Review

Nishant K. Jain, Bavya M. Chathoth, Vinil S. Bhaskar, Himanshu Meena, Rajendra Prasad* and Rohit Srivastava*

Nanoengineered photoactive theranostic agents for cancer

<https://doi.org/10.1515/nanoph-2021-0205>

Received April 30, 2021; accepted June 29, 2021;

published online July 14, 2021

Abstract: Cancer has gained much attention because of slow development of advanced diagnostics and therapeutic strategies. So far, conventional procedures like surgery, radiation therapy and chemotherapy are only available options for cancer treatment which have various limitations. To overcome the limitations of conventional procedures, nano-diagnostics, and therapeutics are emerging approaches for localized diagnosis and treatment of cancer nowadays. So far, various bio-mimicking and stimuli active cancer theranostic platforms have been established but they are limited only for animal studies and their clinical translational progress is slow. Among various cancer theranostics platforms, photo-responsive systems have shown promising outcomes for cancer theranostics applications due to their specific physicochemical properties, biocompatibility, multifunctionality etc. Moreover, these photothermal agents in combination with diagnostics probes and surface functional targeting moieties demonstrate their synergistic response for site selective imaging and ablating cancer cells/tumor. Photoactive principles are rife and with increasing access to light irradiation setups, more the discovery of photoactive products, more would be the success reaped in cancer battle. This review highlights recent developments in cancer nanotheranostics with a special focus on photoactive functional

nanotheranostics. Moreover, the challenges involved in clinical translation of photoactive materials along with their application in vivid areas of cancer nanomedicine and elucidate the future implications on photoactive therapy have been addressed here.

Keywords: cancer therapy; nanotheranostics; photoactive materials; photodynamic probes; photothermal agents.

1 Introduction

Cancer stills remains as one of the leading causes of death worldwide and accounts for about 10 million deaths per year [1, 2]. Approximately 70% of deaths from cancer occur in low- and middle-income countries mainly due to delayed diagnosis and lack of access to diagnosis or treatment facilities [3]. Further, the monetary expenses involved in treating cancer are quite high and results in economic burden. Conventional treatment strategies such as surgery, radiotherapy, and chemotherapy are still widely used in spite of several drawbacks that include nonspecificity, toxicity, and poor therapeutic efficacy [4]. Hence, various researchers across the globe have been trying to explore novel strategies that can overcome these limitations. Nanotechnology has emerged as an innovative technology to cater the unmet needs in the field of cancer therapy [5–7]. Several materials i.e., organic as well as inorganic in origin have been designed to exploit their unique properties at nanoscale dimension. These nanoplat-forms exhibit diverse physicochemical properties and demonstrate significant therapeutic activity in treating cancer by active or passive targeting mechanism. Furthermore, these nanosystems can be surface functionalized with targeting ligands and can also be made bioresponsive resulting in localized action at the tumor site yielding better therapeutic response with less side effects [5–11]. Photothermal therapy (PTT) has emerged as one of the potential modality in treating cancer offering several advantages that includes non-invasiveness, low toxicity, and localized action [12, 13]. It makes use of photoactive agents that generate heat upon irradiation with specific wavelength of light leading to

Nishant K. Jain and Bavya M. Chathoth have contributed equally to this work.

***Corresponding authors: Rohit Srivastava and Rajendra Prasad,** Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Powai, Mumbai, 400076, India, E-mail: rsrivasta@iitb.ac.in (R. Srivastava), rpmeena@iitb.ac.in (R. Prasad). <https://orcid.org/0000-0002-3937-5139> (R. Srivastava). <https://orcid.org/0000-0001-9851-8630> (R. Prasad)

Nishant K. Jain, Bavya M. Chathoth and Himanshu Meena, Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Powai, Mumbai, 400076, India
Vinil S. Bhaskar, Department of Anaesthesia, Saifee Hospital, Girgaon, Mumbai, 400004, India

denaturation of proteins, DNA damage and cellular membrane destruction [14, 15]. This results in ablation of cancer cell with subsequent reduction in size of tumor tissue. Further, the most widely used light for PTT is near infrared (NIR-I) (650–950 nm) often mentioned as first biological window because the specified wavelength reduces NIR absorption of biological tissues mainly blood and water [16, 17]. While, some studies have indicated 1000–1700 nm as second wavelength (NIR-II) or second biological window for which bioimaging of deep rooted tumors show immense progress with improved signal to noise ratio [17]. Recently, several materials of organic and inorganic origin are designed with an aim to improve the photothermal conversion efficiency with high biocompatibility and enhanced localization of nanomedicine at target site for better *in vivo* PTT performance [18, 19]. Additionally, PTT mediated nanomaterials are used in combination with other strategies like chemotherapy, photodynamic therapy, and immunotherapy to achieve synergistic effect for better tumor regression [16, 17, 20]. Moreover, these hybrid systems can be designed as stimuli responsive nanocarriers and functionalized with ligands for on-demand release of chemotherapeutic drug and site-specific localization of the nanomedicine, respectively [21, 22]. The heat generated during the PTT activates the antitumor immunity through immune-stimulatory molecules and release of antigens from the ablating tumor cells [23–25]. Further, it also alters the enzymatic activity and gene expression of living cells that regulates the biological events [26, 27].

In this review, we have highlighted the recent developments in the field of photo-activated nanomaterials and their applications as cancer nanotheranostics. Design of various advanced NIR active hybrid materials for localized imaging and synergistic PTT have been discussed. Further, the principle of heat generation from photoactive materials upon irradiation with NIR light and mechanism of cancer cell death from generated heat has been deciphered. The role of these nanohybrids as an efficient multimode-imaging agent for visualization of tumor area has also been reflected. Besides thermal effect, the synergistic effect achieved with nanohybrids through multimodal therapies with delivery of drug, gene or enzyme, and photodynamic therapy (PDT) has been elaborated. Further, we have summarized the challenges in clinical translation and future perspectives of these photoactive nanotheranostic agents in the field of cancer.

2 Approaches in cancer diagnosis and therapy

2.1 Traditional treatment approaches

Treatment strategies for cancer have undergone huge progress in bringing back patients to live quality life overshadowing the holy grail. According to expert opinion, the advancement in screening and treatment has largely improved or doubled the survival rates in decades after diagnosis. Cancer diagnosis has broadly been divided into traditional and modern screening, with a focus to understand the cell morphology at microscopic level. Traditional procedure includes biopsy, scans (X-ray, computerized tomography, ultrasonography, and magnetic resonance imaging), and endoscopy [28]. Among the above, biopsy is regarded as the gold standard confirmatory test for cancer, for which the abnormal tissue is removed and further delved to understand the cellular pathology. Once the disease is confirmed treatment proceeds based on the severity/degree of the ailment. The treatment options used in the past and still relied to date are radiation, chemotherapy, immunotherapy or a combinatorial approach of chemo-immunotherapy, and surgery [29].

2.2 Modernized techniques for cancer treatment

2.2.1 Photodynamic therapy (PDT)

PDT is a procedure by which photosensitizing agent is targeted onto tumor cells which upon stimulation with visible light of specific wavelength produces reactive singlet oxygen species (Figure 1a) [30]. The procedure requires vigilant selection of photoactive agents capable of tumor localization and metabolic synthesis resulting in irremediable cytolysis of cancer cells [31]. Additionally, tumor vasculature adds to protumorigenic and immunosuppressive microenvironment creating physical barrier to T cell infiltration favoring PDT [32]. The major challenge in this therapy is the photobleaching of sensitizers. Therefore, loading of these photosensitizers in nanocarriers could overcome this issue [33]. Commonly employed sensitizers being hydrophobic, use of nanocarriers has shown to improve the bioavailability [29]. Mainly noble metals are suitable for PDT owing to their absorption capacity compared to that of photoabsorbing dyes [34].

Figure 1: Mechanism of action for photoactive nanotheranostic agent resulting in tumor regression.

(a) Photodynamic therapy (PDT) involving generation of reactive oxygen species (ROS) resulting in cytolysis of tumor cells [78]. (b)

Photothermal therapy (PTT) involving generation of heat upon irradiation resulting in ablation of tumor cells [79].

2.2.1.1 Commonly used agents for PDT

The commonly used photosensitizers in PDT mainly belong to tetrapyrrole family. Among them the most used are the ones found in nature; e.g.: phthalocyanines and porphyrins [35]. Besides, many other compounds also serve as photosensitizers (PS). The suitable commonly used dyes include phenothiazines, phenalenones, squaraines, and indocyanine green (ICG). ICG is negatively charged polymethine dye which serves in eradicating multiple cancers on irradiation with NIR laser at a wavelength range of 800–810 nm and has reduced toxicity to nonsubject host tissue [36, 37]. Studies suggest ICG successfully absorbs light above 800 nm, and the photochemical nature of the compound makes it a suitable candidate for PDT [29, 38, 39]. However, ICG has certain reported drawbacks as well. Stability of ICG differs in different solvents when used for clinical applications, which could be accounted due to its physiochemical nature [40]. Presence of sulfonyl groups promotes water solubility of ICG, while hydrophobic polycyclic groups make it lipophilic [41]. While ICG810 is seen to aggregate or degrade in water which may further result in selfquenching and fluorescent reduction, while the optical properties strictly depend on the dye

concentration [42]. Owing to the amphiphilic nature, ICG has tendency to adsorb lipids [43]. Therefore, in certain cases ICG may interact with normal tissues and may lead to chaos during surgical intervention. Notably, ICG in contact with living tissues bind and exhibits *in vivo* lipoprotein dynamics. Therefore, it is hard to predict the material movement completely using ICG [44–46]. Studies have described that ICG enabled deep light tissue permeability improvising PDT [38, 39]. Apart natural products are also useful as PS [33]. Further, with advancing technology inorganic nanoparticles has contributed enormously which is described in the later part.

2.2.2 Photothermal therapy (PTT)

PTT aims to sentence cancer cell death via engineering heat exposure (electromagnetic radiation) to near infrared light (Figure 1b) [47, 48]. Instilling contrast agents or dyes with weaker emission converts photo energy to thermal energy and results in tumor cell necrosis or apoptosis [39]. Recently, tremendous progress is witnessed in cancer therapy using PTT. NIR absorbents for efficient heat production and incorporating drug delivery system (DDS) for

enhanced heat exposure to abnormal cells has helped PTT to attain success. The notable merit of DDS in PTT is improvising the efficacy and ensuring safety to healthy cells from photothermal damage. The only concern before starting the therapy is the optimization of fluence rate and irradiation time. Later, DDS NIR absorbent and simultaneous PTT is performed irradiating tumor for specified time followed by absorbent administration [49]. However, hurdles exist in determining tumor degree, size, and heterogeneity for which maximum therapeutic effect is hard to exert. At 50 °C or above the risk of thermal damage in healthy tissue raises concern as it might denature protein and may likely cause healthy cell necrosis [50]. Generally, the temperature threshold for PTT therapy is chosen from 40 to 60 °C above which will lead to cell death by coagulation necrosis [51, 52]. Above this temperature, it may affect the integrity of cell membrane and induce the release of cellular contents [51, 53, 54]. When a comparison of PTT is made over PDT, it could be concluded that PTT is more preferred than PDT due to its longer wavelength of light used and is well tolerated by normal cells; additionally the oxygen requirement for the procedure is very minimal [55]. Well, the specificity of photosensitizers restricts extension of PDT [56].

2.2.2.1 Commonly used agents for PTT

Photothermal agents are selected based on their size, shape, and ability to transfer energy from one form to another [33]. Mostly used agents comes in the category of inorganic (metallic, carbon nanostructures, and quantum dots) or organic–inorganic nanohybrids. Inorganic metal-based photoactive agents are selected due to the desired shape and size favoring heat and optical properties [57]. Whereas, various forms of carbon based nanostructures demonstrate ability to transfer energy from one form to another upon light irradiation [58]. Importantly, quantum confinement make quantum dots suitable optically active probes for theranostic applications [59]. Inorganic nanoparticles are not widely used because of the challenges in biodegradability/clearance issue, bioavailability, and toxicity caused for long term [60]. However, hybrids derived from combination of organic and inorganic has demonstrated good biocompatibility, high renal clearance, less toxicity, and high photothermal performance.

2.2.2.2 Principle of photoactive agents

Photoactive agent is the basic element for contrasting phototherapy and need to be selected judiciously. Therefore, these agents basically absorb light of particular wavelength, precisely in near infrared for improved light

penetration. The second criteria for selection; the materials should not interact with cells and should be able to trigger immune responses without external stimuli. Further, for targeted therapies the agents should be capable of clearing from blood and normal tissues for assured phototherapy agent. To brief all these characteristics with good photostability make the material apt for photoactive therapies [60].

The principle involved in the generation of heat by the photoactive materials upon irradiation with NIR light includes absorption of photon resulting in excitement of electron. The excited electron shifts from low excited singlet state (S_0) to highly unstable excited singlet state (S_1) that subsequently comes back to stable S_0 state with release of energy during the relaxation process [61–65]. The energy released can be in the form of fluorescence emission or nonradiative vibrational emission in the form of photothermal energy. Various inorganic structures made from gold, silver, iron oxide, graphene, carbon nanotubes, and upconversion nanoparticles have been explored for photothermal therapy [12, 13, 17, 65, 66], whereas, organic materials like dyes and polymers are also used in photothermal based treatment of cancer. All these nanostructures upon irradiation with NIR light generate heat that ablates the cancer cells. Further, these materials due to their diverse physicochemical properties also aid in the multimodal imaging of the tumor area as well image guided tumor regression. The optical, electronic, and magnetic properties of these materials play a crucial role in contributing to this application [67, 68]. Such nanomaterials which are used for therapy as well as diagnosis of a disease are known as nanotheranostic agents [69]. The field of nanotheranostics is rapidly emerging in cancer with different novel materials being explored by various researchers cross the world. Their application in cancer has revolutionized the treatment regime as they offer several advantages over the conventional treatment like biocompatibility, biodegradability, minimal dose requirement with less frequency, and low systemic toxicity [70].

The most widely used light source for PTT is NIR due to high penetration and less toxicity. The first window of NIR (NIR-I, 650–950 nm) demonstrates lesser penetration when compared to second NIR window (NIR-II, 1000–1700 nm) through biological tissue [68, 71]. Additionally, the maximal permissible exposure (MPE) for skin is higher with NIR-II (1 W/cm² for 1064 nm) when compared to NIR-I (0.33 W/cm² for 808 nm) [72]. Hence, materials with photoexcitation in NIR-II window have recently attracted wide attention in PTT based cancer nanomedicine. This includes inorganic as well organic nanomaterials that are tuned to exhibit distinctive photoexcitation in the NIR window. These photoactive

carriers can be elements or derived as the products of chemical bond with temperature sensitive material. The generated heat from these photoactive materials not only kills the malignant cells but also alters the enzyme activity and gene expression. Further, these NIR photoactivable nanosystems when used in combination with chemotherapeutic drugs, enzymes or gene exhibit synergistic effect with better therapeutic action [73]. Additionally, some of these materials exhibit fluorescence or contrast due to their unique physicochemical properties that aids in imaging of the tumor tissue which are recognized as nanotheranostic agents. Recently, such photoactive nanotheranostic agents are gaining attention and are actively reported for diverse applications in cancer therapy [74].

2.2.3 Combinatorial agents for PDT and PTT

The efficacy could be pronounced with the use of combinatorial therapy of PDT and PTT. The dual therapy is generally made use of two different phosphatidylserine

(PS), which further needs wavelength lasers for activation of two PS [75]. While with the advancement in studies it is recognized that some PS is able to function both in PDT and PTT, e.g.; carbon dots [76]. Besides, ICG loaded liposomes were also equipped in PDT and PTT assisted therapies [77]. An overview of different photoactive agents used in cancer for PDT, PTT and their combinatorial therapy has been provided in Table 1.

2.2.4 PDT versus PTT: curbs in promoting to clinics

PDT has been introduced to clinics in the last 40 years and holds propitious treatment options for cancers of head, neck, breast, bladder, bile duct, pancreas and other vital organs [103]. The therapy is affirmed with the production of reactive oxygen species (ROS). Irradiation triggers the photosensitizer to absorb photons and to get excited to higher electronic states. The singlet state photosensitizer tries to achieve triplet state and further emits energy in the form of fluorescence, heat or light. In this state, the ROS is produced via two mechanisms. The triplet molecular

Table 1: Different photoactive materials used in cancer.

Chemical family of photosensitizer used in PDT	Cancer type	Wavelength (nm)	References
Pyrolipid	4T1 murine breast tumor	669	[80]
	Murine colorectal cancer (MC 38, CT 26)	670	[81, 82]
Porphyrin	Skin, bladder, esophagus, breast, lung, and brain	630	[83–86]
	Basal cell	White light	[87]
Chlorin	Superficial, skin, breast, and colon	660	[88–90]
		633	
Nanomaterials for cancer treatment via PTT			
Carbon nanotubes	RKO (rectal carcinoma cell line), HCT 116 (human colon cancer cells)	1064	[91]
AuNPs	CC 531 (colon carcinoma cells)	808	[92]
Graphene oxide NPs	HCT 116 (human colon cancer cells), human dermal fibroblast	532	[93]
PLGA-ICG-R837	4T1 breast cancer cell line, CT 26 colon rectal cancer cell line	808	[94, 95]
Gold nanostars	MB49 bladder tumor	808	[95]
Combination therapies for cancer			
PTT + CT	HeLa cells (human cervix cancer cell line)	LTH (808) + drug release	[96]
Polydopamine/rGo/MSN			
PTT + CT	Breast cancer	LTH (808) + drug release	[97]
CD AuNP			
PTT + CT	HeLa cells (human cervix cancer cell line)	LTH (808) + drug release	[98]
Polypyrrole/MIL/100DOX			
PTT + PDT	4T1	LTH + ROS (785)	[99]
Te ND	Breast cancer cell line		
GNcHyNA	MDA-MB-231	LTH (808) + ROS (690)	[100]
	Breast cancer cell line		
UCNP-NGO/ZnPC	KB cells (human nasopharyngeal epidermal carcinoma), HeLa cells (human cervix cancer cell line)	LTH (808) + ROS (630)	[101]
CP-TPP/Au/PEG nanospheres	HeLa cells (human cervix cancer cell line)	LTH (808) + ROS (630)	[102]

oxygen in ground state stimulates to produce singlet oxygen species [104–106]. An ideal photosensitizer is equipped with ample biocompatibility and absorbs high light levels. PS can be classified into several categories like metals, organic, inorganic, polymer based and others [107]. Apart from PS selection, it is often a cumbersome task to decide drug to device match and the mode to which the light needs to be applied, or in brief PDT dosimetry (irradiation geometry with parameters which includes fluence rate, wavelength, and total fluence), light source and exposure, PS dose and intervals for drug to light administration is a topic which needs to be worked up diligently [108, 109].

PTT is a technique for treating tumors in local arena. Here, the tissue temperature is raised above 60 °C and results in protein denaturation followed by plasma membrane destruction. The mechanism is that photosensitizers when activated by light of particular wavelength absorbs photons and excites from singlet ground state to excited singlet state. A cascade of event takes place, the electronic excitation energy undergoes vibrational relaxation, a nonradiative decay and comes back to ground state which is mediated by collisions from photothermal agents and other molecules. During this event, tissue temperature elevates as a result of kinetic energy, where heat shock proteins and gene expression changes occurs to overcome the thermal damage [110]. Further, as the temperature goes higher it causes microvascular thrombosis and ischemia [111]. Both PDT and PTT are superior compared to other treatments due to selectivity of PS. In addition, the technique provides less scar formation and can be utilized for treating multiple times [112, 113].

2.2.5 Laser and suitability

Light absorption for PTT and PDT in visible light ranges from 400 to 700 nm while for near infra-red from 700 to

1350 nm. Skin tumors are treated using light emitting diode (LED) with regulated exposure to sunlight [114]. While, most of the lasers are available commercially (Table 2).

2.3 Role of nanoparticles in cancer cell screening and therapy

Nanoparticles (NPs) have growing interest in cancer therapies. Certain nanoparticles are capable of absorbing light and get heated up parallelly with their plasmon band. The optical transmission in tissue is optimal due to possible manipulation of plasmonic band in NPs from visible to infrared favoring deep tissue treatment [121]. Therefore, NPs need to be well orchestrated for; heat generation after absorption of innocuous light in the near infrared range. The efficacy of PTT is largely dependent upon the accumulation of light responsive NPs, excitation time with power density of light, and effectiveness of light energy to heat conversion [47].

Recent studies have demonstrated the use of nanoshells and nanocages of metallic and noble metals in organic polymeric shells to combat cancer [49]. Study conducted by Hirsch et al., revealed that gold–silica nanoshell by thermal ablative therapy on tumor cells demonstrated effective outcomes in breast carcinoma cells. The study was performed tailoring the nanoshells to absorb near infrared where optical transmission was optimally controlled. Photothermal morbidity (with 820 nm, 35 W/cm²) was further confirmed with viable fluorescent staining. Simultaneously the *in vivo* studies conducted substantiated the irreversible thermal damage precisely to the tumor arena, using magnetic resonance imaging (MRI) for concordant planning and temperature monitoring by phase sensitive gradient-echo MRI. Further, magnetic resonance temperature imaging (MRTI) evidence was supported with histopathological findings, proving that nanoshells can be used as potential candidate for thermal ablative tumor destruction [122]. Recent study conducted by Norton et al. on PTT effects of plasmonic metal nanoparticles summarized that it is apt to consider NP whose plasmon resonance is near to therapeutic window for maximum possible light exposure onto soft tissues. Though it is possible to tune the plasmon resonance of nanoshells the absorption is narrow. Therefore, maximum efficacy is obtained when optical wavelength gets along with each other. The study has given more insights to which the NP diffusion can be confined to the tumor region [123].

Table 2: List of commercially available lasers along with their wavelength range [115–120].

Laser	Wavelength range (nm)
Green laser	532
Alexandrite laser	720–800
Dye laser	390–1000
Diode laser	630–1100
Neodymium doped yttrium aluminium garnet laser	1064
LED (red light)	620

3 Nanotheranostic agents in cancer

Conventional treatment of cancer involves chemotherapy, radiation, and surgery. Based on the stage of cancer and extent of tumor area, combination of these strategies is also used for better therapeutic action. The widely used cancer chemotherapy suffers from the drawbacks of non-specificity of drug action leading to poor drug concentration levels in tumor area, toxicity of nontargeted tissue, and multiple dose requirements [124, 125]. However, the emergence of nanotechnology has added new dimension to cancer treatment approach with minimal side effects. They exhibit unique physicochemical properties due to their nanoscale dimension that plays a crucial role in cancer nanomedicine. Various nanotheranostics agents derived from inorganic as well as organic origin have been designed for cancer applications. However, photoactive materials have gained much attention due to their promising potential to overcome the drawbacks of conventional chemotherapy. In addition, the delivery of therapeutic molecules like drugs, enzymes or genes along with these nanohybrids results in synergistic therapy at minimal dose with reduced side effects. Different materials developed for PTT includes metallic nanoparticles (NPs) (gold NPs, silver NPs, and platinum NPs), carbon based NPs (carbon nanotubes and nanodots, graphene based NPs, and Mxene), noncarbon based NPs (upconversion NPs and black

phosphorous), organic/inorganic nanohybrids (lipid/inorganic, polymer/inorganic, semiconductor polymeric dots, and coordination polymeric nanoparticles), and biologically derived photoactive agents etc. (Figure 2) [126–128].

3.1 Gold nanoparticles

Gold nanoparticles (AuNPs) are the most commonly used metallic nanoparticles for PTT applications with vivid morphological structures like nanoshells, nanorods, nanospheres, and nanostars [60]. Of the ones mentioned, nanorods find use in numerous applications due to their unique physiochemical properties and their high efficiency to converts light to heat [129]. Moreover, the ease of surface functionalization and biocompatibility has extended their applications in imaging, diagnostics and cancer therapies [130]. Au nanoshells were the first to get into clinical translation in the year 2008 [131]. *In vivo* studies had confirmed the enhanced permeability and retention (EPR) upon intravenous administration of Au nanoshells in mice, further thermally ablated using 808 NIR laser [122]. Further pre-clinical assessment also confirmed that there was no obvious toxicity although the nanoshells accumulated in liver and spleen. Therefore, full-fledged clinical trials on Au nanoshells are in progress, for which lung cancer (primary/metastasis) patients are given Au nanoshell intravenously and temperature is raised via exposure to

Figure 2: Different types of photoactive nanotheranostic agents used in cancer.

radiation through bronchoscopy. Investigations are still on the adult stage for treatment tumors of head and neck using Au nanoshells [47]. Mooney et al., were successful in showing the distribution of Au nanorods throughout the tumors when transported by neural stem cells in breast cancer xenografts in mice *in vivo*. In doing so, the gold nanorods were able to improve the tumor ablation with tremendous reduction in tumor recurrence. The work also compared the results from free Au nanorods. The authors concluded that a combination of nanotechnology with cell therapy would benefit for cancer curation [132]. Vijayaraghavan et al. [133], showed the complete elimination of deep tumors by the combinatorial treatment with gene silencing (ultralow NIR light)

and PDT employing Au nanoechinus both in *in vivo* and on HeLa cells.

Further, Wang et al., proved Ce-6 Aptamer conjugated Au nanorods for cancer therapy. Aptamer (Sgc8) targeted leukemia T cells and the conjugation through Au-thiol covalent bond. Fluorescence quenching was observed due to the proximity of Ce-6 to Au surface. Upon aptamer binding to cancer cells, Ce-6 released due to DNA structure and purposed as agent for PDT irradiating with NIR (812 nm). The study highlighted PDT/PTT to serve as treatment for targeted multimodal therapy [134]. Yet another study by Lin et al., successfully demonstrated the synergism of PDT/PTT in ruling out cancer (Figure 3). The photosensitizer utilized was Ce-6 loaded plasmonic gold

Figure 3: Morphological characterization of plasmonic gold vesicles (GV) and *in vivo* trimodality imaging using GV loaded with photosensitizer Ce6 (GV-Ce6).

(a) Scanning electron microscopic (SEM) image and (b–d) Transmission electron microscopic (TEM) images of plasmonic gold nanovesicles. (e) NIR fluorescence image at preinjection and postinjection of GV-Ce6 in MDA-MB-435 tumor-bearing mice. (f) Thermal images at postinjection of GV-Ce6 in tumor-bearing mice upon 6 min irradiation with laser of 671 nm (2.0 W/cm²). Red circles indicate the tumor location. (g) Heating curves of tumors upon laser irradiation as a function of irradiation time. (h) *In vivo* photoacoustic (PA) images. Yellow circles indicate the injected location and (i) Average PA intensity of tumor tissues at preinjection and postinjection of GV-Ce6 [135].

vesicles. The technology used was trimodality assisted fluorescence/thermal/acoustic image guided combination with PDT/PTT. The study reported that the absorbance by vesicles in NIR region was strong, and the NIR irradiation (671 nm) was successful in exciting Ce-6 along with Au vesicles producing singlet oxygen species together with heat and eradicated cancer cells. When investigated *in vivo*, the results were fruitful and were visualized via fluorescence/thermal/acoustic signals. There the study clearly describes the importance of combinatorial approach with PDT/PTT in cancer cell destruction [135].

3.2 Silver nanoparticles

Silver nanoparticles (Ag NPs) are popular due to their antibacterial and tumor destructing properties. Besides, their plasmon tunability in the NIR biological window range (650–1200 nm) have paved for increased applications of Ag in medical field [136]. More interesting is its antitumor properties. However, Ag is shown to exhibit cancer killing properties only at higher concentrations [137]. Ag in photoactive therapy seems to aid as NPs for effective drug loading or photosensitizers to improve antitumor therapy [138]. Ag NPs are suitable to load heat labile or water soluble drugs because of the synthesis method (reduction of Ag ions which is devoid of organic solvent or heat) [34]. Studies conducted by Bose et al., demonstrated folate receptor targeted plasmonic Ag NPs intended for breast cancer where, Ag NPs to purport as efficient nanocarrier system for delivery of quercetin thereby inducing PTT. The quercetin folate receptor Ag NPs were synthesized by one pot method and later the hydrogen bond between stabilizer and reductant were tuned according to the need. The outcome of the study was that PTT induced Ag NPs complemented to the antitumor efficiency by hyperthermia induction resulting in selective lysis of abnormal cells with a fate of apoptosis. Further, quercetin incorporated Ag NPs showed double antitumor effect in lab and animal studies. The study successfully proved that quercetin loaded Ag NPs are more effective than free quercetin and can be beneficial for breast cancers [139]. While recent study conducted by Park et al., tried to delve effectiveness and applications of indocyanine green loaded Ag NPs. The study was successful in high loading capacity of indocyanine with good stability against light induced degradation and hepatic clearance. The composite delivery system addressed significant tumor accumulation combining local irradiation of laser at tumor site resulting in tremendous inhibition of tumor growth. The author was

successful to prove that the nanocomposite system purposes to be a promising PTT agent for treating cancer [137].

3.3 Platinum nanoparticles

Platinum (Pt) is a metal that absorbs light in biological range and generates DNA strand breaks [140]. Though Pt NPs act as antioxidants at higher concentration, the toxicity reported is also high in literature [141]. While cancer therapies have also evidenced synergistic effect with the use of these NP's further reducing the side effects, which is a factor of longer time period patient prognosis [142]. To date Pt NPs when used in reduced concentration are apt in biological stability and tolerance [143]. Study conducted by Depciuch et al., was on assessment of size of Pt NPs for PTT therapy. The study concluded that the antitumor activity of Pt NPs like DNA damage and enzyme activity, apart the smaller size could serve as best PS agent [144]. Another study conducted by Song et al., demonstrated Au–Pt NPs uptake with cell targeting folic acid and triphenylphosphine targeting mitochondria in tumor cells. Mitochondria targeting was achieved via loading PS (Ce6) onto Au–Pt NPs. The authors were successful in designing multifunctional theranostic approach with ability to target mitochondria using combinatorial PDT and PTT [145]. While the study conducted by Phan et al., revealed that the prepared Iron–Platinum NPs (Fe–Pt NPs) with polypyrrole coating with evidence of high biocompatibility, NIR absorbance, and photothermal stability can excellently serve as multifunctional system for photo diagnostic application like PDT and photo acoustic imaging (PAI) [141].

3.4 Graphene

Graphene based materials are of major importance in biomedical applications due to their uniqueness in prognosis, diagnosis, and therapeutic agents in cancer therapies [146]. This is due to their easiness in surface modification, for being rich in carboxyl and hydroxyl groups [147]. Graphene lays superior position in cancer treatment due to its toxic effects in tumor cells [148]. Hence, graphene is used actively in battling cancer in PTT, PDT, and imaging [149]. On the other hand, there needs an unmet research to address its biocompatibility and biodegradability [150]. Wang et al., demonstrated in his studies by covalent grafting of nanographene oxide as core shell and upconversion through bifunctional polyethylene glycol, further, loading phthalocyanines on graphene oxide

surface. The study reports the greater efficacy of the prepared nanocomposite system with good biocompatibility. The study leaves a remark that the system can be a great success to be used as upconversion luminescence probe of cells and to image whole body with greater contrast [101]. Recently, a notable study conducted by Thapa et al., revealed that graphene was suitable for prostate cancer treatment, where the authors intratumorally-injected palladium nanoparticle decorated with graphene oxide. The outcome was that the graphene oxide decorated nanoparticulate system showed enhanced local distribution, photothermal ablation, and inhibited cancer cells in PC3 xenograft mouse models, with reduced organ toxicity [151]. Besides, these a study conducted in 2016 by Zhang et al., proved that BaGdF₅ nanoparticles were seemed to get attached intact on graphene oxide surface nanosheets to form the GO/BaGdF₅/PEG nanocomposites. This nanocomposite system exhibited low toxicity, efficient magnetic contrast. The author with evidence suggested that the system could serve as dual imaging (MR and X-ray) models for *in vivo* tumor models [152]. Study conducted by Nurunnabi et al. [153], was yet a further confirmation that graphene nanoparticles being photoluminescent was suitable candidate for PTT and imaging. Notably Nafujjaman et al. [154], through his work elucidated the use of graphene quantum dots in targeted cancer therapy (PDT) and imaging. In short, graphene will be a promising compound in future for treating and imaging cancer, except the challenges faced for its biocompatibility.

3.5 Carbon nanostructures

Carbon dots are basically diamond or graphitic core, which is *sp*² or *sp*³ hybridized. Low dimensional carbon is classified as carbon nanoparticle, carbon nanodot or carbon quantum dot, and fullerenes [155–157]. The ease of surface functionalization of carbon dots with amine (NH₂), carboxylic acid (–COOH–), alcohol (OH), aldehyde (CHO) and production tuning their size together with the ability to deliver photoluminescence has made them popular in cancer therapeutics and imaging [158]. Besides, they have gained much attention in biomedical applications owing to their optical absorption, photostability, high penetration, good electrical conductivity, biocompatibility, high chemical stability, and low toxicity [159, 160]. Study conducted by Serda et al., in 2018 has affirmed the use of fullerene in PDT applications. The authors have developed glycoconjugated C60 derivative for adenocarcinoma. As a result, it was seen that fullerenes completely accumulated in nucleus of stellate pancreatic cells, which is not toxic

upto 1 mg/mL, and was shown to exhibit photoactive ability upon green, blue light activation [161]. Zheng et al., in his studies a solution for hypoxia condition caused in solid tumors. He designed a multifunctional nanocomposite comprising of carbon dots decorated with carbon nitride NPs against hypoxic tumor water splitting. The results were so promising that improved intracellular oxygen concentration with reactive oxygen species under hypoxia and normoxia with light irradiation. While *in vivo* studies confirm that the multifunctional nanosystem surpassed tumor hypoxic condition. The author suggests using water-splitting materials which has the capability of enhancing oxygen level and reversing hypoxia induced PDT resistance and metastasis [162]. A recent study by Sundaram et al., in 2020, was successful in coating hyaluronic acid and Ce6 onto carbon nanotubes which purported as photosensitizer. This further on when tested on CaCo-2 colorectal cancer cells via PDT approach (660 nm) inhibited apoptotic cell death, the study confers the nanocomposite system to be an efficient vehicle for photosensitizer localization in Colorectal cancer cells [163].

3.6 Mxene

MXenes are two-dimensional (2D) novel structures derived from transition metal carbides and nitrides [164]. They are characterized by the presence of layered arrays of transition metal atoms that are interconnected by a carbon or nitrogen atom. The general formula for MXenes is $M_{n+1}X_nTx$ ($n = 1-3$), where M stands for early transition metal carbides (Ti, Hf, Zr, Nb, Ta, V, Mo Sc etc.), X denotes carbon or nitrogen and Tx represent functional groups (–Cl, –F, –OH, and O) terminating the M surface [165–167]. They have attracted increased attention as they exhibit excellent electrical, optical, magnetic, and mechanical properties [168, 169]. These properties can be tuned by modulating the transition metal atom and surface functional groups. Further, they demonstrate thermal stability and extreme biocompatibility that makes them suitable for catalysis, energy storage and biomedical applications [164, 166, 170, 171]. They have structural similarity with graphene and their morphology as well as size can be altered as per the application requirement. Recently, MXenes have emerged as a promising photothermal agent for cancer therapy due to their high surface area, hydrophilic nature, broad absorption band in UV/NIR region and high photothermal conversion efficiency (PCE) [172, 173]. The hydrophilic nature of MXenes can attributed to the presence of hydroxyl (OH), oxygen (O), and fluorine (F). Additionally, their surface can be functionalized to achieve active

targeting as well as combinatorial therapy. Moreover, the planar structure of MXenes can act as a carrier for cargo delivery [172]. Highly photostable MXene QDs with good quantum yield and tunable wavelength demonstrating luminescent properties have been studied extensively for PTT. Therefore, they can be used for imaging guided synergistic PTT integrated with chemotherapy/photodynamic therapy in cancer. The potential of MXene as theranostics agents in cancer has been explored by researchers across the globe.

For instance, the surface of Ti_3C_2 MXenes were been coated with superparamagnetic iron oxide nanoparticles (IONPs) for cancer theranostic applications [174]. The formed composite of Ti_3C_2 -IONPs demonstrated good biocompatibility and high PCE of 48.6% revealed through systemic *in vitro* and *in vivo* studies. Further, the large surface area provided by the nanosheets of MXene acts as a carrier for loading of therapeutic molecules or nanoparticles. Herein, the functionalization of MXene with superparamagnetic IONPs resulted in imaging-guided PTT against cancer through contrast-enhanced T2-weighted MRI and efficient photothermal ablation of cancer cells. Hence, such unique design of safe and efficient photothermal based composite system with high therapeutic efficacy holds promising potential for clinical translation.

Additionally, recent research has been widely focused on photoactive materials that are triggered in NIR-II (1000–1350 nm) biowindow as it shows high tissue penetration with less adverse effects. Lin et al. reported the design of biodegradable Nb₂C nanosheets (150 nm) that demonstrated absorption in both NIR-I (808 nm, PCE 36.4%) and NIR-II (1064 nm, PCE 45.65%) biowindow [175]. Modification of these Nb₂C nanosheets with polyvinylpyrrolidone (PVP) resulted in composite (Nb₂C-PVP) with increased biocompatibility and less toxicity. Results of both *in vitro* as well as *in vivo* experiments confirmed the non-toxic nature and excellent photothermal performance of composite in the NIR-I and NIR-II biological windows. Effective photothermal conversion with considerable tumor regression composite in the NIR-I and NIR-II biological windows was seen *in vivo* and such systems can be highly beneficial for deep tissue PTT applications.

3.7 Upconversion nanomaterials

Upconversion nanomaterials abbreviated as UCNPs makes it unique due to the ability of generating shorter wavelength emissions in longer wavelength excitations [176]. This requires two or more than two low energy NIR photons for high-energy photon generation that ranges from NIR to

ultraviolet/visible. Large Stokes shift, photo-blinking and stable energy levels in micro/milli seconds makes UCNPs outstanding compared to other techniques [177]. Besides, minimal scattering and absorption levels improved penetration depth favors UCNP for *in vivo* biological applications [178, 179]. The host materials selected for UCNP should preferably be of low lattice energy, to lessen non-radiative loss and deliver maximum radiative emission. Nonradiative energy loss needs the presence of phonons in host lattice [180]. UCNP when excited to long wavelengths (e.g.: 980 or 808 nm) the upconversion is to shorter wavelength ranging from deep ultraviolet to near infrared. In turn NIR light excitation results in low auto fluorescence, reducing photo damage and enhancing the penetration depth, and benefitting cell label and imaging in live organisms [181, 182].

Upconversion mechanisms are mainly classified into five types namely; energy transfer, photon avalanche, migration mediated energy upconversion, excited state conversion, and cooperative energy transfer upconversion. Although there is no gold standard procedure for upconversion mechanisms these are purely based on host matrix type and concentration of doped activator [181, 183]. Lanthanide doped UCNPs will be able to get excited with negligible background providing future possibilities in the field of bioimaging. Surface modification of UCNP opens a good possibility for better biocompatibility (silica coating). In addition, efforts to remove the capping ligand on hydrophobic UCNPs were also successful [184]. Though UCNP has high possibility to excel in bio-applications, immense effort is needed to explore and tune the biological and physiochemical properties especially in cellular applications [121, 177, 185].

3.8 Black phosphorous quantum dots (BPQDs)

Black phosphorous (BP) is two-dimensional (2D) material with high surface area and serves as a carrier for drug loading [186, 187]. It also acts as a photosensitizer due to its electronic properties and generates singlet oxygen for PDT [188, 189]. The bulk properties of BP widely differ when they are brought down to single layered structure. Additionally, the nanoparticles (NPs) and quantum dots (QDs) of BP exhibits wide absorption spectrum that can be used for the near infrared (NIR) light triggered PTT [190]. Hence, BP shows huge potential in the field of biomedicine and photo-electronics due to its diverse properties [186, 190–192]. Black phosphorous quantum dots (BPQDs) are nonmetallic, optically active and semiconductor based

material with tunable band gap. They demonstrate absorbance in the NIR region of spectrum. They exhibit diagnostic as well as therapeutic properties for cancer applications. Their surface can be functionalized and can serve as carrier for chemotherapeutic drug. Hence, they can be used to achieve image guided synergistic photodynamic–photothermal–chemotherapy [193–196]. Functionalization of these systems with targeting moieties helps in selective localization in tumor area resulting in precise killing of the cancer cells. Moreover, the BPQDs degrade in aqueous medium yielding nontoxic and biocompatible phosphate and phosphonate [197, 198].

Wang et al., reported a biocompatible folic acid functionalized doxorubicin loaded BPQDs (FA-PEG@BPQD@DOX) that exhibited selective uptake in the cancer cells over expressing folate receptors [199]. Upon NIR irradiation, the generated heat resulted in ablation of cancer cells along with triggering the drug release at tumor site. In addition, considerable reduction in tumor size was observed in nude mice animal model without affecting the noncancerous cells. Hence, the designed nanotheranostic agent aided in

visualized synergistic therapy involving photoacoustic and photothermal imaging. Also, the system demonstrated effective therapeutic response using photodynamic, photothermal, and chemotherapy. Cellular toxicity of targeted system of FA-PEG@BPQD@DOX was approximately 10 times more to that of nontargeted PEG@BPQD@DOX under same condition of irradiation. Such diverse multifunctional targeted systems could serve as an effective treatment modality in cancer. In another study, Liang et al. [200], described a simple, cost-effective protocol for synthesis of BP and BP reduced graphene oxide (BP/rGO) hybrids. The hybrid system demonstrated high stability attributed to the covalent bond formation between carbon from rGO and phosphorous from BP. Further, surface modification of the hybrid with PEG (PEGylated BP/rGO) enhanced the photothermal performance with photothermal conversion efficiency (PCE) of 57.79% at 808 nm. Results of *in vitro* as well as *in vivo* studies with hybrid revealed promising results with significant antitumor efficacy in cancer biomedicine (Figure 4).

Figure 4: Morphological characterization and evaluation of nanotheranostic property of black phosphorous and reduced graphene oxide composite (BP/rGO).

(a) TEM image of BP/rGO composite. Inset shows a typical HRTEM image of dark, small particles; scale bar, 2 nm. (b) TEM image of PEG-coated BP/rGO. Inset shows an enlarged image of a typical PEG-coated BP/rGO particle; scale bar, 100 nm. (c) *In vitro* relative cell viability of SMCC-7721 cells after photothermal ablation using NIR laser irradiation (808 nm, 1.0 W/cm²) for 5 min. (d) *In vitro* relative cell viability of MCF-7, SMCC-7721, B16, and L-O₂ cells after co-incubation with different concentrations (0.01, 0.05, 0.1, and 0.15 g l⁻¹) of PEGylated BP/rGO for 24 h. Error bars represent the standard deviations (SDs) calculated by three parallel samples. (e) *In vivo* real-time IR thermal photos of SMCC-7721 tumor-bearing nude mice exposed to a NIR-laser after intratumor injection of PEGylated BP/rGO (10 μg per mouse). (f) Typical photographs and corresponding growth curves of tumors collected from the mice treated with saline solution, PEGylated GO with NIR laser irradiation, PEGylated RP/rGO with NIR laser irradiation, and PEGylated BP/rGO with NIR laser irradiation. All the relative tumor volumes were normalized to the initial sizes. Data were shown as mean ± SD, ****p* < 0.001, *n* = 5, Dunnett's multiple comparison test [200].

3.9 Organic/inorganic nanohybrids

Recently, organic/inorganic nanohybrids have attracted wide attention due to their desirable properties that extend their applications in cancer nanomedicine. They demonstrate the properties of inorganic materials (such as electrical, optical, and magnetic properties) and at the same time, the organic component helps to improve the biocompatibility, biodegradability, and clearance [201, 202]. Organic materials like polymer, lipids etc., are used to design versatile nanohybrid for biomedical applications. The functional groups present in the organic component also help to functionalize the nanohybrid system with targeting molecules resulting in site-specific localization of nanohybrid. Such nanohybrids can be extensively used for less-invasive imaging as well as imaging-guided PTT.

3.9.1 Polymer/inorganic

Chauhan et al., designed a novel biodegradable and biocompatible plasmonic system for imaging guided photothermal therapy named as Toco-Photoxil (Figure 5) [203]. The nanotheranostic system consisted of vitamin E modified gold-coated poly (lactic-co-glycolic acid) nanoshells loaded with Pgp inhibitor D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS). Toco-Photoxil was tuned to exhibit absorption at 750 nm for effective therapeutic efficacy. Systemic *in vivo* studies demonstrated that Toco-Photoxil passively accumulates in the solid tumor and disintegrates upon NIR light irradiation resulting in generation of heat that ablates the cancer cell. The system upon disintegration is easily cleared from the body minimizing the toxicity issues that can be caused due to accumulation of material. Functionalization of Toco-Photoxil

Figure 5: Morphological characterization and *in vivo* nanotheranostic evaluation of Toco-Photoxil.

(a) FEG-TEM image of Toco-Photoxil. (b) Representative Near Infra-Red Fluorescence (NIRF) imaging at different time points in HT1080 FR(-) xenograft and 4T1 FR(+) orthotopic tumor-bearing mice after systemic delivery of IR780-Toco-Photoxil (top), IR780-FA-Toco-Photoxil (middle), and IR780 dye control (bottom). (c) Qualitative representation of TurboFP fluorescence images of mice bearing HT1080-fluc2-turboFP tumors during the course of photothermal treatment (arrow head indicates the treated tumor region). (d) Quantitative assessment of changes in light output of the TurboFP fluorescent protein ($p < 0.01$). (e) Representative follow up bioluminescence images of mice at day 10 (arrow head indicates the treated tumor region). (f) Fold change in bioluminescence light output between the vehicle control treated mice and mice treated with a combination of Toco-Photoxil and 750 nm laser [203].

with folic acid (FA) and IR780 reduced the stability leading to aggregation and decreased the photothermal transduction potential due to disturbance in plasmon resonance. Computed tomography (CT) imaging studies with Toco-Photoxil revealed comparable contrast to that of iodine based contrast agent Omnipaque at five times lesser concentration due to high X-ray attenuation power. Hence, Toco-Photoxil with high photothermal conversion and localized accumulation can serve as an effective and safe material that can be clinically translated for cancer nanotheranostic applications in future.

Chauhan et al. [204], has also reported a facile and green synthesis of gold deposited zein nanoshells (AuZNS) for image guided plasmonic photothermal therapy. The zein nanoparticles were surface functionalized with cationic glycol chitosan that helps in stabilizing the system and *ex-situ* coating of gold was done over the zein nanoparticles. The designed system demonstrated high biocompatibility and effectively killed cancer cells under NIR light (808 nm) irradiation. Further, it also assisted in diagnosis of tumor through CT imaging and hence the system functions as a nanotheranostic agent in cancer.

Similarly, they have also reported NIR light-triggered thermoresponsive nanoshell for plasmonic PTT based cancer theranostic application [205]. The hybrid nanoshell (Au PNVC NS) was formed by ascorbic acid-driven *in situ* gold coating over thermoresponsive chitosan-grafted poly(*N*-vinyl caprolactam) nanoparticles. The plasmonic absorption peak was tuned in NIR region (750 nm) for its application in PTT and loading of drug in the polymeric core results in controlled release due to hyperthermia triggered shrinkage of polymer. Grafting of chitosan was found to increase the biocompatibility, biodegradability, and elevates the lower critical solution temperature (LCST) to desired value. Au PNVC NS demonstrated superior contrast over Omnipaque in X-ray imaging. *In vitro* studies in mouse normal fibroblast L929 cells confirmed the biocompatible nature of the nanohybrid and studies in breast cancer cells MCF-7 revealed the therapeutic potential of Au PNVC NS. Based on the results, Au PNVC NS could be considered as a promising multifunctional theranostic agent for image-guided PTT and can be explored for in future for combinatorial chemo-photothermal therapy.

Figure 6: Liposomal nanotheranostics (NFGL-FA) for multimode-targeted bioimaging and phototriggered cancer therapy.

(a) Schematic showing folic acid targeting ligand decorated self-assembled liposomal nanohybrid loaded with multimode imaging probes, viz., gold nanoparticles (AuNPs) and graphene quantum dots (GQDs). (b) Localized tumor diagnosis and specific biodistribution measurements after 48 h of time before and after NIR light exposure (750 nm, 1 W/cm² for 10 min) followed by whole body X-ray computed tomography scans with coronal and axial CT slices of mice body (c) Visualization of targeted deep tumor localization in mice body before and after NIR light exposure using the *in vivo* imaging system (IVIS). (d) Measurements of tumor reduction by tumor volume (mm³, $*p < 0.05$) analysis ($n = 3$ mice per group) during various therapeutic conditions using different formulations of NFGL-FA nanotheranostics with and without NIR light exposure (e) Whole body *in vivo* imaging for site-selective 4T1 tumor diagnosis at various time points (1, 24, and 48 h) of intravenously injected NFGL-FA. (f) *Ex vivo* imaging of collected major organs and 4T1 tumor after 48 h from intravenously nanotheranostics injected animals [207].

3.9.2 Lipid/inorganic

Rengan et al. [206], has designed multifunctional and biodegradable gold coated thermosensitive liposomes for multimodal imaging and photothermal therapy. *In situ* reduction of chloro-auroic acid was used to coat gold over the liposomal surface. Upon NIR laser irradiation, these systems degrade into small sized gold nanoparticles that can under renal clearance easily. Also, the nanohybrid demonstrated excellent biocompatibility and high therapeutic efficacy by photo ablation of cancer cells. Besides, they were useful in imaging establishing their potential as a promising nanotheranostic agent for cancer.

Prasad et al. [207], have developed a multifunctional liposomal based nanotheranostic agent for phototriggered chemotherapy. Herein, the liposomal system was used as a carrier to encapsulate doxorubicin (DOX) drug, gold nanoparticles (AuNPs), and emissive graphene quantum dots (GQDs) which was subsequently functionalized with folic acid as targeting ligand (NFGL-FA). The designed system presented imaging bimodality *in vivo* due to the high contrast and emissive nature of encapsulated agents aiding in diagnosis of tumor (Figure 6). Further, *in vivo* studies under NIR light (750 nm) irradiation revealed tumor regression due to generated heat and reactive oxygen species (ROS) production. Additionally, synergistic effect in tumor regression was noticed with combined chemophototherapy when compared to stand-alone therapies (chemotherapy and PTT). Such biodegradable and biocompatible multifunctional-targeted nanotheranostic system results in selective uptake with high therapeutic efficacy can serve as potential platform for image guided synergistic treatment approach by PPT.

3.10 Biological agents for photoactivity

Photosensitizers in nature's list are quite few and is interesting due to their lower toxicity profile in normal cells and the toxic effects shown towards abnormal cells [208, 209]. Besides, the biological compatibility also makes phyto-compounds apt as photosensitizers (absorption maxima 400–700 nm) [210]. Discovery of natural photoactive agents should be supported, as it can contribute photosensitizers of minimal toxicity and adverse effects than synthetic agents. The clinically approved PS of biological origin is Foscan, Levulan, and Photofrin [211, 212]. Describing here are some common phyto-compounds capable of producing photoactivity.

3.10.1 Alkaloids

Alkaloids are nitrogen group containing heterocyclic compounds [213]. Few compounds are shown to exhibit photoactivity among the alkaloid group. Harmine and Berberine are the ones used in PDT till date [214, 215]. Harmine's activity was confirmed upon longer irradiation to ultra violet rays. While, Berberine is extensively used and proven photosensitizer in PDT [216].

3.10.2 Thiophenes and polyacetylene

The compounds are said to get excited at 314–350 nm (nearing the biological absorption) and is capable of producing photoactive effects [217]. Basically, these are unsaturated carbon molecules containing thiophene groups [218]. The produced UV irradiation by these compounds is capable of producing free radicals and has ability to induce apoptosis [212].

3.10.3 Curcumin

Curcumins are one of the most important compounds used in cancer treatment. The absorption peak of curcumin is at 300–500 nm favoring phototoxic reaction at reduced temperatures and therefore can be used as good phyto photosensitizer [219]. Notable, studies have widely used for cancer studies due to its immense ability in producing reactive oxygen species [220]. Study performed by Wu et al., confirmed the photoactivity on human epidermal A431 carcinoma cell. The study also revealed that the more concentration of curcumin used the better is the irradiation permeation [221]. Considering these studies with no doubt could be concluded that curcumin can be used as one of the best photosensitizer, and could reap tremendous results with PDT [222].

3.10.4 Coumarins

Coumarins are present mainly in higher plant species [223]. Photoactivity was evidenced in furanocoumarins when Kim et al., studied the reaction of Grapefruit extract furanocoumarins in eradicating multiple myeloma. The compound successfully inhibited STAT 3 signaling pathway further resulting in chemo sensitization and apoptosis [224].

Among the phyto derivatives, anthraquinone are also fit as photoactive agents. Among this class, soranjidiol and rubradin are the most used in studies [225]. Research is on

its way to explore more anthraquinones suitable to use as photoactive agents [226].

4 Emerging ablation modality

The combination of chemo-photo therapies is yet another option, which can result in synergistic anticancer effects. Photothermal agents upon NIR irradiation aids in killing tumor cells and the heat produced can act as stimuli for release of drug in systematic manner [227]. Optimization of chemotherapeutic system could help eradicate tumors with the support of photothermal therapy [228]. Combined treatment methods could to a vast extent improvise multidrug resistance and minimize metastasis of the lungs [104]. Zhang et al. demonstrated mesoporous silica decorated AuNPs to support light controlled drug release with low intensity NIR radiation chemo-phototherapy for effective destruction of cancer cells [229]. Zheng et al. Through his work has showcased the efficacy of small molecular NIR dyes via chemo-phototherapy. The author successfully incorporated chemotherapeutic drug and NIR dye into nanoparticle by physical interactions. Indocyanine green being the stereotypical NIR dye was coencapsulated with doxorubicin in poly(lactic-co-glycolic acid lecithin poly ethylene glycol (PLGA lecithin PEG NP), upon hike in localized temperature than free ICG, facilitated cellular uptake and drug release [230]. Interestingly, chemo-phototherapy hampered tumor cells and further prevented its reoccurrence. Similar way attempts were made to coencapsulate drugs with NIR dyes in protein, polymeric, metallic, nanogels, and liposomes which landed up in remarkable results [231–233]. Though combinatorial therapy holds promise in future onco clinics, premature leak of drugs and NIR dyes from NPs which could worsen tumor accumulation should be of foremost concern. Covalent conjugation of drugs/dyes to NPs, or surface tailoring can be of solution to a certain extent [233]. Scientists should be vigilant in choosing photothermal agents and NIR dyes for exhibiting good conversion efficiency. Further attention should be given in designing newer nanocarriers with optimized photothermal conversion efficiency and minimal cytotoxicity. Also, the use of FDA approved biomaterials is highly recommended for better biocompatibility and degradation. All the aforementioned points taken into consideration; nanomedicine can create transformation in oncology clinics.

5 Challenges and possible solutions

One of the main challenges faced in photoactive therapy is the thermal damage caused to normal tissues. Scientists are trying their best to eliminate this issue and have come up with more specifically targeted use of photosensitizers. Photoactive materials being dependent on enhanced permeability and retention effect, is largely dependent on particle size that has the ability to penetrate into tumor tissues compared to normal cells. Application of low temperature PTT will be the other solution in surpassing the problem. The other limitation of PTT being uneven dispersion of photosensitizers and is solved by designing mesoporous nanoenzymes by aggregation effect. In addition, the issues associated with ROS were proposed via targeting mitochondria and intervening with its function to attain tumor death [234]. In doing so there will be tremendous reduction in heat resistance of abnormal cells caused due to inhibition of heat shock proteins, while the low temperature will not hamper normal cell physiology. Yet another approach put forward by Du et al. [77], loading of tumor targeting ligands onto NPs with the aim of NPs binding the tumor cells. While Quian et al., tailored Lyp-1 ligand on NPs with intention to target p32 (overexpressed in breast cancer). The authors were successful *in vitro* and *in vivo* in producing anti-tumor effect in mouse with combinatorial PDT/PTT. To brief, targeting photoactive materials can be achieved by tailoring size, properties on NPs and enhancing surface ligands associated with NPs [235, 236].

The next challenge faced is the use of single photoactive therapy. Often the tumor site receives inadequate light penetration leading to recurrence of tumor. This can only be corrected with combinatorial therapeutic approaches, like PTT with chemotherapy, PDT with PTT, or activating body's antitumor immune response. Lam et al., through self-assembled approach synthesized doxorubicin loaded nanoparticulate system delivering photothermal conversion of high efficiency. Nanoparticulate system in combination with PTT-chemo showed good therapeutic efficacy in mouse breast cancer model (xenotransplantation model) treated xenotransplantation cancer. The model was also successful in activating immune activity against tumor [237].

Although PDT under preclinical settings is appealing, when practiced clinically faces some drawbacks, which is one of the unmet needs to be sought out quickly. These include

- (1) The observed side effects for PDT till date is increased risk of dermal toxicity on exposure to sun, which could be accounted due to the complicated composition and the limited absorption to red light [103, 238]. Generally, NIR-II ranging from 1000 to 1700 nm is recommended as light source than the ones with shorter wavelength and the visible light [22].
- (2) The abnormal narrowing of canal or duct was reported using PDT, upon higher dose and light application beyond a certain limit. Due to this, the PS accumulated in organs may likely result in harmful side effects to unintended incidental damage [103, 239].
- (3) This technology seems inept for deeply rooted tumors owing to their poor specificity. Effective penetration depth recommended is not more than 1 cm for the light source used. In certain cases (oral and topical skin cancer) optical fibers can be of help to achieve better therapeutic outcomes [239].
- (4) Besides, the advent of endoscopic techniques, ablation with radiofrequency has gained more efficacy over PDT, which can be advocated due to lack of light reaching the tumor site [240]. This condition could be addressed by designing a site-specific targeted nanoparticle.
- (5) Also, another drawback includes PDT's ineffectiveness in hypoxic tumors as it demands oxygen for therapy. In other terms, molecular oxygen consumption by PS leads to resistance of PDT under hypoxic environment [241]. Hypoxic condition in PDT could be bridled only if newer paradigm like designing oxygen vesicles, hypoxia activated drugs/prodrugs, water splitting nanocomposites, self-oxygen supplementation (to use red blood cells, hemoglobin as oxygen carrier) modification of tumor environment, hypoxia dependent or fractional PDT are brought in as a modification in existing therapeutic regimen [242–244].

PTT/PDT therapy was successfully demonstrated using cationic polyethylenimine to electrostatically adsorbed ICG to Prussian blue NPs. ICG loading with NP helped improving systemic circulation time. Solid tumor in nude mice was efficiently inhibited using PDT/PTT. The work was proceeded by Dong et al., connected monoamine substituted porphyrin photosensitizer to covalent framework, further, loaded naphthalocyanine for light stability. The outcome of PDT/PTT was in lysis of lysosomes and mitochondria demonstrating synergistic effect using PDT/PTT [245, 246].

Nevertheless, PDT/PTT based nanomedicine when combined could revolutionize the field of cancer treatment using tumor specific photosensitizers via localized/

targeted activation. In addition, it also results in minimal adverse effects, which could also be preferred for combining chemo or immunotherapies. Also, as a part of multifaceted nanomedicine, abetment of newer immune adjuncts could be of patient beneficence.

6 Conclusions and perspectives

Various examples of cancer theranostics with their major challenges have been addressed in this review article. Moreover, the importance of integrated nanotheranostics platform has been discussed thoroughly. Among various hybrids nanomedicines, liposomal systems have been recognized as versatile systems for localized diagnostics and therapeutics agents due to their good biocompatibility and easy preparation, and several others as addressed in this article. The clinical aspect of PTT and PDT with advanced development has been highlighted here. Overall, cancer should no longer be contemplated a death sentence. With huge understanding in this field, scientists have brought in new techniques to combat this life intimidating disorder; among them one of the promising therapies being the use of photoactive agents. Photoactive therapy assists people in exploring life's panorama to a complete extend, making "evolve and resistant", theory of Darwinian to meet reality. Therefore, clinically the thought of binary cure needs to be completely erased and concepts of newer techniques to combat cancer should be relied for better care and quality life style of patients. However, modernized photoactive assisted therapies have gained much attention due to its non-invasiveness, spatial control, tumor senescence/assassination capacity, and high specificity. Additionally, the real time monitoring has led photoactive therapies superior when compared with traditional treatment procedures. Many efforts are required to translate photoactive therapies from lab to clinical setting. However, more clinical trials need to be conducted for understanding the exact effectiveness and survival rates when it comes to human subjects. Laser selection, illumination, bowel complications, and security of clinicians are the plausible hurdles to overcome. While, using NPs in therapy, attention is needed for their reproducibility, degradation properties, and toxicity profiles. Alternatives like biological agents/liposomes can be much promising and need to be explored further. Considering all this, photoactive therapy is in its infant stage and can be solved with cutting edge research and more ground breaking studies, where future will regard photoactive therapy as gold standard for cancer treatment.

Acknowledgements: The authors are grateful to Department of Biotechnology (DBT), Government of India for their support. N.K.J. would like to thank Department of Science and Technology, Government of India for providing DST INSPIRE fellowship and Indian Institute of Technology Bombay (IITB) for IPD fellowship.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

- [1] D. M. Parkin, "Global cancer statistics in the year 2000," *Lancet Oncol.*, vol. 2, no. 9, pp. 533–543, 2001.
- [2] M. Heron and R. N. Anderson, "Changes in the leading cause of death: recent patterns in heart disease and cancer mortality," *NCHS Data Brief*, vol. 254, pp. 1–8, 2016.
- [3] A. Sirokman, "AMA policies and code of medical ethics' opinions related to cancer prevention in low-and middle-income countries," *AMA J. Ethics*, vol. 22, no. 2, pp. 112–115, 2020.
- [4] B. Xiao, L. Ma, and D. Merlin, "Nanoparticle-mediated co-delivery of chemotherapeutic agent and siRNA for combination cancer therapy," *Expert Opin. Drug Deliv.*, vol. 14, no. 1, pp. 65–73, 2017.
- [5] R. Misra, S. Acharya, and S. K. Sahoo, "Cancer nanotechnology: application of nanotechnology in cancer therapy," *Drug Discov. Today*, vol. 15, nos 19–20, pp. 842–850, 2010.
- [6] X. Wang, L. Yang, Z. Chen, and D. M. Shin, "Application of nanotechnology in cancer therapy and imaging," *CA Canc. J. Clin.*, vol. 58, no. 2, pp. 97–110, 2008.
- [7] B. Aslan, B. Ozpolat, A. K. Sood, and G. Lopez-Berestein, "Nanotechnology in cancer therapy," *J. Drug Target.*, vol. 21, no. 10, pp. 904–913, 2013.
- [8] S. Jiang, K. Y. Win, S. Liu, C. P. Teng, Y. Zheng, and M.-Y. Han, "Surface-functionalized nanoparticles for biosensing and imaging-guided therapeutics," *Nanoscale*, vol. 5, no. 8, pp. 3127–3148, 2013.
- [9] W. Yu and N. Zhang, "Surface modification of nanocarriers for cancer therapy," *Curr. Nanosci.*, vol. 5, no. 2, pp. 123–134, 2009.
- [10] K. Saravanakumar, X. Hu, D. M. Ali, and M.-H. Wang, "Emerging strategies in stimuli-responsive nanocarriers as the drug delivery system for enhanced cancer therapy," *Curr. Pharmaceut. Des.*, vol. 25, no. 24, pp. 2609–2625, 2019.
- [11] S. Mura, J. Nicolas, and P. Couvreur, "Stimuli-responsive nanocarriers for drug delivery," *Nat. Mater.*, vol. 12, no. 11, pp. 991–1003, 2013.
- [12] A. C. V. Doughty, A. Hoover, E. Layton, C. Murray, E. Howard, and W. Chen, "Nanomaterial applications in photothermal therapy for cancer," *Materials (Basel)*, vol. 12, no. 5, p. 779, 2019.
- [13] C.-F. He, C.-F. He, S.-H. Wang, et al., "Advances in biodegradable nanomaterials for photothermal therapy of cancer," *Canc. Biol. Med.*, vol. 13, no. 3, p. 299, 2016.
- [14] D. Zhi, T. Yang, J. O'Hagan, et al., "Photothermal therapy," *J. Contr. Release*, vol. 325, pp. 52–71, 2020.
- [15] C. Murugan, V. Sharma, R. K. Murugan, G. Malaiamegu, and A. Sundaramurthy, "Two-dimensional cancer theranostic nanomaterials: synthesis, surface functionalization and applications in photothermal therapy," *J. Contr. Release*, vol. 299, pp. 1–20, 2019.
- [16] X. Song, Q. Chen, and Z. Liu, "Recent advances in the development of organic photothermal nano-agents," *Nano Res.*, vol. 8, no. 2, pp. 340–354, 2015.
- [17] J. Cao, B. Zhu, K. Zheng, et al., "Recent progress in NIR-II contrast agent for biological imaging," *Front. Bioeng. Biotechnol.*, vol. 7, p. 487, 2020.
- [18] Y. Yi, H. Wang, X. Wang, Q. Liu, M. Ye, and W. Tan, "A smart, photocontrollable drug release nanosystem for multifunctional synergistic cancer therapy," *ACS Appl. Mater. Interfaces*, vol. 9, no. 7, pp. 5847–5854, 2017.
- [19] Q. Sun, Z. Yang, M. Lin, et al., "Phototherapy and anti-GITR antibody-based therapy synergistically reinvigorate immunogenic cell death and reject established cancers," *Biomaterials*, vol. 269, p. 120648, 2021.
- [20] W. Sang, Z. Zhang, Y. Dai, and X. Chen, "Recent advances in nanomaterial-based synergistic combination cancer immunotherapy," *Chem. Soc. Rev.*, vol. 48, no. 14, pp. 3771–3810, 2019.
- [21] P. Mi, "Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics," *Theranostics*, vol. 10, no. 10, p. 4557, 2020.
- [22] D. Gao, X. Guo, X. Zhang, et al., "Multifunctional phototheranostic nanomedicine for cancer imaging and treatment," *Mater. Today Bio*, vol. 5, p. 100035, 2020.
- [23] R. J. E. van den Bijgaart, D. C. Eikelenboom, M. Hoogenboom, J. J. Fütterer, M. H. den Brok, and G. J. Adema, "Thermal and mechanical high-intensity focused ultrasound: perspectives on tumor ablation, immune effects and combination strategies," *Canc. Immunol. Immunother.*, vol. 66, no. 2, pp. 247–258, 2017.
- [24] Y. Keisari, Ed. *Tumor Ablation: Effects on Systemic and Local Anti-tumor Immunity and on Other Tumor-Microenvironment Interactions*, vol. 5, Netherlands, Springer Science & Business Media, 2012. Available at: <https://doi.org/10.1007/978-94-007-4694-7>.
- [25] L. Xu, W. Zhang, H.-B. Park, et al., "Indocyanine green and poly I: C containing thermo-responsive liposomes used in immune-photothermal therapy prevent cancer growth and metastasis," *J. Immunother. Canc.*, vol. 7, no. 1, pp. 1–14, 2019.
- [26] J. Li, C. Xie, J. Huang, Y. Jiang, Q. Miao, and K. Pu, "Semiconducting polymer nanoenzymes with photothermic activity for enhanced cancer therapy," *Angew. Chem.*, vol. 130, no. 15, pp. 4059–4062, 2018.
- [27] N. Y. Kim, S. Blake, D. De, J. Ouyang, J. Shi, and N. Kong, "Two-dimensional nanosheet-based photonic nanomedicine for combined gene and photothermal therapy," *Front. Pharmacol.*, vol. 10, p. 1573, 2020.
- [28] F. E. Bair, Ed. *Cancer Sourcebook: Basic Information on Cancer Types, Symptoms, Diagnostic Methods, and Treatments, Including Statistics on Cancer Occurrences Worldwide and the Risks Associated with Known Carcinogens and Activities*, vol. 1, Omnigraphics Incorporated, 1990.

- [29] M. Arruebo, N. Vilaboa, B. Sáez-Gutierrez, et al., "Assessment of the evolution of cancer treatment therapies," *Cancers*, vol. 3, no. 3, 2011, <https://doi.org/10.3390/cancers3033279>.
- [30] Q. Peng, J. Moan, and J. M. Nesland, "Correlation of subcellular and intratumoral photosensitizer localization with ultrastructural features after photodynamic therapy," *Ultrastruct. Pathol.*, vol. 20, no. 2, pp. 109–129, 1996.
- [31] J. Moan and K. Berg, "The photodegradation of porphyrins in cells can be used to estimate the lifetime of singlet oxygen," *Photochem. Photobiol.*, vol. 53, no. 4, pp. 549–553, 1991.
- [32] T. J. Dougherty, C. J. Gomer, B. W. Henderson, et al., "Photodynamic therapy," *JNCI J. Natl. Canc. Inst.*, vol. 90, no. 12, pp. 889–905, 1998.
- [33] D. Jaque, L. Martínez Maestro, B. del Rosal, et al., "Nanoparticles for photothermal therapies," *Nanoscale*, vol. 6, no. 16, pp. 9494–9530, 2014.
- [34] X. Huang, P. K. Jain, I. H. El-Sayed, and M. A. El-Sayed, "Plasmonic photothermal therapy (PPT) using gold nanoparticles," *Laser Med. Sci.*, vol. 23, no. 3, pp. 217–228, 2008.
- [35] H. Huang, W. Song, J. Rieffel, and J. F. Lovell, "Emerging applications of porphyrins in photomedicine," *Front. Physiol.*, vol. 3, no. 23, pp. 1–15, 2015.
- [36] S. Parker, "The use of diffuse laser photonic energy and indocyanine green photosensitizer as an adjunct to periodontal therapy," *Br. Dent. J.*, vol. 215, no. 4, pp. 167–171, 2013.
- [37] Z. Zha, X. Yue, Q. Ren, and Z. Dai, "Uniform polypyrrole nanoparticles with high photothermal conversion efficiency for photothermal ablation of cancer cells," *Adv. Mater.*, vol. 25, no. 5, pp. 777–782, 2013.
- [38] K. Urbanska, B. Romanowska-Dixon, Z. Matuszak, J. Oszajca, P. Nowak-Sliwinska, and G. Stochel, "Indocyanine green as a prospective sensitizer for photodynamic therapy of melanomas," *Acta Biochim. Pol.*, vol. 49, no. 2, pp. 387–391, 2002.
- [39] H. Abrahamse and M. R. Hamblin, "New photosensitizers for photodynamic therapy," *Biochem. J.*, vol. 473, no. 4, pp. 347–364, 2016.
- [40] R. Bhavane, Z. Starosolski, I. Stupin, K. B. Ghaghada, and A. Annapragada, "NIR-II fluorescence imaging using indocyanine green nanoparticles," *Sci. Rep.*, vol. 8, no. 1, pp. 1–10, 2018.
- [41] T. Desmettre, J. M. Devoisselle, and S. Mordon, "Fluorescence properties and metabolic features of indocyanine green (ICG) as related to angiography," *Surv. Ophthalmol.*, vol. 45, no. 1, pp. 15–27, 2000.
- [42] R. Manchanda, A. Fernandez-Fernandez, A. Nagesetti, and A. J. McGoron, "Preparation and characterization of a polymeric (PLGA) nanoparticulate drug delivery system with simultaneous incorporation of chemotherapeutic and thermo-optical agents," *Colloids Surf. B Biointerfaces*, vol. 75, no. 1, pp. 260–267, 2010.
- [43] J. Zweck and A. Penzkofer, "Microstructure of indocyanine green J-aggregates in aqueous solution," *Chem. Phys.*, vol. 269, nos 1–3, pp. 399–409, 2001.
- [44] G. R. Cherrick, S. W. Stein, C. M. Leevy, and C. S. Davidson, "Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction," *J. Clin. Invest.*, vol. 39, no. 4, pp. 592–600, 1960.
- [45] K. J. Baker, "Binding of sulfobromophthalein (BSP) sodium and indocyanine green (ICG) by plasma 1 lipoproteins," *Proc. Soc. Exp. Biol. Med.*, vol. 122, no. 4, pp. 957–963, 1966.
- [46] S. Yoneya, T. Saito, Y. Komatsu, I. Koyama, K. Takahashi, and J. Duvoll-Young, "Binding properties of indocyanine green in human blood," *Invest. Ophthalmol. Vis. Sci.*, vol. 39, no. 7, pp. 1286–1290, 1998.
- [47] F. Chen and W. Cai, "Nanomedicine for targeted photothermal cancer therapy: where are we now?" *Nanomedicine*, vol. 10, no. 1, pp. 1–3, 2015.
- [48] D. P. O'Neal, L. R. Hirsch, N. J. Halas, et al., "Photo-thermal tumor ablation in mice using near infrared-absorbing nanoparticles," *Canc. Lett.*, vol. 209, no. 2, pp. 171–176, 2004.
- [49] Y. Omid and J. Barar, "Targeting tumor microenvironment: crossing tumor interstitial fluid by multifunctional nanomedicines," *Bioimpacts*, vol. 4, no. 2, pp. 55–67, 2014.
- [50] B. Tunc and M. Gulsoy, "Tm: Fiber laser ablation with real-time temperature monitoring for minimizing collateral thermal damage: ex vivo dosimetry for ovine brain," *Laser Surg. Med.*, vol. 45, no. 1, pp. 48–56, 2013.
- [51] C. L. West, A. C. V. Doughty, K. Liu, and W. R. Chen, "Monitoring tissue temperature during photothermal therapy for cancer," *J. bio-X Res.*, vol. 2, no. 4, pp. 159–168, 2019.
- [52] Y. Zhang, X. Zhan, J. Xiong, et al., "Temperature-dependent cell death patterns induced by functionalized gold nanoparticle photothermal therapy in melanoma cells," *Sci. Rep.*, vol. 8, no. 1, pp. 1–9, 2018.
- [53] R. M. Fratila and J. M. De La Fuente, *Nanomaterials for Magnetic and Optical Hyperthermia Applications*, Amsterdam, Netherlands, Elsevier, 2018. Available at: <https://doi.org/10.1016/C2017-0-00855-8>.
- [54] X. Wu, Y. Suo, H. Shi, et al., "Deep-tissue photothermal therapy using laser illumination at NIR-II window," *Nano-Micro Lett.*, vol. 12, no. 1, pp. 1–13, 2020.
- [55] A. Pinto and M. Pocard, "Photodynamic therapy and photothermal therapy for the treatment of peritoneal metastasis: a systematic review," *Pleura and Peritoneum*, vol. 3, no. 4, p. 20180124, 2018.
- [56] G. Stüttgen, "The risk of photochemotherapy," *Int. J. Dermatol.*, vol. 21, no. 4, pp. 198–202, 1982.
- [57] Y. Liu, J. R. Ashton, E. J. Moding, et al., "A plasmonic gold nanostar theranostic probe for in vivo tumor imaging and photothermal therapy," *Theranostics*, vol. 5, no. 9, pp. 946–960, 2015.
- [58] Z. M. Markovic, L. M. Harhaji-Trajkovic, B. M. Todorovic-Markovic, et al., "In vitro comparison of the photothermal anticancer activity of graphene nanoparticles and carbon nanotubes," *Biomaterials*, vol. 32, no. 4, pp. 1121–1129, 2011.
- [59] Y. Yong, X. Cheng, T. Bao, et al., "Tungsten sulfide quantum dots as multifunctional nanotheranostics for in vivo dual-modal image-guided photothermal/radiotherapy synergistic therapy," *ACS Nano*, vol. 9, no. 12, pp. 12451–12463, 2015.
- [60] U. Chitgupi, Y. Qin, and J. F. Lovell, "Targeted nanomaterials for phototherapy," *Nanotheranostics*, vol. 1, no. 1, pp. 38–58, 2017.
- [61] Y. He, K. Laugesen, D. Kamp, et al., "Effects and side effects of plasmonic photothermal therapy in brain tissue," *Canc. Nanotechnol.*, vol. 10, no. 1, pp. 1–11, 2019.
- [62] S. Nomura, Y. Morimoto, H. Tsujimoto, et al., "Highly reliable, targeted photothermal cancer therapy combined with thermal dosimetry using a near-infrared absorbent," *Sci. Rep.*, vol. 10, no. 1, pp. 1–7, 2020.
- [63] W. Sheng, S. He, W. J. Seare, and A. Almutairi, "Review of the progress toward achieving heat confinement-the holy grail of photothermal therapy," *J. Biomed. Opt.*, vol. 22, no. 8, p. 080901, 2017.

- [64] J. Kim, J. Kim, C. Jeong, and W. J. Kim, "Synergistic nanomedicine by combined gene and photothermal therapy," *Adv. Drug Deliv. Rev.*, vol. 98, pp. 99–112, 2016.
- [65] M. Kim, J. H. Lee, and J. M. Nam, "Plasmonic photothermal nanoparticles for biomedical applications," *Adv. Sci.*, vol. 6, no. 17, p. 1900471, 2019.
- [66] Q. Xiong, Y. Lim, D. Li, K. Pu, L. Liang, and H. Duan, "Photoactive nanocarriers for controlled delivery," *Adv. Funct. Mater.*, vol. 30, no. 2, p. 1903896, 2020.
- [67] X. Li, X. Li, X.-N. Zhang, et al., "Multimodality imaging in nanomedicine and nanotheranostics," *Canc. Biol. Med.*, vol. 13, no. 3, pp. 339–348, 2016.
- [68] M. S. Muthu, D. T. Leong, L. Mei, and S.-S. Feng, "Nanotheranostics application and further development of nanomedicine strategies for advanced theranostics," *Theranostics*, vol. 4, no. 6, pp. 660–677, 2014.
- [69] R. Prasad, N. K. Jain, J. Conde, and R. Srivastava, "Localized nanotheranostics: recent developments in cancer nanomedicine," *Mater. Today Adv.*, vol. 8, p. 100087, 2020.
- [70] H. Shi and P. J. Sadler, "How promising is phototherapy for cancer?" *Br. J. Canc.*, vol. 123, no. 6, pp. 871–873, 2020.
- [71] M.-F. Tsai, S.-H. G. Chang, F.-Y. Cheng, et al., "Au nanorod design as light-absorber in the first and second biological near-infrared windows for in vivo photothermal therapy," *ACS Nano*, vol. 7, no. 6, pp. 5330–5342, 2013.
- [72] Y. Sun, H. Shi, X. Cheng, et al., "Degradable hybrid CuS nanoparticles for imaging-guided synergistic cancer therapy via low-power NIR-II light excitation," *CCS Chem.*, vol. 3, pp. 1336–1349, 2020.
- [73] I. Yakavets, S. Jenard, A. Francois, et al., "Stroma-rich Co-culture multicellular tumor spheroids as a tool for photoactive drugs screening," *J. Clin. Med.*, vol. 8, no. 10, p. 1686, 2019.
- [74] H. Yang, Y. Zhang, J. Song, et al., "Boosting phototherapeutic efficiency with single NIR laser-activated ultrasmall bismuth sulfide quantum dots," *Chem. Eng. J.*, vol. 375, p. 121941, 2019.
- [75] A. Sahu, W. I. Choi, J. H. Lee, and G. Tae, "Graphene oxide mediated delivery of methylene blue for combined photodynamic and photothermal therapy," *Biomaterials*, vol. 34, no. 26, pp. 6239–6248, 2013.
- [76] P. Huang, J. Lin, X. Wang, et al., "Light-triggered theranostics based on photosensitizer-conjugated carbon dots for simultaneous enhanced-fluorescence imaging and photodynamic therapy," *Adv. Mater.*, vol. 24, pp. 5104–5110, 2012.
- [77] F. Yan, H. Wu, H. Liu, et al., "Molecular imaging-guided photothermal/photodynamic therapy against tumor by iRGD-modified indocyanine green nanoparticles," *J. Contr. Release*, vol. 224, pp. 217–228, 2016.
- [78] E. J. Hong, D. G. Choi, and M. S. Shim, "Targeted and effective photodynamic therapy for cancer using functionalized nanomaterials," *Acta Pharm. Sin. B*, vol. 6, no. 4, pp. 297–307, 2016.
- [79] H. S. Han and K. Y. Choi, "Advances in nanomaterial-mediated photothermal cancer therapies: toward clinical applications," *Biomedicines*, vol. 9, no. 3, p. 305, 2021.
- [80] Y. Liu, P. Maccarini, G. M. Palmer, et al., "Synergistic immuno photothermal nanotherapy (SYMPHONY) for the treatment of unresectable and metastatic cancers," *Sci. Rep.*, vol. 7, no. 1, pp. 1–6, 2017.
- [81] C. He, X. Duan, N. Guo, et al., "Core-shell nanoscale coordination polymers combine chemotherapy and photodynamic therapy to potentiate checkpoint blockade cancer immunotherapy," *Nat. Commun.*, vol. 7, no. 1, pp. 1–12, 2016.
- [82] X. Hou, Y. Tao, Y. Pang, X. Li, G. Jiang, and Y. Liu, "Nanoparticle based photothermal and photodynamic immunotherapy for tumor treatment," *Int. J. Canc.*, vol. 143, no. 12, pp. 3050–3060, 2018.
- [83] I. O. L. Bacellar, T. Tsubone, C. Pavani, and M. Baptista, "Photodynamic efficiency: from molecular photochemistry to cell death," *Int. J. Mol. Sci.*, vol. 16, no. 9, pp. 20523–20559, 2015.
- [84] P. Cramers, M. Ruevekamp, H. Oppelaar, O. Dalesio, P. Baas, and F. A. Stewart, "Foscan® uptake and tissue distribution in relation to photodynamic efficacy," *Br. J. Canc.*, vol. 88, no. 2, pp. 283–290, 2003.
- [85] B. W. Pogue, B. Ortel, N. Chen, R. W. Redmond, and T. Hasan, "A photobiological and photophysical-based study of phototoxicity of two chlorins," *Canc. Res.*, vol. 61, no. 2, pp. 717–724, 2001.
- [86] B. Q. Spring, I. Rizvi, N. Xu, and T. Hasan, "The role of photodynamic therapy in overcoming cancer drug resistance," *Photochem. Photobiol. Sci.*, vol. 14, no. 8, pp. 1476–1491, 2015.
- [87] A. F. dos Santos, D. R. Queiroz de Almeida, L. F. Terra, et al., "Photodynamic therapy in cancer treatment-an update review," *J. Canc. Metastasis Treat.*, vol. 5, p. 25, 2019.
- [88] S. M. Banerjee, A. J. MacRobert, C. A. Mosse, B. Periera, S. G. Bown, and M. R. S. Keshtgar, "Photodynamic therapy: inception to application in breast cancer," *Breast*, vol. 31, pp. 105–113, 2017.
- [89] Z. Chen, K. W. Woodburn, C. Shi, D. C. Adelman, C. Rogers, and D. I. Simon, "Photodynamic therapy with motexafin lutetium induces redox-sensitive apoptosis of vascular cells," *Arterioscler. Thromb. Vasc. Biol.*, vol. 21, no. 5, pp. 759–764, 2001.
- [90] S. Kwiatkowski, B. Knap, D. Przystupski, et al., "Photodynamic therapy-mechanisms, photosensitizers and combinations," *Biomed. Pharmacother.*, vol. 106, pp. 1098–1107, 2018.
- [91] E. G. Graham, C. M. MacNeill, and N. H. Levi-Polyachenko, "Quantifying folic acid-functionalized multi-walled carbon nanotubes bound to colorectal cancer cells for improved photothermal ablation," *J. Nanoparticle Res.*, vol. 15, no. 5, pp. 1–12, 2013.
- [92] A. K. Parchur, G. Sharma, J. M. Jagtap, et al., "Vascular interventional radiology-guided photothermal therapy of colorectal cancer liver metastasis with theranostic gold nanorods," *ACS Nano*, vol. 12, no. 7, pp. 6597–6611, 2018.
- [93] C. Fiorica, N. Mauro, G. Pitarresi, C. Scialabba, F. S. Palumbo, and G. Giammona, "Double-network-structured graphene oxide-containing nanogels as photothermal agents for the treatment of colorectal cancer," *Biomacromolecules*, vol. 18, no. 3, pp. 1010–1018, 2017.
- [94] Q. Chen, L. Xu, C. Liang, C. Wang, R. Peng, and Z. Liu, "Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy," *Nat. Commun.*, vol. 7, no. 1, pp. 1–13, 2016.
- [95] T. Vo-Dinh, et al., "Synergistic immuno photothermal nanotherapy (SYMPHONY) to treat unresectable and metastatic cancers and produce a cancer vaccine effect," in *Advanced Biomedical and Clinical Diagnostic and Surgical Guidance Systems XVI 10484*, International Society for Optics and Photonics, 2018, p. 1048408.
- [96] L. Shao, R. Zhang, J. Lu, C. Zhao, X. Deng, and Y. Wu, "Mesoporous silica coated polydopamine functionalized

- reduced graphene oxide for synergistic targeted chemo-photothermal therapy," *ACS Appl. Mater. Interfaces*, vol. 9, no. 2, pp. 1226–1236, 2017.
- [97] H. Sun, J. Su, Q. Meng, et al., "Cancer cell membrane coated gold nanocages with hyperthermia triggered drug release and homotypic target inhibit growth and metastasis of breast cancer," *Adv. Funct. Mater.*, vol. 27, no. 3, p. 1604300, 2017.
- [98] Y.-D. Zhu, S.-P. Chen, H. Zhao, et al., "PPy@ MIL-100 nanoparticles as a pH-and near-IR-irradiation-responsive drug carrier for simultaneous photothermal therapy and chemotherapy of cancer cells," *ACS Appl. Mater. Interfaces*, vol. 8, no. 50, pp. 34209–34217, 2016.
- [99] T. Yang, H. Ke, Q. Wang, et al., "Bifunctional tellurium nanodots for photo-induced synergistic cancer therapy," *ACS Nano*, vol. 11, no. 10, pp. 10012–10024, 2017.
- [100] H. S. Han, K. Y. Choi, H. Lee, et al., "Gold-nanoclustered hyaluronan nano-assemblies for photothermally maneuvered photodynamic tumor ablation," *ACS Nano*, vol. 10, no. 12, pp. 10858–10868, 2016.
- [101] Y. Wang, H. Wang, D. Liu, S. Song, X. Wang, and H. Zhang, "Graphene oxide covalently grafted upconversion nanoparticles for combined NIR mediated imaging and photothermal/photodynamic cancer therapy," *Biomaterials*, vol. 34, no. 31, pp. 7715–7724, 2013.
- [102] X. Wei, H. Chen, H. P. Tham, et al., "Combined photodynamic and photothermal therapy using cross-linked polyphosphazene nanospheres decorated with gold nanoparticles," *ACS Appl. Nano Mater.*, vol. 1, no. 7, pp. 3663–3672, 2018.
- [103] R. Baskaran, J. Lee, and S.-G. Yang, "Clinical development of photodynamic agents and therapeutic applications," *Biomater. Res.*, vol. 22, no. 1, pp. 1–8, 2018.
- [104] D. E. J. G. J. Dolmans, D. Fukumura, and R. K. Jain, "Photodynamic therapy for cancer," *Nat. Rev. Canc.*, vol. 3, no. 5, pp. 380–387, 2003.
- [105] A. Juarranz, P. Jaén, F. Sanz-Rodríguez, J. Cuevas, and S. González, "Photodynamic therapy of cancer. Basic principles and applications," *Clin. Transl. Oncol.*, vol. 10, no. 3, pp. 148–154, 2008.
- [106] J. P. Celli, B. Q. Spring, I. Rizvi, et al., "Imaging and photodynamic therapy: mechanisms, monitoring, and optimization," *Chem. Rev.*, vol. 110, no. 5, pp. 2795–2838, 2010.
- [107] Y. Liu, P. Bhattarai, Z. Dai, and X. Chen, "Photothermal therapy and photoacoustic imaging via nanotheranostics in fighting cancer," *Chem. Soc. Rev.*, vol. 48, no. 7, pp. 2053–2108, 2019.
- [108] A. Kamkaew, S. H. Lim, H. B. Lee, L. V. Kiew, L. Y. Chung, and K. Burgess, "BODIPY dyes in photodynamic therapy," *Chem. Soc. Rev.*, vol. 42, no. 1, pp. 77–88, 2013.
- [109] B. W. Pogue, J. T. Elliott, S. C. Kanick, et al., "Revisiting photodynamic therapy dosimetry: reductionist & surrogate approaches to facilitate clinical success," *Phys. Med. Biol.*, vol. 61, no. 7, p. R57, 2016.
- [110] E. M. Knavel and C. L. Brace, "Tumor ablation: common modalities and general practices," *Tech. Vasc. Intervent. Radiol.*, vol. 16, no. 4, pp. 192–200, 2013.
- [111] K. Richter, M. Haslbeck, and J. Buchner, "The heat shock response: life on the verge of death," *Mol. Cell*, vol. 40, no. 2, pp. 253–266, 2010.
- [112] R. R. Allison, C. H. Sibata, G. H. Downie, and R. E. Cuenca, "A clinical review of PDT for cutaneous malignancies," *Photodiagnosis Photodyn. Ther.*, vol. 3, no. 4, pp. 214–226, 2006.
- [113] A. Casas, G. Di Venosa, T. Hasan, and A. Battle, "Mechanisms of resistance to photodynamic therapy," *Curr. Med. Chem.*, vol. 18, no. 16, pp. 2486–2515, 2011.
- [114] M. F. Tartaglione, M. E. Zabaleta, R. Lazzarini, et al., "Apoptotic mechanism activated by blue light and cisplatin in cutaneous squamous cell carcinoma cells," *Int. J. Mol. Med.*, vol. 47, no. 4, pp. 1–13, 2021.
- [115] J.-T. Lin, "Progress of medical lasers: fundamentals and applications," *Med. Devices Diagn. Eng.*, vol. 1, no. 2, pp. 36–41, 2016.
- [116] H. Van den Bergh, "On the evolution of some endoscopic light delivery systems for photodynamic therapy," *Endoscopy*, vol. 30, no. 04, pp. 392–407, 1998.
- [117] G. Shafirstein, D. Bellnier, E. Oakley, et al., "Interstitial photodynamic therapy-a focused review," *Cancers (Basel)*, vol. 9, no. 2, p. 12, 2017.
- [118] M. Panjehpour, B. F. Overholt, R. C. Denovo, R. E. Sneed, and M. G. Petersen, "Centering balloon to improve esophageal photodynamic therapy," *Laser Surg. Med.*, vol. 12, no. 6, pp. 631–638, 1992.
- [119] H. Moseley, "Light distribution and calibration of commercial PDT LED arrays," *Photochem. Photobiol. Sci.*, vol. 4, no. 11, pp. 911–914, 2005.
- [120] S. Fitzmaurice and D. B. Eisen, "Daylight photodynamic therapy: what is known and what is yet to be determined," *Dermatol. Surg.*, vol. 42, no. 3, pp. 286–295, 2016.
- [121] Z. Yang, Z. Sun, Y. Ren, et al., "Advances in nanomaterials for use in photothermal and photodynamic therapeutics (Review)," *Mol. Med. Rep.*, vol. 20, no. 1, pp. 5–15, 2019.
- [122] L. R. Hirsch, J. L. West, R. J. Stafford, et al., "Nanoshell-mediated near infrared photothermal tumor therapy," in *Annual International Conference of the IEEE Engineering in Medicine and Biology – Proceedings 2*, 2003.
- [123] S. J. Norton and T. Vo-Dinh, "Photothermal effects of plasmonic metal nanoparticles in a fluid," *J. Appl. Phys.*, vol. 119, no. 8, p. 083105, 2016.
- [124] H. Samadian, S. Hosseini-Nami, S. K. Kamrava, H. Ghaznavi, and A. Shakeri-Zadeh, "Folate-conjugated gold nanoparticle as a new nanopatform for targeted cancer therapy," *J. Canc. Res. Clin. Oncol.*, vol. 142, no. 11, pp. 2217–2229, 2016.
- [125] A. Dadwal, A. Baldi, and R. Kumar Narang, "Nanoparticles as carriers for drug delivery in cancer," *Artif. Cells Nanomed. Biotechnol.*, vol. 46, no. sup2, pp. 295–305, 2018.
- [126] J. Zhang, C. Yang, R. Zhang, et al., "Biocompatible D-A semiconducting polymer nanoparticle with light harvesting unit for highly effective photoacoustic imaging guided photothermal therapy," *Adv. Funct. Mater.*, vol. 27, no. 13, p. 1605094, 2017.
- [127] D. Zhang, H. Xu, X. Zhang, et al., "Self-quenched metal-organic particles as dual-mode therapeutic agents for photoacoustic imaging-guided second near-infrared window photochemotherapy," *ACS Appl. Mater. Interfaces*, vol. 10, no. 30, pp. 25203–25212, 2018.
- [128] X. Liao, Y. Zheng, Z. Lin, et al., "Self-assembled metallo-supramolecular nanoflowers for NIR/acidic-triggered multidrug release, long-term tumor retention and NIR-II fluorescence

- imaging-guided photo-chemotherapy," *Chem. Eng. J.*, vol. 400, p. 125882, 2020.
- [129] B. Jang, J.-Y. Park, C.-H. Tung, I.-H. Kim, and Y. Choi, "Gold nanorod-photosensitizer complex for near-infrared fluorescence imaging and photodynamic/photothermal therapy in vivo," *ACS Nano*, vol. 5, no. 2, pp. 1086–1094, 2011.
- [130] A. Srivatsan, S. V. Jenkins, M. Jeon, et al., "Gold nanocage-photosensitizer conjugates for dual-modal image-guided enhanced photodynamic therapy," *Theranostics*, vol. 4, no. 2, pp. 163–174, 2014.
- [131] C. Loo, A. Lin, L. Hirsch, et al., "Nanoshell-enabled photonics-based imaging and therapy of cancer," *Technol. Canc. Res. Treat.*, vol. 3, no. 1, pp. 33–40, 2004.
- [132] R. Mooney, L. Roma, D. Zhao, et al., "Neural stem cell-mediated intratumoral delivery of gold nanorods improves photothermal therapy," *ACS Nano*, vol. 8, no. 12, pp. 12450–12460, 2014.
- [133] P. Vijayaraghavan, R. Vankayala, C.-S. Chiang, H.-W. Sung, and K. C. Hwang, "Complete destruction of deep-tissue buried tumors via combination of gene silencing and gold nanoechinus-mediated photodynamic therapy," *Biomaterials*, vol. 62, pp. 13–23, 2015.
- [134] J. Wang, M. You, G. Zhu, et al., "Photosensitizer-gold nanorod composite for targeted multimodal therapy," *Small*, vol. 9, no. 21, pp. 3678–3684, 2013.
- [135] J. Lin, S. Wang, P. Huang, et al., "Photosensitizer-loaded gold vesicles with strong plasmonic coupling effect for imaging-guided photothermal/photodynamic therapy," *ACS Nano*, vol. 7, pp. 5320–5329, 2013.
- [136] M. Azizi, H. Ghourchian, F. Yazdian, S. Bagherifam, S. Bekhradnia, and B. Nyström, "Anti-cancerous effect of albumin coated silver nanoparticles on MDA-MB 231 human breast cancer cell line," *Sci. Rep.*, vol. 7, p. 5178, 2017.
- [137] T. Park, S. Lee, R. Amaty, et al., "ICG-loaded pegylated BSA-silver nanoparticles for effective photothermal cancer therapy," *Int. J. Nanomed.*, vol. 15, pp. 5459–5471, 2020.
- [138] V. De Matteis, M. Cascione, C. Toma, and S. Leporatti, "Silver nanoparticles: synthetic routes, in vitro toxicity and theranostic applications for cancer disease," *Nanomaterials*, vol. 8, no. 5, p. 319, 2018.
- [139] P. Bose, A. Priyam, R. Kar, and S. P. Pattanayak, "Quercetin loaded folate targeted plasmonic silver nanoparticles for light activated chemo-photothermal therapy of DMBA induced breast cancer in Sprague–Dawley rats," *RSC Adv.*, vol. 10, no. 53, pp. 31961–31978, 2020.
- [140] E. Porcel, S. Liehn, H. Remita, et al., "Platinum nanoparticles: a promising material for future cancer therapy?" *Nanotechnology*, vol. 21, no. 8, p. 085103, 2010.
- [141] T. T. V. Phan, N. Q. Bui, M. S. Moorthy, K. D. Lee, and J. Oh, "Synthesis and in vitro performance of polypyrrole-coated iron–platinum nanoparticles for photothermal therapy and photoacoustic imaging," *Nanoscale Res. Lett.*, vol. 12, p. 570, 2017.
- [142] J. Kim, T. Shirasawa, and Y. Miyamoto, "The effect of TAT conjugated platinum nanoparticles on lifespan in a nematode *Caenorhabditis elegans* model," *Biomaterials*, vol. 31, no. 22, pp. 5849–5854, 2010.
- [143] M. A. Brook, "Platinum in silicone breast implants," *Biomaterials*, vol. 27, no. 17, pp. 3274–3286, 2006.
- [144] J. Depciuch, M. Stec, B. Klebowski, et al., "Size effect of platinum nanoparticles in simulated anticancer photothermal therapy," *Photodiagnosis Photodyn. Ther.*, vol. 29, p. 101594, 2020.
- [145] Z. Yu, Q. Sun, W. Pan, N. Li, and B. Tang, "A near-infrared triggered nanophotosensitizer inducing domino effect on mitochondrial reactive oxygen species burst for cancer therapy," *ACS Nano*, vol. 9, no. 11, pp. 11064–11074, 2015.
- [146] Z. Youssef, R. Vanderesse, L. Colombeau, et al., "The application of titanium dioxide, zinc oxide, fullerene, and graphene nanoparticles in photodynamic therapy," *Canc. Nanotechnol.*, vol. 8, p. 6, 2017.
- [147] M. Orecchioni, R. Cabizza, A. Bianco, and L. G. Delogu, "Graphene as cancer theranostic tool: progress and future challenges," *Theranostics*, vol. 5, no. 7, pp. 710–723, 2015.
- [148] D. Iannazzo, C. Celesti, and C. Espro, "Recent advances on graphene quantum dots as multifunctional nanoplateforms for cancer treatment," *Biotechnol. J.*, vol. 16, no. 2, p. 1900422, 2021.
- [149] R. Prasad, A. S. Yadav, M. Gorain, et al., "Graphene oxide supported liposomes as red emissive theranostics for phototriggered tissue visualization and tumor regression," *ACS Appl. Bio Mater.*, vol. 2, no. 8, pp. 3312–3320, 2019.
- [150] A. Gazzi, L. Fusco, A. Khan, et al., "Photodynamic therapy based on graphene and MXene in cancer theranostics," *Frontiers in Bioengineering and Biotechnology*, vol. 7, p. 295, 2019.
- [151] R. K. Thapa, Z. C. Soe, W. Ou, et al., "Palladium nanoparticle-decorated 2-D graphene oxide for effective photodynamic and photothermal therapy of prostate solid tumors," *Colloids Surf. B Biointerfaces*, vol. 169, pp. 429–437, 2018.
- [152] H. Zhang, H. Wu, J. Wang, et al., "Graphene oxide-BaGdF₅ nanocomposites for multi-modal imaging and photothermal therapy," *Biomaterials*, vol. 42, pp. 66–77, 2015.
- [153] M. Nurunnabi, Z. Khatun, G. R. Reeck, D. Y. Lee, and Y.-K. Lee, "Photoluminescent graphene nanoparticles for cancer phototherapy and imaging," *ACS Appl. Mater. Interfaces*, vol. 6, no. 15, pp. 12413–12421, 2014.
- [154] M. Nafiujjaman, V. Revuri, H.-K. Park, I. K. Kwon, K.-J. Cho, and Y.-K. Lee, "Enhanced photodynamic properties of graphene quantum dot conjugated Ce6 nanoparticles for targeted cancer therapy and imaging," *Chem. Lett.*, vol. 45, no. 8, pp. 997–999, 2016.
- [155] F. Yuan, S. Li, Z. Fan, X. Meng, L. Fan, and S. Yang, "Shining carbon dots: synthesis and biomedical and optoelectronic applications," *Nano Today*, vol. 11, no. 5, pp. 565–586, 2016.
- [156] R. Prasad, S. Aiyer, D. S. Chauhan, R. Srivastava, and K. Selvaraj, "Bioresponsive carbon nano-gated multifunctional mesoporous silica for cancer theranostics," *Nanoscale*, vol. 8, no. 8, pp. 4537–4546, 2016.
- [157] R. Prasad, D. S. Chauhan, A. S. Yadav, et al., "A biodegradable fluorescent nanohybrid for photo-driven tumor diagnosis and tumor growth inhibition," *Nanoscale*, vol. 10, no. 40, pp. 19082–19091, 2018.
- [158] S. Adrita, K. Tasnim, J. Ryu, and S. Sharker, "Nanotheranostic carbon dots as an emerging platform for cancer therapy," *J. Nanotheranostics*, vol. 1, no. 1, pp. 58–77, 2020.
- [159] P. Namdari, B. Negahdari, and A. Eatemadi, "Synthesis, properties and biomedical applications of carbon-based quantum dots: an updated review," *Biomed. Pharmacother.*, vol. 87, pp. 209–222, 2017.

- [160] E. B. Kang, S. M. Sharker, I. In, and S. Y. Park, "Pluronic mimicking fluorescent carbon nanoparticles conjugated with doxorubicin via acid-cleavable linkage for tumor-targeted drug delivery and bioimaging," *J. Ind. Eng. Chem.*, vol. 43, pp. 150–157, 2016.
- [161] M. Serda, M. J. Ware, J. M. Newton, et al., "Development of photoactive Sweet-C 60 for pancreatic cancer stellate cell therapy," *Nanomedicine*, vol. 13, no. 23, pp. 2981–2993, 2018.
- [162] D. W. Zheng, B. Li, C.-X. Li, et al., "Carbon-dot-decorated carbon nitride nanoparticles for enhanced photodynamic therapy against hypoxic tumor via water splitting," *ACS Nano*, vol. 10, no. 9, pp. 8715–8722, 2016.
- [163] P. Sundaram and H. Abrahamse, "Effective photodynamic therapy for colon cancer cells using chlorin e6 coated hyaluronic acid-based carbon nanotubes," *Int. J. Mol. Sci.*, vol. 21, no. 13, p. 4745, 2020.
- [164] K. Huang, Z. Li, J. Lin, G. Han, and P. Huang, "Two-dimensional transition metal carbides and nitrides (MXenes) for biomedical applications," *Chem. Soc. Rev.*, vol. 47, no. 14, pp. 5109–5124, 2018.
- [165] S. Abdolhosseinzadeh, J. Heier, and C. J. Zhang, "Printing and coating MXenes for electrochemical energy storage devices," *J. Phys. Energy*, vol. 2, no. 3, p. 31004, 2020.
- [166] A. Zamhuri, G. P. Lim, N. L. Ma, K. S. Tee, and C. F. Soon, "MXene in the lens of biomedical engineering: synthesis, applications and future outlook," *Biomed. Eng. Online*, vol. 20, no. 1, pp. 1–24, 2021.
- [167] X. Zhao, X.-J. Zha, L.-S. Tang, et al., "Self-assembled core-shell polydopamine@ MXene with synergistic solar absorption capability for highly efficient solar-to-vapor generation," *Nano Res.*, vol. 13, no. 1, pp. 255–264, 2020.
- [168] X. Jiang, A. V. Kuklin, A. Baev, et al., "Two-dimensional MXenes: from morphological to optical, electric, and magnetic properties and applications," *Phys. Rep.*, vol. 848, pp. 1–58, 2020.
- [169] K. Hantanasirisakul and Y. Gogotsi, "Electronic and optical properties of 2D transition metal carbides and nitrides (MXenes)," *Adv. Mater.*, vol. 30, no. 52, p. 1804779, 2018.
- [170] K. Kannan, K. K. Sadasivuni, A. M. Abdullah, and B. Kumar, "Current trends in MXene-based nanomaterials for energy storage and conversion system: a mini review," *Catalysts*, vol. 10, no. 5, p. 495, 2020.
- [171] K. R. G. Lim, A. D. Handoko, S. K. Nemani, et al., "Rational design of two-dimensional transition metal carbide/nitride (MXene) hybrids and nanocomposites for catalytic energy storage and conversion," *ACS Nano*, vol. 14, no. 9, pp. 10834–10864, 2020.
- [172] A. Szuplewska, D. Kulpińska, A. Dybko, et al., "2D Ti2C (MXene) as a novel highly efficient and selective agent for photothermal therapy," *Mater. Sci. Eng. C*, vol. 98, pp. 874–886, 2019.
- [173] E. A. Hussein, M. M. Zagho, B. R. Rizeq, et al., "Plasmonic MXene-based nanocomposites exhibiting photothermal therapeutic effects with lower acute toxicity than pure MXene," *Int. J. Nanomed.*, vol. 14, p. 4529, 2019.
- [174] Z. Liu, M. Zhao, H. Lin, et al., "2D magnetic titanium carbide MXene for cancer theranostics," *J. Mater. Chem. B*, vol. 6, no. 21, pp. 3541–3548, 2018.
- [175] H. Lin, S. Gao, C. Dai, Y. Chen, and J. Shi, "A two-dimensional biodegradable niobium carbide (MXene) for photothermal tumor eradication in NIR-I and NIR-II biowindows," *J. Am. Chem. Soc.*, vol. 139, no. 45, pp. 16235–16247, 2017.
- [176] J. Zhou, Z. Liu, and F. Li, "Upconversion nanophosphors for small-animal imaging," *Chem. Soc. Rev.*, vol. 41, no. 3, pp. 1323–1349, 2012.
- [177] W. Feng, X. Zhu, and F. Li, "Recent advances in the optimization and functionalization of upconversion nanomaterials for in vivo bioapplications," *NPG Asia Mater.*, vol. 5, no. 12, p. e75, 2013.
- [178] M. Nyk, R. Kumar, T. Y. Ohulchanskyy, E. J. Bergey, and P. N. Prasad, "High contrast in vitro and in vivo photoluminescence bioimaging using near infrared to near infrared up-conversion in Tm^{3+} and Yb^{3+} doped fluoride nanophosphors," *Nano Lett.*, vol. 8, no. 11, pp. 3834–3838, 2008.
- [179] G. Chen, J. Shen, T. Y. Ohulchanskyy, et al., " $(\alpha\text{-NaYbF}_4\text{:Tm}^{3+})/\text{CaF}_2$ core/shell nanoparticles with efficient near-infrared to near-infrared upconversion for high-contrast deep tissue bioimaging," *ACS Nano*, vol. 6, no. 9, pp. 8280–8287, 2012.
- [180] C. Rennero-Lecuna, R. Martín-Rodríguez, R. Valiente, et al., "Origin of the high upconversion green luminescence efficiency in $\text{-NaYF}_4\text{: 2% Er}^{3+}\text{, 20% Yb}^{3+}$," *Chem. Mater.*, vol. 23, no. 15, pp. 3442–3448, 2011.
- [181] X. Ge, J. Liu, and L. Sun, "Controlled optical characteristics of lanthanide doped upconversion nanoparticles for emerging applications," *Dalton Trans.*, vol. 46, no. 48, pp. 16729–16737, 2017.
- [182] L. Sun, X. Ge, J. Liu, et al., "Multifunctional nanomesoporous materials with upconversion (*in vivo*) and downconversion (*in vitro*) luminescence imaging based on mesoporous capping UCNPs and linking lanthanide complexes," *Nanoscale*, vol. 6, no. 21, pp. 13242–13252, 2014.
- [183] H. Dong, L.-D. Sun, and C.-H. Yan, "Energy transfer in lanthanide upconversion studies for extended optical applications," *Chem. Soc. Rev.*, vol. 44, no. 6, pp. 1608–1634, 2015.
- [184] A. Dong, X. Ye, J. Chen, et al., "A generalized ligand-exchange strategy enabling sequential surface functionalization of colloidal nanocrystals," *J. Am. Chem. Soc.*, vol. 133, no. 4, pp. 998–1006, 2011.
- [185] V. Gradinaru, M. Mogri, K. R. Thompson, et al., "Optical deconstruction of Parkinsonian neural circuitry," *Science* (80–), vol. 324, no. 5925, pp. 354–359, 2009.
- [186] X. Qian, Z. Gu, and Y. Chen, "Two-dimensional black phosphorus nanosheets for theranostic nanomedicine," *Mater. Horizons*, vol. 4, no. 5, pp. 800–816, 2017.
- [187] W. Chen, J. Ouyang, H. Liu, et al., "Black phosphorus nanosheet based drug delivery system for synergistic photodynamic/ photothermal/chemotherapy of cancer," *Adv. Mater.*, vol. 29, no. 5, p. 1603864, 2017.
- [188] H. Wang, X. Yang, W. Shao, et al., "Ultrathin black phosphorus nanosheets for efficient singlet oxygen generation," *J. Am. Chem. Soc.*, vol. 137, no. 35, pp. 11376–11382, 2015.
- [189] T. Guo, Y. Wu, Y. Lin, et al., "Black phosphorus quantum dots with renal clearance property for efficient photodynamic therapy," *Small*, vol. 14, no. 4, p. 1702815, 2018.
- [190] Y. Xue, Q. Zhang, T. Zhang, and L. Fu, "Black phosphorus: properties, synthesis, and applications in energy

- conversion and storage,” *ChemNanoMat*, vol. 3, no. 6, pp. 352–361, 2017.
- [191] M. Luo, T. Fan, Y. Zhou, H. Zhang, and L. Mei, “2D black phosphorus-based biomedical applications,” *Adv. Funct. Mater.*, vol. 29, no. 13, p. 1808306, 2019.
- [192] W. Tao, X. Zhu, X. Yu, et al., “Black phosphorus nanosheets as a robust delivery platform for cancer theranostics,” *Adv. Mater.*, vol. 29, no. 1, p. 1603276, 2017.
- [193] Z. Li, H. Xu, J. Shao, et al., “Polydopamine-functionalized black phosphorus quantum dots for cancer theranostics,” *Appl. Mater. Today*, vol. 15, pp. 297–304, 2019.
- [194] M. Luo, W. Cheng, X. Zeng, L. Mei, G. Liu, and W. Deng, “Folic acid-functionalized black phosphorus quantum dots for targeted chemo-photothermal combination cancer therapy,” *Pharmaceutics*, vol. 11, no. 5, p. 242, 2019.
- [195] L. Deng, Y. Xu, C. Sun, et al., “Functionalization of small black phosphorus nanoparticles for targeted imaging and photothermal therapy of cancer,” *Sci. Bull.*, vol. 63, no. 14, pp. 917–924, 2018.
- [196] X. Yang, R. Liu, Z. Zhong, et al., “Platinum nanoenzyme functionalized black phosphorus nanosheets for photothermal and enhanced-photodynamic therapy,” *Chem. Eng. J.*, vol. 409, p. 127381, 2021.
- [197] Z. Wang, Z. Liu, C. Su, et al., “Biodegradable black phosphorus-based nanomaterials in biomedicine: theranostic applications,” *Curr. Med. Chem.*, vol. 26, no. 10, pp. 1788–1805, 2019.
- [198] M. Luo, Y. Zhou, N. Gao, et al., “Mesenchymal stem cells transporting black phosphorus-based biocompatible nanospheres: active Trojan horse for enhanced photothermal cancer therapy,” *Chem. Eng. J.*, vol. 385, p. 123942, 2020.
- [199] J. Wang, D. Liang, Z. Qu, I. M. Kislakov, V. M. Kiselev, and J. Liu, “PEGylated-folic acid-modified black phosphorus quantum dots as near-infrared agents for dual-modality imaging-guided selective cancer cell destruction,” *Nanophotonics*, vol. 9, no. 8, pp. 2425–2435, 2020.
- [200] W. Liang, D. Wang, X. Ren, et al., “Facile sonochemical-assisted synthesis of orthorhombic phase black phosphorus/rGO hybrids for effective photothermal therapy,” *Nanophotonics*, vol. 9, no. 9, pp. 3023–3034, 2020.
- [201] N. Zhao, L. Yan, X. Zhao, et al., “Versatile types of organic/inorganic nanohybrids: from strategic design to biomedical applications,” *Chem. Rev.*, vol. 119, no. 3, pp. 1666–1762, 2019.
- [202] Y. Sasaki and K. Akiyoshi, “Design and function of smart biomembrane nanohybrids for biomedical applications,” *Polym. J.*, vol. 53, no. 5, pp. 587–592, 2021.
- [203] D. S. Chauhan, A. B. Bukhari, G. Ravichandran, et al., “Enhanced EPR directed and imaging guided photothermal therapy using vitamin E modified toco-photoxil,” *Sci. Rep.*, vol. 8, no. 1, p. 16673, 2018.
- [204] D. S. Chauhan, P. Arunkumar, R. Prasad, et al., “Facile synthesis of plasmonic zein nanoshells for imaging-guided photothermal cancer therapy,” *Mater. Sci. Eng. C*, vol. 90, pp. 539–548, 2018.
- [205] D. S. Chauhan, S. Indulekha, R. Gottipalli, et al., “NIR light-triggered shrinkable thermoresponsive PNVC nanoshells for cancer theranostics,” *RSC Adv.*, vol. 7, no. 70, pp. 44026–44034, 2017.
- [206] A. K. Rengan, M. Jagtap, A. De, R. Banerjee, and R. Srivastava, “Multifunctional gold coated thermo-sensitive liposomes for multimodal imaging and photo-thermal therapy of breast cancer cells,” *Nanoscale*, vol. 6, no. 2, pp. 916–923, 2014.
- [207] R. Prasad, N. K. Jain, A. S. Yadav, et al., “Liposomal nanotheranostics for multimode targeted in vivo bioimaging and near-infrared light mediated cancer therapy,” *Commun. Biol.*, vol. 3, no. 1, pp. 1–14, 2020.
- [208] M. Marrelli, G. Menichini, E. Provenzano, and F. Conforti, “Applications of natural compounds in the photodynamic therapy of skin cancer,” *Curr. Med. Chem.*, vol. 21, no. 12, pp. 1371–1390, 2014.
- [209] B. Siewert and H. Stuppner, “The photoactivity of natural products – an overlooked potential of phytomedicines?” *Phytomedicine*, vol. 60, p. 152985, 2019.
- [210] N. B. R. Vittar, J. Awruch, K. Azizuddin, and V. Rivarola, “Caspase-independent apoptosis, in human MCF-7c3 breast cancer cells, following photodynamic therapy, with a novel water-soluble phthalocyanine,” *Int. J. Biochem. Cell Biol.*, vol. 42, no. 7, pp. 1123–1131, 2010.
- [211] E. W. Jeffes, J. L. McCullough, G. D. Weinstein, R. Kaplan, S. D. Glazer, and J. R. Taylor, “Photodynamic therapy of actinic keratoses with topical aminolevulinic acid hydrochloride and fluorescent blue light,” *J. Am. Acad. Dermatol.*, vol. 45, no. 1, pp. 96–104, 2001.
- [212] K. Muniyandi, B. George, T. Parimelazhagan, and H. Abrahamse, “Role of photoactive phytocompounds in photodynamic therapy of cancer,” *Molecules*, vol. 25, no. 18, p. 4102, 2020.
- [213] M. He, C. Qu, O. Gao, X. Hu, and X. Hong, “Biological and pharmacological activities of amaryllidaceae alkaloids,” *RSC Adv.*, vol. 5, no. 21, pp. 16562–16574, 2015.
- [214] J. M. Pérez Martín, V. Labrador, P. Fernández Freire, M. L. Molero, and M. J. Hazen, “Ultrastructural changes induced in HeLa Cells after phototoxic treatment with harmine,” *J. Appl. Toxicol.*, vol. 24, no. 3, pp. 197–201, 2004.
- [215] D. Skalkos, E. Gioti, C. D. Stalikas, et al., “Photophysical properties of *Hypericum perforatum* L. extracts – novel photosensitizers for PDT,” *J. Photochem. Photobiol. B Biol.*, vol. 82, no. 2, pp. 146–151, 2006.
- [216] S. Jantová, S. Letašiová, V. Brezová, L. U. Čipák, and J. Lábaj, “Photochemical and phototoxic activity of berberine on murine fibroblast NIH-3T3 and Ehrlich ascites carcinoma cells,” *J. Photochem. Photobiol. B Biol.*, vol. 85, no. 3, pp. 163–176, 2006.
- [217] K. Park and J. H. Lee, “Photosensitizer effect of curcumin on UVB-irradiated HaCaT cells through activation of caspase pathways,” *Oncol. Rep.*, vol. 17, no. 3, pp. 537–540, 2007.
- [218] W. Jin, Q. Shi, C. Hong, Y. Cheng, Z. Ma, and H. Qu, “Cytotoxic properties of thiophenes from *Echinops grijissi* Hance,” *Phytomedicine*, vol. 15, no. 9, pp. 768–774, 2008.
- [219] K. I. Priyadarsini, “Photophysics, photochemistry and photobiology of curcumin: studies from organic solutions, biomimetics and living cells,” *J. Photochem. Photobiol. C Photochem. Rev.*, vol. 10, no. 2, pp. 81–95, 2009.
- [220] Y. Li, P. Xiao, Z. Huang, et al., “Evaluation of curcumin-mediated photodynamic therapy on the reverse of multidrug resistance in tumor cells,” *RSC Adv.*, vol. 10, no. 1, pp. 298–306, 2019.
- [221] W. H. Chan and H. J. Wu, “Anti-apoptotic effects of curcumin on photosensitized human epidermal carcinoma A431 cells,” *J. Cell. Biochem.*, vol. 92, no. 1, pp. 200–212, 2004.
- [222] S. Banerjee and A. R. Chakravarty, “Metal complexes of curcumin for cellular imaging, targeting, and photoinduced

- anticancer activity," *Acc. Chem. Res.*, vol. 48, no. 7, pp. 2075–2083, 2015.
- [223] N. K. Gibbs, E. Quanten, S. Baydoun, et al., "Photophysical, photochemical and photobiological properties of pyrrolocoumarins; A new class of photoactive compounds," *J. Photochem. Photobiol. B Biol.*, vol. 2, no. 1, pp. 109–122, 1988.
- [224] S. M. Kim, J. H. Lee, G. Sethi, et al., "Bergamottin, a natural furanocoumarin obtained from grapefruit juice induces chemosensitization and apoptosis through the inhibition of STAT3 signaling pathway in tumor cells," *Canc. Lett.*, vol. 354, no. 1, pp. 153–163, 2014.
- [225] S. C. Núñez Montoya, L. R. Comini, B. Rumie Vittar, I. M. Fernández, V. A. Rivarola, and J. L. Cabrera, "Phototoxic effects of heterophyllaea pustulata (rubiaceae)," *Toxicon*, vol. 51, no. 8, pp. 1409–1415, 2008.
- [226] I. Gutiérrez, S. G. Bertolotti, M. A. Biasutti, A. T. Soltermann, and N. A. García, "Quinones and hydroxyquinones as generators and quenchers of singlet molecular oxygen," *Can. J. Chem.*, vol. 75, no. 4, pp. 423–428, 1997.
- [227] D. Luo, K. A. Carter, D. Miranda, et al., "Chemophototherapy: an emerging treatment option for solid tumors," *Adv. Sci.*, vol. 4, no. 1, p. 1600106, 2017.
- [228] P. Agostinis, K. Berg, K. A. Cengel, et al., "Photodynamic therapy of cancer: an update," *CA Canc. J. Clin.*, vol. 61, no. 4, pp. 250–281, 2011.
- [229] Z. Zhang, L. Wang, J. Wang, et al., "Mesoporous silica-coated gold nanorods as a light-mediated multifunctional theranostic platform for cancer treatment," *Adv. Mater.*, vol. 24, no. 11, pp. 1418–1423, 2012.
- [230] M. Zheng, C. Yue, Y. Ma, et al., "Single-step assembly of DOX/ICG loaded lipid-polymer nanoparticles for highly effective chemo-photothermal combination therapy," *ACS Nano*, vol. 7, no. 3, pp. 2056–2067, 2013.
- [231] Y. Deng, F. Käfer, T. Chen, et al., "Let there be light: polymeric micelles with upper critical solution temperature as light triggered heat nanogenerators for combating drug resistant cancer," *Small*, vol. 14, no. 37, p. 1802420, 2018.
- [232] Y. Tan, Y. Zhu, L. Wen, et al., "Mitochondria-responsive drug release along with heat shock mediated by multifunctional glycolipid micelles for precise cancer chemo-phototherapy," *Theranostics*, vol. 9, no. 3, pp. 691–707, 2019.
- [233] A. Zhang, A. Li, W. Zhao, and J. Liu, "Recent advances in functional polymer decorated two dimensional transition metal dichalcogenides nanomaterials for chemo photothermal therapy," *Chem. Eur J.*, vol. 24, no. 17, pp. 4215–4227, 2018.
- [234] X. Deng, Z. Shao, and Y. Zhao, "Solutions to the drawbacks of photothermal and photodynamic cancer therapy," *Adv. Sci.*, vol. 8, no. 3, p. 2002504, 2021.
- [235] W. Li, J. Peng, L. Tan, et al., "Mild photothermal therapy/photodynamic therapy/chemotherapy of breast cancer by Lyp-1 modified Docetaxel/IR820 Co-loaded micelles," *Biomaterials*, vol. 106, pp. 119–133, 2016.
- [236] Y. Chen, Q. Chen, Q. Zhu, et al., "Small molecular theranostic assemblies functionalized by doxorubicin-hyaluronic acid-methotrexate prodrug for multiple tumor targeting and imaging-guided combined chemo-photothermal therapy," *Mol. Pharm.*, vol. 16, no. 6, pp. 2470–2480, 2019.
- [237] L. Zhang, D. Jing, L. Wang, et al., "Unique photochemo-immuno-nanoplatform against orthotopic xenograft oral cancer and metastatic syngeneic breast cancer," *Nano Lett.*, vol. 18, no. 11, pp. 7092–7103, 2018.
- [238] T. J. Dougherty, M. T. Cooper, and T. S. Mang, "Cutaneous phototoxic occurrences in patients receiving Photofrin®," *Laser Surg. Med.*, vol. 10, no. 5, pp. 485–488, 1990.
- [239] X. Li, J. F. Lovell, J. Yoon, and X. Chen, "Clinical development and potential of photothermal and photodynamic therapies for cancer," *Nat. Rev. Clin. Oncol.*, vol. 17, no. 11, pp. 657–674, 2020.
- [240] H. Wu, T. Minamide, and T. Yano, "Role of photodynamic therapy in the treatment of esophageal cancer," *Dig. Endoscopy*, vol. 31, no. 5, pp. 508–516, 2019.
- [241] I. Freitas, "Facing hypoxia: a must for photodynamic therapy," *J. Photochem. Photobiol. B*, vol. 2, no. 2, pp. 281–282, 1988.
- [242] J. Dang, H. He, D. Chen, and L. Yin, "Manipulating tumor hypoxia toward enhanced photodynamic therapy (PDT)," *Biomater. Sci.*, vol. 5, no. 8, pp. 1500–1511, 2017.
- [243] M. Wang, J. Shen, H. Jin, H.-J. Im, J. Sandy, and D. Chen, "Recent progress in understanding molecular mechanisms of cartilage degeneration during osteoarthritis," *Ann. N. Y. Acad. Sci.*, vol. 1240, pp. 61–69, 2011.
- [244] L. Larue, B. Myrzakhmetov, A. Ben-Mihoub, et al., "Fighting hypoxia to improve PDT," *Pharmaceuticals*, vol. 12, no. 4, p. 163, 2019.
- [245] P. Xue, R. Yang, L. Sun, et al., "Indocyanine green-conjugated magnetic prussian blue nanoparticles for synchronous photothermal/photodynamic tumor therapy," *Nano-Micro Lett.*, vol. 10, p. 74, 2018.
- [246] Q. Guan, L.-L. Zhou, Y.-A. Li, et al., "Nanoscale covalent organic framework for combinatorial antitumor photodynamic and photothermal therapy," *ACS Nano*, vol. 13, no. 11, pp. 13304–13316, 2019.