TOPICAL REVIEW — Magnetism, magnetic materials, and interdisciplinary research

Composite magnetic nanoparticles: Synthesis and cancer-related applications*

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Recent advances in the preparation and applications of composite magnetic nanoparticles are reviewed and summarized, with a focus on cancer-related applications.

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1. Introduction

Magnetic nanoparticles (MNPs) have emerged as important nanomaterials. A myriad of highly magnetic materials, including Fe_3O_4, Fe_2O_3, MnO, FePt, Fe, Co, etc., have been prepared as nanoscale particles, and their applications in catalysis,[1–3] biomedicine,[4–7] imaging,[8–11] data storage,[12] environmental remediation,[13,14] nanofluids,[15,16] optical filters,[17] defect sensors,[18] and cation sensors[19,20] have been investigated. On the basis of these advances, there is an interest in preparing magnetic composite nanoparticles, which comprise multiple nanocomponents. Here we consider the particles with at least one magnetic component. Composite nanoparticles of different shapes, such as dumbbell-, core/shell-, and core/satellite-like architectures, have been prepared. Accompanying the developments in synthesis, a new wave of research seeks to harness the unique physical or surface properties of these composite materials for novel applications, especially in bio-related areas.

Manifold benefits are found in multi-component nanosystems. First, the integration means combined physical properties, which often make possible multiple functions. For instance, it is now possible to synthesize nanoparticles consisting of one iron oxide component and one semiconductor component.[21–26] The resulting nanoparticles, boasting both magnetic and optical properties, have a great potential as probes for fluorescence and MRI dual modality imaging.[27] Second, an additional component may function as a protection shell to improve the colloidal or magnetic stability of the core. This is important because many types of high-magnetism nanoparticles easily oxidize in air, diminishing their magnetism.[28,29] A protective layer that resists oxidation can significantly improve the applicability of these materials. Lastly , composite nanoparticles usually possess more than one type of surface, enabling them to be tethered easily, with multiple functionalities and minimal cross-species interference. For instance, it has been shown by us and others that ligands or therapeutics can be selectively conjugated onto the Au and Fe surface of the Au–Fe_3O_4 nanoparticles to achieve multifunctional nanoplatforms.[30–33] Extensive effort has been applied to exploiting the novel bio-applications of these advanced nanostructures. For such applications, delicate control of the size, composition, and architecture is often critical for the physical, physiochemical, and surface features of the nanosystems. This status spurs widespread efforts to improve the synthesis and surface engineering techniques for composite nanoparticles. These advances, in turn, fuel further developments in composite nanoparticle-based diagnosis and therapy. This review summarizes recent progresses in these areas, focusing on cancer-related applications.

2. Controlled synthesis of composite nanoparticles

2.1. Dumbbell-like nanoparticles

Dumbbell-like nanoparticles (NPs) are composites of two nanocomponents that are arranged head-to-head. One example is Au–Fe_3O_4 nanoparticles, which were first reported by Yu *et al.*, who prepared them using a seed-mediated growth method.[34] Briefly, Au nanoparticle seeds were made and then mixed with $Fe(CO)_5$ in 1-octadecene along with oleic acid and oleylamine. The mixture was heated to reflux ($\sim$ 300 °C) to allow Fe_3O_4 to grow on the top of the Au seeds. The size

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of the Au component could be tuned from 2 nm to 8 nm, and that of the Fe_3O_4 component could be tuned from 4 nm to 20 nm. This synthesis approach has been extended to prepare other types of dumbbell-like nanoparticles, such as Pt-Fe_3O_4,[35] Pd–Fe_3O_4,[36,37] Au–CoO,[37] and Pt–CoO[37] nanoparticles. Later, the Doong group reported a one-step synthesis of dumbbell-like Au–Fe_3O_4 nanoparticles using iron–oleate as the iron precursor, achieving a good size control.[38] For instance, 5 nm/14 nm Au–Fe_3O_4 nanoparticles can be prepared by dissolving 0.5 mmol oleic acid, 0.5 mmol oleylamine, 1 mmol iron–oleate complex $Fe(OL)_3$, and 0.1 mmol Au seeds in 5 mL of 1-octadecene, and heating the mixture to reflux.[39] It is also possible to prepare 10 nm/14 nm Au–Fe_3O_4 via a similar approach, using 0.3 mmol of Au seeds as the gold precursors.[38]

Instead of using metal nanoparticles as the seeds, Gu *et al*. used Fe_3O_4 NPs as the starting nanoseeds to prepare Ag-Fe_3O_4 nanoparticles.[40] In their approach, Fe_3O_4 NPs were prepared and then dissolved in an organic solvent, such as dichlorobenzene, dichloromethane, hexane, and dioctyl ether. On the top of the Fe_3O_4 solution, an aqueous solution of silver nitrate was added, forming a two phase mixture. The subsequent sonication of the mixture resulted in the formation of Ag–Fe_3O_4 NPs at the phase interface. It is believed that, due to imperfect coverage or labile ligand-surface interactions, a few Fe(II) sites are exposed on the Fe_3O_4 nanoparticle surface. They act as catalytic centers that facilitate Ag^+ reduction and Ag nanoparticle formation on the Fe_3O_4 surface.

Metal oxide nanoparticles can also grow on the surface of Fe_3O_4 to form composite nanostructures. For instance, Geun *et al.* reported the synthesis of MnO–Fe_3O_4 NPs using Fe_3O_4 NPs as the seeds.[41] Interestingly, the size of the Fe_3O_4 seeds has a strong influence on the shape of the resulting composite nanoparticles. When using Fe_3O_4 seeds of relatively small size (e.g., 5 nm), the synthesis yields core/shell-like nanostructures. Increasing the seed size to 11 nm yields dumbbell-like Fe_3O_4/MnO nanoparticles, and increasing further to 21 nm results in flower-like products. While the Fe_3O_4 nanoparticles are commonly used as T_2 contrast agents, MnO is a paramagnetic material that can efficiently shorten the T_1 relaxation time. Hence, the resulting composite nanoparticles can potentially be used as MRI contrast probes for both T_1- and T_2-weighted imagings.

Hao *et al.* discussed the growth mechanism of dumbbell nanoparticles.[42] As mentioned above, dumbbell NPs can be obtained by the sequential growth of a second component on pre-formed NP seeds. This process relies on promoting limited heterogeneous nucleation on the seeds while suppressing nucleation in the solution. This can be achieved by fine tuning the seed-to-precursor ratio and/or controlling the heating profiles so that the concentration of the precursor remains below the homogeneous nucleation threshold throughout the synthesis. Taking the Au–Fe_3O_4 synthesis as an example, the size of the Fe_3O_4 component is tuned by adjusting the $Fe(CO)_5$/Au ratio. Krylova *et al.* proposed a similar growth model that explained the formation of $CoPt_3$/Au, FePt/Au, and Pt/Au nanodumbbells.[43]

Very recently, Liakakos *et al.* reported the wet chemistry synthesis of Co–Fe composite nanoparticles using a Co nanorod as a seed upon which an iron nanocomponent was grown.[44] The Fe:Co ratio could be adjusted from 1:1 to 12:1 by varying the amount of the Fe precursor (Fig. 1). Interestingly, the mean length of the resulting nanorods was shorter than that of the initial Co seeds, indicating either rod consumption during the Fe growth or its fusion into Fe at the interface. The reason that the growth starts from the tips of the nanorods is probably due to the fact that the termini are less covered by stabilizing ligands and are, therefore, more reactive. A similar growth pattern was also observed with Au–Co heterodimer nanostructures.[45]

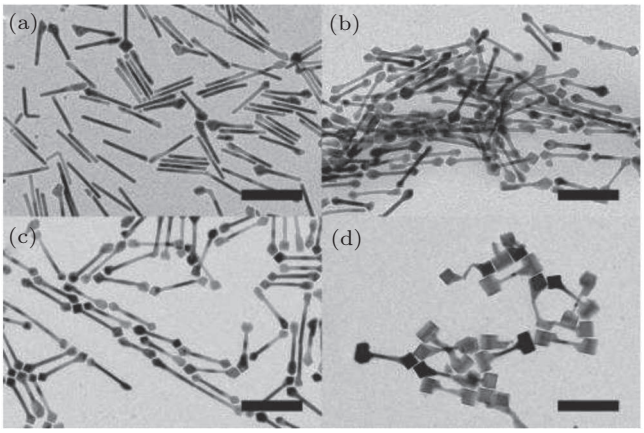


Fig. 1. Co–Fe nanoparticles obtained by tuning the ratio between the iron precursor and the Co nanorod seeds: (a) Fe/Co = 1, (b) Fe/Co = 2, (c) Fe/Co = 4, (d) Fe/Co = 6 (scale bar = 100 nm).[44]

2.2. Core@shell nanoparticles

Core@shell-like nanoparticles comprising at least one magnetic component have also been widely studied, usually with the core being magnetic. Noble metals (Au[46–51] and Pt[52–54]), metal oxides (sulfide) ($Cu_{2-x}S$[27] and TiO_2[55–57]), SiO_2,[58–60] carbon,[61,62] etc. have all been investigated as shell materials that can protect the cores from either oxidation or aggregation.

2.2.1. Gold shell

Due to inertness and unique optical properties, gold is regarded as an excellent material to coat magnetic nanoparticles. Early on, Xu *et al.* reported a convenient means of synthesizing core@shell structured Fe_3O_4/Au by reducing $HAuCl_4$ on the surface of Fe_3O_4 nanoparticle seeds.[47] More recently, Song *et al.* developed a sequential microfluidic process for the

synthesis of Co@Au core@shell NPs, where the shell thickness could be tuned by repeating the Au deposition process (Fig. 2).[63] However, despite the successes, it remains difficult to directly impart one gold shell onto a magnetic nanoparticle.

Recently, the Gao group reported a different, multi-step approach to achieve gold coating. Before adding gold precursors, they first imparted a layer of dielectric polymer, such as phospholipid-polyethylene glycol terminated with carboxylic acid (PL-PEG-COOH) and poly-L-histidine (PLH), onto Fe_3O_4 NPs (Fig. 3).[64] The polymer layer promoted the adsorption of gold precursors onto the particle's surface, facilitating the formation of a gold shell. A similar approach has been used to coat silica onto magnetic nanoparticles prior to gold coating.[65] In that method, the coagulation of tetraethyl orthosilicate (TEOS) at an early stage imparted a silica shell onto Co nanoparticles. This was followed by the adsorption of $\sim$ 2–3 nm gold nanoparticles onto the silica shell. The subsequent reduction of $HAuCl_4$ filled the gaps among the gold seeds to form a relatively homogenous gold shell.

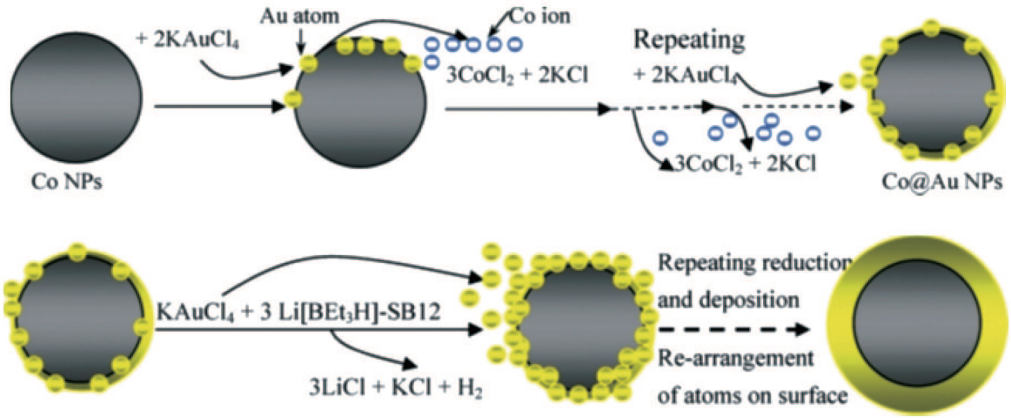


Fig. 2. Co@Au NPs made by a displacement method, where the shell thickness can be tuned by repeating the reduction–deposition process.[63]

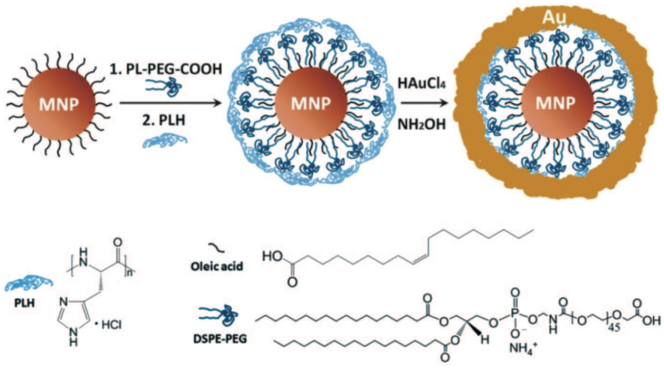


Fig. 3. Key steps in hybrid NP synthesis. Magnetic NPs coated with oleic acids are first solubilized using amphiphilic PL-PEG-COOH. PLH, which is capable of chelating metal ions, is then adsorbed onto the PL-PEG-COOH layer by electrostatic interaction. After the addition of gold ions and a reducing reagent, thin gold shells form on the polypeptide template.[64]

2.2.2. Cu_2S shell

Photothermal nanoparticles have been shown to have potential for cancer therapy applications. While gold-based nanostructures have been the focus of research in this area, copper-containing semiconductor nanocrystals have also attracted much attention recently, given their favorable production cost, stability, nontoxicity, and photothermal conversion efficiency. Shells of these semiconductor materials have been successfully formed around magnetic nanoparticles to obtain particles with dual functions. For instance, Liu *et al.* reported the preparation of Fe_3O_4@$Cu_{2-x}S$ core@shell NPs.[27] These were obtained by first adding an excess amount of sulfur to a Fe_3O_4 solution to yield Fe_3O_4@S core@shell NPs (Fig. 4). The sulfur-coated Fe_3O_4 were subsequently treated with copper(II) acetylacetonate in a mixed solution of oleylamine and chloroform, forming Fe_3O_4@$Cu_{2-x}S$ core@shell nanoparticles.

2.2.3. Carbon shell

Non-metallic materials, such as carbon, can also be used to coat magnetic nanoparticles. For instance, Sharma *et al.* reported the synthesis of Co@C nanoparticles.[66] Li *et al.* reported the preparation of Ni@C core@shell nanoparticles, where a nickel core was surrounded by a 10-nm-thick nitrogen enriched carbon shell.[67] More recently, Sunny *et al.* obtained face centered, cubic nickel NPs with 5-nm-thick carbon layers at relatively low reaction temperatures.[68] The Dai group reported a scalable chemical vapor deposition method to synthesize FeCo@C nanocrystals.[69] Dong *et al.* prepared FeCo@C and FeNi@C nanocapsules by arc discharge in methane.[70–72] Gedanken *et al.* synthesized air-stable FeCo@C alloy NPs via a one-step thermal decomposition process.[73] Yang *et al.* reported the preparation of carbon-coated FeCo alloy NPs with different Co:Fe ratios using a solid-state route with melamine as the carbon source.[74]

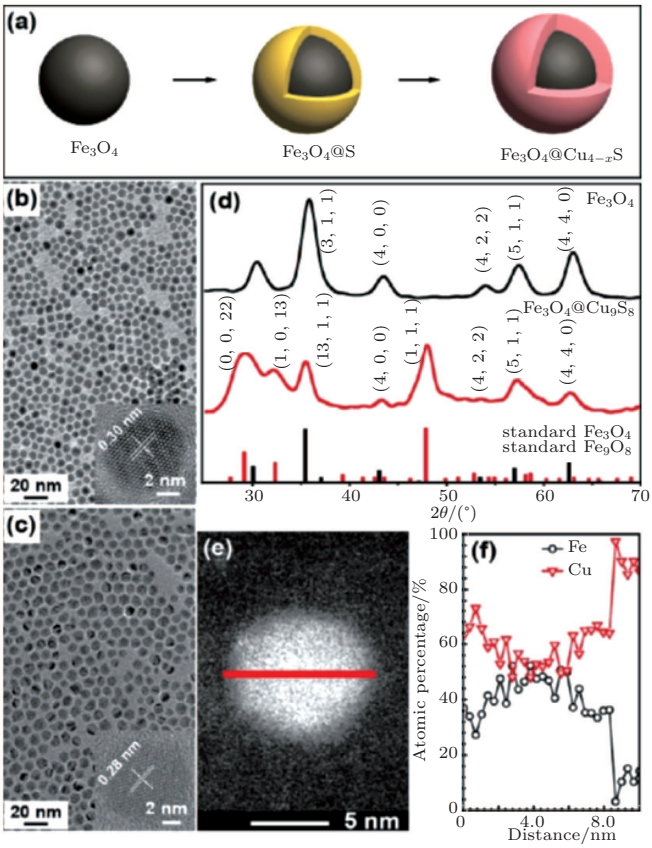


Fig. 4. (a) Schematic diagram of the formation of Fe_3O_4@$Cu_{2-x}S$ core@shell nanostructures. (b) and (c) TEM images of the as-synthesized Fe_3O_4 and Fe_3O_4@$Cu_{2-x}S$ NPs, with corresponding high resolution images in the insets. (d) Powder X-ray diffraction patterns of Fe_3O_4 and Fe_3O_4@$Cu_{2-x}S$ NPs. (e) STEM image of a single Fe_3O_4@$Cu_{2-x}S$ core@shell NP. (f) Corresponding EDX line scan profiles of the core@shell nanoparticle, showing a higher Cu concentration in the peripheral region of the crystal.[27]

2.2.4. Iron oxide shell

Iron oxides can also be coated onto various types of NPs. For instance, Sun *et al.* reported the synthesis of bi-magnetic core@shell $Fe_{58}Pt_{42}$@Fe_3O_4 NPs using a thermal decomposition method.[53] Shavel *et al.* reported that Fe@Fe_3O_4 core@shell NPs can be synthesized by simple thermal decomposition of iron oleate.[75] In a separate study, Fe@Fe_3O_4 core@shell particles were prepared as part of a composite with graphene.[76] More recently, Mahmoud *et al.* reported a two-step synthesis of Fe@Fe_3O_4 core@shell nanocubes (Fig. 5).[77] First, $FeCl_3$ was reduced by $NaBH_4$ in an ethylene glycol solution, with the presence of 2-mercaptopropionic acid (surfactant) and trisodium citrate (cosurfactant). Next, the surfaces of the resulting particles were oxidized with trimethylamine N-oxide, forming a core@shell structure. These nanocubes are promising contrast agents for MRI. Similar approaches have been developed to prepare other core@shell NPs. For instance, Knappett *et al.* reported the synthesis of Co@Fe_3O_4 NPs.[78] Teng *et al.* prepared Pt@Fe_2O_3 NPs by the sequential decomposition of $Pt(acac)_2$ and $Fe(CO)_5$.[79]

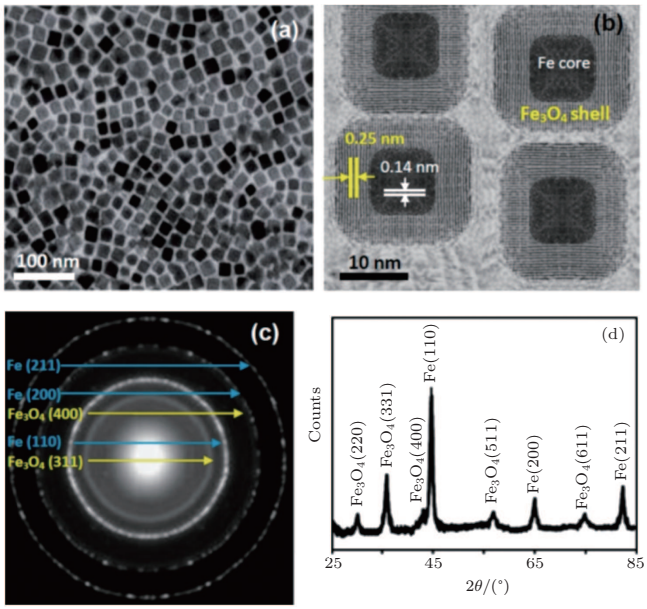


Fig. 5. (a) TEM and (b) HRTEM images of Fe@Fe_3O_4 nanocubes. (c) SAED and (d) XRD analyses of Fe@Fe_3O_4 nanocubes.[77]

2.3. Core/satellite- or flower-like NPs

Another type of nanostructure that is common for composite magnetic nanoparticles is the core/satellite- or flower-like shape. These particles often feature a relatively large core that is surrounded with multiple small nanosatellites. For instance, Cheon *et al.* fabricated core/satellite nanoparticles comprising a dye-doped silica core and multiple Fe_3O_4 NP satellites.[80] These particles can be used for optical and MR dual-modality imaging. Hyeon *et al.* also reported SiO_2/Fe_3O_4 core/satellite nanostructures which embrace multiple 7-nm Fe_3O_4 decorated on the surface of a 100-nm silica sphere.[81] The same group later used mesoporous silica NPs as the core to prepare SiO_2/Fe_3O_4 NPs.[82] The resulting nanoparticles, affording both high drug loading capacity (due to the mesoporous silica) and strong magnetism (due to multiple Fe_3O_4 satellites), have potential as a theranostic agent for MRI and drug delivery. Zhang *et al.* synthesized Fe_3O_4/Au core/satellite NPs using polydopamine as a glue to link the two nanocomponents.[83] Fang *et al.* synthesized Fe_3O_4/SiO_2/Au nanoparticles, this time adsorbing polydopamine on the silica shell to immobilize the gold satellites.[84]

3. Applications

MRI is one of the most important diagnostic tools in the clinic, and magnetic NPs of different forms have been widely investigated as the contrast agents for MRI. These include NPs of high magnetism that can be used to shorten the T_2 relaxation time. Also, paramagnetic NPs such as MnO can enhance signals on T_1-weighted MR maps. Composite magnetic NPs comprising both types of nanocomponents can thus perform as dual-function probes. For instance, Lee *et al.* reported

that Fe_3O_4/MnO nanocrystals of core@shell-, dumbbell-, and flower-like structures can induce both hypointensities on T_2-weighted MR images and hyperintensities on T_1-weighted images due to the release of Mn^{2+}.[41] Bae *et al.* developed carbon-coated iron oxide core@shell NPs, which can also be used as T_1 and T_2 dual functional contrast agents.[85]

Meanwhile, composite NPs, comprising both magnetic and optical properties, can be used as dual-mode imaging probes. For instance, Cheon *et al.* prepared SiO_2/Fe_3O_4 core/satellite NPs consisting of a dye-imbedded SiO_2 core and multiple Fe_3O_4 satellites. These NPs have proven to be effective for both MRI and fluorescence imagings (Fig. 6).[80] Cheng *et al.* reported a layer-by-layer (LBL) assembly approach to synthesize multifunctional NPs comprising an upconversion nanoparticle (UCNP) core, a layer of ultrasmall iron oxide nanoparticles (IONPs) as the intermediate shell, and a thin layer of gold as the outer shell. These nanoparticles can be used for stem cell tracking, enabling the cell movement to be regulated by an external magnetic field while being monitored by both MRI and upconversion luminescence imagings.[86] Very recently, Tian *et al.* reported the synthesis of $NaGdF_4$:Yb/Er@$NaGdF_4$ core@shell UCNPs, which can function as tri-modality imaging probes for upconversion luminescence (UCL), MRI, and X-ray computed tomography (CT).[87]

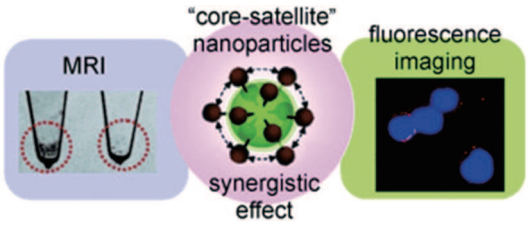


Fig. 6. Dual-mode nanoparticle probes for high-performance magnetic resonance and fluorescence imaging of a "core-satellite" hybrid nanoparticle probe.[80]

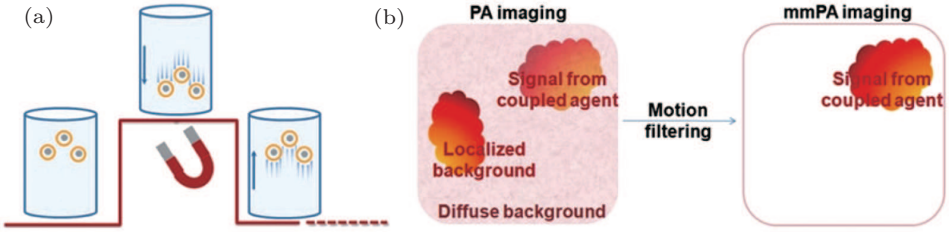


Fig. 7. (a) Schematic diagram of MNP-gold core-shell NPs' response to a magnetic field. The underlying red curve represents the field strength. The coupled agents move as the magnetic field is turned on and off. (b) Schematic diagram of contrast enhancement in mmPA imaging; mmPA imaging suppresses the regions not susceptible to a controlled magnetic field while identifying the regions with coupled agents responsive to a magnetic field.[64]

Composite NPs may also perform as theranostic agents that permit simultaneous diagnosis and therapy. For instance, gold nanoshells are highly absorptive in the near-infrared (NIR) region, a property that can be harnessed for either photoacoustic (PA) imaging or photothermal (PT) therapy. Gao *et al.* prepared iron oxide/gold core/shell NPs and demonstrated that the particles are promising dual-mode probes for simultaneous PA and MR imagings (Fig. 7).[64] Similarly, Tian *et al.* reported that Fe_3O_4@$Cu_{2-x}S$ nanoparticles can serve as T_2 contrast probes while also mediating the energy conversion for photothermal therapy.[27]

4. Summary and perspective

Overall, many synthetic approaches to preparing composite magnetic NPs of different architectures have been developed. The NPs have shown a great potential as multifunctional imaging probes or theranostic reagents. Despite the progress, further investigations are needed to enable the fine tuning of composite NPs in order to achieve desired architectures, compositions, and orientations and, furthermore, to take advantage of the resulting advances to engineer materials for various bioapplications.

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