Vacancy defect-promoted nanomaterials for efficient phototherapy and phototherapy-based multimodal Synergistic Therapy

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Phototherapy and multimodal synergistic phototherapy (including synergistic photothermal and photodynamic therapy as well as combined phototherapy and other therapies) are promising to achieve accurate diagnosis and efficient treatment for tumor, providing a novel opportunity to overcome cancer. Notably, various nanomaterials have made significant contributions to phototherapy through both improving therapeutic efficiency and reducing side effects. The most key factor affecting the performance of phototherapeutic nanomaterials is their microstructure which in principle determines their physicochemical properties and the resulting phototherapeutic efficacy. Vacancy defects ubiquitously existing in phototherapeutic nanomaterials have a great influence on their microstructure, and constructing and regulating vacancy defect in phototherapeutic nanomaterials is an essential and effective strategy for modulating their microstructure and improving their phototherapeutic efficacy. Thus, this inspires growing research interest in vacancy engineering strategies and vacancy-engineered nanomaterials for phototherapy. In this review, we summarize the understanding, construction, and application of vacancy defects in phototherapeutic nanomaterials. Starting from the perspective of defect chemistry and engineering, we also review the types, structural features, and properties of vacancy defects in phototherapeutic nanomaterials. Finally, we focus on the representative vacancy defective nanomaterials recently developed through vacancy engineering for phototherapy, and discuss the significant influence and role of vacancy defects on phototherapy and multimodal synergistic phototherapy. Therefore, we sincerely hope that this review can provide a profound understanding and inspiration for the design of advanced phototherapeutic nanomaterials, and significantly promote the development of the efficient therapies against tumor.

KEYWORDS

nanophotosensitizers, microstructure, vacancy defect engineering, phototherapy, multimodal synergistic phototherapy
Introduction

Cancer, also known as malignant tumor, is one of the major diseases that seriously endanger human health and life (Fan et al., 2017; Parchur et al., 2018). According to the latest medical statistics of the World Health Organization (WHO), cancer has become the second deadliest disease in the world, killing about 10 million people every year. Therefore, the effective diagnosis and treatment of cancer is not only related to human life and health as well as quality of life, but also related to the sustainable development of economy and society. At present, the diagnosis and treatment of malignant tumors mainly rely on traditional methods such as surgical resection, chemotherapy and radiotherapy (Yang et al., 2014; Fan et al., 2017; Zhao et al., 2019). Although they can inhibit the development of tumors to a certain extent, there are still some urgent problems to be solved, such as poor treatment effect, large side effects, easy recurrence and metastasis, easy tolerance and so on (Fan et al., 2017; Zhao et al., 2019). Therefore, the developing more timely, efficient and precise diagnosis and treatment strategies are very important to boost the therapeutic efficacy on cancer and improve patients’ quality of life.

In recent years, with the rapid development of nanotechnology, the emerging phototherapy as a non-invasive light-excited cancer therapeutics, including photodynamic therapy (PDT), photothermal therapy (PTT) and multimodal synergistic phototherapy, has been continuously explored and studied to improve the cancer therapeutic outcomes (Cheng et al., 2014; Liu Y. et al., 2019; Liu et al., 2021). Preclinical studies have confirmed that phototherapy is very promising to achieve accurate diagnosis, targeted recognition and efficient treatment for tumor, which provides a new opportunity to overcome cancer as soon as possible (Cheng et al., 2014; Liu Y. et al., 2019). PDT involves three essentials, i.e., light, photosensitive nanomaterial (nanophotosensitizer), and oxygen (Chatterjee et al., 2008). Among them, nanophotosensitizers can passively accumulate and preferentially remain at the tumor sites via the enhanced permeability and retention (EPR) effect (Maeda et al., 2013; Fan et al., 2017; Zhao et al., 2019). Under the excitation of certain wavelength light, nanophotosensitizers can be selectively activated to produce cytotoxic reactive oxygen species (ROS) in tumor rather than normal tissue, so as to induce cancer cell death and achieve tumor-specific PDT (Cheng et al., 2014; Lu et al., 2015; Fan et al., 2017). Compared with PDT for ROS-induced tumor cell apoptosis through light activation of nanomaterials, PTT is another phototherapy paradigm which utilizes nanomaterials with photothermal conversion effect to generate cytotoxic heat (>45°C) for thermal ablation of tumour (Liu Y. et al., 2019; Guiju et al., 2021). In addition, multimodal synergistic phototherapy (including synergistic PTT and PDT as well as combined phototherapy and other therapies) based on multifunctional nanomaterials can achieve synergistic enhancement of tumor treatment (Cheng et al., 2014; Fan et al., 2017; Liu Y. et al., 2019; Zhao et al., 2019). Notably, the phototherapy is a nanomaterial structure sensitive process, and the effectiveness of phototherapy depends largely on nanomaterials (Cheng et al., 2014; Fan et al., 2016; Lu L. et al., 2018; Liu Y. et al., 2019; Yang et al., 2019; Liu et al., 2021). The ideal nanomaterials for efficient phototherapy should include four key properties (Cheng et al., 2014; Fan et al., 2016; Fan et al., 2017; Liu Y. et al., 2019; Zhao et al., 2019; Liu et al., 2021): 1) It should have strong optical response in the near-infrared (NIR) region, allowing the deeper tissue-penetration and lower light scattering to effectively activate the optical-sensitive nanoparticles accumulated in tumors. 2) It should possess high photoinduced ROS production efficiency (ROS quantum yield) or/and high photothermal conversion efficiency in NIR region, so as to achieve satisfactory treatment efficacy of phototherapy. 3) It should be multifunctional and can be coupled with other therapies (e.g., chemotherapy, radiotherapy, gas therapy, chemodynamic therapy, and sonodynamic therapy), so as to overcome the disadvantages of monotherapy and significantly enhance the comprehensive efficacy for complex tumors. 4) In addition, it should also show low toxicity but high biocompatibility to realize minimized side effects. Recently, thus, a great deal of efforts have been made to develop novel phototherapeutic nanomaterials with well-defined particle sizes, morphology, and compositions, such as various noble metal, semiconductor, and carbon-based nanomaterials (Gao et al., 2018; Gu et al., 2019; Melo-Diogo et al., 2019; Wang L. et al., 2020; Zhou et al., 2020; Chang et al., 2021; Tian et al., 2021; Wang L. et al., 2021; Zhou C. et al., 2021). So far, however, the rational design and controllable synthesis of phototherapeutic nanomaterials in order to satisfy the above four properties simultaneously remains a vitally important and fundamental scientific problem.

The properties/performance of phototherapeutic nanomaterials (e.g., optical, photo-dynamic, photo-catalytic, photo-thermal, and biological properties/performance) are in principle determined by their microscopic electronic/band structure and geometric structure (i.e., atomic arrangement) (Coughlan et al., 2017; Huang et al., 2017; Nosaka and Nosaka, 2017; Chen et al., 2021; Liu et al., 2021). Vacancy-type defect of crystals provides the promising opportunity to effectively regulate microstructure and properties in various nanomaterials for phototherapy (Coughlan et al., 2017; Nosaka and Nosaka, 2017; Lu L. et al., 2018). In past decades, it has been recognized that vacancy-type defects, including but not limited to oxygen vacancy, metal vacancy, carbon vacancy, and sulfur vacancy, ubiquitously exist in solid materials, especially in nanostructure materials with small scale (Banhart et al., 2011; He et al., 2013; Paier et al., 2013; Coughlan et al., 2017; Nosaka and Nosaka, 2017; Xu et al., 2017; Lu L. et al., 2018; Yan et al., 2018). In recent years, with the deepening of the research on vacancy-type defects, it can be found that vacancy defects play a significant impact on the physical and chemical properties of phototherapeutic nanomaterials (e.g., optical, photochemical,
semiconductor, and plasmonic properties) because they can greatly influence and directly change the microstructure of nanomaterials (Wang X. et al., 2019; Guan et al., 2019; Liu H. et al., 2020; Cai et al., 2021). Meanwhile, vacancy defect-engineering has been explored as a very significant and effective strategy to regulate microstructure and properties of phototherapeutic nanomaterials (Liu H. et al., 2020; Bai et al., 2021; Wen et al., 2021; Zhou B. et al., 2021). Thus, more and more attention have been paid to the influence of vacancy defects on microstructure and properties of phototherapeutic nanomaterials, and constructing and regulating vacancy defects has become an important development direction to achieve efficient nanomaterials and improve their phototherapeutic effect against tumor. Recently, the roles of vacancy defects in phototherapeutic nanomaterials have been widely studied and many vacancy defect-promoted nanomaterials have also been synthetized, showing enhanced phototherapeutic efficacy (Wang X. et al., 2019; Guan et al., 2019; Liu H. et al., 2020; Bai et al., 2021; Cai et al., 2021; Wen et al., 2021; Zhou B. et al., 2021). However, due to the diversity and complexity of vacancy defect structures in nanomaterials (e.g., different concentrations, distributions, and types), these influences of vacancy defects on the microstructure and the phototherapeutic efficacy of phototherapeutic nanomaterials still need to be systematically studied and clearly identified. At the same time, more reasonable design and controllable preparation strategy for vacancy defective nanomaterials need to be further developed to achieve efficient phototherapy. Herein, this review systematically summarizes the recent understanding, construction, and application of vacancy defects in phototherapeutic nanomaterials (as shown in Scheme 1). Starting from the perspective of defect chemistry and defect engineering, we also review the types, structural features, and physicochemical properties of vacancy defects in phototherapeutic nanomaterials. Finally, we focus on the vacancy defective nanomaterials (including oxygen, sulfur, metal and carbon vacancy defective nanomaterials) recently applied in phototherapy, and discuss the significant effects of vacancy defects for phototherapy. This review aims to provide useful vacancy engineering strategies for the design and preparation of advanced phototherapeutic nanomaterials.

Vacancy Defect Chemistry and Engineering for Phototherapeutic Nanomaterials

Vacancy Defect Chemistry for Phototherapeutic Nanomaterials

The phototherapy is a nanomaterial microstructure sensitive process (Cheng et al., 2014; Fan et al., 2016; Lu L. et al., 2018; Liu Y. et al., 2019; Yang et al., 2019; Liu et al., 2021). Generally, defect structures can directly and effectively regulate microstructure of nanomaterials, and they are easily formed in nanomaterials by various physicochemical synthesis and modification methods, due to their high surface energy (Banhart et al., 2011; He et al., 2013; Paier et al., 2013; Li et al., 2017; Xu et al., 2017; Yan et al., 2018; Xie et al., 2020; Zhang et al., 2020). With the development of nanotechnology in recent 10 years, defect chemistry of nanomaterials has become a new research field and an important part of the material chemistry, which mainly involves classification, formation, modulation, characterization, and properties of defects in nanomaterials (Banhart et al., 2011; Li et al., 2017; Xie et al., 2020). In defect chemistry, according to the dimensionality of the crystal lattice, defect structures (as schematically shown in Figure 1A) can be mainly classified as point defects (zero-dimensional defects), line defects (one-dimensional defects), planar defects (two-dimensional defects), and volume defects (three-dimensional defects) (Banhart et al., 2011; Li et al., 2017; Xie et al., 2020). Among them, point defects are the main research content of defect chemistry on nanomaterials, while the vacancy-type defects, such as oxygen vacancy, metal vacancy, sulfur vacancy, and carbon vacancy, are the most commonly observed and representative point defect (Banhart et al., 2011; Paier et al., 2013; Jia et al., 2017; Li et al., 2017; Yan et al., 2018; Xie et al., 2020). In terms of formation mechanism, vacancy defect is a typical intrinsic defect, which can be regarded as an intrinsic component like atoms and ions as well as extend from every direction with small or even atomic scale in...
nanomaterials (Wang et al., 2011; Paier et al., 2013; Li et al., 2017; Chen et al., 2019; Xie et al., 2020; Zhang et al., 2020). When vacancy defects are formed by empty lattice sites due to thermal vibration or nonstoichiometric compositions (stoichiometric deviation), they are thermodynamically stable and are known as equilibrium vacancies (Matsunaga et al., 2003; Banhart et al., 2011; Paier et al., 2013; Li et al., 2017; Xie et al., 2020; Zhang et al., 2020). In contrast, when undergoing non-thermodynamic equilibrium processes, such as high energy particle irradiation, quenching from high temperature, or cold working, so-called non-equilibrium vacancies usually related to Frenkel pairs can be generated (Kostrubiec et al., 2002; Nagai et al., 2003; Banhart et al., 2011; Paier et al., 2013; Li et al., 2017; Xie et al., 2020; Zhang et al., 2020). From the space configuration of vacancy, the monovacancy caused by the absence of one atom in nanomaterials is the simplest vacancy-type defect, while multiple vacancies (e.g., double vacancies and vacancy clusters) can be generated either by merging multiple monovacancy or removing several adjacent atoms (Banhart et al., 2011; Paier et al., 2013; Li et al., 2017; Xie et al., 2020). The existence of vacancy defects in nanomaterials will disturb the chemical state of the surrounding atoms or ions to some extent and induce lattice distortion/strain (Matsunaga et al., 2003; Banhart et al., 2011; Wang et al., 2011; Paier et al., 2013; Han et al., 2014; Dai et al., 2016; Li et al., 2017; Xie et al., 2020). This, thus, can effectively change the local bond, atomic coordination and electronic properties around specific atomic positions located at vacancy, including bond breaking and re-forming, the bond length, bond energy, electronic compensation, charge and energy density, potential trap depth, and gap states at the Fermi level (Matsunaga et al., 2003; Banhart et al., 2011; Wang et al., 2011; Paier et al., 2013; Dai et al., 2016; Li et al., 2017; Xie et al., 2020). In particular, vacancy defects bring some unpredictable properties, such as outstanding optical, optothermal, optoelectronic, semiconductor, and plasmonic properties (Han et al., 2014; Dai et al., 2016; Li et al., 2017; Ni et al., 2017; Xu et al., 2017; Liu H. et al., 2020; Zhang et al., 2020; Cai et al., 2021). For instance, the formation of oxygen vacancies in semiconductor nanomaterials can induce defect energy levels and thus effectively regulate their electronic structures and band gap states, enhancing substantially their PTT performances (Zhou et al., 2022). Moreover, oxygen vacancy as the active
Vacancy defect engineering strategies for phototherapeutic nanomaterials

With the establishment of some basic theories of defect chemistry, defect engineering for synthesizing various defective nanomaterials with significantly improved and optimized performance has been widely studied, and effectively used in new phototherapeutic nanomaterials (Jia et al., 2017; Yan et al., 2018; Zhang et al., 2020; Bai et al.,...
2021; Wen et al., 2021; Zhou B. et al., 2021). It is hoped that defect engineering will not only provide a comprehensive insight into the understanding and utilization of defect chemistry in phototherapeutic nanomaterials, but also offer a novel and effective technique to regulate/optimize the microstructure and characteristics of phototherapeutic nanomaterials. To this end, various strategies of defect engineering have been developed, such as vacancies, heteroatomin doping, crystalline form, size effect, dislocations/steps structure effect (Banhart et al., 2011; Jia et al., 2017; Li et al., 2017; Li et al., 2018; Yan et al., 2018; Xie et al., 2020; Zhang et al., 2020). Among them, vacancy engineering strategy is one of the most researched and effective means to synthesize defective nanomaterials and to adjust/optimize their characteristics (Coughlan et al., 2017; Li et al., 2017; Nosaka and Nosaka, 2017; Yan et al., 2018; Xie et al., 2020). For example, vacancy engineering is a very powerful means to modulate band gap structures (Liang et al., 2015; Li et al., 2017). Abundant carbon vacancies are induced through heat treatment of graphite-like carbon nitride. This will not only enhance the mobility of photogenerated charge carriers, but also will extend light absorption into NIR and produce a low and flat potential band. Therefore, vacancy engineering is of great significance for the design of new phototherapeutic nanomaterials, and offer exciting opportunities for controlling their properties and phototherapeutic effectiveness.

Recent advances in vacancy engineering have enabled researchers to exploit many construction methods and manipulation ways of vacancies with high precision, so as to obtain phototherapeutic nanomaterials with specific microstructure (Komaguchi et al., 2010; Naldoni et al., 2012; Ni et al., 2017; Li et al., 2018; Guan et al., 2019; Hu et al., 2019; Lai et al., 2019; Wang X. et al., 2019; Liu H. et al., 2020; Liu Y. et al., 2020; Weng et al., 2020; Bai et al., 2021; Cai et al., 2021; Tamtaji et al., 2021; Wen et al., 2021; Zheng et al., 2021; Zhou B. et al., 2021; Li et al., 2022; Zhou et al., 2022). The construction methods of vacancy defects in phototherapeutic nanomaterials can generally be divided into two broad categories: 1) directly synthesizing vacancy defective nanomaterials; 2) post treatment of nanomaterials to construct vacancies. In terms of the former method, the specific vacancies can be directly induced with the crystal growth by tuning crystallization conditions and methods, or by regulating the ratio of starting materials, or by elemental doping (Li et al., 2017). For instance, constructing ultrathin two-dimensional nanomaterials with thickness of several atomic layers, by the modulation of synthesis methods and conditions, can induce the formation of abundant vacancies (as shown in Figure 2A) (Wang L. et al., 2019; Feng et al., 2020; Liu et al., 2021; Chang et al., 2022). Guan et al. (Wang L. et al., 2019) found a simplistic hydrothermal method to fabricate an ultrathin MnO2 nanosheet with the thickness of ~1.2 nm, much thinner than that of traditional multilayered MnO2 flakes (thickness of ~60 nm). Importantly, this method can form abundant oxygen vacancies in ultrathin MnO2 nanosheets. As obtained ultrathin MnO2 nanosheets exhibited highly efficient vacancy-induced PTT effectiveness in the NIR region. Another example, adjusting the stoichiometry or doping (as shown in Figure 2B) is a direct method to create vacancies in multicomponent nanocompounds (Komaguchi et al., 2010; Han et al., 2014; Dai et al., 2016; Ni et al., 2017; Hu et al., 2019; Liu Y. et al., 2020; Zhao et al., 2020; Zheng et al., 2021; Zhou et al., 2022). Representatively, constructing stoichiometric Cu2−xnx (X = S, Se, Te, 0 ≤ x ≤ 1) can induce Cu vacancies, and tailoring their stoichiometry can control the concentration and distribution of Cu vacancies (Coughlan et al., 2017; Hu et al., 2019; Zhao et al., 2020; Zheng et al., 2021). This can give rise to enhanced LSPR effect in the NIR region as well as a strong NIR absorption. Moreover, the vacancy defects can be induced by aliovalent doping, and the vacancies density can also be controlled by adjusting dopant concentrations (Feng et al., 2020). Chen et al. (Yu et al., 2017; Yu et al., 2018) designed and fabricated Nb-doped TiO2 and Sb-doped SnO2 nanocrystals through aliovalent doping, and formed the defect dipoles of dopants and vacancies in these nanocrystals. These nanocrystals showed broad and strong absorption bands in the NIR-II region as well as enhanced photothermal effects, thereby giving rise to excellent photothermal therapeutic efficacy.

The post treatment like annealing, irradiation, ball-milling, etching, and redox is also an efficient and controllable vacancy construction strategy (Banhart et al., 2011; Jia et al., 2017; Li et al., 2017; Yan et al., 2018; Xie et al., 2020; Zhang et al., 2020; Zhou et al., 2022). Heat treatment is one of the simplest and most common post treatment methods. For most metal oxide nanomaterials, annealing will lead to the loss of lattice oxygen, accompanied by the generation of oxygen vacancies (Li et al., 2017; Nosaka and Nosaka, 2017; Xu et al., 2017; Ji et al., 2019; Zhang et al., 2020). Their distribution and concentration can be controlled through changing sintering temperature, heating and cooling rate (Li et al., 2017; Nosaka and Nosaka, 2017; Xu et al., 2017; Ji et al., 2019; Zhang et al., 2020). Another physical method which has been applied for generating vacancies in transition metal nanocompounds and carbon-based nanomaterials is high-energy electrons or ions irradiation (Banhart et al., 2011; Li et al., 2017; Xie et al., 2020; Zhang et al., 2020). Undergoing an electron or ion beam, the atoms can be sputtered away from their lattice sites and thus generate vacancies (Banhart et al., 2011; Li et al., 2017; Xie et al., 2020). Meanwhile, the number and distribution of vacancies can be regulated by controlling irradiation area, energy and time (Banhart et al., 2011; Li et al., 2017; Xie et al., 2020). In addition, this method can also create vacancies with almost atomic selectivity. For example, according to the much lower bonding energy of Sn–O in oxides than Co–O and Fe–O, Wang et al. have selectively created Sn vacancies in CoFeSn oxides through irradiation (Chen et al., 2018). The ball-milling treatment as a facile physical method can also construct vacancies in phototherapeutic nanomaterials (Zhou Z. et al., 2021; Zhou et al., 2022). For example, the mechanical force can transform...
two-dimensional photosensitive materials into thin and short nanosheets during ball milling and create abundant vacancy defects. Etching is a common and efficient chemical post treatment method to construct vacancies (Xie et al., 2020; Zhang et al., 2020). Etching method has mainly utilized the reaction of some chemical components in nanomaterials with added chemicals to produce specific vacancies (Xie et al., 2020; Zhang et al., 2020; Zhou B. et al., 2021). For instance, the phototherapeutic nanomaterials can be etched through alkaline or acid to create metal or/and oxygen vacancies (Sun et al., 2020; Ji X. et al., 2021). Another example, undergoing the oxidative etching with of H$_2$O$_2$, abundant sulfur vacancies can be induced into MoS$_2$ nanosheets (Xie et al., 2020). In addition, the redox process is also a facile chemical post treatment method. Typical example, the annealing of metal oxides is carried out in a reactive atmosphere like H$_2$, which will cause hydrogen to react with surface oxygen to produce water and evaporate, thus forming oxygen vacancies (Li et al., 2017; Sun et al., 2019; Zhang et al., 2020; Jiao et al., 2021).

Vacancy defective nanomaterials-enhanced phototherapy and multimodal synergistic phototherapy

Phototherapy including PDT and PTT is a non-invasive light-induced therapy, which uses NIR-responsive nanomaterials to achieve effective local treatment in tumor sites and could diminish damage to normal tissues (Cheng et al., 2014; Liu Y. et al., 2019; Liu et al., 2021). Moreover, multimodal synergistic phototherapy (including synergistic PTT and PDT as well as combined phototherapy and other therapies) based on multifunctional nanomaterials can achieve synergistic enhancement of tumor treatment (Cheng et al., 2014; Fan et al., 2017; Liu Y. et al., 2019; Zhao et al., 2019). It is worth noting that various nanomaterials have made significant contributions to phototherapy through both improving targeted therapeutic efficiency and reducing side effects (Cheng et al., 2014; Liu Y. et al., 2019; Liu et al., 2021). Nanomaterials for phototherapy are usually composed of inorganic nanoparticles with strong NIR absorption and rapid NIR activation, such as noble metal, chalcogenide, transition metal oxide, polyoxometalate, transition metal carbide, and carbon-based nanoparticles (Wang X. et al., 2019; Liu G. et al., 2019; Gu et al., 2019; Wang L. et al., 2020; Wang L. et al., 2021; Tian et al., 2021). The most key factor affecting the performance of phototherapeutic nanomaterials is their microstructure (i.e., electronic and geometric structures) which in principle determines their physicochemical properties and the resulting phototherapeutic efficacy (Coughlan et al., 2017; Huang et al., 2017; Nosaka and Nosaka, 2017; Chen et al., 2021; Liu et al., 2021). Thus, the microstructure should be rationally designed and precisely tailored to obtain the phototherapeutic nanomaterials with largely improved phototherapy efficacy. With the deepening of the research on defect chemistry and engineering, it is recognized that the vacancy-type defects, such as oxygen vacancy, metal vacancy, carbon vacancy, and sulfur vacancy, commonly exist in phototherapeutic nanomaterials, which can greatly influence and directly change the microstructure of phototherapeutic nanomaterials (Wang X. et al., 2019; Guan et al., 2019; Liu H. et al., 2020; Cai et al., 2021). Constructing vacancy defects in phototherapeutic
nanomaterials (i.e., vacancy engineering) provides a very important and effective strategy for modulating their microstructure, controlling their properties, and improving their phototherapy efficacy (Liu H. et al., 2020; Bai et al., 2021; Wen et al., 2021; Zhou B. et al., 2021). Meanwhile, a deeper and more detailed understanding of the influence of vacancy defects on phototherapy is also crucial to rational design of new phototherapeutic nanomaterials. In this section, therefore, we will focus on the representative vacancy defective nanomaterials (including oxygen, sulfur, metal and carbon vacancy defective nanomaterials) recently developed through vacancy engineering for efficient phototherapy (as summarized in Table 1), in order to provide the best possible overview of various vacancy engineering strategies and the effects of various vacancies on phototherapy and multimodal synergistic phototherapy.

### Anion vacancy-promoted nanomaterials for phototherapy and multimodal synergistic phototherapy

As a new type of nanomaterials for phototherapy, NIR-responsive metal oxide semiconductor nanomaterials have made great progress in recent years, and show wide application prospect in tumor treatment because of their unique properties (Cheng et al., 2014; Huang et al., 2017; Nosaka and Nosaka, 2017; Liu Y. et al., 2019). Oxygen vacancy as the most common anionic vacancy ubiquitously exists in oxide semiconductor nanomaterials, which is a new state will be formed within the band gap of the O-defected oxide, in which the electrons associated with the metal–O bonds tend to be delocalized, proving to be able to work as the trapping site for photogenerated electron and tends to introduce the occurrence of intermediate energy level (Li et al., 2017; Nosaka and Nosaka, 2017; Wang L. et al., 2019; Guan et al., 2019; Zhou et al., 2022). This can promote the separation of electron and hole, induce band gap narrowing, and produce the related LSPR in the NIR window, which can promote the separation of electron and hole, induce band gap narrowing, and produce the related LSPR in the NIR window, thereby enhancing photothermal conversion efficiency of the MnO2 nanosheets and great potential in NIR-triggered hyperthermia. Moreover, both in vitro and in vivo results confirmed the good biocompatible properties and highly efficient vacancy-induced photothermal therapy of MnO2 nanosheets. Another example, Bu et al. (Ni et al., 2017) synthesized the oxygen-vacancy defective Gd2+-doped Na2WO4 (Na,GdWO4) nanorods by using a facile thermal decomposition approach, with both high-performance MR imaging and outstanding PTT efficacy (Figure 3A). Specifically, oxygen-vacancy-induced small polarons in Na,GdWO4 led to the strong NIR absorption and effective photothermal conversion. Meanwhile, oxygen vacancies could also cause significantly enhanced proton relaxation rates of the Na,GdWO4 (T1 value of 32.1 mM⁻¹ s⁻¹ on a clinical 3.0 T scanner). In addition, both in vitro and in vivo results showed that Na,GdWO4 can be used as an efficient theranostic nanoplatform for MRI-guided photothermal therapy under 980 nm laser irradiation by simply regulating the oxygen vacancy. Thus, the oxygen vacancies were deemed to be responsible for the enhanced MR imaging and efficient PTT treatment. This oxygen vacancy-promoted MRI-guided PTT strategy has certain universality and has recently been extended to Mn2+-doped Na2WO4 (Na,MnWO4) system, giving stable MRI and significant PTT performance (Liu Y. et al., 2020).

Compared to the first near-infrared (NIR-I) window (from 750 to 1,000 nm), the second near-infrared (NIR-II) window (from 1,000 to 1,350 nm) for photothermal therapy exhibits inherent advantages of the deeper tissue-penetration, lower light scattering and higher maximum permissible exposure (Lin et al., 2017; Liu Y. et al., 2019; Liu G. et al., 2019; Tian et al., 2021). Thus, many attempts have been contributed to developing new NIR-II-triggered photothermal nanoagents with satisfactory PTT efficacy through oxygen vacancy engineering (Han et al., 2018; Yin et al., 2018; Zhao et al., 2021; Zhou Z. et al., 2021). For example, Chen et al. (Han et al., 2018) created an oxygen-defective TiO2-x layer onto the surface of TiO2 nanosemiconductors through a facile aluminum-reduction strategy, thus constructing a crystalline-disordered core-shell structure (TiO2@TiO2-x) with black color. Notably, the presence of abundant oxygen vacancies in TiO2-x shell endowed these black nanosemiconductors with a high light absorption in the NIR-II window, inducing an enhanced NIR-II-driven photothermal effect and increased photothermal conversion efficacy. Both in vitro and in vivo evaluations have demonstrated that the photothermal ablation for tumor was enhanced by the black oxygen-defective TiO2-x shell, which could completely eradicate the tumors with high biosafety and no obvious reoccurrence. Another example, Tan et al. (Zhou Z. et al., 2021) reported that the dark blue-colored short, thin and defective MoO3-x nanobelts were synthetized through a facile ball milling process, followed by a simple lithium treatment, showing efficient PTT performance in the NIR-II window. A
| Nanomaterials                                      | Vacancy defect type | Methods                                                                 | Irradiation wavelength (nm) | Irradiation power density (W cm$^{-2}$) | Therapeutic modality          | Imaging mode | Cell lines | References         |
|--------------------------------------------------|---------------------|-------------------------------------------------------------------------|-----------------------------|----------------------------------------|-----------------------------|--------------|------------|-------------------|
| Ultrathin MnO$_2$ nanosheets                      | Oxygen vacancy      | Hydrothermal method                                                     | 808                         | 1.0                                    | PTT                         | PAI, MAI, and thermal imaging | HeLa cells  | Wang L. et al. (2019) |
| PEG-Na$_2$GeWO$_3$ nanorods                      | Oxygen vacancy      | Chemical mixing procedure at different temperatures and subsequent thermal decomposition | 980                         | 1.5                                    | PTT                         | MAI and thermal imaging       | 4T1 cells   | Ni et al. (2017)   |
| Na$_2$MnWO$_3$-PEG nanorods                      | Oxygen vacancy      | Chemical mixing procedure at different temperatures and subsequent thermal decomposition | 980                         | 1.0                                    | PTT                         | Thermal imaging, PAI, and MRI | 4T1 cells   | Liu Y. et al. (2020) |
| J$\text{MoO}_3$-x nanobelts                      | Oxygen vacancy      | Hydrothermal method, followed by ball mulling process and lithium treatment | 1,064                       | 0.75                                   | PTT                         | PAI and thermal imaging       | 4T1 cells   | Zhou Z. et al. (2021) |
| BiOBr$_{1-x}$/Rb$_2$O$_3$ nanocomposites          | Oxygen vacancy      | Hydrothermal method and subsequent heat treatment                       | 520                         | 10.0                                   | PDT                         | FLI                       | HeLa cells  | Guan et al. (2019)  |
| Ca$_{2-x}$Al$_2$O$_4$:Eu, Nd$_2$O$_4$ (CAO) nanosheets | Oxygen vacancy      | Combination of high temperature solid state reaction and subsequent wet-grinding and ultrasound treatment | Pre-excitation with 365 nm UV lamp and re-excitation with white LED | --                        | Self-illuminating PDT        | --           | 4T1 cells   | Chang et al. (2022)  |
| B$_2$TiO$_{5-x}$ nanoparticles                   | Oxygen vacancy      | Mg-thermic reduction of TiO$_2$                                         | 808                         | 0.48                                   | Synergistic PTT/PDT          | Thermal imaging             | B16F10 melanoma cells | Wang X. et al. (2019) |
| Zr$_{1-x}$O$_{2-x}$/PEG/Ce$_6$ nanoparticles     | Oxygen vacancy      | Magnesium reduction procedure and subsequent surface modification        | 660 and 808                 | 0.76 for 660 nm and 2.0 for 808 nm      | Synergistic PTT/PDT          | FLI and PAI                 | 4T1 cells   | Sun et al. (2019)   |
| PEG-MoO$_3$ nanoparticles                        | Oxygen vacancy      | Hydrothermal method                                                      | 808 and 1,064              | 0.75 for 808 nm and 0.6 for 1,064 nm    | Synergistic PTT/PDT          | Thermal imaging             | HeLa cells  | Yin et al. (2018)   |
| TiO$_2$@red phosphorus nanorods                  | Oxygen vacancy      | Vaporization-deposition method                                           | 808                         | 0.85                                   | Synergistic PTT/PDT          | Thermal imaging             | ccRCC cells | Yang et al. (2021)  |
| CaO-SiO$_2$-TiO$_2$ (CST) nanocomposites         | Oxygen vacancy      | Containerless melting technology                                          | 808                         | 0.8 W cm$^{-2}$ and 1.0 W cm$^{-2}$ for NIR irradiation, 10.0 W cm$^{-2}$ for xenon lamp irradiation | Synergistic PTT/PDT          | Thermal imaging             | LM8 cells   | Wang E. et al. (2021) |
| MnO$_2$@Au nanonanomaterials                     | Oxygen vacancy      | One-step reduction method                                                | 808                         | 1.0                                    | Synergistic PTT/CDT          | Thermal imaging             | HeLa cells  | Peng et al. (2020)  |
| NH$_2$-MnO$_2$@BSA nanobelts                     | Oxygen vacancy      | Hydrothermal method, followed by ball mulling                           | 1,064                      | 0.8                                    | Synergistic PTT/CDT          | Thermal imaging             | HUVE, HeLa, 4T1 cells | Zhou et al. (2022)  |

(Continued on following page)
| Nanomaterials                       | Vacancy defect type | Methods                                                                 | Irradiation wavelength (nm) | Irradiation power density (W cm\(^{-2}\)) | Therapeutic modality | Imaging mode | Cell lines | References                |
|------------------------------------|---------------------|-------------------------------------------------------------------------|------------------------------|------------------------------------------|----------------------|--------------|------------|---------------------------|
| Ox-POM@Cu nanocomposites          | Oxygen vacancy      | Chemical mixing procedure at different temperatures                     | 1,064                        | 1.0                                      | Synergistic PTT/CDT | Thermal imaging and PAI | 4T1 and HL-7702 cells | Wang et al. (2022)       |
| Black mica (BM) nanosheets         | Oxygen vacancy      | Combination of calcination, n-butylithium exchange and intercalation, and liquid exfoliating processes | 650 and 808                  | 0.5 for 650 nm and 1.0 for 808 nm         | Synergistic PTT/PTT/PDT/CDT | FLI, PAI, and thermal imaging | A549, Hela, MCF7, and PC3 cells | Ji et al. (2019)         |
| d-Cu-LDH/ICG nanoparticles         | Oxygen vacancy      | Coprecipitation method, followed by isomorphic substitution and acid etching | 808                          | 0.23 and 0.5                             | Synergistic PTT/PTT/PDT/CDT | FLI          | 4T1 cells | Sun et al. (2020)         |
| Functional core layers (FCLc)      | Oxygen vacancy      | Wet-chemical exfoliation method based on allal etching                  | 658 and 808                  | 0.5 for 658 nm and 1.0 for 808 nm         | Synergistic PTT/PTT/PDT/CDT | FLI, PAI, and thermal imaging | A549, HepG2, CCR-25Lu, HEK 293, and THLE-3 cells | Ji X. et al. (2021) |
| As/As\(_x\)O\(_y\)@PDA@M nanosheets | Oxygen vacancy      | Coupling ball-grinding with probe sonication-based liquid exfoliating processes and subsequent surface modification | 660 and 808                  | 0.3 for 660 nm and 1.0 for 808 nm         | Synergistic PTT/PTT/PDT/CDT | FLI          | A549 and MCF-7 cells    | Kong et al. (2021)   |
| WR@hydrogel                        | Oxygen vacancy      | Hydrothermal method and subsequent hydrogenation reaction              | 1,064                        | 1.5                                      | Synergistic PTT/GT  | FLI          | 4T1 and HePG2 cells | Zhao et al. (2021)   |
| ZrO\(_2\)@PEG/cRGD (ZPR) nanoparticles | Oxygen vacancy   | Modified magnesium (Mg) reduction process                              | 1,064                        | 1.0                                      | Synergistic PTT/SDT | PAI, and thermal imaging | 4T1 cells | Jiao et al. (2021)     |
| TiO\(_2\)@TiO\(_2\)@PEG nanoparticles | Oxygen vacancy   | Aluminum (Al) reduction procedure                                      | 1,064                        | 1.5                                      | Synergistic PTT/SDT | Thermal imaging | 4T1 cells | Han et al. (2018)     |
| Bi\(_2\)S\(_3\)-Au nanorods       | Sulfur vacancy      | Solvothermal method and subsequent in situ reduction process            | 808                          | 0.9                                      | PTT                  | CT and thermal imaging | 4T1 cells | Cheng et al. (2018) |
| FeS\(_2\) nanoparticles            | Sulfur vacancy      | Solvothermal method                                                      | 915                          | 1.0                                      | PTT                  | Ultrasound imaging, thermal imaging, and MRI | SMMC-7721 cells | Meng et al. (2016) |
| Bi\(_2\)Se\(_3\) nanodots          | Selenium vacancy    | Scalable biomineralization approach                                     | 1,064                        | 1.4                                      | PTT                  | CT, PAI, and thermal imaging | 4T1 cells | Wen et al. (2021)     |
| PTh@Au nanoconstructs             | Sulfur vacancy      | One-step redox strategy                                                 | 650                          | 50.0                                     | PDT                  | --           | HeLa and U14 cells   | Bai et al. (2021)  |

(Continued on following page)
| Nanomaterials                     | Vacancy defect type | Methods                                                                 | Irradiation wavelength (nm) | Irradiation power density (W cm⁻²) | Therapeutic modality       | Imaging mode          | Cell lines | References |
|----------------------------------|---------------------|------------------------------------------------------------------------|----------------------------|-----------------------------------|---------------------------|-----------------------|-------------|------------|
| MoS₂ quantum dots                | Sulfur vacancy      | Aqueous room temperature bottom-up synthesis                           | 400–800                    | 10.0                              | PDT                       | --                    | SW480 cells | Ding et al. (2019) |
| Fe₃S₄ tetragonal nanosheets      | Sulfur vacancy      | Hot-injection thermal decomposition reaction and subsequent surface modification | 915                        | 0.5                               | Synergistic PTT/PDT       | Thermal imaging, and MRI | HeLa cells  | Guan et al. (2018)  |
| T80-AuPt@CuS nanosheets          | Sulfur vacancy      | In situ reduction process and subsequent surface modification          | 808                        | 1.0                               | Synergistic PTT/radiotherapy | CT and PAI            | 4T1 cells   | Cai et al. (2021)  |
| Cu₉₋ₓSe-PEG-SH nanoparticles     | Cu vacancy          | Aqueous reduction process and subsequent surface modification          | 808                        | 1.5                               | PTT                       | PAI, CT, SPEC, and thermal imaging | 4T1 cells   | Zhang et al. (2016) |
| Ultrathin CuS nanocrystals       | Cu vacancy          | Microwave-assisted synthesis strategy                                  | 980                        | 2.48                              | PTT                       | FLI                   | PC-3/Luc+ cells | Zheng et al. (2021) |
| Cu₂Bi₂S₆ nanocrystals            | Cu vacancy          | Solvothermal method                                                    | 915                        | 1.2                               | PTT                       | CT and thermal imaging | TC71 cells  | Li et al. (2015)   |
| Au@Cu₉₋ₓS nanorods               | Cu vacancy          | Nonepitaxial strategy of tributylphosphine-initialized cation exchange  | 808 and 1,064              | 1.0 for 808 nm and 0.7 for 1,064 nm | PTT                       | --                    | HeLa cells   | Ji et al. (2016)   |
| Ultrasmall Cu₉₋ₓS-PEG nanodots    | Cu vacancy          | One-step redox strategy and subsequent surface modification            | 1,064                      | 1.5                               | Synergistic PTT/CDT       | PAI and thermal imaging | 4T1 cells   | Ha et al. (2019)  |
| CoCuFe-PVP-L-Arg nanosheets      | Cu vacancy          | In situ selenylation treatment of precursor                             | 808                        | 1.0                               | Synergistic PTT/GT        | PAI, thermal imaging, and FLI | HepG2 and 4T1 cells | Wu et al. (2021) |
| Pt-CuS-PNTs nanocomposite        | Cu vacancy          | Co-assembly, followed by biomineralization process and covalent graph method | 808                        | 0.5                               | Synergistic PTT/PDT/ chemotherapy | Thermal imaging       | B16-F10 cells | Lai et al. (2019) |
| MoSe₂/B₈S₆Se₉@PEG-Dox nanocomposites | Mo vacancy        | Ultrasound-assisted exfoliated method and subsequent cation exchange method | 808                        | 0.2, 0.5, and 1.0                 | Synergistic PTT/PDT/ chemotherapy | Thermal imaging, PAI, and CT | L02 and HepG2 cells | Wang Y. et al. (2019) |
| CoFe-mixed metal oxide (CoFe-x) nanosheets | Co vacancy        | Heat treatment of LDHs precursor                                       | 808                        | 1.0                               | PTT                       | PAI and MRI           | HeLa cells   | Wang J. et al. (2020) |
| W₁ₓC₃-BSA nanosheets              | W vacancy           | Solid state sintering, followed by acid etching, exfoliation treatment, and surface modification | 808 and 1,064              | 1.25                              | PTT                       | PAI, FLI, CT, and thermal imaging | 4T1 and L929 cells | Zhou B. et al. (2021) |
TABLE 1 (Continued) Summary of the vacancy defective nanomaterials for phototherapy and multimodal synergistic phototherapy from recent reports in the literature.

| Nanomaterials                      | Vacancy defect type | Methods                          | Irradiation wavelength (nm) | Irradiation power density (W cm⁻²) | Therapeutic modality | Imaging modality | Cell lines | References               |
|-----------------------------------|---------------------|----------------------------------|-----------------------------|-----------------------------------|----------------------|-----------------|------------|--------------------------|
| S-FU/Cu-LDH nanoparticles         | Mg and OH vacancy   | Hydrothermal Method, followed by intercalation treatment and acid etching | 808                         | 1.0                               | PTT                  | MRI and thermal imaging | HCT-116 cells | Li et al. (2018)         |
| Ag@Ag₃O₇/LDHs-Li nanocomposites   | Ag and oxygen vacancy | Modified solvent-free bottom-up approach, followed by in situ spontaneous deposition and surface modification | 1,064                       | 1.0                               | PTT                  | FLI and PAI      | L02, HeLa, and HepG2 cells | Li et al. (2022)         |
| Cu₄(CPPT)·t nanoparticles         | Carbon vacancy      | Pyrolysis of Cu-BTC precursor    | 808                         | 1.6                               | PTT                  | PAI and thermal imaging | Hela cells     | Weng et al. (2020)       |
| Graphene quantum dots             | Carbon vacancy      | Magnetic field-assisted solvothermal method | 1,064                       | 1.0                               | PTT                  | Thermal imaging     | 4T1, Hela, and H196 cells | Liu H. et al. (2020)     |
| Rh₂C@C nanosheets                 | Carbon vacancy      | Hydrothermal method              | 1,064                       | 1.0                               | PTT                  | PAI and FLI       | Hela and HepG2 cells     | Guo et al. (2021)        |
| Pd nanonzyme                      | Carbon vacancy      | Pyrolysis of Pd@ZIF-8 precursor  | 1,064                       | 0.28                              | Synergistic PTT/CDT  | --              | L929 and 4T1 cells     | Chang et al. (2021)      |
| C/Mo₅S₆@MoO₃ nanoparticles        | Carbon vacancy      | Pyrolysis of Mo/ZIF-8 precursor  | 1,064                       | 1.0                               | Synergistic PTT/CDT  | PAI and FLI       | L02 and HeLa cells      | Wang L. et al. (2021)    |

combination study including XPS, EXAFS, HAADF-STEM and EPR indicated the generation of abundant oxygen vacancies in layered MoO₃₋ₓ nanobelts by Li intercalation, leading to partial reduction of Mo atoms from Mo⁶⁺ to Mo³⁺ and thus yielding dark blue-colored MoO₃₋ₓ nanobelts. Such structural changes gave rise to a strong absorption in the NIR-II region and enabled a large extinction coefficient of 18.2 Lg⁻¹ cm⁻¹ at 1,064 nm, thus causing a high photothermal conversion efficiency of 46.9%. As-obtained MoO₃₋ₓ nanobelts can be used as a nanoagent for photoacoustic imaging-guided PTT to achieve efficient ablation and eradication for tumor under 1,064 nm laser irradiation. Therefore, the oxygen vacancy engineering is a powerful strategy to tune microstructure and properties of phototherapeutic nanomaterials and thus boost their PTT effectiveness for tumor.

Oxygen vacancy engineering strategy can also play an important role in photodynamic therapy. It can effectively regulate the energy band structure of phototherapeutic nanomaterials and significantly improve photoinduced ROS production efficiency. Guan et al. (Guan et al., 2019) reported an oxygen vacancy-promoted BiOBr–H/Rub₂d nanocomposite for PDT via a two-step procedure: preparation of oxygen vacancy-rich BiOBr (BiOBr–H) by a hydrothermal method and subsequent heat treatment, followed by the coupling of Ru(bpy)₃C–pyCl₂ photosensitizer (Rub₂d). An experimental-computational combination study demonstrated that the strong electronic interactions between BiOBr–H and Rub₂d resulted in the photogenerated electrons transfer from Rub₂d to the oxygen vacancy-induced intermediate energy level in BiOBr–H (Figure 3B). Thereby this facilitated rapid electron-hole separation and led to enhanced generation of ¹O₂. Specifically, the ¹O₂ yield of BiOBr–H/Rub₂d (0.49) was more than twice that of Rub₂d (0.22). Furthermore, both in vitro and in vivo studies confirmed that the BiOBr–H/Rub₂d nanocomposite was a potent PDT agent for cancer treatment. This strategy of oxygen vacancy-enhanced generation of singlet oxygen also has universal applicability to other photosensitizers (e.g., indocyanine green and zinc phthalocyanine), thus giving great potential in PDT for cancer treatment. In another example of oxygen vacancy-promoted PDT, Feng et al. (Chang et al., 2022) reported that a distinct 2D CaAl₂O₄:Eu, Nd persistent luminescence nanosheets (CAO PLNSs) for irradiation-free PDT. A combination study verified the existence of abundant oxygen vacancies in CAO PLNSs, arising from the introduction of Eu³⁺ and Nd³⁺ ions. Notably, the generation of oxygen vacancies in CAO PLNSs induced formation of trap level
(i.e., defect energy levels), causing a steady stream of $5d-4f$ electronic transition between Nd$^{3+}$ 4$f$ and Eu$^{2+}$ 5$d$ levels and persistent blue luminescence. Thus, CAO PLNSs can continuously produce cytotoxic $^{1}O_2$ through long-lasting self-illuminating PDT without the need for external light excitation, inducing cancer-cell apoptosis. Accordingly, through the systematic evaluation of $in vitro$ and $in vivo$ experiments, persistent luminescence-enhanced PDT showed outstanding antitumor efficacy. Therefore, oxygen vacancy engineering can not only regulate the energy band structure of phototherapeutic nanomaterials and improve $^{1}O_2$ yield, but also enhance the self-luminescence characteristics of phototherapeutic nanomaterials and help the establishment of an efficient self-illuminating PDT systems, so as to overcome the tissue penetration limitation of conventional PDT and provide new avenues for efficient treatment of deep-seated tumors.

Due to the complexity, heterogeneity, and proliferative activity of tumors, the development of multimodal synergistic therapy based on the cooperatively enhanced interactions between PTT and PDT or between phototherapy and other treatments (e.g., chemodynamic therapy), as well as designing more effective multifunctional nanomaterials, are both critical (Fan et al., 2017). The oxygen vacancy engineering provides a new strategy for constructing multifunctional nanomaterial and achieving efficient synergistic therapy. Thus, some oxygen vacancy-engineered nanomaterials have been developed to efficiently combine PDT and PTT to improve the phototherapeutic efficacy against tumor (Sun et al., 2019; Wang X. et al., 2019; Maleki et al., 2021; Yang et al., 2021). For example, Xu et al. (Yang et al., 2021) synthesized the core–shelled TiO$_2$/red phosphorus nanorods (TiO$_2$@RP NRs) as a nanophotosensitizer for synergetic PDT and PTT, through
the vaporization-deposition (VP) method. It can be observed that more oxygen vacancies were created in nanosized TiO2 core after the vaporization-deposition, which led to a significantly enhanced NIR absorption in the range of 640–1,100 nm. This enabled TiO2@RP NRs to effectively kill significant numbers of deep-tissue tumor cells by generating local heat and ROS, and cause low damage to normal cells. Another example, Wu et al. (Wang X. et al., 2019) reported that Mg-containing black titania (B-TiO2-x) nanoparticles were synthesized via the Mg-thermic reduction of TiO2, exhibiting a crystalline/amorphous core–shell structure with abundant oxygen vacancies within the amorphous shell (Figure 4). The existence of abundant oxygen vacancies in the disordered surface layers (Figure 4) caused the band gap narrowing, giving rise to that the light absorption of B-TiO2-x could be effectively extended from the UV to NIR regions. This endowed the B-TiO2-x with simultaneous PTT and PDT effects under single-wavelength NIR laser irradiation, resulting in an outstanding curative effect on skin tumors in vitro and in vivo (Figure 4). Meanwhile, the Mg2+ ions released from B-TiO2-x could stimulate the proliferation, adhesion and migration of normal skin cells, so as to promote wound healing process.

In recent years, chemodynamic therapy (CDT) represents an especially promising anticancer strategy, and utilizes transition metal oxide catalysis or the transition metal oxide-catalyzed Fenton reaction to promote the transformation of tumor-specific H2O2 into ROS, thus inducing tumor cells apoptosis (Liu C. et al., 2019; Tang et al., 2019; Ji S. et al., 2021; Tang et al., 2021). Although CDT is effective in preventing tumor growth and metastasis, it doesn’t have the ability to completely eliminate the tumor because of insufficient endogenous H2O2 (Liu Y. et al., 2020; Ji S. et al., 2021). Thus, oxygen vacancy-promoted synergistic PTT/CDT or PTT/PDT/CDT have been explored to achieve the satisfactory anticancer efficacy, so as to effectively eliminate tumor and inhibit tumor recurrence (Li et al., 2019; Peng et al., 2020; Sun et al., 2020; Ji X. et al., 2021; Kong et al., 2021; Zhang et al., 2021; Wang et al., 2022; Zhou et al., 2022). For instance, Tan et al. (Zhou et al., 2022) reported the dark-blue co-intercalated MoO3-x (denoted as NH–MoO3-x) nanobelts via the ball-milling process and then aqueous Na+H2O co-intercalation as efficient nanozymes for photothermal-enhanced CDT. A combination study verified that the co-intercalation of Na+ and H2O into layered MoO3 nanobelts can induce the formation of the abundant oxygen vacancies. This can provide more active sites for the adsorption and activation of H2O2 to produce the more •OH and O2•, thus improving the catalytic performance of nanozymes. Subsequently, the adsorbed O2 was further reduced to •O2− through the electron transfer between Mo6+ and Mo5+ contained in oxygen defective NH–MoO3-x nanobelts. Moreover, the abundant oxygen vacancies in NH–MoO3-x nanobelts led to the generation of defect energy levels and the narrowing of band gap, boosting its absorption in the NIR-II region and thus enabling its good photothermal effect. Notably, the catalytic activity of nanozyme can be further enhanced by NIR-II light driven photothermal effect. NH–MoO3-x@BSA nanobelts were obtained after surface modification of bovine serum albumin (BSA). In addition, oxygen defective NH–MoO3-x@BSA nanobelts exhibits remarkable synergistic therapeutic efficacy, both in vitro and in vivo, through tumor microenvironment stimulated generation of multiple ROS and NIR-II photothermal activity. The anticancer efficacy can be further strengthened by triple synergistic therapy built on the cooperative enhancement interactions among three treatments and through oxygen vacancy-engineered multifunctional nanomaterials (Ji et al., 2019; Sun et al., 2020; Ji X. et al., 2021; Kong et al., 2021; Zhang et al., 2021). For example, Ji et al. (Kong et al., 2021) designed and fabricated surface-oxidized arsenene nanosheets (As/As2O3 NSs) with type II heterojunction and abundant oxygen vacancies through coupling ball-grinding with probe sonication-based liquid exfoliating processes, showing significant synergistic and photo-enhanced PTT/PDT/CDT. A combination study verified that the As2O3 in As/As2O3 NSs possessed abundant oxygen vacancies and active As2+ and As3+ sites caused by oxygen vacancies. The existence of abundant oxygen vacancies in such heterojunction As/As2O3 NSs caused the narrowing of band gap, promoted the separation of electron holes, and enhanced the adsorption and activation of oxygen. This gave rise to vast •O2− and O2• production in the PDT process (under 660 nm laser irradiation) and obvious NIR-induced photothermal effect in the PTT process (under 808 nm laser irradiation). Moreover, the portion of As2O3 with abundant oxygen vacancies not only can catalyze a Fenton-like reaction of H2O2 to generate •OH and O2• but also inactivate some main anti-oxidants and anti-oxidases to inhibit consumption of ROS. This can directly promote ROS burst and essentially enhance the PDT effect. After polydopamine (PDA) and cancer cell membrane (M) coating, As/As2O3@PDA@M NSs were obtained with remarkable biocompatibility and homologous targeting ability. Both in vitro and in vivo evaluations demonstrated that such oxygen vacancy-promoted As/As2O3@PDA@M NSs with type II heterojunction can efficiently cause a ROS production in cancer cells and successfully integrate PTT/PDT/CDT, thus establishing triple synergistic therapy with high anticancer efficacy.

In addition to metal oxide nanosemiconductors, metal sulfide nanomaterials, such as MoS2, FeS2, and Bi2S3, have attracted extensive attention in the field of phototherapy, because of their superb electronic and optical properties, good biocompatibility, and easily functionalized surface structures (Meng et al., 2016; Cheng et al., 2018; Zhou et al., 2020; Liu et al., 2021). It is worth noting that sulfur vacancy, as another typical anion vacancy, has a profound impact on the microstructures, physicochemical properties and corresponding phototherapeutic efficacy of metal sulfide nanomaterials (Meng et al., 2016; Lu L. et al., 2018; Cheng et al., 2018; Guan et al., 2018; Ding et al., 2019; Hou et al., 2020;
Bai et al., 2021; Cai et al., 2021; Wen et al., 2021). Tan et al. (Cai et al., 2021) reported that an overlap plasmonic AuPt@CuS heterostructure toward synergistic PTT and radiotherapy (RT) were formed by decorating AuPt nanoparticles onto the surfaces of CuS nanosheets (Figure 5). It was found that Au and Pt atoms can strongly bond to S atoms, leading to the formation of sulfur vacancy at the surface of CuS NSs. These interfacial sulfur vacancies enabled an increase of carrier density and then induce intensive surface plasmon resonance effect and strong resonance absorption of NIR light (Figure 5). This resulted in the significantly enhanced photothermal performance of AuPt@CuS NSs upon NIR irradiation. Moreover, the presence of sulfur vacancies in AuPt@CuS NSs promoted radiogenerated electron–hole separation, thus resulting in intracellular glutathione (GSH) depletion and ROS generation. This can give rise to enhanced local radiation energy deposition (Figure 5). T80-AuPt@CuS NSs were obtained after surface modification of Tween 80. Importantly, the T80-AuPt@CuS NSs displayed synergistic therapeutic efficacy in vitro and in vivo upon the combination of PTT and RT, completely killing tumor tissues without later recurrence (Figure 5). In addition, T80-AuPt@CuS NSs possessed the excellent capability of dual-modal computerized tomography (CT)/photoacoustic (PA) imaging, which can effectively guide synergistic radiophotothermal therapy (Figure 5). Another example, Leong et al. (Ding et al., 2019) demonstrated a facile bottom-up route to synthesize sulfur vacancy-defective MoS2 quantum dots (QDs, the uniform sizes of around 3.9 nm) with mild aqueous and room temperature conditions. It is worth noting that the degree of sulfur vacancies can be controlled via tuning precursor stoichiometry, thus providing a window of opportunity to adjust their optical and electrical properties. A strong positive correlation between the degrees of sulfur vacancies and the 1O2 quantum yields (photochemical related 1O2 generation capacity) can be observed in the obtained MoS2 QDs. Further an experimental-computational combination study revealed that the sulfur vacancies in MoS2 QDs reduced band gap and strengthened binding affinity between MoS2 and 1O2. This may have contributed to the intersystem crossing and energy transfer separately in the photosensitizing process, thus leading to the observed enhanced 1O2 generation. Importantly, the resulting MoS2 QDs utilizing tunable defect engineering showed more photodynamic efficiency for killing cancer cells, thereby enhancing their therapy effect while preventing the potential chronic side effects.

Cation vacancy-promoted nanomaterials for phototherapy and multimodal synergistic phototherapy

Metal cation vacancy widely existing in transition metal nanomaterials (e.g., metal chalcogenides, metal oxides, and metal carbides) greatly affects their optical, optothermal,
semiconductor, and plasmonic properties, and therefore largely dominate their efficacy of phototherapy (Coughlan et al., 2017; Wang Y. et al., 2019; Wang J. et al., 2020; Zhou B. et al., 2021). Typically, the copper chalcogenide (Cu_{2-x}X, X = S, Se, Te, 0 ≤ x ≤ 1) nanomaterials can support local surface plasmon resonance (LSPR) from NIR to middle infrared region and the characteristic features of p-type semiconductor, due to Cu vacancies in these nanomaterials, rendering them promising nanomaterials for phototherapy applications (Li et al., 2015; Ji et al., 2016; Zhang et al., 2016; Lu Y. et al., 2018; Hu et al., 2019; Lai et al., 2019; Wu et al., 2021; Zheng et al., 2021). The free carrier concentration of Cu_{2-x}S increases with increasing number of Cu vacancies (x), which gives rise to a broad and strong absorption band in the NIR region and an enhanced photothermal effect (Coughlan et al., 2017; Huang et al., 2017; Zhao et al., 2020). For example, Ma et al. (Zheng et al., 2021) fabricated the ultrathin starch-coated CuS nanocrystals (CuS NCs) with precisely tunable size and LSPR through a simple and rapid microwave-assisted synthesis strategy, exhibiting a prominent photothermal therapeutic effect on human prostate tumor. The plasmonic analysis and simulation revealed that the obtained CuS NCs possessed an increase in the free carrier density while a decrease in the mean free path of carriers, due to high Cu vacancy concentration and starch coating on CuS NCs. This led to a high LSPR absorption of CuS NCs at the NIR wavelength 980 nm and markedly enhanced their photothermal performance. Furthermore, it was found that the free carrier densities of small CuS NCs were higher than that of large CuS NCs because of their structural differences, so small CuS NCs had the higher photothermal performance at 980 nm. In addition, small CuS NCs as efficient photothermal agents displayed a high photothermal ablation efficacy for human prostate cancer PC-3/Luc+ cells and an enhanced biocompatibility. Another example, Wei et al. (Wu et al., 2021) constructed an ultrathin Cu-loaded CoCuFe-selenide (CCFS) through in situ selenylation treatment of CoCuFe-layered double hydroxide (CoCuFe-LDH) precursor, which showed vastly enhanced photothermal conversion efficiency for NIR-triggered PTT. It was found that more Cu vacancies and more free charge carriers can be formed in these selenides via regulating the Cu doping ratio or/and using surface corrosion. Specifically, more Cu vacancies on the surface of the CCFS can be generated with an increase of Cu content from 10% to 30%, while Cu vacancies gradually increased as the pH decreased from 7.4 to 5.4. Correspondingly, CCFS with a 30% Cu doped ratio at pH 5.4 showed maximum Cu vacancies concentration and strongest LSPR absorbance characteristic in the NIR-I region, thus leading to an outstanding photothermal conversion efficiency of 81.0% at 808 nm laser irradiation. Moreover, the surface of CCFS can be further modified with polyvinyl pyrrolidone (PVP) and L-arginine (L-Arg) to obtain CCFS-PVP-L-Arg (CPA) system, permitting localized NO gas therapy (GT) in the tumor site through L-Arg decomposition activated by endogenous H_{2}O_{2}. In addition, both in vitro and in vivo studies have confirmed that the CPA nanocomposites showed excellent synergetic PTT and GT for tumors under NIR irradiation. LSPR coupling effect between noble metal and cationic vacancy defective Cu_{2-x}S can significantly enhance NIR-II-driven PTT. Zhang et al. (Li et al., 2016) constructed an Au@Cu_{2-x}S core–shell nanorods (Au@Cu_{2-x}S NRs) by the non-epitaxial strategy of tributylphosphine- initialized cation exchange, showing strong LSPR coupling effect and enhanced photothermal conversion efficiency under 1,064 nm light irradiation. It was found that LSPR of Au core in Au@Cu_{2-x}S NRs originated from the collective oscillations of electrons. In contrast, the collective oscillations of holes led to LSPR of Cu_{2-x}S shell, due to abundant Cu vacancy induced p-type carriers. Based on experimental and theoretical studies, the formation of Au@Cu_{2-x}S core–shell nanorods could couple the LSPR properties of Au and Cu_{2-x}S NRs to a maximum degree, resulting in a plasmon-enhanced absorption in NIR-II region and heightened photothermal conversion efficiency. Thus, Au@Cu_{2-x}S NRs showed a very strong capacity on killing HeLa cell under 1064 nm laser irradiation.

Due to the presence of Cu vacancies in the lattice, abundant free carriers, excess holes, and more Cu+ active sites can be created in the Cu_{2-x}S semiconductor nanocrystals, which contributes to the generation of ROS (Coughlan et al., 2017; Zhao et al., 2020). Thus, these Cu_{2-x}S can also be designed as the multifunctional nanomaterials for synergistic tumor therapy (e.g., PTT/CDT, PTT/PDT, and PTT/PDT/CDT) (Lu Y. et al., 2018; Hu et al., 2019; Lai et al., 2019). Wu et al. (Hu et al., 2019) reported that the ultrasmall PEG-modified Cu_{2-x}S nanodots (Cu_{2-x}S-PEG NDs) with abundant Cu vacancies were fabricated for photoacoustic imaging-guided synergistic therapy against tumors, through a redox reaction between sulfur and Cu(acac)_{2}, and subsequent DSPE-PEG2000-NH_{2} surface coupling. It was observed that as-obtained ultrasmall Cu_{2-x}S-PEG NDs (their average particle size ≤5 nm) can be efficiently and passively accumulated at the tumor sites through the typical EPR effect. Especially, these Cu_{2-x}S-PEG NDs at the tumor sites can effectively catalyze tumor-overexpressed H_{2}O_{2} to produce a large amount of cytotoxic •OH radicals, thus inducing tumor cell apoptosis. The findings were likely to be attributed to the formation of abundant Cu+ active sites in Cu_{2-x}S-PEG NDs induced by Cu vacancies, improving the catalytic activity of Cu_{2-x}S-PEG NDs for Fenton reaction. Moreover, the presence of Cu vacancies in Cu_{2-x}S-PEG NDs caused also their LSPR and strong light absorption in NIR-II biowindows. These Cu_{2-x}S-PEG NDs, thus, showed significantly enhanced photoacoustic imaging and photothermal effect, which could efficiently monitor the tumor regions and promote photothermal ablation for tumors as well as synergistically enhance Fenton-mediated therapeutic efficacy. In addition, both in vitro and in vivo experiments further demonstrated that Cu_{2-x}S-PEG NDs had good biocompatibility and outstanding synergetic therapeutic effects.
eficacy, providing a new strategy of photoacoustic imaging-guided synergistic therapy for potential clinical application. Another example, Zhang et al. (Lai et al., 2019) synthesized the peptide nanotube-supported Cu$_2$S nanoparticles (CuS−PNTs) with uniform particle size and ordered dispersion. The as-synthesized CuS−PNTs had obvious absorption in the NIR region and significantly enhanced photothermal effect, due to the strong LSPR originated from Cu vacancies in the lattice. Notably, taking the advantage of type I PDT mechanism, CuS−PNTs with the characteristics of p-type semiconductor can induce the efficient generation of $\cdot$O$_2^-$ under NIR laser irradiation, and then the $\cdot$O$_2^-$ can be converted into cytotoxic $\cdot$OH through disproportionation reaction and subsequent Cu$^+$-catalyzed Fenton-like reaction. This resulted in a synergetic PTT and PDT for tumors treatment. Moreover, CuS−PNTs can further be covalently grafted with an oxaliplatin prodrug (Pt−CuS−PNTs) to construct a multifunctional nanoplatform for combined photo- and chemotherapy. Correspondingly, the antitumor studies have confirmed that Pt−CuS−PNTs can significantly inhibit the tumor growth and lung metastasis of melanoma.

For other transition metal nanomaterials such as metal oxides, metal hydroxides, and metal carbides, metal cation vacancy also plays a key role in tailoring microstructure and improving therapeutic efficacy (Naldoni et al., 2012; Li et al., 2018; Wang J. et al., 2020; Zhou B. et al., 2021; Li et al., 2022). Guan et al. (Wang J. et al., 2020) reported that a series of vacancy defects-promoted CoFe-mixed metal oxides (CoFe-x, x represented different calcination temperatures) as efficient photothermal agents were successfully fabricated on the basis of the precise control over the calcination process of CoFe-LDH precursors (Figure 6). A combination study including HRTEM, EXAFS, and XPS verified that the morphology (e.g., particle size) and microstructure (e.g., the concentration of Co$^{2+}$ vacancies) of CoFe-x nanomaterials can be effectively adjusted through tuning different calcination temperature of CoFe-LDH precursors (Figure 6). In particular, with the increase of calcination temperature from 200 to 800°C, the concentration of Co$^{2+}$ vacancies increased first and then decreased, and the maximum Co$^{2+}$ vacancies concentration was present in the sample of CoFe-500 (Figure 6). The optimized nanoagent (CoFe-500, with the highest concentration of Co$^{2+}$ vacancies) via tuning the calcination temperature of CoFe-LDH precursors and Co$^{2+}$ vacancies concentration gave a most efficient photothermal performance under NIR irradiation (Figure 6). Experiments and DFT calculations revealed that Co$^{2+}$ vacancies greatly affected the electronic structure of CoFe-x and resulted in the narrowing of the band gap (Figure 6), so as to increase the non-radiative recombination rate and enhance the NIR-driven photothermal effects. Moreover, in vitro and in vivo results indicated that CoFe-500 had outstanding photothermal therapeutic efficacy, while also acting as a promising agent for biomedical imaging such as near-infrared thermal imaging, magnetic resonance, and photoacoustic imaging (Figure 6).
Another example, Chen et al. (Zhou B. et al., 2021) reported that a distinct BSA-modified W\textsubscript{1.33}C nanosheet (W\textsubscript{1.33}C-BSA) with ordered divacancies was efficiently fabricated through designing a parent bulk laminate in-plane ordered (W\textsubscript{2/3}Y\textsubscript{1/3})\textsubscript{2}AlC ceramic and optionally etching Al and Y elements. Especially, both theoretical simulations and experiments revealed that W\textsubscript{1.33}C-BSA nanosheets with ordered divacancies had a broad and strong absorption band in the NIR region, and resulted in excellent photothermal conversion efficiency under both the NIR-I and NIR-II laser irradiation. Notably, W\textsubscript{1.33}C-BSA nanosheets could be rapidly degraded in normal tissue and easily excluded from the body due to abundant ordered divacancies in these ultrathin nanosheets, while their unique pH-responsive characteristics enabled them to enrich and remain longer at tumor sites. Moreover, benefiting from the superior X-ray attenuation ability and high NIR absorbance of these nanosheets, W\textsubscript{1.33}C-BSA nanosheets exhibited highly effective dual-modal PA/CT imaging-guided photothermal therapy against tumors.

**Carbon vacancy-promoted nanomaterials for phototherapy and multimodal synergistic phototherapy**

In addition to transition metal nanocompounds, carbon-based nanomaterials, including but not limited to graphene, carbon quantum dots, and derivatives of metal–organic frameworks (MOFs), are also promising candidates as nanomaterials for phototherapy (Lu L. et al., 2018; Chen et al., 2021; Tamtaji et al., 2021; Tian et al., 2021). Meanwhile, carbon vacancy defects in carbon-based nanomaterials can significantly influence their configuration and atomic arrangements and effectively regulate the local π-electron system, so as to tailor the global properties of phototherapeutic nanomaterials and to achieve desired phototherapy effects (Liang et al., 2015; Li et al., 2017; Liu H. et al., 2020; Weng et al., 2020; Wang L. et al., 2021; Chang et al., 2021; Chen et al., 2021; Guo et al., 2021; Tamtaji et al., 2021). Guan et al. (Weng et al., 2020) reported that a series of vacancy defective nanocarbon polyhedral-supported Cu nanoparticles (Cu@CPP-\textit{t}, \textit{t} represented different calcination temperatures) as novel photothermal agents were successfully prepared through the controlled calcination of Cu-based MOF (Cu-BTC) precursors at temperatures from 400 to 900°C. Specifically, Cu@CPP-\textit{t} samples comprised partially oxidized Cu nanoparticles dispersed on nanocarbon polyhedra, and their nanocarbon supports were semigraphitic phase with abundant carbon vacancies. It was worth noting that the concentration of carbon vacancies increased with calcination temperature, arising from gradually enhanced interaction between Cu nanoparticles and nanocarbon polyhedral, while the size of the Cu nanoparticles also increased with increasing calcination temperature. At the same time, it can be found that the photothermal effects of as-obtained Cu@CPP-\textit{t} samples were strongly and positively correlated with the concentration of carbon vacancies and the size of copper nanoparticles in the calcination temperature range of 400–800°C. In particular, Cu@
CPP-800 sample showed significantly enhanced photothermal conversion efficiency under NIR-I laser irradiation. The above results were probably due to the following reasons: 1) more carbon vacancies boosted π→π* transitions in the semigraphitic nanocarbon polyhedral, inducing stronger absorption of incident photons; 2) more carbon vacancies as recombination centers promoted non-radiative relaxation processes and thus increased heat release; 3) while Cu LSPR absorptions also enhanced with the increasing of Cu nanoparticle size. However, on increasing the calcination temperature from 800 to 900°C, the photothermal performance decreased due to excessive sintering of the Cu@CPP-900 samples. Thus, increasing the concentration of carbon vacancies together with Cu nanoparticle size via tuning calcination temperature was an effective way to enhance photothermal performance. Moreover, in vitro and in vivo studies confirmed that Cu@CPP-800 was a very effective agent for photothermal cancer treatment and also NIR/ photoacoustic bioimaging. Another example, Wang et al. (Liu H. et al., 2020) reported that a type of graphene quantum dots (9T-GQDs) with strong NIR-II absorption was synthesized by a one-step solvothermal treatment using phenol and hydrogen peroxide as precursor under a high magnetic field with an intensity of 9T. It can be observed that the dissolved oxygen from H2O2 decomposition under external high magnetic field induced the crystallization of small carbon fragments, leading to the formation of abundant vacancy defects in the GQDs. Notably, with the increase in magnetic field intensity, dissolved oxygen and resulted vacancy defects increased. Carbon atoms located round vacancy defects showed high coordination unsaturation and high reactivity, so the defective carbon atoms were easy to react with the superoxide anion and hydroxyl radical intermediates, forming abundant C=O quinone-type groups and C−OH phenol groups on the surface of GQDs. On the one hand, abundant C=O bonds on the 9T-GQDs led to the formation of larger conjugated system containing plentiful delocalized π electrons, thus giving rise to the strong NIR-II absorbance of 9T-GQDs and high photothermal conversion efficacy. On the other hand, abundant C−OH groups as hydrophilic groups ensured small size distribution (3.6 nm), good water-solubility and excellent biocompatibility of 9T-GQDs. Both in vitro and in vivo studies confirmed that as-obtained 9T-GQDs could effectively ablate tumor cells and inhibit the tumor growth under NIR-II irradiation. In addition, the 9T-GQDs displayed enhanced NIR-II imaging of tumor, suggesting a great potential of 9T-GQDs for NIR-II imaging-guided PTT.

**Conclusion and prospects**

Phototherapy including PDT and PTT is a non-invasive light-induced therapy, which uses NIR-responsive nanomaterials to achieve effective local treatment in tumor sites and could diminish damage to normal tissues. Moreover, multimodal synergistic phototherapy (including synergistic PTT and PDT as well as combined phototherapy and other therapies) based on multifunctional nanomaterials can achieve synergistic enhancement of tumor treatment. It is worth noting that the phototherapy is a nanomaterial microstructure (microscopic electronic and geometric structures) sensitive process, and the effectiveness of phototherapy depends largely on nanomaterials. The vacancy-type defects, such as oxygen vacancy, metal vacancy, carbon vacancy, and sulfur vacancy, commonly exist in phototherapeutic nanomaterials, which can greatly influence and directly change the microstructure, properties and phototherapeutic efficacy of nanomaterials. At the same time, the rational design and preparation of vacancy defective nanomaterials as well as the roles of vacancy defect in phototherapy have been paid more and more attention. Therefore, this review focuses on the recent vacancy defect chemistry research and vacancy engineering strategy, as well as efficient vacancy defective nanomaterials and their role in phototherapy and multimodal synergistic phototherapy. The vacancy defect chemistry has become a significant research direction to design and prepare efficient nanomaterials for phototherapy. The existence of vacancy defects in phototherapeutic nanomaterials will disturb the chemical state of the surrounding atoms or ions to some extent and induce lattice distortion/strain. This, thus, can effectively change the local bond, atomic coordination and electronic properties around specific atomic positions located at vacancy, bringing some unpredictable properties (e.g., outstanding optical, optothermal, optoelectronic, semiconductor, and plasmonic properties). Specifically, constructing vacancy defects in phototherapeutic nanomaterials can induce defect energy levels and thus effectively regulate their electronic structures and band gap states, give rise to the strong LSPR absorption in the NIR region, and promote the adsorption and activation of oxygen species. These will result in enhanced photoinduced ROS production efficiency (ROS quantum yield) and high photothermal conversion of phototherapeutic nanomaterials. Moreover, with the deepening of the research on vacancy defect chemistry, vacancy defect engineering for synthesizing various phototherapeutic nanomaterials with significantly improved and optimized performance has been developed. Notably, vacancy engineering not only provide a comprehensive insight into the understanding and utilization of vacancy defect chemistry in phototherapeutic nanomaterials, but also offer a novel and effective technique to regulate/optimize the microstructure, characteristics and phototherapeutic efficacy of nanomaterials. The construction methods of vacancy defects in phototherapeutic nanomaterials can generally be divided into two broad categories: 1) directly synthesizing vacancy defective nanomaterials; 2) post treatment of nanomaterials to construct vacancies. In terms of the former method, the specific vacancies can be directly induced with the crystal growth by tuning
crystallization conditions and methods, or by regulating the ratio of starting materials, or by elemental doping. While the latter post treatment method like annealing, irradiation, ball-milling, etching, and redox is also an efficient and controllable vacancies construction strategy. Additionally, a deeper and more detailed understanding of the influence and role of vacancy defects on phototherapy and multimodal synergistic phototherapy is also crucial to rational design of new phototherapeutic nanomaterials, effective enhancement of their therapeutic efficacy, and systematic development of phototherapeutic applications.

Although more and more studies on vacancy defect-promoted nanomaterials for phototherapy and multimodal synergistic phototherapy have been reported, there are still many scientific and engineering topics to encourage researchers to further explore. First, although these vacancy defect-promoted nanomaterials have been proved to be high anticancer efficacy via preclinical research, their metabolic behavior, potential toxicity and biological effects still need to be deeply and systematically studied through in vitro and in vivo experiments. This will further promote optimization of phototherapeutic nanomaterials and improve their therapeutic outcome, providing an advanced platform for future clinical applications. Second, although the above vacancy engineering strategies have been able to construct various vacancies in phototherapeutic nanomaterials, it is still necessary to find “clean chemistry methods”, that is, more simple, efficient, and controllable vacancy defect construction methods. This will allow large-scale preparation of vacancy defect-promoted nanomaterials, in order to meet the large demand for advanced phototherapeutic nanomaterials in future clinical applications. Third, carbon-based nanomaterials with abundant vacancies, such as vacancy engineered carbon dots and graphenes, should be vigorously developed for future clinical translation, due to their well-defined microstructure, multifunctionality, superior stability, good biocompatibility, and easy manufacturing. Finally, in addition to the application in the field of phototherapy and anticancer, vacancy defect-promoted nanomaterials should also be used in a wider range of biomedical applications, such as biosensing, antibacterials, and antivirals (Macharia et al., 2021; Ren et al., 2022).

In conclusion, vacancy defect chemistry and engineering of phototherapeutic nanomaterials, the role of vacancy defective nanomaterials on phototherapy and their phototherapeutic applications is systematically summarized in this review. In general, the abundant physicochemical properties induced by vacancies, coupled with the recent success in the design of advanced functional nanomaterials for phototherapeutic applications, inspire growing research interest in vacancy engineering and vacancy-engineered nanomaterials for using phototherapy. Therefore, we sincerely hope that this review can provide a profound understanding and inspiration for the design of advanced phototherapeutic nanomaterials, and significantly promote the development of the efficient therapies against tumour.

Author contributions

XX, LW, and SH conceived this article and wrote the manuscript. SH, SG, DL, MZ, and XQ reviewed and revised the manuscript. All authors read and approved the final manuscript.

Funding

We are grateful for the financial support from the Youth Innovation Promotion Association of Chinese Academy of Sciences (No. 2019027) and the Director Foundation of the Technical Institute of Physics and Chemistry, Chinese Academy of Sciences. The authors are grateful for the financial support from National Natural Science Foundation of China (51873214).

Conflict of interest

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

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