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Perspective

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Applications of Colloidal Inorganic Nanoparticles: From Medicine to Energy

Samuel E. Lohse and Catherine J. Murphy*

Department of Chemistry, University of Illinois at Urbana−Champaign, 600 South Mathews Avenue, Urbana, Illinois 61801, United States

ABSTRACT: The synthesis of well-defined inorganic nanoparticles in colloidal solution, which evolved gradually from the 1950s onward, has now reached the point where applications in both the research world and the wider world can be realized. This Perspective explores some of the successes and still-remaining challenges in nanoparticle synthesis and ligand analysis, highlights selected work in the areas of biomedicine and energy conversion that are enabled by colloidal nanomaterials, and discusses technical barriers that need to be overcome by chemists and other scientists in order for nanotechnology to achieve its promise.

INTRODUCTION

Functionalized nanomaterials are transforming many research fields, from biomedicine to energy conversion.[1−24] The intellectual excitement associated with nanotechnology is reflected in the proliferation of specialty "nano"-oriented journals over the past decade. As of March 2012, there were at least 161 such "nano" journals, up from nearly zero in 1990 (Figure 1).[25] The United States infrastructure for nano-

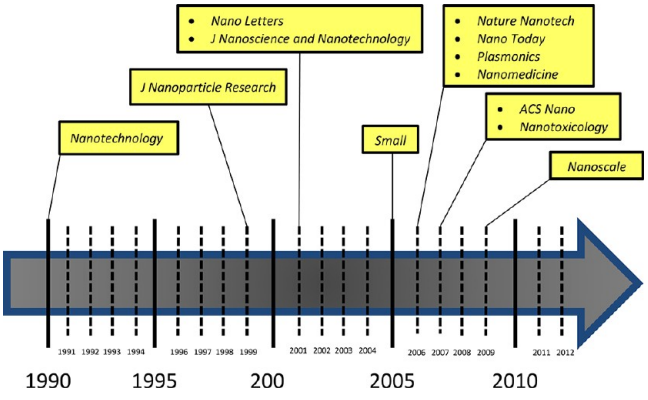

Figure 1. Timeline of selected "nano" journals and their first year of publication.

technology-related research has also increased significantly; a good example is the United States Department of Energy's five Nanoscale Science Research Centers that operate at existing national laboratories: the Center for Nanoscale Materials (Argonne), the Molecular Foundry (Lawrence Berkeley), the Center for Integrated Nanotechnologies (Los Alamos/Sandia), the Center for Nanophase Materials Science (Oak Ridge), and the Center for Functional Nanomaterials (Brookhaven).[26] The National Nanotechnology Infrastructure Network (NNIN) supports 14 nanotechnology user facilities, housed in 14 different universities across the country.[26]

The reason for the widespread interest in nanomaterials research is clear. Nanomaterials (Table 1) possess many of the best properties of both bulk materials and molecules.[14,27−30]

Table 1. A Small Dictionary of Nano Terms

term	definition
nanoscience	fundamental scientific study of matter on the 1−100 nm scale, especially if the properties of matter on the 1−100 nm scale are distinct from those of bulk materials
nanotechnology	applications and devices based on materials on the 1−100 nm scale
nanomaterials	general term for materials (polymers, semiconductors, ceramics, oxides, metals, etc.) with particle sizes in the 1−100 nm range in at least one dimension
nanoparticles (NPs)	1. nanomaterials; 2. nanomaterials that appear to be spherical in electron micrographs

Colloidal nanoparticles (NPs) can be manipulated much like molecules: they can be made by chemical reactions in solutions, injected into biological systems, or self-assembled into structures, which may have superior lithographic resolution than can be achieved using top-down fabrication approaches.[5,18,19,28,29] The large surface area of NPs means that molecules on their surfaces are at high local concentrations yet can be low in "global" concentrations, providing enhanced opportunities for drug delivery or influencing the interaction of NPs with biomolecules.[28,29] Additionally, inorganic NPs can be functionalized with small organics or polymers on their surfaces, meaning that the optical/electronic properties of the inorganic core can be tuned independently of their surface chemistry. Nanomaterials can possess more intense optical absorbance and emission properties (on a per absorber/emitter basis) than molecular absorbers and fluorophores.[1,18] For example, one Au NP possesses an extinction coefficient (ε) over 10 000 times greater than a typical organic dye molecule (although there can be a million gold atoms per NP).[1] As a result, interest in the applications of functionalized nanomaterials continues to increase; over 800 articles were published last year on the *applications* of inorganic NPs

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alone.[31] Though functionalized NPs are a very broad class of materials, much of the interest in nanomaterials applications centers around inorganic colloidal NPs, particularly metal, semiconductor, and insulator NPs.

Although "finely divided" metals and semiconductor minerals have been used as colorants in decorative arts for centuries, colloidal inorganic materials have steadily gained greater importance in a variety of scientific fields, as their nanoscale properties became better understood.[1] As a result, the colloid chemistry subdiscipline, which had migrated from chemistry departments into materials science or chemical engineering departments from the 1960s onward, appears to be making a comeback as nanomaterials chemistry in the mainstream of chemistry. The "nanotechnology revolution" is often said to have begun in the late 1950s with the delivery of Richard Feynman's famous lecture "There's Plenty of Room at the Bottom".[14] Although it is not clear if chemists who developed methods to make nanomaterials actually knew about Feynman's lecture, it is true that major colloidal syntheses of inorganic nanomaterials were developed around this time. Turkevich pioneered the colloidal synthesis of Au NPs in the 1950s.[32] The Stöber preparation for colloidal silica was first developed in the late 1960s.[33] Ferrofluid (colloidal suspensions of iron oxide NPs in organic oils or water) was developed by NASA around the same time.[34] Immunogold (antibody-functionalized Au NPs) was used as early as the 1970s as an electron microscopy contrast agent.[18] The 1980s saw the rise of CdSe and CdS NPs as semiconductor "quantum dots" (QDs), which immediately gained interest for their size-dependent bandgaps and therefore optical properties, which could be understood as quantum confinement of photogenerated excitons.[9] In the 1970s, some of the first commercial products containing nanomaterials (sunscreen containing titanium(IV) oxide or zinc oxide NPs; catalytic converters containing supported Pt, Pd, Rh NPs) entered the market, although the nanoscale nature of the materials was not emphasized to the public. We note that the Project on Emerging Nanotechnologies (http://www.nanotechproject.org) maintains a database of modern consumer products where the nanoscale nature of the materials *is* emphasized to the public. We also note that the International Council on Nanotechnology (http://icon.rice.edu) serves as a clearinghouse for the health, environmental, and regulatory aspects of nanotechnology.

At the research level, the popularity of NPs increased exponentially after Bawendi and Brust demonstrated simple synthetic routes to, respectively, ligand-stabilized QDs and organic-soluble Au NPs.[35,36] Over the past two decades, NP applications have diversified to the point where many different inorganic elements have found an application niche. Colloidal Pt and Pd NPs have found widespread applications as catalysts in organic synthesis.[14,37] Ag NPs release silver ions under physiological conditions, making them very useful antimicrobial agents.[38,39] Au NPs have opened up new opportunities for the development of "theranostic" agents in biomedicine, as their optical properties provide both dia*gnostic* advantages and *thera*puetic options.[1,40] Many different types of NPs can be used for the real-time optical imaging of cells and cellular processes (QDs and dye-doped silica NPs: one-photon emission; Au NPs, two-photon emission and elastic light scattering).[1,8,11,40] Metal oxide NPs have been used in the construction of a variety of next-generation solar cells.[3,41] Even insulator NPs (e.g., silica) have shown considerable promise as drug delivery agents (Figure 2).[16,17]

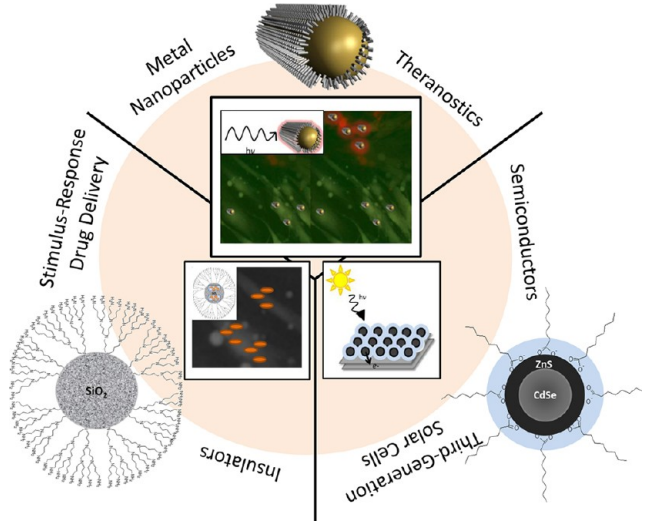

Figure 2. Colloidal inorganic nanoparticles are exciting materials in biomedical and energy conversion research. Metal NPs enable applications in drug delivery, imaging contrast agents, photothermal therapies, and sensing applications. Semiconductor NPs can be harnessed for *in vivo* imaging and contrast agents as well as the development of energy conversion devices (e.g., solar cells). Insulator NPs (e.g., silica) find application in the development of nanoscale phosphors, and mesoporous silica NPs possess functionalized nanoscale pores that can enhance drug delivery applications.

In this Perspective, we briefly revisit the origin of inorganic NPs size-dependent physical properties, paying special attention to the most recent cutting-edge applications in energy conversion and biomedicine. (We exclude carbon nanomaterials such as fullerenes, nanotubes, and graphene.) Our discussion of colloidal NP applications is organized around the three classical electronic groups of materials: metal NPs, semiconductor NPs, and insulator NPs. As we proceed, we will discuss some of the principal challenges associated with refining these NP applications to the point where colloidal NPs and NP-enabled devices can make an impact on the world beyond the research lab. Due to the necessary brevity of this Perspective, we will restrict the discussion of NP applications to those in which colloidal NPs are well-dispersed in solution or to solid state materials that have been directly fabricated from colloidal NPs. The study of NP applications is now so extensive that we strongly recommend that interested readers also consult the reviews referenced and listed here, should they wish to develop a more complete understanding of inorganic NP applications (Table 2).[1−24] In addition, we note that special issues of journals (e.g., *Accounts of Chemical Research* **2008**, *41*(12), 1565−1851; *Chemical Society Reviews* **2012**, *41*(7), 2521−3012; *Langmuir* **2012**, *28*(24) 8825−9180, on colloidal nanoplasmonics; and the June 2012 virtual special issue on TiO_2 in *J. Phys. Chem. Lett.*) are good places to start reading.

THE MOST INTERESTING SIZES AND SHAPES OF COLLOIDAL INORGANIC NANOPARTICLES

Successful nanomaterial-enabled applications require NPs with well-defined physical dimensions, purity, and surface chemistry in order to understand, predict, and take full advantage of their optical, electronic, and magnetic properties.[1,14,42−44] Different inorganic NPs have different nanoscale properties as a result of their size and shape. For instance, metal NPs may have unique electronic, catalytic or optical properties, depending on the

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Table 2. A Selection of Recent Review Articles on the Properties, Synthesis, and Applications of Colloidal Inorganic Nanoparticles

review topic	type of NPs	authors	title; ref	year
NPs in biomedicine	metal NPs	S. Lal, S. E. Clare, N. J. Halas	Nanoshell-enabled photothermal therapy: Impending clinical impact; ref 90	2008
NP synthesis	Au NPs	M. Grzelczak, J. Pérez-Juste, P. Mulvaney, L. M. Liz-Marzán	Shape control in gold nanoparticle synthesis; ref 79	2008
NP sensors	metal NPs	J. N. Anker, W. P. Hall, O. Lyandres, N. C. Shah, J. Zhao, R. P. Van Duyne	Biosensing with plasmonic nanostructures; ref 27	2008
NP electronics	Au NPs	R. Sardar, A. M. Funston, P. Mulvaney, R. W. Murray	Gold nanoparticles: past, present, and future; ref 19	2009
NP synthesis and properties	metal NPs	Y. Xia, Y. Xiong, B. Lim, S. E. Skrabalak	Shape-controlled synthesis of metal nanocrystals: Simple chemistry meets complex physics?; ref 23	2009
NP properties	QDs (CdSe, CdTe, etc.)	A. M. Smith, S. Nie	Semiconductor nanocrystals: Structure, properties, and band gap engineering; ref 45	2010
NP properties	silica	S. H. Wu, Y. Hung, C. Y. Mou	Mesoporous silica nanoparticles as nanocarriers; ref 17	2011
NP synthesis	silica	Q. He, J. Shi	Mesoporous silica nanoparticle based nano drug delivery systems: synthesis, controlled drug release and delivery, pharmokinetics, and biocompatibility; ref 48	2011
NP plasmonics	metal NPs	M. R. Jones, K. D. Osberg, R. J. Macfarlane, M. R. Langille, C. A. Mirkin	Templated technique for the synthesis and assembly of plasmonic nanostructures; ref 24	2011
NPs in biomedicine	Au NPs	E. C. Dreaden, A. M. Alkilany, X. Huang, C. J. Murphy,	The golden age: Gold nanoparticles for biomedicine; ref 40	2012
NP toxicology	QDs	F. W. Winnik, D. Maysinger	Quantum dot cytotoxicity and ways to reduce it; ref 11	2012
NPs in energy	QDs	P. V. Kamat	Boosting the efficiency of quantum dot-sensitized solar cells through the modulation of interfacial charge transfer; ref 104	2012
NPs in energy	metal oxide NPs	T. Froschl, U. Hormann, P. Kubiak, G. Kucerova, M. Pfanzelt, C. K. Weiss, R. J. Behm, N. Husing, U. Kaiser, K. Landsfester, M. Wolfahrt-Mehrens	High surface area crystalline titanium dioxide: potential and limits in electrochemical energy storage and catalysis; ref 41	2012

metal that makes up the NPs core and the size of the core.[19,43,44] Of the various nanoscale phenomena manifested by colloidal metal NPs, the localized surface plasmon resonance (LSPR; the coherent oscillation of conduction-band electrons in response to incident light) is perhaps the most well-known.[1,27] In order to support a plasmon, the metal NP must be large enough to support a conduction band rather than discrete localized states, like a molecule; the general size cutoff is ∼2−5 nm for most metals.[1] The LSPR results in strong absorbance and scattering of light, the energy of which can be tailored by choosing different metal cores with different sizes and shapes. The LSPR absorbance of nanoscale gold has proven to be particularly attractive, as it occurs in the visible region for Au NP spheres (d_{core} 3.0−200.0 nm), making spherical Au NPs ideal for many colorimetric sensing applications or biological contrast agents, but can also be tuned to the near-infrared for anisotropic NPs, making anisotropic Au NPs ideal for *in vivo* imaging and photothermal treatments that rely on a strong near-infrared scatterer (for imaging via dark-field optical microscopy) or absorber (for photothermal therapy).[1,42] Below 3 nm, Au NPs begin to show interesting chemical reactivity and can serve as catalysts, especially if supported on an oxide.[44]

Colloidal semiconductor NPs include chalcogenide QDs (CdSe, ZnSe, ZnS, etc.) and metal oxides (TiO_2, ZnO, FeO_x etc.). Their principal size-dependent properties include their size-dependent bandgaps and therefore emission spectra and superparamagnetism (in the case of FeO_x).[14,45] These properties generally occur in the 1−10 nm size range and make semiconductor NPs useful as *in vivo* biological luminescent tags, photocatalysts, solar cell components, magnetic-responsive therapeutics, or magnetic separation "beads".[8,14,41,46,47] The nanoscale confinement of charge carriers in these species results in band gaps that are blue-shifted with respect to the corresponding bulk materials; the smaller the diameter of the semiconductor NP, the higher the energy of its bandgap. This increases the energy of the excited carriers in the semiconductor NPs and results in higher-energy excitons that can

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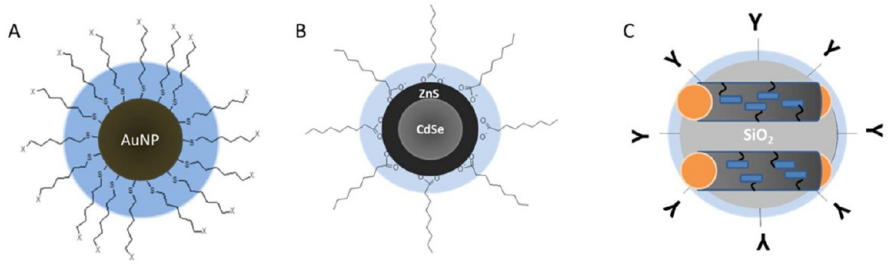


Figure 3. Schematic representations of the general structure of different functionalized inorganic colloidal nanoparticle. (A) Functionalized metal NPs have a metal core with precisely controlled size and shape, protected by a functionalized ligand shell. The functionalized ligand shell provides a means to target the particle in self-assembly and biomedical applications. (B) NPs with a semiconductor core, including metal oxides and quantum dots, are frequently coated with an additional inorganic shell to modify the electronic properties. Usually, these particles are stabilized with long chain carboxylic acids, although they can easily be conjugated to various ligands, including antibodies. (C) Insulator NPs (e.g., mesoporous silica) have a similar structure, stabilized with functionalized ligands; however, the core material is chemically and electronically inert.

do more useful work, whether that work manifests itself as photocatalytic degradation of absorbed organics, converting sunlight into electrical energy, or using the size-dependent fluorescence of QDs to monitor multiple biological processes that are color coded for each dot.[11,12,14,45]

Unlike metal or semiconductor NPs, insulator NPs (such as SiO_2) have no size-dependent optical or electronic properties.[14,17,47,48] However, the inert nature of these NPs in addition to their nanoscale size (30−300 nm) can be turned to advantage, by carefully controlling their structure and composition.[14,48−51] For instance, mesoporous silica NPs (MSNPs) can prepared with precisely controlled pore structures (hexagonal, cubic, etc.) and pore dimensions (2.0−20.0 nm), and these nanoscale pores can be loaded with molecular cargo, such as pharmaceuticals, at much higher capacities than can typically be achieved with polymers or liposomes.[14,49] This high load capacity, combined with their thermal stability and opportunities for surface functionalization, makes them ideal scaffolds for programmed delivery vehicles or nanoprobes for the investigations of nanobio interactions. In addition, solid silica (SiO_2) or fluoride (e.g., $NaYF_4$) NPs can be doped with luminescent ions (e.g., lanthanides) to prepare upconversion phosphors, by virtue of the confinement of the luminescent species within an inert NP matrix.[6,50,51] By implanting luminescent hosts within an "inert" matrix, the frequency of nonradiative transitions between the luminescent species and the host is reduced, increasing the efficiency of the upconversion process and luminescent intensity of the nanocomposite.[51]

DESIGN AND SYNTHESIS OF COLLOIDAL INORGANIC NANOPARTICLES

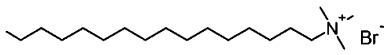
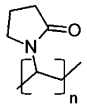
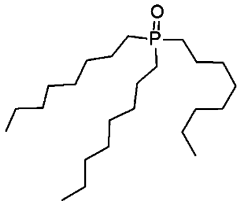
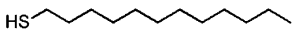
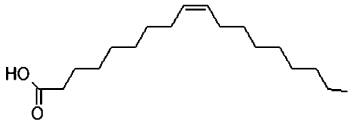
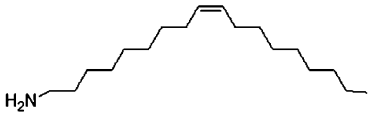
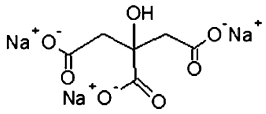
Since "standard" syntheses of some inorganic NPs have appeared in the literature from one to several decades ago (Turkevich, Stöber, Brust, etc.), the impression one can get from the literature is that any NP of any material is easily synthesized for a desired size and perhaps shape.[43] Even for well-known NPs, this impression is not always correct. The ongoing debate about synthetic strategies ("Is particle size and shape controlled by thermodynamics or kinetics?") is still not resolved (*vide infra*); and practically speaking, the first few times one tries a NP prep from the literature frequently fail, usually due to NP aggregation or huge polydispersities in NP size or shape. The ability to fine-tune the dimensions of the NP core during in synthesis is essential; a 2.3 nm QD (CdSe core, ZnS shell) can emit blue light, but a 6.5 nm dot could emit red light.[8] In addition to the core dimensions, knowledge and control of the surface chemistry are also essential to influence effects as diverse as the biodistribution of inorganic NPs, the electronic interactions between the NPs and their environment, and the loading and release of drugs from the NP and dictate the NPs' solubility/self-assembly to facilitate device construction.[8,43,52,53]

Colloidal inorganic NPs, in cartoon form, look very similar (Figure 3): an inorganic core of a particular size and shape is surrounded by a set of ligands (in early days, only one molecular species; now, up to a half-dozen ligands might be proposed to be on the surface of the NPs). The ligand shell can be composed of physisorbed small organic molecules, polymers, dendrimers, chemisorbed thiols, phosphines, or even halides.[43,44] For catalysis, smaller (<2.0 nm) Pd, Pt, or Au NPs protected by labile ligands are typically preferred.[44] For optical applications, large (>5.0 nm) Au NPs are preferred and may be protected with functionalized thiols, polymers (which open up opportunities to prepare multifunctional NPs which couple drug delivery with diagnosis or photothermal therapy), or even nucleic acids.[5,22,53]

Metal NPs are typically prepared in solution by reduction of metal salts with chemical reducing agents or photoreduction.[23,43] The size and shape of the metal NPs are typically controlled through the judicious choice of concentration, reducing agent, and ligand.[43,54] Spherical metal NPs are usually prepared by the direct reduction of the metal salt with a strong reducing agent, such as sodium borohydride in the presence of the ligand.[43] Anisotropic metal NPs, in contrast, are usually prepared using a seeded growth approach, in which a small metal seed particle is exposed to further metal salt in the presence of a weak-reducing agent and a shape-directing ligand.[42,43] Depending on the size and shape required, the surface chemistry may be controlled by simply adding the desired ligand during the initial synthesis (direct synthesis) or may be altered post-synthesis by ligand exchange or polymer coating.[43,55−57]

The ligand shell may serve a very different role in the design of semiconductor or insulator NPs. While the ligand shell can still be used as a means to control solubility or target biomacromolecules, the ligand shell can also mediate the electronic properties of semiconductor NPs (e.g., the longer the chain length of the ligand, the more electronically insulated semiconductor NPs are from their environment).[58,59] In MSNPs, the outer surface of the NP and the surface of the pores is often functionalized with different ligands. The outer surface ligands influence solubility and targeting, while the

Table 3. Common Ligands in Nanoparticle Synthesis

Name	Abbreviation	Structure	Types of NPs Synthesized
Cetyltrimethylammonium bromide	CTAB		Au, Ag, SiO_2, CuO
Polyvinyl pyrrolidone	PVP		Au, Cu, Ag
Trioctylphosphine oxide	TOPO		CdSe, CdTe, ZnS
Dodecanethiol	$C_{12}SH$		Au, Ag, Cu, Pt, Pd
Oleic acid	–		TiO_2, ZnO, FeO_x, CdSe
Oleylamine	OA		CdSe, Au, Pt, Pd $NaYF_4$
Trisodium citrate	Cit		Au, Ag

ligands in the pores are chosen to maximize molecular cargo loading and control cargo release.[48]

Semiconductor NPs are synthesized using a variety of different synthetic approaches. QDs are typically synthesized at high temperatures by combining the metal and chalcogenide precursors as salts and heating to high temperatures (>300 °C) in the presence of a capping agent (often long chain carboxylic acids or trioctyl phosphine oxide) under inert atmosphere conditions.[35,43,60,61] In addition to controlling the size and shape of the QDs, it is also essential to preserve the quality of their surface, as vacancies and faults in the surface can negatively impact their fluorescence and excitation properties.[62] Metal oxide NPs, in contrast, are typically prepared using base hydrolysis reactions of molecular precursors (frequently acetates) in which the size of the NP is controlled by controlling the rate of hydrolysis versus passivation by the ligand, which is typically a carboxylic acid or functionalized silane.[14,43]

Insulator NPs are typically prepared by coprecipitation or sol−gel syntheses, during which NP growth is passivated by the presence of capping agents; usually these are surfactants or long chain hydrocarbons.[16,17,48] For the synthesis of MSNPs, the structure of the mesoporous silica is typically controlled by varying the pH of the synthetic reaction, while if larger pores or hollow MSNPs are desired, the NPs may be grown around soft micellar templates.[16,17,48] Following synthesis the exterior and interior surface of the MSNPs can be functionalized using typical silane monolayer chemistry.[15,63]

While the development of a wide array of ligand-stabilized NP syntheses has facilitated the emergence of many new NP applications, the development of wet chemical NP synthesis strategies is far from complete.[43,60,64,65] Pressing challenges include: (i) the synthesis of truly monodisperse NPs (e.g., diameters of 10.0 ± 0.1 nm); (ii) the development of scalable and high-yielding syntheses to produce grams, or kilograms, of NPs (already achieved for silicas); and (iii) precise control over the number and spatial distribution of ligands within the ligand shell on the NPs.[43,64,65] This last point is particularly acute for studies of multifunctional NPs, in which multiple types of ligands are incubated with the NPs, and the assumption is usually made that the ligands will bind in proportion to their concentrations.[66−68] This is demonstrably true, when measured, for some cases and demonstrably untrue for other measured cases. But at the single particle level, it very well may be that the number and proportion of different ligands bound are far from the average in a batch.[66−68] For example, even for a

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relatively well-defined "NP", like a PAMAM dendrimer, chemical reactions at its terminal groups to give an average of *n* ligands bound can lead to measured Poisson-like distributions as wide as $2n$.[66,67] As a specific example, a solution of generation 5 PAMAM dendrimers with 110 terminal groups that were reacted to produce on average of 14 ligations per dendrimer showed an experimental distribution of 5−25 ligations per dendrimer, with a maximum at 14−15.[67] In experiments in which NPs are to be used in biological applications, a targeting ligand, a polyethylene glycol ligand for biocompatibility, a cell-penetrating peptide ligand, and a ligand bearing a chemical label may all be reacted with the NP solution. At the cellular level, how can we tell which ligand shell composition is the best, from individual NPs going into the cell?

The ligands used to control the growth of inorganic NPs comprise a surprisingly limited list: despite the wide variety of NP core materials, only a half-dozen of ligands are typically used to control NP size and shape during synthesis (Table 3).[14,32,35,36,42,43] Since the surface energies, crystal structures, and binding properties of the different NP core materials to these ligands are extremely diverse, one would not predict that such a small contingent of ligands could effectively control the size and shape of such a wide variety of materials. The question of ligand binding events at growing NP surfaces becomes even more complicated when considering that the presence of tiny impurities in the reaction mixture can effectively compromise the synthesis of many NPs. For instance, Korgel has shown that the presence of parts per million (ppm) amounts of iodide impurities in 0.1 M cetyltrimethylammonium bromide (CTAB) solutions can prevent the formation of gold nanorods (AuNRs) during seeded growth.[69] Mirkin on the contrary has shown that by increasing or decreasing the concentration of a ppm iodide impurity typically found in CTAB, the shape of Au NPs can be controlled with precision![70] Peng and others have observed that impurities in trioctylphosphine oxide can influence the morphology of QDs,[71] while Krauss has found that secondary phosphine chalcogenide impurities are responsible for good QD growth.[72]

The formulation of a general mechanism of NP growth (for the inorganic core, not the organic ligand shells) remains elusive. For a number of years, most researchers have assumed that NP growth was proceeded by a mechanism analogous to the formation of colloidal sulfur species previously postulated by La Mer and modified by subsequent researchers for metal and semiconductor NP growth.[73,74] This model assumes that NPs form by a process of nucleation (new particle formation, frequently described as a "burst") and growth by monomer addition, and the two stages are temporally distinct. While the assumption of this model has motivated a number of important mechanistic developments, recent investigations of NP growth in real time have shown that NPs actually grow by a variety of different processes, including monomer growth, coalescence of two smaller particles to form a larger one, oriented attachment (which is a subset of coalescence, in which specific crystal faces of two or more NPs join and perhaps twist), and even a "popcorn" mechanism in which a small group of NPs suddenly grow to full size, followed by another subset suddenly growing, etc.[75−77] These very different growth trajectories can give rise to what looks like identical NP products. Indeed, for Pt NPs, whose individual growth trajectories were measured *in situ*, both monomer addition and coalescence were observed, leading the authors to conclude that metal NP may grow by different mechanisms, even in the same reaction.[77] The authors furthermore postulated that the growth mechanism of metal NPs may depend heavily on NP size and morphology.[77] Other researchers have suggested that controlling the concentration of truly monodisperse nuclei relative to remaining monomer in solution was the most important criterion in producing a high-yield, monodisperse product.[78] The role of the ligand (or polymer) shell in controlling NP size and shape has likewise been ascribed to numerous mechanisms, all of which have support in different systems: the ligands bind strongly to the inorganic core and stop NP growth; the ligands adsorb with different preferences to different exposed faces of the inorganic core to control NP shape; the ligands are a soft template for NP growth; and the ligands alter the surface energies and strain of the inorganic core facets (which may be a restatement of the previous statements).[79,80] Other studies have recently suggested that NP growth mechanisms may strongly depend on subtle variations in other reaction parameters, particularly pH, which can simultaneously affect ionic strength, redox potentials, protonation states of reagents, etc. While these observations may lead us to doubt that a "unified" mechanism of NP growth will ever be developed, improved understanding of the specific growth conditions for different NPs has already led to the development of syntheses in which NP yield and mondispersity have been greatly improved.[80,81] As new chemical imaging techniques on the nanoscale become more fully developed, we might one day be able to image the ligand composition on a growing NP in real time, with chemical identity information.

■ RECENT HIGHLIGHTS OF COLLOIDAL INORGANIC NANOPARTICLES APPLICATIONS

Metal Nanoparticles. NPs with a variety of metal cores have previously been prepared, each with their own optical, electronic, catalytic, or magnetic properties that can enable a variety of optical and electronic applications. Among metal NPs, the noble metals (Au, Ag, Pd, Pt) have probably received the most attention. Au and Ag NPs possess intense optical absorbance and scattering properties (see above), often with 100 000 times more intense extinction coefficients than individual organic dye molecules.[1] As a result of these optical properties, applications in bioimaging and chemical sensing (via aggregation, to produce bulk solution color changes; or via surface-enhanced Raman scattering) are heavily studied.[1,51,81] Ag NPs actively dissolve under physiological conditions to give silver ions, the active ingredient in potent antimicrobials.[38,39] Both Au and Ag NPs have also received extensive attention as colloidal building blocks for microscale optical and electronic devices, which can be prepared either by self-assembly of the colloidal building blocks or by inkjet-style printing to provide patterning with superior lithographic resolution compared to device fabrication using traditional top-down approaches.[5,84,85] Palladium and platinum NPs generally find use as supported catalysts, and Pd and Pt NPs have been shown to catalyze a variety of C−C bond forming reactions.[37,44,86,87] The organometallic catalysis community has recently recognized that some of their molecular catalysts may actually function as precursors for active Pt or Pd NP catalysts.[87,88] Pt NPs and their alloys, on solid supports, are actively studied for their ability to promote the oxygen reduction reaction to make water, for use in fuel cells.[88] Recently, oxide-supported Pt NPs have been coupled with gold films to produce devices that can follow heterogeneous chemical reactions (such as the oxidation of

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carbon monoxide) at the Pt NP surfaces, by monitoring subtle shifts in the LSPR of the gold film.[13,27,89]

The thermal properties of Au NPs, upon illumination with light, are of special interest. Gold is chemically stable compared to other metal NPs and is biocompatible in the bulk (at the nanoscale, this is another active area of study),[1,18,53] and its absorption wavelengths can be tuned from 500 to 1000 nm depending on particle shape.[1] Simple considerations of Au NP absorption cross sections, laser powers, thermal conductivity and heat capacity of common solvents suggest that illumination into gold's plasmon band can raise the temperature of the system by 4−40 °C in the steady state, with far larger temperature excursions possible near the gold surface for femtosecond pulsed lasers.[90−92] These photothermal effects are sufficient to kill cancer cells or bacteria[93] and, intriguingly, can be used to promote endothermic reactions, since an increase in temperature shifts the reaction equilibrium to the product side.[92,94] Illumination into the plasmon bands of noble metal NPs that are near semiconductor NPs improves the performance of the semiconductor NPs for solar-to-chemical energy conversion in photocatalysis, although the exact mechanisms, such as direct injection of the metal conduction-band electrons into the semiconductor; an increase in exciton formation rate due to the electric fields generated by the LPSR; and improved photon scattering from the metal NPs, are still being worked out.[95]

Plasmon-enhanced thin-film solar cells are part of next-generation solar energy conversion devices. Thin film solar cells, whether made with silicon or with organic polymers, are attractive as lightweight and flexible devices. The idea is that plasmonically active NPs (usually gold or silver) will not only increase the absorption of light in the visible and near-IR regions[62] but also will lead to higher photon capture efficiency within the device by the scattering of light.[96,97] Moreover, the large electric fields generated at the metal surface as a result of illumination into the plasmon bands increase the ability of nearby molecules to absorb light themselves.[98] Finally, the presence of electrically conductive NPs in a solar cell, in principle, could lead to increased efficiency in charge carriers reaching the electrodes. Because the geometry of the plasmonic NPs can be critical to device functioning, devices made via top-down lithographic approaches might be better suited to the application than colloidal dispersions.[99]

The potential for Au NPs to act as "theranostic" (simultaneous therapy and imaging) materials has been extensively explored since it was first shown in 2004 that Au NPs could act as effective imaging/therapy agents *in vivo*.[1,91] Photothermal destruction of tumors by near-IR-absorbing gold nanostructures (gold-coated silica nanoshells, gold nanorods, gold nanocages)[35,90,91] has now successfully been demonstrated *in vivo*, and strategies for maximally efficient *in vitro* and *in vivo* tumor targeting are currently under extensive investigation.[100,101] Recently, besides photothermal therapies alone, multifunctional Au NP agents have been identified that can provide both chemotherapeutic delivery and photothermal treatments, enhancing the efficacy of the chemotherapeutic.[101] Chan and others have shown that Au NPs can act as simultaneous phothermal agents/drug delivery.[21,101,102] Even without photothermal treatments, Au NPs loaded with antitumor agents (such as cisplatin or oxaliplatin's active component) have been found to facilitate improved drug delivery to cancer cells *in vitro*.[21,102] Au NPs loaded with the active component of oxaliplatin have shown enhanced cytotoxicity against A549 (lung) and RKP (colon) cancer cells compared to an equivalent dose of oxaliplatin alone (up to a 6-fold decrease in the IC_{50}).[21] The improved IC_{50} apparently arises from more specific delivery of the drug, which is facilitated by conjugating the drug to the Au NP surface.[21] The Au NP−drug conjugates can even penetrate the cancer cell nuclei, providing an opportunity for what could be highly specific anticancer therapeutics.[21] By coupling the chemotherapeutic to Au NPs, nonspecific drug release is reduced, and new opportunities to target specific organelles within the cancer cells are made possible. Ideally, these drug−Au NP conjugates may reduce traditional difficulties of chemotherapy: side effects and tumor drug resistance (since a nanocarrier enables lower absolute doses of the drug and more specific drug delivery to the leaky vasculature of tumors).[21]

Au NPs conjugated to dense monolayers of thiol-terminated oligonucleotides (either DNA or RNA) are highly effective cellular transfection agents and capable agents for gene therapy.[5] In 1996, Mirkin prepared one of the first well-controlled Au NP−DNA conjugates, which consists of a Au NP conjugated to a dense monolayer of DNA strands.[5] These spherical nucleic acid structures have been shown to be effective agents in a variety of biomedical applications, including colorimetric sensing, gene regulation, and the assembly of 1-D, 2-D, and 3-D DNA−Au NP scaffolds, the geometry of which can be varied by changing the size and shape of the Au NPs or the length of the DNA strands conjugated to the Au NPs.[5] Perhaps most interestingly, these spherical nucleic acids have proven to be very capable cell transfection agents, which resist rapid degradation by DNase enzymes and can even cross cell membranes without the assistance of small chemical chaperones, unlike typical gene regulation agents.[5] Once inside the cells, the spherical Au NPs can mitigate cellular metabolism in a variety of ways, including influencing gene expression by binding and preventing the translation of RNA within the cell.[5] Many of the biomedical applications of DNA-coated Au NPs really just rely on the gold to anchor a large number of DNAs together; however Mirkin has subsequently shown that the gold can be dispensed with entirely, to create true "spherical nucleic acids" with no inorganic core.[5]

While these results have generated significant excitement regarding the potential for novel nanoenabled therapy and diagnostics, the development of design rules to ensure that Au NPs are biocompatible and can selectively target tumors or other malignant tissue in a whole organism remains a challenge. It is usually assumed that by functionalizing NPs with tumor-specific antigens, uptake of NPs by tumors will be enhanced *in vivo*, just as it is *in vitro* in cell cultures. Recently, however, Huang et al. tested whether AuNRs functionalized to specifically bind A549 lung cancer cells (using different peptides targeted to the different receptors displayed on the A549 cell surface) would effectively bind both A549 tumor cells *in vitro* and *in vivo* (Figure 4A).[100] Functionalizing the AuNRs against the A549 tumor cells resulted in increased tumor uptake *in vitro* (Figure 4B).[100] During *in vivo* studies in mice, targeted AuNRs were actually taken up into tumors at a decreased rate versus unfunctionalized (CTAB-stabilized) AuNR, and the majority of AuNRs were sequestered in the liver and spleen regardless of the functionality displayed by the AuNR (Figure 4C).[100] In addition, AuNRs functionalized to target the A549 cells showed decreased blood half-lives versus the unfunctionalized AuNRs.[100] *In vivo*, unfunctionalized AuNRs were actually taken up by tumor tissue at nearly three times the rate of the

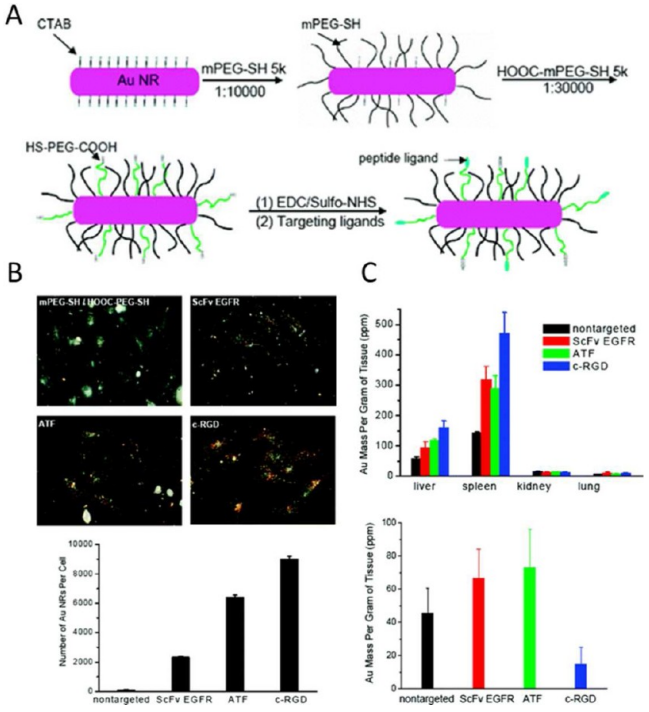

Figure 4. Tumor-specific gold nanorods do not necessarily enhance AuNR uptake by tumors *in vivo*. (A) AuNRs were functionalized toward A549 lung cancer cells using the ScFv, EGFR, ATF, and c-RGD peptides. (B) While this targeting enhanced uptake into A549 cells *in vitro*, (C) the majority of the functionalized AuNRs were retained by the spleen and liver *in vivo*. In fact, unfunctionalized AuNRs (CTAB) were actually taken up by cancer cells at a higher rate *in vivo*. The biodistribution of nanomaterials is governed by a number of competing biological processes, and a more holistic understanding of NP biological interactions is essential to design more sophisticated theranostic Au NPs. Reproduced with permission from ref 100. Copyright 2010 American Chemical Society.

functionalized AuNRs. The surface chemistry of the AuNRs appeared to have a stronger effect, however, on the biodistribution of the AuNRs within the tumor microenvironment, influencing partitioning in and around the tumor vasculature, uptake directly into the cancer cells within the tumor, and even association with different organelles within the cancer cells. These observations highlight the fact that the biological interactions of NPs are difficult to predict; yet it may be possible to selectively bind NPs to different areas of the cellular microenvironment, opening up further options of nanoenabled control of cellular processes and fate.[100,103]

Semiconductor Nanoparticles. As a consequence of their size-dependent bandgaps and tunable emission properties, semiconductor NPs (and iron oxide, which is a semiconductor but usually is classed solely as a magnetic NP) have been used in applications wherein light absorbers, fluorophores, and dyes might be used: biological imaging and contrast agents, solar energy conversion, and magnetic sequestration/therapy applications. Originally, QDs were primarily envisioned to be colloidal components of microscale electronics, much as metal NPs were for microscale optics. Indeed, a variety of advances are still being made in improving solar cell efficiency by using QDs as "luminescent concentrators" in dye-sensitized TiO_2 solar cells.[7,9,10,104−106] However, over the past 5 years or so, functionalized QDs are increasingly finding applications as fluorescent tags in biological systems, in spite of initial and continued worries about biocompatibility.[8,11,45,52] Functionalized QDs can act as nonblinking fluorescent tags in biological systems which are orders of magnitude brighter than fluorescent organic dyes or proteins on a per object basis. As a result, functionalized QDs have been shown to be effective *in vitro* and *in vivo* fluorescent tags for the visualization of a variety of cellular processes.[8,12] QD-enabled fluorescent tags have been used to assist in the visualization of vascular tumor tissue in real-time during surgery,[108] visualize the diffusion of individual protein receptors within neurons, and even image single-molecule biomolecular processes within cells.[111] Functionalized iron oxide NPs have also found extensive application as therapeutic (magnetic thermal heating, somewhat analogous to plasmon heating in metal NPs) and contrast agents (for MRI) in biological systems as well as sequestration agents for environmental remediation by virtue of their magnetic properties.[7109−111]

Quantum dots possess emission events that are generally an order of magnitude (per emitter) more intense than traditional fluorescent biological labels and dyes while possessing similar quantum yields. In addition, QD labels provide superior resistance to photobleaching versus dyes or fluorescent proteins, extending the lifetime over which high contrast images can be collected.[107] In addition, QDs provide larger absorption cross sections (making them superior to the standard green fluorescent protein, GFP, under photon-limited conditions) and generally provide reduced background contrast for in vivo imaging when compared to GFP.[8,107]

One of the most significant problems when using QDs for biological imaging has, until recently, been the tendency of QDs to "blink" on and off during their transport through the cell. This blinking was a severe detriment to effective real-time imaging and is thought to arise from ionization of the QDs within the biological matrix. Originally, this problem was mitigated by overgrowing a thick shell around the QD cores (which kept the QDs "on" more than 97% of the time) but significantly increased the size of the QD (from 5.0 to 13.0 nm), altering its transport through biological media.[50,111,112] In 2009, however, Wang et al. demonstrated that truly nonblinking core−shell QDs (CdZnSe/ZnSe) could be prepared by designing a QD with a core−shell structure in which there is a gradual composition gradient from core to shell (Figure 5).[112] This QD design permits the QD to effectively emit even when the QD is highly ionized, and these nonblinking QDs can be prepared with core diameters from 5 to 7 nm, meaning that they can be transported much more rapidly throughout cells than QDs with a thick outer shell (Figure 5).[45] These nonblinking QDs should be a significant benefit in the real-time imaging of single-molecule biological processes.

Functionalized QDs have recently enabled a significant advancement in energy conversion and storage. One promising advancement in nanomaterial-enabled solar technology over the past few years has been the development of multiple exciton generation (MEG) solar cells, which incorporate QDs to enhance the efficiency of the device. In typical solar cells, although any incident photon with enough energy to exceed the bandgap will generate an electron−hole pair, the energy of the highest-energy excitons is typically lost as waste heat. However, in solar cells that contain QDs, a single high-energy photon could excite multiple excitons, and if these excitons could be collected, the solar cell's efficiency could be substantially improved (Figure 6A).[59,113,114] Initial reports regarding the potential efficiency improvements provided by

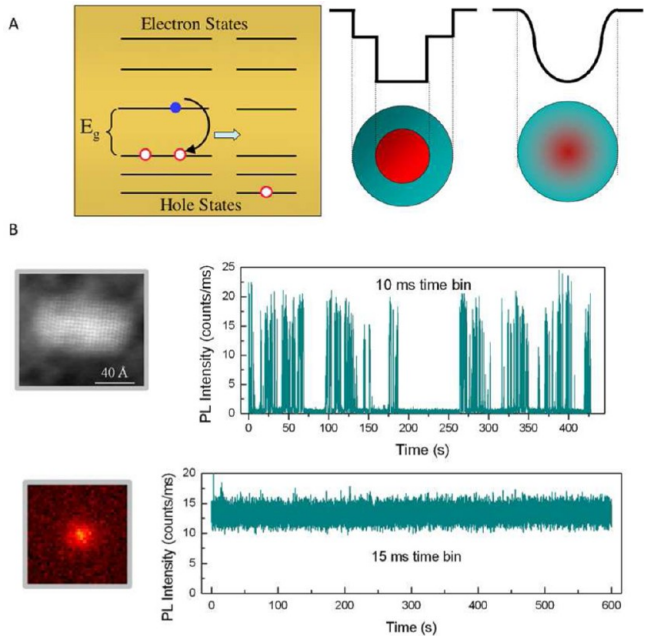

Figure 5. Electronic structure and photoluminescence spectra of nonblinking quantum dots. (A) By developing core−shell QDs in which the core layer and shell layer gradually blend together, the electronic structure of the QD changes, permitting permanent luminescence even when the particle is ionized . (B) The photoluminescence spectra of a core−shell QD compared to a QD in which the core and shell occur over a concentration gradient. The development of nonblinking QDs may permit continuous real-time visualization of single molecule biological processes via fluorescent imaging. Reproduced with permission from ref 112. Copyright 2009 Nature Publishing Group.

the MEG phenomenon sparked significant controversy.[113] However, in the past 2 years, two reports of improved efficiency in QD-enabled solar cells have generated fresh interest and cautious optimism that MEG may make a contribution to solar cell technology. In 2010, Parkinson et al. observed the MEG effect in a QD-impregnated device.[113] Last year, Nozik et al. followed this up by demonstrating the first formal MEG-enabled solar cell, which was impregnated with PbSe QDs (5.0 nm), which produced a measured external quantum efficiency of 114 ± 1% (Figure 6B,C).[59] These PbSe QDs were stabilized with short-chain carboxylic acids, which more easily permit the transition of excitons from the QD surface to the collecting electrode. This MEG solar cell showed an overall 5% conversion efficiency, which is nearly twice the maximum efficiency of previously reported QD-enabled solar cells. It should be noted, however, that this improved efficiency is still far below the overall conversion efficiency of the most efficient bulk solar cells (~20%).[59,113] Still, the rudimentary MEG solar cells provide 30% more electrical charges than photons that actually struck the device's surface. The development of MEG-enabled solar cells is part of the rise of "third-generation" photovoltaics. It should be noted, however, that the most significant improvements in solar photovoltaics are expected to come with engineering of multiple layers of solar cells, rather than relying on MEG.[115]

Iron oxide NPs have recently been shown to remotely activate genes in real time within living organisms. Stanley et al. successfully targeted a temperature-sensitive ion-transport channel (TRPV1) with antibody-coated iron oxide NPs.[110] The magnetic iron oxide NPs can be heated by applying a low-frequency magnetic field, which causes the local temperature to rise, expanding the calcium channel and stimulating calcium-promoted insulin formation.[110] After promising results at the cellular level, the magnetic NP technology was applied to live mice. The blood glucose level of the NP-treated mice showed a 6-fold decrease in blood glucose versus untreated mice, while the level of insulin in the NP-treated mice was increased significantly compared to untreated mice. In addition, the authors demonstrated that ferritin fusion proteins could be used to synthesize iron oxide NPs within the cells themselves and that these iron oxide NPs, synthesized *in vitro*, could produce a similar effect.[110] This is an elegant biomedical application for iron oxide NPs, which suggests that iron oxide NPs can potentially serve as remote-controlled *in vivo* agents to turn cellular processes on or off.

Insulator Nanoparticles. Insulator core materials, particularly silica (SiO_2) NPs, have no inherent size-dependent optical or electronic properties, yet the inert surfaces of these materials can be turned to the researchers' advantage either by implanting luminescent dopants within the inert surface or by carefully controlling their structure to prepare mesoporous nanomaterials for small molecule delivery.[15−17] A variety of insulator NPs, including silica and metal fluorides (MF_x), have be used as inert hosts for the development of NPs that are upconversion phosphors.[6,50,116] Upconversion phosphors are phosphor materials capable of absorbing light of a given wavelength and then emitting light at a higher energy wavelength. A key to the upconversion phenomenon is the presence of luminescent ions, such as lanthanides, doped into a host matrix in which energy losses will be minimized. Therefore, inert matrices, such as silica or fluoride salts, are ideal.[50,51] In addition to being electronically inert, these host materials are chemically and thermally stable, making them ideal host materials. Upconversion phosphor NPs find applications in biosensing, color displays, and solar cells.

Another interesting use of inert NPs for biomedical applications has been the development of functionalized MSNPs as stimuli-responsive drug delivery agents.[15−17] Mesoporous silica is an ideal material for this application, because the nanoscale pores of the silica can be functionalized independently of the NP surface to enhance drug loading and the pores can also be gated with stimulus-responsive molecules to ensure that the molecular cargo can be delivered at exactly the right time. This means that MSNPs provide one of the best chances to achieve controlled drug release only at the desired site of action.[15−17] In addition, MSNPs are thought to be generally biocompatible and nontoxic, making them, in many ways, the ideal biological drug delivery agent.

The principal challenges associated with developing MSNPs for effective drug delivery entail developing appropriate MSNPs that can effectively target specific cells *in vivo* and simultaneously will only release their therapeutic cargo once they arrive in the cells of interest.[15−17] MSNP drug delivery agents are typically targeted to specific cells in the same way that Au NPs or QDs are targeted *in vivo*, by functionalization on the surface with targeting molecules or antibodies. However, with respect to stimulus-responsive gating at the pores, a variety of gating strategies have been explored.[15−17] MSNPs have been gated with a variety of different species, including nucleic acids, QDs bound to disulfides, and photoactive polymers.[15−17,48,49,117,118] Ultimately, the goal of effective gating is to develop a gate that will open the drug-loaded pores only

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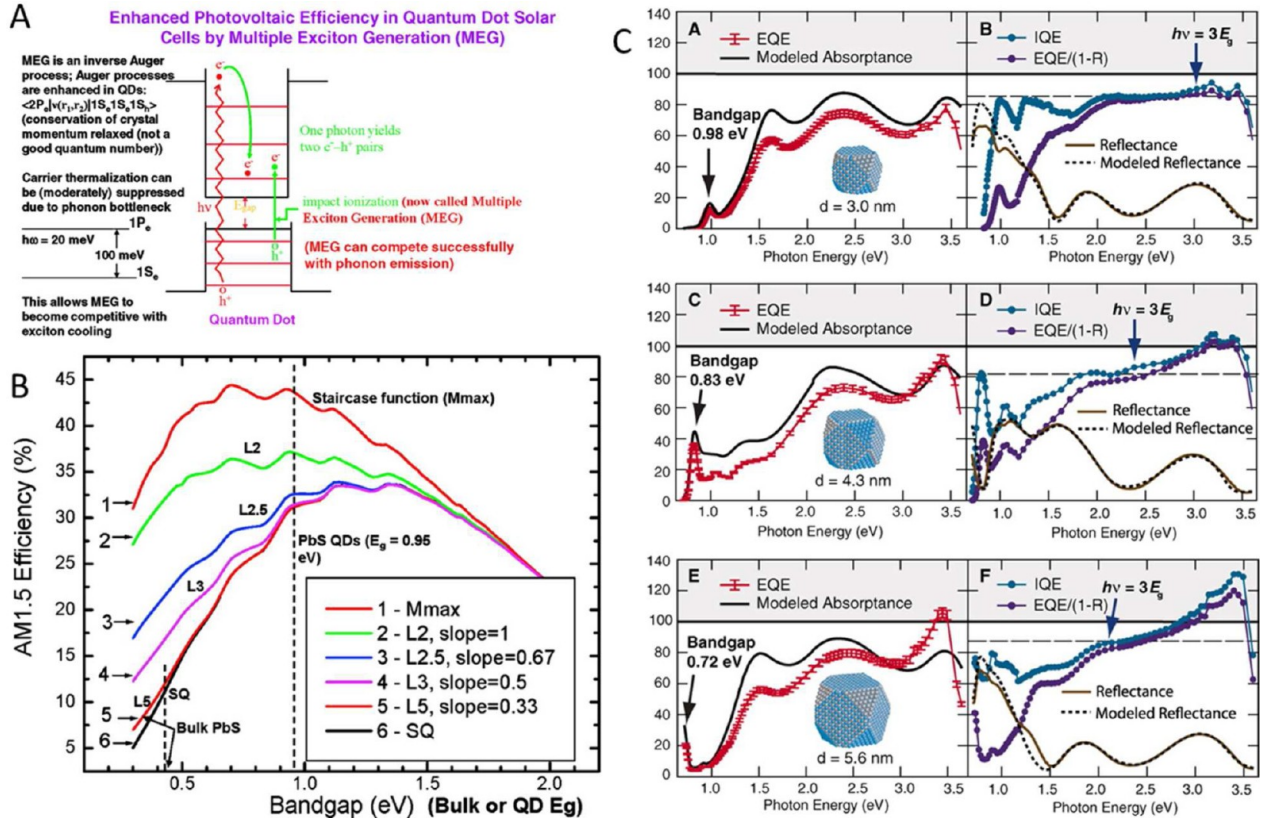

Figure 6. Development of multiple exciton generation third-generation solar cells has the potential to significantly improve the efficiency of quantum dot-impregnated solar cells. The MEG process involves excitation with a high-energy (e.g., UV) photon which generates two excitons. In QDs, the MEG process can compete effectively with phonon relaxation, potentially improving the efficiency of solar cell efficiency. (B) Theoretical comparison of power conversion efficiency between PbSe QD-enhanced solar cells and bulk PbSe. Ideally, the incorporation of QDs into MEG solar cells can raise the maximum 1 sun efficiency from 32% to 44%. (C) A comparison of the external and internal quantum efficiency of PbSe QDs over a range of photon energies (eV). The maximum efficiency absolute efficiency of the QD-impregnated solar depends on the size of the QD. Reproduced with permission from refs 30 and 59. Copyrights 2010 American Chemical Society and 2011 American Association for the Advancement of Science, respectively.

when they have arrived in the cell of interest, and preferably, the opening will be triggered by physiological conditions within the cell itself, rather than external stimuli.[117] Previous MSNP gate-opening stimuli have included redox potential, photo-irradiation, and enzyme action, but many of these stimuli have proven impractical, because the stimulus is difficult to apply or the opening of the gate releases additional toxins into the cell.[15−17,48,49,117]

Recently, a new strategy for stimulus-responsive drug delivery in MSNPs has been demonstrated, which uses a polyvalent nucleic acid−MSNP "click" conjugate as the drug delivery gate (Figure 7A,B).[117] This drug delivery vehicle responds to both external and endogenous release stimuli, responding to both increases in temperature or the presence of deoxyribonuclase I (DNaseI). An increase in temperature or the presence of DNaseI results in the denaturation of the double-stranded DNA holding the nanopure gates closed and releasing the cargo contained in the pores (in this case, rhodamine B). The temperature required to denature the DNA guarding the pores is 50 °C, well above physiological temperatures, making the temperature-mediated release of the cargo not feasible *in vivo*, however, exposure to DNaseI does successfully open the DNA-gated pores and lead to the release of the molecular cargo.[117] After 24 h, up to 81% of the rhodamine dye was released (depending on the concentration of DNase I), implying that DNase I concentration can be used to meter the rate of drug release (Figure 7C).[117] Furthermore, the DNA-gated MSNP delivery vehicle showed enhanced efficiency in killing cancer cells when the MSNP was loaded with camptothecin (CPT), providing an early example of a MSNP drug delivery approach that will release drugs in response to a physiological stimulus.[117]

■ OUTLOOK AND CHALLENGES

Over the past 5 years, there has been more than a 5-fold increase in the number of articles published on colloidal nanoparticle applications, proof enough that the potential applications of functionalized NPs are of significant interest to many scientific fields.[23,31] In addition, the scientific community has seen a variety of advancements enabled by functionalized nanomaterials ranging from tumor-specific cancer therapy (demonstrated both *in vitro* and *in vivo*) to the development of third-generation solar cell technology. Perhaps more importantly, sophisticated biomedical and energy conversion NP applications are quickly moving out of the laboratory and into the commercial sector. The National Cancer Institute lists nine separate NP-enabled anticancer therapy and diagnostic agents that are currently in clinical trials, with many more set to join.[119] These include trials on positron emission tomography imaging agents, cyclodextrin capsules for gene therapy, and nanoscale polymeric and silica spheres for drug delivery; this is substantial progress considering many of these therapies were

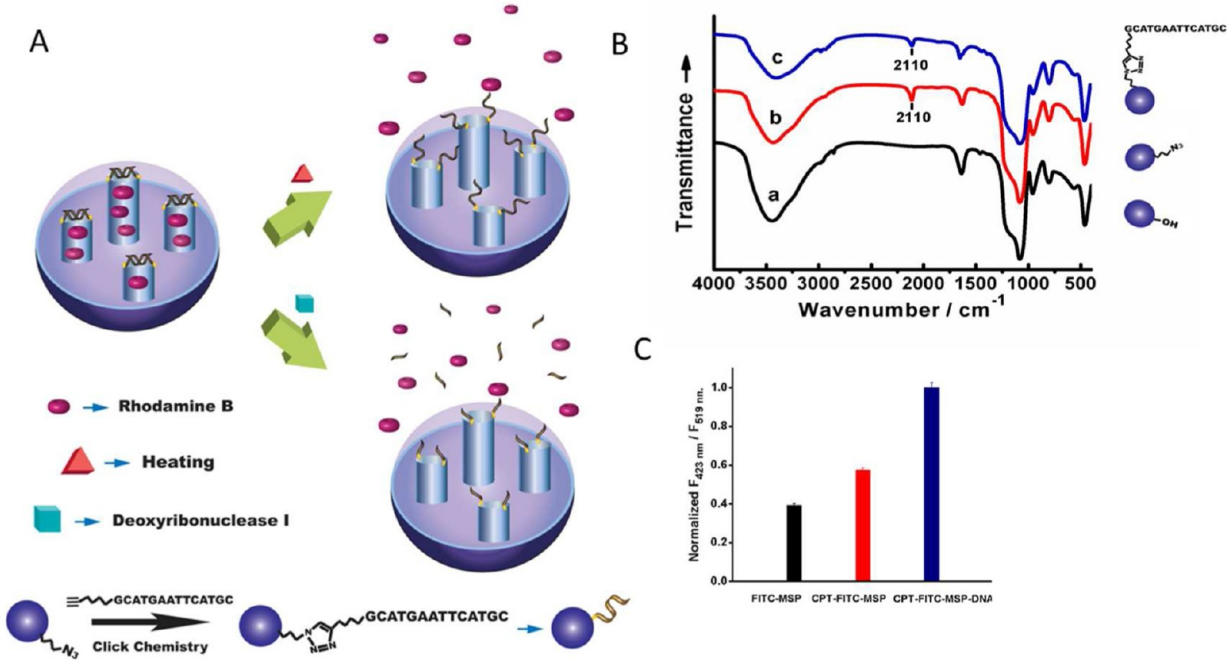

Figure 7. Duplex DNA-gated mesoporous silica nanoparticles for drug delivery. The MSNPs were loaded with rhodamine A as a test cargo. (A) The duplex DNA guarding each pore can be denatured by heat or by the presence of DNase I . (B) The surface functionalization of the MSNP delivery agents was confirmed by FTIR analysis. (C) Luminescent imaging of cells, following treatment with the appropriate stimulus results in enhanced delivery of the rhodamine A to the cancer cells, as a result of the improved drug delivery specificity provided by the silica nanocarrier. Reproduced with permission from ref 117. Copyright 2011 John Wiley and Sons.

first demonstrated less than a decade ago.[119] This is ample reason for excitement and optimism that nanotechnology will have a positive impact in biomedicine.

While interest in nanotechnology applications remains strong and the past decade has seen remarkable demonstrations (in the laboratory) of how nanotechnology can provide elegant solutions to pressing real-world problems, the lasting impact nanotechnology will have on human health and technology is less certain.[63,120−122] A number of significant challenges remain which may ultimately determine whether nanotechnology transforms our society as much as traditional chemical industries have or grows more slowly or stalls, much as nuclear energy has done. Some of these challenges relate to the fundamental chemistry of nanomaterials. As El-Sayed's work showed (*vide supra*), we still know very little about how functionalized nanomaterials behave *in vivo*, and without adequate data to assess the potential hazard and biodistribution of functionalized nanomaterials, it will be difficult to push the development of theranostic nanomaterials forward.[100,121] Fortunately, this challenge is being met with vigor in the scientific community, and the past few years have seen a focused investigation into the fate and transport of nanomaterials in both biological and environmental systems. These types of assessments will also be essential for the development of adequate regulations to govern what will hopefully be a safe and beneficial nanotherapeutics industry.

Other roadblocks in the evolution of nanomaterials into viable commercial products relate more to the practical challenges of developing a new chemical industry out of a science which is still so young.[122] For instance, even the synthesis of large enough quantities of functionalized nanomaterials for clinical trials (or the development of prototype NP-enabled devices) is a significant challenge. Typically, functionalized nanomaterials are still synthesized primarily on the milligram scale, and these syntheses can be difficult to reproduce and scale up and generate excessive waste relative to the small amount of material recovered (10 L of waste to prepare less than 1 g of pure material is still not uncommon).[43,65,122] Thus, while the applications of nanomaterials continue to expand rapidly, the synthesis of functionalized nanomaterials is still very much in the discovery phase. Various strategies are being adopted to enable the cost-effective, reproducible synthesis of functionalized nanomaterials (synthesis in fluidic reactors has proven to be potentially viable path forward),[123] but much more work needs to be done. Without effective synthetic strategies to generate large (kg scale) quantities of functionalized NPs that are monodisperse, pure, and well-characterized, even clinical trials for many types of nanotherapeutics will remain a logistical challenge.[65]

A final significant challenge involves finding new ways to manipulate NP surface chemistry to maximize the efficiency of NPs in their applications, especially for biomedical ones. While it is common to coat NPs with PEG (to limit protein adsorption), or to target NPs to tumor tissue by conjugating antibodies to their surface, the work of many groups now suggests that an extremely sophisticated understanding of NP surface chemistry is essential for *in vivo* targeting and specific binding.[121] The surface chemistry of NPs has been shown to influence binding by proteins in the bloodstream, influence their blood half-lives, and dictate NP biodistribution within biological systems, including tumor tissue microenvironments.[100,121] Accordingly, it will become essential to develop strategies to design NPs with mixed ligands shells, in which the spatial distribution of the ligands can be predictably controlled, as well as strategies for functionalizing different faces of anisotropic NPs in order to control transport and biodistribution *in vivo*.[124]

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CONCLUSION

The past 5 years has seen a surge of interest in the applications of functionalized colloidal nanomaterials. The unique nanoscale optical and electronic properties of these materials, along with the synthetic ability to independently tune their size, shape, and surface chemistry, permit applications that simply cannot be performed by either molecular species or bulk materials. In the past few years, significant advancements have been made in demonstrating the utility of colloidal nanoparticles in biomedical and energy conversion/storage applications, leading to the development of theranostic materials, high-capacity drug delivery agents, and increasingly efficient solar cells. While these applications highlight the fantastic potential of nanotechnology to leave a lasting mark on our society, a number of practical challenges, primarily relating to the evolution of nanotechnology from laboratory science to a viable industry, still remain.

AUTHOR INFORMATION

Corresponding Author

murphycj@illinois.edu

Notes

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