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 cilical 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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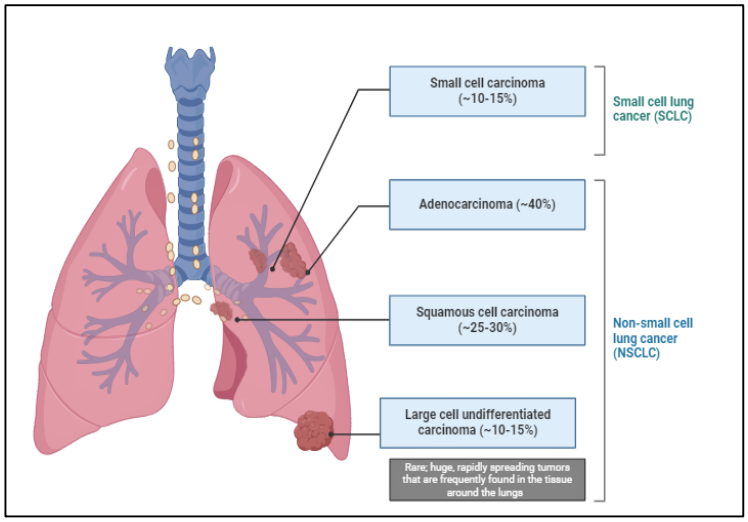

Fig.1.Two main categories of lung cancer.

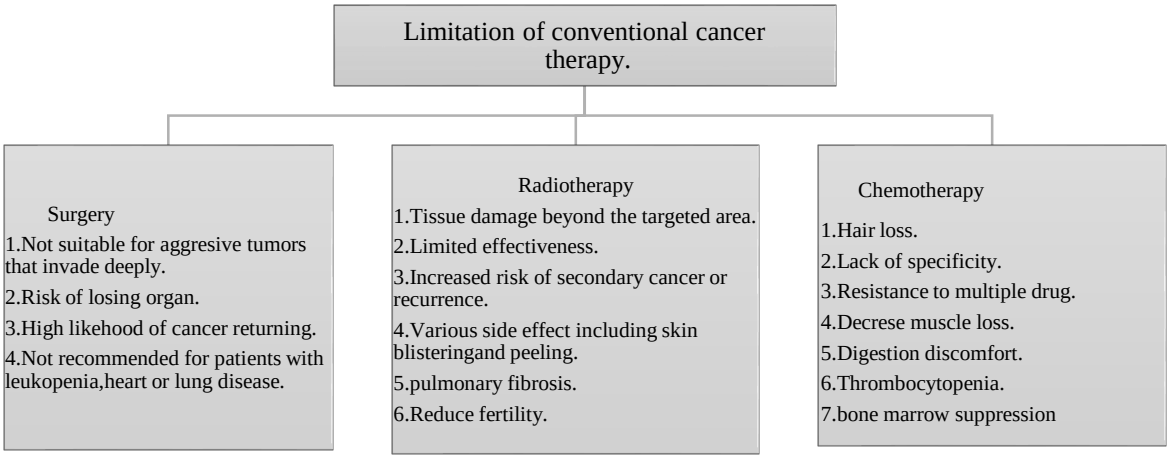

Fig.2.An outline of the limitations of conventional cancer therapy.

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].

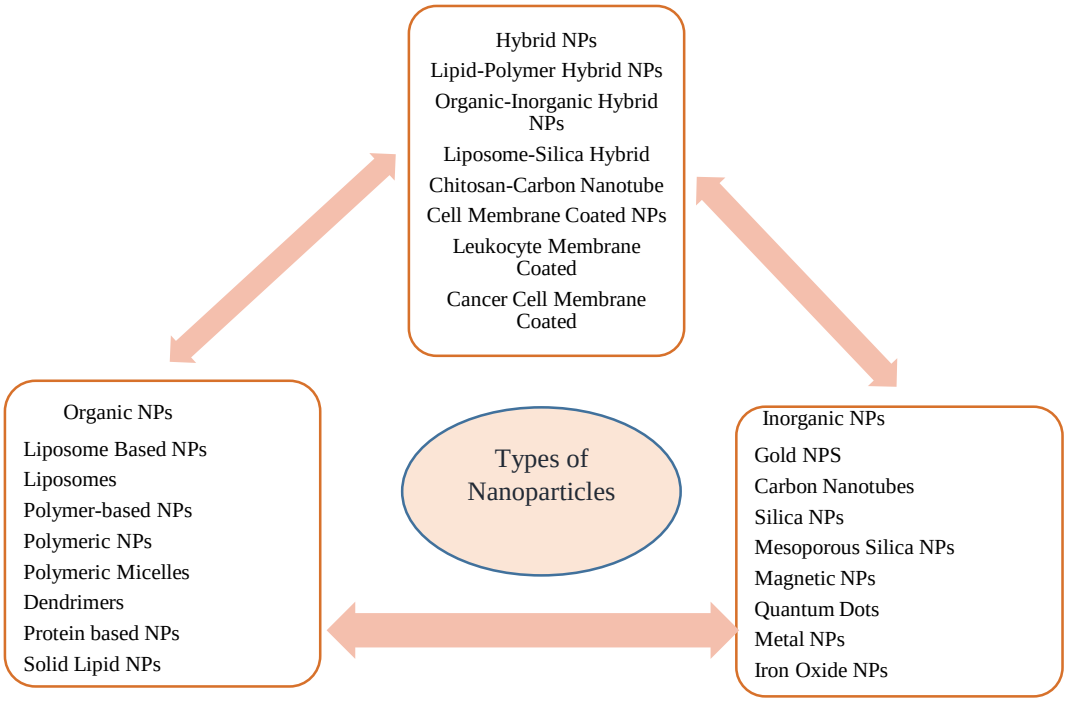

Fig.3. Classification of NPs for cancer therapy: Hybrid, Inorganic, and Organic Types

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 FRα 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 α3β1 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 nanoacarrier used for cancer therapy.

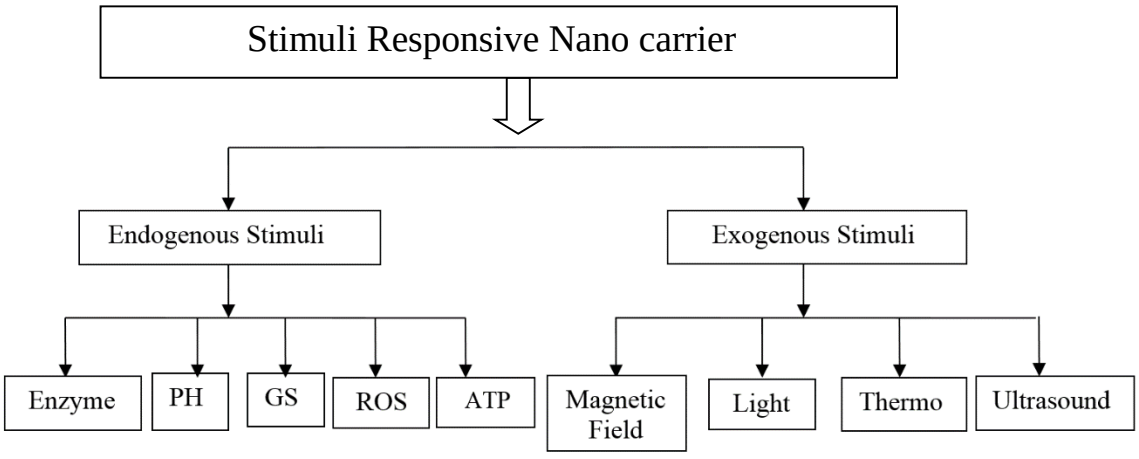

Fig.4.Stimuli responsive nanocarrier for cancer therapy.

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**.**

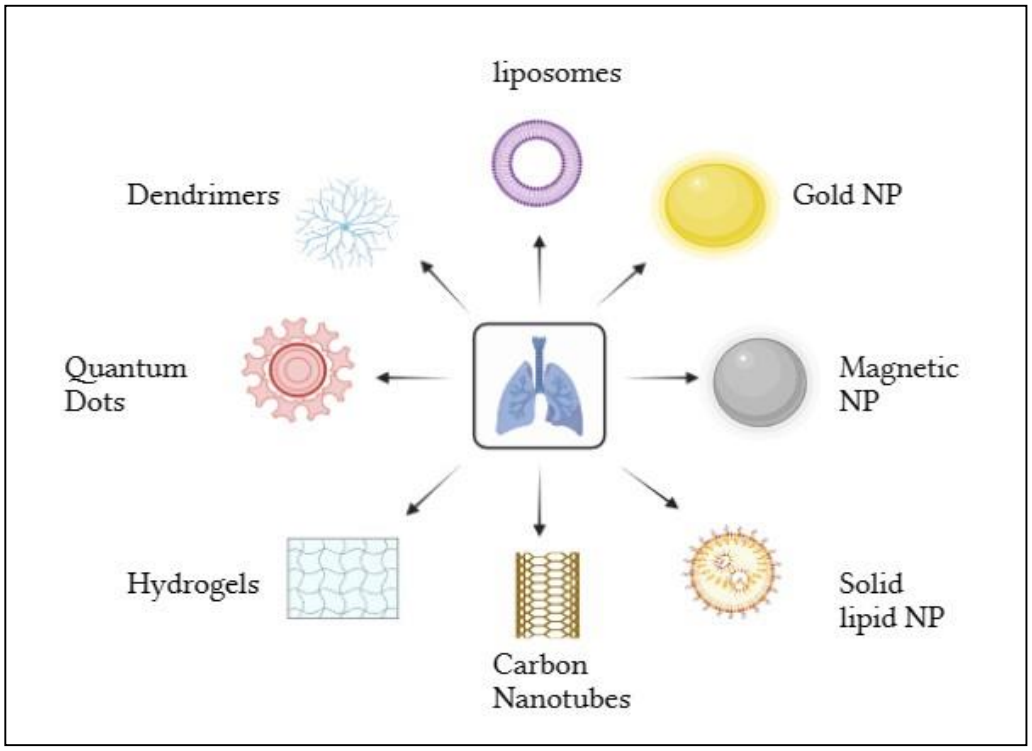

Fig.5. Various types of nanocarriers Utilized in Lung Cancer Therapy.

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	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	100±20	-	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 immunocheckpoint 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].

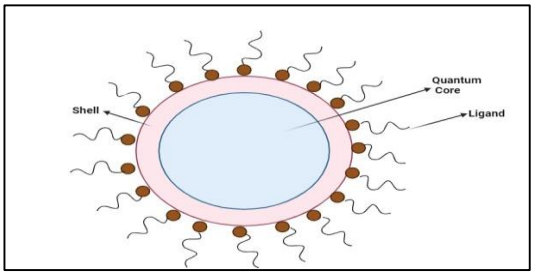

Fig.6. Simplified illustration of a quantum dot.

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.

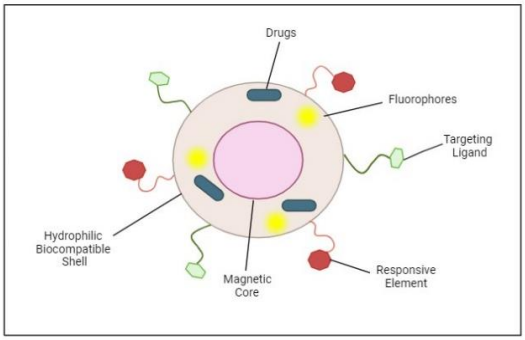

Fig. 7. An illustration of the general structure of a magnetic nanoparticle.

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. Ferucacarbotran, 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].

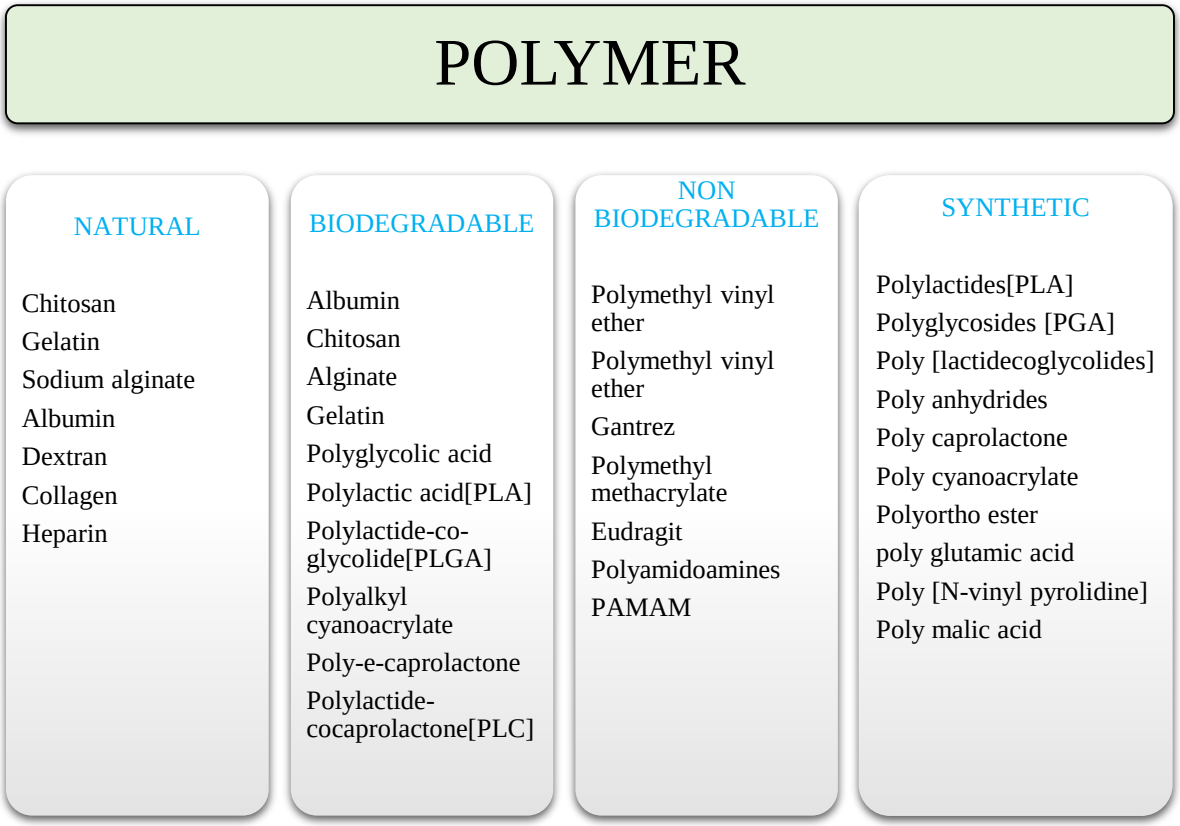

Fig.8. Illustrates various polymers employed in the preparation of PNPs.

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 αvβ6-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.

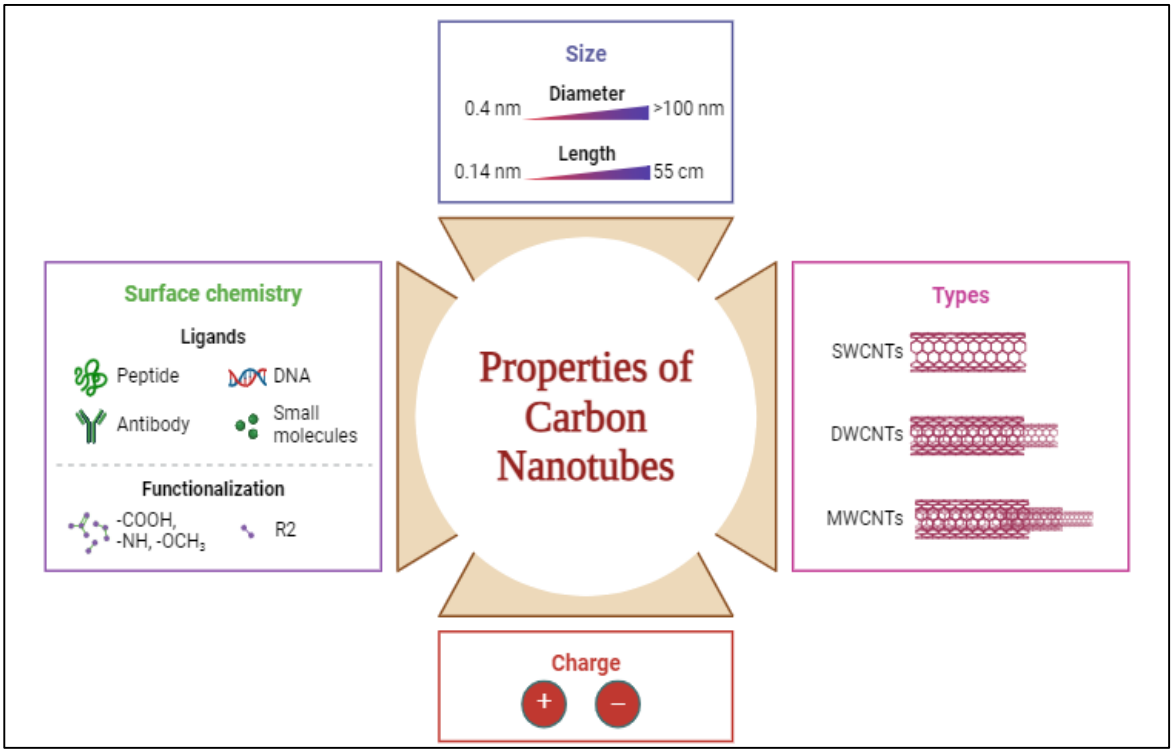

Fig.9. Highlights the characteristics of carbon nanotubes designed to specifically target cancer cells.

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]
	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]
Multiple Wall Coated	SiRNA	CNTs have proven anticancer properties and are effective in therapeutic treatments. In animal models, MWCNTs functionalized with NH+3 and siRNA improve cell survival and suppress tumor growth. Targeting the Polo-like Kinase gene is suggested as a lung cancer treatment option.	[176]
	Doxorubicin	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]
		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	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]
		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 vitroo 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].

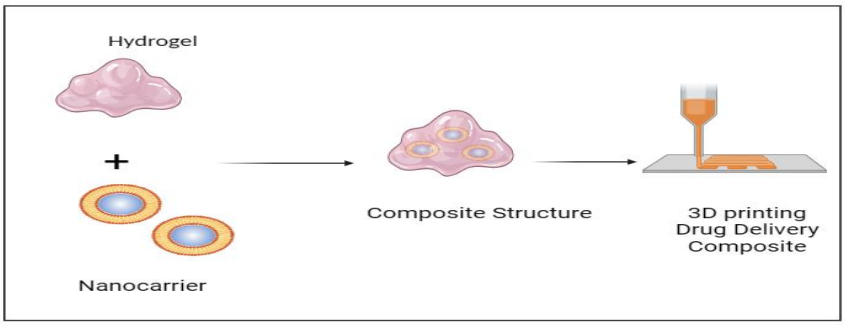

Fig.10. Represents a targeted drug delivery method using a nanocarrier-hydrogel combination.

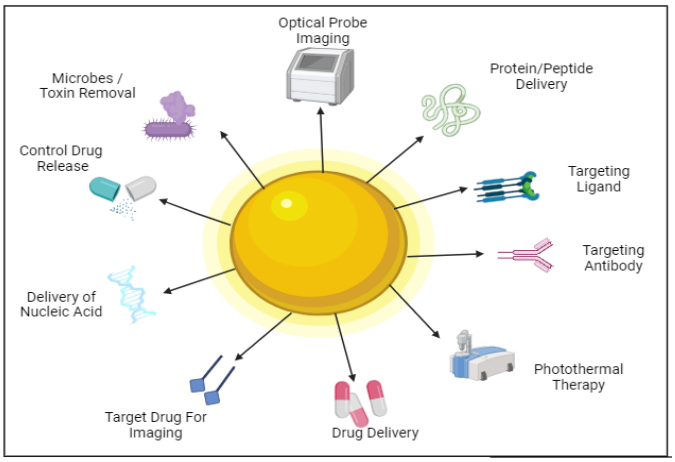

Fig.11. Demonstrate diverse applications of gold NPs are leveraged across various industries.

GNP's 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].

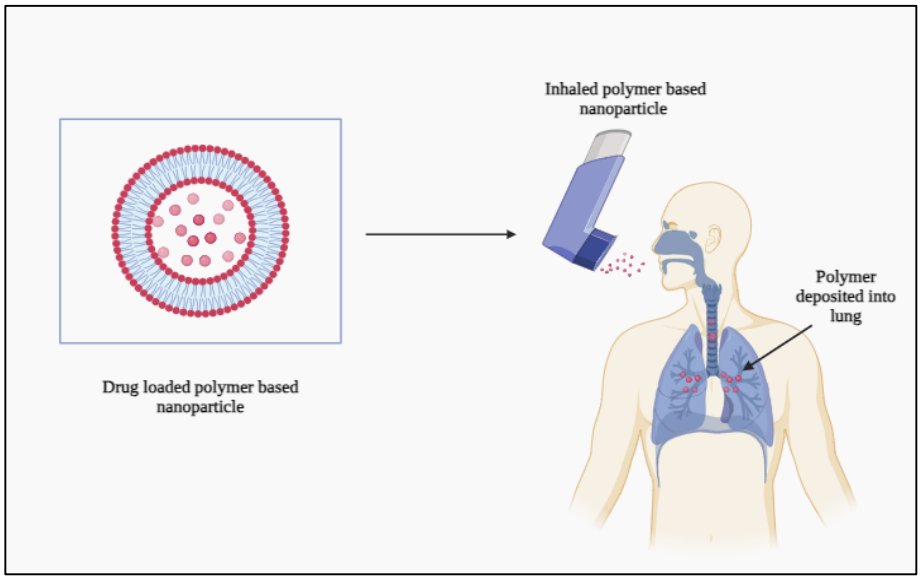

Fig.12.Inhaltion delivery of NPs by dry powder inhaler.

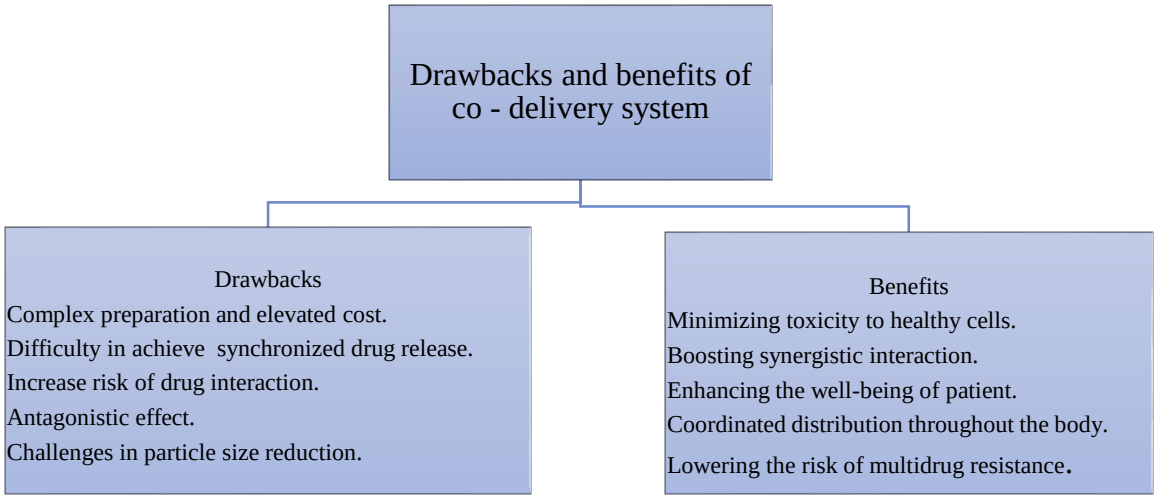

Fig.13. Offers a summary of various co-delivery systems' benefits and drawbacks.

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 treatement 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 ≥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 Erlotinib with TUSC2-NPs in Stage IV Lung Cancer	Terminated	Lung Cancer	Phase1/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-Naï¨ve 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.

REFERENCES

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17–48.
2. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021;149(4):778–789.
3. World Health Organization. 2021. 2021. [Internet]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cancer.
4. Mohtar N, Parumasivam T, Gazzali AM, Tan CS, Tan ML, Othman R, et al. Advanced Nanoparticle-Based Drug Delivery Systems and Cancer Treatment. Cancers (Basel). 2021;(Lc):1–26.
5. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–263.
6. Society American Cancer. Global cancer facts and figures. American Cancer Society. 2024; 1–48.
7. Wheless L, Brashears J, Alberg AJ. Epidemiology of lung cancer. Lung Cancer Imaging. 2013;1–15.
8. Clark SB, Alsubait S. Non–Small Cell Lung Cancer. In Treasure Island (FL); 2024.
9. Basumallik N, Agarwal M. Small Cell Lung Cancer. In Treasure Island (FL); 2024.
10. Shams M, Abdallah S, Alsadoun L, Hamid YH, Gasim R, Hassan A. Oncological Horizons: The Synergy of Medical and Surgical Innovations in Cancer Treatment. Cureus. 2023;15(11).
11. Mokwena MG, Kruger CA, Ivan MT, Heidi A. A review of nanoparticle photosensitizer drug delivery uptake systems for photodynamic treatment of lung cancer. Photodiagnosis Photodyn Ther. 2018;22:147–154.
12. Hristova-Panusheva K, Xenodochidis C, Georgieva M, Krasteva N. Nanoparticle-Mediated Drug Delivery Systems for Precision Targeting in Oncology. Pharmaceuticals. 2024;17(6):1–25.
13. Alshammari MK, Almomen EY, Alshahrani KF, Altwalah SF, Kamal M, Al-Twallah MF, et al. Nano-Enabled Strategies for the Treatment of Lung Cancer: Potential Bottlenecks and Future Perspectives. Biomedicines. 2023;11(2).
14. Wang J, Zhou T, Liu Y, Chen S, Yu Z. Application of NPs in the Treatment of Lung Cancer With Emphasis on Receptors. Front Pharmacol. 2022;12(January):1–14.
15. Bordeianu G, Filip N, Cernomaz A, Veliceasa B, Hurjui LL, Pinzariu AC, et al. The Usefulness of Nanotechnology in Improving the Prognosis of Lung Cancer. Biomedicines. 2023;11(3):1–20.
16. Harish V, Tewari D, Gaur M, Yadav AB, Swaroop S, Bechelany M, et al. Review on NPs and Nanostructured Materials: Bioimaging, Biosensing, Drug Delivery, Tissue Engineering, Antimicrobial, and Agro-Food Applications. Nanomaterials. 2022;12(3).
17. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, et al. Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance. Front Mol Biosci. 2020;7:193.
18. Bhutani M, Gharwan H. EGFR, growth factors. Cancer Ther Targets. 2017;2–2:707–17.
19. Liu TC, Jin X, Wang Y, Wang K. Role of epidermal growth factor receptor in lung cancer and targeted therapies. Am J Cancer Res. 2017;7(2):187–202.
20. Karlsen EA, Kahler S, Tefay J, Joseph SR, Simpson F. Epidermal Growth Factor Receptor Expression and Resistance Patterns to Targeted Therapy in Non-Small Cell Lung Cancer: A Review. Cells. 2021;10(5).
21. Khaddour K, Jonna S, Deneka A, Patel JD, Abazeed ME, Golemis E, et al. Targeting the Epidermal Growth Factor Receptor in EGFR-Mutated Lung Cancer: Current and Emerging Therapies. Cancers (Basel). 2021;13(13).
22. Walser M, Svensson J, Karlsson L, Motalleb R, Åberg M, Kuhn HG, et al. Growth Hormone and Neuronal Hemoglobin in the Brain—Roles in Neuroprotection and Neurodegenerative Diseases. Front Endocrinol (Lausanne). 2021;11(January):1–15.
23. Zhang C, Cui T, Cai R, Wangpaichitr M, Mirsaeidi M, Schally A V., et al. Growth hormone-releasing hormone in lung physiology and pulmonary disease. Cells. 2020;9(10):1–14.
24. Gonzalez T, Muminovic M, Nano O, Vulfovich M. Folate Receptor Alpha-A Novel Approach to Cancer Therapy. Int J Mol Sci. 2024;25(2).
25. Nunez MI, Behrens C, Woods DM, Lin H, Suraokar M, Kadara H, et al. High expression of folate receptor alpha in lung cancer correlates with adenocarcinoma histology and EGFR (corrected) mutation. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2012 May;7(5):833–840.
26. Antony AC. Folate receptors. Annu Rev Nutr. 1996;16:501–521.
27. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-

Angiogenic Therapies. Genes and Cancer. 2011;2(12):1097–1105.
28. Holmes K, Roberts OL, Thomas AM, Cross MJ. Vascular endothelial growth factor receptor-2: structure, function, intracellular signalling and therapeutic inhibition. Cell Signal. 2007;19(10):2003–2012.
29. Al Khashali H, Darweesh B, Ray R, Haddad B, Wozniak C, Ranzenberger R, et al. Regulation of Vascular Endothelial Growth Factor Signaling by Nicotine in a Manner Dependent on Acetylcholine-and/or β-Adrenergic-Receptors in Human Lung Cancer Cells. Cancers (Basel). 2023;15(23).
30. Spagnuolo A, Palazzolo G, Sementa C, Gridelli C. Vascular endothelial growth factor receptor tyrosine kinase inhibitors for the treatment of advanced non-small cell lung cancer. Expert Opin Pharmacother. 2020;21(4):491–506.
31. Li X, Taratula O, Taratula O, Schumann C, Minko T. LHRH-Targeted Drug Delivery Systems for Cancer Therapy. Mini-Reviews Med Chem. 2016;17(3):258–267.
32. Kuzmov A, Minko T. Nanotechnology approaches for inhalation treatment of lung diseases. J Control release Off J Control Release Soc. 2015;219:500–518.
33. Pacini L, Jenks AD, Lima NC, Huang PH. Targeting the Fibroblast Growth Factor Receptor (FGFR) Family in Lung Cancer. Cells. 2021;10(5).
34. Ferguson HR, Smith MP, Francavilla C. Fibroblast Growth Factor Receptors (FGFRs) and Noncanonical Partners in Cancer Signaling. Cells. 2021;10(5).
35. Ahmad I, Iwata T, Leung HY. Mechanisms of FGFR-mediated carcinogenesis. Biochim Biophys Acta. 2012;1823(4):850–860.
36. Templeton AK, Miyamoto S, Babu A, Munshi A, Ramesh R. Cancer stem cells: Progress and challenges in lung cancer. Stem Cell Investig. 2014;2014(APR):1–18.
37. Wang YY, Vadhan A, Chen PH, Lee YL, Chao CY, Cheng KH, et al. Cd44 promotes lung cancer cell metastasis through erk–zeb1 signaling. Cancers (Basel). 2021;13(16):1–15.
38. Luo Z, Wu RR, Lv L, Li P, Zhang LY, Hao QL, et al. Prognostic value of CD44 expression in non-small cell lung cancer: A systematic review. Int J Clin Exp Pathol. 2014;7(7):3632–3646.
39. da Silva EC, Dontenwill M, Choulier L, Lehmann M. Role of integrins in resistance to therapies targeting growth factor receptors in cancer. Cancers (Basel). 2019;11(5).
40. Caccavari F, Valdembri D, Sandri C, Bussolino F, Serini G. Integrin signaling and lung cancer. Cell Adh Migr. 2010;4(1):124–129.
41. Tvaroška I, Kozmon S, Kóňa J. Molecular Modeling Insights into the Structure and Behavior of Integrins: A Review. Cells. 2023;12(2).
42. Bartolazzi A, Cerboni C, Flamini G, Bigotti A, Lauriola L, Natali PG. Expression of alpha 3 beta 1 integrin receptor and its ligands in human lung tumors. Int J Cancer. 1995;64(4):248–252.
43. Rankin EB, Giaccia AJ. The receptor tyrosine kinase AXL in cancer progression. Cancers (Basel). 2016;8(11).
44. Auyez A, Sayan AE, Kriajevska M, Tulchinsky E. AXL Receptor in Cancer Metastasis and Drug Resistance: When Normal Functions Go Askew. Cancers (Basel). 2021;13(19).
45. Zhang G, Wang M, Zhao H, Cui W. Function of axl receptor tyrosine kinase in non-small cell lung cancer (Review). Oncol Lett. 2018;15(3):2726–2734.
46. Li H, Zhang Q, Wu Q, Cui Y, Zhu H, Fang M, et al. IL-22 regulates lung cancer proliferation. 2019;11(7):4077–4088.
47. Kobold S, Völk S, Clauditz T, Küpper NJ, Minner S, Tufman A, et al. Interleukin-22 is frequently expressed in small- and large-cell lung cancer and promotes growth in chemotherapy-resistant cancer cells. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2013;8(8):1032–1042.
48. Fishman P, Bar-Yehuda S, Synowitz M, Powell JD, Klotz KN, Gessi S, et al. Adenosine receptors and cancer. Handb Exp Pharmacol. 2009;(193):399–441.
49. Asgharkhah E, Saghaeian Jazi M, Asadi J, Jafari SM. Gene expression pattern of adenosine receptors in lung tumors. Cancer reports (Hoboken, NJ). 2023;6(3):e1747.
50. Wu B, Chien EYT, Mol CD, Fenalti G, Liu W, Katritch V, et al. Structures of the CXCR4 chemokine GPCR with small-molecule and cyclic peptide antagonists. Science. 2010;330(6007):1066–1071.
51. Fung AS, Kopciuk K, Dean ML, D'Silva A, Otsuka S, Klimowicz A, et al. CXCR4 expression in lung carcinogenesis: Evaluating gender-specific differences in survival outcomes based on CXCR4 expression in early stage non-small cell lung cancer patients. PLoS One (Internet). 2021;16(1 January):1–12.
52. Hughes CE, Nibbs RJB. A guide to chemokines and their receptors. FEBS J. 2018;285(16):2944–2971.
53. Chatterjee S, Behnam Azad B, Nimmagadda S. The intricate role of CXCR4 in cancer. Adv Cancer Res. 2014;124:31–82.
54. Wada E, Way J, Shapira H, Kusano K, Lebacq-Verheyden AM, Coy D, et al. cDNA cloning, characterization, and brain region-specific expression of a neuromedin-B-preferring bombesin receptor. Neuron. 1991;6(3):421–430.
55. Battey JF, Way JM, Corjay MH, Shapira H, Kusano K, Harkins R, et al. Molecular cloning of the bombesin/gastrin-releasing peptide receptor from Swiss 3T3 cells. Proc Natl Acad Sci U S A. 1991;88(2):395–399.
56. Fathi Z, Corjay MH, Shapira H, Wada E, Benya R, Jensen R, et al. BRS-3: a novel bombesin receptor subtype selectively expressed in testis and lung carcinoma cells. J Biol Chem. 1993;268(8):5979–5984.
57. Moody TW, Sancho V, Di Florio A, Nuche-Berenguer B, Mantey S, Jensen RT. Bombesin receptor subtype-3 agonists stimulate the growth of lung cancer cells

and increase EGF receptor tyrosine phosphorylation. Peptides. 2011;32(8):1677–1684.
58. Fitter S, Sincock PM, Jolliffe CN, Ashman LK. Transmembrane 4 superfamily protein CD151 (PETA-3) associates with beta 1 and alpha IIb beta 3 integrins in haemopoietic cell lines and modulates cell-cell adhesion. Biochem J. 1999;338 (Pt 1(Pt 1):61–70.
59. Kwon MJ, Seo J, Kim YJ, Kwon MJ, Choi JY, Kim TE, et al. Prognostic significance of CD151 overexpression in non-small cell lung cancer. Lung Cancer. 2013;81(1):109–116.
60. van Waarde A, Rybczynska AA, Ramakrishnan NK, Ishiwata K, Elsinga PH, Dierckx RAJO. Potential applications for sigma receptor ligands in cancer diagnosis and therapy. Biochim Biophys Acta. 2015;1848(10 Pt B):2703–2714.
61. Georgiadis MO, Karoutzou O, Foscolos AS, Papanastasiou I. Sigma Receptor (σR) Ligands with Antiproliferative and Anticancer Activity. Molecules. 2017;22(9).
62. Villalobos P, Wistuba II. Lung Cancer Biomarkers. Hematol Oncol Clin North Am. 2017;31(1):13–29.
63. Huang H. Anaplastic Lymphoma Kinase (ALK) Receptor Tyrosine Kinase: A Catalytic Receptor with Many Faces. Int J Mol Sci. 2018;19(11).
64. Mousa DP V, Mavrovounis G, Argyropoulos D, Stranjalis G, Kalamatianos T. Anaplastic Lymphoma Kinase (ALK) in Posterior Cranial Fossa Tumors: A Scoping Review of Diagnostic, Prognostic, and Therapeutic Perspectives. Cancers (Basel). 2024;16(3).
65. Kiełbowski K, Żychowska J, Becht R. Anaplastic lymphoma kinase inhibitors-a review of anticancer properties, clinical efficacy, and resistance mechanisms. Front Pharmacol. 2023;14:1285374.
66. Araujo JM, Gomez AC, Pinto JA, Rolfo C, Raez LE. Profile of entrectinib in the treatment of ROS1-positive non-small cell lung cancer: Evidence to date. Hematol Oncol Stem Cell Ther. 2021;14(3):192–8.
67. Gendarme S, Bylicki O, Chouaid C, Guisier F. ROS-1 Fusions in Non-Small-Cell Lung Cancer: Evidence to Date. Curr Oncol. 2022;29(2):641–658.
68. Attia MF, Anton N, Wallyn J, Omran Z, Vandamme TF. An overview of active and passive targeting strategies to improve the nanocarriers efficiency to tumour sites. J Pharm Pharmacol. 2019;71(8):1185–1198.
69. Batool S, Sohail S, Ud Din F, Alamri AH, Alqahtani AS, Alshahrani MA, et al. A detailed insight of the tumor targeting using nanocarrier drug delivery system. Drug Deliv. 2023;30(1):2183815.
70. Bazak R, Houri M, Achy S El, Hussein W, Refaat T. Passive targeting of NPs to cancer: A comprehensive review of the literature. Mol Clin Oncol. 2014;2(6):904–908.
71. Rosenblum D, Joshi N, Tao W, Karp JM, Peer D. Progress and challenges towards targeted delivery of cancer therapeutics. Nat Commun (Internet). 2018;9(1).
72. Chauhan VP, Jain RK. Strategies for advancing cancer nanomedicine. Nat Mater. 2013;12(11):958–62.
73. Stathopoulos GP, Boulikas T. Lipoplatin formulation review article. J Drug Deliv. 2012;2012:581363.
74. Chae YK, Chang S, Ko T, Anker J, Agte S, Iams W, et al. Epithelial-mesenchymal transition (EMT) signature is inversely associated with T-cell infiltration in non-small cell lung cancer (NSCLC). Sci Rep. 2018;8(1):2918.
75. Sousa C, Gouveia LF, Kreutzer B, Silva-Lima B, Maphasa RE, Dube A, et al. Polymeric Micellar Formulation Enhances Antimicrobial and Anticancer Properties of Salinomycin. Pharm Res. 2019;36(6):83.
76. Sunil Gowda SN, Rajasowmiya S, Vadivel V, Banu Devi S, Celestin Jerald A, Marimuthu S, et al. Gallic acid-coated sliver nanoparticle alters the expression of radiation-induced epithelial-mesenchymal transition in non-small lung cancer cells. Toxicol Vitr an Int J Publ Assoc with BIBRA. 2018;52:170–177.
77. Sarma K, Akther MH, Ahmad I, Afzal O, Altamimi ASA, Alossaimi MA, et al. Adjuvant Novel Nanocarrier-Based Targeted Therapy for Lung Cancer. Molecules. 2024;29(5).
78. Yoo J, Park C, Yi G, Lee D, Koo H. Active Targeting Strategies Using Biological Ligands for Nanoparticle Drug Delivery Systems. Cancers (Basel). 2019;11(5).
79. Muhamad N, Plengsuriyakarn T, Na-Bangchang K. Application of active targeting nanoparticle delivery system for chemotherapeutic drugs and traditional/herbal medicines in cancer therapy: a systematic review. Int J Nanomedicine. 2018;13:3921–3935.
80. Wathoni N, Puluhulawa LE, Joni IM, Muchtaridi M, Mohammed AFA, Elamin KM, et al. Monoclonal antibody as a targeting mediator for nanoparticle targeted delivery system for lung cancer. Drug Deliv. 2022;29(1):2959–2970.
81. Singh RP, Sharma G, Sonali, Singh S, Bharti S, Pandey BL, et al. Chitosan-folate decorated carbon nanotubes for site specific lung cancer delivery. Mater Sci Eng C Mater Biol Appl. 2017;77:446–458.
82. Ramalingam V, Varunkumar K, Ravikumar V, Rajaram R. Target delivery of doxorubicin tethered with PVP stabilized gold NPs for effective treatment of lung cancer. Sci Rep (Internet). 2018;8(1):1–12.
83. Mashinchian O, Johari-Ahar M, Ghaemi B, Rashidi M, Barar J, Omidi Y. Impacts of quantum dots in molecular detection and bioimaging of cancer. Bioimpacts. 2014;4(3):149–166.
84. Ebrahimnejad P, Sodagar Taleghani A, Asare-Addo K, Nokhodchi A. An updated review of folate-functionalized nanocarriers: A promising ligand in cancer. Drug Discov Today. 2022;27(2):471–489.
85. Dumontet C, Reichert JM, Senter PD, Lambert JM, Beck A. Antibody-drug conjugates come of age in oncology. Nat Rev Drug Discov. 2023;22(8):641–661.
86. Zhang CW, Zhang JG, Yang X, Du WL, Yu ZL, Lv ZY, et al. Carbohydrates based stimulus responsive nanocarriers for cancer-targeted chemotherapy: a review of current practices. Expert Opin Drug Deliv. 2022;19(6):623–640.

87. Samec T, Boulos J, Gilmore S, Hazelton A, Alexander-Bryant A. Peptide-based delivery of therapeutics in cancer treatment. Mater today Bio. 2022;14:100248.
88. Gao F, Yin J, Chen Y, Guo C, Hu H, Su J. Recent advances in aptamer-based targeted drug delivery systems for cancer therapy. Front Bioeng Biotechnol. 2022;10:972933.
89. Mi P. Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. Theranostics. 2020;10(10):4557–4588.
90. Sun Y, Davis E. Nanoplatforms for Targeted Stimuli-Responsive Drug Delivery: A Review of Platform Materials and Stimuli-Responsive Release and Targeting Mechanisms. Nanomater (Basel, Switzerland). 2021;11(3).
91. Verkhovskii RA, Ivanov AN, Lengert E V., Tulyakova KA, Shilyagina NY, Ermakov A V. Current Principles, Challenges, and New Metrics in pH-Responsive Drug Delivery Systems for Systemic Cancer Therapy. Pharmaceutics. 2023;15(5).
92. Morarasu S, Morarasu BC, Ghiarasim R, Coroaba A, Tiron C, Iliescu R, et al. Targeted Cancer Therapy via pH-Functionalized NPs: A Scoping Review of Methods and Outcomes. Gels (Basel, Switzerland). 2022;8(4).
93. Li M, Zhao G, Su WK, Shuai Q. Enzyme-Responsive NPs for Anti-tumor Drug Delivery. Front Chem. 2020;8:647.
94. Liu H, Yang F, Chen W, Gong T, Zhou Y, Dai X, et al. Enzyme-Responsive Materials as Carriers for Improving Photodynamic Therapy. Front Chem. 2021;9(November):1–8.
95. Ruan L, Chen J, Du C, Lu H, Zhang J, Cai X, et al. Mitochondrial temperature-responsive drug delivery reverses drug resistance in lung cancer. Bioact Mater. 2022;13:191–199.
96. Rahim MA, Jan N, Khan S, Shah H, Madni A, Khan A, et al. Recent Advancements in Stimuli Responsive Drug Delivery Platforms for Active and Passive Cancer Targeting. Cancers (Basel). 2021;13(4).
97. Kohli AG, Kierstead PH, Venditto VJ, Walsh CL, Szoka FC. Designer lipids for drug delivery: from heads to tails. J Control release Off J Control Release Soc. 2014;190:274–287.
98. Jiménez-López J, Bravo-Caparrós I, Cabeza L, Nieto FR, Ortiz R, Perazzoli G, et al. Paclitaxel antitumor effect improvement in lung cancer and prevention of the painful neuropathy using large pegylated cationic liposomes. Biomed Pharmacother. 2021;133:111059.
99. Naik H, Sonju JJ, Singh S, Chatzistamou I, Shrestha L, Gauthier T, et al. Lipidated Peptidomimetic Ligand-Functionalized HER2 Targeted Liposome as Nano-Carrier Designed for Doxorubicin Delivery in Cancer Therapy. Pharmaceuticals (Basel). 2021;14(3).
100. Lin C, Zhang X, Chen H, Bian Z, Zhang G, Riaz MK, et al. Dual-ligand modified liposomes provide effective local targeted delivery of lung-cancer drug by antibody and tumor lineage-homing cell-penetrating peptide. Drug Deliv. 2018;25(1):256–266.
101. Han Y, Zhang P, Chen Y, Sun J, Kong F. Co-delivery of plasmid DNA and doxorubicin by solid lipid NPs for lung cancer therapy. Int J Mol Med. 2014;34(1):191–196.
102. Kim J, Ramasamy T, Choi JY, Kim ST, Youn YS, Choi HG, et al. PEGylated polypeptide lipid nanocapsules to enhance the anticancer efficacy of erlotinib in non-small cell lung cancer. Colloids Surf B Biointerfaces. 2017;150:393–401.
103. Wang JY, Song YQ, Peng J, Luo HL. Nanostructured Lipid Carriers Delivering Sorafenib to Enhance Immunotherapy Induced by Doxorubicin for Effective Esophagus Cancer Therapy. ACS Omega. 2020;5(36):22840–22846.
104. Dilnawaz D, Sahoo S. Augmented Anticancer Efficacy by si-RNA Complexed Drug-Loaded Mesoporous Silica NPs in Lung Cancer Therapy. ACS Appl Nano Mater. 2018;1.
105. Amreddy N, Babu A, Panneerselvam J, Srivastava A, Muralidharan R, Chen A, et al. Chemo-biologic combinatorial drug delivery using folate receptor-targeted dendrimer NPs for lung cancer treatment. Nanomedicine. 2018 Feb;14(2):373–384.
106. Han Y, Li Y, Zhang P, Sun J, Li X, Sun X, et al. Nanostructured lipid carriers as novel drug delivery system for lung cancer gene therapy. Pharm Dev Technol. 2016;21(3):277–281.
107. Kamazani FM, Sotoodehnejad Nematalahi F, Siadat SD, Pornour M, Sheikhpour M. A success targeted nano delivery to lung cancer cells with multi-walled carbon nanotubes conjugated to bromocriptine. Sci Rep. 2021;11(1):24419.
108. Yang Q, Peng J, Xiao Y, Li W, Tan L, Xu X, et al. Porous Au@Pt NPs: Therapeutic Platform for Tumor Chemo-Photothermal Co-Therapy and Alleviating Doxorubicin-Induced Oxidative Damage. ACS Appl Mater Interfaces. 2018;10(1):150–164.
109. Crous A, Abrahamse H. Effective Gold Nanoparticle-Antibody-Mediated Drug Delivery for Photodynamic Therapy of Lung Cancer Stem Cells. Int J Mol Sci. 2020;21(11).
110. Ruzycka-Ayoush M, Kowalik P, Kowalczyk A, Bujak P, Nowicka AM, Wojewodzka M, et al. Quantum dots as targeted doxorubicin drug delivery nanosystems. Cancer Nanotechnol (Internet). 2021;12(1):1–27.
111. Gandhi S, Roy I. Lipid-Based Inhalable Micro- and Nanocarriers of Active Agents for Treating Non-Small-Cell Lung Cancer. Pharmaceutics. 2023;15(5).
112. Zhang Y, Li A, Wang Z, Han Z, He J, Ma J. Antimetastatic activities of pegylated liposomal doxorubicin in a murine metastatic lung cancer model. J Drug Target. 2008;16(9):679–87.
113. Suzuki S, Kawakami S, Chansri N, Yamashita F, Hashida M. Inhibition of pulmonary metastasis in mice by all-trans retinoic acid incorporated in cationic liposomes. J Control release Off J Control Release Soc. 2006;116(1):58–63.
114. Siddikuzzaman, Grace VMB. Anti-metastatic study of liposome-encapsulated all trans retinoic acid (ATRA) in B16F10 melanoma cells-implanted C57BL/6 mice. Cancer Invest. 2014;32(10):507–17.
115. Hamad I, Harb AA, Bustanji Y. Liposome-Based Drug Delivery Systems in Cancer Research: An Analysis of

Global Landscape Efforts and Achievements. Pharmaceutics. 2024;16(3).
116. Fulton MD, Najahi-Missaoui W. Liposomes in Cancer Therapy: How Did We Start and Where Are We Now. Int J Mol Sci. 2023;24(7).
117. Koshkina N V, Waldrep JC, Roberts LE, Golunski E, Melton S, Knight V. Paclitaxel liposome aerosol treatment induces inhibition of pulmonary metastases in murine renal carcinoma model. Clin cancer Res an Off J Am Assoc Cancer Res. 2001;7(10):3258–62.
118. Sawant SS, Patil SM, Shukla SK, Kulkarni NS, Gupta V, Kunda NK. Pulmonary delivery of osimertinib liposomes for non-small cell lung cancer treatment: formulation development and in vitro evaluation. Drug Deliv Transl Res. 2022;12(10):2474–87.
119. Wang X, Cai H, Huang X, Lu Z, Zhang L, Hu J, et al. Formulation and evaluation of a two-stage targeted liposome coated with hyaluronic acid for improving lung cancer chemotherapy and overcoming multidrug resistance. J Biomater Sci Polym Ed. 2023;34(14):1928–51.
120. Omidian H, Gill EJ, Cubeddu LX. Lipid NPs in Lung Cancer Therapy. Pharmaceutics. 2024;16(5).
121. German-Cortés J, Vilar-Hernández M, Rafael D, Abasolo I, Andrade F. Solid Lipid NPs: Multitasking Nano-Carriers for Cancer Treatment. Pharmaceutics. 2023;15(3).
122. Sukumar UK, Bhushan B, Dubey P, Matai I, Sachdev A, Packirisamy G. Emerging applications of NPs for lung cancer diagnosis and therapy. Int Nano Lett. 2013;3(1):1–17.
123. Rosière R, Van Woensel M, Gelbcke M, Mathieu V, Hecq J, Mathivet T, et al. New Folate-Grafted Chitosan Derivative To Improve Delivery of Paclitaxel-Loaded Solid Lipid NPs for Lung Tumor Therapy by Inhalation. Mol Pharm. 2018;15(3):899–910.
124. Naseri N, Zakeri P, Hamishehkar H, Pilehvar Y, Valizadeh H. Development, In Vitro Characterization, Antitumor and Aerosol Performance Evaluation of Respirable Prepared by Self-nanoemulsification Method. Drug Res (Stuttg). 2017;67.
125. Najib Ullah SNM, Afzal O, Altamimi ASA, Alossaimi MA, Almalki WH, Alzahrani A, et al. Bedaquiline-Loaded Solid Lipid NPs Drug Delivery in the Management of Non-Small-Cell Lung Cancer (NSCLC). Pharmaceuticals (Basel). 2023;16(9).
126. Sivadasan D, Ramakrishnan K, Mahendran J, Ranganathan H, Karuppaiah A, Rahman H. Solid Lipid NPs: Applications and Prospects in Cancer Treatment. Int J Mol Sci. 2023;24(7).
127. Mittal P, Saharan A, Verma R, Altalbawy FMA, Alfaidi MA, Batiha GES, et al. Dendrimers: A New Race of Pharmaceutical Nanocarriers. Biomed Res Int. 2021;2021:8844030.
128. Cruz A, Barbosa J, Antunes P, Bonifácio VDB, Pinto SN. A Glimpse into Dendrimers Integration in Cancer Imaging and Theranostics. Int J Mol Sci. 2023;24(6).
129. Crintea A, Motofelea AC, Şovrea AS, Constantin AM, Crivii CB, Carpa R, et al. Dendrimers: Advancements and Potential Applications in Cancer Diagnosis and Treatment-An Overview. Pharmaceutics. 2023;15(5).
130. Zhong Q, Bielski ER, Rodrigues LS, Brown MR, Reineke JJ, da Rocha SRP. Conjugation to Poly(amidoamine) Dendrimers and Pulmonary Delivery Reduce Cardiac Accumulation and Enhance Antitumor Activity of Doxorubicin in Lung Metastasis. Mol Pharm. 2016;13(7):2363–2375.
131. Nguyen H, Nguyen NH, Tran NQ, Nguyen CK. Improved Method for Preparing Cisplatin-Dendrimer Nanocomplex and Its Behavior Against NCI-H460 Lung Cancer Cell. J Nanosci Nanotechnol. 2015;15(6):4106–4110.
132. Wang H, Zheng L, Peng C, Shen M, Shi X, Zhang G. Folic acid-modified dendrimer-entrapped gold NPs as nanoprobes for targeted CT imaging of human lung adencarcinoma. Biomaterials. 2013;34(2):470–480.
133. Hsu HJ, Palka-Hamblin H, Bhide GP, Myung JH, Cheong M, Colley KJ, et al. Noncatalytic Endosialidase Enables Surface Capture of Small-Cell Lung Cancer Cells Utilizing Strong Dendrimer-Mediated Enzyme-Glycoprotein Interactions. Anal Chem. 2018;90(6):3670–5.
134. Zhang WW, Wang YC, Kan XM, Wang XM, Geng DM. Preparation and evaluation of peptide-dendrimer-paclitaxel conjugates for treatment of heterogeneous stage 1 non-small cell lung cancer in 293T and L132 cell lines. Trop J Pharm Res. 2017;16(4):737–42.
135. Ryan GM, Kaminskas LM, Bulitta JB, McIntosh MP, Owen DJ, Porter CJH. PEGylated polylysine dendrimers increase lymphatic exposure to doxorubicin when compared to PEGylated liposomal and solution formulations of doxorubicin. J Control release Off J Control Release Soc. 2013;172(1):128–36.
136. Soni N, Jain K, Gupta U, Jain N. Controlled delivery of Gemcitabine Hydrochloride using mannosylated poly(propyleneimine) dendrimers. J Nanoparticle Res. 2015;17.
137. Ren L, Wang L, Rehberg M, Stoeger T, Zhang J, Chen S. Applications and Immunological Effects of Quantum Dots on Respiratory System. Front Immunol. 2022;12(January):1–10.
138. Hamidu A, Pitt WG, Husseini GA. Recent Breakthroughs in Using Quantum Dots for Cancer Imaging and Drug Delivery Purposes. Nanomater (Basel, Switzerland). 2023;13(18).
139. Nabil M, Megahed F. Quantum Dot Nanomaterials: Preparation, Characterization, Advanced Bio-Imaging and Therapeutic Applications. J Fluoresc. 2023;
140. Liu L, Wu S, Jing F, Zhou H, Jia C, Li G, et al. Bead-based microarray immunoassay for lung cancer biomarkers using quantum dots as labels. Biosens Bioelectron. 2016;80:300–306.
141. Huang X, Chen Q, Li X, Lin C, Wang K, Luo C, et al. CKAP4 Antibody-Conjugated Si Quantum Dot Micelles for Targeted Imaging of Lung Cancer. Nanoscale Res Lett. 2021;16(1):124.
142. Lima-Tenório MK, Pineda EAG, Ahmad NM, Fessi H, Elaissari A. Magnetic NPs: In vivo cancer diagnosis and therapy. Int J Pharm. 2015;493(1–2):313–327.

143. Fathi Karkan S, Mohammadhosseini M, Panahi Y, Milani M, Zarghami N, Akbarzadeh A, et al. Magnetic NPs in cancer diagnosis and treatment: a review. Artif cells, nanomedicine, Biotechnol. 2017;45(1):1–5.
144. Alromi DA, Madani SY, Seifalian A. Emerging Application of Magnetic NPs for Diagnosis and Treatment of Cancer. Polymers (Basel). 2021;13(23).
145. Hosu O, Tertis M, Cristea C. Implication of magnetic NPs in cancer detection, screening and treatment. Magnetochemistry. 2019;5(4).
146. Saadat M, Manshadi MKD, Mohammadi M, Zare MJ, Zarei M, Kamali R, et al. Magnetic particle targeting for diagnosis and therapy of lung cancers. J Control release Off J Control Release Soc. 2020;328:776–91.
147. McEver RP, Luscinskas FW. Cell Adhesion. Hematol Basic Princ Pract. 2017;70:127–134.
148. Tseng CL, Chang KC, Yeh MC, Yang KC, Tang T, Lin FH. Development of a dual-functional Pt–Fe-HAP magnetic NPs application for chemo-hyperthermia treatment of cancer. Ceram Int. 2014;40:5117–5127.
149. Ma J, Zhang Z, Zhang Z, Huang J, Qin Y, Li X, et al. Magnetic nanoparticle clusters radiosensitise human nasopharyngeal and lung cancer cells after alternating magnetic field treatment. Int J Hyperth Off J Eur Soc Hyperthermic Oncol North Am Hyperth Gr. 2015;31(7):800–812.
150. Baskar G, Ravi M, Panda JJ, Khatri A, Dev B, Santosham R, et al. Efficacy of Dipeptide-Coated Magnetic NPs in Lung Cancer Models Under Pulsed Electromagnetic Field. Cancer Invest. 2017;35(6):431–442.
151. Araya T, Kasahara K, Nishikawa S, Kimura H, Sone T, Nagae H, et al. Antitumor effects of inductive hyperthermia using magnetic ferucarbotran NPs on human lung cancer xenografts in nude mice. Onco Targets Ther. 2013;6:237–242.
152. Xiao X, Teng F, Shi C, Chen J, Wu S, Wang B, et al. Polymeric NPs—Promising carriers for cancer therapy. Front Bioeng Biotechnol. 2022;10(October):1–20.
153. Tosi G, Bortot B, Ruozi B, Dolcetta D, Vandelli MA, Forni F, et al. Potential use of polymeric NPs for drug delivery across the blood-brain barrier. Curr Med Chem. 2013;20(17):2212–2225.
154. Dristant U, Mukherjee K, Saha S, Maity D. An Overview of Polymeric NPs-Based Drug Delivery System in Cancer Treatment. Technol Cancer Res Treat. 2023;22:15330338231152084.
155. Gagliardi A, Giuliano E, Venkateswararao E, Fresta M, Bulotta S, Awasthi V, et al. Biodegradable Polymeric NPs for Drug Delivery to Solid Tumors. Front Pharmacol. 2021;12:601626.
156. Jiang ZM, Dai SP, Xu YQ, Li T, Xie J, Li C, et al. Crizotinib-loaded polymeric NPs in lung cancer chemotherapy. Med Oncol. 2015;32(7):193.
157. Kim DW, Kim SY, Kim HK, Kim SW, Shin SW, Kim JS, et al. Multicenter phase II trial of Genexol-PM, a novel Cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. Ann Oncol Off J Eur Soc Med Oncol. 2007;18(12):2009–2014.
158. Wang W, Xi M, Duan X, Wang Y, Kong F. Delivery of baicalein and paclitaxel using self-assembled NPs: synergistic antitumor effect in vitro and in vivo. Int J Nanomedicine. 2015;10:3737–3750.
159. Perumal S, Atchudan R, Lee W. A Review of Polymeric Micelles and Their Applications. Polymers (Basel). 2022;14(12).
160. Kaur J, Gulati M, Jha NK, Disouza J, Patravale V, Dua K, et al. Recent advances in developing polymeric micelles for treating cancer: Breakthroughs and bottlenecks in their clinical translation. Drug Discov Today. 2022;27(5):1495–1512.
161. Wang Q, Atluri K, Tiwari AK, Babu RJ. Exploring the Application of Micellar Drug Delivery Systems in Cancer Nanomedicine. Pharmaceuticals (Basel). 2023;16(3).
162. Zhang Y, Huang Y, Li S. Polymeric micelles: nanocarriers for cancer-targeted drug delivery. AAPS PharmSciTech. 2014;15(4):862–871.
163. Jin GW, Rejinold NS, Choy JH. Multifunctional Polymeric Micelles for Cancer Therapy. Polymers (Basel). 2022;14(22).
164. Guthi JS, Yang SG, Huang G, Li S, Khemtong C, Kessinger CW, et al. MRI-visible micellar nanomedicine for targeted drug delivery to lung cancer cells. Mol Pharm. 2010;7(1):32–40.
165. Zhang Q, Bao J, Duan T, Hu M, He Y, Wang J, et al. Nanomicelle-Microsphere Composite as a Drug Carrier to Improve Lung-Targeting Specificity for Lung Cancer. Pharmaceutics. 2022;14(3).
166. Sharma M, Alessandro P, Cheriyamundath S, Lopus M. Therapeutic and diagnostic applications of carbon nanotubes in cancer: recent advances and challenges. J Drug Target. 2024;32(3):287–299.
167. Gao S, Xu B, Sun J, Zhang Z. Nanotechnological advances in cancer: therapy a comprehensive review of carbon nanotube applications. Front Bioeng Biotechnol. 2024;12(March):1–17.
168. Luanpitpong S, Wang L, Rojanasakul Y. The effects of carbon nanotubes on lung and dermal cellular behaviors. Nanomedicine (Lond). 2014;9(6):895–912.
169. Arya N, Arora A, Vasu KS, Sood AK, Katti DS. Combination of single walled carbon nanotubes/graphene oxide with paclitaxel: a reactive oxygen species mediated synergism for treatment of lung cancer. Nanoscale (Internet). 2013;5(7):2818–2829.
170. Yu B, Tan L, Zheng R, Tan H, Zheng L. Targeted delivery and controlled release of Paclitaxel for the treatment of lung cancer using single-walled carbon nanotubes. Mater Sci Eng C Mater Biol Appl. 2016;68:579–584.
171. Zakaria AB, Picaud F, Rattier T, Pudlo M, Dufour F, Saviot L, et al. Nanovectorization of TRAIL with single wall carbon nanotubes enhances tumor cell killing. Nano Lett. 2015;15(2):891–895.
172. Al Faraj A, Shaik A, Halwani R, Alfuraih A. Magnetic Targeting and Delivery of Drug-Loaded SWCNTs Theranostic Nanoprobes to Lung Metastasis in Breast Cancer Animal Model: Noninvasive Monitoring Using

Magnetic Resonance Imaging. Mol Imaging Biol. 2015;1–10.
173. Singh N, Sachdev A, Gopinath P. Polysaccharide Functionalized Single Walled Carbon Nanotubes as Nanocarriers for Delivery of Curcumin in Lung Cancer Cells. J Nanosci Nanotechnol. 2018;18(3):1534–1541.
174. Cao Y, Huang HY, Chen LQ, Du HH, Cui JH, Zhang LW, et al. Enhanced Lysosomal Escape of pH-Responsive Polyethylenimine-Betaine Functionalized Carbon Nanotube for the Codelivery of Survivin Small Interfering RNA and Doxorubicin. ACS Appl Mater Interfaces. 2019;11(10):9763–9776.
175. Razzazan A, Atyabi F, Kazemi B, Dinarvand R. In vivo drug delivery of gemcitabine with PEGylated single-walled carbon nanotubes. Mater Sci Eng C Mater Biol Appl. 2016;62:614–625.
176. Guo C, Al-Jamal WT, Toma FM, Bianco A, Prato M, Al-Jamal KT, et al. Design of Cationic Multiwalled Carbon Nanotubes as Efficient siRNA Vectors for Lung Cancer Xenograft Eradication. Bioconjug Chem. 2015;26(7):1370–1379.
177. Salas-Treviño D, Saucedo-Cárdenas O, De Jesús Loera-Arias M, Rodríguez-Rocha H, García-García A, Montes-De-Oca-Luna R, et al. Hyaluronate functionalized multi-wall carbon nanotubes filled with carboplatin as a novel drug nanocarrier against murine lung cancer cells. Nanomaterials. 2019;9(11).
178. Lodhi N, Mehra NK, Jain NK. Development and characterization of dexamethasone mesylate anchored on multi walled carbon nanotubes. J Drug Target. 2013;21(1):67–76.
179. Son KH, Hong JH, Lee JW. Carbon nanotubes as cancer therapeutic carriers and mediators. Int J Nanomedicine. 2016;11:5163–5185.
180. Cirillo G, Vittorio O, Kunhardt D, Valli E, Voli F, Farfalla A, et al. Combining carbon nanotubes and chitosan for the vectorization of methotrexate to lung cancer cells. Materials (Basel). 2019;12(18):1–14.
181. Li J, Pant A, Chin CF, Ang WH, Ménard-Moyon C, Nayak TR, et al. In vivo biodistribution of platinum-based drugs encapsulated into multi-walled carbon nanotubes. Nanomedicine. 2014;10(7):1465–75.
182. Tan JM, Karthivashan G, Arulselvan P, Fakurazi S, Hussein MZ. Characterization and in vitro studies of the anticancer effect of oxidized carbon nanotubes functionalized with betulinic acid. Drug Des Devel Ther. 2014;8:2333–2343.
183. Singh RP, Sharma G, Sonali, Singh S, Patne SCU, Pandey BL, et al. Effects of transferrin conjugated multi-walled carbon nanotubes in lung cancer delivery. Mater Sci Eng C Mater Biol Appl. 2016;67:313–25.
184. Zare H, Ahmadi S, Ghasemi A, Ghanbari M, Rabiee N, Bagherzadeh M, et al. Carbon nanotubes: Smart drug/gene delivery carriers. Int J Nanomedicine. 2021;16:1681–1706.
185. Heger Z, Polanska H, Krizkova S, Balvan J, Raudenska M, Dostalova S, et al. Co-delivery of VP-16 and Bcl-2-targeted antisense on PEG-grafted oMWCNTs for synergistic in vitro anti-cancer effects in non-small and small cell lung cancer. Colloids Surf B Biointerfaces. 2017;150:131–140.
186. Kass LE, Nguyen J. Nanocarrier-hydrogel composite delivery systems for precision drug release. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2022;14(2):e1756.
187. Chyzy A, Tomczykowa M, Plonska-Brzezinska ME. Hydrogels as potential nano-, micro- and macro-scale systems for controlled drug delivery. Materials (Basel). 2020;13(1):188.
188. Lee P, Lok CN, Che CM, Kao WJ. A Multifunctional Hydrogel Delivers Gold Compound and Inhibits Human Lung Cancer Xenograft. Pharm Res. 2019;36(4):61.
189. Zubris KA V, Colson YL, Grinstaff MW. Hydrogels as intracellular depots for drug delivery. Mol Pharm. 2012;9(1):196–200.
190. Matsumoto A, Chen J, Collette AL, Kim UJ, Altman GH, Cebe P, et al. Mechanisms of silk fibroin sol-gel transitions. J Phys Chem B. 2006;110(43):21630–8.
191. Jacob S, Nair A, Shah J, Sreeharsha N, Gupta S, Pottathil S. Emerging Role of Hydrogels in Drug Delivery Systems, Tissue Engineering and Wound Management. Pharmaceutics. 2021;13:357.
192. Niżnik Ł, Noga M, Kobylarz D, Frydrych A, Krośniak A, Kapka-Skrzypczak L, et al. Gold NPs (AuNPs)-Toxicity, Safety and Green Synthesis: A Critical Review. Int J Mol Sci. 2024;25(7).
193. Sengupta A, Azharuddin M, Al-Otaibi N, Hinkula J. Efficacy and Immune Response Elicited by Gold Nanoparticle- Based Nanovaccines against Infectious Diseases. Vaccines. 2022;10(4).
194. Jain S, Hirst DG, O'Sullivan JM. Gold NPs as novel agents for cancer therapy. Br J Radiol. 2012;85(1010):101–13.
195. Thambiraj S, Shruthi S, Vijayalakshmi R, Ravi Shankaran D. Evaluation of cytotoxic activity of docetaxel loaded gold NPs for lung cancer drug delivery. Cancer Treat Res Commun. 2019;21:100157.
196. Kumari V, Vishwas S, Kumar R, Kakoty V, Khursheed R, Babu M, et al. Anoverview of biomedical applications for gold NPs against lung cancer. J Drug Deliv Sci Technol. 2023;86:104729.
197. Bardoliwala D, Javia A, Ghosh S, Misra A, Sawant K. Formulation and clinical perspectives of inhalation-based nanocarrier delivery: a new archetype in lung cancer treatment. Ther Deliv. 2021;12(5):397–418.
198. Gupta C, Jaipuria A, Gupta N. Inhalable Formulations to Treat Non-Small Cell Lung Cancer (NSCLC): Recent Therapies and Developments. Pharmaceutics. 2023;15(1).
199. Al Khatib AO, El-Tanani M, Al-Obaidi H. Inhaled Medicines for Targeting Non-Small Cell Lung Cancer. Pharmaceutics. 2023;15(12).
200. Garbuzenko OB, Mainelis G, Taratula O, Minko T. Inhalation treatment of lung cancer: the influence of composition, size and shape of nanocarriers on their lung accumulation and retention. Cancer Biol Med. 2014;11(1):44–55.

201. Yu XY, Jin X, Shou ZX. Surface-engineered smart nanocarrier-based inhalation formulations for targeted lung cancer chemotherapy: a review of current practices. Drug Deliv. 2021;28(1):1995–2010.
202. Choi SH, Byeon HJ, Choi JS, Thao L, Kim I, Lee ES, et al. Inhalable self-assembled albumin NPs for treating drug-resistant lung cancer. J Control release Off J Control Release Soc. 2015;197:199–207.
203. Pontes JF, Grenha A. Multifunctional Nanocarriers for Lung Drug Delivery. Nanomater (Basel, Switzerland). 2020;10(2).
204. Aryal S, Park S, Park H, Park C, Kim WC, Thakur D, et al. Clinical Trials for Oral, Inhaled and Intravenous Drug Delivery System for Lung Cancer and Emerging Nanomedicine-Based Approaches. Int J Nanomedicine. 2023;18:7865–7888.
205. Walker JF, Yu J. A direct injection technique for investigation of lung sensory properties and reflex functions. Exp Physiol. 2021;106(7):1449–1459.
206. Huang TT, Parab S, Burnett R, Diago O, Ostertag D, Hofman FM, et al. Intravenous administration of retroviral replicating vector, Toca 511, demonstrates therapeutic efficacy in orthotopic immune-competent mouse glioma model. Hum Gene Ther. 2015;26(2):82–93.
207. Leijen S, Burgers SA, Baas P, Pluim D, Tibben M, van Werkhoven E, et al. Phase I/II study with ruthenium compound NAMI-A and gemcitabine in patients with non-small cell lung cancer after first line therapy. Invest New Drugs. 2015;33(1):201–14.
208. Wu L, Leng D, Cun D, Foged C, Yang M. Advances in combination therapy of lung cancer: Rationales, delivery technologies and dosage regimens. J Control release Off J Control Release Soc. 2017;260:78–91.
209. Al Bostami RD, Abuwatfa WH, Husseini GA. Recent Advances in Nanoparticle-Based Co-Delivery Systems for Cancer Therapy. Nanomater (Basel, Switzerland). 2022;12(15).
210. Cui T, Sihao Z, Sun H. Co-delivery of doxorubicin and pH-sensitive curcumin prodrug by transferrin-targeted NPs for breast cancer treatment. Oncol Rep. 2017;37(2):1253–1260.
211. Zheng HR, Jiang AM, Gao H, Liu N, Zheng XQ, Fu X, et al. The efficacy and safety of anlotinib combined with platinum-etoposide chemotherapy as first-line treatment for extensive-stage small cell lung cancer: A Chinese multicenter real-world study. Front Oncol. 2022;12:894835.
212. Carrick S, Parker S, Thornton CE, Ghersi D, Simes J, Wilcken N. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev. 2009;2009(2):CD003372.
213. Cancer Nano-Therapies in the Clinic and Clinical Trials - NCI.
214. Desai N. Challenges in development of nanoparticle-based therapeutics. AAPS J. 2012;14(2):282–95.
215. Lv Y, Zou Y, Yang L. Feasibility study for thermal protection by microencapsulated phase change micro/NPs during cryosurgery. Chem Eng Sci. 2011;66:3941–3953.
216. Xia Y, Rao L, Yao H, Wang Z, Ning P, Chen X. Engineering Macrophages for Cancer Immunotherapy and Drug Delivery. Adv Mater. 2020;32(40):e2002054.
217. Love KT, Mahon KP, Levins CG, Whitehead KA, Querbes W, Robert J. in vivo gene silencing. 2010;107(5):2–7.
218. Babu A, Templeton A, Munshi A, Ramesh R. Nanoparticle-Based Drug Delivery for Therapy of Lung Cancer: Progress and Challenges. J Nanomater. 2013;2013:1–11.
219. Sharma A, Tonk R, Shekhar R, Dohare S, Kumar D. Need to focus on inhibitory activity of benzimidazole analogues against indolamine 2,3-dioxygenase-1 (IDO-1). EXCLI J. 2022;21:904–905.
220. Xie L, Xie D, Du Z, Xue S, Wang K, Yu X, et al. A novel therapeutic outlook: Classification, applications and challenges of inhalable micron/nanoparticle drug delivery systems in lung cancer (Review). Int J Oncol. 2024;64(4).