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Review

Advances in Lung Cancer Treatment Using Nanomedicines

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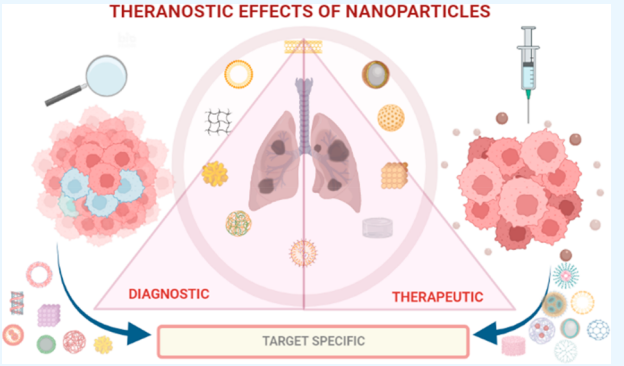
ABSTRACT: Carcinoma of the lungs is among the most menacing forms of malignancy and has a poor prognosis, with a low overall survival rate due to delayed detection and ineffectiveness of conventional therapy. Therefore, drug delivery strategies that may overcome undesired damage to healthy cells, boost therapeutic efficacy, and act as imaging tools are currently gaining much attention. Advances in material science have resulted in unique nanoscale-based theranostic agents, which provide renewed hope for patients suffering from lung cancer. Nanotechnology has vastly modified and upgraded the existing techniques, focusing primarily on increasing bioavailability and stability of anti-cancer drugs. Nanocarrier-based imaging systems as theranostic tools in the treatment of lung carcinoma have proven to possess considerable benefits, such as early detection and targeted therapeutic delivery for effectively treating lung cancer. Several variants of nano-drug delivery agents have been successfully studied for therapeutic applications, such as liposomes, dendrimers, polymeric nanoparticles, nanoemulsions, carbon nanotubes, gold nanoparticles, magnetic nanoparticles, solid lipid nanoparticles, hydrogels, and micelles. In this Review, we present a comprehensive outline on the various types of overexpressed receptors in lung cancer, as well as the various targeting approaches of nanoparticles.



1. INTRODUCTION

Cancer has become one of the paramount and most serious health concerns globally, affecting people in both developing and developed countries.[1,2] Lung cancer is one of the deadliest cancers, accounting for a high mortality rate, and is the most frequent cause of tumor-related fatalities. It is essentially categorized into primary and secondary cancers. Based on the histological assessment, lung carcinoma is subdivided into non-small-cell lung carcinoma (NSCLC), small-cell lung carcinoma (SCLC), mesothelioma, sarcoma, and carcinoid. SCLC and NSCLC are the most commonly occurring, i.e., they represent around 90% of all forms of lung cancers, while the incidence of other types has been rare.[3,4] NSCLC is further subclassified into four types: adenocarcinoma, squamous cell carcinoma, large-cell undifferentiated carcinoma, and Pancoast tumor.[5,6] SCLC is an aggressively growing tumor and is categorized into small-cell and "oat cell" cancer combined.[7] Smoking habits, hereditary factors, urbanization, and environmental factors (like exposure to arsenic, toxins, and asbestos) are the primary causative factors contributing to the pathogenesis of lung cancer.[8−12] As per the statistics released by the World Health Organization (WHO), in 2020 alone there were around 2.21 million diagnosed cases of lung cancers, along with 180 million deaths.[13]

Conventional strategies such as chemotherapy, radiotherapy, and surgical resection, either separately or in combination, have been the mainstay of the current treatment regimens.[14,15] However, severe adverse reactions are well reported with such traditional treatment methods. Moreover, the damage caused by radiotherapy to the surrounding healthy cells is evident, and thus it should not be the preferred treatment in patients who already have severely compromised pulmonary systems, as this may lead to loss in the functionality of the lungs.[16,17] Radiotherapy has also been used in combination with chemotherapy and/or surgery lately.[18] The main principle on which chemotherapy works is by hindering the synthesis of DNA (deoxyribonucleic acid) and mitosis, which eventually leads to the death of rapidly spreading cancerous cells. As the chemotherapeutic agents are non-selective, they tend to impart undesirable adverse side effects to the surrounding normal

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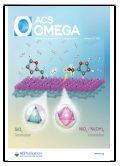

cells, which is one of the major reasons behind the high mortality rate in tumor patients. The drug regimen is, moreover, administered in specific cycles with regular breaks in between, which is essential for the recovery of non-selectively damaged cells. But these breaks may eventually restore even the carcinoma cells which were supposed to be weakened or killed by the therapy. Furthermore, this could also lead to myelosuppression, which requires extending the duration of the break and/or even discontinuation of the agents.[19] In addition, non-targeted cytotoxicity and the prevalence of highly structured physical, physiological, and enzymatic barriers make targeted drug delivery extremely difficult, which restricts drug distribution to the target location.[20] Moreover, the advent of multi-drug resistance (MDR) substantially reduces treatment effectiveness for the majority of malignancies.[21] As a result, nanotechnology has emerged as a widely recognized and promising approach in the battle against cancer.

Nanoparticles (NPs) are colloidal particles with a diameter of less than 100 nm, which are combined with a therapeutic agent that is usually encapsulated inside the particle matrix, which is either adsorbed or conjugated on the surface by structural changes to enhance therapeutic stability and selective targeting. Nanoparticles are effective theranostic agents due to their dimensional resemblance to biomolecules, high surface-to-volume ratio, and potential for surface modification.[22] Theranostic agents are tools that include cancer cell imaging and treatment by incorporating numerous methods that allow for a comprehensive diagnosis, molecular imaging, and a specific treatment regimen all at the same time. Nanoparticles possess a sub-micron size, which allows for deep tissue infiltration, penetration through epithelial fenestrations, and usually effective uptake by targeted cells, which elevates the bioavailability of therapeutic components.[23,24] By fabricating the particle polymer properties, it is possible to maximize the amount and rate of drug release.

Nanotheranostics provide significant advantages over conventional therapeutic, diagnostic, and pharmaceutical approaches (Table 1). As there is a probability of surface modification[25] and a tendency for both passive and active drug targeting,[26] nanoparticles are intriguing agents which can be used in extremely precise *in vitro* and *in vivo* imaging and as targeted treatment sensors.[27,28] The nanotechnology research in this field encompasses a wide variety of component systems that modulate the speed and direct the drug to be released at a specific site.[11] Quantum dots, liposomes, polymeric nanoparticles, inorganic nanoparticles, magnetic nanoparticles, dendrimers, and gold nanoparticles are among the most investigated and promising systems.

Different synthetic and natural compounds have been synthesized and isolated and evaluated against lung cancer cell lines, but still their mechanism of action needs to be explored.[29−33] To overcome the challenges associated with conventional chemotherapy, the development of novel drug delivery systems which can either passively or actively target carcinoma cells is urgently required.[34] Given the larger surface area of the alveolar region, drug delivery to the lungs has provided numerous promising opportunities for enhancing treatment efficacy. Lack of mechanistic insights into the underlying cellular mechanisms behind tumoral heterogeneity has drawn considerable attention to develop the relevant treatment approaches and therapeutic strategies. Because therapeutic responses are generally influenced by the emergence of resistant subpopulations and variations in molecular phenotypes, hence understanding tumor heterogeneity is therapeutically beneficial.[35] For the past two decades, the rise of nano-based delivery systems has created immense opportunities in clinical therapeutics and enhanced bioavailability by demonstrating desirable properties such as the prolonged retention of therapeutics in the lungs, consequently reducing the amount of dose administered and improving patient compliance.[36] This comprehensive review also discusses the applications of novel drug delivery vehicles that employ nanomolecules in the treatment and diagnosis of lung cancer.

Table 1. Various Nanoparticles with Their Theranostic Properties

Nanoparticles (NPs)	Properties contributing to theranostic action
 Liposomes	Liposomes offer various attributes, namely biodegradability, biocompatibility, ease of synthesizing, sustained release of the drug, less toxicity, and the efficiency to incorporate both hydrophilic and lipophilic chemotherapeutic compounds.
 Gold NPs	Gold nanoparticles can absorb and scatter light with strong excitation peaks in the visible as well as near-IR (Infrared) region.
 Dendrimers	They exhibit a number of important attributes in nanomedicine, including homogeneity, chemical modification, tailored multivalency, monodispersity, higher permeation and circulation, reproducibility, and strong spatial distribution of multiple functions on their surface, that are important for the delivery of API (Active pharmaceutical ingredient), Like small and macrocyclic drugs, small interfering RNAs (Ribonucleic acids), and antibodies, for several pharmaceutical applications, including cancer,
 Solid-Lipid NPs	Solid nanoparticles were considered suitable for use as theranostic tools because of their ease in large-scale production, biocompatibility and biodegradability, low toxicity potential, ability to control and modify drug delivery, drug solubility enhancement, and the incorporate both hydrophilic and lipophilic drugs.
 Micelles	Micelles are very stable and biocompatible, with extended blood circulation time, low particle size distribution, controlled release, and ability to high drug loading, and also super-paramagnetic MRI (Magnetic resonance imaging) performance.
 Magnetic NPs	They earned a great attention for cancer theranostics applications because of their unique physicochemical features, MRI contrast, ease of synthesis, simple surface decorating, low toxicity, and remarkable biodegradability.
 Quantum dots	They impart high fluorescent efficiency and photostability with wide range of emission spectra about 400nm to 200nm covering both the visible and near-IR wavelengths.
 Carbon Nanotubes	CNTs (Carbon nanotubes) can be used for cancer diagnosis and therapy in a variety of ways due to their superior optical properties, thermal and electrical conductivity, ease of functionalization, and high drug loading capacity.
 Hydrogels	Due to its controllability, biocompatibility, high drug loading, delayed drug release, malleability, and specific stimuli-sensitivity, hydrogel-based therapies are becoming a viable cancer theranostic approach.
 Polymeric NPs	Polymeric nanoparticles exhibit significant attributes such as ease of fabrication, non-toxicity, non-immunogenicity, targeted drug delivery, biodegradability and biocompatibility which makes them more preferred theranostic tools.

2. OVEREXPRESSED RECEPTORS

2.1. Epidermal Growth Factor Receptor (EGFR). Overexpression of transmembrane protein EGFR plays a crucial role in the advancement of carcinoma. It consists of an intracellular fragment of tyrosine kinase activity and an extracellular section that includes the ligand-binding area responsible for the regulation of tumor growth (invasion, angiogenesis, metastasis, and proliferation of cells).[37] Conformational modifications arise when ligands bind to the attaching area. The binding of ligands and activity of tyrosine kinase further leads to autophosphorylation that triggers alterations in the signaling pathways.[38,39] These tyrosine kinase inhibitors are more effective for altered EGFR in

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cancer.[40] Mutations arising due to the overactivation of EGFR alter the signal transduction pathways. Attachment of ligands present on the outer side of the cell further leads to cell multiplication and anti-apoptosis.[41,42]

2.2. Growth Hormone Receptor (GHR). GHR is a single-pass transmembrane receptor with at least one cytokine receptor homology domain (CRHD) in its extracellular portion. The CRHD has two fibronectin III (FNIII)-like folds. GHR overexpression has been identified in A549 NSCLC and other related cancers.[43,44]

2.3. Folate Receptors. The folate receptors demonstrate a greater binding affinity for folic acid.[45] It comprises four different forms: Folate Receptor Alpha (FRA), Folate Receptor Beta (FRB), Folate Receptor Gamma (FRG), and Folate Receptor Delta (FRD). FRA is a glycosylphosphatidylinositol-anchored glycoprotein present on the cell surface which is referred as FOLR-1 or folate binding protein (FBP) and assists in the delivery of 5-methyltetrahydrofolate (5-MTF) (an active form of folate).[46−48] Overexpression of the FRA has been observed in lung-like solid tumor types and direct or indirect pathway of absorption of folate proves to be advantageous for the growth of cancer cells.[49−51] Several studies have reported on the elevated levels of overexpressed FRA in NSCLC.[52,53] The U.S. FDA (United States Food and Drug Administration) has approved various techniques that target FRA.[54]

2.4. Vascular Endothelial Growth Factor Receptors (VEGFR). The VEGFRs were first recognized as a vascular permeability factor that trigger vascular leakage when exuded by tumor cells.[55,56] FLT-1 (VEGFR1), FLK-1 (VEGFR2), and FLT-4 (VEGFR3) are three major types of tyrosine kinase receptors that exclusively bind to mammalian VEGFR. These receptors feature seven extracellular immunoglobulin-like domains which get stimulated by ligand-mediated dimerization.[57] These receptors are frequently overexpressed in NSCLC and possess an acknowledged significance in angiogenesis, proliferation, and metastasis of tumor cells.[58,59]

2.5. Luteinizing Hormone-Releasing Hormone Receptor (LHRHR). Overexpressed LHRHR found in the cytoplasmic membrane of lung cancer cells could be utilized for targeting the cancer cells without causing any harm to healthy natural cells.[60] Several studies have shown successful targeted screening and delivery of antitumor drugs to the cancerous cells by employing LHRH peptides, by boosting their concentration in the tumor microenvironment and reducing undesirable interactions with the surrounding healthy cells.[61]

2.6. Fibroblast Growth Factor Receptor (FGFR). The extracellular component of FGFR is made up of immunoglobulin resembling domains that possess greater affinity for FGF ligand, consist of a transmembrane region, and possess tyrosine kinase activity.[62] This family of receptors is classified into four groups FGFR1 to FGFR4. Unusual FGF/FGFR signaling, alterations or amplification of genes (oncogenic) may contribute to tumorigenesis and therapy resistance in various cancers such as malignant melanoma and solid tumors.[63,64] Elevated expression of FGFR1 is reported in NSCLC with varying ratios in squamous cell carcinomas and lung adenocarcinomas.[65,66]

2.7. Cluster of Differentiation 44 (CD44). CD44 is a membrane glycoprotein receptor that plays an important role by binding to hyaluronic acid particularly to help normal and cancer stem cells attach, differentiate, perform homing, and migrate.[67] CD44 overexpression was found in pneumocytes (type II) and squamous metaplasia, in lung cancer.[68] The cluster of differentiation 44v6 has been linked to lymph node metastases in NSCLC patients.[69−71]

2.8. Integrins. Integrins belong to transmembrane heterodimeric glycoprotein family that consists of non-covalently linked alpha and beta subunits.[72] They are dependent on the orientation patterns exhibited in the middle of 18 α and 8 β subunits, and there are 24 distinct integrin receptors.[73] Integrins are detected in almost 82% of all NSCLC patients, regardless of differentiation type or degree. On the other hand, just 13% of SCLCs demonstrated an overexpressed $\alpha 3\beta 1$.[74] Downregulated levels of integrin expression have been related to SCLC, as well as the disease's high severity and potential to spread.[75]

2.9. Mer or Axl as Receptor Tyrosine Kinase (RTK). RTKs are members of the group of transmembrane proteins, with a large amount of variation in the extracellular area and a common intracellular tyrosine kinase domain. Axl is a key member of the RTK family TYRO3-AXL-MER (TAM). AXL overexpression was observed in NSCLC ADC (antibody−drug conjugates).[76] The TAM family's second most significant member, MER, was identified from a chicken retrovirus RLP30. Mer overexpression was reported in T-cell acute lung carcinoma.[77,78] Overexpression of these receptors has been linked to chemotherapeutic treatment resistance, tumor growth, and advancement in the cancer metastatic stage.[79]

2.10. Interleukin-22 Receptor. The cytokine interleukin-22 (IL-22) is a member of the IL-10 cytokine family. Expression is shown by macrophages, alveolar cells, and T cells in the lungs and operates entirely on IL-22-R1 (IL-22-receptor 1).[80] Zhang with his team (2008)[349] found IL-22 and IL-22R1 upregulation in cancerous tissue and serum of patients, and since then it has been shown that it protects cancerous cell lines from serum deprivation led cell death triggered by therapeutics.

2.11. Adenosine Receptors (AR). A_1, A_2A, A_2B, and A_3 are the members of G-protein-coupled adenosine receptors. Of these, it is reported that A_3 has been highly expressed in the lung tissues,[81] although the overexpression varies when compared to that of other ARs that are elevated at various degrees in the lung.[82] The Cancer Genome Anatomy Project (CGAP) reported that the expression of A_3AR was higher in malignant tissues as compared to normal tissues of the same patient.[83]

2.12. Chemotactic Cytokine CXCR4 Receptor. Chemotactic cytokine receptors have 7 transmembrane-spanning helixes and belong to the class of G-protein-coupled receptors (GPCR). They bind to a chemotactic cytokine ligand and participate in the migration of a number of cell types.[84] CXC and CC are the two primary types of chemokines. The first two cysteine residues in CXC are separated by an amino acid, whereas it is adjacently placed in chemotactic cytokines.[85] CXCR4 is a chemotactic cytokine receptor that is solely activated through CXCL12.[86] This pair is responsible for the spread of NSCLC cancer. According to Saintigny and Burger (2012), elevation of CXCR4/CXCL12 linkage was related to a later stage of illness and a worsened diagnosis.[87] The receptor linkage was reported in approximately 80% of non-small-cell lung carcinoma tissue sections collected from cancer patients in stages IA to IIB.[88]

2.13. Bombesin Receptor. The GPCR family of human bombesin receptors has three subcategories: the BB1 receptor, which links neuromedin (NMB) with strong potential, the BB2

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receptor, which aids in binding GRP (gastrin-releasing peptide), and the BRS-3 (bombesin receptor subtype-3).[89] Due to its strong structural similarity with the other two bombesin receptors, BRS-3 is categorized as a member of the bombesin receptor family. BB1 and BB2 receptors have been found to be overexpressed in most types of lung carcinoma, and they essentially contribute in enhancing the growth of malignant cells, which frequently function by autocrine mechanisms.[90] When BRS-3 gets activated, it leads to the elevation of intracellular calcium and phospholipase C, further leading to activating PKC (protein kinase C) and MAPK (mitogen-activated protein kinase pathway).[91] Hence, BRS-3 consequently phosphorylates ERK (extracellular signal-regulated kinase) tyrosine and expresses Elk-1 (ETS like-1 protein) and c-Fos, which is the reason behind excessive growth of lung tumor cells.[89]

2.14. PETA-3/CD151. Tetraspanins (Tspan) consist of the following transmembrane domain proteins: (i) N-cytoplasmic domain, (ii) C-cytoplasmic domain, and (iii) two extracellular domains.[92] CD151 (cluster of differentiation 151), CD9, and Tspan12 are three of the 33 human tetraspanin proteins that have shown significance in tumorigenesis.[93] Clinical investigations have found a strong link, associating the expression of CD151 protein with the sufferers of NSCLC, suggesting that it might be an efficient diagnostic tool for NSCLC, especially in patients of adenocarcinoma.[94]

2.15. Sigma (σ) Receptors. σ1 (sigma-1) and σ2 (sigma-2) are membrane-bound protein sigma receptors, each with its own pharmacological profile. Six out of 15 human adenocarcinoma samples and 12 out of 15 human SCLC samples have shown considerable overexpression of σ2 receptors. Various studies conducted on σ2 have demonstrated that it is a promising bioindicator which has the potential to be exploited as a new chemotherapeutic target.[95,96]

2.16. Anaplastic Lymphoma Kinase (ALK) Receptors. The ALK gene is responsible for encoding the human enzyme ALK receptor, also known as CD26. This receptor belongs to the superfamily of insulin receptors and exhibits an enhanced conformance to leukocyte tyrosine kinase. Genetic arrangement had earlier led to the initial identification of ALK receptor in anaplastic large cell lymphomas,[97] following which, it has been reconfigured, mutated, or amplified in a series of cancers including neuroblastoma, lymphoma, and NSCLC.[98]

2.17. ROS Proto-oncogene 1, Tyrosine Kinase Receptor. The ROS1 (c-ros oncogene 1) gene is a receptor tyrosine kinase that structurally resembles the ALK protein. After the first report on ROS1 rearrangements in NSCLC was published,[99] consequently altered ROS1 was identified in patients as a distinct type of molecule.[100]

3. TARGETING APPROACH OF NANOCARRIER

The interactions between nanomaterials and biological systems must be thoroughly investigated in order to develop an efficient nanoparticulate system for delivery of drugs. Three phases must be fulfilled before the nanoparticle-drug delivery system reaches the tumor. They initially circulate through the body and are substantially ingested by macrophages from the reticuloendothelial system (RES).[101] Subsequently, they proceed to permeate and deliver drugs to the tumor. Eventually, they accumulate at the tumor site where they exert pharmacological effects. However, before NPs reach the malignant cells, they are more inclined to interact with immune cells (macrophages and neutrophils) in the RES (liver and spleen) via blood circulation and are eliminated by urinary clearance.[102] Perpetuating the blood circulation is required to reduce RES deposition, however; a prolonged vascular circulation of NPs enhances the likelihood of immunological interactions with the RES. Thus, specific surface alteration can considerably boost the absorption and dispersion of smaller NPs in tumor tissues. Drugs that are hydrophobic are more soluble when they are combined with polyethylene glycol (PEG). It is advantageous to modify the nanoparticle surface of hydrophobic drugs by amalgamating it with PEG because it elevates solubility, prolongs circulation period, and targets specified tumors through an enhanced permeation and retention (EPR) effect.[103] Two generations of PEG conjugation approaches are used: the first generation, also known as PEGylation by randomization, and the second generation, also known as the targeted approach. Specific targeted drug delivery can be achieved by PEGylation, through active and passive routes. Numerous nanoparticles have been synthesized with an improved PK (pharmacokinetic) profile via PEGylation technique. Since such PEGylated NPs can significantly evade RES observation than the control nanoparticles, they are frequently referred to as "stealth" nanoparticles.[103] Strategies involved in the development of target-specific small molecules are respectively modified through inserting a nanocarrier inside the surface-functionalized novel nanosystem or by surface modification of the novel carrier (see Figure 1). Localized drug delivery of nanosystem for lung cancer therapy has fundamental advantages, but an undiscriminating release of anti-cancer drugs can be lethal for non-cancerous cells and the lung parenchyma. Targeted drug delivery systems provide a

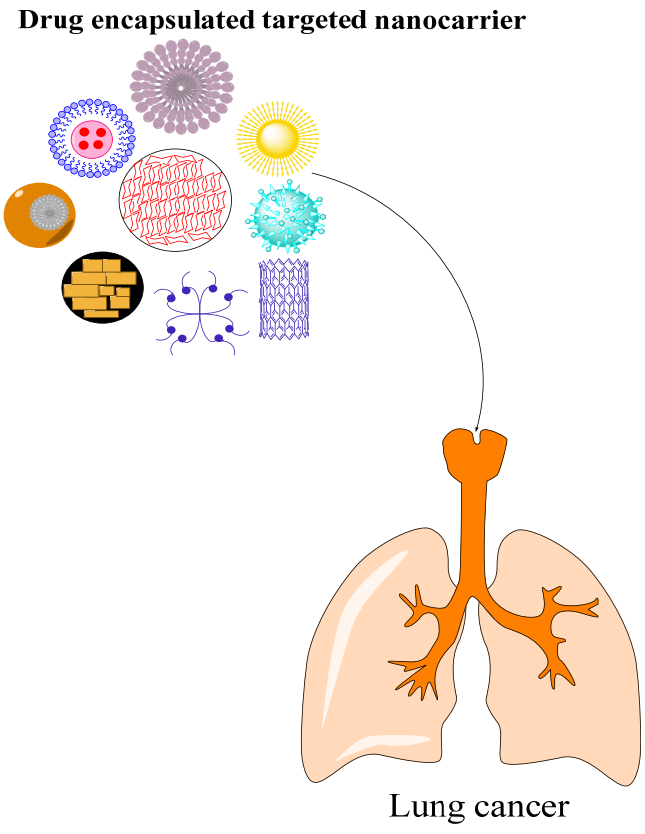

Figure 1. Nanoparticles as an efficient carrier in the therapeutics of lung tumor.

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selective release of the drug directly into the cell. These modified novel delivery compositions are required to reduce cell toxicity. In addition, they also help in increasing the retention time and efficacy of the drug. These novel drug deliveries of small molecules play an important role in lung cancer treatment.

Strategies are generally classified into three categories: (1) receptor-based targeting, (2) passive targeting, and (3) stimuli-responsive system-based targeting.

3.1. Receptor-Based Targeting. Modification of the drug nanocarrier surface results in the delivery of the drug which is specific to the tumor cell by receptor-mediated endocytosis. Folic acid, transferrin, albumin, hyaluronic acid, RGD (arginine-glycine-aspartic acid), and herceptin have been utilized for modifying the surface of nanocarriers and now have improved the tumor-targeting efficiency. Here are some receptor-based targeting approaches which are contributed by many researchers for providing targeted delivery of novel nanocarrier in terms of permeation, cell uptake, and tumor internalization

EGFR Receptor-Based Targeting: Herceptin could be used as an option for receptor-based targeting. Herceptin identifies HER2 receptors overexpressed in breast cancer tumor cells. Paclitaxel (PTX) and docetaxel (DTX) nanocarriers modified with herceptin were employed to avoid drug loss before it reaches the targeted cells and organs. Herceptin-modified nanocarriers could be prepared by adsorption reactions which are carried out overnight with moderate shaking at room temperature. Such modifications have enhanced cellular uptake, improved the release of drugs, and have demonstrated cytotoxic activity.[104]

Transferrin/Folic Acid Receptor-Based Targeting: Paclitaxel nanocarrier was reportedly inserted with apo-transferrin to provide a selective target delivery. Another example of paclitaxel is the modification of the paclitaxel nanocarrier superficially with transferrin surface protein which had previously provided higher tumor inhibition. Selective tumor-targeting peptide, XQ1(HAIYPRHGGGF), binds with transferrin receptors and thus improves the antineoplastic action of camptothecin nanocarriers on HeLa and A549 cell lines.[105]

Vascular Endothelial Growth Factor Receptor-Based Targeting: Oral treatment of bovine lactoferrin (BLF) reduced VEGF overexpression in lung cancer cells, which is linked to vascularization and angiogenesis, as per immunohistochemistry examination. These mechanisms serve as a crucial contributor to the tumor development, including tumor progression, penetration, and metastasis. BLF could block angiogenesis, which makes it useful for treating the carcinoma efficiently.[106]

Luteinizing Hormone-Releasing Receptor-Based Targeting: Tartula et al. discovered that luteinizing hormone-releasing receptor fabricated nanostructured lipid carriers (LHRH-NLC) had success in delivering paclitaxel to the lungs via inhalation. The results showed that Luteinizing hormone-releasing receptor conjugated nanostructured lipid paclitaxel had 16 times better apoptosis than the standard drug and was selectively localized in tumor sites compared to non-targeted NLC nanoparticles.[107]

CD44 Receptor-Based Targeting: Hyaluronic acid-coated lapatinib nanocarriers are used in active targeting of the CD44 receptor which is overexpressed by the cancer cells.[108] Another type of a nanocarrier of paclitaxel was combined with hyaluronic acid that binds to CD44, which is a cell surface receptor upregulated in some other types of cancer (gastric or breast).[109] This intercellular adhesion molecule binds with a receptor for hyaluronic acid-mediated motility for tumor-selective targeting.

Integrin Adhesion Molecule $\alpha_v\beta_3$-Based Targeting: RGD engineered nanocrystals can attach to $\alpha v\beta 3$, an integrin attachment protein seen on tumor cells, and then could be incorporated via receptor-mediated endocytosis. To achieve $\alpha v\beta 3$-based targeting, RGD-modified NCs (nanocapsules), such as RGD-modified PTX NC,[110] may be synthesized via the Schiff base reaction.

Sigma-1 ($\sigma 1$) Receptor-Based Targeting: Ligands include [18F]FTC-146, [18F]fluspidine, donezepil,[111] while for sigma2, it includes [11C]RHM-1, [18F]ISO-1, siramesine, WC-26, DTG (1, 3-ditolyl guanidine), and SV119.[112] Drugs that modulate ion channels and antiproliferative processes, have shown anti-cancer efficacy when acting on the sigma1 and sigma-2 receptors. As a result, the medication acting on receptors makes it an effective potential chemotherapeutic tool in treating lung carcinoma cell lines.[113]

ROS Proto-oncogene 1 Receptor-Based Targeting: Crizotinib was first discovered to have anti-cancer efficacy in individuals with advanced type NSCLC who had a ROS1 fusion.[114] Other examples that inhibit the ROS1 receptor (c-ros oncogene 1) are ROS1 Ceritinib (LDK378),[115] Lorlatinib[116] DS-6051ba[117] and Entrectinib[118]

Other Endocytosis: Targeted drug delivery could be done by the endocytosis pathway such as caveolar or clathrin-mediated endocytosis. Modified paclitaxel nanocarriers are prepared by albumin absorbed paclitaxel nanocarrier and triphenyl phosphonium cation.

3.2. Passive Targeting. Passive targeting approaches enhance the infiltration rate in circulatory vessels in the cancer microenvironment by EPR effect as compared to the usual healthy condition. Enhancing the permeability and retention generally increases 20% to 30% targeting ability as compared to healthy cells.[119,120] Tumors generally grow in unfavorable conditions such as hypoxia or inflammation and rapidly growing cancerous tumors block the new vessels or blood vessels which are present in the surrounding environment. This selectively enhanced permeation of nanosystems might help the tumor stroma and furthermore such enhancement in the permeation in newly generated vessels could improve the retention time. However, drainage of lymph could remove such small molecules and may also decrease the retention time of the drug. Therefore, the regulation of lymphatic drainage is necessary. Physico-chemical characteristics including charge, particle size, and surface-related chemistry are known to improve the EPR effect-based passive targeting to the tumor. It is challenging for a drug molecule which possesses a certain degree of therapeutic value to lodge itself effectively in all target cells.[121] Uneven targeting of tumor cells is the basic limitation that could be overcome by producing more target-specific novel nanocarriers that efficiently link with tumor cells following the irruption process. NDDSs (novel drug delivery systems) containing small molecules improve their pharmacokinetic profile by increasing the retention time and reducing unwanted adverse effects that occur due to the target specificity of the drug.

3.3. Stimuli-Responsive System-Based Targeting. A stimuli-responsive system-based targeting could provide effective and selective therapies. Tumor cells have many key variations in their intracellular cytosolic levels and extracellular tumor microenvironments such as hypoxia, temperature, pH,

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and glutathione levels. Release of the drug from polymers on exposure to a stimulus specific to a tumor cell microenvironment or providing various types of polymers from the surroundings might be a viable strategy for the preparation of such nanocarrier inserted drugs.

pH-Responsive Systems: Over the years, the lower pH of the tumor microenvironment (4.5−6.5 pH) and lysosomes (5.5−6.8 pH) have been explored to directly release of a drug to the extracellular tumor microenvironment or intracellular cytosol, mitochondria, and nucleus. Liang et al.[122] used a pH-responsive peptide and mannitol-based spray-dried powder inhalation system to improve nucleic acid transfection and ensure stability in the prevalence of broncho-alveolar lavage media, delivering payloads to tumor areas with lower pH values.

Temperature-Responsive Systems: As hyperthermia is one of the characteristics of tumorous tissues, modifying the medication release rate in a temperature-dependent way at a specific location has proven highly beneficial in cancer therapy. Moreover, the surface of nanocrystals may be modified using thermo-responsive polymers. To encapsulate 5-Fluorouracil, Wu et al.[123] employed cellulose nanocrystal grafted thermo-responsive PNIPAM [poly(*N*-isopropylacrylamide)] brushes. When the temperature was elevated from 25 °C to 37−40 °C, PNIPAM was shown to produce a multiple-fold increase in drug release from the system. The thermo-responsive release method can also be utilized with stimulus-guided methods, in which the medication is released in response to an external signal.

Enzyme-Responsive Systems: Since specific enzymes are present at the tumor site, it is possible to employ them to selectively release medicines from enzyme-responsive systems. Tagami et al.[124] described a doxorubicin-loaded hybrid liposomal system made up of phospholipids and poloxamer 188 that was sensitive to the PLA2 (phospholipase A2) enzyme expressed in cancer cells. The presence of the PLA2 enzyme resulted in an 8-fold increase in the release of drugs. Enzyme-responsive nanocarriers can be utilized to encapsulate medication nanocrystals and transport them via the pulmonary route for cancer therapy at a local level.

Ligand-Attached Stimuli-Targeted Systems: Pulmonary delivered receptor-based targeting mixed with stimuli-responsive system-based drug delivery can be utilized to improve drug intracellular localization in lung cancer cells. Tseng et al.[125] created gelatin nanoparticle-based aerosols with EGFR receptor targeting for pulmonary administration in mice. The aerosolized method improved the intracellular accumulation of the drug substance in lung cancer cells. Such systems could be exploited to deliver additional treatments such as drug nanocrystals through the lungs. Similarly, the extracellular release of the payload was inhibited when the intracellular concentration of siRNA (small interfering RNA) was enhanced with higher stability by a siRNA-loaded dextran nanogel covered with pulmonary surfactant surface and adorned with folate.

Redox-Responsive Systems: Redox-sensitive systems offer great potential and offer several advantages in cancer therapy. Such stimuli-responsive methods have been proved to be effective for delivering anti-cancer medicines to cancer cells selectively. Tumors, or more particularly, cancer cells, have an increased amount of intracellular ROS, which can be exploited to deliver pulmonary nanoparticle systems to cancer cells. A liposome-based nanosystem comprising of a redox-sensitive cationic oligopeptide lipid with proton sponge effect, soya PC (phosphatidylcholine), and cholesterol was developed for the co-delivery of paclitaxel and anti-survival siRNA in a study done by Chen and co-workers.[126] The synthesized liposomes were quick to release the drug and siRNA into the cytosol, through endo-lysosomal leakage, which consequently resulted in a reduced survival expression and elevated apoptosis induction.

Magnetic Field-Responsive Systems: Using magnetic fields as an external trigger, site-specific delivery of therapeutic substances to the cytosol or extracellularly localized malignancies in the lungs have also been described. Park et al.[127] used PEG-polyethylenimine-DOPA (dopamine) to synthesize a magnetite nanocrystal cluster that exhibited magnetically induced intracellular transport of loaded siRNA into cancer cells.

Multi-Stimuli-Responsive Systems: Multiple multi-responsive delivery methodologies for the pulmonary delivery of biomolecules to cancer cells have been established previously. Qu et al.[128] presented a dual redox and pH-responsive system dependent on a GSH (glutathione) sensitive disulfide linker and a pH-sensitive moiety, which specifically released the drug in the tumor microenvironment with elevated anti-tumor activity.

4. NANOCARRIER-MEDIATED DRUG DELIVERY SYSTEMS

Figure 2 illustrates several types of nanocarriers which are being employed in lung cancer therapy. In addition, due to the regulated drug release pattern and improved *in vivo* efficacy of encapsulated drugs, their acceptance is now well recognized. Various types of natural, semi-synthetic, and synthetic forms of nanomaterials are now utilized as drug delivery vectors.[129]

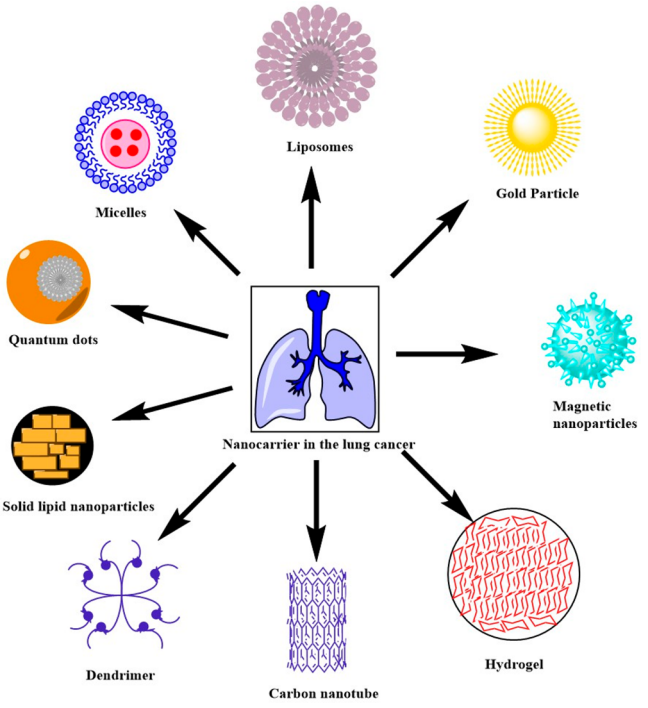

Figure 2. Various nanocarrier-mediated drug delivery systems.

4.1. Liposomes. Liposomes are gaining much significance lately as a potent anti-cancer drug delivery tool. Liposomal

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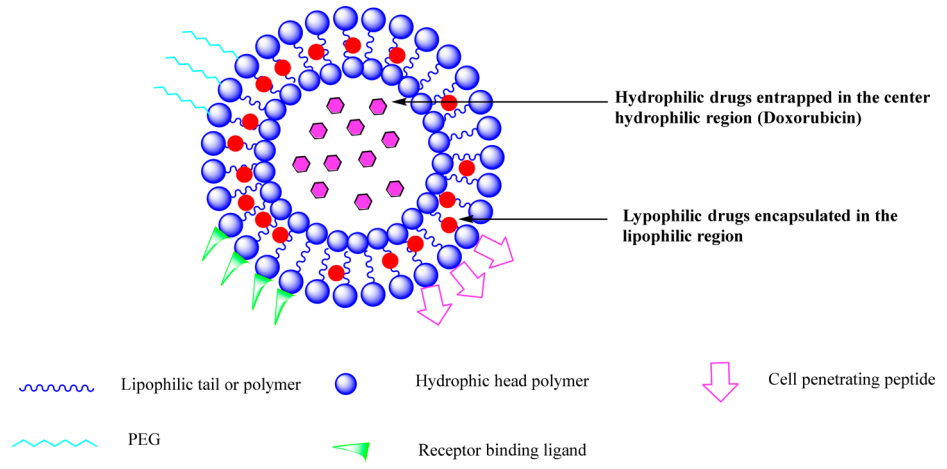

Figure 3. A unilamellar liposome nanoparticle. Lipophilic drugs are contained between the amphiphilic bilayer, while hydrophilic drugs are confined in the central core.

research has expanded in the past decade because of its excellent biocompatibility, resulting in a plethora of newly formed formulations like: archaeosomes, virosomes, temperature-responsive liposomes, and cationic liposomes.[130] Liposomes are nanocarrier tools, synthesized from natural or synthetic lipids and occur as single or multiple bilayer forms.[131] Banham developed liposome-derived phospholipid vesicles in 1965, and they were quickly identified as prospective medication carriers.[132] These are classified as multilamellar vesicles (Figure 3) made of several concentric phospholipid bilayers (1.0−5.0 μm), as well as big (500−1000 Å) and small (300−500 Å) unilamellar vesicles.[133] Several drugs which were approved lung cancer therapy are being continuously developed into liposomal formulations. Etoposide (ETP), doxorubicin (DOX), paclitaxel (PTX), irinotecan (IRI), erlotinib, docetaxel (DTX), vinorelbine (VNB), cisplatin (CPPD), and epirubicin were developed as liposomal formulations. In addition, the antimetastatic efficacy of DOX conjugated liposome and tretinoin have been studied as chemotherapeutic agents for cancers that have spread to the lungs (melanoma, breast cancer).[134−136] The importance of liposomes is associated with its enhanced efficiency and less invasive drug delivery to the bronchial tissues which is a consequence of their prolonged release characteristic and the increased probability to target-specific administration of the therapeutic agents.[137] Remote-loading or gradient methods have been used to load hydrophilic pharmaceuticals such as DOX, which is a hydrophilic weak base molecule. Liposomal-based formulation serves as a solubilizing matrix for hydrophobic, water-insoluble compounds like PTX, as well as a means for lowering medication-related toxicity.[138]

Stealth liposomes or PEGylated liposomes are synthesized through modifying the lipid bilayer surface and by incorporating the synthetic PEG into the mixture. When insertion of cholesterol into the lipoidal layer is executed, attaching the liposomal membrane with PEG allows the liposome to circulate in the blood system for longer periods which results in its diminished absorption by the phagocytic system.[139] Therapeutic activity is initiated, when the drug molecule passes through the cellular membrane to intracellular sites of action. As a result, ligand-targeted liposomes were proposed to improve the selectivity of liposome-mediated administration. This technique has gained considerable attention for utilization in lung cancer-based treatment and research. In lung cancer, the main targeting strategies include (i) specific targeting of the tumor microenvironment (TME), (ii) overexpressed receptor-mediated targeting, and (iii) targeting the organelle in demand. Attaching a target-specific ligand with DSPE-MPEG (1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[maleimide(polyethylene glycol)] integrates the ligand with the membrane during the generation of liposome. Sometimes the ligand gets infiltrated into the lipoplasmic surface. Cetuximab[140] possesses significant inhibitory activity on EGFR and EphA2 (Ephrin A-family) receptors. This ligand was linked to the maleimide group of DSPE-MPEG through the surface of liposomal bilayer. DSPE-PEG was coupled with small molecules such as arginylglycylaspartic acid (which targets overexpressed integrin receptors) and anisamide (which targets overexpressed sigma receptors). A CD44 receptor-targeting hyaluronic acid ligand was reported to be coupled with DOPE (1,2-dioleoyl-*sn*-glycero-3- phosphoethanolamine).[141] Khatri et al.[142] demonstrated that RGD grafted liposomes carrying siRNA were more efficiently absorbed by NSCLC cells from a target-specific and multipurpose-based epirubicin liposomal formulation.[143] The formulated multipurpose epirubicin liposomes were found to have better tumor targeting efficacy, a longer survival time, and a greater anti-cancer effect than non-targeted liposomes liposomes.[144,145] Octreotide is a tumor marker that may be linked onto the liposomal membrane by selectively binding with the overexpressed somatostatin receptors.[146,147]

There are several types of liposomal formulations in various phases of clinical trials to treat NSCLC (Table 2).[148] Several preclinical investigations have shown that targeted and non-targeted liposomal drug delivery methods could improve biodistribution and therapeutic efficacy.[149] Doxil was the first FDA-approved (U.S. Food and Drug Administration) nanodrug in 1995. Utilization of PEGylated nanoliposomes, aided in extending the drug circulation time and preventing RES.[150] Doxil and topotecan have entered phase I clinical trials as potential treatment modules in SCLC. However, no information from this study is available.[151] The chemotherapeutic drug CPPD is the most widely utilized drug in lung cancer treatment regimens. SPI-077 (Alza Corporation) was the first liposomal CPPD to be developed, containing the same lipid makeup as Doxil. Animal studies and preclinical

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Table 2. Liposomal-Based Formulations under Clinical Trials[a]

formulation	application	clinical trial phase
BLP25 liposome vaccine	squamous non-small-cell lung cancer	II
liposomal lurtotecan	small-cell lung cancer	II
cholesterol-fus1 liposome complex	lung cancer	I
irinotecan liposome injection	small-cell lung cancer	II/III
paclitaxel liposome	stage IIIA non-small-cell lung cancer	IV
	stage IIIB non-small-cell lung cancer	
	adenocarcinoma of the lung	
liposomal cisplatin (lipoplatin)	non-small-cell lung cancer	III

[a]Data obtained from U.S. National Institutes of Health Web site (http://clinicaltrials.gov/) on October 4, 2021.

trials revealed promising efficacy in NSCLC treatment and a potential delay in proliferation and growth of tumor cells when compared to CPPD. According to the data provided by phase I/II trials, large doses of liposome-based CPPD when administered are safe and have less toxicity in patients with NSCLC. The potency of lipoplatin in NSCLC was compared in two clinical trials which were randomly conducted (phase II and phase III). Lipoplatin conjugated gemcitabine or lipoplatin conjugated paclitaxel were observed to be as effective as cisplatin conjugated gemcitabine or cisplatin conjugated paclitaxel. Additionally, these formulations were proven to be substantially less toxic.[152] In NSCLC patients (stage III and stage IV), stimuvex exhibited satisfactory results in the initial stage trials.[153] This was the earliest cancer vaccine which entered multiple advanced phase III clinical studies around the world (START, INSPIRE, STRIDE).

The necessity for consistency in biological fluids is one of the concerns with liposomes, when employed as drug delivery vehicles. Drug molecules leak into natural tissues, as a result, producing undesired effects. In conclusion, future research on liposomal conjugated drug delivery could be designed through functionally versatile platforms by administering target-specific theranostic agents for cancerous cells. Liposomes have also shown magnificent biodegradability and biocompatibility for lung cancer as theranostics. Furthermore, liposomes have an advantage over other nanoparticles since they can retain a large number of therapeutic substances and are easy to develop and utilize for long-term drug delivery. For morphological evaluation using MRI, contrasting compounds such as gadolinium (Gd) are often utilized.[154] Although liposomes conjugated with Gd have been proven to have no toxicity or adverse effects in normal cells, these complexes might be used as a promising theranostic tool for cancer therapy if loaded with antitumor agents and coupled with particular ligands of interest. Cheng et al.[155] employed the EGFR binding interactions of a novel peptide GE11 in doxorubicin-encapsulated liposomes to evaluate size range, zeta potential, drug encapsulation efficiency, and shape. In A549 cytotoxicity, it was reported that a 10% GE11 density was optimum. They discovered that GE-11 altered liposomes accumulated and retained 2.2-fold more than unmodified liposomes using a near-infrared (NIR) fluorescence imaging system.[155] Additionally, they will be capable enough for triggering targeted delivery at specific locations where an outcome is required. Furthermore, surmounting the therapeutic resistance will be the objective in modified and improved liposome-based drugs. Advancements in treating lung cancer through therapy, could be achieved by implementing the suggestions discussed, which also aim at minimizing the side effects caused on healthy cells and tissues.

4.2. Polymeric Nanoparticles. Different polymers are employed to encapsulate drugs which constitutes a class of nanoparticles known as polymeric nanoparticles (Figure 4).

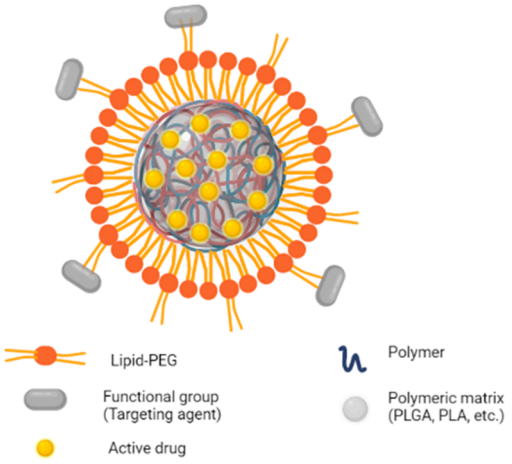

Figure 4. Structural representation of polymeric nanoparticles.

Such polymeric NPs are employed to target-specific tumor cells or tissues by linking them to the ligand and increasing the affinity and stability of the drug.[103] Polymeric nanoparticles are widely demanded for both active and passive strategies of targeting malignant cells. There are several polymers that can be used in the synthesis of polymer nanoparticles. Poly(lactide-*co*-glycolide) (PLGA), poly(lactic acid) (PLA), and a few additional polymers [poly(glycolic acid) (PGA), poly(ε-caprolactone) (PCL), poly(acrylic acid) , etc.] are frequently used polymers in nanoparticles. PLA is a polyester created from lactic acid which is biodegradable. The copolymer of lactic acid and glycolic acid, known as polylactic-*co*-glycolic acid (PLGA), is both biodegradable and biocompatible. The U.S. FDA and EMA (European Medicines Agency) have validated PLGA as a drug delivery vehicle for parenteral route of administration.[156] The use of polymeric nanoparticles in the treatment of lung cancer demonstrates encouraging outcomes. Taxanes-loaded PEG-PLA (polyethylene-glycol-modified poly-lactic acid) nanoparticles have greatly increased the efficacy of chemotherapy and radiation treatment *in vitro* and *in vivo* (A549 lung tumor xenograft model).[157] By co-entrapping paclitaxel and cisplatin within PEG-PLA block copolymers, Kim et al. created nanoparticles for the treating lung cancer,[158] which have entered clinical trial phase II under the name Genexol-PM for advanced NSCLC.

Wang and his team developed a prodrug-based nano-drug delivery system where prodrugs of baicalein (BCL) and paclitaxel (PTX) were used.[159] These NPs were created by nanoprecipitation, and the innermost core was made of PLGA polymer conjugated with BCL and PTX. The MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide) assay was implemented to conduct *in vitro* cytotoxicity tests. In A549 cells, PTX-BCL NPs showed higher cytotoxic effects ($P <$

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0.05) compared to other NP formulations or free-drug solutions. Additionally, PTX-BCL solution demonstrated lower cytotoxicity than PTX-NPs and BCL NPs. Thus, the exponential usage of polymeric nanoparticles is producing chemotherapeutics for tumor treatment which are advanced, revolutionary formulations with least harm to healthy cells and which can be optimally delivered to cancerous tissues.

4.3. Dendrimers. Dendrimers are intensely branched, highly biocompatible, uniformly structured, and complex molecules (having a diameter of 2−10 nm) of spherical or globular appearance. The innermost core of the dendrimer has a tree resembling orientation which has numerous extensions attached to it. It exists in two different forms: high-molecular-weight (hyperbranched, dendronized, and brush polymers) and low-molecular-weight dendrimers (monodispersed and highly symmetrical polymers).[160] The unique properties exhibited by dendrimers are their multivalent nature, their excessively branched core, their uniform globular shape, and their distinguishable molecular weight. These promising features include them in the list of intriguing new drug delivery scaffolds.[161] Their tendency to precisely modify or adjust their size, form, and surface characteristics, make them a typical and adaptable nanocarrier system for the targeted delivery of chemotherapeutics.[162] Dendrimers are made up of three parts: a central core acting as inducer, various interior branches arranged in layered form, and multiple surface end groups for covalent conjugation. The internal central core moiety has reacting sites, with branches extending out from it. The first-generation monomers (G1) are those linked to the center (G0), and surrounding it, a pair of second-generation monomers (G2) are observed. Arrangement of the next generations will be followed by a similar approach (Figure 5).[163] Their wide-ranging nanosized particles, instantaneous

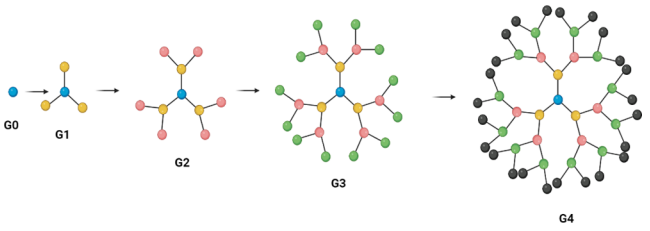

Figure 5. Demonstrated dendrimer generation.

synthesis, tendency to conjugate, and their ability to demonstrate numerous copies of lethal functional groups necessary for rearrangement, make them appealing platforms for drug delivery.[36]

A concise list of dendrimer-based formulations for treating lung carcinoma and their outcomes has been summarized in Table 3. Therapeutic small molecules could be encapsulated in the innermost core through either hydrogen/chemical linkage or lipophilic interaction.[162] To improve bioavailability and target-specific delivery, methods like acylating or PEGylating the active terminal surface and fabrication of dendrimers with receptor proteins could be done, respectively. PEGylated dendrimers are a type of dendrimer which have attracted the interest of formulation scientists because of their prolonged distribution duration in the circulatory system, reduced accumulation in various body organs, and minimal toxicity. Incorporating poly(ethylene oxide) (PEO) with PEG aids in synthesizing PEG-dendrimers.[163] PEGylated dendrimer nanoparticles exhibited promising potential as an aerosol-inhaled drug delivery method when studied in a related investigation.[171] Furthermore, doxorubicin-conjugated PEGylated dendrimers when administered through inhalation routes resulted in sustained duration of residence of drug in carcinoma tissues and efficiently lowered carcinoma load in rats.[172] Commercially available dendrimers are primarily divided into two types: poly(amidoamine) (PAMAM) and poly(propyleneimine) (PPI).[174] The former is found to be used more preferably for delivery of chemotherapeutic and other peptides which must be delivered efficiently and effectively to specified sites.[176] These PAMAM dendrimers are hydrophilic, biocompatible, and nonimmunogenic. They have the capacity for increasing the bioavailability of chemical entities while reducing their frequency of administration which supports their usage as a medication delivery technique.[177] A study was conducted to synthesize a nano drug delivery system of doxorubicin conjugated generation-4 succinamic acid (G4SA) PAMAM dendrimers and to evaluate them in an *in vitro* lung carcinoma 3D model (Scheme 1). It was observed that in comparison with free doxorubicin, dendrimer-based doxorubicin formulation exhibited three times greater permeation rate with 3.1-fold increased rate of aggregation of drug in the innermost core region of co-cultured spheroids. PPI dendrimers could also be incorporated with the drug moiety by diversified techniques which makes them essential for evaluation in biomedical applications.[178] PPI dendrimers exhibit internal hydrophobic properties as a result of the presence of branched alkyl chains. Furthermore, because of the linkage of amides with branched alkyl chains, these PPI dendrimers have a more lipophilic core as compared to PAMAM dendrimers.[179,180] The toxicity of PPI dendritic delivery, like that of PAMAM dendrimers, can be minimized by surface-acetylation or other comparable methods.[181]

Dendrimer-integrated photo-medicinal platforms can be applied as molecular imaging contrast agents to facilitate detection of cancer precisely by coupling the optical features of photoactive agents with the qualities of other distinct components. Luong et al.[173] used a folic acid (FA)-conjugated PAMAM dendrimer with a superparamagnetic iron oxide (SPIO) core to successfully deliver the hydrophobic anti-tumor medication 3,4-difluorobenzylidene curcumin (CDF). Furthermore, incorporating CDF in a FA-PAMAM dendrimer resulted in higher targeting ability, anti-cancer activity, and MRI contrast-enhancing capabilities. Chen et al.[175] demonstrated that a dendrimer complexed with a nanocomposite of Au nanoparticles, cyanine dye (Cy5.5), and Gd(III) could be used as a tri-modal imaging agent for CT (Au nanoparticle), fluorescence imaging (Cy5.5), and MRI (Gd(III)) to impart improved spatial and density resolutions with high specificity. Developing nanomedicines will surely benefit from such integrated multimodal theranostic strategies.

4.4. Nanoemulsions. Administration of chemotherapeutics in the form of nanoemulsions might influence intratumoral chemotherapeutic accumulation, as nanoemulsion delivery employs various pathways for enhanced bioavailability.[182] Nanoemulsions are droplets of water in oil (w/o) or oil in water (o/w) having an average radius of 10−100 nm which are translucent or transparent. These heterogeneous dispersions exhibit a stable thermodynamic profile. They are formed by dispersing aqueous phase in oil phase, as both these phases are immiscible with each other, the dispersion is maintained by reducing the interfacial tension with the help of different

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Table 3. Dendrimer-Based Approaches for Effective Drug Delivery in Lung Cancer

drug	type of dendrimer	formulation	observations	ref
cisplatin	PAMAM [poly(amidoamine)] dendrimer	cisplatin-conjugated dendrimer (NCI-H460 cells)	Through sonication or centrifugation, cisplatin load-bearing capacity of dendrimer was increased. Drug was released at targeted sites with minimum loss. Due to the pH of tumor the drug release rate was higher. Conjugated dendrimer was found to be biocompatible and inhibited proliferation activity in tumor cells.	164
gold NPs	folic acid-conjugated PAMAM dendrimer	folic acid-decorated gold-conjugated PAMAM dendrimer (SPC-A1 cells)	After treatment with Au DENPs-FA (folic acid-modified dendrimer-entrapped gold NPs), the picture of SPC-A1 (human lung adenocarcinoma cell line) cells became clearer. Biocompatibility observed but without any changes in viability of cells.	165
doxorubin (DOX)	PAMAM	doxorubicin-conjugated dendrimer (melanoma (B16−F10) lung metastasis mouse (male C57BL/6) model)	Better stability shown with respect to extracellular pH. Better chemotherapy performance shown instead of I.V. (intravenous). More nodules in lungs were reduced when DOX-conjugated dendrimers were administered instead of free DOX.	166
paclitaxel	peptide-conjugated dendrimer	PTX-conjugated dendrimer (L132 and 293T cells)	Better encapsulation efficiency (95%) was reported with 25% of loading capacity. Sustained release pattern demonstrated higher antiproliferative effect on 293T and L132 cells as compared to free PTX.	167
EndoNt	PAMAM	CTC (circulating tumor cells) detection viability in SCLC (PolySia-positive SCLC cells)	Small-cell lung cancer cells and EndoNt (non-catalytic endosialidase)-immobilized surface have good binding stability. In small-cell lung cancer cells under flow, EndoNt capturing efficiency tends to be higher than that of aEpCAM (epithelial cell adhesion molecule).	168
doxorubicin	PEGylated-PLL (poly L-lysine) dendrimers	sustained and controlled exposure of therapeutic	Doxorubicin shows prolonged and sustained action. After I.T. (intratracheal) administration of dendrimer-incorporated DOX, lung-related toxicity concerns were lower when compared to those with an equivalent dose of DOX solution.	169
gemcitabine	mannose-conjugated PPI [poly(propyleneimine)] dendrimer	mannose-conjugated PPI dendrimer incorporated with gemcitabine (A-549 cell line in albino rats)	Drug loading profile was enhanced. Sustained release with better cytotoxicity against A-549 cell lines. This formulation tends to be a potential drug-delivery tool against lung cancer.	170

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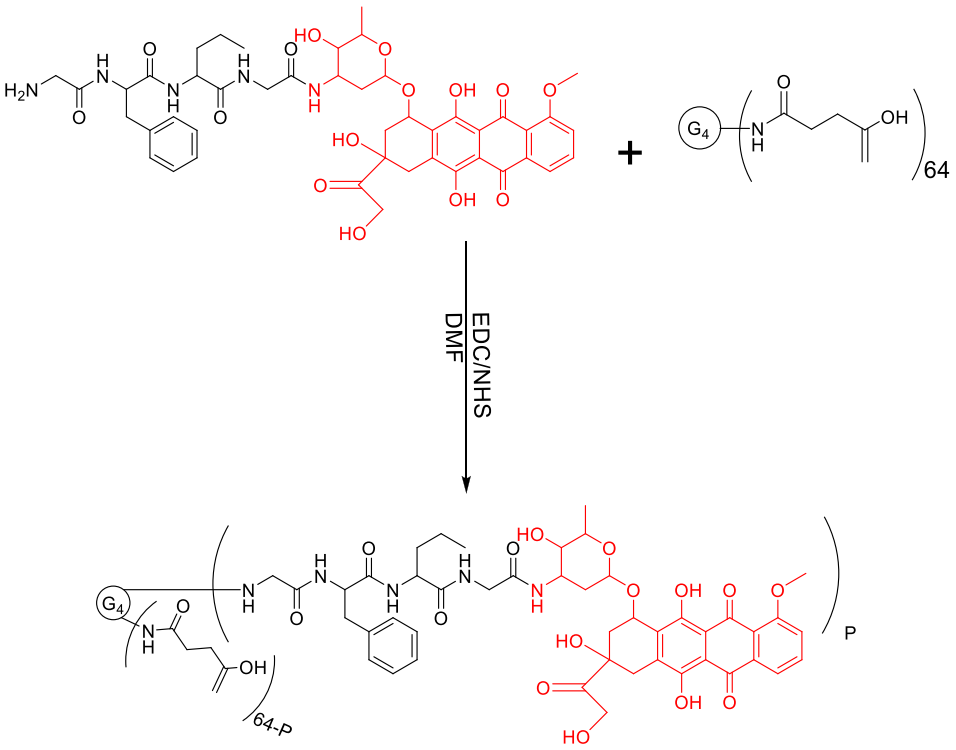
Scheme 1. Synthesis of G4SA-GFLG-DOX (Generation 4 Succinamic Acid PAMAM Dendrimer Conjugated with Doxorubicin)[a]



[a]DMF: dimethylformamide, EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, and NHS: *N*-hydroxysuccinimide.

surfactants and co-surfactants.[183] The distinctive nanoemulsion architecture is administered with hydrophobic or lipophilic chemotherapeutics for creating hydrophilic and lipophilic conditions. Such a design of nanoemulsion aids in reducing liver bypass, inhibits drug decomposition in abnormal environments, eliminates P-glycoprotein outflow, promotes mucosal penetration, and therefore improves the chemotherapeutic systemic availability.[184] Furthermore, decreased stomach emptying and enhanced drug solubility due to a large expansion in the interfacial area is made possible by producing nanoemulsion droplets which may be linked to improved bioavailability.[185] Subsequently, the functionalization of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), lipoid E 80 (agents which elevates permeation) enhance the bioavailability of embedded chemotherapeutics by temporarily opening cellular tight junctions.[185,186] Improved bioavailability of chemotherapeutics in the tumor microenvironment (TME) depends, whether the targeting is active or passive when nanoemulsion is administered intravenously.[182,184] Furthermore, nanoemulsions are advantageous, as they possess enhanced therapeutic absorption due to increased surface area and hence improved drug bioavailability. An additional feature is that it shields the drug from UV (ultraviolet) radiation and oxidative degradation, which improves the drug's stability in the formulation.[187] Nanoemulsions also have the advantage of being resistant to bacteria, fungus, and viruses.[188] Furthermore, its customizable droplet size has the potential to ameliorate the infiltration tendency; for instance, decreased skin irritability was observed when the mean droplet size was smaller, as the small-sized globule easily infiltered into the skin through hair follicles and pores (where the surrounding healthy tissues were undisturbed).[187] Doxorubicin is an anti-cancer substance which is used to treat a variety of malignancies. On the other hand, it has hazardous effects on healthy tissues because of its broader dispersing characteristic feature and a shorter half-life. A pH-responsive lapidated nanoemulsion containing doxorubicin prodrug (DNE) was developed which possesses a significant biocompatibility. The bioluminescent findings from the experiment on the mouse model showed a substantial decrease by DNE in distant lung metastases.[189] Kim and Park created a NSCLC-targeting nanoemulsion having hyaluronic acid-conjugated paclitaxel.[190] While creating the nanoemulsion of conjugated paclitaxel, the formulation was subsequently chelated with the targeting moiety, hyaluronic acid, using a microfluidizer at high pressure. The experiment was carried out on nude mice which had overexpressed CD-44 in NCI-H460 cell tumor xenograft. Cancer progression was more effectively inhibited due to the astounding encapsulation efficiency (>100%).[190−192] Li et al. also reported on a nanoemulsion of docetaxel,[193] a cancer-fighting drug from the same family. Researchers had created an o/w emulsion with the use of medium-chain triglyceride (MCT) composed of the given constituents: (i) poloxamer 188, (ii) oleic acid, and (iii) egg lecithin. In nanoemulsion and commercial formulation groups, histological examination of tumor development indicated necroptosis of cancer cells (by formation of a capsule along the fibrous connective tissues).[193] Due to the absence of breaching of the fibrous connective tissue barrier, malignancy of cancer cells was prevented, and the cancerous cells did not metastasize to other body parts.[194] The production and effectiveness of curcuminoid (derived via *Curcuma longa*) nanoemulsion were observed against cancerous cell lines.[195] The curcuminoids and nanoemulsion of curcuminoids were treated with two distinct cell lines: H460 cells (large cell lung

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cancer) and A549 (adenocarcinoma of lung). The curcuminoid containing nanoemulsion affected the H460 cancerous cells by overexpressing the P21 gene (cyclin-dependent kinase inhibitor) which was followed by reduced cyclin-dependent kinase 1 (CDK1) and cyclin B, which eventually led to the cessation of cell cycle in G2/M phase. Moreover, an elevation in the P53 gene expression of A549 cancerous cells was indirectly responsible for an overexpression of p21 gene which ultimately lowered CDK1 and increased cyclin B levels, halting the cell cycle in the G2/M phase.[195] The o/w carvacrol encapsulated nanoemulsion was developed (by ultrasonication), as a delivery mechanism for carvacrol on a nanoemulsion platform. CANE or Carvacrol nanoemulsion tested against human A549 cancer cell lines (*in vitro*) and against a nude mouse xenograft model (*in vivo*), resulted in a dose-dependent cytotoxic response in the A549 cancerous cell lines.[196] Inhalable nanostructured lipid particles were formulated by Jyoti et al. to administer 9-bromonoscapine, a tubulin-binding alkaloid that inhibits cell growth and induces death in NSCLC cells. The quick incorporation of the formulated nanoemulsion system through a specific mechanism (endocytosis) may be ascribed to the uneven external surface instead of uniform surface of lipid containing nanoemulsions, which may justify the increased apoptosis.[197] Tanshinone conjugated nanoemulsion was synthesized by scientists for testing the ability of nanoemulsion to inhibit the growth of A549 cells. By ultrasonication, Tween 80, Capryol 90, and ethanol were used to create nanoemulsion. The produced formulation had an enhanced storage stability, homogeneity as well as improved encapsulation. Furthermore, as compared to tanshinone extract, the nanoemulsion exhibited substantial tumor cell suppression or death. Tanshinones can indeed halt the G_0/G_1 phase of cell cycle by overexpressing p53 and p21 genes, PJNK (Phospho-c-jun NH_2 terminal kinase) while decreasing the expression of cyclin E1, cyclinD1, and CDK2.[198] Nanoemulsions are drawing much interest in the biomedical application of lung cancer therapy and R&D. However, numerous obstacles need to be addressed in order to ensure the safe and stable administration of nanoemulsions. The major requirements for developing nanoemulsion formulation involves employing the excipients for providing a stable, effective, and target-specific profile by preventing the occurrence of undesirable adverse effects and confirming the biological outcome of the drug.

4.5. Micelles. Micelles are colloidal nanoparticles (Figure 6) which are formed in an aqueous environment when synthetic amphiphilic copolymer or surfactant is greater than a specific concentration, which is essentially the CMC (critical micelle concentration).[199,200]

Smaller size (diameter less than 100 nm) of the polymeric micelles is one of the reasons behind selecting them as an ideal drug delivery tool as they actively escape RES and renal exclusion. They even allow themselves to passively increase the penetration of the endothelial barrier in the area prevailing with the tumor. Polymeric micelles show great potential as hydrophobic drug delivery vehicles.[36] Rapid self-assembling of amphiphilic block copolymers in aqueous environment due to hydrophobic or lipophilic interactions is responsible for designing the distinctive zones which form the structural configuration of micelles. Micelles consist of a hydrophobic center and a hydrophilic barrier which functions by preventing protein linkage, particle agglomeration, and opsonin linkage. These get decomposed in the circulatory pathways, before

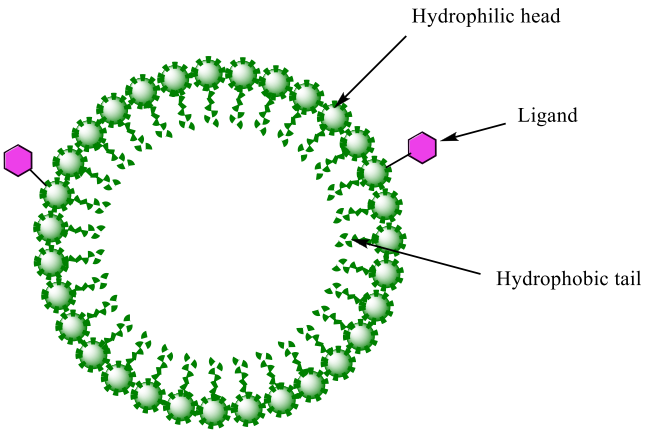

Figure 6. Structural representation of micelles.

entering the targeted region.[201] Liu et al. (2012) covalently functionalized β-CD (β cyclodextrin) fabricated micelles with folic acid (FA), doxorubicin (DOX), and contrast media (DOTA-Gd) which showed decreased cell viability (Scheme 2).[202]

Kataoka et al. demonstrated effective entrapment of doxorubicin (DOX) by poly(ethylene glycol)-poly(-aspartic acid) block copolymer [PEG-PAsp (DOX)] and the formulation is termed as NK911 which is currently being assessed in phase-II clinical trials.[36] Unimeric micelles are more appropriate for drug delivery than diblock (hydrophilic−hydrophobic) or triblock (hydrophilic−hydrophobic−hydrophilic) particles due to their lower molecular mass of polymeric residues after micelle disintegration.[201] Micelles are effective nanocarriers for the delivery of cytotoxic hydrophobic substances like antineoplastic drugs. These medications get enmeshed in the innermost central region, resulting with increased aqueous solubility, reduced toxic profile, tumor cell-specific aggregation and drug resistivity reversal. Furthermore, prolonged blood circulation time could be achieved with hydrophilic shell by inhibiting identification through reticuloendothelial barrier and preventing alveolar uptake. As a result of the tighter particle size characterization and extended plasma circulation (*in vivo*), they specifically aggregate around tumorous sites, which eventually improves therapeutic efficiency and bioavailability of weakly water-soluble drugs.[203] The biodegradability of therapeutic delivery systems is an essential feature which makes this approach a preferable option for formulating anti-cancer and ocular drugs. Drug integration into micelles enhanced circulatory residence time, lowered tumorigenesis, and reduced the toxicity significantly. Various polymeric micelles were conjugated with the purpose of treating lung cancer and were evaluated through preclinical studies which are summarized in Table 4. Distributions based on conjugation with polymeric micelles are preferred because of their inherently adaptable structures. The capacity to influence their surface permits delivery of theranostic chemicals to particular regions, increasing the efficacy, susceptibility, and selectivity of therapeutic and diagnostic approaches. They may also be readily manipulated to increase theranostic solubility and biocompatibility. Micelles conjugated with targeting agents (alpha fetoprotein (AFP) antibodies), surface incorporated with MRI imaging tools (Gd ions), and antitumor drug (paclitaxel) (TGPM) showed growth inhibitory potential, and MRI revealed the deposition of TGPM at the target tissue of H22 tumor containing mice due

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Scheme 2. Schematic Representation of DOX, FA, and DOTA-Gd-Conjugated β-CD-Based Micelles

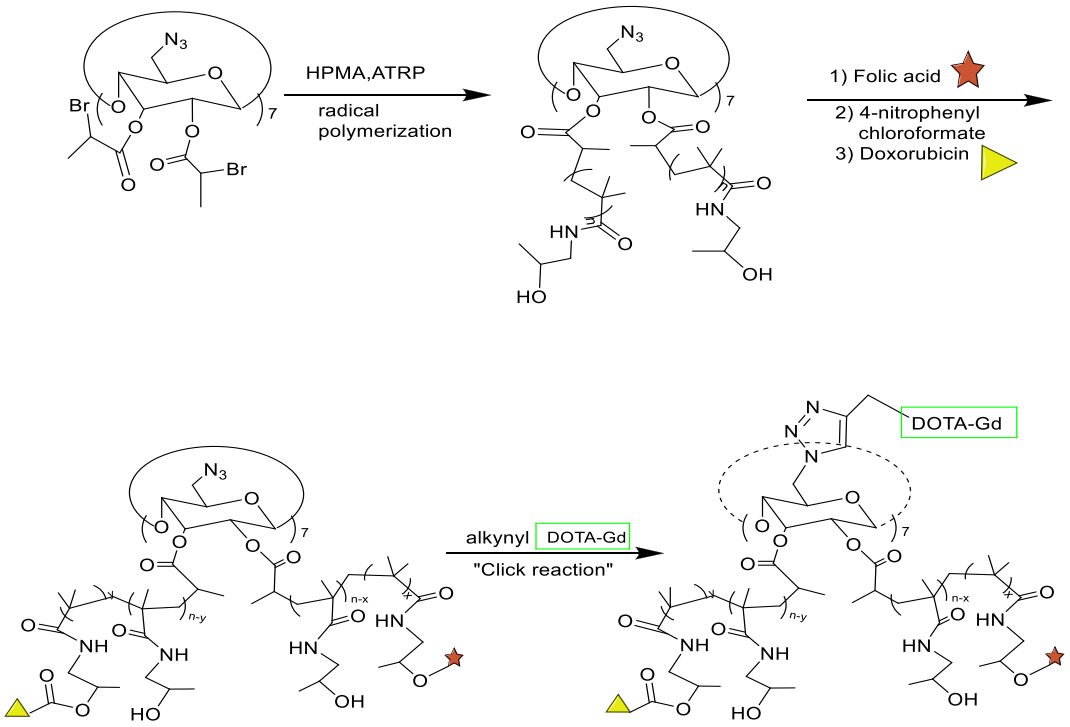

Table 4. Micelle-Based Formulations under Preclinical Trials[a]

drug	conjugation with polymer	phase
cisplatin	PEG-*b*-poly(glutamic acid)	phase Ib/II
paclitaxel	PEG-*b*-PLA copolymer	approved in South Korea (2007) and Europe (2013), Phase II (FDA, USA)
SN-38	PEG-*b*-poly(glutamic acid)	phase II
DACHPt	PEG-*b*-poly(glutamic acid)	phase I
epirubicin	PEG-*b*-poly	phase I (aspartic acid hydrazone)

[a]Data gathered from US National Institutes of Health Web site (http://clinicaltrials.gov/).

to AFP (alpha-fetoprotein) overexpression.[204] Polymeric poly(ethylene glycol)-phosphatidylethanolamine micelles incorporated with paclitaxel and coupled with SPIO nanoparticles imaging agents displayed concurrent MRI and antitumor action.[205]

4.6. Carbon Nanotubes (CNTs). CNTs are lipophilic hollow tubes composed of carbon atoms with diameters ranging from 4 to 100 mm that vary depending on how graphene molecules are arranged.[206] CNTs have the appearance of a single rolled-up sheet of graphene (Figure 7) which is related to the family of fullerene (third allotrope of carbon family).[207] There are two forms in which nanotubes are categorized: (i) having a single wall and (ii) having multiple walls, having an outer diameter of 4−20 Å and 20−1000 Å, respectively. The former can be made when just a single graphene sheet is rolled into a cylinder-like shape, whereas the latter is created when several concentric layers of graphene are rolled to form a cylindrical appearance. Since the past few

Figure 7. Structural representation of a carbon nanotube.

decades, their applications have been investigated to deliver chemotherapeutic substances because of their vast ability to develop new and better delivery systems. However, their negative health effects are a huge concern.[208] Specific biological and physicochemical properties, such as hollow monolith formation, enhanced mechanical efficiency, higher length and diameter ratio, increased surface area, ultra-massive molecular weight, nanoneedle shape, elevated thermal and electrical conductivity, and the ability to alter the surface, make them a promising drug delivery vehicle.[209,210] They can pass through the cellular membrane via endocytosis and then enter the cell because of their needle-shaped features.[11] Drug substances could be injected into the inner chamber of CNTs or bonded to the surface, either covalently or noncovalently. Furthermore, the anchoring of various ligands to the surface of CNTs allows for the targeted therapy of a chemotherapeutic drug to a desired location. Certain chemotherapy drugs, such as doxorubicin, paclitaxel, and cisplatin, have been delivered using CNTs.[211] Three common ways for manufacturing CNTs include laser ablation, thermally enhanced chemical vapor deposition (CVD), and arc discharge.[214] CNTs are a carbon only moiety with a unique chemical structure which has hundredfold strength when compared to steel while weighing only one-sixth of it. They also have an outstanding thermal conductance. It is therefore, considered as a fascinating nanocarrier, which is capable for identification of cancer cells as well as delivering medicines or smaller chemotherapeutics to the carcinomic cells.

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CNTs are fundamentally soluble in neither aqueous nor organic medium. They cause severe toxic effects in biological fluids are a massive concern which needs to be addressed.[215] Chemical variation enhances biocompatibility, lowers toxicity, turns them into water-soluble nanocarriers, and makes them serum-stable substances.[216] The first anti-cancer medication to be coupled with single-walled carbon nanotubes (SWCNTs) to target epidermal growth factor receptors was Cisplatin. The findings revealed that the drug was more effective against squamous cancer cells with high EGFR expression. Furthermore, due to its nano size, it demonstrated improved efficacy in preventing tumorigenesis instead of targeting it passively.[217] *In vitro* and preclinical studies on docetaxel-loaded CNTs in PC3 and S180 (murine sarcoma) cell lines have shown that they are more impactful than free docetaxel.[218] In another study, the efficacy of PEGylated nanotubes incorporated with a chemotherapeutic agent was studied with regard to its mitochondrial apoptosis, cytotoxic profile in NSCLC, its cellular uptake and dynamics. The authors attempted to see that the compound was mostly received by clathrin-mediated endocytosis, which would help the A549 cell line generate early endosomes. In addition, the cytotoxicity studies revealed that PEGylated conjugates induced mitochondrial death at a higher degree than the unconjugated moiety.[219] A549 cancer cell lines were targeted by administering doxorubicin hydrochloride via nanotube/gold hybrids. Non-covalent interactions between aromatic rings ($\pi-\pi$) of doxorubicin and CNTs, resulted in the adsorption of large amounts of doxorubicin on both internal and external surfaces of the nanotubes. Findings from cellular experiments *in vitro* indicated efficient delivery and administration of doxorubicin via nanoparticles.[220] Poloxamer, a hydrophilic non-ionic surfactant, was utilized for stabilizing supramolecular nanotubes containing doxorubicin complexes. For assessing the drug payload capacity of multi-walled carbon nanotubes (MWCNTs), fluorescence spectrophotometry was employed. It was observed that the concentration of CNTs has a significant impact on the intensity of doxorubicin fluorescence.[221] Additionally, a transmission micrograph may be employed to ensure that CNTs are released efficiently. In contrast to doxorubicin−pluronic complexes and simple doxorubicin, cytotoxic assessment on MCF-7 cell lines revealed significant toxicity.[222] According to Arya et al., paclitaxel conjugated single walled nanotubes resulted in an upregulated rate of apoptosis in cancerous tissues. Furthermore, they concluded that synergistic or additional effects (ROS-associated) produced due to CNTs were mostly responsible for the increase in paclitaxel's cytotoxic impact in lung cancer.[223] Sobhani et al. used fabricated CNTs to study the cytotoxicity of paclitaxel. The drug was attached to the surface of MWCNTs using a poly(citric acid) spacer that lowers the nanotube hydrophobicity. Based on their findings, it was concluded that paclitaxel loaded on functionalized CNTs had a greater level of cytotoxicity due to elevated cell infiltration when assessed in comparison with free paclitaxel drug.[224]

CNT linked nanomedicine imparts ways to combine imaging and pharmacological action as a "theranostic" tool in biomedicine. Specifically, CNTs can be combined with other nano-based formulations from various sources to obtain synergetic, imaging and therapeutic effects. These theranostic blended nanoparticles might be applied to identify, visualize, and treat numerous kinds of cancers. Furthermore, unique conjugated nano-platforms can aid in cancer therapy optimization and chemotherapeutic toxicity reduction. Mashal et al. synthesized tissue-mimicking conjugates with varying proportions of SWCNTs and assessed their dielectric characteristics and microwave heating response.[212] In CNT-blended mixes, the researchers noticed a linear temperature rise. Al Faraj et al. synthesized doxorubicin-encapsulated SWCNTs for targeting and monitoring metastasized tumors.[213] Free-breathing MRI and bioluminescence imaging were used to observe the patients. The magnets were implanted in the lungs of tumor-bearing mice at the metastatic tumor locations. The study depicted that amalgamation of non-invasive MRI (to locate tumor areas sensitively) with magnets that promote the magnetic targeting of CNTs improved overall treatment outcome. CNTs may be integrated with a variety of materials, including metals, polymers, and mesoporous silica, for application in theranostics for cancer treatment.

4.7. Gold Nanoparticles (AuNPs). It is well known that drugs, genetic materials, proteins, and tiny molecules can all be delivered using AuNPs, which have been recently identified as a potential delivery vehicle for transporting and releasing drugs into various types of cells. Several enticing characteristics are responsible for making them an excellent tool for delivering chemotherapeutics. To begin with, the innermost section (Figure 8) is safe, biocompatible, and inert, which is the primary reason behind using these particles as an initiating point for building carriers.

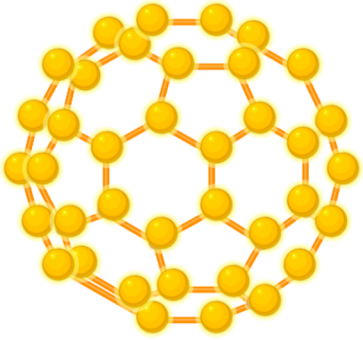

Figure 8. Structural representation of gold nanoparticles.

AuNPs are found in various sizes ranging from 5 nm to 200 nm in diameter, which may also be synthesized by regulated dispersion.[225] In 1951, Turkevitch described a simple, methodical bottom-up approach for synthesizing small gold molecules. Reduction of sodium tetrachloroaurate ions with trisodium citrate, resulted in the formation of nanosized dispersed particles (ca. 20 nm). The technique has then been improvised progressively over time. Several chemical and physical techniques now synthesize AuNPs with controlled particle size and shape.[226] Essentially, drug delivery vehicles must consider both size and dispersion. Finally, AuNPs' highly adjustable and multivalent surface configurations allow for conjugation (covalently or non-covalently) with a variety of drug substances or biomacromolecules on their surfaces. Moreover, the therapeutic applications of the noble metal, gold have been widely explored, including its application in sensitized diagnosis, detection, and classification of lung tumor types.

The flexibility with which AuNPs may be fabricated is one of their most appealing features. AuNPs are beneficial in both active and passive targeting because of their ability to modify

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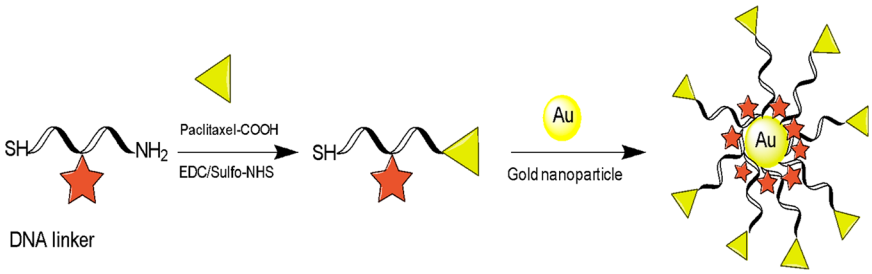
Scheme 3. Synthesis Scheme for Paclitaxel Incorporated with DNA-Linked Gold Nanoparticles



the surface. Due to high water solubility, the drug, methotrexate (MTX) generally has a poor tumor retention capacity, which is responsible for its delayed or weaker therapeutic effect in cancer patients. A mouse model with Lewis lung carcinoma when administered with MTX encapsulated AuNPs, demonstrated a significant accumulation in cancerous tissues which eventually improved the treatment effectiveness.[228] Covalent binding of hydrophobic paclitaxel to AuNPs via DNA linker was demonstrated by Zhang et al. (2011) (Scheme 3),[229] where they reported enhanced *in vitro* cytotoxicity against cancer cells. Gold nanoclusters with fluorescent tagged antibodies on their surfaces have been created with the purpose of specifically targeting overexpressed EGFR tumor cells.[230] This configuration imparts the pathway for gold-based nanoparticles to be applied in both magnetic resonance imaging (MRI) and treatment. Currently, photodynamic therapy (PDT) has been widely employed for AuNPs to transport purpurin-18-*N*-methyl-D-glucamine (Pu-18-NMGA), a water-soluble PDT drug, to A549 cell lines.[231] The photodynamic activity of Pu-18-NMGA-AuNPs was greater than that of free Pu-18-NMGA.

The potential of utilizing gold nanocarriers as medication and biomolecule transporting tools, originates from the versatility of the AuNP monolayer platform.[225] Researchers described a new AuNP carrier system with polyethylene glycol (coating), heptakis-(6-deoxy-6-mercapto)-*block*-cyclodextrin (chemotherapeutic), and anti-EGFR monoclonal antibodies (targeted ligand). Biocompatibility of PEG derivatives is responsible for protecting nanocarriers and the drug encapsulated within it from enzymatic decomposition. Because of the tendency to defend pharmaceuticals from enzymatic, physical, or chemical destruction, cyclodextrins (CDs) are one of the most preferred drug delivery tools. B-Lapachone entrapped within the core cavity of β-CD is recognized for use in the treatment of various carcinomas (like breast, lung, and prostate).[232]

AuNPs have been widely used as cancer theranostics because of their ease of synthesis and functionalization, excellent biocompatibility, and multifunctional theranostic features. Knights et al.[227] recently published a study that showed the size-dependent effects of gold nanorods (AuNRs) on photoacoustic (PA) imaging response and pulsed-wave photothermal therapeutic (PW-PPTT) efficacy, that is critical for AuNRs clinical translation. Additionally, Nanospectra has developed a silica-gold nanoshell stabilized by PEG for the photothermal therapy to the solid tumors using an NIR light source.[233]

4.8. Magnetic Nanoparticles (MNPs). MNPs have extensive pharmaceutical and biomedical applications, mainly in MRI, tailored drug/gene therapy, and cell transfection (magnetofection). The appended ligands influence the magnetic field around the nanocarriers and aid in targeted drug delivery either actively or passively. Application of various MNPs has been approved by the FDA when they are used simultaneously with conventional chemotherapy regimen, resulting in a significant outcome in cancer treatment.[234] Nanoparticles of gadolinium, and platinum are utilized for chemotherapy and other imaging strategies because of their aggregating tendency near the tumor location.[235] MNPs comprise superparamagnetic material with an average size of more than 25 nm.[236] MNPs that are non-biodegradable are covered with a substance that enables the magnetic core to leach thereby aiding in their elimination from the body. Magnetic hyperthermia is a safe lung cancer treatment that uses heat to destroy tumor tissue. The exposure of these MNPs to an external magnetic field results in the induction of thermal effects that eventually cause slower cell death when the temperature is above 42 °C, but instant death when temperature is above 45 °C.[238] Similarly, the exposure of MNPs to alternating current results in the generation of sublethal heat, thereby exacerbating the tissue injury. In a mouse model of NSCLC-based hyperthermic destruction, Sadhukha et al.[239] investigated the efficiency of tumor-targeted SPIO nanoparticles. The SPIO small molecules targeted the overexpressed EGFR which improved drug retention in tumors and reduced cancer progression substantially. Magnetic core and a surrounding functional covering, together constitute MNPs. Elements including iron (Fe), cobalt (Co), gold (Au), and nickel (Ni) make up the innermost core which offers it magnetic characteristics. The surface coat, on the other hand, inhibits aggregation and restricts magnetic core interaction with other particles.[240] This surrounding coat contains a biologically effective therapeutic drug or a ligand. The first experiment with MNPs that can detect lung cancer micrometastasis was carried out by Wang and co-workers.[241] Fabrication with the pan-cytokeratin epithelial tumor cell marker effectively identifies tumor cells in the blood circulation from patients with lung cancer. Drug resistance is subsequently surmounted using MNPs. Using cisplatin-loaded MNPs, an A549 cancer cell xenograft model which is resistant toward cisplatin, can be chemosensitized. Several molecular biologists then concluded that tumors treated with cisplatin-loaded MNPs had a substantial decrease in the concentration of lung resistance-related proteins and elevated cisplatin cytotoxicity.[242] Iron oxide and doxorubicin exhibited magnetic and paramagnetic characters respectively, because of which, they tend to have greater cytotoxic activity.[243] To target EGFR, gold-coated iron oxide nanoparticles were incorporated with 225-antibody, which caused DNA deterioration and cell cycle termination in the M/G2-phase.[244] Another study[245] demonstrated the cytotoxicity through C-225 (Cetuximab) conjugated nanoparticles on NSCLC. Cisplatin (a hydrophobic

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pharmaceutical agent), necessitates the use of a specific carrier to enhance its anti-cancer action. As a result, a functionalized Fe_3O_4 nanoparticle coupled with a PEG-PLGA copolymer has been constructed, demonstrating enhanced cisplatin anti-cancer efficacy in lung cancer.[246] Nanoparticles of lower sizes are well known to be inhaled forming agglomerates in the lungs.[247] MNPs are now encapsulated in micro-sized particles to effectively overcome this challenge. The most frequent materials utilized to make magnetic nanocomposite particles are iron oxide and D-mannitol nanoparticles. This method circumvents therapeutic molecules from diffusing through the bloodstream and transports the drug directly to the specific target location.[248] Iron oxide nanoparticles (IONPs) coupled with gold have been reported to increase nanocarrier bioavailability and are deemed safe for treating lung malignancies.[249] The transport of MNPs to the lungs could be beneficial and worth investigating further as a promising diagnostic tool or a medicine delivery method. In theranostic nanoparticle synthesis, MNPs, particularly IONPs consisting of magnetite (Fe_3O_4) or hematite, have been regarded important nanomaterials (Fe_2O_3) They are used in MRI contrast, medication administration, controlled and prolonged release, and hyperthermia therapy. Even human clinical trials are now being conducted on several of them.[237]

4.9. Solid Lipid Nanoparticles (SLNs). Another type of vehicle for drug and gene delivery are SLNs. SLNs have a myriad of benefits, including the ability to encapsulate hydrophobic drugs more easily, reducing their negative consequences on the GI (gastro-intestinal) tract, and preserving sensitive drugs from an acidic pH (Figure 9).[250]

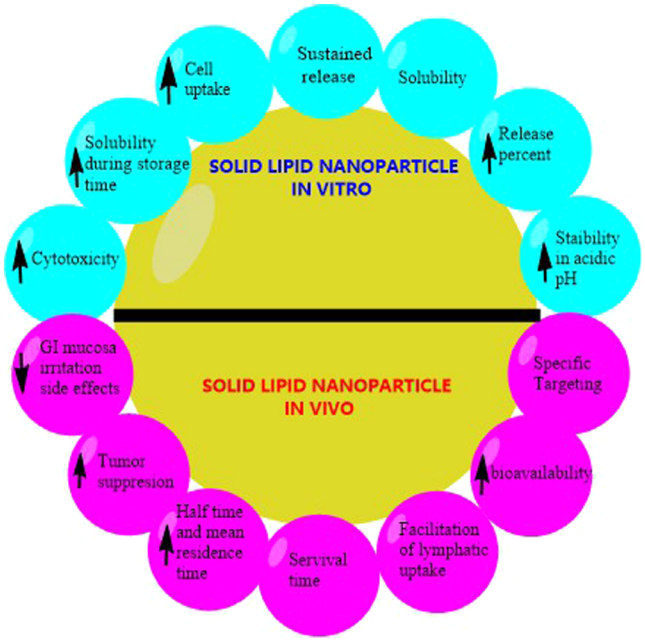

Figure 9. Effects shown by solid lipid nanoparticle-encapsulated drugs.

These particles were first developed in the early 1990s. Many lipophilic or hydrophobic drugs were cytotoxic, so SLNs provided an essential foundation for such medicines to be entrapped. SLNs are colloidal nanocarriers for dissolved and dispersed therapeutics (size ranging from 50 nm to 1 μm) with a highly lipophilic lipid matrix comprising of solid lipids such as monoglycerides, diglycerides, triglycerides, waxes, fatty alcohols, free fatty acids, and steroids.[252] SLNs have a solid lipid content of 0.1−30% (w/w), having the tendency to easily dissolve in aqueous media. Generally, 0.5−5% of surfactants are helpful to stabilize the SLNs.[254] In terms of stability, enhanced biocompatibility, enhanced drug payload, and convenient production on commercial scale, SLNs outperform their lipid counterparts. SEM (scanning electron microscopy) and TEM (transmission electron microscopy) evaluation have indicated that SLNs have a spherical form with a size range of 50 to 1000 nm.[255] A regulated release profile, sustained release characteristics, with a quicker *in vivo* decomposition are all considered benefits of SLN-based drugs when compared to particles composed of PLA or PLGA. Furthermore, as compared to particles produced from certain polymeric materials, SLNs were shown to have better tolerability in the lungs which contributes significantly to their safety profile.[256] As a result, this system is suggested for the administration of pulmonary drugs, in a solution or as a dry powder, without causing inflammation.[257] SLNs combine the properties of fat-emulsion carriers, liposome carriers, and polymeric nanoparticles, making them excellent for targeted drug delivery.[258]

This strategy has demonstrated enormous potential for targeted utilization (particularly intracellular) by manipulating gene expression and cellular communication. Currently, ultra-solid lipid nanoparticles are employed to target the tumor location.[259] Anti-tumor drugs such as doxorubicin, etoposide, and idarubicin[260] are currently administered using these nanocarriers which increase their bioavailability. Furthermore, SLNs[254] are considered as good and efficient gene carriers. Cationic SLNs have demonstrated excellent transfection of p53 gene loaded with chemotherapeutic agents at targeted sites.[261] Trimyristin (high-melting triglyceride) was used to synthesize novel SLNs of DCX (docetaxel). This strategy has resulted in elevated levels of DCX in tumor tissues while lowering them in other organs such as the heart, kidney, liver, and lungs. For optimizing the efficacy of SLNs, usually one or more glycerides (having high melting point) are used for synthesis.[262] Choi et al.[263] transfected SLN-carrier p53 into p53 null lung carcinoma cell line H1299. When compared to commercially available Lipofectin, the authors of this study effectively mapped overexpressed p53 protein which ensured that this system of drug delivery could be employed in genetic transfection with adequate drug payload.

According to a recent study, synergistic effects were observed when amalgamation of paclitaxel and Bcl-2 siRNA were incorporated into SLN.[264] Yuan and colleagues observed that drug-loaded targeted SLNs had a greater proportion of drug uptake in A549 cells, as compared to SLNs incorporated with drug. Hydrophilicity of PEG facilitates an initial burst release, and it was further reported that drug-loaded PEGylated SLNs released more drugs in comparison to target-specific SLNs.[265] When doxorubicin containing SLNs were administered through IV route in mice it was observed that the drug concentration in the lungs was greater than when they were administered with the solution of doxorubicin.[256] According to Leiva et al., *in vitro* anti-cancer activity was considerably improved by paclitaxel-loaded tripalmitin SLN formulation as it facilitated prolonged or sustained release of drug and reduced IC_{50} of paclitaxel which resulted in greater cytotoxicity in lung and breast cancer tissues.[266]

Theranostic applicability, biocompatibility, and biodegradability of created nanomedicine have all been demonstrated in

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previous research studies, as well as the precise *in vivo* screening and drug administration utilizing SLNs. The findings showed that the created SLN theranostic nanoformulation has the potential to make a significant contribution in the field of oncology and diagnosis at the same time. Paclitaxel and siRNA were used as the anti-cancer agent. Paclitaxel and QDs (quantum dots) were distributed throughout the lipid core, whereas anionic siRNA was electrostatically coupled to the external cationic interface. In lung cancer, the integration of the dual therapeutic drug paclitaxel and siRNA loaded in SLN was efficiently deposited and showed synergistic anti-cancer action. Significantly, QD fluorescence in SLN allowed researchers to measure increased *in vivo* cellular uptake of the drug on-site while reducing off-site cancer cell uptake and thus its theranostic action was assessed.[251,253]

4.10. Hydrogels. Hydrogels are polymeric three-dimensional mesh, which has the property of retaining a significant amount of water within their fibers.[267] It is a binary polymer solution system which has a cross-linker. Hydrogels have gained much attention from the last two to three decades because they possess various unique characteristics which are useful in biomedical applications. P-HEMA, or poly(2-hydroxyethyl methacrylate), was the earliest designed hydrogel to be produced by DuPont scientists in 1936. But it was not until 1960 that Wichterle and Lim realized the relevance of P-HEMA hydrogels as good candidates for contact focal point purposes.[268] Based on their cross-linking process, hydrogels may be divided into physical and chemical hydrogels using different production procedures.[269,270] Cross-linking of hydrogels could be done either chemically (ionic, covalent, and atomic) or physically (hydrogen bonding). Chemical-based approaches, such as thermoresponsive, Michael addition, self-assembling hydrogel, and pH-responsive strategies, are therefore recommended for creating hydrogels of various strengths and controlled drug release.

Hydrogels (sol−gel−sol) are generally functionalized with polymers (PEG-PCL-PEG/DDP, PECE/DDP) possessing a polymeric micellar combination of paclitaxel and cisplatin. At room temperature, hydrogels exist in solution form, but when it attains body temperature it gets transformed into a gel. The principal mechanism of this gel form by which it treats cancer, is to form a drug depot through which the medication keeps diffusing gradually. Cisplatin diffuses from the thermosensitive polymer and the gradual release of micellar paclitaxel occurs through the gel state to the nearby cancerous tissues. Hydrogel formulations inhibit tumorigenesis while also prolonging the organism's lifespan. Lung cancer may be potentially treated with hydrogels having two-drug combinations.[271]

For the treatment of NSCLC, scientists have designed a hydrogel-based drug delivery system for intravenous administration.[272] Targeting the cancerous tissues was achieved by two methods. The first stage is passive targeting, followed by IV treatment where GMPs (glycomacropeptides) selectively concentrate in the lungs. Passive targeting yields a 10-times enhancement in anti-cancer medication efficiency with a ten-time decreased peak systemic drug levels, according to preliminary results. The second method is active targeting where two different types of nanoparticles are suggested. Initially, ligands on the NP surfaces are designed for targeting cancerous nodules specifically. The secondary NP group is likewise incorporated with cell surface ligands, but instead of selectively delivering drug contents within the cancer cell, these NPs are intended to firmly attach to cancer cell surface receptors and persist there to block the metastatic signaling cascade. The NPs contained in the GMPs disperse out and approach cancerous cells, once the GMPs have accumulated passively in the lung, resulting in a high level of targeted selectivity.[273]

Following cellular absorption of nanocarriers, expansion of the polymeric nanoparticles is observed in moderately acidic medium because it has evolved to a hydrophilic structure from a hydrophobic structure. This produces nanosized hydrogels, which exhibit intracellular activity and drug depot traits. These nanoparticles are promptly absorbed by A549 cell lines (88.3 ± 0.8% uptake in 24 h), which consequently, expands for releasing the entrapped moieties, and may efficiently deliver the chemotherapeutics *in vitro*. Paclitaxel, an antitumor drug, has been found to have a 3- to 4-fold affinity for enlarged nanoparticles, permitting them to function as intracellular drug depots which facilitates aggregation of the drug locally.[275]

Incorporating SWCNTs with peptide hydrogels may widen tissue engineering applications and may provide hydrogels a broader application-oriented perspective for cell biomaterials. EFK8 is a self-assembling peptide with enhanced mechanical properties. Since phenylalanine is prevalent, it confers stronger hydrophobic interactions. The inclusion of SWCNTs to the EFK8 hydrogel (while maintaining its modulus) yields higher motility in cells comparable to firmer hydrogels, emphasizing the relevance of cell scaffold interactions in metastasis.[276]

In A549 cell line, Khatun et al.[274] reported versatile cancer theranostic uses of graphene-doxorubicin conjugated in hyaluronic acid nanogel. This nanocomposite has been employed for thermal chemotherapy applications, as well as real-time and non-invasive optical imaging and controlled drug release.[274] Carbon dots (CDs) are predominantly used in theranostics and are implanted into the chitosan-containing hydrogel, where the hydrogel serves as a matrix for embedding CDs via non-covalent conjugation. Elimination of cancerous cells is also facilitated by the anti-cancer drug, 5-fluorouracil (5-FU) which is implanted in the hydrogel through hydrophobic interactions and further integrated with CDs to form 5FU@CDs-HY, which has anti-cancer action. The moiety also has properties of a screening agent and is employed for visualization during cellular uptake in cancer cells.[277] The silk nanoparticles of cisplatin were developed by Kim et al. Spray-drying was used to create a composition including silk fibers and cisplatin with or without cross-linkage. Different release profiles result from the presence or absence of a cross-linking agent in the formulation. Without the use of a cross-linker, cisplatin silk nanoparticles showed significant cytotoxicity. The addition of acid and/or ions cause(s) hydrogel sol−gel transitions in silk fibroin nanoparticles.[278,279] Silk strands are more durable and help to keep nanoparticles steady throughout the storage period and *in vivo* investigations. Therefore, anti-cancer medicines are delivered to the lungs using silk fiber nanoparticles, which have greater cytotoxicity and bioavailability.

The anti-cancer drug docetaxel (DTX) and the triblock copolymer hydrogel are employed in the formulation of PLGA-PEG-PLGA triblock copolymer, which does not influence the solubility of DTX but reduces its toxicity concerns. On A-549 lung tumor-bearing BALB/cA mice, a triblock copolymer hydrogel formulation was assessed, and it was found to improve the pharmacokinetic profile over 3 weeks in a sustained release pattern.[280]

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4.11. Quantum Dots (QDs). QDs are nanosized colloidal particles with atom-like characteristics that have recently been synthesized via nanofabrication (Figure 10).[281] These QDs are

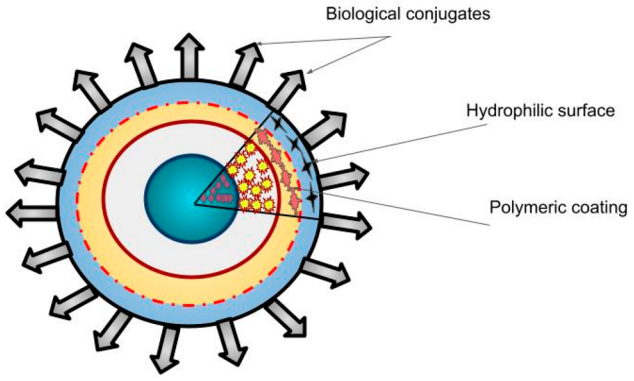

Figure 10. Structural representation of quantum dots.

thought to be a potential treatment option for lung cancer. Modifying the surface of QDs makes it more soluble and biocompatible which converts it to a superior fluorescent probe.[282] The core of the material is composed of a crystalline metalloid which is shielded by a cap or shell which enhances the overall bioavailability.[283]

Large absorption spectra, high photobleaching, and photostability are few of the unique properties exhibited by QDs.[284] Because of the restricted wavelength of the emission spectrum, this nanoparticle system displays redundant fluorescence and excitation cycles.[285] These characteristics have made QDs a trendy topic, particularly for clinical imaging of diseased tissue specimens from patients who had cancer, for identifying the type and phase of disease, directing therapy regimen, and predicting prognosis.[286,293] QDs might potentially be utilized to investigate cell differentiation and development throughout embryogenesis.[287] In general, QDs are made up of elements from groups II−VI/III−V. Cadmium selenide (CdSe), cadmium telluride (CdTe), zinc sulfide (ZnS), and zinc selenide (ZnSe) are among the elements in groups II−IV. Gallium nitride (GaN), gallium arsenide (GaAs), indium phosphide (InP) and indium arsenide (InAs) are among the elements in group IIIV.[288]

When using QDs in biological research investigations, solubility in aqueous medium is a frequent concern for various forms of QDs. Apart from directly synthesizing QDs in aqueous solutions, layering with polymer and exchanging the ligands have efficiently overcome solubility issues.[289] Lipid-coated QDs demonstrate promising outcomes toward tumor cells.[291] An amalgamated treatment strategy was studied and constructed by incorporating several anti-cancer agents (paclitaxel, doxorubicin, and carboplatin) and Bcl-2-targeted siRNA into a novel QD nanocarrier. The findings suggested that the QD-based delivery method resulted in 3- to 4-fold improvement in cytotoxicity for A549 cell lines when compared to free drug therapy. Furthermore, effectiveness of the regimen was improved, revealing that QD-based multifunctional delivery systems could be successfully employed in treating lung cancer when used in combination therapy.

Quantum dots are noted for their high fluorescence emission, which might be valuable for diagnostic and theranostic applications; unfortunately, the heavy metals in their composition could cause severe toxicity, necessitating the employment of alternative imaging strategies. Since tumor cells tend to overexpress biotin, biotinylated graphene QDs might be a viable option for cancer theranostics. Aside from being less cytotoxic than heavy metal QDs, graphene QDs have ideal surface tenability characteristics that provide specific changes and may therefore be developed for a myriad of theranostic purposes.[292] Wu and colleagues described carbon dots functionalized with positively charged polyethylenimine (PEI) and negatively charged siRNA molecules, as well as folate as the tumor-specific moiety for being applied as theranostic agent. Bioluminescence (the dots demonstrate absorbance and emission at 360 and 400 nm, respectively) could be used to track the accumulation of nanomaterials, and the authors were able to report a decline in lung tumor volume *in vivo*.[290]

4.12. Inhalational. The pulmonary route is a more significant, direct, and appealing delivery strategy when compared to conventional methodologies of drug delivery (oral or parenteral). The local approach of delivery of drugs with the help of nanocarriers is to avoid the first-pass metabolism or to overcome the need for injections. Direct therapeutic delivery to the lungs significantly contributes to the local treatment of asthma, cystic fibrosis, and COPD (chronic obstructive pulmonary disease) and advanced treatment of cancer and diabetes. Direct pulmonary targeted delivery has more absorption efficiency compared to conventional administration, and therefore reduces systemic toxicity. Local toxicity could occur due to the deposition of both drugs and excipients. Traditional inhalation methods were not able to achieve specific targets which necessitates the need of developing novel delivery methods.[294] Furthermore, reduced thickness, high surface area, and intense vascularization of the alveoli makes the pulmonary delivery an excellent delivery approach. The prolonged release of drugs, strong tendency for association with drugs, and target specificity are some of the reasons scientists are attracted to explore inhalable nanoparticles. As they can withstand high nebulization forces, they can easily be formulated into aerosols. The duration of the administered drug in the respiratory tract could be enhanced by evading mucociliary transport and phagocytosis by lungs.[295]

Polymeric nanocarriers: Drug delivery through nanotechnology in the treatment of cancer has significantly progressed over the past decades. Polymeric nanocarriers play a vital role in inhalable drug and gene delivery. Doxorubicin released by isobutyl cyanoacrylate polymeric nanoparticles showed that polymeric nanocarrier caused cytotoxicity (secondary) triggered via alveolar phagocytes which provides a superior treatment for lung cancer. After initial phagocytosis, exocytosis of segments of nanoparticles occurs when alveolar phagocytes start imitating the action of Kupffer cells which causes the death of surrounding tumorous cells. Murine macrophages of alveoli were treated with nanocarriers and then were introduced to H460 cells.[294] Free doxorubicin did not produce any secondary cytotoxic effects when it was introduced to macrophages, but in the presence of nanocarriers containing doxorubicin, macrophages demonstrated optimum cytotoxicity after 8 and 24 h. The effects of nanoparticle treatment resulted in the formation of interferon gamma and macrophage inflammatory protein which initiated cellular immunity and inflammation, thus augmenting tumor rejection.

Lipid Nanocarriers: Many *in vivo* and *in vitro* studies have revealed the therapeutic efficacy of 9-nitrocamptothecin (9NC) via an inhalable route instead of oral or i.v. or i.m.

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routes for treating lung cancer. Formulation of 9NC conjugated liposomes with dilauroylphosphatidylcholine [MMAD (mass-mean aerodynamic diameter) 1.2−1.6 μm] inhibited B16 melanoma pulmonary metastases in mice after 16−21 days of treatment. Interestingly, the quantity of inhaled dose of 9NC was 3 to 20 times lower when compared with intragastric, intravenous or intramuscular dosage forms but showed a similar effect.[296] Preparation of solid lipid nanocarrier by amalgamating glycerol and various esters of behenic acid showed greater stability during nebulization time with better inhalable fraction instead of epirubicin (EPI) solution. Inhalable EPI-solid lipid nanocarriers have a greater concentration of drug within the cancer-affected area. In another study with solid lipid nanocarriers, inhalable paclitaxel-solid lipid nanocarriers showed better effect and lesser side effects compared to i.v. formulation.[297] Inhalable celecoxib entrapped lipid nanocarriers demonstrated controlled release of celecoxib. In comparison with celecoxib solution, nebulized celecoxib-encapsulated nanostructure showed 4 times better retention time in the lungs.[298] Nebulizing the drugs enhances the homogeneity and stability of lipid nanocapsules. Paclitaxel−lipid nanocapsules and paclitaxel showed similar cytotoxic effects against lung cancer but lipid nanocapsules influence the stability of the drug in the lungs.[299]

Hybrid Lipid−Polymer Nanoparticles: The innermost core of poly glutamic acid provides viscosity to lipid polymer nanoparticles, which leads to prolonged release of 5-FU when compared to polymeric microspheres and liposomes. Drug release rate of 5-FU is affected through diameter of nanoparticle and thickness of lipid shell.[300] Enhanced release rate of 5-FU was observed (70% to 85%) when the thickness of the shell was reduced from 300 to 100 nm which also influenced the overall size reduction from 1000 to 600 nm. Drug disintegration was affected by the thickness of the shell because it regulated the amount of water which could enter inside the LNPs (lipid NPs). The initial 5-FU concentration in the lungs was 1000 times higher than in the systemic circulation after inhaling LNPs, indicating a larger deposition fraction. Another study was conducted where Paclitaxel-loaded hybrid PEG5000−1,2-distearoyl-phosphatidylethanolamine (PEG5000-DSPE) micelles were administered to deeper alveolar tissues via nebulization.[301] The core moiety of micelles was secured from phagocytosis by PEG chain through macrophages which led to its increased residence in lung tissues. When inhalable micelles conjugated with paclitaxel were administered, 45 times greater AUC (area under the curve) was observed in lungs of rat as compared to administration through intravenous route, which further resulted in significant enhancement in the concentration of drug in the kidneys, liver, and spleen (because of instant absorption through RES macrophages). Overall prolonged release of drug was observed from the core (12 h) with reduced enzymatic degradation of DSPE when compared to free drug which promptly enters the systemic pathway.

Inorganic Nanocarriers: Pulmonary application of metal NPs are limited because of their adverse effects of causing toxicity in lung tissues. Toxicity caused by metal NPs could be regulated by influencing the concentration of inhaled metal, particle size of aerosol, and time of exposure with lung tissues which could enhance their use as a theranostic agent (diagnosis and therapy). Employing nanomagnetic aerosols for targeted delivery of chemotherapeutic agents to various affected regions of lungs through "nanomagnetosols" has an impact on enhancing lung deposition of drugs at tumorous sites while decreasing the toxicity toward healthy tissues.[302] Furthermore, concentration of SPIONs aerosols could be directed greatly toward the central airway instead of the entire lung by regulating the applied magnetic field. When plasmid DNA loaded SPIONs aerosol were administered to mice in the presence or absence of magnetic field, it was observed that the right lung which was influenced with application of magnetic field had a 2-times greater concentration of plasmid DNA as compared to the left lung where magnetic field was absent.[303] In a study conducted to prevent tumorigenesis, PLGA coated Fe_3O_4 nanocarriers were loaded with aerosolized quercetin.[304] Coating avoided agglomeration of particles by improving the size distribution of nanoparticles. In a culture media of cells from human lung epithelium, PLGA-coated MNPs did not show cytotoxicity. But PLGA-MNPs encapsulated with drugs demonstrated cytotoxicity by decreasing the quantity of viable A549 cancerous cell lines.

Actively Targeted Inhalable Nanoparticles: The particle size of inhaled aerosol is critical for precise targeting of tumorous cells which are located in various regions of the lung. Accumulation of aerosol particles with size of 5 μm−10 μm is observed in larger airways and oropharynx while particles with smaller size of 1 μm−5 μm deposits in alveoli and smaller airways.[305] An 8- to 9-fold inclination was observed in the quantity of internalized drug, when administered via nanosized particles (100 nm−150 nm) as compared to microsized particles (3 μm−5 μm).[306] Precisely controlled modification of aerosol particle size is required as it will directly affect the internalization of drug into tumorous tissues and accumulation of drug in lungs.[57,307−309]

5. DIAGNOSTIC AGENTS USED FOR LUNG CANCER

The advantages of timely diagnosis of carcinoma have sparked a lot of scientific interest, since it significantly improves the rate of survival. Early diagnosis of tumors could aid in the total cure of the disease. As a result, the demand for methods that could identify pulmonary nodules in their earlier stages of growth has increased. Early diagnosis is related to a considerably improved survival pattern, highlighting the need for correct LC staging for reasonable treatment regimen selection for maximum anticancer effectiveness. Sputum cytology, chest radiography (CXR), bronchial biopsy, polymerase chain reaction (PCR), fluorescence bronchoscopy, and computed tomography (CT scan) are all widely applied techniques to diagnose LC and to determine the severity and extent of the disease (also known as staging). In the case of inadequate or restricted scope of different traditional diagnostic methods for early-stage tumor identification, NPs have plenty of promise in the clinical environment since they can precisely target the diseased region. In diagnostic radiography, the problem of "missing lung cancer" has also been a subject of concern. These missed detections in LC imaging result in the development of early-stage illness to advanced-stage disease.[310] Nanotechnology is progressing toward the development of novel chemicals for cancer screening, staging, and treatment regimens, resulting in the intriguing potential for biomedical imaging.[311] Particles at the nanoscale size have unique physical and chemical properties that allow detecting tools to be built with increased signal intensity, enumeration, magnification, contrast, and dispersion.[312] Nanomedicines have therefore evolved progressively as a game-changing phenomenon for developing anti-cancer drugs. By regulating nanocarriers they may carry

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screening agents and chemotherapeutic agents for improved imaging and treatment effectiveness.[313−315]

Metallic and Non-metallic Nanocarriers: Noble metal nanoparticles have sparked interest because of their admirable thermal, electrical, and optical characteristics. To begin with, the core is devoid of toxicity, possesses high biocompatibility, and is inert, which makes it a great moiety to start when building a carrier.

Polymeric Nanocarriers: Because of its biocompatibility, biodegradability, noncytotoxicity, and variety of physicochemical characteristics, these have piqued importance in the field of oncology for screening as well as in therapeutic strategies.

Biologically Derived Nanocarriers: These nanocarriers have risen to prominence because of their related biocompatibility, simplicity of morphological changes, and notable tendency of fabricating the surface with multiple active drugs, therefore they are being used in medical procedures.

Table 5 summarizes the many types of nanodiagnostic devices employed for identifying early stages of lung cancer with pulmonary metastases.

6. DRUG DELIVERY CHANGES

Over the past decade, drug delivery strategies based on nanoparticle systems have seen tremendous growth and development. Nanocarriers are most likely three-dimensional constructs of multiple components arranged in the proper spatial arrangement for their operations. Minor modifications in the method or composition might have a deleterious impact on the complex superposition of components. Synthesizing adequately sized nanoparticles for delivering an efficacious payload of therapeutic agent with the capability of targeting the specific site has always made the technique troublesome. In the biological surroundings, various risk factors such as indistinct shape, improper size characterization, inadequate biocompatibility, and unsuitable surface topology are observed. Because of the variations in physical, biological, and chemical profile of the nanoparticles, developing an appropriate and relevant delivery system which could administer medication to the lungs is considered to be arduous. Numerous challenges have to be surmounted by these nanosized systems when they reach clinical and preclinical stages of drug discovery, which include systemic clearance, immunological reactivity, tendency to overcome biological barriers, and target specificity. Certain characteristics must be considered while developing an appropriate nanocarrier system to be used for clinical purposes: Absolute knowledge about critical components with their respective interactions, capability for exhibiting target-specific action by overcoming biological barriers, identifying significant features and their impact on performance, and capacity for replication within manufacturing duration, efficient production in sterile form, convenience for storage and administration and high stability.[343] To achieve successful delivery of chemotherapeutics to the alveolar region several considerations must be met which include formation of definite sized particles for better tumor retention, eluding proteolysis, and overcoming mucus and epithelial absorption barriers (which may affect absorption of drug). The determination of physicochemical parameters is crucial to identify interaction between particles in a biological media, tendency to aggregate, adsorption of the protein surface of nanoparticles, and nanoparticle intracellular trafficking. If any significant change occurs in the parameters, it may affect the therapeutic efficiency (where insufficient drug is delivered) or may cause undesirable side effects which could be toxic. Intravenous injection of particles greater than 500 nm is not recommended since these particles are quickly removed from systemic circulation.[344] Meticulously controlled steps should be carried out for fabrication of polymeric nanoparticles, to obtain a homogeneous size of less than 200 nm. Using standard extrusion techniques, the particle size composition could be modified.[345] When *in vivo* studies are conducted, the fate of the nanocarrier is determined by surface charge. The zeta potential of nanoparticles has a significant impact on particle−particle interactions and aggregation tendencies. Positively charged nanoparticles have a stronger attraction to the body's negatively charged cellular membranes. However, careful examination of these nanoparticle systems is required before testing in an *in vivo* system. In general, multifunctionalization enhances the complexity of the nanoparticles. Although metallic and inorganic nanoparticles have shown potential anti-cancer effects, they also possess the risk of causing damage to normal cells. For example, amorphous silica nanoparticles could trigger inflammatory responses in the targeted site.[346] Titanium dioxide is biologically significant and is used in multiple biomedical purposes but its toxicity to the normal cells is a concerning issue which needs to be resolved.[347] There's a need to improve immunotherapy's adaptability, productivity, and persistence to stimulate the anticancer immune system.[348] To ensure safety, individual assessment of various nanocarrier conjugated systems should be performed (by *in vivo* and *in vitro* toxicity studies) before they are allowed for clinical use.

7. FUTURE PERSPECTIVES

Novel drug delivery systems (NDDSs) are being explored for a broad array of applications. They have shown potential for enhancing the safety, effectiveness, and accuracy of therapeutic regimens. These systems surmount the fundamental concerns with conventional regimens, which include absence of targeted delivery, lower therapeutic efficiency, undesirable adverse effects, and drug resistivity, while also outperforming their predecessors in terms of early metastatic detection. The ability of nanoparticles to distribute medication exclusively to specific targeted tissues via peptide, PEGylation, or receptor ligand linkage delivers an option that creates an optimum local concentration of drug with lower dosages and lower cytotoxicity than topical administration of the free drug. Multiple investigations have reported that embedding chemotherapeutics in nanocarriers reduces cytotoxicity compared to administering them as free drug solutions. With the existing advancements in nano-based systems, they have been hailed as one of the potential strategies for the treatment of lung cancer. However, there are still several unmet needs that must be addressed before they can be formalized. Drug resistance can be caused by insufficient drug release from nanocarriers. Resistance offered by multiple drugs is likely to be resolved using techniques such as enhanced multifunctionalized nanocarriers for targeted drug delivery to specific tumor, endosomal disruption for immediate cytoplasmic release of drug, and providing combination treatment via multiple chemotherapeutics. Further, as we progress from microsized to nanosized particles, there is a decline in size but, inclination in surface area and particle number. Because nanoparticles have a larger surface area, they have more chemical reactivity, which makes it difficult to predict how they would react under varied situations. Nanoparticles have enhanced chemical reactivity

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Table 5. Nano-imaging Diagnostic Methodologies

strategy	formulation	diagnosis	observations	ref
		Metallic and Non-metallic NPs		
IONPs	conjugated iron-oxide/silica nanocomposite	improvement in imaging	In the instance of FA-overexpressing lung cancer cells, improved imaging findings were revealed.	316
	conjugated superparamagnetic iron oxide NPs	MRI	Through targeted administration and improved T_2 relaxivity rates, peptide functionalization boosted lung cancer detection.	317
	immune SPIO-NPs	overexpression of CD44v6 receptors in metastasized lung cancer cells, leading to more accurate detection	Targeted delivery of anti-CD44v6 Ab-attached SPIO-NPs to CD44v6 overexpressing cancer cells improves contrast screening of metastasized lung cancer.	318
	QD/iron-oxide-based nanocomposite	α_v-integrin overexpressing lung cancer cells: targeted administration and improved imaging	Targeted administration of iRGD-attached SPIO-NPs boosted optical and MR diagnostic findings in α_v-integrin-overexpressing lung cancer cells.	319
	ultra-small conjugated SPIO-NPs	lung cancer screening with radionucleotide and optical imaging probe combined US-SPIO-NPs	The use of integrated MR-PET (positron emission tomography) optical imaging resulted in optimal imaging of lung cancers.	320
	functionalized NIR dye-loaded SPIO-NPs	boosted imaging	In the condition of FA-overexpressed lung cancer cells, improved optical imaging and contrast findings were observed.	321
AuNPs	dendrimer-coupled AuNPs (Au DENPs)	X-ray-based CT scan	*In vivo* imaging of a lung tumor that is both precise and biocompatible.	322−324
	aptamer-coupled AuNPs	adherence of aptamer	The presence of cancer cells was indicated by a change in color in the colorimetric assay.	325
	Au-conjugated triangular nanoplates	CT scan based on dual X-ray	Dual CT/PA (computed tomography/pulmonary angiography) screening aids in the determination of the most effective treatment period and gives real-time visual assistance.	326
	AuNP-conjugated electrochemical immunodetectors	enolase-alpha was discovered in patient blood serum	Elevated enolase-alpha levels were linked to a higher risk of lung cancer.	327
	MMP2-conjugated Au nanoclusters (matrix metalloproteinase 2)	fluorescence in near-IR region	Due to the significant buildup of clusters inside tumor cells by passive and active targeting, NIR fluorescence-based identification of lung tumors is effective.	328
	conjugated AuNP interaction	electrochemical probes with hydrophilic characteristics tested on tumor cell surfaces	Lung cancer cells are quantified by evaluating their contact angle and electrochemical characteristics.	329
	AuNPs and iodine NPs-based dual CT scan	X-ray-based CT scan	*In vivo* imaging of lung cancer and its accompanying vasculature.	330
	hollow Au nanospheres (HAuNs)	carcinoembryonicantigen (CEA) detected	CEA levels greater than 5 ng/mL were linked to a higher risk of lung cancer.	331
silica-based NPs	nanospheres of SiO_2 silver-based support shells	single miRNAs detected in lung cancer cells using fluorescent metal nanoshells as molecular diagnostic agents	Lung cancer incidence was confirmed by elevated photostability of NPs and increased emission intensity linked with the genetic signal.	332
	SMART SiO_2 nanoshells	targeted distribution of encapsulated cobalt-ferrite NPs	The overexpression of $\alpha_v\beta_3$-integrin, tenascin-C, and nucleolin in lung cancer cells resulted in improved optical imaging and contrast.	333
carbon-based NPs	graphene-AgNP-conjugated 3D bio-nanosensor	CYFRA21-1 DNA biomarker detected	In preclinical and clinical conditions, the cancer-based nucleic acid may be detected with a sensitivity of 1×10^{-14} M.	334
	SWCNT/AgNP-based nanohybrids	single miRNAs linked to lung cancer revealed	By detecting the related miRNA biomarker, the nanohybrids were able to accurately diagnose lung cancer cells.	335
manganese oxide NPs	fabricated manganese dioxide (MnO_2) NPs	MR contrast imaging applied for NSCLC diagnosis	In the instance of NSLC diagnosis, efficient T1/T2-weighted MR contrast imaging findings with increased transverse relaxivity were seen.	336
	Mn_3O_4-based NPs	overexpressed MMP2 and LHRH-receptor	In metastatic lung cancer cells, targeted administration of MMP2-cleavable peptide and LHRH-targeting peptide-attached Mn_3O_4-NPs resulted in improved MR imaging outcomes.	337
		Polymeric NPs		
albumin NPs	hematoporphyrin-conjugated albumin NPs	diagnosis of metastatic lung cancer *in vitro* and *in vivo*	Based on the results of confocal microscopy and scintigraphic imaging, it was shown that cancer cells could be imaged effectively.	338
chitosan NPs	functionalized glycol-chitosan NPs	*in vivo* imaging	Time-dependent NIRF imaging demonstrated effective imaging of lung cancer by targeted uptake of Cy5.5-labeled gCNPs.	339
gelatin NPs	fabricated gelatin NPs	*in vitro* and *in vivo* diagnosis	Confocal microscopy and *in vivo* imaging provided effective imaging of lung cancer by targeted uptake of FITC-EGFR-labeled gelatin NPs.	340, 341

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Table 5. continued

strategy	formulation	diagnosis	observations	ref
Polymeric NPs				
Biological Nanocarriers				
viral NPs	bioengineered T4-ViNPs	early lung adenocarcinoma detected	Owing to the rapid absorption of Alexa Fluor/Cy3-conjugated viral NPs by cells, the imaging findings are quite sharp.	342

which produces reactive oxygen species (ROS), that can trigger inflammatory responses, DNA deterioration, and oxidative stress, eventually causing cytotoxicity. However, only a few liposomes and nanoparticle-based compositions have received FDA approval so far. Liposomes and lipid-based nanoparticles are prone to oxidative breakdown, and have the tendency to accumulate, leading to reduced therapeutic efficacy and are therefore less stable when compared with other nanocarriers. Even though most lung malignancies are detected at an advanced stage, a suitable delivery approach via an appropriate nanocarrier which can release the drug to peripheral and central lung tissues, along with circulatory pathways, are needed for targeting local and distant metastatic malignant nodules. Additional advancements are needed to facilitate the regulated release of chemotherapeutic drugs through stimuli sensitive carriers. Cancer theranostics includes both diagnosis and target-specific therapy delivered through multi-purpose nanocarriers which include screening and chemotherapeutic chemicals, which might become crucial in the future to regulate cancer therapy. It has the potential for detecting cells with tumors and then eliminating them with minimal adverse effects, and provide instant *in vivo* screening technologies, and demonstrate treatment benefits. As a result, future studies should focus on identifying efficacious nanoparticles that are highly stable, have enhanced deagglomeration potential, and improved infiltrating efficacy. Varying the physical (mass median diameter and porosity) and chemical characteristics of nanoparticles (amphiphilic particles, target ligands, and stable polymers) might help preserve stability and prevent agglomeration during storage. To have a synergistic boosting impact on local and systemic distribution, a drug can be embedded into several nanoparticles, such as liposomes, dendrimers, and micelles.

In addition to the challenges of designing and synthesizing nanocarriers, researchers must also consider the lack of standards in the evaluation of nanomedicines, which involves manufacturing procedures, functional testing, and safety protocols. Therapies including nanocarriers must fundamentally circumvent identical challenges that a newly synthesized drug possesses, which includes: ideal composition and characteristics of compounds, repeatable manufacturing techniques, establishment of analytical techniques to adequately characterize the compound, preferable pharmacological evaluation with toxicity tests, and demonstration of safety and effectiveness in pre-clinical and clinical studies. A single active ingredient is generally found in standard medicines. On the other hand, various active compounds are embedded in nanoparticles which make them complicated. As a result of such a complexity, conventional pharmacokinetic, bioequivalence, and safety inspections must be updated. To strategically tackle the development of new nanoproducts obtained from novel methodologies with ease of drug delivery, regulatory authorities must establish an intensive set of tests with shortened clearance procedures. Substantial investigation in this sector is expected to seek new perspectives and replace the standard dose method with NDDSs in the future, therefore improving health care delivery.

8. CONCLUSION

Lung cancer is one of the most common cancers with a high mortality rate. Early identification and better treatment strategies are highly essential to elevate the efficiency of treatment of carcinoma. Theranostic agents use a distribution

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platform based on nanotechnology, to deliver both therapeutic and imaging compounds to the desired location of the body. Because of unique physical characteristics possessed by nanostructures, they frequently have the capacity to resolve solubility and stability problems of chemotherapeutic drugs by surface modification. Nanotechnology has limitless potential and novel applications are constantly being investigated as it is a discipline that has recently spawned novel methods for lung cancer treatment. Researchers have used several forms of nanocarriers to overcome the shortcomings of traditional treatment by improving active or passive target specificity and reducing cytotoxicity toward healthy cells. Aiming the regimen toward overexpressed targets greatly enhances lung cancer treatment results. The greater surface area of nanoparticles contributes to the larger therapeutic payload as well. Liposomes, SLNs, micelles, dendrimers, MNPs, CNTs, QDs, hydrogels, and nanoemulsions, polymeric NPs are some of the nanocarriers which are formulated to be utilized as theranostics. The quality of nanocarriers is significantly crucial for transferring the drug to the tumor site as it directly affects the infiltration of drug and accumulation of drug in the cancerous tissue. The capacity to identify and quantify cancer at its initial stage with higher resolution and predicting the response of cancer therapy will also depend on the theranostic agent. These significant advancements in lung cancer therapy, as well as the creation of different superior novel drug delivery systems, have helped to boost the morale of patients undergoing cancer treatment.

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Notes

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