Review Paper:

Nanotech approaches in lung cancer research: A review

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Abstract
Advanced medical treatments are desperately needed as the world's leading cause of death is cancer. New nanomaterials and nanocarriers have enabled a significant push to improve the delivery of cancer medications. The multiple pharmacological, biological and physical obstacles that the body presents which frequently obstruct effective treatment, can be circumvented using nanoparticles (NPs). The basic objective of the majority of nanocarrier uses is to prevent the medication from quickly degrading after systemic administration and permit it to penetrate the cancer site at therapeutic concentrations while reducing drug delivery to normal locations as much as possible to reduce adverse effects. Lung cancer is a fatal condition that affects a lot of individuals worldwide and it is becoming more common each year. The use of advanced nanotechnology in the diagnosis and cure of lung tumor have grown in prominence. Recent developments in nanotechnology have increased the field's application to cancer prevention, therapy and diagnosis.

Researchers have access to a variety of alterable molecules for application in cancer attributed to the specific physicochemical properties of substances at the nanostructures. Various NP formulations were created as a result of this understanding and several of these are presently undergoing clinical trials. This study gives a little background on the scientific advancements in the nanotechnology sector, underscoring the significance and necessity in the fight against lung cancer.

Keywords: Drug delivery, tumor, nanoparticles, diagnosis, therapy.

Introduction

The toxicity of some medicines and the complexity of some diseases are driving a growing need for new techniques of delivering drugs. A drug-delivery system is a composition that permits the entry of active components into the body to boost their potency and safety. It accomplishes this by controlling the drug quantity, duration and release the therapeutic target via passing through cellular membranes at the place of action. The histological characteristics of the cancer cells can be used to categorize different types of lung cancer (Fig. 1).[44,47,66]

Nanoparticles-based drug administration system is becoming more technologically advanced (Fig. 2), emphasizing more effective dose control, maintaining the effectiveness of therapy and minimizing the dangers and limitations related to conventional administration routes, concentrating on the active component to the precise location of action as well as limiting the systemic release of the prescribed drugs.[68] In the realm of diagnosis, precise focusing on the conveyance as well as discharge of an alternative material have proven to be very beneficial.[5]

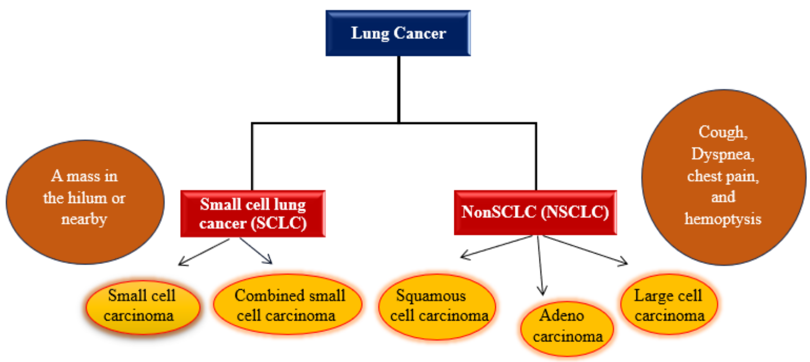

Fig. 1: Types of lung cancer and distinctive features

The second most prevalent cancer worldwide and the major cause of death is lung cancer. Lung cancer is usually identified at a late stage and progresses silently. The field of nanotechnology which has the potential to cure an array of biological problems including cancer, is one of the technological fields with the most rapid pace of growth. Numerous therapies for pain, cancer and infectious diseases are now offered in clinics based on nanoparticles (NPs). NP-based nanomedicine continues to influence cancer detection and treatment. We can get over these chemotherapy-related restrictions by empowering NPs to do theranostic operations which promote the development of novel strategies.

Lung cancer, a malignant tumor, nevertheless has a high mortality rate. A pair of variables prevent lung cancer from being cured: (i) insufficient early diagnosis due to vague or asymptomatic symptoms and (ii) unavoidable development of medication resistance after treatment. Some factors also affect drug resistance (Fig. 3). Drug release could be controlled by altering the nanoparticle system's composition and including more than one active ingredient, which may also facilitate combination therapy. In the realm of diagnosis, precise targeting with the conveyance and release of a contrast agent have proven to be very beneficial.[11]

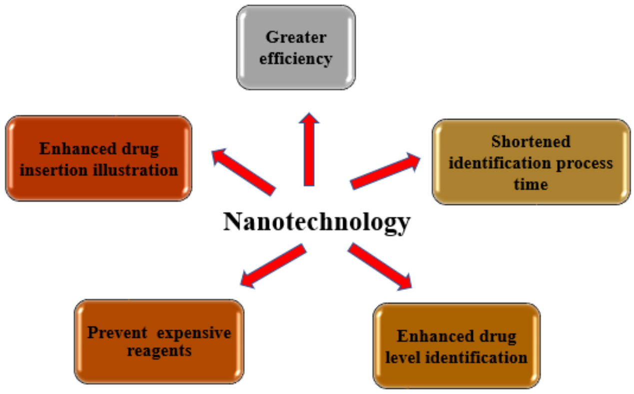

Fig. 2: Tools of Nanotechnology

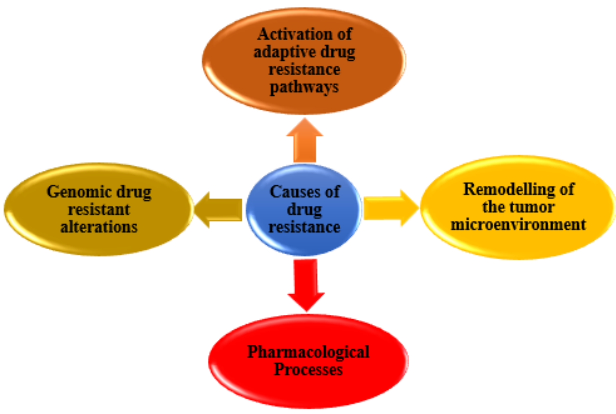

Fig. 3: Variables responsible for medication resistance

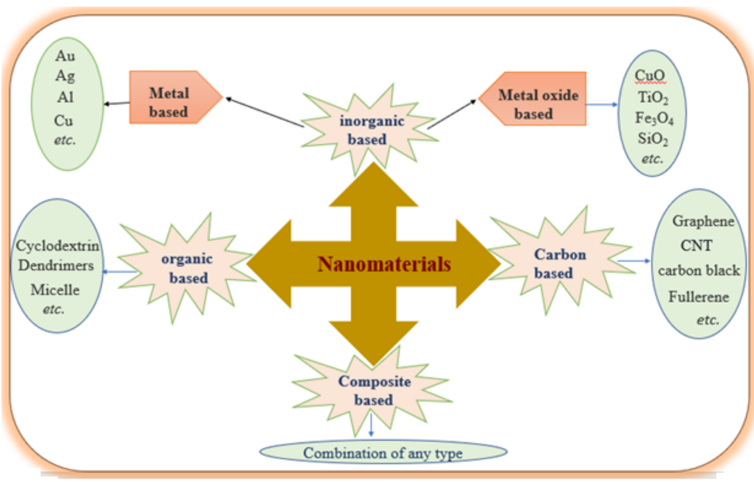

Fig. 4: Types of nanomaterials used in the diagnosis and treatment of cancer[46]

Nanotechnologies have become new, potent tools in a variety of technical applications over the years. Researchers' interest in these applications has grown, leading to notable developments in the creation of nanodevices and nanomaterials. Nanoparticles, which can be made of inorganic, organic, carbon, or composite materials, are used to make nanomaterials[35] using different materials (Fig. 4).

Lung cancer is the most common cancer among the most frequently diagnosed worldwide, with an estimated 1.8 million new cases and an estimated 1.6 million deaths annually.[22,58] About thirteen percent of all cancers globally is triggered by this.

Risk factors responsible for lung cancer

Cigarette smoking: Smoking is a prominent threat to lung tumors. A history of tobacco use occurs in approximately eighty-five percent of lung cancer patients.

Asbestos exposure: The fact is well known that asbestos exposure[13,56] at work enhances the probability of developing lung tumors. According to estimates, asbestos exposure increases the probability of lung cancer by four times higher in persons without a smoking history. All kinds of asbestos are deemed hazardous by the World Health Organization and the Environmental Protection Agency (EPA). Exposure time, amount and asbestos-containing materials fiber variety all increase the probability of infection.

Radon exposure: The radioactive decay of uranium produces radon.[26]

Industrial exposure: Lung cancer risk has been associated with polluted air and industrial exposure to As, Ni and Cr. Rarer substances include polycyclic aromatic hydrocarbons (PAHs), CH_3OCH_2Cl, Ni, As, crystalline SiO_2 and CrO_4^{2-}. Lung cancer growth is influenced by viruses e.g. human papillomaviruses (HPV)[49]. Smoke can often be a lung cancer trigger, especially in developing nations where people rely heavily on stoves and fires for cooking.[2]

In addition to the standard lung cancer treatments of chemotherapy, surgery and radiotherapy, immunotherapy has lately come to light as a potential additional treatment option. To transport medications and genes to specific locations, nanoparticles have become popular in the treatment of lung cancer. Nanoparticles extend the duration that medications and genes circulate in the bloodstream and shield them from unintended interactions.[27]

Several cancer treatments based on nanoparticles have been effective. A substantial amount of drugs used for the treatment of cancer in the lungs may be carried using NPs with greater specific surface areas due to their favorable functionality, which also prevents drug toxicity. Versatile nanomedicines are also made possible by accessible and adjustable characteristics. To prevent harming healthy tissues and lessen adverse effects, chemotherapy drugs can be enclosed in nanomaterials and transported to lung cancer cells. Nanotechnology is being used to treat tumors in a variety of ways and this combined approach to diagnostics and treatment has a significant positive impact on lung cancer patients' survival rates.

Nanotechnology is the process of designing and creating materials at the atomic and molecular level that describes structures with a dimension of up to hundreds of nanometers that are created by the fabrication of individual components either the top-down or bottom-up. The development of drug formulations based on NPs has created new opportunities for the diagnosis and treatment of challenging illnesses. Nanoparticles can be built into smart systems which contain unique physico-chemical features that distinguish nanoparticles by and functionalize construction, precise regulation with tiny size, high surface area and good responsiveness on targeting site. Increased relative surface area and quantum size effects are two parameters that differ nanoparticles from the bulk and are responsible to change the properties.

These characteristics can be used to make medication administration easier to specific tissues to provide controlled release therapy. Encapsulating medications in nanoparticle systems has recently come to light as a novel and intriguing strategy that increases treatment efficacy and minimizes undesirable adverse effects. This drug toxicity is decreased and patient compliance is increased through focused and prolonged drug delivery, which results in less frequent dosing. It has been shown that the use of nanotechnology for the cure of tumors, AIDS and many other types of medical diseases is effective. Drug delivery strategies have been used in the past to treat a variety of illnesses. Medicines often use chemicals with pharmacologically active metabolites to treat diseases.[28]

Numerous novel medications are being created for the treatment of complex health issues, but most of them have serious side effects and in some cases, the benefit exceeds the risk.[29] Apart from smoking, other significant factors that contribute to the rise in patients with respiratory disorders include rapid development, urbanization and environmental pollution.[20] The emergence of nanotechnology in recent decades has opened up new possibilities for targeted therapeutic delivery and has produced nano-based medication delivery components. These systems target the tumor location with a substantial amount of anti-cancer medications while preventing the buildup of such medications in healthy organs.[42,43] To enhance investigative and curative localization and efficiency with higher biocompatibility and less interference, NPs can penetrate biochemical obstacles inside the human body.[10]

Diagnosis

The procedure used to determine whether a patient has a lung tumor, relies on the type (SCLC or NSCLC), the extent and site of the original tumor, the existence of metastases and the patient's general clinical condition.[48] Histological analysis of resected tumors served as the traditional basis for lung cancer diagnosis and was enough to decide the most suitable therapeutic course of action. However, to enable reliable classification of the subtype of cancer, the diagnostic tool kit needs to be expanded due to advancements achieved in the field of molecular biology and alternative therapies.

Traditional methods including surgery, chemotherapy and radiation therapy lack accuracy and the majority of chemotherapeutic drugs act on healthy tissues since they are non-targeting which has unfavorable effects.[1] Numerous diagnostic techniques (Table 1) including fluorescence *in situ* hybridization and more sensitive ones like restriction length fragment polymorphism, mass spectrometry-based genotyping, Sanger sequencing, or PCR-based techniques can help IHC distinguish molecular markers.[50]

Despite being invasive, numerous biopsy samples are the most effective way to gather comprehensive data. It is controversial to make use of CT scans for lung cancer monitoring. The most common imaging approach used to assess the size and location of lung tumors, precise disease staging and identification of ambiguous lung nodules is a combined PET-CT scan (Fig. 5).[18]

Treatment

The most suitable lung cancer therapy depends on the functional evaluation of the patient, the stage of the disease and the histological sort of the tumor.[8] There are presently many NE-based cancer therapies accessible in clinics (Table 2). Innovative NPs that may remain advancing of cancer while reducing the probability of resistance to multiple medicines, have been the focus of recent advances in nanotechnology. Bromocriptine and curcumin nano-liposome joint administration in lung cancer patients revealed cancer-fighting abilities without adverse impacts on normal cells.[52] One of the main chemotherapeutic agents for cancer is cisplatin and by its encapsulation in liposomes and administering the medication intravenously (Fig. 6), the drug's toxicity can be decreased.[55]

Table 1
Biological markers in the serum for the diagnosis of lung tumor

S.N.	Biological markers in the serum	Type of tumor	Function
1	Methylated DNA	All type	Gene expression controlled by epigenetics[38,51,53].
2	CYFRA 21-1[a] and CEA[b]	NSCLC	Lung tumor from benign lung ailments might be distinguished using the combined activity of both markers[40,61,67].
3	Midkine	NSCLC	Growth agent that affects migration, survival, repair, reproduction and gene expression[34,63].
4	SCCA[c]	NSCLC (SCG)	Detection, handling of SCC and involvement in cell migration, apoptosis and existing spreading[37,65].
5	CircFOXP1	NSCLC	It may interact with two important micro RNAs and take part in VEGF signaling pathways that more sensitively and specifically control proliferation and metastasis[32].
6	SAA[d]	All type	It brings cholesterol to the liver and draws immune cells to the areas of acute inflammation during secretion[7,15,59].
7	Neuron specific Enolase	SCLC + NSCLC	Inflammatory and neurotropic activity is caused by the glycolytic enzyme and controls the survival, growth and development of neurons, multiple ions and death[19,21,36].
8	CEA	All type	Glycoprotein regulation on natural immunity, signaling and adherence of cells[17,25,57].
9	Tissue Factor Pathway Inhibitor	All types and a marker of metastasis	Initiates blood coagulation and manages issues associated with bleeding and clotting[4,16].
10	Pro-GRP[e]	SCLC	Control the production of digestive hormones, the continual growth of epithelial cells and the contraction of smooth muscles[39,41,54,62].
11	Complement component 9 proteins	All type	Causes immunological complexes to be cleared, leads to tolerance and targets apoptotic cells[14,64].
12	Haptoglobin β-chain	All type	Response during the acute phase of infection, inflammatory disorders and malignancy[23,31,45].

[a]Cytokeratin 19 fragments [b]Carcinoembryonic antigen [c]Squamous cell carcinoma antigen
[d]Serum amyloid A [e]Pro-Gastrin-Releasing-Peptide

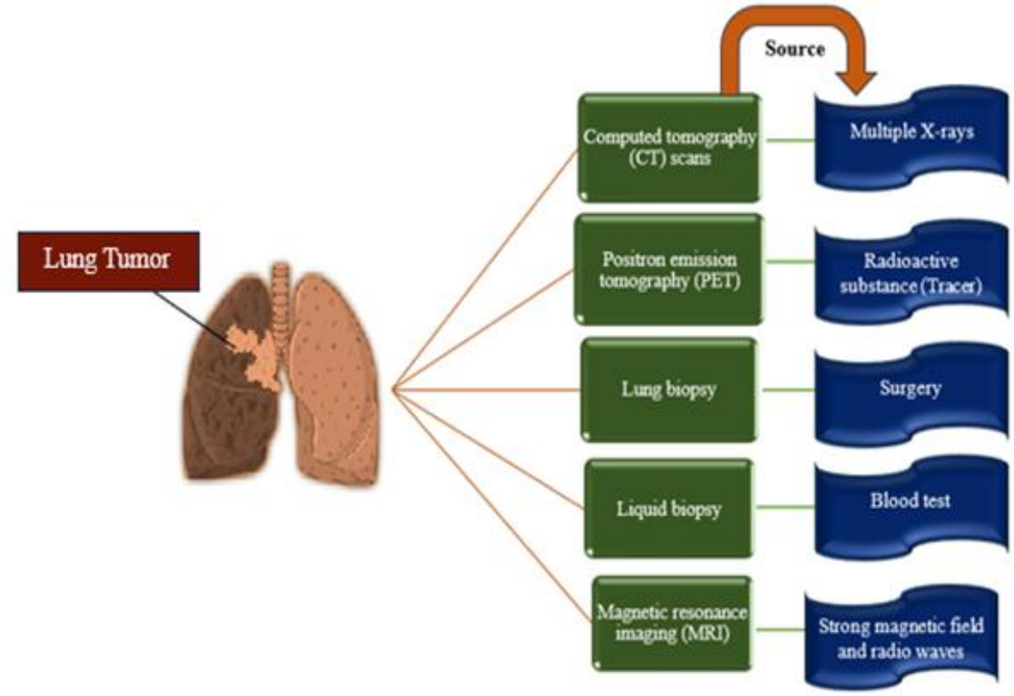

Fig. 5: Techniques and checks used to diagnose lung cancer[33]

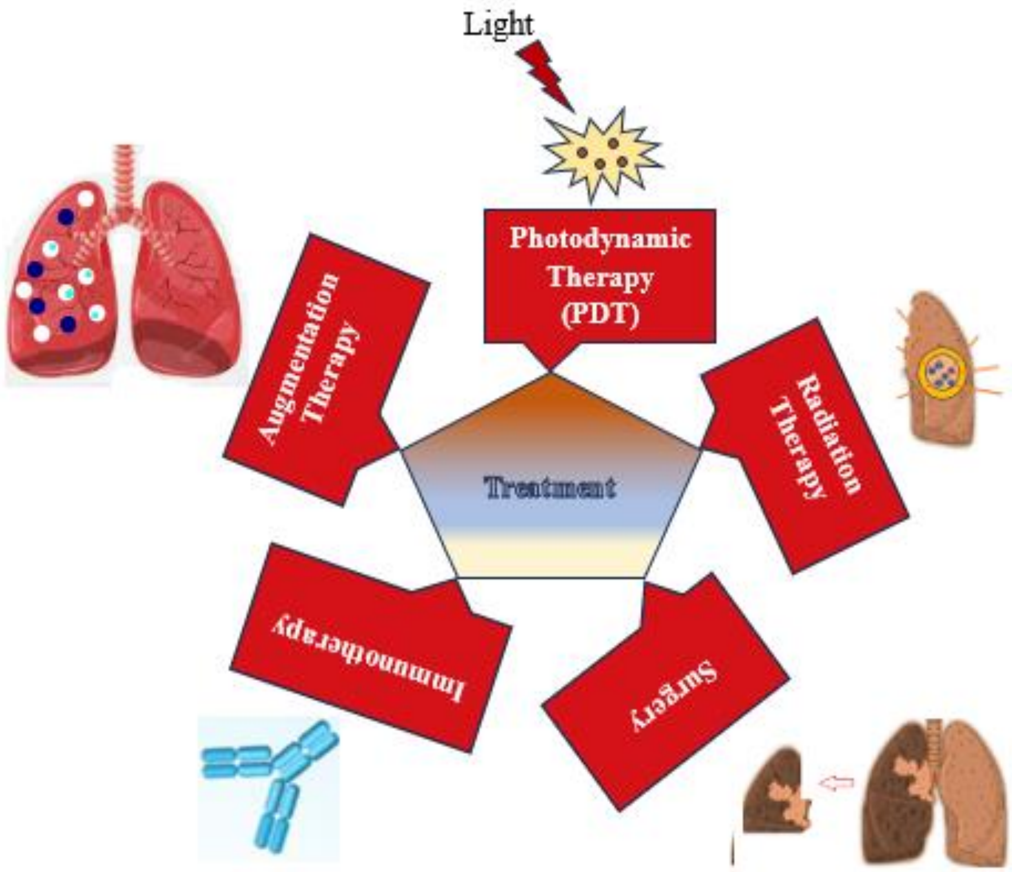

Fig. 6: Treatment methods of lung cancer

Polymeric nanoparticles (PNPs) are a promising method for improving medication stability and endothelial cell permeability while avoiding challenging targets like the mucus barrier in the lungs. Patients who are suspected of having SCLC based on the clinical and radiological findings undergo aspiration using a fine needle, sputum cytology, bronchoscopy, or thoracentesis including transbronchial needle aspiration (TBNA).

Table 2
Nanoemulsion (NE)-based approaches in the improved delivery of chemo-therapeutics to lung cancer

Drug Incorporated	Method Used for Preparation	Composition of NE	Cell Line/Animal Model	Characterization Parameter	Mechanism of Action	Outcomes
HPNs[a 24]	Homogenization under high pressure with microfluidizer	soybean oil + polysorbate 80, ferric chloride + HA + DL-α-tocopheryl acetate	CD44-overexpressing NCI-H460 xenograft tumor	• Size (nm): 85.2±7.55 nm • Morphology: spherical • ζ potential (mV): -35.7 ± 0.25 • PDI: 0.21 ± 0.05	Suspensions of cells were injected via the skin into the flank	• Targetability of HPNs results in a significant reduction in cancer development. • A negligible reduction in organ and body weight in the experimental animals. • Potentially useful nanocarriers for NSCLC.
Curcuminoid[9]	Sonication method	Curcuminoid, Tween 80 and deionized water	A549and H460 cell lines	• Average Particle size (nm): 12.6-13.7 • Shape: spherical	G2/M phase ceased by Curcuminoid NE	• G2/M phase of cell division halted • H460 cells were more susceptible for apoptosis • Caspase-3, Caspase-8, Caspase-9 and Cytochrome C expression increased dose-dependently • Dose-dependent failure in CDK1 expression
Quercetin[3]	High-energy emulsification method	Palm-base esters: Ricinoleic acid,1:1ratio, lecithin, tween 80, glycerol and aqueous phase	A549 cells	• Droplet size (nm): 131.4 ± 0.72 • PDI: 0.257 ± 0.00 • ζ potential (mV): -51.1 ± 0.28	Efficient incorporation and expanded medication availability over time	• Korsmeyer-Peppas mechanism-compliant long-term release profile • Suitable pulmonary system for delivery • A-549 cancer cell line cytotoxicity is dose- and time-dependent • No cytotoxicity appeared in the individual's lung fibroblast MRC5 cell line

Curcumin[60]	Film dispersion-sonication method	CNELNs[b]	A549 cell lines	• Diameter (nm): ~121 • Morphology: spherical • ζ potential (mV): -42	NE + Lipid + Surfactants 1. Evaporation 2. Hydration 3. Cooling ↓ Thin Film	• The NEs absorption constant improved 2.29 to 4.04 folds. • Relative bioavailability of the nanoemulsion to free curcumin was 733.59% • The GI tract's effective permeability values of the NE rise by 4.06 to 8.27 times.
Resveratrol[12]	Nano precipitation methhod. Hot melt homogenization technique. Freeze drying method. Thin film hydration method.	Solid lipid nanoparticles Cyclodextrin liposomes				Improved anti-inflammatory effects.
Naringenin[6]	Aqueous phase titration Thin film hydration	Nanoemulsion Nano complexes				Controlled release and improved skin regeneration Improved ocular bioavailability
Lycobetaine[69]	High pressure homogenization	(LBT–OA–PEG–NE)[c]	LLC cells/C57BL/6mice	• Mean diameter (nm): 146.9 ± 4.3 • ζ potential (mV): −29.6 ± 3.9 • PDI: 0.184 ± 0.012 • Capture effectiveness: 97.32 ± 2.09	Intravenous	• Enhanced pharmacokinetics • Redistribution of tissue profile • Efficacy of treatment is better
Cadmium-selenium quantum dots (QD)[30]	Ultrasonication	L-lyso phosphatidyl choline, Phosphatidyl choline and triolein	H1299lung carcinoma cells	• Dimension of the particle (nm): ~80		• QD-loaded nanoemulsion demonstrated high fluorescence emission and good uniformity. • Enclosed QDs emit fluorescence that is identical to the initial fluorescence • After 4 hours of incubation, QDs were identified inside the H1299 lung cancer cells but

						not in the cytoplasm.

PDI: Polydispersity Index
[a]Hyaluronic acid-complexed paclitaxel NEs [b]Curcumin nanoemulsion-based lipid nanosystems
[c]LBT-Lycobetaine, OA-Oleic acid, PEG-PEGylated, NE-Nanoemulsions

Conclusion

Researchers have access to a variety of alterable molecules for application in cancer attributed to the specific physicochemical properties of substances at the nanostructures. To maximize early identification and therapy of lung cancer via screening programs, a multimodality strategy may be necessary and early attempts at this technique appear promising. To raise awareness of lung cancer, public health outreach programs should be conducted. In addition to this procedure, lung cancer has to be presented in a more favorable image, demonstrating the fact that timely detection saves lives instead of sustaining the adverse perspective. To enhance cancer imaging and cancer diagnostics, nanoparticles can serve as targeting agents that specifically target particular chemicals in cancer cells and can provide a revolutionary change.

NP-based medicine offers endless potential by understanding the biology of the tumor, the microenvironment and the interaction between cancerous cells with recent developments in lung cancer imaging, treatment and detection. Clinical studies are going on for looking at novel immunotherapy combinations with or without chemotherapy treatments to treat lung cancer. Further research directions are required to create new nano-formulated medications that can be investigated in clinical trials.

Acknowledgement

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(Received 15th June 2024, accepted 18th July 2024)

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