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REVIEW

Recent Advances of Emerging Metal-Containing Two-Dimensional Nanomaterials in Tumor Theranostics

Chenxi Li[1,2,*], Xueyang Fang[1,*], Han Zhang[1,3], Bin Zhang[1]

[1]Shenzhen Key Laboratory of Nanozymes and Translational Cancer Research, Institute of Translational Medicine Department of Otolaryngology Shenzhen Second People's Hospital, the First Affiliated Hospital of Shenzhen University, Health Science Center, Shenzhen, 518035, People's Republic of China; [2]Graduate Collaborative Training Base of Shenzhen Second People's Hospital, Heng Yang Medical School, University of South China, Hengyang, Hunan, 421001, People's Republic of China; [3]International Collaborative Laboratory of 2D, Materials for Optoelectronics Science and Technology of Ministry of Education, Institute of Microscale Optoelectronics, College of Physics and Optoelectronic Engineering, Shenzhen University, Shenzhen, 518060, People's Republic of China

*These authors contributed equally to this work

Correspondence: Bin Zhang; Xueyang Fang, Email binzhang@email.szu.edu.cn; FANGXueyang0210@163.com

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Abstract: In recent years, metal-containing two-dimensional (2D) nanomaterials, among various 2D nanomaterials have attracted widespread attention because of their unique physical and chemical properties, especially in the fields of biomedical applications. Firstly, the review provides a brief introduction to two types of metal-containing 2D nanomaterials, based on whether metal species take up the major skeleton of the 2D nanomaterials. After this, the synthetical approaches are summarized, focusing on two strategies similar to other 2D nanomaterials, top-down and bottom-up methods. Then, the performance and evaluation of these 2D nanomaterials when applied to cancer therapy are discussed in detail. The specificity of metal-containing 2D nanomaterials in physics and optics makes them capable of killing cancer cells in a variety of ways, such as photodynamic therapy, photothermal therapy, sonodynamic therapy, chemodynamic therapy and so on. Besides, the integrated platform of diagnosis and treatment and the clinical translatability through metal-containing 2D nanomaterials is also introduced in this review. In the summary and perspective section, advanced rational design, challenges and promising clinical contributions to cancer therapy of these emerging metal-containing 2D nanomaterials are discussed.

Keywords: metal-containing two-dimensional nanomaterials, nanotechnology-based therapy, cancer precision treatment, theranostic platform

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Introduction

Cancer has a significant impact on human health and societal advancement due to its high incidence and mortality rates. There are downsides to using conventional therapeutic approaches including surgery, radiation, chemotherapy, etc.[1] Nanotechnology-based therapy, which includes photodynamic therapy (PDT), photothermal therapy (PTT), chemodynamic therapy (CDT), sonodynamic therapy (SDT) and integrated treatment approaches, etc., has received a lot of interest recently as a potentially promising strategy for cancer suppression.[2]

Two-dimensional (2D) materials are a category of materials with high lateral dimension-to-thickness ratios and a sheet-like structure.[3–5] Numerous 2D nanomaterials have been employed in biomedicine, such as graphene, transition metal dichalcogenides (TMDs), transition metal carbides, nitrides and carbonitrides (MXenes), monoelemental nanosheets like black phosphorus (BP) and graphdiyne, layer like double hydroxides (LDHs), 2D metal-organic frameworks (MOFs), etc.[6–16] Among them, metal-containing 2D materials have become a research frontier in nano-medicine, benefiting from their strong near-infrared (NIR) light absorption, ultrasonic responsiveness and the capacity to produce reactive oxygen species (ROS).[17–20] Currently, there are mainly two types of metal-containing 2D materials, depending

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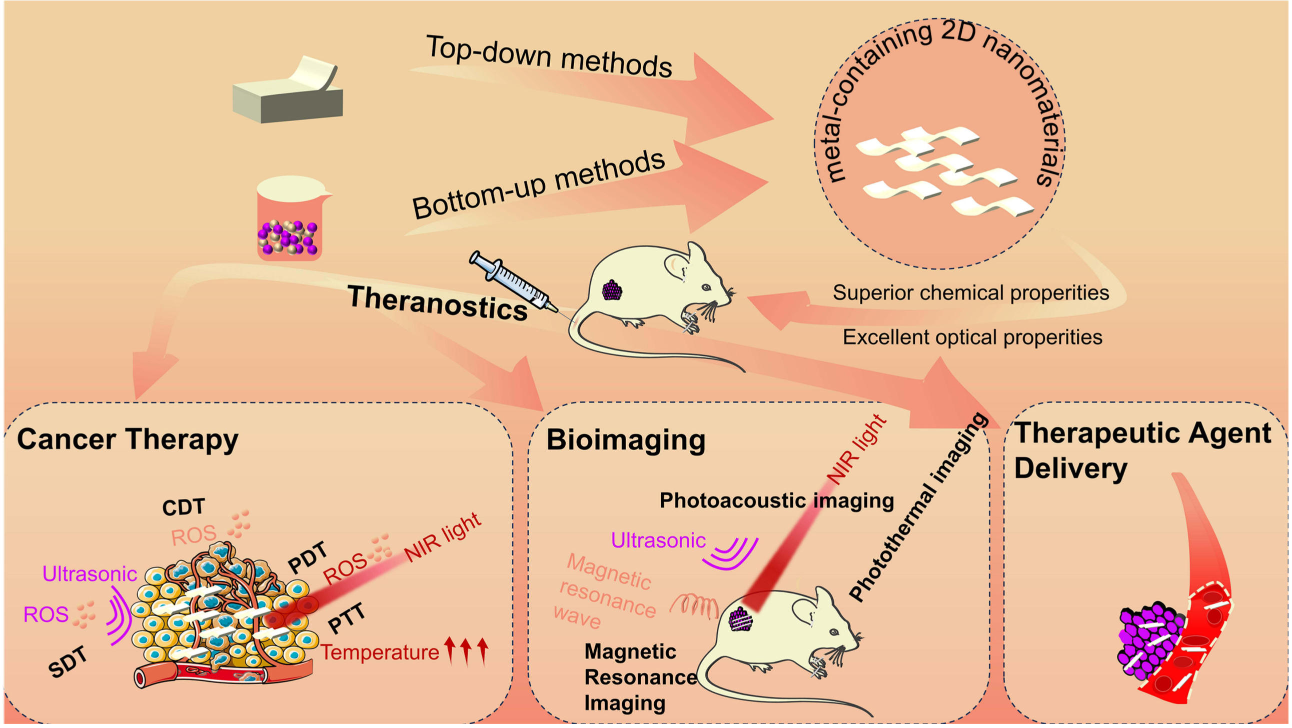
Graphical Abstract



on whether metal species are decorated on the surface of 2D materials or take up the skeleton structures. Thanks to the performance modulation of metal species, which endows 2D materials with highly catalytic performance as well as light and sonic responsive ability, these materials are well suited for cancer PDT, PTT, CDT, SDT, and other types of therapy.[21–25] Due to the large surface area of 2D nanomaterials, various functional molecules, such as chemotherapeutic drugs and fluorescent probes, can be loaded via covalent or non-covalent interactions, as well as various functional nanoparticles (NPs), including Au NPs, Pt NPs and some metal quantum dots.[26–28] These extra molecules and NPs enhance the features of 2D nanomaterials, such as electrochemical performance, magnetic functionality, radioactivity and imaging capabilities. Thanks to their superior physicochemical characteristics, such as their high surface-to-mass ratio, distinctive surface chemical activity and inherent optical features, 2D nanomaterials have emerged as preferred nanoplatforms for biomedicine.[29–31]

Reviews of the categorization and applications of 2D nanomaterials in the literature are reported, but there are limited specific reviews of metal-containing 2D materials discussing the diverse mechanisms of action in the treatment of tumors and the most recent advancements.[32–35] Here, we concentrate on outlining the many approaches that metal-containing 2D nanomaterials have been used to treat cancer in recent years, as well as their use in the integration of cancer diagnostics and therapy. This article conducts a thorough overview of current developments in metal-containing 2D nanomaterials applied to biomedicine, particularly in cancer treatment (Table 1). First, we review the methods used for constructing different kinds of these materials, such as mechanical exfoliation, liquid-phase exfoliation, hydrothermal/solvothermal techniques and Chemical Vapor Deposition (CVD). Then, we discuss the varied applications of these materials in cancer therapy (Figure 1). Afterwards, we analyze the clinical translatability and challenge of metal-containing 2D nanomaterials. Finally, the difficulties now facing them as an integrated nanoplatform for the diagnosis and treatment of cancer are discussed. We have high hopes that this review will stimulate broader interest in the research and development of advantageous uses of metal-containing 2D nanomaterials for cancer treatment.

Table 1 Cancer Treatment of Metal-Containing Two-Dimensional Nanomaterials

2D Nanomaterials	Modification Agents	Preparation Method	Treatment	Experimental Models	Ref.
Bi/BiOx	HOOC–PEG–COOH	Oxidation-assisted liquid exfoliation	PDT	SMCC-7721 cells bearing mice	[36]
BPs	Au@Fe_3O_4	Liquid exfoliating method	PDT	U14 cells bearing mice	[37]
$CaAl_2O_4$	-	High-temperature solid-state reaction	PDT	4T1 tumor-bearing mice	[38]
CoMo-LDH	-	Hydrothermal reaction	PDT	4T1 tumor-bearing mice	[39]
COW-LDH	-	Hydrothermal reaction	SDT	4T1 tumor-bearing mice	[40]
Cu	Ce6-DNAzyme	Hydrothermal reaction and surfactant-assisted method	PDT+ Gene silencing	MCF-7-tumor-bearing mice	[41]
Cu-MOF	MnO_2-FA-TPP-PAH	One-Pot Synthetic Approach	CDT	4T1 tumor-bearing mice	[42]
Cu-MOF	-	Top-down stripping	CDT	CT-26 tumor-bearing mice	[43]
Cu-TCPP-Al	Pt-FA	Self-assembly	PDT+ Immunity	M109 tumor-bearing mice	[44]
FeOCl/ FeOOH	-	Hydrothermal reaction	CDT	MCF7 tumor models	[45]
GeP	NH_2-PEG-FA-DOX	Electrochemical intercalation and ultrasound exfoliation	PTT+ Chemotherapy	H22 tumor-bearing mice	[46]
Germanene	-	High-temperature solid state reaction	PDT	4T1 tumor-bearing mice	[47]
Mg–Mn–Al (LDH)	MoS_2-BSA-Ce6	Hydrothermal method and ultrasonic exfoliation	PTT+PDT	HT29 colorectal carcinoma	[48]
MgO-Fe_2O_3	PEG	Alkali etching and liquid exfoliation	PDT+CDT+PTT	HepG2 tumor-bearing mice	[49]
Mn	-	One-pot templated reaction	PTT	4T1 tumor-bearing mice	[50]
MoO_{3-x}	PVP	Chemical intercalation and exchange, and in situ polymerization	CDT	4T1 tumor-bearing mice	[51]
Sb	HS–PLGA–PEG–FA	High-speed shear exfoliation method	PDT+PTT+ Chemotherapeutic	MCF-7-bearing mice	[52]
SiO_2	Cu-MOF-HA-CQ/HT	Ultrasonication-assisted liquid phase exfoliation strategy	CDT	Hela tumor-bearing mice	[53]
TBP@MOL	-	Hydrothermal reaction	SDT	CT26 and 4T1 tumor-bearing mice	[54]
Ti_3C_2	DOX	Surface synthesis and selective etching-assisted liquid exfoliation	PDT+PTT+ Chemotherapeutic	HCT-116 tumor-bearing mice	[55]
Vermiculite (Fe)	-	Organic solvent-free reflux ion exchange strategy.	CDT	Calu1 tumor-bearing mice	[56]
Vermiculite (Fe)	Arg-PDA-PEG	Top-down stripping (Ultra-assisted)	CDT+SDT	CT26 tumor-bearing mice	[57]
Zn MOF	PVP	Hydrothermal reaction	PDT	4T1 tumor-bearing mice	[58]
Zn–Al–LDH	-	Co-precipitation method	PDT	Hela cells	[59]

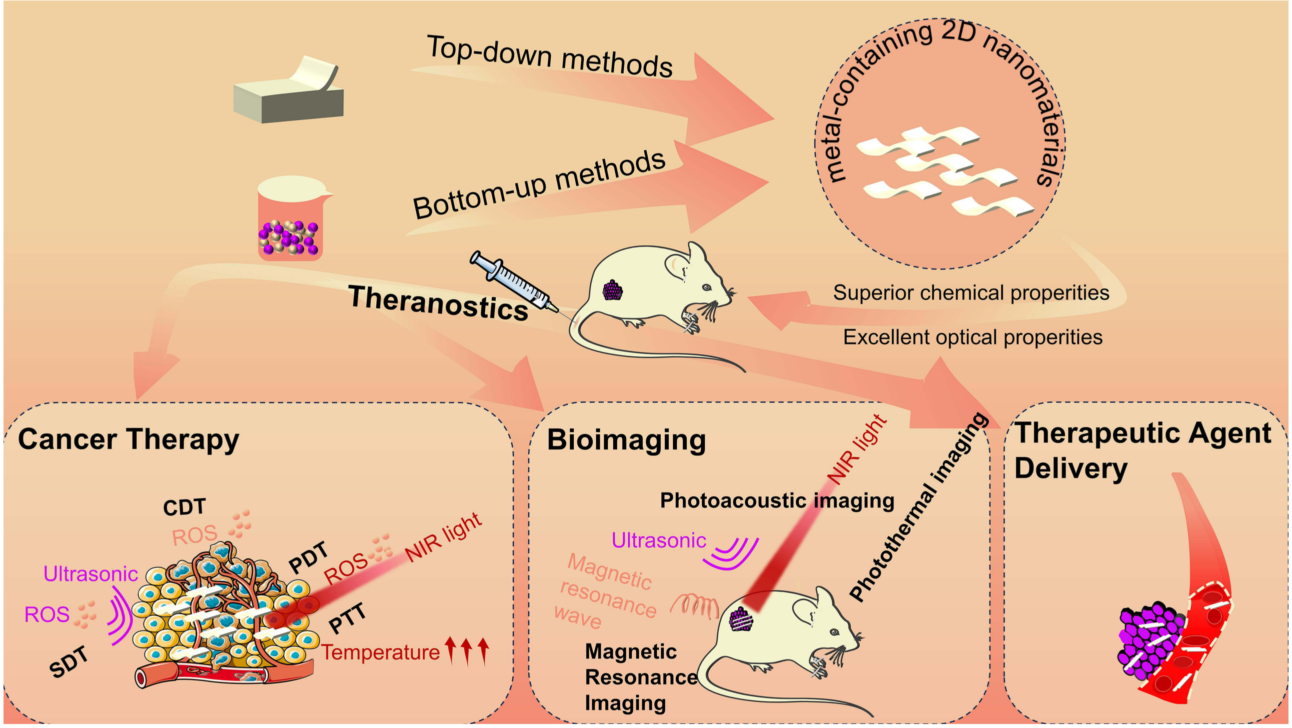


Figure 1 The synthesis and theranostic platform of metal-containing 2D nanomaterials, including cancer therapy, bioimaging and therapeutic agent delivery.

Synthetic Methods of Metal-Containing Two-Dimensional Nanomaterials

The methods for synthesizing metal-containing 2D nanomaterials are mainly classified into two categories: top-down and bottom-up methods (Figure 2A).[60] The former relies on exfoliating bulk materials through physical exfoliation, such as mechanical tearing and sonication exfoliation, and then a single or few layers of metal-containing 2D nanomaterials are obtained.[61] While the latter means preparing metal-containing 2D nanomaterials by chemical reaction of certain

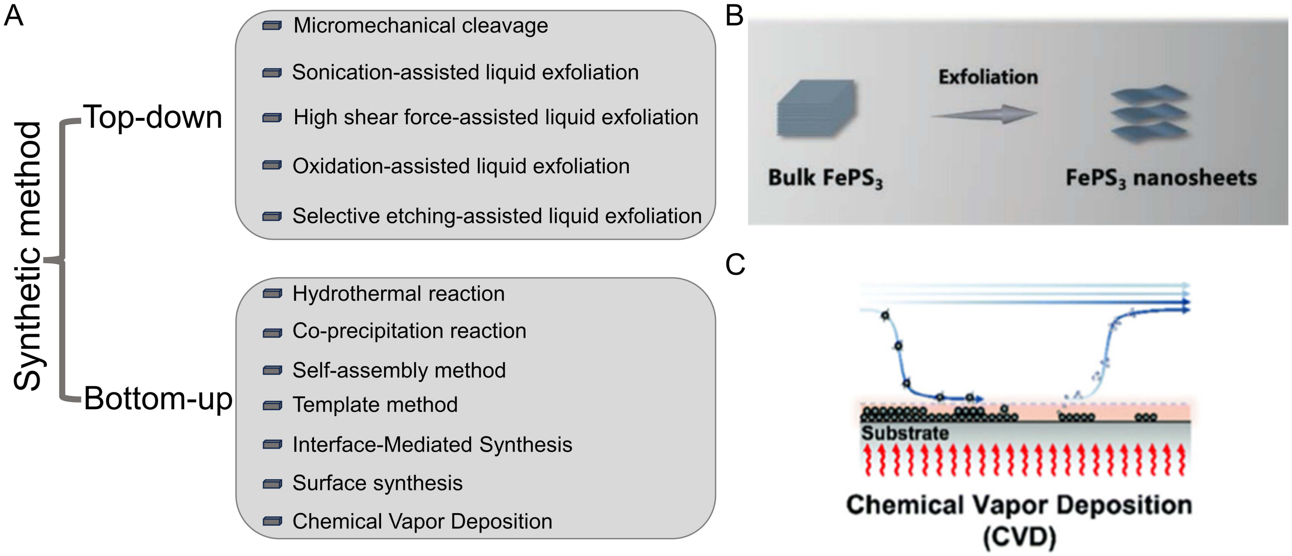


Figure 2 (**A**) The synthetic methods of metal-containing 2D nanomaterials, including top-down and bottom-up methods. (**B**) Top-down synthetic method (Exfoliation) of 2D nanomaterials. Reproduced from Lin S, Yang M, Chen J, et al. Two-Dimensional FePS3 nanosheets as an integrative sonosensitizer/nanocatalyst for efficient nanodynamic tumor therapy. *Small*. 2023;19(8):2204992. [62] Copyright 2022 Wiley-VCH GmbH. (**C**) Bottom-up synthetic method (CVD) of 2D nanomaterials. Reproduced from Huang H, Feng W, Chen Y. Two-dimensional biomaterials: material science, biological effect and biomedical engineering applications. *Chem Soc Rev*. 2021;50(20):11381–11485.[63] Copyright 2021 The Royal Society of Chemistry.

precursors at specific experimental conditions. This article summarizes some common methods in detail for preparing metal-containing 2D nanomaterials in the following parts.

Top-Down Method

The top-down method means stripping bulk materials into a monolayer or a few layers. These methods include micromechanical cleavage (Figure 2B), sonication-assisted liquid exfoliation, shear force-assisted liquid exfoliation, oxidation-assisted liquid exfoliation, selective etching-assisted liquid exfoliation and so on.[64,65] These physical exfoliation methods are simple but not precise because of the uncontrolled synthesis process, thus resulting in low quality and yield.

Micromechanical Cleavage

Micromechanical cleavage is a method that could weaken the van der Waals between the materials by mechanical tearing and then stripping bulk crystals into a single or few layers (Figure 2B). This method has a wide range of applications and can be used to peel various kinds of large 2D crystals. In 2004, Novoselov's group successfully peeled layered graphene for the first time in this way and subsequently applied it to other bulk crystal exfoliation processes.[66] The material stripped by this method has a large lateral dimension, high purity and superior quality. However, it also has many problems including low yield, unprecise control and difficulty in industrial production which hinders its further application.

Sonication-Assisted Liquid Exfoliation

It is the simplest and most common mechanical stripping method. The layered bulk crystals were dissolved in a specific solvent before being treated with sonication. After sonication, the suspension would be purified via centrifugation to obtain the nanosheet suspension. The theory of this method is that ultrasound can create bubbles in the liquid, and when the bubbles burst, microjets and shocks can pass through chunks of crystals, peeling them off into layered nanosheets. Coleman's team first used this method in 2008 which peeled large graphite crystals into layered graphite nanosheets in n-methyl-pyrrolidone (NMP) solution.[67] Subsequently, many kinds of polymers and surfactants were used to adjust the surface energy of liquid solvents, increasing the production of 2D nanomaterials and extending their application range. This method exhibits many advantages such as high yield, low cost and the possibility for large-scale production. However, there are some apparent disadvantages including small lateral size and nanomaterials attaching lots of by-polymers attaching on 2D nanomaterials and low yield of specific monolayers.

High-Shear Force-Assisted Liquid Exfoliation

High-shear force-assisted liquid exfoliation is a method that stripping materials by gradient centrifugation in a specific solvent by a high-shear rotor. The shear rate of the rotor rotator is the most critical factor in determining output and without specific requirements for equipment.[68] Researchers stirred the materials in kitchen Blender and successfully sheared graphene crystals into graphene nanosheets.[69] In this strategy, 2D nanomaterials can be easily synthesized with high yield and low cost. While it has to be carried out at a specific power which induces its low synthetic efficiency.

Oxidation-Assisted Liquid Exfoliation

Oxidation-assisted liquid exfoliation method depends on a strong oxidant to nanomaterials. For instance, the oxidized graphene will generate a large number of oxygen-containing functional groups in the interlayer, which could expand the interlayer distance of graphene, weaken the van der Waals force and peel the big bulk graphene into layers.[70] Although this method exhibits a high yield, it is limited in low safety and results the difficulty in large-scale applications.

Selective Etching-Assisted Liquid Exfoliation

The selective etching-assisted liquid exfoliation method means strip bulk MAX material into nanosheets by strong acid, and then obtaining monolayer 2D MXenes nanomaterials by ultrasonication.[71] This method can be used in tightly bonded layered materials and is easy to perform. However, the strong acid used in the exfoliating process is dangerous, and this method is limited to specific types of materials. It does not apply to all MXenes from the MAX phase, nor can it be applied to graphene, TMD and other 2D nanomaterials.

Bottom-Up Method

The bottom-up synthesis method is a traditional strategy for 2D nanomaterials. It includes hydrothermal reaction, co-precipitation, self-assembly, template, mediated synthesis, surface synthesis CVD (Figure 2C) and so on.[60] These methods are used for the synthesis of 2D nanomaterials through ions or small molecules, and they are widely used for the synthesis of various 2D nanomaterials.

Hydrothermal Reaction

Hydrothermal reaction is a typical method for the synthesis of metal-containing 2D nanomaterials.[72] Hydrothermal reaction can be defined as a method of formation and growth of crystals by chemical reactions in a sealed heated aqueous solution.[73] Li et al synthesized monolayer rhodium (Rh) nanosheets based on poly-vinylpyrrolidone (PVP) for the first time by hydrothermal method.[74] Qiu et al also synthesized 2D Bi/BiOx nanomaterials by this method in 2021.[36] The materials synthetic by this method have high quality, large two dimensions area, controllable thickness and high yield. However, it requires precise control of interior reaction system conditions such as concentration, pH value, time, pressure, organic additives and the exterior reaction environment conditions.[75]

Co-Precipitation Reaction

Co-precipitation reaction is another typical synthesis strategy. The basic idea is to put all kinds of components into one condition and make them react spontaneously.[76] For example, Weicheng et al synthesized CoMo-LDH colloid by reacting (NH_4) $6Mo_7O_{24}\cdot 4H_2O$, Co $(NO_3)_2\cdot 6H_2O$ and NaOH in the N_2 environment.[39] This reaction is simple and easy to operate, but 2D nanomaterials synthesized in this way are always inaccuracy with many by-products.

Self-Assembly Method

The self-assembly method is based on the spontaneous bonding of pre-synthesized nanocrystals through non-covalent interaction.[77] As a typical example, Wu and his group synthesized Cu nanosheets and gold nanosheets through Cu clusters and gold clusters, respectively.[78,79] The thickness of these nanosheets can be adjusted by the concentration of cluster, reaction temperature and reaction time. The operation of this reaction is simple, only need to put materials into the ultrasonic pot. However, the synthetic concentration and temperature need to be precisely controlled, and the quality of this kind of material is relatively low, which is not suitable for large-scale production.

Template Method

The template method is a kind of self-assembly method, which uses the specific shape as a template. For example, Wei et al synthesized half-unit-cell α-Fe_2O_3 nanosheets with a CuO template.[80] In this process, CuO template could be dissolved by acid after Fe_2O_3 nanosheets were synthesized. The method of dissolving the outer template by acid is called the hard template method, while the corresponding soft template method means removing the outer template by cauterization. This method can obtain high-quality nanomaterials, but the synthesis process requires stern conditions and special templates, which hinders its large-scale industrialized production.

Interface-Mediated Synthesis

Interface-mediated synthesis is a typical bottom-up synthesis method.[81] It refers to the process of confining the ligand in the water/air interface and then reacting with salts dissolved in solution to form coordination polymers (CPs) nanosheet. In Bauer's report, hexafunctionalterpyridine-based organic ligand is dissolved in chloroform, and then it is dropwise added into the metal salt solution.[82] Due to the rapid evaporation of chloroform and the low solubility of organic ligands in water, this ligand will be confined to the water/air interface. The ligand at the interface can react with metal ions in solution and finally form a metal coordination polymer. The synthesized nanosheets are located in the interface between water and air, which are easy to transfer into other media. This method has been applied in the synthesis of a variety of metal-containing 2D nanomaterials and it is expected to be further extended.

Surface Synthesis

The surface synthesis method is often used for covalent-organometallic frame (COF) generation. It refers to casting the desired COF monomer onto an appropriate solid substrate and then sealing the solid substrate in a container that is filled with needed volatile monomers. When the container is heated at an appropriate temperature, the volatile monomers in it will gradually volatilize and react with the monomers on the solid substrate. Then, the COF nanosheets will be formed in the shape of the solid substrate. Lei et al first synthesized monolayer imine COF on the surface of highly oriented pyrolytic graphite (HOPG) by this method.[83] With this method, we can synthesize high-quality COF nanosheets with regular shapes, but it requires a constant temperature, which is hard to control.

Chemical Vapor Deposition (CVD)

Due to its high efficiency and controllability, CVD is a popular method in the synthesis of 2D nanomaterials.[84–86] The CVD method involves two main steps: firstly, the preselected substrate is placed into the Furnace Chamber, and then one or more gas/vapor precursors cycle in the chamber and react with the substrate. Under appropriate experimental conditions, ultra-thin metal-containing 2D nanomaterials can be obtained. This method can obtain the desired materials through interatomic reaction and the materials ratio is easy to control. However, there are many factors affecting the synthesis process, including precursors, substrates, catalysts, temperature, atmospheres, etc. Accounting for its complicated synthetic conditions, expensive cost and low yield, it still needs to be optimized.

Biomedical Applications

Cancer Therapy

PDT

PDT is a non-invasive treatment method that differs from traditional surgical treatment due to the fact it can generate cytotoxic ROS by irradiating photosensitizers gathered in tumor sites with laser irradiation, mainly including singlet oxygen ($^1O_2$), hydroxyl radicals ($\cdot OH$) and superoxide ions (O_2^-). In tumor areas, a huge quantity of cytotoxic ROS builds up and thus may trigger intracellular mitochondrial apoptosis or activate immune responses to destroy tumor cells. As a result, the generation of ROS is the most important factor influencing PDT efficiency.[21] Increased production of ROS during the PDT process may be accomplished by strengthening the photosensitizer's properties, increasing the oxygen level in the tumor microenvironment and extending the duration of light exposure.[87]

The ability of photosensitizers to generate ROS is a crucial factor in determining the PDT effect. Ge et al synthesized H-germanene 2D nanosheets with a 1.65eV bandgap as a novel inorganic photosensitizer for PDT, which can generate more ROS than conventional 2D nanosheets with a narrower bandgap such as MXene when exposed to 660nm laser light (Figure 3A and B).[47] Besides, the TME is a hypoxic microenvironment that influences the rate at which oxygen is converted into ROS. Chen et al loaded Pt on 2D Cu-TCPP MOF to alleviate the hypoxia at the tumor site, thereby increasing the production of ROS and enhancing the PDT effect (Figure 3C).[44] In addition, Chang et al developed a sustainable luminescent 2D $CaAl_2O_4$:Eu, Nd persistent luminescence nanosheets (CAO PLNSs), which eliminated the need for external light source irradiation in PDT over the long term (Figure 3D).[38] Their continuous luminescence is caused by Ca and O vacancies in the 2D nanosheets as well as the electronic transition of Eu^{2+} between the 4f and 5d states after illumination (Figure 3E). So, after 10 minutes of irradiation at 365nm, the 2D nanosheets continued to emit light, resulting in the continuous production of ROS that enhanced the tumor-killing effect (Figure 3F). Moreover, the inherent properties of metal-containing 2D nanomaterials, such as their large surface area and ease of modification, are extremely advantageous for PDT.

PTT

PTT means under the irradiating of NIR laser, photothermal agents (PTAs) can elicit protein ablation to eliminate tumor cells through high temperature. The efficacy of PTT is therefore dependent on the photothermal conversion efficiency (PTCE) of metal-containing 2D nanomaterials.[88]

Jiang et al synthesized 2D stanene nanosheets (SnNSs) via a combination of low-temperature exfoliation and liquid phase exfoliation, achieving a PTCE of 48.6% (Figure 4A).[89] According to calculations based on density functional theory (DFT), free electrons in the upper and lower layers of the 2D SnNSs contribute to the conversion of light to heat. As for the therapeutic effect, SnNSs with an 808nm laser irradiation kill tumor cells in vitro; experiments in vivo also validated the local heating and potentially fatal effect of PTT on tumor tissue. As another example, Xu et al prepared a 2D nanocomposite Mn-HDCLwith good stability in aqueous, high photothermal stability, a large extinction coefficient

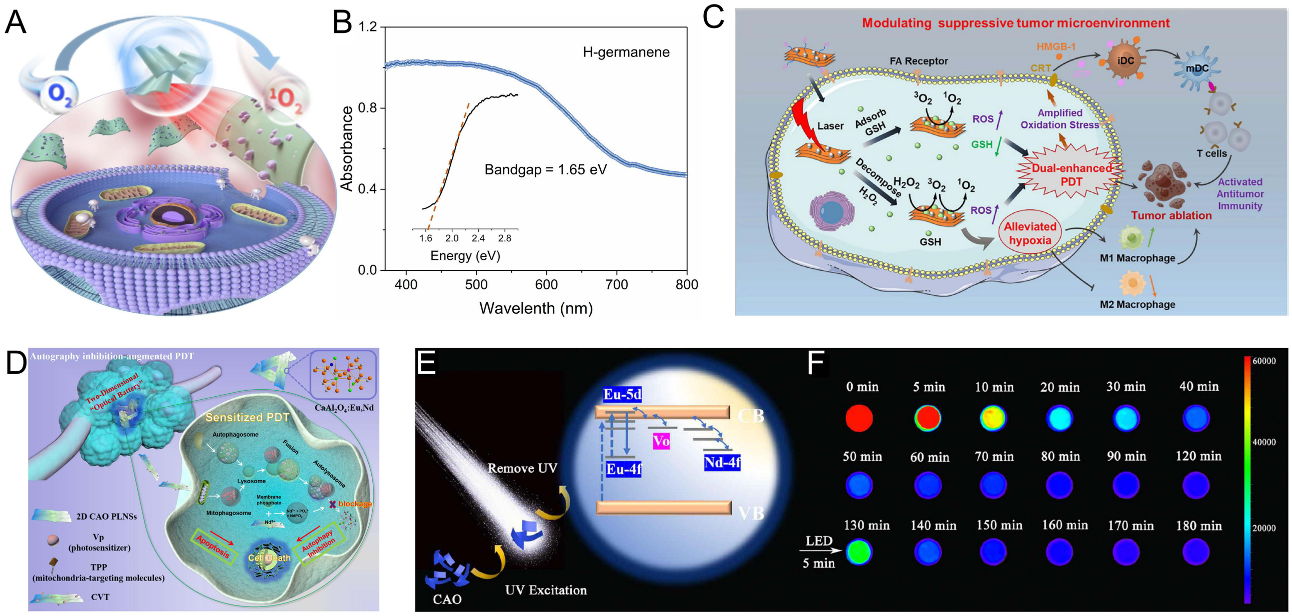


Figure 3 (**A**) Illustrating PDT-induced cell apoptosis on H-germanene under laser irradiation. Reproduced from Ge M, Guo H, Zong M, et al Bandgap-engineered germanene nanosheets as an efficient photodynamic agent for cancer therapy. *Angew Chem Int Ed Engl.* 2023:62.[47] Copyright 2023 Wiley-VCH GmbH. (**B**) UV-vis diffuse reflectance spectra and tauc plots of H-germanene nanosheets. Reproduced from Ge M, Guo H, Zong M, et al Bandgap-engineered germanene nanosheets as an efficient photodynamic agent for cancer therapy. *Angew Chem Int Ed Engl.* 2023:62.[47] Copyright 2023 Wiley-VCH GmbH. (**C**) Schematic illustration of dual-enhanced PDT therapy. Reproduced from Chen Z, Wu Y, Yao Z, et al 2D copper (II) metalated metal-organic framework nanocomplexes for dual-enhanced photodynamic therapy and amplified antitumor immunity. *ACS Appl Mater Interf.* 2022;14(39):44199–44210.[44] Copyright 2022 Journal of the American Chemical Society. (**D**) Schematic diagram of the mechanism of photodynamic tumor nanotherapy. Reproduced from *Nano Today.* Volume 42. Chang M, Dai X, Dong C, et al Two-dimensional persistent luminescence "optical battery" for autophagy inhibition-augmented photodynamic tumor nanotherapy.[38] Copyright 2022, with permission from Elsevier. (**E**) Illustration of persistent luminescence mechanism of CAO PLNSs. Reproduced from *Nano Today.* Volume 42. Chang M, Dai X, Dong C, et al Two-dimensional persistent luminescence "optical battery" for autophagy inhibition-augmented photodynamic tumor nanotherapy.[38] Copyright 2022, with permission Elsevier. (**F**) The persistent luminescence images at different time intervals (0–120 min) of CAO PLNSs after 10 min under irradiation of 365 nm UV lamp, then reactivated by white LED lamp for 5 min (130–180 min). Reproduced from *Nano Today.* Volume 42. Chang M, Dai X, Dong C, et al Two-dimensional persistent luminescence "optical battery" for autophagy inhibition-augmented photodynamic tumor nanotherapy.[38] Copyright 2022, with permission from Elsevier.

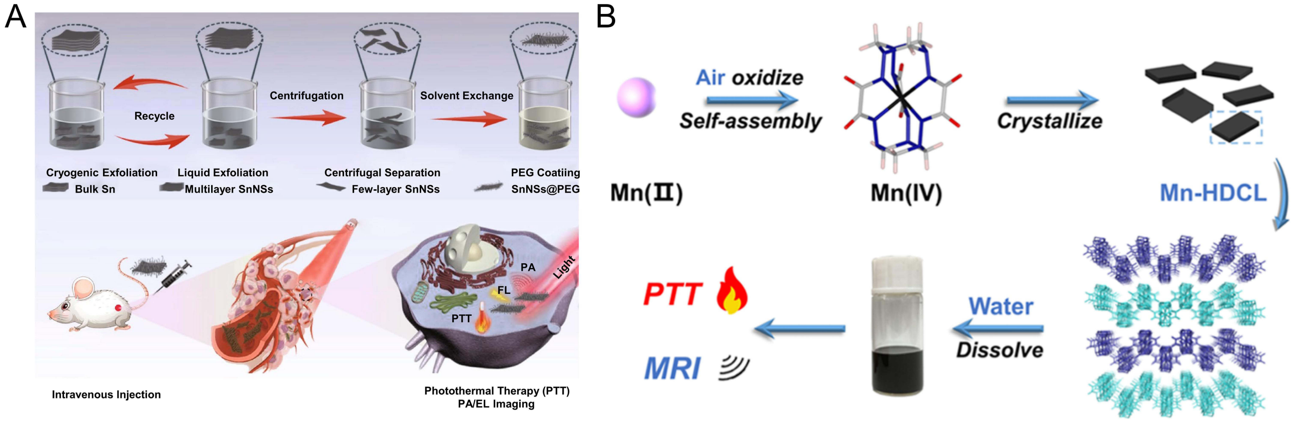


Figure 4 (**A**) Illustrating the synthetic procedure of 2D SnNSs and the Multifunction of SnNSs@PEG in vivo. Reproduced from Ouyang J, Zhang L, Li L, et al. Cryogenic exfoliation of 2D stanene nanosheets for cancer theranostics. *Nanomicro Lett.* 2021;13(1):90,[89] Creative Commons. (**B**) Schematic diagram showing the preparation process of Mn-HDCL and its potential use in MRI and PTT. Reproduced from Xu Y, Li C, Wu X, et al. Sheet-like 2D Manganese (IV) Complex with High Photothermal Conversion Efficiency. *J Am Chem Soc.* 2022;144(41):18834–18843.[50] Copyright 2022 American Chemical Society.

and good PTCE (71%), under the conditions of 730 nm laser light irradiation (Figure 4B).[50] Moreover, GeP nanosheets and 2D silicene nanocomposites have also been noted as outstanding PTAs in the literature, with PTCE reaching 68.6% and 37.7%, under NIR laser irradiation, and both materials also exhibit strong biodegradability and biocompatibility.[46,90] Hence, 2D nanomaterials exhibit powerful PTCE and hold promise as materials for PTT against cancer.

CDT

CDT has received lots of attention in the field of tumor treatment.[91] With the help of the characteristics of weak acid and excessive H_2O_2 in the tumor microenvironment, CDT uses Fenton or Fenton-like reactions to catalyze weakly oxidizing H_2O_2 into strongly oxidizing ·OH, resulting in increased intracellular oxidation levels, DNA necrosis and protein inactivation, lipid oxidation, and ultimately induce apoptosis in cancer cells. Increasing the quantity of ·OH generated by a Fenton or a Fenton-like reaction is therefore the key to enhancing the antitumor effect of CDT.

Kang et al constructed a 2D interfacial heterojunction nanosheets (FeOCl/FeOOH NSs).[45] The holes on the valence band of FeOCl have a superior ability to catalyze H_2O to generate O_2, and the resulting O_2 is subsequently reduced to H_2O_2 by the electrons present on the conduction band of FeOOH (Figure 5A). The proficient generation of ·OH via the Fenton-like reaction, which is facilitated by FeOCl/FeOOH nanosheets, is guaranteed by the commendable self-sufficient capacity of H_2O_2. Another study conducted by Hu et al revealed that superlattice nanosheets polyaniline/MoO_{3-x} (PANI/MoO_{3-x}) facilitated electron transfer with the assistance of good conductivity of PANI through the Fenton reaction, thereby enhancing the efficiency of CDT and exhibiting potent antitumor properties (Figure 5B–D).[51] Besides, due to the high levels of hydrogen sulfide (H_2S) found in colon cancer tumor tissue, Wang's research team created a novel 2D Cu-bipyridine MOF nanosheet called $Cu(bpy)_2(OTf)_2$, which can consume H_2S in tumor tissue to produce ultra-small CuS, thus encouraging the Fenton-like reaction for CDT against

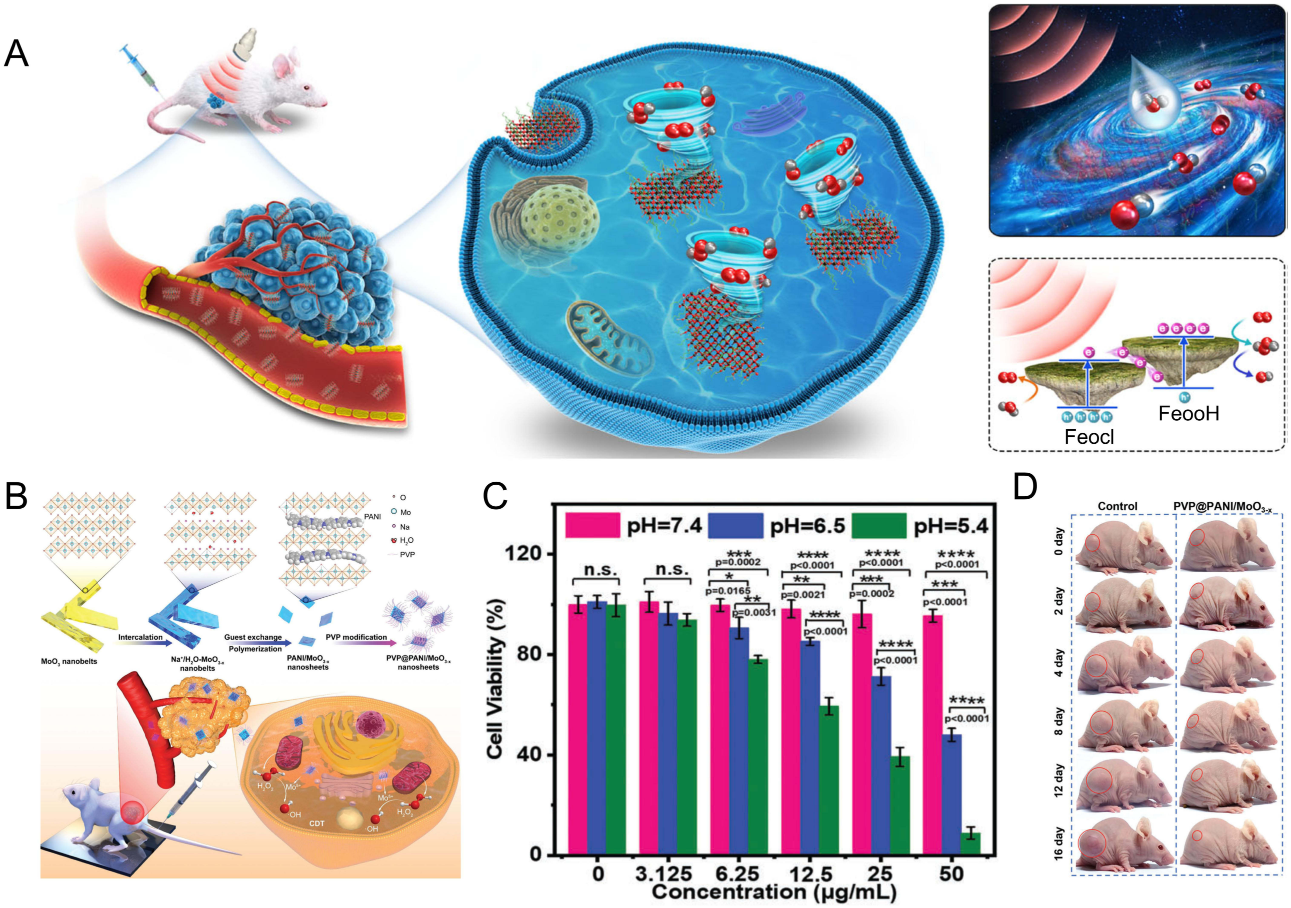


Figure 5 (**A**) Schematic diagram of bioimaging and anti-tumor performance of FeOCl NSs and FeOCl/FeOOH NSs. Reproduced from Kang Y, Mao Z, Wang Y, et al. Design of a two-dimensional interplanar heterojunction for catalytic cancer therapy. *Nat Commun*. 2022;13(1):2425.[45] Copyright 2022 Nature Publishing Group (**B**) The illustration of the preparation of 2D PVP@ PANI/MoO_{3-x} superlattice nanosheets for efficient chemodynamic cancer therapy. Reproduced from Hu T, Xue B, Meng F, et al. Preparation of 2D Polyaniline/MoO3-x superlattice nanosheets via intercalation-induced morphological transformation for efficient chemodynamic therapy. *Adv Healthc Mater.* 2023:12.[51] Copyright 2023 Wiley-VCH GmbH. (**C**) Cytotoxicity of the PVP@ PANI/MoO_{3-x} nanosheets to 4T1 cells at different PH levels in the presence of H_2O_2. Reproduced from Hu T, Xue B, Meng F, et al. Preparation of 2D Polyaniline/MoO3-x superlattice nanosheets via intercalation-induced morphological transformation for efficient chemodynamic therapy. *Adv Healthc Mater.* 2023:12.[51] Copyright 2023 Wiley-VCH GmbH. (**D**) Images of mice after treatment with PBS (control) and the PVP@PANI/ MoO_{3-x} nanosheets at different time points. Reproduced from Hu T, Xue B, Meng F, et al. Preparation of 2D Polyaniline/MoO3-x superlattice nanosheets via intercalation-induced morphological transformation for efficient chemodynamic therapy. *Adv Healthc Mater.* 2023:12.[51] Copyright 2023 Wiley-VCH GmbH.

colon cancer.[43] Taken these together, the utilization of 2D nanomaterials in catalyzing the production of ·OH from H_2O_2 through Fenton or Fenton-like reactions has garnered significant interest in the scientific community, and this method does not necessitate external energy input or O_2 as substrates, thereby presenting a promising avenue for future development.

SDT

Ultrasound is a periodic vibrating mechanical wave with a frequency over 20 kHz. It is extensively used in clinical diagnosis due to its controllability, non-invasiveness and high tissue penetrability.[92] SDT refers to a treatment modality that generates cytotoxic ROS by activating sonosensitizers via ultrasound, similar to the underlying principle of PDT.[93] SDT has been extensively researched as an emergent non-invasive method for eliminating cancer due to its high specificity, low damage to normal cells and deep tissue penetration. The sonosensitizers are the main factor impacting the effect of SDT, specifically, the quantity of ROS generated by the sonosensitizers when activated by ultrasound determines the effect of SDT.

Due to their excellent biocompatibility, acid-responsive biodegradability and varied chemical compositions and structures, 2D LDHs have been demonstrated to be potential nanomedicines across multiple biomedical disciplines. Hu et al designed an ultra-thin 2D CoW-LDH as an efficient SDT sonosensitizer using a simple acid etching process (Figure 6A–C).[40] And the CoW-LDH

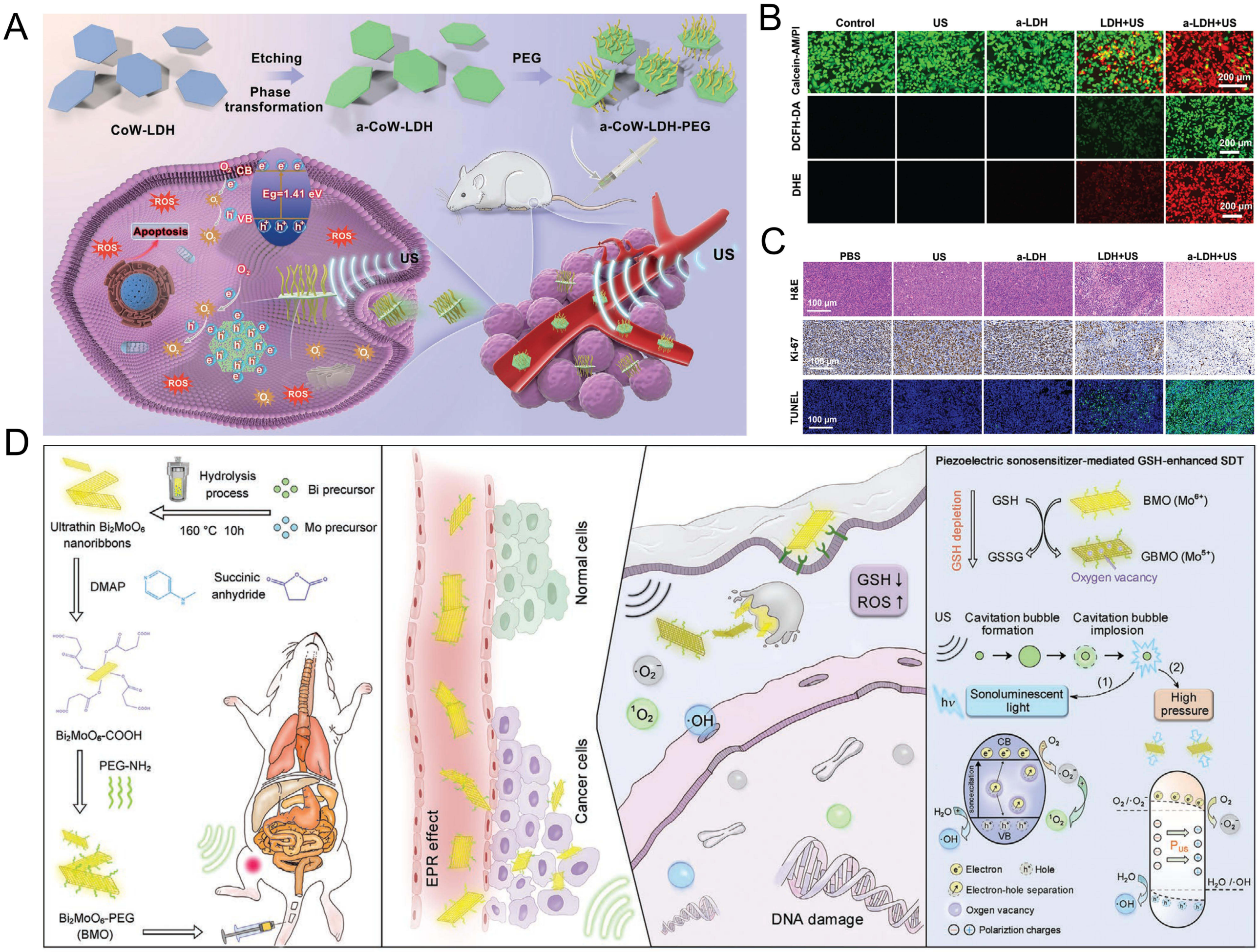


Figure 6 (**A**) Schematic diagram of the preparation of a-CoW-LDH-PEG nanosheets and their application in SDT. Reproduced from Hu T, Shen W, Meng F, et al Boosting the sonodynamic cancer therapy performance of 2D layered double hydroxide nanosheet-based sonosensitizers via crystalline-to-amorphous phase transformation. *Adv Mater.* 2023;35(17):e2209692.[40] Copyright 2023 Wiley-VCH GmbH. (**B**) Calcein-AM/PI co-stained 4T1 cells under different conditions. Reproduced from Hu T, Shen W, Meng F, et al Boosting the sonodynamic cancer therapy performance of 2D layered double hydroxide nanosheet-based sonosensitizers via crystalline-to-amorphous phase transformation. Adv Mater. 2023;35(17):e2209692.[40] Copyright 2023 Wiley-VCH GmbH. (**C**) H&E, Ki-67 and TUNEL staining assays of anti-tumor performance of 4T1 tumor-bearing mice in different groups after 16-day treatment. Reproduced from Hu T, Shen W, Meng F, et al Boosting the sonodynamic cancer therapy performance of 2D layered double hydroxide nanosheet-based sonosensitizers via crystalline-to-amorphous phase transformation. *Adv Mater.* 2023;35(17):e2209692.[40] Copyright 2023 Wiley-VCH GmbH. (**D**) Schematic illustration of the 2D piezoelectric Bi_2MoO_6 sonosensitizer for GSH-enhanced sonodynamic therapy. Reproduced fromDong Y, Dong S, Liu B, et al 2D piezoelectric Bi2 MoO6 nanoribbons for GSH-enhanced sonodynamic therapy. *Adv Mater.* 2021;33(51).[94] Copyright 2021 Wiley-VCH GmbH.

sonosensitizer demonstrated a higher ROS production, which was approximately 17 times greater than that of the commercially applied titanium dioxide sonosensitizer. The enhanced property may be a result of the crystalline-to-amorphous phase transformation-induced bandgap narrowing, electronic structure changing and defect generation, all of which promote the separation of electron–hole pairs and thus enhance ROS generation. Dong et al designed ultrathin 2D Bi_2MoO_6 (BMO NRs) nanocomposites to realize efficient SDT.[94] The ultrathin BMO NRs are piezoelectric, where ultrasonic waves introduce mechanical strain to the nanoribbons leading to piezoelectric polarization and band tilting, which can accelerate the production of ROS (Figure 6D). This process not only provides new options for improving SDT but also broadens the application of 2D nanomaterials as sonosensitizers in SDT. Lin et al reported a kind of high-efficiency sonosensitizers based on 2D tetra(p-benzoate) porphyrin metal-organic layers (TBP@MOL) that created more ROS than TBP ligand and TBP-based MOF, respectively, and showed excellent effectiveness for the treatment of colorectal cancer and breast cancer.[54] In contrast to PDT and PTT which rely on light activation, SDT utilizes ultrasound that does not require precise tumor localization. This characteristic endows SDT with the capability to serve as a feasible and non-intrusive alternative for the treatment of tumors that are located at a significant depth or are of considerable size, and it thus has considerable promise as a therapeutic approach.

Therapeutic Agent Delivery

After years of research, many nanomaterials have been discovered for drug delivery. With a large surface area and easily surface-modified character, 2D nanomaterials can load specific genes or target nanomedicine for smart therapeutic agent delivery.

For the first time, Liu et al developed the 2D PEGylated nanographene oxide (NGO) for the delivery of water-insoluble cancer drugs-SN38 in 2008.[95] The water-soluble NGO-PEG-SN38 complex could afford strong noncovalent banding and exhibit obvious cell toxicity. While no toxicity was measured of plain NGO-PEG without drug loading. This 2D structure and ultrasmall size (down to 5 nm) of NGO-PEG offered unexpected anticancer ability and provided a new idea for a drug delivery application. This promising work paved a way for the subsequent explosion of 2D nanomaterials-related research in cancer therapy. In 2022, a newly 2D Copper (II) based MOF nano complexes (Cu-TCPP(Al)), decorated with folate (FA) and platinum (Pts) NPs, were prepared for specific targeting drug-delivery and tumor therapy (Figure 7A).[44] FA in these nanocomplexes was used for targeting tumor tissue and Pt NPs could produce ROS under laser irradiation, which endows 2D Cu-TCPP(Al) excellent therapeutic efficiency. At the same time, scientists came up with the idea of sandwich-like 2D nanosheets (HA-CQ/HT@$sSiO_2$ NSs), which were modified by $CD44^-$ targeted hyaluronic acid (HA) and ultimately developed targeted 2D nanosheets (Figure 7B).[53] This material has $CD44^-$ targeting specificity which allows it to achieve effective enrichment in tumor cells, and the in vitro and in vivo experiments in this research both collectively demonstrated the superb effect of cancer cell apoptosis and tumor growth inhibition.

Bioimaging

Cancer imaging is essential not only for early detection of cancer but also for determining the specific tumor location and stage, as well as for directing therapy and monitoring for cancer recurrence following treatment. 2D nanomaterials may be employed for a variety of imaging applications due to their superior physical, electronic, chemical and optical properties.

The 2D nanocomplex (Mn-HDCL), as prepared by Xu et al, exhibits a favorable photothermal effect and possesses paramagnetic properties.[50] These characteristics contribute to an enhanced T1-weighted contrast of magnetic resonance images (MRI) in vitro and in vivo, as reported in their study. The study revealed a positive correlation between the concentration of Mn-HDCL in an aqueous solution and the increase in magnetic resonance signal intensity, and Mn-HDCL could passively target tumors and differentiate tumor margins in vivo (Figure 8A–C). Zhang et al introduced an H_2S-responsive nanoplatform known as ZNNPs, which produces a photoacoustic (PA) signal and exhibits an intelligent reaction to H_2S, enabling the quantitative and real-time imaging of endogenous H_2S.[96] This platform therefore offers a method for accurate H_2S -related diagnosis and efficient treatment of diseases such as acute liver toxicity, cerebral hemorrhage and colorectal cancer therapy.

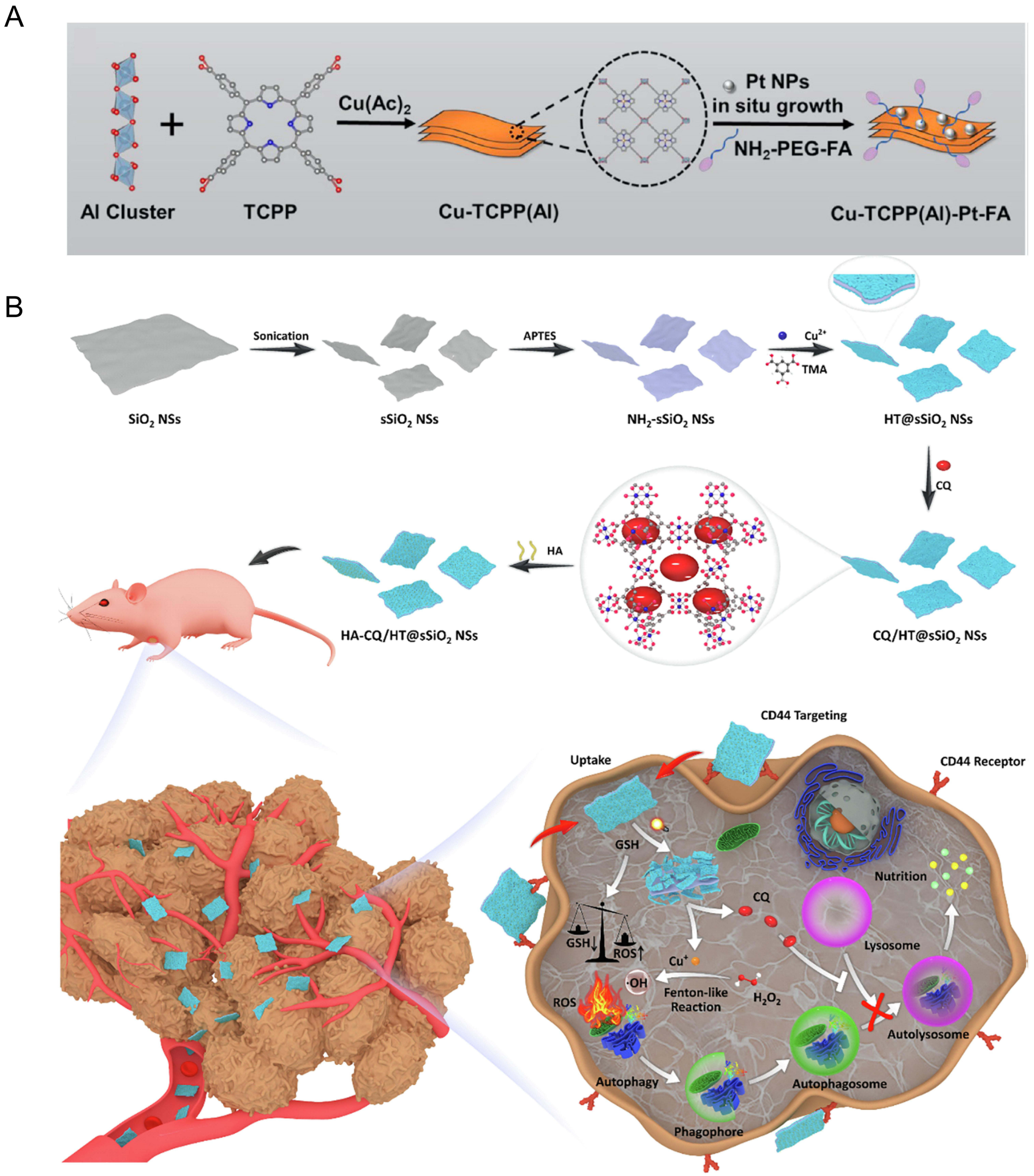


Figure 7 (**A**) The preparation process of Cu-TCPP(Al)-Pt-FA. Reproduced from Chen Z, Wu Y, Yao Z, et al 2D copper (II) metalated metal-organic framework nanocomplexes for dual-enhanced photodynamic therapy and amplified antitumor immunity. *ACS Appl Mater Interf.* 2022;14(39):44199–44210.[44] Copyright 2022 American Chemical Society. (**B**) Fabrication procedure of targeted sandwich-like 2D NSs and schematic illustration of 2D NSs for activatable autophagy inhibition-primed CDT. Reproduced from *Chem Eng J.* Volume 431. Wu H, Wu F, Zhou T, et al Activatable autophagy inhibition-primed chemodynamic therapy via targeted sandwich-like two-dimensional nanosheets.[53] Copyright 2022, with permission from Elsevier B.V.

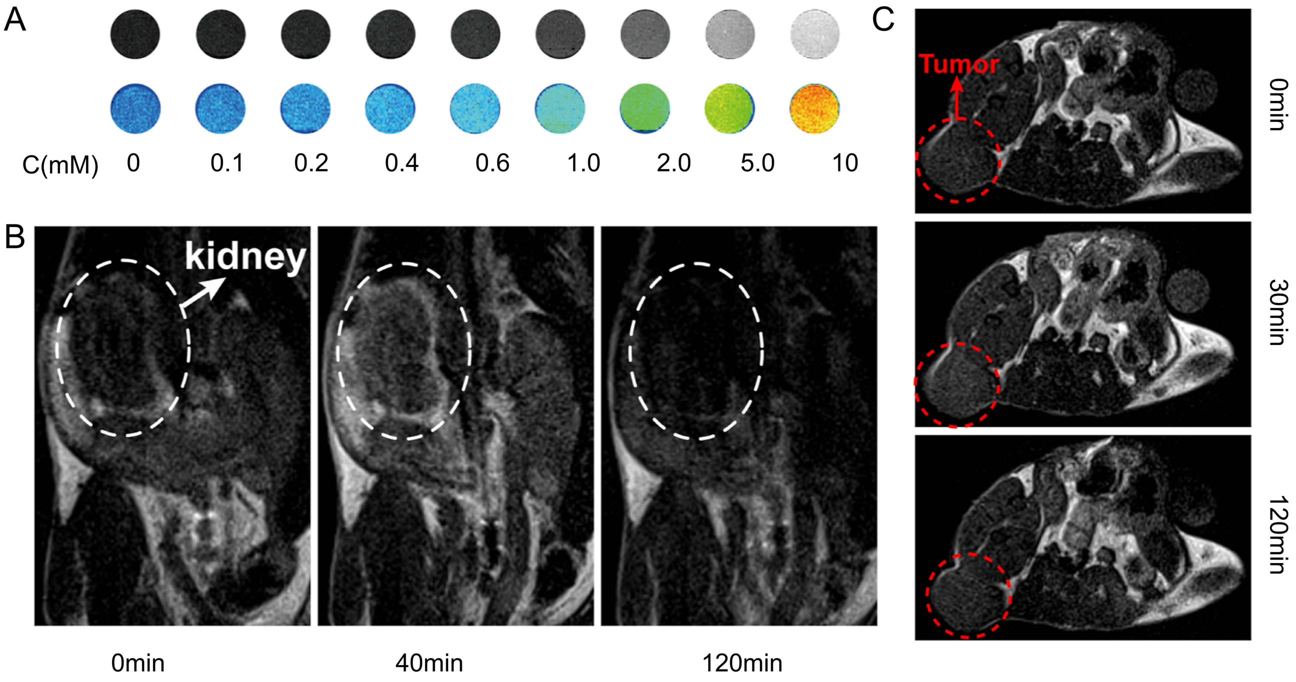


Figure 8 (**A**) T1-weighted and color-mapped phantom MRI for aqueous solutions at different concentrations of Mn-HDCL. Reproduced from Xu Y, Li C, Wu X, et al. Sheet-like 2D Manganese (IV) Complex with High Photothermal Conversion Efficiency. *J Am Chem Soc*. 2022;144(41):18834–18843.[50] Copyright 2022 Journal of the American Chemical Society (**B**) Coronal T1-weighted MR images of a BALB/c mouse at different time points after intravenous injection of Mn-HDCL. Reproduced from Xu Y, Li C, Wu X, et al. Sheet-like 2D Manganese (IV) Complex with High Photothermal Conversion Efficiency. *J Am Chem Soc*. 2022;144(41):18834–18843.[50] Copyright 2022 Journal of the American Chemical Society (**C**) Axial T1-weighted MR images of a BALB/c mouse bearing 4T1 tumor xenografts at different time points after intravenous injection of Mn-HDCL. Reproduced from Xu Y, Li C, Wu X, et al. Sheet-like 2D Manganese (IV) Complex with High Photothermal Conversion Efficiency. *J Am Chem Soc*. 2022;144(41):18834–18843.[50] Copyright 2022 Journal of the American Chemical Society.

Combination Therapy

Synergistic Therapy

As previously stated, the exceptional physical, electronic, chemical and optical characteristics of 2D nanomaterials render them highly promising for potential applications in the field of cancer therapy. Numerous 2D nanomaterials exhibit diverse catalytic functionalities and effectively synergize multiple mechanisms to accomplish cytotoxic effects on tumors.[22]

For combined PDT and PTT, Lu et al incorporated the organic compound chlorophyll (Chl) with metal-supported vanadium carbide (V_2C) nanosheets (Figure 9C).[97] They studied the killing ability of 2D Chl/V_2C NSs on tumor cells under different conditions (Figure 9A), among which 2D Chl/V_2C NSs have PDT effect under 670 nm laser and PTT effect can be produced under 808 nm laser. The killing effect of the two methods on cells is 64% and 80%, respectively. When irradiated with both 670 and 808nm lasers, the killing effect of 2D Chl/V_2C NSs on cells can reach 99%, which verifies that the combined application of PDT and PTT can achieve better tumor-killing effect. The tumor volume of mice also shows the same trend (Figure 9B). In this work, the appropriate heating by PTT enables increased blood flow and improves oxygen supply for enhanced PDT, and PDT can disturb TME conditions and result in increased heat sensitivity of cancer cells. Zhang et al employed the liquid exfoliation method to synthesize $FePS_3$ nanosheets.[98] Their research findings indicate that these nanosheets exhibit a notable PTCE of 43.3% when exposed to 1064nm laser irradiation. This characteristic positions them as a promising type of efficient NIR-II PTA. This iron-based 2D nanosheet exhibits outstanding Fenton catalytic activity that triggers the CDT effect, which is augmented by its photothermal impact, thereby providing a synergistic PTT/CDT therapeutic effect. Liu et al also successfully synthesized 2D $FePS_3$ by liquid phase exfoliation and improved its biocompatibility by modifying it with lipoic acid-polyethylene glycol (LA-PEG).[62] These research findings indicate that $FePS_3$-LA-PEG has the capability to generate ROS when subjected to ultrasound, thereby facilitating the SDT effect (Figure 9D). The intrinsic Fenton catalytic activity of $FePS_3$ can synergistically collaborate with SDT to augment the therapeutic efficacy and efficiently eradicate tumors. 2D nanomaterials, which

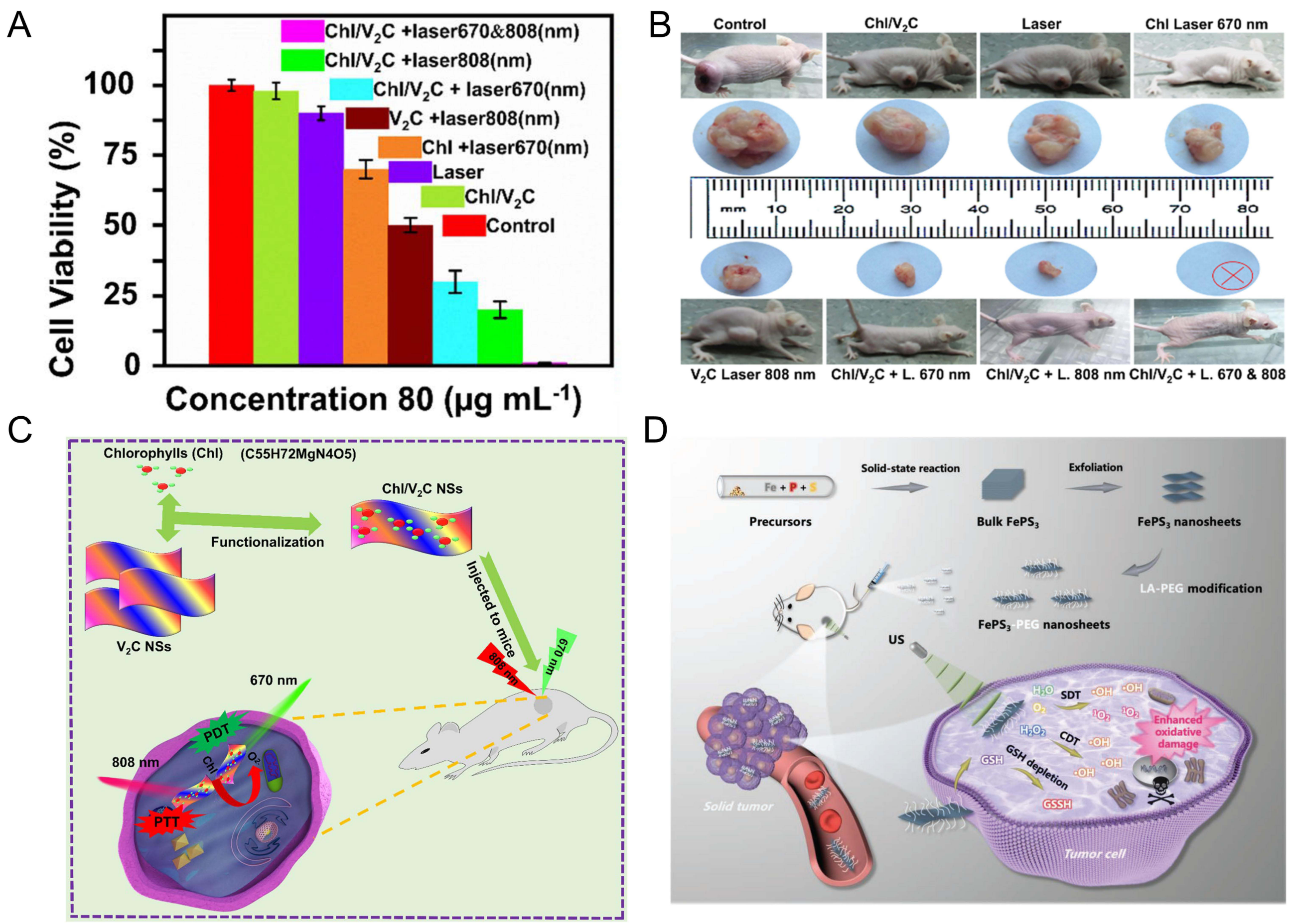


Figure 9 (**A**) MTT analysis of MCF-7 cells under different conditions. Reproduced from Lu H, Zada S, Tang S, et al. Artificial photoactive chlorophyll conjugated vanadium carbide nanostructure for synergistic photothermal/photodynamic therapy of cancer. *J Nanobiotechnology.* 2022;20(1):121.[97] Copyright 2022 BMC (**B**) The images of MCF-7 tumor-bearing mice with different treatments. Reproduced from Lu H, Zada S, Tang S, et al. Artificial photoactive chlorophyll conjugated vanadium carbide nanostructure for synergistic photothermal/photodynamic therapy of cancer. *J Nanobiotechnology.* 2022;20(1):121.[97] Copyright 2022 BMC (**C**) Schematic diagram of Chl/V_2C nanostructure for synergistic PTT/PDT. Reproduced from Lu H, Zada S, Tang S, et al. Artificial photoactive chlorophyll conjugated vanadium carbide nanostructure for synergistic photothermal/photodynamic therapy of cancer. *J Nanobiotechnology.* 2022;20(1):121.[97] Copyright 2022 BMC (**D**) Schematic diagram of the preparation of 2D $FePS_3$-PEG NSs and the proposed mechanism for combinatorial SDT/ CDT. Reproduced from Lin S, Yang M, Chen J, et al. Two-Dimensional FePS3 nanosheets as an integrative sonosensitizer/nanocatalyst for efficient nanodynamic tumor therapy. *Small.* 2023;19(8):2204992.[62] Copyright 2022 Wiley-VCH GmbH.

possess the ability to induce therapeutic effects through various mechanisms, exhibit enhanced efficacy in eliminating tumors and hold significant potential for diverse applications.

Theranostics

The development of an integrated approach of tumor diagnosis and therapy is the primary research objective of scientists due to the increased need for tumor therapy.[99] To address the issue, 2D therapeutic nanosystems were developed, which combine anticancer ability and imaging capability into a unified nanoplatform.[100]

The 2D GeP nanosheets prepared by Ren et al are high-performance PTAs with a PTCE of 68.6% in the NIR region, which can realize multi-modal imaging including PA imaging and photothermal imaging.[46] In addition, GeP nanosheets have a high loading capacity for the anticancer drug doxorubicin (DOX), thereby making the 2D nanocomposite a synergistic platform for chemotherapy and PTT (Figure 10A). Fang et al reported a novel 2D nanomaterials ($FePSe_3$@APP@CCM) for multimodal imaging and synergistic cancer therapy. It exhibited good PTCE of PTT and a significant effect of immunotherapy.[101] Meanwhile, the bioinspired 2D nanomaterials are also used as a new PAI and MRI contrast agent for precise and real-time monitoring. Ji et al synthesized 2D functional core layers (FCLs) nanosheets which were composed of MgO and Fe_2O_3 for cancer theranostics.[49] It has high PTCE, great O_2^- -generation ability under 658nm laser irradiation and enhanced generation capacity of ·OH in TME via the Fenton reaction (Figure 10B). What's

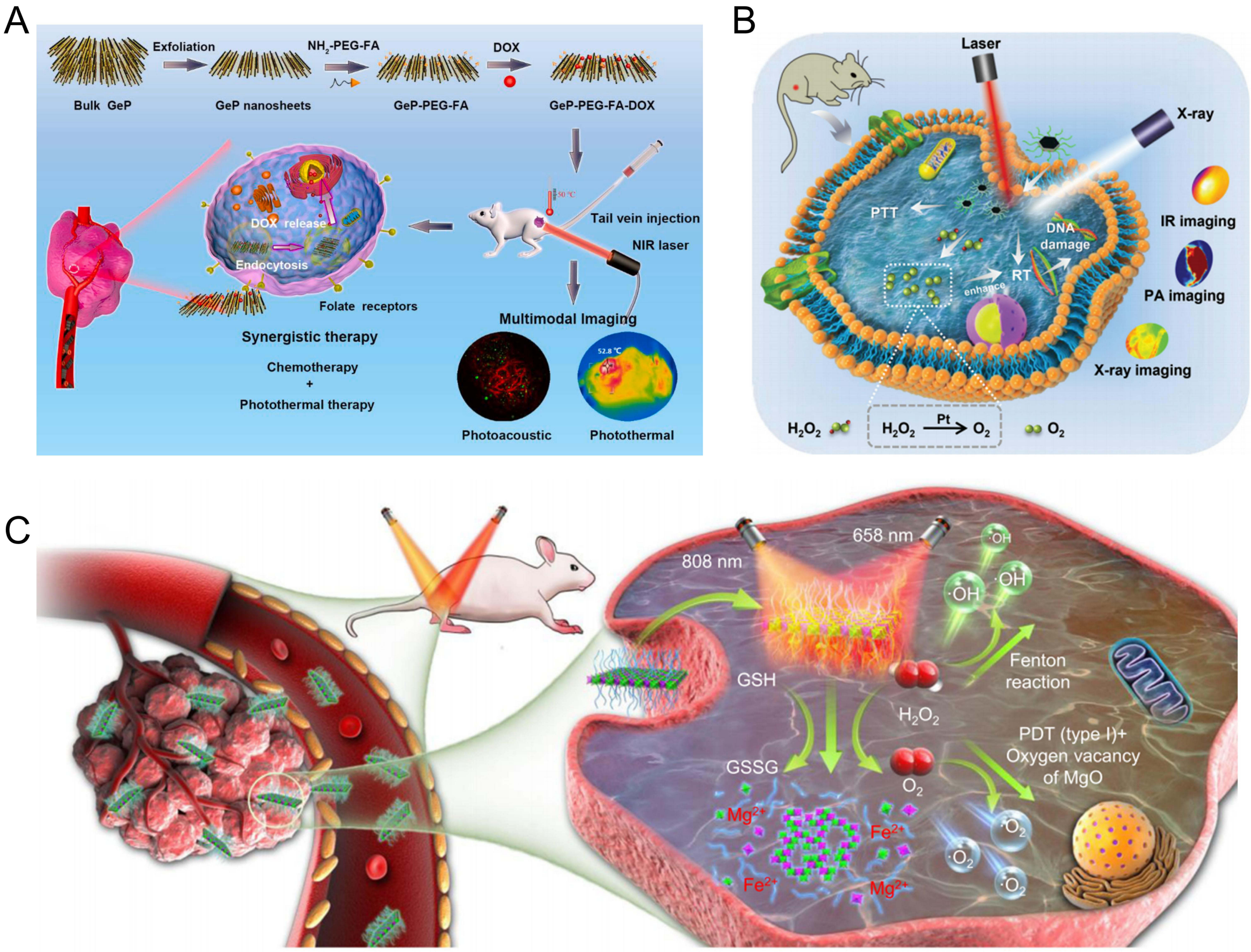


Figure 10 (**A**) The illustration of the 2D GeP nanosheets for cancer theranostics application. Reproduced from Chem Eng J. Volume 431. Ren X, Liu W, Zhou H, et al. Biodegradable 2D GeP nanosheets with high photothermal conversion efficiency for multimodal cancer theranostics.[46] Copyright 2022, with permission from Elsevier B.V (**B**) The photonic therapy-enhanced CDT based on FCL-PEG NSs in tumor-bearing mice. Reproduced from Ji X, Ge L, Liu C, et al. Capturing functional two-dimensional nanosheets from sandwich-structure vermiculite for cancer theranostics. *Nat Commun*. 2021;12(1):1124.[49] Copyright 2021 Nature Publishing Group (**C**) Schematic diagram of the tumor therapy mechanism of PtBi-PEG nanoplates. Reproduced from Liu Y, Li X, Shi Y, et al. Two-dimensional intermetallic PtBi/Pt core/shell nanoplates overcome tumor hypoxia for enhanced cancer therapy. *Nanoscale*. 2021;13(33):14245–14253.[103] Copyright 2021 The Royal Society of Chemistry.

more, FCL-PEG NSs also showed great performance in PA, photothermal and fluorescent imaging, which provides a foundation for its potential application in cancer theranostics. The 2D silicene material demonstrates remarkable light absorption capabilities.[102] Research findings indicate that the 2D silicene nano photosensitizer exhibits outstanding photostability, superior ability to generate $^1O_2$, and effective PA imaging capabilities, making it suitable for applications in tumor theranostics. The 2D PtBi-PEG nanomaterials developed by Liu et al are capable of PTT and radiotherapy (RT) for the treatment of cancer, as well as exhibiting favorable performance in infrared (IR) imaging, PA imaging and X-ray imaging; thus, these capabilities can be applied to image-guided cancer therapy (Figure 10C).[103] As novel multifunctional therapeutic nanoplatforms, 2D nanomaterials with both imaging and therapeutic functions can inspire the design and application of future anticancer nanoplatforms in biology and medicine and have tremendous potential in cancer therapy.

Clinical Translatability and Challenges

With superior physicochemical properties, metal-containing 2D nanomaterials can achieve obvious antitumor effects through therapy modalities such as PDT, PTT, CDT, and SDT. To date, metal-containing 2D nanomaterials have achieved substantial advancements in the field of biomedical science, particularly in cancer therapy. However, to successfully complete the clinical translation, a number of obstacles still need to be overcome.

The poor stability and biocompatibility of metal-containing 2D nanomaterials in physiological environments is an important problem hindering their clinical application.[104] Their large surface areas and easily modified surface properties allow for the enhancement of dispersion, stability and biocompatibility with the addition of surface modifiers such as CS, BSA, PEG, PVP, and others.

The key influencing factor of the biodegradation capacity of metal-containing 2D nanomaterials in non-targeted tissues and eliminating organs is the size of nanomedicine.[105] Liu et al pointed out that 2D Pd NSs with different sizes exhibited good biocompatibility in mice, rats and rabbits.[106] In their work, 5nm PdNSs exhibit a long blood half-life and can be cleared up through the kidney, while larger 2D PdNSs will accumulate in the liver and spleen for a long time. The long-term residence of metal-containing 2D nanomaterials in non-targeted tissues and their toxicity are major concerns that should be taken into consideration for biomedical applications in the clinic. The long-term retention of metal-containing 2D nanomaterials in non-targeted tissues may lead to systemic damage, such as thrombus and endothelial leakiness.[107,108] The cytotoxicity of these metal-containing 2D nanomaterials is highly dependent on their own size, structure and surface chemistry. Therefore, we can work on suitable low-cytotoxicity 2D nanomaterials by controlling the size and surface modification, to reduce their damage to non-target tissues and promote the process of clinical transformation.

At present, the animal models used for the antitumor effect detection of metal-containing 2D nanomaterials still mainly feature subcutaneous xenografts. The preclinical animal tumor models may contribute to the difference between research and predicted clinical performance as they do not reflect clinical tumors and their environment.[105] Genetically engineered mice models or patient-derived xenografts may be more effective in predicting the performance of metal-containing 2D nanomaterials in future clinical applications.

There are two challenges in addressing regulatory standards: the standard definition of metal-containing 2D nanomaterials and their related terms, and the systematic approach for the physical characterization and biological testing of nanomedicine, which have not yet been perfected in many countries and there is still a long way from basic research to clinical application.

Conclusions and Perspectives

In this review, we provide an overview of metal-containing 2D material manufacturing techniques and biomedical applications. These 2D nanomaterials have been successfully synthesized using both top-down and bottom-up techniques. The synthesis of simply layered metal-containing 2D nanomaterials may be accomplished using the top-down method since it is straightforward and practical. The bottom-up approach also produces materials with great accuracy and is appropriate for creating metal-containing 2D nanomaterials with intricate structures. In the field of biomedicine, current research works demonstrate that metal-containing 2D nanomaterials which are highly catalytic active and light/sonic responsive have tremendous potential, particularly for cancer therapy. Precision medicine based on metal-containing 2D nanomaterials in principle is more effective and safer than surgery combined with RT and chemotherapy for cancer patients. Metal-containing 2D nanomaterial-mediated cancer treatment methods, such as PDT, PTT, CDT and SDT, can destroy tumor cells through in situ generation of ROS or local high temperature while causing minimal harm to surrounding normal tissues. Combination therapy can also improve the therapeutic effect without increasing drug toxicity and is more conducive to the healthy recovery of patients. Additionally, most of the atoms in 2D nanomaterials are exposed on the surface, which facilitates material modification and efficient utilization. Moreover, owing to their large specific surface area, 2D nanomaterials may effectively load more chemotherapeutic drugs and tumor-imaging fluorescence probes, and be modified with tumor-targeted molecules more easily, suggesting that they can be utilized for targeted drug delivery, cancer imaging, etc. Therefore, the unique physical and chemical structure of metal-containing 2D nanomaterials, as well as their advantages of high loading capacity, make them the potential platform for the integration of tumor diagnosis and treatment.

Even though metal-containing 2D nanomaterials have a broad variety of applications in biomedicine, there are still certain obstacles and challenges in clinical translatability. First, the synthesis methods of these nanomaterials need to be improved. The top-down synthesis approach is straightforward and practical, but it does not provide the resulting materials with excellent quality and adequate accuracy. In addition, the bottom-up technique, which is the most prevalent approach, is capable of producing optimum nanomaterials; however, it is difficult to generate on a large industrial scale due to the laborious procedure involved in the process of synthesis as well as the high cost. Secondly, in the research on cancer therapy with these nanomaterials, most studies tend to explore the simple mechanism in vitro and in vivo. However, it is necessary to further explain their internal mechanisms, such as the interaction between metal species, the skeleton structures, interfaces and structural proteins, and how these materials affect or regulate various signaling pathways, etc. The in-depth and comprehensive research will help us to gain insight into the influence of the size, shape, chemical composition and surface properties of these nanomaterials on antitumor efficiency. Another existing problem is that some 2D nanomaterials are difficult to degrade in the physiological environment, so they may stay in the body for a long time and may cause damage. However, current research typically evaluates the efficacy of biological safety in just a short period. Therefore, it is essential to study the gene mutations, immune responses and changes in metabolic functions of organs such as the liver and kidney caused by the long-term retention of metal-containing 2D nanomaterials in the body to assess their biosecurity. In short, strict biomedical standards including long-term toxicity, cumulative effects, metabolism, biocompatibility and immunogenicity in animal models should be established systematically and comprehensively.

In summary, as a specified category of 2D nanomaterials, metal-containing 2D materials with large surface areas, unique chemical functions and intrinsic optical/sonic properties are promising nanoplatforms for biomedical applications. Metal-containing 2D nanomaterials present unprecedented opportunities and challenges for technological development in the fields of cancer therapy, drug delivery and diagnostics. We believe that this review will contribute to a better comprehension of metal-containing 2D nanomaterials-mediated cancer therapy and facilitate the future clinical application of nanomedicine.

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Disclosure

The authors declare no conflicts of interest in this work.

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