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Nanoengineered polymers and other organic materials in lung cancer treatment: Bridging the gap between research and clinical applications

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ABSTRACT

Cancer remains a major global health challenge, with increasing incidence and mortality rates projected for the coming years. Lung cancer, in particular, poses significant obstacles due to late-stage diagnosis and limited treatment options. While advancements in molecular diagnostics have been made, there is a critical need to connect the dots between laboratory and hospital for better lung cancer treatment. Systemic therapy plays a crucial role in treating advanced-stage lung cancer, and recent efforts have focused on developing innovative drug delivery techniques. Nanoparticles (NPs) have emerged as a promising approach to lung cancer treatment, offering enhanced drug delivery, active targeting, and reduced toxicity. Organic-based nanomaterials, like polymeric nanoparticles, solid lipid nanoparticles, and liposomes hold great potential in this field. This review examines the application of NPs in lung cancer treatment, highlights current therapies, explores organic nanoparticle-based approaches, and discusses limitations and future perspectives in clinical translation.

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1. Introduction

Annually, nearly 18 million fresh cancer cases are diagnosed, leading to an estimated 9.6 million fatalities [1]. Unfortunately, the International Agency for Research on Cancer anticipates a rise in the number of new cancer cases to 22.2 million and approximately 13.2 million deaths worldwide by the year 2030 [1].

According to a recent report from the World Health Organization (WHO), lung cancer ranks as the sixth leading cause of mortality, accounting for nearly 1.8 % of total deaths. However, the early diagnosis and treatment of lung cancer continue to present significant challenges [2]. Factors such as drastic changes in environmental conditions, unhealthy lifestyles, and exposure to pollutants and radiation contribute to the projection that the number of lung cancer cases could increase by almost 50 % over the next 20 years [3,4]. Despite progress in diagnosing cancer at a molecular level, there remains a gap in translating these advancements into clinically relevant understanding, highlighting the need for further research on lung cancer for effective therapy [5,6].

Among the conventional therapeutic techniques such as chemotherapy, radiotherapy, biological therapy, and surgery, the percentage of patients presenting in the early stage, suitable for local treatments like resection and radiation, is relatively low due to advanced-stage diagnosis or metastasis at the time of presentation [7]. As a result, systemic therapy remains a key component in lung cancer treatment. In recent years, researchers have shifted their focus toward developing new molecules and drug delivery techniques to enhance efficacy while reducing toxicity [8,9].

The shortcomings of conventional chemotherapy treatments have been effectively addressed by advances in drug nanotechnology [10]. Nanoparticles (NPs) are distinguished by their tiny size, high surface area to volume ratio, capacity to be biocompatible and biodegrade, and low cost. Importantly, NPs can passively target tumor cells, and with surface modifications, they can achieve active targeting, therefore, anticancer medications have a greater therapeutic effect and lower toxicity [11–15]. Nanomedicine is a novel therapy modality with the potential to increase medication delivery and therapeutic benefits with reduced collateral damage to healthy tissues [16–18]. Various types of nanoscale organic-based biomaterials, such as dendrimer-highly branched NPs, polymeric NPs (polylactic acid, polylactide, polycaprolactone, gelatine, chitosan, and sodium alginate), nanostructured lipid based delivery systems are being employed in the treatment of lung cancer (Table 1) [9,19–23].

These nanoscale organic-based biomaterials possess intrinsic physicochemical properties like biocompatibility and controlled release capabilities that make them well-suited for drug delivery applications [24]. For instance, polymeric nanoparticles made of PLGA or chitosan are biodegradable by endogenous enzymes and hydrolysis under physiological conditions [25]. Their controlled erosion enables gradual drug release over timescales matching therapeutic needs. Lipid-based nanostructures also exhibit high biocompatibility due to their structural similarity to endogenous lipoproteins [26].

These nanomaterials can also be surface-functionalized with tumor-targeting ligands to impart active targeting and further improve specificity [27]. Common targeting moieties include antibodies, peptides, or small molecules that bind overexpressed receptors on lung cancer cells [28]. Conjugating these ligands enhances nanoparticle adhesion and internalization by cancer cells while avoiding healthy tissue.

The nanoscale size and porous nature of these carriers also facilitate high drug loading capacities, extending circulation half-lives to days or weeks compared to hours for free drug [29]. Their tunable properties can decrease drug leakage in blood circulation and tailored to optimize biodistribution profiles [30]. Controller release then concentrates and retains drug payloads specifically at tumor sites.

In this review, we will explore the potential application of NPs in the treatment of lung cancer. First, current therapy will be introduced and then the organic-based nanomaterials for the treatment of lung cancer will be represented. Finally, the limitations of using organic nanoparticles in the clinical sector will be discussed with future perspectives.

2. Nanoscale organic materials for lung cancer

2.1. Polymers

Polymeric nanoparticles have been the subject of much research as a potential cancer therapy [44]. Due to their favorable chemical and physical properties, polymeric nanoparticles are a promising drug delivery vehicle for anticancer drugs [12,33,45–47] The production of nanoparticles comprises the straightforward manipulation of surface charge and particle size, as well as the capability of enclosing selected ligands into a large range of functional groups, like micelles, colloids, dendrimers, or capsules [48–50]. synthetic and natural polymers with a variety of structural configurations could be employed. Among these organic polymers are of particular interest and they are widely used in cancer treatment [51]. Natural biodegradable polymers and manufactured nontoxic biodegradable polymers are the two main categories of organic polymer materials. Synthetic organic polymers including polyvinylpyrrolidone, polylactide, and polyaniline, as well as naturally occurring organic polymers like chitosan from alkaline deacetylation of chitin, are nontoxic, biocompatible, chemically stable, and ecologically benign. These characteristics broaden the potential applications of organic designed polymers, especially in the medical field [52,53]. Some reports on the use of organic polymer in lung cancer therapy are included in the following paragraphs.

Redox-responsive nano micelles constructed from a disulfide-bond-linked block polymer of polyethylene glycol (PEG) and polylactic acid (PEG-SS-PLA) have been developed as part of a dual-function nano drug

Table 1
Summary of nanoscale organic platforms and key attributes for lung cancer therapy.

Platform	Key constituents	Size range	Key characteristics	Ref.
Polymers	PEG, PLA, PLGA, chitosan	50–400 nm	Biocompatibility, versatile formulation options into nanocarriers, tunable drug release kinetics, non-toxic degradation products	[31–34]
Liposomes	Phospholipids, cholesterol	50–500 nm	Biomimetic, flexible formulations, hydrophobic & hydrophilic drug delivery, capacity for surface modifications, and intrinsic cancer targeting	[35,36]
Dendrimers	Branched polymers with surface groups	1–10 nm	Precise structural control, multifunctional surfaces, high cargo capacity, modular fabrication, ability to penetrate lung tumors, and flexibility to engineer targeted diagnostic/therapeutic systems	[37]
Exosomes	Lipids, proteins, nucleic acids	30–150 nm	Fully biocompatible, biodegradable, intrinsic therapeutic effects, crosses blood–brain barrier	[38–40]
Metal-organic frameworks	EuMOF, ZIF-8, Fe-MOF,	50–300 nm	Ultra high porosity and large surface areas, tunable pore sizes and volumes to accommodate various drug molecules, enable multifunctionality (e.g. targeting, imaging), biocompatibility, facile surface functionalization for targeted lung cancer drug delivery, responsive linkers/structures for microenvironment-triggered drug release	[41–43]

Abrivations: PEG, Polyethylene glycol; PLA, Polylactic acid; PLGA, Poly(lactic-co-glycolic acid); EuMOF, Europium metal–organic framework; ZIF-8, Zeolitic imidazolate framework-8; Fe-MOF, Iron metal–organic framework.

delivery system. These micelles are capable of performing targeted delivery of PEG-SS-PLA drug-loaded vehicles to target cells and tissues by way of glucosamine (AG) modified to PEG-s-s-PLA (AG-PEG).

A dual-function nanoscale carrier has been developed using redox-responsive nano micelles composed of a block polymer i.e., PEG and polylactic acid (PEG-SS-PLA), attached by disulfide bonds. These micelles have the ability to deliver drug-loaded vehicles to specific cells and tissues through modification with glucosamine to form AG-PEG-SS-PLA [54]. These vesicles were designed to target tumor cells through Glucose transporter-1 (GLUT-1) and to regulate drug release via glutathione, both of which have redox-responsive properties. Using paclitaxel (PTX)-resistant A549 lung cells as a model, this bifunctional activity was exploited to defeat drug resistance in cancer cells (Fig. 1**a**). Tumor development was significantly suppressed with the AG-P-SS-P/PTX nanomicelles, as shown by an examination of several formulations containing the same dosage of PTX in resistant A549/ADR-xenografted nude mice (Fig. 1**b**). This work demonstrates that incorporating a disulfide link and AG into functional PTX nanomicelles improves their absorption permeability into drug-resistant tumors, hence increasing their lethal effects on these cancer cells. When comparing AG-P-SS-P nanomicelles to Taxol, Fig. 1**c** shows that the latter does not lead to a significant decrease in body weight. In addition, as there was no difference in toxicity across groups, it was hypothesized that the PEGylated system enhanced the pharmacokinetic profile of the drug, resulting in increased tumor accumulation [54].

Subcutaneous cancer models were used to test the efficacy of glutathione (GSH)-responsive nanomaterials encapsulated with an anticancer medication in targeting and treating non-small cell lung cancer (NSCLC) [55]. Biodegradable polyurethane made up of disulfide links (PU-SS) showed rapid breakdown in the presence of GSH, had excellent cytocompatibility in vitro, and was tissue compatible in vivo. Encapsulation of the anticancer medication cisplatin in PU-SS nanoparticles was employed as a case study (Fig. 2**a**). Cisplatin release kinetics from these nanoparticles were studied in relation to GSH concentrations. In vitro tests measured their blood- and cell-compatibility, their ability to kill cancer cells, and their ability to be taken up by healthy cells. Furthermore, a mouse subcutaneous lung carcinoma model utilizing A549 cells was used to assess the nanoparticles ' in vivo dispersion and therapeutic effectiveness (Fig. 2**b-d).** GPUs' locations in the tumor and other organs of the animal were determined using in vivo biodistribution tests; the findings are shown in Fig. 2**b-d.** There is significant potential in studying and using the cisplatin-loaded glutathione-responsive nanoparticles to boost chemotherapeutic efficacy in lung cancer treatment.

The physicochemical characteristics of a polypyrrole-polyethylenimine nanocomplex have been determined. Its photothermal characteristics intracellularly produced reactive oxygen species, and cytotoxicity mechanism was further described, as was its internalization behavior in lung cancer cells [56]. This synthetic carrier system likely interacts with lung cancer cells by binding to their surface and is

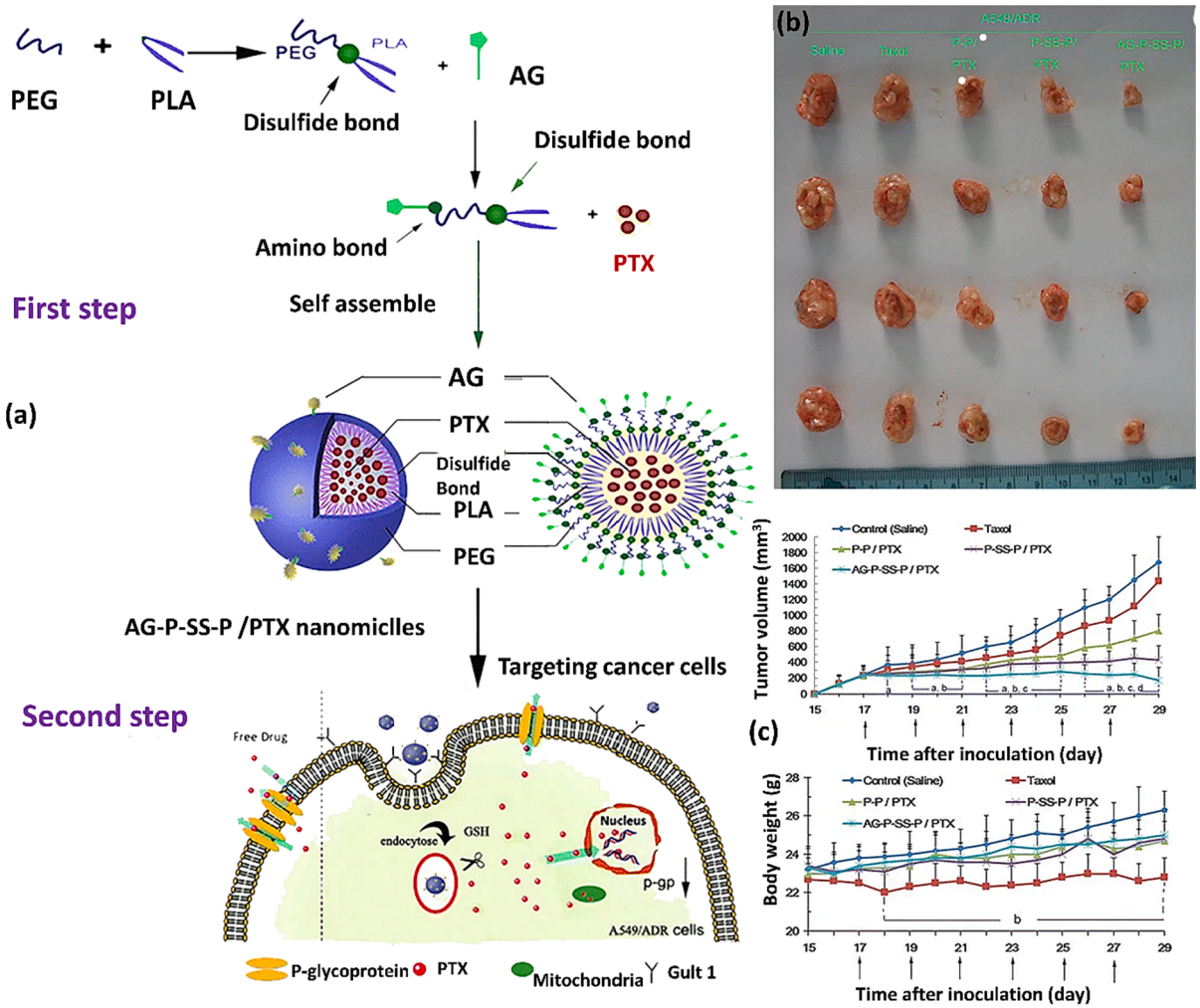

Fig. 1. (a) To reverse multidrug resistance in lung cancer treatment, AG-PEG-SS-PLA nanomicelles are created, targeted to tumors, and internalized by cells, as shown schematically. (b) Images of tumors, and a graph showing how the different formulations affected tumor growth in a mouse model with A549/ADR xenografts (c) Comparison of how much tumor-bearing animals gained or lost as a result of receiving various formulations. Reprinted with permission from ref [54].

Fig. 2. (a) Lung cancer therapy using anticancer agent encapsulated GSH-responsive polymeric nanocarriers, an illustration of drug development. (b) in vivo, fluorescence imaging revealed the localization of cyanine 7-loaded GPU in malignant tissues within 24 h of administration to mice with subcutaneously implanted lung tumors. Estimations based on ex vivo examination of tumor homogenates showed that GPU accumulation in the lung tumor location accounted for approximately 7% (c). Comparing the growth rates of A549 tumors in different treatment groups, (d) demonstrates that mice treated with CGPUs exhibited significantly slower and lower tumor growth compared to those treated with free cisplatin, GPUs, or saline (control). (e) In mice given CGPUs, tumor diameters were reduced as seen in photographs taken ex vivo after removal. Reprinted with permission from ref [55].

then taken in by the cells through endocytosis. The next step would be for the endocytosed nanocomplex to absorb near-infrared and trigger local hyperthermia. Lung cancer ablation may be possible with this photothermal treatment thanks to the induction of intracellularly produced reactive oxygen species.

In another study, To create a smart carrier that can carry two drugs at once, curcumin-loaded niosomes and Rose Bengal were encased in a sphere of chitosan-g-PVCL with an average diameter of 80 nm [57]. Curcumin was selected and placed into the niosome as a model anticancer medication. Afterwards, a chitosan polymer was added to the niosomal carriers; The polymer's muco-adhesive property enhances the adherence of the carriers to mucus, while its positive surface charge facilitates cell attachment. These characteristics have the potential to enhance the bioavailability of the carriers in lung cancer tissue, in addition to the fabrication of stimuli-responsive nanomaterials. A photosensitizer called Rose Bengal, which also has antibacterial properties, was packed away within the transport vehicle. Both kinds of medicines were effectively encapsulated in the synthesized nanocarriers, which also exhibited a temperature and pH-dependent release profile. Both lung cancer cells and Gram-negative bacteria had their growth hindered by these compounds.

2.2. Lipids and liposomes

Submicron colloidal carriers, or solid lipid nanoparticles, have recently gained popularity owing to their potential to be composed of biocompatible components and their capacity to carry both lipophilic and hydrophilic medicines [52,58,59]. Liposomes are vesicles made of phospholipids and are characterized by their spherical shape and double-layer structure. In spite of liposomes' many benefits, including biocompatibility, non-toxicity, and biodegradability, traditional liposomes tend to fuse together, resulting in decreased stability in vivo and increased breakdown through the reticuloendothelial system [60]. Liposomes have had their surface modified by being coated with inert

hydrophilic polymers, such as polyethylene glygocl, to circumvent these restrictions.

Due to its high biocompatibility, liposomes have been the subject of much study over the past decade, leading to the development of several novel formulations like cationic liposomes, temperature-responsive liposomes, virosomes, and archaeosomes [61]. Nanocarriers known as liposomes can have one or more bilayers and can be made from either natural or synthetic lipids [62]. The development of liposomal versions of several authorized medications for lung cancer treatment is ongoing. To treat cancer, scientists created liposomal versions of the drugs etoposide, doxorubicin, paclitaxel, irinotecan, erlotinib, docetaxel, vinorelbine, cisplatin, and epirubicin. Some examples of such materials are

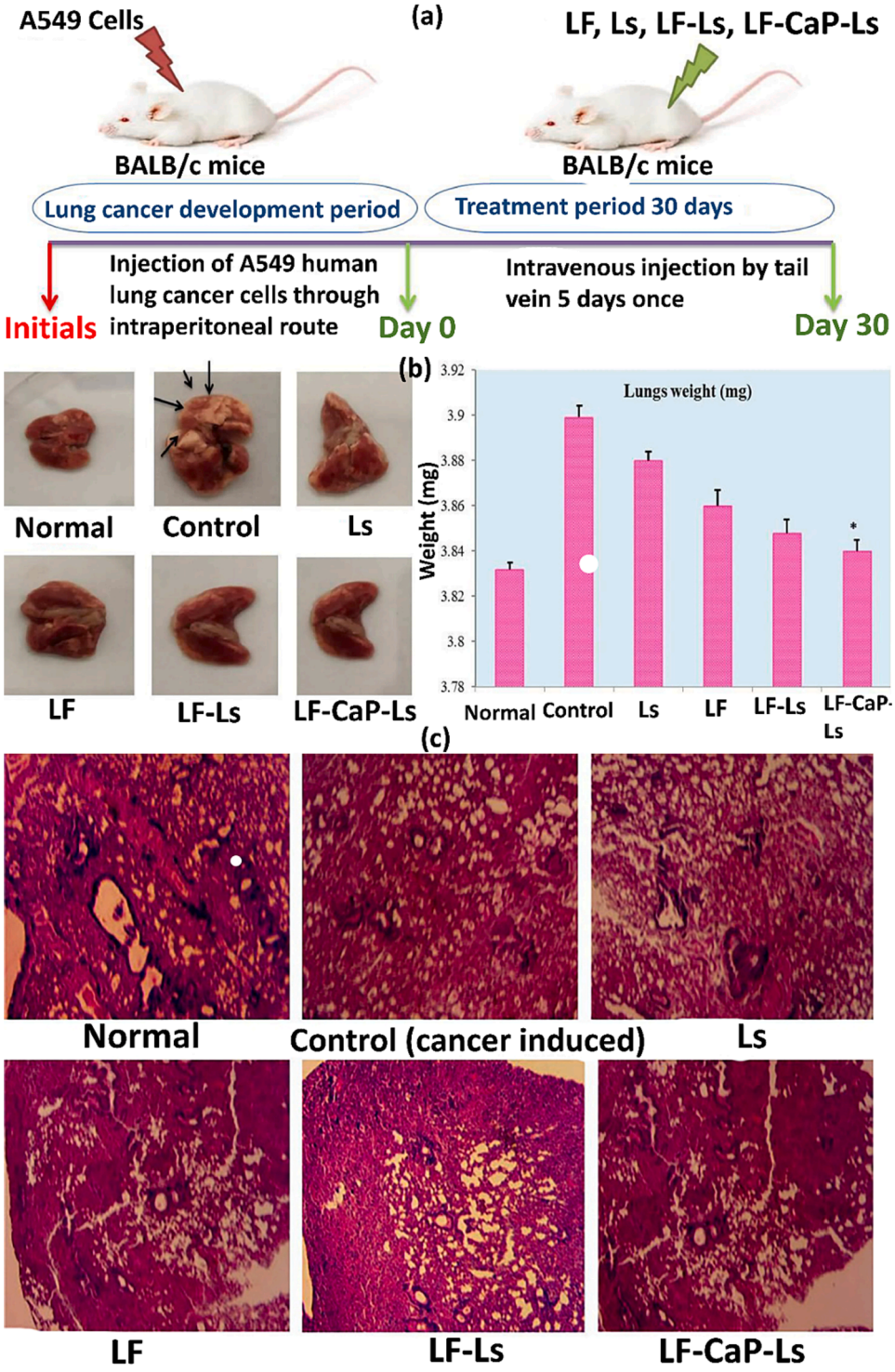

Fig. 3. (a) Illustration of lung cancer growth using A549 cells; animals were treated intravenously once for 5 days with LF, Ls, LF-Ls, or LF-CaP-Ls dependent on their weight. (b) Lung morphology 30 days through various treatment protocols. The normative sample (on the left) has a bloated, deformed, and asymmetrical form. Lung weight (right) as a graphical depiction between treatment groups. (c) Lungs from many groups were histologically examined using H & E staining and displayed under a light microscope with a 10x magnification (normal, control, and tumor-bearing animals). Reprinted with permission from ref [63]. Lf; lumefantrine, Ls; lipid nanoparticles, CaP; nano calcium phosphate.

explained in the following paragraphs.

A pH-sensitive method for umefantrine was created by loading lipid nanoparticles with nano calcium phosphate [63]. The development of lung cancer in BALB/c mice was confirmed, and subsequent anti-tumor testing was undertaken. Lumefantrine, a derivative of artemisinin, was dosed similarly in vivo. A single intravenous dosage of 8 mg/kg was given to BALB/c mice daily for five days (Fig. 3**a**). In Fig. 3**b** pictures of lungs were seen from all the different treatment groups. These findings show that compared to lumefantrine and lumefantrine-CaP- lipid nanoparticles (LF-CaP-Ls), intravenous therapy with LF-CaP-Ls considerably slows the development of lung cancer. Under a light microscope (Motic BA310), lung tissue samples from each group were compared to one another (normal, cancer-induced, LF, LF-Ls, and LF-CaP-Ls) (Fig. 3**c**).

Selective delivery of doxorubicin and siRNA to lung tumor cells while limiting delivery to healthy lung tissue has been shown using lipid nanoparticles targeted to LHRH receptors [64]. Inhalational delivery of paclitaxel was shown to be feasible using nanostructured lipid carriers (LHRHNLC) generated by the luteinizing hormone-releasing receptor. Nanostructured lipid paclitaxel coupled with the luteinizing hormone-releasing receptor demonstrated superior tumor targeting and apoptosis induction relative to both the regular medication and non-targeted NLC nanoparticles. Phospholipids and poloxamer 188 were used to create a hybrid liposomal system loaded with doxorubicin that was vulnerable to the cancer-cell-expressed phospholipase A2 (PLA2) enzyme [65]. Drug release was increased by a factor of 8 due to the presence of the PLA2 enzyme. Nanocrystal medications for localized cancer therapy can be encapsulated in enzyme-responsive nanocarriers and delivered via the pulmonary route.

2.3. Dendrimers

Dendrimers are molecules that have a spherical or globular shape and are intensively branching, as well as extremely biocompatible, evenly organized, and complicated. Their diameter is on the order of 210 nm [66]. The dendrimer's deepest core is shaped like a tree and has several extensions linked to it. This tree-like structure contains the dendrimer's core [67,68]. There are two distinct types of it: high-molecular-weight dendrimers, which include brush, dendronized, and hyperbranched polymers; and low-molecular-weight dendrimers, which include highly symmetrical and monodispersed polymers [69]. Dendrimers are distinguished from other molecules by a number of characteristics, including their ability to take up multiplevalent charges, their core's excessive degree of branching, their spherical uniformity, and their weight. Due to their interesting properties, they have been added to the growing list of novel drug delivery scaffolds [70].

Dendrimers are a common and versatile nanocarrier system for the targeted administration of chemotherapeutics due to their malleability in terms of size, shape, and surface properties [37]. They have a central core that acts as an inducer, a number of inner branches that are organized in layers, and a number of surface end groups that can be used for covalent conjugation. They are attractive platforms for drug administration due to their broad size range of nanoparticles, speed of synthesis, propensity to conjugate, and capacity to display many copies of the deadly functional groups essential for rearrangement [71,72]. The following paragraphs elaborate on some such instances.

Nanocomposites consisting of erlotinib and polyamidoamine dendrimers were developed for the non-invasive treatment of NSCLC [73]. In vivo, comparisons with neutral G5 erlotinib-loaded dendrimers and erlotinib alone revealed that cationic G4 erlotinib-loaded dendrimers exhibited higher selectivity and greater antiproliferative effects against A549 lung cells. These findings suggest that cationic G4 dendrimers hold promise for liberating erlotinib. In a separate study, dendrimers containing doxorubicin (DOX) were synthesized by PEGylating bioactive G3 polyurethane dendrimers [74]. It was observed that the dendrimer coupled with PEG can encapsulate a higher amount of DOX and also exhibited a more sustained release (Fig. 4a-c) [74].

2.4. Metal–organic frameworks (MOFs)

In recent years, various types of porous organic framework materials such as metal–organic frameworks (MOFs) have shown great potential for biomedical applications, especially in the field of cancer therapy [75–78]. MOFs possess unique characteristics that make them well-suited as drug delivery platforms, including their organized structures, high porosity, large surface areas, accessible metal sites, and ease of chemical modification [79–82]. Owing to these advantageous features, researchers have explored the use of MOFs for targeted diagnosis and treatment of different cancer types [83]. Several studies have focused on developing MOF-based nanocarriers for delivering therapeutic agents to lung tumors.

One group synthesized cubic crosslinked cyclodextrin-metal organic framework (CDF-MOF) nanoparticles that can co-deliver the anticoagulant low-molecular-weight heparin and the chemotherapy drug doxorubicin (Fig. 5) [84]. Following intravenous injection, these nanoparticles accumulated 5.8 times more in lung tumors compared to the liver due to functionalization with lung-tumor targeting moieties. In vivo testing showed the CDF-MOF platform significantly reduced lung tumor nodules in murine models by inhibiting cancer cell migration and invasion [84].

In another study, scientists fabricated europium MOF nanoparticles for pH-responsive delivery of the anti-cancer polysaccharide fucoidan. With high drug loading and controlled pH-triggered release, the fucoidan-loaded Eu-MOFs displayed enhanced toxicity against A549 lung cancer cells compared to fucoidan alone [41].

Researchers also recently designed a biomimetic zeolitic imidazolate framework-8 (ZIF-8) based on human bone marrow mesenchymal stem cells. This ZIF-8 platform enabled targeted co-delivery of the gene therapy plasmid pHSVtk and the prodrug ganciclovir to lung tumors. Through a "bystander effect" mechanism, this nano-scaled biological bomb system effectively killed transfected cancer cells and surrounding cells, suppressing lung tumor growth in vivo thanks to evasion of immune clearance and site-specific accumulation after systemic administration[42].

Researchers have also developed a biomimetic iron metal–organic framework (Fe-MOF) nanomedicine that responds to the intracellular microenvironment of non-small cell lung cancer cells to accelerate their death [43]. The Fe-MOF nanoparticles were loaded with the chemotherapy drug doxorubicin (DOX) and designed to mimic biomembranes. In the acidic tumor cell interior, the doxorubicin-loaded biomimetic Fe-MOF (mFe-MOFDOX) underwent enhanced degradation to generate bioavailable Fe^{2+} ions and sustained release of doxorubicin. This intracellular drug delivery system also amplified reactive oxygen species production, which induced ferroptosis - an iron-dependent form of regulated cell death. Specifically, the mFe-MOFDOX nanoparticles decreased levels of the antioxidant enzyme glutathione peroxidase 4 to trigger runaway lipid peroxidation and ferroptosis. In parallel, the released doxorubicin activated the apoptotic cell death pathway. By simultaneously inducing ferroptosis and apoptosis, this multifunctional MOF nanotherapy significantly suppressed growth and metastasis of non-small cell lung cancer cells and tumors. The unique capacity to initiate complementary cell death mechanisms highlights the promise of ferroptosis-inducing biomimetic MOF platforms to improve chemotherapy outcomes [43].

According to above information, MOFs represent promising multifunctional nanocarriers for targeted lung cancer therapy based on their exceptional capacity for loading drugs, genes, and imaging agents combined with flexible conjugation to tumor-recognizing ligands and controlled release properties.

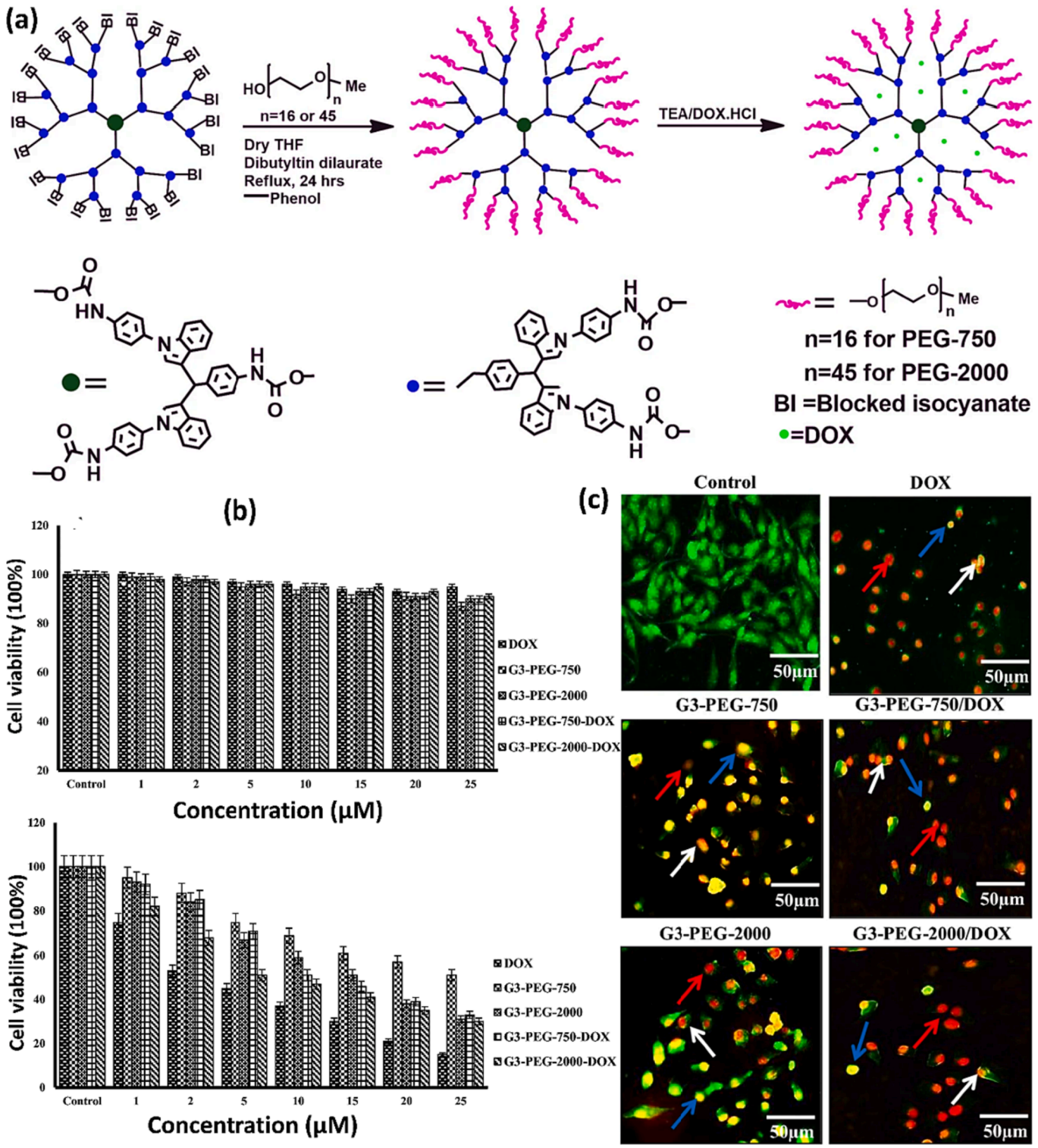

Fig. 4. (a) Doxorubicin (DOX) encapsulation in dendrimers. (b) Cell viability. (c) A double staining with AO and EtBr was used to conduct a qualitative study of apoptosis. Early apoptotic cells are represented by a blue arrow, late apoptotic cells by a white arrow, and DNA fragmentation by a red arrow. Reprinted with permission from ref [74]. THF; Tetrahydrofuran, TEA; triethylamine, DOX; Doxorubicin, PEG; Polyethylene glycol. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. The limitations of nanoparticles in cancer treatment

In spite of the promising preclinical outcomes, the full translation of nanoscale materials into clinical applications for lung cancer treatment still faces several challenges. The reproducibility and scalability of NP formulations are important factors that need to be addressed to ensure consistent and reliable manufacturing processes. Furthermore, there are concerns regarding the potential toxicological and safety hazards associated with NPs, necessitating thorough evaluation and risk assessment.

One key challenge lies in achieving specific targeting of cancer cells with NPs. While active targeting strategies can be employed by modifying the surface of NPs, ensuring efficient and precise delivery to the

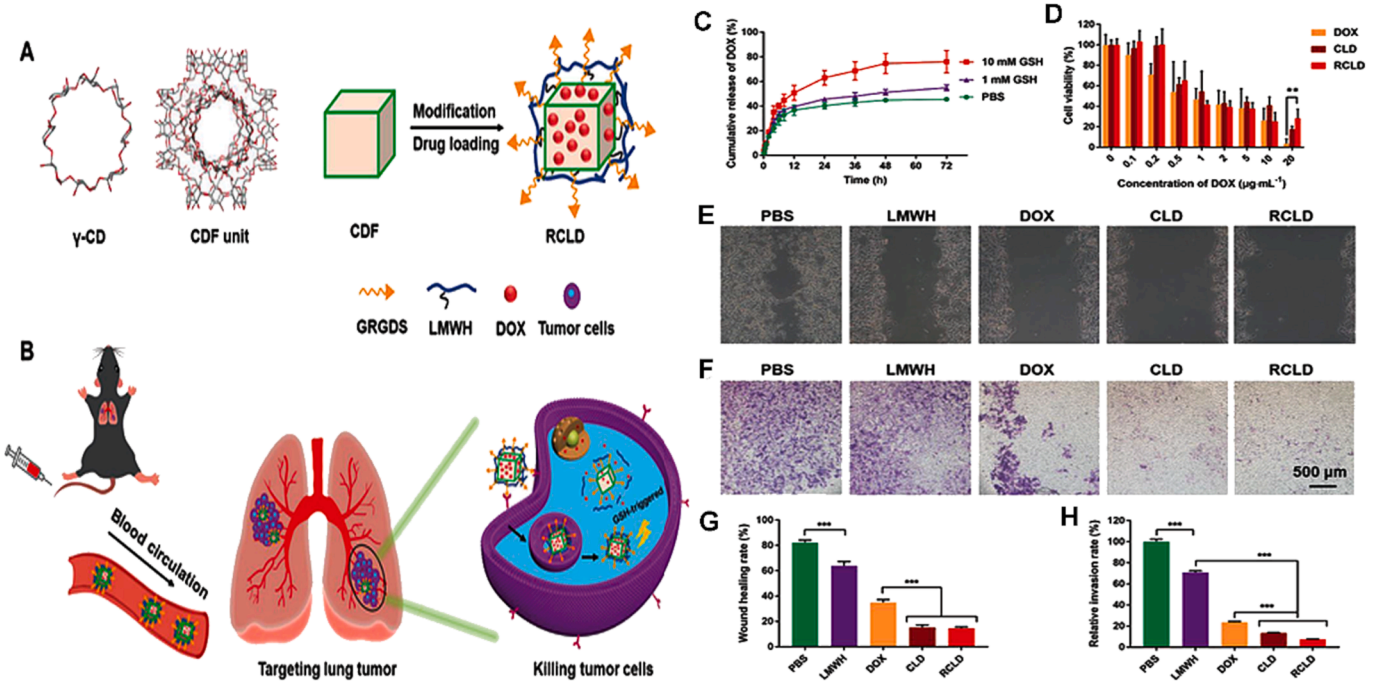

Fig. 5. (A) Structures of building blocks γ-cyclodextrin (γ-CD) and corresponding crosslinked metal–organic framework (CDF) carrier, along with schematic of final particulate system (RCLD). (B) Proposed model for RCLD nanoparticle recognition, accumulation in lung tumors, and inhibition of cancer cell proliferation, migration and invasion. (C) Doxorubicin release kinetics from RCLD nanoparticles as a function of glutathione concentration, validating tumor microenvironment-triggered drug release. (D) In vitro viability of B16F10 melanoma cells after treatment with free doxorubicin, unloaded carrier, or doxorubicin-loaded RCLD formulations. (E,F) Light microscopy images showing impaired wound healing capacity and quantification of migration rates for B16F10 cells incubated with individual agents or combination RCLD particles. (G,H) Invasion assay images and rated invasive potential of B16F10 melanoma cells following exposure to free drugs, blank carrier, or doxorubicin plus low molecular weight heparin co-loaded RCLD system. Reprinted with permission from ref.[84]. Abriviations: γ-CD, γ-cyclodextrin; CDF, cross-linked CD-MOF; RCLD, doxorubicin-loaded RGD-cyclodextrin metal–organic framework-low-molecular weight heparin nanoplatform;PBS, phosphate-buffered saline; LMWH, low-molecular weight heparin;DOX, doxorubicin.

tumor site remains a complex task. The interactions between nanocarriers of different shapes and biological barriers in the human body require further investigation to better understand their impact on NP behavior and efficacy [85].

To overcome these challenges, further research and development are necessary. Improving the reproducibility and scalability of NP formulations, enhancing targeting strategies, and conducting in-depth studies on the toxicological and safety aspects are essential for realizing the full translational potential of NPs in lung cancer therapeutics. Additionally, long-term physiological effects and the metabolic profile of NPs need to be thoroughly investigated to ensure patient safety and efficacy in clinical practice.

4. The clinical situation

The standard approach usually involves a combination of chemotherapy and radiotherapy for lung cancer. Emerging treatments like immunotherapy and personalized medicine are also being explored. However, the complexity arises from the combination of different approaches and the development of resistance patterns. Currently, numerous clinical trials are underway to incorporate advancements in nanoparticle (NP) technology into the clinical stage for these tumors. Prior experients highlighted the effectiveness of nab-paclitaxel for NSCLC as1st-line treatment [86–88]. However, the effectiveness of paclitaxel as a standalone treatment for advanced stages of the disease or in combination with other chemotherapy regimens has not been conclusively determined. Ongoing research is currently exploring the potential use of BIND-014, which is a docetaxel nanoscale formulation designed for injectable suspension, as a second-line treatment for metastatic lung cancer. Encouraging results observed in other tumor sites have provided a basis for further investigation [89,90]. Although no published results are available yet, studies are being conducted (NCT01792479, NCT02283320). Another promising approach is the utilization of CRLX101 (NCT01380769), a nanoparticle comprising conjugated camptothecin and a cyclodextrin-based polymer. Early positive results have been published, as CRLX101 is designed to enhance tumor cell exposure to camptocin while minimizing side effects [91]. It is crucial to monitor its development in the medium term and closely examine ongoing studies, particularly those in advanced stages of development (NCT03088813, NCT04033354), as they have the potential to influence standard treatment protocols.

5. Conclusion and outlook

Despite the significant body of research and numerous studies conducted in the field of nanomedicine, the full potential of this area needs to be understood. Despite the bustling activity and progress, there is a scarcity of clinically approved therapies, indicating that there is still work to be done. The fluctuating confidence in the field reflects its maturation process. However, nanomedicine is currently at a turning point, with researchers increasingly embracing new and emerging concepts while benefiting from the expanding knowledge in neighboring fields.

A deeper comprehension of various aspects is crucial to maximizing the efficacy of nanoscale materials in lung cancer treatment. This includes comprehending the heterogeneity of tumors, exploiting the enhanced permeability and retention effect for efficient delivery of nanoparticles to tumors, understanding the immunological crosstalk between the host and tumor, analyzing the tumor microenvironment, and developing strategies for preventing metastasis. Additionally, the development of more advanced nanocarriers to secrete drugs and genes that can be stimulated by external triggers such as light or biological

stimuli such as pH will allow for the precise spatiotemporal release of therapy and targeted delivery to the diseased site. Another bright future will come from artificial intelligence and machine learning-assisted predictions of nanoscale materials and their outcomes are emerging. Machine learning and artificial intelligence can pave the way for the prediction of lung cancer along with the treatment.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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