

## REVIEW

# Alternative approaches for the treatment of airway diseases: focus on nanoparticle medicine

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### Summary

Despite the various treatment options and international guidelines currently available for the appropriate therapeutic management of asthma, a large population of patients with asthma continues to have poorly controlled disease. There is therefore a need for novel approaches to achieve better asthma control, especially for severe asthmatics. This review discusses the use of nanoparticles for the specific targeting of inflammatory pathways as a promising approach for the effective control of severe persistent asthma as well as other chronic inflammatory diseases.

### Introduction

Although the majority of patients with asthma can be effectively managed with the current corticosteroid-based treatment regimens, about 10% of all patients with asthma have severe/refractory asthma which remains poorly controlled [1]. Importantly, this group accounts for more than 50% of health care expenses related to asthma owing to their higher frequency of hospital admissions, emergency room visits and medication [2–4]. Often, these patients have steroid-resistant disease characterized by a failure for their FEV<sub>1</sub> to increase by at least 15% after 7-day treatment with oral corticosteroids [5].

When systemic corticosteroids do not effectively control moderate-to-severe refractory asthma, antibody-based treatment using humanized neutralizing monoclonal antibodies or receptor antagonists against specific cytokine/chemokine are utilized. However, several reports have concluded that this treatment is most effective only in selected patients with increased levels of

expression or activation of the targeted pathway [6–10]. This means that antibody-based treatment approaches are not effective for many patients with asthma.

High systemic doses of corticosteroids pose serious adverse health effects [11, 12]. Efforts have therefore recently been focused on the development of alternative treatment options. These are expected to introduce effective therapy for steroid-resistant chronic inflammatory lung diseases, with less toxic side-effects.

In the last decade, several treatment approaches, including cell-based therapies, siRNA technology and epigenetic regulation targets, have been investigated for asthma and chronic obstructive pulmonary disease (COPD). However, still there are many unmet medical needs. These treatment options are primarily aimed at blocking specific signal transduction pathways or proteins that are involved in inflammatory responses. However, even these treatment approaches are limited in one way or another, either due to the complexity of the diseases or due to the limitations associated with

inefficient drug delivery which hinders the proper administration, penetration and distribution of the drug. The delivery of most of these therapies to specific sites of the body through the use of nanoparticles ensures that these anti-inflammatory agents avoid normal cells/tissues accumulating in the targeted sites of inflammation. This will allow the drug to achieve a concentration that is many times higher than otherwise expected while causing only a limited effect on normal cells [13]. In addition, nanoparticles can help protect the drug/inhibitor against degradation and increase its half-life in bloodstream allowing better biopharmacokinetics in host tissues.

The development of novel tools to facilitate personalized (or precision) medicine approach is of great interest. This strategy aims to individualize therapeutic interventions, based on genomics, proteomics, metabolomics or histopathological insights, as well as on the potential response of a specific patient to a particular treatment regimen. Nanomedicine enables personalized medicine approaches in many ways. Nano-imaging diagnosis may help understand disease stage and development and hence guide clinical treatment plans. Drug targeting to specific tissue sites or cellular populations may also ensure a personalized, patient-centred therapy. In this review, nanoparticle-based approaches for the treatment of airway chronic inflammatory diseases are discussed.

### Nanoparticle approaches

Nanotechnology has been demonstrated to be a powerful tool to design nanotherapeutics to fulfil different therapeutic and diagnostic purposes. The surface of

nanoparticles can be functionalized with different agents to achieve targeted delivery, improved biocompatibility and high-resolution imaging. The interior of the nanoparticles can also be used to encapsulate various bioactive compounds, such as nucleic acids, drugs and imaging contrast agents (Fig. 1).

Recent advances in material science and characterization techniques have made possible the development of many types of nanoparticles (NPs) with diverse applications. These types of nanomaterial (66) include polymer NPs, metal NPs, dendrimer NPs, liposome, micelles, nanocrystals, nanotubes and other nanostructures (Fig. 2). The usage of nanoparticles has provided several advantages over conventional drug usage. For example, nanotherapeutics have been shown to reduce the required dose of the drugs by increasing the specificity of the drug molecules via targeting and thus enhancing bioavailability and ultimately help in patient compliance. Poorly soluble compounds can be effectively delivered by nanoparticles through more suitable routes of administration which leads to reduced toxicity and increased efficacy (Fig. 2). Another unique aspect of nanocarriers is multimodality enabling the delivery of several diagnostic and therapeutic agents in tandem [14].

These nanocarriers also have disadvantages as drug delivery systems (DDS) [15–23]. The key ones are summarized in the list of *pros* and *cons* in Table 1. The choice of a nanoparticle for drug delivery depends on its unique properties at the nanoscale and the type of application it is intended for. For example, polymeric and lipid nanocarriers (micelles, liposomes, dendrimers, etc.) are commonly used to attain sustained and stimuli-responsive drug release in application such as gene

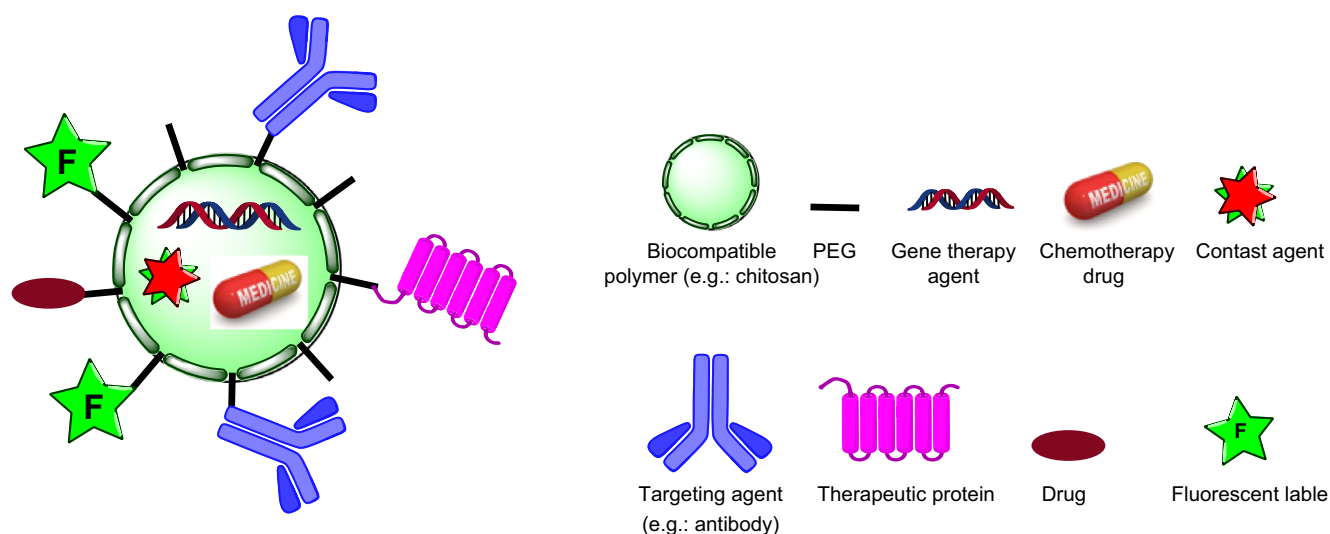


Fig. 1. Schematic of multifunctional nanoparticles. Nanoparticles can be surface-functionalized with different molecules, and the interior core can be encapsulated with various bioactive compounds.

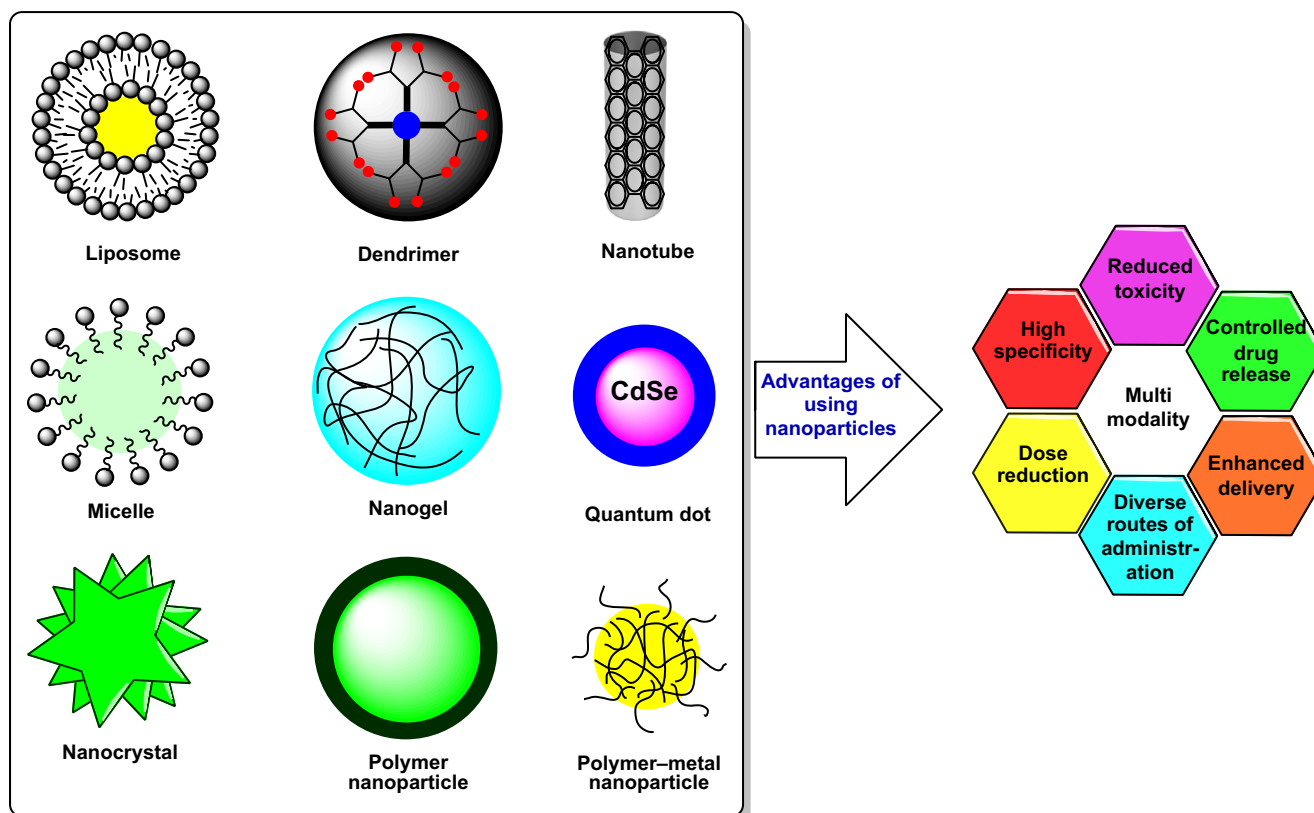


Fig. 2. Various types of nanoparticles and their advantages in nanomedicine.

delivery [24, 25] and photodynamic therapy [26]. Magnetic nanoparticles (such as superparamagnetic iron oxide (SPIO) nanoparticles), on the other hand, have shown success in magnetic resonance imaging (MRI) and magnetically guided drug delivery [27]. Our group has established numerous applications for SPION in the fields of imaging, drug delivery and hypothermia cancer therapy [28–31].

A number of nanoparticle-based drugs have been approved for routine clinical use. Most of these therapeutics have been designed for indications in cancer, infectious diseases and tissue imaging via a parental administration route. For example, Doxil [32], Abraxane [33] and Oncaspar [34] were all developed as anticancer agents and all are administered intravenously. Several other anticancer agents that are nanoparticle based are now in phase II and III clinical trials. For respiratory diseases such as asthma and COPD, development of nanomedicines has been much slower even though these are highly prevalent diseases that affect millions of people world-wide. The next section will highlight some of the pre-clinical studies that have been conducted to assess the role of nanoparticle technology in the control of these diseases.

#### Nanocarriers and the therapeutic potential of nanoparticles in asthma and COPD

The respiratory system is an established drug delivery route for several lung diseases [35]. Inhaling the drug is advantageous as in this case the drug should go directly to the required site of action in contrast to systemic administration. However, the picture is more complicated as inhaled drugs are usually deposited along the whole airways. For these drugs to be therapeutically relevant, they must reach the inflammatory cells in the lower airway at minimally effective doses. Effective pulmonary drug delivery systems can minimize systemic side-effects, provide rapid response and minimize the required dose.

As mentioned earlier, the application of nanotechnology to drug delivery has had tremendous impact on many areas of medicine. A variety of materials have been employed for drug delivery and imaging applications to date (Fig. 2). Since the approval and the commercial success of the nanotechnology platform for Doxil in 1995, a number of nanomedicines have been approved by FDA and several others are in clinical development. Most nanomedicine development has been seen with cancer and infectious

Table 1. Advantages and disadvantages of various nanoparticles used as drug delivery systems

|   | Nanocarriers                     | Advantages                                                                                                                                                                                                                                                                                                                      | Disadvantages                                                                                                                                            |
|---|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Liposomes [22]                   | <ul style="list-style-type: none"> <li>• Biodegradable and biocompatible</li> <li>• Ability to encapsulate and deliver polar and non-polar bioactive agents</li> <li>• Protects entrapped drug and provides sustained release</li> </ul>                                                                                        | <ul style="list-style-type: none"> <li>• Low stability</li> <li>• Tends to agglomerate</li> <li>• Some maybe allergic</li> </ul>                         |
| 2 | Gold nanoparticles [15]          | <ul style="list-style-type: none"> <li>• Biocompatible</li> <li>• Ease of synthesis and conjugation of multiple bioactive agents</li> <li>• Control of particle size</li> </ul>                                                                                                                                                 | <ul style="list-style-type: none"> <li>• Not biodegradable</li> <li>• High cost of large-scale production</li> <li>• Nanoparticle aggregation</li> </ul> |
| 3 | Carbon nanotubes [18]            | <ul style="list-style-type: none"> <li>• Ease of synthesis and conjugation of multiple bioactive agents</li> <li>• Large surface area</li> <li>• Ability to encapsulate and deliver various types of bioactive agents</li> <li>• Protects entrapped drug and provides sustained release</li> </ul>                              | <ul style="list-style-type: none"> <li>• Poorly soluble in water</li> <li>• Not biodegradable</li> <li>• Toxicity concerns</li> <li>• Poor pK</li> </ul> |
| 4 | Quantum dots [16, 21]            | <ul style="list-style-type: none"> <li>• Imaging properties</li> <li>• Theranostic application</li> <li>• Control of particle size</li> </ul>                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>• Toxicity concerns</li> <li>• Instability/air-sensitive</li> <li>• Nanoparticle aggregation</li> </ul>           |
| 5 | Polymeric nanoparticles [17, 20] | <ul style="list-style-type: none"> <li>• Generally, excellent stability</li> <li>• Controlled synthesis and great deal of flexibility in conjugation of multiple bioactive agents</li> <li>• Tailored drug release pattern</li> <li>• Flexibility in administration routes</li> <li>• Accumulates in tumours via EPR</li> </ul> | <ul style="list-style-type: none"> <li>• Agglomeration</li> <li>• Nanotoxicity with non-biodegradable polymers</li> </ul>                                |
| 6 | Dendrimers [19, 23]              | <ul style="list-style-type: none"> <li>• Water soluble and biocompatible</li> <li>• Good PK behaviour</li> <li>• Flexibility in conjugation chemistry</li> <li>• Ability to encapsulate and deliver various types of bioactive agents</li> </ul>                                                                                | <ul style="list-style-type: none"> <li>• Poor drug release profile</li> <li>• Toxicity concerns</li> <li>• Rapid clearance</li> </ul>                    |

diseases; there has been little effort in designing nanoparticles for the treatment of chronic obstructive lung diseases, including asthma. In this section, we will review the literature to highlight some of the recent development efforts aimed at exploring the therapeutic potential of nanoparticles in asthma and COPD.

#### Gene transfer therapy

siRNA-based therapy has great potential in the treatment of asthma and COPD as delivery of therapeutics such as siRNA to airway inflammatory and/or structural cells is likely to reduce toxicity and immunogenicity [36, 37]. However, progress in this area has been hindered due to lack of suitable carriers that can efficiently protect and deliver siRNA/pDNA to desired cells. In an attempt to overcome this obstacle, Kumar *et al.* [38] demonstrated that chitosan interferon (IFN)- $\gamma$ -plasmid DNA (pDNA) nanoparticles therapy can effectively reduce established allergen-induced airway

inflammation and airway hyperresponsiveness (AHR) and is thus a potential therapy for asthma. The same group has also demonstrated that this therapy decreases the number of pro-inflammatory CD8<sup>+</sup> T cells and inhibits the antigen-presenting activity of dendritic cells in mice [39]. As the respiratory system is a viable drug delivery route for asthma and COPD, inhaling the drug may be advantageous as it allows for direct localization of the drug into the site of action. Conti *et al.* [40] reported the formulation of inhalable siRNA using poly (amidoamine) dendrimer nanocarriers that efficiently targeted lung alveolar epithelial cells. Dendrimer-based nanoparticles for the *in vivo* delivery of siRNA to lung vasculature have also been developed by Khan *et al.* [41].

#### Nanocarriers of clinically relevant asthma drugs

Recently, research efforts are focusing on the development of potential drug nanocarriers that can successfully deliver asthma therapeutics to the site of

inflammation. For example, intranasal delivery of theophylline (an anti-inflammatory asthma drug) was successful using thiolated chitosan nanoparticles. The study demonstrated that this drug delivery system augmented the anti-inflammatory effects of the drug compared to theophylline administered alone in a mouse model of allergic asthma [42]. Muco-adhesive nanoparticles for the potential treatment of asthma were also developed. Alonso and co-workers developed chitosan-hyaluronic acid nanoparticles (CS-HA NPs) loaded with heparin to investigate their potential in anti-asthmatic activity. Confocal microscopy experiments showed that fluorescent heparin-loaded CS-HA nanoparticles were internalized by rat mast cells; however, the capacity of free heparin and of heparin-loaded NPs to prevent histamine release was very similar [43]. More recently, the same laboratories demonstrated that heparin-loaded chitosan-cyclodextrin nanoparticles led to significant improvement of the efficacy of the loaded drug, suggesting that these nanomedicines represent promising formulations for asthma treatment [44].

Steroid-loaded nanoparticles have also demonstrated remarkable therapeutic effects compared to free drugs. For example, Matsuo et al. investigated the effect of betamethasone phosphate-loaded polymeric nanoparticles on a murine asthma model. These nanoparticles were found to accumulate at the site of airway inflammation and exhibit anti-inflammatory activity [45]. A recent study has shown that self-assembling nanoparticles containing dexamethasone target the lung and decrease allergic lung inflammation and airways hyperresponsiveness in a mouse asthma model [46]. Another study used a combination of a therapeutic peptide and dexamethasone (Dexa) loaded on the same polymeric nanocarrier in attempt to reduce neutrophilic pulmonary inflammation. In this work, Flt 1 peptide was first conjugated to hyaluronic acid (HA) and the self-assembled nanoparticle was used as a nanocarrier of Dexa for the treatment of asthma [47]. This elegant study showed that the Dexa-loaded nanoparticles reduced the cytokine levels in LPS-stimulated cells more significantly than free Dexa. In addition, the nanoparticles showed remarkable therapeutic effects on both eosinophilic and neutrophilic subtypes of asthma [47]. Recently, a study embarked on the development of oral dispersible tablets containing prednisolone (corticosteroid drug)-loaded chitosan nanoparticles for management of paediatric asthma [48].

Other types of asthma therapeutics can also be delivered to the site of inflammation *via* nanoparticles. Enhanced bioavailability and efficiency of curcumin for the treatment of asthma were demonstrated by its formulation in solid lipid nanoparticles (SL NPs). In an animal model of asthma, curcumin-SL NPs effectively suppressed AHR and inflammatory cell infiltration.

Furthermore, these curcumin-loaded nanoparticles more effectively inhibited the production of Th2 cytokines than curcumin alone [49]. A recent study reports on a new family of biodegradable hydroxybenzyl alcohol (HBA)-incorporated polyoxalate (HPOX) nanoparticles as novel therapeutics of airway inflammatory diseases. The potential of these nanoparticles as an anti-asthmatic agent was evaluated in an asthma animal model, and the results show remarkable reduction in the recruitment of inflammatory cells and expression of pro-inflammatory mediators [50].

### *Other nanoparticle-based approaches*

Several research groups have adopted other approaches to treat airway inflammation. Park et al. [51] have demonstrated the attenuation of allergic airway inflammation and hyperresponsiveness in a murine model of asthma by silver nanoparticles. The study showed that the increased inflammatory cells, airway hyperresponsiveness, increased levels of pro-inflammatory cytokines and NF- $\kappa$ B after OVA inhalation were all significantly reduced by the administration of silver nanoparticles. Our group has recently reported the synthesis, biocompatibility and efficient targeting of PEGylated dextran-coated anti-IL4 receptor (anti-IL4R $\alpha$ ) conjugated SPION to IL4R $\alpha$  within inflamed lung tissue [30]. These optimized anti-IL4R $\alpha$ -NPs were more efficient than free anti-IL4R $\alpha$  in controlling lung inflammation by suppressing the activation and proliferation of lung tissue inflammatory cells [52]. Hardy and co-workers [53] have developed polystyrene 50-nm nanoparticles coated with glycine (PS50G) that modify pulmonary dendritic cell function and inhibit allergic airway inflammation. This research established that exposure to PS50G nanoparticles inhibits key features of allergic airway inflammation including airway epithelial mucus production and serum allergen-specific IgE and allergen-specific Th2 cytokines in the lung-draining lymph node. Although not related to the treatment of asthma *per se*, recently Wang and co-workers developed an ingenious method of delivery of therapeutic nanoparticles across the blood vessel barrier for the treatment of inflammation and infection. The study demonstrated the effective use of activated neutrophils for the delivery of therapeutic albumin nanoparticles to targeted disease sites [54]. Human neutrophils account for nearly 70% of the circulating leucocytes [55], and thus, this study may lead to applications in the treatment of several inflammatory diseases including asthma.

### *Imaging in asthma*

Generally, molecular imaging of inflammatory lung diseases, such as asthma and COPD, has been limited

to date. The most commonly used non-invasive and sensitive methods are magnetic resonance imaging (MRI), fluorescence imaging, radio-imaging and positron emission tomography (PET) imaging. Chen and co-workers have extensively used PET for imaging pulmonary inflammation [56]. Recently, our group has used antibody-conjugated SPIONs for specific targeting and imaging of a particular macrophage subpopulation in lipopolysaccharide-induced COPD mice model [57]. Along with magnetic NPs used by us and others, fluorescent NPs have also been used for imaging macrophages. The laboratory of Low demonstrated that folate-conjugated fluorescent dyes and radio-imaging agents can be specifically targeted to asthmatic lung macrophages, suggesting a potential strategy for the development of diagnostic agents for the imaging of asthma [58]. Recent advances in imaging techniques have allowed the use of multimodal imaging in monitoring disease progression and behaviour. Visible and near-infrared (NIR) light-emitting quantum dots in conjunction with SPIONs have been developed for fluorescence imaging and MRI techniques to monitor the migration of dendritic cells in mice [59]. Recently, Markus *et al.* [60] have developed an imaging approach for tracking inhaled near-infrared fluorescent polystyrene nanoparticles in lungs of SKH-1 mice with allergic airway inflammation. The study showed that fluorescence reflectance imaging (FRI) in combination with NIR is an effective technique to monitor the presence of acute allergic airway inflammation in SKH-1 mice.

### Biosafety of nanoparticle approaches

The most critical determinant factor for nanoparticle development approach is its safety and biocompatibility. Several *in vitro* and *in vivo* (animal) studies have been used to assess the toxicity of nanoparticles. Cells treated with nanoparticles *in vitro* are usually assessed for cell morphology, cytotoxicity, oxidative stress, cytokine release, oxidative stress assays, genotoxicity evaluations, apoptosis and necrosis amongst others. It must be emphasized that the size, shape and surface properties of nanoparticles influence not only the viability of target cells but also their pharmacokinetics and pharmacodynamics [61–64]. Based on their mode of administration, nanoparticles accumulate in spleen, liver, lungs and/or kidneys [65]. Consequently, assessments of acute and chronic toxicity evaluations following either single or multiple doses are performed to confirm biosafety [63, 65].

The risk that nanoparticles can augment allergic pulmonary inflammation cannot be ignored. Several recent reports confirm that certain nanoparticles can aggravate pulmonary inflammation and may put individuals with

asthma at a greater risk. For example, Hussain *et al.* reported that a low intrapulmonary dose of titanium dioxide or gold nanoparticles resulted in an asthmatic response in a mouse model [66]. The laboratory of Bonner demonstrated that nickel nanoparticles caused exaggerated lung and airway remodelling in mice lacking TBX21, a transcription factor that is also significantly less expressed in asthma [67]. Shurin *et al.* [68] have demonstrated that graphene oxide nanoparticles augmented AHR and airway remodelling. Finally, Ronzani *et al.* [69] have reported that exposure to multi-walled carbon nanotubes caused aggravation of airway inflammation and remodelling in a mouse model of asthma.

### Nanoparticle medicine to improve the efficacy of novel treatment approaches

Novel approaches for the treatment of chronic lung inflammatory diseases including cell-based therapies, siRNA technology and epigenetic regulation targets are still at the starting stage of development. Extensive research is still required to prove their efficiency and overcome their challenges.

Stem cells, with their unique self-duplicating ability, provide a great deal of appeal in the treatment of chronic lung diseases [70]. These cells are believed to participate in tissue homeostasis and regeneration of the airways. They may be localized in certain areas within the distal airways [71] or recruited from blood, bone marrow or adipose tissue [72, 73]. One of the main challenges for stem cell research is their effective transplantation and targeting to the site of tissue injury. Nanoparticles could be helpful in this aspect by ensuring correct targeting of delivery. SPION could be targeted specifically to sites within the body non-invasively using magnets [74]. A similar approach could be used to specifically target stem cells to desired lung injury sites.

Gene silencing using RNA interference (RNAi) has attracted lots of interest as a powerful tool to control lung inflammation. RNAi-based therapy carries many advantages over conventional approaches due to its inherent ability to inhibit any chosen gene target with high specificity [36]. Lung diseases are currently one of the main focuses of siRNA-based therapeutics due to the ease of delivery through intra-nasal, intra-tracheal or intra-pulmonary routes [37, 75–78]. Potential treatment options with siRNAs are relatively new to the field of respiratory medicine. Major challenges with this technology that remain to be overcome include the best delivery route, targeting it to the desired site, protecting siRNA against lung tissue environment and the efficacy of the therapy. This could be easily solved using nanoparticles. Nanoparticles

loaded with inhibitory siRNA could be used to control the infiltration, activation and proliferation of lung inflammatory cells or suppress the release of inflammatory cytokines from inflammatory as well as lung structural cells [37, 79–84]. siRNA against inflammatory cytokines (IL-4, IL-13, etc.), chemokines (RANTES, MIP-1 $\alpha$ ) or regulatory pathways (Ex: STAT6 [85] or MAP kinases) could be used to suppress inflammation.

Adaptive changes in epigenetic regulation may cause a series of pathological changes leading to chronic respiratory diseases. Major mechanisms causing epigenetic alterations include DNA methylation of CpG islands, histone modifications and miRNAs [86, 87]. Inhibiting DNA methyltransferase activity and histone deacetylases (HDAC) has reduced airway hyperresponsiveness and abrogated airway constriction in murine asthma models [88, 89]. Currently, clinical trials in asthma and COPD are investigating the potential use of theophylline to alter the acetylation status of nuclear histones. Interestingly, modulating epigenetic regulations is also possible using targeted nanoparticles which may help in reverting pro-inflammatory or induce anti-inflammatory regulations.

Specific immunotherapy (SIT) aiming to induce antigen-specific immune tolerance is widely used for the treatment of allergic diseases. However, this approach requires the use of high doses of soluble antigen for long periods which may carry a high risk of adverse reactions, particularly in highly sensitized patients. Thus, the development of safer, more efficient methods for this approach is critical to advancing allergy treatment. Recently, Smarr et al. [90] have reported the use of PLG NPs containing encapsulated antigen (PLG (Ag)) for the induction of tolerance in a murine model of Th2-mediated, ovalbumin-induced, allergic airway inflammation. These NPs inhibited Th2 responses and airway inflammation both prophylactically and therapeutically. These findings suggest that the NP approach as a biodegradable Ag carrier platform may induce safe and effective inhibition of allergic airway inflammation in animals with established Th2 sensitization.

### Outlook and future prospective

Inhibition of the calcium-sensing receptor has recently emerged as a novel approach for controlling AHR and inflammation in allergic asthma. Recently, Yarova et al. [91] reported that the calcium-sensing receptor (CaSR) is over-expressed in airway smooth muscle cells, causing an increase in their contractility during AHR. Calcilytics, which act as antagonists to the over-active CaSR, reduced AHR and inflammation in

allergen-sensitized mice *in vivo*. Although calcitriol pills are safe as a treatment for osteoporosis, it is not known whether the dose required to be effective in reducing the inflammation found in asthma would be safe. Future studies exploring the use of targeted nanoparticles loaded with CaSR antagonists would be interesting. This approach would increase the availability of the drug to the CaSR at minimal concentrations and hence may lead to a promising treatment for asthma and other chronic lung inflammatory diseases.

To effectively translate these approaches into the clinic, the above-mentioned NP platforms need to demonstrate safety, efficacy, clear therapeutic advantage over existing common asthma treatments and cost-effectiveness in production. This will require the identification of the ideal properties of the nanoparticles to elicit the desired response as well as acquiring in-depth knowledge of the molecular and cellular mechanisms of the disease. The promising results obtained using nano-based delivery of clinically relevant asthma drugs will keep fuelling research to develop multifunctional optimally designed nanoparticles. Novel biocompatible nanocarriers, capable of bypassing the airway defences, will undoubtedly be invaluable for the search for novel treatment of chronic obstructive airway diseases such as asthma and COPD. For example, Hanes and co-workers recently demonstrated that densely coating the surface of nanoparticles with suitable size of PEG molecules enhanced their penetration and distribution through the mucus [92]. The other basic ingredient that is required to control and treat asthma and COPD is the ability to monitor the level of disease progresses including inflammation and tissue remodelling before and after treatment. The continuing advancement in imaging and diagnostic techniques will certainly contribute to fulfilling this need and thus help bring viable asthma treatments closer to market. Cost could also be amongst the challenges for this sophisticated approach. However, nanomedicine field is progressing quickly and expenses are expected to be dramatically reduced in the near future, especially for mass drug production.

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### Conflict of interest

The authors declare no conflict of interest.

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