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Current Opinion in Chemical Engineering

Polymer functionalization of inorganic nanoparticles for biomedical applications

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Inorganic nanoparticles (NPs) are useful materials in the chemical, physical, biological, and medical sciences. Biomedical applications require inorganic NPs to be stable in hydrophilic environments and to avoid premature biodegradation or clearance by the immune system. For this, the NP surface is engineered to enable NP colloidal stability, biocompatibility, and biomedical function. In this review, we present recent advances in polymer coatings of inorganic NPs focusing on polymer composition, ligand architecture, and the resulting coating properties. Further, we discuss how engineering of the polymer coatings governs the NP physicochemical and biological properties, enabling biomedical use as therapeutics, diagnostics , biosensors, and building blocks for material assembly.

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Current Opinion in Chemical Engineering 2022, **37**:100849

This review comes from a themed issue on **Nanotechnology**

Edited by **Inge K Herrmann**

https://doi.org/10.1016/j.coche.2022.100849

Introduction

The nanoscale synthesis of inorganic materials has revolutionized chemistry, physics, biology, and medicine [1–4]. The useful physicochemical properties of inorganic nanoparticles (NPs) are unique to their size and arise, in part, from the large fraction of atoms situated at the surface [5]. The size and composition of inorganic nanomaterials result in magnetic, conductive, radioactive, (photo)thermal, plasmonic, and photoresponsive features. Based on these qualities, inorganic NPs are increasingly applied in biomedicine as therapeutics, diagnostics, biosensors, and material building blocks [6–9].

Despite their potential utility in many clinical applications, the lack of colloidal stability in biological fluids, such as blood serum, can limit clinical translation [4]. Uncontrolled aggregation of NPs can increase adsorption of proteins, resulting in recognition by the immune system or loss of functionality [10,11]. Further, inorganic NPs are usually synthesized in hydrophobic environments, however, their biomedical application requires them to be stable in hydrophilic and aqueous media [12].

The choice of surface modification is a critical design factor governing the colloidal stability, biocompatibility, and function of inorganic NPs for biomedical application [13•]. Modification of the NP surface with non-fouling polymers is an effective strategy to make them colloidally stable, to mitigate clearance, to control their biodistribution, and to limit toxicity (Figure 1) [4]. Altogether, inorganic NP functionalization is of utmost importance as surface ligands create the interface that separates the NP from the biological environment and ultimately determine the NP biological identity.

In this review, we briefly discuss recent advances in NP coating approaches with a focus on polymeric functionalization of inorganic NPs. Throughout, we relate these topics to emerging applications in the field of biomedicine.

Surface engineering of inorganic nanoparticles for biomedical application

Surface hydrophilicity is a key attribute for biomedical application of inorganic NPs. In biological environments, protein fouling and particle aggregation are exacerbated by hydrophobic NP surfaces [14]. Even if some NPs, such as gold NPs, can be synthesized directly in aqueous environments, many inorganic nanomaterials are synthesized under non-aqueous conditions and are therefore stabilized with hydrophobic ligands. To impart the hydrophilicity necessary for biological conditions, and to add other biological functionalities, further processing steps, such as ligand exchange or coating with amphiphilic polymers, are performed (Figure 1).

In the ligand exchange approach, surface ligands are replaced by new ligands with higher binding strength with the NP surface. For applications in biological environments, hydrophobic ligands are usually substituted

Nomenclature

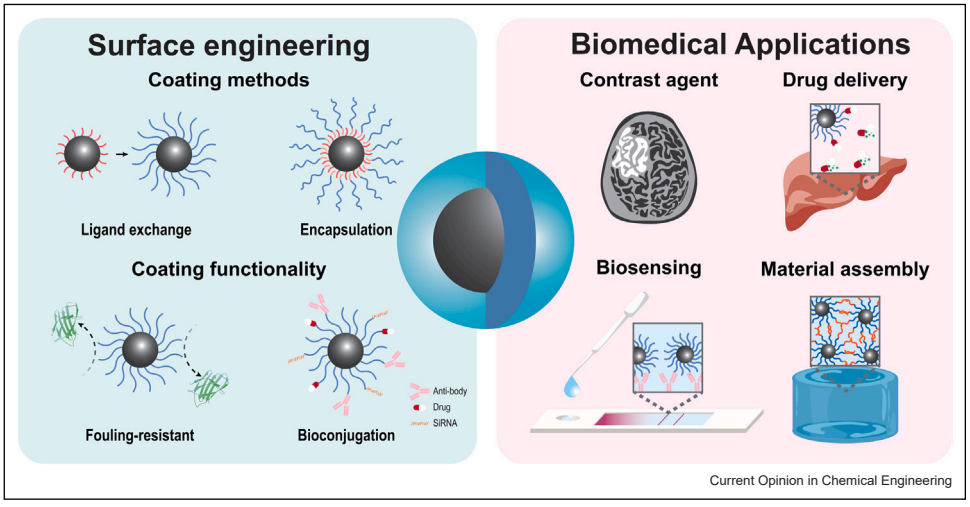
AuNC	Gold nanocrystal
ACE2	human angiotensin-converting enzyme 2
CST	critical solution temperature
MRI	magnetic resonance imaging
NAv	neutravidin
NIR	near-infrared
NP	nanoparticle
PAOXA	polyalkoxazoline
PEG	polyethylene glycol
PIMA	poly(isobutylene-alt-maleic anhydride)
PNG	poly (N-isopropylacrylamide-co-glycidyl methacrylate)
PNP	polymer–nanoparticle
PNIPAm	poly-N-isopropylacrylamide
PET	positron emission tomography
QD	quantum dot
UV	ultraviolet

by hydrophilic ones. For the exchange to occur, the affinity of the new ligands to the surface should be higher than the one of the existing ligands [12,13•]. This is mainly governed by the binding strength of the anchoring group to the NP surface—the ligand affinity to the NP surface determines the coating stability and strength. In practice, the ligand anchor–NP pairs can often be selected following the hard–soft acid–base theory, which states that a soft acid (e.g. Au^{+} and Ag^{+}) will form a stronger bond with a soft base (e.g. R-S^{-} and R_3-PO) while a hard acid (e.g. Fe^{3+} and Ga^{3+}) will result in stronger binding with a hard base (e.g. R-NH_2, R-COO^{-}) [12]. Ligand exchange can be used to obtain hydrophilic NPs in two ways. With the 'grafting to' approach, the hydrophobic ligand of the NP is replaced with a pre-synthesized hydrophilic polymer chain [15,16]. On the other hand with the 'grafting from' approach the initial hydrophobic ligands can be replaced with small molecules or functional ligands suitable for subsequent polymerization from the NP surface [17]. Due to the specificity of the ligands anchoring to NP surface chemistries, a given ligand exchange strategy may be limited in the scope of NPs that it can functionalize [18].

Alternatively, hydrophilicity can be obtained in a non-specific way via encapsulation with amphiphilic polymers. This method creates additional coating layers on top of existing ligands. For example, amphiphilic polymers can adsorb onto the existing hydrophobic NP coating [19]. More precisely, the hydrophobic moieties of the amphiphilic ligands cover the hydrophobic corona of the NPs while the hydrophilic parts form an outer shell. This method can be used to coat hydrophobic NPs independently of the composition of their core and hydrophobic ligands.

Surface modification methods are also leveraged to introduce additional functionality to the inorganic NPs (Figure 1). In the biological milieu, surface composition determines the extent of NP recognition by the innate

Figure 1



Polymer-coating strategies of inorganic NPs for biomedical applications. The design of inorganic NP surfaces is critical for their use in biomedical applications. Surface engineering involves surface modifications (e.g. ligand exchange or encapsulation) using different coating methods and polymers that can have a biological function (e.g. fouling-resistant or bioconjugation). Biocompatible NP surfaces enable biomedical applications as contrast agents for medical imaging, carriers for drug delivery, biosensors, and building blocks for materials assembly.

immune system and regulates the NP biodistribution [10,20]. Therefore, NPs need to be protected from fouling, which involves the unwanted surface adhesion of macromolecules, microorganisms, or suspended debris [21]. NP fouling results in impaired properties, uncontrolled aggregation, premature uptake by the immune system, and ultimately limits the translation of inorganic NPs. To avoid this, hydrophilic polymers impart NP surfaces with a hydration layer, which can limit fouling and improve NP stability. For a precise description of the mechanisms of how hydrophilic polymers limit fouling we recommend the recent works of Zhang et al. and Ozello et al. [22,23].

NP surface composition is also essential to control NP uptake. The use of surface ligands that present specific amino acid sequences, peptides, aptamers, and proteins can improve NP interactions with specific cellular surface moieties and facilitate uptake [24•,25••,26]. As a result, particles can be applied for localized labeling, sensing, imaging, drug delivery, and cancer therapy applications [12]. To conjugate NPs with bioactive ligands, strategies have been developed where surface chemical groups are used to couple biomolecules directly to the NP surface or on NP ligands [13•]. Specific chemical approaches have been thoroughly reviewed [13•,27]. These include reactions involving free thiols, aldehydes, ketones, amines, carboxylates, hydroxyls, and azides.

To conclude, surfaces of inorganic NPs should be designed considering their biocompatibility, stability in the biological milieu, and the necessary physicochemical properties for their application.

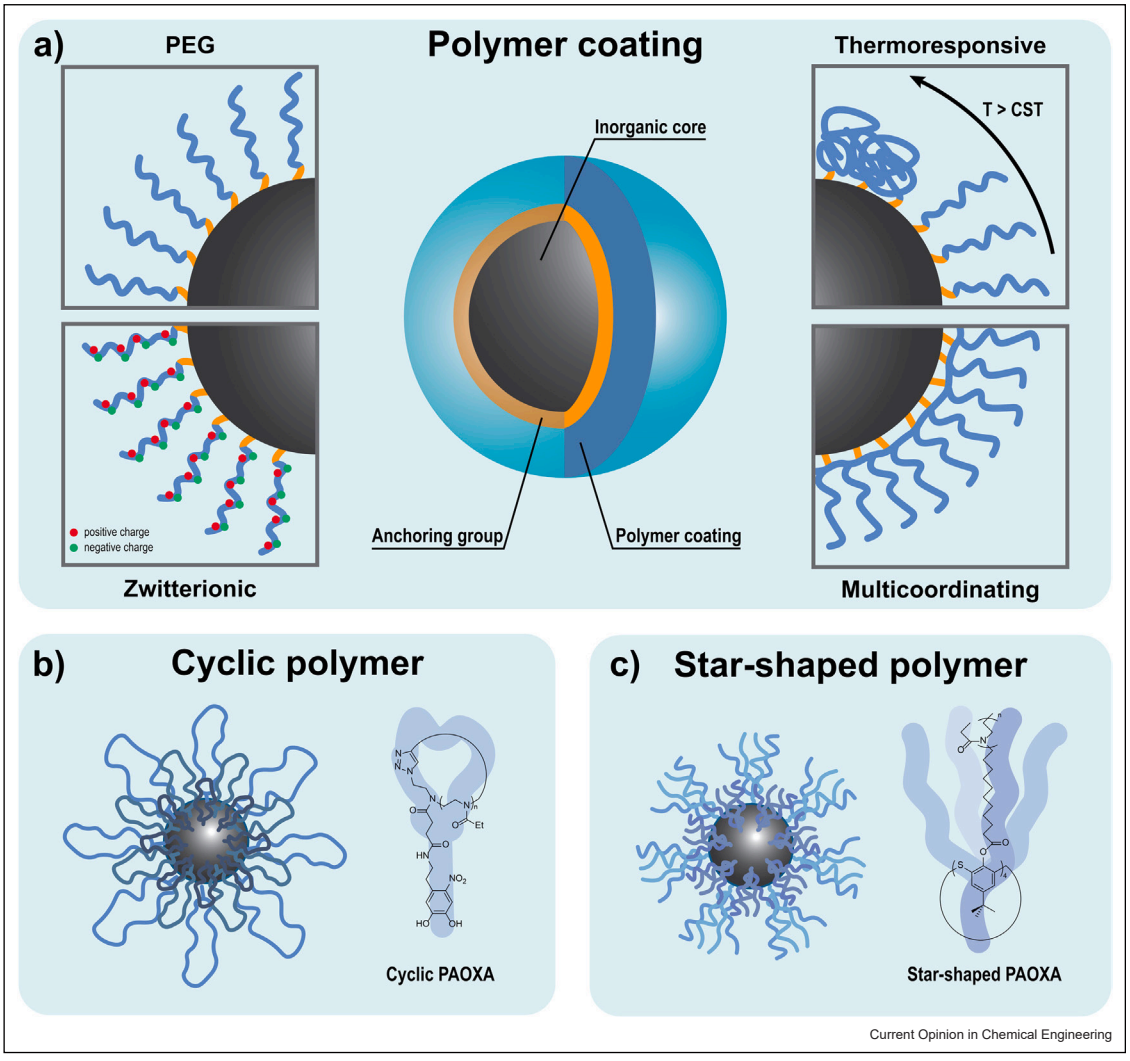
Recent advances in polymer coating of inorganic nanoparticles

Polyethylene glycol (PEG) remains the gold standard polymer for surface coating of biomedical NPs due to its biocompatibility, ease of application on surfaces, and fouling-resistant abilities (Figure 2a) [21,28]. The properties of PEG-based coatings can be tuned by changing the coating layer thickness, polymer architecture, and end-group chemistry. The coating layer thickness increases with increasing PEG molecular weight, and higher grafting densities result in more elongated PEG chains [10]. Yet, PEG and PEG-derivatives can be difficult to graft on certain substrates, are prone to oxidation, and can result in the generation of anti-PEG antibodies [29]. Other polymers have been explored as alternatives to PEG, including Pluronics, polyacrylamides, polyacrylates, polyoxazolines, and polysaccharides [30]. While advances have been made to reduce unwanted immune reactions, further development is needed to increase the clinical translation of polymer-coated inorganic NPs.

Zwitterionic coatings, based on polymers with positive and negative charges, have also been explored based on their capacity to create thick hydration layers that are similar to or stronger than PEG coatings (Figure 2a) [10,28,31]. The differences are caused by the nature of the formed intermolecular interactions between water and the polymer: zwitterionic coatings interact electrostatically with water whereas PEG molecules form hydrogen bonds. The hydrophilicity is often tuned by the choice of the specific anionic groups, as the cationic group in most zwitterionic coatings are quaternary ammoniums. The hydrophilicity increases with decreasing acidity of the anionic group. The antifouling performance of zwitterionic coatings on NPs correlated with their hydration strength [32]. More hydrated zwitterionic polymers were able to completely suppress protein adsorption, whereas a protein corona formed on those with weaker hydration layers. Besides protein resistance, zwitterionic coatings provide NPs with sufficient stability for utilization in biomedical applications. In a recent study, the stability of gold NPs with a zwitterionic coating increased with the addition of a cross-linking agent [33]. Vinyl-containing ligands were grafted on gold NP surfaces and, subsequently, a poly(ornithine methacrylamide) zwitterionic hydrogel was grown on the surface. The particles showed stability at high salt concentrations (saturated solutions) and across a broad range of pH. This coating additionally hindered aggregation of the NPs during lyophilization making them suitable for use with sensitive biologics that degrade rapidly in the liquid state.

To further improve the functionality of the polymer coatings, stimuli-responsive behaviors can be introduced into the surface. Stimuli-responsive polymers undergo physicochemical changes upon alterations in their environment, such as temperature, pH, or light [21]. One of the most studied stimuli-responsive polymers is the thermo- and pH-responsive poly-*N*-isopropylacrylamide (PNIPAm). The solubility of the polymer is determined by its critical solution temperature (CST), which can be tuned by chain length and composition [21]. Below the CST, the polymer is soluble in aqueous conditions. When the temperature increases above the CST, PNIPAm undergoes a phase transition from an extended hydrated state to a collapsed dehydrated and insoluble state (Figure 2). Although the CST of pure PNIPAm, 32 °C, is too low for biomedical applications it can be tuned by copolymerization with hydrophilic co-monomers to increase the CST to be near physiologic temperature [34]. Therefore, PNIPAm coatings are of high interest for stimuli-responsive biomedical applications. Additional responsive polymer coatings were based on surface-initiated reversible addition–fragmentation chain-transfer polymerization to graft a poly (*N*-isopropylacrylamide-*co*-glycidyl methacrylate) (PNG)-based shell from iron oxide NPs. The chain transfer

Figure 2



Engineering of the polymer coating. **(a)** The inorganic NP core can be functionalized with polymers using specific anchoring groups. Different types of functional polymers, such as PEG, zwitterionic, thermoresponsive, and multicoordinating polymers, can be linked to the anchoring groups. Polymer coating properties can be tuned also by varying the architecture, for example through the use of **(b)** cyclic brushes or **(c)** star-shaped brushes.

agent was anchored to the NP and enabled the chain to grow on the surface. The chemotherapeutic doxorubicin was then covalently attached to the PNG shell via pH-sensitive imine bonds [34]. Based on the responsive nature of the coating, doxorubicin was released from the PNIPAm chains in a pH- and temperature-dependent manner. Further, polyalkyloxazolines (PAOXA) are thermoresponsive polymers that have attracted interest for biomedical use [35]. PAOXA are biocompatible and easy to synthesize polymers that can be used to prepare fouling-resistant coatings. Compared to PEG, PAOXA coatings often have an improved stability. In complex physiological media, salinity and additives affect the thermoresponsive behavior, requiring careful tuning of the CST for biomedical applications [36]. Monomer choice can be used to tailor the CST of PAOXA chains — 37°C for isopropyloxazoline to 94°C for ethyloxazoline [36]. This strategy was used, for example, to tailor the aggregation temperature of superparamagnetic iron oxide NPs.

To further improve polymer coating stability and properties, various polymer topologies have been explored. Using PAOXA as an example, a cyclic brush-like coating (Figure 2b) enabled the formation of iron oxide NPs with improved stability compared with those coated with linear PAOXA [37]. The improved stability of the cyclic PAOXA coatings was attributed to the increase in grafting density compared with their linear counterparts, leading to increased stiffness and steric stability. NP

aggregation was induced at increased temperature, and, in the case of the cyclic brushes, individual NPs could be recovered upon reducing the temperature. However, the linear counterpart resulted in irreversible aggregation. In the case of the cyclic brush layers, core–core interactions were thought to be prevented through steric hindrance [38••]. Cyclic PAOXA also showed increased protein resistance and lower friction compared with linear polymer coatings [39]. This behavior was explained by the increased entropic penalty for biomolecule adsorption on the cyclic chains. Other PAOXA topologies have been investigated, including star-shaped PAOXA coatings (Figure 2c) [40]. The star-shaped polymers stabilized Ag NPs as potential hydrophobic drug carriers.

A further step in the design of tunable polymer coatings was developed using multicoordinating polymeric ligands (Figure 2a) [12]. Herein, the polymer ligands offered multisite coordination through the incorporation of several anchoring groups in the backbone. Additionally, secondary polymers can be grafted on the backbone to provide colloidal stability and the desired properties to the NPs. This system enables additional design control and tuning of the properties for specific applications. This approach was used to engineer NPs with surface-reacting functionalities enabling conjugation reactions that were used to link biomolecules to the NPs [12]. For this purpose poly(isobutylene-alt-maleic anhydride) (PIMA) was functionalized with lipoic acid and histamine, anchoring groups for quantum dots (QD). Subsequently, PEG or zwitterionic groups were grafted onto the PIMA backbone to provide hydrophilicity. The functionalized PIMA was then coated on QDs via ligand exchange. By modifying the anchoring groups, this system was applied to a variety of NPs [12]. PIMA was also used to coat NPs for improved stability in biological fluids or saturated buffers [41].

Recent advances in the biomedical application of polymer-coated inorganic nanoparticles

In addition to NP physicochemical properties — such as size, shape, and composition — the surface properties of NPs are critical for their use and can expand their application spectrum enabling unprecedented NP properties and performance in biomedical applications. Here we highlight a few recent examples of how surface engineering of inorganic NPs has been leveraged as diagnostic, therapeutic and sensing NPs, and as building blocks for material assembly (Figure 3).

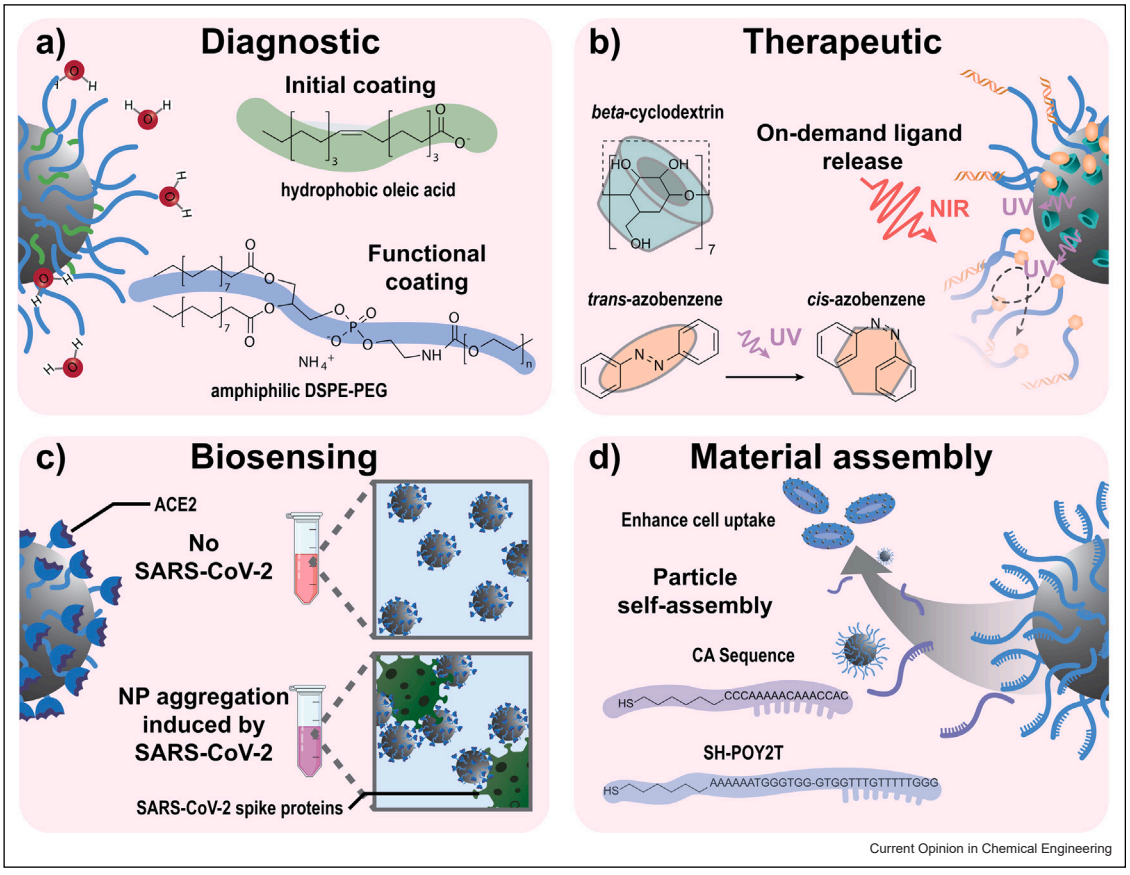
Coatings for diagnostic and therapeutic nanoparticles

In this section, we discuss the use of coatings in diagnostic and therapeutic NPs. NPs combining therapeutic and diagnostic applications are referred to as theranostic materials. The design of polymer coatings for theranostic NPs has recently been reviewed by Shen and coworkers [46]. Therefore, we will direct our focus on coatings for therapeutic or diagnostic applications.

Diagnostic NPs are mainly used as contrast agents for magnetic resonance imaging (MRI), computed tomography, positron emission tomography (PET), and optical imaging [47]. Here we highlight two examples in which the choice of the NP coating was critical for the specific application. MRI contrast agents are widely used in the clinic and are usually made of complexed gadolinium ions. However, high concentrations of gadolinium are toxic and nanomaterials which provide high MRI contrast are clinically important to decrease the dose of injected gadolinium. Gadolinium (III)-based nanocrystals ($NaGdF_4$) were colloidally stabilized by hydrophobic oleic acid and coated with an amphiphilic PEGylated phospholipid, DSPE-PEG (Figure 3a) [42]. The density of DSPE-PEG functionalization modulated the distance between the nanocrystal core and environmental water enabling optimization of T_1 relaxivity; denser coatings increased T_1 water relaxivity. The best-performing nanocrystal contrast agent had a T_1 relaxivity ~25-times higher than clinically used contrast agents which would allow similar MRI contrast with lower gadolinium concentrations. In another example, PEG-diphosphonate ligands were used to stabilize iron oxide NPs in biological environments [48]. Radioactive isotopes rapidly coordinated with the spare coordination sites of the anchoring diphosphonate groups, stabilizing the surface ligands and binding radiotracers to the NPs. The system could be used for PET or single-photon emission computerized tomography. This labeling method was rapid and did not require harsh temperatures or pressures, protecting fast-decaying radioactive tracers and preserving the activity of additional targeting biomolecules. Similar use of polymer coatings enabled the development of inorganic NPs sensitive to different imaging technologies for multimodal imaging. We direct readers interested in inorganic NPs for multimodal imaging to the review of Chen and colleagues [49].

In addition to diagnostic applications, surface immobilization of polymer coatings can be used for therapeutic purposes by delaying the release of pharmaceuticals and to target specific tissues [7,50]. Recent advances include the development of stimuli-responsive coatings for on-demand release. For example, near-infrared (NIR) light-responsive nanocarriers were prepared by surface grafting of a macro-cyclic oligosaccharide (β-cyclodextrin) to lanthanide-based upconverting NPs (Figure 3b) [43]. The incorporated β-cyclodextrin was able to bind ultraviolet-responsive (UV) *trans*-azobenzene ligands. *Trans*-azobenzene-terminated polymer ligands were linked to siRNA and tumor targeting moieties. Deep-penetrating incoming NIR light was converted into surface UV irradiation by

Figure 3



Precise polymer coating design is essential for the use of inorganic NPs in biomedicine. **(a)** Gadolinium(III)-based nanocrystals were formed in a hydrophobic environment and stabilized with oleic acid. DSPE-PEG was adsorbed on the nanocrystals and formed a hydrophilic coating that enabled the tuning of gadolinium(III)–water interactions for MRI contrast. **(b)** The macrocycle of β-cyclodextrin was anchored to the surface of lanthanide-based upconverting NPs. β-cyclodextrin was able to bind *trans*-azobenzene-functionalized PEG–siRNA ligands. The lanthanide-based NPs locally converted incoming NIR light to UV irradiation. UV excitation induced isomerization of *trans*-azobenzene into its *cis*-conformation, releasing the PEG–siRNA-functionalized ligands. **(c)** Gold NPs were functionalized with human ACE2. The ACE2-functionalized gold NPs bound spike protein present on the SARS-CoV-2. NP binding to the viral particles led to a color shift of the suspension following NP aggregation (plasmonic effect). This was used for sensing COVID-19 in a low-cost rapid test kit. **(d)** Gold NPs were functionalized via ligand exchange with thiol-modified oligonucleotides. In the presence of a complementary sequence the coated NPs assembled in sun-flower like aggregates, which lead to enhanced cell uptake. Aspects of the figures were redrawn with permission from references [42–45].

the lanthanide-based core, which isomerized *trans*-azobenzene into its *cis*-conformation. In this manner, NIR irradiation inhibited azobenzene–cyclodextrin interactions and released the therapeutic cargo on demand. Other applications of polymer coatings of inorganic NPs rely on recent understanding of key processes regulating the immune system to rationalize the development of immunomodulating inorganic nanomaterials for therapy. Examples include decorating the surface of inorganic NPs with ligands capable of interacting with immune cells *in vivo* and affecting their behavior, enabling pro-inflammatory or anti-inflammatory effects [8,51••]. Iron oxide NPs were designed to present cell-receptor ligands which modulate immune responses [52]. One of the strategies was to make NPs in the presence of surfactants and the surface ligands were exchanged with dopamine-conjugated PEG, terminated with disease-relevant peptide-major histocompatibility complexes. *In vivo*, ligand density was responsible for antigen-specific regulatory T cell potency, which mitigated auto-immune responses by suppressing auto-reactive T-cells. To summarize, polymer coatings of inorganic NPs have been useful to improve functions, impart stimuli-responsive properties, and control the interactions with the biological milieu.

Coatings for sensing nanoparticles

Advances in polymer-coated inorganic NPs include the fabrication of NP-based sensors and multifunctional nanosensors for *in vivo* disease monitoring. Several groups have engineered inorganic NP coatings to fabricate biosensors for the early diagnosis of SARS-CoV-2

[1,53]. Notably, gold NPs were stabilized with cysteamine and used to make low-cost COVID-19 rapid tests (Figure 3c) [44•]. Human angiotensin-converting enzyme 2 (ACE2) was reacted to free amines present on the NP surface. The natural process by which SARS-CoV-2 infects human cells is through binding of the virus spike proteins to ACE2. In the COVID-19 rapid test, the ACE2-functionalized gold particles aggregated upon binding to the spike proteins. Due to the plasmonic effect, gold NP aggregation led to a visible color shift from red to purple that was used for rapid diagnosis. In another emerging application, surface-coated inorganic NPs have enabled *in vivo* disease monitoring [54]. In one example, protease-cleavable ligands were designed with terminal thiol and biotin functionalities. Gold nanoclusters (AuNCs) were functionalized with the synthesized ligands via thiol–Au bond formation. In the presence of neutravidin (NAv) the biotinylated surface ligands drove nanocluster assembly into larger protease-sensitive AuNC–NAv complexes. Upon intravenous injection in healthy mice, AuNC–NAv complexes were retained in the animals for up to 4 weeks. In tumor-bearing mice, elevated tumor protease activity cleaved the protease-sensitive ligand, liberating the AuNCs which underwent renal clearance. Up to 73% of the injected dose was collected in mice urine 1 h after injection. The presence of NCs in urine samples was measured with a simple colorimetric readout based on the nanozyme activity of AuNCs, allowing quantification of the disease state in mice. This versatile *in vivo* biosensing platform could be deployed directly at the point of care and enable fast and efficient disease detection.

Coatings for dynamic materials design

To further extend the range of applications of inorganic NPs, larger objects have been assembled by engineering the surface coating [44•,55]. NP aggregation, as previously mentioned, can be detrimental if uncontrolled and irreversible. Nonetheless, it is possible to harness the increased uptake of particle aggregates to achieve targeted delivery of particles to specific tissues. By carefully designing coatings of inorganic NPs, assembly can be controlled, leading to increased uptake in targeted regions, and reversed with external stimuli. The disassembled NPs can then act locally as single objects. Sunflower-like NPs were obtained by exchanging surface ligands with triplex-forming NIR-responsive oligonucleotides (Figure 3d) [45]. The assembled materials showed enhanced cellular uptake compared with individual particles in tumors. Upon NIR radiation the aggregates disassembled into ultrasmall NPs leading to a direct release of the gene silencing moieties in proximity to cell nuclei. In another study, iron nanoaggregates were designed as pH-responsive contrast agents for MRI diagnosis of hepatocellular carcinoma in mice [56]. In this study, NPs were used for targeting tumors and also to tune the NP magnetic properties. Through the introduction of a DNA-based ligand via ligand exchange, the NPs formed nanoaggregates at neutral pH with a T_2 contrast capacity. In the presence of acidic pH, as found in tumors, the DNA ligand collapsed, breaking the aggregates, and releasing individual NPs thus altering their magnetic properties exhibiting T_1 contrast.

Furthermore, NPs have been harnessed as building blocks for macroscopic materials design, including the production of moldable or injectable hydrogels [57]. Polymer–nanoparticle (PNP) hydrogels use NPs as structural components of the resultant polymer network [58–60]. Using PEG coated NPs in combination with α-cyclodextrin, PNP hydrogels were formed with a variety of biopolymers, polymeric NPs, and inorganic NPs [61]. The resulting materials demonstrated suitability as cell-laden bioinks for additive manufacturing, as drug delivery platforms, and for the design of conductive or magnetic materials. This paradigm has been extended through the inclusion of magnetic NPs with multifunctional coordinating polymer coatings to form an aerogel suitable for biosensing applications [18]. In this example, Cd/Se, Cd/S, superparamagnetic iron oxide, and Au_3Cu NPs were coated with PIMA, which was cross-linked with calcium ions into a hydrogel and the material was subsequently dried to form the functional aerogel.

Outlook

Surface ligands comprise the interface between nanomaterials and the biological environment and govern how NPs perform in medical applications. Recent advances in polymer coatings have resulted in the creation of inorganic NPs with enhanced biocompatibility and biofunctionality. Through the careful design of the coating, NPs have been engineered to escape from or engage with the immune system, target specific cells or tissues, improve therapy and diagnostics, act as nanoscale biosensors, and assemble into macroscale (bio) materials. Further emphasis should be put on the adaptation of polymer coatings for clinical application. Indeed, the current body of literature on coating such as on PAOXA or PIMA has focused on technical studies on the polymer properties. Application-driven research would enhance the translational potential of those coatings, which remain as lab-scale demonstrations. Indeed, there is a discrepancy between the volume of published articles on the topic of inorganic NPs for biomedical applications and the number of NP-based therapies reaching the clinic. One cause may be that academic studies often focus on the design of complex nanomaterials, overlooking fundamental understanding of how polymer-coated inorganic NPs behave in physiological environments. Therefore, studies that investigate why and how established coating design strategies affect NP performance in the biological milieu, such as the recent

work of Wilhelm et al. and Mittelheisser et al., and detailed reporting of experimental procedures will be key for successful translation to the clinic [62,63]. In addition, there are several practical considerations related to good manufacturing practice, sterilization, and scale-up of polymer-coated NPs. General and standardized metrics for characterization, validation, and safety testing of nanomaterials used in biomedical applications need to be defined [64,65]. The continued convergence of clinicians, chemists, materials scientists, and engineers offers many opportunities in the design and application of polymer-coated inorganic NPs as the field matures.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 956544. This work was supported by the Swiss National Science Foundation under project number 200021_184697 and start-up funds from ETH Zurich. The authors declare no conflict of interest. To prepare aspects of the illustrations, the authors used Adobe stock images under the following licenses 275892405 and 32992365.

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- •• of outstanding interest

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