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Advanced methods to enhance lung cancer immunotherapy through novel drug delivery systems: Lipids and Micelles

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Abstract

The past few decades have witnessed a significant amount of research on lung cancer therapy as one of the leading mortality cause globally. Conventional treatments have disadvantages such as limited water solubility, drug resistance, and the damaging of healthy cells, resulting in decreased efficacy. As this outlook reports, immunotherapy integrated with drug delivery systems has been applied to exploit the synergistic and targeted effects. On the other hand, nanomedicine for cancer therapy has boosted efficacy and mitigated the negative effects substantially. Despite the persistence of obstacles such as drug resistance and insufficiency of stability, clinical studies demonstrated notable improvements in the cytotoxic efficacy of medications and in lowering treatment-related adverse effects. Technical approaches incorporating nanoparticles and innovative delivery strategies to enhance the effectiveness of targeted immunotherapy have been established. In the present review, a summary of the most promising literature aimed to break new ground in the use of immunotherapy and lipid and micelle-based nano drug delivery systems for lung cancer therapy has been presented, along with describing their key benefits, drawbacks, and prospects. The future of lung cancer therapy based on immune modulation will probably be combined with improved drug delivery systems to generate treatment methods of high efficacy.

Keywords: *Immunotherapy, Nanocarriers, Drug delivery, Lung cancer*

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1. Introduction

Cancer is by far the most destructive disease Cancer is by far the most destructive disease accounting for approximately 20 million new cancer cases and also roughly 10 million cancer deaths across the world. The proportion of lung cancer deaths contributes to 18% of the total cancer deaths about more than 1.8 million cases [1,2]. Non-small cell lung cancer (NSCLC) is considered a life-threatening type of lung cancer with the highest mortality rate in the world [3]. Researchers endeavor to find the best approaches in order to cure cancer. The prevailing clinical strategies for lung cancer would be conventional cancer treatment methods including surgery, radiotherapy, chemotherapy, and immunotherapy, and those combinational regimens, as well [4]. Although these aforementioned treatments had increased patients' lifelong somehow, they have deleterious side effects, such as lethargy, hair loss, infections, pain, nausea, mucus, and vomiting, that can considerably decline the standard of patients' life [4-6].

Among those distinct methods of therapies, immunotherapy is now perceived as a better method to address cancer since having an entirely different method to treat cancer. Its strategy would adjust the systemic immune system rather than concentrating on the tumor [7-10]. There are active and passive, and specific and non-specific approaches to immunotherapy for cancer. Cytokines, some synthetic hormones, and molecules as well as some bacterial products are considered active non-specific. Active specific immunotherapy includes the use of vaccines. Adoptive T cell therapy and the utilization of heat-shock proteins and lectins are known as passive non-specific methods, while, passive specific is based on monoclonal antibodies[11]. Among these various types, immune checkpoint proteins, like programmed death-1 (PD-1) or cytotoxic lymphocyte antigen-4 (CTLA-4) are known as significant targets of immunotherapy [12,13]. In particular, immune checkpoint inhibitors (ICIs) were recently integrated into the treatment plan for NSCLC patients without a driver mutation [14]. Even though ipilimumab, Keytruda®, Opdivo ® Tecentriq ®, Imfinzi ®, Bavencio ®, and Libtayo ®) have been approved by FDA as the immune checkpoint blockers [15-19], immunotherapy has encountered some challenges in a range of tumors or patients in clinical steps [20,21]. Some of these issues are immune checkpoints inhibitors resisted to the drug, feeble immunogenicity of therapeutic vaccines, considerable immune-related detrimental events (iRAE), off-target adverse effects [22], etc.

Numerous preclinical studies demonstrated that chemotherapy has the potential to bring advantages to immunotherapy, even those drugs (such as cyclin-dependent kinases 4 and 6 inhibitors) having cytotoxicity can stimulate the immunity of antitumor [23-25]. Chemo-immunotherapy could improve antitumor efficiency and show an optimal synergistic effect since they can settle each other's deficiencies. However, it cannot be denied that it has some challenges such as diverse pharmacokinetics and in vivo propagation of both agents, inadequate tumor specificity and tumor aggregation, unascertainable drug proportion at tumor tissues, and serious hazardous effects [26,27].

In this regard, drug delivery systems (DDSs) have been used as measures for therapeutic purposes of cancer diseases to decrease the side effects of conventional therapies. Although this method showed valuable results, many patients still have suffered from tremendous drawbacks because of limited effectiveness, poor biologic distribution, accumulation of drug resistance, and lack of selectivity of the drug delivery systems [28,29].

Emerging nanotechnology science brought such a revolution in medical sciences. The valuable properties emerging from the special size (10-100 nm diameter) and surface area of nanoparticles pushed scientists to use nanoscience in oncology. In this journey, smart nano-based drug delivery systems (SNDDSs) were introduced as appropriate tools for decreasing the severe drawbacks of naked drugs used in lung cancer therapy. They have a significant role in advancing the in vivo pharmacokinetics behaviors, escalating the stableness of drugs, delivering drugs to target tumor cells, improving biocompatibility, degradability, and permeability, and adjusting the release of drugs [30,31]. Hence, it is more likely to be a suitable way to mitigate the side effects of chemo-immunotherapy [32]. Recently, a wide spectrum of nanoparticles with different chemical structures and formulations have been tested as carriers to improve cancer therapies. Micelles, dendrimers, liposomes, solid lipid nanoparticles, polymeric nanoparticles, carbon nanotubes (CNTs), silica mesoporous nanoparticles, cyclodextrins (CDs), and quantum dots (QDs) have been developed various SNDDSs [33-36]. Figure 1 illustrates schematics of the recently used NDDSs.

Meanwhile, one of the most significant challenges for cancer immunotherapies is the lack of high efficient delivery systems that can keep therapeutic payloads accessible to their targets. Distinct sorts of lipid-based nanoparticles (NPs), including liposomes, lipid nanoparticles (LNPs), exosomes (EVs), and micelles have been developed as promising platforms in order to deliver diverse types of therapeutic agents [37,38]. In comparison to other nanosized delivery systems, lipid-based NPs outperform polymeric NPs and inorganic NPs in terms of mitigating the level of toxicity as well as retaining high water solubility [39]. These benefits have led to lipid-based NPs becoming the most widespread type of FDA-approved nanomedicine [40]. That Liposomes as the most significant tools in DDSs and their countless applications in targeted drug delivery techniques have been recognized as an undeniable fact. Furthermore, the application of some types of micelles helped for the combination therapy. In this review, special attention is devoted to the analysis of the state-of-the-art integrated methods of immunotherapy and NDDSs applied in lung cancer treatment particularly based on lipids and micelles as nanocarriers.

2. Types of lung cancer

Lung cancer is a widespread type, which is also the primary cause of cancer-related mortality. It contributes to 11.6% of the 2.09 million new cancer cases diagnosed in 2018 and 18.4% of the 1.76 million cancer-related deaths. Among all malignant cancers, men are attributed with the highest incidence and mortality rates for lung cancer, whilst women accounted for the second or third highest proportion of lung cancer incidence and deaths, respectively [41]. According to figure 2, lung cancer generally is categorized as small cell lung cancer (SCLC) and NSCLC; NSCLC is designated almost 85% of cases and SCLC makes up for 15%. SCLC depicts 25% of all invasive cancer types worldwide, and it can be seen exclusively in smokers [42]. It stems from neuroendocrine cell precursors. Therefore, it is associated with endocrine and neurologic para neoplastic syndromes (Eaton Lambert syndrome,

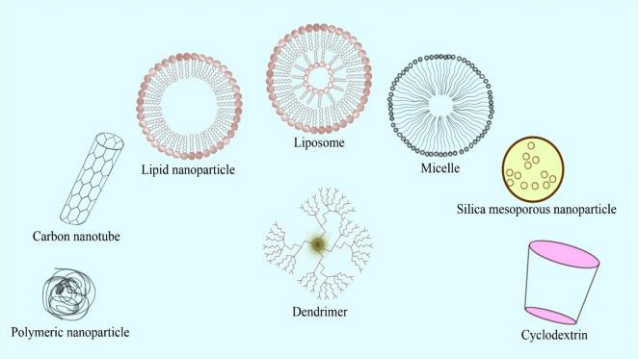

Figure 1: Main types of nano delivery systems

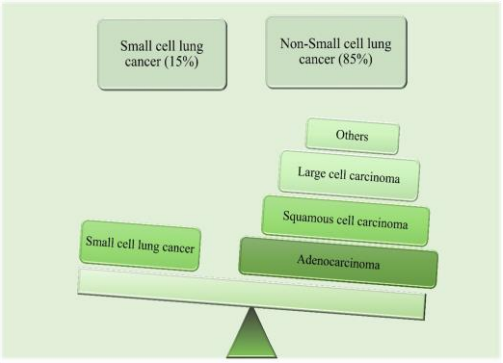

Figure 2: Types of lung cancer by histology

inappropriate antidiuretic hormone secretion, and Cushing's syndrome) [42]. Furthermore, SCLC is attributed to its worse clinical course than that of NSCLC [43,44]. It illustrates resistance to both chemotherapy and radiotherapy courses [45,46]. NSCLC has distinct types including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and mixtures. SCLC can be divided into three subtypes: small cell carcinoma, mixed small cell, large cell carcinoma, and mixed small cell carcinoma. Diverse therapeutic profiles and clinical prognoses are applied for each of these types [47]. Lung cancer is often remedied with surgery, chemotherapy, radiotherapy, and adjuvant therapy [48]. When it comes to traditional chemotherapy cure for lung cancer not only is it unable to treat particularly target tumor cells, but also can considerably destroy normal cells, including bone marrow arrest and gastrointestinal reactions [49], which ends up inhibiting the progress of anticancer drugs.

2.1 Small cell lung cancer (SCLC)

SCLC is a lethal subtype of lung cancer, which includes about 15% of new lung cancer diagnoses [50]. Most patients show metastatic or extensive-stage (ES) in the diagnosis. Progression-free survival (PFS) with platinum doublet therapy is limited to under 6 months with median survival typically shorter than 9 months [51]. Early experience with cancer immunotherapy suggests greater benefit in carcinogen-associated cancers and there is evidence of a relationship between the number of mutations within a tumor (tumor mutational burden, TMB) and the response to immunotherapy [52,53].

Chemo-immunotherapy is now the standard of care for ES-SCLC but the improvement in survival remains modest, though it is very important. SCLC is developed for four reasons: as the first reason, PTEN loss or inactivating mutations are caused by PI3K signaling. According to Yokomizo's research, PTEN/MMAC1 mutations affect SCLC [54]. The second reason for the development of this cancer is due to cell cycle mechanisms, which include an inactivating mutation and loss of the RB gene. It is demonstrated that the RB pathway is disrupted in almost all lung tumors. Cells appear to become resistant to the mitogenic signals required for cell cycle progression when this important RB pathway is dysregulated at any level [55]. Disruption of apoptotic pathways is the third factor. The sentinel network of BCL2 family proteins, which controls the mitochondrial or intrinsic apoptotic response, is what makes SCLC cancer possible. BCL2 overexpression is the main contributing factor to this possibility [56]. The last and fourth reason is TP53, which is deactivated by a mutation that disrupts the transcription mechanisms [57]. The use of molecularly targeted treatments in SCLC, both alone and in conjunction with chemotherapy, has been the subject of numerous pieces of research. Anti-angiogenesis medications including bevacizumab [58], vandetanib [59], and aflibercept [60], as well as histone deacetylase inhibitors like Panobinostat [61], were explored as targeted therapy. In the study of Rudin et al, on the drug Rovalpituzumab tesirine as a target of the dll3, they showed that in patients with progressive SCLC, the one-year survival rate in people with high dll3 was 36%, compared to 12% for conventional treatments [62]. Much research has been done on nanoparticle systems for the treatment of lung cancer. The exceptional properties of nanoparticles help their intravenous injection or inhalation. In the treatment of lung-related disorders, this flexibility is effective in releasing encapsulated drugs to the target cells [63].

2.2 Non-small cell lung cancer

NSCLC is the prevalent type of lung cancer diagnosed in non-smokers. It is apparent that its proportion in females is higher than in males, and it can be observed that in comparison with other types of lung cancer, this type is more common in the youth generations [64].

NSCLC can be categorized, regarding World Health Organization (WHO), into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [65]. Adenocarcinoma is a prevalent form, accounting for around 40% of all diagnoses. It often occurs in both smokers and nonsmokers [66] and originates from small airway epithelial cells that line the lung and alveolar cells; the mucus-secreting cells [67]. Furthermore, it has a moderate growth rate and may spread beyond the lungs. Histologically, adenocarcinoma is distinguished by glandular/acinar growth, papillar differentiation, or a single layer of wallpaper-like dissemination along the alveolar septum and bronchioles [68]. Squamous cell carcinoma arises from the squamous cell type present in the epithelial cells of the airways. These cells line the bronchial passages inside the pulmonary hub. This kind of lung cancer is commonly associated with cigarette usage and accounts for 30% of all lung cancer patients [69]. It is also distinguished histologically by the presence of keratinization or intercellular bridges. 5–10 percent of lung cancer patients have large cell carcinoma. It arises from the center of the lungs, the region next to the lymph nodes, and the chest wall [70]. Rapid growth and dissemination make it more difficult to find an effective treatment solution. Large cell carcinoma is regarded as a non–small cell malignancy with a bad prognosis [48]. Since NSCLC is characterized by multiple gene point mutations and around 70% of NSCLC patients experience somatic mutations in the exons of the epidermal growth factor receptor (EGFR) gene, small-molecule EGFR tyrosine kinase inhibitors (EGFR-TKIs) including erlotinib and gefitinib are known as the second-line cure for NSCLC. As compared with the standard chemotherapeutic regimen, not only EGFR-TKIs considerably enhance the proportion of objective response, but also improve progression-free survival, and quality of life while showing moderate poison. Indeed, the newest EGFR-TKI, osimertinib has been widely adopted as first-line therapy for patients with advanced EGFR-mutant NSCLC, since its approval in April 2018 [71]. This outstanding progress in the use of EGFR-TKIs with the aim of treating NSCLC is recently gaining effect in the field of targeted therapy and precision medicine. Pemetrexed and docetaxel (second line and beyond) are considered other treatment options for patients having metastatic NSCLC who progress after platinum-based chemotherapy [72]. In addition to employing nivolumab and pembrolizumab as inhibitors for anti-program cell death protein-1 (PD-1), atezolizumab is applied for programmed cell death ligand-1 [73]. Pembrolizumab is the first-line remedy for patients who suffer from metastatic NSCLC with high PD-1 expression and was approved by US FDA in 2017 [73]. The combination of nivolumab and ipilimumab (the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitor) was considered the first-line treatment for those patients struggling with metastatic or recurrent NSCLC, with no EGFR or anaplastic lymphoma kinase (ALK) genomic tumor aberrations [74]. These immune checkpoint inhibitors (ICI) illustrated a novel milestone in oncology, and they are likely to be superior to docetaxel in terms of overall survival, progression-free survival, duration of response, and overall response proportion [75]. Irrespective of being highly effective in the curing of NSCLC, all these drugs still encounter several limitations, such as toxicity, fierce side effects, resistance to the drug, requiring high doses for effectiveness, and high treatment costs. Several strategies have been found to overcome these restrictions. One promising approach involves the utilization of nanotechnology for cancer treatment, which has been shown to significantly decline the cost, boost therapeutic efficacy, and decrease systemic toxicity [76].

In fact, NPs must be able to alter the environmental characteristics of the cancerous cells to provide cytotoxicity as they are not inherently producing cytotoxicity. Thus, by developing enhanced permeability and retention (EPR) effects and/or active targeting, they will improve the anti-cancer activity of the drugs. There are three distinct ways by which NPs produce cytotoxicity in tumors including drug release, hyperthermia/thermal ablation, and reactive oxygen species (ROS)-mediated killing [77]. Moreover, surface modification impacts the bioavailability and half-life of the drugs which can be achieved by taking advantage of NPs. On the whole, the promising properties made by NPs will lead to significant therapeutic influences on cancerous cells [78].

3. Limitation of conventional drug delivery systems

Conventional drug delivery systems have some limitations. These restrictions include low water

solubility, precinct targeting, and drug resistance. Because of that, nanoparticle delivery systems are designed to dominate the harms of conventional drug delivery systems. Nowadays, nanoparticle delivery systems are growing fast and they are applicable in various fields of biomedicine. Drug nanocarriers involve liposomes, peptides, water-soluble polymers, dendrimers, micelles, cyclodextrins, mesoporous silica, etc. Some of these nanocarriers are used in clinical therapies. Nanoparticulate drug carriers are also used in antineoplastic drugs to improve the healing process [79].

Chemotherapy's administration of chemical anticancer drugs has several drawbacks. The omission of normal cells is the fundamental concern with chemotherapy. Chemotherapeutic chemicals are cytotoxic to healthy normal cells. Therefore, prolonged exposure to these chemotherapeutic drugs results in significant toxicity to normal cells. Traditional approaches for administering chemotherapeutics may have substantial cytotoxic effects on healthy cells [80]. Low therapeutic index compounds may cause dose-dependent systemic adverse effects [81]. The poor solubility of chemotherapeutic drugs presents additional difficulties in the formulation of drug delivery systems. Intravenous administration of these chemotherapeutic drugs may induce embolization of blood vessels due to their low water solubility [82]. Moreover, tumor cells develop resistance to chemotherapeutic drugs [80]. Conventional drug delivery systems come across hurdles in the path of drugs to malignant tumors. Factors such as the drug's physicochemical properties, and particle charges, comprising the surface composition, and particle size show a significant role in drug transportation [83]. The tumor heterogeneity constraints an unvarying drug delivery into the whole tumor mass. The acidic tumor microenvironment destroys acid-sensitive drugs [80]. Considering all of these details, it seems necessary to seek novel strategies for cancer therapy precisely with novel and more effective delivery techniques.

4. Nano-biocarriers in Immunotherapy

An unregulated proliferation of unhealthy cells creates cancer. Nowadays, some treatments are used for curing cancer such as chemotherapy, radiotherapy, and surgery. Chemotherapy is a conventional form that kills both tumor and healthy cells. Radiotherapy and surgery are both ineffective in eliminating metastases. Due to the limitations of traditional therapies for cancer treatment, it is necessary to use more effective and less harmful methods. Tumor immunotherapy or vaccines are effective treatments [84]. Cancer immunotherapy has essential advantages such as the ability to the identification of tumor cells, induce an antitumor immune response that can control metastases, and develop an immunological memory that can provide long-time protection against the recurrence of a tumor [85]. There are several nanomaterial platforms, such as liposomes, polymer systems, inorganic nanocarriers, cyclodextrins, dendrimers, etc [86,87]. Nanoparticles can improve

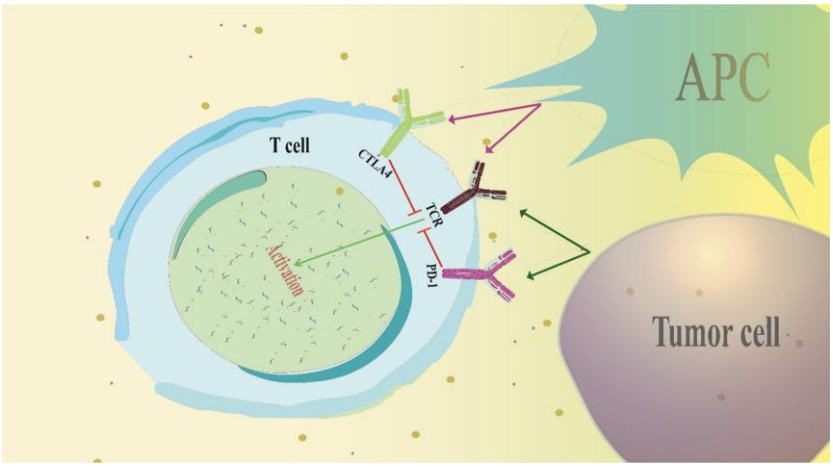

Figure 3: Mechanism of CTLA-4 and PD-1/PD-L1 inhibition

the antitumor effectiveness of cancer immunotherapy, promote medication penetration and retention, and augment the synergistic impact of therapies [88,89]. In recent studies, anti-PD-1, and anti-PD-L1 medications have been identified as the best immunotherapy choices for reducing side effects and enhancing the antitumor activity of antimetabolite therapies [87]. Figure 3 shows CTLA-4 and PD-1/PD-L1 inhibition. In addition, nanocarriers allow for the combination of several treatment techniques. Using a nanocarrier, scientists coupled TKIs with immunotherapy to enhance the effectiveness of targeted treatment [90]. mRNA nanotechnology has also transformed the development of novel cancer therapies that will solve many unresolved therapeutic problems in the foreseeable future. Biocompatibility will increase when nanoparticles are used in mRNA delivery compared to other delivery techniques [91].

4.1 Applications of immunotherapy in lung cancer treatment

Immune checkpoints include various inhibitory mechanisms that maintain tolerance to internal antigens and prevent damage to adjacent tissues [92]. Nevertheless, cancer cells use this factor for their benefit and to escape from the attack of the immune system. CTLA-4 and PD-1 are immune checkpoints. The use of nivolumab and pembrolizumab has been approved as two monoclonal antibodies against PD-1 for the treatment of patients with NSCLC [93,94]. Most patients with SCLC smoke and their tumors have high mutation loads. So, increasing the production of neoantigens available to T cells can predict the benefits of immune checkpoint blockade. Through the development of radiation therapy technology in the early and advanced stages, small improvements have been made in the survival rate of these patients. However, new drugs, such as immune checkpoint inhibitors, are hoped to be developed as a result of a better understanding of the biology of tumors [95].

Immunotherapy is a treatment method, which uses the immune system of patients to treat the disease. Recent strategies for cancer immunotherapy have mainly focused on tumor-associated antigens (TAA), associated with the induction of T cell-mediated immune responses [96,97]. Immunotherapy has created a miracle in the clinical setting by directing the human immune system to attack cancer cells. However, the systemic distribution of these drugs is limited by safety and efficacy issues. Table 1 describes various nanomedicines including nanoparticles, micelles, and liposomes have been investigated in preclinical trials to improve cancer immunotherapy [98,99]. These strategies increase the anti-tumor immune response or reduce their systemic side effects. Micelles provide high accessibility for drug delivery systems [100].

In addition, the behavior of micelles in biological environments (blood circulation and active or passive targeting) largely depends on their chemical composition and physical properties such as dimensions and polydispersity [101]. Small dimensions, convenient preparation, and good dissolution properties make polymeric micelles suitable carriers. These micelles make the drug more accessible and release the targeted and controlled drug, which is useful for reducing side effects [102]. In addition to the advantages of the micellar drug carrier system, hydrophilic polymers are bound to the outer surface of the micelle (corona). For example, polyethylene glycol (PEG), increases circulation time and improves the overall drug kinetics of the delivery system. In addition, the corona is engineered with moieties such as folate, monoclonal antibodies (mAbs), and monosaccharides (mannose, glucose, fructose) to improve target selectivity and binding ability [103]. Table 2 listed the studies in lung cancer treatment based on immunotherapy and different drugs.

5. Combination therapy (Drug and Immunotherapy) against lung cancer

Chemo-immunotherapy is considered a remarkable method having significant synergistic impacts for boosting antitumor efficiency. First and foremost, chemotherapy drugs directly annihilate cancer cells, whilst immunotherapy reactivates immune responses to demolish tumor cells. Moreover, chemotherapy drugs act quickly but they have a short duration of action, whereas immunotherapy can prolong efficacy and produce a strong anticancer effect. Furthermore, immunotherapy could address the imperfection of chemotherapy including killing chemotherapeutical-resistant cells and cancer stem cells [20,104]. Current

Table 1. Various nanomedicines are used in preclinical trials for cancer immunotherapy.

Type	Payload	Mouse Model/Tumor Type	Clinical outcome	Tumor type	Year	Refs
Lipid nanoparticle	Mannose Anti-CTLA-4 antibody mRNA encoding MUC1	4T1 cells	Nanoliposome targeting mannose receptors on DCs increased tumor antigen expression and produced a robust, antigen-specific CTL response against tumor cells.	Breast cancer	2018	[105]
	Mannose Sunitinib Trp2 CpG	B16F10 cells	Increased cytotoxic T-cell infiltration and Th2 to Th1 cytokine expression in tumors	Melanoma	2017	[106]
	tLyp1 peptide Imatinib anti-CTLA-4 mAb	B16/BL6 Cells	Increasing intratumoral CD8+T cells and decreasing intratumoral Treg cells against tumors	Melanoma	2018	[107]
	DOTAP Cholesterol PD-L1 trap plasmid	CT26-FL3 cell B16F10 cells 4T1 cells	Activated DCs were substantially higher in colorectal cancer tumors.	Colorectal cancer	2018	[108]
	Oxaliplatin dihydroartemisinin (DHA)	CT26 and MC38 cells 4T1 cells	Promote intratumoral CD8+ T cell infiltration to boost response.	Colorectal cancer	2019	[109]
	NSC-87877	TRP-SIY prostate tumor model	Increasing CD8+ in prostate cancer	Prostate cancer	2012	[110]
	All-trans retinoic acid (ATRA) Doxorubicin (DOX) interleukin-2 (IL-2)	B16F10 cells	Promotion of cytokines secretion of IFN-γ and IL-12	Melanoma	2017	[111]
	EGFR short peptide vaccine Adjuvant PD-L1-siRNA	A549 cells	Significantly elevated levels of IL-2, IFN-γ, and TNF-α were observed.	Lung cancer	2022	[112]
	Curcumin Paclitaxel	A549 cells	Inhibiting the cell cycle	Lung cancer	2022	[113]
Liposome	siRNA against TGF-β Trp 2 peptide CpG oligonucleotide	B16F10 cells	increased tumor-infiltrating CD8+ T cells and reduced regulatory T cells	Melanoma	2014	[114]
	Indocyanine green (ICG)	CT-26 and B16 cells	ICD-mediated immunotherapy via ROS-based ER stress	colon carcinoma melanoma	2019	[115]
	Doxorubicin sialic acid cholesterol metformin	4T1 cells B16F10 cells	increases intratumoral CD8+ T cell infiltration	breast cancer melanoma	2021	[116]
	CpG	HEK293 cells	Enhanced maturation of DC	N/A	2011	[117]

	Ovalbumin					
	IL-15 IL-21	B16F10 cells	Increasing memory T, CD8+, and CD4+	melanoma	2010	[118]
	Monophosphoryl lipid A (MPLA) nucleoside-modified mRNA	BM-DC model	liposome promoted high antigen expression and active antigen-specific T cell immunity without causing a type I IFN response.	N/A	2017	[119]
	Cyclodextrins TGF-β inhibitor IL-2	B16-F10 cells	activated CD8+ T cells in tumors	Melanoma	2012	[120]
	CpG Oligodeoxynucleotide Ovalbumin	DC2.4 cells	Enhanced antigen presentation and T-cell immune responses	N/A	2013	[121]
	α-GalCer CpG Ovalbumin	B16F10 cells	Increased NK, DC, and T cell activation	Melanoma	2014	[122]
	Trp2 peptide	B16 melanoma	Increase T cell responses	Melanoma	2013	[123]
	E7 peptide	TC-1 cells	Activate antigen-presenting cells and stimulate DCs	Lung cancer	2004	[124]
	RNA	B16F10 cells	Induced effector and memory T cell responses and induced macrophage INF-α release.	Melanoma	2016	[125]
	MART1 mRNA	B16 cells	Induction of anti-tumor cytokines and cellular immune response	Melanoma	2007	[126]
	EPGF MART1 mRNA	B16F10 cells	Enhanced DC activity and tumor-specific immune response	Melanoma	2011	[127]
	Ovalbumin	DC2.4 cells	Increased cytotoxic T cell activity	N/A	2013	[128]
Micelle	Paclitaxel Cyclopamine	Kras PDAC cells	Increased tumor CD8+ T cell infiltration	Pancreatic ductal adenocarcinoma	2018	[129]
	Toll-like receptor 7 agonist imiquimod (IMQ) Doxorubicin Low molecular weight heparin D-α-tocopheryl succinate	4T1 cells	Enhancing the maturation of DCs as well as the CD8+ CTLs/Treg and CD4+ Teff/Treg ratios	Breast cancer	2019	[130]
	Paclitaxel Hyaluronic acid D-α-tocopherol succinate	CT26 cells RAW264.7 cells	Enhance the levels of IL-2, IFN-, and TNF in the tumor region.	N/A	2020	[131]
	Paclitaxel Anti-cancer stem cell agent (thioridazine) PD-1/PD-L1 inhibitor HY19991	MCF-7 cells	Decreases the proportion of CSC and increases the infiltration of T lymphocytes into tumor tissues.	Breast Cancer	2019	[132]

	All-trans retinoic acid (ATRA) PD-L1 mAb	CAL27 cells DOK cells	CD8+ T cells were stimulated in the tumor microenvironment surrounding PD-L1-positive cells.	Squamous cell carcinoma	2020	[133]
	Indoleamine 2,3-dioxygenase inhibitor (LNG919) curcumin (CUR)	B16F10 cells	Increased number of CD8+ and CD4+ T lymphocytes inside tumors	Melanoma	2020	[134]
	Ovalbumin CL264	Bone-marrow derived DC	Enhanced CD40 and CD86 molecule expression	N/A	2018	[135]
	Doxorubicin (DOX) IL-12 plasmid Metformin hydrochloride Hyaluronic acid	4T1 cells	IL-12 expression levels were considerably elevated in both peripheral blood and tumor	Breast cancer	2020	[136]

Table 2. Studies of combining immunotherapy with chemotherapy in lung cancers.

Drug name	**Target**	**Patient (n)**	**Malignancy**	**Clinical outcome**	**Year**	**Refs.**
Ipilimumab	CTLA-4	204	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2012	[137]
Nivolumab	PD-1	272	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2015	[138]
		582	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2015	[139]
		109	Small-Cell Lung Cancer	↑ overall survival ↑ progression-free survival	2019	[140]
		1189	non-small-cell lung cancer	↑ overall survival	2019	[141]
		252	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2020	[142]
		160	small-cell lung cancer	↑ overall survival ↑ progression-free survival	2020	[143]
		1150	non-small-cell lung cancer	↑ overall survival	2021	[144]
		854	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2021	[145]
		834	small-cell lung cancer	None	2021	[146]
		222	small-cell lung cancer	None	2022	[147]

Pembrolizumab	PD-1	495	non-small-cell lung cancer	↑ progression-free survival	2015	[148]
		305	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2016	[149]
		1034	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2016	[150]
		616	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2018	[151]
		559	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2018	[152]
		1274	non-small-cell lung cancer	↑ overall survival	2019	[153]
		78	non-small-cell lung cancer	↑ progression-free survival	2020	[154]
		148	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2021	[155]
		305	non-small-cell lung cancer	↑ overall survival	2021	[156]
Cemiplimab	PD-1	710	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2021	[157]
Atezolizumab	PD-L1	287	non-small-cell lung cancer	↑ overall survival	2016	[158]
		1225	non-small-cell lung cancer	↑ overall survival	2017	[159]
		403	Small-Cell Lung Cancer	↑ overall survival ↑ progression-free survival	2018	[160]
		1202	non-small-cell lung cancer	↑ overall survival	2018	[161]
		724	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2019	[162]
		572	non-small-cell lung cancer	↑ overall survival	2020	[163]
		1280	non-small-cell lung cancer	↑ disease-free survival	2021	[164]
Durvalumab	PD-L1	713	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2017	[165,166]
		1118	non-small-cell lung cancer	None	2020	[167]
		610	non-small-cell lung cancer	↑ overall survival ↑ progression-free survival	2020	[168]
		805	Small-Cell Lung Cancer	↑ overall survival	2022	[169]

investigation proposed that chemo-immunotherapy is bound to bring unparalleled prospects for diagnosing patients [170]. Take the mixture of carboplatin or cisplatin, pemetrexed with pembrolizumab as an example, it is approved by FDA for the first-line cure of NSCLC. To ensure the greatest synergistic anticancer effectiveness, some concerns ought to be dealt with, such as disparate pharmacokinetics and in vivo dispensation of both agents, inadequate cancer specificity and tumor aggregation, undetectable drug proportion at tumor tissues, and deleterious side effects [26,27]. Nano-based drug delivery systems not only promote the in vivo pharmacokinetics behaviors but also increase the steadiness of drugs as well as recognize the targeted delivery and control drug delivery. Therefore, cancer chemo-immunotherapy has been developed as a promising strategy for cancer treatment [171]. Moreover, recent studies have illustrated that nanoparticles can re-model the immunosuppressive tumor microenvironment [172]. Consequently, nowadays researchers tend to focus on cancer treatment through NDDS and chemo-immunotherapy. Hence, the current measures for treating cancer as well as the recent applications of the most popular NDDS including micelle and lipid-based chemo-immunotherapy will be elaborated.

5.1 Immunotherapy-focused micelle-based delivery systems

Recent developments in polymeric micelles showed significant results for cancer immunotherapy. Some studies have investigated the effect of micelles on immunotherapy in the treatment of various cancers. Review of these studies can point to the benefits of using this system in the treatment of NSCLC. Werner et al. used Genexol-PM as a polymeric micellar nanoparticle formulation without chromophore EL of paclitaxel to treat NSCLC about a decade ago, which was more effective than taxol in preclinical settings [173]. Xiao et al. developed folate-modified pH-sensitive micelles with a particle size of 100 nm for the simultaneous administration of metformin and paclitaxel (PTX) as an anticancer strategy with promising results against breast cancer [174]. Guo et al. designed 20 nm micelles as an improved release method for resveratrol and PTX. They studied the possibility of synergistic effects and found sustained release following the first burst release and simultaneous delivery advantage with synergistic effects against MCF-7 cancer cells [175]. Mei et al. developed micelles containing the autophagy inducer rapamycin (RAP) and PTX to have synergistic anti-breast cancer activities. High cellular internalization of micelles, anti-tumor effects with improved drug sensitivity, and synergistic anti-cancer actions of these two medications have been shown in the laboratory [176]. Jin et al. created a pH-responsive polymeric drug release system for simultaneous PTX and siRNA administration. A bivalent cationic PEI-PLA copolymer was produced and self-assembled into a mixed micellar structure that encapsulated PTX in the hydrophobic core and compressed surviving siRNA with a cationic PEI block in the hydrophilic shell [177]. Cai et al. created trilayered telodendrimer micelles for the simultaneous administration of cisplatin and PTX to treat gonadal cancer. Studies conducted in the laboratory have shown significant anti-cancer synergistic effects of these medicines. The nanocarrier increased the drug's blood circulation time and decreased cisplatin's toxicity [178]. Bolu et al. developed docetaxel-loaded micelles containing dendron-polymer conjugates functionalized with trastuzumab. Micelles conjugated to trastuzumab showed lower cell viability and EC50 values in MCF-7 and SK-OV-3 cells [179]. There are other studies on the effects of using micelles to enhance immunotherapy. Bacterial outer membrane vesicles (OMV) cause the activation of host immune responses. Chen et al. proposed a strategy to coat OMVs with drug-loaded polymeric micelles. On one hand, OVM PEGylation improved the stability and on the other hand, the use of Argo-Gly-Asp peptide recovered the targeting treatment. Then, functionalized OVMs were coated on Tegafur (fluorouracil (5-FU) prodrug) micelles to aid in immunotherapy. In this study, mice treated with nanoparticles showed a delay in tumor growth and the tumor volume reached only half of the other group at the end of the treatment period (on the 21st day).The average tumor inhibition rate was about 70%. Also, a higher CD8 + level was observed in the treatment group. [180]. Zhao et al. designed biodegradable polymeric micelles for the simultaneous delivery of PTX and cyclopamine (CPA). Drug-loaded micelles increased vascular density within the tumor, which overcomes the resistance of Pancreatic ductal adenocarcinoma (PDAC) to anti-PD-1 therapy [181]. Another study used low molecular weight heparin-D-

tocopheryl succinate micelles to encapsulate DOX and the toll-like receptor 7 (TLR7) agonist imiquimod for chemotherapy. Micelles enhanced Dendritic cells (DCs), which increased the therapeutic efficiency of the anti-PD-L1 antibody. In addition, an increase in the intratumoral concentration of IFN after treatment with micelles, as well as destruction of tumor cells and increased effect of PTX were seen. Further combination with anti-PD-1 antibody regulated immunosuppressive microenvironment, resulting in a significant elimination of pancreatic cancer cells. Overall, drug delivery systems with chemotherapeutic drugs induce ICD-induced antitumor immunity, which helps in combination with PD-1/PD-L1 blockade immunotherapy [182]. Jiang et al. designed a hyaluronic acid disulfide D-α-tocopherol succinate (HA-SS-TOS, HSST) micelle, which targets cancer cells with CD44. HSST micelles loaded with paclitaxel showed the inhibition of tumor growth and metastasis, which ultimately induced the ICD effect of tumors and optimized the efficacy of anti-PD-1 monoclonal antibody while presenting immune activation [183]. Lang et al. designed a spherical nanodevice, and the outer layer consisted of a copolymer containing a small molecule inhibitor of PD-1/PD-L1, HY19991, an anticancer agent, thioridazine, and another portion of pH-sensitive micelles containing the cytotoxic chemotherapy drug paclitaxel. The strategy aimed to increase antitumor immunity. MCF-7 breast cancer-bearing mice treated with this nanodevice had an 83% longer survival rate after 60 days. There were no survivors in the treatment with micelles containing paclitaxel and non-encapsulated HY19991 after 55 days [184]. Chen et al. developed a PLGA-PEG micelle for the co-delivery of all-trans retinoic acid (ATRA) and PD-L1 mAb to treat oral dysplasia and squamous cell carcinoma. ATRA-PLGA-PEG-PD-L1 has a higher therapeutic efficiency in in vivo than free ATRA, and CD8+ T cells are activated in TME after treatment [185]. According to Dai et al., reducing the dimensions of micelles and inverting their charge led to simultaneous loading of IDO inhibitor (LNG919) and curcumin (CUR) (PCPCD). The combined effect of chemotherapy-enhanced immunotherapy and LNG919-induced IDO immunotherapy showed highly effective inhibition of tumor growth, metastasis, and recurrence in vivo [186]. Li et al. developed a hybrid micelle system based on the bivalent deblock copolymer poly(2-ethyl-2-oxazoline)-poly-(D,L-lactide) (PEOz-PLA) and carboxyl-terminated Pluronic F127. This system can load ovalbumin (OVA) together with the Toll-like receptor-7 agonist CL264 (carboxylated-NPs/OVA/CL264). These mixed micelles greatly promote DC absorption, cytokine production, and better presentation of antigens to CD8+ T cells, which induce antigen-specific cellular immune responses in vivo conditions. In addition, immunization with this co-delivery system greatly inhibited E.G7-OVA tumor growth in C57BL/6 mice [187]. The growth and activity of immune cells are seriously affected by cytokines, which are soluble proteins [188]. Cytokines are released in response to stimuli and instruct the immune system to exert immunomodulatory effects [189]. Cytokines enhance antigenic priming or increase immunological effector cell activity in the TME. Interleukins (ILs), tumor necrosis factors, growth factors, and interferons are considered some examples of immune-stimulating cytokines. Granulocyte-macrophage colony-stimulating factor (GM-CSF), interferons, and interleukins are utilized in clinical conditions [190]. Macrophages, lymphocytes, dendritic cells (DC), and other immune cells are activated during illness through producing interferons [191]. Interleukins affect the activation and differentiation of CD4-/t, CD8 T and B cells and show innate or acquired immune response with a significant anti-angiogenic activity at the tumor site [192]. Cytokines are not effective enough due to their short half-life and limited therapeutic window. CRS (cytokine release syndrome) can occur as a result of taking the maximum dosage required to achieve sufficient therapeutic effectiveness [193]. Sun et al. indicated that PMet-P(cdmPEG2K) micelles with doxorubicin (DOX) and IL-12 plasmid (pIL-12) were more effective in inhibiting tumor growth compared to micelles loaded with DOX or pIL-12 alone [194]. More studies are required to address the abovementioned issues to improve chemotherapy and immunotherapy in the patient's bed by reducing the dose and side effects.

5.2 Immunotherapy-focused lipid-based delivery systems

Liposome systems owing to their bilayer structure can entrap hydrophobic and hydrophilic molecules whose properties resemble the mammalian cell membrane.

Not only does it make penetration easier but also overcomes the obstacles of cellular uptake [195,196]. Liposome has been successfully utilized in clinics since it is unique in terms of both characteristics and adaptability [197]. As a result, they have been approved by the FDA for cancer treatment, drug delivery in vaccines, and fungal and microbial infections [198]. Moreover, agents for immunotherapy range from antigens to adjuvants that can be loaded into the hydrophobic core, adsorbed on the surface of the lipid through charge intercommunication between the lipid and agents, or linked to the lipid bilayer with a chemical [199]. Hence, hydrophilic small-molecule chemotherapeutic agents can be encased inside aqueous cores, as hydrophobic agents might be loaded inside lipid bilayers [200]. Indeed, there are distinct types of chemotherapy agents including platinum, taxanes, gemcitabine, and etoposide (VP-16). Platinum is considered a standard remedy in patients suffering from non-small lung cancer that different sorts of which are cisplatin, carboplatin, and oxaliplatin which attach to the DNA and demolish it, then lead to apoptosis [201,202]. Hence, the side effect of those platinum chemotherapies would be nephrotoxicity, peripheral neuropathy, ototoxicity, or myelopathy [203,204]. Taxanes are another type of chemotherapy agent having the least solubility; paclitaxel, docetaxel, and cabazitaxel are anticancer drugs from the Taxane family. They annihilate the mitotic process and inhibit the cancer cell's proliferation [205]. Nonetheless, Cremophor EL and Polysorbate 80 are applied in conjunction with Taxane drugs to address the lack of solubility-actuated deleterious influences like hypersensitivity reactions, peripheral neuropathy, or myelosuppression [206]. Therefore, those drugs can be encapsulated in liposomes in order to decline their adverse effects. Hence, sorts of approved liposomal products have been widely used in cancer therapy. In addition, liposomes have been investigated because they have the optimal efficacy of chemo-immunotherapy. Hence, Jun Wang et al. in their in vitro and in vivo study generated Cisplatin (DDP) and Oridonin (ORI) co-loaded layer-by-layer NPs (D/O-NPs). Oridonin (ORI) is an extract of Rabdosia rubescens and was found to have anti-tumor effects. It also has the ability to inhibit various types of cancer cells, including lung cancer and other cancers. ORI has a significant role in blocking AKT kinase activity as well as interacting with the ATP-binding pocket of AKT. The most obvious cell toxicity of D/O-NPs might be the clue to the adequacy of layer-by-layer NPs designed in this study. Consequently, the results demonstrated D/O-NPs enable drugs to have the function of sustained release and control toxicity in addition to promising treatment [207]. Yang et al. illustrated that ORI sensitizes cisplatin-instigated apoptosis through AMPK/Akt/mTOR-Dependent autophagosome aggregation in A549 cells [208]. What's more, Ling Zhao et al, reported that the primary goal of this study was to improve the therapeutic potential of a PTX and curcumin (CU) combination regimen utilizing solid lipid nanoparticles (SLNs). PC-SLN plays a key role in inhibiting cancer cells. The cell cycle in the G2-M phase can be blocked as a result of promoting A549 apoptosis by PC-SLN which is likely to curb the proliferation of cancer cells. PC-SLNs not only prohibit the phosphorylation of Akt in the PI3K/Akt pathway but also increase the expression of Bax protein and inhibit the expression of Bcl-2. Consequently, PC-SLNs can prevent P-glycoprotein efflux, reverse MDR, and down-regulate the NF-jB pathway. PC-SLNs are potential antineoplastic agents that are more effective and less toxic in treating lung cancer [113]. In addition, Wang, Ying, et al. investigated the synergistic effect of Docetaxel (DTX) considered a first-line of treatment for non-small lung cancer encapsulated in exosomes as a carrier in the in vivo and in vitro. Hence, exosomes are separated from A549 tumor cells by ultracentrifugation method, and also DTX was loaded into exosomes applying electroporation. The study demonstrated that not only EXO-DTX had a favorable sustained release of the drug, but also it extended the time of drug release. Furthermore, EXO-DTX has the potential to ban proliferation, uphold apoptosis, deter A549 tumor cells from migrating, stimulate ROS generation as well as disrupt the cell cycle on the grounds of that employing exosomes which are escalated the drug absorption ratio. Moreover, in the in vivo, the effect of Cy5.5-EXO-DTX was assessed on A549 tumor-bearing nude mice resulting in prohibiting the growth of the tumor, imperceptible weight alteration in the body, boosting the targeting proportion, and extending the retention time in tumor cells. Therefore, it showed the most effective therapy in both in vitro and in vivo [209]. Similarly, Li, Huizhen, et al. reported that the co-delivery of chemotherapeutic DOX and chemosensitizer LND

with EVs had a considerable influence on increasing anticancer treatment both in vitro and in vivo. Hence, they withdrew 16k EVs and 120k EVs from A549 cells and generated them by applying low-speed centrifugation and ultra-high-speed centrifugation method. EVs were obtained with 68 and 53 nm, respectively. This combination of damaging DNA, inhibiting ATP, and also producing ROS could inhibit cancer proliferation. Therefore, it demonstrated the most effective anticancer impact in vivo, as well [210]. Yang et al. studied the synergistic effect of PD-L1-siRNA and EGFR short peptide blended lipid nanoparticles that were made by PEI-LNP (EPV-PEI-LNP-siRNA) in vitro. Indeed, siRNA and EGFR short peptide can be delivered into cells in an inefficient way, when T cells were co-cultured with EPV-PEI-LNP-siRNA cured A549 cells led to escalating the IFN-γ and TNF-α levels, whilst the IL-10 proportion considerably declined. EPV-PEILNP-siRNA performed in a specific way in blocking immune checkpoint as well as decreasing side effects of immunotherapy. Moreover, liposome nanocarriers illustrated higher compatibility with the cell membrane and also eliminated the challenges of siRNA penetration. Furthermore, loaded siRNA via liposomes can boost the PD-L1 downregulation. Additionally, EPV-PEI-LNP-siRNA can be applied in order to deliver EGFR short peptides to immune cells resulting in generating immune-stimulating cytokines, adjusting immunosuppressive TEM, and having a long-lasting effect on antitumor immunity, as well [211]. It is perceived as promising method to treat non-small-cell lung cancer.

6. Perspective: Challenges and Opportunities

Identifying the exact triggers of cancer immunity, comprehending the fundamental mechanism of immune evasion, maximizing tailored methods via biomarkers, and optimizing combination regimens for long-term survival are a few of the crucial aspects highlighted by the researchers [212]. There have been several advancements in the usage of this approach; nonetheless, significant constraints, such as multi-drug resistance, treatment efficacy, high treatment costs, and efficacy of drug delivery methods, must be addressed [213,214]. Identifying cancer genetic mutations, biomarkers, tumor antigens, combined treatment methods based on targeting antigens, identifying and targeting resistant tumor cells, and developing an efficient delivery method for cancer immunotherapy are required for cancer treatment. Each case's improvement has the potential to considerably enhance cancer treatment outcomes. Oral administration is a common route of pharmacological administration. The improved approach of using nanocarriers such as liposomes, dendrimers, and solid lipid nanoparticles may enable the use of oral drugs for the treatment of cancer [215].

7. Conclusion

Cancer is one of the leading global causes of mortality. Lung cancer accounts for around one-fifth of all cancer-related death. Immunotherapy by stimulating the body’s immune system and drug delivery approaches are considered to be two highly potent tools for lung cancer therapy. However, conventional drug delivery techniques for malignant tumors, particularly lung cancer, have serious challenges. It is important to notice the severe cytotoxic effects on healthy cells, dose-dependent systemic side effects, poor solubility, embolization of blood vessels after intravenous injection, and the resistance of cancer cells to chemotherapy drugs. With the breakthrough in drug delivery methods, particularly nanoparticle-based systems, and integrating with immunotherapy researchers are closer than ever before to developing an effective cancer therapy. Nanocarriers can be delivered to tumors by passive targeting via improved penetration and persistence or by active targeting employing tumor-dependent ligands to overcome present obstacles in cancer immunotherapy and increase its therapeutic efficacy. Among various nanocarriers, lipids can more likely enable effective and selective drug delivery to lymph nodes and tumors for particular immunological action, hence optimizing therapeutic benefits and minimizing systemic toxicity. As an integrated system for delivering customized therapies and modulating the immune system against cancer cells, drug delivery systems have been extensively used to improve the effectiveness of immunotherapy and decrease off-target cytotoxicity. Future advancements in drug delivery technologies and combination treatments will increase the effectiveness of immunotherapy in the treatment of cancer, particularly lung cancer. Continuous attempts

to develop nanoparticle-based delivery techniques for clinical applications provide a significant chance to fully realize the therapeutic promise of immunotherapy, which may represent a new stride in cancer treatment.

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