

## Correspondence

## Reply

To the Editor:

We appreciate the comments of Lipworth et al<sup>1</sup> about the role of the  $\beta_2$ -adrenergic receptor ( $\beta_2$ AR) in asthmatic patients<sup>2</sup> and agree that important clinical questions remain unanswered. Human studies are needed to establish whether other  $\beta_2$ AR ligands, in addition to  $\beta_2$ -agonists, are viable asthma drugs. Basic science investigations using human and nonhuman models also are required to fully understand the complexity of  $\beta_2$ AR signaling and function in the lung.

Lipworth et al<sup>1</sup> refer to preclinical studies that demonstrate that chronic but not acute administration of nadolol, an inverse agonist, attenuates airway hyperresponsiveness, airway inflammation, and mucin content, 3 key features of asthma in a mouse model of allergic lung inflammation.<sup>3</sup> Similar results of an attenuated asthma-like phenotype were obtained by using pharmacologic and genetically modified mice deficient in the epinephrine- $\beta_2$ AR axis.<sup>4</sup> Conversely, prolonged treatment with formoterol, a long-acting  $\beta$ -agonist (LABA), restored the asthma features in these animals.

The potential clinical relevance of these findings was tested in patients with mild asthma during an open-label pilot study that demonstrates a dose-dependent reduction of airway hyperresponsiveness with the chronic administration of nadolol.<sup>5</sup> This is associated with a quantitative effect comparable with the improvement with chronic inhaled corticosteroids (ICSs) demonstrated in some clinical trials. Although encouraging, treatment of asthma with chronic administration of an inverse  $\beta_2$ -agonist demands double-blind, placebo-controlled clinical trials with asthmatic patients of varying disease severity to prove its safety and efficacy. Moreover, it is thought that the harmful effects of chronic  $\beta_2$ -agonist treatment result from  $\beta_2$ AR signaling away from the canonical Gs protein - cAMP pathway and biased toward the  $\beta$ -arrestin-2 pathway. Therefore efforts should continue to develop asthma medications that preferentially activate the canonical signaling cascade, inhibit the  $\beta$ -arrestin-2 pathway, or both. The cell type or types involved in the detrimental effects of  $\beta_2$ -agonists also should be delineated.<sup>6</sup>

$\beta_2$ AR agonists are excellent bronchodilator medications. The Global Initiative for Asthma guidelines recommend the use of

LABA only with ICSs. The beneficial effects of ICSs might stem from their capacity to prevent  $\beta_2$ -agonist-induced downregulation of  $\beta_2$ ARs and mRNA expression. Importantly, a combination therapy of the ICS budesonide with formoterol is more effective than budesonide alone to improve asthma symptoms, pulmonary function, and eosinophilic inflammation and to reduce airway wall thickness (remodeling) in patients with mild-to-moderate persistent asthma.<sup>7</sup> Furthermore,  $\beta_2$ ARs can associate with different intracellular molecules. These interactions might influence receptor localization and downstream signaling cascades without necessarily affecting  $\beta_2$ AR density or intracellular cAMP levels.

Scientific biomedical progress happens always more slowly than desirable. However, in the meantime,  $\beta_2$ AR agonists remain a cornerstone of asthma therapy.

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