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*Teaser Identifying novel inhaled therapies could address significant unmet need in respiratory diseases. Such undertakings are regarded as particularly challenging and risky; therefore, here we discuss potential approaches to overcoming these challenges.*



# Current approaches to the discovery of novel inhaled medicines

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**Inhaled administration is underutilised because the drug discovery process is viewed as challenging, risky, and expensive. However, unmet medical need continues to grow, and significant opportunities exist to discover novel inhaled medicines delivering the required lung concentrations while minimising systemic exposure. This profile could be achieved by a combination of properties, including lung retention and low oral bioavailability. Property-based rules exist for orally administered compounds, but there has been limited progress defining *in silico* predictors to guide the discovery of novel inhaled drugs. Recently, the use of informative cell- and tissue-based screens has greatly facilitated the identification of compounds with optimal characteristics for inhaled delivery. Here, we address opportunities for novel inhaled drugs, and the key challenges and uncertainties hampering progress.**

## Background

### *The inhaled revolution for the treatment of asthma and chronic obstructive pulmonary disease*

The first inhaled β2-adrenergic agonist, salbutamol (albuterol), was introduced for the treatment of asthma during the 1960s [1]. Although inhaled salbutamol demonstrated clear therapeutic and safety advantages, compared with treatment using subcutaneous or intravenous dosing, its utility was restricted by its short duration of action (~4 h). This prompted efforts to identify longer acting compounds, resulting in the development of salmeterol, the first, long-acting, inhaled β2-adrenergic agonist (LABA) [2], which enabled twice-daily dosing for the management of asthma (Fig. 1).

Asthma is an inflammatory condition and the availability of oral cortisone therapy during the 1950s resulted in striking clinical efficacy. The subsequent introduction of potent oral corticosteroids, such as prednisolone, was accompanied by unacceptable systemic adverse effects, which led to the development of inhaled corticosteroids (ICS), such as beclometasone dipropionate (BDP), during the early 1970s [3]. By reducing the unacceptable systemic adverse effects, the ICS class transformed the management of mild–moderate asthma. The development of combined ICS–LABA therapy [e.g., salmeterol/fluticasone propionate (FP)] yielded unexpected therapeutic

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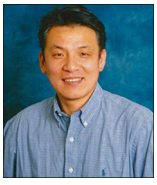

**Kazuhiro Ito** is a co-founder of, and director of biology at, Pulmocide. Kaz worked for 13 years for Sankyo Co. Ltd (Japan) before moving to National Heart and Lund Institute, Imperial College in 2002, as a principle investigator (and then reader, and currently honorary principal research fellow), specialising in epigenetics, steroid resistance, ageing and biomarkers in respiratory disease. Kaz has published extensively and is a highly cited researcher in the chronic obstructive pulmonary disease (COPD)/asthma area. Kaz was a co-founder of Respivert and was responsible for the discovery and development of novel inhaled anti-inflammatory molecules to treat steroid-insensitive chronic inflammatory respiratory disease.

**Garth Rapeport** is the CEO of Pulmocide, a company that focuses on new treatments for lung *Aspergillus* and respiratory syncytial virus (RSV) infections. He a medical graduate who undertook postgraduate training in general medicine and clinical pharmacology at the Universities of Glasgow and Oxford. He joined Pfizer Central Research in 1988, contributing to the early development of a range of compounds. Moving to GSK, he headed the Respiratory Centre of Excellence for Drug Discovery, leading to the development of new, long-acting inhaled therapies for COPD and asthma. He co-founded Respivert in 2006, which was acquired by Centocor Ortho Biotech, a division of Johnson & Johnson, in June 2010.


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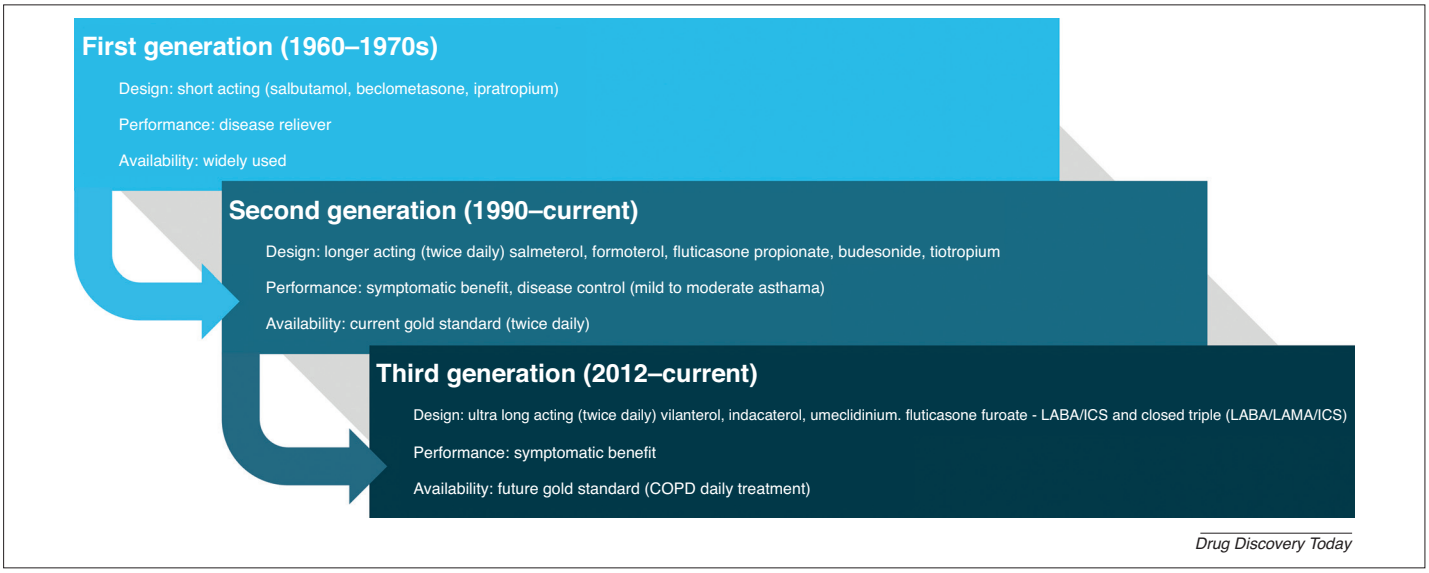


**FIGURE 1**

Generations of inhaled therapies for asthma and chronic obstructive pulmonary disease (COPD). Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β-adrenoceptor agonist, LAMA, long-acting muscarinic receptor antagonist.

synergy [4,5] for patients with mild–moderate asthma. This use of fixed-dose ICS/LABA combinations, such as salmeterol/FP and formoterol/budesonide, evolved as the new standard of care for patients whose asthma was inadequately controlled by low-dose inhaled steroids.

The recent development of once-daily, ultra-long-acting LABA and ICS treatments, such as vilanterol/fluticasone furoate, has enabled the introduction of convenient once-daily inhaled products. Despite these significant advances, patients with severe asthma (10–20% of the total patient population) require improved therapies and the search for more effective anti-inflammatory agents is a major area of current research (Fig. 1).

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by persistent inflammation, recurring infection, lung tissue destruction, and the scarring of small airways. Bronchoconstriction in patients with COPD is controlled by cholinergic neural pathways. Ipratropium bromide, a short-acting muscarinic receptor antagonist, was introduced during the 1970s as a bronchodilator therapy for COPD. Since then, several long-acting muscarinic receptor antagonists (LAMA) have been introduced, including tiotropium, umeclidinium and aclidinium. Compared with ipratropium, tiotropium exhibits higher affinity for muscarinic receptors, and slower dissociation from M3 muscarinic receptors [6], which is believed to enable once-daily dosing with LAMAs. Despite the availability of ICS and LAMA agents, COPD is recognised as a complex disease, with progressive inflammation that is refractory to corticosteroids.

The development of inhaled products culminated in the introduction of Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol), the first closed triple combination to be approved for once-daily therapy (Fig. 1) [7]. Although offering greater convenience, these products do not appear to offer significant additional therapeutic benefits and the need remains for new disease-modifying treatments for asthma and COPD [8].

### *A range of opportunities exists for new inhaled drugs*

The standard approach to the treatment of asthma and COPD has not changed significantly since the introduction of inhaled corticosteroids, β2 agonists, and muscarinic antagonists [9], despite the range of opportunities that exists for new inhaled drugs (Box 1). Although mild–moderate asthma can be effectively managed, the treatment of progressive, corticosteroid-insensitive inflammation in patients with severe asthma remains a therapeutic challenge [10].

In common with severe asthma, the identification of effective treatments for COPD has been hampered by a poor understanding of the underlying inflammatory mechanisms responsible for disease progression [11–13]. COPD is marked by persistent inflammation in lung epithelium and influx of macrophages, both of which persist after smoking cessation and are refractory to corticosteroids. Disease heterogeneity is an additional complication for COPD and severe asthma populations, because the multiple disease phenotypes identified suggest the need for different treatment approaches. In recent years, research has been focussed on the identification of anti-inflammatory agents that address corticosteroid-insensitive inflammation and can slow or reverse disease progression [14].

Cystic fibrosis (CF) is an autosomal, recessive, hereditary disorder resulting from a mutation in a single gene [the CF transmembrane regulator (*CFTR*)]. Characterised by thick viscid mucus, recurrent lung infections and progressive damage to airways and lung parenchyma [15], the disease occurs at a rate of 1 in 3000 births. Despite the introduction of the CFTR conductance regulator, ivacaftor, treatment needs include more-effective anti-inflammatory agents in addition to inhaled antibiotic and anti-fungal therapies.

Significant unmet need also exists for the management of idiopathic pulmonary fibrosis [16] and idiopathic pulmonary hypertension. Currently available treatments are not curative but aim to slow disease progression. The opportunity exists for


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