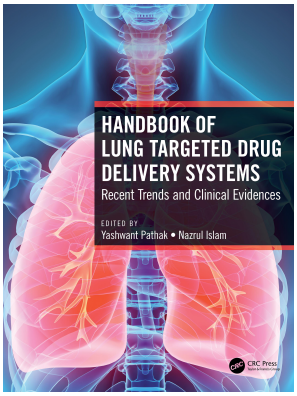

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

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Emerging Applications of Nanoparticles for Lung Cancer Diagnosis and Therapy

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Emerging Applications of Nanoparticles for Lung Cancer Diagnosis and Therapy

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28.1 Introduction

Cancer is the main health concern throughout the world. As per the 2020 estimation, new cases of cancers diagnosed will be 1,806,590, and 606,520 people die from cancers in the United States. It is expected by 2040, there will be 29.5 million new cases per year and the cancer deaths will be 16.4 million (1). Development of cancer is a complex and multiscale biological process that is correlated with the mutations or molecular changes of vital proteins regulating the cellular functions of the body. Tumors have special physiological properties with abnormal expression of receptors, growth factors, and leaky vasculature. The main objective of any cancer therapy was to improve the patient's survival and quality of life by reducing the systemic toxicity of therapy. The challenges involved in targeting are as follows: setting the goal for the disease, investigating the agent to treat effectively, and how the therapeutic agent is given. Lung cancer has the second major cancer-related mortality in the United States among all the cancer-related deaths. The estimations of new lung cancer cases for 2020 are 228,820 and 135,720 deaths from lung cancer in the United States (1). The patients, when diagnosed with lung cancer, had advanced non small cell lung cancer, because of its asymptomatic nature, thereby necessitating specific and effective treatment after diagnosis. Genetic and epigenetic alterations in the lung epithelium are the causes of lung cancer and make it a heterogenous disease. Therapeutic failures of anti-cancer drugs resulted from the drugs' cytotoxicity and the complexity in treatments. Encapsulation of lung cancer drugs in nanoparticles may facilitate intact drug delivery, avoid first-pass metabolism, and reduce cytotoxicity to normal cells, as well as being attractive to patients. The formulated nanoparticles should facilitate entrance, deposition, retention, and permeability on targeted lung tissues, and escape phagocytosis and mucociliary clearance.

Causes of lung cancer: The major contributing factor in lung cancer is cigarette smoking. Other factors contributing to lung cancer are genetic predisposition, workplace exposure (nickel, asbestos, chromium, arsenic), and environmental exposure (radon, second-hand smoke and air pollution, rapid urbanization, lifestyle change, unhealthy regimen) (2).

28.2 Classification of Lung Cancers

Based on the histological classification, lung cancer is divided into two types: small cell lung cancer and non small cell lung cancer. The small cell lung cancer also called *oat cell cancer* because the cells look like oats under a microscope. The small cell lung cancer is a not very common but aggressive cancer and difficult to treat; it accounts for about 15% of lung cancers. These originate in the inner layer of the wall of bronchi but can migrate to other parts of the body. The earlier symptoms of this cancer are infection, breathing difficulty, and sore throat. Smoking is the main cause of this cancer and other causes are inhalation of radon gas and consuming arsenic in drinking water. The advancement of disease causes difficulty in swallowing, coughing with blood, and fatigue. Non small cell lung cancer is the most common, accounting for 85% of the total lung cancers, and grows slowly when compared to small cell lung cancer. The non small cell lung carcinoma (NSCLC) patients frequently have a poor diagnosis due to diagnostic modalities issues, late detection, increased relapse rate, and rate of metastasis. NSCLC is further classified into three subtypes: adenocarcinoma, large cell carcinoma, and squamous cell carcinoma. Diagnosis of the NSCLC was done by using immunohistochemical (IHC) staining, histological alterations, molecular and mutational genetics analysis, and imaging techniques for the confirmation of the subtype of NSCLC. The adenocarcinoma found centrally in the lung at the joint of trachea and bronchi, the part of the lung which secretes mucus and helps us to breathe. The gene mutations of KRAS, BRAF, EGFR, and ELM4-ALK were exclusive to adenocarcinoma and a complement to the histological analysis to grade accurately the progression of the disease. Squamous-cell carcinoma is the second most common NSCLC subtype and accounts for 20–30% of the all NSCLC cases, and is most common in men. This cancer originates from the central airway. However, there are no specific markers, but the expression of cytokeratin-5, desmocollin-3 and p63 is used to differentiate SCC from other NSCLC variants. Large-cell carcinoma is the third most common NSCLC subtype, accounting for 3–9% of the NSCLC. Inconclusive results were observed in 70% cases

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based on the conventional histological methods due to the misrepresentative sampling of the tumor which, indeed, emphasises the need to investigate a more targetable phenotype in relation to which therapeutic approaches to pursue.

28.3 Detection of Lung Cancer

The early detection of lung cancer is very important as it augments the survival rate of the people affected by lung cancer (3). The early detection of cancer lowers the suffering, strain, and overall cost of the treatment for curing the disease, and it is easy to treat the cancer initially. Therefore, there is a dire need to find novel ways to detect the cancer at the early stage (4). The detection of lung cancer is by several histological and biochemical assays, imaging techniques like fluorescence bronchoscopy, chest radiograph, polymerase chain reaction (PCR), bronchial biopsy, computed tomography (CT), and sputum cytology. The above-mentioned methods need specialized equipment and make detection of tumors expensive. The low dose spiral (helical) CT technique is more sensitive than CT in detecting lung cancer, but these techniques need to be cost-effective and sensitive enough to detect the patients affected by lung cancer (5,6). The lung cancer screening with the advent of new technologies should allow accurate detection of cancer in individuals who are at risk of developing the disease (7). The primary role of screening is to detect the presence of disease in asymptomatic patients and the early screening will aid in the survival rate. On cthe other hand, the results may give false positives, leading to more damage to the patient (8). The radiography of the chest is the first procedure to check the individual suspected to have lung cancer and provides the first information, but it is not useful to determine the stage of cancer. Bronchoscopy is the procedure used for imaging and biopsy and it depends on the location of the tumor. Staging of cancer can be determined by whole-body CT scanning or positron emission tomography (PET), and the information gathered is very vital as this provides a prognosis and cancer can be managed efficiently. Many research efforts focused on the predictive biomarkers of lung cancer showed the role of specific genes in lung cancer progression (9). These biomarkers of cancer information allow us to design the therapy and route of therapeutic agent taken. The route of lung cancer treatment is determined by the stage of the cancer. The most common treatments available are surgical resection, radiotherapy, radiofrequency ablation, chemotherapy, radiotherapy, immunotherapy, and palliative therapy (10).

28.4 Treatments Available for Lung Cancer

The most common and effective option available for lung treatment is surgical resection. Patients with poor health and with Stage I cancer may be unable to undergo surgery (11). Radiotherapy is another option if surgery is not viable for the patient. The radiotherapy causes damage to the surrounding cells of the lungs which significantly affects the lung functionality. Radiotherapy is not recommended for patients with compromised pulmonary systems (12). The common side effects of traditional methods were hair loss, lymphedema, blood clot, dental and bone problems, weight loss, vomiting, and blood in urine and stools. Hence, there is a need to develop advanced approaches that effectively kill cancer cells, not harm the healthy cells, and have reduced side effects when compared to surgery and radiotherapy (13).

The first line of treatment options available for late stage (advanced) lung cancer is chemotherapy, which circulates throughout the body, ultimately destroying both cancerous and healthy tissues. The US FDA-approved drugs used for the treatment of lung cancer are abitrexate, avastin, carboplatin (14), docetaxel (15), gefitinib (16), afinitor, doxorubicin (17), folex, tethotrexate (18), and Topotecan hydrochloride (19). Platinum-based drugs such as carboplatin and cisplatin were the standard first-line chemotherapy regimens for lung cancer treatment (20). However, platinum-based regimes pose dose-limiting side effects which include cardio- and neprotoxicity, intestinal injury, anemia, and peripheral neuropathy. To overcome these untoward effects, platinum-based drugs were used in combination with other anti-cancer drugs (20). The anti-cancer drugs used for the chemotherapy lack tumor targeting ability, which also affects normal cells and inconveniences the patients (adverse side effects) (21). To overcome this problem, targeted drug delivery attracted much attention (22). The introduction of the inhibitors targeting receptors like epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) (23–25), and other small molecule inhibitors targeting the atypical protein kinase C (aPKC) (2,26–29), which are some of the major causes of lung cancer, yielded some promising results, but their clinical translation has yet to be investigated. This approach delivers the drugs to the tumor and reduces its distribution to other normal tissues and organs (30).

28.5 What Makes Treating Lung Cancer Difficult

There are many fundamental factors present at the lung cancer perplexity: unique tumor heterogenicity of each patient, diagnosis difficulty, the evident gaps in bridging innovative developments, and translating problems to achieve clinical success (31). Chemotherapy is the most widely used treatment strategy for lung cancer among all the available treatments for cancers. The major impediment retarding the clinical success of lung cancer therapies is an adequate amount of drug concentration in the tumor tissues. To overcome this uphill therapeutic challenge, drugs are given at high concentrations, which leads to adverse side effects. The very common side effect originates from the cytotoxic nature of drugs affecting the normal body tissues, apart from the cancerous tissues. These lacunae in the conventional therapies may be attributed to the lack of diagnosis approaches at the early stage of lung cancers (32). The overall survival rate is in question as a majority of patients are diagnosed at the advanced stage (metastatic state), which poses treatment challenges. Of the risk factors associated with the lung cancer, the prominent ones are tobacco smoking, carcinogens, air pollution, and second-hand smoke. The critical determinant of tumorigenesis is the

microenvironment of the tumor, which encompasses mesenchymal cells, infiltrating immune cells, close association with vasculature, and extracellular matrix (33). Each patient has unique microenvironment based on the tumor's genetic background, immune architecture, and somatic cells. Furthermore, the main reason that lung cancer is incurable is the development of therapeutic resistance (34). The efficacy of the treatment was low because of the poor biodistribution and non-specific distribution leading to undesirable side effects. The new chemical entities are significantly failing in later stage clinical trials mainly due to lack of safety and efficacy. Thus, there is an emergency in developing novel therapeutic modalities to treat lung cancer effectively.

Lung Characteristics for Drug Delivery: For drug delivery, lung cancer is unique. Fast drug absorption is ensured by the lung's large surface area, rich blood supply, and thin epithelium layer. These special characteristics aid in treating lung diseases, as well as systemic applications of the drugs (35). The metabolic rate was low in lungs when compared to the liver and GI tract. Thus, drugs bypass metabolism when they are delivered straight to the lungs. The most attractive feature of drugs administered to the lungs is its non-invasiveness and chance of self-administration (36).

28.6 Emergence of Nanotechnology in Lung Cancer Treatment

The advent of nanotechnology revolutionized cancer treatment and management. Nanoparticles possess various physical and chemical properties which can be used to investigate their applications in the oncology field.

28.6.1 Advantages of Nanoparticles (37–49)

- Availability of extensive surface area per unit volume
- Tunability of electronic, magnetic, optical, and biological properties
- Ease of engineering to have various shapes, sizes, solid, hollow, and porous structures
- Can be made from diverse materials: metals, silicates, carbon, polymers, metal oxides, lipids, biomolecules
- Existence in many morphologies like cylinders, spheres, platelets
- Ability to carry any nature of drugs (hydrophilic and hydrophobic)
- Nano-drug delivery systems can overcome drug resistance
- Use for specific target drug delivery
- Use in designing novel drug delivery systems
- Improves the stability of drugs
- Can be used as both active and passive drug targeting
- Better image and diagnostic tool for early detection of cancer cells in the biologic system
- Less amount of dosage form is required
- More rapid onset of therapeutic action
- Ability to show multifunctionalities
- Very good biocompatibility and the ability to overcome clearance by the kidney

28.6.2 Disadvantages of Nanoparticles

- Synthesis process is complex
- Subtle changes in the composition of nanoparticles may yield adverse effects
- In vivo clearance and release kinetics of the drug can be complicated by their physicochemical properties
- Induction of immunologic response
- Lack of standards for nanoparticle testing
- From the regulatory perspective, there is a dire need to develop an exhaustive list of tests and a smooth and streamlined approval process which facilitate translation of nano-based drugs to the clinic

In the past two decades, there has been tremendous growth and development of drug delivery systems utilizing nanotechnology. The current research efforts in the nanomedicine are expected to yield safe, efficient, and feasible drug delivery, highly sensitive,disease monitoring, and improved imaging agents for diagnosis. On the other hand, nanomedicine research is obstructed by many challenges in bridging rapidly developing novel ideas and translating them into clinicals.

28.7 Nanoparticles in the Treatment of Lung Cancer

For the treatment of lung cancer, the use of nanoparticles unlocks new avenues to develop novel treatment strategies which are efficient and overcome the shortcomings of the traditional methods. There are many classifications of the nanoparticles used to treat lung cancers. After reviewing the literature, we classify the nanoparticles as follows (50–55) (Figure 28.1):

There are many investigations of different nanoparticles used to treat lung cancer. In this, we will focus on the very recent developments of nanotechnology in lung cancer.

Liposomal nanoparticles have been explored as drug delivery vehicles for their biocompatibility and their safety profile and the ability to carry small and large molecule therapeutics of both hydrophilic and hydrophobic nature. PEG surface modification of liposomes prolongs their half-life in circulation. The liposomes, different from conventional liposomes, are referred to as "Intelligent liposomes" or "smart liposomes." These contain a bilayer of phopsholipids and surface modifiers and these decrease the chances of multi-drug resistance (MDR), apart from precisely targeting the tumor (56). Stealth liposomes, a different type of long-circulating liposome, has more residing and circulation time, which increases the drug delivery of drug at targeted site and improved the interaction of receptors and therapeutic agent in the tumor cells (57). Paclitaxel is insoluble in aqueous solvents and use of this drug is limited due to multi-drug resistance. In the study, the paclitaxel was delivered using polysaccharide nanoparticles while overcoming issues of solubility

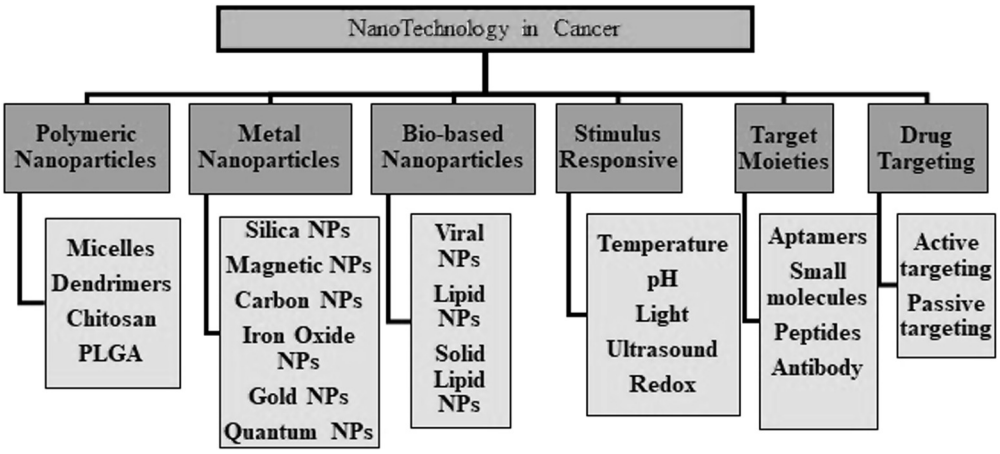

FIGURE 28.1 Classification of the Nanoparticles

and drug resistance. The biocompatible biopolymer galactoxyloglucan used to prepare nanoparticles and the study data provided the evidence that the PST-PTX nanoparticle induces apoptotic cell death and overcomes multi-drug resistance (58).

Table 28.1 presents some of the nanoparticle's advantages and applications in lung cancer treatment.

Nanoparticles are used as drug carriers and there are many research efforts exploiting the advantages of nanoparticles in this therapeutic area (Table 28.2).

28.8 Nanoparticles in the Diagnosis of Lung Cancer

In addition to the applications of nanoparticles in treatment, they can be employed for diagnostic applications. Contrast agents like radionuclides, fluorescent dyes, and gadolinium-based probes have been used for magnetic resonance imaging (MRI), positron emission tomography (PET), optical imaging, computed tomography (CT), single-photon emission computed tomography (SPECT), ultrasound (US) imaging, and photoacoustic imaging (PA) (89). The above molecular imaging methods had greater potential for the detection and diagnosis of the cancer and monitor pathological processes of the body at molecular and cellular levels, including proliferation, apoptosis, signal transduction pathways, angiogenesis, perfusion, and tumor cell metabolism (90).

The imaging technology of the cancerous tissue enables the detection of cancer at an earlier stage. The detection of metastasis in lung cancer is made easy by MRI imaging with the use of immune superparamagnetic iron oxide nanoparticles (SPIONS) (91). The SPIONS that can be delivered directly to the lungs were developed by researchers (92). The application of nanoparticles in the biosensors improves the sensitivity and detection of the test. The gold nanoparticles as biosensors were tested and

TABLE 28.1

Summary of the Different Types of Nanoparticles in the Treatment of Lung Cancer

Type of Nanoparticles	Advantages	Application in Lung Cancer Treatment	References
Liposomes	Improved stability, enhanced circulation of time of drugs, biocompatable, biodegradable	B-amino polymer used in controlled drug delivery, stealth liposomes with PEG in the composition, doxorubicin liposomes, liposomal cisplatin	(59–64)
Solid lipid nanoparticles (SLNs)	Wide range of drug adaptability, suitable for different routes of administration	SLN carrier p53, loaded SLNs with Bcl-2 siRNA	(65,66)
Polymeric nanoparticles	Ease of incorporation of water insoluble drugs, good stability, avoids macrophages phagocytosis, ease of surface functionalization, controlled drug release	Genexol-PM, peptide-Taxol (AEYLR-PNPs),	(67–69)
Dendrimers	Had strong EPR, stable nature, can accommodate multiple functional groups on surface, drug release profile can be customized	Antibody-dendrimer conjugates, PAMAM dendrimers, PEG dendrimers	(68–74)
Bio- nanoparticles	Overcome biological barriers, biocompatable, biodegradable, reduced toxicity and immunogenic response	Human serum albumin modified erlotinib NPs, microRNAs, mesenchymal stem cells (MSC) as drug delivery vehicle with NPs loaded with drugs, albumin NPs	(75–77)
Metal nanoparticles	Simple synthesis process, multifunctional surface modifications	Gold NPs, silver NPs, iron oxide NPs	(78–80)

TABLE 28.2

Summary of Nanoparticles as Drug Carriers to Treat Lung Cancer

Nanocarrier	Carrier	Drug	Vital outcomes	References
Chitosan polyplexes	Mannitol	siRNA	Improved aerosolization and dispersibility by manual grinding	(81)
PBCA NPs	Lactose	DOX	Cytotoxicity of DOX-NPs on both A549 and H460 cells was increased	(82)
SPIONS	Polyrotaxan	5-FU	Improved lung disposition of cubic nanoaggregates by lower PR content	(83,84)
Liposomes	Trehalose	ETP and DTX	Enhanced apoptosis by ETP and DTX ny pre-treatment and co-administration of p53 tumor suppressor genes	(85)
SLNs	Mannitol and leucine	TP5	Increased the bioavailability and activity of TP5	(86)
CUR NS	Mannitol	CUR	Higher cellular uptake and increased cytotoxicity to lung cancer cells	(87)
CS-PLGA NPs	Lactose, leucine, ploxamer	2-ME	Deep lung deposition improved by mucoadhesive properties of chitosan	(88)

able to differentiate lung cancer histologies. The lung cancer detection is efficient with the use of biosensors based on AuNPs and microRNAs (93). Development of biosensors made from the 11-Mercapto-1-undecanol aptamers bound to AuNPs were sensitive and selective to A549 cells (94). The detection of micrometastasis in the peripheral blood of lung cancer was achieved by the development of quantum dots linked to the NSCLC micrometastasis marker lung-specific Xprotein (LUNX) and the surfactant protein-A (SP-A) antibody (95).

Radiomics: The comprehensive method which utilizes datamining and machine-learning advancements to analyze medical images is referred to as radiomics (96). Radiomics provide quantitative data that may aid in the accuracy of diagnosis and therapy assessments. In lung cancer diagnosis, evaluation of treatment, and prognosis, radiomics is widely used. A deep learning model based on CT images yielded more precise results for the malignant lung nodule when compared to previous methods (97,98). CT radiomic signatures combined with clinical risk factors were used to predict the distant metastasis in a Chinese cohort of 348 lung cancer patients (99)and on a US cohort of 182 pathologically confirmed lung adenocarcinoma patients (100). These studies revealed the good performance of radiomics on distant metastasis (M staging). Radiomics was also used for the prediction of the gene mutation in lung cancers and many studies provide evidence for the detection of EGFR mutation by using CT radiomic features (99). Radiomic signature data from the Chinese cohort study revealed it can serve as a diagnostic factor for the histologic subtype classification of the NSCLC. In addition, radiomics can be used to evaluate the treatment of lung cancer. The delta-radiomic characteristics were used to predict the outcomes in NSCLC stage III patients undergoing radiotherapy (101). The EGFR mutation status in NSCLC before treatment and after gefitinib response, and prediction of progression-free survival after TKI therapy was predicted by CT radiomic features (102).

28.9 Nano-theranostics

The science of integration of both diagnosis and therapeutic applications of nanoparticles is referred to as nano-theranostics and emerged as a propitious paradigm in cancer treatment. It combines the advantages of both therapeutic and diagnostic worlds: nanocarriers to ferry cargo while loading on them both therapeutic and diagnostic agents. The nano-theranostic agents offer many advantages over other theranostic agents because of the sophisticated capabilities in one single platform, which include multimodality therapy/diagnosis or quality performance (e.g. autophagy inhibition, oral delivery) (103–108), stimulus-responsive drug release (e.g. magnetism, temperature, pH, and ultrasound) (109,110), targeted delivery, and synergistic performance (e.g. combination therapy, siRNA delivery) (111–113). There are four crucial aspects in designing efficient therapeutic platforms based on nanoparticles: (a) selection of therapeutic agent, (b) choosing a suitable carrier, (c) adopting a targeting and drug release approach, and (d) carefully isolating the imaging agent. Nano-theranostics was able to monitor drug distribution in the body, drug action site, drug release patterns, and the efficacy of the therapy. There is in vivo data available for either therapeutic or diagnostic agents but not for theranostics. Currently there are only a few studies showing evidence of in vivo results of real theranostic nanomedicines.

Stimulus response	Title of the Theranostic Approach Study	Reference
Heat	Thermosensitive liposomal drug delivery systems: state of the art review	(114)
Light	Near-infrared light-activatable polymeric nanoformulations for combined therapy and imaging of cancer	(115)
Ultrasound	Mechanical force-triggered drug delivery	(116)
Magnetic field	Magnetically triggered nanocomposite membranes: a versatile platform for triggered drug release	(117)
Redox	Self-cross-linked polymer nanogels: a versatile nanoscopic drug delivery platform	(118)
pH	Tailor-made dual pH-sensitive polymer–doxorubicin nanoparticles for efficient anticancer drug delivery	(119)
Microenvironment	Tumor targeting and microenvironment-responsive nanoparticles for gene delivery	(120)

Other triggers	Multifunctional, stimuli-sensitive nano-particulate systems for drug delivery, smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems	(121,122)

28.10 Innovative Strategies Showed Promising Theranostic Applications in Treating Lung Cancer (35)

The novel strategy to enhance lung cancer treatment with five essential elements is an innovative multi-tier biotechnology treatment approach utilizing the RNA interference mechanism, induction of cell death by anti-cancer agent, local delivery of nanoparticles by inhalation (passive targeting), active targeting of the peptide system to minimize the adverse side effects of traditional agents (harming the normal cells), and constructing the tumor-targeted nanostructured lipid carriers (NLCs) to increase the stability, solubility, and cellular penetration of the drug and siRNA. The most feasible carrier for the inhalatory delivery of siRNA and drug is a lipid-based system selected after screening various nanocarriers like micelles, liposomes, polymers, dendrimers, gold, silica, and NLC nanoparticles. The criteria used for the selection is preferential accumulation and retention of a carrier, siRNA and drug in lungs when compared to other organs. The authors prepared NLC comprising positively charged drug to form complexes with negatively charged siRNAs. The anti-cancer drug, paclitaxel (TAX), which is lipophilic in nature, is used to encapsulate the lipids of NLC. Furthermore, paclitaxel has been used in clinics for the treatment of advanced NSCLC. For improving the treatment efficiency, a dual targeting approach was employed. First, the therapeutic agent was limited to the lungs by its nanoparticle's delivery by inhalation. Secondly, a luteinizing hormone-release hormone (LHRH) peptide was incorporated into the system to shift the preferential accumulation (active targeting) in cancer cells. The data from the study revealed the novel tumor-targeted LHRH-NLC-siRNAs-paclitaxel delivery system is efficient in delivering the active payloads (paclitaxel and siRNA) to cancer cells. The dual active and passive targeting strategies enabled the delivery of the toxic active components specifically to the lungs with tumor and their preferential accumulation in cancer cell, and limiting their adverse effects in the normal (non-cancerous) cells. The data from the study showed all individual components were less effective when compared to the complex tumor-targeted (LHRH-NLC-siRNAs-TAX) system.

Theranostic Applications of Gold Nanorods (123): Accessibility of lung cancer tissues is the limiting factor which makes it difficult to treat lung cancer. Because of the space limitations, a single laser fiber can be used to integrate the diagnostic and therapeutic applications and this is achieved by pulse wave, plasmonic photothermal therapy (PWPPTT technology). The optimization of AuNRs and employing a laser source enabled successful translation of AuNRs for theranostic applications. The size of the AuNR is the most influential characteristic and also exhibits SPR phenomena. The theranostic potential of AuNRs combined with PW lasers is demonstrated for application in the lung cancer.

28.11 Challenges of Nanoparticles in Cancer Treatment

Despite tremendous development and explorational research efforts into the use of nanoparticles to treat cancers, there are vital issues that need to be addressed. Some of the hurdles/challenges to overcome are as follows:

A very good understanding of nanoparticle toxicity, biocompatibility, degradation, and biodistribution is required to exploit their potential in medicinal applications. The nanoparticles' physical and chemical properties, such as their surface size, charge, and shape, will determine the biological response. The rod-shaped nanoparticles are more toxic and harmful when compared to sphere-shaped nanoparticles. New materials used for the applications of nanoparticles and assessment of their nanotoxicity is complicated by the surface modifications, which in turn alter the biologic response (57). There are many possibilities to modify the nanoparticle characteristics that have a significant impact on the biological action (64). Therefore, it is absolute necessity to explore the safety of each material individually. From the perspective of the regulatory agencies and patients, the primary concern is the toxicity of the materials used to make the nanoparticles. There is a possibility of nanoparticles to induce autophagy, which plays an important role in cancer (124). Some of the materials used are not biodegradable, which can cause serious issues that limit their use in nanomedicine. There are no controls or gold standards to validate the functioning of the materials at nanoscale. The productive cost of these nanoparticles is high; to overcome this challenge we must adopt novel production methods, and seek government support and more demand from the consumers.

28.12 Conclusion

Researchers are continuously exploring the infinite potential of nanotechnology and innovative applications in the diagnosing, detecting, imaging, and treating of various cancers. The efforts in this field have already aided in overcoming problems associated with traditional medical methods such as low therapeutic efficiency, undesired side effects, drug resistance, and non-specific targeting. Development of a wide range of applications in the NDDS have shown promising results in treating diseases with more safety, efficacy, and precision. The NDDS approaches aids in targeting the active drugs to a specific site apart from regulating the desired drug level in the blood. Nanotechnology is not ideal or flawless, despite its applications and benefits. The nanoparticles have more surface area, which results in augmented chemical reactivity leading to uncertainty on how these particles behave in different environments. The augmented chemical reactivity produces reactive oxygen radicals, which may produce inflammation,

damage to proteins, DNA, and oxidative stress, ultimately leading to toxicity. In lung cancer treatment, NDDS approaches will flourish and unlock a new dimension which replaces traditional dosage approach, which in turn improves health care delivery.

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