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Current Opinion in Pharmacology

Editorial overview: Respiratory: Pulmonary pharmacology–The emergence of new treatments in pulmonary medicine is finally providing real therapeutic perspectives

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The growing interest surrounding the lungs and their diseases, with a real explosion in the last year and a half caused by the appearance and spread of COVID-19, is motivated by our poor understanding of the triggering events and natural history of different lung diseases. Because of this lack of understanding, the treatment of various lung diseases is still insufficient to induce complete recovery of the patient. An exception to this is the treatment of infectious diseases, although the emergence of bacterial resistance, and an upsurge of novel bacterial, viral, and fungal respiratory pathogens that are becoming increasingly challenging to treat, are making our therapeutic approach to these diseases increasingly problematic [1]. Nonetheless, the development of new treatments for different pulmonary diseases/disorders seems finally to provide real novel therapeutic perspectives.

Despite the high prevalence of asthma and chronic obstructive pulmonary disease (COPD), treatment of these two disorders is still largely based on bronchodilators and inhaled corticosteroids, although new treatment options have emerged for more severe forms of asthma. These new options are the focus of the article by Calzetta et al. [2]. The therapeutic benefits of currently approved biological therapies are driving research to identify additional potential molecular targets and to develop the next generation of biologicals directed against these emerging targets upstream of both T2-high and/or T2-low inflammation.

Improving the treatment of COPD is more problematic. Research is currently focused on the persistent inflammation that characterises COPD. Several molecules have been synthesised that have been shown to regulate the inflammatory process in animal models of COPD, but currently available anti-inflammatory therapies provide little or no benefit in COPD patients. It is likely that the redundancy of effects induced by signal-transmitting substances can still induce or maintain the

2021), he is the top-rated expert in COPD and in bronchodilator agents in the world.

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inflammatory state even when a specific pathway is switched off. Nevertheless, as pointed out by Matera et al. [3], there are therapeutic possibilities that have already been tested in humans and could be useful in specific subgroups of COPD patients.

The many similarities between the ageing process in the lungs and COPD suggest that accelerated ageing may be a pathogenic mechanism in COPD [4]. Cellular senescence associated with shortened telomeres and epigenetic changes, including DNA methylation, histone modifications, and altered expression of noncoding RNA molecules presumably participates in COPD pathogenesis. Certainly, ageing causes high levels of inflammation and oxidative stress and is associated with changes in the innate and adaptive immune responses (immunosenescence) that characterise COPD [5]. For these reasons, COPD may be an expression of accelerated premature ageing of the lungs. Based on these concepts, Barnes has elegantly illustrated in his article [6] the different existing or future drugs that may inhibit the development of cellular senescence, dividing them into senostatics if they are able to inhibit pathways that lead to cellular senescence and senolytics if they selectively remove senescent cells. His suggestions to use senotherapies in the early stages of the disease are worthy of attention and future studies because this approach may even reverse the disease process.

More immediate possibilities for influencing oxidative stress and thus also acting in a senolytic mode lie in the use of thiol-based drugs, although at present their use is not really proving to be totally effective [7]. However, increased knowledge about the role of oxidative stress caused by reactive oxygen species (ROS) in lung disease is facilitating the development of other possible antioxidant therapeutic strategies. Sharma et al. [8], after a clear and concise description of current knowledge on the topic, outlined several present and future classes of ROS modulators to be used for treating different lung diseases. Nevertheless, they correctly pointed out that this use is still in its infancy, and more research is needed to establish the role of ROS modulators in pulmonary medicine.

Although an important pathogenetic role for senescence has been identified also in idiopathic pulmonary fibrosis (IPF), a progressive interstitial lung disease that has a poor prognosis, and there is documentation that *N*-acetylcysteine, a thiol-based drug, in combination with an antifibrotic drug may be a reasonable option in a minority of IPF patients, probably those with the rs3750920 (TOLLIP) TT genotype [9], the current treatment of this disease is based on the use of two antifibrotic drugs, nintedanib and pirfenidone [10]. Antifibrotic treatment with pirfenidone and nintedanib has been shown to slow disease progression, although prognosis remains poor. Antoniou et al. [10] in their review highlighted the current understanding of IPF and pointed out the need to improve biogenomic and metabolic research, and to translate it into clinical accuracy and optimal service through patient-centredness to support effective treatment of IPF [10]. They also described the novel therapeutic options currently under investigation based on the major pathogenic pathways and molecular targets driving IPF and the therapeutics being explored in clinical trials for the treatment of this devastating disease.

Regenerative or stem cells have been proposed as a potential therapy for IPF owing to their multipotency and role in tissue repair and wound healing [10]. Current evidence suggests that these cells may participate in lung tissue homeostasis and regeneration after injury [11]. A growing body of evidence from animal and human studies has shown that tissue-specific stem cells and bone marrow-derived cells contribute to the regeneration

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and protection of lung tissue, and therefore the administration of exogenous stem/progenitor cells or humoral factors responsible for the activation of endogenous stem/progenitor cells may be a potent next-generation therapy. In their overview, Khedoe et al. [12] discussed existing treatment targets, as well as new strategies for the development of pharmacological and cell therapy-based regenerative treatment for a variety of lung diseases. Emphasis has been placed on the use of more advanced culture models, such as lung-on-chip models that recapitulate the mechanochemical environment and physiological functions of human lungs or a more realistic culture environment for lung alveolar cells based on biomimetically curved track-etched membranes, restoring the geometry of the cells' native microenvironment. These models have the potential to better mimic the lung environment and may help reduce the need for animal models. Obviously, there is a need to consider different treatment approaches and combinations for pulmonary regenerative medicine. In addition, the choice for a therapy may be determined by the stage of the disease with pharmacological interventions (retinoids and retinoic acid receptor agonists, senolytics and senostatics) being feasible at earlier disease stages than cell therapy.

Although idiopathic pulmonary arterial hypertension (PAH) is a rare disease characterised by elevated pulmonary artery pressure with no apparent cause [13], the high prevalence of PAH in COPD patients [14] and in those with IPF [15] is the reason why there is a real interest in finding effective and disease-modifying therapies. Actually, the drugs currently available for the treatment of PAH are relatively ineffective and most patients eventually become drug-resistant and die. In their article, Ali et al. [13] described the most promising new therapies targeting key pathological pathways involved in PAH. In recent years, many cellular and molecular mechanisms such as bone morphogenetic protein receptor 2 signalling, DNA damage, modulation of sex hormones, the immune system and inflammation have been described as playing key roles in the pathogenesis of the disease. Consequently, several potential and exciting new therapeutic strategies focusing on anti-remodelling and supporting right ventricular dysfunction mechanisms have been identified in preclinical studies and are currently proposed or have progressed to early clinical trials with promising results.

Cystic fibrosis, the most common autosomal recessive disease in the Caucasian population, which is characterised by a functionally defective ion channel, caused by inheritable mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and clinically by a combination of recurrent respiratory infections, and pancreatic insufficiency, is more frequent than previously thought and now recognised in many regions of the world [16]. The most common mutation at least in Western countries is a codon deletion in exon 10 for phenylalanine at position 508 (*p.Phe508del*) in the encoded CFTR polypeptide [17]. The development of new therapies targeting the underlying defect in cystic fibrosis is a key research area considering the need for progress in the treatment of this disease [16]. Gramegna et al. [18], through a narrative review that summarised the current preclinical and clinical evidence for adding a next-generation CFTR corrector, elexacaftor, to the existing CFTR modulator dual combination of tezacaftor plus ivacaftor, illustrated the additional benefit that this triple combination provides to people with cystic fibrosis homozygous for the *p.Phe508del* mutation. They also highlighted the need to demonstrate the effectiveness of this therapeutic approach in as many genotypes as possible to further expand the treatable population.

We have already highlighted the emergence of bacterial strains resistant to currently available anti-bacterials. Drug resistance is one of the major threats to the treatment of tuberculosis (TB) [19]. Like all pathogens, *Mycobacterium tuberculosis* has continually evolved to resist antagonistic drugs, resulting in the emergence of resistant strains that have given rise to 'multidrug-resistant TB (MDR-TB)', and 'extensively drug-resistant TB (XDR-TB)', and eventually even unmanageable 'totally drug-resistant TB' [20]. Mondoni et al. [21] in their article focused on the recent therapeutic advances in the field of MDR/XDR-TB. They described the main pharmacological characteristics and clinical aspects of new drugs such as bedaquiline, delamanid, pretomanid and new regimens based on combinations of new, old, and repurposed drugs, as well as complementary therapeutic strategies to standard chemotherapy (i.e. new approaches to drug delivery, direct host therapy, surgery, new collapse therapy, rehabilitation and palliative care).

There are still substantial issues that must be overcome in order to continually innovate and improve targeted inhaled drug delivery to the lungs [22]. A potentially extremely useful innovation in pulmonary medicine is the development of nanotechnology, which has been developed to produce particles with submicron diameter sizes in the range of 1−100 nm, as drug delivery vehicles [22]. The transport of nanoparticles to the lungs, the loading of appropriate therapeutic drugs and the incorporation of intelligent functions to surmount the various lung barriers have relevant perspectives as they can help to find exactly target tissues and can improve the therapeutic effect by reducing systemic adverse events [23]. Doroudian et al. [24] provided a concise but interesting historical overview of the application of nanomedicine to respiratory diseases and potential applications in the diagnosis, treatment, and clinical staging of disease. The description of the latest cutting-edge approaches such as nanoparticle-mediated combination therapies, the novel dual-target non-pharmaceutical delivery system for targeting, stimulant-reactive nanoparticles, and therapeutic imaging in the diagnosis and treatment of lung diseases supports their view that nanotherapeutics as applied to the lung and other organs will 'open new doors' and change the way we practice medicine in the near future.

Conflict of interest statement

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