BIODEGRADABLE PLGA-BASED NANOPARTICLES FOR TARGETED CANCER PREVENTION AND STRATEGIES, CHEMOTHERAPY: MECHANISTIC INSIGHTS, FORMULATION AND TRANSLATIONAL CHALLENGES

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Abstract
Biodegradable flag-based nanoparticles represent a promising frontier in targeted cancer prevention and chemotherapy, merging precision delivery with minimized systemic toxicity. These nanocarriers are engineered with surface "flag" motifs—ligands such as peptides, antibodies, or aptamers—that selectively recognize and bind to tumor-associated biomarkers, enabling enhanced uptake by malignant cells while sparing healthy tissues. This review synthesizes current mechanistic insights into how flag-decorated nanoparticles navigate biological barriers, leverage receptor-mediated endocytosis, and facilitate controlled drug release within tumor microenvironments. Key formulation strategies are examined, including the selection of biodegradable polymers (e.g., PLGA, chitosan, PEGylated systems), optimization of flag density and orientation for maximal targeting efficiency, and co-delivery of chemotherapeutics with immunomodulatory agents to overcome multidrug resistance. Emphasis is placed on design parameters that influence particle stability, circulation time, and bioavailability. Finally, translational challenges are critically discussed, highlighting issues such as scalable manufacturing, reproducibility, regulatory pathways, immunogenicity concerns, and variability in tumor heterogeneity that impede clinical adoption. By integrating material science, molecular targeting, and therapeutic efficacy, biodegradable flag-based nanoparticle systems hold significant potential to advance precision oncology, yet require concerted multidisciplinary efforts to realize clinical translation.

Introduction

Cancer remains one of the most formidable global health challenges, accounting for millions of deaths annually despite substantial advances in diagnostics, therapeutics, and preventive strategies. Conventional cancer management relies heavily on surgery, radiotherapy, and systemic chemotherapy, either alone or in combination. While chemotherapy continues to play a central role in the treatment of both solid and haematological malignancies, its clinical utility is often constrained by several inherent limitations, including poor tumor selectivity, systemic toxicity, rapid clearance, and the emergence of multidrug resistance. These challenges not only compromise therapeutic efficacy but also significantly impair patient quality of life, thereby underscoring the urgent need for more precise, safer, and effective therapeutic approaches (Ara & Hafeez, 2024; Banthia *et al.*, 2022; Gomes-da-Silva *et al.*, 2012; Narvekar *et al.*, 2014; Sunoqrot *et al.*, 2024).

In parallel with therapeutic interventions, cancer prevention has gained increasing attention as a complementary and cost-effective strategy to reduce cancer incidence, progression, and recurrence.

Chemoprevention involves the use of natural or synthetic agents to inhibit, delay, or reverse carcinogenesis at various stages, including initiation, promotion, and progression. However, many chemopreventive agents—particularly phytochemicals such as polyphenols, flavonoids, and alkaloids—suffer from poor aqueous solubility, low oral bioavailability, rapid metabolism, and limited tissue accumulation. These pharmacokinetic shortcomings have significantly restricted their clinical translation, despite compelling preclinical evidence of anticancer potential. Consequently, innovative drug delivery systems capable of enhancing the stability, bioavailability, and target specificity of both chemotherapeutic and chemopreventive agents are of paramount importance (AbouAitah *et al.*, 2024; Chae *et al.*, 2024; Duan *et al.*, 2021; Khan *et al.*, 2022; Zhao *et al.*, 2023).

Nanotechnology-based drug delivery systems have emerged as a transformative platform in oncology, offering unprecedented opportunities to overcome the limitations associated with conventional formulations. Nanoparticles, typically ranging from 10 to 500 nm in size, can be engineered to improve drug solubility, protect labile molecules from degradation, prolong systemic circulation, and enable controlled or stimuli-responsive drug release. More importantly, nanocarriers can exploit tumor-specific pathophysiological features, such as leaky vasculature and impaired lymphatic drainage, to preferentially accumulate at tumor sites through the enhanced permeation and retention (EPR) effect. In addition to passive targeting, surface modification with ligands allows for active targeting of tumor-associated receptors, thereby further improving cellular uptake and therapeutic selectivity (Bayat *et al.*, 2020; Duan *et al.*, 2021; Hussain, 2016; Lansner *et al.*, 2020; Yaghmur *et al.*, 2023; Yan *et al.*, 2025; Zhao *et al.*, 2023).

Among the various polymeric nanocarriers investigated to date, poly(lactic-co-glycolic acid) (PLGA) has emerged as one of the most extensively studied and clinically relevant biodegradable polymers. PLGA is a copolymer composed of lactic acid and glycolic acid monomers, both of which are naturally metabolized via the Krebs cycle. Its biodegradability, biocompatibility, and favourable safety profile have led to regulatory approval by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for multiple biomedical applications, including drug delivery systems, implants, and injectable depots. These regulatory endorsements provide a strong foundation for the translational development of PLGA-based nanomedicines in oncology (Bai *et al.*, 2023; Bose *et al.*, 2016; Dong *et al.*, 2020; Jeswani *et al.*, 2021; Saxena *et al.*, 2022; Yang *et al.*, 2019).

The versatility of PLGA lies in its highly tunable physicochemical properties, which can be modulated by altering the lactic acid to glycolic acid ratio, molecular weight, end-group chemistry, and particle size. Such flexibility enables precise control over drug encapsulation efficiency, degradation rate, and release kinetics, allowing PLGA nanoparticles to be tailored for short-term, sustained, or pulsatile drug delivery. Furthermore, PLGA nanoparticles are capable of encapsulating a wide spectrum of therapeutic agents, including hydrophobic chemotherapeutics, hydrophilic drugs, proteins, peptides, nucleic acids, and plant-derived bioactives. This broad compatibility makes PLGA an attractive platform for both cancer chemotherapy and chemoprevention (Benedetto *et al.*, 2025; Chen *et al.*, 2025; Dölen *et al.*, 2021; Godse *et al.*, 2025; Puri *et al.*, 2022; Shahbaz *et al.*, 2022; You & Zhang, 2025).

In the context of targeted cancer therapy, PLGA-based nanoparticles offer multiple advantages beyond controlled drug release. Surface functionalization strategies such as polyethylene glycol (PEG) coating can be employed to enhance colloidal stability and evade recognition by the reticuloendothelial system, thereby prolonging circulation time. Additionally, conjugation with targeting ligands—including folic acid, transferrin, antibodies, peptides, and aptamers—enables receptor-mediated uptake by cancer cells, improving intracellular drug delivery while minimizing off-target toxicity. These features are particularly valuable in addressing tumor heterogeneity and reducing systemic adverse effects commonly associated with conventional chemotherapy (Fonseca-Gomes *et al.*, 2020; Gangapurwala *et al.*, 2020; Giacon *et al.*, 2024; Gupta *et al.*, 2022; Kömür *et al.*, 2025; Liang *et al.*, 2020; Rocha *et al.*, 2022; Umar *et al.*, 2021).

Beyond therapeutic applications, PLGA nanoparticles have demonstrated significant promise in cancer prevention strategies. Encapsulation of chemopreventive agents within PLGA matrices has been shown to enhance their stability, protect them from premature degradation, and facilitate sustained exposure at target tissues. By improving pharmacokinetic profiles and enabling site-specific delivery, PLGA-based systems may allow lower doses of chemopreventive agents to achieve meaningful biological effects, thereby reducing the risk of long-term toxicity. Such attributes are especially relevant for preventive interventions, which often require chronic administration. Despite these advantages, the clinical translation of PLGA-based

nanoparticles is not without challenges. Issues related to large-scale manufacturing, batch-to-batch reproducibility, long-term stability, and variability in tumor accumulation continue to pose significant hurdles. Moreover, the reliance on the EPR effect for passive targeting has shown inconsistent outcomes across different tumor types and patient populations. A critical and balanced evaluation of these limitations, alongside emerging solutions, is essential to guide future research and development efforts (Fonseca-Gomes *et al.*, 2020; Gangapurwala *et al.*, 2020; Giacon *et al.*, 2024; Gupta *et al.*, 2022; Kömür *et al.*, 2025; Liang *et al.*, 2020; Rocha *et al.*, 2022; Umar *et al.*, 2021).

In this context, the present review aims to provide a comprehensive and critical overview of biodegradable PLGA-based nanoparticles for targeted cancer prevention and chemotherapy. The review systematically discusses the physicochemical properties of PLGA, formulation and surface engineering strategies, targeting mechanisms, and preclinical and translational evidence supporting their use in oncology. By integrating insights from chemoprevention and chemotherapy perspectives, this article seeks to highlight the dual potential of PLGA nanoparticles as both preventive and therapeutic tools, while also identifying key challenges and future directions necessary for successful clinical translation.

1. Poly(lactic-co-glycolic acid): Physicochemical and Biological Considerations Poly(lactic-co-glycolic acid) (PLGA) is a synthetic, aliphatic polyester that has gained extensive acceptance in pharmaceutical nanotechnology owing to its predictable biodegradation, excellent biocompatibility, and adaptable physicochemical properties. As a copolymer derived from lactic acid and glycolic acid monomers, PLGA occupies a unique position among biodegradable polymers, particularly in cancer drug delivery, where long-term safety and controlled drug release are critical prerequisites. An understanding of its chemical structure, degradation behavior, and biological interactions is fundamental for rational design

of PLGA-based nanoparticles intended for cancer prevention and chemotherapy (Latronico *et al.*, 2021).

The chemical composition of PLGA is defined by the molar ratio of lactic acid to glycolic acid, commonly expressed as PLGA 50:50, 65:35, 75:25, or 85:15. This ratio plays a decisive role in determining polymer hydrophobicity, crystallinity, glass transition temperature, and degradation kinetics. Glycolic acid units, being more hydrophilic, promote faster water penetration and hydrolytic cleavage, whereas lactic acid units impart increased hydrophobicity and steric hindrance due to the presence of a methyl side chain. Consequently, PLGA 50:50 typically exhibits the fastest degradation rate, while higher lactic acid content leads to more sustained polymer erosion. This tunability allows formulation scientists to tailor drug release profiles to meet the specific requirements of anticancer or chemopreventive therapies (Bao *et al.*, 2022).

Molecular weight is another critical determinant of PLGA performance in nanoparticle systems. Low-molecular-weight PLGA degrades more rapidly, resulting in faster drug release, whereas high-molecular-weight polymers provide prolonged release over weeks or months. In cancer chemotherapy, sustained release formulations are often desirable to maintain therapeutic drug concentrations at tumor sites while minimizing peak-related toxicity. In contrast, chemoprevention strategies may benefit from moderate, continuous drug exposure over extended periods. End-group chemistry, whether ester-terminated or carboxyl-terminated, further influences degradation behavior and drug—polymer interactions. Acid-terminated PLGA tends to degrade more rapidly and may enhance encapsulation of basic drugs through ionic interactions (Nag, 2021).

The biodegradation of PLGA occurs primarily through hydrolytic cleavage of ester linkages, resulting in the formation of lactic acid and glycolic acid. These monomers are subsequently metabolized via the tricarboxylic acid cycle and eliminated as carbon dioxide and water.

Importantly, this degradation process does not require enzymatic involvement, making PLGA degradation relatively predictable across different physiological environments. However, localized accumulation of acidic degradation products within nanoparticles or tumor tissues may influence drug stability and biological responses. Careful optimization of particle size, polymer composition, and drug loading is therefore essential to mitigate potential pH-related effects, particularly when delivering acid-labile anticancer agents (Dong *et al.*, 2020).

From a biological standpoint, PLGA nanoparticles exhibit favorable interactions with biological systems, which has contributed to their widespread use in preclinical and clinical studies. Their biodegradation products are non-toxic at clinically relevant concentrations, and PLGA has demonstrated minimal

immunogenicity in most applications. Particle size and surface characteristics significantly influence cellular uptake, biodistribution, and clearance pathways. Nanoparticles in the range of 100-200 nm are generally considered optimal for tumor accumulation via the enhanced permeation and retention effect, while avoiding rapid renal clearance or excessive uptake by the mononuclear phagocyte system. Surface properties of PLGA nanoparticles are particularly important in determining their in vivo fate. Unmodified PLGA nanoparticles tend to adsorb plasma proteins upon systemic administration, leading to opsonization and clearance by macrophages in the liver and spleen. This limitation has been effectively addressed through surface modification strategies, such as PEGylation, which creates a hydrophilic steric barrier that reduces protein adsorption and prolongs circulation time. Extended systemic circulation is especially beneficial for both chemotherapeutic and chemopreventive applications, as it increases the probability of nanoparticle accumulation at target sites (Bai *et al.*, 2023; Bose *et al.*, 2016; Creemers *et al.*, 2021).

PLGA's compatibility with a wide range of drugs further enhances its utility in oncology. Hydrophobic chemotherapeutic agents such as paclitaxel, docetaxel, and curcumin readily partition into the polymer matrix, achieving high encapsulation efficiencies. Hydrophilic drugs,

proteins, and nucleic acids can also be incorporated using double emulsion or specialized formulation techniques. This versatility enables the development of multifunctional nanoparticles capable of delivering single agents, drug combinations, or therapeutic agents alongside imaging probes.

Importantly, the regulatory acceptance of PLGA distinguishes it from many other experimental nanomaterials. Several PLGA-based products have already received clinical approval in non-oncological indications, including long-acting injectables and implantable systems. This established regulatory track record significantly lowers the translational barrier for PLGA nanoparticles in cancer prevention and chemotherapy. Nevertheless, when used at the nanoscale, PLGA systems must still undergo rigorous evaluation for pharmacokinetics, biodistribution, toxicity, and long-term safety.

In summary, the physicochemical and biological properties of PLGA provide a robust and adaptable foundation for the design of nanoparticle-based cancer delivery systems. Its tunable degradation kinetics, favorable safety profile, and compatibility with diverse therapeutic agents make PLGA an exceptionally versatile platform for both targeted cancer chemotherapy and chemoprevention. A thorough understanding of these properties is essential for optimizing nanoparticle performance and ensuring successful translation from laboratory research to clinical application.

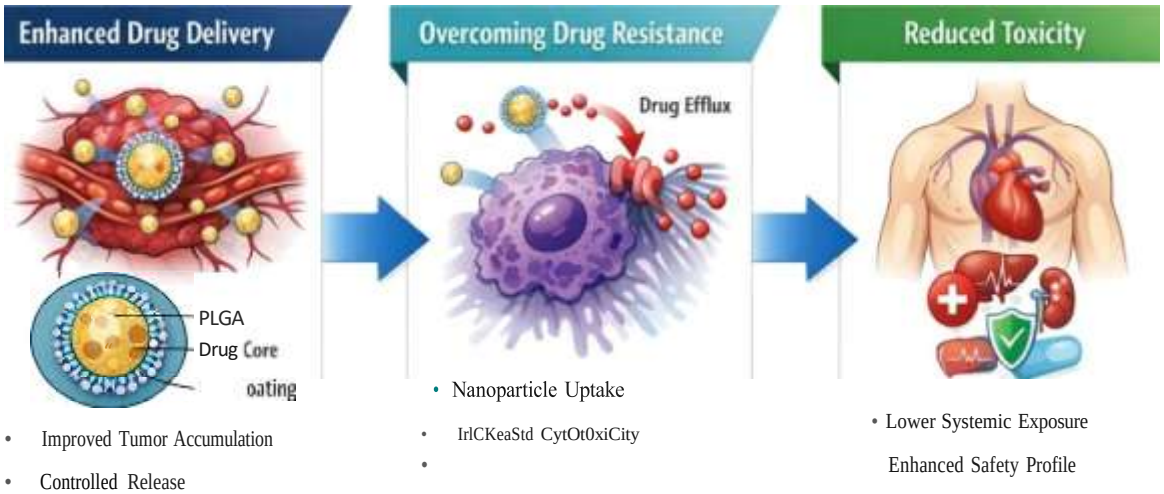

Figure 1. Key advantages of PLGA nanoparticles in cancer therapy

2. Formulation Strategies for PLGA-Based Nanoparticles

The formulation strategy adopted for PLGA-based nanoparticles plays a decisive role in determining their physicochemical characteristics, drug loading efficiency, release behavior, stability, and biological performance. In the context of cancer prevention and chemotherapy, formulation approaches must be carefully optimized to ensure reproducible particle size, high encapsulation efficiency, controlled drug release, and compatibility with targeting or surface-modification strategies. Over the years, several preparation techniques have been developed and refined to accommodate the diverse physicochemical properties of anticancer and chemopreventive agents.

Among the most widely employed methods for preparing PLGA nanoparticles is the emulsion solvent evaporation technique. This approach is particularly suitable for encapsulating hydrophobic anticancer drugs such as paclitaxel, docetaxel, and curcumin. In a typical process, PLGA and the drug are dissolved in a volatile organic solvent, such as dichloromethane or ethyl acetate, which is subsequently emulsified into an aqueous phase containing a stabilizer, commonly polyvinyl alcohol. Upon solvent evaporation under reduced pressure or continuous stirring, solid nanoparticles are formed as the polymer precipitates. The simplicity, scalability,

and relatively high encapsulation efficiency of this method have contributed to its widespread adoption. However, careful control of formulation parameters—including polymer concentration, solvent type, emulsifier concentration, and homogenization speed—is essential to achieve narrow particle size distribution and consistent drug loading.

For hydrophilic drugs, proteins, peptides, and nucleic acids, the double emulsion (water-in-oil-in-water) solvent evaporation method is frequently employed. In this technique, the aqueous drug solution is first emulsified into an organic phase containing dissolved PLGA, followed by a second emulsification step into an external aqueous phase. This method enables the incorporation of water-soluble agents within the inner aqueous compartment of the nanoparticles. Although double emulsion techniques expand the scope of PLGA-based delivery systems, they are often associated with lower encapsulation efficiencies and potential drug leakage during processing. Optimization of phase volumes, emulsification energy, and stabilizer concentration is therefore critical, particularly when formulating biologically sensitive anticancer agents.

Nanoprecipitation, also known as the solvent displacement method, represents another widely used formulation strategy, especially for small-molecule chemotherapeutics and chemopreventive agents. In this approach, PLGA and the drug are dissolved in a water-miscible organic solvent, such as acetone or acetonitrile, and rapidly injected into an aqueous phase under continuous stirring. The instantaneous diffusion of the organic solvent into the aqueous medium results in polymer precipitation and nanoparticle formation. Nanoprecipitation offers advantages such as operational simplicity, avoidance of high shear forces, and relatively narrow particle size distribution. However, this method is less suitable for hydrophilic drugs and may yield lower drug loading for highly water-soluble compounds.

Advanced formulation approaches have been explored to improve reproducibility and scalability of PLGA nanoparticle production. Microfluidic-based techniques have gained considerable attention due to their ability to precisely control mixing dynamics, resulting in uniform particle size and improved batch-to-batch consistency. In microfluidic systems, controlled laminar flow enables rapid and reproducible nanoprecipitation of PLGA nanoparticles, making this approach particularly attractive for translational research and industrial scale-up. Despite these advantages, the requirement for specialized equipment and potential limitations in production throughput remain challenges that must be addressed for widespread adoption.

Spray drying has also been investigated as a scalable alternative for producing PLGA nanoparticles, particularly in the context of dry powder formulations for pulmonary or oral delivery. In this method, a solution or suspension containing PLGA and the drug is atomized into a hot drying chamber, leading to rapid solvent evaporation and particle formation. Spray drying offers advantages such as continuous processing and suitability for large-scale manufacturing. However, exposure to elevated temperatures may compromise the stability of thermolabile anticancer agents, necessitating careful process optimization.

Beyond particle formation techniques, drug encapsulation strategies are central to the performance of PLGA-based nanoparticles. Hydrophobic drugs generally exhibit high affinity for the PLGA matrix, enabling efficient encapsulation and sustained release. In contrast, encapsulation of hydrophilic drugs and macromolecules often requires additional formulation strategies, such as polymer blending, ion pairing, or the use of stabilizing excipients. The selection of an appropriate encapsulation approach is particularly important in cancer chemoprevention, where prolonged and predictable drug exposure is essential for efficacy.

Surface modification and functionalization represent critical extensions of PLGA nanoparticle formulation strategies, particularly for targeted cancer therapy. Polyethylene glycol (PEG) is frequently grafted onto the surface of PLGA nanoparticles to impart steric stabilization and reduce opsonization by plasma proteins. PEGylation prolongs systemic circulation time and enhances tumor accumulation, thereby improving the therapeutic index of encapsulated anticancer agents. The density and molecular weight of PEG chains must be carefully optimized, as excessive PEGylation may hinder cellular uptake and intracellular drug release. Active targeting strategies involve the conjugation of ligands to the surface of PLGA nanoparticles to facilitate receptor-mediated uptake by cancer cells. Commonly used targeting ligands include folic acid, transferrin, hyaluronic acid, antibodies, peptides, and aptamers. Ligand conjugation can be achieved through covalent coupling to functional groups present on the PLGA or PEG chains. These targeted systems have demonstrated enhanced cellular uptake, improved intracellular drug delivery, and superior anticancer efficacy in preclinical models. In chemopreventive applications, targeting strategies may also be employed to direct bioactive compounds to high-risk tissues, thereby improving preventive outcomes while minimizing systemic exposure.

Co-delivery and combination therapy represent another important formulation strategy enabled by PLGA nanoparticles. The ability to encapsulate multiple therapeutic agents within a single carrier allows for synchronized delivery of drugs with complementary mechanisms of action. For example, PLGA nanoparticles have been used to co-deliver chemotherapeutic agents with chemosensitizers, antioxidants, or molecular inhibitors to overcome drug resistance and enhance therapeutic efficacy. Such combination systems are particularly relevant in the treatment of heterogeneous tumors and in strategies aimed at preventing cancer recurrence.

Overall, formulation strategies for PLGA-based nanoparticles are highly adaptable and can be tailored to meet the specific demands of cancer prevention and chemotherapy. The choice of preparation method, encapsulation strategy, and surface modification must be guided by the physicochemical properties of the drug, the intended route of administration, and the desired biological outcome. Rational formulation design, supported by systematic optimization and quality-by-design principles, is essential to maximize the therapeutic potential of PLGA nanoparticles and facilitate their successful translation into clinical oncology.

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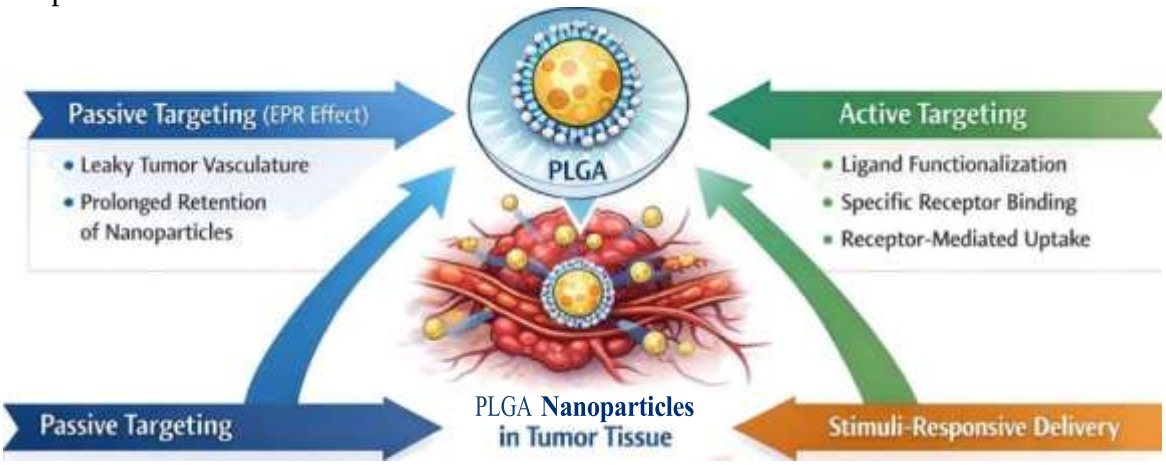
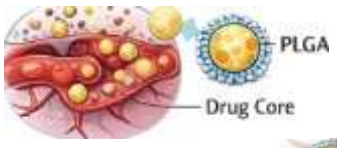
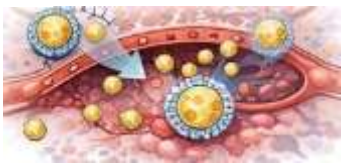


- Leaky Tumor Vasculature
- Prolonged Retention of Nanoparticles



- pH-Responsive
- Enzyme-Responsive
- Redox-Responsive



PLGA Nanoparticles in Tumor Tissue

Figure 2. Targeting strategies for PLGA nanoparticles for cancer therapy

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4. Targeting Strategies in Cancer Prevention and Chemotherapy

Targeted drug delivery represents a cornerstone in the rational design of nanoparticle-based cancer therapeutics, as it directly addresses the fundamental limitations of conventional chemotherapy, namely poor tumor selectivity and systemic toxicity. PLGA-based nanoparticles offer a versatile platform for implementing both passive and active targeting strategies, as well as stimuli-responsive approaches, thereby enabling preferential drug accumulation at tumor sites and enhanced intracellular delivery. In the context of cancer prevention and chemotherapy, effective targeting is critical not only for maximizing therapeutic efficacy but also for minimizing off-target effects during long-term or repeated administration. Passive targeting relies primarily on the enhanced permeation and retention (EPR) effect, a phenomenon

arising from the unique pathophysiological features of solid tumors. Tumor vasculature is typically characterized by rapid and aberrant angiogenesis, resulting in leaky blood vessels with enlarged endothelial gaps. In addition, impaired lymphatic drainage in tumor tissues leads to prolonged retention of macromolecules and nanoparticles. PLGA nanoparticles, when engineered within an optimal size range of approximately 100-200 nm, can exploit the EPR effect to preferentially accumulate within tumor interstitium following systemic administration. This passive accumulation enhances local drug concentration at the tumor site while reducing exposure to healthy tissues.

Despite its widespread acceptance, the EPR effect exhibits considerable variability across tumor types, stages, and individual patients. Factors such as tumor size, vascular density, stromal composition, and interstitial fluid pressure can significantly influence nanoparticle penetration and distribution. Consequently, reliance on passive targeting alone may result in inconsistent therapeutic outcomes, particularly in poorly vascularized or highly fibrotic tumors. These limitations have prompted the integration of active targeting strategies to complement and enhance passive accumulation mechanisms.

Active targeting involves the functionalization of PLGA nanoparticles with ligands that specifically bind to receptors overexpressed on cancer cells or within the tumor microenvironment. Upon ligand—receptor interaction, nanoparticles are internalized through receptor-mediated endocytosis, leading to enhanced intracellular drug delivery. Commonly targeted receptors include folate receptors, transferrin receptors, epidermal growth factor receptors, CD44, and integrins, among others. The selection of an appropriate targeting ligand is dictated by the molecular profile of the target cancer and the intended therapeutic or preventive application.

Folic acid is one of the most extensively studied targeting ligands due to its small size, stability, low immunogenicity, and high affinity for folate receptors, which are overexpressed in several malignancies, including ovarian, breast, lung, and colorectal cancers. PLGA nanoparticles conjugated with folic acid have demonstrated significantly enhanced cellular uptake and cytotoxicity in folate receptor—positive cancer cells compared to non-targeted systems. Similar advantages have been reported with transferrin-functionalized nanoparticles, which exploit the elevated iron demand of rapidly proliferating cancer cells.

Antibody-based targeting offers high specificity and strong binding affinity but presents challenges related to immunogenicity, manufacturing complexity, and stability. Nevertheless, monoclonal antibodies and antibody fragments have been successfully conjugated to PLGA

nanoparticles for targeted delivery of chemotherapeutic agents in preclinical models. Peptides and aptamers represent attractive alternatives to antibodies, offering improved tissue penetration, lower immunogenicity, and greater chemical stability. These ligands have been increasingly explored in both therapeutic and chemopreventive nanoparticle systems.

In cancer prevention strategies, targeting approaches may be employed to direct chemopreventive agents to tissues at high risk of malignant transformation, such as the colon, breast, or prostate. Targeted delivery of bioactive compounds using PLGA nanoparticles can enhance local drug concentration, improve preventive efficacy, and reduce systemic exposure during long-term administration. This is particularly important for preventive interventions, where safety and tolerability are paramount considerations.

Beyond ligand-mediated targeting, stimuli-responsive PLGA nanoparticles have emerged as an advanced strategy to achieve site-specific drug release in response to tumor-associated triggers. These systems are designed to respond to internal stimuli such as acidic pH, elevated enzyme levels, or redox gradients, which are characteristic of the tumor microenvironment. For instance, pH-responsive PLGA nanoparticles can be engineered to release their payload preferentially in the mildly acidic conditions of tumor tissues or within endo-lysosomal compartments following cellular uptake. Such systems enhance intracellular drug availability while minimizing premature drug release in circulation.

Enzyme-responsive PLGA nanoparticles exploit the overexpression of specific enzymes, such as matrix metalloproteinases or cathepsins, within the tumor microenvironment. By incorporating enzyme-cleavable linkages or coatings, these nanoparticles can achieve selective drug release at tumor sites. Similarly, redox-responsive systems take advantage of the elevated intracellular glutathione levels in cancer cells to trigger drug release through cleavage of disulfide bonds. These approaches are particularly promising for overcoming multidrug resistance and improving therapeutic selectivity.

The integration of multiple targeting mechanisms within a single PLGA nanoparticle system has also been

explored to further enhance specificity and efficacy. For example, nanoparticles combining PEG-mediated stealth properties, ligand-based active targeting, and stimuli-responsive release have demonstrated superior antitumor activity in preclinical studies. Such multifunctional systems reflect a growing trend toward increasingly sophisticated nanocarrier designs aimed at addressing the complex and heterogeneous nature of cancer.

In summary, targeting strategies are central to the successful application of PLGA-based nanoparticles in cancer prevention and chemotherapy. While passive targeting via the EPR effect provides a foundational mechanism for tumor accumulation, active targeting and stimuli-responsive approaches offer additional layers of specificity and control. The rational integration of these strategies holds significant promise for improving therapeutic outcomes, reducing toxicity, and advancing the clinical translation of PLGA-based nanomedicines in oncology.

5. PLGA Nanoparticles in Cancer Chemoprevention

Cancer chemoprevention refers to the use of natural or synthetic agents to inhibit, delay, or reverse the process of carcinogenesis before the onset of invasive disease. Unlike chemotherapy, which is typically administered after cancer diagnosis, chemopreventive strategies are often intended for long-term or repeated use in high-risk populations. Consequently, the success of chemoprevention critically depends on the safety, bioavailability, and tissue-specific delivery of preventive agents. In this context, PLGA-based nanoparticles have emerged as a promising delivery platform to address many of the pharmacokinetic and biological limitations associated with conventional chemopreventive formulations.

Chemopreventive agents exert their effects at various stages of cancer development, including initiation, promotion, and progression. These agents encompass a broad range of compounds, such as polyphenols, flavonoids, isothiocyanates, carotenoids, and certain synthetic molecules.

Despite their demonstrated anticancer potential in vitro and in vivo, many chemopreventive compounds suffer from poor aqueous solubility, chemical instability, rapid metabolism, and limited systemic or tissue exposure. These challenges have significantly hindered their translation into clinically viable preventive interventions. Encapsulation within PLGA nanoparticles offers an effective strategy to overcome these barriers by enhancing drug stability, improving bioavailability, and enabling controlled release.

Natural polyphenols such as curcumin, resveratrol, quercetin, and epigallocatechin gallate have been extensively investigated as chemopreventive agents due to their ability to modulate multiple molecular pathways involved in carcinogenesis. However, their clinical utility has been restricted by low oral bioavailability and rapid clearance. PLGA nanoparticle-based delivery systems have demonstrated substantial improvements in the pharmacokinetic profiles of these compounds. Encapsulation protects the bioactive agents from premature degradation and allows sustained release, resulting in prolonged systemic exposure and enhanced tissue accumulation. Preclinical studies have consistently reported improved anticancer efficacy of nanoparticle-encapsulated chemopreventive agents compared to their free counterparts.

Table 1. Key physicochemical properties of PLGA influencing nanoparticle performance in cancer prevention and chemotherapy

PLGA parameter	**Description**	**Impact on nanoparticle behaviour and therapeutic performance**
Lactic acid Glycolic acid ratio	Determines hydrophobicity and crystallinity of the polymer	Higher glycolic content accelerates degradation and drug release, while higher lactic content provides sustained release suitable for long-term chemotherapy or chemoprevention

Molecular weight	Represents polymer chain length	Higher molecular weight prolongs degradation and drug release; lower molecular weight favors faster release and clearance
End-group chemistry	Ester-terminated or acid-terminated PLGA	Acid-terminated PLGA degrades faster and may enhance encapsulation of basic drugs
Particle size	Typically 50-300 rim for oncology applications	Sizes between 100-200 nm favor tumor accumulation via the EPR effect and reduce renal clearance
Surface charge (zeta potential)	Reflects surface electrostatic properties	Neutral or slightly negative surfaces reduce opsonization and prolong circulation time
Degradation products	Lactic acid and glycolic acid	Metabolized via the Krebs cycle, ensuring biocompatibility and low systemic toxicity

At the molecular level, PLGA nanoparticle-mediated delivery of chemopreventive agents has been shown to enhance modulation of key signaling pathways implicated in cancer development. These include inhibition of nuclear factor kappa B signaling, suppression of cyc1ooxygenase-2 expression, regulation of phosphoinositide 3-kinase/Akt and mitogen-activated protein kinase pathways, and induction of apoptosis through mitochondrial mechanisms. By improving intracellular uptake and sustained exposure, PLGA nanoparticles amplify the biological effects of chemopreventive agents at lower doses, thereby reducing the risk of dose-related toxicity during long-term use.

Targeted delivery further strengthens the role of PLGA nanoparticles in chemoprevention. Surface functionalization with ligands enables preferential accumulation of chemopreventive agents in tissues at elevated cancer risk. For instance, folate-functionalized PLGA nanoparticles have been explored for targeted delivery in tissues overexpressing folate receptors during early carcinogenic transformation. Similarly, colon-targeted PLGA-based systems have been investigated for colorectal cancer prevention, exploiting local delivery to minimize systemic exposure. Such targeted approaches are particularly valuable in chemoprevention, where safety margins must be carefully maintained.

Sustained and controlled drug release is another key advantage of PLGA nanoparticles in preventive applications. Chronic exposure to chemopreventive agents at sub-therapeutic yet biologically effective concentrations is often required to achieve meaningful preventive outcomes. PLGA nanoparticles can be engineered to release their payload over extended periods, ranging from days to weeks, depending on polymer composition and particle size. This controlled release profile reduces dosing frequency, enhances patient compliance, and maintains consistent tissue drug levels.

In vivo studies have provided encouraging evidence supporting the chemopreventive potential of PLGA-based nanoparticle systems. Animal models of chemically induced carcinogenesis have demonstrated reduced tumor incidence, delayed tumor onset, and suppression of preneoplastic lesions following administration of nanoparticle-encapsulated chemopreventive agents. These outcomes are often accompanied by reduced systemic toxicity and improved tolerability compared to free drugs. Importantly, the biodegradation of PLGA into non-toxic metabolites supports the feasibility of long-term administration, which is a critical requirement for preventive interventions.

Despite these promising findings, several challenges remain in the development of PLGA nanoparticles for cancer chemoprevention. Long-term safety data, particularly with repeated or chronic exposure, are still

limited. Variability in individual risk profiles and differences in tissue-specific carcinogenic pathways further complicate the design of universally effective preventive strategies. Additionally, regulatory pathways for approving nanoparticle-based chemopreventive agents are not as well established as those for therapeutic drugs, necessitating careful consideration of risk—benefit profiles.

In summary, PLGA-based nanoparticles represent a highly promising platform for cancer chemoprevention by addressing key limitations of conventional preventive formulations. Through enhanced stability, improved bioavailability, controlled release, and targeted delivery, these systems enable effective modulation of carcinogenic pathways at reduced doses. While further translational and clinical studies are required, the integration of PLGA nanoparticle technology into chemopreventive strategies holds significant potential for reducing cancer burden in high-risk populations.

6. PLGA Nanoparticles in Cancer Chemotherapy

Cancer chemotherapy remains a central component of oncological treatment across a wide range of malignancies; however, its clinical effectiveness is frequently compromised by systemic toxicity, non-specific biodistribution, short plasma half-life, and the development of multidrug resistance. These limitations not only restrict the therapeutic window of anticancer drugs but also contribute to treatment failure and disease recurrence. PLGA-based nanoparticles have been extensively investigated as a strategy to overcome these challenges by improving drug solubility, enhancing tumor accumulation, enabling controlled release, and facilitating intracellular drug delivery.

One of the most significant advantages of PLGA nanoparticles in chemotherapy is their ability to improve the delivery of poorly water-soluble anticancer agents. Many frontline chemotherapeutics, including paclitaxel, docetaxel, etoposide, and camptothecin derivatives, exhibit low aqueous solubility, necessitating the use of toxic solubilizing agents in conventional formulations. Encapsulation within PLGA nanoparticles eliminates the need for such excipients, thereby reducing formulation-related toxicity. Furthermore, the polymeric matrix protects the drug from premature degradation and allows sustained release, resulting in prolonged therapeutic exposure at the tumor site.

Table 2. Common formulation techniques for PLGA nanoparticles and their suitability for anticancer applications

Formulation technique	**Type of drug encapsulated**	**Advantages**	**Limitations**	**Typical oncology application**
Emulsion solvent evaporation	Hydrophobic drugs	High encapsulation efficiency, scalable	Use of organic solvents, batch variability	Paclitaxel, docetaxel, curcumin delivery
Double emulsion (W/O/W)	Hydrophilic drugs, proteins	Enables macromolecule loading	Drug leakage, lower encapsulation efficiency	Protein drugs, gene delivery

Nanoprecipitation	Small molecules	Simple process, narrow size distribution	Limited hydrophilic drug loading	Chemopreventive polyphenols
Microfluidics-based methods	Broad range	High reproducibility, scalable	Specialized equipment required	Translational nanomedicine
Spray drying	Small molecules	Industrial scalability, dry powders	Thermal stress on drugs	Oral and pulmonary delivery

PLGA nanoparticles also play a crucial role in modifying the pharmacokinetic behavior of chemotherapeutic agents. Following systemic administration, nanoparticle-encapsulated drugs typically exhibit extended circulation time, reduced clearance, and enhanced tumor accumulation compared to free drugs. These pharmacokinetic improvements are largely attributed to particle size optimization, surface modification strategies such as PEGylation, and reduced recognition by the mononuclear phagocyte system. By maintaining therapeutic drug concentrations within the tumor microenvironment for extended periods, PLGA nanoparticles enhance antitumor efficacy while minimizing peak-related systemic toxicity.

Intracellular drug delivery is another critical aspect of effective chemotherapy that is addressed by PLGA-based nanocarriers. Many chemotherapeutic agents exert their cytotoxic effects by interacting with intracellular targets, such as DNA, microtubules, or specific enzymes. However, efflux transporters, particularly P-glycoprotein, often limit intracellular drug accumulation in cancer cells, contributing to multidrug resistance. PLGA nanoparticles can bypass these efflux mechanisms by entering cells via endocytic pathways, thereby enhancing intracellular drug retention. Several preclinical studies have demonstrated that PLGA-encapsulated chemotherapeutics exhibit superior cytotoxicity in drug-resistant cancer cell lines compared to free drugs.

Combination chemotherapy represents a well-established strategy for improving cancer treatment outcomes by targeting multiple pathways simultaneously and reducing the likelihood of resistance development. PLGA nanoparticles provide a versatile platform for co-delivery of multiple therapeutic agents with distinct mechanisms of action. Co-encapsulation ensures synchronized delivery and controlled release of drug combinations at the tumor site, thereby maximizing synergistic effects. For example, PLGA nanoparticles have been explored for the co-delivery of paclitaxel with chemosensitizers, antioxidants, or molecular inhibitors to enhance cytotoxicity and overcome resistance. Such combination systems are particularly valuable in the treatment of heterogeneous tumors with complex molecular profiles.

Targeted PLGA nanoparticles further enhance the therapeutic potential of chemotherapy by improving selectivity and reducing off-target effects. Surface conjugation with tumor-specific ligands facilitates receptor-mediated uptake by cancer cells, resulting in higher intracellular drug concentrations and improved therapeutic outcomes. Targeted delivery is especially advantageous in chemotherapy, where dose-limiting toxicity often restricts the use of otherwise effective agents. By concentrating the drug within tumor tissues, PLGA nanoparticles enable dose reduction without compromising efficacy, thereby improving patient tolerability.

In vivo studies have consistently demonstrated the superior antitumor efficacy of PLGA-based nanoparticle formulations compared to conventional drug solutions. Animal models of solid tumors have shown significant reductions in tumor volume, delayed tumor progression, and improved survival following treatment with nanoparticle-encapsulated chemotherapeutics. These therapeutic benefits are often accompanied by reduced systemic toxicity, as evidenced by lower hematological, hepatic, and renal adverse effects. Such findings highlight the potential of PLGA nanoparticles to improve the therapeutic index of

established chemotherapeutic agents.

Despite these promising outcomes, several challenges remain in the clinical translation of PLGA-based chemotherapeutic nanoparticles. Tumor heterogeneity, variable vascular permeability, and differences in tumor microenvironment characteristics can influence nanoparticle accumulation and drug release. Additionally, large-scale manufacturing, reproducibility, and long-term stability of nanoparticle formulations remain significant hurdles. Regulatory considerations, including comprehensive safety evaluation and quality control, further complicate the development pathway for nanoparticle-based chemotherapies. Nevertheless, the growing body of preclinical and translational evidence supports the continued exploration of PLGA nanoparticles as a powerful tool in cancer chemotherapy. Their ability to enhance drug solubility, improve pharmacokinetics, overcome resistance, and reduce systemic toxicity positions them as a promising platform for next-generation cancer therapeutics. With ongoing advancements in formulation science, targeting strategies, and manufacturing technologies, PLGA-based nanoparticles are poised to play an increasingly important role in the future of cancer chemotherapy.

7. Preclinical Evaluation and Translational Evidence

Rigorous preclinical evaluation forms the backbone of successful translation of PLGA-based nanoparticles from laboratory research to clinical oncology. Given the complex interactions between nanocarriers, therapeutic payloads, and biological systems, comprehensive in vitro and in vivo assessments are essential to establish safety, efficacy, and translational feasibility. In the context of cancer prevention and chemotherapy, preclinical studies not only validate therapeutic performance but also provide critical insights into pharmacokinetics, biodistribution, and mechanism of action.

In vitro evaluation serves as the initial screening platform for PLGA nanoparticle formulations. Cytotoxicity studies using cancer cell lines are commonly employed to assess the anticancer efficacy of nanoparticle-encapsulated drugs in comparison with free drug controls. Assays such as MTT, XTT, and resazurin-based viability tests are routinely used to quantify dose-dependent cytotoxic effects. PLGA nanoparticles have consistently demonstrated enhanced cytotoxicity against cancer cells, which is attributed to improved cellular uptake, sustained intracellular drug release, and protection of labile drugs from extracellular degradation. In chemopreventive studies, in vitro assays are often designed to evaluate antiproliferative effects at sub-cytotoxic concentrations, reflecting the preventive rather than therapeutic intent.

Cellular uptake and intracellular trafficking studies provide further mechanistic insight into the performance of PLGA nanoparticles. Fluorescent labelling of nanoparticles enables visualization and quantification of cellular internalization using confocal microscopy and flow cytometry. These studies have shown that PLGA nanoparticles are predominantly internalized via endocytic pathways, including clathrin-mediated and caveolae-mediated endocytosis. Targeted nanoparticles generally exhibit significantly higher uptake in receptor-overexpressing cancer cells compared to non-targeted systems, underscoring the importance of ligand-mediated delivery. Additionally, intracellular localization studies reveal accumulation of nanoparticles within endo-lysosomal compartments, followed by gradual drug release into the cytosol.

In vivo evaluation represents a critical step in establishing the translational potential of PLGA-based nanoparticle systems. Animal models of cancer, including xenograft, orthotopic, and chemically induced tumor models, are commonly used to assess therapeutic efficacy, biodistribution, and safety. Following systemic administration, PLGA nanoparticles typically demonstrate prolonged circulation time and enhanced tumor accumulation relative to free drugs. Biodistribution studies using radiolabelling or fluorescence imaging techniques have shown preferential accumulation of nanoparticles in tumor tissues, with reduced off-target distribution to healthy organs.

Pharmacokinetic studies further highlight the advantages of PLGA nanoparticle-based delivery. Encapsulation within PLGA matrices often results in increased area under the plasma concentration—time curve, reduced peak plasma concentrations, and extended half-life of anticancer agents. These pharmacokinetic improvements translate into enhanced therapeutic efficacy and reduced systemic toxicity. In chemopreventive applications, sustained plasma and tissue drug levels achieved through nanoparticle delivery are particularly valuable for maintaining long-term biological activity at lower doses.

Toxicological evaluation is a critical component of preclinical assessment, especially for nanoparticle systems intended for repeated or long-term administration. PLGA-based nanoparticles generally exhibit

favorable safety profiles, with minimal acute or chronic toxicity observed in animal studies. Hematological, hepatic, and renal parameters are commonly assessed to evaluate systemic toxicity, while histopathological examination of major organs provides insight into potential tissue-level adverse effects. The biodegradable nature of PLGA and its metabolism into non-toxic byproducts support its suitability for both therapeutic and preventive oncology applications.

Translational evidence for PLGA nanoparticles is further strengthened by their established regulatory acceptance in non-oncological applications. Several PLGA-based formulations have already received clinical approval as long-acting injectables and implantable systems, demonstrating the feasibility of large-scale manufacturing and regulatory compliance. This existing clinical experience significantly reduces the translational barrier for PLGA-based nanomedicines in cancer therapy. Moreover, early-phase clinical trials investigating PLGA-based nanoparticle formulations for cancer treatment have reported encouraging safety and efficacy outcomes, although widespread clinical adoption remains limited.

Table 3. Applications of PLGA nanoparticles in cancer chemoprevention and chemotherapy

Application domain	**Representative agents**	**Role of PLGA nanoparticles**	**Therapeutic/preventive advantage**
Cancer chemoprevention	Curcumin, resveratrol, quercetin, EGCG	Enhances stability and bioavailability	Sustained exposure, reduced dose requirement
Conventional chemotherapy	Paclitaxel, doxorubicin, etoposide	Improves solubility and tumor accumulation	Reduced systemic toxicity
Targeted chemotherapy	Ligand-functionalized drug systems	Enables receptor-mediated uptake	Higher intracellular drug delivery
Combination therapy	Drug + chemosensitizer systems	Co-delivery and synchronized release	Overcomes multidrug resistance
Long-term preventive therapy	Natural bioactives	Controlled release over extended periods	Improved compliance and safety

Despite these advances, the translation of PLGA nanoparticles from preclinical models to clinical practice faces several challenges. Differences in tumor physiology between animal models and human patients can lead to discrepancies in nanoparticle accumulation and therapeutic outcomes. Variability in the enhanced permeation and retention effect, tumor heterogeneity, and immune system interactions may influence clinical performance. Additionally, scaling up nanoparticle production while maintaining consistent quality and performance remains a significant hurdle.

In summary, preclinical evaluation provides compelling evidence supporting the potential of PLGA-based anoparticles in targeted cancer prevention and chemotherapy. Enhanced cytotoxicity, improved pharmacokinetics, favourable biodistribution, and acceptable safety profiles collectively underscore their translational promise. Continued refinement of preclinical models, combined with advances in formulation science and manufacturing technologies, will be essential to bridge the gap between experimental success and clinical implementation.

8. Challenges and Limitations of PLGA-Based Nanoparticles

Despite the considerable promise of PLGA-based nanoparticles in targeted cancer prevention and chemotherapy, several scientific, technological, and regulatory challenges continue to limit their widespread clinical adoption. A critical examination of these limitations is essential to provide a balanced perspective and to guide future research efforts toward more effective and translatable nanomedicine platforms. One of the most frequently cited challenges in the clinical translation of PLGA nanoparticles is the variability of tumor targeting, particularly when relying on passive accumulation through the enhanced permeation and retention effect. Although the EPR effect has been extensively validated in preclinical models, its manifestation in human tumors is highly heterogeneous. Differences in tumor vascularization, interstitial pressure, stromal density, and lymphatic drainage can significantly influence nanoparticle penetration and retention. As a result, PLGA nanoparticles may demonstrate excellent tumor accumulation in certain cancer types while exhibiting limited efficacy in others. This variability complicates patient selection and limits the predictability of therapeutic outcomes in clinical settings.

Manufacturing and scalability represent another major hurdle for PLGA nanoparticle-based systems. While laboratory-scale production methods such as emulsion solvent evaporation and nanoprecipitation are well established, translating these techniques to large-scale, reproducible manufacturing remains challenging. Batch-to-batch variability in particle size, drug loading, and release characteristics can compromise product consistency and regulatory compliance. The use of organic solvents, stringent processing conditions, and complex purification steps further complicates large-scale production. Advanced manufacturing technologies, such as microfluidics, offer improved reproducibility but are not yet widely implemented in industrial settings. Stability during storage and distribution is an additional concern that must be addressed to ensure the practical viability of PLGA nanoparticle formulations. Nanoparticles are prone to aggregation, drug leakage, and physicochemical degradation over time, particularly under suboptimal storage conditions. Lyophilization is commonly employed to enhance stability; however, this process requires careful optimization of cryoprotectants to prevent particle aggregation and loss of drug activity. Ensuring long-term stability without compromising therapeutic performance remains a significant formulation challenge.

From a biological perspective, interactions between PLGA nanoparticles and the immune system warrant careful consideration. Although PLGA is generally regarded as biocompatible, nanoparticle formulations may still elicit immune responses depending on their size, surface properties, and route of administration. Uptake by the mononuclear phagocyte system can lead to rapid clearance and reduced tumor delivery. Moreover, repeated administration of nanoparticle formulations may result in altered immune responses over time, which could impact both efficacy and safety, particularly in chemopreventive applications requiring chronic exposure.

Regulatory and translational challenges further complicate the development of PLGA-based nanomedicines. Nanoparticle formulations often fall into complex regulatory categories that require extensive characterization, including detailed analysis of physicochemical properties, in vivo behavior, and long-term safety. Standardized guidelines for evaluating nanoparticle-based drug delivery systems are still evolving, leading to uncertainties in regulatory expectations. This complexity increases development costs and extends timelines, potentially limiting commercial interest and investment.

Another limitation lies in the incomplete understanding of nanoparticle behavior within the tumor microenvironment. Factors such as extracellular matrix composition, cellular heterogeneity, hypoxia, and acidic pH can influence nanoparticle penetration and drug release.

While stimuli-responsive PLGA nanoparticles have been developed to address some of these challenges, their complexity may introduce additional manufacturing and regulatory hurdles. Balancing system sophistication with practical feasibility remains a key consideration in nanoparticle design.

In chemopreventive applications, the long-term safety of PLGA nanoparticles is of particular importance. Preventive strategies often require administration over extended periods, potentially spanning months or years. Although PLGA degrades into non-toxic metabolites, the cumulative effects of repeated nanoparticle exposure have not been fully elucidated. Comprehensive long-term toxicological studies are therefore essential before widespread adoption of PLGA-based chemopreventive systems can be achieved. In summary, while PLGA-based nanoparticles offer substantial advantages for targeted cancer prevention and chemotherapy, their clinical translation is constrained by challenges related to targeting variability, manufacturing, stability, immune interactions, and regulatory complexity. Addressing these limitations through interdisciplinary research, technological innovation, and regulatory harmonization will be crucial to unlocking the full potential of PLGA nanotechnology in oncology.

9. Future Perspectives and Emerging Trends

The field of PLGA-based nanoparticle drug delivery continues to evolve rapidly, driven by advances in materials science, molecular oncology, and translational nanomedicine. While substantial progress has been made in the application of PLGA nanoparticles for targeted cancer prevention and chemotherapy, emerging trends suggest a shift toward more personalized, multifunctional, and clinically adaptable nanocarrier systems. Addressing existing limitations while harnessing new technological innovations will be central to the future success of PLGA-based nanomedicines in oncology.

One of the most promising directions in this field is the integration of personalized medicine principles into nanoparticle design. Tumor heterogeneity at the genetic, molecular, and microenvironmental levels significantly influences therapeutic response. Future PLGA nanoparticle systems are expected to be tailored based on patient-specific tumor profiles, including receptor expression patterns, metabolic characteristics, and immune status. Such personalization may improve targeting efficiency and therapeutic outcomes while minimizing unnecessary exposure to ineffective treatments. Advances in molecular diagnostics and biomarker identification will play a critical role in guiding the rational selection of targeting ligands and therapeutic payloads.

Hybrid nanoparticle systems represent another emerging trend with considerable potential. By combining PLGA with other materials, such as lipids, inorganic nanoparticles, or natural polymers, hybrid systems aim to integrate the advantages of multiple platforms within a single delivery vehicle. Lipid—polymer hybrid nanoparticles, for instance, combine the structural stability and controlled release properties of PLGA with the biomimetic and membrane-fusogenic characteristics of lipids. These systems have demonstrated enhanced cellular uptake, improved drug loading, and superior in vivo performance compared to conventional PLGA nanoparticles. Such hybrid approaches may offer more efficient solutions to challenges related to drug delivery, targeting, and immune evasion.

Stimuli-responsive PLGA nanoparticles are expected to undergo further refinement and clinical exploration. Future systems may incorporate multi-responsive elements capable of reacting to multiple tumor-associated triggers, such as pH, redox gradients, enzymatic activity, and external stimuli. These advanced systems aim to achieve highly precise spatiotemporal control over drug release, thereby maximizing therapeutic efficacy while minimizing off-target effects. However, balancing system complexity with manufacturability and regulatory feasibility will be essential to ensure successful translation.

Artificial intelligence and machine learning are increasingly being recognized as transformative tools in nanomedicine development. Data-driven approaches can be applied to optimize formulation parameters, predict nanoparticle behaviour, and identify relationships between physicochemical properties and biological performance. AI-guided design frameworks may significantly reduce experimental burden, accelerate formulation optimization, and improve reproducibility. In the context of PLGA nanoparticles, such approaches could facilitate the rational selection of polymer composition, particle size, surface modifications, and drug combinations tailored to specific cancer types or preventive strategies. Another

important future direction involves the exploration of PLGA nanoparticles in combination with emerging cancer therapies, such as immunotherapy and gene therapy. PLGA-based systems have already shown potential for delivering immunomodulatory agents, antigens, and nucleic acids. Combining chemotherapy or chemopreventive agents with immune-targeting strategies within a single nanoparticle platform could enhance antitumor immune responses and improve long-term disease control. Such combination approaches may be particularly valuable in addressing tumor recurrence and metastasis.

From a translational perspective, greater emphasis is expected to be placed on scalable manufacturing technologies and regulatory alignment. Advances in continuous manufacturing, microfluidics, and quality-by-design frameworks are likely to improve batch-to-batch consistency and facilitate large-scale production. Early engagement with regulatory authorities and the development of standardized characterization protocols will be critical to streamlining approval pathways for PLGA-based nanomedicines.

In summary, the future of PLGA-based nanoparticles in targeted cancer prevention and chemotherapy lies in the convergence of personalization, multifunctionality, and translational practicality. Emerging technologies, including hybrid systems, stimuli-responsive designs, and AI-guided optimization, offer promising avenues to overcome current limitations. With continued interdisciplinary collaboration and a focus on clinical relevance, PLGA-based nanocarriers are well positioned to play a transformative role in the next generation of cancer prevention and treatment strategies.

10. Conclusion

Biodegradable PLGA-based nanoparticles have emerged as a highly versatile and clinically relevant platform for targeted cancer prevention and chemotherapy. Their unique combination of biocompatibility, tunable physicochemical properties, and regulatory acceptance positions PLGA as one of the most promising polymeric materials for oncological drug delivery. By addressing fundamental limitations of conventional chemotherapy and chemopreventive strategies—such as poor solubility, non-specific biodistribution, systemic toxicity, and inadequate bioavailability—PLGA nanoparticles offer a rational and effective approach to improving therapeutic and preventive outcomes in cancer management. The ability of PLGA nanoparticles to encapsulate a wide range of anticancer and chemopreventive agents, including small-molecule drugs and bioactive natural compounds, enables controlled and sustained drug release while protecting payloads from premature degradation. Targeting strategies, encompassing passive accumulation via the enhanced permeation and retention effect, active ligand-mediated targeting, and stimuli-responsive release mechanisms, further enhance tumor selectivity and intracellular drug delivery. Collectively, these attributes contribute to improved pharmacokinetic profiles, enhanced antitumor efficacy, and reduced systemic toxicity, as demonstrated across numerous preclinical studies.

Importantly, PLGA-based nanoparticles have shown potential not only in therapeutic oncology but also in cancer chemoprevention, where long-term safety, controlled exposure, and patient compliance are critical considerations. By enhancing the stability and bioavailability of chemopreventive agents and enabling targeted delivery to high-risk tissues, PLGA nanoparticles provide a promising avenue for reducing cancer incidence and recurrence in susceptible populations. Despite these advances, significant challenges remain in translating PLGA-based nanomedicines from bench to bedside. Variability in tumor targeting, manufacturing scalability, long-term stability, immune interactions, and regulatory complexity continue to limit widespread clinical adoption. Addressing these challenges will require continued interdisciplinary efforts, combining advances in formulation science, tumor biology, manufacturing technology, and regulatory science.

In conclusion, PLGA-based nanoparticles represent a mature yet evolving nanotechnology platform with substantial potential to transform both cancer prevention and chemotherapy. Continued refinement of targeting strategies, integration of emerging technologies such as artificial intelligence and hybrid nanocarriers, and a strong focus on translational feasibility will be essential to fully realize the clinical impact of PLGA nanomedicines. With sustained research and collaborative innovation, PLGA-based nanoparticle systems are poised to contribute meaningfully to the future of precision oncology.

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