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CHAPTER

# Chronic respiratory diseases: An introduction and need for novel drug delivery approaches

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## 1 Introduction

The burden of chronic respiratory diseases (CRDs) that affect both adults and children is constantly increasing globally. The mortality and morbidity cause of respiratory diseases is unclear; however, recent statistics published by WHO and other agencies found an estimate of around 400 million people around the globe are suffering with mild to moderate conditions of Asthma and COPD alone. In addition, lower respiratory tract infection caused by *Haemophilus influenzae* has a death toll ranging between 250,000 and 500,000 deaths yearly. In 2015 alone lower respiratory tract infection caused by *Mycobacterium tuberculosis* infected 10.4 million worldwide and killed 14% of the patients. Other noninfectious conditions like lung cancer caused by tobacco smoking or inhalation of environmental carcinogens were found to kill 1.6 million people yearly with an alarmed increased trend. In addition to death toll, respiratory disorders directly account for 10% of total disability-adjusted life years (DALYs) in human workforce [1].

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Based on disease pathology and mode of transmission, the respiratory diseases could be broadly categorized into communicable, that is, infectious diseases (e.g., tuberculosis and pneumonia), and noncommunicable (NCD), that is, diseases that do not have an infectious etiology (e.g., asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, interstitial pulmonary fibrosis, and lung cancer) [2]. These respiratory diseases have a set of varied causes and are diagnosed very differently. However, especially the noncommunicable CRDs are treated similarly; that is, the treatment of these diseases generally includes a bronchodilator, corticosteroids, and antibiotics. Moreover the focus on understanding the pathology of COPD has only been initiated in the last two decades, and the regions with substantial disease burden lack a credible disease diagnosis and prevention/management strategy [3]. This is particularly a cause of concern in low- and middle-income countries such as India, China, and countries in multiple regions, including those in Asia Pacific, Latin America, and Africa [4].

Despite constantly increasing burden of CRDs, the treatment options are limited [3]. This is primarily due to lack of understanding the underlying mechanisms that may lead to discovering promising targetable targets, either molecular or immunological. Moreover the mode of delivery of existing drugs is also variable, thus warranting further research into enhancing the deposition and efficacy of currently prescribed drugs [5].

We will be summarizing the basic introduction of respiratory diseases, including the burden, pathology, and pathophysiology of CRDs. We will also discuss the currently available treatment options for major respiratory diseases.

## 2 Lungs: Morphology and physiology

The respiratory system in humans is subdivided into two major parts: the upper respiratory tract (URT) and the lower respiratory tract (LRT) [6]. The URT is composed of nose/nostrils, mouth, and the initial portion of trachea. The LRT includes the trachea that progressively bifurcates into the bronchi, bronchioles, and finally to the functional units known as alveoli [6]. The airways are supported by the lung parenchyma, and the gas exchange takes place with pulmonary vasculature. The most important function of the respiratory system is the exchange of gases, that is, absorption of oxygen ($O_2$) and release of carbon dioxide ($CO_2$) [6]. This gas exchange into the pulmonary capillaries takes place through the single membranes of the pulmonary alveolus. The process of breathing includes inhalation, that is, the intake of air into the lungs primarily via expansion of chest volume, and the inhaled air then moves through the progressively smaller "conductive" airways; and exhalation, that is, the expulsion of air from the lungs, which is the result of contraction of chest volume [6, 7]. The process of inhalation/exhalation is facilitated by predominantly two types of muscles, that is, diaphragm and intercostal muscles. The internal surface area of lungs is approximately 50–75 $m^2$ [7]. The average weight of a normal human lungs is approximately 1 kg, with around half (40%–50%) of which is attributed to blood

in the pulmonary vasculature [6]. Measuring the volume and action of inhalation/exhalation of air is key to establish the presence of restrictive and/or obstructive lung diseases, such as asthma and COPD [6].

Pulmonary mechanics includes efficient gas exchange that requires multiple components, with various measurements that are routinely utilized for monitoring the normal functioning of the lungs [6]. The measurement of lung functionality is achieved by spirometry, which is a safe, practical, and reproducible maximum breathing test that is used in almost all the clinical laboratories to determine the ventilatory capacity of the lungs [8]. Modern spirometers have the added advantages of yielding immediate computer-generated feedback to the operator on the quality and repeatability of the test, as well as real-time graphical display of the flow-volume curve. The standard lung volumes that are measured include tidal volume (TV), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), and residual volume (RV). Other standard lung capacities that are routinely measured are inspiratory capacity (IC), functional residual capacity (FRC), vital capacity (VC), and total lung capacity (TLC) [9]. A summary of these lung volumes and capacities are represented in Fig. 1 (Adapted from Ref. [9]).

A normal human lung comprised several cell types that have highly specialized functions. The major cell types include airway epithelial cells, goblet cells, ciliated cells, Clara cells, neuroendocrine cells, basal cells, and type I and type II alveolar cells. In addition, there are immune cells, stem cells, and adipose cells in the lungs [10]. One or more cell types are also linked to various respiratory diseases. For instance, glandular cells in the lungs are associated with induction of lung adenocarcinomas in the presence of risk factors [11]. The functionality of specific cell types is also linked to disease. For instance, the secretion of surfactant proteins and lipids has been linked to pathology of respiratory diseases, such as neonatal respiratory failure, interstitial lung disease (ILD), alveolar proteinosis, and other rare lung diseases [12]. Moreover, in addition to the airway epithelia being the first line of defense and acting as a physical barrier that separates host-environment axis, it also serves as an important modulator in pulmonary inflammation and immune cell activation, as well as a crucial component of pulmonary remodeling and repair [13]. In addition, changes in the pulmonary vasculature include intimal hyperplasia and smooth muscle hypertrophy/hyperplasia, likely attributed to chronic hypoxic vasoconstriction of the small pulmonary arteries [14]. Moreover, basal cells in the airway epithelium are increasingly regarded as extremely important in airway remodeling [15].

A major cause of concern remains the lack of effective treatment and/or management strategies for the CRDs, especially noncommunicable diseases (e.g., asthma, COPD, CF, and IPF) [16]. This is attributed to several factors, including lack of comprehensive understanding vis-a-vis the underlying mechanisms that could be implicated in the initiation and progression of CRDs [16]. Consequently the currently available treatments reflect the same, as these only target the major symptoms of the disease without offering any long-term relief, both in terms of prevention and cure. Moreover the drugs that are available lack in terms of targeting the biological entities

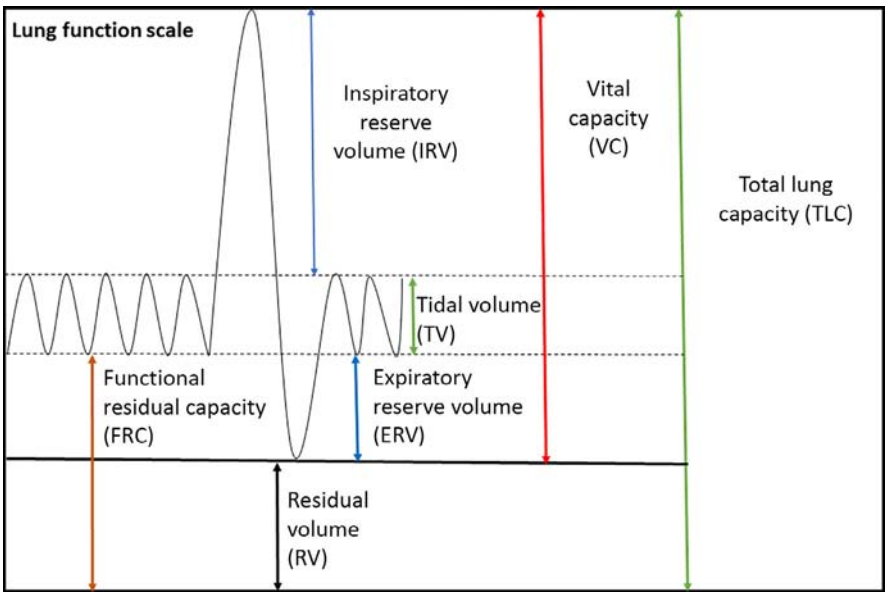


**FIG. 1**

Standard lung volumes and capacities from a spirometer trace. The *solid black and gray arrows* indicate lung volumes and capacities, respectively.

*Reproduced with permission from Lutfi MF. The physiological basis and clinical significance of lung volume measurements. Multidiscip Respir Med 2017;12(1):3. doi:10.1186/s40248-017-0084-5.*

fully, thus requiring more effective drug delivery approaches to alleviate symptoms of CRDs [17, 18]. We will discuss these key issues in the present chapter.

## 3 Overview of respiratory disease

Growing population complemented with a changed lifestyle of the 21st century has opened a window for a wide range of diseases that are currently threating human life across the borders. Among these, respiratory disorders were found to be most prominent affecting the large-scale populations of both middle- and lower-income countries worldwide. Despite their high prevalence, respiratory diseases are often ignored or receive very little attention than required. Human lungs are the only internal organ that is regularly exposed to a wide range of environmental pollutants, composed of organic/inorganic/biological agents from various natural and anthropogenic sources, and are at a constant threat of developing simple to complex pulmonary disorders, which may compromise the quality of life and ultimately leads to demise. Some of the respiratory diseases that are currently threatening millions of life across the globe are briefly discussed in the succeeding text.

## 3.1 Asthma

Asthma is a heterogeneous and complex lung disease that is characterized by variable airflow obstruction, hyperresponsiveness of the airways (bronchial), and, importantly, increased airway inflammation [19]. Asthma affects roughly 10% of adult population in almost all countries, amounting to approximately 300 million individuals globally [20]. Moreover, asthma is estimated to be a direct cause of 383,000 deaths worldwide, with over 80% asthma-related deaths reported from low- and middle-income countries [21]. Asthma also accounts for substantial economic burden, totaling up to $USD 3100 per person per year [22].

Asthma is a common yet poorly understood lung disease that can manifest at any age. The risk factors for asthma include indoor pollutants (house dust mite and pollution), exposure to outdoor allergens (pollen, molds, and pollution), tobacco smoke, occupational exposure to chemical fumes, and air pollution [21]. Asthma is a complex disease and could manifest as disease "episodic," that is, periods when symptoms appear and resolve upon treatment. Also the disease could also be "persistent" in individuals, which is characterized by the presence of characteristic clinical symptoms of asthma. The major symptoms of asthma include wheezing, dyspnea (breathlessness), shortness of breath, and cough [23]. Symptoms may become more pronounced due to various factors, such as exposure to known/unknown allergens, irritants, respiratory tract infections with virus or bacteria, bacterial sinusitis, physical exercise, thunderstorm, and cold weather [23].

Recent understanding in asthma pathophysiology has led to categorization of asthma into various phenotypes and/or endotypes [24]. This is essential for effective treatment of patients with asthma, which has been recommended by the recent Lancet commission that outlines identification of "treatable traits" in patients with asthma and then specifically targets these traits for the management of disease [24]. Further, based on the triggers, asthma can be grouped into allergic asthma—caused by allergens like pollen, house dust mite, mold, and biological/organic environmental containments. In contrast, nonallergic asthma is associated with risk factors like tobacco smoke, viral/bacterial infections, cold air, exercise, and diet. Studies reveal that in majority of cases, asthma is driven by Th2 responses, where the type 2 T-helper cells are recruited into airways in response to external/internal trigger and produce the cytokines like IL-4, IL-5, IL-9, and IL-13 at elevated concentrations. Among which, IL-4 plays a vital role in IgE switch in B cells, which results in increased production of immunoglobulin E, which in turn induces the production of inflammatory mediators like histamine and cysteinyl leukotrienes, whereas IL-5 is exclusively involved with recruitment of eosinophils, leading to development of allergic rhinitis in upper airways. IL-13 and IL-4 alongside with inflammatory mediators cause the contraction of smooth muscles, which leads bronchospasm, excess mucus production, and increased influx of immune cells, resulting in reduced airway diameter along with airway hyperresponsiveness in lower airways, which ultimately reduces the airflow ($FEV_1$) [25]. The airway epithelium was found to play a substantial role in controlling the Th2 responses by producing master regulators like thymic

stromal lymphopoietin (TSLP), IL-25, or IL33 that regulate the expression of Th2 cytokines and cause an early onset of asthma during childhood [26].

The initial stage of asthma is characterized by wheezing, airway hyperresponsiveness to nonspecific stimuli, however, during later stages (severe forms) due to increased inflammation aided with other local (viral/bacterial infections) or systemic factors, results in airway remodeling with subsequent exacerbations. The early observations from animal models have misled asthma to be an allergic, eosinophilic, Th2-driven inflammatory disease. However, clinical trials in humans showed that some forms asthma are involved with less or no Th2 responses [26], which confirmed the presence of different phenotypes of the long-studied respiratory disease. Studies in patients suffering with severe asthma showed elevated levels of neutrophilic populations with steady or no change in eosinophilic populations. Moreover the neutrophilia (excess of neutrophilic population) was found to be commonly observed in severe asthmatics who are being treated or were treated in the past with inhaled corticosteroids (ICS), which may raise the question that ICS might be responsible for this peculiar phenotype. The asthmatics with neutrophilia were found to have less/no effect with ICS treatment. At present, clinicians are relying on negative skin test for objectifying the nonallergic asthmatics from allergic asthmatics, where the skin cells are challenged to aeroallergens to detect their ability to produce IgE [27]. In addition, genome-wide association studies of asthma in both adults and children identified some key polymorphisms in IL33, ILRL1, IL18R1, IL2RB, and SMAD3 on chromosome 17q21, alongside with ZPBP2, GSDMB, and ORMDL3 gene expressions. These set of genes are responsible to maintain the epithelial barrier integrity and function [28]. However, the exact genetic markers underlying the development of asthma in early stages or adult are not well understood. Recent studies have linked intrinsic factors like obesity in increasing the onset of asthma, where the white adipose tissues were found to secrete IL-1, IL-6, and TNF with additional oxidative stress through inflammatory macrophages. Further, transition of epithelial to mesenchymal, thickness of basement membrane, and collagen deposition lead to airway remodeling and increased stress on airways, which worsens the existing asthmatic exacerbations [26, 29]. These findings highlight the extreme heterogeneity of asthma and an immediate need of new therapies and strategies to counter the problem.

### 3.1.1 Treatments

Clinicians account more than a single factor in treating the people suffering with asthma. The lung function analysis paired with sputum analysis including preexisting respiratory conditions and ongoing treatments is accounted before the treatment. Initially, glucocorticoids were the medication of choice for the treatment of majority of asthmatics (suppress the Th2 responses); however, the steroid treatment had its fair share of cons. Prolonged steroid treatment was found to have several local to systemic side effects, which includes dysphonia, candidiasis, osteoporosis, and adrenal suppression [26]. However, the patients suffering with neutrophilic asthma or low Th2 response phenotypes were found to resistant. Studies showed that allergic asthma (pollen) responds well to $\beta_2$-agonist in inhaled corticosteroid (ICS);

however, nonallergic patients (virus/bacterial) are often treated using systemic corticosteroid (SCS). Additionally, short-acting beta-agonists (SABAs) like albuterol and levalbuterol are used at high concentrations in accordance to EPR-3 regulations; oxygen are used as a primary treatment in acute asthmatics; however, at later stages (chronic), these medication are replaced with epinephrine, magnesium sulfate, noninvasive positive pressure ventilation (NPPV), and hospitalization [20].

In recent years, long-term treatment with azithromycin became a popular choice to treat the patients suffering with severe asthma; however, it remains controversial. Gibson and his team showed that azithromycin as an add-on therapy (combination with ICS) was successful to reduce the yearly exacerbations by 50% in severe asthmatics [30]. However, epidemiological data published by Tian et al. show no significant efficacy of azithromycin in controlling the severe asthmatic exacerbations; to conclude and confirm the potential of azithromycin as an effective drug against asthma, we are in need of additional human cohorts [31]. In contrast a recent study highlighted that the long-term usage of azithromycin (antibiotic and macrolide) has reduced the *H. influenzae* in severe asthmatics; however, they observed increased antibiotic resistance against azithromycin in the long run [32], which highlights a major limitation to use the famous antibiotic in treatment/management of asthma.

Usage of monoclonal antibodies in treatment of diseases has attracted the attention of scientific communities around the world in recent decade. Biological inhibitors like anti-IL-5 (mepolizumab) and anti-IgE mAB (omalizumab), currently approved for human use, were found to be effective in controlling the exacerbations in severe asthmatics; omalizumab forms an irreversible complex with the immunoglobulin IgE and blocks the production of inflammatory mediators and immune cells (mast cells and basophils), thus effectively controlling the disease pathogenesis. Busse et al. showed that usage of omalizumab has significantly reduced the exacerbations in severe asthmatics compared with other groups (placebo and ICS) [33]. Further, efficacy and safety of using omalizumab or other mAB were confirmed and published [34, 35]. Though usage of biological inhibitors (mAB) is effective and reduces the economic burden on medication, the costs involved in production, transport, and storage of mAB still remain challenging.

## 3.2 Chronic obstructive pulmonary disease

COPD or chronic obstructive pulmonary disease is a coherent term used to represent a group of progressive, obstructive-irreversible pulmonary conditions like emphysema, chronic bronchitis, small airway deterioration, and chronic asthma [36, 37]. According to WHO [38] the global burden of disease study reported 251 million COPD cases across the globe, among which 90% were from low- and middle-income countries. An estimate of 3.17 million deaths, which account 5% of total deaths, occurred in the year 2015 alone, which was increase by 11.6% compared with 1990 [39, 40]. In addition to mortality the Centers for Disease Control and Prevention (CDC) estimated an economic burden of USD $32.1 billion by 2010 toward the medical costs and days of work lost due to COPD and expected to further raise to

USD $49.0 billion by 2020 in the United States [41, 42]. However, the exact number of COPD cases globally is still a debate, due to the fact that most of the asthma cases in elderly are often mistaken to be COPD and the absence of data sets from developing or underdeveloped nations of Asia and Middle East regions, which may raise the mortality count by few millions.

The patients suffering with any form of COPD exhibit wide range of symptoms, among which breathlessness or shortness of breath during day-to-day activities is a primary indicator, which worsens with time, while patients suffering from severe forms of COPD and asthma experience frequent exacerbations and subsequent ER visits around the year. This is due to partial destruction of alveoli (emphysema) [43] or accumulation of excess mucus and inflammatory cells in bronchioles (chronic bronchitis), especially in smokers and exsmokers suffering with COPD [44], which decreases the gas exchange capability of lungs and causes obstruction to the airflow, resulting in decreased blood oxygen levels (hypoxemia) and subsequent organ failure [45]. In addition, patients suffering with any form of COPD may exhibit common symptoms like persistence cough (with or without mucus), tiredness, wheezing, and tightness in chest; in most cases these symptoms are misunderstood to be age factors. Some patients may not exhibit symptoms until the disease exacerbates. Despite of extensive research over the decades, there is no cure that exists to regenerate the damaged tissue and revoke the lung function. Moreover, COPD is a progressive disease, which worsens with aging. The existing treatments are designed to slow down the progression of pathogenesis and provide temporary ease to patients but not capable of restoring the lost function of damaged regions. According to the existing data sets, the single most common cause of COPD was found to be tobacco smoking. Recent reports show that long-term exposure to noncigarette smoke irritants (e.g., airborne dust particles, geogenic dust, and metal contaminants) as a crucial risk factor implicated in development (nonsmokers) or exacerbation (smokers) of COPD, which still remains largely underinvestigated [46]. In addition, studies confirm the role of hereditary factors/genetic predisposition like deficiency of alpha-1-antitrypsin (AAT) deficiency, which leads to development of COPD; the exact underlying mechanisms are largely unexploited. However, the individuals with AAT deficiency are more prone to respiratory infections, and the genetic factors constitute 1% of total COPD cases, highlighting tobacco smoking and air pollutants as major culprits. It is interesting to note that not all the smokers or exsmokers develop the disease, only 20%–30% of the active- or exsmokers may develop the disease during their lifetime. The studies even identified passive smoking (51.2%, $n=87$) to be one of the risk factors for developing COPD; the exact underlying mechanisms still remain unclear [47].

The disease pathogenesis of COPD is mainly driven by obstruction of airflow and influx of inflammatory cells, especially CD8+ T lymphocytes, neutrophils, macrophages in alveolar and peripheral spaces in response to tobacco smoke, or environmental particles/gases. However, the response of immune system was found to be different for different subtypes of COPD. Chronic bronchitis, characterized by excess mucus production, increased inflammatory cells, overexpression of MUC5AC gene in response to secreted serine proteases, elevated levels of ROS from inhaled

smoke, or activated macrophages, restricts the air space and subsequent damage of adjacent cells, resulting in remodeling (fibrosis) of airways leading to loss of lung elasticity, whereas the emphysema (centrilobular and panlobular) is a direct result of cigarette smoke. The inhaled smoke elevates the inflammation in territory bronchioles and alveolar sacs, leading to gradual destruction of alveolar sacs and smaller airway walls, leading loss of alveolar structure, function, and recoil. The activation of innate and adaptive immune responses in COPD patients is not entirely clear. However, the overexpression of CXC, IL8, and MMP by immune cells or production of proinflammatory mediators like TNFα, IL1β (Th1 responses), leukotriene B4, and transforming growth factor beta (TGFβ) induce local fibrosis and imbalance of oxidant-antioxidant percentage (ROS/RNS) and were taught to be some of the crucial factors for exacerbation of disease [48, 49].

To diagnose and estimate the severity of disease progression, clinicians often relay on noninvasive spirometry and GOLD staging system developed by Global Initiative for Chronic Obstructive Lung Disease (GOLD) [50]. The GOLD staging system is a measure of pulmonary function, forced expiratory volume/forced vital capacity ratio (FEV1/FVC), that is, the amount of air exhaled by patient in 1 s after a single deep breath, and categorizes the individual in one of the four following stages:

- **Stage 1:** If the individual has a FEV1/FVC ratio of ≥ 80% of normal, categorized as mild COPD.
- **Stage 2:** If the individual has a FEV1/FVC ratio between 50% and 80% of normal, categorized as moderate COPD.
- **Stage 3:** If the individual has a FEV1/FVC ratio between 30% and 50% of normal, categorized as severe emphysema.
- **Stage 4:** If the individual has a FEV1/FVC ratio of ˂ 30% of normal or stage 3 with low blood oxygen levels, categorized as very severe form of emphysema or COPD.

The individuals diagnosed with GOLD stage 1 or stage 2 COPD gradually lose the FEV1 ratio and head toward stage 3 and 4, at which patients experience severe symptoms and lose the quality of life. At this moment apart from spirometry, imaging techniques like chest X-rays and high-resolution CT scans can be used to disease progression. In addition, blood gas analyzer can be used to monitor levels of oxygen, and carbon monoxide in blood samples can be helpful.

COPD is a preventable but irreversible disease. The existing treatments are designed to ease symptoms and slow down the progression of disease but not complete recovery, which can be only possible with a lung transplant, which is not a feasible approach. Using medications like bronchodilators, corticosteroids, glucocorticosteroids, phosphodiesterase-4 inhibitors, theophylline, and antibiotics can relax the airway muscles, increase the airflow, and decrease inflammation in lower airways. In case of stage 3 and 4, clinicians often suggest for oxygen therapy to restore the blood oxygen levels to baseline; however, it is temporary, and upon dislodging the oxygen supply, the patient's condition deteriorates quickly back to original. Changing lifestyle like quitting smoking, avoiding air pollution, and restricted dietary intake can also slow down the progression [51].

## 3.3 Interstitial lung diseases

Interstitial lung diseases (ILDs) are a wide group of pulmonary diseases, regrouping over 100 disorders, that cause scaring and fibrosis of the lung [52, 53]. The hallmark manifestations of ILDs are variable and comprise respiratory symptoms (cough and dyspnea), decline pulmonary capacities, abnormalities on chest radiographies and abnormal fibrosis, and inflammation on biopsies [53]. According to some of those specific clinical, physiological, radiological, and histopathological features, ILDs can be classified in individual disorders [53]. For instance, the presence of granulomatous inflammation (and no parenchymal fibrosis) is indicative of sarcoidosis, while broad pulmonary fibrosis and distortion of the lung are specific to idiopathic pulmonary fibrosis (IPF) [52]. The complexity of making a clear diagnostic have compromised the capacity to precisely estimate the incidence rates of ILDs [54]. However, it appears that IDLs are present worldwide and affect principally adult. The most common ILD is IPF, with (1) estimation of approximately 3 million persons suffering from IPF worldwide and 130,000 persons in the United States and (2) increasing rate of incidence reported [55–57]. According to each disorders the epidemiology of ILDs can vary [54, 58, 59]. For instance, IPF is most common in older people (over 65 years old), while sarcoidosis appear to be more frequent in African Americans and Northern Europeans [58, 59].

The outcome of ILDs is heterogeneous and ranges from partially reversible fibrosis to chronic progressive fibrotic ILDs that can be deadly. More specifically, IPF, the most common chronic progressive fibrotic disease, has a very poor prognosis, with a median survival estimated to only 2–5 years following diagnosis [60, 61]. IPF patients often suffer from acute exacerbations that can be fatal [62]. High interindividual and intraindividual heterogeneity is present in the progression of IPF, with some patients having slow progress of their diseases, while other suffer from rapid lung function decline, and, in the same patient, periods with low changes in lung function can alternate with periods of rapid deterioration [63]. Sarcoidosis, another common ILD with considerable levels of morbidity, also displays heterogeneous progression and outcome according to patients, ranging from an acute onset with spontaneous regression to a chronic progressive disease [64]. Often, ILDs have comorbidities, and/or they lack specific symptoms, which can complicate diagnosis, hence causing delay in treatments and prejudicing the prognosis for the patient [52, 53], with, for example, a study that identified a delay of approximately 2.1 years before diagnosis of IPF patients [65].

In most cases, ILDs are idiopathic diseases, which mean that the cause of the lung injury and subsequent fibrosis are unknown. However, in some cases, ILDs have been linked to systemic disorders (such as an autoimmune disease like rheumatoid arthritis), infections, or exposure to environmental agents that specifically damage the lungs (such as tobacco smoke or asbestos) [54, 66–70]. Moreover, some cases of ILDs have been linked with genetic mutations, with the alteration of specific set of genes being associated with increase fibrosis or being the cause of the ILDs called Hermansky-Pudlak syndrome [52, 71]. Additionally, patients that underwent

lung transplant and hematopoietic stem cell transplantation have been shown to have higher risks of developing bronchiolitis obliterans, a rare type of ILD [72].

The mechanisms involved in the development of IDLs are still relatively unknown, but they appear to be multifactorial and to include aging and lung epithelium injuries. Two of the key features of ILDs are the presence of abnormal inflammation and fibrosis in the lungs, which are, respectively, characterized by excessive number of inflammatory cells (macrophages, lymphocytes, etc.) and abnormal deposition of collagens and other extracellular matrix components in the lungs [73]. However, concerning IPF, the contribution of inflammation remains controversial and poorly understood, despite evidence showing that polymorphonuclear cells infiltrate in the lungs or that alternatively activated macrophages can display profibrotic characteristics [73, 74]. The key recognized feature causing the development of fibrosis in IPF lung appears to be the local proliferation of fibroblasts, myofibroblasts, and their production of collagen and other extracellular matrix components following chronic injury to the lung alveolar epithelium. The mechanisms driving fibroblast and myofibroblast accumulation and activation remain unclear, but there might have multiple pathways involved, with different dynamics, explaining the large diversity of clinical manifestations in different patients [75].

Treatment strategies are often based on the specific ILD diagnosis and the severity of disease. In circumstances of ILDs of known cause, one of the recommended methods to prevent progression of the disease is to avoid the triggering agent. However, as mentioned previously, most cases of ILDs are idiopathic and, therefore, cannot be prevented, other than by reducing the contact with risk factors (cigarette smoking, exposure to environmental and microbial stimuli, etc.) [52, 76]. The treatment regimen options for ILDs are dependent on the specific disease and have been extensively reviewed by Kim et al. [76] and Richeldi et al. [77]. They often comprised the use of corticosteroids and/or immunosuppressive agents (such as prednisone, cyclophosphamide, or azathioprine) to preserve lung function, reduce the frequency of acute exacerbations, and improve patients' survival [76, 78, 79]. However, in the most severe cases of progressive fibrosis, the administration of those therapies have not seemed to provide long-term improvement for patients [76]. For instance, to date, IPF has no demonstrated treatment able to prolong the life of patients. Two approved antifibrotic agents have been shown to help preventing the decline in lung function and slow the progression of the disease in patients suffering from IPF and other progressive ILDs [77, 80–82]. They appear to target multiple pathways, which might explain their efficiency. Their mechanism of action remains poorly understood. Nintedanib appears to inhibit some of the intracellular tyrosine kinase receptors involved in IPF, including the profibrotic mediators, platelet-derived growth factor receptor, fibroblasts growth factor receptor, and vascular endothelial growth factor receptor, while pirfenidone seems to have broad antifibrotic, antiinflammatory, and antioxidant properties (which include reducing TGFβ and TNFα) [83–85]. However, those two antifibrotic agents have been shown to have some adverse events, including gastrointestinal events (such as diarrhea), which can lead patients to discontinue their treatments if no counseling and personalized practical management of those

events are put in place [80–82, 86]. Clinical trials have showed that the antioxidant *N*-acetylcysteine (in monotherapy or in combined therapies with corticosteroids or pirfenidone) appears promising in improving the lung function and slowing the progression of the disease in IPF patients [87]. Despite some promising preliminary results of candidate biological immunomodulatory drugs designed to prevent the progression of IPF (such as the use of treatment with interferon gamma-1b), clinical trials have often not identified improvement in patients [79, 88]. However, many treatment options remain on clinical trials and give hope to patients. For instance, mesenchymal stem cell-based therapies have shown promising preclinical results, but more research remain to be conducted to confirm or invalidate those outcomes [89]. As no therapies exist to date, the last option for patients suffering for advanced progressive cases of IDLs is lung transplantation, which has been shown to increase survival. However, the median survival after transplantation remains low, with, for instance, a survival mean of 6 years of posttransplantation in IPF patients, highlighting the need for novel treatment options [90].

Taken together, ILDs remain a major health concern for whom therapies are not often effective. While some progress has been made recently in understanding ILDs, the discovery of a cure for the most aggressive chronic progressive ILDs remains relatively distant. Currently, medical research on ILDs combines basic research (combination of cell culture and animal work) and clinical research (clinical trials and real-world studies) in the aim of identifying the mechanistic and the molecular pathways involved in the development of abnormal pulmonary inflammation and fibrosis. The subsequent objectives of those studies are (1) to find new biological markers to simplify the diagnosis of ILDs and follow their progression and (2) to develop novel therapies (for currently incurable ILDs) to improve the quality of life and survival of affected patients.

## 3.4 Cystic fibrosis

Cystic fibrosis (CF) is a seriously disabling genetic condition that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [91]. The CFTR gene encodes a protein that aids in translation of chloride-containing transmembrane channel, which regulates anion transport and mucociliary clearance mechanism in the airways [92]. The genetic risk factor contributes to majority of cases of CF (~70%) [93]. The specific gene responsible for initiation of CF is "delta Phe508," which commonly occurs as a triple-base deletion that results in loss of amino acid phenylalanine at residue 508 of the predicted 1480 amino acid CFTR protein [94]. Moreover, till date, >2000 mutations have been identified that may modulate the CFTR function in humans [92]. These mutations could be broadly categorized as protein production mutations (Class 1) (i.e., nonsense and splice mutations that interfere with protein production), protein processing mutations (Class 2) (i.e., mutation resulting in addition or deletion of amino acids), gating mutations (Class 3) (i.e., mutation causing the CFTR protein to remain closed), conduction mutations (Class 4) (malfunction in protein functionality), and insufficient protein

mutations (Class 5) [95, 96]. Notably, CFTR mRNA transcripts are expressed in the epithelial cells throughout respiratory tract, including the epithelial cells of nasal, tracheal, and bronchial origin, although the expression of CFTR mRNA in these epithelial cells is quite low (~ 1–2 copies per cell) [94].

Approximately 70,000 individuals are affected by CF globally, predominantly in children of Northern European ethnicity (~ 1 in every 2500–3000 births) [97]. The disease has high rate of mortality, with survival estimated to be between 33 and 50 years in different parts of the world [21, 96, 98]. In addition, the economic burden of CF is only beginning to be unraveled. The cost of management of CF patient costs from €17,551 per patient-year in Germany [99] to approximately €48,603 in the United Kingdom [100].

The cellular mechanisms involved in CF are primary driven by genetic mutations and recurrent and/or persistent bacterial infections [101]. Importantly the CFTR mutation leads to misfolded or malfunctioning protein that may lead to dehydrated mucus, subsequently leading to impaired mucociliary clearance [102], although mucus is constantly produced by the goblet cells and submucosal glands, which is not adequately cleared by cilia, potentially leading to formation of mucus plugs [103]. These mucus plugs could contribute to local tissue hypoxia, particularly epithelial cell surface [103]. Local tissue hypoxia is further associated with local inflammation and increased risk of bacterial infections [104]. In addition, both recurrent and persistent bacterial infections of the large airways are the most important risk factors for CF progression, especially in the first few years of life [102].

There is an inherent need for better drug delivery mechanisms that could effectively deliver the therapeutic drug to the site of pathology. This could be achieved by a number of strategies that involve novel ways of delivering the drug via nasal and/or pulmonary routes, for instance, the usage of common absorption enhancers, such as surfactants (e.g., bile salts, phospholipids and fatty acids, and derivatives), cationic polymers, enzymatic inhibitors, cyclodextrins, and tight junction modulators [105]. Other strategies could be investigating the efficacy of nanoparticles, which are utilized as "drug carriers." Specific examples include polystyrene-based mucopenetrating particles (MPP) [106].

## 3.5 Tuberculosis

Tuberculosis (TB) is currently the leading cause of mortality worldwide due to a single infectious agent. In 2018 alone, there were an estimated 10 million people who became ill and 1.5 million who died from the disease globally [107]. Geographically the burden of TB is not evenly distributed. Approximately, two-thirds of TB cases in 2018 presented in the World Health Organization (WHO) is found in the regions of South-East Asia (44%) and Africa (24%) with a substantially lower proportion of incidences found in Europe (3%) and the Americas (3%). The highest number of TB cases in 2018 occurred in India (2.69 million) followed by China (866,000) and Indonesia (845,000) [107].

TB in humans is primarily caused by the acid-fast bacterial species *M. tuberculosis* with a relatively smaller number of zoonotic cases, 143,000 in 2018, due to the animal-adapted species *M. bovis* [107]. Although lacking many of the classical virulence factors that are found in other bacterial pathogens such as exotoxins, *M. tuberculosis* is still highly infectious when transmitted in aerosols from the lungs of patients with active TB through sneezing, coughing, or spitting. Exposure of a susceptible individual to droplets containing the bacterium results in inhalation of the pathogen into the alveoli of the lower respiratory tract. There, resident macrophages, normally the first cells of the immune system to engage with *M. tuberculosis* in the lung, proceed to internalize the bacterium [108].

The bacterium harbors a suite of virulence genes whose inactivation results in a loss of pathogenicity in an experimental model of TB but not an impairment of mycobacterial growth under optimum in vitro conditions in the absence of stress or starvation. The virulence factors of *M. tuberculosis* can be grouped into categories that include lipid metabolism enzymes, cell envelope proteins, inhibitors of macrophage function, protein kinases, proteases, metal transporters, gene regulators, and proteins of undefined function such as PE and PE_PGRS proteins [109]. Once phagocytosed by alveolar macrophages, *M. tuberculosis* is able to withstand the activity of reactive oxygen and nitrogen intermediates and also impede phagosome acidification and lysosomal fusion [110, 111]. These functions are key to persistence of the pathogen in the host during latent TB and, in addition, facilitate bacterial replication and ultimately tissue dissemination and damage in active TB cases and downstream person-to-person transmission. Types of structural lung damage that occur during pulmonary TB may include fibrosis, cavitation, traction bronchiectasis, bronchostenosis, and parenchymal destruction [112, 113].

In terms of treatment the standard WHO-recommended therapeutic regimen for drug-susceptible pulmonary TB requires that patients take four drugs, that is, isoniazid, rifampicin, pyrazinamide, and ethambutol, for 2 months followed by isoniazid and rifampicin for a further 4 months [114]. Among patients whose TB was detected, reported, and treated in 2017, the overall global treatment success rate with this regimen was 85% [107]. This success rate, however, drops to 56% for cases of TB that are resistant to both isoniazid and rifampicin, that is, multidrug resistant (MDR) or are rifampicin resistant (RR). Worldwide, there were 484,000 cases of MDR/RR-TB in 2018, which constituted 3.4% of new TB cases and 18% of previously treated cases [107].

MDR-TB involves an even longer treatment duration with the standard regimen recommended by the WHO consisting of an intensive 8 month phase, with at least four effective second-line TB drugs plus pyrazinamide, followed by a continuation phase, with at least three potent second-line anti-TB drugs, which stretches the treatment duration to a total of 20 months [115]. A shorter WHO-recommended treatment regimen has become available, which entails a 4- to 6-month intensive phase with seven drugs, that is, moxifloxacin, kanamycin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by a 5-month continuation phase with moxifloxacin, clofazimine, pyrazinamide, and ethambutol [38].

In addition to the lower success rate and increased duration associated with MDR-TB treatment, it is also more expensive to administer with per-case costs estimated at USD $134,000 in the United States and €57,213 in 15 European Union (EU) countries compared with USD $17,000 and €10,282, respectively, for drug-susceptible TB [116, 117]. Therefore methods that deliver drugs more effectively in patients and reduce the cost and/or duration of anti-TB treatment are needed.

Developments in drug delivery systems have the potential to improve the efficacy of existing TB drugs. These systems offer better targeting of TB drugs, improved release and bioavailability, and reduced adverse reactions. In terms of TB control, possible outputs of new drug delivery systems could include improvements in patient adherence to TB treatment regimens along and an accompanying decrease in the incidence of default TB cases and treatment failures, as well as the generation of new therapeutic regimens with shorter durations.

First-line treatment of drug-susceptible TB with isoniazid, rifampicin, ethambutol, and pyrazinamide primarily utilizes the oral route of delivery [114]. In addition, a number of the second-line drugs used in the treatment of MDR-TB, that is, amikacin, kanamycin, and capreomycin, are administered through intramuscular or intravenous injection [115]. The pulmonary route is now being investigated as a potential route for administering of TB drugs as it is believed that it could target the drugs more effectively to the lungs, the principal portal entry of *M. tuberculosis* and primary site of TB disease [118]. Recently the use of a gastric resident delivery system has also been explored and found to provide multigram dosing of TB drugs for several weeks in a swine model [119].

A wide range of new vehicles are also being examined with regard to the carriage of TB drugs. These include the use of liposomes (typically 50–450 nm) of phosphatidylcholine and cholesterol, microparticles (1–1000 μm) of polylactic acid (PLA) or polylactic-*co*-glycolic acid (PLGA), and nanoparticles (1–100 nm in at least one dimension) of alginate, PLA, PLGA, or poly-ε-caprolactone (PCL) [120, 121]. Several TB drugs have been successfully incorporated into liposomes, microparticles, and/or nanoparticles and include each of the first-line drugs isoniazid, rifampicin, ethambutol, and pyrazinamide and second-line drugs such as levofloxacin, ofloxacin, and capreomycin [121–123]. In one study the use of aerosolized PLGA nanoparticles was shown to increase the bioavailability of isoniazid, rifampicin, and pyrazinamide and eliminate *M. tuberculosis* from the lungs of infected guinea pigs more effectively than standard orally administered drugs [124].

Due to their small size, liposomes, microparticles, and nanoparticles have the potential to be taken up by macrophages and concentrate TB drugs selectively in the main host cell of invading *M. tuberculosis* [125]. This would serve to reduce the dosage and duration that would be required to achieve eradication of the infection and, thereby, reduce the toxic side effects associated with current TB treatment regimens. It is also possible to design vehicles that discharge their drug cargo after entry into macrophages. For example, nanoparticles have been developed with cyclodextrin-based pH-operated valves that function to release isoniazid only in an acidic environment such as in the acidified endosomes of human macrophages [126].

Novel delivery systems that specifically target drugs to the main focus of TB infection and pathology in humans have the potential to significantly advance TB control by shortening the duration and dosage required to achieve successful chemotherapy. This would not only decrease healthcare costs but also, more importantly, reduce the adverse effects of TB drugs experienced by patients and promote higher levels of treatment compliance and success. It is therefore hoped that further research and testing of new drug delivery systems will translate into superior but affordable treatments for both drug-susceptible and drug-resistant TB.

## 4 Lung cancer

Globally, lung cancer-related mortality is majorly caused by the late diagnoses and inadequate treatment interventions of 70% of lung cancer patients mostly present with advanced stage disease (stage III or IV). It is extremely invasive, rapidly metastasizing, and prevalent malignancy in both men and women. Statistically, in the United States, the mortality rate due to lung cancer is higher than the combined mortality rate of other four leading causes of cancer (prostate, breast, colon, and pancreas) [127]. Twenty or more years of smoking history seems to be significantly associated with its frequency of development and mortality. The tobacco-induced susceptibility of lung cancer is considered to be highly dependent on competitive gene-enzyme interactions at the level of procarcinogens and resultant extent of DNA damage. For this reason, lung cancer is also believed to be generally preventable by smoking prevention and cessation. Public awareness/education is required to reduce or eradicate cigarette smoking to circumvent the unavoidable rise in respiratory cancers in countries where smoking has increased [128].

The major cause of cancer-related death, worldwide, both in men and women is caused by lung cancer [129]. According to a study by Martin et al., estimated new cases of lung cancer in 2012 were approximately 1.8 million, accounting for 12.9% of all new cancer diagnoses. According to the Global Burden of Disease Study 2020, the healthcare burden and expense assigned to lung cancer were extensive worldwide [9]. One study indicated that level of economic progress is not correlated with cancer fatalities in men. Surprisingly the study also showed that economic development status of a country is indeed associated with lung cancer fatalities in women. The major cause of deaths due to cancers in women of developing countries remains breast cancer [130].

The prevalence and mortality of lung cancer are significantly associated with the history of cigarette smoking. Interestingly the trend of both lung cancer and mortality in men and women has been observed to be increasing with time, indicative of increased smoking rates, followed by a decline, which could be perhaps due to formulation and implementation of comprehensive smoking cessation policies [131]. Data from the United States and the United Kingdom suggest that both lung cancer prevalence and mortality are considerably reducing since 1990s. In contrast the low- and middle-income countries (LMICs), in particular, the BRICS nations, that is, Brazil, Russia, India, China, and South Africa, report significantly increasing rates of cigarette

smoking irrespective of gender. The LMICs also have a higher mortality rate due to lung cancer despite constituting smaller disease incidence when compared with the higher-income countries. This is most likely due to the disproportionately accessible healthcare facilities, which then limits timely diagnosis and treatment challenging. The other key factors include environmental pollution and/or contamination, as well as sociocultural taboos [132]. It highlights the need of preventive approaches like the WHO Framework Convention on Tobacco Control that should be further strengthened in these nations, through tax policy, smoke-free areas, monitoring, cessation assistance, education about the impairs of tobacco, and prohibitions on tobacco advertising [133].

Complex heterogeneity of lung cancer is based on its origin in different locations in the bronchial tree and variable presentations of patient's symptoms and signs according to its type and anatomic location. Traditionally, lung cancer is classified into two primary groups: small-cell lung carcinoma (SCLC) (15% of all lung cancers) and non-SCLC (NSCLC) (85% of all lung cancers). NSCLCs are usually subcategorized into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [134]. This particular stratification of lung cancer was further complemented with specific histopathologic characteristics and reliable immunohistochemical markers, which allows clear distinction between invasive adenocarcinomas and preinvasive lesions. Furthermore the advent of molecular characterization of lung cancers and evergrowing arsenal of available therapies has substantially resulted in the ways lung cancer is nowadays classified. Data imply that lung cancer indicates a group of histologically and molecularly heterogeneous diseases even within the same histological subtype [135].

Statistically, among all lung cancer subtypes, squamous cell lung cancers are important because of higher prevalence (25%–30%) and site of origin (main bronchi) in the lung and metastases (carina—bifurcation site of trachea in bronchi). In contrast, peripherally located adenocarcinomas constitute 40% of all lung cancers with its localized manifestations like lobar atelectasis and pneumonitis [136]. Reclassification of bronchioloalveolar cancers (BAC) has also been done according to their origin in alveoli and their localized spread into interalveolar compartments. This reclassified lung cancers further into adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) [137]. Small-cell lung cancers (SCLC) (10%–15% of all lung cancers) derived from the neuroendocrine cells (APUD cells) in the bronchus called Feyrter cells are considered extremely aggressive tumor with rapid disseminating ability into nearby lymphatic vessels and associated regional lymph nodes [138].

More than 70% of NSCLC patients are diagnosed in advanced stages or metastatic disease. The possibilities and cycle of treatments for NSCLC are determined corresponding to the site and stage of tumor while observing the involvement and the performance status of patient as well. Outlined are some traditional and ongoing treatments for NSCLC according to their stage, metastasis, and recurrence.

**(a)** Stage I and II—NSCLC

Surgery is the most common primary treatment for resectable stage I and II disease [139, 140]. Postsurgical adjuvant platinum-based chemotherapy is also proposed and proved to be valuable for stage II NSCLC patients [141, 142].

**(b)** Stage III—NSCLC
Complex heterogeneity of stage III NSCLC divides its treatment option in resectable and nonresectable disease, which is highly dependent on the involvement of regional lymph nodes. It ranges from resectable tumors with microscopic metastases to regional lymph nodes to nonresectable stage III disease with distant nodal involvement. Traditionally, stage IIIA resectable disease treatment is surgery followed by chemotherapy alone. In contrast, nonresectable stage IIIA disease treatment consists of chemotherapy alone or chemoradiation (combined chemotherapy and postchemoradiation therapy) [143]. Traditional therapy of stage IIIB NSCLC comprises of either a sequential combination of chemotherapy or external radiation therapy.

**(c)** Stage IV—NSCLC
Due to complex nature of disease, 40% of the recently diagnosed NSCLC patients exhibit stage IV. For this reason, treatment options are mostly based on combination therapy in the form of combination chemotherapy, combination chemotherapy and targeted therapy, and external radiation therapy with internal endoscopic radiation therapy as required [144].

**(d)** Recurrent NSCLC
Recurrence or relapse of NSCLC following an initial treatment with surgery, radiation therapy, and/or chemotherapy. For stage IV NSCLC patients, the treatment plan is the same as that of stage IV NSCLC, that is, chemotherapy. In contrast, patients with recurrence, after receiving chemotherapy treatment options, may vary, which comprise of (1) external palliative radiation therapy [145], to relieve pain and other tumor-associated symptoms; (2) cytotoxic chemotherapy [146]; (3) EGFR inhibitors (TKIs) in patients with or without EGFR mutations; and (4) EML4-ALK inhibitor (crizotinib) in patients with EML-ALK translocations [147, 148].

Apart from surgical resection, chemotherapy-based NSCLC treatment also proved to have valuable effect on patient survival rate. Different classes of chemotherapies are currently used and much more under trial for the benefit of NSCLC patients. Several key treatment strategies are follows.

### *4.1.1 Angiogenesis inhibitors*

Angiogenic pathways are always considered a critical target in NSCLC treatment as tumor exhibits development of new blood vessel in desmoplastic stroma for its growth and progression. Targeting various proangiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) is always considered pivotal to block angiogenesis required for tumor growth. Presently, anti-VEGF monoclonal antibody bevacizumab is approved for first-line treatment of advanced NSCLC, in combination with platinum-based chemotherapy [149]. Studies also recommended that bevacizumab might be beneficial for the treatment of patient with adenocarcinoma as well [150]. However, it is also observed that eventually all patients show resistance to treatment with anti-VEGF agents. This leads to development of multiple tyrosine kinase inhibitor (TKI)

sorafenib that targets VEGFR-2/3, PDGFR-β, c-Kit, Raf, and Flt-3, which showed promising response in multiple phase I and II trials especially in NSCLC patients with K-Ras mutation [149].

### 4.1.2 Insulin-like growth factor inhibitors

The insulin-like growth factor system (IGF system) composed of two receptors: insulin-like growth factor 1 receptor (IGF-IR) and IGF-IIR with their corresponding intracellular ligands. These ligands are overexpressed in multiple cancers including lung cancer [151]. Figitumumab (anti-IGF-1R monoclonal antibody) furnished remarkable response in comparison with chemotherapy alone in a phase II trial in formerly untreated, locally advanced, or metastatic NSCLC patients [152]. Two other monoclonal antibodies against IGF ligands, cixutumumab and dalotuzumab, are also under trial as well [153].

### 4.1.3 Histone deacetylase inhibitors

Histones are a family of basic proteins that associate with DNA in the nucleus and help condense it into chromatin. Histone deacetylases (HDACs) regulate the expression and activity of numerous proteins involved in both cancer initiation and cancer progression [153]. Targeting several intracellular proteins involved in cell growth and proliferation, several HDAC inhibitors have been developed and reported to alter the acetylation of these key cellular proteins. These target cellular proteins include tumor suppressor protein (p53), HSP90, STAT3, subunits of NFκ-B, and α-tubulin [153–155]. FDA has already approved two HDAC inhibitors for cutaneous T-cell lymphoma, including suberoylanilide hydroxamic acid and romidepsin. Several HDAC inhibitors are still under trial for NSCLC treatment, which consists of entinostat, Pivanex, CI-994, panobinostat, and romidepsin [156].

### 4.1.4 Proapopototic agents

Nearly all cancer cells evade normal apoptotic mechanism by either upregulation of antiapoptotic factors or downregulation of proapoptotic mechanisms or both [157]. For the treatment of NSCLC, conatumumab (anti-DR1) and YM155 (antisurvivin), both apoptotic promoter agents, are currently under clinical trial. It has been observed that these proapoptotic agents have exhibited remarkable outcomes in combination with chemotherapy in comparison with chemotherapy alone [153, 158, 159].

Despite of all continuing research and advancement of developing numerous new targeted agents, more investigations are still required to identify early detection and treatment of these cancers that may help radically in the patients' long-term survival. Pulmonary drug delivery turns out to be increasingly significant because of its specific physiological environment and better absorption and treatment organ. For 10 years the quest of optimizing the delivery of the cancer therapeutic drug to the lungs has been accelerated. The landmark approval of Pfizer's Exubera [human insulin (rDNA origin)], which is an inhalation powder, has been pivotal in similar strategy being tested for many more potential drug. Several microscopic scaled (e.g., micrometer- and nanometer-sized) drug carrier systems, such as liposomes, polymer conjugates, polymeric micelles, microparticles, and nanoparticles (NPs),

are now being aggressively researched for targeted delivery of a wide range of potential anticancer therapeutic molecules specifically to the part of lung showing cancer pathology.

## 5 Challenges of current therapeutic strategies

Though the disease pathology and epidemiology of different infectious and noninfectious respiratory diseases were studied in detail, the development of more effective therapies is still under trial phases. Asthma and COPD being most common noninfectious diseases are affecting large populations of both higher- and lower-income countries worldwide. The disease pathology and progression differ widely among different demographics and largely narrow down to personal lifestyle. Widely used bronchodilators like albuterol and ipratropium and newly developed long-acting $\beta_2$ agnostics (LABAs) and long-acting muscarinic antagonists (LAMAs) are being effective to treat the patients with mild to moderate symptoms of chronic respiratory disorders; however, the effectiveness of the drugs in patients with chronic asthma and COPD was found to be not fully effective. Moreover, personal lifestyle habits like smoking or exposure to occupational dust for longer periods have rendered the effectiveness of existing therapeutics. Moreover the severe forms of the disease are characterized by irreversible damage of lung tissue leading to scarring, which cannot be treated using the commercially available therapeutics.

In contrast the respiratory diseases caused by infectious agents are being a major concern, since most of these diseases are seasonal and continue to manifest within or outside human body. The natural selection, mutations, and overusage of antibiotics have led to development of new potent mutants with increased drug resistance causing different pandemics worldwide. Recent studies also highlight the cross-transfer of various infectious agents among different species (animals to humans and vice versa) affecting the global populations at a larger scale. Recent outbreak of COVID-19 is one good example that is caused by a distinct relative of coronavirus family, due to lack of natural immunity to the newborn mutants, and can cause severe threat to global health.

## 6 Summary and conclusion

The burden of chronic respiratory diseases (CRDs) is enormous and increasingly becoming more prevalent globally, primarily due to aging populations and lack of effective measures to reduce the risk factors associated with the development/progression of these pulmonary diseases. Furthermore the lack of effective treatments that could potentially be utilized for treating and/or preventing these chronic lung diseases further compounds both the societal and economic burden associated with chronic lung diseases. In addition to further research into discovering novel treatments for

CRDs, efforts should be made to ensure optimal delivery of treatments to the site of pathology, that is, airway epithelium, parenchyma, and bronchioles. Additionally, the treatments should target specific cell types that might be playing a crucial role in the progression of the diseases. There are multiple biomolecular entities that could be utilized for maximizing the drug delivery and absorption/adsorption of prescription drugs in CRDs. Further research is warranted in ascertaining both the efficacy and safety of these drug delivery vehicles.

## Conflict of interest

None to declare.

## Author contribution

Conceptualization, SDS; literature search and drafting of manuscript, all authors; editing and revisions, SDS, SKV, and RFOT.

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## References

[1] World Health Organization, https://www.who.int/gard/publications/The_Global_Impact_of_Respiratory_Disease.pdf.

[2] Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386(9995):743–800. https://doi.org/10.1016/s0140-6736(15)60692-4.

[3] Khaltaev N, Axelrod S. Chronic respiratory diseases global mortality trends, treatment guidelines, life style modifications, and air pollution: preliminary analysis. J Thorac Dis 2019;11(6):2643–55. https://doi.org/10.21037/jtd.2019.06.08.

[4] Salvi S, Kumar GA, Dhaliwal RS, Paulson K, Agrawal A, et al. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990-2016. Lancet Glob Health 2018;6(12):e1363–74. https://doi.org/10.1016/s2214-109x(18)30409-1.

[5] Gross NJ, Barnes PJ. New therapies for asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2017;195(2):159–66. https://doi.org/10.1164/rccm.201610-2074PP.

[6] Chaudhry R, Bordoni B. Anatomy, thorax, lungs. In: StatPearls. Treasure Island, FL: StatPearls Publishing LLC; 2019.

[7] Hasleton PS. The internal surface area of the adult human lung. J Anat 1972;112(Pt 3):391–400.
[8] Johns DP, Walters JAE, Walters EH. Diagnosis and early detection of COPD using spirometry. J Thorac Dis 2014;6(11):1557–69. Retrieved from: http://jtd.amegroups.com/article/view/3088.
[9] Lutfi MF. The physiological basis and clinical significance of lung volume measurements. Multidiscip Respir Med 2017;12(1):3. https://doi.org/10.1186/s40248-017-0084-5.
[10] Franks TJ, Colby TV, Travis WD, Tuder RM, Reynolds HY, Brody AR, et al. Resident cellular components of the human lung: current knowledge and goals for research on cell phenotyping and function. Proc Am Thorac Soc 2008;5(7):763–6. https://doi.org/10.1513/pats.200803-025HR.
[11] Travis WD, Garg K, Franklin WA, Wistuba II, Sabloff B, Noguchi M, et al. Bronchioloalveolar carcinoma and lung adenocarcinoma: the clinical importance and research relevance of the 2004 World Health Organization pathologic criteria. J Thorac Oncol 2006;1(9 Suppl):S13–9.
[12] Whitsett JA, Wert SE, Weaver TE. Alveolar surfactant homeostasis and the pathogenesis of pulmonary disease. Annu Rev Med 2010;61:105–19. https://doi.org/10.1146/annurev.med.60.041807.123500.
[13] Hiemstra PS, McCray Jr. PB, Bals R. The innate immune function of airway epithelial cells in inflammatory lung disease. Eur Respir J 2015;45(4):1150–62. https://doi.org/10.1183/09031936.00141514.
[14] Harkness LM, Kanabar V, Sharma HS, Westergren-Thorsson G, Larsson-Callerfelt AK. Pulmonary vascular changes in asthma and COPD. Pulm Pharmacol Ther 2014;29(2):144–55. https://doi.org/10.1016/j.pupt.2014.09.003.
[15] Rock JR, Randell SH, Hogan BL. Airway basal stem cells: a perspective on their roles in epithelial homeostasis and remodeling. Dis Model Mech 2010;3(9–10):545–56. https://doi.org/10.1242/dmm.006031.
[16] Barnes PJ, Bonini S, Seeger W, Belvisi MG, Ward B, Holmes A. Barriers to new drug development in respiratory disease. Eur Respir J 2015;45(5):1197–207. https://doi.org/10.1183/09031936.00007915.
[17] Dua K, Malyla V, Singhvi G, Wadhwa R, Krishna RV, Shukla SD, et al. Increasing complexity and interactions of oxidative stress in chronic respiratory diseases: an emerging need for novel drug delivery systems. Chem Biol Interact 2019;299:168–78. https://doi.org/10.1016/j.cbi.2018.12.009.
[18] Dua K, Shukla SD, de Jesus Andreoli Pinto T, Hansbro PM. Nanotechnology: advancing the translational respiratory research. Interv Med Appl Sci 2017;9(1):39–41. https://doi.org/10.1556/1646.9.2017.1.02.
[19] McCracken JL, Veeranki SP, Ameredes BT, Calhoun WJ. Diagnosis and management of Asthma in adults: a review. JAMA 2017;318(3):279–90. https://doi.org/10.1001/jama.2017.8372.
[20] Fergeson JE, Patel SS, Lockey RF. Acute asthma, prognosis, and treatment. J Allergy Clin Immunol 2017;139(2):438–47.
[21] Ravindra K, Sokhi R, Van Grieken R. Atmospheric polycyclic aromatic hydrocarbons: source attribution, emission factors and regulation. Atmos Environ 2008;42(13):2895–921.
[22] Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. Asthma Res Pract 2017;3(1):1. https://doi.org/10.1186/s40733-016-0029-3.

[23] Ray A, Oriss TB, Wenzel SE. Emerging molecular phenotypes of asthma. Am J Phys Lung Cell Mol Phys 2015;308(2):L130–40. https://doi.org/10.1152/ajplung.00070.2014.
[24] Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet 2018;391(10118):350–400. https://doi.org/10.1016/s0140-6736(17)30879-6.
[25] Quirt J, Hildebrand KJ, Mazza J, Noya F, Kim H. Asthma. Allergy Asthma Clin Immunol 2018;14(Suppl. 2):50. https://doi.org/10.1186/s13223-018-0279-0.
[26] Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. Nat Rev Immunol 2015;15(1):57.
[27] Romanet-Manent S, Charpin D, Magnan A, Lanteaume A, Vervloet D, Group, E. C. Allergic vs nonallergic asthma: what makes the difference? Allergy 2002;57(7):607–13.
[28] Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet 2018;391(10122):783–800. https://doi.org/10.1016/S0140-6736(17)33311-1.
[29] Mohanan S, Tapp H, McWilliams A, Dulin M. Obesity and asthma: pathophysiology and implications for diagnosis and management in primary care. Exp Biol Med 2014;239(11):1531–40.
[30] Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV, Price DB. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. Thorax 2018;73(2):116–24. https://doi.org/10.1136/thoraxjnl-2017-210531.
[31] Tian BP, Xuan N, Wang Y, Zhang G, Cui W. The efficacy and safety of azithromycin in asthma: a systematic review. J Cell Mol Med 2019;23(3):1638–46.
[32] Taylor SL, Leong LE, Mobegi FM, Choo JM, Wesselingh S, Yang IA, et al. Long-term azithromycin reduces *Haemophilus influenzae* and increases antibiotic resistance in severe asthma. Am J Respir Crit Care Med 2019;200(3):309–17.
[33] Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Della Cioppa G, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108(2):184–90.
[34] Katsaounou P, Buhl R, Brusselle G, Pfister P, Martínez R, Wahn U, Bousquet J. Omalizumab as alternative to chronic use of oral corticosteroids in severe asthma. Respir Med **150**, 2019, 51–62;.
[35] Lai T, Wang S, Xu Z, Zhang C, Zhao Y, Hu Y, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. Sci Rep 2015;5:8191.
[36] Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182(5):598–604.
[37] Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet 2004;364(9434):613–20.
[38] World Health Organization. Factsheet—the shorter MDR-TB regimen. Geneva, Switzerland: World Health Organization; 2016.
[39] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3(11):e442.
[40] Organization, W. H. Chronic obstructive pulmonary disease (COPD). Retrieved from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd; 2017.
[41] Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. Clinicoecon Outcomes Res 2013;5:235.

[42] Sullivan J, Pravosud V, Mannino DM, Siegel K, Choate R, Sullivan T. National and state estimates of COPD morbidity and mortality—United States, 2014-2015. Chronic Obstr Pulm Dis 2018;5(4):324.
[43] Shah PL, Herth FJ, van Geffen WH, Deslee G, Slebos D-J. Lung volume reduction for emphysema. Lancet Respir Med 2017;5(2):147–56.
[44] Kesimer M, Ford AA, Ceppe A, Radicioni G, Cao R, Davis CW, et al. Airway mucin concentration as a marker of chronic bronchitis. N Engl J Med 2017;377(10):911–22.
[45] Kent BD, Mitchell PD, McNicholas WT. Hypoxemia in patients with COPD: cause, effects, and disease progression. Int J Chron Obstruct Pulmon Dis 2011;6:199.
[46] Rajendra K, Shukla SD, Gautam SS, Hansbro PM, O'Toole RF. The role of environmental exposure to non-cigarette smoke in lung disease. Clin Transl Med 2018;7(1):1–12.
[47] Terzikhan N, Verhamme KM, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam study. Eur J Epidemiol 2016;31(8):785–92.
[48] MacNee W. Pathogenesis of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2(4):258–66.
[49] MacNee W. Pathology, pathogenesis, and pathophysiology. BMJ 2006;332(7551):1202–4.
[50] Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. Available from: http://goldcopd.org; 2019.
[51] Barnes PJ. Chronic obstructive pulmonary disease. N Engl J Med 2000;343(4):269–80. https://doi.org/10.1056/nejm200007273430407.
[52] Meyer KC. Diagnosis and management of interstitial lung disease. Transl Respir Med 2014;2:4. https://doi.org/10.1186/2213-0802-2-4.
[53] Ryu JH, Daniels CE, Hartman TE, Yi ES. Diagnosis of interstitial lung diseases. Mayo Clin Proc 2007;82(8):976–86. https://doi.org/10.4065/82.8.976.
[54] Raghu G, Nyberg F, Morgan G. The epidemiology of interstitial lung disease and its association with lung cancer. Br J Cancer 2004;91(Suppl. 2):S3–10. https://doi.org/10.1038/sj.bjc.6602061.
[55] Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J 2015;46(3):795–806. https://doi.org/10.1183/09031936.00185114.
[56] Martinez FJ, Collard HR, Pardo A, Raghu G, Richeldi L, Selman M, et al. Idiopathic pulmonary fibrosis. Nat Rev Dis Primers 2017;3:17074. https://doi.org/10.1038/nrdp.2017.74.
[57] Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. Adv Ther 2018;35(5):724–36. https://doi.org/10.1007/s12325-018-0693-1.
[58] Costabel U. Sarcoidosis: clinical update. Eur Respir J Suppl 2001;32:56s–68s. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11816825.
[59] Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev 2012;21(126):355–61. https://doi.org/10.1183/09059180.00002512.
[60] Ley B, Collard HR, King Jr. TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;183(4):431–40. https://doi.org/10.1164/rccm.201006-0894CI.
[61] Torrisi SE, Palmucci S, Stefano A, Russo G, Torcitto AG, Falsaperla D, et al. Assessment of survival in patients with idiopathic pulmonary fibrosis using quanti-

tative HRCT indexes. Multidiscip Respir Med 2018;13:43. https://doi.org/10.1186/s40248-018-0155-2.
[62] Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King Jr. TE, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176(7):636–43. https://doi.org/10.1164/rccm.200703-463PP.
[63] Sauleda J, Nunez B, Sala E, Soriano JB. Idiopathic pulmonary fibrosis: epidemiology, natural history, phenotypes. Med Sci (Basel) 2018;6(4):https://doi.org/10.3390/medsci6040110.
[64] Nagai S, Handa T, Ito Y, Ohta K, Tamaya M, Izumi T. Outcome of sarcoidosis. Clin Chest Med 2008;29(3):565–74. x, https://doi.org/10.1016/j.ccm.2008.03.006.
[65] Hoyer N, Prior TS, Bendstrup E, Wilcke T, Shaker SB. Risk factors for diagnostic delay in idiopathic pulmonary fibrosis. Respir Res 2019;20(1):103. https://doi.org/10.1186/s12931-019-1076-0.
[66] Azadeh N, Limper AH, Carmona EM, Ryu JH. The role of infection in interstitial lung diseases: a review. Chest 2017;152(4):842–52. https://doi.org/10.1016/j.chest.2017.03.033.
[67] Bes C. Comprehensive review of current diagnostic and treatment approaches to interstitial lung disease associated with rheumatoid arthritis. Eur J Rheumatol 2018;6(3):146–9. https://doi.org/10.5152/eurjrheum.2019.19036.
[68] Fischer A, Distler J. Progressive fibrosing interstitial lung disease associated with systemic autoimmune diseases. Clin Rheumatol 2019;38(10):2673–81. https://doi.org/10.1007/s10067-019-04720-0.
[69] Gulati M, Redlich CA. Asbestosis and environmental causes of usual interstitial pneumonia. Curr Opin Pulm Med 2015;21(2):193–200. https://doi.org/10.1097/MCP.0000000000000144.
[70] Hagmeyer L, Randerath W. Smoking-related interstitial lung disease. Dtsch Arztebl Int 2015;112(4):43–50. https://doi.org/10.3238/arztebl.2015.0043.
[71] Devine MS, Garcia CK. Genetic interstitial lung disease. Clin Chest Med 2012;33(1):95–110. https://doi.org/10.1016/j.ccm.2011.11.001.
[72] Estenne M, Hertz MI. Bronchiolitis obliterans after human lung transplantation. Am J Respir Crit Care Med 2002;166(4):440–4. https://doi.org/10.1164/rccm.200201-003pp.
[73] Bagnato G, Harari S. Cellular interactions in the pathogenesis of interstitial lung diseases. Eur Respir Rev 2015;24(135):102–14. https://doi.org/10.1183/09059180.00003214.
[74] Bringardner BD, Baran CP, Eubank TD, Marsh CB. The role of inflammation in the pathogenesis of idiopathic pulmonary fibrosis. Antioxid Redox Signal 2008;10(2):287–301. https://doi.org/10.1089/ars.2007.1897.
[75] Maher TM, Wells AU, Laurent GJ. Idiopathic pulmonary fibrosis: multiple causes and multiple mechanisms? Eur Respir J 2007;30(5):835–9. https://doi.org/10.1183/09031936.00069307.
[76] Kim R, Meyer KC. Therapies for interstitial lung disease: past, present and future. Ther Adv Respir Dis 2008;2(5):319–38. https://doi.org/10.1177/1753465808096948.
[77] Richeldi L, Varone F, Bergna M, de Andrade J, Falk J, Hallowell R, et al. Pharmacological management of progressive-fibrosing interstitial lung diseases: a review of the current evidence. Eur Respir Rev 2018;27(150):https://doi.org/10.1183/16000617.0074-2018.
[78] Baughman RP, Grutters JC. New treatment strategies for pulmonary sarcoidosis: antimetabolites, biological drugs, and other treatment approaches. Lancet Respir Med 2015;3(10):813–22. https://doi.org/10.1016/S2213-2600(15)00199-X.

[79] Karampitsakos T, Vraka A, Bouros D, Liossis SN, Tzouvelekis A. Biologic treatments in interstitial lung diseases. Front Med (Lausanne) 2019;6:41. https://doi.org/10.3389/fmed.2019.00041.
[80] Margaritopoulos GA, Trachalaki A, Wells AU, Vasarmidi E, Bibaki E, Papastratigakis G, et al. Pirfenidone improves survival in IPF: results from a real-life study. BMC Pulm Med 2018;18(1):177. https://doi.org/10.1186/s12890-018-0736-z.
[81] Noble PW, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, et al. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. Eur Respir J 2016;47(1):243–53. https://doi.org/10.1183/13993003.00026-2015.
[82] Rivera-Ortega P, Hayton C, Blaikley J, Leonard C, Chaudhuri N. Nintedanib in the management of idiopathic pulmonary fibrosis: clinical trial evidence and real-world experience. Ther Adv Respir Dis 2018;12:https://doi.org/10.1177/1753466618800618.1753466618800618.
[83] Knuppel L, Ishikawa Y, Aichler M, Heinzelmann K, Hatz R, Behr J, et al. A novel antifibrotic mechanism of nintedanib and pirfenidone. Inhibition of collagen fibril assembly. Am J Respir Cell Mol Biol 2017;57(1):77–90. https://doi.org/10.1165/rcmb.2016-0217OC.
[84] Lopez-de la Mora DA, Sanchez-Roque C, Montoya-Buelna M, Sanchez-Enriquez S, Lucano-Landeros S, Macias-Barragan J, Armendariz-Borunda J. Role and new insights of pirfenidone in fibrotic diseases. Int J Med Sci 2015;12(11):840–7. https://doi.org/10.7150/ijms.11579.
[85] Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, Kolb M. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J 2015;45(5):1434–45. https://doi.org/10.1183/09031936.00174914.
[86] Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, et al. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. Eur Respir Rev 2017;26(146):https://doi.org/10.1183/16000617.0057-2017.
[87] Feng F, Zhang J, Wang Z, Wu Q, Zhou X. Efficacy and safety of N-acetylcysteine therapy for idiopathic pulmonary fibrosis: an updated systematic review and meta-analysis. Exp Ther Med 2019;18(1):802–16. https://doi.org/10.3892/etm.2019.7579.
[88] King Jr. TE, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet 2009;374(9685):222–8. https://doi.org/10.1016/S0140-6736(09)60551-1.
[89] Tzouvelekis A, Toonkel R, Karampitsakos T, Medapalli K, Ninou I, Aidinis V, et al. Mesenchymal stem cells for the treatment of idiopathic pulmonary fibrosis. Front Med (Lausanne) 2018;5:142. https://doi.org/10.3389/fmed.2018.00142.
[90] Laporta Hernandez R, Aguilar Perez M, Lazaro Carrasco MT, Ussetti Gil P. Lung transplantation in idiopathic pulmonary fibrosis. Med Sci (Basel) 2018;6(3):https://doi.org/10.3390/medsci6030068.
[91] Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989;245(4922):1066–73. https://doi.org/10.1126/science.2475911.
[92] Elborn JS. Cystic fibrosis. Lancet 2016;388(10059):2519–31. https://doi.org/10.1016/s0140-6736(16)00576-6.
[93] Davies JC, Alton EW, Bush A. Cystic fibrosis. BMJ 2007;335(7632):1255–9. https://doi.org/10.1136/bmj.39391.713229.AD.

[94] Trapnell BC, Chu CS, Paakko PK, Banks TC, Yoshimura K, Ferrans VJ, et al. Expression of the cystic fibrosis transmembrane conductance regulator gene in the respiratory tract of normal individuals and individuals with cystic fibrosis. Proc Natl Acad Sci USA 1991;88(15):6565–9. https://doi.org/10.1073/pnas.88.15.6565.
[95] Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet 2015;16(1):45–56. https://doi.org/10.1038/nrg3849.
[96] Cystic Fibrosis Foundation. https://www.cff.org/What-is-CF/Genetics/Types-of-CFTR-Mutations/.
[97] https://www.who.int/genomics/public/geneticdiseases/en/index2.html#CF.
[98] Taylor-Robinson D, Archangelidi O, Carr SB, Cosgriff R, Gunn E, Keogh RH, et al. Data resource profile: the UK cystic fibrosis registry. Int J Epidemiol 2018;*47*(1):9–10e. https://doi.org/10.1093/ije/dyx196.
[99] Frey S, Stargardt T, Schneider U, Schreyogg J. The economic burden of cystic fibrosis in Germany from a payer perspective. PharmacoEconomics 2019;37(8):1029–39. https://doi.org/10.1007/s40273-019-00797-2.
[100] Angelis A, Kanavos P, Lopez-Bastida J, Linertova R, Nicod E, Serrano-Aguilar P. Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom. BMC Health Serv Res 2015;15:428. https://doi.org/10.1186/s12913-015-1061-3.
[101] Clunes MT, Boucher RC. Cystic fibrosis: the mechanisms of pathogenesis of an inherited lung disorder. Drug Discov Today Dis Mech 2007;4(2):63–72. https://doi.org/10.1016/j.ddmec.2007.09.001.
[102] Knowles MR, Robinson JM, Wood RE, Pue CA, Mentz WM, Wager GC, et al. Ion composition of airway surface liquid of patients with cystic fibrosis as compared with normal and disease-control subjects. J Clin Invest 1997;100(10):2588–95. https://doi.org/10.1172/jci119802.
[103] Worlitzsch D, Tarran R, Ulrich M, Schwab U, Cekici A, Meyer KC, et al. Effects of reduced mucus oxygen concentration in airway Pseudomonas infections of cystic fibrosis patients. J Clin Invest 2002;109(3):317–25. https://doi.org/10.1172/jci13870.
[104] Shukla SD, Walters EH, Simpson JL, Keely S, Wark PAB, O'Toole RF, Hansbro PM. Hypoxia-inducible factor and bacterial infections in chronic obstructive pulmonary disease. Respirology 2019;https://doi.org/10.1111/resp.13722.
[105] Ghadiri M, Young PM, Traini D. Strategies to enhance drug absorption via nasal and pulmonary routes. Pharmaceutics 2019;11(3):https://doi.org/10.3390/pharmaceutics11030113.
[106] Schneider CS, Xu Q, Boylan NJ, Chisholm J, Tang BC, Schuster BS, et al. Nanoparticles that do not adhere to mucus provide uniform and long-lasting drug delivery to airways following inhalation. Sci Adv 2017;3(4):e1601556. https://doi.org/10.1126/sciadv.1601556.
[107] World Health Organization. Global tuberculosis report. Retrieved from: Geneva, Switzerland: World Health Organization; 2019, https://www.who.int/tb/publications/global_report/en/.
[108] Pieters J. *Mycobacterium tuberculosis* and the macrophage: maintaining a balance. Cell Host Microbe 2008;3(6):399–407. https://doi.org/10.1016/j.chom.2008.05.006.
[109] Forrellad MA, Klepp LI, Gioffre A, SabioyGarcia J, Morbidoni HR, de la Paz Santangelo M, et al. Virulence factors of the *Mycobacterium tuberculosis* complex. Virulence 2013;4(1):3–66. https://doi.org/10.4161/viru.22329.

[110] Echeverria-Valencia G, Flores-Villalva S, Espitia CI. Virulence factors and pathogenicity of Mycobacterium. In: Mycobacterium—research and development. Wellman Ribón: IntechOpen; 2018. p. 231–55.
[111] Zhai W, Wu F, Zhang Y, Fu Y, Liu Z. The immune escape mechanisms of *Mycobacterium tuberculosis*. Int J Mol Sci 2019;20(2):https://doi.org/10.3390/ijms20020340.
[112] Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GA. Lung remodeling in pulmonary tuberculosis. J Infect Dis 2005;192(7):1201–9. https://doi.org/10.1086/444545.
[113] Jordan TS, Spencer EM, Davies P. Tuberculosis, bronchiectasis and chronic airflow obstruction. Respirology 2010;15(4):623–8. https://doi.org/10.1111/j.1440-1843.2010.01749.x.
[114] World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva, Switzerland: World Health Organization; 2017.
[115] World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: World Health Organization; 2014.
[116] Bhakta S, Besra GS, Upton AM, Parish T, Sholto-Douglas-Vernon C, Gibson KJ, et al. Arylamine N-acetyltransferase is required for synthesis of mycolic acids and complex lipids in *Mycobacterium bovis* BCG and represents a novel drug target. J Exp Med 2004;199(9):1191–9. https://doi.org/10.1084/jem.20031956. jem.20031956 [pii].
[117] Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J 2014;43(2):554–65. https://doi.org/10.1183/09031936.00079413.
[118] Goyal AK, Garg T, Bhandari S, Rath G. Advancement in pulmonary drug delivery systems for treatment of tuberculosis. In: Nanostructures for drug delivery. Elsevier; 2017. p. 669–95.
[119] Verma M, Vishwanath K, Eweje F, Roxhed N, Grant T, Castaneda M, et al. A gastric resident drug delivery system for prolonged gram-level dosing of tuberculosis treatment. Sci Transl Med 2019;11(483): https://doi.org/10.1126/scitranslmed.aau6267.
[120] Mehta P, Bothiraja C, Kadam S, Pawar A. Potential of dry powder inhalers for tuberculosis therapy: facts, fidelity and future. Artif Cells Nanomed Biotechnol 2018;*46*(sup 3):S791–806. https://doi.org/10.1080/21691401.2018.1513938.
[121] Pham DD, Fattal E, Tsapis N. Pulmonary drug delivery systems for tuberculosis treatment. Int J Pharm 2015;478(2):517–29. https://doi.org/10.1016/j.ijpharm.2014.12.009.
[122] du Toit LC, Pillay V, Danckwerts MP. Tuberculosis chemotherapy: current drug delivery approaches. Respir Res 2006;7:118. https://doi.org/10.1186/1465-9921-7-118.
[123] Miranda MS, Rodrigues MT, Domingues RMA, Torrado E, Reis RL, Pedrosa J, Gomes ME. Exploring inhalable polymeric dry powders for anti-tuberculosis drug delivery. Korean J Couns Psychother 2018;93:1090–103. https://doi.org/10.1016/j.msec.2018.09.004.
[124] Pandey R, Zahoor A, Sharma S, Khuller GK. Nanoparticle encapsulated antitubercular drugs as a potential oral drug delivery system against murine tuberculosis. Tuberculosis (Edinb) 2003;83(6):373–8. https://doi.org/10.1016/j.tube.2003.07.001.
[125] Saifullah B, Hussein MZ, Hussein Al Ali SH. Controlled-release approaches towards the chemotherapy of tuberculosis. Int J Nanomedicine 2012;7:5451–63. https://doi.org/10.2147/IJN.S34996.
[126] Clemens DL, Lee BY, Xue M, Thomas CR, Meng H, Ferris D, et al. Targeted intracellular delivery of antituberculosis drugs to *Mycobacterium tuberculosis*-infected

macrophages via functionalized mesoporous silica nanoparticles. Antimicrob Agents Chemother 2012;56(5):2535–45. https://doi.org/10.1128/AAC.06049-11.
[127] Society, A. C. Cancer facts & figures 2014. Atlanta: American-Cancer-Society; 2014.
[128] Prüss-Üstün A, Corvalán C. Preventing disease through healthy environments: towards an estimate of the environmental burden of disease. vol. 12. Brasil: SciELO; 2006.
[129] Collaboration, G. B. o. D. C. The global burden of cancer 2013. JAMA Oncol 2015;1(4):505–27. https://doi.org/10.1001/jamaoncol.2015.0735.
[130] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(2):87–108. https://doi.org/10.3322/caac.21262.
[131] Youlden DR, Cramb SM, Baade PD. The international epidemiology of lung cancer: geographical distribution and secular trends. J Thorac Oncol 2008;3(8):819–31. https://doi.org/10.1097/JTO.0b013e31818020eb.
[132] Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, Fan L, Li J, Chavarri-Guerra Y, et al. Challenges to effective cancer control in China, India, and Russia. Lancet Oncol 2014;15(5):489–538. https://doi.org/10.1016/S1470-2045(14)70029-4.
[133] Burci GL. World Health Organization (WHO): framework convention on tobacco control. Int Leg Mater 2003;42(3):515–39.
[134] Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. Introduction to the 2015 World Health Organization classification of tumors of the lung, pleura, thymus, and heart. J Thorac Oncol 2015;10(9):1240–2. https://doi.org/10.1097/jto.0000000000000663.
[135] Zhang Y, Li ZY, Hou XX, Wang X, Luo YH, Ying YP, Chen G. Clinical significance and effect of AEG-1 on the proliferation, invasion, and migration of NSCLC: a study based on immunohistochemistry, TCGA, bioinformatics, in vitro and in vivo verification. Oncotarget 2017;8(10):16531–52. https://doi.org/10.18632/oncotarget.14972.
[136] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6(2):244–85. https://doi.org/10.1097/JTO.0b013e318206a221.
[137] Rubin P, Hansen JT. TNM staging atlas. Philadelphia, PA: Lippincott Williams & Wilkins; 2008169–78.
[138] Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. J Clin Oncol 2013;31(8):992–1001. https://doi.org/10.1200/jco.2012.46.9270.
[139] da Cunha Santos G, Shepherd FA, Tsao MS. EGFR mutations and lung cancer. Annu Rev Pathol 2011;6:49–69. https://doi.org/10.1146/annurev-pathol-011110-130206.
[140] Sangha R, Price J, Butts CA. Adjuvant therapy in non-small cell lung cancer: current and future directions. Oncologist 2010;15(8):862–72. https://doi.org/10.1634/theoncologist.2009-0186.
[141] Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143(5 Suppl):e278S–313S. https://doi.org/10.1378/chest.12-2359.
[142] Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26(21):3552–9. https://doi.org/10.1200/jco.2007.13.9030.
[143] Rowell NP, O'Rourke NP. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2004;(4)Cd002140. https://doi.org/10.1002/14651858.CD002140.pub2.

[144] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649–55.

[145] Sundstrom S, Bremnes R, Aasebo U, Aamdal S, Hatlevoll R, Brunsvig P, et al. Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: a national phase III trial. J Clin Oncol 2004;22(5):801–10. https://doi.org/10.1200/jco.2004.06.123.

[146] Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372(9652):1809–18. https://doi.org/10.1016/s0140-6736(08)61758-4.

[147] Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363(18):1693–703. https://doi.org/10.1056/NEJMoa1006448.

[148] Shaw AT, Yeap BY, Solomon BJ, Riely GJ, Gainor J, Engelman JA, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol 2011;12(11):1004–12. https://doi.org/10.1016/s1470-2045(11)70232-7.

[149] Ellis PM, Al-Saleh K. Multitargeted anti-angiogenic agents and NSCLC: clinical update and future directions. Crit Rev Oncol Hematol 2012;84(1):47–58. https://doi.org/10.1016/j.critrevonc.2012.02.004.

[150] Sandler A, Yi J, Dahlberg S, Kolb MM, Wang L, Hambleton J, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. J Thorac Oncol 2010;5(9):1416–23. https://doi.org/10.1097/JTO.0b013e3181da36f4.

[151] Neal JW, Sequist LV. Exciting new targets in lung cancer therapy: ALK, IGF-1R, HDAC, and Hh. Curr Treat Options in Oncol 2010;11(1–2):36–44. https://doi.org/10.1007/s11864-010-0120-6.

[152] Karp DD, Paz-Ares LG, Novello S, Haluska P, Garland L, Cardenal F, et al. Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751, 871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small-cell lung cancer. J Clin Oncol 2009;27(15):2516–22. https://doi.org/10.1200/jco.2008.19.9331.

[153] Capelletto E, Novello S. Emerging new agents for the management of patients with non-small cell lung cancer. Drugs 2012;72(Suppl. 1):37–52. https://doi.org/10.2165/1163028-s0-000000000-00000.

[154] Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. Nat Rev Cancer 2006;6(1):38–51. https://doi.org/10.1038/nrc1779.

[155] Schrump DS. Cytotoxicity mediated by histone deacetylase inhibitors in cancer cells: mechanisms and potential clinical implications. Clin Cancer Res 2009;15(12):3947–57. https://doi.org/10.1158/1078-0432.Ccr-08-2787.

[156] Zhang W, Peyton M, Xie Y, Soh J, Minna JD, Gazdar AF, Frenkel EP. Histone deacetylase inhibitor romidepsin enhances anti-tumor effect of erlotinib in non-small cell lung cancer (NSCLC) cell lines. J Thorac Oncol 2009;4(2):161–6. https://doi.org/10.1097/JTO.0b013e318194fae7.

[157] Haura EB, Cress WD, Chellappan S, Zheng Z, Bepler G. Antiapoptotic signaling pathways in non-small-cell lung cancer: biology and therapeutic strategies. Clin Lung Cancer 2004;6(2):113–22. https://doi.org/10.3816/CLC.2004.n.025.

[158] Kelly RJ, Thomas A, Rajan A, Chun G, Lopez-Chavez A, Szabo E, et al. A phase I/II study of sepantronium bromide (YM155, survivin suppressor) with paclitaxel and carboplatin in patients with advanced non-small-cell lung cancer. Ann Oncol 2013;24(10):2601–6. https://doi.org/10.1093/annonc/mdt249.

[159] Paz-Ares L, Balint B, de Boer RH, van Meerbeeck JP, Wierzbicki R, De Souza P, et al. A randomized phase 2 study of paclitaxel and carboplatin with or without conatumumab for first-line treatment of advanced non-small-cell lung cancer. J Thorac Oncol 2013;8(3):329–37. https://doi.org/10.1097/JTO.0b013e31827ce554.