Edge modification facilitated heterogenization and exfoliation of two-dimensional nanomaterials for cancer catalytic therapy

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The rapid recombination of electron-hole pairs and limited substrates are the most critical factors astricting the effect of catalytic therapy. Thus, two-dimensional interplanar heterojunction (BiOCl/Bi2O3) that prolongs the lifetime of excited electrons and holes and extends the selectivity of substrates under ultrasound irradiation is prepared to facilitate high-performance cancer therapy. An edge modification displacing marginal BiOCl to Bi2O3 of excited electrons and holes is prepared to construct the interplanar heterojunction, promoting ultrathin nanosheets exfoliation due to the enhanced edge affinity with H2O. The spontaneously aligning Fermi levels mediate a built-in electric field–guided Z-scheme interplanar heterojunction, retard electron-hole pairs recombination, and improve redox potentials. Hence, these high-powered electrons and holes are capable of catalyzing diverse and stable substrates, such as the reduction reactions, O2 –→ O2•– and CO2 –→ CO, and oxidation reactions, GSH –→ GSSG and H2O –→ OH. The Z-scheme interplanar heterojunction with the extending substrates selectivity completely breaks the tumor microenvironment limitation, exhibiting high anticancer activity.

INTRODUCTION

Catalysis is an omnipotent “tool” creating an enchanting world for human survival and development through millions of years of evolution (1–6). Recently, the combination of catalysis and medicine, viz., catalytic medicine, integrates catalytic technology to solve medical problems. Moreover, it provides efficient treatment strategies against various pathological abnormalities, including cancer, bacterial infection, inflammation, and other diseases (7–10). Undoubtedly, the physical and chemical properties of the catalyst, such as activity, selection, and stability, are integral to the curative effect of catalytic medicine.

Three crucial factors and steps essentially determine the catalytic efficiency in medicine applications, namely, (i) excitation energy (light or ultrasound) absorption, (ii) electron-hole pairs separation and migration from the bulk to the surface, and (iii) surface catalysis reactions (11–14). The mainly used catalytic medicine focuses on reactive oxygen species (ROS) generation from O2•– or H2O2– induced oxidative damage to cancer cells (15). Nevertheless, the effect of these redox imbalance–based catalytic therapies is extremely limited by the unique tumor microenvironment (TME). For instance, hypoxia and limited H2O2 concentration restrict the ROS generation efficacy, and high expression glutathione (GSH) and peroxidase consume ROS (16–20). Therefore, developing previously unidentifed cancer catalytic medicine is desired, notably expanding the range of substrates and therapeutic products.

On the basis of the perspective of catalytic chemistry, the catalyst must have a high valence band (VB) and conduction band (CB) levels with enough redox potential energy to broaden the range of substrates and therapeutic products (11, 13, 21, 22). However, the bandgap, the energy level difference between VB and CB, will increase with the increase of VB and CB levels, which would inevitably lead to the difficulty of separating electron-hole pairs and poor catalytic activity (23). Therefore, there is an irreconcilable contradiction between broadening the catalytic reaction type and the catalytic activity for a single catalyst (14).

The construction of heterojunction is one of the most practical and effective strategies to break through this contradiction, simultaneously accelerating the separation of the electron-hole pairs and extending the species of substrate and therapeutic product selection (23–27). Z-scheme heterojunction with excellent properties of natural photosynthesis owns many advantages over single catalysts and other types of heterojunctions. Two photosensitizers are activated simultaneously, and the electrons within the lower CB of one photosensitizer combine with the lower VB of the other so that the higher CB and VB of these photosensitizers would have separate electrons and holes having high reduction/oxidation potentials (23, 25, 28, 29). The primary advantage of biomimetic Z-scheme heterojunction is that it improves the separation efficiency of charges and promotes reduction and oxidation potentials, directly broadening the catalytic reaction range and activity.

Two-dimensional (2D) nanomaterials representing a previously unidentified class of nanomaterials have been exhaustively used in developing catalysis due to their sizeable bandgap, good conductivity, fast electron transfer, and photoelectrochemical activity (30–37). In particular, 2D heterostructures integrating the advantages of 2D nanomaterials and heterojunction are conducive to elevating energy conversion capacity and improving oxidation and reduction (11, 13, 21, 22). Here, a 2D interplanar Z-scheme heterojunction (BiOCl/Bi2O3) was developed through a smart wet-chemical method integrating interplanar heterojunction synthesis and 2D ultrathin heterojunction exfoliation within one step. As exhibited in Fig. 1, after the bulk layered bismuth oxychloride (BiOCl) was synthesized using a hydrothermal process, the edges of BiOCl were selectively
modified and transformed into Bi$_2$O$_3$, which constructed an interesting interplanar heterojunction. Moreover, it also facilitated the exfoliation by improving affinity with water molecules. At this interplanar heterojunction BiOCl/Bi$_2$O$_3$ nanosheets (NSs) interface, a built-in electric field was formed by the aligning Fermi levels of BiOCl and Bi$_2$O$_3$, guiding excited electron and hole redistribution. Using US irradiation, the ultrasound (US)–excited electrons on the CB of Bi$_2$O$_3$ will be combined with the holes on the VB of BiOCl, using the driving force of the built-in electric field in their interface, leaving stronger reduction/oxidation potentials of separated electrons and holes over the CB of BiOCl and the VB of Bi$_2$O$_3$, respectively. Hence, a built-in electric field–facilitated Z-schemed catalytic mechanism was constructed, which endowed that the electrons and holes were separated thoroughly and had the most powerful reduction and oxidation potentials, respectively. Thus, two active catalytic sites located at the CB of BiOCl and the VB of Bi$_2$O$_3$ were capable of catalyzing both conventional reactions, such as O$_2$ + e$^-$ → ·O$_2$$^-\ + $ and GSH + h$^+ \rightarrow $ GSSG, and difficult reactions, such as CO$_2$ + 2H$^+$ + 2e$^-$ → CO + H$_2$O and H$_2$O + h$^+$ → ·OH + H$. The extension of substrates and therapeutic products based on the 2D interplanar Z-scheme heterojunction breaks the limitation of the TME to catalytic therapy. It exhibits excellent antitumor performance both in vitro and in vivo. Hence, this work provides a smart strategy to intelligently synthesize 2D ultrathin heterojunction and an advanced strategy to enhance the efficiency and application range of catalytic therapy by increasing the selectivity of nanocatalysts.

![Fig. 1. Schematic illustration of the edge selective modification preparation facilitated exfoliation and heterogenization of the 2D nanomaterials (BiOCl/Bi$_2$O$_3$ NSs) by extending catalytic selectivity to bypass the TME restrictions.](image)

(A) BiOCl/Bi$_2$O$_3$ NS preparation with Z-schemed heterojunction. (B) Top and side views of the fully optimized BiOCl and Bi$_2$O$_3$ NSs. (C) Optimized geometries of H$_2$O molecule on the surface of BiOCl and Bi$_2$O$_3$ NSs. (D) Equilibrium distance (d) between the NS and H$_2$O. The intramolecular bond angle (θ) and bond length (l$_1$ and l$_2$) of H$_2$O, respectively. The adsorption energy (E$_{ad}$) and charge transfer (Q) for each adsorption system.

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RESULTS
Preparation and characterization of BiOCl/Bi$_2$O$_3$ NS-based interplanar heterojunction

The layered BiOCl powder was synthesized using a hydrothermal process applying Bi(NO$_3$)$_3$·5H$_2$O as the substrate (fig. S1A). Subsequently, the interplanar heterojunction BiOCl/Bi$_2$O$_3$ was synthesized through in situ reductions and oxidation of layered BiOCl powder (fig. S1B). After being immersed in KBH$_4$ for 10 min, the edges of layered BiOCl powder were reduced to Bi (Fig. 1). Then, the Bi edges of BiOCl were oxidized to Bi$_2$O$_3$ after reacting with H$_2$O$_2$. The change in color from white (BiOCl) to faint yellow (BiOCl/Bi$_2$O$_3$) depicted the first evidence of successful BiOCl/Bi$_2$O$_3$ synthesis (fig. S1). Next, the BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs were liquid exfoliated in water under ultrasonic treatment to avoid additional toxicity from organic solvents. BiOCl/Bi$_2$O$_3$ is much easier to peel off in an aqueous solution than BiOCl. However, for exfoliation of BiOCl NSs in water solution, 12-hour ultrasonic treatment was required for nanoscale BiOCl NSs. Hence, the edge modification not only constructed an interplanar heterojunction but also facilitated the exfoliation of layered NSs. The mechanism of this exciting phenomenon is illustrated in Fig. 1. As shown in Fig. 1B, the models for BiOCl and Bi$_2$O$_3$ were established with supercells of 3 × 3 × 1 and 2 × 2 × 1 unit cells, respectively. Inside the sandwich layer structure of BiOCl, Cl atoms were distributed on both sides of the Bi$_2$O$_3$ layer. The average distance between Cl and O was 3.30 Å. Bi$_2$O$_3$ had a network-like voids between the layers, the intramolecular bond length, bond angle of H$_2$O before application, the adsorption energy, and charge transfer for each system are given in Fig. 1D. We observed that the H$_2$O-Bi$_2$O$_3$ system had a smaller equilibrium distance of 0.41 Å and a much lower adsorption energy of ~0.87 eV. These findings indicated that Bi$_2$O$_3$ is more hydrophilic than BiOCl. The intermolecular hydrogen bond forming contributes to the high affinity between Bi$_2$O$_3$ and H$_2$O after H$_2$O exposure. Therefore, the improved hydrophilicity of BiOCl/Bi$_2$O$_3$ may be more conducive to the exfoliation of ultra-thin NSs in water.

As exhibited in Fig. 2A, the size of the prepared BiOCl powder was about 1000 nm, and the layered structure was revealed in the scanning electron microscope (SEM) image of BiOCl. After 12 hours of continuous sonication, the BiOCl NSs with a thickness of 10- and 176-nm size were prepared (Fig. 2, B and C, and figs. S2A and S3A). The high-resolution transmission electron microscopy (HRTEM) images of BiOCl NSs were observed in Fig. 2D. A clear interference fringe and d-spacing of 0.73 nm was corresponding to the plane of BiOCl. For BiOCl/Bi$_2$O$_3$ NSs, after edge modification, the edges of BiOCl/Bi$_2$O$_3$ began to curl, and the layered structure became more evident (Fig. 2E). A thickness of 6 nm and a size of 156 nm of BiOCl/Bi$_2$O$_3$ NSs were obtained after 5 hours of ultrasonic treatment (Fig. 2, F and G, and figs. S2B and S3B). The HRTEM images revealed the clear interference fringe and d-spacing of 0.73 and 0.33 nm, corresponding to the plane of BiOCl NSs and Bi$_2$O$_3$ NSs (Fig. 2H). Next, x-ray photoelectron spectroscopy (XPS), x-ray diffractionometry (XRD), and Raman spectra analyzed the chemical composition and structures of as-prepared BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs. In the XRD spectra of BiOCl/Bi$_2$O$_3$ NSs (Fig. 21), two respective crystal structures were observed, corresponding with the tetragonal structure of BiOCl [Joint Committee on Powder Diffraction Standards (JCPDS) no. 06-0249] and the monoclinic structure of Bi$_2$O$_3$ [JCPDS no. 06-0294]. In the Raman spectra (Fig. 2J), BiOCl NSs showed two distinctive bands at 144 cm$^{-1}$ (assigned to $A_{1g}$ internal Bi-Cl stretching mode) and 197 cm$^{-1}$ (assigned to $E_p$ internal Bi-Cl stretching mode). After edge modification, the characteristic peaks of Bi$_2$O$_3$ were exhibited in the spectrum of BiOCl/Bi$_2$O$_3$ NSs. The 119-cm$^{-1}$ modes came from Ag symmetry caused primarily by the participation of Bi atoms. Modes of 138 ($A_g$) and 153 cm$^{-1}$ ($B_g$) could come from the displacements of both Bi and O atoms in the Bi$_2$O$_3$ lattice. The Raman peaks with the higher-frequency modes 183, 211, 279, 313, 410, 446, and 521 cm$^{-1}$ were attributed to the displacements of the O atoms in Bi$_2$O$_3$. During the XPS analysis (Fig. 2K), the specific peaks of Bi 4f, O 1s, and Cl 2p were observed. As shown in Fig. 2 (L and M), the typical high-resolution XPS spectra of Cl 2p of BiOCl NSs were much higher than that of BiOCl/Bi$_2$O$_3$ NSs. For typical high-resolution XPS spectra of Bi 4f of BiOCl/Bi$_2$O$_3$ NSs, other than the specific peaks of Bi 4f from BiOCl NSs, two other specific peaks of Bi 4f from Bi$_2$O$_3$ NSs were also observed. More obvious evidence was demonstrated in the high-resolution XPS spectra of O 1s. As shown in Fig. 2 (P and Q), apart from these specific peaks of O 1s BiOCl NSs and absorbed O$_2$, another specific peak of O 1s of Bi$_2$O$_3$ NSs was also observed. These characterizations further demonstrated the successful edge modification. Biocompatibility and dispersibility are crucial for biomedical applications. The as-prepared BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs were modified using polyethylene glycol 5k [PEG(5k)]–NH$_2$ through electrostatic attraction between positively charged PEG(5k)–NH$_2$ and negatively charged NSs (fig. S4). Moreover, thermogravimetric analysis was applied to quantify the PEG(5k)-NH$_2$ coated on the surface of the NSs [≈20% (w/w)] (fig. S5). PEGylation of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs improved dispersion in water, phosphate-buffered saline (PBS), and cell culture medium than with the bare NSs (fig. S6 and table S1). Enhanced dispersion in a solution would provide more active sites of catalysts. Moreover, the improved hydrophilicity would decrease the distance between catalysts and substrates, notably improving the catalytic reaction rate. Therefore, PEGylation is essential for nanomedicine used in vivo and the catalytic properties, and in vitro and in vivo experiments were carried out after PEGylation of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs. Fourier transform infrared absorption bands of the PEGylated BiOCl/Bi$_2$O$_3$ NSs at ~2900 and ~1250 cm$^{-1}$ corresponded to the –CH and =O stretching vibration in the PEG-NH$_2$ segment (fig. S7). The energy dispersive spectrometer (EDS) mappings observed in Fig. 2 (R and S) exhibited a homogeneous Bi, O, and Cl distribution in BiOCl NSs. They reduced the concentration of Cl in BiOCl/Bi$_2$O$_3$ NSs. Moreover, the ratio of BiOCl to Bi$_2$O$_3$ in prepared BiOCl/Bi$_2$O$_3$ NSs was determined. As shown in table S2, after edge modification, the atomic percent of Bi in BiOCl/Bi$_2$O$_3$ NSs was consistent with that in BiOCl NSs, without any impurities during edge modification. The atomic percent of Cl decreased from 31.32 to 23.38%, converting nearly 25.35% of BiOCl to Bi$_2$O$_3$. Hence, the ratio of BiOCl to Bi$_2$O$_3$ in prepared BiOCl/Bi$_2$O$_3$ NSs was evaluated to be 2.94:1. In addition, from the...
Fig. 2. Characterization of BiOCl/Bi$_2$O$_3$ NSs. (A) SEM, (B) TEM, (C) 2D atomic force microscopy (AFM), and (D) HRTEM images of BiOCl NSs. (E) SEM, (F) TEM, (G) 2D AFM, and (H) HRTEM images of BiOCl/Bi$_2$O$_3$ NSs. (I) XRD, (J) Raman, and (K) XPS spectra of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs. HRXPS spectra of (L) Cl, (M) Bi, and (N) O of BiOCl NSs. Energy dispersive spectrometer (EDS) mapping of the (R) BiOCl NSs and (S) BiOCl/Bi$_2$O$_3$ NSs. Scale bars, 1000 nm (A and E), 100 nm (B, C, F, G, R, and S), 5 nm (D and H). a.u., arbitrary units.
viewpoint of practical applications, the stability of the BiOCl/Bi$_2$O$_3$ NSs within different acidic solutions (pHs 5.0, 7.4, and 8.0) was analyzed. As shown in fig. S8, after being immersed in the above solutions for 48 hours, the morphology and structure of NSs did not alter obviously. The XPS, XRD, and Raman spectra of BiOCl/Bi$_2$O$_3$ NSs remained nearly the same before and after 48 hours of acid and alkaline environment treatments (fig. S9), demonstrating the notable stability of prepared BiOCl/Bi$_2$O$_3$ NSs.

**Analysis of catalytic performance and mechanism**

Specific catalysis is one of the excellent properties of catalysts (38–40). However, because of the lack of substrate concentration in the TME, the application of catalysts with high specificity is limited (41–43). Therefore, broadening the catalytic selectivity of catalysts could achieve the efficiency of catalytic medicine. First, diphenyl isobenzofuran (DPBF) as a $\cdot$O$_2^-$ probe was applied to detect the $\cdot$O$_2^-$ generation through O$_2$ reduction (Fig. 3A). As shown in Fig. 3B and fig. S10, the treatment through US, BiOCl NSs, and BiOCl/Bi$_2$O$_3$ NSs alone could not generate $\cdot$O$_2^-$. Coupling NS-based catalyst and US, different content $\cdot$O$_2^-$ was developed, in which BiOCl/Bi$_2$O$_3$ NSs depicted stronger $\cdot$O$_2^-$-generating ability than BiOCl NSs.

The $\cdot$O$_2^-$-generating performance was detected under BiOCl NSs + US and BiOCl/Bi$_2$O$_3$ NSs + US treatments within a hypoxic environment to verify that O$_2$ is the substrate of $\cdot$O$_2^-$ and simulate a hypoxic TME in vitro. Much less $\cdot$O$_2^-$ yields were obtained and exhibited in Fig. 3B. Second, the CO yield developed from CO$_2$ reduction was determined qualitatively and quantitatively using myoglobin and gas chromatography (Fig. 3C). Similar to the $\cdot$O$_2^-$ generating a profile, no detectable CO was treated with US, BiOCl NSs, and BiOCl/Bi$_2$O$_3$ NSs alone. On the basis of the excitation of US, the BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs began to catalyze CO$_2$ reduction, and BiOCl/Bi$_2$O$_3$ NSs exhibited efficient CO generation. Enhanced CO yields were observed under the hypoxic environment. Because of the CO$_2$ and O$_2$ reductions being undergone by the excited electrons, there was a certain amount of competition between them. Compared with CO$_2$ reduction, O$_2$ reduction was much easier, so this heterojunction catalyst preferred to catalyze the reaction under normal O$_2$ concentration. Hence, many more excited electrons were saved from catalyzing CO$_2$ reduction under a hypoxic environment.

Third, dithiobisnitrobenzoic acid (DTNB) was applied as a GSH probe to assess the consumption of GSH. Negligible GSH change was obtained using coupling BiOCl/Bi$_2$O$_3$ NSs with US excitation (Fig. 3F), in which a noticeable GSH consumption was observed in Fig. 3F, in which the excited electrons transition across the bandgap to the catalyst CB, while the holes remain in the VB. Then, under the guidance of built-in electric field, the electrons in the CB of Bi$_2$O$_3$ were recombinated with the holes in the VB of BiOCl, leaving more substantial reduction/oxidation potentials within the CB of BiOCl and the VB of Bi$_2$O$_3$. Moreover, the $E^0$ of oxidation of H$_2$O/·OH (2.73 eV) and GSH/GSSG (0.3 eV) was lower than that of the VB of Bi$_2$O$_3$, respectively. The $E^0$ reduction of O$_2$/·O$_2^-$ (−0.28 eV) and CO$_2$/CO (−0.53 eV) was lower than that of the CB of BiOCl.

In practice, defects are inevitable, playing an essential role in the properties of crystals (44, 45). Using vacancy formation energy, we further considered the difficulty of forming point defects in BiOCl and Bi$_2$O$_3$. Figure 4C illustrates the formation energies of all possible point vacancies in BiOCl and Bi$_2$O$_3$. In BiOCl, only one type of Bi, O, and Cl monovacancy could be formed, and the corresponding formation energies were 10.92, 7.29, and 4.68 eV, respectively. At the same time, there were two and three types of Bi and O monovacancy in Bi$_2$O$_3$, with the formation energies ranging from 6.39 to 10.19 eV. Cl@BiOCl had the lowest formation energy, meaning that Cl vacancy was most likely to appear in the BiOCl/Bi$_2$O$_3$ heterojunction. Work function is an essential parameter reflecting the field-emission properties of materials. Density functional theory (DFT), therefore, understands the work function of pristine BiOCl, Cl-defective BiOCl, and pristine Bi$_2$O$_3$. Figure 4D shows the planar-averaged electrostatic potentials of all the considered systems. Moreover, the vacuum and Fermi levels were marked using blue and red lines, respectively. Compared with the BiOCl NSs, the Bi$_2$O$_3$ NSs had a lower vacuum level but a significantly higher Fermi level. The work function of BiOCl and Bi$_2$O$_3$ was found to be 6.68 and 4.81 eV, respectively. However, the phenomenon was reversed after Cl vacancy was introduced into BiOCl. The Fermi level of BiOCl was elevated higher than Bi$_2$O$_3$ (the vacuum energy level was taken as 0 eV) by the Cl vacancy, resulting in a lower work function, and electrons could quickly form BiOCl. When Cl-defective BiOCl was in contact with Bi$_2$O$_3$, electrons migrated spontaneously from BiOCl to Bi$_2$O$_3$ until the Fermi level reached the same, resulting in a built-in electric field, which is the key to Z-scheme electron transmission. The BiOCl is positively charged at the interface, while the Bi$_2$O$_3$ is negatively charged. This result was consistent with the charge transfer from BiOCl to Bi$_2$O$_3$, as revealed by XPS results. As displayed in Fig. 2, Fe 2p, Cl 2p, and O 1s in BiOCl/Bi$_2$O$_3$ NSs were shifted from 0.2 to 0.5 eV toward higher binding energy compared with those of pristine BiOCl NSs. The results demonstrated that the electrons transferred from BiOCl to Bi$_2$O$_3$ upon hybridization due to the difference in their work functions and Fermi levels. Such electron transfer also showed that a built-in electric field was constructed within the interfaces that connected BiOCl to Bi$_2$O$_3$. Moreover, it facilitated the construction of Z-scheme BiOCl/Bi$_2$O$_3$ heterojunction without any redox mediator, efficiently separating the charge carriers and thus promoting the reduction and oxidation reactions catalyzed by separated electrons and holes. The built-in electric field–facilitated Z-scheme charge transfer in the BiOCl/Bi$_2$O$_3$-based heterojunction was presented in Fig. 4E. US irradiation excited the electron-hole pair separation in the VB of BiOCl and Bi$_2$O$_3$ synchronously, in which the excited electrons transition across the bandgap to the catalyst CB, while the holes remain in the VB. Then, under the guidance of built-in electric field, the electrons in the CB of Bi$_2$O$_3$ were recombinated with the holes in the VB of BiOCl, leaving more substantial reduction/oxidation potentials within the CB of BiOCl and the VB of Bi$_2$O$_3$. Moreover, the $E^0$ of oxidation of H$_2$O/·OH (2.73 eV) and GSH/GSSG (0.3 eV) was lower than that of the VB of Bi$_2$O$_3$, respectively. The $E^0$ reduction of O$_2$/·O$_2^-$ (−0.28 eV) and CO$_2$/CO (−0.53 eV) was lower than that of the CB of BiOCl.
Therefore, on the basis of US irradiation, it is feasible and convenient for H\textsubscript{2}O oxidation to produce ·OH and GSH oxidation through the holes in the VB of Bi\textsubscript{2}O\textsubscript{3} and the reducing O\textsubscript{2} and CO\textsubscript{2} to produce ·O\textsubscript{2}\textsuperscript{−} and CO (Fig. 4E). Although the sites of catalytic oxidation reactions (GSH → GSSG and H\textsubscript{2}O → ·OH) were located on Bi\textsubscript{2}O\textsubscript{3}, it does not mean that the occurrence and efficiency of the two oxidation reactions attribute to Bi\textsubscript{2}O\textsubscript{3} alone. The extended lifetime of the excited electrons and holes due to unique Z-schemed electron transport should be the primary reason for efficient catalytic water splitting and GSH oxidation. To further confirm the superiority of Z-scheme BiOCl/Bi\textsubscript{2}O\textsubscript{3} heterojunction, the ·OH production, and GSH oxidation were investigated using Bi\textsubscript{2}O\textsubscript{3} alone as a catalyst based on US irradiation. As shown in fig. S15, without the support of 2D nanostructure and Z-scheme heterojunction, Bi\textsubscript{2}O\textsubscript{3}-based nanocatalyst has very low efficiency in catalyzing GSH oxidation and ·OH generation. It cannot effectively induce tumor cell apoptosis. Although the BiOCl/Bi\textsubscript{2}O\textsubscript{3} NS–based heterojunction has two active centers for catalytic oxidation and reduction, the degree of its catalytic reverse reaction, such as oxidation reactions (·O\textsubscript{2}\textsuperscript{−}/O\textsubscript{2} and CO/CO\textsubscript{2}) or reduction reactions (GSSG/GSH and ·OH/H\textsubscript{2}O), should be very low. There are two main reasons: First, in the TME, compared with O\textsubscript{2}, CO\textsubscript{2}, GSH, and H\textsubscript{2}O, the contents of their redox products such as ·O\textsubscript{2}\textsuperscript{−}, CO, GSSG, and ·OH are much lower. According to the catalytic reaction equilibrium theory, the catalyst preferentially catalyzes the high concentration substrate, so the reversible reaction proceeds in a positive direction as a whole. In addition, ROS, including ·O\textsubscript{2}\textsuperscript{−}, ·OH, and CO, all have a very short lifetime, which will immediately oxidize and damage the surrounding

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**Fig. 3.** Catalytic performance and mechanism of BiOCl NSs and BiOCl/Bi\textsubscript{2}O\textsubscript{3} NSs. The mechanism (A) and performance (B) of ·O\textsubscript{2}\textsuperscript{−} generation with US-excited electrons. The mechanism (C) and performance (D) of CO generation with US-excited electrons. The mechanism (E) and performance (F) of GSH consumption with US-excited holes. The mechanism (G) and performance (H) of ·OH generation with US-excited holes.
tumor cell membrane, organelles, DNA, etc. and quickly consume up. Therefore, the reaction will continue in the positive direction based on equilibrium theory of reversible catalytic reaction.

The adsorption of reactant and catalyst is the first step within a catalytic reaction and determines the possibility and efficiency of the reaction. We estimated the adsorption behavior for each reactant on the corresponding catalyst in this study. The initial distance between the reactant and catalyst was set to be 3.0 Å, and all possible molecular orientations and conformations were evaluated. We analyzed the density of states of pristine Bi$_2$O$_3$- and Cl-defective BiOCl to determine the initial adsorption sites, respectively. As illustrated in fig. S14, the VB maximum of Cl-defective BiOCl has

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Fig. 4. Analysis of the catalytic mechanism of BiOCl/Bi$_2$O$_3$ NSs. (A) Bandgaps and (B) the valance band of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs. (C) The formation energy of different vacancies of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs. (D) The DFT computationally calculates BiOCl, Cl@BiOCl, and Bi$_2$O$_3$. (E) Mechanism of the Z-schmed heterojunction based on BiOCl/Bi$_2$O$_3$ NSs.
Bi characters, indicating that Bi atoms participate in the reduction reactions. In contrast, O characters contribute to the CB minimum of pristine Bi$_2$O$_3$. Thus, the oxidation reactions will occur around the O atoms of Bi$_2$O$_3$. There are three types of O atoms present in the Bi$_2$O$_3$ primitive cell; the Wyckoff position for the O atoms are O1 (0.44, 0.40, 0.50), O2 (0.42, 0.64, 0.45), and O3 (0.25, 0.37, 0.51). The favorite adsorption energies of H$_2$O molecules at the three binding sites were calculated to be $-0.70$, $-0.88$, and $-0.71$ eV. Therefore, position O$_2$ was the most favorable site for oxidizing H$_2$O molecules. The results were consistent with the prediction of hydrophilic properties, establishing that the self-consistent methodology in this work could become self-consistent. After adsorbing to Bi$_2$O$_3$, the length of the O─H bond near the adsorption surface was elevated to 1.021 Å.

The electrons between the O atom and the H atom in the H$_2$O molecule close to Bi$_2$O$_3$ is reduced significantly. Thus, adsorption causes the H$_2$O molecule to dissociate more efficiently, and ·OH is generated. For adsorbing GSH on Bi$_2$O$_3$, the most favorable adsorption configuration with $-3.54$ eV is shown in Fig. 5B. The conformation of GSH underwent some adjustments, mainly reflected in the rotation of the sulfhydryl group toward the surface of the Bi$_2$O$_3$ NS to achieve a stable adsorption state. The bond length of the H─S bond in adsorbed GSH was 0.02 Å longer than the isolated one. The adsorption energy of the GSH-Bi$_2$O$_3$ complex was calculated to be $-3.54$ eV, indicating that the GSH molecule was chemisorbed on the NS. This is due to the three hydrogen bonds and one O─Bi bond that formed between GSH and Bi$_2$O$_3$.

Among them, the hydrogen bond formed between the sulfhydryl group and Bi$_2$O$_3$ makes the O atom near the sulfhydryl group accepts 0.76 electrons from the GSH molecule. The results indicate that chemical adsorption made the GSH molecule anchors the sulfhydryl group on the Bi$_2$O$_3$ NS, reducing its consumption of the ROS molecules. In addition, the adsorption process also provides a prerequisite for Bi$_2$O$_3$ to catalyze GSH and generate GSSG, conducive to ROS accumulation within the TME. For the O$_2$ adsorption system, the Bader charge analysis was used to obtain the specific charges of the O$_2$ molecule and BiOCl. As shown in Fig. 5C, the electrons flowed from the BiOCl to O$_2$ during the adsorption process. Furthermore, the obtained adsorption energy is $-0.06$ eV, allowing the O$_2$ molecule to escape after accepting electrons from BiOCl. Dissociative adsorption of CO$_2$ after being exposed to Cl-defective BiOCl is displayed in Fig. 5D: One of the C─O bonds breaks, and the dissociated O atom forms a chemical bond with two Bi atoms of BiOCl. Meanwhile, one CO molecule is physisorbed on the BiOCl NS through the van der Waals force. The results further support the catalytic activity for CO$_2$ reduction on the BiOCl NSs.

**Antitumor strategy and biocompatibility in vitro**

Next, the in vitro catalytic performance and the antitumor effect of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs were investigated. The biocompatibility of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs with normal cells, including human embryonic kidney cells (HEK293), normal human liver cells (HL-7702), and normal human mammary epithelial cells (MCF-10A) were detected through the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) assay. Moreover, the cytotoxicity of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs with or without PEGylation was determined to confirm the function of PEGylation. As shown in Fig. 6A and fig. S16, the BiOCl/Bi$_2$O$_3$ NSs exhibited concentration-dependent cytotoxicity against the detected normal human cells before PEGylation. However, BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs exhibited good biocompatibility and safety toward normal cells after PEGylation, demonstrating the notable role of PEGylation in nanomedicine. Next, specific cytotoxicity to cancer cells of PEGylated NSs was evaluated. In contrast, the PEGylated BiOCl/Bi$_2$O$_3$ NSs showed specific cytotoxicity toward cancer cells (Fig. 6B for HepG2 and fig. S17 for MCF-7). Two potential factors contributed to the cytotoxicity of BiOCl/Bi$_2$O$_3$ NSs: The Fenton-like reaction catalyzed by BiOCl/Bi$_2$O$_3$ NSs and GSH absorption on BiOCl/Bi$_2$O$_3$ NSs, synergistically inducing intracellular redox equilibrium disruption. The Fenton-like effect of BiOCl/Bi$_2$O$_3$ NSs with Cl defect was investigated through calculation and experiments to analyze the mechanism of the specific cytotoxicity to tumor cells. At first, to understand the behavior of overexpressed H$_2$O$_2$ in the TME after the heterojunction catalyst treatment, the “Gibbs free energy change ($\Delta G$) of the Fenton-like reaction was determined using the following pathway

$$^*H_2O_2 \rightarrow ^*OH + ^.-OH \quad (a)$$

$$^*OH \rightarrow ^+.-OH \quad (b)$$

where $^*OH$ stands for the catalyst-hydroxide pair.

The free energy of the Fenton-like reaction is illustrated in fig. S18. The total energy required for a Fenton-like response is 2.31 eV, independent of the catalyst species. For Bi$_2$O$_3$ and BiOCl, one H$_2$O$_2$ molecule undergoes step (a) to generate one $^.-OH$ molecule with a
Fig. 6. The biocompatibility and cytotoxicity of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs. (A) The biocompatibility of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs for HEK293, HL-7702, and MCF-10A. (B) The cytotoxicity of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs–based treatments for HepG2. (C) The live/dead staining images of HepG2 cells under various treatments. Scale bar, 100 μm. (D) Apoptosis behaviors of HepG2 cells under different treatments were detected using flow cytometry. (E) The intracellular ROS generation, (F) CO generation, (G) early DNA damage, and (H) mitochondrial membrane potential change of HepG2 cells under various treatments. (I) The intracellular ROS generation, CO generation, early DNA damage, and (J) the mitochondrial membrane potential change of HepG2 cells under different treatments were detected through flow cytometry. The nuclei were stained with 4′,6-diamidino-2-phenylindole (DAPI; blue). The intracellular ROS were stained with DHE (green). The intercellular CO was stained with the FL-CO-1 CO probe (yellow). The γH2AX foci per nucleus were stained with an anti-γH2AX antibody (red). The mitochondrial membrane potential loss was stained by JC-1 (green). The live and dead cells were stained with calcein AM (green) and propidium iodide (PI) (red). Scale bars, 50 μm.
ΔG of 1.17 and 2.22 eV, respectively, and then proceeds to release one ·OH molecule with a ΔG of 1.13 and 0.08 eV. Thus, Fenton-like reactions with Bi2O3 and BiOCl as catalysts could be endothermic and nonspontaneous. Although the ΔG of step (b) was raised to 3.63 eV, the ΔG of the Cl-defective BiOCl catalytic system was reduced to −1.33, implying a marked reversal of the spontaneity of step (a). Therefore, we hypothesize that the Cl defect leads to the spontaneous partial Fenton-like reaction, which mediates tumor cytotoxicity. Besides, the ·OH production of prepared BiOCl/Bi2O3 NSs was also detected. As shown in figs. S19 and S20, there was no ·OH generation based on reactions between BiOCl or Bi2O3 with H2O2. However, a certain amount of ·OH was produced using the Fenton-like effect of BiOCl/Bi2O3 NSs with Cl-defective BiOCl, consistent with the computer simulation.

In addition, coupling BiOCl NSs with US irradiation, the O2 was catalyzed to ·O2−. Moreover, CO2 could be catalyzed to CO using the US-excited electrons of BiOCl NSs due to the hypoxic micro-environment. Z-scheme BiOCl/Bi2O3 NSs-based interplanar heterojunction exposed to US irradiation exhibited the highest cytotoxicity to cancer cells. More than 85% of tumor cells were dead with BiOCl/Bi2O3 NSs (100 μg/ml) and 5 min of US irradiation (Fig. 6B). The leading cause of this excellent antitumor performance of BiOCl/Bi2O3 NSs should be attributed to the extended catalytic selectivity, including two reductions (O2/·O2− and CO2/CO) and two oxidation (H2O/OH and GSH/GSSG) reactions. The extended catalytic selectivity of BiOCl/Bi2O3 NSs effectively avoids the TME limitation and synergistically induces tumor apoptosis. Moreover, the cytotoxicity of different treatments to the cancer cell and their apoptosis behaviors were evaluated using fluorescent staining and flow cytometry. The live/dead fluorescent staining and flow cytometry exhibited the excellent antitumor performance of BiOCl/Bi2O3 NSs coupling with US irradiation (Fig. 6, C and D). Some rescue experiments were carried out, including adding GSH or vitamin (Vc) as a ROS inhibitor to verify the antitumor mechanism and the catalytic therapy of BiOCl/Bi2O3 NSs. As shown in fig. S21, after adding GSH and Vc, the cell viabilities were improved under the treatment of BiOCl/Bi2O3 NSs, BiOCl NSs + US, and BiOCl/Bi2O3 NSs + US, further demonstrating the excellent antitumor mechanism of BiOCl/Bi2O3 NSs through catalytic therapy. Next, the properties of BiOCl/Bi2O3 NSs interplanar heterojunction-mediated catalytic effects were investigated on a cellular level using immunofluorescence staining inside the HepG2 cells. Figure 6 (E to H) demonstrated the immunofluorescence images of intracellular ROS content (green), CO generation (yellow), early DNA damage (pink), and mitochondrial membrane injury (green). Excessive ROS directly damages the DNA double strand in the nucleus. In contrast, excessive CO in the cell will directly change the polarization potential of the mitochondrial membrane, causing early DNA damage and mitochondrial membrane damage. Because of the high biocompatibility of BiOCl NSs, on the basis of the control and US group, BiOCl NS treatment exhibited a negligible chance of the above indicators. Because of the Fenton-like reaction catalyzed by BiOCl/Bi2O3 NSs and GSH absorption, the intracellular ROS content was elevated by being treated with BiOCl/Bi2O3 NSs, leading to evident early DNA damage. Coupling with US irradiation, BiOCl NSs could catalyze O2 reduction and a small amount of CO2 reduction, generating ·O2− and CO (Fig. 6, E and F). Subsequently, the early DNA damage and polarization potential of the mitochondrial membrane responded accordingly in Fig. 6G within 6 hours. For BiOCl/Bi2O3 NSs + US treatment, large amounts of ROS and CO contents were observed in Fig. 6 (E and F) due to the omnipotent and synergistic catalytic effects, leading to extensive DNA and mitochondrial membrane damages. Moreover, the intracellular ROS and CO generation, early DNA damage, and mitochondrial membrane potential change were further analyzed by flow cytometry (Fig. 6, I to J), which further demonstrated the specific and efficient antitumor performance based on BiOCl/Bi2O3 NSs coupling with US irradiation. For the flow cytometry analysis of mitochondrial membrane potential change under different treatments (Fig. 6J), the treatments of US and BiOCl NSs did not change the membrane potential of cancer cells, and 5,5′,6,6′-Tetram chloro-1,1′,3,3′-tetraethyl-imidacarbocyanine (JC-1) enters the mitochondria through the polarity of the mitochondrial membrane and forms a polymer emitting red fluorescence due to the increase in concentration. Because of the generation of ROS treated by BiOCl/Bi2O3 NSs inducing apoptosis, the mitochondrial transmembrane potential depolarizes, JC-1 is released from the mitochondria, and the concentration decreases, reversing to the monomer form emitting green fluorescence. Moreover, BiOCl/Bi2O3 NSs + US treatment mediated much more cell apoptosis, which emitted more green fluorescence. Therefore, changes in mitochondrial membrane potential can be detected qualitatively (shift of cell population) and quantitatively (fluorescence intensity of cell population) by detecting green and red fluorescence.

**Biodistribution and antitumor strategy in vivo**

The in vivo therapeutic performances of BiOCl/Bi2O3 NSs were investigated. At first, the biodistribution of BiOCl/Bi2O3 NSs was determined through intravenous injection of Cy5.5-loaded BiOCl/Bi2O3 NSs to the HepG2 xenograft tumor model. Figure 7A demonstrated the biodistribution of BiOCl/Bi2O3 NSs. Figure 7B showed the fluorescent images of the major organs and tumor after 24 hours after injection, indicating a specific accumulation of nanoscale BiOCl/Bi2O3 NSs at the tumor site due to enhanced permeability and retention effect (46–48). In addition to fluorescence imaging, BiOCl/Bi2O3 NSs could also be computed tomography (CT) imaging agents based on the high x-ray attenuation coefficient of Bi. As shown in Fig. 7 (C and D), BiOCl/Bi2O3 NSs have a good linear relationship between concentration and the Hounsfield units (HU) value. Then, the in vivo CT imaging potential of BiOCl/Bi2O3 NSs was investigated by intravenously injecting them into HepG2 tumor-bearing mice. As observed in Fig. 7E, the results showed that enhanced contrast was discerned in the HepG2 tumor from coronal CT images, with HU values increasing from 7.0 to 93.2, at 24 hours following intravenous injection of BiOCl/Bi2O3 NSs into HepG2 tumor–bearing nude mice. Therefore, BiOCl/Bi2O3 NSs could be an efficient CT imaging agent during in vivo cancer diagnosis. Pharmacokinetic analysis (fig. S22) depicted the long circulation time of BiOCl/Bi2O3 NSs. In addition, an inductively coupled plasma (ICP) emission spectrometer was applied to precisely analyze the in vivo biodistribution of BiOCl/Bi2O3 NSs. As shown in fig. S23, the concentration of NSs inside the major organs and tumors over 24 hours was exhibited, in which an excellent tumor accumulation of the prepared NSs was also depicted. However, the biodistribution of BiOCl/Bi2O3 NSs, especially in the tumor, is inconsistent between fluorescent imaging and ICP. The degradation of Cy5.5 catalyzed by BiOCl/Bi2O3 NSs mediated the Fenton-like effect in the entire TME (fig. S24).

The in vivo therapeutic performance of BiOCl NSs and BiOCl/Bi2O3 NSs was carried out considering the high tumor accumulation.
Fig. 7. In vivo imaging, biodistribution, and antitumor study of the BiOCl/Bi$_2$O$_3$ NSs. (A) In vivo fluorescence images of nude mice at different time points after intravenous injection using Cy5.5-labeled NSs and ex vivo fluorescence images of tumor and major organs at 24 hours after injection. (B) Semiquantitative biodistribution of Cy5.5-labeled NSs in nude mice was detected using the average fluorescence intensity of tumors and the major organs per gram. F.L., Fluorescein. (C) The CT images of BiOCl/Bi$_2$O$_3$ NSs with different concentrations. (D) The CT values (HU) of BiOCl/Bi$_2$O$_3$ NSs. (E) Time-dependent whole-body CT imaging of the tumor-bearing mouse after intravenous injection of NSs. The green circle indicates a tumor. (F and G) Tumor growth curves under different treatments. (H) Mouse survival curves under various treatments. (I) Tumor images after 14 days of various treatments. (J) The cure mechanism of BiOCl/Bi$_2$O$_3$ NSs through US irradiation.
HepG2 tumor–bearing mice were randomly separated into six groups and received different treatments: treatment 1, saline; treatment 2, US; treatment 3, BiOCl NSs; treatment 4, BiOCl/Bi$_2$O$_3$ NSs; treatment 5, BiOCl NSs + US; and treatment 6, BiOCl/Bi$_2$O$_3$ NSs + US. The BiOCl NS and BiOCl/Bi$_2$O$_3$ NS dose intravenously injected into mice in treatments 3, 4, 5, and 6 was 4 mg/kg. The US treatment (1 MHz, 0.8 W cm$^{-2}$, 50% duty cycle) in treatments 5 and 6 were performed 24 hours after injection of NSs (fig. S25). As shown in Fig. 7 (F and G), no significant tumor growth inhibition was observed in control (treatment 1), US only (treatment 2), and BiOCl NSs (treatment 3). However, to a certain extent, tumor growth inhibition was exhibited in BiOCl/Bi$_2$O$_3$ NSs alone treated mice (treatment 4). It was attributed to the Fenton-like reaction and absorption of GSH by BiOCl/Bi$_2$O$_3$ NSs, inducing intracellular REDOX imbalance. Treatment 5 provided a better therapeutic effect than treatment 3, indicating the advantages of US irradiation for triggering O$_2$ and CO$_2$ reduction. Treatment 6 demonstrated extreme inhibition of tumor growth due to the omnipotent and synergistic catalytic effects through BiOCl/Bi$_2$O$_3$ NS–based interplanar heterojunction with expansive catalytic selectivity. Therefore, the tumors treated with BiOCl/Bi$_2$O$_3$ NSs coupling with US irradiation were nearly eliminated. The dissected tumors (Fig. 7I) provided direct evidence for the therapeutic outcomes of interplanar heterojunction–mediated catalytic therapy. Correspondingly, the BiOCl/Bi$_2$O$_3$ NSs coupled with US treatment were associated with a significantly high survival rate (Fig. 7H). In addition, no noticeable side effects were observed based on different treatments (fig. S26).

**Antitumor mechanism and biocompatibility analysis in vivo**

To further confirm the specific targeted antitumor mechanism and biocompatibility of BiOCl/Bi$_2$O$_3$ NS–based catalytic therapy, the histological analyses through the hematoxylin and eosin (H&E) staining, CO contents through Spiro[isobenzofuran-1(3H),9′-[9H]-xanthen]-3-one (COP-1), DNA damage levels through γ-H2AX staining, and apoptosis levels using cleaved caspase-3 (C-CAS3) staining were undergone in vivo. As depicted in Fig. 8, although partially intravenously injected BiOCl/Bi$_2$O$_3$ NSs were accumulated within other organs and nearly no CO generation, DNA damage, cell apoptosis, and the destruction of normal organs (including heart, liver, spleen, lung, and kidney) were demonstrated without direct US irradiation. In the histological analyses of the H&E staining image of the tumor, there was extensive destruction of the tumor tissue (Fig. 8A). As shown in Fig. 8B, a large amount of CO was produced through BiOCl/Bi$_2$O$_3$ NSs coupling with US irradiation. Moreover, many DNA damages and apoptosis of cancer cells were observed using the immunofluorescence staining images of tumors treated with BiOCl/Bi$_2$O$_3$ NSs + US (Fig. 8C). The current in vivo analysis further established that the intrinsic interplanar heterojunction of BiOCl/Bi$_2$O$_3$ NS–based catalytic therapy mediated an efficient, targeted cancer therapy by improving the REDOX potential energy and extending substrate selectivity. Moreover, it also guarantees an excellent biosafety for normal organs.

Considering that the in vivo toxicity of the materials has an essential role in translation from bench to practical applications, we set forth to evaluate the toxicity of BiOCl/Bi$_2$O$_3$ NSs. Immune analysis, histology examination, and hematology assay were additionally detected. Blood examination was carried out at 1, 7, and 14 days after intravenous injection of BiOCl/Bi$_2$O$_3$ NSs for the histology and hematology assay. As shown in fig. S27, no statistically significant differences in the levels of aspartate aminotransferase (AST), lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase (ALT), or blood urea nitrogen (BUN) were detected in mice receiving BiOCl/Bi$_2$O$_3$ NSs than the control mice. For immune analysis, the amount of interleukin 6 (IL-6), interferon-γ (IFN-γ), tumor necrosis factor–α (TNF-α), and IL-12 + P40 were measured in serum samples from mice at 2 and 24 hours after intravenous injection of BiOCl/Bi$_2$O$_3$ NSs. As exhibited in fig. S28, the cytokine levels from the BiOCl/Bi$_2$O$_3$ NS–treated group revealed no noticeable difference compared with the control group. It also established that the prepared BiOCl/Bi$_2$O$_3$ NSs showed good biocompatibility and biosafety in vivo.

**DISCUSSION**

Chemotherapy is the primary choice for most cancer patients due to its broad spectrum and reliable curative effect. However, the clinical use of small-molecule chemotherapy drugs depicts some problems, including poor selectivity, low bioavailability, and obvious toxic side effects (49–52). Catalytic therapy converts the substrate within the TME into effective therapeutic drugs by addressing the specific internal microenvironment or exogenous stimulation of the tumor site. Moreover, it uses the in situ catalytic reaction in the tumor initiated by nontoxic or low toxic nanocatalysts to achieve tumor cell–specific oxidative damage and cell death without obviously affecting the normal tissue (7). However, the clinical application of catalytic therapy has the following two problems: (i) The traditional nanocatalysts have weak catalytic power due to the fast recombination rate of excited electrons and holes; (ii) the types and concentrations of substrates catalyzing in the microenvironment are minimal, leading to low catalytic efficiency.

Our work creates an interplanar heterojunction based on 2D BiOCl/Bi$_2$O$_3$ NSs capable of prolonging the life span of electrons and holes and extending substrate selectivity. Moreover, its proof-of-concept application becomes a new heterojunction-based catalytic therapy platform for effective cancer therapy. First, an intelligent edge modification was developed to integrate interplanar heterojunction synthesis and exfoliate the ultrathin NSs. After PEGylation, the engineering BiOCl/Bi$_2$O$_3$ NSs functionalized through a characteristic interplanar heterojunction to efficiently catalyze O$_2$ and CO$_2$ reduction and H$_2$O and GSH oxidation under US irradiation. In the interplanar heterojunction BiOCl/Bi$_2$O$_3$ NSs, BiOCl and Bi$_2$O$_3$ parts with different Fermi levels and energy band structures contacting each other induce charges to redistribute at their interfaces by the aligning Fermi levels. Thus, it mediates the construction of a built-in electric field in its interface. Under US irradiation, the US-excited electrons at the CB of Bi$_2$O$_3$ were combined with the holes at the VB of BiOCl guided by the built-in electric field at their interface, leaving more substantial reduction/oxidation potentials of separated electrons and holes at the CB of BiOCl and the VB of Bi$_2$O$_3$. Meanwhile, a Schottky barrier was formed because of band bending at their interface, preventing the electron flow from BiOCl to Bi$_2$O$_3$ and enhancing their Z-schmed charge transfer. Hence, a built-in electric field and Schottky barrier facilitated a Z-schmed catalytic mechanism. The holes on the VB of Bi$_2$O$_3$ with high oxidation potential had a remarkable ability to oxidize H$_2$O and GSH, generating -OH and GSSG. Meanwhile, the electrons on the CB of BiOCl with high reduction potential showed a notable ability to reduce O$_2$ and CO$_2$, developing -O$_2$ and CO. The obtained BiOCl/Bi$_2$O$_3$ NSs...
**Fig. 8. BiOCl/Bi$_2$O$_3$ NSs based on specific targeted therapy and biocompatibility.** (A) H&E staining images. Scale bars, 500 μm. (B) CO staining images and (C) immunofluorescent images of the major organs and tumors obtained from mice through BiOCl/Bi$_2$O$_3$ NSs + US treatment. Scale bars, 500 μm. The apoptotic cells were stained using the apoptosis marker C-CAS3 (green), the damaged DNA was stained with γH2AX foci (red), the generated CO was stained with COP-1 (orange), and the nucleus was stained with DAPI (blue).
with highly efficient catalytic effects exhibited excellent anticancer performance both in vitro and in vivo.

The overall objective of this study was to understand whether a 2D interplanar heterojunction platform could prolong the life span of electronics and holes, extend substrate selectivity, and promote tumor catalytic therapy. As a test case, we selected HepG2 subcutaneous transplanted tumor as the tumor model. The data showed that BiOCl/Bi2O3 NS–based interplanar heterojunction successfully catalyzed the O2 and CO2 reduction and H2O and GSH oxidation under US irradiation in vitro and HepG2 subcutaneous transplanted tumors. Therefore, this study not only defines an excellent strategy for intelligent synthesizing 2D ultrathin interplanar heterojunction. It also solves the fundamental problem that limits the efficiency of catalytic therapy, providing a specific incentive to make valuable contributions in other possible fields in the future. In addition, more robust formulation strategies could be required to scale up biocompatibility of BiOCl NSs and BiOCl/Bi2O3 NSs. First, BiOCl/Bi2O3 composite was within probe sonication–assisted liquid exfoliation in water for 12 hours. After exfoliation, the unexfoliated BiOCl/Bi2O3 was removed through centrifugation at 3000 rpm for 5 min. Afterward, the supernatant was centrifuged at 12,000 rpm for 5 min, and the as-prepared BiOCl/Bi2O3 NSs were stored at 4°C.

**PEGylation of BiOCl NSs and BiOCl/Bi2O3 NSs**

NSs were modified with PEG(5k)-NH2 to improve the stability and biocompatibility of BiOCl NSs and BiOCl/Bi2O3 NSs. First, PEG(5k)-NH2 (10 mg) was added to NS suspension, and then the suspension was ultrasonicated and stirred for 30 min and 12 hours, respectively. The mixture was washed thrice by centrifugation at 2500 rpm (4°C) for 30 min to remove the unattached PEG(5k)-NH2. Afterward, the PEGylated NSs were resuspended in PBS and stored at 4°C for future use.

**Characterization**

SEM (JSM-6700F, JEOL, Japan), TEM (JEM-2100UHR, JEOL, Japan), and atomic force microscopy (AFM; FastScan Bio, Germany) were used to analyze the microstructure and morphology of prepared BiOCl NSs and BiOCl/Bi2O3 NSs. Moreover, XPS (ESCALAB 250Xi, Oxford, UK) evaluated the elementary composition and chemical structures of NSs. At room temperature, ultraviolet-visible (UV-vis)–near-infrared spectra of NSs were recorded using an Infinite M200 PRO spectrophotometer.

**Modeling and calculation details**

We used the VASP code to perform the whole spin-polarized DFT calculations. The convergence threshold was set to be $1 \times 10^{-7}$ Ha in energy and 0.01 Ha/Å in force. The Perdew-Burke-Ernzerhof formalism of the generalized gradient approximation dealt with the electron exchange–correlation term. The cutoff energy was set to be 500 eV for the plane-wave expansion. The projector augmented wave approach was adopted to handle the electron-ion interactions. The DFT–D2 method of Grimme was considered the van der Waals interactions. The $3 \times 3 \times 1$ and $2 \times 2 \times 1$ supercells of BiOCl and Bi2O3 were repeated periodically in the x-y plane. A vacuum region of 15 Å was added to eliminate interlayer interference. The Brillouin zone integration was sampled through $4 \times 4 \times 1$ and $4 \times 5 \times 1$ Monkhorst-Pack k-points meshes for BiOCl and Bi2O3, respectively.

The adsorption of H2O on BiOCl and Bi2O3 was studied more than the hydrophilic properties of the two materials. The initial binding sites for H2O were searched through Monte Carlo annealing simulations, which allowed a rotatable molecule to randomly translate on the surface of the substrate until the local energy minima were reached.
The following equation calculated the vacancy formation energies of defective BiOCl and Bi$_2$O$_3$

$$E_{\text{formation}} = E_{\text{defective}} + E_{\text{atom}} - E_{\text{pristine}}$$

Here, $E_{\text{formation}}$ is the vacancy formation energy; $E_{\text{defective}}$ is the total energy of BiOCl or Bi$_2$O$_3$; $E_{\text{atom}}$ is the energy of an isolated Bi, O, or Cl atom; and $E_{\text{pristine}}$ is the total energies of BiOCl or Bi$_2$O$_3$.

The work function ($\Phi$) was calculated to determine the minimum energy required for an electron to escape from the surface of a material to the vacuum as follows

$$\Phi = E_{\text{vac}} - E_F$$

where $E_{\text{vac}}$ and $E_F$ represent the electrostatic potential of vacuum and Fermi levels, respectively.

The adsorption energy ($E_{\text{ad}}$) per H$_2$O molecule was calculated as follows

$$E_{\text{ad}} = E_{\text{com}} - E_{\text{sub}} - E_{\text{H}_2\text{O}}$$

where $E_{\text{com}}$ and $E_{\text{sub}}$ are the energy of BiOCl or Bi$_2$O$_3$ with or without an H$_2$O molecule, respectively. $E_{\text{H}_2\text{O}}$ is the energy for one isolated H$_2$O molecule. A negative magnitude $E_{\text{ad}}$ indicated an exothermic adsorption process.

Bader’s charge analysis was performed to estimate the charge transfer ($\Delta Q$) between the substrate and the molecule. $\Delta Q$ can be defined as

$$\Delta Q = Q_1 - Q_0$$

where $Q_0$ and $Q_1$ are the number of electrons occupied by each substrate before and after adsorption. A negative magnitude $\Delta Q$ infers that the electrons flow from the substrate to the molecule.

**GSH degradation in vitro**

First, a final 0.1 mM concentration of GSH solution was mixed with DTNB with a final 0.2 mg/ml concentration. Then, the above solution was treated with the following treatments: (i) US, (ii) BiOCl NSs, (iii) BiOCl/Bi$_2$O$_3$ NSs, (iv) BiOCl NSs + US, and (v) BiOCl/Bi$_2$O$_3$ NSs + US. The final concentration of NSs was 0.1 mg/ml. US treatment conditions were 1 MHz, 0.8 W cm$^{-2}$, and 50% duty cycle. During the 30-min reaction, the absorbance of DTNB was detected every 5 min using the UV-vis spectroscopy.

**·OH generation in vitro**

MB was applied as a ·OH indicator for detecting the generation of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs. The ·OH production performance was seen in the following groups: (i) US, (ii) BiOCl NSs, (iii) BiOCl/Bi$_2$O$_3$ NSs, (iv) BiOCl NSs + US, and (v) BiOCl/Bi$_2$O$_3$ NSs + US. The final concentration of NSs was 0.1 mg/ml. US treatment conditions were 1 MHz, 0.8 W cm$^{-2}$, and 50% duty cycle. During the 30-min reaction, the absorbance MB was recorded every 5 min through UV-vis spectroscopy.

**·O$_2^-$ generation in vitro**

The ·O$_2^-$ generating ability of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs within the suspension was evaluated through the probe of DPBF. The ·O$_2^-$ production performance was detected through the following group: (i) US, (ii) BiOCl NSs, (iii) BiOCl/Bi$_2$O$_3$ NSs, (iv) BiOCl NSs + US, (v) BiOCl/Bi$_2$O$_3$ NSs + US, (vi) BiOCl NSs + US-hypoxia, and (vii) BiOCl/Bi$_2$O$_3$ NSs + US-hypoxia. The final concentration of NSs was 0.1 mg/ml. US treatment conditions were 1 MHz, 0.8 W cm$^{-2}$, and 50% duty cycle. During the 30-min reaction, the DPBF absorbance was recorded every 5 min through UV-vis spectroscopy.

**CO generation in vitro**

The CO-generating ability of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs was evaluated in the suspension using a tandem gas chromatograph (Agilent GC-7890) by observing and comparing the chromatographic peaks with various standards. The CO production performance was detected with the following group: (i) US, (ii) BiOCl NSs, (iii) BiOCl/Bi$_2$O$_3$ NSs, (iv) BiOCl NSs + US, (v) BiOCl/Bi$_2$O$_3$ NSs + US, (vi) BiOCl NSs + US-hypoxia, and (vii) BiOCl/Bi$_2$O$_3$ NSs + US-hypoxia. The final concentration of NSs was 0.1 mg/ml. US treatment conditions were 1 MHz, 0.8 W cm$^{-2}$, and 50% duty cycle.

**Biocompatibility of NSs in vitro**

The biocompatibility of BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs was tested with normal human and cancer cell lines, including the human embryonic kidney cells (HEK293), normal human liver cells (HL-7702), normal human mammary epithelial cells (MCF-10A), human breast cancer cells (MCF-10A), human breast cancer cells (MCF-7), and human liver cancer cells (HepG2). The cells were seeded into two 96-well plates at a density of 5000 cells in every well and incubated for 24 hours. Afterward, BiOCl NSs and BiOCl/Bi$_2$O$_3$ NSs (0 to 150 μg/ml) were added to the above-mentioned normal cells and coincubated for another 24 hours. Last, cell viabilities were detected using the MTT cell viability assay.

**Intracellular ROS generation**

The ROS probe, dihydroethidium (DHE), tested the intracellular generation of ROS through confocal laser scanning microscopy (CLSM) imaging. HepG2 cells were seeded into 96-well plates for 24 hours (37°C, 5% CO$_2$). Then, the cells were treated with the following: (i) US, (ii) BiOCl NSs, (iii) BiOCl/Bi$_2$O$_3$ NSs, (iv) BiOCl NSs + US, and (v) BiOCl/Bi$_2$O$_3$ NSs + US. The final concentration of NSs was 0.1 mg/ml. The condition for US treatment was 1 MHz, 0.8 W cm$^{-2}$, and 50% duty cycle, for 5 min. Afterward, DHE with the final 0.2 μM concentration was added to the above-treated cells. After 1-hour incubation, the treated HepG2 cells were washed thrice with PBS. Last, the intracellular ROS concentration was determined using CLSM and flow cytometry.

**Intracellular CO generation**

The CO probe, COP-1, tested the intracellular generation of CO through CLSM imaging. The HepG2 cells were seeded into 96-well plates for 24 hours (37°C, 5% CO$_2$). Then, the cells were treated using the following: (i) US, (ii) BiOCl NSs, (iii) BiOCl/Bi$_2$O$_3$ NSs, (iv) BiOCl NSs + US, and (v) BiOCl/Bi$_2$O$_3$ NSs + US. The final concentration of NSs was 0.1 mg/ml. The US treatment condition was 1 MHz, 0.8 W cm$^{-2}$, and 50% duty cycle, for 5 min. After that, a CO probe with the final 1 μM concentration was added to the above-treated cells. After 0.5-hour incubation, the treated HepG2 cells were washed three times with PBS. Last, the intracellular ROS concentration was determined using CLSM and flow cytometry.
Intracellular DNA damage
The phosphorylated H2AX is the marker of early DNA damage. Cellular phosphorylated H2AX (γH2AX) under different treatments were determined using Alexa Fluor 647 mouse anti-H2AX (pS139) antibody to characterize the early DNA damage. Briefly, HepG2 cells were seeded into the 96-well plates for 24 hours (37°C, 5% CO2). Then, the cells were treated as follows: (i) US, (ii) BiOCl NSs, (iii) BiOCl/Bi2O3 NSs, (iv) BiOCl NSs + US, and (v) BiOCl/Bi2O3 NSs + US. The final concentration of NSs was 0.1 mg/ml. The condition for US treatment was 1 MHz, 0.8 W cm−2, and 50% duty cycle, for 5 min. Then, the cells were stained using a 5 μl per test of Alexa Fluor 647 mouse anti-H2AX (pS139) antibody based on the manufacturer’s instructions. After incubating for 30 min, the treated HepG2 cells were washed thrice with PBS. Last, the cellular phosphorylated H2AX (γH2AX) was evaluated with CLSM and flow cytometry.

Detection of intracellular mitochondrial membrane potential
A mitochondrial membrane potential assay kit with JC-1 was used to detect the mitochondrial membrane potential. HepG2 cells were seeded into 96-well plates for 24 hours (37°C, 5% CO2). Then, the cells were treated with the following: (i) US, (ii) BiOCl NSs, (iii) BiOCl/Bi2O3 NSs, (iv) BiOCl NSs + US, and (v) BiOCl/Bi2O3 NSs + US. The final concentration of NSs was 0.1 mg/ml. The condition for US treatment was 1 MHz, 0.8 W cm−2, and 50% duty cycle, for 5 min. Then, 1 ml of JC-1 staining solution was added to each well, mixed, and incubated at 37°C for 20 min. Then, the supernatant was aspirated and washed twice using the JC-1 staining buffer (1×). Last, the mitochondrial membrane potential was determined with CLSM and flow cytometry.

Antitumor therapy in vitro
The MCF-7 and HepG2 cells were incubated into 96-well plates for 24 hours (37°C, 5% CO2). Subsequently, the old culture medium was replaced with a fresh one and treated within the following groups: (i) BiOCl NSs, (ii) BiOCl/Bi2O3 NSs, (iii) BiOCl NSs + US, and (iv) BiOCl/Bi2O3 NSs + US. The final concentration of NSs was 0.1 mg/ml. The condition for US treatment was 1 MHz, 0.8 W cm−2, and 50% duty cycle, for 5 min. The US treatment was carried out after NSs treated for 12 hours and removed from plates using PBS after washing thrice. Last, cell viabilities were determined using MTT assay (Life Technologies) based on the manufacturer’s instructions. In addition, the flow cytometry was applied to analyze the cell apoptosis under different treatments.

Pharmacokinetic study
To understand the pharmacokinetics of BiOCl/Bi2O3 NSs in vivo, 200 μl of Cy5.5-PEG-NH2-modified BiOCl/Bi2O3 NSs was intravenously injected into healthy C57BL/6 mice, and the dose of BiOCl/Bi2O3 NSs was 4 mg/kg. Afterward, 20 μl of blood was taken from the mice at different time intervals. Then, the fluorescence intensity of Cy5.5-PEG-NH2-modified BiOCl/Bi2O3 NSs in blood was detected through a BioTek microplate reader.

Xenograft tumor model
All animal experiments were conducted on the basis of the Guidelines for the Care and Use of Laboratory Animals of Tianjin University. The experiments were approved by the Animal Ethics Committee of the Tianjin University Laboratory Animal Center (Tianjin, China). This study used 6- to 8-week-old female Balb/c nude mice and female C57BL/6 mice (purchased from Tianjin Medical Laboratory Animal Center, Tianjin, China). Five mice were kept in one cage with free access to food and water. The cages with five mice per cage were placed inside conventional rooms with controlled photoperiod (07:00 to 19:00 white light, ± 200 lux at 1 m above the floor; 19:00 to 07:00 red light, ± 5 lux at 1 m), temperature (20°C to 22°C), relative humidity (50 to 60%), and ventilation (15 air changes hour−1). The HepG2 tumor models were established using the subcutaneous cell injection (2 × 106 cells in 100 μl of serum-free cell medium) within the right hind leg of Balb/c nude mice. When the size of the tumors reached about 100 mm3, the mice were divided randomly into different groups for various treatments.

Fluorescence imaging and biodistribution study in vivo
BiOCl/Bi2O3 NSs with Cy5.5-PEG-NH2 was intravenously injected into the HepG2 tumor–bearing mice through the tail vein. Maestro2 in vivo imaging system detected the fluorescence at different times after injection. Subsequently, the major organs (e.g., heart, liver, spleen, lung, and kidney) and tumors of mice were obtained and imaged after the mice were killed through cervical dislocation. The fluorescence intensity of Cy5.5 was measured using ImageJ to depict the accumulation of NSs in tumors and organs. Then, the intensity values were divided using the weight (grams) of each organ. For accurate quantitative determination of the biodistribution of BiOCl/Bi2O3 NSs, the HepG2 tumor–bearing mice were intravenously injected with BiOCl/Bi2O3 NSs (200 μl per mouse; dosage, 5 mg kg−1). The control group was intravenously injected with 200 μl of PBS. The mice were euthanized, and the major organs, including heart, liver, spleen, lungs, kidney, and tumor, were collected after 24 hours after injection. Those organs were added with 10 ml of aqua regia and heated to 200°C for 3 hours. After being cooled to room temperature, each sample was diluted to 10 ml using deionized water and passed through a 0.22-μm filter to remove undigested tissues. The amount of Fe was measured using ICP atomic emission spectrometry.

CT imaging in vivo
A small mouse x-ray CT (Gamma Medica-Ideas) was used to in vivo CT imaging. Imaging parameters were as follows: field of view, 80 mm by 80 mm; slice thickness, 154 μm; effective pixel size, 50 μm; tube voltage, 80 kV; tube current, 270 μA. The reconstruction was done by using the filtered back projection method. The reconstruction kernel used a Feldkamp cone beam correction and SheppLogan filter. The CT images were analyzed using amira 4.1.2. In detail, tumor-bearing nude mice were intravenously injected with 200 μl of BiOCl/Bi2O3 NSs (10 mg/ml) before imaging. After 12 and 24 hours, tumor-bearing mice were imaged by a small animal x-ray CT. The mice whole-body 360° scan lasted about 20 min under isophane anesthesia.

Antitumor therapy in vivo
The HepG2 tumor–bearing mice were randomly divided into six treatment groups with five mice for each group as follows: (i) PBS, (ii) US, (iii) BiOCl NSs, (iv) BiOCl/Bi2O3 NSs, (v) BiOCl NSs + US, and (vi) BiOCl/Bi2O3 NSs + US. The injection dose of NSs was 4 mg/kg. The NSs were reconstituted within PBS solution with a 0.2 mg/ml concentration for administration into the mice and delivered as a
single bolus dose. The condition for US treatment was 1 MHz, 0.8 W cm\(^{-2}\), and 50% duty cycle. The exposure time of treatment with the US was 10 min. For groups 5 and 6, the mice were exposed to the US successively at 24 hours after injection. The tumor size and body weight of each group were measured using a digital scale and caliper every 2 days for 14 days during the treatment. Then, the tumor volume was calculated.

**Biosafety in vivo**

Healthy C57BL/6 mice were intravenously injected with BiOCl/\(\text{Bi}_2\text{O}_3\) NSs in PBS (10 mg/ml) to conduct the biosafety experiment. Twenty-four hours after injection, the representative cytokines, including IL-6, TNF-\(\alpha\), and IFN-\(\gamma\), were determined using enzyme-linked immunosorbent assay based on the manufacturer’s instructions. Subsequently, the relative indexes in blood, including BUN, creatinine, albumin, total protein, ALT, and AST, were measured to evaluate the biocompatibility and immune response of BiOCl/\(\text{Bi}_2\text{O}_3\) NSs. After 1 month of treatment, the main organs (heart, liver, spleen, lung, and kidneys) were retrieved for analysis using H&E staining.

**SUPPLEMENTARY MATERIALS**

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View/request a protocol for this paper from Bio-protocol.

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