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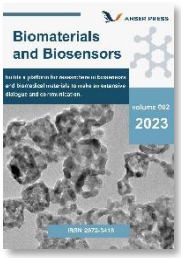

Advances in Novel Tumor Therapeutics Based on Nanomaterial Technologies

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ABSTRACT

Cancer is the leading cause of death in the world, throughout the global researches of cancer treatment, people have a deeper understanding of cancer, and the treatment methods are constantly breakthrough. Conventional surgery, chemotherapy and radiotherapy have serious adverse effects and patients' quality of life is not significantly improved. Now, photodynamic therapy, photothermal therapy and thermodynamic therapy based on nanotechnology and materials technology are booming, and the development of these novel cancer therapies and their combination therapies brings more possibilities for cancer treatment. This review summarizes the research progress of novel cancer therapies based on nano and material technology from the aspects of mechanism of action and therapeutic methods, hoping to provide reference for their clinical application.

KEYWORDS

Novel cancer therapies; Nano and material technology; PDT; PTT; TDT

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1. Introduction

Cancer, as one of the leading causes of death in the world, seriously threatens people's lives. The global incidence of malignant tumors is increasing year by year. Worldwide, an estimated 19.3 million new cancer cases and about 9.95 million cancer deaths occurred in 2020. The global cancer burden is estimated to be 28.4 million cases in 2040, a 47% rise from 2020[1, 2]. Many types of cancer are characterized by high mortality and recurrence rates. Traditional treatments include surgery, chemotherapy, and radiation therapy, however, many contraindications, serious adverse reactions and other limitations can not significantly improve the quality of life of patients. Moreover, most tumors are occult and metastases have already occurred when diagnosed, and some tumors are not sensitive to radiotherapy and chemotherapy. Therefore, surgery is still the main treatment at present. The process of complete excision of cancer tissue by surgery is limited due to the unclear boundary of cancer tissue. Therefore, there is an urgent need for extensive therapeutic modalities with minimal adverse reactions[3, 4]. New therapeutic modalities such as gene therapy, epigenetic therapy and immunotherapy are all gradually developing. Surprisingly, although there are many modalities such as gene therapy, RNA interference therapy and cell therapy, the overall survival time of tumor patients does not seem to be prolonged due to intratumoral heterogeneity and tumor competitive metastasis, so that, new tumor treatment modalities need to be established. For the past few years, photodynamic therapy (PDT), photothermal therapy (PTT) and thermodynamic therapy (TDT) have gradually come into people's vision with the continuous efforts of researchers.

The emergence of nanotechnology and material technology has promoted the continuous development of new forms of anti-tumor drugs, which realized the targeted therapy that can accurately deliver drugs to tumor tissues. These new drug forms, with their stronger specificity, deeper delivery range and other characteristics, provide the possibility for humans to deepen the understanding of the anti-tumor regulatory mechanism. Moreover, with the rapid development of nanotechnology, the applications of PDT, PTT and TDT have gained a broader platform.

2. Photodynamic therapy in oncology

2.1. The mechanism of photodynamic therapy (PDT)

PDT is a new form of cancer treatment with noninvasive and highly selective. Although still emerging, it is already a successful and clinically approved therapeutic modality used for the management of neoplastic and nonmalignant diseases. PDT consists of 3 essential components: photosensitizer (PS), light (harmless visible or near-infrared light of the appropriate wavelength corresponding to the absorption range of PS), and oxygen. The specific light stimulates PS to an excited state, excited photosensitizer delivers energy to surrounding oxygen, reactive oxygen species (ROS) including singlet oxygen are produced. The latter can rapidly cause significant toxicity on surrounding tissues and cells, leading to death via apoptosis or necrosis (Figure 1)[5-7]. It is worth noting that hydrogen peroxide (H_2O_2), a component of ROS, can either induce autophagy in cells or transform into hydroxyl group with stronger oxidative activity, which is also more cytotoxic. The laser power required for this process is low, therefore it does not cause thermal damage to cells and tissues[6]. In addition, it is found that none of the clinically approved PSs can enter the nucleus of target cells, limiting DNA damage which can lead to mutations that make cells resistant to treatment, therefore the occurrence of PDT resistance can be prevented to a certain extent. PDT has been widely used to treat tumors such as esophageal cancer and skin cancer. However, the application of PDT in the treatment of deep tissue diseases such as deep tumors is limited due to the low solubility of most photosensitizers,

the lack of targeting, and the insufficient penetration of excitation light source to skin and tissue. There are two approaches may increase the antitumor effectiveness of PDT: one is sensitization of tumor cells to PDT and another is interference with cytoprotective molecular responses induced by PDT in surviving tumor or stromal cells[7].

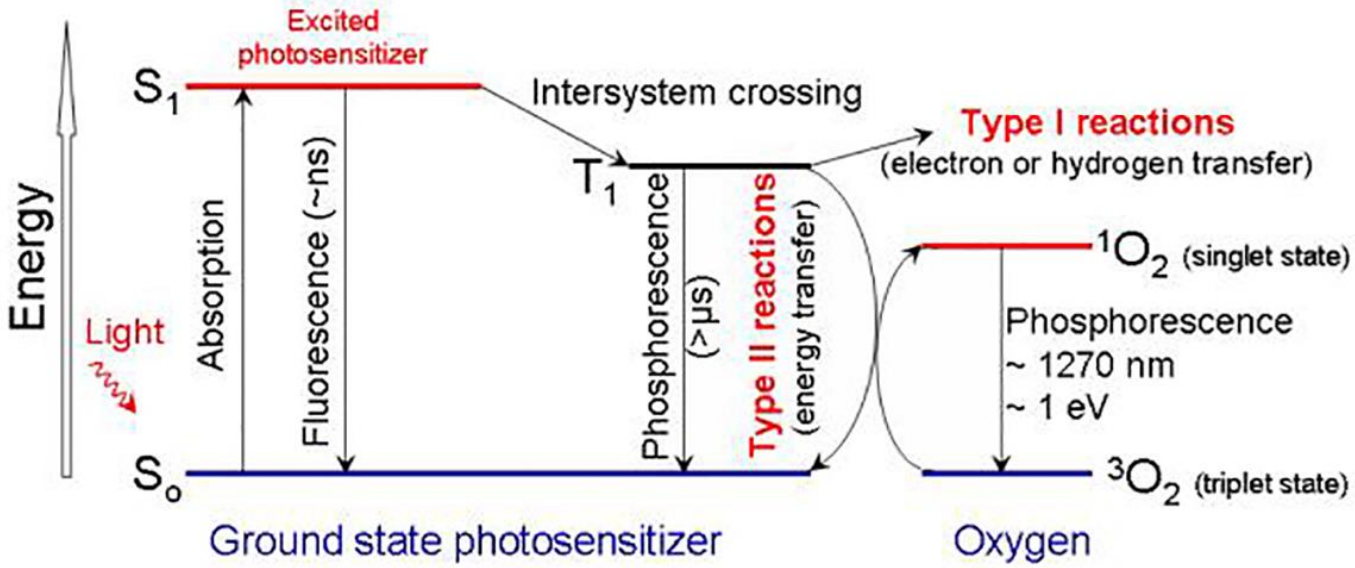


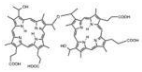
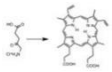
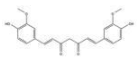
Figure 1. Photosensitization processes[8]. A photosensitizer, is irradiated with a light wavelength and is converted from the singlet basic energy state S_0 into the excited singlet state S_1 because of the photon absorption. The molecule in S_1 may undergo intersystem crossing to an excited triplet state (T_1) and then either form radicals or, more likely, transfers its energy to molecular oxygen ($^3O_2$) and form singlet oxygen ($^1O_2$), which is the major cytotoxic agent involved in PDT.

2.2. Photosensitizers

Photosensitizers are catalysts for the generation of ROS in the process of PDT, which is an important factor determining the effect of PDT. The choice of photosensitizer is related to the type of disease and the route of administration[9]. Currently, photosensitizers can be divided into three generations. The first generation is represented by hematoporphyrin derivatives, and the active components are mainly dihematoporphyrin ethers or esters. The second generation includes phthalocyanines, porphyrins derivatives and gecycloquinones which uses longer wavelength excitation light, achieve a stronger tissue penetration, deeper treatment, higher ROS production rate and better therapeutic effect compared with the first generation of photosensitizers (Table 1). The third generation is formed by the combination of the second generation photosensitizers and targeting ligands, including photosensitizers of immune targeting, photosensitizers of epidermal growth factor receptor targeting, photosensitizers of mRNA targeting and so on, which further improve the targeting of photosensitizers and the efficiency and safety of PDT[10-15].

Tetrapyrrole absorption spectrum showing porphyrins, chlorins and bacteriochlorins.

Table 1. Classification of PSs[16]

Class	Name	Structure	λ_{max}	Application
Porphyrin	Photofrin[17]		630 nm	Cancer, *in vitro*, *in vivo*, clinical
	ALA-induced protoporphyrin IX[18]		635 nm	Cancer, *in vitro*, *in vivo*, clinical
	5,10,15,20-Tetrakis(1-methylpyridinium-4-yl) porphyrin tosylate[19]		White	antimicrobial, *in vitro*, *in vivo*
Chlorin	Foscan, m-tetrahydroxyphenylchlorin[20]		652 nm	Cancer, *in vitro*, *in vivo*, clinical
	Chlorin(e6)[21]		660 nm	Cancer, *in vitro*, *in vivo*, clinical
	HPPH[22]		660 nm	Cancer, *in vitro*, *in vivo*, clinical
Phthalocyanine	Liposomal ZnPC[23]		670 nm	Cancer, *in vitro*, *in vivo*, clinical
	Chloroaluminium sulfonated phthalocyanine (CASP)[24]		670 nm	Cancer, *in vitro*, *in vivo*
	Silicon phthalocyanine (PC4)[25]		675 nm	Cancer, *in vitro*, *in vivo*, clinical
Perylenequinone	Hypericin[26]		570 nm	Cancer, antimicrobial, *in vitro*, *in vivo*
Perylenequinone	Hypocrellin[27]		470 nm	Cancer, antimicrobial, *in vitro*, *in vivo*, clinical
Curcuminoid	Curcumin[28]		420 nm	Antimicrobial, *in vitro*, *in vivo*, clinical

Photosensitizers, as an important part of PDT, are limited in application due to their own defects, for example, most photosensitizers are fat-soluble, poorly targeted, and have potential phototoxicity. While the use of nano drug delivery system to deliver photosensitizers can foster strengths and circumvent weaknesses, reduce the non-specific accumulation of photosensitizers in normal tissues, reduce phototoxicity and so on. Moreover, the surface modification with functional or targeting groups can further strengthen the targeting, reduce the dosage and adverse reactions, so as to improve the efficacy of PDT[9]. As an excellent photosensitizer of PDT, porphyrin MOFs material has high efficiency PDT performance, which is mainly attributed to the advantages of the material itself, such as high load capacity of porphyrin, good biocompatibility and so on. In a recent study, researchers synthesized porphyrin MOFs nanodots (MOF QDs) by a simple method and used them as renal scavable nanoreagents to enhance PDT. MOF QDs has high renal clearance rate and abundant tumor accumulation, which can greatly overcome the long-term toxicity caused by residual drugs after systemic administration. Compared with nanometallic organic framework (NMOF), MOF QDs showed better PDT treatment effect than NMOF under the same treatment conditions[29]. Meanwhile, a novel intelligent oxygen (O_2) releasing PDT nanoparticles (Mn NPs) are synthesized by coating manganese dioxide (MnO_2) nanosheets on porphyrin MOFs materials for tumor targeted therapy and dual-

mode imaging, it provides a new idea for cancer cell imaging and PDT therapy[30].

2.3. PDT therapy in tumor

In modern oncology, it is a common idea to combine several different therapeutic methods in malignant tumor therapy. Since the potentiated toxicity of the combinations is localized, so the combination of PDT and other therapies also has no significant systemic toxicity. This is especially important for elderly or debilitated patients who may tolerate more intensive therapeutic regimes poorly. Furthermore, the combination of PDT and other therapies is not likely to induce cross-resistance in the body because PDT is mainly dependent on the cytotoxic effects of relatively specific reactive oxygen species[31].

Now, there have been many reports on the treatment of tumor by PDT combined with other therapies at home and abroad. PDT is commonly used for highly selective treatment of tumors combined with surgical therapy, chemoradiotherapy, chemoradiotherapy, and especially fluorescence endoscopy[32, 33]. On the one hand, the delivery efficiency of the photosensitizer to the target tissue can be enhanced to improve the therapeutic efficiency of PDT, for example, by coupling monoclonal antibody to the photosensitizer to enhance the tumor targeting of the photosensitizer. On the other hand, PDT in combination with drugs that inhibit the excretion of photosensitizers can greatly enhance the sensitivity of tumor cells to PDT, which is limited to those photosensitizers that have clearly acted on an transport protein (such as ABCG2) as a substrate[34]. Recently, it has been reported that cyclooxygenase (COX) inhibitors, anti-angiogenic drugs, and monoclonal antibodies against neovascular growth factors (such as VEGF) can significantly enhance the inhibition effect of PDT on the growth of tumor cells[35, 36]. The combination of PDT and antibodies related to signal transduction pathway such as epidermal growth factor antibody cetuximab can also significantly enhance the therapeutic effect of PDT[37]. Geldanamycin, an Hsp-90 protein inhibitor, can increase the sensitivity of tumor cells to PDT by regulating the function of Hsp-90[38]. The proteasome inhibitor bortezomib, a drug used for hematopoietic disorders, is found to increase the cytotoxic effect of PDT by further enhancing ER stress[39]. Researches have shown that rapamycin, Bcl-2 antagonists, urdeoxycholic acid, ceramide analogues, and inhibitors of enzymes involved in ROS scavenging (such as superoxide dismutase SOD, HO-1, or NOS) are found to enhance the antitumor effect of PDT[40-42].

PDT has many advantages compared with chemoradiotherapy, such as less systemic adverse reactions, resistant to drug resistance, repeatable application and can combine with other therapies to improve the efficacy further. In addition, in recent years, the research on the photosensitizer, light source and oxygen, three factors of PDT, has become more and more in-depth, and the three factors have been continuously optimized. Hence, more and more PDT combination therapies have been continuously researched and put into clinical application.

3. Photothermal therapy in oncology

3.1. The mechanism of photothermal therapy (PTT)

PTT is a new noninvasive tumor treatment method that uses photothermal agent (PTA) to convert light energy into heat energy to kill tumor cells under the irradiation of near-infrared (NIR) and other external light sources. PTA absorb energy from photons under NIR irradiation and are transformed from their ground singlet state to an excited singlet state. The electronic excitation energy then undergoes vibrational relaxation, a non-radiative form of decay, and returns to the ground state is mediated by collisions between the excited PTA and their surrounding molecules. Consequently, increased kinetic energy will heat up the surrounding microenvironment, resulting in thermal effects (Figure 2)[43]. It has shown significant advantages owing to noninvasive, targeted and high-efficiency compared with most traditional cancer therapy[44]. PTT can be divided into traditional photothermal therapy (≥45°C)

and mild photothermal therapy (MPTT) (<45°C). The temperature of traditional PTT is relatively higher, and the killing ability to tumor tissue is stronger, but also to normal tissue. In contrast, MPTT has less damage to normal tissues, while it also has lower killing capacity. It is mostly used as a regulatory mechanism, rather than directly used to kill tumor tissues at present.

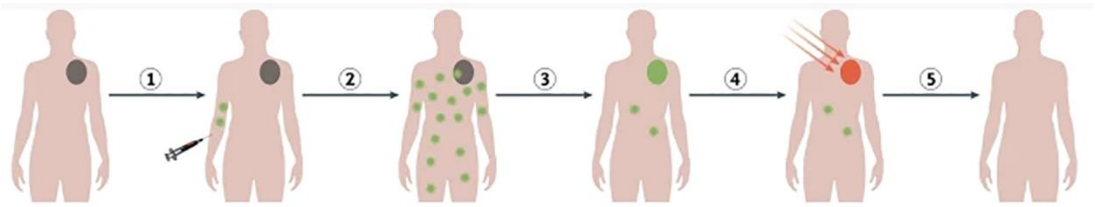


Figure 2. The treatment of PTT[43]. The PTA (small green circles) is administered intravenously to the patient, and then subsequently distributed around the body. Accumulation of PTA in tumour tissues (indicated by previously grey ovals, representing the tumour, turning green) can be achieved through active and/or passive targeting strategies and optional molecular activation exploiting, for example, proteases or hypoxia in the tumour microenvironment. While, local application of light of a specific wavelength to the tumour tissues can stimulate PTA from a ground single state to an excited singlet state (indicated by red oval). Finally, tumour ablation following excitation of the PTA results predominantly from thermal and chemical damage, respectively.

3.2. The core of PTT is PTA

PTA, can transform light energy into heat energy under the irradiation of NIR and other external light sources to kill tumor cells. At present, there are a lot of researches on photothermal converter, and a variety of new materials are frequently produced which mainly concentrated on nanometer level material roughly divided into inorganic PTA and organic PTA (Table 2). Inorganic PTA has the advantages of high stability and strong photothermal conversion efficiency, and mainly includes precious metals (Au, Pd, etc.), carbon-based (carbon nanotubes (CNT), graphene (GE), graphene oxide (GO), carbon quantum dots (CQDs), etc.) and transition metals (metal sulfides and metal oxides). In recent research, a kind of relatively small sized (35 nm) and slightly-hollow degree gold-silver nanocages (GSNCs) with an absorbance locked at 532 nm has been successfully synthesized which can enhance the intrinsic photoacoustic imaging performances for blood vessels around tumor sites, and it may assist PAM-based tumor diagnosis and induce a tumor targeted PTT effect[45].

Table 2. Classification of PTA

Class	Nano drug delivery system	PTA	Drug
Inorganic PTA	Mn-ICG@pHis-PEG/GA[46]	ICG	GA
	mPEG-PCL-g-PEI- IR820 @Lyp-1-DTX[47]	IR820	DTX
	PNOC-PDA/DOX[48]	PDA	DOX
	MPEG-AuNR@VER-M[49]	Au	VER-155008
Organic PTA	GO-FA-SNX-2112[50]	GO	SNX-2112
	Ir@Fe_3O_4 NPs[51]	Fe_3O_4	Ir

3.3. PTT treat tumor

PTT, as a new tumor therapy, has the advantages of non-invasive, small adverse reactions and high targeting, which has great potential in the development of tumor therapy. Whereas the single use of PTT also faces such problems as not being able to completely kill the whole tumor tissue, damage the surrounding normal tissue and

biological safety of photothermal materials. Hence, a series of combination therapies based on PTT have been extensively studied to address the limitations of PTT monotherapy, including chemotherapy, PDT, gene therapy and immunotherapy.

Chemotherapy, as one of the traditional ways of tumor treatment, has been widely used in clinical practice, but it is limited by problems such as insufficient local drug concentration, serious adverse reactions and drug resistance. Nanomaterials loaded with chemotherapy drugs could effectively solve these problems by passive targeting enhanced permeability and retention effect or active targeting by surface-to-binding molecules. In addition, local heating during PTT can also improve the permeability of cell membrane and cytotoxicity of drugs, achieving the effect of "1+1>2"[52]. Synergetic treatments that combine chemotherapy with PTT/PDT have been developed as promising new strategies for cancer therapy, especially for drug-resistant cancers. Polycaprolactone (PCL) nanoparticles loaded with IR780 and paclitaxel (PTX) and modified with luteinizing hormone releasing hormone (LHRH) peptide are prepared by emulsion method using bovine serum albumin (BSA) as stabilizer, and used for combinational phototherapy and chemotherapy. The PCL-LHRH NPs can efficiently hinder the growth of drug-resistant xenografts in vivo with the assistance of an 808 nm NIR laser (100%) and the effect is stronger than that without NIR (17.8%)[53]. Similarly, the research of Lee also proved that the single use of chemotherapy and PTT both had certain defects, and the combination of the two could maximize the efficacy[54].

It has been reported that PTT could enhance the efficacy of PDT by increasing the cell absorption of Chlorin e6 (Ce6)[55]. Au for PPT and Ce6 nanocomposite for PDT are successfully synthesized, and the researches in vitro and in vivo both proved that PPT combined with PDT has greater efficacy than the single use[56, 57]. A nanocomplex composed of the thermosensitizers Fe_3O_4 and the PTA curcumin is prepared and used in a BALB/c mice triple-negative breast cancer model, resulting in a 27% reduction in tumor volume in the last day of treatment compared to the initial volume, significantly superior to PTT and PDT treatment alone[58]. Similarly, a nanoplatform (PDA-ICG-TPZ NPs) integrated with thermal sensitizer polydopamine (PDA), photosensitizer ICG and chemotherapeutic agent tirapazamine is constructed by loading TPZ, a hypoxic-activated chemotherapy drug, using the hypoxic microenvironment in the treatment of PTT combined with PDT. The synergistic treatment of PTT, PDT and chemotherapy is realized, and remarkable inhibitory effect is obtained against subcutaneous tumor cell line U87MG and in situ tumor cell line B16F10[59].

Gene therapy aims to treat disease at its root by correcting or compensating for faulty and abnormal genes, rather than simply alleviating its symptoms. In the early stage, the development of gene therapy has been limited due to the lack of ideal vector, whereas the rapid development of nanomaterials has also driven the rapid progress of gene therapy. While killing tumor cells, the photothermal effect can promote gene release by breaking chemical bonds between genes and nanomaterials[60]. For the past few years, PTT combined with gene therapy has shown remarkable therapeutic effect in the treatment of hepatoma and pancreatic cancer[61, 62].

Tumor immunotherapy can activate the body's own defense system to recognize, attack and destroy tumor cells, which is a research hotspot in recent years. It has been reported that tumor associated antigens (TAAs) can be released from the thermogenic effects of tumor, while the TAAs are recognized by dendritic cells (DCs) and presented to T cell receptors with the help of immune adjuvants to activate the immune response[63]. As a branch of PTT, MPTT plays a significant role in tumor immunity and microenvironment. Although it does not directly reduce tumor size like PTT, it can inhibit the progression of tumor cells by changing the "soil" of tumor cell growth and metastasis, providing a new strategy for tumor immunotherapy[64, 65].

As an emerging tumor therapy, PTT has shown great potential in the clinical application of cancer. In recent years, the application of PTT based on different PTAs is also more efficient and extensive with the rapid development of nanomedicine. However, although different types of PTA show unique advantages, a photothermal material with

low cost, good water solubility, strong biosafety and high photothermal conversion efficiency is still to be explored. In addition, compared with traditional therapy, PTT has advantages such as small adverse effects and strong targeting, but, it also has shortcoming such as incomplete elimination of tumors, high recurrence rate, and ineffective treatment of distant lesions, and thermal damage to normal tissue has always been a difficult problem to solve. The problem has long puzzled researchers that how to balance killing efficiency with normal tissue protection. To some extent, the combined application of other therapies can solve the above problems faced by a single PTT, but the synergistic effect of these therapies should be fully explored firstly, rather than the simple combination of different therapies. For example, more drugs and other ingredients can be loaded into nanosystems while it may affect the therapeutic effect of PTA, so the internal mechanism of the combination also needs to be improved.

4. Thermodynamic therapy in oncology

4.1. The mechanism of thermodynamic therapy (TDT)

TDT has recently emerged as an attractive approach for cancer therapy. It uses heat to activate thermosensitizers and produce reactive active chemicals, including ROS and other free radicals unrelated to oxygen[66, 67]. In TDT, ROS, free radicals and other active species can be obtained directly from the thermosensitizers during heating, showing a property unrelated to oxygen, and not limited to the anoxic environment in the tumor, which could overcome the hypoxia limitation of the clinical tumor therapy (Figure 3)[68, 69]. In consequence, TDT has incomparable advantages over PTT and PDT, and is considered as a novel, flexible and promising cancer treatment method, which has recently received special attention from researchers[66, 68, 69]. In contrast to PTT, the heat source of TDT can be obtained in a variety of ways, such as chemical reactions, light, ultrasound, and microwave[70]. However, TDT also has some problems and limitations, for instance the need to rely on external energy, the availability of fewer thermosensitizers. When obtaining heat source from light, TDT also has similar problems as PTT, such as limited penetrating power of NIR laser, uneven distribution of heat generated by photothermal action, poor accumulation of photothermal conversion materials at tumor sites. Moreover, cells adapt to the living environment of oxidative stress to produce the mechanism of resistance to high levels of ROS and the body's own oxidative stress response, which will weaken the effect of TDT on tumor killing[71]. These problems and limitations make it difficult to eliminate the tumor completely with TDT alone, which inevitably leads to tumor recurrence and metastasis. Fortunately, combining TDT with other drugs or therapies to construct a multi-modal synergistic therapy system can compensate for this deficiency, even achieve a better synergistic therapeutic effect.

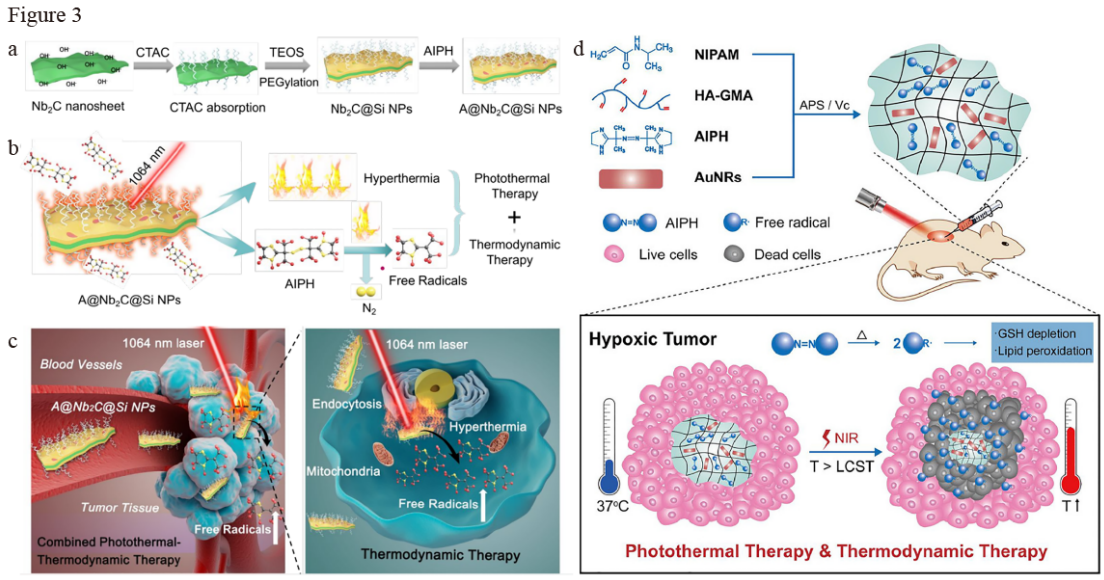


Figure 3. Schematic illustration synthesis and action of thermosensitizers[68, 69]. a, the preparation of AIPH@Nb2C@mSiO2 NPs; b, the thermal decomposition of AIPH for radical production; c, the systematic delivery of AIPH@Nb2C@mSiO2 NPs as a photo-sensitive nanomedicine for multifunctional imagingguided synergistic photothermal thermodynamic therapy and thermodynamic therapy; d, the schematic diagram of the formation of the hydrogels composed of HA-GMA and NIPAM, loaded with AIPH and AuNRs, and the combination of the photothermal and thermodynamic therapy for hypoxic tumor therapy. CTAC is abbreviated for cetyltrimethylammonium chloride, TEOS is abbreviated for tetraethylorthosilicate, AIPH is abbreviated for 2, 2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride, A@Nb2C@Si NPs are abbreviated for AIPH@Nb2C@mSiO2 NPs and Nb2C@Si NPs are abbreviated for Nb2C@mSiO2 NPs in the Figure 3 (a-c).

4.2. The key of TDT-Thermosensitizers

Thermosensitizers, can absorb heat and decompose to produce ROS or other free radicals unrelated to oxygen. These active chemicals can cause the damage of DNA and mitochondrial, lipid peroxidation, and then activate apoptosis pathways, thus killing tumor cells and inhibiting tumor growth. To date, there are not many thermosensitizers reported in the literature. A few diazo (isobutyronitrile) derivatives, which are not heat-resistant, can decompose easily to produce free radicals during thermal activation, and can be used as thermal sensitive agents of TDT[72, 73]. Among them, 2,2' -azadidi (2-imidazoline) dihydrochloride (AIPH or AIBI) has been used in the application study of TDT[67, 69].

4.3. The application of TDT

The combination of TDT and PTT is also the most studied in tumor therapy[68, 74, 75]. It is found that artesunate (ARS) could produce ROS upon heating. Therefore, a pH-sensitive liposomal nanoplatform (ICG-ARS@NPs) composed of indocyanine green (ICG) and ARS is prepared for photoinduced TDT as well as PTT. ICG-ARS@NPs exhibited highly efficient anti-cancer therapeutic efficacy in H_{22} tumor-bearing mice owing to their specific tumor targeting and synergistic photothermal and thermodynamic effects[76]. A NIR-triggered thermo-responsive long-acting hydrogels, composing of HA-GMA and NIPAM, loading with AuNRs and AIPH, could combine PTT induced by AuNRs and TDT induced by free radicals. And this new thermodynamic therapeutic strategy is an oxygen-independent and showed great advantages to the hypoxia tumor therapy. Furthermore, the carrier has good safety

and biocompatibility due to the biodegradable of hydrogel[69].

The nanocomposites BMT@AIBI NCs are prepared by using black mesoporous titanium dioxide (BMT) with large pore size as the support of AIBI. In BMT@AIBI NCs, the BMT, as a light transducer, can convert NIR light energy into thermal energy and chemical energy (·OH), contributing to PTT and PDT respectively. Meanwhile, the heat generated by BMT triggers the decomposition of AIBI to produce a large number of alkyl radicals (·R) for TDT. High levels of free radicals produced by BMT@AIBI NCs under NIR light cause DNA double strand breaks, and ultimately inducing apoptosis of cancer cells. Since free radical production is independent of oxygen, BMT@AIBI NCs exhibit excellent anti-cancer effects in vitro and in vivo under hypoxic conditions. PTT/PDT/TDT combined therapy can overcome the problem of tumor hypoxia and enhance the anti-cancer effect[67]. There have also shown that MCN-AR@PCM combined with PTT/TDT/CT therapy can cause large area of HeLa cell death under both normal and hypoxia conditions, and can completely eliminate the tumor of HeLa cervical cancer bearing mice without recurrence, which has a significant anti-cancer effect[77].

TDT combined with other therapies has achieved good therapeutic effect in animal researches, but there are still a lot of problems to be solved. We should develop other ways to capture heat energy, find and develop more available heat-sensitive agents. And we can take advantage of the flexibility in the design of nanomaterials to further explore to introduce other anti-tumor drugs or molecules for therapeutic purposes into the nanomaterial structure, so as to realize the combination of TDT with tumor therapy techniques such as PTT, PDT, radiotherapy, microwave therapy, ultrasound therapy, immunotherapy, gene therapy and so on, further improve the therapeutic effect of tumor and provide technical support and experimental basis for the clinical application of TDT.

5. Conclusions

As an emerging cancer therapy, PDT, PTT and TDT have shown great potential in the clinical application of cancer. The rapid development of nanotechnology and material technology in recent years has also made these applications more efficient and extensive. These novel treatment modes combined with other therapies still lack the accumulation of researches and the support of a large number of research data, as well as relatively immature technology and uncertain biological safety and other problems. Moreover, the solubility and biosafety of PTA, thermosensitizers and photosensitizers used in these novel therapies also need to be addressed. In the future, it should be focused on solving the existing problems of PTT, PDT and TDT to remove the obstacles, so as to further improve the therapeutic effect of tumor, and provide technical support and experimental basis for their clinical application.

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Conflict of interest

All the authors claim that the manuscript is completely original. The authors also declare no conflict of interest.

Author contributions

Conceptualization: Chen Li, Yi Liu; Investigation: Chen Li; Summarization: Chen Li; Writing–original draft: Chen Li; Writing – review & editing: Yi Liu. All authors contributed to the article and approved the final manuscript.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; 71: 209-249. 2021/02/05. DOI: 10.3322/caac.21660.
2. Cao W, Chen HD, Yu YW, et al. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J (Engl)* 2021; 134: 783-791. 2021/03/19. DOI: 10.1097/cm9.0000000000001474.
3. Jabaji RB, Fischer H, Kern T, et al. Trend of Surgical Treatment of Localized Renal Cell Carcinoma. *Perm J* 2019; 23: 18-108. 2019/01/10. DOI: 10.7812/tpp/18-108.
4. Wang JJ, Lei KF and Han F. Tumor microenvironment: recent advances in various cancer treatments. *Eur Rev Med Pharmacol Sci* 2018; 22: 3855-3864. 2018/06/28. DOI: 10.26355/eurrev_201806_15270.
5. MacCormack MA. Photodynamic therapy. *Adv Dermatol* 2006; 22: 219-258. 2007/01/26. DOI: 10.1016/j.yadr.2006.09.008.
6. Kessel D. Death pathways associated with photodynamic therapy. *Med Laser Appl* 2006; 21: 219-224. 2006/11/15. DOI: 10.1016/j.mla.2006.05.006.
7. Greenwald BD. Photodynamic therapy for esophageal cancer. Update. *Chest Surg Clin N Am* 2000; 10: 625-637. 2000/09/01.
8. Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. *CA Cancer J Clin* 2011; 61: 250-281. 2011/05/28. DOI: 10.3322/caac.20114.
9. Xie S and Fu S. Therapeutic characteristics and clinical evaluation element of the photosensitive drugs. *CHINESE NEW DRUGS JOURNAL* 2008; 17: 618.
10. Wu H, Minamide T and Yano T. Role of photodynamic therapy in the treatment of esophageal cancer. *Digestive Endoscopy* 2019; 31: 508-516. DOI: 10.1111/den.13353. DOI: 10.1111/den.13353.
11. Chiu W-T, Tran T-TV, Pan S-C, et al. Cystic fibrosis transmembrane conductance regulator: a possible new target for photodynamic therapy enhances wound healing. *Advances in Wound Care* 2019; 8: 476-486. DOI: 10.1089/wound.2018.0927.
12. Namvar MA, Vahedi M, Abdolsamadi H-r, et al. Effect of photodynamic therapy by 810 and 940 nm diode laser on Herpes Simplex Virus 1: An in vitro study. *Photodiagnosis and photodynamic therapy* 2019; 25: 87-91. DOI: 10.1016/j.pdpdt.2018.11.011.
13. Matoba Y, Banno K, Kisu I, et al. Clinical application of photodynamic diagnosis and photodynamic therapy for gynecologic malignant diseases: A review. *Photodiagnosis and photodynamic therapy* 2018; 24: 52-57. DOI: 10.1016/j.pdpdt.2018.08.014.
14. Cruess AF, Zlateva G, Pleil AM, et al. Photodynamic therapy with verteporfin in age-related macular degeneration: a systematic review of efficacy, safety, treatment modifications and pharmacoeconomic properties. *Acta ophthalmologica* 2009; 87: 118-132. DOI: 10.1111/j.1755-3768.2008.01218.x.
15. Moore C, Nathan T, Lees W, et al. Photodynamic therapy using meso tetra hydroxy phenyl chlorin (mTHPC) in early prostate cancer. *Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery* 2006; 38: 356-363. DOI: 10.1002/lsm.20275.
16. Abrahamse H and Hamblin MR. New photosensitizers for photodynamic therapy. *Biochem J* 2016; 473: 347-364. 2016/02/11. DOI: 10.1042/bj20150942.
17. Kessel D. Photosensitization with derivatives of haematoporphyrin. *Int J Radiat Biol Relat Stud Phys Chem Med* 1986; 49: 901-907. 1986/06/01. DOI: 10.1080/09553008514553131.
18. Lee PK and Kloser A. Current methods for photodynamic therapy in the US: comparison of MAL/PDT and ALA/PDT. *J Drugs Dermatol* 2013; 12: 925-930. 2013/08/30.

19. Liu AH, Sun X, Wei XQ, et al. Efficacy of multiple low-dose photodynamic TMPYP4 therapy on cervical cancer tumour growth in nude mice. *Asian Pac J Cancer Prev* 2013; 14: 5371-5374. 2013/11/02. DOI: 10.7314/apjcp.2013.14.9.5371.
20. Senge MO and Brandt JC. Temoporfin (Foscan®, 5, 10, 15, 20-tetra (m-hydroxyphenyl) chlorin)—a second-generation photosensitizer. *Photochemistry and photobiology* 2011; 87: 1240-1296. DOI: 10.1111/j.1751-1097.2011.00986.x.
21. Biswas R, Moon JH and Ahn JC. Chlorin e6 derivative radachlorin mainly accumulates in mitochondria, lysosome and endoplasmic reticulum and shows high affinity toward tumors in nude mice in photodynamic therapy. *Photochem Photobiol* 2014; 90: 1108-1118. 2014/03/29. DOI: 10.1111/php.12273.
22. Shafirstein G, Rigual NR, Arshad H, et al. Photodynamic therapy with 3-(1'-hexyloxyethyl) pyropheophorbide-a for early-stage cancer of the larynx: Phase Ib study. *Head Neck* 2016; 38 Suppl 1: E377-383. 2015/01/13. DOI: 10.1002/hed.24003.
23. Soriano J, Villanueva A, Stockert JC, et al. Vehiculization determines the endocytic internalization mechanism of Zn(II)-phthalocyanine. *Histochem Cell Biol* 2013; 139: 149-160. 2012/08/18. DOI: 10.1007/s00418-012-1012-6.
24. Stern SJ, Flock ST, Small S, et al. Photodynamic therapy with chloroaluminum sulfonated phthalocyanine in the rat window chamber. *Am J Surg* 1990; 160: 360-364. 1990/10/01. DOI: 10.1016/s0002-9610(05)80543-4.
25. Anderson CY, Freye K, Tubesing KA, et al. A comparative analysis of silicon phthalocyanine photosensitizers for in vivo photodynamic therapy of RIF-1 tumors in C3H mice. *Photochem Photobiol* 1998; 67: 332-336. 1998/04/02. DOI: 10.1111/j.1751-1097.1998.tb05206.x.
26. Theodossiou TA, Hothersall JS, De Witte PA, et al. The multifaceted photocytotoxic profile of hypericin. *Mol Pharm* 2009; 6: 1775-1789. 2009/09/11. DOI: 10.1021/mp900166q.
27. Zhenjun D and Lown JW. Hypocrellins and their use in photosensitization. *Photochem Photobiol* 1990; 52: 609-616. 1990/09/01. DOI: 10.1111/j.1751-1097.1990.tb01807.x.
28. Tonon CC, Paschoal MA, Correia M, et al. Comparative effects of photodynamic therapy mediated by curcumin on standard and clinical isolate of Streptococcus mutans. *J Contemp Dent Pract* 2015; 16: 1-6. 2015/04/17. DOI: 10.5005/jp-journals-10024-1626.
29. Wang H, Yu D, Fang J, et al. Renal-clearable porphyrinic metal–organic framework nanodots for enhanced photodynamic therapy. *ACS nano* 2019; 13: 9206-9217. DOI: 10.1021/acsnano.9b03531.
30. Zhang D, Ye Z, Wei L, et al. Cell membrane-coated porphyrin metal–organic frameworks for cancer cell targeting and O2-evolving photodynamic therapy. *ACS applied materials & interfaces* 2019; 11: 39594-39602. DOI: 10.1021/acsami.9b14084.
31. Kessel D and Erickson C. Porphyrin photosensitization of multi-drug resistant cell types. *Photochem Photobiol* 1992; 55: 397-399. 1992/03/01. DOI: 10.1111/j.1751-1097.1992.tb04253.x.
32. Szokalska A, Makowski M, Nowis D, et al. Proteasome inhibition potentiates antitumor effects of photodynamic therapy in mice through induction of endoplasmic reticulum stress and unfolded protein response. *Cancer Res* 2009; 69: 4235-4243. 2009/05/14. DOI: 10.1158/0008-5472.Can-08-3439.
33. Weinberg BD, Allison RR, Sibata C, et al. Results of combined photodynamic therapy (PDT) and high dose rate brachytherapy (HDR) in treatment of obstructive endobronchial non-small cell lung cancer (NSCLC). *Photodiagnosis Photodyn Ther* 2010; 7: 50-58. 2010/03/17. DOI: 10.1016/j.pdpdt.2009.12.002.
34. Liu W, Baer MR, Bowman MJ, et al. The tyrosine kinase inhibitor imatinib mesylate enhances the efficacy of photodynamic therapy by inhibiting ABCG2. *Clin Cancer Res* 2007; 13: 2463-2470. 2007/04/18. DOI: 10.1158/1078-0432.Ccr-06-1599.
35. Ferrario A, von Tiehl KF, Rucker N, et al. Antiangiogenic treatment enhances photodynamic therapy responsiveness in a mouse mammary carcinoma. *Cancer Res* 2000; 60: 4066-4069. 2000/08/17.

36. Bhuvaneswari R, Yuen GY, Chee SK, et al. Hypericin-mediated photodynamic therapy in combination with Avastin (bevacizumab) improves tumor response by downregulating angiogenic proteins. *Photochem Photobiol Sci* 2007; 6: 1275-1283. 2007/11/30. DOI: 10.1039/b705763f.
37. Cengel KA, Hahn SM and Glatstein E. C225 and PDT combination therapy for ovarian cancer: the play's the thing. *J Natl Cancer Inst* 2005; 97: 1488-1489. 2005/10/20. DOI: 10.1093/jnci/dji360.
38. Ferrario A, Rucker N, Wong S, et al. Survivin, a member of the inhibitor of apoptosis family, is induced by photodynamic therapy and is a target for improving treatment response. *Cancer Res* 2007; 67: 4989-4995. 2007/05/19. DOI: 10.1158/0008-5472.Can-06-4785.
39. Golab J, Nowis D, Skrzycki M, et al. Antitumor effects of photodynamic therapy are potentiated by 2-methoxyestradiol. A superoxide dismutase inhibitor. *J Biol Chem* 2003; 278: 407-414. 2002/11/01. DOI: 10.1074/jbc.M209125200.
40. Nowis D, Legat M, Grzela T, et al. Heme oxygenase-1 protects tumor cells against photodynamic therapy-mediated cytotoxicity. *Oncogene* 2006; 25: 3365-3374. 2006/02/08. DOI: 10.1038/sj.onc.1209378.
41. Henderson BW, Sitnik-Busch TM and Vaughan LA. Potentiation of photodynamic therapy antitumor activity in mice by nitric oxide synthase inhibition is fluence rate dependent. *Photochem Photobiol* 1999; 70: 64-71. 1999/07/27. DOI: 10.1111/j.1751-1097.1999.tb01950.x.
42. Ferrario A, Von Tiehl K, Wong S, et al. Cyclooxygenase-2 inhibitor treatment enhances photodynamic therapy-mediated tumor response. *Cancer Res* 2002; 62: 3956-3961. 2002/07/19.
43. Li X, Lovell JF, Yoon J, et al. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat Rev Clin Oncol* 2020; 17: 657-674. 2020/07/24. DOI: 10.1038/s41571-020-0410-2.
44. Ban Q, Bai T, Duan X, et al. Noninvasive photothermal cancer therapy nanoplatforms via integrating nanomaterials and functional polymers. *Biomater Sci* 2017; 5: 190-210. 2016/12/19. DOI: 10.1039/c6bm00600k.
45. Qin Z, Du T, Zheng Y, et al. Glutathione Induced Transformation of Partially Hollow Gold-Silver Nanocages for Cancer Diagnosis and Photothermal Therapy. *Small* 2019; 15: e1902755. 2019/07/28. DOI: 10.1002/smll.201902755.
46. Yang Y, Zhu W, Dong Z, et al. 1D Coordination Polymer Nanofibers for Low-Temperature Photothermal Therapy. *Adv Mater* 2017; 29 2017/08/24. DOI: 10.1002/adma.201703588.
47. Li W, Peng J, Tan L, et al. Mild photothermal therapy/photodynamic therapy/chemotherapy of breast cancer by Lyp-1 modified Docetaxel/IR820 Co-loaded micelles. *Biomaterials* 2016; 106: 119-133. 2016/08/27. DOI: 10.1016/j.biomaterials.2016.08.016.
48. Ding Y, Du C, Qian J, et al. NIR-Responsive Polypeptide Nanocomposite Generates NO Gas, Mild Photothermia, and Chemotherapy to Reverse Multidrug-Resistant Cancer. *Nano Lett* 2019; 19: 4362-4370. 2019/06/15. DOI: 10.1021/acs.nanolett.9b00975.
49. Tang X, Tan L, Shi K, et al. Gold nanorods together with HSP inhibitor-VER-155008 micelles for colon cancer mild-temperature photothermal therapy. *Acta Pharm Sin B* 2018; 8: 587-601. 2018/08/16. DOI: 10.1016/j.apsb.2018.05.011.
50. Deng X, Guan W, Qing X, et al. Ultrafast Low-Temperature Photothermal Therapy Activates Autophagy and Recovers Immunity for Efficient Antitumor Treatment. *ACS Appl Mater Interfaces* 2020; 12: 4265-4275. 2020/01/07. DOI: 10.1021/acsami.9b19148.
51. Qiu K, Wang J, Rees TW, et al. A mitochondria-targeting photothermogenic nanozyme for MRI-guided mild photothermal therapy. *Chem Commun (Camb)* 2018; 54: 14108-14111. 2018/12/01. DOI: 10.1039/c8cc08570f.
52. Li Z, Chen Y, Yang Y, et al. Recent Advances in Nanomaterials-Based Chemo-Photothermal Combination Therapy for Improving Cancer Treatment. *Front Bioeng Biotechnol* 2019; 7: 293. 2019/11/07. DOI: 10.3389/fbioe.2019.00293.
53. Pan Q, Tian J, Zhu H, et al. Tumor-Targeting Polycaprolactone Nanoparticles with Codelivery of Paclitaxel and IR780 for Combinational Therapy of Drug-Resistant Ovarian Cancer. *ACS Biomater Sci Eng* 2020; 6: 2175-2185. 2021/01/19. DOI: 10.1021/acsbiomaterials.0c00163.

54. Lee SY and Shieh MJ. Platinum(II) Drug-Loaded Gold Nanoshells for Chemo-Photothermal Therapy in Colorectal Cancer. *ACS Appl Mater Interfaces* 2020; 12: 4254-4264. 2020/01/14. DOI: 10.1021/acsami.9b18855.
55. Tian B, Wang C, Zhang S, et al. Photothermally enhanced photodynamic therapy delivered by nano-graphene oxide. *ACS Nano* 2011; 5: 7000-7009. 2011/08/06. DOI: 10.1021/nn201560b.
56. Chuang CC, Chen YN, Wang YY, et al. Stem Cell-Based Delivery of Gold/Chlorin e6 Nanocomplexes for Combined Photothermal and Photodynamic Therapy. *ACS Appl Mater Interfaces* 2020; 12: 30021-30030. 2020/07/01. DOI: 10.1021/acsami.0c03446.
57. Wu F, Liu Y, Wu Y, et al. Chlorin e6 and polydopamine modified gold nanoflowers for combined photothermal and photodynamic therapy. *J Mater Chem B* 2020; 8: 2128-2138. 2020/02/20. DOI: 10.1039/c9tb02646k.
58. Ashkbar A, Rezaei F, Attari F, et al. Treatment of breast cancer in vivo by dual photodynamic and photothermal approaches with the aid of curcumin photosensitizer and magnetic nanoparticles. *Sci Rep* 2020; 10: 21206. 2020/12/05. DOI: 10.1038/s41598-020-78241-1.
59. Huang X, Wu J, He M, et al. Combined Cancer Chemo-Photodynamic and Photothermal Therapy Based on ICG/PDA/TPZ-Loaded Nanoparticles. *Mol Pharm* 2019; 16: 2172-2183. 2019/04/13. DOI: 10.1021/acs.molpharmaceut.9b00119.
60. Kim J, Kim J, Jeong C, et al. Synergistic nanomedicine by combined gene and photothermal therapy. *Adv Drug Deliv Rev* 2016; 98: 99-112. 2016/01/10. DOI: 10.1016/j.addr.2015.12.018.
61. Liu Y, Tan M, Zhang Y, et al. Targeted Gene Silencing BRAF Synergized Photothermal Effect Inhibits Hepatoma Cell Growth Using New GAL-GNR-siBRAF Nanosystem. *Nanoscale Res Lett* 2020; 15: 116. 2020/05/26. DOI: 10.1186/s11671-020-03340-x.
62. Jia X, Xu W, Ye Z, et al. Functionalized Graphene@Gold Nanostar/Lipid for Pancreatic Cancer Gene and Photothermal Synergistic Therapy under Photoacoustic/Photothermal Imaging Dual-Modal Guidance. *Small* 2020; 16: e2003707. 2020/08/28. DOI: 10.1002/smll.202003707.
63. Chang M, Hou Z, Wang M, et al. Recent Advances in Hyperthermia Therapy-Based Synergistic Immunotherapy. *Adv Mater* 2021; 33: e2004788. 2020/12/09. DOI: 10.1002/adma.202004788.
64. Huang L, Li Y, Du Y, et al. Mild photothermal therapy potentiates anti-PD-L1 treatment for immunologically cold tumors via an all-in-one and all-in-control strategy. *Nat Commun* 2019; 10: 4871. 2019/10/28. DOI: 10.1038/s41467-019-12771-9.
65. Nicolas-Boluda A, Laurent G, Bazzi R, et al. Two step promotion of a hot tumor immune environment by gold decorated iron oxide nanoflowers and light-triggered mild hyperthermia. *Nanoscale* 2021; 13: 18483-18497. 2021/11/10. DOI: 10.1039/d1nr03201a.
66. Fenn A. The Celsion adaptive thermodynamic therapy (TDT) drug delivery system for treating deep-seated cancer. *Drug Deliv Tech October* 2002; 2.
67. Wang M, Zhao Y, Chang M, et al. Azo Initiator Loaded Black Mesoporous Titania with Multiple Optical Energy Conversion for Synergetic Photo-Thermal-Dynamic Therapy. *ACS Appl Mater Interfaces* 2019; 11: 47730-47738. 2019/12/04. DOI: 10.1021/acsami.9b17375.
68. Xiang H, Lin H, Yu L, et al. Hypoxia-Irrelevant Photonic Thermodynamic Cancer Nanomedicine. *ACS Nano* 2019; 13: 2223-2235. 2019/01/10. DOI: 10.1021/acsnano.8b08910.
69. Sun X, Liu D, Xu X, et al. NIR-triggered thermo-responsive biodegradable hydrogel with combination of photothermal and thermodynamic therapy for hypoxic tumor. *Asian J Pharm Sci* 2020; 15: 713-727. 2020/12/29. DOI: 10.1016/j.ajps.2019.11.007.
70. Xu H, Sheng G, Lu L, et al. GRPr-mediated photothermal and thermodynamic dual-therapy for prostate cancer with synergistic anti-apoptosis mechanism. *Nanoscale* 2021; 13: 4249-4261. 2021/02/18. DOI: 10.1039/d0nr07196j.

71. Trachootham D, Alexandre J and Huang P. Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach? *Nat Rev Drug Discov* 2009; 8: 579-591. 2009/05/30. DOI: 10.1038/nrd2803.
72. Prucker O and Rühe J. Synthesis of poly (styrene) monolayers attached to high surface area silica gels through self-assembled monolayers of azo initiators. *Macromolecules* 1998; 31: 592-601. DOI: 10.1021/ma970660x.
73. Goto A, Kwak Y, Fukuda T, et al. Mechanism-based invention of high-speed living radical polymerization using organotellurium compounds and azo-initiators. *Journal of the American Chemical Society* 2003; 125: 8720-8721. DOI: 10.1021/ja035464m.
74. Wu S, Liu X, Ren J, et al. Glutathione Depletion in a Benign Manner by MoS(2) -Based Nanoflowers for Enhanced Hypoxia-Irrelevant Free-Radical-Based Cancer Therapy. *Small* 2019; 15: e1904870. 2019/11/22. DOI: 10.1002/smll.201904870.
75. Wan Y, Lu G, Zhang J, et al. A biocompatible free radical nanogenerator with real-time monitoring capability for high performance sequential hypoxic tumor therapy. *Advanced Functional Materials* 2019; 29: 1903436. DOI: 10.1002/adfm.201903436.
76. Zhao PH, Ma ST, Hu JQ, et al. Artesunate-Based Multifunctional Nanoplatform for Photothermal/Photoinduced Thermodynamic Synergistic Anticancer Therapy. *ACS Appl Bio Mater* 2020; 3: 7876-7885. 2020/11/16. DOI: 10.1021/acsabm.0c01026.
77. Liu Z, Wan P, Liu Z, et al. Photothermal Generation of Oxygen-Irrelevant Free Radicals with Simultaneous Suppression of Glutathione Synthesis for an Enhanced Photonic Thermodynamic Cancer Therapy. *ACS Biomater Sci Eng* 2020; 6: 6186-6194. 2021/01/16. DOI: 10.1021/acsbiomaterials.0c00889.