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# TARGETED DELIVERY AND CONTROLLED RELEASE USING POLYMERIC NANOPARTICLES (PNPs) IN CANCER THERAPY

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## ABSTRACT
Nanoparticle-based drug delivery systems have revolutionized the landscape of cancer therapy. These nanocarriers, including polymeric nanoparticles, micelles, dendrimers, and lipid-based systems, offer enhanced bioavailability, prolonged circulation, and preferential tumour accumulation through passive and active targeting mechanisms. Ligand-mediated strategies, using folate, transferrin, antibodies, and aptamers, further improve selective cellular uptake. Intelligent, stimuli-responsive nanocarriers that triggered by pH, redox, enzymes, or hypoxia would provide spatiotemporal control over drug release and thus enhancing therapeutic precision. Multifunctional platforms allow the co-delivery of chemotherapeutics, siRNA, natural compounds, and immunomodulators, thereby addressing multidrug resistance and enabling synergistic effects. Recent innovations also support the delivery of genome-editing tools such as CRISPR/Cas9, positioning nanoparticles at the forefront of genetic therapy in oncology. Biodegradable polymers, implantable devices, microneedles, and in situ-forming hydrogels have been developed for localized and sustained drug release, improving treatment efficacy and patient compliance. This review presents a comprehensive overview of the design strategies, targeting mechanisms, and therapeutic applications of nanoparticle-based drug delivery systems in cancer therapy.

**KEYWORDS:** ligand-mediated targeting, biodegradable polymers, siRNA and gene delivery.

## INTRODUCTION
Cancer remains one of the most formidable challenges in modern medicine, characterized by complex pathophysiology, genetic heterogeneity, and dynamic tumour microenvironments. Despite substantial progress in diagnostic techniques and therapeutic modalities, conventional treatments such as chemotherapy, radiotherapy, and surgery still encounter significant limitations. These include systemic toxicity, drug resistance, non-specific targeting, and limited efficacy against metastatic and deep-seated tumours. Consequently, there is a pressing need for innovative strategies that can selectively deliver therapeutic agents to malignant tissues while minimizing harm to healthy cells.

Nanotechnology has emerged as a transformative force in cancer therapy, offering novel platforms for the targeted delivery of chemotherapeutic agents. Nanoparticles, by virtue of their size, surface characteristics, and functional versatility, are uniquely suited to traverse biological barriers and exploit the distinctive features of the tumour microenvironment, such as leaky vasculature and impaired lymphatic drainage known as the enhanced permeability and retention (EPR) effect, underpins passive tumour targeting, a foundational principle in nanoparticle-based drug delivery systems.

However, passive targeting alone is often insufficient, particularly for tumours located in remote or hypoxic regions where vascularization is poor. To overcome these barriers, active targeting strategies have been developed, wherein nanoparticles are functionalized with ligands—such as antibodies, peptides, aptamers, or small molecules—that bind specifically to overexpressed receptors on cancer cells. Ligand-directed approaches dramatically improve the selectivity and accumulation of nanocarriers in tumour tissues, thereby enhancing therapeutic efficacy and reducing off-target effects. Among the various nanocarrier systems, polymeric nanoparticles including micelles, dendrimers, and polymersomes are particularly attractive due to their tunable physicochemical properties, high drug loading capacity, and biodegradability. mPEG–PCL polymersomes loaded with methotrexate have

demonstrated potent cytotoxicity against cancer cells while exhibiting favorable pharmacokinetic profiles. Similarly, dual-functional nanocarriers combining photodynamic therapy and chemotherapy have shown synergistic anti-tumour effects in hepatocellular carcinoma models, underscoring the potential of multifunctional systems in overcoming the limitations of monotherapies.

Natural polymers such as chitosan and dextran also play a significant role in non-parenteral drug delivery. Their biocompatibility, mucoadhesive properties, and ease of functionalization make them ideal candidates for various administration routes, including oral, nasal, and transdermal delivery4–6. Dextran-based nanocarriers, in particular, offer unique opportunities for targeted delivery due to their ability to be modified with responsive linkers and targeting ligands.

The incorporation of tumour-specific ligands further enhances the potential of nanocarriers. Doxorubicin-loaded hyaluronan-based polymersomes exhibit selective uptake by cancer cells overexpressing CD44 receptors, improving intracellular drug accumulation and cytotoxicity. Mesoporous silica nanoparticles (MSNs) provide a versatile platform for drug delivery owing to their high surface area, tuneable pore size, and ease of surface modification. Functionalization with biomolecules such as folate9 or transferrin18 enables these carriers to engage in receptor-mediated endocytosis, promoting site-specific drug release.

Folate receptor-targeted systems have gained significant traction in recent years due to the overexpression of folate receptors in many cancer types. Folate-functionalized nanocarriers facilitate the targeted delivery of a wide range of therapeutic agents, including chemotherapeutics, genes, and photosensitizers. These carriers demonstrate improved therapeutic indices and reduced systemic toxicity. Similarly, aptamer-based systems offer high specificity and affinity for target molecules, enabling precision targeting at the molecular level. Such systems are highly adaptable and can be engineered to recognize a broad spectrum of cancer biomarkers, providing a customizable approach to targeted therapy.

Active targeting strategies are further complemented by the design of stimulus-responsive nanocarriers capable of releasing their payload in response to specific internal or external triggers. These include pH, redox gradients, enzymes, and external stimuli such as light or heat. For example, hypoxia-activated systems leverage the oxygen-deficient environment of solid tumours to trigger drug release, offering enhanced selectivity and effectiveness in poorly vascularized tumour regions.

Multifunctional and co-delivery nanocarriers are increasingly being explored to simultaneously deliver multiple therapeutic agents, including chemotherapeutics, gene silencers, and immunomodulators. These platforms can address the multifaceted nature of cancer by targeting multiple pathways or cell populations within the tumour microenvironment. Moreover, by integrating imaging agents, nanocarriers can serve dual functions as theragnostic tools—facilitating both treatment and real-time monitoring of therapeutic response.

Despite the considerable promise of nanocarrier-based cancer therapies, several challenges remain. Tumour heterogeneity, immunogenic responses, and the complexity of scaling up production under Good Manufacturing Practice (GMP) conditions are major obstacles to clinical translation. Furthermore, the dynamic nature of the tumour microenvironment necessitates adaptive and intelligent delivery systems capable of responding to the ever-changing biochemical landscape. This has spurred interest in developing AI-guided and smart nanocarriers, which represent the next frontier in precision oncology.

In brief, the rational design of targeted nanocarriers presents a compelling strategy to address the limitations of conventional cancer therapies. By harnessing both passive and active targeting mechanisms, incorporating stimulus-responsive features, and leveraging natural and synthetic materials, nanocarriers offer unprecedented control over drug delivery. The ability to deliver therapeutics precisely to tumours in remote or hypoxic regions not only enhances treatment efficacy but also opens avenues for the treatment of otherwise intractable cancers. As research continues to evolve, integrating these systems with emerging technologies such as artificial intelligence, genomics, and immunotherapy will likely define the next generation of cancer therapeutics.

**Insights Into Targeted Cancer Therapy**

Polymeric nanocarriers are reshaping the paradigm of cancer therapy by addressing longstanding challenges such as poor drug solubility, systemic toxicity, and nonspecific drug distribution. Both synthetic and natural polymers are being engineered into sophisticated delivery systems that enhance therapeutic index through targeted and controlled drug release. This review presents recent advancements in polymeric nanocarriers, focusing on hybrid systems, multimodal therapies, and stimuli-responsive platforms that offer high precision and efficacy in oncological applications.

Hybrid Polymeric Systems for Enhanced Delivery: Combining synthetic and natural polymers has emerged as a powerful strategy to exploit the benefits of both material types. For instance, chitosan-modified PLGA nanoparticles exhibit enhanced mucoadhesive properties, better encapsulation efficiency, and controlled release profiles. The positive surface charge from chitosan promotes stronger interactions with negatively charged cancer cell membranes, improving cellular uptake and therapeutic efficacy. Modifications improve colloidal

stability and extend shelf life, making these carriers more viable for clinical application.[1]

Structural Versatility and Drug Retention: Polymersomes, particularly those based on amphiphilic block copolymers like mPEG-PCL, offer structural advantages for encapsulating both hydrophobic and hydrophilic drugs. Their bilayer architecture supports sustained release and improves cytotoxicity in cancer models such as breast cancer. Unlike traditional micelles, polymersomes demonstrate improved mechanical stability, drug-loading capacity, and in vivo predictability, establishing them as a promising alternative for long-term chemotherapy applications.[2]

Multimodal Nanocarriers: Dual-function polymeric nanocarriers integrate multiple therapeutic strategies within a single platform. Nanovesicles composed of PEG-PDLLA, co-loaded with chemotherapeutic and photodynamic agents, exemplify this approach. By enabling drug release in response to external stimuli like light, these systems offer spatiotemporal control over therapy, reducing off-target toxicity and improving antitumor activity. This multimodal integration represents a crucial advancement in overcoming tumour heterogeneity and treatment resistance.[3]

Non-Parenteral Delivery via Natural Polymers: Non-invasive delivery routes, including oral, nasal, and ocular pathways, are increasingly being explored using natural polymer-based nanoparticles. Chitosan nanoparticles stand out due to their mucoadhesive and permeation-enhancing properties. Their ability to transiently open epithelial tight junctions enhance absorption of chemotherapeutic agents, while chemical modifications further expand their functional applications. These systems offer patient-friendly alternatives to injectable formulations.[4]

Dextran-Based Responsive Systems: Dextran and its derivatives are valued for their biocompatibility and chemical tunability. Responsive dextran systems can be engineered to release drugs in response to environmental stimuli such as pH or redox conditions, typical of the tumor microenvironment. Their molecular weight and branching can be fine-tuned to influence pharmacokinetics and release kinetics, while site-specific drug conjugation improves therapeutic targeting and efficacy.[5,6]

Nanogels are found to be an Intelligent Depots for Tumour-Specific Release. Natural polymer-based nanogels offer a high degree of structural flexibility, enabling them to respond dynamically to the tumour environment. Their high water content and swelling capacity allow for efficient drug entrapment and controlled release under tumour-specific pH or thermal conditions. Enhanced permeability and retention characteristics further support their accumulation in solid tumors, offering a smart and adaptable platform for next-generation delivery.[7]

Co-Delivery Systems to Combat Drug Resistance: Combination therapy using co-encapsulated drugs, such as cisplatin and paclitaxel, has demonstrated synergistic cytotoxicity and enhanced therapeutic efficacy in models of ovarian cancer. Polymeric nanocarriers facilitate this by enabling co-loading, synchronized release, and improved tumour accumulation. This strategy not only increases treatment success rates but also addresses the critical issue of multidrug resistance—a major challenge in recurrent and refractory cancers.[8]

The evolution of polymeric nanocarriers signifies a transformative shift in cancer therapeutics. By integrating biological responsiveness, structural versatility, and multimodal capabilities, these systems address many limitations of traditional treatments. As clinical translation progresses, a focus on biocompatibility, scalability, and long-term safety will be essential. Nonetheless, the current trajectory suggests that precision nanomedicine, powered by advanced polymeric systems, will become an integral part of future oncological care.

**Ligand-Mediated Targeting Strategies**

Ligand-mediated targeting represents a pivotal advancement in the precision of cancer nanomedicine. Various ligands—such as folate, transferrin, antibodies, and aptamers—are employed to actively target tumor-specific receptors, enhancing cellular uptake, reducing off-target effects, and improving therapeutic indices.

Folate-functionalized nanocarriers exploit the high expression of folate receptors in many tumors, enabling selective drug delivery and minimizing systemic toxicity. They exhibit enhanced design flexibility in ligand density and nanoparticle surface chemistry across various cancer types, including osteosarcoma, where folate-conjugated micelles have shown targeted curcumin delivery with promising therapeutic outcomes.[9,10]

Transferrin-modified systems target transferrin receptors overexpressed in numerous malignancies, supporting improved drug internalization and overcoming drug resistance. Silica-based nanocarriers and transferrin-conjugated micelles have both demonstrated increased tumour specificity and the ability to bypass multidrug resistance mechanisms.[11,12]

Aptamer-functionalized nanocarriers offer nucleic acid-based targeting with high specificity and low immunogenicity. These systems facilitate site-specific delivery of therapeutic agents and enhance the precision of tumor targeting. They show strong binding affinity and internalization efficiency while serving as a safer alternative to antibodies.[13,14]

Polymeric nanoparticles conjugated with various ligands, including peptides and small molecules, emphasize the importance of rational design, particularly in ligand selection, nanoparticle stability, and surface density. Such strategies allow for improved tumour penetration, reduced clearance, and higher intracellular accumulation of anticancer agents.[15,16]

Multi-ligand strategies, such as dual targeting with folate and transferrin on gold nanoparticles or polymeric micelles, address tumour heterogeneity by engaging multiple receptors. These approaches result in enhanced cellular uptake, superior therapeutic outcomes, and improved pharmacokinetics.[17,18]

Collectively, ligand-mediated strategies represent a powerful toolkit in the evolution of cancer nanotherapy. By enhancing receptor-specific delivery and minimizing systemic side effects, these approaches contribute to more effective and personalized treatment regimens. Innovations in ligand combinations, nanoparticle engineering, and tumour microenvironment responsiveness continue to push the boundaries of targeted cancer therapy.

**Tumor Microenvironment-Responsive Nanocarriers**

The tumour microenvironment (TME) presents a complex array of biological and physicochemical features, such as acidity, hypoxia, high redox potential, and enzyme overexpression, that can be harnessed to achieve targeted and controlled drug delivery. Recent advances in nanocarrier engineering have focused on developing smart, stimuli-responsive systems that are selectively activated by these TME characteristics, improving therapeutic efficacy while minimizing systemic toxicity.

pH and Hypoxia Dual-Responsive Nanocarriers enhances the chemotherapy. TME-responsive nanocarriers that simultaneously respond to acidic pH and elevated $H_2O_2$ concentrations have shown promising results in modulating hypoxia and enhancing therapeutic outcomes. Systems utilizing $MnO_2$-based platforms not only promote site-specific drug release but also generate oxygen in situ, alleviating hypoxic conditions and improving photodynamic therapy (PDT) efficacy. Similar strategies using hypoxia-sensitive prodrugs demonstrate the potential of co-opting the tumour's own environment to enhance therapy.[19,20]

Dual-responsive nanocarriers exploiting both acidic pH and elevated intracellular glutathione (GSH) levels offer another robust approach for controlled release. These platforms remain stable under physiological conditions but undergo structural changes within the TME, ensuring precise drug delivery. Such systems have demonstrated improved antitumor performance across various models, including gliomas, through co-delivery mechanisms and improved intracellular targeting.[21,22]

**Enzyme-Responsive Nanocarriers play a vital role in chemo-dynamic and sonodynamic therapy.** The overexpression of enzymes such as matrix metalloproteinases (MMPs) and hyaluronidase in the TME can be leveraged for selective drug release. Nanocarriers utilizing enzyme-cleavable linkers achieve site-specific activation, reducing off-target effects and enhancing drug concentration at the tumour site. Broader studies have also explored the use of enzyme-mimetic systems for TME modulation, further enhancing treatments like chemo-dynamic and sonodynamic therapy.[23,24]

**Role of Redox-Manipulating Nanocarriers in the enhancement of chemo-dynamic therapy:** Redox-responsive nanocarriers designed to deplete intracellular antioxidants and trigger oxidative stress provide a powerful mechanism for inducing cancer cell death. These systems typically incorporate disulfide linkages that cleave in reductive environments, releasing cytotoxic agents. Specific applications have been demonstrated in glioma models, where glutathione depletion synergizes with reactive oxygen species generation for enhanced chemo-dynamic therapy.[25,26]

Glutathione (GSH)-Responsive Injectable Hydrogels play a key role in site-specific therapy establishing control over tumour verses normal cells. Injectable hydrogel systems responsive to elevated GSH levels in the TME represent a novel avenue for localized drug delivery. These hydrogels degrade selectively within the tumour milieu, enabling controlled, sustained release of therapeutics directly at the site of action. Compared to systemic nanocarrier approaches, GSH-responsive hydrogels offer an alternative for site-specific therapy with reduced systemic exposure.[27,28]

The integration of TME-responsive features into nanocarriers has opened new possibilities for precision oncology. By harnessing endogenous tumour signals such as pH shifts, redox gradients, enzyme activity, and hypoxia, these smart systems enable site-specific activation and enhance therapeutic outcomes. Ongoing research into multi-responsive and hybrid systems will likely further refine the specificity and clinical applicability of nanocarrier-based cancer therapies.

**Comparative Strategies in Polymer–Drug Conjugates and Physically Encapsulated Drug Delivery Systems**

The design of drug delivery systems that can achieve controlled, sustained, and stimuli-responsive release remains a cornerstone in the development of next-generation therapeutics. Polymer–drug conjugates (PDCs) and physically encapsulated drug systems represent two complementary strategies for improving drug bioavailability, targeting, and therapeutic efficacy. This section explores recent advances in these two domains, emphasizing their respective design principles, functional mechanisms, and clinical potential in cancer therapy.

PDCs offer a versatile platform for integrating therapeutic and diagnostic functions (theranostics), enabling real-time monitoring of drug distribution and treatment response. Their modular design allows for the conjugation of drugs via cleavable linkers that respond to biological stimuli, such as pH, enzymes, or redox potential. This strategy ensures site-specific drug activation, minimizing systemic toxicity. Furthermore, the incorporation of imaging agents into PDCs expands their utility beyond therapeutic delivery, contributing to precision medicine approaches.[29,30]

**Rational Design and Clinical Translation of PDCs**

Key design parameters in PDCs, such as the nature of the polymer backbone, drug loading strategy, and linker chemistry, directly influence therapeutic performance. Advances in synthetic strategies have enabled the development of PDCs with tenable pharmacokinetics, improved solubility, and controlled release. These systems are increasingly entering clinical and preclinical pipelines, affirming their translational promise. In contrast, physically encapsulated systems like microparticles offer simpler loading mechanisms and predictable release kinetics based on structural factors such as particle size, although they may lack the molecular precision of conjugates.[31,32]

**Electroactive Polymers and On-Demand Drug Release**

Emerging technologies such as electroactive polymers allow drug release to be triggered in real-time through external stimuli (e.g., electric fields), offering highly controllable and reversible delivery systems. These materials align well with personalized medicine strategies that demand adaptable dosing. Meanwhile, polymer conjugates have also been adapted for combination chemotherapy, using structural versatility to deliver multiple agents simultaneously and synergistically.[33,34]

**Polymeric Nanocarriers and Material-Specific Approaches**

General advancements in polymeric vehicles continue to improve the stability and release profiles of encapsulated drugs. Broad-spectrum systems, including hydrogels, micelles, and nanoparticles, offer sustained release and enhanced bioavailability. Specific polymer families, such as polyurethanes, are being tailored to modulate release kinetics in response to the physicochemical properties of the loaded drug, offering a material-driven approach to delivery customization.[35,36]

**Stimuli-Responsive Hydrogels and Temperature-Dependent Systems**

Hydrogel-based systems, particularly those derived from biopolymers like pectin, have shown potential in controlled release through pH sensitivity, there by enable the targeted delivery in acidic tumour microenvironments. Complementary strategies involve temperature-responsive systems, which release therapeutic agents upon exposure to localized hyperthermia. The use of smart polymers such as poly(N-isopropylacrylamide) (PNIPAM) demonstrates the ongoing innovation in stimuli-responsive PDCs tailored for specific tumour microenvironments.[37,38]

Both polymer–drug conjugates and physically encapsulated systems provide viable, yet distinct, pathways toward achieving controlled and targeted drug delivery. While PDCs offer high specificity and functional versatility, encapsulated systems bring simplicity and scalability. Continued cross-disciplinary innovation, spanning materials science, chemistry, along with nanomedicine is vital to optimizing these platforms for clinical deployment in cancer therapy and beyond.

**Intracellular Delivery and Endosomal Escape: Mechanisms and Strategies For Enhanced Therapeutic Efficacy**

Effective intracellular delivery of therapeutics remains a major challenge in nanomedicine, particularly due to the complexity of cellular uptake and the barrier posed by endosomal entrapment. Overcoming these obstacles is essential for the success of gene therapies, mRNA-based therapeutics, and nanoparticle-mediated drug delivery systems. This review outlines key cellular internalization pathways, highlights critical mechanisms involved in endosomal escape, and evaluates the role of cationic polymers and the proton sponge effect in facilitating cytosolic release of therapeutic payloads.

**Mechanisms of Cellular Uptake:** Understanding the predominant endocytic pathways is vital for optimizing intracellular delivery. Caveolae-mediated endocytosis has emerged as a particularly efficient route for the uptake of nanoparticles in slow-dividing cells, offering advantages in non-degradative trafficking and enhanced delivery to the cytoplasm.[39] In contrast, clathrin-mediated endocytosis (CME) remains a well-characterized and widely exploited pathway, with insights into vesicle formation and the involvement of accessory proteins such as dynamin providing a foundation for targeted delivery strategies.[40] Comparative studies of these pathways reveal how tailoring nanoparticle design to exploit specific uptake mechanisms can significantly influence therapeutic efficacy.

**Overcoming Endosomal Entrapment:** Once internalized, nanocarriers are typically sequestered within endosomes and subjected to lysosomal degradation. A major determinant of successful intracellular delivery is the ability of the therapeutic agent to escape from these compartments. Various approaches have been explored to address this barrier, including the use of polymeric nanoparticles engineered with pH-responsive or membrane-disruptive functionalities.[41] Among these, the proton sponge effect has received considerable attention for its capacity to induce endosomal swelling and rupture through osmotic

pressure generated by cationic polymers such as polyethylenimine (PEI).[42]

Design innovations in pH-responsive polymers further refine this strategy by facilitating endosomal disruption in response to acidic environments, thus minimizing off-target effects and cytotoxicity.[43] Parallel approaches involving cationic amphiphilic drugs (CADs) offer an alternative chemical-based mechanism for destabilizing endosomal membranes, expanding the toolkit for endosomal escape enhancement.[44]

**Multi-Modal Endosomal Escape Strategies:** A combination of biochemical, biophysical, and material-driven strategies has broadened the scope of endosomal escape enhancement. These include the use of cell-penetrating peptides, redox-sensitive linkers, reactive oxygen species (ROS) generators, and small molecules with membrane-disruptive potential.[45] The proton sponge effect remains a cornerstone mechanism, but it is increasingly integrated with other functionalities to achieve synergistic effects in delivery systems.[46]

**Role of Cationic Materials and Liposomes:** Cationic liposomes and polymers continue to play a pivotal role in intracellular delivery due to their electrostatic interactions with negatively charged cell membranes and endosomal membranes. These interactions promote both cellular uptake and endosomal escape, particularly when combined with stimuli-responsive design elements.[47] Furthermore, comprehensive analyses of cellular internalization and intracellular trafficking highlight the necessity of integrating endosomal escape mechanisms into early-stage nanoparticle design to maximize delivery efficiency and target engagement.[48]

The interplay between cellular uptake pathways and endosomal escape mechanisms determines the ultimate success of intracellular delivery platforms. Advances in understanding clathrin- and caveolae-mediated endocytosis, combined with innovations in polymer design and chemical enhancers, provide multiple avenues for optimizing therapeutic delivery. Continued integration of biological insight and material engineering will be key to translating these strategies into clinically effective systems.

**Nanoscale Co-Delivery Systems in Cancer Therapy: Advancing Synergistic Treatment Strategies**

The complexity of cancer pathophysiology and the emergence of drug resistance necessitate the use of multi-modal treatment strategies. Co-delivery systems in nanoscale platforms engineered to simultaneously deliver multiple therapeutic agents. They are gaining attention for their ability to enhance efficacy, reduce side effects, and overcome mechanisms of resistance. By combining chemotherapeutics with genetic materials such as siRNA or immunomodulators, these systems enable synergistic effects that improve treatment outcomes in both preclinical and clinical settings. This section outlines recent advances in nanoparticle-based co-delivery strategies, focusing on combination approaches involving chemotherapy, siRNA, immunotherapy agents, and natural products.

Chemotherapy and siRNA Co-Delivery: Combining chemotherapeutic drugs with siRNA targets key oncogenic pathways while simultaneously inhibiting resistance mechanisms, offering a dual approach to cancer treatment. Nanoparticle-mediated systems facilitate the synchronized release of both agents within the tumour microenvironment, increasing intracellular drug accumulation and gene silencing efficiency.[49] Broader applications of siRNA co-delivery strategies further support this approach, showcasing its capacity to modulate gene expression and sensitize tumours to chemotherapeutics.[50]

Chemoimmunotherapy Co-Delivery: Integrating chemotherapy with immunomodulators within a single nanocarrier has shown potential to activate tumour-specific immune responses while directly killing cancer cells. This strategy enhances the recruitment and activation of cytotoxic T lymphocytes, contributing to long-term immune surveillance and tumour control.[51] Advances in delivery platforms for immunotherapy support this approach by offering improved payload stability, targeting efficiency, and immunomodulatory activity.[52]

Multi-Drug Co-Delivery Systems: The co-encapsulation of multiple chemotherapeutic agents within a nanoparticle system enables synchronized release and spatial-temporal drug distribution, resulting in enhanced synergy and reduced off-target toxicity. Core-shell nanoparticle systems, for instance, have demonstrated high levels of drug deposition in tumours and strong inhibition of tumour growth.[53] Broader analyses confirm that co-delivering multiple drugs using nanocarriers outperforms traditional monotherapy approaches by achieving enhanced pharmacokinetics and therapeutic indices.[54]

Natural Compounds and siRNA Co-Delivery: Natural compounds with inherent anticancer properties can complement siRNA-mediated gene silencing when co-delivered via nanoparticles. These systems allow for enhanced intracellular uptake and sustained release, resulting in potentiated antitumor effects.[55] Complementary evidence from broader studies confirms the synergistic potential of combining phytochemicals and small RNAs, offering a promising strategy for low-toxicity cancer therapies.[56]

Design Strategies and Delivery Mechanisms: The performance of co-delivery systems is largely influenced by design parameters such as drug loading capacity, release kinetics, and targeting capability. Recent reviews highlight the importance of rational design in developing efficient co-delivery vectors that can respond to tumour-

specific stimuli and release therapeutic payloads in a controlled manner.[57] Additional insights emphasize the need for multifunctional carriers capable of bypassing biological barriers and facilitating endosomal escape, which remain key challenges in current system development.[58]

Co-delivery systems represent a transformative approach in cancer therapy, offering the ability to tackle multiple therapeutic targets simultaneously. By combining chemotherapeutic agents, siRNA, immunomodulators, or natural compounds within a single nanoscale platform, these strategies enable synergistic effects, improved bioavailability, and reduced toxicity. Continued innovation in nanocarrier design, drug combination optimization, and tumour-targeting mechanisms will be critical for translating co-delivery strategies into clinical success.

**Polymeric Nanocarriers for Crispr/Cas9 Delivery: Overcoming Barriers To Precision Gene Editing**

The clinical translation of CRISPR/Cas9 gene editing hinges not only on the system's inherent precision but also on the development of effective delivery vehicles. Viral vectors, though efficient, are limited by immunogenicity, insertional mutagenesis, and cargo capacity constraints. In contrast, polymeric nanocarriers offer a promising non-viral alternative due to their biocompatibility, structural versatility, tunable release profiles, and ability to encapsulate diverse molecular formats such as DNA, mRNA, and ribonucleoprotein complexes. A growing body of research has focused on optimizing these nanocarriers to overcome the key barriers in CRISPR/Cas9 delivery: extracellular stability, targeted cellular uptake, endosomal escape, and nuclear localization.

Overview of Polymeric Nanocarriers in CRISPR Delivery: Polymeric nanocarriers are emerging as adaptable platforms for therapeutic gene delivery, enabling the protection and transport of CRISPR components to target cells. They can be engineered to respond to stimuli such as pH or redox gradients, allowing controlled release of payloads in intracellular environments. This flexibility makes them particularly suitable for delivering CRISPR/Cas9 systems to diseased tissues with high specificity and reduced systemic toxicity.[59] These delivery systems must address unique challenges such as nucleic acid degradation, off-target effects, and immune activation. A deeper understanding of nanoparticle–cell interactions has led to advanced designs tailored for efficient cytosolic and nuclear delivery.[60]

CRISPR/Cas System Compatibility and Delivery Modalities: Given the diversity of CRISPR/Cas formats including plasmids, mRNA, and RNPs are polymeric carriers and must be optimized for each modality. RNP delivery, for example, provides rapid gene editing with reduced off-target activity, but requires carriers capable of preserving protein activity and facilitating nuclear transport. Non-viral vectors, including polymeric micelles, dendrimers, and cationic polymers, offer distinct advantages in terms of tunability and safety for such applications.[61] While in vivo genome editing remains a significant hurdle, advances in polymer chemistry and nanoparticle architecture continue to enhance biodistribution and tissue-specific targeting.[62]

Biomedical Applications and Non-Viral Delivery Strategies: Polymer-based nanocarriers have shown promise in diverse biomedical applications which range from correcting genetic disorders to cancer immunotherapy. These systems enable functional delivery of CRISPR components in preclinical models, providing a framework for their use in treating monogenic diseases, viral infections, and malignancies.[63] As concerns around viral vectors persist, there is a growing emphasis on nanoparticle-mediated systems that combine high editing efficiency with improved biosafety profiles.[64] Multifunctional carriers integrating targeting ligands, imaging agents, or responsive release mechanisms further enhance the potential of CRISPR-based therapeutics.

Biomaterial Innovation and Cancer Applications: Biomaterials-based strategies expand the design space for CRISPR delivery, allowing incorporation of biodegradable polymers, hydrogels, and organic nanoparticles to suit specific therapeutic contexts. These platforms offer sustained, localized release and can be engineered for co-delivery with adjuvants or immune modulators.[65] In oncology, polymeric and organic nanoparticles enable tumour-targeted gene editing, enhancing therapeutic outcomes while minimizing off-target effects.[66]

**Delivery Efficiency and Future Perspectives:** Efficient gene editing requires high-fidelity delivery systems capable of overcoming cellular and nuclear barriers. Enhancing transfection efficiency while maintaining cellular viability remains a key objective. Polymeric nanocarriers designed with endosomal escape mechanisms and nuclear localization signals are critical to achieving this balance.[67] Continuous innovation in nanoparticle design, including surface modifications and charge optimization, is essential for refining delivery strategies.[68]

Polymeric nanocarriers represent a transformative platform for CRISPR/Cas9 delivery, offering safer and more versatile alternatives to viral vectors. By addressing key challenges such as payload stability, targeted delivery, and intracellular trafficking, these systems enable precise genome editing with therapeutic potential across a wide range of diseases. Future efforts should prioritize clinical translation through scalable manufacturing, long-term safety assessment, and integration with disease-specific delivery frameworks.

**Personalized And Precision Nanomedicine in Cancer Therapy: Integrating Tumour Profiling, Responsive Carriers, And Theranostics**

The rise of personalized medicine has redefined cancer therapy, prioritizing individualized treatment strategies based on the molecular and phenotypic characteristics of a patient's tumour. Within this paradigm, precision nanomedicine plays a pivotal role, offering engineered nanocarriers tailored to patient-specific tumour profiles and capable of overcoming delivery barriers while integrating therapeutic and diagnostic functions. By leveraging nanotechnology, therapeutic agents can be selectively delivered to diseased tissues, reducing off-target effects and enabling real-time monitoring of treatment efficacy.

Tailoring Nanomedicine to Tumour Heterogeneity: Personalized nanomedicine emphasizes the customization of nanocarriers based on tumour-specific markers, vascular architecture, and microenvironmental cues. Such stratified approaches are critical in addressing inter- and intra-tumoral heterogeneity, which often limits the efficacy of conventional therapies. Advances in nanomaterial science now allow for the engineering of multifunctional carriers capable of adapting to the dynamic tumour environment, offering both precision in targeting and flexibility in formulation design.[69] Beyond tumour targeting, precision nanomedicine also involves overcoming biological barriers such as immune clearance, dense extracellular matrices, and abnormal vasculature that impair drug delivery.[70] Strategies incorporating surface modifications, stealth coatings, and environment-responsive elements are being used to address these limitations, resulting in enhanced tumour accumulation and cellular uptake.[71,72]

Stimuli-Responsive Nanocarriers for Site-Specific Delivery: An essential feature of precision nanomedicine is the development of stimuli-responsive systems that activate drug release selectively in the tumour microenvironment. These systems respond to endogenous cues such as pH, redox potential, and enzymatic activity as well as external stimuli like temperature and light, to achieve controlled and localized therapeutic action.[73] This responsiveness not only enhances treatment precision but also mitigates systemic toxicity. Liposomal nanocarriers have emerged as a leading class of stimuli-responsive vehicles, offering modularity in drug loading and surface functionalization. Innovations in dual- and multi-responsive nanocarriers further enable synchronized responses to complex tumour microenvironments.[74]

Theranostics: Dual Integration of Therapy and Diagnosis: Theranostic nanomedicine, which combines therapeutic and diagnostic functionalities into a single platform, marks a significant advancement in personalized cancer care. Barcoded nanoparticles capable of real-time tracking and quantitative imaging provide dynamic feedback on biodistribution and therapeutic response, facilitating treatment adjustments on-the-fly.[75] This approach not only enhances treatment accuracy but also supports longitudinal monitoring and outcome prediction. The integration of imaging agents into nanocarriers enables non-invasive visualization of drug delivery pathways and accumulation sites, fostering adaptive treatment strategies.[76] Multifunctional nanomedicines incorporating chemotherapeutics, contrast agents, and targeting ligands demonstrate potential for simultaneous tumour localization, therapy, and outcome assessment.[77] These platforms also support combination therapies, such as co-delivery of gene therapy and chemotherapy, further expanding their therapeutic reach.[78]

Precision and personalized nanomedicine represent a transformative direction in cancer treatment, aligning therapeutic design with the molecular and physiological complexities of individual tumours. Stimuli-responsive carriers and theranostic platforms are critical enablers of this shift, offering both enhanced therapeutic specificity and real-time monitoring capabilities. Continued innovation in nanomaterials, bio-responsive systems, and integrated diagnostics is essential for translating personalized nanomedicine from concept to clinical reality.

**Emerging Formulation Platforms in Cancer Therapy: Long-Acting Injectables, In Situ Gels, And Implantable Depots**

Innovations in formulation platforms are reshaping the delivery landscape for cancer therapeutics, offering sustained, localized, and patient-friendly alternatives to conventional administration routes. Long-acting injectable nanoparticles, in situ forming gels, and implantable polymeric depots represent three major classes of delivery systems that address key limitations in current cancer treatments namely poor bioavailability, frequent dosing, and systemic toxicity.

**Injectable Long-Acting Nanoparticles:** Long-acting injectable (LAI) systems have emerged as a transformative strategy for enhancing patient adherence and maintaining therapeutic plasma concentrations over extended periods. Nanoparticle-based LAIs are formulated using polymeric conjugates, biodegradable nano/microparticles, and depot-forming excipients that enable sustained drug release profiles while reducing dosing frequency.[79] These systems are particularly advantageous in oncology, where frequent administrations can compromise patient quality of life and contribute to suboptimal adherence. Advances in materials engineering, including PEGylation and biodegradable polymers, have improved the stability and biocompatibility of these nanoparticles. Nevertheless, challenges such as injection-site reactions, dose uniformity, and scale-up for manufacturing remain critical areas for development.[80]

**In Situ Forming Gels for Local Tumour Therapy:** In situ forming hydrogels represent a highly effective platform for postoperative cancer management, especially in preventing local recurrence. These injectable systems undergo sol-to-gel transition upon exposure to physiological conditions, forming a drug-laden depot that conforms to irregular tissue geometries.[81] The ability to localize therapy at the surgical site minimizes systemic toxicity and allows high local drug concentrations at residual tumour margins. Recent progress in thermo-sensitive and pH-responsive gels has expanded the applicability of these systems in various tumour microenvironments. Furthermore, their capacity to incorporate chemotherapeutic agents, immune modulators, or radiosensitizers supports multimodal treatment strategies.[82]

**Implantable Polymeric Depots:** Implantable drug delivery systems (IDDSs) offer a versatile and sustained release mechanism for site-specific therapy in oncology. These depots, fabricated from synthetic or naturally derived polymers, provide controlled drug release over weeks or months, reducing the need for repeated interventions.[83] They are particularly well-suited for solid tumours where consistent intra-tumoral drug exposure is required. Implantable platforms can also be engineered to respond to environmental cues, adding a layer of responsiveness to their extended-release profile. While promising, limitations related to biodegradation rates, biocompatibility, and surgical implantation must be addressed to optimize clinical adoption.[84]

The integration of advanced formulation platforms in cancer therapy signifies a paradigm shift toward more effective, patient-centric treatment modalities. Long-acting nanoparticles enhance adherence and systemic exposure control, in situ gels deliver localized and sustained therapy with minimal invasiveness, and implantable depots provide prolonged and controlled release at tumour sites. Together, these systems offer distinct yet complementary approaches to overcoming longstanding barriers in oncology drug delivery and hold considerable potential for improving treatment outcomes.

**Biocompatibility, Biodegradability, And Safety in Polymeric Biomaterials For Drug Delivery**

The success of polymeric materials in biomedical applications hinges critically on their biocompatibility, biodegradability, and safety profiles. These factors not only determine therapeutic efficacy and device longevity but also govern patient outcomes by minimizing adverse immune reactions and toxicities. Understanding and optimizing these parameters is essential for advancing polymer-based drug delivery systems.

Immunogenicity and Immune Interactions: Immunogenicity remains a pivotal consideration in polymer design. Ideally, polymers used in drug delivery and implantable devices should evade immune recognition to prevent inflammation, fibrosis, or rapid clearance. Yet, even widely used biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) can provoke immune responses due to acidic degradation products accumulating locally, which may induce inflammatory cascades and compromise biocompatibility.[85] Additionally, stealth polymers like polyethylene glycol (PEG), while improving circulation times, have been shown to elicit anti-PEG antibodies upon repeated exposure, posing challenges for long-term use.[86] The interplay between polymer molecular architecture, surface properties, and implantation site strongly influences immunogenic potential, necessitating tailored formulation strategies.

Biodegradation Mechanisms and Byproducts: Biodegradable polymers are engineered to degrade within physiological environments into non-toxic metabolites. Synthetic polymers such as PLGA and polylactic acid (PLA) primarily undergo hydrolytic cleavage of ester bonds, yielding lactic and glycolic acids that enter endogenous metabolic pathways.[87] In contrast, natural polymers like chitosan and collagen degrade enzymatically, a process influenced by local enzyme concentrations and tissue microenvironment.[88] The degradation kinetics must be carefully modulated to maintain structural integrity throughout the therapeutic window while preventing accumulation of acidic or reactive byproducts that could provoke toxicity or impair healing.

Long-Term Safety and Off-Target Effects: Despite their biodegradable nature, polymeric materials are not free from long-term safety concerns. Chronic exposure to degradation products or polymer residues may cause organ toxicity, immunosuppression, or dysbiosis, as observed in studies with starch-based bioplastics which revealed unexpected metabolic and microbiota disturbances.[89] These findings emphasize the critical need for extensive in vivo biocompatibility and toxicological evaluations extending beyond acute phases. The development of smart polymeric carriers with stimuli-responsive degradation profiles and integrated monitoring capabilities presents promising avenues to mitigate off-target effects while maintaining therapeutic efficacy.[90]

Advances in polymer science have substantially expanded the toolkit for designing safer, more effective drug delivery systems. However, balancing the complex demands of immune invisibility, controlled biodegradation, and long-term safety remains a formidable challenge. Emerging strategies focusing on intelligent polymer architectures, precise degradation control, and comprehensive safety assessments are vital to translating polymer-based nanomedicines into clinical success. Continuous innovation in this space will enable the development of next-generation biomaterials that optimize therapeutic outcomes while minimizing adverse effects.

**Clinical Translation and Regulatory Challenges of Polymeric Nanocarriers**

The clinical translation of polymeric nanocarrier systems represents one of the most promising yet complex frontiers in nanomedicine. These systems offer numerous advantages over conventional drug delivery approaches, including targeted delivery, improved solubility and stability, and the potential for controlled or stimuli-responsive drug release. However, despite encouraging preclinical outcomes, relatively few polymeric nanocarriers have reached clinical use. This translational gap reflects a range of interrelated challenges, including regulatory scrutiny, scale-up limitations, and reproducibility issues. Addressing these hurdles is essential to advance polymer-based therapeutics from bench to bedside.

Polymeric Nanocarrier Systems in Clinical Evaluation: Polymeric nanocarriers encompass diverse architectures like micelles, nanoparticles, nanogels, and dendrimers that have been engineered to improve pharmacokinetics and site-specific drug accumulation. In the oncology space, where drug toxicity and resistance often limit therapeutic success, polymeric formulations have shown significant promise. Several systems have reached clinical trials, demonstrating enhanced efficacy or reduced toxicity in early-phase evaluations. Among these, nanoparticle-based delivery of chemotherapeutics such as docetaxel, paclitaxel, and camptothecin derivatives have been investigated for their capacity to bypass multidrug resistance and extend circulation half-life.

While some of these systems have progressed to advanced trial stages, broad clinical translation remains limited. This limitation is not due to a lack of innovation but rather to the complexities of validating clinical efficacy, stability, and patient-specific pharmacodynamics under tightly controlled conditions. Moreover, the variability in disease biology and the difficulty in standardizing nanoscale systems complicate trial designs and outcome interpretation.[91]

Efforts are underway to optimize trial methodologies and harmonize endpoints specific to nanocarrier therapies. For example, incorporating companion diagnostics, patient stratification, and real-time biodistribution imaging is becoming increasingly common to evaluate in vivo performance and improve clinical predictability. Nevertheless, the leap from successful early-phase trials to regulatory approval remains a significant bottleneck.[92]

Regulatory Hurdles: FDA and EMA Perspectives

The regulatory frameworks governing polymeric nanocarriers are still evolving. Unlike conventional pharmaceuticals, nanomedicines are not regulated under a unified classification but are instead evaluated case-by-case due to their structural diversity and complex behavior in vivo. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued preliminary guidance and reflection papers, but no universally accepted criteria currently exist for nanomedicine approval.[93]

Comprehensive Physicochemical Characterization: The FDA emphasizes the need for detailed analytical characterization of nanomaterials—particle size distribution, surface charge, morphology, and aggregation behaviour are all critical factors that can influence safety, efficacy, and clearance rates.[94]

Reproducibility and Batch Consistency: Nanocarrier formulations must demonstrate batch-to-batch reproducibility, which is often complicated by their sensitivity to minor variations in formulation and processing parameters. The lack of harmonized assays across laboratories complicates the comparability of data submitted for regulatory review.

Risk-Based Evaluation: The EMA encourages developers to adopt a risk-based approach, integrating preclinical toxicity data, biodistribution profiles, and immunogenicity assessments. However, long-term toxicity, especially related to accumulation and degradation products, remains difficult to predict in short duration trials.[95]

Clinical Trial Design Considerations: Traditional pharmacokinetic and toxicity metrics may not fully capture the behaviour of nanocarriers, especially when targeted delivery or stimuli-responsive release is involved. Regulatory agencies call for innovative trial designs that reflect the unique mechanisms of action of these systems.

These challenges highlight the necessity of early and sustained dialogue between developers and regulatory authorities to ensure a smoother transition through the development pipeline.

Manufacturing, Scale-Up, and Quality Control: A major barrier to the widespread adoption of polymeric nanocarriers is the scalability and industrial reproducibility of nanoscale formulations. While many polymeric systems perform well under lab-scale conditions, scaling up to commercial manufacturing without compromising quality or efficacy poses significant technical challenges.

Scale-Up Challenges: Lab-scale methods often rely on batch production with high control over mixing, solvent evaporation, or emulsification. Translating these into continuous or semi-continuous industrial processes can lead to variations in particle size, polydispersity, drug encapsulation efficiency, and surface characteristics. Process analytical technologies (PATs) are being explored to monitor and control critical quality attributes in real-time during scale-up.

Reproducibility and Batch Integrity: Minor inconsistencies in the raw polymer materials or environmental conditions can result in heterogeneity that affects pharmacological performance. Polymers often lack mono dispersity, and variations in molecular weight distribution or functional group density can affect self-assembly and drug release profiles. These issues necessitate rigorous quality assurance protocols and validate analytical techniques.

Quality Control and GMP Compliance: Manufacturing of polymeric nanocarriers must adhere to Good Manufacturing Practices (GMP), with validated processes and stability testing over time. Novel analytical tools, such as nanoparticle tracking analysis and cryo-electron microscopy, are increasingly used to assess product attributes, but standardization remains a challenge across regulatory jurisdictions.[96]

Cost Considerations: Economic viability also impacts clinical translation. The complexity of nanocarrier synthesis, purification, and characterization may inflate production costs compared to conventional small-molecule drugs. Establishing cost-effective production platforms is essential to make polymeric therapies viable for large-scale clinical use.

The translation of polymeric nanocarriers into clinically approved therapeutics is fraught with scientific, regulatory, and manufacturing challenges. Despite these hurdles, the promise of enhanced therapeutic precision, reduced systemic toxicity, and tailored drug release profiles continues to drive innovation in the field. A multidisciplinary effort that encompasses material scientists, pharmacologists, regulatory agencies, and manufacturing experts. They are essential to overcome these translational barriers.

Standardization of characterization techniques, proactive regulatory engagement, and investment in scalable manufacturing technologies will be pivotal in converting preclinical success into clinical and commercial reality. Ultimately, aligning technological advances with regulatory and industrial frameworks will determine the extent to which polymeric nanocarriers can revolutionize patient care.

**Future Directions**

The convergence of nanotechnology with artificial intelligence (AI) and machine learning (ML) is redefining the landscape of polymeric nanocarrier development. These emerging technologies offer unprecedented opportunities to design intelligent, adaptive, and patient-specific drug delivery systems that align with the goals of precision medicine. As the complexity of disease pathophysiology and therapeutic modalities increases, the need for sophisticated, data-driven solutions in nanomedicine has become more pronounced.

Integration of AI and Machine Learning in Nanocarrier Design: Traditional approaches to nanocarrier design have relied on iterative experimental procedures, which are time-consuming and resource intensive. The integration of AI and ML is revolutionizing this process by enabling predictive modelling of nanocarrier properties and biological interactions. Through the analysis of large, multidimensional datasets, AI algorithms can identify patterns and correlations that inform the optimal combination of physical, chemical, and biological parameters such as particle size, surface charge, hydrophobicity, and targeting ligand density to maximize therapeutic efficacy and biocompatibility.[97]

ML models have been utilized to forecast the pharmacokinetic behaviour and organ distribution of polymeric nanocarriers, offering insight into their clearance pathways and biodistribution profiles in vivo. This predictive capability supports the rational design of systems tailored to specific patient populations or disease environments, enhancing the translational potential of these platforms.[98] Furthermore, AI-powered simulation tools can anticipate potential immunogenic responses or toxicity profiles, reducing the risk of late-stage clinical failure.[99]

Emergence of Responsive and “Intelligent” Nanocarriers: Another transformative innovation is the development of real-time responsive or "smart" nanocarriers. These systems can sense and adapt to microenvironmental cues such as pH gradients, enzymatic activity, or oxidative stress to trigger site-specific drug release. This responsiveness significantly enhances drug bioavailability at the pathological site while minimizing systemic exposure and associated toxicity.[100]

Recent advances have seen the incorporation of AI frameworks into the operation of these smart nanocarriers. For example, nanocarriers embedded with AI-driven feedback loops can monitor biochemical parameters in real-time and dynamically adjust their release kinetics. This creates an interactive therapeutic platform that responds adaptively to the evolving pathophysiological state of the patient.[101] The coupling of stimuli-responsive materials with onboard logic-based AI circuits has opened the door to nanodevices capable of decision-making processes such as halting drug release in response to off-target effects or activating treatment upon detection of a tumour-specific biomarker.

Such intelligent systems represent a paradigm shift toward autonomous therapeutic agents that can make informed decisions within the biological milieu, moving beyond passive delivery toward active therapeutic engagement.

Clinical Impact and Roadmap Ahead: The clinical integration of AI-enabled polymeric nanocarriers presents immense opportunities for personalized

medicine. These technologies offer capabilities in early disease detection, real-time treatment monitoring, and adaptive therapeutic regimens, positioning them as valuable assets in the future of clinical oncology, neurology, infectious diseases, and beyond. AI-driven models are already being explored to personalize drug combinations based on patient-specific tumor genomics and immune profiles, supporting the development of individualized treatment blueprints.[102]

However, realizing this potential requires overcoming several barriers. The regulatory environment for AI-integrated nanomedicines remains nascent, with limited precedent for approval pathways. Standardization of data, interpretability of ML models, and validation in clinically relevant populations are essential prerequisites for regulatory acceptance. Furthermore, the manufacturability and scalability of such complex systems must be addressed to ensure cost-effective and reproducible production. Ethical concerns related to data privacy, algorithmic bias, and autonomous decision-making also warrant careful consideration as these technologies move closer to clinical application.

Continued interdisciplinary collaboration among material scientists, clinicians, bioinformaticians, and regulatory bodies is imperative to ensure that AI-guided nanomedicine evolves responsibly and effectively. Investment in infrastructure to support integrated computational-experimental workflows and clinical data sharing will further accelerate the translation of intelligent nanocarriers from bench to bedside.

The fusion of AI and ML with polymeric nanocarrier technology is not merely an enhancement—it represents a foundational shift in how therapeutic systems are conceptualized, designed, and deployed. By leveraging computational intelligence, future nanocarriers will possess capabilities of adaptation, real-time decision-making, and patient-specific optimization that were previously unattainable. These innovations herald the dawn of a new era in drug delivery: one that is intelligent, responsive, and deeply personalized. As technological, regulatory, and clinical frameworks evolve in tandem, the realization of AI-integrated nanomedicine promises to reshape the therapeutic landscape for years to come.

## CONCLUSION

Nanoparticle-based drug delivery systems have emerged as a transformative approach in the fight against cancer, offering unprecedented precision, control, and multifunctionality in therapeutic interventions. With advancements in polymeric nanocarriers, stimuli-responsive systems, and ligand-targeted formulations, these platforms address critical challenges such as poor bioavailability, off-target toxicity, and multidrug resistance. Passive and active targeting mechanisms, such as folate, transferrin, aptamers, and antibody-mediated targeting, have significantly improved tumour localization and cellular uptake.

Moreover, the integration of co-delivery system which simultaneously transporting chemotherapeutic agents, siRNA, immunomodulators, or natural compounds has shown enhanced synergistic effects and therapeutic efficacy. This multi-agent strategy aligns with modern trends toward combination therapy, particularly in hard-to-treat cancers like pancreatic and hepatocellular carcinoma. Simultaneously, intelligent nanocarriers designed to respond to endogenous stimuli, such as pH, redox gradients, enzymes, and hypoxia, ensure spatiotemporal control of drug release, minimizing systemic toxicity.

Cutting-edge research in CRISPR/Cas9 delivery and nanocarrier-mediated genome editing further exemplifies the growing convergence of nanotechnology and genetic medicine, offering precise gene regulation and therapeutic correction at the molecular level. In parallel, biodegradable polymers, microneedles, in situ hydrogels, and implantable systems are contributing to the development of long-acting and localized therapies with sustained release profiles, particularly for post-surgical cancer management.

Personalized nanomedicine driven by theragnostic platforms and AI-guided design promises to further tailor treatments to individual patient profiles, enhancing efficacy while reducing adverse effects. However, challenges remain, including regulatory hurdles, endosomal escape inefficiencies, large-scale production, and clinical translation. Continuous innovation, interdisciplinary collaboration, and robust clinical validation will be crucial to realizing the full potential of these sophisticated delivery platforms. As the landscape evolves, nanoparticle-based cancer therapeutics stand at the forefront of a new era in precision oncology.

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