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Polymer-based nanoparticles for cancer theranostics: advances, challenges, and future perspectives

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Abstract

Polymer-based nanoparticles have emerged as powerful multifunctional platforms in cancer theranostics, offering the ability to integrate diagnostic imaging and targeted therapy within a single system. These nanocarriers enable improved tumor localization, enhanced contrast agent delivery, and controlled therapeutic release, addressing limitations associated with conventional contrast agents such as poor specificity, rapid clearance, and systemic toxicity. Advances in polymer chemistry and nanoparticle fabrication methods, including solvent evaporation, nanoprecipitation, emulsion-diffusion, and emulsion polymerization, have allowed precise control over particle size, surface charge, and drug-loading efficiency, optimizing biodistribution and imaging performance. Hybrid polymer-inorganic nanoparticles further expand functionality by incorporating magnetic, optical, or radiopaque components, enabling multimodal imaging and stimuli-responsive drug release while maintaining biocompatibility. Key factors influencing the efficiency of polymer nanoparticle-based contrast agents include physicochemical properties such as particle size, morphology, surface functionalization, and responsiveness to tumor microenvironmental stimuli. These attributes collectively govern circulation time, cellular uptake, and accumulation in tumor tissues via passive and active targeting strategies. While promising, the clinical translation of these systems faces challenges including immunogenicity, pharmacokinetic variability, long-term safety concerns, and manufacturing scalability. Recent innovations in ligand functionalization, biomimetic coatings, and multifunctional nanoparticle design continue to advance therapeutic specificity and imaging precision, positioning polymer nanoparticles as versatile candidates for personalized oncologic care. This review provides a comprehensive synthesis of current methods for contrast agent integration, the role of physicochemical properties in performance, biological interactions, safety considerations, recent design innovations, translational barriers, and future research directions for polymer nanoparticle-based cancer theranostics.

Keywords

Polymer nanoparticles, cancer theranostics, contrast agent delivery, targeted drug delivery, nanoparticle functionalization

Introduction

The integration of polymer-based nanoparticles into cancer theranostics has revolutionized the landscape of modern oncology by combining targeted therapy and precise diagnostics within a single platform [1, 2]. Unlike conventional contrast agents, which often suffer from short circulation times, poor specificity, and dose-limiting toxicities, polymeric nanoparticles offer a versatile and tunable delivery system capable of overcoming biological barriers while simultaneously enhancing imaging quality and therapeutic efficacy [3, 4]. These nanocarriers are engineered to encapsulate a wide array of contrast agents, including magnetic, radioactive, and fluorescent materials, alongside chemotherapeutics, immunotherapeutics, or genetic cargo, enabling real-time monitoring of treatment delivery and response [5].

Central to the success of polymer-based theranostics is their physicochemical adaptability. Parameters such as particle size, shape, surface charge, and hydrophilic-hydrophobic balance directly influence circulation time, tumor accumulation, and cellular uptake, with nanoparticles in the 10–200 nm range exploiting the enhanced permeability and retention (EPR) effect for passive tumor targeting [6–8]. Advances in polymer chemistry and synthesis methods, including solvent evaporation, nanoprecipitation, emulsion-diffusion, and emulsion polymerization, have enabled precise control over these parameters, allowing for the design of highly specialized and reproducible systems [9, 10].

Recent efforts have focused on the development of hybrid nanoparticles that combine inorganic components, such as gold or iron oxide, with polymer matrices, enhancing multifunctionality for multimodal imaging [e.g., Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET)] and combined therapeutic approaches [11–13]. These hybrid systems leverage the optical, magnetic, and electrical properties of inorganic cores while benefiting from the biocompatibility and functional flexibility of organic coatings [9, 14, 15]. Stimuli-responsive designs, sensitive to changes in pH, temperature, or enzymatic activity, further refine the precision of drug release and contrast activation at the tumor site, minimizing off-target effects and systemic toxicity [16, 17].

Despite these promising advances, the clinical translation of polymer-based theranostic nanoparticles remains limited by key challenges. These include achieving optimal pharmacokinetic profiles, controlling immunogenicity, ensuring long-term safety, and addressing large-scale manufacturing and regulatory barriers [18]. In cancer theranostics, they are engineered to serve both as nanocarriers and as multifunctional systems with integrated capabilities. In many formulations, contrast agents and therapeutic drugs are physically loaded or chemically conjugated onto preformed polymer matrices. However, recent advances in polymer chemistry have enabled the direct incorporation of diagnostic and therapeutic functionalities into the nanoparticle during synthesis. For example, stimuli-responsive polymers can release drugs in response to tumor microenvironmental cues, and copolymerization techniques can embed fluorophores or chelators into the backbone, eliminating the need for post-synthetic modifications. This duality, between modular loading and integrated function, underpins the versatility of polymer-based platforms and is a central theme of this review.

This review synthesizes the current state of research on polymer-based nanoparticles for cancer theranostics, detailing the key methods for integrating contrast agents, the influence of physicochemical properties, biological interactions, biocompatibility considerations, recent design innovations, and the challenges and future directions for clinical translation. By consolidating the latest evidence and insights, we aim to provide a comprehensive understanding of how these nanoplatforms are reshaping diagnostic and therapeutic strategies in oncology.

Integration methods of contrast agents in polymer nanoparticles

Polymeric nanoparticles are becoming an essential part of advancing imaging techniques, particularly in cancer therapy. By engineering nanoparticles to carry contrast agents, researchers are improving the effectiveness of diagnostic methods such as CT, MRI, and PET, offering sharper images and better disease detection.

Theranostic platforms, which combine therapy and diagnostics into a single system, often rely on different types of organic polymeric nanoparticles. These include polymer conjugate complexes, polymeric nanospheres, micelles, and dendritic polymers. In parallel, inorganic nanoparticles, such as iron oxide, quantum dots, silica, and gold, have made their way into medical imaging because of their distinctive magnetic and optical properties, which enhance contrast with minimal toxicity. This blending of contrast agents and nanoparticles not only improves diagnostic precision but also reduces side effects traditionally seen with standalone contrast media. Adding therapeutic drugs into the same nanoparticles introduces a dual functionality: The particles not only illuminate tumors for imaging but also deliver treatment directly to the diseased tissue, opening the door for more targeted and effective therapies.

Today's research moves beyond simply loading contrast agents into nanoparticles. Scientists are creating intelligent nanocarriers that can respond to specific biological triggers, such as pH changes in tumors or oxidative stress, to release their payloads precisely where needed [1, 2]. These smart designs are helping to solve long-standing challenges such as poor drug penetration and unwanted side effects, making treatments more personalized and effective.

Choosing suitable polymers, contrast agents, and fabrication techniques is key. Material choice affects everything from nanoparticle size and surface charge to circulation time and imaging clarity [3, 4]. With careful design, nanoparticles can now travel through the body undetected by the immune system, accumulate preferentially at tumor sites, and provide high-quality imaging signals while delivering therapy at the same time.

Following the rapid advances in nanotechnology and material science, a wide variety of polymer-based and hybrid nanoparticles have been developed to function as carriers for contrast agents in cancer theranostics. These systems can be broadly categorized into four main types: organic polymer nanoparticles, inorganic nanoparticles, polymer-inorganic nanocomposites, and polymer-coated inorganic nanoparticles. Each category offers distinct advantages depending on the intended imaging modality, therapeutic payload, and biological behavior required. Moreover, the choice of synthesis method plays a critical role in determining nanoparticle properties such as size, surface characteristics, and stability, all of which directly influence imaging performance and therapeutic efficacy. In the following sections, we explore the main types of nanoparticles employed for contrast agent integration, along with an overview of the key synthesis strategies used to produce them.

Organic polymer nanoparticles

Organic polymer nanoparticles are colloidal systems composed of biodegradable or biocompatible polymers that can encapsulate, adsorb, or conjugate therapeutic agents and contrast agents [5]. These nanoparticles can be fabricated using a range of synthesis techniques such as solvent evaporation, nanoprecipitation, emulsion-diffusion, ionic gelation, and polymerization-based methods, each offering precise control over size, surface charge, and drug loading efficiency [9, 10]. Organic polymer nanoparticles are particularly valued for their ability to enhance targeted drug delivery through both passive accumulation in tumors via the EPR effect and active targeting by surface modification with ligands specific to tumor biomarkers [19, 20]. Moreover, their customizable surface chemistry allows the integration of imaging agents, creating multifunctional nanocarriers that can simultaneously diagnose and treat cancers. The synthesis process, polymer choice, and functionalization strategies all critically determine the stability, targeting capability, and therapeutic success of these nanoparticle systems [10, 14].

The synthesis technique directly influences the size, structure, stability, and drug-loading capacity of polymeric nanoparticles. Several established methods are commonly used to produce high-quality nanoparticles tailored for targeted delivery and imaging. This section focuses on four widely adopted fabrication approaches: solvent evaporation, nanoprecipitation, emulsion-diffusion, and emulsion polymerization.

Among the most widely adopted fabrication techniques for organic polymer nanoparticles are solvent evaporation, nanoprecipitation, emulsion-diffusion, and emulsion polymerization. Solvent evaporation enables encapsulation of hydrophobic agents with moderate control over particle size and loading efficiency, though concerns remain over residual organic solvents [9, 10]. Nanoprecipitation, also known as solvent displacement, offers high precision in size control and is well suited for hydrophobic drugs, though it tends to yield lower encapsulation efficiencies for hydrophilic agents [15, 21, 22]. Emulsion-diffusion provides good size uniformity and encapsulation performance using biodegradable polymers such as poly(lactic-*co*-glycolic acid) (PLGA), but it generally requires more time and careful optimization to prevent aggregation [22, 23]. Emulsion polymerization, by contrast, is a robust method that produces uniformly sized nanoparticles with high solid content and biocompatibility, although the need for rigorous purification to remove surfactants and residual monomers is a key consideration [24, 25].

Furthermore, each synthesis method distinctly influences the physicochemical attributes of the resulting nanoparticles. Solvent evaporation generally yields particles in the range of 100–400 nm with moderate drug loading efficiency, commonly applied for hydrophobic compounds [9, 10, 26]. Nanoprecipitation offers precise control over particle size (typically 50–200 nm) and yields relatively monodisperse formulations, though it is less efficient for encapsulating hydrophilic agents [22]. Emulsion-diffusion techniques can improve size uniformity and reproducibility but often require careful optimization of surfactant content and solvent ratios to prevent particle aggregation. Emulsion polymerization produces nanoparticles with high drug loading efficiency and narrow size distributions, particularly effective for hydrophilic drugs, although extensive purification may be necessary to remove residual surfactants and monomers [25]. Ionic gelation, while less consistent in size control, allows fabrication under gentle conditions suitable for sensitive biomolecules [10]. These characteristics directly influence in vivo behavior, including circulation time, biodistribution, and tumor penetration, which are essential parameters in cancer theranostics. Table 1 summarizes the characteristics of each synthesis method.

Table 1. Summary of key characteristics for common nanoparticle synthesis methods, including size control, drug loading efficiency, and agent compatibility

Synthesis method	Particle size control	Drug loading efficiency	Suitable for	References
Solvent evaporation	Moderate (100–400 nm)	Moderate (30–45%)	Hydrophobic agents (e.g., paclitaxel, curcumin)	[26, 27]
Nanoprecipitation	High (50–200 nm)	Moderate to High (50–80%)	Hydrophobic agents (e.g., docetaxel); limited for hydrophilic (e.g., doxorubicin)	[28–30]
Emulsion-diffusion	Good (100–300 nm)	Low (< 10%)	Hydrophobic agents (e.g., indomethacin)	[31, 32]
Emulsion polymerization	Good (100–300 nm)	High (80–95%)	Hydrophilic agents (e.g., 5-FU)	[33]

Inorganic nanoparticles

Inorganic nanoparticles are nanoscale materials composed of metals, metal oxides, or semiconductors that exhibit unique magnetic, optical, and electrical properties. These characteristics make them highly attractive for medical imaging applications, such as MRI, CT, and photoacoustic imaging [13]. Various synthesis techniques have been developed to control their size, crystallinity, surface chemistry, and dispersibility, which are crucial factors for their biomedical performance. Commonly used synthesis methods include co-precipitation, sol-gel processing, hydrothermal synthesis, and solution combustion [13, 34]. Each of these techniques offers specific advantages in producing inorganic nanoparticles with tunable properties for targeted imaging and therapeutic delivery.

Several established methods are used to synthesize inorganic nanoparticles for imaging and therapeutic applications, each offering unique advantages in terms of particle morphology, crystallinity, and scalability. Co-precipitation remains one of the most common approaches for fabricating magnetic metal oxides such as Fe_3O_4 and γ-Fe_2O_3, offering simplicity and scalability, though it often requires strict control over pH and temperature to minimize aggregation and size heterogeneity [13, 18, 35]. Sol-gel processing enables precise tuning of particle size, composition, and porosity, producing highly homogeneous nanoparticles at low processing temperatures, albeit with potential challenges like shrinkage and cracking during drying [11, 18, 36]. Hydrothermal synthesis facilitates the formation of well-crystallized, dopant-tunable oxides (e.g., ZnO, TiO_2, Fe_3O_4) under elevated pressure and temperature in aqueous environments, although it typically demands specialized equipment and extended reaction times [18, 37]. Solution combustion, by contrast, is a rapid, energy-efficient method relying on exothermic redox reactions to yield crystalline nanoparticles such as CeO_2, ZnO, and MgO; while it supports large-scale, low-cost production, achieving uniformity remains challenging due to the fast reaction kinetics [18, 34].

Hybrid nanoparticles

Hybrid nanoparticles are multifunctional systems that combine the structural benefits of inorganic cores with the biocompatibility and functional flexibility of organic polymer shells [12]. These systems include polymer-coated inorganic nanoparticles and polymer-inorganic nanocomposites, both designed to enhance stability, targeting, and responsiveness in diagnostic and therapeutic applications. Depending on how the organic and inorganic phases are integrated, synthesis approaches are broadly classified as ex-situ or in-situ methods [18]. Ex-situ techniques include melt blending and solution mixing/solvent casting, while in-situ strategies encompass hydrolysis, microemulsion polymerization, and grafting techniques for forming well-dispersed and chemically bonded hybrid nanostructures.

Among ex-situ methods, melt blending enables solvent-free incorporation of inorganic fillers such as Fe_3O_4 or ZnO into molten polymer matrices like PMMA, though it often requires surface modification or compatibilizers to mitigate agglomeration and ensure homogeneous dispersion [11, 25]. Similarly, solution mixing (solvent casting) facilitates uniform embedding of preformed nanoparticles into polymer solutions, suitable for materials such as PMMA, chitosan, or alginate; however, solvent evaporation can lead to uneven distribution or aggregation, typically addressed via surfactants or sonication [38, 39]. In contrast, in-situ approaches chemically generate nanoparticles within the polymer phase. Hydrolysis enables uniform nucleation of metal oxides (e.g., Fe_3O_4) by reacting metal ions within the polymer matrix, resulting in enhanced dispersion and interface bonding. Microemulsion polymerization, using nanodroplet reactors, produces narrowly distributed core-shell nanocomposites like Fe_3O_4/PS and SDS-stabilized $CoFe_2O_4$, offering high monodispersity and size control in the 2–100 nm range [29]. Lastly, grafting approaches, either "grafting to" or "grafting from", enable chemical attachment of polymer chains to inorganic surfaces, improving colloidal stability and biocompatibility. Grafted systems include polyethylene glycol (PEG)-Fe_3O_4 and PMMA-coated γ-Fe_2O_3, often synthesized via controlled radical polymerization methods such as ATRP or RAFT [12, 38–43].

Physicochemical factors influencing contrast agent efficiency

The efficiency of contrast agents delivered through polymer-based nanoparticles in cancer imaging and therapy is intimately linked to the nanoparticles' physicochemical characteristics. Key parameters such as particle size, morphology, surface charge, surface chemistry, and responsiveness to stimuli govern not only the biodistribution and tumor-targeting capacity of these systems but also their imaging performance and safety profile. Compared to conventional contrast agents such as iodinated small molecules, polymeric nanoparticles offer significant advantages, including the capacity for higher payloads, longer systemic circulation, tunable surface modification, and potential for multi-functionality [44].

Size

Nanoparticle size plays a pivotal role in determining their circulation behavior, tumor penetration, clearance route, and imaging resolution [7]. Typically, nanoparticles ranging from 10–200 nm can exploit the EPR effect to passively accumulate in tumor tissues through leaky vasculature [6–8]. This size range is large enough to load substantial amounts of contrast-generating material, yet small enough to penetrate tumor interstitial spaces [45, 46].

Smaller nanoparticles (e.g., < 10 nm) are rapidly cleared by the kidneys via renal filtration, while particles larger than 200 nm are generally sequestered by the mononuclear phagocyte system, particularly in the liver and spleen [47]. On the other hand, nanoparticles within the optimal range tend to exhibit slower clearance, prolonged retention, and enhanced contrast signal at tumor sites [48, 49].

Surface properties

Surface charge

Surface charge influences nanoparticle stability, cellular interactions, protein adsorption, and systemic clearance. Highly charged particles tend to repel one another electrostatically, preventing aggregation in suspension [50]. Additionally, surface charge governs the formation of the protein corona, a layer of biomolecules that adsorb onto the nanoparticle surface upon entry into biological fluids [51, 52]. This corona affects biodistribution, cellular uptake, and recognition by the immune system [53–55].

Positively charged nanoparticles often demonstrate enhanced cellular uptake due to electrostatic attraction with negatively charged cell membranes, but may also provoke higher systemic toxicity and rapid clearance [56, 57]. In contrast, neutral and zwitterionic surfaces offer prolonged circulation times, reduced immune recognition, and improved tumor accumulation via passive targeting [58].

Surface functionalization

Functionalizing nanoparticles with ligands such as folic acid, transferrin, or hyaluronic acid enhances their specificity for cancer cells overexpressing corresponding receptors [59, 60]. This ligand-receptor targeting mechanism facilitates selective accumulation of contrast agents at tumor sites, boosting imaging precision and therapeutic efficacy [61].

Surface morphology

The morphological features of the nanoparticle surface, including roughness and texture, influence cellular uptake and retention. Rougher or irregular surfaces provide increased surface area for contrast agent loading and stronger interactions with cell membranes [56–58]. These features not only enhance internalization and local drug/contrast agent concentration but also improve imaging signal strength and persistence [62, 63].

Hydrophilicity and hydrophobicity

Surface hydrophilicity enhances nanoparticle solubility and minimizes aggregation, improving circulation time and tumor accumulation. Hydrophilic coatings, especially PEG, can form a stealth layer that shields nanoparticles from immune detection, thereby extending their systemic half-life [64, 65].

Biodegradability and biocompatibility

The use of biodegradable and biocompatible polymers, such as PLGA or chitosan, ensures that nanoparticles are safely metabolized without provoking adverse immune reactions [66–68]. Biodegradable carriers support controlled release of contrast agents, allowing for sustained signal during imaging procedures [69, 70]. Biocompatibility further reduces immunogenicity, enhances circulation times, and promotes passive tumor targeting [71].

Magnetic properties

Magnetic polymeric nanoplatforms, particularly those containing Superparamagnetic Iron Oxide Nanoparticles (SPIONs), are widely utilized in MRI due to their strong T2 (transverse) contrast-enhancing capabilities [72]. SPIONs create localized magnetic field inhomogeneities that accelerate transverse relaxation, resulting in darkened tumor regions on T2-weighted images, thereby improving lesion visibility [73, 74]. These magnetic characteristics are essential in enhancing spatial resolution and contrast specificity in MRI.

Responsiveness to physiological stimuli

Stimuli-responsive nanoparticles can release contrast agents in response to specific tumor microenvironmental cues such as pH, temperature, or enzyme activity. pH-responsive polymers with ionizable groups can release payloads selectively in acidic tumor tissues. Thermo-responsive polymers such as poly(*N*-isopropylacrylamide) (PNIPAM) exhibit a phase transition at physiological temperatures, enabling heat-triggered release of contrast agents during hyperthermia-based interventions [75]. Enzyme-sensitive nanoparticles constructed from degradable polymers such as PLA or PCL can be selectively cleaved by tumor-overexpressed enzymes such as proteases and esterases, triggering localized contrast agent release [76].

Figure 1 schematically illustrates a multifunctional nanoparticle integrating size, surface properties, magnetic behavior, and stimulus responsiveness.

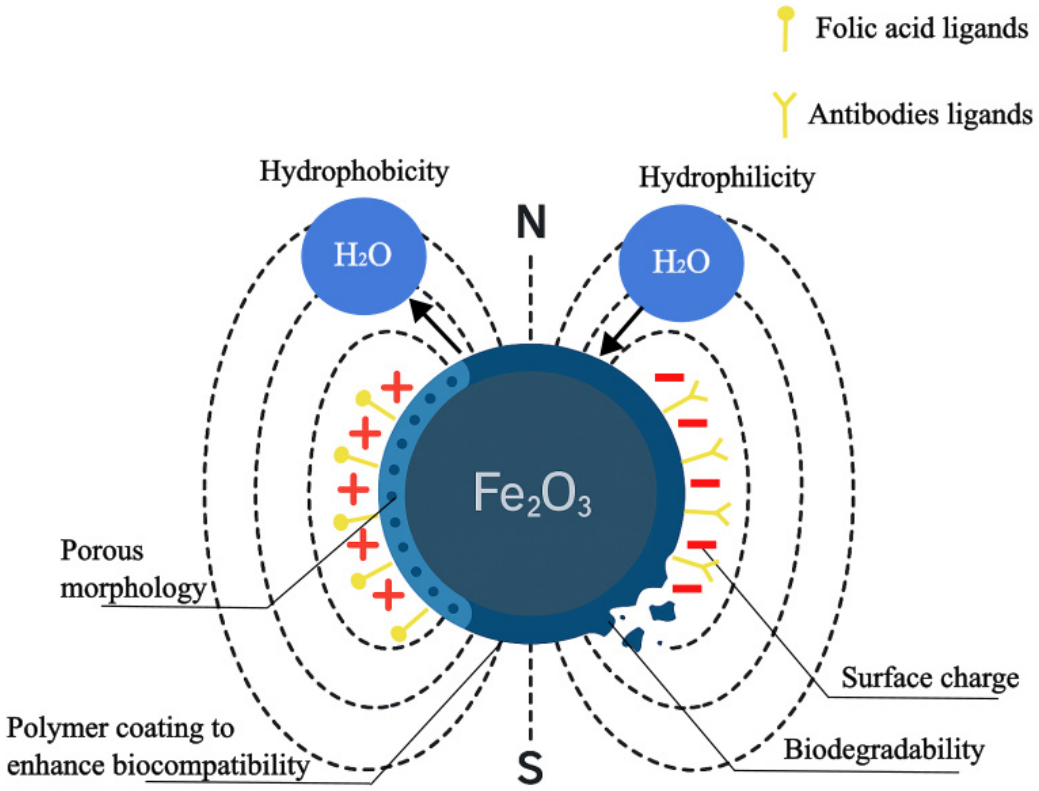

Figure 1. Schematic representation of a polymer-coated Fe_2O_3 nanoparticle illustrating key physicochemical and biological characteristics that influence biodistribution and imaging performance. Surface charge (depicted by red '+' and '–' signs), hydrophilicity and hydrophobicity interactions with water molecules (H_2O), surface functionalization with folic acid and antibody ligands (yellow structures), and porous surface morphology all contribute to cellular uptake, targeting, and circulation behavior. Magnetic field lines (dashed) indicate superparamagnetic properties relevant for MRI and hyperthermia. Biodegradability and biocompatibility are enhanced through surface polymer coatings, which also modulate immune evasion and clearance. This multifunctional design enables precise control over pharmacokinetics and biological interactions in cancer theranostics

These diverse integration strategies lay the foundation for optimizing the composition and architecture of nanoparticles, which is critical for achieving desired imaging and therapeutic outcomes. The following section examines how these material configurations influence key physicochemical properties relevant to clinical performance.

Biological interactions and biodistribution patterns

The biological performance of polymer nanoparticles used as contrast agent carriers is shaped by their interaction with various components of the body, which in turn influences their biodistribution, cellular uptake, clearance, and overall safety. These interactions are largely dictated by key physicochemical parameters such as size, surface charge, morphology, and hydrophilicity. Understanding and controlling these interactions is essential for improving nanoparticle circulation time, minimizing unintended organ accumulation, and reducing potential toxic effects. Notably, without careful control, partial clearance and off-target biodistribution can contribute to adverse outcomes such as immunotoxicity, organ-specific toxicity, or unwanted inflammatory responses [77, 78].

Among the primary factors influencing biodistribution is cellular uptake, which is closely linked to the nanoparticle's surface characteristics. Positively charged and smaller nanoparticles tend to show enhanced cellular internalization due to electrostatic interactions with negatively charged cell membranes [79–81]. This phenomenon is well illustrated in Figure 2, which shows the enhanced cellular uptake of surface charge-switchable theranostic nanoparticles under acidic conditions. These nanoparticles, initially neutral at physiological pH, undergo protonation in the acidic tumor microenvironment, thereby increasing their surface positive charge and promoting internalization via electrostatic attraction [82]. In contrast, hydrophilic and neutrally charged particles typically avoid recognition by opsonins and evade the complement system, which helps prevent rapid clearance and supports extended circulation in the bloodstream [83, 84]. Once in systemic circulation, nanoparticles are internalized by cells through multiple endocytic routes. These include clathrin-mediated endocytosis, which generally favors nanoparticles around 100–150 nm, caveolae-mediated pathways for smaller particles, and macropinocytosis, which allows the uptake of particles exceeding 500 nm [85–87]. After internalization, polymer nanoparticles are typically trafficked into endosomes or lysosomes, where the acidic environment degrades the polymeric matrix, triggering the release of encapsulated contrast agents [88]. In addition to non-specific uptake mechanisms, targeted delivery can be achieved by modifying the nanoparticle surface with ligands that selectively bind to receptors overexpressed on tumor cells. This strategy, which often involves functionalizing nanoparticles with molecules such as folic acid, transferrin, or tumor-specific peptides, enhances selective accumulation in tumor tissues and improves imaging accuracy by increasing contrast where it is most needed [89–92]. Furthermore, antimicrobial polymer-based nonviral gene vectors demonstrate that optimizing polymer architecture, such as introducing cationic moieties and tuning hydrophobic-hydrophilic balance, can significantly enhance cellular uptake via clathrin- and caveolae-mediated endocytosis, offering a parallel strategy for improving receptor-targeted nanoparticle internalization in cancer theranostics [93]. Targeted uptake not only improves diagnostic precision but also supports better therapeutic outcomes by increasing payload delivery to malignant tissues. Multifunctional polymeric platforms have also enabled co-delivery strategies that combine chemotherapeutic agents with immunomodulators, offering synergistic effects in resistant tumor environments [94].

Immune compatibility is another critical consideration for nanoparticle systems. The use of biocompatible polymers such as PEG has become standard practice for minimizing immunogenicity and extending systemic circulation. However, not all polymers are equally benign. Certain materials, such as dextran and polyvinyl alcohol (PVA), have been reported to provoke mild immune responses, often attributed to incomplete removal of monomers or the presence of antibody-binding motifs [95, 96]. Similarly, degradation products from PLGA can create local acidity, occasionally leading to mild inflammatory reactions [97]. Surface engineering to reduce immune recognition plays an important role in ensuring nanoparticle persistence in circulation and enhancing their imaging and therapeutic potential [98].

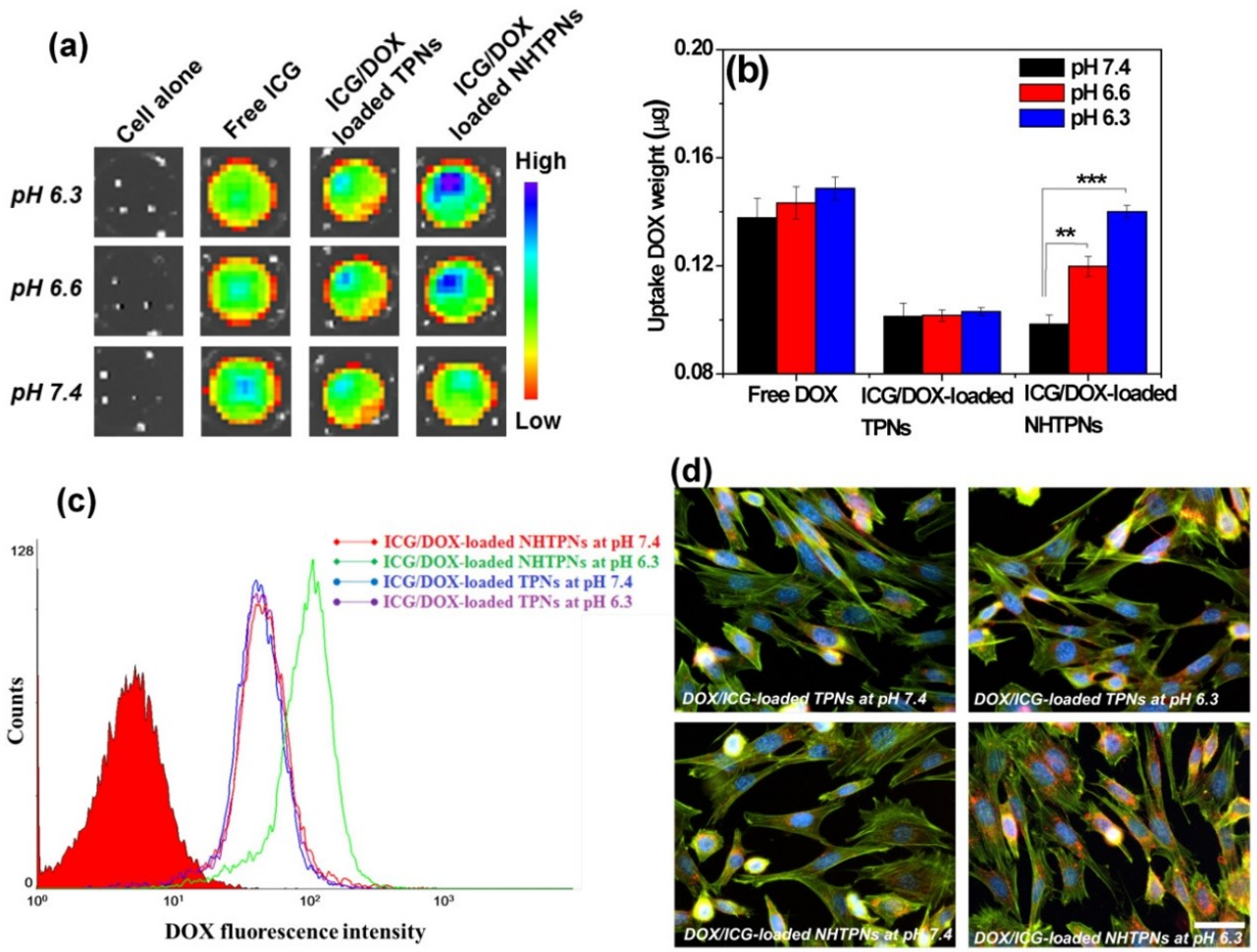

Figure 2. pH-Responsive cellular uptake and imaging of ICG/DOX-loaded TPNs and NHTPNs. (**a**) Fluorescence images of ICG molecules from TRAMP-C1 cells incubated with free ICG and ICG/DOX-loaded TPNs and NHTPNs, respectively, under different pH conditions attained by IVIS. (**b**) Intracellular DOX amount of TRAMP-C1 cells incubated with various DOX formulations. (**c**) Flow cytometric histograms TRAMP-C1 cells treated with ICG/DOX-loaded TPNs and NHTPNs at pH 7.4 and 6.3 for 2 h (DOX concentration = 20 μM). (**d**) Fluorescence images of TRAMP-C1 cells incubated with ICG/DOX-loaded TPN and NHTPNs at pH 7.4 and 6.3 for 1.5 h (DOX concentration = 10 μM). Nuclei and F-actin cytoskeleton were stained with Hoechst and F-actin marker, respectively. Scale bar is 50 μm. Reproduced with permission from Hung et al. [82], Theranostics 2016;6:302–317, © Ivyspring International Publisher. Under the terms of CC BY-NC license (https://creativecommons.org/licenses/by-nc/4.0/)

Once administered, nanoparticles distribute through various organ systems depending on their physicochemical profile and route of administration. In general, uncoated or unmodified nanoparticles show preferential accumulation in the liver, spleen, and kidneys, largely due to filtration by the mononuclear phagocyte system. In some studies, up to 90% of uncoated nanoparticles have been detected in the liver, with lower concentrations observed in the spleen and bone marrow [99, 100]. This organ-specific accumulation presents both opportunities and challenges, offering a route to target tumors in these organs while also posing risks of toxicity. Polymer coatings such as PEG have proven effective at reducing non-specific accumulation and prolonging systemic circulation. For example, PEGylated dendrimers show significantly reduced uptake in non-target organs and demonstrate improved pharmacokinetics, including lower toxicity and longer residence time in blood [101].

Excretion pathways for polymer nanoparticles are primarily renal or hepatobiliary, depending on particle size and degradability. Nanoparticles smaller than 5 nm are typically cleared rapidly via renal filtration, while larger particles are more likely to be processed and excreted through the liver and biliary system [102]. The use of biodegradable polymers allows nanoparticles to break down into smaller fragments that can be more easily excreted, helping to avoid long-term accumulation and potential toxicity. Moreover, polymer-based contrast agents have shown lower toxicity compared to traditional agents such as iodinated compounds, particularly with respect to excretion profiles [103, 104].

A critical feature that enhances the effectiveness of polymer nanoparticles in tumor imaging is their ability to leverage the EPR effect. Tumor vasculature is characteristically leaky and poorly drained by lymphatics, allowing nanoparticles in the optimal size range to passively accumulate in tumor tissues. This phenomenon significantly increases the concentration of contrast agents in tumors relative to healthy tissues, improving imaging contrast and diagnostic clarity [105–107]. The EPR effect is further enhanced through polymer surface modifications such as PEGylation, which extends nanoparticle circulation and reduces immune clearance. The result is a system that enables higher local delivery of contrast agents, requires lower dosages, and allows less frequent administration while maintaining excellent imaging contrast and tumor specificity [108, 109].

Understanding the structural advantages and limitations of each nanoparticle type is essential, but it is equally important to consider how their physical and chemical attributes affect in vivo performance. We therefore next examine the physicochemical factors that govern contrast agent efficiency.

Strategies to enhance targeting and retention in tumors

To maximize the diagnostic and therapeutic potential of polymer nanoparticles loaded with contrast agents, several strategies have been developed to improve their targeting specificity and retention within tumor tissues. These approaches can be broadly divided into passive and active targeting mechanisms, as well as the use of stimuli-responsive release systems, all designed to overcome biological barriers and improve nanoparticle accumulation at the tumor site.

Passive targeting relies heavily on the EPR effect, a phenomenon observed in solid tumors due to their abnormal, leaky vasculature and deficient lymphatic drainage. This microenvironment allows nanoparticles to preferentially accumulate in tumor tissues compared to normal tissues, effectively increasing local concentrations of contrast agents [110]. By extending circulation time and improving nanoparticle stability, passive targeting enhances the overall imaging signal. One well-established strategy to boost passive accumulation is the use of polymer coatings, such as PEG, which provide steric stabilization and reduce immune clearance, further amplifying the EPR effect. This process is illustrated in Figure 3, which depicts the intravenous administration of PEGylated mesoporous silica nanoparticles (MSNs), their circulation through the bloodstream, and their passive accumulation in tumor tissues via the EPR effect

In addition to passive targeting, active targeting strategies are widely employed to further enhance nanoparticle localization and retention at cancerous sites. This is achieved through surface modification, where targeting ligands are conjugated to the nanoparticle surface to enable specific binding to overexpressed receptors on tumor cells. A diverse array of molecules has been explored for this purpose, including peptides [112], anti-bodies [113], saccharides [114], lipoproteins [115], and small molecules [116–118]. These surface modifications not only promote selective tumor targeting but also improve colloidal stability, enhancing both retention and imaging performance (Figure 4).

Among physical triggers, thermo-responsive polymers are designed to release their payload in response to elevated temperatures typically found within tumor environments. Such polymers exhibit a critical solution temperature, above which their solubility decreases and structural changes occur, leading to the release of encapsulated contrast agents. This behavior, known as inverse temperature dependence, is driven by the presence of hydrophobic groups (e.g., methyl, ethyl, propyl) that strengthen inter-polymer interactions at higher temperatures [120]. Similarly, electro-responsive polymers, often based on polyelectrolytes with ionizable groups, respond to electric fields by shrinking or swelling, facilitating controlled release when activated by technologies such as sonophoresis, iontophoresis, or infusion pumps [121–123]. Beyond physical stimuli, recent advances have introduced programmable polymeric nanocarriers that respond to tumor-specific biochemical cues such as pH changes, enzymatic activity, or redox gradients, allowing precise spatiotemporal control over payload release [124].

Magnetically responsive systems exploit the application of external magnetic fields to guide and retain magnetic nanoparticles at tumor sites. The use of SPIONs is particularly advantageous, as they exhibit enhanced penetration under magnetic fields, significantly improving retention times. Studies have shown

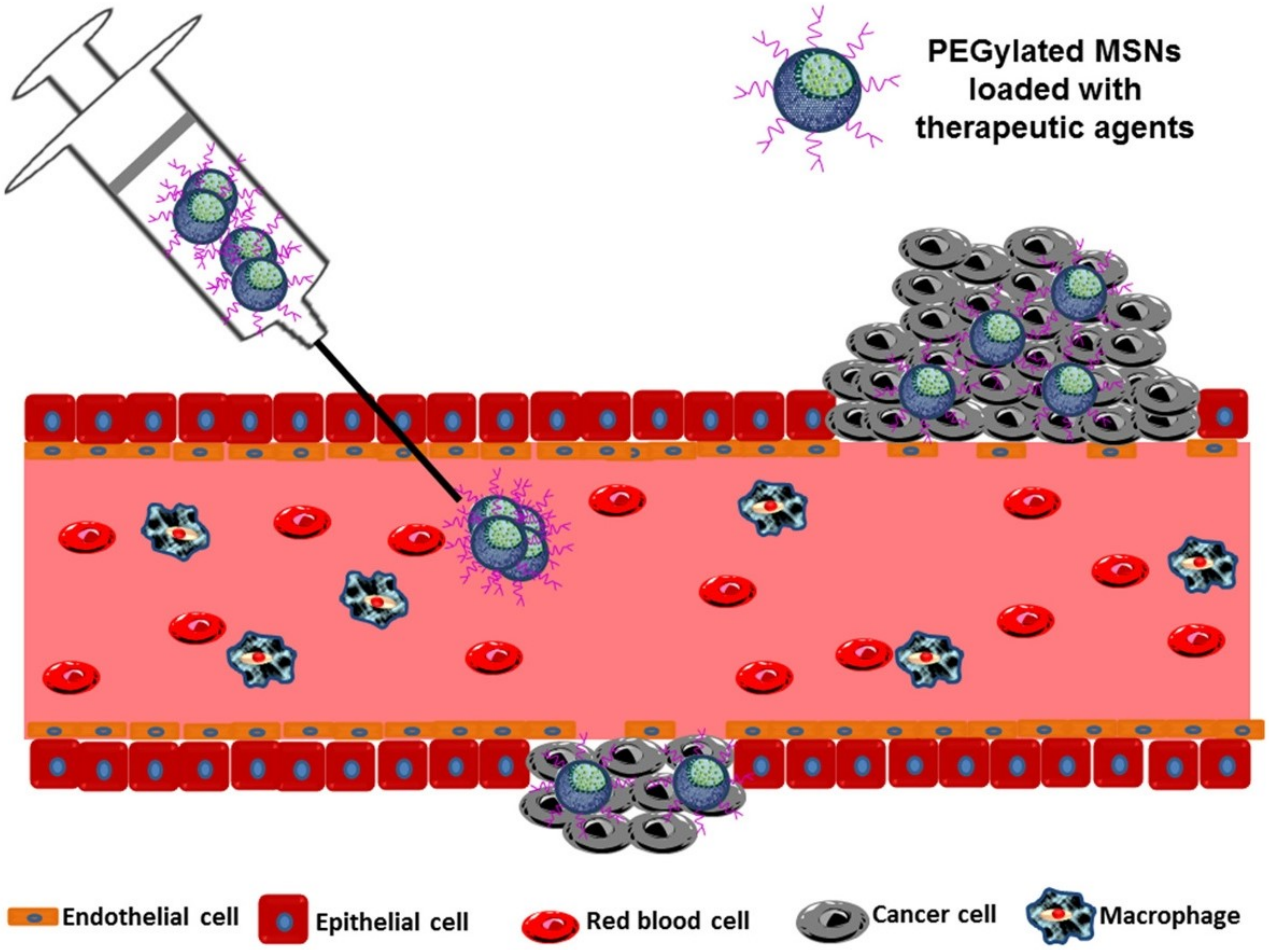

Figure 3. Schematic illustration of EPR effect. Reproduced from Martínez-Carmona et al. [111], Nanomaterials 2015;5:1906–1937, © The Author(s). Under the terms of CC BY license (http://creativecommons.org/licenses/by/4.0/)

that applying an external magnetic gradient can increase magnetic nanoparticle accumulation in the brain by up to 25-fold [16, 35, 125–128]. Chemical stimuli offer another avenue for precise, tumor-specific release. pH-Responsive polymers are designed to take advantage of the acidic microenvironment characteristic of tumors, caused by hypoxia-induced lactic acid buildup. These polymers undergo structural changes such as swelling, shrinking, or degradation when exposed to the slightly acidic extracellular pH of tumors (6.5–7.2) or the highly acidic conditions within lysosomes (pH 4.5–5.0) following cellular uptake, enabling precise and controlled release of contrast agents [129]. Enzyme-responsive polymers target overexpressed tumor enzymes such as cathepsin B or dextranase, undergoing selective degradation to release their payloads specifically at the disease site [130]. Additionally, inflammation-responsive systems capitalize on the presence of inflammatory mediators and immune cell infiltration (including polymorphonuclear leukocytes and macrophages) within tumors, enabling site-specific nanoparticle degradation and localized contrast delivery (Figure 5) [120].

These physicochemical parameters directly influence how nanoparticles interact with biological systems. The next section explores how such interactions determine biodistribution, targeting efficiency, and safety profiles.

Biocompatibility and safety profiles

Polymer nanoparticles have garnered significant attention for contrast agent delivery in cancer therapy due to their promising biocompatibility and generally favorable safety profiles. One of their greatest advantages lies in their capacity to safely transport a diverse array of contrast and therapeutic agents, while

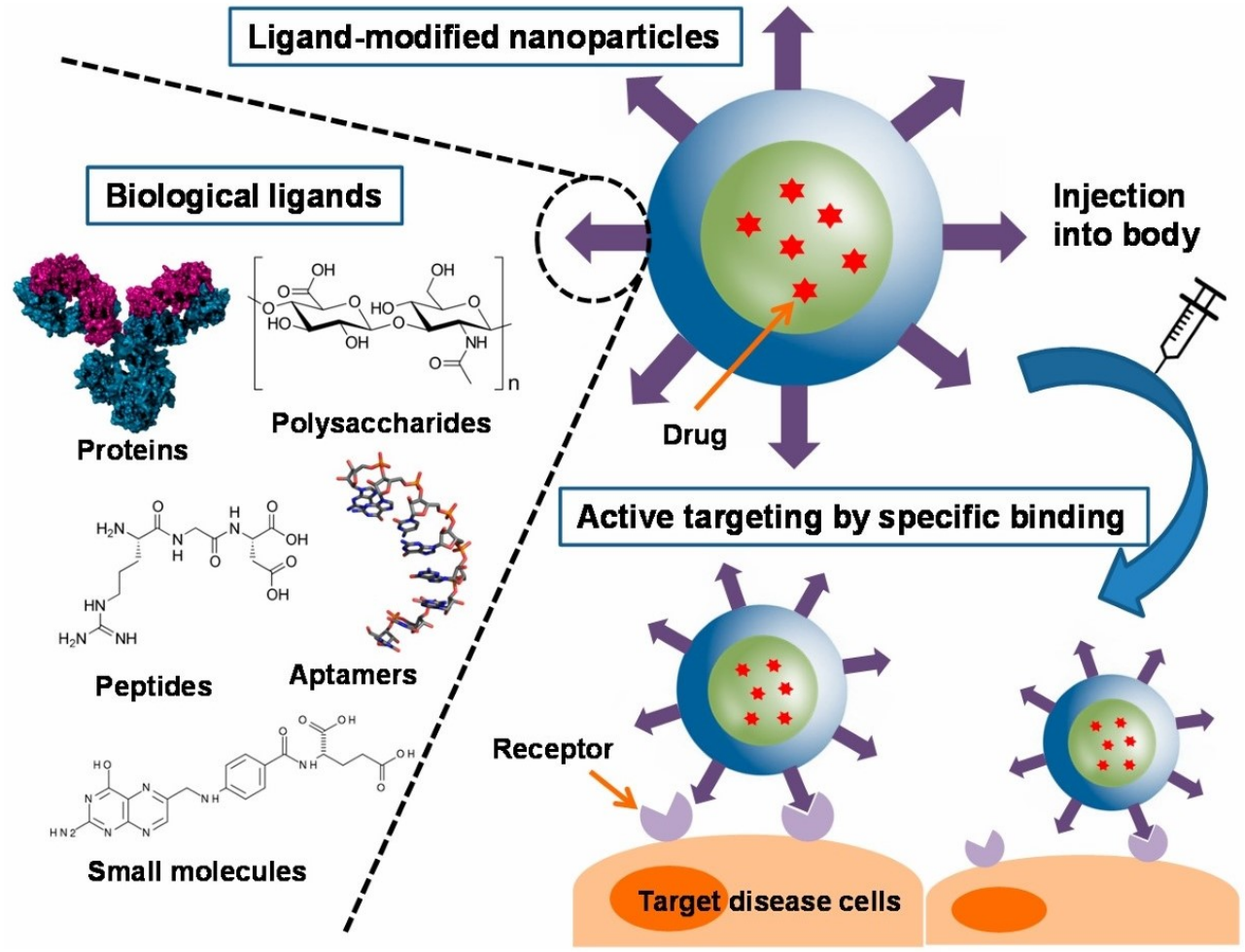

Figure 4. Illustration of biological ligands for active targeting of nanoparticle drug carriers. Reproduced from Yoo et al. [119], Nanomaterials 2019;11:640, © The Author(s). Under the terms of CC BY license (http://creativecommons.org/licenses/by/4.0/)

demonstrating reduced toxicity compared to conventional contrast agents [132]. These attributes make polymer nanoparticles appealing candidates for advancing imaging technologies and improving diagnostic precision in oncology.

Biocompatibility

Organic polymer nanoparticles, by nature, are largely biocompatible, offering minimal risk when used in biological systems. However, the integration of inorganic components, common in hybrid nanoparticles designed for theranostic applications, can complicate this profile by potentially eliciting immune responses that trigger inflammation or other adverse reactions [133]. Additionally, advanced polymer systems engineered to respond to tumor hypoxia, acidity, or redox gradients can further refine release kinetics and reduce off-target effects [134]. As a result, thorough investigations are essential to evaluate the safety and immunogenicity of hybrid systems before their widespread clinical adoption.

Evidence from studies examining hybrid organic-inorganic nanoparticles indicates that smaller, spherical particles with smooth surfaces are more effective at evading immune detection and thus present better biocompatibility [135]. In contrast, larger particles or those with irregular and rough surfaces have been shown to provoke stronger immune responses, leading to inflammation and raising concerns about potential health risks [136]. Importantly, even beyond physical characteristics such as size and shape, the material composition itself plays a critical role; for instance, gold nanoparticles have been documented to activate the immune system and incite inflammatory reactions, underscoring the multifactorial nature of nanoparticle biocompatibility [137].

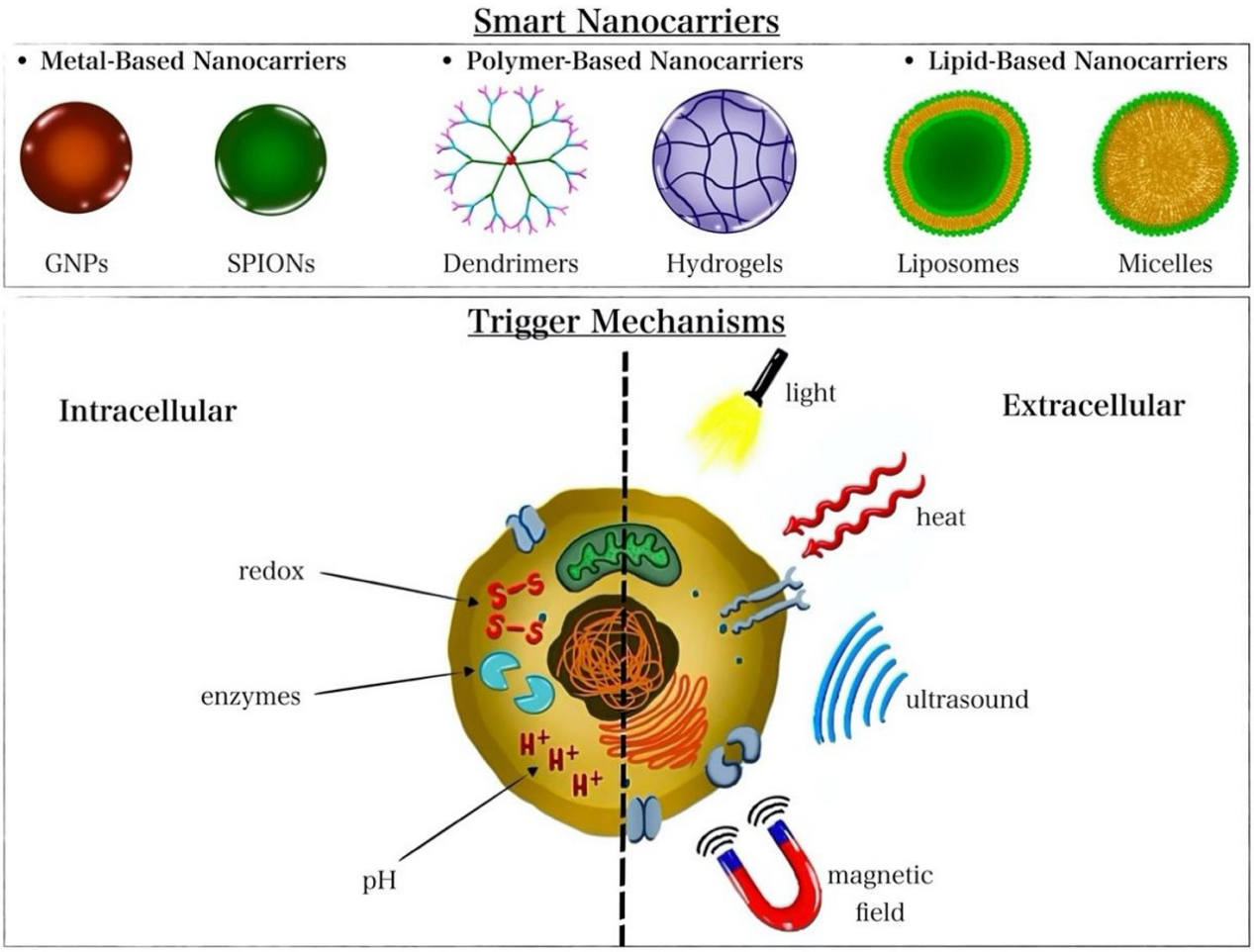

Figure 5. Illustration of the different nanocarrier types and release-triggering mechanisms. Reproduced from Abdulraqeb Ali et al. [131], Nanomaterials 2022;12:3706, © The Author(s). Under the terms of CC BY license (http://creativecommons.org/licenses/by/4.0/)

Toxicity

Building on the preceding discussion of biodistribution and immune recognition, this subsection addresses the toxicological concerns associated with nanoparticle accumulation and degradation in vivo.

Compared to traditional small-molecule contrast agents, polymer nanoparticles such as those made from PLGA exhibit markedly reduced toxicity, making them favorable for clinical use. Notably, Heidel et al. [138] conducted one of the earliest comprehensive toxicology studies of a targeted polymeric nanoparticle system in non-human primates, aiming to address critical concerns regarding their systemic effects. The results were encouraging, revealing that intravenously administered polymeric nanoparticles were well-tolerated, even after repeated dosing over several weeks. In parallel, extracellular vesicle-based systems are emerging as low-immunogenicity alternatives due to their natural origin. Recent work by Djeungoue Petga et al. [139] demonstrated a scalable approach to isolate EVs using polyethylenimine polymers, enabling efficient cellular delivery while minimizing systemic immune responses. These pivotal findings paved the way for investigational new drug applications, marking a major milestone in translating polymeric nanoparticle platforms toward human use.

Despite these advances, it remains crucial to continue rigorous in vitro and in vivo testing to ensure that these nanoparticles do not inadvertently damage healthy tissues, particularly as newer formulations and functionalizations are introduced [140].

Additionally, while targeted ligand modifications enhance tumor-specific accumulation, they may also introduce unintended toxicities and immunological risks. Ligands such as antibodies, peptides, or folic acid derivatives can trigger off-target binding to normal tissues that express low levels of the target receptor,

particularly in the liver, kidneys, or spleen [141, 142]. Such off-target accumulation may induce localized toxicity or organ dysfunction, especially when the payload includes cytotoxic agents or metal-based contrast materials. Moreover, repeated administration of ligand-functionalized nanoparticles can elicit immunogenic responses, including anti-ligand antibody production or complement activation, which compromise treatment efficacy and provoke systemic adverse effects [79]. These risks underscore the importance of rigorous in vivo evaluation and ligand screening to balance targeting specificity with biocompatibility.

Side effects

While polymer nanoparticles generally demonstrate good safety profiles, potential side effects, both short-term and long-term, must be carefully considered and monitored.

Short-term effects often include localized or systemic immune activation, which can manifest as inflammation. This is particularly relevant for nanoparticles employed in cancer immunotherapy, where immune engagement is part of the therapeutic strategy. For example, Zhou et al. [143] reported that semiconducting polymer nanoparticles, despite their favorable biocompatibility, were associated with observable immune-related side effects.

Long-term effects are significantly mitigated when biodegradable polymers, such as PLGA, are used. These materials naturally degrade into biocompatible byproducts (lactic acid and glycolic acid), which are metabolized and excreted without accumulating or causing toxicity [144, 145]. Long-term studies have consistently demonstrated that PLGA-based nanoparticles exhibit minimal adverse effects over extended periods, further supporting their suitability for clinical applications. However, it is important to acknowledge that even biodegradable systems are not entirely risk-free, as some studies suggest they may increase cardiovascular risks by contributing to endothelial dysfunction and inflammation under certain conditions [146].

In contrast, non-biodegradable polymer systems pose a greater risk of chronic toxicity due to the long-term accumulation of non-degradable particles in organs such as the liver, spleen, kidneys, and bones. Prolonged exposure to these materials can lead to persistent inflammation and associated health complications [147].

To fully characterize the chronic safety of polymer nanoparticles, particularly in repeated or long-term therapeutic contexts, further extended-duration studies are warranted to assess their biodegradation behavior, clearance mechanisms, and potential for bioaccumulation [148].

Theranostic applications: combining therapy and diagnosis

The application of nanoparticles as theranostic agents, integrating both therapeutic and diagnostic functionalities, has emerged as a highly promising strategy in modern oncology [149]. By uniting these two functions, theranostics enables real-time monitoring of drug accumulation, tissue distribution, and release kinetics, thereby significantly enhancing treatment efficacy and precision. Polymer-based theranostic nanoparticles, in particular, stand out due to their capacity to combine diverse materials within a single system, offering multiple advantages over conventional nanosystems. Key benefits include controlled and sustained drug release, improved pharmacokinetics and biodistribution, precise targeted delivery to tumour tissues, enhanced multimodal imaging, prediction of therapeutic response, and simultaneous reporting of both biochemical and morphological disease features, all while minimizing systemic toxicity and reducing effective drug doses [150–152].

Polymer nanoparticles amplify the theranostic potential of cancer treatments by seamlessly merging diagnostic and therapeutic functions into a unified platform [2]. This dual-functionality approach not only allows non-invasive, real-time imaging but also supports efficient drug delivery strategies [153–155]. In the realm of drug delivery, polymer nanoparticles provide an especially attractive solution by overcoming common challenges such as drug resistance, while simultaneously boosting therapeutic efficacy and reducing systemic side effects associated with high-dose treatments [156–158]. Among the various

contrast-enhancing strategies used in theranostic nanoparticles, magnetic properties warrant dedicated discussion due to their strong integration with the polymer matrix and their unique dual function in both diagnosis and therapy. Magnetic nanoparticles, such as SPIONs, are often embedded within the polymer core during synthesis, influencing the nanoparticle's overall size, stability, and magnetic relaxivity. This differs from optical, radioactive, or ultrasound-based contrast agents, which are typically conjugated post-synthetically or co-loaded into the carrier system without significantly altering the nanoparticle structure. For this reason, magnetic systems represent a structurally and functionally distinct class within polymer-based theranostics, justifying their separate treatment in this review.

Numerous anticancer drugs, including chemotherapeutics such as doxorubicin, have been effectively encapsulated within polymeric carriers to enhance delivery to tumour sites. For example, doxorubicin-loaded PLGA nanoparticles have demonstrated markedly greater anticancer activity compared to free doxorubicin, highlighting the powerful synergy between nanoparticle delivery systems and conventional anticancer agents [159]. This multifunctional capacity positions polymer nanoparticles at the forefront of advancing personalized nanomedicine, where precise localization, targeted treatment, and ongoing disease monitoring are integrated within a single system.

Real-time monitoring and feedback

Perhaps the most transformative advantage of the theranostic approach is its ability to deliver continuous, real-time feedback on disease progression and therapeutic response by simultaneously coupling imaging with treatment [160]. Recent theranostic systems integrate both imaging agents and active targeting ligands into a single polymeric platform, improving both localization accuracy and functional imaging depth [161]. This dual-action capability enables clinicians to estimate safe drug dosages, identify adverse reaction patterns, and monitor therapeutic efficacy over time [162]. Real-time tracking of therapeutic agent distribution offers immediate feedback on whether drugs are effectively reaching the tumor site, empowering clinicians to make rapid, evidence-based adjustments to dosing regimens or nanoparticle concentrations as needed [163]. Such dynamic treatment adjustments improve both safety and efficacy, offering a level of precision not achievable through conventional monofunctional therapies.

Improved dosing accuracy

The capacity to visualize nanoparticles in vivo during treatment plays a critical role in optimizing dosing accuracy. By allowing clinicians to monitor the spatial distribution of nanoparticles in real time, the risk of under- or overdosing is minimized, thus reducing side effects and improving therapeutic outcomes [164]. Furthermore, diagnostic feedback derived from theranostic imaging supports the customization of patient-specific treatment plans, tailoring therapy to the individual tumor microenvironment and molecular characteristics [165]. This level of personalization enhances targeting efficiency, maximizes treatment impact, and aligns closely with the goals of precision oncology.

The multifunctional potential of polymer-based theranostic nanoparticles is shaped by their ability to integrate diagnosis, targeted therapy, and feedback-driven dosing within a single platform. Table 2 summarizes the key insights from this section, highlighting current advantages, challenges, and future directions supported by recent literature.

Table 2. Summary of theranostic applications of polymer nanoparticles: current status, challenges, and future directions

Aspect	Current status	Challenge/Limitation	Future strategy/Direction	Reference
Theranostic integration	Polymer nanoparticles integrate therapy and diagnosis.	Balancing imaging and therapeutic components.	Optimize multifunctional designs for personalized nanomedicine.	[141–144]
Controlled drug delivery	Provide sustained, targeted delivery and minimize systemic toxicity.	Drug resistance and suboptimal drug accumulation at target site.	Develop smart release platforms and improve targeting precision.	[145–147]
Real-time monitoring and feedback	Enables clinicians to track nanoparticle distribution and drug release dynamically.	Need for high-resolution imaging and integration with therapeutic control.	Design real-time feedback loops to adjust dosing based on live data.	[152–154]

Table 2. Summary of theranostic applications of polymer nanoparticles: current status, challenges, and future directions (*continued*)

Aspect	Current status	Challenge/Limitation	Future strategy/Direction	Reference
Dosing accuracy	In vivo tracking supports dosing and reduces risk of under/over-treatment.	Variation in patient-specific tumor microenvironments.	Leverage diagnostic data for adaptive dosing protocols.	[155, 156]
Enhanced efficacy with reduced side effects	Multifunctional systems improve specificity to cancer cells.	Ensuring safe systemic circulation.	Advance biocompatible coatings.	[148–151]

Translational optimization of polymer nanoparticles: from design to clinical integration and future directions

Innovations in nanoparticle design

Recent years have witnessed remarkable progress in the design and functionalization of polymer nanoparticles, significantly advancing their utility for contrast agent delivery in cancer imaging and therapy. These innovations aim to enhance biocompatibility, targeting precision, and imaging performance, collectively improving diagnostic accuracy and therapeutic success.

Among the critical parameters influencing nanoparticle behavior, shape optimization has emerged as a key factor in improving cellular uptake, biodistribution, and therapeutic impact. Non-spherical, anisotropic nanoparticles, such as nanorods, have demonstrated superior tumor penetration and retention compared to traditional spherical counterparts [166]. The elongated geometry and high aspect ratio of nanorods provide an increased surface area for functionalization and improved ability to traverse biological barriers, enhancing their efficacy for targeted delivery [167, 168]. Beyond nanorods, alternative shapes, including disks and ellipsoids, are actively being explored for their unique transport dynamics and binding behaviors [169].

In parallel, precise control over nanoparticle size is essential for tuning pharmacokinetics, tissue penetration, and excretion profiles. Techniques such as microfluidics, seed-mediated growth, and ligand engineering have enabled the production of size-tunable nanoparticles with high uniformity [170]. For instance, thiol-containing ligands have been used to regulate the growth of gold nanoparticles with exceptional precision [171]. Post-synthesis refinement approaches, including size exclusion chromatography and dialysis, further enhance purity and consistency [172]. Notably, size-reversible nanoparticles that dynamically alter their dimensions in response to tumor microenvironmental cues such as hypoxia or abnormal vasculature represent a promising new frontier for improving tumor selectivity and treatment outcomes [173–179].

Another promising innovation is the development of core-shell hybrid structures, which combine functional materials such as gold and iron oxide to create nanoparticles capable of multimodal imaging and therapy. Gold enhances X-ray attenuation for CT, while iron oxide confers magnetic responsiveness for MRI, enabling dual-modality diagnostics within a single polymeric construct [180].

To enhance biocompatibility and translational potential, researchers are increasingly incorporating natural and biological coatings onto polymer nanoparticles. Alginate, a biopolymer derived from brown seaweed, offers a non-toxic, stabilizing shell that reduces immunogenicity and improves physiological stability. Similarly, nanoparticles cloaked in red blood cell membranes form biomimetic platforms capable of evading immune recognition, thereby prolonging systemic circulation and improving delivery efficiency [181]. Hyaluronic acid-functionalized nanoparticles exploit CD44 receptor overexpression in tumor cells to enhance selective uptake [182], while gelatin-coated nanoparticles provide biodegradable, tunable platforms ideal for dual diagnostic and therapeutic applications due to their rich surface chemistry [183].

Finally, the integration of targeting ligands further expands the functionality of polymer nanoparticles. Multifunctional systems that incorporate therapeutic agents, imaging moieties, and targeting ligands have demonstrated significant promise in precision oncology [184–186]. For example, gadolinium-loaded polymeric nanoparticles functionalized with anti-VEGF antibodies exhibit enhanced MRI contrast and liver

tumor specificity [187]. Likewise, anti-HER2 PLGA-PEG nanoparticles have shown improved selectivity and uptake in HER2-positive breast cancer models, underscoring the clinical relevance of combining ligand targeting with polymer-based theranostics [91].

Challenges in clinical translation

Despite the tremendous promise of polymer nanoparticles as carriers for contrast agents in cancer therapy, their clinical translation has faced numerous challenges. While nanoparticles have shown considerable success in preclinical research, only a few, such as iron oxide-based formulations, have made it into clinical practice. This gap stems largely from hurdles related to optimizing pharmacokinetics, maintaining consistent manufacturing quality, ensuring biocompatibility, and satisfying safety and regulatory requirements.

One of the most pressing issues is rapid elimination and toxicity risk. Nanoparticles are often sequestered by phagocytic cells in the liver and spleen shortly after administration, which limits their bioavailability and reduces therapeutic efficacy. Moreover, prolonged retention of non-biodegradable components or their byproducts in vital organs has been associated with adverse outcomes such as chronic inflammation, organ fibrosis, or dysfunction [188, 189]. For instance, iron oxide nanoparticles can release free iron ions that catalyze the formation of reactive oxygen species (ROS), causing oxidative stress and mitochondrial damage, particularly in hepatic tissues. These effects are implicated in the pathogenesis of neurodegenerative disorders such as Parkinson's and Alzheimer's disease [190–193]. Thus, the development of biodegradable and metabolically safe nanoparticle systems is a critical priority.

Closely related are the pharmacokinetic challenges that determine the efficacy and safety of nanoparticle-based contrast agents. Key pharmacokinetic parameters, absorption, distribution, metabolism, and excretion, are profoundly influenced by nanoparticle properties and vary widely across patient populations [194]. This variability complicates dose optimization and therapeutic predictability, necessitating robust in vivo validation strategies that are reproducible and adaptable to personalized treatment contexts.

Immunogenicity and rapid clearance also represent a significant barrier to clinical translation. Immune recognition mechanisms, particularly those governed by innate immunity, can accelerate nanoparticle clearance and provoke systemic hypersensitivity. Addressing this issue requires innovative surface engineering approaches that reduce immunogenic potential without compromising targeting specificity.

Mechanistically, immunogenic responses to polymeric nanoparticles are primarily triggered by innate immune recognition systems. One major pathway involves activation of the complement system via the classical, lectin, or alternative routes, leading to opsonization, phagocytic uptake, and rapid clearance [57, 79]. In parallel, TLR signaling, particularly TLR2 and TLR4, can be activated by specific nanoparticle surface patterns or degradation products, resulting in cytokine release and inflammation [195]. To mitigate these effects, surface modification strategies such as PEGylation are commonly employed to create hydrophilic "stealth" layers that reduce protein adsorption and immune recognition [96]. More recently, biomimetic coatings derived from red blood cell membranes, cancer cell membranes, or extracellular vesicles have been developed to camouflage nanoparticles from immune surveillance, minimize complement activation, and extend circulation half-life [196, 197]. These approaches hold promise for reducing immunotoxicity while maintaining targeting and therapeutic functionality.

Additional theranostic-specific challenges include the need to finely calibrate nanoparticle dosage and release kinetics for both therapeutic and imaging functions. Ensuring that neither function compromises the other requires precise control over nanoparticle composition and responsiveness. Limitations in signal-to-noise ratio, susceptibility to photobleaching, and inadequate sensitivity of certain imaging agents further complicate real-time tracking and interpretation of treatment data [198].

On the manufacturing front, large-scale production and cost remain substantial obstacles. The synthesis of complex, multifunctional nanoparticles often involves multi-step protocols that are costly and

difficult to scale while maintaining batch consistency. Variables such as ligand conjugation efficiency, encapsulation reproducibility, and physicochemical uniformity all require stringent quality control.

Efforts to address batch-to-batch variability have been quantified in several nanoparticle production studies. For example, microfluidics-based synthesis platforms have demonstrated < 5% variation in size and encapsulation efficiency compared to > 20% in conventional batch methods [199]. Standardization frameworks have been introduced by organizations such as the National Cancer Institute's Nanotechnology Characterization Laboratory, which provides a panel of standardized assays for preclinical validation of nanoparticle properties [200]. Additionally, ISO/TR 10993-22:2017 offers technical guidance on biological evaluation of medical devices containing nanomaterials [201]. However, widespread adoption remains limited, and significant gaps exist in global harmonization of quality control procedures, particularly for complex hybrid or ligand-functionalized systems.

These manufacturing and cost-related challenges must be weighed alongside regulatory and safety requirements, which are critical considerations for successful clinical translation. The final section outlines forward-looking strategies aimed at overcoming these barriers.

Lastly, regulatory and safety approval processes represent one of the final and most formidable steps toward clinical implementation. Preclinical animal testing is required but can be hampered by poor translational fidelity due to species-specific physiological differences [202, 203]. Long-term human toxicity profiles remain largely unknown for many nanoparticle systems, underscoring the need for dedicated nanotoxicology protocols. The lack of harmonized international regulatory standards specific to nanomedicine further exacerbates this bottleneck, making it difficult to navigate the approval landscape efficiently.

Overcoming these multifaceted challenges, scientific, manufacturing, regulatory, and economic, is essential for enabling polymer-based nanoparticles to fulfill their potential in cancer diagnosis and treatment.

The integration of contrast agents into polymeric nanoparticles has emerged as one of the most promising avenues for transforming cancer diagnosis and treatment. Advances in polymer nanoparticle design and functionalization have already paved the way for more efficient, safer, and cost-effective diagnostic and therapeutic strategies. These innovative nanomedicine platforms not only deliver therapeutic agents but also enable simultaneous, real-time monitoring of treatment responses, embodying the core principles of theranostics [132].

Future strategies and technologies

Future research is increasingly focused on the development of deterministic delivery systems, nanoparticles engineered to autonomously respond to complex biological environments with high spatial and temporal precision. These intelligent polymeric platforms are being designed to dynamically adjust their pharmacokinetics and biodistribution, enabling them to localize exclusively at tumor sites and release their therapeutic payloads in response to specific stimuli such as pH, enzymatic activity, or oxidative stress. The ultimate goal is to move beyond co-delivery and imaging, toward systems that can actively navigate biological barriers, home to disease sites, and remain localized for maximal therapeutic effect. Another promising direction involves engineering tissue-specific delivery of extracellular vesicles. Deng et al. [204] proposed novel administration routes and targeting strategies that could be translated to polymeric nanocarriers, offering enhanced selectivity and reduced off-target toxicity.

In parallel, ensuring batch-to-batch consistency in particle size, morphology, and drug-loading capacity remains a priority, as these parameters are critical to achieving reproducibility, regulatory compliance, and clinical efficacy. Computational modeling and in silico simulations are increasingly used to guide experimental design, reduce trial-and-error iterations, and de-risk translational research [205]. These advances are helping to close the gap between bench-scale development and scalable, patient-ready systems.

Recent innovations in advanced biomaterials and targeting strategies have further expanded the capabilities of polymeric nanoparticles. Modified natural and synthetic biomimetic polymers have improved the ability of these systems to evade immune recognition, extend circulation time, and selectively accumulate in tumor tissues [206]. Advances in peptide and aptamer conjugation, antibody engineering, and receptor-specific surface chemistry have allowed for more sophisticated and tunable targeting schemes that increase the therapeutic index while reducing systemic toxicity.

Personalized nanomedicine also represents a major frontier in the evolution of polymer-based theranostics. By leveraging patient-specific genetic, metabolic, and proteomic data, nanoparticle systems can be tailored to deliver bespoke therapeutic regimens. These personalized strategies aim to optimize efficacy, reduce side effects, and account for interpatient variability. For example, siRNA (small interfering RNA)-loaded nanoparticles have demonstrated significant potential in silencing tumor-driving genes in cancers such as breast cancer and melanoma [207, 208]. The integration of ligand-receptor compatibility screening and tumor microenvironment profiling will play a vital role in fine-tuning these approaches.

Looking ahead, several transformative technologies may reshape the design and validation of polymer-based nanoparticles. Artificial intelligence and machine learning are being increasingly applied to predict optimal nanoparticle compositions, surface chemistries, and biological interactions, accelerating the discovery process and reducing experimental burden [209]. High-throughput screening platforms integrated with AI models can identify non-intuitive structure-function relationships that inform smarter nanocarrier design. In parallel, organ-on-chip systems are emerging as promising in vitro models to replace animal testing, offering dynamic, tissue-relevant environments for assessing nanoparticle biodistribution, toxicity, and therapeutic efficacy [210]. These bioengineered platforms can capture organ-level responses with greater human relevance and may soon become a cornerstone in regulatory toxicology for nanomedicine.

Conclusions

Polymer-based nanoparticles have demonstrated significant promise as multifunctional platforms for contrast agent delivery and integrated cancer theranostics. The growing body of research highlights their advantages over traditional contrast agents, including enhanced biocompatibility, prolonged systemic circulation, targeted accumulation in tumor tissues, and the capacity for controlled and stimuli-responsive release. These features, coupled with the flexibility of polymer chemistry, enable the development of highly tailored nanocarriers capable of addressing diverse imaging and therapeutic challenges.

Among the major observations, the physicochemical properties of polymer nanoparticles, namely size, surface charge, morphology, hydrophilicity, and responsiveness to biological stimuli, were consistently shown to influence their biodistribution, cellular uptake, immune recognition, and clearance. Nanoparticles in the 10–200 nm range, especially those with neutral or slightly negative surface charges and stealth coatings such as PEG, exhibited favorable pharmacokinetic profiles, exploiting the EPR effect for passive tumor targeting. Surface functionalization with ligands such as folic acid, transferrin, and antibodies further improved active targeting and imaging precision.

Hybrid systems incorporating inorganic components such as iron oxide, gold, or quantum dots provided added imaging modalities (e.g., MRI, CT, PET) and introduced magnetic or optical functionalities. Synthesis techniques, ranging from solvent evaporation and nanoprecipitation to microemulsion and grafting, allowed precise control over particle size, drug loading efficiency, and stability, each offering specific benefits depending on the application. Despite this progress, clinical translation remains limited due to several interrelated barriers.

A critical limitation involves the complexity of nanoparticle design and the reproducibility of large-scale synthesis. Ensuring uniformity in particle characteristics across batches remains a challenge, especially when multifunctional designs require intricate fabrication protocols. Moreover, the immunogenicity and potential long-term toxicity of some materials, particularly hybrid or non-degradable components, continue to raise safety concerns. While polymers such as PLGA and PEG have favorable

biocompatibility and biodegradability profiles, degradation products and immune interactions must still be rigorously evaluated, especially under repeated dosing or chronic exposure scenarios.

Pharmacokinetic variability across patient populations is another key limitation, complicating dose optimization and individualized treatment planning. The interactions of nanoparticles with the protein corona, and their susceptibility to rapid clearance by the mononuclear phagocyte system, further limit their effectiveness. Although surface engineering strategies can mitigate these effects, their long-term in vivo behavior remains insufficiently understood, necessitating comprehensive toxicological and pharmacodynamic studies.

Looking ahead, future research should prioritize the development of "smart" nanoparticles that respond dynamically to the tumor microenvironment. Stimuli-responsive systems capable of releasing contrast agents or therapeutics in response to pH, enzyme activity, temperature, or magnetic fields offer improved localization and safety. Furthermore, biomimetic coatings and cell membrane-camouflaged nanoparticles hold great potential for enhancing immune evasion and prolonging circulation.

Integration with personalized medicine approaches represents another frontier. By incorporating ligands or payloads tailored to tumor-specific biomarkers, polymer nanoparticles can support patient-specific diagnostics and therapies. Advances in high-throughput screening, machine learning-based formulation design, and in silico modeling may accelerate the development of next-generation nanotheranostics with predictable performance and minimal off-target effects.

In conclusion, polymer-based nanoparticles offer a highly adaptable and multifunctional platform for contrast agent delivery in cancer theranostics. Continued innovations in material design, surface engineering, and synthesis techniques are likely to address current limitations and unlock their full clinical potential. Achieving this will require concerted efforts in translational research, standardization of characterization protocols, and collaboration across materials science, oncology, and regulatory disciplines.

Abbreviations

CT: Computed Tomography

EPR: enhanced permeability and retention

MRI: Magnetic Resonance Imaging

PEG: polyethylene glycol

PET: Positron Emission Tomography

PLGA: poly(lactic-*co*-glycolic acid)

SPIONs: Superparamagnetic Iron Oxide Nanoparticles

Declarations

Author contributions

KS: Conceptualization, Investigation, Methodology, Writing—original draft. DC: Conceptualization, Investigation, Methodology, Writing—review & editing. WN: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing—review & editing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Not applicable.

Consent to participate

Not applicable.

Consent to publication

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Availability of data and materials

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