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Delivery of Drugs, Proteins, and Nucleic Acids using Inorganic Nanoparticles

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Abstract

Inorganic nanoparticles provide multipurpose platforms for a broad range of delivery applications. Intrinsic nanoscopic properties provide access to unique magnetic and optical properties. Equally importantly, the structural and functional diversity of gold, silica, iron oxide, and lanthanide-based nanocarriers provide unrivalled control of nanostructural properties for effective transport of therapeutic cargos, overcoming biobarriers on the cellular and organismal level. Taken together, inorganic nanoparticles provide a key addition to the arsenal of delivery vectors for fighting disease and improving human health.

Keywords

drug delivery; inorganic nanoparticles; gold; silica; iron oxide; lanthanide upconversion particles

1. Introduction

Nanotechnology provides a potent tool for delivery and programmed release of therapeutics. Many therapeutics suffer from poor stability, inability to cross the cell membrane, and rapid clearance *in vivo* [1,2]. The biomimetic size and tunable properties of nanomaterials provide unique advantages for therapeutic delivery agents. [3,4,5]. A broad range of inorganic nanoparticles have been explored as carriers to deliver therapeutic cargos into living systems for the controlled, targeted management of diseases like cancer [6,7].

Today, three main classes of therapeutic are of central interest for the treatment of disease: small molecule drugs, nucleic acids, and recombinant proteins [8,9,10]. Small molecule drug delivery is a broad field that has been explored extensively for many applications, including inhibition of cellular processes [11,12], enhanced cell signaling [13,14], and targeted cytotoxicity [15]. Delivery and controlled release of these materials provides a

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strong value-added proposition, with the potential to maximize efficacy and minimize off-target effects [16].

Many diseases are considered ‘undruggable’ using standard small molecule therapeutics [17]. Many of these challenges, however, can be addressed using biomacromolecular therapeutics [18]. Nucleic acid therapeutics are one broad class, and include plasmid DNA (pDNA) and messenger RNA (mRNA), which induce expression of proteins in the cell [19], as well as RNA interference (RNAi) techniques such as small interfering RNA (siRNA) [20] and micro RNA (miRNA) [21], which ‘knock down’ protein expression. Nucleic acids are highly charged, making them essentially impermeable to the cell membrane [22]. They are also relatively fragile, and benefit from nanocarrier-mediated protection against endogenous nucleases [23].

Proteins present a second family of biomacromolecular therapeutics [24]. Both native and engineered proteins can function directly in the cell and can induce or suppress specific biological processes [25]. Proteins are generally large and do not generally penetrate the cell membrane on their own. [26,27,28]. While peptide (e.g. cell-penetrating peptides) [29] and other bioconjugation strategies can enable delivery into cells, these strategies often result in endosmal entrapment and degradation [30]. Nanocarriers provide access to critically important tools for effecting delivery of large and highly charged nucleic acids and protein species across the otherwise impermeable cell membrane, as well as the benefits of targeting and controlled release.

The different delivery challenges presented by small molecules, nucleic acids and proteins necessitate distinct strategies for complexation/conjugation and delivery [27]. Nanomaterials derived from gold, iron, silica, and lanthanides feature a range of unique physio-chemical characteristics and structural capabilities distinct from the properties of their bulk materials that have made them promising carrier platforms for therapeutics (Fig. 1) [31,32,44]. Many of these attributes, such as high surface-volume ratio [33], long-term stability [34], and optical responsiveness [35], make these materials promising candidates for drug loading and targeted release [36,37]. Certain types of nanocarrier technology have also significantly enhanced delivery efficiency for all three classes of cargo through triggered or localized release [38].

In this review, we highlight the evolution of inorganic nanoparticles for delivery applications, from earlier landmarks to more recent clinical translation. We will also discuss challenges still faced with inorganic nanoparticles, and finally provide our perspective on the opportunities presented by this expansive and fertile field of research. The range of nanomaterials employed for delivery is vast. For this review we have focused on four major classes of materials: gold [39], silica [40], iron oxides [41], and lanthanides [42,43].

2. Gold Particles

AuNPs emerged in the late 1990s as attractive candidates for delivery of diverse payloads [38]. Gold has since proven a versatile and useful core material for delivery applications; it can be formed into monodisperse nanostructures [44] with a high degree of specificity, is

essentially chemically inert and nontoxic [45], and can be functionalized with a wide variety of ligand species and chemical moieties [46,47].

Gold can be directly conjugated using thiolated (-SH) molecules to form stable monolayer-protected particles (Fig. 2) in an interaction that is partially covalent (~35%) and mostly electrostatic (~65%) [48,49]. The monolayer stabilizes the core and can be tailored with a range of functionalities to provide effective cellular uptake, controlled payload release, and cell-specific targeting [50]. Direct covalent attachment to the gold core can be used to deliver thiolated fluorophores [51] or small molecule drugs into the cell and into tumor tissue [52] with improved efficacy over free drug [53]. These coverings are stable outside cells but labile intracellularly due to much higher glutathione levels inside cells than extracellularly, providing a mechanism for internal release [54]. The monolayer also allows for non-covalent loading with large amounts of pharmaceuticals, effectively rendering a 'drug reservoir' for controlled and sustained release [55,56].

AuNPs are made through reduction of gold salts in the presence of an appropriate stabilizing agent, and can be synthesized with a highly controllable core size, ranging from ultrasmall (≤2 nm) to as large as 150 nm [39]. Size differences influence physio-chemical characteristics [57], pharmacokinetic behavior [58], and especially optical properties [59]; small AuNPs, including gold nanoclusters, typically have a high surface-to-volume ratio, and can exhibit photoemission (gold nanoclusters (AuNCs, typically < 2 nm), while larger particles show a characteristic surface plasmon resonance [60, 61, 62]. Numerous strategies utilize the advantageous physio-chemical properties of gold nanomaterials to provide robust platforms for intracellular delivery of everything from small molecule drugs [39] to large biomolecules like proteins [27] and pDNA [50].

2.1. Covalent AuNP cargo attachment

Small AuNCs and AuNPs can penetrate cells without disrupting the cell membrane structure [63,64]. Ultrasmall particles also benefit from a tunable biodistribution [65,66], as well as enhanced uptake into the nucleus [67,68] and into tumors [69,70], making them excellent candidates for drug delivery vehicles. Early work demonstrated intracellular delivery of a thiolated small molecule dye covalently bound to a 2 nm AuNP gold core [71]. AuNPs are efficient quenchers of fluorescence, providing the AuNP platform with a robust 'turn-on' fluorescence signal to monitor delivery (Fig. 3). Similar approaches using ultrasmall AuNPs enhance small molecule drug delivery for photodynamic therapy [72,73] as well as chemotherapy [74] and at the time of this writing are undergoing clinical trials for treatment of childhood brain cancer [75]. Covalent drug conjugation to a photocleavable head group is a versatile alternative approach to photo-regulated drug delivery [76,77]. 'Caging' the anticancer drug 5-fluorouracil to the ligand through a photo-responsive *o*-nitrobenzyl linkage followed by UV-A radiation triggered photolytic cleavage and drug release, providing effective *in vitro* anticancer activity [78].

The optical behavior of gold nanoparticles ≥ 2 nm is based on plasmonic properties and gives AuNPs the ability to absorb and scatter light with extraordinary efficiency [79]. Plasmonic properties can be tuned to absorb specific wavelengths based on shape and aspect ratio [80]. AuNPs of mid-to-large core size differ from their ultrasmall counterparts in

several ways, one of the most notable being efficient light-to-heat conversion. This property of AuNPs was originally used to destroy cancerous tissue through conversion of NIR irradiation into heat for photothermal therapy [81,82]. AuNPs for photothermal therapy can be combined with other treatment strategies, providing opportunities for multimodal cancer treatment [83,84,85,86]. However, the high-power density of irradiation and poor selectivity remain challenges for this approach [87]. Today, the photothermal properties of AuNPs (in particular hollow nanoshells) are being investigated in the clinic as a treatment for prostate cancer [88].

Peptide conjugation to particle surfaces can serve multiple purposes. First, peptide presentation on the particle surface can provide targeting elements for a specific cell type [89, 90, 91, 92]. Work by Russell utilized AuNPs conjugated with a phthalocyanine dye, polyethylene glycol (PEG) for stability, and HER-2 antibody to provide breast cancer cell targeting [93]. PEG conjugation is a common approach to increasing ‘stealth’ character of nanomaterials otherwise identified as foreign by the body [94,95,96,97]. These studies resulted in selective cancer cell death in cultured cells. Peptides with therapeutic activity can also be conjugated to the particle surface for intracellular delivery [98]. Recently, 2 nm AuNPs bound to small antigenic peptides have been used in clinical trials as an immunotherapeutic treatment for type I diabetes, a promising step forward in medical nanotechnology [99,100].

Nucleic acid strands can be readily modified and bound to gold nanoparticle cores [101] in a selective and cooperative manner, most commonly through thiol moieties [102,103,104]. Mirkin synthesized a class of polyvalent nucleic acid AuNPs (13–15 nm core) with thiolated oligonucleotides. These particles exhibited optical properties governed by aggregate size and were initially used as a diagnostic method to detect DNA [105,106]. They also covalently conjugated 13 nm gold core AuNPs with thiolated antisense oligonucleotides as a gene interference strategy, first using the oligonucleotides themselves [107], and then using complementarily bound siRNA strands (Fig. 4) [108], demonstrating tunable gene knockdown using both approaches [109]. This conjugation strategy is not limited to DNA; thiolated siRNA for example, can also be stably conjugated directly to the gold core [110,111] or attached to polymer-modified gold cores [112,113]. This bioconjugation has notably been shown to be dependent on AuNP shape [114]. Mirkin and Paller demonstrated the capability of spherical nucleic acid-13 nm core AuNP conjugates dispersed in moisturizing ointment to penetrate the skin and down-regulate gene targets responsible for insulin resistance in diabetic mice [115,116]. Conboy and Murthy utilized covalent conjugation to 15 nm gold core for delivery of the CRISPR/Cas9 gene repair machinery with their ‘CRISPR-Gold’ platform [117]. Thiolated complementary olignonucleotides bound to the core held the ‘donor’ DNA needed for gene repair, while the Cas9/RNA complex was encapsulated by a cationic polymer. These studies demonstrated efficient genetic repair, with follow-up studies resulting in therapeutic gene correction of a murine muscular dystrophy model [118].

2.2. Non-covalent AuNP cargo complexation

Non-covalent cargo encapsulation provides an alternative to covalent delivery strategies that avoids the challenges associated with covalent conjugation arising from modification of the cargo, and issues related to detachment [55,119,120]. Drug encapsulation within a hydrophobic pocket such as that present in PEG-conjugated (PEGylated) AuNPs can provide significant loading capacity. Burda reported 5 nm core PEGylated AuNPs with a phthalocyanine photosensitizer small molecule encapsulated within the PEG layer. Intravenous injection provided tumor localization to a much greater extent than free drug [121].

The AuNP ligand monolayer also provides opportunity to encapsulate and deliver drugs. Hydrophobic small molecule anticancer drugs can be loaded into the monolayer of 2 nm core AuNPs for delivery to cancer cells [122]. In this work, AuNP ligands were comprised of hydrophobic alkanethiol chains with zwitterionic head groups, to prevent non-specific adhesion. Several hydrophobic anticancer drugs, including bodipy, tamoxifen, and β-lapachone were encapsulated and demonstrated *in vitro* anticancer activity significantly greater than free drug alone [123]. Monolayer encapsulation is a versatile strategy; biorthogonal catalysts, such as transition metal catalysts, have also been delivered. These cargos provide an alternative approach to delivery, through localized ‘prodrug’ activation, with the potential for selective intra/extracellular drug activation, based on ligand functionality [124,125,126,127].

Mixed-monolayer AuNPs have the ability to stabilize the interface between immiscible fluids, and form Pickering emulsions [128]. Self-assembled capsules have been demonstrated extensively for encapsulation and delivery, and benefit from the advantages of incorporated AuNPs [129]. Rotello reported 2 nm AuNP-stabilized capsules (NPSCs) with highly controllable physical properties that could encapsulate and deliver small molecule drugs [130]. Follow-up studies demonstrated these systems for delivery of siRNA [131,132,133] through a combination of encapsulation and lateral interaction at the NPSC surface. In this work, siRNA that silenced TNF-α expression was delivered to macrophages LPS-challenged mice. *In vivo* studies showed directed delivery of NPSCs to the spleen after intravenous administration, with 70% gene silencing, demonstrating NPSC platforms as efficient vectors for immunomodulation in treatment of inflammation (Fig. 5). Macrophages are the first line phagocytes of the innate immune system and are being investigated as therapeutic targets using AuNPs for treatment of several diseases, including inflammation and cancer [134,135,136].

The AuNP monolayer can be tailored to interact with a diverse range of targets, including large biomolecules through electrostatic interaction. One study prepared cationic 2 nm core AuNPs capable of electrostatic surface recognition of a large anionic protein, β-galactosidase. This recognition was used first for intracellular binding and inactivation of the protein [137], and later for intracellular delivery of the same protein [138]. However, this approach relied on inefficient endosomal uptake and escape pathways. In later work, Rotello reported direct cytosolic protein delivery using supramolecular protein-AuNP complexes. Electrostatic interaction between cationic AuNPs and poly(glutamic acid)-tagged proteins generated hierarchically-structured complexes that delivered protein cargo of various sizes

and isoelectric points (pI) into the cytosol of mammalian cells [139,140]. This highly effective cytosolic delivery system avoids the endosomal entrapment challenges faced by other strategies [141] and demonstrate the unique structural and dynamic properties that can be obtained using AuNPs [10,39]. This AuNP platform was notably used for intracellular delivery of the CRISPR/Cas9 gene editing machinery, providing efficient (30%) knockout of the *PTEN* gene in HeLa cells [142]. This approach was effective *in vivo* as well, as demonstrated by efficient (>8%) knockout of the *PTEN* gene in splenic macrophages, following systemic administration of the CRISPR/Cas9-AuNP assemblies in *BALB/c* mice (Fig. 6) [143].

Cationic small AuNPs can non-covalently bind nucleic acids through electrostatic interactions with the highly anionic phosphate backbone [144,145]. Early work demonstrated the ability of mixed monolayer AuNPs to complex [146] with pDNA and transfect mammalian cells with low toxicity [147]. Translation of these platforms to *in vivo* applications [148,149,150] has shown promising results, with potential advantages over viral carriers in terms of safety and efficacy [151,152,153].

Multilayer assembly is an encapsulation approach that electrostatically complexes cargo within complementarily charged coatings [154,155]. Tung employed multilayered 40 nm core AuNPs fabricated with poly-L-lysine and siRNA (up to 4 layers) in alternating coatings to provide a protease-degradable siRNA carrier [156]. The authors observed a gene knock-down effect correlated with the number of siRNA layers. Co-assembly with the organic transfection reagent polyethylene imine (PEI) is a commonly used approach to promote uptake of AuNPs for delivery of siRNA or miRNA [157]. Incorporation is often done through multilayering of PEI and RNA [158], but supramolecular complexation and delivery has also been demonstrated using AuNPs with dendritic ligands [145]. In recent work, Liang *et al.* developed self-assembled and crosslinked clusters based on 2 nm AuNPs, containing an anticancer oligonucleotide, into a sunflower-like superstructure that dissociated and enhanced cell uptake upon irradiation with near-IR (NIR) light [159]. This strategy notably utilized the uptake capabilities of small AuNPs as well as the photo-responsive properties of larger gold clusters to achieve targeted delivery *in vivo* [160].

The optical responsiveness of gold nanomaterials has garnered especial interest in gold nanorods (AuNRs), elongated Au-based nanoscale materials with optical properties that can be finely tuned through the aspect ratio of the rods [161,162,163]. Upon wavelength-specific irradiation, AuNRs generate heat, potentially providing for localized payload release [164,165,166]. AuNRs have been extensively explored for delivery applications [167], perhaps most notably of nucleic acids including DNA [168,169,170,171] and siRNA [172]. In 2008, Murphy encapsulated a model hydrophobic small molecule in the surfactant bilayer bound to the nanorods, demonstrating their high drug loading capacity [166]. More recently they have been explored as delivery vehicles for nucleic acids. Wei demonstrated the electrostatic adsorption of dithiocarbamate-modified siRNA duplexes to a AuNR surface, minimizing premature siRNA desorption and release [173]. These carriers released their cargo upon NIR irradiation and demonstrated significant knockdown of a target gene related to metastatic ovarian cancer. AuNRs provide for efficient non-covalent cargo loading and benefit from their photo-responsiveness, however they also tend to suffer from aggregation,

and sufficient purification from surfactants and other chemicals used in their fabrication can be a challenge [174].

2.3. Gold nanoclusters

Gold nanoclusters (AuNCs) are smaller gold-based nanomaterials consisting of tens to hundreds of gold atoms. The properties of AuNCs bridge the gap between nanoparticles and atoms, as they possess unique properties distinct from their bulk counterparts [175]. Unlike AuNPs, AuNCs are mixed-valence species that have discrete energy levels and show multiple absorption bands. These photophysical properties can allow for fluorescence in the NIR region [176] and for other unique photodynamic properties [177] that position AuNCs as potential vehicles for delivery.

Cui et al reported a facile method of assembling monodisperse and stable self-assembled nanoparticles (NPs) in water using chlorin e6 (Ce6) molecules to cross-link AuNCs. These GNCs-Ce6 NPs were conjugated with CD3 antibody to create a cell-specific drug delivery system for cytokine-induced killer cells (CIK). This system exhibited high tumor-targeting efficiency and excellent therapeutic efficacy toward MGC-803 tumor-bearing mice [178]. Antibody-based tumor targeting can be extended to include multiple targeting elements [179,180,181]. Chen developed a AuNC platform for doxorubicin (dox) delivery to tumors, using a dual-targeting strategy. AuNCs were covalently conjugated with both a peptide specific for integrins on the surface of tumor tissues (cRGD) and an aptamer with high affinity to nucleolin overexpressed in the cytoplasm of tumor cells (Apt), for extra- and intracellular tumor targeting, respectively (Fig. 7) [182]. dox was immobilized onto the dual targeting platform and was shown to release and trigger tumor cell death in both cultured cell models and *in vivo*, with enhanced accumulation in the tumor.

Like AuNPs, cationic AuNCs can electrostatically complex nucleic acids to enhance cellular delivery. In a recent study, Jiang [183] complexed siRNA targeted at *NGF* (a tumor-associated gene) with < 3 nm cationic AuNCs. The authors demonstrated enhanced siRNA stability in serum, enhanced cellular uptake and gene silencing in cells, and tumor accumulation *in vivo*. Notably, AuNCs with cores < 3 nm often exhibit robust fluorescence, enabling imaging applications. Wang [184] demonstrated carborane NCs that provide accurate tumor imaging and long-term accumulation in tumor sites by the EPR effect.

AuNPs and AuNCs are both versatile platforms that benefit from their stability and tunable surface functionalization. AuNP-based delivery platforms are also among the few that have reported for direct cytosolic delivery, critical for future development of efficient therapeutic delivery systems for biologics [139,142]. Gold is inherently inert and has even been called the ‘noblest’ of metals [185]. Work by Xu [186] demonstrated that even direct incubation of gold nanoparticles with zebrafish embryos had minimal effect on development. Despite being mostly accumulated in the liver and spleen of animal models, gold nanomaterials did not induce any hepatic or renal toxicity [187]. Although some uncertainty in regards to the biological fate of the gold nanomaterials is to be considered, there are ways to overcome this limitation by controlling the surface properties such as surface charge [66] which will be critical to the future advancement of gold-based delivery platforms. [143,188].

3. Silica Nanoparticles

Silica-based nanocarriers offer many advantages in terms of loading capacity and can be easily functionalized for a variety of applications [189,190,191]. Silica nanomaterials and especially porous nanoparticles have gained interest as delivery platforms for their potential to address key therapeutic issues including drug solubility and extended drug release rate [192,193]. Mesoporous silica nanoparticles (MSNPs) are nanoscale silica particles with a honeycomb-like structure featuring hollow channels and are the most commonly used silica-based delivery vehicles [31,194]. The generation of MSNP structures was advanced considerably in the early 1990s by with scientists at Mobil Oil working to develop a new family of molecular sieves [195]. MSNPs have since become attractive delivery vehicles due to their chemical inertness, thermal stability, extended cargo loading, and tunable structure [196,197,198]. The synthesis of MSNPs generally relies on a cationic surfactant to provide a template for the base-catalyzed sol-gel process (Fig. 8) [199]. The process itself and choice of template are highly controllable, so resulting MSNPs can be finely tuned for particle size, pore quantity, and pore radius [200,201]. MSNPs generally encapsulate cargo within their pores through non-covalent binding, but delivery strategies can also benefit from rationally designed covalent surface modifications to provide targeted or controlled cargo release [197].

3.1. Non-covalent cargo encapsulation by MSNPs

Pore size and surface functionalization play crucial roles in the drug loading capacity and tunable release rate of MSNPs [202]. Typically, cargo molecules are loaded in MSNPs through weak non-covalent interactions, such as hydrogen bonding, physical adsorption, electrostatic interaction, or aromatic stacking [203]. Altering pore characteristics can significantly influence charge density and steric effects within the pore, modulating weak electrostatic interactions, and impacting cargo release [204,205]. MSNPs with small pores can provide tunable release rate for small molecule drugs: in early studies, Pérez-Pariente reported that by employing different pore sizes, release of pore-loaded ibuprofen could be tuned from burst release to long-term sustained release [206]. In later work by Tian, MSNPs with pore sizes ranging from 3 nm to 10 nm were loaded with the chemotherapeutic drug paclitaxel [207]. The release rate of paclitaxel loaded MSNPs was measured in solution and in cultured cells, and it was found that larger pores provided higher loading capacity, faster release rate, and greater *in vitro* anticancer activity. Later however, Yin's *in vivo* antitumor experiments added complexity to these conclusions by demonstrating that MSNs with a pore size of ~5 nm induced the most apoptosis and showed best tumor reduction in H22 tumor bearing mice [208].

Recently the ability of MSNPs with small pores to isolate encapsulated materials from the environment has been used for biorthogonal applications [209,210,211]. Mascareñas and coworkers reported a hollow 'nanoreactor' consisting of 3 nm pore MSNPs as a nano-shell, doped with an inner layer of palladium nanoparticles [212]. These nanoreactors facilitated palladium-catalyzed *in situ* de-caging reactions and Suzuki-Miyaura intermolecular cross-couplings in living systems, providing a promising platform for biorthogonal prodrug activation [213,214].

Biomolecules such as proteins and nucleic acids are multi-nanometer scale, and thus require larger pore sizes. Lin used MSNPs with a large average pore diameter (5.4 nm) to deliver cell membrane-impermeable protein cytochrome *c* into mammalian cells through endocytosis [215]. The authors observed that enzymes adsorbed and released from MSNPs retained their catalytic activity, suggesting that loading did not impact protein structure. As mentioned above, pore size can be used to regulate release of proteins. Shi prepared a series of MSNPs with varying average pore size (ranging from 2.7 to 4.6 nm) to evaluate encapsulation of cytochrome *c* [216]. The authors observed increased loading capacity up to 4.6 nm pore size, indicating the importance of pore size in efficient loading of protein cargo.

Small nucleic acids can be loaded into MSNP pores using hydrogen bonding, but only if the repulsive negative charges of the nucleic acids and the MSNP surface are shielded from each other [217]. In early studies, Zink and Tamanoi [218] developed PEI-coated 100 nm MSNPs with ~2.5 nm pores to encapsulate and deliver functional siRNA to knock-down enhanced green fluorescent protein (eGFP) and functional genes related to signaling in cultured PANC-1 human cancer cells. Gu and Xia similarly packaged functional siRNA into MSNPs featuring ~3.7 nm pores and then mixed them with PEI to form a polymer layer on the external surface [219]. Delivery to reporter cell lines demonstrated efficient knockdown of target genes eGFP and *Bcl-2*. MSNP pore sizes can also be expanded to tens of nanometers to accommodate larger nucleic acids. Min reported that compared to smaller pore sizes, ‘ultralarge’ pore size (> 15 nm) provided higher pDNA loading capacity and was able to protect luciferase pDNA (4.8 kbp) from degradation (Fig. 9) [220].

Surface modification provides an avenue for stimuli-responsive delivery, using ‘gatekeeper’ moieties. Gatekeeper molecules are generally bound to the outside of the pore, and sterically block cargo release until they are detached. Joo and Ryu [221] developed a gatekeeping strategy by capping drug-loaded MSNP pores with disulfide cross-linkable polymers that would degrade in the cytosol, triggering drug release. The authors reported high loading capacity of dox and cisplatin, with a varied cytotoxic response upon intracellular release. Tan and Zhao [222] developed similar MSNP platforms for targeted delivery of dox to MDA-MB-231 xenograft model breast cancer *in vivo* models. MSNPs loaded with dox were gated with amino-β-cyclodextrin bridged by cleavable disulfide bonds and grafted with folate tumor targeting moieties. The drug cargo was released after delivery by the decrease in intracellular pH in endosomes and increased intracellular glutathione levels. After intravenous injection, significant decrease in tumor growth was seen in treated mice over 30 days without decrease in body weight (Fig. 10).

A variety of non-covalent and covalent gatekeeping strategies have been developed for triggered cargo release, more of which will be highlighted in the following section [223].

3.2. Covalent surface modification of MSNPs

Covalent modification of the MSNP surface can greatly influence cargo loading, protein adsorption, and rate of release [224,225]. MSNP surfaces are typically negatively charged but can be covalently modified to have cationic surfaces. These modified cationic MSNPs can bind with highly negatively charged cargos, generating complexes with potential for delivery. Shi used MSNPs covalently grafted with cationic rhodamine B to enhance

encapsulation of the negatively charged cardiovascular drug salvianolic acid B [226]. The authors reported protection of encapsulated drug from degradation, a sustained rate of release, and increased uptake over free drug in LX-2 hepatic cells. Similar approaches to modify MSNP surfaces for adsorption and delivery of nucleic acids have included a variety of other cationic macromolecules as modifiers, including PEI [227,228], dendrimers [229], and lipids [230]. Work by Cristini and Brinker [231] examined the biological fate of MSNPs with varied sizes, surface chemistries and routes of administration through single photon emission computed tomography integrated with computed tomography (SPECT/CT) imaging, with tandem mathematical modeling used to interpret the results. These studies revealed cationic MSNPs with surface exposed amines (PEI) are rapidly sequestered into the liver and spleen but show less total excretion than MSNPs with surface-shielded amines.

Covalently bound gatekeeper moieties can provide carrier stability, and potentially stimuli-responsive release. Stimuli-responsive gatekeepers provide a method for targeted delivery at a desired locale through endogenous or exogenous stimuli [232,233]. Several families of covalent gatekeepers have been used for controlled release, including cyclodextrins [234], azobenzenes [235,236], and complementary DNA [237]. In a notable study, Zhu developed dox-loaded MSNPs gated with a DNA hybrid complementary to miR-21 miRNA [238]. Upon binding miR-21, conformational changes in the DNA hybrid released dox and effectively killed HeLa cells. Interestingly the DNA hybrid also provided miR-21 silencing, inducing apoptosis and providing complementary chemotherapeutic mechanism.

Stimuli-responsive polymers provide versatile gatekeepers for release of payloads under disease-relevant environmental conditions like the low pH found in tumors [239] and bacterial biofilms [240]. Chu and coworkers [241] developed a pH-responsive release system for delivery of the anticancer cytokine protein TNF-α. Hollow MSNPs loaded with TNF-α were conjugated with pH-sensitive chitosan for controlled release in the acidic tumor microenvironment (Fig. 11). Chitosan was further conjugated with ErbB 2 antibody to provide enhanced breast cancer cell targeting. Under acidic conditions, the chitosan amino groups were protonated, stretching the polymers and triggering TNF-α release. These platforms eliminated 70% of MCF-7 cells *in vitro*, and upon intraperitoneal administration to mice with implanted MCF-7 tumors, reduced tumor weight by 50% *in vivo*.

Conformational changes in engineered gatekeeping polymers can be triggered by exogenous stimuli including ultrasound waves and light [242]. Vallet-Regi [243] designed thermally responsive co-polymer-grafted MSNPs for ultrasound-triggered small molecule delivery. Thermally triggered conformational changes in the polymer allowed the MSNP pores to be loaded with small molecule therapeutic cargo at 4°C and to encapsulate their cargo at 37 °C. Triggered by ultrasound waves, conformational changes in polymer tetrahydropyranyl moieties on the surface of the MSNP increased hydrophilicity and concomitantly the exposure of carboxylates, resulting in payload release (Fig. 12). dox-loaded MSNP hybrids showed significant efficacy relative to free drug in prostate adenocarcinoma (LNCaP) cells. Recent work by Zink [244] has applied ultrasound-stimulation for MRI-guided MSNP platforms capable of triggered spatiotemporal small molecule release. These vectors were demonstrated for delivery of an MRI contrast agent in a proof-of-concept study but provide opportunity for future image-guided theragnostic applications. Related work by Jokerst

[245] examined MRI-guided MSNPs for delivery of the pro-survival protein insulin-like growth factor (IGF) in cultured cells.

Ultrasound has been used for targeted disruption of microbubbles for delivery. Zhang and coworkers [246] adopted this strategy for delivery of MSNP-loaded cargo. A small molecule chemotherapeutic (Tanshinone IIA) was encapsulated in folate-conjugated MSNPs that were then incorporated within microbubble surfaces. These microbubbles protected the MSNPs from non-specific release of drug and enhanced circulation time. Ultrasound disrupted the microbubble structure and provided drug release from the MSNP at the desired locale, providing ~30% tumor growth suppression *in vivo* after intravenous administration to H22-tumor bearing mice.

Photoisomeric moieties such as azobenzene are useful gatekeeper moieties that undergo isomerization upon exposure to specific wavelengths of light [247,248]. In recent work, Fu [249] developed dox-loaded MSNPs capable of triggered release by both acidic pH and exposure to UV light. dox-loaded MSNPs were covalently conjugated with supramolecular switches consisting of hydrazone-based bonds, azobenzene moieties, and α-cyclodextrins to sterically block drug release from the pores. Trans-azobenzene has a strong host-guest interaction with cyclodextrin, while the cis-state inhibits interaction due to changes in polarity and steric hindrance. Acidic pH led to rapid hydrolysis of the hydrazone-based bonds, while exposure to UV light (365 nm) triggered *cis-trans* isomerization of the azobenzene moiety. The authors demonstrated that either stimulus alone was sufficient to trigger cargo release, and demonstrated delivery through phagocytosis, and efficient killing of MCF-7 human breast cancer cells.

UV-triggered delivery strategies are of course limited by the poor tissue penetration of UV light compared with longer wavelength radiation (e.g. NIR) [250]. Several NIR light-responsive platforms have been developed including MSNPs embedded with upconversion nanoparticles (such as lanthanide nanoparticles) [251] or iron oxide nanoparticles [252,253,254,255]. These platforms will be further discussed in later sections.

A major challenge facing clinical translation of MSNPs is the surface-exposed silanol groups on the particle surface. Silanol moieties interact with surface phospholipids on red blood cells, potentially causing hemolysis [256]. MSNPs have also been implicated in promoting the growth of malignant melanoma through altered ROS production *in vivo* [257]. Coupled with this is the concern of accumulation in the body; much recent research has focused on understanding the biodegradability of silica-based nanocarriers [258,259], even as a tumor-specific delivery strategy [260]. Notable work by Maggini and De Cola [261] explored ‘breakable’ MSNPs held together by disulfide linkages that degraded in the cytosol, providing a biodegradable carrier vehicle. This vehicle was also shown to be capable of a functional protein, cytochrome *c* to cultured cells [262]. Despite these challenges the advantages of porous silica nanocarriers have positioned them as competitive platforms for delivery of both small molecules and biologics.

4. Iron Oxide Nanoparticles

Iron oxide nanoparticles feature inherent magnetic properties coupled with tunable size and functionality that provide excellent potential for therapeutic applications [263]. The two predominant forms of iron oxide nanoparticles used for biomedical applications are maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4), due to their relative colloidal stability [264–268]. Magnetite has a ferromagnetic structure arising from alternating lattices of Fe(II) and Fe(III) [269]. Nanoparticles composed only of magnetite with a mesoporous structure have been demonstrated for encapsulation and delivery of small molecule drugs [270,271]. Maghemite has the same lattice structure as magnetite and exhibits similar ferromagnetic properties, however all iron atoms are in Fe(III) oxidation state. Fe(III) ions are commonly found in the human body, and are less toxic than Fe(II) that can effect Fenton chemistry, making maghemite a favorable core material [272].

Iron oxide nanoparticle delivery vectors typically consist of a magnetic core, an outer coating (often a polymer or metal) to provide a surface for grafting, and finally surface functionality (Fig. 13). Cargo may be bound to surface moieties, or alternatively can be encapsulated either inside the particle shell or within co-embedded mesoporous particles. Stimuli-responsive elements for encapsulation can provide triggered cargo release, for synergistic combination with the hyperthermic properties of the iron oxide [273,274].

Superparamagnetic iron oxide nanoparticles (SPIONs) are a special class of iron oxide particles that display superparamagnetic properties, i.e. the ability to strongly magnetize when the material is exposed to an alternating magnetic field (AMF) no residual magnetization when the magnetic field is removed. Notably, this is an effect of size; superparamagnetism usually arises only in small (< 30 nm) ferromagnetic particles or larger particles with nanodomains [275,276]. SPIONs have been explored extensively in the past decade for their ability to penetrate and kill biofilms, as well as their utility in magnetic resonance imaging (MRI) [277]. Biological fate, labelling efficiency, and magnetic characteristics heavily affect the efficiency of SPION-based MRI contrast agents, as notably reported by Lévy [278].

One of the main applications of iron oxide nanoparticles historically has been in magnetic hyperthermia. Upon excitation with an alternating current magnetic field, iron oxide nanoparticles generate localized heat due to Néel [279] and Brown [280] relaxation pathways. First proposed by therapeutically by Gilchrist [281] in the 1950s, iron oxide nanoparticles provide localized heat sources for destroying diseased tissue [282] or dispersal of biofilms [283,284]. SPIONs in particular generate a significant amount of heat under an applied magnetic field (42–45 °C) [285] and have been used for cancer treatment through magnetic hyperthermia [286–290]. Taratula [291] recently developed magnetic nanoclusters composed of cobalt- and manganese-doped hexagonal iron oxide nanoparticles encapsulated in PEG-based polymer nanocarriers for hyperthermia treatment of ovarian cancer (Fig. 14). The authors reported accumulation at the tumor site after intravenous injection and increased local temperature at the tumor up to 44 °C, resulting in inhibited tumor growth. Magnetic nanoparticles have also been utilized by several groups for cancer detection and ablation

through tandem MRI and hyperthermic treatment after localization at the tumor site [292–298]. Today these properties are used synergistically with therapeutics, as discussed here.

Widder and Senyi first demonstrated the use of magnetic fields to manipulate nanoparticles for drug delivery in the late 1970s [299,300]. Magnetic targeting involves the attachment of therapeutic cargo to magnetic nanomaterials, followed by injection and guidance of these particles to the site of interest, providing localized drug delivery at a controllable rate [301,302,303]. This directed motion can provide targeting to regions that are traditionally difficult to deliver to, such as the brain [304]. Work by Polyak [305] demonstrated that small magnetic nanoparticles could be localized to brain tumor tissue in murine glioma models, while larger particles (1 μm) could not. Iron oxide nanoparticles can be magnetically directed to a disease site, tracked via contrast imaging, heated at the effected sites, and provide triggered drug release [306,307,308]. Several strategies have been taken for attachment of therapeutic cargo to these nanoparticles, to provide enhanced stability, targeting, and in some cases, controlled release.

4.1. Functionalization of Magnetic Nanomaterials by Covalent Conjugation

Covalent linkages can be used for conjugation of small molecules and biologics to iron oxide particles. Alexiou [309] used a covalent strategy for delivery of cisplatin, developing 4.5 nm magnetite SPIONs coated with cisplatin-bound hyaluronic acid. The authors observed two-stage drug release *in vitro*, with burst release in the first 30 minutes, followed by slow release for a 48-hour time span. The Kim group [310,311] utilized thermally crosslinked magnetite SPIONs featuring PEG and carboxylic acid moieties to engineer a co-delivery system for a protein and the small molecule chemotherapeutic paclitaxel. Magnetically responsive host-guest complexes were generated between a polymerized β-cyclodextrin conjugate (pCD) and paclitaxel, with enhanced anticancer activity in CT26 tumor-bearing mice relative to the free drug (Fig. 15).

Covalent modification has also been utilized for delivery of biologics including DNA [312]. Licandro recently reported the covalent conjugation of SPIONs with peptide nucleic acids (PNAs), synthetic polyamide mimics of natural DNA and RNA [313]. PNAs were functionalized with terminal maleimide moieties, allowing conjugation with SPION surface-exposed thiol groups through Michael addition. These particles exhibited hyperthermic and superparamagnetic properties, making them promising carriers for delivery.

In recent years, iron oxide technologies have been commercialized for tumor-targeted delivery of chemotherapeutic delivery with hyperthermic tumor ablation. Chemicell GmbH developed TargetMAG nanoparticles that feature a multidomain magnetite core and a crosslinked starch matrix with terminal cations, that can be loaded with dox [314] or cisplatin. Hilger [315] demonstrated that bound cisplatin would desorb in PBS with hyperthermal (42 °C) or thermal ablative (60 °C) temperatures used for therapeutic approaches. A 20–40 nm iron oxide nanoparticle (MagNaGel) hydrogel featuring different targeting ligands is also produced by Alnis Biosciences for loading and delivery of chemotherapeutic agents [316]. In conjunction with MRI and inductive heating, these platforms provide multimodal treatment for cancer.

4.2. Non-Covalent Conjugation

Electrostatic attachment is useful for iron oxide nanoparticle-mediated delivery of biologics, particularly nucleic acids. Many of these approaches rely on surface-engineered cationic iron oxide nanoparticles that can electrostatically interact with anionic nucleic acid cargos. Scherer [317] demonstrated non-viral gene delivery to cultured cells using PEI-coated SPIONs with sizes ranging from 400–1000 nm. Application of a magnetic field *in vitro* provided an increase in efficiency and speed of transfection over several commercial reagents. This method, known as magnetofection, was adapted by several groups following Scherer's initial report as a simple method to deliver DNA [318], antisense oligonucleotides [319] and siRNA to cultured cells, with applicability for *ex vivo* applications.

PEI-modified iron oxide particles have been used for delivery *in vivo*. Dou [320] recently utilized PEI-coated SPIONs modified with galactose for the siRNA-mediated treatment of hepatocellular carcinoma. Intravenous tail vein injection to C57BL/6 murine luciferin-expressing hepatic tumor models demonstrated efficient hepatic tumor localization, with fluorescence knockdown using luciferin-silencing siRNA, and inhibiting tumor growth through silencing of the c-Met gene. Addition of a permanent magnet placed on the skin above the tumor for 2 hours post-injection did not significantly affect efficiency. Delivery of pDNA *in vivo* has also been approached using similar methods. Zhang [321] reported high gene expression levels in a C6 xenograft mouse model following intravenous injection of pDNA-conjugated SPIONs. These SPION particles were surface-grafted with PEG-PEI for biocompatibility and bound with chitosan to allow for pDNA condensation. Transfection of eGFP-encoded pDNA *in vivo* revealed high expression levels in tumor sites after 48 hours, as confirmed by MRI imaging. Later work by Sersa [322] aimed at adenocarcinoma treatment in BALB/c (TS/A tumors) and C57Bl/6 (B16F1 tumors) murine models through cancer immuno-gene therapy and SPION-mediated gene delivery. SPIONs modified with PEI and endosomolytic polyacrylic acid (PAA) were injected intratumorally, and magnetically stimulated to deliver to cells in a process considered *in vivo* magnetofection. These studies revealed high expression levels first of GFP in a model study, and then immunostimulatory cytokine interleukin 12 (IL-12) in experimental work. Tumor IL-12 expression resulted in a significant decrease in tumor growth over a course of 20 days (Fig. 16).

Micellar lipid coatings have been used to adsorb and layer nucleic acids. Anderson reported a technique for iron oxide nanoparticle coating using nucleic acid-loaded lipidoids [323]. These 50–100 nm particles encapsulated siRNA and plasmid DNA with high efficiency, and demonstrated efficient *in vitro* transfection, with future potential for magnetically guided treatment and magnetic hyperthermia *in vivo*. Later work by Chertok [324] demonstrated lymph node targeting using size-controlled lipidoid-iron oxide nanoparticles, suggesting a promising route for design of theranostic platforms.

Iron oxide nanoparticles have been utilized to some extent for recombinant protein delivery as well, however the relatively large size and complex surfaces of proteins makes interfacial recognition with iron oxide particles challenging. Silica-embedded iron oxide particles have been demonstrated in the past as enhanced MRI contrast agents [325]. Khashab [326] utilized mesoporous silica nanoparticles to overcome this issue, using biodegradable silica-

iron oxide propylamine nanohybrids featuring ultra large pores capable of protecting and delivering a large protein (mTFP-Ferritin, ~530 kDa) to cancer cells (Fig. 17). These large proteins were electrostatically immobilized into mesoporous cavities of the particles and were released under acidic pH or magnetic stimuli in HeLa cells.

Hyperthermic applications are challenging due to natural thermoregulatory processes make it difficult to locally increase temperature in the body, and hyperthermic heating is dependent on particle concentration at the target site [327]. At the time of writing, the only clinically available AMF system, NanoActivator® (MagForce AG, Germany) is capable of operating frequency up to 100 kHz [328]. Limited data is available regarding clinically tolerable AMF dosage [329,330], and future studies must critically evaluate tumor temperature. Magnetic field depth is another important consideration, and several studies have implanted internal magnets using minimally invasive surgery [331,332]. Finally, the degradation of iron oxide particles in the body, and the potential accumulation of magnetic nanoparticles and their by-products in tissues and organs [333] has elicited concerns over toxicity [334]. Dissociated iron oxide particles promote the formation of reactive oxygen species and hydroxyl radicals, and as a result may lead to cytotoxicity as well as impaired cell metabolism and an increase in apoptosis [335]. Despite the several advantages that iron oxide nanoparticles offer, it is important to consider ways to overcome iron ion-induced toxicity. Toxicity of these nanomaterials to a large extent is concentration as well as exposure time dependent [336]. in mouse models that at lower concentrations these particles can be cleared from the body without significant toxicity [337]. Therefore, iron oxide nanoparticles have a potential for nanomedical applications if we understand and mitigate potential risks.

5. Lanthanide Upconversion Particles

As discussed above, light-triggered drug delivery is a promising strategy to spatiotemporally control the drug release *in vivo*, boosting local effective drug accumulation while minimizing side effects [32]. However, most light-triggered drug carriers require short wavelength UV/visible light, resulting in high phototoxicity with limited penetration depth *in vivo* [338,339]. Lanthanide upconversion nanoparticles (UCNPs) are a unique class of optical nanomaterials that absorb and convert low-energy near-infrared (NIR) photons into high-energy UV/visible light through a nonlinear anti-Stokes process [340,341] Multiple lanthanide-doped UCNPs have been studied, and today ytterbium (Yb^{3+}), erbium (Er^{3+}), thulium (Tm^{3+}), and holmium (Ho^{3+}) are the most widely used lanthanide dopants [341]. UNCPs offer several advantages such as low toxicity and deep light penetration in tissues, making them excellent candidates for controlling *in situ* drug release via photochemical processes [342,343].

Three common approaches have been developed to load photosensitive compounds onto UCNPs for drug delivery, with perhaps the most common being encapsulation within a mesoporous silica shell [344]. Compound loading has also been accomplished using covalent conjugation [345,346,347] and non-covalent adsorption [348,349,350] to the particle. Drug release can then be controlled by three mechanisms, namely i) bond cleavage between the molecule and the carrier; ii) destruction of the carrier, or iii) photoisomerization.

5.1. Covalent UCNP cargo attachment

UCNPs have been employed as a NIR-triggered delivery vehicle by covalently binding drug molecules onto the nanoparticle surface to control the drug release [351–353]. O-nitrobenzyl (ONB) esters are the most commonly used photosensitive compounds for modification as they will undergo irreversible deformation when triggered by UV/visible light [354]. Krull [355] conjugated a chemotherapeutic agent 5-fluorouracil (5-FU) to core-shell UCNPs (~20 nm) via an ONB photolabile linker. Upconverted UV and blue light from the UCNPs matches the absorption profile of caged 5-FU and cleaves the drug-UCNPs linker using a NIR laser (Fig. 18). In a similar manner, the Hartman group [356] developed a photo-responsive drug delivery system by attaching dox directly onto the surface exposed UCNPs ($LiYF_4$:Tm^{3+}/Yb^{3+}) through a nitrobenzyl derivative. The authors observed ~40% drug release after exposure to NIR irradiation.

In a theranostic approach, the Lin group [357] conjugated dox to the surface of UCNPs ($NaYF_4$: Yb/Tm) by acid-labile hydrazone-based bonds (~25 nm) to generate a luminescence-monitored drug delivery system. In the design, the spectral overlap between emission of donor UCNPs (452 nm and 477 nm) and the broad absorbance of acceptor dox (480 nm) enabled luminescence resonance energy transfer (LRET) to quench the upconversion luminescence of UCNPs under NIR irradiation. This quenching effect was used as a probe to confirm the dox conjugation and monitor drug release *in vitro*. More recently, this group attached dox onto $BaGdF_5$: Yb/Tm-UCNPs using the same hydrazone linker to develop a multifunctional nanoplatform (sub-10nm) for simultaneous diagnosis and therapy [358]. This UCNP exhibited strong upconversion fluorescence after delivery to cultured cells under NIR irradiation and can be used as well for T_1-weighted magnetic resonance and X-ray computed tomography imaging. Peptide conjugation to the UCNP surface was used in the targeted delivery of siRNA to cancer cells. Ye [359] functionalized the silica coated UCNPs ($NaYF_4$: Yb/Tm) with an Anti-Her2 antibody by reaction of its terminal amino group via carbodiimide chemistry (~30 nm). Under NIR irradiation, UCNPs enabled the real-time tracking of siRNA due to their superior optical properties. The silencing effect of siRNA on luciferase gene was studied *in vitro* and ~50% down-regulation was observed. Recently, covalent conjugation strategies for UCNPs have included quantum dots [360], fluorescent proteins [361], and fluorophores [362] and focusing largely on photodynamic therapy, theragnostics [363] and imaging [364].

5.2. Non-covalent cargo attachment to UCNPs

By incorporating appropriate photosensitive moieties into polymer structure, photochemical reactions such bond cleavage can result in disassembly of the carrier due to photoinduced structural and/or property changes [365]. UCNPs can be encapsulated into polymer micelles to act as internal UV/visible light sources upon NIR irradiation, with the upconverted light activating photoreactions to trigger micelle disruption and release co-loaded hydrophobic drugs [366]. Almutairi [367] utilized cresol monomers functionalized with ONB groups to fabricate micelles (ranging in size from 0.3 μm to 1 μm) that can degrade through a cascade of cyclization and rearrangement reactions in response to upconverted UV light by UCNPs (Fig. 19). Cleavage of ONB moieties triggered by upconverted UV light rapidly increased water permeability and facilitated cargo release.

Zhao's group [368] developed a photosensitive micelle composed of hydrophilic polyethylene oxide and a hydrophobic polymethacrylate modified with ONB groups. The upconverted UV light photocleaved the ONB groups and thus released the drug by destabilization of micelles. In follow-up work, this group developed a hybrid UCNP-hydrogel system which allows the use of NIR light to induce gel-sol transition and release large, inactive biomacromolecules on demand, after which bioactivity could be recovered [368]. In a proof-of-concept study, they entrapped the enzyme trypsin and UCNPs into the hydrogel which has a crosslinked hybrid polyacrylamide-poly(ethylene-glycol) structure held together by photosensitive ONB groups and observed an immediate release of protein upon exposure to NIR light.

Incorporating UCNPs into mesoporous silica nanoparticles (MSNPs) is a common approach to non-covalent drug loading. Wu [369] employed the previously mentioned MSNP gatekeeping strategy using blue-light-cleavable ruthenium (Ru) complex to control drug release. UCNPs were first coated with porous silica and then loaded with dox. A Ru-based complex was covalently grafted onto UCNPs, encapsulating dox within the pores. that was released after 5h exposure to NIR irradiation. Cell culture studies showed a significant inhibition to the growth of HeLa cells after incubation for 3–6 h followed by NIR irradiation. Lanthanide-doped UCNPs coated with MSNPs were also used to deliver siRNA. Ju [370] loaded siRNA and photosensitizer hypocrellin A (HA) into MSNP pores and then wrapped the obtained complexes with PEG polymer 'tape' using an ONB-based photocleavable linker (Fig. 17c). Under NIR irradiation, the UV light emitted by UCNPs broke photocleavable linkers to release siRNA and activate HA to generate reactive oxygen species (ROS), disrupting the endosomal membrane. This combination of two photosensitive moieties led to a significant enhancement in gene silencing.

As discussed previously [235,236], photoisomerizable molecules such as azobenzene undergo spatial conformation changes reversibly under UV/visible illumination [371]. Changing between the two isomers can be used as a switch to control drug release [372]. In 2013, Shi [373] reported NIR-induced drug delivery using UCNPs coated with an azobenzene-modified mesoporous silica shell (Fig. 20) (~54 nm). Since the azobenzene molecular impeller is only activated under upconverted UV light, the amount of the released drug could be controlled through tuning the intensity and/or time duration of NIR light. Studies *in vitro* confirmed that the dox released in cytoplasm could migrate into nucleoplasm to kill the cancer cells.

The trans-cis transformation of azobenzene was later adapted for UCNP-mediated siRNA delivery by Gong [374]. In this study, siRNA strands tagged with azobenzene were complexed onto UCNPs modified with cyclodextrin via a host-guest interaction. This NIR-activated UCNPs core emitted UV light which efficiently isomerized azobenzene to the cis state, thus releasing siRNA as a result of unmatched host-guest pairs. This group further conjugated GE11 and TH peptides onto the carrier surface to facilitate the cellular uptake and endosomal/lysosomal escape of the nanoparticles. The amount of released siRNA was controlled by adjusting NIR irradiation time, demonstrating 85% siRNA release within 20min.

A major challenge of delivery with NIR-absorbing UCNPs is the strong absorption of water molecules at 980 nm. UCNPs have a limited number of available excitation wavelengths, with 980 nm being one of the most common. Irradiation at this wavelength will cause the surrounding solution to heat, potentially causing a complication for *in vivo* applications [375]. However, studies have shown an appreciable lack of toxicity from *in vivo* administration of UCNPs, encouraging their biomedical use [376]. The versatile chemical nature and low toxicity of UCNPs lends them great promise for future delivery applications.

6. Conclusions and perspective

Inorganic nanoparticles offer a versatile, multimodal approach to the intracellular delivery of therapeutic molecules. With a vast diversity of therapeutic targets comes a similar diversity of therapeutic cargo- from small molecule drugs to large multimeric proteins, effective treatment of disease requires a wide range of delivery vehicles featuring a broad spectrum of structure and activity properties. Inorganic nanoparticles in their many forms offer structural versatility that can accommodate these different cargos. Each class of inorganic nanoparticle offers unique structural properties, each with their own potential advantages such as stimuli-responsive release, favorable biodistribution, and photothermal reactivity [377]. Table 1 summarizes the notable advantages and challenges of each inorganic material in the context of therapeutics delivery, with focus on clinical translatability.

Challenges remain to the development of clinically translatable delivery vehicles, partly because hurdles exist in clinical applications that are overlooked in fundamental research [378]. One of these is entry into the cytosol [379,380]. Many delivery platforms enter the cell through endosomal uptake. Recent studies have shown that <10% of carriers escape from degradative endo/lysosomal pathways, making endosomal delivery and escape an extremely inefficient process [381,382]. Another challenge remaining in delivery is localization at the disease site *in vivo*. Nanocarriers in general exhibit a degree of colloidal stability in circulation [383] due to their small size. Specific delivery to a cell type or organ remains challenging, however. Particles above a certain size will invariably accumulate in the major clearance organs of the mononuclear phagocyte system, such as liver and spleen [384,385,386]. Moreover cellular uptake has been shown to decrease with increasing particle size, but increase significantly with increased cationic surface charge [387]. Surface functionalization with specific chemical moieties or recognition elements can promote cell type-specific delivery, but proteins in the blood bind nanoparticle surfaces electrostatically, potentially skewing biodistribution and masking surface-exposed recognition elements [388,389].

Nanomaterial shape also dictates organ-level biodistribution, tissue penetration, and cellular uptake. The shape and aspect ratio of MSNPs have been shown to significantly effect tissue residence time and cell internalization rate [390,391] with small, spherical particles exhibiting the most favorable trends of circulation and tissue residence. Similar results have been demonstrated with PEGylated polystyrene-core nanoparticles [392], and gold nanoparticles of various sizes and shapes [393,394]. Importantly, particle shape has been shown to directly relate to uptake in macrophage cells, suggesting critical implications in terms of clearance from the body [393]. While small, spherical particles generally

exhibit enhanced uptake and greater circulation time, this can prove a challenging target for nanocarrier development. Furthermore, rationally designed surface functionality may provide benefits to localized delivery beyond what can be achieved by relying on size alone.

Stimuli-responsive materials provide a promising avenue for localized delivery and have demonstrated promising results in numerous inorganic nanoparticle-based platforms, especially using NIR light-triggered release or assisted accumulation through magnetism. Notably however several reported systems took advantage of the enhanced permeability and retention, or EPR effect for increased particle accumulation in tumor tissue *in vivo.* This effect has been observed in murine models and may not directly apply to humans [395]. Finally, although many inorganic nanoparticle platforms exhibit low toxicity on a cellular level, accumulation *in vivo* can exacerbate toxic effects, making degradability and clearance critical safety measures in carrier design [396].

The approaches highlighted herein demonstrate the immense progress made toward development of efficacious delivery platforms in the past decade alone. Inorganic nanomaterials provide versatile scaffolds with high surface-to-volume ratio for cargo loading, generally low toxicity, and highly tunable structural properties. From proof-of-concept to systems with real clinical relevance, gold, silica, iron oxide, and UCNP delivery platforms have been advanced significantly to overcome the challenges faced in therapeutics delivery. Inorganic nanoparticle-based platforms remain a front-line approach for delivery and with continued advancement will doubtlessly see extensive clinical application in the future.

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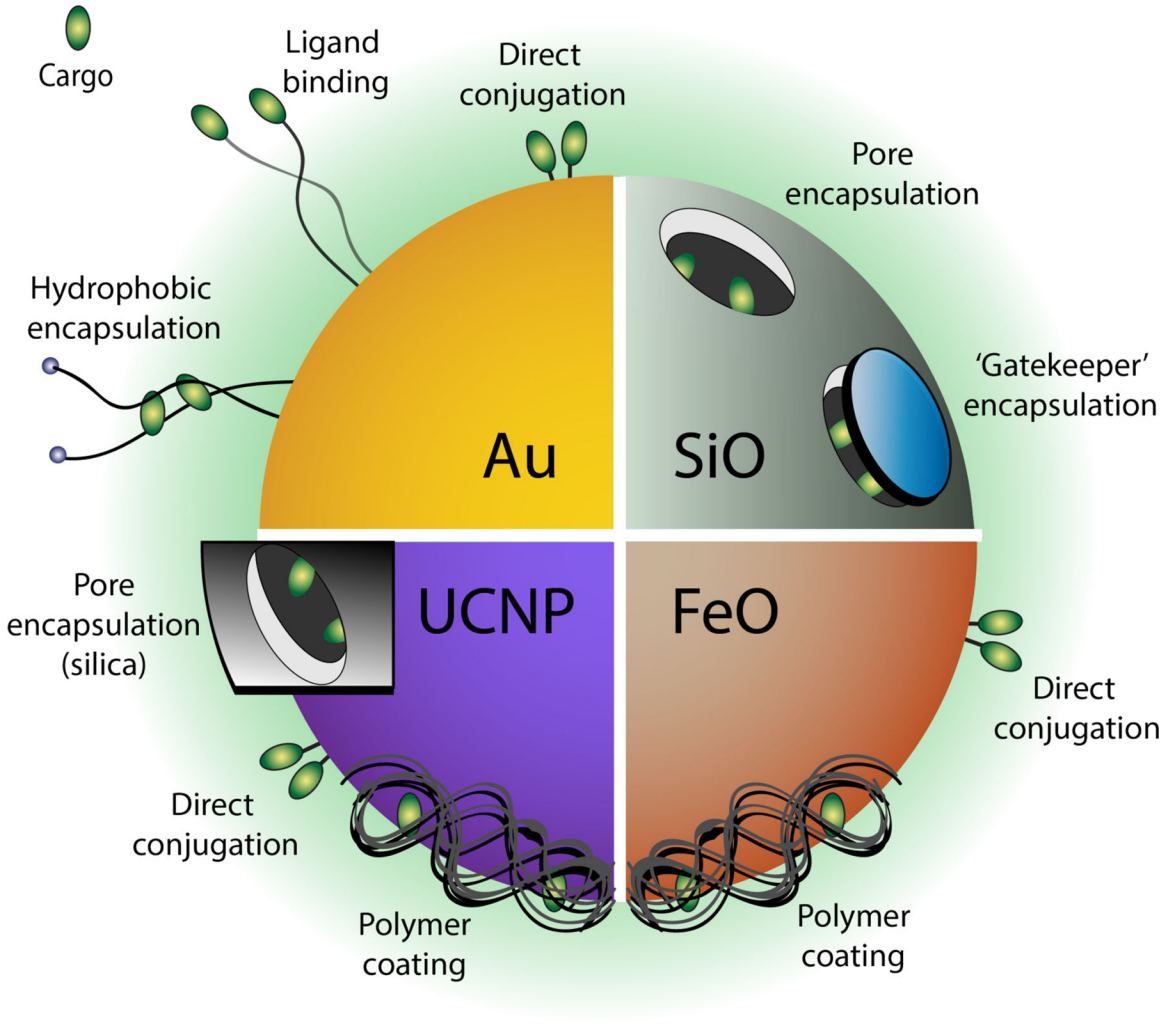

Fig. 1.

Gold, silica, iron oxide, and upconversion nanoparticle (UCNP)-based platforms provide diverse structural features for covalent or non-covalent conjugation with therapeutic cargo, as shown through representative modalities.

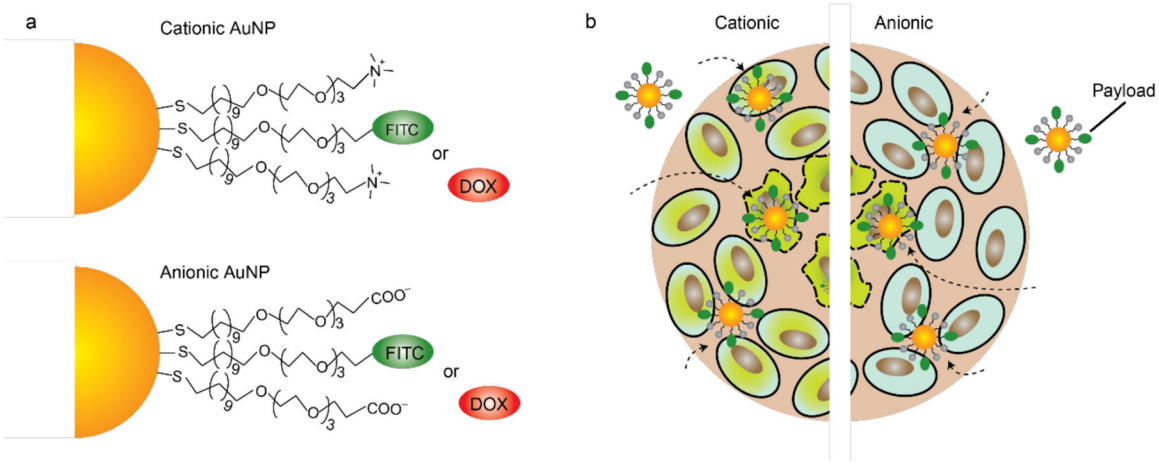

Fig. 2.

(a) Mixed monolayer-protected gold nanoparticles can be loaded with dyes or small molecule drugs, like thioalkylated FITC or Doxorubicin (Dox). (b) Cellular uptake and FITC-SH release by thiol-mediated replacement reactions within the cell. Particle uptake is dictated by surface functionality. (Adapted from ref. 52).

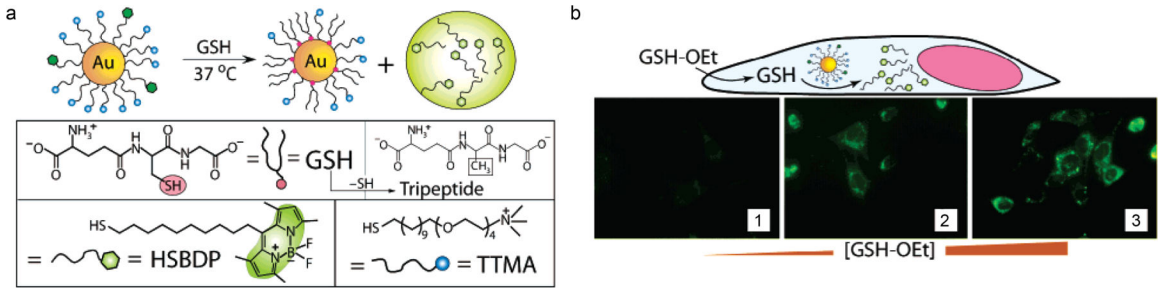

Fig. 3.

(a) Schematic depiction of AuNP carrier and glutathione-mediated surface monolayer exchange reaction to release the dye. (b) Schematic representation and fluorescence images using glutathione (GSH-OEt) as an external stimulus to trigger release of HSBDP from AuNPs. GSH-OEt concentrations were varied from 0, 5, and 20 mM in panels 1, 2, and 3, respectively (Adapted from ref. 71).

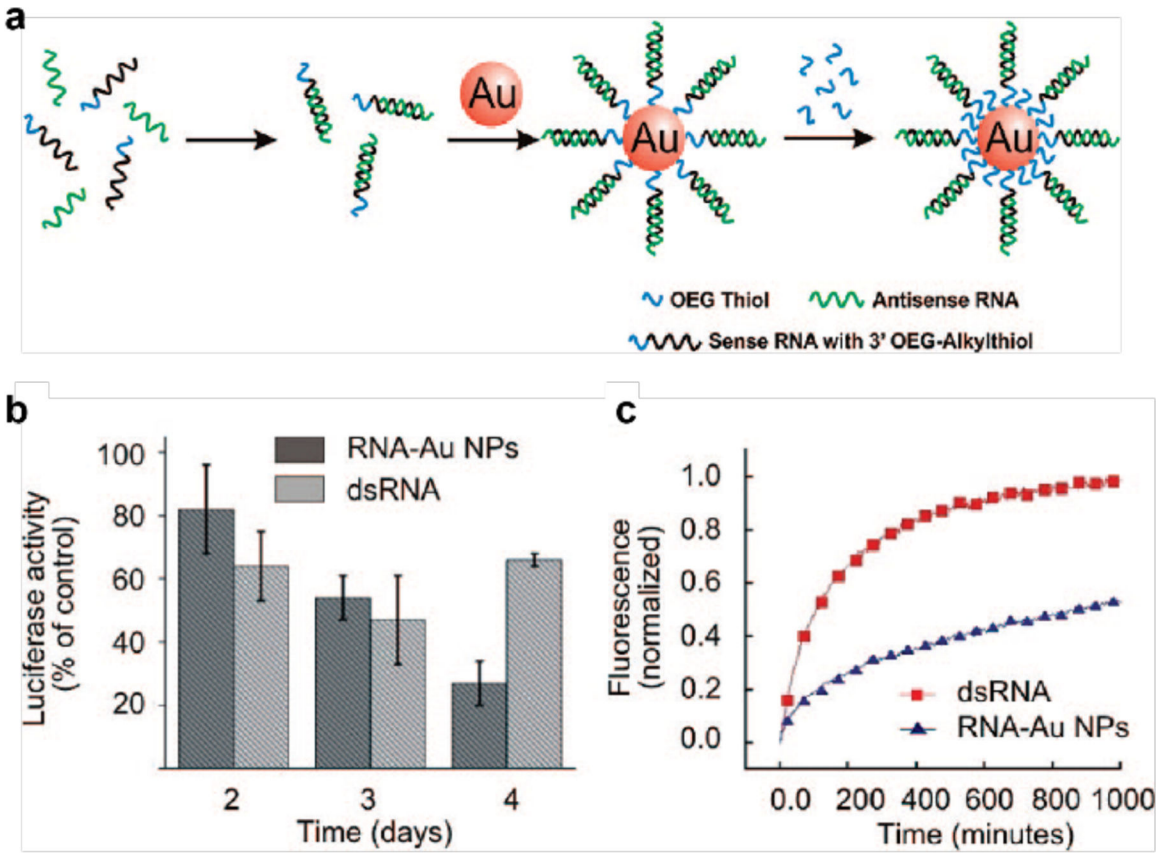

Fig. 4.

(a) Schematic depiction of the synthesis of polyvalent RNA-AuNP conjugates. (b) Knockdown of luciferase expression in HeLa cells over 4 days using polyvalent RNA–AuNP conjugates (3 nmol/L nanoparticle (NP) concentration, ~100 nmol/l RNA duplex concentration) or double-stranded (ds) RNA (100 nmol/l). (c) Stability of RNA–AuNPs. Comparison of the stability of cyanine 5-labeled double-stranded (ds)RNA (red) and RNA–AuNPs (blue) in 10% serum. The increase in fluorescence intensity demonstrates the distance-dependent release of the fluorophore from the gold core, which is an efficient quencher of the fluorescence. (Adapted from ref. 107).

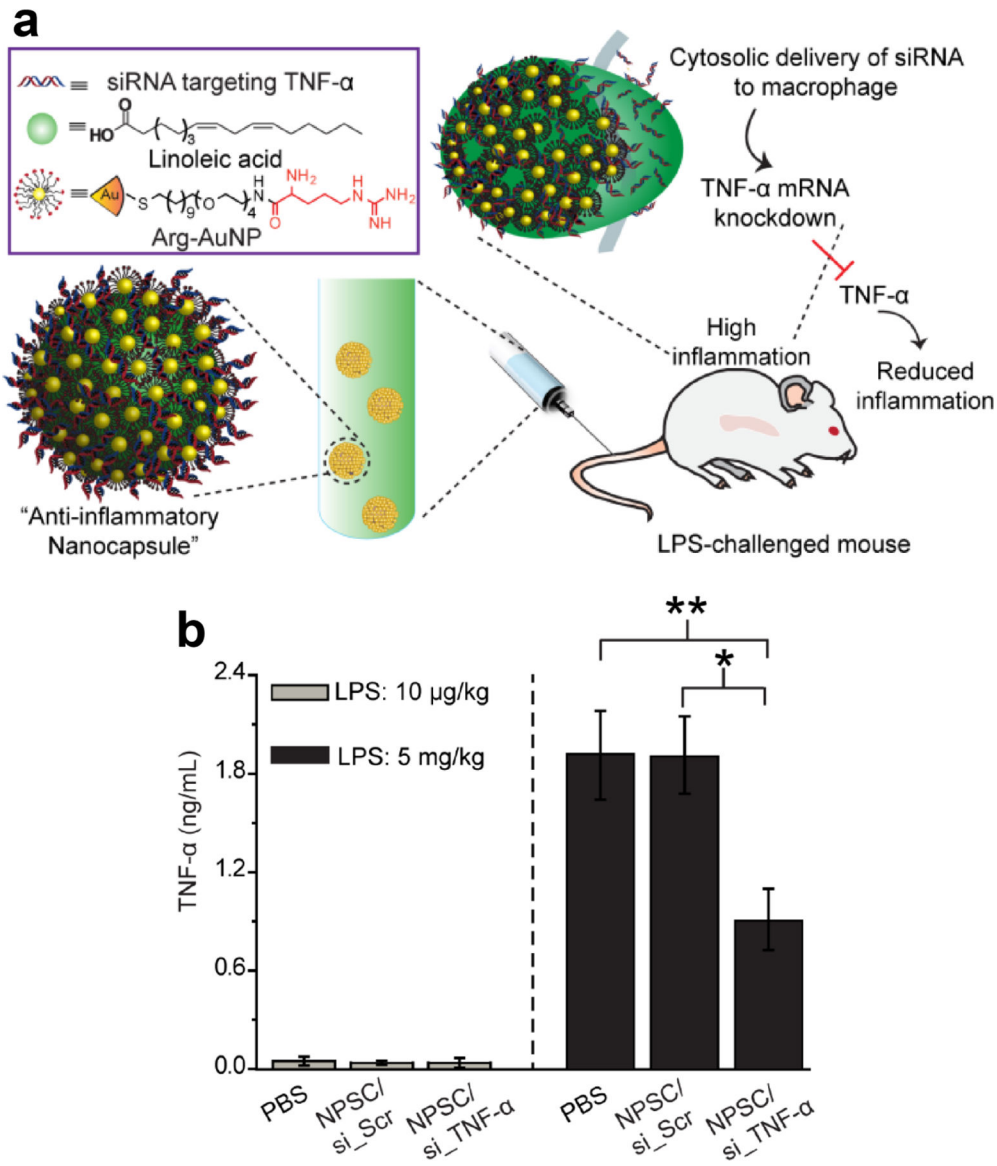

Figure 5.

(a) Schematic of NPSC/siRNA-mediated *in vivo* TNF-α silencing in LPS-induced inflammation. The anti-inflammatory NPSC was prepared by assembling TNF-α targeted siRNA with arginine functionalized AuNPs, with the ensemble self -assembled onto the surface of fatty acid nanodroplets to form a NPSC/siRNA nanocomplex. (b) *in vivo* delivery of NPSC/si_TNF-α decreased serum TNF-α production from LPS-induced inflammation. (Adapted from ref. 132)

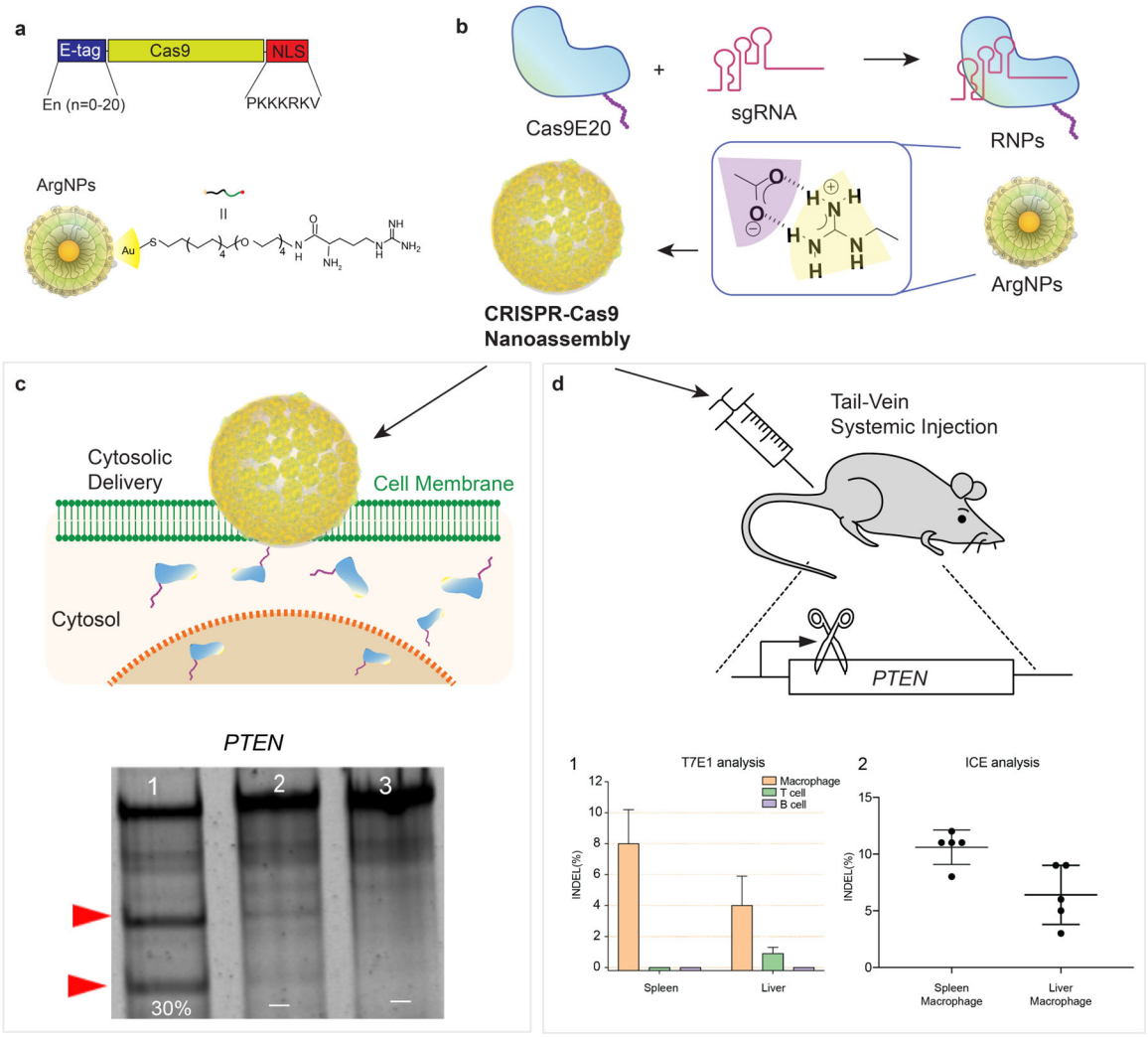

Fig. 6.

(a) Schematic depiction of E-tagged Cas9 (Cas9E20) protein construct and arginine-functionalized AuNPs (ArgNPs). (b) Cas9E20 was pre-assembled with single guide RNA (sgRNA) to form ribonucleoprotein (RNP) complexes. Cas9E20 RNPs self-assembled with ArgNPs to escalate particle protein nanoassemblies. (c) AuNP-protein nanoassemblies associated with the cell membrane and delivered protein through a membrane fusion-type mechanism in cultured HeLa cells. Gene edited was evaluated by *T7* endonuclease I (T7E1) assay in experimental samples (1), with no editing observed in controls with no ArgNPs (2) and cell only (3). (d) Nanoassemblies administered to the tail vein of *BALB/c* mice exhibited gene editing in the spleen and liver, as determined by T7E1 assay and Interference of CRISPR Edits (ICE) sequencing analysis. (Adapted from refs. 142 and 143).

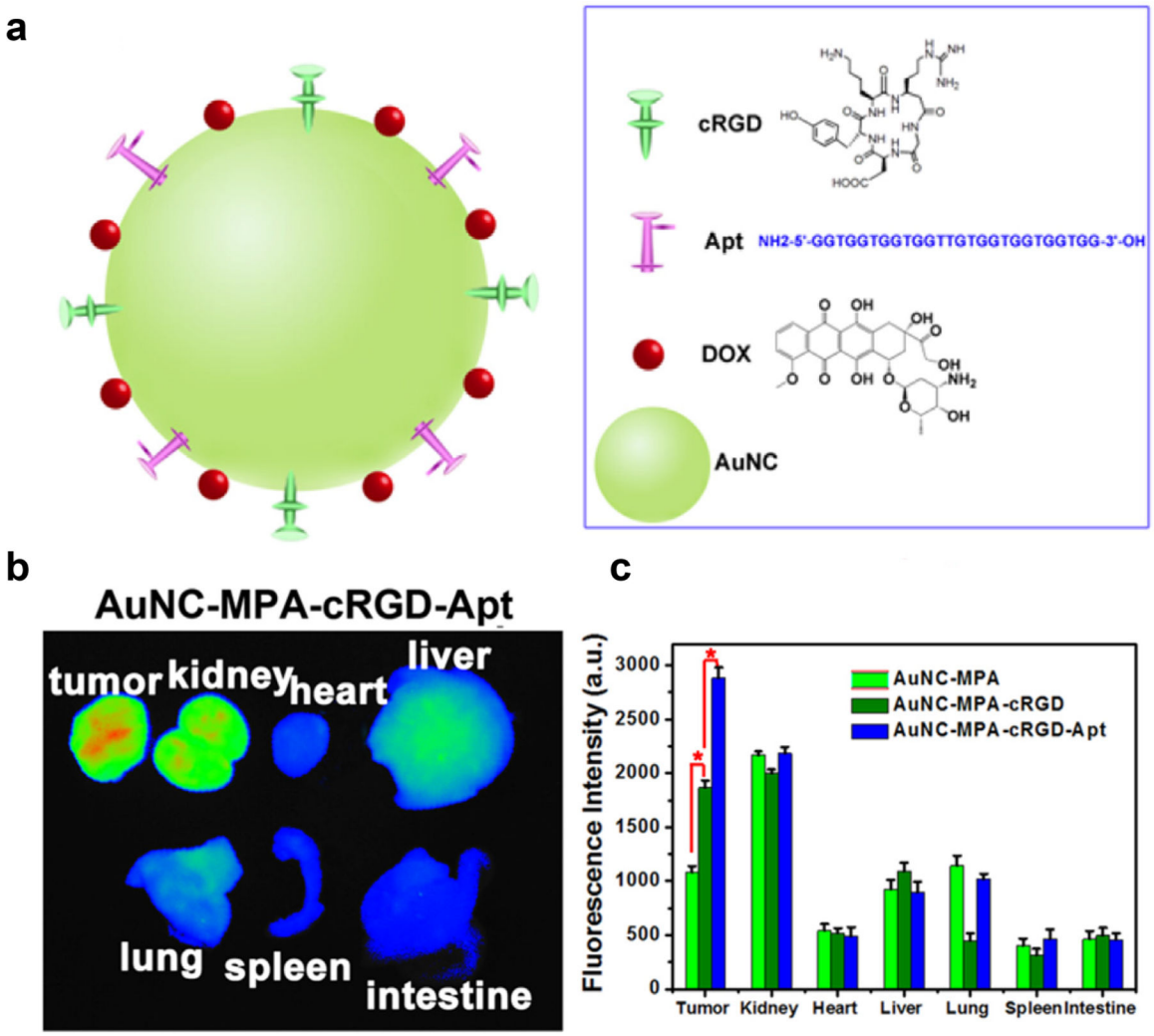

Fig. 7.

(a) Schematic structure of dox-loaded antibody/aptamer (cRGD/Apt)-conjugated AuNC. (b) *ex vivo* fluorescence images of isolated organs from tumor-bearing mice at 8 h post-injection. (c) Fluorescence intensity of isolated organs at 8 h post-injection with different sample formulations (Adapted from ref. 182).

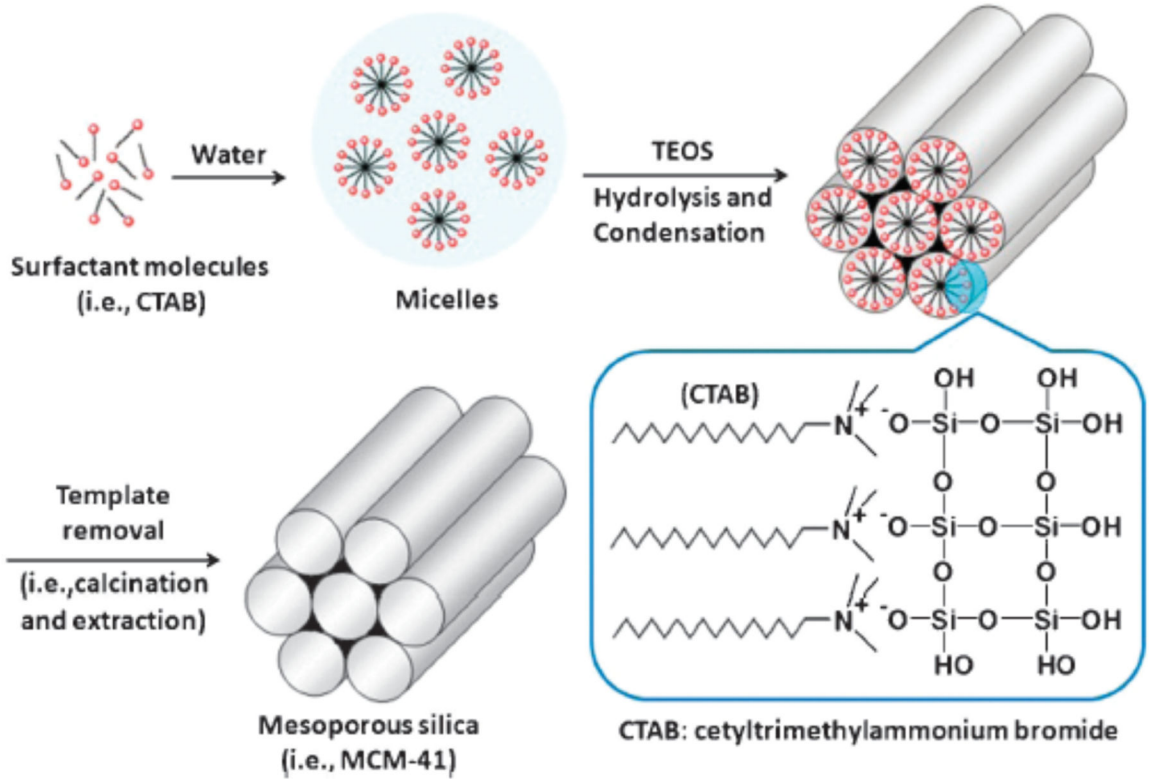

Fig. 8.
General synthetic scheme for preparation of MSNPs. (Adapted from ref 202).

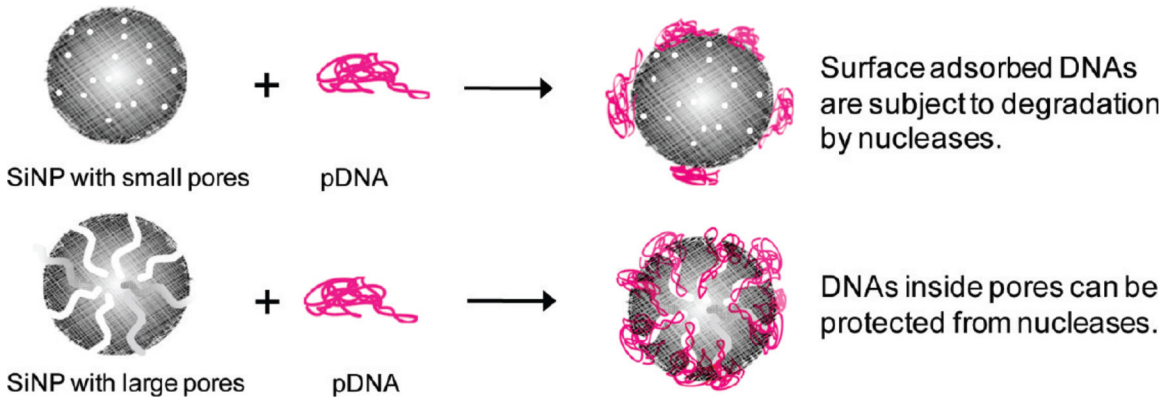

Fig. 9.

Monodisperse MSNPs with large pores provide higher loading capacity for pDNA and better protection from nucleases compared to those with small pores. (Adapted from ref. 220).

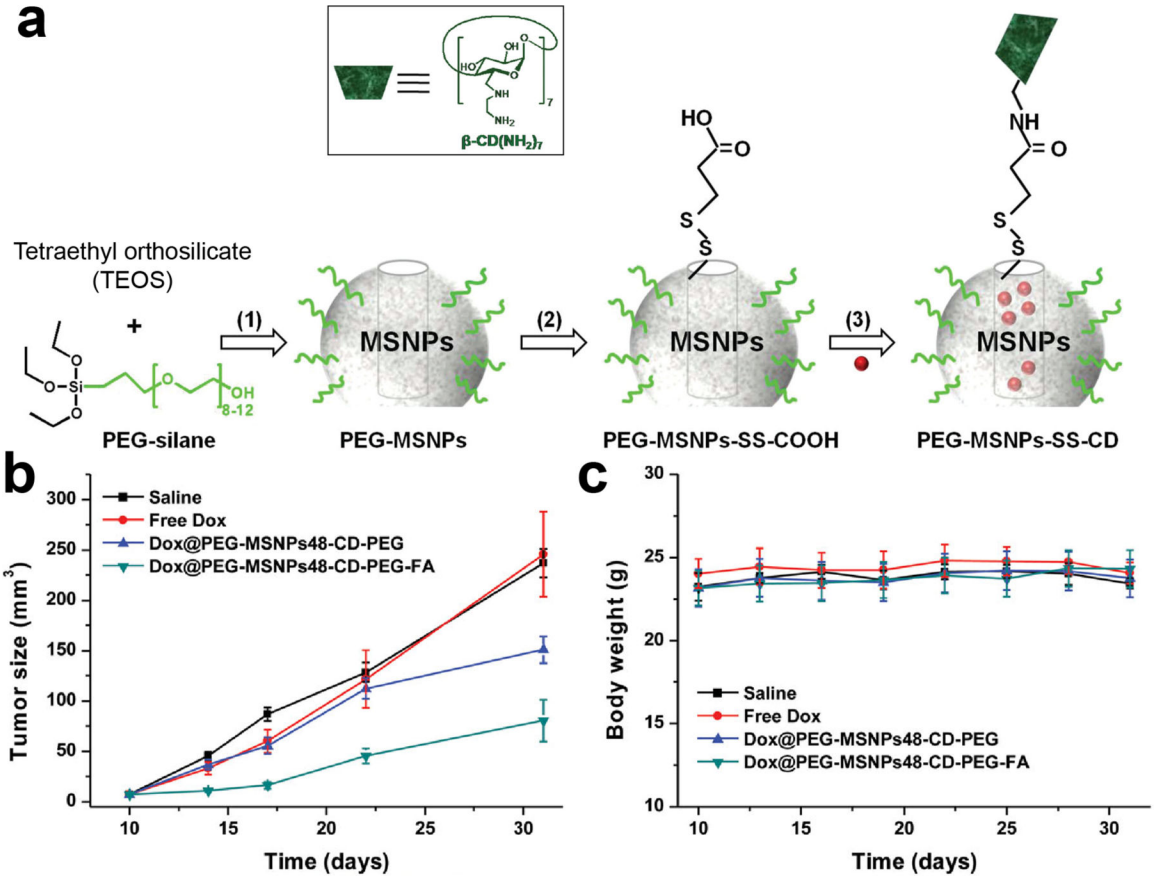

Figure 10.

(a) Schematic representation of the cargo-loaded PEG-MSNPs-SS-CD prior to folate conjugation. (b) Tumor volume changes from different treatment groups. (c) Body weight changes of MDA-MB-231 tumor-bearing mice.

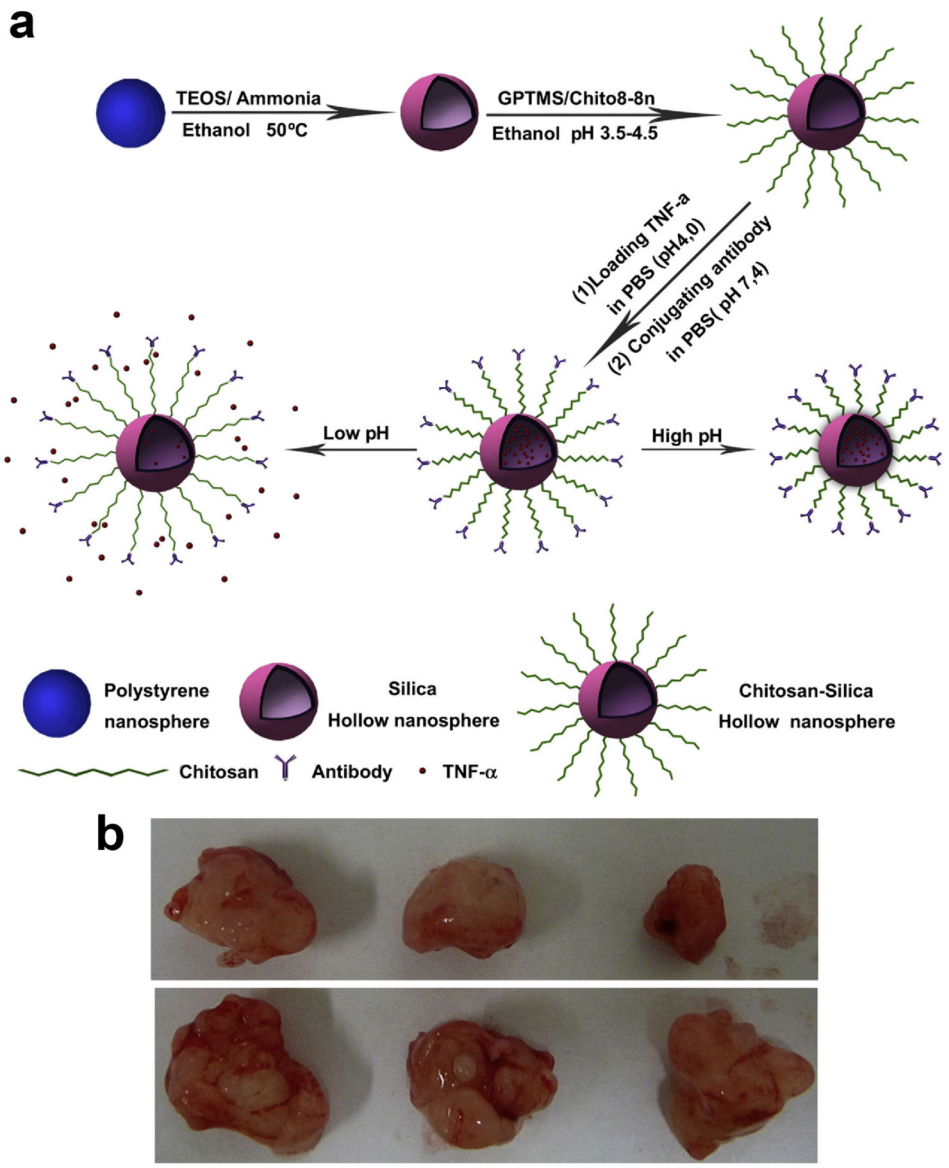

Fig. 11.

(a) Schematic diagram illustrating the formation of nanocarriers (MSNP-chitosan-TNF-a conjugated with antibody) and the drug release behavior at different pH values. This structure blocks and restricts drugs release from the hollow interior. (b) Photos of tumors collected from mice in Nano group; nanocarriers composed of CS-SiO_2,HNPs, TNF-a and antibody were injected into the mice (top); PBS (pH 7.4) only was injected into the mice (bottom). (Adapted from ref.241).

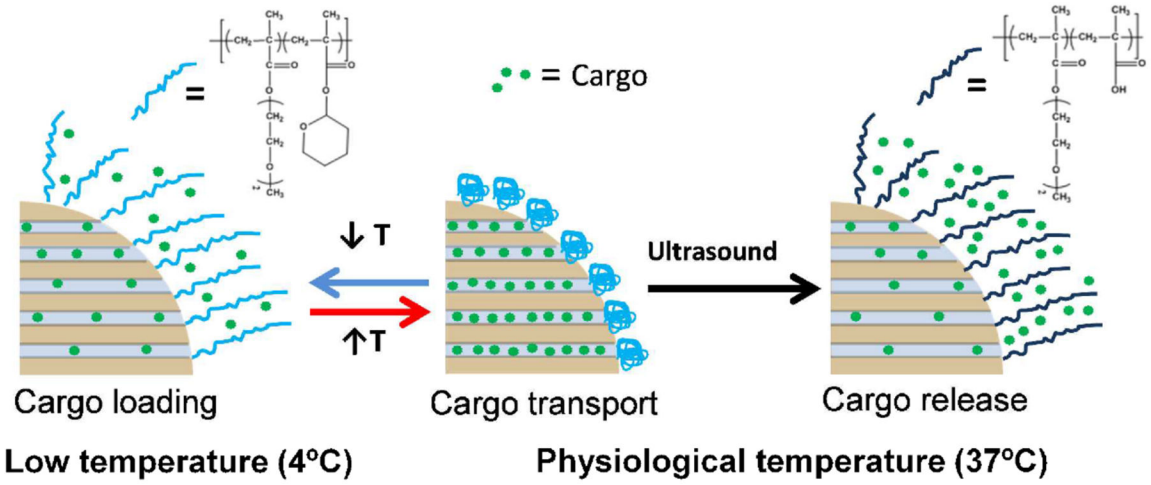

Fig. 12.

Scheme of polymeric ultrasound sensitive “nano-gate” on MSNPs. Loading was achieved at lower temperature. Ultrasound waves triggered cargo release at physiological temperature. (Adapted from ref 243).

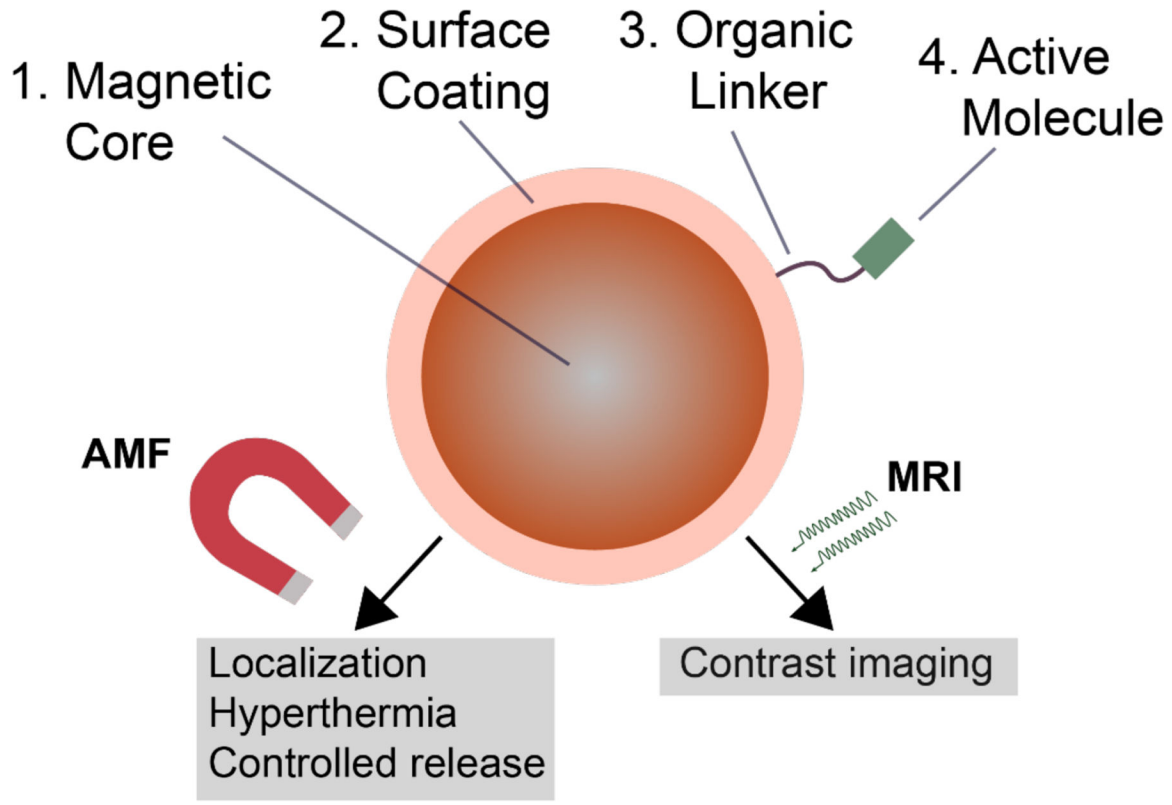

Fig. 13.
Schematic representation of typical magnetic iron oxide nanoparticle structure, with potential applications for delivery, theragnostics, and imaging.

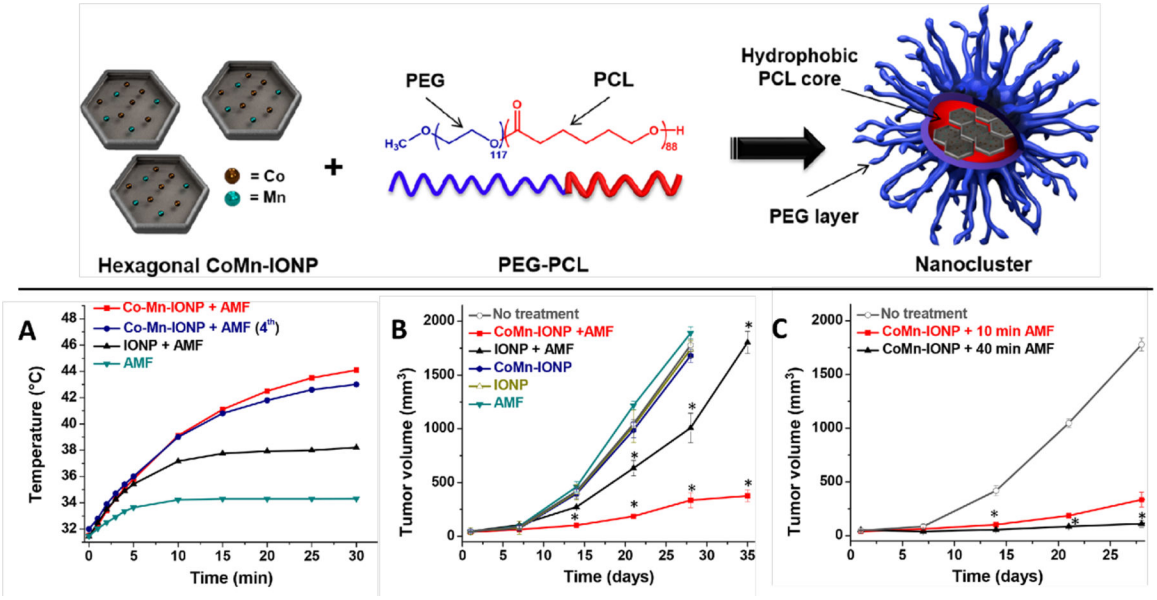

Fig. 14.

(top) Schematic depiction of hexagonal cobalt- and manganese-doped iron oxide nanoparticles encapsulated within polymeric nanocarriers. (bottom) (a) Representative intratumoral temperature profiles during AMF (420 kHz, 26.9 kA/m) exposure of mice injected with a single dose of 5% dextrose (AMF), cobalt and manganese-doped iron oxide nanoclusters (Co-Mn-IONP), and IONP nanoclusters. The navy curve shows the intratumoral temperature during the fourth cycle in a mouse that was treated with CoMn-IONP nanoclusters (6 mg Fe/kg) and AMF once a week for 4 weeks. (b) Tumor growth profiles of mice with ES-2 xenografts after four cycles of the following treatments; *$p < 0.05$ when compared with nontreated animals. (c) Tumor growth profiles of mice with ES-2 xenografts after treatment with AMF for 10 min. or 40 min. (Adapted from ref. 291).

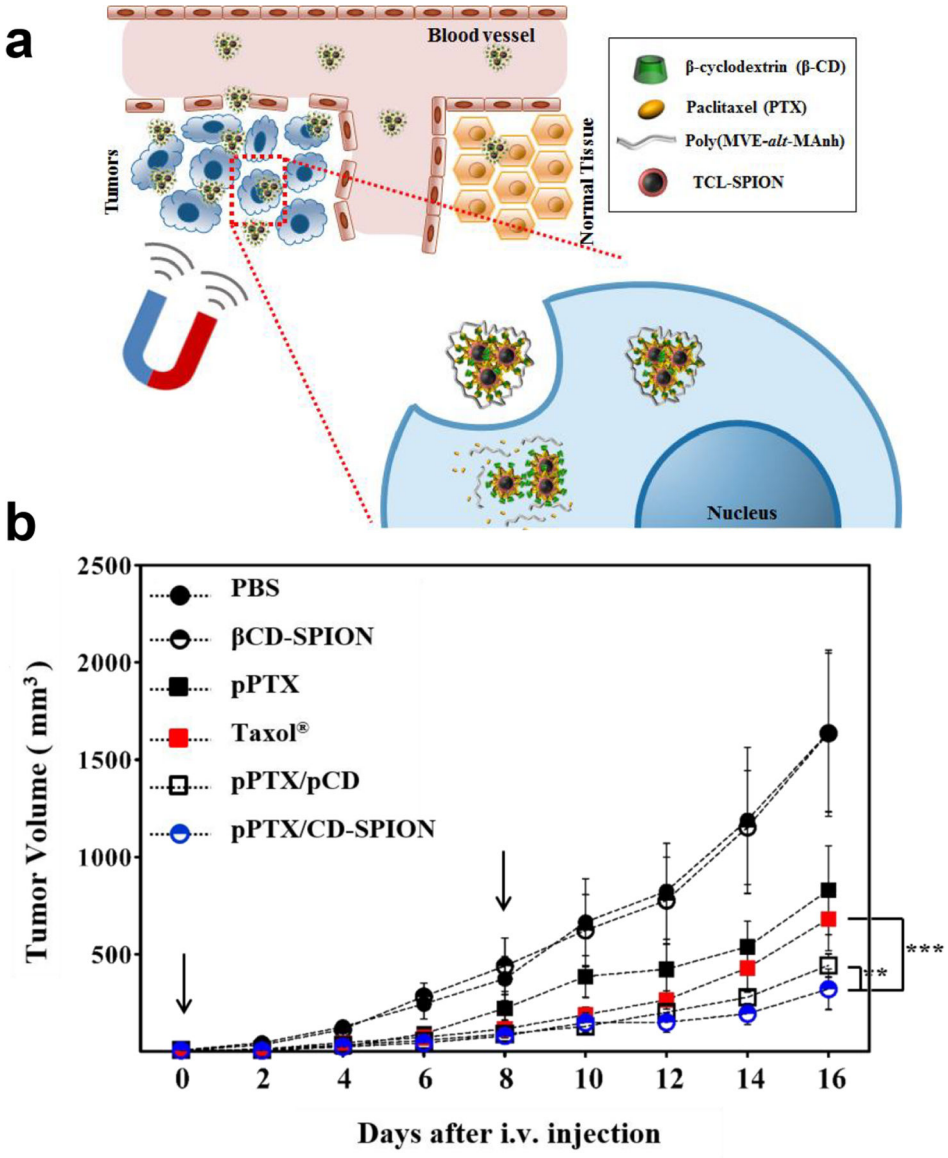

Fig. 15.

(a) Schematic illustration of polymerized β-cyclodextrin and paclitaxel conjugated to SPIONs. Delivery complexes were magnetically guided to the tumor site. (b) CT26 tumor growth profile for different treatment groups. Data represent mean ± S.E.M. from n=4 (*P<0.05; **P<0.01; ***P<0.001). Each arrow represents the time of intravenous injection of samples. (Adapted from ref. 311).

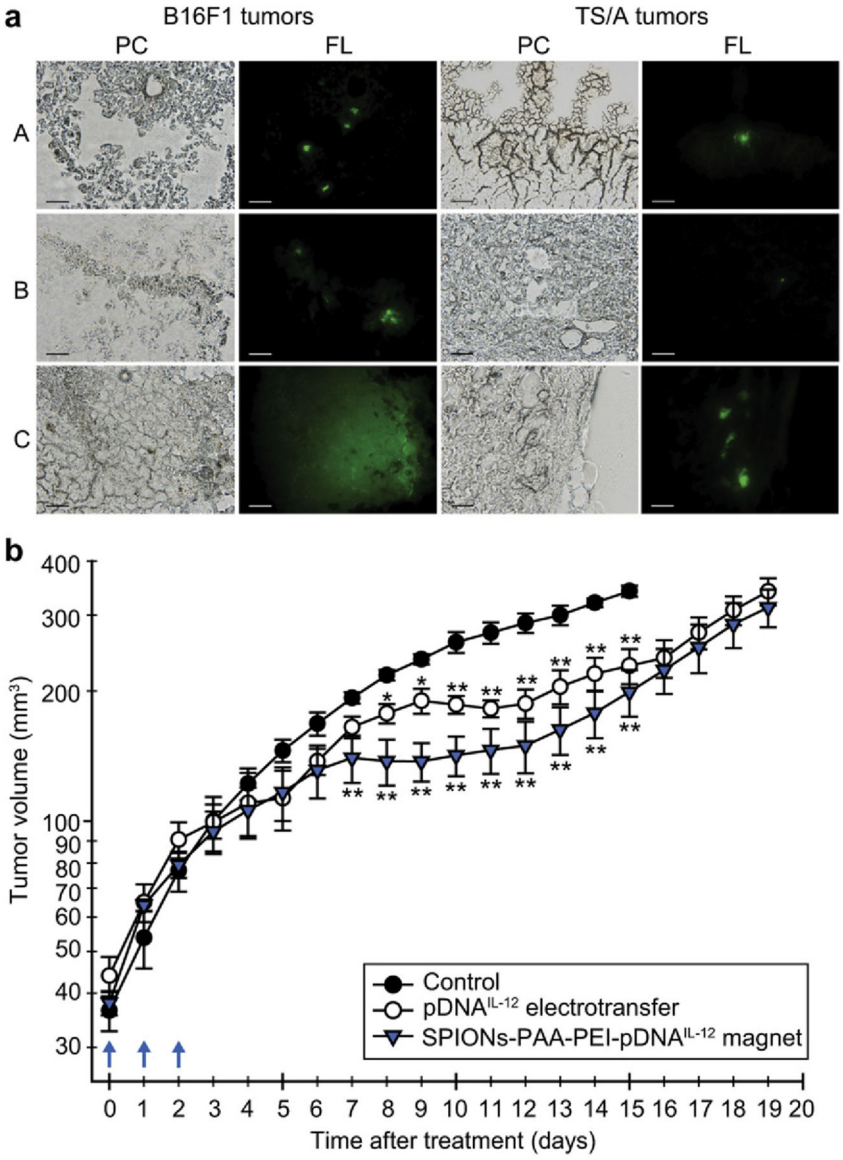

Fig. 16.

Magnetofection of tumors with pDNA^{GFP} or pDNA^{IL-12} using SPIONs-PAA-PEI: (a) Micrographs of frozen murine melanoma B16F1 and mammary adenocarcinoma TS/A tumor sections under phase contrast (PC) and epi-fluorescence illumination (FL) after transfection with pDNA^{GFP} using (A) magnetofection, (B) SPIONs-PAA-PEI in the absence of magnetic field, (C) electrotransfer. Scale bar, 50 mm. (b) Antitumor effect of intratumoral administration of pDNA^{IL-12} on TS/A mammary adenocarcinoma tumors after magnetofection with SPIONs-PAA-PEI and electrotransfer. Blue arrows represent three consecutive treatments with pDNA^{IL-12}. Tumor growth delay was calculated on the 10th day. (Adapted from ref. 304).

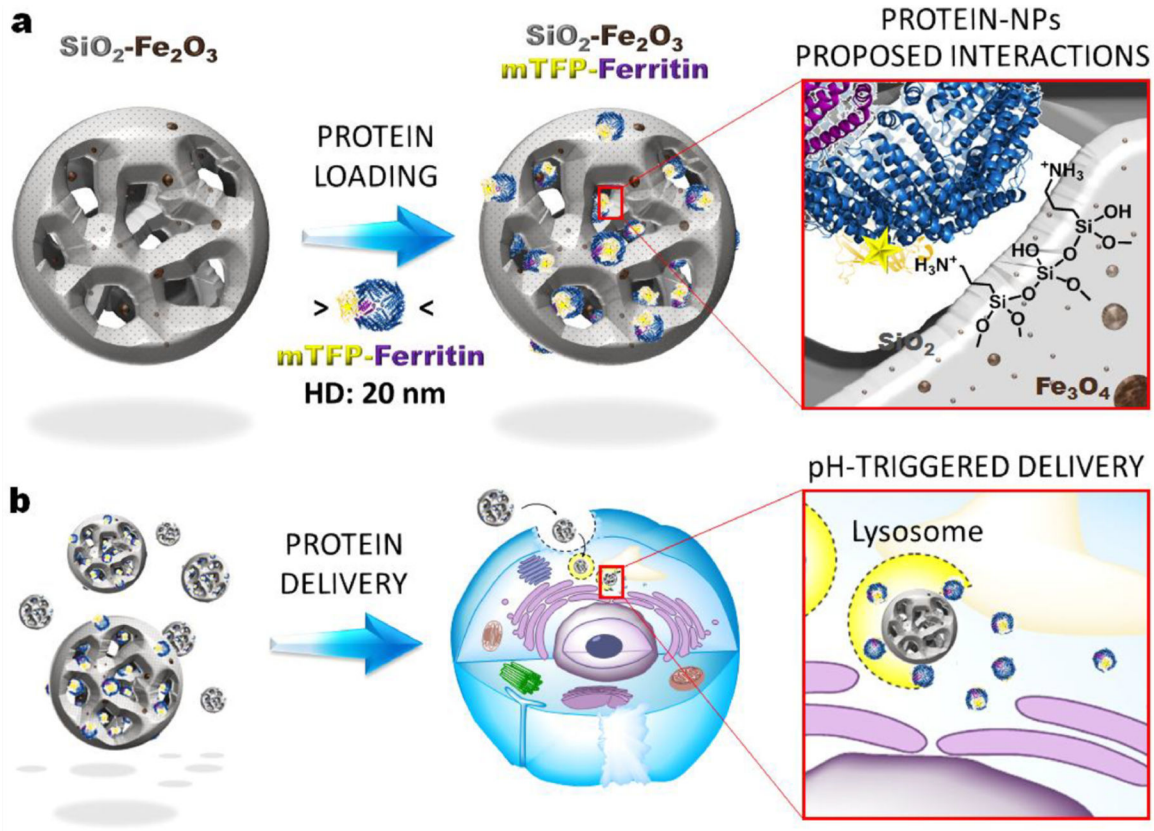

Fig. 17.

Schematic illustration of silica-iron oxide propylamine nanocomposites, with (a) proposed loading interactions for large proteins with the particles and (b) representation of pH-driven intracellular delivery. (Adapted from ref. 326).

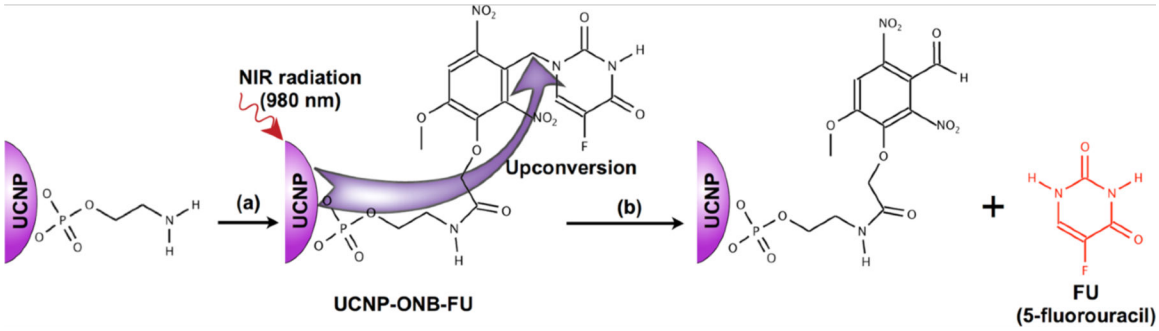

Fig. 18.

NIR excitation (980 nm) of the UCNPs resulted in upconverted UV emission at 364 nm used for photocleavage subsequent release of 5-fluorouracil from the UCNP surface. (Adapted from ref. 355).

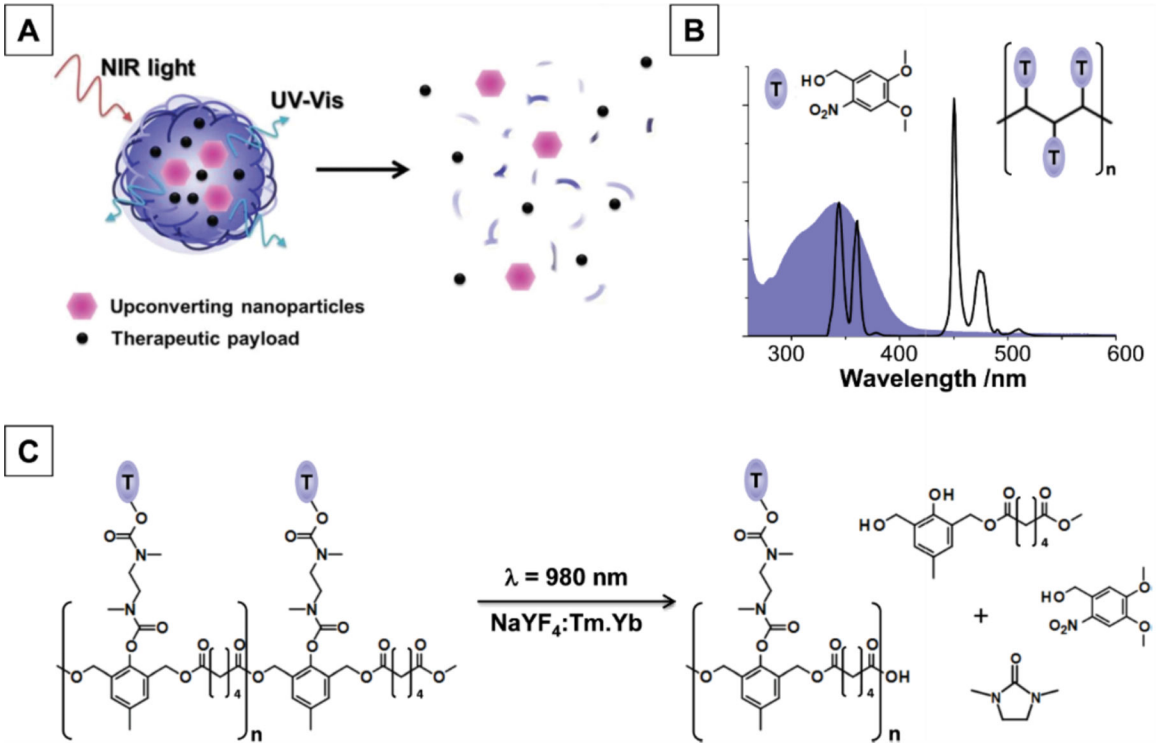

Fig. 19.

Schematic representation: (a) upconverted luminescence triggers degradation and release from light-sensitive nanoparticles; (b) spectral overlap between the UV emission profile of NaYF 4 :Yb.Tm core-shell UCNPs (black trace) and the absorption spectrum (shaded blue) of ONB triggering groups; (c) photochemical mechanism of light-triggered degradation. (Adapted from ref. 367).

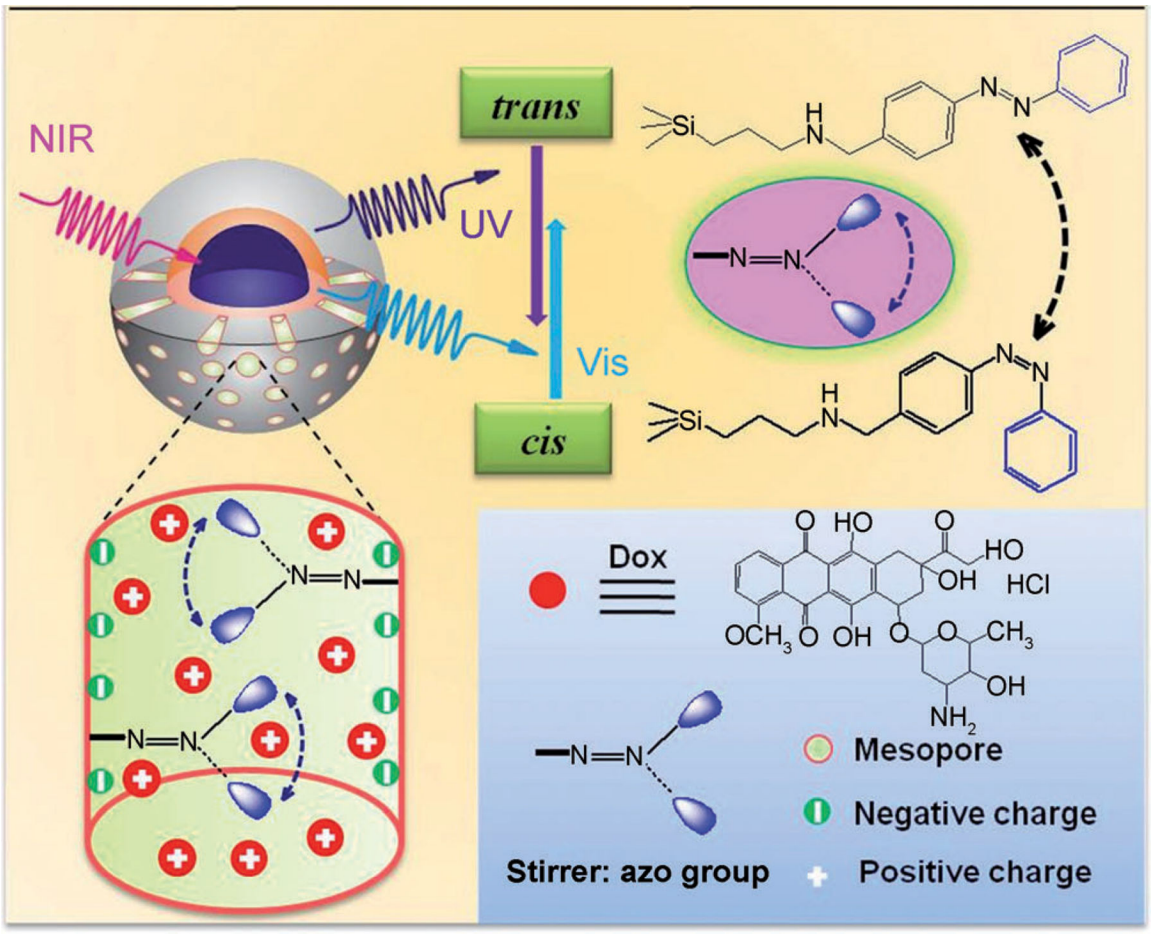

Fig. 20.

Schematic illustration of NIR light-triggered dox release by making use of the upconversion properties of UPNCs and trans–cis photoisomerization of azobenzene molecules grafted on a mesoporous silica layer. (Adapted from ref. 373).

Table 1.
Comparison of inorganic materials for delivery purposes.

Summarized advantages and potential issues of gold, silica, iron oxide, and UCNP platforms for *in vivo* delivery of therapeutics, with key references for delivery of each form of therapeutic cargo.

Material	Advantages	Challenges	References
Gold	tunable size and shape, optical reactivity, flexible monolayer design, inherently non-toxic	uncertain biological fate, nuanced synthetic process	*Small molecule* 71–78, 81–86, 88, 122–127, 130–136, 165 *Protein* 93, 99, 100, 138–140, 142, 143 *Nucleic acid* 105–118, 146–153, 156, 159, 160, 173
Silica	high loading capacity, controllable release rate, flexible platforms for triggered release	toxicity from surface-exposed silanol groups, increased ROS production	*Small molecule* 225, 242, 243, 245, 248, 205–213, 220, 221 *Protein* 230, 240, 244, 214, 215 *Nucleic acid* 237, 217–219
Iron Oxide	hyperthermic properties, potential for contrast imaging or magnetic localization	particle accumulation/ degradation *in vivo* produces toxic byproducts	*Small molecule* 308, 309, 313–315 *Protein* 310, 325 *Nucleic acid* 311, 312, 316–323
Lanthanide Upconversion Particles	NIR-triggered release for localized drug release, low toxicity	limited available excitation wavelengths, need for silica components	*Small molecule* 348–355, 363, 364, 365, 367, 371 *Protein* 366 *Nucleic acid* 356, 368, 372

NIR: Near-infrared radiation

ROS: Reactive oxygen species