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Advances in Nanotechnology-Based Drug Delivery Systems for Lung Cancer Therapy: A Review

Zoha Waheed Abbasi[1], Sania Ikram[1], Ayesha bibi[2], Falak Naz[3], Aziz Ahmad Khan[3], Sana Hayat[3], Shakir ullah Shakir[3], Attique Ur Rehman[3], Muhammad Naseer Abbas[3*]

[1]Department of Biological Sciences, National University of Medical Sciences (NUMS), Rawalpindi, Pakistan

[2]Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad, Pakistan

[3]Department of Pharmacy, Kohat University of Science and Technology (KUST), Kohat, Khyber Pakhtunkhwa, Pakistan

Email: dr_naseer86@yahoo.com

Abstract – Lung cancer remains one of the deadliest cancers globally, with conventional therapies often falling short due to their systemic toxicity, poor specificity, and limited efficacy against resistant tumors. Nanotechnology-based drug delivery systems have emerged as a promising solution to these challenges, offering targeted, controlled, and sustained release of therapeutic agents directly at the tumor site. This review explores the potential of nanotechnology in revolutionizing lung cancer therapy by examining various nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, nanomicelles, inorganic nanoparticles, and exosomes. These systems enable enhanced drug delivery through passive targeting (via the enhanced permeability and retention effect) and active targeting (through ligand-receptor interactions), significantly improving drug efficacy and reducing off-target toxicity. Furthermore, nanocarriers facilitate the co-delivery of multiple therapeutic agents, including chemotherapy, gene therapy, and immunotherapy, overcoming issues such as multidrug resistance and tumor heterogeneity. We also highlight the integration of nanotechnology with diagnostic agents for therapeutic applications, enabling real-time monitoring of therapeutic progress. While challenges such as large-scale production and safety concerns remain, the continued development of nanomedicine holds immense promise for the future of personalized lung cancer treatment, offering new hope for improved patient outcomes.

Keywords – Nanotechnology, Lung Cancer, Drug Delivery Systems, Targeted Therapy, Multidrug Resistance (MDR).

1. Introduction

Lung cancer is the most fatal malignancy worldwide, with non-small cell lung cancer (NSCLC) constituting approximately 85% of all cases [1, 2]. Despite recent advancements in diagnosis and treatment, the prognosis for lung cancer patients remains poor, particularly in the late stages. Primarily, this poor prognosis stems from frequent treatment resistance and tumor metastasis [3]. These challenges, coupled with the limitations of conventional therapeutic strategies such as systemic toxicity, lack of specificity and inadequate drug accumulation in tumor tissues significantly reduce treatment efficacy especially in advanced stages[4]. These limitations has driven the urgent need for more efficient and targeted treatment modalities [5]. Nanotechnology has emerged as a promising strategy to enhance the precision and therapeutic efficacy of cancer treatment [6, 7]. Among various applications, nanoparticle-based drug delivery systems have offer significant advantages such as improved pharmacokinetics, precise tumor targeting, reduced side effects, and the potential to overcome drug resistance.

Nanoparticles can be engineered to exploit the enhanced permeability and retention time of encapsulated therapeutic agent (EPR) effect, allowing selective accumulate of encapsulated therapeutic agents within tumor and improving drug localization at tumor site [6-8]. Beside these nano-systems can be further modified with targeting ligands to improve specificity toward cancer cells [9-12]. Together, these nanotechnology-based drug delivery systems offer a transformative approach to overcoming the limitations of conventional treatments [13].

Nanocarriers can be customized in terms of size, shape, surface charge, and composition to optimize their pharmacokinetics and biodistribution. This versatility enables the simultaneous delivery of multiple therapeutic agents, including immunomodulators, gene therapy vectors, and chemotherapeutics, on a single nanoplatform, enabling synergistic treatments outcomes [14, 15]. Several studies have demonstrated that these smart drug delivery systems can improve therapeutic outcomes while minimizing adverse effects [16-19].

This review provides an overview of nanotechnology-based drug delivery systems in the treatment of lung cancer. It begins by summarizing conventional therapeutic approaches and their limitations, followed by an in-depth discussion of

various types of nanocarriers, their mechanisms, and applications. Recent advancements, ongoing challenges, and future directions in the field of nanomedicine are also highlighted, with a focus on improving clinical outcomes for lung cancer patients.

1. Conventional Therapies and its Limitations

2.1. Lipid-Based Nanoparticles

The current standard treatment options for lung cancer include surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy [20-22]. Surgery is typically the first-line option for patients diagnosed in the early stages of NSCLC, where the tumor is localized and operable [23-26]. Chemotherapy is commonly used in both early and advanced stages, either alone or in combination with radiation [27]. Platinum-based chemotherapeutics such as cisplatin and carboplatin are widely used non-small cell lung cancer but are associated with significant systemic toxicity and a narrow therapeutic window [28-31].

Targeted therapies and immune checkpoint inhibitors have revolutionized the treatment landscape by allowing for more personalized interventions [32-34]. Drugs targeting mutations in EGFR, ALK, and KRAS genes have shown improved progression-free survival in selected patient populations[35-39]. Similarly, immunotherapeutic agents such as PD-1 and PD-L1 inhibitors have been associated with significantly prolonged overall survival in certain patient subsets [40-42]. However, resistance development, adverse immune reactions, and limited effectiveness in unselected patients remain major drawbacks of these newer treatments. Despite these advancements, the majority of lung cancer patients are either present with advanced diseases or develop resistance to initial therapy [43, 44]. Conventional drug delivery systems are unable to effectively concentrate the therapeutic agents at the tumor site without affecting normal tissues[45-48]. The lack of target specificity often results in dose-limiting toxicities, reduced patient compliance, and sub-optimal treatment outcomes [49].

These persistent challenges highlight the critical need for innovative drug delivery approaches that can enhance therapeutic efficacy while minimizing collateral damage.

The primary limitations of conventional lung cancer therapies stem from their systemic nature and inability to distinguish between malignant and healthy cells [2, 50, 51]. Chemotherapy, for instance, circulates throughout the body and affects rapidly dividing cells indiscriminately, leading to adverse effects such as immunosuppression, hair loss, gastrointestinal and renal toxicity [43, 52].

Furthermore, these therapies often fail due to low drug accumulation in cells. Adequate intracellular concentration of anti-tumor drugs may be compromised by reduced cellular uptake, increased efflux or the combination of both mechanisms[53, 54]. Drug resistance poses another significant obstacle, with cancer cells developing mechanisms such as drug efflux, DNA repair, and mutation of target molecules to evade treatment [55-58]. This resistance often renders subsequent lines of therapy less effective and contributes to disease recurrence. Additionally, the blood–tumor barrier and other physiological barriers hinder the transport of drugs to the tumor, further limiting their efficacy [59]. The inability to achieve sustained and localized drug concentrations continues to undermine the long-term success of conventional treatments [58, 60]. Moreover, many therapeutic agents have short half-lives and poor solubility, requiring high doses or frequent administration, which further compounds systemic toxicity. The lack of real-time monitoring and controlled drug release mechanisms adds another layer of unpredictability to treatment outcomes[61]. These challenges have prompted the search for smarter, more targeted drug delivery approaches, most notably through the application of nanotechnology.

3. Nanotechnology-Based Drug Delivery Systems

3.1. Overview of Nanocarriers

Pharmaceutical nanocarriers are submicron-size delivery materials that are designed to deliver therapeutic agents directly to targeted sites in the body, offering numerous advantages over conventional drug delivery methods [62, 63]. The primary features that define a nanocarrier include its size, surface area, surface charge, and biocompatibility [64-66]. Nanocarriers typically range from 1 to 200 nm in diameter, enabling enhanced accumulation in tumor tissues via the enhanced permeability and retention [67, 68]. These carriers small enough to navigate the body's vasculature and extracellular spaces[69] . The surface area of nanocarriers is crucial for their ability to encapsulate and release drugs. A higher surface area-to-volume ratio allows for better drug loading, increasing their therapeutic efficiency [70, 71] [72]. The surface charge of nanocarriers influences their interaction with biological tissues, cells, and the immune system. Positively charged particles may interact more readily with negatively charged cell membranes [73, 74], while neutral or negatively charged particles may reduce non-specific binding, leading to reduced toxicity and immune response [75, 76]. Biocompatibility is essential to minimize any adverse immune reactions or systemic toxicity. As such, nanocarriers must be composed of materials that are non-toxic and able to safely degrade or clear from the body [77].

3.2. Types of Nanocarriers

3.2.1 Liposomes

Liposomes are spherical vesicles composed of a lipid bilayer that can encapsulate both hydrophilic (water-soluble) and hydrophobic (lipid-soluble) drugs. These biocompatible carriers are one of the

most widely studied and FDA-approved nanocarriers, with products such as Doxil (liposomal encapsulated doxorubicin) being used in the clinic for cancer therapy [78]. Liposomes have the ability to protect their encapsulated drugs from premature degradation, offering increased bioavailability and sustained drug release [79, 80]. Additionally, their lipid-based composition allows for biocompatibility and the ability to merge with the lipid bilayers of cell membranes, enhancing cellular uptake.

The size and surface properties of liposomes can be modulated to improve targeting to specific tumor cells. By modifying the surface of liposomes with targeting ligands, they can specifically bind to overexpressed receptors on cancer cells, allowing for selective drug delivery and reduced off-target effects [81]. Liposomes have shown promise in improving drug efficacy and reducing systemic side effects when compared to free drug formulations [82, 83].

3.2.2 Polymeric Nanoparticles

Polymeric nanoparticles are solid or semi-solid particles composed of biodegradable and biocompatible polymers such as poly (lactic-co-glycolic acid) (PLGA) or polycaprolactone (PCL) [84], These nanoparticles are highly versatile and can be engineered to release their payload in a controlled manner over an extended period. The degradation rate of the polymer can be tailored to match the therapeutic needs of the drug, ensuring a sustained release profile that maintains drug concentration at the target site for longer durations [85].

Polymeric nanoparticles are particularly valuable for co-delivery of multiple drugs or therapeutic agents, such as chemotherapy and gene therapies, within a single platform [86-88]. The surface of polymeric nanoparticles can be functionalized with targeting ligands (e.g., antibodies or peptides) to enhance specificity for cancer cells [89]. Moreover, their relatively high stability and ease of modification make them attractive candidates for developing combination therapies and improving the pharmacokinetics of poorly soluble drugs [90].

3.2.3 Dendrimers

Dendrimers are highly branched, tree-like structures with a well-defined and uniform shape, offering high surface area and precise control over molecular weight and functional groups [91]. Their unique architecture allows them to encapsulate a variety of

therapeutic agents, including small molecule drugs, nucleic acids, and proteins [91]. The surface of dendrimers can be easily modified with functional groups, making them highly customizable for drug delivery and targeting [92]. The controlled size, shape, and surface characteristics of dendrimers provide several advantages over other nanocarriers [93]. They can deliver their payloads more efficiently, reduce toxicity, and improve solubility for poorly soluble drugs [94].

Their precise molecular weights and uniformity help in reproducible manufacturing processes. Furthermore, dendrimers have the ability to penetrate biological barriers, including the blood-brain barrier in some cases, opening up new avenues for the treatment of brain cancers [95, 96].

3.2.4 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are composed of solid lipids that provide a stable matrix for drug encapsulation. These particles combine the advantages of liposomes and polymeric nanoparticles, offering both structural stability and controlled drug release. SLNs are well-suited for the delivery of both hydrophobic and hydrophilic drugs and can improve the solubility and bioavailability of poorly soluble drugs [97, 98].

The lipid matrix in SLNs offers excellent biocompatibility, making them safe for use in vivo. Moreover, they are easily scalable for large-scale production[99]. SLNs have been used in various clinical applications, and their potential in cancer therapy lies in their ability to carry chemotherapeutics to the tumor site while minimizing systemic toxicity. Recent research has focused on enhancing their targeting abilities and improving their stability during storage and in circulation [100, 101].

3.2.5 Nanomicelles

Nanomicelles are amphiphilic nanoparticles composed of surfactant molecules that spontaneously self-assemble into spherical structures with a hydrophobic core and hydrophilic shell [102]. They are particularly effective for the delivery of poorly water-soluble drugs. The hydrophobic core can encapsulate hydrophobic drugs, while the hydrophilic outer layer stabilizes the structure in an aqueous environment.

Nanomicelles offer several advantages, including small size, ease of preparation, and the ability to solubilize poorly soluble drugs [103, 104]. They also have enhanced permeability across biological membranes, making them excellent candidates for targeted drug delivery. Nanomicelles can be modified by targeting ligands or pH-sensitive groups to enhance drug release specifically at the tumor site. They are often used in combination with other types of nanocarriers to improve drug loading and release kinetics [103].

3.2.6 Inorganic Nanoparticles

Inorganic nanoparticles, such as gold nanoparticles (AuNPs), silica nanoparticles, and iron oxide nanoparticles (IONPs), offer unique

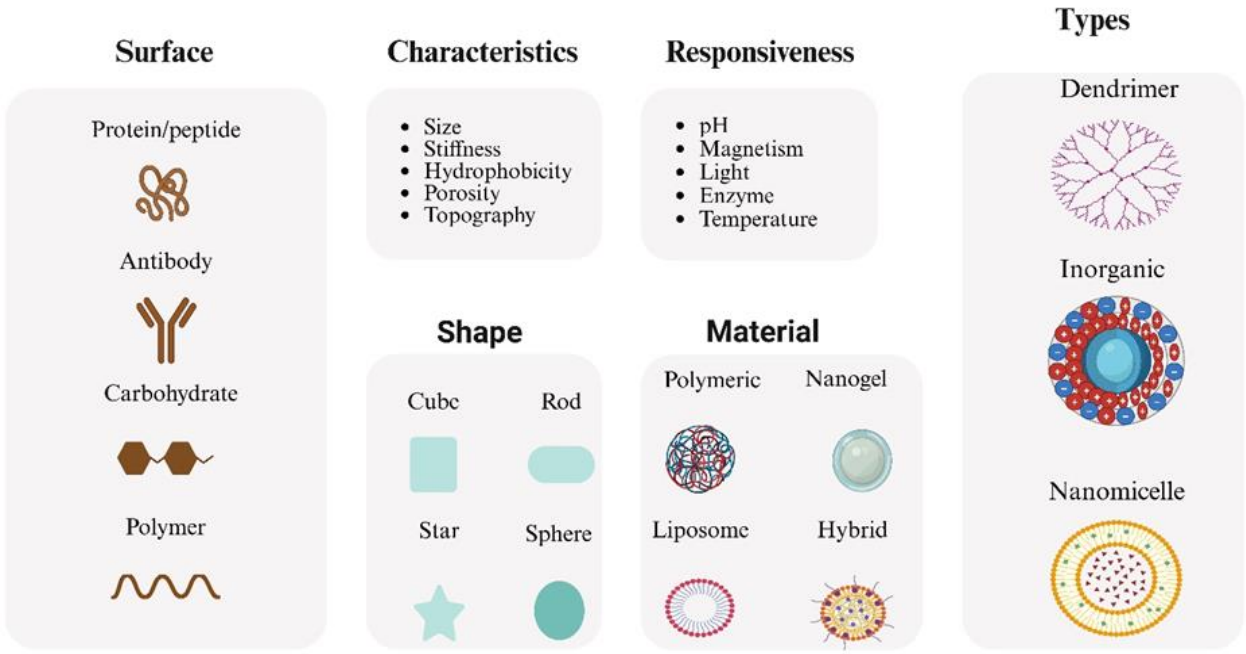

Figure 1. Overview of key physiochemical traits of nanocarriers including surface ligands, structural characteristics, shapes, materials and common carrier types

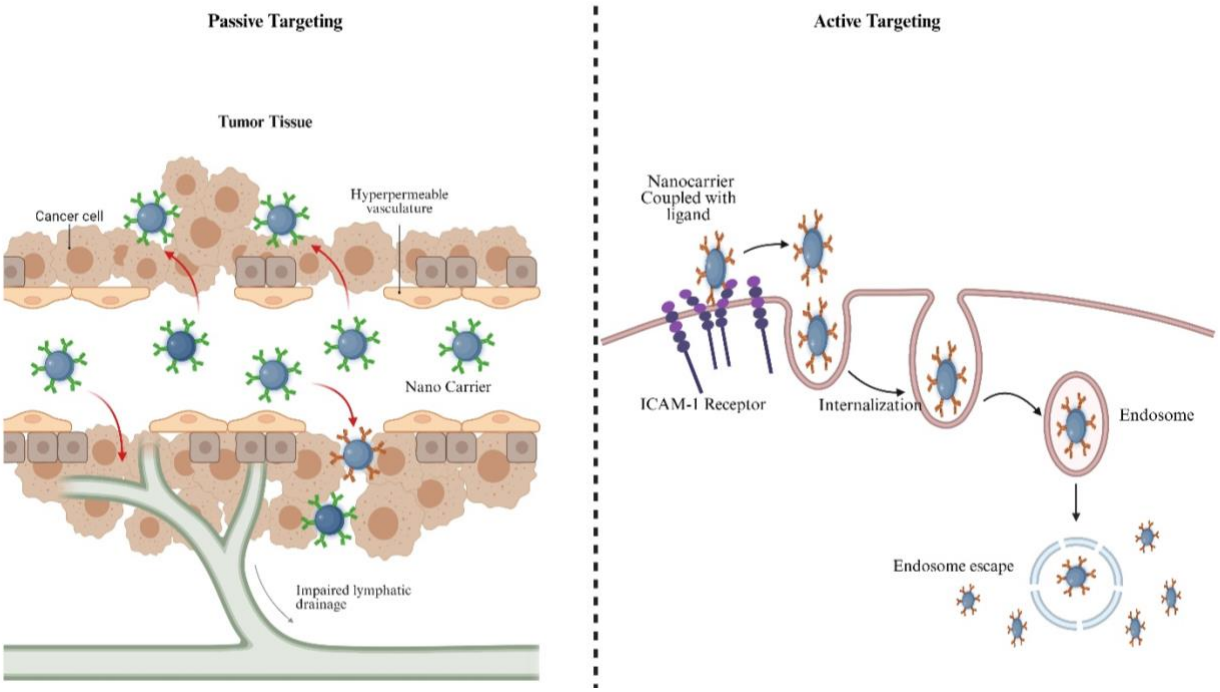

Figure 2. . Illustration of passive and active targeting strategies for nanocarriers. Passive targeting operates via the enhanced EPR effect in tumor tissue, whereas active targeting utilized ligand-receptor interaction to achieve targeted delivery and cellular uptake.

properties that make them ideal for both therapeutic and diagnostic applications. Gold nanoparticles are particularly useful in photothermal therapy, where they absorb light and generate heat to destroy tumor cells. Iron oxide nanoparticles are frequently used for magnetic resonance imaging (MRI) [105]. and have the added benefit of magnetic targeting, allowing for more precise drug delivery to tumor sites [106, 107]. These nanoparticles are also highly customizable in terms of size, shape, and surface properties, enabling them to be used for a wide range of applications, including targeted drug

delivery, imaging, and combination therapies [106]. The versatility of inorganic nanoparticles lies in their ability to integrate with other therapeutic modalities, such as gene therapy and immunotherapy, to improve overall treatment efficacy.

3.2.7 Exosomes

Exosomes are naturally occurring extracellular vesicles secreted by cells that are involved in intercellular communication [108]. These vesicles, typically ranging from 30 to 150 nm in size, can be engineered to encapsulate therapeutic agents such as small molecules, proteins, or RNA. Exosomes are attractive drug delivery vehicles because they can naturally evade immune detection, possess excellent biocompatibility, and can be easily modified for targeted drug delivery. Exosomes offer the unique advantage of being derived from cells, which can provide inherent targeting properties based on the origin of the exosome [109-111]. For example, exosomes derived from cancer cells may preferentially deliver their cargo to other cancer cells, while exosomes derived from immune cells may enhance immune responses. As a result, exosomes are considered a promising carrier for targeted cancer therapies, especially in the context of gene delivery and immunotherapy [112].

4. Nanotechnology in Lung Cancer Therapy

Nanotechnology has revolutionized drug delivery systems, offering numerous advantages over conventional treatment approaches, particularly in the context of lung cancer therapy. Below are some of the key benefits that nanotechnology brings to the field of oncology:[113]

4.1. Nanotechnology in Lung Cancer Therapy

One of the most significant advantages of nanotechnology in cancer therapy is its ability to deliver drugs directly to the tumor site, minimizing damage to healthy tissues. This can be achieved through passive targeting, primarily via the enhanced permeability and retention (EPR) effect [113, 114]. Tumor tissues exhibit a leaky vasculature [115] and poor lymphatic drainage [116], which allows nanoparticles to accumulate preferentially at the tumor site. This phenomenon enables higher local drug concentrations and improved therapeutic efficacy without affecting surrounding healthy tissue.

Additionally, active targeting allows for even more precise delivery. Nanocarriers can be functionalized with targeting ligands such as antibodies, peptides, or small molecules that specifically bind to overexpressed receptors on cancer cells. This ligand-receptor interaction enhances cellular uptake and ensures that the therapeutic agent is delivered directly to the cancer cells, further increasing treatment specificity and reducing off-target effects [117-120].

4.2. Controlled/Sustained Release of Therapeutics

Another key advantage of nanotechnology is the ability to design nanocarriers that offer controlled and sustained drug release. Many traditional drug delivery systems release their therapeutic payload rapidly, often leading to high peak concentrations followed by a steep decline, which can result in suboptimal treatment and unwanted side effects. In contrast, nanocarriers can be engineered to release drugs at a steady rate over extended periods, maintaining therapeutic levels at the tumor site for longer durations [121-124]. This sustained release reduces the need for frequent dosing, improves patient compliance, and ensures that drug levels remain within the therapeutic window, thus optimizing treatment efficacy [125]. Moreover, stimuli-responsive nanocarriers can further enhance this feature by releasing their payload in response to specific triggers found in the tumor microenvironment, such as pH changes, temperature shifts, or the presence of certain enzymes [126, 127]. This ensures that the drug is released specifically at the tumor site, minimizing systemic exposure and maximizing therapeutic benefits.

4.3. Reduced Systemic Toxicity and Enhanced Therapeutic Index

Traditional chemotherapy often results in significant systemic toxicity, as the drugs are not only delivered to the cancer cells but also to healthy tissues throughout the body. This systemic toxicity can lead to serious side effects, including damage to the immune system, gastrointestinal issues, and hair loss [128]. Nanotechnology helps to mitigate this problem by ensuring that the drug is delivered more selectively to the tumor, minimizing exposure to normal tissues. Nanocarriers can be engineered to reduce immune recognition and clearance, allowing the therapeutic agents to circulate for longer periods, thereby improving drug bioavailability at the tumor site. In addition, the controlled release of drugs from nanoparticles reduces peak plasma concentrations, further decreasing the likelihood of side effects. As a result, the therapeutic index (the ratio between the effective dose and toxic dose) is significantly enhanced, making treatments more effective and less harmful to the patient [129, 130].

4.4. Capability for Co-Delivery of Drugs and Genes

Nanotechnology enables the co-delivery of multiple therapeutic agents within a single nanoparticle system [131, 132]. This capability is especially important in the treatment of lung cancer, where combination therapies can enhance treatment outcomes by targeting multiple pathways simultaneously. For example, chemotherapeutic drugs can be combined with gene therapies (e.g., RNA, DNA, or small interfering RNA [siRNA])

that target specific oncogenes or tumor suppressor genes. This dual delivery allows for synergistic effects, where the chemotherapeutic agent works to kill cancer cells while the gene therapy modulates the tumor's genetic profile to enhance treatment response.

Co-delivery can also extend to immunotherapeutic agents, such as checkpoint inhibitors or cytokines which can be combined with chemotherapeutic drugs to stimulate the immune system while targeting tumor cells directly[133-135]. This integrated approach may not only improve treatment efficacy but also help overcome challenges such as tumor heterogeneity and resistance to single-drug therapies [131].

4.5. Potential for Overcoming Multidrug Resistance (MDR)

One of the most significant challenges in cancer treatment is multidrug resistance (MDR), where tumors become resistant to a range of chemotherapy drugs, often due to mechanisms such as drug efflux, altered drug targets [136, 137], and enhanced DNA repair [138]. Nanotechnology-based drug delivery systems have shown promise in overcoming MDR by enhancing the intracellular accumulation of drugs and bypassing some of the cellular mechanisms that cause resistance[139].

Nanoparticles can be designed to evade drug efflux pumps, which are often overexpressed in resistant cancer cells. Additionally, combination nanocarriers can deliver chemotherapeutics along with agents that inhibit the drug efflux mechanisms or modulate the tumor's resistance pathways. This approach increases the likelihood of a successful therapeutic response even in resistant tumors.

5. Conclusion

Nanotechnology has ushered in a new era in cancer therapy, offering revolutionary solutions to many of the limitations associated with conventional treatment modalities. Through enhanced targeting, controlled drug release, and integration with novel therapeutic techniques such as phototherapy, gene delivery, and immunotherapy, nanocarriers have shown great potential to transform oncological care. Clinically approved nanoformulations already demonstrate improved efficacy and reduced side effects, validating the relevance of nanotechnology in modern cancer treatment. However, the journey from bench to bedside remains fraught with scientific, technical, and regulatory hurdles. Challenges such as nanotoxicity, inconsistent biodistribution, tumor heterogeneity, and complex manufacturing processes must be systematically addressed. Furthermore, standardization in regulatory pathways and long-term clinical studies are essential to establish the safety and efficacy of nanomedicines at scale.

Nonetheless, emerging innovations such as AI-driven nanoparticle design, personalized medicine, and organoid-based testing platforms are expected to accelerate the development and clinical translation of next-generation nanotherapeutics. The exploration of biomimetic and multifunctional nanostructures offers new hope for overcoming biological barriers and enhancing patient-specific treatment responses. In conclusion, while nanotechnology in cancer therapy is still evolving, its impact is undeniably transformative. A future that combines intelligent design, translational research, and clinical precision may finally fulfill the promise of safe, targeted, and effective cancer nanomedicine paving the way for longer survival, improved quality of life, and potentially curative outcomes.

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Conflict of Interest

Authors have no conflict of interest to declare.

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