Optimizing nanoparticle design and surface modification toward clinical translation

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The field of nanomedicine is a rapidly evolving field driven by the need for safer and more efficient therapies as well as ultrasensitive and fast diagnostics. Although the advantages of nanoparticles for diagnostic and therapeutic applications are unambiguous, in vivo requirements, including low toxicity, long blood circulation time, proper clearance, sufficient stability, and reproducible synthesis have, in most cases, bedeviled their clinical translation. Nevertheless, researchers have the opportunity to have a decisive influence on the future of nanomedicine by developing new multifunctional molecules and adapting the material design to the requirements. Ultimately, the goal is to find the right level of functionality without adding unnecessary complexity to the system. This article aims to emphasize the potential and current challenges of nanoparticle-based medical agents and highlights how smart and functional material design considerations can help to overcome many of the current limitations and increase the clinical value of nanoparticles.

Introduction

Nanomedicine is a rapidly evolving field that has just recently gained worldwide attention through the US Food and Drug Administration (FDA) emergency use authorization of two nanoparticle-based vaccines provided by BioNTech/Pfizer and Moderna in the fight against the acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Nanoencapsulation, in this case, provides protection from degradation for the enzyme-labile messenger RNA (mRNA). Being the first mRNA-based vaccines in clinical use represents a milestone in fighting the current COVID-19 pandemic, but also demonstrate a huge achievement in the field of nanomedicine and underlines its yet unexploited potential.

To date, precise engineering on the nanoscale has enabled the synthesis of numerous materials in the 1–100 nm dimension range with tailororable and unique properties for versatile medicinal applications. In order to achieve the specificity, stability, and compatibility required for each application, nanoparticles are often modified and functionalized in multiple steps. While an increasing functionality is beneficial in many ways, the related increase in complexity often implies reproducibility and scalability issues leading to the question: How complex do nanomaterials have to be for applications in medicine? According to R. Weissleder, a world-leading scientist and clinician with decades of experience in the field of nanomedicine, the answer is simple: “Just enough and no more.”

A closer look at current nanomaterials approved for their use in clinics by the FDA or European Medicines Agency (EMA) reveals dozens of different agents used as drug delivery vehicles, imaging agents, dietary supplements, and vaccines. Interestingly, most of them consist of only few components and thus demonstrate a rather low level of complexity. For instance, most drug delivery applications are based on the use of cell-membrane mimicking liposomes or lipid nanoparticles that encapsulate anticancer drugs and, with few exceptions, even avoid co-formulations with stabilizing polymers such as poly(ethylene glycol) (PEG). In contrast, the functional complexity of nanomaterials in fundamental research has increased tremendously over the years. In fact, thousands of research projects are published every year in the field of nanomedicine encompassing complex multicomponent architectures and sophisticated surface modifications driven by the need of being more and more innovative. As a result, nanoparticles with extraordinary properties have been described, including those that are responsive to internal or external trigger,
accumulate preferentially in a specific cell type, provide enhanced contrast for multimodal imaging, possess superior stability and anti-fouling behavior or degrade to nontoxic clearable side-products over time.

These additional functionalities can be beneficial for in vivo applications and have the potential to overcome some of the current limitations of conventional agents and nanoformulations, including their lack of specificity and fast clearance from circulation. Indeed, more and more of these modifications have received clinical visibility with the result that out of 45 investigated nanoparticles in 2019 seven possessed targeting functionality and six were stimuli-responsive. Basic research thus has the potential to have a major impact on the development of new diagnostics and therapeutics if it takes place in close collaboration with clinicians. In other words, it is essential to understand the needs for therapeutics and diagnostics from a clinical perspective and develop problem-oriented solutions in order to enhance the translational potential of nanoparticles.

What makes a good therapeutic?
The success of therapeutics can be measured by their therapeutics efficacy and lack of side effects. Nevertheless, many potent chemotherapy treatments have limited clinical use related to their low bioavailability and their strong adverse effects to healthy tissues and cells. Transport of therapeutics with nanoparticles has demonstrated to be suitable to overcome these limitations. Clinically relevant carrier systems are mostly related to liposomes, lipid nanoparticles (LNP), and polymeric nanoparticles. The most prominent example is Doxil, a liposomal encapsulated doxorubicin formulation which was first approved in 1995 and has shown improved cardiac safety compared to conventional doxorubicin. Since then, multiple other drug delivery approaches were FDA approved, including DaunoXome (liposomal daunorubicin), Myocet (liposomal doxorubicin), Onivyde MM-398 (liposomal irinotecan), and Abraxane (albumin-bound paclitaxel) just to name a few. The success of these delivery vehicles is based on multiple factors, including their high biocompatibility, their capability of transporting both hydrophilic and hydrophobic drugs, and their accumulation in tumor tissue.

Besides improving the safety of encapsulated therapeutics, nanoparticles can be employed to limit peak toxicities through slow release or transport of otherwise unstable compounds such as RNA, which are prone to rapid extracellular degradation by RNases. In 2018, the FDA approved Onpattro, the first short interfering RNA (siRNA) drug that uses lipid nanoparticles as encapsulating and delivery agents. This first successful translation has encouraged researchers to make further use of RNA interference (RNAi) for treating various diseases and developing mRNA-based vaccines.

Although nanotechnology is central in the development of novel therapeutics, multiple key requirements have to be fulfilled to achieve safe and efficient agents. For instance, given the high surface-to-volume ratio of nanoparticles, the surface composition of employed carriers plays a decisive role during cellular interaction and determines the immune response, blood circulation time as well as accumulation in tissues and organs. PEG represents one of the most commonly employed and FDA approved surface modifications and has demonstrated prolonged drug circulation times and avoidance of degradation and clearance through the reticuloendothelial system (RES).

Generally, the payload itself can be versatile, although highest benefits for nanoparticle encapsulated drugs are observed for those that are quickly degraded or cleared, possess a short-half-life, are insoluble or cause potential harm to healthy cells. The latter thereby critically depends on the biocompatibility of the carrier itself and its capability to lower the toxicity of payloads, as shown for liposomal formulations. Moreover, systemic toxicity can be significantly reduced if delivery of the payload to target organs can be enhanced. Currently, most nanotherapeutics rely on passive targeting approaches where accumulation occurs due to the enhanced permeability and retention (EPR) effect. This effect is most effective in neovascularized solid tumor tissues and thus usually requires a sufficient tumor size. Alternatively, active targeting approaches through attachment of cell-specific target units might allow for treatment of diseased cells at an earlier stage (see next chapter).

Additionally, higher local concentrations of therapeutics can be achieved through triggered release systems. While first examples of temperature or ultrasound sensitive liposomes are currently in clinical trials, multiple alternative treatment options have been developed based on the triggered generation of heat or reactive oxygen species (ROS) at the site of interest. One example are negatively charged phosphate coated hafnium oxide nanoparticles (NBTRX3/Hensify) that have recently been FDA approved as radio enhancers for the treatment of squamous cell carcinoma, releasing cell death triggering electrons to their surrounding upon external radiation. Since particles are administered intratumorally, radiotherapeutic effects could be significantly enhanced in tumors while reducing side effects in surrounding healthy tissues. Moreover, thermal ablation of prostate tumors is currently investigated in clinical trials based on PEG coated core–shell silica-gold nanostructures. Heat is generated by the metal shell upon external near infrared (NIR) laser radiation while accumulation in the tumor relies on passive targeting strategies. Heat treatments of tumor tissues, so-called hyperthermia, has been alternatively shown by magnetic nanoparticles.

The ideal nanotherapeutic hence either contains a highly potent but insoluble and/or unstable drug that demonstrates significantly lower toxicity and/or higher stability upon encapsulation into a nanosized matrix or generates a cytotoxic environment upon external stimuli. In both cases, particles should provide a high blood half-life, high biocompatibility and chemical functionality to attach targeting units (Table 1).
Different imaging techniques that have been described in detail and have been developed for a multitude of different dosages, which has so far limited the clinical relevance of theranostics, with the exception of radiotheranostics.

In favor of safety, the carrier composition is still limited to few materials for in vivo diagnostics. For this reason, a large number of materials with outstanding optical, electronic or magnetic properties, including metal nanoparticles, quantum dots, rare-earth doped nanoparticles and carbon nanotubes, have not yet found application for in vivo diagnostics. However, compared to in vivo imaging agents, toxicity and biodegradability play subsidiary roles for in vitro diagnostics and therefore enables the use of the entire material spectrum, including complex composite and hybrid materials like core–shell, hollow, rattle-type or Janus-type particles. Instead, the key requirements in this application field include aspects such as stability, quantum yield, upscaling potential and low manufacturing costs. Employed materials typically change their physicochemical properties with high sensitivity in the presence of analytes, which is usually achieved through surface modification of particles with target-selective molecules. To date, biosensors have been developed for a vast variety of analytes, including cancer cells and extracellular vesicles, nucleic acids, and antibodies and antigens, with the latter being currently particularly relevant for diagnosing COVID-19.

Obtaining a high signal-to-noise ratio remains pivotal to detect even rare aberrant species in biological fluids. Therefore, analyte purification and signal amplification strategies have been developed (e.g., based on the incorporation of magnetic beads that allow for magnetic extraction and concentration). Indeed, integration of nanomaterials into point-of-care (POC) diagnostic devices has been shown to be highly beneficial for diagnosing and monitoring diseases at low costs and short time yet high sensitivity and specificity. 

### What makes a good diagnostic?

Similar to therapeutics, in vivo use of nanomaterial-based imaging agents and diagnostics requires low toxicity, high blood circulation times in combination with efficient clearance and sufficient stability in a biological environment (Table II). Nanodiagnostics have been developed for a multitude of different imaging techniques that have been described in detail in previous reviews.

A look at currently FDA approved agents reveals that compared to therapeutics, the number of diagnostic agents is significantly smaller, which is likely related to differences in market sizes. Interestingly, while organic materials are predominant in therapeutic applications, the strength of nanoimaging agents often relies on inorganic materials. Popular examples are dextran encapsulated superparamagnetic iron oxide nanoparticles such as Feridex, Resovist, and Ferumoxytol. While Feridex and Resovist were approved as contrast agents for magnetic resonance imaging (MRI) of liver lesions, Ferumoxytol has been originally approved for iron supplementation in anemic patients but has received increasing interest as MRI contrast agent (e.g., for pancreatic cancer) (NCT00920023). Moreover, ultrasound (US) contrast agents based on lipid micron-sized bubbles have been FDA approved for cardiovascular imaging. They consist of an inert gas encapsulated by a shell that can either be made up of lipids, phospholipids or proteins and are designed to be injected into the bloodstream with a half-life in the range of minutes. A recent research study even demonstrates the future potential of these contrast agents for transcranial imaging of deep vasculature in the adult human brain at macroscopic resolution.

Recently, a trend toward clinical use of ultrasmall (< 10 nm) yet complex nanoparticles for diagnostics has been observed, which comes with two advantages: (1) renal elimination of the nanoparticles after intravenous administration and (2) prolonged blood circulation times and stability compared to the free contrast agent. One example are Cornell dots, 6–7 nm core–shell hybrid silica particles that possess an organic dye labeled core and radionuclide labeling on the surface and are currently evaluated in clinical trials regarding simultaneous positron emission tomography (PET)–optical imaging. Besides possessing a carrier size with favorable pharmacological properties, Cornell dots are surface decorated with cRGDY peptides for molecular targeting αvβ3 integrin-expressing tumors. Additionally, diagnostic and therapeutic functionalities can be incorporated into one carrier matrix, leading to so-called theranostics. For instance, AGuIX represents a clinically tested theranostic comprised of ultrasmall nanoparticles made of polysiloxane and gadolinium chelates that provide MRI contrast enhancement in combination with radiotherapy of solid tumors. Although image-guided therapies are expected to be of great clinical value, therapy and diagnosis usually require different dosages, which has so far limited the clinical relevance of theranostics, with the exception of radiotheranostics.

In favor of safety, the carrier composition is still limited to few materials for in vivo diagnostics. For this reason, a large number of materials with outstanding optical, electronic or magnetic properties, including metal nanoparticles, quantum dots, rare-earth doped nanoparticles and carbon nanotubes, have not yet found application for in vivo diagnostics. However, compared to in vivo imaging agents, toxicity and biodegradability play subsidiary roles for in vitro diagnostics and therefore enables the use of the entire material spectrum, including complex composite and hybrid materials like core–shell, hollow, rattle-type or Janus-type particles. Instead, the key requirements in this application field include aspects such as stability, quantum yield, upscaling potential and low manufacturing costs. Employed materials typically change their physicochemical properties with high sensitivity in the presence of analytes, which is usually achieved through surface modification of particles with target-selective molecules. To date, biosensors have been developed for a vast variety of analytes, including cancer cells and extracellular vesicles, nucleic acids, and antibodies and antigens, with the latter being currently particularly relevant for diagnosing COVID-19. Obtaining a high signal-to-noise ratio remains pivotal to detect even rare aberrant species in biological fluids. Therefore, analyte purification and signal amplification strategies have been developed (e.g., based on the incorporation of magnetic beads that allow for magnetic extraction and concentration). Indeed, integration of nanomaterials into point-of-care (POC) diagnostic devices has been shown to be highly beneficial for diagnosing and monitoring diseases at low costs and short time yet high sensitivity and specificity.

### Table I. Demands to nanotherapeutics.

| Requirement                  | Feature                        |
|------------------------------|-------------------------------|
| Low toxicity of carrier      | High encapsulation efficiency  |
| Long blood circulation time  | Reduce toxicity of payloads   |
| Timely and proper clearance  | Triggered release of payload  |
| Sufficient stability         | Enhance solubility of payloads |
| Reproducible synthesis       | Protect payload from degradation |

### Table II. Demands to nanodiagnostics.

| Requirement                  | Feature                        |
|------------------------------|-------------------------------|
| Low toxicity of carrier      | Strong contrast enhancement    |
| Long blood circulation time  | High sensitivity              |
| Timely and proper clearance  | High selectivity              |
| Sufficient stability         | Low cost production           |
| Reproducible synthesis       |                               |
What are the current challenges that can be addressed by chemistry and material design?

Aforementioned examples have demonstrated that nanoparticles possess considerable potential for advanced treatments and earlier diagnosis of multiple ailments. However, it remains a major challenge to meet the demanding requirements for their in vivo use such as low toxicity, long blood circulation and adequate clearance time, accumulation at the site of interest, high encapsulation efficiency and storage stability. Diagnostic applications additionally require high signal-to-noise ratios, high specificity and sensitivity and a low cost yet scalable production. Nevertheless, it is important to understand that chemistry and design strategies can help to minimize and even overcome these hurdles (Figure 1). The following sections therefore present some examples on how researchers can efficiently modify nanomaterials in order to enhance their translation potential. Since additional modification steps usually bring synthetical drawbacks in terms of reproducibility, scalability, time investment and cost with them, the actual challenge is to find the sweet spot between complexity and functionality.

Enhance target-specificity of carriers

Independent of the application in diagnostics or therapy, accumulation of nanoparticles in the target organ, in some cases even target cell type, is a key requirement to overcome drawbacks of free drugs and reduce the overall side effects in healthy tissue. While the majority of currently approved nanomedicines rely on the EPR effect and thus passively accumulate, its efficiency is still highly debated given the fact that the effect varies depending on patient’s pathological and physiological characteristics. For cases where the EPR effect is insufficient, active targeting strategies have been developed based on the surface modification of nanoparticles with peptides, polysaccharides, hormones or proteins to enhance their target affinity. These molecules are usually covalently attached to the particle surface and are recognized by receptors or transporters expressed on the cell membrane of target cells. In order to reduce off-target accumulations, it is essential to choose an accessible yet specific or at least overexpressed cellular target. Contrary to the assumption “the more the merrier,” there is evidence that larger numbers of cell-targeting ligands on nanoparticle surfaces are not beneficial for particle–cell interactions, but instead suffer from steric hindrance and undesired receptor clustering. While active targeting has brought significant advantages in vitro, active targeting approaches in vivo are still suffering from low efficacies and might only be of relevance for few conditions such as treating hematological malignancies. In fact, studies have reported that antigen targeting does not significantly increase tumor uptake relative to untargeted particles. The discrepancy between in vitro and in vivo results is likely related to (1) potential opsonization of nanoparticles, (2) carrier instability and degradation, and (3) patient dependent cellular heterogeneity. However, the tumor microenvironment itself can be therapeutically primed to achieve accumulation of nanoparticles. For instance, accumulation of nanoparticles into tumor-associated macrophages (TAMs) can be exploited in a therapeutically beneficial manner, since TAMs have demonstrated to function as a reservoir for nanotherapeutics and allow for their sustained release in the tumor environment. Additionally, short local tumor irradiation can substantially increase the concentration of TAMs at the tumor site through vascular bursting and therefore lead to a remarkable sixfold increase in nanoparticle accumulation at the tumor site.

Visualization of nanoparticle accumulation is very beneficial to predict the therapeutic efficacy of nanomedicine and has been successfully performed through coinjection of nanoparticle-based MRI contrast agents.

Enhance blood circulation time and reduce nonspecific binding

Drug delivery vehicles are commonly administered intravenously and generally require sufficiently long blood circulation times to reach the therapeutic target site. While smaller particles usually circulate longer than larger ones, ultrasmall nanoparticles (<10 nm) are cleared from the blood via the kidneys. However, the majority of nanoformulations are in the range of 10–200 nm and once administered to the blood stream, are quickly covered by circulating proteins, so-called opsonins, which leads to recognition and subsequent elimination by the mononuclear phagocyte system (MPS). Formation of
a protein corona can additionally camouflage target-specific surface ligands resulting in off-target accumulations of the carriers (i.e., in the liver).\textsuperscript{55} Multiple factors influence the protein corona formation and RES elimination, including particle size, charge, and hydrophobicity.\textsuperscript{56} For instance, cationic particles are known to be cleared much faster compared to neutral or slightly negative vehicles.\textsuperscript{57} As demonstrated by FDA approved drug delivery vehicles such as Doxil and Onivyde, PEGylation is a widely accepted method to enhance stealth effects; however, recent clinical research revealed the formation of anti-PEG antibodies in patients.\textsuperscript{58}

Alternatively, zwitterionic molecules have become popular alternatives to obtain nanomaterials with anti-fouling surface yet without immunogenicity.\textsuperscript{59} The neutral charge at physiological pH and high hydration capability in combination with the presence of chemically reactive groups make zwitterionic molecules an outstanding class of materials for the surface coating of nanomaterials.\textsuperscript{60} Moreover, zwitterionic anti-fouling modifications are not only advantageous for drug delivery vehicles, but have also shown to enhance the selectivity and sensitivity of sensors when applied to the sensing surface, ultimately leading to higher signal-to-noise ratios of nanodiagnostic systems.\textsuperscript{61} Finally, coating nanoparticles with cell membranes from autologous leukocytes or red blood cells, or by attaching CD47, an immunosuppressive signaling molecule has been shown to reduce MPS elimination and enhance blood circulation times.\textsuperscript{53}

**Enhance nanoparticle stability and biocompatibility**

One of the major prerequisites for in vivo applications of nanoparticles is their nontoxicity, which usually refers to the carrier itself, not necessarily its payload. The toxicity of nanoparticles is influenced by many factors, including the material itself, its stability in a biological environment, toxicity of potential degradation products, potential accumulation in clearance organs as well as systemic distribution and release of payloads. Moreover, toxicological profiles are highly dependent on the anatomical environment and might thus differ from one location to another making in vitro biocompatibility analyses difficult to translate to in vivo conditions.\textsuperscript{62} The majority of FDA approved nanomedicines is based on organic materials such as lipids, proteins or polymers given their overall high biocompatibility. Since long-term toxicity of nanoparticles is often observed due to accumulation in liver and spleen upon RES clearance, it is desirable to design nanoparticles that degrade over time to smaller particles which are subject to rapid renal elimination. Therefore, biodegradable polymers have found increasing popularity as they are readily excreted from the body upon degradation under physiological conditions. Some of the most prominent examples include, among many others, polymers made from albumin, gelatin, polysugars and poly(lactic-co-glycolic acid) (PLGA).\textsuperscript{63} Toxicity concerns have commonly been raised in terms of inorganic nanoparticles, except for those made from iron oxides, which have shown to be cleared via the liver where released iron is reincorporated in the natural cell metabolism.\textsuperscript{64} In contrast, gold nanoparticles, which have long been seen as inert material have been shown to induce severe immunotoxicity.\textsuperscript{65} Surface coating of these materials with biocompatible molecules is thus a fundamental requirement for their in vivo use.

During their in vivo journey, nanoparticles have to surmount multiple biological barriers and are subjected to pH changes and the presence of potentially interfering enzymes. While these conditions might jeopardize nanoparticle stability, environmental changes can be useful for the controlled degradation and release of loaded functional molecules. Stimuli-responsive delivery vehicles are desired to reduce dose-limiting toxicity as well as to lower toxic side effects induced due to off-target release of payloads.\textsuperscript{66} Most approaches have been described for nanotherapeutics, with more and more reaching clinical trials,\textsuperscript{4} but recent studies suggest that this approach might be likewise interesting for diagnostic applications.\textsuperscript{67}

**Future needs and perspective**

In order to develop nanoformulations with high translational potential, it is essential to understand the needs from clinical perspective, which requires enhanced dialog between researchers and clinicians. In fact, the current COVID-19 pandemic has demonstrated nanomedicine’s adaptability and capability to react quickly to new challenges.\textsuperscript{68} With successful mRNA vaccine deliveries and first FDA approved siRNA loaded carriers, RNAi is likely to become one of the future drivers in nanoparticulate therapeutics. While most nanotherapeutics already demonstrate a distinct reduction in toxicity compared to the free drug, nanomedicine’s promise of being potentially revolutionary is largely dependent on a significant improvement in efficacy.\textsuperscript{69} Advanced surface modifications that allow for cellular targeting as well as the use of composite structures that enable combinations of multiple functionalities into one carrier represent potential solutions. Although huge advancements have already been made during the last decades, the diversity of approved and currently investigated drugs demonstrates that there is no one-fits-all solution that can overcome patient specific heterogeneity. Instead, the solution is based on a range of highly efficient and specific nanoformulations that target a subset of patients and is the basis of our modern personalized medicine.\textsuperscript{70} In this context, the preselection of patients that are most likely to respond to nanomedicine therapies is a key step for the establishment of superior therapies.\textsuperscript{71}

Additionally, many clinically available imaging techniques are still unable to provide single-cell sensitivity and specificity. The high signal-to-noise ratio provided by nanomaterials, however, offers great potential to achieve these goals in the future and allow for in-depth analyses of diseases.\textsuperscript{25,72}

Generally, many of the current challenges on the way to clinical translation can be overcome through smart material design. For instance, multifunctional materials such as the zwitterionic polymers introduced by the Jiang group can provide particle stability, enhanced pharmacokinetics, reduced
immune response, anchor points for further functionalization and even enhanced sensitivity for diagnostic POC sensors.73 Likewise, poly(β-amino esters) represent a new class of multifunctional polymers that can combine biodegradability with stimuli-responsiveness and targeting capability depending on the chemical modification.74,75 Moreover, careful design and combination of materials can even allow for the transport of nanoparticles across highly protected biological barriers such as the blood–brain-barrier and provide hope for future treatments of nervous system related diseases.76 In this context, active targeting approaches are not only limited to ligand design but can also rely on noninvasive magnetic targeting strategies as recently demonstrated for magnetoelectric nanoparticles which could be successfully relocated to the brain upon intranasal administration using external magnetic fields.77 The power of chemistry is additionally demonstrated through combinatorial chemical libraries as provided by the Anderson group on alginate hydrogels and demonstrates its predictive screening capability to determine derivatives with mitigated foreign body response.78 In the end, the development of chemical protocols for the surface modification of nanoparticles will be essential to guarantee reproducibility of designed nanomedicines. 

With the potential of nanotechnology in medicine being far from exhausted, the number of clinically approved nanoformulations is expected to increase further during the next years. This trend can be supported by innovation-driven research through design of multifunctional smart components that lead to a balanced equilibrium between particle complexity and functionality.

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References

1. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19 (2021)
2. Nature Nanotechnology 15, 963 (2020)
3. L. Zhang, F.X. Gu, J.M. Chan, A.Z. Wang, R.S. Langer, O.C. Farokhzad, A.C. Herr, A. Gronchi, L. Mangel, T. Sy-Torin, P. Hohenberger, T. de Baire, A. Le Cesne, S. Helfre, E. Saada-Bouzid, A. Borkowska, R. Anghel, A. Co, M. Gebhart, G. Kantor, A. Montero, H.H. Loong, R. Vérès, L. Lapeire, S. Dema, G. Kacso, A. Lesten, M. Houang, Z. Papai, V. Servois, E. Wadelmann, J. Buser, A.J. Lazar, J.M.G. Bowée, C. Pléchoux, Z. Popa, P. Wiertz, M. Witzigmann, J.A. Kulkarni, R. van der Meel, P.R. Cullis, U. Wiesner, H. Kalaigian, H. Schöder, H.W. Strauss, S.M. Larson, U. Wiesner, M.S. Bradbury, A.M. Humm, M. Gönen, H. Schöder, H.W. Strauss, S.M. Larson, U. Wiesner, M.S. Bradbury, Sci. Transl. Med. 6, 260ra149 (2014)
4. F. Lux, V.L. Tran, E. Thomas, S. Dufort, F. Rossetti, M. Martinelli, C. Truillet, T. Doussineau, G. Bort, F. Denat, F. Boscetti, G. Angelovski, A. Detappe, Y. Crémieux, Y. Nigmet, B.-T. Doan, B. Larnat, S. Meriaux, E. Barbier, S. Roux, P. Fries, A. Müller, M.-C. Abadjan, J. Buser, P. Carreaux, J. Balosso, M. Evans, J. Sidi-Boumedine, M. Janier, K. Butterworth, S. McMahon, A. Allouch, J.-L. Perfettini, C. Chargari, E. Deutsch, G. Le Duc, O. Tillement, S. Roux, B. Larrat, S. Meriaux, E. Barbier, S. Roux, P. Fries, A. Müller, M.-C. Abadjan, J. Buser, P. Carreaux, J. Balosso, M. Evans, J. Sidi-Boumedine, M. Janier, K. Butterworth, S. McMahon, A. Allouch, J.-L. Perfettini, C. Chargari, E. Deutsch, G. Le Duc, O. Tillement, Br. J. Radiol. 82, 20180365 (2019)
5. J.W. Jokors, S.S. Gambhir, Acc. Chem. Res. 44, 1050 (2011)
6. K. Herrmann, M. Schweiger, J.S. Lewis, S.B. Solomon, B.J. McNeil, M. Baumann, S.S. Gambhir, H. Hricak, R. Weissleder, Lancet Oncol. 21, e146 (2020)
7. D. Kim, K. Shin, S.G. Kwon, T. Hyeon, Adv. Mater. 30, e1802309 (2019)
8. H.M. Azzazy, M.M. Mansour, Br. J. Radiol. 82, 1584 (2006)
9. D. Kim, K. Shin, S.G. Kwon, T. Hyeon, Adv. Mater. 30, e1802309 (2019)
10. M.-T. Aloy, D. Ardail, C. Rodriguez-Lafrasse, E. Porcel, S. Lacombe, R. Berbeco, A. Allouch, J.-L. Perfettini, C. Chargari, E. Deutsch, G. Le Duc, O. Tillement, Br. J. Radiol. 82, 20180365 (2019)
11. J.W. Jokors, S.S. Gambhir, Acc. Chem. Res. 44, 1050 (2011)
12. K. Herrmann, M. Schweiger, J.S. Lewis, S.B. Solomon, B.J. McNeil, M. Baumann, S.S. Gambhir, H. Hricak, R. Weissleder, Lancet Oncol. 21, e146 (2020)
13. D. Kim, K. Shin, S.G. Kwon, T. Hyeon, Adv. Mater. 30, e1802309 (2019)
Optimizing Nanoparticle Design and Surface Modification Toward Clinical Translation

49. M.M. Schmidt, K.D. Wittrup, *Mol. Cancer Ther.* **8**, 2861 (2009)
50. M.A. Miller, Y.R. Zheng, S. Gadde, C. Pfirshcike, H. Zope, C. Engblom, R.H. Kohler, Y. Iwas moto, K.S. Yang, B. Askevold, N. Kolishetti, M. Pittet, S.J. Lippard, O.C. Farokhzad, R. Weissleder, *Nat. Commun.* **6**, 8692 (2015)
51. M.A. Miller, R. Chandra, M.F. Cuccarese, C. Pfirshcike, C. Engblom, S. Stapleton, U. Adhikary, R.H. Kohler, J.F. Mohan, M.J. Pittet, R. Weissleder, *Sci. Transl. Med.* **9**, eaal0225 (2017)
52. M.A. Miller, R. Weissleder, *Nat. Rev. Cancer* **17**, 399 (2017)
53. S. Jiang, Z. Cao, *Adv. Mater.* **22**, 920 (2010)
54. Y. Liu, Y. Li, D. Keskin, L. Shi, *Adv. Healthc. Mater.* **8**, e1801359 (2019)
55. D.M. Lynn, R. Langer, *J. Am. Chem. Soc.* **122**, 101 (2000)
56. E.A. Wyatt, M.E. Davis, *Mol. Pharm.* **17**, 717 (2020)
57. M. Pardo, E.R. Roberts, K. Pimentel, Y.A. Yildirim, B. Navarrete, P. Wang, E. Zhang, P. Liang, S. Khizroev, *Nanomedicine* **32**, 102337 (2020)
58. A.J. Vegas, O. Veiseh, J.C. Doloff, M. Ma, B.R. Bacon, C.C. Compton, D.L. White, P. Jacobs, J. Lewis, *Adv. Healthc. Mater.* **8**, 166 (2020)
59. G.T. Kozma, T. Shimizu, T. Ishida, J. Szebeni, *Adv. Drug Deliv. Rev.* **154–155**, 163 (2020)
60. C. Sanchez-Cano, M. Carril, *Int. J. Mol. Sci.* **21**, 1007 (2020)
61. G. Level, J. Zhang, J. Brown, O. Hammond, B. Hannigan, L. Stella, P. Nockemann, M. Blesic, *J. Colloid Interface Sci.* **562**, 391 (2020)
62. Y. Hu, B. Liang, L. Fang, G. Ma, G. Yang, Q. Zhu, S. Chen, X. Ye, *Langmuir* **32**, 11763 (2016)
63. S. Naahidi, M. Jafari, F. Edalat, K. Raymond, A. Khademhosseini, P. Chen, *J. Control. Release* **166**, 182 (2013)
64. R. Rampado, S. Crotti, P. Caliceti, S. Pucciarelli, M. Agostini, *Front. Bioeng. Biotechnol.* **8**, 166 (2020)
65. E. Blanco, H. Shen, M. Ferrari, *Nat. Biotechnol.* **33**, 941 (2015)
66. T.U. Wani, S.N. Raza, N.A. Khan, *Polym. Bull.* **77**, 3865 (2020)
67. Y.N. Zhang, W. Poon, A.J. Tavares, I.D. McGilvray, W.C.W. Chan, *J. Control. Release* **240**, 332 (2016)
68. V.H. Nguyen, B.J. Lee, *Int. J. Nanomed.* **12**, 3137 (2017)
69. J.M. Caster, A.N. Patel, T. Zhang, A. Wang, *Nanomed. Nanobiotechnol.* **9**, e1416 (2017)
70. M.J. Mitchell, M.M. Billingsley, R.M. Haley, M.E. Wechsler, N.A. Peppas, R. Langer, *Nat. Rev. Drug Discov.* **20**, 101 (2021)
71. J.I. Hare, T. Lammers, M.B. Ashford, S. Puri, G. Storm, S.T. Barry, *Adv. Drug Deliv. Rev.* **188**, 25 (2017)
72. M.A. Miller, R. Weissleder, *Nat. Rev. Cancer* **17**, 399 (2017)
73. S. Jiang, Z. Cao, *Adv. Mater.* **22**, 920 (2010)
74. Y. Iwamoto, K.S. Yang, B. Askevold, N. Kolishetti, M.J. Pittet, O.C. Farokhzad, R. Weissleder, *Sci. Transl. Med.* **7**, 314ra183 (2015)
75. J.I. Hare, T. Lammers, M.B. Ashford, S. Puri, G. Storm, S.T. Barry, *Adv. Drug Deliv. Rev.* **108**, 25 (2017)
76. K.S. Soppimath, T.M. Aminabhavi, A.R. Kulkarni, W.E. Rudzinski, *J. Control. Release* **70**, 1 (2001)
77. R. Weissleder, D.D. Stark, B.L. Engelstad, B.R. Bacon, C.C. Compton, D.L. White, P. Jacobs, J. Lewis, *Adv. Healthc. Mater.* **8**, e1801359 (2019)
78. D.M. Lynn, R. Langer, *J. Am. Chem. Soc.* **122**, 10761 (2000)
79. E.A. Wyatt, M.E. Davis, *Mol. Pharm.* **17**, 717 (2020)
80. A.J. Vegas, O. Veiseh, J.C. Doloff, M. Ma, H.H. Tam, K. Bratlie, J. Li, A.R. Bader, E. Langan, K. Oleijnik, P. Fenton, J.W. Kang, J. Hollister-Locke, M.A. Bochenek, A. Chiu, S. Siebert, T. Tang, S. Jhunjhunwala, S. Aresta-Dasilva, N. Dholakia, R. Thakrar, T. Vietti, M. Chen, J. Cohen, K. Sinisikowicz, M. Qi, J. McGarrigle, A.C. Graham, S. Lyle, D.M. Harlan, D.L. Greiner, J. Oberholzer, G.C. Weir, R. Langer, D.G. Anderson, *Nat. Biotechnol.* **34**, 345 (2016)

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