

Advances in nanotechnology and asthma

Lingwei Wang[#], Mengjie Feng[#], Qiuwen Li[#], Chen Qiu, Rongchang Chen

Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Southern University of Science and Technology, Second Clinical Medical College of Jinan University, Shenzhen People's Hospital, Shenzhen Institute of Respiratory Diseases, Shenzhen 518020, China

Contributions: (I) Conception and design: C Qiu, R Chen; (II) Administrative support: C Qiu, R Chen; (III) Provision of study materials or patients: L Wang, M Feng, Q Li; (IV) Collection and assembly of data: L Wang, M Feng, Q Li; (V) Data analysis and interpretation: L Wang, M Feng, Q Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Chen Qiu; Rongchang Chen. Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Southern University of Science and Technology, Second Clinical Medical College of Jinan University, Shenzhen People's Hospital, Shenzhen Institute of Respiratory Diseases, Shenzhen 518020, China. Email: qiuchen@email.jnu.edu.cn; chenrc@vip.163.com.

Abstract: According to the World Health Organization, Asthma is the fastest-growing disease in the world alongside HIV/AIDS, and its socioeconomic burden exceeds the sum of HIV/AIDS and tuberculosis. Its high disability and mortality rates have become serious social and public health concerns. Asthma is a heterogeneous disease in which genetic polymorphisms interact with the environmental factors. While no specific treatment has been available for asthma due to its complex pathogenesis, the advances in nanotechnology have brought new hope for the early diagnosis, treatment, and prevention of asthma. Nanotechnology can achieve targeted delivery of drugs or genes, reduce toxic effects, and improve drug bioavailability. The nano-modifications of drugs and the development of new nano-drugs have become new research directions. Studies have demonstrated the safety and effectiveness of nanocarriers. However, many challenges still need to be overcome before nanotherapy can be applied in clinical practice. In this article we review the new research highlights in this area, with an attempt to explore the great potential and feasibility of nanotechnology in treating asthma.

Keywords: Nanotechnology; asthma; nano-modifications of drug; new nano-drugs; nanotherapy

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Asthma

Asthma is one of the most common chronic and non-communicable diseases in children and adults. At present, more than 300 million people are living with asthma worldwide, among whom about 30 million asthmatic patients are in China (1). In recent years, the global asthma prevalence is rising annually. Asthma is a heterogeneous disease in which genetic polymorphisms interact with environmental factors. It can be divided into different phenotypes according to clinical characteristics (e.g., the age of onset and disease severity), triggers (exercise and viral infection), and inflammation types (e.g., eosinophilic, neutrophilic, paucigranulocytic, and mixed granulocytic)

(2,3). While no specific treatment has been available for asthma due to its complex pathogenesis, long-term standardized therapies can effectively alleviate symptoms, reduce attacks, and improve the prognosis (*Figure 1*). Most asthmatic patients respond well to corticosteroid inhalation. The combinations of steroids with bronchodilators such as long- or short-acting beta-receptor agonists (LABA or SABA) or leukotriene receptor antagonists (LTRAs) are considered to be the first-line control strategy for asthma (4). However, asthma control is still poor in some asthmatic patients, even after the use of the maximum dose of corticosteroids (4). Importantly, the expenditure in these patients accounts for more than 60% of asthma-related

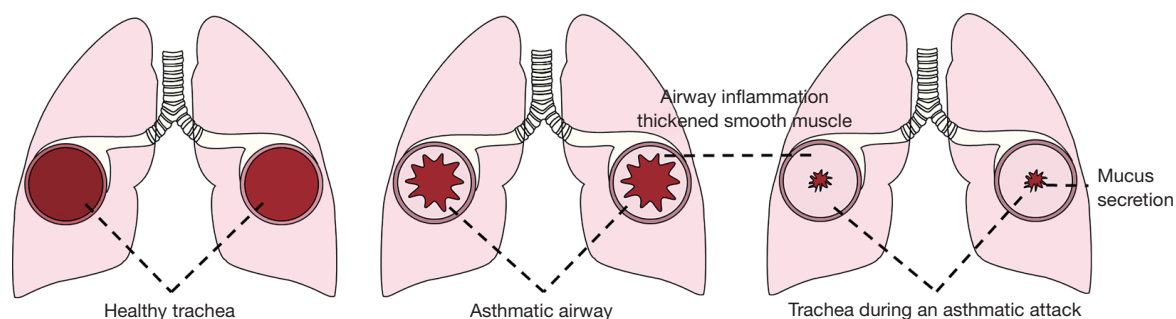


Figure 1 Airway changes in asthmatic patients.

medical costs (5). In addition to inhaled glucocorticoids, human monoclonal antibodies and cytokine/chemokine antagonists have been used to treat moderate to severe refractory asthma. However, these strategies can only achieve limited success due to the heterogeneity of asthma (6–8).

Nanotechnology

Nanotechnology is a multidisciplinary field of research, which manipulates and controls atoms and molecules sized 0.1–100 nm and manufactured relevant materials or structures (9). As a powerful driving force for the development of biomedicine, nanotechnology has stretched over fields including the early diagnosis, treatment, and prevention of diseases and the bioengineering studies, showing promising prospects. Thousands of nanomaterials have been used in biomedical research. Nanoparticles are one of the most widely studied drug delivery systems, as described in over 25,000 articles in the past decade (10). The Doxil nanotechnology platform was approved in 1995 and has become commercially successful. Since then, many nano-drugs have been approved by the US FDA, and some other drugs are also in clinical development. Nanomedicine is mainly focused on cancer and infectious diseases. For instance, doxorubicin liposomes (11), albumin-bound paclitaxel (12), and pegaspargase (13) have been developed as intravenous anticancer drugs. Other anticancer drugs are so far in phase II and III clinical trials. However, few studies have focused on the design of nanoparticles for the treatment of asthma. Here we will review the literature to highlight some of the recent advances in this field, with an attempt to further explore the potential of nanoparticles in asthma treatment.

Potentials of nanotechnology in asthma treatment

The currently available nano-drugs can be divided into two categories: (I) traditional molecular drugs improved by nanotechnology; and (II) the brand-new nano-drugs. The former is an improvement on traditional medicines, while the latter emphasizes the use of nanomaterials themselves as drugs. Here we will separately elucidate the application of these two categories of nano-drugs in asthma management (*Table 1*).

Application of nano-modified anti-asthma drugs

The nano-modification technology of traditional drugs mainly includes the research and development of nano-particle carriers with precise surface patterns, the carrying of existing drugs through drug-targeting reagents, and so on, to achieve targeted drug delivery, reduce toxic and side effects, and improve the solubility of insoluble drugs.

The prevention and treatment of asthma require long-term medication. The traditional anti-asthma drugs are mainly administered intravenously, orally, or by inhalation. The inhaled agents are the mainstream medications to maintain good asthma control, and their sizes are closely related to their bioavailability and efficacy. Compared with systemic drug administration, the targeted drug delivery by inhalation enables the drugs to directly reach the lungs, thus avoiding the first-pass effect and improving bioavailability (*Figure 2*). Glucocorticoid is the most effective drug to control airway inflammation caused by asthma (29). After a glucocorticoid is inhaled, it has a potent topical anti-inflammatory effect. The drug directly acts on the respiratory tract, which requires less dosage and has fewer systemic adverse reactions. A multi-center clinical

Table 1 Application of the traditional asthma drugs modified by nanotechnology and the brand-new nano-drugs

Authors	Findings
Modifications of anti-asthma drugs and their applications	
Chen <i>et al.</i>	Half of the Global Initiative for Asthma-recommended dose of inhaled corticosteroids (ICS) in the management of Chinese asthmatics could achieve similar efficacy as the recommended ceiling dose (14)
Nasr <i>et al.</i>	Poly-amidoamine (PAMAM) can be used as a carrier of beclomethasone dipropionate (BDP) and other insoluble drugs. It can improve drug solubility and increase its lung accumulation capacity, thereby improving the bioavailability of the drug, reducing dosage and dosing frequency, and reducing toxic and side effects (15)
Kenyon <i>et al.</i>	The non-toxic telomere dendrimer could also deliver hydrophobic drugs (e.g., dexamethasone) into the lungs directly, thus reducing allergic pulmonary inflammation and decreasing the eosinophils and inflammatory cytokines. Therefore, compared with the same dose of dexamethasone, it could improve airway hyperresponsiveness to a greater extent (16)
Matsuo <i>et al.</i>	Compared with free steroids, nanocarrier-encapsulated steroids could achieve better and more lasting therapeutic effects in airway inflammation sites (17)
Bhavna <i>et al.</i>	A nanocarrier could be tightly bound to salbutamol, yielding stronger interaction with pleura. The effective drug concentration could be maintained at the target site for a long period to achieve long-term relief of bronchospasm (18)
Chen <i>et al.</i>	Liposomes prolonged the retention of salbutamol sulfate in the lungs and maintained the effective drug concentration for more than 10 hours. Thus, they could achieve significantly higher efficacy than the free drug solution (19)
Application of brand-new nano-drugs	
Liu <i>et al.</i>	Nanoliposomes effectively transfected p53 gene into nasopharyngeal carcinoma cells, thus inhibiting the growth of tumor cells and inducing apoptosis (20)
Kumar <i>et al.</i>	Chitosan-IFN- γ pDNA nanoparticles (CIN) significantly reduced airway hyperresponsiveness and lung histopathology in BALB/c mice with allergic asthma induced by ovalbumin (21)
Kong <i>et al.</i>	CIN effectively inhibited the production of pro-inflammatory factors in lung OVA-specific CD8 + T lymphocyte population and lowered the activation level of dendritic cells. Its efficacy in treating allergic asthma might be related to the effective regulation of Th1/Th2 immune response. Once the regulatory T cells detected the up-regulation of IFN- γ expression, it up-regulated the expressions of Th1 cytokines and down-regulated the expressions of Th2 cytokines (22)
Oyarzun-Ampuero <i>et al.</i>	Thiolated chitosan nanoparticles and nanoparticles containing chitosan and cyclodextrin had also been used as lung delivery systems to prolong drug retention in the respiratory tract and enhance their anti-inflammatory effect (23)
Dahlman <i>et al.</i>	After the polyethylene glycol (PEG) nanoparticles were injected into the mouse body, they could reach the lungs, as shown by DNA sequencing (24). Further experiment showed that nanoparticles are reaching the lungs delivered a small-molecule RNA into lung cells and inhibit the expressions of target genes successfully (24)
Merkel <i>et al.</i>	Due to its high cationic charge density, polyethyleneimine (PEI) can effectively concentrate the negatively charged DNA into nano-scale complexes, thus protecting it from nuclease degradation. However, such a positive charge can be toxic and makes PEI a bad carrier for gene therapy of asthma. The PEG/PEI complex, modified by PEG, can also activate the complement system and induce the expressions of apoptosis-related genes (25,26)
Mastorakos <i>et al.</i>	Highly dense and biodegradable DNA nanoparticles could overcome the mucus barrier for inhaled lung gene therapy and have good safety. There was no obvious toxicity after intratracheal administration (27)
Salem <i>et al.</i>	Recently, a promising vaccine loaded with cytokine-phosphate-guanine (CpG) nanoparticles has been developed, which can be used for the treatment of allergic diseases caused by factors such as dust mites. Also, as an effective adjuvant, it could transform the Th1 cell immune response and inhibit asthma induced by Th2 cells (28)

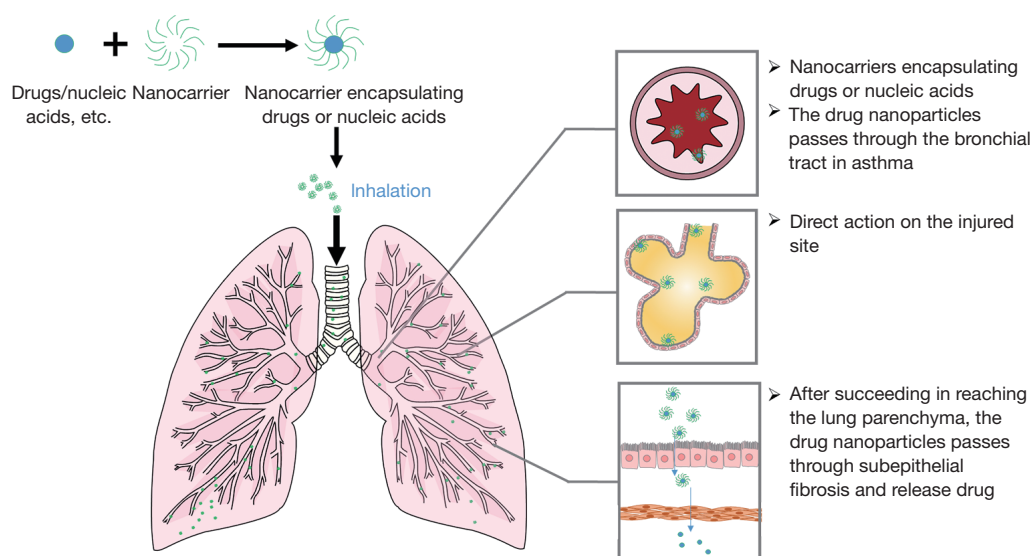


Figure 2 Advantages of inhaled nanoparticles. The inhaled nanocarriers loaded with drugs or nucleic acids can pass through the bronchial tract and directly reach the lungs and act on the site of injury in asthma. After succeeding in reaching the lung parenchyma, the drug nanoparticles pass through subepithelial fibrosis and release drug.

trial of fluticasone in the treatment of asthma in China many years ago showed that half of the Global Initiative for Asthma-recommended dose of inhaled corticosteroids (ICS) in the management of Chinese asthmatics achieved similar efficacy as the recommended ceiling dose (14). Although hormone inhalation therapy dramatically reduces the side effects (compared with systemic hormones), long-term high-dose hormone inhalation will inevitably bring some adverse reactions such as inhibition of adrenal axis, oral fungal infection, and osteoporosis. To reduce the side effects of long-term high-dose hormone inhalation and further improve the bioavailability of hormones, PEGylated Poly(amidoamine) (PAMAM) dendrimer, a typical dendrimer, has been widely studied and applied. According to Nasr *et al.*, PAMAM could be used as a carrier of beclomethasone dipropionate (BDP) and other insoluble drugs. It could improve drug solubility and increase its lung accumulation capacity, thereby improving the bioavailability of the drug, reducing dosage and dosing frequency, and reducing toxic and side effects (15). Also, the well-defined non-toxic telomere dendrimer has also been reported to be an efficient nanocarrier with greater loading capacity and better stability than micelles (for more than 6 months) (30). This nanocarrier can also deliver hydrophobic drugs (e.g., dexamethasone) into the lungs directly, thus reducing allergic pulmonary inflammation

and decreasing the eosinophils and inflammatory cytokines. Therefore, compared with the same dose of dexamethasone, it can improve airway hyperresponsiveness to a greater extent (16).

At present, the most commonly used drugs for alleviating symptoms included inhaled β_2 -receptor agonists, anticholinergic drugs, and short-acting theophylline. These drugs can rapidly relieve bronchospasm, usually within a few minutes, and the therapeutic effect can last for several hours. They are the first choice for alleviating acute symptoms in patients with mild to moderate asthma and also can be used for preventing exercise-induced asthma. These drugs should be used on demand, and long-term, excessive use of one single agent should be avoided. Their adverse reactions include skeletal muscle tremor, hypokalemia, and arrhythmia. Also, long-term use of a single LABA was associated with an increased risk of death from asthma (31).

According to Matsuo *et al.*, compared with free steroids, nanocarrier-encapsulated steroids achieved better and more lasting therapeutic effects in airway inflammation sites (17). Also, a nanocarrier can tightly be bound to salbutamol, yielding stronger interaction with pleura. The effective drug concentration could be maintained at the target site for a long period to achieve long-term relief of bronchospasm (18). Based on the above two studies, Chen

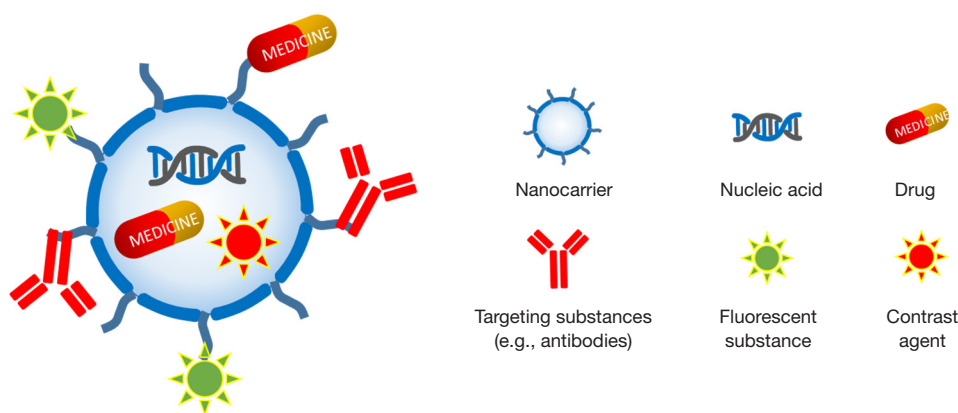


Figure 3 Schematic diagram of a multi-functional nanocarrier. Different molecules can functionalize the surface of a nanocarrier. The internal nuclei include various biologically active compounds including nucleic acids, drugs, and fluorescent substances.

et al. found that liposomes prolonged the retention of salbutamol sulfate in the lungs and maintained the effective drug concentration for more than 10 hours. Thus, they achieved significantly higher efficacy than the free drug solution (19). Compared with the micronized salbutamol sulfate, the nanoparticles loaded with the same drug were less affected in the human oropharynx and had higher peripheral deposition, which indicated that the nanoparticles had smaller size and greater topical bioavailability and could last for a longer period (32).

While no specific treatment has been available for asthma due to its complex pathogenesis, long-term standardized asthma treatment can effectively control asthma symptoms, prevent asthma attacks, and protect normal lung function. At present, the priority of asthma treatment has also changed from the use of bronchodilators to the treatments for fighting against inflammation and reducing airway responsiveness. Also, gene therapy and molecularly targeted therapy have also become hot research topics.

Application of brand-new nano-drugs

New nano-drugs are highly effective and low-toxicity therapeutic drugs or diagnostic drugs based on new nano-particles by utilizing new nanostructures or nano-characteristics. Since few studies have explored the new nanotherapy of asthma and the attack of asthma is closely related to the abnormal expressions of multiple genes, the effective combination of nano-gene carriers with genes represents a new direction in asthma therapy. Nano-sized gene carriers, with nanoparticles as the gene transfer vectors, wrap DNA and RNA in nanoparticles or adsorb

them on the surface of nanoparticles; meanwhile, specific target molecules such as specific ligands and monoclonal antibodies are coupled on the surface of nanoparticles. By binding the target molecules with specific receptors on the surface of cells, the nanoparticles can enter cells via cellular uptake, thus achieving safe and effective targeted drug and gene therapies (Figure 3). Therefore, selecting and constructing appropriate nanocarriers are cutting-edge topics in the gene therapy of asthma.

In recent years, new nano-gene therapy has become an alternative therapy for asthma patients. How to deliver DNA or RNA molecules to the target cells has long been a challenge in gene therapy. Due to the presence of a defense mechanism against foreign genetic material in the human body, free DNA and RNA molecules will be degraded rapidly and thus cannot achieve the desired therapeutic effects. It has been proposed that lipid molecules can be made into nanoparticles for wrapping DNA and RNA molecules. After their sizes and chemical compositions are changed, these nanoparticles can be safely transported into lung tissue. The nanocarrier-based gene delivery system provides a highly adjustable platform for therapeutic gene delivery, but the inability to achieve sustained, high-level gene expression *in vivo* is another major obstacle (27).

Many non-viral vectors based on liposomes and macromolecule polymers have been developed to convert nucleic acids into nanoparticles for lung delivery (33). Polyethyleneimine (PEI) is one of the most important polymeric gene carriers (34). Applications of nanoparticles such as chitosan (35), polyamidoamine dendrimers (36), and biodegradable poly(lactic-co-glycolic) acid (PLGA) (37) in the delivery of nucleic acids to lungs have also been described.

Nanoliposomes could effectively transfect *p53* gene into nasopharyngeal carcinoma cells, thus inhibiting the growth of tumor cells and inducing apoptosis (20). Due to the toxicity of nanoparticles, however, microbubble nanocarriers have also been considered. They are composed of pulmonary surfactants and newly synthesized amphiphilic compounds, which are safe, biocompatible, and biodegradable. Some inventors are also trying to obtain patents of inhaled liposomes and liposome-drug-liposomes in treating lung diseases or systemic diseases or in gene therapy (38). A new solid lipid nanoparticle with a particle size of 50-1000 nm has also shown promising future. With good biocompatibility, it can protect compounds from degradation and can better control drug release (39).

According to Kumar *et al.*, Chitosan-IFN- γ pDNA nanoparticles (CIN) can significantly reduce airway hyperresponsiveness and lung histopathology in BALB/c mice with allergic asthma induced by ovalbumin (21). In another study, they found CIN could effectively inhibit the production of pro-inflammatory factors in lung OVA-specific CD8⁺ T lymphocyte population and lower the activation level of dendritic cells. Its efficacy in treating allergic asthma may be related to the effective regulation of Th1/Th2 immune response. Once the regulatory T cells detect the up-regulation of IFN- γ expression, it will up-regulate the expressions of Th1 cytokines and down-regulate the expressions of Th2 cytokines (22). Thiolated chitosan nanoparticles and nanoparticles containing chitosan and cyclodextrin have also been used as lung delivery systems to prolong drug retention in the respiratory tract and enhance their anti-inflammatory effect (23).

After the polyethylene glycol (PEG) nanoparticles are injected into the mouse body, they can reach the lungs, as shown by DNA sequencing (24). The further experiment shows that nanoparticles reaching the lungs can successfully deliver a small-molecule RNA into lung cells and inhibit the expressions of target genes (24). Due to its high cationic charge density, polyethyleneimine (PEI) can effectively concentrate the negatively charged DNA into nano-scale complexes, thus protecting it from nuclease degradation. However, such a positive charge can be toxic and makes PEI a bad carrier for gene therapy of asthma. The PEG/PEI complex, modified by PEG, can also activate the complement system and induce the expressions of apoptosis-related genes (25,26). Therefore, we need safer and more effective biodegradable carriers. Mastorakos *et al.* introduced highly dense and biodegradable DNA nanoparticles that could overcome the

mucus barrier for inhaled lung gene therapy and have good safety. There was no obvious toxicity after intratracheal administration (27). Recently, a promising vaccine loaded with cytokine-phosphate-guanine (CpG) nanoparticles has been developed, which can be used for the treatment of allergic diseases caused by factors such as dust mites. Also, as an effective adjuvant, it could transform the Th1 cell immune response and inhibit asthma induced by Th2 cells (28).

To sum up, asthma is a highly complex chronic airway inflammatory disease, involving a variety of cells and cellular components. Therefore, asthma has many potential molecular targets including cytokines, chemokines, transcription factors, tyrosine kinases, and their receptors, as well as costimulatory molecules for gene silencing or over-expression of specific targets, which can be delivered together with drugs through nanoparticles.

Summary and prospect

This article reviews the potential benefits of nanocarrier-based drugs and gene therapy for asthma patients. As a potentially useful technique for the treatment and diagnosis of lung diseases, nanotechnology has become one of the top priority research areas. Pre-clinical studies using nanocarriers have demonstrated the safety and effectiveness of nanocarriers. However, many challenges still need to be overcome before nanotherapy can be applied in clinical practice. A thorough understanding of the mechanism of nanocarriers and the improved chemical structures of these materials are essential for the design and implementation of more reasonable clinical studies.

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Footnote

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