# Nano-Enabled Strategies for the Treatment of Lung Cancer

Subjects: Oncology

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Lung cancer is acknowledged to be the major driver of cancer death attributable to treatment challenges and poor prognosis. Classical cancer treatment regimens, such as chemotherapy or radiotherapy, can be used to treat lung cancer, but the appended adverse effects limit them. Because of the numerous side effects associated with these treatment modalities, it is crucial to strive to develop novel and better strategies for managing lung cancer. Attributes such as enhanced bioavailability, better in vivo stability, intestinal absorption pattern, solubility, prolonged and targeted distribution, and the superior therapeutic effectiveness of numerous anticancer drugs have all been boosted with the emergence of nano-based therapeutic systems. Nano-based approaches are pioneering the route for primary and metastatic lung cancer diagnosis and treatment.

Keywords: nanotechnology ; lung cancer ; nanoparticles

## 1. Targeting of Nano-Formulations for Lung Cancer

Long-circulating nanosized therapeutics are kept in the tumor bed by diminished lymphatic outflow after preferentially penetrating tumor tissue through the permeable tumor vasculature. The said phenomenon is termed the enhanced permeability and retention (EPR) effect [1]. Due to the unique traits of the tumor milieu, which are not typically encountered in normal healthy tissues, passive targeting makes it easier for nano-vectors to be deposited at the tumor site [2]. Along with variables intrinsic to the nanoparticle, such as particle size, shape, and zeta potential, the tumor microvasculature also performs a function in the delivery of nanoparticles [3]. Targeting technologies have advanced significantly over the years to improve the preferential internalization of nanoparticles into tumor cells [4]. Targeting markers overexpressed by cancerous cells require the attachment of biorecognition molecules or ligands to the surface of the formulated nano-vectors. These tactics have been given the moniker “active targeting”, demonstrating greater specificity and effectiveness in attaining the desired consequence [5]. Some of the widely used targeting ligands are transferrin, folic acid, hyaluronic acid, aptamers, etc. [6]. The pictorial representation of passive and active targeting strategies is presented in **Figure 1**.

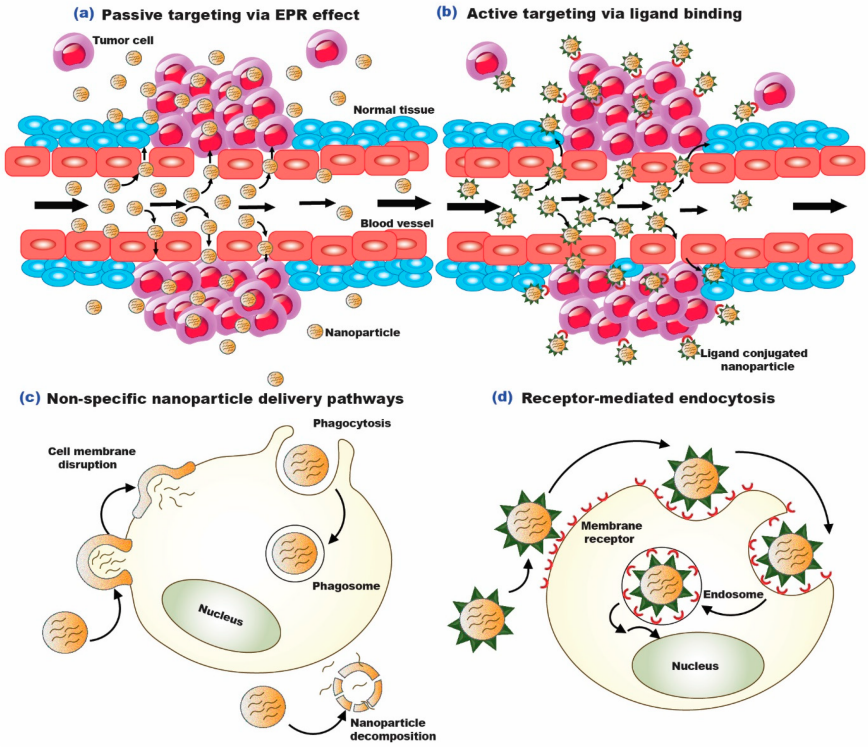


**Figure 1.** Targeting apoptotic pathway: (**a**). Passive targeting via EPR effect; (**b**). Active targeting via ligand binding; (**c**). Nonspecific nanoparticle delivery pathways; (**d**). Receptor-mediated endocytosis [7].

The FDA has approved a handful of nano-formulations for use in the treatment of cancer, including stealth TMPEGylated liposomal doxorubicin (Doxil or Caelyx). In 1995, the FDA approved Doxil® as the first nanoparticle-based drug delivery system. In phase I/II research, patients with small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) showed significant responses to Doxil when combined with other standard therapies and supportive growth factors [8]. Albumin-bound paclitaxel, commonly known as Abraxane, was another FDA-approved nano-formulation for metastatic NSCLC. Either alone or in combination with other chemotherapeutics, Abraxane has demonstrated superior therapeutic efficacy with reduced toxic effects [9].

### 1.1. Passive Targeting of Nano-Formulations for Lung Cancer

A surge of NPs enters tumor locations because of the atypical blood vessel development and absence of typical vascular basement membrane features. The “passive targeting” method of nanoparticle buildup in tumors is made possible by a phenomenon known as the EPR effect. Drug accumulation occurs at the tumor site due to this mechanism, which is predicated on the physiochemical characteristics of nanoparticles and intrinsic tumor traits [10]. Through the EPR effect, NP features such as size, shape, and surface qualities influence the effectiveness of drug delivery. It is preferable for nanoparticles between 40 and 400 nm to stay in the biological environment for a protracted time. The risk of NPs being cleared by the spleen and kidney depends on the type of NPs formulated. Hence, it is critical to formulate NPs with adequate physicochemical attributes to prevent the elimination of NPs from systemic circulation [11][12][13].

The advancement of novel methods and approaches to combat malignancy has been greatly aided by the proposal of gene therapy to combat cancer development, but the effectiveness of the proposed strategies has not yet reached the level needed to fully realize the potential of gene therapy in the clinic. Despite the wide range of gene modulation techniques available, such as gene silencing, antisense treatment, RNA interference, and gene and genome editing, it has proven difficult to effectively transport these effectors to the targeted cell or tissue. A number of cutting-edge platforms have been proposed by nanomedicine to avoid this problem [14]. In the past decades, the synthesis of nanoparticles for the transport of DNA or pDNA has received much attention in cancer therapy. Owing to their superior gene transfection and silencing effectiveness, recent research implies that the targeted administration of short RNAs such as siRNA and miRNA is growing in popularity in cancer therapy [15].

### 1.2. Active Targeting of Nano-Formulations for Lung Cancer

Active targeting promotes drug delivery effectiveness by increasing the cellular internalization of NPs at tumor locations [16][17]. The said approach is possible by surface decorating the NP to bind exactly to cell receptors on tumor cells. The effectiveness of the treatment is improved, adverse effects are reduced, the drug amount at the tumor location is increased, and the dosage of the drug to be administered is decreased [18]. A plethora of chemotherapeutics has been

reported to be designed to deliver to tumor areas using various targeted nano-drug delivery systems by focusing on overexpressed receptors on the tumor surface.

For NSCLC-targeted drug administration, an RGD peptide-modified chitosan-based nanoparticle formulation (CSNP)-RGD was developed [19]. Chitosan was employed to boost adhesion, limit drug release, and enhance particle stability. The integrins αvβ3 and α5β1 on the surface of cells are recognized by the linear peptide known as GRGDSP. The targeted formulation entrapping paclitaxel was 217 nm in size. Since integrin αvβ3 overexpression is present in NSCLC cells such as A549 and H1299, PTX-PLGA-CSNP-RGD was very selective for these cells. The formulation entered cells through endocytosis, which was regulated by integrin αvβ3. This protein suppressed the G2/M cell cycle and triggered apoptosis in tumor cells, although it was noted to be mostly nontoxic to healthy bronchial epithelial cells.

To effectively treat lung cancer, a group of researchers in 2017 synthesized multi-wall carbon nanotube loaded with chitosan-folate-conjugated digitoxin. The cytotoxicity assay revealed substantial intracellular levels and enhanced cellular internalization of the nanocarrier. By incubating in A549 cells, the nano-formulation reached 89 times the therapeutic efficacy in IC50 measures compared with the commercial product DOCELTM. The targeted and untargeted formulations exhibited lower toxicity profiles and offered a promising framework for effective lung cancer therapy [20].

Doxorubicin (Dox) conjugated on the surface of gold nanoparticles with PVP was formulated. Compared to free doxorubicin, they found that the targeted formulation combination significantly increased cellular penetration with a notable intracellular release of Dox when evaluated in lung cancer cells [21].

To aid in the diagnosis, staging, prognosis, and therapeutic usage, quantum dots (QDs) may be crucial to the imaging of tumors [22]. QDs are promising prospects for constructing multimodal theranostics due to their distinct optical characteristics and ability to functionalize with biomolecules [23]. Multispectral investigations showed a narrow fluorescence emission (570 nm) following stimulation (400 nm). As a result, it may be stated that doxorubicin-conjugated bi-functionalized InP/ZnS QD may be employed as a theragnostic for lung cancer treatment and diagnostics at the same time [24].

Another NP that uses hyaluronic acid (HA) as a targeting agent is DTX/PPN@PPY@HA. The nanoparticle consisted of a fatty-acid phase-changing core and an exterior layer made of photoresponsive polypyrrole, HA, and docetaxel [25]. Laser activation of polypyrrole in tumor cells, along with irradiation exposure, induces local hyperthermia, which leads to the melting of the fatty acid core ending up in drug release that is activated by heat. The research shows that NP DTX/PPN@PPY@HA demonstrated outstanding photothermal chemotherapeutic efficacy with a superior cellular absorption profile. PPN@PPY@HA did not cause cytotoxicity in vitro or harm healthy tissue when evaluated in vivo. Additionally, in vivo evaluations showed that the intra-tumoral injection of NPs was capable of total tumor eradication, while intravenous administration suppressed tumor growth.

## 2. Drug Resistance in Lung Cancer

Due to the emergence of drug resistance in cancer cells, the therapeutic potential of chemotherapeutics is known to be constrained [26]. Drug resistance refers to the tumor cells' capacity to generate a specific strategy to counteract and suppress chemotherapeutics' cytotoxic or inhibitory action, lowering their therapeutic efficacy. Approximately 90% of clinical metastasis occurrences result from chemotherapeutic failure due to drug resistance. Chemotherapeutic drugs must be provided at larger doses and more frequently to combat resistance, which may lead to significant toxicity and a decrease in the overall patient survival rate. To establish a synergistic impact and lower the rate of resistance, two or more chemotherapeutics drugs may be combined to achieve potentially high therapeutic effectiveness [27]. The various factors responsible for the emergence of drug resistance in tumor cells are presented in **Figure 2**.

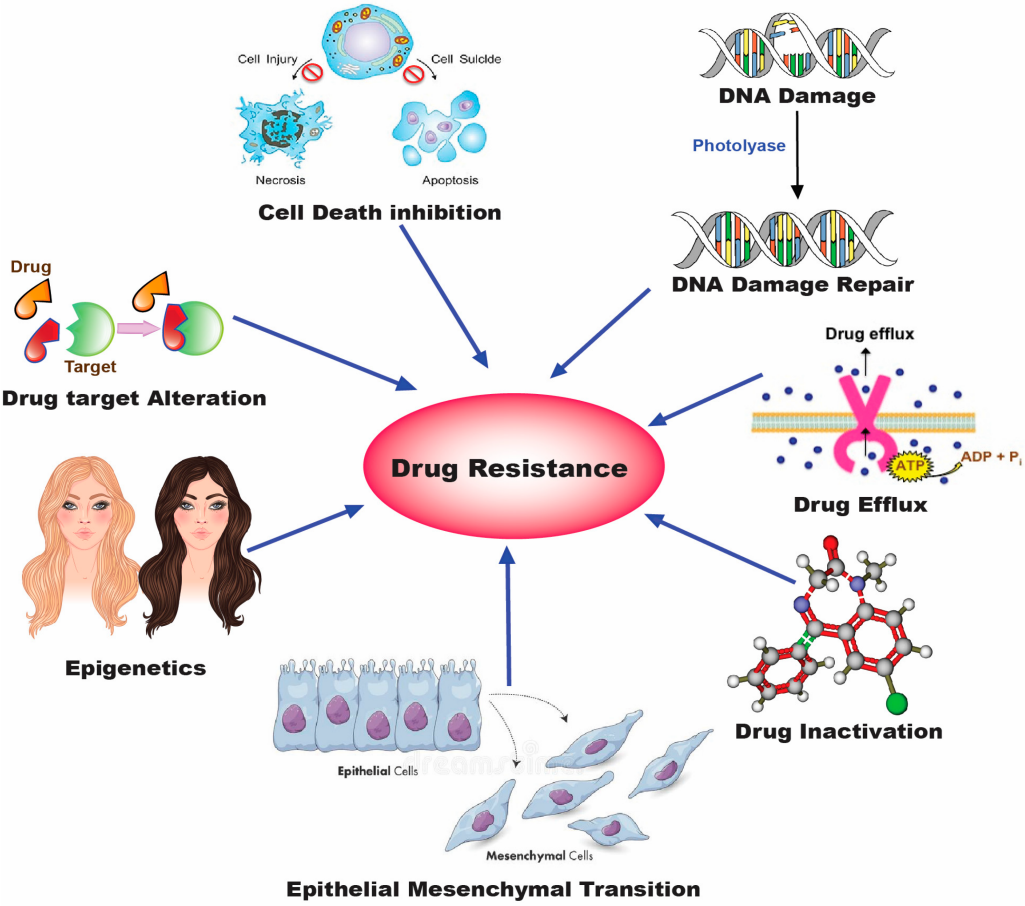


**Figure 2.** Various techniques employed by human cancer cells for direct or indirect drug resistance.

Patients with later episodes of LC are frequently treated with platinum-based compounds such as cisplatin. ROS and DNA damage is produced when the chemotherapeutics enter cancer cells, which results in cellular apoptosis [28]. By rendering the platinum medications ineffective through various resistance processes, including increased DNA repair, decreased cellular internalization, and anti-apoptosis, the resistance to LC inevitably evolves. According to several research investigations, the active SH-group in glutathione has an affinity to attach to platinum-based pharmaceuticals and prevent their DNA targeting owing to their strong interaction with anticancer medications. This can prevent DNA targeting. The cells become cisplatin-resistant because of the increased drug efflux through the GS-X pump and the increased glutathione content in the cells [29].

The overexpression of the ABC pumps in resistant LC cells following paclitaxel (PTX) treatment resulted in the proliferation of genes in the MDR1/ABCB1 chromosomal domain that code for P-gp. This led to PTX's intracellular aggregation being reduced, its egress from cancer cells increasing, and the emergence of drug resistance [30]. Chemotherapeutic drugs can avoid the ABC drug efflux pumps by being encapsulated in nanoparticles or conjugated to polymeric nanocarriers, rendering them unidentifiable as export platforms. DOX was entrapped in liposomes containing anti-MRP-1 and anti-Bcl2 siRNA. The nanocarrier system reduced the activity of efflux pumps with a notable internalization of the chemotherapeutics in resistant LC cells [31].

## 3. Combinatorial Therapy for Lung Cancer Treatment

For resistant tumors, combination therapy using various chemotherapeutics is effective due to its synergistic action, reduced toxicity, and lack of drug resistance [32]. Other combination strategies also include photothermy, hyperthermia, or ultrasounds, in combination with stimuli-responsive nanoparticles [33][34]. Platinum drugs, which were frequently used with paclitaxel, docetaxel, gemcitabine, or irinotecan, in addition to radiation, continue to be the most effective treatment for advanced NSCLC [35]. However, the unique physicochemical characteristics and in vivo pharmacodynamics and pharmacokinetics of the various drugs present challenges for combinatorial therapy, making it difficult to optimize dose and administration timing [36]. Exploiting various nanotools in such a pursuit curtails the associated challenges and presents enhanced therapeutic effectiveness.

Research studies have been conducted on the ability of nanoparticles to transport the immune modulators that function in immunotherapy. In this regard, some studies have suggested that nanoparticles may transport molecules that successfully modulate the immune response. In such a pursuit, ARAC (Antigen Release Agent and Checkpoint Inhibitor), a

nanoparticle-based immunotherapy created to boost the effectiveness of PD-L1 inhibitors, was developed [37]. ARAC is a nanoparticle that simultaneously delivers the PD-L1 antibody and PLK1 inhibitor, volasertib. In a metastatic lung tumor model (LLC-JSP), ARAC was noted to reduce the effective doses of volasertib and PD-L1 antibody by five times, and the impact was mostly mediated by CD8+ T cells.

## 4. Clinical Studies of Nanocarriers in Lung Cancer

Progressive forms of LC typically necessitate a standard combination of chemotherapy and radiotherapy treatment in conjunction with additional cutting-edge treatments such as immunotherapy or tailored therapeutics. Nevertheless, the usage of these agents is complicated by resistance tendencies and combination perspectives.

In the trial BIND-014, total docetaxel (DTXL) plasma concentrations remained at least 100-fold greater than solvent-based docetaxel (sb-DTXL) for more than 24 h in tumor-bearing mice, rats, and nonhuman primates treated with targeted docetaxel (DTXL-TNP) [38]. These results were consistent with an extended circulation of NPs in the vascular compartment and regulated release of DTXL. DTXL-TNP exhibited a pharmacological profile distinct from sb-DTXL, including pharmacokinetic character traits consistent with preclinical data and instances of tumor shrinkage at doses below the dose of sb-DTXL usually used in the clinic, according to preliminary clinical data in patients with advanced solid tumors.

For clinical study NCT00077246, on days 1, 8, and 15 of a 28-day cycle, NAB-paclitaxel at a dose of 125 mg/m$^2$ was given, and it showed encouraging single-agent activity [39]. No premedication with corticosteroids was given, and no hypersensitive reactions were seen. It was needed to conduct more research on both platinum-based combinations and single-agent NAB-paclitaxel.

## 5. Challenges Associated with the Use of Nanomedicine in Cancer

### 5.1. Challenges Associated with Non-Targeted (Passively Targeted) Nano-Formulations

First-generation passively tailored nanomedicines make up most nanocarrier-based cancer treatments [40]. The pathophysiological characteristics of cancers and the environment around them have been employed for passive targeting, especially in cases when the EPR effect substantially encourages the buildup of nanomedicine in cancer cells. As a result, the passive targeting of neoplasms using nanomedicine is possible through diffusion and convection without the need to attach a specific chemical to the surface of the nanocarrier. However, it is generally acknowledged that directed delivery offers more advantages than passive targeting based on EPR effects on cytotoxic medication side effects.

The delivery of drugs through a passive targeting approach may be significantly impacted by the complexity of cancer and its stroma, such as hypoxic gradients, leading to decreased or eliminated transport of substances into neoplasms [41]. Recent studies have concentrated on standardizing the neoplasm vasculature before beginning cancer treatment. Furthermore, passive targeting does not stop the aggregation of nanocarriers in former fenestrated endothelial organs such as the liver and spleen, supporting next-generation nanomedicine development with cutting-edge practicalities [42].

### 5.2. Challenges Associated with Targeted (Ligand Anchored/Active Targeted) Nano-Formulations

Actively targeted nano-formulations used to deliver macromolecules encounter extra physiological obstacles due to their interactions with the target cells. Escape from the endocytic route is one of the main obstacles noted. Intracellular trafficking pathways drive NCs to subcellular regions following endocytosis, which may harm the fate of nano-formulations. For instance, transferrin-targeted nano-formulations that are ingested through clathrin-mediated endocytosis would transit the degradative route and ultimately be digested in lysosomes [43]. Various methods have been explored, including pore-formation peptides, proteins, and pH-buffering compounds that use the “proton sponge effect” to help nano-formulations egress from endosomes and enter the cytosol. The endosomal escape of NCs in vivo is still exceptionally challenging, though.

The enormous diversity within and between tumors and the prevalence of tumor and metastasis-supportive stroma add to the complexity [44]. Many active, cell-specific nano-formulations ignore tumor heterogeneity and favor the persistence of resilient clones by targeting a single cell-surface receptor on cancer cells. Because of this, current therapy frequently produces visible partial or complete cures, which are typically followed by resistant tumor recurrence and mortality [45].

Approaches for active targeting are substantially more intricate than those for passive methods. To understand the challenges brought on by physiological barriers and tumor heterogeneousness, a significant barrier is presented by the intricate design and manufacturing of these nano-formulations, which may make the scale-up steps more difficult [46]. Due to the significant processes of chemical synthesis and purification, the manufacturing process for conjugating ligands targeting nanocarriers is more complicated than it is for passively targeted ones.

Immunological and hematological problems are significant issues with cancer nanomedicine and its advancement. Metallic nanoparticle translation is initially concerned with specific responses known as anaphylactic reactions [47]. These issues are connected to the polymeric coating materials employed to eliminate the agents present in their commercialized forms. Furthermore, endotoxin contamination and related complications such as activation and pyrexia are crucial problems when employing nanomedicine as therapeutics and cancer therapies.

The toxicity aspects of nanoparticles are an important factor to consider as they impede clinical translation [48]. Electrostatic interactions between nanoparticles with positive surface charges and pulmonary surfactants have been demonstrated [49]. It has been hypothesized that these interactions may alter how nanoparticles interact with cells. The lack of vesicles encircling the ingested nanoparticles or nanoparticle aggregates revealed that the nanoparticles entered the cells via a non-endocytosis pathway. The membrane was also harmed at the point where the cells entered [50]. In such cases, suitable surfactants need to be employed during the formulation of nanoparticles which may help in reducing the toxicity impacts.

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