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Recent Advances in Photothermal Therapies Against Cancer and the Role of Membrane Transporter Modulators on the Efficacy of This Approach

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Abstract

Recently, much research is focused on the use of photothermal therapy (PTT) as an advanced method to treat various types of cancer. The PTT approach primarily utilizes nanoparticles (NPs) made from metals, carbon, or semiconductors that can convert near-infrared laser irradiation, which penetrates tissues, into local heat that induces cancer cell death. An alternative approach is to utilize NPs (such as liposomes) to carry suitable dye molecules to the same end. Numerous studies concerning PTT have shown that local heat released in cancer cells may suppress the expression of membrane transporter proteins such as P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP1), thus enhancing cytotoxicity and reverse multidrug resistance. In addition, because NPs may be loaded with different substances, researchers have designed multifunctional NPs for PTT by including several agents such as membrane transporter modulators, anticancer drugs, and photothermal agents. This review will focus on the recent advances in PTT utilizing various types of NPs, and their components and characteristics. In addition, the role of membrane transporters in PTT will be highlighted and different methods of transporter modulation will be summarized from several PTT studies in which multifunctional NPs were used to treat cancers *in vitro* and *in vivo*.

Keywords

photothermal therapy, gold nanoparticles, monoclonal antibodies, and membrane transporters

Abbreviations

ADCC, antibody-dependent cellular cytotoxicity; ABC, ATP binding cassette; BPQDs, Black phosphorus quantum dots; CTAB, cetyltrimethylammonium bromide; CT, chemotherapy; CDC, complement-dependent cytotoxicity; EPR, enhanced permeability and retention; EGFR, epidermal growth factor receptors; GO, graphene oxide; ICG, indocyanine green; IONPs, Iron oxide nanoparticles; mAbs, monoclonal antibodies; MRP1, multidrug resistance-associated protein 1; MWCNTs, multiple-walled carbon nanotubes; NGS, nanographene sheets; NPs, nanoparticles; NIR, near-infrared; P-gp, P-glycoprotein; PTT, Photothermal therapy; PEG, polyethylene glycol; PEI, polyethyleneimine; PLGA, polylactic-co-glycolic acid; QD, Quantum

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dots; RT, radiotherapy; ROS, reactive oxygen species; SPNs, semiconducting polymer-based nanoparticles; SWCNTs, single-walled carbon nanotubes; SLC, solute carrier; SPR, surface plasmon resonance; TPP, triphenylphosphonium.

Introduction

Cancer is a group of diseases that affects millions of patients annually. According to the World Health Organization (WHO), cancer accounted for nearly 10 million deaths in 2020; and the most common types of cancer affected the breast, lung, colon, prostate, skin, and stomach.[1] For instance, in 2022, 1 918 030 new cancer cases were projected to occur in the United States,[2] and around 3 million people are currently living with cancer in the UK.[3] These horrible numbers could adversely progress due to the Coronavirus disease 2019 (COVID-19) pandemic that led to delays in both diagnosis and treatment.[4]

The main cancer treatment modalities are surgery, radiotherapy (RT), chemotherapy (CT), and biotherapeutic antibodies. However, these therapies could be either associated with severe side effects or not being sufficiently effective.[5,6] The recent technological advances have enhanced our understanding of cancer and the importance of using multidisciplinary approach to tackle this disease. Photothermal therapy (PTT) is an approach that has attracted extensive research attention as a noninvasive and selective treatment strategy for numerous cancers.[7] The photothermal concept depends on photothermal agents that convert light (typically near-infrared) energy into heat, thus increasing the temperature of surrounding tissue and triggering cancer cell death.[8] These agents typically possess the ability for specific targeting and high photothermal conversion efficiency without excessive thermal damage to surrounding tissues.[9]

Various review articles have focused on different aspects of the PTT including properties of the implemented nanoparticles, temperature optimization, and their clinical development.[10–12] In addition, several articles showed that the heat generated from PTT may enhance the cytotoxicity of PTT in cancer cells.[13–15] This enhancement was related to the effect of heat on the expression of membrane transporters which is one of the major causes of the multidrug resistance phenomenon. Much research thereafter has shown that the loading of PTT nanoparticles with membrane transporter modulators improved the outcomes of PTT both *in vitro* and *in vivo*.[16–18] Consequently, this review will specifically provide an updated summary of the current advances in this field and will highlight the important role of membrane transporters on the efficacy of the PTT approach.

The Nanoparticle Component of PTT

Nanotechnology has rapidly evolved over the past few years to provide significant potential in combating cancer.[19] Nanoparticles exhibit unique characteristics that enhance their application in the field of cancer treatment. These mainly include their selective accumulation into tumor tissues, their versatile structures which facilitate their surface modification for enhanced targeting, along with their ability to load various types of therapeutic agents.[20] The large surface-to-volume ratio of nanoparticles represents an additional advantage[21]; the nanoparticle surfaces can be densely coated with different molecules that have targeting properties[22] as well as other functionalities.

In order to meet the high nutrient and oxygen demands, tumor tissues are characterized by massive and irregular neovascularization with structural and functional abnormalities in the blood vessels presented as very dense and tortuous with fenestrated structure. This will facilitate the penetration of macromolecular compounds with sizes above 40 kDa.[23,24] Moreover, these tissues do not have efficient lymphatic drainage system which will result in the trapping of the penetrated macromolecules inside the tumor tissues for prolonged period of time.[25,26] Together, the increase in the penetration of macromolecules and their retention in the tumor tissues, form the enhanced permeability and retention (EPR) phenomena. The EPR phenomenon has been observed in various solid tumors in rodents, rabbits, dogs, and humans.[27–29] This effect has been later used in the targeting of anticancer therapeutics into the solid tumor by controlling the size and the characteristics of the drug delivery system.[30] Nanoparticles can be effectively used for this purpose since they can accumulate in cancer tissues due to the EPR effects.[31] Different factors seem to affect the use of nanoparticles in PTT including their size, surface properties, shape, and concentration.[32]

A wide range of nanoparticles has been adopted in PTT-based cancer treatments, such as metal nanomaterials (platinum and gold), carbon nanomaterials (graphene and carbon nanotubes), semiconductor nanomaterials (copper), and conducting polymers.[33,34]

Iron oxide nanoparticles (IONPs) are metal-based nanoparticles with magnetic properties. They are safe, biocompatible, with a high ability to absorb both visible, and NIR light and generate heat for PTT.[35] Similar to other nanoparticles, IONPs can accumulate in the tumor tissues based on the EPR effect and the generated heat from the IONPs can result in intense cancer cell death. Moreover, since these nanoparticles have magnetic properties, their accumulation in the cancer tissues can be increased by applying an external magnetic field before exposing them to NIR light. This external magnetic field can also result in the generation of magnetic hyperthermia with subsequent destruction to cancer cells.[36] Moreover, the iron present in these nanoparticles can contribute to iron hemostasis in the body after the metabolism of these IONPs into elemental iron.

Carbon nanotubes are a class of carbon-based nanoparticles that are employed in PTT based on their ability to absorb light energy at wavelengths from 750 to 1000 nm followed by heat

generation. The implementation of carbon nanotubes in sensing/monitoring of cancer has been comprehensively reviewed.[37] Carbon nanotubes are present as either single-walled carbon nanotubes (SWCNTs) or multiple-walled carbon nanotubes (MWCNTs) based on the number of the tube wall layers. The SWCNTs, developed by Liang et al, exhibited an effective destruction of metastatic tumors in an *in vivo* mice model. This was a result of the accumulation of these SWCNTs in the tumor followed by heat generation in response to light irradiation.[38] Yang et al developed PEGylated nanographene sheets (NGS) coated with polyethylene glycol with a size of 10–50 nm in the form of 1–2 layers which showed high tumor accumulation through passive targeting. These NGS showed strong optical absorbance in the NIR region which resulted in a temperature increase by more than 30 °C with a subsequent efficient tumor ablation based on this PTT.[39]

Semiconducting polymer-based nanoparticles (SPNs) used for PTT exhibit favorable properties such as biological compatibility and excellent optical properties. Li et al synthesized highly biodegradable SPNs with photothermic activity which upon NIR irradiation resulting in a local temperature increase up to 45 °C leading to collagen digestion in the tumor extracellular matrix.[40]

Quantum dots (QD) contain several types of materials and are characterized by their small size which promotes their use in PTT. The optical properties of QD can be adjusted by controlling their size and composition, which can result in improved heat generation, high production of reactive oxygen species (ROS), and fast metabolic rate to avoid long exposure toxicity. Black phosphorus quantum dots (BPQDs) are one type of QD that exhibit novel PTT. BPQDs with a lateral size around 2.6 nm have efficient NIR photothermal performance with high photostability. Under irradiation with 808 nm laser, BPQDs resulted in complete *in vitro* killing of cancer cells. Moreover, in the absence of irradiation, these types of nanoparticles have negligible toxicity even at high concentrations resulting in high biocompatibility profile.[41]

Manganese dioxide (MnO_2) nanosheets have been also applied in the field of PTT. pH-/H_2O_2-responsive MnO_2 nanosheets anchored with up-conversion nanoprobes were developed by Fan et al. These can exert excellent PTT under hypoxic conditions by the conversion of the NIR into short-wavelength light which will result in a local temperature increase. In this system, the pH and the H_2O_2 consumption at tumor sites will result in oxygen production to enhance the PTT and at the same time the emitted light quenching in this system protects the normal tissues from ROS-mediated damage.[42]

Gold nanoparticles (AuNPs) are another important type of metal-based nanoparticles that exhibit excellent photothermal activities due to their ability to passively accumulate in the tumor tissues by the EPR effect and their strong absorbance of NIR light. The NIR exposure of these nanoparticles will enhance the resonance of the high number of free electrons present within the metal and on its surface and induce surface plasmon resonance (SPR). This will result in high photothermal conversion activity which will promote apoptosis and necrosis in the cancerous tissues. Once accumulated at the tumor tissues, AuNPs can strongly absorb the laser irradiation and immediately generate heat locally with minimal damage to the adjacent normal tissues.

AuNPs have been extensively investigated in the field of PTT. The ability of AuNPs to absorb light in the visible as well as the near-infrared (NIR) region depends on the AuNP shape and dimension, which influence the SPR required for the photothermal effect. Depending on the dimensions, AuNPs can be classified into three categories. One-dimensional AuNPs include gold nanobelts, nanowires, nanotubes, and gold nanorods. Two-dimensional AuNPs include dimpled AuNPs, truncated triangles, square or rectangular nanoparticles, and hexagonal nanoparticles. All these two-dimensional AuNPs are referred to as gold nanoplates. Three-dimensional AuNPs include nanodumbbells, nanotadpoles, nanostars, nanodendrites, and nanopods. The last three types are further classified as branched gold nanoparticles.[43] These different types of AuNPs have various characteristics and applications. They differ from each other in terms of their physicochemical characteristics, SPR, optical, and electronic properties.[44,45] These differences resulted from the variability of the size, shape, and aspect ratio. The availability of different types of AuNPs which can be easily synthesized has resulted in various applications in many fields such as diagnosis and imaging, targeted drug delivery into specific diseased tissue or organ, biosensing, and most importantly photothermal and photodynamic therapy.[46]

By changing the size and shape of AuNPs, the SPR can be tuned to the NIR region, which imparts high-depth photothermal penetration in tissues.[47] Laser wavelength is also crucial in determining the outcomes of the AuNPs action, in the majority of the AuNPs studied, 808 nm PTT laser wavelength was used. A few studies have employed other wavelengths, including 650, 980, and 1064 nm. However, the use of 808 nm has proven to cause the most effective temperature enhancement.[48]

For more efficient cancer treatment, several types of the nanoparticles used to exert PTT can also be loaded with some chemotherapeutic anticancer agents to achieve an enhanced synergistic effects between the chemotherapy and the PTT. In this regard, the nanoparticle will act as a carrier to deliver the loaded drug into the target cancer cells based on the EPR effect, and the same nanocarrier will absorb the NIR light to induce PTT. This will improve the therapeutic outcomes of chemotherapy when combined with PTT using the same nanocarrier. This can be seen in the work of Wu et al who developed an engineered versatile nanoplatform based on graphene oxide (GO) coated with mesoporous silica for synergetic effect between the PTT and doxorubicin. The GO is used for improved photothermal effects, and the mesoporous silica will enhance the doxorubicin loading. The *in vivo* study demonstrated that these nanoplatform could accumulate in the cancer cells by the EPR effect and the NIR can trigger doxorubicin release and result in a local temperature increase to above 50

°C exhibiting excellent antitumor synergy between chemotherapy and PTT.[49] Other platforms have employed Cisplatin as a loading agent. Similar to Doxorubicin, Cisplatin have showed enhanced localized antitumor effects by improving hypoxia at the site of action.[50]

Liposomes, which are the most studied type of nanoparticles, are also investigated in PTT. Liposomes are composed of phospholipids, cholesterol, and other components which will self-assemble into a bilayer structure upon hydration.[51] Liposome components by themselves have poor light absorption properties, however, their use in PTT is based on loading NIR absorbing dyes, such as indocyanine green (ICG), IR780, IR820, and IR792. Following the accumulation of these loaded liposomes into the target cancers, the dyes will be released and used for PTT.[52] The used irradiation wavelength will depend on the selected dye loaded into the liposomes. Moreover, liposomes have another advantage in the context of PTT in that additional molecules can be co-loaded into liposomes such as chemotherapeutic agents for a synergetic effect between PTT and chemotherapy. Xu et al developed ICG-loaded liposomes wrapped with C6 glioma cell membranes for potential application in PTT. The liposomes enhanced the accumulation of the ICG dye in glioma tumors in BALB/c nude mice which showed a peak absorption at 808 nm resulting in complete tumor eradication within 18 days.[53]

Other types of nanoparticles that can also be used in PTT include sulfide nanoparticles,[54] silver nanoparticles,[55] silica,[56] palladium,[57] and polymeric nanoparticles.[58] Each one of them has different features and specific applications in the field of PTT with highly promising future outcomes.

The Targeting Component of PTT

The excellent properties of nanoparticles can be improved through the conjugation of targeting molecules, such as monoclonal antibodies (mAbs), onto the surfaces of nanoparticles to enhance the targeting effect on certain cancer cells.[59] Antibodies are widely used in cancer due to their versatile targeting capability.[60] In addition, antibodies can directly target cancer cells while concurrently promoting the induction of long-lasting anti-cancer immune responses.[61] For example, antibodies could target tumor antigens, tumor microenvironment to reduce tumor growth, or to target cells of the immune system to enhance the antitumor immune responses.[60] In addition, antibodies could manipulate the host immune response to tumors through either antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), or the induction of adaptive immune responses.[9,62]

The microenvironment of cancer comprises several factors that can inhibit the immune responses against cancer, promote cancer cell growth, and induce pro-tumorigenic angiogenesis.[63] Targeting these critical factors and proteins within the cancer microenvironment was proven clinically through the successful approval of several antibodies against different forms of cancer. Consequently, mAbs represent major tools to fulfill this requirement.

Several articles highlighted the utilization of AuNPs-mAbs conjugates within various photothermal approaches (Table 1). Different shapes of AuNPs were used, including nanorods (AuNR), nanoshells (AuNSH), nanostars (AuNST), and nanocages (AuNC). The high representation of AuNR could be attributed to their excellent physical properties represented by strong NIR absorption due to the longitudinal localized SPR band.[64] The mAbs that have shown promising efficacy (Table 1) included anti-HSP mAb that was used to target HSP70 expression in 4T1 cell lines.[65] In addition, an anti-HER2 mAbs were tested on SKBR3, MDA-MB-231, MCF-7 and CIK cells, and C57BL/6 and MCF-7 tumor-bearing mice.[66] Another mAb that provided significant results is the anti-CD33 antibody that was conjugated with AuNST.[67]

Different researchers have also investigated the coating of these AuNPs with other molecules like bovine serum albumin, polylactic-co-glycolic acid (PLGA), chitosan, and indocyanine green (ICG) to increase the stability of the AuNPs.[68–70] The implemented antibodies have mainly targeted epidermal growth factor receptors (EGFR) in multiple cancer cell lines, since EGFR is the most commonly overexpressed membranous oncogenic protein in cancer.[71] Numerous cell lines were used to test these particles as, for example, in glioblastoma (U373-MG and 1321N1 cell lines),[72] breast cancer (MDA-MB-231 and HeLa cells),[73] lung cancer (A549 cells),[74] and oral cancers (HOC313 clone 8 and HSC 3).[8]

Diverse types of gold nanoparticles were utilized in various articles that we examined (Supplemental Table 1). One of the most utilized shapes of gold nanoparticles was AuNR followed by AuNST, AuNP, and AuNC (Figure 1). However, it was noted that a large number of the AuNPs that do not utilize mAbs were coated or had alternative surface modifications.

One of the common surface modifications is polyethylene glycol (PEG). In 13 AuNPs, PEG utilization is linked to its ability in improving the distribution of the AuNP throughout blood circulation.[79] Other platforms tended to assist the AuNPs by using mesoporous silica as a coating agent, because it possesses favorable biocompatibility, thermal stability, and desirable chemical properties. As drug carriers, they facilitate the effective loading and subsequent controlled release of the drugs to the target sites.[80] The use of hyaluronic acid (HA) as a coating agent has also proved its efficacy in multiple studies.[66] The combination of AuNPs and HA increases the mobility of the AuNPs, resulting in a better distribution over the cancer site. Other articles have implemented the use of polyethyleneimine (PEI), as it is the most widely used cationic polyelectrolyte for preparing positively charged AuNPs. They feature dual roles as stabilizing/reducing agents for gold ions and their chemical stability.[81]

Most of the AuNPs analyzed were studying the efficacy and safety in breast cancer, followed by lung, cervical, and colon cancers (Figure 2). This focus is interestingly reflecting the incidents of these types of cancer. In addition, breast cancer is associated with challenges like treatment-related adverse events, poor outcomes in triple-negative breast cancer and balancing the treatment with quality of life.[82] The use of AuNPs might be a crucial

Table 1. Summary of Targeted Therapy Utilization in Gold Nanoparticles.

Shape	Coating and Load	Targeting Agent	Target	Size (nm)	Laser Wavelength (nm)	Laser Power Density (W/cm^2)	Duration of Radiation (min)	Cancer Cell Line	Temperature (°C)	Cancer Type (Indication)	Reference
AuNC	-	Anti-HSP monoclonal antibody	HSP70	61.2 ± 4.85	808	1	5	4T1 and Female BALB mice	-	Breast	[65]
AuNR	-	Anti-EGFR antibody	EGFR	-	808	2.5	40 and 75	U373-MG and 1321N1	-	Glioblastoma	[72]
	-	Anti-EGFR antibody	EGFR	10 × 40	808	1.5	3	MDA-MB-231	$T_{max} = 43$	Breast	[73]
	-	Anti-HER2 antibody and HA	HER2 and CD44	55.1 × 14.1	808	2	10	MCF-7 and MCF-7 tumor bearing mice	≈ 55	Breast	[66]
	-	Anti-EGFR antibody	EGFR	40	850	1.5	5	A549	-	Lung	[74]
	Coated with BSA	R837	DCs, CD8 + T cells	122.1	1064	1	10	B16-F10	-	Melanoma	[75]
AuNSH	Coated with PLGA	Anti-HER2 antibody	EGF/ HER-2/ CD133 antibody	248.3	808	1	10	SKBR3 and MDA-MB-231	-	Breast	[76]
	Chitosan-layered, Paclitaxel loaded	Anti-EGFR antibody	EGFR	9	808	1.2	5	HeLa and MDA-MB-231 cells/ MDA-MB-231 tumor-bearing mice	$T_{max} = 52.5$	Breast	[77]
AuNST	ICG	Anti-HER2 antibody (Trastuzumab)	EGF/ HER-2/ CD133 antibody	135.3	808	0.5	3	CIK cells, SKBR3/ C57BL/6 and BALB/c nude mice	-	Breast	[78]
	-	Anti-CD33 antibody	EGF/ HER-2/ CD133 antibody	120	808	0.8	5	PC3 cell-line/male BALB/c athymic nude mice	-	Prostate	[67]

Abbreviations: AuNC, gold nanocage; AuNR, gold nanorod; AuNSH, gold nanoshell; AuNST, gold nanostar; BSA, bovine serum albumin; PLGA, polylactic-co-glycolic acid; ICG, indocyanine green; HSP, heat shock proteins; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; R837, imiquimod; CD33, transmembrane receptor; HSP70, family of conserved ubiquitously expressed heat shock proteins; CD44, cell-surface glycoprotein antigen; DCs, antigen-presenting cells for activating native T cells; CD8, transmembrane glycoprotein; CD133, prominin-1; PTT, photothermal therapy; 4T1, cell line posing 6-thioguanine resistance; U373-MG, human glioblastoma cell line; 1321N1, human astrocytoma cell line; MDA-MB-231, triple-negative breast cancer cell line; MCF-7, human breast cancer cell line; A549, lung carcinoma epithelial cell line; B16-F10, cell line of murine melanoma; HOC313, human oral squamous-cell-carcinoma cell line; HSC3, human oral squamous carcinoma cell line; SKBR3, human breast cancer cell line; HeLa, HeLa cell line; CIK, cytokine-induced killer cells; C57BL/6, Inbred strain of laboratory mouse; PC3, prostate cancer cell line.

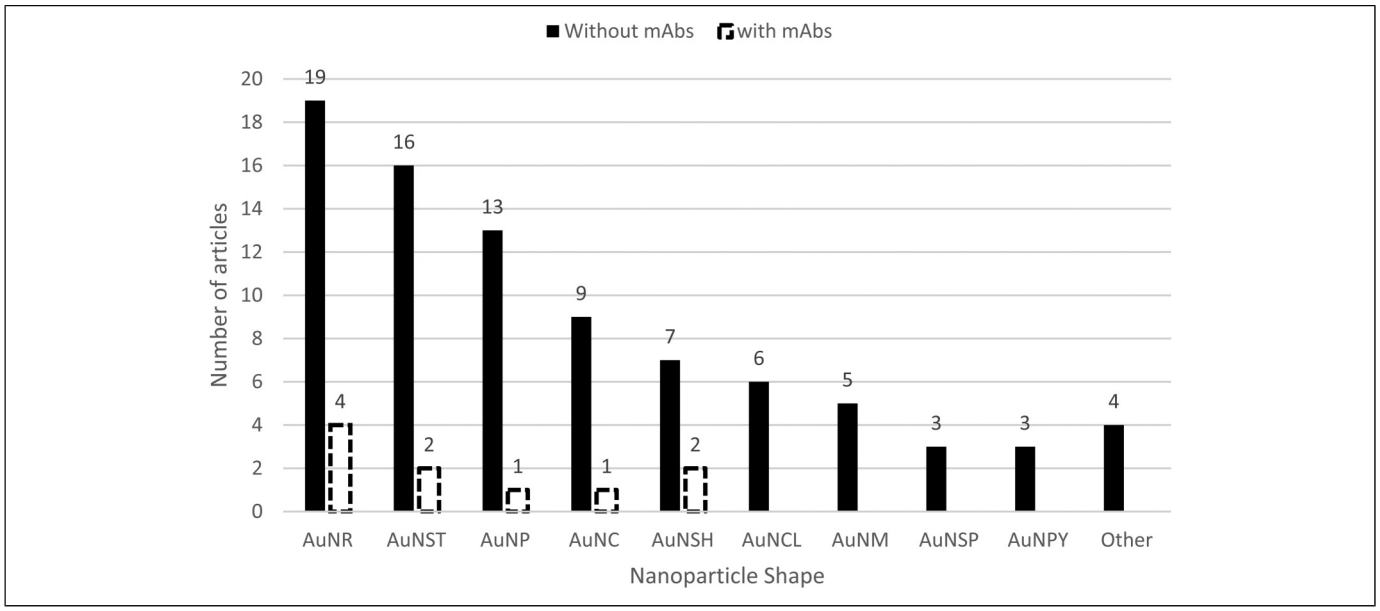

Figure 1. Number of examined publications utilizing AuNPs classified by shape. AuNR (gold nanorod), AuNST (gold nanostar), AuNP (gold nanoparticles), AuNC (gold nanocages), AuNSH (gold nanoshell), AuNCL (gold nanoclusters), AuNM (gold nanomaterials), AuNSP (gold nanospheres), and AuNPY (gold nano pyramids). Others include one article for each of the AuNU (gold nanourchins), AuNPR (gold nanoprisms), AuNF (gold nanoflower), and AuND (gold nanodumbbells). The articles were covering the period 2015–2022, as summarized in Supplemental Table 1 and Table 1.

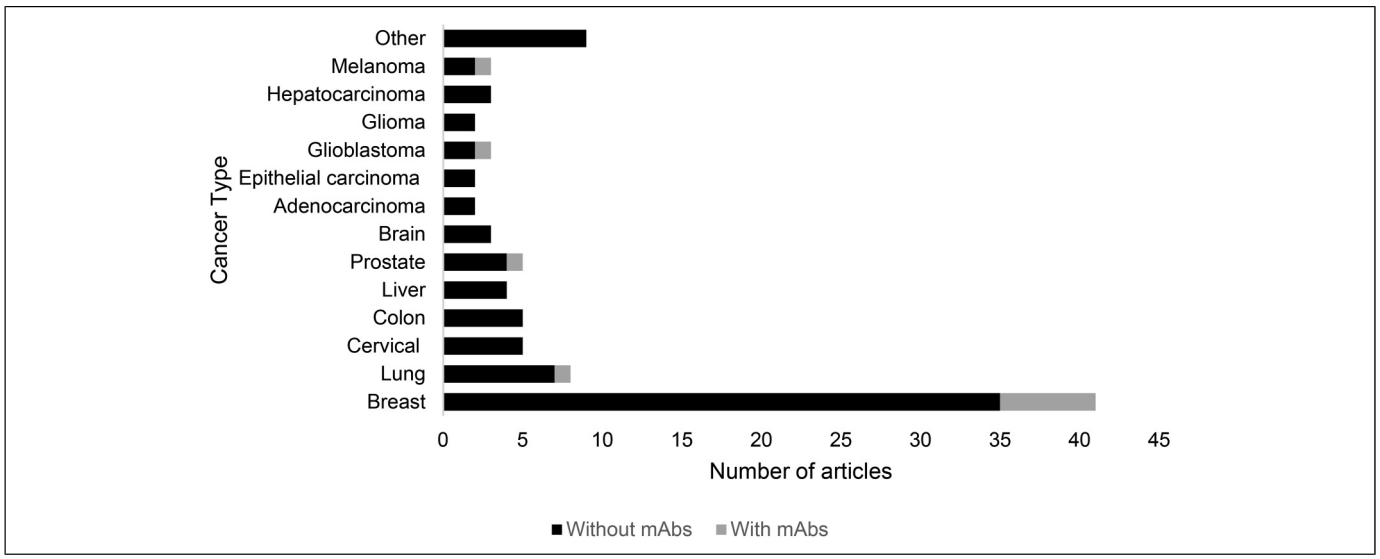

Figure 2. Number of publications classified by cancer type. The articles covered a wide range of cancers. Others include one article focusing on squamous cell, squamous vulvar, osteosarcoma, sarcoma, hepatoma, gastric, lymphoma, and pancreas cancers. The articles were covering the period 2015–2022, as summarized in Supplemental Table 1 and Table 1.

treatment option due to breast cancer's high prevalence and the increased focus on localized treatment methods of noninvasive nature. Huang et al prepared gold nanorods that are conjugated to antibodies to specifically bind to the cancer cells before exposing these nanoparticles to continuous red laser at 800 nm to photothermally induce cancer cell killing.[8] However, gold nanoparticles suffer from some limitations in terms of their long exposure toxicity and their relatively weak optical signal.[12]

Other promising approaches for enhanced phototherapy might focus on improving the efficiency of photosensitizers. Mitochondria-targeted nanomedicines are being developed to focus on damaging the mitochondria DNA, disturbing respiratory chain and redox balance, and increasing reactive oxygen species (ROS). Such attempts to enhance the photothermal efficacy have been comprehensively reviewed by Gao et al.[83] For instance, targeting the mitochondria, by diketopyrrolopyrrole-based

photosensitizer,[84] has demonstrated an efficient approach to produce thermal energy and singlet oxygen under 635 nm laser irradiation with ideal cytocompatibility and highly effective antitumor effects. Furthermore, Lv et al[85] have utilized polydopamine-coated hollow copper sulfide nanoparticles as the photothermal nanoagents and thermosensitive drug carriers for loading hypoxia-activated prodrug. Chlorin e6 (Ce6) and triphenylphosphonium (TPP) were conjugated onto the surface of the nanoplatform. The former can generate ROS and simultaneously exacerbate the cellular hypoxia, while the latter aided accumulation of the nanoplatform in mitochondria to restore the drug activity and avoid drug resistance. Consequently, this approach highlights the potential of using additional molecules and substances to synergize the photothermal effect in cancer treatment. In a similar vein, we will focus on the use of membrane transporters in the following section.

The Role of Membrane Transporters in PTT

Membrane transporter proteins, which transport drug substances, are usually referred to as drug transporters in biomedical sciences. Two major families of membrane transport proteins are the ATP binding cassette (ABC) family and solute carrier (SLC) family. Solute carriers mediate the transport of ions or other solutes including vitamins, minerals, peptides, toxins, as well as numerous drug substances across cell membranes.[86,87] ABC transporters efflux molecules from the cell membrane in a process requiring energy in the form of ATP[86,88]; while SLC is both cellular influx and efflux carriers not directly dependent on ATP use, but often utilize the ion gradient across the cell membrane found for eg Na^+ or H^+.[89] In humans, membrane proteins are expressed in different tissues and organs such as the intestine, liver, kidney, blood-brain barrier, and testes.[90] Importantly, ABC transporters were found to be highly expressed in cancer cells which may lead to efflux of diverse structurally and mechanistically unrelated anticancer drug substances, and this is a major cause of multidrug resistance.[91,92] ABC transporters of importance in multidrug resistance are mainly permeability glycoprotein 170 (P-glycoprotein, P-gp which is encoded by the *ABCB1* gene), multidrug resistance-associated protein 1 (MRP1, encoded by *ABCC1*), and breast cancer resistance protein (BCRP, encoded by *ABCG2*).[91–94]

Recently, photothermal therapy used in cancer treatment was found to influence the expression of membrane transporters through the effect of hyperthermia which may either denaturate membrane transporters such as P-gp and MRP1 or increased the expression of heat shock factor-1 (HSF-1) which in turn decreased the expression of membrane transporters in cancer cells.[13,14,16] In addition, the substantial progress in designing nanoparticles that may accommodate different types of molecules such as anticancer drug substances, surfactants, and biological materials such as RNA and monoclonal antibody, enabled nanoparticles containing a photothermal agent and a membrane transporter modulator. These nanoparticles have been investigated *in vitro* and *in vivo*.[17,95–97]

Nanoparticles for Photothermal Effect and Modulation of Membrane Transporters In Vitro

In order to obtain a synergistic effect of ablating the cancer cells and reversing the multidrug resistance related to overexpression of ABC transporters, different methods were utilized to modulate membrane transporter abundance. Molecules or biological materials that have been combined with photothermal nanoparticles include (1) Photothermal agent which produces heat when exposed to NIR light and the released heat may decrease the expression of membrane transporters such as P-gp[13] and MRP1,[14] or induce P-gp denaturation,[15] (2) P-gp monoclonal antibody,[96] (3) Nonionic surfactants such as Pluronic P123 and TPGS,[17,95] (4) siRNA to downregulate the expression of a membrane transporter protein,[18,97] (5) Nitric oxide donor molecule to liberate nitric oxide which decreases the expression of membrane transport proteins,[98,99] (6) Natural product with specific P-gp inhibitory properties such as curcumin,[100] and (7) Combination of different methods (Table 2).

Wang and coworkers used gold nanoparticles which were loaded with the anticancer drug substance doxorubicin (P-gp substrate).[13] They found that hyperthermia increased the expression of HSF-1 which depressed the expression of P-gp, thus decreased the efflux of doxorubicin and enhanced the cytotoxic effect in MCF-7/ADR cells.[13] When cyanine dye-loaded nanoparticles were exposed to NIR laser irradiation, the ensuing hyperthermia was found to decrease the expression of MRP1, thus increasing cisplatin-prodrug cytotoxicity in A549 and A549R cells, and enhancing the ablation effect of the nanoparticles.[14]

Previous research has also reported that hyperthermia decreased MRP1 expression in HeLaMRP1 cells.[16] In addition, P-gp monoclonal antibodies were included in oxidized carbon nanoparticles to reverse P-gp activity and to decrease etoposide (P-gp substrate) efflux in A549 and A549R cells.[96] Besides the photothermal effect mediated by oxidized carbon nanohorns, utilization of the P-gp monoclonal antibody suppressed the efflux activity of P-gp and increased the intracellular concentration of etoposide, and enhanced the cytotoxic effect of the nanoparticles.[96]

Zeng et al[18] were able to augment the photothermal effect of polydopamine-modified black phosphorus by inclusion of doxorubicin (P-gp substrate) and P-gp siRNA in nanosheets. P-gp siRNA downregulated P-gp and enhanced the anticancer cytotoxicity in MCF-7 and MCF-7/ADR cells. Moreover, Cheng et al[97] included a P-gp siRNA in polydopamine nanoparticles decorated with folic acid and these nanoparticles showed outstanding photothermal effect, P-gp downregulation, and a selective cell targeting ability mediated by the presence of folic acid in the formulation.

Nonionic surfactants which were shown to inhibit P-gp *in vitro* and *in vivo*[105–109] were included in the design of photothermal nanoparticles.[95,102] TPGS is a nonionic surfactant with P-gp inhibitory properties[110] and was included in nanoparticles containing a photothermal agent indocyanine green, and doxorubicin.[102] In the latter study, it was shown that TPGS decreased the expression of P-gp and enhanced the cytotoxicity

Table 2. Nanoparticles for Photothermal Therapy and Modulation of Membrane Transporters *In Vitro* and *In Vivo*.

Nanoparticle Components	Targeted Transporter	Transporter Substrate	Transporter Modulator	Effect of Transporter Modulator *In Vitro*	Effect of Nanoparticle + NIR Light *In Vivo*	Reference
Gold, silicon dioxide, doxorubicin	P-gp	Doxorubicin	Hyperthermic effect	Hyperthermia increased the expression of heat shock factor-1 (HSF-1). HSF-1 depressed the expression of P-gp on cell membrane of MCF-7/ADR cells		13
Cyanine dye, cisplatin prodrug	MRP1	Cisplatin prodrug	Hyperthermic effect	Hyperthermia inhibited the expression of MRP1 and enhanced the cytotoxicity in A549 cells and resistant A549R cells	Successful ablation of A549R tumor and A549 tumor in mice without regrowth, and no effect on other organs	14
Oxidized carbon nanohorns, PEG, etoposide, P-gp monoclonal antibody	P-gp	Etoposide	P-gp monoclonal antibody	P-gp inhibited by direct interaction between the antibody and P-gp. Decrease the cellular efflux of etoposide in A549 and A549R cells	Significant reduction of relative tumor volume (RTV) in A549R tumor-bearing mice	96
Polydopamine, doxorubicin, PEG, folic acid, P-gp siRNA	P-gp	Doxorubicin	P-gp siRNA	P-gp expression was downregulated by 57% in MCF-7/ADR cells	Significant reduction in tumor volume and weight in mice bearing MCF-7/ADR tumor	97
Polydopamine, black phosphorus, doxorubicin, P-gp siRNA, PEG, aptamers	P-gp	Doxorubicin	P-gp siRNA	P-gp expression decreased by 68% and the cellular efflux of doxorubicin decreased, thus the cytotoxicity improved in MCF-7 and MCF-7/ADR cells	Significant tumor ablation in MCF-7/ADR tumor-bearing nude mice, and no effect on other organs	18
IR820 dyes, doxorubicin, porous silicon attached with amine group	P-gp	Doxorubicin	Hyperthermic effect	Hyperthermia induced P-gp denaturation in MCF-7 cells and MCF-7/ADR cells		15
P-Cypate, doxorubicin, pluronic P123	P-gp	Doxorubicin	Pluronic P123, Hyperthermic effect	Pluronic P123 inhibited P-gp activation by depleting ATP production in MCF-7/AD. Hyperthermia increased the expression of HSF-1, which in turn depressed the expression of P-gp	Tumor growth was completely inhibited in MCF-7/ADR tumor-bearing mice	95
Polydopamine, doxorubicin, TPGS	P-gp	Doxorubicin	TPGS	The cytotoxicity of doxorubicin increased by TPGS due to P-gp inhibition effect in MCF-7/ADR cells. It was suggested that TPGS reduced the transmembrane potential of mitochondria and consequently inhibited the ATP-production activity		101
Indocyanine green, Doxorubicin, TPGS	P-gp	Doxorubicin	TPGS	TPGS inhibited P-gp expression and enhanced the cytotoxicity of doxorubicin inSCG7901/VCR cells		102,103
Polydopamine, 12-aminododecanoic, BNN6, doxorubicin, TPGS-Galactose	P-gp MRP3	Doxorubicin Rhodamine 123	TPGS Nitric oxide	Nitric oxide decreased the expression of P-gp and MRP3 in HepG2/ADR cells. TPGS decreased the intracellular ATP content and P-gp expression on cell membrane, and this inhibited P-gp and	Inhibited the tumor growth in HepG2/ADR-tumor-bearing mice. Significant reduction in tumor weight without affecting the body weight of the mice	17

(continued)

Table 2. (continued)

Nanoparticle Components	Targeted Transporter	Transporter Substrate	Transporter Modulator	Effect of Transporter Modulator *In Vitro*	Effect of Nanoparticle + NIR Light *In Vivo*	Reference
				enhanced doxorubicin accumulation in the cells		
Indocyanine green, curcumin, molybdenum disulfide	P-gp		Curcumin	Nanoparticles containing curcumin inhibited the expression of P-gp in HepG-2 cells	Tumor volume and weight reduced significantly in hepatocellular carcinoma H22 tumor-bearing mice	104
Copper selenide, N-diazeniumdiolate, doxorubicin	P-gp	Doxorubicin	Nitric oxide	The released nitric oxide gas inhibited P-gp expression by (≈ 40%) in MCF-7/ADR cells	Tumor growth was completely inhibited (TIR = 100%), with no side effects on other organs	98
N-doped graphene oxide (N-GO), BNN6, mitoxantrone	P-gp	Mitoxantrone	Nitric oxide	The released nitric oxide gas inhibited P-gp expression on the membrane of MCF-7/ADR cells	Significant decrease in tumor volume in MCF-7/ARD tumor-bearing nude mice without side effects on other organs	99

Abbreviations: BNN6, nitric oxide donor agent, NN′-di-sec-butyl-N,N′-dinitroso-1,4-phenylenediamine; PEG-b-PDPA, cypate-conjugated poly(ethylene glycol)-block-poly(diisopropanolamino ethyl methacrylate; TPGS, diblock copolymer, D-α-tocopheryl polyethylene glycol 1000 succinate; A549, nonsmall cell lung cancer cell line; A549R, multidrug resistant variant of A549 cells; MCF-7, breast cancer cells; MCF-7/ADR, adriamycin resistant cell line of MCF-7; SGC7901/VCR, vincristine-resistant human gastric cancer cell line; HCC, hepatocellular carcinoma; TIR, tumor inhibitory rate; HepG-2 cells, human hepatoma cells.

of doxorubicin in SGC7901/VCR cells.[102] To potentiate the photothermal effect of nanoparticles, inclusion of several molecules to inhibit membrane transporter activities was also investigated. Du et al included TPGS and nitric oxide donor molecules (N,N′-di-sec-butyl-N,N′-dinitroso-1,4-phenylenediamine [BNN6]) in polydopamine/doxorubicin nanoparticles.[17] TPGS and the released nitric oxide decrease P-gp and MRP3 expression, and reduced intracellular ATP content, thus enhanced intracellular doxorubicin, and increased the cytotoxicity in HCC cells. Other studies reported using nitric oxide donor molecules as P-gp modulators in order to enhance the photothermal effect of nanoparticles.[98,99] In these studies, nitric oxide decrease the expression of P-gp on MCF-7 and MCF-7/ADR cells, thus reversed multidrug resistance and potentiated the effect of anticancer drug substances included in the nanoparticles, consequently, the photothermal effect was augmented.[98,99]

Nanoparticles for Photothermal Effect and Modulation of Membrane Transporters In Vivo

In vivo studies were conducted in mice to compare the effect of multifunctional nanoparticles in the presence or absence of NIR light (Table 2). In these studies, researchers designed and characterized nanoparticles containing a photothermal agent, membrane transporter modulator, and/or a chemotherapeutic agent. Membrane transporter modulators used in *in vivo* studies were nonionic surfactants, siRNA, monoclonal antibody, and/or nitric oxide donor compounds to reverse multidrug resistance in tumors.[14,17,18,95,96,98,99,104] Xenograft tumors were implanted into mice to investigate the effect of the multifunctional nanoparticles, with or without NIR light, on tumor volume, and the overall tumor growth in animals. Several studies showed a significant reduction in tumor volume and weight in mice treated with nanoparticles and exposed to NIR laser compared to control (without laser exposure; Table 2).[14,17,18,95,96,98,99,104] Histopathological studies were also performed to assess the effect of nanoparticles components on other tissues and no side effects were reported on other organs such as heart, liver, and kidneys.[14,17,18,95,96,98,99,104]

Pharmacokinetic studies conducted in Sprague–Dawley rats showed prolonged systemic circulation time of photothermal nanoparticles in blood compared to circulation of anticancer drug substances not loaded in nanoparticles.[18,97] The prolonged circulation time may increase the exposure of photothermal agents and anticancer drug substances to the tumor sites, enhance the uptake of the nanoparticles by the tumors, and achieve a maximum inhibition of cancer growth. Interestingly, one study reported a 152- and 12-fold increase in the maximal plasma concentration (C_{max}) and in the area under the plasma concentration time profile (AUC), respectively, in rats received intravenous P-cypate micellar formulation containing doxorubicin compared to control (rats receiving doxorubicin only).[95] After intravenous administration, a single dose of polydopamine nanoparticles containing

doxorubicin, researchers reported a prolonged blood circulation of doxorubicin administered in the nanoparticles formulation noted as a seven-fold increase in half-life ($t½$) compared to rats received equivalent dose of free doxorubicin.[17] The results from these preclinical studies in animals indicated a promising future for photothermal therapy when included in multifunctional nanoparticles to simultaneously reverse multidrug resistance by membrane transporter modulation and ablate human tumors.

Conclusions

Photothermal therapy seems a promising approach to treat patients with cancer diseases in the future. Gold nanoparticles are the most utilized type of nanoparticles in PTT. Targeting cancer by conjugating the PTT nanoparticles with monoclonal antibodies or by alternative coatings enhances the therapeutic efficacy of the PTT approach. In addition, the inclusion of membrane transporter modulators in PTT nanoparticles enhanced the efficacy of the formulation *in vitro* and *in vivo*. It seems that the current advancement in designing multifunctional nanoparticles will assist researchers to create more effective and safe nanoparticles for PTT by the inclusion of different substances in the formulation, with each having a specific role in the treatment of cancer diseases.

Despite the remarkable progress in the development of the photothermal concept, different challenges are still to be fine-tuned, and these can mainly affect the safety and efficacy of the developed therapies. The improvements could be directed toward the three components of the photothermal therapies: targeting molecules, linkers, and nanoparticles. The development of gold nanorods that are free from cetyltrimethylammonium bromide (CTAB), which, for example, is currently implemented by companies like Sona Nanotech Inc.,[111] could significantly reduce any potential toxicity of CTAB. Further research could also enhance the NIR penetration depth by optimizing the aspect ratio, shape, and composition of the selected nanoparticles. The targeting molecules could be optimized through the implementation of smaller antibody fragments or multispecific antibodies. The selection of efficient linkers that can specifically bind to the antibodies, without affecting the binding regions, while remaining stable within the physiological system is also essential and is currently the focus of different companies like SiMologics Ltd[112] and BroadPharm.[113] Other enhancements could be achieved through the utilization of membrane transporter modulators, heat resistance blockers, and optimization of the cancer cell-death mechanisms (apoptosis vs necroses), and successful regulation of the tumor microenvironment. Moreover, many studies currently investigating the effect of PTT in cell cultures and animal models require follow-on clinical trials to confirm the overall efficacy in humans.

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The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Mohammed Al Qaraghuli is employed by the company SiMologics Ltd.

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