New frontiers in polymeric nanomedicine for cancer therapy

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Abstract

Cancer remains a leading cause of mortality worldwide, and the limitations of conventional treatments underscore the urgent need for more effective and targeted therapeutic strategies. Polymeric nanoparticles (PNPs) have emerged as highly versatile platforms for cancer therapy, offering tunable physicochemical properties, improved pharmacokinetics, and the potential for site-specific drug delivery. Recent advances in polymer chemistry and nanofabrication have enabled precise control over particle size, surface chemistry, and drug release profiles, facilitating passive and active tumor targeting, as well as responsiveness to tumor-specific stimuli. This review critically examines the design and functionalization of PNPs, their applications across chemotherapy, gene therapy, immunotherapy, and combination treatments, and the incorporation of multifunctional and theranostic capabilities. We also discuss the translational challenges—such as manufacturing scalability, tumor heterogeneity, and safety concerns—and explore emerging trends including biomimetic nanocarriers, AI-driven formulation optimization, and personalized nanomedicine approaches. By integrating recent findings from, this work provides a comprehensive overview of the current landscape and future opportunities for PNPs as next-generation cancer therapeutics.

1. Introduction

Cancer treatment still wrestles with a narrow therapeutic window, systemic toxicities, and heterogeneous drug exposure in solid tumors. Polymeric nanoparticles (PNPs)—built from degradable backbones such as PLGA, PEG-block copolymers, and natural polysaccharides—aim to widen this window by improving solubility and stability of payloads, prolonging systemic circulation, increasing tumor accumulation, and enabling on-demand release via endogenous (pH, redox, enzyme) or exogenous (light, heat, ultrasound, electric/magnetic field) triggers (Chang et al., 2021; Darge et al., 2024; Li et al., 2022; Yu et al., 2020; Ulkoski et al., 2019; Dennahy et al., 2022).

Beyond single-agent chemotherapy, PNPs now support combination regimens (chemo–immuno, chemo–photo, drug–gene) and theranostics that pair treatment with imaging to guide dosing and patient selection (Jiang et al., 2024; Mamuti et al., 2021; Zhang et al., 2023; Haidar et al., 2025). Parallel advances in tumor model fidelity (3D, organoids, murine “avatars”) and image-guided delivery are clarifying when and where nanomedicines succeed in vivo, and why they sometimes fail (Zhang et al., 2025; Jiang et al., 2021; Achterberg et al., 2021; Austria Jr et al., 2025). This review synthesizes design rules and translational lessons, centering on developments from the last five years.

2. Design and Functionalization of Polymeric Nanoparticles

The design of polymeric nanoparticles (PNPs) for cancer therapy requires careful consideration of the core material, fabrication method, physicochemical parameters, and surface modifications to optimize therapeutic performance while maintaining safety and biocompatibility. PNPs are typically synthesized from biodegradable synthetic polymers such as *poly(lactic-co-glycolic acid) (PLGA)*, *poly(lactic acid) (PLA)*, *polycaprolactone (PCL)*, and *poly(alkyl cyanoacrylate)*, or natural polymers such as chitosan, hyaluronic acid, alginate, and gelatin. Synthetic polymers often offer more predictable degradation profiles and mechanical properties, whereas natural polymers can provide inherent biological functionalities such as receptor affinity or bioadhesion (Zhang et al., 2020, *Nano Today*).

2.1 Fabrication Methods

Multiple fabrication techniques exist for PNP production, each influencing particle size distribution, encapsulation efficiency, and drug release kinetics:

- Emulsion–solvent evaporation and nanoprecipitation remain the most widely used due to their scalability and compatibility with hydrophobic drugs.
- Microfluidic platforms allow for highly uniform particle size and precise tuning of formulation parameters, enabling continuous production under controlled conditions (Chen et al., 2021, *ACS Nano*).
- Self-assembly of amphiphilic block copolymers enables encapsulation of both hydrophobic and hydrophilic therapeutics, facilitating co-delivery systems (Wang et al., 2023, *Advanced Drug Delivery Reviews*).
- Electrospraying and spray-drying are emerging approaches offering solvent-free production and the possibility of large-scale manufacturing.

2.2 Tuning Physicochemical Properties

The size of PNPs plays a pivotal role in biodistribution and tumor accumulation. Typically, particles in the range of 50–200 nm exploit the enhanced permeability and retention (EPR) effect, while avoiding rapid renal clearance or splenic filtration. Surface charge also governs circulation half-life and cellular uptake; near-neutral or slightly negative zeta potentials tend to minimize opsonization and clearance by the reticuloendothelial system (RES), whereas positively charged PNPs enhance uptake by negatively charged cell membranes but may induce higher cytotoxicity.

The core composition and crystallinity affect degradation rates, with highly crystalline polymers (e.g., PCL) degrading more slowly than amorphous ones (e.g., PLGA). The choice of polymer must therefore balance sustained drug release with timely biodegradation to avoid long-term accumulation (Li et al., 2022, *Nano Today*).

2.3 Surface Functionalization Strategies

Surface engineering is critical for imparting targeting capabilities, stealth properties, and stimuli-responsiveness:

- PEGylation is widely employed to extend circulation time by reducing protein adsorption and immune recognition. However, repeated administration may induce anti-PEG antibodies, prompting exploration of alternative hydrophilic polymers such as poly(2-oxazoline)s (Zhu et al., 2023, *ACS Nano*).
- Active targeting ligands, including antibodies, antibody fragments, peptides (e.g., RGD, iRGD), aptamers, and small molecules (e.g., folic acid), can be conjugated to PNP surfaces to selectively bind tumor-associated receptors.
- Charge-switchable coatings can transition from neutral in circulation to positive in the acidic tumor microenvironment, enhancing tumor penetration and endosomal escape (Xu et al., 2021, *Advanced Drug Delivery Reviews*).
- Enzyme-cleavable linkers enable on-demand drug release in response to matrix metalloproteinases (MMPs) or cathepsins, enzymes overexpressed in tumor tissue.

2.4 Stimuli-Responsive and Multifunctional Platforms

Next-generation PNPs are increasingly designed to respond to intrinsic stimuli (e.g., pH, redox gradients, enzyme activity) or extrinsic stimuli (e.g., temperature, magnetic fields, ultrasound, light). For instance, disulfide-crosslinked polymer micelles remain stable in systemic circulation but rapidly disassemble in the high-glutathione intracellular environment of tumor cells, releasing their payload (Wang et al., 2020, *Nano Today*).

Moreover, multifunctional PNPs integrate diagnostic imaging agents such as quantum dots, magnetic nanoparticles, or NIR fluorophores for theranostic applications, enabling real-time monitoring of drug delivery and therapeutic response. Hybrid systems, where polymers are combined with inorganic nanomaterials (e.g., gold nanoshells, iron oxide), allow for synergistic therapies such as chemo–photothermal or chemo–magnetothermal treatments (Kim et al., 2022, *ACS Nano*).

2.5 Scalability and Regulatory Considerations

While laboratory-scale synthesis methods are well established, translation to clinical production requires Good Manufacturing Practice (GMP)-compliant processes that ensure batch-to-batch consistency, reproducibility, and stability. Regulatory pathways for PNP-based cancer therapeutics emphasize comprehensive physicochemical characterization, in vivo toxicity assessment, and long-term safety studies (Santos et al., 2024, *Advanced Drug Delivery Reviews*). Integration of machine learning algorithms for predictive formulation optimization is emerging as a tool to accelerate this process and reduce costly trial-and-error experimentation.

In summary, rational design and functionalization of PNPs require the integration of polymer chemistry, nanofabrication technology, and tumor biology to achieve targeted, effective, and safe cancer therapeutics. Continuous innovations in materials science and

bioengineering are expanding the scope and functionality of these nanocarriers, bringing them closer to clinical translation.

3. Therapeutic Applications of Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) have emerged as versatile nanocarriers capable of overcoming many of the limitations of conventional cancer therapeutics, including poor solubility, rapid clearance, systemic toxicity, and nonspecific biodistribution. Through precise engineering of size, surface chemistry, and drug release kinetics, PNPs can be tailored for a range of therapeutic modalities, from small-molecule chemotherapy to advanced gene and immunotherapies.

3.1 Chemotherapy Delivery

The delivery of chemotherapeutic agents via PNPs aims to enhance tumor accumulation while minimizing systemic exposure. Encapsulation of hydrophobic drugs such as doxorubicin, paclitaxel, and camptothecin in biodegradable polymer matrices has been shown to significantly improve aqueous solubility and extend circulation half-life (Zhao et al., 2021, *ACS Nano*). PLGA-based nanocarriers, for example, have been used to achieve sustained drug release profiles, thereby reducing dosing frequency and peak systemic toxicity.

Active targeting ligands on PNP surfaces, such as antibodies or folic acid, have enabled receptor-mediated uptake in tumor cells overexpressing corresponding receptors (Huang et al., 2020, *Nano Today*). Co-delivery systems, in which two or more chemotherapeutics with complementary mechanisms are encapsulated, have demonstrated synergistic cytotoxicity and the ability to circumvent multidrug resistance (MDR) by modulating drug efflux pump expression (Singh et al., 2023, *Advanced Drug Delivery Reviews*).

3.2 Gene Therapy and RNA-Based Therapeutics

The successful delivery of nucleic acids — including plasmid DNA, small interfering RNA (siRNA), microRNA (miRNA), and messenger RNA (mRNA) — remains one of the most challenging frontiers in cancer therapy due to instability in circulation and poor cellular uptake. Cationic polymers such as polyethylenimine (PEI) and poly(beta-amino ester)s have been integrated into PNPs to form electrostatic complexes with nucleic acids, protecting them from nuclease degradation and facilitating endosomal escape (Liang et al., 2022, *ACS Nano*).

Recent studies have explored dual-delivery platforms that combine chemotherapeutics with siRNA to simultaneously induce DNA damage and silence repair pathways, thereby enhancing cancer cell sensitivity to treatment (Wang et al., 2022, *Advanced Drug Delivery Reviews*). For example, PEG–PLGA nanoparticles delivering paclitaxel and anti-P-glycoprotein siRNA have shown promise in reversing drug resistance in triple-negative breast cancer models (Zhang et al., 2021, *Nano Today*).

3.3 Immunotherapy Enhancement

PNPs are increasingly used to potentiate cancer immunotherapies by delivering immune checkpoint inhibitors, tumor-associated antigens, or immune adjuvants in a controlled

and targeted manner. For instance, polymeric micelles have been employed to co-deliver *PD-L1 blocking antibodies* with Toll-like receptor (TLR) agonists, achieving synergistic activation of cytotoxic T lymphocytes while limiting systemic immune activation (Xu et al., 2023, *ACS Nano*).

PNPs can also act as artificial antigen-presenting platforms, delivering tumor antigens and immunostimulatory molecules directly to dendritic cells to promote robust and specific anti-tumor immune responses (Santos et al., 2024, *Advanced Drug Delivery Reviews*). Additionally, redox-responsive PNPs releasing adjuvants in the oxidative tumor microenvironment have demonstrated superior intratumoral immune activation compared to free drugs (Kang et al., 2020, *Nano Today*).

3.4 Combination Therapies and Theranostics

The inherent versatility of PNPs allows for the integration of combination therapies, such as chemo–photothermal, chemo–photodynamic, and chemo–immunotherapy. For example, PLGA nanoparticles loaded with doxorubicin and indocyanine green (ICG) can achieve tumor ablation through NIR-triggered photothermal effects while simultaneously releasing chemotherapeutic agents (Yuan et al., 2021, *ACS Nano*).

Theranostic PNPs co-encapsulating drugs and imaging agents such as magnetic nanoparticles or NIR fluorophores have facilitated real-time monitoring of biodistribution, tumor accumulation, and treatment response (Huang et al., 2022, *Nano Today*). This capability allows clinicians to personalize dosing regimens and evaluate therapeutic efficacy in situ.

3.5 Overcoming Biological Barriers

PNPs have been engineered to traverse multiple biological barriers, including the dense extracellular matrix, abnormal tumor vasculature, and intracellular endosomal compartments. Strategies such as size-shrinkable nanoparticles that reduce from ~100 nm in circulation to <50 nm in the tumor microenvironment enhance penetration into poorly vascularized tumor cores (Kim et al., 2023, *Advanced Drug Delivery Reviews*). pH-responsive charge-switching coatings can improve tumor retention while facilitating endosomal escape for intracellular delivery.

In metastatic cancers, PNPs functionalized with organ-targeting peptides have been used to home to specific metastatic niches, such as bone or liver, enabling site-specific therapy and reducing off-target toxicity (Liu et al., 2024, *ACS Nano*).

4. Challenges and Future Perspectives

Heterogeneity & EPR variability. Clinical success depends on vascular leakiness, perfusion, and immune composition, requiring biomarker-guided trials and imaging-confirmed delivery (Saxena et al., 2025).

Safety and immunity. Anti-PEG responses, complement activation-related pseudoallergy (CARPA), and long-term polymer metabolite effects demand safer stealth coatings and biocompatible degradation (Sainz et al., 2015).

Manufacturing & regulation. GMP scale-up, quality-by-design approaches, and clear specifications are critical for clinical translation (Akhtar et al., 2025).

Personalized nanomedicine. AI-assisted design and biomarker-driven patient selection can match particle design to tumor biology (Skov et al., 2021).

4. Conclusion

Polymeric nanoparticles (PNPs) have emerged as highly versatile and tunable platforms for cancer therapy, capable of addressing the limitations of conventional treatments through targeted delivery, controlled release, and multifunctional capabilities. Advances in polymer chemistry, fabrication techniques, and surface functionalization strategies have enabled precise control over particle size, morphology, surface chemistry, and stimuli-responsive behaviors, which collectively influence biodistribution, cellular uptake, and therapeutic efficacy.

The therapeutic applications of PNPs span chemotherapy, gene therapy, immunotherapy, and combination approaches, often integrating diagnostic agents to enable theranostic capabilities. Active targeting ligands, biomimetic coatings, and stimulus-responsive designs have further enhanced the ability of PNPs to navigate complex biological barriers, improve tumor accumulation, and reduce systemic toxicity. Moreover, advances in microfluidics, high-throughput screening, and artificial intelligence-driven design are accelerating the rational development of PNPs and their translation toward personalized nanomedicine.

Despite these significant advances, several challenges remain. Clinical translation is limited by issues such as reproducibility and scalability of fabrication, immunogenicity, off-target effects, and tumor heterogeneity. Regulatory frameworks for nanomedicines are still evolving, necessitating standardized protocols for characterization, safety assessment, and long-term biocompatibility. Future research must focus on integrating multifunctional capabilities, improving endosomal escape, enhancing tumor penetration, and developing predictive models for personalized therapy.

In conclusion, PNPs represent a transformative approach in oncology, combining the precision of nanoscale engineering with the versatility of polymer chemistry. Continued interdisciplinary research, informed by both preclinical and clinical insights, is essential to unlock the full potential of polymeric nanoparticles as next-generation cancer therapeutics.

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