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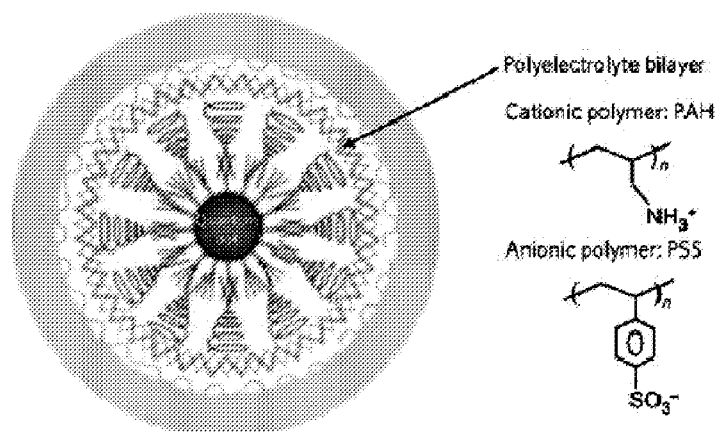
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(54) Title: METAL-COATED NANOSTRUCTURES AND RELATED METHODS

**Fig. 1B.**

(57) Abstract: Metal-coated nanostructures, methods for making metal-coated nanostructures, methods for using metal-coated nanostructures, and devices that include metal-coated nanostructures.

METAL-COATED NANOSTRUCTURES AND RELATED METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/270,476, filed July 8, 2009, and U.S. Provisional Application No. 61/349,170, filed May 27, 2010, each expressly incorporated herein by reference in its entirety.

STATEMENT OF GOVERNMENT LICENSE RIGHTS

This invention was made with Government support under RO1 CA131797 and RO1 CA140295 awarded by the National Institutes of Health, and under 0645080 awarded by the National Science Foundation. The U.S. Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

The development of multifunctional nanoprobe enabling new imaging modalities beyond the intrinsic limitations of individual components is of considerable interest to many research areas, ranging from fundamental biology to molecular imaging and medical diagnostics. Recent advances in nanotechnology have produced a variety of nanoparticle probes such as semiconductor quantum dots (QDs), magnetic nanoparticles (MNPs), and metallic NPs. Their unique electronic, magnetic, optical, and structural properties have addressed a broad spectrum of biomedical applications, such as ultrasensitive detection, medical imaging, and targeted therapeutics. Although combining multiple discrete components into a single multifunctional nanoparticle could be useful in a variety of applications, retaining the unique properties of each component after nanoscale integration is a long-standing problem.

Combining fluorophores, such as semiconductor quantum dots, with plasmonic materials, such as gold, is particularly difficult because gold and other metals quench fluorescence. To date, the combination of quantum dot fluorescence with plasmonically active gold has only been demonstrated on flat surfaces.

Plasmonic engineering of nanomaterials has the potential to revolutionize a variety of research fields ranging from optoelectronics and nanophotonics to nanomedicine. For example, deposition of silver nanoparticles on thin-film solar cells has resulted in greater than ten-fold enhancement in light absorption due to localized surface plasmons. Similarly, when quantum dots (QDs) were spread on a rough gold film

or a gold nanoparticle film, striking new spectral features including a five-fold increase in fluorescence intensity and 1,000 times faster excited-state lifetime were observed.

Despite these recent advances achieved on surfaces or based on nanoparticle clusters in solutions, a long-standing barrier has been how to functionalize single QDs with plasmonic materials such as gold while still maintaining the unique electronic and optical properties of each nanocomponent. Although selective growth of gold tips onto single-semiconductor QDs, quantum rods, and tetrapods has been demonstrated, the signature optical property of the semiconductor nanostructures, fluorescence, is nearly completely quenched in such arrangements owing to the direct coupling of the gold and the semiconductor. The key to solving this problem is to precisely tune the spacing between the gold and QDs and the plasmon band of the gold (for example, by coating the QDs with a gold shell of tunable thickness). Unfortunately, making discrete hybrid structures with tunable separation in the nanometer regime is extremely difficult, and current success remains on the theoretical analysis level.

Similar to conventional small molecule-based imaging probes, each type of nanoprobe displays distinct advantages as well as limitations. MNPs have become an important contrast agent in T2-weighted magnetic resonance imaging (MRI) because MRI offers high-resolution and excellent tissue penetration depth. However, MRI is not as sensitive as optical imaging or positron emission tomography, and is difficult to visualize in microscopic tissue examination. Similarly, although gold NPs are often used in scattering based imaging and offer high sensitivity, high resolution, and multiplexing capability, tissue penetration depth of optical imaging is limited to millimeters.

Engineering molecular probes with integrated functionalities, while maintaining compact size, remains a challenge. Nanoprobes with coupled functionalities will enable new imaging modes not available from each individual component for enhanced contrast specificity.

Due to a number of desirable properties including magnetic attraction, near-infrared (NIR) absorption, photon scattering, and ease of biomolecular conjugation through the stable thiolate-gold interaction, noble metal (e.g., platinum, gold) coated MNPs with precisely controlled shell thickness and smooth surface are a long sought after coupled imaging probe. Several attempts have been made by directly coating gold onto MNPs or MNP-silica composites (utilizing the low dielectric permittivity of silica). However, neither approach simultaneously provides nanoparticles with NIR response

(critical for in vivo imaging and therapy) and while maintaining compact particle size (desirable for tissue penetration and plasma circulation). For example, gold coating on MNP-silica composites often results in large particles of 100-200 nm in diameter with uneven surfaces.

5 Similarly, direct coating of gold onto iron oxide NPs requires both a large core particle and thick gold coating for NIR response. This is because, in contrast to silica-gold core-shell NPs whose absorption profile red-shifts with decreasing shell thickness, iron oxide-gold core shell particles absorb at longer wavelengths with increasing shell thickness. As a consequence, compact MNPs with thin gold coatings
10 only absorb in the visible spectrum. For NIR response, MNP-gold core-shell particles must be large in overall size (100-400 nm).

Despite the advances noted above with regard to multifunctional nanoprobe, a need exists for improved multifunctional nanoprobe. The present invention seeks to fulfill this need and provides further related advantages.

15 SUMMARY OF THE INVENTION

The present invention provides metal-coated nanostructures, methods for making the metal-coated nanostructures, methods for using the metal-coated nanostructures, and devices that include the metal-coated nanostructures.

In one aspect of the invention, a metal-coated nanostructure is provided. In one
20 embodiment, the nanostructure comprises (a) a nanostructure core, (b) a metal shell surrounding the core, and (c) a cationic polymer intermediate the core and the shell. Representative nanostructures include quantum dots, magnetic nanoparticle, carbon nanotubes, and biological particles. In one embodiment, the shell comprises a template grown metal. In one embodiment, the shell is a gold shell. In one embodiment, the
25 nanostructure further includes a material intermediate the core and polymer. The material may further include one or more polyelectrolyte bilayers. In certain embodiments, the distance between the core and the shell is from about 0.1 to about 200 nm. In certain embodiments, the shell has a thickness of from about 0.1 to about 30 nm. In other embodiments, the shell has a thickness of from about 2 to about 3 nm.

30 Use of a nanostructure of the invention as an agent for hyperthermic treatment is also provided.

In one embodiment, the invention provides a gold-coated quantum dot, comprising (a) a quantum dot core, (b) a gold shell surrounding the core, and (c) a

cationic polymer intermediate the core and the shell. Use of a quantum dot of the invention for optical and/or fluorescent imaging is also provided.

In another embodiment, the invention provides a gold-coated magnetic nanoparticle, comprising (a) a magnetic nanoparticle core, (b) a gold shell surrounding the core, and (c) a cationic polymer intermediate the core and the shell. Uses of a magnetic nanoparticle of the invention as a contrast agent for magnet resonance imaging and for magnetomotive photoacoustic imaging are also provided.

In another aspect, the invention provides a method for making a metal-coated nanostructure. In one embodiment, the method comprises:

- 10 (a) dispersing nanostructures in water to provide a plurality of individual nanostructures;
- (b) adding a cationic polymer to the plurality of individual nanostructures dispersed in water to provide a plurality of nanostructures having cationic polymer attached thereto;
- 15 (c) adding a reducible metal ion complex to the plurality of nanostructures formed in step (b); and
- (d) adding a reducing agent to the mixture of the reducible metal ion complex and the plurality of nanostructures having cationic polymer attached thereto to provide metal-coated nanostructures.

20 In one embodiment, the method further comprises adding a polyamine to the plurality of individual nanostructures in water followed by adding a polyanionic material to provide a plurality of nanostructures comprising a polyelectrolyte bilayer, prior to adding the cationic polymer. In another embodiment, the method further comprises adding a polyamine to the plurality of nanostructures comprising a polyelectrolyte bilayer followed by adding a polyanionic material to provide a nanostructure comprising two polyelectrolyte bilayers, prior to adding the cationic polymer.

In a further aspect of the invention, methods for imaging are provided. In one embodiment, the methods comprise administering to a subject or contacting a tissue with a nanostructure, a quantum dot, or a nanoparticle of the invention. In one embodiment, 30 the nanostructure is a magnetic nanoparticle and imaging is magnetic resonance imaging. In another embodiment, the nanostructure is a magnetic nanoparticle and imaging is magnetomotive photoacoustic imaging. In another embodiment, the imaging is fluorescent imaging. In another embodiment, the imaging is based on light scattering.

In another aspect, the invention provides a method for sensing or detecting an analyte. In one embodiment, the method comprises contacting a sample containing an analyte with a nanostructure, a quantum dot, or a nanoparticle of the invention, and measuring a change in absorption and/or scattering of the nanostructure, quantum dot, or nanoparticle shell, wherein the change in absorption and/or scattering is indicative of the presence of the analyte in the sample.

In a further aspect of the invention, a method for treating a condition is provided. In one embodiment, the method comprises administering to a subject a therapeutically effective amount of a nanostructure of the invention, and irradiating the subject with a wavelength of light sufficient to cause the metal shell to generate heat effective for hyperthermic therapy. In one embodiment, the nanostructure further includes a targeting agent to direct the nanostructure to a site of interest.

In another aspect, the invention provides a photovoltaic device comprising an active layer comprising a quantum dot of the invention.

In a further aspect, the invention provides a light-emitting device comprising an active layer comprising a quantum dot of the invention.

In another aspect of the invention, a metal-coated surface is provided. In one embodiment, the surface comprises (a) a continuous surface, (b) a metal coating, and (c) a cationic polymer intermediate the surface and the coating.

In a further aspect, the invention provides a method for sensing or detecting an analyte. In one embodiment, the method comprises contacting a sample containing an analyte with a surface of the invention, and measuring a change in fluorescence, absorption, and/or scattering of the surface, wherein the change in fluorescence, absorption, and/or scattering is indicative of the presence of the analyte in the sample.

DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings.

FIGURE 1A is a schematic illustration of a method for producing a representative gold-coated nanostructure of the invention: a gold-coated quantum dot (QD). In the method, hydrophobic QDs coated with trioctylphosphine oxide (TOPO) on QD surface were solubilized with a lipid-PEG-COOH conjugate to provide water-soluble QDs, which

were then coated with poly-L-histidine (PLH) to facilitate immobilization of gold ions (Au^{3+}) ions at high density. Addition of a mild reducing agent (hydroxylamine) provided gold nucleation on the PLH template and formation of a thin gold shell.

FIGURE 1B is a schematic illustration of a representative gold-coated nanostructure of the invention, a gold-coated quantum dot (QD), in which the distance between the QD core and the gold shell is tuned by coating QDs with polyelectrolyte bilayers (cationic polyallylamine (PAH) and anionic polystyrene sulfonate (PSS)) by layer-by-layer (LBL) assembly before PLH coating.

FIGURES 2A-2D presents transmission electron microscopy (TEM) images: FIGURE 2A is a TEM image of QD-gold hybrid nanoparticles in chloroform; FIGURE 2B is a TEM image of lipid-PEG-COOH conjugate-coated water-soluble QDs; FIGURES 2C and 2D are TEM images of representative gold-coated nanostructures of the invention, gold-coated QDs, shown at a magnification of 245 K and 340 K, respectively. These TEM images demonstrate that virtually every QD is encapsulated by a thin gold shell (2-3 nm) and having a gap between the shell and the nanoparticle core.

FIGURES 3A and 3B illustrate optical properties of representative gold-coated nanostructures of the invention, gold-coated QDs. FIGURE 3A compares the UV-Vis absorption spectra of QDs before and after gold encapsulation (QD/PLH is the water-soluble PLH-coated QD). After gold shell formation, the QD absorption was obscured by a strong surface plasmon resonance (SPR) band centered at 583 nm (QD/PLH/Au). FIGURE 3B compares the fluorescence spectra of the original organic-soluble QDs (QD/ CHCl_3), water-soluble QDs in the presence of Au^{3+} ions (QD/PLH/ Au^{3+}), and gold-shell-encapsulated QDs (QD/PLH/Au).

FIGURE 3C compares the quantum yield of fluorescence of representative gold-coated nanostructures of the invention, gold-coated QDs. Although the peak position did not change, the fluorescence intensity decreased 51.9% upon addition of Au^{3+} salt, and decreased another 23.7% after gold shell formation. To improve the QD fluorescence efficiency, polyelectrolyte bilayers composed of cationic PAH and anionic PSS were deposited onto the QD surface before PLH coating to increase the spacing between the QD core and the gold shell. Quantitative spectroscopic measurements indicated that the QD fluorescence was significantly improved with one to two layers of polyelectrolyte coating. The final QD quantum yield increased to 32.8% with one layer of PAH/PSS (QD/1-bl/PLH/Au) and 39.0% with two layers of PAH/PSS (QD/2-bl/PLH/Au).

FIGURES 3D and 3E compare TEM images of representative gold-coated nanostructures of the invention, QD-gold core-shell nanoparticles with one and two layers of polyelectrolyte spacers, respectively.

FIGURE 3F1-3F3 are histograms comparing the core-shell separation distribution of representative particles of the invention having no polyelectrolyte bilayer (0-bilayer, 3F1), one bilayer (1-bilayer, 3F2) and two bilayers (2-bilayer, 3F3). Each histogram was plotted based on 100 nanoparticles. Insets show the TEM measurements of representative particles.

FIGURE 4A compares normalized photoluminescence (PL) intensity over time for a representative gold-coated nanostructure of the invention, gold-coated QDs (QD/PLH/Au): normalized fluorescence intensities of organic soluble QDs (QD/organic), water-soluble QDs (QD/PLH), and gold-coated QDs (QD/PLH/Au). Under identical illumination conditions (480/40 nm), the QD-gold nanoparticles are significantly more photostable than the lipid-PEG-coated water-soluble QDs, and slightly outperformed the original organic-soluble QDs.

FIGURES 4B-4G compare fluorescence and darkfield imaging of single representative nanoparticles of the invention spread between two glass coverslips. For QDs without gold shell coating (FIGURES 4B-4D), only fluorescence signals were observed, but no scattering signal. In contrast, because of the metallic gold shell, the encapsulated QDs (FIGURES 4E-4G) not only exhibited strong fluorescence, but also are probes for surface plasmon scattering.

FIGURES 5A and 5B are TEM images of representative nanostructures of the invention: gold-coated iron oxide nanoparticles (FIGURE 5A) and gold-coated liposomes (FIGURES 5B). The inset in FIGURE 5A shows original iron oxide nanoparticles before gold shell encapsulation. No TEM image of liposome before gold shell encapsulation is shown because liposomes are not electron-dense materials suitable for TEM visualization.

FIGURES 6A-6F present transmission electron microscopy (TEM) images: FIGURE 6A is a TEM image of QD-gold hybrid nanoparticles in chloroform; FIGURE 6B is a TEM image of lipid-PEG-COOH conjugate-coated water-soluble QDs; FIGURES 6C, 6D, and 6E are TEM images of representative gold-coated nanostructures of the invention, gold-coated QDs, shown at a magnification of 245 K, 340 K, and 1050 K, respectively. In FIGURE 6E, the crystal lattice fringe becomes visible. Due to the

uneven shell thickness and the polycrystalline structure, some shell areas have low contrast. FIGURE 6F shows the signature crystal lattice of Au, confirming the existence of a thin shell. The lattice spacing in CdSe core measured at 0.37 nm corresponds to CdSe (100) lattice planes, and 0.23 nm in the shell corresponds to the (111) planes of face-centered cubic (fcc) Au.

FIGURE 7 is a schematic illustration of representative photovoltaic device incorporating a representative gold-coated nanostructure of the invention in the active layer.

FIGURE 8 is a schematic illustration of representative light-emitting device incorporating a representative gold-coated nanostructure of the invention in the active layer.

FIGURE 9A is a schematic of illustration of a method for producing a representative gold-coated nanostructure of the invention: a gold-coated magnetic nanoparticle (MNP-gold core-shell NPs). In the method, monodisperse hydrophobic MNPs coated with oleic acids are first solubilized using amphiphilic phospholipid (PL), PL-PEG-COOH. PLH, which is capable of chelating metal ions, is then adsorbed onto PL-PEG-COOH via electrostatic interaction. Upon addition of gold ions and a reducing reagent, thin gold shells form on the polypeptide template rather than directly on the core nanoparticles. The molecular structures of oleic acid, PL-PEG-COOH, and PLH are shown.

FIGURE 9B is a schematic illustration of the response of a representative gold-coated nanostructure of the invention, MNP-gold core-shell NP, to a magnetic field, where the underlying curve represents field strength. The coupled agents vibrate as the magnetic field is turned on and off.

FIGURE 9C is a schematic illustration of the mechanism of background suppression in magnetomotive photoacoustic (mmPA) imaging: mmPA imaging suppresses regions not susceptible to a controlled magnetic field while identifying regions with coupled agents responsive to a magnetic field.

FIGURES 10A-10D present transmission electron microscopy (TEM) images and FIGURES 10a1-10d1 present size distribution histograms of PL-PEG-COOH / PLH coated MNPs (polymer layer not visible under TEM due to low electron density) (FIGURE 10A), and MNP-gold core-shell NPs with various shell thickness (FIGURE 10B, about 1-2 nm; FIGURE 10C, 2-3 nm; FIGURE 10D, 4-5 nm). The

particle size histograms in FIGURE 10a1-FIGURE 10d1 are plotted from analysis of > 150 particles for each sample.

FIGURES 10E and 10F are HR-TEM images of representative MNP-gold core-shell NPs with shell thickness of about 2-3 nm. The lattice spacing of the MNP core measures at 0.48 nm corresponding to the (111) plane of Fe_3O_4 ; whereas the (111) plane of face-centered cubic (fcc) Au shows 0.23 nm lattice spacing

FIGURE 11A compares extinction spectra of representative gold-coated nanostructures of the invention, MNP-gold core-shell NPs (MNP/Au) successively coated with PL-PEG-COOH and PLH, and with gold nanoshells of various thickness, 1-2 nm, 2-3 nm, and 4-5 nm. As the gold nanoshell thickness increases, the spectral intensity increases and the peak center blue shifts.

FIGURE 11B compares magnetization as a function of magnetic field at room temperature for MNP and MNP/Au (2-3 nm shell thickness). The gold shell coating has negligible effect on MNPs' magnetic behavior. The insets show the absence of magnetic hysteresis and magnetic separation of the MNP-gold NPs.

FIGURE 11C compares photothermal stability of MNP-gold NPs with gold nanocages and nanorods. Extinction peak shifts as a function of laser fluence indicate that nanocages and nanorods start to quickly degrade at 5 mJ/cm^2 , whereas the MNP-gold hybrid NPs remain stable against laser irradiation of approximately three times higher fluence. TEM images of the nanocages and nanorods are shown as insets, scale bars are 50 and 100 nm for nanocages and nanorods, respectively.

FIGURES 12A-12E show multimodality imaging using MNP-gold hybrid NPs in accordance with an embodiment of the invention. FIGURES 12A and 12B are dark-field imaging of single MNPs spread on glass coverslips before and after gold nanoshell coating. The coated MNPs are readily detectable under current experiment conditions (insets show corresponding TEM images). FIGURE 12C shows T2-weighted MR images of the bare and gold-coated MNPs at various dilutions. The signal strength is indicated by the darkness of the images. At the same concentrations, the MR images are indistinguishable between the two series indicating unchanged magnetic properties before and after gold nanoshell coating. FIGURES 12D-12E are cross-sectional photoacoustic (PA) images of a tube filled with 5 nm MNPs and 5 nm MNP-gold NPs on a dB scale. 0 dB corresponds to the maximum signal level among both images. Note that a different

dynamic range was used for better visualization. Signal-to-noise ratio can be improved by 1 order of magnitude (20 dB) when MNP-gold NPs are used.

FIGURES 13A-13G show data processing in magnetomotive photoacoustic (mmPA) imaging in accordance with a representative method of the invention.

5 FIGURE 13A is a conventional PA image sequence acquired in synchrony with a magnetic pulse. FIGURE 13B is an image showing the maximum displacement achieved at the end of the magnetic pulse tracked using this sequence with the magnetic pulse spanning the first 5 seconds. FIGURE 13C compares three displacement courses and their fitted curves for pixels in different inclusions. The maximum positive

10 (FIGURE 13D) and maximum negative (FIGURE 13E) velocities were derived from fitted displacement curves, and used to create a weighting image (FIGURE 13F). The product shown in FIGURE 13A and FIGURE 13F produced an mmPA image (FIGURE 13G), where the gold nanorod inclusion is completely suppressed. The display ranges are 40 dB dynamic range in FIGURE 13A and FIGURE 13A, [0 (dark), 30 (light)] μm in (FIGURE 13B), [-20, 20] $\mu\text{m/s}$ in FIGURE 13D and FIGURE 13E with -20 $\mu\text{m/s}$,

15 0 $\mu\text{m/s}$, and 20 $\mu\text{m/s}$, and [0, 1] in FIGURE 13F.

FIGURES 14A, 14B, 14D, and 14E show TEM images of representative gold-coated nanostructures of the invention, gold shell encapsulated MNPs, having 10 nm (FIGURES 14A and 14B) and 50 nm MNP core size (FIGURES 14D and 14E). (a-c)

20 TEM and extinction spectrum of gold coated 10nm MNPs.

FIGURES 14C and 14F show extinction spectra of TEM images of representative gold-coated nanostructures of the invention, gold shell encapsulated MNPs, having 10 nm (FIGURE 14C) and 50 nm MNP core size (FIGURE 14E).

FIGURES 15A and 15B compare curves of magnetization versus temperature of

25 25 nm iron oxide NPs before (15A) and after (15B) coating of thin gold layers (about 2-3 nm) measured under ZFC and FC conditions (in a 500 Oe field), respectively.

FIGURE 16 compares lateral position displacements and velocities for a MNP inclusion and a MNP-gold NP inclusion.

FIGURE 17 is a TEM image of a representative gold-coated nanostructure of the

30 invention, gold core (Au core) encapsulated with magnetic nanoparticles (MNP).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides gold-coated nanostructures, methods for making the gold-coated nanostructures, methods for using the gold-coated nanostructures, and devices that include the gold-coated nanostructures.

5 In one aspect, the invention provides a metal-coated surface. In one embodiment, the metal-coated surface includes (a) a continuous surface, (b) a metal coating, and (c) a cationic polymer intermediate the surface and the coating. In the surfaces, the cationic polymer intermediate the surface and the coating provides a spacing or gap between the surface and the coating.

10 In another aspect, the invention provides a metal-coated nanostructure. In one embodiment, the nanostructure includes (a) a nanostructure core, (b) a metal shell surrounding the core, and a cationic polymer intermediate the core and the shell. As noted above, the cationic polymer intermediate the core and the shell provides a spacing or gap between the core and the shell.

15 Representative nanostructures include quantum dots (i.e., semiconductor nanoparticles), metal nanoparticles, metal oxide nanoparticles, metalloid nanoparticles, metalloid oxide nanoparticles, polymer nanoparticles, silica nanoparticles, nanoscale micelles, nanoscale liposomes, and clusters and combinations thereof. As used herein, the term "nanoscale" refers to a particle having at least on nanoscale (up to 1000 nm)
20 dimension.

In one embodiment, the nanoparticle is a magnetic nanoparticle. Representative magnetic nanoparticles include metal nanoparticles, metal oxide nanoparticles, metalloid nanoparticles, metalloid oxide nanoparticles. In one embodiment, the metal and metal oxide nanoparticles are selected from the group consisting of gold, silver, copper, titanium, and oxides thereof. In another embodiment, the metal and metal oxide nanoparticles are lanthanide series metal nanoparticles. Suitable magnetic nanoparticles include particles that are responsive to a magnetic field. Representative magnetic nanoparticles include particles that include a suitable metal or metal oxide. Suitable metals and metal oxides include iron, nickel, cobalt, iron platinum, zinc selenide, ferrous
25 oxide, ferric oxide, cobalt oxide, aluminum oxide, germanium oxide, tin dioxide, titanium dioxide, gadolinium oxide, indium tin oxide, cobalt iron oxide, magnesium iron oxide, manganese iron oxide, and mixtures thereof.
30

As noted above, in one embodiment, the nanoparticle is a quantum dot. The nanoparticle can be a single color quantum dot, a multicolor quantum dot, or a combination of quantum dots (multiple single color quantum dots), which can be used to provide a multicolor combination. Suitable quantum dots include those known to those of skill in the art and include those that are commercially available. Other suitable quantum dots include those described in U.S. Patent Nos. 5,906,670, 5,888,885, 5,229,320, 5,482,890, 6,468,808, 6,306,736, and 6,225,198, the description of these quantum dots and their preparations are incorporated herein by reference.

Representative nanostructures include nanoparticles such as quantum dots (e.g., CdSe/ZnS), carbon nanotubes (e.g., SWCNTs, MWCNTs), magnetic nanoparticles (e.g., iron oxide), and biological particles (e.g., liposome or cell).

In one embodiment, the shell has a thickness of from about 2 to about 3 nm. In one embodiment, the shell is transmissive.

In one embodiment, the nanostructure core is a quantum dot, the shell comprises a plasmonic metal, and the nanoparticle is fluorescent.

In one embodiment, the invention provides a gold-coated quantum dot that includes (a) a quantum dot core, (b) a gold shell surrounding the core, and (c) a cationic polymer intermediate the organic material and the shell.

In another embodiment, the invention provides a gold-coated magnetic nanoparticle that includes (a) a magnetic nanoparticle core, (b) a gold shell surrounding the core, and (c) a cationic polymer intermediate the organic material and the shell.

In one embodiment, the distance between the core and the shell is from about 0.1 to about 200 nm. In certain embodiments, the shell has a thickness of from about 2 to about 3 nm. In one embodiment, the shell is transmissive.

In one embodiment, the nanostructure core is a quantum dot, the shell comprises a plasmonic metal, and the nanoparticle is fluorescent.

In the above-noted metal-coated surfaces and metal-coated nanostructures, the coating is a template grown metal coating. Representative template grown metals include gold, silver, copper. In one embodiment, the coating includes a plasmonic metal. In one embodiment, the coating is a gold coating.

In certain embodiments, the surfaces or cores include a hydrophobic material. The hydrophobic material provides a material on the surface or core that facilitates build up the surface or core and for receiving the cationic polymer. Representative

hydrophobic materials include an $O=PR_3$ compound, an $O=PHR_2$ compound, an $O=PHR_1$ compound, a H_2NR compound, a HNR_2 compound, a NR_3 compound, a HSR compound, a SR_2 compound, and combinations thereof. In the above chemical compounds, "R" can be a C_1 to C_{24} hydrocarbon, such as but not limited to, linear hydrocarbons, branched hydrocarbons, cyclic hydrocarbons, substituted hydrocarbons (e.g., halogenated), saturated hydrocarbons, unsaturated hydrocarbons, and combinations thereof. A combination of R groups can be attached to P, N, or S. In particular, the chemical compound can be selected from tri-octylphosphine oxide (TOPO), oleic acid, stearic acid, and octyldecyl amine.

10 In certain embodiments, the surfaces or cores further comprise a material intermediate the surface or core and the polymer. The material may be an organic material or an inorganic material. In one embodiment, the material comprises polyethylene glycol. Representative materials include lipid-polyethylene glycol conjugates (e.g., DSPE-PEG2000 CO_2H). In one embodiment, the material comprises one or more polyelectrolyte bilayers (e.g., poly(allylamine) hydrochloride/polystyrene sulphonate bilayer). In one embodiment, the material comprises silica.

In the above surfaces and nanostructures, the cationic polymer is a polyamine (e.g., a polypeptide, such as polyhistidine or poly-L-histidine). In one embodiment, the cationic polymer is a metal chelator.

20 In the surfaces and nanostructures of the invention, the metal coatings and shells do not directly contact the surfaces or cores. In certain embodiments, the distance between the surface and the metal coating, or the core and the shell is from about 0.1 to about 200 nm.

In certain embodiments, the metal coating has a thickness of from about 0.1 about 30 nm. In certain embodiments, the shell has a thickness of from about 2 about 6 nm.

In another aspect of the invention, methods for making metal-coated surfaces and nanostructures are provided.

In one embodiment, the invention provides a method for making a metal-coated nanostructure, comprising:

30 (a) dispersing nanostructures in water to provide a plurality of individual nanostructures;

(b) adding a cationic polymer to the plurality of individual nanostructures dispersed in water to provide a plurality of nanostructures having cationic polymer attached thereto;

(c) adding a reducible metal ion complex to the plurality of nanostructures
5 formed in step (b); and

(d) adding a reducing agent to the mixture of the reducible metal ion complex and the plurality of nanostructures having cationic polymer attached thereto to provide metal-coated nanostructures.

In one embodiment, the method further comprises adding a polyamine (e.g., PAH)
10 to the plurality of individual nanostructures in water followed by adding a polyanionic material (e.g., PSS) to provide a plurality of nanostructures comprising a polyelectrolyte bilayer, prior to adding the cationic polymer.

In one embodiment, the method further comprises adding a polyamine to the plurality of nanostructures comprising a polyelectrolyte bilayer followed by adding a
15 polyanionic material to provide a nanostructure comprising two polyelectrolyte bilayers, prior to adding the cationic polymer.

In one embodiment, the cationic polymer is a polyamine (e.g., a polypeptide, such as polyhistidine or poly-L-histidine).

In one embodiment, the reducible metal ion complex is a gold complex (e.g., a
20 gold (IV) complex, HAuCl_4).

In one embodiment, the reducing agent is hydroxylamine.

In another aspect, the invention provides methods for imaging using the metal-coated nanostructures of the invention. In one embodiment, the method comprises administering to a subject or contacting a tissue with a nanostructure of the invention
25 (e.g., gold-coated quantum dot or gold-coated magnetic particle).

In one embodiment, the imaging is fluorescent imaging. In another embodiment, the imaging is based on light scattering.

In one embodiment, the nanostructure is a magnetic nanoparticle and imaging is magnetic resonance imaging. In another embodiment, the nanostructure is a magnetic
30 nanoparticle and imaging is magnetomotive photoacoustic imaging.

In a further aspect of the invention, a method for sensing or detecting an analyte is provided. In one embodiment, the method includes contacting a sample containing an analyte with a surface or a nanostructure of the invention, and measuring a change in

absorption and/or scattering of the surface coating or nanoparticle shell, wherein the change in absorption and/or scattering is indicative of the presence of the analyte in the sample. In one embodiment, the sensing or detecting is measured by surface plasmon resonance.

5 In another aspect, the invention provides a method for treating a condition. In one embodiment, the method includes administering to a subject in need thereof a therapeutically effective amount of a nanostructure of the invention and irradiating the subject with a wavelength of light sufficient to cause the nanostructure's metal shell to generate heat effective for hyperthermic therapy. In one embodiment, the nanostructure
10 further includes a targeting agent to direct the nanoparticle to a site of interest. As used herein, the term "targeting agent" refers to a chemical moiety associated with (i.e., covalently coupled or otherwise stably associated with the complex that direct the complex to a specific site where the complex can then be imaged or where the complex delivers its associated therapeutic agent. Suitable targeting agents include those known in
15 the art. Representative targeting agents are one of a binding pair. In one embodiment, the targeting agent is an antibody or fragment thereof or its antigen. The antigen can be a small molecule, peptide, protein, polynucleotide, or polysaccharide. In one embodiment, the targeting agent is a nucleic acid or its complement. The nucleic acids can be DNAs and RNAs. In one embodiment, the targeting agent is an enzyme or its substrate. In one
20 embodiment, the targeting agent is a receptor or its ligand. In one embodiment, the targeting agent is a nucleic acid or its partner protein. In one embodiment, the targeting agent is a ligand for a cell, a cell membrane, or an organelle.

 In another aspect, the invention provides a composition containing a nanostructure of the invention and an acceptable carrier or diluent. For therapeutic and/or diagnostic
25 applications, in which the composition is administered to a subject in need thereof, the composition includes a pharmaceutically acceptable carrier or diluent. The composition can be administered parenterally, for example, orally, transdermally (e.g., patch) intravenously (injection), intraperitoneally (injection), and locally (injection).

 In other aspects of the invention, devices that include a nanostructure of the
30 invention are provided.

 In one embodiment, the invention provides a photovoltaic device having an active layer that includes a nanostructure of the invention. A schematic illustration of a representative photovoltaic device is shown in FIGURE 7. Referring to FIGURE 7,

photovoltaic device 150 includes a first electrode 105', a photovoltaic layer 110', and a second electrode 115'. Typically, one of the electrodes 105' or 115' is a transparent conductor, such as indium-tin oxide (ITO), and the other electrode is a metal, such as aluminum. The photovoltaic layer 110' comprises a nanostructure of the invention that
5 utilizes the energy from incident electromagnetic radiation (e.g., visible light) to form free carriers, such as holes and electrons. The work functions of the electrodes 105' and 115' create an energetic state of the device 150 such that holes will flow to a hole-collecting electrode (e.g., 115'), and electrons will flow to an electron-collecting electrode (e.g., 105'). The holes and electrons generated in the photovoltaic layer 110'
10 migrate towards their respective electrodes for collection, and electrical current is generated. When the electrodes 105' and 115' are connected to a device (e.g., a battery or electrical circuit) in need of electricity, current flows to the device. The optional electron-transporting layer 106 forms an intermediary layer between the photovoltaic layer 110' and the electron-collecting electrode 105', such that electrons are allowed to
15 pass favorably through the electron-transporting layer 106 and holes are blocked. A hole-transporting layer 111 is also optional in the device 150 and forms an intermediary layer between the photovoltaic layer 110' and the hole-collecting electrode 115' such that holes are favorably passed through the hole-transporting layer 111 and electrons are blocked. Finally, an optional substrate 120 is illustrated abutting the hole-collecting
20 electrode 115'. It will be appreciated that in another embodiment, a substrate can alternatively abut the electron-collecting electrode 105' instead of the hole-collecting electrode 115'. A typical photovoltaic device 150 is fabricated on a substrate 120 of plastic- or glass-coated indium-tin oxide (ITO). Because ITO is typically sold pre-coated on glass or plastic substrates, the hole-collecting electrode (ITO) is essentially tied to the
25 substrate when fabricating devices. Thus, the substrate 120 also acts as the hole-collecting electrode 115' when an ITO-coated glass or plastic substrate is used for device fabrication.

In one embodiment, the invention provides a light-emitting device having an active layer that includes a nanostructure of the invention. A schematic illustration of a
30 representative light-emitting device is shown in FIGURE 8. Referring to FIGURE 8, representative device 200 includes first substrate layer 210, indium-tin oxide (ITO) anode layer 220, emissive layer 230 comprising a nanostructure of the invention, electron transporting and protective layer 240, anode 201, and cathode 202.

In one aspect, the invention provides a gold-coated fluorescent nanoparticle having fluorescent and plasmonic activities. The combined functionality in a single nanoparticle is achieved by controlling the spacing (e.g., gap) between the nanoparticle (e.g., quantum dot) core and the thin gold shell. The spacing is controlled with
5 nanometer precision through layer-by-layer assembly. In one embodiment, the invention provides a method for the deposition of an ultrathin gold layer onto virtually any discrete nanostructure or continuous surface. The method provides nanostructures useful for multimodal bioimaging, interfacing with biological systems, reducing nanotoxicity, modulating electromagnetic fields, and contacting nanostructures.

10 The preparation and characteristics of a representative nanostructure of the invention, a gold-coated quantum dot, are described in Example 1.

The nanostructures are produced from a homogeneous solution-based method that provides an ultrathin gold coating on both isolated nanostructures and continuous surfaces, and has direct relevance to problems frequently encountered in engineering
15 sophisticated electronic devices and bioimaging probes, such as connecting molecules with electric sources in molecular electronics, producing multimodality imaging probes, and creating anchor points for simple biomolecule conjugation. In addition, encapsulation of QDs made from toxic chemical elements (for example, CdSe) with a thin layer of gold, which is biocompatible and highly stable, may address concerns
20 regarding QD toxicity, which is the determining factor for translational and clinical applications of QDs.

To encapsulate QDs with a gold shell and yet maintain their fluorescence, a number of problems are addressed: (a) gold nanostructures are known fluorescence quenchers for both organic fluorophores and QDs; (b) a thick surrounding gold shell will
25 block QD fluorescence transmittance; (c) the gold precursor, chloroauric acid (HAuCl_4), is highly acidic and corrosive, and can irreversibly damage QDs; (d) the QD structural scaffold for gold shell growth is small (a few nanometers); and (e) the space between the QD core and the gold shell must be precisely controlled. Although the preparation of gold nanoshells coated on large silica particles (120 nm) with shell thicknesses ranging
30 from 5 to 20 nm has been reported, the core and Q1 shell contact each other, which would completely quench fluorescence when the core is a QD. Furthermore, these gold shells are too thick for efficient QD fluorescence transmission, and the thickness cannot be

further reduced because the gold surface roughness is already 4 nm because of the large size of the gold nuclei.

The present invention provides fluorescent gold-coated nanostructures using biomolecules as the structural scaffold. In the method for preparing the nanostructures, lipid-stabilized water-soluble QDs are coated with a layer of polyamine (e.g., peptide such as poly-L-histidine (PLH)), which serves as the gold deposition template. In contrast to the commonly used primary amines, an important feature of PLH is that its histidine groups are capable of immobilizing Au^{3+} ions at very high packing density for deposition of thin and smooth gold shells. For QD encapsulation, because HAuCl_4 is highly acidic, the pH of the reaction solution was adjusted to 9-10 with NaOH to avoid QD damage. The separation between the QD core and the gold shell is determined by the size of the polyethylene glycol (PEG) chains and can be increased with nanometer precision by adding alternating polyelectrolyte monolayers, such as polyallylamine hydrochloride (PAH, cationic) and sodium polystyrene sulphonate (PSS, anionic), a process also known as layer-by-layer (LBL) assembly (see FIGURE 1B).

FIGURES 2A-2D show representative transmission electron microscopy (TEM) images of the QD-gold core-shell nanoparticles (FIGURES 2C and 2D) and the original organic-soluble QDs (FIGURE 2A) and water-soluble QDs (FIGURE 2B) coated with lipids and PLH. Commercial QDs with narrow emission peaks (full-width at half-maximum (FWHM), 32 nm) centered at 655 nm were used as the starting materials, which were insoluble in water. The lipid-based QD surface-coating method was highly efficient in transferring QDs into aqueous solutions yielding well dispersed particles (FIGURE 2B). The soluble QDs remained single with successive adsorption of PLH and gold ions. After further gold deposition using a mild reducing reagent, hydroxylamine, the core-shell structure was revealed by TEM (FIGURES 2C and 2D). The shell thickness was about 2-3 nm, with a transparent gap of 3 nm observed between the core and shell because the sandwiched organic materials are not electron-dense enough for TEM visualization. This separation unambiguously shows that the gold deposition was not directly on (i.e., contacting) the core particle surface, but was templated by the polymer outer layer.

The optical properties of the QD-gold nanoparticles were characterized. The QDs absorbed over a broad spectrum with increasing molar extinction coefficient towards shorter wavelengths and a first quantum confinement peak of 646 nm (FIGURE 3A).

After gold shell encapsulation, the QD absorption was obscured by the strong gold surface plasmon resonance (SPR) peak centered at 583 nm. A key question was whether the encapsulated QDs would remain fluorescent, because gold nanostructures are known fluorescence quenchers and a gold shell will also limit photon transmittance.

5 Quantitative spectroscopy measurements revealed that the original organic-soluble QDs and the lipid coated water-soluble QDs shared a similar quantum yield (QY) of 75%, whereas that of the QD-gold nanoparticles decreased to 18% (FIGURE 3C). Despite this fluorescence intensity decrease, the emission peak position did not shift. Detailed stepwise investigation of the synthesis revealed that the quenching occurred

10 instantaneously upon the introduction of Au^{3+} ions, and this process accounted for approximately half of the total quenching effect. Although the exact mechanism is unclear at this time, likely a small number of Au^{3+} ions penetrated through the PEG layer and directly interacted with the QD surface. Several lines of evidence support this observation. The quenching effect was also observed for the control experiment without

15 the PLH coating layer, indicating that the quenching was not due to the Au^{3+} ions adsorbed on the polymer. For QDs solubilized with small-molecule mercapto compounds, the fluorescence was completely quenched due to the higher accessibility of Au^{3+} to the QD surface. In addition, a similar effect has been observed previously with Ag^+ , Pb^{2+} and Cu^{2+} ions and has been attributed to cation exchange in the nanocrystals'

20 lattice.

Another factor that could affect the fluorescence is the thickness of the gold shell. The thicker the shell, the more fluorescence will be blocked. Based on the peptide templated gold deposition, a 2-3 nm thin gold layer was achieved. Under the experiment conditions (excitation 400 nm and emission 655 nm), the light transmittance values for

25 excitation and emission were 86% and 92% through the thin gold shell, collectively resulting in about 20% fluorescence attenuation. The QD fluorescence decreased gradually with slight increase of the gold shell thickness and was significantly quenched when this was greater than 5 nm. A further factor that affects the QD fluorescence is the gold shell SPR, which can simultaneously quench and enhance the QD fluorescence

30 (competing processes) depending on the spacing between the two materials and the spectral overlap between the QD fluorescence and the gold SPR. At short separation distance and significant overlap between QD emission and gold SPR bands, the

quenching effect dominates, whereas long distance and spectral overlap of QD absorption and gold SPR result in more pronounced field enhancement.

To optimize the QD-gold nanoparticle synthesis for improved fluorescence, the QD core and gold shell separation was increased with successive adsorption of cationic and anionic polymers by means of LBL assembly, which is capable of reducing Au³⁺ diffusion to the QD surface and tuning the distance between the QD and gold with nanometer precision. Unlike on flat surfaces, however, LBL on nanometer-sized particles requires multiple rounds of centrifuge-based purification for every layer of polyelectrolyte deposition (experiments described herein use three rounds for every polymer coating layer), which consequently results in an overall low QD recovery. From the TEM images, small but statistically meaningful increments of the gap between the two electron-dense materials were measured. FIGURE 13F shows the histograms of the gap distribution obtained from more than 100 particles with zero, one and two bilayers. The average separations are 3.0 ± 0.5 , 3.9 ± 0.6 and 4.6 ± 0.6 nm, respectively, which are smaller than the previously reported PAH/PSS bilayer thickness (about 1.2 nm) and could originate from the limited TEM image resolution and slight gold shell infiltration into the polyelectrolyte bilayers. Nevertheless, reproducible and quantitative fluorescence spectroscopy shows that the QD quantum yield increased to 33% with one additional bilayer of polyelectrolyte coating and 39% for two bilayers.

As well as the preserved QD fluorescence, two additional striking features were observed for the QD-gold core-shell nanoparticles of the invention. First, although QDs are known for their stability against photobleaching, the gold-encapsulated QDs exhibited significantly improved photostability over the lipid-stabilized water-soluble QDs, and even outperformed the original organic-soluble QDs under identical illumination conditions (FIGURE 4A). This surprising feature is likely due to limited diffusion of oxygen through the gold shell because QD photobleaching is mainly caused by surface oxidation. Second, the strong scattering property of the gold shell renders the QD-gold an excellent dual-modality imaging probe. As shown in FIGURES 4B-4G, samples of dilute uncoated and gold-shell-encapsulated QDs were spread on glass coverslips, resulting in spatially isolated single nanoparticles on the surface. Fluorescence and dark-field imaging show that the uncoated QDs were fluorescent but not plasmonic. In contrast, the QD-gold nanoparticles in the fluorescence and dark-field imaging micrographs show nearly complete overlap, which also confirms the successful

encapsulation of QDs with thin gold shells. It is widely known that each type of nanoprobe has distinct advantages as well as limitations. This new class of multimodality nanoprobe will allow imaging with both fluorescence and scattering as well as light-triggered photo thermal treatment (particularly when the surface plasmon band is
5 tuned to the NIR region). These modes of imaging and therapy cannot be achieved simultaneously with the traditional small molecule-, amphiphilic polymer-, and silica-coated QDs.

The present invention provides gold-shell encapsulated QDs prepared by peptide-templated shell growth. Although gold nanoparticles have been demonstrated as
10 efficient fluorescence quenchers, the spacing between the QD core and the gold shell in the gold-coated nanostructures of the invention resulted in QDs with a quantum yield of 39%. The thin gold shell also exhibits strong surface plasmon scattering, which makes the QD-gold nanoparticles an excellent dual-modality imaging probe. In addition, because recently reported monodisperse nanostructures often have a similar surface
15 chemistry as QDs (for example, monolayer of hydrophobic ligands), this technology can serve as a general route for encapsulating a variety of discrete nanomaterials and modulating their surrounding electromagnetic field. Because the degradation rate of the gold shell under physiological conditions is significantly lower than those of small-molecule, silica and amphiphilic polymer coating layers, the gold-coating
20 methodology described herein can prevent toxic chemicals from being released into the biological environment. This improved stability represents a potential solution to converting toxic nanomaterials into biocompatible materials, a critical step towards translational nanotechnology.

In another aspect, the present invention provides compact, uniform, NIR-
25 responsive MNP-gold core-shell nanostructures having a gap between the particle core and shell. The nanostructures of the invention are magnetically-sensitive having with strong NIR and MR responses, and enable a new modality, magnetomotive photoacoustic (mmPA) imaging. Compared to photoacoustic (PA) imaging using conventional metallic NPs, mmPA imaging with a coupled agent provides the same sensitivity, but with
30 markedly improved contrast specificity. Indeed, all PA signals not created by the coupled NP potentially can be suppressed to the electronic noise limit of the imaging system.

In contrast to particles in which gold shells are deposited directly on iron oxide or iron oxide-silica composites, the core and shell of the nanostructures of the present

invention are spatially separated with a dielectric polymer layer. This method allows formation of uniform MNP-gold particles simultaneously being compact in size and responsive in the NIR spectrum, which have not been achieved previously. The resulting NPs show highly integrated properties including electronic, magnetic, optical, acoustic, and thermal responses, which allow multimodality imaging. Beyond conventional NP based imaging modalities such as TEM, optical imaging, MRI, and photoacoustic (PA) imaging, coupling of magnetic motion with photothermal conversion enables magnetomotive photoacoustic (mmPA) imaging, a new modality with remarkable contrast enhancement compared to conventional PA imaging. The gold-coated nanostructures have a surface that allows simple conjugation with biomolecular targeting ligands to develop all-in-one nanostructures for noninvasive imaging, molecular diagnosis, and hyperthermia-based treatment of complex diseases.

The preparation and characteristics of a representative nanostructure of the invention, a gold-coated magnetic nanoparticle, are described in Example 2.

In certain embodiments, MNP-gold NPs can be manipulated for mmPA imaging. For example, during real-time PA data acquisition, a pulsed magnetic field can be applied wherein voxels within the imaging region experience a force induced by the local field and magnetization. When the field is on, MNP-gold NPs move as a result of their strong magnetization, creating a moving source within a PA image. When the field is turned off, MNP-gold NPs return to their original positions. In one embodiment, the magnetic field can be pulsed on and off such that a shaking motion is achieved. Non-magnetic PA sources do not move coherently with the applied field during this entire interval. Consequently, coherent motion processing of a PA image sequence can identify sources related to MNP-gold NPs and reject all background signals whether from diffuse or localized sources. Such processing can greatly enhance the contrast specificity of the NP (e.g., by suppressing background signal in molecular imaging).

A schematic illustration of the preparation of a representative gold-coated magnetic nanoparticle of the invention (MNP-gold NP) is shown in FIGURE 9A. In the method, monodisperse MNPs with hydrophobic surface ligands (e.g., oleic acid) are first solubilized into aqueous solution using phospholipids (PL)-polyethylene glycol terminated with carboxylic acid (PL-PEG-COOH). The hydrophobic PL segment interdigitates with oleic acids through hydrophobic interactions, and the PEG block facing outward renders the MNPs water-soluble and negatively charged due to the

terminal carboxylic acids. To create anchor points for gold shell growth, a layer of positively charged peptide, poly-L-histidine (PLH), is adsorbed onto the outer surface of MNP-PEG via charge-charge interaction at pH 5-6. Zeta potentials of the PEG solubilized MNPs before and after coating with PLH were -15.5 and +9.1 mV, respectively. This surface charge inversion suggests a successful layer-by-layer surface coating of polyelectrolytes (ionic polymers) on the NP surfaces.

In contrast to commonly used primary amines, the histidine groups in PLH are capable of immobilizing Au^{3+} ions on QD surfaces at high packing density. The multilayer organic molecules coated on the MNP surface (oleic acid, PL-PEG, and PLH) act as an effective barrier preventing gold ions from direct growth on the iron oxide core. Further reduction of Au^{3+} with a reducing reagent leads to the formation of multifunctional MNP-gold core-shell particles with clear separation and only small size increase over the original MNPs. The resulting MNP-gold nanoprobe provides contrast not only for conventional modalities such as TEM, optical imaging, PA imaging, MRI, but also for the new modality of mmPA imaging.

FIGURE 9B illustrates how MNP-gold NPs can be manipulated for mmPA imaging. During real-time PA data acquisition, a pulsed magnetic field is applied. Voxels within the imaging region experience a force induced by the local field and magnetization. When the field is on, MNP-gold NPs move as a result of their strong magnetization, creating a moving source within a PA image. When the field is turned off, MNP-gold NPs return to their original positions. Non-magnetic PA sources do not move coherently with the applied field during this entire interval. Consequently, coherent motion processing of a PA image sequence (FIGURE 9C) can identify sources related to MNP-gold NPs and reject all background signals whether from diffuse or localized sources. Such processing can greatly enhance the contrast specificity of the NP. By comparison, bare MNPs are not a suitable contrast agent for PA or mmPA imaging even though they can respond to magnetic field. Bare MNPs do not absorb efficiently in the NIR and, consequently, exhibit poor PA efficiency. Large NIR absorption per particle is required for all PA applications.

Although the methods for making MNP-gold NPs of the invention apply to MNPs of various sizes, the synthesis, characterization, and applications of the coupled nanoprobe discussed below are focused on one representative MNP having a 25 nm diameter (FIGURE 10A). TEM images show MNP-gold core-shell NPs with different

shell thickness and a gap of about 3 nm between core and shell due to the low electron density of the embedded organic molecules. In contrast to conventional approaches in which only thick gold nanoshells can be coated onto NPs, PLH templated gold deposition can be controlled with nanometer precision to form an ultrathin and relatively smooth
5 shell layer. As a result, a gold nanoshell less than 3-4 nm thick enabled direct observation of the internal structure of the MNP-gold core-shell NPs (FIGURES 10B and 10C). When the shell thickness was slightly increased to 4-5 nm, the core-shell internal structure disappeared and manifested as solid dark dots (FIGURE 10D). Note that the 4-5 nm shell thickness was not directly measured (not visible under TEM), but was
10 derived from the overall particle size increase compared with original MNPs and MNPs coated with thin gold layers (FIGURES 10D and 10d1).

Given that TEM imaging under inappropriate focusing conditions could possibly show blurred ring structures around NPs, high resolution TEM (HR-TEM) was also performed to ensure that the core-shell structure observed was not an imaging artifact.
15 Two representative images are show in FIGURES 10E and 10F. Despite their relatively low contrast compared to low-magnification images on ultrathin nanomaterials, the signature crystal lattices of the MNP core and the gold shell are clearly visible, which unambiguously confirms the core-shell structure.

The optical and magnetic properties of the gold-coated magnetic nanoparticles as well as their stability against NIR laser irradiation was characterized. The core-shell NPs display shell-type NIR absorption. FIGURE 11A shows the extinction spectra of MNP-gold core-shell hybrid particles corresponding to the TEM images shown in FIGURES 10A-10D. In comparison to MNPs successively coated with PL-PEG-COOH and PLH polymer layers exhibiting negligible NIR absorption, the surface plasmon
20 resonance (SPR) band appeared in the NIR spectrum with formation of thin gold nanoshells. The SPR peaks of the core shell structures are significantly enhanced (intensity well above that of the original MNP core), which is desirable for photoacoustic imaging. Note that the elevated curves are part of the extinction signals instead of noise, which is commonly seen in shell-type plasmonic materials. For 1-2 nm thick gold shells,
25 the SPR band centered around 900 nm. As the thickness increased to 2-3 nm and 4-5 nm, SPR extinction peak blue-shifted to 760 nm and 660 nm, respectively, following a similar trend to that of silica-gold nanoshells. This spectroscopic measurement confirms the
30 electron microscopy results of FIGURE 10 showing that the gold shell is separated from

the iron oxide core (red-shift in the visible spectrum with increasing shell thickness would be expected otherwise). The extinction peaks of hybrid NPs are broader than theoretical values. This kind of line broadening is commonly seen in virtually all gold shell nanostructures and has been attributed to the combination of a number of factors including phase retardation effects, size distribution of both cores and shells, and electron scattering at the shell interfaces.

The magnetization of the hybrid NPs (2-3 nm gold shell) was measured using superconducting quantum interference device (SQUID) magnetometry. The temperature dependence of the zero-field-cooled/field-cooled (ZFC/FC) magnetization is shown in FIGURE 15. The two curves overlap at high temperature and quickly depart from each other as the temperature decreases. The ZFC curves show maxima at 275 K and 270 K (blocking temperature, T_b) for MNPs before and after coating with thin Au shells, which is characteristic behavior of superparamagnetism. The T_b s of MNPs are well below room temperature and the slight decrease after surface coating has been previously observed as well. It is believed to reflect the decreased coupling of the magnetic moments as a result of the increased interparticle spacing of magnetic cores, which is due to a combination of the Au and the polymer capping shells for the hybrid NPs. For superparamagnetic colloids, the M - H curve should not show hysteresis when measured above T_b . Indeed, no hysteresis was detected at room temperature after MNPs were coated with a thin gold shell and the saturation magnetization of the magnetic cores was only reduced slightly (FIGURE 11B). The compact core-shell NPs do not aggregate in solution, but respond magnetically. When an external magnetic field was applied, the NPs were slowly isolated by the magnetic force ($> 3h$). The remaining liquid became colorless, indicating that the plasmonic response was indeed due to gold nanoshells on MNPs instead of self-nucleated gold NPs (FIGURE 11B inset).

Particle stability under NIR laser irradiation was characterized because the biomedical applicability of these gold-coated magnetic nanoparticles strongly depends on probe stability. Compared with two popular gold-based NIR-responsive nanoprobes, nanorods and nanocages, each of which have been used in imaging and therapy, the MNP-gold core-shell NPs exhibited remarkable stability under identical laser irradiation. As shown in FIGURE 11C, both gold nanorods and nanocages were stable at laser fluences below 2 and 6 mJ/cm², respectively. Above these fluences, significant SPR peak shifts were observed indicating nanoprobe degradation. In contrast, only slight peak

shifts were observed for the MNP-gold NPs when the laser fluence was increased to 10-15 mJ/cm². Significant spectral shifts were also observed when the laser fluence was further increased.

To demonstrate the use of the gold-coated magnetic nanoparticles for multimodality imaging, the MNP-gold NPs tested with conventional modalities, including dark field, and PA and MR imaging. In addition to the TEM images shown in FIGURE 10 based on the high electron density of both core and shell materials, MNP and gold have highly complementary features for other imaging modes. As shown in FIGURES 12A and 12B, the strong scattering property of gold nanoshell makes the NPs an excellent optical imaging probe. Samples of dilute uncoated and gold shell encapsulated MNPs were spread on glass coverslips, resulting in spatially isolated single NPs on the surface. Under dark field imaging conditions, the MNP-gold NPs are easily detectable while the original MNPs are not. Although scattering-based imaging does not allow deep tissue imaging, MRI does. To demonstrate the MRI capability of the gold-coated magnetic nanoparticles, they were compared to conventional MNPs. Serial dilutions of MNPs with and without the gold nanoshell coating exhibited nearly identical image contrast (FIGURE 12C), which confirmed the SQUID results that the MNPs maintained their magnetic properties after coating with thin gold shells.

In addition to scattering, the second feature unique to the gold nanoshell is the strong NIR absorption, and companion energy release in the form of heat, which can be utilized for photothermal therapy and PA imaging. Compared with the shallow photon penetration depth of scattering techniques, PA imaging can sample optical phenomena within tissue to a depth of several centimeters. It is also significantly less expensive to operate and more portable than MRI. Absorption of pulsed NIR laser light creates acoustic sources within tissue, where the source strength is proportional to the local absorption of the optical pulse. An image is formed using conventional ultrasound technology, where PA contrast is directly related to optical absorption.

To test the efficacy of MNP-gold particles as PA contrast agents, water solutions consisting of no particle, 5 nm MNPs, and 5 nm MNP-gold NPs were injected sequentially into a polycarbonate tube and illuminated with a 750 nm pulsed laser. FIGURES 12D and 12E show cross-sectional PA images of the tube corresponding to the different solutions on a decibel (dB) scale, with 0 dB corresponding to the maximum signal level across all images. Compared to the MNP solution, MNP-gold of the same

concentration improved image signal-to-noise ratio by nearly 1 order of magnitude (i.e., 20 dB) due to the strong gold-shell SPR absorption.

MNP-gold NPs' strong magnetization and NIR absorption were demonstrated to enable mmPA imaging with significantly improved contrast specificity compared with conventional PA imaging. A 3-mm thick, 10% polyvinyl alcohol (PVA) disk was constructed as an imaging phantom. It contained three 2-mm diameter cylindrical inclusions made of 10% PVA mixed with 8% 15-um polymer beads. The first, containing gold nanorods with comparable absorption coefficient as 3 nm MNP-gold hybrid NPs, serves as a magnetic reference, i.e., a localized "background" region to be suppressed in mmPA imaging. The second, containing 3 nm MNP-gold hybrid NPs, serves as an object of interest. Third, containing 3 nm MNPs, serves as an optical reference. An electromagnet generating 5-s 0.7-Tesla pulses was placed under a water tank holding the phantom. FIGURE 13A shows a cross-sectional PA image on a dB scale of the PVA phantom at 720 nm optical wavelength with 0 dB corresponding to the maximum signal level across all images. The inclusion with MNP-gold hybrid NPs (middle) is one order of magnitude (i.e., 20 dB) brighter than the one with MNPs (right), in agreement with FIGURE 11A. While the inclusion with gold nanorods (left) has comparable PA strength to that with MNP-gold hybrid NPs, it is suppressed in the mmPA image shown in FIGURE 13G.

An mmPA image can be derived from a series of PA images in a variety of ways. FIGURE 13 illustrates the current signal processing scheme. A conventional PA image (FIGURE 13A) sequence was acquired in synchrony with a magnetic pulse. The displacement of each pixel in a PA image from its initial position was tracked using a conventional speckle tracking algorithm over the entire 10 second interval, with the magnetic pulse spanning the first 5 seconds. FIGURE 13B shows the maximum displacement at the end of the magnetic pulse. For each pixel, the displacement was fitted as linear functions of time over the two 5-second intervals when the field was on/off. A pixel with positive slope in the first half and negative slope in the second half was subsequently fitted to two cascaded exponential functions using nonlinear least squares curve fitting. Three representative fitted curves are shown in FIGURE 13C for three pixels within the inclusions. Using these curves at every pixel, the velocity was computed over the full 10-second interval (not shown), and the maximum positive and negative velocities, shown in FIGURES 13D and 13E, were used to create a weighting

image (FIGURE 13G) based on the magnitude of the difference between the peak positive velocity in the first half and the peak negative velocity in the second half. FIGURE 13G shows the mmPA image produced from the product of FIGURE 13A and FIGURE 13F, where the gold nanorod inclusion is almost completely suppressed.

5 Although the principle of suppressing strong PA sources not susceptible to an applied magnetic field (e.g., the gold nanorod inclusion above) in mmPA imaging has been demonstrated, finite background motion in real clinical imaging from physiological sources such as cardiac motion and respiration can interfere with induced motion. Other imaging modalities, such as acoustic radiation force impulse (ARFI) imaging and thermal
10 strain imaging (TSI), have a similar problem of tracking small induced displacements during physiologic motion. Robust signal processing methods have been developed to track induced motion by synchronizing the data acquisition sequence with physiologic motion. Similar methods can be developed for clinical applications of mmPA imaging.

 In mmPA imaging, the induced motion depends not only on the magnetic field,
15 but also on tissue elastic properties. Therefore, in biomedical applications, it is hard to quantitate the contrast agent concentration based on motion alone. For example, displacements and velocities in the MNP inclusion were slightly greater than those in the MNP-gold hybrid NP inclusion primarily because of differences in the elasticity of the inclusions (FIGURE 16). However, the induced motion, regardless of scale, is coherent
20 with the applied magnetic field. By detecting motion in response to a time-varying magnetic field, contrast can be greatly improved. The ability to enhance regions with targeted contrast agents makes mmPA imaging an attractive modality for molecular diagnostics. In addition, because the displacement time course depends on tissue elastic properties (e.g., after the magnetic field is turned off, displaced tissue moves back to its
25 original position subject only to intrinsic elastic properties such as relaxation), mmPA imaging can potentially also be used for elasticity imaging.

 The following examples are provided for the purpose of illustrating, not limiting the invention.

EXAMPLES

30 Materials and General Methods

 Unless specified, chemicals were purchased from Sigma-Aldrich and used without further purification. Organic soluble CdSe/ZnS QDs (QDOT[®] 655 ITK[™]) were purchased from Invitrogen. Lipid (PL)-PEG-COOH (DSPE-PEG₂₀₀₀ carboxylic acid)

was purchased from Avanti Polar Lipids. Poly(allylamine hydrochloride) (M_{w3} , 15,000) and polystyrene sulphonate (Na salt) (M_w , 8,000, Polysciences) were used for the LBL polyelectrolyte deposition. Poly-L-histidine hydrochloride (PLH) ($M_w \geq 5,000$) was used as the template to direct gold nucleation and growth. Oleic acid-capped monodisperse superparamagnetic iron oxide nanocrystals of different sizes were a gift from Oceannanotech LLC. A UV-2450 spectrophotometer (Shimadzu) and a Fluoromax4 fluorometer (Horiba Jobin Yvon) were used to characterize the absorption and emission spectra. A table-top ultracentrifuge (Beckman TL120) was used for nanoparticle purification and isolation. Particle size was measured on a CM100 transmission electron microscope (Philips EO, Netherlands). HRTEM analysis was performed on a FEI TECNAI G2 F20 S-TWIN electron microscope. Fluorescence and dark-field images were obtained with an IX-71 inverted microscope (Olympus, San Diego, CA) and a Q-color5 digital color camera (Olympus). For fluorescence imaging, broadband excitation in the blue range (460-500 nm) was provided by a mercury lamp. A long-pass dichroic filter (505 nm) and emission filter (510 nm, Chroma Technologies) were used to reject the scattered light and to pass the Stokes-shifted fluorescence signals. SQUID magnetometry was measured at 300K on a Quantum Design MPMS-5S SQUID Magnetometer (Quantum Design, San Diego, CA).

Example 1

Representative Gold-Coated Nanostructures: Gold-Coated Quantum Dots

In this example, the preparation and characteristics of a representative gold-coated nanostructure of the invention, gold-coated quantum dots, are described.

Organic-soluble QD₆₅₅ nanoparticles (1 μ M solution in decane, 100 μ l) were first flocculated by using a 4x methanol/isopropanol mixture (v/v 75/25), and resuspended in chloroform (1 ml). Lipid-PEG-COOH (3 mg) was added to the solution and sonicated for 5 min followed by removal of the chloroform by evaporation. The residual solid was heated to 80 °C for 5 min, followed by addition of deionized (DI) water (1 ml). Excess lipids were purified out from the solubilized QDs using repeated ultracentrifugation (30,000 r.p.m. for 1 h, 3 times). The purified nanoparticles were redispersed in DI water (3 ml), to which PLH (1.5 mg) was added. The QDs and PLH were incubated at room temperature for about 1 h to allow PLH to adsorb onto the QD surface by electrostatic interaction. Excess PLH molecules were again removed by ultracentrifugation. The

purified QD-PLH with a final concentration of 5.2 nM was dispersed in DI water and stored for use.

For gold shell growth, 890 μ l of DI water and 10 μ l of HAuCl_4 (w/w 1%) aqueous solution (pH adjusted to 9-10 with NaOH) were added to 100 μ l of the QD-PLH, and incubated for about 10 min. A reducing agent NH_2OH (20 mM, 20 μ l) was then introduced to initiate the surface-confined gold shell growth. Upon mixing, the colloidal solution changed from colorless to brownish blue over a few minutes, indicating formation of gold nanoshells. After synthesis, PEG-SH can be used to enhance the colloidal stability.

To adjust the QD core and gold shell separation, PAH and PSS stock solutions (10 mg ml^{-1} in 1 mM NaCl solution) were used for the LBL polyelectrolyte deposition onto the lipid-PEG-coated QDs before deposition of PLH and gold. In a typical preparation, 0.5 ml of PAH solution was added and mixed with 3 ml of the above synthesized water-soluble QDs suspended in 1 mM NaCl. After 30 min incubation, unbound PAH was removed by ultracentrifugation (three rounds). The same procedure was repeated for additional layers of polyelectrolytes and finally capped with a layer of PLH for gold nucleation and growth.

The QD quantum yield (QY) was determined relative to rhodamine 101, as its QY is well documented. During each step of polyelectrolyte coating, the QY of the QD-polymer complex can be easily determined in the same manner. However, after gold shell formation on the surface of the QDs, the QD first extinction peak was buried by the strong gold plasmon peak, and as a consequence the QD concentration can no longer be determined using UV absorbance. Fortunately, due to the high reaction yield, virtually all QDs are encapsulated with a gold shell (confirmed with many randomly selected TEM images). Because the concentration of QDs before and after gold shell formation remained the same, the QY values of QD-gold can be calculated using QD-PLH as a reference in fluorescence spectroscopy measurements.

Example 2

Representative Gold-Coated Nanostructures: Gold-Coated Magnetic Nanoparticles

In this example, the preparation and characteristics of a representative gold-coated nanostructure of the invention, gold-coated magnetic nanoparticles, are described.

Solubilization of MNPs with PL-PEG-COOH was performed by first mixing 1.0 mg of the oleic acid coated MNPs with 1.4 mg of PL-PEG-COOH in 1 mL of

chloroform followed by slow evaporation of chloroform. The residual solid was heated to 80 °C for 5 min to completely removed chloroform. The MNPs became soluble after adding deionized (DI) water (1 ml) and brief sonication. Excess lipids were purified out from the solubilized MNPs with repeated ultracentrifugation (25,000 rpm for 1h X 3 times). The purified MNPs were redispersed in 4 mL of DI water, to which 1.1 mg of PLH was added. The pH of the solution was adjusted to 5-6 using 0.1 N HCl. After incubation of 60 min, MNPs coated with PLH were again purified with ultracentrifugation and dispersed in 5 mL DI water.

For gold nanoshell growth, 890 μ L of DI water and 10 μ L of HAuCl₄ (w/w 1%) aqueous solution (pH adjusted to 9-10 with NaOH) were added to 100 μ L of the MNP-PLH solution, and incubated for 20 min. A reducing agent NH₂OH (20 mM, 20 μ L) was then introduced to initiate the surface-confined Au shell growth. Upon mixing, the colloidal solution changed color from brownish-black to dark blue over a few minutes, indicating formation of gold nanoshells. The resultant gold shells are typically about 2-3 nm in thickness, which can be facilely tuned by changing the amount of gold ions. After synthesis, PEG-SH was used to enhance the colloidal stability.

For PA imaging, particle samples were injected into a polycarbonate tube (CTPC167-200-5, Paradigm Optics, Vancouver, WA; 167 and 200 μ m inner and outer diameters, respectively). A frequency doubled YAG pulsed laser (Surelite I-20, Continuum, Santa Clara, CA) with 5-ns pulse width pumped an optical parametric oscillator (Surelite OPO Plus, Continuum) to illuminate the tube at 750 nm wavelength and 3.3 mJ/cm² fluence. PA signals were received by the central 32 elements of an ultrasound linear array (L 14-5/38, Ultrasonix, Burnaby, BC, Canada) and recorded by an ultrasound scanner (Sonix RP, Ultrasonix). A delay-and-sum beam forming algorithm was used for image reconstruction. For NP stability against laser irradiation, samples were subjected to 30-min continuous irradiation at wavelengths close to the SPR peaks of each particle sample at fixed laser fluence.

For mmPA imaging, a phantom of 10% polyvinyl alcohol (PVA) disk with 3-mm thickness was constructed using three short freeze-thaw cycles. Three 2-mm diameter cylindrical inclusions made of 10% PVA mixed with 8% 15- μ m polymer beads (Bangs Laboratories, Inc., Fishers, IN) were placed within the phantom: the first one contained gold nanorods with about the same absorption coefficient as 3 nm MNP-gold hybrid NPs, the second contained 3 nm MNP-gold hybrid NPs, and the third contained 3 nm MNPs.

An electromagnet integrated with a DC power amplifier, a current amplifier, and a function generator (Agilent 33250A, Santa Clara, CA), producing 5-s 0.7-Tesla pulses, was placed under a water tank holding the phantom. A frequency doubled YAG pulsed laser (Surelite I-20, Continuum, Santa Clara, CA) with 5-ns pulse width pumped an optical parametric oscillator (Surelite OPO Plus, Continuum) to illuminate the PVA phantom at 720 nm wavelength and 2.3 mJ/cm² fluence. A 15-MHz single element transducer (Olympus, Waltham, MA) was translated to scan 1D PA images. The RF signal was acquired using an amplifier (AM-1300, MITEQ, Hauppauge, NY) and a digital oscilloscope (LeCroy, Chestnut Ridge, NY).

For MR imaging, samples were scanned with a 3.0T whole body MRI scanner (Achieva, Philips Healthcare) using a phased array wrist coil. MR images were obtained using a 2D multi-slice-multi-echo spin echo (SE) sequence with various echo times. The imaging parameters were as following: repetition time, 2500 ms; echo times, 10/30/50/70/100 ms; field of view, 10 cm; matrix, 256x256; and thickness, 2 mm.

While illustrative embodiments have been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A metal-coated nanostructure, comprising:
 - (a) a nanostructure core;
 - (b) a metal shell surrounding the core; and
 - (c) a cationic polymer intermediate the core and the shell.
2. The nanostructure of Claim 1, wherein the nanostructure core is a quantum dot.
3. The nanostructure of Claim 1, wherein the nanoparticle core is a carbon nanotube.
4. The nanostructure of Claim 1, wherein the nanostructure core is a magnetic nanoparticle.
5. The nanostructure of Claim 1, wherein the nanostructure core is a biological particle.
6. The nanostructure of any one of Claims 1-5, wherein the shell comprises a template grown metal.
7. The nanostructure of any one of Claims 1-6, wherein the shell comprises a plasmonic metal.
8. The nanostructure of any one of Claims 1-7, wherein the shell is a gold shell.
9. The nanostructure of any one of Claims 1-8, wherein the nanostructure core further comprises a hydrophobic surface.
10. The nanostructure of any one of Claims 1-9 further comprising a material intermediate the core and polymer.

11. The nanostructure of Claim 10, wherein the material is an organic material or an inorganic material.

12. The nanostructure of any one of Claims 10 or 11, wherein the material comprises polyethylene glycol.

13. The nanostructure of any one of Claims 10-12, wherein the material comprises a lipid-polyethylene glycol conjugate.

14. The nanostructure of any one of Claims 10-13, wherein the material further comprises one or more polyelectrolyte bilayers.

15. The nanostructure of any one of Claims 10-14, wherein the material comprises silica.

16. The nanostructure of any one of Claims 1-15, wherein the cationic polymer is a metal chelator.

17. The nanostructure of any one of Claims 1-16, wherein the cationic polymer is a polyamine.

18. The nanostructure of any one of Claims 1-17, wherein the distance between the core and the shell is from about 0.1 to about 200 nm.

19. The nanostructure of any one of Claims 1-18, wherein the shell has a thickness of from about 0.1 to about 30 nm.

20. The nanostructure of any one of Claims 1-19, wherein the shell is transmissive.

21. The nanostructure of any one of Claims 1-20, wherein the shell has a thickness of from about 2 to about 3 nm.

22. The nanostructure of Claim 1, wherein the nanostructure core is a quantum dot, the shell comprises a plasmonic metal, and the nanostructure is fluorescent.

23. A gold-coated quantum dot, comprising:

(a) a quantum dot core;

- (b) a gold shell surrounding the core; and
- (c) a cationic polymer intermediate the core and the shell.

24. The quantum dot of Claim 23, wherein the core further comprises a hydrophobic surface.

25. The quantum dot of any one of Claims 23 or 24 further comprising a material intermediate the core and polymer.

26. The quantum dot of Claim 25, wherein the material is an organic material or an inorganic material.

27. The quantum dot of any one of Claims 25 or 26, wherein the material comprises polyethylene glycol.

28. The quantum dot of any one of Claims 25-27, wherein the material comprises a lipid-polyethylene glycol conjugate.

29. The quantum dot of any one of Claims 25-28, wherein the material further comprises one or more polyelectrolyte bilayers.

30. The quantum dot of any one of Claims 25-29, wherein the material comprises silica.

31. The quantum dot of any one of Claims 23-30, wherein the cationic polymer is a metal chelator.

32. The quantum dot of any one of Claims 23-31, wherein the cationic polymer is a polyamine.

33. The quantum dot of any one of Claims 23-32, wherein the distance between the core and the shell is from about 0.1 to about 200 nm.

34. The quantum dot of any one of Claims 23-33, wherein the metal coating has a thickness of from about 0.1 about 30 nm.

35. The quantum dot of any one of Claims 23-34, wherein the shell is transmissive.

36. The quantum dot of any one of Claims 23-35, wherein the shell has a thickness of from about 2 to about 3 nm.

37. The quantum dot of any one of Claims 23-36, wherein the quantum dot is fluorescent.

38. A gold-coated magnetic nanoparticle, comprising:

- (a) a magnetic nanoparticle core;
- (b) a gold shell surrounding the core; and
- (c) a cationic polymer intermediate the core and the shell.

39. The magnetic nanoparticle of Claim 38, wherein the core further comprises a hydrophobic surface.

40. The magnetic nanoparticle of any one of Claims 38 or 39 further comprising a material intermediate the core and polymer.

41. The magnetic nanoparticle of Claim 40, wherein the material is an organic material or an inorganic material.

42. The magnetic nanoparticle of any one of Claims 40 or 41, wherein the material comprises polyethylene glycol.

43. The magnetic nanoparticle of any one of Claims 40-42, wherein the material comprises a lipid-polyethylene glycol conjugate.

44. The magnetic nanoparticle of any one of Claims 40-43, wherein the material further comprises one or more polyelectrolyte bilayers.

45. The magnetic nanoparticle of any one of Claims 40-44, wherein the material comprises silica.

46. The magnetic nanoparticle of any one of Claims 38-45, wherein the cationic polymer is a metal chelator.

47. The magnetic nanoparticle of any one of Claims 38-46, wherein the cationic polymer is a polyamine.

48. The magnetic nanoparticle of any one of Claims 38-47, wherein the distance between the core and the shell is from about 0.1 to about 200 nm.

49. The magnetic nanoparticle of any one of Claims 38-48, wherein the shell has a thickness of from about 0.1 about 30 nm.

50. The magnetic nanoparticle of any one of Claims 38-49, wherein the shell has a thickness of from about 2 to about 3 nm.

51. A method for making a metal-coated nanostructure, comprising:

(a) dispersing nanostructures in water to provide a plurality of individual nanostructures;

(b) adding a cationic polymer to the plurality of individual nanostructures dispersed in water to provide a plurality of nanostructures having cationic polymer attached thereto;

(c) adding a reducible metal ion complex to the plurality of nanostructures formed in step (b); and

(d) adding a reducing agent to the mixture of the reducible metal ion complex and the plurality of nanostructures having cationic polymer attached thereto to provide metal-coated nanostructures.

52. The method of Claim 51 further comprising adding a polyamine to the plurality of individual nanostructures in water followed by adding a polyanionic material to provide a plurality of nanostructures comprising a polyelectrolyte bilayer, prior to adding the cationic polymer.

53. The method of any one of Claims 51 or 52 further comprising adding a polyamine to the plurality of nanostructures comprising a polyelectrolyte bilayer followed by adding a polyanionic material to provide a nanostructure comprising two polyelectrolyte bilayers, prior to adding the cationic polymer.

54. The method of any one of Claims 51-53, wherein the cationic polymer is a polyamine.

55. The method of any one of Claims 51-54, wherein the reducible metal ion complex is a gold complex.

56. The method of any one of Claims 51-55, wherein the reducing agent is hydroxylamine.

57. A method for imaging, comprising administering to a subject or contacting a tissue with a nanostructure of any one of Claims 1-22, a quantum dot of any one of Claims 23-37, or a nanoparticle of Claims 38-50.

58. The method of Claim 57, wherein the nanostructure is a magnetic nanoparticle and imaging is magnetic resonance imaging.

59. The method of Claim 57, wherein the nanostructure is a magnetic nanoparticle and imaging is magnetomotive photoacoustic imaging.

60. The method of Claim 57, wherein the imaging is fluorescent imaging.

61. The method of Claim 57, wherein the imaging is based on scattering.

62. A method for sensing or detecting an analyte, comprising contacting a sample containing an analyte with a nanostructure of any one of Claims 1-22, a quantum dot of any one of Claims 23-37, or a nanoparticle of Claims 38-50, and measuring a change in fluorescence, absorption, and/or scattering of the nanostructure, quantum dot, or nanoparticle shell, wherein the change in absorption and/or scattering is indicative of the presence of the analyte in the sample.

63. The method of Claim 62, wherein the sensing or detecting is measured by surface plasmon resonance.

64. A method for treating a condition, comprising administering to a subject a therapeutically effective amount of a nanostructure of any one of Claims 1-22, and irradiating the subject with a wavelength of light sufficient to cause the metal shell to generate heat effective for hyperthermic therapy.

65. The method of Claim 64, wherein the nanostructure further includes a targeting agent to direct the nanostructure to a site of interest.

66. A photovoltaic device, comprising an active layer comprising a quantum dot of any one of Claims 23-37.

67. A light-emitting device, comprising an active layer comprising a quantum dot of any one of Claims 23-37.

68. Use of a quantum dot of any one of Claims 23-37 for optical and/or fluorescent imaging.

69. Use of a magnetic nanoparticle of any one of Claims 38-50 as a contrast agent for magnet resonance imaging.

70. Use of a magnetic nanoparticle of any one of Claims 38-50 as a contrast agent for magnetomotive photoacoustic imaging.

71. Use of a nanostructure of any one of Claims 1-22 as an agent for hyperthermic treatment.

72. A metal-coated surface, comprising:

- (a) a continuous surface;
- (b) a metal coating; and
- (c) a cationic polymer intermediate the surface and the coating.

73. The surface of Claim 72, wherein the continuous surface is a nanostructure surface.

74. The surface of any one of Claims 72 and 73, wherein the continuous surface is a nanoparticle surface.

75. The surface of any one of Claims 72-74, wherein the coating comprises a template grown metal coating.

76. The surface of any one of Claims 72-75, wherein the coating comprises a plasmonic metal.

77. The surface of any one of Claims 72-76, wherein the coating is a gold coating.

78. The surface of any one of Claims 72-77, wherein the continuous surface comprises a hydrophobic material.

79. The surface of any one of Claims 72-78 further comprising a material intermediate the surface and polymer.

80. The surface of Claim 79, wherein the material is an organic material or an inorganic material.

81. The surface of any one of Claims 79 or 80, wherein the material comprises polyethylene glycol.

82. The surface of any one of Claims 79-81, wherein the material comprises a lipid-polyethylene glycol conjugate.

83. The surface of any one of Claims 79-82, wherein the material further comprises one or more polyelectrolyte bilayers.

84. The surface of any one of Claims 79-83, wherein the material comprises silica.

85. The surface of any one of Claims 72-84, wherein the cationic polymer is a metal chelator.

86. The surface of any one of Claims 72-85, wherein the cationic polymer is a polyamine.

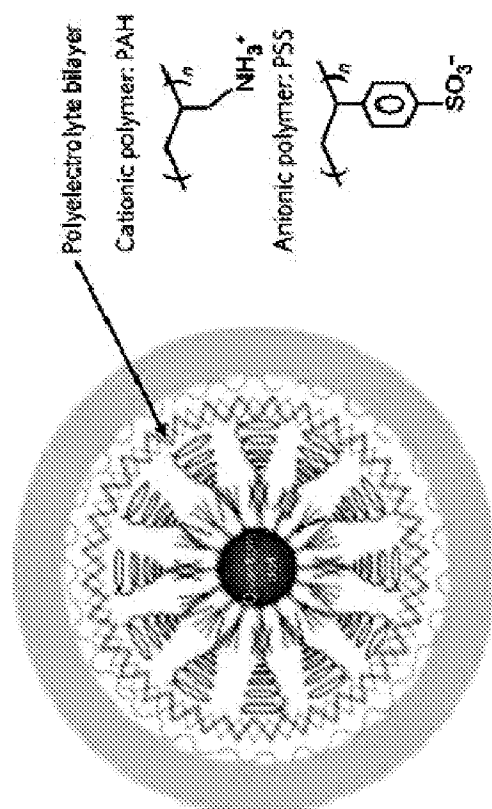
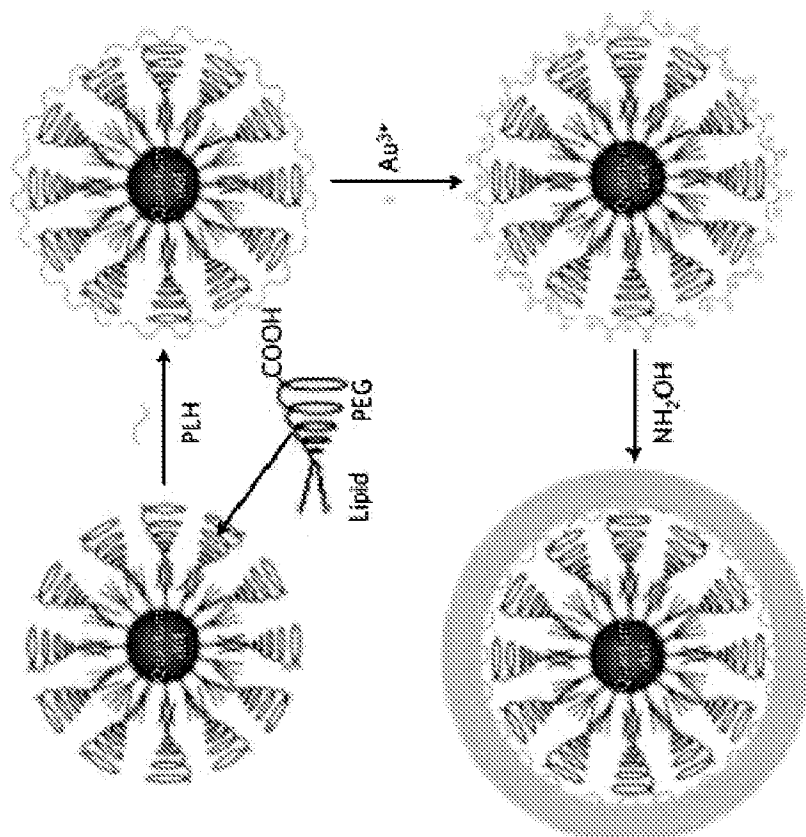
87. The surface of any one of Claims 72-86, wherein the distance between the continuous surface and the metal coating is from about 0.1 to about 200 nm.

88. The surface of any one of Claims 72-87, wherein the metal coating has a thickness of from about 0.1 about 30 nm.

89. A method for sensing or detecting an analyte, comprising contacting a sample containing an analyte with a surface of any one of Claims 72-88, and measuring a change in fluorescence, absorption, and/or scattering of the surface, wherein the change in fluorescence, absorption, and/or scattering is indicative of the presence of the analyte in the sample.

90. The method of Claim 89, wherein the sensing or detecting is measured by surface plasmon resonance.

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**Fig. 1B.****Fig. 1A.**

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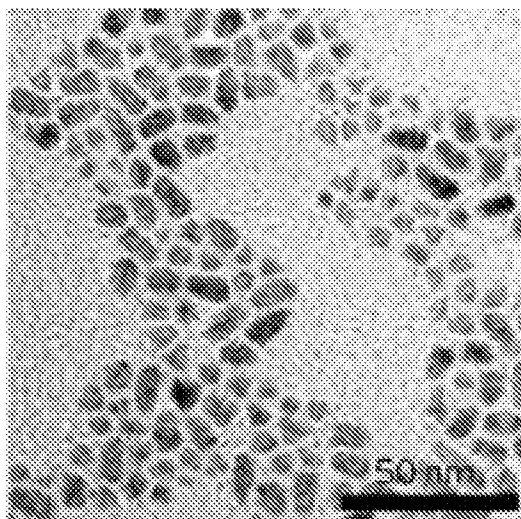


Fig. 2A.

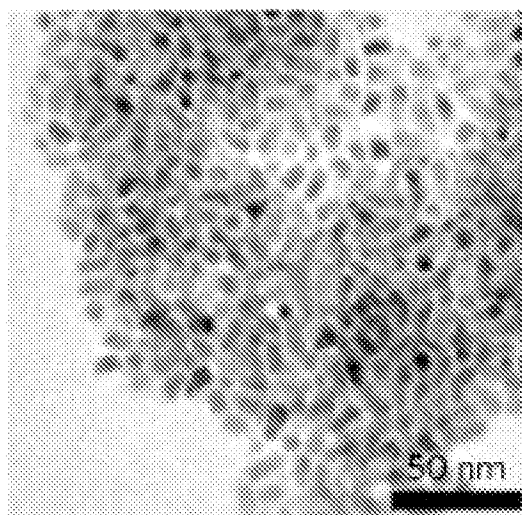


Fig. 2B.

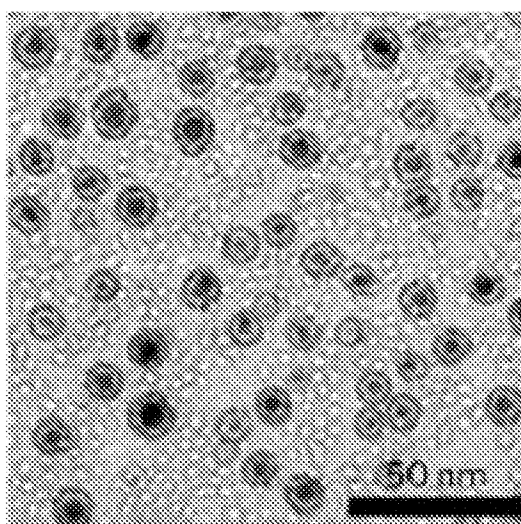


Fig. 2C.

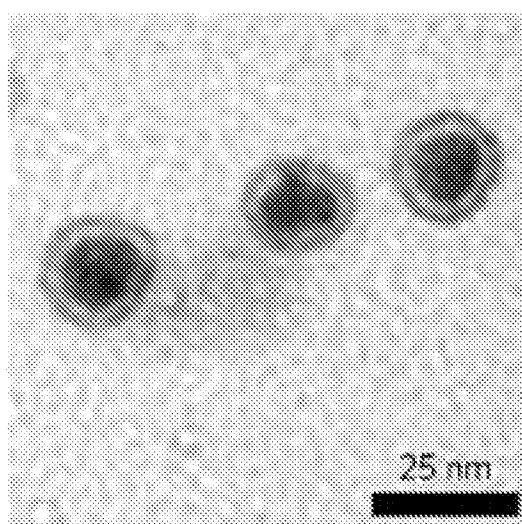
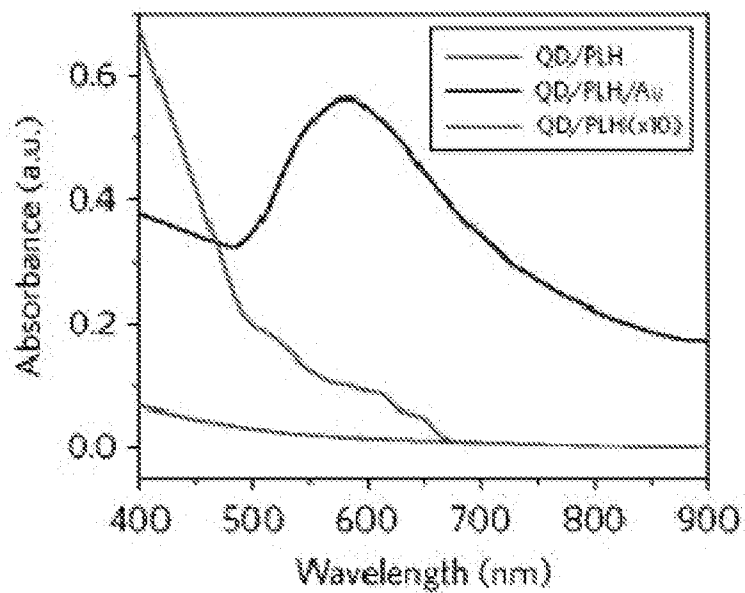
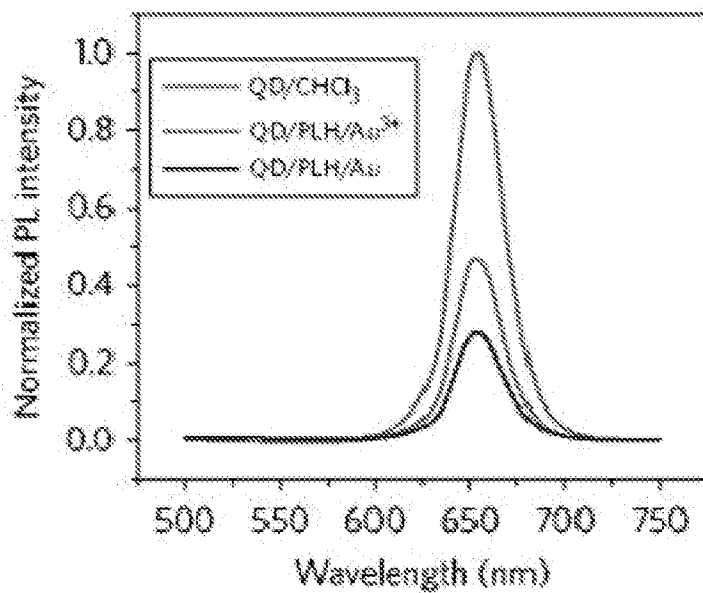
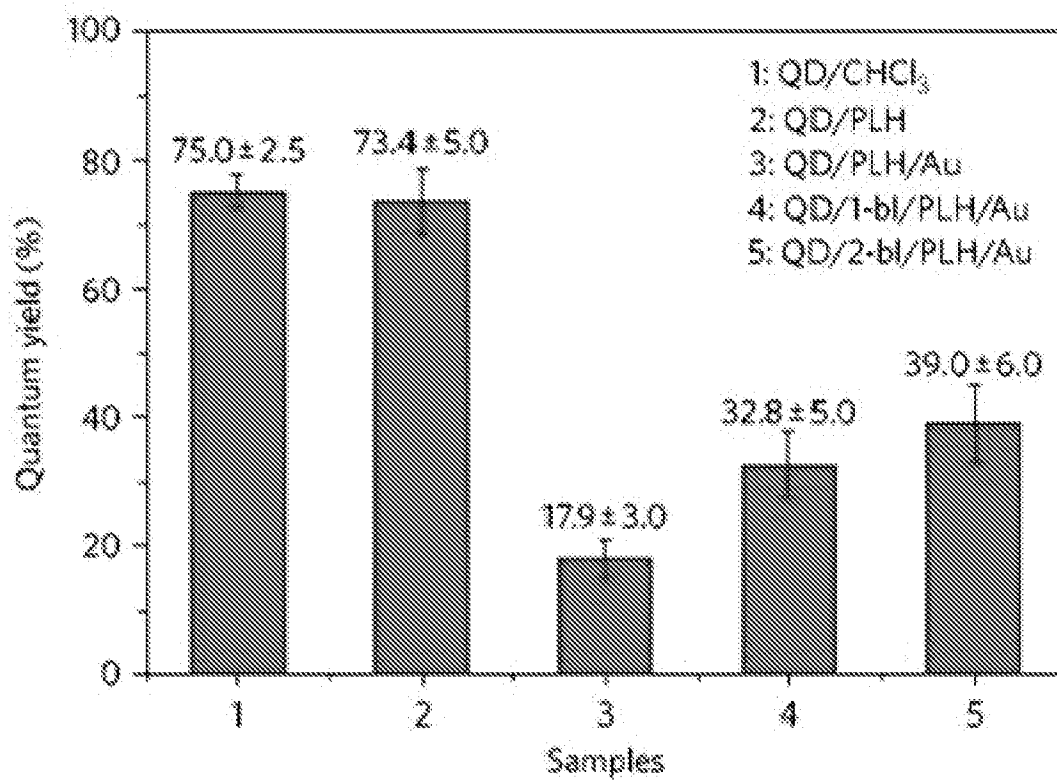


Fig. 2D.

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***Fig.3A.******Fig.3B.***

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*Fig.3C.*

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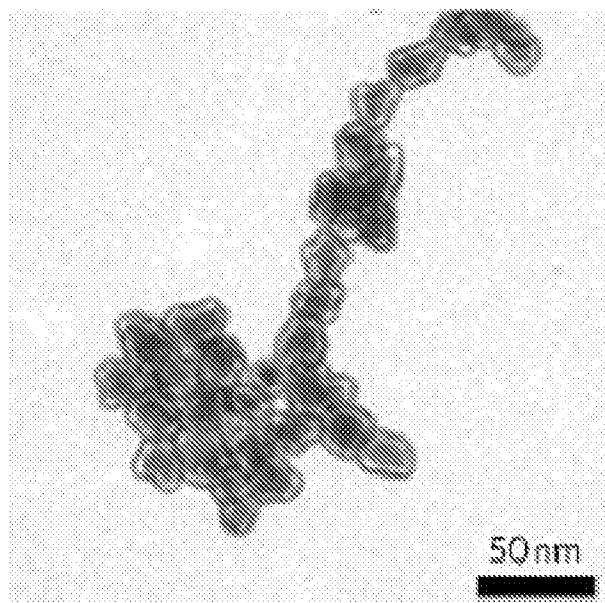


Fig.3D.

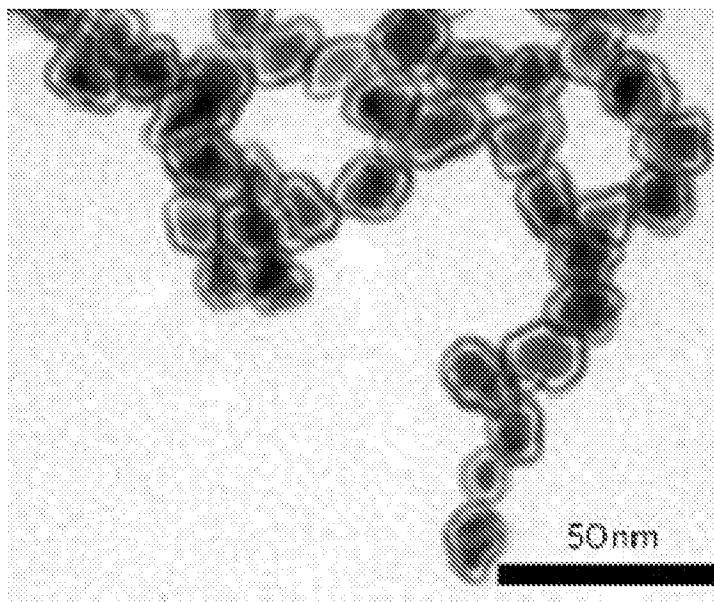
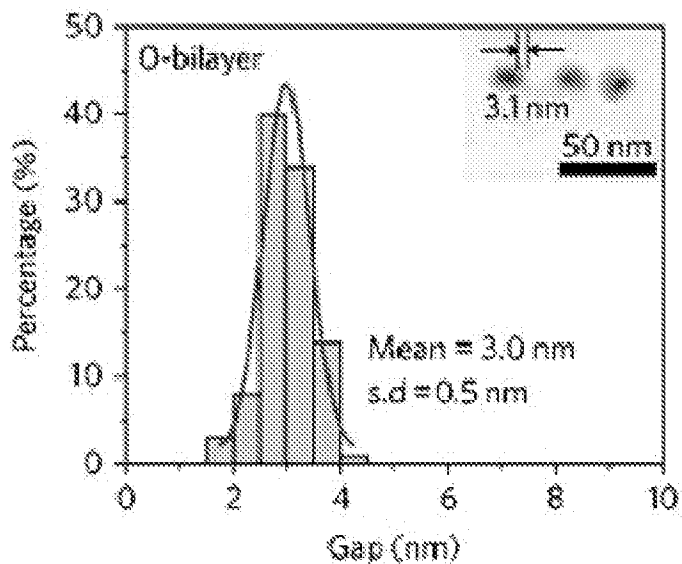
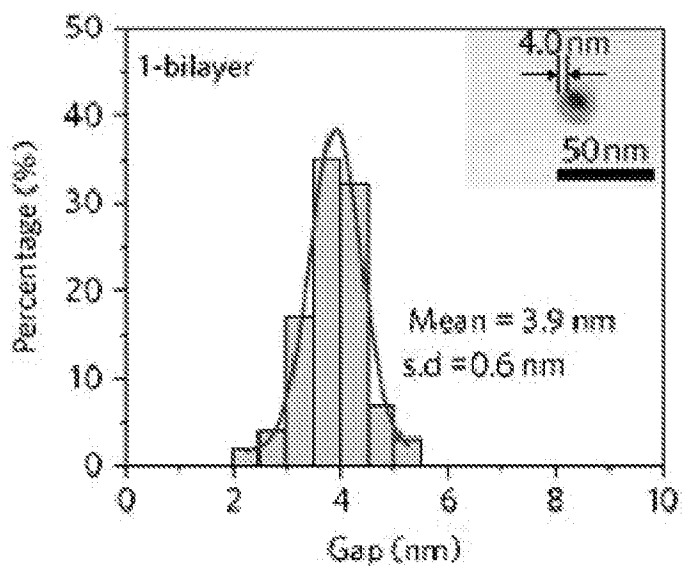
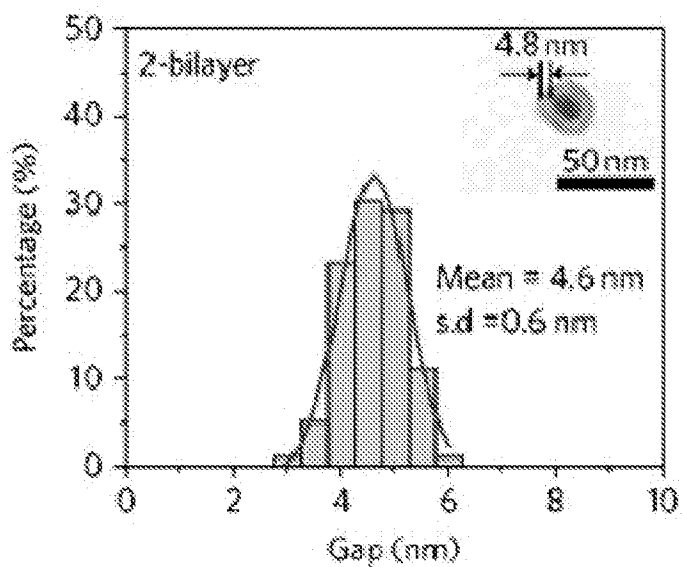
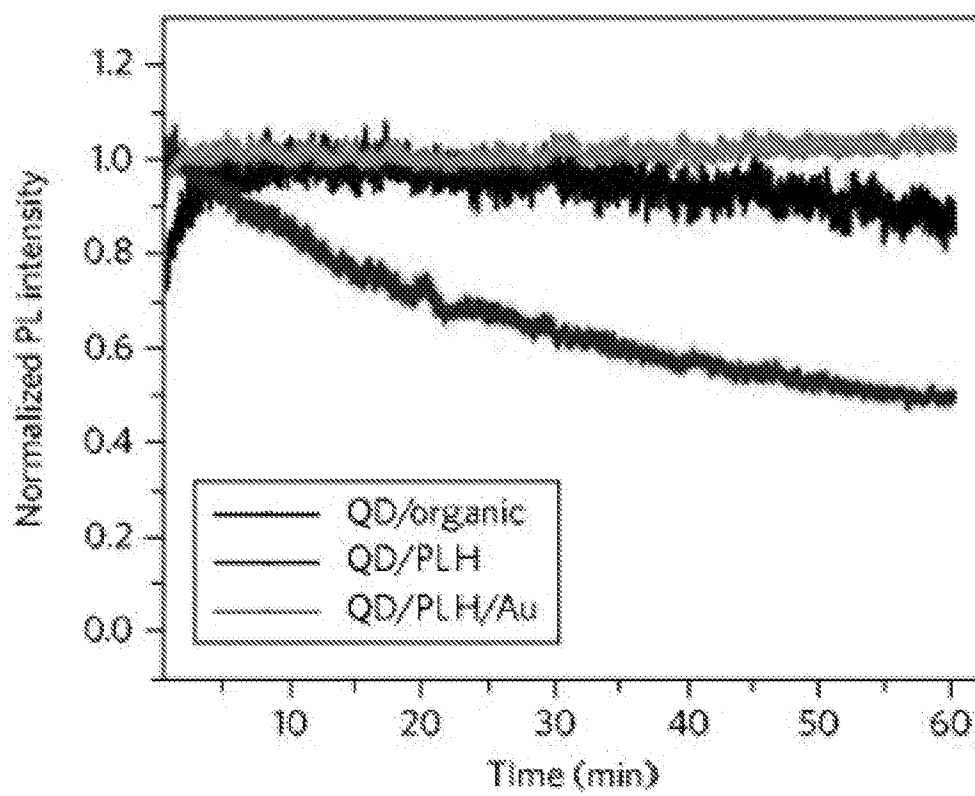


Fig.3E.

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***Fig.3F-1.******Fig.3F-2.******Fig.3F-3.***

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***Fig.4A.***

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QD

Fig.4B.



Fig.4C.

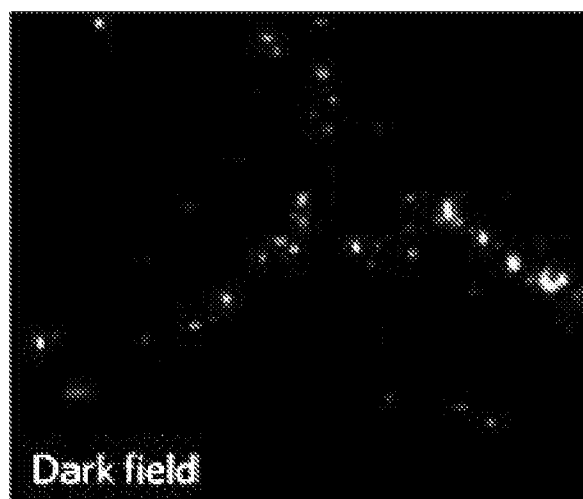
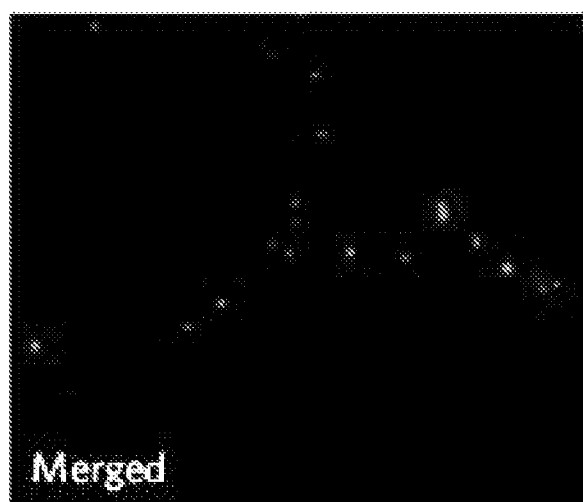


Fig.4D.



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QD-Au

Fig.4E.*Fig.4F.**Fig.4G.*

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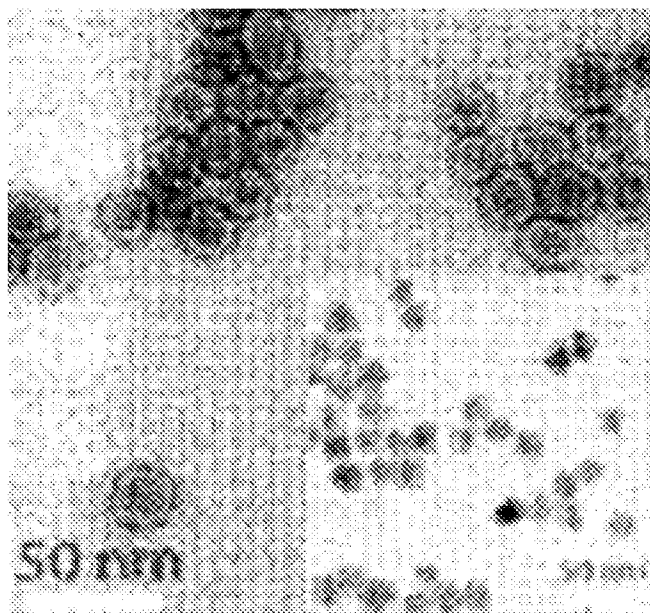


Fig.5A.

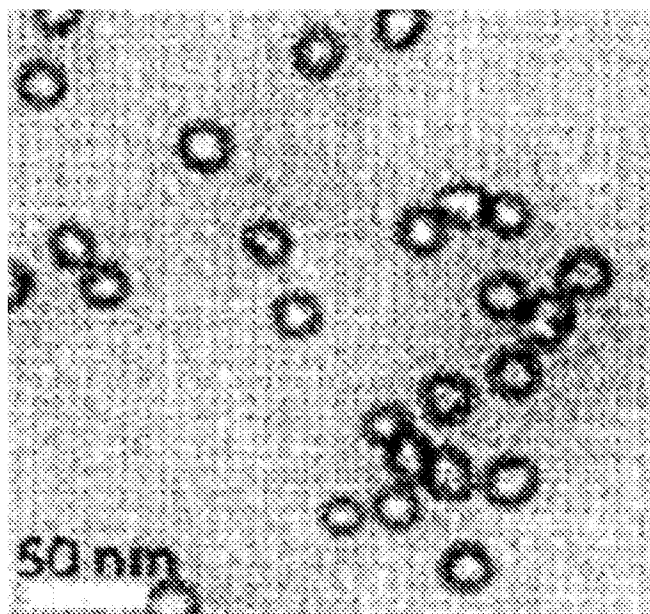


Fig.5B.

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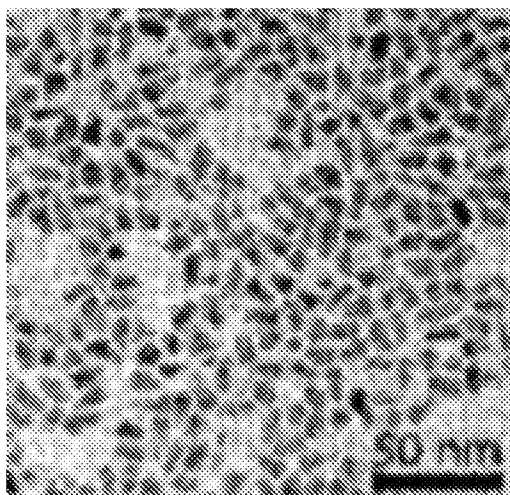


Fig. 6A.

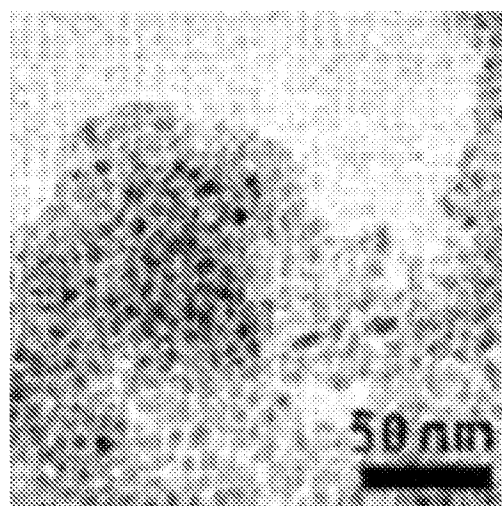


Fig. 6B.

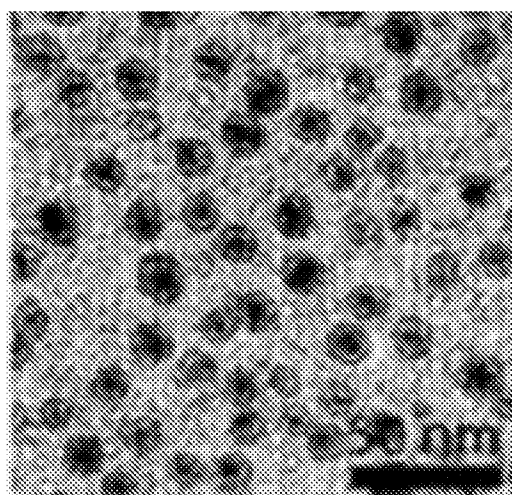


Fig. 6C.

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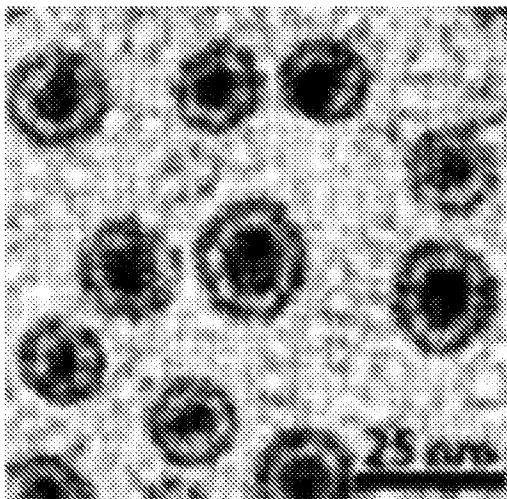


Fig. 6D.



Fig. 6E.

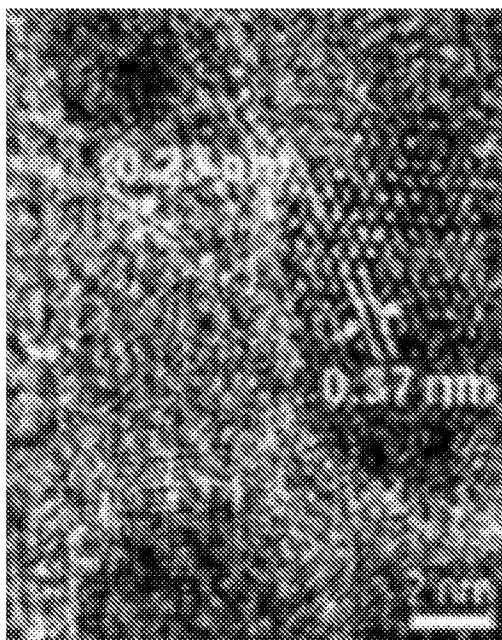


Fig. 6F.

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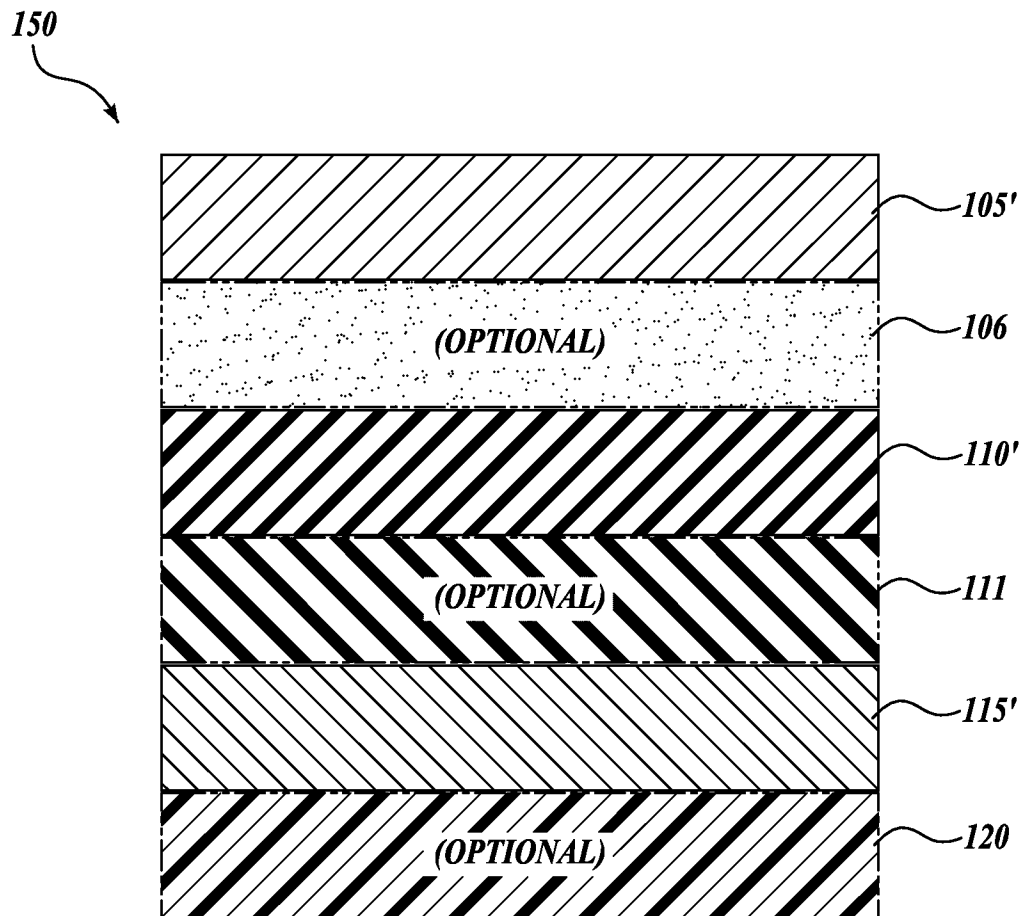


Fig. 7.

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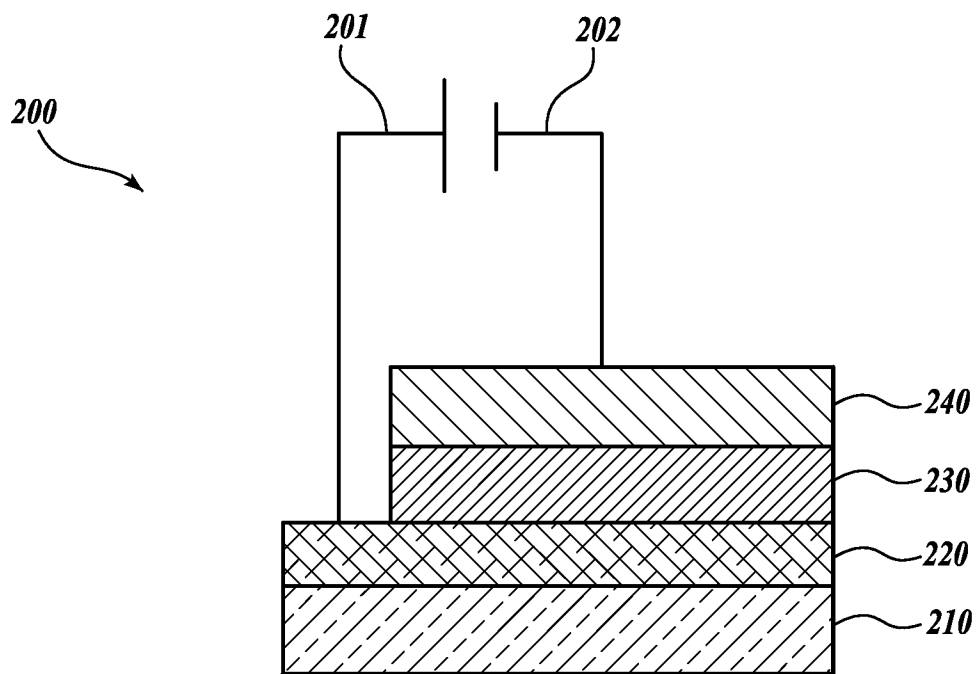


Fig. 8.

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Fig. 9A.

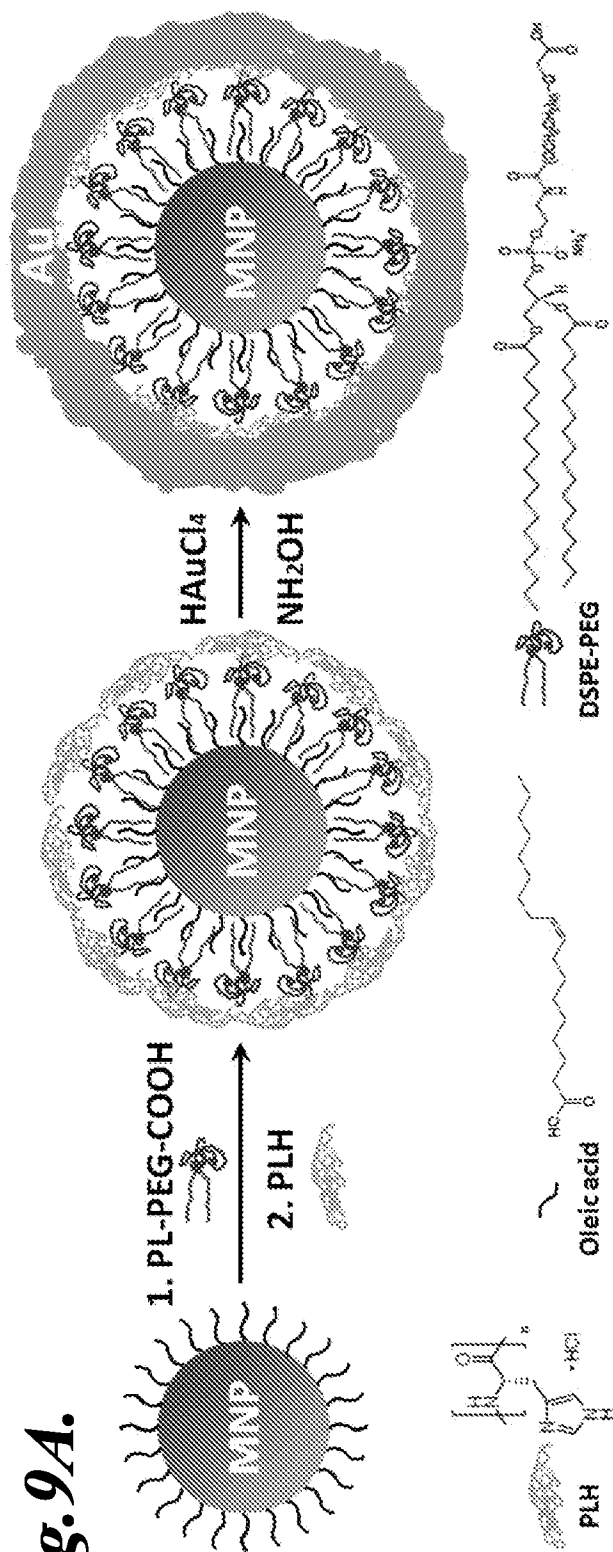


Fig. 9B.

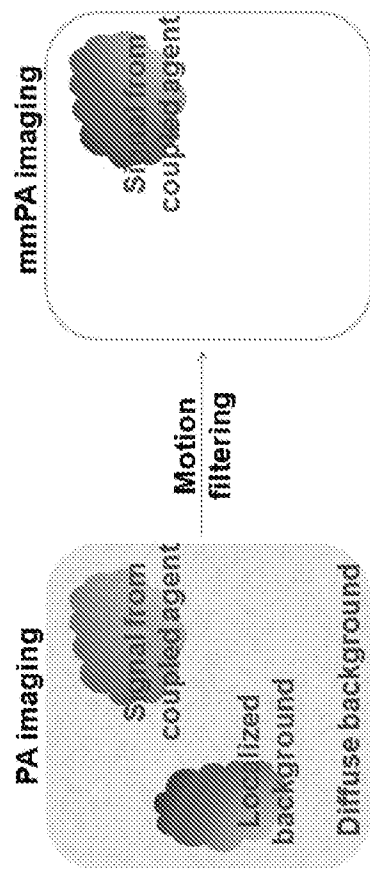
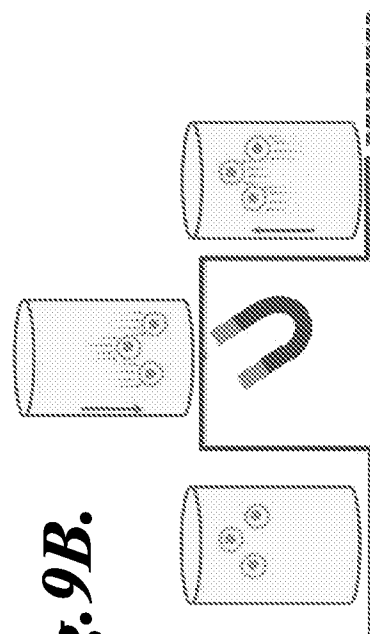
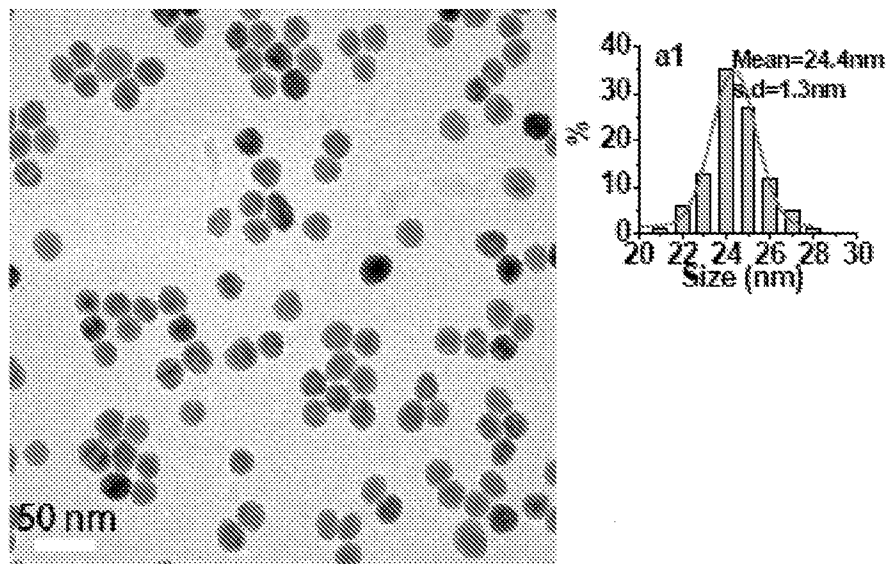
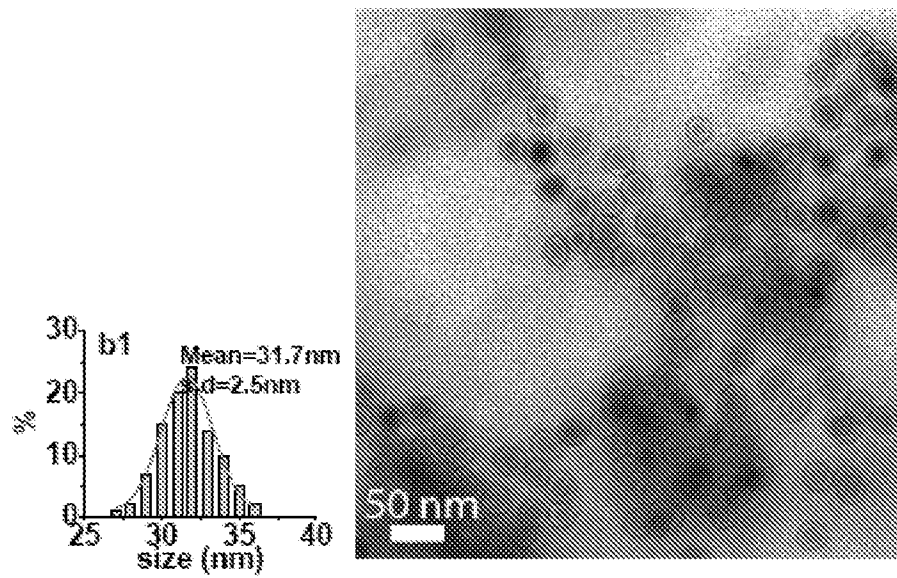
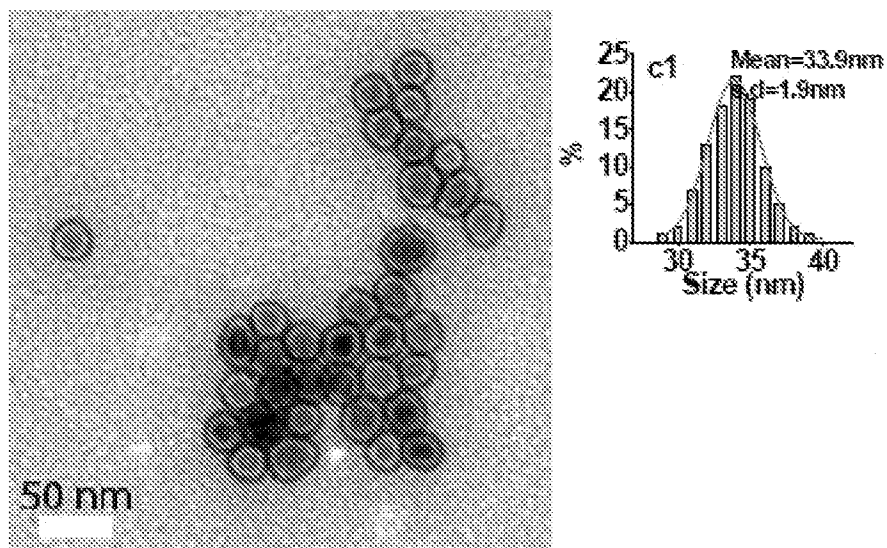
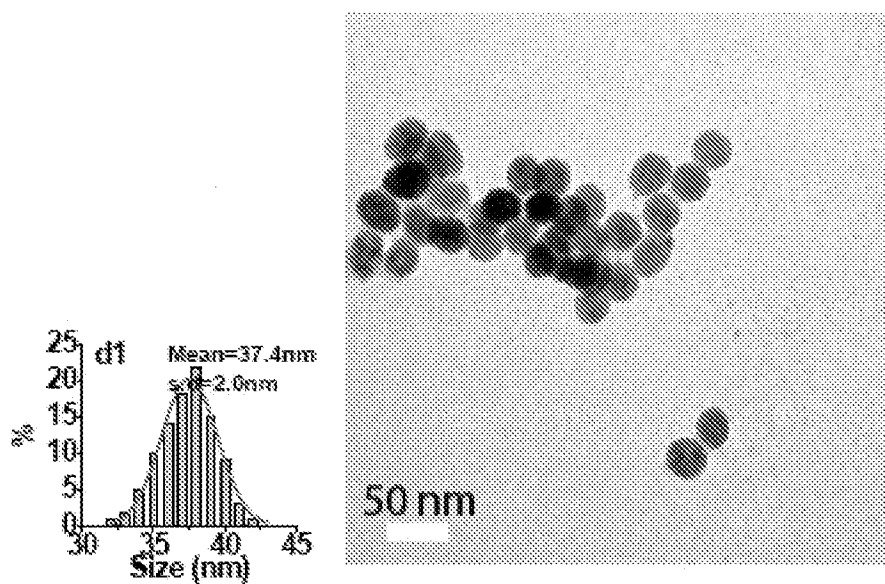


Fig. 9C.

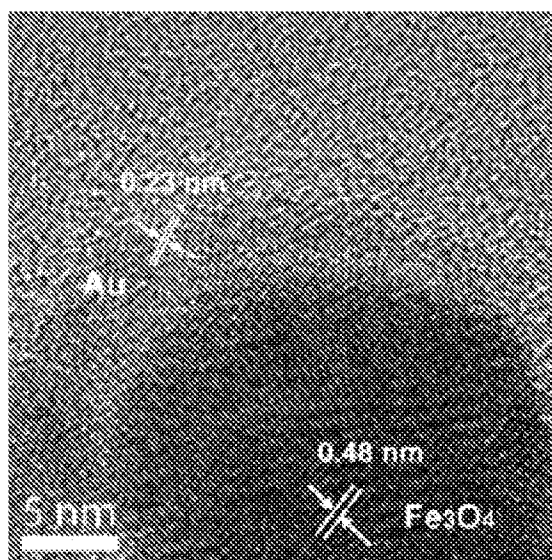
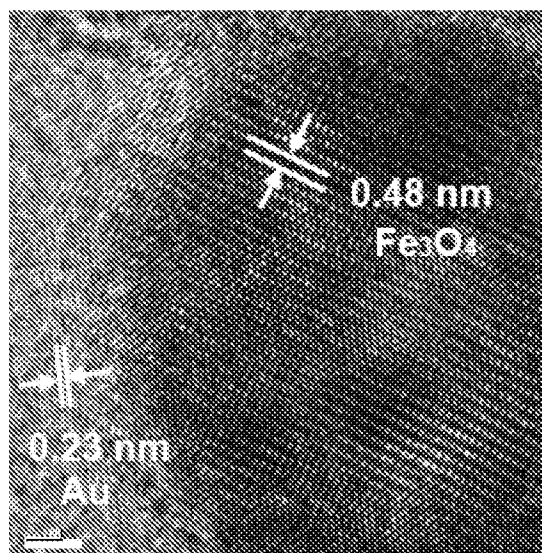
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*Fig. 10A.**Fig. 10B.*

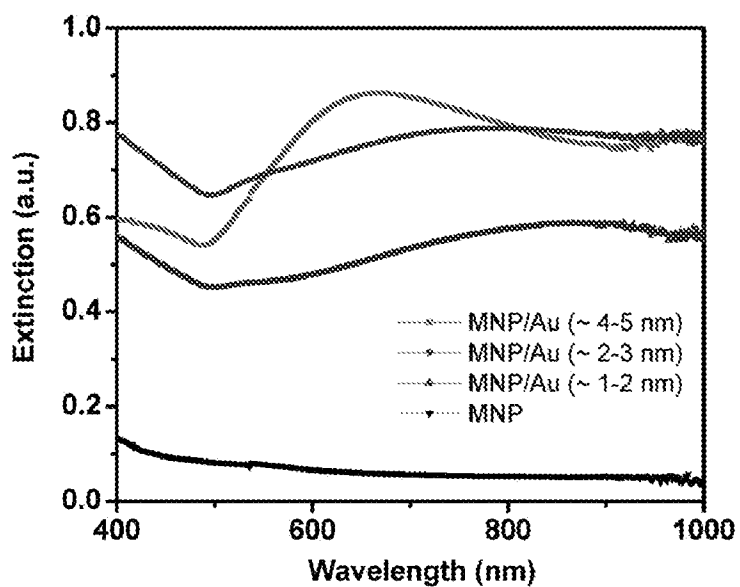
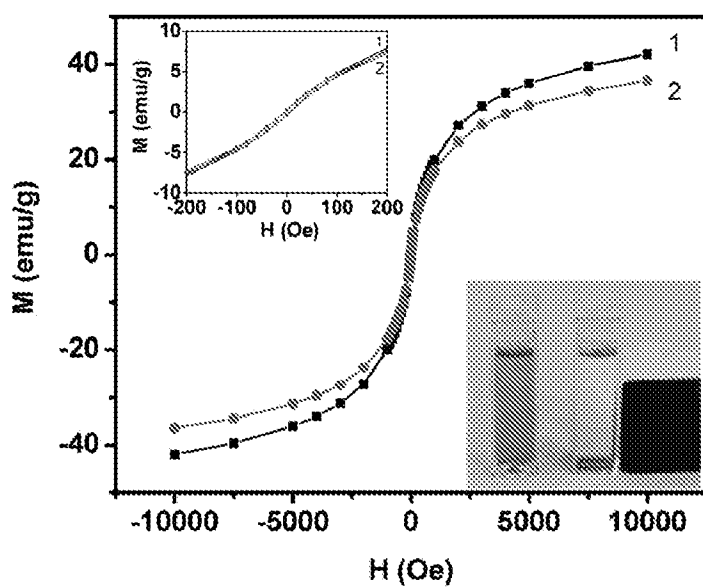
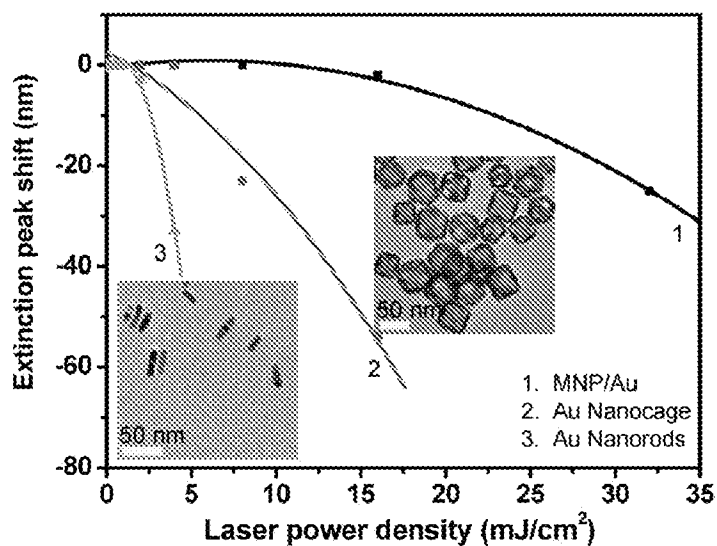
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*Fig. 10C.**Fig. 10D.*

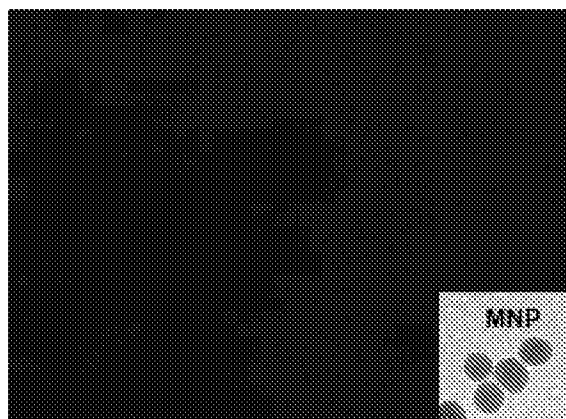
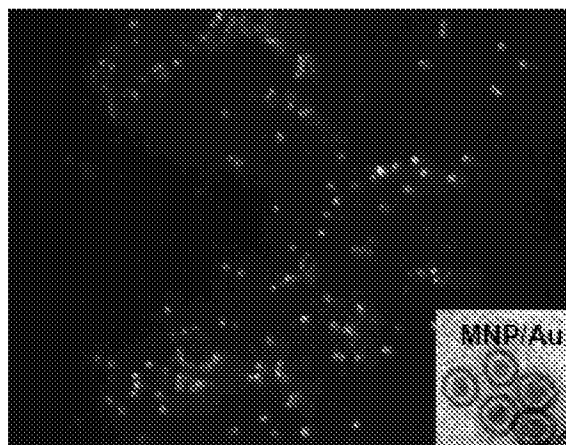
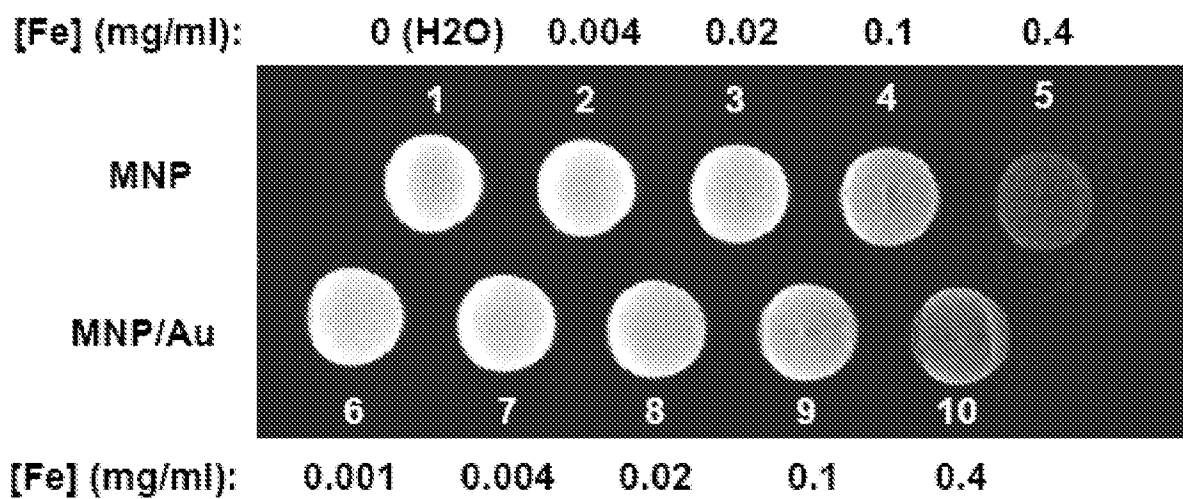
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*Fig. 10E.**Fig. 10F.*

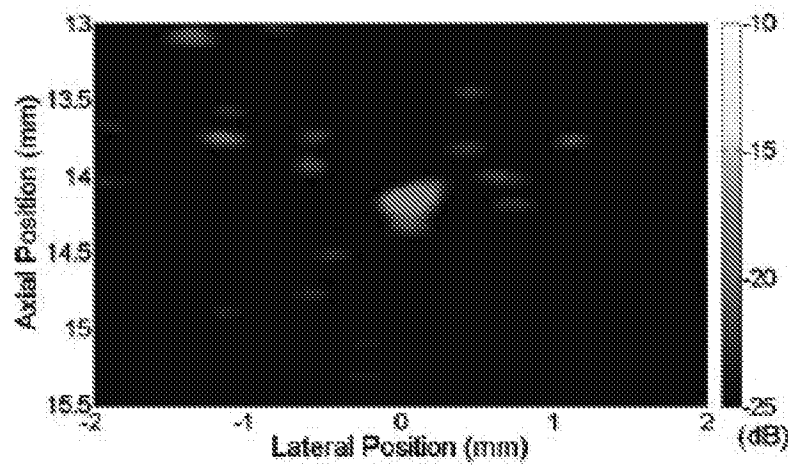
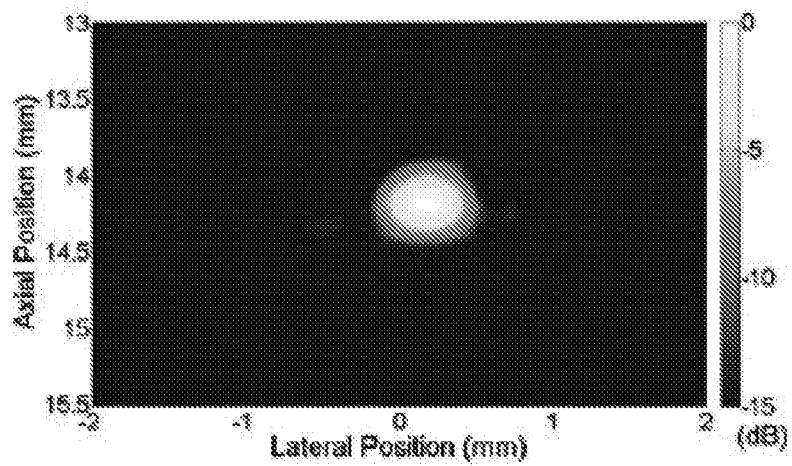
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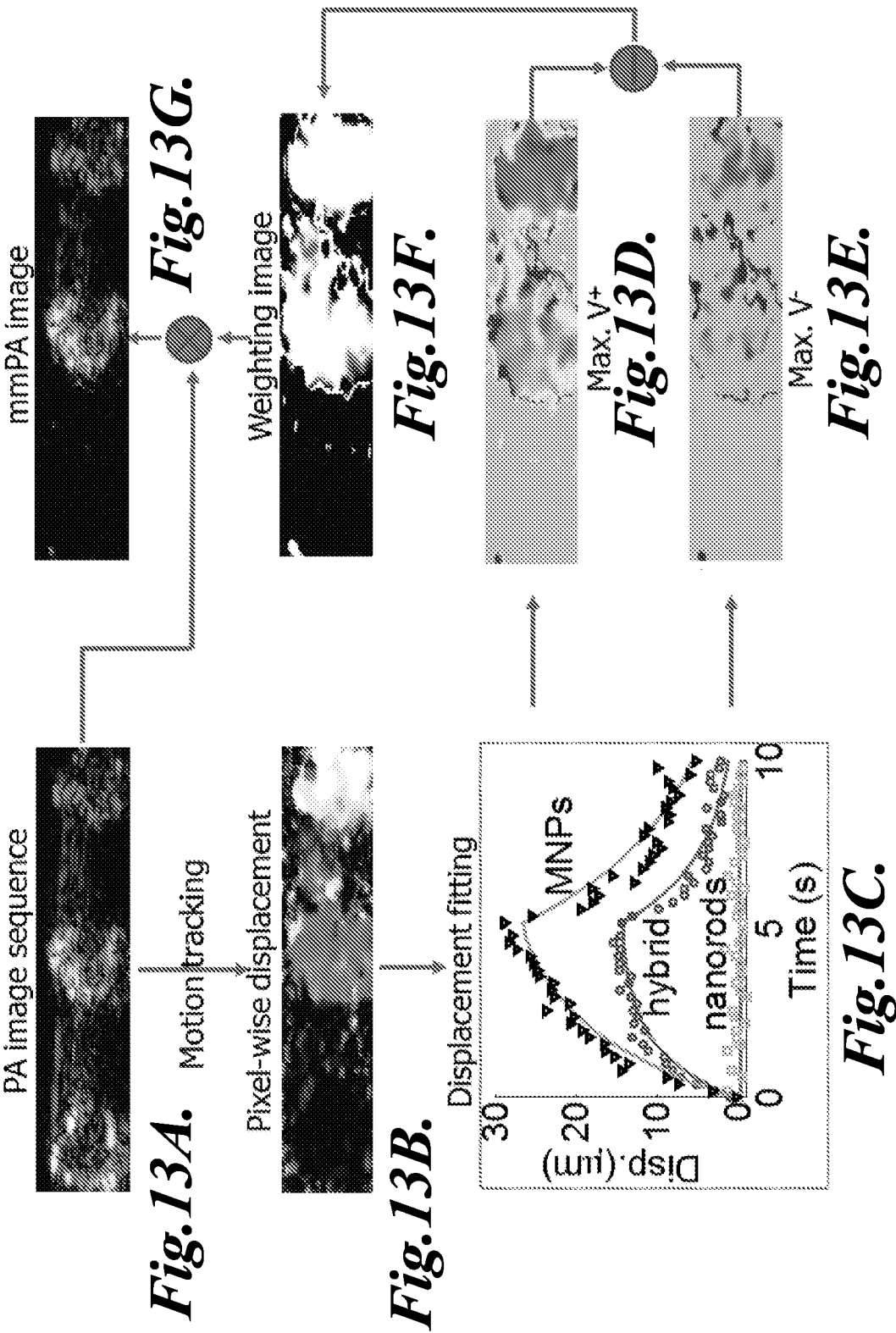
*Fig.11A.**Fig.11B.**Fig.11C.*

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*Fig.12A.**Fig.12B.**Fig.12C.*

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*Fig.12D.**Fig.12E.*



MNP core size: 10 nm

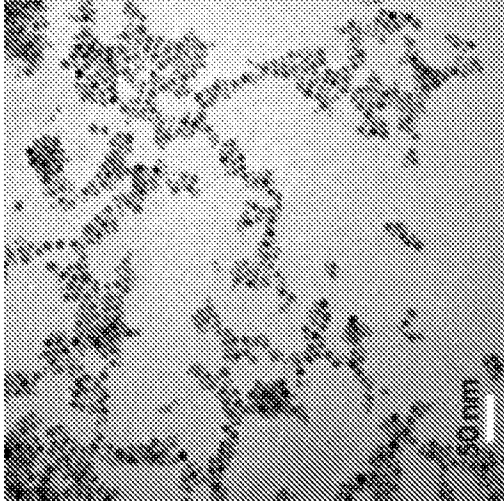


Fig. 14A.

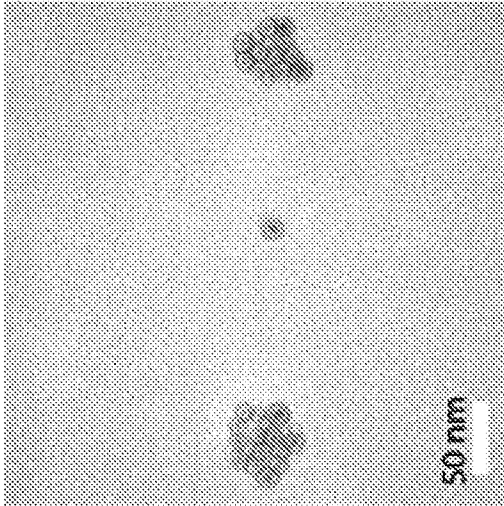


Fig. 14B.

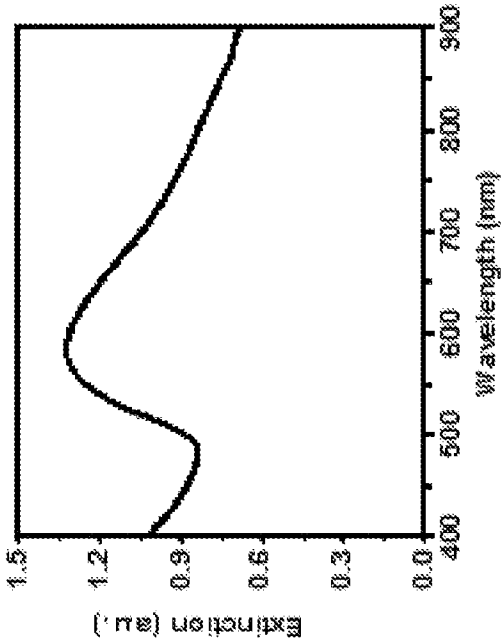


Fig. 14C.

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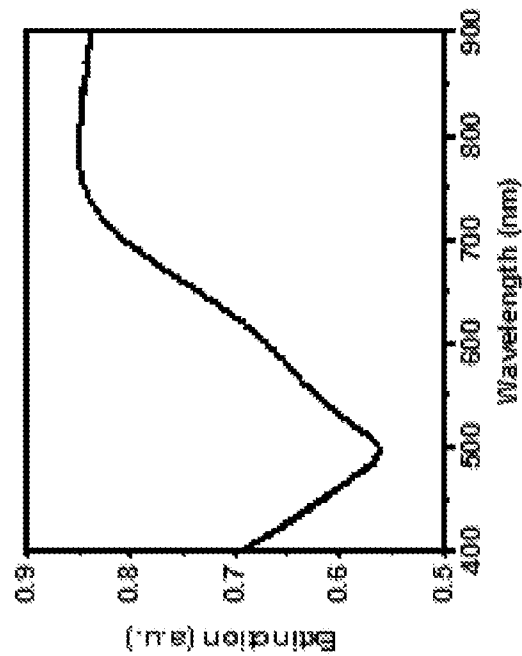


Fig. 14F.

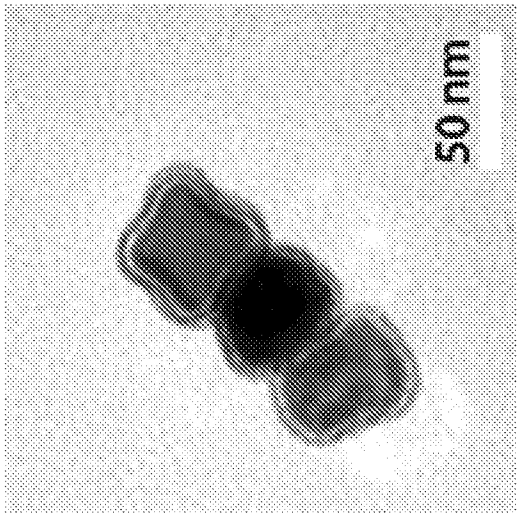


Fig. 14E.

MNP core size: 50 nm

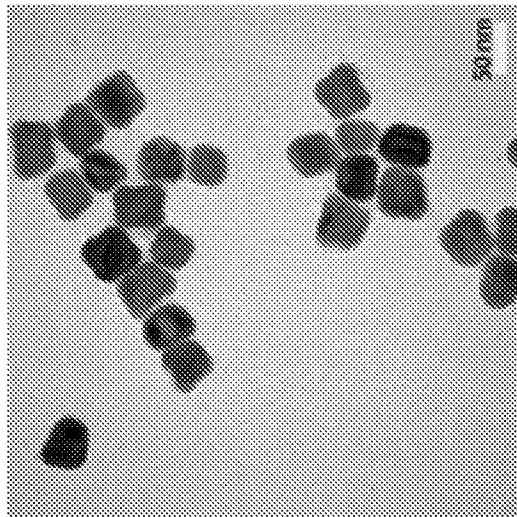


Fig. 14D.

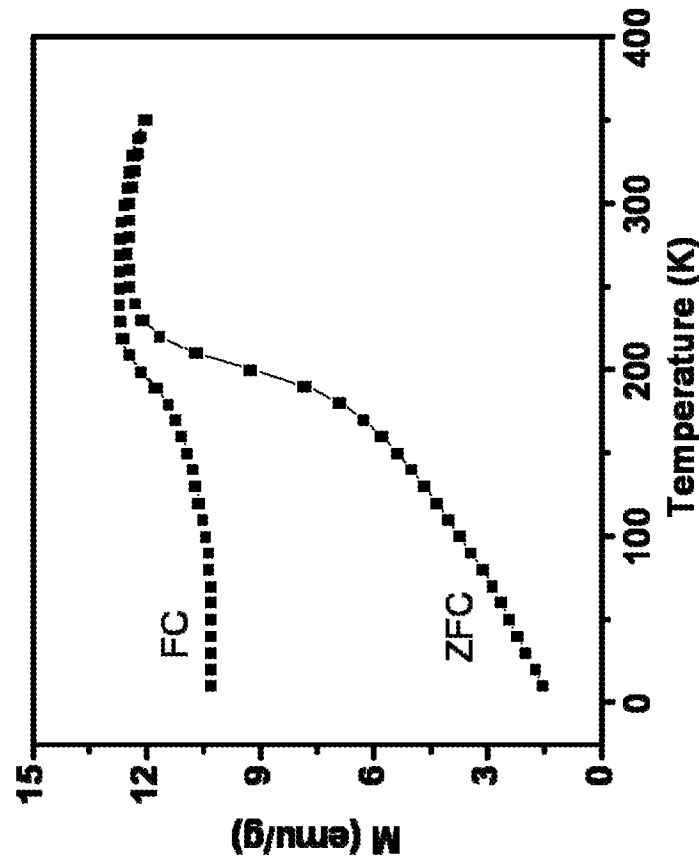


Fig.15B.

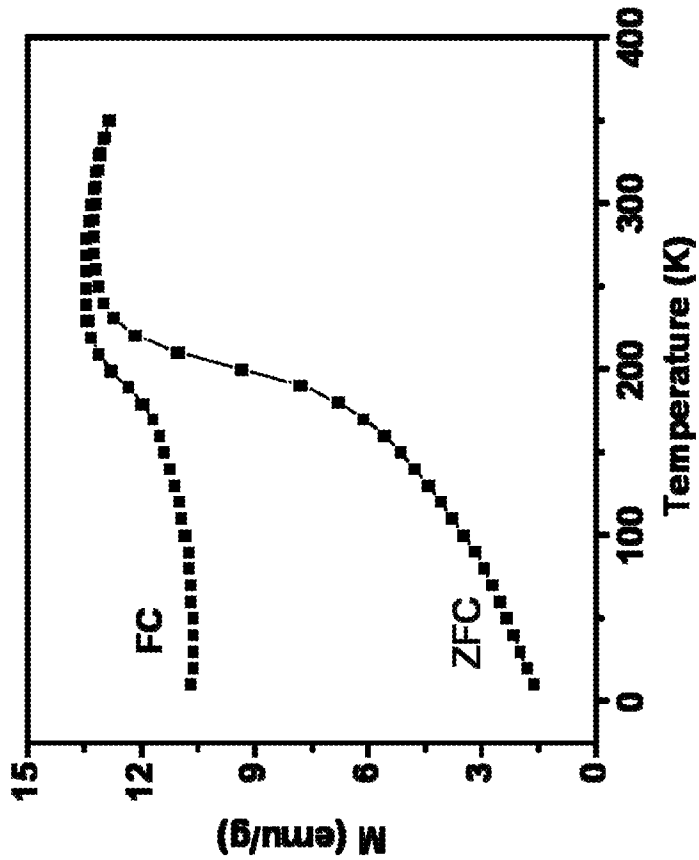


Fig.15A.

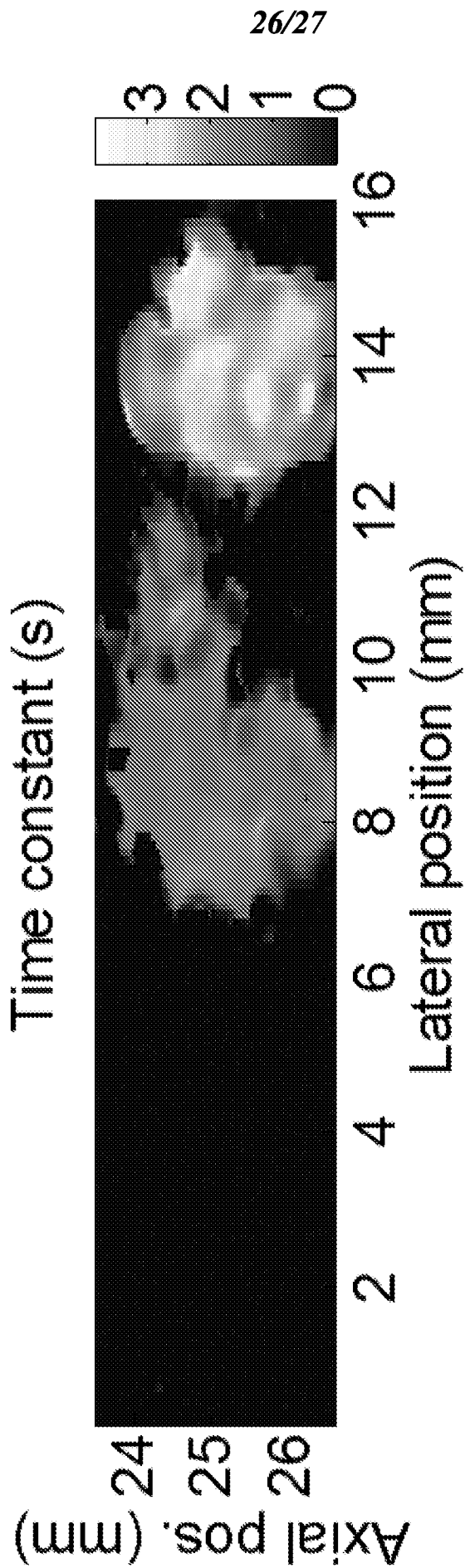
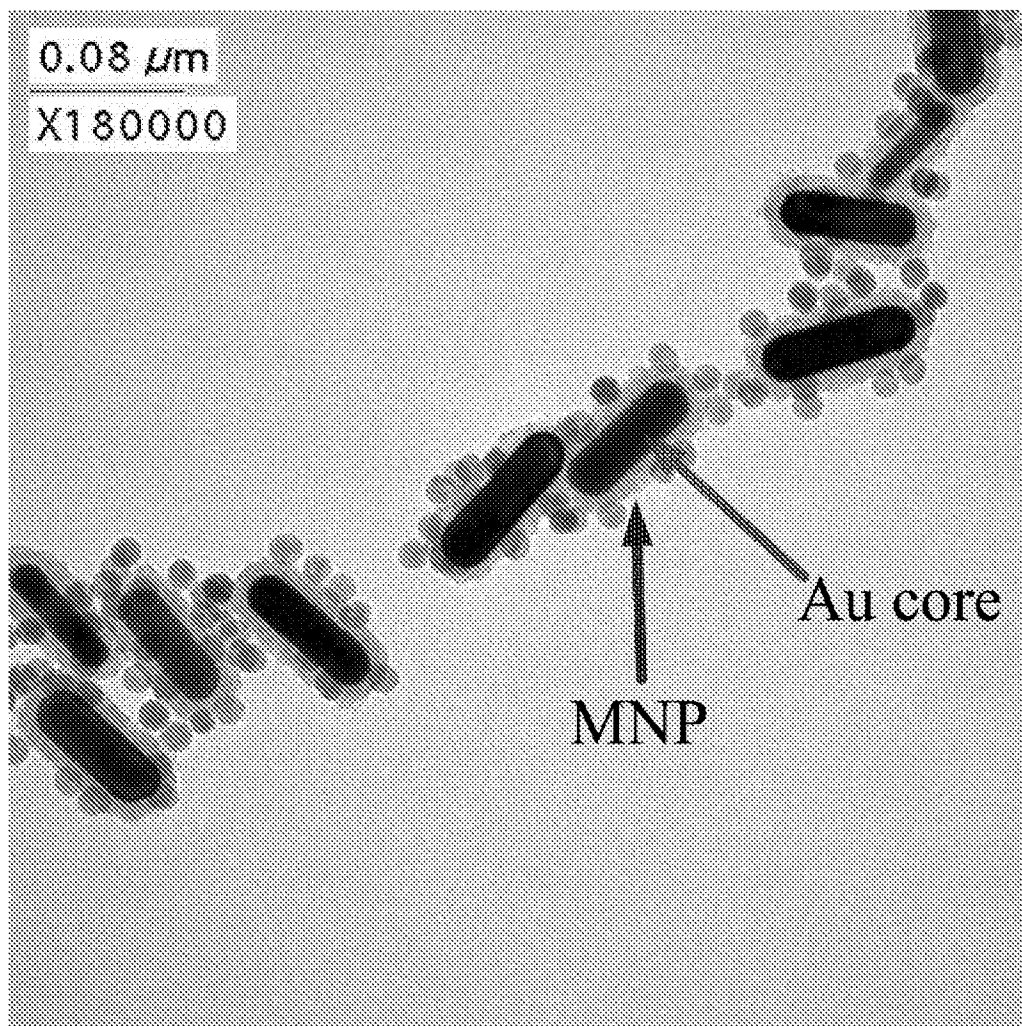


Fig. 16.

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*Fig.17.*