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Editorial overview: Respiratory: GPCR signaling and the lung

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The influence of G-protein-coupled receptor (GPCR) signaling in lung biology has a rich history, which is also reflected by a recurring theme among Nobel laureates. For the airways and heart, the pre-GPCR observation of Wilhelm Einthoven in 1892 that electrical stimulation of the vagus nerve resulted in bradycardia (decrease in heart rate, HR;) and bronchoconstriction (airway narrowing) was a seminal observation in the journey towards cardiopulmonary GPCR therapeutics [1]. A contextual review of the 1994 Noble Prize [2] for Gilman and Rodbell concluded that ‘Elucidation of the universal role and mechanism by which G proteins transduce signals across the plasma membrane has provided a unifying view of diverse biological processes of extraordinary explanatory power.’ The 2012 Nobel prize for Lefkowitz and Kobilka for studies of GPCRs marked the cloning of a major target in asthma, the β_2 adrenergic receptor (β_2 AR) coupled with the evolving role of intracellular second messenger amplification, signaling and structure that continues to shed new light on the therapeutics associated with GPCRs in the airways [3]. GPCR structural biology has a major impact on the understanding and design of novel therapeutic approaches that target the airways (see Kruse *et al.* and Rominger *et al.*, in this issue).

The reviews contained in this Special Respiratory Issue on obstructive airway disease collectively summarize new complexities with respect to GPCR signaling pathways and highlight the therapeutic opportunities afforded by this new understanding. Rominger *et al.* provide a novel view of the potential for biased signaling to influence drug discovery and draw attention to the therapeutic opportunities within and beyond lung disease (Figure 1).

Pera and Penn shed light on the mystery of muscarinic and beta-2-adrenergic receptor crosstalk in mediating airway inflammation, resistance and remodeling and explore the possibility of using biased ligands to avoid pathogenic signaling. Similarly, Dale *et al.* compare muscarinic and adrenergic receptor regulation of smooth muscle tone in two different organs (airway and bladder) to gain insight into the use of combined therapy targeted at both receptors. Thanawala *et al.* elegantly explain evolving receptor theory and apply it to beta-blocker effectiveness, which, as they point out, is better examined in terms of ligand bias than ‘class effects’. Walker and DeFea relate the paradoxical effects of receptor activation to dual GPCR signaling pathways and highlight the possibilities of exploiting this signaling paradigm for biased ligand therapeutics. Although dual signaling pathways make receptor signaling more complex, selective targeting of one pathway over

the other using biased ligands provides the opportunity for the development of drugs that are more efficacious, while having fewer side-effects.

Kruse *et al.* provide a state-of-the-art overview of advances in M2 and M3 muscarinic receptor structure deduced by X-ray crystallography, as well as novel insight into the interactions between the current anti-muscarinic antagonist of choice for obstructive lung disease, tiotropium, and the M3 muscarinic receptor. Kummer and Kastreva-Christ outline the remarkable potential for the non-neuronal cholinergic system to influence airway function via auto-/paracrine inputs. Downstream GPCR signaling is reviewed by Giembycz and Maurice with respect to phosphodiesterase (PDE) biology, potential novel therapeutics for PDE inhibitors and the future impact of cellular compartmentalization of PDE function. Piedimonte and Perez outline the novel developmental biology associated with mechanisms of respiratory syncytial virus transmission via the placenta, which raises many questions regarding the etiology of postnatal airway disease, airway responsiveness and GPCR function. Wasilewski *et al.* discusses asthma guidelines from a global and functional perspective relative to β_2 AR agonists and the potential emerging role(s) and mechanisms for anti-muscarinic and β_2 AR therapy.

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Biographies

Dr. Julia Walker received her PhD in Physiology from Queen's University at Kingston and postdoctoral training in the Department of Cell Biology at Duke University. As an Assistant, and then Associate, Professor in Duke's Division of Pulmonary, Allergy and Critical Care Medicine, Dr. Walker has studied the role for GPCR regulatory proteins in the pathophysiology of asthma with the support of grants from NIH, VA and pharmaceutical companies. Dr. Walker was recently appointed to associate professor in the Duke University School of Nursing, where she continues to study how GPCR biased signaling can be exploited for improved asthma treatments.

Dr. John Fisher is a Professor of Biomedical & Molecular Sciences and Respiriology (Dept. Medicine), a member of the Cardiac Circulatory & Respiratory research group and Director

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Figure 1.

Factors contributing to the muscarinic receptor (MR) as a therapeutic target via G-protein-coupled receptor (GPCR) signaling and structure: Excessive airway narrowing or bronchoconstriction (center and lower left) is a hallmark feature of obstructive lung diseases such as asthma or COPD. The ‘classic’ rationale for GPCR as therapeutic targets focused on the prevention of G_α second messenger signaling of actetylcholine (ACh), which causes smooth muscle contraction via muscarinic receptors (MR). However, modern paradigms now include bias signaling through the arrestin protein (see Rominger *et al.*; Walker and DeFea; and others this issue), as well as novel approaches to antagonist design elucidate by MR and other GPCR structures (upper and lower right; see Kruse *et al.*, [4]), such as the M3 MR receptor shown with the antagonist tiotropium within the receptor structure. * from Kruse *et al.* [4].