

REVIEW PAPER

Innovations in nanoparticle-based drug delivery for lung cancer: recent developments and future horizons

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ABSTRACT

Lung cancer is a serious disease with a low overall survival rate due to delayed detection and ineffective conventional therapy. Advances in material science have led to the development of unique nanoscale-based theranostic agents, providing renewed hope for lung cancer patients. Nanocarrier-based drug delivery is an emerging modality for treating lung cancer, offering enhanced bioavailability, in vivo stability, better solubility, greater safety, and sustained, controlled targeted drug delivery. Various types of nanocarriers have been investigated against lung cancer, including liposomes, polymer-drug conjugates, NPs, micelles, dendrimers, carbon nanotubes, and nanofibres. This review aims to provide an overview of various receptors overexpressed in lung cancer, the various targeting approaches of NPs, and the therapeutic involvement of nanosized carriers as targeting tools for lung cancer treatment. It also highlights the progress in the development and design of nano carrier-based pulmonary as well as co-delivery systems, as well as insights into clinical trials, formulation challenges, and physicochemical characteristics of nanocarriers affecting their in vitro and in vivo performance.

Keywords: Nanoparticle, Lung cancer, Nanocarrier

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INTRODUCTION

The American Cancer Society predicts 609,820 cancer-related deaths and 1,958,310 new cases in the US in 2023, based on information from national cancer registries and the National Center for Health Statistics[1]. In 2020, breast and lung cancer were the most widespread cancer forms, with lung cancer leading the cause of 1.80 million fatalities, and 400,000 children receive annual cancer diagnoses[2,3]. Smoking is an essential risk factor for lung cancer, however variations in ethnic and geographic populations may indicate that other variables are also involved [4]. The International Agency for Research on Cancer [IARC] released its 2022 report, revealing a 20 million increase in cancer cases, despite a slight decrease in deaths from 9.96 million in 2020 to 9.7 million in 2022. The report also highlighted the potential role of air pollution in the rise in lung cancer cases[5]. The American Cancer Society conducted research that implies in the case that current incidence rates remain unchanged, there will be around 35 million cases of cancer worldwide by the year 2050. This increase is primarily due to ageing

populations and population expansion[6].

As illustrated in Fig. 1, there are two main categories of lung cancer according to the type of cells that give rise to the disease: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).

As per to the 2015 WHO classification, NSCLC can take a variety of forms. The most prevalent kinds are neuroendocrine tumors squamous cell carcinoma [SCC], and adenocarcinoma, which originates in glandular cells. Neuroendocrine tumors include carcinoid tumors, small cell carcinoma (SCLC), and large cell neuroendocrine carcinoma (LCNEC)[7]. There are two forms of small cell lung cancer: oat cell carcinoma and mixed SCLC. Treatment strategies differ according to the stage; common treatments with a view of treating are chemotherapy and radiation therapy[8,9]. Traditional medicine, particularly surgery, can be harmful to healthy cells, organs, and tissues, especially when combined with radiation therapy and chemotherapy for advanced stages of cancer[10]. Surgery is effective for lung cancer, but inadequate removal can cause recurrence. Chemotherapy and radiation therapy shrink tumors, reduce pain, and kill cancer cells, but can damage healthy organs[11]. An outline of the drawbacks and adverse consequences of conventional cancer treatments, as shown in Fig 2 [12].

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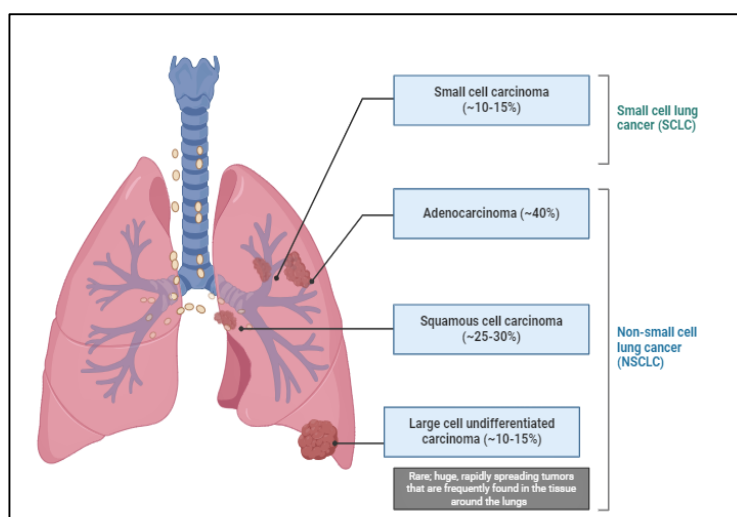


Fig.1.Two main categories of lung cancer.

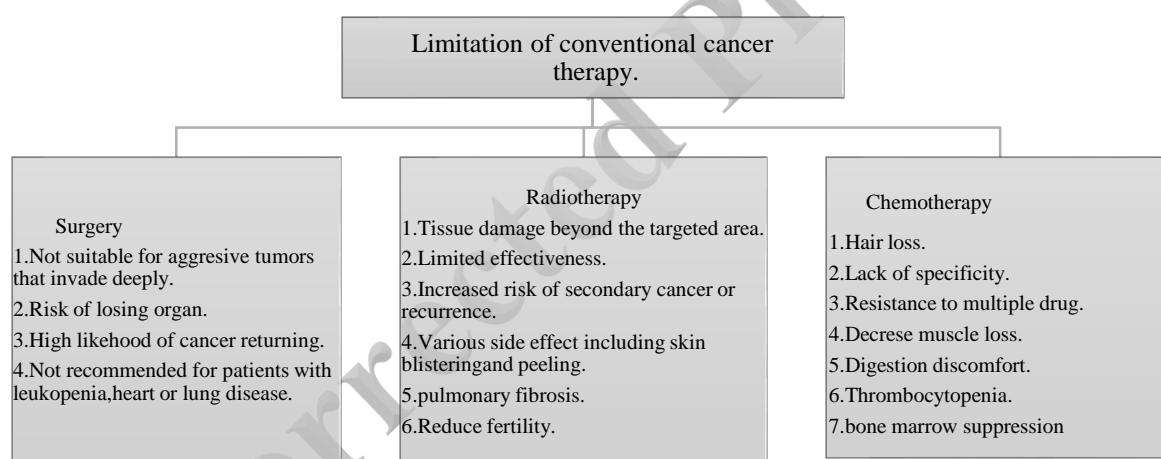


Fig.2.An outline of the limitations of conventional cancer therapy.

Traditional therapeutic techniques face limitations such as poor penetration, immune response aggravation, serum breakdown, quick clearance, and off-target side effects, often leading to treatment failure[13]. "The challenges require an innovative approach, including the use of nanoscale materials and nanotechnology integration, to offer a novel solution. The study aims to offer an extensive assessment of the state of our knowledge on the use of nanotechnology in diagnosing, treating, and managing lung cancer, highlighting its potential benefits and limitations, and presenting a novel solution to address challenges in this area." [14].

Nanotechnology

Nanotechnologies offer promising solutions to conventional cancer therapies, enhancing their effectiveness. These techniques enable targeted medication administration, increased intracellular

uptake, and precise navigation across tumor microenvironments. Nanoparticles (NPs) can target specific cell types and influence the immune system, making them potential for lung cancer detection and therapy[15].

Researchers are exploring the potential of nanomaterials in biomedical and therapeutic applications, focusing on small particles (1-100 nanometers) and larger ones [up to 500 nanometers] made from basic materials like metals, carbon, or polymers[16]. Nanoparticles (NPs) have been thoroughly studied for use in drug delivery systems and other cancer therapeutic applications. They are categorized into hybrid, inorganic, and organic classes based on their properties and composition each offering unique advantages and features for targeted and effective cancer treatment. Various types of NPs for cancer therapy as depicted in fig.3[17].

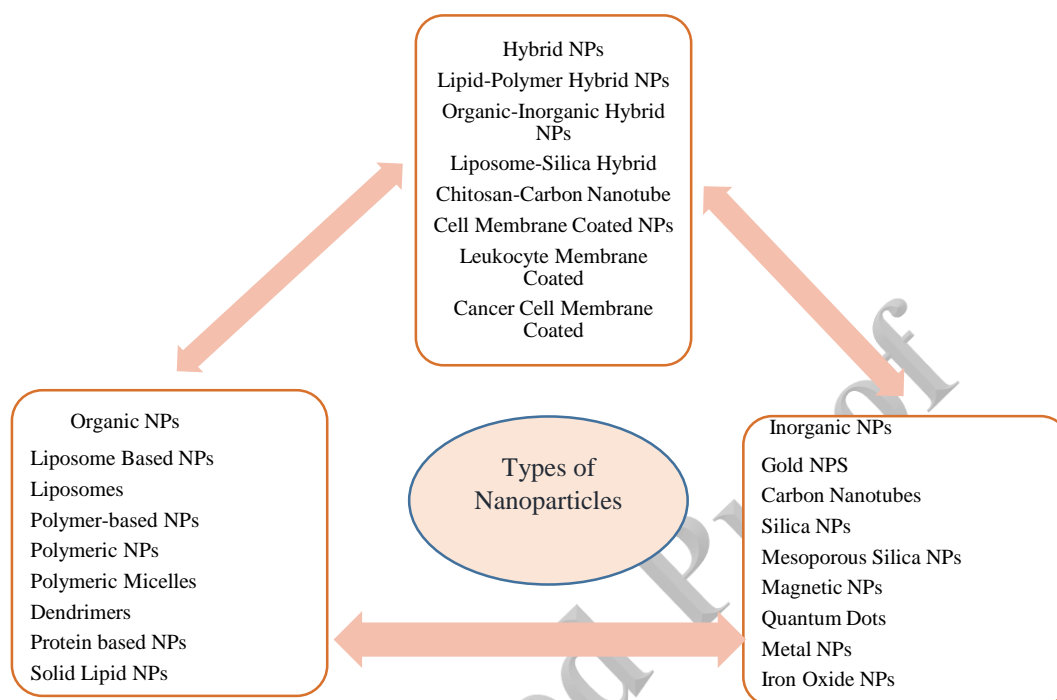


Fig. 3. Classification of NPs for cancer therapy: Hybrid, Inorganic, and Organic Types

Overexpressed receptors

The onset and spread of lung cancer are significantly influenced by the overexpression of certain receptors. Notably, Table 1 lists a number of important receptors that have been found to be overexpressed in lung cancer.

Targeting strategies of nanocarriers in lung cancer treatment

Targeted drug delivery systems (DDS) offer benefits like preserving healthy cells, reducing side

effects, and targeting drug-resistant cancer cells. The nucleus is often the ultimate target for treatments like cancer, neurological disorders, and cardiovascular diseases. NPs improve drug delivery by allowing selective cellular uptake and precise trafficking, ensuring therapeutic agents reach their intended sites in effective concentrations. However, internalizing a drug into the cytoplasm doesn't guarantee interaction with its subcellular target, so appropriate nanoparticle design and optimization are crucial for efficient nuclear and cellular targeting[68].

Table 1. Receptors that are overexpressed in lung cancer.

Sr.NO	Receptors	Overview	References
1.	Epidermal growth factor receptor (EGFR)	Tyrosine kinase inhibitors [TKIs] target EGFR, a key factor in lung cancer development, with a high response rate of 50%-77%, particularly in Asian patients with minimal smoking history. Over 85% of EGFR mutations are somatic, causing lung cancer.	[18–21]
2.	Growth hormone receptor (GHR)	The GHR signaling system significantly influences biological processes like cell cycle regulation, growth, and metabolism through JAK/STAT and SRC pathways. Membrane receptors release extracellular domains to control GH levels, and various lung cells express the GHRH gene.	[22,23]
3.	Folate receptor (FR)	The FR protein, found in kidneys, lungs, and intestines, is crucial for tumor growth and development, with FR α being more expressed in NSCLC. Human placental FR is essential for folate transfer.	[24–26]
4.	Vascular endothelial growth factor receptor (VEGFR)	VEGF and VEGFR are crucial for angiogenesis and cancer, with nicotine affecting VEGF signaling, promoting lung cancer cell survival, and understanding these mechanisms could aid in developing new treatments.	[27–30]
5.	Luteinizing hormone-releasing hormone (LHRH)	GnRH, the regulation of reproductive processes, is often overexpressed in various malignancies, leading to the development of targeted medication delivery techniques. LHRH receptor levels are typically too low in healthy organ cells.	[31,32]
6.	Fibroblast growth factor receptor (FGFR)	Lung cancer is linked to FGFRs, which regulate cell survival, proliferation, migration, differentiation, and metabolism. NSCLC is particularly affected by FGFR signaling disruptions. The human FGFR family consists of four receptor genes.	[33–35]
7.	CD44	CD44, a transmembrane glycoprotein found in cancer stem cells, affects lung cancer cell motility and invasion. Overexpression increases ZEB1 levels, reduces	[35–37]

Sr.NO	Receptors	Overview	References
		Claudin-1 expression, and enhances ERK phosphorylation, requiring further clinical research.	
8.	Integrin	Integrins, cell surface receptors in mammals, are responsible for generating 24 receptor types that communicate with cytoskeletal proteins and signaling chemicals. In NSCLC, 82% have integrins, while only 13% have $\alpha 3\beta 1$ overexpression.	[38–42]
9.	AXL	The AXL receptor tyrosine kinase, a member of the TAM family, represents a potential therapeutic target in NSCLC due to its role in tumor development, metastasis, and treatment resistance. Several AXL inhibitors are currently in clinical trials, including BGB324 [R428].	[43–45]
10.	Interleukin(IL)-22	Chronic inflammation-producing lymphocytes produce IL-22, a member of the IL-10 superfamily. High IL-22-R1 expression in cisplatin-resistant cell lines stimulates cell division. IL-22 is the most commonly expressed gene in 58% and 46% of lung cancer cases.	[46,47]
11.	Adenosine	The overexpression of adenosine receptors A3AR and A2aAR in lung cancers suggests their significant role in tumor growth and potential therapeutic targets, suggesting that adenosine plays a crucial role in lung cancer.	[48,49]
12.	Chemokine	G protein-coupled receptors (GPCRs) control cell migration in leukocytes. Elevated CXCR4 expression in advanced malignancies like ovarian, breast, head, neck, and NSCLC leads to poor prognosis and elevated risks of lymph node metastasis and tumor recurrence, with the CXCR4/CXCL12 axis being a key factor.	[50–53]
13.	Bombesin	The mammalian bombesin receptor family comprises BB1, BB2, and BRS-3, which affect signaling pathways like phosphatidylinositol turnover and ERK tyrosine phosphorylation, affecting NSCLC cell proliferation. Peptide receptor antagonists can stop cell proliferation.	[54–57]
14.	CD151	CD151, a protein found in various cells, is overexpressed in NSCLC, leading to aggressive tumor features and poor survival rates. Anti-CD151 monoclonal antibodies can prevent cell migration and metastasis in high-CD151 cancers, potentially paving the way for targeted antibody-based drugs.	[58,59]
15.	Sigma	Sigma receptors, initially opioid receptors, now belong to different protein classes with distinct pharmacological properties, and large-cell carcinomas like NCI-H1299 and NCI-H838 overexpress both types.	[58,59]
16.	Anaplastic lymphoma kinase (ALK)	The tyrosine kinase receptor known as ALK is encoded by the ALK gene. First-generation ALK inhibitor crizotinib has a limited overall CNS impact but is somewhat effective in treating CNS metastases in NSCLC. ALK inhibitors are permitted for use in IMT and metastatic NSCLC.	[60–65]
17.	ROS	The ROS1 gene, also known as MCF3, ROS, and c-ros-1, is crucial for controlling brain metastases in metastatic ROS1-positive NSCLC, with targeted treatments like entrectinib and lorlatinib.	[66,67]

Passive targeting

Low molecular weight drug-loaded nanocarriers ability to passively target tumors is limited by the pathophysiology and immunochemical environment of the tumor, which also affects how long the nanocarriers can stay at the tumor site. targeting the cellular and nuclear systems[69]. NPs aggregate in tumor tissues due to enhanced permeability and retention (EPR) effect, nanoparticle size, and tumor tissue features like leaky blood arteries and impaired lymphatic drainage[70]. Passively targeted nanocarriers are being used in medical applications like Genexol-PM in Korea, SMANCS in Japan, Myocet in Europe, Doxil in the US, and Onivyde in the US[71]. The therapeutic efficacy of nanocarriers is influenced by differences in EPR effect between and within tumors, with liposome-enclosed formulations like Lipoplatin showing significant nephrotoxicity reduction[72]. Lipoplatin with promising clinical results, may become a practical therapy for lung cancer in the future due

to its potential to promote metastasis through the epithelial-mesenchymal transition process[73,74]. Therapeutic NPs, like Salinomycin, have been shown to significantly suppress EMT in lung cancer cells, decreasing migration capacity without negatively impacting cell proliferation[75]. Silver NPs can suppress EMT-mediated spread of lung cancer cells by administering therapeutic drugs like gallic acid, demonstrating that passive targeted drug delivery systems can treat almost all rapidly growing solid tumors[75,76].

Active targeting

Active targeting involve altering NPs through biomimicry or surface modification, allowing targeted cells to absorb ligands like antibodies, proteins, peptides, nucleic acids, vitamins, carbohydrates which bind to overexpressed receptors in sick organs or tissues[77]. Various types of targeting ligands their structures, benefits, and drawbacks is reflected in Table 2.

Table 2. Various types of targeting ligands: Overview of their structures, benefits, and drawbacks.

Targeting ligand	Drawbacks	Benefits	Structure	References
Folic acid	Limited capacity for transport and constrained targeting capabilities.	Compact size, simplistic chemical structure, secure for living things, and affordable prices.	A three-part water-soluble vitamin that is formed by glutamic acid, p-aminobenzoic acid, and pteridine.	[84]
Antibodies	High the development expenditures and complications with modification of chemicals.	Strong immunogenicity, minimum cross-reactivity, excellent levels of purity, sensitivity, and precision.	A type of immunoglobulins that affix itself to antigens.	[85]
Carbohydrates	fluctuations in targeting and affinity along with structural complexities.	Existing naturally, getting associated with biological systems, and reflecting a variety of structural diversity.	organic compound consisting of atoms of hydrogen, carbon, and oxygen.	[86]
Peptides	Short duration of action, high the manufacturing costs, and uneven stability.	Adaptable and capable of biodegrading effortlessly.	Molecules which are produced when 10–100 amino acids are dehydrated and condense. They are moderately flexible.	[87]
Aptamers	Weakened metabolic instability and immunogenicity.	It's easy synthesizing, outstanding specificity and affinity, replicability, and chemical modification amenability.	A brief oligonucleotide sequence or brief polypeptide found via in vitro screening; high affinity and specificity; obvious to synthesis.	[88]

Active targeting involves specific biological interactions between NPs and target cells, unlike passive targeting which relies on EPR. Several biological ligands have been studied for improved targeting[78]. Biological ligands bind to specific cell surface receptors, enhancing therapy efficacy by increasing cellular absorption of drug-loaded NPs[79]. Active targeting systems aim to reduce toxicity by directing NPs to malignant tissue. A CSNP-RGD formulation was developed for NSCLC treatment. The formulation, containing polyvinylpyrrolidone-coated gold NPs with conjugated doxorubicin, showed enhanced intracellular release and penetration in lung cancer cells. Quantum dots (QDs) have unique optical properties and can be functionalized with proteins, making them useful for tumor detection, staging, prognosis, and treatment[80–83].

Stimuli responsive targeting

Recent developments have developed stimuli-responsive nanocarriers which may alter their size, charge, and conformation in response to pathological and physicochemical conditions in disease sites. They can also control the release of medications, activate bioactive compounds, probes, and ligands, and target them. These attributes facilitate sensing and signaling processes, allow for accurate assessments and healthcare goods, and overcome multidrug resistance[89]. The increasing number of proof-of-concept studies has significantly enhanced the toolkit for efficient drug delivery systems in cancer treatment[90]. Fig 4. Shows stimuli responsive nanoacacrier used for cancer therapy.

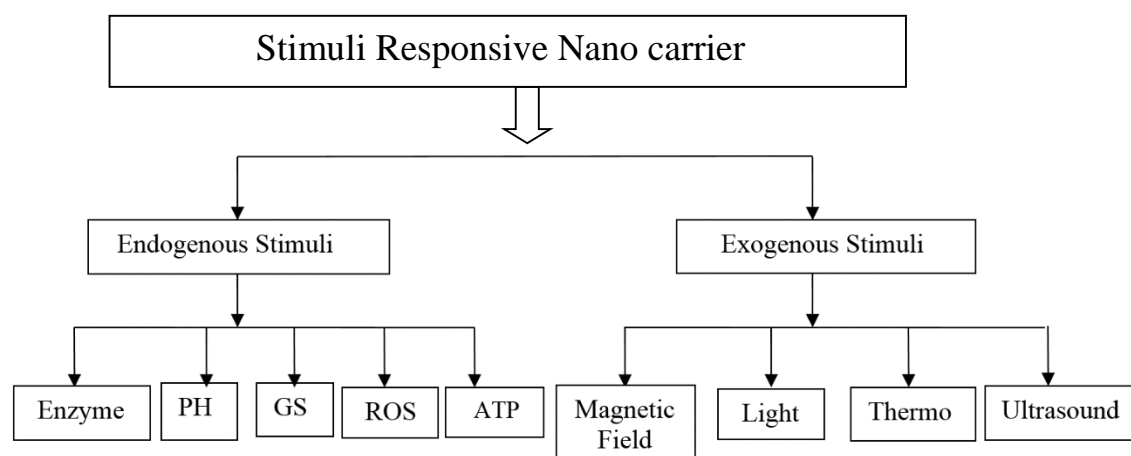


Fig.4. Stimuli responsive nanocarrier for cancer therapy.

pH responsive systems

The minimize pH of tumor microenvironments allows for more effective drug delivery through pH-responsive delivery systems, targeting the acidic tumor microenvironment and cancer cell metabolism, thereby enabling targeted treatment of malignant tumors[91]. pH-responsive NPs are effective at pH values below 6.5, crucial for clinical outcomes. Enhancing sensitivity is essential due to tumor microenvironments occurring at pH levels between 6.8 and 7.2, allowing medication release similarly[92].

Enzyme responsive systems

Enzyme-responsive NPs show potential for tackling drug accumulation in inflammatory or tumorous regions through modifications to enzyme activity. Targeting particular biological regions, these alterations have the ability to initiate drug release mechanisms. The overexpression of enzymes in malignant cells and tissues presents a unique opportunity for the development of enzyme-responsive materials [ERMs] that provide photosensitizers to tumor cells and tissues only. Several ERMs that combine the selectivity of enzyme response with the features of nanomaterials have been researched and generated, offering a number of benefits[93,94].

Thermo responsive systems

Thermoresponsive nanocarriers have demonstrated superiority in increasing intracellular DOX levels, optimizing DOX targeting to mitochondria, and augmenting DOX accumulation in malignancies. In cellular and mouse models of DOX-resistant small-cell lung cancer, effective resistance reversal was achieved through thermoresponsive transportation [95]. Thermoresponsive carriers, like polymeric micelles, liposomes, or NPs, are designed to be inert at normal body temperatures but efficiently release medications in high-temperature environments like malignant tumors, retaining the drug payload at body temperature[96].

Nanocarrier-mediated drug delivery systems for lung cancer

Several kinds of nanocarriers employed for lung cancer therapy are reveals in the fig. 5. These encapsulated medications have gained widespread popularity due to their increased in vivo efficacy and controlled medication release. Currently, a variety of synthetic, semi-synthetic, and natural nanomaterials are used as for drug delivery vehicles [97]. Table 3. Illustrates multiple nanocarriers for targeted therapy of lung cancer.

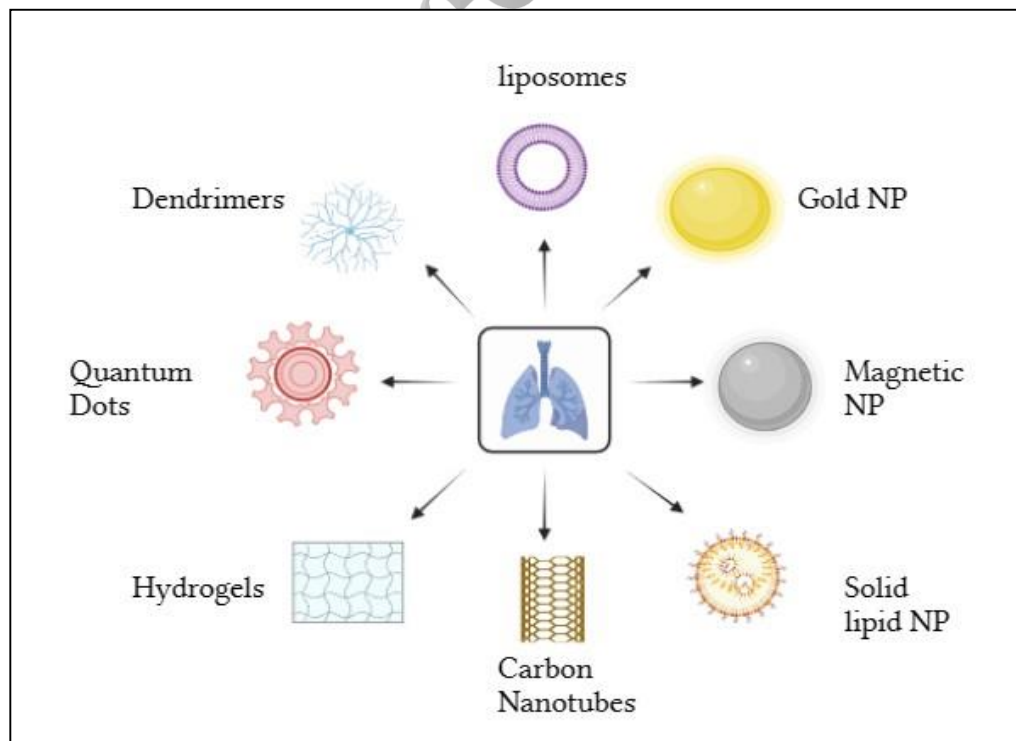


Fig.5. Various types of nanocarriers Utilized in Lung Cancer Therapy.

Table.3 Nanocarriers for lung cancer targeted therapy.

Sr.No	Nanocarrier	Anticancer drug	Particle size (nm)	Cell Line	Remarks	References
1.	PEGylated large liposome	Paclitaxel	183 ± 29.1	LL2, A549	Decreased painful neuropathy and antitumor activity	[98]
2.	Peptidomimetic conjugate (SA-5)liposome	Doxorubicin	107.19 ± 2.90	BT-474, MCF-7, A549	Antiproliferative activity	[99]
3.	Liposome modified with CPP33 peptide and monoclonal anti-CA IX antibody	Triptolide	137.6± 0.8	A549	Targeting specific tumors and boosting tumor cell penetration without affecting the general health.	[100]
4.	Transferrin-conjugated SLN	Doxorubicin	286.5±3.9	A549	Enhances anticancer efficacy	[101]
5.	PEGylated polypeptide lipid nanocapsules	Erlotinib	182± 25 100±20	HCC-827 and NCI-H358-20	Improved cell toxicity was noted in a contrast with erlotinib on its own, without the drug being loaded into a nanocarrier.	[102]
6.	Folic acid nanostructured lipid nanocarrier	Doxorubicin,sorafenib	-	-	The substance aids in overcoming the obstacles posed by the tumor microenvironment, enhances the immune response, and enhances cytotoxicity.	[103]
7.	Folic acid conjugated si-RNA Complexed Drug-Loaded Mesoporous Silica NPs	siRNA, myricetin	161± 3	NCI-H1299,A549	The substance accumulates in the tumor microenvironment (TME) and inhibits colony formation by increasing the radio sensitivity of cancer cells.	[104]
8.	Folic acid conjugated polyamidoamine dendrimers	siRNA, cis-diamine platinum	280±14.5	H1299,A549, MRC9.	Recommended for delivering siRNA and cytotoxic agents together	[105]
9.	Transferrin nanostructured lipid carriers .	Enhanced green fluorescence protein containing plasmid	157.3 ± 4.9	A549	Delivery of medications via gene targeting	[106]
10.	Multiwalled carbon nanotubes coupled with bromocriptine	Bromocriptine	26.3± 6.3	(A549 & QU-DB)	Proliferation of cancer cell in the tumor microenvironment(TME)increases their radiosensitivity, limiting colony development	[107]
11.	Porous Au-Pt NPs	Doxorubicin	85.3 ± 4.8	MDA-MB-231cell	Porous Au-Pt NPs modified with cRGD and loaded with doxorubicin exhibit better anticancer activity and superior drug release patterns.	[108]
12.	Aluminum (III)phthalocyanine chloride tetrasulfonic acid and anti-CD133 bioconjugated goldNP	Gold NP	63.91±5	A549	The gold NPs' photothermal activity gets improved by the bioconjugate	[109]
13.	QDs	Doxorubicin	14±4.8	A549	Enhanced cytotoxicity, genomic toxicity, and migrating inhibitory effectiveness against A549 lung cancer cells were shown by the modified QD nanocrystals	[110]

Liposomes

These NPs, which are primarily made up of phospholipids, form both multilamellar and unilamellar vesicular structures. Hydrophilic or hydrophobic drugs may be included in liposomes of this composition. It's fantastic that both types of drugs can be contained in a single nano-formulation, as this increases the drug's efficacy and diversity [111]. Liposomal versions of approved lung cancer medications like erlotinib, vinorelbine, cisplatin, ETP, DOX, paclitaxel, IRI, and epirubicin are being developed for potential chemotherapeutic interventions [112–114]. Liposome-encapsulated immuncheckpoint inhibitors (ICIs) have potential in treating various tumors, including lung cancer, ovarian cancer, and melanoma renal cell carcinoma can be combined with other anticancer medicines [115]. Liposomes are formed by dissolving phospholipids in organic solvents and loading them using techniques like microfluidics, reverse phase evaporation, dehydration-rehydration, and thin lipid film hydration[116].

Paclitaxel, a common lung cancer drug, can cause peripheral neurotoxicity, resulting in the discontinuation and failure of treatment. Encapsulating PTX in large cationic liposomes, SUV and MLV, with a polyethylene glycol coating, may mitigate this effect and improve patient outcomes. This approach offers a promising new strategy for lung cancer chemotherapy, with direct inhalable medication delivery offering advantages like minimal impact, less intrusiveness, comfort, and smaller dosages. Lipid-based micro- and nanocarriers are widely used for NSCLC treatment[117]. Sawant et al. created inhalable OB liposomes to administer osimertinib to lung cancer tumor sites. They used active and passive loading techniques, achieving 78% drug encapsulation efficiency and 82% aerosolization. The liposomes significantly reduced IC50 values in vitro and demonstrated anti-cancer activity, inhibiting tumor growth using 3D spheroid technology, indicating potential for localized medication delivery[118].

A two-step procedure was used to create a targeted liposome (HA/TT LP/PTX) to target mitochondria selectively in treating NSCLC. The

HA/TT LP/PTX formulation showed improved stability and safety compared to uncoated cationic liposomes. This mitochondrial targeting increased apoptosis and improved anticancer efficacy in disrupted cells, overcoming multidrug resistance in the treatment of NSCLC [119].

Advancements in liposome-based medications enable precise delivery to beneficial sites, tackling therapeutic resistance and improving lung cancer treatment by minimizing negative impact on tissues and healthy cells.

Solid lipid nanocarrier

Solid lipid NPs [SLNs] are biocompatible with human tissue, improving drug delivery routes, safety, bioavailability, therapeutic efficacy, circulation time, and enzyme breakdown [120]. SLNs offer benefits like low water absorption, biocompatibility, reduced erosion susceptibility, and loading of hydrophobic and hydrophilic medicines. They are taken up by cells via endocytosis, and can be modified with specific targeting moieties to improve treatment targeting compared to traditional, non-specific medications[121]. Researchers have found that SLNs can enhance the absorption of anti-tumor medications like doxorubicin, etoposide, and idarubicin in rats[122]. The drug's pharmacokinetic features, including maximum plasma concentration and mean residence time were linked to this accelerated absorption. The addition of paclitaxel to SLNs reduced its inhibitory concentration against M109HiFR lung cancer cells [123,124]. Shehla Nasar et al. developed Bedaquiline-Loaded SLNs for lung cancer treatment using UPLC-MS/MS technology. The formulation, with a polydispersity index of 0.324 and particle size of 144 nm showed promising pharmacokinetic properties, decreased tumor volume, and enhanced BQ accumulation in lung tumors. It maintained gastrointestinal stability at pH 1.2 and 6.8, and showed long-term stability at 25°C and 60% relative humidity. The IC50 value was 3.46 times lower than BQ suspensions [125]. Table 4 shows some products that are presently on the market that make employing solid lipid nanoparticle technology [126].

Table 4. The current marketed products utilize solid lipid nanoparticle technology.

Trade name	Producer	Drug	Delivery Route	Field of Use
Cipro	Bayer HealthCare Pharmaceuticals Inc.	Ciprofloxacin	Oral	Pharmaceuticals
Mucosolvan Retard	Boehringer	Ambroxol	Oral	Pharmaceuticals
Nanobase	Yamanouchi	-	Dermal	Cosmeceuticals

Table.5. Effective Drug Delivery Techniques for Lung Cancer Using Dendrimers.

Class of Dendrimer	Drug	Cell Line	Remark	References
PAMAM [poly(amidoamine)] dendrimer	Doxorubin (DOX)	Mouse melanoma cell line (B16-F10)	significantly reduced lung nodules compared to intravenous delivery, enhancing chemotherapy effectiveness.	[130]
PAMAM [poly(amidoamine)] dendrimer G3.5	Cisplatin	NCI-H460 cells	cisplatin-loading capacity was enhanced, allowing for precise drug release and increased drug retention, while its biocompatibility and effective tumor cell inhibition were achieved in an acidic tumor environment.	[131]
Folic acid-conjugated PAMAM dendrimer	-	SPC-A1 cells	Au DENPs-FA, which are dendrimer-entrapped gold NPs modified with folic acid, significantly enhanced the visibility of SPC-A1 cells, a human lung adenocarcinoma cell line.	[132]
PAMAM	Endosialidase	NCI-H69 and SW2 cells.	Small-cell lung cancer cells exhibit good binding stability to surfaces immobilized with EndoNt. EndoNt showing better capture effectiveness than aEpCAM under flow conditions.	[133]
Peptide-conjugated dendrimer	Paclitaxel	NSCLC cell lines 293T and L132.	The compound, encapsulated with a 25% loading capacity, demonstrated a 95% encapsulation efficiency and a potent antiproliferative effect on L132 and 293T cells relative to free PTX.	[134]
PEGylated-PLL (poly L-lysine) dendrimers	Doxorubicin	-	Doxorubicin, when incorporated with dendrimer, significantly reduces lung-related toxicity when administered intratracheally compared to an effective dose of doxorubicin solution.	[135]
Mannose-conjugated PPI [poly(propyleneimine)] dendrimer	Gemcitabine	A-549 lung adenocarcinoma cellline	The formulation showed improved medication loading and higher cytotoxicity against A-549 cell lines, indicating potential as a targeted drug delivery technique for lung cancer.	[136]

Dendrimers

Nanoscale molecules referred to as dendrimers have unique chemical and physical properties which allow regulated growth and make them highly compatible with biological systems. They enable significant drug payloads and effective tissue accumulation in drug conjugate applications in medicine and biology. Advanced uses of dendrimers, such as gene transfer, boron neutron capture therapy, and MRI contrast agents, are also being explored [127].

Dendrimers, such as polyamidoamine (PAMAM) and polypropylene imine (PPI), are studied for their hydrophilic, biocompatibility, and non-immunogenic properties. PAMAM uses a divergent approach, PPI uses double Michael addition processes, and PL has an asymmetrical structure. Phosphorus-based dendrimers are promising for cancer treatment, and carbosilane dendrimers have antimetastatic properties [128].

Dendrimers are essential in cancer diagnosis, enhancing MRI imaging and targeting cancers. They also aid in immunodiagnostics by producing visible signals when antibodies attach to antigens. Their higher density of light-emitting molecules increases immunodiagnosis sensitivity, making them a valuable tool in cancer research [129]. Table 5 shows successful drug administration techniques for lung cancer using dendrimers.

QDs

Nanoscale semiconductor crystals called QDs (QDs) have unique optical and electrical characteristics, like chemically reactive surfaces and near-infrared emission. Biomedical applications like as drug delivery, therapy, and imaging utilize them more and more [137]. QDs have surface activation, photoluminescence quantum yield, and stability in chemical and photoreaction reactions. They are composed of up of a surface coating, a shell, and a core. Photostability, decay kinetics, and fluorescence quantum yield are all affected by the shell's stabilizing effect on the core. Stability, dispersibility, and biological interactions are all governed by the surface layer. Both hydrophilic and hydrophobic QDs are achievable. Fig.6 Represents a shortened picture of a quantum dot [138].

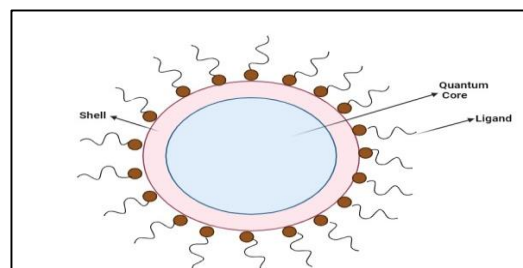


Fig.6. Simplified illustration of a quantum dot.

Three main types of QDs are semiconductors (II–VI), semiconductors (III–V), and silicon. Materials like InAs, GaAs, and GaN are semiconductors (III–V), whereas PbSe, CdTe, and CdSe are semiconductors (II–VI). Conventional silicon, which is used in the semiconductor and chip sectors, turns into silicon QDs. These materials are usually used to create the core of QDs, which are then covered with a broad band-gap semiconductor shell to improve quantum yield and reduce surface defects [139]. QDs offer potential benefits in the management of lung cancer, the eradication of pulmonary arterial hypertension, and the fight against bacteria linked to pulmonary infections. According to research by Sun et al., QDs can prevent lung cancer cells from expressing the P-glycoprotein gene and protein, which is connected to multidrug resistance. Since miR-185 and miR-34b mediate this impact, QDs might be effective targets for lung cancer treatment [140].

Huang and colleagues developed Si QD micelles which are water-dispersible (CKAP4), with a 78.8 nm average diameter and a strong 640 nm fluorescence. These spherical micelles successfully targeted lung cancer cells and tissues in vitro and in vivo, implying promise as a fluorescent contrast agent for surgical navigation in lung cancer treatments [141].

Magnetic NPs

Chemotherapy drugs are non-specific and may harm cancer-causing as well as healthy cells. By developing an external magnetic field once released, magnetic NPs [MNPs] can be employed to precisely transport medications to the desired location. MNP-based controlled drug delivery systems can control medication levels, reduce adverse effects, and prevent overdoses [142]. Currently, direct intra-tumoral injection is necessary for the use of MNPs, limiting their clinical applicability. The development of targeted surface coatings for superparamagnetic iron oxide NPs could improve the selectivity of nanoparticle distribution to tumor cells [143]. Due to its favorable physicochemical characteristics, such as superparamagnetism, distinct behaviors, and structural features, as well as their biocompatibility, stability, low toxicity, and many other uses, iron oxide MNPs are often used in the medical sciences [144]. MNPs can transport targeted ligands, fluorophores, and responsive components for a variety of biochemical uses in addition to medications as expressed in fig. 7.

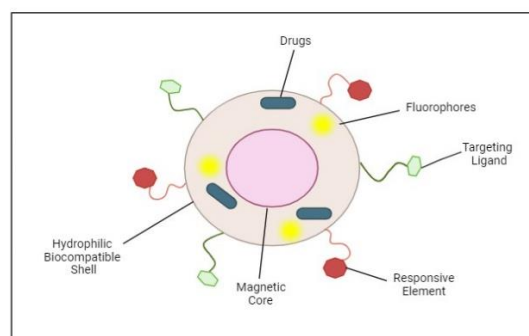


Fig. 7. An illustration of the general structure of a magnetic nanoparticle.

MNPs offer prevention and monitoring through MRI and specific sensor devices, making them potential for cancer screening, diagnosis, and treatment. They can also be deployed as medication delivery devices in cancer therapy, which will improve treatment results [145]. Lung cancer is being managed with magnetic particle targeting, which targets particular tissues and lowers drug accumulation [146]. An alternating magnetic field can be used to remotely heat the embedded iron oxide MNPs in magnetic nanocomposite microparticles. This makes thermal therapy an excellent way to treat lung cancer since it enhances particle movement, activates medications, and induces hyperthermia [147].

The study investigates the heating efficiency of MNP clusters coated with polyacrylic acid under an alternating magnetic field. It has been shown that this approach can delay the growth of tumors in vivo and radiosensitize NCI-H460 human lung cancer cells. Pulsed electromagnetic fields may cause lung cancer cells to die. Ferucarbotran, an MRI contrast agent, and doxorubicin-loaded porous MNPs with a polyethylene glycol coating have shown promising results against human lung adenocarcinoma cells [148–151].

Polymeric NPs

Polymeric NPs [PNPs] are crucial in cancer treatment, enhancing drug delivery, improving tumor retention, reducing cytotoxicity, and ensuring prolonged drug release when combined with anticancer medication or encapsulated [152]. Polymeric NPs, including PLA, PLGA, PGA, PCL, and acrylic acid, are crucial for targeting malignant cells. Fig. 8 illustrates various polymers employed in the preparation of PNPs on the basis of origin and degradability. PLGA, a biocompatible and biodegradable polymer, has been authorized by the FDA and EMA for use as an injectable medication delivery vehicle [153]. Due to their outstanding efficacy and few side effects, PLGA NPs have an exciting future in the treatment of cancer [154].

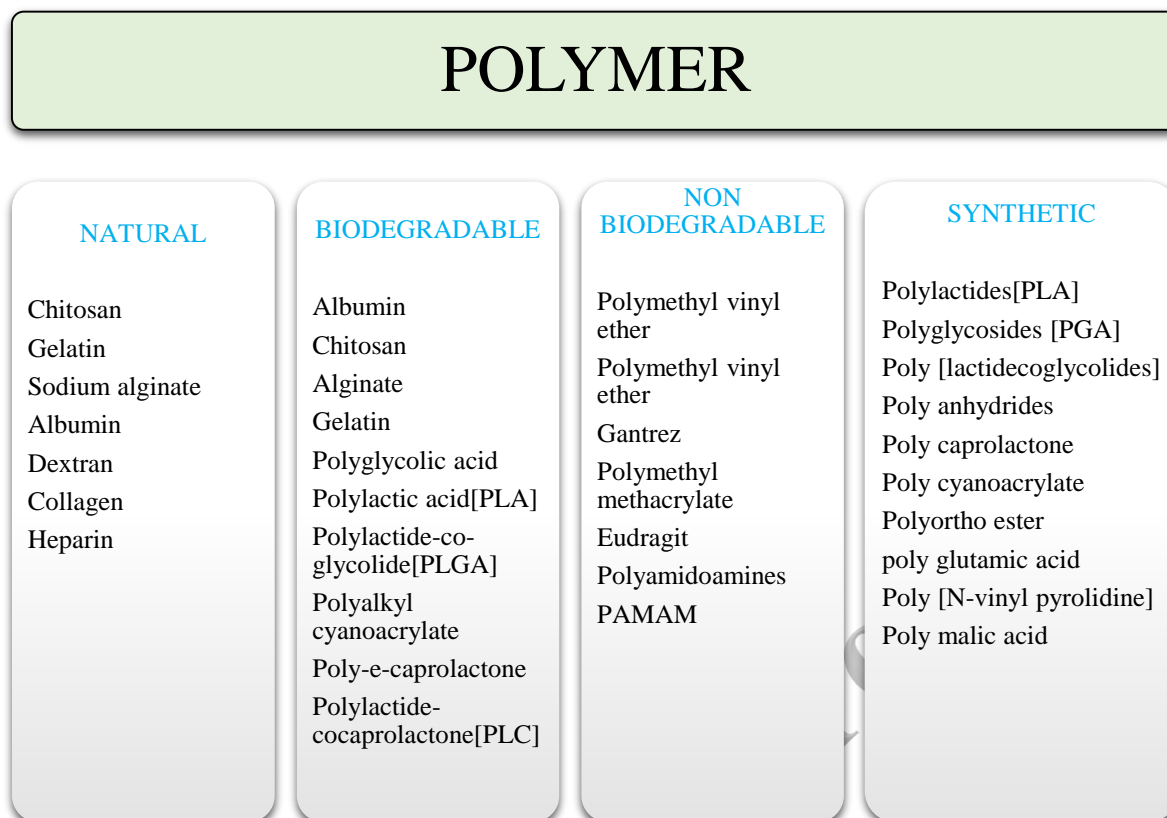


Fig.8. Illustrates various polymers employed in the preparation of PNPs.

Techniques like emulsification, supercritical anti-solvent method, nanoprecipitation, solvent evaporation and salting out are essential for producing PNPs, which can be referred to as nanospheres or nanocapsules [155].

Jiang et al. have developed a polylactide-tocopheryl polyethylene glycol 1000 succinate PLA-TPGS-based nanosystem for delivering crizotinib, a hydrophobic drug, to improve its anticancer efficacy in therapy of lung cancer, demonstrating its stability and ideal characteristics for cancer treatment [156]. Kim et al. have developed therapeutic NPs, Genexol-PM, for lung cancer treatment, currently undergoing Phase II clinical trials for advanced non-small cell lung cancer [157].

Wang and his team created a nanodrug delivery system using paclitaxel and baicalein prodrugs, conjugated with a PLGA polymer core. In vitro cytotoxicity experiments showed PTX-BCL NPs had greater lethal effects and reduced cytotoxicity. This highlights the potential of PNPs in developing effective chemotherapeutic formulation[158].

Micelles

Micelles are formed when polymer concentrations are higher than the critical micelle concentration. These micelles give MNPs improved

pharmacokinetics, biocompatibility, adherence, targeted distribution, and extended stability, which makes them beneficial in biomedical settings [159]. Polymeric micelles [PMs] are being explored for cancer treatment due to their surface functionalization, stability, responsiveness, drug release regulation, and improved penetration and retention, and their potential as nanocarriers [160]. Micelles are utilized in cancer treatments due to their unique properties, such as response to stimuli like pH, temperature, light, or enzymes, and their increased permeability and retention [161]. PMs made of polyesters and polyamides, are crucial for therapeutic applications due to their biocompatibility and biodegradability. Clinical trials have advanced various PMs technologies, including Genexol-PM, paclitaxel, and formulations like NK105, SP1049C, and NK911. Phase I clinical studies have also been completed [162].

PEG-PLA copolymer-based micelles have higher concentrations in tumor tissue and better anticancer activity, Korea approved them in 2007 for use against breast, lung, and ovarian cancers. One such medication is Genexol®-PM [163]. Guthi et al. have created a prototype multifunctional micelle system using a lung cancer-targeting peptide, enabling magnification detection and

improved cell targeting and micelle uptake compared to SP-encoded MFM or $\alpha\beta 6$ -negative H460 cells [164].

Zhang et al. created a nanomicelle-microsphere composite system by modifying PEG-PCL micelles with spermine and doxorubicin. The system showed improved cytotoxicity and cellular uptake in vitro and in vivo in C57BL/6 mice. It also demonstrated efficient tumor targeting and increased DOX accumulation in the lungs, suggesting potential for targeted lung cancer therapy [165]. Many micellar formulations are now being investigated in different phases to treat lung cancer. The purpose of these trials is to look at potential benefits of micellar drug delivery methods in oncology. Table 6 provides an overview

of the specific data related to these clinical studies. The data was retrieved from clinicaltrials.gov on July 30, 2024.

Carbon nanotubes

Carbon nanotubes (CNTs) are unique carbon allotropes with electronic polyaromatic framework, high surface area, and chemical stability, making them potential drug carriers for biomedical uses, including cancer treatment, enhancing treatment efficacy and reducing traditional medication side effects. Fig. 9 illustrates the properties of carbon nanotubes, which are designed to target cancer cells, thereby increasing treatment efficacy and reducing the negative effects of traditional medication molecules [166].

Table 6. Overview of clinical trials investigating micellar drug delivery for lung cancer.

Sr.No	Drug	Condition	Status	Phases	NCT NO	Location
1.	Paclitaxel	Lung cancer	Recruiting	Phase2	NCT06199895	China
2.	Paclitaxel	Non-squamous NSCLC	Not yet recruiting	Phase2	NCT05782426	China
3.	Pegsitacianine	Lung cancer	Completed	Phase2	NCT05048082	United States
4.	Paclitaxel	Advanced Solid Tumors	Recruiting	Phase1	NCT04778839	China
5.	ONM-100	NSCLC	Completed	Phase2	NCT03735680	United States
6.	Paclitaxel	NSCLC	Unknown	Phase3	NCT02667743	China
7.	Genexol-PM/Gemcitabine	NSCLC	Completed	Phase2	NCT01770795	Republic of Korea
8.	Paclitaxel	NSCLC	Completed	Phase2	NCT01023347	Republic of Korea

NSCLC: Non Small Cell Lung Cancer, ONM-100:Oncogenic Nanoparticle Marker.

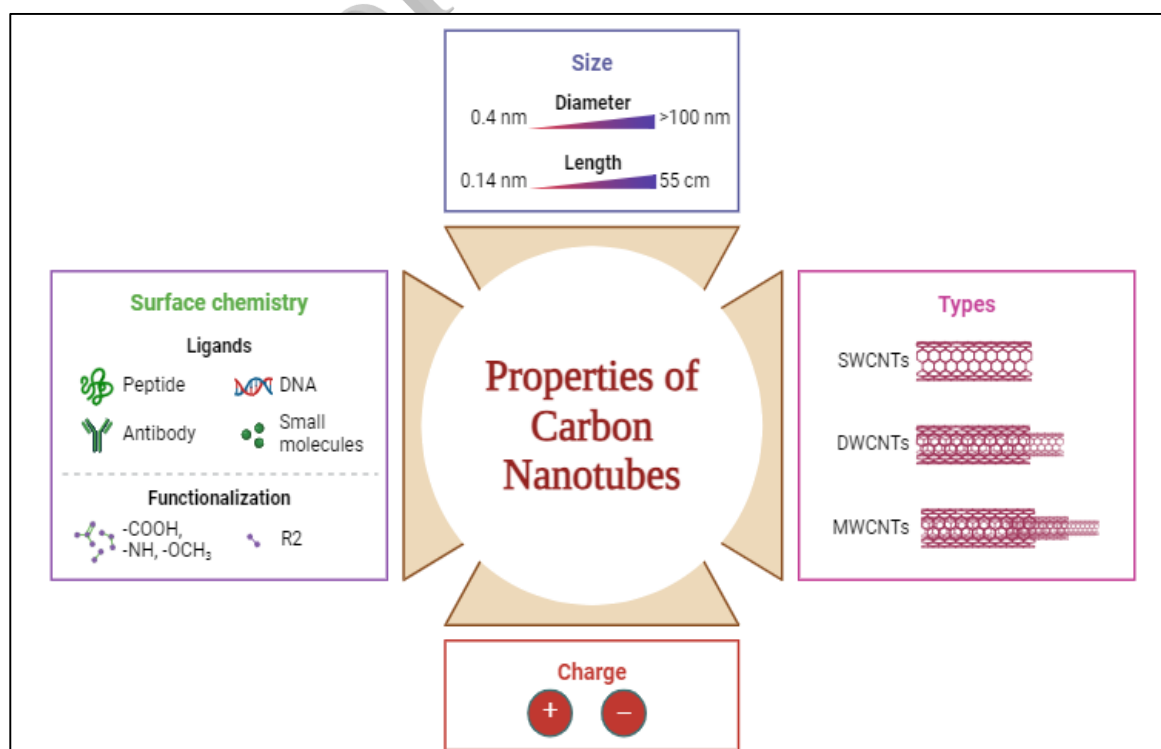


Fig.9. Highlights the characteristics of carbon nanotubes designed to specifically target cancer cells.

EGFR inhibitors are cancer drugs that inhibit the interaction between EGFR and its ligands, potentially aiding in the treatment of certain cancers [167]. Single-walled nanotubes with outer diameters from 4 and 20 Å and multi-walled nanotubes with diameters from 20 and 1000 Å are two distinct types of nanotubes [168]. CNTs can induce cancer cell apoptosis by targeting

mitochondrial organelles, with enhanced precision when functionalized with polyethylene glycol, varying based on CNT type, drug administration, and targeted proteins.

Table 7 represents investigations based on targeted proteins, medication delivery, and CNT type.

Table 7. Researches based on CNT type, drug delivery, and targeted proteins.

Type of carbon nanotubes	Drug/Protein	Outcome	References
Single Wall Coated	Paclitaxel	A nanostructure combining graphene oxide and SWCNTs with paclitaxel has been developed, enhancing the drug's activity and promoting cell death in A549 and NCI-H460 cancer cells.	[169]
		Paclitaxel is enhanced in vivo by incorporating chitosan-modified SWCNTs, and a layer of hyaluronic acid and chitosan is mixed to precisely target A549 cells.	[170]
	TRAIL	TRAIL, a cancer cell apoptotic protein, can be enhanced by combining it with SWCNTs, enhancing its solubility in the bloodstream, thereby expediting the removal of pulmonary malignancies.	[171]
	Doxorubicin	Doxorubicin's improved drug distribution and magnetic localization may enhance targeting and increase therapeutic efficacy, as demonstrated in mice studies, supported by MRI techniques.	[172]
	Curcumin	A 2018 study found curcumin nanoform, functionalized with alginate polysaccharides and chitosan, may have therapeutic effects against A549 cancer cells when used as a carrier.	[173]
	Survivin siRNA and Doxorubicin	A 2019 study demonstrated that using doxorubicin and survivin siRNA with a SWCNT carrier can increase apoptosis by inhibiting survivin expression, with polyethyleneimine and betaine functionalized to enhance carrier efficacy.	[174]
Multiple Wall Coated	Gemcitabine	A clinical trial on gemcitabine, found that SWCNTs, with their high drug-loading capacity, long distribution time, and cell membrane permeability, are efficient drug delivery vehicles, demonstrating their potential in treating NSCLC.	[175]
	SiRNA	CNTs have proven anticancer properties and are effective in therapeutic treatments. In animal models, MWCNTs functionalized with NH ₂ and siRNA improve cell survival and suppress tumor growth. Targeting the Polo-like Kinase gene is suggested as a lung cancer treatment option.	[176]
		Hyaluronic acid and MWCNTs were combined with doxorubicin, a cancer-inhibiting drug, to enhance apoptotic effects on A549 cancer cells, without toxicity to liver, heart, or kidneys.	[177]
	Doxorubicin	Lodhi et al. found that MWCNTs, when combined with Dexamethasone and Doxorubicin HCL, can effectively target epithelial cancer cells, enhancing their cytotoxicity and reducing hemolytic effects.	[178]
		Methotrexate and MWCNTs can effectively treat lung cancer, reducing waste and improving drug delivery precision, with no harmful effects on kidney, liver, or heart.	[179]
	Methotrexate	chitosan-coated carbon nanotubes as methotrexate transporters, enhancing its anti-tumor efficacy against lung cancer cells (H1299) and reducing its toxicity to healthy lung cells (MRC-5).	[180]
	Cisplatin	Li et al. found that conjugating MWCNTs with cisplatin enhanced treatment efficacy, reduced liver and renal toxicity, and expedited platinum build-up in target organs like the lungs.	[181]
	Betulinic Acid	UV light and thermogravimetric analysis can evaluate the anti-cancer properties of betulinic acid-loaded MWCNTs, with lung cancer cells showing increased susceptibility to specific doses.	[182]
	Docetaxel	Singh et al. found that docetaxel combined with a MWCNT carrier with transferrin protein was 136 times more effective than alone, and its absorption was greater in A549 cancer cells.	[183]
		It was discovered in 2017 that docetaxel was 89 times more effective at targeting A549 cells when loaded onto MWCNTs together with chitosan-folate.	[184]
	Etoposide	The study utilized functionalized MWCNTs to deliver Bcl-2 and VP-16 antisense medicines, aiming to enhance their anti-cancer efficacy in various lung cancer cell types.	[185]

Hydrogels

Hydrogels are biocompatible, biodegradable, and hydrophilicity polymers used in medical drug delivery. They encapsulate hydrophilic drugs, providing sustained release. Engineered devices reduce administration frequency and enhance patient compliance. Nanocarriers enhance control, flexibility, and mechanical strength [186].

Hydrogels, in various forms like microparticles, NPs, micelles, and films, are vital for the distribution of drugs into the human body. The size of these particles affects their release route, and drug immobilization within a polymer matrix ensures controlled release. Various therapeutic benefits have been developed for in vitro and in vivo applications [187].

Lee et al. developed a multifunctional hydrogel formulation containing Gold(III) Amino-Functionalized Porphyrin (AUP) in an Interpenetrating Network (IPN) system for targeted local delivery against human lung cancer cell lines, inhibiting tumor development and reducing angiogenesis in mice, without systemic toxicity [188].

Researchers are developing an intravenous hydrogel-based drugs delivery system for the treatment of NSCLC [189]. Kim et al. created

cisplatin-loaded silk NPs using spray drying, demonstrating significant cytotoxicity and sol-gel transitions. These silk strands enhance durability and stability, making them ideal for delivering anti-cancer medications to the lungs[190]. Kass et al. discussed two major advancements in hydrogel fabrication for targeted drug release. They highlighted the use of nanocarriers to enhance drug loading adaptability and the use of 3D printing for precise control over drug dose and release kinetic[191]. A nanocarrier-hydrogel composite delivery device for targeted drug release gets displayed in Fig. 10.

Gold NPs

In recent years, the scientific community has grown more fascinated with gold NPs, also known as AuNPs, due to their various uses in a multitude of industries. These typically 1-100 nm-sized NPs show a lot of promise to improve many technological developments [192]. Gold NPs (GNPs') remarkable adjuvant properties may strengthen the host's immune response. Diverse immune responses are triggered by features like as size, shape, charge, and surface modifications, when they are existent. Fig. 11. provides an example of these attributes [193].

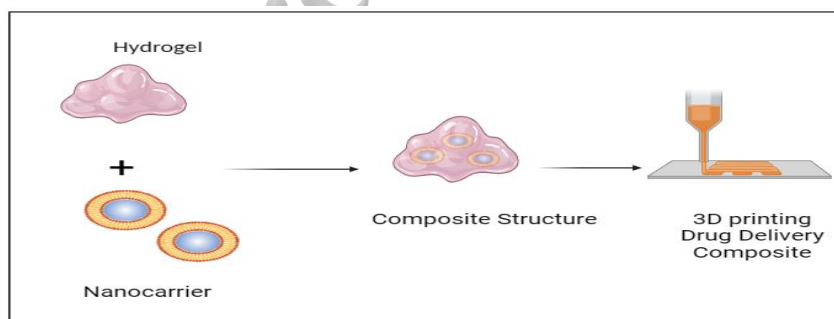


Fig.10. Represents a targeted drug delivery method using a nanocarrier-hydrogel combination.

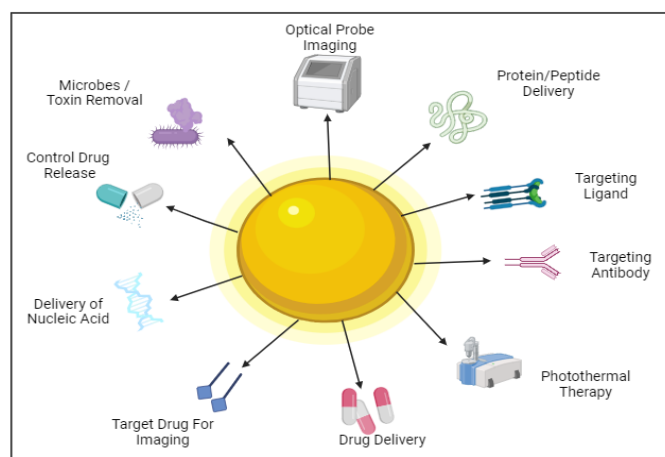


Fig.11. Demonstrate diverse applications of gold NPs are leveraged across various industries.

GNPs offer the ability to treat tumor because their small size, enhanced permeability, and capacity to bind to drugs and proteins. Cancer cells that overexpress specific surface receptors can be their target. GNPs can be hazardous in both in vivo and in vitro conditions, despite their biocompatibility. They raised the potency of radiation therapy, absorb kilovoltage X-rays, and supply heat for targeted photothermal therapy [194].

Thambiraj et al. developed a safe, efficient nanocarrier for targeted drug delivery using GNPs. Using UV-vis, Raman, FT-IR, and X-ray diffraction, they tested the nanoconjugates against the H520 lung cancer cell line, showing a 50% drop in cell survival, suggesting potential cancer therapeutic use [195]. Over the past three years, many incisive reviews on the various uses of GNPs have been published. Some of these reviews include those published by Barabadi et al. (2020), Sehgal et al. (2022), Niloy et al. (2021). highlighted that biosynthesized GNPs demonstrate beneficial effects against lung cancer and normal cells [196].

Pulmonary delivery of NPs

Inhalation based delivery system

A concentrated dosage of the drug is delivered to the lungs through inhalation administration, which reduces its impact on other organs and improves the therapeutic ratio [197]. Inhalable formulations for lung cancer treatment can be achieved using aerosols, liposomes, and dry-powder inhalers. Fig. 12. Gives schematic view of

delivery of drugs by dry powder inhaler. These nano-carriers target deep lung tissues and lung malignancies via various routes, opening up new possibilities for cancer therapy by encapsulating medications directly in the lungs [198].

A number of variables, including particle size, velocity, density, charge, hygroscopicity, shape, and surface properties, must be taken into consideration in order to deposit anticancer medications in the lungs. Techniques involve lung imaging, pharmacokinetic studies, and direct drug concentration detection [199]. Garbuzenko et al.'s 2014 study reveals that lipid-based nanocarriers have higher accumulation and retention in the lungs post-inhalation delivery, making them ideal for successful lung cancer treatment [200]. Researchers have developed 190 nm-sized lactoferrin-chondroitin sulfate nanocomplexes to co-deliver doxorubicin and ellagic acid for lung cancer treatment. These nanocomplexes, which are identified by lung cancer cells through overexpression of lactoferrin and CD44 receptors, are believed to be ingested through endocytosis mediated by clathrin. The nanocomplexes are microencapsulated for optimal delivery [201].

The combination of doxorubicin (Dox), TNF-related apoptosis-inducing ligand (TRAIL), and human serum albumin (HAS) has been used to create inhalable NPs to combat resistant tumors. Preliminary testing showed that Dox and TRAIL significantly improved cytotoxicity, reducing cell viability from 60% to a lower level [202,203].

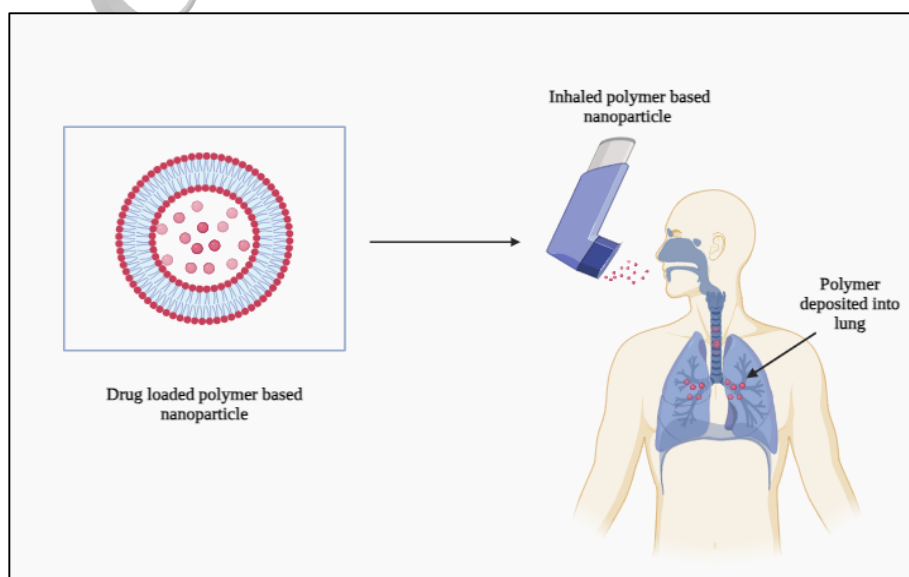


Fig.12. Inhalation delivery of NPs by dry powder inhaler.

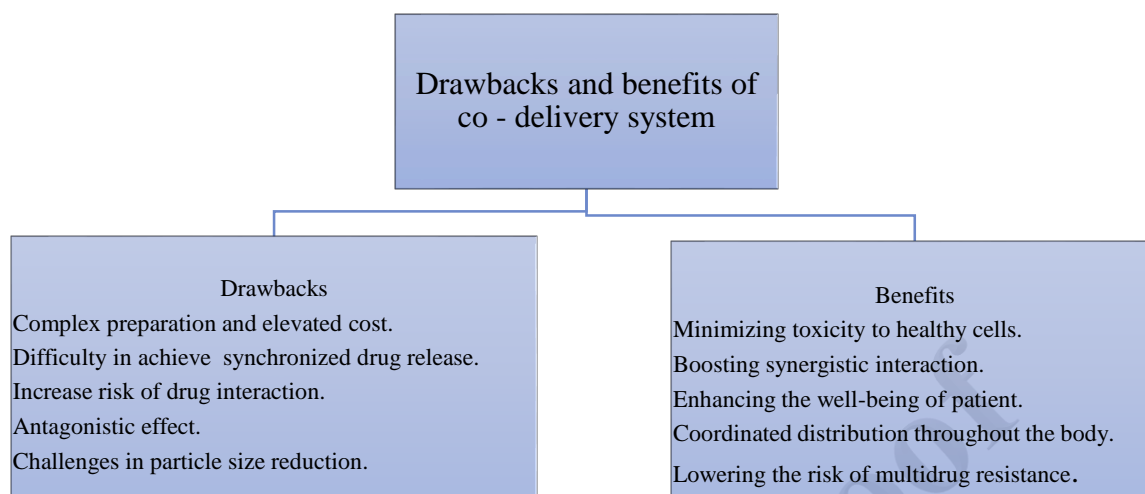


Fig.13. Offers a summary of various co-delivery systems' benefits and drawbacks.

Direct injection into lungs

IV administration provides quick and high drug concentration in the bloodstream by injecting drugs directly into a vein using a needle or tube. The medicine can enter the bloodstream quickly, have a high bioavailability, and effectively get past physiological obstacles to absorption thanks to this technique, which bypasses the gastrointestinal tract [204].

The ability to assess pulmonary sensory qualities and reflex functions has improved due to DIT. Implementing DIT in conjunction with other methodologies and evaluating diverse reflex responses presents a significant prospect for enhancing comprehension of pulmonary sensory receptors and their capabilities [205].

The efficacy and safety of cetuximab with chemoradiotherapy (CRT) for treating unresectable stage III NSCLC has been studied by Blumenschein et al. Preclinical research on the monoclonal antibody cetuximab, which targets EGFR, indicates radiosensitizing effects. When comparing the combined therapy to prior results published by the Radiation Therapy Oncology Group, there was a notable improvement in both median and overall survival [206].

After first-line therapy for NSCLC, the combination of gemcitabine and the intravenous ruthenium-based therapy NAMI-A (Novel Anti-tumor Metastasis Inhibitor A) has been studied by Leijen et al.[207].

Combinatorial therapy used in lung cancer

Combination therapy enhances the effectiveness of individual medications by adjusting their timing or co-administration. This approach has been extensively studied in oncology and other complex disorders, reducing side effects, reducing drug resistance, and improving therapeutic effectiveness compared to single-drug treatments [208].

Several inorganic and organic NPs are being explored for novel co-delivery systems. Typical inorganic nanocarriers are silica, iron oxide, gold, and QDs, while organic nanocarriers involves polymeric micelles [209]. Co-delivery systems use nanotechnology to target multiple therapeutic agents simultaneously to cancer sites, involving the design and construction of nanocarriers and the integrated application of these agents within cells [210].

As a first-line treatment for patients with ES-SCLC, the multicenter real-world trial sought to evaluate the efficacy and safety of anlotinib combined platinum-etoposide chemotherapy [211]. Despite the fact that nanotechnology has made significant strides in co-delivery systems, there are still a number of issues that need to be addressed before creating drug delivery systems that work well together. Fig. 13. Offers a summary of various co-delivery systems' benefits and drawbacks [212]. The FDA-approved combination therapy treatments for lung cancer will be displayed in the Table 8 Data accessed from <https://lcfamerica.org/> August 2,2024.

Table.8. Combination therapies treatment for lung cancer approved by the FDA.

Drug	Biomarkers	Description	Approved for	Approved year
Trametinib	BRAF	It's used with dabrafenib for NSCLC that has spread. Patients whose cancer have a specific mutation in the BRAF gene are offered trametinib.	NSCLC	2024
Dabrafenib	BRAF	When treat metastatic NSCLC, trametinib is also employed. Only people whose cancer has a certain mutation in the BRAF gene are treated with dabrafenib.	NSCLC	2024
Durvalumab	-	As an initial phase of treatment for patients with advanced illness, it is given in conjunction with etoposide phosphate and either carboplatin or cisplatin.	SCLC	2024
Atezolizumab	PD-L1	Adults with PD-L1-expressing cancer who do not have EGFR or ALK gene mutations, along with those whose disease worsened after receiving or undergoing platinum-based chemotherapy, are being treated with atezolizumab as a first-line therapy.	NSCLC	2023
Encorafenib	BRAF	Encorafenib with binimetinib has been granted FDA approval for use in adult patients suffering from metastatic NSCLC with a BRAF V600E mutation.	NSCLC	2023
Pembrolizumab	-	Pembrolizumab has been approved by the FDA as an adjuvant therapy for NSCLC in phases 1B (T2a \geq 4 cm), 2A, or 3A follows surgery and platinum-based chemotherapy.	NSCLC	2023
Cemiplimab-rwlc	-	The FDA has authorized cemiplimab-rwlc when combined with platinum-based chemotherapy for adult patients with advanced NSCLC that have no EGFR, ALK, or ROS1 mutations.	NSCLC	2022
Tremelimumab	-	The FDA has approved the use of tremelimumab together with durvalumab and platinum-based chemotherapy for adult patients with metastatic NSCLC who do not have sensitizing EGFR mutations or ALK genetic abnormalities.	NSCLC	2022

BRAF: B-Raf proto-oncogene, serine/threonine kinase, SCLC: Small Cell Lung Cancer, EGFR: Epidermal Growth Factor Receptor, ALK: Anaplastic Lymphoma Kinase, ROS-1: ROS proto-oncogene 1

Clinical trial and translation research

Nanotechnology's usefulness to cancer detection and therapy is still mostly in its early stages, a number of medications based on nanocarriers are now available on the market, and numerous other nano-based treatments are presently undergoing clinical studies. Nanotechnology in cancer refers to the application of carefully designed materials to produce novel treatments and devices. These developments are intended to decrease toxicity, increase therapeutic efficacy, and improved drug administration[213].

The potential application of NPs in the therapy for lung cancer was covered in this review. Some of these approaches had been tested in different clinical trials, the outcomes of which were either recently released or still pending. Still, the majority of them were still in the clinical trial recruitment stage. The table 9 provides a concise overview of the latest clinical trial studies on nano medicines used to treat lung cancer. Data accessed from <https://clinicaltrials.gov/> in Aug 3, 2024.

Table.9. An overview of current clinical trials exploring the utilization of nanomedicines to treat lung cancer.

NCT Number	Description	Study Status	Type of Lung Cancer	Phases
NCT06096844	In individuals who are older and have stage IIIB–IV lung cancer, chemotherapy with immunotherapy is superior than immunotherapy itself.	Recruiting	Advanced NSCLC	Phase3
NCT06048367	Iron Loaded using Carbon NPs [CNSI-Fe(II)] for the Management of Advanced Solid Tumor.	Recruiting	Advanced Solid Tumor	Phase1
NCT05703971	Maintenance Therapy having Atezolizumab and Quaratusugene Ozeplasmid [Reqorsa] in Patients with ES-SCLC.	Recruiting	SCLC	Phase1/Phase2
NCT05501665	Utilizing Pembrolizumab in Split Course Adaptive Radiation Therapy With or Without Chemotherapy for Stage IV Lung Cancer.	Suspended	Lung Non-Small Cell Carcinoma	Phase1/Phase2
NCT05157542	Durvalumab combined with Neoadjuvant LDRT for Potentially Resectable Stage III NSCLC.	Unknown	NSCLC	Phase1
NCT04789486	Nano-SMART: NPs With MR Guided SBRT in Centrally Located Lung Tumors and Pancreatic Cancer.	Recruiting	NSCLC	Phase1/Phase2
NCT04314895	Trial of NanoPac Intratumoral Injection in Lung Cancer	Completed	NSCLC	Phase2
NCT04310007	To compare standard chemotherapy for NSCLC to the addition of the pill chemotherapy medication cabozantinib to the standard immune therapy drug nivolumab.	Active not recruiting	Non-Squamous NSCLC	Phase2
NCT03361319	Combination of Nintedanib with Nab-paclitaxel (N-P) or N-P and Placebo for Relapsed NSCLC.	Withdrawn	NSCLC	Phase1/Phase2
NCT02769962	Trial of Camptothecin with Olaparib Nanoparticle EP0057 in Subjects with Relapsed or Refractory Small Cell Lung Cancer.	Recruiting	SCLC	Phase1/Phase2
NCT02240238	Combination treatment for advanced solid tumors or non-small cell lung, biliary, or bladder cancer with NC-6004 and gemcitabine.	Completed	Solid Tumors	Phase1/Phase2
NCT01969955	Nab-paclitaxel as a Secondary Treatment for Metastatic or Locally Advanced Squamous Lung Cancer.	Unknown	Squamous Cell Carcinoma of Lung	Phase2
NCT01455389	TUSC2-NPs and Erlotinib in Stage IV Lung Cancer	Terminated	Lung Cancer	Phase1/Phase2
NCT00729612	Erlotinib with TUSC2-NPs in Stage IV Lung Cancer	Completed	Lung Cancer	Phase2
NCT00729612	Utilizing Paclitaxel Albumin-Stabilized Nanoparticle Formulation with Carboplatin to Treat Patients with Recurrent NSCLC in Stage IV, Stage IIIB, or Stage IV.	Completed	Lung Cancer	Phase2
NCT00470548	Considering Advanced Solid Tumors, Abraxane and Alimta.	Terminated	Solid Tumor	Phase1/Phase2
NCT00077246	Management of Patients with Chemotherapy-Naïve Stage IV NSCLC With ABI-007.	Completed	Lung Cancer	Phase1/Phase2
NCT00073723	Weekly Delivery of ABI-007 in Patients with Advanced NSCLC Without Chemotherapy.	Completed	NSCLC	Phase1/Phase2

Challenges

The prognosis for lung cancer may be enhanced by using drug delivery systems comprised of NPs. However, the complex formulae and structures of numerous drugs provide difficulties for large-scale

industrial manufacture. In order to address these challenges, it is crucial to rationally design nanomaterials by optimizing their characteristics to improve medication absorption, limit cell efflux, and lower toxicity. It's also critical to address drug

stability and scalability difficulties. The production of nanomedicines requires careful observation and improvement at every stage. Additional development necessitates improved comprehension of biological mechanisms, developments in nanotechnology, and animal models that are applicable in therapeutic settings [214].

Nanotechnology is contributing to a huge increase in research on NPs, yet very few of these investigations go to clinical trials. Due to issues with technology, biology, and research design, most nano formulations have unique challenges in their clinical translation. Overcoming biological barriers includes things like biodistribution and administration routes. Accurate behavior prediction of NPs, scaling up of synthesis, and performance optimization are examples of technological challenges. Aspects of the study design have the potential to greatly impact the outcomes of clinical trials [215–217].

For polymeric NPs smaller than 200 nm in diameter, precise control is required; nevertheless, extrusion methods can lead to issues including instability and burst drug release. Inorganic and metal-based NPs have potential, but there's also a big chance they could be harmful. Because they can cause inflammatory reactions and pose a risk to healthy cells, amorphous silica NPs should only be utilized in small amounts during cancer treatment. Titanium dioxide and carbon nanotubes can cause lipid peroxidation and malfunctioning mitochondria. Both in vitro and in vivo toxicity assessments are needed to ensure the safety of these nanoparticle systems [218]. To optimize immunotherapy's ability to activate the immune system against cancer, it is imperative to increase its adaptability, productivity, and persistence. Every nanocarrier-conjugated system must pass a stringent evaluation process that involves both in vitro and in vivo toxicity testing before receiving a license for clinical usage. This is done with the aim to ensure safety [219].

Inhalation therapy for lung cancer treatment faces challenges due to differences in lung architecture, airway anatomy, and respiratory physiology between humans and rodents. Challenges include inhaled drug technologies, formulation, storage, and delivery, as well as biocompatibility of nanomedicines. The distribution of inhaled free anticancer medicines in the lungs is not tumor-specific, and drug release from NPs is challenging. Long-term data on lung parenchymal therapy's adverse effects is lacking,

making it uncertain for early-stage lung cancer [220].

Future aspects

Novel drug delivery systems (NDDSs) hold considerable potential to improve the safety, precision, and efficacy of medicinal interventions. These methods, particularly the ones that incorporate NPs, provide targeted drug delivery to specific tissues, improving local drug concentrations, at lower doses and with less cytotoxicity. However, there are still problems, such as inflammation, severe oxidative damage, and treatment resistance. Future research should focus on producing stable, effective NPs with improved mechanisms for release and deagglomeration. Theranostics developments in cancer could lead to early tumor detection and tailored treatment. Simplifying regulatory processes can enhance both the broader use of NDDSs and the general delivery of healthcare.

CONCLUSION

In spite of its high fatality rate and incidence, lung cancer demands better treatment options and early detection. Theranostic medication overcome solubility and stability problems by employing nanotechnology to deliver therapeutic and imaging chemicals to specific regions. Researchers are investigating different nanocarriers to enhance target specificity and reduce harm on healthy cells. Nanotechnology has tremendous potential for treating lung cancer. Treatment success can be considerably enhanced by concentrating on overexpressed targets. Regarding theranostic applications, several kinds of nanocarriers have been created, such as solid lipid NPs, liposomes, dendrimers, micelles, magnetic NPs, carbon nanotubes, QDs, hydrogels, nanoemulsions, and polymeric NPs. The efficiency of these nanocarriers affects drug penetration and accumulation in malignant tissues, which is crucial for drug delivery. Moreover, theranostic agents' capability to precisely recognize and evaluate cancer at an early stage and anticipate therapy responses is crucial to the advancement of lung cancer treatment. Patients receiving treatment have hope and encouragement from these improvements in the management of lung cancer and the invention of complex medication delivery methods.

AUTHORS CONTRIBUTION

P. S. Sonawane design and drafted the manuscript. R. S. Shendage and S. B. Khade reviewed and approved the finale version

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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