Review

A Review on the Scope of Photothermal Therapy—Based Nanomedicines in Preclinical Models of Colorectal Cancer

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Abstract

Oncologic thermal ablation involves the use of hyperthermic temperatures to damage and treat solid cancers. Thermal ablation is being investigated as a method of treatment in colorectal cancers and has the potential to complement conventional anticancer treatments in managing local recurrence and metastatic disease. Photothermal therapy utilizes photosensitive agents to generate local heat and induce thermal ablation. There is growing interest in developing nanotechnology platforms to deliver such photosensitive agents. An advantage of nanomedicines is their multifunctionality, with the capability to deliver combinations of chemotherapeutics and cancer-imaging agents. To date, there have been no clinical studies evaluating photothermal therapy—based nanomedicines in colorectal cancers. This review presents the current scope of preclinical studies, investigating nanomedicines that have been developed for delivering multimodal photothermal therapy to colorectal cancers, with an emphasis on potential clinical applications.

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Introduction

Colorectal cancer (CRC) is one of the major causes of cancer-related mortalities worldwide. There is an increasing trend in CRC incidence, especially in more economically developed countries, attributed in part to lifestyle choices such as dietary and physical activity patterns.[1,2] Surgical intervention remains the cornerstone of CRC management, with around 80% of new CRC patients presenting with localized disease amenable to curative resection.[3] Surgery is the first line of treatment, primarily for patients with stage I to III CRC. However, up to half of patients diagnosed with early-stage CRC experience recurrent disease after surgical resection and may also develop metastatic disease, typically in the liver or lungs.[3,4] Patients with metastatic and stage IV CRC are usually treated with chemotherapy as the first option because of the unresectable nature of the cancer. If possible, chemotherapy is often used as an adjunct to surgery for downstaging or reducing the risk of recurrence. Treatments based on 5-fluorouracil, such as FOLFOX (folinic acid, fluorouracil, and oxaliplatin) and FOLFIRI (leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin), have been developed for patients with metastatic CRC. These treatment regimens have been found to improve treatment response, progression-free survival, and overall survival rates.[5-7] More recently, treatment with FOLFOXIRI (leucovorin, 5-fluorouracil, oxaliplatin, and irinotecan) has been studied and found to be an effective and aggressive approach to treat metastatic CRC.[8] Targeting biological agents such as bevacizumab, cetuximab, and panitumumab have also been studied as part of treatment regimens in combination with FOLFOX and FOLFIRI.[9-14] Studies on these combination treatment regimens have demonstrated improved treatment response and survival rates in patients with metastatic CRC.

Despite the benefits of the current chemotherapeutic regimens, a recent review by Schuurhuizen et al[15] highlighted the fundamental limitation of systemic chemotherapeutic and biological drugs that are routinely used to treat late-stage and metastatic colorectal disease. Although these treatment methods increase overall survival rates and improve prognosis, systemic toxic effects often have dire consequences on the patients' quality of life. In current clinical practice, there remains a need for novel treatment methods that can improve survival rates while minimizing life-affecting adverse toxicities.

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Thermal ablation and laser-induced thermotherapy are treatment methods that may be able to address this unmet clinical need.[16] These treatments utilize hyperthermia to eradicate cancers and have been evaluated for treatment of metastatic CRC.[17] Clinical studies are currently being performed to evaluate the safety and efficacy of such treatment strategies.[18,19] Similar to the heat-mediated cytotoxicity observed in thermal ablation, photothermal therapy (PTT) is a noninvasive technique that involves the administration of a photosensitive agent, which can convert photonic energy into heat upon light irradiation.[20] With absorption of photonic energy from light, ground-state electrons are elevated to an excited energy state. The excited electrons then relax, and the released kinetic energy overheats the local environment, resulting in cell and tissue damage.[21] Hyperthermia can induce cell death through apoptosis, necrosis, and necroptosis (programmed necrosis).[22,23] Intracellular temperatures between 40°C to 47°C cause irreversible damage to cellular proteins and impair DNA function, often resulting in apoptotic cell death. In PTT, it is common for the intracellular temperature of cancer cells to reach 50°C, resulting in necrosis and rapid cell death.[22,24]

In recent years, there has been much interest in developing new nanomedicines for PTT, especially for the treatment of CRC. Nanomedicines and nanoparticle-based therapies have advantages over conventional treatments, which are hindered by low specificity and poor pharmacokinetics. This has led to the development of various nanostructures for biomedicinal applications.[21,25] Nanomedicines that can deliver combined payloads of chemotherapeutics, and cancer-imaging agents show great promise for potential clinical applications.[26] This review highlights the preclinical studies that have evaluated PTT-based nanomedicines as a method of treating and managing CRC. To date, no clinical studies have been reported assessing PTT-based nanomedicines in CRC patients.

This review is categorized according to the different classes of materials and structures that have been used to develop PTT-mediating nanomedicines. The aim of this review is to explore the current state of PTT nanotechnologies in preclinical models of CRC. Table 1 summarizes all the studies included in this review.

Gold-Based Nanomedicines

Gold-based nanoparticles (AuNP) are attractive agents for PTT and form the basis of many anticancer platforms. They are efficient in converting light energy into heat, and their structural dimensions permit the tailored tuning of AuNP particles to specific absorption spectra, including maximum absorption in the near-infrared (NIR) light region for optimal tissue penetration. Other benefits of AuNP are good biocompatibility, passive accumulation within tumors via the enhanced permeability and retention effect, and the ability to functionalize their surfaces with targeting ligands and therapeutic molecules.[63,64] AuNP can also be used for optical imaging because of the capacity to absorb and scatter light in the visible and NIR regions.[65]

O'Neal et al[27] conducted one of the earliest studies of AuNP-mediated PTT in CRC. The authors coated polyethylene glycol (PEG)-ylated silica nanoshells with gold and evaluated the efficacy of PTT in vivo in murine CT26 CRC tumor xenografts. After the intravenous injection of gold-coated nanoshells, tumors were irradiated with NIR light. Control animals exposed to NIR light only demonstrated ongoing rapid tumor growth. Treated tumors, however, all showed significant tumor regression, and the animals appeared healthy and tumor free for more than 90 days after treatment. A subsequent study by Goodrich et al[28] found that CT26 tumor xenograft–bearing animals treated with PEGylated gold nanorods (AuNR) and NIR irradiation survived for longer than control animals (NIR light irradiation only or AuNR only). AuNR was found to selectively accumulate in the tumors, and histologic analysis confirmed no toxicity in vital organs. This study demonstrated the safety and efficacy of AuNR-mediated PTT in CRC tumors.

The versatility of nanomedicines, especially in theranostic applications, has driven clinical interest in combining PTT with chemotherapy. Combined treatments have previously been described as synergistically improving anticancer activity by reducing the systemic drug dose and unwanted side effects.[66] Guo et al[29] prepared multifunctional nanocarriers based on AuNR and chitosan, and loaded them with the chemotherapeutic drug cisplatin. They were able to use the inherent optical properties of AuNR to image LoVo CRC cells in vitro in real time via dark-field optical microscopy. Upon NIR irradiation, no cell death was observed at 1 W/cm^2, but increasing the light output to 3 W/cm^2 resulted in mass cell death. Cisplatin was found to synergistically accentuate the therapeutic effects. This study successfully showcased the ability of nanoparticles to act as single platforms for drug delivery, cell imaging, and PTT.

Kirui and colleagues[32,31,30] conducted a series of experiments investigating single-chain A33-targeting, antibody-functionalized AuNP-mediated PTT in CRC. The cell surface antigen A33 is overexpressed in CRC and may serve as a useful biomarker.[67] The authors synthesized gold and iron oxide hybrid nanoparticles functionalized with the A33 antibody. Intracellular accumulation and PTT cytotoxicity after nanoparticle administration was significantly increased in SW1222 cells (A33 positive) as compared to HT29 cells (A33 negative) in vitro. Apoptosis was the primary mode of cell death at 5.1 W/cm^2, with necrosis observed at higher laser power.[30] In a follow-up study, the authors designed AuNR functionalized with the A33 antibody. Similar to their previous study, selective uptake of the functionalized AuNR was observed in SW1222 cells, and PTT-mediated cytotoxicity was only observed in NIR-irradiated, AuNR-treated SW1222 cells treated with functionalism AuNR.[31] The authors then conducted an in vivo analysis using immunofunctionalized gold and iron oxide hybrid nanoparticles. Magnetic resonance imaging revealed selective accumulation of the nanoparticle after intravenous injection in SW1222 tumor xenografts. PTT treatment of SW1222 CRC xenografts resulted in a reduction in the size of tumors. Histopathologic examination revealed features of thermonecrosis, as indicated by the loss of nucleus, cell shrinkage, and coagulation in treated xenografts with minimal damage in control animals.[32] This study demonstrated targeted AuNP as an attractive adjunct for image-guided treatment in CRC, combining the optical imaging properties of the nanoparticle with its ability to induce tumor death via PTT.

Lee et al[33] combined chemotherapy and PTT by developing doxorubicin (DOX)-loaded AuNP conjugated to anti–death receptor 4 (DR4) antibody. Animals bearing DOX-resistant DLD1 CRC tumor xenografts were treated with AuNP and irradiated with

Table 1 Summary of Studies Evaluating Photothermal Therapy Nanomedicines in Colorectal Cancer

Class of Nanomedicine	Study	Preclinical Model of Colorectal Cancer	Intended Application of Nanomedicine	Treatment Outcome
Gold nanoparticles	O'Neal 2004[27]	CT26 tumor xenografts in vivo	PTT	Tumor growth regression
	Goodrich 2010[28]	CT26 tumor xenografts in vivo	PTT	Treated animals were free of tumor growth
	Guo 2010[29]	LoVo cells in vitro	PTT, cell imaging, cisplatin delivery	Synergistic chemo- and PTT cytotoxicity
	Kirui 2010[30]	SW1222 and HT29 cells in vitro	Targeted PTT	PTT-induced cytotoxicity
	Kirui 2011[31]	SW1222 and HT29 cells in vitro	Targeted PTT	PTT-induced cytotoxicity
	Kirui 2013[32]	SW1222 and HT29 tumor xenografts in vivo	Targeted PTT, tumor imaging	Tumor regression and confirmed tissue necrosis
	Lee 2014[33]	DLD1 cells in vitro and tumor xenografts in vivo	Targeted PTT, doxorubicin delivery	Synergistic chemo- and PTT tumor growth regression
	Hosseinzadeh 2017[34]	HT29 and SW480 cells in vitro	Targeted PTT, SN38 delivery	Synergistic chemo- and PTT cytotoxicity
	Seo 2014[35]	CT26 cells in vitro	PTT, PDT	Synergistic PDT and PTT cytotoxicity
	Azhdarzadeh 2016[36]	HT29 cells in vitro	Targeted PTT, cell imaging	PTT-induced cytotoxicity
	White 2017[37]	Liver metastasis of orthotopic CC531 deposits in vivo	Targeted PTT, tumor imaging	PTT-induced confirmed tissue necrosis
	Parchur 2018[38]	Liver metastasis of orthotopic CC531 deposits in vivo	PTT, tumor imaging	PTT-induced confirmed tissue necrosis
	Chen 2018[39]	HT29 cells in vitro and tumor xenografts in vivo	PTT, tumor imaging	PTT-induced cytotoxicity and complete tumor regression
	Wang 2014[40]	SW620 cells in vitro	Targeted PTT	PTT-induced cytotoxicity
Dye-based nanoparticles	Peng 2011[41]	HCT116 cells in vitro and tumor xenografts in vivo	PTT, tumor imaging	Tumor regression and confirmed tissue necrosis
	Shih 2017[42]	HCT116 and SW620 cells in vitro and tumor xenografts in vivo	Targeted PTT	Tumor growth regression
	Tsai 2017[43]	HCT116 tumor xenografts in vivo	PTT, cell imaging, SN38 delivery	Synergistic chemo- and PTT tumor growth regression
	Lin 2018[44]	HT29 cells in vitro and tumor xenografts in vivo	PTT, cell imaging, doxorubicin delivery	Synergistic chemo- and PTT improvement in survival
	Chen 2017[45]	HCT116 tumor xenografts in vivo	PTT, doxorubicin delivery	Synergistic chemo- and PTT tumor growth regression
	Wang 2017[46]	Lymph node metastasis of HCT116 tumor xenografts in vivo	PTT	Necrosis and pyknosis in lymph nodes
Carbon nanotubes	Tan 2012[47]	HT29 cells in vitro	PTT	PTT-induced cytotoxicity
	Graham 2013[48]	HCT116 and RKO cells in vitro	Targeted PTT	PTT-induced cytotoxicity
	Levi-Polyachenko 2009[49]	HCT116 and RKO cells in vitro	PTT, oxaliplatin/mitomycin C delivery	Synergistic chemo- and PTT cytotoxicity
Graphene oxide nanoparticles	Fiorica 2017[50]	3-D co-culture model of HCT116 CRC cells and human dermal fibroblasts	Targeted PTT, irinotecan delivery	Synergistic chemo- and PTT cytotoxicity
	Einafshar 2018[51]	HT29 cells in vitro	PTT, SN38 delivery	Synergistic chemo- and PTT cytotoxicity
	Lu 2018[52]	CT26 tumor xenografts in vivo	Targeted PTT, doxorubicin delivery	Tumor regression and confirmed tissue necrosis
Transition metals-based nanoparticles	Lee 2010[53]	CT26 cells in vitro	PTT	PTT-induced cytotoxicity
	Liu 2015[54]	SW620 tumor xenografts in vivo	PTT, tumor imaging	Tumor growth regression
	Zhang 2016[55]	HT29 cells in vitro and tumor xenografts in vivo	PTT, tumor imaging	PTT-induced cytotoxicity, tumor growth regression, and confirmed tissue necrosis
	Hessel 2011[56]	HCT116 cells in vitro	PTT	PTT-induced cytotoxicity
	Li 2016[57]	CT26 cells in vitro and tumor xenografts in vivo	PTT	PTT-induced cytotoxicity and tumor growth regression

Table 1 Continued

Class of Nanomedicine	Study	Preclinical Model of Colorectal Cancer	Intended Application of Nanomedicine	Treatment Outcome
Polymerically structured nanomedicines	Hong 2011[58]	CT26 cells in vitro and tumor xenografts in vivo	PTT	PTT-induced cytotoxicity and tumor growth regression
	MacNeill 2013[59]	HCT116 and RKO cells in vitro	PTT	PTT-induced cytotoxicity
	Zhou 2013[60]	HCT116 cells in vitro and tumor xenografts in vivo	PTT	PTT-induced cytotoxicity and tumor growth regression
	Kelkar 2016[61]	CT26 cells in vitro	Dual-wavelength PTT	Synergistic dual-wavelength PTT-induced cytotoxicity
	Yang 2017[62]	HT29 cells in vitro and tumor xenografts in vivo	PTT, PDT, tumor imaging, SN38 delivery	Synergistic PTT, PDT, and chemo-induced cytotoxicity, tumor growth regression, and confirmed tissue necrosis

Abbreviations: PDT = photodynamic therapy; PTT = photothermal therapy.

NIR light. The greatest inhibition in tumor xenografts growth was observed in DR4-targeted, DOX-loaded AuNP- and PTT-treated animals. This was compared to free DOX alone, DOX-loaded AuNP alone, and AuNP + NIR light-treated animals. Combined PTT and chemotherapy from a single nanoparticle platform was found to be the most effective method of treatment. Packaging DOX into AuNP allowed the chemotherapeutic to be retained for longer in the cancer cells. Furthermore, the amount of DOX loaded into nanocarriers was 1.8% the amount used in DOX-only treated animals, showing that lower doses of chemotherapeutics could be effectively administered with minimal adverse effects to treat multidrug-resistant tumors. Hosseinzadeh et al[34] also investigated combined cancer-targeting chemotherapy and AuNP-mediated PTT. The anticancer drug SN38 was deposited onto the surface of AuNP via hyaluronic acid and electrostatic interactions, and the AuNP were functionalized with MUC1 targeting aptamers. MUC1-positive (HT29 and SW480 CRC cell lines) and MUC1-negative (CHO) cell lines were treated with the nanoparticles in vitro. Uptake of nanoparticle and subsequent cytotoxicity in HT29 and SW480 cells was found to be highest in MUC1 aptamer SN38-loaded AuNP. Again, this was compared to free SN38 alone, nonaptamer SN38-loaded AuNP, and PTT-only treated cells. Furthermore, cotreatment of cells with MUC1 aptamer SN38-loaded AuNP and light irradiation limited their ability to migrate.

The ability to combine dual treatments into one nanocarrier and synergize anticancer effects has been evaluated in photodynamic therapy (PDT) and PTT dual therapy. Similar to PTT, PDT involves the administration of photosensitizing agents, which upon excitation transfer energy to oxygen and superoxides, and produce reactive oxygen species that cause intracellular oxidative stress and cell death.[68] Seo et al[35] developed methylene blue (MB)-loaded AuNR for dual PDT-PTT therapy. CT26 CRC cells were treated with MB-loaded AuNR and irradiated with NIR light in vitro. Cytotoxicity was enhanced in the nanocomposites compared to MB-PDT or AuNR-PTT alone. Interestingly, the NIR light used in this study was remote from the optimal absorption wavelength for MB (visible light region). However, the production of reactive oxygen species was still enhanced, which may be due to the transfer of energy from the excited electrons in AuNR to MB. Similar to previous studies, the concentration of MB packaged into the nanocomposites was low but still resulted in a significant anticancer response.

The transmembrane protein mucin 1 (MUC1) is associated with increased proliferation and metastasis in CRC.[69] As described above, Hosseinzadeh et al[34] exploited the overexpression of MUC1 in CRC to target nanoparticles to MUC1-positive cells. Similarly, Azhdarzadeh et al[36] synthesized gold-coated superparamagnetic iron oxide nanoparticles (SPIONs) functionalized with MUC1 aptamers. SPIONs are popular theranostic agents, especially for magnetic resonance imaging (MRI), with the gold coating conferring biocompatible and photothermal properties.[70] MRI confirmed the uptake of nanoparticles into MUC1 HT29 CRC cells. Upon NIR irradiation, nanoparticle treated cells showed significant cell death, while control cells (nanoparticle only and no light irradiation) remained viable. White et al[37] evaluated PTT in anti−mucin 5B (MUC5B) antibody−conjugated AuNP in liver metastatic models of CRC. Similar to MUC1, the overexpression of MUC5B is associated with carcinogenesis and metastasis in gastric and CRC cancers.[71] Metastasis was modeled by implanting CC531 CRC cells into the liver of rats. Anti-MUC5B–conjugated AuNP were injected through the tail veins, and MRI confirmed the selective uptake of AuNP into hepatic metastatic deposits. After light treatment, histologic analysis confirmed large areas of tumor necrosis induced by PTT. No toxicity was observed in any of the major organs. Recently Parchur et al[38] reported a multimodal nanoparticle consisting of a gadolinium oxide shell coated on AuNR. Using a similar liver metastasis model, gadolinium-mediated MRI confirmed a significant accumulation of AuNR into metastatic deposits. Histopathologic analysis confirmed thermal damage in the tumor regions after fiber optic delivery of NIR light and photothermal ablation, with minimal damage to adjacent liver tissue. Pathologic hypoxia in solid cancers plays an important role in aiding the progression and dissemination of cancer.[72] The expression of carbonic anhydrase IX (CAIX) is up-regulated under hypoxic conditions as a result of the highly induced activity of hypoxia-inducible factor 1α.[73] In CRC cells, CAIX has been shown to promote the invasive potential and survival in cells. In addition, CAIX protein expression correlates with poor prognosis in solid tumors.[74] To exploit the importance of CAIX, Chen et al[39] developed AuNR constructs conjugated to anti-CAIX antibody. Under hypoxic conditions, the binding and uptake of CAIX-targeted AuNR into HT29 CRC cells in vitro was higher compared to nontargeted AuNR-treated cells. Upon NIR irradiation, CAIX-targeted, AuNR-treated cells were found to experience significantly higher cell death compared to control AuNR and untreated cells. Hyperspectral imaging in vivo confirmed a high accumulation of intravenously administered CAIX-targeted AuNR in HT29 xenografts, with penetration into the hypoxic areas of the tumors. In vivo NIR light irradiation of tumor xenografts resulted in complete tumor regression in CAIX-targeted, AuNR-treated animals. Transient tumor regression followed by recurrence was observed in nontargeted AuNR-treated animals.

The studies described above utilized CRC targeting antibodies and aptamers to direct and catalyze AuNP-mediated PTT. Wang et al[40] constructed gold and silver hybrid nanorods conjugated to CRC-specific phage fusion proteins. Selective uptake into SW620 CRC cells was confirmed via electron microscopy, and the gold and silver hybrid nanorods were efficient in inducing PTT-mediated cell death.

Dye-Based Nanomedicines

NIR dyes are small organic molecules that can absorb light in the NIR region and are of interest in anticancer theranostic applications. NIR dyes have great versatility and can be used in a wide variety of clinical applications. This includes fluorescent imaging, PDT, and PTT.[75] IR780 is a lipophilic NIR heptamethine cyanine dye that has shown great promise in anticancer-related applications.[76] Because of its hydrophobic nature, IR780 can be packaged into nanoparticles to improve uptake into cancer cells.[76,41] Peng et al[41] developed IR780-loaded micelles for NIR fluorescence and PTT. The micelles were also labeled with the radionuclide rhenium-188 for nuclear imaging. HCT116 CRC cells treated with the IR780 micelles and irradiated with NIR exhibited significant cell death in vitro compared to IR780 micelles treated alone or NIR irradiation alone. Animals bearing HCT116 CRC tumor xenografts were fluorescently imaged after the administration of the IR780 micelles and showed a high uptake at 96 hours. After NIR light irradiation, substantial tumor regression was observed in animals treated with IR780 micelles compared to controls. Photothermal ablation in treated tumors was confirmed by histopathologic analysis, which showed large areas of thermonecrosis, irreversible tissue damage, increased apoptosis, and increased expression of heat shock proteins. Shih et al[42] took this concept one step further by conjugating the epidermal growth factor receptor (EGFR)-targeting monoclonal antibody cetuximab onto IR780-loaded micelles. NIR fluorescence showed high in vitro and in vivo uptake of the micelles into HCT116 CRC (high EGFR expression) cells compared to SW620 CRC (low EGFR expression) cells. After NIR irradiation, all HCT116 tumor xenografts treated with cetuximab-conjugated IR780 micelles had significant tumor regression. In comparison, SW620 tumor xenografts relapsed after 13 days.

Tsai et al[43] described a multiplatform and multifunctional nanoparticle composed of IR780 and SN38 as the core of the structure. The structure was PEGylated and was functionalized with the $\alpha v\beta 3$ integrin targeting peptide cRGD. The dual function of IR780 enabled noninvasive NIR fluorescent imaging to verify nanoparticle accumulation in tumor xenografts and NIR irradiation to generate heat for PTT. HCT116 CRC tumor xenografts treated with the nanoparticle and irradiated with NIR light exhibited a rapid increase in temperature, reaching 52°C in 60 seconds. Combining PTT with SN38 further enhanced tumor regression in a synergistic fashion. Lin and Shieh[44] designed and evaluated grenade-like nanocages to deliver DOX to CRC cells. The nanocage was composed of DOX in the core with the NIR dye ADS-780 on the surface. After the administration of the DOX-loaded nanocages to HT29 CRC cells, NIR fluorescent imaging was used to track the uptake of the nanocages. Upon NIR light irradiation, cell death and tumor regression were observed in vitro and in vivo, respectively. The thermal effects of ADS-780 also triggered the explosion of nanocages into smaller clusters, and the acidic intracellular pH triggered the release of DOX from the clusters. NIR light– and nanocage-treated groups had a longer survival, with histologic analysis showing great anticancer effects. There were no signs of cytotoxicity in other major organs.

Indocyanine green (ICG) is a well-known NIR dye, and its inherent fluorescent properties have been utilized in many medical and surgical specialities.[77] ICG is also a photosensitizing agent and can produce reactive oxygen species, as well as heat, upon light irradiation.[78] Chen et al[45] created ICG- and DOX-loaded nanoparticles and took advantage of ICG's ability to produce reactive oxygen species and trigger the intracellular release of DOX. HCT116 CRC tumor xenograft–treated mice exhibited enhanced cytotoxicity and tumor growth regression after treatment with DOX- and ICG-loaded nanoparticle with NIR light irradiation. Thermal imaging confirmed PTT, as tumor xenograft temperatures rose to around 50°C after light treatment. Hyperthermia also aided the increased accumulation of ICG in the tumor.

Serendipitously, Chinese traditional ink, a conventional writing material, was found to share similar optical and chemical properties as artificially synthesized NIR dyes. Wang et al[46] explored the photothermal effects of Chinese traditional ink in lymph node metastatic models of CRC. HCT116 CRC cells were subcutaneously implanted into mice, and the animals that developed metastases in sentinel lymph nodes were used for experiments. After the administration of the ink and NIR light irradiation, thermal imaging was used to map the location of the ink, with temperatures in the sentinel lymph nodes reported to be around 60°C. Several days after PTT, the lymph nodes were histopathologically examined and showed signs of necrosis and pyknosis. In contrast, intact morphology of cells with no anticancer effects was observed in control lymph nodes. Furthermore, Chinese traditional ink was found to be safe and biocompatible, as indicated by no pathologic damage to any of the major organs.

Carbon Nanotube–Based Nanomedicines

Carbon nanotubes (CNT) have attracted the interests of biomedical researchers because of their electrical, thermal, and spectroscopic properties. CNT offer a potentially useful platform for developing photothermal agents because of their ability to efficiently convert NIR light energy into heat.[79] Tan et al[47] developed modified multiwalled CNT by functionalizing CNT with the nanocomposite polyhedral oligomeric silsesquioxane poly (carbonate urea) urethane (POSS-PCU). POSS-PCU functionalizing plays a similar role to PEGylation in that it improves biocompatibility, addresses inherent toxicity, and prolongs the degradation of nanomedicines in the systemic circulation.[80] In this study, the authors treated HT29 CRC cells with the POSS-PCU—functionalized CNT and irradiated cells with NIR light. There was a 95% reduction in cell viability and negligible reduction in cell viability in cell cultures treated with the modified CNT but not irradiated with NIR light. Graham et al[48] also investigated multiwalled CNT by conjugating folic acid onto the surfaces. Folate receptor is known to be overexpressed in many cancers, including CRC, and has been exploited to target imaging agents and therapeutic compounds toward cancerous tissues.[81] After incubation with the folic acid—functionalized CNT and NIR light irradiation, cytotoxic analysis showed a significant reduction in cell viability in HCT116 and RKO CRC cells. Similar to the previous study, no cell death was observed in cells treated with CNT but not irradiated with NIR light. Levi-Polyachenko et al[49] explored the hyperthermia-inducing ability of CNT to improve the uptake and delivery of oxaliplatin and mitomycin C. The clinical relevance for this is its potential use in hyperthermic intraperitoneal chemotherapy to treat peritoneal metastasis.[82] The authors loaded the chemotherapeutics into multiwalled CNT and incubated it with HCT116 and RKO CRC cells. There was a rapid accumulation of the chemotherapeutics into cells (tens of seconds), and the intracellular amount of anticancer drugs was found to be similar to cells incubated with the chemotherapeutics for 2 hours under nonhyperthermic conditions. Cell viability analysis showed a synergistic effect on cell death, mediated by combined CNT-PTT and oxaliplatin/mitomycin C toxicity.

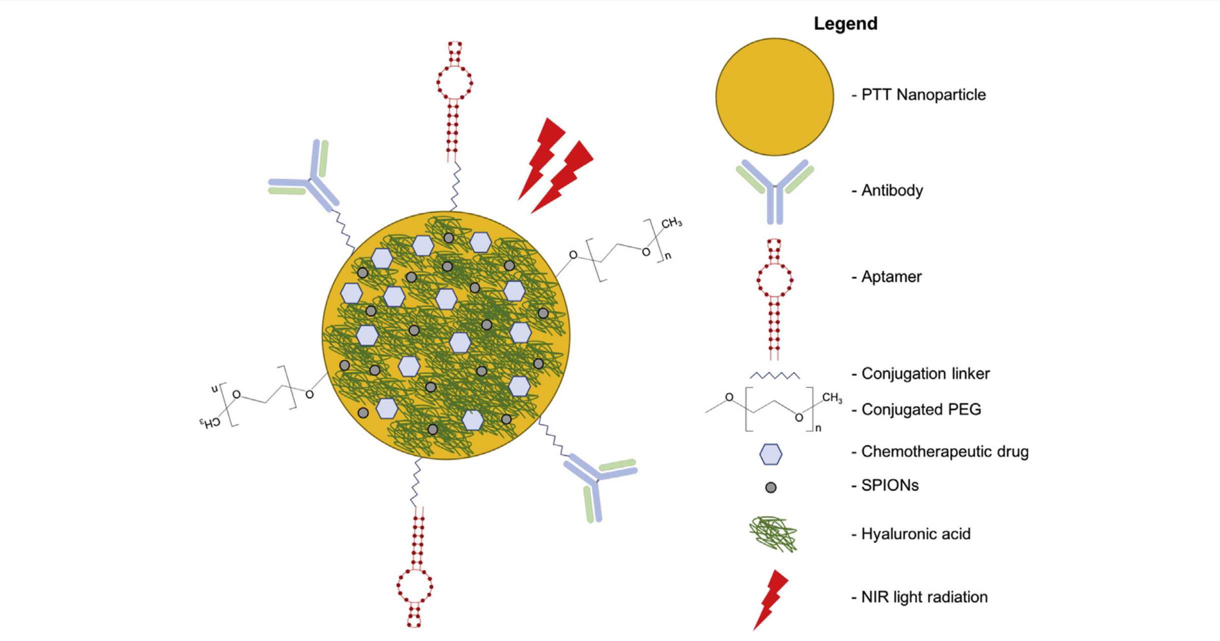
Graphene Oxide–Based Nanomedicines

Graphene is the fundamental building block in graphitic materials. It can be fashioned into many different geometrical structures. Graphene, graphene oxide, and other derivatives have been extensively explored for theranostic applications in nanomedicines because of their low cost, large molecular surface area, chemical and mechanical stability, low toxicity, and biocompatibility. Graphene also exhibits high photonic energy absorption in the NIR range, making it a suitable candidate for PTT.[83,84] Fiorica et al[50] developed a hyaluronic acid—based nanogel network with graphene oxide incorporated into the nanostructure. The anticancer drug irinotecan was loaded into the core of the nanostructure. The authors evaluated the multimodal activities of the nanogel in 3-D spheroidal coculture models of CRC composed of HCT116 CRC cells and human dermal fibroblasts. The 3-D models were directly injected with the nanogel constructs, mimicking intratumoral injections. The nanogel was taken up by HCT116 cells, which may have been due to the recognition of hyaluronic acid by overexpressed cancer cell surface markers, such as CD44.[85] After NIR light irradiation, the destruction of both HCT116 CRC and healthy fibroblasts was observed in irinotecan-loaded, nanogel-treated 3-D models. Cytotoxicity was observed throughout the 3-D model. This contrasted with necrosis alone being observed in the light irradiation spot on 3-D models treated with non—irinotecan-loaded nanogels. Viable HCT116 and fibroblasts were still present around the light irradiation spot.[50] Einafshar et al[51] used sheets of graphene oxide to produce biocompatible nanocarriers of SN38. The nanoparticles were composed of SPIONs and were functionalized with cyclodextrins to improve aqueous solubility and confer biocompatibility. HT29 CRC cells were treated with the nanoparticle in vitro, and the results indicated a synergistic mode of cell death with combined graphene oxide—PTT and —SN38 chemotherapy. This study also highlighted the effectiveness of designing nanoplatforms to be used as dual carriers of chemotherapeutic and PTT agents. Lu et al[52] developed a dual-targeting nanoparticle to deliver PTT and chemotherapy to CT26 CRC tumor xenografts. Magnetic nanoparticles were deposited on graphene oxide, which was then functionalized by PEGylation, and cetuximab was conjugated onto the nanoparticles. DOX was then loaded onto the nanoparticles. Magnetic guidance was used to attract the nanoparticle toward the tumor xenografts, with cetuximab binding to cells overexpressing EGFR. The nanoparticles were taken up via endocytosis, followed by the intracellular release of DOX. After intravenous injection and application of magnetic field and NIR light irradiation, substantial regression in tumor growth was observed in treated animals. In comparison, the other animal groups (free DOX alone, DOX-loaded nanoparticle alone, DOX-loaded nanoparticle + magnet alone) showed an initial regression in tumor growth, but tumors relapsed after a few days. Histopathologic analysis revealed large areas of necrosis in tumor xenografts from treated animals.

Transition Metals–Based Nanomedicines

The use of transition metals as oxides, hybrid structures, and alloys is being evaluated in an effort to create more efficient biofunctional nanomaterials and platforms with high photothermal effects.[86] Lee et al[53] reported the use of titanium oxide nanotubes (TONT) as mediators of PTT. Compared to AuNP and CNT, TONT absorb more NIR light energy and convert light to heat more efficiently. In vitro cytotoxicity analysis found CT26 CRC to respond to TONT treatment and NIR light irradiation, with a

Figure 1 Schematic Diagram of Multimodal Targeted PTT Nanomedicine. Multimodal Nanomedicines Combine Different Therapies Such as Near-infrared (NIR) Light-absorbing Nanoparticles to Mediate Photothermal Therapy (PTT) and Conventional Chemotherapeutic Drugs (ie, Doxorubicin, SN38, and Oxaliplatin). Nanomedicines Can Be Functionalized With Superparamagnetic Iron Oxide Nanoparticles (SPIONs) to Facilitate Magnetic Resonance Imaging and Polyethylene Glycol (PEG) to Improve Biocompatibility and Prolong Systemic Circulation. Cancer-targeting Ligands Such as Antibodies, Aptamers, and Hyaluronic Acid Can Be Conjugated Onto Nanomedicines to Improve Delivery and Uptake of Nanomedicines in Cancers



significant reduction in cell viability. TONT was also found to be nontoxic when incubated with cells and devoid of NIR light irradiation. Liu et al[54] developed a theranostic agent by combining MRI and PTT into a single nanoparticle. The nanoparticles were assembled using iron (Fe^{3+}), gallic acid, and poly(vinylpyrrolidone). Because of the small size of the nanoparticles, they were found to preferentially accumulate in SW620 CRC tumor xenografts. The intratumoral acidic pH enhanced MRI, and after NIR light irradiation, tumors were completely ablated as a result of the PTT-mediating properties of Fe^{3+}. Zhang et al[55] created a multimodal iron-based hybrid anisotropic nanoparticle. Cell viability analysis showed cytotoxicity in nanoparticle- and laser irradiation—treated HT29 cells in vitro. After the injection of the iron nanoparticle into HT29 CRC tumor xenograft—bearing animals, photoacoustic imaging and MRI were used to track the uptake and dissemination of nanoparticles. Once the optimal time for intratumoral accumulation was identified, NIR light irradiation was applied to the tumor xenografts. Two days after irradiation, tumor sizes in treated mice had regressed significantly. Histopathologic analysis of tumor sections confirmed a high therapeutic efficacy with apparent extensive necrosis.

Compared to gold and other inorganic materials, copper is cheap, easily obtainable, and biocompatible; it also possesses efficient photothermal properties. This makes it advantageous for the mass production of copper-based nanoparticles. Hessel et al[56] developed copper selenide nanocrystals, which exhibited strong NIR optical absorption. Cellular destruction was observed after the treatment of HCT116 CRC cells in vitro, with copper selenide nanocrystals and NIR light irradiation. Li et al[57] investigated PEGylated copper nanowires (CuNW) as PTT-mediating agents. CuNW was found to efficiently generate heat upon NIR light irradiation. In vitro analysis showed CuNW intertwining around CT26 CRC cells, and upon light irradiation, heat was transmitted to cells, triggering thermal-induced cell ablation. CT26 CRC tumor xenograft—bearing animals were then injected with CuNW and irradiated with NIR light. Tumoral temperatures rose and tumor growth was suppressed. Necrosis was found to be the primary mode of cell death, as indicated by release of the damage-associated molecular pattern molecule HMGB1.

Polymerically Structured Nanomedicines

Hong et al[58] evaluated porous silicon as a PTT-mediating agent and found that, in combination with NIR light irradiation, CT26 CRC cells experienced substantial cytotoxicity in vitro. Porous silicon or NIR light irradiation alone did not influence cell viability. In vivo treatment of animals bearing CT26 CRC tumor xenografts with porous silicon and NIR light irradiation resulted in tumor regression, with the animals remaining healthy and free of tumor for more than 3 months. Furthermore, surrounding healthy tissue was found to be free from thermal damage. Similarly, MacNeill et al[59] developed a novel chemically modified polymer nanoparticle. The nanoparticle was stable and nontoxic under non-NIR light conditions. Upon NIR light irradiation, the nanoparticle generated temperatures above 50°C in vitro. Photothermal ablation was seen in HCT116 and RKO CRC cells treated with the nanoparticle and NIR light irradiation. Recently polyaniline-based nanoparticles (PANP) have been developed with strong NIR optical absorption properties.[87] Zhou et al[60] investigated PANP and found that the cytotoxicity of PANP was dependent on NIR light irradiation in vitro. HCT116 CRC tumor xenograft−bearing mice were treated with PANP and NIR light irradiation. Complete tumor regression was observed 5 days after treatment, and tumors did not regrow.

Ideally, nanomedicines that have been developed for PTT should possess strong optical absorption in the NIR range (700-2000 nm, typically 800 nm) of the electromagnetic spectrum.[88] Kelkar et al[61] developed a dual-wavelength-absorbing nanoparticle for PTT. The nanoparticle could absorb light at 450 and 800 nm. The rationale was that the shorter wavelength would be better suited to treat superficial lesions, whereas the longer wavelength could penetrate into deeper tumors. In vitro cell viability analysis in CT26 CRC cells showed that irradiation at both wavelengths resulted in a nanoparticle dose-dependent reduction in cell viability. Simultaneous application of both wavelengths was found to be better than blue (450 nm) and NIR (800 nm) wavelengths alone. Yang et al[62] investigated SN38-loaded nanoporphyrin micelles. This trimodal therapeutic platform could impart PTT, PDT, and chemotherapeutic effects. Under nonlight conditions, the micelles were stable, but upon light irradiation, they resulted in a controlled release of SN38. In vitro analysis showed a dose-dependent uptake and light-dependant reduction in cell viability in HT29 CRC cells. Because of the small size of the micelles, they were retained longer in tumors compared to the major organs in animal models. Complete tumor regression was observed in animals bearing HT29 CRC tumor xenografts treated with SN38-loaded nanoporphyrin micelles and light. Histopathologic analysis showed signs of necrosis and pyknosis.

Potential Clinical Applications

As highlighted in this review, there are many classes, derivatives, and highly modified multimodal nanomedicines that can deliver PTT to CRC. The studies evaluated in this review are preclinical in nature and show great promise. However, there is still a long way to go before these techniques can be clinically applied. AuNP are the most favored class of nanoparticles in PTT because of their many inherent advantages in optical imaging, eliciting PTT, and serving as effective nanocarriers. AuNP were the first class of nanoparticles to be evaluated for PTT in CRC, and they are still being studied today. In addition, as summarized in Table 1, there are more AuNP-based PTT preclinical studies in CRC compared to other classes of PTT-mediating nanoparticles.

Stern et al[89] published the findings of a small-scale clinical study evaluating the toxicity of AuNP in patients with prostate cancer. The primary end point of this study was patient safety; the clinical safety profile of AuNP was found to be excellent and strongly supported further investigation. On the basis of the preclinical findings in this review and the aforementioned clinical study, there is ample evidence suggesting that AuNP-based PTT nanomedicine is an attractive method of treatment in CRC; it is a strong candidate that would greatly benefit from early-phase clinical evaluation in the near future.[90]

Intraoperative PTT shows great clinical potential as a treatment option for metastatic CRC. Because PTT is similar to PDT, there are similarities in the clinical application of both treatment methods. In PDT, after the systemic administration of the photosensitizing agent, light is delivered laparoscopically through optical fibers to the site of tumor growth. This method for practicing intraoperative PDT has been shown to be the best and safest route for treating patients.[91] Without light-mediated activation, photosensitizing agents are unable to elicit cytotoxicity. It would therefore be practical to use the same technique for PTT. Because of the flexibility of optical fibers, light delivery can be localized and made accessible to any organ, making it ideal for precisely targeting metastatic CRC lesions.

Limitations of Nanomedicines

The enhanced permeability and retention (EPR) effect is often described as a potential drawback in the clinical application of nanomedicines. Briefly, the EPR effect describes the extravasation of intravascular fluids from systemic circulation, carrying plasma proteins and macromolecules into the interstitial spaces within the tumor microenvironment. This is usually brought on by the leakiness and compromised structure of the tumor vasculature.[92] Coupled with the ineffective lymphatic filtration system in the tumor microenvironment, extravasated macromolecules are prevented from being removed back into systemic circulation.[93] The EPR effect is the basis on which nanomedicines are delivered to the tumor. Paradoxically, a major obstacle to this system is the buildup of colloid osmotic pressure as a result of the EPR effect.[94] The continuous extravasation and accumulation of intravascular fluids can increase the interstitial fluid pressure and impede the delivery of nanomedicines.

Off-target effects of nontargeted nanomedicines and challenged pharmacokinetics—that is, the inability to penetrate through multiple layers of tissues—can also result in the inefficient delivery of nanomedicines and treatment of tumors. There is ongoing research to potentially improve the delivery of nanomedicines to tumors, which includes the use of magnetic nanoparticles and ultrasound, through the exploitation of tumor-specific physiology.[95]

Conclusion

This review highlights the preclinical evaluations of nanomedicines for PTT in CRC. Thermal ablation is an effective method for treating solid cancers, and via nanocarriers, nanoparticles, and similar platforms, it is possible to directly deliver photothermal agents to cancers. As detailed in this review, multimodal PTT nanomedicines have been produced in various forms, which can deliver combinations of cancer-imaging agents and chemotherapeutics in addition to the photothermal agent (Figure 1). To date, the results are limited to preclinical (cancer cell line and tumor xenograft) models. The next steps are to investigate PTT-based nanomedicines for CRC in a clinical setting. This would involve setting up phase 1 small-scale pilot or feasibility studies evaluating nanomedicine toxicity, safety of NIR light irradiation, and treatment efficacy of PTT-based nanomedicines. These clinical studies can be used to investigate this technique as either a standalone method of treatment or one combined with surgery. These vital studies are necessary to demonstrate the clinical benefit of this technology in human CRC.

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Disclosure

The authors have stated that they have no conflict of interest.

References

1. Wong CKH, Chen J, Yu CLY, Sham M, Lam CLK. Systematic review recommends the European Organization for Research and Treatment of Cancer colorectal cancer—specific module for measuring quality of life in colorectal cancer patients. *J Clin Epidemiol* 2015; 68:266-78.
2. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 2009; 18:1688-94.
3. Gustavsson B, Carlsson G, MacHover D, et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. *Clin Colorectal Cancer* 2015; 14:1-10.
4. Kaveh S, Ebrahimi P, Rezapour A, Mozafari M, Sayehmiri K. Bevacizumab and erlotinib versus bevacizumab for colorectal cancer treatment: systematic review and meta-analysis. *Int J Clin Pharm* 2019; 41:30-41.
5. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; 22:23-30.
6. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005; 23:4866-75.
7. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; 22:229-37.
8. Leal F, Ferreira FP, Sasse AD. FOLFOXIRI regimen for metastatic colorectal cancer: a systematic review and meta-analysis. *Clin Colorectal Cancer* 2017; 16:405-9.e2.
9. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; 25:1539-44.
10. van Houdt WJ, Hoogwater FJH, de Bruijn MT, et al. Oncogenic *KRAS* desensitizes colorectal tumor cells to epidermal growth factor receptor inhibition and activation. *Neoplasia* 2010; 12:443-52.
11. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; 360:1408-17.
12. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor *KRAS* and *BRAF* mutation status. *J Clin Oncol* 2011; 29:2011-9.
13. Douillard JY, Siena S, Cassidy J, et al. Randomized, Phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; 28:4697-705.
14. Wilkinson NW, Yothers G, Lopa S, Costantino JP, Petrelli NJ, Wolmark N. Long-term survival results of surgery alone versus surgery plus 5-fluorouracil and leucovorin for stage II and stage III colon cancer: pooled analysis of NSABP C-01 through C-05. A baseline from which to compare modern adjuvant trials. *Ann Surg Oncol* 2010; 17:959-66.
15. Schuurhuizen CSEW, Braamse AMJ, Konings IRHM, et al. Does severe toxicity affect global quality of life in patients with metastatic colorectal cancer during palliative systemic treatment? A systematic review. *Ann Oncol* 2017; 28:478-86.
16. Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. *Nat Rev Cancer* 2014; 14:199-208.
17. Vogl TJ, Eckert R, Naguib NNN, Beeres M, Gruber-Rouh T, Nour-Eldin NEA. Thermal ablation of colorectal lung metastases: retrospective comparison among laser-induced thermotherapy, radiofrequency ablation, and microwave ablation. *AJR Am J Roentgenol* 2016; 207:1340-9.
18. Gillams A, Goldberg N, Ahmed M, et al. Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, the Interventional Oncology Sans Frontières meeting, 2013. *Eur Radiol* 2015; 25:3438-54.
19. Gurusamy K, Corrigan N, Croft J, et al. Liver resection surgery versus thermal ablation for colorectal LiVer MetAstases (LAVA): study protocol for a randomised controlled trial. *Trials* 2018; 19:1-13.
20. Huang X, El-Sayed MA. Plasmonic photo-thermal therapy (PPTT). *Alexandria J Med* 2011; 47:1-9.
21. Huang X, Jain PK, El-Sayed IH, El-Sayed MA. Plasmonic photothermal therapy (PPTT) using gold nanoparticles. *Lasers Med Sci* 2008; 23:217-28.
22. Spyratou E, Makropoulou M, Efstathopoulos EP, Georgakilas AG, Sihver L. Recent advances in cancer therapy based on dual mode gold nanoparticles. *Cancers (Basel)* 2017; 9:E173.
23. Mouratidis PXE, Rivens I, Ter Haar G. A study of thermal dose—induced autophagy, apoptosis and necroptosis in colon cancer cells. *Int J Hyperthermia* 2015; 31:476-88.
24. Cherukuri P, Glazer ES, Curley SA. Targeted hyperthermia using metal nanoparticles. *Adv Drug Deliv Rev* 2010; 62:339-45.
25. Tran S, DeGiovanni PJ, Piel B, Rai P. Cancer nanomedicine: a review of recent success in drug delivery. *Clin Transl Med* 2017; 6:44.
26. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer* 2017; 17:20-37.
27. O'Neal DP, Hirsch LR, Halas NJ, Payne JD, West JL. Photo-thermal tumor ablation in mice using near infrared—absorbing nanoparticles. *Cancer Lett* 2004; 209:171-6.
28. Goodrich GP, Bao L, Gill-Sharp K, Sang KL, Wang J, Payne JD. Photothermal therapy in a murine colon cancer model using near-infrared absorbing gold nanorods. *J Biomed Opt* 2010; 15:018001.
29. Guo R, Zhang L, Qian H, Li R, Jiang X, Liu B. Multifunctional nanocarriers for cell imaging, drug delivery, and near-IR photothermal therapy. *Langmuir* 2010; 26:5428-34.
30. Kirui DK, Rey DA, Batt CA. Gold hybrid nanoparticles for targeted phototherapy and cancer imaging. *Nanotechnology* 2010; 21:105105.
31. Kirui DK, Krishnan S, Strickland AD, Batt CA. PAA-derived gold nanorods for cellular targeting and photothermal therapy. *Macromol Biosci* 2011; 11:779-88.
32. Kirui DK, Khalidov I, Wang Y, Batt CA. Targeted near-IR hybrid magnetic nanoparticles for in vivo cancer therapy and imaging. *Nanomedicine* 2013; 9:702-11.
33. Lee SM, Kim HJ, Kim SY, et al. Drug-loaded gold plasmonic nanoparticles for treatment of multidrug resistance in cancer. *Biomaterials* 2014; 35:2272-82.
34. Hosseinzadeh H, Atyabi F, Varnamkhasti BS, et al. SN38 conjugated hyaluronic acid gold nanoparticles as a novel system against metastatic colon cancer cells. *Int J Pharm* 2017; 526:339-52.
35. Seo SH, Kim BM, Joe A, et al. NIR-light—induced surface-enhanced Raman scattering for detection and photothermal/photodynamic therapy of cancer cells using methylene blue-embedded gold nanorod@SiO_2 nanocomposites. *Biomaterials* 2014; 35:3309-18.
36. Azhdarzadeh M, Atyabi F, Saei AA, et al. Theranostic MUC-1 aptamer targeted gold coated superparamagnetic iron oxide nanoparticles for magnetic resonance imaging and photothermal therapy of colon cancer. *Colloids Surf B Biointerfaces* 2016; 143:224-32.
37. White SB, Kim DH, Guo Y, et al. Biofunctionalized hybrid magnetic gold nanoparticles as catalysts for photothermal ablation of colorectal liver metastases. *Radiology* 2017; 285:809-19.
38. Parchur AK, Sharma G, Jagtap JM, et al. Vascular interventional radiology-guided photothermal therapy of colorectal cancer liver metastasis with theranostic gold nanorods. *ACS Nano* 2018; 12:6597-611.
39. Chen Y, Bian X, Aliru M, et al. Hypoxia-targeted gold nanorods for cancer photothermal therapy. *Oncotarget* 2018; 9:26556-71.
40. Wang F, Liu P, Sun L, Li C, Petrenko VA, Liu A. Bio-mimetic nanostructure self-assembled from Au@Ag heterogeneous nanorods and phage fusion proteins for targeted tumor optical detection and photothermal therapy. *Sci Rep* 2014; 4:6808.
41. Peng CL, Shih YH, Lee PC, Hsieh TMH, Luo TY, Shieh MJ. Multimodal image-guided photothermal therapy mediated by ^{188}Re-labeled micelles containing a cyanine-type photosensitizer. *ACS Nano* 2011; 5:5594-607.
42. Shih YH, Luo TY, Chiang PF, et al. EGFR-targeted micelles containing near-infrared dye for enhanced photothermal therapy in colorectal cancer. *J Control Release* 2017; 258:196-207.
43. Tsai MH, Peng CL, Yang SJ, Shieh MJ. Photothermal, targeting, theranostic near-infrared nanoagent with SN38 against colorectal cancer for chemothermal therapy. *Mol Pharm* 2017; 14:2766-80.
44. Lin CY, Shieh MJ. Near-infrared fluorescent dye—decorated nanocages to form grenade-like nanoparticles with dual control release for photothermal theranostics and chemotherapy. *Bioconjug Chem* 2018; 29:1384-98.
45. Chen Y, Li H, Deng Y, Sun H, Ke X, Ci T. Near-infrared light triggered drug delivery system for higher efficacy of combined chemo-photothermal treatment. *Acta Biomater* 2017; 51:374-92.
46. Wang S, Cao Y, Zhang Q, et al. New application of old material: Chinese traditional ink for photothermal therapy of metastatic lymph nodes. *ACS Omega* 2017; 2:5170-8.
47. Tan A, Madani SY, Rajadas J, Pastorin G, Seifalian AM. Synergistic photothermal ablative effects of functionalizing carbon nanotubes with a POSS-PCU nanocomposite polymer. *J Nanobiotechnology* 2012; 10:1-8.

48. Graham EG, MacNeill CM, Levi-Polyachenko NH. Quantifying folic acid--functionalized multi-walled carbon nanotubes bound to colorectal cancer cells for improved photothermal ablation. *J Nanoparticle Res* 2013; 15:1649.
49. Levi-Polyachenko NH, Merkel EJ, Jones BT, Carroll DL, Stewart JH. Rapid photothermal intracellular drug delivery using multiwalled carbon nanotubes. *Mol Pharm* 2009; 6:1092-9.
50. Fiorica C, Mauro N, Pitarresi G, Scialabba C, Palumbo FS, Giammona G. Double-network-structured graphene oxide-containing nanogels as photothermal agents for the treatment of colorectal cancer. *Biomacromolecules* 2017; 18: 1010-8.
51. Einafshar E, Asl AH, Nia AH, Mohammadi M, Malekzadeh A, Ramezani M. New cyclodextrin-based nanocarriers for drug delivery and phototherapy using an irinotecan metabolite. *Carbohydr Polym* 2018; 194:103-10.
52. Lu YJ, Lin PY, Huang PH, et al. Magnetic graphene oxide for dual targeted delivery of doxorubicin and photothermal therapy. *Nanomaterials* 2018; 8:193.
53. Lee C, Hong C, Kim H, Kang J, Zheng HM. TiO_2 nanotubes as a therapeutic agent for cancer thermotherapy. *Photochem Photobiol* 2010; 86:981-9.
54. Liu F, He X, Chen H, Zhang J, Zhang H, Wang Z. Gram-scale synthesis of coordination polymer nanodots with renal clearance properties for cancer theranostic applications. *Nat Commun* 2015; 6:1-9.
55. Zhang R, Cheng K, Antaris AL, et al. Hybrid anisotropic nanostructures for dual-modal cancer imaging and image-guided chemo-thermo therapies. *Biomaterials* 2016; 103:265-77.
56. Hessel CM, Pattani VP, Rasch M, et al. Copper selenide nanocrystals for photothermal therapy. *Nano Lett* 2011; 11:2560-6.
57. Li KC, Chu HC, Lin Y, Tuan HY, Hu YC. PEGylated copper nanowires as a novel photothermal therapy agent. *ACS Appl Mater Interfaces* 2016; 8:12082-90.
58. Hong C, Lee J, Zheng H, Hong SS, Lee C. Porous silicon nanoparticles for cancer photothermotherapy. *Nanoscale Res Lett* 2011; 6:321.
59. MacNeill CM, Coffin RC, Carroll DL, Levi-Polyachenko NH. Low band gap donor-acceptor conjugated polymer nanoparticles and their NIR-mediated thermal ablation of cancer cells. *Macromol Biosci* 2013; 13:28-34.
60. Zhou J, Lu Z, Zhu X, et al. NIR photothermal therapy using polyaniline nanoparticles. *Biomaterials* 2013; 34:9584-92.
61. Kelkar SS, McCabe-Lankford E, Albright R, Harrington P, Levi-Polyachenko NH. Dual wavelength stimulation of polymeric nanoparticles for photothermal therapy. *Lasers Surg Med* 2016; 48:893-902.
62. Yang X, Xue X, Luo Y, et al. Sub-100 nm, long tumor retention SN-38-loaded photonic micelles for tri-modal cancer therapy. *J Control Release* 2017; 261:297-306.
63. Riley RS, Day ES. Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2017; 9.
64. Norouzi H, Khoshgard K, Akbarzadeh F. In vitro outlook of gold nanoparticles in photo-thermal therapy: a literature review. *Lasers Med Sci* 2018; 33:917-26.
65. Tong L, Wei Q, Wei A, Cheng J. Gold nanorods as contrast agents for biological imaging: optical properties, surface conjugation and photothermal effects. *Photochem Photobiol* 2009; 85:21-32.
66. Kemp JA, Shim MS, Heo CY, Kwon YJ. "Combo" nanomedicine: Co-delivery of multi-modal therapeutics for efficient, targeted, and safe cancer therapy. *Adv Drug Deliv Rev* 2016; 98:3-18.
67. Wong NACS, Adamczyk LA, Evans S, Cullen J, Oniscu A, Oien KA. A33 shows similar sensitivity to but is more specific than CDX2 as an immunomarker of colorectal carcinoma. *Histopathology* 2017; 71:34-41.
68. Dolmans DEJGJ, Fukumura D, Jain RK. Photodynamic therapy for cancer. *Nat Rev Cancer* 2003; 3:380-7.
69. Zeng Y, Zhang Q, Zhang Y, et al. MUC1 predicts colorectal cancer metastasis: a systematic review and meta-analysis of case controlled studies. *PLoS One* 2015; 10: 1-17.
70. Jin R, Lin B, Li D, Ai H. Superparamagnetic iron oxide nanoparticles for MR imaging and therapy: design considerations and clinical applications. *Curr Opin Pharmacol* 2014; 18:18-27.
71. Lahdaoui F, Messager M, Vincent A, et al. Depletion of MUC5B mucin in gastrointestinal cancer cells alters their tumorigenic properties: implication of the Wnt/β-catenin pathway. *Biochem J* 2017; 474:3733-46.
72. Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia (Auckl)* 2015; 3:83-92.
73. Chiche J, Ilc K, Laferrière J, et al. Hypoxia-inducible carbonic anhydrase IX and XII promote tumor cell growth by counteracting acidosis through the regulation of the intracellular pH. *Cancer Res* 2009; 69:358-68.
74. Sansone P, Piazzi G, Paterini P, et al. Cyclooxygenase-2/carbonic anhydrase-IX up-regulation promotes invasive potential and hypoxia survival in colorectal cancer cells. *J Cell Mol Med* 2009; 13(9B):3876-87.
75. Yuan A, Wu J, Tang X, Zhao L, Xu F, Hu Y. Application of near-infrared dyes for tumor imaging, photothermal, and photodynamic therapies. *J Pharm Sci* 2013; 102:6-28.
76. Alves CG, Lima-Sousa R, de Melo-Diogo D, Louro RO, Correia IJ. IR780 based nanomaterials for cancer imaging and photothermal, photodynamic and combinatorial therapies. *Int J Pharm* 2018; 542:164-75.
77. Baiocchi GL, Diana M, Boni L. Indocyanine green-based fluorescence imaging in visceral and hepatobiliary and pancreatic surgery: state of the art and future directions. *World J Gastroenterol* 2018; 24:2921-30.
78. Topaloglu N, Guney M, Aysan N, Gulsoy M, Yuksel S. The role of reactive oxygen species in the antibacterial photodynamic treatment: photoinactivation vs. proliferation. *Lett Appl Microbiol* 2016; 62:230-6.
79. Singh R, Torti SV. Carbon nanotubes in hyperthermia therapy. *Adv Drug Deliv Rev* 2013; 65:2045-60.
80. Solouk A, Cousins BG, Mirzadeh H, Solati-Hashtjin M, Najarian S, Seifalian AM. Surface modification of POSS-nanocomposite biomaterials using reactive oxygen plasma treatment for cardiovascular surgical implant applications. *Biotechnol Appl Biochem* 2011; 58:147-61.
81. Zwicke GL, Mansoori GA, Jeffery CJ. Targeting of cancer nanotherapeutics. *Nano Rev* 2012; 1:1-11.
82. Dehal A, Smith JJ, Nash GM. Cytoreductive surgery and intraperitoneal chemotherapy: An evidence-based review—past, present and future. *J Gastrointest Oncol* 2016; 7:143-57.
83. Liu J, Cui L, Losic D. Graphene and graphene oxide as new nanocarriers for drug delivery applications. *Acta Biomater* 2013; 9:9243-57.
84. Lim JH, Kim DE, Kim EJ, Ahrberg CD, Chung BG. Functional graphene oxide-based nanosheets for photothermal therapy. *Macromol Res* 2018; 26: 557-65.
85. Lesley BJ, He Q, Miyake K, Hamann A, Hyman R, Kincade PW. Requirements for hyaluronic acid binding by CD44: a role for the cytoplasmic domain and activation by antibody. *J Exp Med* 1992; 175:257-66.
86. Gulyaev PY, Kotvanova MK, Omelchenko AI. Nanotechnologies of the treatment and production of complex transition metal oxides with high photothermal effect. *Inorg Mater Appl Res* 2018; 9:540-5.
87. Yang J, Choi J, Bang D, et al. Convertible organic nanoparticles for near-infrared photothermal ablation of cancer cells. *Angew Chem Int Ed Engl* 2011; 50:441-4.
88. Zhang M, Kim HS, Jin T, Woo J, Piao YJ, Moon WK. Near-infrared photothermal therapy using anti-EGFR-gold nanorod conjugates for triple negative breast cancer. *Oncotarget* 2017; 8:86566-75.
89. Stern JM, Kibanov Solomonov VV, Sazykina E, Schwartz JA, Gad SC, Goodrich GP. Initial evaluation of the safety of nanoshell-directed photothermal therapy in the treatment of prostate disease. *Int J Toxicol* 2016; 35:38-46.
90. Sztandera K, Gorzkiewicz M, Klajnert-Maculewicz B. Gold nanoparticles in cancer treatment. *Mol Pharm* 2019; 16:1-23.
91. Shafirstein G, Battoo A, Harris K, et al. Photodynamic therapy of non-small cell lung cancer. Narrative review and future directions. *Ann Am Thorac Soc* 2016; 13: 265-75.
92. Klein D. The tumor vascular endothelium as decision maker in cancer therapy. *Front Oncol* 2018; 8:367.
93. Wagner M, Wiig H. Tumor interstitial fluid formation, characterization, and clinical implications. *Front Oncol* 2015; 5:1-12.
94. Heldin CH, Rubin K, Pietras K, Östman A. High interstitial fluid pressure—an obstacle in cancer therapy. *Nat Rev Cancer* 2004; 4:806-13.
95. Nehoff H, Parayath NN, Domanovitch L, Taurin S, Greish K. Nanomedicine for drug targeting: Strategies beyond the enhanced permeability and retention effect. *Int J Nanomedicine* 2014; 9:2539-55.