Hydrogen sulfide (H$_2$S) is of vital importance in several biological and physical processes. The significance of H$_2$S-specific detection and monitoring is emphasized by its elevated levels in various diseases such as cancer. Nanotechnology enhances the performance of chemical sensing nanoprobes due to the enhanced efficiency and sensitivity. Recently, extensive research efforts have been dedicated to developing novel smart H$_2$S-triggered/therapeutic system (SHTS) nanoplatforms for H$_2$S-activated sensing, imaging, and therapy. Herein, the latest SHTS-based nanomaterials are summarized and discussed in detail. In addition, therapeutic strategies mediated by endogenous H$_2$S as a trigger or exogenous H$_2$S delivery are also included. A comprehensive understanding of the current status of SHTS-based strategies will greatly facilitate innovation in this field. Lastly, the challenges and key issues related to the design and development of SHTS-based nanomaterials (e.g., morphology, surface modification, therapeutic strategies, appropriate application, and selection of nanomaterials) are outlined.

1. Introduction

Hydrogen sulfide (H$_2$S) is a highly toxic gas known for its causticity, flammability and distinct odor of rotten eggs. However, endogenous H$_2$S is the third major gasotransmitter in addition to carbon monoxide (CO) and nitric oxide (NO). The misregulation of this signaling molecule is associated with numerous diseases, such as Alzheimer’s disease, diabetes, and cancer. Since H$_2$S has such a crucial role, an effective H$_2$S detection method would facilitate the understanding of the implicated diseases and permit early diagnosis. Currently, the most-used techniques include high-pressure liquid/gas chromatography (HPLC/GC) and mass spectrometry, which efficiently detect and image hydrogen sulfide via chemiluminescence or mass spectrometry. However, the high cost and tedious processing time severely restrict their practical application in detecting H$_2$S in biological samples, especially for real-time measurements. In comparison, novel small molecules ranging from colorimetric and fluorescent probes have demonstrated substantial advantages for dynamic and in situ H$_2$S sensing/imaging via various chemical strategies. Several fluorescent probes, such as sulfidefluor-1/2 (SF-1/2) and hydrogen sulfide imaging probe-1 (HSip-1) present desirable selectivity and can “turn on” an H$_2$S-activated fluorescent signal for H$_2$S detection (e.g., living cell imaging), with limits of detection (LOD) (all the abbreviations could be found in Table 1) reported around 5 × 10$^{-6}$–10 × 10$^{-6}$ M. While well-designed small molecule probes have been applied for H$_2$S-selective detection in live cells and in vivo imaging.

Recently, novel nanoprobes have been developed for H$_2$S sensing, which efficiently detect and image hydrogen sulfide via 1) chemical features of the loaded smart fluorophore (e.g., Azide reduction, metal precipitation and nucleophilic attack), 2) change of luminescence/Förster resonance energy transfer (LRET/FRET), 3) variation of absorbance (colorimetric assay) or fluorescent probing, 4) surface metal precipitation, 5) change of luminescence/Förster resonance energy transfer (LRET/FRET), or 6) electrochemical reaction. More importantly, a series of therapeutic strategies (e.g., photothermal therapy and photodynamic therapy, etc.) could be intelligently triggered by the activation of endogenous H$_2$S from the targeting area. Additionally, exogenous H$_2$S delivery has been successfully achieved via nanoplatforms, which can induce H$_2$S-mediated gas therapy (via physical damage) or tissue protection (e.g., the heart I/R injury) within the disease regions. These multifunctional nanoplatforms may generate novel treatments available for various H$_2$S-related diseases.
As such a promising field, smart H$_2$S-triggered/therapeutic system (SHTS)-based nanomedicine is expected to significantly accelerate the development of disease diagnosis and therapeutic strategy by enhancing accuracy and efficiency. Given the vital role of hydrogen sulfide in biological processes and advantages of nanotechnology, we provide an overview of recent progress in H$_2$S detection, imaging and related disease therapy via SHTS-based nanomedicine (Figure 1). Within this review, various nanoagents such as noble metal nanomaterials, metal-organic framework, copper-based nanomaterials, and carbon nanodot for H$_2$S sensing, different imaging (including fluorescence, localized surface plasmon resonance, upconversion luminescence, near-infrared, photoacoustic and positron emission tomography imaging) and therapeutic strategies (e.g., the endogenous H$_2$S-triggered therapy or exogenous H$_2$S delivery) are summarized. As such, we aim to highlight these powerful nanoprobases in this emerging field and offer an overview for the development of next-generation of SHTS-based nanomedicine.

2. Roles of H$_2$S in Biological Systems

Endogenous H$_2$S is mainly produced from cysteine by three enzymes: 3-mercaptoppyruvate sulflotransferase (3-MST), cystathionine $\beta$-synthase (CBS), and cystathionine $\gamma$-lyase (CSE).[58–61] The H$_2$S generated is a vital gas transmitter that affects various biological and physical functions within the body, ranging from antiinflammation to regulation of neuronal transmission.[62–65] For instance, it has been reported that H$_2$S donors promote the production of ATP and electron transport in mitochondrial.[66] Furthermore, H$_2$S is able to protect the cell by attenuating apoptosis. Thus, it has been widely applied as a novel reagent for preserving organs from ischemia-reperfusion injury during various surgeries and organ transplantsations.[67–69] Also, the increased secretion of endogenously H$_2$S is strongly associated with the progress of tumor.[4,70]

Notably, the H$_2$S generating enzymic system including 3-MST, CBS, and CSE have been widely identified in many cancer types.[4,71] The overexpression of CBS has been particularly reported within various colon and ovarian cancers,[72,73] indicating the significant role of H$_2$S in promoting tumor development. The hydrogen sulfide derived from cancer cells also promotes tumor growth and proliferation by acting as an autocrine and paracrine factor.[74] After introducing a CBS inhibitor, the growth of colon cancer could be greatly attenuated by efficiently reducing H$_2$S generation and inhibiting peritumor angiogenesis.[61] However, the fast catabolism and regulation of this toxic gas show a great challenge for real-time detection within the tissues.[74] As one of the most dangerous gases, the concentration of H$_2$S within the air needs to be monitored as well. While this toxic gas easily noted because of its rotten-egg smell, the exposure to H$_2$S can cause a serial of symptoms including lung irritations ($\leq$20 ppm), damage of eye (300–500 ppm), unconsciousness, or even death ($\geq$700 ppm).[75] Therefore, successful detection/imaging of hydrogen sulfide would be immensely valuable for disease diagnosis and treatment, as well as risk management.

3. H$_2$S Detection with SHTS-Based Nanomedicine

To monitor H$_2$S in solutions and air, various nanomaterials have been developed as novel sensors, including noble metal nanoparticles (e.g., Au, Ag, and Au/Ag alloy), metal-organic frameworks (MOF), copper nanomaterials, carbon nanodots, among others (e.g., ruthenium nanoparticles, etc.). In this section, a series of SHTS-based nanosensors will be summarized (Table 2).

3.1. Noble Metal Nanomaterials

Gold and silver are two major noble metals that have been widely used in daily life for centuries. For instance, colloidal gold
Table 1. Full names and the corresponding abbreviations.

| Full name                                                                 | Abbreviation | Full name                                      | Abbreviation |
|---------------------------------------------------------------------------|--------------|------------------------------------------------|--------------|
| 3-mercaptopyruvate sulfotransferase                                        | 3-MST        | Myocardial infarction                           | MI           |
| Aerosol-assisted chemical vapor deposition                                | AACVD        | Metal-organic frameworks                        | MOF          |
| Alzheimer’s Disease                                                        | AD           | 11-mercaptoundecanoic acid                      | MUA          |
| Anethole dithiolethione                                                    | ADT          | Mesoporous silica nanoparticles                 | MSNs         |
| Aggregation-induced emission                                               | AEI          | Near Infrared                                   | NIR          |
| Anethole dithiolethione (ADT)-loaded magnetic nanoliposome                | AMLs         | Noble metal clusters                            | NMCs         |
| Amino-oxyacetic acid                                                       | AOAA         | Photoacoustic                                   | PA           |
| Adenosine triphosphate                                                    | ATP          | Positron emission tomography                    | PET          |
| Carbon nanodots                                                            | C-dot        | Photodynamic therapy                            | PDT          |
| Cystathionine β-synthase                                                   | CBS          | Polymeric nanoparticles                         | PMNs         |
| Carbon nanotubes                                                           | CNTs         | Plasmonic nanoparticles                         | PNP s        |
| Cystathionine γ-lyase                                                     | CSE          | Polystyrene sulfonate                           | PSS          |
| Dialyl sulfide                                                            | DATS         | Photothermal therapy                            | PTT          |
| Functional graphene sheets                                                 | FGS          | Reactive oxygen species                         | ROS          |
| Ischemia/reperfusion                                                       | I/R          | S-adenosyl-l-methionine                          | SAM          |
| Inner filter effect                                                        | IFE          | Smart H₂S-triggered/therapeutic system          | SHTS         |
| Intercellular adhesion molecule-1                                          | ICAM-1       | Tris(2-chloroisopropyl)phosphate                | TCPP         |
| Limits of detection                                                       | LOD          | 3,3',5,5'-tetramethylbenzidine                  | TMB          |
| Liposome nanoparticles                                                     | LNPs         | 1-(10-mercaptodecy1)-5-methylprimidine-2,4-dione | TSH          |
| Luminescence/Förster resonance energy transfer                            | LRET/FRET    | Triphenyltetrazolium chloride                   | TTC          |
| Longitudinal surface plasmon resonance’s                                  | LSPR         | Upconverting nanoparticles                      | UCNPs        |
| Vascular cell adhesion molecule-1                                          | VCAM-1       | Upconversion luminescence                        | UCL          |

Figure 1. The H₂S-specific detection, imaging, and therapy mediated by the smart H₂S-triggered/therapeutic system (SHTS).
and optical properties, gold, silver, and alloy nanomaterials have been widely developed and applied for biomedical engineering applications. The LSPR is a key characteristic of noble metal nanomaterial that is easily influenced by the size, shape, and environment.

![Image](https://www.advancedsciencenews.com)

| Material | Nanoparticle | Size [nm] | Mechanism | Assay | Sample Phase | LOD | Ref. |
|----------|--------------|----------|-----------|-------|--------------|-----|------|
| Au | Au NRs | ≈60 | Aggregation | Colorimetry (A730) | Solution | 24 × 10⁻⁶ m | [76] |
| AE AuNPs | 13.3 ± 1.6 | Aggregation | Colorimetry (A520/720) | Solution | 20 × 10⁻⁶ m | [44] |
| GSH-AuNP | 13 | Aggregation | Colorimetry (A700/520) | Solution | 3 × 10⁻⁶ m | [77] |
| BSA-AuNCs-HSIP-1 | ≈1 | Aggregation | Metal precipitation (IS19/IS32) | Solution | 0.73 × 10⁻⁶ m | [78] |
| TSH-MUA-AuNDs | 1.9 ± 0.3 | Anti-aggregation | Fluorescence (Em510) | Solution | 0.5 × 10⁻⁶ m | [79] |
| Cu@Au NPs | N/A | Competitive binding | Colorimetry (A650/520) | Solution | 0.3 × 10⁻⁶ m | [80] |
| Au/SiAu NPs | N/A | Reduction | Colorimetry (A414) | Solution | 0.28 × 10⁻⁶ m | [81] |
| FSN-AuNRs | 30.8 ± 2.125 ± 1 | Aggregation | Colorimetry (A518/A648) | Solution, Serum | 0.2 × 10⁻⁶ m | [82] |
| Au NPs | 8.1 ± 1.1 | Catalyst | Colorimetry (A652) | Solution | 80 × 10⁻⁹ m | [83] |
| Au NPs | 13 | Anti-aggregation | Colorimetry (A520) | Bubble gas | 30 × 10⁻⁹ m | [84] |
| Au@TPI-NCs | 17.1 | Catalyst | Colorimetry (A650) | Solution/Evaporated gas | 7.5 × 10⁻⁹ m | [85] |

**Table 2.** The nanosized materials as SHTS for H₂S detection.

- **Au/Au**: Core–shell Au@Ag NCs
- **C-dot**: CD-Hg²⁺/Ag⁺

*LOD* is the limit of detection, which is an important parameter for the sensitivity of the assay.
distance, and composition.\cite{104} Based on this property, a variety of detection methods have been developed by the formation/dispersion of aggregation or change of the surface, including the specific detection for hydrogen sulfide (Table 2).

With proper surface functionalization using different ligands such as glutathione,\cite{77} fluorosurfactants,\cite{82} or small molecules (e.g., thiolated azido derivates and active esters),\cite{44} gold nanosensors quickly aggregate when they encounter with H$_2$S. This results in a redshift of absorbance wavelengths and LOD ranging from $0.2 \times 10^{-6}$ to $20 \times 10^{-6}$ m. In comparison, hydrophobic surface modification (e.g., fluorescent probe, 1-(10-mercaptodecyl)-5-methylpyrimidine-2,4-dione, TSH) force the AuNDs coated with TSH and MUA (11-mercaptoundecanoic acid) to aggregate. The presence of H$_2$S could disassemble the aggregation surface adsorption of H$_2$S and HS, recovering the quantum yield back to 1.61.\cite{79} Similarly, Zhang et al. developed a simple sensing strategy by using bubbling H$_2$S to stabilize the AuNPs (13 nm), with the existence of NaCl ($80 \times 10^{-3}$ m) and Tween 80 (Figure 2A).\cite{84} This cost-effective method provides a high sensitivity toward H$_2$S with LOD values reaching around $14 \times 10^{-9}$ m for the naked eye and $30 \times 10^{-9}$ m for machine detection, which is more efficient than that afforded by TSH-MUA-AuNDs ($0.5 \times 10^{-6}$ m).

While other approaches, such as the change of LSPR induced by surface reduction and competitive binding between S-Au and I-Au (forming clusters or larger nanoparticles),\cite{80,81} have been used with gold-based sensors, the sensing limits only reach about $0.3 \times 10^{-6}$ m for H$_2$S detection. Comparably, catalysis mediated by Au based nanosensors has excellent sensitivity.\cite{83,85} A catalysis Au@TPt-NCs (Au core with an ultrathin platinum shell) nanoplatform was developed by Gao et al. to detect dissolved H$_2$S gas (Figure 2B).\cite{85} The H$_2$S evaporated or dissolved interacts with and deactivates the nanoclusters, attenuating the chromogenic reaction between H$_2$O$_2$ and 3,3',5,5'-tetramethylbenzidine (TMB) and showing an extremely low LOD value at $7.5 \times 10^{-9}$ m. More importantly, the approach is also visible to the naked, providing flexibility for applications (Figure 2C,D).

Additionally, the Au/Ag alloy has also been recruited for sensing H$_2$S by fluorescence quenching.\cite{86,87} Among all, a sensitive DNA-templated Au/Ag NCs was successfully developed by Chen et al (Figure 2E,F).\cite{87} In the presence of H$_2$S, the prepared

---

Figure 2. A) The scheme of AuNPs for detecting bubbling H$_2$S with the coordination of NaCl and Tween-80. Reproduced with permission.\cite{84} Copyright 2014, American Chemical Society. B) Schematic demonstration of the Au@TPt-NCs-based platform for detecting dissolved hydrogen sulfide via a colorimetric strategy. C) The deactivated assays of Au@TPt-NCs (Au core @ ultrathin platinum shell nanoclusters) via H$_2$S (the testing groups included: a) Au@TPt-NCs; b) H$_2$O$_2$ + TMB (3,3',5,5'-tetramethylbenzidine); c) $0.1 \times 10^{-6}$ m H$_2$S + H$_2$O$_2$ + TMB; d) Au@TPt-NCs + H$_2$O$_2$ + TMB; e) Au@TPt-NCs + $0.1 \times 10^{-6}$ m H$_2$S + H$_2$O$_2$ + TMB; f) Au@TPt-NCs + $0.1 \times 10^{-6}$ m H$_2$S + H$_2$O$_2$ + TMB; g) Au@TPt-NCs + $0.5 \times 10^{-6}$ m H$_2$S + H$_2$O$_2$ + TMB; h) Au@TPt-NCs + $1 \times 10^{-6}$ m H$_2$S + H$_2$O$_2$ + TMB). D) the detection of H$_2$S at various concentrations (a) $0 \times 10^{-6}$ m; b) $0.1 \times 10^{-6}$ m; c) $0.2 \times 10^{-6}$ m; d) $0.5 \times 10^{-6}$ m) via the catalysis of Au@TPt-NCs platform (n = 3). Reproduced with permission.\cite{87} Copyright 2015, American Chemical Society. E,F) Schematic illustration of DNA-Au/Ag NCS Probe’s synthesis and detection of H$_2$S; H$_2$S-induced fluorescent quenching of DNA-Au/Ag NCS in the presence of S$^{2-}$ ions over G) $0 \times 10^{-6}$ –$0.01 \times 10^{-6}$ m and H) $0.01 \times 10^{-6}$–$9 \times 10^{-6}$ m. Reproduced with permission.\cite{88} Copyright 2011, American Chemical Society.
Au/Ag NCs showed a linear relationship ($0 \times 10^{-6}$–$0.01 \times 10^{-6}$ m and $0.01 \times 10^{-6}$–$9 \times 10^{-9}$ m) between the H$_2$S concentration and fluorescence intensity, with a quantum yield of 4.5% and a LOD of $0.83 \times 10^{-9}$ m (Figure 2G,H). Among Ag-based platforms, only several polymer-coating Ag nanoparticles have been investigated and relatively-low efficiency was demonstrated for H$_2$S detection ($0.2 \times 10^{-6}$–$3.3 \times 10^{-9}$ m) compared with that provided by Au-based nanoprobes.[42,43,88]

3.2. Metal-Organic Framework (MOF)

The past decade has seen a great deal of attention to metal-organic framework (MOF) due to their excellent physiochemical features.[105–110] These nanomaterials are composed of different combinations of metal ions, organic linkers, and modifications and have vast application possibilities (e.g., gas storage, chemical sensing, chiral separations, etc.).[111] With the tremendous surface area ($\approx 7000$ m$^2$ g$^{-1}$) and rigid pores that could host various functional molecules, MOF has also been investigated as a potential sensor for chemical and toxic gas detection, such as hydrosulfide.[112] Through the formation of the metal sulfides (e.g., CuS),[46,89,90] amine group,[39] or N–S bond[91] with S$^{2-}$, several novel MOFs could recover the fluorescence/photoluminescence that was quenched and trigger a detectable signal for sensing H$_2$S with a desirable sensitivity. For instance, the presence of Tb$^{3+}$/Cu$^{2+}$ ions enables the Tb$^{3+}$@Cu1/Cu2 MOF complex to generate multiwavelength luminescences and produce an enhanced ratiometric signal ($I_{544}/I_{390}$) after the interaction with the H$_2$S exposed, with a LOD of S$^{2-}$ at about $1.2 \times 10^{-6}$ m.[89] Similarly, Qian Lab synthesized an Eu$^{3+}$@UiO-66-(COOH)$_2$ MOF that induced a fluorescent signal via the interaction between Cu$^{2+}$ and S$^{2-}$.[46] Although such MOF exhibits a uniform nanostructure (80–100 nm) and comparable H$_2$S LOD (5.45 $\times 10^{-6}$ m), the fluorescence intensity generated could be affected by amino acids containing thiol and nitroxy groups, which strongly lowers selectivity toward H$_2$S.[46] Comparably, the novel sensors, Zr(TBAPy)$_3$(TCP) and aluminum-based MOF (Al-MIL-53-NO$_3$) demonstrate desirable H$_2$S detection and selectivity via reduction, with LOD of $\approx 92.31 \times 10^{-9}$ m and $\approx 1$ ppb, respectively.[39,91] The Zr(TBAPy)$_3$(TCP) were synthesized with a uniform nanostructure (with a diameter around 100 nm) after incorporation of Tris(2-chloroisopropyl)phosphosphate (TCP) (Figure 3A,B).[91] This synthesized nanoparticle was very sensitive to H$_2$S (with a LOD around $50 \times 10^{-9}$ m), and only showed fluorescence after the introduction of H$_2$S, demonstrating a desirable linear relation between fluorescence and the concentration of H$_2$S (Figure 3C,D,F). More importantly, the reaction of Zr(TBAPy)$_3$(TCP) and H$_2$S was completed within 10 s, providing an opportunity for real-time detection (Figure 3E).

As alternatives to single substrate MOFs, probes for the detection of multiple biomolecules are highly desirable for large scale detection in environmental or clinical assay. Recently, a Eu$^{3+}$-Cu$^{2+}$ based MOF was developed.[90] With two specific and separate binding areas for ascorbic acid (AA) and H$_2$S, it simultaneously detected both biomolecules. Due to the high sensitivities, the as-prepared MOF can identify H$_2$S and AA concentrations as lower as $130 \times 10^{-9}$ and $55 \times 10^{-9}$ m, respectively. Additionally, desirable recovery rate (94.7–104.1%) was attained in assays using human serum. After incorporating various elements and molecules, novel MOF-based probes for multiple biomolecule detection have significant promise for biomedical applications.

**Figure 3.** A) Representative TEM and B) HR-TEM images of Zr(TBAPy)$_3$(TCP); C) The photoluminescence emission spectra among Zr(TBAPy)$_3$(TCP) (black), NU-1000 (red), TBAPy (blue), and TCPP (cyan). D) The variation of fluorescence generated by Zr(TBAPy)$_3$(TCP) with a series of S$^{2-}$ concentrations and E) the change of fluorescence intensity at various time points post the addition of S$^{2-}$ into the Zr(TBAPy)$_3$(TCP) solution; F) Fluorescence pictures ($\lambda_{em} = 365$ nm) of Zr(TBAPy)$_3$(TCP) aqueous solutions with different anions. Reproduced with permission.[91] Copyright 2018, Wiley.
3.3. Copper Based Nanomaterials

Copper (Cu), the most-used cation for H2S sensing (via the metal precipitation), has been widely incorporated into small organic molecules (e.g., HSIP-1) and the other nanosized probes.[78,80] The addition of Cu to nanomaterials in the form of Cu, CuO, or Cu2O is also employed for H2S-specific detection.[52] Coating the surface of nanoparticle sensors (e.g., nanowires, nanoneedles, or nanotubes) with Cu, CuO, or Cu2O enables rapid detection of H2S due to variations in conductivity after reduction. As such, the concentration of H2S in the solution or air can be determined.[53,92,93] For example, a Cu2O NPs (2–3 nm) coated WO3 nanoneedles were prepared via aerosol-assisted chemical vapor deposition (AACVD).[53] This system was able to detect H2S levels as low as 300 ppb within two seconds. A major limitation of the Cu2O-WO3 nanoneedles was the high temperature required (390 °C) that makes practical application difficult. A Quasi-2D-Cu2O/SnO2 consisting of P-type Cu2O and N-type SnO2 was successfully developed for H2S gas detection at room temperature, with a LOD at 0.5 ppm.[94] Notably, laser illumination further reduced the heterojunction barrier and enhanced the response of Quasi-2D-Cu2O/SnO2 by 20%. The Chen lab synthesized a Cu2O-FGS (functional graphene sheets) by in situ growth that provided desirable surface accessibility, contacting area (Cu2O was prepared without surfactant) and sensitivity (LOD is around 5 ppb) for H2S gas sensing under normal atmospheric conditions (Figure 4A–C).[52]

Several studies have confirmed that the aggregation of organic Cu NCs (e.g., cysteine or penicillamine (PAE) template) can activate an enhanced fluorescence referred to as aggregation-induced emission (AIE).[95,96] By incorporating polystyrene sulfonate (PSS) into the system, PSS-PAE-Cu NC aggregates were designed H2S detection in drinking water (Figure 4D).[95] With the 0.05 wt% PSS, as-prepared PSS-PAE-Cu NCs aggregates (173 nm) generated red photoluminescence (665 nm) that was extinguished when as little as 650 × 10−9 M H2S was present (Figure 4E,F).

3.4. Carbon Nanodot

Since the first discovery at 2004, carbon nanodots (C-dots or CDs) have been widely investigated for biomedical, catalytic, and sensing applications due to its attractive features of high solubility, biocompatibility, and photostability.[113–115] Among all, several novel C-dots have been designed for H2S detection/imaging.[51,97,116,117] For example, two metal ion (Ag+/Hg2+) based C-dots were synthesized for sensing sulfide ions. In the presence of H2S as low as 0.32 × 10−6 and 0.43 × 10−6 m respectively, the fluorescence of CD-Hg2+/Ag2+ would be quenched by the inner filter effect (IFE) mediated by the Hg2S/Ag2S formed. Meanwhile, the formation of Ag2S significantly changes the Ag–C-dot’s electrochemiluminescence that shows a desirable sensitivity with a LOD at 27 × 10−9 M.[56,57]

Figure 4. A) Schematic demonstrating the in situ approach for synthesizing the Cu2O-FGS (functional graphene sheets) platform; B) Representative SEM image of the Cu2O–FGS established on the Si/SiO2 substrate with gold interdigitated electrodes coverage; C) Sensitivity limits of Cu2O–FGS and FGS based detector in series of concentrations of atmospheric H2S. Reproduced with permission.[52] Copyright 2013, Royal Society of Chemistry. D) Schematic illustration of the polystyrene sulfonate (PSS) mediated PSS-PAE-Cu NC synthesis. E) Optical images of PSS-PAE-Cu NC aggregates prepared via various concentrations of PSS (0.005–0.5 wt%) without (upper row) and with UV illumination; F) The photoluminescence spectra of the PSS-PAE-Cu NC aggregates under various concentrations of H2S and the linear relationship between the photoluminescent intensity of PSS-PAE-Cu NC aggregates and the concentration of H2S with sodium phosphate buffer (10 × 10−3 M, pH 3.0). Reproduced with permission.[95] Copyright 2016, Nature Research.
3.5. Other Nanosensors

Other nanomaterials such as Pb-based NPs, graphene supporting and polymeric nanocomposites, and ruthenium NPs have been investigated as nanosensors for H$_2$S detection (Table 2).\[44,98–103\] Given the great conductivity of graphene, a SnO$_2$-rGO (reduced graphene oxide) nanosheet was successfully developed via a one-step colloidal synthesis for H$_2$S sensing (Figure 5A).\[100\] H$_2$S gas was adsorbed (i.e., chemisorption) and detected within 2 s at room temperature with a desirable sensitivity (with LOD at 43 ppb) (Figure 5B,C). Two polymeric nanoparticles, the PPy/WO$_3$ (50–70 nm) and cyclen-FPNs (33–40 nm) were designed for identifying this gas as well.\[99,101\] After electrochemical electron transfer (i.e., H$_2$S $^+$ + 3O$_2^-$ $\rightarrow$ 2H$_2$O $+ 2SO_2 + 3e^-$) and the formation of CuS (i.e., the recovery of fluorescence), H$_2$S concentrations could be well determined by PPy/WO$_3$ and cyclen-FPNs (Table 2). Recently, Zhao et al. developed a colorimetric approach via the catalysts mediated by ruthenium nanoparticles (Ru NPs) (Figure 5D).\[44\]

The synthesized Ru NPs (1.7 ± 0.2 nm) degraded the organic dye—Orange I. The resulting color fade occurred about 4, 47, and 165 times faster than for platinum (Pt), iridium (Ir) based NPs, and control groups. Exposure of the Ru NPs and Orange I to H$_2$S protected the Orange I by deactivating Ru NPs (Figure 5E). The superior catalytic capability of Ru NPs demonstrated an excellent LOD (about 0.6 × 10$^{-9}$ m), but it had a relatively poor selectivity to H$_2$S as cross-reaction with Cys and GSH occurred (Figure 5F).\[44\]

4. H$_2$S Imaging with SHTS-Based Nanomedicine

As we have mentioned, micro- or nano-probes have been widely applied for H$_2$S measurements in clinical samples and has greatly facilitated bench efforts. However, the real-time imaging of H$_2$S secretion in patients for disease diagnosis, especially tumor tracking, is still highly demanded. Among all the in vitro and in vivo imaging candidates, nanocarriers have shown great potential as fluorescent, LSPR, upconversion luminescence (UCL), near infrared (NIR), photoacoustic (PA) and positron emission tomography (PET) imaging probes (Table 3). In comparison with the fluorescence and UCL imaging, only a few of nanoprobes has been used for H$_2$S imaging via NIR, LSRP, PA, and PET. These nanosensors would be described in detail in this section.

4.1. Fluorescence Imaging

With the innovation of imaging technology, two- and multiphoton microscopy has been used for fluorescence imaging, which greatly improved the depth of penetration (~1 mm).\[118,119\] However, most fluorescent agents have generally employed for living cell or tissue section based imaging. For instance, the incorporation of organic components (azide or unsaturated C=C bond) enabled MOF to be used for specific imaging in a series of cancer cell lines (e.g., PC12 and J774A.1 cells) via reduction mediated by H$_2$S.\[120,121\] Comparably,
Further functionalization with Cu^{2+} based ligands (e.g., Cyclam-Cu^{2+}) enabled the C-Dots to visualize H_{2}S within cells via fluorescence initiated after CuS precipitation.\textsuperscript{[40,116,117,122]} These nanosensors demonstrated desirable biocompatibility and efficiently detected H_{2}S in Hela or L929 cells, with LOD ranging from around 90 \times 10^{-9} \text{ to } 780 \times 10^{-9} \text{ m}. Notably, C-Dot-TPEA-Cu^{2+}, a two-photon nanoprobe, exhibited excellent tumor penetration that could be used for sensing H_{2}S in A549 tumor sections. This system provided an emission wavelength (560 nm) suitable to minimize background for H_{2}S and nuclei imaging, compared with those (\approx 460 nm) offered by other C-dots.\textsuperscript{[116]}

Internal Förster resonance energy transfer (FRET) is able to aid specific imaging of H_{2}S in vivo. The FRET acceptor (e.g., CuO coated on the surface) or probe structure changes could initiate or terminate FRET in response to H_{2}S.\textsuperscript{[45,49,50]} Notably, carried fluorophores can change its excitation or emission wavelength to act as the imaging trigger when exposed to H_{2}S.\textsuperscript{[49]} For instance, boron-dipyrromethene (BODIPY), with a small Stokes shift and high fluorescent quantum yields, has been widely employed in various nanosized platforms for probing H_{2}S. A micellar nanomaterial was designed by incorporating an amphiphilic copolymer (mPEGDSPE), semi-cyanine-BODIPY hybrid dye (BODInDCI), and BODIPY1 as the energy donor for H_{2}S copolymer (mPEGDSPE), semi-cyanine-BODIPY hybrid dye (BODInDCI), and BODIPY1 as the energy donor for H_{2}S.

### Table 3. The novel nanosensors as SHTS for H_{2}S imaging.

| Imaging strategy\textsuperscript{a} | Material | Nanoparticles | Size [nm] | Mechanism | Assay | Sample(s) | LOD \textsuperscript{b} | Ref. |
|-------------------------------------|----------|---------------|-----------|-----------|-------|-----------|----------------|------|
| FL                                 | MOF      | UiO-66-CH = CH\textsubscript{2} | 20–30     | Reduction (C = C) | Em = 370 | PC-12 cell | 6.46 \times 10^{-6} M | [120] |
|                                    | [Al(OH)(IPA-N3)]·3.2 H\textsubscript{2}O·0.4DMF | N/A | Reduction | Em405 | J744A.1 cell | 2.65 \times 10^{-6} M | [121] |
|                                    | CuO@TO@UiO-66 | N/A | FRET interruption (Turn-off) | Em520-650 | A549 and HepG2 cell | 0.51 \times 10^{-6} M | [45] |
| C-dot                              | C-dot-Ligand-Cu\textsuperscript{2+} |= 5 | Metal precipitation | Em455 | Hela and L929 cell | 0.78 \times 10^{-6} M | [117] |
|                                    | C-dot-TPEA-Cu\textsuperscript{2+} |= 5 | Metal precipitation | Em560 | Hela cell and A549 tumor slide | 0.7 \times 10^{-6} M | [116] |
| Cyclam-CDs (CCDs)                  | = 2 | Metal precipitation | Em460 | Hela cell | 130 \times 10^{-9} M | [122] |
| FCDs-Cu\textsuperscript{2+}        | 4 | Metal precipitation | Em452 | Hela cell | 88.9 \times 10^{-9} M | [40] |
| CD-based sensor                    | = 5 | FRET induction (Turn-on) | IS26/IS425 | Hela and L929 cell | 10 \times 10^{-9} M | [50] |
| Other                              | FAM-DNA/AgNP | 10 \pm 3 | Reduction | Em520 | Hela cell | 10 \times 10^{-9} M | [47] |
|                                    | NanoBODIPY | = 10 | FRET interruption (Turn-on) | Em589 | Raw 264.7 cell | 7 \times 10^{-9} M | [49] |
| LSPR                               | Au/Ag PNPs | 74.19 | LSPR shift | A702 (Dark field imaging) | HepG2 and Hela cell | 0.1 \times 10^{-4} M | [41] |
| UCL                                | UCNPs    | Cy7-UCNPs | 11.27–44.6 | LRET shift (Turn-on) | Em800 | Hela and MCF-7 cell; Zebra fish | 510 \times 10^{-9} M | [123] |
|                                    | TPAMC-UCNPs@PEG | = 35 | LRET shift (Turn-on) | IS30/IS660 | Hela and MCF-7; HCT-116 bearing mice | 0.22 \times 10^{-4} M | [48] |
|                                    | NaYF4: 20% Yb, 2% Er, 0.2% Tm | 94 | LRET shift (Turn-on) | I\textsubscript{green}/I\textsubscript{red} | Hela cell | 0.58 \times 10^{-4} M | [124] |
|                                    | CHC\textsubscript{1}-UCNPs | 24 | LRET shift (Turn-on) | I\textsubscript{ex700}/I\textsubscript{em650} | Hela cell and Mice (LPS) | 0.13 \times 10^{-4} M | [125] |
|                                    | PAA-NaYF 4:Yb/Er/Tm | 12 | LRET shift (Turn-on) | IS40/IS800 or IS650/IS800 | Hela cell | N/A | [34] |
| NIR                                | Silica   | ZX-NIR | = 66 | Nucleophilic substitution | Em900-1300 | HepG2, HCT-116 cell and tumor-bearing mice | =37 \times 10^{-9} M | [126] |
| PA                                 | Silica   | Si@BODPA180 | = 75 | Nucleophilic substitution | ex780 | HCT-116 bearing mice | 53 \times 10^{-9} M | [38] |
| Liposome                           | AzHD-LP | = 12 | Reduction | ex700 | HCT-116 cells and HCT-116 bearing mice | 91 \times 10^{-9} M | [127] |
| PET                                | ^{64}\textsuperscript{Cu}\textsuperscript{2+} | N/A | Metal precipitation | PET | Mice and Rat | 0.15 \times 10^{-4} M (=1% g\textsuperscript{-1}) | [128] |

\textsuperscript{a}FL: fluorescence; UCL: Upconversion luminescence; NIR: Near infrared; PA: photoacoustic imaging; PET: positron emission tomography.

The novel nanosensors as SHTS for H_{2}S imaging.
finished within 140 s, demonstrating high efficiency for H$_2$S detection. [129] Additionally, this nanoBODIPY probe was able to track endogenous H$_2$S in a macrophage cell line (RAW 264.7) based on the ratio between the dual-color images (Figure 6C,D). [49]

4.2. LSPR Dark-Field Imaging

Plasmonic nanoparticles (PNPs), such as gold nanorods (AuNR), can provide extremely bright signal compared with organic fluorescent dyes. [130,131] By further coating Ag on the AuNR, Xiong et al. successfully applied the gold nanorod-silver (AuNR-Ag) core–shell PNPs for mapping H$_2$S in living cells via dark-field imaging. [41] The AuNR-Ag PNP (74 × 19 nm core and 2.1 nm shell) generated Ag$_2$S and changed its LSPR wavelength when it encountered with H$_2$S (Figure 7A,B). Notably, a linear logarithmic was observed between the spectral shifts and sulfide concentrations (ranging from 0.01 nm to 10.0 × 10$^{-6}$ m) at various time points (1–30 min), indicating extremely high sensitivity. In addition, the AuNR-Ag PNP demonstrated excellent H$_2$S selectivity compared to other inorganic sulfur ions. Using this nano platform, the fluctuations of sulfide (0 × 10$^{-9}$–100 × 10$^{-9}$ m) and real-time H$_2$S mapping/calculation around single AuNR-Ag PNP within live cells (from 5.8 × 10$^{-9}$–4.18 × 10$^{-9}$ m or 0.5 × 10$^{-9}$–3.8 × 10$^{-9}$ m for P1 or P2 respectively) was successfully achieved (Figure 7C–E).

4.3. UCL Imaging

Upconversion nanoparticles (UCNPs) convert continuous-wave (CW) NIR wavelengths to visible light with a sizeable anti-Stokes shift of several hundred nanometers. [132–137] Compared to organic dyes and inorganic semiconductor nanoparticles, UCNPs display superior features, such as scarcely autofluorescence from biological samples, [138] a remarkable light penetration depth (up to 10 mm), [139] no photobleaching in bio-applications, [140,141] and less damage to biological samples than UV excitation source. [142] As a result, UCNPs are ideal probes for visualizing living cells and whole-body animals. [143–145] To achieve a sensing function, UCNPs need to combine with other chromophores with recognition sites, through the luminescence resonance energy transfer (LRET) process. Several UCNPs-chromophores based LRET nanosystems have been developed for detecting critical biological species and toxins, such as DNA, O$_2$, CN$^-$, Hg$_2^{2+}$, and Zn$_2^{2+}$. [146–150] In these applications, the UCNPs (donor) transfer energy to the organic chromophores (acceptor) and results in changes to the UCL emission. Thus, UCNPs-chromophores are excellent candidates for H$_2$S sensing probes.

Since the multicolor luminescence of UCNPs can be tuned by doping different ions, a series of chromophores with different absorption bands could be combined and designed for H$_2$S-specific response. For example, Peng et al. compared three H$_2$S-responsive chromophores combined with different doping ions UCNPs (NaYF$_4$:Yb/Er/Tm, NaYF$_4$:Yb/Er/Mn). This library
of H₂S sensors had responsive emission signals ranging from the visible to the NIR region. These UCNPs-chromophores showed various R RET efficiency (11.8–25.1%), but all exhibited high excellent selectivity and rapid responsiveness in live cells and blood serum. Doping Tm³⁺ into UCNPs introduces UCL signals at 800 nm that can be utilized as an internal standard for ratiometric detection of H₂S to improve sensitivity. As an example, Liu et al. employed NaYF₄:20%Yb,2%Er,0.2%Tm@mSiO₂-merocyanines for ratiometric detection of H₂S using multielement UCL.[151] UCNPs@mSiO₂-MC showed an enhanced ratiometric signal (I₅₄₀/I₈₀₀) for higher sensitivity with LOD at ~0.58 × 10⁻⁶ M, which was lower than that of another merocyanine-based H₂S probe (1.0 × 10⁻⁶ M).[152] Similarly, Zhou et al. used NaYF₄:20%Yb,1.8%Er,0.5%Tm@α-cyclodextrin (CD)-coumarin hemicyanine (CHC1) dye as a ratiometric UCL probe (Figure 8A).[153] By measuring the ratio of I₅₈₀/I₈₀₀, this UCNPs was able to measure H₂S concentrations as low as 0.13 µM, much more sensitive than single UCL signals (1.85 µm) in aqueous solution (Figure 8B). This UCNPs@CD-CHC1 could be used for ratiometric UCL monitoring of pseudo-enzymatic H₂S production in living cells, and also showed for ability to detect lipopolysaccharide (LPS)-induced inflammation in the liver tissues of mouse models for the first time (Figure 8C).

UCNPs have also been developed for detecting or imaging of small molecules, biomacromolecules, organs, and tumors. Li et al. developed a merocyanine derivative modified UCNPs (NaYF₄: 20%Yb, 2%Er, 0.2%Tm@PEG) as a ratiometric UCL probe for H₂S detection in mitochondria of live cells and live-tissues (Figure 9A–C).[154] This probe was used for locating the HCT116 (human colorectal cancer cell line) tumor in vivo by using NIR UCL imaging (Figure 9D–F). Additionally, this system was capable of monitoring mitochondrial H₂S within tumor slices via a ratiometric UCL measurement (Figure 9G).

To monitor H₂S using UCL imaging both ex vivo and in vivo, Wang et al. proposed a PAA-UCNPs (NaYF₄:Yb/Tm@NaYF₄) loaded with a cyanine chromophore (Cy7-Cl) as a NIR probe for H₂S response. (Figure 10A).[155] This nanoprobe was able to emit luminescence at 800 nm (Figure 10B,C) and demonstrated superb sensitivity toward H₂S (Figure 10D,E). In addition to imaging exogenous and endogenous H₂S in living cells (Hela and MCF-7 cells), the Cy7-UCNPs were successfully employed for sensing H₂S in tumor-bearing zebrafish in real time, with high penetration depth and low autofluorescence background (Figure 10F,G). Thus, the UCNPs-chromophores were capable of monitoring H₂S in living cells and small animals by UCL imaging. Ratiometric UCL-based nanosystems provide a new design strategy for sensing and imaging of H₂S that might be further utilized by novel probes for highly sensitive in vivo imaging studies.

4.4. NIR Imaging

Various fluorescent probes have been successfully employed for detection of cellular H₂S. However, most of these fluorescent probes emit in the ultraviolet or visible light region (450–750 nm) that is impeded by cell autofluorescence. In contrast, long wavelength probes with emission in the NIR region are optimal for biological imaging applications due to minimal photodamage to biological samples and interference from background autofluorescence in living systems.[156,157] Additionally, NIR light (700–900 nm) can well improve the...
Figure 8. A) Schematic demonstrating the LRET process between the energy acceptor (CHC1) and energy donor (UCNPs). B) The change of CHC1-UCNPs' UCL emission patterns under a series of H$_2$S concentrations ($0 \times 10^{-6}$–$90 \times 10^{-6}$), and the ratiometric values ($I_{541}/I_{800}$) along with optical image of green UCL emission are presented as inserted figure and photo. C) The UCL imaging of H$_2$S expressed endogenously in mouse liver: a) the in vivo UCL imaging of the mice with inflammatory (for 24 h) after intravenous injection with CHC1-UCNPs; b–d) The UCL images of liver section obtained from the mice injected with PBS and CHC1-UCNPs only; e–g) The UCL images of liver section harvested from the mice administrated with LPS (20 mg kg$^{-1}$) and CHC1-UCNPs; h) The average UCL ratiometric values among different tissues. Images were acquired under an excitation 980 nm, with a green channel around 500–560 nm and red channel at 600–700 nm. Reproduced with permission.[153] Copyright 2014, Wiley.

Figure 9. A) Schematic of the cellular targeting process and mitochondrial H$_2$S detection mediated by the TPAMC-UCNPs@PEG nanoplatform. B) Schematic of the LRET mechanism between UCNPs and TPAMC with or without H$_2$S. C) The chemical structures of TPAMC and TPAMC-SH. D) The UCL imaging obtained from HCT116 tumor-bearing mice post-intravenous administration of TPAMC-UCNPs@PEG. E) The ex vivo UCL images and F) the corresponding fluorescence quantifications of the major organs at 24 h post the TPAMC-UCNPs@PEG injection ($n=3$). G) The two single channels and ratiometric UCL images of the tumor sections from the mice intravenously administrated with TPAMC-UCNPs@PEG and further injected with PBS (top raw) and S-adenosyl-l-methionine (SAM) (button raw). The green (500–560 nm) and red (600–680 nm) signal of UCL were obtained under a 980 nm excitation. Reproduced with permission.[156] Copyright 2018, American Chemical Society.
Figure 10. A) Schematic of luminescent strategy employed by PAA-UCNPs, and the chemical structures of Cy7-Cl and Cy7-SH. B) The luminescence spectra of PAA-UCNPs, Cy7-UCNPs, and Cy7-UCNPs + Na2S (50 × 10−6 M). C) The UV–vis absorption spectra of Cy7-Cl (black) along with Cy7-Cl + Na2S (blue), and the UCNPs’ luminescence spectrum (red). D) The change of luminescence spectra upon the addition of various Na2S concentrations (0 × 10−6–100 × 10−6 M). E) The enhancement of fluorescence ratio accompanied by increasing concentrations of Na2S. F) In vivo UCL images of exogenous and endogenous H2S in zebrafish via the Cy7-UCNPs imaging system: a,b) normal zebrafish were injected with PBS, followed by an administration of Cy7-UCNPs 30 min later; c,d) tumor-bearing zebrafish was administrated with PBS, followed by an injection of Cy7-UCNPs 30 min later; e,f) tumor-bearing zebrafish was first injected with NMM (the scavenger of intracellular H2S), followed by an injection of Cy7-UCNPs 30 min later; g,h) tumor-bearing zebrafish was administrated with L-Cys (the precursor of H2S), followed by the administration of Cy7-UCNPs 30 min later; the length of scale bar is 500 µm. G) The corresponding average UCL intensities of data in (a,c,e,g). Reproduced with permission.[157] Copyright 2018, Elsevier.

4.5. PA Imaging

Among imaging methods that are not fluorescence-based, PA imaging is a newly emerging technique. This modality is based on the PA effect of translation of excitation light into ultrasonic waves, which bridges the traditional depth and resolution limits of conventional optical imaging techniques.[165,166] As the acoustic waves are generated by pulsed laser light, noninvasive biomedical images with sharp optical absorption contrast and high ultrasonic resolution are produced.[167,168] The development of chemical PA probes proposed a new perspective for monitoring therapeutic response and real-time molecular imaging.[169,170] For H2S detection, Shi et al. first presented a PA probe by encapsulating semi-cyanine-BODIPY hybrid dyes into the core–shell silica nanocomposites (Si@BODPA), enabling real-time imaging of H2S-related biological processes (Figure 12A).[171] Based on the thiol-halogen nucleophilic substitution reaction, the Si@BODPA produced emission at 780 nm after the hydrogen sulfide activation, leading to a 44-fold turn-on response within 15 s (Figure 12B,C). The LOD was determined to be as low as 53 × 10−9 M, a sufficient sensitivity for detecting endogenous H2S within living systems. Due to its rapid response, Si@BODPA was then employed for the real-time monitoring of endogenous H2S generation in HCT116 tumor-bearing mouse to verify elevated level of H2S due to CBS upregulation (Figure 12D).

Ratiometric PA probes are able to further eliminate some of the shortcomings of a single responsive PA signal by self-calibration. Thus, the combination of two PA responsive signals at two separated wavelengths would efficiently improve the accuracy of results. For example, Ma et al. developed a ratiometric
photoacoustic nanoprobe AzHD (H$_2$S-responsive NIR dye) that was carried by a liposome for monitoring and imaging of H$_2$S in cells, brain tissues, and live mice. [127] With H$_2$S-mediated reduction of the azide, the AzHD-LP absorption centered at 600 nm gradually decreased, and a new absorption band at 700 nm subsequently appeared (Figure 13A). Through this design, the ratio of PA700/PA532 increased about 4.5-fold after reactive with H$_2$S, which was about 23-fold higher than a single

![Figure 11. A) Schematic of the formation of NIR-II@Si nanoprobe and the chemical structures of components including ZX-NIR and NIRII-HS. B) The variation of NIR-II spectra of as-prepared NIR-II@Si at different time points after the addition of 100 × 10$^{-3}$ μ NaHS, and the NIR-II images of NIR-II@Si after H$_2$S activation (10 mm ZXNIR) in the presence of 100 mm NaHS (inserted photo). C) The NIR-I and NIR-II fluorescent images of the H$_2$S-activated NIR-II@Si covered by pork skin with various thicknesses. The NIR-I and NIR-II imaging of the D) HCT116 tumor, C) HepG2 tumor, and F) normal tissue from tumor-bearing mice or normal mice at different time points (5, 15, and 30 min) after intratumor or on-site injection of NIR-II@Si nanoprobe. E) The NIR-II images of HCT-116 tumor-bearing mice at 5, 15, and 30 min postinjection of NIR-II@Si nanoprobe along with AOAA (amino-oxyacetic acid, the inhibitor) or SAM (S-adenosyl-L-methionine, the activator). Reproduced with permission.[166] Copyright 2018, Wiley.](image)

![Figure 12. A) Schematic of the Si@BODPA nanoprobe. B) The change of absorbance of the Si@BODPA1 along with Si@BODPA2 with and without NaHS (100 × 10$^{-3}$ μ). C) The reaction times among BODPA2-Si@BODPA30 (13 min), BODPA2-Si@BODPA90 (6 min), BODPA1-Si@BODPA30 (5 min), BODPA1-Si@BODPA90 (2 min), BODPA1/2-Si@BODPA180/270 (within 15 s), and H$_2$S (100 × 10$^{-3}$ μ). D) In vivo photoacoustic images of the mice bearing HCT-116 tumor via the subcutaneously-injected BODPA1-Si@BODPA180: a) the tumor regions with saline injection; b) the normal area with nanoprobe injection; c) the tumor regions with nanoprobe administration; d) the tumor area from the pretreated mice (100 nmol AOAA, 12 h in advanced) with nanoprobe administration; e) the tumor area from the pretreated mice (300 nmol SAM, 12 h in advanced) with nanoprobe injection; f) the corresponding PA intensities in a series of time points post BODPA1-Si@BODPA180 injection. Reproduced with permission.[173] Copyright 2017, Royal Society of Chemistry.](image)
PA signal alone (Figure 13B, C). The LOD of ratiometric PA signals was determined to be $91 \times 10^{-9}$ M. This enabled the ratio of PA700/PA532 PA signal of healthy and Alzheimer’s disease (AD) mice brains (homogenate supernatant) to increase by 6.5 and 1.2-fold, respectively, following AzHD-LP introduction (Figure 13D, E). Additionally, further conjugating the RGD targeting group to the AzHD-LP allowed for successful monitoring of H2S in the HCT116 tumor-bearing mice using time-dependent dual-channel ratiometric PA signals (Figure 13F–I). Therefore, the newly designed ratiometric PA probes of H2S sensing system provides a powerful analytical and imaging tool for further exploration of the roles of H2S in living complex organisms.

### 4.6. PET Imaging

Although fluorescence-based imaging techniques are primarily utilized for H2S detection, their applications in live-animal imaging are limited because of the limited quantitative analysis. PET provides a highly sensitive non-invasive technology for molecular imaging assays of metabolism, signal transduction, and gene expression from mice to patients. [172–174] unsurprisingly, targeted and sensitive PET probes have also been developed for H2S over other potential competitors, including polysulfides. Due to the physical differences, the intravenously injected $^{64}$Cu-cyclen and $^{64}$Cu-cyclam were quickly cleared from the body, while the insoluble $^{64}$Cu nanoparticles were immobilized for more than 4 h after encountering H2S (Figure 14B). When $^{64}$Cu-cyclam was administered into mice intravenously, an elevated H2S concentration within the inflamed paw was visualized and quantified by both PET imaging and Cerenkov luminescence (Figure 14C, D). Moreover, the $^{64}$Cu-cyclam could be also used to detect the defect site in the myocardium from an acute myocardial infarction (MI) model (Figure 14E–H). As such, this radioactive probe demonstrated great potential as a powerful nanoplatform providing efficient detection, accurate quantification, and nuclear imaging of H2S within living animals.

### 5. SHTS-Based Nanomedicine for Disease Therapy

Following disease diagnosis, an effective, timely, and in situ treatment is highly demanded. In comparison to imaging agents, smart nanoplatforms could combine imaging, diagnosis, and therapy simultaneously. As highly-expressed H2S within the disease area as a trigger, multifunctional
nanoagents can serve as imaging and therapeutic agents simultaneously. As mentioned previously, the H$_2$S functions as an important biological indicator and also has vital roles in a series of physiological functions, such as factors for protecting or killing cells. However, the application of most H$_2$S donors is restricted by the short half-life and low hydrophilic property. Due to these limitations, several H$_2$S-releasing nanomaterials were developed for various disease therapies. In this following section, these latest nanoagents designed for tumor diagnosis and treatment enabled by endogenous H$_2$S activation will be discussed (Table 4). Additionally, the exogenous H$_2$S delivering nanoplatforms employed for tumor therapy, ischemic/reperfusion protection, and transplanted organ preservation will be summarized.

5.1. Endogenous H$_2$S-Triggered Photodynamic Therapy

Under a specific wavelength (e.g., near-infrared light), photosensitizing agents generate reactive oxygen species (ROS) for treatment of diseases such as bacterial infection or cancers, referred to as photodynamic therapy (PDT). Compared with conventional therapies such as chemotherapy and radiotherapy, PDT is an ideal strategy to treat cancer (i.e., lead the cellular apoptosis and necrosis via the ROS activated) since it is non-invasive, safe, and convenient. However, photosensitizing agents (e.g., porphyrin) typically cannot elicit an antitumor PDT effect due to their physiochemical features (e.g., hydrophobic) nor are able to diagnose cancer. As such, nanomaterial alternatives have arisen as an attempt to effectively implement this therapeutic strategy. As an example, Ma et al. developed a smart, H$_2$S-triggered MOF nanosensor acted as a photosensitizer after exposure to H$_2$S (Figure 15). This novel MOF, (Cu$_2$(ZnTcpp)·H$_2$O)$_n$ (NP-1) was synthesized using a reverse microemulsion system followed by a hydrothermal treatment. NP-1 reacted quickly with H$_2$S within one minute to recover red fluorescence ($\approx$Em$_{610}$ and Em$_{660}$). A linear logarithmic relationship was found for the fluorescence intensity and NaHS concentration (from $10^{-7}$ to $10^{-6}$ M) (Figure 15A,B). As a potential photosensitizer, the NP-1 showed better PDT efficacy than the ZnTCPP precursor (Figure 15C). Specifically, NP-1 ($10 \times 10^{-6}$ M) responded only to laser irradiation (600 nm) to generate...
(Nano-PT) was synthesized via self-assembly of a H2S acti-

vity is strongly required. Recently, an innovative nanoagent
tissues after a laser applied. Therefore, targeting or selective
nanoagent would cause further damage to surrounding normal

However, the temperature of the Nano-PT solution only slightly
° can reach around 55
C after 10 min of irradiation (Figure 16C).

1O2 when H2S (50 × 10−6 m) was present. In comparison, when
not irradiated or H2S was absent, NP-1 was unable to damage to
HepG2 human liver cancer cells (Figure 15C). After intra-
tumoral injection and irradiation, NP-1 was detrimental to the
HCT-116 cells (high H2S levels) and nearly eradicated the entire
tumor (Figure 15D–G). Tumor shrinkage was also observed for
mice injected with ZnTcpp following irradiation, but the therapeu-

tic effect was relatively poor compared with NP-1. The role
of H2S in irradiation-induced damage was confirmed using
HCT-116 cells (Figure 15H). Although this intelligent nanoplat-
form, NP-1 shows significant potential as a H2S-selective pho-
tosensitizing agent for PDT of cancer, further functionalization
using PEGylation to enable the whole body circulation is highly
recommen

5.2. Endogenous H2S-Triggered Photothermal Therapy

As an additional photodynamic treatment, photothermal
therapy (PTT) can damage or kill cancer cells by gener-
ating vibrational energy in the form of heat after elecromag-
netic radiation.[37,182–185] Many nanomaterials, including gold
nanorods and graphene, have been employed as PTT photosen-
sitizers using NIR excitation.[157,186] Nevertheless, the scatted
nanoagent would cause further damage to surrounding normal

was loaded with the H2S donors, anethole dithiolethione
metabolism and has a toxic effect on tumor cells. [4] Exploiting
Low concentrations of H2S are widely known to aid the prolif-

mediated by Nano-PT successfully ablated the HCT-116 tumor
and limited any noticeable damage to the surrounding healthy
tissue (Figure 16F,G).

By intratumorally or subcutaneously administration, these
nanoplatforms are able to treat noticeable tumors with PDT
and PTT. However, these strategies are limited for clinical
applications that often require simultaneous diagnosis and
therapy. To achieve this, Yang’s lab recently designed a H2S
activated nanomaterial, Cu2O (21 nm), for colon cancer
(HCT-116, CBS overexpression) theranostics (Figure 17A).[54]
After encountering endogenous H2S at the tumor site, Cu2O
formed Cu9S8 which absorbed NIR irradiation (808 nm) and
increased the tumor tissue temperature by 20.7 °C. Addition-
ally, the formation of Cu9S8 provided a stable PA imaging
agent that was unaffected by pH variations or GSH. For better
efficiency, SAM (S-adenosyl-L-methionine) or AOAA (ami-
oxoyacetic acid) were administered by intravenous injection as
a CBS activator and inhibitor, respectively. After supplemen-
tation of Cu2O with SAM, increased PA intensity was found
at the tumor site (Figure 17B,C). While PA signal from Cu2O
was detected, it failed to identify the tumor area due to its
relatively lower intensity. Similarly, the CBS activator dramati-
cally enhanced the temperature elevation with SAM + Cu2O
 treatment (15 °C), which was twice that of the Cu2O treated
mice (Figure 17D,E). After two weeks of treatment with
SAM + Cu2O and laser irradiation, HCT-116 tumor-bearing
mice were completely eradicated (Figure 17F–H). In com-
parison, the size of the tumor treated with Cu2O + irradiation
only slightly decreased. Thus, the reported Cu2O nanoparticle
was an intelligent theranostic agent for clinic application after
supplementation with SAM.

5.3. Nanoplatforms as Exogenous H2S Delivery System

Low concentrations of H2S are widely known to aid the prolif-
eration of cancer cells and surrounding vessels.[4,61] However,
sufficient H2S quickly released in tumor tissue affects cellular
metabolism and has a toxic effect on tumor cells.[4] Exploiting
this, Liu et al designed a H2S-generating "nanobomber" for
cancer therapy (Figure 18A).[60] This nanoliposomes (AML)
was loaded with the H2S donors, anethole dithiolethione
(ADT) and magnetic nanoparticles (MNPs), and had a dia-
meter around 200 nm. The ADT could be activated enzymati-
cally to continuously release significant H2S gas, eventually

Table 4. Multifunctional nanoplatforms for SHTS-based imaging and therapy.

| Imaging strategya | Material | Nanoparticles | Size [nm] | Therapeutic mechanism | Administration | Disease | Ref. |
|------------------|---------|--------------|----------|-----------------------|---------------|--------|-----|
| FL               | MOF     | Cu1(ZnTcpp)H2O | 120      | Photodynamic          | Intratumoral  | Colorectal cancer | [55] |
| NIR              | Polymer | Nano-PT      | 8.4–15   | Photothermal          | Subcutaneous  | Colorectal cancer | [175]|
| PA               | Cu      | Cu2O         | 21       | Photothermal          | Intra-vascular| Heart I/R injury | [176]|
| US/MRI           | Liposome| AML          | −200     | Bubble/H2S bomb      | Intra-vascular| Hepatocellular cancer | [56]|
| N/A              | Silica  | DATS-MSN     | −225 ± 35| GSH triggered-release | Intra-vascular| Heart I/R injury | [176]|
|                  |         | DATS-MSN     | −225 ± 35| GSH triggered-release | Intra-vascular| Myocardial I/R Injury | [57]|
|                  |         | DATS-MSN     | 175 ± 35 | GSH triggered-release | Preoperative treatment | CAV | [177]|

aI/R: Ischemic/reperfusion; US: Ultrasound; MRI: Magnetic resonance imaging; CAV: Cardiac allograft vasculopathy; MSN: Mesoporous silica nanoparticles.
forming microsized bubbles (Figure 18B). The H₂S bubbles rapidly occupied most of the intracellular space and caused the apparent morphology changes, which was strongly cytotoxic to HepG2 cells, with more than 40% death after 12 h (Figure 18C). These microbubbles were detected using ultrasonic imaging. After loading with MNPs, the AML accumulated in the tumor area under a magnetic field, which was around 3.4 times of that of Als (without MNPs) at 4 h postinjection (Figure 18D–F). Ultrasonic treatment was then applied to burst the intratumoral microsized bubbles and subsequently induce physical damage and H₂S-induced cytotoxicity to the tumor tissue. The magnetic-guided therapy successfully induced cell apoptosis (with 21.5 ± 7.4%) and suppressed the tumor growth up to 7 days. However, treatment without the magnetic field showed relatively lower therapeutic effect and decreased apoptosis rates (15.4 ± 4.5%) (Figure 18G). In conclusion, this combined imaging system strongly enhanced the targeting accuracy during the treatment will also providing the “H₂S air bomber” for a novel cancer therapy strategy.

Supplementation of H₂S can help preserve organs and protect injuries triggered by ischemia/reperfusion by various antiapoptotic, antiinflammatory and antioxidative methods. However, most H₂S donors cannot produce decent protection due to burst release and poor solubility, such as the NaHS or diallyl sulfide (DATS). Mesoporous silica nanoparticles (MSNs) have arisen as ideal nanoplatforms due to their large surface

---

**Figure 15.** A) The change of fluorescence spectra of NP-1 after incubating with HS⁻ (0 × 10⁻⁶ to 10 × 10⁻⁶ M). B) The linear relationship between the fluorescence intensity of MOF NP-1 and the NaHS’s concentration. C) Confocal images obtained from the HepG2 cells with calcein-AM and PI staining after the following treatments: a) 10 × 10⁻³ M MOF NP-1; b) 10 × 10⁻³ M MOF NP-1 + 50 × 10⁻³ M NaHS; c) 10 × 10⁻³ M MOF NP-1 + irradiation; d) 10 × 10⁻³ M MOF NP-1 + 50 × 10⁻³ M + irradiation. D) Optical images of the nude mice bearing HCT-116 tumor with different treatments (before treatment, upper raw; after treatment, down raw): a) PBS administration; b) PBS injection followed by irradiation; c) ZnTcpp administration followed by irradiation; d) Cu(ZnTcpp) (MOF NP-1) injection; e) Cu(ZnTcpp) injection followed by irradiation. E) The growth inhibition curve of tumor among different treatment groups. F) The body weight of mice from different therapy. G) Optical images of tumors extracted from MOF NP-1 (upper row) and control (down row) groups after irradiation. H) The MTT assay of the HCT116 cells treated with various concentrations of MOF NP-1 with or without irradiation. Reproduced with permission.© 2016, Wiley.
area that can be diversely functionalized, adjustable pore size for loading various cargo (e.g., the hydrophobic drug), and overall biocompatibility.\cite{190,191} Recently, Wang's lab successfully developed DATS-loaded MSNs as a H\(_2\)S-generating platform for protecting organs from I/R injury and transplantation.\cite{57,176,177} These MSN (175–225 nm) efficiently carried DATS at the surface pore (≈2 nm) because of the high affinity between DATS and Si-OH, with an entrapment rate around 99% (Figure 19A).\cite{176} A sustained DATS release profile (reaching about 80 min) was achieved after loaded on MSN and in the presence of GSH in the solution. In turn, the amount of H\(_2\)S released from DATS alone quickly declined after only one hour. The supplementation of DATS-MSN in the preserving solution effectively reduced inflammation in the transplanted organ by downregulating the expression level of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VACM-1).\cite{177} Notably, the DATS-MSN continuously released H\(_2\)S into the plasma for up to 12 h, while NaHS and DATS quickly decreased after one or three hours respectively (Figure 19B).\cite{57} The administration of DATS-MSN reduced myocardial apoptosis by approximately 15% at 24 h post-reperfusion. Additionally, DATS-MSN and substantially decreased I/R injury in myocardial tissues, which was confirmed using TTC staining (percentage of infarction area (INF)/area at risk (AAR)) (Figure 19C,D). More importantly, the DATS-MSN exhibited superior protection of the heart after I/R injury in comparison to GYY4137, a conventional H\(_2\)S donor with slow release kinetics (Figure 19E,F).

Figure 16. A) Schematic of Nano-PT synthesis, the chemical structures of the components, and the transformation of SSS after the presence of H\(_2\)S. B) Schematic illustration of the NIR-II-guided photothermal therapy for colorectal cancer mediated by Nano-PT nanoplatform. C) The temperature curves of PBS, Nano-PT, and Nano-PT + NaHS (100 \times 10^{-6} \text{ M}) under laser irradiation. D) The change of NIR-II fluorescence spectra of Nano-PT during a series of time points (0–15 min) with NaHS (100 \times 10^{-6} \text{ M}), and the NIR-II image of Nano-PT after the H\(_2\)S activation. E) The NIR-II in vivo images of the normal and HCT-116 tumor tissue on nude mice after on-site subcutaneous injection of Nano-PT at different time points. F) The ratios of tumor weight (W\(_{d15}/W_{d0}\)) among tumors collected from different groups (1) Control; 2) Nano-PT; 3) Laser; 4) Nano-PT + Laser) at day 15 and the corresponding photos of representative tumor tissues. G) The optical images of representative mice from different treated groups (1) Control; 2) Nano-PT; 3) Laser; 4) Nano-PT + Laser) at a series of time points; tumor sites has been indicated by red circles. Reproduced with permission.\cite{177} Copyright 2018, Wiley.
Figure 17. A) The characterization of Cu$_2$O and Cu$_9$S$_8$ nanoparticles: a) Schematic of the H$_2$S-induced transformation of Cu$_2$O to Cu$_9$S$_8$; b) XRD patterns of the Cu$_2$O and Cu$_9$S$_8$ nanoparticles; c,d) TEM images of the Cu$_2$O and Cu$_9$S$_8$ nanoparticles; e,f) HR-TEM images of the Cu$_2$O and Cu$_9$S$_8$ nanoparticles; g,h) SAED patterns of the Cu$_2$O and Cu$_9$S$_8$ nanoparticles. B) In vivo PA images of the mice bearing HCT-116 tumor at various time points with different treatments. C) The corresponding PA intensities within the tumors. D) The in vivo thermal imaging of the mice carrying HCT-116 tumor through a period of time after different treatments. E) The corresponding temperature change curve post 5 min irradiation. F) The optical images of representative mice bearing tumor from various therapeutic groups at day 16 posttreatment. G) The growth curve of tumor from different groups from 0 to 16 days. H) The representative tumor tissue harvested at day 16 postdifferent treatments. Reproduced with permission.[54] Copyright 2018, Wiley.

Figure 18. A) Schematic of the combination tumor therapy mediated by the AMLs (anethole dithiolethione (ADT)-loaded magnetic nanoliposome) nanoplatform. B) The optical images of the cellular morphology change and the bubble generated inside at 12 and 24 h after the incubation with AMLs (upper raw), ALs (middle raw), and liposomes (down raw) respectively; the generated bubbles and the serious membrane disruption have been indicated by red arrows. C) The HepG2 cell viability after the incubations with various samples for different time periods; the statistical difference is shown by *p < 0.01 and **p < 0.05. D) The in vivo ultrasonic and E) T2 MR imaging of the HepG2 tumor area at 12 and 24 h post the injections of AMLs (upper raw), ALs (middle raw), and liposomes (down raw). F) The DiR-fluorescence images of a HepG2 bearing mice with the injection of DiR-AMLs under external magnetic field (down raw) or no (upper raw) at 12 and 24 h. G) The TUNEL assay on tumor tissue obtained. Scale bars = 20 µm. Reproduced with permission.[56] Copyright 2017, American Chemical Society.
6. Conclusion and Future Outlook

Undoubtedly, early diagnosis significantly contributes to attaining successful therapeutic interventions. Early diagnosis—especially for cancer—is likely to increase the efficacy of nearly every therapy, ranging from surgery, chemotherapy, radiotherapy to immunotherapy. In addition to screening specific diseases' biomarkers (e.g., tumor surface markers), proper surveillance of the influential gasotransmitters would effectively aid disease diagnosis at early stages. Of these, H$_2$S is vitally important in a series of signaling pathways associated with various physiological (e.g., antiinflammation and antiapoptosis) and pathological effects (e.g., tumor progress, etc.). Additionally, the high toxicity of H$_2$S further emphasizes the importance of monitoring H$_2$S, especially for potential air exposures. Currently, several organic probes have been implemented for detecting/imaging H$_2$S. However, widespread applicability is restricted by their poor physiochemical conditions, including relatively weak sensitivity and limited circulation.

Advanced nanomaterials have demonstrated desirable properties as multifunctional platforms for imaging and therapy. In recent years, nanomaterials have been continually developed as novel probes for H$_2$S-triggered detection, imaging, and therapy (Figure 1). This review summarizes and discusses all SHTS-based nanomedicines to date, focusing on H$_2$S imaging of cancer cells and in tumor-bearing mice as well as for disease therapy (e.g., cancer or I/R injury) (Table 5). More specifically, various H$_2$S imaging approaches using fluorescence, LSPR, UCL, NIR, PA, and PET modalities are summarized. Therapeutic strategies, such as photodynamic and photothermal therapy, influenced by the presences of H$_2$S are also discussed in detail. To provide more ideas for the H$_2$S related treatments, the H$_2$S generated nanoplatforms have been included as well. Undeniably, the development of SHTS-based nanomedicine has seen much progress accelerated by the efforts of researchers. However, there are still several principles and challenges that need to be addressed in future H$_2$S-nanoprobe designs. Below we provide a series of considerations regarding these crucial issues for future SHTS-base nanomedicine innovation and translation (Figure 20).

6.1. Challenge

Due to physiochemical properties, H$_2$S quickly dissolves in water and results in the formation of HS$^-$ and S$^2-$ that introduce interference. Additionally, toxic H$_2$S generated from cells is processed rapidly by anabolism and catabolism. Due to this dynamic nature, real-time imaging of H$_2$S is highly demanded to inform the location/status of disease (e.g., cancer) following therapy. In summary, a specific, sensitive, and multifunctional H$_2$S sensor with excellent circulation (for reaching the specific area) is ideal for H$_2$S detection and therapy.
6.2. Influence of Size, Shape, and Charge

The morphology of nanomaterials, especially size, directly affects the optical features (e.g., LSPR) and contacting area. Both of these aspects are strongly related to the sensitivity toward H2S. Additionally, large nanoparticles (>200 nm) tend to absorb more serum proteins (34% absorbance) compared with smaller ones (80 nm, with 6% absorbance). This results in only smaller nanoparticles having a circulation half-life suitable for imaging.[196] Additionally, the nanomaterials biodistribution is significantly affected by their shape and surface charge. [197–199] For instance, tumor tissue accumulation is enhanced with negatively charged NPs.[198,199] Thus, varying the diameter, shape, and charge alter biodistribution and tumor penetration and subsequently influence the efficiency of imaging and therapy.[200,201]

6.3. Surface Modification

Although the H2S detection (e.g., solution, serum or H2S in the air) can be performed with unmodified nanomaterials, surface modifications (e.g., PEGylation, acetylation, amino acid or ligand/antibody functionalization) greatly increase their stability, biocompatibility, circulation and targeting for in vivo sensing/delivery.[202,203] Other surface modifications of functional groups or material (e.g., Cyclam-Cu2+ or FRET acceptor)[45,122] can impart an alternative strategy that affords a specific nanomaterial (such as Au nanorod with photothermal strategy) with H2S-selectivity.

6.4. Accuracy of Real-Time H2S Concentration

During in vivo imaging, interfering background signal from tissue autofluorescence (e.g., skin) greatly affects H2S visualization. Although most in vivo NIR or PET imaging agents limit the autofluorescence background, the accuracy of H2S detection or imaging would be further influenced by the variation among individuals. As an ideal imaging system, UCNPs can greatly reduce autofluorescence. Additionally, the unique ratiometric strategy applied (i.e., the ratio of specific emission/contro emission) ensure sensing accuracy. Thus, we believe the incorporation of a reference emission using surface modification or reagent loading will increase imaging accuracy during diagnosis and therapy.

6.5. Sensitivity Enhancement for In Vivo Imaging

As mentioned above, the biological half-life of H2S is short. Typically, biological concentrations are generally lower than the LOD of most nanoagents. To improve the detection performance, an enhancement (e.g., SAM) agent is strongly
recommended, especially for H$_2$S-triggered therapeutic nanoplatforms.$[^{54}]$

6.6. Therapeutic Strategy

A series of combined therapies including photodynamic, photothermal, and gas-generated treatments, have been listed in this review. These smart nanoplatforms are all H$_2$S-regulated and mitigate damage to surrounding tissue. However, the potential problems, including the releasing speed and the concentration of H$_2$S generated within a certain area, must be controlled. Meanwhile, additional agents, such as chemical drugs or vaccine adjuvants (e.g., CpG ODN) could be further loaded for combined chemotherapy or immunotherapy after H$_2$S activation.

6.7. Applications and Selection of Nanosensor

Given diverse applications for SHTS-based nanomedicine, proper nanoplatform selection is critical. For the detection of H$_2$S in solution, biosample, and air, the priority of nanosensor selection is the selective, sensitivity, and practicality. For instance, the sensors with a physical supporting (e.g., supporting membrane) or an eye-visible colorimetric examination would be more practical and convenient. Alternatively, biocompatibility and circulation half-life are the key factors for in vivo imaging and therapy. Although great progress has been made in the development of nanomaterials as H$_2$S sensors with high sensitivity and selectivity, only a few can apply in the in vivo assay due to the bad biocompatibility and circulation. Thus, to promote the real application of SHTS based nanomedicine and its following clinic translation, more efforts should be dedicated to investigating these aspects.

In a sharp comparison of general strategies, the advances of nanotechnology enable us to combine various functions into one nanoagent. With SHTS-based nanomedicine, we are able to detect and imaging H$_2$S for different applications, and also induce specific therapy following the diagnosis. The increasing interest in real-time H$_2$S imaging and high performance of SHTS would encourage the further investigation of the following translation in the clinic, which will greatly improve the diagnosis of various H$_2$S diagnosis and benefit the patients via a safe and efficient therapeutic strategy.

Acknowledgements

The authors acknowledge the financial support from the University of Wisconsin-Madison and the National Institutes of Health (P30CA014520).

Conflict of Interest

The authors declare no conflict of interest.

Keywords

- gas delivery
- H$_2$S-specific detection
- H$_2$S-triggered therapy
- hydrogen sulfide
- novel nanoplatforms

Received: July 8, 2019
Revised: September 13, 2019
Published online: October 14, 2019
[195] D. L. Ni, C. A. Ferreira, T. E. Barnhart, V. Quach, B. Yu, D. W. Jiang, W. J. Wei, H. S. Liu, J. W. Engle, P. Hu, W. B. Cai, J. Am. Chem. Soc. 2018, 140, 14971.
[196] F. Alexis, E. Pridgen, L. K. Molnar, O. C. Farokhzad, Mol. Pharmaceutics 2008, 5, 505.
[197] X. Huang, L. Li, T. Liu, N. Hao, H. Liu, D. Chen, F. Tang, ACS Nano 2011, 5, 5390.
[198] C. He, Y. Hu, L. Yin, C. Tang, C. Yin, Biomaterials 2010, 31, 3657.
[199] K. Xiao, Y. Li, J. Luo, J. S. Lee, W. Xiao, A. M. Gonik, R. G. Agarwal, K. S. Lam, Biomaterials 2011, 32, 3435.
[200] Z. Popovic, W. H. Liu, V. P. Chauhan, J. Lee, C. Wong, A. B. Greytak, N. Insin, D. G. Nocera, D. Fukumura, R. K. Jain, M. G. Bawendi, Angew. Chem., Int. Ed. 2010, 49, 8649.
[201] N. Khlebtsov, L. Dykman, Chem. Soc. Rev. 2011, 40, 1647.
[202] Y. Y. Cheng, L. B. Zhao, Y. W. Li, T. W. Xu, Chem. Soc. Rev. 2011, 40, 2673.
[203] A. E. Nel, L. Madler, D. Velegol, T. Xia, E. M. Hoek, P. Somasundaran, F. Klaessig, V. Castranova, M. Thompson, Nat. Mater. 2009, 8, 543.