



Published in final edited form as:

Prog Mater Sci. 2019 January ; 99: 1–26. doi:10.1016/j.pmatsci.2018.07.005.

Nanomaterials as photothermal therapeutic agents

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Abstract

Curing cancer has been one of the greatest conundrums in the modern medical field. To reduce side-effects associated with the traditional cancer therapy such as radiotherapy and chemotherapy, photothermal therapy (PTT) has been recognized as one of the most promising treatments for cancer over recent years. PTT relies on ablation agents such as nanomaterials with a photothermal effect, for converting light into heat. In this way, elevated temperature could kill cancer cells while avoiding significant side effects on normal cells. This theory works because normal cells have a higher heat tolerance than cancer cells. Thus, nanomaterials with photothermal effects have attracted enormous attention due to their selectivity and non-invasive attributes. This review article summarizes the current status of employing nanomaterials with photothermal effects for anti-cancer treatment. Mechanisms of the photothermal effect and various factors affecting photothermal performance will be discussed. Efficient and selective PTT is believed to play an increasingly prominent role in cancer treatment. Moreover, merging PTT with other methods of cancer therapies is also discussed as a future trend.

Keywords

Nanomaterials; Photothermal therapy; Cancer

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1. Introduction

Cancer is a continuing crisis to public health worldwide due to its mortality and invasion. At present, two commonly used therapies, radiotherapy and chemotherapy, are usually accompanied by broad collateral damage. Drugs for chemotherapy may also cause collateral damage to normal cells via oxidative stress while killing cancer cells [1], and radiation used in the radiotherapy may result in sequelae like radiodermatitis during or after treatment [2]. Consequently, studies on invasive and selective therapies have been hot topics in the medical field. One of the most promising therapies is light stimulation therapy, including photothermal therapy (PTT) and photodynamic therapy (PDT).

Photothermal-induced elevated body temperature could be beneficial for recovery from certain diseases [3–6]. When the body temperature rises, pathogens may slow down growth and the enzymes in viruses may become inactivated because the temperature of the internal environment is no longer optimal for them. Accordingly, the thermal effect has been utilized as an anti-bacterial [7–10] and an anti-cancer [11,12] medical treatment. Thermal treatments against cancer rely on the susceptibility of cancer cells to heat. In other words, heat causes irreversible damage to cancer cell membranes and initiates protein denaturation [7–13]. Compared to normal cells, cancer cells have a lower ability to endure elevated heat [14]; this precondition makes thermal treatment a selective treatment. This means that thermal treatments can be considered a promising and selective treatment for various cancers; this holds especially true for photothermal therapy.

Laser irradiation was applied as a cancer treatment at an early stage; however, heat produced only by an external laser device may burn lesions as well as surrounding healthy tissues [15,16]. This limited selectivity restricted its clinical use. Thus, the photothermal effect used to induce local heating has started attracting great attention. Some nanomaterials called ablation agents can initiate the photothermal effect by absorbing particular light irradiation and converting this energy to heat [17–28]. With the use of ablation agents, it is possible to generate heat in the lesions themselves, making the treatment selective and non-invasive to surrounding healthy tissues. To generate heat internally, the light irradiation utilized should be able to go through healthy tissues without causing any side effect. Unlike ultraviolet light and visible light, near-infrared (NIR) light can penetrate deep tissues while doing relatively mild damage [29–31]. In more detail, the NIR region is known as the biological window [32], where water and biomolecules absorb minimal amounts of light, making NIR advantageous to PTT. On the other hand, the ablation agents should be biocompatible, allowed to congregate in tumors and should be capable of converting NIR light energy to heat effectively. Various nanomaterials can be remarkable candidates as the result of their photothermal effect in the NIR region and passive localization in tumors.

It must be considered that PTT has its own limits. Nanomaterials are able to pass through cancer cell membranes [33], leading to accumulation of nanomaterials in lesions and heightening treatment efficacy. Nevertheless, there may be accumulation of nano-materials in other healthy tissues during and after PTT as well. A concern that still needs further research is the possible long-term cytotoxicity of accumulated and aggregated nanomaterials, since it is still quite difficult to detect and eliminate nanoscale materials. As

for most nanomaterials, the surface property plays a great role in the photothermal effect and other physicochemical properties [34–39]. Surface modification is usually required to satisfy PTT demand and biocompatibility. After surface modification process, nanomaterials used for PTT could own better biocompatibility and greater NIR conversion efficiency, which would avoid side effect from nanomaterials and make it unnecessary to use a large density of laser beyond standard.

Our article will review the development of nanomaterials including noble metal, semiconductor, carbon-based, and conducting polymers for PTT; additionally, mechanisms of their photothermal effect are introduced. At the end of this review article, synergic therapies containing PTT are predicted as promising cancer treatments in the near future. Although the development of individual nanomaterials for PTT has been reviewed by other groups [40–42], this review emphasizes using composite nanomaterials for a greater photothermal effect or synergic light-responsive systems for a better anti-cancer effect.

2. Light-tissue interaction

Light has been applied in the medical field for imaging diagnosis and surgery for quite a long time [43–46]. The invasion of light should be minimized during imaging diagnosis, while operations for lesion removal need the energy of a laser to ‘cut’ the targeted lesion. Both applications are related to the interaction between light and tissues. Thus, it is very important to cognize the interaction between light and tissues. Similar to the situation in an external environment, the reflection, scattering, absorption and transmission of light may occur during the light’s penetration through tissues [47]. Light may affect biological activities by, for example, oxygen consumption [48]. Light irradiation may result in the thermal effect [47] or the catalysis effect [49], which could influence biological activities by changing enzyme activity. Given these realities, interaction between light and tissues should be considered before the use of light in clinical treatments.

The interaction between light and tissues depends on the optical property of tissues and the wavelength of light. Since the optical property of tissues and biomolecules is barely modifiable, selection of light of a particular wavelength for medical use should be the primary focus. As reported [47–49], reflection, absorption and scattering are the main optical activities in the interaction between light and tissues. The absorption of light could accumulate energy from light irradiation, making it a useful tool for lesion ablation during surgery, but unnecessary thermal effect may do harm to normal tissues as well. Moreover, these three optical activities could be detected and used for diagnosis purposes.

Here we will discuss three commonly used lights in different wavelengths, X-ray, ultraviolet light (UV) and NIR; light in these specific wavelengths are used to analyze the interaction between light and tissues. X-ray has been increasingly used since the inception of computed tomography (CT) since the 1970s [50]. Though it is well-known that overexposure to X-rays may increase the risk on patient health, it is still widely used under strict guidelines because of its ability to provide three-dimensional views of deep body structure [51–54]. X-ray regions refer to the wavelength between 0.001 and 10 nm. X-rays have a relatively high frequency and high energy, leading to the high penetrability of X-rays. X-rays are applied in

the scanning of different body structures, for example, bones and soft tissues. The density and thickness of target objects greatly affect the absorption of X-rays, resulting in differentiated images between bones and organs for diagnostic imaging applications. A dual-energy X-ray system, which could produce low and high energy X-rays, is applied for the measurement of bone density [55] or muscle mass [56]. It should be noted that, metal with high density can also be detected by the use of X-rays [57], thus, X-ray systems can be used to monitor ablation agents like gold nanomaterials [57,58]. However, during the interaction between X-rays and tissues, X-rays with high energy could generate primary and secondary electrons, which are considered a major cause of damage in creatures [59]. In more detail, the electron excited by an X-ray may cause the production of radicals, which could result in damage to DNA and the development of cancer [60], therefore X-rays should be used under strict guidelines. As for ultraviolet light, liquid water shows a high affinity for absorption [61]; this indicates that UV can barely penetrate through tissues. Therefore, both the application of and protection from UV is focused on human skin and eyes. UV light could be subdivided into three wavelengths, including ultraviolet A (UVA, 320–400 nm), ultraviolet B (UVB, 280–320 nm) and ultraviolet C (UVC, 200–280 nm) [62]. Similarly, the wavelengths of these UV lights determine their properties. For example, UVA is barely filtered by the ozone layer in the atmosphere due to its long wavelength and low energy, making it the main UV content in sunlight that reaches the earth's surface [62–64]. Among solar radiation, UVA can penetrate relatively deep into skin while UVB can only penetrate the upper layers of the epidermis. UVC can barely go through the ozone layer in the atmosphere or reach the earth's surface, but the high energy of UV light, especially UVC, may lead to burns on the skin or eye [63,64]. Furthermore, long-term exposure of UV light may result in sunburn, aging of skin, erythema, suppression of the immune system of skin, wrinkling, carcinoma and other symptoms. Various methods have been applied to shelter people from sunlight or UV light; conversely, UV light has been employed in phototherapy. As reported, UV light may induce the in vivo production of cytokines, neuropeptides and other natural molecules, which could help improve anti-inflammatory effect or immunosuppressive effects of human skin [65–68]. According to previous research (Fig. 1), light in NIR region has a relatively low absorption coefficient and deep penetration ability [30]. In fact, the NIR region is known as the biological window, where biological systems have minimal absorption [69,70]. Therefore, NIR is considered a useful tool for diagnosis and therapy for deep-seated lesions. According to relevant research [71], in the NIR region the light with longer wavelengths has deeper penetration in tissues. NIR light exhibits a higher level of penetration in tumor tissues than in normal tissues. For example, wavelengths of 630 nm penetrate through normal brain tissue for about 0.9 mm, while the penetration through lung carcinoma is about 1.6 mm. From this information it can be reasoned that NIR light can be used in selective phototherapy [71].

Apart from wavelength, the power of laser light also plays a great role in the interaction between light and tissues. With regard to NIR light (the NIR lasers most commonly used in PTT are 808 and 980 nm), the safe power density limit is $\sim 0.33 \text{ Wcm}^{-2}$ for the 808 nm NIR laser and $\sim 0.726 \text{ Wcm}^{-2}$ for the 980 nm NIR laser according to the American National Standard for the Safe Use of Lasers [72,73]. It is important to note that exposure time and

focal spot size can also affect the interaction. In practical application, all of the above mentioned parameters should be taken into account for safety.

3. Light stimulation therapy

Current anti-cancer treatments, such as chemotherapy and radiotherapy, have severe side-effects [1,2]. These treatments cause damage to normal cells while killing cancer cells. To lower the side-effects of cancer treatment, specific target therapies against cancer cells have been proposed [74]; target therapies like nanomedicines have been widely studied for selectively killing cancer cells [75]. To precisely control the expression of nanomedicine, stimulation-responsive nano-systems have been suggested. Since tumors may be deep-seated, it is a challenge to stimulate nano-systems in lesions and avoid overexpression in normal tissues. Overall, NIR light is considered a fine candidate as a stimulation source; this is because low power NIR light could penetrate tissues deeply without causing serious damage or absorption by body fluids [69,70]. Therefore, NIR induced imaging and selective treatment has recently attracted a lot of attention (see Fig. 2). NIR fluorescence has been applied to diagnosis and labeling due to the high penetrability of NIR light through tissues [76–80]. As for anti-cancer treatment, PTT [81] and PDT [82] are two current NIR-induced therapies and have been applied for causing damage to cancer cells with heat and reactive oxygen species (ROS), respectively. In addition, NIR could induce the photothermal effect, which leads to the transformation of heat-transducing nanoparticles, in order to trigger controllable nano-systems for drug delivery [83].

4. Nanomaterials for photothermal therapy

The current research on ablation agents mainly focuses on nanomaterials. Nanomaterials have many different properties compared to their macroscopic counterparts. It is important to note that the photothermal effect is related to the nanoscale properties of materials. For example, due to surface plasmon resonance (SPR), gold nanoparticles (NPs) are able to convert excited state photon energy into heat [11,84]. In addition, nanomedicines have an advantage in passive tumor targeting during tumor treatment through a mechanism of nanoparticle induced endothelial leakiness (NanoEL) [85–87] or enhanced permeability and retention (EPR) of NPs for immature and mature tumors, respectively. In NanoEL, NPs with a certain size and density would interact with the endothelial cells' adherens junction protein and induce micro-sized gaps between endothelial cells, improving the permeability and accumulation of the nanomedicines [85–87]. The size [34], shape [37] and surface chemistry [38,39] of the NPs play a great role in the bio-compatibility and photothermal performance. In the past, noble metal nanomaterials [26,37], as one of the first PTT ablation agents, were widely studied. In recent years, many new nanomaterials, like nanoarchitected conducting polymers [88–90], have been developed for the application of PTT.

4.1. Noble metal nanomaterials for photothermal therapy

In the past few decades, research on agents for PTT have mainly focused on noble metal nanomaterials, such as platinum-based nanomaterials [91] and gold-based nanomaterials [37,84]. Noble metal nanomaterials have a strong optical absorption property and a relatively high photothermal conversion efficiency without causing quick photobleaching problems;

this is a common phenomenon in the use of organic dyes as ablation agents [92]. As mentioned previously, SPR results in the photothermal effect of noble metal nanomaterials [11,84]. When interacting with light, noble metal nanomaterials convert light energy into heat if their oscillation is resonant at the practical frequency of the light [93]. For instance, M. Manikandan et al. studied the photothermal effect of platinum NPs [91]. They found that platinum NPs with sizes ranging from 5 to 6nm could be used as ablation agents for photothermal ablation of Neuro 2A cells.

Recently, the studies about the use of gold nanomaterials for PTT have attracted attention among noble metal nanomaterials. Gold NPs without modification, for example, have an SPR effect in the region of visible light [11,94]. Pitsillides et al. [94] used 20 ns laser pulses at 532 or 565 nm for the light irradiation. Although these wavelengths were not exactly in the biological window, the short laser pulses were applied to avoid over diffusion of heat. However, the SPR effect strongly depends on the size and the shape of gold nanomaterials according to the Mie theory [34,95], making it possible to shift the SPR wavelength to the NIR region. In order to tune the SPR and enhance the photothermal performance, different gold nanomaterials have been developed (Table 1), including gold nanorods (NRs) [32], gold nanoshells [96] and gold nanohexapods [37].

Gold NRs have two characteristic optical absorptions [97], the transverse and the longitudinal, corresponding to the diameter and the length of the rods, respectively. Thus, by means of adjusting the aspect ratio (i.e., length/diameter ratio), the SPR region could be tuned and shifted to the NIR region for PTT. Link et al. studied the relationship between the absorption maximum resulting from the longitudinal plasmon resonance and the aspect ratio [97]. According to their research, though the transverse plasmon absorption is located in the visible light region like traditional gold NPs, the longitudinal plasmon absorption could be shifted to 740 nm when the average aspect ratio reached 3.3 (Fig. 3). With tunable longitudinal plasmon absorption, the photothermal effect of these gold NRs could be induced by NIR, making it more suitable for medical application.

Apart from the gold nanomaterials with various shapes, dendritic gold nanoparticles have also been studied for possible application on photothermal therapy, because their properties vary according to their hyperbranched nanostructures. The connection between photothermal property and degree of branching of gold nanodendrites has been studied [98]. It is found that the optical property of gold nanodendrites was tunable and the gold nanodendrites with relatively low degree of branching owned better photothermal therapy efficiency within the second NIR window.

Additionally, gold nanomaterials can be employed not only for PTT but also for other medical applications. Gold nanomaterials have been synthesized as drug carriers and imaging contrast agents [99–101], implying their potential role in serving as multifunctional medical agents. A hollow gold nanostructure shape, for example, the gold nanocage, was proposed as a PTT ablation agent with further medical value. The hollow gold nanomaterials possess great NIR absorption for PTT and the unique hollow nanostructure is likely what made them able to act as the drug carriers and/or the contrast agents for imaging [102]. Yavuz et al. [103] covered gold nanocages with a poly(N-isopropylacrylamide)-co-

polyacrylamide polymer coating. When heated by the photothermal effect of gold nanocages, the polymer coating would undergo a phase transition and form open pores, allowing the drugs inside the gold nanocages to diffuse. Wang et al. [104] designed drug-loaded gold NRs for combinational chemo-photothermal therapy against cancer. It was reported that the gold NRs were coated with DNA via the self-assembly method of electrostatic interaction. Hence, the NRs could load DOX. Gold NRs played a role as ablation agents as well as DOX release thermal-trigger in the combinational chemo-photothermal therapy (Fig. 4). Recently, gold-shelled silica NPs [105] and gold-shelled Fe₃O₄ NPs [106] were also proposed. These composites exhibited high optical absorption in NIR region because of the hollow nanostructure of gold nanoshells. In addition, the core composition has the potential to play a great role in further medical applications. For example, the silica nanocores could act as nanosized drug carriers with high thermal stability and the Fe₃O₄ magnetic NPs could help improve thermal performance.

Though noble metal nanomaterials have provided an outstanding photothermal effect for cancer treatment, some problems remain to be solved. For example, gold nanomaterials are non-biodegradable and thus further detection on gold nanomaterials after treatment is necessary. The photostability of gold nanomaterials is also a concern, since some structures are relatively weak due to the ‘melting effect’ [96]. When exposed to NIR irradiation continuously, some specific gold nanomaterials deform and their photothermal effect reduces. Thus, further study on noble metal nanomaterials viability is needed.

4.2. Semiconductor nanomaterials for photothermal therapy

Besides noble metal nanomaterials, some semiconductor nanomaterials, like semiconductor copper chalcogenide nanomaterials [107,108], have gained their recognition as PTT ablation agents by reason of their low cost and low cytotoxicity. However, under the common NIR light of 808 nm, the relatively low photothermal conversion efficiency of some Cu-based nanomaterials may require higher NIR power to achieve tumor ablation. For example, the use of CuS NPs as ablation agents could cause cell death by photothermal effect under the irradiation of 808 nm NIR light as high as 16 and 24 W cm⁻² [108,109]. To surmount this obstacle, NIR light of 980 nm is often selected as an alternative for some Cu-based NPs. 980 nm NIR light proves to be a relatively high limit for human skin exposure and its penetration through biological tissues could reach several centimeters [72,110]. In this aspect, the power of NIR laser could be reduced while the effect of the treatment can be retained.

The size and the shape of Cu-based nanomaterials play a prominent role in the photothermal performance [111–115]. Thus, to improve the photothermal performance of Cu-based semiconductors, adjustment of the size and shape of the Cu-based nanomaterials has been proposed. Hu’s group [116] successfully synthesized CuS NPs with uniform 3-dimensional flower-like morphology, which helped improve the photothermal conversion efficiency. It was hypothesized that such superstructures could serve as the laser-cavity mirrors of a 980 nm laser, leading to the improvement of reflection and subsequent enhancement of photothermal conversion efficiency. They also developed hydrophilic Cu₉S₅ plate-like nanocrystals with photothermal conversion efficiency up to 25.7%, slightly higher than that of gold NRs under the same 980 nm light irradiation [117]. Besides, a self-assembly process

was applied to construct the shuttle-like CuS bundles nanostructures for the better photothermal conversion efficiency (Fig. 5) [118]. Accordingly, when undergoing the self-assembly process, the CuS NPs would form primarily CuS nanorods, and finally shuttle-like CuS bundles. Due to the change of interparticle distance and generation of new electronic structures, the molar extinction coefficient of shuttle-like CuS bundles had a notable increase when compared with the one of CuS NPs, which suggested that the shuttle-like CuS had the better photothermal conversion efficiency than CuS NPs. According to these studies, the nano-architectures of Cu-based materials play a great role in photothermal performance.

In terms of photothermal mechanisms, the NIR light absorption of CuS NPs has been theorized to be intrinsic and derives from the d-d transition of Cu^{2+} . Therefore, the optical absorption property of CuS NPs would not be affected by environment. On the contrary, optical absorption of noble metal NPs would be affected by the environment because it is related to the dielectric constant of the surrounding matrix, which probably results in the difference of maximum absorption peaks between in vivo and in vitro [116]. Since the light absorption ability is derived from the energy band transition of Cu^{2+} , the maximum absorption peak could not be shifted along with the change of particle morphology, but relies instead on the state of the Cu atom. This implies that the enhancement of the photothermal conversion efficiency is related to the 'utilizing rate' of NIR, which may result from the NIR light reflection or other optical behavior. For example, as discussed before, the flower-like CuS superstructure could serve as a laser-cavity mirror for the 980 nm laser [116], which may result in improvements on light reflection and absorption, and finally the rise of photothermal efficiency. Recently, Burda et al. discussed the NIR absorption of Cu_{2-x}S [119]. The optical absorption of Cu_{2-x}S was assigned to the Cu deficiencies, which led to a high density of holes and exhibited strong free carrier absorption. According to their study [119], the NIR absorbance of all samples resulted from free carriers, making it dependent on stoichiometry. Furthermore, along with the decrease of x, the degree of doping decreased, which led to the loss of the available energy band; this process resulted in a drop of absorption intensity consequently (Fig. 6). When x was tuned down to 0, the valence band of Cu_{2-x}S (or Cu_2S) was filled and no free carrier absorption occurred.

As for the practical use of such nanomaterials for PTT, CuS NPs have been used in research involving the effects of PTT on Hela cells [108]. The dependent effect of the laser dose and CuS particle concentration was then studied. In this research, though a NIR laser (808nm) as high as 24 W cm^{-2} was applied, relatively specific cancer killing was achieved. The NIR laser or CuS NPs alone showed mild effect on killing cells. In addition, the low cytotoxicity of CuS NP was verified individually in this research, implying that CuS NP-induced PTT was non-invasive for normal cells. Moreover, modified $\text{Cu}_{7.2}\text{S}_4$ nanocrystals with a photothermal conversion efficiency of up to 56.7% were prepared [120]. Such $\text{Cu}_{7.2}\text{S}_4$ nanocrystals were capable of killing cancer cells efficiently by a low dose concentration and with a low power 980 nm laser. With specific ablation effect, low cytotoxicity and low cost considered, CuS NPs could be applied for PTT as an exceptional ablation agent [108,118,120].

Still, there are some concerns on the PTT use of Cu-based nanomaterials. As reported, some Cu-based nanomaterials require a high powered NIR laser when the stimulation wavelength

is 808 nm, which explains why studies have started focusing on PTT with 980 nm NIR. However, 980 nm NIR can be absorbed by water, which means temperature elevation will occur in exposed tissues, healthy or not, under 980 nm NIR without ablation agents. It was reported that temperature elevation of a PBS solution was about 10 °C under irradiation of 980 nm NIR light with a power density of 0.7 W cm⁻² [73]. It is a lurking peril that needs to be investigated before the practical use of 980 nm NIR laser in PTT can be implemented.

4.3. Carbon-based nanomaterials for photothermal therapy

Carbon nanotubes (CNTs) have drawn tremendous attention in the optoelectronics industry [121,122]. Recently, due to the optical properties and excellent thermal behaviors [122,123], CNTs have been studied in the medical fields for use in thermal treatment [124,125]. Applications of CNTs in the medical field have included drug carriers [126,127] and bioimaging probes [128,129]. CNTs can also be either covalently or noncovalently modified with different chemical groups. By binding or wrapping, CNTs can be easily functionalized with other medical molecules [130], like magnetic NPs [131] and anti-cancer drugs [132]. In this way, the photothermal performance of CNTs could be improved and synergic therapies can be developed.

Various factors, like size, dose, surface chemistry and elemental components, are relevant to the toxicity of nanomaterials, including CNTs [133–135]. As mentioned previously, CNTs can be modified with different surface chemical properties, making them valuable for the catalysis industry [136], but it's possible for CNTs to produce a high dose of toxic compounds [133,135]. Therefore, surface functionalization for a decrease in toxicity must be addressed.

Like other ablation agents [107,137], carbon-based nanomaterials are usually functionalized by PEG coatings. Generally speaking, PEG coatings can help improve biocompatibility, avoid aggregation and prolong blood circulation time [138,139], which is considered as advantageous in nanomaterials applied as ablation agents. Liu et al. [38] investigated the effect of a PEG-PMHC₁₈ coating on PTT using single-walled carbon nanotubes (SWNTs). It turned out that the polymer coating played a substantial role in extending the blood circulation half-life of the SWNTs, which is related to the biodistribution of the SWNTs. It was found to be noteworthy that with the extension of the blood circulation half-life, the SWNTs tumor uptake increased while the SWNTs skin uptake also showed increasing trends (Fig. 7). Such instances as an increase of SWNTs in skin uptake may possibly cause skin damage and reduce treatment efficacy, though high tumor uptake was thought to be positive for the treatment. Therefore, it was highlighted that adjustment of blood circulation half-life needed greater attention for the balance of SWNTs uptake.

To demonstrate the mechanism of PTT mediated by CNTs, Burke et al. [140] characterized the response of breast cancer stem cells (BCSCs) to hyperthermia using water bath or photothermal effect induced by multi-walled carbon nanotubes (MWNTs). It turned out that across a range of temperatures BCSCs were resistant to hyperthermia; but the photothermal effect induced by multi-walled CNTs could overcome the resistance by promoting necrotic cell death. This was hypothetically theorized from the interaction between cancer cell membranes and NIR-stimulated MWNTs with high surface temperature.

Graphene, a planar sheet of carbon atoms, is a relatively new carbon nanomaterial with excellent mechanical and physical properties [141–143]. Gradually, the application of graphene as an anti-tumor option has been demonstrated as better understanding has been obtained [144–147]. Similar to CNTs, graphene-based nanomaterials have a strong optical absorption in NIR region as well as high surface activity [148–151], making it a promising PTT ablation agent with the potential use in the synergic therapies. To clarify the mechanism of PTT induced by graphene, Markovic et al. [152] analyzed the type of cell death resulting from graphene-induced PTT. According to their characterizations, cells died by both necrosis and apoptosis. Despite necrosis, the general cell death modality triggered by PTT, hyperthermia would potentiate oxidative stress/superoxide production and finally cause apoptosis as well (see Fig. 8).

Overall, both CNTs and graphene have shown similar features. Their surface activities could result in further functionalization as well as harmful degeneration in contrast. Thus, both CNTs and graphene need further modification to be functionalized for synergic therapies. As for the mechanism, it has been suggested that photothermal effects mediated by CNTs and graphene could result in necrosis and apoptosis, showing greater anti-cancer effect when compared with single hyperthermia.

4.4. Conducting polymers for photothermal therapy

The conducting polymers (CPs), such as polyaniline (PANI) [153,154] and polypyrrole (PPy) [155], have been used in bioelectronics and biomedical applications. In addition, their optical absorption abilities make it possible to employ CPs for use in PTT. CPs as a PTT ablation agent has attracted significant attention, because they show lower cost than noble metal nanomaterials and better biocompatibility than inorganic nanomaterials [156–158]. The mechanism to induce the photothermal effect of CP-based nanomaterials is thought to be quite different from the inorganic nanomaterials. When excited by specific light stimulation, a bio-polaron is formed that subsequently decays into a photon band while generating heat [159,160]. Furthermore, nanoarchitected CPs could shift their optical absorption peak during the doping process [161–163]. In more detail, dopants would help generate an interband gap that could finally result in the change of the excitation-energy level, which is often applied to improve the conductivity of conducting polymers. It is suggested that such a doping process would also change the optical properties of CPs. For example, the water soluble PANI NPs were synthesized by the chemical oxidative polymerization method and the doping-dedoping process [164]. According to this research, the PANI NPs could result in tumor ablation when under the irradiation of NIR. The NIR absorption ability of these PANI NPs was dependent on pH. Moreover, the transformation of PANI NPs from the emeraldine base state to the emeraldine salt state during NIR stimulation was confirmed (Fig. 9). It has been reported that these CPs can convert the NIR light energy into heat. However, as some studies mentioned [164,165], the photothermal conversion efficiency of PANI was relatively low and bare Poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) NPs were found to be toxic to cells. Therefore, some modifications like PEG-coating [165] have been utilized and more novel CPs-based nanomaterials are under research.

To improve the performance of PEDOT:PSS NPs, Cheng's group synthesized PEG-coated PEDOT:PSS NPs [165]. Their research demonstrated that these NPs owned a long blood circulation half lifetime (21 h) and a high tumor uptake (28%), resulting in an impressive effect on tumor ablation according to the in vivo experiment. Recently, PPy nanomaterials have been utilized as a PTT ablation agent. Among the CPs, PPy nanomaterials have a relatively fine biocompatibility and have been studied in medical fields as biosensors and neural probes [144,166–168]. PPy nanomaterials have fine photostability and high photothermal conversion efficiency. As reported, sub-100 nm PPy NPs showed strong optical absorption at 808 nm ($2.38 \times 10^{10} \text{M}^{-1} \text{cm}^{-1}$) and a high photothermal conversion efficacy (44.7%) [89]. Dai's group [88] studied the cancer cell ablation ability of PPy NPs. They synthesized uniform PPy NPs with average size of 46 nm via aqueous dispersion polymerization. In vitro study showed that Hela cells incubated with PPy NPs were destroyed when exposed to the irradiation of NIR (Fig. 10). These studies demonstrate that PPy NPs could work as an ablation agent to offer a selective therapy with low side effects.

PPy is relatively biocompatible, stable and easily synthesized [166–168]; thus, PPy could be an outstanding candidate as polymer coating for other nano-drugs. As mentioned previously, gold NPs have a strong SPR effect in the region of visible light, but not in the exact NIR window without further modification. It limits the use of gold NPs in PTT. To tune the responsive region to NIR, PPy-coated chainlike gold NP architectures were produced [169]. This PPy-gold composite had greater photothermal transduction in the NIR region and showed specific effect in inhibiting tumor growth (Fig. 11). Regarding this study as an example, PPy nanomaterials could be used as a photothermal coating for synergic treatments or multiple PTT.

In a conclusion, CP-based nanomaterials have shown remarkable photothermal abilities and potential use in clinical PTT due to their high photostability. Similar to gold-based nanomaterials, nanoarchitected PPy nanomaterials could work as drug carriers. Alternately, various synthesis methods, like chemical oxidation [88] and electrochemical deposition [170], were applied to synthesize nanoscale PPy-functionalized coating for enhanced medical systems. Thus, PPy nanomaterials could work as outstanding ablation agents as well as accessories for modified medical systems involving synergic therapies.

Overall, the nanomaterials as ablation agents cover noble metals, semiconductors, carbon-based materials, conducting polymers and so on (Table 2). The diversity makes it possible to fabricate composite ablation agents with different nanomaterials for greater photothermal effect.

5. Further development of photothermal therapy

Traditional therapies like radiation therapy and chemotherapy have been clinically used in cancer treatment [171–173] whereas PTT is a relatively new method showing great promise for anti-cancer capabilities. However, because the power of light may decrease along with the penetration through tissues, the therapeutic effect of PTT may decay in practical use [174]. Therefore, for a thorough cure, it's reasonable to combine PTT with traditional therapies. Here we emphasized the synergic therapies containing PTT and other therapies.

First of all, synergic therapies help lower side effects because the dose of each therapy can be reduced, while the total treatment effect can be maintained [175–177]. Interaction among therapies could lead to greater efficiency; for example, heat produced by the photothermal effect could improve the effect of some anti-cancer drugs [176,177]. The thermal effect, called hyperthermia in medical fields, may not directly cause tumor ablation by heat, but could improve the efficiency of other therapies. Furthermore, some nanomaterials as ablation agents, like CP based nanomaterials and gold nanomaterials, which could be stimulated by electricity [178] or irradiation [179], could work as controllable carriers for anti-cancer drug delivery. Thus, many nanosystems have been fabricated for synergic therapies and some actively responsive nanosystems have been developed.

5.1. Imaging guided photothermal therapy

PTT can be initiated after the ablation agents are associated with the tumors through the mechanisms such as EPR or NanoEL. To detect the distribution of ablation agents and assess PTT performance on tumors, real time imaging techniques are needed.

X-ray imaging is a traditional tomographic method for diagnosis of various pathologies [180], including cancer. In some cases, when noble metal nanomaterials are applied as the ablation agents, X-ray imaging is available for PTT performance observation. Metals with a high atomic number (e.g. gold) can be detected by X-ray [181]. Other than X-rays, a number of imaging techniques have been applied for diagnosis. Although the images have a lower resolution, ultrasound imaging still has some advantages over other techniques [182–184]. Ultrasound imaging provides a low-cost and portable way for diagnosis. More importantly, ultrasound could provide instant, dynamic and multidimensional images, making it suitable for locating the PTT ablation agents and observing the ablation of tumors in real time. Contrast agents are necessary for ultrasound imaging, but not all ablation agents can act also as contrast agents and be observed by ultrasound imaging. Gold nanoshells [185] and PPY hollow microspheres [186] can be used as both ablation agents and contrast agents for ultrasound imaging simultaneously. These agents have hollow structures similar to microscale bubbles [187], the traditional contrast agents for ultrasound imaging due to their oscillation at the practical ultrasound wave. Recently, research has paid great attention to the combination of photoacoustic (PA) detection and PTT [188–190]. PA is a promising imaging method because it is non-invasive and has the capability to image deep biological tissues [191–194], where tumors are usually located. More importantly, NIR could be chosen to induce ultrasound signals in PA imaging [189]. Thus, it is possible to use NIR to induce photothermal effect as well as gain tumor ultrasound images, potentially achieving PA-guided PTT [195]. TaO_x@PPy NPs with a core-shell structure was proposed for more precise detection by PA [196]. PPy shells would act as an ablation agent as well as the PA contrast agent while the TaO_x core operated as an X-ray computed tomography (CT) contrast agent. In this way, bimodal imaging guided PTT could be applied (Fig. 12).

Apart from radiographing, surface-enhanced Raman scattering (SERS) assays have gained great attention in imaging guided PTT [197–199]. SERS can label and detect cells through NIR laser stimulation, making it a noninvasive detection method. Cai's group [200] reported an aptamer-Ag-Au shell-core nanomaterials; the aptamer was applied in this research to

distinguish A549 cells (lung adenocarcinoma cells) from normal tissue. These shell-core nanomaterials could detect A549 cells through SERS signaling, leading to the success in monitoring the PTT induced by the Au core (see Fig. 13).

Many strategies have been proposed to achieve imaging and monitoring of PTT. SERS is considered the most promising one for practical use as it shows many advantages [200]. For example, SERS could detect targeted cells with the use of a specific aptamer. Furthermore, SERS imaging could be stimulated by NIR laser, which may cause relatively mild damage to tissues compared to X-rays. Different from NIR-based fluorescence imaging, NIR SERS imaging makes it possible to detect cancer cells as well as eradicate them with PTT simultaneously with same laser source. NIR SERS imaging could be applied as a dye-free method [201], which allows it to avoid the photobleaching problem. Therefore, we emphasized NIR SERS imaging as a promising imaging method for guiding PTT (see Fig. 14).

Modification on ablation agents for imaging during PTT has been proposed; detecting and tracking these nanomaterials after PTT is also needed because most nanomaterials as ablation agents (e.g. gold NPs, PPy NPs) are non-biodegradable. Observation on the metabolism and excretion of these ablation agents is necessary to avoid a potential bio-hazard. However, the follow-up survey on the toxicity of nanomaterials is usually by histological analysis. Imaging methods for real-time tracking on nanomaterials after treatment have been seldom reported. Therefore, real-time imaging and detection of nanomaterials after PTT is a topic that must be studied in order to gain a better understanding of the long term effect of these ablation materials.

5.2. Hyperthermia for improving traditional therapy

Thermal therapy can be divided into two categories. The first one is the aforementioned PTT, a treatment of ablating cancer cells by heat directly. The second one, called hyperthermia, is usually by heating below 44 °C; cell ablation is not fully expected in hyperthermia. It is applied to induce 'fever', elevated locally or throughout the whole body, in order to boost the treatment [202–206]. The traditional cancer treatment may cause severe side effects, for example, chemotherapy and radiotherapy kill cancer cells and normal cells at the same time. With the development of the treatments including hyperthermia, the therapies mentioned above could be improved [207–209]. Hyperthermia can enhance the effect of drugs or irradiation, resulting in improved therapeutic effect or reduced dose. For example, gold NRs were applied to induce localized mild hyperthermia [210]. This treatment could increase vascular permeability, in order to enhance transport of macromolecules for chemotherapy [210] (see Fig. 15). In the application of hyperthermia on anti-cancer treatment, heat is usually produced by photothermal agents, such as the nanomaterials capable of selectively locating and accumulating in tumors. The locally elevated temperature makes tumors more sensitive to these therapies while surrounding healthy tissues suffer mild effects. Nanomaterials with photothermal effects can act as a heat-triggered drug delivery system, making it possible to control drug release [211]. It is reported that a photo-responsive protein-- graphene-protein (PGP) capsule was constructed for heat-triggered drug delivery, which induced an enhanced therapeutic effect [212]. This

work shows that such capsules could work as drug carriers with controllable delivery characteristics, improving the cell uptake of the capsule and release of the drug. The interaction of heat and drugs improved cellular drug uptake and DNA damage [212]. In summary, hyperthermia is a common phenomenon in the application of ablation agents during PTT. It is an important characteristic to consider when designing a responsive drug delivery system and a prerequisite for the synergic therapies with PTT.

5.3. Photothermal-photodynamic synergic therapy

Both PTT and PDT are medical treatments induced by light. Under light irradiation, PDT agents could be activated and form singlet oxygen, which is cytotoxic to cells nearby due to oxidative stress [213–215]. In PDT, in terms of penetration, the NIR region is highly desired [216–218], similar to PTT. Therefore, a synergic therapy consisting of PTT and PDT could be an efficient treatment for cancer. Some PTT agents, such as gold NPs [82], could act as PTT ablation agents and the carriers of PDT agents simultaneously. Since singlet oxygen has a short half-life and relatively narrow diffusion range [219,220], the PDT agents should be ideally transported to the subcellular level before treatment. Hence, PTT agents would improve the efficiency of PDT.

A nanosystem for photodynamic-photothermal synergistic therapy was proposed [221]. Specifically, methylene blue (MB), a traditional PDT drug, was combined with magnetic core-plasmonic shell nanoparticles (Fig. 16). The magnetic core served as an imaging contrast agent whereas the plasmonic shell, known as a gold nanoshell in this study, worked as a PTT ablation agent. The study demonstrated that this nanosystem resulted in NIR-induced photodynamic-photothermal synergistic therapy.

In addition, Guo et al. [222] proposed an innovative way to transport PTT and PDT agents for the photothermal/photodynamic synergic therapy. They used micelles to load Ce₆ (PDT agents) and Cypate (PTT agents). Such a system could translocate both agents into subcellular environments while working as contrast agents for PA imaging and near-infrared fluorescence imaging (Fig. 17). This research developed a multi-functional platform for a dual imaging-guided and synergic light-induced treatment. Recently, Kalluru et al. [223] reported that nano-graphene oxide decorated with PEG and folate could produce singlet oxygen and achieve temperature elevation as well when under the irradiation of NIR (980 nm) light. Their work could shed light on the application of PTT-PDT synergic therapy with the use of one single photo-sensitive agent.

Although PTT and PDT could be applied simultaneously with one NIR light source, theoretically, there are some unsolved problems. First, there is a possibility that the maximum absorption wavelengths among the NIR region of PTT agents and PDT agents are not exactly the same. NIR light with a single wavelength can't fully induce both the photothermal effect and photodynamic effect at the same time, while broadband NIR light may bring an unexpected negative effect. Synergic therapies combining PTT and PDT are supposed to provide a better therapeutic effect. However, since both treatments are NIR-induced, it may be difficult to target deeply seated tumor due to the decrease of NIR during the penetration through tissues. In this case, these synergic therapies may be a total failure with inefficient NIR irradiation.

5.4. Photothermal-immuno/chemo synergic therapy

Like PTT, immunotherapy is a promising treatment for cancer. Unlike the traditional treatments such as radiotherapy and chemotherapy, immunotherapy relies on the immune system of patients themselves rather than external, fierce stimulation [224–226]. Cancer cells suppress the immune system, for example, by reducing T cells stimulation [226,227], so that the immune system is unable to respond efficiently. Immunotherapy aims at inducing an immune anti-cancer response by delivering vaccines or adjuvants. As for chemotherapy, the biggest challenge is to lower its side-effects. Targeted therapy is thought to be a useful strategy; therefore, it is reasonable to functionalize ablation agents with chemotherapy drugs, because ablation agents in nanoscale would passively target tumors through NanoEL or EPR effects for immature or mature tumor, respectively. In this case, drugs could also be delivered into tumors and reduce damage to normal tissues.

Since both ablation agents and immuno/chemo medicines have greater therapeutic effect when inside a tumor, a lot of research is focused on the development of a nanosystem for drug delivery. Chen's group [228] invented nanocookies as a drug delivery nanosystem and applied this nanocomposite for synergic photo-chemothermal therapy (Fig. 18). This nanocomposite contained mesoporous silica as a drug carrier and amorphous carbon for improving drug delivery capacity. Alternatively, reduced graphene oxide and (S)-(+)-camptothecin (CPT) were used as PTT agents and anti-cancer drugs, respectively. Further experimentation showed that this nanocomposite had a remarkable efficacy for killing cancer cells.

Since some ablation agents could be applied as drug carriers, direct functionalization on ablation agents with anti-cancer drugs for synergic therapies was proposed. For example, Wang et al. [132] synthesized polyethylenimine functionalized single-walled carbon nanotubes with the remarkable sustained-release effect of doxorubicin (DOX). Carbon nanotubes in this study worked as a NIR-induced drug carrier. To achieve tumor immunotherapy and chemo-photothermal therapy, gold NRs were also applied as an ablation agent as well as a carrier for cytosine-guanosine (CpG) oligodeoxynucleotides (ODNs) and DOX by conjugation [209]. Zandberg et al. [229] demonstrated the photothermal-induced release of small molecules from gold NPs in live cells. In this study, as a model drug, a fluorescent dye was anchored on the surface of gold NPs. Heat induced by photothermal effect of gold NPs triggered the release of the fluorescent dye, the fluorescent appearance of cells would change and the success of the photothermal effect can then be detected. Furthermore, when real anti-cancer drugs are anchored on gold NPs, a nanosystem combined with ablation agents and controllable drug carriers for synergic therapy can be achieved.

In conclusion, the synergic therapy with photothermal and immunotherapy/chemotherapy is not only a simple accumulation of these treatment's effects. First of all, hyperthermia caused by the photothermal effect could improve the treatment effect of immunotherapy/chemotherapy. Secondly, some ablation agents could be used as drug carriers, so it is reasonable to functionalize ablation agents with other anti-cancer drugs. This allows the blood circulation time of anti-cancer drug to be extended while ablation agents could be functionalized for other needs, such as better biocompatibility and specificity targeting.

Moreover, when ablation agents work as drug carriers, their photothermal effect could make them a temperature responsive drug delivery system. These coupled therapy options provide prospective options for the future that should continue to be investigated and developed.

There are more and more nano-systems being constructed for synergic therapies with PTT. The main purpose is to (1) monitor the process of tumor ablation during PTT treatment, (2) improve the therapeutic effect with the use of PDT or chemical drugs and (3) improve the selectivity of the ablation agents to targeted lesions. For example, gold-coated Fe₃O₄ nanoroses, is another model that is being researched [230]. The nanoroses possess five medical functions for anti-cancer treatment, including magnetic resonance imaging (MRI), optical imaging, integrating aptamer-based targeting, PTT and chemotherapy (see Fig. 19). Though more specific clinical experiments are needed to verify their potential clinical use, this study highlights the importance of the combination of targeting, real-time imaging and synergic therapies against cancer.

6. Challenges

The cytotoxicity of foreign matter, especially the one on a nanoscale, must be investigated before practical use can be explored. The ablation agents for PTT are no exception; especially since most of the ablation agents mentioned above are non-biodegradable. As a matter of fact, the cytotoxicity of nanomaterials has been one of the greatest concerns when incorporating nanomaterials into medical use [231,232]. First of all, compared with their macroscopic counterparts, nanomaterials can pass through skins, blood vessels and cell membranes easily, making them hard to track or detect; consequently, the cytotoxic nanomaterials could enter systemic circulation and reach end organs [233,234]. Secondly, nanomaterials may exhibit high surface activity due to the surface effect [235–237], which may make them easily modified by toxic compounds and harmful for cells through inflammation or production of ROS. As mentioned previously, CNTs may pose a health risk due to their surface effect. According to the pulmonary toxicity investigation [135], CNTs are more toxic than carbon black to lungs, indicating that the airborne CNTs could become a biological hazard under certain conditions. It has also been found that two commercially available carboxylated SWNTs are significantly cytotoxic [133]. The examples above suggest that CNTs must be prepared cautiously and assessed before medical use. As for gold nanomaterials, cytotoxicity of gold nanoparticles has been studied widely since they are one of earliest candidates for PTT and other medical uses. Though studies [238,239] have indicated certain kinds of gold NPs taken up by cells will not cause acute cytotoxicity, there have been conflicting opinions suggesting that the cytotoxicity of gold NPs is size dependent [240]. Thus, in order to synthesize gold NPs with low cytotoxicity, precise control of particle size is mandatory. Conversely, changes of size/shape of gold NPs could greatly affect the photothermal effect of such nanomaterials [34,37]. Therefore, we can conclude that precise synthesis and modifications to gold NPs in order to lower their cytotoxicity while maintaining or improving their photothermal effect is a great challenge. Among conducting polymers, PPy nanomaterials are considered promising candidates for PTT, due to the biocompatibility of PPy. According to the research of Zheng's group [89], histological analysis showed that PPy NPs caused no noticeable damage to the liver, spleen or kidney after acting as ablation agents in tumor-bearing mice. Although some nanomaterials when

used as ablation agents have been proven harmless or accumulated in liver and spleen through histological analysis, long-term observation for the tracking of nanomaterials and the toxicity to host is still needed. To improve the biocompatibility of ablation agents, it is common to functionalize the nanomaterials with safe coatings. For example, PEG coatings have been widely studied on the functionalization on nanomaterials [38,139], because some medical use of PEGs and medicines developed with PEGs have been approved by the Food and Drug Administration (FDA). Such coating strategies could lower the core material's cytotoxicity but maintain their photothermal efficiency. It may also help prolong blood circulation time [139], improving the PTT effect. Although such modifications may lower cytotoxicity of ablation agents in PTT, enhanced ability to detect ablation agents is still needed in order to observe the metabolism and excretion of these ablation agents.

The surface properties of nanomaterials also affect medical performances other than biocompatibility as well. Nanomedicines could passively target immature or mature tumors through the NanoEL or EPR effect [85–87], respectively, and unstable nanomedicines may aggregate during blood circulation. The increase of size may result in the detection or absorption of ablation agents by the immune system. Moreover, the change of size may also affect the photothermal efficiency [34,37] and cytotoxicity [240]. Or even worse still, aggregation may block blood vessels, which can cause safety concerns to rise [241]. Therefore, with the unexpected increase of size, nanomedicines like ablation agents may become invalid. Under ideal circumstances, the diameter of nanomaterials should be between 20 and 100 nm [242–244], in order to avoid filtration by kidney and clearance by the reticuloendothelial system (RES). To synthesize stable nanomaterials with good aqueous dispersion, surface coatings, such as PVP ligand [241] and silica shell [245] have been applied for surface modification of nanomaterials. Furthermore, the surface properties play a great role in the medical performance of ablation agents, because surface properties, such as hydrophilicity [246,247] and surface charge, [248] affect the blood circulation time of ablation agents. In more detail, hydrophilic surfaces prevent interaction and absorption by proteins and clearance by RES [249–251]. Similarly, the surface charge also affects absorption by proteins and recognition by macrophages; it has also been reported that macrophage uptake increases with the increase of absolute value of the zeta potential of ablation agents [244,252–254]. It has been suggested that prolonged blood circulation time results in a greater chance of ablation agent accumulation in tumorous tissue before elimination of ablation agents by RES [244]. In this aspect, ablation agents with the capacity to meet the requirements above can be applied to achieve effective tumor uptake, and the risk of safety problems may decrease. Therefore, surface properties of nanomaterials for PTT should be modified and assessed before medical use.

Besides, the tumor-targeting ability of nanomaterials should be emphasized. It is a common understanding that ablation agents attached with or internalized in cancer cells will lead to greater therapy efficiency than those around the lesion. To increase the amount of the effective ablation agents is beneficial to avoid over dose of nanomaterials or NIR laser. Various methods were studied to induce greater the EPR effect for better accumulation of anti-cancer agents in tumor, such as surface charge adjustment [255,256] and the generation of nitric oxide (NO) [257]. Based on the relative results above, researchers started to focus on the surface modification and the NO release system on anti-cancer agents, in order to

enhance the EPR effect and improve the therapeutic efficacy. However, the EPR effect has its own negative consequences. For example, since the EPR effect is related to the nutrients and oxygen transport, the over expression of the EPR effect could facilitate tumor growth [258]. Therefore, there is a need in a novel method to improve ablation agent accumulation in tumor for better therapeutic efficacy through NanoEL or EPR [85–87]. Moreover, to achieve this goal, we proposed a strategy for delivering the anti-cancer agents with the use of mesenchymal stem cells (MSCs) as a drug carrier [259]. It has been accepted that MSCs own a natural high tumor affinity. Besides, MSCs can be obtained from patients and re-implanted without immune rejection, which is an enormous advantage compared with the artificial compounds. By using MSCs to deliver photosensitizers, the tumor growth was inhibited after PDT treatment. It is reasonable to assume that such MSCs carriers could be applied to load different anti-cancer drugs, including the photosensitizers and ablation agents. This work may shed light on a novel approach to improve the targeting and accumulation of ablation agents in tumor. Specifically, bio-carriers could be fine candidates to help delivery of the ablation agents. Moreover, we introduced another strategy for anti-cancer drug delivery with the use of bacteriophage as a bio-carrier [260–263]. In one of these works, filamentous bacteriophage was considered as a nanowireshaped carrier that genetically displayed cancer-targeting peptide and chemically conjugated with photosensitizers (Fig. 20) [260]. In this way, targeted PDT with a bio-carrier was achieved. Such a strategy was also applied on gold NPs, the nanomaterials used in PTT [264]. Therefore, we could draw a conclusion that biological systems can be used as carriers of ablation agents.

As for light sources, as mentioned previously, the safe limit of power density should be taken in to consideration. It should be noted that absorption of NIR light by tissues may occur, this situation may lead to the reduction of NIR light power and unexpected thermal effects. For example, it was reported that under irradiation of a 980 nm NIR light with a power density of 0.7 Wcm^{-2} , the temperature of PBS solution rose $10 \text{ }^\circ\text{C}$ [73], inferring absorption of 980 nm NIR light by PBS solution. In this case, the temperature elevation could also occur on normal tissues and the targeting function of PTT may become invalid. Moreover, though NIR light has been seen as a non-invasive light with high penetration, NIR light energy decreases along with the penetration through tissues due to light scattering and absorption, leading to lowered therapeutic efficacy [174]. To make up for the losses of therapeutic efficacy, synergic therapies combined with PTT and other light stimulation therapies have been studied [132,221,222,265].

7. Conclusion and perspective

Many nanomaterials have been introduced into PTT, showing great promise for this selective and non-invasive cancer treatment. Though the experiments are still in the early stage, some biological research for PTT has shown welcome results. Although the mechanisms of all these ablation agents are quite different, it was found that the photothermal effect could usually be tunable by adjusting the shape and the size of PTT agents. On one hand, with many promising candidates and ablation agents for PTT and with the use of nano effects, we may be capable of synthesizing a compound with better photothermal efficiency for PTT. On the other hand, the potential threat of nanomaterials to patients and the environment should

not be ignored. As for the safety of the PTT agents, though different methods, such as PEG-coating, have been applied, the limitations of solubility, hydrophilicity and aggregation are still uncertain in the complicated internal environment. Precise modification to satisfy both good biocompatibility and high photothermal efficiency remains a great difficulty. Like other medical studies on nanomaterials, the tracing of nanomaterials after treatment is challenging, so an advanced technology for tracking and researching the nanomaterials over a long-period in the patients is needed. Furthermore, it is worth noting that not all ablation agents described in this article were stimulated by a NIR source with safe power according to safety limit from the American National Standard. Inappropriate light for stimulation may result in severe absorption by water and lower PTT efficiency against tumors.

In conclusion, PTT continues to be developed for clinical applications. In the near future, PTT will probably satisfy the need for anti-tumor treatments and safety concerns will be eliminated. Nevertheless, to improve curative effects, the future work should focus on PTT integration into synergic therapies. The PTT ablation agents themselves also need further evolution to become multifunctional. As introduced previously, some PTT ablation agents possess the potential to work as contrast agents or drug carriers. In this way, real-time imaging PTT or PTT combined with chemotherapy could be achieved. According to these studies, synergic therapies containing PTT could be realized in order to avoid over-dosing concerns or secondary treatments, and achieve better anticancer abilities. Photothermal nanomaterials and their applications have been widely studied and some positive results have been emphasized. Potential synergic therapies with PTT should be valued in the future.

Acknowledgements

This work was supported by the National High Technology Research and Development Program of China (863 Program) (2015AA033502), the National Natural Science Foundation of China (51541201 and 51673168), National Key Research and Development Program of China (2016YFA0100900), Science and Technology Planning Project of Guangdong Province, China (2014A010105048), the Natural Science Foundation of Guangdong Province (2015A030313493, 2016A030308014) and State Key Laboratory for Mechanical Behavior of Materials, China (Grant No. 20141607). YZ and CBM also thank the financial support from National Institutes of Health (CA200504, CA195607, and EB021339).

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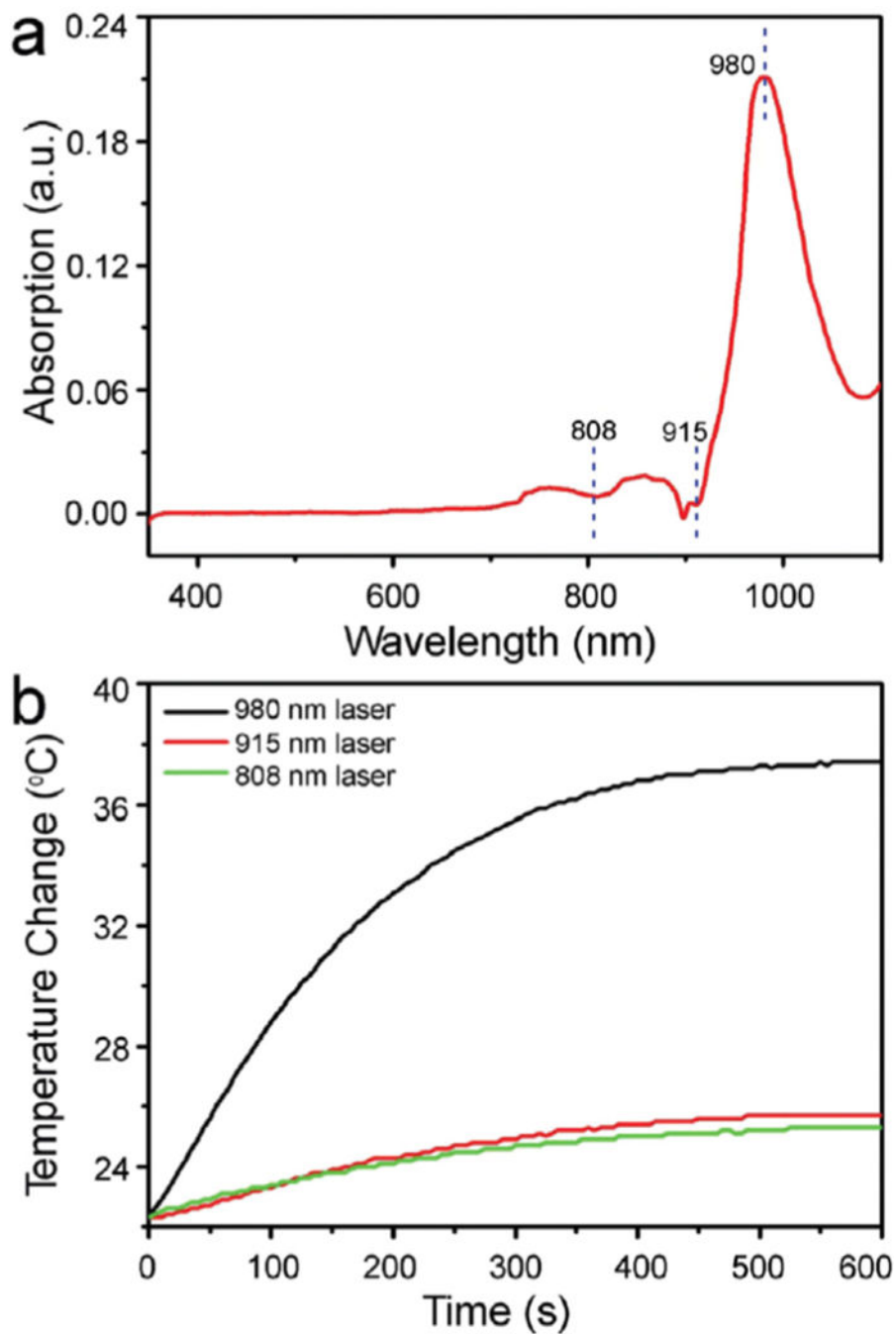


Fig. 1. (a) UV-vis absorption spectrum of the pure water. (b) Temperature elevation of the pure water under the irradiation of 808 nm, 915 nm and 980nm lasers with the same power density of 1.0Wcm^{-2} for 10min [73].

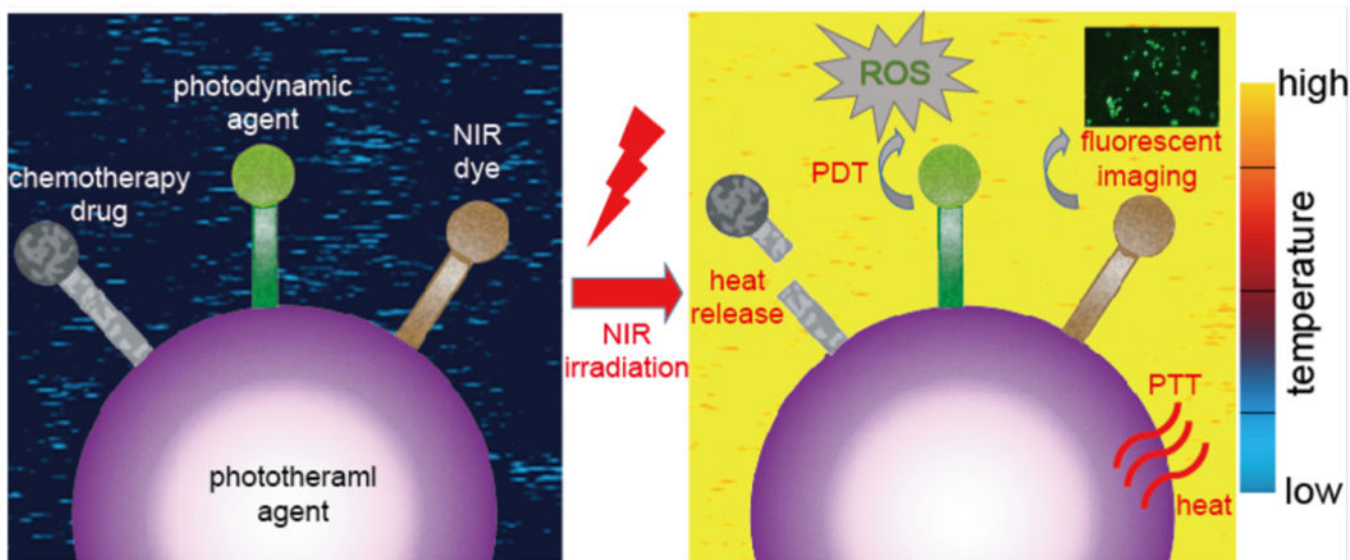


Fig. 2. Schematic illustration of photothermal therapy and the synergistic medical applications combined with photothermal therapy and other light-induced treatment, such as light-induced release of drugs for chemotherapy, photodynamic therapy and NIR fluorescent imaging. The color of background indicates the change of temperature during the photothermal therapy according to the color map on the right.

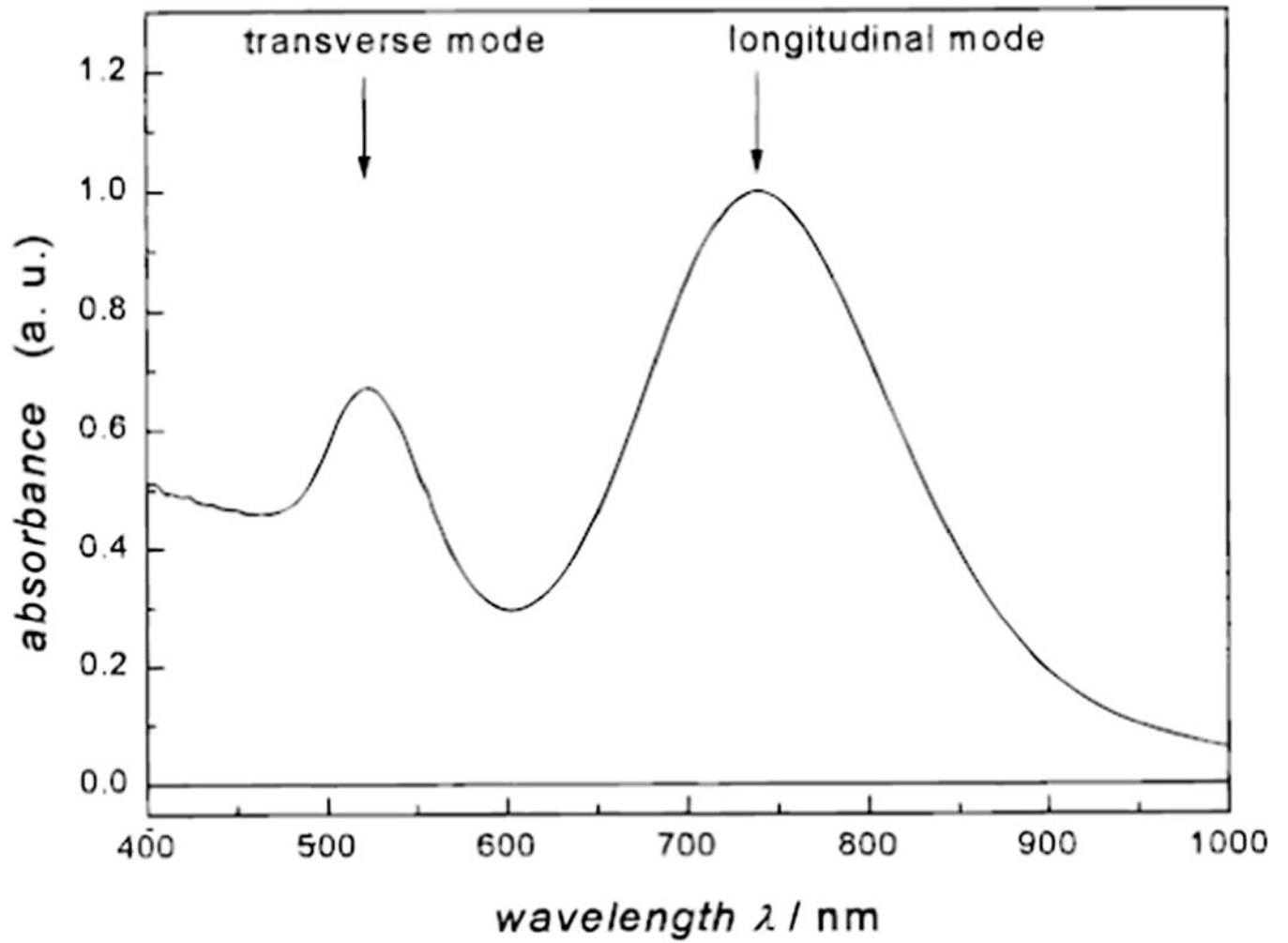


Fig. 3. UV-vis absorption spectrum of gold nanorods with an average aspect ratio of 3.3. The band at 740 nm is referred to as the longitudinal plasmon absorption [97].

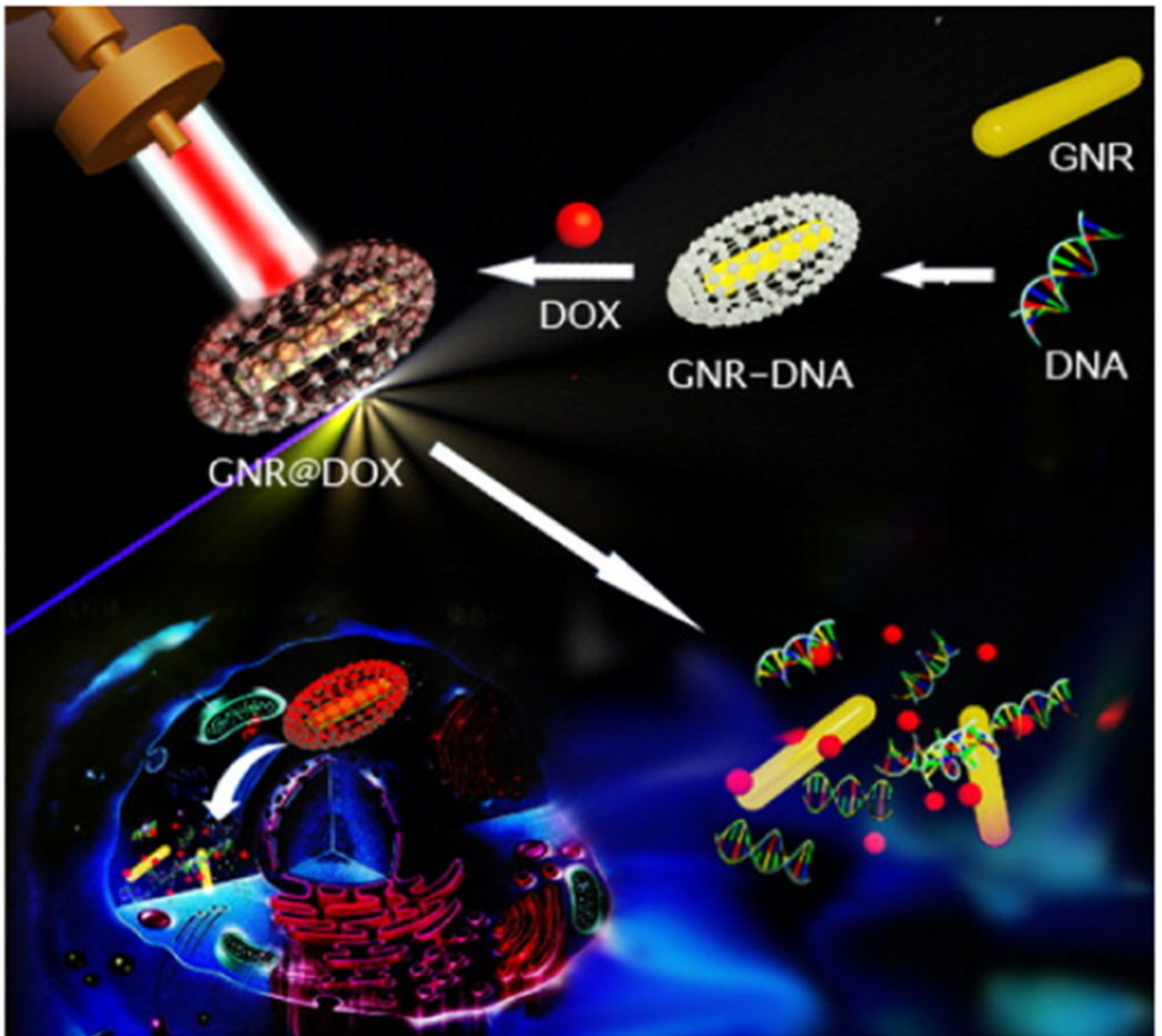


Fig. 4. Representative scheme illustrating the fabrication of DNA-wrapped GNRs with DOX loading, and cellular mechanism for combinational chemo and PTA cancer therapy [104].

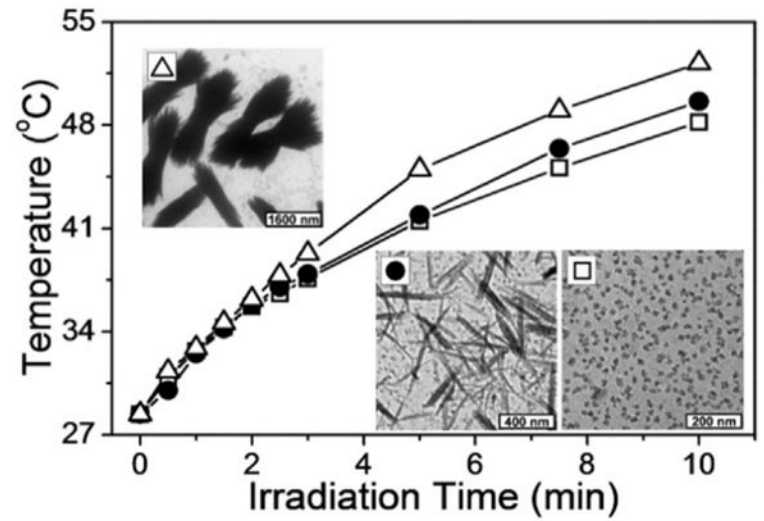
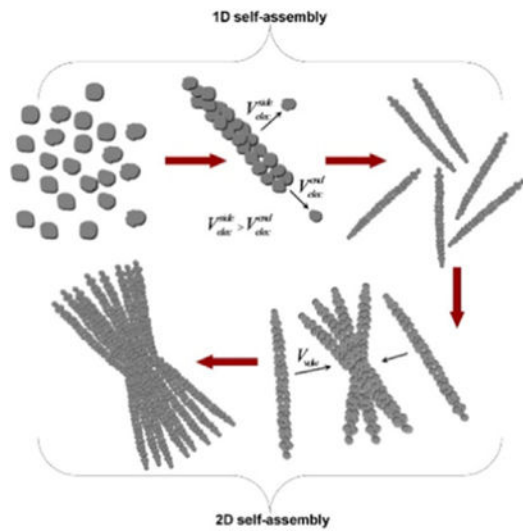


Fig. 5. Schematic Illustration of the Stepwise Self-Assembly of CuS NPs to Primary Nanorods and Secondary Shuttle-like Bundles and the photothermal effect improvement from CuS NPs to Primary Nanorods and Secondary Shuttle-like Bundles [118].

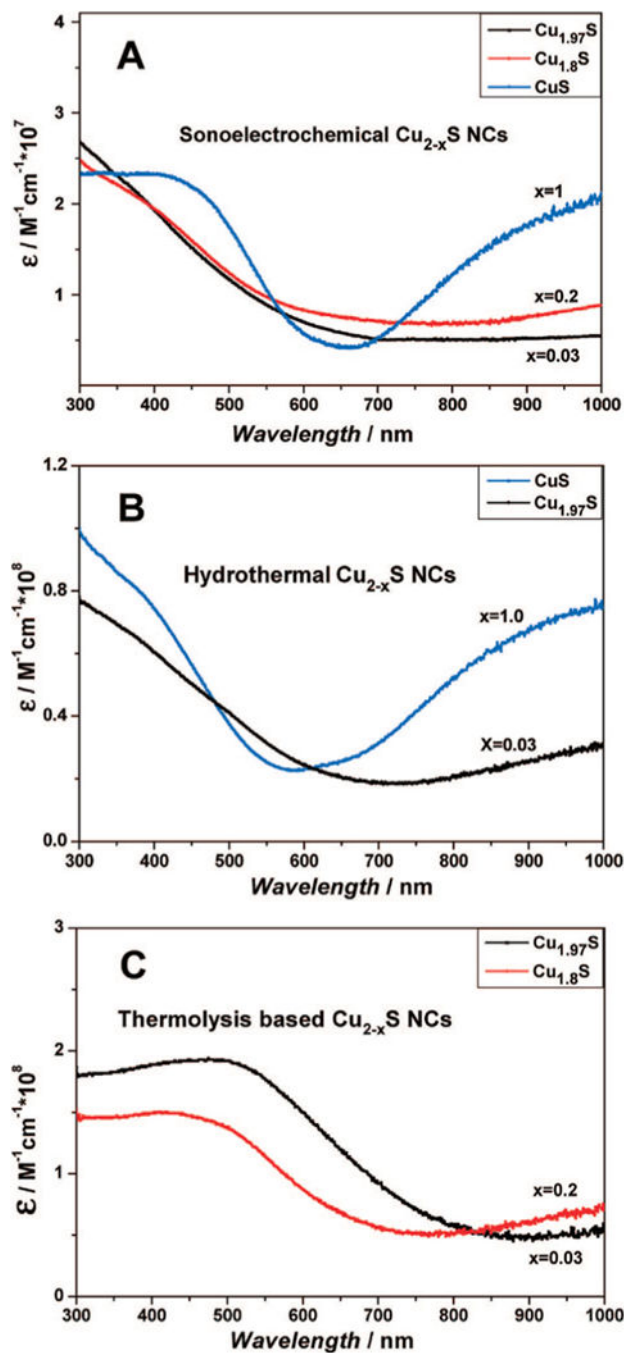


Fig. 6. UV-vis spectra of Cu_{2-x}S NCs prepared by (A) sonoelectrochemical, (B) hydrothermal, and (C) thermolysis methods [119].

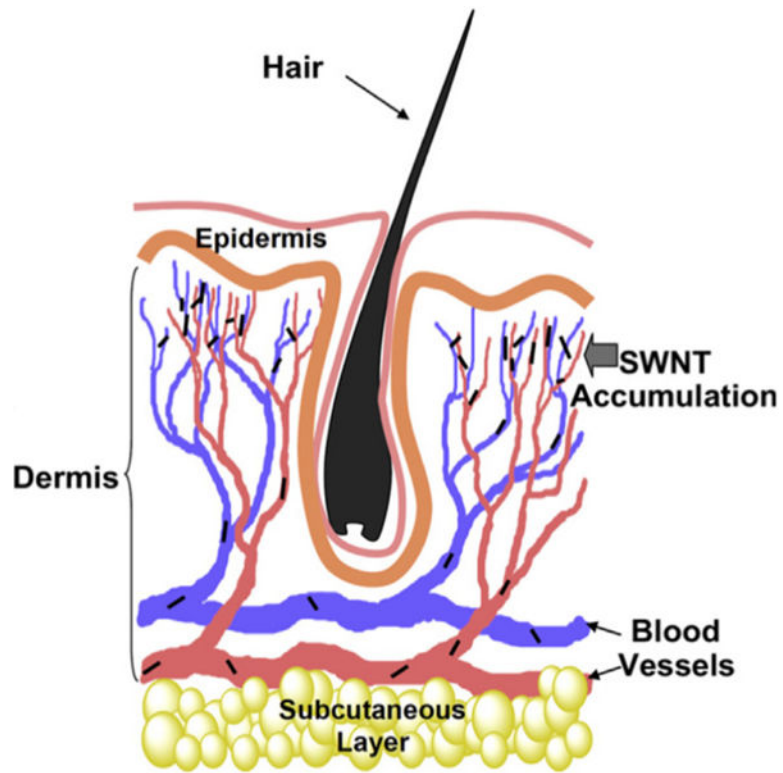


Fig. 7. A proposed scheme to explain SWNT skin accumulation. The micro-vessels with diameters as small as 5 mm enriched in the skin dermis may tend to trap SWNTs overtime once nanotubes have an ultra-long blood circulation half-life [38].

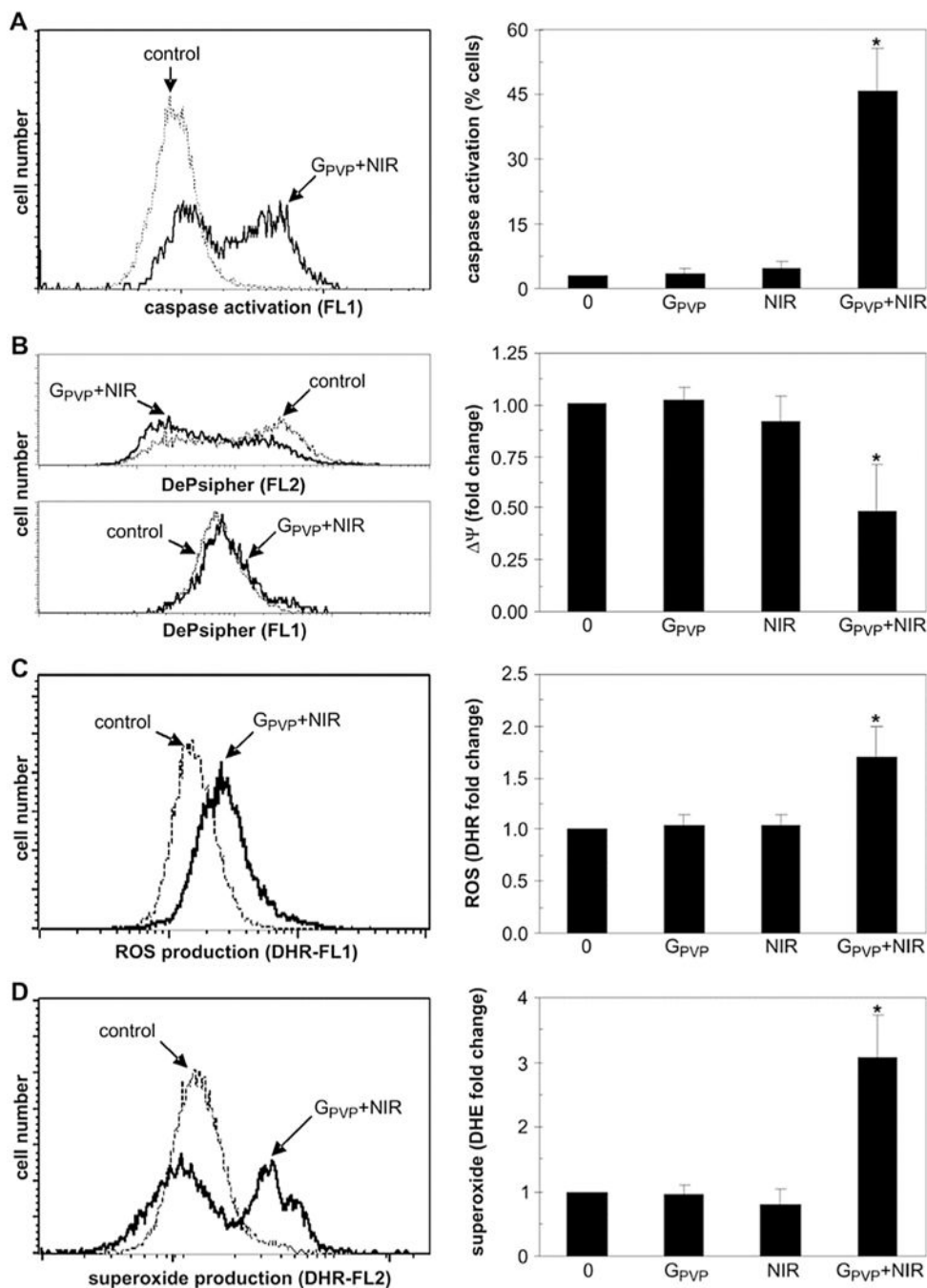


Fig.8. The intracellular mechanisms of graphene-induced photothermal cell death. (A-D) U251 cells were exposed for 3 min to NIR laser (808 nm, 2Wcm^{-2}) in the absence or presence of GPVP (10mg/ml). After 24h, flow cytometry was used to assess caspase activation (ApoStat staining; A), while the mitochondrial membrane potential (Ψ) (DePsipher staining; B), production of ROS (DHR staining; C) and superoxide (DHE staining; D) were measured after 4 h. The representative photomicrographs, histograms and dot plots are shown. The

results are mean \pm SD values from three experiments (*p < 0.05 refers to untreated cells and cells treated with NIR or GPVP alone; ANOVA). [152]

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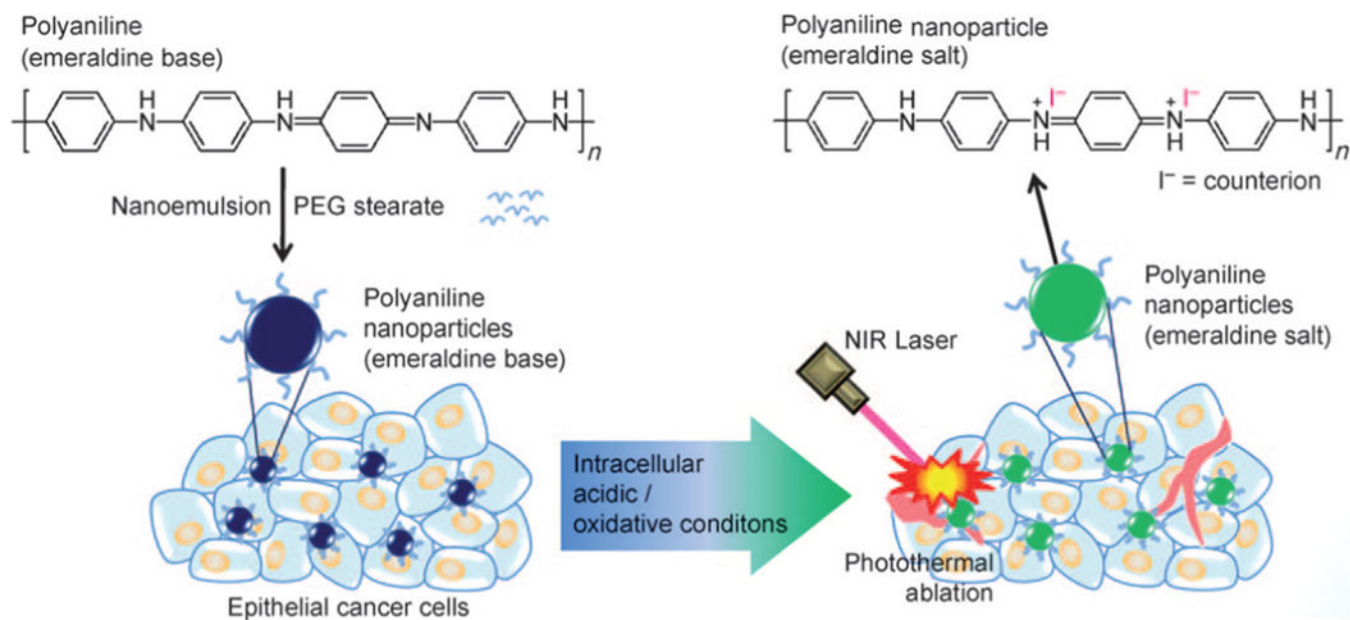


Fig. 9. Schematic illustration of the preparation of organic photothermal agents based on polyaniline nanoparticles and their application for the photothermal ablation of epithelial cancer cells by NIR laser irradiation [164].

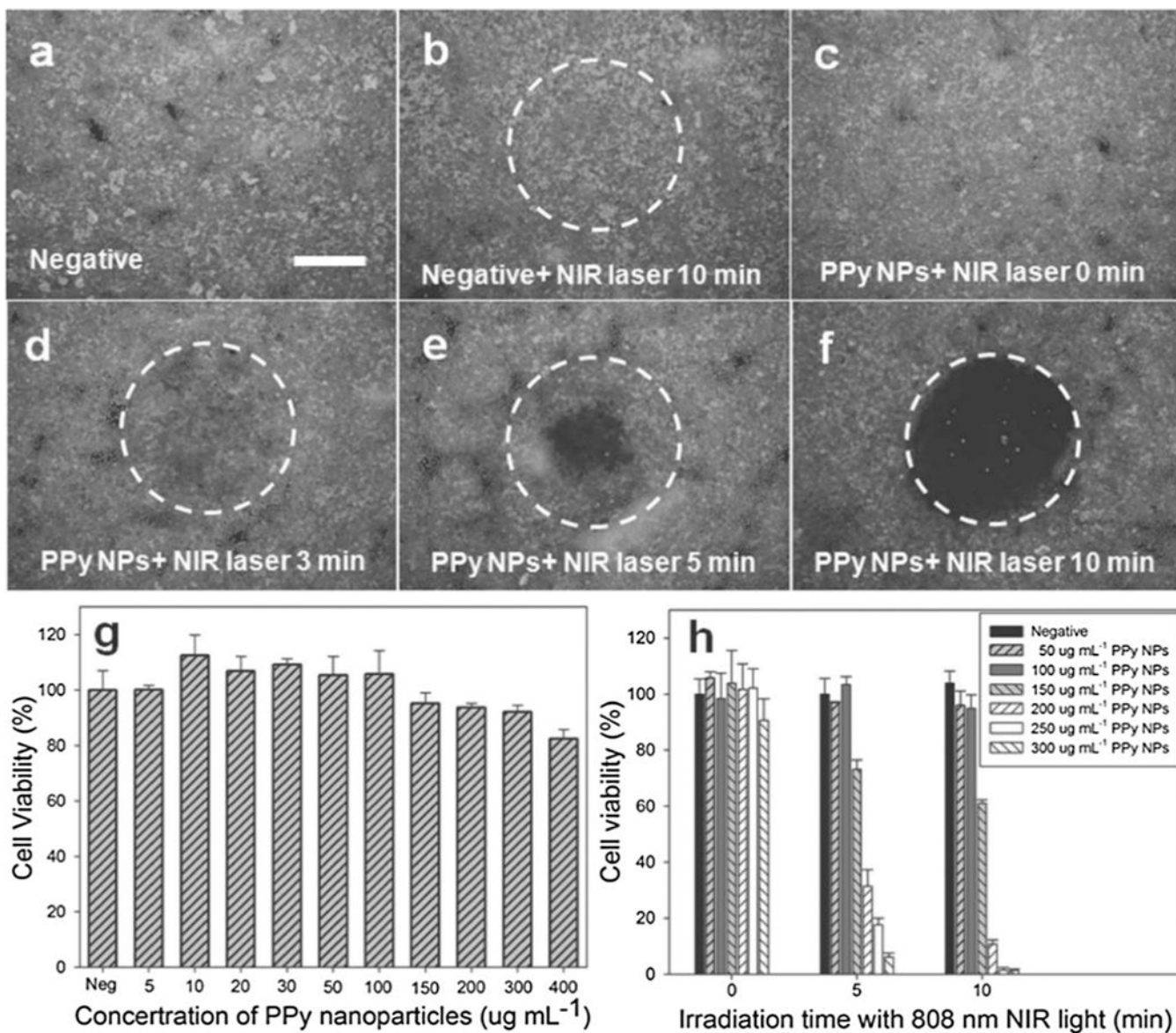


Fig. 10. Photothermal destruction of HeLa cells with or without PPy NPs and NIR laser (808 nm, 6Wx m^{-2}) treatments (a, b, c, d, e and f). White circle indicates the laser spot; live/dead stain for viability. Scale bar = 800 μm . (g) Cell viability of HUVECs with 24 h exposure to various concentrations of PPy NPs. (h) Cell viability after treatment with different concentrations of PPy NPs and different NIR laser irradiation time [86].

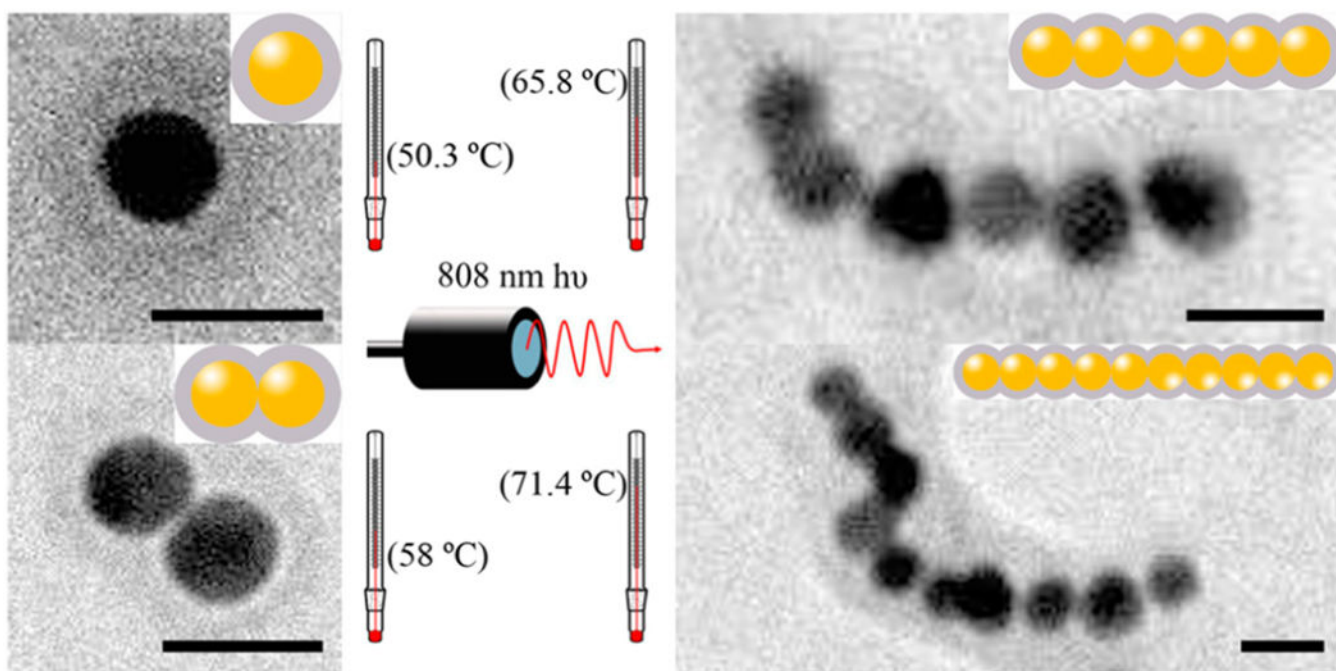


Fig. 11. Schematic illustration of photothermal effect of PPy-coated chainlike gold NPs [169].

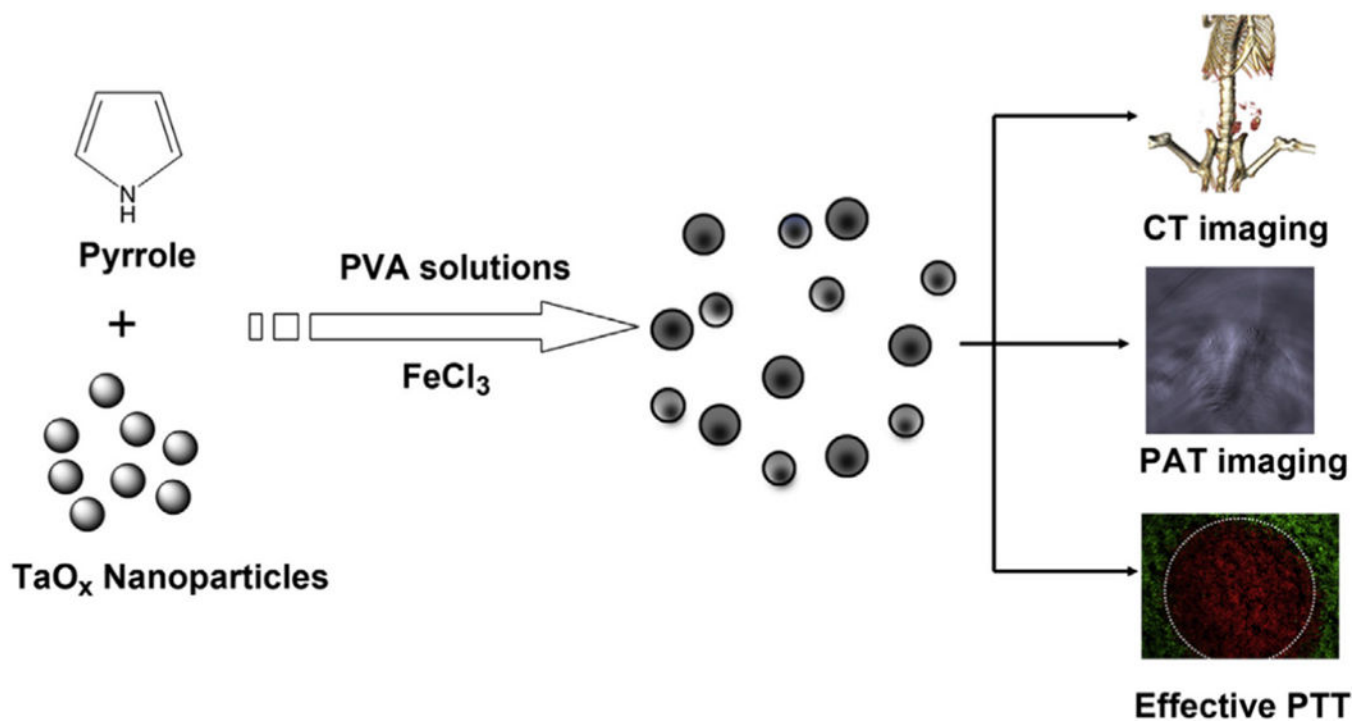


Fig. 12. Schematic illustration of the formation of TaO_x@PPy NPs for combined CT/PA imaging and PTT [196].

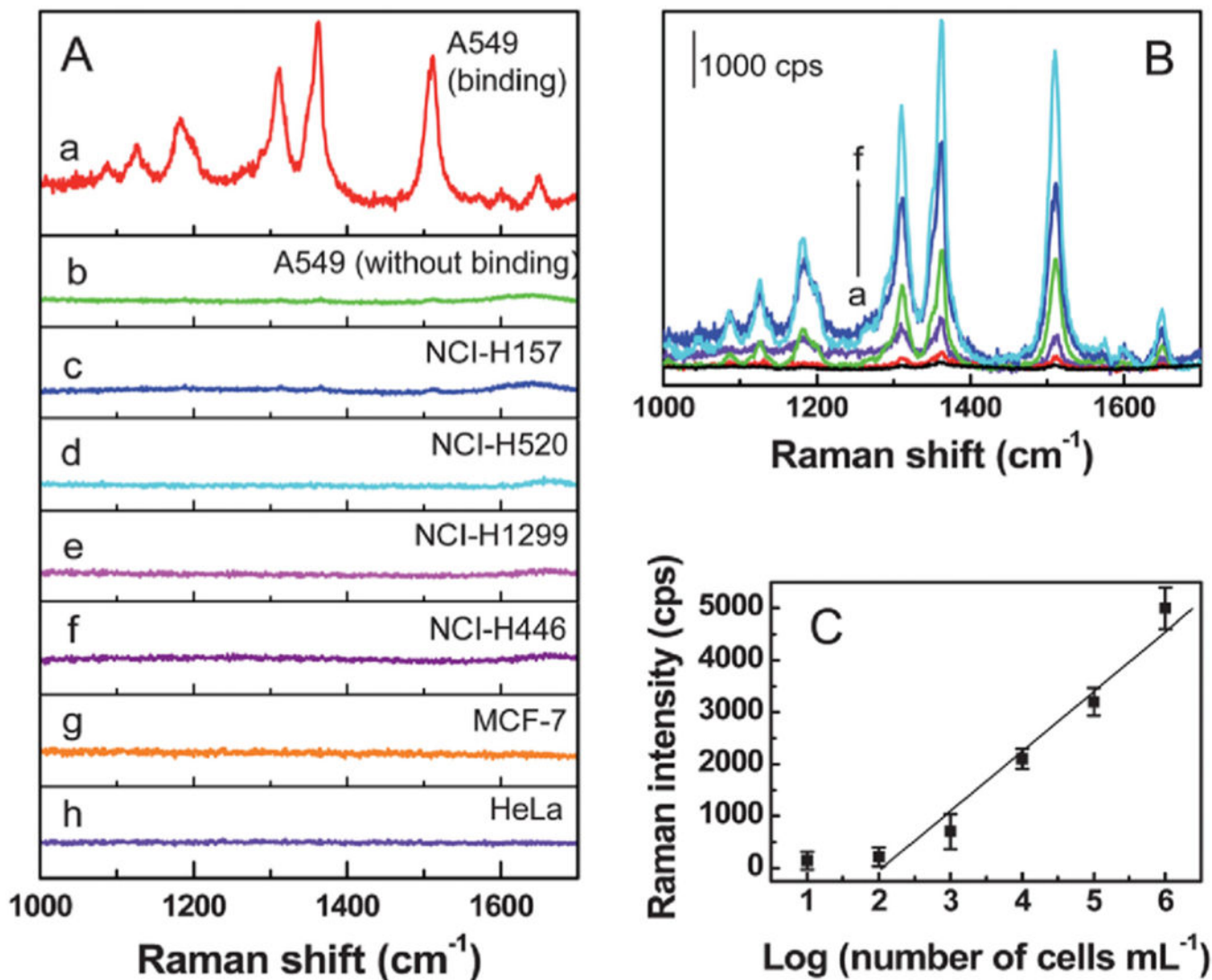


Fig. 13.

(A) SERS spectra of the A549 cells with (a) and without (b) binding of the Rh6G-labeled aptamer-Ag-Au nanostructures. (c-h) SERS spectra of the NCIH157, NCI-H520, NCI-H1299, NCI-H446, MCF-7, and HeLa cells, respectively, after incubating with the Rh6G-labeled aptamer-Ag-Au nanostructures. (B) SERS spectra of the A549 cells after binding of the Rh6G-labeled aptamer-Ag-Au nanostructures at the cell number (cells per mL) of (a) $\sim 1 \times 10^1$, (b) 1×10^2 , (c) 1×10^3 , (d) 1×10^4 , (e) 1×10^5 , and (f) 1×10^6 , respectively. (C) Dependence of the SERS signals at 1363 cm^{-1} on the A549 cell numbers (in cells per mL) [200].

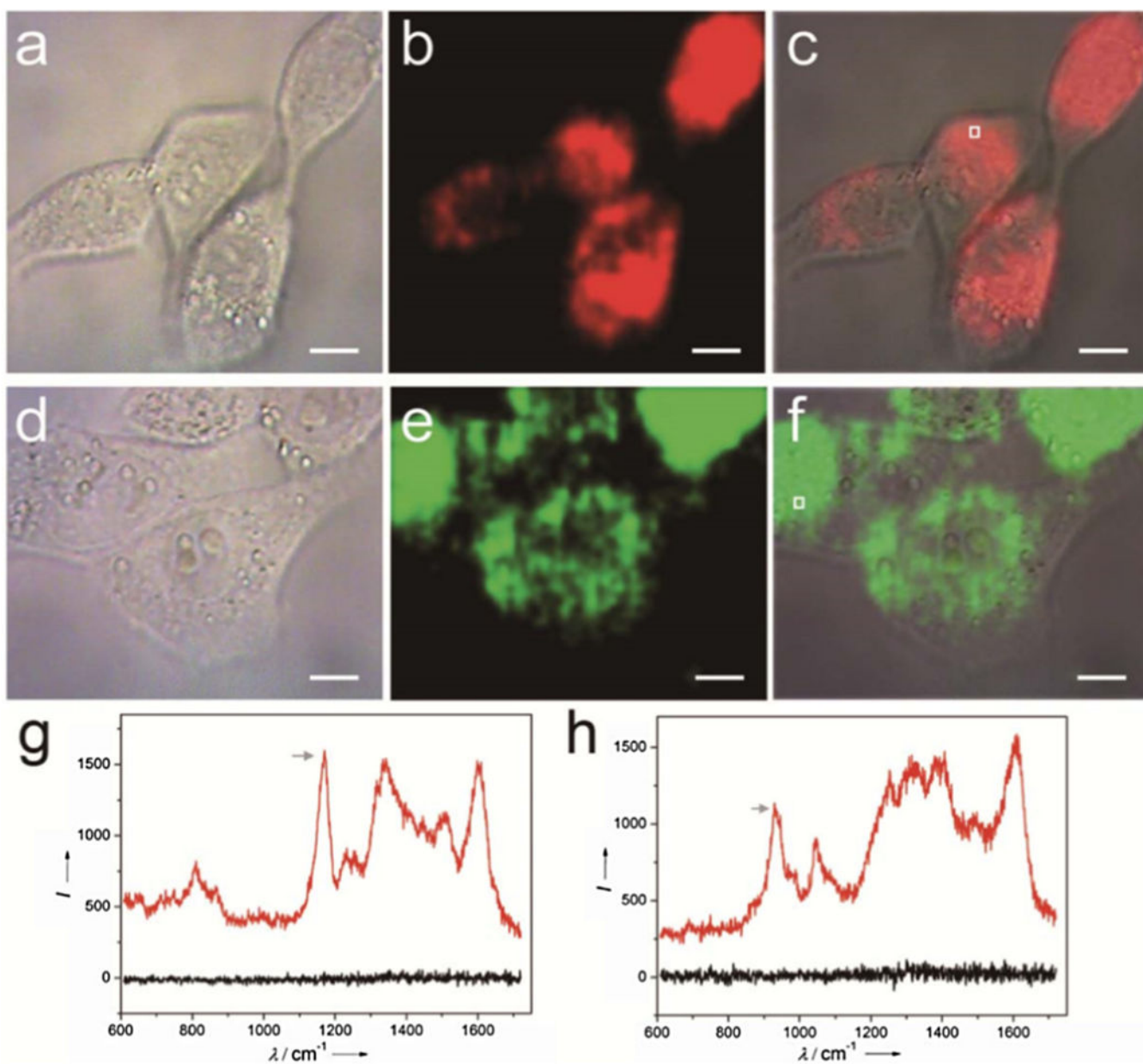


Fig. 14. NIR SERS imaging of 4T1 cells using GNR-PANI (a-c) or GNR-PPy (d-f) as nanotags. (g and h) SERS spectral lines acquired from the 4T1 cells incubated with GNR-PANI (c) and GNR-PPy (f), respectively. Black lines are the background lines. Scale bar: 10 μm [201].

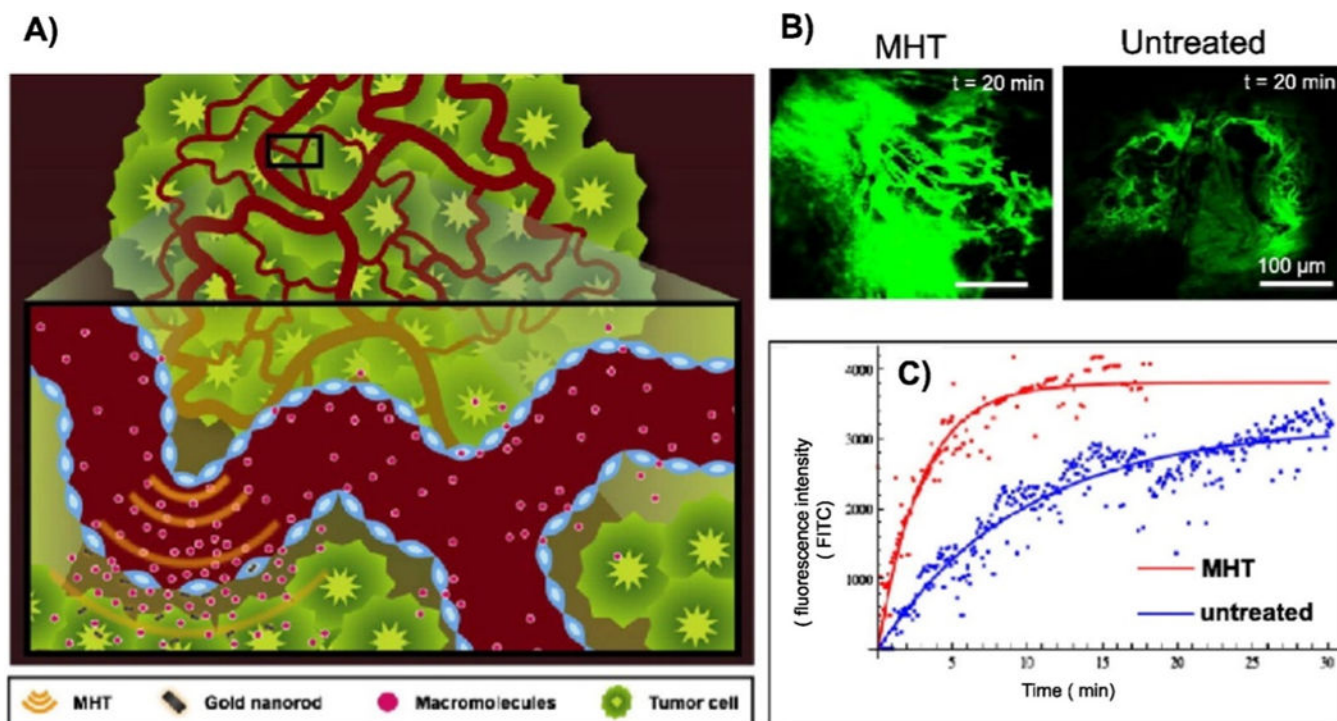


Fig. 15.

Illustration of hyperthermia-driven transport. Mild heat is generated by near infrared laser irradiation aided by heat-absorbing gold nanorods (A). Effect on tumor transport was studied by intravital microscopy with images demonstrating increased macromolecular accumulation (fluorescent intensity) in tumors receiving heat treatment versus control (B). Mathematic modeling was further used to quantify enhancements which revealed that the rate of extravasation increased by 30% while the total macromolecule accumulation increased by 200% (C) [210].

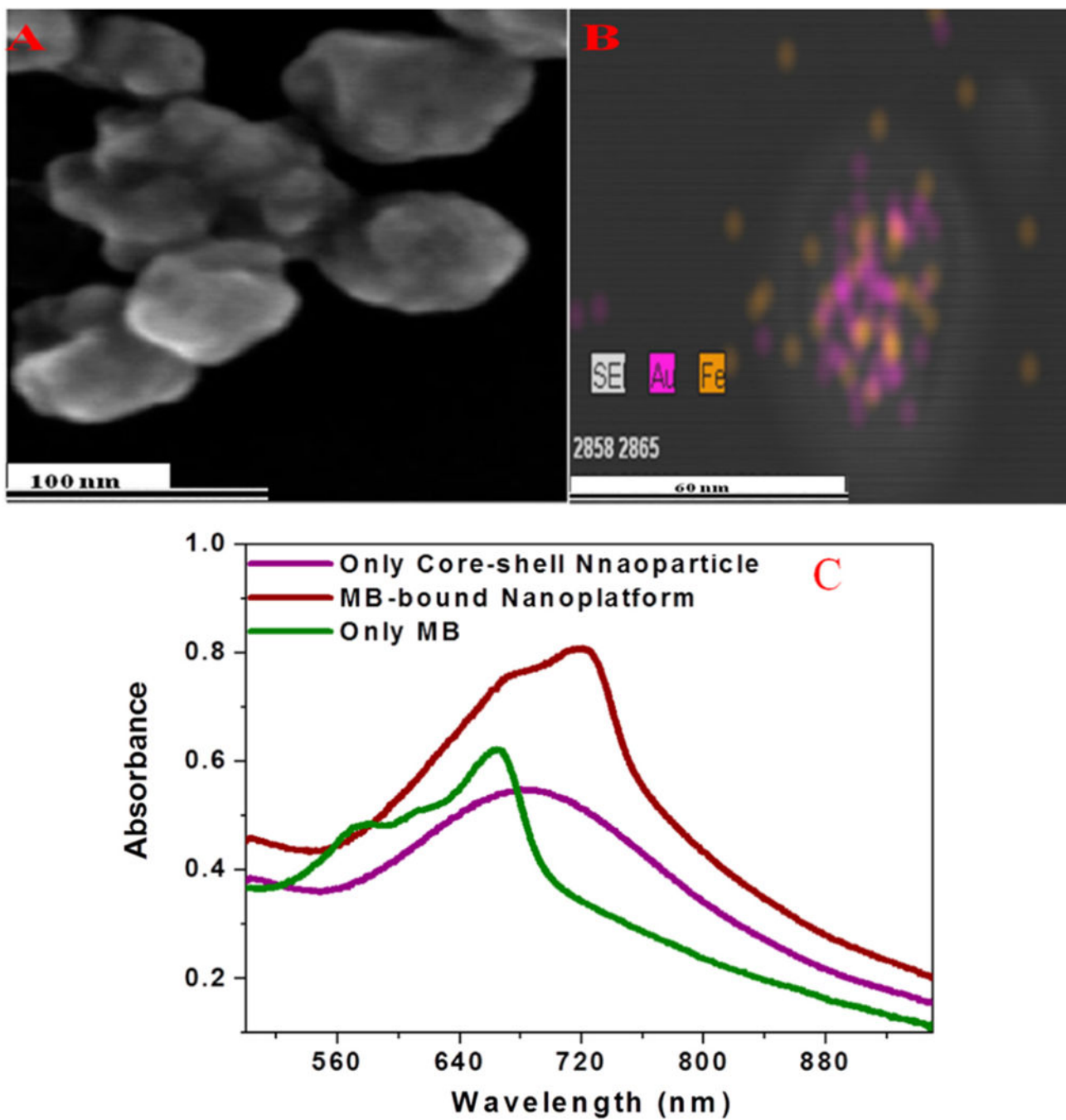


Fig. 16. (A) SEM images of freshly prepared core-shell plasmonic nanopopcorn. (B) EDX mapping shows the presence of Fe and Au in a core-shell nanoparticle. (C) Absorption spectra of core-shell nanoparticle, methylene blue, and methylene blue conjugated nanopopcorn [221].

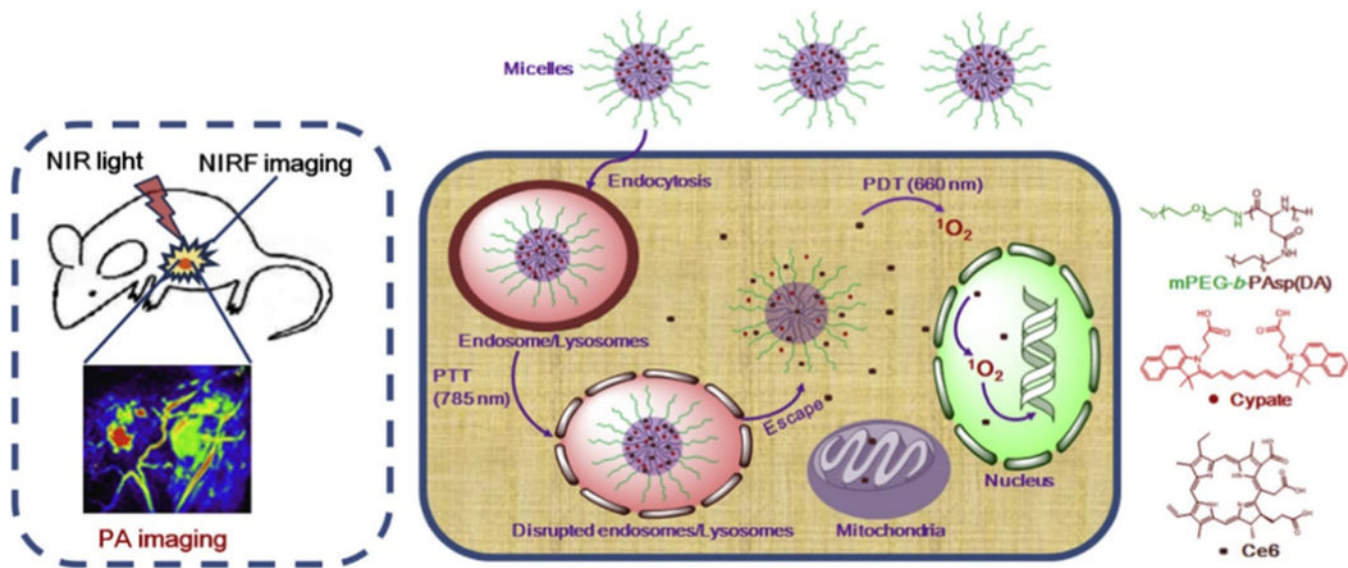


Fig. 17. Schematic illustration of PS-loaded micelles integrating cyanine dye for dual-modal cancer imaging and synergistic therapy of PTT and PDT via an enhanced cytoplasmic delivery of PS [222].

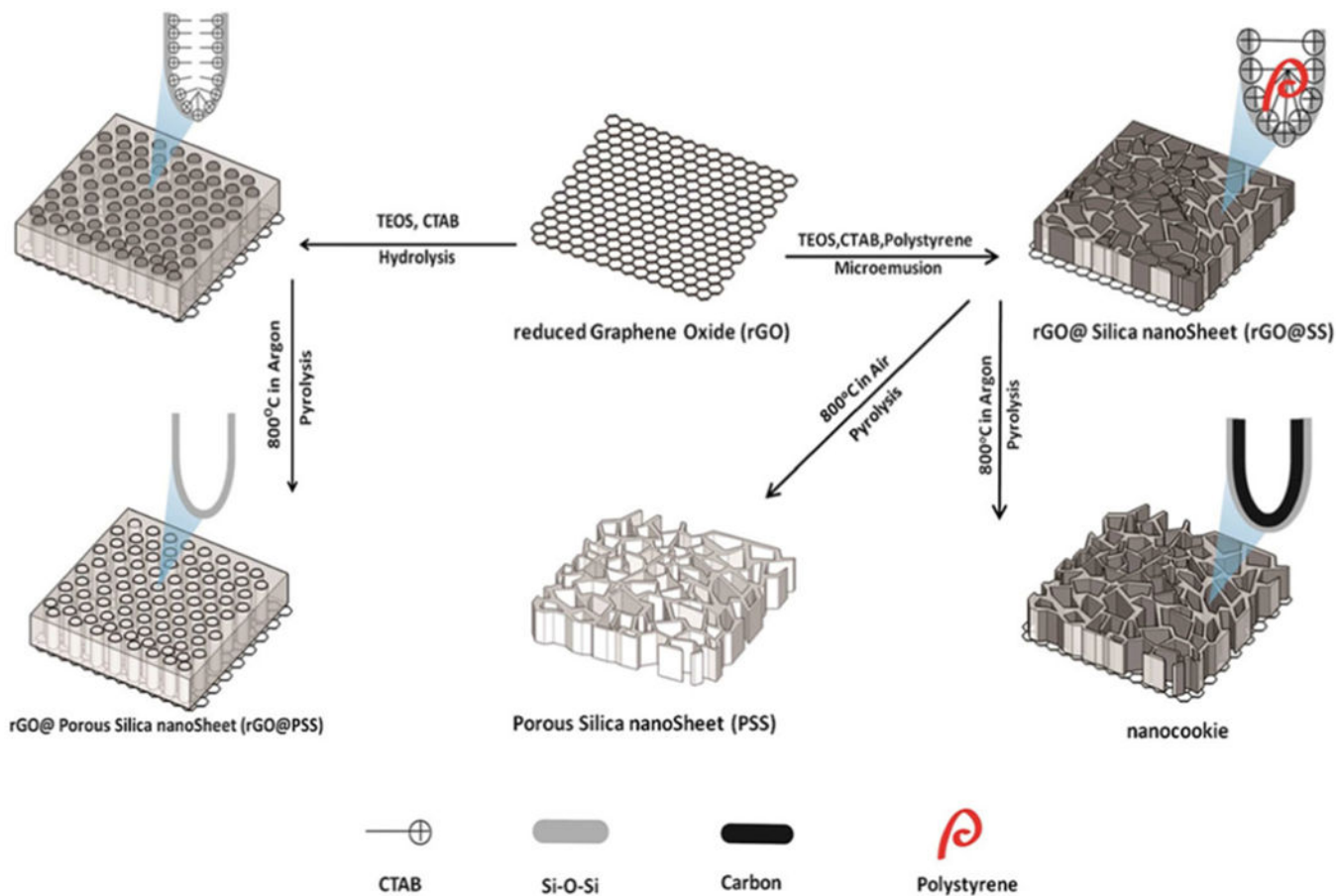


Fig. 18. Schematic illustration of synthesis and microstructure of reduced Graphene Oxide (rGO), Porous Silica nanoSheet (PSS), rGO@Silica nanoSheet (rGO@SS), GO@Porous Silica nanoSheet and nanocookie [228].

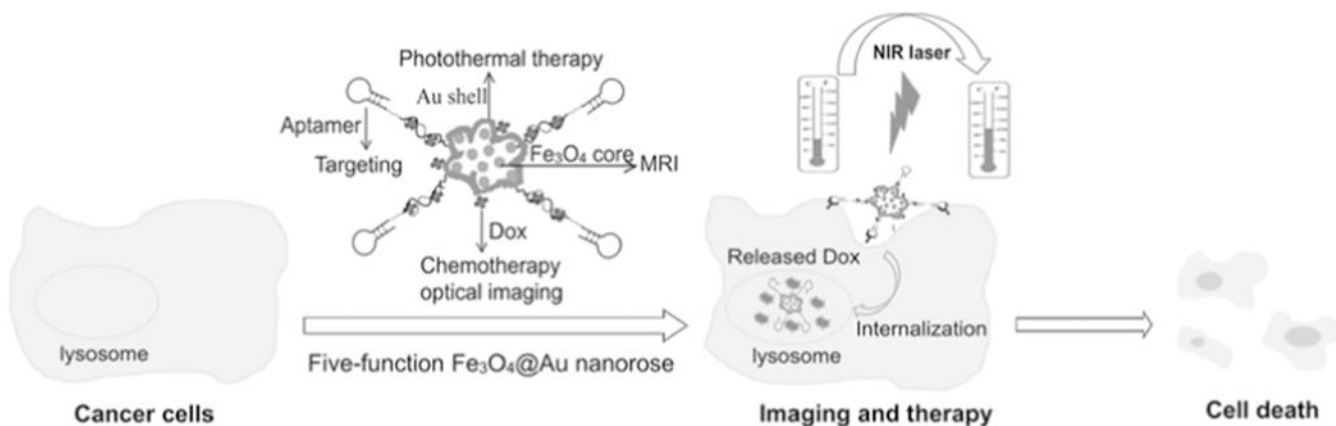


Fig. 19. Schematic representation of five-function $\text{Fe}_3\text{O}_4@Au$ nanorose for cancer cell targeting, MRI, optical imaging, photothermal and chemotherapy. Sgc8 aptamers are conjugated on the surface of nanoroses for targeting of CCRF-CEM cancer cells. Anticancer drug (Dox) is specifically delivered into cancer cells for chemotherapy and optical imaging. $\text{Fe}_3\text{O}_4@Au$ nanorose is an efficient MRI agent and photothermal agent; therefore, MRI and photothermal therapy can be achieved for cancer cell imaging and therapy [230].

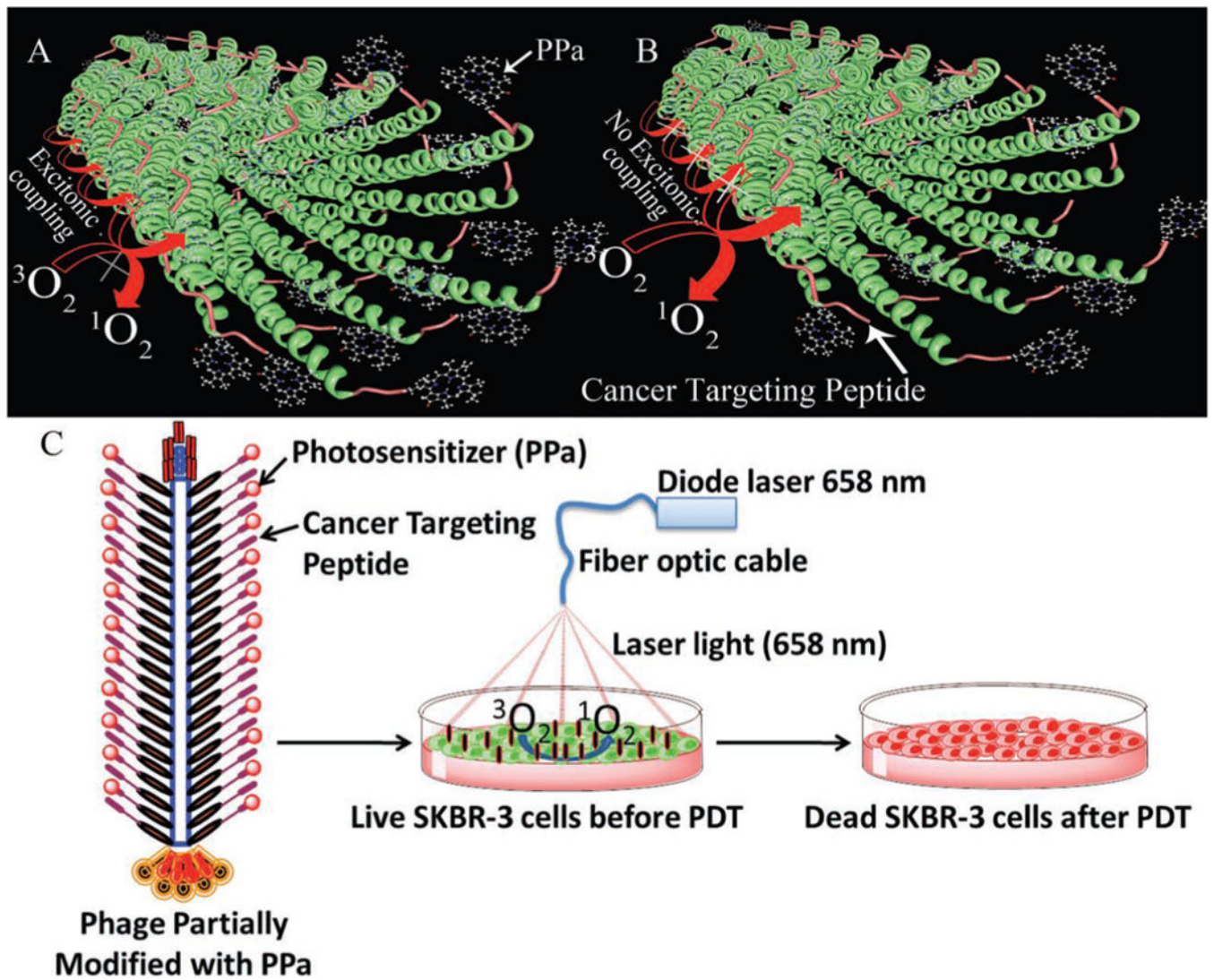


Fig. 20. Schematic diagram of photosensitizer conjugation onto biological nanowire and its targeted photodynamic therapy [260].

Table 1

Molar extinction coefficient of indocyanine green (molecular dye) and some common gold nanomaterials, including gold nanospheres, gold nanorods, gold nanoshells and gold nanohexapods.

Photosensitizers	Dimension (nm)	Molar extinction coefficient ($M^{-1} \times cm^{-1}$)	Wavelength (nm)	Ref.
Indocyanine green	Molecular	1.1×10^4	778	[17]
Gold nanospheres	Radius = 20	7.7×10^9	528	[34]
Gold nanorods	Length = 27 Width = 10	1.9×10^9	695	[96]
Gold nanoshells	Outer radius = 65 Inner radius = 55	2×10^{11}	800	[11]
Gold nanohexapods	Octahedral core = 25 Arm length = 16 Arm width=14	5.5×10^9	805	[37]

Table 2

Nanomaterials as ablation agents for PTT.

Nanomaterials	Size (nm)	Shape	Wavelength (nm)	application	Ref.
Au nanoparticles	10–50	Nanospheres	528	Cervical carcinoma	[34]
		Nanorods	695		[96]
		Nanoshells	800	Breast epithelial carcinoma, etc.	[11]
		Nanohexapods	805		[37]
Pt nanoparticles	1–20	Nanospheres	1064	Neuroblastoma	[91]
CuS nanoparticles	1–20	Nanospheres	808	Cervical carcinoma	[108]
					[109]
	500–800	Flower-like	980	Glioblastoma, etc.	[116]
					[120]
carbon nanotubes	50–500	Multiwalled/	1064	Breast cancer	[140]
		single-walled nanotubes	808		[38]
Graphene	50–360	Nanospheres	808	Glioblastoma	[152]
PANI	100–150	Nanospheres	808	Epidermoid carcinoma	[164]
PEDOT:PSS	80–130	Nanospheres	808	Breast cancer	[165]
PPy	40–60	Nanospheres	808	Breast cancer	[88]
					[89]