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Nanomedicine for the Treatment of Lungs Cancer Its Challenges and Future Perspective-A Review

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Abstract

Abstract: A major public health concern with a global reach,lungs cancer necessitates cutting-edge techniques to treatment. Nanomedicine is a new technology that is currently being used to treat and diagnose lung cancer. This review examines the difficulties in using nano medicine to treat lung cancer and shows the promising directions for this rapidly developing field of study. The issues raised in this review cover a wide range of topics, such as medication delivery, targeted precision, toxicity, and legal obstacles. Approaches based on nanomedicine have the potential to get through these barriers thanks to improvements in drug delivery to lung cancer cell, a decrease in side effects, and increased therapeutic effectiveness. Additionally, this study explores the potential applications of nanomedicine for the treatment of lung cancer, highlighting the significance of cutting-edge technology including personalized medicine techniques,theranostic nanosystems, and targeted nanoparticles. These developments carry the possibility of individualized treatment plans, improved therapeutic results, and reduced side effects.

Nanomedicine offers a multifaceted approach to address the challenges of lung cancer treatment, bringing new hope to patients and clinicians alike. By overcoming existing limitations and harnessing the potential of emerging technologies, nano medicine is poised to play a pivotal role in the future of lung cancer therapy. This review serves as a comprehensive overview of the field, shedding light on the path forward in the fight against lung cancer.

INTRODUCTION

A specialized field of medicine known as "nanomedicine" utilizes nanotechnology in disease identification, treatment, and prevention. Substances and technologies at the nanoscale, which is typically between 1 and 100 nanometers (one billion of a meter), constitute the topic of nanotechnology.With over 200 different

kinds, cancer is one of the leading causes of death internationally.The most prevalent kind of cancer and the primary reason for cancer-related fatalities is lung cancer. Lung cancer accounted for 11.6% of the 2.09 million new cancer cases and 18.4% of the 1.76 million cancer-related fatalities in 2018. Men are more likely than women to develop lung cancer, which has the third- and second-highest incidence and fatality rates among all cancers that are malignant, respectively [1].By the middle of this decade, according to recent data, lung cancer will have surpassed breast cancer as the leading cause of cancer death among European women [2]. About 220,000 new cases of lung cancer were estimated to have been diagnosed in the USA in 2013 (118,080 in men and 110,110 in women), with 85% of these instances categorised as non-small-cell lung carcinoma (NSCLC) and the rest being classified as small-cell lung carcinoma (SCLC)[3].A mix of hereditary and environmental factors, as well as their interactions, influence the risk of lung cancer. Despite the fact that smoking is the primary cause of lung cancer, other factors such as secondhand smoke exposure, radon exposure, workplace toxins including asbestos and arsenic, and air pollution significantly raise the risk of developing the disease. According to recent research, men and female smokers have a lung cancer mortality risk ratio of 14.6 and 17.8, respectively[4].A branch of nanotechnology known as nanomedicine focuses on the development, maintenance, and repair of human biological systems at the nanoscale (1-100 nm) using nanotechnology standards (http://www.nano.gov).These developments in science might translate the molecular insights gained from genomics and proteomics into substantial benefits for patients.The majority of previous diagnostic and treatment techniques involved invasive medical procedures (such as random biopsy and surgery) and non-specific treatments like irradiation and chemotherapy. In the realm of nanomedicine, efforts to apply Paul Ehrlich's "magic bullet" idea to chemotherapy utilising nanoparticles are crucial for increasing treatment effectiveness and promoting the welfare of cancer patients[5].For improved effectiveness and less toxicity, nanoparticles can be created to incorporate a variety of chemotherapeutic drugs and to directly and specifically target the tumour location[6].Additionally, nanocarriers can manipulate their size and surface features to avoid their opsonization, sustaining prolonged drug solubility and protecting the drug from degradation the flow of blood[7]. Due to their useful characteristics, nanoparticles are one of the topics of nanomedicine that are being explored the most.

2. CONCEPT AND PRICIPLE OF CANCER TREATMENT USING NANOMATERIAL

2.1 Active targeting

Active targeting is a technique used in nanomedicine to improve the delivery of therapeutic drugs to a target place inside the body. This site is often a disease site, like a tumor or an inflammatory tissue. Specifically created nanoparticles or nanocarriers are used in this method, and they are loaded with ligands, antibodies, peptides, or other compounds that can interact with particular molecules or receptors on the surface of target cells. The objective is to improve drug delivery's accuracy and efficiency while reducing off-target effects. For increased and/or targeted management active targeting entails the use for conjugated targeting moieties that recognise receptors or proteins expressed in cells of tumours, which are additionally referred to as tumor-associated antigens[8]. This technique was first applied in the 1980s using liposomes to improve targeted distribution by covalently adding a specific antibody (known as an immune liposome).[9].This is one of the most well-known strategies for increasing the efficacy of nanomedicine, and it was frequently used by scientists studying drug delivery with nanoparticles.[10]. Due to their significant selection and high affinity for either cancer or their associated endothelium, the moieties for conjugating particles are typically ligands or targeting antibodies, which subsequently enhance their localization and accumulation in the tumour. .However, several studies have shown that antibody-based targeting only enhances internalisation and does not improve tumour localisation. This implies that biodistribution still depends on passive targeting to tissues with fragile blood vessels, and that targeting moieties only initiate endocytosis subsequent to extravasation into the tumour.[11]. Long circulation times would enable a significant accumulation of nanoparticles at the tumour location by the EPR effect, followed by an increase in endocytosis brought on by the targeting molecules. Activating targeting with targeting moieties enhances the delivery of therapeutics to the specific tumour site, regardless of the precise processes involved. Although not fully understood, the most likely way for nanoparticles to enter cells is through endocytosis, and the internalisation of drugs by nanoparticles after attachment is essential to preserving the effectiveness of some anticancer medications, particularly in gene delivery, siRNA silencing, and other biotherapeutics[12]. Various targeting compounds are employed for active targeting. The most often used tiny organic compound among them is folate.When comparing many cancer cells to normal tissue, the folate receptor is considerably overexpressed, often by a factor of 100–300. Folate has a high affinity for this receptor[13]. The human epidermal growth factor receptor 2 (HER2), which is overexpressed in one-fourth of breast tumours, is the target of the anti-HER2-antibody trastuzumab (Herceptin), which also targets a tar-getting moiety. Recently, anti-HER2 antibodies were functionalized with liposomes containing topotecan, a topoisomerase-I inhibitor, to target breast

tumours[14]. The anticancer activity of HER2-targeted liposomes increased by more than twofold and fivefold, respectively, in comparison to nontargeted liposomes and free topote. As an additional possibility for active targeting of nanoparticles, the cyclic peptide cRGD (Arg-Gly-Asp-D-Phe-Lys) has been studied because of its high affinity for avd3, which is overexpressed in blood vessels during angiogenesis. [15].

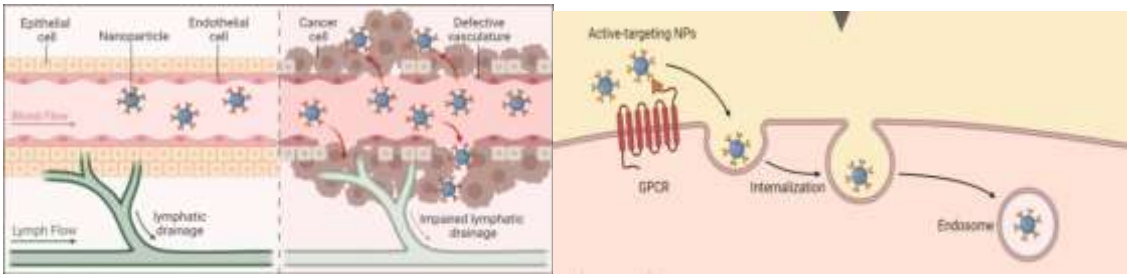

Fig.1 Concept of passive and active targeting.

(a) Passive targeting of nanocarriers.Nanocarriers reach tumors selectively through the leaky vasculature surrounding the tumors. Schematic representation shows the influence of size on retention in the tumor tissue. Small molecular therapeutics (green) diffuse freely in and out the tumor blood vessels because of their small size and thus their effective concentrations in the tumor decrease rapidly. On the other hand, drug-loaded nanocarriers (blue) cannot diffuse back into the bloodstream due to their huge size, which causes gradual accumulation—the EPR effect. (b) Strategies for active targeting. Target-ligands that have been grafted onto the surface of nanocarriers attach to receptors that are overexpressed by vascular endothelial cells or cancer cells.

2.2 Passive Targeting

Nanomaterials enhanced permeability and retention (EPR) effect and prolonged circulation period can be largely blamed for passive targeting of the materials and accumulation of their therapeutic cargo in tumour tissues. The EPR effect refers to a molecule's propensity to accumulate in tumour tissue at a higher rate than in normal tissue. Obstacles must be overcome in the areas of nutrition supply, waste excretion, and oxygen consumption since tumour tissue has a diffusion limit at a volume of 2 mm3 or above[16]. By expanding the surrounding vasculature, tumours overcome these obstacles in a procedure known as angiogenesis.Angiogenesis is characterised by aberrant deformation, abnormalities in the basement membrane, and a deficiency of pericytes lining the endothelial cells. Owing to this defective tumour vasculature, depending on the kind of cancer, arteries are encased with leaky gaps ranging from 100 nm to 2 μm[17]. In addition, as tumors lack a well-defined lymphatic system, interstitially accessed drugs and nanoparticles have higher retention times in tumor tissues than in normal tissues, because the EPR effect results from the combination of leaky vasculature and poor lymphatic drainage . Smaller than vascular fenestrations nanoparticles have the ability to pass through the interstitium and gather inside tumours. [18].

3. Nanoparticle Drug Delivery for Lung Cancer Therapy

Anticancer medications can be enclosed in nanocarriers, which is one extremely effective method of delivering drugs to sick locations. Targeted administration of significant chemotherapy doses agents by improving their pharmacokinetic characteristics, which leads to enhanced drug efficacy, lower non-specific toxicity, better anticancer effects, and tumour localization, is the primary clinical advantage of nanocarrier-based approaches over free medicines[19-21]. Over the past few years, several nanoparticle formulations, such as liposomes and polymers, have been developed that are intended to effectively deliver anticancer medications and nucleic acids like DNA and siRNA to metastatic lung cells. These formulations have the potential to become candidates for the next-generation therapy for lung cancer that has progressed to an advanced stage[22,23].In most nanocarrier-based approaches, the drug is combined with a carrier, a targeted moiety that is joined to the carrier by a particular conjugation chemistry, and a medicine. Carriers can be in the form of lipids, polymeric nanoparticles, inorganic nanoparticles, or dendrimers..High affinity ligands, antibodies, and nucleic acids are a few examples of targeting moieties that can be attached to carriers using a range of chemistries.

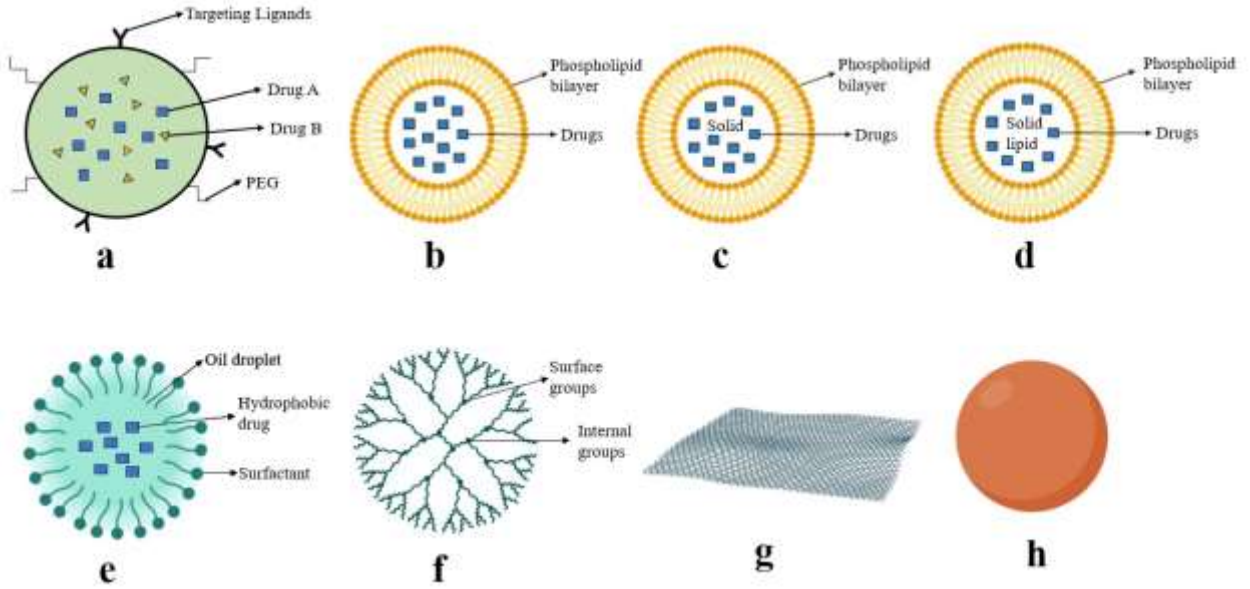

Fig.2 Categories of nanomaterials applied in the treatment of cancer. a.Nanoparticles, b.Liposomes, c.Solid lipid nanoparticles, d.Nanostructures lipid carriers, e.Nanoemulsions, f.Dendrimers, g.Graphene, h.Mettalic nanoparticles.

3.1Mettalic and Magnetic nanoparticle

Metallic materials can be conjugated in a variety of ways with adaptable carriers such liposomes, dendrimers, NPs, or CNMs. Magnetic nanomaterials are mainly applied in MRI imaging. Guided by external magnetic feld, magnetic NPs loaded with chemical drugs can target cancer cells, and therefore sid been extensively studied in bio-imaging and drug delivery[24]. When metal particles are conjugated, the nanosystem is capable of PTT and bioimaging. Fe3O4/Ag-based iron oxide nanoparticles (IONPs) were enclosed in a gold shell. Due to the gold shell in the NIR region, IONPs and PTT demonstrated MRI contrast capabilities [25]. Highly oxidative hydroxyl radicals (OH), which are generated in cancer cells similarly to peroxidative dye transfer (PDT), are toxic and cause permanent damage to proteins, lipids, and DNA by initiating chain reactions with nearby organic molecules.[26].In the treatment of cancer, metallic elements are frequently employed in PTT, PDT, CDT, and immunotherapy.[27]FeS2, Fe2P, Fe3O4, SnFe2O4, and amorphous iron are a few examples of iron-based nanostructures that increase the disproportionation of H2O2 to create OH radicals [28, 29, 30]. NIR triggered materials are crucial for PTT and PDT because they have a far higher capability for tissue penetration than UV and visible light. compared to PDT, where ROS such as OH, singlet oxygen (1O2), and superoxide (O2) trigger deadly reactions, PTT involves the heat destruction of cancer cells in order to produce energy. In these therapies, metallic substances like Au (gold), Cu (copper), and Fe (iron) are typically used[31]. The disadvantage of metallic nanomaterials lies in their toxicity. Attarilar et al. summarized the mechanisms of metallic NPs: ROS generation and infuence on cell structures, characteristics of metallic NP toxicity are similar to other NPs, that toxicity is related to size, shape, dimensionality, surface charge [32]. Therefore, metallic NPs should be carefully examined before use on human patients.

3.2 Liposomes and solid lipid NPs

Sphere-shaped, two-layer vesicular structures made of phospholipids are known as liposomes[33].Because of these vesicles' capability for carrying chemotherapeutic medications, whether they are hydrophobic and embedded in the bimembrane or hydrophilic and enclosed in the aqueous core, research into them is expanding. Even while liposomes have numerous advantages, such as their biocompatibility, non-toxicity, and ability to biodegrade, conventional liposomes have a tendency to fuse together, which leads to decreased stability in vivo and accelerated breakdown of the reticuloendothelial system (RES)[34].In order to get over these restrictions, the liposomes' surface has been altered by coating it with inert hydrophilic polymers like PEG. These polymers give the liposomal surface stability and provide a barrier that prevents RES from recognizing them right away, lengthening the period that the liposomes spend circulating in the blood.[35].Drugs like doxorubicin have been encapsulated using this modification. Multiple Phase III studies for ovarian cancer have validated PEGylated Liposomal Doxorubicin, and the results are encouraging [36]. Solid lipid NPs, often referred to as a submicron colloidal carriers, have recently gained popularity because of their capacity to transport both hydrophilic and lipophilic medicines as well as their high stability, extended blood retention time, and potential for

composition with biocompatible components [37]. Because of the advantages they offer, such improved pharmacokinetic qualities or diminished side effects of particular chemotherapeutic treatments, interest in using liposomes in drug design has grown over time. Patients with locally advanced illness get platinum-based chemotherapy as the usual treatment for NSCLC [38]. However, 20–40% of individuals who receive cisplatin also experience acute nephrotoxicity [39].Lipoplatin was created in order to lessen these adverse effects and increase response rates.Encased in a liposomal NP, cisplatin has been demonstrated to dramatically lower the likelihood of side effects such nephrotoxicity, peripheral neuropathy, ototoxicity, or myelopathy[40,41]. In order to compare the effectiveness of combination treatment with Lipoplatin and paclitaxel versus cisplatin and paclitaxel in patients with advanced non-small cell lung cancer (NSCLC), Stathopoulos et al. developed a randomised Phase III clinical trial. The results showed a statistically significant increase in the response rate in those patients treated with Lipoplatin[42].A randomized Phase III clinical trial was developed by Stathopoulos et al. to compare the effectiveness of Lipoplatin and Paclitaxel versus Cisplatin and Paclitaxel in treating patients with advanced NSCLC, and the results showed that Lipoplatin treatment resulted in a statistically significant improvement in response rates [43].

3.3 Dendrimers

A certain class of unusual macromolecules known as dendrimers have defined hyperbranched structures. Their enormously branching and elongated shapes are dendrimers' most noticeable attribute surfaces that are simple to modify. The dimensions of these diamonds. The majority of polymers have sizes between 1 and 10 nm, while some huge, expertly crafted dendrimers can reach sizes between 14 and 15 nm[44].The dendrimer particles are composed of three primary structural pieces: a central core that encapsulates therapeutic substances in a noncovalent manner, branches that include the internal pyramidal structure, and an outside surface conjugated with functional surface groups. For the treatment of cancer, a number of dendrimers have been created, particularly polyamidoamine (PAMAM), polypropylenimine (PPI), poly(ethylene glycol), bis(2,2-bis(hydroxymethyl)propionic acid), 5-ALA (5-aminolevulinic acid), and triethanolamine (TEA). Dendrimers different from other nanoparticles due to their particular structure, which provides them benefits over them such as specified molecular weight, flexible modifiable branches, a low polydispersity index, and better solubility and bioavailability of hydrophobic medicines. Dendrimers can be effective nucleic acid nanocarriers because electrostatic the dendrimers with electrically charged surfaces are capable of creating compounds with nucleic acids. Two widely researched dendrimers with different application strategies are PAMAM and PPI[45]. Using fuorescence imaging, a PAMAM dendrimer/carbon dot nanohybrid was created to regulate MDRs and simultaneously monitor cancer cells.Separate complexes were made for each. The first component was a CDs/DOX complex made up of non-covalent contacts between blue-emitting carbon dots (CDs) and the anticancer medication DOX. The other component was G5-RGD TPGS, which comprised of generation 5 (G5) PAMAM den drimers targeting the drug efflux inhibitor d-tocopheryl polyethylene glycol 1000 succinate (TPGS) and the cyclic arginine-glycine-aspartic (RGD) peptide[46]. An electrostatic connection between two components created a dual drug-loaded nanohybrid system. The luminescence of CDs was used to generate in vitro fluorescent properties, and the presence of RGD ligands, which target v3 integrin receptors overexpressed in cancer cells, was used to accomplish targeting specificity.The findings demonstrated that TPGS significantly inhibited the growth of cancer cells.The co-delivery capability of dendrimers can also be employed to deliver compounds that are entirely different. Colon cancer patients frequently receive DOX treatment. A vital component of the apoptotic pathway, the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) can bind to the death receptors 4 and 5 (DR4 and DR5), which are overexpressed in a variety of cancer cells. The Pishavar group combined the TRAIL and DOX plasmids to create a dendrimer nanocarrier, which showed a greater anticancer impact than modified carriers containing just the TRAIL or DOX plasmid. [47]. In order to treat liver cancer cells using chemotherapy and photothermal therapy, a PAMAN nanocarrier based on dendrimer was created. The drawbacks of tough PAMAN dendrimers without modification.

3.4Nanoemulsion

Emulsifying agents, aqueous phase, and oil combine to generate colloidal nanoparticles called nanoemulsions (NE).A nanoemulsion's size ranges from 10 to 1000 nm..Drug nanocarriers known as nanoemulsions, which are typically solid spheres with amorphous and lipophilic surfaces, are commonly employed who show a negative charge.Because nanoemulsions are heterogeneous mixtures made of aqueous and oil droplet nanodroplets are dispersed over media with a small size, and it is possible to create the following three types of nanoemulsionswater in an oil nanoemulsion system, where (a) water is dispersed in an aqueous medium; (b) an oil-in-water nanoemulsion system where oil is dispersed in an aqueous (c) a medium;a bi-continuous nanoemulsion[48,49].In comparison to the majority of lipid-based nanomaterials

and nanoparticles, nanoemulsions have a number of benefits, including optical clarity, thermodynamic stability, large surface area, ease of production, biodegradability, and optimal drug release profle [50].A wide range of membrane-modified nanoemulsions have been studied. Using nanoemulsions for co-delivery can enhance both the bioavailability and therapeutic effectiveness. The anti-tumor effects of PTX could be enhanced by modulating immunity through Toll-like receptor 4/nuclear factor kappa B (TLR4/NF-B) signaling pathways, according to test results of a NE drug carrier system loaded with spirulina polysaccharides and PTX [51].To treat metastatic melanoma, a nanoemulsion system containing temozolomide, rapamycin, and bevacizumab was developed. In vitro human and animal cell models demonstrated enhanced cytotoxicity against melanoma cells, as well as better tumour relapse, migration, and angiogenesis suppression, following parenteral dosing.[52].

Table 1 Examples of nanocarriers used in cancer treatment.

Nanotechnology platform	Description	Pharmaceutical ingredients	Disease	Status	References
Polymeric nanoparticle	somatostatin analog decorations	Cetuximab	Colon cancer	Stage-1	NCT03774680
Nanoparticle	When used with enzalutamide	Camptothecin	prostate cancer with metastatic castration resistance	Stage-2	NCT03531827
Liposome	Liposome	irinotecan	lung cancer with little cells	Stage-3	NCT03088813
Nanoemulsion	PDT therapy with a photosensitizer	Nanoemulsion of aminolevulinic acid	cancers of the basal cells	Stage-2	NCT02367547
Quantum dot	coated with a drug	veldoreotide	Breast cancer	Stage	NCT04138342

Conclusion and Future Perspectives

An important development in the realm of oncology is the use of nanoparticles in the treatment of lung cancer. The potential of nanoparticles as a diverse and effective tool against this fatal disease has been the subject of intensive study and development over the years, which has yielded useful insights. As we wrap up, it is abundantly evident that nanoparticles have enormous potential for overcoming the particular difficulties presented by lung tumors.One of the most significant advantages of nanoparticles in the treatment of lung cancer is improving medication delivery. Nanoparticles have the potential to boost the therapeutic efficacy of anticancer drugs while reducing systemic toxicity by increasing drug solubility, extending circulation periods, and enabling targeted delivery to tumor locations.

Moreover, by improving drug solubility, prolonging circulation times, and facilitating targeted delivery to tumour sites, nanoparticles have the potential to increase the therapeutic efficacy of anticancer medications while lowering systemic toxicity.Additionally, nanoparticles can serve as versatile platforms that aid in both therapy and diagnosis.In order to enable prompt intervention and individualized treatment plans, theranostic nanoparticles with imaging agents can help with the early identification and monitoring of lung malignancies. A paradigm shift in the treatment of cancer is represented by this convergence of diagnostics and therapies.

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