Heterojunction Nanomedicine

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Exogenous stimulation catalytic therapy has received enormous attention as it holds great promise to address global medical issues. However, the therapeutic effect of catalytic therapy is seriously restricted by the fast charge recombination and the limited utilization of exogenous stimulation by catalysts. In the past few decades, many strategies have been developed to overcome the above serious drawbacks, among which heterojunctions are the most widely used and promising strategy. This review attempts to summarize the recent progress in the rational design and fabrication of heterojunction nanomedicine, such as semiconductor–semiconductor heterojunctions (including type I, type II, type III, P–N, and Z–scheme junctions) and semiconductor–metal heterojunctions (including Schottky, Ohmic, and localized surface plasmon resonance–mediated junctions). The catalytic mechanisms and properties of the above junction systems are also discussed in relation to biomedical applications, especially cancer treatment and sterilization. This review concludes with a summary of the challenges and some perspectives on future directions in this exciting and still evolving field of research.

1. Introduction

Catalysis, as a utility strategy, is closely related to our survival and development because of its irreplaceable ability in controlling the rate of chemical reactions by decreasing the activation energy. In many aspects, catalysis has expressed its crucial importance in fields, for example, organic decomposition[1] and energy regeneration,[2] which provide the necessary conditions for our daily life. In the past years, catalysis technology has been wildly used to solve medical problems by virtue of its unique and excellent properties, providing new inspiration for the treatments of diverse pathological abnormalities. This new and promising field is called catalytic medicine in which non-toxic catalysts instead of traditional drugs are employed for the treatment of diseases by catalyzing the reaction at the disease site to produce therapeutic products. According to the operation mode and treatment principle, catalytic therapy can be divided into two categories: endogenous catalytic therapy and exogenous stimulation catalytic therapy. Fenton or Fenton-like reactions catalyzed by reductive metal ions or metal nanomaterials are representative of endogenous catalytic therapy, which is also called chemodynamic therapy (CDT).[3] In Fenton or Fenton-like reactions, hydroxyl radicals (-OH) derived from the decomposition of hydrogen peroxide are the main therapeutic product to eliminate tumor cells or pathogens in this treatment mode, which is independent of extra stimulation. However, the therapeutic efficacy is hindered by the monotonous catalytic substrate type with limited content at the lesion site.[4] By virtue of the cooperation of various exogenous stimulants and catalysts, exogenous stimulation catalytic therapy, including photodynamic therapy (PDT),[5] sonodynamic therapy (SDT),[6] and other exogenous stimulation-excited dynamic therapies,[7] has the advantages of diverse catalytic substrates, high catalytic efficiency, and low limitation by the internal microenvironment. According to the mechanism of catalytic therapy, the physical and chemical properties of the catalyst are the key to the success of catalytic therapy.

Many emerging single semiconductor nanomaterials with improved biocompatibility, higher catalytic efficiency, and unique band structure have been prepared to enhance the generation of reactive oxygen species (ROS) from oxygen (O2) in a rational and simple way.[8] The semiconductors are mostly crystals, and their valence electrons can be transferred between adjacent atoms and are affected by the potential field of the surrounding atoms due to the close arrangement of the constituent atoms, which results in splitting of energy levels and formation of energy bands. Analysis of the band structures of semiconductors is necessary, as they are the critical factors that determine a variety of the semiconductor properties. As shown in Figure 1, a forbidden band without energy level is located between the energetically lower valence band (VB) and the energetically higher conduction band (CB). Due to the narrow forbidden band of semiconductors, the electrons in the VB can be transferred into the CB after absorption of
exogenous energy (e.g., light, ultrasound, X-rays). As a result, holes are left in the VB, which is a prerequisite for catalysis, and the separated carriers can take part in redox reactions.  

Based on this, semiconductor-mediated catalytic therapy involves at least the following steps: a) Accumulation. It is essential for catalysts to be targeted and enriched at the tumor site to reach the therapeutic dose. b) Excitation. Stimulation provides enough energy for electrons to overcome the bandgap ($E_g$) of the therapeutic agents and thus induce electron–hole pairs. c) Migration. After excitation, some excited carriers migrate to the surface of the material, while most of them recombine and release energy. d) Reaction. Electrons and holes at the surface undergo redox reactions with surrounding reactants to form ROS, such as superoxide anion ($\cdot O_2^-$) ($O_2 + e^- \rightarrow \cdot O_2^-$, $-0.33$ eV vs normal hydrogen electrode (NHE)) and $\cdot$OH ($OH^- + h^+ \rightarrow OH$, $1.99$ eV vs NHE), leading to irreversible permanent damage and apoptosis of tumor cells.

Semiconductors exhibiting a bandgap with more positive VB potential and more negative CB potential are promising candidates to expand the pool of substrates and products for cancer treatment. On the other hand, such a band structure with a large bandgap brings about the difficulties of electron–hole pair separation and requirement on high energy light. Due to this contradiction, various and efficient ROS generation methods for single semiconductors can be hardly achieved at the same time. To overcome these disadvantages, various methods have been proposed, including surface modification, element doping, control of morphology, and construction of heterojunctions.

Considering the efficiency and feasibility, the construction of heterojunctions using different photocatalysts is undoubtedly the most promising strategy to improve the photocatalytic ability. The band structures of catalysts can be tailored by reasonably designing the heterostructure. Compared with single semiconductors, heterojunction structures are more feasible and effective in applying external light with wavelengths in the biowindow for photoexcitation and inhibit the recombination of photoinduced electron–hole pairs. Apart from these advantages, heterojunctions containing various compounds have many unique functions while retaining the properties of a single component. Hence, in addition to the benefits in energy supply, pollutant disposal, and photodetectors optimization, fabricating appropriate heterojunctions also goes a long way towards the treatment of diseases, especially cancer treatments. As one of the biggest killers of human life and health, cancer urgently needs effective, safe, and reliable treatment strategies. Traditional treatment methods, such as surgery, chemotherapy, radiotherapy (RT), etc., inevitably bring great side effects to patients while treating cancer. Catalytic therapy, which replaces traditional drugs with safe and non-toxic catalysts, achieves specific treatment of cancer by generating therapeutic products in situ in tumor tissues and greatly reduces the side effects of cancer treatment. However, due to the limited catalytic efficiency of single catalyst, the shielding effect of biological tissue on excitation energy source, and the complex inhibitory microenvironment of tumor tissue (hypoxia, high glutathione expression, etc.), the therapeutic efficiency of traditional catalytic therapy is seriously affected. Heterojunction nanomedicine can not only effectively inhibit excited electron-hole recombination, improving the effective utilization efficiency of external excitation energy, but also contain multiple reactive active sites, expanding substrate selectivity and effectively regulating tumor inhibition microenvironment. Therefore, using heterojunction technology, development of novel and efficient heterojunction nanomedicine can achieve efficient and safe catalytic treatment of cancer.

This review article focuses on the specific principles and preparation methods of heterojunctions (Scheme 1). In addition, the recent design and application of various heterojunctions in biomedicine are introduced. Then, the optimization of existing heterojunctions as well as future applications and potential heterojunctions in other therapeutic approaches are presented, and prospects are discussed. The introduction of heterojunctions into biomedicine will greatly accelerate the development of multiple treatments, and we hope this review can provide some ideas to promote the further development of heterojunctions as high-efficiency “medicine” in the field of biomedicine.

2. Working Principles of Different Heterojunction Photocatalysts

As promising candidates for overcoming the drawbacks of single-component catalysts, heterojunction catalysts are formed by coupling two different functional materials. According to the conductivity of the materials, heterojunctions can be classified into two types: a) semiconductor–semiconductor (S–S) heterojunctions and b) semiconductor–metal (S–M) heterojunctions.

2.1. S–S Heterojunction

The formation of semiconductor heterojunctions is a promising strategy for the preparation of high-performance catalysts for...
the full conversion of light. Through surface engineering, such as doping and defect engineering, various intrinsic p- or n-type semiconductors with different mechanical, physical, and chemical properties can be fabricated, providing abundant raw materials for the development of S–S heterojunctions. In general, the positions of the electronic band edges and the work functions of two semiconductors are important metrics to determine the electron transfer mechanism of a semiconductor heterojunction, which directly affects its catalytic performance. Based on the transfer mechanism of photoinduced electrons, S–S heterojunctions can be divided into type-I, type-II, and Z-scheme heterojunctions (Figure 2).

In type-I heterojunctions, the energy band structures of the two catalyst systems are nested. As shown in Figure 2, the VB and the CB of the narrow-bandgap photocatalyst are both located in the forbidden band of the wide bandgap photocatalyst. Since the band edges of narrow bandgap photocatalysts are lower upon light irradiation, the photoinduced electrons and holes will be transferred from the wide bandgap photocatalyst to the CB and VB of the narrow-bandgap photocatalyst, respectively. This electron transfer route facilitates the recombination of the photoinduced carriers, which is beneficial for potential applications in light-emitting devices but not conducive to photocatalytic reactions.

In type II heterojunction photocatalysts, the VB and CB edges of one semiconductor (catalyst I) are higher than those of the second semiconductor (catalyst II). The Fermi level of catalyst I is lower than that of catalyst II. Due to the rearrangement of the Fermi levels after contact of the catalysts, catalyst II acts as an electron donor to transfer electrons to catalyst I. Consequently, the energy bands of catalyst I bend downwards, while the energy bands of catalyst II bend upwards at the semiconductor interface. Under light irradiation, the photoinduced electrons and holes accumulate in the CB of catalyst II and the VB of catalyst I. Compared with type I heterojunctions, the photoinduced electrons and holes in type II heterojunctions are trapped in two spatially separated potential wells, which effectively increases the lifetime of the photoinduced carriers. However, the increase in the lifetime of photoinduced carriers is at the expense of a reduced recombination capacity of the two semiconductor catalysts. In addition, the migration of photoinduced carriers is inhibited by the existing photoinduced carriers in another phase.

Type III heterojunctions are formed when the VBM of one photocatalyst is higher than the CBM of the second

Scheme 1. A schematic summarization of the classification, properties, and biomedical applications of heterojunction nanomedicine.
As shown in Figure 2, the bandgaps of these two photocatalysts are completely separated. Therefore, photoinduced carrier separation and migration hardly occur between the two phases, and the efficiency of the photocatalytic reactions are thus not improved.

Inspired by natural photosynthesis, which realizes the electron transport by connecting two different photocatalytic systems via an electron transfer medium, A. J. Bard first proposed the liquid-phase Z-scheme heterojunction photocatalyst in 1979. The liquid-phase Z-scheme heterojunction photocatalyst consists of two semiconductors acting as catalytic centers and free redox mediators (Fe$^{3+}$/Fe$^{2+}$, IO$_3^–$/I$^–$, etc.) As illustrated in Figure 2, photoinduced electron and hole pairs are generated in catalyst I and catalyst II under light irradiation. Then, the photoinduced holes in the VB of catalyst I and the photoinduced electrons in the CB of catalyst II are consumed by free redox ion pairs. In contrast, the photoinduced electrons in the CB of catalyst I with higher reduction potential and the photoinduced holes with higher oxidation potential in the VB of catalyst II will undergo redox reactions with the substrates. In addition, for the effective separation of photoinduced electron–hole pairs, the solid phase Z-scheme heterojunction also retains the original strong redox capability of the semiconductors. However, shortcomings, such as a limited application environment, low electron transfer efficiency, light-shielding effect, and serious side reactions, limit the further application of liquid-phase Z-scheme heterojunctions in the field of catalysis.

To overcome these shortcomings of liquid-phase Z-scheme heterojunction photocatalysts, all-solid-state Z-scheme heterojunction photocatalysts were subsequently developed. Conductive materials (e.g., precious metals, graphene) were adopted as electron transfer mediums in all-solid-state Z-scheme heterojunction photocatalysts. Although the solid electron transfer medium expanded the application of Z-scheme heterojunctions, the high cost of precious metals and difficulties in the design are remaining problems.

In 2001, Grätzel et al. first coupled nano-sized transition metal oxides (WO$_3$ or Fe$_2$O$_3$) with dye-sensitized TiO$_2$. They found that photoinduced holes in the VB of WO$_3$ or Fe$_2$O$_3$ can effectively catalyze the oxidation of H$_2$O, while the photoinduced electrons accumulate in the CB of TiO$_2$. Since then, Z-scheme heterojunctions without electron mediators have gradually entered the field of vision of researchers. Yu et al. reported a g-C$_3$N$_4$/TiO$_2$ Z-scheme heterojunction in 2013. This type of Z-scheme heterojunction was reported for the first time; it does not require an electron mediator and was named direct Z-scheme heterojunction. Direct Z-scheme heterojunctions, which are formed by two semiconductors that are in direct contact, do not require an additional electron transfer medium but still effectively follow the Z-scheme electron transfer mechanism. The basic design principle of direct Z-scheme heterojunctions is that the two semiconductors have a staggered gap, and the semiconductor with the higher potential (catalyst I) has a lower work function than the semiconductor with the lower potential (catalyst II). After contact with the two semiconductors, the electrons of catalyst I are transferred to catalyst II until the two Fermi levels reach equilibrium. Consequently, the bands of catalyst I bend upwards, while the bands of catalyst II bend downwards, providing the basis for the combination of the photoinduced holes in the VB of catalyst I and the photoinduced electrons in the CB of catalyst II through the tunneling effect. In addition, the internal electric field generated by the rearrangement of the Fermi level further enhances the separation of photoinduced electron–hole pairs.
level can further promote the combination of the above photoinduced electron–hole pairs. Moreover, the internal electric field effectively inhibits the combination of the photoinduced electrons on the CB of catalyst I with high reduction potential and the photoinduced holes in the VB of catalyst II with high oxidation potential. As a result, the direct Z-scheme heterojunction possesses not only a wide catalytic substrate range but also a high catalytic efficiency.

In practice, intrinsic semiconductors are artificially and accurately endowed with various physical and chemical properties through doping engineering to meet various application requirements. In particular, by doping a specific proportion of heteroatoms or introducing defects, properties related to the catalytic ability of the semiconductor, such as the carrier type, Fermi level, and band structure, are modulated to obtain ideal raw materials for the preparation of excellent heterojunction photocatalysts. According to the type of the major carrier, the modified semiconductors can be divided into n- and p-type semiconductors. The major carriers in n- and p-type semiconductors are electrons and holes, respectively. According to the conductivity type of the semiconductor, heterojunctions can be divided into homotype heterojunctions (n-n type and p-p type) and heterogeneous p-n junctions. [34] Since the two semiconductors in a homotype heterojunction have the same conductivity type, carrier diffusion caused by Fermi level rearrangement is unidirectional. It is worth noting that when an n-type semiconductor is connected with a p-type semiconductor, electrons in the n-type semiconductor near the p-n interface will diffuse to the p-type semiconductor, forming a positively charged area. Furthermore, the holes in the p-type semiconductor near the p-n interface will diffuse to the n-type semiconductor, forming a negatively charged area. Charge diffusion will continue until the Fermi levels of the n- and p-type semiconductors are in equilibrium. Due to the carrier concentration gradient, a stronger internal electric field will eventually be generated in p-n junctions, effectively promoting the separation of photoinduced electrons and holes.

2.2. S–M Heterojunction

The characteristics of metal–semiconductor contacts, which can be divided into Schottky junction and Ohmic contact, are related to the type of the semiconductor (i.e., n- or p-type) and the relative work function between the metal and the semiconductor. [35] In 1874, Schottky found that a surface potential-energy barrier (Schottky barrier) exists in the semiconductor phase of some specific metal–semiconductor contacts (Schottky contacts; Figure 3). [36]

In general, Schottky junctions are built by connecting a metal with higher work function (Φ) and an n-type semiconductor with lower Φ or by connecting a metal with lower Φ and a p-type semiconductor with higher Φ. Taking a Schottky junction formed by an n-type semiconductor and a metal as an example, after the semiconductor and the metal come in contact, the electrons flow from the semiconductor with higher Φ to the metal with lower Φ until their Fermi levels reach equilibrium. Due to the limitation of the free electron density, a positively charged region forms in the semiconductor. Furthermore, the energy band of the semiconductor bends upward. Thereby, the rectification property of Schottky junctions makes it possible to control the production and flow of excited electrons, and the Schottky junction can serve as an electron trap to effectively promote the separation of excited electrons and holes. However, as a minority carrier in the n-type semiconductor, the holes exhibit a decreased potential after the formation of a Schottky contact, resulting in a restricted oxidation ability.

Contrary to Schottky contacts, Ohmic junctions are formed by connecting an n-type semiconductor with lower Φ and a metal
with higher $\Phi$ or by connecting a p-type semiconductor with higher $\Phi$ and a metal with lower $\Phi$. Taking an n-type semiconductor/metal Ohmic junction as an example, the band edges of the semiconductor bend downward after connection with the metal, which cannot effectively prevent the flow of excited electrons back to the VB of the semiconductor and the subsequent recombination of electron–hole pairs. Therefore, the Ohmic junction is not an ideal photocatalyst candidate due to its inefficient regulation of the photoinduced electron–hole separation.

If the frequency of the incident photon matches the vibration frequency of the overall free electrons of the precious metal nanoparticles in the Schottky contact, the metal will show a strong absorption of photon energy, which is the localized surface plasmon resonance (LSPR). The LSPR effect promotes the generation of photoinduced electrons with high energy, which are enticed hot electrons, in the noble metal. Then, the hot electrons cross the Schottky barrier and are injected into the semiconductor, while the photoinduced holes remain in the metal. At present, Au and Ag are the common plasmon-resonance metals to alter the light absorption ability with resonance absorption peaks located at 580 and 530 nm respectively.

Di et al. designed an Ag quantum dots-modified BiOBr ultrathin nanosheet (Ag QDs/BiOBr) with high photocatalytic activity. Using photoluminescence spectroscopy, they proposed another explanation of the mechanism of the transfer and separation of photoinduced electron–hole pairs based on the LSPR effect. In the Ag QDs/BiOBr Schottky junction, the holes generated in the Ag QDs via the LSPR effect can combine with excited electrons from the VB of BiOBr, leaving the excited hot electrons to catalyze the reduction of specific reaction substrates. At the same time, the holes left in the VB of the BiOBr nanosheet can catalyze the oxidation. Based on this mechanism, in the Schottky junction, the metal not only serves as an electron reservoir, but the electrons have also sufficient catalytic activity through the LSPR. In addition, the precious metal quantum dots with nano-sized diameters dispersed on the surface of the semiconductor ultrathin nanosheet can provide more catalytic sites due to the larger specific surface area.

In addition to traditional metals, some materials that generate a large number of free carriers under certain circumstances can also be adopted as conductors for the development of S–M heterojunctions. For instance, the resistance of certain functional nanoceramics represented by $\text{ZrO}_2$ and $\beta$-$\text{Al}_2\text{O}_3$ will change with the changes in external fields such as mechanical force, temperature, and irradiation. Structural modification can further modulate the electrical conductivity of functional ceramics. Na-$\beta$-$\text{Al}_2\text{O}_3$ ceramics are a family of ceramics with fast ionic conductivity, which have been widely used as battery separators. Moreover, some layered nanomaterials, such as graphene and transition metal carbide as well as nitride or carbonitride (MXene), represented by $\text{Ti}_x\text{C}_y$, also have excellent superior conductivity, which undoubtedly provides a broad range of material candidates for the design of S–M heterojunctions.

3. Preparation Methods of Heterojunctions

At present, the devised and studied conventional heterojunction materials are mostly composed of two kinds of semiconductors. To improve the photoresponsiveness and enhance the separation efficiency of photoinduced carriers, it is vital to consider the semiconductor properties in detail, including morphology features, crystal structures, and band arrangement. Therefore, the appropriate construction method of heterojunctions plays a crucial role in optimizing their optical and catalytic performances. After decades of development, several strategies for the construction of heterojunctions have been established. In the following, typical methods for the construction of heterojunctions will be elaborated, including mechanical assembly, chemical deposition, surface oxidation, and the electron transfer chain-mediated strategy.

3.1. Mechanical Method

As a common strategy, physical methods are applied to combine different semiconductors by mechanical forces, such as grinding, stacking, and stirring.

In the process of grinding, the materials’ grain sizes are decreased and the materials are mixed adequately to increase the interfacial interaction and strengthen the intermolecular force. You et al. reported $\text{g-C}_3\text{N}_4/\text{Bi}_2\text{NbO}_6\text{Cl}$ with a tight interface, which was prepared through a simple ball-grinding method at high energy. The transmission electronic microscopy (TEM) images (Figure 4A,B) showed dark $\text{Bi}_2\text{NbO}_6\text{Cl}$ particles and the corresponding lattice fringe on $\text{g-C}_3\text{N}_4$, illustrating the successful composition, which was confirmed by energy dispersive X-ray (EDX) elemental mapping (Figure 4C–G).

The structures of most layered heterojunctions are held together by van der Waals forces resulting from the vertical stacking of semiconductors, which increases the contact area between different components for broad applicability. Nie et al. integrated exfoliated black phosphorus (BP) and MoS$_2$ into a BP/MoS$_2$ heterojunction with type-II band alignment (Figure 4H) through direct stacking. In Figure 4I, the superimposed outlines demonstrate the integration of BP and MoS$_2$, and that MoS$_2$ coverage prevented the BP from fast degradation. To appraise the band structure and the heterostructure construction, the photoluminescence of MoS$_2$ and BP/MoS$_2$ was measured, and the spectra shown in Figure 4J reveal a 30% reduction of the photoluminescence intensity attributed to formation of the BP/MoS$_2$ heterojunction, suggesting the occurrence of type-II charge transfer.

In addition, stirring is an effective way to enhance the interactions between materials to induce the mechanical assembly into heterojunctions. Kong et al. synthesized a BP/g-$\text{C}_3\text{N}_4$ heterojunction through the modification of layered g-$\text{C}_3\text{N}_4$ with BP quantum dots and the corresponding TEM images are displayed in Figure 4K,L. In simple terms, the layered g-$\text{C}_3\text{N}_4$ owned abundant free electrons and a large specific surface area to support the strong adsorption ability, which is beneficial to BP modification via stirring under vacuum.

Apart from adsorption, electrostatic attraction enables materials to assemble and form a contact surface. Nie et al. fabricated direct Z-scheme g-$\text{C}_3\text{N}_4$/ZnO microspheres via the preparation method shown in Figure 4Q to achieve an improved photocatalytic ability. In brief, the mixed dispersion of g-$\text{C}_3\text{N}_4$ and ZnO was stirred to construct the heterojunction by electrostatic self-assembly of positive ZnO and negative g-$\text{C}_3\text{N}_4$ (Figure 4R). In contrast, the components are bound by electrostatic attraction
more tightly, resulting in a more stable electronic structure. The characterization of this heterostructure is presented in Figure 4S–W.

This implementation is determined by the mechanical method, which is largely mediated by intermolecular forces and is a simple and effective method. However, it is difficult to form tight contacts in some heterojunctions only by physical forces, which could lead to shedding, cracking, or deformation. Thus, it is vital to explore other methods to stabilize heterojunction composites for photocatalysis in different systems.

3.2. Chemical Deposition

In the typical fabrication process of film heterojunction composites, the layered component is deposited onto the basement through chemical deposition, including liquid phase deposition (LPD), chemical vapor deposition (CVD), and electrochemical deposition (ECD). Compared with other strategies, the film prepared by chemical deposition is uniform and compact. Moreover, this bottom-up approach provides outstanding repeatability and stability.

LPD has been specially developed as a simple and efficient method for the formation of oxides films. Yuan et al. reported a mild route for the preparation of TiO₂/boron-doped-diamond heterojunctions by LPD. These composites showed an average length of 2 μm, outside diameter of 100–150 nm, and wall thickness of 35–40 nm, exhibiting an improved photocatalytic ability for azo dyes. Zhang et al. reported WO₃/TiO₂ heterojunction films obtained by LPD which expanded the response range to light to improve the photoelectrocatalytic activity for organic contaminants. In addition, in the field of photoelectric
direct Z-scheme Sn–In2O3/In2S3 heterojunction nanowires with In2021, Ma et al. used CVD and sulfidation methods to prepare which is beneficial to the photoresponsivity and response speed. photodetector. As shown in Figure 5F,G, two lattice spacings playing potential application in space detection as solar-blind outstanding, but the low mobility and high recombination of carriers hamper their further application to some extent. The introduction of heterojunctions allows the remodeling of band structures to broaden the responsive spectrum of the materials, and the electron migration paths are also optimized to improve the photocatalysis ability.

Thus, surface oxidation has become one of the efficient strategies to modify and optimize the catalytic performance of photocatalysts. Zeng et al. designed the Z-scheme ternary heterojunction system Zn1(VO4)2/ZnV2O4/ZnO through the combination of the hydrothermal method and a calcination process. [57] Figure 6A,B shows that lots of small nanosheets were formed on the surface when the nanocomposite underwent partial phase transformation of Zn1(VO4)2 at 700 °C for 2 h. Analysis of the crystal planes based on the lattice fringes proved the existence of Zn1(VO4)2, ZnV2O4, and ZnO (Figure 6C), which constitute the ternary heterojunction. During thermal oxidation, temperature control is a critical factor determining the photocatalytic effect. In a comparative study, Zn1(VO4)2/ZnV2O4/ZnO nanosheets (after treatment at 700 °C (S-700)) presented an improved photocatalytic degradation ability, which is displayed in Figure 6D,E.

In addition to calcination, ultrasonication is another efficient method for the introduction of surface oxides. In 2019, our group synthesized thermally oxidized pyrite nanosheets (TOPY NSs) with Z-scheme heterojunction as an efficient photocatalyst for PDT. [58] In short, we employed ultrasonication under different atmospheres to simultaneously achieve liquid-phase exfoliation and thermal oxidation. This was not only beneficial for the formation of nanosheets but also overcome the shortcomings of oxide impurity formation in regular liquid-phase exfoliation for the introduction of heterojunctions in photocatalysis. For further verification, a series of characterization methods was conducted. As shown in Figure 6F, the average size of TOPY NSs was 106 nm, and the thickness was 7 nm, providing numerous active sites for reactions. After coating with PEG–NH2 to impart biocompatibility and hydrophilicity, the size and thickness of the TOPY-PEG NSs were altered to 95 and 10 nm, respectively (Figure 6G). XRD, Raman spectroscopy, and XRD presented in Figure 6H–J confirmed the successful construction of the TOPY-PEG NS heterojunction with intimate contact between the Fe2O3 shell and the FeS2 core, which could accelerate the photogenerated electron transfer to facilitate ROS generation. Finally, energy dispersive spectrometry (EDS) mapping revealed a homogeneous distribution of Fe, S, O, C, and N in the TOPY-PEG NSs, confirming that the heterojunction had a high oxide content and PEG attached to the surface of the TOPY-PEG NSs (Figure 6K).

3.3. Surface Oxidation

Due to inspiration from photocatalytic water splitting via TiO2, a large number of oxide semiconductors with appropriate bandgap, high photocatalytic efficiency, and low cost have been reported. Perovskite oxides, such as Pb2ZrO3, BaTiO3, PbTiO3, and SrTiO3, [53] play an important role in photocatalytic water splitting and photovoltaic applications. Moreover, the narrow bandgap of the BiVO4 photocatalyst makes it a suitable candidate for photocatalytic applications in the visible light region, [54] and various photocatalysts based on it have been explored. The TiO2-based photocatalytic system has the advantages of easy operation, desired catalytic activity, and excellent stability. [55] In addition, hematite (Fe2O3) is also valued for its advantages of high photocurrent density and strong photocorrosion resistance. [56] In general, the optical performance of oxide-based photocatalysts is outstanding, but the low mobility and high recombination of carriers hamper their further application to some extent. The introduction of heterojunctions allows the remodeling of band structures to broaden the responsive spectrum of the materials, and the electron migration paths are also optimized to improve the photocatalysis ability.

Apart from the redox reaction employed in LPD and CVD, the external electric field can be utilized to prepare heterojunction composites in electrolyte solution via ion oxidation/reduction during ECD. This method has many advantages, such as diverse substrate shapes, controllable film thickness, and relatively low cost. Zhang et al. fabricated a Cu2O/ZnO/ITO nanotube array heterostructure for CO2 reduction to methanol after ECD (Figure 5N). [51] As presented in Figure 5O,S, the TiO2 nanotube array heterostructure formed via a two-step anodization approach is highly ordered with a tube diameter of 30 nm and a tube length of ≈500 nm. After ECD, the graphene sheets and Cu2O nanoparticles (≈100 nm) were successfully deposited, which was confirmed by EDX (Figure 5T). As an effective method to fabricate films, ECD is often employed in conjunction with other strategies for heterojunction preparation. Wang et al. combined the strategies of ECD, [52] heating treatment, and photoreduction to synthesize Bi/BiVO4, which manifested an improved photocurrent response and photoelectrochemical performance compared with pure BiVO4.

In contrast to the LPD, in CVD, substances are introduced in the gaseous or vapor state for deposition on the substrate, providing products with high crystallinity and purity. Yu et al. employed CVD to fabricate uniform TiO2-boron-doped diamond heterojunctions [47] with an improved ability in the photo-mediated decomposition of dyes. In addition, through one-step CVD, Zhao et al. designed highly crystallized ZnO–Ga2O3 microwires with core–shell heterostructures (Figure 5B–E), [48] displaying potential application in space detection as solar-blind photodetector. As shown in Figure 5F,G, two lattice spacings were detected, and the lattice interface between constituents was homogeneous and atomically sharp with few structural defects, which is beneficial to the photoresponsivity and response speed. In 2021, Ma et al. used CVD and a sulfidation method to prepare direct Z-scheme Sn–In2O3/In2S3 heterojunction nanowires with 1D structure (Figure 5H). [49] These nanowires not only avoided the lattice mismatch and the inherent interfacial defects between the two components but also provided effective channels to shorten the charge transmission path and diminish the recombination of carriers. As displayed in Figure 5J,K, Sn–In2O3 synthesized via CVD is smooth without obvious defects or grain boundaries. The X-Ray diffraction (XRD) patterns (Figure 5L) show that the sharp characteristic diffraction peaks of Sn–In2O3 matched those of In2O3 well, demonstrating high crystallinity and phase purity, which was confirmed by Raman spectroscopy (Figure 5M).

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Figure 5. A) Illustration of the ultraviolet solid–liquid heterojunction photodetector. Reproduced with permission. \cite{46} Copyright 2020, Elsevier. B) Photograph of ZnO–Ga2O3 microwires with core–shell structure. C–E) Representative SEM images of ZnO–Ga2O3, ZnO, and Ga2O3 and the corresponding cross-sectional images. HRTEM images of ZnO–Ga2O3 of F) the core and shell layers, G) core part, and H) shell part. Reproduced with permission. \cite{48} Copyright 2017, Wiley-VCH. I) Scheme of the fabrication of the Sn–In2O3/In2S3 heterojunction. SEM images of J) Sn–In2O3 and K) Sn–In2O3/In2S3. Characterization of different samples by L) XRD and M) Raman spectroscopy. Reproduced with permission. \cite{49} Copyright 2021, Royal Society of Chemistry. N) Preparation method of Cu2O/graphene/TiO2. Scanning electron microscope (SEM) images of O) TiO2, P) graphene/TiO2, Q) Cu2O/ TiO2, and Cu2O/graphene/TiO2 at R) low and S) high magnification. T) EDS analysis of Cu2O/graphene/TiO2. Reproduced with permission. \cite{51} Copyright 2016, Elsevier.
3.4. Electron Mediator

In spite of a huge improvement in photocatalysis due to heterojunction construction, the electron mediator needs to be introduced into the system as a bridge to transfer carriers for further promotion of the photocatalytic efficiency, especially in the Z-scheme heterojunction. With the development of heterojunctions, electronic mediators are also being optimized and upgraded. In contrast to the shortcomings of the liquid phase heterojunction system in the potential reverse reaction of redox pairs, which might abate the separation efficiency of charges in the contact area, the all-solid heterojunction significantly facilitates the capability of carriers to cross the interface depending on the solid electron mediator. Noble metals, such as Ag, Au, and Pt, are regarded as good candidates due to their excellent electrical conductivity. Su et al. fabricated the ternary heterostructure Ag–SrTa2O6/g-C3N4 with improved light absorption and photocatalytic activity.\(^{[59]}\) Figure 7A shows a close contact of SrTa2O6 and g-C3N4, and Figure 7B,C confirms the modification with Ag through morphology characterization and crystal structure analysis. Ag not only separated the electron–hole pairs via LSPR but also acted as a mediator to transfer the photogenerated electrons from the CB of g-C3N4 to the CB of SrTa2O6 (Figure 7D). Similarly, Li and co-workers modified the C3N4/TiO2 heterojunction with Au,\(^{[60]}\) and the corresponding TEM images are shown in Figure 7E–G. As a mediator, Au in this heterostructure system facilitated the recombination of electrons in the CB of BWO and the holes in the VB of CN, causing higher redox potentials for ROS generation (Figure 7H).

Despite the excellent electron transfer performance of precious metals, high cost impeded further research. Carbon materials with low cost, such as graphene, are characterized by an excellent photoelectric performance, which is ascribed to the outstanding \(\pi\)-electron transfer characteristics and the large specific surface area. Wu et al. inserted oxide graphene (RGO) into C3N4-TiO2 to form g-C3N4-RGO–TiO2 nanoheterojunctions,\(^{[61]}\) as presented in Figure 7I–K. Notably, these nanocomposites with 10% RGO mass ratio displayed an optimized photocatalytic activity compared with the direct Z-scheme C3N4-TiO2 heterojunction (Figure 7L). This was attributed to the increase and tightness of the contact area, as well as the improved surface adsorption and reaction kinetics. Apart from RGO, carbon dots served as the mediator to inhibit the recombination of photocarriers and expand the light absorption range. Zhang et al. fabricated a BiOBr/CDs/g-C3N4 heterojunction by a facile polymerization method\(^{[62]}\) and the TEM images of this heterojunction are presented in Figure 7M–O. CDs, as the charge transmission bridge connecting BiOBr and g-C3N4, not only enhance light absorption in the infrared region but also induce the immigration of...
Figure 7. TEM images of A) SrTa$_2$O$_6$/g-C$_3$N$_4$ and B) Ag-SrTa$_2$O$_6$/g-C$_3$N$_4$. C) HRTEM image of Ag-SrTa$_2$O$_6$/g-C$_3$N$_4$. D) Schematic diagram of the Ag-SrTa$_2$O$_6$/g-C$_3$N$_4$ heterojunction exposed to visible light irradiation. Reproduced with permission.\cite{59} Copyright 2015, Elsevier. TEM images of E) BWO and F) CN/Au/BWO. G) HRTEM images of CN/Au/BWO. H) Diagrammatic sketch of the CN/Au/BWO heterojunction photocatalyst. Reproduced with permission.\cite{60} Copyright 2020, Elsevier. I) SEM images of GO. J, K) HRTEM images of g-C$_3$N$_4$-RGO–TiO$_2$. L) Mechanism of the photocatalytic degradation of MB by g-C$_3$N$_4$-RGO–TiO$_2$. Reproduced with permission.\cite{61} Copyright 2017, Elsevier. TEM images of M) CDs/g-C$_3$N$_4$ and N) BiOBr/CDs/g-C$_3$N$_4$. O) HRTEM image of BiOBr/CDs/g-C$_3$N$_4$. P) Illustration of photocatalysis mediated by BiOBr/CDs/g-C$_3$N$_4$. Reproduced with permission.\cite{62} Copyright 2019, Elsevier.

Electrons into the CB of BiOBr and holes into the VB of g-C$_3$N$_4$ for photocatalysis on higher potential (Figure 7P). Interestingly, transformation of the heterojunction type through alteration in the direction of carrier migration can be achieved by the rational introduction of electron mediators.

Interestingly, in addition, to promote the separation of charges, the transfer direction of electrons could be changed by decoration of the mediators. Palanivel et al.\cite{63} inserted CD mediators into NiFe$_2$O$_4$/g-C$_3$N$_4$ to prepare a ternary heterojunction via the simple wet chemical impregnation method. For the binary heterojunction, the photogenerated carriers accumulated at a relatively low position through type-II transfer, which was insufficient to catalyze ·O$_2^-$ generation. In contrast, the Z-scheme transfer of the photogenerated electrons after the introduction of CD excites electrons to a higher potential to participate in the production of ·O$_2^-$, improving the catalytic efficacy remarkably.

4. Application of Different Heterojunction Photocatalysts in Biomedicine

4.1. Type II Heterojunctions

Type II heterojunction is one of the most best-known and widely used heterojunctions. For type II heterojunction, the band structures (VB and CB) of the two catalysts are interlaced, for example, the VB and CB edges of one semiconductor (catalyst I) are higher than those of the second semiconductor (catalyst II). The Fermi level of catalyst I is lower than that of catalyst II. Due to the rearrangement of the Fermi levels after contact of the catalysts, catalyst II acts as an electron donor to transfer electrons to catalyst I. Consequently, the energy bands of catalyst I bend downwards, while the energy bands of catalyst II bend upwards at the semiconductor interface. Under exogenous energy irradiation, the ex-
cited electrons and holes transfer spontaneously and accumulate in the CB of catalyst II and the VB of catalyst I. Compared with other heterojunctions, type II heterojunction can avoid the waste of catalytic energy caused by the recombination of excited electrons and holes by gathering excited electrons and holes in the CB of different catalysts.

Recently, Guo and co-workers reported a strategy for the fabrication of BiO1-based photocatalysts.\[^{64}\] In simple terms, after the preparation of BiO1 via a hydrothermal reaction, nanoparticles with an average size of 100 nm were formed by anion exchange and BSA modification on the BiO1@Bi2S3 type II heterojunction (SHNPs; Figure 8A, b). The composite structure of this heterojunction was verified through element analysis and XRD spectra (Figure 8C). In addition, this system with high-Z elements could be excited by X-rays for the purpose of RT and PDT. Specifically, due to the interlaced band structure and Fermi levels of BiO1 and Bi2S3, under X-ray irradiation, the excited electrons moved easily to the CB of BiO1, while the excited holes were transferred to the VB of Bi2S3 (Figure 8A). Then, the excited electrons and holes reacted with O2 and OH−, respectively, to generate ROS for cancer treatment. The photocurrent response of SHNPs under X-ray irradiation shown in Figure 8E reveals that the SHNPs are X-ray sensitive, which implies the higher yield efficiency due to the transfer of photogenerated carriers. As a result, X-ray exposure of the BiO1@Bi2S3 type II heterojunction resulted in a superior ROS generation ability compared with that of pure BiO1, as indicated by the fluorescence change of the ROS probe sodium terephthalate (Figure 8F). In addition, the excellent photothermal (PT) conversion capability endowed SHNPs with the ability to ablate tumor cells. The results displayed in Figure 8G, H revealed the disappearance of the tumor in the SHNPs+NiR+X-ray group, illustrating the desirable effect of synergistic treatments on the basis of SHNPs-triggered RT/PDT/PTT. Moreover, after formation of the heterojunction, SHNPs were expected to act as computerized tomography (CT) and photoacoustic (PA) contrast agents to achieve a “one for all” cancer theranostic nanoplatform.

Similarly, Dong et al. reported a strategy for a combined therapy on the basis of WO2.9−WSe2 (Figure 8I).\[^{65}\] On the premise of the type II heterojunction construction, the X-ray-triggered charges moved in the direction shown in Figure 8J for the enhanced separation of electron–hole pairs, which led to the occurrence of cytotoxic −OH facilitating immunogenic cell death (ICD). Furthermore, the PT effect of the WO2.9−WSe2 heterojunction was able to induce ICDD, which improved the immunogenicity and triggered specific immune responses at the tumor site in synergy with checkpoint blockade immunotherapy (CBT). Through the analysis of tumor-infiltrating T cells at remote tumor sites (Figure 8K), they found that the number of T cells increased during the treatment with WO2.9−WSe2, and the strongest immune response was triggered after treatment with WO2.9−WSe2 and anti-PD–L1 antibody under NiR and X-ray irradiation. This result demonstrated that heterojunction-dependent RT/PTT/CBT plays a crucial role in both antitumor effect and immune response, which is in agreement with the immunostaining assay results (Figure 8L). In an in vitro assay (Figure 8M), WO2.9−WSe2 displayed the outstanding ability of ROS generation upon X-ray and NiR irradiation. In vivo, the negligible tumor growth demonstrated the great inhibitory activity of WO2.9−WSe2 with irradiation and programmed death ligand-1 (PD–L1) against primary and distant tumors. Taken together, these studies not only proved that a reasonably matched energy band would strengthen the therapeutic effect through the separation of charges but also confirmed the potential of the heterojunction in various treatments.

To further promote photocatalysis, a series of accessory compounds were added to the type II heterojunction system. Liu et al. introduced Au into CdSe/Bi2Se3 with type II band alignment to take advantage of the plasmon-induced local field enhancement and hot electron injection for the enhancement of heat generation resulting from type II separation of charge pairs.\[^{66}\] In addition, Zhang and co-workers integrated the upconversion particles NaYF4:Yb3+·Tm3+ into the Zn2GeO4:Mn2+ (ZGM)/g-C3N4 heterojunction to match the irradiation frequency and the band structure of ZGM/g-C3N4 for function enhancement of type II separation,\[^{67}\] which contributed to ROS production.

As an antioxidant widely present in tumor sites, glutathione (GSH) plays a significant role in the redox equilibrium of tumors. Notably, the strong reduction property of GSH hampers ROS-induced cell death, leading to the inefficiency of most photocatalytic therapies. Given this issue, Ji et al. proposed type II-based As/AsxOy@PDA@M NSs for ROS burst,\[^{68}\] which were synthesized through ball grinding, liquid exfoliation, and further coating with polydopamine and cancer cell membrane (Figure 9A). Figure 9B shows that the obtained As/AsxOy NSs had a layered structure with an average size of 93 nm. Owing to this, plenty of active sites were provided for the generation of photocatalytic singlet oxygen (O2·−) and O2·−. In addition, the presence of abundant oxygen vacancies on the surface induces the disproportionation of H2O2, which not only contributes to ·OH generation but also complements O2 to facilitate self-enhanced PDT. On the other hand, ROS become more destructive because the photo-triggered type II electron transfer resulted in the accumulation of sufficient holes for the oxidation of GSH, and the AsxOy NSs inactivated some main anti-oxidases in the tumor site (Figure 9G).

As shown in Figure 9H, irreversible DNA damage was caused in MCF-7 cells treated with As/AsxOy@PDA@M NSs plus laser irradiation, which resulted from ROS burst and O2·− generation (Figure 9I). A consistent conclusion was drawn based on further exploration in vivo (Figure 9J–L). In general, the synergism between the tripartite ROS generation and two main ROS consumption pathways improved the weak curative effect of the common type II heterojunction, providing a new cancer therapeutic strategy with superior efficacy and biosafety.

Although the catalytic activity increased due to the improved charge separation efficiency and the addition of adjuvants, this kind of type II charge transfer, similar with that of the type I heterojunction, decreases the redox potentials and redox capacity, resulting in a limited variety of therapeutic products. Moreover, it is physically unfavorable for the photoinduced electrons or holes to migrate through the type II heterojunction due to the electrostatic repulsion by the electron-rich CB or the hole-rich VB, respectively. Thus, it is necessary to further promote the development of heterojunctions.

4.2. Z-Scheme Heterojunction

As mentioned before, based on the medium, Z-scheme heterojunction could subdivide into three different subclasses,
including Z-scheme heterojunction with redox pairs, Z-scheme heterojunction with transfer bridge, and Z-scheme heterojunction without medium. Similar to type II heterojunction, the band structures (VB and CB) of the two catalysts are interlaced. However, the transfer path and mode of excited electrons and holes of Z-scheme heterojunction were totally different from that of type II heterojunction. Specifically, the excited electrons at lower CB of catalyst II would be combined with the holes at lower VB of catalyst I, leaving excited electrons and holes at higher CB of catalyst I and higher VB of catalyst II.

Similar to natural photosynthesis, the Z-scheme heterojunction can achieve effective photocatalytic reactions at high redox...
Figure 9. A) Schematic diagram of the fabrication of and tumor theranostics with As/As$_2$O$_3$@PDA@M NSs. B) TEM images of As/As$_2$O$_3$ NSs (scale bar: 100 nm). C) HRTEM images of As NSs (scale bar: 1 nm). D) HRTEM images of As/As$_2$O$_3$ NSs (red and blue circles indicate lattice fringes and As$_2$O$_3$ amorphism, respectively; scale bar: 1 nm). TEM images of E) As/As$_2$O$_3$@PDA NSs and F) As/As$_2$O$_3$@PDA@M NSs (scale bar = 100 nm). G) ROS burst induced by As/As$_2$O$_3$@PDA@M NSs. H) Confocal laser scanning microscopy (CLSM) images of MCF-7 in different groups (scale bar: 50 μm). I) Generation of ROS and O$_2$ in vitro. Detection of J) ROS and K) O$_2$ generation in tumor tissue by DCFH and pimonidazole (PIMO) via fluorescence microscopy (scale bar: 1000 μm). L) Immunofluorescence staining of tumors in different treatments groups (scale bar: 1000 μm). Reproduced with permission.[68] Copyright 2021, Springer Nature.
potentials in contrast to the type II heterojunction. Inspired by the above-mentioned fundamental principles, Ji et al. synthesized TOPY NSs with Z-scheme heterojunction via ultrasound-assisted surface oxidation, as described above, as an efficient photocatalyst for PDT (Figure 10A). To verify the function of the Z-scheme heterojunction, ROS analysis was performed (Figure 10B). More specifically, 5,5-dimethyl-1-pyrroline-N-oxide was used as a spin trapping agent for electron spin resonance (ESR) detection. Signals attributed to -O$_2$- and -OH indicated the formation of TOPY NSs with Z-scheme heterojunction and the superior photocatalytic performance. In an in vivo assay (Figure 10C,D), TOPY NSs exhibited an enhanced therapeutic...
effect upon 650 and 808 nm laser irradiation compared with other groups owing to the optimized photocatalytic effect induced by the heterojunction. Notably, the synergism with the TOPY NS-mediated Fenton reaction provided not only additional ·OH for CDT but also O2 supplement to alleviate hypoxia in the tumor site for PDT, which further improved the tumor-killing activity.

To verify the universality of ultrasound-assisted surface oxidation, highly oxidized ilmenite nanosheets (HOIL NSs) were prepared in a similar way. Such an excellent therapeutic effect was also presented by the system of HOIL-PEG NSs. On the other hand, the potential of HOIL-PEG NSs for fluorescence imaging and thermal imaging allowed the development of a multimodal imaging-guided synergistic treatment (Figure 10E).

Recently, Wu et al. successfully prepared a Z-scheme MnO2/g-C3N4 heterojunction on Ti implants (MnO2/g-C3N4-Ti) by the in situ growth of MnO2 on g-C3N4 (Figure 10F,G). The photocatalytic property of MnO2/g-C3N4-Ti was evaluated by electrochemical impedance spectroscopy (EIS) measurements. The EIS results shown in Figure 10H revealed that MnO2/g-C3N4-Ti had the smallest arc among all samples, indicating the lowest charge transfer resistance and greatest electron/hole separation efficiency. Moreover, MnO2/g-C3N4-Ti more easily triggers more carriers and promotes charge separation under light irradiation. According to the curves shown in Figure 10I, an increase of the photoconversion efficiency of MnO2/g-C3N4 of 21.11% compared with g-C3N4 was calculated, which was due to the acceleration of photoinduced charges and the blocked recombination of electron–hole pairs, facilitating ROS-induced antibacterial therapy under visible light irradiation. The MnO2 weight ratio was related to the photocatalyst activity of the Z-scheme heterojunction MnO2/g-C3N4. Too high or too low MnO2 loading is detrimental to the photocatalytic performance, as less MnO2 is related to less charge trapping sites, while excess results in the conversion of trapping sites to recombination sites. Thus, the resulting PDT enhancement was utilized for sterilization. Compared with g-C3N4-Ti, the photo-triggered antibacterial efficacy against S. aureus and E. coli of MnO2/g-C3N4-Ti reached 99.96% and 99.26%, respectively (Figure 10K,L). Apart from that, severe damage of E. coli under illumination is displayed in the corresponding SEM images (Figure 10J), indicating enhanced PDT after the introduction of the heterojunction. In addition, the PDT efficiency was further enhanced through the regulation of the GSH level by MnO2/g-C3N4-Ti (Figure 10M,N).

Furthermore, Cheng and co-workers synthesized Z-scheme hetero-structured photocatalysts and PT agents based on Bi2S3@Bi nanorods (NRs) via combining the solvothermal method with hydrazine treatment. In particular, due to the different Fermi levels of Bi2S3 and Bi, charge migration after the contact of Bi2S3 and Bi results in the formation of a built-in electric field (E-field). This facilitates the diffusion of electrons from the CB of Bi2S3 to holes in the VB of Bi, resulting in higher redox potentials for the formation of ROS (Figure 11A,B). The calculated charge density difference (CDD) are shown in Figure 11C, revealing the electron transfer and the presence of the E-field. Through transient photovoltage (TPV; Figure 11D) and transient absorption spectroscopy (TAS; Figure 11E), the process of charge migration was further illustrated, which suggested the successful formation of the Bi2S3@Bi Z-scheme heterojunction architecture. Thus, under NIR irradiation, O2 and ROS were generated in the VB of Bi2S3 and in the CB of Bi, respectively (Figure 11F), by spatiotemporal synchronization to achieve phototherapy of tumors under hypoxic conditions. In an in vitro assay, the Bi2S3@Bi NR heterojunction presented excellent biocompatibility under dark conditions. Flow cytometry analysis (Figure 11G) revealed that 56.1% of apoptotic/necrotic cells were induced by the Bi2S3@Bi NRs exposed to an 808 nm laser, suggesting NIR-triggered cytotoxicity. Moreover, superior tumor inhibition in vivo demonstrated their general potential for clinical application (Figure 11H). In 2021, Wang et al. reported Cu2-xSe/Bi2Se3 with Z-scheme heterojunction for anticancer treatment, and the band structure after optimization displayed 6-times greater ROS generation than the pure sample (Figure 11J). Likewise, Kang and co-workers designed an antimone nanosheet-based Z-scheme heterostructure, which also facilitated improved photonic therapy due to the Z-scheme heterojunction (Figure 11K).

Compared with type II heterojunction, some of the excited electrons and holes in the Z-scheme heterojunction recombine at the interface, resulting in a certain degree of waste. However, the separated electrons and holes were located at higher levels of CB and VB of Z-scheme heterojunction, in which the potential energy of electron-hole catalytic REDOX reaction is increased. Hence, the type of catalytic reactions and therapeutic products are greatly expanded.

4.3. P-N Heterojunction

Similar to traditional type II heterojunction, the band structures (VB and CB) of the two catalysts are interlaced and the transfer path of excited electrons and holes were as same as that of type II heterojunction. However, due to the presence of electric field in the interface between p-type semiconductor and N-type semiconductor, the transfer directionality and efficiency of excited electrons and holes at p-n heterojunction are much higher than that of conventional type II heterojunction. Meanwhile, the defect of p-n node is the same as that of type II heterojunction. Although the separation efficiency of excited electrons and holes is improved, the REDOX potential is reduced, which reduces the ability of catalytic REDOX reaction.

To date, a lot of efforts have been placed on p-n heterojunctions for PDT. For example, the integration of PDT and photochemotherapy was proposed by Wang and co-workers through the construction of the Fe3O4@MIL-100(Fe)-UCNPs-PEG (FMUP) nanoplatform. The Fe3O4@MIL-100(Fe) (FM) heterojunction was obtained by a layer-by-layer assembly strategy, and the upconversion nanoparticles (UCNPs) were modified by covalent attachment, which enabled to make use of the advantages of NIR and UV/vis light (Figure 12A). Based on the Hall test, the FM was proved to be both an n- and p-type semiconductor, which implied the formation of an FM p-n heterojunction. Accordingly, cytotoxic ·OH was produced by photoinduced charge transfer in the presence of the internal electric field and electron–hole pair separation by the p-n heterojunction. In addition, UV/vis light, converted from NIR by UCNPs, could induce the Fe-ion-based Fenton reaction even in tumor microenvironment where the pH did not meet the requirements (pH = 5–4) to assist PDT in the production of apoptosis-inducing ROS. In an
in vivo assay, the gradual increase of the body weight over time in all groups showed good biosafety and no adverse drug reaction (Figure 12B). The obvious decrease in the tumor volume and the clear damage of cancer tissue suggested an excellent tumor-killing ability of FMUP under light irradiation (Figure 12C–E).

In cancer treatment, hypoxia in the tumor site is another reason restricting PDT application. To overcome this limitation, Zhen et al. developed a p–n heterostructure to simultaneously achieve effective type-I and O2 self-supplying type-II PDT by hydrothermal coupling of BiOI and BiOIO3.[74] When BiOI/BiOIO3 was exposed to a 650 nm laser, the photoinduced electrons and holes accumulated in the CB of BiOIO3 and the VB of BiOI, respectively, according to their electronic band structure (Figure 12F), which was further improved due to the internal electric field. In the BiOI/BiOIO3 formation mechanism (Figure 12G), O2 was shared by BiOI and BiOIO3, resulting in an intimate contact, which significantly enhanced the migration of photoinduced charges. Irrespective of the hypoxic microenvironment of cancer, the clustered electrons converted H2O2 into most cytotoxic ·O2, while the collective holes reacted with H2O to generate not only ·OH but also O2. O2 was further converted into toxic 1O2 to simultaneously realize the two types of PDT. Fluorescence analysis of...
Figure 12. A) Illustration of photocatalysis mediated by Fe₃O₄@MIL-100(Fe). B) Bodyweight curves and C) tumor growth curves of mice in different treatment groups. D) Photographs of tumors dissected from mice treated under diverse conditions, and photographs of the corresponding mice. E) Tumor tissue stained with H&E after the treatment. Reproduced with permission. Copyright 2018, Elsevier. F) Schematic diagram of the preparation and therapeutic mechanism of BiO/I/BiOIO₃. G) Formation mechanism of BiO/I/BiOIO₃. CLSM images of HeLa cells after staining with H) SOSG, I) HPF, and J) DCFH-DA under different treatments. Reproduced with permission. Copyright 2019, Royal Society of Chemistry. K) Diagrammatic drawing of the synthesis and function of p-MoS₂/n-rGO–MnO₂–PEG. L) Mott–Schottky plots of the bare FTO glass substrate, p-type MoS₂, n-rGO, and MoS₂/rGO–PEG. M) Overlay of the Mott–Schottky plots of p-MoS₂/n-rGO–PEG and p-MoS₂/n-rGO–MnO₂–PEG. N) Fluorescence microscopy images of HeLa cells incubated with a) DCFH-DA, b) DCFH-DA + MoS₂/rGO–PEG, c) DCFH-DA + p-MoS₂/n-rGO–PEG, or d) DCFH-DA + p-MoS₂/n-rGO–MnO₂–PEG under NIR irradiation for 5 min and in the presence or absence of NaN₃. Reproduced with permission. Copyright 2018, Royal Society of Chemistry.
MoS₂/n-rGO–MnO₂-PEG plus irradiation, while an obvious re-
strong fluorescent intensity in the cells after treatment with p-
ROS level in cells after different treatments. Figure 12N shows
Specifically, DCFH-DA was employed as an indicator to detect the
ROS. This hypothesis was proved by ROS detection in vitro.
Regarding O₂ self-providing PDT via the Fenton reaction,
Kapri et al. designed a p-MoS₂/n-rGO–MnO₂-PEG nanocompos-
ite as a p-n heterojunction.⁷⁷ which was fabricated through a se-
ries of methods, including liquid exfoliation and hydrothermal
reaction (Figure 12K). The Mott–Schottky plots shown in Fig-
ure 12LM revealed the p-type nature of MoS₂ and the n-type
nature of rGO. As for p-MoS₂/n-rGO–MnO₂-PEG nanosheets,
Mott–Schottky plots with an inverted “V-shape” verified p-n het-
erojunction characteristics. Acting as a photosensitizer, the p-
MoS₂/n-rGO–MnO₂-PEG was triggered under NIR irradiation
so that the resulting separated charge carriers converted O₂ into
ROS. This hypothesis was proved by ROS detection in vitro.
Specifically, DCFH-DA was employed as an indicator to detect the
ROS level in cells under different treatments. Figure 12N shows
strong fluorescent intensity in the cells after treatment with p-
MoS₂/n-rGO–MnO₂-PEG plus irradiation, while an obvious re-
duction in fluorescence was detected after the addition of NaN₃
scavenger, suggesting outstanding ROS generation by the p-n
heterojunction. In addition, the further fluorescence enhance-
ment in the group of p-MoS₂/n-rGO–MnO₂-PEG plus irradiation
proved that self-providing of O₂ improved PDT.

4.4. S–M Heterojunction

In contrast to semiconductor-semiconductor heterojunctions,
there is a large class of heterojunctions that are composed of
semiconductors and metals. Semiconductor–metal heterojunc-
tions mainly include Schottky, Ohmic, and LSPR–mediated junc-
tions. Schottky junctions are built by connecting a metal with
higher work function (Φ) and an n-type semiconductor with
lower Φ or by connecting a metal with lower Φ and a p-type
semiconductor with higher Φ, which could facilitate the sepa-
rated and trap the excited electrons and prevent the recombin-
ation of electron-hole pairs. Contrary to Schottky contacts, Ohmic
junctions are formed by connecting an n-type semiconductor with
lower Φ and a metal with higher Φ or by connecting a p-
type semiconductor with higher Φ and a metal with lower Φ,
which are bad for the separation of electron-hole pairs. In addi-
tion, the LSPR effect promotes the generation of photoinduced
electrons with high energy (hot electrons) in the noble metal.
Then, the hot electrons cross the Schottky barrier and are injected
into the semiconductor, while the photoinduced holes remain
in the metal, which provides more negative electrons. Although
semiconductor–metal heterojunctions have great potential in the
field of catalysis, the strict requirements for semiconductors and
metals have severely limited its development in the biomedical
field.

Recently, Wang et al. reported Au–Bi₂S₃ heterojunction
nanoparticles⁷⁸ prepared by the in situ growth of Au on the sur-
face of Bi₂S₃ (Figure 13A). Due to the construction of the Schot-
tky barrier between Bi₂S₃ and Au, the electrons transferred to the
CB under the irradiation of X-ray could be trapped in Schottky
barrier, which inhibited the combination of electron-hole pairs
and facilitated H₂O₂ as electron acceptor to be decomposed into
·OH for tumor destruction. The catalytic performance was an-
alyzed by measuring the photocurrent under X-ray irradiation,
showing that the current density induced by Au–Bi₂S₃ was 1.5
times as high as that obtained by pristine Bi₂S₃, which directly
proved that the Au–Bi₂S₃ heterojunction enhanced the separa-
tion of X-ray-excited electrons and holes (Figure 13B). The pho-
tocatalytic ability of the Au–Bi₂S₃ heterojunction in the genera-
tion of free radicals is 1.6 times as high as that of the Au and
Bi₂S₃ mixture under the same conditions (Figure 13C), demon-
strating that the formation of the heterojunction strengthened
the photocatalytic effect. Furthermore, the triggered low energy
electrons in the Au–Bi₂S₃ heterojunction are captured by Au
via the electron trap of the Schottky barrier to react with overex-
pressed H₂O₂ and generate ·OH, which was verified by the signifi-
cant fluorescence increase of terephthalate (specific indicator for
·OH) after hydroxyl radical detection (Figure 13D). Interestingly,
Figure 13E reveals a significant increase of free radicals in the
group of Au–Bi₂S₃/H₂O₂+X-ray+Ar, manifesting that the pho-
toconversion of H₂O₂ to ROS broke the limitation by hypoxia.

To evaluate the anticancer activity, DNA damage was analyzed
by γ-H₂AX foci detection. Figure 13G shows that the green flu-
cesence of cells co-incubated with Au–Bi₂S₃ composite plus
X-ray irradiation was 5.6 times stronger than in the group only
exposed to X-ray irradiation, demonstrating that the radiosensi-
tization enhancement was caused by the heterojunction. Inter-
estingly, the green fluorescence was further strengthened when
the cells were exposed to X-ray and NIR irradiation after incuba-
tion with Au–Bi₂S₃. This was attributed to the improved uptake
of Au–Bi₂S₃ by the cells due to the change in transmembrane permea-
ability under the PT effect of Au–Bi₂S₃ nanoparticles exposed to
NIR irradiation. The JC-1 assay proved cell damage resulting from
free radicals by the loss of the mitochondrial membrane po-
tential. Overall, phototherapy based on Au–Bi₂S₃ is independent
of oxygen so that it is more suitable for treating cancer in hypoxic
environment than conventional PDT.

LSPR is a useful method that plays a significant role in im-
proving photocatalysis. Chang et al. combined the hydrothermal
method with a reduction to prepare NdVO₄/Au heterojunction
nanocrystals as plasmonic photocatalysts,⁷⁷ and the corre-
sponding TEM and HR–TEM images are presented in Figure 13H, I.
Due to the LSPR effect, the plasmonic metal Au interacted
strongly with the laser, which resulted in an enhanced light
absorption and the formation of an electromagnetic field.
Therefore, under laser irradiation, the LSPR-triggered plas-
mon resonance energy transfer (PRET) from Au to NdVO₄
surmounted the wide bandgap of NdVO₄ (Figure 13J), which
allowed the formation of a considerable number of electron–hole
pairs to participate in redox reactions so that the photocatalytic
performance was strengthened for ROS generation. Accord-
ingly, the solar-driven photocatalytic activity was tested by analyzing
the degradation of methyl orange. Figure 13K,L shows that methyl
orange was almost completely decomposed in the presence of
NdVO₄/Au under solar irradiation, and no obvious deactivation
of the photodegradation ability was detected even after four
consecutive cycles, which further demonstrated the outstanding
photocatalytic performance of NdVO₄/Au. In addition, the
enhanced PT conversion efficiency and improved thermal expansion effect endowed the nanocomposites with the potential of PT/PA imaging. The real-time PT image of mice injected with NdVO$_4$ or NdVO$_4$/Au under NIR laser irradiation (Figure 13F,G) showed an obvious variation of the temperature after NdVO$_4$/Au treatment, indicating the superior potential of NdVO$_4$/Au as a PT agent. Among different treatments, NdVO$_4$/Au treatment of U14-tumor-bearing mice exhibited the strongest photoacoustic (PA) signal, indicating the good PA imaging ability of NdVO$_4$/Au (Figure 13H,I).

Moreover, Dai et al. fabricated g-C$_3$N$_4$ coated with Au nanoparticles by the joint approach of liquid-phase exfoliation and photo-deposition (Figure 14A). As a semiconductor material with great photocatalytic activity, g-C$_3$N$_4$ has a wide bandgap of 459 nm, which severely hinders its application in PDT. They reported that Au makes use of the laser energy to move and accumulate electrons in the CB of g-C$_3$N$_4$, which improves the separation efficiency of photoexcited charges and facilitates ROS generation from H$_2$O (Figure 14B). In addition, on account of the Au modification, the photo-absorption range of the g-C$_3$N$_4$/Au heterojunction could be extended to the NIR region (Figure 14C). When the Au content reached 1.0%, g-C$_3$N$_4$/Au exhibited the best photocatalytic ability to induce tumor cell death even in the absence of oxygen (Figure 14D). This was ascribed to the high number of ROS formed from H$_2$O by the g-C$_3$N$_4$/Au heterojunction, which was confirmed by the flow cytometry assay (Figure 14E).

Compared with Au, Ag exhibits many advantages, including the relatively low cost and extraordinary plasmonic properties. Chang et al. reported a CeVO$_4$/Ag nanohybrid heterojunction with outstanding photoconversion capability for ROS production. Under NIR laser irradiation, hot electrons formed...
Figure 14. A) Illustration of γ-C3N4–Au-based PDT. B) High-angle annular dark field-scanning transmission electron microscope (HAADF-STEM) image of γ-C3N4–Au (scale bar = 200 nm). C) UV–vis spectrum of γ-C3N4–Au. D) Anticancer effect of γ-C3N4–1.0% Au in a hypoxic atmosphere. E) Flow cytometry images of MCF-7 after different treatments in a hypoxic atmosphere: ① MCF-7; ② MCF-7 + light; ③ MCF-7 + γ-C3N4–1.0% Au; ④ MCF-7 + γ-C3N4–1.0% Au + 20 min light irradiation (γ-C3N4–1.0% Au concentration: 200 μg mL⁻¹). Reproduced with permission. [78] Copyright 2021, American Chemical Society. F) Schematic illustration of enhanced phototherapy based on CeVO₄/Ag. G) ROS generation capability of CeVO₄ and CeVO₄/Ag. H) Fluorescence images of HeLa cells stained with DCFH-DA under different treatments. I) Representative images showing the changes of tumor volume and body weight in an in vitro assay. Reproduced with permission.[79] Copyright 2019, Royal Society of Chemistry. J) Schematic diagram of CN@MS heterojunction-mediated PDT. K) ROS generation based on the CN@MS heterojunction. L) Band structure of the CN@MS heterojunction. CDD M) top and N) side view of the CN@MS heterojunction. The upper layer is MS and the lower layer is CN. Purple, yellow, brown, and silver indicate Mo, S, C, and N atoms, respectively. The isosurfaces were set to 1.23 × 10⁻⁶ e A⁻³. O) Fluorescence intensity of DCFH after different treatments. P) Fluorescence images and the corresponding flow cytometry analysis of (a) cell; (b) cell + light; (c) cell + CN@MS; and (d) cell + CN@MS + light after different treatments (scale bar = 50 μm). Changes of the Q) body weight and R) tumor growth curves under different conditions. Reproduced with permission. [80] Copyright 2019, Elsevier.

After absorption of resonant photons by Ag and moved into the CB of CeVO₄ to effectively separate electrons and holes and facilitate the generation of O₂⁻ and ·OH in the CB and VB of CeVO₄, respectively (Figure 14F). As shown in Figure 14G, the gradual decrease in the absorption intensity of 1,3-diphenylisobenzofuran (DPBF) and methylene blue over time indicated the continuous ROS generation after laser irradiation of the CeVO₄/Ag heterojunction. According to Figure 14H, enhanced ROS generation was proved by the changes in the intracellular fluorescence of 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA), and green fluorescence indicated the superb ROS production ability of CeVO₄/Ag via photocatalysis. The ROS-mediated antitumor activity was further analyzed by in vivo experiments, as displayed in Figure 14I, showing that the tumor suppression ratio after CeVO₄/Ag plus NIR illumination treatment was superior to that of other treatment groups, implying the enormous potential of the CeVO₄/Ag heterojunction in antitumor treatment.
Apart from noble metals, metallic transition metal dichalcogenides can be employed to transfer photoinduced electrons. Dai and co-workers integrated graphitic carbon nitride (CN) and metallic molybdenum disulfide (MS) into a CN@MS heterojunction system[80] in which MS acted as the antenna to respond to the incident light and induce the injection of photogenerated electrons into the CN for electron–hole separation (Figure 14J,K). To prove the successful construction of this heterostructure, DFT calculations were performed. Figure 14L shows that the calculated valence band maximum (VBM) and the conduction band minimum (CBM) were located at K and G points, respectively, indicating that pure CN has the characteristics of an indirect band-gap semiconductor. The CDD plot demonstrated that the heterojunction formation was contributed by the electron rearrangement at the stacking interface and the noncontact surface (Figure 14M,N). Figure 14O shows that massive ROS generation resulted from the construction of the CN@MS heterostructure due to fluorescence quenching of DCFH-DA. An in vitro assay confirmed ROS-induced cell apoptosis via fluorescent staining and flow cytometry (Figure 14P). To further assess the anticancer effect, the experiment was conducted in vivo. Figure 14Q,R shows body weight and tumor growth curves, which exhibited little fluctuation and thus good biosafety and a good therapeutic effect, indicating that the CN@MS heterojunction is a promising candidate for clinical application.

5. Summary and Future Perspectives
As an effective strategy to enhance the catalytic efficacy, heterojunctions have been intensely studied for application in the energy conversion field, yet comparable studies in biomedicine are just in their infancy but promise huge potential. Over decades, some heterojunction-based catalytic systems have been designed for biomedical applications (Table 1). Herein, recent achievements and the development of heterojunctions in the medical field are introduced through some examples, including the design procedures, synthetic methods, specific applications, and treatment efficacy, showing that the heterojunction-based catalytic system has promising biomedical properties and prospects. To achieve the desired effect, the requirements, including the rational alignment of energy bands and ideal migration of photogenerated electron–hole pairs, the shape uniformity preparing through simple, economical, but efficient ways, need to be met. And the clinical application of heterojunction medicine has never appeared, because several problems have not been solved yet. 1) Basically, the balance between biosafety and therapeutic efficacy of heterojunctions should be realized. The higher doses of heterojunctions, the higher potential of side effects. Further research needs to enhance the therapeutic effect of per unit dose, such as the increase in the number of active sites and the targeting to specific lesions. Development of biodegradable and metabolizable materials is another way. 2) Current studies almost focus on the common, existing other properties, such as the bioimaging ability, determined by the composition of the materials should be focused on to realize multi-functional integration. 3) Turning basic research into clinical application require a large amount of time and money. To speed up the process, we believe that the in-depth theoretical
research can guide the future research directions of heterojunction nanomedicine.

5.1. Enhance Catalytic Efficiency and Biosafety

The toxicity of heterojunctions to normal tissue restricts the in vivo application. Compared with the uniform distribution of catalytic sites of homogeneous photocatalysts, active sites of heterogeneous photocatalysts restrict the photocatalytic capability. Thereby, enlarging the specific surface area is one of the effective strategies to achieve the exposure of sufficient active sites. Compared with conventional 3D materials, the surface effects and the huge specific surface area of the emerging 2D structures, due to the atomic layer thickness, not only present the unique photoelectric performances of materials but also provide a considerable number of active sites for an increased responsiveness. And the band gap of 2D materials can be controlled by changing the number of layers to achieve a response to different wavelengths for various applications. Many examples proved that some heterojunctions can uptake the advantages and exhibit better function than the only use of the component. BP, a typical 2D material used for tumor treatment, has an adjustable bandgap. When the thickness decreases from five layers to a single layer, the bandgap increases from 0.59 to 1.51 eV, enabling BP to absorb light in the UV–vis–NIR region and overcome the shortcomings of Si-based photodetectors in response to NIR laser irradiation. And it is reported that photodetectors with high responsivity by the formation of a heterojunction of BP and Si. The key role 2D heterojunction materials playing in the technology of photoelectrical detection makes us speculate that band-gap-matched heterojunction materials based on 2D structures, including but not limited to BP, may exhibit better properties for biomedical use than conventional materials in the medical field.

In addition to controlled bandgap, BP is profitable for practical application due to the biodegradability of it and the biosafety of the degradation product, phosphate. Also, quantum dots with the size of several nanometers are safer than other materials with large size, because they can be eliminated through kidney. Similar to other agents, targeting promises better therapeutic results with less dose. In a word, heterojunctions consisting of biodegradable materials and targeting systems have a larger potential to turn into clinic.

5.2. Expand Catalytic Reaction and Application Types

With the continuous research and development of nanomedicine, multimodal therapies have been utilized for antitumor therapies. Apart from ROS generation, heterojunctions can be utilized in catalyzing several biological and chemical reactions due to the controlled band structure, and therefore adopted for many therapeutic methods due to their superior optical properties.

Gas therapy, as an emerging antitumor treatment, is used to kill cancer cells through the specific accumulation of toxic gas at the tumor site. However, this treatment still faces challenges because of the uncontrollable and ineffective release of therapeutic gas in vivo. To solve this problem, Wang and co-workers proposed a CO nanogenerator synthesized by partially oxidized SnS2, which had an excellent antitumor effect. Also, hydrogen treatment possesses a superb regulation function in physiology and pathology. It can be employed to not only inhibit tumors but also reduce ischemia reperfusion injury and improve rheumatoid arthritis. To hinder the adverse nature of hydrogen (e.g., uncontrollable diffusion), the heterojunction photocatalyst for hydrogen generation through the coupling of graphene and g-C3N4 has been fabricated, taking advantage of the optical properties of graphene for the effective separation of photoinduced charges. The results show that as a strategy to improve the permeability and photocatalytic efficiency of gases, the heterojunction nanoplatform is a promising candidate to be introduced in the field of gas therapy to control the gas production with high accuracy.

In addition, heterojunctions can also play a role in PT therapy. Deng et al. introduced the CuS@Cu2S@Au nanohybrid as a PT agent. After the formation of CuS on the surface of Cu2S and Au, the gas production increased and more circuit paths are provided for charge migration, which contributed to increasing the PT conversion efficiency. Moreover, Cui et al. reported a composite resulting from coupling Au and Cu2S to ablate tumors via PTT. After the formation of Cu2S, Au heterodimers, the LSPR absorption was changed, and the response of this system was optimized to 808 nm laser irradiation so that the PT effect was strengthened.

5.3. Equip with Theoretical Strategies

Theoretical strategies such as first-principles calculations and molecular dynamics simulations have been widely adopted in material design, functional evaluation, and mechanism analysis. Combination of experimental research and theoretical calculations can improve the efficiency of heterojunction development and save costs. In addition, the application of theoretical calculations can provide an in-depth supplement to the mechanism study of heterojunction photocatalysts. At present, many constructive results have been achieved in theoretical calculations based on the vertical heterojunction stacked by van der Waals forces. However, due to the more complicated factors at the interface in the transverse heterojunction, the existing theoretical researches are limited to graphene-like materials and 2D transition metal sulfides. Therefore, to better provide theoretical support for the development of heterojunction, extending the scope of application through reasonable construction of the initial structure and optimization of the parameters has become a necessary matter.

In summary, the recent progress of heterostructure nanomedicine is presented in this review. This field of medicine provides an effective approach to optimize anti-tumor effects. We hope that this review provides a new perspective for the application of heterostructure nanomedicine to advance the further development of this novel field of medicine in biomedicine.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (32071322, 81801826) and National Natural Science Funds for Excellent Young Scholar (32122044 and 31922042).
Conflict of Interest
The authors declare no conflict of interest.

Keywords
catalytic therapy, electron-hole pairs, heterojunction, nanomedicine, semiconductor

Received: December 11, 2021
Revised: January 29, 2022
Published online: February 17, 2022
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