NIR light-assisted phototherapies for bone-related diseases and bone tissue regeneration: A systematic review

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Abstract

Recently, the rapid development of biomaterials has induced great interest in the precisely targeted treatment of bone-related diseases, including bone cancers, infections, and inflammation. Realizing noninvasive therapeutic effects, as well as improving bone tissue regeneration, is essential for the success of bone-related disease therapies. In recent years, researchers have focused on the development of stimuli-responsive strategies to treat bone-related diseases and to realize bone regeneration. Among the various external stimuli for targeted therapy, near infrared (NIR) light has attracted considerable interests due to its high tissue penetration capacity, minimal damage toward normal tissues, and easy remote control properties. The main objective of this systematic review was to reveal the current applications of NIR light-assisted phototherapy for bone-related disease treatment and bone tissue regeneration. Database collection was completed by June 1, 2020, and a total of 81 relevant studies were finally included. We outlined the various therapeutic applications of photothermal, photodynamic and photobiomodulation effects under NIR light irradiation for bone-related diseases and to realize bone regeneration, based on the retrieved literatures. In addition, the advantages and promising applications of NIR light-responsive drug delivery systems for spatiotemporal-controlled therapy were summarized. These findings have revealed that NIR light-assisted phototherapy plays an important role in bone-related disease treatment and bone tissue regeneration, with significant promise for further biomedical and clinical applications.

Key words: Near infrared light, phototherapy, drug delivery systems, bone-related diseases, bone tissue regeneration

Introduction

Bone-related diseases such as cancers, infection, and trauma, are common clinical problems that lead to irreparable bone defects, which remains an intractable problem for clinicians, leading to ongoing suffering for patients, and representing a burden to healthcare systems [1]. To develop a precise treatment to minimize the adverse influence on the surrounding healthy tissues and to maximize the efficacy of osteogenesis and bone tissue regeneration, selective targeted therapeutic strategies have been investigated [2]. Various strategies have been proposed for the targeted therapy of disease regions. A noninvasive technique utilizing external stimulation to control the therapeutic effect on the targeted tissues is an ideal solution [3-5].

Among several external stimuli-responsive therapy approaches, those using light irradiation have attracted significant attention. The commonly used
light for photoresponsive therapies can be generally divided into three subcategories: ultraviolet (UV) (200–400 nm), visible (Vis) (400–700 nm), and near infrared (NIR) (700–1300 nm) lights [3]. The choice of different phototherapies in clinical applications is related to the tissue penetration depth of light, which is wavelength-dependent. Compared with UV and Vis lights, NIR light exhibits a higher tissue penetration depth because of its minimum refraction and attenuation by endogenous biomolecules and chromophores (e.g., water, blood, and melanin). For instance, the tissue penetration depth of the rat skin is 7.5 ± 0.5 mm at λ = 705 nm, 6.3 ± 0.5 mm at λ = 633 nm, and only 1.0 ± 0.02 mm at λ = 408 nm, respectively [6]. In vivo studies in male rats also showed that an 810 nm laser could penetrate 51% through the skull and 40% through the scalp and skull combined in the prefrontal regions. In terms of 660 nm, only 5.8% of light could pass through the scalp plus skull and reach the cortical surface [7]. Moreover, the NIR light can be easily controlled in space and time, representing a promising alternative for precisely targeted therapies in vitro and in vivo. The controlled use of NIR light as an external stimulus is also highly biocompatible, with little toxicity or injurious effects on normal tissues [8]. Therefore, NIR light-assisted phototherapy, which realizes effective, noninvasive, precisely controlled therapeutic effects, has attracted increased research attention, leading to multiple solutions in a wide range of fields.

With the rapid development of nanotechnology, a series of NIR light-responsive nanomaterials with specific light absorbance and conversion abilities in NIR light windows have revealed marked potential for phototherapy strategies. Many kinds of nanomaterials, such as carbon-based nanomaterials, metal nanostructures, metal sulfides or oxides, and other organic or inorganic nanostructures, have attracted interest because of their NIR light-responsive properties [9]. These NIR light-responsive nanomaterials have been widely exploited not only for disease diagnosis, but also for photothermal therapy (PTT), photodynamic therapy (PDT), and drug delivery systems because of their good photostability, efficient photothermal conversion ability, and minimal toxicity to normal cells and tissues. One commonly used phototherapy strategy, PTT, directly utilizes photosensitizing agents to convert the photo energy of the penetrating NIR light into thermal effects, which can be used to ablate nearby abnormal tissues, with minimal damage to normal cells. Contrasting, during PDT, photosensitizer molecules can generate reactive oxygen species (ROS) under NIR light irradiation, which have a targeted phototherapeutic effect on pathological tissues [2, 8].

The local hyperthermia and high ROS concentration have shown stable anticancer performance in vitro and in vivo [10, 11]. Furthermore, NIR light-responsive drug delivery systems have been proposed based on the photothermal and photodynamic effects of nanomaterials. These NIR light-responsive drug delivery systems are able to trigger the controlled release of the encapsulated therapeutics to enhance their therapeutic efficacy [12].

As a noninvasive spatiotemporal controlled treatment technology, NIR light-assisted phototherapy has played an important role in clinical therapies of many diseases. To date, existing published reviews have mainly summarized the development of NIR light-responsive nanomaterials and their clinical applications for biomaging and phototherapeutic effect in cancer therapies [11, 13, 14]. However, few reviews have discussed NIR light-assisted phototherapies for bone-related diseases and bone tissue regeneration. Recent studies have reported NIR light-induced antibacterial and anti-inflammatory therapeutic effects for the treatment of bone-related diseases [15-18]. At the same time, several studies have demonstrated that NIR light triggered mild localized heat, and the photoelectronic microenvironment could accelerate bone tissue regeneration [19, 20]. Moreover, NIR light-responsive drug delivery systems have not only been used for targeted cancer therapies, but also for the delivery of growth factors for bone tissue regeneration [21, 22]. These latest studies have revealed that NIR light-assisted phototherapy is likely to realize more precise and less invasive therapeutic solutions not only for bone cancers, but also for implant infections, osteochondral inflammation, and bone tissue regeneration. In addition, another photoinduced strategy, photobiomodulation therapy, has been proposed for bone disease treatment and tissue regeneration. However, the above applications of NIR light-assisted treatment have not yet been reviewed.

Therefore, this article systematically reviews the recent progress of NIR light-associated phototherapies for bone-related diseases and bone tissue regeneration, intending to reach a general audience comprising not only medical scientists and clinicians, but also material scientists and engineers. Moreover, the current challenges and perspectives within the development of NIR light-assisted phototherapies for further clinical applications are proposed and discussed. A systematic understanding of NIR light-assisted phototherapies would help to achieve the desired therapeutic effects in the treatment of bone-related diseases, providing penetrating insights into precision medicine and regenerative medicine.
Methods

A primary database collection was constructed for all relevant publications in English (January 1, 1950 – June 1, 2020) based on three databases (PubMed, MEDLINE, and the Web of Science). The following keywords and their combination were used: (NIR OR (near infrared) OR (near infrared light) OR (near infrared laser)) AND bone AND (therapy OR treatment). The keyword search resulted in 1333 initial articles (June 1, 2020). The initial articles were screened based on the following inclusion and exclusion criteria:

Inclusion criteria: 1) Articles focused on bone disease treatment, such as bone cancers, bone infections, osteoarthritis, bone metabolic diseases, bone defect repair, and bone tissue regeneration; 2) only studies using NIR light as the treatment method; and 3) only phototherapies under the NIR light irradiation within the biological window of NIR light (700–1300 nm).

Exclusion criteria included: 1) Duplicate studies; 2) books, reviews, meetings, letters, literature updates, and laboratory protocols; 3) studies using NIR light in the detection and imaging of bone-related diseases (such as NIR spectroscopy for skeletal muscle oxygenation and hemodynamics monitoring, NIR spectroscopy for progressive degeneration of cartilage and bone monitoring, NIR spectrometry for material characterization, and NIR fluorescence for in vivo molecule, cell or tissue imaging); 4) articles in languages other than English; and 5) articles without full text (abstract only).

Titles or abstracts of the initially retrieved articles were evaluated for inclusion. Each article was reviewed by two researchers independently. When the title and abstract could not be excluded, the full text of the article was evaluated. This resulted in 71 articles fulfilling the eligibility criteria. In addition, reference tracking of the included publications was completed and all the relevant articles were checked and added. Finally, a total of 81 articles were fully examined for discussion in this systematic review (Figure 1).

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**Figure 1.** Flowchart for the study screening and selection process, and reasons for inclusion/exclusion. N = number of publications. NIR, near infrared.
Results

Literature search output

Among the 81 included studies, PTT and PDT were used in 39 and 3 studies, respectively, while 11 studies introduced a combined use of PTT and PDT for the treatment of bone-related diseases. NIR light-assisted phototherapies have been used to treat different bone-related diseases (44 studies). The most common types of diseases were osteosarcoma (19 studies), bone metastasis of breast cancer (6 studies), implant-related infections (8 studies), rheumatoid arthritis (3 studies), and osteoarthritis (1 study). Meanwhile, NIR light-assisted phototherapies have been used to accelerate bone tissue regeneration (13 studies). Twelve of these studies focused on NIR light-responsive delivery systems to trigger the spatiotemporal controlled release of drugs or molecules to enhance the therapeutic effects to treat bone-related diseases.

Moreover, 24 studies reported the photobiomodulation effects of NIR light irradiation upon cells and tissues, including 8 studies that discussed the photobiomodulation effects on stem cells, and 16 studies that focused on the effect of photobiomodulation therapy on bone healing and dental treatment (Figure 2).

Summary of NIR light-responsive nanomaterials and NIR light radiation conditions

In the 81 included studies, 28 types of photosensitive agents were reported for their superior photothermal and photodynamic performances. These agents comprised a series of biocompatible photothermal transduction agents or photosensitizers based on metal, carbon, transition metal dichalcogenides, polymers, and semiconductors, which have significant NIR light-absorption ability and superior light-responsive capabilities [15, 23-26]. They have high photothermal conversion efficiency to generate heat and good photocatalytic characteristics to produce ROS in the NIR region [20, 27, 28]. They can also convert NIR light into the secondary local energy, which induces structural changes in drug carriers to trigger drug release [29]. The most commonly used NIR light-responsive biomaterials in the included studies were carbon-based nanomaterials (13 studies), metal nanostructures (11 studies), metal oxide nanoparticles (8 studies), metal sulfide nanostructures (9 studies), and black or red phosphorus (7 studies). The current most commonly used NIR light-responsive nanomaterials are summarized in Figure 3.

Moreover, to investigate the most suitable radiation conditions, we obtained an overview of the wavelength of the NIR light, the power density and the radiation time used in the different studies and their photothermal or photodynamic effects. The most commonly used window of NIR light for biological application was the NIR-I window (700–1000 nm). NIR light can be generated via many types of available lasers, such as Nd:YAG (neodymium-doped yttrium aluminum garnet) or diode lasers. Most studies (45/81) delivered the NIR light irradiation via an 808 nm diode laser module with fiber coupling. By contrast, phototherapies using NIR coherent (lasers) or noncoherent infrared light (light-emitting diodes, LED) have been investigated for their photobiomodulation effects on stem cells and bone tissue regeneration. Eighteen studies reported the photobiomodulation effect of low level or high frequency NIR laser therapy, while six studies investigated the effect of NIR LED photobiomodulation on cells and tissues.

Figure 2. A pie chart representing the number and distribution of different applications of NIR light-assisted phototherapies in the included articles. NIR, near infrared.
Figure 3. A summary of the current most commonly used NIR light-responsive nanomaterials. NIR, near infrared.

| Nanomaterials            | Graphene nanosheets | Carbon nanotubes | Gold nanoparticles | Gold nanorods | Gold nanocages | Magnetic nanoparticles | MoS₂ nanosheets | Ti₃C₂ nanosheets | Nb₃C nanosheets | Black phosphorus | Indocyanine Green | Polydopamine coating |
|--------------------------|---------------------|------------------|--------------------|---------------|----------------|----------------------|-----------------|-----------------|-----------------|------------------|------------------|---------------------|

Discussion

The results of the literature search showed NIR light-assisted phototherapy exhibited great potential for the precise and controlled treatment of bone-related diseases and bone tissue regeneration because of its deep tissue penetration ability, high spatiotemporal resolution, and the unique biocompatibility of NIR light irradiation. Compared with other traditional therapy strategies, these phototherapies are considered as more minimally invasive, easily controlled, and precise to achieve the desired therapeutic effects and avoid damage to normal tissues. In this systematic review, these NIR light-assisted treatment strategies for bone-related disease and bone tissue regeneration are summarized, based on their mechanisms and applications.

**NIR light-assisted phototherapy for bone cancers**

Bone cancers generally refer to malignant bone tumors, including autologous skeletal system cancers (such as osteosarcoma and chondrosarcoma) and bone metastasis of cancers from other tissues (primary cancers in the lung, breast, and prostate) [30, 31]. Compared with traditional cancer radiotherapy strategies, NIR light-assisted targeted phototherapies, inducing PTT and PDT, mainly occur in cancer tissues and cause no obvious damage to normal tissues, thus minimizing adverse side effects [32-34]. PTT can exploit a local heating effect to realize the ablation of cancer tissues by combining light-absorbing materials with NIR light irradiation. The use of NIR light as an external stimulus allows for remote and high spatiotemporal control of local heating, leading to irreversible destruction of cancer tissue [35]. Hyperthermia over 50 °C, followed by NIR light irradiation, can cause irreversible DNA and protein denaturation in cancer regions [36]. Contrastingly, in PTT, the photosensitizer enters an excited state after NIR light radiation and generates various ROS from molecular oxygen. This NIR light-induced release of ROS in PDT can kill cancer cells and damage the cancer vasculature, depriving the cancer of oxygen and nutrients [12, 37].

With the rapid development of nanotechnology, a series of NIR light-responsive nanomaterials have emerged and shown great advantages for efficient bone cancer phototherapy by serving as photothermal agents for PTT or as photosensitizers for PDT. [38-40]. According to the different administration methods, there are three main applications of these NIR
light-responsive nanomaterials for bone cancer therapy. Firstly, these nanomaterials could be injected intravenously. The prolonged blood circulation time and the targeted tumor accumulation effects of these nanomaterials make highly efficient \textit{in vivo} PTT and PDT possible, offering promising options for the treatment of the primary bone cancers or problematic cancer bone metastasis from other tissues [41]. However, the direct intravenous injection of nanomaterials might cause \textit{in vivo} toxicity. The biosafety of these NIR light-responsive nanomaterials should be confirmed by testing normal hematology parameters to minimize the potential side effects [42]. Secondly, these NIR light-responsive nanomaterials can be integrated into scaffolds for combinatory bone cancer therapy and tissue regeneration. Considering that a few bone tumor cells inevitably remain around the bone defect after surgical intervention, the implanted bifunctional scaffolds could exhibit not only prominent photothermal and photodynamic performances, but also outstanding bone regeneration capabilities, which provide optimal alternatives for the treatment of large bone tumors and tumor-initiated bone defects [31, 43-45]. Thirdly, these NIR light-responsive nanomaterials could also be integrated into NIR light-triggered drug release systems, exhibiting versatility via their precise and controlled release of anticancer drugs [12]. NIR light-absorbing nanomaterial-doped drug-carriers could exhibit outstanding photothermal and photodynamic therapeutic effects, as well as superb anticancer drug encapsulation efficiency, through intravenous administration, serving as promising candidates for bone cancer therapies [46]. In this section, we will introduce these three applications of NIR light-assisted phototherapy for bone cancers based on three different administrations. The mechanisms of these applications are shown in Figure 4.

\textbf{Figure 4.} Schematic illustration showing the applications of NIR light-responsive nanomaterials, NIR light-responsive bone scaffolds, and NIR light-triggered drug delivery systems for bone cancer therapy. The NIR light-responsive nanomaterials (A) and scaffolds (B) with the specific features of highly efficient photothermal conversion and controllable ROS release provide an effective biomaterial platform for the phototherapy of bone cancers. C. The NIR light-triggered drug delivery systems can realize controlled release of the encapsulated anti-tumor drugs for bone cancer chemotherapy. NIR, near infrared; ROS, reactive oxygen species.
NIR light-responsive nanomaterials in the phototherapy of bone cancers

The efficiency of anticancer phototherapy depends on the photothermal and photodynamic performances of the employed NIR light-responsive nanomaterials. Several nanomaterials, such as carbon-based nanomaterials [47], metal nanoparticles [48], and ceramic-based nanomaterials [32] are being developed for bone cancer phototherapies because of their efficient photothermal conversion function under NIR light irradiation after direct intravenous administration. A series of carbon-based nanomaterials have been widely used in NIR light-assisted phototherapies because of their excellent photothermal performances under the NIR light irradiation. For example, nanosized graphene oxide (GO) has been used as a localized, minimally invasive therapeutic approach for osteosarcoma therapy by inducing hyperthermia-mediated membrane damage of cancer cells under 808 nm NIR irradiation [47]. Similarly, multi-walled carbon nanotubes (MWNTs) can also result in an efficient hyperthermia under 808 nm NIR irradiation and could remarkably suppress the growth of tumors, reducing the amount of cancer-induced bone destruction [49]. At the same time, metal nanoparticles, such as the classical platinum nanoparticles, could display enhanced accumulation at cancer-bearing bone lesions and inhibit the growth of bone cancer via PTT under an 808 nm NIR laser irradiation [48, 50]. Jie et al. reported a novel kind of oxygen vacancy-rich tungsten bronze nanoparticle (Na₅WO₃) against breast cancer osteolytic bone metastasis, which acts via the desirable photothermal effect under NIR laser irradiation [51]. This treatment strategy could also inhibit the osteoclastic RANKL and Sclerostin expression from tumor cells, thus further attenuating downstream osteoclastogenesis. Notably, the shapes of these nanoparticles can change their photo-responsive properties, and NIR absorbing nanorods and nanocages have been preferred for in vivo applications [4]. The heat released by these nanoparticles under NIR light irradiation would efficiently kill cancer cells via photothermal ablation. Meanwhile, these nanosized particles can be cleared efficiently via the kidneys, decreasing their long-term toxicity in clinical applications [50].

Alternatively, the tissue penetration efficacy of NIR light would also influence the efficiency of anticancer phototherapies. The biological window of NIR light can be divided into NIR-I (700–1000 nm), and NIR-II (1000–1300 nm) biowindows [32, 52]. To date, the NIR-I biowindow has been more commonly used in phototherapies because most kinds of NIR light-responsive nanomaterials have exhibited favorable photothermal and photodynamic properties in the NIR-I biowindow. Considering that the tissue penetration depth of light increases with increasing wavelength, the NIR-II biowindow exhibits deeper tissue penetration compared with the NIR-I light. It would be helpful to develop efficient photoresponsive nanomaterials with high NIR-II absorbance [35, 42]. Recently, a new family of two dimensional (2D) nanomaterials, named MXenes, have generated great interest because of their unique physiochemical performance and excellent photothermal conversion efficiency [53]. These 2D nanomaterials, which comprise transition metal carbides, nitrides, or carbonitrides, have displayed highly efficient in vivo photothermal performance in both the NIR-I and NIR-II windows [54]. For example, Lin’s group reported a 2D niobium carbide (Nb2C), a novel kind of MXene, with an extraordinarily high efficiency of photothermal conversion for bone tumor ablation [32]. They revealed its highly efficient in vitro and in vivo photothermal cancer therapies in both NIR-I (36.4%) and NIR-II (45.65%) biowindows. Similarly, hybrid carbon dots (CDs)/WS₂ heterojunctions have also been reported for NIR-II enhanced PTT of osteosarcoma. These CDs/WS₂ heterojunctions exhibited improved cancer targeting ability after intravenous injection and efficient photothermal conversion under the 1064 nm laser irradiation. The deep tissue penetration ability in the NIR-II biowindow means that the satisfying ablation of cancer tissues can be realized at relatively low laser exposure, even when being covered by a 10 mm thick additional tissue. Although the NIR-II biowindow has attracted great attention for tumor xenografts, to date, it has rarely been used for bone cancer therapies, mainly because of a lack of suitable photosensitive agents with desirable strong absorption and high efficiency of photothermal conversion in the NIR-II biowindow [32, 55-57]. More effort should be made to develop efficient light-responsive nanomaterials with high NIR-II absorbance to broaden the application prospects of NIR light-assisted phototherapies for bone cancer.

Meanwhile, nanomaterials can serve as an effective photosensitizer to generate ROS after NIR light irradiation for photodynamic therapy in bone cancer therapy. Pd-bacteriochlorophyll has been reported as a photosensitizer that induces PDT, leading to hypoxia, necrosis, and eradication of prostate cancer bone metastasis [41]. This photosensitizer could target the tumor vasculature after direct intravenous administration and is cleared rapidly from the circulation within a few hours. Raucci et al. [58] proposed ultrathin 2D black
phosphorous (BP) as a promising candidate for osteosarcoma therapy because of its photodynamic effect. 2D BP could inhibit the metabolic activity of osteosarcoma cells and induce the proliferation and osteogenic differentiation of human preosteoblast cells in vitro, thus playing important roles in anticancer therapies and regenerative medicine. The nanomaterials and the different radiation conditions used in current bone cancer phototherapies are summarized in Table 1. These nanomaterials show great promise for bone cancer therapy and bone tissue engineering.

NIR light-responsive scaffolds for the phototherapy of bone cancers

Massive cancer-induced bone defects and residual cancer cells are two critical problems in the prognosis of bone cancers. It is essential to fabricate multifunctional scaffolds endowed with the ability to eradicate cancer cells and remodel bone tissue simultaneously during bone cancer therapy [31]. In the present review, a series of strategies have been proposed to combine NIR light-responsive nano-

Table 1. NIR light-responsive biomaterials for bone cancer phototherapy

| Phototherapies | Photoresponsive agents | Wavelength (nm) | Power density (W cm⁻²) | Time (min) | irradiation condition | In vitro phototherapeutic effects | In vivo phototherapeutic effects | References |
|---------------|------------------------|----------------|------------------------|-----------|----------------------|-----------------------------------|----------------------------------|------------|
| PTT           | Nanographene oxide sheets | 808            | 1.5 W cm⁻²           | 5         |                      | Effective decrease of osteosarcoma cell viability | -                                | Cucuændez et al. [47] |
| Multi-walled carbon nanotubes (MWNTs) | 808 | 1.25 W cm⁻² | 1 | Effective decrease of breast cancer cell viability to 74.3% | Significantly suppressed growth of breast cancer bone metastasis | Lin Z. et al. [49] |
| Platinum nanoparticles | 808 | 3.5 W cm⁻² | 7 | Obvious G1 arrest in cancer cells | Efficient bone-targeted anticancer activity | Zhou Z. et al. [48] |
| Na₂WO₄ nanoparticles | 800 | 2.5 W cm⁻² | 10 | Effective decrease in tumor cell viability | Effective inhibition of tumor growth in a bone metastasis model | Wang C. et al. [50] |
| 2D NbC nanosheets | 808 | 1.5 W cm⁻² | 5 | Remarkable decrease in breast cancer cell viability | Significant decrease in tumor volume | Jie S. et al. [51] |
| Carbon dot/WS₂ nanosheets | 1064 | 0.6 W cm⁻² | 5 | Effect of human osteosarcoma cell viability | Complete eradication of osteosarcoma without recurrence | Geng B. et al. [42] |
| PDT           | Pd-bacteriopheophorbide | 650-808 | 360 J/cm² | 30 | Complete eradication of osteosarcoma | Complete tumor elimination in 50% | Koudinova N. V. et al. [41] |
| Black phosphorus | 650-808 | - | 15 | Inhibited metabolic activity of osteosarcoma cells | - | Raucci M.G. et al. [58] |

PTT: Photothermal therapy; PDT: Photodynamic therapy.

Table 2. NIR light-responsive scaffolds for bone cancer phototherapy

| Photoresponsible agents | References | Scaffolds | Irradiation condition | Step 1 mechanism | Step 2 mechanism | In vivo phototherapeutic effects: Bone tumor bearing model of nude mice | In vivo bone tissue regeneration |
|------------------------|------------|----------|----------------------|-----------------|----------------|---------------------------------------------------------------|-------------------------------|
| Bismuth (Bi)           | Wang L. et al. [60] | Bi-doped BG scaffolds | 808 | 1.5 W cm⁻², 10 min | Photothermal effect of Bi | Osteoconductivity and osteo-inductivity of BG | Complete elimination at day 3 (rat osteosarcoma cells, 15 days) | NM |
| Hydrogenated black TiO₂ (H-TiO₂) | Zhang W. et al. [61] | Hydrogenated black TiO₂ coating | 808 | 0.4 W cm⁻², 2 days after implantation | Photothermal effect of H-TiO₂ | Osteogenesis abilities of H-TiO₂ coating with hierarchical micro/nano-topographies | Enhanced cellular adhesion, spread, proliferation, and osteogenic differentiation of rBMSCs (in vitro) |  |
| Photo-responsive agents | References | Scaffolds | Irradiation condition | Step 1 mechanism: Anti-cancer effects | Step 2 mechanism: Bone tissue regeneration | In vivo phototherapeutic effects: Bone tumor bearing model of nude mice | In vivo bone tissue regeneration |
|-------------------------|------------|----------|-----------------------|----------------------------------------|-------------------------------------------|-------------------------------------------------|------------------------------|
| Fe$_3$O$_4$             | Zhao P. et al. [62] | GdPO$_4$/Chitosan/Fe$_3$O$_4$ scaffolds | 808 nm, 4.6 W cm$^{-2}$, 3 min for 14 days | Photothermal effect of Fe$_3$O$_4$-nanoparticles (a) | Osteogenesis abilities of as-released Gd$^{3+}$ ions | Significantly reduced tumor growth (human breast cancer bone metastasis tumor cells, 14 days) | BV/TV: 61.23 ± 2.12% (calvarial-defect model of SD rats, 12 weeks) |
| SrFe$_2$O$_4$          | Yang F. et al. [63] | Multifunctional magnetic mesoporous calcium/silicate/chitosan porous scaffolds | 808 nm, 0.3 W cm$^{-2}$, 6 min post-implantation | Photothermal effect of SrFe$_2$O$_4$ (a) | Osteogenesis abilities of magnetic nanoparticles and calcium silicate | Significantly decreased tumor growth (osteosarcoma MNNG cells, 12 days) | More newborn bone formation, BV/TV: 57.32 ± 3.53% (calvarial-defect model of SD rats, 12 weeks) |
| Lu J. et al. [64] | Magnetic SrFe$_2$O$_4$ nanoparticles modified mesoporous bioglass/chitosan porous scaffold | 808 nm, 0.3 W cm$^{-2}$, 6 min | Photothermal effect of SrFe$_2$O$_4$ nanoparticles | Osteoconductivity of bioglass and SrFe$_2$O$_4$ nanoparticles | Tumor cell necrosis rate: 84.6% (osteosarcoma MNNG cells, 12 days) | More newborn bone formation, BV/TV: 63.4% (calvarial-defect model of SD rats, 24 weeks) |
| Cu-TCPP               | Dang W. et al. [65] | Cu-TCPP/TCP composite scaffolds | 808 nm, 0.9 W cm$^{-2}$, 10 min every day in the first week, once every two days in the second week | Photothermal effect of Cu-TCPP nanosheets | Osteogenesis abilities of constituent elements (Cu, Ca and P) | Effective ablation and restrained growth of tumor (Saos-2 cells, 18 days) | Excellent bone-forming bioactivity (femoral defect model of New Zealand white rabbits, 8 weeks) |
| CuFe$_3$S$_4$          | Dang W. et al. [63] | CuFe$_3$S$_4$ nanocrystals integrated 3D printed BG scaffolds | 808 nm, 0.55 W cm$^{-2}$, 10 min every day in the first week, every 2 days in the second week | Photothermal effect of CuFe$_3$S$_4$ nanocrystals | Osteogenesis abilities of constituent elements (Cu, Fe, Se, Ca, S, P) | Tumor cell necrosis rate: 96% (Saos-2 cells, 14 days) | Good bone-forming capacity (femoral defect model of New Zealand white rabbits, 8 weeks) |
| MoS$_2$               | Wang H. et al. [66] | MoS$_2$/PLGA coating BG scaffolds | 808 nm, 2 W cm$^{-2}$, 10 min at day 1, 2, 4 and 8 | Photothermal effect of MoS$_2$ nanosheets | Osteogenesis abilities of constituent elements (Mo, Si, Ca, P) | Decreased tumor size to 15% (human osteosarcoma cells, 14 days) | Excellent osteogenic ability (calvarial-defect model of SD rats, 3 months) |
| DTC crystal           | Xiang H. et al. [45] | DTC@3D printed BG scaffolds | 808 nm, 1.5 W cm$^{-2}$, 10 min | Photothermal effect of DTC | Osteoconductivity and osteo-inductivity of BG | Promoted substantial tumor suppression (Saos-2 cells, 2 weeks) | Better newborn bone formation BV/TV: 43.5 ± 2.7% (calvarial-defect model of SD rats, 8 weeks) |
| Graphene oxide (GO)   | Xu C. et al. [71] | Tricalcium silicate/GO bone cement | 808 nm, 0.66 W cm$^{-2}$, 10 minutes every two days | Photothermal effect of GO | Osteogenesis abilities of constituent elements (Ca, Si) | Decreased tumor volume, progressive apoptosis, and necrosis (Saos-2 cells, 14 days) | Enhanced cellular adhesion, spread, proliferation, and osteogenic differentiation of MC3T3-E1 cells (in vitro studies) |
| Ma H. et al. [59]     | GO/TCPP 3D printed scaffold | 808 nm, 0.42 W cm$^{-2}$, 10 min | Osteoconductivity and osteoinductivity of TCP | | Tumor cell necrosis rate: 83.28% (osteosarcoma MG-63 cell, 15 days) | Promoted bone-forming bioactivity (calvarial-defect model of New Zealand white rabbits, 8 weeks) |
| Carbon dots (CD)      | Lu Y. et al. [68] | Zero-dimension al CD doped chitosan/nanohydroxyapatite scaffold | 808 nm, 1.0 W cm$^{-2}$, 10 min | Photothermal effect of CD | Osteoconductivity and osteo-inductivity of nano-hydroxyapatite | Effective suppression of tumor growth (UMR-106 osteosarcoma cells, 14 days) | Enhanced osteoinductivity (glutears maximus muscle pouch of SD rats, 4 weeks) |
| MXene                 | Yang Q. et al. [44] | 2D mesoporous silica/NbC MXene integrated 3D printed BG scaffolds | 808 nm, 1.0 W cm$^{-2}$, 10 min, 1 day after implantation | Photothermal effect of NbC MXene (a) | Phosphorus and calcium components degraded from BG | Complete elimination without recurrence (Saos-2 cells, 2 weeks) | Excellent osteogenic performance (calvarial-defect model of SD rats, 24 weeks) |
| Pan S. et al. [31]    | 2D Ti$_3$C$_2$ MXene | 808 nm, 1.0 W cm$^{-2}$, 10 min, 1 day after implantation | Photothermal effect of Ti$_3$C$_2$ MXene | Osteoconductivity and osteo-inductivity of BG | Complete elimination without recurrence (Saos-2 cells, 2 weeks) | Better newborn bone formation (calvarial-defect model of SD rats, 24 weeks) |
The classical metal nanomaterials have generated great interest because of their excellent photothermal conversion performance in anticancer therapies. It has been reported that bismuth-doped BG scaffolds displayed high photothermal conversion efficiency to induce hyperthermia for osteosarcoma treatment [60]. Meanwhile, multiple kinds of metal oxide nanoparticles have been used as photoabsorbers to kill cancer cells. Zhang’s groups have reported a black TiO2 nanoparticles-coated Ti6Al4V implant for the reconstruction of large bone defects followed by surgical resection of bone cancers [61]. The black TiO2 nanoparticle coating endowed the implant with good biocompatibility, strong NIR light absorbance, and efficient photothermal conversion ability under 808 nm laser irradiation. Similarly, magnetic iron oxide nanoparticles, such as Fe3O4 nanoparticles and M-type ferrite nanoparticles (SrFe12O19), could serve as photothermal agents in scaffolds. These scaffolds could exhibit photothermal anticancer therapeutic abilities and enhanced bone regeneration simultaneously [62-64]. Meanwhile, metal-organic frameworks (MOFs), such as copper coordinated tetraakis (4-carboxyphenyl) porphyrin (Cu-TCPP) also have strong NIR light absorption [65]. The released bioactive ions of the Cu-TCPP combined with TCP scaffolds can simultaneously stimulate osteogenesis and angiogenesis in the bone defect. Moreover, a copper-based CuFeSe2 nanocrystal, a kind of semiconductor, has been reported to act as a new class of efficient photothermal agent. By functionalization with the CuFeSe2 nanocrystals, 3D printed BG scaffolds exhibited excellent photothermal performance under 808 nm laser irradiation [43]. Another kind of PTT agent, MoS2 nanosheets, has also been introduced into BG scaffolds for anticancer treatment and bone tissue regeneration [66]. Besides these inorganic nanomaterials, a kind of NIR light-absorbing organic charge-transfer cocrystal with great photothermal conversion performance has also been integrated into BG scaffolds to fabricate bifunctional therapeutic implants [45]. Additionally, organic NIR light-responsive biomaterials modification, such as dopamine modification, would also provide scaffolds with an excellent NIR photothermal effect [67]. These modified bifunctional scaffolds could be implanted precisely into the tumor sites and could induce effective local hyperthermia (over 50 °C) under the NIR light irradiation, which resulted in enhanced tumor cell apoptosis and tumor ablation. After irradiation, the mesenchymal stem cells (MSCs) could migrate to the bone defects gradually and attach, proliferate, and differentiate on the bioactive scaffolds, leading to long-term bone regeneration.

In addition, carbon-based nanomaterials, such as GO and single-/multi-walled carbon nanotubes, offer great promise for cancer photothermal therapies because of their strong NIR light absorbance, excellent photothermal performance and satisfactory cytocompatibility [68-71]. It also has been reported that carbon-based nanomaterials can effectively improve bone regeneration by inducing the directional migration and osteogenic differentiation of BMSCs [72, 73]. For example, GO-modified biofunctional tricalcium silicate bone cement and TCP bone scaffolds have been fabricated for cancer therapy and bone tissue regeneration [59, 71]. The MWNT-modified scaffold also exhibited high photothermal performance in the treatment of cancer related bone defects [70]. Zero dimensional carbon dots are another kind of carbon-based nanomaterial. They can bind specifically to calcified bones and have been used to eliminate osteosarcoma and enhance bone tissue regeneration [68]. In vitro and in vivo studies of these carbon-based nanomaterial-coated scaffolds have successfully demonstrated their bifunctional properties of photothermal therapy and bone regeneration, which could pave the way for the design and fabrication of novel implants with simultaneous bone cancer killing and bone tissue-remodeling capacity.

With the rapid advance of nanotechnology, a series of new nanomaterials, including MXenes and Lanthanide (Ln) nanomaterials, have also been incorporated into bone scaffolds for cancer phototherapies recently. MXene nanosheets, such as 2D Ti3C2 MXene and Nb2C MXene, have unique...
structural characteristics, including a large specific surface area and adjustable physicochemical properties. They display enriched photothermal and photodynamic therapeutic effects in both the NIR-I and NIR-II biowindows, providing intriguing biomaterial platforms for the diversified treatment of bone cancers [31, 44]. LaB₆, a chemical compound of La and B elements, also shows efficient NIR photothermal conversion ability. The LaB₆-modified TCP scaffold is an ideal option for both the ablation of bone cancers and the repair of defect regions [74]. The emergence of these novel photothermal agents has provided the possibility for the development of NIR light-responsive scaffolds, offering new avenues to construct highly efficient therapeutic platforms for bone caners.

**NIR light-triggered drug delivery systems for bone cancer chemotherapy**

Controlled drug delivery systems exhibit an enhanced therapeutic efficiency as well as reduced systemic toxicity compared with conventional bone cancer chemotherapies. Photothermal (generation of heat) and photodynamic (production of ROS) mechanisms could be used to break, isomerize, or rearrange molecules and achieve drug release. After reaching the cancer tissues, the drug delivery systems can be triggered by NIR light to realize controlled release of the encapsulated therapeutics [12]. The energy of NIR light radiation could be converted into heat in photothermal systems. This heat conversion can change the physicochemical properties of thermostimulated agents in drug delivery systems, resulting in drug release [12, 75]. In the photodynamic-induced release system, the photosensitizer generates singlet oxygen (¹O₂) from molecular oxygen after NIR light radiation and mediates the PDT. The highly active ¹O₂ interacts with the specific molecule in the drug delivery system, leading to a structural change that triggers drug release [12, 75].

Considering that the well-distributed porous structure of mesoporous silica nanoparticles (MSNs) is promising for drug loading and encapsulation, a series of NIR light-absorbing agent-doped MSNs have been designed for photochemotherapy of bone cancer. For example, Lu et al. [46] designed novel bismuth sulfide (BS)@MSNs to deliver doxorubicin (DOX), a classical anticancer drug, to treat osteosarcoma. The outstanding photothermal effect of the BS nanoparticles not only controlled the release of DOX, but also induced cell death, exerting a combined bone-targeted chemothermal therapeutic effect. Xue’s group also engineered a biodegradable polydopamine (PDA) coated bioactive glass nanoparticle platform for on-demand NIR light-triggered anticancer drug (DOX) release and photothermal ablation of bone cancers [76]. Similarly, Sun’s group have designed a gold nanorod-decorated mesoporous silica nanoparticle to deliver zoledronic acid (ZOL), which exhibits strong bone affinity and efficient anticancer abilities for breast cancer bone metastasis [77].

In addition, mussel-inspired FDA nanoparticles also possess efficient photothermal conversion and intrinsic drug anchoring abilities [78, 79]. They have been used widely as versatile carriers for anti-tumor drug delivery in the photochemotherapy of bone cancer. For example, Wang’s groups have designed alendronate (ALN)-anchored PDA nanoparticles to release the anticancer drug, 7-ethyl-10-hydroxycamptothecin [80]. Similarly, injectable chitosan hydrogels containing PDA-decorated hydroxyapatite (HAp) nanoparticles could realize localized controlled and sustained release of cisplatin when exposed to NIR light [81]. Moreover, a kind of dual responsive drug delivery system, which could be triggered by both NIR laser irradiation and acidic stimulus, has been developed for bone cancer therapy. Gu et al. [82] reported a bovine serum albumin-bioinspired iridium oxide nanosystem for chemophotothermal therapy of osteosarcoma. This nanosystem displayed both NIR light and pH-responsive DOX release profiles in vitro, which enhanced the therapeutic anticancer effect. The above anticancer drug carrier systems could be administrated through intravenous injection and are mainly distributed to, and accumulated in, bone cancer tissues, displaying efficient photochemotherapeutic performance under NIR laser irradiation. The radiation parameters of NIR light-induced phototherapies, as well as the encapsulation and release efficiencies of these anticancer drug delivery systems, are summarized in Table 3.

**NIR light-assisted phototherapy for bone infection and inflammation**

In recent years, NIR light-assisted phototherapy has been recognized as a promising strategy, not only for anticancer therapy, but also for antibacterial and anti-inflammation therapies [15, 58, 83]. The NIR light-responsive nanomaterials could be coated onto the bone implants, exhibiting outstanding photothermal and photodynamic therapeutic effects to destroy bacterial integrity or biofilm structure via hyperthermia and ROS generation [16]. Meanwhile, NIR light-responsive nanomaterials can be directly injected into the inflamed joints, inducing local heat under NIR irradiation and delivering ROS simultaneously to remove inflamed tissues [83]. Therefore, the current applications of NIR light-assisted phototherapies for classical implant-related...
bone infections, as well as common chronic arthritis, will be introduced and summarized in this section (Figure 5).

Figure 5. Schematic illustration revealing the mechanisms of NIR light-assisted phototherapy for bone infection and inflammation. A. NIR light-induced hyperthermia increases the bacterial membrane permeability under ROS stimulation, accelerating the eradication of the biofilm formed on the surface of the implants. B. The NIR light can penetrate the inflamed joints and generate local heat and ROS to eliminate inflamed tissues, decreasing the generation of inflammatory cytokines, synovial erosion, and tissue destruction. NIR, near infrared; ROS, reactive oxygen species.

Table 3. NIR light-triggered drug delivery systems for bone cancer photo-chemotherapy

| Nanocarriers structure | Photo-responsive agents | Radiation conditions | The mechanisms of phototherapeutic effects | Anticancer drugs | Encapsulation efficiency | Release efficiency | Application | References |
|------------------------|-------------------------|----------------------|------------------------------------------|-----------------|------------------------|-------------------|-------------|------------|
| Bismuth sulfide (Bi2S3)@mesoporous silica nanoparticles (MSNs) | Bi2S3 | 808 | 1 | 10 | The outstanding photothermal conversion efficiency of Bi2S3 nanoparticles | DOX | 99.85% | Almost 30% | Osteosarcoma | Lu Y. et al. [46] |
| PDA coated bioactive glass nanoparticle (BGN) | PDA | 808 | 1.4 | 10 | The stable NIR light-excited photothermal effects of PDA coating | DOX | 59% | Almost 10% (50th day, pH = 5.5) | Bone cancer therapy and bone tissue regeneration | Xue Y. et al. [76] |
| Gold nanorods enclosed inside mesoporous silica nanoparticles | Gold nanorods | 808 | 1.2 | 10 | The outstanding photothermal conversion efficiency of gold nanorods | ZOL | 35.4% | Almost 90% | Breast cancer bone metastasis | Sun W. et al. [77] |
| PDA-alendronate/SN38 nanoparticles | PDA | 808 | 3.6 | 30 | Highly efficient photothermal effects of PDA nanoparticles | SN38 | - | Over 50% | Malignant bone tumors and osteosclerosis | Wang Y. et al. [80] |
| PDA-decorated nano-hydroxyapatite chitosan hydrogel | PDA | 808 | 2 | 2 | The excellent photothermal effects of PDA coating | Cisplatin | 91.49% | Sustained release: 71% (9th day) | Breast cancer bone metastasis and bone tissue regeneration | Luo S. et al. [81] |
NIR light-assisted phototherapy for implant-related infections

Massive bone defects caused by bone cancers, infections, fractures, and the increasing number of orthopedic diseases have led to a high demand for artificial implants [84]. Bacteria-induced infections of artificial implants and insufficient bone tissue integration are still the main problems after implantation, which could lead to implant failure [85, 86]. The implant surface could provide appropriate conditions for bacteria to adhere and proliferate. Once a pathogenic biofilm forms on the implant surface, the host defense and conventional antibiotic treatment cannot work, leading to infections of the surrounding tissues [87, 88]. The implants coated with the NIR light-responsive nanomaterials have received increased attention because of their outstanding photothermal and photodynamic therapeutic performances. These implants could exhibit controlled, noninvasive, and nonsurgical antibacterial properties by generating heat and ROS. The antibacterial efficiency reached about 97% for Staphylococcus aureus at a hyperthermia of 88.8 °C for 15 min when photothermally triggered by NIR light [28]. Moreover, releasing ROS, such as \(^1\)O\(_2\), can damage cell membranes and cell walls of bacteria and kill the pathogens [89]. However, when using photothermal or photodynamic therapy alone, the excessive temperature caused by the photothermal effect or release of ROS during the photodynamic therapy could damage normal tissue and induce serious side effects. Therefore, it is desirable to combine the two therapies to kill bacteria. A high temperature of 50 °C can facilitate permeability of the bacterial membrane, making it easier to kill bacteria via ROS [27, 28]. In addition to efficient antibacterial properties, ideal bone implants should also display good biocompatibility and promote osteogenic capabilities. Based on these mechanisms, several studies have reported NIR light-assisted antibacterial coating on the surface of bone implants to treat implant-related infections. These NIR light-assisted antibacterial strategies are discussed in more detail below and are summarized in Table 4.

For example, mussel-inspired PDA is emerging as an excellent photothermal agent because of its good biocompatibility and efficient NIR light-responsive photothermal conversion. It has been reported that photosensitizer-loaded mesoporous PDA nanoparticles, as well as MoS\(_2\)/PDA-arginine-glycine-aspartic acid (RGD) decorations of bone implants, displayed synergistic photothermal and photodynamic effects for antibacterial therapy [16, 17]. Similarly, a hybrid BS@Ag\(_3\)PO\(_4\) coating on bone implants also exhibited good photothermal effects using BS as photocatalyst [90]. The integration of Ag\(_3\)PO\(_4\) also endows the implant with bacteriostatic properties. This NIR light-triggered inorganic hybrid semiconductor heterojunction-decoration system is biocompatible and effective to eliminate biofilms. In addition, red phosphorus has been proven to be an efficient photothermal coating on bone implants because of its good biocompatibility and more effective photothermal ability compared with BP. Its degradation products are mainly phosphate, which plays an important role in bone tissue regeneration [91]. Tan’s group have reported a red phosphorus-IR780-RGDC (arginine-glycine-aspartic-acid-cysteine)-coated antibacterial titanium (Ti) bone implant [28, 92]. The outstanding photothermal effects of red phosphorus and the stable photodynamic effects of IR780 meant that the biofilm could be eliminated efficiently under a safe 808 nm NIR light irradiation at 50 °C, \(in vitro\) and \(in vivo\), without damaging the normal tissues. At the same time, the RGDC decoration on the surface of the Ti implant enhanced the adhesion, proliferation, and osteogenic differentiation of MSCs. These coating strategies on the surfaces of bone implants have provided great promise for clinical orthopedic applications.

Hang et al. [27] have reported another dual light coirradiation system, including both 660 nm visible light and 808 nm NIR light, for biofilm elimination and osteointegration of bone implants. They designed a biocompatible TiO\(_2\)/MoS\(_2\)/PDA/RGD nanorod array on Ti implants, which could kill bacteria under dual light coirradiation and promoted the osteogenic capabilities of the implants. While the photothermal conversion ability of 660 nm is relatively weak, the yield of ROS under dual light irradiation is almost the sum of individual light irradiation, which enhanced the antibacterial ability of the implants. The physical puncture of the nanorods also contributed to the

| Nanocarriers structure | Photo-responsive agents | Radiation conditions | The mechanisms of photothermal effects | Anticancer drugs | Encapsulation efficiency | Release efficiency | Application | References |
|------------------------|------------------------|----------------------|--------------------------------------|-----------------|------------------------|------------------|-------------|------------|
| Bovine serum albumin (BSA)-iridium oxide (IrO\(_2\)) nanoparticles | IrO\(_2\) | Wavelength (nm) 808 | Power density (W cm\(^{-2}\)) 1 | Radiation time (min) 5 | The superior photothermal conversion efficiency of IrO\(_2\) nanoparticles | DOX 27.4 wt% | Osteosarcoma | Gu W. et al. [82] |

DOX: Doxorubicin, PDA: Polydopamine, ZOL: Zoledronic acid, SN38: 7-ethyl-10-hydroxycamptothecin.
antibacterial properties of the implants. In addition, a novel photo-sonotherapy strategy has also been designed by fabricating an oxygen deficient S-doped TiO2 coating on Ti implants, which exhibited significant sonodynamic and photothermal abilities [15]. This system achieved an extremely high antibacterial efficiency of 99.995% against Staphylococcus aureus under 15 min NIR light irradiation combined with ultrasound treatment. In addition, besides coating on the surface of bone implants, the NIR light-responsive nanomaterials could also be injected into the knee joint for the clinical treatment of periprosthetic joint infection. Liu et al. [93] has reported curcumin-upconversion nanoparticles (curcumin–UCNPs) for the efficient eradication of drug-resistant bacteria in a deep joint infection by producing singlet oxygen under NIR light irradiation. Curcumin is an extract from the plant Curcuma longa, which has intrinsic antibacterial and anti-inflammatory properties. Compared with traditional therapeutic strategies, this research might offer a new alternative for periprosthetic joint infection.

In summary, the NIR light-assisted phototherapies have shown stable antibacterial photothermal and photodynamic therapeutic performances in vitro and in vivo, representing promising strategies to treat bone infections.

NIR light-assisted phototherapy for arthritis

Worldwide, the prevalence of arthritis is high, and includes over 100 types, of which the most common are rheumatoid arthritis, osteoarthritis, and inflammatory arthritis [94]. NIR light has sufficient penetration depth to reach the deep inflamed joints, which guarantees the efficacy of phototherapies and desirable therapeutic outcomes. NIR light-responsive nanomaterials could exhibit outstanding photothermal and photodynamic therapeutic effects for the anti-inflammation therapy via intra-articular injection, which is similar to the mechanisms in anticancer and antibacterial therapies. These photothermal materials could convert NIR light into localized heat and suppress the inflammatory reaction. In parallel, the photosensitizers in PDT can also be excited into their singlet state under NIR light irradiation, producing ROS to treat inflamed cells and tissues [83, 95]. These synergistic photothermal and photodynamic effects of NIR light-assisted phototherapies might decrease the synovium erosion, chronic inflammation activity, and bone and cartilage destruction, providing a promising approach for arthritis treatment [95].

Rheumatoid arthritis (RA) is a common chronic inflammatory disease that seriously affects the quality of life of the patients, leading to long standing synovitis, degradation of cartilage and bone tissue, and increased disability. Recently, NIR light-assisted phototherapy including PTT and PDT, has received increased attention for noninvasive and spatiotemporal controlled RA treatment [96-98]. Nanoparticles with good biocompatibility, excellent photo-responsive ability, and intrinsic osteogenic/chondrogenic capabilities have significant advantages for RA phototherapies. Lu et al. [95] prepared novel L-cysteine (Cys) assisted Cu7:2S4 nanoparticles to serve as photothermal agents for PTT and photosensitizers for PDT simultaneously. This kind of nanoparticle can be injected into the disease region and has full potential for RA treatment. Meanwhile, a novel therapeutic system that combined NIR light-responsive BP nanosheets with a platelet-rich plasma (PRP)-modified chitosan thermoresponse hydrolgel has been prepared to treat RA [83]. The BP nanosheets generate mild local hyperthermia upon NIR light irradiation and release ROS into the inflamed joints simultaneously to eliminate hyperplastic synovial tissue. In addition, the degradation products of BP enhance the osteogenic process and the thermoresponse hydrolgel can serve as an anti-inflammation drug carrier, reducing the friction between the surrounding tissues at the same time. These Injectable NIR light-responsive systems can be used as efficient alternatives to anti-inflammation therapies for RA. The above-mentioned NIR light-responsive phototherapy systems for RA are summarized in Table 5.

Moreover, NIR light-triggered drug delivery systems have been developed for arthritis treatment. As NIR light-triggered drug delivery systems for bone cancer chemotherapies, the photothermal and photodynamic mechanisms of NIR light could also be used to achieve drug release in arthritis treatment. Zhao et al. [99] reported a highly efficient photothermal-triggered drug delivery platform based on the molybdenum disulfide (MoS2) nanosheets to control the release of dexamethasone for osteoarthritis therapy. This nanosystem could be used to treat osteoarthritis in vivo through intra-articular injection and the NIR light could control dexamethasone release remotely in the disease region, which could be modulated by adjusting the light-radiation behavior. Similarly, cell membrane penetrating peptide-modified mesoporous silica nanoparticles (MSNs) were reported to realize the efficient controlled release of triptolide, which is a traditional Chinese herbal medicine used to treat RA [100]. The MSNs modified with indocyanine green, a kind of photothermal agent, could effectively regulate the release of triptolide under 808 nm laser irradiation, leading to
the development of noninvasive therapeutic approaches for RA. These strategies could serve as references for the design of other intra-articular drug delivery nanosystems and have marked potential for the clinical treatment of arthritis.

**NIR light-assisted phototherapy for bone tissue regeneration**

Recently, several strategies to accelerate bone tissue regeneration via NIR light-assisted phototherapies have been proposed. The mild localized heat or photoelectric microenvironment triggered by NIR light irradiation can achieve noninvasive, remote, and spatiotemporally controlled cell differentiation behaviors, providing a unique strategy for bone tissue regeneration [19, 20]. In addition, considering that NIR light-responsive biosystems have been applied to realize the remote and controlled release of anticancer or antibacterial drugs, it also could be used to facilitate the controlled release of biological molecules (such as ions, drugs, or proteins) to promote bone tissue regeneration or promote tissue regeneration via a nonpharmacological and noninvasive strategy. At the same time, it is suggested that photobiomodulation therapy under NIR light irradiation could have a positive effect on bone metabolism, providing more inspirations for clinical applications in bone-related disease treatment. At the cellular level, stem cells and progenitor cells appear to be particularly susceptible to photobiomodulation effects. NIR light-induced photon absorption mainly occurs in mitochondria. Numerous signaling pathways could be activated via the promoted oxidative metabolism within the mitochondria, leading to the activation of a series of transcription factors [101]. These transcription factors can lead to increased expression of genes that modulate the attachment, proliferation, and osteogenic differentiation of cells, playing important roles in accelerating wound healing and bone tissue regeneration [102]. Therefore, NIR light-assisted phototherapies have several advantages for bone tissue regeneration (Figure 6). These applications are summarized in the following sections.

| Table 4. Phototherapy based on NIR light-responsive biomaterials for implant-related infections |
|-----------------------------------------------|-----------------------------------------------|
| Reference                                      | Surface modification | Phototherapeutic agents | Antibacterial mechanism | Wavelength (nm) and power density (W cm⁻²) | In vitro studies | In vivo studies |
| Yuan Z. et al. [16]                            | Mesoporous PDA nanoparticles (MPDA) + ICG + RGD coating | PDA                      | (a) accelerated bacterial death due to hyperthermia produced by photothermal conversion of MPDA, (b) ROS produced by released ICG with the assistance of heat | 808 nm, 0.75 W cm⁻² in vitro, 2.0 W cm⁻² in vivo | 51.2°C (5 min), 99.7% (S. aureus, 5 min), 51.3°C (the femur of Sprague Dawley rats, 10 min), 95.4% (S. aureus, 10 min) |
| Yuan Z. et al. [139]                           | MoS₃/PDA-RGD coating | MoS₃ coating | (a) hyperthermia produced by photothermal effect, (b) accelerating GSH oxidation induced by NIR, (c) intrinsic ROS-independent oxidative stress of Mo₃ nanosheets | 808 nm, 0.5 W cm⁻² in vivo, 1 W cm⁻² in vivo | 56.4°C (8 min), 92.7 % (S. aureus, 8 min), 95.1 % (E. coli, 8 min), 51.5°C (rabbits' tibia near knee joint, 10 min), 94.6% (S. aureus, 10 min) |
| Hong L. et al. [90]                            | Bismuth sulfide (Bi₅Se₆) @ trisilvere phosphate (Ag₃PO₄) coating | Bi₂Se₃                           | (a) hyperthermia produced by photothermal conversion of Bi₂Se₃, (b) ROS produced by Bi₅Se₆, (c) bacteriostatic properties of Ag₃PO₄, (d) hyperthermia produced by photothermal conversion of red phosphorus, (b) ROS produced by IR780 under NIR light | 108 nm, 0.05 W cm⁻² | 52.4°C within 3 min, 0.5 W cm⁻², 3 min, 0.25 W cm⁻², 12 min, 99.5% (S. aureus), 99.74% (E. coli) |
| Huang B. et al. [92]                           | Red phosphorus/IR80/RGDC coating | Red phosphorus                     | -                            | - | 1.5 W cm⁻² + 1 W cm⁻² to maintain 50°C (Sprague Dawley rats' tibia near the knee joint) 50°C within 10 min (rats' tibia near knee joint) Only a few bacterial colonies (S. aureus) |
| Tang L. et al. [28]                            | TiO₂/MoS₃/PDA /RGAD nanorod arrays coating | TiO₂/MoS₃                        | (a) ROS produced by 660 nm VL and 808 nm NIR light, (b) hyperthermia produced by photothermal conversion of MoS₃ doped TiO₂ NAs, and (c) physical puncture of the nanorods. | 808 nm, 0.5 W cm⁻² in vivo | 53.2°C (250 s), 89.3% (S. aureus, 10 min), 50°C after 2 min of irradiation (rats' tibia near knee joint) 96.2% (S. aureus, 10 min) |
| Zhang G. et al. [27]                           | Oxygen-deficient Ti–S–TiO₃ coating | Oxygen-deficient Ti–S–TiO₃ coating | (a) ROS produced by 808 nm NIR light and ultrason, (b) hyperthermia produced by photothermal conversion of Ti–S–TiO₃ coating | 808 nm, 0.35 W cm⁻² | 54.9°C (5 min), 99.99% (S. aureus, 5 min), 99.43% (the bilateral tibial plateaus of Wistar rats, S. aureus, 15 min) |

PDA: Polydopamine, ICG: Indocyanine Green, RGD: Arginine-glycine-aspartic acid, ROS: Reactive oxygen species, GSH: Glutathione, RGDC: Arginine-glycine-aspartic acid-cysteine.
Table 5. NIR light-responsive phototherapy systems for rheumatoid arthritis

| References | Phototherapy systems | Step 1: Phototherapy | Step 2: Osteogenesis | In vitro studies |
|------------|----------------------|----------------------|----------------------|-----------------|
| Pan W. et al. [83] | BPNs/Chitosan/PRP thermos-responsive hydrogel | Photothermal and photodynamic properties of BPNs | 808 nm, 1.0 W cm⁻², 8 min | Distinct ROS generation | DBA1/J mouse rheumatoid arthritis model |
| Lu Y. et al. [18] | Cu₇.₂S₄ nanoparticles | Photothermal and photodynamic properties of Cu₇.₂S₄ NPs | 808 nm, 1.0 W cm⁻², 10 min | Singlet oxygen production and intracellular ROS generation | CIA models (SD rats) |

BPN: Black phosphorus nanosheets, PRP: Platelet-rich plasma, CIA models: Type II collagen induced rheumatoid arthritis models, UCNP: Upconversion nanoparticle, PJI models: Periprosthetic joint infection models.

Figure 6. Schematic illustration of the NIR light-induced photobiomodulation, photothermal effect, and NIR light-triggered osteogenic molecule release systems to regulate new bone formation. **A.** Photobiomodulation therapy under NIR light irradiation can modulate the attachment, proliferation, and differentiation of stem cells. **B.** Phototherapy based on the NIR light-responsive nanomaterials can induce mild local heat under NIR light irradiation, which enhances new bone formation. **C.** NIR light-responsive release systems can realize the controlled release of osteogenic molecules, such as ions, drugs, and cytokines, to accelerate new bone formation. NIR, near infrared.

Phototherapy based on NIR light-responsive nanomaterials for bone tissue regeneration

Controlling cell fate through noninvasive in vitro stimulation can achieve precise and orchestrated biological activities in tissue engineering. It represents an appealing strategy to use NIR light radiation as a kind of tissue penetrative stimuli to gain nonpharmacological and noninvasive control of cell differentiation behaviors. For example, Fu et al. [20] designed a bismuth sulfide/hydroxyapatite (BS/HAp) film to build a rapid and repeatable NIR light-sensitive photoelectric extracellular microenvironment around Ti implants. The photoelectrons created under 808 nm laser radiation could tune the behavior of MSCs and control cell fate by regulating downstream gene expression towards osteogenic differentiation. This BS/HAp modification on an implant is highly encouraging and could achieve more precise control of cell fates in biological...
therapies. Similarly, Tiwari et al. reported a kind of NIR light-absorbing carbon nitride (C₃N₄) sheet, which enhances cellular proliferation and differentiation through runt-related transcription factor 2 (RUNX2) activation. The photocurrent upon two photon excitation of this small sized C₃N₄ sheet would induce a charge transfer and increased cytosolic Ca²⁺ accumulation, resulting in enhanced osteogenic differentiation of stem cells and new bone formation. In addition, single-walled graphene nanoribbons have been reported to generate photoacoustic signals under 905 nm NIR laser radiation, which could serve as an anabolic stimulus for noninvasive bone defect repair in a rodent femoral fracture site [103].

By contrast, mild local heat (40–43 °C) has been reported to facilitate healing of bone defects via inducing the earlier differentiation of human MSCs (hMSCs) and promoting the maturation of osteoblasts differentiated from MSCs [104]. Several studies have reported the application of NIR light-triggered photothermal technology in bone tissue engineering. For example, classical NIR light responsive nanomaterials, such as metal nanoparticles, could serve as hyperthermal agents to promote bone tissue regeneration by producing mild localized heat. A kind of NIR light-responsive gold nanorod doped gelatin/HAp composite microsphere was successfully synthesized, which exhibited an efficient NIR light-triggered photothermal properties [105]. Zhang et al. [19] reported a photothermal strategy for in situ bone regeneration using porous AuPd alloy nanoparticles (pAuPds) as photothermal agents. The mild localized heat (around 40–43 °C) could greatly enhance cell proliferation and bone tissue regeneration via upregulating the expression of a series of osteogenesis-related genes and proteins. RNA sequencing analysis demonstrated that the Wnt signaling pathway was involved in in situ bone regeneration. Moreover, a new class of 2D BP nanosheets have been employed as photothermal agents for the remote control of bone regeneration [106, 107]. These BP nanosheets could upregulate the expression of heat shock proteins in human BMSCs and thus enhance bone tissue regeneration by remote control of NIR light irradiation. Moreover, BP can degrade into nontoxic phosphates and phosphonates in the biological environment, providing good nucleation sites for biomineralization [108, 109]. The BP-combined osteoimplants have good photothermal properties, biodegradability, and osteogenic abilities, thus providing new insights for orthopedic applications.

NIR light-responsive release systems for bone tissue regeneration

Although the use of NIR light-responsive drug delivery systems combining chemotherapy and photothermal therapy has exhibited versatility in bone cancer therapies, NIR light-responsive release systems for bone tissue regeneration have not been widely used. NIR light has good tissue penetration, as well as accurate and spatiotemporal control properties. Remote control of cell fate could provide a versatile method to regulate bone regeneration therapies. Combining the use of tissue penetrative NIR light stimuli with NIR light-responsive nanomaterials is a delicate and efficient strategy for the intracellular control of stem cells. Recently, several strategies have been proposed to regulate the differentiation of stem cells based on NIR light-responsive release nanosystems. Kang et al. [110] designed an upconversion nanotransducer (UCNT)-based nanosystem to regulate intracellular calcium by encapsulating either a calcium chelator or a calcium supplier under NIR light stimuli. An increase in calcium can promote the differentiation of hMSCs into osteoblasts. Strontium (Sr) is another osteoinductive element that could enhance bone formation. An NIR light-triggered Sr²⁺ delivery system was developed by incorporating SrCl₂ and BP nanosheets into poly(lactic-co-glycolic acid) (PLGA) microspheres for bone tissue regeneration [29]. The spatiotemporal release of Sr²⁺ controlled by NIR light significantly improved bone tissue regeneration. These NIR light-triggered ion-release systems are suitable for bone regeneration therapies that require precise control at specific times.

Alternatively, the on-demand release of therapeutic proteins holds great promise for bone tissue regeneration. Tuncaboylu et al. [111] designed a shape-memory poly(e-caprolactone) network to release several proteins, including stromal cell-derived factor 1α (SDF-1α), a chemotactic protein relevant to bone tissue regeneration. The diameter of these shape-memory tubes decreases under NIR light irradiation and expels the payload protein. Yin et al. [22] provided another strategy to fabricate a biomimetic anti-inflammatory nanocapsule (BANC). The BANC is coated with lipopolysaccharide-treated macrophage cell membranes, loading resolvin D1 inside a gold nanocage as an “M2 polarization inducer”. Controlled release could be triggered under NIR light irradiation, promoting the healing process during bone tissue repair. Moreover, another heat-activated and dimerizer-dependent transgene expression system was designed based on an NIR light-responsive hydrogel to achieve spatiotemporal control of bone morphogenetic protein-2 (BMP-2) [21].
The photothermal effect of hollow gold nanoparticles in hydrogels induced mild hyperthermia, which stimulated the cell constructs to express BMP-2 in the bone defect. These protein-release systems promote the formation of new mineralized bone tissue, providing promising strategies for bone tissue regeneration. These NIR light-responsive drug release systems are summarized in Table 6.

**Photobiomodulation therapy under NIR light irradiation for bone tissue regeneration**

Photobiomodulation describes the photochemical reactions of cells and tissues achieved under red or NIR light irradiation with lower energy densities compared with other heat-mediated laser therapies, which induce tissue ablation or coagulation after irradiation [102, 112]. This light-based technique involves irradiation of tissue using lasers or LEDs. Laser light can reach the target tissue regions via a continuous or pulsed mode. The transmitted energy will trigger photochemical reactions instead of inducing a thermal effect, which can modulate cellular metabolic processes, including cell viability, proteins synthesis, and DNA/RNA expression [113]. Currently, photobiomodulation therapy under NIR light irradiation has been used clinically to reduce inflammation, edema, and pain, and to repair multiple damaged tissues, representing a promising alternative for bone disease treatment and bone tissue regeneration [112, 114]. For photobiomodulation therapy, two critical challenges must be overcome: One is the uncertainty about the mechanism underlying its beneficial effects, and the other is the optimal irradiation parameters [12]. In the following sections, the effects of photobiomodulation therapy on cellular behavior, the bone healing process, and dental treatments are discussed based on the published literature.

**The effects of photobiomodulation therapy on cellular behavior**

Stem cell therapy has attracted great interest in tissue regenerative medicine. Photobiomodulation therapy might increase the biological functions of MSCs. The primary action site of photobiomodulation under red or NIR light irradiation is the mitochondria, more specifically, cytochrome c oxidase. It is hypothesized that inhibitory nitric oxide dissociated from cytochrome c oxidase could restore electron transport and increase the mitochondrial membrane potential. By contrast, NIR light irradiation could trigger light or heat-gated ion channels and activate the change of transient receptor potential. These potential changes to mitochondria could increase the rate of respiration and ATP production, leading to a marked effect on stem cells via mitochondrial redox signaling [112]. Our literature review showed that the effect of photobiomodulation therapy for bone tissue regeneration not only depends on the type of cells, but also on the category of lasers, wavelength, density of energy, and the duration of photobiomodulation therapy. There is a wide variation in the parameters between different studies, making it difficult to compare the efficacy of photobiomodulation. Different types of cells, such as adipose-derived stem cells (ASCs) and BMSCs, might have different responses to photobiomodulation therapy [112]. It has been reported that photobiomodulation therapy with a combination of 630 and 810 nm lasers irradiation significantly enhanced cell viability and decreased the apoptosis of human ASCs and BMSCs in vitro, in which NIR light irradiation induced more in vitro cell viability of ASCs than BMSCs [115].

In addition, the effects of photobiomodulation therapy within different wavelengths are still being explored. Wavelengths from blue to NIR light have been demonstrated to enhance bone regeneration. Kunimatsu’s group have reported that irradiation with a high frequency NIR diode laser is highly efficient to increase cell division and migration of osteoblasts via MAPK/ERK signaling and improved the bone tissue regeneration [116]. Under 1064-nm irradiation, equine MSCs remained viable and expressed increased concentrations of interleukin (IL)-10 and vascular endothelial growth factor (VEGF), which enhanced the tissue healing process by decreasing the inflammatory reaction and promoting angiogenesis [117]. The cellular responses to NIR light irradiation demonstrate the great potential for the photobiomodulation effect on MSCs to enhance their therapeutic properties. Meanwhile, it has been reported that low-power irradiation by 635 and 809 nm lasers might not have obvious effects on osteoblast viability and proliferation [114]. Moreover, Wang’s group have demonstrated that although red (660 nm) or NIR (810 nm) photobiomodulation therapies stimulated the proliferation of hASCs, the blue (415 nm), green (540 nm) wavelengths are more effective to stimulate the osteogenic differentiation of hASCs [118, 119]. Similarly, Tani et al. [120] reported that photobiomodulation therapy with a 635 nm laser was a more effective option to enhance the viability, proliferation, adhesion, and osteogenic differentiation of human MSCs compared with those of 808 nm and 405 nm irradiation. Therefore, the most promising range of wavelengths to promote the proliferation of osteoblasts and tissue regeneration is still controversial [114]. It is important to use appropriate irradiation parameters during laser treatment for bone tissue engineering.
Moreover, guiding the differentiation of MSCs by light is particularly attractive for bone tissue engineering and regenerative medicine. Yan’s group constructed a controlled UCNPs-based substrate to guide multi-directional differentiation of MSCs by NIR light irradiation [121]. Under NIR light irradiation of different power densities, MSCs tend to differentiate into adipocytes (low power, 0.5 W cm\(^{-2}\)) or osteoblasts (high power, 6 W cm\(^{-2}\)). The NIR light triggered anti-adhesive effect of a 4-(hydroxy-methyl)-3-nitrobenzoic acid modified poly(ethylene glycol) coating on a substrate demonstrated these differentiation properties of MSCs, providing a new way to modulate bone regeneration in tissue engineering.

**The photobiomodulation therapy under NIR light irradiation for bone healing**

Several studies have demonstrated that NIR light irradiation therapy could be used to improve bone healing and the regeneration process. NIR light therapy at 790 nm was reported to guide bone tissue regeneration on rabbits’ tibial fractures with wire osteosynthesis or internal rigid fixation [122-124]. In addition, 850 nm NIR light phototherapy demonstrated the same ability to stimulate cell proliferation and guide bone tissue regeneration in a rodent model [125]. Moreover, linear polarized NIR light irradiation (830 nm) could enhance the mechanical expansion of the rat sagittal suture by controlling the growth of the craniofacial skeleton [126]. These NIR light irradiations showed deep penetration in the bone defect region and stimulated bone healing, resulting in an increased deposition of calcium hydroxyapatite in the radiation regions [122].

Furthermore, Gokmenoglu et al. [127] reported that photobiomodulation therapy under NIR light irradiation could change the biochemical markers in peri-implant cervical fluid and the biological activities in the wound healing process. In that study, an LED device at a wavelength in the NIR region was applied to the surgical region, leading to a positive effect on the osseointegration process and implant stability after surgery. Similarly, the effect of LED (945 nm) therapy on the bone healing and tissue regeneration processes has also been investigated [128]. These studies demonstrated that low power LED therapy within the NIR region has a positive effect on tissue regeneration, especially in the early stage of repair. The results from those studies have shown that NIR light irradiation can accelerate the process of fracture healing and promote the formation of new bone tissue, providing great potential for the clinical treatment of bone fractures.

**The photobiomodulation therapy under NIR light irradiation for dental treatment**

Tooth movement during orthodontic therapy is usually associated with bone resorption on the pressure side and bone regeneration on the tension side [129]. Several strategies have been proposed to decrease the treatment time in orthodontic therapy. A multicenter clinical trial demonstrated that photobiomodulation under 850 nm NIR light changed the rates of tooth movement and promoted orthodontic alignment significantly in the early phase of treatment [130]. NIR light irradiation at a power density of 60 mW cm\(^{-2}\) was performed on the surface of the patients’ cheek for 20 or 30 min every day or 60 min every week. Another study supported this conclusion, providing evidence that low level laser therapy accelerates bone remodeling and inhibits root resorption during orthodontic tooth movement in a rodent model [131]. The laser irradiation (810 nm, 5 W cm\(^{-2}\)) in that study was performed on the labial and palatal sides of the tooth for 15 s every other day. Moreover, Gunji et al. [129] examined the effect of high frequency NIR diode laser irradiation with a wavelength of 910 nm on tooth movement. They reported that 910 nm NIR laser irradiation on periodontal tissue resulted in metabolic activation, which ultimately enhanced tooth movement during

**Table 6. NIR light-responsive release systems for bone tissue engineering**

| Release systems                                      | Photosensitive agents | Wavelength (nm) | Power density | Osteogenic agents | Mechanisms                                                                 | References     |
|------------------------------------------------------|-----------------------|-----------------|---------------|-------------------|----------------------------------------------------------------------------|----------------|
| Photocaged UCNTs@mesoporous silica nanoparticles     | Photocaged UCNTs      | 980             | 1 W cm\(^{-2}\) | Cal\(^{2+}\) | Photocaged UCNTs regulate the intracellular calcium and stem cells differentiation by NIR light | Kang H. et al. [110] |
| BP-SrCl\(_2\)/PLGA microspheres                      | BP nanosheets         | 808             | 1 W cm\(^{-2}\) | Sr\(^{2+}\)    | NIR light triggers a local temperature rise and destroys the PLGA shells to release Sr\(^{2+}\) | Wang X. et al. [29] |
| Poly(\(\varepsilon\)-caprolactone) (PCL) networks    | IR-26 dye             | 1064            | 50 mJ         | SDF-1a          | NIR light triggers the shape switch of PCL networks to release SDF-1a       | Tunçaboylu D. C. et al. [111] |
| Biometric anti-inflammatory nanocapsule (BANC)        | Gold nanocage         | 808             | 3 W cm\(^{-2}\) | RvD1            | NIR triggers the release of RvD1 to induce the M2 polarization of macrophage cell | Yin C. et al. [22] |
| Heat-activated and dimerizer-dependent transgene expression system | Hollow gold nanoparticles | 808 | 11-17 mW mm\(^{-2}\) | BMP-2           | Hyperthermia triggered by NIR laser activates the BMP-2 expression of cell constructs | Sanchez-Casanova S. et al. [21] |

UCNTs: Upconversion nanotransducer, BP: Black phosphorus, PLGA: Poly(lactic-co-glycolic acid), SDF: Stromal cell-derived factor, RvD1: Resolvin D1, BMP: bone morphogenetic proteins.
orthodontic treatment. Recently, the combined effects of mechanical force loading and Nd:YAG laser irradiation on bone metabolism have been investigated [132]. NIR laser irradiation at a wavelength of 1064 nm activated the expression of genes related to bone metabolism in osteoblast-like cells, enhancing bone remodeling and tooth movement.

Besides the reported capability to enhance tooth movement, NIR light-assisted phototherapy has also been applied to regulate the inflammatory and repair processes of dental trauma. LED phototherapy (940 nm) of the periodontal ligament stimulated the proliferation of fibroblasts and increased the synthesis of the extracellular matrix, accelerating periodontal tissue repair [133]. Irradiation could also decrease the migration of inflammatory cells into periodontal tissues, thus reducing root resorption. Another study demonstrated that 810 nm laser phototherapy on the root surface, in continuous or pulsed modes, could reduce root resorption during the treatment of tooth replantation [134]. These studies suggested that NIR light-assisted phototherapy might be efficient to decrease root resorption and enhance periodontal tissue healing after injury to periodontal tissue. However, Mitihiro et al. [135] reported that NIR LED (940 nm) phototherapy up to 48 h after tooth replantation did not improve the healing process, and even delayed periodontal ligament repair. Although phototherapy seems to show a promising effect in decreasing the inflammatory reaction, it may not be effective to avoid pulp necrosis, which damages the process of tissue repair after tooth replantation. The results of our literature search literature suggested that caution should be taken when using NIR light-assisted phototherapy in dental treatment. Determining the irradiation parameters, such as the wavelength, power density, mode of emission (discontinuous or continuous), duration of irradiation, and the irradiated region, is essential for successful dental treatment.

**Current challenges and perspectives**

In summary, NIR light can serve as an effective *in vitro* stimulation for targeted therapy because of its good tissue penetration ability, minimal invasiveness and high selectivity [50]. NIR light-assisted phototherapies have shown great potential to treat bone-related diseases and bone regeneration. Most of these phototherapies are based on a series of unique NIR light-responsive nanomaterials. These nanomaterials could exert their functions via multiple methods administration according to different therapeutic goals. They could be injected directly, or serve as a part of bioactive scaffolds and drug delivery systems, exhibiting efficient therapeutic performance in the pathological regions via generating local hyperthermia and increasing ROS concentrations under NIR light irradiation. The different applications of NIR light-responsive nanomaterials to treat bone-related diseases and bone regeneration are summarized in Table 7. However, the photobiomodulation effect under the direct NIR light irradiation has also shown great potential to regulate cellular behaviors and the process of bone tissue regeneration. To date, a series of *in vitro* and *in vivo* studies have demonstrated the encouraging advantages of the NIR light-assisted phototherapies for bone-related disease and bone regeneration. However, it remains challenging to translate preclinical studies into clinical applications.

### Table 7. Current applications of NIR light-responsive nanomaterials in bone-related diseases phototherapies

| Applications                      | Administration of nanomaterials | Therapeutic mechanisms                                                                 | Advantages                                                                 | Drawbacks                                                                 |
|----------------------------------|---------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Anticancer therapy               | Direct intravenous injection    | Photothermal and photodynamic properties of nanomaterials (a) photothermal and photodynamic properties of nanomaterials, (b) osteogenic capability of bioactive scaffolds | Targeted accumulation in tumor sites, easy controllability, Efficient anticancer properties as well as osteogenic capability | In vivo toxicity of non-degradable nanomaterials, unsuitable hyperthermia for normal cells as well as relatively complex design |
|                                 | Implanted bone scaffolds       |                                                                                        | Combined photo-chemotherapeutic effects                                      |                                                                          |
|                                 | Drug delivery systems (intravenous injection) |                                                                                      |                                                                            |                                                                          |
| Antibacterial therapy            | Coating on the surface of bone implants |                                                                                      | Efficient noninvasive treatment of infection in deep tissue as well as simultaneous osteogenic activity |                                                                          |
| Anti-inflammation therapy        | Intra-articular injection      | (a) photothermal and photodynamic properties of nanomaterials, (b) osteogenic capability of implants | Efficient NIR light induced anti-inflammation capability, controlled release of anti-inflammation drugs as well as simultaneous osteogenic activity |                                                                          |
|                                 |                                 | (a) photothermal and photodynamic properties of nanomaterials, (b) combined chemotherapeutic of anti-inflammation drugs, (c) osteogenic capability of co-delivery systems |                                                                            |                                                                          |
| Bone regeneration                | Implantation                   | Mild local heat to promote bone regeneration Controlled release of osteogenic ions, drugs and proteins | Controllable bone regeneration for precise medicine | Difficulty in controlling a suitable temperature |
|                                 | Drug delivery systems (local injection) |                                                                                      |                                                                            |                                                                          |

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Firstly, the biosafety of NIR light-responsive nanomaterials should be considered. With the rapid development of nanotechnology, several kinds of nanomaterials, such as metal-based nanomaterials, carbon-based nanomaterials, and other related photosensitive nanostructures, have been involved in NIR light-assisted phototherapies to make them “smart”. Apart from their efficient photosensitive properties and attractive biocompatibility, there are still many challenges to overcome before clinical applications. Above all, the components of these nanomaterials should be nontoxic and biodegradable. The acute and long-term toxicity of these nanomaterials depend on their physicochemical properties, including their composition, size, shape, and surface charge. The acute and chronic pathological toxicity during the treatment period of these nanomaterials, as well as their renal or hepatobiliary elimination from the body, should be evaluated to guarantee their in vivo safety for further clinical translation [32]. In current phototherapies, most applied NIR light-responsive nanomaterials might have long-term toxicity, especially the nonbiodegradable inorganic nanoparticles. The nanomaterials with excellent biocompatibility and biodegradability, such as black and red phosphorus, are the preferred selections for various phototherapies. In addition, the size, shape and surface charge of the nanomaterials should be modified to minimize their cellular interactions with normal tissues, thereby avoiding nonspecific damage to normal cells. For example, the emerging MXenes have exhibited satisfactory photosensitive abilities, hydrophilic nature, and unique physiochemical properties, allowing them to meet the strict requirements of biomedicine. The large surface area and facile surface modification of the MXenes also endow them with better in vivo performance because of their reduced toxicity, enhanced colloidal stability, and extended circulation within the body [53, 54]. Providing nanomaterials with a biological mimic coating, such as liposomes and cell membranes, could also be a promising alternative for clinical translation [11]. In conclusion, these NIR light-responsive nanomaterials should not induce any adverse effects and must receive Food and Drug Administration (FDA) approval before human use. Currently, few FDA-approved phototherapeutic agents, such as indocyanine green, have been applied in NIR light-assisted phototherapies [136, 137]. Increased efforts should be made to synthesize and design more nanomaterials with both high phototherapeutic efficiency and outstanding biocompatibility.

Secondly, NIR light-induced hyperthermia should be well controlled according to different therapeutic needs. The main side effect of NIR light-induced phototherapies for bone-related disease treatment is that local hyperthermia followed by NIR light irradiation can not only eliminate the cancer cells, bacteria, and inflammatory cells, but also might damage the normal cells and tissues when the temperature is above the threshold. The precise regulation of photothermal effect during the NIR light irradiation treatment is essential to promote the efficacy of phototherapies and minimize the damage. Considering the different therapeutic goals in the treatment of bone-related diseases, the parameters of NIR light irradiation to generate targeted hyperthermia within a reasonable temperature range should be carefully selected [21]. Generally speaking, local hyperthermia over 50 °C exerts highly effective phototherapeutic effects on pathological tissues, which is favorable for the treatment of bone cancers, infections, and inflammations. Under NIR light irradiation, the cancer tissues can be effectively ablated by photonic hyperthermia (over 50 °C) without recurrence [31, 44, 66]. Similarly, hyperthermia at almost 55 °C achieved a high antibacterial efficiency (99.995%) in the treatment of bone infections [15]. For bone regeneration therapies, the proposed mild local hyperthermia (40–42 °C), which is only about 3–5 °C higher than the normal human body temperature (37 °C), is recommended because of its abilities to accelerate bone healing and enhance the mineralization process in bone tissue regeneration [106]. Meanwhile, the temporary photothermal therapy within a suitable irradiation time might have a minimal impact on the tissue regeneration of the defect areas. The local inflammatory reaction secondary to PTT is similar to the primary phase of bone healing, which could accelerate bone tissue regeneration by recruiting precursor cells. Considering the effects of photobiomodulation on the adhesion, proliferation, and differentiation of stem cells, suitable mild local hyperthermia might have positive therapeutic effects on bone regeneration [44]. In future studies, more accurate and sensitive real-time monitoring techniques should be developed to adjust the irradiation parameters and avoid unnecessary damage following overheating [11].

Furthermore, the administration of NIR light could also be optimized. Although NIR light has deeper tissue penetration than the UV and Visual light, more effort should be made to overcome the laser penetration problem for the treatments of deep-seated bone cancer, infection, or inflammation. The optimization of excitation conditions and the improvement of nano-bio interactions are also important. Local implantation and injection, rather than intravenous injection, could deliver effective
amounts of photosensitive nanomaterials to targeted sites to obtain better therapeutic outcomes. Recently, phototherapy using an optical fiber NIR laser device was combined with surgery, in which the deep pathological lesions could be directly exposed to laser irradiation [138]. These emerging techniques using light administration could promote the efficiency of NIR light phototherapy, and advance its further translation into clinical applications.

In conclusion, NIR light-assisted phototherapies have shown great potential to treat bone-related disease and bone tissue regeneration. This noninvasive, precisely targeted treatment strategy could be considered as an effective tool to promote therapeutic efficacy. With better understandings of this technology, NIR light-assisted phototherapy could serve as a promising alternative for clinical applications.

Abbreviations

NIR: near infrared; PTT: photothermal therapy; PDT: photodynamic therapy; ROS: reactive oxygen species; Nd:YAG: neodymium-doped yttrium aluminum garnet; LED: light-emitting diodes; GO: graphene oxide; MWNTs: multi-walled carbon nanotubes; CDs: carbon dots; BP: black phosphorus; BMSCs: bone mesenchymal stem cells; DNA: deoxyribonucleic acid; BA: bioactive glass; Cu: copper; CTPP: copper coordinated tetrakis (4-carboxyphenyl) porphyrin; TCP: tricalcium phosphate; 2D: two dimensional; O2: singlet oxygen; DOX: doxorubicin; PDA: polydopamine; BGN: bioactive glass nanoparticle; ZOL: zoledronic acid; ALN: alendronate; HAP: hydroxyapatite; S. aureus: Staphylococcus aureus; UCNP: upconversion nanoparticles; RGD: arginine-glycine-aspartic acid; RGD: arginine-glycine-aspartic-acid-cysteine; RA: rheumatoid arthritis; PRP: platelet-rich plasma; PA: photoacoustic; BS: bismuth sulfide; MSCs: mesenchymal stem cells; RUNX2: runt-related transcription factor 2; Sr: Strontium; PLGA: poly(lactic-co-glycolic acid); SDF-1α: stromal cell-derived factor 1a; BANC: biomimetic anti-inflammatory nanocapsule; BMP-2: bone morphogenetic protein-2; ASCs: adipose-derived stem cells; hMSCs: human mesenchymal stem cells; CCO: cytochrome c oxidase; IL: interleukin; VEGF: vascular endothelial growth factor.

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Competing Interests

The authors have declared that no competing interest exists.

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