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Photothermal nanohybrid hydrogels for biomedical applications

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In the past decades, diseases such as wound infection, cancer, bone defect and osteoarthritis have constantly threatened the public health. However, the traditional treatment has many insufficiencies, such as high cost, easy recurrence and high biological toxicity. Hydrogel is a material with three-dimensional network structure, which has a series of advantages, such as injectability, self-heal ability, easy loading and controllability of drug release, and excellent biocompatibility. Therefore, it is extensively used in drug delivery, antibacterial, anti-cancer and other fields. However, the traditional hydrogels have the single performance, and therapeutic efficacy is often rely on the drugs loaded on them to cure diseases, which cannot achieve sustainable therapeutic effect. In order to solve this problem, photothermal nano hydrogel with photothermal agent (PTA) has become an ideal material due to its excellent physical and chemical properties. Photothermal nano hydrogels used in photothermal therapy (PTT) can exploit the photothermal effect of photothermal agent to increase local temperature and control the sol-gel phase transition behavior of hydrogels, so they are widely used in drug release, photothermal sterilization, photothermal inhibition of cancer cells and enhancement of bone repair. To sum up, this paper introduces the preparation of hydrogels with photothermal nanomaterials, and discusses their applications in the fields of drug release, photothermal sterilization, photothermal cancer cell inhibition and enhanced bone repair.

KEYWORDS

biomedical hydrogel, photothermal therapy, photothermal antibacterial, photothermal cancer suppressor, photo-controlled drug release

Introduction

Hydrogel is a kind of soft material with a three-dimensional network structure, which is made up of networks with hydrophilic polymers, and is crosslinked by physical or chemical bonds between strong water absorption. By simulating the composition, physical and chemical properties of the natural extracellular matrix (ECM), the hydrogel performs good biodegradability and biocompatibility. (Cao et al., 2021; Pei et al., 2021). And the hydrogels exhibit stimulus response and self-healing properties under the stimulation of

external environment can meet the needs of hydrogels in medical materials, which has attracted extensive attention of researchers (Ou & Tian, 2021; Xie et al., 2021; Zhang & Lucia, 2021). In recent years, hydrogels have been widely used in biomedical fields, such as drug delivery, antibacterial therapy, biosensors and cancer cell inhibition (Xu et al., 2022a; Xu et al., 2022b; Zhang et al., 2022).

Photothermal nano hydrogel is a kind of hydrogel with photothermal nano materials added during the preparation of hydrogel. Photothermal therapy (PTT) generated by photothermal nano hydrogel is a typical photon triggered therapy method. It can use the photothermal effect of photothermal agent (PTA) to extract energy from visible light/near-infrared light, convert it into heat, increase the temperature of the surrounding environment, and achieve the effect of ablating of tumor cells and killing bacteria. (Chen et al., 2021; Guedes et al., 2021). It is highly necessary to choose the appropriate photothermal agent. The ideal photothermal agents with appropriate NIR band gap and high response to near-infrared light irradiation can effectively convert light energy into heat energy under near-infrared light irradiation, and improve the therapeutic effect (Lu Y. et al., 2021). Photothermal treatment has many advantages. It can reduce the pain of patients during treatment. Secondly, it has short processing time and obvious therapeutic effect. More importantly, the materials used for photothermal treatment are of low toxicity or even non-toxic, causing less harm to the human body. So far, many forms of photothermal therapy have been studied and applied to the field of anti-cancer and antibacterial (Yu et al., 2019; Zhao et al., 2022).

Photothermal agent (PTA) is an crucial factor of photothermal therapy and the selection of appropriate photothermal agent is very important to the success of photothermal therapy (Guedes et al., 2021; Zhang et al., 2021). PTA should have high photothermal conversion efficiency, easy to prepare and good biocompatibility. However, many photothermal agents with high thermal efficiency have certain toxicity, which is not suitable for medical application. Hydrogels made by combining materials with photothermal agents with high biocompatibility can not only retain the high photothermal conversion effect, but also reduce biological toxicity and make them more biocompatible. In this paper, several typical photothermal nanohydrogels are reviewed and their applications in biomedical fields are also discussed.

Photothermal nanomaterials for hydrogel fabrication

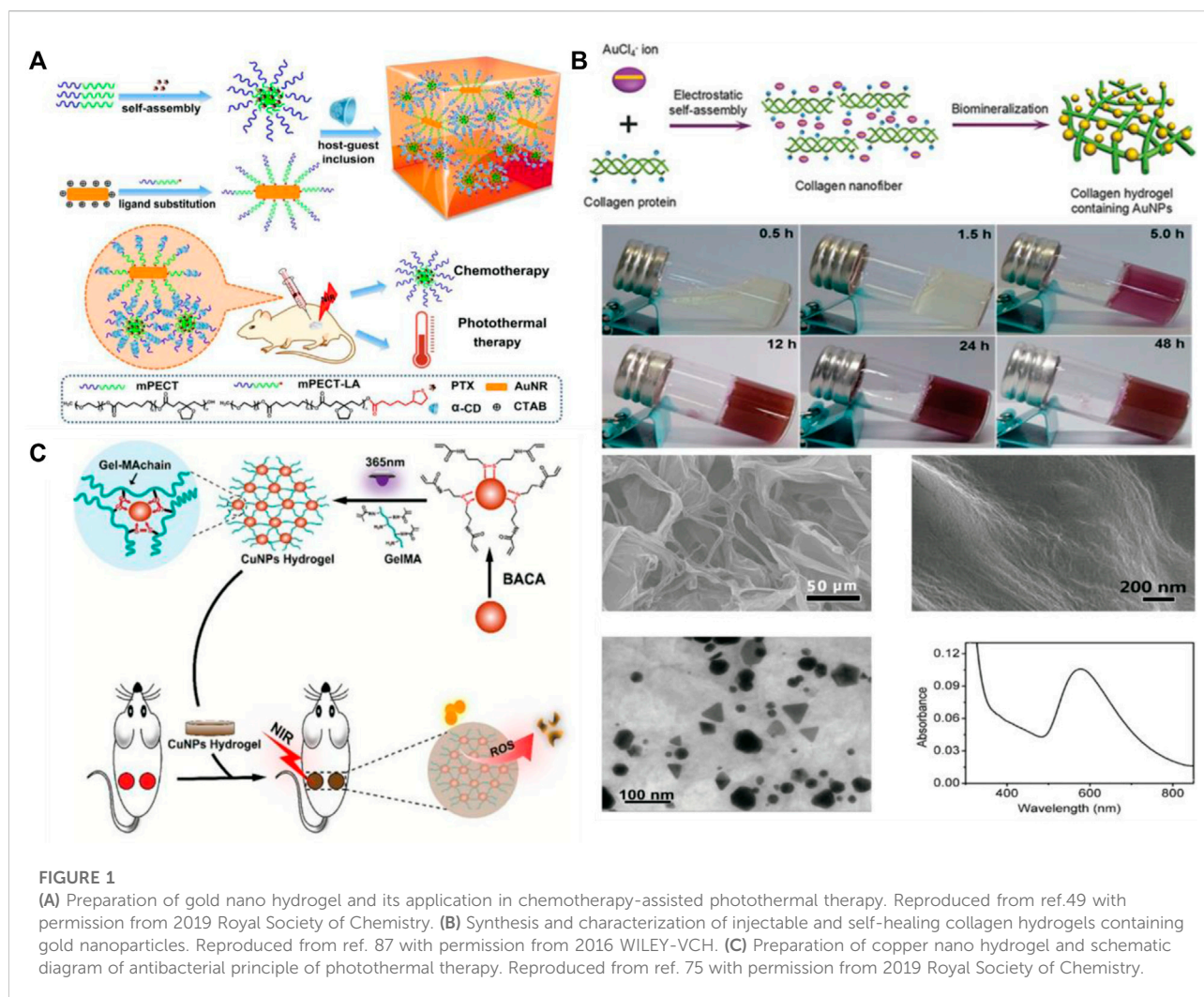
The preparation of photothermal nanohydrogels mainly relies on the photothermal nanomaterials. The most widely used ones mainly include Metal nanomaterials, Carbon based

nanomaterials, Metal sulfide/oxide nanomaterials, Black phosphorus nanomaterials, MXenes nanomaterials, Polymer nanomaterials, Organic dye nanomaterials, etc. In the following, the development of different photothermal materials for the preparation of photothermal nanohydrogels will be discussed in detail.

Metal nanomaterials

The properties of metal nanomaterials are very excellent. It has a strong surface plasmon resonance (LSPR) effect. When the incident photon frequency matches the overall vibration frequency of the metal nano material, the nano material will have a strong absorption effect on the photon energy, and a strong resonance absorption peak will appear in the spectrum. (Ai et al., 2021). Moreover, metal nanomaterials have excellent thermal properties, high absorption cross section and high field conversion efficiency in the near infrared region. Metal nanomaterials combine with peptides, antibodies, biocompatible polymers, chemical drugs and immune factors, and have great potential in the field of biomedicine (Park et al., 2018). The metal nanomaterials most explored and studied in PTT are gold nanomaterials, silver nanomaterials and copper nanomaterials, All of them have the advantages of strong absorption, excellent adjustable physical properties, optical properties and biocompatibility (Xu H. et al., 2020; Lu X. et al., 2021).

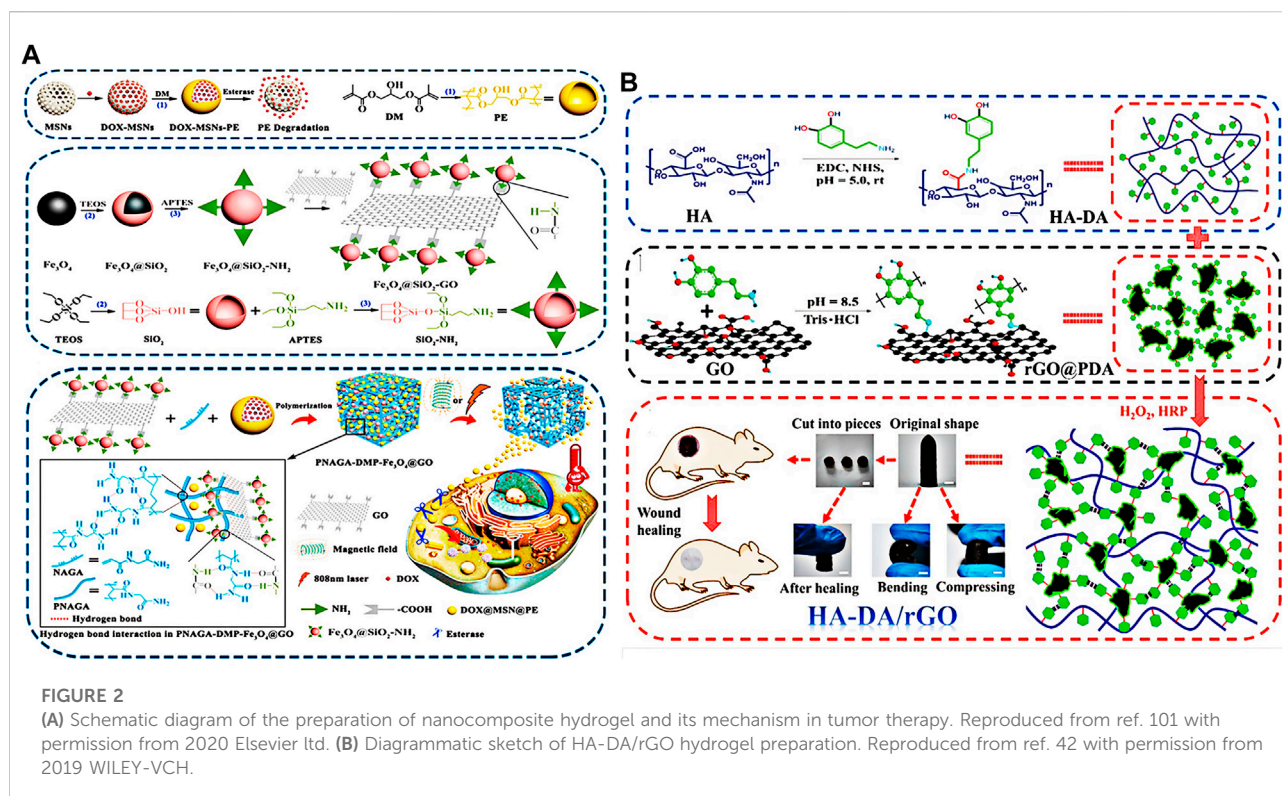
At present, various configurations of nanostructures based on gold have been developed. Among them, gold nanorods (GNR) have attracted much attention because of their simple biological coupling, strong and adjustable plasma absorption. In particular, there are two plasmon resonance surfaces on the surface of GNR, the transverse band represented in the visible region (650 nm–950 nm) and the longitudinal band represented in the near infrared region (1000 nm–1350 nm), so the radiation can penetrate tissues to the maximum extent, making it an ideal material for biomedical applications (Zhang Y. et al., 2020; Gupta & Malviya, 2021). GNR have biofilm activity and are an attractive therapeutic method for photothermal therapy. The hydrogel added with gold nanoparticles (GNP) shows certain advantages in biomedical applications. On the one hand, the hydrogel has good biocompatibility and degradability. On the other hand, the GNP are used as light absorbers, making the hydrogel well used in photothermal therapy. Bermudez-Jimenez et al. prepared gold nanorod hydrogels by embedding GNR into a non-toxic, biocompatible and biodegradable chitosan hydrogel (Bermudez-Jimenez et al., 2020). Combined with PTT treatment, it can effectively control the pathogenic bacteria in the mouth. In another study, Liu et al. modified gold nanorods by a two-block copolymer, an injectable nanocomposite hydrogel was prepared by the interaction of α -cyclodextrin (Figure 1A)(Liu M. et al., 2019). The hydrogel can not only improve the



biocompatibility of AuNR, but also realize local photothermal treatment. Moorcroft et al. co loaded IRIKIRIKONH₂ (IK8) and GNR into polyethylene glycol (PEG) hydrogels, and achieved the bactericidal effect on *Staphylococcus aureus* by photothermal triggering the release of IK8 (Moorcroft et al., 2020). At the same time, relevant experiments further confirmed that the hydrogels loaded with GNR had certain photothermal damage to the biofilms. At present, photothermal ablation (PTA) based on nanotechnology, as a highly effective treatment method for solid tumors, has been widely explored. Gold nanoparticles, as strong light absorbers, can absorb NIR and achieve local fever through photothermal conversion effect, which can reduce the damage to tissues around the wound to the maximum extent while treating the wound (Zhang R. et al., 2020). Xing et al. proposed a method based on biomimetic mineralization trigger for the first time to prepare collagen hydrogels with adjustable mechanical properties (Figure 1B) (Xing et al., 2016). Through electrostatic bonding between collagen chains (positively charged) and inorganic anion clusters, GNP were formed, which were controlled as cross-linking

agents for mechanical properties, to prepare hydrogels with advantages of *in vivo* injection. When the stress relaxation of the hydrogel is caused by the non-covalent interaction between GNP and collagen chains, the hydrogel can recover rapidly under the condition of applied stress. This study expands the application of GNP hydrogel.

Silver nanoparticles (Ag NP_s) have similar photothermal properties to GNP. Because of their photothermal effects, toxicity of silver, and wide applicability in the pharmaceutical field, they have always attracted the attention of researchers. (Awasthi et al., 2020; Ren et al., 2021). Silver nanoparticles have become a good photothermal agent because of their high photothermal conversion efficiency, easy synthesis and multifunctional adjustability of their surface properties (de Oliveira Lima et al., 2022). Recently, Amatya et al. prepared hydrogel films with good photothermal activity through bovine serum protein (BSA) and Ag NP_s and applied them *in vivo* (Amatya et al., 2021). Under 0.6 W low laser power, the temperature can be reached 45 °C which is ample for tumor ablation.



Due to local surface plasmon resonance, copper nanoparticles show strong light absorption in visible and near infrared, similar to that of silver and gold nanoparticles. Nano copper has been widely used in wound healing due to its high redox potential, low production cost and broad-spectrum antibacterial activity. Chen et al. successfully embedded nanoparticles into guar gum hydrogel to form copper nanoparticle hydrogel (Chen et al., 2017). The copper nanoparticles embedded in the hydrogel have a good photo thermal conversion rate. After 10 min of laser irradiation, the temperature of the hydrogel can rise to 67°C. This rapidly rise in temperature contributes to the high antibacterial performance of copper on irradiated nanoparticle hydrogels. Tao et al. reported a MA modified copper nanoparticle hydrogel (Figure 1C) (Tao et al., 2019). In combination with 808 nm NIR radiation, copper NPs embedded in the hydrogel can produce reactive oxygen species (ROS), and effectively convert NIR laser energy into local heat. It can eradicate *Escherichia coli* and *Staphylococcus aureus* bacteria *in vitro* antibacterial experiments. Most importantly, the hydrogel can also promote wound healing and realize multi-functional application of hydrogel.

Carbon-based nanomaterials

Graphene is a new material with a single-layer two-dimensional honeycomb lattice structure, which is closely

packed with sp^2 hybrid connected carbon atoms (Deng X. et al., 2020). The sp^2 hybrid carbon atoms of Graphene oxide in the hexagonal lattice structure allows to absorb light of different wavelengths, and its photothermal capacity can be enhanced with the increase of photoabsorption, which make it a good photothermal heating material (Falke et al., 2020; Huang, 2022). Lee et al. used graphene oxide and modified it with polyethylene glycol to develop a wavelength independent hydrogel system, to improve the dispersion of graphene oxide in aqueous solution (Lee et al., 2020). Under the irradiation of 532 nm, 785 nm and 980 nm lasers, the temperature of graphene oxide polyethylene glycol solution can reach 43°C, and free radical polymerization can be triggered at this temperature. Yuan et al. prepared a magnet and light double response hydrogel by introduced Fe_3O_4 -GO nanocomposite as a magneto photothermal agent. Fe_3O_4 -GO nanocomposite can convert the external magnetic field and near-infrared (NIR) light into heat, which can effectively improve the local temperature in the hydrogel (Figure 2A) (Yuan et al., 2020). Li et al. modified graphene oxide with polyethyleneimine, an amine terminal polymer branch, and prepared a hydrogel (Li et al., 2019). The hydrogel is not only structurally stable, but also can provide continuous drug delivery and near-infrared photothermal effect. Also many researchers studied the reduction of graphene oxide to improve the photothermal properties of graphene oxide. Liang and his colleagues prepared a series of hyaluronic acid grafted dopamine and

reduced graphene oxide (rGO) hydrogels using the $\text{H}_2\text{O}_2/\text{HPR}$ (horseradish peroxidase) system (Figure 2B) (Liang et al., 2019). The hydrogels have good self-healing properties, antioxidant activity and tissue adhesion. And most importantly, the enhanced antibacterial properties of the hydrogels through near-infrared (NIR) radiation, make them a good wound dressing. Liu and his colleagues prepared the hydrogel by functionalizing and reducing graphene oxide with pH responsive carboxymethyl chitosan (Liu W. et al., 2019). The hydrogel not only has excellent degradability and biocompatibility, but also has better photothermal conversion efficiency than many other photosensitizers, reaching 86.7%.

Metal sulfide/oxide nanomaterials

Metal sulfides/oxides which cost less than precious metals are also used in PTT. Copper sulfide nanostructures have excellent photothermal properties. Unlike the infrared absorption of gold nanostructures, the infrared absorption of copper sulfide nanoparticles comes from the energy band transition (Sun et al., 2019; Xie et al., 2022). Fu and his colleagues reported an injectable and thermosensitive hydrogel encapsulating copper sulfide nanoparticles (Fu et al., 2018). Nanodots are uniformly distributed in the hydrogel matrix, and their particle size remains unchanged. The hydrogel not only shows the ability of forming *in-situ* gel with thermal response, and the chemical toxicity of copper sulfide was reduced by “composing” nano dots in the matrix. In another study, Lin et al. incorporated copper sulfide nanoparticles (CuS NPs) into hyaluronic acid (HA) to construct hydrogels (Lin et al., 2021). By combining the photothermal characteristics of CuS NPs, the sterilization of low temperature photothermal therapy is realized, also the improvement of the antibacterial efficiency and minimization of the damage to normal tissues. The team combined the photothermal effect and antibacterial effect provides a new idea for the new type of wound bandage.

Silver sulfide quantum dots are semiconductor materials with strong light stability and high biocompatibility. Because of their unique properties such as broadband absorption, convenient preparation, good chemical stability and low toxicity, they have attracted extensive attention. Recently, Hou et al. encapsulated the near-infrared silver sulfide quantum dots as photosensitizers in the hydrophobic cavity by self-assembly of polypeptide hydrogels, and then integrated the drugs DOX and Bestin into the hydrogels, thus prepared a multifunctional gene engineering polypeptide hydrogel encapsulating silver sulfide quantum dots (Hou et al., 2020). Due to the photothermal properties of silver sulfide quantum dots, the release of DOX from hydrogels is promoted, thus the overall therapeutic effect is improved.

Bismuth sulfide (Bi_2S_3) is a promising PTT agent with a narrow direct band gap ($E \approx 1.3$ eV). Bi_2S_3 nanostructures have been used as CT contrast agents, its cost is much lower than other metal elements (such as gold, platinum and tantalum). Bi_2S_3

nanoparticles also have biocompatibility and metabolism, and have low toxicity. Different types of Bi_2S_3 nanoparticles, such as Bi_2S_3 nanorods, nano porous bladder and nanodots are more commonly used. Smaller Bi_2S_3 nanoparticles are thought to have better light absorption and can be excreted from the bladder. Wu et al. embedded the ultra-small (less than 3 nm) Bi_2S_3 nano point into the hydrogel to improve the stability of the Bi_2S_3 nano point and endow the injectability of hydrogel (Figure 3A) (Wu et al., 2021). The hydrogel can maintain the same photothermal performance after being stored for 3 months. In another study, Wu et al. designed and synthesized $\text{MoS}_2/\text{Bi}_2\text{S}_3$ -PEG (MBP) nano sheets (Figure 3B). And they dispersed them together with DOX into agar solution to build a hydrogel system with photothermal conversion performance, and achieve tumor PTT and chemotherapy under the guidance of computer tomography (CT)/photoacoustic (PA) dual model imaging (Wu et al., 2018).

MoS_2 is another representative sulfide. Jin et al. designed to load positively charged DOX and negatively charged PC10A onto the surface of molybdenum disulfide nano sheets to prepare mixed PC10A/DOX/ MoS_2 nano particles and dispersed them in hydrogels (Jin et al., 2020). Molybdenum disulfide nano sheets were used as both photothermic agent and photodynamic agent in hydrogels. The production of hot oxygen and reactive oxygen can cause immune response and promote photothermal therapy on tumors. Zhou et al. reported a simple method to prepare sodium alginate (ALG) - Fe^{3+} (MAF) hydrogel containing molybdenum disulfide and glucose oxidase (GOx) (Zhou L. et al., 2020). The hydrogel has high photothermal conversion capacity of molybdenum disulfide, and an enzymatic reaction could occur in the hydrogel, which provides an effective way for the use of enzymes in cancer treatment.

Black phosphorus nanomaterials

Black phosphorus nanomaterials (BP) nano sheet is a kind of two-dimensional nano material with unique properties such as adjustable band gap, high NIR absorption and high photothermal conversion efficiency (Eswaraiah et al., 2016; Ren et al., 2017). BP nano sheet has the characteristics of highly efficient single oxygen generation, and has extensive NIR absorption and photothermal conversion characteristic under whole visible light region, and is extensively used in photothermal therapy. As an inorganic nano agent, BP nano tablets are attractive due to their biocompatibility. Because phosphorus is an important element in human bones, accounting for about 1% of human body weight. Qin et al. used the biocompatible copolymer F127 as the matrix to construct the thermosensitive hydrogel together with the photothermal therapeutic agent BP nano sheet (Qin et al., 2019). The hydrogel has the characteristics of near infrared

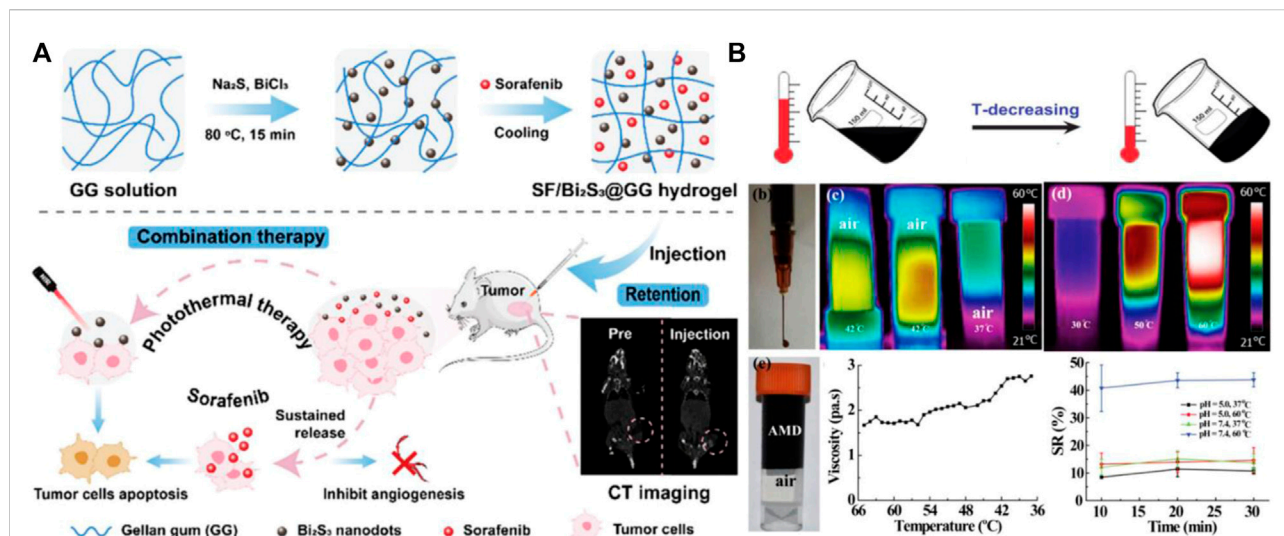


FIGURE 3 (A) Preparation of SF/ Bi₂S₃@GG photothermal nanohydrogel and its application in tumor therapy. Reproduced from ref. 83 with permission from 2021 Royal Society of Chemistry. (B) The formation principle of AMD hydrogel and its photothermal performance test. Reproduced from ref. 81 with permission from 2017 Published by Elsevier Ltd.

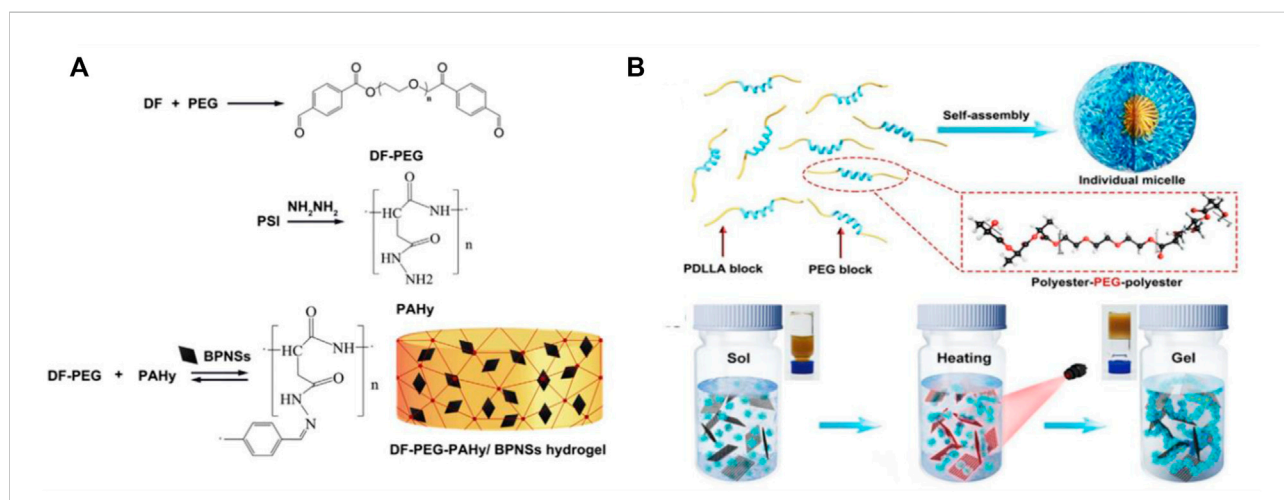
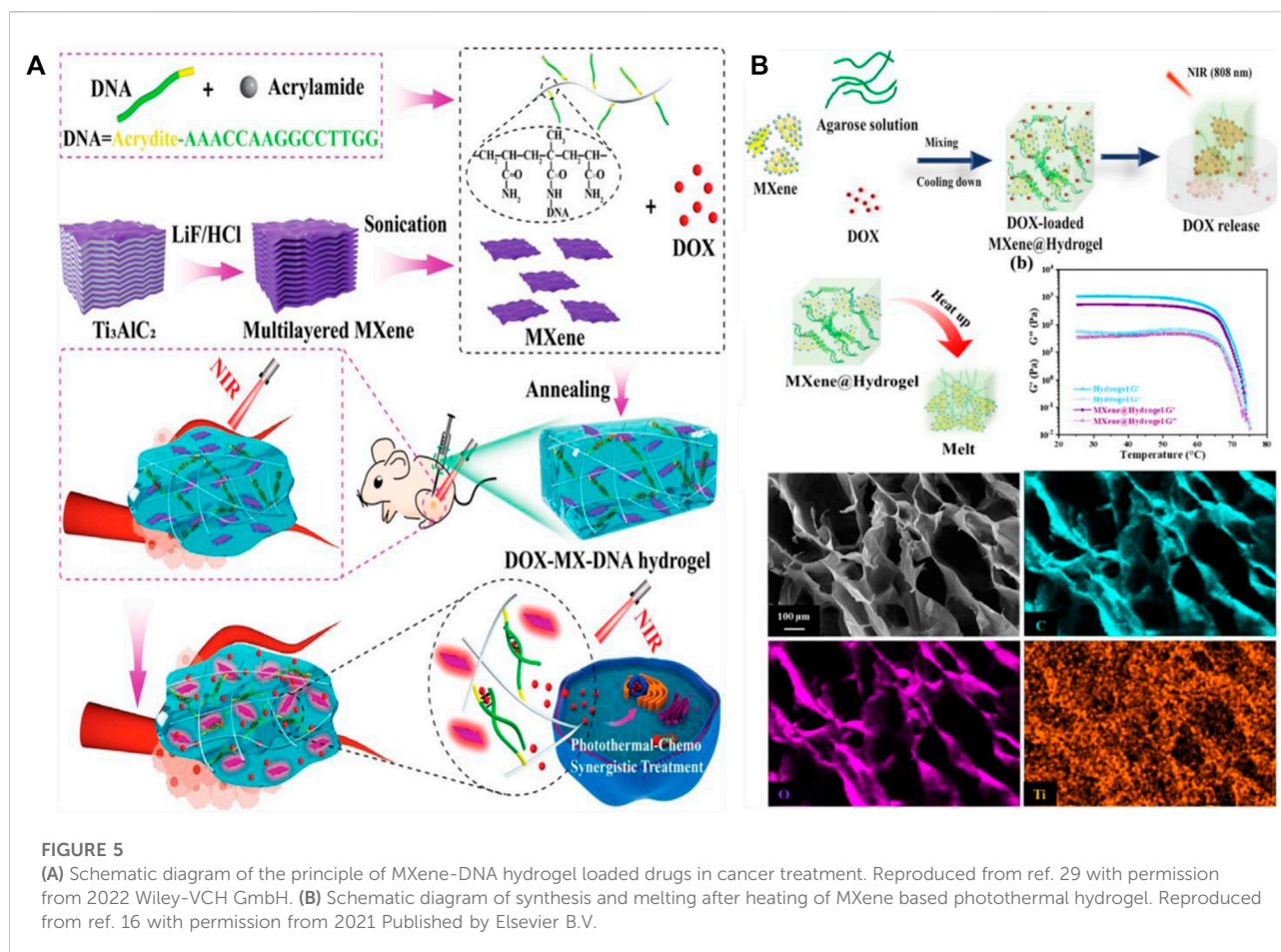


FIGURE 4 (A) Schematic diagram of preparation of black photothermal nanohybrid hydrogels. Reproduced from ref. 82 with permission from 2019 Published by Elsevier Inc. (B) Preparation of black phosphorus nano hydrogel and its schematic diagram of gel sol transition under infrared light irradiation. Reproduced from ref. 70 with permission from 2018 The Authors. Published by WILEY-VCH.

photothermal conversion, photothermal stability and biodegradability. Wu et al. prepared a pH sensitive DF-PEG-PAHy/BPNSs hydrogel by adding black phosphorus nanoparticles (BPNSs) into the hydrogel formed by diphenylaldehyde functionalized polymer and polyaspartic hydrazine polymer (Figure 4A) (Wu et al., 2019). This study shows that the hydrogel has good gel characteristics, pH sensitivity and near-infrared response. Due to the photothermal effect of BP NPs, NIR accelerates the release of

drugs in the hydrogel. In addition, BP nano tablets are naturally degraded in the physiological environment, in the form of harmless PO₄³⁻ as the final degradation product. Shao and his colleagues combined BP nano tablets with thermosensitive hydrogels to prepare hydrogels for photothermal therapy after cancer surgery (Figure 4B) (Shao et al., 2018). The research shows that the hydrogel has excellent NIR PTT performance, good biodegradability and biocompatibility. It can promote the rapid transformation of sol gel under NIR irradiation safely. A gel film

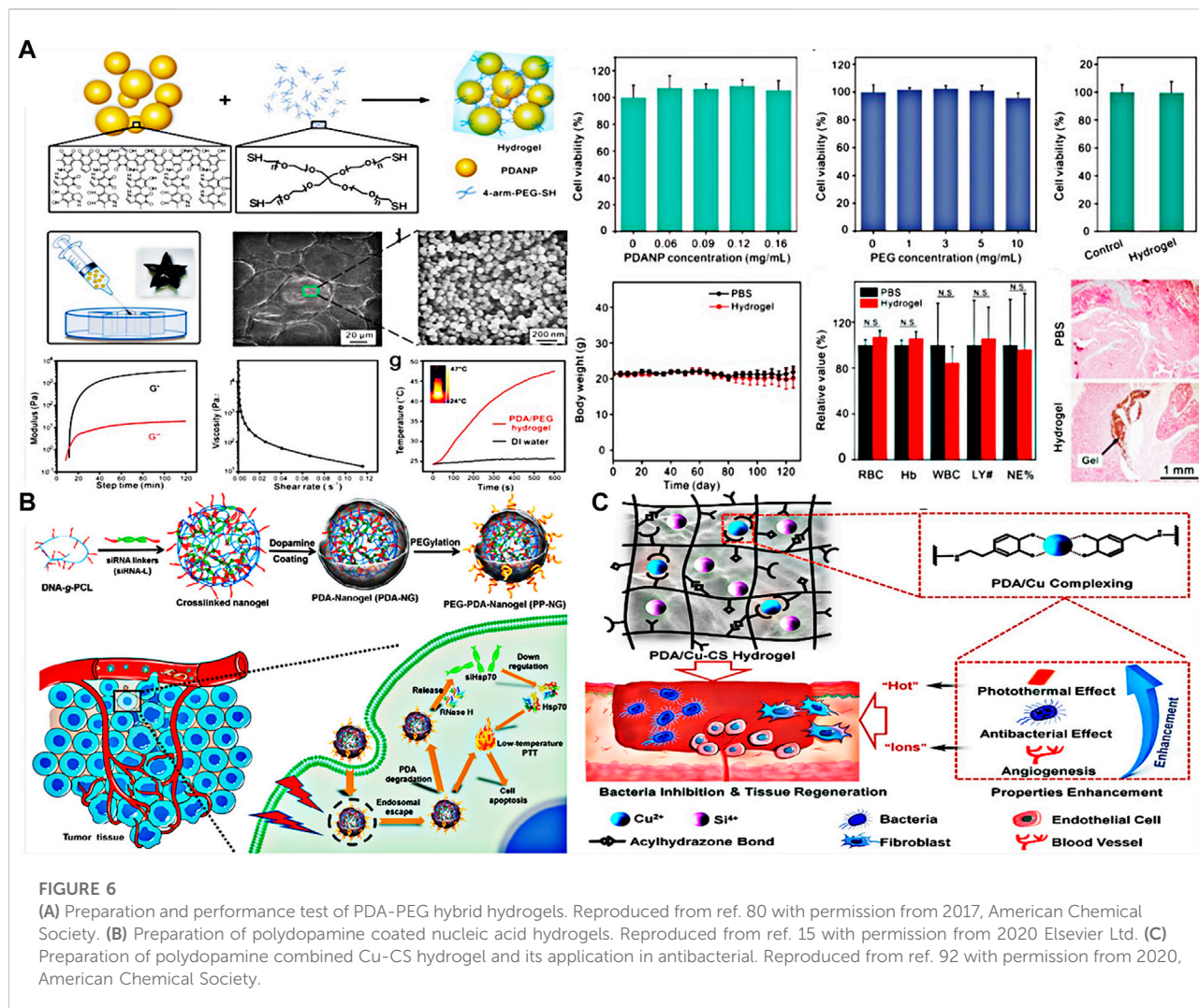


can quickly form by spraying the hydrogel under NIR irradiation on the wound, which performed a high PTT effect and can eliminate the residual tumor tissue.

MXenes nanomaterials

After the discovery of titanium carbide ($Ti_3C_2T_x$) by Naguib et al., in 2011, transition metal carbides, nitrides, and carbon nitrides (often referred to as MXene) have attracted widely attention because of their unique planar structures, excellent physicochemical properties, and chemical diversity (Naguib et al., 2011). The general formula for these materials is $M_{n+1}X_nT_x$ ($n = 1, 2, \text{ or } 3$), where M is an early transition metal, X is carbon and/or nitrogen, and T is the surface end inherited from the synthesis process, like -OH, -O, and -F (Xu D. et al., 2020). As a photothermal agent, MXene nanosheets exhibit strong light absorption in the near infrared range, high specific surface area and negative charge, which make abundant anchoring position of the therapeutic agent, so MXene nanosheets are widely used in photothermal therapy

(Lin et al., 2017; Lin et al., 2018). He and his colleagues used MXene as photothermal agent and doxorubicin as loading chemotherapy agent, and combined it with DNA hydrogel to establish a photothermal-chemical synergistic therapy system for highly effective local cancer treatment (Figure 5A) (He et al., 2022). Under local near-infrared light irradiation, the MXene nanosheet converts light energy into heat energy and triggers the reversible transformation of hydrogel from gel to solution, releasing DOX therapeutic agent. The experimental results showed that the hydrogel had excellent biocompatibility and showed effective local cancer treatment. Dong and colleagues prepared a drug-loaded MXene/ agarose hydrogel (Dong et al., 2021). They first prepared a two-dimensional MXene nanosheet with high photothermal conversion efficiency and photothermal stability, then introduced the MXene nanosheet into the low melting point agarose gel skeleton. The temperature of the loaded hydrogel can rapidly rise to 60°C under near-infrared light and hydrolyze to release the encapsulated drug (Figure 5B). The kinetics of drug release can be regulated by agarose concentration, MXene concentration, irradiation intensity and irradiation



time. This research provides a new way to develop smart hydrogel-based drug delivery systems for local cancer treatment. Li et al. prepared an anisotropic MXene@PVA hydrogel by directed cryoassisted salting-out. (Li Y. et al., 2022). Because of the good photothermal properties of MXene, the hydrogel can be used in local hyperthermia treatment of the infected site under near-infrared laser (808 nm) irradiation. In addition, the hydrogel has excellent mechanical properties, with stress up to 0.5 MPa and strain up to 800%. Bacterial experiments showed that the hydrogel had broad spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria. Li and colleagues designed a hydrogel film with MXene nanosheets embedded with heat-responsive gelatin (Li Y. et al., 2022). They used an epithelial cell adhesion molecule antibody to modify the hydrogel membrane so that it could specifically recognize and isolate CTCs from whole blood. The captured CTCs can be released without damage through

temperature responsive release and photothermal site release.

Polymeric nanomaterials

Dopamine (DA) is a biocompatible neurotransmitter in human body. It can synthesize polydopamine (PDA) by oxidative self-polymerization, and has different photothermal properties. Biologically inspired poly (dopamine) (PDA) based hydrogels have attracted great attention because of their well-known adhesion and biocompatibility (Han et al., 2017; Zhou D. et al., 2020). Wang et al. described a polydopamine nanoparticle conjugated polyethylene glycol hydrogel that could be used for on-demand drug delivery and combined chemotherapy-photothermal therapy under near-infrared irradiation (Figure 6A) (Wang et al., 2017). Most importantly, the hydrogel had good biocompatibility and would not cause

inflammation *in vivo*, and the hydrogel-mediated chemophotothermal therapy could effectively inhibit tumor growth. Zheng et al. designed a new injectable thermosensitive nano hydrogel by loading PDA NP and chemotherapy drugs (Zheng et al., 2020). The hydrogel has anti protein adsorption and photothermal effects, and the injectable amphoteric ion thermosensitive hydrogel has the advantage of low pollution. Ding et al. designed a nucleic acid nanogel coated with polydopamine (PDA) (Figure 6B) (Ding et al., 2020). After being coated with a layer of polydopamine, the nanogel not only protects the nanogel from enzymatic degradation, but also enables the nanogel to have good photothermal conversion ability under near-infrared (NIR) light irradiation. The study shows that the surface temperature of medical implants coated with PDA can be increased under NIR irradiation, which can effectively kill the adhering microorganisms on the implant surface. In addition, Xu et al. synthesized multifunctional composite hydrogels with PDA and Cu-doped calcium silicate ceramics (Cu-CS) as the main components (Figure 6C) (Xu Q. et al., 2020). Copper doped calcium silicate bioceramics have unique biological activity. The composition of PDA and Cu-CS enhanced the antibacterial performance through the “thermionic effect” of copper ions and photothermal materials synergetic antibacterial function.

Organic dye nanomaterials

Organic dye nanomaterials are also a common photothermal nanomaterials. Indocyanine green (ICG) is a water-soluble anionic tricarbocyanine dye with NIR absorption properties of 808 nm laser irradiation (Lee & Chang, 2017; Ma et al., 2019). Because of its low toxicity, it is widely used. In one study, Pan et al. prepared an ICG alginate gel with good photothermal treatment and good biocompatibility. Most importantly, hydrogels have a strong ICG fixation ability, which facilitates the accumulation of photothermal agents (Pan et al., 2019). This fixation can also reduce the potential side effects of ICG spread to surrounding tissues and improve biocompatibility.

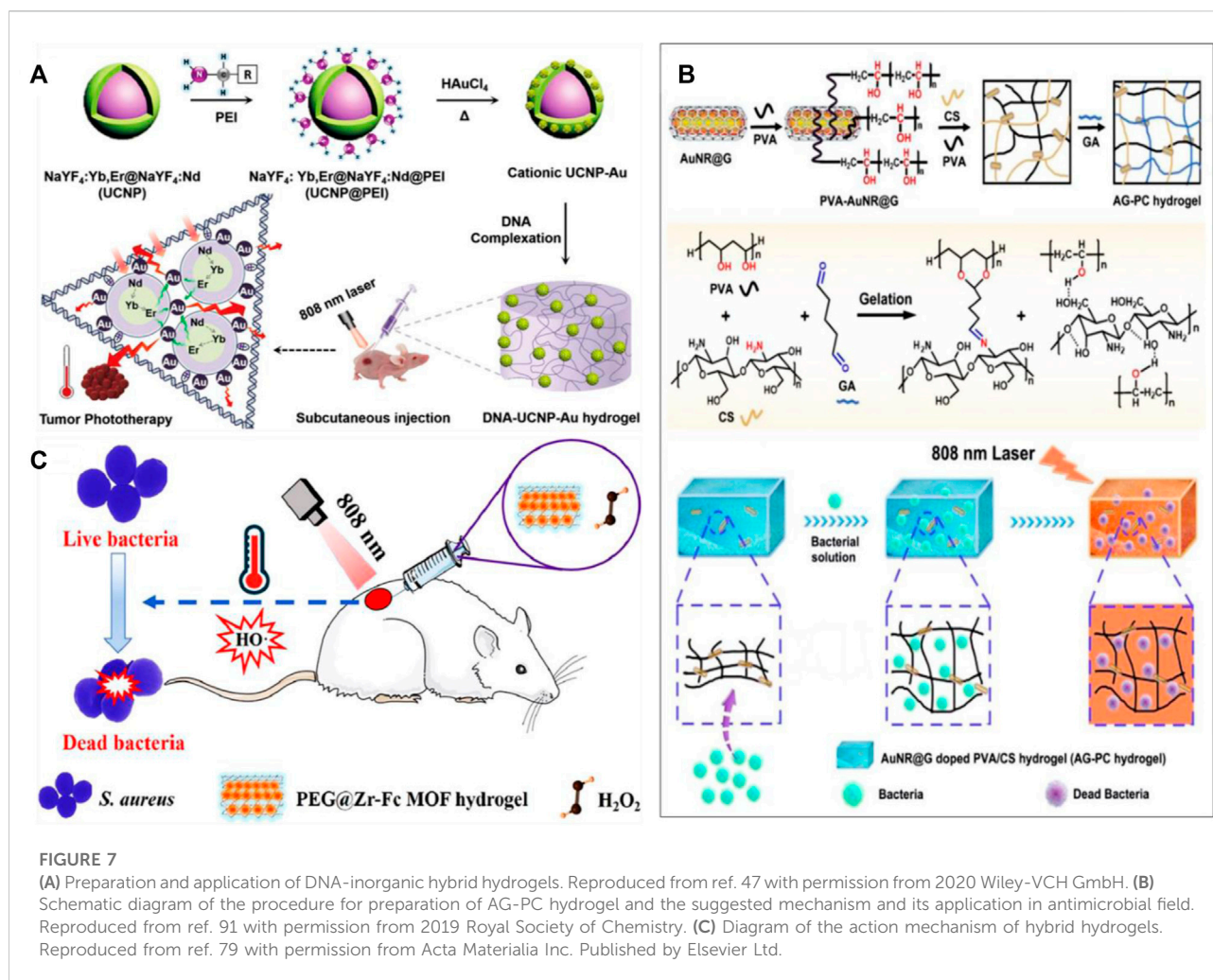
Prussian blue (PB) is also a common organic dye nanomaterial. It was called a pigment in history. PB can be prepared in colloidal form by direct synthesis method. It has a strong charge transfer centered at ~700 nm and a large tail in the near-infrared range. The radiation of this band will lead to thermal relaxation, and local hyperthermia can be generated by irradiating in the so-called bio transparent near-infrared window. PB nanoparticles have complete biocompatibility (PB has been approved by FDA) and biodegradability. Fu et al. established an injectable hydrogel containing Prussian blue nanospheres for cancer photothermal therapy (Fu J. et al., 2019). The hydrogel showed satisfactory serum stability and photothermal conversion ability. In addition, the hydrogel

containing the photosensitizer nanospheres has better photothermal conversion efficiency than the nanospheres.

Biliflavin is a dark green bile pigment that is a by-product of the breakdown of hemoglobin. In recent years, the endogenous metabolite biliverin has been shown to have high photothermal conversion properties, as well as cell-protective effects with antioxidant and anti-inflammatory properties. Yao et al. designed a bioinspired green hydrogel (BVSF) (Yao et al., 2020). They incorporated biliverdin into a naturally derived silk fibroin matrix and the resultant hydrogel could be used for anti-glioma, photothermal therapy and wound healing. In the presence of biligreen, the temperature of the hydrogels can rapidly increase to higher than 45°C under NIR irradiation. Meanwhile, BVSF hydrogels can stimulate cell proliferation, migration and adhesion, and perform anti-inflammatory properties, and significantly accelerate wound repair and regeneration.

Composite nanomaterials

During the construction of hydrogel, in addition to the single photosensitive material, two kinds of composite hybrid materials may play a better effect. Liu et al. prepared a hybrid hydrogel by electrostatic complexation of DNA with upconverted rare-earth Au hybrid nanoparticles (Figure 7A) (Liu et al., 2020). The hybrid hydrogel had a higher photothermal efficiency (42.7%) due to the network formed between DNA and rare-earth Au hybrid nanoparticles. Local administration under 808 nm laser irradiation can achieve tumor eradication without recurrence. Xu and his colleagues prepared AG-PC hybrid hydrogels without antibiotics (Figure 7B) (Xu M.-L. et al., 2019). The hydrogel prepared by doping polyvinyl alcohol (PVA)/chitosan (CS) is highly stable. Because AuNR@G has the photothermal conversion characteristics. Therefore, the hybridized hydrogel showed a highly effective inhibition against both gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus* under 808 nm laser irradiation. Xing and his colleagues synthesized a collagen hydrogel using self-assembly initiated by gold biomineralization (Xing et al., 2016). Due to the reversible weak interaction between collagen chains and gold nanoparticles, the hydrogel has shear thinning and self-healing functions. This hybrid hydrogel of gold nanoparticles and collagen chains can be used in local drug delivery and sustained release, and provides novel strategy for a wide range of biomedical applications such as drug delivery and tissue engineering. Wang and colleagues synthesized a carrageenan based hybrid hydrogel functionalized with ZR-Fc MOF nanosheets using COOH-PEG-COOH as a carrier (Figure 7C) (Wang X. et al., 2021). The hybrid hydrogel can trap Gram-negative and Gram-positive bacteria by destroying ROS. The hybrid hydrogel can synergistically kill bacteria by decomposing H₂O₂ into toxic hydroxyl radicals and photothermal effects.



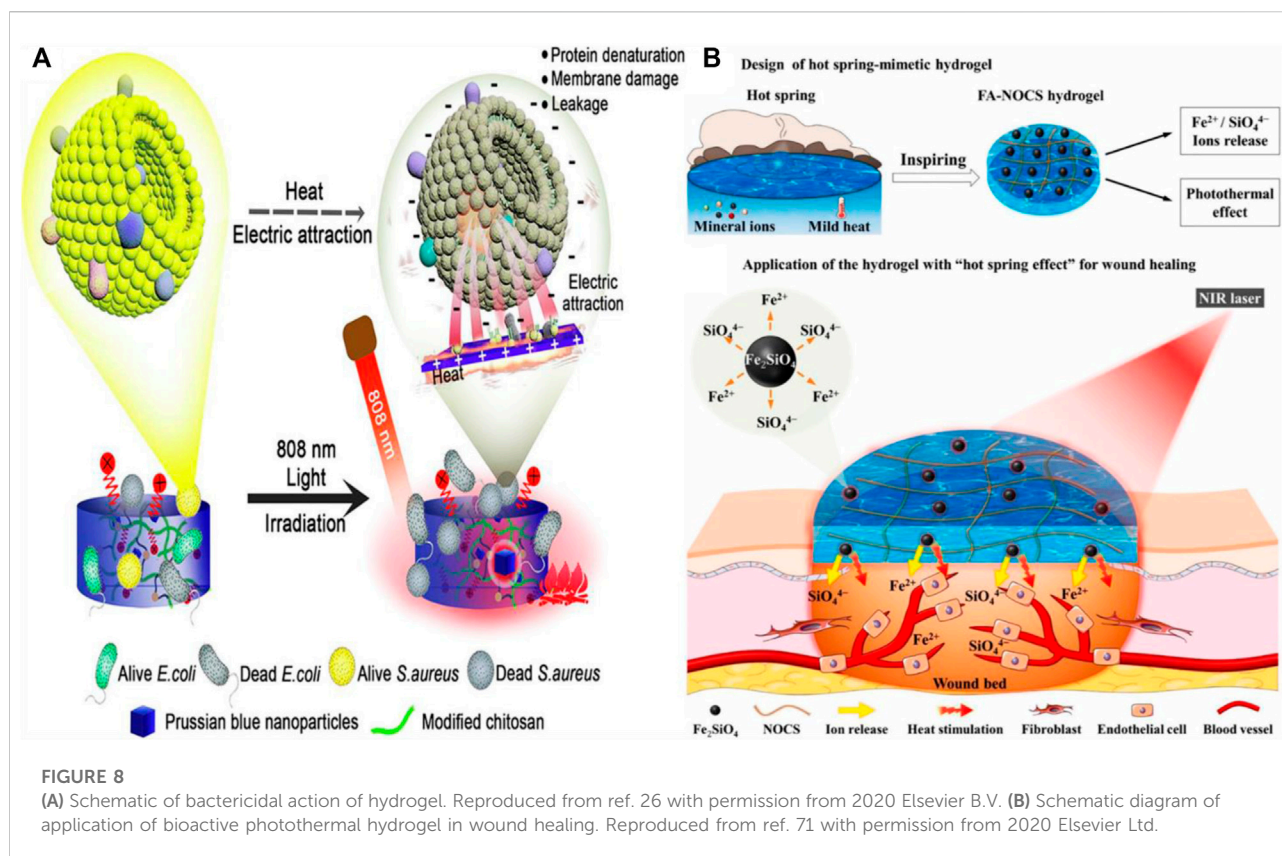
Other nanomaterials

In addition to the above eight photothermal nano-hydrogel materials, there are some other photothermal nano-materials for hydrogel preparation. Ma et al. synthesized a multifunctional Nd Ca Si silicate glass and glass/alginate composite hydrogel (Ma et al., 2020). The hydrogel has fluorescence temperature monitoring performance. Most importantly, due to the addition of bioactive silicate components, the hydrogel has the ability to repair the thermal damage caused by PTT. Therefore, the hydrogel can not only obtain the appropriate PTT temperature for effective treatment of tumors, but also minimize the damage to normal tissues. Han and his colleagues synthesized a new type of photosensitive antibacterial hydrogel (Figure 8A) (Han et al., 2020). The hydrogel can capture bacteria by electrostatic adsorption, and then kill a large number of adsorbed bacteria by high temperature generated by Russel blue MOF particles under near-infrared light. The inhibition rate of *Staphylococcus aureus* and

Escherichia coli could reach 99.97% and 99.93%, respectively. Sheng and his colleagues synthesized a novel bioactive photothermal nanohybrid hydrogel using Fe-bauxite (Fe_2SiO_4) bioceramics and N, O-carboxymethyl chitosan as matrix (Figure 8B) (Sheng et al., 2021). The photothermal nanohybrid hydrogel has good $\text{Fe}^{2+}/\text{SiO}_4^{4-}$ release and photothermal properties, which can simulate the therapeutic effect of hot spring. Animal Experiments have proved that hydrogels can promote angiogenesis and have great application potential in the field of wound repair materials.

Biomedical applications of photothermal nanocomposite hydrogels

The application of photothermal nanocomposite hydrogel in biology mainly depends on the photothermal effect of hydrogel itself and the special role of drug loading. Photothermal



nanocomposite hydrogels can kill bacteria, inhibit tumor and control drug release through photothermal effect. Drugs released through the photothermal effect can further enhance the killing effect on bacteria and tumors. In addition, the photothermal nanocomposite hydrogel can also enhance the repair of bone tissue. These are described in detail below.

Photothermal-controlled drug delivery

One of the main applications of photothermal nanohydrogels is to control the release of drugs by their photothermal properties (Liu C. et al., 2019; Dong et al., 2021). The synergistic treatment of light and heat promotes drugs has better therapeutic effect on diseases. Sun and colleagues combined 5'-guanosine monophosphoric acid, indocyanine green, hemin, and metformin to construct a hydrogel HMI@GEL for breast cancer treatment (Figure 9A) (Sun et al., 2022). Due to the photothermal effect of ICG, the hydrogel has good NIR photo-triggering and continuous drug delivery characteristics. Most importantly, the loading concentration of metformin on the hydrogel was as high as 300 mg ml^{-1} . This is the highest reported in the literature. The combination of metformin and catalase mimic Hemin@mil88 can not only significantly inhibit mitochondrial respiration in tumors, but also achieve high oxygen production *in situ*. The hydrogel

successfully achieves the synchronization of drug synergistic therapy and photo-controlled release under 808 nm laser irradiation, which provides a more reliable direction for the treatment of breast cancer. Zheng and his colleagues prepared a temperature sensitive injectable hydrogel of poly (N-isopropylacrylamide-co-sulfonamide methacrylate) (PNS) in the zwitterionic structure (Zheng et al., 2020). The aqueous dispersion of the nano gel is colloidal at room temperature, and the hydrogel is formed due to thermal sensitivity at 36°C . After the chemotherapeutic drug DOX and photothermal agent PDA nanoparticles are loaded on the hydrogel, DOX can be continuously released from the hydrogel, and the drug release can be accelerated by near-infrared laser irradiation. The synergistic effect of photothermal therapy and local chemotherapy shows a better anti-cancer effect. Geng and his colleagues prepared polyacrylic acid-B-N-isopropylamid-B-acrylic acid/polypyrrole the temperature sensitive composite polymer nanogel through redox polymerization in PNA micelles dissolved in pyrrole (PPy@PNA) (Figure 9B) (Geng et al., 2020). The hydrogel has sensitive sol-gel phase transition behavior, shear dilution characteristics and excellent photothermal properties. It can induce drug release through NIR, and promote drug penetration in tumors. Hou et al. synthesized a powerful injectable agarose hydrogel containing sodium humate and doxorubicin (Figure 9C) (Hou et al., 2018). Under near-infrared

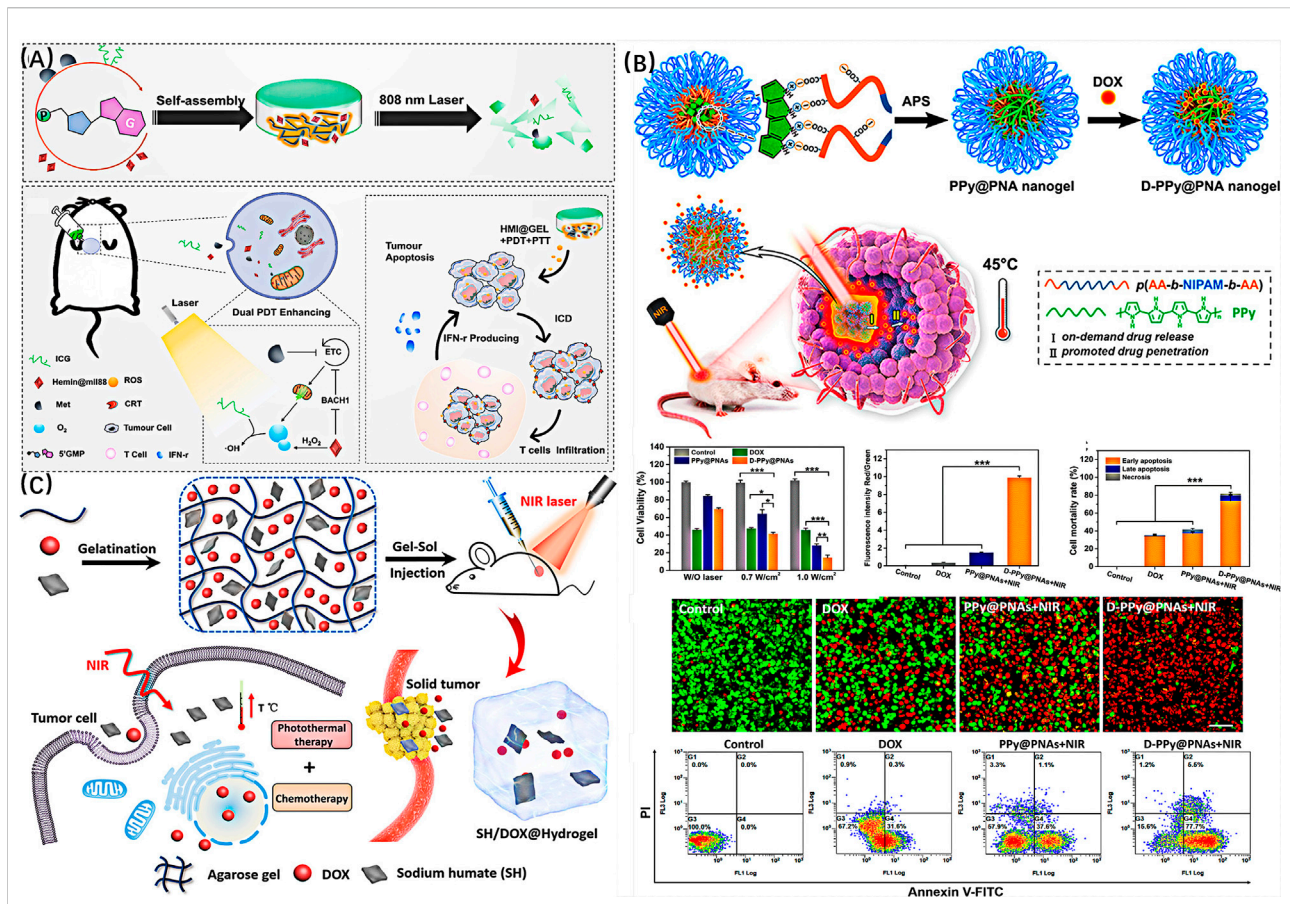


FIGURE 9

(A) Schematic illustration of HMI@GEL. Reproduced from ref. 72 with permission from 2022 Elsevier Ltd. (B) Schematic diagram of preparation of temperature sensitive nano hydrogel and its application in temperature controlled drug release for tumor treatment. Reproduced from ref. 22 with permission from 2020, American Chemical Society. (C) Schematic diagram of the principle of SH/DOX @ hydrogel controlling drug release and tumor ablation by using photothermal effect. Reproduced from ref. 31 with permission from 2018, American Chemical Society.

light irradiation, SH can effectively convert light energy into heat energy, thereby inducing local high temperature, and continuously release drugs through typical gel sol transition. The drug release rate can be controlled by changing the concentration of agarose, SH and DOX, or the laser power density and irradiation time. Animal experiments show that this light triggered drug release and local hyperthermia combined with chemotherapy photothermal therapy have excellent tumor inhibition.

Photothermal bacterial killing and wound repair

The harm caused by bacterial infection has been puzzling people. Antibiotics can be used for wound healing to avoid bacterial infection. Long term use of antibiotics may lead to drug resistance. The commonly used gold ion antibacterial is reduced because of its toxicity. Therefore, photothermal therapy

has been introduced into the field of antibacterial, it provides an effective treatment strategy for wound infection (Xu J.-W. et al., 2019; Chen et al., 2020).

Wang et al. combined pH sensitive bromothymol blue and near-infrared absorption conjugated polymer into heat sensitive chitosan hydrogel (Figure 10A) (Wang et al., 2020b). Diagnose of the biofilm of *Staphylococcus aureus* (*Staphylococcus aureus*) and the acidic microenvironment of infected wounds were carried out by visible color changes in hydrogels. After rapid diagnosis, hydrogels can be used to treat infect sites, even stubborn biofilms that are difficult to eradicate, by hyperthermia under the irradiation of NIR laser (808 nm). Through thermotherapy, it has broad-spectrum antibacterial activity against gram positive, gram negative and drug-resistant bacteria. Han and his colleagues prepared a GelDA/PGO hydrogel through dopamine grafted gelatin (GelDA) and polydopamine coated graphene oxide (PGO). The introduction of graphene oxide makes hydrogels have excellent photothermal antibacterial

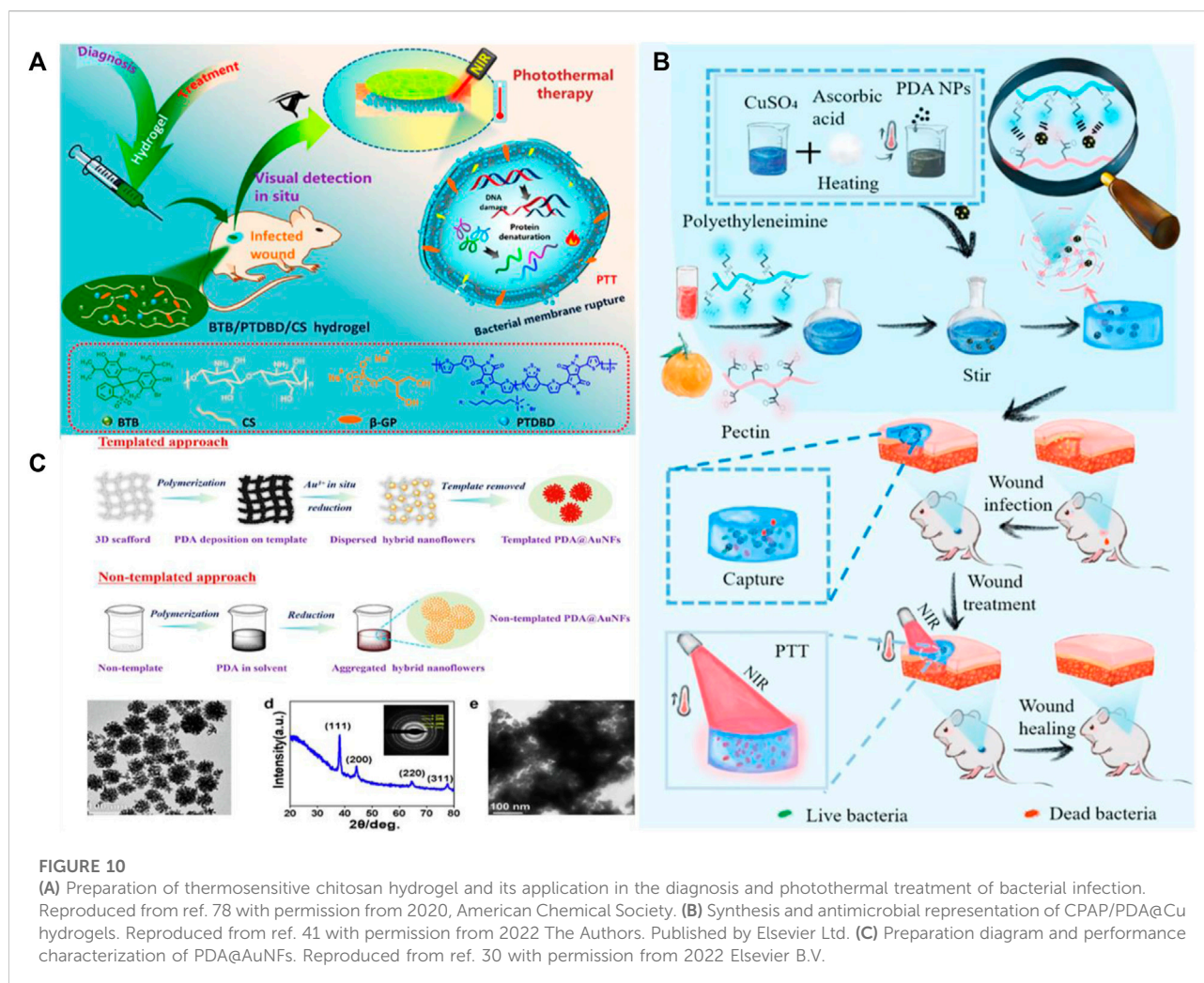


FIGURE 10

(A) Preparation of thermosensitive chitosan hydrogel and its application in the diagnosis and photothermal treatment of bacterial infection. Reproduced from ref. 78 with permission from 2020, American Chemical Society. (B) Synthesis and antimicrobial representation of CPAP/PDA@Cu hydrogels. Reproduced from ref. 41 with permission from 2022 The Authors. Published by Elsevier Ltd. (C) Preparation diagram and performance characterization of PDA@AuNFs. Reproduced from ref. 30 with permission from 2022 Elsevier B.V.

properties and is beneficial to enhance wound healing *in vivo* (Han et al., 2022). Deng et al. put single fatty acid Fe (III) (TA Fe) nanoparticles in agarose (AG) hydrogel (Deng H. et al., 2020). When the NIR was irradiated for 10 min, the temperature sharply increased to 58°C, indicating that the nanocomposite hydrogel produced had significant photothermal effects. Through *in vitro* antibacterial test, the hydrogel can effectively kill nearly 99% of bacteria under 10min NIR irradiation. Li and his colleagues prepared a hydrogel with photothermal properties by *in-situ* culturing Cu NPs on the surface of polydopamine and introducing an electrolyte hydrogel precursor (Figure 10B) (Li Z. et al., 2022). Its photothermal properties are better than those of pure polydopamine nanoparticles, and it also can capture and kill bacteria through electrostatic adsorption, which helps to improve the antibacterial performance. In addition, You and others also put forward their own views. They prepared a multifunctional hydrogel wound dressing using copper/tannic acid nanosheets (You et al., 2022). In addition to absorption exudate, the dressing has adjustable photothermal antibacterial

and reactive oxygen species scavenging properties. These properties can not only play the role of hemostasis, antibacterial and anti-inflammatory, but also achieve wound repair and restore skin physiological function by reducing inflammation. Hong et al. selected the bacterial cellulose scaffold as the template platform for polydopamine deposition, controlled the growth of mixed polydopamine and gold nanoparticles through *in situ* deposition and reduction technology, and controlled the template platform within 100 nm (Figure 10C) (Hong et al., 2022). Under the irradiation of NIR, the template showed good photothermal performance, and the photothermal temperature could rise from 45°C to 55°C, with good antibacterial effect. Yin et al. used the photothermal properties of copper disulfide nanoparticles to prepare hydrogels through metal coordination (Yin et al., 2022). The photothermal antibacterial efficiency of hydrogels against *Staphylococcus aureus* and *Escherichia coli* can reach 99%. At the same time, it can reduce inflammation and promote skin tissue.

Photothermal cancer cell inhibition

In today's society, tumors threaten people's life and health, but the effect of traditional surgical resection and chemotherapy is not very ideal. People began to care about other effective treatments to treat tumors. The application of photothermal nanomaterials in disease therapy has attracted great attention (Ruhi et al., 2018; Yan et al., 2022). Yang and his colleagues developed a methylcellulose hydrogel platform with photothermal properties and injectable properties (Yang et al., 2021). The hydrogel can be rapidly heated to more than 50.0°C under near-infrared irradiation to achieve the goal of killing tumor cells and preventing tumor recurrence after surgery *in vivo*. The addition of MP in hydrogels can not only improve the strength of hydrogels, but also facilitate the attachment of normal breast cells and adipocytes to promote breast reconstruction. Liu et al. developed a bio-inorganic hybrid hydrogel with near-infrared light response (Liu et al., 2020). The addition of DNA in the NIR response system makes the hydrogel a porous interconnected structure. The interaction between adjacent DNA strands and UCNP-Au nanoparticles makes the photothermal efficiency of the hydrogel as high as 42.7%, and the tumor can be eradicated under 808 nm laser irradiation. Zhou and his colleagues reported an injectable self-healing hydrogel system based on CuS nanoparticles (Zhou et al., 2021). Hydrogels were constructed by forming a 3D network of polyethylene glycol functionalized CuS nanoparticles with surface amino groups with oxidized dextran and PEG with amino terminal groups. The introduction of CuS NPs endows hydrogels with excellent photothermal properties and can inhibit tumor growth in a subcutaneous skin-tumor model. Interestingly, the hydrogel also continuously releases Cu²⁺, which can promote the proliferation of fibroblasts and vascular endothelial cells. Lee and his colleagues synthesized a biodegradable hemoglobin hydrogel (Lee et al., 2019). The hydrogel was constructed by the rapid formation of PEG linkage between hemoglobin and polyethylene glycol *in situ*. The hemoglobin hydrogel was heated to 60°C under near-infrared laser irradiation, which could effectively inhibit A549 lung cancer cells. Most importantly, the hemoglobin has good biocompatibility and can be completely degraded in 21 days after implantation.

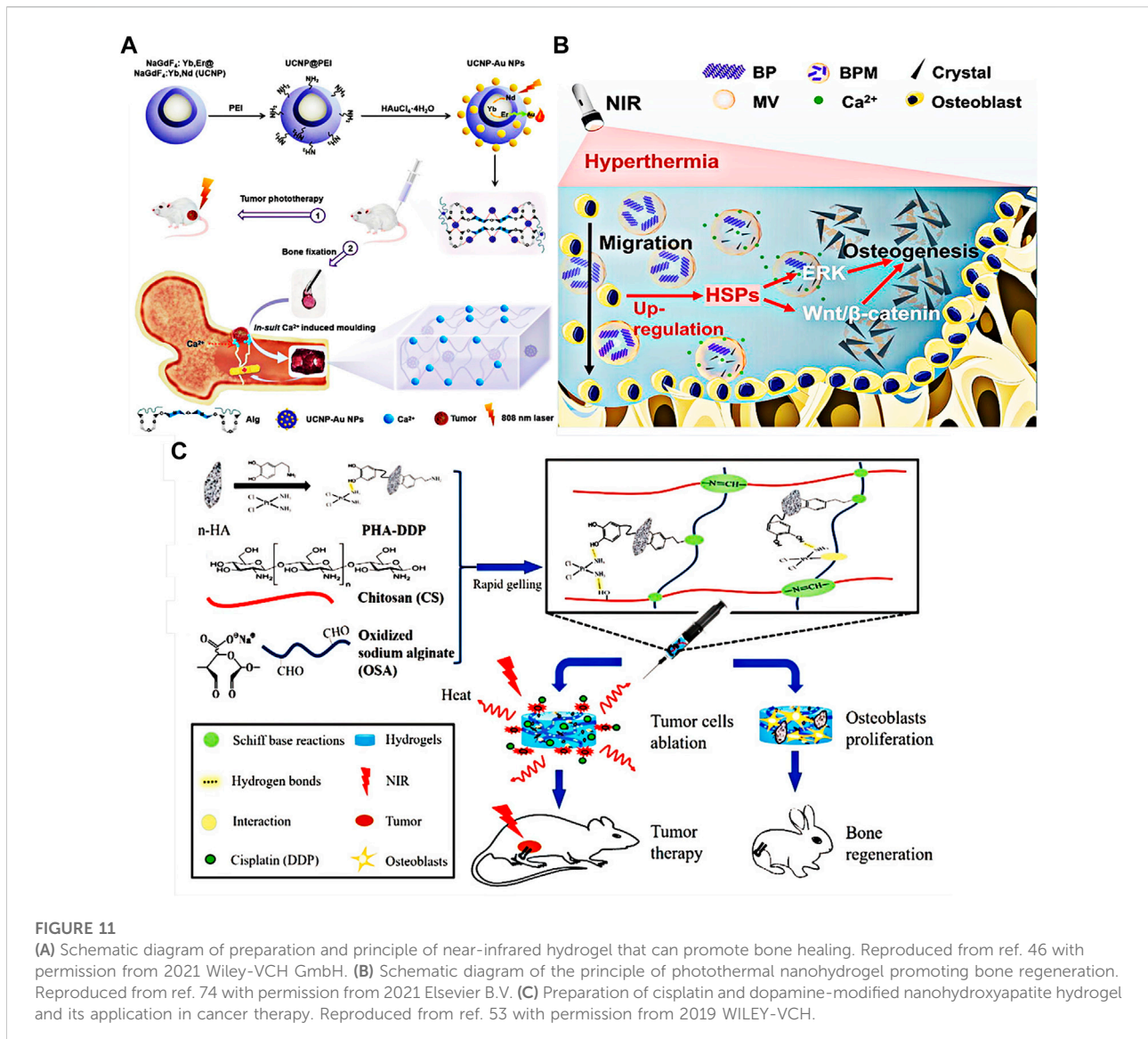
Photothermal-enhanced bone tissue regeneration

The number of patients with bone defects and osteoarthritis is increasing. It not only brings pain to patients, but also is a major problem in clinical treatment. The main reason for the failure of bone defect and osteoarthritis repair is the loss of osteoblasts and chondrocytes. (Marchev et al., 2017). The biomineralization of calcium and phosphorus ions in

extracellular matrix is the key to bone regeneration. (de Melo Pereira & Habibovic, 2018; Cheng et al., 2020). At present, many scholars have introduced photothermal therapy into orthopedic repair, providing a new strategy for this field (Wang et al., 2020a; Chang et al., 2022). Wu et al. prepared hydrogels by using the photothermal properties of polydopamine nanoparticles and methacryloyl gelatin (Wu et al., 2022). Animal studies have shown that, hydrogels can promote the alkaline ALP activity and the formation of extracellular calcified nodules. Polydopamine nanoparticles can provide mild photothermal treatment and have better bone repair ability. Liu et al. synthesized a new NIR hydrogel with high photoresponse and mechanical strength using rare-earth gold hybrid nanoparticles and alginate molecules (Figure 11A) (Liu et al., 2021). The hydrogel can not only eradicate tumors by local photothermal therapy, but also effectively promote bone repair as an internal matrix.

Miao and his colleagues prepared nanocomposite hydrogels through BP nano sheets (Miao et al., 2019). Under near-infrared radiation, nanocomposite hydrogels have effective photothermal antibacterial properties. In the absence of bone induction factors, hydrogel matrix could enhance mineralization and bone regeneration, and promote bone formation *in vitro*. Tan et al. prepared EMC simulated hydrogel through BP nano sheet coated by MSC membrane (Figure 11B) (Tan et al., 2022). Under NIR irradiation, they activated heat shock proteins mediated matrix metalloproteinases (MMPs) to induce mild photothermal effect and stimulate the recruitment of osteoblasts. At the same time, the thermal decomposition of BP will release phosphate ions into the surrounding medium and attract calcium ions to form hydroxyapatite in the ECM, which is conducive to the migration and differentiation of osteoblasts and achieves the effect of bone repair.

In addition, Qing et al. added MgO nanoparticles and black phosphorus nanoparticles into poly (vinyl alcohol)/chitosan hydrogels (Qing et al., 2022). The hydrogel can kill more than 99.9% of *Staphylococcus aureus* and *Escherichia coli* under NIR irradiation. The released Mg ions stimulate mesenchymal stem cells to migrate to the hydrogel, and cooperate with the released phosphate to promote osteogenic differentiation, then synergistic photothermal antibacterial and bone regeneration can be achieved. Luo et al. successfully synthesized hydrogels containing cisplatin and dopamine-modified nanohydroxyapatite by Schiff base reaction between aldehyde group on sodium alginate and amino group on chitosan (Figure 11C) (Luo et al., 2019). The results show that the photothermal properties of hydrogels under near-infrared laser (808 nm) irradiation can effectively ablate tumor cells *in vitro* and inhibit tumor growth *in vivo*. Most importantly, because of the abundant functional groups on dopamine, hydrogels can also promote the adhesion and proliferation of bone marrow mesenchymal stem cells, further promote the formation of bone tissue.



Other biomedical applications

The eye is an important and special organ of the human body, with unique physiological and anatomical characteristics. If eye diseases occur, it is difficult to cure. With the frequent use of lighting screens, eye diseases have become an increasingly serious phenomenon (Li et al., 2021). Although there are many drugs for relieving or treating eye in drops, powders and ointments on the market, there are many deficiencies in their use, such as low permeability, low bioavailability, short stay time, frequent administration, etc. The intraocular bioavailability of

these drugs is very low, usually only 1–5% (Wang F. et al., 2021). At present, some non-traditional ocular drug delivery systems have been extensively studied, such as nano carriers, hydrogels, liposomes, etc. Researchers began to introduce photothermal nano hydrogels into ocular drug delivery systems. Pang et al. developed a mini eye patch based on photothermal conversion hydrogel (Pang et al., 2019). The hydrogel eye piece was prepared by cross-linking gelatin and gold nanoparticles. The heating performance of eye piece was obtained through infrared temperature profile and cycling temperature experiments. The results show that the eye system can perceive a variety of visible

light and react through spontaneous heating. Through the hydrogel patch, it can convert all kinds of light into heat, stimulate the lacrimal gland to produce more tears to alleviate dry eye.

Microfluidics refers to the science and technology involved in the system of using micro pipes (tens to hundreds of microns in size) to process or manipulate micro fluids (nano liters to a liter in volume). Through electrical stimulation to regulate and transfer plasma nanomaterials, photosensitive materials are introduced to prepare a hydrogel based microfluidic platform with photothermal response, which can effectively provide photothermal therapy in tumor treatment. Ha and his colleagues developed one microfluidic platform based on electric response hydrogel for brain tumor targeting and photothermal therapy (Ha et al., 2020). Electroresponsive hydrogels are composed of silver nanowires (Ag NWs) with high conductivity and biocompatible collagen type I gels. The electroresponsive hydrogel based microfluidic actuator platform can deliver the electroresponsive smart nanomaterials, while the vasopeptide coupled gold nanorods provide photothermal therapy. The combination of electric response and photothermal therapy can promote the release of tumor drugs and effectively improve the therapeutic effect. Fu et al. introduced the principle of photothermal sensor into the analysis device based on microfluidic paper (μ PADs), a photothermal microfluidic sensing platform with multi-channel dual-mode quantitative readout driven by a NIR laser is developed (Fu G. et al., 2019). Prussian blue was used as an analyte related photothermal agent, which was synthesized *in situ* in the thermal reaction poly (n-isopropylacrylamide) hydrogel as a photothermal sensor on the chip. The photothermal effect driven by the NIR laser not only triggered the dose dependent heat generation on the chip, but also triggered the phase change induced release of hydrogel dye, and enabled the dual-mode vision based on thermal image and distance to read the analyte concentration quantitatively in a multi-channel manner. The elevated temperature of the hydrogel on the tablet and the moving distance of the dye solution released are directly proportional to the concentration of PB.

Conclusion and perspectives

The application and development of metal nanomaterials, carbon-based nanomaterials, metal sulfide/oxide nanoparticles, black phosphorus nanomaterials, MXenes nanomaterials, polymer nanomaterials and organic dye materials in the preparation of photothermal nano hydrogels are reviewed in this paper. The applications of photothermal nano hydrogels in drug release, photothermal sterilization, photothermal cancer cell

inhibition and bone repair enhancement were introduced in detail. Photothermal nano hydrogels can inhibit the growth of bacteria and tumor cells through the high temperature generated by the photothermal effect, and control the sol-gel transition behavior of hydrogels through the photothermal characteristics, thus control the drug release. The synergistic effect of photothermal therapy and chemotherapy can greatly enhance the therapeutic effect and reduce the drug toxicity. There is no doubt that the photothermal therapy of local hyperthermia combined with chemotherapy will have further applications in medical engineering.

Author contributions

FD: Investigation, Conceptualization, Writing-original draft. LZ: Investigation, Writing-original draft. XC: Investigation, Review and editing. WY: Investigation, Review and editing. LN: Investigation, Review and editing. MW: Conceptualization, Supervision, Writing-review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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