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Review Article

Advances in nanotechnology for early cancer diagnosis: emerging nanoplatforms and multimodal imaging approaches

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Abstract: Nanotechnology has revolutionized the field of cancer diagnosis, by enabling the development of innovative platforms for diagnosis that offer the potential to identify malignancies at an early stage, and they possess an unprecedented degree of sensitivity and specificity. This review focuses on the combination of nanotechnology and different imaging modality such as magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT) and optical imaging which demonstrate the potential to target tumour with high precision. We delve into the physicochemical characteristics of nanoparticles such as size, surface charge and functionalization that allow nanoparticles to cross the biological barriers, preferentially accumulate in tumor sites and deliver diagnostic and therapeutic payloads. Special attention is paid to the achievements in multimodal and theranostics platforms, where a single nanoparticle is able to perform both imaging and therapy at the same time. While these have great potential, there are challenges with clinical translation of these technologies ranging from biodistribution, toxicity, immunogenicity and regulatory hurdles. Despite these hurdles the accumulating amount of clinical evidence indicates that nanotechnology will have a significant role in precision oncology that will move from the experimental stages to routine clinical use, thus changing the paradigms of cancer detection and treatment.

Keywords: Nanotechnology-driven imaging, multimodal nanoplatforms, precision diagnostics, theranostic nanocarriers, molecular imaging

Introduction

Cancer is classified as one of the major health challenges of the twenty-first century by the World Health Organization (WHO) in regards to incidence, with an estimated 20 million new cases and almost 10 million deaths in 2022 alone [1, 2]. The growing occurrence of this complex disorder, as well as its heterogeneity and spreading early, this disorder has been relegated to be one of factors of the leading causes of death not only in the developed countries, but also in the developing countries [3]. Although much progress in the terms of the therapeutic options has been achieved, the stage of the disease is a decisive factor in the outcomes of patients at the moment of the diagnosis [4]. On some malignancies, the five year survival rate can be 90 percent and up when the disease is caught early in a localized state and comes crashing down to zero when the disease is caught late on advanced stages or in metastasized forms which heralds a critical clinical need of sensitive specific and minimally invasive diagnostic platforms that can detect the disease at an early stage to receive precise treatment [5, 6].

Conventionally, tumor detection and characterization has been based on magnetic resonance imaging (MRI) [7], imaging technology (PET and SPECT) [8], and optical imaging [9]. The methods are long-standing staple of oncological practice which gives significant anatomical and functional information on the state of the disease. Nonetheless, even though they have been widely used clinically, these modalities have inherent limitations that are associated

with spatial and temporal restrictions, sensitivity to detect early molecular alterations, and sensitivity to very low volumes of disease [10]. Consequently, the problem of capable detection of subtle malignancies or microscopic metastases at an early stage with the help of the traditional techniques is urgent and frequently leads to the failure to apply therapeutic treatment at the appropriate time, and thus to the decrease in the prognosis of patients [11]. In that regard, nanotechnology has become a disruptive and revolutionary technology that is changing the ground in early cancer detection. The full range of physicochemical attributes of nanoparticles such as size, surface charge, shape, composition and surface chemistry can be designed in a highly specific way to enable very specific interactions in (complex) biological environments [12]. These characteristics have led to the development and construction of a broad spectrum of nanoprobes tailored to search and characterize important molecular and cellular functions occurring at an early stage of carcinogenesis [13]. Nanoparticles can be used to achieve sensitive imaging and high contrast based on their preferential accumulation in neoplastic tissue based on the exploitation of both passive targeting strategies including the enhanced permeability and retention (EPR) effect and active targeting methods based on ligands, peptides or antibodies [14, 15].

Additionally, the development of nanomaterials has fueled the breakthrough in multimodal and theranostics platforms, whereby a single nanoprobe is capable of providing molecular and structural imaging with high resolution as well as acting as a delivery vehicle of therapeutic cargo [16]. The resulting nanoplatforms have shown deep potential towards real time tracking of disease progression, evaluation of therapeutic efficacy as well as precision guided interventions [17]. By doing this nanotechnology can transform the paradigm of clinical oncology which is currently conventional reactive treatment of advanced disease to early, precision driven detection and intervention and therefore be consistent with the fundamentals of precision medicine [18]. Notably, imaging has been also accelerated by the progress of molecular biology, genomics, and proteomics that allowed to translate into clinics nanotechnologies [19].

Based on deep learning - increased processing of signals of nanomaterials, it is possible to provide advanced image analysis, highly specific characterization of pathophysiological states and distinction benign and malignant pathologies [20]. Potentially, there is a lot of promise in the clinical translation of nanotechnology-based diagnostic platforms, but there exists a wide variety of scientific, engineering and regulatory challenges. Issues associated with long term biocompatibility, immunogenicity, biodistribution and clearance need to be very closely tackled to guarantee the safety of the patient [21]. Additionally the reproducibility and scale of nanomaterials to multiple manufacturing environments and the process of the development of characterization and quality control of nanomaterials via standardized methods are also essential towards regulatory and clinical acceptance [22].

In this review, we have critically analyzed the advances, challenges and future of nanotechnology based driving approaches towards early cancer detection. The physicochemical design of nanoparticle, functionalization of nanoparticles in order to allow precise targeting, and application of nanoparticles in MRI, optical, PET/Spect and multi modal systems are the issues on which we pay attention. We also discuss the role of emerging trends like theranostics nanoparticle, intelligent nanoprobes powered by bio-degradable platforms will play in the future of precision oncology. This review will provide an authoritative state of the art synthesis of the literature in an effort to explain the critical importance of nanotechnology in enabling an entirely new paradigm capability to detect earlier, more accurate and more actionable cancer, which will ultimately benefit patient outcomes and transform clinical practice.

Novelty and scope of the present review

Although there have been several good reviews on the recent progress of nanotechnology-based imaging applications in cancer, the current article is unique both in scope and analysis of the subject. Recent reviews from Wang et al. [23] focus mainly on signal transduction mechanisms and modulation of therapeutic response mediated by nanomaterials with very little discussion regarding imaging-guided early detection and integration of the clinical workflow.

Table 1. Comparison of recent reviews vs. the present work

Review	Main Focus	Imaging Modality Analysis	Clinical Translation	AI/Smart Nanoplatforms	Unique Contribution
Wang et al., 2024 [23]	Signal transduction & therapy	Limited	Moderate	Minimal	Therapeutic signaling mechanisms
Andoh et al., 2024 [24]	Nanocarrier formulation	General	Limited	Not addressed	Delivery systems overview
Puttasiddaiah et al., 2025 [25]	Broad nanomedicine	Modality-agnostic	Moderate	Minimal	Diagnostic-therapeutic overview
This review	Cancer imaging-centric	MRI, PET/SPECT, optical, multimodal (systematic)	Strong	Integrated	Imaging-driven early detection framework

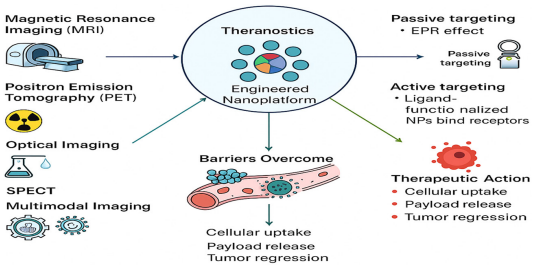

Figure 1. Nanotechnology and its applications in cancer imaging.

Similarly, Andoh et al. [24] give an excellent review of nanocarrier platforms but does not focus too much on formulation strategies and efficiency of delivery but rather on modality-specific imaging performance and translational imaging benchmarks. More recently, the applications of nanomedicine in the diagnostics and therapy have been reviewed by Puttasiddaiah et al. [25], however, their analysis is mainly modality agnostic and does not provide a systematic comparison of physicochemical design principles for MRI, PET/SPECT [26], optical and multimodal imaging systems (**Table 1**).

In contrast, the present review presents modality-centric clinically-oriented synthesis of nanotechnology-driven cancer imaging, with a special focus on: (i) how physicochemical properties of nanoparticles determine imaging sensitivity and specificity of different modalities, i.e., MRI, optical and nuclear; (ii) rational consideration of multimodal and theranostic nanoplatforms from the structure function point of view; and (iii) the translational pathway from nanomaterial engineering to real clinical imaging workflows. Furthermore, this review presents unique integration of emerging concepts such as A.I. assisted nanoparticle design, image analytics and biodegradable/bioinspired platforms in the scope of early cancer detection rather than therapy only.

The convergence of nanotechnology and cancer imaging

The advent of nanotechnology has opened a pivotal change in the areas of biomedical engineering and clinical oncology with a sophisticated method of early detection and characterization of diseases that was unimaginable. At the heart of this shift is the capability of manipulating matter at the nanometer scale within the scope of 1-100 nanometer (nm) in most cases which results in the emergence of a new generation of diagnostic platforms bridging the gap between molecular biology and clinical practice [23]. By precisely controlling physicochemical characteristics such as size, shape, surface charge and surface composition, nanoparticles can be designed to navigate the complexities of the human body [24] providing unprecedented precision in the detection, characterization and monitoring of neoplasia (**Figure 1**).

A basic benefit of nanoparticles is that they can circulate in the bloodstream for an extended period of time to extravasate into the highly irregular microvasculature of tumor [26]. Particles with a size of approximately 10-100 nm are in an optimum balance between in body and tissue penetration [27]. Unlike the smaller molecular agents which are filtered out by the kidneys too quickly, or larger particles which are removed by the reticuloendothelial system, nanoparticles in this range can circulate long enough to accumulate within the abnormal fenestrated endothelium which characterizes the neovascular architecture of tumors [28]. The phenomenon produced by this liposome nanotechnology is the enhanced permeability and retention (EPR) effect that enables nanoparticles to passively accumulate inside the tumor microenvironment because of a combination of disordered, leaky vasculature and deficient lymphatic clearance [29]. This passive

targeting mechanism gives nanomaterials a basic level of specificity in their use in oncology and has been at the heart of progress in early detection and therapeutic delivery [30].

Although the EPR effect gives a good foundation for accumulation, improvements in surface engineering has allowed nanoparticles to move beyond passive accumulation and develop into highly-specific platforms for precision molecular targeting [31]. By functionalizing the surface of NPs with ligands such as antibodies, peptides or aptamers, it has become feasible to guide these platforms towards antigens, growth factor receptors and other disease associated molecular markers expressed inside the tumor microenvironment [32]. This approach enables the nanoparticles to selectively bind to cellular and stromal targets to enable internalization and increase residence in tumors [33]. The synergistic effect of EPR effect and active molecular adhesion has significantly improved the specificity and sensitivity of nanoparticles in early diagnosis of diseases, and early diagnosis of diseases is so good that it is possible to distinguish the neoplastic tissue from the environment with remarkable precision [34].

Achieving this level of specificity, however, is dependent upon a sophisticated understanding of the nanobio interface the complex interplay between nanomaterials and the biological environments that they live in [35]. Upon entry to the bloodstream, nanoparticles quickly adsorb a coat of biomolecules (mainly proteins and lipids), forming a dynamic characteristic "protein corona" that determines their biological identity, biodistribution, cellular uptake, and clearance kinetics [36]. Controlling this interface has become one of the important design problems facing nanomedicine [37, 38]. To overcome this, the development of surface engineering has led to the introduction of various types of stealth and bio orthogonal coatings, such as polyethylene glycol (PEG), polymers that are charged in both directions and natural or bio-mimetic membranes [39]. These surface treatments have shown to reduce the opsonization and clearance of particles, increasing circulation time and making it possible create a more predictable and specific interaction between the nanoparticles and the chosen target tissue [40].

Modern advancements in molecular probe design have gone beyond these principles and provided the opportunity to create multi-functional nanoparticles with various diagnostic and therapeutic capabilities in one platform [41]. These platforms can be designed with magnetic cores for MRI, radionuclide labels for PET and SPECT or fluorophores for optical detection [42]. The resultant multi modal nanoparticles allow a thorough characterization of the tumor in both spatial and temporal scales, which allows for the detection of malignancy from its very inception, the molecular characterization of subtypes, and the determination of the dynamics of disease progression with unprecedented precision [43].

Taken together, the convergence of nanotechnology and cancer imaging has brought about a new age in precision medicine. The ability to engineer the physicochemical characteristics of nanoparticles and utilise passive and active targeting mechanisms, as well as optimise the biological interface has established a foundation for the development of highly sensitive, specific and multi-functional diagnostic platforms. In this manner, nanotechnology has gone from being a promising experimental technology to a transformative, clinically relevant technology, changing the face of cancer detection and therapy in the future.

State-of-the-art nanoparticles for cancer imaging

Magnetic nanoparticles for MRI

The exceptional spatial and temporal resolution, deep tissue penetration and ability to generate high contrast, three dimensional soft tissue morphological images have long since made magnetic resonance imaging an influential instrument in clinical oncology practice [44]. However, as is well known, despite its extensive application in clinical practice, MRI is frequently hampered with inherent poor sensitivity as far as the early diagnosis of cancer is concerned [45]. This limitation is especially seen in its ability to make favorable in the accuracy of detecting the microscopic lesions, low-frequency molecular markers, as well as early neovascularization [46]. In clinical practice MRI is unable to detect tumors until they have reached a relatively large size, equivalent of a grid of 105-106 cells, and a size of several mil-

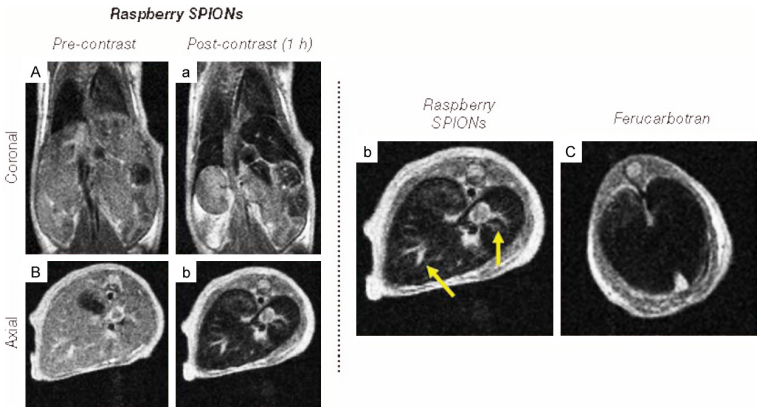

Figure 2. T2-weighted MRI images before and after contrast administration show raspberry SPIONs (A, B) and Ferucarbotran (C). Both agents darken the liver, but raspberry SPIONs reveal hepatic vessels (arrowed), unlike Ferucarbotran (n = 1) [52].

limeters (mm). The detection of smaller lesions or low volume of disease is very difficult [47]. Further, its ability to differentiate between the malignant and benign tissue is limited by the low signal differentiation that traditional contrast agents give [48]. The degree of such restriction of sensitivity indicates a dire need to develop intensely efficient contrast platforms with sufficient reliability in clarifying the initial changes of molecules and cells in tumors [49]. Here, magnetic nanoparticles were found good candidate overcoming these shortcomings and increasing the clinical use of MRI in early cancer diagnosis. In this respect, magnetic nanoparticles raised great hope that they would help it to overcome these shortcomings and increase the scope of clinical application of MRI.

Preclinical animal experiments have repeatedly demonstrated that SPIONs can be used to enhance the contrast in an MRI image because of their preferential uptake in tumor tissue because of the enhanced permeability and retention (EPR) effect and because of ligand-mediated targeting. These results have been confirmed primarily in murine and rat tumor models with SPIONs providing an improvement in lesion conspicuity and sensitivity over conventional contrast agents.

In contrast, the clinical evidence for SPION based imaging is limited. While many formulations of iron oxide have been approved previously for clinical MRI applications especially for liver and lymph node imaging some of these agents have been withdrawn from the market because of safety concerns and suboptimal clinical performance or lack of clinical benefit. Current clinical investigations are therefore aimed at the optimization of particle size, coating chemistry and dosing in order to increase the safety and translational reliability.

Superparamagnetic iron oxide nanoparticles (SPIONs) are nowadays the most common magnetic nanomaterials for MRI [50]. These nanoparticles typically have a core of an iron oxide (Fe304 or v-Fe203) surrounded by biocompatible substances such as dextran, polyethylene glycol or phospholipids. Their superparamagnetic nature ensures negligible remanent magnetization in the absence of any external magnetic field, so that aggregation is minimized and prolonged circulation is possible. Exposed to the magnetic field of an MRI, SPIONs induce large local inhomogeneities in the magnetic fields. These inhomogeneities lead to rapid dephasing of the nearby proton spins resulting in greatly reduced transverse relaxation times (T2/T2*) and also significant loss of signal (dark contrast) on images [51]. Previous studies [52] report T2-weighted MRI (TE 20 ms) showing discernable hepatic vessels 1 h after administration of raspberry SPIONs a feature which was absent with Ferucarbotran despite comparable darkening of the liver (**Figure 2**). This mechanism is the basis of their application in tumor detection, since SPIONs may be conjugated with targeting ligands (antibodies, peptides, small molecules) specific to the antigens that are overexpressed in tumors. Furthermore, SPIONs preferentially accumulate in neoplastic tissue because of the enhanced permeability and retention (EPR) effect that is influenced by the leaky vasculature in tumors (extravasation and lymphatic drainage issues can promote retention) can increase their diagnostic potential for early disease [53].

In parallel, nanocarriers with gadolinium have developed into being very prominent as very effective T1 contrast agents [54]. The paramagnetic gadolinium ion (gadolinium ion) (Gd^{3+})

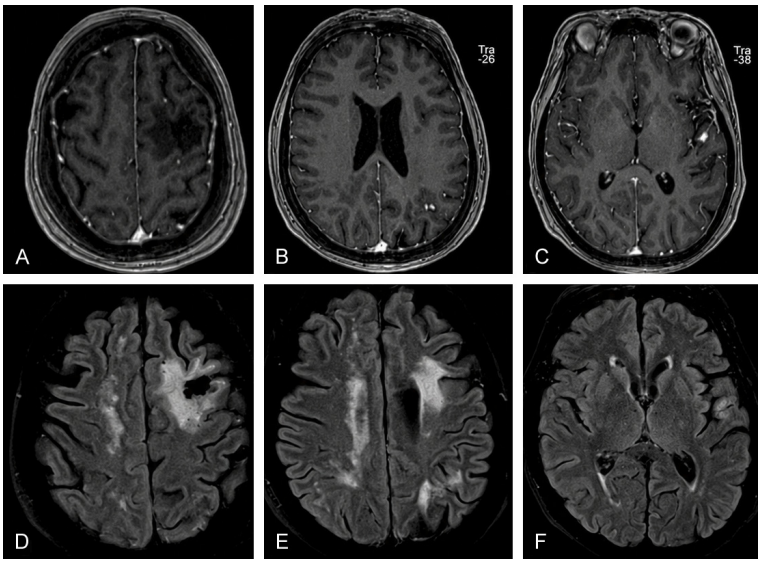

Figure 3. MRI (4 years later) with gadolinium shows: (A-C) T1 images with new nodular enhancement in the left frontal cortex (D), two small lesions in the left parietal cortex (E), and changes in the left temporal cortex (F). T2 reveals edema in the left frontal cortex and bilateral hyperintensities on T2 FLAIR [55].

has seven unpaired electrons. This is a strong magnetic moment, which is efficient in interacting with the neighboring water protons and causes longitudinal relaxation of the protons, which in turn gives a lot of T1 relaxation time and therefore produces a bright signal (positive contrast) for protons in T1-weighted MRI imaging. Encapsulation of Gd^{3+} in nanoparticles or dendrimers in addition to increasing safety (minimizing free ion exposure and risk of nephrogenic systemic fibrosis) also gives the possibility of targeted delivery by surface functionalization. Advances in this direction have led to nanocarriers with improved pharmacokinetics and high relaxivity significantly improving the sensitivity in early stage detection of tumor. In some studies [55], greater lesion conspicuity and better small cortical abnormalities detection have been shown by these agents compared to conventional contrast media as given in **Figure 3**.

There has now been much progress in the design of the multifunctional magnetic nanoprobes having SPIONs in addition to the nanocarriers with the Gd doping on the same platform. The mechanism of these hybrid probes is based on their complementary contrast mechanism: The SPION part of the probe induces high T2/T2* dark contrast whereas the Gd^{3+} part of the probe induces bright T1 contrast. This enables dual-modal (T1/T2) MRI simultaneously, providing more rich and complementary information about tissue structure, molecular markers and microenvironmental conditions - and so compensate for limitations that single contrast imaging has. Recent improvements in surface engineering allow to functionalize these nanoprobes with highly specific ligands (affibodies, aptamers, antibodies) for specific targeting of overexpressed tumor antigens (e.g., HER2, EGFR, integrins), for their specific guidance to diseased locations apart from passive EPR accumulation [56]. This integration has the advantage to transform magnetic nanoparticles from being passive contrast agents to an active tool for targeted molecular characterization, in vivo monitoring of disease progression and MR guided interventions. These innovations are further strengthened with high field MRI platforms and advanced pulse sequences to perfect the signal-to-noise ratio and sensitivity to nanoparticles for early detection. Collectively, magnetic nanoparticles SPIONs, Gd-doped carriers and multimodal platforms - are transforming MRI from being a tool of structural imaging to a precision tool in early detection of targeted cancer.

Quantum dots and upconversion nanoparticles for optical imaging

During the last 20 years, revolutionary developments in nanotech have radically changed the face of biomedical imaging, and optical methods in general [57]. Optical imaging has remained a mainstay of biomedical research and clinical diagnostics for decades for its unsurpassed ability to provide highly sensitive, real-time and spatially resolved information on molecular interactions, cell dynamics and disease progression. Its great appeal is in the inherent benefits of light which is a non-invasive, cost effective and exquisitely adaptable modality that can provide insights into the

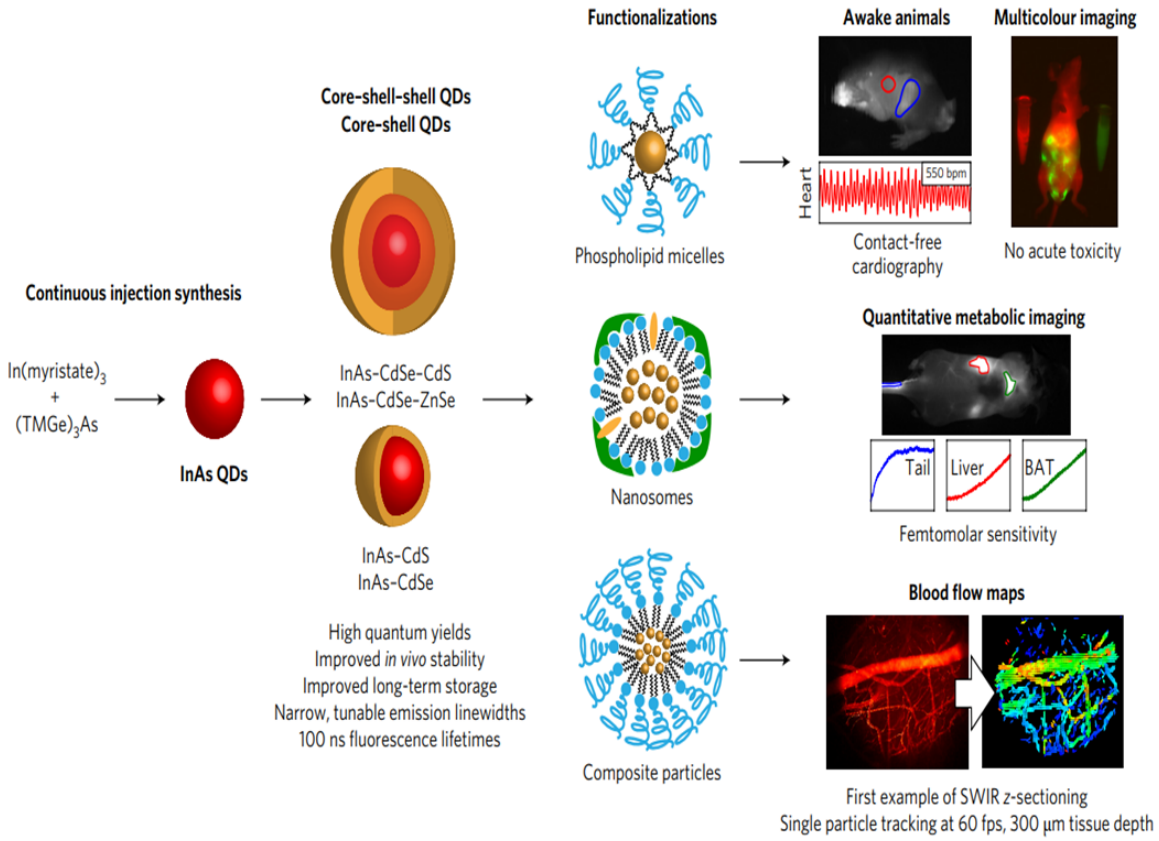

Figure 4. Short-wave infrared quantum dots for next generation in vivo optical imaging [62].

behaviour of cells, the microarchitecture of tissues and the pathological evolution of lesions with extraordinary specificity. Nevertheless, traditional optical probes such as organic dyes and small molecule fluorophores have been limited by serious limitations in the past: rapid photodegradation, wide and overlapping emission spectrum, and intrinsically shallow tissue penetration depth (~ <1-2 mm), and low signal-to-noise ratios due to ubiquitous tissue autofluorescence [58]. To overcome these limitations, researchers have developed sophisticated nanomaterial platforms that have been designed to display exceptional photostability, tunable brilliance, deep tissue operability and multiplexing capabilities to help visualize the pathogenesis of diseases at their earliest, most targetable stages with unprecedented lucidity.

Quantum dots (composites of precisely sized semiconductor nanocrystals, such as CdSe/ZnS, PbS or recently developed cadmium free InP/ZnS) harness the effects of quantum confinement in order to offer unprecedented control over emission wavelengths in the visible to near-infrared-II (NIR-II, 1000-1700 nm) range by simple manipulation of their physical dimensions (**Figure 4**) [59]. Compared to conventional fluorophores, QDs exhibit orders of magnitude greater brightness and amazingly narrow and symmetric emission bands (<30 nm full-width-at-half-maximum) and near-complete resistance to photobleaching. This enables the longitudinal and high fidelity tracking of complex cell processes, tumor-host interactions as well as dynamic molecular events in complex microenvironments over extended periods of time [60]. Strategic surface functionalization will further enable QDs: Conjugation with high-affinity targeting ligands such as monoclonal antibodies, tumor homing peptides or such as structured nucleic acid aptamers will offer exquisite specificity for disease associated antigens (e.g., HER2, EGFR, PSMA, CA-IX). This molecular precision makes it easier to unambiguously discriminate the malignant from the healthy tissue on the cellular resolution level [61, 62].

Upconversion nanoparticles have been viewed as a potential alternative to such difficulties in

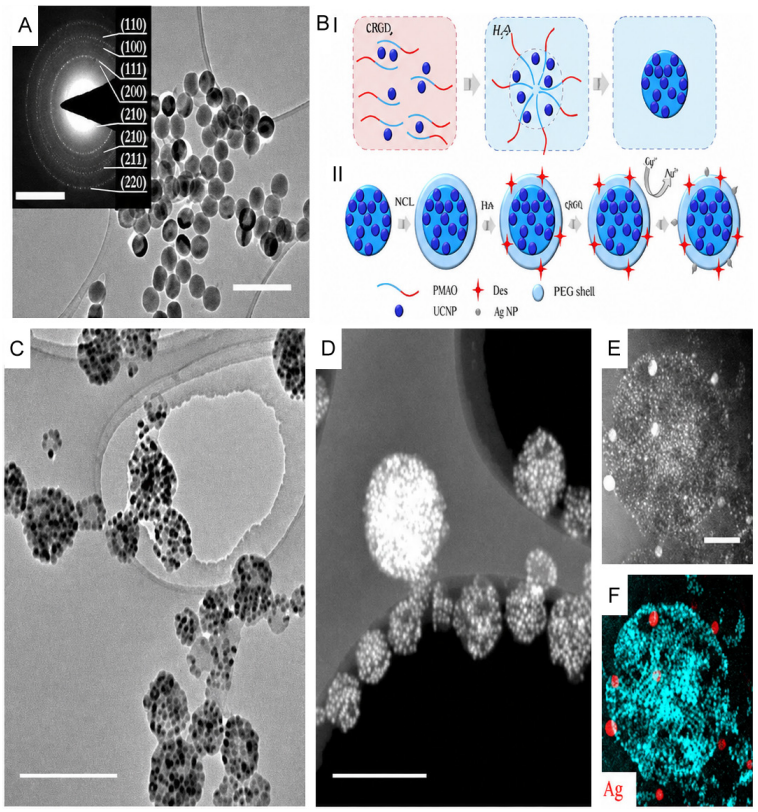

Figure 5. (A) TEM images of as-synthesized core/shell NaYF4:Yb^{3+}/Tm^{3+}@NaYF4 UCNPs (scale bar - 100 nm) and selected area electron diffraction pattern of UCNPs on insert (scale bar - 5 nm^{-1}). (B) Schematic illustration of the rational design of multifunctional UCNP complexes: I. step 1: PMAO hydrocarbon moiety interaction with oleate ligand on the surface of UCNP in organic solvent; PMAO self-assembly into large spherical micelles with several UCNPs intercalated in the micelle core after transfer into water; crosslinking of large spherical micelle with diamine to form stable polymer particles (UCNP-PMAO); II. step 2: UCNP-PMAO modification with PVCL; step 3: embedding the therapeutic agents; step 4: Ag^{+} adsorption on the UCNP-PMAO-PVCL surface, followed by reduction; (C) TEM and (D) HAADF-STEM image of UCNP-PMAO-PVCL complexes. Scale bar is 500 nm; (E) HAADF-STEM image and (F) EDX elemental mapping of UCNP-PMAO-PVCL containing in situ-formed Ag NPs. Scale bar is 200 nm [66].

which a fundamentally different photophysical mechanism is exploited [63]. UCNPs, as they are typically comprised of crystalline host lattices that contain pairs of sensitizer/activator lanthanide ions (i.e. NaYF4:Yb^{3+}/Er^{3+}/NaYF4:Yb^{3+}/Tm^{3+}/), absorb low-energy near-infrared (NIR) photons (typically 980 nm) and convert it later to higher-energy visible or NIR emissions through a process of photon upconversion. This anti-Stokes shift leads to very sharp multi-line emission spectra with no broad background fluorescence as is the case with conventional probes and this gives dramatically enhanced signal-to-noise ratios and near-zero autofluorescence interference [64, 65]. Crucially, UCNPs operate efficiently within the NIR biological transparency windows (NIR-I: 700-900 nm; NIR-II: 1000-1700 nm), which are where scattering and absorption of tissues are minimised. This unique property allows for unprecedented optical penetration depths of several centimeters (>4-8 cm) which can be used to image deeply buried tumors and micro-metastases in organs such as the liver, pancreas or brain, much deeper than can be imaged using traditional fluorescence or QDs. In order to study the structures and functions of the multifunctional nanomaterials, UCNP ATPaseu-PMAO-PVCL based nanocomposites with embedded therapeutics and in situ formed Ag NPs were rational designed and characterized via TEM, HAADF-STEM and EDX mapping as given in **Figure 5**.

Sophisticated surface engineering makes UCNPs biocompatible and target specific: inert silica or amphiphilic polymers for stability and circulation and conjugation to tumor-targeting ligands (e.g., folic acid, RGD peptides, trastuzumab fragments) for targeted accumulation within neoplasms. This powerful combination of deep tissue penetration, low background and molecular specificity has made UCNPs indispensable tools of real-time intraoperative guidance [66, 67]. Surgeons take advantage of their bright confined signal by the tumor to microscopically delineate malignant margins perfectly (>95% accuracy in preclinical models) allowing radical resection while preserving critical adjacent structures - significantly decreasing positive margin rates and collateral damage. Previous studies [68] have led to the preparation of heterogeneously doped core@shell UCNPs as well with a controllable energy migration and doping scheme, thus enabling customizable multiple-step energy cascades, orthogonal emissions under dual

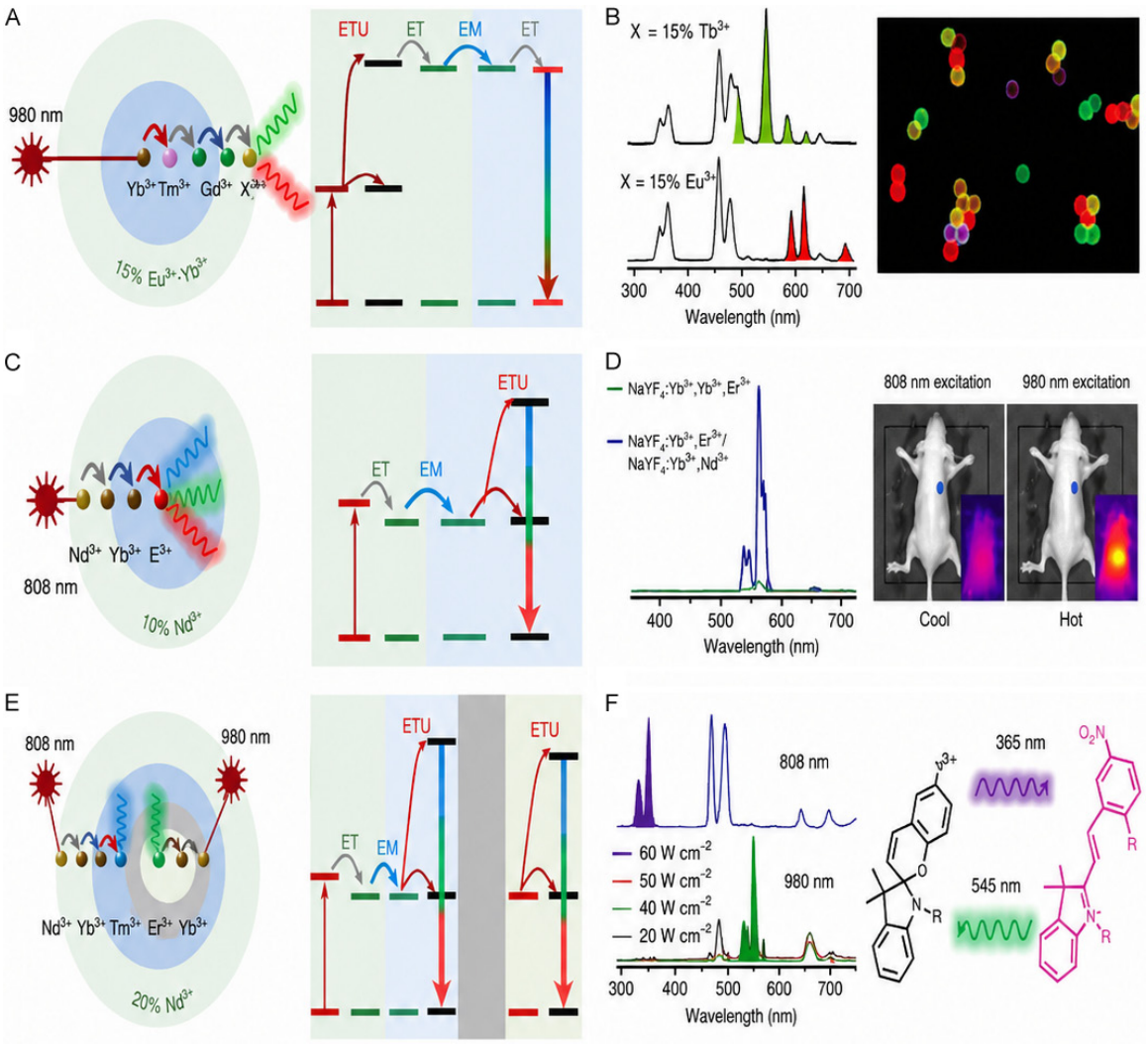

Figure 6. Heterogeneously doped core@shell upconversion nanoparticles address concentration quenching. A. Schematic of core@shell design with energy migration at the emission site. B. Upconversion spectra with tunable wavelengths via a $Yb^{3+}\rightarrow Tm^{3+}\rightarrow Gd^{3+}\rightarrow Eu^{3+}/Tb^{3+}$ energy cascade, plus luminescence micrograph of polystyrene beads tagged with nanoparticles. C. Schematic showing energy migration at the excitation site, with $E^{3+} = Er^{3+}$, Tm^{3+}, or Ho^{3+}. D. Emission spectra of $NaYF4:Yb^{3+},Er^{3+}@NaYF4:Yb^{3+},Nd^{3+}$ core@shell and homogeneous-doped nanoparticles, plus in vivo imaging under 808 nm and 980 nm excitation. E. Doping location control with an energy transfer blocking layer. F. Core@multishell UCNPs ($NaYF4:Yb^{3+},Nd^{3+},Tm^{3+}@NaYF4@NaYF4:Yb^{3+},Er^{3+}$) with orthogonal emissions under 800 and 980 nm, used for reversible spiropyran isomerization [68].

NIR excitation (800/980 nm), as well as sophisticated applications such as in vivo imaging and reversible molecular switching (**Figure 6**). The complementary evolution of QD and UCNP technologies has provided another motivation to the development of complex multifunctional theranostics platforms. By combining magnetic elements (e.g., SPIONs for providing MRI contrast), positron-emitting radionuclides (e.g., ^{89}Zr, ^{64}Cu for PET imaging) or therapeutic moieties (chemotherapeutics, siRNA, photosensitizers) within the same nanoconstruct, researchers have developed unified agents with the ability to simultaneously diagnose, treat and monitor treatment [69]. Stimuli-responsive designs that are activated by unique pH, redox or enzymatic activity of the tumor microenvironment guarantee spatially and temporally controlled drug release or signal activation at the site of disease. The complex high-dimensionality spatial and temporal information produced by QD and UCNP imaging has the potential to be processed by intelligent algorithms for the extraction of

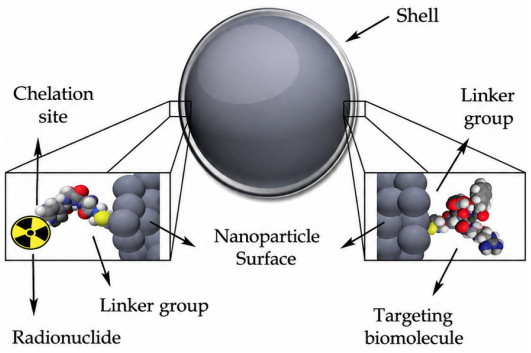

Figure 7. Radionuclide nanoparticles for molecular imaging [72].

subtle and prognostic patterns that reveal information on micro-metastatic niches, or the prediction of early therapeutic resistance, or the quantitative measurement of the dynamics of biomarker expression at a level that is imperceptible by conventional analysis or human observation.

The emergence of quantum dots as well as upconversion nanoparticle is a significant paradigm shift in biomedical optical imaging. Through a step-by-step elimination of limitations of legacy probes, and the use of synergistic breakthroughs in surface bioconjugation, materials chemistry and computational intelligence, these nano-materials have been able to lay the cornerstone of a new era of precision medicine. Their potential for illuminating occult deep tissue malignancies with molecular specificity, guiding lifesaving surgical intervention with cellular precision in real-time and for easy integration into multimodal diagnostic and therapeutic work flows makes QDs and UCNPs important future tools to change the clinical course of oncology. In doing so, they are actively in redefining the gold standards of early molecular detection, intraoperative accuracy and personalised therapeutic strategy ushering in a transformative future where cancer is intercepted preemptively, and treated with exquisite precision and with minimal disruption to the patient's life.

Radiolabeled nanoparticles for PET and SPECT imaging

Radioactively labeled nanoparticles (**Figure 7**) have become powerful tools in molecular imaging and allow a higher degree of precision and specificity than traditional radiotracers [70]. These nanoplatforms benefit from the high sensitivity of nuclear imaging in combination with the physicochemical versatility of nanomaterials to enable early detection of disease and precise discrimination of pathological and healthy tissue and monitoring molecular events in vivo in real-time. The addition of radionucles to engineered nanocarriers has resulted in the development of diagnostic agents with long circulation, high target affinity and stability in complex biological environments [71, 72].

Various nanomaterials can be successfully radiolabeled using chelator based or chelator free strategies and include liposomes, dendrimers, polymeric micelles, silica based systems, metallic nanoparticles and hybrid composites as can be seen in **Figure 8** [73]. Chelator based approaches include the conjugation of bifunctional chelators such as DOTA, NOTA or DTPA to the surface of the nanoparticle allowing for stable complexation with radiometals such as ^{64}Cu, ^{68}Ga, ^{89}Zr or ^{177}Lu. These systems are well used due to the high radiochemical and well-characterized stability. In contrast, chelator-free strategies exploit inherent chemical interactions between radionuclides and the core of the nanoparticle (e.g., gold, cerium oxide or carbon dots), obviating the requirement for the use of synthetic linkers; this improves in vivo radiostability [74]. Chelator-free ^{64}Cu labeled copper sulfide nanoparticles, and ^{89}Zr doped silica or titania systems have demonstrated high labeling efficiency and good imaging performance without any impact on the integrity and biofunctionality of the nanoparticles [75].

Surface engineering of such nanoparticles allows for the dual target capability by both the passive mechanism (e.g., enhanced permeability and retention effect) and the active mechanism (e.g., disease-specific ligands). Functionalization with polyethylene glycol (PEG) results in improved pharmacokinetics with stealth properties and conjugation of antibodies, peptides or small molecule ligands allows for receptor mediated targeting of pathological tissues. This custom design permits selective accumulation at the site of disease and longer retention time which is important for imaging small or small stage lesions. Compared to conventional radiotracers, radiolabeled nanoparticles

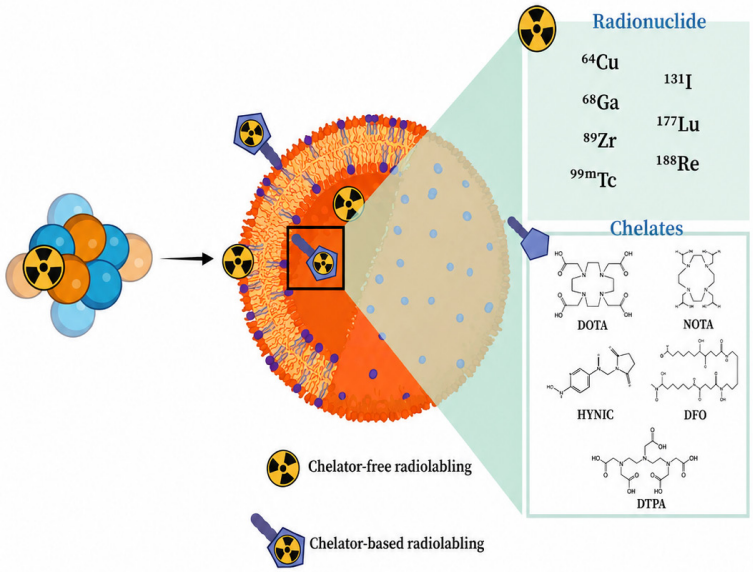

Figure 8. Radiolabeling of nanoparticles through two main strategies: chelator-based and chelator-free radiolabeling. Radionuclides and chelators typically used in radiolabeling of nanoparticles for multimodal cancer imaging and theranostic applications are depicted [76].

have much longer circulation that ranges from hours to days depending on the formulation and coating [76, 77].

Nanoparticles are free to carry a variety of isotopes that can be used for various types of imaging. Positron emitters such as ^{64}Cu, ^{68}Ga and ^{89}Zr are typically used for PET imaging due to their favourable half-lives and decay properties. For SPECT isotopes such as ^{99}mTc and ^{111}In allow for long term imaging with a high number of photons. Radiolabeled nanoparticles are hence versatile imaging platforms that can be applied for single or multimodal imaging applications. In the field of oncology where molecular profiling and early stage early detection are extremely important, these nanoplatforms have been very effective. Studies based on ^{64}Cu-labeled liposomes and ^{89}Zr-labeled iron oxide nanoparticles have shown higher level of localization to tumors compared to traditional PET tracers with signal retention of 48-72 hours [78]. ^{111}In- and ^{99}mTc-based nanoparticles have enabled high-resolution SPECT imaging based on tracking disease progression, angiogenesis or therapeutic response over time [79].

Advances in theranostics have brought new dimensions in the clinical applications of radiolabeled nanoparticles. By combining therapeutic isotopes, e.g., ^{177}Lu or ^{225}Ac, with diagnostic isotopes [80], it is possible to integrate both real-time imaging and targeted radionuclide therapy with one nanoparticle system as given in **Figure 9**. For example, liposomes simultaneously loaded with ^{64}Cu and ^{177}Lu have combined PET and therapeutic efficacy in preclinical models of prostate and breast cancer [81]. Such dual function agents provide the potential for adaptive treatment regimens, where physicians can monitor the delivery of treatments and adjust dosing in real-time, optimizing efficacy while avoiding off target toxicity. Recent advances in nanomedicine have also been observed in multimodal formulations with combination of contrast agents for both MRI, fluorescence and photoacoustic imaging. Hybrid nanoparticles labeled with ^{64}Cu for PET and Gd for MRI for example, provide both a high resolution picture of the anatomy and functional metabolic information to obtain a complete picture of disease phenotype. This combination of anatomical and molecular information enables the improvement of the diagnostic accuracy and is used in the planning for surgery or treatment of therapy [16].

Moreover, by using predictive models tools, nanoparticles are now designed according to the simulation of biodistribution and pharmacokinetics of nanoparticles, but also the accumulation of nanoparticles in tumors, in a variety of patient profiles. These technologies not only increase the speed of development but also help to the development of patient specific nanotheranostics. Several first in human and phase I clinical studies have established the translational potential of radiolabeled nanoparticles. For example, ^{64}Cu- and ^{89}Zr-labeled liposomes have shown favorable safety profile and tumor targeting efficacy in PET imaging trials in glioblastoma and HER2-positive breast cancer. ^{99}mTc- and ^{111}in-labeled formulations are already in clinical use for sentinel lymph node mapping and bone metastasis detection; thus proving its feasibility and impact [82]. These

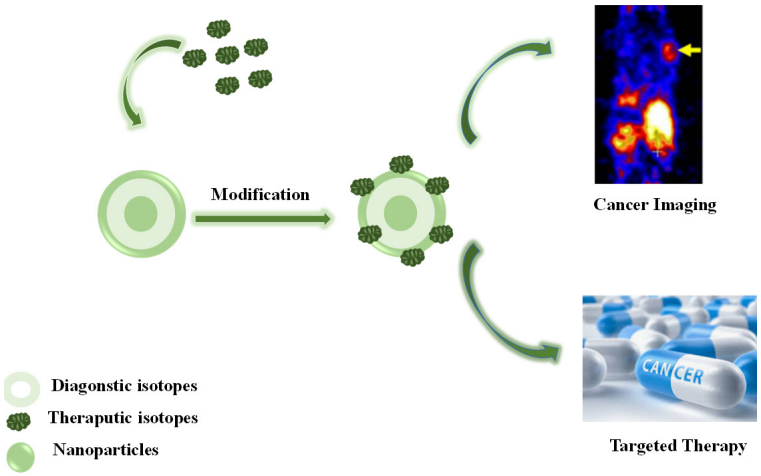

Figure 9. Modification of nanoparticles with isotopes for cancer imaging and therapy.

innovations are a part of the evolution towards precision medicine, in which diagnostic tools are combined with therapy and monitoring as one formulation. Radiolabeled nanoparticles can offer a consolidated platform for pre-symptomatic diagnosis, real-time correction of treatment and longitudinal monitoring of disease. As GMP manufacturing and regulatory alignment continues to move forward, such platforms are expected to be a key part of routine clinical work flows. Their emergence is a revolution towards predictive, personalized and preventive healthcare.

A consolidated summary of radionuclides, nanomaterial platforms, imaging modalities and clinical or preclinical applications is given in **Table 2**.

Multimodal and theranostic nanoparticles

The search for precision medicine has raised the development of nanoplatforms with both diagnostic and therapeutic functions now integrated into a single platform. In this fast-changing environment, the concept of multimodality has become one of the most revolutionary innovations in the field of molecular medicine research allowing nanoparticles to perform in a multitype of imaging techniques. By exploiting the complementary power of MRI, PET, SPECT and the optical imaging modalities including fluorescence and therapeutic functionalities researchers have developed sophisticated carriers where it is possible to detect the disease early, to characterize it precisely and to treat it in a targeted manner, all as part of a single workflow. Through these platforms, there has been a blurring of traditional boundaries between diagnosis and therapy, and the era for the treatment of disease has emerged where it can be diagnosed, monitored and treated by the same, highly adaptable agent [17].

The basic advantage of dual- or triple-modality nanoparticles is to overcome the limitations of the technique of individual imaging. The MRI provides an excellent spatial resolution as well as soft tissue contrast and is limited in sensitivity [83]. PET and SPECT allow for high sensitivity and quantitative information about molecular processes but are limited in their spatial resolution, i.e. their ability to provide information about anatomic localization in detail [84]. Optical imaging modalities including fluorescence and bioluminescence have high specificity and enable for real time visualization but are limited due to poor penetration in the tissues [85]. When these modalities are combined into a single nanocarrier their respective strengths are combined to produce sensitive and anatomically precise and molecularly specific information on the biological scale. The result is a full picture of disease to support a more informed clinical decision-making process with clarity like no other. The realisation of such multifunctional capabilities is based on the development of nanomaterials engineering. Central to these platforms is a nanocarrier such as a liposome, polymeric micelle, dendrimer or inorganic nanoparticle capable of encapsulating/connecting a number of functional agents. In one common design, an iron oxide core is utilized to provide the contrast for MRI, a chelator is attached on the surface of the carrier to bind PET radioisotopes such as ^{64}Cu or ^{89}Zr, and a conjugated near infrared fluorophore can be used to provide intraoperative fluorescence detection. Other systems have combined gadolinium-based MRI agents with radionuclide tags and optical dyes, to produce very versatile nanoparticles that are available for preoperative planning, intraoperative guidance and postoperative surveillance. These platforms are providing a multilayered

Table 2. Radionuclides nanomaterials

Parameter	Description	Nanomaterials Involved	Radionuclides Used	Clinical/Preclinical Applications	Advantages
Platform Type	Core structure of the nanoparticle	Liposomes, polymeric micelles, dendrimers, gold NPs, silica, SPIONs	^{64}Cu, ^{68}Ga, ^{89}Zr, ^{99}mTc, ^{111}In, ^{177}Lu, ^{225}Ac	PET/SPECT probes for tumor imaging, lymph node mapping, radiotherapy	Versatility, biocompatibility, high loading capacity
Surface Functionalization	Surface-engineering for targeting and stability	PEGylation, zwitterionic polymers, targeting ligands (e.g., PSMA, RGD)	Labeled on chelators or surface moieties	Active targeting to tumor biomarkers, longer circulation, immune evasion	Enhanced targeting, prolonged circulation, immune stealth
Targeting Mechanism	How the nanoparticle homes in on diseased tissue	Passive (EPR effect), Active (ligand-receptor binding)	Not specific depends on imaging needs	Tumor-specific imaging, metastatic niche visualization	High specificity, early diagnosis, reduced background signal
Imaging Modalities Supported	Type of molecular imaging techniques used	Multimodal platforms (e.g., PET/MRI, PET/optical)	PET: ^{64}Cu, ^{68}Ga, ^{89}Zr SPECT: ^{99}mTc, ^{111}In	Multi-parametric tumor characterization, intraoperative imaging	High sensitivity, deep tissue penetration, real-time tracking
Theranostic Capabilities	Combined diagnosis and therapy	Hybrid nanoplatforms (e.g., liposome + radiotherapeutic)	^{177}Lu, ^{225}Ac (therapy) + ^{64}Cu/^{89}Zr (diagnosis)	Simultaneous therapy delivery and monitoring	Personalized treatment, reduced off-target toxicity
Pharmacokinetics	Circulation time, biodistribution	Modified via PEG, size (~100 nm), charge tuning	All suitable isotopes	Tumor retention over hours/days, minimized RES uptake	Optimized delivery, enhanced accumulation in tumors
Regulatory Progress	Translation from lab to clinic	GMP-compliant systems, standardized formulations	All clinically relevant isotopes	^{64}Cu-labeled liposomes, ^{111}In-SPIONs entering Phase I/II trials	Enhanced reproducibility, safety, and regulatory compliance
AI Integration	Use of AI for image analysis and design	Deep learning models for image interpretation	Not dependent on isotope	Radiomics, lesion classification, patient stratification	Automation, predictive diagnostics, real-time analysis
Multimodal Applications	Integration with other contrast agents	Iron oxide (MRI), quantum dots (optical), gold (CT)	Dual-labeled: e.g., PET/MRI, SPECT/optical	Comprehensive anatomical + functional imaging	Synergistic resolution, anatomical mapping with molecular signals
Challenges and Future Scope	Barriers and directions	Biodegradable materials, DNA origami, immune modulation	Future isotopes: ^{161}Tb, ^{149}Tb	Preventing long-term toxicity, improving specificity, personalized nanoparticle synthesis	Scalable synthesis, deep-tissue targeting, early-stage disease monitoring

diagnostic approach where MRI allows for accurate anatomical mapping, PET allows sensitive detection and quantification of disease and fluorescence imaging allows for surgical resection and margin evaluation in real-time [86].

These benefits are particularly evident in the oncology field, where early detection and targeted treatment have a substantial impact on patient outcomes. The dual functionality of nanoparticles as both diagnostic and therapeutics has given rise to emergence of theranostics platforms single agents which can both localize to the disease site, monitor and treat it. These systems are in the capacity to give therapeutic delivery of radionuclides, chemotherapeutic, photosensitizer or immunotherapeutics, as well as imaging moieties [11]. For example, the same nanoparticle can have a cytotoxic drug within the center, can be radiolabeled for PET or SPECT tracking, as well as tagged with a fluorophore for intraoperative visualization. This multifunctional approach allows clinicians to monitor the delivery of therapy and assess the efficacy in real-time and tailor treatment regimens accordingly. A hallmark feature of theranostic nanoparticle is that they can combine the diagnostic clarity with the precision of the therapy. In both clinical and preclinical research, liposomal and polymeric nanocarriers have been used for the delivery of drugs such as doxorubicin and paclitaxel and combine them with imaging agents for PET or MRI [87]. In some studies, such as is shown in **Figure 10**, iron oxide-based PET/MRI probes functionalized with DOTA and RGD have been able to target- or imaging tumors in U87MG mice as observed by T2-weighted MRI and ^{64}Cu PET and competitive blocking validation [88]. These platforms have enabled researchers to view biodistribution in real-time, assess tumor accumulation and observe therapeutic response in real-time. In previous studies, ^{64}Cu-DOTA-IO-RGD nanoparticles showed targeted accumulation into tumor in PET/MRI imaging studies confirmed by MR and PET scan in the presence and absence of c(RGDyK) blocking. Similarly, nanoparticles of radioisotopes such as ^{177}Lu or ^{225}Ac can be used to ablate diseased tissue and at the same time report the progress of treatment (by imaging) to develop a closed feedback loop that can enhance efficacy and reduce toxicity [89].

Equally important is the ability of these platforms to operate on multiple spatial and temporal scales, dealing with an important challenge of modern medicine: that the disease is dynamic and heterogeneous. Cancer, for example, is not a static disease, with fluctuation in the expression of antigens, metabolism and vascularization which makes traditional treatment strategies difficult. Agnostic nanoparticles with long-circulating properties and molecular targeting ligands for tracking disease based on these biological variations. PET and SPECT offer sensitive longitudinal change information of tumor biology; MRI offers the detailed anatomic localization; and optical imaging offers accurate and complete resection information intra-operatively. Collectively such features culminate in truly personalized therapy that changes in response to the evolution of disease. These innovations, however, are also altering the design of clinical trials and the way the patient is grouped. By combining both diagnostic and therapeutic functionality in a single agent, researchers can be able to evaluate drug delivery and efficacy in a single patient at the same time. This capability enables smaller trials with reduced inter-patient variability, quicker biomarker-facilitated trial stratification and stronger clinical data. The result is a faster and more targeted translation of new therapies from bench to bedside - leading to a more efficient translation of precision medicine to the patient [90].

Early clinical trials for nanoparticles with PET/MRI capabilities have led to better detection of lymph node metastases in breast and prostate cancer, better staging and impact treatment strategies. Meanwhile, theranostics systems using radioisotopes and chemotherapy combinations have made treatment more efficacious and less systemic toxic for a variety of malignancies [91]. Taken together, these advances point to the game-changing potential of multimodal and theranostic nanoparticles in clinical practice. By the combination of sensitive, specific and spatially precise diagnostic capabilities with targeted therapy such systems represent a new paradigm of personalized medicine.

Their ability to work on biological time scales from molecular signatures to organ level mapping make them important tools in the next generation of healthcare. Enabled by innovation in nanotechnology, surface engineering and an AI powered approach to analytics these

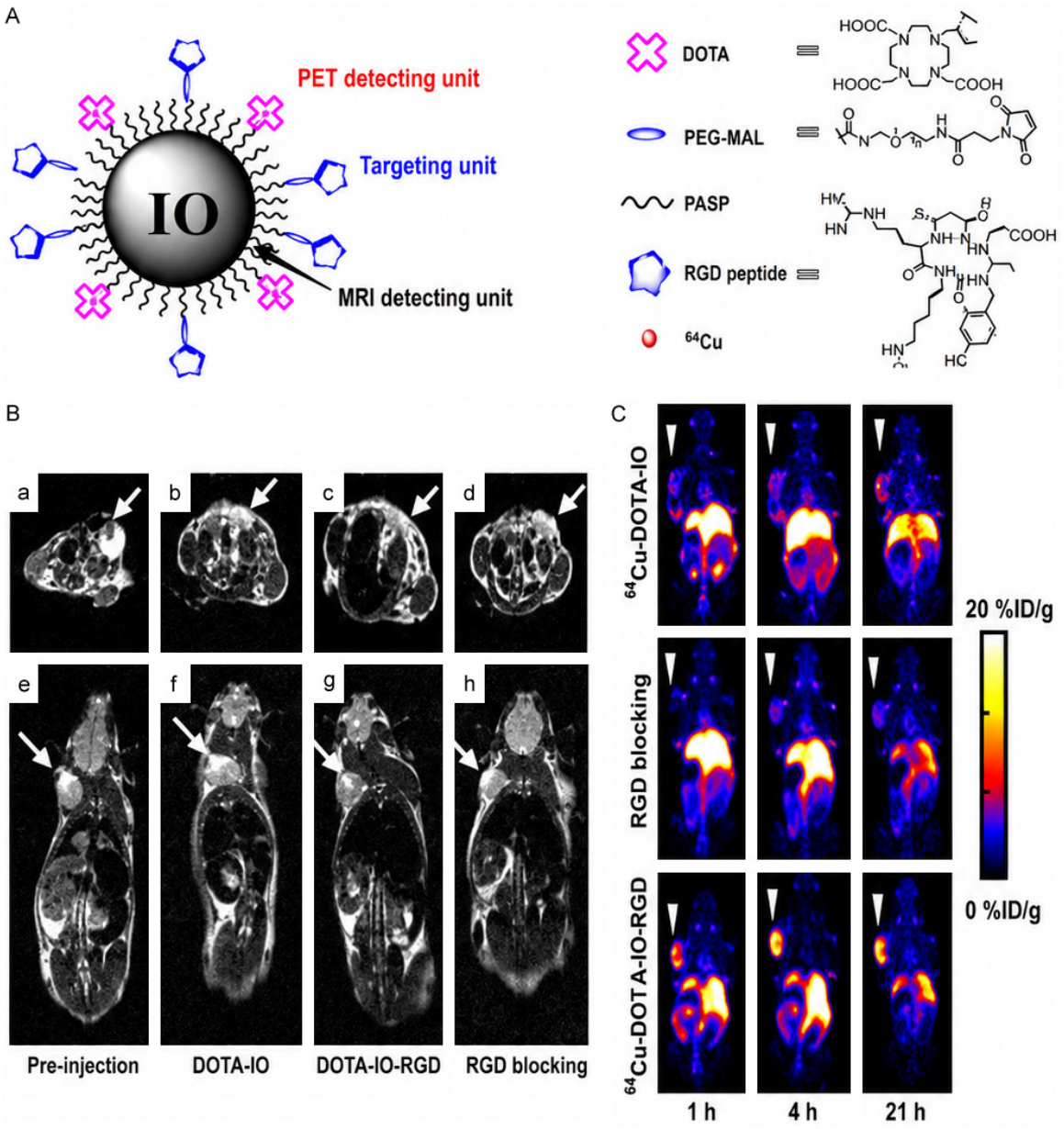

Figure 10. (A) Schematic illustration of PET/MRI probe based on iron oxide (IO) nanoparticle. (B) T2-weighted MR images of nude mice bearing U87MG tumor before injection of IO nanoparticles ((a) and (e)) and at 4 h after tail-vein injection of DOTA-IO ((b) and (f)), DOTA-IO-RGD ((c) and (g)), and DOTA-IO-RGD with blocking dose of c(RGDyK) ((d) and (h)). (C) Decay-corrected whole-body coronal PET images of nude mouse bearing human U87MG tumor at 1, 4, and 21 h after injection of 3.7 MBq of 64 Cu-DOTA-IO, 64 Cu-DOTA-IO-RGD, or 64 Cu-DOTA-IO-RGD with 10 mg of c(RGDyK) peptide per kilogram (300 μg of iron-equivalent IO particles per mouse) [88].

platforms are driving a future in which diagnosis and therapy are no longer discrete processes but integrated strategies and individualised to the individual patient. This convergence is changing the way medicine is practiced and bringing precision, efficacy and personalization at a level that was almost unheard of a decade ago.

Biocompatibility, toxicity, and immunogenicity challenges of nanomaterials

While nanotechnology-enabled imaging platforms provide a lot of benefit in early cancer detection, biocompatibility and safety over a long period of time are very important barriers for clinical translation, especially for inorganic

or non-biodegradable nanomaterials. Recent studies increasingly put emphasis on the fact that toxicity is not determined solely by nanoparticle size and dose but rather also by its elemental composition, degradation behaviour and immune interactions [92, 93].

Heavy-metal-based quantum dots (QDs), and cadmium-based quantum dots in particular (such as CdSe/ZnS) have raised a lot of safety issues due to the propensity to long-term bioaccumulation (**Table 3**). Investigations showed that gradual degradation of the shell may lead to release of toxic Cd2+ ions and accumulation in the liver, spleen and kidney with induction of oxidative stress and inflammatory responses with repeated exposure. These findings have led to the faster development and use of cadmium-free alternatives such as indium phosphide and carbon-based quantum dots which have been shown to have a better clearance profile and less systemic toxicity [94, 95].

Iron oxide nanoparticles (IONPs) are generally considered relatively biocompatible and are already being used clinically, however the literature is beginning to point out the presence of dose related magnetotoxicity limits. Excessive iron loading or prolonged retention has been shown to lead to breakdown of iron homeostasis, production of reactive oxygen species through Fenton reactions and activation of macrophage-mediated inflammatory pathways. Studies highlighted the necessity of strict dose control, ultrasmall particles design and biodegradable coating for reducing the risk of iron overload and inflammation [96].

Surface coating induced immunogenicity, in particular of polyethylene glycol (PEG), has become an important translational problem. Recent clinical and preclinical reports have confirmed the evidence of PEGylated nanomaterials being able to elicit anti-PEG antibodies, resulting in faster blood clearance, lower imaging efficacy and in some instances, hypersensitivity reactions. These observations have led to the discovery of alternative approaches to stealth, such as the use of Zwitterionic polymers, polysaccharide coatings and biomimetic camouflage of cell membranes exhibiting lower immunogenicity with retained circulation stability [97].

Collectively, such findings underscore the importance of accounting for biocompatibility and toxicity as key design constraints to keep in mind as opposed to secondary considerations.

Challenges and limitations

Although nanoparticles have demonstrated tremendous potential as highly sensitive and specific platforms for cancer imaging and therapy, clinical adoption of these nanoparticles is confronted by substantial barriers that must be overcome if the potential of nanoparticles is to be fully realized. These hurdles are an outgrowth of the complex interplay of physicochemical design, biological behaviour and the demands of clinical practice. Such limitations, understanding and overcoming them is important to the development of nanoplatforms from the experimental setting to routine clinical practice. One of the major limitations of nanoplatforms is the biodistribution and clearance profiles. Unlike the low molecular weight agents, nanoparticles have a scale of action where physicochemical properties, such as size, shape and surface charge prevail in determining their behaviour in the bloodstream and in the microenvironment of the tumours. Particles falling into the range of approx. 10-100 nm are ideal for extravasation through the fenestrated vasculature of tumors through the enhanced permeability and retention (EPR) effect but this size range is also associated with challenges of showing significant clearance and accumulation. Particles that are smaller than about 5-7 nm are at risk of being fast cleared by the kidney and removed from circulation before therapeutically or diagnostically effective. On the other hand, nanoparticles larger than approximately 100-150 nm are likely to be recognized and bound by the mononuclear phagocyte system (MPS), with deposition in the liver, spleen and lymph nodes. This contributes to major off target distribution and can result in a decrease of overall specificity and efficacy of formulation [93]. The major issues involved in imaging of cancer with nanotechnology and emerging approaches of mitigation are presented in **Table 4**.

The interplay between biodistribution and clearance have far reaching implications for diagnostic and therapeutic nanoparticles. Prolonged circulation times are able to provide target accumulation and increased signal detection, but this has to be balanced against the potential risk of prolonged tissue retention

Table 3. Quantitative performance comparison of SPIONs, quantum dots (QDs), and upconversion nanoparticles (UCNPs) for cancer imaging

Nanoplatform	Primary Imaging Modality	Key Quantitative Metrics	Typical Performance Range	Evidence Level	Key Strengths	Key Limitations
SPIONs	MRI (T_2/T_2*)	Transverse relaxivity (r_2)	~100-300 $mM^{-1}s^{-1}$ (3 T)	Preclinical + limited clinical	Deep tissue imaging; high spatial resolution; clinical familiarity	Lower sensitivity than nuclear/optical imaging; dose-dependent magnetotoxicity
Quantum dots (QDs)	Optical (fluorescence)	Quantum yield; signal-to-noise ratio (SNR)	Quantum yield: 30-90%; SNR: >10-100 × dyes	Mainly preclinical	Exceptional brightness; multiplexing; photostability	Heavy-metal toxicity (Cd-based); limited tissue penetration
UCNPs	Optical (NIR upconversion)	Upconversion efficiency; background autofluorescence	Upconversion efficiency: ~0.1-1%; near-zero autofluorescence	Preclinical	Deep tissue penetration; minimal background; high contrast	Lower absolute brightness than QDs; complex synthesis

Table 4. Challenges and their solutions

Challenge	Description	Implications	Emerging Solutions
Biodistribution & Clearance	Nanoparticle size, shape, and charge affect EPR effect, renal clearance (<5-7 nm), and MPS uptake (>100-150 nm).	Non-specific organ accumulation; suboptimal tumor targeting.	Optimized size (10-100 nm), stealth coatings (PEGylation), surface charge tuning.
Toxicology & Immunogenicity	Surface properties and composition can trigger complement activation, oxidative stress, or immune responses.	Inflammatory reactions; species-specific discrepancies between preclinical and clinical models.	Biocompatible materials, species-relevant models (e.g., humanized mice), reduced immunogenicity surface designs.
Scalability & Reproducibility	Complexity in synthesis and functionalization causes batch-to-batch variability in size, charge, or drug/labeling consistency.	Inconsistent efficacy/safety; regulatory delays.	Standardized protocols, quality-by-design (QbD), automation in nanoparticle synthesis and characterization.
Regulatory Complexity	Multifunctional nature (diagnostic + therapeutic) challenges conventional regulatory frameworks (drug/device/biologic hybrids).	Slower approvals; high development costs.	Harmonized global guidelines; nanomedicine-specific regulatory pathways; early engagement with regulatory bodies.
Cost & Commercialization	High R & D and production costs; specialized infrastructure; uncertain reimbursement and IP issues.	Investment barriers; slow market uptake.	Demonstration of superior cost-effectiveness; modular, scalable manufacturing; strong IP strategies.
Patient-to-Patient Variability	Tumor heterogeneity and diverse immune/metabolic profiles affect nanoparticle targeting and performance.	Inconsistent outcomes; difficult patient stratification.	Personalized nanomedicine approaches; AI-driven patient profiling and adaptive nanoparticle design.
Preclinical-Clinical Translation	Discrepancies between animal models and human physiology limit predictive accuracy of nanoparticle behavior.	Failed translation; unexpected toxicity.	Humanized models, patient-derived xenografts, multi-omics integration for better predictive modeling.
Multifunctional Complexity	Integration of imaging, therapy, and targeting functions increases design complexity and potential for failure points.	Increased development risk; more stringent validation.	Modular design strategies; AI-assisted structure-function analysis; robust validation at each functional layer.

and possible toxicity. The design of nanoparticle with precise physicochemical characteristics, surface chemistry minimizing protein coronation and stealth properties to minimize clearance by the MPS is an area of active research. Yet striking this balance across populations of patients where factors such as immune status, metabolism and comorbidities are often significantly different is an ongoing challenge. Closely related to biodistribution is the problem of toxicology and immunogenicity [94]. The very features that attribute to nanoparticles being able to cross into the tumor and cellular compartments can also cause undesirable biological interactions such as the triggering of the complement system, the producing of oxidative stress or the triggering of unwanted immune responses. Surface charge, composition and morphology may play a role in internalization by the cell, as well as the activation of inflammatory cascades. In some instances, nanoparticles that are well tolerated in preclinical animal models may have significant immunogenic or toxic effects in human subjects because of species specific differences between metabolism and immunology. The risk of long term accumulation and potential toxicity within critical organs such as the liver, spleen or kidneys, also adds to the challenge of advancing them to clinical translation [95].

There are additional limitations arising from the challenge to scale up and replicate. The very specific physicochemical properties of the nanoparticles enabling the nanoparticles to perform their desired diagnostic or therapeutic function need to be maintained during manufacture. Yet the complexities of nanoparticles synthesis, surface functionalization and radiolabeling can lead to a variability from one batch to another that makes quality control and clinical translation difficult. Variations in the particle size, surface coating or radioisotopic labeling can have a substantial impact on biodistribution, as well as clearance profiles and targeting of disease. To overcome these limitations, it is important to implement stringent protocols for synthesis, purification and characterization of nanoparticles with the goal to preserve their desired physicochemical and biological characteristics during the scale-up production [96]. This has been difficult if not impossible for many platforms, especially when transitioning from the experimental, or preclinical, setting into clinical trials and commercial manufacturing. The path to clinical translation is also complicated by a complex and changing regulatory landscape. The combination of multiple functionalities into one nanoplatform such as combined diagnostic and therapeutic functionality leads to huge regulatory complexities. Such platforms are often blurring the lines between pharmaceuticals, medical devices and biological products, creating problems in traditional review systems. In many cases, the requirements for nanoparticles to be used in preclinical studies include in depth toxicology studies, long term biodistribution assessments and detailed characterization of their physicochemical properties. The fact that there are no standardized metrics to evaluate safety, efficacy and replicability of nanomaterials makes this process of review more difficult and leads to delays and higher costs associated with the development of nanomaterials [97].

Similarly, commercialization of nanoplatforms have hurders associated with intellectual property, market positioning and reimbursement. The design and manufacture of nanoparticles can often require highly specialist equipment and expertise, which means that the cost of producing nanoparticles can be significant. Coupled with the length of the timeline to clinical translation and an unknown path to market adoption, this has limited investment and slowed down the clinical adoption of many promising platforms. In a medical environment that is increasingly defined by both cost and evidence based practice, clinical efficacy and cost effectiveness of nanomedicines needs to be clearly demonstrated over established alternatives [98]. Finally, despite the advancements made in surface engineering and delivery to target, patient to patient variability in disease biology and treatment response, is a fundamental challenge for the nanoplatforms. The microenvironment of tumors is very heterogeneous from patient to patient so it is very difficult to design “one size fits all” nanoparticles that will reliably provide the desired biodistribution and therapeutic outcome. The balance between the biology of the disease and the particular features of patients call for highly adaptable platforms, which can be tailored to the individual patient profile and adds to difficulties of their clinical translation [99].

Although these limitations pose great challenges, continued development of nanomaterials design, surface engineering as well as multi parametric characterization provides avenues for their minimization. Researchers are focusing on development of nanoparticles with well-controlled physicochemical properties and stealth surface chemistries capable of predictable behaviour across populations of patients. New synthesis and characterization techniques, coupled with progress on quality by design approaches are making it possible to achieve reproducibility over manufacturing scales. Meanwhile, advances in preclinical models such as patient derived xenografts and humanized mouse models will help to make better predictions of clinical behavior and immunogenicity. Regulatory agencies are also starting to adapt to the complexity presented by nanoplatforms, and are addressing the issue by looking into new paradigms for review and guidance documents that reduce the path to approval for combined diagnostic therapeutic platforms. The advent of artificial intelligence (AI) driven analytics allows for greater characterization of the structure function relationships to provide a sound scientific foundation for evaluation of efficacy and safety across patient populations. With greater innovation in the different fields, these constraints can become roadblocks and guideposts as they guide the design and clinical translation of nanoparticles to realize their potential.

Emerging directions and innovative concepts

The roadmap of nanotechnology in biomedical imaging is rapidly gaining momentum and an increasing emphasis is on those platforms, which in addition to the elucidation of disease biology, are able to adapt and respond to the complex microenvironment in which disease resides. The second generation nanoparticle far exceeds the titration of passive local tensors, to include smart designs which combine responsiveness, precision targeting and capture of multi parametric details within a single formulation. Such innovations have the possibility to change the way diseases are solved and treated, and the once dreamed of notion of precision, personalized and molecularly targeted medicine has become a reality [100].

One of the strongest trends is development of intelligent nanoparticles which react to physiological features of microenvironments of diseases. In contrast to a more passive system that conventional platforms are, these nanoparticles can be developed to identify, detect and change according to a highly specific stimuli that may exist inside a tumor or pathological tissue. The microenvironment of a lot of tumors is a bit acidic, and the design of such carriers, as pH responsive ones, uses this aspect. These structures are always stable under physiological PH (~7.4) but break-down or spill their cargo when exposed to the lower PH (6.5-6.9) of the tumoral environment. Analogous approaches have been made with enzyme-responsive nanoparticles, oxidant-responsive nanoparticles and hypoxiaresponsive nanoparticles. Via utilisation of these physiological signals, the smart nanoparticles allow extremely regional activation, which will reduce a systemic exposure and off target effects [101].

More advanced designs have come thereafter to combine several triggers in one form of configuration. The dual/multi responsive nanoparticles may combine the pH dependent sensitivity with enzyme or thermal activation with a precision similar to disease heterogeneity. These systems provide very spatiotemporally specific delivery of diagnostic or therapeutic cargo and it is now possible to monitor disease development and therapeutic response in ways that were not previously possible with historical probes. In tandem with development of smart nanoparticle engineering is use of artificial intelligence (AI) and deep learning in nanoparticle design and interpretation of imagery. The extreme complexity of biological setting has always been a problem to the nanoplatform design which is expected to have predictable behavior across a population of patients. This process is being revolutionized today through the use of AI powered methods. Machine learning algorithms can be used in the analysis of large data sets of physicochemical properties, cell interactions, clinical effects, to identify the latent structure of design and the design rules for the in vivo behaviour of nanomaterials. Such developments allow the researchers to go beyond the concept of empirical trial-and-error and take it to the realm of guiding the logical tailoring of nanoparticles with a highly individualized biodistribution, clearance and targeting [102].

The interpretation of molecular imaging data produced by nanoparticles has also changed

with the current use of AI. When used in PET, MRI, SPECT or optical studies, deep learning platforms are able to determine disease defining patterns over multi parametric data sets to draw out information that could otherwise be missed by current techniques of analysis. These strategies enable the early diagnostics, precise planning of treatment and get high level of prediction of treatment results. The combination of AI and nanoplatform design is inconvenient, which is how it is coming possible to tailor the measure of diagnostic and treatment to the needs of peculiar individuals, which conforms to the requirements of precision medicine. Another major trend that is addressing molecular imaging and therapy is that of biodegradable and bioinspired nanoparticles. Unlike some of the first generations nanoplatforms, which tended to be inorganic core based or to have long circulatory vectors which can result in accumulation and potential long term toxicity, new generations of nanoparticles take their cues directly out of nature. Highly biocompatible carriers degradable in physiological conditions may be built on the basis of natural biopolymers, e.g., chitosan, silk fibroin, or alginate, or may be based on DNA origami platforms. These carriers may get degraded and cleared out from the body through clearance routes and lessen the opportunities of long term toxicity and immunogenicity [103].

It is also possible to make biodegradable nanoparticles relevant to very specific biomedical (applications), including highly localized form of therapy in tumors, and targeted delivery of genes, RNAs and immunomodulatory agents. These platforms are also given stimuli responsive qualities and the result could be smart carriers with the kind of specificity and efficiency of the biological molecular machines. The future challenge is to generate nanop article carrier systems that would behave in a similar way to that of the cells and follow the physiological design principles to be designed, therefore, achieving safer and more competent therapeutic and diagnostic systems. Perhaps the sternest frontier in nanomedicine is to gain molecular specificity, single cell resolution in the diagnosis and treatment of diseases. Disease tracking and characterization such as at the level of individual cellular units have been a holy grail to biomedical science, as this would help detect disease way before it becomes manifest anatomically. Newer developments, in the area of nanoprobe design, means that such a target is even within reach. Truly small nanoparticles e.g., plasmonics based on quantum dots, rare earth nanocrystals or surface enhanced Raman scattering platforms can be designed to bind to highly specific markers on the surface of cells with great specificity and the individual disease bearing cell within a complex tissue environment can then be individually detected [16].

Integration platforms which combine single cell targeting with ultrasensitive optical or nuclear detection are giving a heretofore-unseen clarity in clinical assays. However, through the principles of surface engineering these nanoparticles can be biased to preferentially bind cellular antigens, disease associated lipids or cellular exosomes, giving a highly specific signature that may be imaged with optical or PET/SPECT imaging systems. These developments can lead in the early detection in order to allocate and isolate the disease and also can describe the phenotypes of cells related to therapy resistance, disease advancement or metastatic progress. Simultaneously, recent improvements in the intra-operative optical probes allow detection and removal of the microscopic disease providing more comprehensive resections and better patient outcomes [104].

Notably, such developments are obtaining more and more consistency with the principles of the precision and personalized medicine. The extremely specific nature of both diagnosis and therapy is achieved due to the possibility to combine both genomic, proteomic and metabolomic data with highly targeted nanoparticles. On such platforms disease can be detected, the molecular signature thereof mapped and the release of therapeutic payloads can be timed, in reaction to cellular and tissue level signals. This is shaping nanomedicine to be transforming out of an experimental venture into a purely translational platform that will work through the spectrum on either side of disease diagnosis, classification as well as treatment [105].

The advances are revolutionizing clinical trials, patient stratification and therapy design. Precision therapy: Even highly heterogeneous tumors can be treated using smart nanoparticles that respond to microenvironmental signals. This has been a long running obstacle to

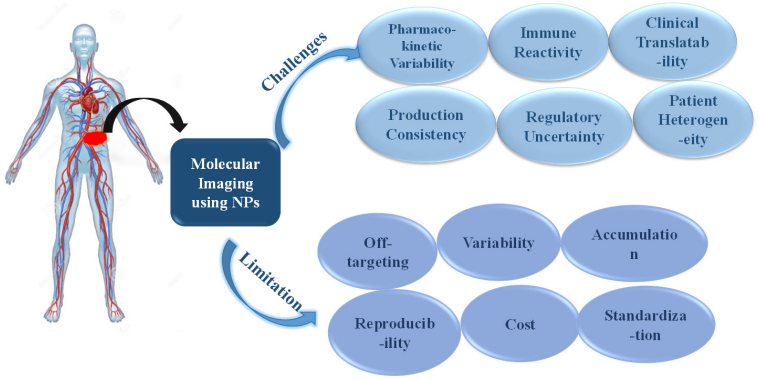

Figure 11. Challenges and Limitation of nanomaterials in cancer imaging.

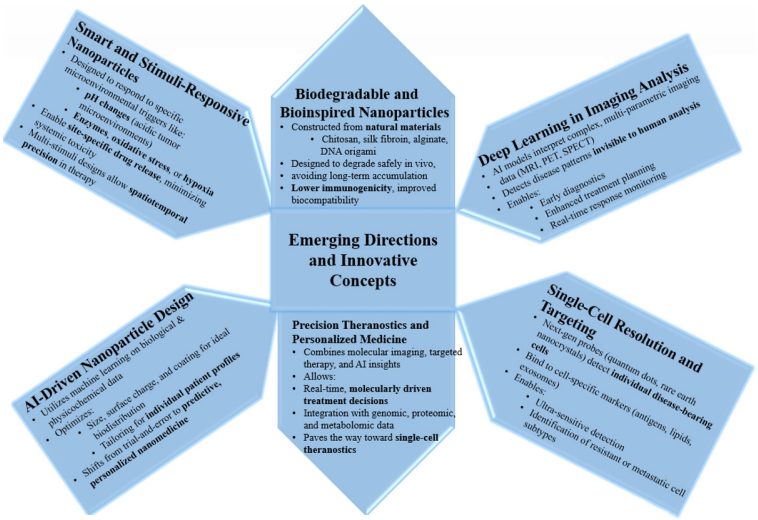

Figure 12. Innovative concepts of nanomaterials in cancer imaging.

effective disease treatment. The extremely customized nature of carriers can be brought about by AI-optimized design platforms that can personalize the nanoparticles to suit the patient profile particularly well, and which change with any shifts in disease dynamics. Long term toxicity may be avoided by use of biodegradable and bioinspired platforms hence making long term monitoring of therapy and administration possible among the patients [106].

The most attractive of all is the vision of realization of the goal of the so-called single cell theranostics: the ability to identify, characterise and treat the disease of a patient with the precision which can act at the cellular and molecular level. In this model, nanoparticle as carrier/contrast agent transforms into intelligent platforms which play as an active role in disease diagnosis and treatment. With the intersection of multi-modality platforms, the use of AI in design and an ability to move to a biomimetic engineering approach, this goal is now becoming a reality and a forthcoming change with regards to detection and treating disease.

As numerous advances continue to be made in different fields such as precision engineering and multi-modality design, artificial intelligence and bioinspired materials, nanomedicine is shaping the future of medical practice. The overarching motivating factor is that in the next decade we are bound to see realization of these platforms out of the experimental systems and into the everyday clinical practice requiring redefinition of the limits of precision diagnosis and targeted therapy. The age of highly specific, multi-functional and intelligent nanoparticle based platforms has dawned and new territories in patient care are being conquered and precision medicine is becoming an even more realizable possibility (**Figure 11**).

Clinical translation and outlook

The exponential progressions in design of nanoparticles suitable in medical imaging has predestined the slow replacement of nanoparticles as instrumentation out of the experiment lab and into the clinical setup (**Figures 12** and **13**). However, comparison of the preclinical evidence of their efficacy and specificity is as wide as it can be, the use of nanoplatforms in the clinic seems to be slower than it should. They are complex; matters of regulatory stringency, industrial reproducibility, life-long safety and clinical work-flow integration (**Figure 14**). However, a growing number of clinical trials and other early research studies have now begun to bring a plausible pathway

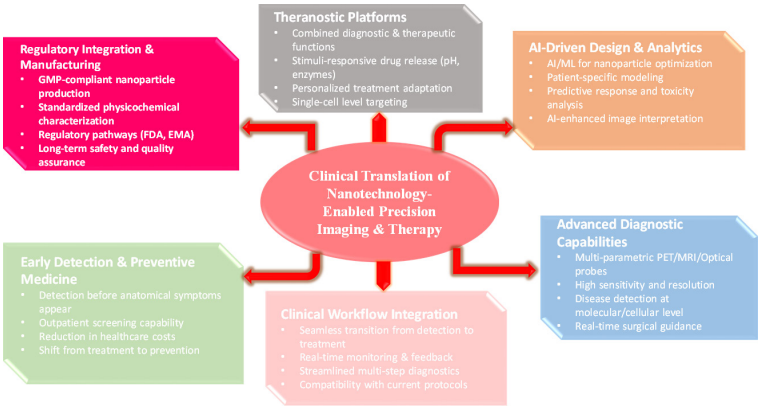

Figure 13. Clinical translation of nanotechnology enabeled precision imaging and therapy.

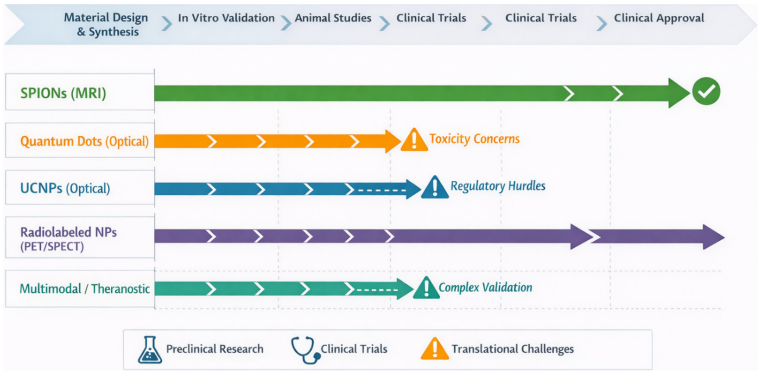

Figure 14. Clinical translation timeline of nanoplatforms for cancer imaging.

into the mainstream use of nanotechnology enabled diagnostic platforms and adopting precision medicine as a clinical norm into clear view.

An overview of the Nano-based imaging technology in terms of clinically relevant trials show potential and limitation. Liposomes and polymeric nano-particles have come furthest and formulations like lipext ^{64}Cu labelled liposomes have shown an ability to localize and quantitate tumors in clinical trials, long circulating carriers of PET and PET/CT studies. Correspondingly, iron oxide nanoparticles were used as MRI contrast agents in the detection of liver and lymph nodes and are clinical candidate in some formulations with desirable biocompatibility characteristics and compatibility with protocols in use. Targeted nanoparticles such as prostate specific membrane antigen directed nanoparticle or integrin expressing tumor directed nanoparticle have moved on to early phase trials and have given very specific images that may be used to construct the correct description of the disease and staging [14].

Even though clinical translation of some platforms particularly that based on very complex surface chemistries, or multi-modality payloads have proven difficult, incremental progress has paved the way to potentially stronger clinical trials in the medium-term. Recent families of nanoparticles have been focused on improved reproducibility and precise design, and hence new generations will be appealing subjects of clinical testing. The clinical potential of medicines based on nanotechnology has been substantially improved by new capabilities to manufacture nanoparticles in Good Manufacturing Practice (GMP) conditions. Conversely, the improvement in characterization methodology has enhanced the capability of the developer and regulators to carry out physicochemical characterization, biodistribution data and long term toxicity elevated in patient grouping [21].

One of most urgent directions which the field should use is the creation of the channels of nanotechnology introduction to regular diagnostic practice. Such pathways should be able to strike a balance between scientific innovations and patient safety and clinical feasibility, economic viability (**Table 5**). The use of nanoparticles to improve sentinel lymph node mapping is an early example; iron oxide nanoparticle has been shown to have a good risk benefit-structure in clinical trials against breast and other malignancies. In such cases nanoparticles have replaced conventional radiocolloids to allow very sensitive and specific intraoperative localization and reduce the exposure of radiations to the patients and achieve accuracy of surgery. The same progression has been made in the fields of PET and MRI nanoparti-

Table 5. Innovative domain

Innovation Domain	Key Breakthroughs	Mechanistic Insights	Translational Potential
Smart Stimuli-Responsive Nanocarriers	pH-, redox-, enzyme-, hypoxia-sensitive nanoparticles	Remain inert in normal tissue; activated in diseased microenvironments (e.g., tumor acidity, oxidative stress)	Spatially-confined activation; minimal off-target toxicity; effective in heterogeneous pathologies
Multi-Stimuli Platforms	Dual- and tri-modal responsive systems (e.g., pH + enzyme + temperature)	Sequential or synergistic release mechanisms for complex microenvironmental cues	Enables programmable cargo release tailored to tumor subtypes and dynamic states
AI-Driven Nanoparticle Engineering	Machine learning-guided material selection, size/charge tuning, and ligand optimization	AI models trained on physicochemical & biological datasets predict in vivo behavior, clearance, and efficacy	Rapid, patient-specific nanoparticle design with reduced trial-and-error; higher translational fidelity
AI-Enhanced Imaging Interpretation	Deep learning applied to multi-modal data (PET/SPECT/MRI/optical)	Identifies sub-voxel heterogeneity, early resistance patterns, and micro-metastatic niches	Diagnostic precision beyond human perception; real-time adaptive therapy planning
Biodegradable & Bioinspired Nanoplatforms	Carriers from chitosan, alginate, silk, DNA origami	Mimic physiological degradation and clearance; avoid accumulation in organs	Ideal for chronic applications, pediatric use, and regulatory approval; minimizes immunotoxicity
Single-Cell and Molecular Resolution Targeting	Rare-earth UCNPs, SERS probes, QDs with high-affinity bioconjugates	Target single tumor cells, circulating exosomes, or therapy-resistant clones within tissue	Enables “invisible” disease detection; facilitates early intervention and therapy re-stratification
Multifunctional Theranostics	One nanoparticle = imaging (PET/SPECT/optical/MRI) + therapy (siRNA, photosensitizers, radionuclides)	Integration of diagnostic and therapeutic roles with stimuli-responsive release and real-time feedback	Allows continuous monitoring of therapeutic efficacy and adaptive treatment cycles
Intraoperative Optical Imaging	Real-time probes for surgical navigation (tumor margin detection, nerve-sparing surgery)	Fluorescence, Raman, or photoacoustic signals for intra-surgical visualization	Increases resection accuracy, lowers recurrence rates, and enhances functional preservation
Biomimetic & Cell-Inspired Designs	Nanoparticles that mimic leukocytes, vesicles, or ECM-binding properties	Use of natural membranes, proteins, and enzymatic functions to enable stealth and homing	Next-gen biocompatibility and immune evasion for enhanced targeting and circulation
Personalized Precision Nanomedicine	AI-powered nanoplatforms tailored to patient genomics, proteomics, and tumor microenvironment	Modular designs adapted dynamically to disease evolution and host response	Foundation

cles to diseases staging and detection that have culminated in platforms that are easily incorporated into standard medical practices [107].

With the development in nanomedicine, the role of regulatory authorities has also changed, leading to the development of new guidance documents and review paradigms of the use of nanoparticles, taking into consideration their special property as a multi parametric platform of both diagnostics and treatment. A number of the international regulatory authorities such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA) and so on have implemented specific review pathways devoted to nanotechnology based medical products including the requirement to characterize these products and also address issues of quality and long term safety. These have helped in the study conducted clinical trials on nanoparticles which work cross boundary integrating the diagnostic and therapeutic loads on the same platform. Further harmonization of the review and approving of nanomaterials has also resulted in the creation of standardized measures that can be used to evaluate the physicochemical properties of the nano materials, biodistribution, and long-term toxicity which makes clinical translations close to achievable since there has been much more harmonization to the process [108].

The next step will be the clinical translation of nanotechnology based platforms to which artificial intelligence and deep learning will be leveraged to achieve accurate patient stratification, modeling of patient response to therapy and the ability to detect disease at a high sensitivity in complex populations of patients. The use of AI upgraded analytics already changed the clinical trial industry by mining unknown patterns out of multi parametric data, and allowing scientists to better understand the action of nanoparticles on different groups of patients. Precision medicine is also possible and cost effective because in clinical practice, these platforms can support highly personalized diagnostic and therapeutic interventions which change according to the dynamics of the disease [109].

It can be said that the biggest impact of nanotechnology on the clinical practice will be directly predictive role in personalized medicine and precision imaging in the future. The possibility to engineer nanoparticle surfaces incorporating very specific chemistries, multi parametric payload and response to stimuli, in combination with the ease of having multiple, affinity based binding events in a single design is giving the opportunity to abandon traditional one size fits all approaches to disease detection and treatment. Nanoparticles, which work in MRI, PET, optical and therapeutic scales, will make possible in the next years highly specific and patient-tailored systems that can spot disease, describing the molecular and cellular dynamics, target therapy to where it is required [16].

More generally, the clinical use of nanotechnology based platforms has the potential to fundamentally redefine the role of molecular imaging within patient care. In the conventional clinical setting, the process of disease detection, characterization, therapy, and follow up are separate steps involving different teams, and often represent delays and inconsistencies in the patient experience. In contrast, nanoparticles have evolved into multi parametrics and theranostics that facilitate these steps to be combined and streamlined in a single seamless process. By combining highly sensitive diagnostic capabilities, accurate molecular characterization, targeted therapy and monitoring over time, these platforms have the potential to simplify the multi stage workflow into a highly coordinated and simplified clinical protocol. Such advances have the potential to reduce delays between detection and initiation of treatment, optimize treatment planning and enable more accurate, patient specific disease management. Ultimately, the integration of nanotechnology based platforms into clinical practice is set to enhance patient outcomes in a wide range of disease contexts, bringing us precision medicine that operates with unprecedented efficiency and efficacy [110].

It will also be possible to initiate clinical nanoplatforms that will support the possibility of changing the state of empirical treatment to evidence based therapy design. Nanoparticles will facilitate the transition of statistical population based therapy to precision medicine by providing highly sensitive and multi parametric information on the biology of the disease and the therapy response to the disease. Such changes fundamentally change the way patient

care occurs in that today, it could be possible to design a treatment that changes according to the dynamic of the disease and the patient biology resulting in an improved outcome, reduced side effects, and more efficient clinical pathways [111].

With a changing nature of these platforms, there will arise an increase in the radius of their application beyond traditional clinical settings. It will become possible to detect disease many years before it is anatomically obvious as the possibility occurs to create highly sensitive, multi parametric diagnostic platforms that operate at the molecular and cellular level and will allow detection to be carried out early and successfully intervened in an outpatient or screening setting. This in its turn can transform disease management into prevention and early intervention with far reaching consequences to patient outcomes and lessening the burdensome long term costs of healthcare [112-117].

An overview of clinical translation pathways, regulatory progress and expected clinical impact of nanotechnology-based imaging platforms is presented in **Table 6**.

In the next few decades, the development of nanomaterials engineering, artificial intelligence and precision medicine will allow the medical application of nanoparticles through experimental platforms to clinical practice. Development of a well-established manufacturing and characterization pipeline and regulatory review and clinical trial design breakthroughs should help nanoparticles to mature into valuable platforms in precision medicine. By so doing, nanotechnology will transform the customary scope of clinical practice with highly sensitive, multi parametric, and patient centred platforms becoming the staple of the clinical workflow paving the way to the new generation of disease detection, characterization, and therapy by precision methods.

Manufacturing scalability and cost constraints

Despite their promising imaging performance, the limited manufacturing scalability and high production costs of many nanoplatforms remain major barriers to clinical translation. For example, the large scale synthesis of SPIONs entails a strict control over the particle size distribution, crystallinity and surface coating to ensure reproducible magnetic relaxivity, which often involves multi-step wet chemical/thermal decomposition processes, which involves a higher cost and batch-to-batch variation. Similarly, quantum dots, especially cadmium-based systems are based on high temperature organometallic synthesis and shell passivation that is complex, limiting the scalable production of quantum dots using Good Manufacturing Practice (GMP) compliance as well as the associated to regulatory and environmental compliance costs [118].

Upconversion nanoparticles (UCNPs) pose an even greater challenge as synthesis normally involves rare-earth dopants, high temperature reactions and low quantum efficiency, making the yield low and the cost of materials high as compared to the increase in optical performance. In contrast, radiolabeled nanoparticles have the advantages of existing radiopharmaceutical manufacturing infrastructure, but half-lives of radionuclide limit time constraints, specialized facilities, and high operational costs [119]. Collectively, these case studies pull out the point that complexity of manufacturing, quality control needs and regulatory compliance vs. material cost alone are some of the driving forces behind the high production cost of nanotechnology based imaging agents.

Limitations of the enhanced permeability and retention (EPR) effect

The EPR effect is widely known to be an important mechanism for passive tumor targeting of nanoplatforms; however, there has been a growing body of evidence that shows the use of EPR for targeting is not a reliable mechanism for consistent and clinically reliable tumor accumulation. Significant inter-patient variability and heterogeneity of tumors are major obstacles to effective EPR-based delivery. Differences in vascular permeability, interstitial fluid pressure, stromal composition and lymphatic drainage result in highly variable nanoparticle extravasation and retention from patient to patient and tumor type to tumor type. As a result, whereas highly vascularized tumors may show pronounced EPR effects, desmoplastic or hypovascular tumors such as pancreatic and some breast cancers, may show limited nanoparticle penetration.

To overcome these limitations, more and more attention has been paid to hybrid approaches

Table 6. Clinical translation of nanotechnology

Domain	Key Focus Areas	Highlights/Advances	Clinical Impact
1. Nanoplatform Development	- Liposomes -Polymeric NPs - Iron oxide particles	- ^{64}Cu-labeled liposomes in PET/CT - MRI contrast via SPIONs - Targeted PSMA/integrin NPs	High-resolution tumor detection and staging
2. Manufacturing & Design	- GMP scale-up - Surface chemistry refinement	- Batch reproducibility - Complex payload stability	Enables safe, scalable, trial-ready platforms
3. Clinical Integration	- Sentinel lymph node mapping - Surgical imaging agents	- Replaces radiocolloids - Minimizes radiation - Enhances intraoperative accuracy	Integrates easily into surgical & diagnostic workflows
4. Regulatory Pathways	- FDA & EMA guidelines - Long-term safety protocols	- Standardized evaluation of biodistribution & toxicity - Defined approval tracks for theranostics	Accelerates safe approval of multifunctional nanomedicines
5. Artificial Intelligence	- Predictive analytics - Patient stratification - Trial modeling	- Deep learning enhances diagnosis - Multi-parametric image interpretation - Therapy response prediction	Enables data-driven precision therapy
6. Theranostics & Multi-Functionality	- Dual imaging & therapy - Molecular targeting - Stimuli-responsive designs	- Combines PET/MRI/Optical with therapy - Personalized, adaptive payload release	Streamlines diagnosis, treatment & monitoring in one system
7. Personalized Medicine Transition	- Disease-specific tailoring - Affinity-based binding	- Abandons “one-size-fits-all” model - Adjusts therapy to molecular & cellular dynamics	Reduces side effects, increases efficacy
8. Workflow Simplification	- Integrated imaging, therapy & follow-up	- Replaces fragmented, multi-step protocols - Increases speed & coordination	Efficient, seamless patient management
9. Long-term Vision	- Disease interception before symptoms - Outpatient screening tools	- Sub-anatomical early detection - Molecular profiling of asymptomatic patients	Shifts care from treatment to prevention
10. Future Outlook	- AI + Nanotech + Biomimicry	- Ultra-sensitive, smart, biodegradable platforms - Real-time decision support	Redefines precision diagnostics & therapy; sets new clinical standard

which integrate passive EPR targeting with active targeting mechanisms. Active targeting usually includes surface modification of nanoplatforms with ligands such as peptides (e.g., RGD), antibodies or small molecules that interact with tumor-associated receptors, increasing cellular binding and tumor retention after extravasation. Preclinical studies have continuously shown that actively targeted nanoparticles have higher tumor uptake and better imaging contrast than the non-targeted systems based only on EPR. Emerging clinical imaging evidence has further suggested receptor-mediated targeting partial compensation of poor or heterogeneous EPR effects by inter-patient variability reduction.

Conclusion

The symbiotic meeting of nanotechnology and cancer imaging and therapy has led to a new era of precision medicine. The capability of nanoparticles for molecularly specific tumor targeting, combined with the implementation of the nanoparticles into multimodal and theranostic platforms, promises to revolutionize the early cancer detection and treatment. These advanced nanoplatforms can make high-resolution imaging, specific molecular characterization, and targeted therapeutic delivery possible, thus making it possible to diagnose and treat cancer at its earliest stages. However, the clinical implementation of nanotechnology-based platforms is faced with several challenges, including biocompatibility and long-term toxicity issues, manufacturing scalability and regulatory approval.

Despite these barriers, ongoing development of nanoparticle design, artificial intelligence and bioinspired engineering is aiding the clinical translation of these devices. Looking to the future, there is the opportunity to transform the status of care for oncology with nanotechnology-based personalized, early and minimally invasive diagnostic and therapeutic solutions to help improve patient outcome and reduce the burden of healthcare. The continued process of developing nanoplatforms, harmonization of regulations and improvements in clinical trial design will enable the integration of nanotechnology into routine medical practice leading to a future where cancer care will be more predictive, precise and patient-centric.

Disclosure of conflict of interest

None.

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