Cancer Insight
Homepage: https://www.anserpress.org/journal/CI

Recent Progress in the Transition Metal Sulfide/Phosphide for Cancer Theranostic Applications

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ABSTRACT

Transition metal sulfides/transition metal phosphides (TMS/TMP) has shown great potential in cancer diagnosis and treatment due to its unique structural, optical, acoustic and magnetic properties. TMS/TMP can be formed from sulfur/phosphorus source and metal into binary compounds, or from the interaction of hydrogen sulfide (or hydrogen sulfuric acid) with metal oxides or hydroxides. It has a series of unique properties, such as high conductivity, metalloid properties, a variety of valence states and adjustable structure and so on. These advantages make it have great potential in biomedical applications, such as diagnostic imaging, disease therapy and drug/gene delivery. This review presents the latest research progress of TMS/TMP on tumor imaging, diagnosis and treatment. Here, we first illustrate the synthesis approaches and surface modification of TMS/TMP. Then, its emerging applications in tumor diagnosis and therapy are highlighted. Moreover, the challenges of TMS/TMP-mediated diagnosis/treat are provided and the prospective for this field are discussed.

KEYWORDS: Transition metal sulfides; Transition metal phosphides; Nanomedicine; Drug delivery; Cancer diagnosis and therapy

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ISSN 2972-3388
doi: 10.58567/ci01020005
Received 2 December, 2022; Accepted 15 December, 2022; Available online 22 December, 2022

Introduction

Cancer is one of the major diseases threatening human health. Although the traditional treatment (surgery, chemotherapy and radiotherapy) has been used for many years, the prognosis of surgical treatment is poor, easy to relapse, and the side effects of radiotherapy and chemotherapy are great, which seriously threaten the physical and mental health of cancer patients.[1-3] The application of nanomaterials in cancer treatment brings hope for the diagnosis and treatment of tumors, especially the functional nanoparticles (NPs) with unique physical and chemical properties, which has attracted extensive attention.[4-6] Researches of nanomaterials for cancer diagnosis and treatment mainly focus on imaging, phototherapy, drug delivery or combination of these methods.

Due to the difference in the physiochemical properties between transition metal elements and other metal elements, there may be a single d electron in the atom or ion of the transition metal. The spin of the electron determines the magnetism of the atom or molecule. Many transition metals have paramagnetism. Ferromagnetism can also be observed in iron, cobalt and nickel. The transition element has an empty d orbital and a high charge/radius ratio, which makes it easy to form stable coordination compounds with various ligands. [7] Transition metal sulfides (TMS) are widely used in photocatalysis due to their narrow band gap and good photoelectric properties. Transition metal phosphides (TMP) have higher stability and conductivity than oxides, thus making them mainly utilized for photocatalysis. Different structures of the same transition metal can cause changes in properties. Some TMS/TMP with unique structures, such as ultrasmall quantum dots, one-dimensional or two-dimensional lamellar structures, hollow structure, multi-layer core-shell structure will be endowed with unique electrical, optical and catalytic properties, which interests many scientists. Different preparation methods have great influence on the morphology and structure of the materials. Representative TMS/TMP materials include Ag_2S,[8-11] MoS_2, [12-14] CuS,[15-21] WS_2,[22-27] FeP,[28-30] CoP,[31-32] NiP,[33] CuP,[34] The fabrication methods mainly contain stripping method, chemical vapor deposition method (CVD), water/solvothermal method and wet chemical method. TMS/TMP materials synthesized by different methods is suitable for photoelectrocatalysis, new energy resources, biomedical and other research fields. In recent years, studies have focused on the complex structure and morphology design of TMS/ TMP in order to improve the absorption range and efficiency.

Due to their unique structure, they have shown great potential in the fields of photocatalysis and biomedicine, such as tumor imaging, phototherapy, drug delivery. Some transition metal sulfides are quantum dots (QDs)with low dimensional structure. QDs are widely used in biosensors, tumor imaging, photothermal therapy and immunoassay due to their remarkable optical properties and biocompatibility.[10, 35-36] For example, Ag_2S QDs have strong absorption in the visible and near infrared (NIR) light, and show good photothermal and photoacoustic response under a certain wavelength excitation.[8] In this review, we systematically summarize the latest progress of TMS/TMP nanomaterials in biomedical field, especially in tumor imaging and treatment (scheme 1). Firstly, the synthesis methods and applications of TMS/TMP nanomaterials are introduced. Then, the latest progress of tumor imaging with TMS/TMP nanomaterials are presented, including computed tomography (CT), fluorescence imaging (FI), magnetic resonance imaging (MRI), positron emission computed tomography (PET), and photoacoustic imaging (PAI). Moreover, tumor treatment methods are introduced, including radiotherapy (RT), phototherapy (PTT/PDT), chemodynamic therapy (CDT) and its application in drug delivery and gene delivery. Finally, the problems TMS/TMP may

encounter as a nanoplatform for cancer diagnosis and treatment and the future development prospects are discussed.

1. Synthesis approaches and Surface Modification of TMS/TMP

The excellent biomedical properties of TMS/TMP based nanomaterials largely depend on their structures. Different preparation methods have great influence on the structure. In this paper, the common preparation methods of TMS/TMP materials are summarized, including mechanical striping, CVD, solvothermal/hydrothermal, wet chemistry method. In order to improve the biocompatibility, absorption and metabolism of materials, various surface modification strategies have been implemented.

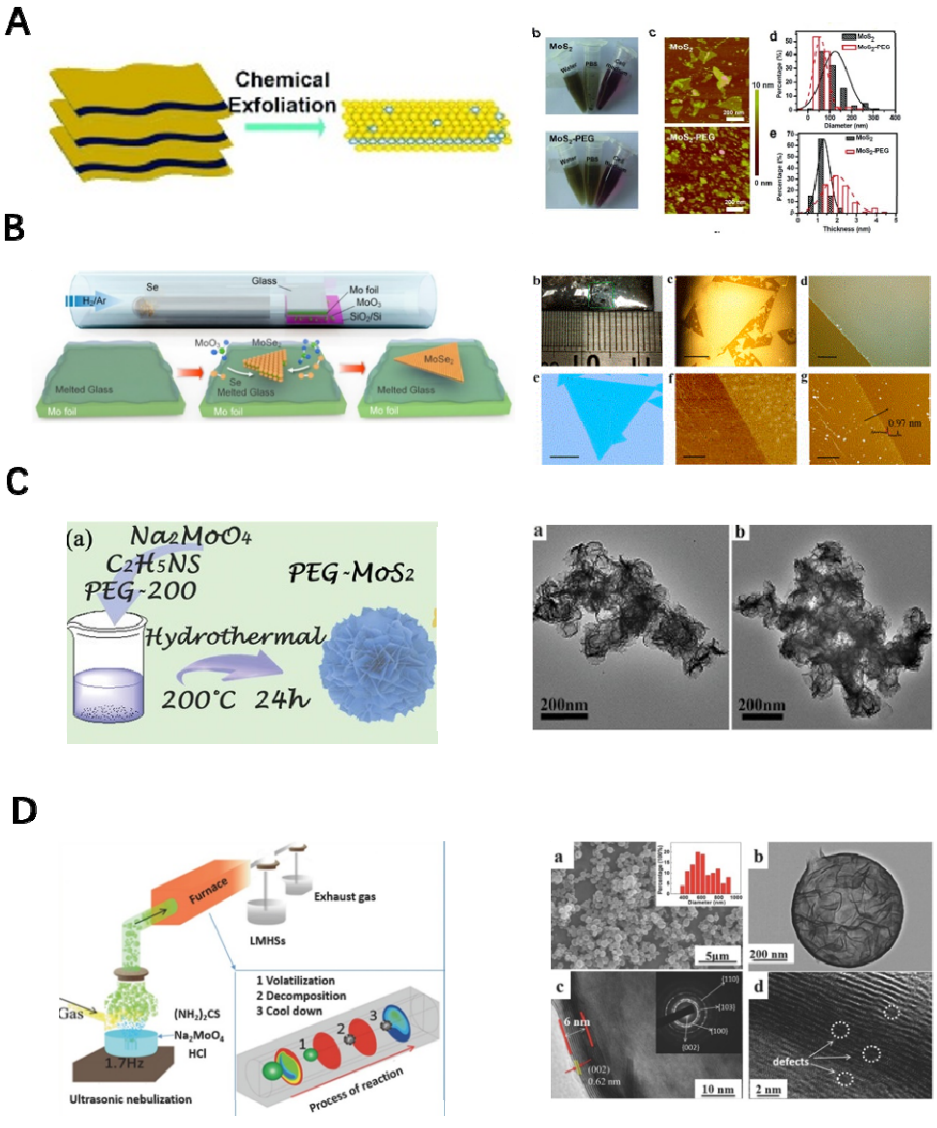

Figure 1. The synthesis method of TMS/TMP and the corresponding morphology diagram: A. Preparation of MoS_2 nanosheets by stripping method.[37] Copyright 2014, Wiley-VCH.B. Preparation of single layer $MoSe_2$ crystal on molten glass by CVD.[38] Copyright 2017,American Chemical Society. C. Nanoflowers with a diameter of 200 nm were prepared by hydrothermal method.[39] Copyright 2019, Wiley-VCH. D. The layered hollow

structure of MoS_2 was prepared by chemical aerosol flow method. The method is one-step, simple, fast and can be expanded.[40] Copyright 2016,Wiley-VCH.

1.1 Synthesis strategies of TMS/TMP

1.1.1 Mechanical stripping method

In 2004, Geim and co-workers used mechanical exfoliation for the first time to successfully exfoliate highly oriented thermally cracked graphite and observed a single layer of graphene.[41] As soon as the mechanical stripping method was successfully found, it generated a research upsurge of two-dimensional (2D) materials. Researchers used this method to prepare other 2D materials such as MoS_2. The nanosheets of MoS_2 were prepared by ball milling in the presence of ammonia or hydrocarbon ethylene gas. The obtained nanosheets can maintain their single crystal structure and low defect density even after a long time of grinding. [42]Generally speaking, the materials prepared by mechanical stripping method have many advantages, such as less defects, smooth surface and high mobility. However, this method is limited by poor controllability, low production efficiency and cannot be industrialized in mass production, thus restricting its wider application.

Also, layered 2D materials can be peeled from bulk materials via liquid phase peeling method. The liquid phase peeling method is a common method that the key structure and average thickness of the layered material can be controlled by adjusting the parameters of the ultrasonic cell disruptor or selecting different surfactants. Coleman and co-workers used the liquid phase exfoliation method to exfoliate the bulk crystals of MoS_2 and WS_2 in a common solvent to obtain monolayer and multilayer nanoflake.[43]Liu and co-workers used chemical exfoliation to prepare MoS_2 nanosheets with an average diameter of 120 nm and an average thickness of 1 nm.[37] Zhao and co-workers reported a simple, high-yield, low-cost method to design a single-layer MoS_2 nanosheet with a controllable size through a modified oleum treatment exfoliation process.[44] Liquid phase stripping method is universal and favorable for large scale synthesis of materials. Nevertheless, there are still some problems, such as high requirements for reaction conditions and solvent-induced toxicity.

1.1.2 Chemical vapor deposition (CVD)

CVD is a novel technology for preparing inorganic materials developed in recent years. It is a process in which gaseous substances react on a solid surface to form solid sediments. One advantages of CVD is that the composition of the final product can be controlled by adjusting the ratio of precursors, and the good interface between the nanostructure and the substrate is conducive to charge transfer. Many materials are prepared by CVD, such as graphene, transition metal dichalcogenides. For example, Lin and co-workers synthesized large area MoS_2 atomic layer by CVD.[45] Cheng and co-workers demonstrated a double additive CVD (DA-CVD) method to prepare MoS_2 with large dimensions and doped with Mn.[46] Conventional Ti_2 thin films are prepared using CVD. [47] However, the main disadvantages are that the requirements of reaction temperature, pressure and gas flow are relatively high, and the deposition rate is low (generally only a few μm to several hundred μm per hour), so it is difficult to deposit locally. In conclusion, CVD is suitable for manufacturing materials with large size, controllable thickness and high requirements, but CVD is not suitable for materials requiring mass production.

1.1.3 Solvothermal/hydrothermal approach

Hydrothermal reaction process refers to as the general term of chemical reactions in water, aqueous solution or steam under certain temperature and pressure. Solvothermal method is developed on the basis of hydrothermal method, which is usually carried out in organic medium with high boiling point, and nucleation and crystal growth can be controlled in the reaction process. Different solvents can be used to obtain products with different morphologies and sizes. Qu and co-workers used solvothermal method to prepare MoS_2 nanoflowers.[39] Liu and co-workers obtained ultra-small MoS_2 nanodots by one-step solvothermal decomposition of ammonium tetrathiomolybdate.[12] Zhu and co-workers prepared nanocrystals with a particle size of about 30 nm and octahedral FeS_2 samples with a size of 350 nm were prepared by thermal decomposition method and solvothermal method (using ethylene glycol as solvent), respectively.[7] Zhang and co-workers synthesized Copper(I) phosphide and Fe_2P by organic solvothermal method, which had hexagonal structure with the particle size around 22 nm and 1D rod-like structure with a size of 10 × 180 nm, respectively.[30, 34] However, the crystallization rate of some transition metal-based nanocrystals prepared by solvothermal and hydrothermal methods is too fast. High temperature may aggravate the formation of nanocrystals, leading to rapid accumulation and internal growth. Some researchers have proved that polymer coating can effectively control the rapid accumulation rate of crystals. For example, Shi and co-workers and co-workers used solvothermal method to control the size of MoS_2 nanosheets by adding PEG-400.[48] Hydrophobic Ag_2S QDs were synthesized by thermal decomposition of $(C_2H_5)_2NC_2Ag$ using 1-dodecanethiol (DT) as surface capped ligand for the first time.[8] Bimetallic sulfides can also be synthesized by hydrothermal method. Wu and co-workers dissolved $CuCl_2$, $CoCl_2$, thiourea and PVP in deionized water, then added ethylenediamine and heated at 160°C for 20 h to obtain $CuCo_2S_4$ with a size of about 10 nm.[49] Liu and co-workersand co-workers synthesized small size metal sulfides (CuS, Ag_2S, Bi_2S_3 and Cds, NPs) coated with proteins by a simple hydrothermal method.[50] Hydrothermal/solvothermal process is characterized by high purity, good dispersion, good crystal shape and low production cost. Generally speaking, Hydrothermal/solvothermal synthesis of micro-structured crystals is a promising preparation strategy with a simple and high yield.

1.1.4 Wet Chemistry

The methods of preparing materials through chemical reactions with the participation of liquid phases are collectively referred to as wet chemical methods, such as chemical liquid deposition (CBD), electrochemical deposition (electroplating), sol-gel, etc. Liu and co-workers prepared metal ion (M) doped WS_2 nanoflakes (M = Fe^{3+}, Co^{2+}, Ni^{2+}, Mn^{2+} and GD^{3+})) by a simple wet chemical method to guide PTT and RT under multimodal imaging. The specific process is as follows: a mixture of WCl_6: MClx was added to the flask (containing oleamine and 1-octadecene). The flask was filled with N_2 and stirred to remove water and oxygen. The temperature of the solution was rapidly raised to 300°C and kept for 30 minutes to obtain the mixed solution. Then, the sulfur solution prepared in advance at 300°C was injected into the above mixed solution, and then reacted at 300°C for 30 min. After cooling to room temperature, the nanosheets were precipitated.[51]Meng and co-workers prepared layered hollow MoS_2 nanospheres using wet chemical methods using sodium molybdate ($Na_2MoO_4·H_2O$) and thiourea $(NH_2)_2CS$ as precursors. [40]

1.2. Surface Modification

The target of tumor treatment is organism, so any nanomaterial with therapeutic effect must have biocompatibility, can be absorbed and metabolized by the body, increase blood circulation time and reduce side effects. For better combination with biomolecules and minimized toxicity to the body, the surface of nanomaterials requires some functional groups, such as amine, dopamine, etc. So it is very crucial to modify the surface of nanomaterials.[52]

Many kinds of polymers are used for surface modification, such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hyaluronic acid (HA), amphiphilic gelatin (AG). Because PEG is non-toxic, nonirritating, water-soluble and miscible with many organic components, many researchers use it to modify nanomaterials. There are many examples of transition metal sulfides treated with PEG, such as Ag_2S,[8, 53] MoS_2[48, 54] ,CoS[55-56], CuS[16, 20, 57-58], MnS[59-61]. Hu and co-workers modified Fe_3S_4 nanosheets with PVP, which increased the effective accumulation of materials in the tumor site. [62] HA can recognize and target CD44 protein on some cell membranes, so the surface functionality with HA can not only improve the biocompatibility of nanomaterials, but also actively target cells to optimize the utilization rate of materials. [63] Zhang and co-workers used HA to modify CuS surface. Superficial HA not only provides targeting capability, but also acts as a stable protective layer for CuS to survive in blood circulation. In some tumor sites overexpressing hyaluronidase (HAase), CuS would be exposed once the HA is degraded, which can play the key role of PTT mediated by CuS and induce cell apoptosis. AG was also reported to be a coating layer of CuS to improve biocompatibility.[64]

Besides polymers, many biomolecules are also used for surface modification, such as bovine serum albumin (BSA), human serum albumin (HSA), ferritin (FN), soybean phosphoripid (SP) molecule and so on. The excellent biocompatibility of these native macromolecules has made them promising for sueface functionalities. BSA was used as sulfur source to provide binding sites for metal ions. Encapsulation of drug loaded nanoparticles with erythrocyte membrane and cancer cell membrane can improve the targeting accuracy and biocompatibility. [65-69] Ag_2S nanoparticles can be synthesized by precisely controlling the growth of Ag_2S in HSA.[10] These reactions are based on electrostatic interactions and subsequent reduction/precipitation reactions to nucleate and grow into metal sulfide nanoparticles. The whole process is easy to operate, reproducible and biocompatible. No matter what kind of modification, the ultimate goal is to meet the practical needs of biomedicine and make current tumor diagnosis and treatment more precise and accurate.

2. Applications in tumor imaging, biodetection and therapy

A variety of researches focused on metal elements have been conducted in tumor imaging. The metal elements with higher atomic number like Bi and I have stronger absorption of X-ray and are suitable for CT imaging. There are also some imaging methods related to the optical and acoustic properties of materials, such as fluorescence imaging and photoacoustic imaging. Additionally, magnetic materials can serve as a contrast enhancer for magnetic resonance imaging. Materials labeled with radionuclides are feasible for positron emission computed tomography (PET), which utilizes nuclear medicine for imaging. In modern research, with the rapid development of nanomaterials, varied materials are explored with multimodal imaging capability, which can achieve more accurate tumor diagnosis. The application of nanomaterials in

tumor therapy is mainly based on its intrinsic physiochemical properties, such as the high atomic number of materials for radiotherapy, optical properties for photothermal and photodynamic therapy, acoustic properties for kinetic therapy, and high reaction activity with overexpressed H_2O_2 in tumor microenvironment to generate reactive oxygen species (ROS) to generate cytotoxicity. Some nanomaterials have large specific surface area or can react with some chemotherapeutic drugs to form chemical bonds, which endows them as drug or gene carriers. Therefore, the targeted specificity of tumor cells can be effectively improved, and the on-demand rlease of tumor site with lower side effects to other nornal tissues are achieved.

2.1 Tumor imaging

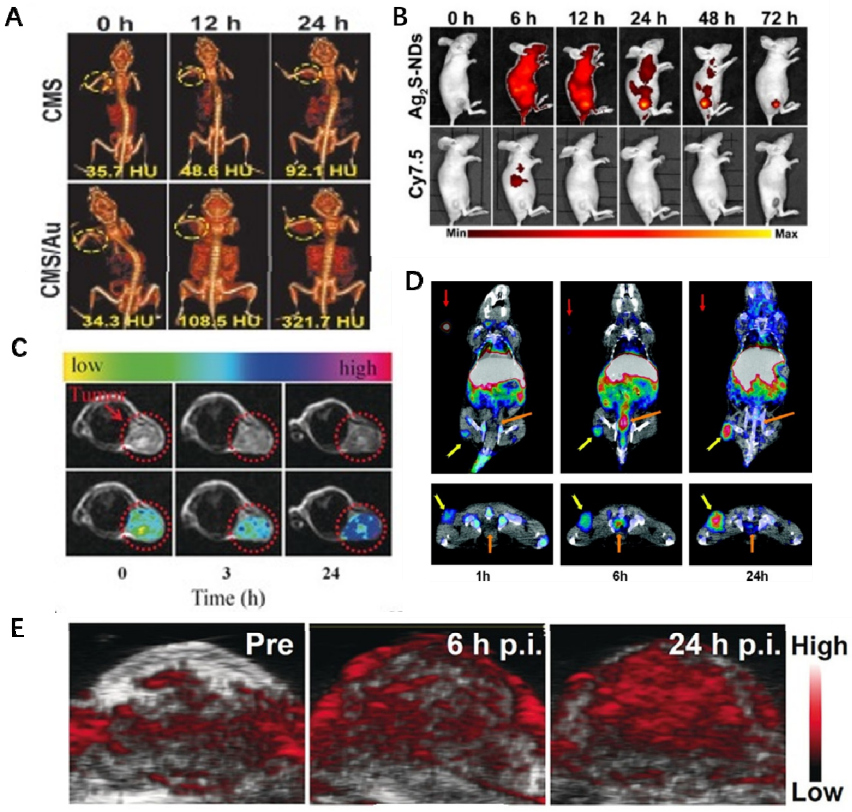

Figure 2. A. The CT signal intensity of Cu_2MoS_4 (CMS) and CMS/Au solutions with different concentrations showed a linear relationship with the material concentration.[70] Copyright 2020. B. Ag_2S nanodots for Second Near-Infrared FI. [10] Copyright 2017. C. Fe_2P for MRI.[30] Copyright 2019. D. PEG-[^{64}Cu] CuS for Micro-PET/CT images. [71]Copyright 2010. E. VS_2 nanodots for PAI.[72] Copyright, 2017.Reproduced/Adapted with permission.

2.1.1 CT

Computer X-ray tomography (referred to as X-CT or CT) is a device that can display the fault structure of various parts of the human body after X-ray tomography. Before CT examination, the examiners need to inject contrast agent which further enters various parts of the human body for metabolism. The metabolism of contrast medium in the lesion site is very large, and a large amount of contrast agent will be concentrated in the lesion area, which can be easily detected by CT scanning. Hence, the contrast medium is significant to get a good contrast CT result. Materials containing elements with high atomic number and strong X-ray

absorption capacity, such as MoS_2, TaS_2 and WS_2, can be used as CT contrast agents to enhance CT imaging. Tantalum (Ta) has a high atomic number and high X-ray attenuation characteristics. Unlike other Ta-based compounds, TaS_2 has a small size-dependent band gap, which can be well exerted for tumor treatment under the guidance of CT images.[73] WS_2 nanoplates can serve as a contrast agent for in vivo enhanced X-CT imaging, and assist image-guided therapy of tumors.[22] The hydrophilic Cu_3BiS_3 nanocrystals prepared by Hu and co-workers has a CT imaging response due to the large X-ray attenuation coefficient of bismuth.[74] Compared with comprehensive treatment, single CT imaging cannot meet the needs of modern tumor treatment, so it is urgently needed to create multimodal imaging and treatment.

2.1.2 FI

Fluorescence imaging (FI) is an imaging technology based on luminescent groups, which has the advantages of fast acquisition time and high imaging temporal and spatial resolution. QD_S are a new kind of fluorescent labeling materials. Compared with traditional organic fluorescent agents, QD_S fluorescence has the advantages of strong emission intensity, high photochemical stability and adjustable color. Wang and co-workers used Ag_2S QDs as imaging contrast agent, which emitted bright fluorescence in the NIR-II window for positioning in deep organs, dynamic tumor contrast and rapid tumor detection.[53, 75-76] By controlling the growth of Ag_2S in hollow human serum albumin nanotubes, Chen and co-workers can accurately synthesize Ag_2S nanoparticles, which can produce effective fluorescence and unique photoacoustic intensity in the NIR-II.[10] Based on the fluorescence properties of CdSe/ZnS QDs, some researchers have investigated the effect of fluorescence intensity modulation on ROS in cancer cells during radiotherapy and chemotherapy.[77] The photoluminescence wavelength of Cd_3P_2 quantum dots synthesized by Miao can span the visible to near-infrared spectral region, which is conducive to expanding the application of biological fluorescent labeling.[78]

2.1.3 MRI

Compared with CT, MRI has the advantages of high tissue resolution, spatial resolution, no hard artifact, no radiation damage, and so on. At the same time, exposed to different contrast conditions, MRI can monitor the blood flow changes of blood vessels and heart, which is widely used in clinical practice.[72] In order to obtain more accurate molecular structure or internal structure of human body, appropriate contrast agent is necessary. TMS/TMP have made great progress in the field of MRI because of their unique magnetic properties and good ion carrying capacity. Iron based, cobalt based, nickel based and manganese based therapeutic agents, such as FeS, CoS, FeP, Co-P, NiP and MnS have been exploited for MR imaging-guided cancer therapy.[7, 49, 55, 59, 61-62, 79-82] Liu and co-workers synthesized VS_2 @ lipid PEG nanoparticles for the first time to achieve high-efficiency photothermal tumor ablation guided by MRI in vivo.[72] FeP nanoparticles were successfully synthesized by thermal decomposition, which could react to acidic microenvironment and produce significant T1 enhancement of MRI in tumor area. Consequently, FeP nanomaterial is a potential alterative MRI contrast agent for tumor diagnosis.[29]

2.1.4 PET

Positron emission computed tomography (PET) is an advanced clinical imaging technology in nuclear medicine. The necessary substance during metabolic procedure of living body is labeled with radionuclide, and the health condition can be reflected by the accumulation of the necessary substance in the metabolism

in vivo, so as to achieve the purpose of diagnosis. Because TMS/TMP have good loading capacity and biocompatibility, combining elements with nuclear imaging capability can obtain good nuclear imaging capability. Li and co-workers demonstrated the preparation of simple and stable [^{64}Cu] CuS nanoparticles for PET imaging and photothermal ablation.[71]

2.1.5 PAI

Photoacoustic imaging (PAI) is a new non-invasive and non-ionizing biomedical imaging method, which has the advantages of deep penetration, good contrast and high spatial resolution. In particular, it can be combined with PTT. The photothermal effect produced by photothermal agent can locally produce sound waves, which can be converted into photoacoustic signals. TMS/TMP have good light absorption and photothermal properties, so have the potential to be used as PAI agent. Liu and co-workers reported a novel biodegradable amphiphilic gelatin (AG) coated with doxorubicin (DOX)-loaded, a common anticancer drug, copper sulfide (CuS) composite for PAI guided tumor therapy.[64] Chen and co-workers have successfully synthesized ultra-small CuS nanoparticles in the FN cage cavity via biomimetic method, which shows excellent photoacoustic tomography in quantitative ratio PAI.[83] In addition, the same group further prepared PEGylated $Cu_{2-X}S$ nanodots with particle size less than 5 nm, which are suitable for PAI guided collaborative nanocatalytic therapy/PTT anti-tumor.[20] TMP considerable photothermal properties can also be used in PAI.

2.1.6 Multi-modal imaging

Single-modality imaging technology has made great contributions to disease diagnosis. However, in the face of complex and changeable diseases and prognostic diagnosis and therapy, single-modality exposure has many shortcomings, and the development of multiple imaging technologies has become very urgent. TMS/TMP has made a lot of progress in multimodal imaging, integrating many imaging modes, such as CT, FI, MRI, PET, PAI, US, etc. For example, MnS@Bi_2S_3-PEG nanoparticles were designed for MRI, CT and PAI of cancer cells.[59] And CuS@MnO_2-FITC NPs were prepared for in vivo FL, PT, MR, and CT imaging.[84]Biodetection

2.2 Tumor therapy

2.2.1 Radiotherapy

Radiotherapy (RT) is the treatment of malignant tumor and some benign diseases by using one or more kinds of ionizing radiation. The method of radiotherapy is ionizing radiation. By introducing high-Z nanomaterials as radiosensitizer, the local radiation dose can be remarkably enlarged. Liu and co-workers have proved that X-ray irradiation affects the uptake and excretion of different types of nanoparticles by cancer cells.[58]To study the combination of photothermal ablation (PTA) and radiotherapy (RT), Shi and co-workers modified ultra-small CuS nanoparticles on the surface of silica (SiO_2)-coated rare earth upconversion nanoparticle.[85] Au@MnS@ZnS-PEG has good stability and negligible cytotoxicity in different physiological solutions, which has potential applications in MRI guided RT therapy.[61]

2.2.2 PT

Phototherapy (PT), including photothermal therapy (PTT) and photodynamic therapy (PDT), is a non-invasive therapy mode, which can effectively eliminate tumor cells and has attracted extensive attention. PT can stimulate an immune response to kill residual and metastatic cancer cells.[86-88] The Cu_2MoS_4/Au

heterostructure prepared by Lin and co-workers can be used as a contrast agent for PAI and CT under NIR, and has enhanced PTT and PDT effects. Moreover, it proved that phototherapy can activate the immune system and prevent tumor metastasis. [70]

PTT is another widely studied therapy approach that applies materials with high efficiency of light and heat conversion. When injected into the living body, those light-activated materials would gather near the tumor sites by targeted recognition technology, and converts light into heat energy to kill cancer cells under the irradiation of external light source (generally near-infrared light). For the improved effect of photothermal therapy, it is necessary to develop novel materials with high efficiency of photothermal conversion and enrichment in tumor site. TMS/TMP have been developed and proved to be a promising and efficient PTT reagent, such as cobalt sulfate,[49, 55-56, 89] copper sulfide,[57, 64, 67, 83, 90-91]iron sulfide,[7, 81-82]molybdenum sulfide,[14, 37, 40, 54, 92]iron phosphide,[28-30]cobalt phosphide,[31-32, 93] nickel phosphide.[33]

Wang and co-workers synthesized a novel rhombic dodecahedral and poly(vinylpyrollidone)-modified triangular SnS nanocrystals for PTT.[94-95]The nanomaterials prepared by Zhang and co-workers are composed of upconversion nanoparticles surrounded by HA-modified CuS, which are used for deep tumor PTT.[63] Liu and co-workers prepared hexagonal FeS crystals with different cubic structure to form nanoplates instead of spherical nanoparticles, which could realize MRI-guided PTT.[82] One more study was reported about a nanocomposite comprised of Platinum (Pt) -modified gold nanorods and Ag_2S core satellite. This nanoparticles present excellent properties for CT imaging and photoacoustic imaging functions to quantify intracellular MIR (miR-21) and photothermal therapy for tumors.[9]

Different from PTT, PDT does not rely on the laser-induced thermal ablation, and is less detrimental to the tissues around tumor cells.[96] PDT is to irradiate the tumor site with a specific wavelength, which causes photochemical reaction of photosensitive drugs gathered in tumor tissue to generate singlet oxygen. Singlet oxygen can react with the nearby biomacromolecules to produce cytotoxicity and kill tumor cells. Recently, many researchers have realized that tumor microenvironment (TME) is different from normal cells, and specializes in low oxygen content and excessive glutathione production. However, a highly efficient PDT therapy extremely relies on oxygen generation and glutathione elimination, of which the therapeutic effect may be largely impaired by the characteristics of TME. The design and fabrication of TMS and TMP with oxygen generating capacity to improve the tumor hypoxia and glutathione consumption capacity brings hope for enhancing the efficacy of PDT.

Compared with individual treatment of PTT or PDT, the coordination of PTT and PDT shows more superior therapeutic effects against tumor cells. Zhao and co-workers used WS_2 nanoplates coated with BSA as photosensitizer carrier for the combined application of PDT and PTT.[65] Yang and co-workers developed an IR-808 dye-sensitized upconversion nanoparticles, of which the outer sphere was modified with Ce6-containing SiO_2 layer for PDT reagent. These presynthesized nanocomposite were then grafted onto MoS_2 nanosheets to realize the combined treatment of PDT and PTT.[97] The MoS_2@Fe_3O_4-ICG/Pt(IV) Nanoflowers nanocomposites designed by Lin and co-workers can realize the synergistic therapy of PTT/PDT/chemotherapy.[98] In this system, the author proved that the effect of PDT was improved because of ICG. Both ICG molecules and MoS_2 nanomaterials show wide absorption in the NIR region, which are used for PTT. Furthermore, Fe_3O_4 has high transverse relaxativity, which is used for MRI. Cai and co-workers designed multifunctional nuclear satellite nanostructures by inserting porphyrin molecules on the surface of [^{89}Zr] labeled mesoporous SiO_2 nano shells, with copper sulfide (CuS) nanoparticles assembled on the surface. The interaction between CuS-mediated PTT and porphyrin mediated PDT effectively eliminated tumor without

visible recurrence or side effects.[16] Lin and co-workers formed CMS/Au heterostructures by depositing plasmon Au nanoparticles on CMS nanosheets, showing better PDT and PTT effects than purine CMS.[70] Another work conducted by Qu and co-workers proposed intriguing nanostructures composed of Co_3S_4 and nitrogen doped carbon, which promoted PDT and PTT, and generated nearly twice as much ROS as pure Co_3S_4.[99] Utilizing varied imaging approaches for adjuvant therapy, the precise treatment of tumor with TMS/TMP can be further reinforced. For example, Liu and co-workers prepared a novel biodegradable AG-coated nanocomposite composed of dendrimers loaded with DOX and CuS. This nanocomposite could be used for PTT and PDT dual phototherapy and synergetic chemotherapy under the guidance of PAI.[64] FeS_2@BSA-Ce_6 nanomaterials can achieve the synergistic treatment of PTT and PDT with the assist of three imaging modes (optical imaging/ magnetic resonance imaging/ photoacoustic imaging).[66] FeS_2-PEG prepared by Bu and co-workers can achieve PTT/CDT synergistic therapy under the guidance of MRI.[81]

2.2.3 CDT

Chemodynamic therapy (CDT) is a highly specific therapeutic method for tumor cells, which can trigger Fenton or Fenton-like reactions in tumor microenvironment. Then, the high level of H_2O_2 in TME can be catalyzed to generate toxic hydroxyl radical (·OH) and other strong oxidative active species, thus ultimately activating cell apoptosis and causing cell death. Cheng and co-workers assembled monodisperse CoS_2 nanoclusters (CoS_2 NCs) formed by oligomerization of ultra-small nanocrystals to achieve CDT of cancer cells.[100] Lin and co-workers constructed a multifunctional cascade bioreactor using hollow mesoporous Cu_2MoS_4 loaded glucose oxidase as the carrier, which was used for the synergistic treatment of CDT/starvation therapy/phototherapy/immunotherapy.[15]

2.2.4 SDT

Sonodynamic therapy (SDT) is utilizing ultrasound as a stimulating source to treat cancer due to its favorable tissue penetration. Of note, focused ultrasound can concentrate ultrasonic energy on deep tissue without trauma, and activate some sound sensitive drugs (such as hematoporphyrin) to produce anti-tumor effect. It has been suggested that ultrasound irradiation is helpful to the production of ROS, which proves that ultrasound is an effective strategy to improve the efficiency of Fenton reaction.[30, 101] Compared with PDT, SDT has a deeper penetration depth and a better therapeutic effect on deep tumors. However, in the hypoxic tumor microenvironment, the therapeutic effect cannot achieve the desired effect. In the Pt-CuS system designed by Lin and co-workers, the heat generated by Pt-CuS under 808 nm laser irradiation can accelerate the catalytic activity of Pt and increase the O_2 level, thus further promoting the effect of SDT.[19]

3.3 Drug Delivery and Gene Delivery

2.3.1 Drug delivery

Chemotherapy is one of the main methods of tumor treatment, but it has strong toxic and side effects. So it is urgent to design controllable nano carriers to improve the selectivity and safety of chemotherapeutic drugs. TMS/TMP have great potential as a drug carrier due to the advantages of structural diversity, adjustable porosity, large specific surface area and responsiveness to tumor microenvironment. Among relevant studies, Wang and co-workers encapsulated DOX in phospholipid PEG-Ag_2S QDs and combined with ring RGD (cRGD), a integrin specific recognition peptide, to form a nano drug delivery system with tumor vascular targeting specification, which can cause extensive tumor apoptosis.[76] Zhou and co-workers

prepared mesoporous cobalt sulfide (CoS) nanomaterials through DNA template hydrothermal method for PTT and drug delivery. The heat shock proteins (HSP) inhibitor epigallocatechin gallate (EGCG) and immunogenic cell death (ICD) inducer oxaliplatin (OXA) were encapsulated in porous cobalt sulfide nanomaterial. The drug release was triggered under pH and temperature.[79] Some nanomaterials with core-shell structure were used as drug carriers, and the drugs were controllably released in response to pH.[102-104] Huang and his colleagues loaded Cu^{2+}, GOD and chemotherapeutic drug doxorubicin (DOX) directly into CaP nanomaterials. The DOX loaded in CaP can be specifically released under acidic TME to reduce its side effects on normal tissues. More importantly, the drug delivery system loaded with GOD and Cu^{2+} has a variety of treatment modes of starvation treatment and CDT, which can effectively inhibit the growth of cancer cells and solid tumors.[105]

2.3.2 Gene delivery

Gene therapy is considered as a treatment that can treat oncological diseases via genetic manipulation of mutating target cells. This kind of Nucleic acid-based therapeutics have been proved to be a promising strategy for inhibiting cancer by correcting the fundamental genetic errors in tumors.[106] The purpose of gene reprograming is to transport nucleic acid molecules to the cytoplasm or nucleus to modify the gene expression of tumor cells. [107] Due to the fragile structure of nucleic acid in vitro, gene delivery needs to meet some requirements, such as cell uptake, escape from the endosome, cytoplasmic release and on-demand release.[108-110] Similar to drug therapy, in order to overcome these difficulties and achieve efficient gene delivery, carriers with special structures and unique physical and chemical properties are required. Previously, a variety of viral and non-viral vectors were used to achieve efficient gene transfection. Virus vectors have high transduction efficiency, complex assembly process mediated by cells, and different virus vectors show distinct expression characteristics. However, the negative realities of carcinogenesis, host immune response and high production cost greatly limit the further use of viral vectors. Therefore, non-viral vectors including polymers, liposomes and inorganic materials have attracted people's attention. Sun and co-workers studied the interaction between CdSe/ZnS mercaptopropionic acid and CdSe/ZnS glutathione with P-glycoprotein (P-gp). The results showed that both of them could significantly inhibit the expression of P-gp gene and protein in A549 cells to inhibit proliferation of tumor cells.[111] Biju and co-workers studied the strand break and base damage of plasmid DNA (pDNA) induced by streptavidin functionalized CdSe-ZnS QDs under different photoactivation conditions.[112]Some researchers have developed CdSe/ZnS QDs loaded with siRNA to silence the expression of TERT gene, which can significantly inhibit the proliferation of glioblastoma cells.[113]

2.4 Multimodal Imaging and therapy

For cancer patients, accurate and timely diagnosis of the disease is very important. However, due to low bioavailability, low targeting and metabolic burden, conventional drug diagnosis or treatment alone cannot meet the clinical demand. The development of nanomaterials, which can combine multimodal imaging with therapeutic measures, brings hope to solve this problem. Yu and co-workers achieved high contrast three mode imaging (PA, IRT and MRI) based on the strong near infrared absorption and T_2-MR contrast of CoS-PEG-NSs, providing a direction for accurate/efficient cancer diagnosis and treatment.[55] Cai and co-workers assembled CuS nanoparticles on the [^{89}Zr] labeled SiO_2 surface filled with porphyrin molecules, which could be used for PET imaging. When combined with fluorescence/Cerenkov luminescence/Cerenkov

radiation energy transfer, the composite nanoparticles could quickly and accurately depict and guide the treatment of tumors.[16] Liu and co-workers added ^{131}I to the preparation of iodine doped CuS nanoparticles. The I-doped CuS NPs were subsequently functionalized with PEG to form CuS/[^{131}I]I-PEG nanoparticles, which were used for RT and PTT, respectively, mainly based on their inherent high near-infrared absorption and doped ^{131}I radioactivity.[57] Gadolinium doped with ultrasmall size (about 9 nm) CuS @ BSA nanoparticles, which can be activated upon NIR irradiation, have high photothermal conversion efficiency and good optical stability, thus could realizing combinatorial imaging of PA and MRI.[67] Hu and co-workers prepared hexagonal hydrophilic Cu_3BiS_3 nanoplates by simple solvothermal method, which inherited the advantages of binary metal sulfides for CT and IR imaging, thus guiding photothermal therapy.[74] Fe_3O_4@CuS hybrid nanoparticle is another kind of ideal multifunctional probe for MRI, infrared thermography and PTT.[18, 114] Via multi-step hydrothermal method, Hu and co-workers prepared PVP coated Fe_3S_4, which could achieve dual-mode MRI/IR imaging guided PTT/PDT anti-tumor therapy. The mechanism of mineralogical transformation from Fe_3S_4 to FeOOH under physiological conditions and the metabolic process in organism circulation were also investigated.[62] Miao and co-workers synthesized MnS@Bi_2S_3 by solvothermal method, of which the functional Mn and Bi elements qualified these NPs with T1/T2-weighted MRI and strong X-ray attenuation ability to enhance CT and RT signals, and ultimately realized the synergistic therapy of PDT and RT guided by MRI/ CT/PAI.[59]

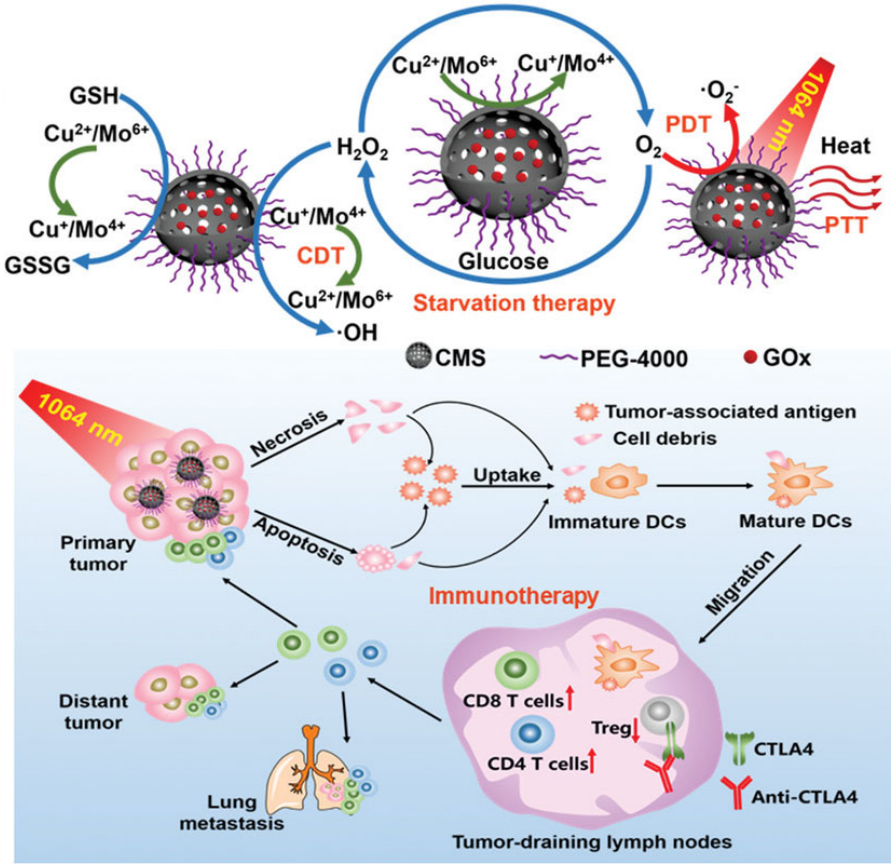

Figure 3. The mechanism of Cu_2MoS_4 (CMS) as a multifunctional cascade bioreactor for chemo-dynamic therapy/starvation therapy/phototherapy/immunotherapy of cancer. The mechanism of antitumor immune responses induced by CMS@GOx-based phototherapy and checkpoint blockade therapy.[15] Copyright 2019. Wiley-VCH.

A typical example is the work recently published by Lin and co-workers The hollow structure of Cu_2MoS_4 (CMS) loaded with glucose oxidase (GOx) was synthesized by hydrothermal method. The presence of Cu^+/Cu^{2+} and Mo^{4+}/Mo^{6+} redox pairs in CMS made CMS produce sufficient hydroxyl radical (·OH) to realize CDT, and consumed GSH to reduce tumor antioxidant capacity. Moreover, the CAT-like activity of CMS enable itself to decompose with H_2O_2 in TME to generate O_2, which activates GOx to catalyze glucose oxidation, accompanied by H_2O_2 regeneration in tumor. Thus, smart nanomaterials have appliable prospects in augmented tumor therapy by the priority of realizing trimodal therapy of chemodynamic therapy/starvation therapy/phototherapy/immunotherapy. [15]

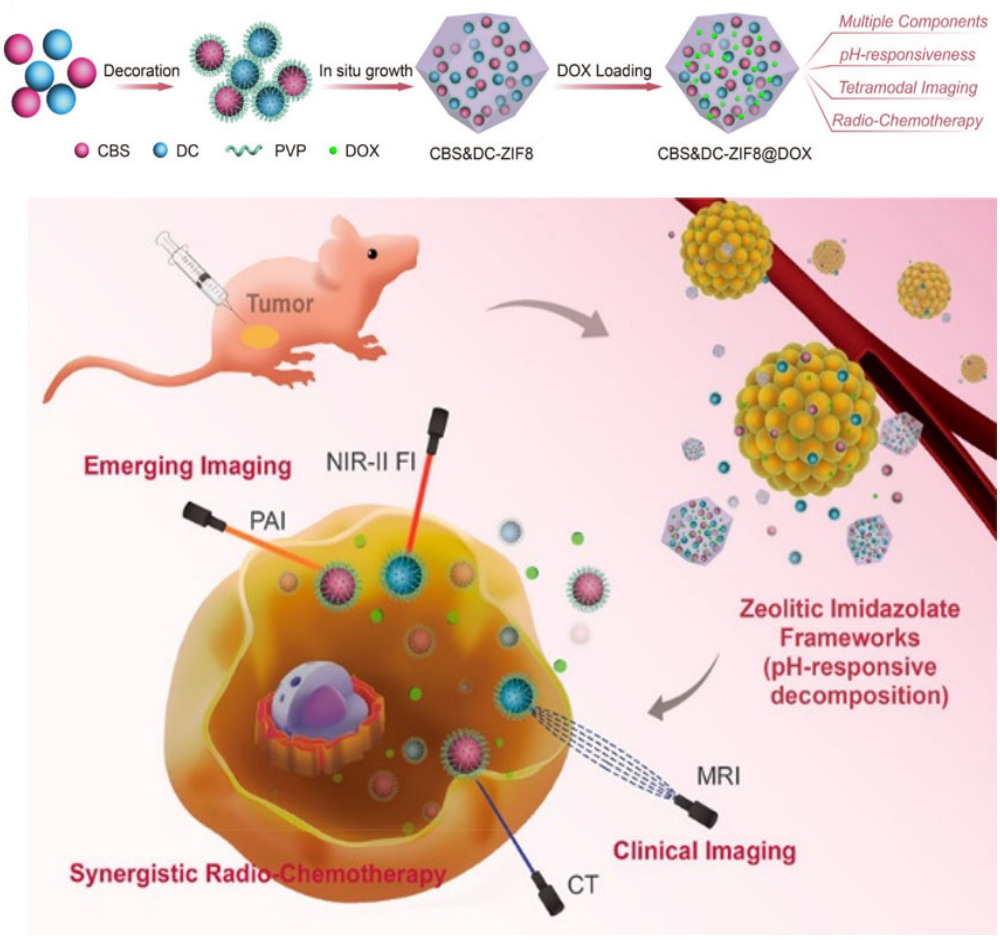

Figure 4. Fabrication process and potential biomedical applications of CBS&DC-ZIF8@DOX composites.[104] Copyright 2020. American Chemical Society.

Another mentionable example is the research recently proposed by Qiu and co-workers In this paper, they encapsulated the small semiconductor CBS and down-conversion (DC) nanoparticles into the larger ZIF8 nanoparticles, and then loaded with DOX. CBS has strong absorption of X-ray and NIR. Rare earth down conversion nanomaterials have strong and sharp NIR-II emission under the excitation of 808 nm laser. Therefore, the system can be applied not only for CT and MRI imaging, but also for photoacoustic imaging and fluorescence imaging. After DOX loading, pH-responsive release was achieved in the tumor site. Additionally, the synergistic chemoradiotherapy of this responsive platform could reach high tumor inhibition efficiency about 87.6%. [115]

3 Conclusions and perspectives

In this review, the characteristics and synthetic methods of TMS/TMP, the biomedical applications in tumor diagnosis and therapy are mainly introduced. TMS/TMP have special structures, such as ultra-small quantum dots, one-dimensional or two-dimensional lamellar structures, and some have unique electrical, optical, magnetism and catalytic properties. Their excellent structural and physiochemical properties determine that these nanomaterials can produce marked effects on tumors by itself or serving as carrier for drugs and nucleic acid. Firstly, the synthesis strategies of TMS/TMP are introduced, including stripping, CVD, water/solvothermal method and wet chemical method. Secondly, we decipher the application of TMS/TMP in tumor imaging (CT/FI/MRI/PET/PAI), which mainly utilize the X-ray attenuation, strong optical, magnetic properties and acoustics of materials. Then, its functions and application in tumor therapy and as drug and gene carrier are discussed, mainly concentrating on RT, PTT, PDT, CDT. Single diagnosis and treatment can no longer meet the clinical needs, so the development direction of next-generation nanomaterials is to achieve multimodal imaging guided precise treatment. It is hoped that the introduction of the latest progress of TMS/TMP will be helpful for the design and synthesis of nanostructured materials and provide guidelines for biological applications in the future.

In recent years, the application of nanomaterials in biomedicine has achieved good results, but the transformation process from laboratory to clinical still faces great challenges. The main problems in the application of nanomaterials in biomedicine are safety, circulation time, absorption and metabolism, potential immune response, etc. Full considerations should be taken with respect to the aspects in the size of the material, the dispersion in water, the ability of the material to target and accumulate in the tumor site, and the degradation under physiological conditions to solve these main problems. For example, many literatures have proved that ultra-small quantum dots (6-8 nm) can be metabolized by kidney.[8, 12, 53] Surface treatment of materials is also a way to improve biocompatibility and targeting accuracy. There are also some enzyme-like nanomaterials, which can be metabolized slowly in organisms. In order to meet the clinical needs, it is often necessary to combine two or more imaging modes to guide tumor treatment. However, using a single material to achieve the cooperation of multiple treatment methods puts forward higher requirements for the structure and performance of the materials. In conclusion, the challenges and properties of the development for TMP/TMP coexist, which leaves a brilliant room for further research.

Table 1. Representative examples of TMS/TMP nanomaterials for combinatorial therapy.

synthetic method	Materials	Imaging mode	therapeutic method	Ref.
Mechanical stripping	MoS2-PEG/DOX	Near-Infrared Imaging	Photothermal and Chemotherapy	[37]
	MoS2			[42]
	MoS2 and WS_2			[43]
	Single Layer MoS_2 Nanosheets	Near-Infrared Imaging and CT	chemotherapy and PTT	[44]

CVD	Large-area MoS2 films			45
	Mn-Doped 2D MoS_2			46
	TiS_2 nanosheets	PAI	PTT	47
Solvothermal/hydrothermal	FeS_2 Nanoparticles	MRI and Near-Infrared Imaging	PTT	7
	PEGylated-Ag_2S QDs	FI		8
	MoS_2 nanodots	PAI	PTT	12
	PEG-MoS_2 nanoflowers	Near-Infrared Imaging	Remove GSH	39
	PEGylated MoS_2 nanosheets		PTT	48
	Ultrasmall $CuCo_2S_4$ Nanocrystals	Near-Infrared Imaging and MRI	PTT	49
	Ag_2S, Bi_2S_3, CdS, and CuS NPs	Near-Infrared Imaging	PTT	50
Wet Chemistry	WS_2 nanosheets	CT and PAI	PTT	51
	MoS_2	CT and Near-Infrared Imaging	PTT	40

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