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Review

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Applications of nanotechnology in the treatment of pulmonary diseases

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Abstract

This review article discusses the utilisation of nanotechnology in the treatment of pulmonary diseases, including asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, pneumonia, lung infections, and lung cancer. It highlights the importance of early diagnosis and novel drug delivery systems for successful disease management. Specifically, nanoformulations administered via the pulmonary route have shown effectiveness in managing asthma and COPD, while targeted drug delivery is crucial for improving therapeutic outcomes and minimising systemic side effects in lung infections and cancer. The article also explores the role of nanotechnology in gene therapy for cystic fibrosis, showcasing the development of nonviral vectors. Overall, this review provides a comprehensive overview of the causes of pulmonary diseases and the advancements in nanoscience and nanotechnology for their treatment.

Keywords: Pulmonary diseases, nanoparticles, COPD, asthma, lung cancer, respiratory diseases, pulmonary administration

INTRODUCTION

Pulmonary diseases include any disease conditions affecting the respiratory system[1]. It is mainly caused by air pollutants, smoking tobacco, infections, and genetic disorders. These include lung cancer, cystic fibrosis (CF), asthma, pulmonary embolism, pneumonia, and other pulmonary infections. However, there are several barriers to the pulmonary absorption of proteins and peptides, such as mucus, surfactants,

mucociliary clearance, alveolar lining, basement membrane, enzymes, and macrophages[2]. In such cases, porous microspheres are versatile in tissue regeneration, high-speed chromatography, alveoli-targeted drug delivery, and gastro-retentive drug delivery due to their low density and proper aerodynamic diameter. Recently, the severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2) virus has caused a deadly pandemic through lung infection. Millions of people died globally[3].

The lung is a complicated organ. Its architecture and homeostatic maintenance systems are highly complex[2]. Administration of drugs through the oral route or intravenous (i.v) route is not always very effective. Direct delivery of medicine through the pulmonary route is desirable[2]. Particles or droplets inhaled with a size of 1 to 5 μm can reach the central and peripheral airways within the lungs, but they struggle to pass through the mucus layer that lines the respiratory tract[2]. Instead, they are efficiently removed from the lungs by pulmonary macrophages.

Nanotechnology has rapidly developed nanoparticles (NPs) for medical purposes, including pulmonary disease therapy[4]. However, these foreign materials can have adverse effects on the lung, including oxidase stress, inflammation, fibrosis, and genotoxicity. Specially designed nanoparticles or nanocapsules are efficient in treating pulmonary diseases. They can efficiently overcome different biological barriers to reach the target site. Nanoscience discusses a new frontier for fast, risk-free, and potentially inexpensive diagnostics of respiratory diseases using exhaled breath-based volatile organic compounds (VOCs)[5]. It covers overlaying concepts, exhaled breath chemistry, and various sensors used for disease detection. Figure 1 describes nanotechnologies associated with different pulmonary diseases including asthma, CF, lung cancer, and lung infections. Nanomaterials like quantum dots are popular as diagnostic agents, whereas nanocarriers like liposomes, solid lipid nanoparticles (SLN), nanovesicles, and nanodroplets are suitable for the targeted delivery of anticancer chemotherapeutic agents. Nanoparticles of diameter < 100 nm can target the lung tumor passively. Properly designed multifunctional nanoparticles can target lung tumors actively. Nanoparticles of inorganic materials such as silver, gold, copper, zinc, iron, *etc*., have potent anticancer and antimicrobial activity. They are suitable for treating cancer and other respiratory infections such as tuberculosis.

PULMONARY DISEASES

Lung cancer

It is the deadliest disease in the world due to the lack of efficient early identification and the limits of standard therapy methods for advanced-stage patients as a highly invasive thoracic malignancy with rising frequency[6]. The main contributors to the development of lung cancer are tobacco smoking, exposure to polluted air, and hereditary disorders passing from one generation to another[7]. The rapidly growing non-small cell lung cancer often appears near the outer layer of the lung. It displays poor cell differentiation and rapidly spreads to other parts of the body[8].

Pathophysiology

The maintenance of blood vessel growth is achieved through a delicate balance between chemicals that promote and prevent apoptosis. Meanwhile, lymphatic tubes eliminate metabolic waste from the tissue spaces, allowing the vasculature to supply linked cells with adequate oxygen and nutrients[9,10]. There is the rapid proliferation of tumor tissue during its progression. As a tumor grows to a certain extent, the cells located at a distance from the supplying blood vessels become deprived of oxygen and nutrients, leading to apoptosis or necrosis death to limit tumor growth. On the other hand, this hypoxia induces the generation of abnormal blood vessels, known as Neo-angiogenesis[11]. This tumor vasculature has uneven branches and defective endothelial cells and basement membranes. Though neo-angiogenesis is not as well-regulated as embryonic angiogenesis, it promotes tumor development and provides a route for metastasis[11].

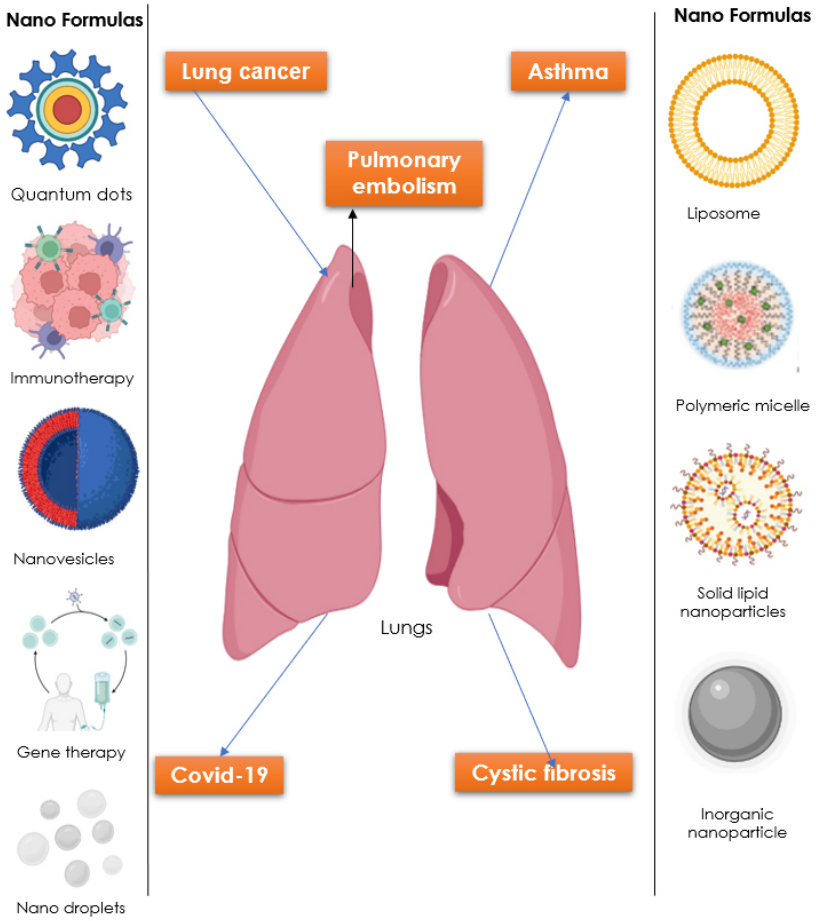

Figure 1. Role of nanocarriers in treating pulmonary diseases like asthma, cystic fibrosis, lung cancer, and lung infections. Nanomaterials like quantum dots are popular as diagnostic agents, whereas nanocarriers such as liposomes, solid lipid nanoparticles (SLN), nanovesicles, and nanodroplets are suitable for the targeted delivery of anticancer chemotherapeutic agents. Nanoparticles of inorganic materials such as silver, gold, copper, zinc, iron, *etc.*, have potent anticancer and antimicrobial activity. They are suitable for treating lung cancer and other respiratory infections like tuberculosis.

The blood vessels in tumors have a decreased surface-volume ratio, making it challenging to deliver nutrients and oxygen[10]. This results in a hypoxic microenvironment within the tumor cells, providing a favorable condition for the survival of apoptosis-resistant cells. The regulation of hypoxia-induced apoptosis is governed by multiple factors, including hypoxia-inducible factor (HIF-1) prolyl hydroxylase 1 (PHD1), which is accountable for the proline hydroxylation effect and oxygen-sensory action[10]. The HIF-1 transcriptional complex decreases the need for oxygen and regulates vascular endothelial growth factor (VEGF) which overexpresses to increase permeability of the tumors' blood vessels[12]. In contrast, BRAF is a serine-threonine kinase protein that functions by activating MEK through phosphorylation[13]. These genetic alterations can result from environmental exposure and cause modifications to DNA in lung cells, leading to aberrant cell growth and potentially resulting in cancer[14].

Treatment

There are various FDA-approved treatment strategies for lung cancer. Emerging drugs based on targeted delivery of siRNA to the lungs have opened up the intriguing potential for treating various lung disorders[15]. Localized siRNA administration to the lungs has been demonstrated to result in significantly more lung accumulation than the systemic approach while limiting non-specific distribution in other

organs[15]. Paclitaxel is a broad-spectrum anticancer agent that binds with the microtubule and arrests the cells at the G2/M phase[16]. Cisplatin binds with DNA and inhibits the repair mechanism causing cell death[17]. In low-oxygen environments, the prolyl hydroxylase PHD1 is activated by docetaxel. This leads to cell death in cancer cells and decreased HIF-1 protein[18]. Bevacizumab is an antiangiogenic agent that inhibits the growth of blood vessel cells by suppressing the VEGF receptor pathway[19]. Some Tyrosine-kinase inhibitors, such as Erlotinib, prevent the activation of EGFR by blocking mutations in the tyrosine kinase domain located in exons 18 to 21[20]. The first generation of EGFR-targeted tyrosine kinase inhibitors, including gefitinib and erlotinib, have shown high efficacy in treating lung cancers with two commonly occurring mutations, either exon 19 deletions or the L858R mutation in exon 21[20]. These mutations cause EGFR to become overactive without any stimulus from ligands, leading to cell growth and resistance to cell death[21]. However, the presence of an exon 20 activation mutation typically signifies a natural resistance to these treatments.

Limitation

The use of the conventional delivery system of chemotherapeutic agents frequently results in severe and undesirable side effects due to their nonselective biodistribution destroying healthy tissues, particularly the fast-growing tissues such as blood cells, digestive system cells, and skin cells[22]. Common side effects of chemotherapy include decreased immunity, decreased production of blood cells, digestive discomfort, fatigue, hair loss, increased risk of additional cancers, decreased fertility, mental decline, and toxicity to organs[23]. Moreover, standard chemotherapeutic treatments are prone to developing MDR. The harsh consequences of chemotherapy on the patient's health significantly lower their quality of life and can even lead to death[24]. Therefore, developing novel nanoformulations of anticancer agents is essential to overcome the side effects.

Nanotechnology

Even with significant advances in early detection, combination therapy, and the knowledge of the molecular basis of drug resistance, the overall success rate in curing lung disease remains low. The unique physical and chemical properties of nanoscale materials provide researchers with ample opportunities for diagnosis and drug delivery strategies.

Liposome

The USFDA has approved doxorubicin (DOX) loaded PEGylated liposome (Doxil^{M}/Caelyx) for the treatment of lung cancer[25]. It has prolonged the mean residence time (MRT) of loaded drugs in plasma with targeted delivery of drug at the tumor cells[25]. During phase I clinical studies, it was found to have a special effect of single agent PEGylated doxorubicin on metastatic or locally advanced non-small cell lung cancer (NSCLC)[26]. In a separate study, advanced NSCLC patients who had not undergone prior chemotherapy were treated using a combination of three drugs (Doxil^{M}, gemcitabine, and docetaxel)[27].

In an attempt to treat metastatic lung cancer, scientists developed nanoformulations for the pulmonary administration of cisplatin and doxorubicin[28]. They had synthesized the methoxy-Poly-ethylene-glycol-poly(L-glutamic acid) (MPPLG) copolymer to prepare nanoparticles for targeted delivery of loaded cisplatin and doxorubicin to the lung tumor[28]. The results indicated that this nanoformulation was more effective in treating metastatic lung cancer compared to cisplatin or doxorubicin alone.

Solid lipid nanoparticle

SLN are nanoparticles of fatty acids, fatty alcohols, or fatty esters. Their size is less than 200 nm. They are suitable for the delivery of lipophilic drugs such as paclitaxel (PTX) which is popularly used in lung

tumors[16]. Figure 2 describes the mechanism of nanocarriers to augment tumor cell death. However, its poor water solubility, limited oral bioavailability, and potent cytotoxicity make its usage challenging. Dastidar *et al.* (2019) developed 78 nm PTX loaded nanoparticles core shell nanoparticle[16]. PTX was loaded within the core and the shell was made up of cetyl alcohol. The drug encapsulation efficiency was 98%. It enhanced the potency and efficacy against A549 cells by 6.8 times. Moreover, this nanoformulation was also effective against PTX resistant A549 cells[16]. The oral bioavailability in SD rats was 95%. When tested *in vivo* in syngeneic BALB/C mice model, it enhanced the potency and efficacy of PTX. Interestingly, this cetyl alcohol nanoparticle was capable of targeting the $ALDH^+$ cancer stem cells[16].

Researchers developed a novel treatment for lung cancer using calprotectin-loaded porous microspheres made from acetylated dextran (Ac-DEX)[29]. The release of medication can be controlled by choosing Ac-DEX with different molecular weights. This allows for the regulation of release over short periods orally[29].

Polymeric micelle

Cisplatin (CDDP) is a broad-spectrum antineoplastic agent that targets DNA[30]. However, prolonged use or spontaneous mutations in tumor cells can lead to drug resistance, reducing its efficacy during therapy. NC-6004 comprises a block co-polymer-metal complex of the sodium salt of poly- (glutamic acid) and cisplatin at the core surrounded by a shell of Polyethylene glycol[31]. Pharmacokinetic studies showed that NC-6004 had a longer half-life in the blood circulation than cisplatin and exhibited a sustained release of platinum species[31]. Recently, researchers reported the findings of long-lasting antitumor activity combined with NC-6004 and gemcitabine in patients with advanced lung cancers[32].

Nanoformulations in immunotherapy

Investigations have shown that the human gene PDL1 plays a critical role in maintaining the survival of cancer cells through its intrinsic signaling capacities[33]. Researchers have extensively explored using gold nanoparticles (GNPs) in tumor imaging and treatment because of their exceptional properties[34]. This nanoplatform can not only be used as a photothermal agent for lung cancer treatment, but also can decrease the expression of programmed death ligand 1 (PD-L1)[34].

Lipid nanoparticle

Cationic lipid nanoparticles are suitable for incorporation of anionic nucleic acids such as miR-660. A study using a mouse model of lung cancer showed that the disruption of expression of miR-660 leads to the progression of lung cancer[35]. Furthermore, the systemic delivery of miR-660 increased its level in the tumor, significantly slowed the growth of cancer, and adverse reactions on two different p53 metastasized xenografts from lung cancer patients[35]. The results showed that the developed miR-660 lipid nanoparticles did not cause any immunological off-target or acute/chronic harm[35].

Nanovesicle

The side effects of anticancer drugs primarily arise from their toxicity towards healthy tissues, particularly in the case of traditional therapies[36]. To maximize clinical effectiveness while minimizing these adverse effects, researchers have explored the use of cancer-targeted nanoparticles in cancer therapy[37]. These nanoparticles take advantage of their unique nanoscale size and the specific pathological environment of tumors, allowing them to easily penetrate and accumulate within tumor tissues[38]. Liu *et al.* developed an innovative and highly efficient doxorubicin-loaded nanomicelle[39]. This formulation exhibited potent anticancer activity against pancreatic ductal adenocarcinoma (PDAC)[39].

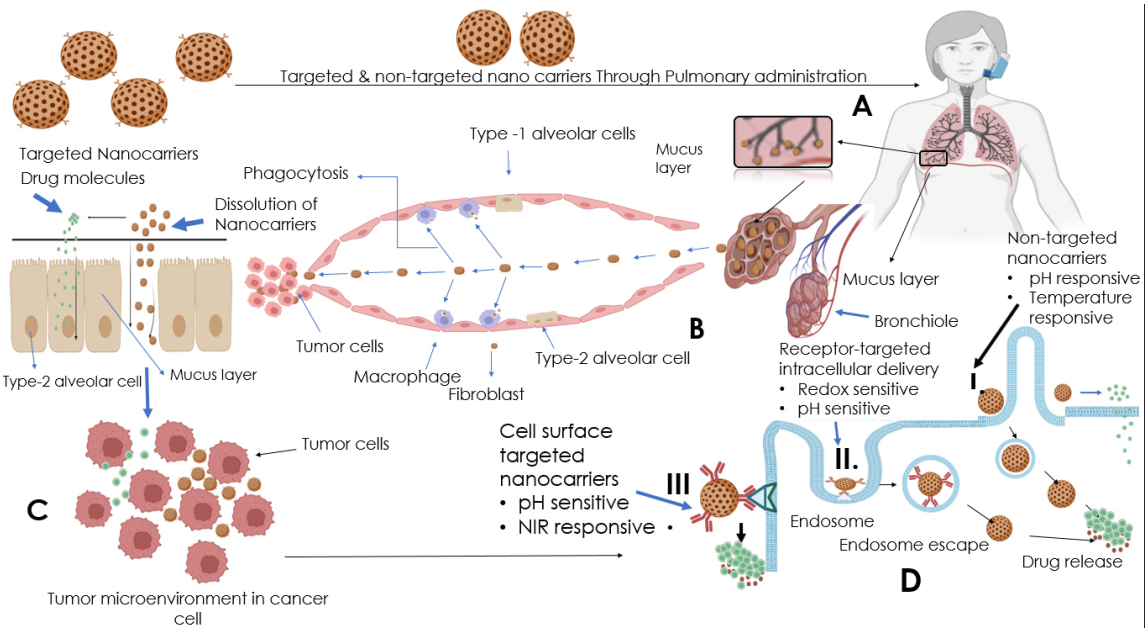

Figure 2. Nanocarrier-loaded surface-functionalized nanocarriers for pulmonary delivery in lung cancer. It describes that targeted nanocarriers have been administered through the pulmonary route. (A) Nanocarriers undergo through the mucus layer of human lungs. (B) In the mucus layer, different cells are present such as Type 1 alveolar cell, Type 2 alveolar cell, macrophage cell, Fibroblast, and Tumor cells. Drug nanocarriers attach to the tumor cells by the process of phagocytosis. (C) Nanocarriers dissolve with the tumor cells and penetrate the surfactant layer of mucus in a microenvironment. (D) Three types of nanocarriers are intended for drug delivery to tumor cells. (I) stimuli (pH, temperature) triggered intracellular delivery of drugs in tumor cells using passively targeted nanocarriers. (II) stimuli (pH, temperature) triggered intracellular delivery of drug in tumor cells using actively targeted nanocarriers (III) Cell surface targeted nanocarriers bind with the target receptors on tumor cells and release the drug upon stimuli such as a change in pH or generation of heat using NIR radiation.

Quantum dot

The advent of quantum dots (QDs) has opened up new prospects for optical imaging[40]. It also offers several advantages over traditional methods. To enhance sensitivity, resolution, and signal-to-noise ratio, imaging in the NIR-I range (700-900 nm) reduces auto-fluorescence, scattering, and absorption effects[40]. Among the most promising NIR-emitting QDs with promising biomedical applications are Ag_2S QDs, which are superior to traditional cadmium- or telenium-based QDs such as Cd@Te or core/shell quantum dots[40]. Researchers have demonstrated a targeted cancer therapy approach using cyclic RGD peptide (cRGD) that is used as a radiotracer for invasive monitoring of tumor metastasis that tagged with Ag_2S QDs which was coated with thiophene-based methamphetamine derivative (MPA), loaded with the drug doxorubicin[41]. These Near IR-emitting Ag_2S QDs, stabilized with bovine serum albumin (BSA), have been conjugated with vascular endothelial growth factor (VEGF) antibodies for targeted cancer imaging. To deliver drugs to cancer cells that overexpress the folate receptor, folate-targeted Ag_2S QDs loaded with doxorubicin were designed and utilized[41]. In other words, molecularly targeted medications can potentially improve patient outcomes and reduce side effects compared to conventional chemotherapy methods. Duman *et al.* developed PEGylated Ag_2S quantum dots functionalized with cetuximab (Cet) antibodies and the incorporation of 5-fluorouracil (5FU)[40]. The synergistic effect of these combinations led to a significant increase in apoptotic cell death[40].

Stimuli-responsive nanoparticles

Promising results have been seen in preclinical and clinical studies of photo-responsive nanoformulations. When exposed to light, Chlorine-6 (Ce6) generates reactive oxygen species (ROS) that lead to the

destruction of cancer cells[42]. In another study, researchers created pH-responsive nanoparticles (NPs) to encapsulate DTX and evaluate its drug release profile and anticancer effects. The NPs were designed to increase in size in the tumor microenvironment's acidic pH, facilitating faster and more efficient drug release[43]. On the other side, double-stranded small interfering RNA (siRNAs) molecules work by inhibiting the production of specific proteins through the RNA interference pathway[44]. However, the challenge with siRNAs is their entrapment in endosomes. To overcome this issue, researchers have explored using pH-responsive NPs that can release siRNAs in response to the acidic endosomal pH[44].

Cystic fibrosis

It is an uncommon genetic condition that impacts the respiratory system. It causes the production of thick, sticky mucus that clogs the airways and makes breathing difficult[45].

Pathophysiology

It is caused by severe impairment in the functioning of CFTR protein[46]. The airway tissues have the greatest level of CFTR expression. Recent research has established a model that describes how airway surface fluids and mucus hydration are regulated[47]. The periciliary region may be kept hydrated indefinitely by drawing water from a reservoir produced by secreted mucins, namely MUC5AC, MUC5B, and MUC2. Lack of oxygen triggers cellular signaling processes, affecting angiogenesis, inflammation, and fibrosis. Ceramide levels increase cell death, DNA release, bacterial adhesion, and chemokine release[48].

Treatment strategy

To date, about 2,500 mutations associated with CF have been discovered. However, only a limited number of these mutations account for the majority of cases[49]. Innovations such as pancreatic enzyme replacement therapy and improved nutritional management were introduced in the 1970s[50]. In addressing respiratory difficulties, recent advancements include inhaled medications such as dornase alfa. This medication aids in the breakdown of neutrophil DNA in the nasal passages, lowering mucus discharge accumulation[51]. Aside from hypertonic saline, it also operates osmotically by increasing mucus fluid intake[52]. Instead of targeting the root cause, the previously mentioned therapies all address the symptoms and side effects of reduced CFTR function[53].

Limitations

CF requires continuous treatment, but recent advancements increase survival but increase costs. Understanding long-term expenses and treatment costs changes is crucial for cost-effectiveness analysis[54]. Poor treatment persistence can result in increased morbidity, death, and medical costs for chronic illnesses due to forgetfulness, side effects, and resource limits. The level of adherence to CF treatment plans is influenced by several factors, such as understanding of the disease and its treatments, communication between patient and healthcare provider, and the nature of the treatment regimen itself[55]. Effective collaboration between patients and healthcare providers is crucial in determining and implementing treatment plans, addressing patients' worries, and ensuring their comprehension of treatment advice[56].

Nanotechnology

Mucus permeating nanoparticles

The disease leads to high rates of death and illness due to bacterial infections and respiratory issues[57]. Mucus blocks the cilia from removing bacteria and causes infections. To overcome this barrier, NPs can be coated with polymers such as polyethylene glycol that do not interact with mucus. Nanoparticles can be coated with non-mucoadhesive polymers to improve their ability to penetrate CF sputum[58]. In this disorder, thin, sticky mucus has been formed that can hinder the delivery of medications to the affected

areas[58]. Once the muco-inert particles reach the underlying lung tissue, they can exert their therapeutic effects. Suk *et al.* have explored the use of muco-inert particles to decrease the viscosity of the mucus[58]. By reducing the viscosity, the mucus becomes less sticky and easier to clear from the airways, which can help improve lung function.

PEGylation

Researchers developed flash nanoprecipitation (FNP) technique to prepare ibuprofen-loaded nanoparticles[59]. They used these NPs to examine the degree and structure of PEGylation on mucus penetration[59]. They varied the % of PEG to study the role of PEG density on particle surface to penetrate the tough mucus. The conformation of PEG molecules is also important. Ivacaftor is a potentiator of CFTR protein. In an attempt to deliver ivacaftor through the pulmonary route, researchers developed PEGylated poly(N-2-hydroxyethyl)-d-aspartame that penetrates CF artificial mucus[59]. They found that a “brush-like” PEG corona was more effective rather than a "mushroom" conformation in mucus penetration. It also avoided the hydrophobic interaction between mucin and nanoparticles.

Mucolytics

Mucolytic drugs penetrate CF mucus, reduce viscoelasticity, and increase NP mobility[60]. In a study, the combination of N-acetyl cysteine (NAC) was observed to enhance penetration through the mucus in cystic fibrosis[61].

Viscoelastic sputum also hinders efficient nanoparticle drug and gene delivery in the patients[58]. Suk *et al.* covalently conjugated low MW (3.4 kDa) diamine polyethylene glycol (PEG) to polystyrene particles (PEG-PS)[58]. The dense PEG coating was confirmed by the near-neutral surface charge of PEG-PS. Uncoated particles are highly negatively charged. A fluorometric assay revealed that all the Particles coated with low MW PEG exhibited greatly improved transport rates in CF sputum[58]. Scientists also conducted a study to determine the ability of 10 kDa polyethylene glycol (CK30PEG10k/DNA) NPs to penetrate the mucus[61]. These NPs are about 350 nm in length and are made of poly-l-lysine with 10 kDa of PEG and non-specific DNA. They evaluated the penetration of NPs by exposing mucolytic agents[61]. Suk *et al.* conducted an assay to assess the impact of mucolytics such as DNase and NAC on diffusion[62].

Nanocarriers in bacterial infection

One particular strain of Pseudomonas aeruginosa has been found to thrive and form a biofilm on the extracellular matrix of epithelial cells in the lungs. This type of lung infection is most commonly seen in individuals with the disease. However, the therapeutic level of free-form Tobramycin cannot be achieved because it is rapidly eliminated and unable to permeate the mucosal membrane[63]. In another study, human bronchial cells have been cultured with *P. aeruginosa* to make a biofilm at the air-liquid interface to show the safety and efficiency of aerosolized anti-infective nanocarriers[64]. This biofilm was transferred to filter-grown monolayers of the human CF cell line (CFBE41o-). This methodology provides a suitable time window for depositing aerosolized ciprofloxacin-loaded nanocarriers. When administered after 1 h, the nanocarriers eliminated all bacteria and decreased the pathogen’s biofilm fraction of pathogen, although CFBE41o- viability and barrier qualities were preserved[64].

Lipid nanoparticles

Scientists developed a new delivery system, Tobramycin-loaded nanostructured lipid carriers (Tb-NLCs), to enhance the delivery of Tobramycin and bypass the mucosal membrane[63]. mRNA treatment by nanoparticles is a powerful method for transferring genetic material to cells with vast, broad populations, such as airway epithelia. Introducing a therapeutically relevant lipid-based nanoparticle (LNP) into patient-

derived bronchial epithelial cells increased membrane-localized CFTR and restored its primary function as a chloride channel[65].

Polymeric nanoparticle

The results of an isothermal titration calorimetry study revealed a significant interaction between alginate and tobramycin[66]. To stabilize the medication and alginate mixture, chitosan was introduced as a supplementary polymer. The NPs were also functionalized with DNase to help break down the DNA polymers found in mucus. NPs showed low cytotoxicity and high survival rates in *Galleria mellonella* larvae model[66]. Gram-negative bacteria are attracted to silver nanoballs due to the positive charges on their surface in solution. The positive charge also weakens the interaction between the nanoballs and bacteria but enhances their interaction with mucus. The antibacterial properties of the nanoballs were evaluated using various species of gram-negative bacteria after a 24-h incubation period[66]. The results showed that nanoballs have enhanced the antimicrobial activity against gram-negative bacteria. Inhaled siRNA therapy has the potential by using lipid-polymer hybrid nanoparticles that consist of a poly(lactic-co-glycolic) acid (PLGA) core and a lipid shell of dipalmitoyl phosphatidylcholine (DPPC) that facilitates nucleic acid transport[67]. SiRNA pool encapsulated in LpNPs against nuclear factor-B (siNFB) with a non-PEGylated (DPPC) or PEGylated (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly-(ethylene glycol) or DSPE-PEG) lipid shell that impacts lung occupancy and mucin type in donor patients[67]. Overall, the results highlight the potential of non-PEGylated LpNPs as carriers for pulmonary delivery of siRNA for the treatment of disease[67].

Nanoparticles for gene delivery

Creating safe and effective nonviral delivery vehicles for gene therapy, especially in treating CF, remains a fundamental challenge. The newly developed poloxamine-based copolymers have shown promising potential for *in vivo* gene delivery compared to conventional cationic polymers or lipids [Figure 3]. Researchers presented the ability of peptides created through modular design to self-assemble into compact and uniform nanoparticles when combined with poloxamines and nucleic acids[68]. Peptide-poloxamine nanoparticles significantly enhance *in vitro* and *in vivo* expression of messenger RNA and plasmid DNA while exhibiting low toxicity. These nanoparticles have the potential to effectively and safely repair long-term deficits in the CF transmembrane conductance regulator[68]. Pharmacological therapies, such as ivacaftor, are limited in efficacy, as they only work for a specific type of CFTR mutation and provide temporary symptom relief through a single mechanism. Leal *et al.* investigated nanoparticles for delivering CFTR-specific Lipid NPs, revealing monodisperse particle size distribution and neutral to slightly negative surface charge in PLGA-LNA NPs[69]. This suggests promising lung-targeted CF therapeutic approaches.

CFTR gene entrapping nanoparticle

Scientists developed a method for developing PLGA and chitosan nanoparticles (NPs) loaded with locked nucleic acids (LNAs) to target, attach to, and turn off the microRNAs[70]. They utilized double-emulsion and self-assembly techniques to fabricate PLGA and chitosan particles that contained two separate 16-base LNAs. The resulting NPs tended to endocytose monocytes[70]. These nanoparticles (NPs) demonstrated an efficiency of up to 70% in loading LNAs, and their physical and chemical properties remained intact after being used for nebulization to deliver the particles to the lungs.

Pulmonary embolism

This is an acute respiratory disorder involving blood clots from the legs blocking arteries, causing inflammation and difficulty breathing[71].

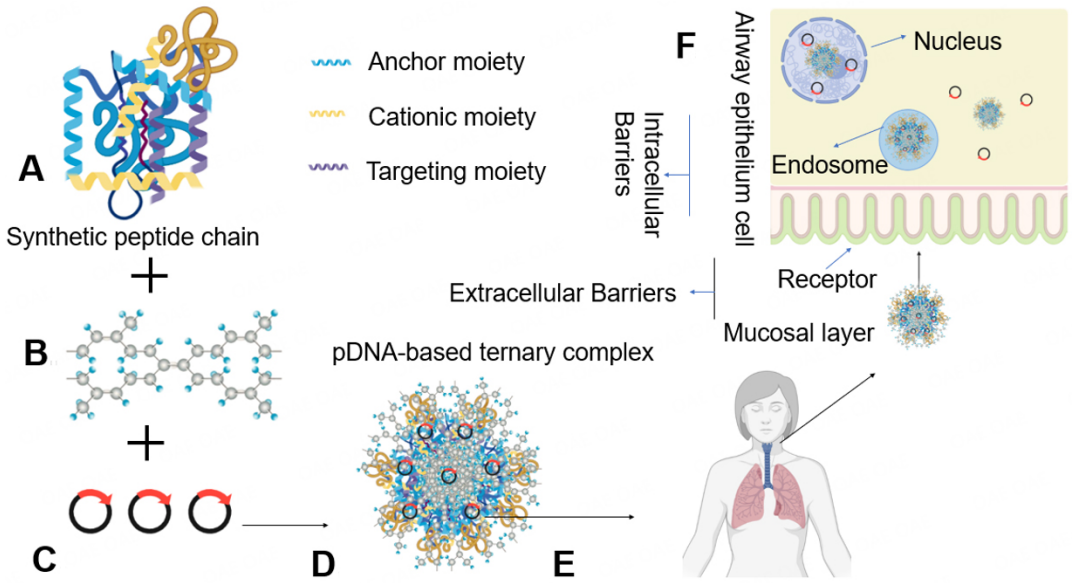

Figure 3. Schematic diagram of the multi-modular peptide-based gene transfection platform used in cystic fibrosis treatment. (A) Structures of the synthetic multi-modular peptide. (B) Structure of polyoxamine-704. (C) Structure of pDNA. (D) Schematic showing nanoparticle formation: pDNA-based ternary complex (pDNA-TC) was prepared via self-assembly of the synthetic peptide, T-704, and pDNA. (E) A suggested method for delivering pDNA-TC to the lungs. (F) The pDNA of the pDNA-TC payloads translocate into cells by passive diffusion, even though all of these nanocomplexes could cross extracellular barriers in the lung tissue thanks to T-704. By overcoming the intracellular barriers, the multi-modular peptide in ternary complexes, in contrast, allows for the effective transport of genetic payloads into target cells and organelles.

Pathophysiology

Pulmonary Embolism (PE) originates from clots formed in the deep veins of the legs. The formation of these clots in the deep veins of the legs is the starting point of PE[72]. Thrombosis, or the formation of clots, takes place in regions where blood flow is slowed, such as valve flaps and furrows, and grows due to local increases in coagulation and reduced oxygen levels caused by blood concentration and hypoxia[73]. Pelvic vein deep vein thrombosis (DVT) has the potential to cause pulmonary emboli, but they usually occur due to specific causes such as pregnancy, pelvic surgery, or pelvic infection. Unlike DVTs located in the upper limbs, those situated in the lower central part of the body have a higher likelihood of causing emboli and resulting in a PE[74]. PE ranges in severity from being asymptomatic to causing hemodynamic collapse and death. The main contributor to its high mortality rate is the impact it has on the body's hemodynamic balance[75].

Treatment strategy

Rapid and reliable diagnosis is important for the management of this disease that is followed by an assessment of the risk level to develop a tailored treatment approach[76]. Accurate detection, threat assessment, and anticoagulant therapy serve as the cornerstones of contemporary PE treatment[77]. The level of expertise required from radiologists, and specialists in angiographies can vary based on the specifics and severity of the acute PE case[77]. At each hospital, the optimum management entails a coordinated, interdisciplinary strategy that adheres to consensus-based protocols[78]. When administering thrombolytic medication, it is recommended to use a high concentration and administer it briefly[78].

Limitations

Having an understanding of the underlying pathophysiology helps in assessing the risk level of patients and choosing the most appropriate treatment option. A small percentage of individuals at higher risk may

require a more intensive form of thrombolytic intervention[77]. Clinical factors associated with a poor prognosis include advancing age, cancer, congestive heart failure, low systemic arterial blood pressure, chronic obstructive pulmonary disease, and dysfunction of the right ventricle. Before undergoing any thrombolytic treatment, all patients should undergo thorough screening to identify potential contraindications, such as a history of brain conditions, and recent surgical procedures[77]. Catheter-directed thrombolysis has been utilized to treat blood clots in the groin area[79]. This augmented different clot-dissolving medications such as alteplase aided in breaking down the clot and restoring the blood flow. Therefore, different nanotechnology approaches have been developed as represented in Figure 4.

Nanotechnology

Polymeric micelle

Researchers developed FXIIIa-targeted near-infrared scanning and thrombolytic nanoparticles known as IR780/FPHM/LK NPs, resulting in fibrin polymerization[80]. Limited therapeutic interval and bleeding consequences of traditional therapy limit clinical applicability; polymeric hybrid micelles with PCL-PEI and PCL-PEG can be used as codelivery of diagnostic sensors and medications[81]. Complex and time-consuming production is commonly essential to modify the structure of the polymers in order to control the ratio of cationic sections. So, compared to traditional polymeric nanocarriers, a highly generic polymeric nanocarrier with adaptable features is probably preferable[82]. Reversible addition-fragmentation chain transfer (RAFT) was implemented to construct a series of pH-responsive di block polymers that constituted of poly[(ethylene glycol)-b-[(2-(dimethylamino)-ethyl methacrylate)-co-(butyl methacrylate)], PEG-(DMAEMA-co-BMA)[82]. In comparison to the benchmark polymer, NPs improve siRNA biodistribution, gene silencing, and organ function[82].

Carbon dot

Studies have been conducted to assess the risks of thrombolysis and determine the patient groups in which the benefits outweigh the dangers.

A novel form of protein-carbon dot nanohybrid has been developed by incorporating carbon dots into thrombolytic drugs through covalent bonding[83]. The nanohybrids exhibit both fluorescent traceability and thrombolytic capability simultaneously, making them a unique example of the integration of fluorescent nanomaterials and thrombolytic agents[84]. A novel sort of carbon dot (CDOT) nanoparticle has been developed that significantly lowered collagen-stimulated human platelet aggregation[85]. It also inhibited the activation of collagen-activated protein kinase C (PKC) and the phosphorylation of Akt (protein kinase B), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK)[85]. This study suggests that CDOT has the potential to be utilized as a therapeutic agent in the treatment of arterial thromboembolic disorders.

Nanodroplet

Nanodroplets (NDs) can potentially penetrate retracted clots by enhancing clot lysis due to their small size to enhance drug delivery[86]. The researchers also evaluated nanodroplet-mediated sonothrombolysis with MB and tPA-mediated methods[86]. Compared to typical MB and tPA-mediated sonothrombolysis procedures in retracted blood clots, combined ND- and tPA-mediated sonothrombolysis considerably improved retracted clot lysis[86].

Multimodal molecular imaging can provide much information about thrombi[87]. This study presents phase transition multimodal and multifunctional nanoparticles (EWVDV-Fe-Ink-PFH NPs) for thrombus detection and targeting thrombolysis. The NPs were constructed using a three-step emulsification and

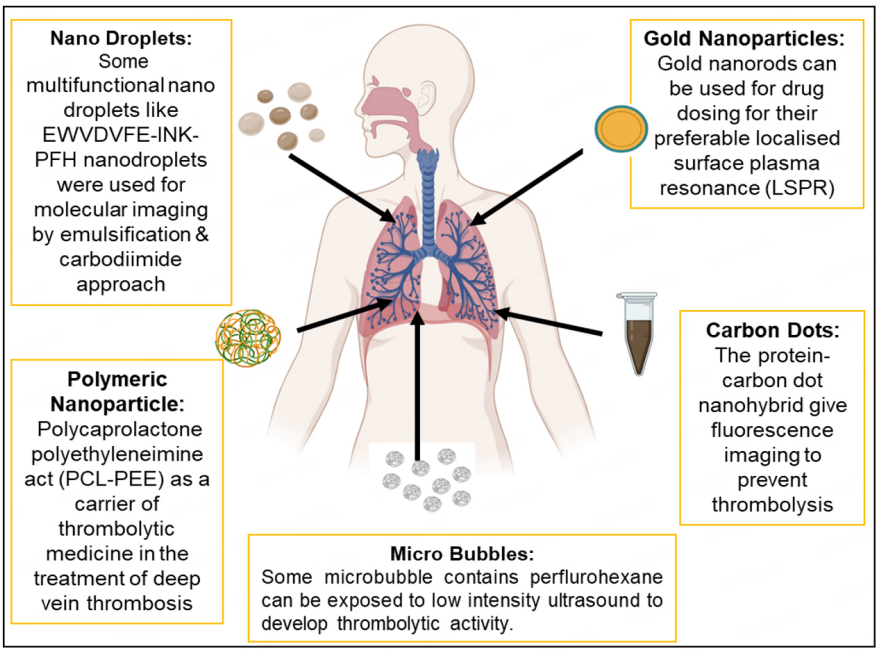

Figure 4. Application of nanotechnology in Pulmonary embolism. Nanotechnologies such as nanodroplets, polymeric nanoparticles, microbubbles, gold nanoparticles, and carbon dotes are suitable for targeted delivery in the treatment of pulmonary embolism.

carbodiimide method, and their physical and chemical properties were investigated[87]. The NPs effectively targeted P-selectin of thrombi, with deep penetration depths and perfluoro-hexane phase transition induced by ultrasound irradiation[87]. These NPs offer a simple, effective, and non-invasive approach for diagnosing and treating thrombosis.

Inorganic nanoparticle

Nanoparticle-based drug delivery systems promise to accurately diagnose and treat various disorders by delivering medications and imaging contrast agents to specific areas[88]. Thrombi, comprised primarily of activated platelets and fibrin, can cause fatal vascular dysfunction by obstructing the blood supply to healthy organs. These systems can potentially target thrombi and improve treatment outcomes[88].

Gold nanorods (AuNRs) have garnered attention as effective nanomaterials for drug delivery and photothermal therapy[88]. This is because of their exceptional ability to produce localized surface plasmon resonance (LSPR). As a result, Near IR (NIR) photothermal thrombolytic systems have the potential to directly dissolve blood clots or enhance the action of thrombolytic agents by inducing localized hyperthermia[88]. The application of nanomaterial-based hyperthermia has the potential to enhance the efficacy of thrombolytic drugs and reduce the required dose. This is because hyperthermia can break down noncovalent bonds in blood clots through the process of lysis[88].

Researchers demonstrated the use of a new activatable fluorescence/micro-CT dual imaging system, utilizing TAP-SiO2@AuNPs, for the first time[89]. This system provides the simultaneous visualizations of thrombin activity and the anatomy of thrombotic lesions in a live animal model. This imaging system utilizes an FDA-approved agent for NIR fluorescence diagnostic imaging[89]. So, the study concludes that the Si-AuNR nanocomposite targeted towards P-selectin by providing NIR-II fluorescence imaging, making it a promising solution for thrombosis treatment[89].

Microbubble

An alternative approach is the use of switchable nanodroplets, also known as nanoexcavators or nanobombs, that can transform into microbubbles. These can also induce thrombolysis through a phenomenon known as cavitation, which involves the destruction of clots through microbubble explosions[90]. In addition to causing thrombolysis, these microbubbles can enhance penetration into clots, further improving the thrombolytic effect. Other research teams have similarly demonstrated that these microbubbles can enhance ultrasound signals, making it a useful tool for particle imaging and forming a convenient theragnostic system[91]. Specifically, these particles only become microbubbles in response to low-intensity focused ultrasound activation, allowing for simultaneous imaging and therapeutic capabilities at the site of a thrombus[91]. Other researchers added MRI and photoacoustic imaging capabilities to these particles by incorporating iron oxide nanoparticles (IONPs)[92]. However, this made the fabrication process more challenging. Despite their wider range of applications, these multimodal particles might not be as practical from a therapeutic standpoint because of their higher cost[90].

Liposomal delivery

Revitalizing blood flow by breaking up clots is crucial for many medical conditions, and the only FDA-approved thrombolytic therapy for ischemic stroke is recombinant tissue plasminogen activator (rtPA). This substance hastens the transformation of plasminogen into plasmin, effectively breaking down clots[87]. Figure 5 represents the mechanism of nanoparticles used in thrombolytic activity. A new liposome-based nanocarrier (T7&SHp-P-LPs/ZL006) was created to target areas of ischemia and penetrate the blood-brain barrier. This nanocarrier is loaded with a neuroprotectant (ZL006) that can help to prevent ischemic stroke. The ex vivo fluorescence imaging results showed that T7&SHp-P-LPs, tagged with DiR, could efficiently cross the blood-brain barrier and were mostly found to aggregate in the ischemic region rather than the normal cerebral hemisphere of MCAO rats. These findings suggest that T7&SHp-P-LPs/ZL006 may potentially improve the prevention of ischemic stroke *in vivo*[93]. Bai *et al.* developed cationic liposomal formulations of low molecular weight heparin utilizing 1,2-dioleoyl-3-trimethylammonium-propane (chloride salt), cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)-2000][94]. The mean particle size of the liposomes was 104.8 ± 20.7 nm, and the drug entrapment efficiency was 90.3% ± 0.1%[94]. The formulations demonstrated thrombolytic effects that are comparable to low molecular weight heparin subcutaneous administration.

Asthma

It is a common respiratory disorder that affects people worldwide. This causes narrowing, swelling, mucus production, causing breathing challenges, and coughing[95].

Pathophysiology

It is a chronic inflammatory disorder[96]. Lungs, with 75 m^2 surface area, are susceptible to microorganisms and environmental contaminants[97]. A wide range of clinical symptoms characterizes the complex heterogeneity of asthma, the manifestation of which depends on the interactions between several environmental factors and numerous susceptibility genes. Asthma is a diverse condition with various clinical symptoms influenced by environmental factors and susceptibility genes, with airway epithelium influencing inflammation[98]. T helper-2 (TH-2) cells influence allergic disorders by producing unique IgE antibodies to aggravating allergens[99]. TH-2 cells mobilize and enhance eosinophils and mast cells, causing goblet cell hyperplasia and increasing bronchial hyperreactivity[100]. The airway obstruction that characterizes the clinical presentation of asthma occurs in cycles of symptom-free intervals and varying intervals of aggravation, which are often triggered by a trigger or other stimuli[101].

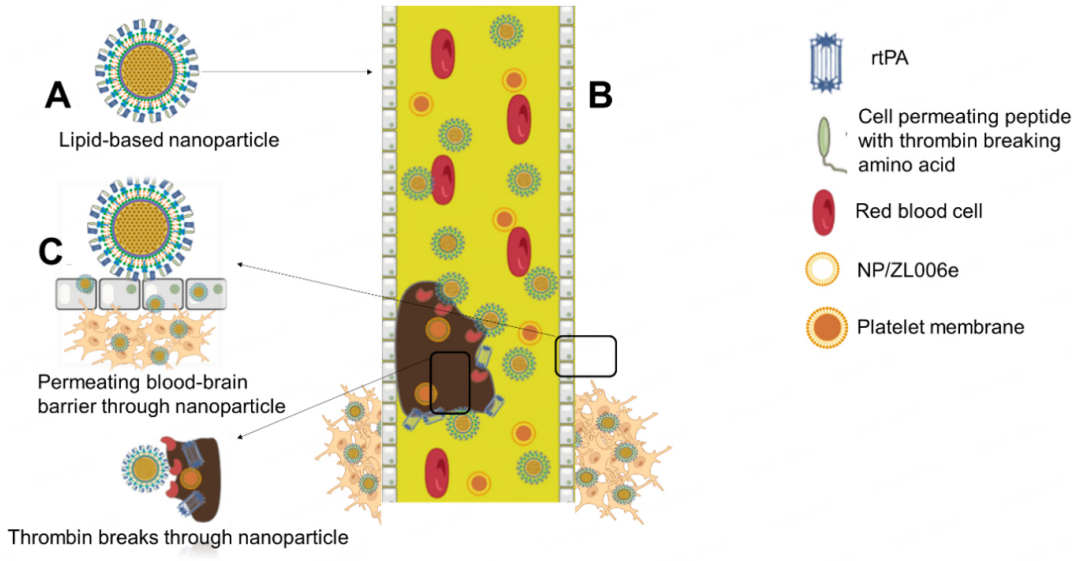

Figure 5. Novel application nanotechnology in pulmonary embolism. (A) specially designed lipid nanoparticle named tP-NP-rtPA/ZL006e. (B) tP-NP-rtPA/ZL006e was injected intravenously. It is directed to the thrombus for the thrombin-triggered release of rtPA. (C) Tat-mediated transcytosis helps in the transfer of nanocarriers into the brain.

Treatment strategies

Various medications have been developed to manage asthma, including anti-inflammatory drugs and antibiotics that can impact the lung microbiome[102]. Anti-inflammatory treatment is crucial for asthma management, with budesonide/formoterol therapy being more effective than Short-Acting Beta Agonist (SABA) reliever in controlling asthma and reducing exacerbations SABA in controlling asthma and reducing exacerbations[102]. Conversely, free corticosteroids interact with cytoplasmic glucocorticoid receptors through the cell membrane. Once activated, the receptors are transported to the nucleus, where they regulate the transcriptional activity of target genes through mechanisms such as gene transactivation and transrepression[103]. Inhaled short-acting beta-agonists (SABAs), such as salbutamol and terbutaline, are the most effective bronchodilators for quickly alleviating asthma symptoms. They bind to the 2-adrenoceptor, activating the Gs protein, which stimulates adenylate cyclase and increases the production of cyclic adenosine 3′5′-monophosphate (cAMP). Inhaled long-acting beta-agonists (LABAs), such as formoterol and salmeterol, are also used to treat asthma and provide bronchodilation for at least 12 h[104]. (TH2) cells play a major role in mediating the asthmatic response by secreting cytokines such as IL-4, IL-5, and IL-13. There are also efforts to shift the TH2-TH1 cell balance towards TH1, which can have anti-asthmatic effects by suppressing TH2-cell cytokines or promoting TH1-cell responses through cytokine-based therapy.

Limitations

Asthma patients face obstacles to adherence, including challenging regimens, undesirable side effects, inhaled medications, Overuse of Short-Acting Beta Agonists (SABA), and inconsistent efficacy[102]. Factors such as the dose of medications required, the frequency of doses, and the method of administration can all play a role in a patient's adherence to medication[105]. Thus, a prolonged acting controlled release delivery system for pulmonary administration is required to overcome these limitations.

Nanotechnology

Liposomal nanoparticle

These increase therapeutic efficacy in the treatment of asthma by minimizing extra-pulmonary side effects. A study showed that curcumin-loaded liposomes with an average diameter of 270 nm and low zeta potential suppressed proinflammatory biomarker secretion, such as Interleukin (IL), better than a group treated with lipopolysaccharide (LPS). This suggests that liposomal curcumin may be an effective treatment for asthma[106]. Some researchers studied the association between bioavailability and the anti-asthmatic efficacy of an aerosolized liposome formulation for delivering anti-asthmatic medication to the lungs[107]. Salbutamol sulfate, with its high-water solubility and quick absorption, was selected as the model treatment. Results showed that liposome-encapsulated salbutamol sulfate was more effective in the treatment of asthma than traditional treatment methods[107]. Konduri *et al*. investigated weekly budesonide encapsulation effectiveness in reducing allergic inflammation in ovalbumin-sensitized mice[108]. C57/Black ovalbumin-sensitized six mice exposed to budesonide in stealth liposomes showed reduced lung inflammation and eosinophil peroxidase activity, reducing serum IgE levels[108].

Solid lipid nanoparticle

For efficient respiration, Phospholipids are found in abundance in the lungs. In order for the alveolar surface to have optimal surface tension and minimize friction in the lung tissue, it is crucial that phospholipid-surfactant proteins be active at this location. Scientists demonstrated a 3:7 SLN phospholipid/triglyceride proportion for pulmonary administration. The quercetin was then incorporated into the solid lipid matrix to form the microparticles. These SLMs have been shown to have improved bioavailability and sustained release of quercetin, making them a promising candidate for asthma therapy[109].

Some studies found the antioxidant activity of rhynchophylline-SLNs and prevented airway remodeling better than traditional rhynchophylline [Figure 6]. The Rhy-SLNs reduced allergic asthma by inhibiting the p-38 signaling pathways[110].

Nanopolymeric particle

Research showed that functionalization with hyaluronic acid improved the thermal stability and therapeutic effectiveness of ferulic acid by facilitating increased interaction with the mucus barrier[111]. Lipopolysaccharide was utilized to create and evaluate nanoparticles containing quercetin for their anti-inflammatory effects. Due to their ability to decrease the secretion of proinflammatory cytokines such as IL-8, IL-1, and IL-6, quercetin-loaded and surface-modified crystalline nanoparticles may prove to be a viable therapeutic option for individuals suffering from asthma[112]. Other research suggests that the interferon response pathways can be re-established because the administration of locked nucleic acid/DNA oligonucleotides into the bloodstream has the potential to impact lung inflammation[113]. The study results showed that delivering medication through the lungs was more effective and efficient compared to oral administration.

Dendrimer

Dendrimers are nano-sized components with tree-like branches made up of a set of macromolecules with finely tuned structures that are controlled via cyclical synthesis. However, PAMAM dendrimers contain NH_2 terminal functionalities and can thus be easily modified according to the specified structure, making them the most versatile dendrimers for uses, particularly in drug delivery and biological applications[114]. PAMAMs dendrimers require modifying cationic groups to avoid toxicity and liver accumulation[114]. PAMAM dendrimers offer high solubility and modification capabilities for solubilizing hydrophobic asthma drugs such as dexamethasone, rifampicin methylprednisolone, and beclomethasone dipropionate[115]. After

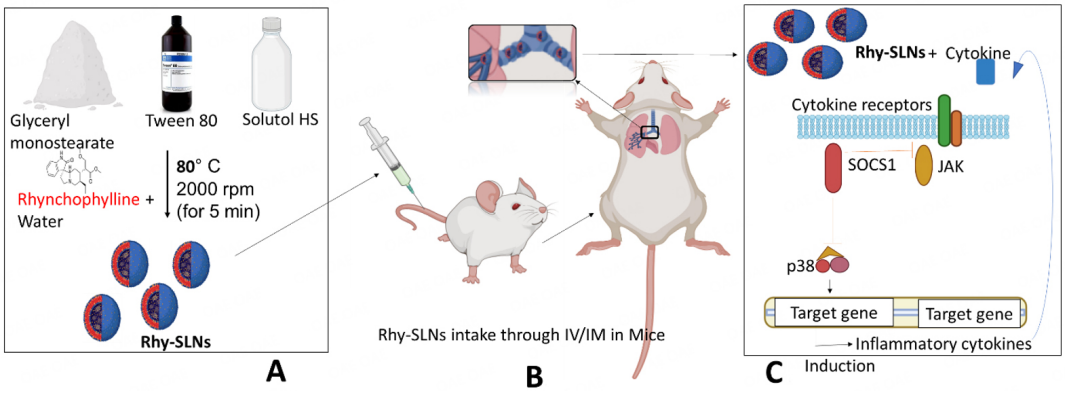

Figure 6. Schematic Diagram of nanotechnology-based treatment against allergic asthma. (A) Glyceryl monostearate, Tween 80, and Solutol are mixed with the aqueous solution of Rhynchophylline at 80 °C at 2,000 rpm for 5 min to form a Rhynchophylline-Solid lipid nanoparticle. (B) Upon intravenous injection in mice, the nanoparticle gets accumulated in the lungs. (C)The released rhynchophylline inhibits the p38 signaling pathway to lower the cytokine level.

binding to PAMAM dendrimers, these drugs significantly enhanced the drug accumulation in the lungs and their bioavailability. Another study showed that the methylprednisolone-dendrimer combination resulted in a substantial decrease of 65% to 85% compared to daily doses of methylprednisolone alone. The research indicated that dendrimer-bound methylprednisolone improves its ability to reduce inflammation caused by allergens, potentially by increasing its duration of action in the lungs[115].

Nanosuspension

Curcumin is a potential asthma supplement with immune system modulation and inflammation reduction. However, limited solubility and bioavailability hinder its therapeutic impact. Researchers have developed water-based nanosuspension Isoliquiritigenin (ILQ) with self-nano emulsifying drug delivery system (SMEDDS) with uniform particle size and 200 nm diameter[116]. ILQ-SMEDDS significantly increased bioavailability in the simulated gastrointestinal tract, with 3.95 times higher than that of ILQ suspension. Another study established a multicomponent formulation for water-based nanosuspensions (NS) including curcumin (CUR) and beclomethasone dipropionate (BDP)[117]. P188 stabilizer optimized single component formulation curcumin nanosuspension (CUR-NS) for long-term stability and nanocrystal solubility in single and multicomponent formulations[117].

Nanomicelle

These are many effective ways to treat asthma. According to a study by scientists, the use of intranasal micellar curcumin was found to be effective in treating chronic asthma. Both dexamethasone and curcumin-micelles were shown to have a similar impact in reducing intracellular levels of reactive oxygen species[118]. The research also demonstrated that the micellar form of curcumin was effective in reducing the production of nitric oxide. Intratracheal administration of the beclomethasone dipropionate (BDP-SSMs) prior to a challenge resulted in a significant reduction in the number of inflammatory cells in bronchoalveolar lavage fluid, compared to the administration of solubilized BDP[119]. When the siRNA was injected intravenously, they specifically targeted alveolar macrophages. The results showed a decrease in airway irritation and mucus production, and inhibition of Chil3 and Chil4 expression, through the use of these ternary complexes[119]. The self-assembled micellar form of chafuroside A was found to be equally effective in reducing airway inflammation caused by ovalbumin, with a 1.0 mg/kg dose. The study suggests that the improved solubility of the self-assembled micellar form of chafuroside-A has a greater therapeutic effect[120].

Coronavirus disease 2019

The novel *severe acute respiratory syndrome-coronavirus-2* (SARS-CoV-2) has caused severe respiratory illness leading to the pandemic in 2020[121]. COVID-19 causes respiratory system effects such as cough, shortness of breath, fever, and multi-organ failure based on the immune system, age, and comorbidities[121].

Pathophysiology

The Spike protein interacts with ACE-2 receptors [Figure 7], causing internalization into lung cells. The viral capsid and lysosomal membrane initiate a cascade of molecular events leading to viral replication and host cell damage[122]. Additionally, SARS-CoV-2 induces cytokine storm in some patients, leading to a hyperinflammatory response, acute respiratory distress syndrome (ARDS), and eventually organ failure. SARS-CoV-2 also causes vascular anomalies, such as enhanced branching and tortuosity of pulmonary vasculatures[122].

Treatment strategy

There are many possible therapeutic strategies (as represented in Figure 8) for the treatment of COVID-19. They include targeting viral entry into host cells, blocking virus replication, and mitigating the host immune response[123]. The combination of Remdesivir and chloroquine went many clinical trials[124]. Favipiravir as a prodrug was also found effective to inhibit the viral multiplication. The combination therapy of lopinavir-ritonavir was also tested in thousands of COVID-19 patients[125]. A combination of azithromycin and hydroxychloroquine was also initially recommended. Since SARS-CoV-2 invades the target cells through ACE-2 receptor protein, ACE-2 inhibitors such as Fluvastatin were found to combat the COVID-19 infection[126,127].

Limitations

No treatment strategies were found significantly effective in covid-19 disease. When compared to routine supportive treatment, researchers failed to demonstrate a significant reduction in the mortality of hospitalized patients[125]. Moreover, many adverse effects were associated with the use of remdesivir and hydroxychloroquine[128,129].

Nanotechnology

Liposome

These produce bilayer vesicular structures when phospholipids become dispersed in water. They are small vesicles with a lipid bilayer-based membrane wrapping an aqueous volume. The liposome is a multimodal drug delivery method for both polar and phobic medicinal molecules [Figure 9]. Additionally, it has been shown that liposomes are quite effective at delivering specific drugs via the lungs[130]. Injecting vancomycin in a liposomal formulation improves the biodistribution of medication in the lung. The medicine concentration in the lung tissue is increased after the liposome has been PEGylated[131]. Researchers invented beclomethasone dipropionate-loaded multilamellar vesicles using the freeze-drying method liposomes[132]. Lipoquin™ and Pulmaquin™ nanoproducts are used as biosensors to detect biomarkers like proteins, DNA, RNA, and antibodies. These nanopharmaceutical approaches enhance local antibiotic delivery in the lung[132].

Polymeric nanoparticle

Polymeric nanosystems improve targeted drug delivery to lung regions by improving therapeutic effects in COVID-19 treatment using biodegradable, biocompatible polymers. Polymeric-based nanoparticles, ranging from 10 to 999 nm, offer specificity, tunable release kinetics, and multimodal drug composition, overcoming limitations in traditional drug development[133]. The other research suggests the Voriconazole-

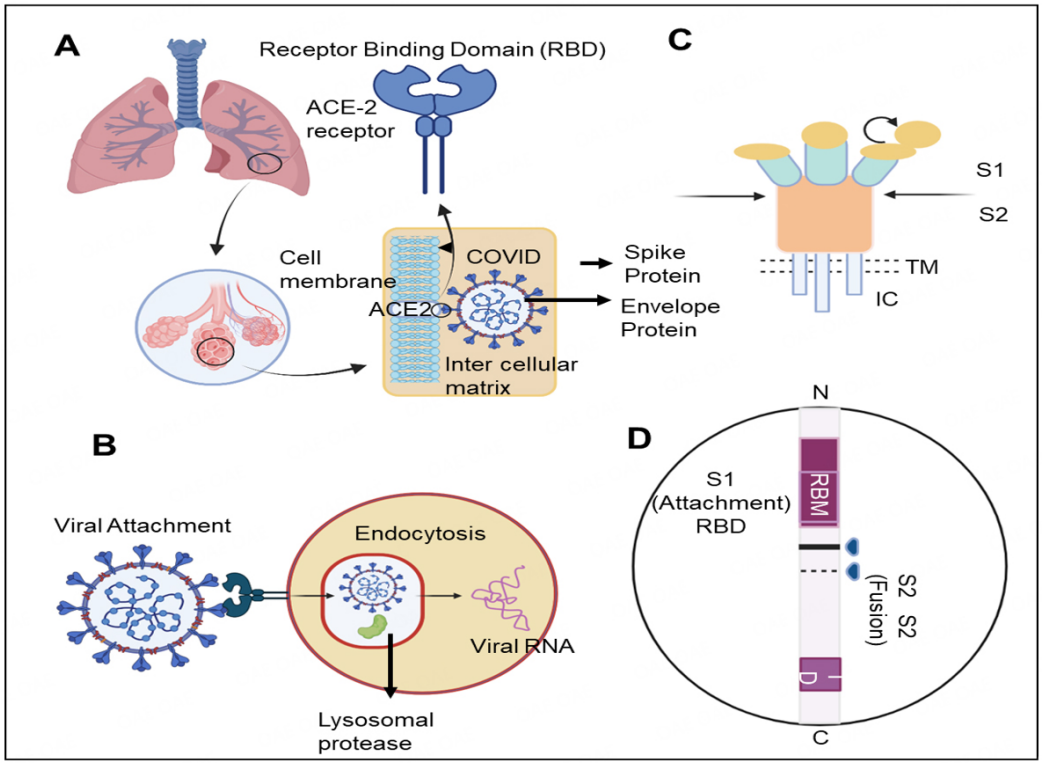

Figure 7. The diagram presents a schematic representation of the various events during the entry of coronaviruses into a host cell. In (A), the ACE2 receptor's RBD (receptor binding domain), which is present in the host cell membrane, binds with the terminal end of the spike protein (specifically S1) of the coronavirus. Cell surface proteases, responsible for activating coronavirus spike proteins, assist SARS-CoV-2 in entering the host cell. Following attachment in the host cell, lysosomal proteases aid in the breakdown of the ACE2-S protein complex, facilitating the release of viral RNA into the cytoplasm through endocytosis, as shown in (B). Moreover, (C) illustrates the 3D structure of the spike protein of coronavirus, highlighting its functional components such as S2 (stalk for membrane fusion), TM (trans-membrane domain), IC (intracellular part), receptor binding domain (RBD), receptor binding motif (RBM), and transmembrane domain (TD). Additionally, (D) displays the diagram of the spike protein, featuring the receptor binding domain (RBD), receptor binding motif (RBM), transmembrane domain (TD), and protease cleavage sites (S1/S2, S2').

loaded-chitosan-coated PLGA nanoparticles for inhaling lactose using a dry powder inhaler[134]. Nanoparticles access deep lung tissue, carrying drugs for structural and local measures. New lipid-modified polymer poly (β-amino esters) developed through enzyme-catalyzed esterification and PLGA-PEG formulation for gene delivery, enhancing efficacy, stability, and self-assembly[135]. This enhanced transfection efficacy, sustained gene release behavior, and excellent stability for at least 12 months of storage at -20 °C after lyophilization without loss of transfection efficacy[135]. In another research, lipid polymer hybrid nanoparticles (LPH NPs) were utilized as a platform for the delivery of azithromycin or niclosamide in combination with piroxicam[136]. The obtained systems were successfully loaded with both azithromycin and piroxicam ($LPH_{Azi-Pir}$) with entrapment efficiencies (EE%) of 74.23% ± 8.14% and 51.52% ± 5.45%, respectively, or niclosamide and piroxicam ($LPH_{Nic-Pir}$) with respective EE% of 85.14% ± 3.47% and 48.75% ± 4.77%[136]. These results provide a rationale for further *in vivo* pharmacological and toxicological studies to evaluate the potential activity of these drugs to combat the COVID-19 outbreak, especially the concept of combination therapy.

Solid lipid nanoparticle

Lipid nanoparticles (LNPs) have a high potential for delivering nucleic acids such as mRNAs. The US-FDA granted emergency use authorization (EUA) to two mRNA-based vaccines, BNT162b2 (Pfizer-BioNTech)

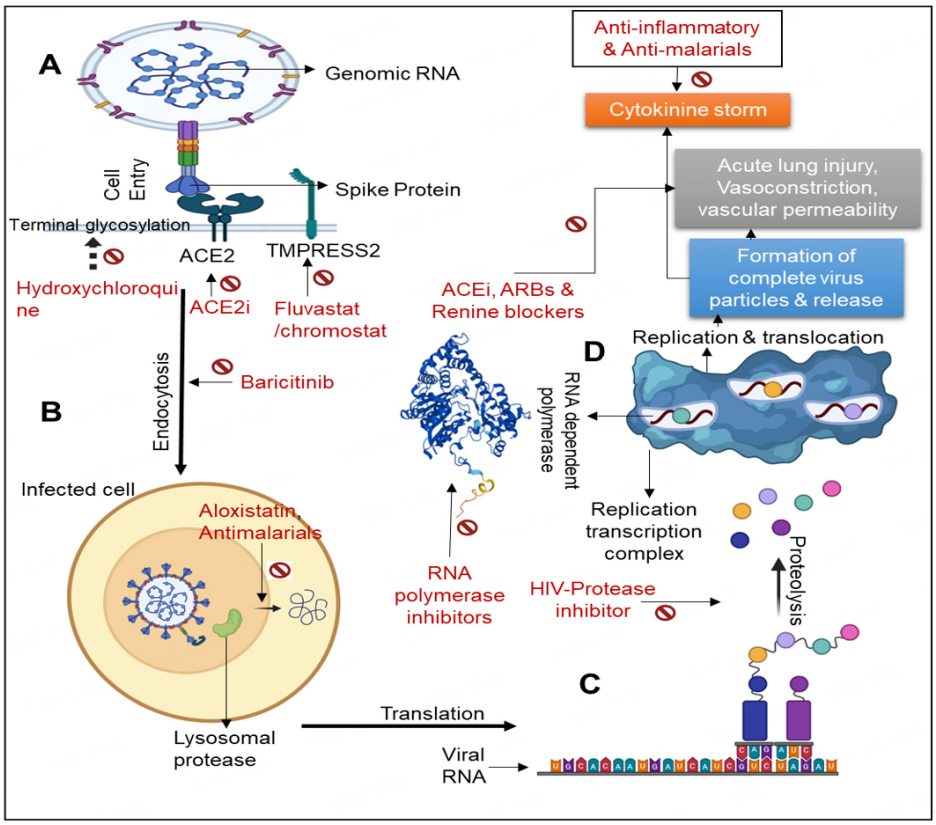

Figure 8. The diagram illustrates the different stages of SARS-CoV-2 infection and potential treatment strategies to target specific steps. (A) SARS-CoV-2 is activated by TMPRSS2, which allows it to attach to the glycosylated ACE2 receptor found on alveolar epithelial cells. The fusion of the viral capsid with the host cell membrane results in endocytosis. (B) Under optimal acidic conditions in the endosome and lysosome, ss(+) viral RNA is generated through fusion. (C) The RNA is then transcribed and translated to synthesise polyproteins which undergo further maturation through cleavage by HIV proteases, resulting in non-structural proteins. (D) The non-structural proteins combine within double-membrane vesicles (DMVs) to form the replication-transcription complex (RTC). The RTC increases the number of RNA copies and generates essential proteins. Assembling the necessary components leads to the formation of the complete viral particle. The release of the complete virion particle is associated with increased cytokine levels and acute lung injury. The figure also highlights possible treatment inhibitors for each step, such as monoclonal antibodies (mAb) targeting specific viral proteins, ACE2 inhibitors (ACE2i), TMPRSS2 inhibitors, Cathepsin B/L inhibitors, ACE inhibitors (ACEi), angiotensin receptor blockers (ARBs), and Janus-Associated Kinase inhibitors (JAKi).

and mRNA-1273 (Moderna), to prevent SARS-CoV-2 induced COVID-19 (Wilson & Geetha, 2022), and the vaccines were produced utilizing LNPs[137]. This research focuses on the potential application of LNPs in developing and delivering mRNA vaccines for COVID-19. mRNAs have self-adjuvating characteristics as they can bind with toll-like receptor 7 (TLR7) and improve cellular immunity. The mRNA vaccines can induce antibody production and T-cell induction as the protein antigen is generated in the cells after vaccination[137]. In another research, SLNs have been invented in which cells are absorbed in lipid layer[16]. This technique has been described in Figure 9. Amikacin has a logP value of 8.8 and is a water-soluble medication.

This poorly water-soluble drug has been encapsulated with stearic acid or cetyl alcohol[138]. Therefore, potential doses with high lipophilicity and low water solubility are suitable for inhalation as SLN.

Quantum dots

A portable smartphone-based quantum barcode serological assay device has been developed for real-time

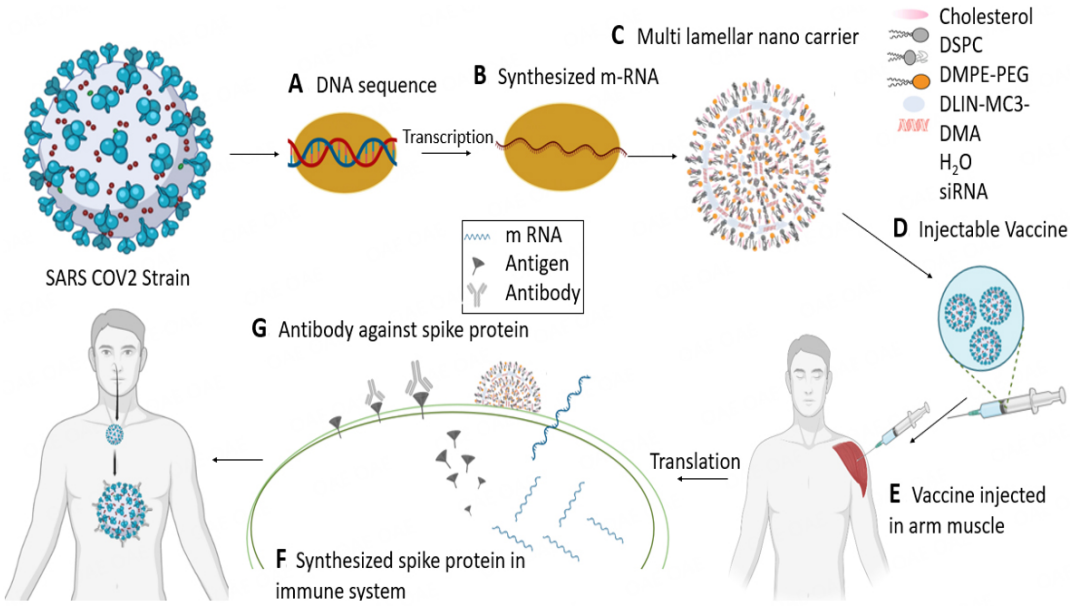

Figure 9. Lipid-based nanoparticles are utilized to effectively deliver a vaccine against SARS-CoV-2. Initially, the viral spike protein's DNA is replicated (A). Then, mRNA is synthesised by transcribing the DNA sequence (B). To encapsulate the mRNA, a multilamellar liposome incorporating cholesterol, distearoyl phosphatidylcholine (DSPC), and 1,2-Bis-(dimethylphosphino)-ethane is prepared (C). This liposome is then formulated for injectable administration (D). The vaccine is administered through intramuscular injection into the subject (E). Within the target cell, the mRNA is released from the lipid and get translated into the desired antigen (F). As a result, the antigenic protein circulates and stimulates the production of antibodies, specifically against the spike protein of the virus (G).

surveillance of SARS-CoV-2 patients[139]. The device has a 90% clinical sensitivity and 100% specificity, outperforming lateral flow assays by 34% and 100%, respectively. The device has ~3 times greater clinical sensitivity because it is ~140 times more analytically sensitive than lateral flow assays. It can diagnose SARS-CoV-2 at different sampling dates and infectious severity, providing instantaneous results for patients, physicians, and public health agencies. Researchers have been exploring the use of carbon nanomaterials in the fight against human coronaviruses. Pang *et al.* produced peptide inhibitors and demonstrated the potential of a series of bioisosteres created from triazole-functionalized heteroatom co-doped carbon quantum dots (TFH-CQDs) to prevent viral entry or inhibit replication enzymes such as helicase[140]. CQDs-2 can be produced through the hydrothermal method by heating citric acid, p-phenylenediamine, and borax at 1,800 °C for 5 h. The triazole moiety in the CQDs-2 can bind with spike proteins, leading to antiviral activity. Improved antiviral activity was observed when the CQDs were surface-functionalized with boronic acid. The triazole moiety is believed to play a role in the antiviral activity, as seen when the boronic acid functional groups were blocked. The co-doping of N and B in the CQDs showed more significant antiviral activity, as demonstrated by the 50% effective inhibitory concentration (EC50). These findings suggest that triazole moieties hold promise as antiviral medicines. In another research, It developed the one-step synthesis of new luminous polyamine quantum dots (PA@CQDs) derived from apricots[141]. The inclusion of molnupiravir significantly reduced the relative fluorescence intensity (RFI) of the produced quantum dots[141]. The fluorescent probe was successfully utilized in a pharmacokinetic study of MOL with a maximum plasma concentration (C_{max}) of 920.2 ± 6.12 ng mL^{-1} without any matrix interference.

Vaccine delivery

In clinical settings, many antibodies have been assessed. So many vaccinations were either subjected to clinical examinations or obtained their approval in recent years[142]. COVAX-19™ vaccine is designed to induce T cells against the spike protein. COVAX-19 vaccine will induce durable high-titer neutralizing

antibodies and T-cell responses against the SARS-COV-2 virus. Different nanomedicines are recommended for mRNA, DNA, and protein vaccinations. Ionizable lipids, PEGylated lipids, structured lipids, and cholesterol are all frequently utilized in the development of mRNA vaccine nanomaterials; for instance, Pfizer-BioNTech developed the nucleoside-modified RNA (modRNA) vaccine BNT162b2 (Comirnaty)[143]. BNT162b2 offers 95% protection against Covid-19 in 16+ adults with short-term pain, exhaustion, and headache, similar to previous viral vaccinations. Over a median of two months, safety was identical to that of previous viral vaccinations.

CONCLUSION

The potential of nanotechnology in treating pulmonary diseases is truly remarkable, as revealed by this comprehensive evaluation. Nanotechnology utilizes the size and shape of particles to unlock a vast array of possibilities. By targeting specific receptors in the lungs, nano drugs can be more efficiently distributed, leading to a significant impact on structures such as bronchioles and alveoli. Additionally, the use of trigger or controlled release methods can further improve the effectiveness of nano drugs, thereby reducing the risk of harmful side effects and resulting in better therapeutic outcomes. The integration of nanotechnology into medical treatment plans can greatly enhance their efficacy, providing a valuable alternative for patients who have not responded well to conventional medication-based approaches. This groundbreaking technology has the potential to revolutionize the field of pulmonary medicine, offering a promising avenue for the treatment of a wide range of respiratory conditions.

DECLARATIONS

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Authors' contributions

Conceptualized the study, guided other authors, and edited the manuscript: Dastidar DG
Reviewed the literature and made the first draft of the manuscript: Dey RK, Jana B

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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