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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.

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 goals are both to highlight the promise of these materials and to provide areas where questions remain and better understanding is required.

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 a 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 (UCPs) 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

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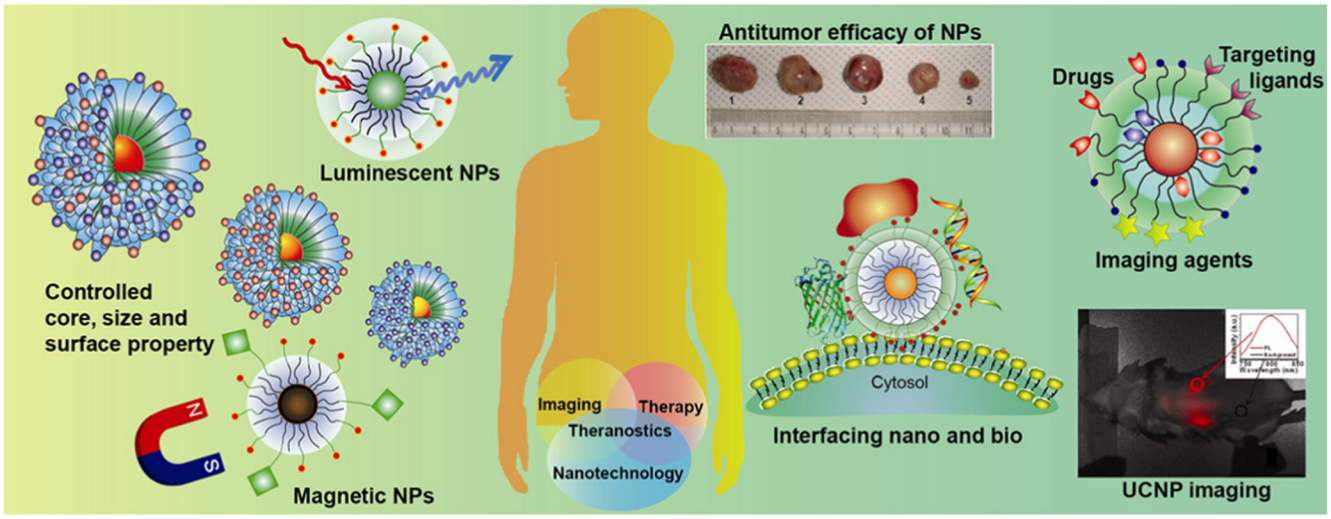

Fig. 1. Use of the core properties and structure of nanoparticle in biomedicine.

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 hydrophobicities 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 oxide 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 the 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.