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Inorganic Nanoparticles for Therapeutic Delivery: Trials, Tribulations and Promise

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Abstract

Inorganic nanomaterials have a wide array of physical and structural properties that make them attractive candidates for imaging and therapeutic delivery. Nanoparticle platforms have been intensely studied for these applications, and examples are starting to enter the clinic. This review looks at why inorganic particles provide promising platforms for biomedicine, and what issues need to be addressed for them to reach their potential.

Keywords

inorganic nanomaterials; bio-nano interface; drug delivery; up converting nanoparticles; theranostic; imaging agent

1. Introduction

Inorganic nanoparticles come in a wide variety of sizes [1–3] and shapes [4], and possess an array of physical properties that arise from the quantum properties of their core materials [5, 6]. The diversity of both structure and properties enables new strategies for the design of therapeutics and imaging agents [7, 8] (Fig. 1), with examples of nanoparticle-based systems starting to enter the clinic. New issues that arise from the interactions of these materials with biosystems, however, balance the promise of nanomaterials [9–13]. Some of these issues are insurmountable, some require research to overcome, and some provide new directions that were unexpected yet potentially quite powerful.

This review takes a look at the current status of inorganic nanoparticles as imaging and therapeutic agents. Our goal is to both highlight the promise of these materials and to provide areas where questions remain and better understanding is required.

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2. Nanoparticle Cores—Physics in Action

The core sizes of smaller nanoparticles impart unique properties arising from quantum confinement [14]. Quantum dots (QDs) provide very stable fluorescent probes [15] that are size tunable and very resistant to photobleaching [16–19]. Tailoring the surface of QDs with suitable ligands may confer desirable properties such as high quantum yield and long-term stability under broad range of conditions (high electrolyte concentration, a broad pH range, and biogenic thiols). Mattoussi *et al.* have demonstrated that QDs capped with multidentate lipoic acid ligand possessing a zwitterionic head group bring out compact and highly biocompatible nanomaterials [20, 21]. These attributes have made QDs attractive materials for *in vitro* and *in vivo* imaging applications [22–24]. Extension of these studies to the clinic has been hampered by two major challenges. First, the core materials of these QDs are frequently fabricated using toxic heavy metals such as cadmium and lead [25–27]. While other less toxic QDs have been developed [28], they generally have excitation/emission wavelengths that are too short for practical use or present challenges in terms of functionalization. The other issue with QDs is that most are active in the visible range where tissue penetration is quite poor [29]. While this is not an issue in mice, where most of the organs are close to the surface, it is quite important for clinical imaging applications.

Upconverting particles (UCP) avoid many of the issues of QDs. First, these systems are often excited by near-infrared (NIR) or infrared radiation [30, 31]. UCPs are typically designed to emit visible light upon NIR-light excitation, with excitation occurring in the wavelength range where tissue has maximum transparency to allow the light source to penetrate more deeply into living tissues [32, 33]. Recently, Han *et al.* have used (α-$NaYbF_4$:Tm^{3+})/CaF_2 core/shell UCP for high contrast deep tissue bioimaging [34]. In their design, a 35-fold increase in the intensity of UC photoluminescence (PL) was obtained as a result of suppressing the quenching effect by heteroepitaxial growth of biocompatible CaF_2 shell. Rat femoral bone under centimeter-deep soft tissues and pork tissue under 3.2 cm were successfully imaged (Fig. 2). Besides deep tissue penetration, an additional benefit of UCPs is that they can be made using less toxic materials such as lanthanides [35, 36]. UCPs, however, can have challenges in terms of surface modification, and are difficult to fabricate in “ultra-small” (<15 nm diameter) sizes [37].

3. The interface between nanoparticles and biosystems

What is on the surface of a nanoparticle dictates how that particle interacts with biosystems [38]. Much of the work on nanomaterials has focused on non-interactive “stealth” coatings designed to minimize interactions of nanomaterials with cells and the immune system. The most popular coatings are poly(ethylene glycol) (PEG)-based. These polymers are relatively good at minimizing interactions with biosystems [39] (Fig. 3), however recent studies have shown that PEG polymers can cause inflammation through complement activation [40–42]. Zwitterionic coatings, i.e. ones featuring paired cationic and anionic centers are rapidly increasing in popularity [43–45], though the immune system effects of these coverages are not fully understood.

Understanding the behavior of nanomaterials *in vivo* is complicated by the fact that serum proteins adsorb to the surface of particles, generating a "protein corona" [46, 47]. The composition of this corona is dictated by the surface of the particle [48, 49], but generally provides a barrier between the particle and the bio-environment. While complicating the behavior of nanomaterials, the corona plays a useful role, reducing the damage to red blood cells that can be caused by nanoparticles. For example, Rotello *et al.* have used a library of gold NPs (AuNPs) with different surface hydrophobicity to investigate the effect of surface functionality on hemolysis [50]. Although in the absence of serum media a linear hemolytic behavior with increasing hydrophobicity was observed, in the presence of plasma proteins no hemolysis was observed within 30 min (Fig. 4).

4. Biomedical applications of nanomaterials

4.1. Inorganic nanomaterials in imaging

Imaging strategies are key tools for diagnosing a wide range of diseases. Magnetic resonance imaging (MRI) is one of the most useful techniques, and one where nanomaterials can provide unique imaging agents [51, 52]. Superparamagnetic iron oxides nanoparticles (SPIONs) provide effective MRI contrast agents that rely on the magnetic nature of the core [53]. These systems have been explored extensively *in vivo*, with tumor targeting ligands used to image tumors [54, 55]. While potentially quite useful, the relaxation mechanism induced by SPIONs causes targeted tissue to have reduced signal, the opposite of more desirable "turn on" agents such as gadolinium.

In addition to the UCPs described above, AuNPs provide optical imaging agents, exploiting the size and shape dependent optical properties of nanoscale gold. Nanospheres, nanocages [56], nanorods [57] and nanoshells [58] made from AuNPs have all been used as contrast agents in preclinical investigations. In one strategy, photoacoustic imaging with nanoparticles was combined with deep tissue imaging provided by ultrasound (Fig. 5) [59].

4.2. Application of inorganic nanomaterials in drug delivery

The size, shape [60], and surface properties [61] of nanoparticles make them promising platforms as drug delivery vehicles [62, 63]. Two strategies are used for these vectors: covalent attachment and non-covalent association. Covalent attachment has the advantages of being able to control release through attachment chemistry (e.g. release of thiol-based payloads via glutathione release inside the cells) [64] and the fact that the dissociation of the carrier and payload requires a chemical reaction, making the systems stable in solution. On the other hand, covalent attachment of drugs generally (but not always) requires conversion from the particle-bound prodrug to the free drug [65, 66]. Additionally, a number of covalent carrier systems for biomolecules (e.g. siRNA) have a large proportion of the delivered particle trapped in endosomes where it is not active [67].

Non-covalent supramolecular complexes provide a means of delivering unmodified drugs. For instance, Rotello *et al.* have used hydrophobic pockets of AuNP monolayers to encapsulate highly hydrophobic dyes/drugs and deliver them into MCF-7 cells through cell membrane mediated release (Fig. 6) [68]. Non-covalent strategies, however, require careful tuning to prevent either premature or overly slow payload release.

One of the ways for NPs to improve drug efficacy is the release of the cargo on the targeting site by using a wide range of release stimuli. Design of "smart" surface functionalities is a general method adopted to obtain stimuli-responsive NPs. Stimuli-responsive carriers can be designed from NPs that respond either to an internal stimulus (such as a change in pH, glutathione (GSH) or enzymatic cleavage) or to an external stimulus (such as an applied magnetic field or exposure to a specific wavelength of light) [69]. These stimuli are used as triggers to break covalent bonds between the carrier and cargo, or to destabilize non-covalent interactions, facilitating the release of cargo once the carrier has reached the destination.

The efficiency of both covalent and non-covalent delivery systems can be enhanced through targeting [70]. Targeting comes in two forms: passive and active targeting. Passive targeting takes advantage of physical properties that arise from particle size. Inorganic NPs are generally in the correct size range to take advantage of the enhanced permeation and retention (EPR) effect [71, 72]. The EPR effect relies on the leaky nature of tumor vasculature to concentrate nanomaterials in tumors. On it's own, the EPR effect provides a modest enhancement in therapeutic concentration at tumor sites—helpful but not game changing [73, 74].

Active targeting focuses on cell surface molecules, in particular receptors that are overexpressed on tumor cells [75, 76]. Active targeting has been effective *in vivo*, however translation to the clinic has been less rapid than one would expect for a "silver bullet" approach. There are a number of challenges that arise with active targeting. Foremost, even though receptor overexpression can be substantial in tumor cells, there are many more healthy cells than tumor cells in the typical patient, where tumor sizes of 1–10 g are normal. This challenge in lab-to-clinic translation is exacerbated by the large tumor burdens typically used in mouse models—often equivalent to human tumors of over 1 kg.

4.3. Theragnostic applications of inorganic nanomaterials

One of the burgeoning areas in delivery is the field of theragnostics—the combination of imaging and therapeutic modalities [77]. This approach can be quite powerful, providing tumor visualization and treatment at the same time [78]. As an example, Jon *et al.* have used doxorubicin (Dox) loaded thermally cross-linked (TCL) SPIONs as a drug-delivering MR contrast agent (Fig. 7a) [79]. After 4.5 hours of injection, darkening was noticeable due to accumulation of TCL-SPIONs in the vicinity of tumor (Fig. 7b). In addition, the highest tumor growth inhibition was observed when the mouse was injected with Dox@TCL-SPIONs compared to mice treated with 5% glucose, TCL-SPION, Dox (0.64 mg kg^{-1}) and Dox (5 mg kg^{-1}) (Fig. 7c). As with all multifunctional systems, however, it can be challenging to balance the different functions. As an example, imaging and delivery have very different requirements, and balancing limits of detection for imaging with payload amount is non-trivial. Additionally, multiple functions increase the potential for failure—simplicity is a virtue in pharmaceutical design.

4.4. Additional challenges in translation of nanoparticles to the clinic

Nanoparticles have challenges that arise from their novel structures, such as the corona effects described above. There are other challenges with these systems, however, that arise from our experimental approaches. First, there is the issue of characterization [80]. Many studies using nanomaterials feature poorly characterized particles (Fig. 8). As a result, it is difficult to differentiate artifacts from real effects caused by nanomaterials in biological systems, compromising also the reproducibility of the results [81]. Given the rigorous characterization and quality control that is required for the clinic, it can be hoped that there will be a "trickle down" effect that will foster enhanced characterization of nanomaterials for *in vitro* and *in vivo* studies [82, 83].

Perhaps the most significant challenge to creation of effective nanotherapeutics arises from the combinatorial approach of the research in nanotechnology. Particles come in different sizes and shapes, surface coverages have different structures/charges/lengths, and targeting ligands can have different attachment strategies and densities on the particle. Each of these parameters is important, and will affect the behavior of the resulting vehicle (Fig. 8) [84]. Current research tends to focus on one parameter at a time, for example particle size or targeting functionality. As a result we still have a fairly weak understanding of structure-function correlations for nanomaterials, an issue that will need to be addressed if we are to generate systems that are optimized for function and suitable for the clinic [85].

5. Conclusions

Nanoparticles provide highly promising platforms for therapeutics and imaging agents. Proper engineering of core and surface properties enable us to tune parameters such as toxicity, penetration depth, and uptake. For examples of core modifications, gold nanoparticles provide low toxicity for delivery applications, while upconverting nanoparticles provide less toxic analogs of quantum dots for imaging applications. In terms of surfaces, we are rapidly gaining experience in creation of surfaces with desired interactions, but the study is still quite empirical, making generalization challenging.

Like all new technologies, however, there are growing pains in nanomedicine. One thing that should be kept in mind is that effective use of any tool requires understanding of how it works. If the potential impact of nanomaterials in medicine is to be realized, we must balance our pursuit of novel applications with strong effort applied to understanding the fundamentals of nanoparticle interactions with biosystems. In this way, combinatorial designs could be used to fabricate multifunctional platforms for various applications besides helping discovery and understanding of principles lying underneath.

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Highlights

- Inorganic nanoparticles provide platforms for biomedicine.
- Numerous nanoparticle systems with useful properties have been developed.
- Characterization is a very important but often neglected topic in nanomedicine.
- We do not yet have an integrated understanding of nanobiosystems.
- Lack of fundamental understanding means limited predictive capabilities.

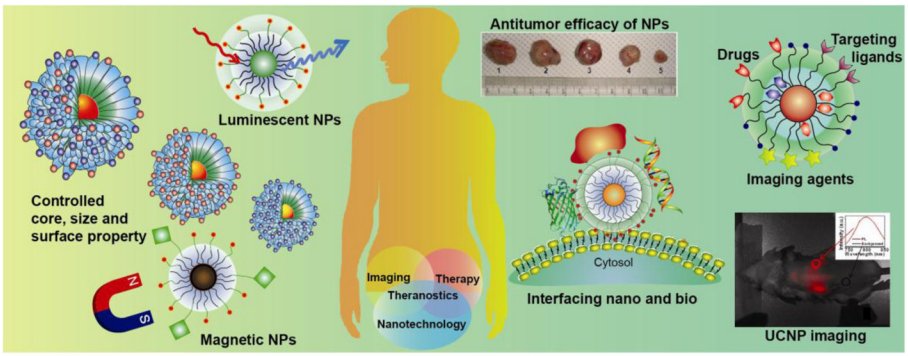

Fig. 1.

Use of the core properties and structure of nanoparticle in biomedicine

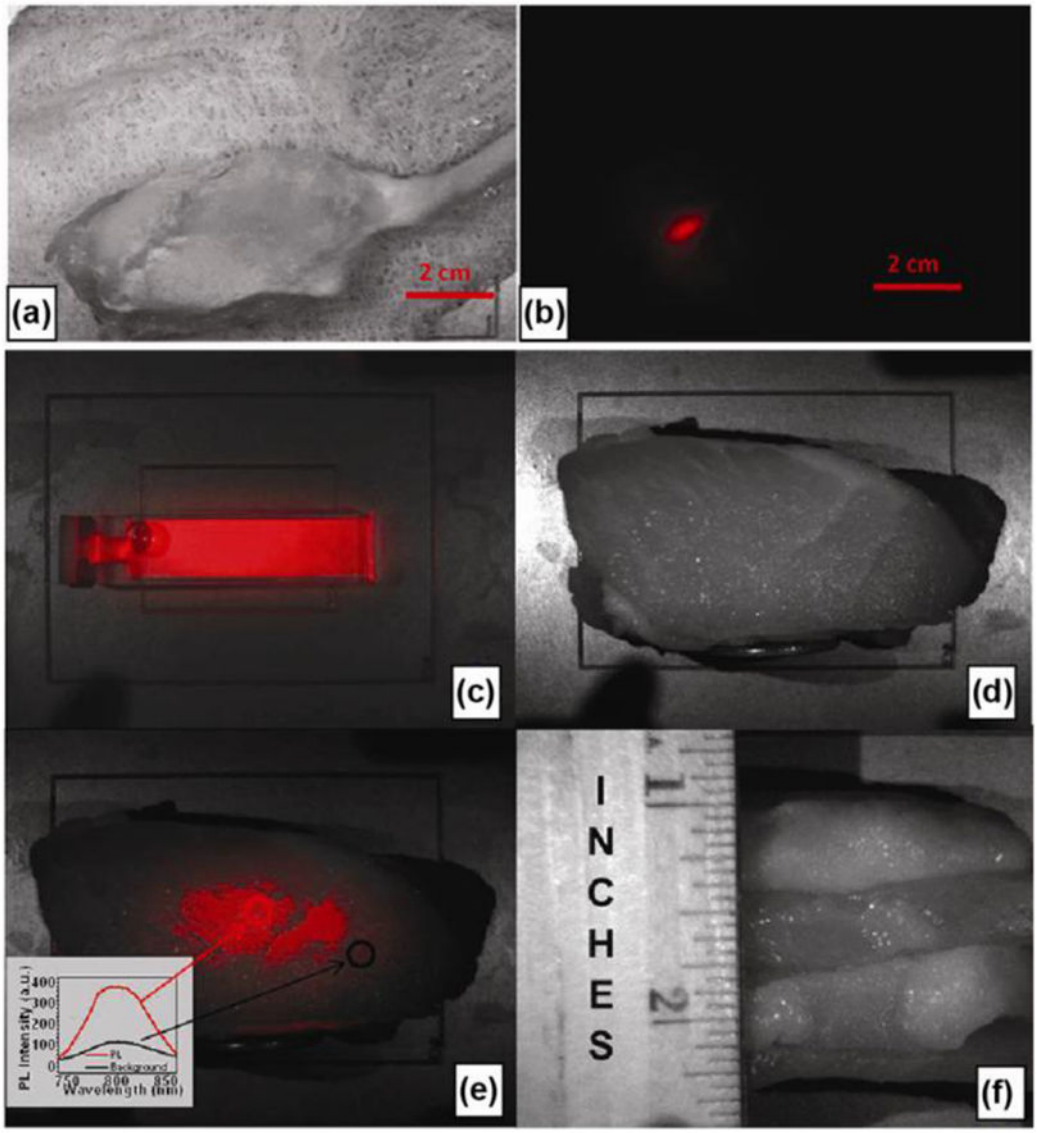

Fig. 2.

(a) Bright-field image of the rat hind leg after embedding UCNP-loaded synthetic mesh and suturing muscle and skin. (b) PL image of the rat femur seven days after UCNP-loaded mesh implantation. Scale bar: 2 cm. (c) PL bright-field image of a cuvette filled with a suspension of UCNPs. (d) Bright-field image of the pork tissue with the cuvette under and a quarter coin placed aside indicating the thickness, (e) Merged UCPL/bright-field image of the pork tissue. (f) Side view of the pork tissue. Adapted from [34].

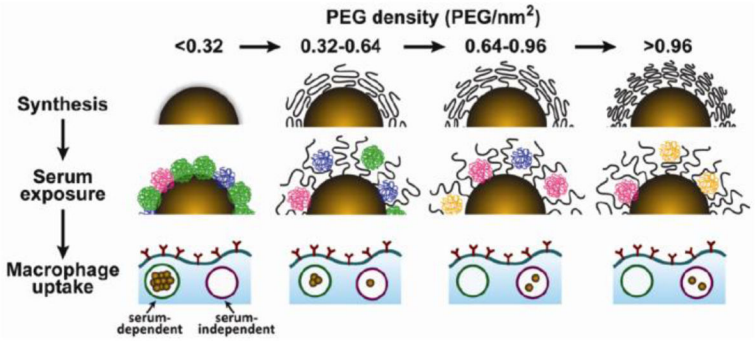

Fig. 3.

Schematic illustration showing how PEG density affects the adsorption of serum proteins to gold nanoparticles. As PEG density increases, the amount of serum proteins adsorbed to the gold NP surface decreases and as a result macrophage uptake is driven mainly by a less efficient serum-independent mechanism. Adapted from [39].

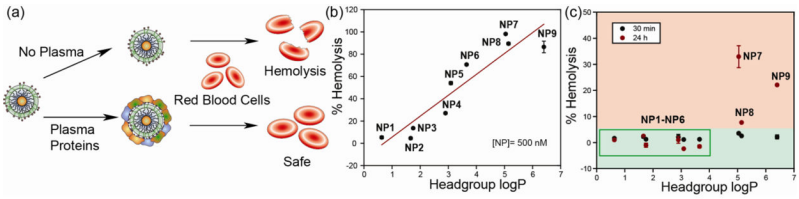

Fig. 4.

(a) Schematic illustrating that the formation of a plasma protein corona on the NP surface protects red blood cells from NP-mediated hemolysis. (b) Hemolysis percentage of NP1–NP9 versus headgroup logP in the absence of plasma proteins. (c) Hemolysis percentage of NP1–NP9 versus headgroup logP in the presence of plasma proteins. Adapted from [50].

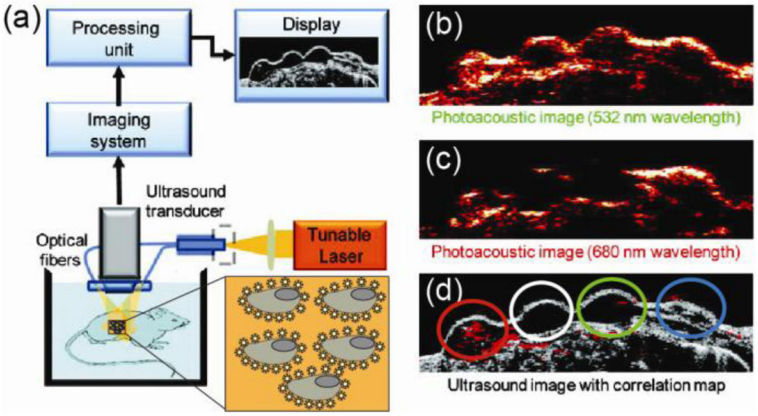

Fig. 5.

(a) Scheme for ultrasound and photoacoustic imaging system. (b) Photoacoustic image at 532 nm wavelength. (c) Photoacoustic image at 680 nm wavelength (d) Ultrasound of gelatin implants in mouse tissue *ex vivo*. The cells with targeted AuNPs (red), control cells (white), the cells mixed with mPEG-SH coated Au NPs (green), and NIR dye (blue) are shown on the ultrasound image. Adapted from [59].

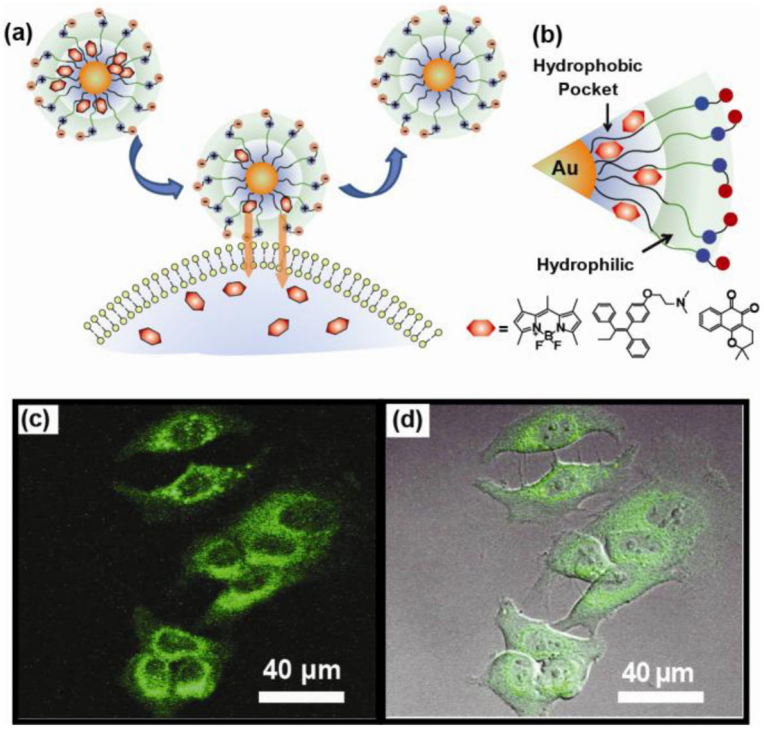

Fig. 6.

(a) Payload delivery to cell through monolayer-membrane interactions. (b) Schematic illustration of guest molecules (bodipy, tamoxifen and lapachone) trapped in the hydrophobic pocket of NPs. Confocal laser scanning microscopy images of MCF-7 cell treated with bodipy encapsulated NPs (c) green channel, (d) overlapped with bright field. Adapted from [68].

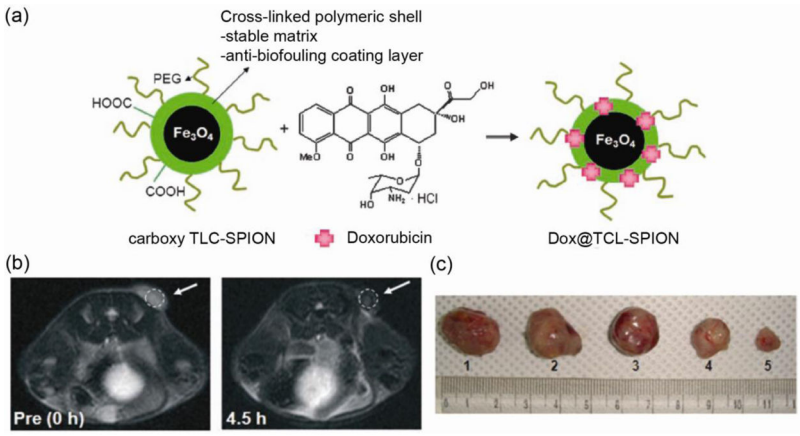

Fig. 7.

(a) Schematic illustrating doxorubicin loading into TLC-SPIONs. (b) Images taken at 0 and 4.5 h at level of tumor on the right back of mouse. (c) Changes in tumor volume when mice were treated with (1) 5% glucose, (2) TCL-SPION, (3) Dox (0.64 mg kg^{-1}) and (4) Dox (5 mg kg^{-1}) and (5) Dox@TCL-SPION (0.64 mg Doxkg^{-1}). Adapted from [79].

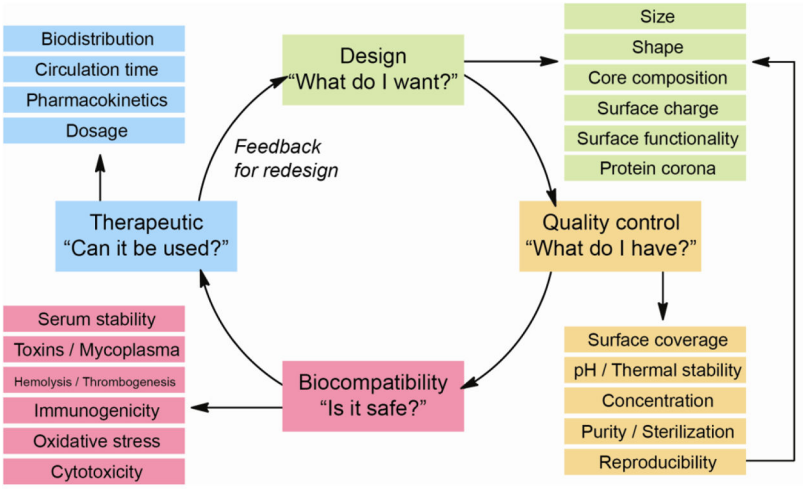

Fig. 8.
Characterization cycle in nanomaterials research.