Chapter 13

Functional Inorganic Nanohybrids for Biomedical Diagnosis

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55266

1. Introduction

Functional hybrid inorganic nanomaterials have received substantial attention for their promising performance in nanotechnological applications.[1] A combination of more than one nanocomponent into a hybrid structure gives rise to new collective properties different from the constituents.[1] The hybrid nanostructures not only have multifunctional properties, but also may induce synergistic properties, arising from interfacial particle-particle interactions.[2] Coupling of two or more components produces a hybrid nanostructure that allows electronic transfer across the junction to change local electronic structure. The engineering chemical reactivity on the particle surface is thus dependent on the internal and external interfacing capacilities and the particle size distribution of the deposited particles onto the nanosupports.[1, 3] These behaviours make them to generally have potential applications in solar energy conversion, catalysis, and potential biomedical methods for drug delivery, bioimaging, and cancer theragnosis.[4-6]

The morphology of the hybrid nanostructures impacts a critical factor affecting their active performance.[7] The shape-controlled synthesis of these materials have been made in recent years. This objective could be performed by conducting heterogeneous nucleation-growth kinetics during the synthesis. Wet-chemistry methods, such as seed-mediated growth, ion-exchange deposition, thermal decomposition, hydro-solvothermal process used to synthesize single nanoparticles have been extended to the hybrid nanostructures. The nanohybrids with specific shapes (e.g., dumbbell and core-shell) formed by sequential growth of second components onto the preformed seeds through directed attachment. The hybrid structures formed during heterogeneous growth are dependent on organic linkers used and lattice parameters of each components, which is relative to the electron transferred capacity at the particle-particle interfaces. A combination of synthetic control along with

understanding of the interfacial interactions is therefore a significant basis for the fabrication of the multifunctional hybrid nanomaterials.

The functional inorganic hybrid nanomaterials with combined plasmonic-magnetic, plasmonic-fluorescent, or magnetic-fluorescent structures have unique optoelectronic properties for biomedical applications.[5, 8-10] The optical, electronic, magnetic properties could be controlled by adjusting their sizes, shapes, compositions, and surface chemistry. Several types of the hybrid nanostructures are potentially useful for biomedical applications.[5, 8] For example, the plasmonic-fluorescent materials would be interesting as dual-use biological tags, giving the ability to visualize labeled cells using both magnetic resonance and fluorescence imaging techniques, while external magnetic fields could be employed for the directed assembly of such materials.[11] In order to be compatible with biomedical environment, the surface of the nanohybrids is functionalized with appropriate amphiphilic polymer, silica, targeting ligand through chemisorption, covalent linkage, and ligand exchange.[12] After surface modification, the coated hybrid nanoparticles have the possibility of highly colloidal stabilization in aqueous media compatible with bioconjugation.[13] The delivery of the hybrid nanoparticles to targeted cells is an important and challenging approach in medical diagnosis and therapy. Development of biomolecule-conjugated strategies allows the hybrid nanoparticles delivering to targeted tissues through either antibody-antigen or ligand-receptor interactions.[12] Biomolecules, such as small molecules (vitamin, peptide, lipid, sugar) and larger ones (protein, DNA, antibody, enzyme, carbohydrate), are often used to conjugate onto the hybrid particles. Biomolecule-conjugated nanohybrid colloids have the possibility of highly selective binding with alive organ made them to be “biocompatible” behaviour and superior bioactivity at the supermolecular level.[5, 14, 15] These features have potentially applied in smart drug delivery vehicles, contrast agents, and theranostic biomedical applications.

This Chapter reviews the design, fabrication, and theranostic biomedical applications of the inorganic hybrid nanomaterials with combined plasmonic-magnetic, plasmonic-fluorescent, or magnetic-fluorescent structures. New collected properties of the hybrid nanostructures arising from the particle-particle interactions and the geometries are discussed from specific results of recent publications. The functionalizations of the hybrid nanostructures with amphiphilic polymer and silica coatings yielded water-soluble nanohybrid colloids are described. The subsequent conjugation of biomolecules with the coated nanohybrids afforded cellular targeting agents and the use of them as multimodal bioprobes for multimodal imaging and therapy are highlighted.

2. Seed-mediated growth toward hybrid nanostructures

Wet-chemically seed-mediated growth provides an effective method for the synthesis of the hybrid nanoparticles with well-controlled structures, where the secondary species attach and sequentially grow on the preformed seeds. To ensure the deposited species well-dispersed on the supports, heterogeneous nucleation and growth through atomic addition must be achieved and homogeneous nucleation should be avoided. Significant progress has

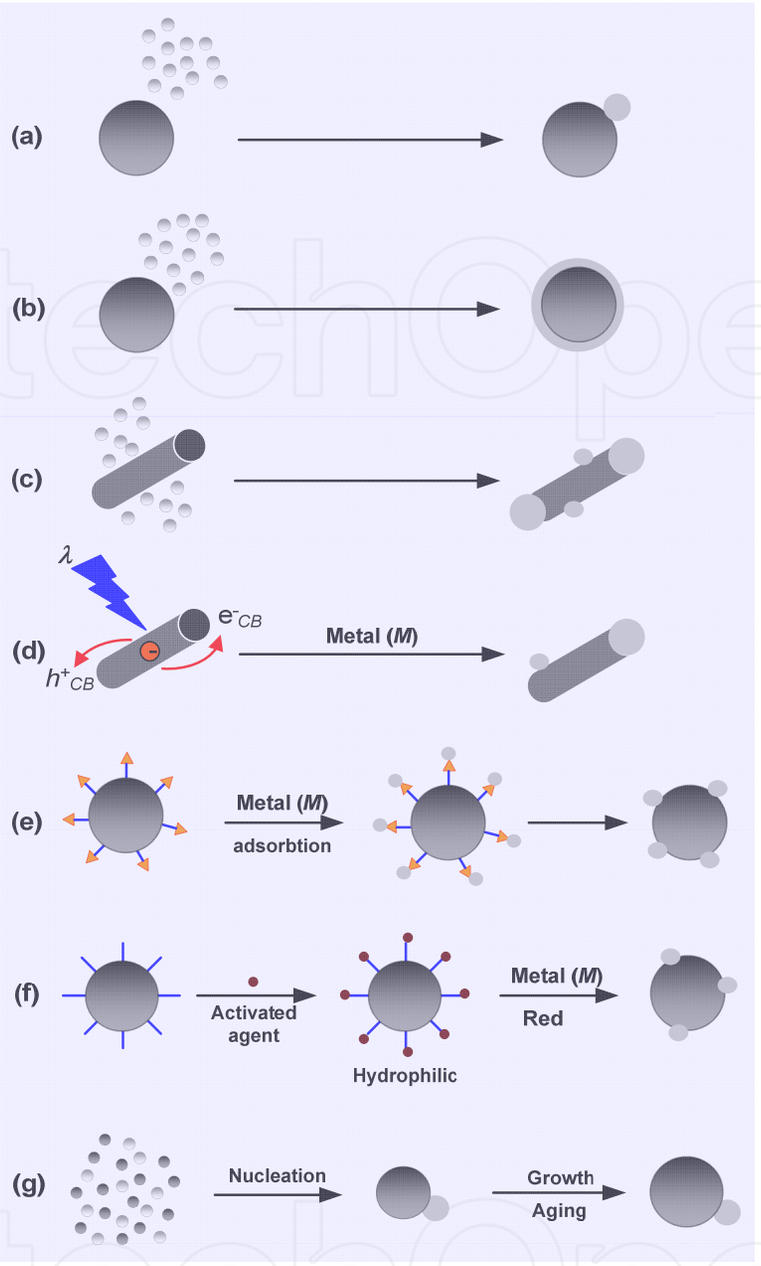

Figure 1. A general sketch of reaction mechanisms for the formation of the hybrid nanostructures: (a-c) Heterogeneous nucleation and growth of secondary precursors on the preformed seeds; (d) Secondary precursors adsorbed on the opposite charged surfaced supports by photo-irradiation; (e) Reduced precipitation of secondary precursors on hydrophilic-surfaced supports; (f) Secondary precursor growth on the activated-surfaced supports; (g) One-pot self-controlled nucleation-growth.

been achieved in the synthesis of the core-shell and dumbbell nanoparticles combining two different components. When the individual components involved have similar crystal structures and lattice parameters, each component fuses together giving the dumbbell shape. In a dumbbell structure consisted of one particle-bounded another, charged transfer across nanoscale junction could significantly change local electronic configuration that give the remarkable properties. While large lattice space difference of the individual components

results in the core shell-shaped structure obtained by growing a uniform layer of a shell material around colloidal particles. An isolation of core from surroundings could create the specific materials with emerged properties to those of the bare nanoparticles.[16, 17]

The colloidal nanohybrids are generated upon reaction of molecular precursors in solution in the presence of surfactants. Once the synthesis is activated at a suitable temperature, monomers are generated, and then induced nucleation of nanoparticles and sustain their subsequent enlargement. The organic surfactants play key roles along the courses of the hybrid formation. **Figure 1** shows general growth models for the fabrication of dumbbell- and core shell-shaped hybrid nanostructures, that can be classified into the synthetic routes: (i) the direct heterogeneous growth of secondary precursors on the sites or tips of the preformed seeds (Figure 1 a-c); (ii) metal clusters adsorbed on the opposite-charged surface of the supports by photo-irradiation (Figure 1d); (iii) reduced precipitation of secondary precursors adsorbed on the hydrophilic-surfaced nanohybrids through ion-exchange deposition (Figure 1e); (iv) secondary precursor growth on the support surface after the chemical activation of their surface (Figure 1f); (v) one-pot growth of secondary precursors on the supports through self-assembled control (Figure 1g). Following these pathways, a large variety of the nanohybrids including metal-metal, metal-oxide, oxide-oxide, metal-semiconductor structures has been synthesized successively. In the following sections, we present types of the plasmonic-magnetic, plasmonic-fluorescent, and magnetic-fluorescent hybrid nanomaterials synthesized using seed-mediated growth methods along functionalization and subsequent bioconjugation of the hybrid nanostructures for biomedical applications.

2.1. Synthesis of plasmonic-magnetic hybrid nanostructures

Plasmonic-magnetic nanohybrids provide a promising platform for developing optical and magnetic multifunctional probes for cell imaging applications. Materials researchers have recently been efforted to synthesize the hybrid nanostructures. Alivisatos et al.[18] synthesized gold-iron oxide core-shells via thermolysis of $Fe(CO)_5$ at the surface of gold nanoparticles in octadecene/oleylamine/oleic acid. These hybrid nanostructures were formed by deposition of an iron shell around the gold core and subsequent oxidation of the metallic iron shell to form an iron oxide hollow through Kirkendall effect. The heterogeneous growth of iron precursors on the gold seeds was dependent on the molar ratio of oleylamine/oleic acid capping agents. The thinnest oxide shell (~2 nm) surrounded the gold nanoparticles was formed at oleylamine/oleic acid ratio of 1:1. Irregular polycrystalline iron oxide shells connected with the gold core were formed in the presence of oleylamine without oleic acid. With increasing the oleic acid concentration led to the iron nucleation and growth to be slowed because of the formation of stable iron oleate complex in high-temperature reaction. The gold-iron oxide core-shells exhibited the surface plasmon resonance shift of the gold particles and the magnetic hysteresis loop shift of the iron oxide particles, originating from the core-shells with particle-particle interactions. Sun et al.[19] synthesized Au-Fe_3O_4 dumbbells via thermolysis of $Fe(CO)_5$ on Au particles and subsequent

oxidation in 1-octadecene. The sizes (~2-8 nm) of Au particles were controlled either by tailoring $HAuCl_4$/oleylamine molar ratio or by controlling temperature at which $HAuCl_4$ precursors was injected. The sizes (~4-20 nm) of Fe_3O_4 particles were tuned by adjusting the $Fe(CO)_5$/Au ratio. Hyeon el al.[20] synthesized metal/oxide core-shells (Au-Fe_3O_4, Ni- Fe_3O_4, Au-MnO, Pt-Fe_3O_4) through thermolysis of the mixtures of transition metal-oleate (Fe, Mn) complexes and metal-oleylamine (Au, Ag, Pt, Ni) complexes in oleylamine/octadecene. These complexes were prepared from transfer-phase reaction of the inexpensive metal salts and surfactants. Due to the high solubility of the prepared complex precursors in 1-octadecene solvent, this method was able to large-scale synthesis of the well-shaped nanohybrids per a singe preparation. The Au-Fe_3O_4 particles became soluble in water by encapsulating their surface with a PEG-phospholipid shell. The amino-functionalized Au-Fe_3O_4 nanohybrids conjugated with thiolated oligonucleotide sequences exhibited the red shift of the surface plasmon resonance of the gold particles and the enhanced signal intensity of the Fe_3O_4 particles in T_2-weighted magnetic resonance imaging. These conjugated hybrid nanostructures have potential in multimodal biomedical probes.

Figure 2 shows plasmonic-magnetic Au-Co core-shell and Au-Ni spindly nanostructures synthesized by Li et al.[21] through one-pot solvothermal reaction of $HAuCl_4$ and metal

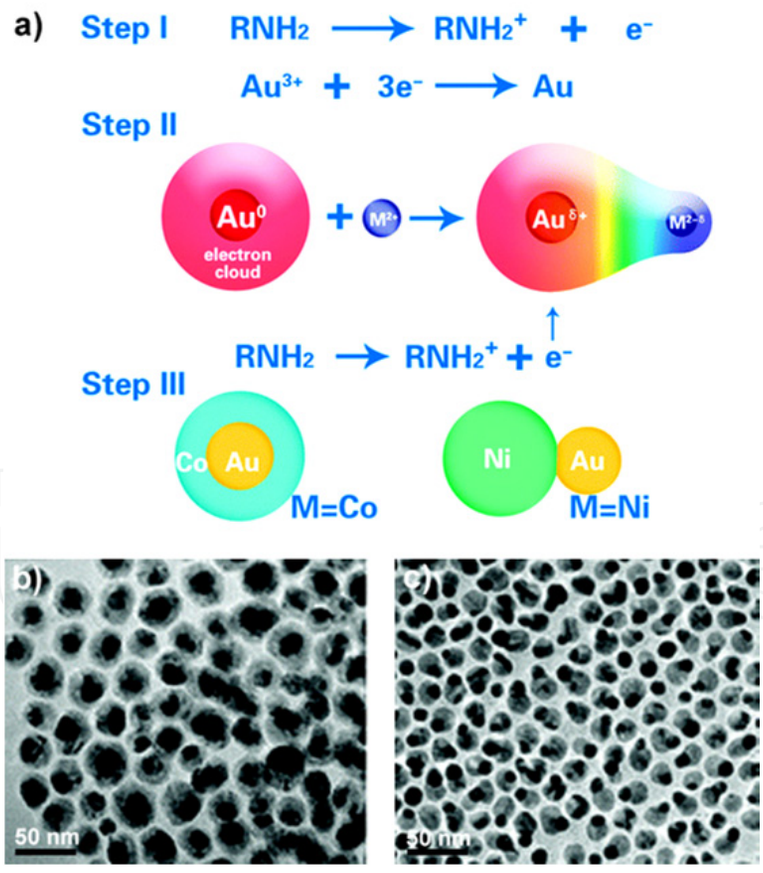

Figure 2. One-pot protocol for plasmonic-magnetic hybrid nanostructures via noble-metal-induced reduction process. (a) Schematic illustration of the noble-metal-induced reduction process. TEM images of Au-Co core-shell (b) and Au-Ni spindly nanostructures (c). Reproduced with permission from ref. [21]. Copyright 2010, American Chemical Society.

nitrate ($Co(NO_3)_2 \cdot 6H_2O$ or $Ni(NO_3)_2 \cdot 6H_2O$) in octadecylamine used as both solvent and surfactant. The formation of the hybrid structures was illustrated by metal-induced reduction process namely, octadecylamine-supplied electron cloud surrounded Au atoms reduced transition metal ions to form the nanohybrids. The strong magnetism of the plasmonic-magnetic nanohybrids and the CO superior catalytic activity of the Au-Co core-shells were showed as a result of incorporating magnetic heterometals into gold particles. The authors [22] also synthesized bifunctional Au-Fe_3O_4 nanohybrids through the conjugation of Au particles to thiol-modified Fe_3O_4 nanoparticles. Lysine contained both amino and carboxylic groups played dual roles as both linker and capping agent in attaching metals on Fe_2O_3 particles. The hybrid nanostructures can be used for magnetic separation of biosubstances and for protein separation. The authors [27] also synthesized hexagonal pyramid-like shaped Au-ZnO nanohybrids based on the growth of ZnO particles derived from a mixture of zinc acetate/oleylamine/dodecanol on Au seeds. The nanopyramids composed of Au particles as the tip and hexagonal ZnO pyramid as the tail. The Au-ZnO hybrid nanopyramids with homogeneous composition and controlled morphology showed better photocatalytic efficiency than ZnO nanocrystals.

2.2. Synthesis of plasmonic-fluorescent and fluorescent-magnetic hybrid nanostructures

Plasmonic-fluorescent hybrid nanostructures have seen a renewed interest in photocatalytic degradation of organic contaminants and photocatalytic water splitting.[4] Banin et al.[1, 3] synthesized various classes of these materials via photodeposition of metals on semiconductors. Au/CdSe/CdS hybrid nanorods were synthesized through growing Au precursors on the reactive facets exposed tips of the seeded rods.[23] Under UV excitation, large Au domains were exclusively deposited at one end of the seeded CdSe/CdS rod because of electron migration to one of the reactive facets of the tips. The strong Au-Se coordination allowed Au precursors at high concentration to grow further on the side facets of the seeds. Au-CdSe pyramids were obtained by growth and reductive transformation of a gold shell around a CdSe pyramid under electron beam irradiation. The deposition of the Au clusters along the anisotropic semiconductors was strongly influenced by reaction temperature and ligand-mediated defect sites. Decreasing the amount of surfactant allowed the Au tips to interact and coalesce, forming disordered networks of the fused hybrid nanostructures. The selective growth of the Au precursors on the tips of the CdSe rod, tetrapod, pyramid exhibited a significant modification of the optical property compared to the corresponding singe components.

Figure 3 shows Au-CdSe rod- and pyramid-shaped hybrids synthesized by Klinke et al.[24] via growth and reductive transformation of the Au shell around the pyramidal CdSe nanocrystals in the presence of chlorine under either electron beam irradiation or addition of reducing agent. The size of the deposited Au dots can be tuned from 1.4 to 3.9 nm by varying the synthesis conditions, such as ligands and shape of the CdSe. The shape rod and pyramid were thermodynamically favored for the size-controlled growth of Au precursors

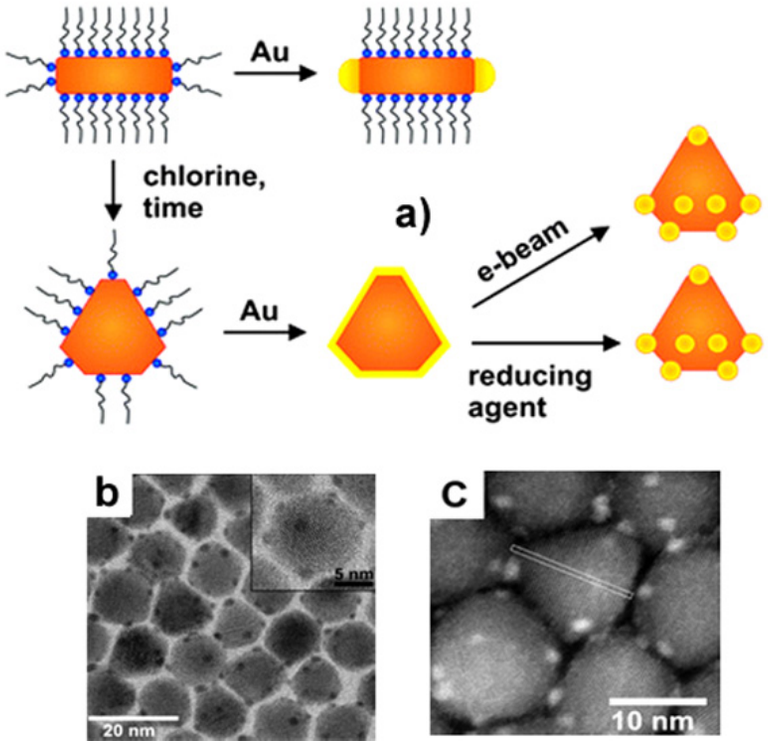

Figure 3. Growth of Au shell around pyramidal CdSe nanocrystals. (a) Scheme of the Au growth process onto CdSe nanocrystals. (b) Incubation of CdSe with Au-tetra-*n*-butylammonium borohydride/dodecyltrimethylammonium bromide led to Au clusters positioned at apexes of the CdSe pyramids. (c) STEM image of Au/CdSe hybrids with sharp angles as reactive sites for the nucleation of Au particles. Reproduced with permission from ref. [24]. Copyright 2010, The Royal Society of Chemistry.

on the corners and tips of the CdSe nanocrystals through the suitable choice of the metal precursor and the surface ligand concentration. The pyramid structure provided relatively sharp angles which were highly reactive sites for the nucleation of the gold particles. Banin et al.[25] also synthesized cage-shaped Ru/Cu_2S nanohybrids by adding $Ru(acac)_3$ to Cu_2S seed suspension in octadecylamine. Metallic Ru selectively grew on the crystal edges of the Cu_2S nanocages to form a symmetrical cage around a Cu_2S core. The cage formation could be due to the capping of thiol ligands on the Cu_2S facets to block the growth of these crystal facets. These Ru/Cu_2S nanocages were used as an excellent electrocatalyst for H_2O_2 sensing with catalytic activity higher than Cu_2S electrode.

The recent progress made in the synthesis of magnetic-fluorescent nanohybrids with combined magneto-transport properties has been reported. Cozzoli et al.[26] reported the two-step seeded-growth for the selective synthesis of Co-tipped CdSe/CdS core-shell nanorods. A two-step procedure consisted of injection of tri-n-octyl phosphine sulphide/CdSe seeds to Cd-surfactant complexes and heated at 350-380 °C to form CdSe/CdS core-shells. Co clusters were then attached with the CdSe/CdS seeds by injecting $Co_2(CO)_8$ solution into octadecene solvent containing CdSe/CdS seeds at 200-240 °C under inert atmosphere. An excess volume of oleic acid was added to the growing mixture to stabilize the hybrid nanostructures formed after reaction completion. The formation of the

nanohybrids with matchstick-like topology was predicted by crystal-oriented-attachment occurred the directional fusion of the generated Co nanocrystals to the nanorod tips. These Co-tipped CdSe/CdS heterostructures exhibited unusual room-temperature ferromagnetism and fluorescent emission despite photoexcited charge transfer from the semiconductor to the metal domain. Talapin et al.[27] synthesized FePt/PbS and FePt/PbSe nanohybrids with magneto-transport properties by coupling ferromagnetic FePt particles with either PbS or PbSe in form of core-shells or dumbbells. The formation of the hybrid products by injecting bis(trimethylsilyl) sulfide to reaction mixture containing FePt nanoparticles, oleic acid, Pb-oleate complex dissolved in octadecene at 120-150 °C. The nanohybrid shape was controlled by capping of the ligand on the surface of the FePt seeds and the reaction temperature. These magnet-in-the-semiconductor hybrid nanostructures showed semiconductor-type transport properties with magnetoresistance characteristic of combining the advantages of both functional components. The maghemite-metal sulphide (ZnS, CdS, HgS) nanohybrids were synthesized by adding sulphur and appropriate metallorganic precursors to the Fe_2O_3 particles followed by heating treatment.[28] In other reports, the large lattice mismatch between Fe_2O_3 and metal sulphide resulted in the formation of non-centrosymmetric nanostructures. The formations of trimers and oligomers were observed for ZnS and dimers for CdS and HgS nanocomposites. Alloy-cadmium selenide core-shells including FePt/CdSe, NiPt/CdSe, FePt/CdSe, NiPt/CdSe were synthesized by hydrolysis of cadmium stearate in oleylamine, hexadecylamine/octyl ether, 1,2-hexadecandiol in the presence of alloy seeds.[29]

3. Surface modification of hybrid nanostructures

Functionalization of the hybrid nanostructures has received a great deal of interest because of their biomedical applications in targeted drug delivery, diagnosis and therapy. The synthesis of the hybrid nanomaterials has mostly been achieved in organic and aqueous media containing either hydrophobic or hydrophilic organic linkers. The hybrid nanostructures synthesized usually involves organic linkers binding to the surface of two or more components to stabilize the nuclei and larger nanoparticles against aggregation by repulsive force for controlled growth of the sized and shaped nanohybrids. As capped by the linkers, the resulting hybrid nanostructures become hydrophobic character and is insoluble in water, resulting in incompatible with biological systems. A surface modification of hydrophobic-surfaced nanohybrids to produce water-soluble functional nanohybrids are therefore a indispensable step prior to biomedical applications. These interactions with the environment ultimately affect the colloidal stability of the particles and may yield to the delivery of the appropriate functional nanoparticles to targeted species. There are common functionalization strategies of silica and amphiphilic polymer coatings. Since the coated hybrid nanostructures retained their original physical properties, the resulting nanocomposites showed the multifunctional properties. These routes can serve as a powerful paradigm for the further fabrication of antibody-conjugated nanohybrids for multifunctional theranostic applications.

3.1. Polymer adsorption

The nanohybrid colloids could be soluble in water by adsorbing amphiphilic polymers onto hydrophobic molecules-capped nanohybrids. The amphiphilic polymer adsorption are carried out through hydrophobic interaction of hydrocarbon chains and van der Waals force between the molecules. The desorption of polymer molecules from the nanoparticles is usually prevented because numerous contact points formed from the interactions of organic linkers and polymer chains. Advantage of this approach is mainly not dependent on the types of the inorganic hybrid cores and the organic linkers, and the physiochemical surface properties of the coated particles are significantly unchanged. A popular example is the gold particles in aqueous media prepared by citrate reduction. Citrate ions adsorbed on the gold surface resulted in their negative charge and colloidal stability within several years by electrostatic repulsion. The citrate layer was replaced by stronger-binding ligands of mercaptocarboxylic acids. The surface modification of the particles with mercaptocarboxylic acids allowed for achieving concentrated particle solutions, that can precipitate out of particles by salt-induced aggregation and redissolved in low-salt buffers.[30] The surface functionalization of TOP/TOPO-capped CdSe/ZnS quantum dots was substituted phosphine-based hydrophobic ligands with hydrophilic mercaptocarboxylic acid molecules.[31] The quantum dots in aqueous solution stabilized with mercaptoacetic acid were modified by co-adsorption of polyethylene glycol and peptides.

Polyethylene glycol (PEG) is a linear polymer consisted of ethylene oxide units and well soluble in water. PEG is high biocompatibility due to its inertness and non-toxic properties.[32] Apart from the post-modification approach by covalent chemistry, PEG-modified nanoparticles can be obtained by PEG-contained ligand molecules with functional group that can bind to the particle surface.[33] Owing to the solubility of PEG itself, the PEG-coated particles can also be dispersed in polar organic solvents.[34] **Figure 4** shows the modular design toward The synthesis of the amphiphilic polymer of poly(maleic anhydride-alt-1-octadecene) (PMAO)-polyethylene glycol was carried out through reaction between maleic anhydride and primary amine-terminated polyethylene glycol methyl ethers and subsequent coating of PMAO-polyethylene glycol amphiphilic polymer with hydrophobic ligand-capped quantum dots.[35] The functionalized materials dissolved in water had the same optical spectra and quantum yield as those pre-synthesized quantum dots. The water-soluble encapsulated nanoparticles contain free carboxylic acid groups for conjugating anti-Her2 antibody to the polyethylene glycol-coated nanoparticles. The antibody-conjugated quantum dots were used as a probe to recognize human breast cancer cells with Her2 receptor with nonspecific binding of polyethylene glycol with cell receptors on the particle surface. Mattoussi et al.[33] achieved the capping of water-soluble ligand of mixed dihydrolipoic acid (DHLA) and poly(ethylene glycol) (PEG) on quantum dots. These ligands are consist of a poly(ethylene glycol) (PEG) segment attached anchoring DHLA group on one end to drive binding to the quantum dot. Cap exchange with these hydrophilic ligands made quantum dots to be stabilized in water over extended periods of time and over a broad pH range. The quantum dots capped with DHLA-PEG-biotin interacted with streptavidin coupled to proteins which were subsequently taken up by live cells. Yu et al.

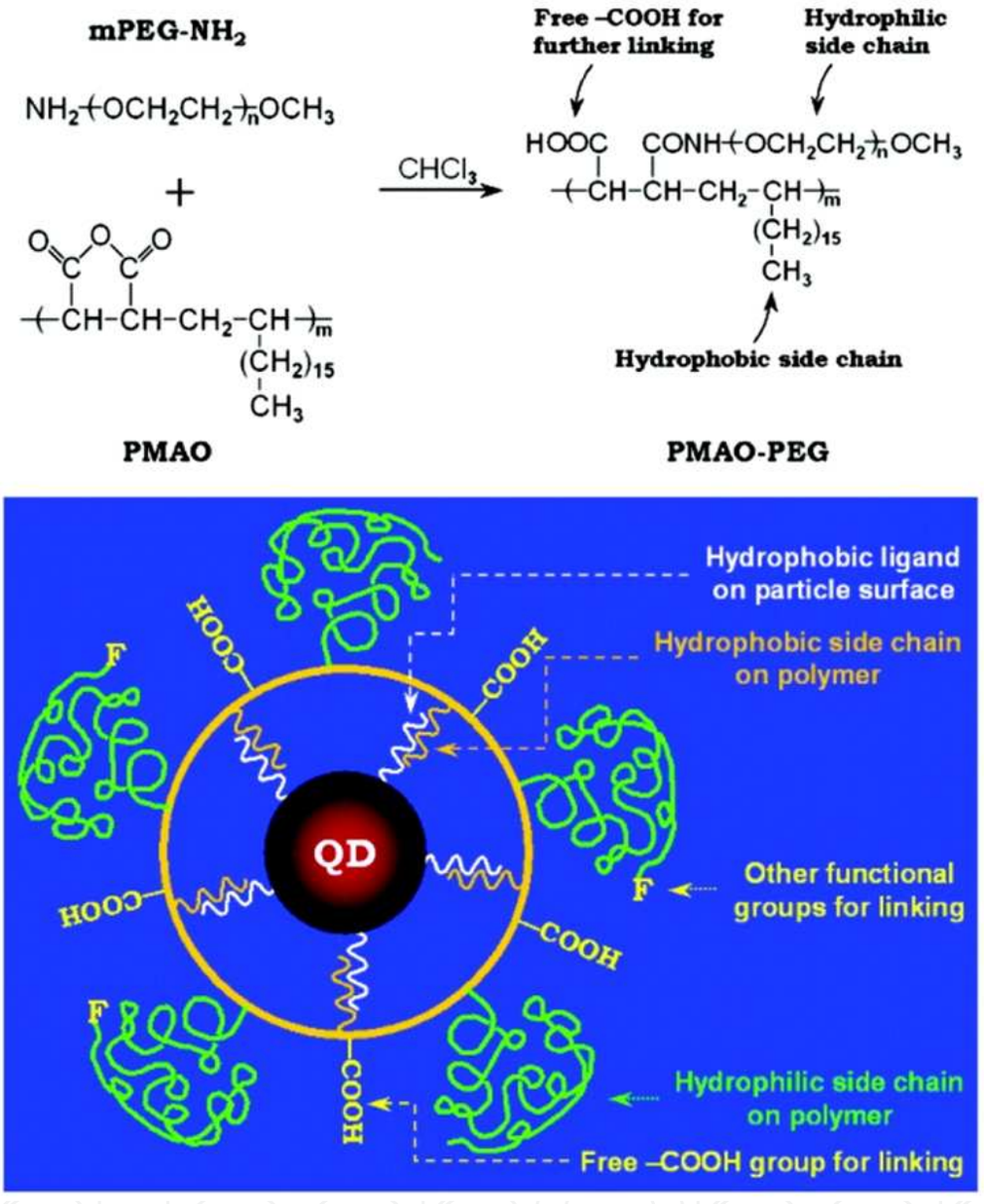

Figure 4. Forming biocompatible and nonaggregated nanocrystals in water using amphiphilic polymers. Top: one-step formation of poly(maleic anhydride-alt-1-octadecene) (PMAO)-polyethylene glycol (PEG) amphiphilic polymers through reaction between maleic anhydride and amino groups. Bottom: schematic structure of water-soluble quantum dots (F stands for a functional group instead of -OCH_3, such as -OH, -COOH, -NH_2). Quantum dots were encapsulated by PMAO-PEG amphiphilic polymer hydrophobic interaction. Reproduced with permission from ref. [35]. Copyright 2007, American Chemical Society.

[35] prepared amphiphilic polymer of PMAO-PEG through reaction between poly(maleic anhydride-alt-1-octadecene) (PMAO) and primary amine-terminated polyethylene glycol methyl ethers (PEG). The quantum dots were mixed with PMAO-PEG in chloroform. These PMAO-PEG-coated quantum dots were found to have the optical properties and recognized the cancer cells with Her2 receptor.

Poly(acrylic acid)-based polymers with hydrophobic side chains were usually used for surface modification with aliphatic amine- or thiol-capped particles.[36] These polymers are soluble in organic solvent and can bind to the hydrophobic particle surface. After solvent evaporation, the particle solids can be dissolved in aqueous buffer, providing stable water-soluble particles. Poly(acrylic acid) was coated onto hydrophobic dodecylamine-capped CdTe/CdSe quantum dots to form amphiphilic double-layered nanohybrids soluble in either water or organic media.[37] The coating of these polymers can carry out in ethanol solvent, resulting of poly(acrylic acid) backbone linked with mixed octylamine and isopropylamine, giving numerous hydroxyl groups on the particle surface.[38, 39] The hydrophobic side chains of the polymers commonly cover or intercalate the hydrophobic ligand molecules, and the exposed hydrophilic backbone outwards to aqueous media. In addition, poly(maleic anhydride) copolymers prepared from copolymerization of maleic anhydride with olefin are used as alternating copolymers. In aqueous media, the maleic anhydride rings hydrolyze and open giving two carboxylic groups, which gives access to further functionalization. Each maleic anhydride ring yields a free carboxylic group, indicating that the surface of the polymer-coated particles could be covalently grafted to amino acids for biomolecule conjugation.

Poly(vinyl pyrilidone) was also used to graft directly on the surface of the particles through one-pot process.[37] The further surface functionalization of the grafted products can be achieved by adding a next layer or exchanging original capping agents. Other polymers contained a mixture of aliphatic side chains and others with primary amines at their ends can bind to the nanoparticle surface through the amino groups.[40] Additionally, poly(acrylic acid) modified with free thiol and amino groups at the ends of the side chains was demonstrated as coating for quantum dots to form a thin shell with little effect on the quantum yield of the coated particles. The hydrophobic-hydrophilic block-copolymers formed in micellar structure dispersible in solvent were also used for the coating of the nanoparticles. The coating by block-copolymer micelles yields the particle aggregates instead of the monodisperse particles that could be suitable for further generation of the multifunctional porous materials.

3.2. Silica coating

Coating of a cross-linked silica shell to protect the organic agent-capped hybrid cores from external environment is carried out to produce the silica-coated hydrophobic nanohybrids. Coating with silica layer is one of the most widely used methods for surface modification of the inorganic nanoparticles, because the unique properties of the nanoparticles can be preserved by silica shells. After silica coating, the colloids stabilized in aqueous media and have low nonspecific interaction with biosystems and inert silica layer against degradation of optical properties. Silica can also be easily surface modified to link bioconjugators with interesting biofunctionalities. To this goal, water-to-oil microemulsion and Stober sol-gel have generally been achieved for silica coating.

Reverse microemulsion is a promising method for the synthesis of the monodisperse silica-coated nanoparticles.[41] Ying et al.[42] developed the reverse microemulsion-mediated route to encapsulate the hydrophobic trioctylphosphine oxide (TOPO)-capped quantum dots and magnetic particles within silica shells to form the silica-coated quantum dot-magnetic hybrid structures. **Figure 5** describes the water-in-oil (W/O) reverse microemulsion system for silica coating of the hydrophobic particles, where water droplets are stabilized by nonionic Igepal surfactant in a continuous oil phase (e.g., cyclohexane). After the addition of silane (TEOS), hydrolysis and condensation occur at W/O interface or in water phase to encapsulate the inorganic particles within a silica shell. The magnetic particles and quantum dots were confined in the silica layer to afford the hybrid structure. The silica-coated magnetic-quantum dot nanohybrids preserved the magnetic property of γ-Fe_2O_3 and optical property of CdSe quantum dots. The authors also used this route to synthesize silica-coated oleylamine-coated Au and Ag core-shells and subsequent conjugation with activated polymeric dextran.[43] The resulting materials were potentially used as glycobiological

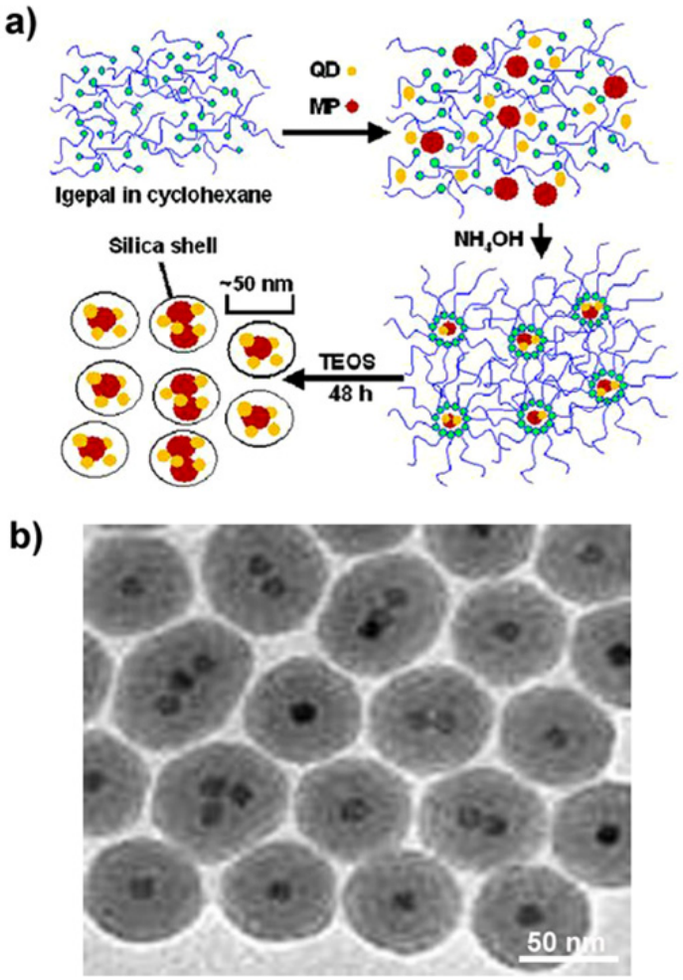

Figure 5. Silica-coated magnetic-quantum dot hybrid nanoparticles. (a) A scheme of the reverse microemulsion system for the synthesis of silica-coated magnetic-quantum dot nanohybrids; (b) TEM image of the silica-coated magnetic-quantum dot nanohybrids. Reproduced with permission from ref. [42]. Copyright 2005, American Chemical Society.

probes. Similarly, the SiO_2-coated Fe_2O_3 rattle-type nanoball structures were also synthesized and used as support for decorating the Pd nanoclusters onto the support surface by mercapto- or amino-functionalized silica.[44]

The reverse microemulsion process was also used by other research groups. Meijerink et al. [45] elucidated the mechanism of incorporating hydrophobic quantum dots into monodisperse silica spheres. In water-in-oil reverse microemulsion system, the hydrolyzed TEOS had a high affinity for the quantum dot surface for replacement of hydrophobic amine ligands, which enabled the transfer of the quantum dots to the hydrophilic interior of the micelles where silica growth occurred. Serna et al.[46] achieved in-situ synthesis and further silica coating of the Fe nanoparticles in microemulsion system. The lamellar-like coated nanostructures were formed through the subtle interplay controlling the formation of nanospherical silica particles by the ammonia base-catalyzed hydrolysis of tetraethoxysilane (TEOS) in water-in-oil. Kang et al.[47] designed the reverse microemulsion based on the Igepal CO-520 surfactant to produce the silica-coated NiPt nanohybrids prepared from the reduction of nickel acetylacetionate and platinum acetylacetonate in oleic acid/oleylamine. Tsang et al.[48] reported that the templated sol-gel encapsulation of CTAB-stabilized micelles cOntaining metal precursors with ultra-thin porous silica coating allows solvent extraction of organic based stabilizer from silica-coated Ag-Pt alloys. The water-in-oil microemulsion for silica coating on $Y_3Al_5O_{12}$:Ce nanoparticles was presented by Chen et al. [49] through hydrolysis of tetraethyl orthosilicate. The silica shell thickness can be turned from 8-16 nm by varying the ratio of NiPt particles to TEOS precursor.

The Stober method of base-catalyzed hydrolysis and condensation of tetraethyl orthosilicate (TEOS) to produce silica used to coat on the hybrid cores. [50] This reaction has several advantages such as mild conditions, low cost, without surfactant used. Earlier, Kotov et al.[51] coated hydrophilic CdTe quantum dots within 40-80 nm silica spheres using modified Stober method, which resulted in reduced emission intensity with broadening of the spectrum. The quantum dots acted as seeds for the silica growth in ethanol/water. This method yielded single or multiple quantum dot per silica sphere, but the size and dispersion of the silica-coated quantum dots were hard to control. Alivisatos et al.[52] achieved Stober silanization approach for the functionalization of mercapto-silane/(3-mercaptopropyl-trimethoxysilane) siloxane with thiol and/or amine groups to produce silica shell-coated hydrophobic CdSe/ZnS core-shells. Mercaptopropyltris(methyloxy)silane (MPS) was replaced TOPO molecules on the surface. The methoxysilane groups (Si-OCH_3) of (MPS) hydrolyzed into silanol groups (Si-OH), and formed a primary polymerization layer. The silane precursors containing functional groups (F = -SH, -NH_2) were then incorporated into the shell and may tailor the nanoparticle surface functionality. Adopting the Stober method, **Figure 6a** shows the seminal silica coating of citrate-reduced Au particles by Mulvaney et al. [53] involved the weak surface attachment with bifunctional (3-aminopropyl) trimethoxysilane in aqueous media. The -NH_2 groups were bound to the gold surface and -$Si(OEt)_3$ groups and facilitated for hydrolysis and condensation with sodium silicate to deposit a surface-coated silica layer. Later, the thicker silica shells can be grown on the surface-stabilized Au particles by further hydrolysis/condensation of tetraethyl orthosilicate (TEOS).

In some cases prior to silica coating, the particle surface should be attached with hydrophilic molecules to create the surface-protected nanoparticles stabilized in aqueous media. This could facilitate hydrolysis/condensation of tetraethyl orthosilicate. For example, Han et al. [54] synthesized the monodisperse silica-coated gold particles derived from the citrate-stabilized gold particles. The prepared citrate-reduced gold particles are low stable for silica coating in alcoholic media. The colloidal stability needs to be increased by introducing a certain amount of sodium citrate into the synthetic solution to replace the surface charge of the gold particles. Chang et al.[55] presented the synthesis of the silica nanohybrids composed of the $CuInS_2/ZnS$ quantum dots and magnetite nanocrystals. The outside silica shell grafted with poly(ethyleneglycol) and amine groups to provide better biocompatibility and to allow further bioconjugation. These materials exhibited the exert excellent properties for drug delivery vehicles and magnetic resonance imaging. The conjugation of Pt(IV) anticancer drug onto the nanohybrids resulted in higher cytotoxicity than the free Pt(IV) anticancer drug, indicative of the multifunctional feature of the synthesized nanohybrids.

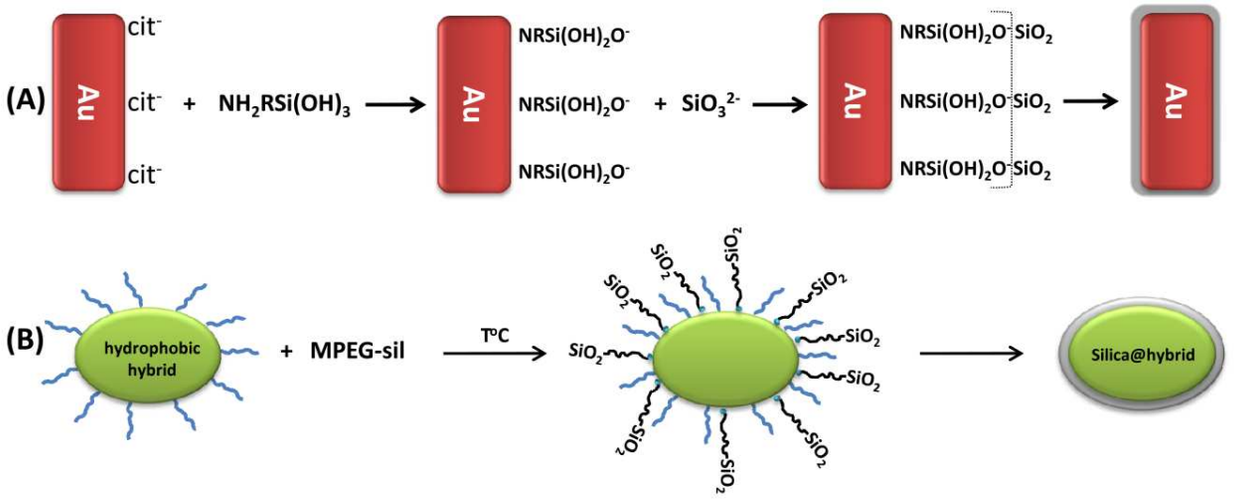

Figure 6. Schemes of silica coatings of hydrophilic (a) and hydrophobic (b) nanoparticles.

Figure 6b shows a successful example involved the surface adsorption of methoxypoly(ethylene glycol) silane to replace oleylamine capped on silver nanoparticles by Yang et al.[56] The functionalized silver nanoparticles were then hydrolyzed and condensed further to form thin silica layer-stabilized silver nanoparticles followed by thick silica coating with the Stober process. Bifunctional $Gd_2O(CO_3)_2{\cdot}H_2O$/silica/Au hybrid nanoparticles prepared by condensation of TEOS followed by conjugation with the gold shells were demonstrated potential as a MRI and therapeutic agent.[57] The hybrid particles showed the capability of absorbing NIR radiation for photothermal destruction of cancer tumors, in which the Au shell thickness strongly influenced the NIR optical absorption and photothermal effect. Pratsinis et al.[58] achieved coating of a thin silica shell on Ag/Fe_2O_3 Janus-shaped hybrids via one-step flame aerosol method. The silica coating still intacted their shape and plasmonic-magnetic properties but minimizes the release of toxic Ag^+ ions from the Ag particle surface and their direct contact with live cells. Well-defined $Au/SiO_2/CdSe$ hybrid nanostructures constituted a gold core overcoated with a silica shell

followed by a dense monolayer of CdSe quantum dots were formed via multistep procedure.[59] The formed products involved the synthesis of the gold particles, gold surface activation, silica-shell deposition, modification of the silica surfaces with -NH_2 groups, and final self-assembly of the CdSe quantum dots onto the particle surfaces. In order to the surface activation of the gold particles, (3-mercaptopropyl)-trimethoxysilane was found to be better than (3-aminopropyl)-trimethoxysilane because of stronger binding of -SH groups to the gold surfaces. These hybrid structures were used to perform the accurate quantitative analysis of the effect of the metal on quantum dot photoluminescence intensity. Khlebtsov et al.[60] preformed the silica coating on Au-Ag nanocages through adding water-ammonia solution and TEOS to the reaction solution containing Au-Ag particles. Silica-coated Au-Ag nanocages were then functionalized with photodynamic sensitizer Yb-2,4-dimethoxyhematoporphyrin to form the nanocomposites potential in multifunctional capability of IR-luminescence detection, photosensitization, and photothermolysis.

4. Nanotechnology in cancer treatments

Cancer is the greatest challenge in human healthcare today. It is a result of unregulated cell division leading to the uncontrolled growth and spread of abnormal cells. This behaviour causes the formation of malignant tumors consisted of cancer cells plus some healthy cells (normal tissue) invade nearby parts of the body. At early growth stages, the cancer cells mostly do not look or act like the normal cells because they are readily disguised by the healthy cells on their surface. This mainly behaves an extremely danger of the cancer cells. Tumor cells have a strong tendency to displace healthy cells until the tumor reaches a diffusion-limited maximal size, frequently resulting of changes to the DNA (mutations), leading to deaths.

Traditional cancer diagnosis and treatment modalities basically include post-surgical chemotherapy, radiotherapy, hormone therapy, and immunotherapy.[61] Each of these modalities has constantly limitations in treatment and also contribute to the rising costs of healthcare. Because of most human cancers relevant to solid tumors, so that the current cancer therapies are usually achieved some surgeries for removal of tumors, followed by chemotherapy and radiotherapy to kill the remaining tumor cells. However, the efficacy of the chemotherapy, serious side-effects on different healthy organs, the increased costs are a great obstruction by the fact that cancer stem cells be still survive and could continue to spread back. It is reasonably why cancer symptoms come back within relative short duration in patients who has passed through the post-surgical chemotherapy.

Thermal therapies (hyperthermia) have often employed a variety of heat sources including laser light, focused ultrasound, microwaves to destroy the solid tumors.[62] The benefits of hyperthermia are minimally or non-invasive, relatively simple to perform in the absence of surgical resection. However, simple heating techniques have trouble discriminating between tumors and surrounding healthy tissues, and often heat intervening tissue between source and target site. To irradiating beams reached underlying tumors or dispersed into large

tumors, high activating energy source must achieve at long duration of time, leading to sufficiently penetrate and damage healthy tissues.

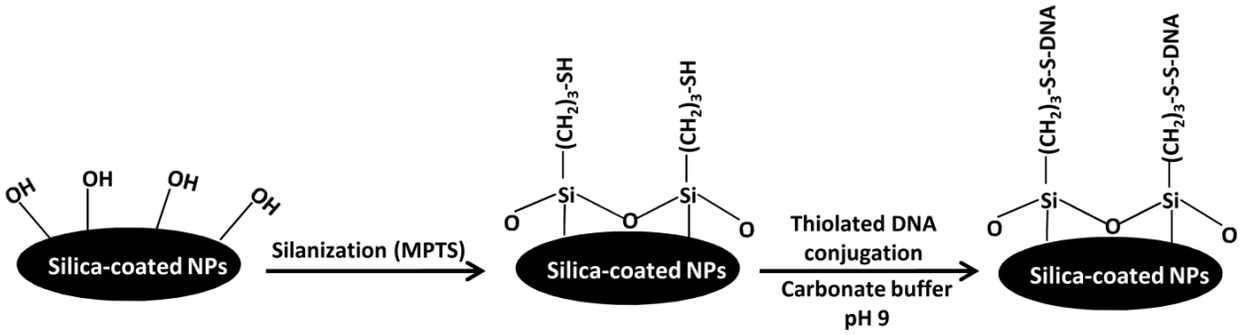

Figure 7. A scheme of thiolated DNA conjugation onto the silica-coated nanoparticles.

To the goal of the cost and performance, the development of new efficient approaches based on an advanced combination between "smart drug delivery" chemotherapy and photoradiation companied by "near-infrared (NIR) laser-adsorbing nanomaterials" to create the most effective results have been interested in medicine technology.[63] Lack of target specificity is one of the major disadvantages of many drugs. When drugs administered into human body are distributed to all organs through bloodstream, rather than to specific target organ that needs the pharmacological treatment. Biochemical and physiological barriers of certain organs also limit drug delivery to the desired organ. Chemotherapeutic drugs may destroy the cancer cells along with destroy the healthy tissue and cytotoxic effect of the drugs. To overcome these disadvantages, newer and effective methods should be developed to safely shepherd a pharmacological agent to avoid specific organs, where healthy tissue might be adversely affected.

The nanoparticles with the size smaller 100-10,000 times than the cells can be conjugated with various complementary biomolecules including DNA strands and antigens, as shown in **Figure 7**. The conjugated nanoparticles can easily pass through the cell membrane and accumulate into target sites by manipulation, which is advantageous in targeted imaging, diagnosis, and delivery.[64] The functionalization of the silica-coated nanohybrids is usually achieved by adsorption or chemical conjugation of the biomolecules to the particle surface. The silica-coated gold-based nanohybrid colloids can be surface-functionalized with mercapto-, amino-, carboxy-terminated silanes for biomolecule conjugation. Homogeneously water-dissolved biomolecules-conjugated silica-coated nanoparticles could bind to the surface of the cancer cells with greater affinity than to the noncancerous cells.

5. Gold nanorods-activated NIR laser plasmonic photothermal therapy

The targeted delivery of gold-based nanohybrids to solid tumors is one of the most important and challenging problems in cancer medicine. The strongly plasmonic absorption and photothermal conversion of the gold nanoparticles have been exploited in cancer

therapy through the selective localized photothermal heating of the cancer tumors.[65] To treat a tumor, the gold particles conjugated with biomolecules can be selectively targeted to cancer cells without significant binding to healthy cells. The nanoparticles in the bloodstream generally have to firstly move across the tumor blood vessels. The tumors are then exposed to an excitation source, such as NIR laser light, radiowave, or an alternating magnetic field. When the gold nanoparticles are exposed to the light radiation at their resonance wavelength, the electric field of light causes the collective oscillation of the conduction-band electrons at the particle surface. The coherent oscillation of the metal free electrons in resonance with the electro-magnetic field is called the surface plasmon resonance (SPR). The excitation of the maximum SPR absorption results in enhancement of the photophysical properties of gold particles.[66] The gold nanoparticles absorb the incident energy and convert them to heat, which raises the temperature (~42°C) of the tissue and ablates the cancerous cells by disrupting the cell membrane. The photoradiations do not often kill healthy cells because the laser power requires to heat/destroy the cancer cells much low than the healthy cells to which nanoparticles do not bind specifically. The physical heating mechanism of ablative therapies would provide an advantage against chemotherapy-resistant cancers, as well as improved tumor response when combined with chemotherapy and photoradiation.

Key features to consider when selecting a compatible particle for hyperthermia are the wavelength of maximal absorption, absorption cross-section, and shape/size of the particle. NIR laser light is ideal for in-vivo hyperthermia applications because of its low absorption by tissue chromophores (hemoglobin and water), which prevents them from damaging healthy tissue. The absorption coefficient of these tissue chromophores is as much as two orders of magnitude greater in the visible region (400-600 nm) as compared to the NIR region (650-900 nm).[66] Gold-nanoparticle-mediated photothermal therapy is predominantly designed to operate in this window of wavelengths ("NIR window") to minimize energy interaction of light-tissue, preventing damaging heating of healthy tissue. Upon tumor laser irradiation, NIR light is absorbed by the nanoparticles and heat dissipation is generated as a consequence of electron-phonon interactions. For successful cancer ablation, the tissue must be heated to a minimum temperature for a minimum duration of time to induce tumor cell death.

The plasmon absorbance of the gold particles can be easily tuned from the visible region into the NIR by simple manipulation of their aspect ratio (from sphere to rod).[66] For the gold nanospheres, this resonance occurs in the visible spectral region at about 520 nm, originating from the brilliant colour of the gold particle solution. Owing to their distinctive rod shape, the gold nanorods have two absorption peaks attributed to the free electron oscillation along the longitudinal and transverse axis, resulting in a stronger resonance band in the NIR region and a weaker band in the visible region (~520 nm for gold nanospheres). The synthesis of the colloidal gold nanorods would therefore prove effectively for photothermal therapy because they can absorb low-energy NIR light and convert it to heat in the usual way.

The gold species conjugated to antibodies can be selectively targeted to cancer cells without significant binding to healthy cells. In general, the routes to nanoparticle delivery are mainly based on an "active" mechanism and a "passive" mechanism.[67] In the active mode, the molecule ligands of antibodies, DNA, and peptides are used to recognize specific receptors on the tumor cell surface. In the passive mode, the nanoparticles without targeting ligands are accumulated and retained in the tumor interstitial space mainly. In both mechanisms, the nanoparticles in the bloodstream must first move across the tumor blood vessels. Some reports were used PEG ligand to attach the lysine-capped Au nanoparticles through lysine-terminated PEG link.[68] The targeted delivery of the gold nanoparticles to solid tumors is one of the most important and challenging problems in cancer nanomedicine. It was recently observed that the colloidal gold nanoparticles were found in dispersed and aggregated forms within the cell cytoplasm and provided anatomic labeling information. The anti-EGFR antibody-conjugated nanoparticles homogeneously bind to the surface of the cancer type cells with greater affinity than to the noncancerous cells. These results were detected by using SPR scattering imaging and SPR absorption spectroscopy, in which a relatively sharper SPR absorption band with a red shifted maximum compared to that observed on noncancerous cells.[69] We recently reviewed the aqueous-based synthetic pathways of the metal nanocrystals potential in biomedical applications.[67]

6. Hybrid nanostructures for biomedical diagnosis and therapy

6.1. Plasmonic-magnetic hybrid nanostructures

Magnetic nanoparticles with unique magnetic properties are a direct consequence of the behaviour of electrons within the particle. The electrons are similar to tiny bar magnets, with a surrounding magnetic field that corresponds to the electron spin in an applied field. When electrons move between different energy levels, they absorb energy and can generate light or heat.[13] Because of their low toxicity and good sensitivity, the magnetic particles conjugated with biomolecules are widely studied and applied in biomedicine, where these particles are used as magnetic carriers that could travel to targeted cancer tumors under orientation of an external magnetic field. The magnetic carriers then absorb externally magnetical energy and convert them to heat to kill the cancer cells. Magnetic resonance imaging (MRI) is presently one of the most powerful diagnosis tools for imaging the central nervous system and for detecting tumors and cancer cells. The paramagnetic gadolinium chelate complexes (e.g., Gd-DTPA) were widely used for MRI contrast agents.[70] The porous/hollow iron oxide nanocapsules made by wrap-bake-peel process from FeOOH nanorods via silica coating were used for this goal.[14]

The plasmonic-magnetic nanohybrids retain plasmonic properties and strong response to magnetic fields, where scattering of the plasmon alongside with magnetic contrast could be envisioned. Many researchers have recently developed the plasmonic-magnetic nanohybrids to improve the contrasting abilities with extra functions. As a typical material for cancer diagnostics and therapeutics, the Au/Fe_3O_4 nanohybrids as a bifunctional probe offer two functional surfaces for attachment of the plasmonic and magnetic particles.[71]

The Au and Fe_3O_4 particles both in a hybrid system are known to be highly compatible with biomedicine and a consequence of extending for diagnostics and therapeutics. The Au and Fe_3O_4 interfaces result in drastically change the local electronic structure, leading to an enhancement of their synergistic properties. The plasmonic and magnetic properties of the nanohybrids could be optimized by adjusting the size of the two particles. In comparison with the single Au and Fe_3O_4 particles, the Au/Fe_3O_4 hybrids possessing simultaneous plasmonic and magnetic detection facilitate for cancer diagnosis and therapy. When the biomolecules-conjugated Au/Fe_3O_4 hybrids are dispersed in body, they could travel to the targeted cancer tumors by influence of external magnetic field. The Au and Fe_3O_4 particles in the hybrid system adsorb energy from irradiating laser light and from exposing external magnetic field, respectively, and convert them into heat to kill the cancer cells. By using these bifunctional materials, an abundant amount of synergistic heating within the cancer tumors is created by a simultaneous adsorption-conversion of Au and Fe_3O_4 species facilitating the heating of the cancer cells.

Figure 8 shows the use of S6 aptamer-conjugated plasmonic-magnetic Au-Fe_3O_4 nanohybrids for the targeted diagnosis, isolation, and photothermal destruction of human breast cancer cells.[72] Cy3-modified S6 aptamers were attached to magnetic/plasmonic nanoparticles through -SH linkage. In the multifunctional nanoparticles, gold plasmonic shells were used as both a photothermal agent and a nanoplatform; the magnetic core was used for cell isolation. The S6 aptamer-conjugated magnetic/plasmonic nanoparticles attached to the cancer cells due to the S6 aptamer-cancer cell interaction. The bioconjugated magnetic/plasmonic nanoparticles highly selectively bind to the cells, which can be used for targeted imaging and magnetic separation of a specific kind of cell from a mixture of different cancer cells. The photothermal destruction results showed a selective irreparable cellular damage to most of the cancer cells, due to the absorption of 670 nm continuous NIR irradiation of the hybrid nanostructures.

Sun et al.[10] was achieved the thermolysis of $Fe(CO)_5$ on the surface of the Au nanoparticles in octadecene to produce Au-Fe_3O_4 dumbbells followed by coupling with Herceptinand Pt complex. The cisplatin complex was linked to Au surface by reacting Au-S-$CH_2CH_2N(CH_2COOH)_2$ with cisplatin. The coating of Herceptin antibody on Fe_3O_4 particles was performed by PEG3000-CONH-Herceptin. Cisplatin-Au-Fe_3O_4-Herceptin nanohybrids were tested to HER2-positive breast cancer cells and HER2-negative breast cancer cells. The cisplatin-Au-Fe_3O_4-Herceptin hybrids revealed a high efficiency in the killing of HER2-positive cancer cells. The presence of the hollow inside the nanohybrids was witnessed as an efficient carrier for targeted delivery and controlled release of cisplatin. These materials illustrated the possibility of acting as a multifunctional platform for target-specific platin delivery. Besides, other plasmon-magnetic materials of FePt/Fe_2O_3 yolk-shells[6] and mesoporous silica-coated Au-Fe_3O_4 core shells[73] were also synthesized and extensively studied for strong MRI contrast agent enhancement and carriers for anticancer drug delivery.

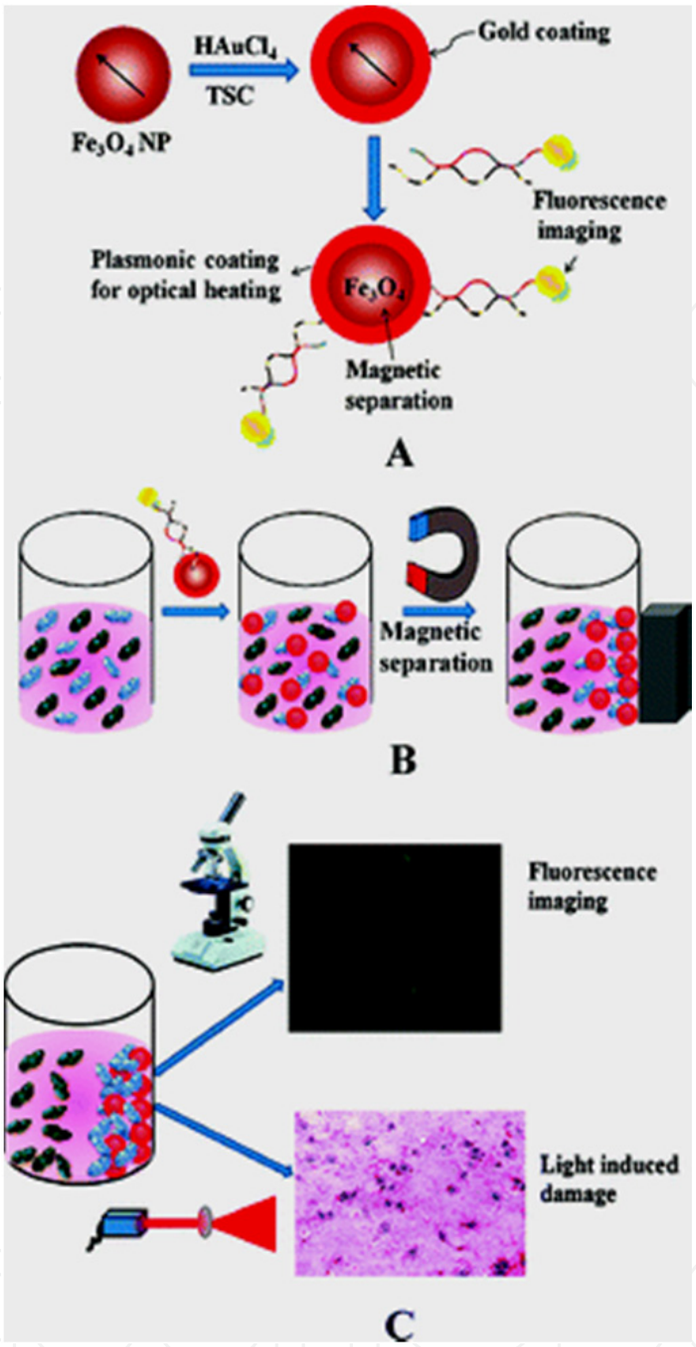

Figure 8. Plasmonic-magnetic Au-Fe_3O_4 shell cores for targeted diagnostics, isolation, and photothermal destruction of tumor cells. (a) Scheme showing the synthesis of S6 aptamer-conjugated core shells. (b) Scheme showing the separation of breast cancer cells using S6 aptamer-conjugated plasmonic-magnetic nanoparticles. (c) Scheme showing the selective fluorescence imaging and targeted photothermal destruction of breast cancer cells. Reproduced with permission from ref. [72]. Copyright 2012, American Chemical Society.

6.2. Fluorescent-magnetic hybrid nanostructures

In comparison with conventional organic dyes and fluorescent proteins, the quantum dots have unique optoelectronic properties with size-tunable light emission, superior signal

brightness, resistance to photobleaching, and broad absorption spectra for simultaneous excitation of multiple fluorescence colours. In order to establish the utility of the quantum dots for biological sensing application, the quantum dots are injected into desired cells of animals (e.g., mouse), emitted green and red labels are spectrally resolved to the eye clearly under the excitation of a single light source by a laser scanning microscope. For example, Liu et al.[74] used the synthesized triantennary dendritic galactoside-capped ZnS/CdSe nanohybrids as a hydrophilic, fluorescent, multivalent probe for detecting metastatic lung cancer cells. The water-soluble nanohybrids were selectively uptaken by lung cancer cells enriched with membrane-bound asialoprotein receptors. The results suggested the stronger interaction between polyhydroxylended nanohybrids in the membrane composition and cancer cells.

Nevertheless, the use of the quantum dots for biosensor application still has some limitations. Namely, the quantum dots are frequently emitted at UV and visible regions, meanwhile biological samples (water and tissues) also induce autofluorescence by the absorption of ultraviolet and visible light, possibly leading to an inexact diagnosis. Moreover, if the biological samples are prolonged exposure to UV radiation, it would cause the photo-damage and mutation. Therefore, the use of the quantum dots emitted in the near-infrared spectrum is an alternative approach for the imaging of tumour structures in vivo. The fluorescent emission peaks of these desired nanoparticles are in the low-energy NIR (800-1000 nm), distant from the typical UV-vis spectrum (400-600 nm) of tissue autofluorescence. This unique properties of the near-infrared quantum dots makes probes easily recognisable under near-infrared light, even in the tissues with high fluorescent background.

To overcome this barrier, one novel approach is based on the conjugation of two components in a fluorescent particle. The fluorescent emission peaks of the quantum dots could be shifted from ultraviolet to near-infrared region, arising from particle-particle interface. Because the quantum dots did not show the magnetism, consequently, the quantum dots coupled with superparamagnetic particles could provide the two-in-one multimodal fluorescent-magnetic nanohybrids, which could act as multi-targeting, multi-functional and multi-treating tools. The bifunctional magnetic-fluorescent nanoprobe allows for a preoperative diagnosis via MRI owing to the magnetic-fluorescent properties. They ally the high sensitivity and resolution of the fluorescence phenomenon to the high spatial resolution and noninvasiveness of MRI. Furthermore, the interaction between quantum dots and magnetic particles could result in NIR fluorescent emission of the nanohybrids.

Visual sorting and manipulation of tumor cells through using fluorescent-magnetic-biotargeting multifunctional nanobioprobes were reported by Pang et al.[75] Avidin-conjugated fluorescent CdSe/ZnS-magnetic γ-Fe_2O_3 nanohybrids synthesized were used to perform detection and extraction of multiple types of cancer cells via high affinity between antigens and antibodies. **Figure 9** presents the synthetic procedure for these materials. CdSe/ZnS and γ-Fe_2O_3 were coupled together in the chloroform/butanol suspension containing hydrazine-treated poly-(styrene/acrylamide) copolymer. Avidin-coupled fluorescent-magnetic nanohybrids were then obtained by incubating aldehyde-containing

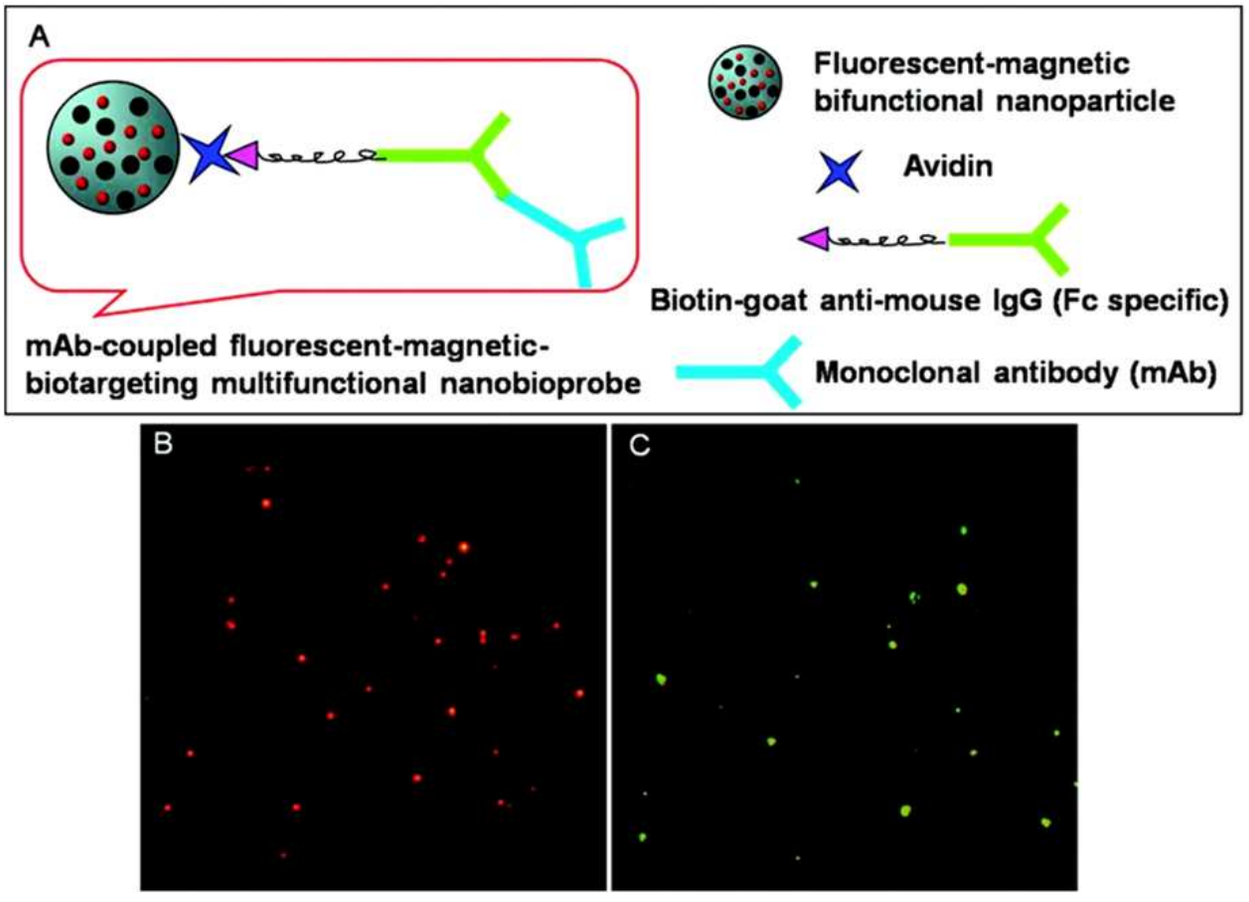

Figure 9. Fluorescent-magnetic biotargeting nanobioprobes for detecting and isolating tumor cells. (a) Scheme of avidin-coupled fluorescent-magnetic nanohybrids. Fluorescent-magnetic nanohybrids were covalently coupled with avidin and then coated with biotinylated goat anti-mouse IgG via biotin-avidin interaction. Mouse monoclonal antibody (mAb) was then attached to the nanohybrids via binding to goat antibody; (b) Fluorescence microscopic images of anti-CD3 mAb-coupled red nanobioprobes; (c) Anti-prostate-specific membrane antigen mAb-coupled yellow nanobioprobes. Reproduced with permission from ref. [75]. Copyright 2011, American Chemical Society.

avidin with fluorescent-magnetic nanohybrids. The authors demonstrated that the avidin-coupled fluorescent-magnetic nanobioprobes detected and extracted two different types of tumor cells from complex samples containing both normal cells and the target cancer cells and the capture efficiencies were of about 96% and 97%, respectively. Upon exposing magnet and fluorescence microscopes, these multifunctional materials were sensitively detect and isolate target tumor cells at low concentration of 0.01% in the mixed cells. Shi et al. [76] synthesized fluorescent-magnetic nanospheres by co-embedding quantum dots and magnetite nanoparticles into hydrazide-functionalized copolymer nanospheres followed by coupled on the surface with IgG, avidin and biotin to form the fluorescent-magnetic bio-targeting trifunctional nanospheres. The nanoscale biocomposites can selectively link to apoptotic cells, allowing their visualisation and isolation. The fluorescent-magnetic particles were inert with respect to cell proliferation and tumour formation and served as both a negative contrast agent for in vivo MRI, as well as a fluorescent tumour marker for optical imaging in vivo and in vitro. The multifunctional capability of the nanocomposite nanoparticles as MRI and

fluorescence imaging probes, along with their potential as drug delivery vehicles made them novel candidates for simultaneous cancer diagnosis and therapy.

The surface functionalization of the nanohybrids consisted of a polymer-coated maghemite superparamagnetic core and a CdSe/ZnS quantum dot shell, with anticycline E antibodies was permitted the separation of MCF-7 breast cancer cells from serum solution. The surface immobilised anticycline E antibodies bound specifically to cyclin, a protein which is expressed on the surface of breast cancer cells. The separated cells were monitored by fluorescence imaging microscopy, due to the strong luminescence of these nanohybrids.[42] An interesting external magnetic motor effect on floating cells, treated with fluorescent-magnetic nanocomposites, was reported by Lee et al.[77] In an another report, CdS:Mn/ZnS fluorescent-magnetic core-shells were prepared by using water-in-oil microemulsion. The peptide-conjugated fluorescent-magnetic core-shells possessing fluorescent, radio-opacity, and paramagnetic properties were used to label and visualise brain tissue without manipulating the blood-brain-barrier. The fluorescent visualisation of the whole rat brain was achieved using a simple low power handheld UV lamp, indicating that these materials are potentially applicable for advanced multimodal detection.[78]

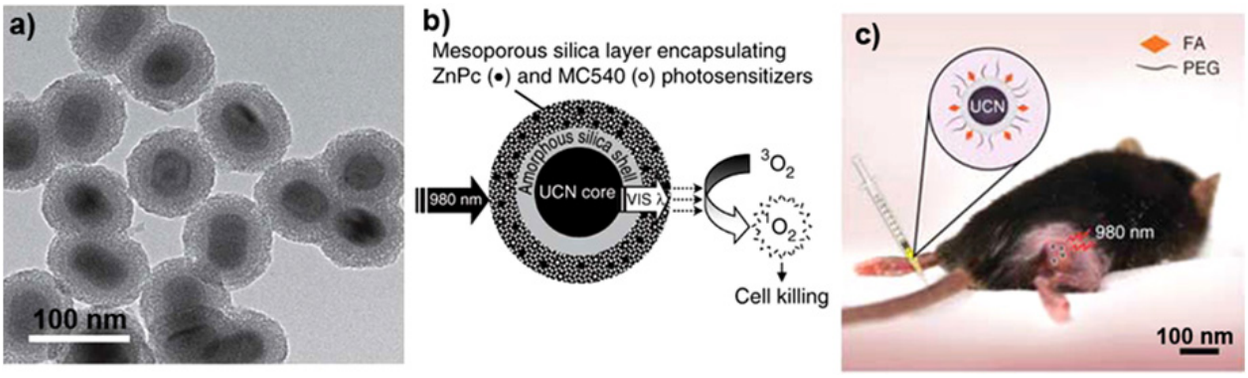

Figure 10. In vivo photodynamic therapy using mesoporous silica-coated $NaYF_4$:Yb,Er upconversion fluorescent nanoparticles (UCNs) as remote-controlled nanotransducers. (a) TEM image of the mesoporous silica-coated UCNs, scale bar = 100 nm. (b) Change in tumor size as a function of time after treatment to assess the effectiveness of UCN-based mediated targeted PDT in tumor-bearing mice intravenously injected with folic acid (FA)-PEG-UCNs. (c) Photograph showing showing UCN-based targeted conventional photodynamic therapy (PDT) in a mouse model of melanoma injected with UCNs surface modified with FA and PEG moieties. Reproduced with permission from ref. [82]. Copyright 2012, Nature.

One of the main problems in the preparation of the fluorescent-magnetic nanohybrids is the risk of quenching of the fluorophore on the surface of the particle by the magnetic core. This quenching process could be occurred because of the fluorophore contact with the particle surface, resulting in an energy transfer process. The problem of quenching can be partially resolved by coating of a stable shell (e.g., coating of a thin silica layer) on the magnetic nanoparticles prior to the introduction of the fluorescent molecules. As a proof-of-concept, Ying et al.[79] employed the silanization in a reverse microemulsion to produce a thin silica coating on the bare quantum dots or magnetic particles with surface NH_2 groups. The

silanized particles were conjugated to oleyl-O-poly(ethylene glycol)succinyl-N-hydroxysuccinimidyl ester through binding of the surface amine groups with heterofunctional polyethylene glycol. The biocompatible silica-coated can effectively target the cell membranes of HepG2 human liver cancer cells, NIH-3T3 mouse fibroblast cells, and 4T1 mouse breast cancer cells. These results demonstrated that these materials have potential for drug loading and delivery into cancer cells to induce cell death.

The biological applications of the down-conversion luminescent materials are currently restricted because they frequently emit at UV and visible regions, given the autofluorescence from biological tissues. These limitations would be breakthrough if we discover an alternate materials emitted in near-infrared (NIR)-to-vis upconversion.[80] This expectation was proved by Stucky et al.[81] who recently developed the new mesoporous multifunctional materials based on the combination of both up-converting luminescent and magnetic properties. Nanorattle hollow spheres consisted of the rare-earth-doped $NaYF_4$ shells with a SiO_2-coated Fe_3O_4 inner particle fabricated through ion-exchange process. The silica coating of the Fe_3O_4 nanoparticles were carried out by hydrolysis of TEOS in reverse-microemulsion system. The $Fe_3O_4@SiO_2@Y_2O_3$/Yb,Er magnetic upconversion oxide nanospheres were prepared by coating with the layer of Y/Yb,Er$(OH)CO_3.H_2O$ via homogeneous precipitation in the aqueous solution of yttrium nitrate and urea and subsequent calcination at 550 ^oC for 2 h. The $Fe_3O_4@SiO_2@\alpha$-$NaYF_4$/Yb,Er magnetic upconversion fluoride nanorattles were formed via ion-exchange of the $Fe_3O_4@SiO_2@Y_2O_3$/Yb,Er particles in HF and NaF solution. To demonstrate the material's potential use as a drug delivery system, the magnetic upconversion fluoride nanorattles were conjugated with antitumor drug doxorubicin. Through in vitro experiments in mice cells, the authors demonstrated that the material emits visible luminescence upon NIR excitation and can be directed by external magnetic field to specific target, making it an attractive system for targeted chemotherapy. **Figure 10** shows the use of mesoporous silica-coated $NaYF_4$:Yb,Er upconversion fluorescent nanoparticles (UCNs) as a remote-controlled nanotransducer for photodynamic therapy reported by Zhang et al.[82] The nanoparticle matrix can efficiently upconvert the energy of penetrating near-infrared light to visible light and transfer it to the encapsulated photosensitizers. The UCN materials exhibited a spectral overlap between the emitted visible light and the maximum absorption wavelengths of the photosensitizers to generate cytotoxic singlet oxygen in water. The authors discovered that the inhibition of tumor-cell growth in mice as a result of singlet oxygen generation from the UCNs, even at a very low 980-nm laser powers. This enabled selective fluorescent labelling, imaging and potentially sorting of the cells opening new prospects in cancer diagnostics and therapy.

7. Conclusions and outlooks

Most strategies of conjugating functional surfaced nanoparticles with biomolecule imaging agents produce antibody-conjugated particles that are considered as efficient biomedical diagnosis agents and universal platforms for engineering of multifunctional nanodevices. Inorganic nanohybrids containing more than one component have drawn considerable interest

in materials science. In the multicomponent system, one can expect unique properties originated from collective interactions between the constituents. The outstanding understanding of how growth joining of two individual materials could allow for controlling the nanohybrid geometries with unexpected properties. In this Chapter, we review theranostic biomedical applications of diverse types of the colloidal inorganic nanohybrids synthesized using seed-mediated growth. The structure and shape of the nanohybrids are predominantly dependent on the crystal structure and lattice parameter of each component and seed-to-precursor ratio in heterogeneous growth. A major goal in nanomedicine is the coherent implementation of multifunctional platforms within a single targeted nanodelivery system, which would simultaneously perform diagnosis, targeted delivery and efficient therapy. With the goal of creating synergistic properties, multifunctional hybrid materials with combined plasmonic-magnetic, plasmonic-fluorescent, fluorescent-magnetic structures are reviewed. These hybrid structures were then functionalized with either silica or amphiphilic polymer layers to convert water-soluble particles compatible with biomedical applications, while retaining their individual functional characteristics. For theranostic biomedical applications, the water-soluble nanomaterials were conjugated with biomolecules (antibody, DNA, peptide). The resulting bioconjugated hybrid nanoparticles show to be viable not only as dual-functional probes for imaging but also as an anticancer drug delivery vehicle even orientation of NIR excitation and external magnetic field. Through in vitro experiments demonstrated that these conjugated hybrid nanoparticles were actively delivered and targeted to the tumor sites in alive organs.

Since recent efforts on the synthesis of the multifunctional hybrid materials and studies them on animal species for theranostic biomedical applications, however it still presents major challenges for transferring into the clinical practices. Integrated collaborations of materials scientists with biologists and clinicians to be interdisciplinary teams should be established to systematic demonstrate and evaluate specific properties of the preformed hybrid nanomaterials, such as long-term toxicity, pharmacokinectics, and disinfection byproduct effects. In the future, the unexpected properties of these materials effective to human cancer cells are conducted by medical doctors, the multifunctional hybrid nanomaterials will provide powerful tools for simultaneous diagnosis and therapy of cancer diseases.

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Acknowledgement

This work was supported by the National Foundation for Science and Technology development of Vietnam-NAFOSTED (No. 104.03-2012.54).

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