



## Editorial

## The Future of Bronchodilators in COPD and Asthma

### El futuro de los broncodilatadores en la EPOC y el asma



Bronchodilators are still key elements in the treatment of both COPD and asthma and are likely to remain so for years to come. Therefore, requirement of new bronchodilators is critical. However, in recent decades there has been no discovery of new classes that could overcome efficacy and even safety concerns of what we currently have, namely  $\beta_2$ -agonists and  $M_3$  muscarinic receptor (mAChR) antagonists, and albeit less effective, theophylline, which is a non-selective phosphodiesterase (PDE) inhibitor.

The development of new classes of bronchodilators is proving difficult and also burdened by great economic uncertainties because the costs involved in their research and development may outweigh any incremental improvement such drugs might have. Consequently, the logical approach has been to improve these “old” classes to ensure greater specificity and effectiveness as well as greater practicality of use.

#### Improving “Old” Classes of Bronchodilators

Over the past two decades,  $\beta_2$ -agonists and  $M_3$  mAChR antagonists with longer half-lives and inhalers containing a combination of several classes of long-acting bronchodilator have been developed, and there is still a considerable amount of research to develop more potent long-acting  $\beta_2$ -agonists (LABAs) and long-acting muscarinic receptor antagonist (LAMAs).<sup>1</sup>

A number of LABAs, such as bedoradrine, abediterol, and trantinterol,<sup>2</sup> and LAMAs, such as imidafenacin, revfenecin, mequitazine and CHF-5407,<sup>3</sup> are currently under clinical development, but these compounds cannot be understood as real innovation.

On the contrary, allosteric ligands that allow a specific modulation of G protein-coupled receptors (GPCRs) not obtainable with orthosteric ligands and therefore a greater degree of selectivity of the subtype compared to classical orthosteric ligands activating ( $\beta_2$ -agonists) or blocking ( $M_3$  mAChR antagonists) the specific receptor could represent the possible advancement in these two classes of bronchodilators.<sup>1,2</sup> Such allosteric agents can influence the potency and efficacy of orthosteric ligands, may possess agonistic or inverse agonist activity in their own right, and reduce the risk of adverse events compared with orthosteric ligands.

Currently, there is a great scientific and economic interest in the use of LABA/LAMA fixed dose combinations because they induce appreciable synergistic bronchorelaxant effect in human airways, especially when the medications are combined at isoeffective

concentrations.<sup>4</sup> Furthermore, they optimize bronchodilation and represent an easier approach to the development of triple therapies that also include an inhaled corticosteroid to be used both in COPD and asthma.<sup>4</sup>

A novel approach to “dual” bronchodilator therapy relates to the development of a series of new bifunctional (or dual pharmacophore) drugs called MABAs, which have both mAChR antagonism and  $\beta_2$ -agonist activity in the same molecule.<sup>5</sup> Batefenterol is the MABA in the most advanced clinical development stage.<sup>1</sup> Navafenterol, AZD-2115, AZD8999, AZD-2115, and CHF6366 are other MABAs under clinical development.<sup>3</sup> MABA compounds are believed to be a better opportunity than LABA/LAMA combinations to be coformulated in “triple therapy” combinations. Indeed, batefenterol/fluticasone furoate is already under clinical development.<sup>5</sup>

To overcome the limits of theophylline, research has focused on more effective and safe PDE inhibitors.<sup>6</sup> Although roflumilast, the only PDE4 inhibitor to enter the market, is burdened with consistent adverse effects, research has continued and is currently concentrated on inhaled PDE4 inhibitors such as tanimilast, and PDE3/PDE4 inhibitors such as ensifentrine that induces bronchodilatory and anti-inflammatory effects simultaneously.<sup>6,7</sup>

Since compounds that inhibit PDE4 enzymes together with a second PDE family could provide a therapeutic benefit at a concentration that does not cause emesis, the research is focused on the development of drugs capable of interacting simultaneously with different PDEs and also molecules specifically designed to have multivalent (multifunctional) ligands, which contain two or more pharmacophores (dual PDE4 inhibitors/ $\beta_2$ -agonists and dual PDE4 inhibitors/mAChR antagonists).<sup>6,7</sup>

#### Developing New Classes of Bronchodilators

Alongside these approaches aimed at improving what is already available, the interest in identifying and possibly developing new classes of bronchodilators, even with all the difficulties that this entails, has never ceased.

The focus is currently mainly on eight possible new classes (1) bitter-taste receptor (TAS2Rs) agonists; (2) E-prostanoid receptor 4 agonists; (3) Rho kinase inhibitors; (4) calcilytics; (5) agonists of peroxisome proliferator-activated receptor- $\gamma$ ; (6) agonists of relaxin receptor 1; (7) soluble guanylyl cyclase activators; and (8) pepducins.<sup>1,7</sup> Three of these eight classes deserve particular consideration.

TAS2R agonists are promising, at least on a preclinical level.<sup>8</sup> TAS2Rs, which are members of a GPCR subfamily and evoke relaxation by means of a mechanism that is  $G_{\beta\gamma}$  protein-, phospholipase C  $\beta$ -, and inositol trisphosphate receptor-dependent, are expressed on human airway smooth muscle (ASM) cells, with subtypes 10, 14, and 31 being the most abundant.<sup>9</sup> There are approved drugs including some prescribed antibiotics, such as azithromycin, and anti-inflammatory and analgesic compounds, such as flufenamic acid, that are TAS2R ligands but their potency against TAS2Rs is not enough for their repurposing to TAS2R-driven diseases. It is still problematic to find specific TAS2R ligands despite being listed more than 600 molecules that taste bitter to humans.<sup>9</sup> Difficulties in developing specific agonists reside above all in identifying palatable compounds and in the fact that bitter compounds can be agonistic to one TAS2R but antagonistic to another TAS2R.<sup>9</sup>

There is also some interest in identifying drugs capable of interfering with the Ras-homologous (Rho)A/Rho-associated coiled-coil forming kinase (ROCK) pathway that plays an important role in the regulation of myosin light chain (MLC) phosphatase that is critical in removing phosphate from the phosphorylated MLC to induce ASM relaxation.<sup>1,7</sup> Several preclinical studies suggest that ROCK inhibitors may be effective bronchodilators and also that these agents may act synergistically with other classes of bronchodilators.<sup>1,7,10</sup> Three Rho-kinase inhibitors, fasudil, ripasudil and netarsudil, have been approved in some countries for clinical use,<sup>11</sup> but not as bronchodilators. There are other novel ROCK inhibitors under development, including hydroxyfasudil, HA-1152P, netarsudil (AR-13324), AMA0076 and Y-39983. However, their implementation is limited because of the highly identical kinase domains in ROCK-1 and ROCK-2, which makes it difficult to assign specificity to the inhibitors.<sup>12</sup> The potential for undesirable cardiovascular adverse events caused by the abundant expression of these enzymes in the cardiovascular system is suggesting the development of such compounds for inhalation.<sup>1,7</sup>

Pepducins are the third class to mention. They are cell-penetrating, membrane-tethered lipid (usually palmitate)-peptides that are conjugated with sequences derived from the intracellular loops of the targeted GPCR. These compounds are designed to target the intracellular region of a GPCR in order to allosterically modulate the receptor's signaling output.<sup>1,7,13</sup> Pepducins stabilize the GPCR conformation and affect its signaling by interacting with the receptor-G protein intracellular interface. They can function as broad-based antagonists of  $G_q$  signaling, and consequently  $G_q$ -mediated contraction in ASM.<sup>13</sup> However, pepducins from the third intracellular loop (ICL3) of the  $\beta_2$ -adrenoceptor mediate  $G_s$ -biased signalling, and those from the first intracellular loop (ICL1) mediate  $\beta$ -arrestin-biased signaling.<sup>1,7,13</sup> P4pal-10 is a protease activated receptor 4-derived pepducin that exhibits efficacy toward multiple  $G_q$ -coupled receptors including  $M_3$  mAChR.<sup>14</sup> ATI-2341 has been predicted to interact with most of the residues located in ICL1-ICL3 and promote specific  $G_i$ -mediated signaling without  $G_{13}$ -coupling or  $\beta$ -arrestin recruitment.<sup>7</sup> Despite pepducins have a polypharmacological

nature ascribable to their derivation from regions of homology between closely-related receptors and some of them may have therapeutic limitations (tissue access, potency, efficacy), it has been shown that these intracellular agents can bring new pharmacological opportunities. The occurring development of lipidated peptide agonists and antagonists of other classes of cell-surface receptors<sup>15</sup> suggests that in the not too distant future pepducins will be available that will allow for more specific regulation of ASM contractility and airway resistance in obstructive lung diseases.<sup>13</sup>

## Financial/nonfinancial Disclosures

None to declare.

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