Introduction
Chronic obstructive pulmonary disease (COPD) and asthma are the two of the most common chronic inflammatory lung diseases (CILDs) and affect > 500 million people worldwide. Conventional treatments mainly focus on easing the symptoms by mitigating inflammation with corticosteroids (CSs) or by bronchodilators (BDs). However, these are proven to be ineffective preventing the progression of CILD and particularly of COPD. Furthermore, the CS, which is used in routine, has adverse health effects when systematically applied in high doses. Therefore, there is an urgent need for new, effective therapeutics that can treat, and ultimately cure, patients who suffer from CILD. This review will evaluate the hallmarks of CILD and the therapeutics that are currently used for treatment. Then elucidate the area of liposome-based theranostics as an improvement to these therapies and exemplify the research that has done in the area.

Hallmarks of Chronic Inflammatory Lung Disease and Conventional Treatments
COPD is the fourth largest cause of death worldwide, and it is expected to be the third by 2020. COPD is an inclusive term for a group of conditions, such as emphysema and chronic bronchitis, which causes the persistent difficulty in exhaling air from the lungs. Cigarette smoking is the major cause of COPD, and it induces chronic inflammation that leads to irreversible destruction of lung alveoli and the promotion of mucus secretion, which further blocks the airway and causes cilia damage in the respiratory track and makes lungs vulnerable to chronic infections.

Asthma is a common type of CILD that occurs in airways in the lung and affects >300 million people worldwide. Inflammation leads to swelling and narrowing of the airways, therefore obstructing breathing. In contrast to COPD, airflow obstruction in mild to moderate asthma is usually reversible naturally or with treatment. Even though inflammation in the respiratory track is common to both of them, the nature of inflammation usually differs particularly in terms of anatomical

Abstract
Chronic obstructive pulmonary disease and asthma affect millions of people worldwide. Conventional treatments are not sufficient at preventing the progression of these diseases. The treatments are unspecific, and when administered systematically, and in high doses, they have adverse health effects. Further, the current diagnostic methods are poor and they are not capable of identifying the accurate state of the disease. Nanoparticle-based theranostics (NBTs) are well-established systems that simultaneously provide treatment and diagnostics. Various nanocarriers can be used in NBT and are designed according to the need. In this review, liposome-based theranostic systems are evaluated and possible modifications that could provide better drug delivery and accumulation and diagnosis are exemplified. These systems can be applied to conventional therapeutics to avoid side effects and perhaps overcome the challenges that interfere with their cellular accumulation.

Keywords: Asthma, chronic obstructive pulmonary disease, imaging, liposomes, magnetic resonance imaging, superparamagnetic iron oxide nanoparticle, theranostics

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distribution, inflammatory cells, mediators, and response to anti-inflammatory therapy.\(^{[5,9]}\)

Although asthma and COPD are two distinct diseases and have different management strategies, they are often treated with the same medications.\(^{[10]}\) Some patients show symptoms similar to both asthma and COPD, which is termed asthma-COPD, overlap syndrome (ACOS).\(^{[10]}\) Even though ACOS has several phenotypes that require different therapeutic approaches, the patients are also treated with conventional asthma therapeutics.\(^{[10]}\) The current treatments for asthma, COPD, and ACOS solely focus on eliminating the inflammation with CS and dilated bronchi with BD. The aerosol formulations containing these medicines have relatively fast pharmacokinetic profile; therefore, they are required to be administered frequently.\(^{[11]}\) CS is a strong anti-inflammatory and immunosuppressive medicine, which either induces anti-inflammatory or represses pro-inflammatory genes to reduce inflammation.\(^{[12,13]}\) CS treatments are effective to keep asthma under control when delivered locally; however, patients who have severe asthma have remained difficult to be treated.\(^{[14]}\) Severe asthma requires high doses of CS and a second controller or systemic CS to be restrained; otherwise, it may remain uncontrollable.\(^{[14]}\) CS insensitivity may occur in severe asthma patients, which could further contribute to the severity of the disease.\(^{[15]}\) Moreover, long-term systemic CS therapy has adverse effects such as osteoporosis, adrenal suppression, diabetes, and cardiovascular diseases.\(^{[12,13,16]}\) Most of the severe asthma patients tend to develop at least some of these pathologies overtime.\(^{[16]}\) In contrast to asthma, CS is not effective to suppress inflammation in COPD patients due to decreased activity of gene transcription suppressors, histone deacetylases (HDACs).\(^{[17]}\) It has been found that activated glucocorticoid receptors recruit HDAC2 to nucleus to repress the transcription of inflammatory genes and relieve the inflammation in healthy or non-COPD smoker, whereas in COPD patient, this system may fail to function.\(^{[17]}\)

**Liposomes as Nanotheranostics**

Nanotechnology offers great potential as the future of medicine due to its capability of delivering appropriate amounts of a therapeutic to a target area sustainably and monitoring the disease state concurrently. Their improved pharmacokinetics and biodistribution profiles via the enhanced permeability and retention (EPR) effects make them valuable tools in the design of therapeutics.\(^{[19]}\) Until 1995, nanotechnology applications were limited to the cosmetics industry. Doxil\(^{[4]}\), the first liposome-based nanomedicine that carries an anticancer agent, was approved by the Food and Drug Administration and marketed in 1995 which made nanoparticles a promising tool in the pharmaceutical industry.\(^{[19]}\)

Liposomes are among the most established drug delivery platforms due to their flexibility, biocompatibility, biodegradability, and nonimmunogenicity.\(^{[20,21]}\) They are self-assembled structures constructed by amphiphilic phospholipids and have spherical lipid bilayer structure containing an aqueous core [Figure 1].\(^{[22]}\) Due to containing both hydrophilic and hydrophobic sites, liposomes are suitable to carry drugs that have different molecular entitites toward water, which makes them convenient for combination therapy that holds great importance in CILD treatment.\(^{[23,24]}\)

The main drawbacks of liposomes are their instability and short blood circulation time.\(^{[24]}\) However, these problems may be solved by simple surface modifications. Liposomes’ surface can be modified by ligand coating, which enhances their properties such as stability, permeability, circulation time, mucoadhesiveness, or cellular uptake.\(^{[33]}\) Coating the surface of liposomes with poly (ethylene) glycol is the most common modification, and it stabilizes the liposome in the blood while preventing it from opsonization and promoting them for target localization.\(^{[26,27]}\) Furthermore, mucoadhesive polymer coating with chitosan, carbopol, or hyaluronic acid gives mucoadhesiveness to the liposomes that could be a desired feature when targeting COPD and/or asthma as increased mucus secretion is observed in both diseases.\(^{[28,29]}\) Liposomes’ surfaces are modified not only to increase stability but also to enhance targeting specificity. Antibodies or ligands, such as peptides or polysaccharides, can be attached to liposomes’ surface to increase specificity\(^{[30]}\) (For more details see “Targeting and Delivery” section).

Liposomes can be designed to have different electrostatic properties. Consistent with their lipid composition, liposomes can either be positively or negatively charged. Positively charged liposomes, as known as cationic liposomes, are easily taken up by cells due to the negatively charged nature of their membranes and widely used in gene delivery.\(^{[31,32]}\) However, the strong interaction between the cell surface and the liposome membrane may lead unspecific Toll-like receptor binding that could result in leukocyte activation.\(^{[33]}\) Negatively charged, anionic liposomes can be internalized by macrophages that might be an effective approach to target alveolar macrophages for COPD treatment since these cells have key roles in the pathogenesis of COPD.\(^{[24,31]}\)

![Figure 1: Structural illustration of liposomes. The lipid bilayer is capable of containing hydrophobic or lipophilic drugs. The hydrophilic core can contain hydrophilic drug poly (ethylene) glycol coating which prolongs the blood circulation and stabilizes the liposomes](image)
Liposomes are very felicitous to develop nanoparticle-based theranostics (NBTs), which contain imaging agent in addition to therapeutics, and allow therapy and diagnosis simultaneously. Synchronized imaging is essential for monitoring the disease state during, and after, the therapy to assess treatment efficiency. NBTs have shown great efficacy in cancer diagnosis and treatment in the past decade by delivering the correct doses of chemotherapeutic drugs to tumorous areas in a reliable manner and allowing consistent imaging instantaneously.[34,36] There are four important assets to consider when designing a successful NBT: first, to choose an effective therapeutic, either a small molecule compound peptide or nucleic acid; second, to find a stable transporter; third, to decide on a targeting and drug release strategy; finally, to select a contrast agent or dye for imaging.

THERAPY

Liposomes are used in various lung diseases, carrying vasodilators for pulmonary arterial hypertension,[37] antimicrobials for chronic bacterial airway infections,[39,38,40] anticancer agents for lung cancer,[41,42] recombinant gene for cystic fibrosis gene therapy,[32] and CS and BD for asthma, acute lung injury, and acute respiratory distress syndrome (ARDS).[11,12,43-47] They have been studied for asthma therapy since the early 1990s. Vidgren et al. examined liposomal beclomethasone dipropionate (Bec-L) in human volunteers and found that they have a prolonged anti-inflammatory effect as compared to any soluble drug.[45] They also used radioactive labeling $^{99m}$Tc to observe drug release patterns and confirmed that Bec-L provides sustained release.[45] These liposomes are found to be tolerable, and they have no significant pulmonary or systemic adversities in healthy individuals.[43] Following these improvements in 2003, Konduri et al. developed stealth liposomes, which are more stable versions of unmodified liposomes, containing budesonide to reduce the frequency of CS administration for patients who are suffering from CS’s side effects.[49] As a result, weekly therapy with liposomal budesonide could substitute daily budesonide administration as well as reduce toxicity and improve compliance in mice.[49] Researchers also encapsulated BD in liposomes for sustained delivery and frequency reduction of the administered drug. Chen et al. encapsulated salbutamol sulfate (SBS) into liposomes and delivered them in an aerosol form to guinea pigs and observed that liposomal SBS displayed anti-asthmatic effects for up to 18 h whereas free SBS had lasted for only 6 h.[11]

Liposomes are preferred transporters to carry combinations of therapeutics in a single platform to increase treatment efficiency.[49] Patients with CILD are generally prescribed CS and BD because the combination of inhaled CS and long-acting $\beta_2$ antagonists (LABAs) provides greater control over asthma.[44,50] Indeed, in ACOS, which has suffering and mortality of both disorders, combination therapy might be a necessary solution.[41] In fact, in 2002, Saari et al. studied LABA formoterol in addition to Bec-L treatment in nine asthma patients to observe the effect of LABA on lung deposition pattern of Bec-L and found that formoterol enhanced lung functions and peripheral lung deposition of Bec-L.[44] This study was the first combination therapy for asthma although BD and CS were separately, but concurrently, administered. Currently, there are inhalers containing combination of BD and CS, but these formulations are mixed either physically or mechanically, which may lack homogeneity and prevent the association of these two drugs at the target site.[48] Parikh et al. had drawn attention to the fact that there is a synergistic effect on inflammation when these two drugs combined together at the target side as each drug enhances the biochemical and pharmacological effects of other.[50] In other words, delivering CS and BD to the pathological area simultaneously in the same platform, which could be liposomes, might increase the treatment efficiency.

TARGETING AND DELIVERY

Since most of the liposome-based theranostics are mainly studied in the area of cancer, the preferred administration method is intravenous. However, pulmonary delivery has become an attractive method and of great interest in the healthcare research area, when targeting respiratory track diseases, lung cancer, or CILD due to the ability to deliver the drug directly to the pathological site without getting metabolized rapidly.[7,42,52,53,55] Pulmonary delivery has been also used for systemic delivery of drugs such as insulin, human growth hormone, and calcitonin.[53,54] Due to the lungs’ large absorptive surface area, approximately 70–140 m², high permeability, limited proteolytic activity, and good blood supply, pulmonary route is now considered one of the most effective approaches for drug administration.[7,53,56,57]

Pulmonary delivery uses three main inhalation devices: metered-dose inhalers, dry powder inhalers, and nebulizers.[58] These devices generally use two forms of therapeutics: liquid spray or dry powder form.[58] Although, in this review, these devices are not explained in detail, the technical feature of these devices should be taken into consideration when designing an NBT, since the preparation of liposomes may differ according to the form of delivery. It is stated that liposomal formulations opened a new era in jet nebulizers as their applicability used to be limited to water-soluble drugs.[50] However, due to the structure of liposomes, aerosol form of water-insoluble or lipophilic drugs can be used in jet nebulizers.[59] Waldrep et al. indicated that aerosolized Bec-L is well tolerated in humans and practical for elderly people and young children who cannot efficiently use dry powder inhalers or metered-dose inhalers.[43] However, Elhissi et al. argued that in liquid spray form in aqueous solution, hydrolysis rate of the liposomes and oxidation of phospholipids might increase and these could jeopardize their stability.[60] They suggested that freeze-dry lyophilization method could overcome this problem as in this method liposomes are lyophilized in the presence of cryoprotectants, such as carbohydrates, to preserve their stability.[60] Using this technique, they successfully developed
a stable liposomal carrier containing a combination of asthma drugs; beclomethasone dipropionate, a synthetic glucocorticoid to reduce inflammation, and SBS, a short-acting β2 adrenergic agonist as relaxant.\[60]\]

Liposomes are found to be highly effective in pulmonary delivery; however, their size must be tuned carefully. Depending on the size, the deposition of liposomes in the upper respiratory track could be prevented, and the residence time of the deposited material in lower airways would be prolonged.\[45]\]

Figure 2 shows the particle sizes that can reach to certain place in the lung. Mucociliary transport is mainly responsible for airway clearance, and it is particularly successful with particles larger than 6 μm.\[61]\] The particles can be removed by mucociliary system from the lungs and excreted by feces within 24 h.\[61,62]\] Smaller particles can be engulfed by airway macrophages, but particles <5 μm in size enter the alveolar region, where alveolar macrophages reside.\[61]\] Since there is no mucus transport in the lung periphery, the clearance is slower as compared to the airways.\[62]\] Depending on the size and surface properties, particles can remain in parenchyma longer than 24 h.\[62]\] Considering an average size of a liposome, which is approximately 200 nm, they can remain in the lungs for a period of time and provide a prolonged release of the loaded drug compound.\[63]\]

Although tuning the size of the liposomes is important to prevent opsonization by macrophages, sometimes, when the aim is to target the macrophages, liposome sizes can intentionally be altered to make them identifiable by these cells. It is proposed that mannosylated liposomes that are 1000 nm in size can be used as a model therapeutic for cells. It is proposed that mannosylated liposomes that are 1000 nm in size can be used as a model therapeutic for respiratory infections and deliver drugs to macrophages effectively.\[40,65,66]\] Liposomal surface modifications with mannose make these carriers specific to alveolar macrophages as mannose receptors are highly expressed on their surface.\[66]\] Targeting alveolar macrophages may be a convenient drug delivery approach with oversized liposomes as using this method specific targeting and internalization steps could be bypassed.

Two main approaches are used in NBT targeting: active and passive targeting. Active targeting uses chemically conjugated ligands that recognize receptors or distinct peptides or polysaccharides on the cell surface.\[21]\] When these receptors recognize the ligand, they induce ligand-induced internalization by endocytosis. This method is highly beneficial when pathological tissues express specific biomarkers. Targeting these biomarkers precisely is necessary for the liposomes to accumulate only in diseased tissues at high levels and not in healthy tissues.\[26]\] In 2013, Chen et al. developed a liposomal dexamethasone delivery system with antibody targeting surfactant protein A, which is abundantly expressed by type II alveolar epithelial cells, in rats with ARDS, and found that liposomal steroid have better therapeutic effect and fewer side effects, compared to rats receiving free dexamethasone sodium phosphate.\[12]\] Although active targeting is successful at targeting specific cells, nonspecific binding is usually a drawback.\[67]\] Since the accumulation of nanoparticles solely depends on the biomarker, there is a possibility that it may accumulate in other tissues that express the same biomarker.\[68]\] However, this would be more likely if the NBT injected intravenously, but via inhalation, this problem could be eliminated.

In pulmonary diseases, passive targeting gets particular attention when combined with inhalation route. Under certain conditions such as inflammation and tumor development, the endothelial lining of the blood vessel wall becomes more permeable than in healthy tissues.\[69]\] Therefore, molecules ranging from 10 to 500 nm in size are able to accumulate deep in those tissues.\[69]\] This impulsive accumulation is called EPR. Passive targeting is a strategy that benefits from the EPR effect of either tumor or inflamed tissues.\[21,70]\] Inflamed areas have increased blood flow and capillary permeability causing edema and the fluid flux into the target site, which promotes plasma protein localization.\[26]\] When liposome concentration is high in the capillaries, they also flux into the inflamed area naturally, similar to plasma proteins.\[26]\] Liposomal systems particularly have distinct advantages over nano-based carriers in pulmonary delivery. The most important feature of liposomes is to be internalized subsequently in the lungs, which makes passive targeting more attractive. Lungs secrete a mixture of surfactants that contain high levels of dipalmitoylphosphatidylcholine (DPPC), which is one of the main phospholipids used in liposomal membrane; therefore, the mechanism of surfactant uptake eases the internalization of liposomes.\[25,58]\] A study by Saari et al. shows that Bec-L constructed by DPPC deposited easily in the lung, showing slower clearance and providing sustained release.\[71]\]

Although pulmonary delivery is a successful method for treatment, there are several obstacles such as enzymatic activities in the respiratory track, airway geometry, mucociliary escalator, and mucus hypersecretion.\[72,73]\] One of the most studied passive targeting techniques is magnetic targeting. To overcome these problems, magnetic targeting is widely used technique in cancer research due to its practicality. Drugs
containing magnetic nanoparticles (e.g., magnetoliposomes) can be physically dragged by a permanent magnet and concentrated into tumors through leaky blood vessels.\cite{70,74,75} Yet, McGill et al. suggested that magnetic nanoparticles are also important in lung diseases indicating mucus hypersecretion as they might act as a nano-knife and could disrupt high viscosity long-chain polymers via thermal degradation or break mechanically through oscillation.\cite{72} Superparamagnetic iron oxide nanoparticles (SPIONs) are commonly used in NBT due to their magnetic properties, capability to be used as contrast agents in magnetic resonance imaging (MRI) and as hyperthermia agents due to their ability of producing heat when alternating current magnetic field (ACMF) is applied.\cite{73} Their superparamagnetism provides a greater magnetic response than bulk magnetism and presents rapid response to a magnetic stimulus.\cite{76} The only downside of SPIONs is their tendency to agglomerate; however, appropriate coating with surfactants can stabilize them and prevent sedimentation, and also, according to the coating material, it allows them to gain different entities toward water.\cite{37} SPIONs can also be encapsulated into liposomes, and when encapsulated, they do not only preserve their magnetic properties but also gain improved pharmacokinetic profiles.\cite{72} SPIONs are biodegradable and nontoxic nanomaterials and have been studied extensively in tumor targeting and diagnosis.\cite{63,73} They have also recently been used in the diagnosis of different lung diseases. For instance, Nahar et al. investigated sustained and targeted release of Fasudil, which is a vasodilator, in pulmonary arterial hypertension in rats.\cite{37} They observed that liposomes that contain magnetic nanoparticle suspensions provided increased cellular uptake and a slower pharmacokinetic profile and most importantly targeted and prolonged vasodilation.\cite{173}

**DRUG RELEASE AND IMAGING**

Liposomes are capable of providing controlled and sustained drug release that could reduce frequency of dosing, keep therapeutic drug levels constant over a period of time, and only release the drug when it reaches the target area.\cite{52} This is one of the essential reasons to prefer a liposome-based system over free drugs. Drug release can be triggered by various factors, internally or externally.\cite{77} Liposomal carriers can be designed using lipids with different properties to gain sensitivity to temperature, pH, or certain enzymes, which are essential qualities in drug release mechanisms.\cite{77} For example, pathological tissues that contain inflammation are known to be slightly more acidic than healthy tissues; hence, when targeting the inflammation, pH sensitive liposomes could be advantageous.\cite{169} However, external control such as hyperthermia could be more favorable to internal control since this can be applied to specific area to induce drug release.\cite{68,73} Liposomes can gain thermosensitivity by altering the composition of the lipid bilayer to undergo a temperature-dependent gel to liquid phase transition in temperature range of 42°C–44°C.\cite{78,79} This can be arranged by changing the molar ratio of the lipids that have different gel to liquid transition temperatures. Nevertheless, thermosensitive liposomes may not be able to achieve clinical effectiveness if drug concentration does not reach the required level.\cite{68} If the designed NBT use thermosensitive liposomes that contain SPIONs, enhanced drug accumulation and heat-triggered release could be achieved. As it is mentioned earlier, SPIONs are capable of accumulating in the desired area and generating heat when an ACMF is applied, and this accumulation can also be monitored concurrently through MRI.\cite{80}

MRI has high spatial resolution and therefore is considered one of the best noninvasive imaging techniques for medical diagnosis.\cite{81} In MRI, image contrast is produced by variances in proton density and MR relaxation times of the tissues.\cite{81} SPIONs, after tissue penetration, reduce the spin-spin relaxation time by giving hypointense signals in T2/T2*-weighted images, producing dark regions, and therefore enhancing the contrast.\cite{82} To date, the use of SPIONs is focused on cancer diagnosis, and marketed SPIONs are to enhance the MRI contrast of liver tumors (Feridex®, Resovist®), metastatic lymph nodes (Compatix™), and gastrointestinal lining (GastroMARK®). However, monitoring the lung with MRI is challenging as lungs contain significant airspace that makes them weak at proton density with short T2/T2* relaxation times.\cite{81,83} That might be the main reason that MRI was not considered as an option of diagnosis technique of CILD. Nonetheless, researchers managed to monitor pulmonary ventilation imaging with high spatial resolution using hyperpolarized 3He.\cite{83} Hyperpolarized noble gas MRI uses 3He or 129Xe for inhalation into the lungs, and when these gases polarize and give increased MR signal, it makes pulmonary ventilation monitoring feasible.\cite{84,83} Al Faraj et al. observed the biodistribution of ultrafine SPIONs with combination of 3He and proton MRI, and they showed that this technique has the potential to introduce MRI as a reliable diagnosis technique for lung diseases.\cite{81} However, this system is very costly, and it requires sophisticated equipment; therefore, its application is limited.\cite{73} It is proposed that the ultra-short time of the echo could provide a good contrast for the detection of inflammation, and it is sufficient to visualize the lung parenchyma.\cite{73} Further, SPIONs detection in the lung parenchyma has been achieved in inflamed lungs by arranging the system to different relaxation properties of SPIONs.\cite{73} Recently, SPIONs have also become favored for imaging inflammation. SPIONs uptake by macrophages can be monitored on MRI, and it has an essential role in the diagnosis of chronic inflammatory diseases and chronic infections.\cite{86}

Computed tomography (CT) and chest X-ray imaging are two imaging methods that are used in CILD. According to the Global Strategy for the diagnosis, management, and prevention of COPD 2017 report, thoracic imaging is considered as additional investigations, and main diagnosis is based on spirometry.\cite{87} Diagnosis of asthma based on spirometry and imaging with X-ray or CT is only recommended to exclude other diagnoses.\cite{88} CT and X-ray imaging are based on the absorption of X-rays by high electron density atoms.\cite{83}
While X-ray imaging creates two-dimensional images, CT is capable of creating three-dimensional images, and yet CT uses higher radiation doses as compared to conventional X-ray. A contrast achieved in both system through atoms that have high atomic numbers such as iodine and barium. While barium sulfate is used in imaging of the gastrointestinal track, it is contraindicated for lung imaging as it potentially causes granulomas and asphyxiation. Therefore, iodine is commonly used as a lung imaging contrast agent; however, sometimes, it is challenging to achieve desired concentration in the lung and to disseminate it to periphery of the lungs.

Spirometry is commonly used as a diagnostic method in chronic airway diseases, yet this may not provide adequate information about the disease progression and the disease state to clinicians, which may lead to clinical problems and insufficient treatment. Diagnosis and monitoring inflammation is critical because inflammation-induced tissue changes occur before necrosis and loss of function; therefore, early diagnosis would enable clinical intervention. Despite the challenges of the imaging methods mentioned above, it is important to find an effective method to monitor CILD patients regularly as these patients may be more prone to develop other diseases such as cancer. It has been found that there is a strong association between emphysema and lung cancer.

Quantitative CT can measure pathological changes in COPD including emphysema and low-dose CT is now recommended to the patient with COPD in the USA for regular control, yet this is not a common practice worldwide. CT is also considered as an invasive method, which may not be applied to routine practice, as the amount of radiation may have an adverse effect on patients’ health.

**Conclusion and Future Indications**

In CILD, the challenge is delivering and accumulating the drug into pathological sites effectively as there are physical barriers that interrupt the competence of the medication used. However, it might be possible to enhance the efficiency of the current treatment by improving the drug delivery systems. This could also reduce the administrative dosage or frequency that may help eliminate side effects and decrease drug resistance. In the last two decades, NBTs are considered to be very successful in reducing therapeutics’ side effects and cytotoxicity. They can also provide sustained and controlled drug release and allow for the simultaneous monitoring the disease state. Therefore, NBT could be suitable candidates for the new form of therapeutics for CILD treatment.

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**References**

1. Durham AL, Caramori G, Chung KF, Adcock IM. Targeted anti-inflammatory therapeutics in asthma and chronic obstructive lung disease. Transl Res 2016;167:192-203.
2. Keskin O, Uluca U, Keskin M, Gogebakan B, Kucukosmanoglu E, Ozkars MY, et al. The efficacy of single-high dose inhaled corticosteroid versus oral prednisone treatment on exhaled leukotriene and 8-isoprostane levels in mild to moderate asthmatic children with asthma exacerbation. Allergol Immunopatol (Madr) 2016;44:138-48.
3. Parasaram V, Nosoudi N, LeClair RJ, Binks A, Vyavahare N. Targeted drug delivery to emphysematous lungs: Inhibition of MMPs by doxycycline loaded nanoparticles. Pulm Pharmacol Ther 2016;39:64-73.
4. Barnes PJ. Cellular and molecular mechanisms of chronic obstructive pulmonary disease. Clin Chest Med 2014;35:71-86.
5. Ratemi E, Sultana Shaik A, Al Faraj A, Halwani R. Alternative approaches for the treatment of airway diseases: Focus on nanoparticle medicine. Clin Exp Allergy 2016;46:1033-42.
6. Mannino DM, Kiriz VA. Changing the burden of COPD mortality. Int J Chron Obstruct Pulmon Dis 2006;1:219-33.
7. Vij N, Gorde A. Theranostic applications of nanotechnology in chronic obstructive lung diseases. Int: Vij N, editor. Pulmonary Medicine: Diagnostics, Imaging, and Therapeutics. Florida, U.S: CRC Press; 2012.
8. Pawankar R. Allergic diseases and asthma: A global public health concern and a call to action. World Allergy Organ J 2014;7:12.
9. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: Molecular and cellular mechanisms. Eur Respir J 2003;22:672-88.
10. Barnes PJ. Therapeutic approaches to asthma-chronic obstructive pulmonary disease overlap syndromes. J Allergy Clin Immunol 2015;136:531-45.
11. Chen X, Huang W, Wong BC, Yin L, Wong YF, Xu M, et al. Liposomes prolong the therapeutic effect of anti-asthmatic medication via pulmonary delivery. Int J Nanomedicine 2012;7:1139-48.
12. Chen XY, Wang SM, Li N, Hu Y, Zhang Y, Xu JF, et al. Creation of lung-targeted dexamethasone immunoliposome and its therapeutic effect on bleomycin-induced lung injury in rats. PLoS One 2013;8:e58275.
13. Ito K, Barnes PJ, Adcock IM. Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits interleukin-1beta-induced histone H4 acetylation on lysines 8 and 12. Mol Cell Biol 2000;20:6891-903.
14. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
15. Chung KF. Clinical management of severe therapy-resistant asthma. Expert Rev Respir Med 2017;11:395-402.
16. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol 2015;9:30.
17. Ito K, Ito M, Elliott WM, Cosio B, Caramori G, Kon OM, et al. Decreased histone deacetylase activity in chronic obstructive pulmonary disease. N Engl J Med 2005;352:1967-76.
18. Sahoo B, Devi KS, Banerjee R, Maiti TK, Pramanik P, Dhara D. Thermal and pH responsive polymer-tethered multifunctional magnetic nanoparticles for targeted delivery of anticancer drug. ACS Appl Mater Interfaces 2013;5:3884-93.
19. Barenholz Y. Doxil® – The first FDA-approved nano-drug: Lessons learned. J Control Release 2012;160:117-34.
20. Zamuni Vahed S, Salehi R, Davaran S, Sharifi S. Liposome-based drug co-delivery systems in cancer cells. Mater Sci Eng C Mater Biol Appl 2017;71:1327-41.
21. Shahidian A, Asfahar H, Habibi MR, Ghasemi M. Therapeutic nanostructures: Application of mechanical engineering in drug delivery. In: Holban AM, Grumezescu AH, editors. Nanobiotechnology for Smart Delivery and Drug Targeting. Oxford, U.K: William Andrew; 2016. p. 3-34.

22. Joo Ki, Xiao L, Liu S, Liu Y, Lee CL, Conti PS, et al. Crosslinked multilamellar liposomes for controlled delivery of anticancer drugs. Biomaterials 2013;34:3098-109.

23. Liu Y, Fang J, Kim YJ, Kong MK, Wang P. Codelivery of doxorubicin and paclitaxel by cross-linked multilamellar liposome enables synergistic antitumor activity. Mol Pharm 2014;11:1651-61.

24. Pinheiro M, Lúcio M, Lima JL, Reis S. Liposomes as drug delivery systems for the treatment of TB. Nanomedicine (Lond) 2011;6:1413-28.

25. Mosgoeller W, Prassl R, Zimmer A. Nanoparticle-mediated treatment of pulmonary arterial hypertension. In: Abelson JN, Simon MI, editors. Methods in Enzymology. Oxford, U.K: Elsevier; 2012. p. 325-54.

26. Schifferles RM, Bakker-Woudenberg IA, Storm G. Localization of sterically stabilized liposomes in experimental rat Klebsiella pneumoniae pneumonia: Dependence on circulation kinetics and presence of poly (ethylene) glycol coating. Biochim Biophys Acta 2000;1466:553-61.

27. Konduri KS, Nandedkar S, Rickaby DA, Düzgünes N, Gangadharam PR. Aerosol therapy and multifunctional platforms. Appl Biochem Biotechnol 2009;71:88-95.

28. Hua S. Targeting sites of inflammation: Intracellular adhesion molecule-1 as a target for novel inflammatory therapies. Front Pharmacol 2013;4:127.

29. Kelly C, Jefferies C, Cryan SA. Targeted liposomal drug delivery to monocytes and macrophages. J Drug Deliv 2011;2011:72724.

30. Wheeler CJ, Felgner PL, Tsai YJ, Marshall J, Sukhu L, Doh SG, et al. A novel cationic lipid greatly enhances plasmid DNA delivery and expression in mouse lung. Proc Natl Acad Sci U S A 1996;93:11454-9.

31. Robertson JD, Ward JR, Avila-Olías M, Battaglia G, Renshaw SA. Targeting neutrophilic inflammation using polymersome-mediated cellular delivery. J Immunol 2017;198:5396-604.

32. Fernandez-Fernandez A, Manchanda R, McGroron AJ. Theranostic applications of nanomaterials in cancer: Drug delivery, image-guided therapy, and multifunctional platforms. Appl Biochem Biotechnol 2011;165:1628-51.

33. Fan Z, Fu PP, Yu H, Ray PC. Theranostic nanomedicine for cancer detection and treatment. J Food Drug Anal 2014;22:3-17.

34. Li R, Liu B, Gao J. The application of nanoparticles in diagnosis and theranostics of gastric cancer. Cancer Lett 2017;386:123-30.

35. Nahar K, Absar S, Patel B, Ahsan F. Starch-coated magnetic liposomes as an inhalable carrier for accumulation of fusidin in the pulmonary vasculature. Int J Pharm 2014;464:185-95.

36. Liu C, Shi J, Dai Q, Yin X, Zhang X, Zheng A. In-vitro and in-vivo evaluation of ciprofloxacin liposomes for pulmonary administration. Drug Dev Ind Pharm 2015;41:272-87.

37. Ellbogen MH, Olsen KM, Gentry-Nielsen MJ, Preheim LC. Efficacy of liposome-encapsulated ciprofloxacin compared with ciprofloxacin and ceftriaxone in a rat model of pneumococcal pneumonia. J Antimicrob Chemother 2003;51:839-91.

38. Chono S, Tanino T, Seki T, Morimoto K. Influence of particle size on drug delivery to rat alveolar macrophages following pulmonary administration of ciprofloxacin incorporated into liposomes. J Drug Target 2006;14:557-66.

39. Patel AR, Chougule MB, IT, Patilolla R, Wang G, Singh M. Efficacy of aerosolized celexobin encapsulated nanostructured lipid carrier in non-small cell lung cancer in combination with docetaxel. Pharm Res 2013;30:1435-46.

40. Lin C, Wong BCK, Chen H, Bian Z, Zhang G, Zhang X, et al. Pulmonary delivery of triptolide-loaded liposomes decorated with anti-carboxic anhydrase IX antibody for lung cancer therapy. Sci Rep 2017;7:1097.
surface-mannose modification on aerosolized liposomal delivery to alveolar macrophages. Drug Dev Ind Pharm 2010;36:102-7.

67. Al-Jamal KT. Active drug targeting: Lessons learned and new things to consider. Int J Pharm 2013;454:525-6.

68. Lin W, Xie X, Yang Y, Fu X, Liu H, Yang Y, et al. Thermosensitive magnetic liposomes with doxorubicin cell-penetrating peptides conjugate for enhanced and targeted cancer therapy. Drug Deliv 2016;23:3436-43.

69. Shaji J, Lal M. Nanocarriers for targeting in inflammation. Asian J Pharm Clin Res 2013;6 Suppl 3:3-12.

70. Bai J, Wang JT, Rubio N, Protti A, Heidari H, Elgogary R, et al. Magnetic-responsive nanoparticles for drug delivery. Nano Today 2007;2:22-32.

71. Saari M, Vidgren MT, Koskinen MO, Turjanmaa VM, Nieminen MM. Pulmonary distribution and clearance of two beclomethasone liposome formulations in healthy volunteers. Int J Pharm 1999;181:1-9.

72. McGill SL, Cuylear CL, Adolphi NL, Osinski M, Smyth HD. Magnetically responsive nanoparticles for drug delivery applications using low magnetic field strengths. IEEE Trans Nanobioscience 2009;8:33-42.

73. Al Faraj A, Shaik AS, Afzal S, Al-Muhsen S, Halwani R. Specific targeting and noninvasive magnetic resonance imaging of an asthma biomarker in the lung using polyethylene glycol functionalized magnetic nanocarriers. Contrast Media Mol Imaging 2016;11:172-83.

74. Gu FX, Karnik R, Wang AZ, Alexis F, Levy-Nissenbaum E, Hong S, et al. Targeted nanoparticles for cancer therapy. Nano Today 2007;2:14-21.

75. Arruebo M, Fernández-Pacheco R, Ibarra MR, Santamaria J. Magnetic nanoparticles for drug delivery. Nano Today 2007;2:22-32.

76. Chen SY, Hu SH, Liu TY. Magnetic-responsive nanoparticles for drug delivery. In: Schneider HJ, Shahinpoor M, editors. Smart Materials for biomedical and biotechnology research. Singapore: Springer Science+Business Media Singapore; 2012. p. 479-98.

77. Kono K. Thermosensitive polymer-modified liposomes. Adv Drug Deliv Rev 2001;53:307-19.

78. Gogoi M, Jaiswal MK, Banerjee R, Bahadur D. Magnetic liposomes and hydrogels towards cancer therapy. In: Thanh NT, editor. Magnetic Nanoparticles: From Fabrication to Clinical Application. Florida, U.S: CRC Press; 2012. p. 479-98.

79. Kong G, Anyarambhata G, Petros WP, Braun RD, Colvin OM, Needham D, et al. Efficacy of liposomes and hyperthermia in a human tumor xenograft model: Importance of triggered drug release. Cancer Res 2000;60:6950-7.

80. Xie J, Gu N, Zhang Y. Controlled synthesis and surface modification of magnetic nanoparticles with high performance for cancer theranostics combining targeted MR imaging and hyperthermia. In: Dai Z, editor. Advances in Nanotheranostics II: Springer Series in Biomaterial Science and Engineering 7. Singapore: Springer Science+Business Media Singapore; 2016. p. 39-73.

81. Al Faraj A, Lacroix G, Alsaaid H, Elgrabi D, Stupar V, Robidel F, et al. Longitudinal 3He and proton imaging of magnetite biodistribution in a rat model of instilled nanoparticles. Magn Reson Med 2008;59:1298-303.

82. Ungureanu BS, Teodorescu CM, Safioiu A. Magnetic nanoparticles for hepatocellular carcinoma diagnosis and therapy. J Gastrointestin Liver Dis 2016;25:375-83.

83. Rollér J, Laschke MW, Tschernig T, Schramm R, Veith NT, Thorlacius H, et al. How to detect a dwarf: In vivo imaging of nanoparticles in the lung. Nanomedicine 2011;7:753-62.

84. Fain S, Schiebler ML, McCormack DG, Parraga G. Imaging of lung function using hyperpolarized helium-3 magnetic resonance imaging: Review of current and emerging translational methods and applications. J Magn Reson Imaging 2010;32:1398-408.

85. Liu Z, Araki T, Okajima Y, Albert M, Hatabu H. Pulmonary hyperpolarized noble gas MRI: Recent advances and perspectives in clinical application. Eur J Radiol 2014;83:1282-91.

86. Neuwelt A, Sidhu N, Hu CA, Mladý G, Eberhardt SC, Sillerud LO. Iron-based superparamagnetic nanoparticle contrast agents for MRI of infection and inflammation. AJR Am J Roentgenol 2007;120 5 Suppl: S94-138.

87. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med 2017;195:557-82.

88. National Asthma Education and Prevention Program. Expert panel report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol 2007;120 5 Suppl: S94-138.

89. Aillon KL, El-Gendy N, Dennis C, Norenberg JP, McDonald J, Berkland C. Iodinated NanoClusters as an inhaled computed tomography contrast agent for lung visualization. Mol Pharm 2010;7:1274-82.

90. Mets OM, de Jong PA, van Ginneken B, Gietema HA, Lammers JW. Quantitative computed tomography in COPD: Possibilities and limitations. Lung 2012;190:133-45.

91. de Torres JP, Bastarrrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest 2007;132:1932-8.