



MoS₂-based nanocomposites for cancer diagnosis and therapy

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ABSTRACT

Molybdenum is a trace dietary element necessary for the survival of humans. Some molybdenum-bearing enzymes are involved in key metabolic activities in the human body (such as xanthine oxidase, aldehyde oxidase and sulfite oxidase). Many molybdenum-based compounds have been widely used in biomedical research. Especially, MoS₂-nanomaterials have attracted more attention in cancer diagnosis and treatment recently because of their unique physical and chemical properties. MoS₂ can adsorb various biomolecules and drug molecules via covalent or non-covalent interactions because it is easy to modify and possess a high specific surface area, improving its tumor targeting and colloidal stability, as well as accuracy and sensitivity for detecting specific biomarkers. At the same time, in the near-infrared (NIR) window, MoS₂ has excellent optical absorption and prominent photothermal conversion efficiency, which can achieve NIR-based phototherapy and NIR-responsive controlled drug-release. Significantly, the modified MoS₂-nanocomposite can specifically respond to the tumor microenvironment, leading to drug accumulation in the tumor site increased, reducing its side effects on non-cancerous tissues, and improved therapeutic effect. In this review, we introduced the latest developments of MoS₂-nanocomposites in cancer diagnosis and therapy, mainly focusing on biosensors, bioimaging, chemotherapy, phototherapy, microwave hyperthermia, and combination therapy. Furthermore, we also discuss the current challenges and prospects of MoS₂-nanocomposites in cancer treatment.

1. Introduction

Cancer is one of the main causes of human death. The global cancer statistics released by the World Health Organization show that there were 18.1 million new cancer cases and 9.7 million deaths from cancer in 2018 [1]. The current main methods of cancer treatment are surgery, chemotherapy, and radiotherapy [2]. These therapies can only show limited efficacy [3]. The size of nanomaterials is between the size of biomolecules and cells. In theory, carefully designed nanomaterials can realize the regulation of cell state and function like organelles and exosomes. Nanomaterials for cancer treatment have been intensively

studied in the past two decades. The latest advances in nanotechnology have made it possible to engineer complex nanostructures with unique physical properties and surface chemistry. Currently, nanomedicines for cancer have shown great potential compared to traditional therapeutic agents. Nanomaterials such as MoS₂, gold nanoparticles, MnO₂, iron oxide, carbon nanotubes and others have been widely developed for detection of cancer markers, imaging diagnosis, and treatment of cancer. Gold nanomaterials have a unique SPR effect and high X-ray attenuation coefficient, and can be used as efficient photothermal reagents and CT contrast agents for cancer. MnO₂ nanoparticles can catalyze H₂O₂ to generate oxygen (O₂), relieving tumor hypoxia and inhibiting cancer cell

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proliferation and migration. Carbon nanotubes can be used as a good carrier of anti-cancer drug. Iron oxide nanoparticles (IONPs) that are one of the most promising magnetic resonance imaging (MRI) contrast agent precursors, which can be used for cancer diagnosis [4]. At the same time, IONPs can convert the magnetic energy of an alternating magnetic field into heat energy, effectively ablating cancer cells at high temperatures [5].

Among many nanomaterials, MoS₂ nanomaterials are extremely attractive in cancer diagnosis and treatment [6–9]. First, MoS₂ is a two-dimensional (2D) semiconductor nanomaterial, so it has the unique characteristics of 2D materials and the properties of semiconductors. These characteristics make it have great application prospects in cancer marker detection, cancer imaging, and treatment. Second, MoS₂ are easy to achieve controllable preparation. Many 2D nanomaterials such as graphene, Ti₃C₂T_x MXene, black phosphorus and others are generally prepared in a top-down manner. It is difficult to control the size, morphology and surface properties of 2D nanomaterials. MoS₂ nanomaterials can be synthesized in two ways, top-down and bottom-up. As a result, the controllable and precise synthesis of MoS₂ nanomaterials can be achieved according to the needs of cancer diagnosis and treatment. Third, MoS₂ nanomaterials is easy to functionalized with biomolecules and combined with other nanomaterials. Mo is a transition metal element with multiple valence states (from +1 to +6). MoS₂ nanomaterials is extremely flexible and easy to achieve surface modification and doping of other elements. Therefore, MoS₂ nanomaterials can also be used as a platform material to integrate other nanomaterials to form a multifunctional nanomedicine according to the require of cancer

diagnosis and treatment. Finally, unlike many inorganic nanomaterials, such as gold nanomaterials, up-conversion nanomaterials, MoS₂ (sulfur and molybdenum) are composed of elements that exist in the human body. Mo is a trace element necessary for human survival [10]. Molybdenum-bearing enzymes play a key role in human metabolism, such as xanthine oxidase, aldehyde oxidase and sulfite oxidase. Insufficient intake of molybdenum in humans can lead to esophageal cancer [11]. Many studies have shown that MoS₂ nanomaterials has very good biocompatibility. In general, these advantages make MoS₂ nanomaterials very promising in cancer treatment and diagnosis.

MoS₂, as a diamagnetic compound with the property of semiconductor, exhibits excellent chemical and thermal stability. As shown in Fig. 1a, MoS₂ has a typical two-dimensional layered structure, which belongs to the hexagonal crystal system. Each layer consists of two sulfur (S) atoms and a molybdenum (Mo) atom, forming an S–Mo–S sandwich plate with a spacing of 0.315 nm. Meanwhile, each Mo atom and six S atom coordinating ligand to form a triangular prism or octahedral structure [12,13]. The layers with the spacing of 0.349 nm connected through the weak van der Waals force, as well as the stacking order of different S–Mo–S layers for the C axis constitute various MoS₂ crystal structures (Fig. 1b) [14].

As shown in Fig. 1c, 1T-MoS₂, 2H-MoS₂, and 3R-MoS₂ are three different crystal structures of MoS₂. The 1T-MoS₂ has a metastable phase structure that Mo atoms adopt octahedral coordination, while each S–Mo–S unit constitutes a crystal cell, resulting in metalloid or metallic properties of MoS₂. The 2H-MoS₂ structure is more stable that Mo atoms adopt trigonal prismatic coordination, in which two S–Mo–S units form

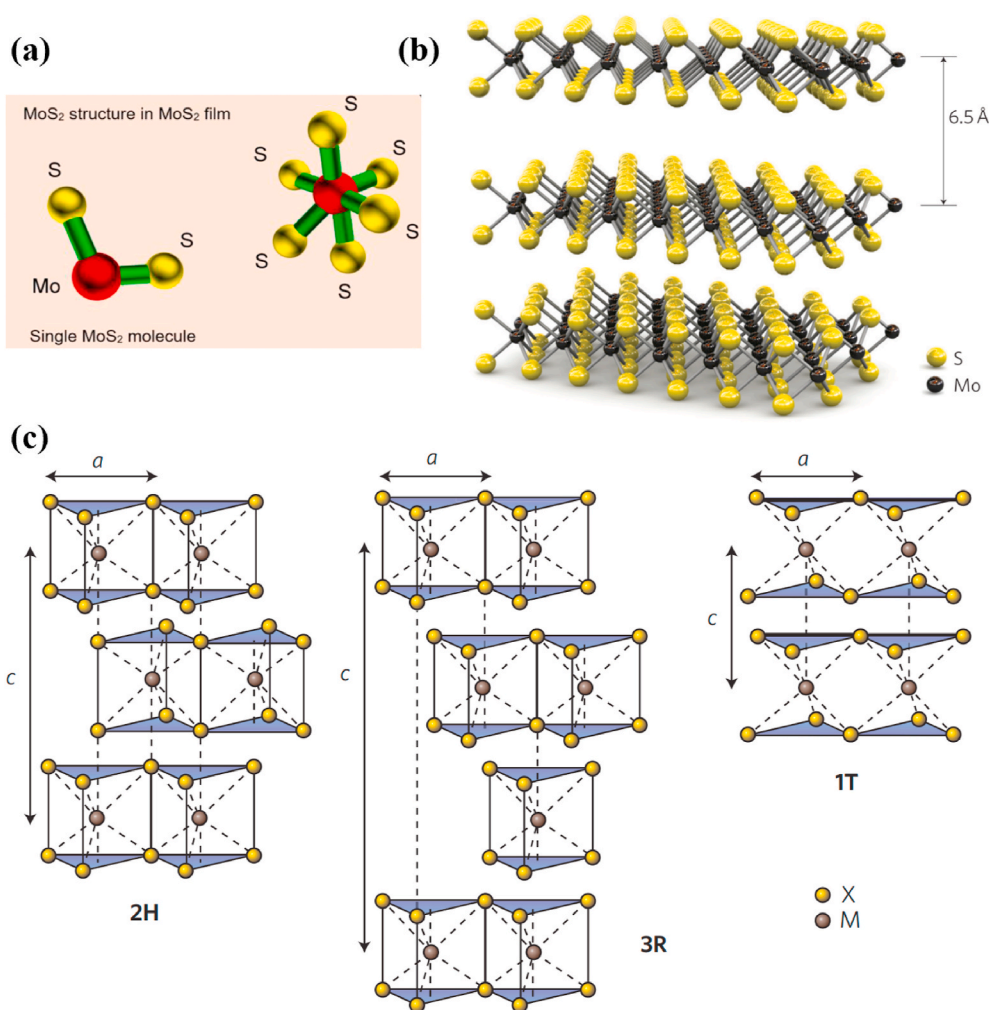


Fig. 1. (a) Structure of a single molybdenum disulphide molecule and an elemental unit of molybdenum disulphide film. Reprinted with permission from Ref. [13]. Copyright 2019, Journal of Physics D: Applied Physics. (b) Three dimensional representation of the structure of MoS₂. Reprinted with permission from Ref. [14]. Copyright 2011, Nature Nanotechnology. (c) Schematics of the structural polytypes: 1T (tetragonal symmetry, one layer per repeat unit, octahedral coordination), 2H (hexagonal symmetry, two layers per repeat unit, trigonal prismatic coordination) and 3R (rhombohedral symmetry, three layers per repeat unit, trigonal prismatic coordination). Reprinted with permission from Ref. [15]. Copyright 2012, Nature Nanotechnology.

a unit cell. The 3R-MoS₂ structure is also a metastable phase and Mo atoms adopt trigonal prismatic coordination, while every three S–Mo–S units form a crystal cell [15].

MoS₂-nanomaterials have been widely used in a lot of fields, on account of the unique physical and chemical properties, including electronic devices, a transistor, and a catalytic energy storage device [15–17]. In recent years, MoS₂-nanomaterials have attracted more attention in cancer diagnosis and treatment [7]. Firstly, MoS₂ has the large specific surface area and can effectively adsorb various molecules through covalent or non-covalent interactions, such as nucleic acids, proteins, drugs, fluorescent probes, and other molecules, forming MoS₂-nanocomposites with radioactivity, magnetism and imaging, also achieving excellent controlled release by specifically responding to the tumor microenvironment [18]. Secondly, the high absorption rate of MoS₂ in a wide wavelength range promotes its application in phototherapy, including the energy receptor of fluorescence resonance energy transfer, photodynamic therapy agent, and photothermal therapy agent. Meanwhile, a large number of negative charges are distributed on the surface of the MoS₂-nanocomposite, which enables them to be stably dispersed in the aqueous medium without obvious aggregation [19]. Finally, MoS₂ has the advantages of high electron mobility, tunable energy band, photoluminescence, good flexibility, and biocompatibility [14,20–24], which further promote its application in the biomedical field.

However, research MoS₂-nanocomposites in the biomedical field is still at an early stage, especially in terms of diagnosis and treatment of cancer [25]. In this review, we describe the latest developments of MoS₂-nanocomposites in cancer diagnosis and treatment systematically, mainly focusing on bioimaging, chemotherapy, phototherapy, and various combination therapy, with brief introduction of achievements in microwave thermotherapy. Subsequently, we discussed the existing problems and the future foreground of MoS₂-nanocomposites in cancer treatment, providing new ideas for designing nanocomposites to diagnose and treat cancer.

2. Biosensors

The unique microenvironment and abnormal expression of specific biomarkers in cancer cells promote the occurrence and development of cancer. Therefore, accurate, sensitive, and rapid detection of biomarkers is very important for disease diagnosis and treatment [26]. Due to the extremely low concentration of biomarkers, outstanding methods for their detection have attracted a lot of attention [26–28].

As an excellent tool in detection of biomolecules, biosensors have high specificity and sensitivity [29]. The biosensor generally consists of a biorecognition element and a transducer, which can convert the interactions between the biorecognition element and the specific target into an output signal that can be detected and displayed by the processor [30]. However, traditional label-based detection methods have many defects including tedious sample processing, high operation cost, inconvenient portability and limited application in real-time monitoring [31,32]. Label-free biosensors based on nanostructure are superior to the traditional methods in detection speed, sensitivity, cost, and versatility [33]. MoS₂ has the large specific surface area that can cause charge transfer by adsorbing small molecules, resulting in changes in its electron mobility. Meanwhile, MoS₂ is an outstanding energy receptor for quenching fluorescence. Therefore, MoS₂ biosensors can be used as detection devices of biomolecules. In this review, we mainly discuss their application in field-effect transistor sensors, fluorescence resonance energy transfer-based sensors, and electrochemical sensors.

2.1. Field effect transistor (FET) biosensors

FET sensor has advantages of small size, high sensitivity, large detection range and low energy consumption. It has broad application prospects in the detection of cancer markers, especially in the point-of-

care testing of cancer markers. FET biosensor is mainly composed of four parts: channel, drain, source and substrate. Among them, the channel is the core part of FET biosensor. FET biosensors can detect the binding events of biomolecules and gate dielectrics or semiconductor channels by monitoring changes in channel conductance [34,35]. The biggest bottleneck of FET biosensors comes from channel materials. The channel materials must be easy to be functionalized with the bioreceptor, and have good semiconductor properties. MoS₂ nanomaterial can be used as a very good channel material of FET biosensors thanks to its unique physical and chemical properties. Controllably switching between the conductive and insulating states of MoS₂ nanostructures can be achieved because MoS₂ has an adjustable bandgap [36]. A larger bandgap provides a better state switching capability, which is very important for isolating any current leakage during device shutdown while improving detection sensitivity and accuracy [37]. MoS₂-based FET biosensors can better control static electricity and reduce low-frequency flicker noise due to interface traps and low surface roughness in its pristine surfaces.

PSA is a biomarker for diagnosing prostate cancer, the second most common cancer among men worldwide [1]. The survival time of prostate cancer patients can be prolonged if it is detected early. Wang et al. [38] designed a label-free FET sensor based on MoS₂ to detect PSA detection, which was the first demonstration and application of the biological functionalization of MoS₂ nanosheet field-effect devices in the liquid phase. The specific binding of PSA with the antibody fixed to the mechanical exfoliated MoS₂ membrane caused a significant change of drain current. The method had high sensitivity, high specificity, and timeliness. However, the mechanical exfoliation method for obtaining single-layer or multi-layer MoS₂-nanomaterials has many limitations, such as long synthesis time, low yield, and batch-to-batch variations [39, 40]. Kukkar et al. [41] obtained few-layered MoS₂ nanosheets by electrolytic intercalation of sodium (Na⁺) ions into an original molybdenum sheet to produce Mo ions which could combine with S ions. During the process, the raw materials were easy to obtain, and the preparation of few-layered MoS₂ nanosheets was simple, without inorganic or organic byproducts. The MoS₂ nanosheets and anti-PSA antibodies were introduced into FET microdevices for constructing a particular PSA immunosensor that had a wider detection area (10^{−5} to 75 ng/mL). Although many studies have reported the sensitivity and specificity of FET sensors, the repeatability and accuracy have not been explored. Park et al. [42] prepared a MoS₂-based FET in which the 30–45 nm thick MoS₂ flakes had high field-effect mobility ($\mu = 30\text{--}50\text{ cm}^2/(\text{V}\cdot\text{s})$ on SiO₂/Si substrate), and Al₂O₃ could improve the electrical performance of the device and it was easy to be functionalized by 3-aminopropyltriethoxysilane (APTES) and glutaraldehyde (GA). The anti-PSA was fixed to the CHO end of GA via the reaction of lysine and aldehyde. Casein is used as a blocking agent to reduce non-specific molecular binding events in the immune response while uniformly chemisorbed anti-PSA on the surface of MoS₂, which could reliably and quantitatively detect PSA in a non-aqueous environment with excellent accuracy and repeatability (Fig. 2). Most traditional methods of diagnosing PSA are laboratory tests, which are inconvenient and expensive. In contrast, point-of-care (POC) testing has become a trend with the development of biosensors [43]. Yoo et al. [44] designed an epidermal skin-type POC device for real-time monitoring of PSA, which integrated the MoS₂ FET biosensor, readout circuit, along with the light-emitting diode (LED) that as an indicator into a system. PSA antibody could physically absorb on MoS₂ channel by van der Waals force without pre-surface chemical treatment. Meanwhile, the channel conductance of the MoS₂ FET could be affected when anti-PSA combined with PSA. Therefore, highly sensitive detection of PSA could be achieved through the current change of MoS₂ channel. The POC testing device had good electrical performance and mechanical durability under various mechanical stress conditions, and its detection limit (1 pg/mL) was much less than the clinical cut-off.

Recently, Yang et al. [45] prepared a FET sensor based on MoS₂ nanosheets to simultaneously detect the bladder cancer biomarkers (NMP22 and CK8) in patients' urine. The recognition molecules of

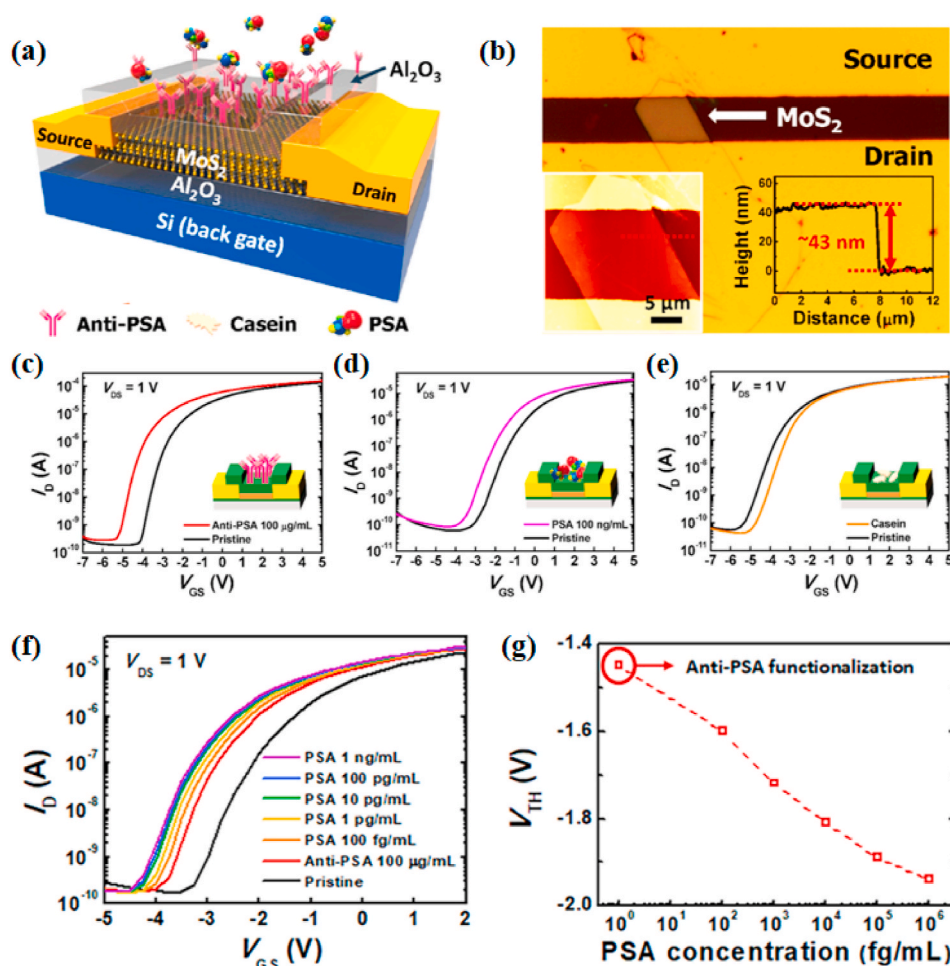


Fig. 2. (a) The pseudo-double-gate structure of a MoS₂ biosensor. (b) Optical image of the MoS₂ bio-FET with insets representing a tapping-mode AFM image and its thickness profile. Shifts in the transfer curves for the MoS₂ bio-FET immobilized with (c) anti-PSA of 100 µg/mL, (d) PSA of 100 ng/mL and, (e) casein of 1% (w/v). (f) Transfer characteristics with PSA concentrations from 100 fg/mL to 1 ng/mL on the anti-PSA-immobilized MoS₂ bio-FET. (g) Plot of V_{th} against PSA concentrations. Reprinted with permission from Ref. [42]. Copyright 2017, ACS Applied Materials & Interfaces.

NMP22 and CK8 were conjugated on different sensing channels of MoS₂ nanosheets, and the channel current would change and achieve highly sensitive detection of NMP22 and CK8 when NMP22 and CK8 bound to their specific recognition molecules (the detection limits of NMP22 and CK8 as low as 0.027 aM and 0.019 aM, respectively).

2.2. Fluorescent biosensors

The traditional fluorescence methods easily are interfered with background fluorescence, leading to inaccurate detection results [46]. Fluorescence resonance energy transfer (FRET) requires the transfer of energy from donor to the recipient to sensitively detect biomolecules [47]. Fluorescence sensors based on nanomaterials can overcome the shortcomings of traditional fluorescence methods and selectively combine with target substances to ensure a high labeling success rate, obtain strong fluorescence detection signals, facilitate detection equipment to capture signals, and significantly improve detection sensitivity and reliability. MoS₂ has been regarded as an effective energy receptor for quenching fluorescence, on account of its high surface area and particular optical characteristics [48]. Meanwhile, MoS₂ is suitable for intracellular analysis due to its low cytotoxicity [49].

miRNAs play important roles in molecular pathways and are promising molecular biological markers to predict the early tumorigenesis or metastasis [50]. Currently, miRNAs are mainly detected by end-point technologies, including northern blotting, qualitative reverse transcription-polymerase chain reaction (qRT-PCR) [51], Northern blotting [52], and microarrays [53], which require a good deal of samples simultaneously take a long time. MoS₂ nanomaterial-based fluorescent biosensors can overcome the above defects and improve

detection sensitivity and specificity [54,55]. Xiao et al. [56] found that polycytosine (polyC) DNA could non-covalently functionalize MoS₂ nanosheets to retain DNA activity and increase the recognition ability of probes. They synthesized diblock molecular beacons that possessed polyC tails attached to MoS₂ nanosheets to detect miRNA. During co-incubation with layered MoS₂, the van der Waals force make the polyC-MB adsorbed on MoS₂ [57], and then the fluorescence of the dye is quenched by FRET [58]. DNA/RNA heteroduplex could be formed with the target miRNA because of the specific affinity between MB block and miRNA, while the duplex-specific nuclease (DSN) would cleave it, leading to fluorescence recovery. Furthermore, DSN could cause signal amplification by target recirculation. Considering that the extracellular detection of miRNA is complicated and time-consuming, Oudeng et al. [59] prepared the folic acid (FA)-poly (ethyleneglycol)-modificatory MoS₂ nanosheets and used fluorescent-labeled ssDNA probes to fix it (ssDNA-MoS₂-PEG-FA) for the first time, realizing one-step in-situ to detect endogenous miRNAs in the single cancer cell. After the cancer cells internalized the ssDNA-MoS₂-PEG-FA, the high binding force of miRNA-21 and ssDNA made the probe fall off from the MoS₂ nanosheet, resulting in the rapid fluorescence recovery (Fig. 3 a, b). Nevertheless, there are many challenges in intracellular detection due to the high homology, small size and low abundance of miRNAs. For example, the signals read by a single step of in situ hybridization are relatively low and the sensitivity of miRNA detection is limited [59]. Besides, false-positive signals may be caused by the complex intracellular environment, nuclease degradation, or non-specific binding. A living cell detection strategy related to isothermal amplification and enzyme-catalyzed cycling reaction can increase the sensitivity of the intracellular analysis [60,61]. To this end, Zhu et al. [62] used the DNA

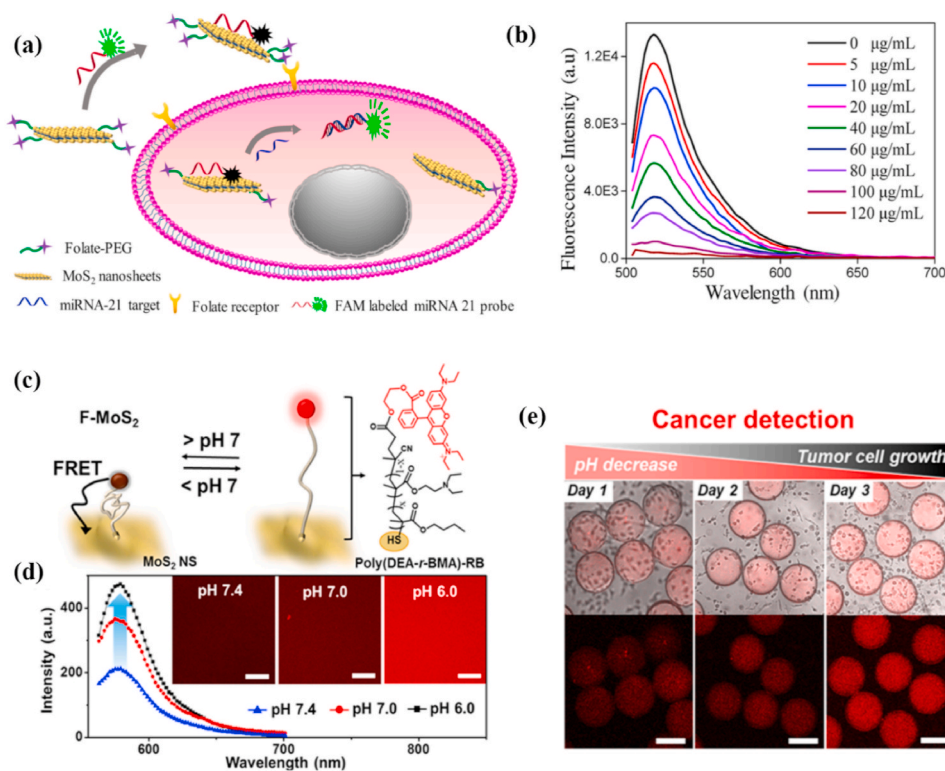


Fig. 3. (a) Schematic of ssDNA-MoS₂-PEG-FA probe-based FRET platform for intracellular miRNA-21 detection. (b) Photoluminescence spectra of FAM-labeled miRNA-21 probes incubated with MoS₂ nanosheets with a series of concentrations. Reprinted with permission from Ref. [59]. Copyright 2018, ACS Applied Materials & Interfaces. (c) Schematic illustration showing the construction of the F-MoS₂ NSs and pH-dependent FRET, which is mediated by a conformation change of poly (DEA-r-BMA). (d) PL spectra of F-MoS₂ NSs at three different pH values of 7.4, 7.0, and 6.0. Insets are the corresponding confocal microscopy images of the solution. Scale bars are 100 µm. (e) Series of overlaid bright-field and fluorescence confocal microscopy images (top) and confocal microscopy images (bottom) showing the progressive enhancement of fluorescence intensity in the microcapsules during the growth of A549 tumor cells. Scale bars are 200 µm. Reprinted with permission from Ref. [63]. Copyright 2018, ACS Applied Materials & Interfaces.

catalytic hairpin supported by MoS₂ as a signal amplifier to detect the low expression of miRNA-21 in living cells. Three kinds of DNA molecular beacons modified with Cy3 in the terminal consist of the three-branched catalyzed hairpin assembly (TB-CHA) probes that form “Y”-shaped three-branched duplex nanostructure when miRNA-21 is presented, releasing from the surface of the MoS₂ nanosheet. In the microenvironment of living cells, multi-site fluorescence modification and cyclic reaction enable TB-CHA probe to achieve significant fluorescence recovery.

Cancer cells secrete lactic acid to maintain their weakly acidic microenvironment (pH 6–7). Therefore, tumor sites can be confirmed by pH [64]. Detecting the regional pH of the tumor microenvironment via traditional ways (e.g., a pH meter or litmus test paper) is difficult because of its limited accessibility. pH-responsive polymers [65] with good biocompatibility can link the fluorescent molecules and optical quenchers to produce pH-dependent FRET compounds [66,67]. The MoS₂ nanosheets have a large specific surface area and abundant sulfur binding sites, thus the oligomeric or polymeric molecules can briefly functionalize them under mild conditions [68,69]. Park et al. [63] synthesized a FRET-based microsensor and encapsulated it in a microcapsule by attaching a pH-responsive polymer that contain a fluorescent terminal to the surface of a MoS₂ nanosheet (F-MoS₂ NSs). The pH-sensitive polymer could respond to subtle pH changes through conformational changes and converted it into FRET signals at a lower pH for detecting cancer cells. The microcapsules ensured that MoS₂ NSs did not leak while preventing the entry of adhesion proteins and lipids, avoiding the inactivation of encapsulated MoS₂ NSs, meanwhile realizing home position pH monitoring (Fig. 3 c-e).

EpCAM protein can be applied as a biomarker for cancer diagnosis, treatment, and prognosis because its overexpression was found in most cancer [70–72]. The majority of EpCAM-based diagnoses and treatments depend on anti-EpCAM antibodies, which cannot supply accurate clinical outcomes due to their instability and large-size under the physiological condition [73,74]. Aptamers, with small size and high specificity towards biomolecules, have been widely used in the sensor field [75]. On the other hand, Graphene quantum dots (GQDs) can serve as good

FRET donors to detect specific biomarkers because of their high light stability [76]. Meanwhile, MoS₂ has a good light absorption capacity at a wide wavelength range and can be used as an efficient energy acceptor. For these reasons, Shi et al. [77] designed a novel GQD-PEG-aptamer/MoS₂ “turn-on” fluorescent biosensors based FRET mechanism for the rapid and sensitive detection of EpCAM. Since EpCAM aptamer and the EpCAM protein have a stronger affinity, the separation of MoS₂ nanosheet and GQD-PEG-EpCAM aptamer could be promoted in the existence of EpCAM proteins, causing the restoration of fluorescence intensity. The biosensor could sensitively and selectively detect EpCAM in the detection range of 3 nM–54 nM, with a low detection limit (450 pM).

Recently, Xu et al. [78] synthesized silver nanocluster (AgNC) @ MoS₂ to detect ATP in Hela cells. ATP aptamer was as templates to prepare DNA-AgNCs, which was as a fluorescent label and an Ag element tag to quantitatively analyze ATP. In addition, DNA-AgNC was loaded on MoS₂ nanosheets by van der Waals forces, and its fluorescence was quenched by MoS₂ nanosheets. The interaction between DNA-AgNCs and MoS₂ nanosheets could be weakened when ATP specifically bound to its aptamer. As a result, DNA-AgNC was released from the surface of MoS₂ nanosheets, and its fluorescence was recovered. The detection limits of this nanoplatfrom as low as 0.18 nmol/L. Similarly, Zhao et al. [79] used fluorescein (FAM) labeled DNA to functionalize MoS₂ for detecting CA15-3. The fluorescence of FAM-DNA was quenched by MoS₂ via FRET and was restored when CA15-3 bound to FAM-DNA. The fluorescent biosensor not only had a low detection limit (0.0039 U/mL) but also displayed high sensitivity.

2.3. Electrochemical biosensors

The electrochemical biosensor converts the interaction of biomarkers and bioreceptors into electrical signals, which has many advantages such as simple preparation, low cost, simple operation, fast speed, good stability, strong specificity, high sensitivity. The introduction of nanomaterials in electrochemical biosensor systems can further enhance the detection signal, improve detection specificity and

accuracy, and has been widely used in the biomedical field. As a semiconductor that possesses an indirect energy band of 1.29 eV, MoS₂ has good electrocatalytic activity due to the enhancement of planar electrical transmission performance [80]. Furthermore, MoS₂ modified by monometallic, bimetallic or even trimetallic nanoparticles exhibits higher catalytic performance [81,82]. Currently, the MoS₂-based electrochemical sensors have detected multiple tumor markers, such as H₂O₂, carcinoembryonic antigen (CEA), circulating tumor cells (CTCs) and miRNA.

MoS₂-based nanocomposites can electrochemically catalyze the reduction of H₂O₂ to produce H₂O and O₂, detecting H₂O₂ via the current change induced by redox reaction [83]. In situ detecting H₂O₂ secreted by cells is extremely significance because the intracellular H₂O₂ concentration level is a key physiological parameter for early screening and diagnosis of primary cancer [84]. Electrochemical methods can be utilized for detecting H₂O₂ secreted from living cells because they can offer an interface to bridge cells and sensing electrodes [85]. However, electrochemical sensors currently used for in situ detecting H₂O₂ not only require complicated manufacturing processes but also are not feasible for cell adhesion and growth. Dou et al. [86] synthesized Au–Pd–Pt nanoflower-modified MoS₂ nanosheet-based sensor through a wet chemical method to in-situ monitor the secretion of H₂O₂ that from living MCF-7 cancer cells, which enhanced the electrochemical catalytic activity through synergistic action of the MoS₂ nanosheets and the highly dispersed tri-metal hybrid nanoflower, and improved the biocompatibility of cell adhesion and growth by immobilizing laminins on the surface of nanocomplexes. Although loading noble metals on MoS₂ can improve detection sensitivity, it would decrease stability and increase costs. Interlayer expanded MoS₂ (IE-MoS₂) without noble metal nanoparticles can also provide high sensitivity, clarity, and resolution for H₂O₂ detection. Shu et al. [87] used excessive thiourea to synthesize IE-MoS₂ with a wide interlayer spacing of 9.40 Å via the one-step hydrothermal reaction with good electrical conductivity and strong combining ability with *OH intermediates, realizing the rapid kinetics reduction of H₂O₂ ($\text{H}_2\text{O}_2 + 2\text{e}^- \rightarrow 2\text{OH}^-$). The sensitivity of the first-rank IE-MoS₂ is considerably high (1706.0 $\mu\text{A}/(\text{mM}\cdot\text{cm}^2)$), while the detection limit is very low (0.2 μM). Thanks to Mo₂C advantages of high conductivity, Mo₂C@MoS₂ co-axial nanorods had a higher sensitivity of H₂O₂ (1080 $\mu\text{A}/(\text{mM}\cdot\text{cm}^2)$) and lower detection limit (0.2 μM) than IE-MoS₂. At the same time, Mo₂C@MoS₂ had rich surface amino groups, and could be used to specifically detect MDA-MB-231 cells after functionalized folate ligand [88]. Besides, studies found that self-supporting nanoarrays with a three-dimensional (3D) structure could further enhance the sensitivity of H₂O₂ detection because they had more catalytic sites and larger contact areas than the two-dimensional electrode [89]. Du et al. [90] designed a MoS₂ nanosheet array that distributed over the carbon cloth (MoS₂/CC) for ultrasensitive detection of trace amounts of H₂O₂ secreted by living cells. MoS₂/CC with low charge transfer resistance and abundant surface area as a good electron conductor facilitated the electron transfer from the MoS₂/CC electrode to reduce H₂O₂, which led to significant current changes to sensitively detect the concentration of H₂O₂. As a result, MoS₂/CC afforded an outstanding sensitivity of 5300 $\mu\text{A}/(\text{mM}\cdot\text{cm}^2)$. Recently, Yang et al. [91] prepared 3D MoS₂/reduced graphene oxide composite (3D-MoS₂/rGO) as a sensitive sensor of H₂O₂. Graphene could not only serve as the supporting structure for the growth of MoS₂ but also increase the specific surface area of MoS₂/rGO to promote reaction with H₂O₂. The 3D-MoS₂/rGO sensor had a good anti-interference ability, a lower detection limit (0.19 μM), and a wider linear range (2 μM –23.18 mM).

CEA (tumor-associated glycoprotein) is a crucial marker to detect multiple tumors but its concentration is ultralow in the early stages of cancer. Hence, in order to early diagnosis cancer, high sensitivity detection of CEA is very vital. MoS₂ can easily modify with specific antibodies to prepare highly sensitive electrochemical sensors to detect tumor-specific antigens. Wang et al. [92] integrated MoS₂–Au with strong catalytic activity and Ag nanospheres (AgNPs) with good

electricity into an electrochemical immunosensor for detecting CEA. MoS₂–Au used as the solid support for CEA primary antibody (Ab₁) and AgNPs were served as the supporter of glucose oxidase (GOx) and CEA secondary antibody (Ab₂), which could combine with CEA respectively to form a sandwich-type immunosensor. The H₂O₂ was produced after glucose was added and MoS₂–Au could catalyze reduction of H₂O₂ to cause the current to vary with the concentration of CEA. The biosensor had a range of linearity from 1 pg/mL to 50 ng/mL and a limit of detection of 0.27 pg/mL. Analogously, Ma et al. [93] also synthesized a sandwich-type electrochemical immunosensor with a broader detecting range (10 fg/mL to 100 ng/mL) and a lower limit of detection (3.09 fg/mL). The trimetallic yolk-shell Au@AgPt nanocubes (Au@AgPt YNCs) with good catalytic activity loaded on amino-modified MoS₂ nanoflowers to form MoS₂ NFs/Au@AgPt YNCs as the marker of Ab₂, which could catalyze the reduction of H₂O₂ more effectively and thus amplify the current signal. At the same time, gold triangle nanoprisms (Au TNPs) as substrate materials offered a steady environment for immunosensors. The reduction reaction of H₂O₂ was triggered to realize the detection of CEA concentration when CEA was combined with Au TNPs and MoS₂ NFs/Au@AgPt YNCs respectively. Jia et al. [94] used MoS₂/CuS–Au as sensing platform and Au@PtPd porous nanorods (Au@PtPd MP–Ab₁) as signal amplifiers to fabricate sandwich-type biosensor for detecting CEA. MoS₂/CuS–Au could increase the loading rate of Ab₁ and the electron transport rate. Au@PtPd MP–Ab₁ had excellent catalytic activity and could generate highly sensitive current signal, which could efficiently detect CEA in human serum samples. Despite tremendous progress of electrochemical immunosensors have been achieved, ultra-sensitive high-performance immunosensors with multiple amplified signals are still challenging [95]. In order to further improve their detection performance and amplify detection signal of CEA, the reducing substrate (o-phenylenediamine[o-PD], Cu₂O, and Ferrocene[Fc]) and enzyme amplifiers were introduced into the detection system of MoS₂ and H₂O₂ [96–99]. Su et al. [100] used MoS₂ nanocomposites (MoS₂–AuNPs) decorated with gold nanoparticles to construct an enzyme-assisted signal amplification sensor for CEA analysis. MoS₂–AuNPs could load anti-CEA (Ab₁) after being modified onto the cleaned glassy carbon electrode (GCE) to form anti-CEA/MoS₂–AuNPs/GCE. Meanwhile, HRP-anti-CEA (Ab₂) was loaded on the surface of MoS₂–AuNPs to produce HRP-anti-CEA/MoS₂–AuNPs nanoprobe for blocking the nonspecific absorption. The effective amplification of the electrochemical signal is attributed to the following three strategies. Firstly, MoS₂–AuNPs catalyze the reduction of H₂O₂ to produce *OH intermediates which could oxidize o-PD to form o-PDox, amplifying the changes of current response signal. Second, the HRP-anti-CEA could also generate the above reaction to further amplify the current change. Third, the introduction of HRP could not only prevent non-specific adsorption but also catalyze the redox reaction of H₂O₂ and o-PD to enhance the electrochemical properties of the sensor. Such immunosensor has a lower limit of detection of 1.2 fg/mL.

CTCs, are the malignant cells found in biological fluids and indicate the invasion and metastasis of tumor, which ultimately lead to the death of the patient [101,102]. At present, multifarious methods have been used to capture and detect CTCs, such as immunomagnetic separation [103], microfluidic chip [104], as well as flow cytometry [105]. Nevertheless, majority of methods are complicated to operate or require expensive instruments [106–108]. Label-free detection of CTCs by electrochemical methods will greatly simplify analytical techniques and accelerate the capture of CTCs [109,110]. MoS₂ is a semiconductor that possesses good electrical conductivity and easily functionalized surface, and it is thus a very suitable candidate for electrodes. Chen et al. [111] constructed MoS₂/FA-modified AuE (AuE/MoS₂/FA) by using folic acid-modified two-dimensional MoS₂ (MoS₂/FA) as a signal indicator and assembling it on the surface of the gold electrode (AuE), which could detect CTCs by an alternating current (AC) impedimetric method. Since the conductivity of MoS₂ (0.14 S/m) and cancer cells (0.13–0.23 S/m) is approximate, the sensitivity of the MoS₂ electrochemical sensor

may be enhanced after adding cancer cells. This is because that an insignificant change in the conductivity caused by cancer cells causes a conspicuous change in the impedance of the semiconductor electrode. Meanwhile, MoS₂/FA with a high specific surface area might increase the contact sites between semiconductor and CTCs, further improving the sensitivity. Besides, the FA loaded on 2D MoS₂ could specifically recognize HeLa cells that is enrichment of folate receptor (FR), significantly increasing the impedance even in the presence of a few HeLa cells, because MoS₂ is loaded with a lot of FA. Therefore, the prepared electrochemical sensor could detect cancer cells in a linear range of 1 to 10⁵ cell/mL, and the limit of detection is 0.43 cell/mL (S/N = 3) (Fig. 4).

However, the captured CTCs were incapable of effectively releasing, greatly hindering the further proliferation and downstream biomedical applications of cells [112]. It is known that most of the current cell release strategies based on enzymes or other chemical methods would seriously damage cells, reduce cell viability and affect analysis results [106,107]. Light-induced cell release has highly precise controllability [108]. MoS₂ nanosheets (NFs) can be used as the NIR-regulated control element to effectively release CTCs. Wang et al. [113] designed a NIR optical switch biological platform to capture, detect, and release CTCs. Firstly, the surface of ITO was modified with PEG-MoS₂ NFs@ gelatin as the working electrode. The MUC1 aptamer is then fixed to its surface by amination between the aptamer and gelatin. Thus, it could specifically bind to the MUC1 protein overexpressed on the membrane of MCF-7. The rapid electron transfer between the nanoplateform and the redox probe could result in a significant change of impedance when cancer cells were added, which was attributed to the quite high conductivity of MoS₂ NFs. Meanwhile, MoS₂ with strong photothermal ability could make the NIR-light transform into heat that would melt the solid gelatine, releasing cancer cells. Notably, the nanoplateform had a remarkable release efficiency of 92.5% and the released cells remained in good cellular shape and proliferative ability.

In addition, electrochemical sensors based on MoS₂ can also sensitively detect miRNA, triiodothyronine, cytokeratin 19 fragment antigen 21-1, EpCAM, and α -methylacyl-CoA racemase [114–119]. These probes were prepared by functionally modifying specific ligands at the MoS₂-based nanocomposites. The current or impedance of the probes

would change when the target substances and the ligands on the probe surface specifically interacted. In this way, highly sensitive detection of target substances could be achieved. For example, Su et al. [120] prepared highly sensitive miRNA-21 probe (MLNP) by functionally modifying specific DNA (specifically binds to miRNA-21) on MoS₂-AuNPs. In the presence of miRNA-21, MLNPs formed a typical “sandwich” structure to cause changes of impedance. The miRNA-21 detection limit of the probe was as low as 38 aM and the detection range was as wide as 10 aM - 1 μ M.

2.4. Other biosensors

Surface-enhanced Raman scattering (SERS) overcomes the inherent limitations of traditional Raman spectroscopy and improves its sensitivity by SERS substrates [121]. SERS substrates are dependent on plasmonic effects in electromagnetic “hotspots” and highly concentrated charges originating from surface roughness [122]. SERS biosensors have obvious advantages, such as fingerprint recognition and single-molecule sensitivity. Recently, MoS₂ were prepared MoS₂/precious metal nanocomposites to fabricate highly sensitive SERS substrates [123]. For example, Liu et al. [123] designed Ti₃C₂ (MXene)/MoS₂@ Au nanoparticles (AuNPs) (MMA) to detect miRNA-182. AuNPs not only were used to enhance the signal of SERS, but also could graft the hairpin probe DNA labeled with Cyanine 5 (Cy5) via Au-S bonds. Cy5 were released from the MoS₂ nanocomposites when the probe DNA bound with miRNA-182, and then reduced the intensity of the SERS peak at 1362 cm⁻¹. In this way, miRNA-182 could be detected with high sensitivity and the detection limit of miRNA-182 was 6.61 aM.

MoS₂ nanomaterials usually have weak peroxidase activity. Recently, Sun et al. [124] found that the peroxidase activity of MoS₂ could be greatly increased by modifying MoS₂ with gold nanoparticles. On this basis, the MoS₂/Au could catalyze H₂O₂ to generate *OH with strong oxidizing properties that could oxidize 3,3',5,5'-tetramethylbenzidine (TMB) to the colorimetric assay of H₂O₂. Electrochemiluminescence (ECL) has many advantages, such as low background, high sensitivity, simple operation, good controllability. Recently, MoS₂ nanocomposites also have been used in ECL biosensors

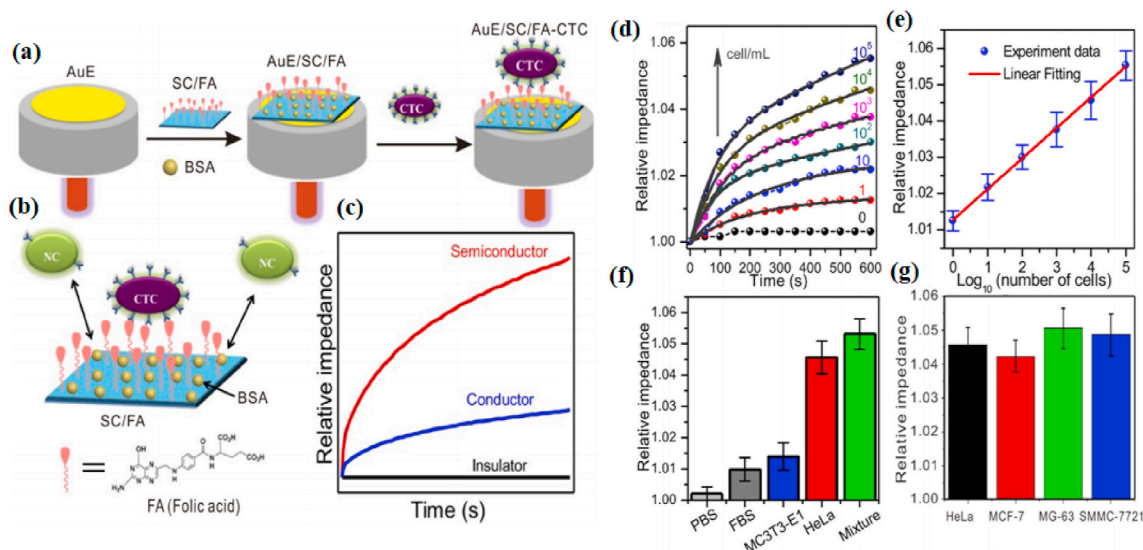


Fig. 4. (a) The fabrication of AuE/SC/FA for CTC capture. (b) Schematic model of HeLa cell binding with FA and repelling NC on a negatively charged AuE/SC/FA electrode surface. (c) The corresponding impedance curves. SC: Semiconductor; AuE: gold electrode; BSA: albumin from bovine serum; CTC: circulating tumor cells; FA: folic acid; NC: normal cells with low folate receptor expression. (d) Relative impedance at 10 Hz with time for AuE/MoS₂/FA electrodes scanned while being immersed in HeLa cell with different concentrations in PBS. The grey solid lines indicate fittings using exponential association. (e) Calibration plots of relative impedance at 10 min for determining HeLa cells at AuE/MoS₂/FA electrodes while changing the concentration of HeLa cell in PBS. (f) Relative impedance at 10 min at AuE/MoS₂/FA electrodes for PBS, 10% FBS solution, MC3T3-E1 cell suspension, HeLa cell suspension and the mixture of all, indicating a good selectivity of AuE/MoS₂/FA electrodes. (g) Relative impedance at 10 min at AuE/MoS₂/FA electrodes for HeLa, MCF-7, MG-63 and SMMC-7721 cancer cell suspensions. Three replicates were performed. Reprinted with permission from Ref. [111]. Copyright 2019, Biosensors & Bioelectronics.

due to their strong fluorescence quenching ability and electrocatalytic performance [125,126]. For example, Delnia Bahari et al. [127] prepared MoS₂ based electrochemiluminescence sensor (GO-HBP-Ru-complex-NCND-anti-CA19-9 Ab₁) to detect carbohydrate antigen 19-9 (CA19-9). In this sensor, amine-rich nitrogen-doped carbon nanodots (NCNDs) linked to Ru(bpy)₂(phen-NH₂)²⁺ was loaded on graphene oxide grafted hyperbranched aromatic polyamide (GO-HBP) to generate and amplify the ECL signal, and MoS₂ was used as a strong quencher. The sandwich complex of GO-HBP and MoS₂ would be formed and cause ECL signal quenching via FRET effects when CA19-9 antigen and MoS₂-Ab₂ were added.

3. Bioimaging

Early biological behavior analysis and high-precision positioning of tumors improve the accuracy of tumor qualitative, tumor staging and curative effect analysis. Therefore, high-precision imagological examinations play an increasingly important role during the treatment process to achieve personalized medicine, optimize treatment effect, and monitor the treatment response [128–132]. The common tumor imaging method is fluorescence (FL) imaging which has good selectivity, fast response, high resolution that can observe subcellular structures and realize real-time imaging. For example, Zhang et al. [133] fabricated poly(N-isopropylacrylamide) (PNIPAM)-peptide-Au nanospheres with red fluorescence for observing its endocytosis pathway in HeLa cells. FL imaging usually obtained under ultraviolet rays or visible light irradiation, but hemoglobin and other biomolecules have strong absorption of visible light and ultraviolet rays, leading to a weaker penetration depth of FL imaging. Most tumors are located inside the body that requires imaging methods have longer penetration depth and high resolution, implying that common FL is not very suitable for deep tumor imaging.

Currently, there are many imaging methods used to overcome the above difficulties. These methods are mainly divided into three categories: The first category mainly uses near-infrared light as the excitation light source or detection signal, including near-infrared fluorescence imaging (NIRF), two-photon imaging (TPF), and photoacoustic imaging (PA); The second category is to use ultra-short wavelength, high-energy rays as the excitation light source or detection signal, including positron emission tomography (PET, γ -photons) and X-ray computed tomography (CT, X-ray); The third category is the use of ultra-long wavelength electromagnetic waves as the excitation light source (such as MRI). The penetration depth of these imaging is longer than common FL imaging (Table 1). MoS₂ has various physicochemical properties (such as strong near-infrared absorption and easy functional modification), which enables it to be combined with other materials to fabrication powerful imaging platforms. MoS₂ nanocomposites have aroused great concern from scientific researchers in recent years (Table 2). In this part, we will introduce the NIRF imaging, PA imaging, CT imaging, PET imaging and MRI based on MoS₂ nanomaterials

according to the penetration depth from shallow to deep.

3.1. FL imaging

Near-infrared light can be divided into two areas: the first area (NIR-1, 650–900 nm) and the second part (NIR-2, 1000–1700 nm). NIR-1 and NIR-2 both have a longer penetration depth in the body than visible light because biological tissues have a low absorption for them [134–136], indicating that NIR-1 and NIR-2 are biological transparent windows. Meanwhile, the normal biological tissues hardly get damage and not emit light (without background fluorescence) when exposed to the NIR light. Once special nanomaterials absorb NIR light and then transform into required signal or energy at tumor site, good contrast imaging of tumor can be achieved by NIR light irradiation, as shown in Fig. 5. These advantages have made NIRF imaging widely used in cancer imaging in recent years.

NIRF imaging is a novel in vivo imaging method with low background signal, high resolution, and high stability. Zero-dimensional (0D) semiconductor nanocrystals, commonly called quantum dots (QDs), have a variety of special optical characters, including wide excitation and narrow emission spectra, strong fluorescence, and high photobleach resistance [137]. Therefore, QDs have become a fluorescent labels for biomedical imaging [138]. Nevertheless, it is difficult to prepare multifunctional MoS₂ nanoplateform with excellent luminescence due to the strong quenching effect when QDs directly bind with MoS₂. Zhang et al. [139] prepared RGD-QD-MoS₂ nanosheets (NSs) that could successfully be used for targeted fluorescence imaging under NIR (785 nm) laser. MoS₂ NSs adsorbed BSA (bovine serum albumin) on its surface by the van der Waals force, and BSA was conjugated QDs (CdSe/ZnS, 580 nm) by forming amide bonds. Subsequently, RGD (arginine-glycine-aspartic) with outstanding tumor-targeting capability combined with the carboxyl-activated QDs to obtain RGD-QD-MoS₂ NSs. BSA not only acted as an anchor to conjugate QDs but also decreased the fluorescence quenching of QDs by broadening the distance between QDs and MoS₂ NSs. Meanwhile, MoS₂ NFs with lots of defect sites could be efficiently modified with thiolated PEG to enhance their colloidal stability. Compared with QD-MoS₂ NSs (without RGD), RGD-QD-MoS₂ NSs could specifically combine with integrin $\alpha\beta_3$ that is highly expressed on HeLa cells membrane, which is beneficial to produce a stronger fluorescence signal on the HeLa cell membrane and in the tumor areas of HeLa tumor-bearing Balb/c nude mice when treated with RGD-QD-MoS₂ NSs (Fig. 6 a-d).

MoS₂ must be modified by NIR fluorescent substance to obtain the function of NIRF imaging because themselves cannot emit NIR light [142,143], which requires careful design and complex synthesis process. The TPF excitation is a kind of fluorescence process, in which simultaneously absorb two photons to excite the fluorophore. The excitation light source of TPF usually is near-infrared laser which can emit fluorimetry under the visible light region. Compared with traditional fluorescence (SPF) imaging technology, TPF imaging technology has deeper tissue penetration, lower tissue autofluorescence and less photobleaching [144,145]. Monolayer MoS₂ has great photoluminescence because of their indirect-direct band gap transition, but its applications in TPF imaging are rare due to its extremely low room-temperature TPF quantum yield (QY) ($\Phi \approx 1\%$) [146–151]. Different from monolayer MoS₂, MoS₂ quantum dots (QDs), their size are below 10 nm have unique optical and electrical properties that attributed to the size and quantum confinement effect [152,153]. MoS₂ QDs have a higher two-photon absorption cross-section than organic dyes and common semiconductor QDs, representing it can be applied to TPF imaging [154]. Dai et al. [140] fabricated controllable-size MoS₂ QDs which had high TPF QY ($\Phi = 9.65\%$), long fluorescence lifetime (4.66 ns), and favourable fluorescent stability in the pH range of 4–10. The bright blue fluorescence could be observed in HeLa cell treated by MoS₂ QDs when irradiated by NIR-1 (700 nm) and the fluorescence brightness had not changed significantly after continuous excitation 30 min, indicating that

Table 1
Principle and depth of imaging detection.

Imaging modality	Incident radio	Detection signal	Depth	Resolution
Common FL imaging	350–650 nm	Vis	~1 mm	0.2–0.4 μ m
NIRF imaging	650–900 nm	NIR	~6 mm	0.35–0.5 μ m
TPF imaging	1000–1700 nm	Vis-NIR	~7 mm	0.3–1 μ m
PA imaging	650–950 nm	Ultrasonic	~50 mm	20–300 μ m
CT imaging	0.01 nm–10 nm	X-rays	No limit	50–500 μ m
PET imaging	~0.002 nm (511 KeV)	γ -photons	No limit	2–7 mm
MR imaging	~7 m (42.6 MHz)	Radio wave	No limit	25–100 μ m

Table 2MoS₂-based nanocomposites for cancer imaging and therapy.

Materials	Physically trigger	Therapy	Imaging modes	In vivo models	Therapeutic effect	Refs
DOX-MoS ₂ /Pt	/	drug delivery	/	/	/	[378]
DOX-PSMS-PEG	NIR laser(808 nm)	drug delivery	/	/	/	[206]
DOX/DNA/MoS ₂ -NS	ATP	drug delivery	/	/	/	[379]
MoS ₂ /GO@DOX	GO-targeting	drug delivery	/	Mice bearing B16 tumor	Completely eradicate tumor	[213]
DOX@MoS ₂ -PEI-HA	NIR laser(808 nm)/pH/HAase	drug delivery	PET	Mice bearing MCF-7-ADR tumor	Completely eradicate tumor	[181]
F-MoS ₂ NSs.	NIR laser(808 nm)	PTT	/	/	/	[63]
MoS ₂ -CS-Cype	NIR laser(808 nm)	PTT	/	/	/	[380]
MoS ₂ -PEG nanoflakes	NIR laser(808 nm)	PTT	/	Mice bearing 4T1 tumor	/	[244]
MoS ₂ -PEG	NIR laser(808 nm)	PTT	/	Mice bearing 4T1 tumor	Delay tumor growth	[240]
MoS ₂ -PPEG	NIR laser(808 nm)	PTT	/	Mice bearing 4T1 tumor	Reduce tumor volume	[258]
MoS ₂ -GSH nanodots	NIR laser(808 nm)	PTT	PA	Mice bearing 4T1 tumor	Completely eradicate tumor	[252]
RGD-QD-MoS ₂ NSs	NIR laser(785 nm)	PTT	NIRF	Mice bearing HeLa tumor	Reduce tumor volume	[139]
MoS ₂ @PZAC	NIR laser(808 nm)	PTT	MRI	Mice bearing 4T1 tumor	Reduce tumor volume	[178]
MoS ₂ -Gd-BSA	NIR laser(808 nm)	PTT	MR/PA	Mice bearing 4T1 tumor	Completely eradicate tumor	[305]
Layered MoS ₂ hollow spheres	NIR laser(808 nm)	PTT	CT/IR	Rabbit bearing VX2 tumor	Completely eradicate tumor	[242]
HA-MoS ₂	NIR laser(808 nm)	PTT	FL/PA	Mice bearing HCT116 tumor	Reduce tumor volume	[293]
⁶⁴ Cu-MoS ₂ -IO-(d)PEG	NIR laser(808 nm)	PTT	MRI/PA/PET	Mice bearing 4T1 tumor	Reduce tumor volume	[177]
p-MoS ₂ /n-rGO-MnO ₂ -PEG	NIR laser(980 nm)	PDT	/	/	/	[262]
MoS ₂ -PEG/Ce6	NIR laser(808 nm)/660 nm	PTT/PDT	/	Mice bearing 4T1 tumor	Delay tumor growth	[269]
MoS ₂ -LA-K11(DMA)-TBO (MKT)	NIR laser(808 nm)/630 nm	PTT/PDT	/	Mice bearing SCC-7 tumor	Reduce tumor volume	[270]
MoS ₂ -UCNPs-FA/ZnPc	NIR laser(808 nm)/980 nm	PTT/PDT	NIRF	Mice bearing HCC38 tumor	Delay tumor growth	[289]
PEG-MoS ₂ -Au-Ce6	NIR laser(808 nm)/660 nm	PTT/PDT	CT/NIRF	Mice bearing 4T1 tumor	Reduce tumor volume	[381]
Cy5.5-BSA-MoS ₂	NIR laser(808 nm)	PTT/PDT	FL/PAT	Mice bearing HepG2 tumor	Completely eradicate tumor	[292]
MoS ₂ -UCNPs@Ce6@SiO ₂	NIR laser(808 nm)	PTT/PDT	CT/MRI/UCL	Mice bearing U14 tumor	Reduce tumor volume	[382]
BSA-MoS ₂	MW irradiation	MW thermal therapy	/	Mice bearing H22 tumor models	Completely eradicate tumor	[279]
MoS ₂ encapsulated in microcapsules	MW irradiation	MW thermal therapy	CT	Rabbit bearing VX2 tumor	Completely eradicate tumor	[280]
sandwich-like MoS ₂ @MOS	NIR laser(808 nm)	PTT/drug delivery	/	/	/	[334]
Fe ₃ O ₄ @MoS ₂ @ZnO-DOX	NIR laser(808 nm)	PTT/drug delivery	/	/	/	[320]
HMSNs/DOX@MoS ₂ /Tf	NIR laser(808 nm)	PTT/drug delivery	/	/	/	[207]
Mn-doped Fe ₃ O ₄ @MoS ₂	NIR laser(808 nm)	PTT/drug delivery	MRI	/	/	[307]
PMO-DOX@MoS ₂ -PEG	NIR laser(808 nm)	PTT/drug delivery	/	Mice bearing MCF-7 tumor	Delay tumor growth	[322]
MoS ₂ -HPG-DOX	NIR laser(808 nm)	PTT/drug delivery	/	Mice bearing B16 tumor	Delay tumor growth	[325]
MoS ₂ -PEG-FA/DOX	NIR laser(808 nm)	PTT/drug delivery	/	Mice bearing 4T1 tumor	Delay tumor growth	[68]
MoS ₂ /HSA-DOX	NIR laser(808 nm)	PTT/drug delivery	/	Mice bearing MCF-7 tumor	Completely eradicate tumor	[328]
HA-PEI-LA-MoS ₂ -PEG@ (DOX/Mel)	NIR laser(808 nm)/pH	PTT/drug delivery	/	Mice bearing MCF-7 tumor	Reduce tumor volume	[314]
MoS ₂ -Lipid-DOX	NIR laser(808 nm)/pH	PTT/drug delivery	/	Mice bearing 4T1 tumor	Reduce tumor volume	[326]
NIR-CD/DOX/MoS ₂	NIR laser(808 nm)	PTT/drug delivery	CT	Mice bearing 4T1 tumor	Completely eradicate tumor	[383]
MoS ₂ -HA-DTPA-Gd/Gef	NIR laser(808 nm)	PTT/drug delivery	MRI	Mice bearing A549 tumor	Reduce tumor volume	[384]
Fe ₃ O ₄ @MoS ₂ -PEG(DOX)-2DG	NIR laser(808 nm)	PTT/drug delivery	MRI	Mice bearing MDA-MB-23 tumor	Reduce tumor volume	[303]
MoS ₂ -CS-DOX	NIR laser(808 nm)	PTT/drug delivery	CT	Mice bearing Panc-1 tumor	Reduce tumor volume	[237]
PLGA/MoS ₂ /DOX (PMD)	NIR laser(808 nm)	PTT/drug delivery	PA	Mice bearing 4T1 tumor	Completely eradicate tumor	[290]
MoS ₂ /Cu _{1.8} S/DOX	NIR laser(980 nm)	PTT/drug delivery	PLI/PAT/PTI	Mice bearing A549 tumor	Completely eradicate tumor	[295]
MoS ₂ @Fe ₃ O ₄ -ICG/Pt(IV)	NIR laser(808 nm)	PTT/PDT/drug delivery	MR/IR/PA	Mice bearing H22 tumor	Completely eradicate tumor	[301]
MoS ₂ -PEG-PEI/siPLK1	/	gene delivery	/	/	/	[352]
G5-MoS ₂ /Bcl-2 siRNA	NIR laser(808 nm)	PTT/gene delivery	/	Mice bearing 4T1 tumor	Delay tumor growth	[363]
FA/MoS ₂ /siRNA (HDAC1+KRAS)	NIR laser(808 nm)	PTT/gene delivery	/	Mice bearing Panc-1 tumor	Delay tumor growth	[361]

(continued on next page)

Table 2 (continued)

Materials	Physically trigger	Therapy	Imaging modes	In vivo models	Therapeutic effect	Refs
MoS ₂ -AKT scaffolds	NIR laser(808 nm)	PTT/tissue regeneration	/	Mice bearing Saos-2 tumor	Reduce tumor volume	[346]
AuNPs@MoS ₂	NIR laser(808 nm)	PTT/CDT	TPF	/	/	[369]
MoS ₂ @PANI	NIR laser(808 nm)	PTT/RT	CT/PA	Mice bearing 4T1 tumor	Delay tumor growth	[189]
MoS ₂ -PEG-CpG	NIR laser(808 nm)	PTT/immunotherapy	/	/	/	[366]
FePt/MoS ₂ -FA	NIR laser(808 nm)	PTT/drug delivery/immunotherapy	CT/MRI	Mice bearing 4T1 tumor	Completely eradicate tumor	[374]
PC ₁₀ A/DOX/MoS ₂	NIR laser(808 nm)	PTT/PDT/drug delivery/immunotherapy	/	Mice bearing 4T1 tumor	Completely eradicate tumor	[377]

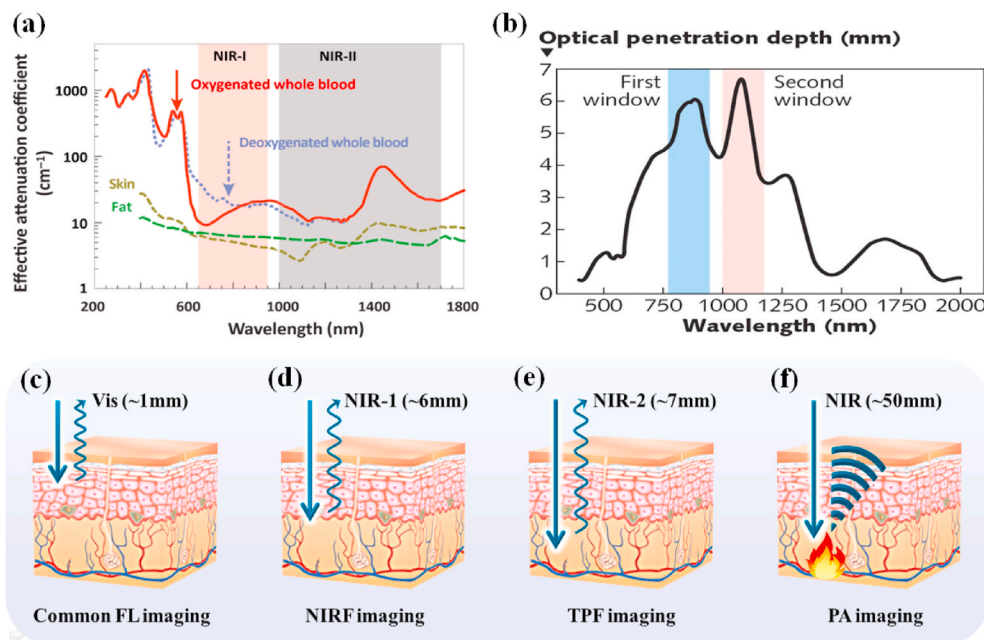


Fig. 5. (a) Effective attenuation coefficient of various biological components, including oxygenated blood, deoxygenated blood, skin, and fatty tissue. Reprinted with permission from Ref. [135]. Copyright 2019, Trends in Chemistry. (b) The optical penetration depth of light into skin over the wavelength range from 400 to 2000 nm. Reprinted with permission from Ref. [136]. Copyright 2005, Journal of Physics D: Applied Physics. The penetration depth of (c) common FL imaging (d) NIRF imaging (e) TPF imaging (f) PA imaging, respectively.

MoS₂ QDs was an outstanding multiphoton imaging probe (Fig. 6 e). NIR-2 has a longer penetration depth in the living body, lower phototoxicity and better image contrast than NIR-1 [155–160]. Sweet et al. [141] designed a water-soluble anti-PSMA antibody-conjugated MoS₂ QD-based TPF probe for targeted bioimaging of LnCaP prostate cancer cells. Firstly, they used LA-PEG to modify MoS₂ quantum dots (QDs) to improve the stability in physiological environment. LA can effectively form a covalent bond with Mo on the edge of molybdenum sulfide. Subsequently, anti-PSMA antibody conjugated with MoS₂ QDs via PEG to make the TPF probe has targeting ability for prostate cancer cells. The QY of MoS₂ QDs was as high as 54% and their two-photon brightness was detected to be 4.7×10^3 GM, which indicated that MoS₂ QDs were a good TPF imaging probe under the excitation of NIR-2 light (1064 nm). Furthermore, the TPL imaging data proved that anti-PSMA antibody-conjugated MoS₂ QDs could selectively target LnCaP prostate cancer cells and achieve effective TPL imaging in living cells (Fig. 6f and g).

3.2. PA imaging

The principle of PA imaging is that a NIR laser pulse is transmitted into biological tissue, and some of the laser energy is absorbed and transformed into heat, causing a transient thermoelastic expansion, resulting in broadband ultrasonic emission. The resulting ultrasonic waves are then examined by ultrasonic transducers, which are ultimately analyzed to produce an image. The penetration depth of PA imaging can reach ~50 mm thanks to strong penetration of ultrasonic

wave. PA imaging technology combines advantages of optical imaging and ultrasound imaging to achieve the tissue image of high resolution and high contrast [161–165]. MoS₂ has outstanding photothermal conversion efficiency and excellent NIR absorption capacity, which can be used for high-quality PA imaging. Yu et al. [166] developed a MoS₂/Fe₃O₄ composite (MSIOs) for photoacoustic tomography (PAT) imaging. MSIOs were prepared by attaching Fe₃O₄ nanoparticles to the surface of the MoS₂ nanoflakes. It's worth noting that MSIOs was a highly sensitive PAT imaging contrast agents and the PAT signals of MSIOs exhibited a concentration-dependent manner with a good linear relationship ($r^2 = 0.995$). The data in vivo showed that the PAT signals were remarkably increased with the prolonging of time after intravenously injecting MSIOs into PANC-1 tumor bearing mice, confirming the gradual accumulation of MSIOs into tumor sites to generate strong PAT contrasts. Furthermore, the relatively long residence time (24 h) of MSIOs in tumors further improved their PAT imaging effect, realizing more effective cancer diagnosis.

In order to further enhance the effect of PA imaging and obtain more accurate information of cancer diagnosis, it is a very effective way to modify nanomaterials with specific targeting functional groups of cancers. Jiang et al. [167] developed transmembrane peptide LNP-modified porous MoS₂ nanoflowers (MNFPPPL) as PA contrast agents that could actively target breast cancer. MNFPPL was spiny nanoparticle composed of three dimensional (3D)-stacked MoS₂ nanosheets with large surfaces and abundant pores and the 3D nanostructure could trap the near-infrared light through multiple reflection to strengthen the signal of PA imaging. MNFPPL and porous MoS₂ nanoflowers (MNF) had

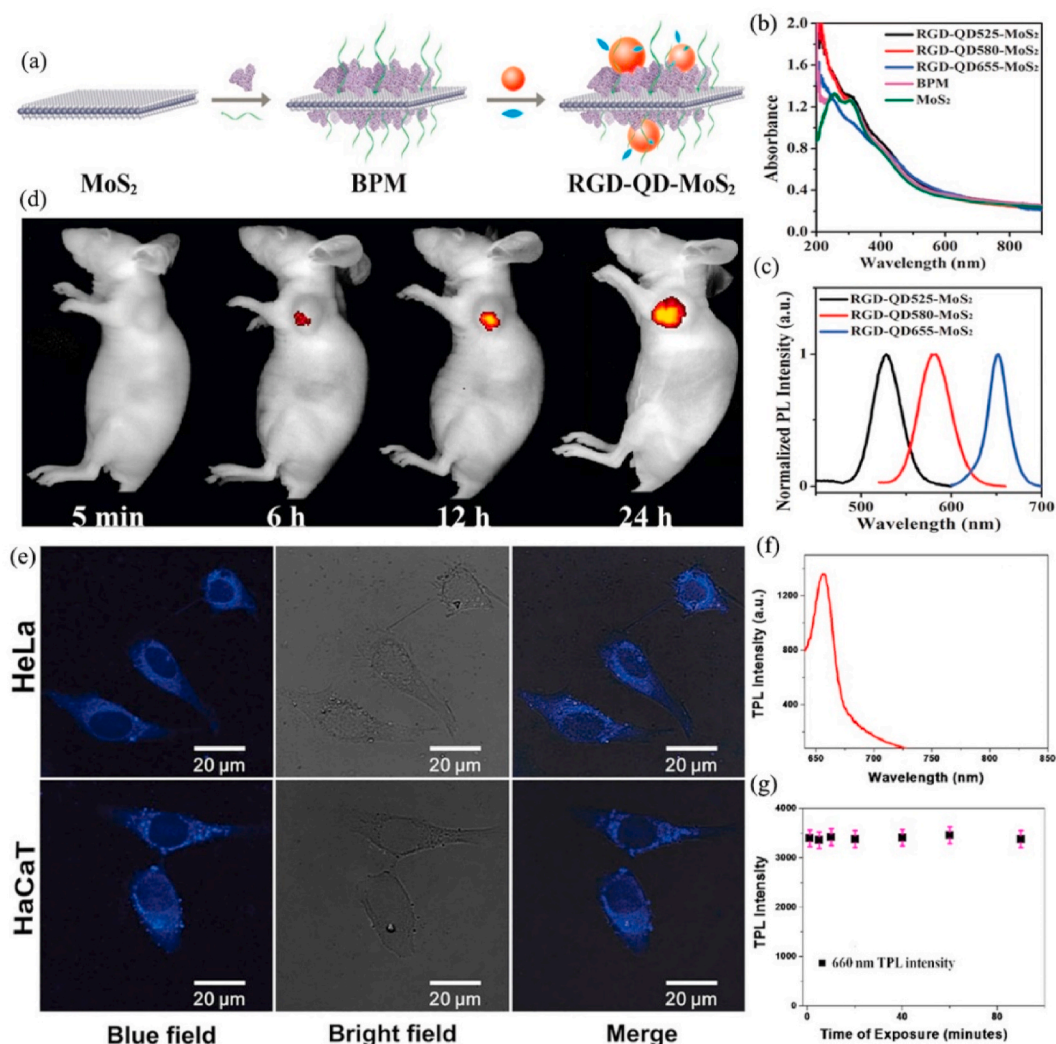


Fig. 6. (a) The preparation of RGD-QD-MoS₂ NSs. (b) Ultraviolet-visible-near infrared (UV-Vis-NIR) absorption spectra of MoS₂ NSs, BPM NSs, and RGD-QD-MoS₂ NSs. (c) Normalized photoluminescence spectra of RGD-QD-MoS₂ NSs. (d) Fluorescence images of HeLa tumor-bearing Balb/c nude mice at different times after i. v. injection of RGD-QD655-MoS₂ NSs. Reprinted with permission from Ref. [139]. Copyright 2017, Nanoscale. (e) The multiphoton luminescence image of HeLa and HaCaT cells with internalized MoS₂ QDs. Excitation wavelength was 700 nm and detection wavelength in the 420–460 nm range. Reprinted with permission from Ref. [140]. Copyright 2015, Small. (f) TPL intensity of the MoS₂ QDs at 1064 nm excitation. (g) Variation in the TPL intensity with time, indicating that anti-PSMA antibody-attached MoS₂ QDs exhibit very good photostability. For this experiment, we used a laser power density of 40 W/cm². Reprinted with permission from Ref. [141]. Copyright 2017, ACS omega.

similar near-infrared absorption curves around 808 nm, manifesting that the modification of transmembrane peptide LNP did not change the NIR absorption of MNF. Meanwhile, MNFPPL was absorbed by tumor cells faster and more efficiently than MNF. This result could be attributed to the targeting effect of transmembrane peptide LNP. After intravenously injected MNFPPL or MNFPP (MAL-PEG-PEI-MoS₂), the PA signals reached the maximum at 4 h in carcinoma tissues of 4T1 tumor-bearing mice but PA signal of MNFPPL more rapidly enhanced than MNFPP, which implied that MNFPPL could target the tumor site (Fig. 7 a-c).

Highly sensitive PA signals of MoS₂ can also be obtained by reducing the its layers. The PA signal of MoS₂ will further increase along with the number of layers lessen because MoS₂ with less layers has a higher light absorbance. Currently, PA molecular imaging of deep cerebral tumors remains a challenge partly because the available PA molecular probe has insufficient sensitivity and limited selectivity [168,169]. Chen et al. [170] directly obtained single-layer (S-MoS₂), few-layer (F-MoS₂), and multi-layer (M - MoS₂) nanosheets through albumin-assisted exfoliation without further surface modification. The results showed that reducing the number of nanosheet layers from M - MoS₂ to S-MoS₂

could improve the elasticity of nanomaterials and enhance the absorption of near-infrared light, greatly increasing the PA effect. Meanwhile, S-MoS₂ could be effectively endocytosed by U87 glioma cells and generated a strong PA signal to detect brain tumor cells with high sensitivity. Tumor tissue with a size less than 1.5 mm of skull was still observed in vivo (Fig. 7 d-h).

3.3. CT/PET/MR imaging

NIF-based imaging technology usually can only detect tumors whose subcutaneous depth is less than 50 mm (Table 1). Ultra-short electromagnetic wave like X-rays, γ -photons and long-wavelength electromagnetic wave (42.6 MHz, its wavelength is 7 m) all have extremely longer tissue penetration depth that represents CT/MRI/PET imaging based on these rays can realize a better imaging effect in most tumors located inside the body, as shown in Table 1.

CT is a kind of medical imaging technology, it uses computer to handle multiple X-ray measurements taken from different angles combined to generate the tomographic image of human body. CT imaging

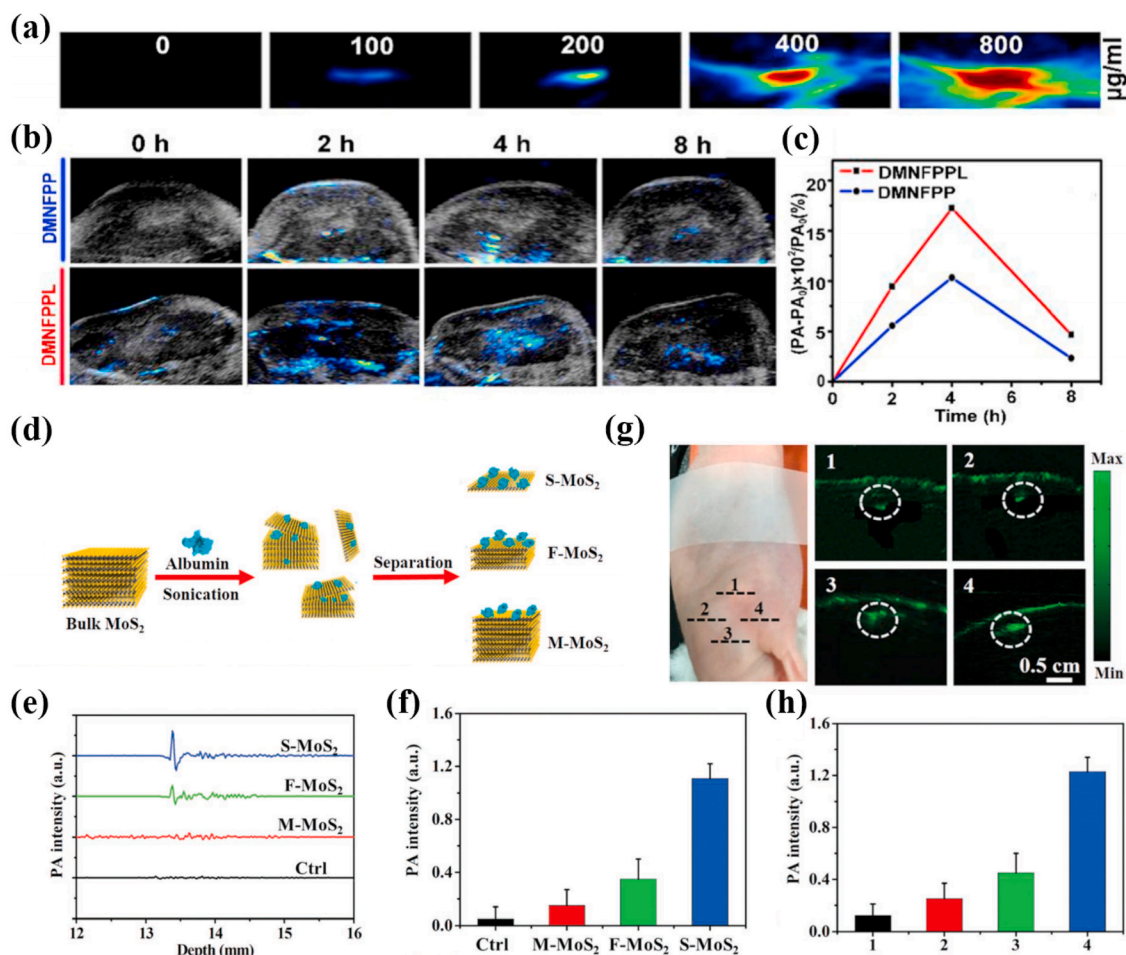


Fig. 7. (a) In vitro PA images of DMNFPPL with different concentrations. (b) Real-time PA images of 4T1 tumor-bearing mice at different time points after intravenous administration of DMNFPPL and DMNFPPL. (c) The curves of PA signal rate changed with administration time periods. Reprinted with permission from Ref. [167]. Copyright 2020, International journal of pharmaceuticals. (d) Schematic illustration of the synthesis procedure of MoS₂ nanosheets with various layered nanostructures. (e) The PA signals produced by S-MoS₂, F-MoS₂, and M-MoS₂ and (f) their quantitative results. (g) PA images of S-MoS₂, F-MoS₂, and M-MoS₂ in subcutaneous tissue of mice and (h) their quantitative results. 1: Control group, 2: M-MoS₂ treated group, 3: F-MoS₂ treated group, 4: S-MoS₂ treated group. Reprinted with permission from Ref. [170]. Copyright 2016, Advanced functional materials.

with fast detection speed can provide tissue density distribution of a certain section and visualize deep cancer structures in the body [171, 172]. MoS₂ nanomaterials can be applied to contrast agents in CT imaging [68,173,174] because Mo atom with high absorption coefficient and atomic number has stronger X-ray attenuation than the components of the body. Liu et al. [175] synthesize antitumor nanocomposites (PEG-MoS₂-Au-Ce6) through adsorbing chlorin e6 (Ce6) onto PEG-MoS₂ nanosheets decorated with gold nanoparticles (AuNPs). The Hounsfield unit (HU) value, represents CT contrast ability, was increased from 121.0 ± 20.1 (0 h) to 245.7 ± 18.6 (6 h) when intravenously injected PEG-MoS₂-Au-Ce6 into 4T1 tumor bearing Balb/c nude mice, indicating excellent CT imaging effect (Fig. 8 a-c). Besides, Researchers found that MoS₂ nanocomposites had a stronger CT imaging ability in tumor-bearing mice than iohexol [171] or iopromide [176], both are common clinical X-ray contrast agents.

PET imaging has outstanding sensitivity, excellent temporal resolution and superb tissue penetration, which makes it receive much attention in cancer diagnosis, staging and treatment monitoring [179]. Isotope-labeled drugs (PET imaging agents) with positron emission can happen annihilation effects during the physiological metabolism after injecting them into body, producing two γ -photons with equal energy and opposite directions. Radioisotope ^{64}Cu (the half-life of the positron emitter is 12.7 h) could successfully modify MoS₂ for PET imaging [180]. Liu et al. [177] straightforwardly efficiently labeled ^{64}Cu onto

double-PEGylated MoS₂-iron oxide (MoS₂-IO-(d)PEG) by mixing $^{64}\text{CuCl}_2$ with MoS₂-IO-(d)PEG, which was attributed that the Cu^{2+} ions could anchor on the Mo defect sites of MoS₂ nanosheets. The serum stability test indicated that ^{64}Cu -MoS₂-IO-(d)PEG had a strong stability within 48 h and quantitative PET data, a percentage injected dose per gram of tissue (%ID/g), and confirmed that the enhancement of ^{64}Cu signal was time-dependent. Therefore, ^{64}Cu -MoS₂-IO-(d)PEG could be applied to PET imaging contrast agent for real-time monitoring the body distribution of MoS₂-IO-(d)PEG and therapeutic effect in 4T1 tumor-bearing mice (Fig. 8 d-f). Furthermore, HA could specifically bind to a CD44 receptor overexpressed in MCF-7-ADR cancer cells to improve the tumor-targeting of PET imaging contrast agent. Dong et al. [181] also synthesized ^{64}Cu -NOTA labeled MoS₂-PEI-HA for PET imaging of MCF-7-ADR tumor-bearing mice. PET imaging indicated that the signals at tumor site were remarkably stronger in the HA-targeted group than no targeting group when ^{64}Cu -NOTA labeled MoS₂-PEI-HA and MoS₂-PEI were intravenously injected into MCF-7-ADR tumor-bearing mice for 4 h. Meanwhile, the quantitative results of biodistribution for the MoS₂-PEI and MoS₂-PEI-HA acquired by γ -counter indicated that the accumulation of ^{64}Cu -MoS₂-PEI-HA-NOTA was 10.486 ID/g in MCF-7-ADR tumor area at 4 h post-injection but ^{64}Cu -MoS₂-PEI-NOTA was only 5.015 ID/g, which proved that MoS₂-PEI-HA has high targeting ability to achieve more accurate PET imaging.

MRI is a non-invasive bioimaging technology with a high spatial

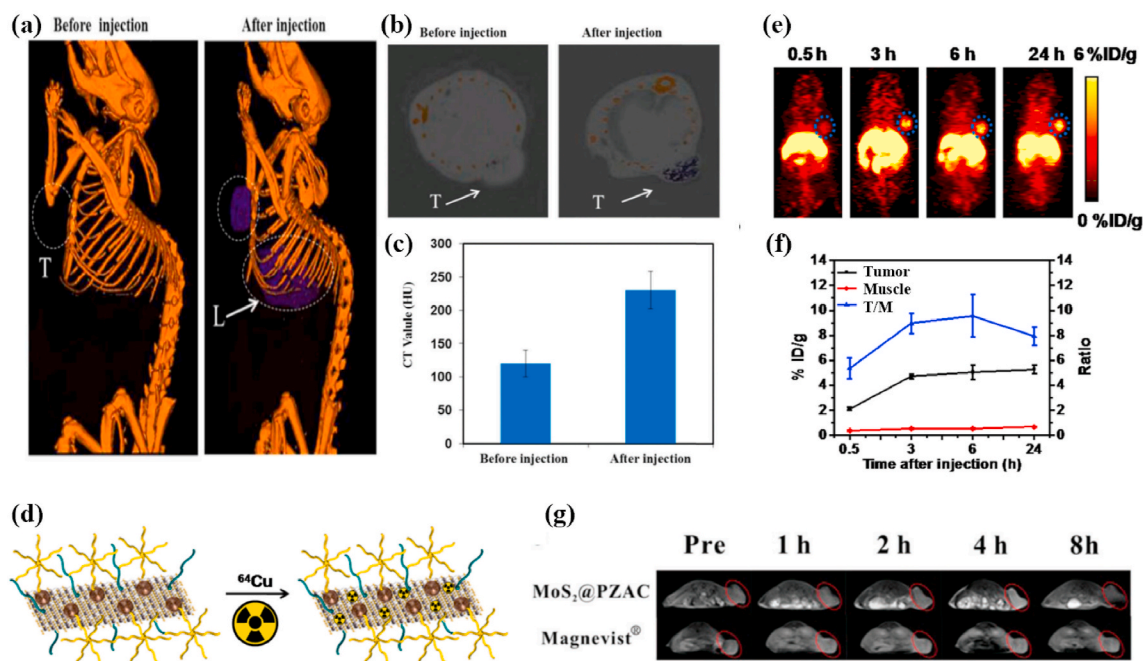


Fig. 8. (a) In vivo CT images of 4T1 tumor-bearing mice before and 6 h after intravenous injection with PEG-MoS₂-Au-Ce6 nanocomposites, tumor (T) and liver (L). (b) In vivo CT images of tumors on mice before and 6 h after intravenous injection with PEG-MoS₂-Au-Ce6 nanocomposites. (c) Corresponding HU value of PEG-MoS₂-Au-Ce6 nanocomposites in the tumor before injection and 6 h after injection. Reprinted with permission from Ref. [175]. Copyright 2017, Journal of materials chemistry. (d) Scheme presenting the ⁶⁴Cu labeling on MoS₂-IO-(d)PEG via a chelator-free manner. (e) PET images of 4T1 tumor-bearing mice taken at various time points post iv injection of ⁶⁴Cu-MoS₂-IO-(d)PEG. The blue dot circles highlight the 4T1 tumor site of mice. (f) Quantification of ⁶⁴Cu-MoS₂-IO-(d)PEG uptake in the tumor and muscle, as well as the tumor/muscle (T/M) ratio at various time points pi. Reprinted with permission from Ref. [177]. Copyright 2015, ACS nano. (g) In vivo T1-weighted MR images of Balb/c mice after injection at different time points (pre-injection, 1 h, 2 h, 4 h, 8 h). Reprinted with permission from Ref. [178]. Copyright 2018, Journal of materials chemistry.

resolution [182] and the image contrast can be enhanced between the diseased and the tissues normal tissues [183,184]. Using long-wavelength electromagnetic waves pulses with a specific frequency (the frequency must match the magnetic field strength) to stimulate the hydrogen nucleus in the body, making the hydrogen nucleus absorb energy and generate resonance. The hydrogen nucleus releases the absorbed energy and emits electromagnetic wave signals after the long-wavelength electromagnetic waves pulses is stopped, which is gathered by a receiver in vitro and treated through an electronic computer for obtaining the MRI image. Gadolinium (Gd) complexes are commonly clinical T1-weighted MRI contrast agents, but free Gd³⁺ has high biotoxicity. Zwitterions are expected to be a substitute to PEG because they have systemic circulating stability and can avoid nonspecific protein adsorption [185,186]. Also, the carboxybetaine monomers of zwitterionic polymers are rich in -COOH groups which can coordinate with MoS₂ to form a stable conjugated system [187]. Yu et al. [178] prepared paramagnetic zwitterionic amphiphilic copolymer (PZAC) by introducing the zwitterionic monomer carboxybetaine methacrylate (CBMA) into the amphiphilic copolymer backbone to lengthen systemic circulation, and the paramagnetic crosslinker was the Gd³⁺-monomer complex. Subsequently, PZAC interacted with ammonium tetrathiomolybdate (ATTM) to form MoS₂@PZAC under microwave irradiation. The synergistic effect of the combination between the edge Mo atoms in MoS₂ and the -COOH groups of the CBMA chain in PZAC and the non-covalent interactions between Mo and N on the CBMA promoted the hybridization of MoS₂ and PZAC. The result showed that MoS₂@PZAC had a higher relaxivity ($r_1 = 11.2 \text{ mM}^{-1} \text{ s}^{-1}$) than Magnevis (r_1 of approximately $4.4 \text{ mM}^{-1} \text{ s}^{-1}$) due to two reasons. One was that the hydrophilic CBMA enhanced the rotational correlation time and water exchange rate based on Solomon-Bloembergen-Morgan (SBM) theory, and the other was that the multiple Gd³⁺ centres in the MoS₂@PZAC could also enhance the relaxivity. Meanwhile, the circulation time could be prolonged because MoS₂@PZAC had an appropriate and uniform size

($28.5 \pm 5.5 \text{ nm}$). Therefore, the PZAC in the spherical MoS₂ nanohybrid (MoS₂@PZAC) acted as a T1-weighted MRI contrast agent to effectively guide MRI imaging in Balb/c mice bearing 4T1 tumors (Fig. 8 g).

3.4. Multi-mode imaging

Single-mode imaging usually has its inherent limitations, such as FL imaging has high resolution but limited penetration, while CT/PET/MRI has strong penetration but low resolution. Multi-mode imaging can overcome the deficiency of single-mode imaging, increasing the accuracy of a cancer diagnosis. In the field of multi-mode imaging, nanocomposites based on MoS₂ have attracted extensive attention because of their unique physicochemical property [188–190].

The most common is to combine the two imaging modes to achieve highly sensitive cancer diagnosis. For instance, Gao et al. [191] prepared rod-shaped heterogeneous Bi₂S₃-MoS₂ nanoparticles (BMNPs) served for CT/PA dual-mode imaging contrast agents. The slope of the HU value against the Bi concentration (8.84 HU L/mmol) was twice higher than commercial I (4.47 HU L/mmol) and BMNPs had a stronger CT imaging brightness. In the meantime, the CT value in 4T1 tumor-bearing mice increased from 37.43 HU to 160.66 HU after injection of BMNPs, manifesting BMNPs possessed excellent CT imaging ability. Moreover, PA signals could be generated by BMNPs even at low aqueous solution concentration (6.25 mM) based on Bi and the intensity of PA signal is positively correlated with concentration of BMNPs within the linear range of $3.125\text{--}25 \text{ mM}$. BMNPs with CT/PA imaging capability could improve the precision in cancer diagnosis. Tang et al. [192] also constructed a micrometer-sized materials (mPEG-PLGA@DMF) that integrated MoS₂ nanosheets and Fe₃O₄ nanoparticles into methoxy poly(ethylene glycol) poly(lactic-co-glycolic acid) (mPEG-PLGA) microcapsules. T2-weighted intensity of Fe₃O₄ nanoparticles became gradually stronger and CT signal intensity of MoS₂ nanosheets was progressively enhanced with the increase of mPEG-PLGA@DMF concentration in

vitro. Meanwhile, the tumor site was markedly darkened that observed by MRI and the CT signal was increased from 45 HU to 356 HU after injecting mPEG-PLGA@DMF into VX-2 liver orthotopic transplantation tumor, which proved that microcapsules could be successfully applied to MR/CT dual-modal imaging.

Triple-modal or Multi-modal imaging has also been designed to further increase the accuracy of cancer diagnosis. Liu et al. [194] obtained a multifunctional nanocomposites based on an aluminum phthalocyanine chloride (AlPc) loaded MoS_2 nanodot core/ SiO_2 shell, which coated by chitosan (CS) to form AlPc- MoS_2 @ SiO_2 -CS. AlPc used as the NIRF imaging contrast agent and MoS_2 nanodot served as PA and CT imaging contrast agent, realizing NIRF/PA/CT imaging in the 4T1 tumor-bearing mice and the signals of the three types of imaging all increasing with the concentration of AlPc- MoS_2 @ SiO_2 -CS increased. NIRF imaging in vivo displayed that AlPc- MoS_2 @ SiO_2 -CS widely distributed all over the body at the early stages after injection and subsequently the NIRF signal at tumor sites gradually increased and reached peak value at 8 h after injection, which implying that the nanocomposites could circulate in the bloodstream and quickly targeted tumors to achieve high precision imaging. MoS_2 nanosheets also have the ability of multispectral optoacoustic tomography (MSOT) imaging due to their strong NIR light absorbance. Yang et al. [193] synthesized mesoporous silica nanoparticles (MSNRs)@ MoS_2 -HSA/Ce6 nanocomposites for FL/MSOT/CT triple-modal imaging in 4T1 tumor-bearing nude mice. Human serum albumin (HSA) which used as tumor-targeting agents to increase the accumulation of MSNR@ MoS_2 -HSA/Ce6 in tumor cells via albumin receptor (gp60) and albumin-binding protein SPARC. The FL and MSOT imaging signals showed that the accumulation of MSNR@ MoS_2 -HSA/Ce6 in the tumor site was gradually increased after 8 h and the peaked at 12 h.

Meanwhile, CT signals were positively correlated with the concentration of MSNR@ MoS_2 -HSA/Ce6 (Fig. 9).

4. Chemotherapy

Compared with surgery and radiotherapy, chemotherapy is a means of systemic treatment. However, chemotherapy usually produces significant side effects due to its low solubility, poor stability, and easy absorption by non-cancer tissues. Hence, it ought to be design effective drug delivery systems (DDSs) to enhance the stability and load rate of drugs, and control the drug release in the tumor tissue, enhancing the therapeutic effect [195–197]. MoS_2 -nanomaterials have many merits, including effective load rate, good stability, excellent biocompatibility, and are easy to be functionalized, which can be used as carriers to deliver drugs. Meanwhile, the nanostructure will be destroyed to achieve the release of drugs under the NIR irradiation because MoS_2 can effectively convert the absorbed NIR light into heat energy. Therefore, MoS_2 -nanomaterials are promising candidates for drug delivery (Table 2).

Traditional DDSs can successfully deliver drugs to the treatment site, such as ethyl cellulose/chitosan/g- C_3N_4 / MoS_2 core-shell nanofibers could co-deliver folic acid and doxorubicin into MCF-7 and HeLa cells [198]. The latest researches focus on how to control drug release to reduce side effects. Drugs can be released accurately and controllably by increasing the sensitivity of DDS to the applied stimuli [199,200]. The pH value of tumor microenvironment (TME) is about 6.5, which is lower than that of normal cells, so pH can act as an excellent internal stimulus to promote the effective release of drugs at cancer sites [201]. Among various stimuli, NIR light with low cytotoxicity can penetrate deep tissues that make it have prominent advantages [202,203]. Local heating

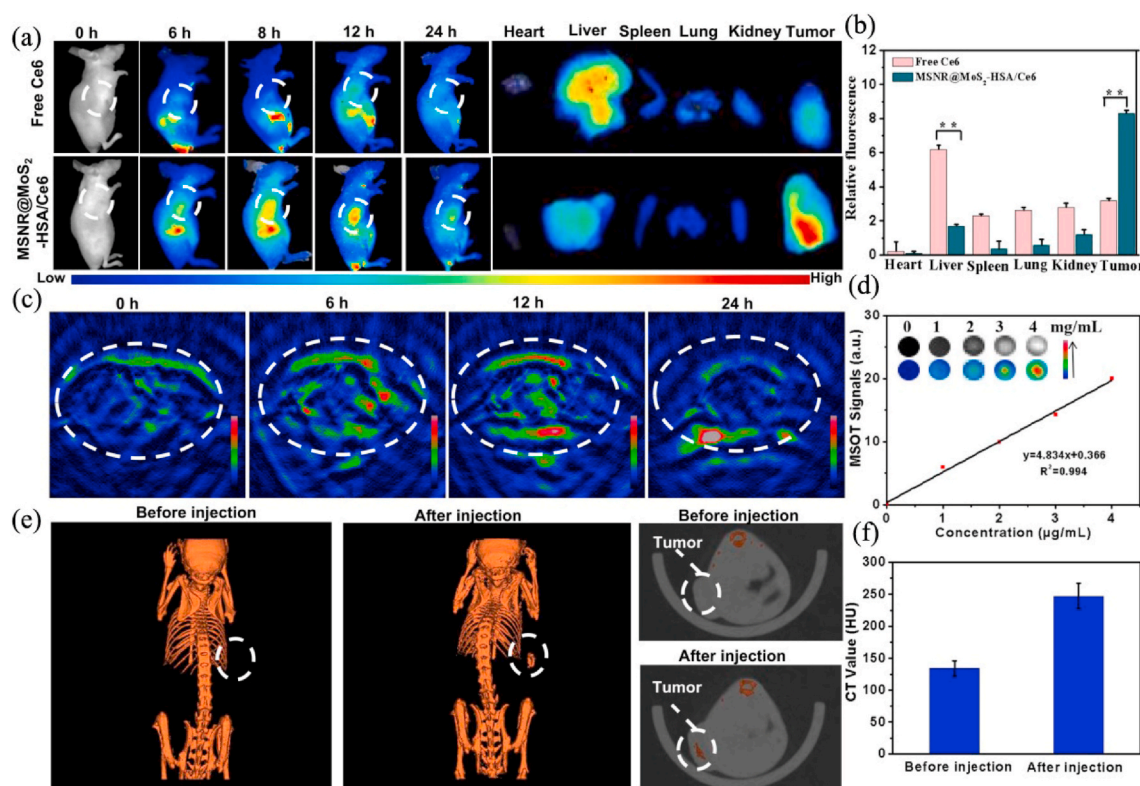


Fig. 9. (a) Fluorescence images of nude mice at different time points after administration of free Ce6 and MSNR@ MoS_2 -HSA/Ce6; the right panel shows the ex vivo images examined at 24 h. (b) Average fluorescence signals of Ce6 in major organs examined at 24 h. (c) MSOT images of 4T1 tumor-bearing mice after being intravenously injected with MSNR@ MoS_2 -HSA/Ce6. (d) Photoacoustic intensity linearly fit to the concentration of MSNR@ MoS_2 -HSA/Ce6 aqueous solutions; inset: the corresponding PA images. (e) CT images of tumor site before and after intratumor injection with MSNR@ MoS_2 -HSA/Ce6. (f) Corresponding HU value of MSNR@ MoS_2 -HSA/Ce6 nanocomposites in the tumor before injection and 12 h after injection. Reprinted with permission from Ref. [193]. Copyright 2019, Theranostics.

will destroy the stability of the endosomal membrane, promoting the escape of drugs and their carriers from the endosomal. The single-layered MoS_2 obtained by lithium intercalation is easily prepared into a dispersion in aqueous solution, which is appropriate for biomedical applications [19]. However, the newly synthesized single-layered MoS_2 has a strong aggregation in the aqueous solution, and thus further modification is needed to increase the stability of the dispersion [204,205]. Related studies showed that using polymer or silica to modify the MoS_2 surface can significantly improve drug loading and colloidal stability. Lee et al. [206] synthesized a photothermal controlled nanoplate to load anticancer drug DOX, which consisted of single-layered MoS_2 coated with porous silica and modified with polyethylene glycol (PEG). The modification of porous silica and PEG significantly enhanced the colloidal stability of the nanocomposite. Meanwhile, the escape of the carrier from the endosome and the release of DOX from nanoplateform were both achieved upon exposure to NIR light radiation. The corresponding half maximal inhibitory concentration (IC_{50}) values of the MoS_2 -nanocarrier against HeLa, HepG2, and HCT-8 cell was 1.4-, 36-, and 12-fold that of free DOX respectively, suggesting that MoS_2 -nanocarrier had a stronger anti-cancer effect (Fig. 10).

DDSs with a single stimulus-response can only release the drug under a specific stimulus. Therefore, DDSs sensitizing to double or multiple stimuli have attracted more concerns to further improve the therapeutic effect. Since GSH can reduce disulfide bonds ($-\text{S}-\text{S}-$), it is possible to develop GSH-sensitive DDS by capping hollow mesoporous silica nanoparticles (HMSN) with disulfide cross-linkable polymers to achieve

controlled release of drugs. Zhao et al. [207] prepared a dual-functional DDS ($\text{HMSN@MoS}_2/\text{Tf}$) that could effectively release DOX from HMSN when degraded by GSH and high temperature. Firstly, they used MoS_2 nanosheets to cap the pores of HMSNs via disulfide linkage after encapsulating DOX into HMSNs. Then transferrin (Tf) was covalently attached on the surface of HMSNs@ MoS_2 by forming $-\text{S}-\text{S}-$ to improve the tumor-targeting of $\text{HMSN@MoS}_2/\text{Tf}$. MoS_2 , a NIR light response element, could not only prevent the pre-release of DOX but also realize controlled drug release by NIR and intracellular reducing agents such as GSH, realizing more accurate release of DOX.

To reduce the absorption of non-cancer tissues during drug delivery and decrease the side effects of chemotherapy, it is essential to explore DDSs with good biocompatibility that can target cancer tissues. Graphene oxide (GO) is capable of localizing in the lung through various pathways (e.g., intravenous (iv) injection) [208–211] and has a high water-solubility [212]. Liu et al. [213] synthesized a MoS_2/GO nanocomposite with high dispersion and excellent biocompatibility that could selectively target the lung. Results showed that the accumulation of MoS_2/GO in the lung is 9-fold greater than bulk MoS_2 and 50-fold greater than Lys- MoS_2 and FA- MoS_2 . Meanwhile, compared with GO, the MoS_2/GO possessed better biocompatibility, such as lessened pro-inflammatory effects, improved lung fibrosis and compromised macrophagic activation, which attributed to the decreased reactivity of MoS_2 in the complexes. Furthermore, the drug loading and the killing effect for cancer cells were both increased, and metastatic tumor growth of B16 cells in the lung of mice was also dramatically repressed by MoS_2/GO nanocomplexes.

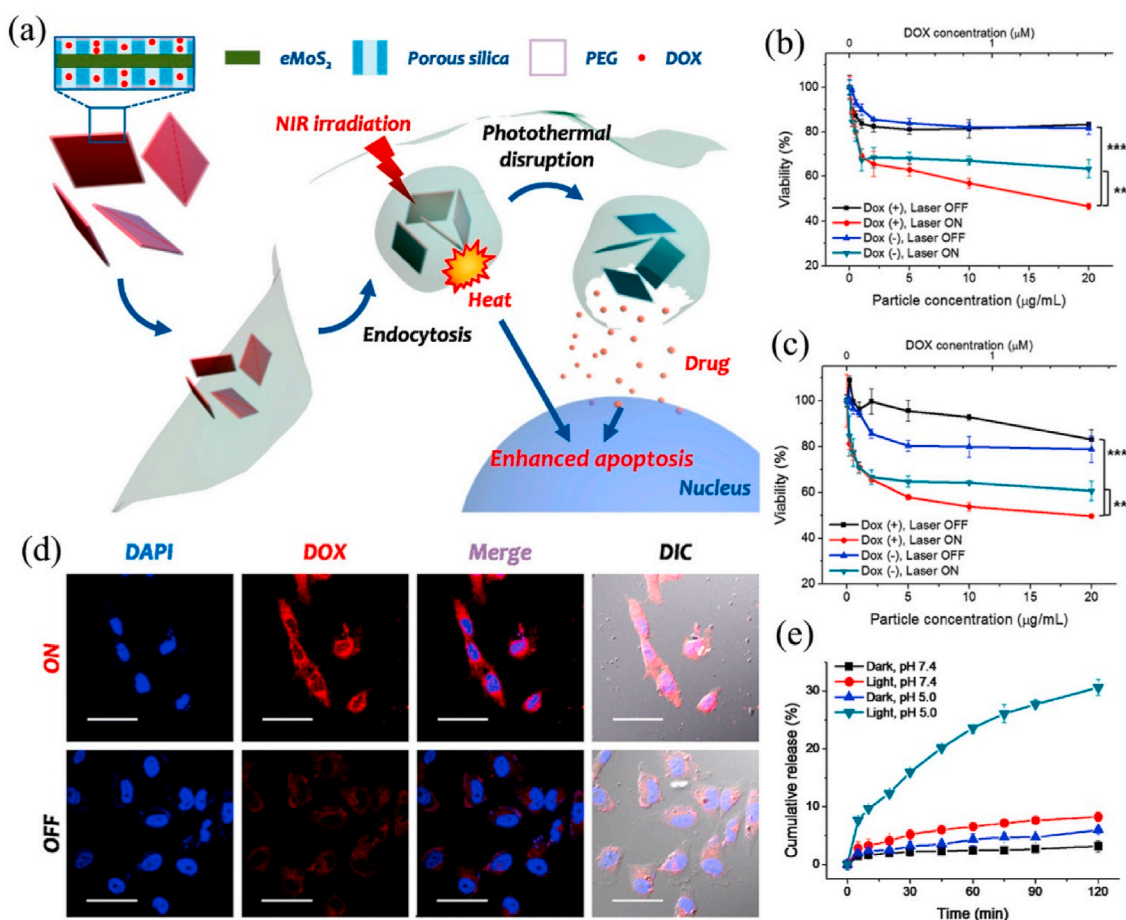


Fig. 10. (a) Schematic illustration of single-layered MoS_2 -based nanoplate as a NIR-responsive system. NIR-induced cytotoxicity of DOX-PSMS-PEG or PSMS-PEG against (b) HeLa and (c) HCT-8 cell line (** $p < 0.01$, *** $p < 0.001$). (d) Confocal microscopic images of DOX-PSMS-PEG treated HeLa cells which were further irradiated or not irradiated by 808 nm laser (5 W/cm^2). Nucleus was stained by DAPI (blue) and DOX was false-imaged as red (scale bar = $50 \mu\text{m}$). (e) Photo-responsive drug release of DOX from DOX-PSMS-PEG in vitro. Reprinted with permission from Ref. [206]. Copyright 2016, Chemistry of Materials.

Multidrug resistance (MDR) will reduce the accumulation of drugs in the tumor tissue, reducing the therapeutic effect during cancer chemotherapy [214,215]. Overexpression of p-glycoprotein (P-gp) is the main reason for MDR [216], inhibiting its expression can therefore enhance the therapeutic effect. Hyaluronic acid (HA) with excellent biocompatibility can specifically bind to the CD44 receptors that are highly expressed in drug-resistant cancer cells [217], and be degraded by hyaluronidase (HAase) overexpressing in the tumor microenvironment [218]. Dong et al. [219] designed polyethyleneimine (PEI) and HA-modified multifunctional MoS₂ nanofibers (MoS₂-PEI-HA) for actively targeting drug-resistant MCF-7-ADR cells with high expression of CD44. MoS₂-PEI-HA could be effectively absorbed by MCF-7-ADR, and then released DOX under stimulation of HAase and NIR laser. Importantly, the nanocarrier could significantly inhibit the expression of P-gp to improve sensitivity of chemotherapy, which attributed to the combination of HA targeting and mild NIR laser stimuli. The results indicate that DOX@MoS₂-PEI-HA + NIR groups had a stronger therapeutic effect than DOX@MoS₂-PEI-HA groups, MoS₂-PEI-HA + NIR groups and DOX groups in MCF-7-ADR tumor-bearing mice.

5. Phototherapy

Although nanomedicine and nanobiotechnology have made tremendous progress and promoted the early diagnosis and treatment of cancer [220], cancer still is the most serious and challenging illness and the leading cause of death [221–225]. Therefore, it is urgent to explore new strategies with high treatment efficiency and low toxic reaction. Phototherapy including photothermal therapy (PTT) and photodynamic therapy (PDT) is an emerging alternative therapy for traditional cancer treatments [226,227]. Different from traditional cancer therapy, phototherapy has its own unique advantages. On the one hand, phototherapy can precisely be controlled by selection of irradiation location, time and intensity. The limitation of phototherapy is the limited depth of tissue penetration. Nanomaterials with NIR absorption ability can improve the efficiency of phototherapy to a certain extent. The rich van Hove singularity peaks in the electronic density of states ensures the strong light-matter interactions in MoS₂, which leads to high NIR light absorption [228]. Meanwhile, MoS₂ also has a strong photothermal conversion capability that promotes its applications for phototherapy (Table 2).

5.1. Photothermal therapy

PTT is a strategy mediated by PTT agents [229,230] which can effectively turn absorbed NIR light into heat [231], killing cancer cells with minimal side effects because tumor cells are more sensitive to heat [232,233]. Compared with traditional methods, PTT has smaller invasiveness, higher accuracy and spatiotemporal selectivity, achieves a high degree of localization and can be applied to areas where surgery is difficult [234]. NIR light in the range of 700–1100 nm has high transparency in biological tissues, blood, and water, which can be used to induce photothermal therapy [235,236].

Previous studies have found that MoS₂ nanosheets modified with PEG, L-cysteine or chitosan could be used as PTT agents [68,237–239]. However, the process of obtaining MoS₂ through chemical exfoliation based on “top-down” strategy is time-consuming, and cannot control the thickness and morphology of the MoS₂ nanosheets. Besides, complicated surface modification is required to ensure its stability in the physiological environment. Therefore, the typical “bottom-up” strategy is the other choice to produce high-quality 2D MoS₂ nanosheets. Wang et al. [240] used the PEG-400 aqueous solution as the solvent, for the first time, to synthesize PEGylated MoS₂ nanosheets through the one-pot solvothermal reaction. Notably, the modification of PEG could promote the small-size MoS₂ to remain stable under physiological conditions and have strong photothermal conversion capacity. Meanwhile, the anti-cancer effect of PEGylated MoS₂ nanosheets could be further

improved because surface-grafted PEG macromolecules could increase the blood circulation time to generate more heat (Fig. 11 a, b). Fu et al. developed interlayer-expanded MoS₂ (E-MoS₂) nanosheets through solvothermal reaction as PTT agents [241]. The photothermal conversion efficiency of E-MoS₂ nanosheets was as high as 62% thanks to their wide interlayer spacing (0.94 nm). The wide interlayer spacing could improve the accessibility of water, which conducted to increase the capacity of near-infrared light absorption and the ability of repeated light reflections. Furthermore, the heat storage and transport of E-MoS₂ nanosheets could be improved by the large interlayer spacing.

Although MoS₂ nanosheets with controllable size can increase the therapeutic effect of PTT, how to successfully construct tumor-targeted PPT agents is still a challenge. Studies have shown that adjusting the size of PTT agents to 50–300 nm can enhance their targeted delivery capabilities [243]. Feng et al. [244] synthesized a three-dimensional flower-shaped MoS₂ nanoflake with an average size of 90 nm, which had good colloidal stability after modifying with lipoic acid-terminated polyethylene glycol (LA-PEG). Compared to single modification with thiol PEG, the LA-PEG molecule with two S atoms has stronger binding force to MoS₂. The nanocomplexes could destroy the lysosomal membrane and reduce the adhesion of tumor cells when radiated by NIR light at 808 nm, promoting cancer cell death.

Although changing the size of the PPT agent can heighten its tumor targeting, most of them would be cleared by the reticuloendothelial system (RES), so only less than 5% of them could reach the cancer tissue after intravenous injection [245,246]. Notably, the PTT agents can arrive at tumor areas directly via transarterial administration (TA) [247]. Tan et al. [242] constructed layered MoS₂ hollow spheres (LMHSs), which had higher photothermal conversion efficiency (34.46%) than MoS₂ nanosheets (24.37%). At the same time, intra-arterial (i.a.) injection in New Zealand white rabbits with hepatic metastasis of VX 2 carcinoma demonstrated significantly improved the tumor-targeting efficiency of LMHSs. Studies showed that cancer cells could be ablated by single NIR light irradiation (Fig. 11 c, d).

With the deepening of research, the biodegradability of PTT agents has attracted more attention because most inorganic nanomaterials cannot be degraded by the body, significantly hindering their clinical application [248,249]. Nanomaterials can be quickly excreted from the body via the renal-clearance pathway when the hydrodynamic diameter of nanoparticles is less than the glomerular filtration threshold (less than 10 nm) [250,251]. Liu et al. [252] synthesized ultra-small MoS₂ nanodots by one-step solvothermal decomposition. The hydrodynamic diameter of the MoS₂-GSH nanodots was less than 10 nm and without aggregation in physiological buffers when being modified with GSH. The MoS₂-GSH nanodots could induce local high temperature to ablate tumor cells, and was almost completely cleared by the kidney within 7 days at the injected dose.

Although the retention time of ultra-small nanoparticles with a size smaller than the glomerular filtration threshold in normal organs is decreased [253,254], the accumulation concentration and retention time in tumor tissues will also be affected due to the relatively short cycle time and weakened enhanced permeability and retention (EPR) effect [255]. Therefore, biodegradable nanomaterials with large size can not only exert the advantage of inorganic nanoparticles but also avoid long-term biotoxicity [256,257]. Chen et al. [258] used polyacrylic acid (PAA) to synthesize biodegradable MoS₂ nanosheets. Amino-terminated PEG could conjugate with active carboxyl groups in PAA of MoS₂-PAA via the amide reaction to form PEGylated MoS₂ nanoflakes (MoS₂-P-PEG). PAA not only promoted the modification of PEG, but also made MoS₂ nanosheets degradable. Meanwhile, MoS₂-PPEG had excellent stability and photothermal properties in various media. Importantly, the degradation rate of MoS₂-PPEG was distinct under different pH conditions, probably because the concentration of hydroxide ions played an important role, and the primary Mo^{IV} in MoS₂-PPEG was ultimately oxidized to Mo^{VI} during the degradation process. MoS₂-PPEG degraded rapidly in neutral pH solution but slowly in the acidic

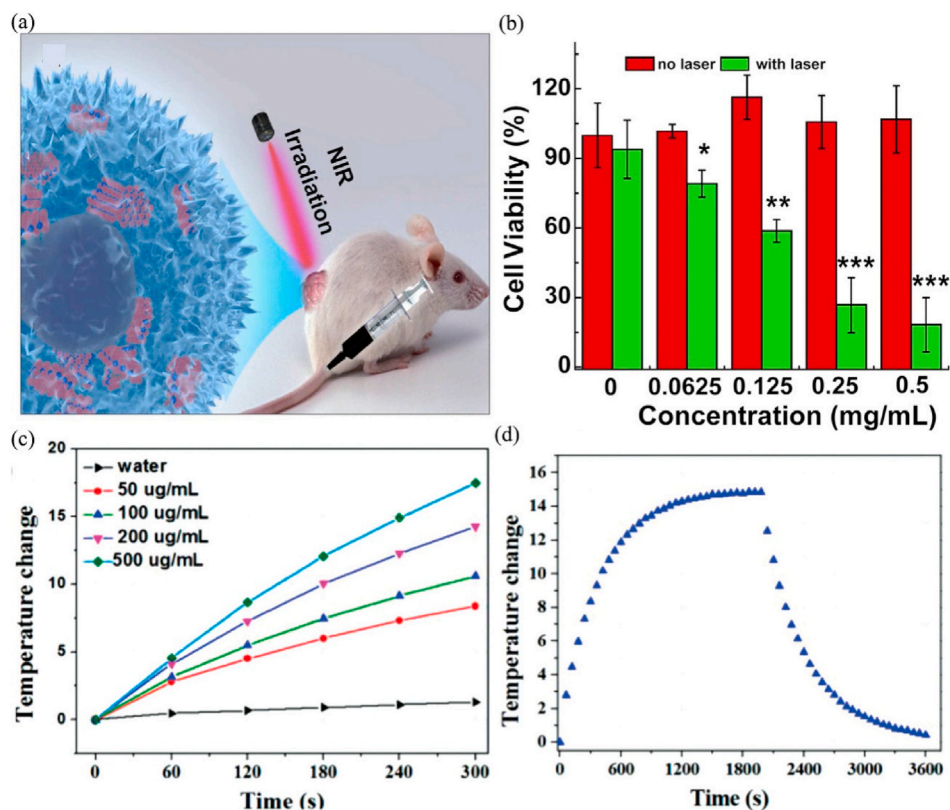


Fig. 11. (a) Schematic illustration of PTT, mouse was intravenously injected with MD₈₀-PEG dispersion and irradiated with NIR laser. (b) Cell viability assay of 4T1 cells after treated with or without 808 nm NIR laser (5 min, 1 W/cm²), cells were pre-incubated with MD₈₀-PEG (0.5 mg/mL) for 4 h before laser irradiating (mean ± SD, n = 3). Reprinted with permission from Ref. [240]. Copyright 2015, Biomaterials. (c) The temperature elevation of LMHSs with different concentrations under the NIR laser irradiation. (d) The photothermal response of the LMHSs aqueous solution with NIR laser irradiation and then the laser was shut off. Reprinted with permission from Ref. [242]. Copyright 2016, Small.

microenvironment, promoting its accumulation in tumor tissues and enhancing the anti-cancer effect.

5.2. Photodynamic therapy

PDT is mediated by photosensitizer (PS) [259]. Under light

irradiation, PS transitions to the excited singlet state and subsequently returns to the ground state, and transfer the energy released from the process to oxygen molecules in the medium to generate ROS. ROS with high reactivity can oxidize biomolecules such as lipids, proteins, and DNA, leading to cell death [260,261]. PDT has the characteristics of minimally invasive. It can also eliminate small recessive cancer nests

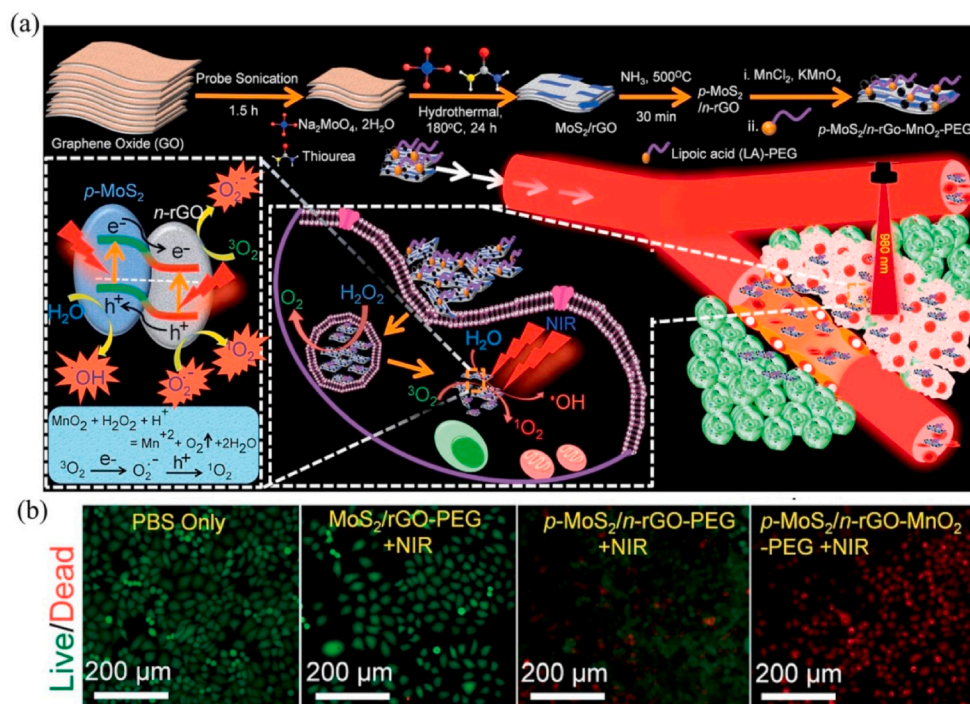


Fig. 12. (a) Schematic illustration of the fabrication of p-MoS₂/n-rGO-MnO₂-PEG nanosheets. While the hybrid nanosheets generate ROS via electron-hole separation under 980 nm laser irradiation, the MnO₂ NPs trigger the decomposition of endogenous H₂O₂ into O₂, simultaneously enhancing the PDT effect. (b) Merged epifluorescence microscopy images of HeLa cells co-stained with fluorescein diacetate (green emission for live cells) and PI (red emission for dead cells) under 0.4 W/cm² laser irradiation for 5 min. Reprinted with permission from Ref. [262]. Copyright 2018, Chemical Science.

and reduce the chance of tumor recurrence.

Local hypoxia of the tumor microenvironment can result in increased synthesis of lactic acid, promoting proliferation and migration of cancer cells. Photosensitive nanomaterials are capable of alleviating local hypoxia to improve the therapeutic effect of cancer. Kapri and Bhattacharyya [262] adopted the concept of p-n heterojunction to synthesize p-MoS₂/n-rGO nanosheets (p-MoS₂/n-rGO-MnO₂-PEG) as a PDT agent, which could obtain effective electron-hole separation to promote the generation of ROS in tumor tissues when irradiated by NIR (980 nm) light. Meanwhile, p-MoS₂/n-rGO-MnO₂-PEG could alleviate the hypoxic microenvironment because MnO₂ can reduce H₂O₂ to produce O₂ via the Fenton reaction. Therefore, the cell mortality rate of p-MoS₂/n-rGO-MnO₂-PEG was 3 times and more than 5 times that of MoS₂/rGO-PEG or p-MoS₂/n-rGO-PEG, respectively, at the same concentration (Fig. 12).

PTT and PDT have inherent limitations due to their distinct mechanisms. PTT usually requires high-power laser irradiation to generate sufficient heat [263]. Besides, the self-protective effect of cancer cells will cause a heat shock response, weakening the curative effect during PTT [264,265]. Meanwhile, the therapeutic effect of PDT will be suppressed by the hypoxic microenvironment, because of the strong dependence on the oxygen concentration [266,267]. Studies found that the photothermal effect may increase blood flow in the tumor area, subsequently increasing the tumor area's oxygen supply and improving the efficiency of PDT [268]. Therefore, the combination of PTT and PDT will provide new strategies for cancer treatment.

For example, Liu et al. [269] utilized PEGylated MoS₂ (MoS₂-PEG) to physically adsorb the photodynamic agent chlorin e6 (Ce6) for PDT treatment. Compared with free Ce6, MoS₂-PEG/Ce6 could enhance cell uptake and the curative effect of PDT via mild NIR light radiation, given the fact that moderate hyperthermia can increase cell membrane permeability. The synergistic effects of PDT and PTT could achieve more effective cancer cell killing when simultaneously irradiated at 808 nm and 660 nm. Peng et al. [270] designed a 2D MoS₂-based pH-responsive nanosystem that firstly used pH-responsive charge-switchable peptide (lipoic acid (LA)-K₁₁(DMA)) to modify MoS₂, then loaded the toluidine blue O (TBO, photosensitizer) on MoS₂ by physical adsorption. The negatively charged LA-K₁₁(DMA) peptides were turned into a positively charged peptide under acidic conditions, whose charge conversion reduced the binding force between positively charged TBO and MoS₂, resulting in the release of TBO and realizing fluorescence imaging. Besides, the positively charged nanoplateforms were easily endocytosed by cancer cells. The pH-responsive MoS₂ nanosystem combined PTT and PDT into a platform which possessed highly specific and effective anti-tumor effects. Multidrug resistance is one of the main obstacles to cancer treatment, and p-glycoprotein (P-gp) is the main protein to mediate multidrug resistance. Curcumin (Cur) can inhibit the effect of P-gp and reduce the efflux of nano-drugs by cancer cells. Li et al. [271] integrated indocyanine green (ICG), Cur and layered MoS₂ hollow spheres (LMHSs) into one nanoplateform for PTT-PDT. LMHSs and ICG could trigger PTT and PDT respectively under 808 nm NIR radiation. Meanwhile, Cur repressed the activity of P-gp to increase the accumulation of ICG&Cur@MoS₂. The LMHSs had a very good anti-cancer effect because it effectively overcame multi-drug resistance. In their experiment, ICG&Cur@MoS₂ + NIR group exhibited the strongest anti-cancer ability than ICG@MoS₂ + NIR group and MoS₂ + NIR group.

6. Microwave hyperthermia

The microwave beam can be focused with a suitable shape to concentrate the energy. This feature makes it suitable for local minimally invasive treatment of tumors. Compared with other hyperthermia methods, the main advantages of microwave hyperthermia are longer penetration depth, quicker heat generation, larger ablation area. However, due to the irregular tumor or the large tumor volume, there is the possibility of incomplete microwave ablation. These surviving tumor

cells will become a hidden danger of tumor recurrence and metastasis. Researchers have shown that the space between MoS₂ layers can retain molecules or ions [21,272,273]. Meanwhile, dipole polarization and ionic conduction are the two main causes of microwave hyperthermia [274]. The dipoles or ions would arrange in the oscillating electric field under MW irradiation, and generate heat through molecular friction and dielectric loss [275]. Besides, the sandwich structure of nanometer scale-spaces (NSSs) can markedly enhance the heating effect by changing the state of dipoles and ions [276–278], which promotes the application of MoS₂ in microwave hyperthermia (Table 2). Wang et al. [279] prepared layered MoS₂ nanoflowers and used them as the MW sensitizer for MW hyperthermia for the first time. BSA-MoS₂ nanoflower had low systemic toxicity and outstanding microwave sensitivity. MoS₂ nanoflowers were composed of many NSSs and the layered structure enhanced the microwave heating effect. There were two reasons that might result in enhancement of the MW heating effect of NSSs: (1) layered nanoflowers could efficiently recruit and enrich ions due to their large specific surface, enabling a high concentration of ions within BSA-MoS₂; and (2) the frictional collision frequency of dipoles or ions markedly increased because the small volume prolonged the contacting time by repressing the precursor diffusion. In vivo results showed that the tumor could be 100% eliminated after MW radiation at 1.8 W and 450 MHz.

However, microwave hyperthermia is still not feasible for treating large tumors due to insufficient heat accumulation around the whole tumor, owing to the heat-sink effect (HSE) [281–283]. Arterial embolism (TAE) and chemoembolization (TACE) are two common clinical treatments that can block tumor blood vessels to treat unresectable hepatocellular carcinoma (HCC). The means of combining TAE with a specific targeted embolization agent can be utilized for blocking the tumor blood vessels and alleviating the HSE [284,285]. Fu et al. [280] synthesized a microwave embolization agent (MSMC) by encapsulating MoS₂ nanosheets in sodium alginate microcapsules (MCs) for effectively treating large tumors. Compared with free ions participating in microwave hyperthermia, the microwave-heat conversion ability of ions confined in the MC is much higher due to the lamellar structures that could divide the microcapsule into smaller spaces, which would further raise the temperature surrounding solution. Besides, MSMC could be simultaneously used as an outstanding embolic and a microwave sensitizer for dual-enhanced microwave ablation therapy. MR imaging showed that the ablation area of MSMC was larger than that of the microwave treatment alone after injection of MSMC to the VX2 liver cancer tissue via hepatic artery. Meanwhile, persistent hyperthermia could nearly completely ablate the large tumor and prevent its recurrence (Fig. 13).

7. Multifunctional nanoplateforms for cancer therapy

Multifunctional nanoplateforms are mainly divided into two categories: cancer treatments combining different therapy methods and cancer theranostics. The combination of multiple treatment methods can improve the treatment effect, eliminate residual lesions, and prevent metastasis and recurrence for prolonged the survival time of patients. Cancer theranostics is a multifunctional nanoplateforms that combines cancer imaging and treatment. The multifunctional nano-platforms can accurately and timely provide diagnostic information and pharmacokinetics to doctors, which not only make doctors to design personalized treats according to the cancer patient's condition, but also accurately obtain the information of the therapeutic effect for prognosis. Compared with traditional treatment methods, the main advantage of cancer theranostics is that it can distinguish cancer lesions from healthy tissues, which minimize systematic toxicity of cancer treats and improve curative effects. However, multifunctional nanoplateforms need a key flexible platform material that can combine many different functional components together. MoS₂ nanomaterials is easy to functionalized with biomolecules and combined with other nanomaterials. Therefore, MoS₂

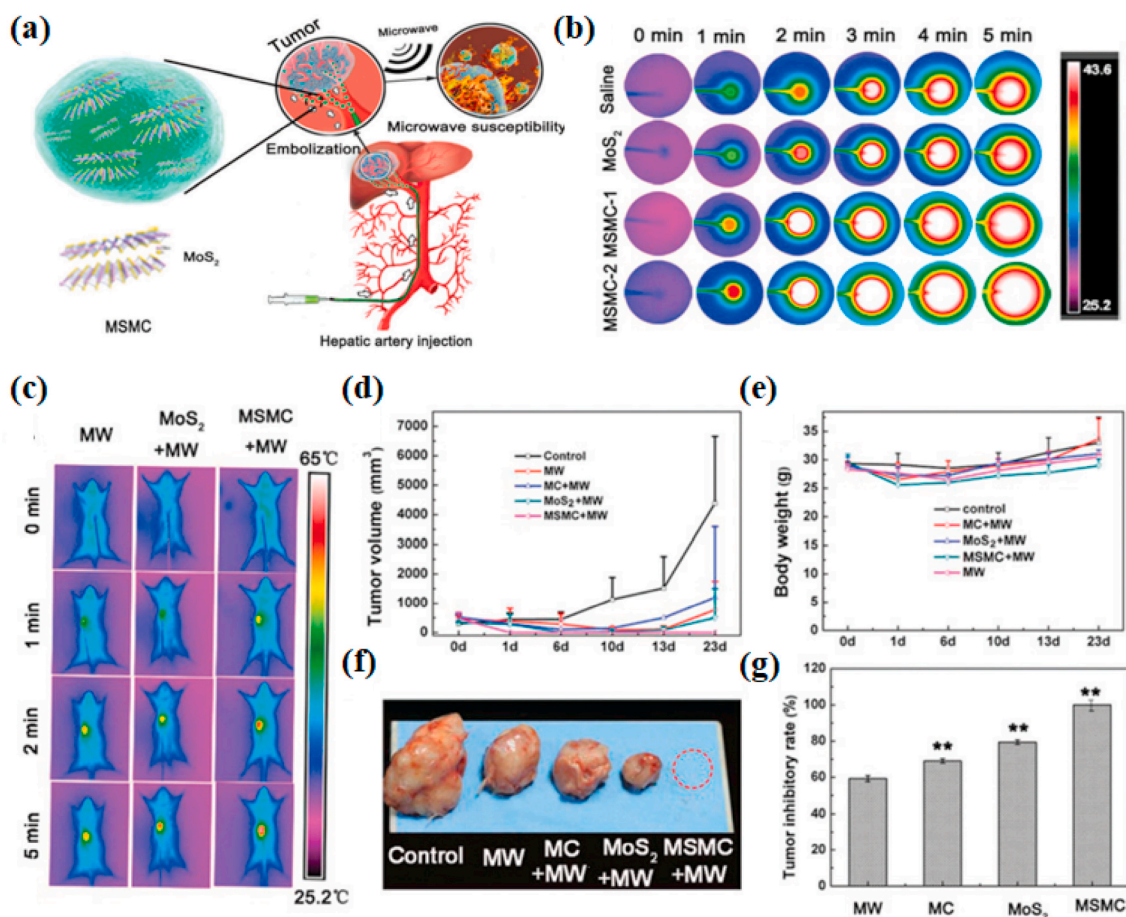


Fig. 13. (a) Schematic illustration of the MSMC used for the microwave ablation and the TAC therapy. (b) Near-infrared thermography images with different MW susceptible agents. (c) Infrared thermal imaging of mice bearing H22 cells after the intratumoral injection of MSMC, MoS₂ nanosheets, and saline at 50 mg/kg under the MW irradiation for 5 min at 5 W. (d) The changes of tumor volume and (e) body weight of the mice in different groups. (f) Tumor tissues removed from the mice and (g) tumor inhibition rate of different groups at 23 day. ***p* < 0.01. Reprinted with permission from Ref. [280]. Copyright 2017, Nanoscale.

nanomaterial can be used as a good platform material for building multifunctional nanoplateforms [286–288] (Table 2).

7.1. Near-infrared/PA imaging-guided cancer therapy

Han et al. [289] prepared a multifunctional nanocomplex MoS₂-UCNPs-FA/ZnPC by integrating PTT, PDT and up-conversion luminescence (UCL) imaging into one platform to strengthen the anti-cancer effect. First, chitosan-functionalized MoS₂ (MoS₂-CS) with good biocompatibility was covalently grafted with hydrophilic COOH-functionalized upconverted nanoparticles (UCNPs). Thereafter, MoS₂-UCNPs were conjugated with FA through a carbodiimide cross-linking reaction between the –COOH of MoS₂-UCNPs and the –NH₂ of FA. Finally, phthalocyanine (ZnPC), was loaded on the surface of MoS₂ to construct MoS₂-UCNPs-FA/ZnPC. Results showed that the nanoplateform could convert optical energy into heat by MoS₂ and generate ROS by ZnPC under NIR light irradiation at 808 nm and 980 nm, respectively. Meanwhile, the unique UCL emission afforded a significant method for cell bioimaging, achieving a more effective therapeutic effect of tumors.

However, the sensitivity and spatial resolution of UCL imaging are relatively lower than those of PA imaging. PA imaging possesses stronger penetration, higher contrast, and more sensitive spatial resolution on account of combining the advantages of optical imaging and acoustic imaging. Wang et al. [290] dissolved polylactic acid-glycolic acid copolymer (PLGA), MoS₂, and DOX into N-methylpyrrolidone (NMP) for preparing PLGA/MoS₂/DOX (PMD) oleosol with good injectability, which did not diffuse into the body fluid circulation and could be

biodegraded in vivo. MoS₂ nanosheets serve as high-performance contrast agents to monitor the position of solid PMD implants via PA imaging. Besides, MoS₂ could also be used as PPT agent to control the release of DOX and generate heat, enhancing the anti-cancer effect in tumor-bearing nude mice. Compared with NIR-1, NIR-2 has a longer penetration depth and better image contrast. Zhou et al. [291] developed 1T-MoS₂ nanodots as effective nano-agents for PA imaging-guided PTT in the NIR-2 window. 1T-MoS₂ nanodots gave an extinction coefficient of 25.6 L g^{−1} cm^{−1} and photothermal power conversion efficiency (PCE) of 43.3% under 1064 nm laser irradiation. The strong NIR-2 absorption of 1T-MoS₂ could be attributed to the metallic properties. In an attempt to further enhance the sensitivity of imaging, Song et al. [292] designed the “four-in-one” nanoplateform consisting of fluorescent imaging, PA imaging, PTT, and PDT to achieve imaging-guided phototherapy. BSA-MoS₂ could simultaneously generate local high temperatures, singlet oxygen, and PAT signals after 808 nm NIR laser excitation. Besides, the biodistribution of nanocomplex at the tumor site could be detected by fluorescence imaging when MoS₂ conjugates with Cy5.5 fluorescent molecules, realizing multimode imaging-guided precision treatment.

Enhancing the tumor targeting of multifunctional nanomaterials can reduce the side effects on normal tissues. Shin et al. [293] reported a multifunctional HA-MoS₂ with the tumor-targeting capability as well as integrated fluorescence imaging, PAT, and PTT. Thiolated HA (HA-SH) was first prepared by chemically modification of hyaluronate (HA) with cystamine. The as prepared HA-SH was then conjugated with MoS₂ via the disulfide bond formation. HA promoted the accumulation of

HA-MoS₂ at the tumor site through HA receptor-mediated endocytosis. Meanwhile, the disulfide bond of HA-MoS₂ could be reduced by GSH in the cytoplasm, releasing MoS₂ sheets to strengthen the optical signal and photothermal conversion efficiency, realizing effective tumor ablation effect in Balb/c nude mice inoculated with HCT116 (Fig. 14 a-f).

The synergistic effect between MoS₂ and other photothermal

conversion agents can increase the photothermal conversion efficiency and the therapeutic effect of PTT, also enhancing the sensitivity of PA imaging. Copper sulfide (CuS) is an excellent photothermal conversion material because of its good thermostability, photostability and high photothermal conversion efficiency [294]. For this reason, Meng et al. [295] prepared a multifunctional nanoplatform (ATPMC) through

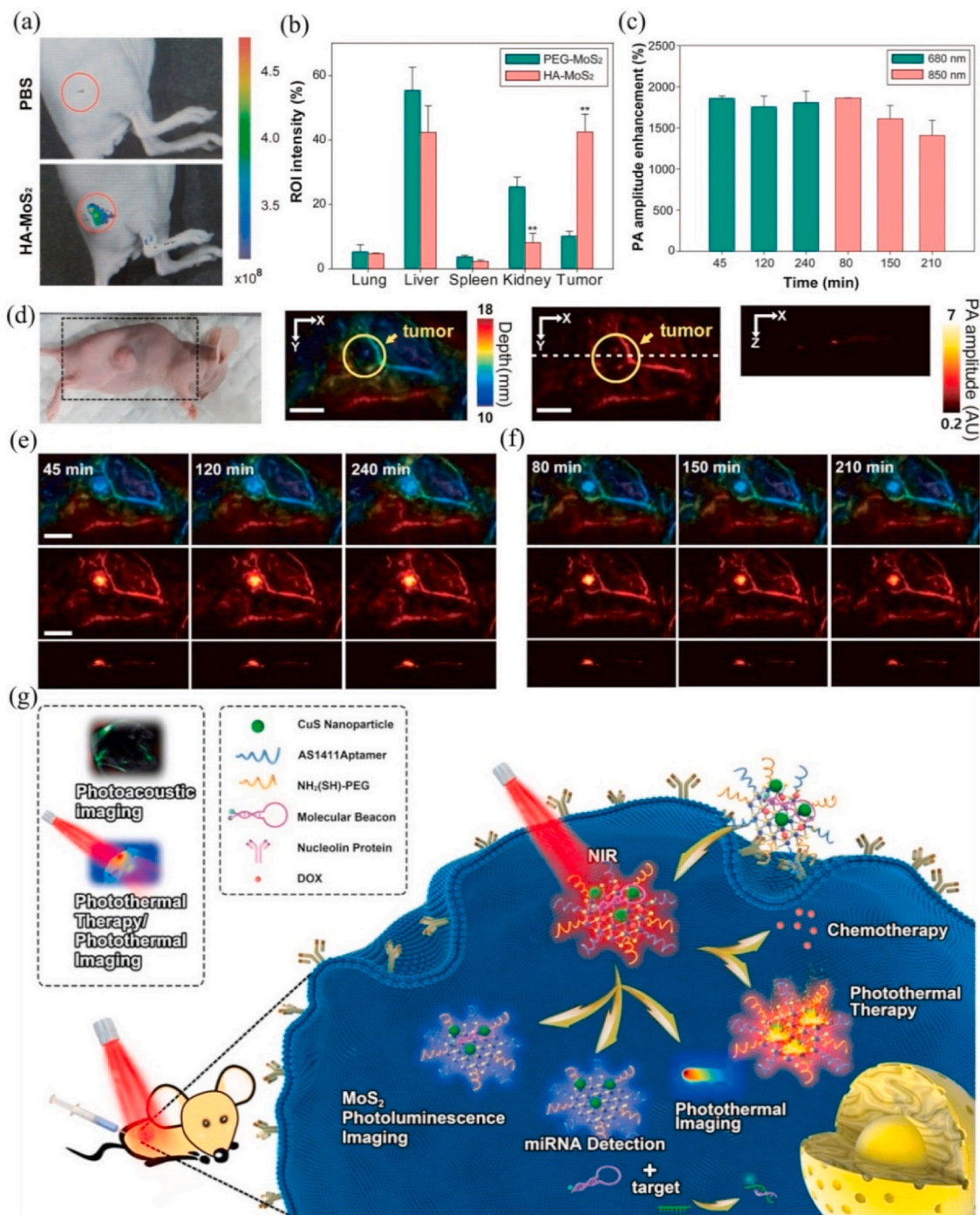


Fig. 14. In vivo fluorescence and PA imaging of HA-MoS₂ conjugates. **(a)** IVIS imaging of PBS and HA-MoS₂ conjugates after intradermal injection into the tumor (red circle) region. **(b)** Quantitative fluorescence analysis of PEG-MoS₂ and HA-MoS₂ conjugates in the organs for the assessment of tumor targeting affinity (**p < 0.01, PEG-MoS₂ vs HA-MoS₂ conjugates). **(c)** The PA amplitude enhancement of HA-MoS₂ conjugates compared to the control (PBS) image at both 680 and 850 nm wavelengths with the depth profile of the highest signals for 240 min. **(d)** A photo-image and PA MAP image of mouse in respect to depth (left) and amplitude (right) before injection of HA-MoS₂ conjugates. The PA signals at 30 and 240 min after intratumoral injection of HA-MoS₂ conjugates at **(e)** 680 and **(f)** 850 nm wavelengths in respect to depth (upper) and intensity (bottom). Reprinted with permission from Ref. [293]. Copyright 2019, Advanced Healthcare Materials. **(g)** ATPMCD (ATPMC nanoplatform loaded with DOX) for multimodality bioimaging and NIR-laser irradiation-induced chemotherapy. Reprinted with permission from Ref. [295]. Copyright 2017, Advanced Functional Materials.

conjugating aptamer and PEG on the surface of $\text{MoS}_2\text{-Cu}_{1.8}\text{S}$, which not only served as photoluminescence/PA/photothermal imaging contrast agent but also used as carriers of DOX and miRNA-155 probe, realizing triple-modal bioimaging-guided diagnosis and synergistic therapy. The combined effect of MoS_2 and $\text{Cu}_{1.8}\text{S}$ made ATPMC have stronger heat conversion ability (32.5%) than MoS_2 or $\text{Cu}_{1.8}\text{S}$ alone, which indicated that ATPMC was a superb photothermal conversion agent. Meanwhile, ATPMC could selectively release DOX under NIR light radiation to kill lung cells (Fig. 14 g).

7.2. MRI-guided cancer therapy

Due to the different relaxation times of normal tissues and cancerous tissues, MRI can provide anatomical information. Conventional MRI cannot recognize the boundary and microstructure of tumor lesions due to its relatively low resolution [296]. Nanoparticle-based MRI contrast agents can provide high-quality and sensitive anatomical information [297,298]. For example, superparamagnetic Fe_3O_4 nanoparticles are commonly used as T2-weighted MRI contrast agents [299,300]. A novel

multifunctional complex (Mo@Fe-ICG/Pt) was prepared by covalently grafting Fe_3O_4 nanoparticles (≈ 6 nm) on MoS_2 and then loading indocyanine green molecule (ICG, photosensitive agent) and platinum (IV) prodrug. The resulting multifunctional nanoparticles possessed remarkable bioimaging capacity of MRI ($r_2 = 71.8 \text{ mM}^{-1} \text{ s}^{-1}$)/infrared thermal/PA and could trigger PTT, PDT, and chemotherapy under NIR light irradiation [301]. Notably, the T2-weighted contrast ability may be affected by the morphology and size of Fe_3O_4 nanoparticles [302]. Generally, the larger cubic iron oxide (IO) nanoparticles have lower r_2 value and higher imaging sensitivity. Xie et al. [303] combined MoS_2 (MS) film with IO nanocubes (≈ 100 nm) to form $\text{Fe}_3\text{O}_4\text{@MoS}_2$ nanocubes (IOMS NCs), which could easily load DOX for MRI-guided chemo-photothermal therapy. Compared with the nanomaterials containing small-size Fe_3O_4 nanoparticles ($r_2 = 71.8 \text{ mM}^{-1} \text{ s}^{-1}$), the IOMS NCs containing large-size Fe_3O_4 nanoparticles displayed more sensitive MRI capabilities ($r_2 = 48.86/(\text{mM}\cdot\text{s})$) (Fig. 15).

T1-weighted MRI contrast agents, as positive contrast agents, can enhance the signal in the affected area, thus making this area brighter than other areas. Nanoparticles containing Gd^{3+} are commonly used as

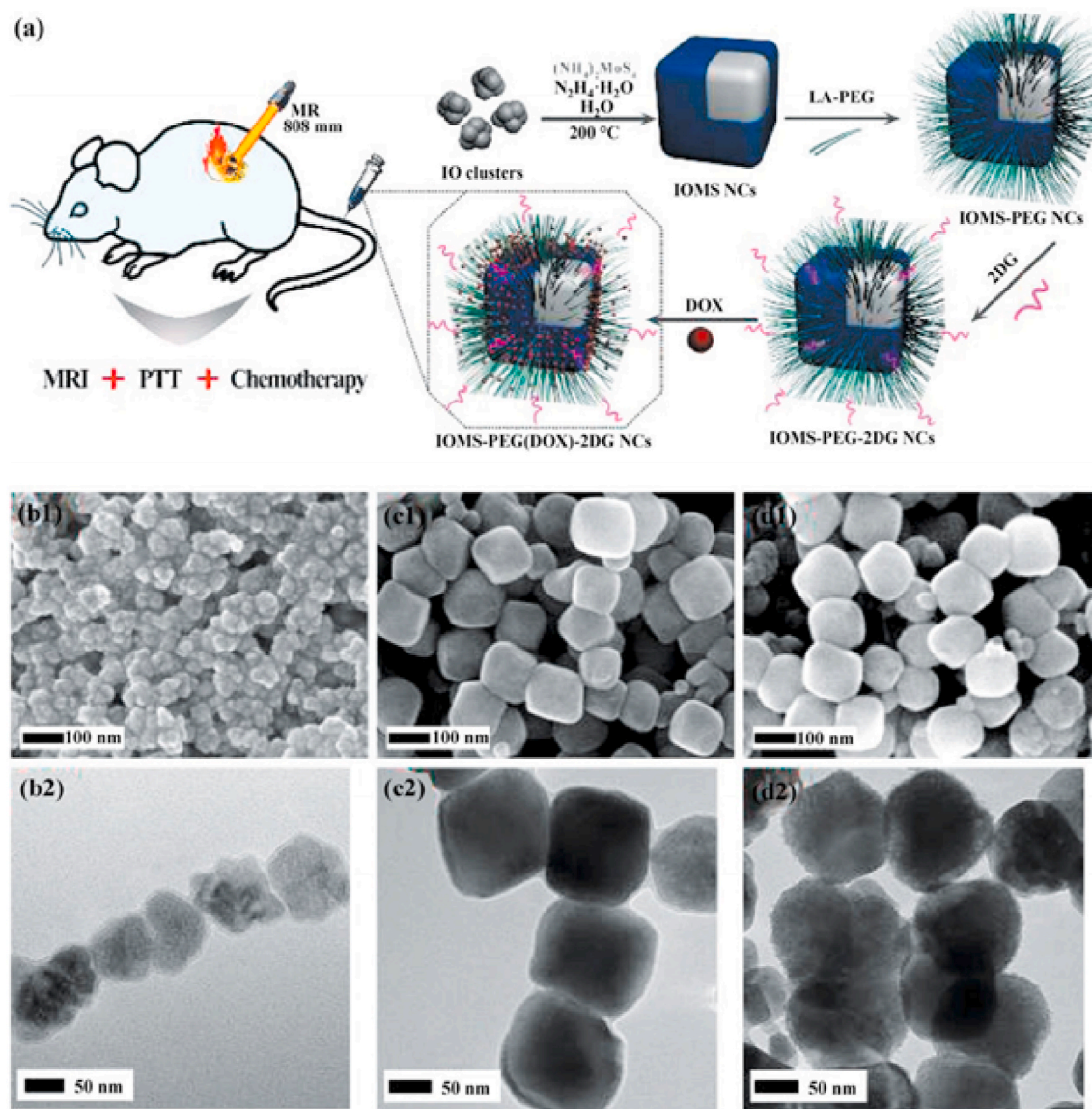


Fig. 15. (a) Schematic illustration of the fabrication process of IOMS-PEG(DOX)-2DG NCs for MRI-guided chemo-photothermal therapy of cancer. (b1) and (b2) SEM and TEM images of IO clusters. (c1) and (c2) SEM and TEM images of IOMS NCs. (d1) and (d2) SEM and TEM images of IOMS-PEG NCs. Reprinted with permission from Ref. [303]. Copyright 2018, Nano Research.

T1-weighted MRI contrast agents [304]. Chen et al. [305] synthesized the multifunctional MoS₂-Gd-BSA through conjugation of BSA-gadolinium (Gd) complexes with MoS₂ nanosheets via an amide bond. BSA-Gd complexes were served as MRI contrast agents, while MoS₂ nanosheets used for PTT agents and PA imaging contrast agents, realizing dual-mode MRI/PA imaging-guided PTT in tumor-bearing mice. Besides, Mn²⁺ also serves as T1-weighted MRI contrast agents [306]. The generated T1/T2-weighted MRI contrast agents have demonstrated a higher sensitivity than single-mode contrast agents in cancer identification. Therefore, Mn-doped Fe₃O₄ nanoparticles can be utilized for T1/T2-weighted MRI bimodal probes. Jing et al. [307] synthesized multifunctional nanosystems by loading chitosan (CS) and metformin (MET) on Mn-doped Fe₃O₄@MoS₂ nanoflowers. The Mn-doped Fe₃O₄@MoS₂ nanoflowers were applied to the T1/T2-weighted MRI with high sensitivity ($r_2 = 18.46 \text{ mM}^{-1} \text{ s}^{-1}$, $r_2 = 63.75 \text{ mM}^{-1} \text{ s}^{-1}$) and had a quick magnetic response. Meanwhile, it could suppress and kill hepatoma cells when MET was released from the nanosystems under NIR irradiation or weakly acidic tumor microenvironment. Therefore, T1/T2 MRI-guided chemo-photothermal combined therapy was realized *in vitro*. Furthermore, Researchers discovered that incorporating MoS₂ nanosheets and Fe₃O₄ into microcapsules can be used in MRI/CT-guided microwave hyperthermia for HCC [192].

7.3. Combination of phototherapy with chemotherapy

Studies have shown that PTT-induced hyperthermia can interfere with DNA repair [308] and increase membrane permeability [309,310], promoting the entry of drugs into the tumor cells and improving the sensitivity of tumor cells to drugs. Meanwhile, PDT can enhance the penetration of tumor blood vessels and increase the intake of nanoparticles, improving the anti-tumor efficacy of nanodrugs [311,312].

Overall, the combination of phototherapy and chemotherapy can achieve a better therapeutic effect [313–324].

Liu et al. [68] firstly discovered that MoS₂ could be used as a novel 2D nanocarrier to deliver drugs and also used for PTT. The PEGylated MoS₂ nanosheets with the large specific area could efficiently deliver DOX via hydrophobic action and had strong NIR light absorption efficiency. Results displayed that about 95% of cancer cells died when they co-incubated with MoS₂-PEG-FA/DOX and radiated by the 808 nm laser at 1.07 W/cm^2 for 5 min, which was much higher than DOX or PPT treatment alone (Fig. 16 b–f). Furthermore, studies demonstrated that MoS₂ nanosheets modified by chitosan [237], hyperbranched polyglycidyl (HPG) [325] or egg yolk phospholipids [326] could also serve as nanoplateforms with good colloidal stability and biocompatibility to realize the synergistic treatment of chemotherapy and PTT. Time-staggered administration of erlotinib (Er) and DOX can enhance the anticancer effect, but its clinical application is limited due to different administration routes and formulation parameters. Recently, Liu et al. [327] designed a MoS₂-based nanoplateform to co-deliver Er and DOX. Under NIR irradiation, the MoS₂-based nanoplateform could simultaneously release Er and DOX, and greatly improve the anti-cancer effect by synergistic treatment of Er and DOX.

Because MoS₂ with a large specific surface area is easy to modify, many molecules can be combined with MoS₂ to construct various types of multifunctional nanoplateforms for combined phototherapy and chemotherapy. Many outstanding characters, such as organic-group-doped frameworks, high surface area, and excellent blood compatibility, making periodic mesoporous organosilicas (PMOs) become ideal platforms for drug delivery [329–331]. MoS₂ nanosheets might efficiently wrap the PMOs due to its excellent flexibility in chemical reaction [332–334]. To this end, Shao et al. [322] designed PMO-DOX@MoS₂-PEG that has high DOX loading efficiency (160 µg/mg

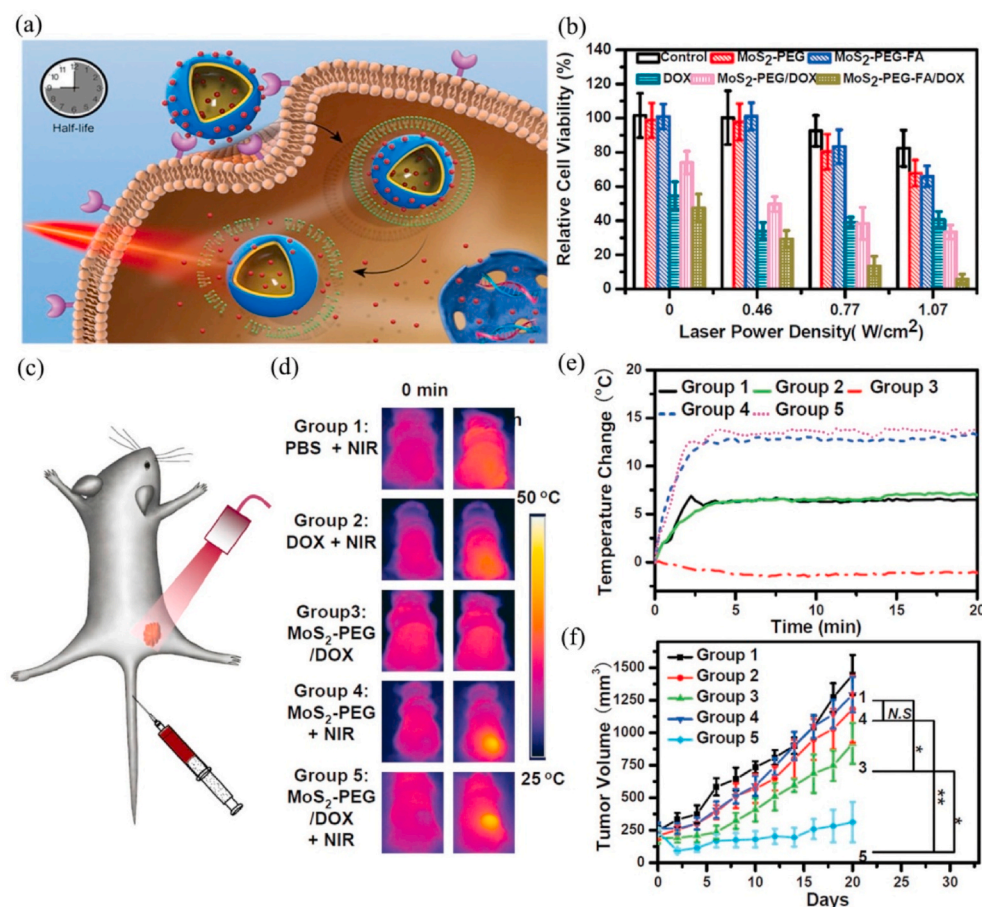


Fig. 16. (a) Schematic illustration of MoS₂/HSA-DOX nanocapsules targeting a cancer cell surface receptor (gp60) and their transcytosis into the cytoplasm. After irradiation, MoS₂ generates heat, and free DOX is released, achieving synergistic photothermal-chemotherapeutic efficacy. Reprinted with permission from Ref. [328]. Copyright 2018, Advanced Functional Materials. (b) Relative viabilities of KB cells after various treatments indicated. In this experiment, KB cells were incubated with MoS₂-PEG, MoS₂-PEG-FA, free DOX, MoS₂-PEG/DOX and MoS₂-PEG-FA/DOX for 1 h, and then irradiated with the 808-nm laser at different power densities for 5 min or kept dark as controls. Afterwards cells were washed with PBS, placed into fresh cell medium, re-incubated for additional 24 h before the MTT assay. Error bars were based on four parallel samples. (c) Scheme of combination therapy based on intratumorally injected MoS₂-PEG/DOX. (d) IR thermal images of 4T1 tumor-bearing mice recorded by an IR camera. The doses of DOX and MoS₂-PEG were 5 mg/kg and 3.4 mg/kg, respectively, in this experiment. Laser irradiation was conducted by using 808-nm NIR laser at the power density of 0.56 W/cm^2 for 20 min on the tumors. (e) Temperature change of tumors monitored by the IR thermal camera in different groups during laser. (f) Tumor volume growth curves of mice after various treatments (5 mice for each group). Reprinted with permission from Ref. [68]. Copyright 2014, Advanced Materials.

PMO) and outstanding photothermal conversion capacity, which could successfully release DOX with the irradiation of NIR laser. The release of DOX in PMO-DOX@MoS₂-PEG could be controlled by NIR laser. Benefiting from these properties, a combination therapy of chemotherapy and PTT in multiple cancer cells was achieved.

Researchers have found that improving the tumor targeting and specific response-ability of multifunctional nanomaterials to the tumor microenvironment can further enhance the anticancer effect. Yang et al. [320] prepared a novel type of cabbage-like Fe₃O₄@MoS₂@ZnO nanocomposite with magnetism, extensive pore structure, large surface area, and high DOX loading capacity, which could effectively deliver drugs to tumor lesion areas under magnetic targeting. Meanwhile, the efficient PTT could be realized because MoS₂ has strong photothermal conversion ability, and the controlled release of DOX in slightly acidic environments (pH 6.5) could be achieved by using the pH-dependent ZnO as an encapsulating component to cover the mesopores. Xu et al. [328] synthesized MoS₂/HSA with strong photothermal conversion ability which constructed with MoS₂ hollow nanocapsules and human serum albumin (HSA) by a layer-by-layer coating method. The MoS₂/HSA were uniform in size (280 nm), large in the cavity, low in Young's modulus (222 ± 20 MPa), and high in load rate of DOX (27 wt%). The uptake rate of MCF-7 cells was dramatically increased due to the targeting ability of HSA. Simultaneously, the longer mean retention time (170.9 h) of MoS₂/HSA made it has a higher tumor tissue accumulation (27%) than its solid counterpart, dramatically improving the treatment effect of breast cancer (Fig. 16 a). Melanin (Mel) is a biocompatible biopolymer that exists in human tissues and has the ability to absorb NIR light. Our groups developed dopamine-melanin colloidal nanospheres (Dpa-melanin CNSs) as efficient PTT agents for cancer therapy [335]. The combination of Mel and MoS₂ nanosheets would further strengthen the photothermal effect. Yang et al. [314] synthesized a multipurpose nanosystem based on MoS₂ and Mel nanocomposites (HPMP@(DOX/-Mel)) that could deliver DOX. They first prepared the multi-functional HA-PEI-LA-MoS₂-PEG (HPMP). HA could selectively bond with CD44 receptor which expresses highly in MCF-7 cells to enhance the targeting ability of HPMP, while PEI made HPMP to obtain the function of responding to pH. Subsequently, melanin and DOX were loaded into HPMP to prepare HPMP@(DOX/Mel). The efficiency of HPMP@(DOX/Mel) photothermal conversion could reach 55.3% due to the synergistic enhancement of Mel and MoS₂, which was higher than Mel and MoS₂. The DOX could be released from HPMP@(DOX/Mel) with the dual stimuli of weakly acidic environment and NIR light irradiation at 808 nm. Besides, experiments *in vivo* demonstrated that chemo-photothermal therapy had a better treatment effect than single therapy. Recently, Zhang et al. [336] constructed urchin-like MoS₂@C with high photothermal conversion ability (40.8%) and high DOX loading rate (52.34%), which could effectively release DOX under the mediation of pH and temperature. The cumulative release rate of DOX was as high as 64.59% when irradiated by NIR, which was about twice as high as that without laser irradiation, and the survival rate of MCF-7 cells was only 25.8%.

7.4. Combination of phototherapy with other therapy

In addition to the synergistic effect of chemotherapy and phototherapy, PTT can also be combined with radiation therapy, tissue regeneration, gene therapy, immunotherapy, and catalytic therapy to overcome the inherent limitations of monotherapy for enhancing anticancer effects and prolonging the survival period of patients.

Nevertheless, PTT alone hardly completely eliminates tumors due to its depth-dependent. Radiation therapy (RT) without depth restriction generally utilizes ionizing radiation to generate oxygen-centered radicals which can promote cancer cell death by causing the DNA damage [337,338]. But the hypoxic tumor microenvironment is the main barrier to RT. Moderate high temperature induced by PTT may increase the bloodstream within the tumor lesions and improve the tumor hypoxic

microenvironment, making the cancer cells more sensitive to RT. MoS₂ with high Z value is expected to be a candidate of RT radiosensitizers [339]. Wang et al. [189] designed inorganic-organic nano-hybrid particles based on MoS₂ quantum dots@polyaniline (MoS₂@PANI), which not only enhanced PA/CT signals but also performed RT and PTT for cancer. Firstly, they dispersed MoS₂ QDs powder in the water when polyvinylpyrrolidone (PVP) existed and PVP served as a dispersing and stabilizing agent to control the size of MoS₂ QDs during the process. Subsequently, MoS₂ QDs could absorb aniline molecules onto its surface to form MoS₂@PANI-COOH via the electrostatic forces and then conjugated with PEG-NH₂ by forming the amide bond, constructing MoS₂@PANI nanohybrids. The MoS₂ QDs could be used as fluorescence probes and PANI could serve as a PTT agent due to its strong photothermal conversion efficiency capacity. Besides, MoS₂@PANI could also serve as CT imaging agents because the molybdenum has a high X-ray absorption coefficient. Results showed that oxygenation at the tumor site could be enhanced under moderate PTT. PTT/RT combination therapy guided by PA/CT images could nearly eliminate tumors in 4T1 tumor-bearing mice (Fig. 17 a, b). Besides, MoS₂ can also be combined with other nanoradiosensitive agents to form a PTT-RT combined treatment platform. Hafnium dioxide (HfO₂) nanoparticles have strong X-ray attenuation ability, and are regarded as potential radiosensitive agents. Recently, Fu et al. [340] integrated MoS₂, HfO₂ and dextran into new nanoplatforms (M/H-D) for CT/PA imaging-guided PTT/RT. HfO₂ produced ROS to kill cancer cells under X-ray irradiation. Meanwhile, local high temperature caused by MoS₂ could relieve the hypoxia of tumor cells and improve the therapeutic effect of RT under NIR irradiation. In addition, MoS₂ could catalyze H₂O₂ to produce hydroxyl radicals to further damage cancer cells. M/H-D could eliminate tumors in MMC-7721-fluc tumor-bearing mice after X-ray and NIR irradiation.

Malignant bone tumor is usually treated with a collaborative strategy of surgery, chemotherapy, and radiotherapy [233,341], but cannot thoroughly ablate cancer cells and lead to large bone defects which need bioactive graft materials to repair [342,343]. Fortunately, the osteogenesis and angiogenesis can be induced by three-dimensional (3D)-printed bioceramic scaffolds with bioactive elements [344,345], while these scaffolds gradually degrade with the formation of new bone tissue. Wang et al. [346] prepared new dual-function scaffolds (MS-AKT scaffolds) via the technology that combines a 3D printing technique and a hydrothermal method. First, they immersed AKT bioceramic scaffolds prepared by 3D printing into an aqueous precursor solution including (NH₄)₆Mo₇O₂₄·4H₂O and H₂NCSNH₂. Next, H₂NCSNH₂ would be decomposed and attach on the surface of AKT scaffolds under hydrothermal conditions. Finally, AKT scaffolds were used as templates to promote the nucleation and growth of the sheet-like MoS₂ *in situ*, producing MS-AKT scaffolds. MoS₂ nanosheets with photothermal properties and bifunctional three-dimensional (3D) scaffolds with osteogenic potential could be used to induce PTT and repair bone defects caused by large tumors, respectively. PTT significantly increased the death rate of osteosarcoma cells and breast cancer cells, and the MS-AKT scaffold could support the attachment, proliferation, and osteogenic differentiation of bone mesenchymal stem cells, inducing tissue regeneration *in vivo* (Fig. 17 c-k).

Gene therapy (GT) induced by small interfering RNA (siRNA) promises to be an alternative means for traditional treatment. It can selectively kill cancer cells by silencing specific genes [347]. However, the naked siRNA with negative charges is easily degraded by nuclease and difficult to cross the negatively charged cell membranes. Therefore, safe and effective carriers are highly needed [348]. MoS₂ can efficiently deliver genes to the target area for cancer therapy due to its flexible physicochemical properties. Polo-like kinase 1 (PLK1), a vital regulatory factor of cell cycle and overexpressed in various cancer. The proliferation of cancer cells will be inhibited by silencing PLK1 expression [349–351]. Kou et al. [352] developed a PLK1 siRNA nano-transport system based on MoS₂ (MoS₂-PEG-PEI nanosystem). In this nanosystem, PEG could prevent nonspecific binding of proteins and

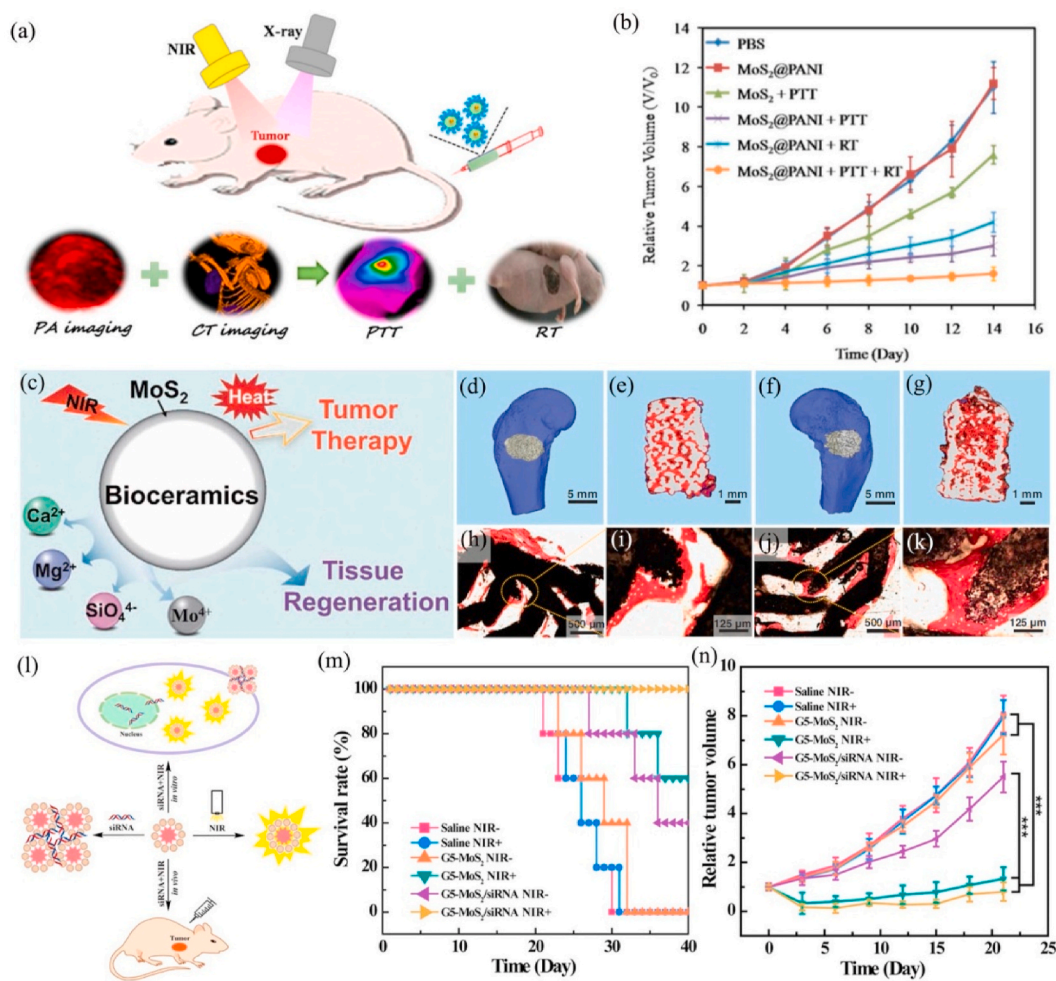


Fig. 17. (a) Scheme of MoS₂@PANI nanohybrids used for dual modal imaging and combined PTT and RT therapy. (b) Tumor growth in different groups of mice after various treatments. Reprinted with permission from Ref. [189]. Copyright 2016, ACS Applied Materials & Interfaces. (c) Schematic illustrations of the bifunctions of tumor therapy and tissue regeneration of MoS₂ nanosheets grew on 3D-printed bioceramic scaffolds. Micro-CT analysis for the bone regeneration after implanting with MoS₂-modified akermanite (MS-AKT) (d), (e) and AKT (f), (g) scaffolds in the critical-sized femoral defects of rabbits for 8 weeks. Red color stands for the formation of new bone (e), (g). Histological analysis of MS-AKT (h), (i) and AKT (j), (k) scaffolds by Van Gieson staining after implanting for 8 weeks. Reprinted with permission from Ref. [346]. Copyright 2017, NPG Asia Materials. (l) Schematic illustrations of G5-MoS₂/Bcl-2 siRNA used for the gene therapy and PTT. (m) Survival rate of the tumor-bearing mice after different treatments at different time periods and (n) relative tumor volume. Reprinted with permission from Ref. [363]. Copyright 2017, ACS Applied Materials & Interfaces.

nanomaterial to strengthen the stability of MoS₂ in serum and positive charge amino end of PEI could promote the combination of MoS₂-PEG-PEI and siRNA due to the electrostatic interaction. The expression of PLK1 was significantly decreased and the flow cytometry analysis demonstrated that the number of apoptotic cells were increased markedly when HepG2 cells treated by MoS₂-PEG-PEI/siPLK1. Pancreatic carcinoma usually has properties including a very poor prognosis and a high mortality rate. Therapeutic effects of pancreatic carcinoma are mainly suppressed by the high molecular heterogeneity and surrounding stromal and inflammatory components [353–356]. Combination therapy of GT and PTT could improve the therapeutic effect and prolong survival of pancreatic cancer patients. Histone deacetylase 1 (HDAC1) and the mutational KRAS gene both promote the development of pancreatic cancers by regulating cell survival, transformation, invasion, and metastasis [357–360]. Yin et al. [361] designed a multi-gene delivery nanoplatform based on MoS₂ (MoS₂/LA/PEG/FA/PAH) for co-delivering HDAC1 and KRAS siRNAs into pancreatic tumor cells. FA-PEG polymers and polyallylamine hydrochloride (PAH) were used to functionalize the surface of MoS₂ nanosheets, which was conducive MoS₂/LA/PEG/FA/PAH to bond with siRNA and internalize by Panc-1 cells. The growth rate of Panc-1 cells and tumor volume was decreased

by 70% and 80% respectively thanks to the synergistic effect of GT and PTT. By targeting antiapoptotic B-cell lymphoma-2 (Bcl-2) that over-expresses on tumor cells [362]. Kong et al. [363] synthesized dendrimer-modified MoS₂ nanosheets as carriers to condense Bcl-2 siRNA, realizing combination therapy of gene silencing and PTT. The results indicated that G5-MoS₂/siRNA polyplexes with the hydrodynamic size (300 nm) and positive surface potential could be used to deliver siRNA. Meanwhile, the inhibition rate of G5-MoS₂/Bcl-2 siRNA polyplexes on the expression of Bcl-2 gene was 47.3%. Under 808 nm NIR laser radiation, the survival rate of cells treated with G5-MoS₂/Bcl-2 siRNA complex was only 21.0%, which is much lower than PTT (45.8%) or GT (68.7%) alone (Fig. 17 l–n). In conclusion, MoS₂-based nanocomposites could effectively load siRNAs of specific genes which over-expressed in a variety of cancer cells and successfully delivered them to tumor cells, inhibiting the proliferation and migration of cancer cells to delay cancer progression through synergistic effect of GT and PTT.

Tumor immunotherapy aims to activate the immune system of the body and kill tumor cells via the immune reaction, and is emerging as a promising anti-tumor strategy [364]. Cytosine-phosphate-guanine (CpG) can be absorbed by lysosomes, inducing the generation of innate immune responses characterized by Th1 cells and

proinflammatory factors [365]. However, CpG is difficult to penetrate cell membranes and easily degraded by nucleases. Therefore, an ideal vector is needed to transport CpG to target cells and protect them from degradation. Han et al. [366] designed a uniform MoS₂-PEG-CpG for photothermal enhanced immunotherapy. First, the few-layered MoS₂ nanosheets obtained from bulk MoS₂ via Li ion intercalation and ultrasonication. Then SH-PEG and CpG modified MoS₂ nanosheets through the Mo-S bond. Importantly, MoS₂-PEG-CpG with uniform morphology had a mean diameter of 100 nm after probe sonication and modification, which more applicable to immune response. The enhanced immune response could be attributed to two aspects: (1) MoS₂-mediated photothermal effect enhanced the permeability of the cell membrane, promoting the endocytosis of MoS₂-PEG-CpG; (2) MoS₂-PEG-CpG could protect CpG from degradation by nucleases. Therefore, the production of pro-inflammatory factors and Th1 cells could be induced by increasing the uptake of CpG under near-infrared irradiation, realizing a stronger anti-cancer effect.

Chemodynamic therapy (CDT) uses the weakly acidic microenvironment of the tumor as the reaction conditions, H₂O₂ as the reaction raw material, and nanomaterials with enzyme-like activity as the catalyst. Therefore, it can induce Fenton or Fenton-like reactions in tumor cells to reduce H₂O₂ to ROS with strong oxidizing property, promoting cancer cell apoptosis [367]. MoS₂ nanosheets have a peroxidase-like activity (POD) that can detect H₂O₂ and glucose in serum [368]. Maji et al. [369] designed hybrid gold nanopyramid nanocomposites coated with MoS₂ (AuNBPs@MoS₂) that possessed enzymes-like activity and could be used for anticancer treatment and TPF bioimaging. The AuNBPs@MoS₂ possessed significantly localized surface plasmon resonance (LSPR) performance under excitation ascribing to its anisotropic nature and the rich electron density in MoS₂. Meanwhile, the peroxidase-like activity of AuNBPs@MoS₂ could further heighten in the presence of TMB and H₂O₂ that due to LSPR speciality, leading to in situ photogeneration of ROS. TPF imaging demonstrated that AuNBPs@MoS₂ was endocytosed into tumor cells, and synergistic treatment of CDT and PTT was achieved in the presence of H₂O₂ and NIR laser irradiation, which promoted cancer cells death. Similarly, Mei et al. [370] synthesized MoS₂@CGTC NCR by co-loading tirapazamine (TPZ) and glucose oxidase (GOx) on the surface of MoS₂ for combination therapy of CDT and chemotherapy. First, GOx could catalyze glucose to generate H₂O₂ and gluconic acid, which could promote the reduction reaction between MoS₂ and H₂O₂ to produce a great deal of ·OH. MoS₂ also could react with GSH to decrease the consumption of ·OH. Second, TPZ could convert into toxic TPZ radical under hypoxia conditions to kill cancer cells. MoS₂@CGTC NCR could effectively ablate A549 cells in vivo and in vitro. Recently, copper ions and iron ions have been incorporated into MoS₂ to enhance the CDT effect of MoS₂ [371,372]. For example, Jiang et al. [373] prepared MoS₂-CuO heterostructures to promote the generation of ·OH by inducing Fenton or Fenton-like reactions.

To further strengthen the anticancer effect, Zhang et al. [374] integrated immunotherapy, CDT, and PTT into a platform (FePt/MoS₂-FA-CpG ODN), eliminating tumor and prevent tumor recurrence. The multipurpose FePt/MoS₂-FA nanocomplexes were constructed by immobilizing FePt nanoparticles (FPMF NCs) and FA on MoS₂ nanosheets. FePt nanoparticles used as competent iron death agents to catalyze Fenton reaction for generating ROS, and MoS₂ nanosheets could ablate primary tumor cells by PTT. Furthermore, oligodeoxynucleotides containing cytosine-guanine (CpG ODNs) anchored on the surface of MoS₂ nanosheets could strengthen the body's immune reaction to antigens, which combined with systemic checkpoint blockade therapy using an anti-CTLA4 antibody could effectively eliminate the metastatic tumor. At the same time, the combination of CpG ODNs and Toll-like receptor-9 (TLR9) could up-regulate the expression of co-stimulatory factors, promote the secretion of inflammatory factors, and enhance the immune response of CD8⁺ T cells. Compared with FA receptor-negative L02 cells, FA receptor-positive 4T1 cells had a lower

survival rate, indicating that FePt/MoS₂-FA-CpG ODN had a strong targeting ability, which could effectively kill cancer cells and inhibit tumor growth. What's more impressive was that this synergistic treatment had obtained a strong immune memory, thereby inhibiting cancer recurrence (Fig. 18). Phototherapy could trigger body's immune response to improve the effectiveness of cancer therapies [259, 375–377]. Cancer cells were destroyed by phototherapy and then released tumor associated antigens which can be captured by antigen presenting cells (particularly dendritic cells, DCs) and presented to T cells, subsequently inducing immune reactions to kills tumor cells. Jin et al. [377] synthesized an injectable PC₁₀A/DOX/MoS₂ hydrogel that could be used for chemotherapy, phototherapy and immunotherapy of 4T1 tumor. MoS₂ nanosheet loaded with positively charged DOX and negatively charged PC₁₀A to form hybrid PC₁₀A/DOX/MoS₂ nanoparticles by electrostatic interaction and then dispersed them in PC₁₀A hydrogel to prepare the multifunctional PC₁₀A/DOX/MoS₂ hydrogel. MoS₂ nanosheets were used as efficient PTT agents and PDT agents to generate hyperthermia and ROS, respectively. Meanwhile, the secretion of immune-stimulatory cytokines would increase when PDT and PTT could promote the maturation of DCs, which was contributed to the activation of T cells. The result showed that the number of mDCs, CD4⁺ T cell, CD8⁺ T cell, and immune-stimulatory cytokines was significantly increased and the anti-cancer effect was remarkably enhanced due to the combination of chemotherapy, phototherapy and immunotherapy.

8. Conclusions and perspectives

Efficient and reliable cancer diagnosis and treatment methods can extend the survival period of patients and improve the quality of life [385]. Two-dimensional nanomaterials (MoS₂, MoSe₂, WS₂, WSe₂, and etc.) have attracted great interest in the biomedical field [8,18, 386–397], especially MoS₂-based nanocomposites due to their outstanding physico-chemical properties and good biocompatibility. MoS₂ with a large specific surface area can load various biomolecules, drugs, fluorescent molecules, and other nanomaterials to improve its colloidal stability and tumor targeting, increase its sensitivity and accuracy in detecting specific biomarkers, and enhance its specific response to the stimulation of tumor microenvironment, which reduces side effects during treatment. At the same time, the strong photothermal conversion capacity and near-infrared light absorption ability of MoS₂ have promoted its application in phototherapy, PA imaging. Moreover, MoS₂-nanocomposites can be used for bioimaging, microwave hyperthermia, radiation therapy, immunotherapy, and combination therapy. However, most the research of MoS₂-nanocomposites for cancer diagnosis and treatment are still at an early stage, and there are still many problems to be solved [16].

Firstly, the long-term safety of MoS₂-nanocomposites in biomedical applications needs to be considered. Most experiments in vivo are limited to animal models, and only the short-term effects of these nanocomplexes on animal major organs, hematological indexes and blood biochemical indexes have been tested. Whether their long-term toxicity and efficacy in humans are consistent with the results of animal models has not been confirmed [398]. Quantum size effects and surface effects of MoS₂-nanocomposites may cause toxicity or enhance toxicity in organisms. MoS₂-nanocomposite may interact with channel proteins and various receptors on the surface of the cell membrane or inside the cell, resulting in conformational changes of proteins, changing of signal transduction pathways, and leading to dysfunction of the body. At present, there is no research to prove whether nanomaterials can interfere with the reproductive system and affect offspring [394]. In summary, the realization of clinical transformation of nanomaterials still faces great challenges, and more efforts are needed to fully demonstrate their long-term bio-safety.

Additionally, the bioavailability of MoS₂-nanocomposites in human tumor sites should be considered. It is very important to design MoS₂-nanomedicines that can specifically respond to the tumor

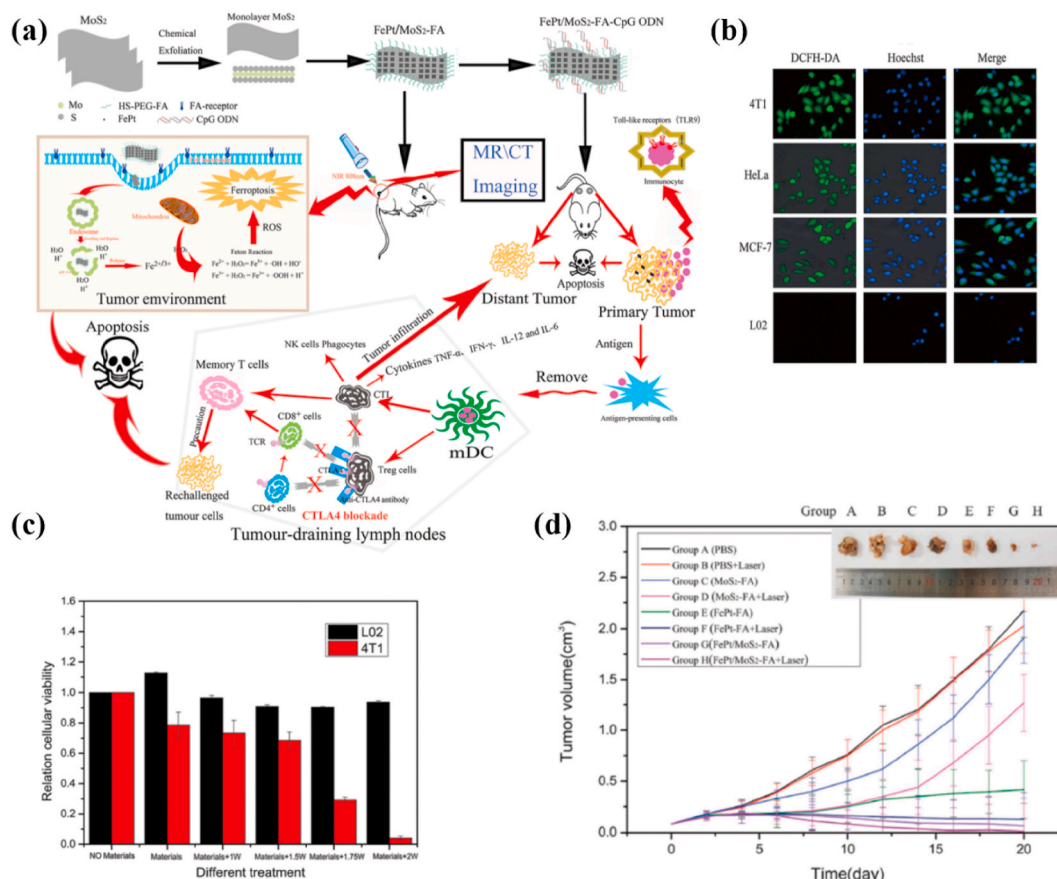


Fig. 18. (a) The fabrication process of FPMF nanocomposites and the mechanism of anti-tumor immune responses by FPMF@CpG ODN nanocomposites by combining immunotherapy, CDT, and PTT for anticancer therapeutic applications. (b) Fluorescence microscopy images of DCFH-DA labeled 4T1, HeLa, MCF-7 and L02 cells incubated with FPMF NPs for 6 h at the Fe concentration of 80 mg/mL. (c) Viabilities of 4T1 and L02 cells treated with different times at the same Fe concentration of 80 mg/mL. (d) The volume of tumors in tumor-bearing mice during different treatments. (Group: A: PBS, B: PBS + laser, C: MoS₂-FA, D: MoS₂-FA + laser, E: FePt-FA, F: FePt-FA + laser, G: FePt/MoS₂-FA, and H: FePt/MoS₂-FA + laser, n = 5). Reprinted with permission from Ref. [374]. Copyright 2019, Nanoscale.

microenvironment to enhance efficacy. For example, designing nanomaterials that can selectively bind to tumor cell-specific receptors to increase their accumulation in tumor sites and reduce the uptake of non-cancerous tissues. The rapidly established mouse orthotopic tumor model has an obvious EPR effect. However, the cancer progression and growth rate of many patients is much lower than that of mouse models, resulting in the patients' EPR effect is not obvious. Therefore, the uptake of nanomaterials through the EPR effect may not be suitable for the cancer patients. It is necessary to synthesize nanomaterials that can enter human tumor sites through other effects for improving their bioavailability in the human body.

Finally, synthesis of MoS₂-nanocomposites with stable performance is another challenge. On the one hand, the size and thickness are the key factors that affect the physicochemical property of MoS₂. Although there are existing methods to adjust the size and thickness of MoS₂, the cost is expensive, the operation steps are cumbersome and the morphology of MoS₂ will be affected. Therefore, exploring a simple and easy synthesis method can not only reduce costs, but also better optimize the properties of MoS₂ and improve its therapeutic effect. On the other hand, excellent stability is a necessary condition for nanomedicines to achieve clinical transformation. Therefore, it is urgent to optimize experimental methods to improve the stability of nanomaterials, prolonging their storage time and promoting clinical transformation.

Declaration of competing interest

The authors declare no conflict of interest, financial or otherwise.

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