Archives of Materials Science and Engineering

Volume 119
Issue 2
February 2023
Pages 71-85

International Scientific Journal
published monthly by the
World Academy of Materials
and Manufacturing Engineering

DOI: 10.5604/01.3001.0053.4743

Nanomedicine - a boon for respiratory disease management

D. Balasubramanian, S.J. Lavanya, A. Girigoswami, K. Girigoswami*
Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Chettinad Health City, Kelambakkam, 603103, Tamilnadu, India
* Corresponding e-mail address: koyelig@care.edu.in
ORCID identifier: https://orcid.org/0000-0003-4441-7863 (D.B.); https://orcid.org/0000-0002-1541-7293 (S.J.L.); https://orcid.org/0000-0003-0475-2544 (A.G.); https://orcid.org/0000-0003-1554-5241 (K.G.)

ABSTRACT

Purpose: Respiratory diseases affect the lungs and other parts of the respiratory system. The respiratory disease affects hundreds of millions of humans, and premature death is observed in nearly four million people yearly. The major cause of the increase in this disease is the increased level of air pollution and higher tobacco usage in public places.

Design/methodology/approach: We have used the search engines PubMed and Google Scholar for the keywords Respiratory diseases, Nanomaterials, diagnosis, Nanomedicine, and Target drug delivery; recent and relevant articles are selected for reviewing this paper.

Findings: Nanomedicine is a recent field of research that deals with monitoring, repairing, theragnosis, and development of human biological systems at the sub-atomic level, where we utilize engineered nanodevices and nanostructures. The conventional therapeutic strategies designed for respiratory diseases have limited solubility and bioavailability. Moreover, the robust effect of the drugs led to adverse side effects due to their high dose requirement. The local delivery of therapeutic Nanoparticles (NPs) or drug-loaded nano vehicles to the lung is a safe technique for managing various respiratory tract-related diseases like chronic obstructive pulmonary diseases, cystic fibrosis, lung cancer, tuberculosis, asthma, and infection. To overcome the difficulties of conventional treatment with antibiotics and anti-inflammatory drugs, nano-enabled drug delivery, nanoformulations of drugs as well as drug nanoencapsulation have been used recently. In this mini-review, we will discuss the importance and application of nanomedicine for diagnosis, treatment and clinical research involved in the different types of respiratory diseases.

Practical implications: Nanomedicine provides an alternative delivery of drugs with the help of various nanocarriers, which enhances controlled drug delivery at the pulmonary region and can be used for treating and diagnosing respiratory diseases in vivo and in vitro studies. Further experiments followed by clinical examination are warranted to prove the potential application of nanomedicine in treating respiratory disease.

Originality/value: This mini-review will help the readers and budding scientists apply new methods for developing highly efficient drugs with low side effects and improved targeted sites of action.

Keywords: Nanomedicine, Asthma, Chronic obstructive pulmonary diseases, Cystic fibrosis, Respiratory diseases

Reference to this paper should be given in the following way:
D. Balasubramanian, S.J. Lavanya, A. Girigoswami, K. Girigoswami, Nanomedicine - a boon for respiratory disease management, Archives of Materials Science and Engineering 119/2 (2023) 71-85. DOI: https://doi.org/10.5604/01.3001.0053.4743

1. Introduction

Respiratory diseases are the leading causes of death and disability in the world. There are two major categories of respiratory diseases based on their causative agent-infectious and chronic respiratory disorders. There are five major respiratory diseases with which most of the world's population gets infected, and about 4 million people die yearly. These are chronic obstructive pulmonary disease (COPD), pneumonia, cystic fibrosis (CF), asthma, tuberculosis (TB), and lung cancer [1]. Various medicines are used to treat these disorders, but most of them are steroids with severe adverse effects. The treatment of respiratory illnesses and infections remains a significant problem. Much progress has been made in altering the administration of therapeutic medications for respiratory illnesses and infections. Currently, there is a rush of interest in applying nanotechnology-based delivery systems of drugs, which helps to enhance the treatment and diagnosis of respiratory diseases and infections [2]. Various kinds of NPs, such as liposomes, micelles, nanoclusters, etc., are used in various fields of science and technology, such as military and security affairs, spatial, food industry, agriculture, terrestrial and naval/marine industries, animal husbandry and health sciences like wound dressing, diabetes [3,4]. Other nanotechnology applications include targeted drug delivery, theranostics, biosensing and biomedical imaging [5-12]. One of the most important applications of nanotechnology is nanomedicine.

The advantage of nanotechnology research involves investigating and manipulating the matter at molecular levels that may result in drastic changes in society [5]. The definition of nanomedicine is observing, repairing, developing, and influencing human biological systems at their sub-atomic level, for which we can utilize designed nanodevices and nanostructures. Nanoformulations are thermodynamically stable, transparent, low viscosity, and isotropic dispersions of oil and water; they also have a photocatalytic activity maintained by an interfacial coating of cosurfactant and surfactant [13]. Nanotechnology is increasingly being used in consumer goods, cosmetics, and medicine, and it may have an impact on respiratory medicine [14]. NPs loaded with nutraceuticals are reported to have anticancer activity [15], and also different forms of nanoclays were used for food packaging [16]. Local delivery of therapeutic NPs to the lung is ideal for treating different respiratory diseases, including CF, asthma, COPD, cellular breakdown in the lungs, etc. This mucus fluid in the lungs gets cleared within 10 min to 20 min removing the inhaled materials loaded with nanomedicines etc. [17].

2. Nanomedicine for respiratory diseases

A wide range of nanoscale materials has shown some promising effects in managing respiratory diseases, although the role of each type of NPs is not the same [2]. There are various types of nanoparticles used in managing respiratory diseases, which are mentioned in Figure 1. The management of respiratory infections with the aid of nanotechnology follows three fundamental principles:

1. Nanotechnology involves diagnosis and imaging,
2. Targeted drug delivery,
3. Reconstructive surgery.

The ability of NPs to transfer the drugs to specific sites inside the airway can be used to treat respiratory diseases, such as pulmonary diseases (COPD, CF, TB, lung cancer) etc. These aspects will be discussed in other sections [17].

2.1. Nanotechnology involves diagnosis and imaging in respiratory medicine

The final destination is to recognize the disease at the initial stage of the disease at its molecular level [18]. NPs (< 6 nm), which were delivered via the intratracheal route, could reach the bloodstream by crossing the air-blood barrier and can enter the circulation through lung capillaries and lymph nodes [19,20]. Faraj et al. identified a promising strategy for the identification of pulmonary inflammatory disease using the non-invasive MRI by coupling superparamagnetic iron oxide (SPIO) NPs with a cluster of differentiation (CD) 86- and CD206 which identifies the M1 and M2 macrophages localized at the site of inflammation [21]. A similar study was done by Gao *et al.* for the detection of lung cancer in the early stage using nano-size chistosan/Fe_3O_4-enclosed bispecific antibodies (BsAbCENS) that can target the neuron-specific enolase (NSE) and carcino-embryonic antigen (CEA) present in the lung cancer cells

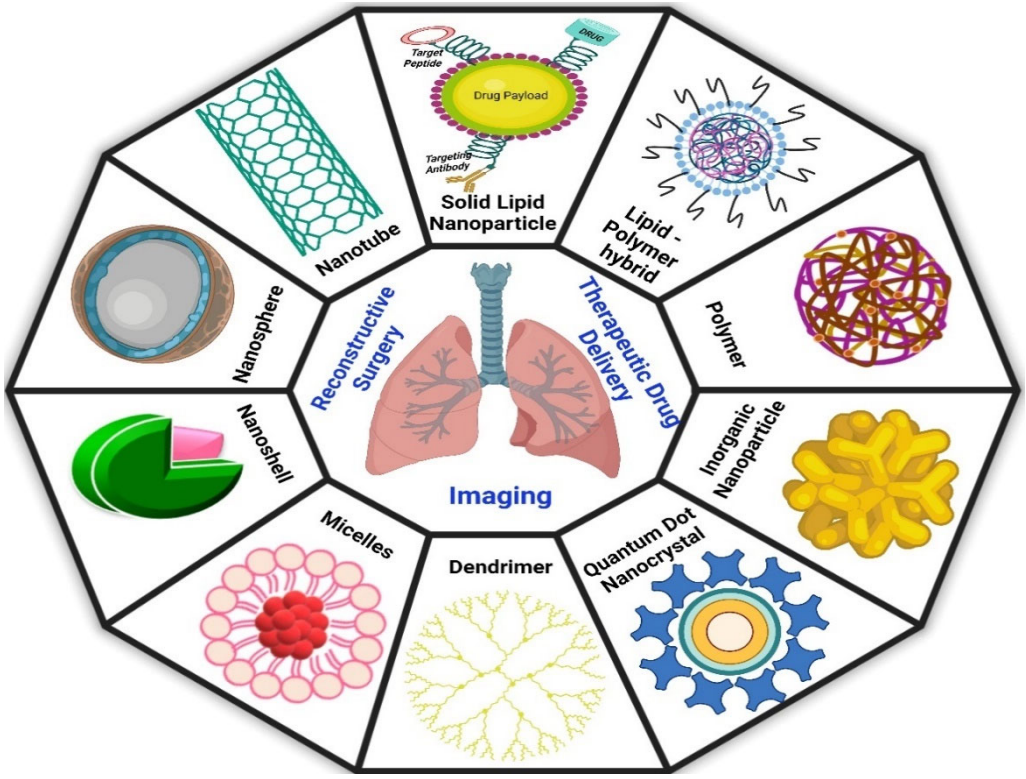

Fig. 1. Various types of NPs used in different fields of respiratory disease management

using contrast-enhanced MRI with BsAbCENS (CEMRI-BsAbCENS). The diagnosis data have shown that the CEMRI-BsAbCENS was diagnosed in 142/182 lung cancer cases, whereas contrast-enhanced MRI can detect only 98/182. This type of detection of lung cancer using specific antibodies encoded in NPs helps in the early detection of lung cancer which leads to the extension of the patient's lifetime [22]. In another study, polystyrene NPs loaded with a near-infrared fluorescent dye (ItrybeNPs) (100 nm) were used for lung imaging. In the lung tissues, the uptake of ItrybeNPs is higher in the alveolar region and M2 macrophages in an ovalbumin (OVA)-based allergic airway inflammation (AAI) model in hairless SKH-1 mice. Fluorescence reflectance imaging (FRI) shows that the fluorescence in the mice AAI lungs is enhanced compared to the control after the administration of ItrybeNPs via the intranasal tract [23]. Gong et al. used two nanoformulations silica coated fluorescence NPs (SFNPs) and silica-coated superparamagnetic to improve the sensitivity and specificity of detection of the SARS-CoV gene during PCR testing NPs (SMNPs). SFNPs help identifies specific cDNA, and the SMNPs bind to the target cDNA and remove it from the bulk sample solution leading to the amplification of specific DNA [24]. Stringer et al. identified a feasible way for porcine reproductive and respiratory syndrome virus (PRRSV) detection using an optical biosensor developed based on Quantum dots and gold NPs (AuNP) labelled with PRRSV-specific capture antibody attached with a fluorescent dye bound to a protein. When in contact with PRRSV, the antibody and antigen will combine to give fluorescence emission that can be identified using a spectrofluorometer. This study showed the advantages of AuNP for the rapid, sensitive and specific detection of PRRSV with a detection limit of 3 particles/µl using FRET platform [25]. Xu et al. studied the active targeting of the biomarker of tumour angiogenesis $\alpha_v\beta_3$-integrin using the perfluorocarbon (PFC) nanoparticle in an orthotopic lung cancer rabbit model. PFC nanoparticle is administered via intratracheal and intravenous pathways and then subjected to the samples in ^{19}F MRI to identify the amount of PFC nanoparticle that has reached the targeted site. Compared to intravenous, intratracheal administration, the PFC NPs showed more quantity of binding that provided a quantitative analysis of tumour angiogenesis [26]. To overcome the limitation in diagnosing various respiratory diseases NPs such as SPIO, PFC, AuNP, SFNPs, SMNPs, etc., can be improved via MRI, FRET, PCR methods, as in Figure 2.

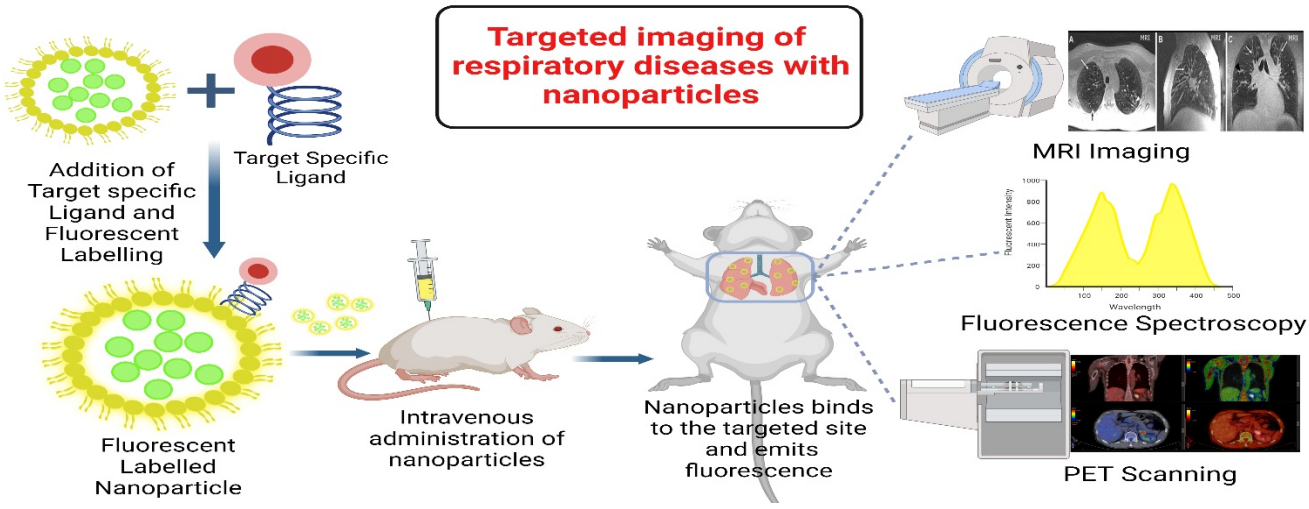

Fig. 2. Fluorescently labelled nanoparticles for identification of respiratory diseases

2.2. Nanotechnology target-based drug delivery in respiratory diseases

In the therapeutic field, the use of nanotechnology offers many advantages that allow the more controllable release of therapeutic compounds and enhanced targeted drug delivery. The controlled drug release and targeted drug delivery focus on the management of drug pharmacokinetics, pharmacodynamics, immunogenicity, and the system of biorecognition for exerting improved efficacy. The two features of nanostructure in drug development are the route of administration and drug formulation [27]. CF is most commonly due to the gene mutation leading to the misfolding of ΔF508-CFTR protein. Various "Corrector" molecules can recover the misfold of ΔF508-CFTR protein like PS-341 (pyrazylcarbonyl-Phe-Leuboronate, a.k.a. Velcade or bortezomib) [28]. The same group of researchers formulated a nano-based biodegradable vehicle using PEGylated PLGA(PLGA-PEG) encapsulated with PS-341 (PLGA-PEG$^{ps\text{-}341}$) to enhance the target base drug delivery and also to provide sustained drug release. PLGA-PEG$^{ps\text{-}341}$ was tested for its sustained drug release in CF cells, and it was identified that they could inhibit the growth of cells maximum on the 7th day after incubation. *In vivo* study done using fluorescent-labelled PLGA-PEG$^{ps\text{-}341NileRed}$ was also tested in C57BL6 mice. Based on the changes in the proteasomal activity of the misfolded ΔF508-CFTR, the misfolding is rectified up to 2-fold after three days of administration of the nano-drug compared to the control.

The fluorescence was used to identify whether the nanoparticle, administered intravenously, reached the target site, using optical imaging 24 h after administration. The presence of PLGA-PEG$^{ps\text{-}341NileRed}$ was found in both murine mice lung and bladder (excreted nanoparticle). The results have also shown sustained drug release from day 1 to 11. They identified PLGA-PEG$^{ps\text{-}341}$ also inhibits *Pseudomonas aeruginosa* (Pa)-LPS which decreases inflammation in the CF conditions, which occurs due to oxidative stress in Chronic CF [29]. Guthi *et al*. developed a multifunctional micellar nanoparticle encapsulated with superparamagnetic iron oxide (SPIO) and doxorubicin (Doxo) for targeted drug delivery and MRI that is encoded with Lung cancer targeting peptide (LCP) target $\alpha_v\beta_6$ (LCP-MFM). The signal intensity of the cells measured using MRI specifically for $\alpha_v\beta_6$ showed the uptake of peptide-encoded MFM NPs in a dose and time-dependent manner. The results indicated that the uptake of LCP-MFM is two times higher compared to control in H2009 cells. This study shows that target-specific MFM NPs can serve as a potential vehicle to target therapeutics for lung cancer [30]. NPs coated with target-specific ligands specific for respiratory diseases were used to overcome the pulmonary barriers which inhibited the drugs from reaching the lungs due to their large size. Therapeutic agents which can prevent and control this disease are listed in Table 1.

When administered intravenously for cell therapy, the mesenchymal stem cells (MSC) get trapped inside the lungs, giving rise to cell-based therapy's major disadvantage. Wang et al. used this disadvantage for targeting lung cancer using the nanoparticle-loaded lung cancer drug docetaxel (DTX). They fluorescently labelled the nanocomposite with IR-780 dye and tagged it to the DTX in NP. This nanodrug was administered along with the MSC to the lungs, which resulted in higher drug uptake at 12 h after administration.

In both rabbit and monkey models, the trio combination DXT/NP/MSC inhibited the cancer growth predominantly at a low dose (1×10^6 MSCs loaded with DXT in NP). The MRI showed that the deposition of MSC is more in the lungs after 24 h administration via intravenous route [31]. This showed that MSC could be used as lung-based targeted delivery for various respiratory diseases. For the treatment of asthma, targeting of the epithelial cells which are present in the airways was executed using various NPs that are loaded with different drugs such as theophylline, betamethasone disodium phosphate, cytosine-phosphateguanosine, polyinosinic-polycytidylic acid, procaterol hydrochloride, etc. which can decrease the number of eosinophils in Bronchoalveolar lavage fluid (BALF). Inhibition of mucus hypersecretion, reduction of bronchial damage, etc., which are the major causes of asthma, was found to be controlled in a superior way using the nano drugs [32]. NPs coated with target-specific ligands specific for respiratory diseases were used to overcome the pulmonary barriers which inhibited the drugs from reaching the lungs due to their large size. Therapeutic agents which can prevent and control this disease are listed in Table 1.

Table 1.
List of various therapeutic agents used for the treatment of respiratory diseases

Respiratory	Therapeutic agents
Asthma	Leukotriene receptor antagonists (LTRAs), Glucocorticoid drug, Cytokine\chemokine antagonists, Theophylline [33].
Cystic fibrosis	Antibiotics (tobramycin, aztreonam lysine, piperacillin, ciprofloxacin), Symptomatic therapy, CFTR gene [2,34].
Tuberculosis	Three Anti-tubular drugs (Isoniazid, pyrazinamide rifampicin) [18].
COPD	Inhaled bronchodilators drugs: long-acting bronchodilator as initiative therapy salmeterol xinafoate, tiotropium bromide and formoterol fumarate, short-acting bronchodilators: Albuterol sulfate Ipratropium bromide [35].
Lung cancer	Alpha-interferon [36].

2.3. Nanotechnology-based regenerative surgery in respiratory diseases

Regenerative medicine focuses on the own body repair system for the prevention of chronic diseases that can disable us, such as diabetes, allergies, obstructive lung diseases and degenerative disorder of the cardiovascular system, etc. It also identifies the viable method to start the control of the regenerative interaction [18]. Reconstruction of the trachea is required when the patient is discovered with tracheal abnormality, in which tracheal stenosis (TS) affects only 1 % of the population. Most commonly, infants lesser the one month show a mortality rate of nearly 70%. TS was divided into two types based on the lesions in the tracheal ring- short segment (SSTS) and long segment (LSTS). LSTS is considered a critical one because 50-70% of the airway is infected in this type. The treatments for SSTS are endoscopic repair, tracheal resection and reanastomosis, whereas for LSTS, slide tracheloplasty is performed for this treatment. Tracheal reconstruction is done using rapid prototyping and three-dimension (3-D) printing, and they synthesize patient specific 3-D models which can be utilized for tracheobronchial stenosis of patient-specific bioresorbable implants. After tracheal resection and reconstruction, 40% of the patients face complications [37]. These complications were due to various anastomotic factors such as length of resected trachea, prior tracheal resection, pre-existing trachea and patients with medical complications such as diabetes. This complication can be prevented by modifying some procedures in treatment or during the implantation.

Granulation of tissues can be reduced by changing the suture from nonabsorbable (polyester) to absorbable (vicryl) substance. Restenosis is seen earlier after an operation and in some cases, it occurs after a month, which is treated with dilation; if it fails, t-tubes can be used [38]. Three-dimension tissue reconstruction of cartilages using thermoreversible polymer and the biodegradable polymer was done both *in vitro* and *in vivo*. The first model they used is thermoreversible gelation polymer (TGP) as a 3D scaffold. Chondrocytes from a calf shoulder were suspended in TGP, and various growth factors were provided. After eight weeks of incubation, the 3D shape of cartilage was formed, which remained unaltered even at four °C. The polyglycolic scaffold was used to get the shape of cartilage which acted as a scaffold to grow cells for three weeks. To maintain the shaper further, this cell-containing scaffold was warped in silica, and a white shape artificial trachea was formed. This intervention was ineffective after implantation due to a lack of growth factors [39].

2.4. Nanomedicine in asthma

Asthma is a widespread and noncontagious disorder in children and adults. More than 30 million people have recently been affected by asthma, a heterogeneous disease. In this disease, there is an interaction between genetic

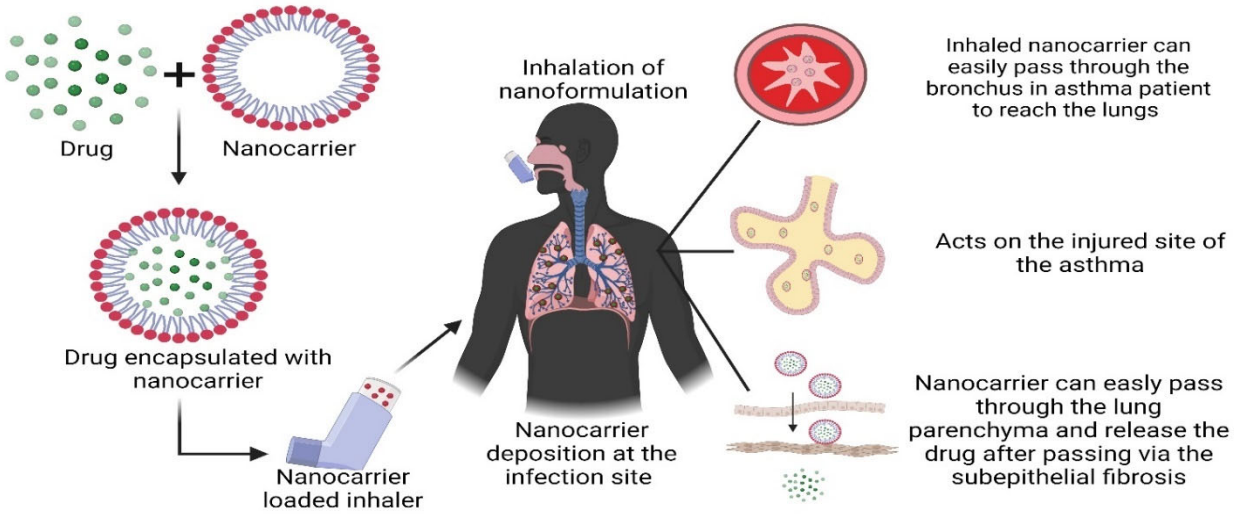

Fig. 3. Advantages of inhalation of nanoparticles in asthma management

polymorphisms with environmental factors. The drug has a combination of steroids with bronchodilators which are short or long-acting beta-receptor agonists that are considered the primary line of control priority for asthma [33]. On the other hand, corticosteroids can cause long-lasting side effects. They may also not provide immediate relief, thereby minimizing adherence to patient treatment, accelerating the progression of the disease and lung remodelling, and leading to further loss of lung function [40]. Nebulizers can be helpful at home in treating asthma problems in children and other patients with COPD who need the medication at higher doses. Inhalation of nanoparticles with the drugs helps in easy penetration of the drug to the injured site, and target-specific release of the drug can be achieved, as shown in Figure 3 [33]. In several studies, it was demonstrated that gene therapy through NPs can be an effective asthma treatment. Kumar *et al*. have used an asthma model (BALB/c mice) and showed that chitosan-IFN-γ pDNA loaded NPs (CIN) can be utilized very effectively to reduce the airway hyperresponsiveness, decrease pro-inflammatory OVA-explicit CD8+ T cells, and reduces the action of dendritic cells in OVA [41]. An intranasal IFN-γ q gene therapy proceeds towards the asthma therapy where adenovirus-interceded IFN-γ gene transfer was utilized. It reduced Th2 cytokine levels, lung inflammation, and airway hyperresponsiveness, but the frequency of gene delivery restricted this methodology. The frequency of gene delivery depended on the potential acute inflammation of airways caused by viral disease and the immune response due to the viral infection. In this manner, a non-viral intranasal IFN-γ using gene delivery mediated by chitosan NPs gives an effective way to deal with the treatment of asthma.

The above study used a BALB/c mouse model, which was induced with allergic asthma and the impacts of chitosan-IFN-γ pDNA NPs (CIN) were observed. The outcomes showed that CIN treatment significantly prevents the synthesis of hypertrophy, airway inflammation IL-5, IL-4, and OVA-specific serum IgE expression, which are responsible for acute asthma. Recombinant IFN-γ administration turns contamination in murine models and conventional airway disease, and it can be used in treatment for asthma. Still, it has limitations due to the short half-life of IFN-γ *in vivo* and the feasibly acute adverse impacts related to high-dose administration [42]. Metal NPs, for example, in the chemistry of gold and silver, are mainly used for therapeutic purposes in many diseases. Considering the inflammation of asthma as a consequence of enhanced oxidative stress in the route of airways, silver (AgNP) and AuNP were used as a potential therapeutic agents for the treatment of asthma. The application of NPs for therapeutics has various benefits over prevailing respiratory system drugs, including uniform drug distribution, increased solubility or rate of disintegration, sustained release, delivery of macromolecule, and appropriate cell disguise.

The advantages of NPs include incorporated help to target the drug and direct delivery of medicine and biological materials where required [43].

2.5. Nanomedicine in cystic fibrosis

CF is a recurrent genetic disease that is caused due to mutations in transmembrane conduction proteins. Seventy thousand people worldwide have been affected by this CF, and there is a need to develop more effective treatment

methods for CF [44]. The gene CFTR mutation airways cause CF. In general, there exist two vector types for the CFTR gene transfer to the subjects- non-viral vectors and viral vectors. Compared to viral vectors, the non-viral vectors, such as, nanomaterials are less expensive and less challenging for the production, have a long shelf life, and show reduction in immunomodulatory responses with better repetitive tolerance treatment. Non-viral vectors were often constructed with some charge, forming an electrostatic bond with nucleic acid that is negatively charged, for the treatment and also improved the particle function in CF mucus. It is because the CF mucus contained a high concentration of negatively charged macromolecules, e.g., mucus and actin filaments [45]. CF causes many chronic lung complications such as bacterial contamination, inflammation, thickened bodily fluid, loss of lung function, and eventually, death of the patient. Compliance in current clinical consideration for CF treatment was drowned in preventing and treating diseases [46]. The CFTR gene is responsible for CF located on 7q31.2, 'F508del being the first common mutation. The CFTR gene has six different mutations, based on their effects on CFTR protein, class1 (defective production due to premature protein truncation) (e.g., G542X), class II (defective processing/trashing) (e.g., F508del), class III (defective regulation/gating) (e.g., G551D), class IV (defective conductance) (e.g., R117H), class V (reduced synthesis) (e.g., A455E), and class VI (reduced protein uptake on the cell surface stability) (e.g., c.120del23) mutations. The first three classes are considered severe, while the other three are mild-form diseases [47]. Most of the symptoms of this treatment have been addressed on the manifestation of CF condition, but there is currently a drop back and no cure to stop the progression of CF. If a patient has been diagnosed with CF, the treatment plans prioritize maintaining lung function as well as nutritional therapy as the second choice. Nebulized hypertonic saline is used to reduce mucus levels and helps keep the airways clear. Antibiotics are utilized to prevent infection [48].

Therapy for cystic fibrosis

Various therapies for CF include inhalation of anti-microbials, systemic anti-inflammatories, mucolytics, and nutritional support, and these adjunct therapies are widely used to improve life expectancy over time. Dexamethasone, prednisone and ibuprofen can prevent morbidity and progressive lung deterioration in CF. Anti-inflammatory drugs are now widely used for CF that address the correction of some of the most basic defects of this disease [49]. Various microorganisms play an important role in the pathogenesis of lung function, such as *Staphylococcus aureus, Burkholderia cepacian, Haemophilus influenza, Stenotrophomonas maltophilia,* although most CF patients are affected by the airways because of the common pathogen *Pseudomonas Aeruginosa* (PA). Various types of NPs can inhibit bacterial growth and gene-related causes in CF. Liposomes loaded with drugs such as polymyxin, polyxin-B, β_1Tobramycin exhibited antibacterial, antibiofilm activity against PA. The enhancement in antibacterial activity was due to improved penetration of the antibiotics inside the microbe. Dendrimers loaded with siRNA and cysteamine has been shown to regulate the growth of PA, and it aids in the CFTR gene rescue. Polymeric NPs loaded with curcumin, ciprofloxacin, tobramycin, dec-ODN, plasmid DNA reduce chronic lung inflation by inhibiting NF-Kb transcription activity and mucus formation and enhancing drug delivery [34,44]. Researchers have formulated self-assembling polymer lipid oligonucleotide NPs with three well-known drugs, polyxin B, tobramycin, and cathelicidin LL-37 and tested them against the bacterial population present in CF, such as PA. They found the NPs showed minimum inhibitory concentration at five µg/ml [49]. Inorganic NPs were used for the treatment of CF; for example- AgNP recovered CF multi-drug repellent pathogens, such as *P. aeruginosa, Stenotrophomonas maltophilia, Burkholderia cepacia* and *S. aureus strains* [47]. Mucolytics, osmotic agents and bronchodilators are considered to recover the airway, and it can clear the sputum. In the airway, the main therapeutic agents in the treatment of CF are delivered via inhalation using pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs) and nebulizers [34].

Gene therapy

This therapeutical methodology has a lasting effect and allows interference at the chromosomal level of a particular gene, thereby adjusting for mutations related to all diseases. CFTR function can be retrieved either by altering endogenous genes or by embeddings in the wild-type CFTR at a protected harbour location such as AAVS1. Among the different types of genes, the three important genes that alter the procedures and are investigated as potential CF treatment approaches are- (i) zinc finger nucleases (ZFNs), (ii) clustered regularly intercepted palindromic repeats (CRISPR)/CRISPR-related systems (Cas), and (iii) transcription activator-like effector nucleases (TALENs) [50]. ZFN-based gene effectively improved the F508del mutation in CFTR29 cells; nonetheless, variable efficiency was low. In CF patients, the same methodology was practised by induced pluripotent stem cells (iPSC) that have differentiated in the airway like epithelial cells by the TALEN gene editing strategy. When co-cultured with CFBE41o-cells, the reactivation of the electrophysiological property was reported. However, the CRISPR/Cas method is recommended because these two strategies are more difficult. This process is basic and has low production costs.

Moreover, a variation of the CRISPR/Cas system that is competent for exact rectification without a double-strand mutagen disruption is currently accessible. In non-gene therapy, currently, the conventional treatment of CF is mainly used to control the symptoms of the disease without treating the underlying cases, and gene therapy may reduce the disease progression and enhance the patient's lifetime. The discovery of modulators of CFTR in recent times has given advancement in CF treatment and can be utilized to improve the function of CFTR and other related complications [47].

2.6. Nanomedicine in COPD

COPD is an infection categorized by the limitations of airflow, which is partially reversible [51]. COPD can be classified concerning both the phenotype and severity of the disease. Due to the diversity, the researchers cannot develop different perspectives on COPD prevention. Forty years ago: the British hypothesis stated that the presence of cough and sputum was an important factor in COPD, and the Dutch hypothesis indicated the presence of increased airways response. A little well-known thinking is the hypotheses part of genetic factors (the Swedish hypothesis) and the role of non-disruptive remediation processes in the development of emphysema (the American hypothesis) [52]. The airflow limitation is related to an abnormal inflammatory response to the lungs. Alveolar macrophages play an important role in these inflammatory responses by delivering inflammatory mediators, including leukotrieneLTB4, monocyte chemotactic peptide (MCP)-1, interleukin (IL)-6, IL-8, tumour necrosis factor-α (TNF-α), and volatile oxygen species. Current treatment possibilities for COPD, including β2-agonists, inhaled corticosteroids, and anticholinergics, control the symptoms but do not cure the underlying disease (Global Initiative for Chronic Obstructive Lung Disease) [53]. Geiser et al. demonstrated the AuNP delivery as an effective management strategy aimed at alveolar therapy epithelial cells and macrophages in COPD. This study compared the cellular uptake of AuNP (21 nm) in Scnn1b-transgenic mice as a model for COPD with healthy Wild type (wt.) mice. The results showed that 0 h after inhalation of NPs, 76.0 ± 5.9% NPs attached to the epithelial surface of both alveolar cell types in the COPD model, whereas in wt. mice, 38.3 ± 36.4 % got attached. The attachment of NPs to BLA-macrophages was 24.0 ± 5.9 % in the COPD model and 58.3± 41.4% in wt. After 24 h incubation, the uptake was reduced in epithelial cells; 37.0 ± 19.0 % in the COPD model and 11.7 ± 6.6 % in wt. mice, whereas the attachment of NPs to BLA-macrophages increased predominantly in the COPD model, which was 51.7,% but in wt., it was 62.4%.

On the other hand, the uptake of AuNP in alveolar epithelial type I cells gradually increased from 6.7 ± 1.2% at 0 h to 19.9 ± 12.0% after 24 h. In type II cells, the increment was 0.1 ± 0.2% at 0 h to 3.5 ± 0.4% at 24 h. Based on this observation, the uptake of AuNP can be used to target drug delivery based on alveolar epithelial type I cells [53]. Metallic NPs are tested as potential nanocarriers for COPD treatment. The main evidence for COPD is that its direct relationship with tobacco smoke leads to the most dangerous causes of cigarette smoking risk factors [51]. Nano-based theranostics provide several benefits for CF and COPD patients, such as continuous determination of lung inflammatory conditions and treatment. Especially for patients with fewer adverse effects of the drug, this includes developing multifunctional airway targeting nanocarriers [54]. The gold standard for diagnosing COPD is currently spirometry, which can detect any obstruction in airflow. This method has limited sensitivity for changes in the airway pathway, and therefore, air pressure measurement by NPs is very powerful, especially because they take less time, are more cheap, easy to use and easy to interpret [40]. Currently, multivariate polymer vesicles synthesized by combining the two synthetic polymers, namely, polyethylene glycol and poly lactic-co-glycolic acid (PLGA-PEG) and were utilized for COPD/CF drug delivery (prednisolone, theophylline, corticosteroid and/or anti-inflammatory bronchodilator, etc.) and also to deliver the molecular probes that can have therapeutic applications in case of obstructive lung diseases. Such investigations and drug-loaded nanocarrier treatment serve as a theranostic system for CF and COPD [40]. Gene therapy is one of the most promising strategies for treating COPD [54].

2.7. Nanomedicine in tuberculosis

Tuberculosis is the second most disastrous infectious disease after AIDS, caused by Mtb bacterium [55]. The Central Scientific Instruments Organization of India has designed a nanotechnology-based TB diagnostic tool currently in the clinical trial phase. The device does not need expert technicians for use and provides efficiency, portability, simplicity and availability for less than US$1 [56]. MDR (TB isolate)+XDR(Extensive drug resistant) are formed due to the prolonged treatment requirement, usage of various drugs and low compliance with the program of administration [57]. Culture filtrate protein 10 (CFP-10) and antigenic 6 (ESAT-6) are the two orthologous proteins that are vital in transmitting Mtb infection. They induce the temporary Ca^{2+} release from the intracellular compartments of the immune cells in humans, which can protect the bacteria against immune responses, thereby stimulating intracellular survival [50]. Chemotherapy of TB is complicated due to the need for a multi-drug regimen that should be controlled over a wide range. Poor patient

compliance is the most common cause of chemotherapy failure in TB. Delivery systems such as follicles and microcephalous have been produced for the persistent delivery of anti-TB drugs. They have been found to have superior chemotherapeutic efficacy during investigation in animal models (e.g., mice). The important technical advantages of NPs as drug carriers are- high stability (i.e., long shelf life); high carrier capacity (i.e., many medication molecules can be fused into the molecule matrix); the possibility of incorporation of both hydrophilic and hydrophobic substances; and practicality of variable routes of organization, including oral administration and inhalation [5,56]. First-line drugs are used to treat the TB as a combination treatment with Rifampin, pyrazinamide, isoniazid and ethambutol for a few months. These drugs are controlled orally and adequately against Mtb. Second-line drug: When Mtb strains are repellent for first-line drugs, they improve a more complex system of TB known as MDR-TB. Second-line drugs are treated with MDR-TB aminoglycosides such as kanamycin, amikacin and polypeptides such as viomycin, enviomycin, and capreomycin. The second-line drugs are higher in cost than first-line drugs, and the treatment may last much longer. The third-line drugs: Used to treat the TB includes linezolid, rifabutin, arginine, vitamin D, thioridazine and macrolides such as thioacetazone and clarithromycin. Many different types of drug delivery systems are designed to deliver drugs for TB [55]. PLG nanoparticles were used to load the three drugs of tuberculosis- rifampin, isoniazid, and pyrazinamide and it was found that these drugs were in circulation for 6 to 9 days compared to free drugs which got cleared the body within 24 h. There was also complete clearance of the microorganisms from organs found after such treatment in mice [57]. CeO_2 NPs doped with Cu showed antimicrobial activity, and similarly, various NPs loaded with antibiotic agents enhanced the bactericidal activity [58].

2.8. Nanomedicine in lung cancer

Lung cancer is a worldwide disease classified into two subtypes: small cell lung cancer and non-small cell lung cancer [59]. Genexol-PM is the first nanotherapeutics approved for the therapy of non-small-cell lung cancer (NSCLC) [50]. Squamous cell carcinoma forms at the major bronchi and adenocarcinoma, whereas large cell carcinoma arises mostly in peripheral areas of the lungs [59]. For example, silver and gold noble metals have been used for theranostic applications, that includes their detection, sensitive diagnostic imaging and use in classifying lung cancer [60]. AuNPs are used to design biosensors that can detect lung cancer from a person's breathing analysis. AuNP has also been successfully tested as a sensor for differentiating and classifying various lung cancer histology. The sensor could differentiate between two subtypes- normal and cancerous cells, SCLC and NSCLC. AuNP also dispensed anticancer drugs for enhanced therapeutic efficacy. For example, the high water solubility of methotrexate (MTX) has poor tumour retention ability, which probably transmits it to slow or poor therapeutic reaction in patients [61]. An automated computer-aided diagnostic (CAD) system was used to determine the location and analysis of lung cancer CT images. In the early years, image processing techniques have been widely used in the medical field in various ways to improve detection and treatment stages.

At that time, various cancerous tumours, such as breast and lung cancer, can be detected soon for early treatment onset [62]. The major risk factors for cancer in the lung are air pollution, indirect smoke inhalation, smoking, and random exposure to air pollutants. On the other hand, adenocarcinoma is also found in non-smokers. Surgery IIIA is the therapy for patients with stage I NSCLC. Treatment for NSCLC may include radiotherapy and chemotherapy post-surgery. The aim of targeted therapies, particularly the antiviral endothelial growth mediator agent bevacizumab (Avastin), has been investigated in patients with advanced-stage (IIIB and IV) non-squamous carcinoma. Survival with chemotherapy alone was combined with bevacizumab chemotherapy. Chemotherapy (combined with radiotherapy in limited-stage disease) is the mainstay of treatment for small cell carcinoma [63]. Currently, for the treatment of cancer, gene therapy has been introduced for lung cancer and has been demonstrated to have a beneficial effect [59]. There are various nanoformulation with various drug conjugations that have been studied for their potential activity in the inhibition of lung cancer are listed in Table 2.

3. Future challenges for nanomedicine for respiratory diseases

The concept of nanomedicine offers various novel therapeutic options in pharmacotherapy [64]. Nanomedicine provides the option for targeted drug delivery and nanostructure-assisted drugs which are required in very less amount than bulk drugs. Moreover, specific delivery of drugs to the organs can reduce the side effect of the drug on other non-targeted organs. Personalized medicine can also be developed using nanomedicine. However, we are at the beginning of the nanomedicine phases in treating respiratory diseases. More human data with a lot of investment are needed before they can be seen as a common objective for diagnosis and treatment [45]. Nanomedicine, dependent on

Table 2.
List various nanoformulation and their activity against lung cancer

Nanoformulation	Cancer Model used	Observation	Ref.
PLGA nanoparticles coated with erlotinib-cyclodextrin (Erlo-CD)	NSCLC cells	Erlo-CD nanoparticles inhibited the growth of NSCLC cells in lower concentrations by inducing apoptosis. The nanoformulation was found to reduce the colony-forming units also. The nanoformulation improved the anticancer ability of Erlo-CD	[65]
Zinc oxide nanoparticles synthesized using Mangifera indica leaves (ZnO NPs)	A549 cells	The nanoformulation showed a dose-dependent cytotoxicity effect on the cancer cell. The antioxidant activity of the nanoformulation was also improved	[66]
Methoxy poly (ethylene glycol)-poly(ethylenimine)- poly(L-glutamate) (mPEG-OEI-PLG) copolymers were synthesized as a carrier for the co-delivery of DOX and CDDP	B16F10 cells and male C57BL/6 mice	The cytotoxicity effect of nanoformulation was found to be higher compared to free drugs in B16F10 cells. The pulmonary administration of nanoformulation in mice models showed a higher accumulation of drugs at the cancer site.	[67]
DOX and DTX-loaded PLGA-b-PEG-FITC nanoparticle with Mesenchymal stem cell (MSC) as co-delivery system	A549 cells and Nu/Nu mice, KrasG12D mice, and Rabbits	In both in vitro and in vivo experiments, accumulation of drug was found in the target site, and tumour reduction was also higher when compared to the only drug in MSC as a co-delivery system	[31]
Hyaluronic acid (HA)-modified chitosan nanoparticles (CS NPs-HA) loaded with cyanine 3 (Cy3)-labelled siRNA	A549 cells and Female BALB/c mice	The nanoformulation regulated tumour growth by downregulation of BCL 2. In the *in vivo* model, nanoformulation delivers the Cy3-labeled siRNA to the tumour site leading to the down-regulation of BCL2. This was found to be unmodified in naked Cy3-labeled siRNA.	[68]
Paclitaxel-loaded galactoxyloglucan nanoparticle (PST-PTX nanoparticle)	A549, SK-OV-3, 4T1, and A375 Cells	PST-PTX nanoparticle down-regulated the multidrug-resistant protein P-gp and BCRP in drug-resistant cancer cells.	[69]
AgNPs biosynthesized from *Gossypium hirsutum*	A549 cells	The nanoparticle induced apoptosis in cancer cells via the mitochondrial pathway. They also arrested the cell cycle at the G2/M phase	[70]
zinc oxide (ZnO) nanoparticles	NCI-N417 (N417), H82, and H187, BEAS-2B human bronchial epithelial cells, and MCF-7 human breast cancer cells and BALB/cAJcl-nu/nu mice	The nanoformulation was found to have less cytotoxicity on normal cells and inhibited cancer growth both *in vitro* and *in vivo.* ROS synthesis was found higher in cancer cells, and DNA leakage was observed.	[71]
Myricetin (Myr)-loaded mesoporous silica nanoparticles (MSN)	NSCLC, A549, and NCI-H1299 cells.	Nanoformulation reduced the cell viability of lung cancer cells. They minimized colony-forming units, and an expression of caspase-3 and PARP was also identified.	[72]
Mesoporous silica nanoparticle coated with ten kDa branched PEI	A549 (CCL-185), H460 (HTB-177), H1437 (CRL-5872), and H1944 (CRL-5907) NSCLC cells, KLN205 (CRL-1453), B16F10 (CRL-6475), 4T1 (CRL-2539) cells and naïve C57BL/6 mice	The formulated nanoparticle improved the efficacy and also reduced the toxicity. Due to the addition of PD-L1 antibody to the nanoparticle.	[73]
chitosan (CST) encapsulated myogenic (Talaromyces purpureogenus (Tp)) gold nano-particles (Apt-CST-Tp-AuNPs)	HEK293 cells and A549 cells	The nanoformulation triggered cell cycle arrest at M1 phase and also regulated apoptosis-related proteins like Bcl-2 and Bax expression	[74]

various materials and capacities, has been created and applied in the therapeutic treatment of respiratory diseases in the recent twenty years. The use of the polymer, lipid or metal-based nanoparticle system in the field of targeted gene delivery has developed tremendously and indicated promising therapeutic efficacy for in vivo or in vitro tests. However, interpreting these novel NPs - mediated gene delivery techniques in clinical practices is a major challenge. The challenge of applying NPs in mediated gene delivery inside the body has come with limitations; for example, maintaining the stability of nanoparticle and gene molecules during delivery in the biological system, controlling the bio dissemination and pharmacokinetics, infiltrating organic obstructions and minimizing the potential cytotoxicity of the NPs, needs to be considered and defeated before entering into clinical preliminaries. Size control and aggregation are the other parameters which limit the use of nanostructures in nanomedicine. However, the gap between the ideas of nanomedicine-distributed clinical data into experimental data is huge [64].

4. Conclusions

With the development of nano-sized carriers that include NPs, or liposomes in respiratory infections, there is great potential to find and move forward with the delivery system for immunomodulation. NPs can effectively regulate the active components of immunity for acute or chronic lung diseases. The use of nanotechnology for drug delivery can have implications in many areas of medication, especially for lung diseases. An alternative delivery innovation prompting the drug explicitly to lung areas could be based on nanocarriers that can be controlled by the external magnetic field through focusing. In this context, by addressing these challenging issues, without a doubt new nanocarrier-based items containing locally-acting drugs that have more prominent pulmonary bioavailability are proposed. This review briefly discusses the importance and application of nanomedicine for the diagnosis, and treatment of respiratory diseases. In the future, experimental and clinical examinations are needed to reveal the diagnostic and therapeutic potential of nanomedicine.

Acknowledgements

The authors are grateful to the Chettinad Academy of Research and Education for providing fellowship to D.B. and providing the infrastructure. We are thankful to the Council of Scientific and Industrial Research (CSIR), INDIA, for the grant with Scheme No. 01(2868)/17/EMR- II.

Additional information

The work presented in this paper was presented in “Two Days Virtual National Meet on Nano Interface Science (NIS-2021)”, Chettinad Academy of Research & Education, Chennai, India, 2021.

References

[1] Forum of International Respiratory Societies, The Global Impact of Respiratory Disease, Second Edition, European Respiratory Society, Sheffield, 2017.

[2] H. Swai, B. Semete, L. Kalombo, P. Chelule, K. Kisich, B. Sievers, Nanomedicine for respiratory diseases, WIREs Nanomedicine and Nanobiotechnology 1/3 (2009) 255-263. DOI: https://doi.org/10.1002/wnan.33

[3] B. Amanzadi, E. Mirzaei, G Hassanzadeh, P. Mahdaviani, S Boroumand, M. Abdollahi, A.H. Abdolghaffari, R.F. Majidi, Chitosan-based layered nanofibers loaded with herbal extract as wound-dressing materials on wound model studies, Biointerface Research in Applied Chemistry 9/4 (2019) 3979-3986.
DOI: https://doi.org/10.33263/BRIAC94.979986

[4] P.K. Gaur, H. Pal, D. Puri, N. Kumar, S.K. Shanmugam, Formulation and development of hesperidin loaded solid lipid nanoparticles for diabetes, Biointerface Research in Applied Chemistry 10/1 (2020) 4728-4733.
DOI: https://doi.org/10.33263/BRIAC101.728733

[5] S. Ghosh, K. Girigoswami, A. Girigoswami, Membrane-encapsulated camouflaged nanomedicines in drug delivery, Nanomedicine 14/15 (2019) 2067-2082. DOI: https://doi.org/10.2217/nnm-2019-0155

[6] N. Akhtar, S.K. Metkar, A. Girigoswami, K. Girigoswami. ZnO nanoflower based sensitive nano-biosensor for amyloid detection, Materials Science and Engineering: C 78 (2017) 960-968.
DOI: https://doi.org/10.1016/j.msec.2017.04.118

[7] P. Sharmiladevi, V. Haribabu, K. Girigoswami, S.F. Abubacker, A. Girigoswami, Effect of Mesoporous Nano Water Reservoir on MR Relaxivity, Scientific Reports 7 (2017) 11179.
DOI: https://doi.org/10.1038/s41598-017-11710-2

[8] A. Girigoswami, W. Yassine, P. Sharmiladevi, V. Haribabu, K. Girigoswami, Camouflaged Nanosilver with Excitation Wavelength Dependent High Quantum Yield for Targeted Theranostic, Scientific Reports 8/1 (2018) 16459. DOI: https://doi.org/10.1038/s41598-018-34843-4

[9] S.K. Metkar, K. Girigoswami, Diagnostic Biosensors in Medicine - a Review, Biocatalysis and Agricultural Biotechnology 17 (2019) 271-283. DOI: https://doi.org/10.1016/j.bcab.2018.11.029

[10] P. Sharmiladevi, N. Akhtar, V. Haribabu, K. Girigoswami, S. Chattopadhyay, A. Girigoswami, Excitation Wavelength Independent Carbon Decorated Ferrite Nanodots for Multimodal Diagnosis and Stimuli Responsive Therapy, ACS Applied Bio Materials 2/4 (2019) 1634-1642. DOI: https://doi.org/10.1021/acsabm.9b00039

[11] V. Haribabu, K. Girigoswami, P. Sharmiladevi, A. Girigoswami, Water-Nanomaterials Interaction to Escalate Twin-mode Magnetic Resonance Imaging, ACS Biomaterials Science and Engineering 6/8 (2020) 4377-4389. DOI: https://doi.org/10.1021/acsbiomaterials.0c00409

[12] K. Girigoswami, A. Girigoswami, A Review on Role of Nanosensors in Detecting Cellular miRNA Expression in Colorectal Cancer, Endocrine, Metabolic and Immune Disorders 21/1 (2021) 12-26. DOI: https://doi.org/10.2174/1871530320666200515115723

[13] O. Mukhopadhyay, S. Dhole, B.K. Mandal, F.R.N. Khan, Y.C. Ling, Synthesis, characterization and photocatalytic activity of Zn^{2+}, Mn^{2+} and Co^{2+} doped SnO_2 nanoparticles, Biointerface Research in Applied Chemistry 9/5 (2019) 4199-4204. DOI: https://doi.org/10.33263/BRIAC95.199204

[14] A.J. Omlor, J. Nguyen, R. Bals, Q.T. Dinh, Nanotechnology in respiratory medicine, Respiratory Research 16/1 (2015) 64. DOI: https://doi.org/10.1186/s12931-015-0223-5

[15] H. Arzani, M. Adabi, J. Mosafer, F. Dorkoosh, M. Khosravani , H. Maleki, H. Nekounam, M. Kamali, Preparation of curcumin-loaded PLGA nanoparticles and investigation of its cytotoxicity effects on human glioblastoma U87MG cells, Biointerface Research in Applied Chemistry 9/5 (2019) 4225-4231. DOI: https://doi.org/10.33263/BRIAC95.225231

[16] Z. Afsharian, K.K. Darani, Application of nanoclays in food packaging, Biointerface Research in Applied Chemistry 10/1 (2020) 4790-4802. DOI: https://doi.org/10.33263/BRIAC101.790802

[17] M. Bahadori, F. Mohammadi, Nanomedicine for respiratory diseases, Tanaffos 11/4 (2012) 18-22.

[18] U. Pison, T. Welte, M. Giersig, D.A. Groneberg, Nanomedicine for respiratory diseases, European Journal of Pharmacology 533/1-3 (2006) 341-350. DOI: https://doi.org/10.1016/j.ejphar.2005.12.068

[19] H.S. Choi, Y. Ashitate, J.H. Lee, S.H. Kim, A. Matsui, N. Insin, M.G. Bawendi, M.S. Behnke, J.V. Frangioni, A. Tsuda, Rapid translocation of nanoparticles from the lung airspaces to the body, Nature Biotechnology 28/12 (2010) 1300-1303. DOI: https://doi.org/10.1038/nbt.1696

[20] A.K Mohammad, L.K. Amayreh, J.M. Mazzara, J.J. Reineke, Rapid lymph accumulation of polystyrene nanoparticles following pulmonary administration, Pharmaceutical Research 30/2 (2013) 424-434. DOI: https://doi.org/10.1007/s11095-012-0884-4

[21] A.A. Faraj, A.S. Shaik, S. Afzal, B.A. Sayed, R. Halwani, MR imaging and targeting of a specific alveolar macrophage subpopulation in LPS-induced COPD animal model using antibody-conjugated magnetic nanoparticles, International Journal of Nanomedicine 9/1 (2014) 1491-1503. DOI: https://doi.org/10.2147/IJN.S59394

[22] J. Gao, L. Li, X. Liu, R. Guo, B. Zhao, Contrast-enhanced magnetic resonance imaging with a novel nano-size contrast agent for the clinical diagnosis of patients with lung cancer, Experimental and Therapeutic Medicine 15/6 (2018) 5415-5421. DOI: https://doi.org/10.3892/etm.2018.6112

[23] M.A. Markus, J. Napp, T. Behnke, M. Mitkovski, S. Monecke, C. Dullin, S. Kilfeather, R. Dressel, U. Resch-Genger, F. Alves, Tracking of Inhaled Near-Infrared Fluorescent Nanoparticles in Lungs of SKH-1 Mice with Allergic Airway Inflammation, ACS Nano 9/12 (2015) 11642-11657. DOI: https://doi.org/10.1021/acsnano.5b04026

[24] P. Gong, X. He, K. Wang, W. Tan, W. Xie, P. Wu, H. Li, Combination of functionalized nanoparticles and polymerase chain reaction-based method for SARS-CoV gene detection, Journal of Nanoscience and Nanotechnology 8/1 (2008) 293-300. DOI: https://doi.org/10.1166/jnn.2008.18130

[25] R.C. Stringer, S. Schommer, D. Hoehn, S.A. Grant, Development of an optical biosensor using gold nanoparticles and quantum dots for the detection of porcine reproductive and respiratory syndrome virus, Sensors and Actuators B: Chemical 134/2 (2008) 427-431. DOI: https://doi.org/10.1016/j.snb.2008.05.018

[26] X. Xu, R. Zhang, F. Liu, J. Ping, X. Wen, H. Wang, K. Wang, X. Sun, H. Zou, B. Shen, L. Wu, ^{19}F MRI in orthotopic cancer model via intratracheal administration of $\alpha_v\beta_3$-targeted perfluorocarbon nanoparticles, Nanomedicine 13/20 (2018) 2551-2562. DOI: https://doi.org/10.2217/nnm-2018-0051

[27] J. Griesser, G. Hetényi, C. Federer, C. Steinbring, H. Ellemunter, K. Niedermayr, A.B. Schnürch, Highly mucus permeating and zeta potential changing self-emulsifying drug delivery systems: A potent gene

delivery model for causal treatment of cystic fibrosis, International Journal of Pharmaceutics 557 (2019) 124-134.
DOI: https://doi.org/10.1016/j.ijpharm.2018.12.048

[28] N. Vij, S. Fang, P.L. Zeitlin. Selective inhibition of endoplasmic reticulum-associated degradation rescues DeltaF508-cystic fibrosis transmembrane regulator and suppresses interleukin-8 levels: therapeutic implications, The Journal of Biological Chemistry 281/25 (2006) 17369-17378.
DOI: https://doi.org/10.1074/jbc.M600509200

[29] N. Vij, T. Min, R. Marasigan, C.N. Belcher, S. Mazur, H. Ding, K.T. Yong, I. Roy, Development of PEGylated PLGA nanoparticle for controlled and sustained drug delivery in cystic fibrosis, Journal of Nanobiotechnology 8 (2010) 22.
DOI: https://doi.org/10.1186/1477-3155-8-22

[30] J.S. Guthi, S.G. Yang, G. Huang, S. Li, C. Khemtong, C.W. Kessinger, M. Peyton, J.D. Minna, K.C. Brown, J. Gao, MRI-Visible Micellar Nanomedicine for Targeted Drug Delivery to Lung Cancer Cells, Molecular Pharmaceutics 7/1 (2010) 32-40. DOI: https://doi.org/10.1021/mp9001393

[31] X. Wang, H. Chen, X. Zeng, W. Guo, Y. Jin, S. Wang, R. Tian, Y. Han, L. Guo, J. Han, Y. Wu, L. Mei, Efficient lung cancer-targeted drug delivery via a nanoparticle/MSC system, Acta Pharmaceutica Sinica B 9/1 (2019) 167-176.
DOI: https://doi.org/10.1016/j.apsb.2018.08.006

[32] S. Kan, D.M. Hariyadi, C. Grainge, D. Knight, N.W. Bartlett, M. Liang, Airway epithelial-targeted nanoparticles for asthma therapy, American Journal of Physiology. Lung Cellular and Molecular Physiology 318/3 (2020) L500-L509.
DOI: https://doi.org/10.1152/ajplung.00237.2019

[33] L. Wang, M. Feng, Q. Li, C. Qiu, R. Chen, Advances in nanotechnology and asthma, Annals of Translational Medicine 7/8 (2019) 180.
DOI: https://doi.org/10.21037/atm.2019.04.62

[34] C. Velino, F. Carella, A. Adamiano, M. Sanguinetti, A. Vitali, D. Catalucci, F. Bugli, M. Iafisco, Nanomedicine Approaches for the Pulmonary Treatment of Cystic Fibrosis, Frontiers in Bioengineering and Biotechnology 7 (2019) 406. DOI: https://doi.org/10.3389/fbioe.2019.00406

[35] E.R. Sutherland, R.M. Cherniack, Management of chronic obstructive pulmonary disease, The New England Journal of Medicine 350/26 (2004) 2689-2697. DOI: https://doi.org/10.1056/NEJMra030415

[36] A. Trapani, S.D. Gioia, S. Castellani, A. Carbone, G. Cavallaro, G. Trapani, M. Conese, Nanocarriers for respiratory diseases treatment: recent advances and current challenges. Current Topics in Medicinal Chemistry 14/9 (2014) 1133-1147. DOI: https://doi.org/10.2174/1568026614666140329225817

[37] S. Walton, D. Rogers, Tracheal Reconstruction, in: StatPearls [Internet], Treasure Island (FL): StatPearls Publishing 2021 Jan., Updated 2021 Aug 1, ebook, Available from:
https://www.ncbi.nlm.nih.gov/books/NBK564393/

[38] H.G. Auchincloss, C.D. Wright, Complications after tracheal resection and reconstruction: prevention and treatment. Journal of Thoracic Disease 8/2 (2016) S160-S167. DOI: https://doi.org/10.3978/j.issn.2072-1439.2016.01.86

[39] S. Liao, C.A. Vacanti, K. Kojima, 6.8 Cartilage Regeneration in Reconstructive Surgery, in: P. Ducheyne (ed), Comprehensive Biomaterials II, vol. 6, Elsevier, Amsterdam, 2017, 135-141. DOI: https://doi.org/10.1016/B978-0-08-100691-7.00047-1.

[40] A.L.D. Silva, F.F. Cruz, P. Rocco, M.M. Morales, New perspectives in nanotherapeutics for chronic respiratory diseases, Biophysical Reviews 9/5 (2017) 793-803. DOI: https://doi.org/10.1007/s12551-017-0319-x

[41] B. Yang, H. Choi, S.H. Kim, H.J. Yoon, H. Lee, How will nanotechnology lead to better control of asthma?, Annals of Translational Medicine 7/20 (2019) 515. DOI: https://doi.org/10.21037/atm.2019.09.129

[42] M. Kumar, X. Kong, A.K. Behera, G.R. Hellermann, R.F. Lockey, S.S. Mohapatra, Chitosan IFN-gamma-pDNA Nanoparticle (CIN) Therapy for Allergic Asthma, Genetic Vaccines and Therapy 1/1 (2003) 3. DOI: https://doi.org/10.1186/1479-0556-1-3

[43] A.L.D. Silva, L.A. Silva, F.F. Cruz, P. Rocco, M.M. Morales, Application of novel nanotechnologies in asthma, Annals of Translational Medicine 8/5 (2020) 159. DOI: https://doi.org/10.21037/atm.2019.12.40

[44] V. Ong, V. Mei, L. Cao, K. Lee, E.J. Chung, Nanomedicine for Cystic Fibrosis, SLAS Technology 24/2 (2019) 169-180.
DOI: https://doi.org/10.1177/2472630318824334

[45] M. Doroudian, R. MacLoughlin, F. Poynton, A. Prina-Mello, S.C. Donnelly, Nanotechnology based therapeutics for lung disease, Thorax 74/10 (2019) 965-976. DOI: https://doi.org/10.1136/thoraxjnl-2019-213037

[46] F.A. Almughem, A.M. Aldossary, E.A. Tawfik, M.N. Alomary, W.S. Alharbi, M.Y. Alshahrani, A.A. Alshehri, Cystic Fibrosis: Overview of the Current Development Trends and Innovative Therapeutic Strategies, Pharmaceutics 12/7 (2020) 616. DOI: https://doi.org/10.3390/pharmaceutics12070616

[47] M. Marangi, G. Pistritto, Innovative Therapeutic Strategies for Cystic Fibrosis: Moving Forward to CRISPR Technique, Frontiers in Pharmacology 9 (2018) 396. DOI: https://doi.org/10.3389/fphar.2018.00396
[48] M.E. Chirgwin, M.R. Dedloff, A.M. Holban, M.C. Gestal, Novel Therapeutic Strategies Applied to Pseudomonas aeruginosa Infections in Cystic Fibrosis, Materials 12/24 (2019) 4093. DOI: https://doi.org/10.3390/ma12244093
[49] J. McDonald, "Smart" polyelectrolyte nanomedicine for cystic fibrosis pneumonia, MSc Thesis, Rutgers University Community Repository, 2019. DOI: https://doi.org/doi:10.7282/t3-wyca-d222
[50] J. Vagedes, E. Helmert, S. Kuderer, K. Vagedes, J. Wildhaber, F. Andrasik, The Buteyko breathing technique in children with asthma: a randomized controlled pilot study, Complementary Therapies in Medicine 56 (2021) 102582. DOI: https://doi.org/10.1016/j.ctim.2020.102582
[51] R.A. Pauwels, K.F. Rabe, Burden and clinical features of chronic obstructive pulmonary disease (COPD), The Lancet 364/9434 (2004) 613-620. DOI: https://doi.org/10.1016/S0140-6736(04)16855-4
[52] D.M. Mannino, A.S. Buist, Global burden of COPD: risk factors, prevalence, and future trends, The Lancet 370/9589 (2007) 765-773. DOI: https://doi.org/10.1016/S0140-6736(07)61380-4
[53] M. Geiser, O. Quaile, A. Wenk, C. Wigge, S.E. Berthou, S. Hirn, M. Schäffler, C. Schleh, W. Möller, M.A. Mall, W.G. Kreyling, Cellular uptake and localization of inhaled gold nanoparticles in lungs of mice with chronic obstructive pulmonary disease, Particle and Fibre Toxicology 10 (2013) 19. DOI: https://doi.org/10.1186/1743-8977-10-19
[54] M. Passi, S. Shahid, S. Chockalingam, I.K. Sundar, G. Packirisamy, Conventional and Nanotechnology Based Approaches to Combat Chronic Obstructive Pulmonary Disease: Implications for Chronic Airway Diseases, International Journal of Nanomedicine 15 (2020) 3803-3826. DOI: http://doi.org/10.2147/IJN.S242516
[55] M. Nasiruddin, M. Neyaz, S. Das, Nanotechnology-Based Approach in Tuberculosis Treatment, Tuberculosis Research and Treatment 2017 (2017) 4920209. DOI: https://doi.org/10.1155/2017/4920209
[56] J.P. Mathuria, Nanoparticles in Tuberculosis Diagnosis, Treatment and Prevention: A Hope for Future, Digest Journal of Nanomaterials and Biostructures 4/2 (2009) 309-312.
[57] R. Pandey, S. Sharma, G.K. Khuller, Nebulization of liposome encapsulated antitubercular drugs in guinea pigs, International Journal of Antimicrobial Agents 24/1 (2004) 93-94. DOI: https://doi.org/10.1016/j.ijantimicag.2004.04.004
[58] G. Killivalavan, A.C. Prabakar, K.C.B. Naidu, B. Sathyaseelan, G. Rameshkumar, D. Sivakumar, K. Senthilnathan, I. Baskaran, E. Manikandan, B.R. Rao, Synthesis and characterization of pure and Cu doped CeO_2 nanoparticles: photocatalytic and antibacterial activities evaluation. Biointerface Research in Applied Chemistry 10/2 (2020) 5306-5311. DOI: https://doi.org/10.33263/BRIAC102.306311
[59] D.A. Bölükbaş, Development of novel nanoparticle-based therapeutics for treatment of lung cancer, PhD Thesis, Ludwig Maximilian University of Munich, Munich, 2017.
[60] G. Peng, U. Tisch, O. Adams, M. Hakim, N. Shehada, Y.Y. Broza, S. Billan, R.A. Bortnyak, A. Kuten, H. Haick, Diagnosing lung cancer in exhaled breath using gold nanoparticles, Nature Nanotechnology 4 (2009) 669-673. DOI: https://doi.org/10.1038/nnano.2009.235
[61] A. Babu, A.K. Templeton, A. Munshi, R. Ramesh, Nanoparticle-Based Drug Delivery for Therapy of Lung Cancer: Progress and Challenges, Journal of Nanomaterials 2013 (2013) 863951. DOI: https://doi.org/10.1155/2013/863951
[62] D. Sharma, G. Jindal, Identifying lung cancer using image processing techniques, Proceedings of the International Conference on Computational Techniques and Artificial Intelligence "ICCTAI'2011", vol. 17, Penang, Malaysia, 2012, 872-880.
[63] L.G. Collins, C. Haines, R. Perkel, R.E. Enck, Lung cancer: diagnosis and management, American Family Physician 75/1 (2007) 56-63.
[64] S. Beg, M. Rahman, M.A. Barkat, M.A., F.J. Ahmad (eds), Nanomedicine for the Treatment of Disease: From Concept to Application, First Edition, Apple Academic Press, New York, 2019. DOI: https://doi.org/10.1201/9780429425714
[65] B. Vaidya, V. Parvathaneni, N.S. Kulkarni, S.K. Shukla, J.K. Damon, A. Sarode, D. Kanabar, J.V. Garcia, S. Mitragotri, A. Muth, V. Gupta, Cyclodextrin modified erlotinib loaded PLGA nanoparticles for improved therapeutic efficacy against non-small cell lung cancer, International Journal of Biological Macromolecules 122 (2019) 338-347. DOI: https://doi.org/10.1016/j.ijbiomac.2018.10.181
[66] S. Rajeshkumar, S.V. Kumar, A. Ramaiah, H. Agarwal, T. Lakshmi, S.M. Roopan, Biosynthesis of zinc oxide nanoparticles using *Mangifera indica* leaves and evaluation of their antioxidant and cytotoxic properties in lung cancer (A549) cells, Enzyme and

Microbial Technology 117 (2018) 91-95. DOI: https://doi.org/10.1016/j.enzmictec.2018.06.009
[67] C. Xu, Y. Wang, Z. Guo, J. Chen, L. Lin, J. Wu, H. Tian, X. Chen, Pulmonary delivery by exploiting doxorubicin and cisplatin co-loaded nanoparticles for metastatic lung cancer therapy, Journal of Controlled Release 295 (2019) 153-163. DOI: https://doi.org/10.1016/j.jconrel.2018.12.013
[68] W. Zhang, W. Xu, Y. Lan, X. He, K. Liu, Y. Liang, Antitumor effect of hyaluronic-acid-modified chitosan nanoparticles loaded with siRNA for targeted therapy for non-small cell lung cancer, International Journal of Nanomedicine 14 (2019) 5287-5301. DOI: https://doi.org/10.2147/IJN.S203113
[69] P.L. Reshma, B.S. Unnikrishnan, G.U. Preethi, H.P. Syama, M.G. Archana, K. Remya, R. Shiji, J. Sreekutty, T.T. Sreelekha, Overcoming drug-resistance in lung cancer cells by paclitaxel loaded galactoxyloglucan nanoparticles, International Journal of Biological Macromolecules 136 (2019) 266-274. DOI: https://doi.org/10.1016/j.ijbiomac.2019.06.075
[70] N. Kanipandian, D. Li, S. Kannan, Induction of intrinsic apoptotic signaling pathway in A549 lung cancer cells using Silver nanoparticles from Gossypium hirsutum and evaluation of in vivo toxicity, Biotechnology Reports 23 (2019) e00339. DOI: https://doi.org/10.1016/j.btre.2019.e00339
[71] R. Tanino, Y. Amano, X. Tong, R. Sun, Y. Tsubata, M. Harada, Y. Fujita, T. Isobe, Anticancer Activity of ZnO Nanoparticles against Human Small-Cell Lung Cancer in an Orthotopic Mouse Model ZnO Nanoparticles Inhibit Growth of Small-Cell Lung Cancer, Molecular Cancer Therapeutics 19/2 (2020) 502-512. DOI: https://doi.org/10.1158/1535-7163.MCT-19-0018
[72] Y. Song, B. Zhou, X. Du, Y. Wang, J. Zhang, Y. Ai, Z. Xia, G. Zhao, Folic acid (FA)-conjugated mesoporous silica nanoparticles combined with MRP-1 siRNA improves the suppressive effects of myricetin on non-small cell lung cancer (NSCLC). Biomedicine and Pharmacotherapy 125 (2020) 109561. DOI: https://doi.org/10.1016/j.biopha.2019.109561
[73] M. Reda, W. Ngamcherdtrakul, M.A. Nelson, N. Siriwon, R. Wang, H.Y. Zaidan, D.S. Bejan, S. Reda, N.H. Hoang, N.A. Crumrine, J.P. Rehwaldt, A. Bindal, G.B. Mills, J.W. Gray, W. Yantasee, Development of a nanoparticle-based immunotherapy targeting PD-L1 and PLK1 for lung cancer treatment, Nature Communications 13/1 (2022) 4261. DOI: https://doi.org/10.1038/s41467-022-31926-9
[74] X. Hu, K. Saravanakumar, A. Sathiyaseelan, V. Rajamanickam, M.H. Wang, Cytotoxicity of aptamer-conjugated chitosan encapsulated mycogenic gold nanoparticles in human lung cancer cells, Journal of Nanostructure in Chemistry 12/4 (2022) 641-653. DOI: https://doi.org/10.1007/s40097-021-00437-2