Critical Considerations on the Clinical Translation of Upconversion Nanoparticles (UCNPs): Recommendations from the European Upconversion Network (COST Action CM1403)

Helena Oliveira,* Artur Bednarkiewicz, Andreas Falk, Eleonore Fröhlich, Darja Lišjak, Adriele Prina-Mello, Susanne Resch, Christa Schimpel, Ivana Vinković Vrček, Edyta Wysokińska, and Hans H. Gorris* © 2018 The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim DOI: 10.1002/adhm.201801233

1. Introduction

Nanotechnology is considered as one of the key-enabling technologies (KETs) that has brought fundamental research on nanomaterials (NMs) to applications in industry, medicine, and pharmacology. Despite numerous known advantages of NMs for biomedical use, growing concerns have been expressed on their potential adverse effects on human and animal health, as well as the environment. With the advent of nanoenabled products, their toxicological evaluation has become critical, as many NMs find applications in biomedical and healthcare settings such as therapeutic, diagnostic, or combined theranostic systems. Such applications decisively depend on biocompatible products without or with negligible hazard for human cells, tissues, and organs.

Lanthanide (Ln)-doped crystalline nanoparticles are an emerging type of NMs that exhibit many useful properties for biomedical applications. The unique photoluminescent properties of upconversion nanoparticles (UCNPs) have attracted worldwide research interest and inspired many bioanalytical applications. The anti-Stokes emission with long luminescence lifetimes, narrow and multiple absorption and emission bands, and excellent photostability enable background-free and multiplexed detection in deep tissues. So far, however, in vitro and in vivo applications of UCNPs are restricted to the laboratory use due to safety concerns. Possible harmful effects may originate from the chemical composition but also from the small size of UCNPs. Potential end users must rely on well-founded safety data. Thus, a risk to benefit assessment of the envisioned combined therapeutic and diagnostic (“theranostic”) applications is fundamentally important to bridge the translational gap between laboratory and clinics. The COST Action CM1403 “The European Upconversion Network—From the Design of Photon-Upconverting Nanomaterials to Biomedical Applications” integrates research on UCNPs ranging from fundamental materials synthesis and research, detection instrumentation, biofunctionalization, and bioassay development to toxicity testing. Such an interdisciplinary approach is necessary for a better and safer theranostic use of UCNPs. Here, the status of nanotoxicity research on UCNPs is compared to other nanomaterials, and routes for the translation of UCNPs into clinical applications are delineated.
applications.\[^{[1,2]}\] In particular, their anti-Stokes luminescence under near-infrared (NIR) excitation, photostability, and long luminescence lifetimes have attracted wide attention. Translation of upconversion nanoparticles (UCNPs), however, faces similar challenges as other NMs. These challenges include (1) a reproducible synthesis, (2) full control over the NP size and shape, (3) the preparation of a biocompatible surface architecture with biorecognition elements for labeling target sites, (4) light activation, (5) theranostics, and drug delivery as well as (6) instruments for low background optical detection and imaging.\[^{[3]}\] We have established the COST Action CM1403 “The European Upconversion Network—From the Design of Photon-Upconverting Nano-materials to Biomedical Applications” as an interdisciplinary research network to address (1) materials research and photophysical characterization, (2) surface functionalization, (3) instrument development, (4) assays, sensors, and imaging, and (5) toxicity.

Upconversion in Ln-doped crystals and glasses has already been known for decades\[^{[4]}\] and has found many different applications in physics and technology, such as solid-state lasers, displays, phosphors, and anti-counterfeiting. The unique luminescent properties of Ln-doped crystals originate from the optical transitions and properties of Ln ions—i.e., the forbidden transition between optically active $f$-$f$ electrons on the 4f shell, which is protected from chemical environment by electrons of higher 5s and 5p shells. These fundamental aspects determine crystal field splitting of the multiplets, multiple spectrally narrow absorption and emission bands and long luminescence lifetimes (micro-to-milliseconds). These photophysical features lead to an extremely photostable multicolar emission.

2. Advantages of UCNPs for Biomedical Applications

A significant breakthrough for the wider application of Ln-doped crystals in the field of nanotechnology and biomedicine was the development of new bottom-up syntheses that yield well-defined UCNPs with tunable size.\[^{[5]}\] Their first applications in bioassays followed quickly and initiated a worldwide growing interest in using UCNPs for biomedicine (Figure 1).\[^{[6-9]}\] Various companies are testing the suitability of UCNPs as a detection label in their specific applications.

Organic fluorescent labels are typically excited by short wavelength light (i.e., in the UV, blue and green), which simultaneously excites many endogenous fluorophores of biological origin (the so-called autofluorescence) due to their broadband and overlapping absorption spectra. Additionally, damage can occur to cellular biomolecules (e.g., DNA, proteins), cells or tissues by photochemical reactions (e.g., radical generation) originating from short-wavelength photoexcitation. Thus, the most advantageous feature of UCNPs is the capability to operate (i.e., they can be photoexcited and emit) in the NIR spectral region ranging between 650 and 1000 nm, as well as in the II\[^{[10]}\] and III\[^{[11]}\] optical windows, where endogenous chromophores, tissues, or bioanalytes neither absorb nor autofluoresce and light scattering is strongly reduced. For these reasons, many systems ranging from single cells up to small animals and in cellular nanothermometry show a high signal-to-noise ratio as well as enhanced imaging contrast.\[^{[10]}\]

Conventional UCNPs are photoexcited at 980 nm based on Yb$^{3+}$ sensitizers used for energy upconversion to other luminescent Ln$^{3+}$ ions. Water molecules, however, also absorb 980 nm light, which leads to biological sample heating. Therefore, novel core–shell UCNPs architectures have been developed that use Nd$^{3+}$ ions as a sensitizer because it absorbs light at 808 nm.\[^{[11-14]}\] where the absorption coefficient of water is over 20-fold smaller compared to 980 nm light. Additionally, UCNPs have been developed that can be excited efficiently by 745 or 1532 nm laser lines. These alternative excitation wavelengths reduce the sample heating, improve the light penetration depth and enhance the photobiocompatibility.\[^{[11]}\] The multiple emission lines have been employed to design specific UCNPs signatures that can be spectrally resolved. In this way, different labels can be detected simultaneously for multiplexed applications.\[^{[13]}\] Further advantages relate to the flexible Ln-dopant composition of UCNPs. By adjusting the material composition, multiple functionalities can be obtained in a single type
of UCNP for multimodal imaging in vivo including magnetic resonance imaging, computed tomography, and positron emission tomography.[16]

UCNPs have also attracted considerable attention for photodynamic therapy (PDT) in deep tissues.[6] Under NIR excitation, UCNPs can emit UV–vis light, which activates surface-bound photosensitizers via resonance energy transfer. The photosensitizers generate reactive oxygen species (ROS) that kill cancer cells in a locoregional area. Several studies have demonstrated the efficiency of UCNP-based PDT against cancer in vitro and in vivo.[17–21] For instance, in vivo studies showed a significant reduction in melanoma growth using 980 nm excited FA-PEG-UCNPs and a synergism between merocyanine 540 (MC540) and zinc phthalocyanine as a photosensitizer.[19] Moreover, the combined therapy based on doxorubicin-induced chemotherapy and Ce6-triggered PDT exhibited a high therapeutic efficacy in vitro.[22] Such applications are promising to further develop UCNP-enabled medicines, medical devices and in vitro diagnostics.

In addition to accidental contacts with the human body, the intentional injection of UCNPs leads to a direct interaction with human physiological fluids, cells, and tissues. For this reason, the scientific community jointly with the research, development, and innovation (R&D&I) community are responsible not only to evaluate the specific biomedical gains and efficiency of UCNPs, but also to determine and quantify their safety and possible risks for both human health and the environment.

3. Regulatory Requirements for Clinical Translation of Nanomaterials

Only a limited number of nanoproducts have entered routine clinical application because there is no or only a limited benefit-to-risk ratio compared to the existing standard of care (SoC). Safety concerns and socioeconomic uncertainties strongly impede translational activities in nanomedicine.[23] Current concepts for the safety evaluation are not sufficient to efficiently manage the multidisciplinary nature of nanotechnology and its associated risks. The European REACH (registration, evaluation, authorization, and restriction of chemicals) legislation defines the estimation and characterization of risks as the ratio of exposure levels to hazard levels (risk characterization ratio, RCR) (https://echa.europa.eu/regulations/reach/legislation). A quantitative risk assessment of NMs, however, is not feasible.
because standardized, validated and specific methods providing quantitative data and limits on human (worker, consumer, patients) or environmental exposure have not been specified, yet. A large number of potential nanoenabled products fail because the lack of physicochemical characterization leads to contradictory results on the efficacy, biocompatibility, product sterility, and safety.

From the regulatory and industrial point of view, the efficacy, quality, and safety (EQS) for end-users are critical aspects when a new biomedical application of UCNPs is designed. It is recommended to engage with the national regulatory authorities as soon as the intellectual property rights for the biomedical application have been secured to meet the strictest regulatory directives for the commercialization of UCNPs. A product classification during the early exploratory phase can eliminate possible risks in advance. Risk-mitigation approaches include risk assessment, life cycle analysis, and risk management. The factors and conditions that most strongly influence the EQS evaluation of NMs for biomedicine are still uncertain. Therefore, robust scientific data on their physicochemical properties, transformation patterns, and the nano–bio interactions under different biological and (pre)clinical conditions are necessary to support the key benefits of the nanoenabled product compared to the possible risks.

4. Analytical Techniques for the EQS Evaluation of UCNPs

Due to their nanospecific properties, UCNPs, like all other NMs, are subject to a plethora of possible interactions and transformation patterns that affect all stages of their life cycle including various biological environments, storage, and waste treatment. Thus, UCNPs must be characterized with respect to (1) their physicochemical properties, (2) their interaction with the biological environment, and (3) possible toxic interactions in vitro and in vivo. The characterization should include batch-to-batch variability, batch aging, dispersibility, biomolecular corona formation, exchange of surface compounds, dissolution, and their propensity to undergo redox reactions. Table 1 provides an overview of specific techniques to investigate the physicochemical properties of UCNPs.

The interactions of UCNPs at the nano–bio interface are dominated by a long-lived “hard protein corona” and a short-lived “soft protein corona,” which cover the surface of NPs. The corona may strongly influence the hydrodynamic size, electrophoretic mobility, and surface composition of NMs, but its biological role is still poorly understood. The adsorbed biomolecules, such as proteins, may also enable UCNPs to enter cells through the so-called “Trojan horse” effect. On the other hand, the “Trojan horse” effect is important for bioapplications of UCNPs as a drug and/or gene delivery system. A list of techniques to analyze interactions of UCNPs at the nano–bio interface is provided in Table 2.

Biological interactions and biotransformations may strongly affect the absorption, distribution, metabolism, and excretion pattern, mechanisms of toxicity, interactions with the immune system, autophagy activities, and interference with reproductive functions. The safety evaluation should take into account all expected exposure routes when interacting with biofluids, cells, and tissues, as well as hazard and biokinetic data. It is further necessary to consider environmental fate indicators (e.g., partitioning coefficients, persistence) and reactivity indicators (e.g., surface chemistry).

Table 1. Experimental techniques for evaluating the physicochemical properties and stability of UCNPs.

| Analytical technique | Information on                                    |
|---------------------|--------------------------------------------------|
| Dynamic light scattering (DLS) | Hydrodynamic diameter |
| Analytical ultracentrifugation (AUC) | Hydrodynamic diameter and surface charge |
| Nanoparticle tracking analysis (NTA) | Surface charge |
| Agarose gel electrophoresis | Size, shape, crystal structure, and material composition |
| Zeta potential measurement | Size and surface shape |
| Transmission electron microscopy (TEM) | Crystal size and structure |
| Scanning electron microscopy (SEM) | Surface chemistry |
| Atomic force microscopy (AFM) | Specific surface area |
| X-ray diffraction (XRD) | Concentration of dissolved ions and dissolution of UCNPs |
| X-ray photoelectron spectroscopy (XPS) | Dissolution of NMs or energy transfer (FRET) to organic fluorophores (important for biosensing, presence of quenching components, photosensitizers) |
| Time of flight secondary ion mass spectrometry (ToF SIMS) | |
| transmission electron microscopy | |
| X-ray fluorescence spectroscopy | |
| Luminescence spectroscopy | |
| Luminescence spectroscopy | |
| Mass spectrometry (MS) | |
| Atomic absorption spectroscopy | |
| Voltammetry | |
| Isothermal calorimetry | |
| Isothermal calorimetry | |
| Quartz crystal microbalance (QCM) | |
| Electric cell-substrate impedance sensing (ECIS) | |
| Atomic force microscopy (AFM) | |
| Separation techniques (capillary electrophoresis, liquid chromatography, flow-field fractionation, gel electrophoresis) | |
| Hyphenated to speciation analysis (DAD, UV–vis, MS/MS, ICP-MS, DLS, NTA, AUC) | |

Table 2. Experimental techniques for evaluating the interactions of UCNPs with the biological environment.

| Analytical technique | Information on                                    |
|---------------------|--------------------------------------------------|
| Microscopy and spectroscopy (fluorescence, UV–vis, circular dichroism, Raman, NMR) | Interactions with the chemical environment or cells. Spectral changes may result from the interactions with biomolecules. |
| Isothermal calorimetry | Binding constants and thermodynamic parameters |
| Quartz crystal microbalance (QCM) | Interactions result in mass changes |
| Electric cell-substrate impedance sensing (ECIS) | Interaction with cells |
| Atomic force microscopy (AFM) | Adhesion forces and surface free energy during the biomolecular corona formation |
| Separation techniques (capillary electrophoresis, liquid chromatography, flow-field fractionation, gel electrophoresis) | Nano–bio interactions, purity, biomolecular corona formation |
| Hyphenated to speciation analysis (DAD, UV–vis, MS/MS, ICP-MS, DLS, NTA, AUC) | |
These considerations raise critical questions regarding the most suitable in vitro or in vivo testing model or assay. Presently, the primary steps for the safety assessment of UCNPs are in vitro testing strategies including (1) cell viability and proliferation assays and mechanistic assays for the identification of ROS, apoptosis, necrosis, DNA damage, (2) microscopic evaluation of uptake and intracellular localization (SEM, TEM, AFM, confocal microscopy), (3) gene expression analysis, (4) high-throughput systems, (5) in vitro hemolysis, and (6) genotoxicity.[39] While in vitro model systems provide a rapid and effective means to establish concentration-dependent effects and thresholds in cells, they are not suitable to identify effects upon repeated or long-term exposure.[35]

Developers and regulators rather rely on a set of endpoints obtained from commercial bioassays in order to assess the safety of UCNPs and to get information how UCNPs interact with living cells. Compared to soluble chemicals, however, it is more challenging to test the safety and toxicity of UCNPs due to their specific properties such as size, density, composition, surface functionalities, solubility, and aggregation. Many testing methods need to be adapted to account for these specific properties. The EQS evaluation of UCNPs further relies on metrology and reference materials. For example, metrology requires the definition of a dosing system for NMs. While the effect of two chemicals such as pharmaceuticals or toxins can be compared by using the same number of molecules per volume (molar concentration), a dose definition of NMs is much more difficult because the size, mass, and number of NMs per volume can differ for each batch. Another metrological problem originates from the experimental setup during in vitro experiments. Typically, cells grow as a monolayer at the bottom of the experimental chamber. UCNPs added to the culture media may not be evenly distributed in volume, but rather sediment at the bottom of the wells and cover the cells. As the volume of the culture medium can change between the assays, the actual dose may change, too. Furthermore, correlation between the density of the cell culture (confluence) and the actual number of UCNPs per cell density is an important metrology-related shortcoming of in vitro testing that may strongly affect the conclusions and make it difficult to compare the effect of the same UCNPs concentration in different assays or the results of different studies. There is also the need to assess any possible interference of UCNPs—or their biotransformation products after biological interactions—with the assay system to avoid false positive or false negative results. Such interferences may include optical interactions due to the luminescence of UCNPs, chemical reactions between UCNPs and assay compounds, and adsorption of assay molecules to the nanoparticle surface.[40,41]

Finally, many cytotoxicity tests are performed on cells grown in cell culture (in vitro). Most cell lines, however, have been generated either by immortalizing cells via virus transfection or by searching for spontaneously immortalized normal or tumor cells. It is not possible to extrapolate the nanosafety data obtained from tumor cell lines directly to other cells and tissues because immortalized cells are in a nonphysiological state. As oncogenesis affects cell functions, the endocytosis may be affected too, leading to increased or decreased uptake of UCNPs and associated cytotoxicity. Cell lines maintain cell-specific functions to a variable extent. Higher than normal proliferation rates and cell death resistance may affect the reaction to UCNPs. Primary cells, on the other hand, may mimic the cell-specific phenotype in a better way. The main problems in using them for cytotoxicity screening consist in donor-dependent, variable quality of the isolated cells and the difficulty to maintain them for a prolonged time to perform a series of assays. The isolation of primary cells from human blood is relatively easy and may be a better option for assessing toxic effects than animal models.

5. Studies on the Safety of UCNPs

We surveyed a large number of research studies that address the safety of UCNPs (Figure 2). From 1811 publications on UCNPs designed for biomedical applications, almost a third investigated the efficacy and quality of UCNPs, while only 18% of papers evaluated the toxicity or safety of these UCNPs. Studies performed so far indicate negligible or low toxicity of UCNPs in vitro, in cells and tissues.[42,43] It is, however, difficult to compare the results of different safety studies since they depend on the nature of the UCNP coating, the cell model and the mode of exposure.[44] Furthermore, most studies were performed only over limited ranges of concentrations and exposure times and did not take into account degradation and transformation products of UCNPs in the biochemical environment.[38,43]

Transformations of UCNPs may result from a myriad of processes, including aggregation, dissolution, exchange of surface compounds, and interactions with biomolecules. For example, the chemical decomposition (dissolution) of UCNPs releases Ln$^{3+}$ ions, which may lead to oxidative stress after cellular uptake.[43,45–49] Oxidative stress is a consequence of a redox disequilibrium, in which the production of ROS overwhelms the antioxidant defense capacity of the cell, thereby leading to adverse biological consequences such as damage to DNA, proteins, and lipids. This will subsequently affect cell proliferation, apoptosis, lipid peroxidation, or mutagenicity.[32,33] Oxidative stress can be determined (1) directly by measuring ROS levels, (2) by measuring the damage to biomolecules, or (3) by measuring the level of antioxidant enzymes and other molecules that serve to counterbalance the generated ROS.

Toxicity tests on Ln$^{3+}$ oxides indicated that the dissolution of UCNPs in lysosomal compartments released Ln$^{3+}$ ions. Ln$^{3+}$ precipitated with cellular phosphates and formed needle-like structures, which showed toxic effects.[43,50] Furthermore, the common codopant gadolinium (Gd$^{3+}$) has been linked to toxic effects such as nephrogenic systemic fibrosis.[50] Suitable coatings that prevent direct contact between the UCNPs surface and the medium can avoid such chemical threats. Surface coatings should also provide colloidal stability and biocompatibility. Good and promising examples are block copolymers and phosphonates with multiple phosphonic groups.[51,52] Inorganic shells can be an alternative solution to prevent dissolution of UCNPs.[53] A silica coating may be used for this purpose, but it cannot completely inhibit the UCNPs dissolution due to the relative porosity of the silica shell.[54] A fluoride shell (e.g., CaF$_2$)
on the NaYF₄-based core UCNPs has also been proposed, but the shell may be partially dissolved. Li et al. suggested that the Ln³⁺ phosphate coating could prevent toxic effects due to the very low solubility of Ln³⁺ phosphate salts under physiological conditions. The design of an optimum protective coating should take into account the application, the optical performance, biocompatibility, and safety of UCNPs.

Data on the EQS of UCNPs in vivo are scarce but inevitable prior to any clinical use. Recently, toxicity assessments of UCNPs have been carried out in Caenorhabditis elegans and zebrafish. C. elegans incubated with NaYF₄:Yb,Tm nanocrystals showed normal ingestion behavior. Moreover, protein expression, life span, egg production, egg viability, and growth rate of C. elegans fed with UCNPs have almost the same pattern and ratio like the untreated control. Zebrafish embryos treated with β-NaYF₄:Ce,Tb showed no phenotypic abnormalities when treated with concentration up to $0.5 \times 10^{-9}$ m. At this concentration also the morphology of the heart was similar as the untreated control group.

Similar results were obtained by Wang et al. in zebrafish embryos treated with LaF₃:Yb,Er@SiO₂, where no malformations were found at concentrations below 200 µg mL⁻¹. The biosafety of UCNPs was also assessed in vivo by introducing UCNP-treated bean sprouts into the stomach of mice. Single-photon emission computed tomography imaging confirmed excretion of UCNPs with the feces (without adsorption or retention) and hematoxylin eosin staining indicated no detectable toxic effects in the main organs of UCNP-treated mice.

6. Recommendations for the EQS Evaluation of UCNPs from the European Upconversion Network

Since conventional methods can only provide an initial EQS assessment of UCNPs, customized protocols, and validated analytical techniques are required that comply with the demands of metrology. Controls and reference materials must be in line with biomedical applications and commercial applications in order to bridge the translational gap of UCNPs. The general need for a standardized assessment of NMs has been recognized all over the world. For example, the Nanotechnology Characterization Laboratory in the US (NCI-NCL) (https://ncl.cancer.gov/) and the European Union Nanomedicine Characterization Laboratory (EUNCL) (http://www.euncl.eu/) provide state-of-the-art physical, chemical and biological characterization of NMs at the preclinical stage in order to accelerate the process of clinical translation. In the future, the safety evaluation of UCNPs should be addressed on a global level (e.g., US-EU-Communities of Research, EU-Asia dialogue on NanoSafety) to enable knowledge transfer and drive further developments in this field.

The European Upconversion Network (COST Action CM1403) has been established to define and develop innovative techniques and approaches for the characterization of UCNPs. For example, recently the luminescent properties of the same batch of UCNPs were compared in a round robin test. The shortcomings of conventional in vitro and in vivo testing systems that do not allow for comparing the effect of the same UCNPs concentration in different assays have been discussed in Section 4. Therefore, the partners of the European Upconversion Network have collaborated to identify suitable assays taking into account the selection of cell and tissue models as well as quality controls. These efforts are in line with other European councils, infrastructures, and networks that are focused on the characterization and safety evaluation of NMs. For example, the European Materials Characterisation Council (EMCC, www.characterisation.eu), the EU-funded Horizon 2020 project NanoCommons and the working group on data management of the EU NanoSafety Cluster develop databases and infrastructures for the EQS evaluation of NMs and offer...
services to make nanosafety knowledge widely available. These initiatives connect and integrate data from individual EU-funded nanosafety projects (e.g., BIORIMA, ITS nano, Go4Nano, NanoREG, NanoREG II, ProSafe NanoSafe2, Nanosmile, EC4SafeNano) as well as nanomaterial projects (e.g., NanoFASE, MAGPRO²LIFE, NANOVALID). Promoting transparency of NM safety aspects among developers, end-users, but also the general public, is essential for the translation of NMs. These joint efforts aim to provide guidelines to pass through the bottlenecks of translation for each specific type of application.[62]

Based on the extensive knowledge from various European initiatives, projects and networks, the COST Action CM1403 recommends a multimethod approach for developing UCNP-based applications from the early phases of research (Tier 1) to the final product (Tier 3). Since the large surface-to-volume ratio makes the behavior of NMs unpredictable, it is necessary to evaluate UCNP dispersions in biofluids such as blood plasma. Once discharged into the biosystem, UCNPs are subject to alterations through biotransformation and interactions with various biomolecules.[32,33,35] Transformations in vitro or in vivo depend on pH, ionic strength, thermodynamic activity, concentration, and the redox conditions of the biological media. Factors such as natural colloids, biomolecules, sunlight, and oxidants/reductants also determine the behavior of UCNPs in real biological environments, likely resulting in deviations from in vitro assays.[63] The tools for the EQS evaluation shown in Figure 3 should define the critical physicochemical properties, possible biological interactions, and the mode of interaction in vivo over relevant exposure times and closely follow the course of product development.

Such a prioritized EQS evaluation should identify the most important safety issues of UCNP-based biomedical applications on human health including all dynamic aspect of exposure and pharmacokinetics. Furthermore, the preclinical in vivo EQS evaluation should be carefully planned for each particular theranostic application.[28] The EQS evaluation should consider all applications in theranostics, sensing, whole-animal imaging, bioassays, and tumor targeting. The path for the development and applicability of UCNPs for the different types and modalities of applications can be selected based on the go/no-go decision tree shown in Figure 4, which may strongly reduce the costs and accelerate the translation of UCNPs.[64]

The European Upconversion Network has strived to solve the needs for well-established and validated methodologies (specific or standardized), nanospecific metrology, and UCNP reference materials for physicochemical and biological characterization, as well as for preclinical and clinical assessment of UCNPs. We will focus future collaborative activities on (1) the time- and cost-effective identification of physicochemical and biological properties that are critical for theranostics, (2) establishing harmonized and validated standards and methodologies for the EQS evaluation of novel UCNPs products, and (3) supporting the infrastructure for the translation of UCNPs into clinical applications. Additional funding for these investigations, however, will be needed to bring benefit to patients and thus to society.

In conclusion, it is essential to guide the development of new UCNP-based biomedical applications by time- and cost-efficient strategies and evaluate the EQS of UCNPs in real biological environments. All these efforts will bridge the translational gap between research laboratories and medical and biomedical...
setups and pave the way for a better and safer theranostic use of UCNPs.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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