Review

Nanoformulations in the Treatment of Lung Cancer: Current Status and Clinical Potential

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ABSTRACT

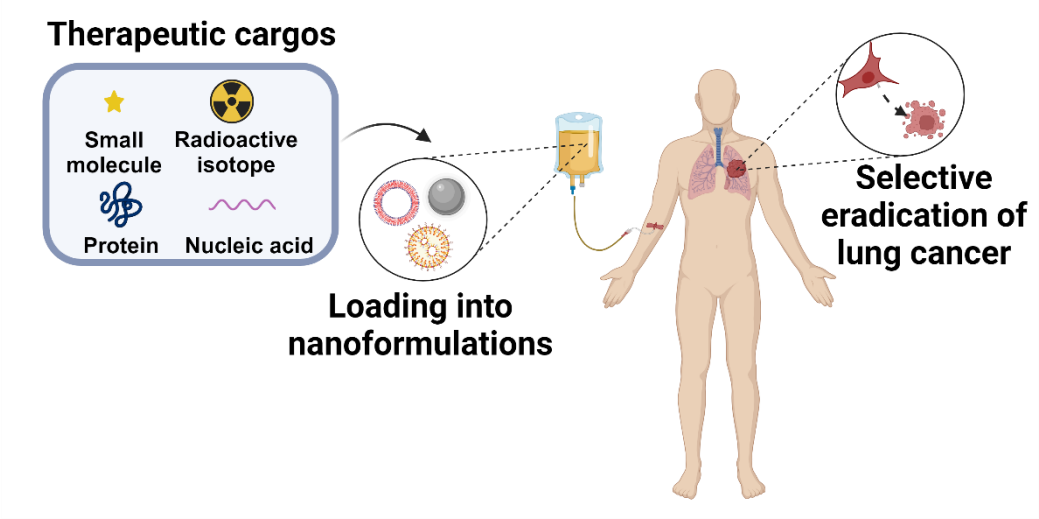
Objective: Recent developments in nanotechnology have regained the hope in enabling the eradication of lung cancer, while overcoming the drawbacks of the classic therapeutics. Nevertheless, there are still formidable obstacles that hinder the translation of such platforms from the bench into the clinic. Herein, we shed the light on the clinical potential of these formulations and discuss their future directions.

Significance of review: The current article sheds the light on the recent advancements in the recruitment of nanoformulations against lung cancer, focusing on their unique features, merits, and demerits. Moreover, inorganic nanoparticles, including gold, silver, magnetic, and carbon nanotubes are highlighted as emerging drug delivery technologies. Furthermore, the clinical status of these formulations is discussed, with a particular attention on the challenges that they encounter in their clinical translation. Lastly, the future perspectives in this promising area are inspired.

Key findings: Nanoformulations have a promising potential in improving the physico-chemical properties, pharmacokinetics, delivery efficiency, and selectivity of lung cancer therapeutics. The key challenges that encounter their clinical translation include their structural intricacy, high production cost, scale-up issues, and unclear toxicity profiles. The application of biodegradable platforms improves the biosafety of lung cancer-targeted nanomedicine. Moreover, the design of novel targeting strategies that apply lower number of components can promote their industrial scalability and deliver them to the market at affordable prices.

Conclusions: Nanomedicines have opened up new possibilities for treating lung cancer. Focusing on tackling the challenges that hinder their clinical translation will promote the future of this area of endeavor.

GRAPHICAL ABSTRACT



Keywords: Lung cancer; Nanomedicines; Targeted drug delivery; Biosafety; Clinical translation.

1. Introduction

Lung cancer is a major global health concern, affecting millions worldwide, and is considered as a leading cause of death [1, 2]. Lung cancer is linked to certain risk factors such as smoking, tobacco use, and an imbalanced diet [3, 4]. According to clinical investigations, it has been found that approximately 69% of patients who undergo medical examinations are diagnosed with a progressive illness. This means that their condition is likely to worsen over time and may require an ongoing medical attention [5]. Whereas only 15% of patients diagnosed with lung cancer manage to survive for five years or more after their diagnosis. These figures highlight the severity of lung cancer and the challenges that patients encounter in their battle against this disease. Individuals need to take preventive measures and undergo regular check-ups to detect potential illnesses at an early stage [6]. Lung cancer diagnosis methods include medical history, physical exam, and imaging techniques [7]. Meanwhile, lung cancer treatment options include surgical interventions, radiotherapy, chemotherapy, and targeted immunotherapy [8]. Unfortunately, chemotherapy, which is a common therapeutic tool for advanced lung cancer, lacks target specificity, leading to off-target toxicities and side effects [9, 10, 11].

Nanotechnology has recently achieved significant advancements in the diagnosing and treatment of lung cancer [10, 12]. Nanoparticles (NPs), which are tiny particles ranging in size from 1 to 1000 nm, have been found to have a large amount of surface energy that allows for the encapsulation or loading of a wide diversity of hydrophilic and hydrophobic molecules [13, 14]. NPs possess high drug loading capacities and can be decorated with multiple ligands to promote their selectivity. This holds special importance in lung cancer therapeutics and diagnostics, as NPs can surpass the bronchial epithelium barrier and accumulate in the deep lung tissues [15, 16]. In addition, the application of NPs in lung cancer has been practical due to their small size, which allows them to accumulate mainly in cancer cells as they penetrate out of the leaky vasculature in the nearness of tumor cell mass [17]. Structurally, NPs can be natural or synthetic. However, most NPs are synthetic particles that are artificially produced

through various physical or chemical methods [18]. Depending on their composition, NPs can be classified into diverse classes, such as polymeric NPs (PNPs), lipid NPs (LNPs), or inorganic NPs [19]. **Fig. 1** illustrates the most common types of nanoparticles that can be used in the treatment of lung cancer.

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In spite of such a promise, the journey of lung cancer nanotherapeutics from the bench to the bedside still encounters multiple obstacles [9]. In the present article, we shed the light on the recent advancements in the application of nanomedicines for lung cancer treatment. The different classes of NPs as well as their unique features, merits, and limitations are discussed. Moreover, inorganic nanoparticles, including gold, silver, magnetic, and carbon nanotubes are highlighted as emerging drug delivery technologies that can contribute to combating lung cancer. Furthermore, the past and current clinical status of these formulations are discussed, with a superior concentration on the challenges that encountered their clinical translation. Eventually, we inspire the future directions in this promising area of endeavor.

2. Current status of lung cancer nanotherapeutics

2.1. Liposomes

Liposomes are spherical NPs composed of one or more phospholipid bilayer(s) [20]. The number of bilayers, size, and preparation method can be used to categorize them. Multilamellar vesicles have multiple bilayers, while small unilamellar vesicles have a single bilayer with an average diameter of less than 100 nm. Meanwhile, large unilamellar vesicles have a diameter greater than 100 nm [21, 22]. Vesicles can transport chemotherapeutic drugs, whether hydrophobic or hydrophilic, to their desired site of action. Studies have shown that liposomal nanoformulations of chemotherapeutic drugs such as paclitaxel and doxorubicin can improve drug efficacy and reduce side effects in lung cancer treatment [23]. Liposomal nanoformulations have also been tested with radiotherapy, and results have shown enhanced tumor regression [24]. Another promising application of liposomal nanoformulations in lung

cancer treatment is using them for anticancer immunotherapy [25]. Liposomes can be designed to carry immunomodulatory agents, such as checkpoint inhibitors, which can enhance the immune response against cancer cells [26]. Checkpoint inhibitors are a type of immunomodulatory agent that can block the mechanism by which cancer cells evade their detection by the cytotoxic T cells, thus promoting cancer eradication by the host cellular immunity [27]. They can be encapsulated within liposomes to easily target the tumor site, which minimizes off-target effects and maximizes the therapeutic efficacy. Furthermore, conventional systemic delivery of immunomodulatory agents usually encounters a rapid clearance from the body, limiting their accumulation at the tumor site and thereby diminishing their curative influence. Formulations such as liposomes can improve the pharmacokinetic profile of these agents and enable a sustained release of the cargo at the desired rate [28]. Additionally, the physicochemical characteristics of liposomes can help them cross biological barriers and penetrate the tumor tissues deeply [29]. Thanks to these benefits, liposomes have become a popular choice in drug delivery systems and are being extensively studied for their potential in treatment of various disorders, including lung cancer [30]. **Fig. 2** sketches the general composition of liposomes and their versatile applicability for targeted drug delivery. **Table 1** sheds the light on some representative studies that recruited liposomal drug delivery systems for the delivery of lung cancer therapeutics.

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Please, insert Table 1 here

Nevertheless, classic liposomes tend to fuse, making them less stable inside the body and more prone to clearance by the reticulo-endothelial system (RES) [31]. To overcome such a pitfall, the surface of liposome can be modified with inert (inactive) hydrophilic polymers, such as polyethylene glycol (PEG). These polymers provide stability and improve the activity to the liposomal surface which indeed create a protecting layer that slows down their recognition by the RES. This leads to an increase in the circulation time of liposomes in the blood [32]. However, excessive PEGylation can also exert negative impacts on the cellular uptake

efficiency of the nanocarriers and their subsequent intracellular trafficking, which is referred to as “PEG dilemma” [33]. To tackle these challenges, liposomes can be equipped with diverse targeting moieties, such as peptides, carbohydrates, or antibodies, which can bind to specific receptors on cancer cells, allowing for selective drug delivery, which is referred to as “active targeting” [34, 35].

2.2. Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are considered a pivotal constituent in lung cancer drug delivery. These NPs exhibit various attributes that make them ideal for targeted delivery, such as their biocompatibility, controlled drug release, and capability to encapsulate both hydrophilic and hydrophobic drugs. SLNs utilize lipid-based materials, that are solid at the room temperature, to encapsulate and deliver therapeutic agents to the target site. SLNs range in size from 50 to 1,000 nm and have garnered substantial interest due to their ability to enhance the drug solubility, bioavailability, and stability [36]. Common solid lipids that produce SLNs include triglycerides such as Dynasan 112 and Compritol, which are highly biocompatible and have excellent drug-loading capacities. Solid lipids like carnauba wax, cetyl alcohol, beeswax, cholesterol, emulsifying wax, and cholesterol butyrate are also employed to produce SLNs. Triglyceride-based SLNs are particularly effective in delivering hydrophobic drugs, such as paclitaxel and curcumin, to cancer cells. They can also cross the blood-brain barrier (BBB), making them a promising candidate for treating neurodegenerative diseases.

Poor aqueous solubility is a critical parameter that limits the bioavailability of a substantial proportion of drugs [37, 38]. Herein, SLNs can offer a promising platform to improve the aqueous solubility of a huge diversity of hydrophobic chemical entities. SLNs have been used to improve the bioavailability of a wide diversity of chemotherapeutic drugs, including idarubicin, doxorubicin, camptothecins, paclitaxel, and etoposide [39]. In addition to their use as carriers for anticancer drugs, SLNs have been shown to effectively deliver nucleic acid therapeutics to the lung cancer cells [40]. Furthermore, the safety of SLNs has been investigated in a study involving repeated inhalation exposure to BALB/c mice. The results showed that SLNs made from homogenized triglycerides and phospholipids are safe for

inhalation exposure at concentrations lower than 200 µg [41]. Additional examples of studies that recruited SLNs for drug delivery to lung cancer are summarized in **Table 2**.

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From a mechanistic point of view, SLNs differ from liposomes in that they possess a hydrophobic core that can accommodate hydrophobic chemical entities. In addition, the unique self assembly of their constituting amphiphilic lipid molecules forms hydrophilic chambers inside the core that also allows for the encapsulation of hydrophilc cargos, especially gene therapies [42] (see **Fig. 1** for structural differences between SLNs and liposomes). Furthermore, SLNs are made of lipids that are solid at room temperature, which improves their stability, reduces aggregation tendencies, and improves the controlled-release pattern of their drug cargos [43].

2.3. Nano-structured lipid carriers (NLCs)

Despite their attractive features, SLNs have been challenged with their relatively limited drug loading capacity that arises from their rigid and perfectly ordered structures. Subsequently, NLCs have been developed as the second generation of SLNs in the 1990s to cope with this challenge. NLCs incorporate liquid lipids in their composition (approximately 30%); thus, their structures become less ordered, enabling them to load drugs at a higher capacity than the classic SLNs. Meanwhile, their high content of solid lipids (~70%) makes them also solid at room temperature to keep the stability advantages and other attractive features of their parent SLNs [44, 45].

In the area of lung cancer, NLCs have shown a promising potential. For example, Rawal *et al.* engineered the surface of NLCs with folate for lung cancer-targeted delivery of a combination of docetaxel (DT) and curcumin (CR) via a solvent-free high-pressure homogenization approach. The developed NLCs showed improved bioavailability of DT that exceeded the commercial product, Taxotere®, by approximately 25-fold. *In vivo* application to a murine model of lung carcinoma revealed enhanced anticancer activities with lower side effects compared to the standard chemotherapy regimen [46]. In another study, Rodenak-Kladniew and co-workers encapsulated the natural product, Geraniol (GOH), into biocompatible

NLCs for a lung cancer-targeted therapy. The prepared NLCs demonstrated an outstanding encapsulation efficiency of the drug (95%) and homogenous physicochemical properties (an average particle diameter of 110 nm, a polydispersity index (PDI)<0.2, and a zeta potential of -10 mV). Moreover, the developed NLCs were biosafe upon incubation with blood and showed enhanced anticancer activities against a human lung cancer cell line, A549 [47]. **Table 3** summarizes additional examples from studies that applied NLCs for lung cancer-targeted treatment.

Please, insert Table 3 here

2.4. Polymeric nanoparticles (PNPs)

PNPs have been extensively studied as a potential treatment option for lung cancer. These NPs are tiny particles of polymers that can be formulated to be delivered loaded with drugs to cancerous lung cells. PNPs offer several advantages over traditional chemotherapy, including increased drug efficacy, reduced toxicity, and improved patient outcomes. Researchers continue exploring the potential of PNPs in lung cancer treatment, hoping to develop more effective and targeted therapies for this devastating disease [48]. Due to their unique physical and chemical properties, PNPs have gained significant attention as potential carriers for anticancer drugs. These NPs offer a range of advantages over conventional drug delivery systems, including improved pharmacokinetics, enhanced cellular uptake, and reduced toxicity. The development of PNPs involves the manipulation of various parameters, such as surface charge, particle size, and surface functionalization [17, 49]. PNPs can be designed in various forms, such as dendrimers, capsules, micelles, or colloids, to fulfill specific drug delivery requirements. The surface charge of PNPs can be easily manipulated to control the release rate of the drug, improve cellular uptake, and enhance the stability of the NPs. Similarly, the particle size of PNPs can be controlled to optimize the drug's pharmacokinetics, improve the drug's diffusion into the tumor tissue, and reduce the clearance by the innate immune system [50]. Furthermore, attaching various targeting ligands to the surface of PNPs allows for the development of multifunctional PNPs that can target specific cell types or tissues, improving the therapeutic efficacy and reducing the side effects. These properties make PNPs promising

drug delivery systems for treating cancer and other diseases [51] PNPs can be designed by self-assembling block copolymers with different hydrophobicity between blocks. These polymers are suitable for administration via oral, topical, nasal, or intravenous routes [52]. Studies have shown that aerosols containing PNPs can improve the efficacy and safety of therapeutic medications for targeting lung disorders such as cancer, asthma, infections, and chronic obstructive pulmonary disease [53]. In alternative study, a hyaluronan-cisplatin was delivered as conjugate through the lungs showed improved drug concentration in the lungs compared to an intravenously-administered cisplatin after 24 hours. Also, the tissue-to-plasma ratio was lower in the CNS and kidneys, thus reducing dose-limiting toxicities [54]. Nevertheless, developing PNPs that effectively target lung cancer is complex and challenging. One of the main challenges is ensuring that the PNPs can precisely target cancer cells whereas avoiding the healthy cells [55]. Another challenge is optimizing the particle size, shape, and surface properties of such formulations to maximize their efficacy. Additionally, there are challenges related to the stability and biocompatibility of the PNPs once they are introduced into the body [29, 55]. Overcoming these challenges requires a deep understanding of the biology of lung cancer and the properties of the materials used to create the nanoparticles, as well as careful design and testing. **Fig. 3** summarizes the most common subclasses of PNPs and their merits for the treatment of lung cancer.

Please, insert Fig. 3 here

The choice of the constituting polymer of PNPs have a crucial role in defining their characters, performance, and safety. Structurally, polymers are molecules that consist of repeating structural units. They can be either natural origin or synthetic. Natural polymers, such as albumin, polypeptides, chitosan, and gelatin, are commonly used in various applications due to their unique properties, such as their high biocompatibility, biodegradability, and safety [56]. Albumin is considered protein located in egg whites and blood plasma and is widely used in pharmaceuticals for drug delivery. Polypeptides are chains of amino acids, and they are commonly used in tissue engineering and drug delivery due to their ability to mimic the natural proteins [57]. Chitosan is a polysaccharide derived from chitin, found in crustaceans' exoskeleton. It is used in wound dressings, drug delivery, and tissue-engineering technologies

due to its biocompatibility and antimicrobial properties [58]. Moreover, it has been reported to possess an intrinsic affinity to certain cancer cells, and it can be used as a functional coating to modulate the *in vivo* biodistribution of other nanocarriers [59, 60]. Gelatin is defined as a protein derived from collagen. It is used in food, pharmaceuticals, and cosmetic industries due to its gelling and emulsifying properties [61].

Despite the attractive characteristics, abundance, and economic resources of the natural polymers, a substantial focus has been directed to their synthetic counterparts thanks to their scalability and flexibility for tailored chemical modifications. Synthetic polymers can be also tailored for specific applications and can be designed to have various properties such as biodegradability, biocompatibility, and conductivity. However, their synthetic nature may not be as biocompatible or biodegradable as natural polymers [62]. **Table 4** summarizes the key advantages and disadvantages of natural and synthetic polymers in the area of lung cancer-targeted PNPs.

Please, insert Table 4 here

Synthetic polymers are crucial in various fields, including biomedical engineering, drug delivery, and tissue engineering. These highly versatile polymers offer several desirable properties such as biocompatibility, tunable degradation rates, and controlled release of drugs. Some of the regularly used synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), polycaprolactone (PCL), and polylactic acid (PLA). PLGA is often utilized for drug delivery and tissue engineering applications [63]. PEG is known for its excellent water solubility and biocompatibility and is often used in drug delivery and surface modification of medical devices. PCL is a biodegradable polyester that is often used in tissue engineering thanks to its slow degradation rate and mechanical properties. PLA, on the other hand, is considered biodegradable and biocompatible that is widely used in drug delivery and tissue engineering applications [62]. Herein, we shed the light on the most common synthetic polymers that represent the fundamental component of PNPs used for the delivery of lung cancer therapeutics.

Poly (D, L-lactide-co- glycolic acid*)*

Poly(lactic-co-glycolic acid), commonly known as PLGA, is considered a biodegradable that is gained significant attention in drug delivery. PLGA is composed of lactic acid and glycolic acid monomers, which makes it highly versatile and tunable in terms of its physical properties. Due to its biocompatibility and biodegradability, it was approved by the FDA for use in drug delivery systems. These systems are designed to encapsulate drugs within nanoscale particles, allowing for targeted delivery to specific sites in the body. PLGA-based drug delivery systems have successfully treated various diseases, including cancer, infectious diseases, and inflammation [64].

Several studies have looked into using PLGA NPs for anticancer therapy, and there have been some promising results. In one study, researchers loaded paclitaxel and afatinib into PLGA-inhaled microspheres. These microspheres were found to have higher biocompatibility, meaning that they were less likely to be rejected by the body and could maintain higher lung concentrations. At the same time, they demonstrated lower concentrations in other tissues, which reduces the risk of undesired side effects. These benefits make targeted PLGA a helpful and effective strategy for treating resistant lung cancer. Overall, this research suggests that PLGA NPs have great potential for cancer therapy, and further studies are needed to explore their full range of applications [65]. Doxorubicin is a potent cytotoxic drug in lung cancer treatment. However, its clinical use is limited due to its toxicity and poor bioavailability. Doxorubicin-loaded PLGA NPs have shown promise in increasing the bioavailability of the drug and reducing its toxicity [66]. Paclitaxel is another chemotherapeutic drug commonly used to treat lung cancer. Paclitaxel-loaded PLGA NPs have been presented to increase the bioavailability of the drug and enhance its therapeutic efficacy [67]. Curcumin is a natural turmeric compound with anti-cancer properties. However, its clinical use is limited due to its poor solubility and bioavailability. Curcumin-loaded PLGA NPs have been shown to increase the solubility and bioavailability of curcumin, making it a promising candidate for lung cancer treatment [68]. Epidermal growth factor receptor (EGFR) is expressed in various types of malignancy such as lung cancer. EGFR-targeted PLGA NPs have been developed to target EGFR-expressing cancer cells. They have shown promise in enhancing the efficacy of chemotherapeutic agents and reducing their toxicity [69]. Small interfering RNA (siRNA) is a

hopeful technology for cancer treatment [70, 71]. siRNA-loaded PLGA NPs have been developed to transport siRNA to cancer cells while also is used as a silence for expression of explicit genes involved in cancer cells' growth and survival. This technology has shown promise in preclinical studies and is presently being estimated in clinical trials [72].

In conclusion, PLGA NPs are a promising technology for treating lung cancer. These NPs have shown promise in enhancing the bioavailability and efficacy of chemotherapeutic agents and delivering siRNA to cancer cells. Further research is needed to fully understand this technology's potential and develop new and innovative treatments for lung cancer.

Poly (Ethylene glycol) (PEG)

PEG is a biocompatible and nontoxic polymer used extensively in drug delivery systems. It has several advantages, including increased solubility, improved bioavailability, and prolonged circulation time. [73, 74] Researchers have found that PEG NPs can effectively target lung cancer cells, making them a promising option for treating this disease [75]. One of the most promising applications of PEG NPs for treating lung cancer is the delivery of chemotherapeutic drugs. By encapsulating such drugs in PEG nanoparticles, researchers aim to improve their efficacy and safety [19]. Another promising application of PEG NPs for lung cancer treatment is the delivery of RNA-based therapies. RNA-based therapies have shown promise in cancer treatment but are challenging to deliver to cancer cells. PEG NPs can encapsulate RNA-based therapies and deliver them precisely to lung cancer cells [76]. Moreover, According to a previous study, PEG-modified NPs have hopeful results in augmenting the efficacy of combined chemotherapy and radiotherapy in human lung cancer cells and non-small cell lung cancer (NSCLC) *in vitro* [77]. Furthermore, several studies have reported the development of a formulation of Crizotinib, a drug used for treating EML4-ALK fusion-positive lung cancer. This formulation has exhibited continuous release and increased cytotoxicity in lung cancer cells. Additionally, noticeable early and late apoptosis was reported in lung cancer cells treated with this formulation. These findings suggest that PEG-modified NPs and the Crizotinib-PLA-TPGS formulation had a promising potential as effective treatments for lung cancer [78].

Despite their promise, there are several challenges associated with the use of PEG NPs. One of the primary challenges is the limited ability to penetrate the tumor tissues, especially when fibrotic tissues or dense extracellular matrix are developed, which reduces the efficiency of the treatment [79, 80]. Another challenge is the potential for systemic toxicity [81]. While PEG NPs are biocompatible, there is still a toxicity risk when administered in high doses which lead to severe adverse effects that may lead to organ damage. The stability of the NPs is also a concern. PEG NPs can be affected by temperature, pH, and salt concentration. This can impact the NPs' stability and ability to effectively deliver the drug payload to the tumor site [82]. Additionally, the immune system can identify and exclude the NPs, reducing their effectiveness. The immune system recognizes NPs as foreign objects. This can lead to the elimination of the NPs from the body before they can reach the tumor site and deliver their drug payload [83]. An additional challenge is the difficulty in scaling up the production of PEG NPs. Producing NPs at a large scale can be costly and time-consuming, which can limit their availability and affordability for both manufacturers and patients [84, 85]. Finally, more knowledge is needed on the long-term effects of PEG NPs on the body. While they have shown promise in preclinical studies, there is still much to learn about their safety and efficacy when administered to humans over extended periods [86].

Dendrimers

Dendrimers are a unique class of highly branched macromolecules with a precisely controlled size and shape. They are composed of numerous branched monomers arranged in a tree-like structure. Due to their unique composition, dendrimers have various applications in various fields, including medicine, catalysis, and electronics [87]. One of the most remarkable properties of dendrimers is their ability to self-organize. The molecular structure of dendrimers allows them to form well-defined supramolecular structures, which can be tailored to meet specific requirements. This property makes dendrimers ideal for drug delivery systems, as they can be designed to encapsulate drugs and release them at a desired rate. Additionally, dendrimers are used as promoters in biochemical reactions due to their high surface area and capability to bind to metal ions [88]. Dendrimers consist of a core, branches or end groups, and a surface formed by polymerization from monomers [89]. Dendrimers can connect to

NPs, liposomes, and anticancer compounds. They can also become biocompatible with high bio-permeability and low cytotoxicity [90]. Dendrimers demonstrate multiple advantages, such as a high drug-loading capacity, nano-size, promising selectivity, and ability to enhance the solubility of poorly soluble anti-neoplastic drugs [91]. Furthermore, dendrimers can be decorated with targeting ligands to impart actively-targeted drug delivery [92].

Table 5 highlights additional examples for the use of PNPs from either natural or synthetic sources for the delivery of lung cancer therapies.

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2.5. Inorganic/metallic NPs

Inorganic/metallic nanoparticles (MeNPs) are multifunction agents that demonstrate various possibilities in diverse biomedical purposes, for example, diagnostic imaging [93], radiotherapy development [94], and thermal ablation [94]. MeNPs show great promise in the treatment of lung cancer thanks to the strong electromagnetic attraction on the surface of the MeNPs, their broad optical properties, ease of the synthesis, simplicity of its surface chemistry, and feasibility of surface functionalization [95, 96]. Modifying the surface of MeNPs with biocompatible polymers such as PEG improves the permanency of drug action and is also imparts targeted drug/gene delivery [97, 98]. Numerous MeNPs, such as gold, iron, and silver NPs, the most common type used in lung cancer, have been investigated in cancer therapy [99, 100]. Herein, we highlight some MeNPs-based approaches currently being studied for lung cancer treatment. **Table 6** summarizes the major subclasses of MeNPs and their merits and demerits.

Please, insert Table 6 here

Gold nanoparticles (AuNPs)

Gold nanoparticles (AuNPs) are a popular choice for researchers, due to their unique optical and surface properties. These particles consist of a gold core and a surface coating and can be synthesized in various sizes. Additionally, they are biocompatible and can be loaded

with various molecules, including chemotherapy drugs, making them ideal for multiple applications [101, 102]. The optical properties of AuNPs are primarily utilized in ultra-sensitive detection and imaging of lung cancer [103, 104]. Nanoshells were the first near-infrared absorbents used in photothermal therapy (PTT), and they were evidence-based in effectiveness. They were developed in the 1990s as PEGylated silica-cored gold nanoshells and later appeared in 2008 as absorbent agents for AuroLase® Therapy [105].

AuNPs have unique properties that make them ideal for cancer treatment. When these NPs are injected into the body, they can selectively target cancer cells, because cancer cells have a higher concentration of proteins on their surface, which attracts AuNPs [106]. Another advantage of AuNPs is that they can be easily conjugated with other molecules to enhance their effectiveness. For example, researchers have found that attaching a chemotherapy drug to AuNPs can increase its potency and reduce its toxicity. Consequently, lower doses of chemotherapy drugs can be used and the side effects can be reduced [106]. **Table 7** highlights some successful studies that applied AuNPs for the treatment of lung cancer.

Please, insert Table 7 here

Despite these advantages, there are also some limitations to the use of AuNPs in lung cancer. Because they are so small, they can be easily filtered out of the body before they reach their target. Researchers are currently working on developing delivery systems that can overcome this challenge, such as through coating the AuNPs with a protective layer that allows them to evade fast clearance [19]. Another limitation of AuNPs is that they are expensive to produce. However, as more research is conducted and new technologies are developed, the cost of producing AuNPs will likely decrease in the future [107].

Silver Nanoparticles (AgNPs)

AgNPs have several biomedical applications, including anti-cancer, and bio-imaging applications [108]. The cytotoxicity of AgNPs mainly due to their size, shape, and surface properties [109]. AgNPs are tiny particles of silver that are only few nanometers in size. They

have a large surface area-to-volume ratio, which makes them highly reactive materials. This property is particularly important in drug delivery, as it allows for targeted and controlled release of drugs to specific areas of the body [110]. In the case of lung cancer, AgNPs can be formulated to load chemotherapeutic agents to the cancerous cells in the lungs using various targeting methods [111]. One of the major advantages of using AgNPs as a good drug delivery transporter is their capability to penetrate the cell membrane. This is because AgNPs are small enough to pass through the gaps in the cell membrane and enter the cell. Once they get inside the cell, they release the drug and exert their therapeutic effect [73].

AgNPs have been recruited as either anticancer modality or as a nanocarrier for other anticancer drugs. A previous study reported on the anticancer activity of AgNPs against lung cancer such as H1299 lung cancer cells [112]. Another study explored the basic mechanism of hypoxia on AgNPs that caused apoptosis, demonstrating the upregulation of HIF-1α expression under hypoxic and normoxic conditions. Furthermore, the AgNPs treatment generated programmed cell death in lung cancer cells while is considered safe with healthy cells [113]. As a nanocarrier, AgNPs have been successfully conjugated to a wide variety of chemotherapeutics. One example is AgNPs-cisplatin. The AgNPs help in enhancing the drug's effectiveness while reducing its toxic side effects. In a recent study, this formulation was highly effective in killing lung cancer cells *in vitro* [114]. Another example is AgNPs-paclitaxel, which have been found to be highly effective in killing lung cancer cells *in vitro*. In addition, it has been found to be more effective than paclitaxel alone in reducing the size of lung tumors in animal models [115]. A third example is AgNPs-curcumin, which demonstrated an improved anticancer performance [116]. Overall, the above examples demonstrate the potential of AgNPs as a treatment for lung cancer. Nevertheless, more studies are needed regarding the *in vivo* biosafety, pharmacokinetics, clearance, as well as the scale-up of such nanosystems to promote their clinical translatability [117].

Iron Oxide Nanoparticles (IONPs)

IONPs form an interesting subclass of MeNPs with a diverse tunable properties and versatile applicability. In the area of lung cancer, IONPs can reduce the side effects of the chemotherapy drugs and improve their efficacy [118]. In a study conducted on mice, IONPs were used to deliver doxorubicin to the lung cancer cells. The study showed that this approach was more effective in treating lung cancer than using doxorubicin alone [119].

Magnetic Iron Oxide Nanoparticles (MIONPs) are a type of IONPs widely used in cancer treatment. They are composed of iron oxide that is coated with a biocompatible polymer. MIONPs have magnetic properties that allow them to be guided to the cancerous cells in the lung. Once they reach the cancerous cells, they can be heated up using magnetic fields, which destroys the cancerous cells [120]. In a study conducted on mice, MIONPs could selectively target the cancer cells in the lung and destroy them using magnetic fields [121].

Superparamagnetic Iron Oxide Nanoparticles (SPIONs), another type of IONPs, have been investigated for their potential use in treating lung cancer. They are similar to MIONPs in that they have magnetic properties but they are smaller in size. This allows them to penetrate deeper into the lung tissue and target the cancer cells [122]. SPIONs have a wide range of biomedical applications. They are often used as an MRI contrast agent and can also be used as a delivery carrier in cancer theranostics. In particular, they have been utilized in lung cancer for drug delivery, MRI imaging, magnetic hyperthermia, and cancer theranostics [123]. A study demonstrated that the usage of EGFR-SPIONs significantly inhibited lung tumor growth *in vivo*. Magnetic hyperthermia treated by EGFR-targeted SPIONs caused significant inhibition of the lung cancer growth in an *in vivo* orthotropic animal model [124]. In another study conducted on rats, SPIONs were able to selectively target the cancer cells in the lung and induce cytotoxicity [125].

Magnetic nanoparticles (MNPs)

Magnetic nanoparticles have many potential uses in diagnosing and treatment of numerous diseases [126]. The FDA has approved the usage of MNPs along with chemotherapy

[127]. MNPs are made up of superparamagnetic materials with an average particle size >25 nm [128]. Their high (surface-to-volume ratio), and they can be recognized and controlled by remote magnetic fields make them extensively recruited in research. MNPs efficiently deliver drugs to the tumors with minimal damage to the healthy tissues [129]. The biocompatibility of these particles is influenced by several factors: their structure, size, shape, surface properties, concentration, and biodegradability. Regarding the surface properties, it has been shown that MNPs with neutral surface charge demonstrate delayed circulation time and fewer uptake via the mononuclear phagocyte system due to reduced opsonization [130]. MNPs are composed of iron oxide NPs such as maghemite (γ-Fe2O3) and magnetite (Fe_3O_4) [131]. These NPs are either non-biodegradable or biodegradable [128]. Non-biodegradable MNPs are coated with a certain material that causes the magnetic core to leach and simplifies the excretion of the particles through the kidneys [132]. When an external magnetic field is applied, they demonstrate thermic effects, which initiate cellular apoptosis at temperatures above 42 °C and induce direct killing at 45 °C. Iron oxide and D-mannitol are the most common materials used to synthesize magnetic nanocomposite nano-sized particles [133]. **Figure 4** outlines the concept of MNPs and their prospective applications in the identification and treatment of lung cancer. **Table 8** gives some examples for MNPs that have been investigated in this area.

Please, insert Fig. 4 here

Please, insert Table 8 here

Carbon nanotubes (CNTs)

CNTs are graphene sheets have a diameter of 0.4−3 nm and 20−1000 nm in length [134]. There are two forms of CNTs, single-walled and multi-walled CNTs. CNTs are effective in treating lung cancer via the activation of the apoptotic pathway through targeting mitochondria in cancer cells. CNTs linked to PEG could concentrate better on cancer cell repertoires, enhancing Nano-drug delivery performance. The first type of CNTs is single-walled CNTs, which are formed of a single sheet of graphene that is flexible due to Van der Waals' forces. Due to the low toxicity of SWCNTs, they were widely employed in drug delivery and

cancer therapy. A study used Paclitaxel as an antitumor drug connected with SWCNTs besides graphene oxide. This nanostructure enhanced effectiveness and induced death in NCI-H460 and A549 cancer cells [135]. Another study using doxorubicin with SWCNTs demonstrated that thanks to their magnetic localization and better distribution, SWCNTs can enhance the targeting and increase therapeutic efficiency [136]. The second type of CNTs is multi-walled CNTs, composed of multiple sheets of coaxial cylinders surrounding a single layer of graphene. A study reported that MWCNT conjugated with doxorubicin and hyaluronic acid had more toxicity and apoptosis effects on A549 cells. This complex demonstrated freedom from toxicity for the heart, kidneys, and liver. Scintigraphic techniques could be used to identify the location and operation of the complex [137]. Another study demonstrated that chitosan-coated CNTs were employed as carriers of methotrexate. In this *in vitro* research, the developed platform enhanced the anticancer activity against a cancerous cell line, H1299, compared to a healthy lung cell line, MRC-5 [138]. Also, another study using MWCNTs conjugated with Cisplatin as a chemotherapeutic agent improved the therapeutic effects and reduced toxicity to the liver and kidney as a common side effect seen with the classic therapies [139].

3. Market and clinical Status of lung cancer nanotherapeutics

Currently, many nanoparticle-based therapeutic advances are under preclinical investigation, clinical trials, or waiting for approval by the FDA or EMA [140]. In the case of advanced lung cancer tumors, the regular care involves a recipe of chemotherapy and radiotherapy. Both therapies have been shown to be successful in supervisory the growing and spreading of cancer cells. However, despite the effectiveness of this combined approach, there are currently only two nanomedicines approved by both the FDA in the USA and the EMA in EU for the healing of non-small cell lung cancer (NSCLC). These drugs have been shown to be effective in combating NSCLC tumors in clinical trials. **Table 9** offers a concise outline of the marketed lung cancer nanotherapeutics and their key features.

Please, insert Table 9 here

Furthermore, a plethora of clinical trials are currently in progress, focusing on integrating these advances into the treatment of tumors. **Table 10** lists the completed and ongoing clinical trials that recruited nanomedicines for the curing of lung cancer as of 2023.[141]

Please, insert Table 10 here

4. Discussion

Nanotechnology has a promising potential for tackling medical problems, including incorporating multiple chemotherapeutic drugs for the treatment of lung cancer. Our review of literature revealed that the top three nanoparticle platforms suitable for this purpose are liposomes, PNPs, and MNPs. The three platforms possess competitive features that allow for efficient drug delivery to the lung cancer in comparison with the other dosage forms.

Liposomes are widely used in drug delivery systems due to their unique properties alluded to above. Liposomes can deliver therapeutic agents through specific targeting strategies like passive, active, or stimuli-responsive approaches including pH-responsive, magnetic-responsive, and thermo-responsive approaches [142]. It has been reported that Cisplatin causes acute nephrotoxicity in 20-40% of patients, in addition to peripheral neuropathy, ototoxicity, and myelopathy [143]. Herein, liposomes hold promise to reduce these side effects through targeted drug delivery. Yet, liposomes have some shortcomings such as low encapsulation efficiency and long-term stability. To overcome these issues, recruiting more advanced technologies such as SLNs or NLCs can be considered. Moreover, merging the classic liposomes to other technologies such as PNPs can result in hybrid platforms, e.g. hybrid lipid-polymer NPs, that integrate the powers of their parent technologies while overcoming their drawbacks.

PNPs are solid and colloidal micelles with a size range of 10−1000 nm [144]. The most common forms of PNPs are nanocapsules and nanospheres. Within these two large categories, NPs are divided further into subclasses based on their morphology and properties such as micelles, polymersomes, and dendrimers. Several studies have recruited various types of PNPs in the treatment of lung cancer. A Phase III clinical trial compared PNPs of paclitaxel (pm-Pac) plus cisplatin versus solvent-based paclitaxel plus cisplatin as first-line treatment for advanced NSCLC. The study found better response rates in the experimental group, but no significant difference in overall survival or serious adverse events [145]. Additional studies have been highlighted in the previous sections of this article. Nevertheless, the disadvantages of PNPs include an increased risk of particle aggregation and toxicity.

MNPs are composed of a magnetic core that is surrounded by a functional coat. The magnetic core is made up of materials like cobalt, gold, iron, and nickel, which provide the core with magnetic properties. Because of the biocompatibility of Fe_3O_4, NPs conjugated with iron oxide are the most widely employed for lung cancer treatment [146]. Iron oxide has strong MRI contrast properties and low systemic toxicity. Commonly, MNPs with a diameter less than 50 nm are superparamagnetic, especially superparamagnetic iron oxide nanoparticles (SPIONs) [147]. The magnetic properties of MNPs facilitate their enrichment, isolation, purification, and targeting upon exposure to an external magnetic field [148]. Moreover, MNPs have a magnetocaloric effect in a high-frequency magnetic field that lead to indirect killing of tumor cells [149]. At present, a variety of SPIONs have been utilized in preclinical research as well as clinical trials [150]. According to many studies, SPIONs have high specificity and no side effects and are widely used in MRI imaging [151, 152]. SPIONs were approved by the FDA for use in the clinic as a form to diagnose tumors and for targeted delivery of anticancer drugs. Although SPIONs are biocompatible and biodegradable, the risk of toxicity is still cannot be totally avoided, for example, due to reactive oxygen species (ROS) production [153].

One of the leading challenges in healing lung cancer is supplying the drugs to the tumor site. The lung is a complex organ, and getting drugs to the tumor can be challenging. However, NPs can be designed to target the tumor specifically. Another advantage of using NPs is that they can be formulated to control the release of drugs over time. This means that the drug can

be delivered over a period of days or weeks rather than all at once. This can assist minimizing the adverse effects and increase the effectiveness of the treatment [154]. In addition, NPs can be also used to enhance the effectiveness of radiotherapy. Furthermore, NPs can be used to monitor the progression of lung cancer, for example through attaching a fluorescent probe to them, their biodistribution [155]. Immunotherapy is an additional promisinbg area for the eradication of cancer, where NPs play a pivotal role in the efficient, selective, and safe delivery of antigens to the immune cells of interest [25]. Despite promise, there are multiple obstacles that encounter the clinical translation of lung cancer nanotherapeutics. One of the challenges is the scalability of NPs production. Another challenge is the safety of NPs, as some NPs have been shown to cause toxicity in animal studies. Despite these challenges, the potential benefits of nanoformulations in cancer treatment are significant, and the field of nanomedicine continues to evolve rapidly. The use of nanoformulations in lung cancer treatment has shown promising results, and further research is needed to realize this technology's potential fully.

5. Concluding remarks and future perspectives

NPs are a promising tool in the field of cancer treatment due to their unique properties. They have a high surface area-to-volume ratio, enabling them to carry a larger drug payload to the tumor site. This has the potential to reduce the amount of toxicity to the surrounding healthy cells. There are two major types of NPs targeting: active and passive. Active targeting involves the attachment a moiety to the surface of the NP that can bind specifically to a receptor on the cancer cell. Passive targeting, on the other hand, relies effect due to (enhanced permeability and retention effect) (EPR), which permits NPs to accumulate in the tumor due to its leaky blood vessels. However, several challenges still need to be addressed before NPs can be widely used in cancer treatment. One of the main issues is the cost of production and scale-up problems. Another challenge is the challenging pharmacokinetic profiles, which can limit their effectiveness. Imaging methods can be used to track the NPs, but this requires the development of specific probes that can be attached to the surface of the NPs. There are also concerns about the toxicity of NPs, as they can potentially cause damage to healthy cells.

Regulatory guidelines and hurdles must be addressed to ensure the safe and effective use of NPs in cancer treatment.

Despite these challenges, nanotechnology has made tremendous progress in the past decade and continues to be an area of active research. Further advancements in NPs production, imaging, and regulation will be necessary to realize the full potential of NPs in diagnosing and treating cancer. This paradigm shift operates in concert with the ever-increasing knowledge gained from other fields, such as immunology and molecular biology. However, more knowledge on the heterogeneity of tumors, the utility of the EPR effect, transport of NPs to tumors, nano-bio interactions, the immunological crosstalk between host and tumor, the tumor microenvironment, and the prevention of metastasis will significantly improve the efficacy of nanomedicines. Furthermore, the advent of more sophisticated drug delivery systems, triggered by intrinsic biological stimuli or extrinsic mechanisms, will encourage the greater release of therapy as well as adroit targeting to the site of disease.

Because the lungs are highly vascularized, NPs can be designed to accumulate preferentially in lung tumors, allowing for more effective treatment. Another promising area of research in the field of nanotechnology is the development of imaging agents that can detect lung cancer at an early stage. Early detection is critical for improving the prognosis of lung cancer, as it allows for earlier intervention and more effective treatment. NPs can be designed to bind specifically to lung cancer cells, allowing for the early detection of tumors using imaging techniques such as MRI or PET. One of the challenges of using NPs for cancer treatment is the potential for toxicity. Because NPs are so small, they can easily enter cells and interact with cellular components which lead to unintentional adverse effects, such as inflammation or damage to healthy cells. To address this challenge, researchers are developing NPs that are biocompatible and biodegradable, meaning that they can be safely metabolized by the body.

Declaration of competing interests

The authors report no conflict of interests associated with this work.

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Figure legends

Fig. 1. Different types of nanoparticles that are used in the treatment of lung cancer. *The figure was created with BioRender.com, with a publication license.*

Fig. 2. A schematic diagram showing the general composition of liposomes and their versatile applicability. A) A liposome for the delivery of small molecular hydrophilic/hydrophobic drugs. B) A targeted liposome for theranostic applications. C) A liposome modified with both PEG and targeting moieties for the delivery of anticancer therapeutics to the tumor. D) A PEGylated liposome for tumor targeting based on the enhanced permeability and retention (EPR) effect. *The figure was created with BioRender.com, with a publication license.*

Fig. 3. Examples of the most common types of PNPs used for the delivery of lung cancer therapies and their common merits. *The figure was created with BioRender.com, with a publication license.*

Fig. 4. A diagrammatic representation of how Magnetic Nanoparticles (MNPs) can be used in targeting drug delivery and cancer treatment, in vivo imaging, and the various mechanisms of action involved in different therapeutic agents. The MNPs can be coated with polymers, loaded with therapeutic payloads and imaging agents, and functionalized with targeting ligands to ensure precise delivery to the intended site. *The figure was created with BioRender.com, with a publication license.*

Figures

Fig. 1.

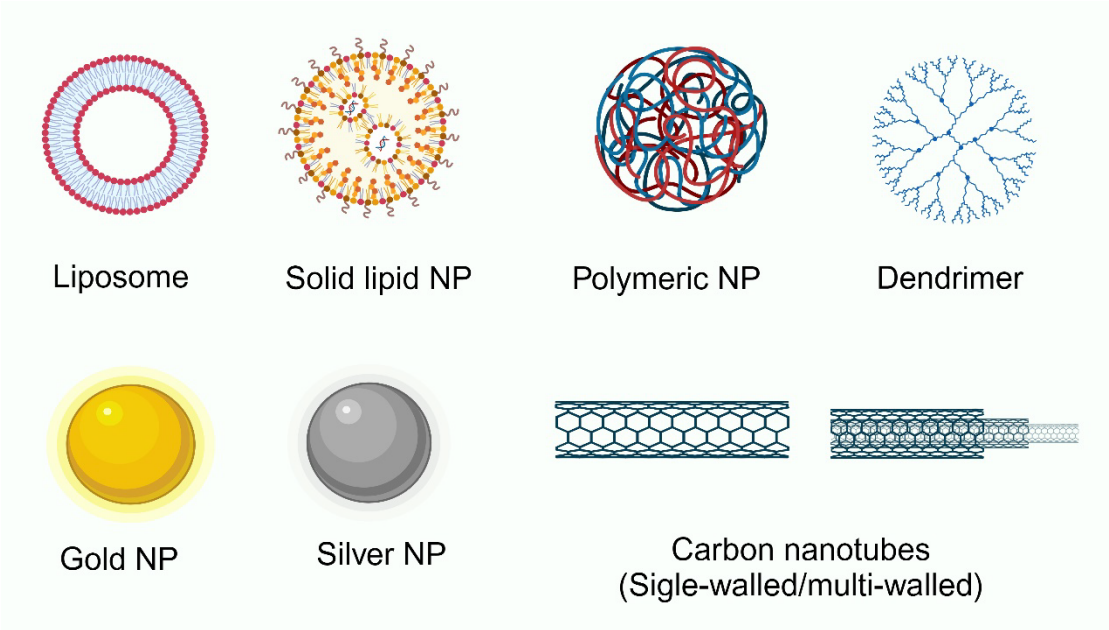


Fig. 2.

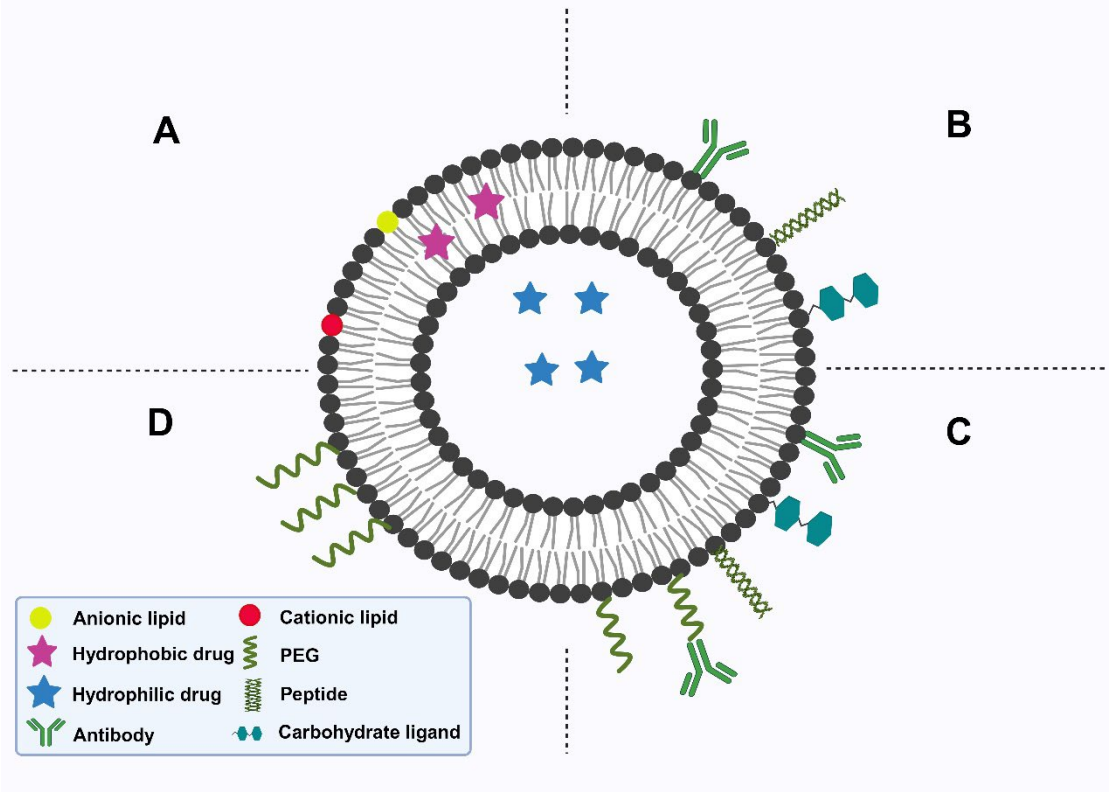

A
B
C
D
Anionic lipid
Cationic lipid
Hydrophobic drug
PEG
Hydrophilic drug
Peptide
Antibody
Carbohydrate ligand

Fig. 3.

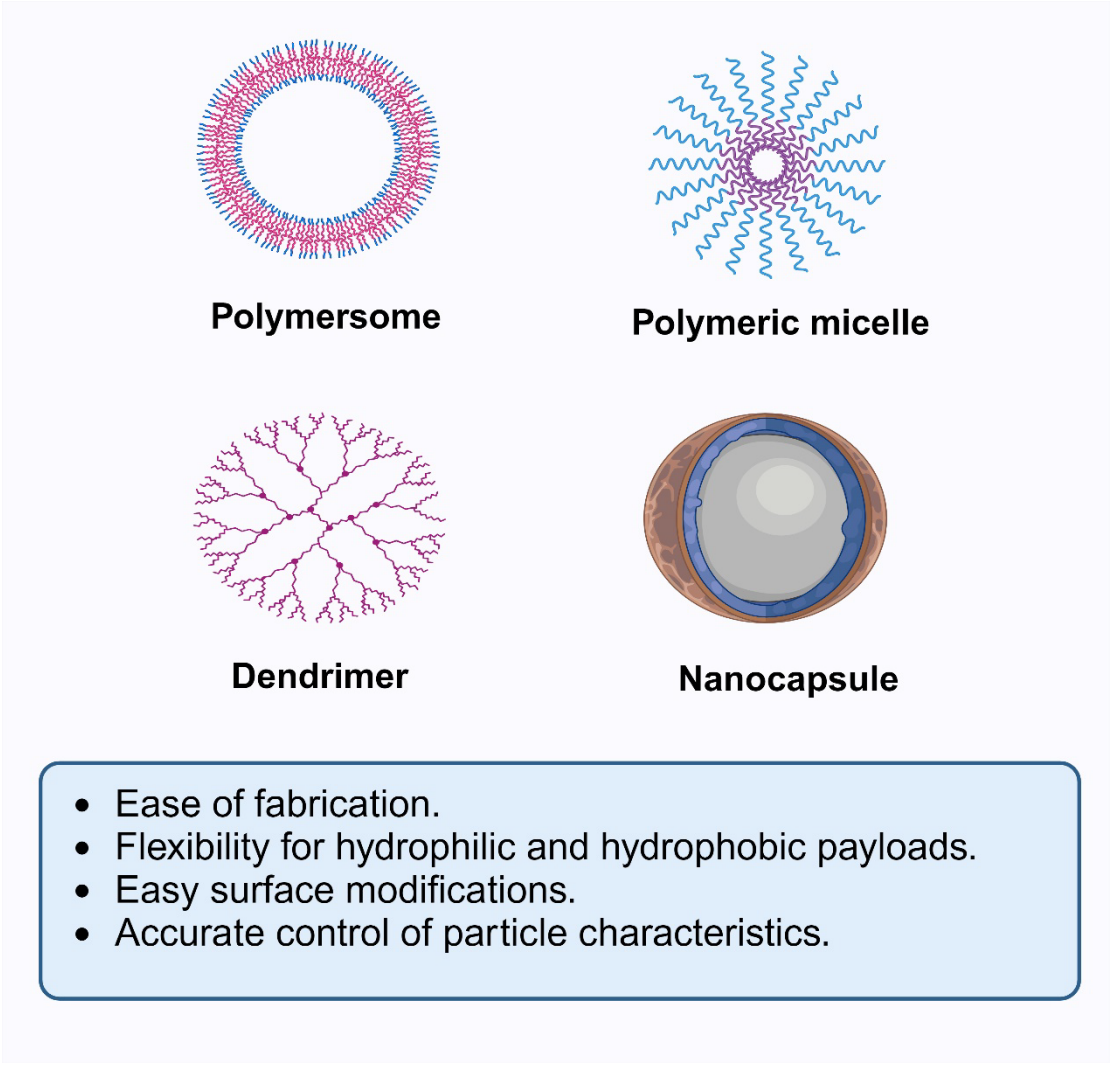
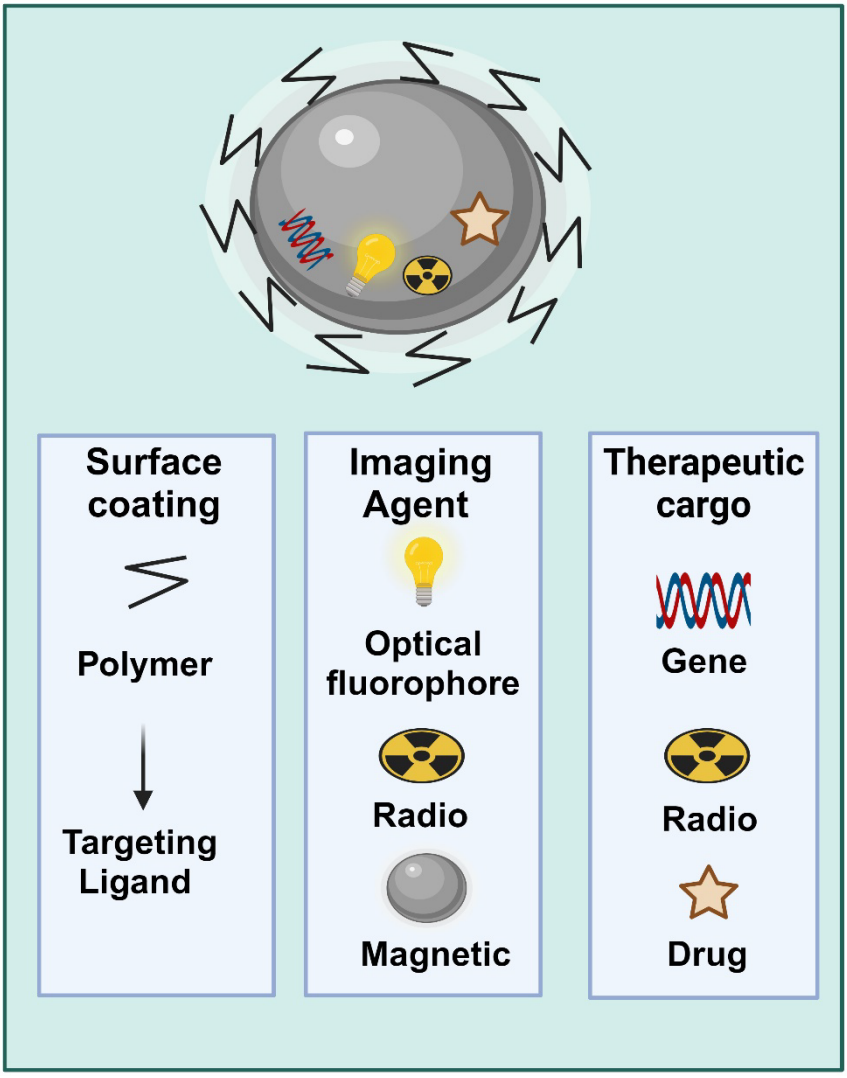

Polymersome
Polymeric micelle
Dendrimer
Nanocapsule
• Ease of fabrication.
• Flexibility for hydrophilic and hydrophobic payloads.
• Easy surface modifications.
• Accurate control of particle characteristics.

Fig. 4.


Surface coating
Polymer
Targeting Ligand
Imaging Agent
Optical fluorophore
Radio
Magnetic
Therapeutic cargo
Gene
Radio
Drug

Tables

Table 1. A summary of some representative studies that recruited liposomes for the treatment of lung cancer.

Drug	Nanocarrier	Study type	Key outcomes	References
Cisplatin	Lipoplatin	Phase III	Increased therapeutic response	[156]
Paclitaxel	RGD-modified liposome	Preclinical	Improved efficacy *in vitro* and *in vivo*	[157]
Irinotecan	PEGylated liposome	Phase II/III	High overall response rate and biosafety	[158]
SN-38	PEGylated liposome	Phase II	Inhibition of tumor growth	[159]

Table 2. Examples of studies that applied SLNs for drug delivery to lung cancer.

Drug	Nanocarrier	Study type	Key outcomes	References
Paclitaxel and Curcumin	PC-SLNs	Preclinical	Improved delivery efficiency and synergistic oncotherapy	[160]
Silymarin	SLNs	Preclinical	Enhanced apoptotic and cytotoxic effects	[161]
Bedaquiline	SLNs	Preclinical	Enhanced bioavailability and biodistribution, reduced tumor volume and weight in NSCLC	[162]
Artemether	PEGylated SLNS	Preclinical	Enhanced cytotoxicity, downregulation of MMP-9, HIF-1a, and VEGF	[163]
Phyllanthi Tannin (PTF)	SLNs	Preclinical	Improved anti-tumor efficacy and safety	[164]

Abbreviations: MMP-9, Matrix metalloproteinase-9; HIF-1a, Hypoxia-inducible factor-1a; VEGF, Vascular endothelial growth factor.

Table 3. A summary of some representative studies for the use of NLCs for lung cancer-targeted delivery of drugs.

Drug	Nanocarrier	Study type	Key outcomes	References
Docetaxel and Curcumin	Folate-NLCs	Preclinical	Enhanced bioavailability, lower side effects, synergistic oncotherapy	[46]
Geraniol	NLCS	Preclinical	Enhanced bioavailability and improved anticancer activity	[47]
Celecoxib and Docetaxel	NLCs	Preclinical	Synergistic diminution in NSCLC	[165]
Paclitaxel and Doxorubicin	NLCs	Preclinical	Inhibited tumor growth *in vitro* and *in vivo*	[166]

Table 4. A brief summary of the fundamental advantages and disadvantages of the natural and synthetic polymers in lung cancer-targeted PNPs.

Polymer class	Advantages	Disadvantages	References
Natural (e.g. albumin, polypeptides, chitosan, and gelatin)	• Less/non-toxic. • Enhanced aqueous solubility. • Biocompatible. • Biodegradable. • Fewer side effects.	• Uncontrolled hydration rate. • Batch-to-batch variation. • Complex structures. • Complicated and expensive extraction methods. • A high degree of variability.	[167]
Synthetic (e.g. PLGA, PEG, PCL, and PLA)	• Scalability. • Greater conjugation properties. • Better in selectivity and specificity.	• Less biocompatible. • Expensive and difficult synthesis procedures. • Poor aqueous solubility. • Absence of intrinsic bioactivity.	[168]

Table 5. A summary of some representative studies that recruited PNPs for the treatment of lung cancer.

Drug	Nanocarrier	NP resource	Study type/status	Key outcomes	References
Paclitaxel	Nab-paclitaxel	Natural	FDA-approved	Treatment of NSCLC	[169]
Carboplatin/Paclitaxel	Albumin NPs	Natural	Phase II	Management of non-resectable Stage III NSCLC	[170]
Paclitaxel	PLGA NPs	Synthetic	Approved in South Korea/Europe	Management of lung cancer	[171]
Taxanes	PEG NPs	Synthetic	Preclinical	Enhanced efficacy in A549 cells	[77]
Crizotinib	PLA-TPGS	Synthetic	Preclinical	Promote cytotoxicity in NCIH3122 cells	[78]
Doxorubicin	PAMAM	Synthetic	Preclinical	Increased therapeutic efficacy and selectivity	[172, 173]

Abbreviations: PLA-TPGS, Polylactic tocopheryl PEG 1000 succinate; PAMAM, Poly(amidoamine) dendrimers.

Table 6. A summary of the major subclasses of MeNPs as well as their advantages and disadvantages.

MeNPs subclass	Advantages	Disadvantages	References
Gold nanoparticles (AuNPs)	• Easy synthesis and conjugation to multiple agents. • Control of particle size. • Biocompatible.	• Non-biodegradable • High cost for large-scale production • Controversial safety.	[174]
Silver Nanoparticles (AgNPs)	• Scalability. • Controlled drug delivery. • Long-term stability.	• Low drug loading capacity. • Low capacity of loading lipophobic drugs.	[73, 175]
Iron Oxide Nanoparticles (IONPs)	• Unique electrical, and optical properties. • Suited for theragnostic applications. • variable in size and structure.	• Toxicity concerns. • Solubility limitations.	[176]
Magnetic nanoparticles (MNPs)	• Large surface-to-volume ratio. • Easy synthesis. • Excellent biodegradability. • Low cytotoxicity.	• Poor dispersion abilities. • Limitations in production processes. • Biodistribution depends on the environment compatibilities.	[177]
Carbon nanotubes (CNTs)	• Large surface area. • Ability to encapsulate and deliver several types of agents. • Protects entrapped drug and provides sustained release.	• Non-biodegradable. • Toxicity concerns. • Poorly soluble in water.	[178]

Table 7. Examples of studies that applied AuNPs for the treatment of lung cancer.

Drug	Nanocarrier	Study type	Key outcomes	References
Bortezomib	PEGylated AuNPs	Preclinical	Enhanced selectivity and anticancer activity *in vitro*.	[179]
Doxorubicin	PVP-AuNPs	Preclinical	Enhanced anticancer activity compared to free drug	[180]
Afatinib	AuNPs	Preclinical	Enhanced anticancer potency by 3.7x *in vitro*, reduced proinflammatory cytokines	[181]

Abbreviations: PVP, Polyvinylpyrrolidone.

Table 8. Some examples for the use of MNPs in the treatment of lung cancer.

Drug	Nanocarrier	Study type	Key outcomes	References
Doxorubicin/ cetuximab	Dextran-coated IONPs	Preclinical	Suppression of A549 cell proliferation	[133]
Paclitaxel	Core-shell MNPs+atmospheric plasma	Preclinical	Synergistic inhibition of A549 cell growth	[182]
Actein (AT)	Actein conjugated MNPs (AT-MNPs)	Preclinical	Apoptosis induction and inhibition of NSCLC growth.	[183]
Cisplatin	Fe_3O_4 associated with PEG-PLGA	Preclinical	Enhanced antitumor activity	[184]

Table 9. Marketed Nanopharmaceuticals for lung cancer therapy.

Product	Active drug	Nanoplatform	Advantages	Approval status (Year)
Abraxane	Paclitaxel	Colloidal Albumin NPs	↑ Blood circulation time ↑ Drug solubility ↑ Tumor uptake (EPR) ↓ Severe toxicity	FDA (2005) EMA (2008)
Pazenir	Paclitaxel	Dispersable Albumin NPs Powder for infusion	↑ Blood circulation time ↑ Drug solubility ↑ Tumor uptake (EPR) ↓ Severe toxicity	EMA (2019)
Genexol-PM	Paclitaxel	Polymeric micelles	↑ Blood circulation time ↑ Drug solubility ↑ Tumor uptake (EPR) ↓ Severe toxicity	South Korea/India (2007)

Table 10. Registered clinical trials involved nanomedicines for the treatment of lung cancer as of 2023.*

NCT identifier	Phase	Description	Enrolled subjects	Recruitment status
NCT01792479	Phase II	Study on BIND-014 for NSCLC second-line therapy.	64	Completed
NCT01620190	Phase II	Albumin-stabilized NPs of paclitaxel for the treatment of advanced NSCLC in previously treated patients.	26	Completed
NCT00729612	Phase II	Studying paclitaxel albumin-stabilized NPs with carboplatin for treating NSCLC patients.	63	Completed
NCT00077246	Phase I/II	Paclitaxel NPs for treating patients with stage IV NSCLC.	64	Completed
NCT00553462	Phase II	Concurrent unresectable Stage III NSCLC treatment with carboplatin, paclitaxel albumin-stabilized nanoparticle formulation, radiation therapy, and erlotinib.	78	Completed
NCT04033354	Phase III	HLX10 + chemo (carboplatin-nab-paclitaxel) as 1st line treatment for stage IIIB/IIIC or IV NSCLC.	537	Active, not recruiting
NCT02769962	Phase I/II	Safety and efficacy of combining CRLX101 and olaparib in treating SCLC.	123	Recruiting
NCT04789486	Phase I/II	Nano-SMART: NPs with MR Guided SBRT in Centrally-located lung tumors.	100	Recruiting
NCT04486833	Phase I/II	Efficacy and safety of GPX-001+ Osimertinib in NSCLC patients.	158	Recruiting

Abbreviations: SCLC, Small-cell lung cancer; NSCLC, Non-small-cell lung cancer; SBRT, Stereotactic Body Radiation Therapy.

*The information were obtained from Clinicaltrials.gov database[141] and were classified by the authors.