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REVIEW ARTICLE

Targeting the ACE2 receptor using nanomedicine: Novel approach to lung cancer therapy

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ABSTRACT

The angiotensin-converting enzyme 2 (ACE2) receptor gained prominence in 2020, having been identified as a prime receptor for entry of the novel coronavirus COVID-19, which has led to the current global pandemic. Many studies have reported that lung cancer patients have a higher risk of contracting COVID-19 due to the up-regulated expression of ACE2 in lung cancer cells. Lung cancer is a heterogeneous disease and the most frequently occurring cancer globally. It is more prevalent in men than in women and accounts for an estimated 40% of cancer cases. Over the years, many studies have reported on the ACE2 expression in lung cancer. Conventional methods currently available for the detection and treatment of lung cancer face numerous challenges. Nanomedicine has risen to many challenges facing cancer therapy and drug delivery. With the array of nano delivery systems available, nanomedicine can be used to develop alternative methods to help overcome these challenges and improve the therapeutic efficiency in cancer therapy. Hence, this review focuses on lung cancer, the ACE2 receptor, and the use of nanomedicine in formulating a novel targeted cancer treatment strategy directed at the ACE2 receptor. This may serve as a stepping stone for exploring further targeting strategies and therapies.

Keywords: ACE2 Receptor; Nanomedicine; Lung Cancer; Therapy; Targeting

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1. Introduction

Lung cancer is a complex heterogeneous disease and is one of the most frequent causes of cancer-related deaths worldwide. It can be subdivided into non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). According to World Health Organization (WHO) statistics, cancer was responsible for approximately 10 million deaths in 2020, with lung cancer contributing 2.21 million cases and 1.8 million deaths[1]. This could be attributed to the late-stage diagnosis of the disease, which is asymptomatic in its early stages[2,3]. Therefore, early detection methods and improved treatment strategies are needed to combat lung cancer.

Current detection methods such as computed tomography scan, bronchial biopsy, PCR-based sputum assay and fluorescence bronchoscopy are invasive and can produce false positive results[4]. Breath testing and liquid biopsies are alternative non-invasive detection methods. Current treatment options for lung cancer include surgical resections, chemotherapy, radiotherapy, and immunotherapy[5]. However, these conventional treatments are challenged with drug resistance, lack of specificity, low efficacy, low solubility, and systemic toxicity[4,5]. They can cause severe side effects in patients, such as lung

damage causing reduced pulmonary function, fatigue, nausea, weight loss, hair loss, anemia, myelosuppression, intestinal injury, cardiotoxicity, and nephrotoxicity[5].

The use of nanomedicine in cancer therapy can overcome the challenges faced by conventional treatment and detection methods. Nanomedicine, a branch of medicine that uses nanotechnology for medical purposes, has the potential to challenge traditional treatment strategies by providing a novel efficacious therapeutic approach. Nanomedicine utilizes nanomaterials to improve the specificity and sensitivity of diagnostic imaging for early cancer detection, in addition to their formulation as nanodrug or gene delivery systems. Targeted drug delivery can improve patient compliance, reduce nonspecific delivery, and increase therapeutic efficacy. It can be personalized by identifying specific mutations and amplified biomarkers, in lung cancer tissues, by profiling of epigenetic factors[4]. This allows for the specific targeting of overexpressed receptors in different types of cancer.

One such receptor is the angiotensin-converting enzyme 2 (ACE2) receptor, which is overexpressed in lung cancers such as lung adenocarcinoma (LUAD)[6]. ACE2 is a zinc-type I carboxypeptidase that regulates the renin-angiotensin system (RAS). The ACE2 receptor gained popularity during the global pandemic of the novel coronavirus (COVID-19), since it was the crucial receptor for the entry of COVID-19[7]. Due to the overexpression of ACE2 in lung cancer cells and the subsequent metastasis, lung cancer patients were most vulnerable to COVID-19[8]. Therefore, the therapeutic targeting of ACE2 could be beneficial in combating LUAD.

2. Lung cancer

Lung cancer is the most common cause of death worldwide in men and the second most common in women[3]. Lung cancer consists of glandular differentiation or mucin production and is classified as a malignant epithelial neoplasm. It is a complex and diverse disease comprising various subtypes (**Figure 1**)[3,9].

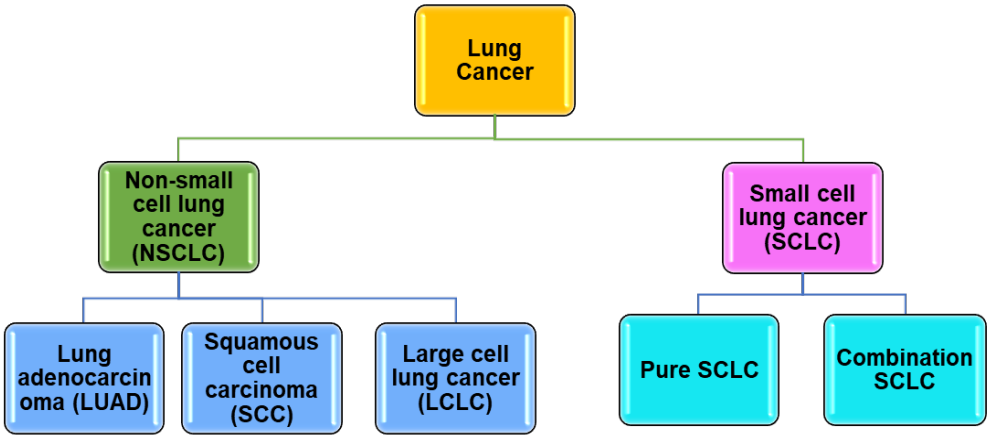

Figure 1. A simple breakdown of the subtypes of lung cancer.

Lung cancer can be classified as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)[9]. A mutation in the p53 gene is the most common cause of tumorigenesis found in NSCLC[10]. NSCLC possesses subtypes such as lung adenocarcinoma (LUAD), large cell lung cancer (LCLC) and squamous cell carcinoma (SCC)[2,3]. SCLC has two subtypes, namely pure SCLC and combination SCLC that contain components of NSCLC. SCLC, an aggressive form of lung cancer, accounts for approximately 20% of lung cancer cases. Most SCLC cases can be treated non-surgically, whereas NSCLC cases are treated with surgery and other therapies. In NSCLC, approximately 40% to 80% of patients exhibit overexpression of epithelial growth factor receptor (EGFR)[9]. LUAD is the most common NSCLC and accounts for approximately 40% of cancer cases. LUAD generally forms masses located peripherally with central fibrosis and pleural puckering[9].

Tobacco smoke contributes to lung cancers from air pollution, occupational exposure, chronic obstructive lung disease, radiation, radon, and hereditary susceptibility. It is implicated in approximately 80% of lung cancers in males and 50% of females[3]. On average, 1 in 6 tobacco smokers is diagnosed with cancer, with second-hand smoke posing an increased risk factor in non-smokers[2,3]. However, less than 20% of smokers are diagnosed with lung cancer, suggesting that genetic susceptibility plays a role in developing lung cancer. Several lung cancer susceptibility genes have been identified on chromosomes, 5p15.33, 6p21, 15q24 to 25.1, 6q23 to 25, and 13q31.3[3].

Radon, an inert gas, also contributes to the development of lung cancer. Radon found in building materials and the soil is considered an occupational exposure, with approximately 20,000 radon-related lung cancer cases reported in the United States. Aluminium production also contributes to lung cancer development because of the carcinogenic agents used in the production process. Other occupational contributors include coke and coal gasification fumes, asbestos, nickel, and arsenic[2,3].

2.1 Lung adenocarcinoma

Lung adenocarcinoma (LUAD) is the most recurrent, aggressive, and fatal subtype of NSCLC. LUAD is a heterogeneous disease that affects the mucosal glands and accounts for an estimated 40% of cancer cases[10,11]. It usually occurs along the periphery of the lung and can be found in scar tissues with areas of chronic inflammation. It is characterized by a high level of genetic mutation and a survival rate of less than 5%[11]. The early stages of LUAD tend to be asymptomatic, with later-stage symptoms including cough, weight loss, haemoptysis, and, in some cases, shortness of breath due to pleural infusions. Patients with a loco-regional spread may display symptoms such as phrenic nerve palsy, Horner syndrome, brachial plexus compression, and superior vena cava obstruction. A family history of LUAD is an added risk factor. LUAD has become common in recent years, surpassing the number of cases of squamous cell carcinoma[12].

CT scans for LUAD can appear as invasive mucinous, lepidic predominant non-mucinous adenocarcinoma, minimally invasive adenocarcinoma, and adenocarcinoma *in situ*. LUAD could also mimic the appearance of thoracic malignancies and pneumonia in the lungs, making the diagnosis tricky[13]. The genes DNA topoisomerase IIα (TOP2A), aurora kinase A (AURKA), and cell division cycle 20 (CDC20) are all up-regulated in LUAD. The AURKA gene is associated with lymphatic metastasis, while the TOP2A and CDC20 genes are associated with tumorigenesis. CDC20 overexpression correlates to poor prognosis of the disease with the upregulation of AURKA and TOP2A leading to increased tumour sizes and lymphatic metastases[11]. The common somatic mutations occur in TP53, KRAS, KEAP1, STK11, and EGFR[14] and are vital for tumour growth and division. The EGFR mutation has been observed to stimulate cancer growth in LUAD. Importantly, LUAD overexpresses the protein ACE2, which has various roles in cancer progression, tumorigenesis, metastasis and carcinogenesis[6]. The role of ACE2 in LUAD is still being investigated and shows great promise in cancer research.

3. The ACE2 receptor

LUAD and SCC exhibit increased levels of ACE2 compared to normal tissue, independent of the cancer stage. DNA methylation has been proposed to be responsible for increased ACE2 expression, acting as a tumorigenesis regulator[8]. Samad *et al.*[15] confirmed the up-regulation of ACE2 in LUAD and SCC, with ACE2 inhibiting apoptosis in human rat alveolar epithelial cells and reducing cell invasion and mitigation of NSCLC. When overexpressed, ACE2 reduces UGT1AG levels, which detoxifies toxic and carcinogenic agents in lung cancers. ACE2 could act as a protective agent for cancers, exhibiting anti-tumour effects and inhibiting tumour angiogenesis. The up-regulation of ACE2 in LUAD and SCC was associated with decreased cellular proliferation and oncogenic effects. The increase in ACE2 favoured the reduction of malignancies[8,15]. It was also reported that LUAD exhibited decreased DNA methylation levels, in-

creased ACE2 expression, and increased regulation of ACE2 RNA expression[6].

3.1 Structure of ACE2

The main features of ACE2 are illustrated in **Figure 2**. ACE2 comprises 805 amino acids and two functional domains: the N-terminal peptidase and C-terminal Collectrin domain, which includes a transmembrane sequence, a neck domain and a 43 amino acid cytoplasmic tail. The N-terminal peptidase domain contains two catalytic subdomains, with the active site sandwiched in-between[16]. The N-terminal peptidase domain reportedly has four key sites: the active carboxypeptidase site, the hinge region, the claw-like surface and the dimerization interface. The claw-like surface plays a role in the interaction with the receptor binding domain (RBD) of COVID-19[17].

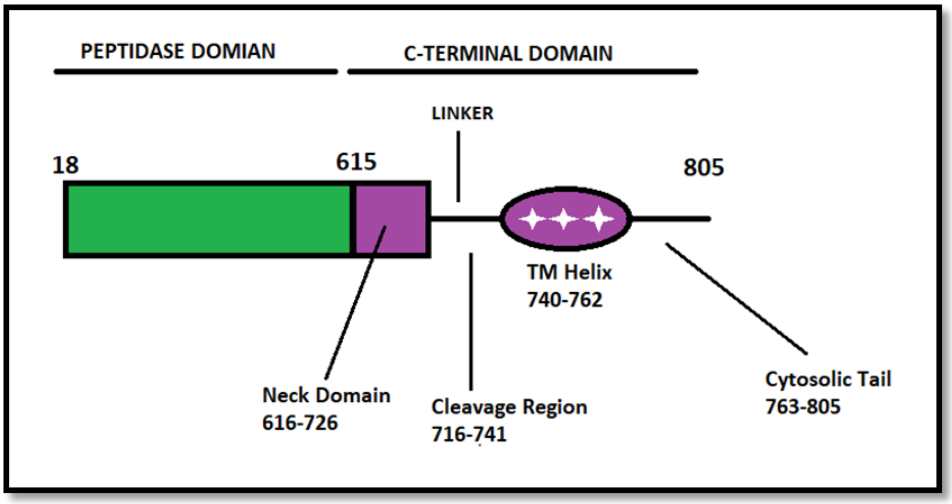

Figure 2. Diagram of the ACE2 motifs and domains: the N-terminal domain (green), the peptidase domain (PD), the C-terminal domain (purple), and the Collectrin domain (CLD).

3.2 Roles of ACE2

In the renin-angiotensin system (RAS), ACE converts Angiotensin I (Ang I) to Angiotensin II (Ang II). Ang I is an inactive decapeptide, while Ang II is a versatile bioactive peptide associated with hypertension, vasoconstriction, inflammation, and endovascular thrombosis and can promote vascular injury by preventing nitric oxide production[18]. ACE2 functions to reduce these adverse effects by degrading Ang II into Ang (1–7), which displays cardiovascular protective properties by alleviating cardiac inflammation, increasing endothelial function, suppressing cardiomyocyte growth in vitro, inhibiting vascular smooth muscle cell proliferation and migration, and suppressing myocardial infarction-induced ventricular hypertrophy *in vivo*[19]. ACE2 cleaves Ang I into an inactive peptide Ang (1–9), reducing Ang I substrate availability for ACE. ACE2 can also stop inflammation, fibrosis, and cell growth by activating the angiotensin type 2 receptor[7]. **Figure 3** provides a summary of the roles of ACE2 in RAS.

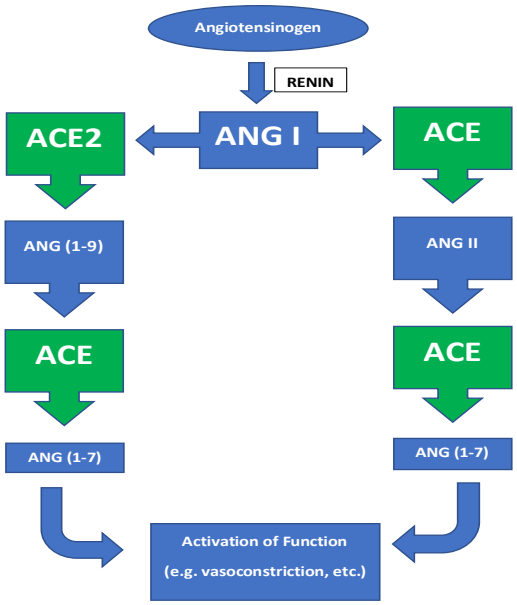

Figure 3. Summary of the function of ACE2 in regulating the renin-angiotensin system.

ACE2 also functions as an amino acid transporter. The association of ACE2 with amino acid

transport stems from its C-terminal domain's transmembrane homology with Collectrin, a binding partner for amino acid transporters. In the intestines, ACE2 binds to the sodium-dependent neutral amino acid transporter B(0)AT1, which aids in the absorbing of amino acids. When ACE2 interacts with B(0)AT1, it undergoes hetero-dimerization that allows for surface expression of transport proteins and the supply of amino acid substrate to the transporters[20]. **Figure 4** summarizes the various roles of ACE2.

3.3 Biodistribution of ACE2

ACE2 is found in different parts of the body, with varying levels of expression (**Figure 5**).

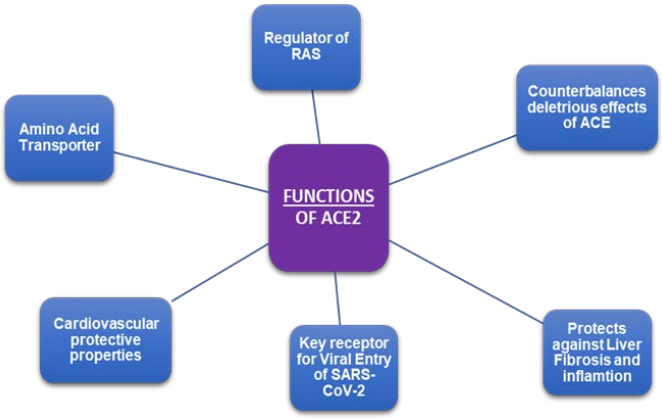

Figure 4. Summary of the different roles played by ACE2.

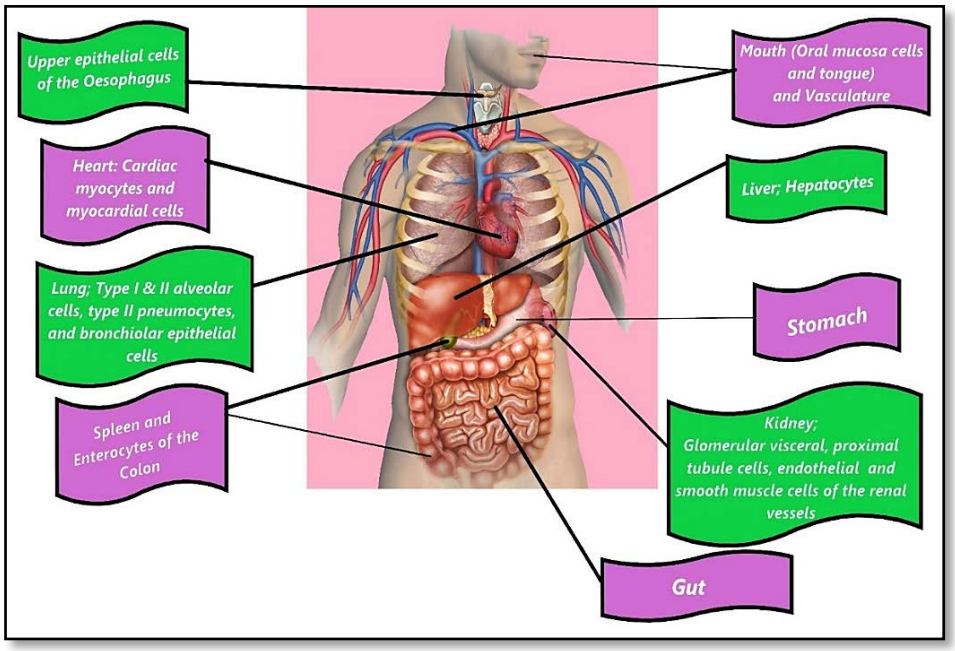

Figure 5. Biodistribution of ACE2 expression in the human body.

ACE2 expression has been identified in the oral mucosa cavity, tongue, kidney proximal tubule cells, myocardial cells, urothelial bladder cells, lung type II alveolar cells, colon enterocytes, prostate, liver hepatocytes, epithelial cells of the oesophagus, cholangiocytes[14], the placenta of pregnant women, bronchiolar epithelial cells, endothelial and smooth muscle cells of the renal vessels, proximal tubular brush border of the kidneys, brain, spleen, glomerular visceral, arterial smooth muscle cells, cardiac myocytes, type I alveolar epithelial cells, nasal goblet secretory cells, lung type II pneumocytes, and ileum absorptive enterocytes[21].

4. Nanomedicine

Nanomedicine, the branch of medicine utiliz-

ing nanotechnology, can overcome the challenges experienced by conventional lung cancer treatments and detection methods. With its array of nanomaterials, nanomedicine has revolutionized and opened up novel strategies that can improve cancer therapy. Nanoparticles (NPs) that have impacted medicine can be classed as organic, inorganic, and carbon-based NPs. Organic NPs include lipid-based NPs, micelles, and polymers; inorganic NPs include gold, silver, selenium, mesoporous silica, iron oxide, quantum dots, and platinum; and carbon-based NPs include carbon nanotubes, graphene, and fullerenes. NPs can be easily optimized for utilization in various biomedical applications and offer many advantageous properties ranging from their nano-size to surface morphology[22,23]. Their favourable surface-to-mass ratio allows them to conjugate therapeutic biomolecules for target-specific drug or gene delivery.

Quantum dots can be used as fluorophores for biomedical imaging, and as contrast agents to improve diagnostic imaging sensitivity, specificity, image resolution, and signal strength[24]. Magnetic NPs and quantum dots were used to screen macrometastases in patients with lung cancer for early diagnosis and to prevent a recurrence. Gold NPs (AuNP) have been used for *in vitro* and *in vivo* imaging and in the development of biosensors that can distinguish between normal and cancer cells and allow for the classification and the histology of different lung cancers[5]. AuNPs possess ideal properties such as good biodegradability, easy bioconjugation, inertness, low cytotoxicity, tuneable stability, controlled drug release, simple synthesis and functionalization, and easy chemical modification. They also offer protection from systematic degradation to conjugated therapeutics, reducing their toxic side effects, and improving their bioavailability[25–27]. Importantly, the upper limit for toxicity for any NP must be determined before application.

Silver NPs (AgNPs) have been shown to have better physical, chemical, and biological properties than their bulk form. AgNPs offer ease of synthesis, good chemical stability, biocompatibility, optical, thermal, and electrical conductivity, as well as antiviral, anti-inflammatory, antifungal, antibacterial, anticancer, antiangiogenic and catalytic properties[28–30]. NSCLC cells treated with AgNPs showed significant dose-dependent growth inhibition *in vitro*, with stimulation of apoptosis indicating a potential for chemotherapy and chemoprevention *in vivo*[31]. Lung cancer cells (A549) treated with phytosynthesised AgNPs carrying the anticancer drug cisplatin showed a significant level of cytotoxicity compared to cisplatin alone. These AgNPs exhibited apoptosis, anti-metastasis and anti-proliferative effects on the lung cancer cells[28].

Selenium is an essential trace element required by various organisms. It plays a role in immune responses and cancer prevention and has gained much interest in material chemistry, nanomedicine, and bioengineering[32,33]. Selenium nanoparticles (SeNPs) offer favourable characteristics such as good bioavailability, low toxicity, antioxidant properties, high biological activity, biocompatibility, low cytotoxicity, anticancer, and apoptotic effects[34,35]. SeNPs can be used as a radiosensitizer to minimize the side effects of radiation therapy. A combination of radiotherapy and SeNPs, exhibited good anticancer activity, promoted apoptosis, and inhibited migration, invasion, and proliferation of the lung cancer cells[32]. Furthermore, lung cancer cells treated with SeNPs conjugated with hyaluronic acid and paclitaxel inhibited the migration, invasion, and proliferation of lung cancer cells[33]. SeNPs can promote apoptosis by activating the overproduction of intracellular peroxides that activate the p53 and MAPK pathways and inhibit tumour growth[20].

Copper, another essential trace element needed for metabolic processes in animals and plants[36], functions in maintaining the immune system and fighting against inflammation. Copper NPs (CuNPs) offer favourable properties such as oxidation resistance, low toxicity, biocompatibility, antifungal, antibacterial, and antiviral activity[37], suggesting their potential for use in nanomedicine. Copper oxide (CuO) NPs can regulate oncogenes and tumour suppressor genes, mRNA and protein expression and can induce apoptosis and anticancer activity in lung cancer (A549) cells[38].

One of the most popular uses of NPs is as de-

livery vehicles for therapeutic agents to tumour sites. NPs less than 100 nm in size have the ability to penetrate physiological barriers, including those found in the lung, blood, nervous system, and tumour vasculature[39]. Thus, the development of nanodelivery systems can potentially improve cancer therapy and overcome challenges faced by conventional treatments such as chemotherapy and radiation therapy. These delivery systems can also enhance aqueous solubility, drug distribution, biocompatibility, drug efficacy, reduce toxic side effects, protect against drug inactivation and biodegradation, increase circulation time, reduce dosage frequency, overcome multi-drug resistance, chemical and biological barriers, passively or actively target tumours, deliver therapeutic molecules for synergistic effects in a singular platform and generate immunostimulatory responses to aid in the generation of anti-tumour immunity[24].

Nanomedicine has promoted the development of targeted drug delivery systems for lung cancer through non-invasive methods, such as aerosols for administration via inhalation, that deliver the anticancer drugs directly into the lungs, reducing systemic drug exposure, distribution, and toxicity. The conjugation of receptor-cognate ligands to NPs has improved cell-specific uptake in various organs. Therefore, the use of a NP modified using an ACE2 targeting ligand can selectively bind to lung cancer cells that over-express the ACE2 receptor. Pulmonary drug delivery is an effective delivery route since the lung possesses a noteworthy surface area of alveoli and a large vascular bed. Delivery via the pulmonary route would achieve a higher local drug concentration, avoid clearance by mucociliary and lung phagocytic mechanisms, and achieve a rapid therapeutic effect with minimized systemic absorption[38].

The personalized drug delivery to overexpressed receptors identified in different lung cancers can be highly beneficial. Targeted drug delivery can improve patient compliance, reduce drug accumulation at nontarget sites, and increase the drug's therapeutic efficacy. **Table 1** summarises the various NPs that have been used in lung cancer therapy.

Table 1. Some relevant *in vitro* applications of selected nanoparticles in lung cancer studies from 2016–2021

Nanoparticle	Cell	Study	Results
Gold[40]	A549	Bio-synthesized AuNP using marine bacteria *Enterococcus sp.*	Increased anticancer effects with increased concentration
Selenium[33]	A549	Delivery of paclitaxel	Inhibition of cell growth, invasion, migration
Palladium[41]	A549	Chemically synthesized nanoparticles	Dose-dependent cytotoxicity
Silver[42]	A549	Bio-synthesised AgNPs from of *Pinus roxburghii* needles	Induced apoptosis and increased intracellular ROS in cells

5. Nanoparticles in clinical trials

Several clinical trials have been conducted over the years, with many trials mentioning lung cancer, but only a few of these reported clinical trials that focus specifically on lung cancer therapy using NPs[43]. Several trials were withdrawn or terminated prematurely. **Table 2** summarizes and highlights some of the relevant studies completed from 2003 to date. Chemotherapeutics such as nab-paclitaxel have been reported, but its potency in the latter stages of lung cancer or combination therapy remains to be determined. Most NP formulations were drug: paclitaxel albumin-stabilized NPs, with no NPs such as those mentioned in **Table 1** yet in clinical trials. Some studies started in 2021 are still in the recruiting phase and have not been included in **Table 2**. Interestingly, none of these clinical trials exploited the ACE2 receptor or has examined targeted treatment via this receptor in previous studies. Therefore, this novel review highlights the immense potential of targeting the ACE2 receptor using NPs as a more effective means of lung cancer therapy. The role of nanomedicine in lung cancer therapy is yet to be realized.

Table 2. Selected completed or ongoing lung cancer-focused clinical trials from 2003 to 2023 utilizing nanoparticles in lung cancer therapy (adapted from ClinicalTrials.gov[43])

Title of trial	Lung cancer	Approach	Start & end dates
⁎ ABI-007 in treating patients with chemotherapy-naïve stage IV NSCLC	NSCLC	Drug: paclitaxel albumin-stabilized nanoparticles	December 2003–October 2008
Carboplatin and paclitaxel albumin-stabilized nanoparticle formulation followed by radiation therapy and Erlotinib in treating patients with Stage III NSCLC that cannot be removed by surgery	NSCLC	Drugs: carboplatin, erlotinib hydrochloride, paclitaxel albumin-stabilized nanoparticles + radiation therapy	March 2008–June 2015
Neoadjuvant chemotherapy of nanoparticle albumin-bound paclitaxel/carboplatin vs. paclitaxel/carboplatin in stage#B and IIIA squamous cell carcinoma of the lung	NSCLC	Drug: albumin-bound paclitaxel/carboplatin nanoparticles	October 2012 –December 2017
Paclitaxel albumin-stabilized nanoparticle formulation in treating patients with previously treated advanced NSCLC	Recurrent and stage IV NSCLC	Drug: paclitaxel albumin-stabilized nanoparticles	December 2012–April 2019
Nab-paclitaxel as second-line therapy in locally advanced or metastatic squamous lung cancer	Squamous Cell Carcinoma	Drug: nanoparticle albumin-bound paclitaxel	September 2013–July 2015
Neoadjuvant chemotherapy of nanoparticle albumin-bound paclitaxel in lung cancer	NSCLC	Drug: nanoparticle albumin-bound paclitaxel	January 2014–March 2016
⁎BIND-014 (Docetaxel nanoparticles for injectable suspension) as second-line therapy for patients with KRAS positive or squamous cell NSCLC	Squamous NSCLC	Drug + nanoparticles	September 2014–April 2016
⁎Feasibility study of SBRT plus chemotherapy for NSCLC	NSCLC (Stage I & II)	Drugs carboplatin and paclitaxel albumin-stabilized nanoparticles + radiation	February 2016–January 2017
⁎TUSC2-nanoparticles and Erlotinib in stage IV lung cancer	Lung Cancer	Drugs: erlotinib, dexamethasone, diphenylhydramine. DOTAP: Chol: TUSC2 nanoparticles	February 2018–September 2020
A randomized, double-blind, Placebo-controlled Phase III study to investigate efficacy and safety of first-line treatment with HLX10 + chemotherapy (Carboplatin-nanoparticle albumin bound (Nab) Paclitaxel) in patients with Stage IIIB/IIIC or IV NSCLC	Squamous NSCLC	Drugs: carboplatin nanoparticles and nab-paclitaxel	August 2019–January 2023

Note: NSCLC = Non-small Cell Lung Cancer
(⁎) Trials that have been terminated or completed

6. Conclusion

Nanomedicine has opened up attractive possibilities for developing improved cancer detection and treatment strategies. It can help to enhance traditional treatment methods while reducing current shortcomings. This review highlighted the potential for ACE2 in nanomedicine to help combat lung cancer. Exploiting the ACE2 receptor in combination with nanomedicine can serve as a stepping stone to explore new targeting strategies that are highly beneficial for the delivery of anticancer drugs or therapeutic genes with improved efficacy in lung cancer cells. Nano-delivery systems possess immense potential to provide efficient cancer therapy with little or no side effects.

Lung cancer in its early stages is generally asymptomatic, often resulting in late diagnosis. Traditional treatments have shortcomings such as off-target toxicity, damage to normal tissue, low efficacy, and drug resistance. Nanotherapeutics has revolutionized many treatment strategies by creating more disease and target-specific therapies that overcome the shortcomings experienced by traditional chemotherapy. The increasing knowledge of both tumour and molecular biology is fundamental for effecting changes in cancer treatment. Identifying key receptors overexpressed in various lung cancers and targeting these receptors will provide the gateway for formulating advanced treatment regimens that are potent against cancer cells. This review has identified a niche for the prospect of nanomedicine-influenced targeted therapies in lung cancers that take advantage of the ACE2 receptor. More research is required to conceive such therapies, optimize them and deliver these targeted therapies from the bench to the patient.

Conflict of interest

The authors declare that they have no conflict of interest.

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