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Review

Onco-Receptors Targeting in Lung Cancer via Application of Surface-Modified and Hybrid Nanoparticles: A Cross-Disciplinary Review

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Abstract: Lung cancer is among the most prevalent and leading causes of death worldwide. The major reason for high mortality is the late diagnosis of the disease, and in most cases, lung cancer is diagnosed at fourth stage in which the cancer has metastasized to almost all vital organs. The other reason for higher mortality is the uptake of the chemotherapeutic agents by the healthy cells, which in turn increases the chances of cytotoxicity to the healthy body cells. The complex pathophysiology of lung cancer provides various pathways to target the cancerous cells. In this regard, upregulated onco-receptors on the cell surface of tumor including epidermal growth factor receptor (EGFR), integrins, transferrin receptor (TFR), folate receptor (FR), cluster of differentiation 44 (CD44) receptor, etc. could be exploited for the inhibition of pathways and tumor-specific drug targeting. Further, cancer borne immunological targets like T-lymphocytes, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and dendritic cells could serve as a target site to modulate tumor activity through targeting various surface-expressed receptors or interfering with immune cell-specific pathways. Hence, novel approaches are required for both the diagnosis and treatment of lung cancers. In this context, several researchers have employed various targeted delivery approaches to overcome the problems allied with the conventional diagnosis of and therapy methods used against lung cancer. Nanoparticles are cell nonspecific in biological systems, and may cause unwanted deleterious effects in the body. Therefore, nanodrug delivery systems (NDDSs) need further advancement to overcome the problem of toxicity in the treatment of lung cancer. Moreover, the route of nanomedicines' delivery to lungs plays a vital role in localizing the drug concentration to target the lung cancer. Surface-modified nanoparticles and hybrid nanoparticles have a wide range of applications in the field of theranostics. This cross-disciplinary review summarizes the current knowledge of the pathways implicated in the different classes of lung cancer with an emphasis on the clinical implications of the increasing number of actionable molecular targets. Furthermore, it focuses specifically on the significance and emerging role of surface functionalized and hybrid nanomaterials as drug delivery systems through citing recent examples targeted at lung cancer treatment.

Citation: Sabir, F.; Qindeel, M.; Zeeshan, M.; Ul Ain, Q.; Rahdar, A.; Barani, M.; González, E.; Aboudzadeh, M.A. Onco-Receptors Targeting in Lung Cancer via Application of Surface-Modified and Hybrid Nanoparticles: A Cross-Disciplinary Review. *Processes* **2021**, *9*, 621. https://doi.org/10.3390/pr9040621

Academic Editor: Carla Vitorino

Received: 1 March 2021
Accepted: 29 March 2021
Published: 1 April 2021

Keywords: lung cancer; nanoparticles; toxicity; surface modification; hybrid nanocarriers

1. Introduction

Lung cancer is one of the most prevalent diseases and the leading causes of death worldwide [1]. It is more common in males than in females and based on an estimation, this type of cancer caused 154,050 deaths in 2018 [2]. One of the most common causes of this devastating disease is chronic tobacco usage. The major reason for its high mortality is the late diagnosis of the disease, and in most cases, lung cancer is diagnosed at the fourth stage when the cancer has already metastasized to the nearby organs [3]. Among lung cancer patients, 85% exhibit nonsmall cell lung cancer (NSCLC) while the rest (15%) of the patients have small cell lung cancer (SCLC). The survival of the patients suffering from lung cancer mainly depends upon the early diagnosis and efficient surgical removal of the tumor tissues. Among the different treatments, chemotherapy is the most recommended therapy to treat lung cancer. However, the major limitation of conventional chemotherapy is related to the presence of inefficient drugs at the target site, which ultimately compromises the therapeutic efficacy [4]. To reduce this problem, repeated administration of systemic chemotherapy at higher concentrations is required, which is allied with dose-related systemic toxicities. Moreover, in conventional therapies the uptake of the cytotoxic agents by the healthy cells can increase the chances of cytotoxicity in these normal cells. Hence, novel approaches are required for both the diagnosis and treatment of lung cancers [5].

Due to numerous limitations associated with these conventional methods, several researchers have exploited nanotechnology-based approaches for the efficient diagnosis and delivery of therapeutic agents [6]. Among various nanoparticle-mediated drug delivery systems, the most frequently used ones for lung cancer treatment include polymeric nanoparticles [7,8], liposomes [9,10], bionanoparticles [11,12] and metallic nanoparticles [13,14]. These nanoparticles have been very effective due to their small size, large surface area, high biocompatibility and reduced renal clearance. Although the use of nanoparticles has shown several advantages [15], their site-specific delivery is still a problem for which passive and active-targeting approaches are necessary [16,17].

The passive targeting approach utilizes the exploitation of the enhanced permeability and retention (EPR) effect. In many disease conditions, including lung cancers, the endothelial lining of the blood vessels exhibits higher permeability than in normal conditions [17,18]. The presence of this leaky vasculature allows the higher permeation of the nanoparticles into the target site [19]. Moreover, the lack of a normal lymphatic drainage system in the tumor site contributes to higher levels of retention of the nanoparticles. However, this idiosyncratic property cannot be applied to low molecular weight drugs which have a small residence time and rapid excretion from the tumorous cells. Low molecular weight drugs can be encapsulated in unionized drug carriers to improve their pharmacokinetics (elongated systematic circulation), increasing tumor selectivity and lowering side effects. This phenomenon of tumor-targeting is called "passive" and depends upon the properties of the carrier molecule (its molecular weight and residence time) and the tumor anatomy (vascularity, porosity, etc.), but does not have any ligands for specific cells' binding sites. The EPR effect provides a 20–30% higher concentration of the drug targeted delivery of the tumorous site compared to normal body tissues [20,21].

EPR effect is extremely dependent on the intrinsic pathways of tumor cells' growth and it is controlled specifically by the rate of angiogenesis and lymphangiogenesis, the rate of perivascular tumor development, stromal thickness response and the intratumor pressure. All these elements, along with the physicochemical properties of nanoparticles, can influence the efficiency of the drug's targeted delivery [22]. However, the extrusion properties of the newly formed tumor's blood vessels have an impact on the nanomedicine impregnation; it causes an increase in the interstitial pressure, which may hinder the retention of the drug carriers in the tumor tissues. Furthermore, due to the imbalance

between the pro- and antiangiogenetic signaling in different points of the tumorous tissues, the blood vessels are deviant with enlarged, curvy and saccular pathways, unorganized interconnection processes and branching. This miscellaneous blood circulation causes an irregular growth of the tumor cells and those cells surrounding the blood vessel grow rapidly compared to those that are far away, because of low oxygen and nutrition supply. This explains why the outer sites of large tumorous tissues have less blood supply (i.e., 1–2 cm in diameter in mice) and why is most often difficult for nanomedicines to reach the cores of tumor cells. Although the interstitial pressure is high in the inner portion of the tumor, the extrusion rate is unexpectedly small. This pattern was observed in some different types of murine and human tumor cells. The increased interstitial pressure does not only hinder the drug supply to the core tumorous tissues but also retards the growth of new blood vessels. This causes a higher blood supply to flow towards the tumor cells' periphery, indicating that there is the possibility of modifying the EPR effect chemically or mechanically to improve the growth of the blood vessels for the retention of the drug-loaded nanocarriers. It is worth mentioning here that some types of EPR enhancers like bradykinin (kinin), nitric acid, peroxynitrite, prostaglandins, etc. may cause hypertension that could enhance tumor extrusion [23].

To further improve the targeted delivery of the imaging modalities and therapeutic agents against lung cancer, many researchers have also exploited the receptor-mediated delivery of theranostics [24]. Several receptors are overexpressed in lung cancer, like oxytocin, vasopressin, chemokine, epidermal growth factor, bradykinins, bombsein, folate and tyrosine receptors. The majority of the lung cancer receptors are categorized as G-protein coupled receptors. These receptors have a potential role in the formation, progression and metastasis of lung cancer and are involved in angiogenesis process during tumor development and also during the progression of the cancer to the nearby organs [25]. The overexpression of several kinds of receptors in lung cancer has been exploited by researchers for the site-specific delivery of theranostics. As compared with the passive targeted approach, a higher amount of the drug can be made to reach the target site through active targeted delivery of the imaging modalities and therapeutic agents.

Active targeting is compulsory for the proper distribution of drugs, genes and theranostics to the action site so the therapeutic effect on normal body tissue can be avoided. By using active targeting, a sufficient amount of drug is placed at the tumor site increasing the drug efficiency by many folds. Thus, active targeting nanosystems are more efficient than passive targeting ones. Active targeting is possible exclusively when the nanocarriers are enriched with ligands that are specific for the overexpressed receptors in lung cancers [26]. This phenomenon enhances the binding capacity of the drug and imaging modalities to the tumor tissues and thus increases the drug entrapment capacity at the tumor site. Hundreds of ligands and antibodies have been discovered against the abovementioned receptors and are exploited for targeted delivery of the drug cargoes to the target site. A strong ligand/receptor binding affinity serves as role model to promote active binding technology. This can improve the targeted delivery of theranostics and therapeutic agents on the one hand and overcome the problems allied with conventional approaches on the other hand [26]. The visual illustration of various nanotechnology-based theranostic delivery approaches are shown in Figure 1.

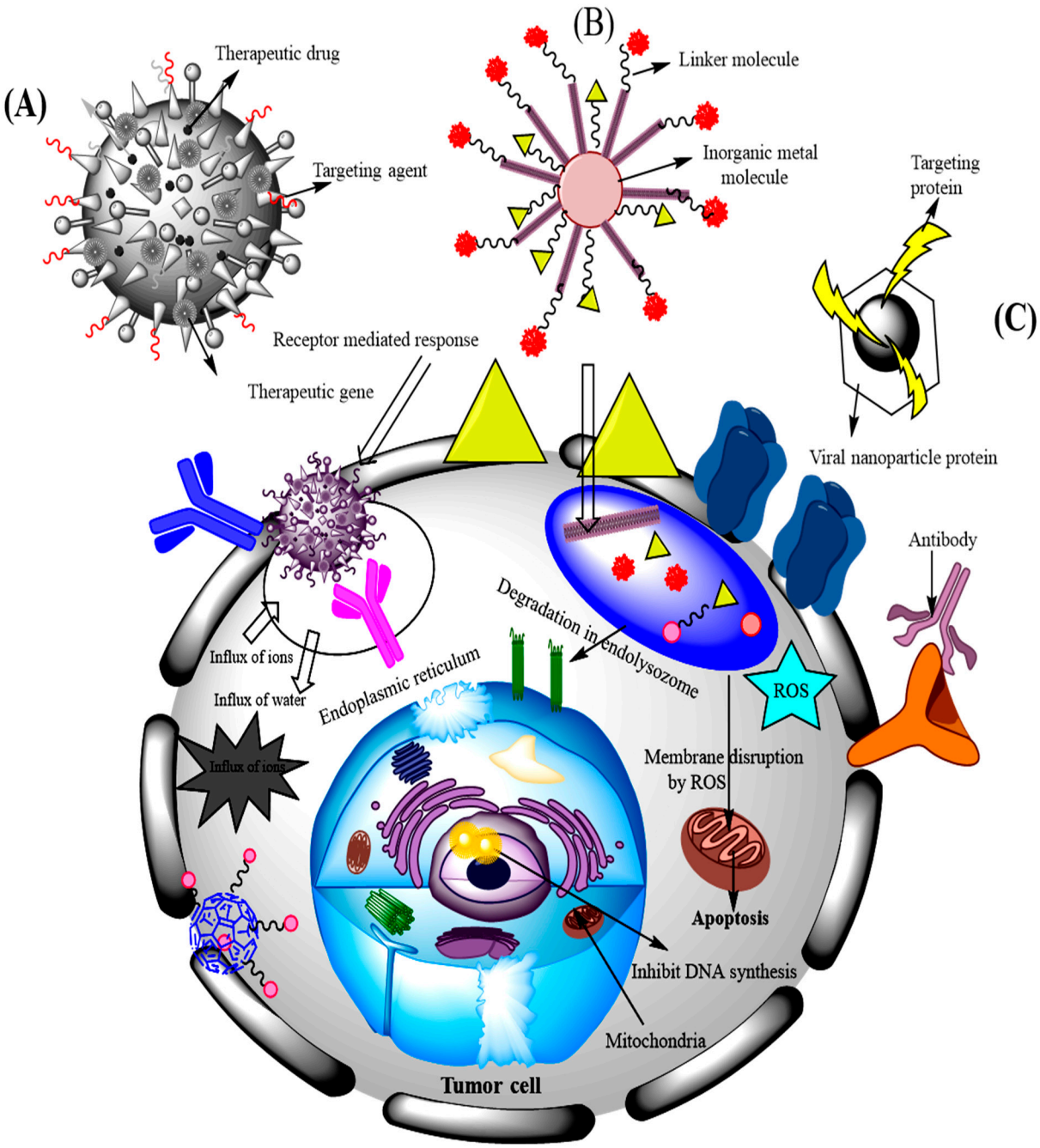

Figure 1. Schematic presentation of various methods for delivery of therapeutic agents against lung cancer including (**A**) polymeric nanoparticle-based approach, (**B**) metallic nanoparticle-based approach and (**C**) bioparticle-based approach.

This review first summarizes the current knowledge of the pathways implicated in the different types of lung cancer with an emphasis on the clinical implications of the increasing number of actionable molecular targets. The utilization of different targeting approaches to combat the toxicity of the chemotherapeutic agents is discussed here. The mechanism through which this targeted delivery is attained is also described. In this context, this review could attract the interest of medical scientists who are involved in biological systems. The second specific focus of this review is on the role of the surface-modified and hybrid nanomaterials as drug delivery systems in combating lung cancer. This spotlight was achieved through citing most the recent and representative examples

targeted at lung cancer treatment. From this perspective, it could be highly interesting for material scientists.

The fields of biology and material science are traditionally rather separated, as much as they naturally rely on the very same basic principles. Through the novel cross-disciplinary focus of this review, we attempt to overcome this gap and create a more synergetic perspective on both areas, which will be highly beneficial for the scientific community given the plethora of discussions and discoveries that can be envisaged.

2. Pathways for Targeting Lung Cancer

Lung cancer is histologically classified into NSCLC and SCLC. The complex interplay between pathological changes and oncogenic mutations alters the signaling of multiple pathways and the expression of chemokines and various receptors. In turn, a modified tumor microenvironment facilitates the growth, proliferation, angiogenesis, metastasis and survival of the cancer cells. Traditional treatment strategies for the lung cancer include chemotherapy, radiotherapy and surgical excision. However, conventional chemotherapeutic agents have compromised therapeutic efficacy owing to pharmacokinetic issues, solubility problems and nonspecific action in normal cells with resultant toxicities. Moreover, high drug doses, tumor-associated alteration of pathways and subsequent treatment with multiple therapies will contribute to the occurrence of tumor resistance against chemotherapeutic agents [27] Therefore, the focus is now laid on the suppression of upregulated pathways including EGFR, RAS-RAF-MEK-ERK/MAPK, JAK-STAT, PI3K/AKT/mTOR through newly designed, specifically targeted small molecule inhibitors and antibodies (Figure 2). For instance, specific EGFR inhibitor (erlotinib) and PI3K/AKT/mTOR inhibitor (everolimius) replaced the first-line chemotherapy [28]. The most common genetic mutations in the lung cancer, along with their mode of aberration and the associated small molecule inhibitors to target specific pathways, are mentioned in Table 1. Nevertheless, the small-molecule-mediated targeted therapy is relatively successful and increases survival rates but is prone to therapeutic failure because of cancer relapse, and increased drug resistances due to targeting site mutations [29].

Hence, developing a highly targeted drug delivery system for specific action into the tumorous cells at an optimal dose is of great necessity. Broadly, lung cancer can be targeted through either passive or active targeting mechanisms or both. Passive drug delivery follows a certain principle to be deposited into the lung tissues under the EPR effect. EPR is attributed to leaky vasculature and deteriorative epithelial integrity that allows residence and accumulation of small sized particles into the lung tumorous tissue [30], which act either as a carrier to deliver the drug or act directly as a therapeutic moiety. In passive targeting, particle size is the main determinant for distribution and deposition in the lungs. For instance, large particles around >5 μm have fewer chances to concentrate and are mostly exhaled out of the lungs. Particles in the range of 1–5 μm are phagocytosed by the alveolar macrophages and particles with size <1 μm could be deposited in the alveolar cells with minimal clearance by the immune cells [31].

To achieve improved tumor-specific targeting and to avoid possible threats with dislocation and clearance of passively targeted delivery carriers, active targeting of overly expressed onco-receptors with specific ligands brings better outcomes [30]. The inhibition of overexpressed receptor functions through specifically targeting moieties modulates the expression of cancer projectors and improves drug action in the tumor-specific lung tissues. Various overexpressed receptors in the tumor microenvironment include EGFR, TFR, FR and CD44 receptor [32]. Tumor receptors and tumor-associated immune cells have a role in cancer growth, proliferation, metastasis and angiogenesis. Therefore, receptor-mediated targeting and immune cell targeting alter the onco-proteins' expression and inhibit oncogenic pathways to stop cancer growth and progression.

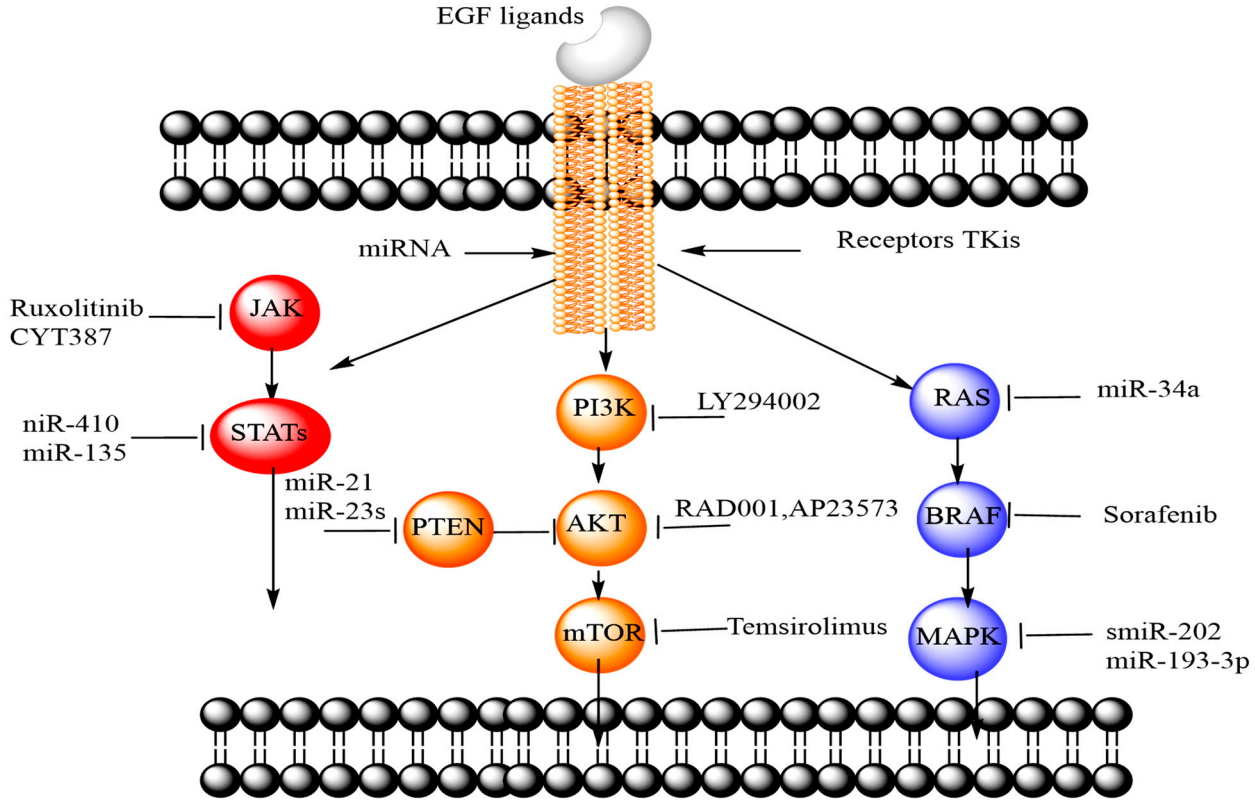

Figure 2. Oncogenic signaling pathways and drugs targeting abnormal signaling of EGFR, VEGFR, PI3/AKT/mTOR, RAS/BRAF/MAK, JAK/STAT pathways. Reproduced from the reference [27].

Table 1. Most common mutations in lung cancers and their relevant mechanisms.

Oncogene	Aberration	Activation Mechanism	Type of Lung Tumor	Targeted Drug Inhibitors	References
EGFR	Gatekeeper or oncogene mutation/ Amplification	Ligand binding → Activation of tyrosine kinase → phosphorylation of EGFR	NSCLC, ADC	Erlotinib, Gefitinib, Cetuximab,	[33–35]
EML/ALK	Fusion	Fusion of amino terminal of EML4 to intracellular kinase → ALK tyrosine kinase receptor rearrangement leads to activation	NSCLC, ADC	Lorlatinib, ensartinib, crizotinib, alectinib	[34,36,37]
BRAF	Mutation/fusion/kinase duplication	Autophosphorylation of kinase loop and MEK protein binding	NSCLC, ADC	Dabrafenib, Vemurafenib	[34,38]
PI3K	Modified/Activated	PIP2 and PIP3 phosphorylation → placement of serine threonine kinase AKT into membrane → PI3K phosphorylation	NSCLC, SCLC	LY294002, wortmannin	[39–41]

Table 1. *Cont.*

Oncogene	Aberration	Activation Mechanism	Type of Lung Tumor	Targeted Drug Inhibitors	References
mTOR	Activated	PIP2 and PIP3 phosphorylation → placement of serine threonine kinase AKT into membrane → mTOR phosphorylation	NSCLC, SCLC	Ridaforolimus, Rapamycin, sirolimus	[39,40]
RAS	Mutation	Conversion of GDP to GTP to activate G-protein (RAS) receptor	NSCLS, ADC	Tipifarinib, Lonafarinib, salirasib, sorafenib	[34,42]
p53	Mutation/Deletion	Inactivating of missense gene mutations	ADC, SCLC	Advexin (adenoviral vector)	[33,43,44]
MEK	Activated	RAS activation	NSCLS, ADC	Selumetinib, sorafenib, trametinib	[45,46]
c-KIT	Overexpression	Regulatory and functional c-KIT mutations → activation of protein kinase	SCLC	Imatinib, STI-571 (Gleevec)	[47,48]
VEGF	Overexpression	HIF-1 or EGR-1 upregulation → VEGF expression	SCLC, NSCLS	Bevacizumab	[33,49,50]
ROS1	Rearrangement	Autophosphorylation	NSCLS	Crizotinib	[51,52]

Epidermal growth factor receptor (EGFR); small cell lung cancer (SCLC); nonsmall cell lung cancer (NSCLC); adenocarcinoma (ADC); phosphatidylinositide-3 kinase (PI3K); hypoxia-inducible factor-1 (HIF-1); early growth response-1 (EGR-1); guanine diphosphate (GDP); guanine triphosphate (GTP); vascular endothelial growth factor (VEGF); echinoderm microtubule associated proteinlike-4 (EML4); phosphatidylinositol 4,5-bisphosphate (PIP2); phosphatidylinositol 3,4,5-bisphosphate (PIP3).

3. Onco-receptor Targets in Lung Tumors and Vasculature

3.1. Epidermal Growth Factor Receptor (EGFR)

The EGFR is a cell surface peptide receptor from the ErbB family of tyrosine kinase. It consists of the extracellular region with two homologous ligand-binding domains and two cysteine-rich domains, a single slanging transmembrane domain and an intracellular region comprising juxtamembrane, a tyrosine kinase domain and a regulatory region [53]. EGFR regulates growth, differentiation and migration of the alveolar and bronchial epithelial cells under normal conditions, while overfunctioning in cancer facilitates the proliferation, metastasis, and invasion of lung cancer cells [54]. EGFR is among the highly expressed onco-receptors in 85% of NSCLC, with negligible involvement in SCLC [55]. Various monoclonal antibodies (panitumumab, cetuximab) and tyrosine kinase inhibitors (erlotinib, gefitinib, lapatinib) are used to target EGFR to treat lung cancer [55]. Furthermore, antisense oligonucleotides, affibodies, peptides, and nanobodies worked to inhibit EGFR [56]. Recently, it has been observed that ligand anchored nanocarriers specifically bind to extracellular domains of EGFR to release the drugs intracellularly for the tumor-specific inhibition of the signaling pathway. Under this approach, biotinylated-EGF ligand-bound gelatin nanocarriers have delivered increased concentrations of cisplatin to the lung cancer cells and significantly reduced tumor volume via inhalation route [57]. Similarly, DNA aptamer conjugated chitosan-liposome complexes have delivered erlotinib specifically to the lung cancer cells via EGFR [58]. Additionally, monoclonal antibody linked polymeric nanoparticles have shown promising results against acquired EGFR-kinase resistance in cancer cell lines and could be designed to suppress EGFR resistant pathways in the lung tumor [59]. Ligand-bound nanocarriers favor site-specific tyrosine kinase inhibitors or

monoclonal antibodies' delivery to the lung cancer cells, reduce off-site toxicities and endosomal clearance, and improve therapeutic efficacy with sustained drug release rate.

3.2. Transferrin Receptor (TFR)

Transferrin (TF) is a nonheme glycoprotein (~180 kDa), mainly responsible for iron (ferric ions) transport in the body [60]. Therefore, TFR (CD71) is expressed by the normal epithelial and immune cells. In tumors, the overexpression of TFR facilitates fast iron transport to accomplish the nutritional demand of the cancer cells. The expression of TFR in cancer cells is 10-fold higher than the expression in normal cells [54]. Overexpressed TFR can be targeted by the ligands including TF, ferritin and anti-TFR antibody, thus improving the tumor targeting efficiency of the carrier system. TFR is highly upregulated in lung cancer; about 88% of NSCLC cases have elevated TFR-1 levels [61]. In one study, the blocking of TFR through the anti-TFR antibody significantly retarded the cell proliferation of the lung adenocarcinoma cell lines [62]. Furthermore, TF conjugated doxorubicin (DOX) liposomes increased cellular internalization in A549 lung cancer cells compared to alveolar type *I* (AT*I*) and alveolar type *II* (AT*II*) cells [63]. Similarly, antibodies and peptides targeted TFR and inhibited tumor growth or induced apoptosis of the tumor cells [64].

3.3. α. vβ3 Integrin Receptor

Integrins belong to the transmembrane heterodimeric glycoproteins family, consisting of the 18 α and 8 β subunits [65]. Integrins are expressed in multiple forms in many tumor-associated cell types. In lung cancer, the integrins αv, α5, β1, β3 and β5 have been demonstrated to develop the survival and metastasis of cancer cells [66]. The role of integrins encompasses cell–matrix adhesion, the maintenance of cellular morphology, differentiation and proliferation [54]. About 82% of NSCLC cases have higher integrin expression, while only 13% of SCLC expressed integrins [67]. The widespread functions of integrins in lung cancer suggest that their inhibition could be beneficial in tumor targeting and therapy. It was demonstrated that the inhibition of the αvβ3 and αvβ5 integrins with targeted ligands can block the endothelial cell angiogenesis and tumor metastasis [66]. In this context, arginylglycylaspartic acid (RGD) peptide has the potential to target αvβ3 integrin, thus facilitating drug delivery to the lung cancer. In one study, RGD anchored poly(lactide-co-glycolide) (PLGA)-chitosan nanocarriers successfully delivered paclitaxel (PTX) specifically to lung cancer, while normal human bronchial epithelial cells with poor integrin expression had negligible cytotoxic effects of PTX [68]. Furthermore, cyclic peptide anchored formulation elevated the localized drug concentration and suppressed the tumor cells in the subcutaneous and orthotopic A549 xenograft mice models as compared to the free drug controls [69].

3.4. Folate Receptors (FRs)

FRs are from a family of glycoproteins (35–40 kDa) having a strong binding affinity for folic acid (FA). FRs are differentiated into four isoforms including FRα, FRβ, FRγ and FRδ [70]. Normal human cells have a very low content of FRs, whereas FRs are overexpressed in a variety of tumor cells—the first two isoforms (FRα, FRβ) are the most common [70,71]. In NSCLC, FRα is overly expressed especially in adenocarcinoma [54]. Therefore, FA or FR monoclonal antibodies could serve as a ligand to target lung cancer. Folate can be conjugated to chemotherapeutic agents, microparticles, nanocarriers, lipidic systems and oligonucleotides to directly target FR-positive tumor cells. Folate-PEG-modified cytochrome **c** nanomicelles have demonstrated selective targeting and internalization by FR expressed on the HeLa cells compared to FR negative cell lines [72]. Similarly, DOX and small interfering RNA (siRNA) were loaded into folate-biotin conjugated starch nanoparticles for codelivery into human lung cancer cells (A549). Folate-mediated codelivery has shown enhanced cytotoxicity and reduced proliferation of the A549 cells. The cytotoxicity was competitively inhibited in the presence of free folate; further, the expres-

sion of insulinlike growth factor 1 receptor (IGF1R) proteins was decreased through the treatment [73].

3.5. Cluster of Differentiation 44 (CD44)

CD44 is a cell-surface based glycoprotein receptor with a specific affinity for hyaluronic acid (HA). The binding of HA to the receptor regulates cell adhesion and the differentiation and migration of the normal cells [74]. In tumors, CD44 has the important functions of cell adhesion, growth, proliferation, metastasis and induction of the cancer cell resistance [74,75]. CD44 is highly upregulated in squamous cell metaplasia and NSCLC [76] and is involved in metastasis of NSCLC to the lymph node [77]. HA, as an anionic glycosaminoglycan and a polymeric ligand, can be anchored to the surface of the particles or itself is able to self-assemble to target the lung cancer [78,79]. For instance, HA anchored polyethyleneimine-PEG nanoparticles specifically delivered siRNA to lung cancer cells [78]. Furthermore, enzyme hyaluronidase-1 expressed heavily in the malignant tumors degraded HA, thus facilitating drug release from HA in the target cancer cells [80].

3.6. Other Onco-Receptors

Several other receptors are heavily expressed in the lung tumor microenvironment including luteinizing hormone-releasing hormone (LHRH) receptors [81], chemotactic chemokines receptor 4 (CXCR4) [82], fibroblast growth factor receptor [83], tyrosine kinase AXL receptor [84], vascular endothelial growth factor receptor (VEGFR) [85], death receptor/TNF-related apoptosis-inducing ligand-receptor (DR4/TRAIL-R1) [86], β2-adrenergic receptors (β2-AR) [87] and lectin receptors [88]. Targeting these receptors through specific ligands can inhibit lung cancer survival, growth and metastasis.

4. Extracellular Nanovesicles in Targeting Lung Cancer

The concept of applying nanoparticles for lung cancer targeting shares a lot of similarities with the function of extracellular vesicles (EVs). In this regard, we briefly review these particles in this section. EVs are cell-derived, membrane-bound particles known to mediate intercellular signaling and are sensitive in organ-specific metastasis. Depending on the biogenesis pathways or their subcellular origin and size, EVs are also referred to as apoptotic bodies, microvesicles or exosomes [89–91]. EVs confined from distinct body fluids transport immune response-related and immune-modulatory molecules. These molecules include proteins, lipids, and nucleic acids. Recent studies considered EVs as one of the main components in the tumor microenvironment. In the tumor microenvironment, the EVs are able to transport the biomolecules to the less malignant cells. As the result, the less malignant cells receiving the EVs may continue to show increased metastatic and migratory behavior [92].

Integrin receptors are enriched in small EVs and are major players in mediating EV functions. For example, αvβ3 integrin is upregulated during cancer progression and is known to account for the migration of cancer cells. These nanovesicles' signaling is capable of modifying the tumor cell's structure, characteristics and functionality, such as overcoming drug resistance [93,94]. In their study, Hoshino et al. demonstrated that the tumor-derived lung-tropic EVs carry integrins α6β1 and α6β4, which are favorably taken up by lung fibroblasts and surfactant protein C-positive epithelial cells. The authors demonstrated that the incorporation of EVs by lung resident cells enhanced the expression of the proinflammatory gene S100 and promoted the lung metastasis [95].

From the therapeutic perspective, EVs are novel drug delivery systems and have more biosafety and biocompatibility characteristics than other synthetic surface functionalized or hybrid nanoparticles. In this context, EVs can be divided into unmodified and modified EVs [96]. Similar to nonfunctionalized nanoparticles, unmodified EVs have shown less efficacy in various performed studies. Therefore, scientists are now developing modified EVs through the introduction of therapeutic molecules into EVs or modifying the surface components of EVs to enhance their efficacies in terms of tissue targeting and

site specificity [97]. For example, Nakase et al. modified EVs with octaarginine peptide, which resulted in enhanced cellular EV uptake via the active induction of macropinocytosis without cytotoxicity. Additionally, the increased accumulation of EVs at the targeting site showed greater therapeutic effect [98]. Recent studies on EV-mediated lung cancer targeting at a specific site highlighted that there are many limitations involved in the modification of these nanovesicles, as the strategies adopted for modification may damage the EV membrane and consequently compromise the therapeutic efficacy of the EVs [99–103]. To overcome these limitations, surface modification of the synthetic nanoparticles has demonstrated more promising results. For instance in a recent report, α3β1 integrins were targeted in NSCLC through cyclic peptide linked polymersome containing docetaxel. The results demonstrated better cellular uptake of cyclic peptide anchored formulation by A549 human lung cancer cells than by free docetaxel (DTX) and nontargeted polymersome.

5. Immunological Targets in Lung Cancer

Since the tumor is associated with pathophysiological, cellular and biochemical alterations, several immune cells like T-lymphocytes, macrophages, natural killer cells, B cells, MDSCs and dendritic cells infiltrate the lung tumor microenvironment. Hence, TAMs, MDSCs and regulator T-cells can be targeted through different ligands and strategies to modulate the tumor activity and reduce tumor progression [104].

5.1. Tumor-Associated Macrophages (TAMs)

Traditionally, activated macrophages of different phenotypes have commonly been categorized as M1 and M2 macrophages. M1 macrophages are activated through the classical pathway and are involved in proinflammatory response, while M2 macrophages are alternatively activated and associated with anti-inflammatory action. At first, macrophages polarize to M1 to assist the host immune response against an antigen, then they attain M2 phenotype to repair the damaged tissues. Macrophages linked with tumors are known as TAMs and are classified into two phenotypes—M1 and M2 (M1 type TAMs suppress cancer progression, while M2 type TAMs promote it). TAMs are characterized by increased M2/M1 ratio and play a crucial role in tumor progression, metastasis, matrix remodeling, angiogenesis and tumor resistance [105,106]. TAMs produce cytokines, growth factors like epithelial growth factor, matrix metalloproteinase-9, angiopoietin, etc. to assist tumor development. Therefore, TAM targeting can bring benefits to treat lung cancer. TAMs can be targeted through different ways including the repolarization of M2 into M1 cells, the prevention of macrophage recruitment into the tumor or the direct termination of M2 cells [104]. Moreover, several receptors such as C-type lectin, CD44, FRs have been expressed on the surface of TAMs, which can be specifically targeted for tumor eradication [107–109]. C-type lectin receptors are Ca^{2+} dependent carbohydrate recognition proteins and have multiple types including mannose receptor, macrophage galactose-type lectin-C and dectin receptor. Hence, different carbohydrate moieties are used to target C-type lectin receptors like mannose, glucose, D-galactose, N-acetyl-D-glucosamine (NAG) and maltose [110]. Recently, various mannose receptor targeting strategies involving mannose anchored liposomes, solid lipid nanoparticles, polymeric nanocarriers, niosomes, dendrimers and quantum dots have been fabricated to modulate macrophage function in the tumor [110]. In this quest, biotin and mannose conjugated lipid-coated calcium zoledronate nanocarriers have shown higher internalization in both TAMs and cancer cells, restraining tumor growth, progression and angiogenesis [111].

5.2. Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are the heterogeneous immature population of cells, comprised of myeloid progenitor cells, immature macrophages, immature dendritic cells and immature granulocytes [112]. MDSCs release immunosuppressive cytokines to retard immune system action against the tumor and thereby facilitating the tumor progression [113]. Thus, MDSCs are

the major target cells in cancer immunotherapy. Several strategies have been designed to suppress MDSCs function in lung cancer including:

(a) Differentiation of MDSCs into mature myeloid cells [113];
(b) Suppression of MDSCs amplification through inhibition of stem cell function [114], VEGF [115] or STAT3 pathway [116];
(c) Direct elimination of MDSCs by antibodies or chemotherapeutic drugs like gemcitabine [117];
(d) Attenuating MDSCs functioning [118];
(e) Inhibition of the immune checkpoint to restore the antitumor immune response [119].

Nowadays, nanocarriers employing different options to target MDSCs, promote MDSCs maturation and modulate their function to regress tumor progression and angiogenesis [120]. Furthermore, MDSCs cell membrane coated iron oxide magnetic nanoparticles successfully evaded the immune system, actively targeted cancer cells along with magnetic and photothermal-induced ablation of the cancer cells [121].

5.3. Regulators T-Cells

Infiltrated regulatory T-cells in the tumors have downregulated the activation and response of cytotoxic T-cells against lung cancer [122,123]. Regulatory T-cells play an integral role in tumor development; thus, they could be targeted to suppress the tumor. For instance, glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR) ligand was linked to PLGA nanoparticles for active targeting of regulator T-cells. The complex nanosystem, together with photothermal and photodynamic therapy, has remarkably reduced the tumor growth and recurrence [124,125].

6. Delivery Routes of Nanoparticles in Targeting Lung Cancer

The delivery of nanomedicines to the lungs increases the sustained local drug concentration to treat lung cancer [32]. Most chemotherapeutics act on normal tissues due to their nontargeting nature, leading to adverse effects [126]. Therefore, targeted drug delivery requires a low dose, which results in fewer systemic side effects. Although drugs can be administered through oral, intravenous or inhalational routes, the research on oral drug delivery to lungs has not shown promising results, as only a limited amount of the drug molecules are delivered to the lung tumors [127]. Additionally, the majority of the anticancer formulations are used as intravenous dosage forms. However, as most of the chemotherapeutic agents for lung cancer treatment are hydrophobic in nature, high doses and/or surface modification are needed to improve their systemic bioavailability [128]. On the other hand, the inhalational route is the most attractive option due to lower side effects and high biodistribution [129]. A safe and effective mean of lung cancer theranostics are the chemotherapeutic agents formulated by nanotechnology-based carriers, which are a novel targeted drug delivery "inhalational nanomedicine" that can be administered through the inhalational route [130]. In this context, the easiest way of drug delivery is inhalation by aerosols to target the cancerous tissues of the lung. The differential accumulation of drug particles or aerosol droplets in different regions of the lungs depends on their sizes. Drugs can be formulated as solutes or particles in aerosol droplets of appropriate size and used in drug delivery [131].

Okamoto et al. formulated gene powders with chitosan as a nonviral vector and mannitol as a dry powder carrier to compare their gene expression and therapeutic adequacy to intravenous or intratracheal gene solutions in mice having pulmonary metastasis prepared by injecting CT26 cells. In both normal and tumorous tissues, the genes expressed by intratracheal powder were higher than the one expressed by intravenous or intratracheal solutions, indicating that therapeutic gene powders are efficient for lung cancer treatment [132]. In another study, Dames et al. revealed that the targeted delivery of aerosols to the affected lung tissue might improve therapeutic efficiency and reduce undesired side effects. The authors showed theoretically that targeted aerosol delivery with superparamagnetic iron oxide nanoparticles along with a target-directed magnetic

gradient field can be achieved to treat localized lung disease [133]. Ngwa et al. examine the potential of nanoparticle drones (smart nanomaterials) in targeting lung cancer. They compared and assessed inhalation (air) versus the traditional intravenous routes of navigating physiological barriers using such drones. They concluded that the inhalation route might be more promising for targeting tumor cells with radiosensitizers and cannabinoids in terms of maximizing the damage to lung tumor cells while minimizing any collateral damage or side effects [134].

7. Surface Modification of Nanoparticles to Combat Toxicity in Lungs Cancer

One of the challenging factors in the delivery of drugs to the lungs is to understand the interactions of the nanoparticles with the biological systems. The chemotherapeutic agents in the form of NDDSs are cell nonspecific, resulting in the undesired attack of healthy cells (an important factor in the failure of conventional nanotechnology cancer therapy). This is the reason why still further advancements need to be carried out in the field of NDDSs. The fast clearance of nanoparticles decreases the efficiency of sustained drug delivery and their translocation might bring nanoparticles to undesired areas of the body causing toxicity. Due to the complex nature of nanoparticles, research studies have led to different views of the nanomaterials' safety [135,136]. The physical properties of nanoparticles, such as morphology, geometry, dimensions and surface charge, have been found to change their therapeutic effect. Rod-shaped particles are more toxic than spherical particles. Long fibers cause inflammation because they are less likely to be engulfed by macrophages, thus minimizing their elimination from the system [136]. Nanoparticles produce pulmonary toxicity by oxidative stress because of the production of reactive oxygen species within the biological system [137]. It is evident from a research study that cytotoxicity occurs due to the production of free radicals after exposure to 3.5 to 23.3 μg/mL cerium oxide (CeO_2) nanoparticles. It causes oxidative stress in the cells by reducing glutathione and α-tocopherol levels and elevating the production of malondialdehyde and lactate dehydrogenase, which are indicators of lipid peroxidation and cell membrane damage, respectively [138]. The accumulation of nanoparticles in the tissue due to slow clearance produces potential free radicals as well as the prevalence of numerous phagocytic cells in the organs of the reticuloendothelial system (RES) making the lungs the main targets of oxidative stress [139].

According to a research study, 15 nm and 46 nm silicon dioxide (SiO_2) nanoparticles significantly reduced cell viability in a dose-dependent and time-dependent manner in bronchoalveolar carcinoma-derived cells at 10–100 μg/mL dosage. Both types of SiO_2 nanoparticles have higher cytotoxicity than the positive control material (Min-U-Sil 5). The reactive oxygen species (ROS) generated by exposure to 15 nm SiO_2 nanoparticles produces oxidative stress in these cells as reflected by reduced glutathione levels and the elevated production of malondialdehyde and lactate dehydrogenase, indicative of lipid peroxidation and membrane damage [140].

Surface functionalized nanoparticles have received tremendous importance as drug carriers. The physicochemical or biological properties of the nanoparticles can be altered by modifying their surfaces with different functional groups through covalent or non-covalent bonding, such as the adsorption of biologically active molecules (i.e., proteins, surfactants, enzymes, antibodies or nucleic acids) [141]. Nanoparticles functionalized with biodegradable polymers could be evaluated as the best chemotherapeutic delivery system. The surface chemistry of these nanoparticles must be carefully controlled as it is the shell of the nanoparticles that is in contact with body organs and fluids. As an example, nanoparticles have been coated with hydrophilic polymers or functionalized with ligands or proteins to enhance their circulation time or to achieve site specific delivery, respectively [142]. In another example, it was shown that the coating of nanoparticles with polymers could reduce their toxicity by changing their half-life distribution, disposition, stimuli reactivity and therapeutic application [30]. The oily nature of the nanocapsule's core can accommodate high loadings of lipophilic anticancer drugs [143]. Moreover, magnetic

nanoparticles functionalized with polymers, monoclonal antibodies, peptides, heparin, hormones or other biologics are very effective and highly specific for cell biology and cancer therapeutic applications [144]. Surface modification of the NDDSs allows the targeted delivery of therapeutic agent such as antibodies and ligands (i.e., TF, FA, lactoferrins, lectins and mannose derivatives) into the tumors [135]. Additionally, surface PEGylation (the process by which polyethylene glycol chains are attached to biological molecules) does not only enhance the colloidal stability of nanoparticles but also increases their accumulation at the tumor site and decreases opsonization [145]. It was shown that surface-modified nanoparticles with 1, 2 dipalmitoylphosphatidylcholine (DPPC) are less prone to phagocytosis. The presence of phospholipids inhibits the adsorption of opsonic proteins on the inhaled nanoparticles, allowing them to escape phagocytosis [146]. In one research study, multiwalled carbon nanotubes (MWCNTs) were functionalized with amine-terminated poly (amidoamine) (PAMAM) dendrimers modified with fluorescein isothiocyanate (FI) and FA. This modified system acted as both a drug targeted system and a pH-responsive system for delivering DOX into cancerous cells [147]. Meenach et al. used an advanced organic spray-drying method to manufacture inhalable lung surfactant-based carriers comprising synthetic phospholipids, DPPC and dipalmitoylphosphatidylglycerol (DPPG), loaded with PTX, for targeted pulmonary delivery as high-performing nanoparticulate dry powder inhalers [148]. Li et al. suggested that a tumor-targeted PEGylated LPD formulation (liposome-polycation-DNA complex) enhanced cellular uptake by specific receptor-mediated pathways. They showed that the targeted drug delivery system caused a strong gene-silencing mediated by RNAi through delivering siRNA to the tumor cells after intravenous administration [149,150]. Grabowski et al. described the cytotoxicity and inflammatory action of nanoparticles made of PLGA through in vitro analysis on A549 human lung epithelial cells. Three different neutral, positively or negatively charged PLGA nanoparticles (230 nm) were obtained by using different types of stabilizers (polyvinyl alcohol, chitosan, or Pluronic® F68). For comparison, polystyrene nanoparticles were used as nonbiodegradable polymeric nanoparticles and titanium dioxide (anatase and rutile) as inorganic nanoparticles. As the result, the PLGA-based and polystyrene nanoparticles were less toxic than or equally toxic to titanium dioxide nanoparticles. On the contrary, the inflammatory response measured by the release of interleukin 6 (IL-6), IL-8, monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor α (TNF-α) cytokines was low for all nanoparticles [151]. The PLGA-based nanoparticles led to a higher inflammatory response, which was correlated with a higher uptake of these nanoparticles. The authors claimed that both the coating of the PLGA nanoparticles and the nature of the core play a key role in the cell response.

8. Comparison between Surface-Modified Nanoparticles with Other Targeting Methods in Lung Cancer Treatment

There are many ongoing contributions of nanoparticles in the field of targeting lung cancer. However, there are a few limitations that inhibit amplifying their applications, including low stability, greater immunogenicity, nonuniform distribution, increased rate of clearance, poor ability in encapsulating imaging and targeting agents and unspecified internalization (via passive delivery method) at the malignant site. The morphology of the lung itself is a big barrier for the optimal transformation of agents into it. Therefore, it is important to design nanoparticulate systems that could reduce these complications. The functionalized nanoparticles can be used as powerful theranostic tools to enhance the delivery of drugs to the malignant site [34]. Many studies have been carried out comparing the performance of functionalized and nonfunctionalized nanoparticles in lung cancer targeting. For example, Chung et al. developed and compared the PLGA nanoparticles ligated with heparin, chitosan and pluronic with nonconjugated PLGA nanoparticles. The viability tests for both normal and tumor cells showed the less cytotoxic effect of the nanoparticles. The in vitro cellular uptake of the nanoparticles for both chitosan and heparin functionalization showed the desired effects. The in vivo tumor model study exhibited that there was a positive but insufficient effect of chitosan decorated nanoparticles,

although it showed enhanced accumulation that was almost 2.4-fold higher than that of the control nanoparticles. The results concluded that the surface functionalization of the PLGA nanoparticles with chitosan and heparin may be an efficient strategy for the enhanced tumor theranostics [152]. Patil et al. performed a study with the aim of achieving targeted delivery through the single-step surface functionalization of nanoparticles with a tissue recognition ligand. They used biotin and a folic acid ligand to functionalize the PLA-PEG nanoparticles. The surface modification was confirmed through NMR, transmission electron microscopy and tumor cell uptake study. In comparison to the bare nanoparticles, the functionalized nanoparticles showed more precise and efficient results with greater binding affinity at the delivery site. The in vivo study result of the surface-modified PTX-loaded PLA-PEG nanoparticles showed an enhanced efficacy in comparison to the nonmodified nanoparticles [153]. The same authors in another study developed biotin functionalized PLGA nanoparticles encapsulating a combination of PTX and P-glycoprotein (P-gp) inhibitor tariquidar to overcome tumor drug resistance. The dual agent nanoparticles showed higher cell inhibition in the cell line study in comparison to only PTX-loaded ones. Additionally, performing in vivo studies in a mouse model, these nanoparticles demonstrated considerably enhanced inhibition of tumor growth. The authors concluded that these dual agent nanoparticles could be applied as an efficient system to overcome tumor drug resistance [154]. In another report, Xia et al. developed DOX-loaded selenium (Se) nanoparticles and functionalized them with cyclic peptide (Arg–Gly–Asp–$_{D}$-Phe–Cys [RGDfC]) to fabricate tumor targeting delivery. The aim of the study was to improve the antitumor efficacy of DOX in NSCLC. This nanodrug carrier displayed an efficient cellular uptake in A549 cells and entered the A549 cells mainly by clathrin-mediated endocytosis. Interestingly, comparing active targeting with the passive targeting delivery system, the authors concluded that the RGDfC functionalized DOX-loaded Se nanoparticles provide a promising approach for lung carcinoma therapy [155]. Perepelyuk et al. studied the therapeutic efficacy and in vivo efficacy of mucin1-aptamer-modified miRNA-29-loaded hybrid nanoparticles in a lung tumor model. The results displayed that the presence of MUC1-aptamer conjugates increase the delivery of miRNA-29b to the tumor cells. Moreover, the downregulation of DNMT3B by MAFMILHNs resulted in the inhibition of tumor growth in a mouse model [156]. Table 2 presents a summary of the recent studies on comparison between surface-modified and unmodified nanoparticles in lung cancer treatment.

Table 2. Summary of the recent studies on comparison between surface-modified and unmodified nanoparticles in lung cancer treatment.

Nanodrug Carrier Type	Encapsulated Drug	Ligand/Targeting Moiety	Outcomes	Reference
Cationic lipid nanosystems (CLNs)	Curcumin	Surface charged particle	Greater bioavailability pharmacokinetics inhibitory effect on cell growth and invasion, enhanced apoptosis in LL/2 cells, increased antitumor effect of curcumin loaded, CLNs in C57BL/6 J mice compared with control, reduced tumor volume and growth	[157]
Solid lipid nanoparticles (SLNPs)	Gemcitabine	Mannose	Reduced hemolysis due to the presence of cationic ammonium on the surface of SLNs, significant toxicity on A549 cells in vitro, greater uptake into A549 cells by receptor mediated endocytosis, enhanced concentration in lungs in in vivo studies	[158]

Table 2. *Cont.*

Nanodrug Carrier Type	Encapsulated Drug	Ligand/Targeting Moiety	Outcomes	Reference
Cationic liposomes	Vinblastine	Peptide nucleic acid (PNA)	Greater internalization of targeted liposome into LL/2 cells in vitro, inducing apoptosis in LL/2 cells, greater antitumor efficacy of PNA-modified vinblastine cationic liposome in tumor-bearing mice, increased survival rate of animals treated with PNA-modified liposomes	[159]
Polylactic acid (PLA)	Gemcitabine	Cetuximab	Greater uptake into A549 cells via EGFR mediated endocytosis, enhanced antiproliferative activity of targeted nanoparticles against lung cancer cells compared with nonmodified nanoparticles	[160]
Cationic liposome	Erlotinib/oxygen	Anti-EFGR aptamer	Greater cellular uptake, greater erlotinib resistance in vitro, inhibiting the tumor growth in xenograft model, accumulation of targeted liposomes at the site of tumor compared with other organs	[161]
Albumin self-assembly	Doxorubicin/ TRAIL protein	Not applicable (N/A)	Enhanced antiproliferative activity of doxorubicin and TRAIL protein on lung cancer (H226) cells, significant antitumor efficacy in BALB/c nu/nu mice having H226 cell induced tumor.	[162]
Multiwalled carbon nanotube (MWCNT)	Docetaxel/ curcumine-6	Transferrin	Greater uptake of targeted MWNT into A549 cells, cell cycle arrest in phase (sub-G1),significantly reduced lung toxicity of targeted MWNT.	[163]
pH sensitive liposomes	Afatinib	N/A	Enhanced stability of CL and PSL, induction of apoptosis in H-1975 cells	[164]
Silk fibroin	Gemcitabine	SP5–52 peptide	Increased potential in LL/2 cells targeting in both in vitro and in vivo studies, enhanced reduction in proliferation of tumor cells, greater accumulation of targeted nanoparticles at the site	[165]
Silica	10-Anthraquinone-2-carboxylic Acid (OCAq)/rose bengal (RB)	N/A	Enhanced efficacy of silica nanoparticles conjugated with dyes for photodynamic therapy, two folds phototoxicity on A549 cells by generating oxygen radicals	[166]
Thermally crosslinked supermagnetic iron oxide (TCL-SPION)	Cyanine/ Doxurubicin	N/A	Greater fluorescent intensity of TCL-SPION at tumor site compared to other tissues, greater accumulation of DOX encapsulated TCL-SPION at the tumor site.	[167]
Gold nanoparticles	N/A	N/A	For diagnosis of lung cancer by analyzing the volatile organic compounds in cancer patients	[168]
Polyamidoamine dendrimer	Cis-diamine platinum	Folate/HuR siRNA	Greater antiproliferative effect on H1299 cells by codelivery of anticancer drug and siRNA, enhanced toxicity of targeted formulation in comparison to nontargeted at tumor site	[169]

9. Different Types and Applications of Surface-Modified and Hybrid Nanoparticles for Targeting Lung Cancer

Nanoparticles are included in the drug delivery systems to overcome certain issues such as low solubility and permeability related to tumor targeting. The most significant advantages of nanoparticles are their excellent loading capacity and high surface to volume ratios. Various organic and inorganic nanomaterials have emerged as novel tools for cancer diagnosis and therapy due to their unique characteristics. In this review, based on the main structural moiety of nanoparticle we broadly divide them into three types: organic nanoparticles, inorganic nanoparticles and hybrid nanoparticles. The combinatorial therapeutic approach via hybrid nanoparticles is discussed in a separate subsection too.

9.1. Organic Nanoparticles

Organic nanoparticles can be defined as solid particles composed of organic compounds (mainly polymers, lipids or proteins). They have been widely studied for decades, presenting a large variety of materials and exciting applications in cancer therapies. There are many biopolymeric nanoparticles that are utilized in the drug delivery systems. For example, PLGA is a biodegradable copolymer approved by the US Food and Drug Administration (FDA) for use in distinct biological products. PLGA nanoparticles can be used to obtain extended and sustained delivery of therapeutic agents including protein, peptide, RNA, DNA and small molecules to their particular target sites [170,171]. As an example, Karra et al. developed cetuximab functionalized PLGA nanoparticles and loaded them with PTX. The results confirmed the in vitro targeting performance and enhanced the cellular internalization along with cytotoxicity of this targeted delivery system in lung cancer cells overexpressing EGFR. The intravenous administration of the nanoparticles to mice results in the considerable inhibition of tumor growth and the reduction of mortality rates. Pharmacokinetics studies results showed no increase in the aggregation of nanoparticles at the tumor tissue site. The authors concluded the promising potential of this system for enhanced efficacy against lung cancer [172]. In another report, Patil et al. compared YSA peptide functionalized and nonfunctionalized PLGA nanoparticles to improve delivery to bleomycin treated cultured endothelial cells in a bleomycin induced lung injury mouse model. When human umbilical vein endothelial cells (HUVEC) were treated with bleomycin, the 3 h uptake of both types of nanoparticles was increased up to 2-fold. The results showed that in mice the bleomycin injury led to 2.3 and 4.7 times increases in the lung concentrations of the nonfunctionalized and YSA-functionalized nanoparticles, respectively. The authors stated that PLGA nanoparticle delivery to cultured vascular endothelial cells and mouse lungs in vivo was higher directly after bleomycin treatment, with the delivery likely to be higher for YSA-functionalized nanoparticles [173].

Single chain technology is a new term developed in nanotechnology in order to broaden the functions of soft nano-objects through chain compaction. Using single chain technology, individual copolymer chains of different natures, compositions and molar masses have been folded intramolecularly to develop single chain nanoparticles (SCNPs). This leads to very small size polymer nanoparticles in the sub-20 nm size [174,175]. The folding is achieved by the self-assembly or crosslinking of functional groups on the precursor polymer, or rather moderated by the external cross-linker. There are several ways to develop SCNPs including dynamic and irreversible covalent crosslinking reactions such as cycloaddition. Moreover, there are huge number of SCNPs that have been introduced, from single and multiblock to star particles, hairpins and tadpole molecules. There are only a few examples present where a functionalized group has been incorporated into SCPNs [176]. However, these functionalized SCNPs still have not been used for lung cancer targeting. In this context, an insight was given by Benito et al. who evaluated the use of SCPNs based on poly(methacrylic acid) in targeting pancreatic adenocarcinoma. They functionalized SCPNs with somatostatin analogue PTR86 as a targeting moiety since these somatostatin receptors are overexpressed in pancreatic cancer. The imaging results showed a higher accumulation of targeted SCPNs in the tumor compared to the nontargeted nanoparticles,

which was due to the enhanced retention in the tissues [177]. Later, Kröger et al. also reported the greater potential of these types of nanoparticles for cellular targeting [178,179].

Dendrimers are another class of polymers that are constructed by the stepwise addition of layers (generations) of molecules around a central core. This unique physicochemical properties of dendrimers enable a facile utilization of them as templates to funcionalize nanoparticles [180]. In this regard, a group of researchers reported greater penetration and higher stability of siRNA by implementation of surface-modified poly(propyleneimine) dendrimers. The siRNA nanoparticles were coated by a dithiol bearing cross linker that followed by a layer of PEG. In addition, a synthetic derivative of LHRH was linked at the end of the PEG polymer to conduct siRNA nanoparticles to the cancer cell. The developed system showed time- and concentration-dependent cellular uptake under in vitro conditions. It was proposed by the authors that this approach could be used for the in vivo systemic delivery of siRNA for efficient cancer therapy [181].

Solid lipid nanoparticles or lipid nanoparticles are nanoparticles composed of lipids as a matrix which are exceptionally biodegradable and biocompatible. They possess superior properties such as high drug payload, increased drug stability, large scale production and sterilization [182]. For instance, in one study Pooja et al. developed and evaluated TF conjugated and etoposide loaded solid lipid nanoparticles. The tissue distribution and pharmacokinetics were studied in Balb/c mice. The nanoparticles showed great anticancer activity of etoposide via antiproliferative assay and induced apoptosis in A549 cells. It was concluded that over expressed TF-receptors showed enhanced efficacy in NSCLC [183]. Liposomes are similar in design to lipid nanoparticles, but slightly different in composition and function. Riaz et al. developed the TF-7 surface functionalized liposomes loaded with quercetin (QR) for lung cancer therapy. These liposomes were evaluated for cellular uptake and in vitro cytotoxicity study and they exhibited higher cytotoxicity and S-phase cell cycle arrest. The in vivo study showed enhanced liposomes accumulation in the lungs and sustained release up to 96 h [184].

Considering that albumin has remarkable roles in human body, it can be used in the area of medicine and disease treatment. As an example, Yang et al. used hematoporphyrin (HP) functionalized albumin nanoparticles for cancer therapy. These nanoparticles further modified with gamma emitting nuclides (^{99m}Tc). HP-albumin nanoparticles showed improved accumulation in A549 and CT-26 cancer cell lines. The evaluation of the pharmacokinetics of ^{99m}Tc chelated HP-albumin nanoparticles via the scintigraphic imaging of rabbits resulted in acceptable imaging properties in the rabbit with a longer biological half-life compared to ^{99m}Tc-HP. The authors concluded these modified albumin nanoparticles could be applied as a diagnostic tool for cancer as well as the obvious application for photodynamic therapy [185].

9.2. Inorganic Nanoparticles

Inorganic nanoparticles including gold, silver, iron oxide and silica nanoparticles have been widely studied as therapeutic agents for cancer treatments in biomedical fields [186]. Among them, gold nanoparticles are attractive constituents for nanoparticle polymer hybrid materials as they support localized surface plasmon resonances, and the wavelength region of the surface plasmon resonance peak can be adjusted finely through the geometric parameters of the particles [187,188]. In one study, Heo et al. developed the gold nanoparticles surface-functionalized with PEG, biotin and rhodamine B and linked beta-cyclodextrin (β-CD). The specific interactions of these nanoparticles with cancer cells such as HeLa, A549 and MG63, as well as normal NIH3T3 cells, were evaluated. The authors observed that the modified nanoparticles were more effectively involved with the cancer cells. Confocal laser scanning microscopy (CLSM), fluorescence-activated cell-sorting (FACS) and cell viability analyses showed that the surface functionalized nanoparticles played a significant role in the diagnosis and treatment of the cancer cells, and could be used in theranostic agents [189]. Guo et al. developed a multifunctional nanocarrier encapsulated with methotrexate via electrostatic interaction between gold nanocluster conjugate chitosan and

nucleolin targeting aptamer (AS1411). The in vivo study demonstrated that intravenous administration of nanodrug carrier systems into BALB/c mice caused the accumulation of methotrexate at the tumor site. The results suggested that the developed functionalized system can be applied for an effective delivery for anticancer agents and shows enhanced potential in clinical applications [190]. João Conde et al. fabricated the gold nanoparticles conjugated with siRNA/RGD and studied in a lung cancer murine model. The RGD treatment showed a significant downregulation followed by tumor growth inhibition and the increased survival of the tumor bearing transgenic mice. The results demonstrated that RGD gold nanoparticles stimulate the delivery by intratracheal application in mice that leads to the suppression of tumor cell proliferation. The enhanced targeted delivery of gold nanoparticles encapsulated with siRNA to cancer cells works towards effective silencing of the oncogene. The study showed gold nanoparticles stimulated the inflammatory and immune responses that can promote the therapeutic effect of the siRNA to reduce the tumor size at very low doses [191]. The schematic illustration of this study is described in Figure 3, which shows the enhanced efficacy of siRNA loaded into functionalized nanoparticles.

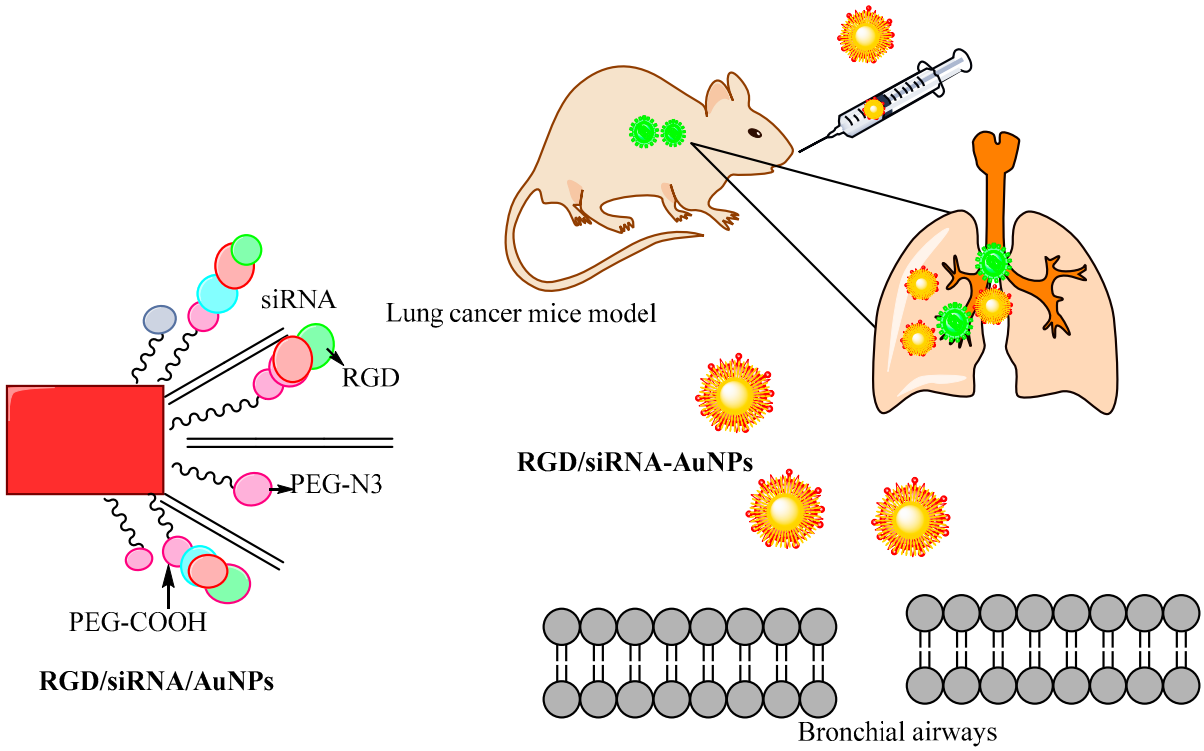

Figure 3. Inflammatory response and therapeutic siRNA silencing via RGD nanoparticles in a lung cancer mouse model.

Applications of silica or silicon dioxide (SiO_2) as another inorganic nanoparticle are broadly investigated in drug delivery. For example, Munaweera et al. prepared cisplatin and cisplatin/nitricoxide-loaded amine functionalized mesoporous silica nanoparticles for the treatment of lung cancer. The results demonstrated that for nonsmall lung cancer cell lines (i.e., H596 and A549), the toxicity of cisplatin/nitric oxide-loaded silica nanoparticles was higher than that of silica nanoparticles loaded with only cisplatin. The nitric oxide-activated sensitization of the tumor cell death, which showed that nitric oxide is a potential enhancer of platinum-based lung cancer therapy [192]. Another type of inorganic nanoparticles with biomedical applications is zirconium oxide (ZrO_2). In one study, ZrO_2 nanoparticles were coated with aminopropilsilane, tetraoxidecanoic acid or acrylic acid. The studied results showed dose-dependent signs of effectiveness. It was concluded that surface modifications of the ZrO_2 nanoparticles had very small effects on the inflammatory lungs of rats and mice but it had very clear efficacy in the allergic mouse

model used. The results stated that the allergic mice are more responsive to exposure to surface-modified nanoparticles [193]. The unique properties of molybdenum disulfide (MoS_2) make it an attractive candidate for drug delivery applications [194]. In their study, Wei Zhang et al. developed the riboflavin 5′-monophosphate sodium salt functionalized 2D MoS_2 nanosheets prepared by the simple ultrasonication method, then they applied this nanocomposite having fine electrochemical redox activity as a platform to immobilize DNA probe. The results showed that the signal detection platform showed greater sensitivity with the limit of detection of 1.2×10^{-17} mol L^{-1} for PIK3CA gene from lung malignancy. The constructed biosensor was easy to achieve and could detect different pathogenic DNA without an intricate label process [195].

Magnetic nanoparticles can produce heat under the magnetic field and can also deliver drugs to the lung cancer site [196,197]. Among them, iron oxide nanoparticles are widely studied systems for biomedical applications [198,199]. In their study, Huang et al. reported the synergy effect of superparamagnetic iron oxide nanoparticles along with an anticancer drug (β-lapachone) for improved cancer therapy. The authors suggested that combination of superparamagnetic iron oxide nanoparticles with reactive oxygen species-producing drugs could conceivably enhance drug efficiency, thus presenting a synergistic strategy to integrate imaging and therapeutic functions in the discovery of theranostic nanomedicine [200]. In another study, dextran coated iron oxide nanoparticles were modified with the TAT peptide and they were used to improve the efficiency of the radiation. After performing the internalization study, it was revealed that TAT functionalized nanoparticles enhanced the generation of the reactive oxygen species in comparison to the nanoparticles without any surface modifications. These modified nanoparticles also affected the mitochondrial integrity of A549 cells in combination with the radiation, which resulted in a synergistic decrease in cell viability [201,202].

9.3. Hybrid Nanoparticles

In order to enhance the efficacy of the therapeutic regimen in lung cancer, it is necessary to develop new systems that can increase the survival rates. The development of hybrid nanoparticles (that could comprise both inorganic and organic structural moieties) in conjugation with other genes, biomolecules and other drugs are promising therapeutics systems for efficient targeting [203]. These types of nanoparticles are important for targeting the tumor site, for its early diagnosis and to measure the risk of malignancy in neighboring cells. These hybrid types are classified into diagnostics, therapeutic and theranostic nanoparticles. Figure 4 graphically shows the different types of hybrid nanoparticles that have been applied for lung cancer targeting.

In this regard, Sacko et al. studied anticancer effect of a combination therapy of miRNA-29b and genistein loaded in mucin-1 (MUC 1)-aptamer functionalized hybrid nanoparticles in NSCLC A549 cell line. This nanodrug carrier displayed a superior antiproliferative effect compared to individual genistein and miRNA-29b-loaded nanoparticles, thus, it can be considered a potential treatment modality for A549 cell line [204]. The same research group studied the pharmacokinetic response of novel antineurotensin receptor 1 monoclonal antibody (anti-NTSR1-mAb)-functionalized antimutant K-*ras* siRNA-loaded hybrid nanoparticles and compared it with that of naked siRNA formulation. As with the main findings, the plasma terminal half-life of the siRNA-loaded nanoparticle-delivered was 11 times higher than that of the naked siRNA formulation. In addition, high performance liquid chromatography (HPLC) analysis showed that the hybrid carrier system could protect the encapsulated siRNA against degradation in systemic circulation. The authors concluded that these hybrid nanoparticles can function as an effective nonviral vector for siRNA delivery for both experimental and clinical uses [205].

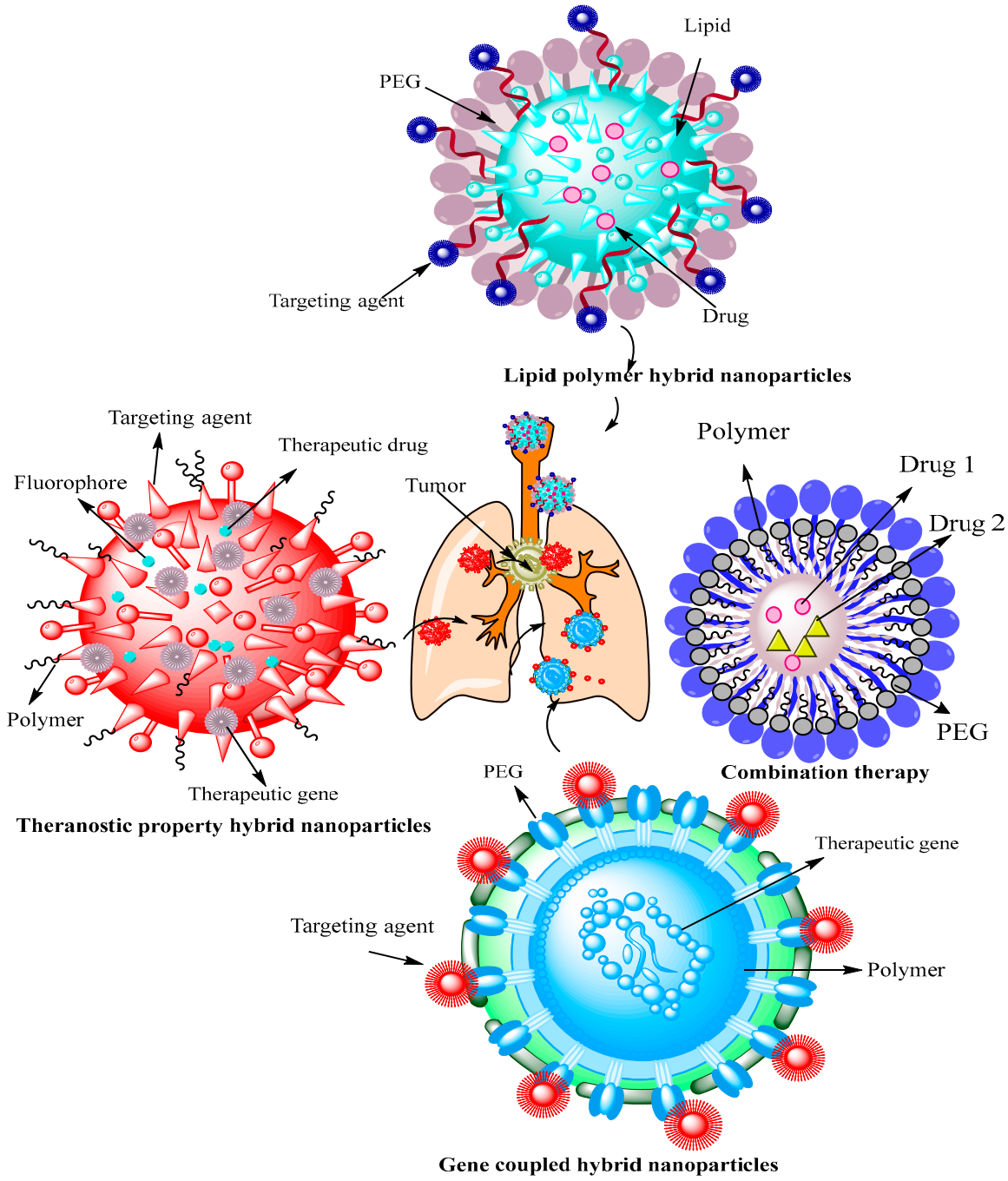

Figure 4. Schematic representations of different types of hybrid nanoparticles used for lung cancer targeting (i.e., theranostic hybrid nanoparticles, gene hybrid nanoparticles, combination therapy of hybrid nanoparticles and lipid polymer hybrid nanoparticles).

In another study, EGFR-targeted superaparamagnetic iron oxide nanoparticles (SPIONs) were conjugated to carboxy-terminated pluronic F127. The authors investigated the inhalation delivery of these nanoparticles as a potential approach for lung cancer treatment. As in the main findings, EGFR targeting enhanced tumor retention of SPIONs while minimizing systemic exposure. Additionally, magnetic hyperthermia using these nanoparticles resulted in a significant inhibition of in vivo tumor growth [206].

Another type of hybrid delivery system are lipid polymer nanoparticles or core shell lipid polymer nanoparticles, which combine the good biodegradability of polymeric nanoparticles with the excellent biomimetic characteristics of liposomes, and they are

effective carrier systems for the delivery of anticancer drugs into the tumor site [207]. In this context, Bivash Mandal et al. showed that a hybrid system containing biodegradable polycaprolactone (as the core) and phospholipid-shell was able to deliver erlotinib into the lung cancer cells. Performing cell viability studies by this erlotinib-loaded hybrid system, a significant decrease in proliferation of A549 cells was observed, which affords this system a potential application to deliver erlotinib into lung cancer cells [208]. A similar study was carried out by Song et al. in which they showed the enhanced properties of EGFR-targeted lipid polymer hybrid nanoparticles in the codelivery of resveratrol and DTX. They developed this nanocarrier system by the conjugation of EGF and target the EGFR on the surface of the lung cancer cells in order to increase the endocytosis. Resveratrol (as an antioxidant) improved the production of reactive oxygen species through inducing cytotoxicity. The results exhibited the enhanced antitumor efficacy of resveratrol and DTX in both in vitro and in vivo studies [209]. Another related study reports the synthesis and characterization of lipid-coated poly D,L-lactic-co-glycolic acid nanoparticles that were modified with TF to deliver the DOX into A549 cells. These DOX-loaded hybrid nanoparticles exhibited higher cytotoxicity against lung cancer cells and showed an improved therapeutic effect in the lung cancer-bearing nude mice in comparison to their nontargeted counterparts. This finding marks this approach as an efficient targeted drug-delivery system for lung cancer therapy [210]. In another study, naturally occurring chitosan and hyaluronic acid were deposited on negatively charged hybrid solid lipid nanoparticles through layer-by-layer (LbL) assembly. Next, this hybrid system was loaded with DOX/dextran sulfate complex with the aim of tumor specific targeting. Employing this approach under in vivo studies, the DOX half-life was increased and its elimination rate was decreased compared to those measured for the uncoated solid lipid nanoparticles [211].

Another interesting type of nanocarriers in cancer therapy are hydrazine-based pH-sensitive nanoparticles. For example, Li et al. designed a dual-ligand lipid based nanoparticle system, in which TF conjugated PEG hydrazone nanoparticles were used for the codelivery of DTX and baicalein into A549 cells. Decorating the lipid nanoparticle with TF could internalize them into the cancer cells. Moreover, this hybrid nanocarrier achieved significant synergistic effects, the best tumor inhibition ability and the lowest systemic toxicity [212]. A recent progression in lung cancer therapy is gene therapy of lung cancer by applying siRNA hybrid nanoparticles [213]. Applying hybrid nanoparticles was useful to carefully transport the siRNA into the cytoplasm and cross the limitations of the traditional gene therapy [214]. For instance, the encapsulation of siRNA in calcium phosphate nanoparticles coated with DOPA (dioleoylphosphatydic acid) could target H460 lung cancer cells [215].

An overview of some other recent studies (that were not mentioned in this section) on developing nanoparticle-based delivery systems as a therapy against lung cancer is presented in Table 3.

Table 3. Summary of some recent studies on design of nanoparticle-based delivery approaches for therapy against lung cancer.

Nanoparticles Type	System Description and the Main Finding	Reference
Silver NPs [1] (AgNPs)	- Poly vinyl pyrrolidone coated AgNPs were used in this study. - After exposure to AgNPs, DNA damage induced by ROS was detected as an increase in bulky DNA adducts by ^{32}P postlabeling and these NPs were suggested as a mediator of ROS-induced genotoxicity.	[216]
Gold NPs (AuNPs)	- Glucose-bound AuNPs combined with radiation, can increase cytotoxicity on A549 cells not only by arresting the G2/M phase, but also by increasing apoptosis.	[217]

Table 3. *Cont.*

Nanoparticles Type	System Description and the Main Finding	Reference
Quantum dot (QD)	- The QD-pulsed dendritic cell vaccine was introduced as a new combination therapy to amplify antitumor immunity. - This combination boosts antigen-specific T-cell immunity and actively inhibits local tumor growth and tumor metastasis in vivo.	[218]
Liposome	- A liposomal curcumin dry powder inhaler for inhalation treatment of primary lung cancer was developed. - This liposomal system showed higher anticancer effects than the other medications regarding pathology and the expression of many cancers.	[219]
Graphene	- Graphene oxide/TiO_2/DOX loaded polymer composites were developed in the forms of nanofibers. - In the presence of magnetic field, these nanofibers showed higher proliferation inhibition effect on target lung cancer cells.	[220]
Carbon nanotubes (CNT)	- PEG-coated CNT nanodrugs were designed that improves the mitochondrial targeting of lung cancer cells. - This system increased the anticancer efficacy by increasing mitochondria accumulation rate of cytosol released anticancer nanodrugs.	[221]
Niosome	- A noisome-based formulation containing gemcitabine and cisplatin was presented for lung cancer treatment. - This system reduced cytotoxicity effects against both MRC5 and A549 comparing to with control (gemcitabine and cisplatin alone) after 72 h of treatment.	[222]
Solid lipid NPs (SLNPs)	- Sclareol-loaded SLNPs was formulated and tested for potential geno-cytotoxicity upon A549 lung cancer cells. - Flow cytometry analyses determined early and late apoptosis in sclareol and sclareol-loaded SLNPs treated cells.	[223]
Hydrogel	- A poloxamer-based thermoresponsive hydrogel was developed to exert local tumor control. - This hydrogel demonstrated a dose-dependent cancer cell-specific toxicity in vitro and was retained in situ for at least 14 days in the xenograft model.	[224]
Iron oxide magnetic NPs	- DOX and cetuximab were co-conjugated to dextran-coated Fe_3O_4 magnetic nanoparticles. - These NPs significantly suppress cell proliferation of A549 cells as compared with A549 cells treated with NPs only conjugated with DOX.	[225]
Nanoemulsion system	- Naringenin nanoemulsions for oral delivery were developed using employing a Box–Behnken design. - These nanoemulsion were more effective than the naringenin solution in reducing Bcl2 expression, while increasing proapoptotic Bax and caspase-3 activity.	[226]

Table 3. *Cont.*

Nanoparticles Type	System Description and the Main Finding	Reference
Porous $Se@SiO_2$ NPs	- Porous $Se@SiO_2$ NPs were fabricated with antioxidant properties. - These NPs significantly increased the resistance of airway epithelial cells under oxidative injury and shifted lipopolysaccharide-induced gene expression profile closer to the untreated controls.	[227]
Metal–organic frameworks (MOFs)	- A hydrolytically stable mesoporous gadolinium -MOF was prepared. - This nanostructure provided lewis basic sites for 5-Fu delivery and inhibition of human lung cancer cells in vivo and in vitro.	[228]

[1] NPs: Nanoparticles.

9.4. Combinatorial Therapeutic Approach via Hybrid Nanoparticles

The encapsulation of different drugs with multiple sites of action is considered to be an efficient method for targeting malignant cells. The application of combinatorial therapeutic approaches will reduce the dose and resistance of the applied anticancer drugs. However, each anticancer drug has a specific biochemical activity; therefore, combined administration would be inappropriate and ineffective in targeting lung cancers. Moreover, combining more drugs can cause harmful effects on healthy organs [229]. Various hybrid combination therapies have been designed for lung cancer targeting. Multifunctional hybrid nanoparticles have gained more recognition as a combinatorial therapeutic approach. For example, in one study an amphiphilic triblock copolymer functionalized with deoxycholate was synthesized and was used as a nanocarrier to codeliver DOX and PTX into lung cancer cells. Each residue of the copolymeric system comprises a unique property for the complex construction. The codelivery of DOX and PTX using hybrid nanovesicles exhibited an enhanced antitumor effect by reducing the growth of the A549 cells in lung cancer [230]. Another study demonstrated the enhanced efficacy of dual drug delivery in lung cancer therapy, in which PLGA/methacrylic acid copolymer nanoparticles were developed for the codelivery of DOX and chrysin. This nanoformulation significantly reduced the proliferation of A549 cells. The loaded agents showed higher antitumor activity under the in vitro cell line study [231]. Based on several studies, it is concluded that the combination therapies using two or more drugs in a single nanoparticle might be more useful for tumor targeting. Hybrid nanoparticle-based combination therapy, including chemotherapy with hyperthermia, can help to reduce the mortality rate in lung cancer patients. Through combining hyperthermia therapy with chemotherapy, upon increasing the temperature of tumor environment up to 40–45 °C, the malignant cells are killed but the healthy cells are not affected [232]. The hybrid magnetic nanoparticles can be used for combination therapy (chemo and hyperthermia) to achieve better antitumor efficacy. In one study, hydroxyapatite nanoparticles encapsulated with cisplatin were developed to target lung cancer by combining chemotherapy with hyperthermia. The results of this study showed a greater uptake of nanoparticles in A549 cells by activation of the (ERK) signaling pathway [233]. Figure 5 presents a schematic graphic design of combination therapy approaches via different types of nanoparticles.

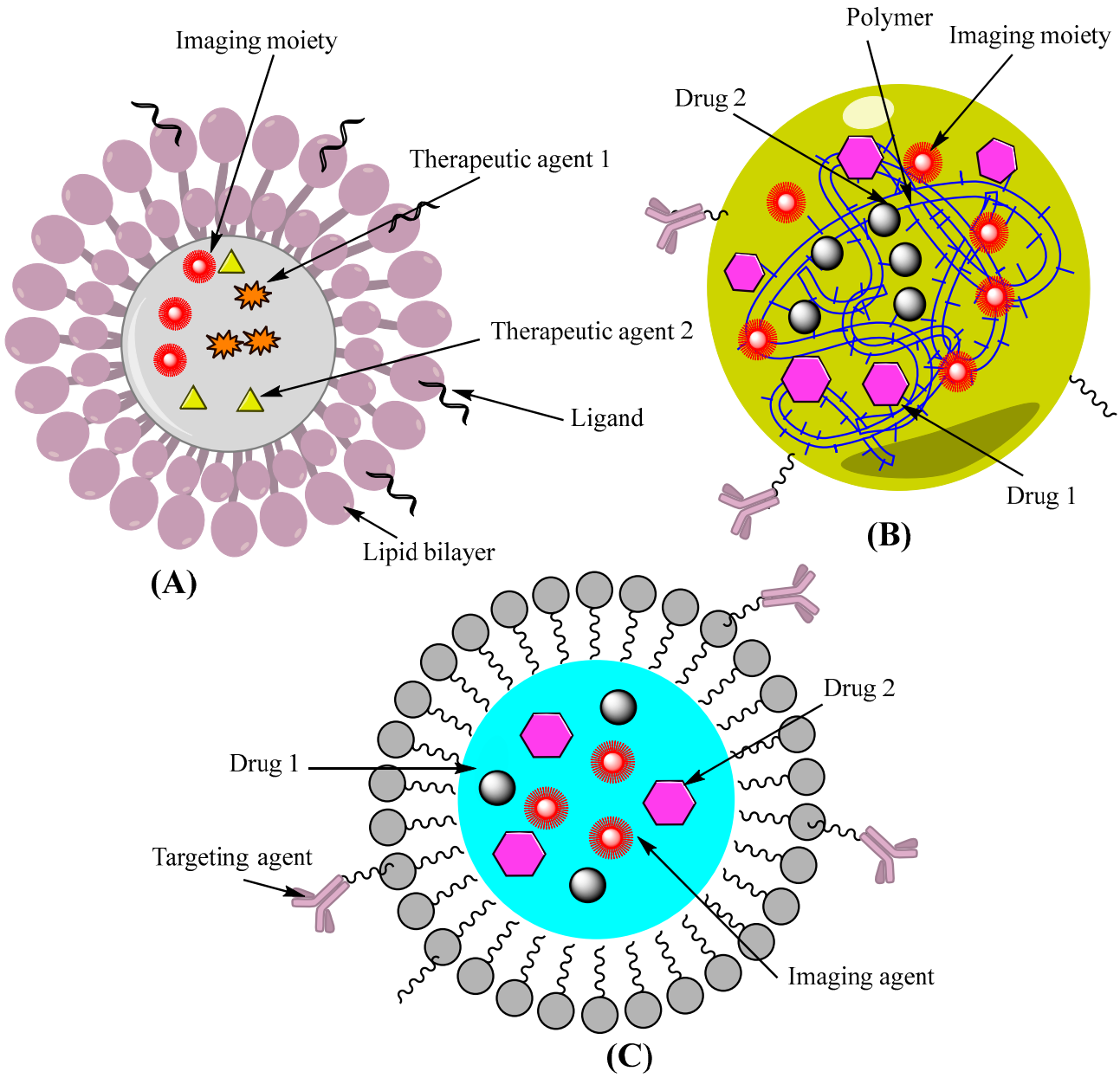

Figure 5. Schematic representation of combination therapy approaches in targeting lung cancer. (**A**) Combination lipid nanoparticles with imaging and therapeutic moiety (**B**) Polymer based nanocapsule hybrid therapy with imaging and targeting moiety along with therapeutic agent (**C**) Inorganic-polymer combination nanoparticle coencapsulated with drug molecule, targeting agent and imaging moiety.

10. Some Clinical Studies and Marketed Formulation of Nanoparticles for Lung Cancer Treatment

The application of nanoparticle-based drug delivery systems for lung cancer treatments is still in the development phase. Nevertheless, there are already some nanoparticle-based drugs in the market and various nanobased therapeutics are being used in clinical studies. Abraxane is the first nanotechnology-based drug for lung cancer therapy that has passed regulatory scrutiny and is already on the market and can be used to treat breast and pancreatic cancer as well. In this formulation, PTX is bonded to albumin nanoparticles as a delivery vehicle [234]. Genexol-PM is another PTX-loaded formulation, which is based on polymeric (PEG-PLA) nanoparticle micelles and has been approved in Europe and South Korea for the treatment of breast cancer and NSCLC [235,236].

In recent years, the US FDA has approbated numerous investigational new drug (IND) applications for nanoformulations, enabling clinical trials for lung cancer. Considering these developments, it seems that nanotechnology could improve the drugs' effects, overcoming their inherent conventional limits. In Table 4, a list of the FDA approved nanoparticle-based drug delivery systems and a list of INDs being tested in clinical trials are shown [237,238].

Table 4. List of FDA approved and under investigation nanoparticles encapsulated with anticancer drugs.

List of FDA Approved Anticancer Drug Loaded Nanoparticles			
Trade name	**Generic name**	**Benefits of encapsulation via nanoparticles**	**Reference**
Doxil (Janssen)	Doxorubicin HCl liposome injection	Increased delivery to disease site, decreased systemic toxicity of free drug	[239,240]
Marqibo (Spectrum Pharmaceuticals)	Liposomal vincristine	Increased delivery to tumor site, decreased systemic toxicity	[241]
Onivyde (Ipsen Biopharmaceuticals)	Liposomal irinotecan	Increased delivery to tumor site, decreased systemic toxicity	[241]
Vyxeos (Jazz Pharmaceuticals)	Liposomal daunorubicin and cytarabine	Increased efficacy through synergistic delivery of coencapsulated agents	[242]
List of INDs encapsulated by modified and unmodified nanoparticles under clinical trials			
Nanoparticle type (Investigation ID)	**Encapsulated Drug**	**Clinical trial phase**	**Reference**
Pegylated Liposomal MM-302	DOX	Phase 1	[243]
HER2-Targeted Liposomes	DOX	Phase 1	[244]
Thermo sensitive Liposome Thermodox (Celsion Corp.)	DOX	Phase 3	[244]
Conjugate Cyclodextran-PEG polymeric nanoparticle CRLX101	Camptothecin	phase1 and 2 clinical trials	[243]
Polymeric nanoparticle Conjugated CRLX301	Docetaxel	phase $\frac{1}{2}$a	[243]
Polyglutamic acid-conjugated nanoparticle (poliglumex) Opaxio	Paclitaxel	Phase3	[239]

11. Conclusions and Future Perspectives

In spite of the achieved advances in the drug delivery systems for lung cancer targeting, this cancer type is still the main cause of many deaths in the world. The major problem with the present treatment strategies is a lack of tools and smarter carrier systems for the drug targeting of malignant cells. It is evident from numerous research studies that the surface modification strategy reduces toxicity by changing the half-life, distribution, disposition, stimuli reactivity and therapeutic application. All the applications of surface-modified and hybrid nanoparticles paved the way for the clinical therapeutics through engineered and fine-tuned delivery to the lung tumor while reducing its side effects. These nanomaterials for lung cancer targeting are categorized into diagnostic, therapeutic, and theranostic multifunctional systems. The alteration of the onco-receptor function and modulating their pathways through specific strategies inhibit tumor growth and development through enhanced tumor-specific action. Surface-modified and hybrid nanoparticles can also help to advance the diagnosis process of lung cancer by stepping ahead from anatomical to molecular imaging for more precise diagnosis. However, the chemo-physiological aspects of these carriers should be carefully evaluated for optimal diagnosis. There are several conjugated nanodrugs recently filed in the list of the FDA's new drug applications. Camptothecin, a potent antineaoplastic agent being studied alone and in combination with

other drugs, has been included in various phase 1 and phase 2 clinical trials for targeting lung cancer (SCLN and NSCLC) and other solid tumors. For evaluating the surface-modified and hybrid nanoparticles it is mandatory to evaluate the in vivo toxicity and biodistribution of the nanohybrid carriers. By addressing the challenges in the development of optimized modified/functionalized nanoparticles, it will be possible to translocate these systems for clinical applications. The current review described why and how hybrid or surface-modified nanocarrier systems have the potential to be the most insolent delivery system for targeting lung cancer. We anticipate that this cross-disciplinary review could inspire further research and discovery on the design and performance of surface-modified and hybrid nanoparticles for targeted drug delivery and lung cancer therapy.

Author Contributions: Conceptualization, A.R.; writing—original draft preparation, F.S., M.B., M.Z., M.Q., Q.U.A. and E.G.; writing—review and editing, A.R. and M.A.A.; supervision, A.R. and M.A.A. All authors have read and agreed to the published version of the manuscript.

Funding: The APC was funded through PHOTO-EMULSION project. Financing entity: European Union H2020-MSCA-ITN-2017.

Acknowledgments: M.A.A. would like to thank Radmila Tomovska for her great help in providing APC funding.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AgNPs	silver nanoparticles
anti-NTSR1-mAb	antineurotensin receptor 1 monoclonal antibody
ATI	alveolar type I
ATII	alveolar type II
AuNPs	gold nanoparticles
β2-AR	β2-adrenergic receptors
β-CD	beta-cyclodextrin
CCL2	chemokine (C-C motif) ligand 2
CD44	cluster of differentiation 44
CeO2	cerium oxide
CLNs	cationic lipid nano-systems
CLSM	confocal laser scanning microscopy
CNT	carbon nanotubes
DNA	deoxyribonucleic acid
DPPC	1, 2 dipalmitoylphosphatidylcholine
DPPG	dipalmitoylphosphatidylglycerol
DOPA	dioleoylphosphatydic acid
DOX	doxorubicin
DR4/TRAIL-R	death receptor/TNF-related apoptosis inducing ligand-receptor
DTX	docetaxel
EGFR	epidermal growth factor receptor
EGR-1	early growth response-1
EML4	echinoderm microtubule-associated protein-like 4
EPR	enhanced permeability and retention
ERK	extracellular signal-regulated kinase
EVs	extracellular vesicles
FA	folic acid
FACS	fluorescence-activated cell-sorting
FDA	food and drug administration
FI	fluorescein isothiocyanate
FR	folate receptor
GDP	guanine diphosphate
GITR	glucocorticoid-induced tumor necrosis factor receptor-related

GTP	guanine triphosphate
HA	hyaluronic acid
HIF-1	hypoxia-inducible factor-1
HP	hemamiddleorphyrin
HPLC	high performance liquid chromatography
HUVEC	human umbilical vein endothelial cells
IL-6	interleukin 6
IND	investigational new drug
JAK-STAT	janus kinase-signal transducer and activator of transcription
KLF2	Krüppel-like Factor 2
KLF4	Krüppel-like Factor 4
LbL	layer-by-layer
LHRH	luteinizing hormone-releasing hormone
LPD	liposome-polycation-DNA complex
MAA	methacrylic acid
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemoattractant protein-1
MDSCs	myeloid-derived suppressor cells
MoS2	molybdenum disulfide
MWCNTs	multi-walled carbon nanotubes
NAG	N-acetyl-D-glucosamine
NDDS	nanodrug delivery systems
NPs	Nanoparticles
NSCLS	non-small cell lung cancer
OCAq	9,10-anthraquinone-2-carboxylic acid
PAMAM	poly(amidoamine)
PEG	polyethylene glycol
PI3K/AKT/mTOR	phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin mTOR
PIP2	phosphatidylinositol 4,5-bisphosphate
PIP3	phosphatidylinositol 3,4,5-bisphosphate
PLA	polylactide
PLGA	poly(lactide-co-glycolide)
PNA	peptide nucleic acid
PNIPAAm	poly-(N-isopropylacrylamide)
PTX	paclitaxel
QD	quantum dot
(QR	quercetin
RAF	rapidly accelerated fibrosarcoma
RB	rose bengal
RES	reticuloendothelial system
RGD	arginylglycylaspartic acid
RNA	ribonucleic acid
RNAi	RNA interference
ROS	reactive oxygen species
SCNP	single chain nanoparticle
SCLC	small cell lung cancer
SiO2	silicon dioxide
siRNA	small interfering RNA
SLNPs	solid lipid nanoparticles
SPIONs	superaparamagnetic iron oxide nanoparticles
TAMs	tumor-associated macrophages
TCL-SPION	thermally crosslinked supermagnetic iron oxide
TF	transferrin
TFR	transferrin receptor
TLR3	toll-like receptor 3
TNFα	tumour necrosis factor α
VEGFR	vascular endothelial growth factor receptor
ZO1	zonula occludens 1
ZrO2	zirconium oxide

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