An Official American Thoracic Society Research Statement

Prakash, Y S; Halayko, Andrew J; Gosens, Reinoud; Panettieri Jr., Reynold A; Camoretti-Mercado, Blanca; Penn, Raymond B; Burgess, Janette K; ATS Assembly on Respiratory Structure and Function

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An Official American Thoracic Society Research Statement: Current Challenges Facing Research and Therapeutic Advances in Airway Remodeling

Y. S. Prakash, Andrew J. Halayko, Reinoud Gosens, Reynold A. Panettieri, Jr., Blanca Camoretti-Mercado, and Raymond B. Penn; on behalf of the ATS Assembly on Respiratory Structure and Function

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Background: Airway remodeling (AR) is a prominent feature of asthma and other obstructive lung diseases that is minimally affected by current treatments. The goals of this Official American Thoracic Society (ATS) Research Statement are to discuss the scientific, technological, economic, and regulatory issues that deter progress of AR research and development of therapeutics targeting AR and to propose approaches and solutions to these specific problems. This Statement is not intended to provide clinical practice recommendations on any disease in which AR is observed and/or plays a role.

Methods: An international multidisciplinary group from within academia, industry, and the National Institutes of Health, with expertise in multimodal approaches to the study of airway structure and function, pulmonary research and clinical practice in obstructive lung disease, and drug discovery platforms was invited to participate in one internet-based and one face-to-face meeting to address the above-stated goals. Although the majority of the analysis related to AR was in asthma, AR in other diseases was also discussed and considered in the recommendations. A literature search of PubMed was performed to support conclusions. The search was not a systematic review of the evidence.

Results: Multiple conceptual, logistical, economic, and regulatory deterrents were identified that limit the performance of AR research and impede accelerated, intensive development of AR-focused therapeutics. Complementary solutions that leverage expertise of academia and industry were proposed to address them.

Conclusions: To date, numerous factors related to the intrinsic difficulty in performing AR research, and economic forces that are disincentives for the pursuit of AR treatments, have thwarted the ability to understand AR pathology and mechanisms and to address it clinically. This ATS Research Statement identifies potential solutions for each of these factors and emphasizes the importance of educating the global research community as to the extent of the problem as a critical first step in developing effective strategies for: (*1*) increasing the extent and impact of AR research and (*2*) developing, testing, and ultimately improving drugs targeting AR.

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ORCID IDs: 0000-0002-2968-224X (Y.S.P.); 0000-0003-0598-2632 (B.C.-M.).

Correspondence and requests for reprints should be addressed to Y. S. Prakash, M.D., Ph.D., Department of Anesthesiology, 4-184 W Jos SMH, Mayo Clinic, Rochester, MN 55905. E-mail: prakash.ys@mayo.edu; or Raymond B. Penn, Ph.D., Department of Medicine, Thomas Jefferson University, Room 543, Jefferson Alumni Hall, 1020 Locust Street, Philadelphia, PA 19107. E-mail: raymond.penn@jefferson.edu

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Overview

Airway remodeling (AR) can be collectively considered a process encompassing changes in structural cells and tissues of the airway in obstructive disease (particularly asthma). The last two decades have witnessed a profound, progressive increase in AR research (Table 1), with appreciation that AR is part of the pathogenesis and a cardinal feature of chronic airway disease. Unfortunately, numerous factors have thwarted our ability to understand AR pathology and mechanisms and to address it clinically. In this Research Statement, we discuss specific scientific, technological, economic, and regulatory issues that deter progress of AR research and development of therapeutics targeting AR, and we propose approaches and solutions to these specific problems. This Statement is not intended to provide clinical practice recommendations on any disease in which AR is observed and/or plays a role. Indeed, unlike scientific review articles that typically summarize research findings on a scientific theme, an American Thoracic Society (ATS) Research Statement provides a more appropriate platform for articulating the challenges—scientific, logistical, and monetary—of advancing specific research and its clinical application as well as providing recommendations for addressing these challenges.

Specific Challenges for Enabling AR Research and Advancing AR Therapeutics

- *Lack of consensus regarding the importance of multiple features of AR.* Although numerous airway cell types and processes are involved in AR, a majority of studies have focused on a subset of features (Table 1) or simply noted the existence of AR-relevant changes in different disease models, with some attempts to implicate specific effectors. Importantly, the pathophysiological role of specific AR indices in more well-accepted asthma features (airway hyperreactivity [AHR], airway impedance independent of AHR, or inflammation) is largely conceptual and associative/correlative but does not demonstrate necessity and sufficiency of AR in disease, leading to lack of clear direction and rationale for AR research, identification of therapeutic targets, and development of anti-AR drugs (Table 2).
- *Fundamental methodological limitations*, including cost, lack of standardized methodology, relevance of nonhuman model systems, prolonged time frame of AR development in humans, and inherent limitations of tools/techniques.
- *Difficulty of proposing "deliverables"* for research testing anti-AR drugs due to lack of prioritized AR outcomes and lack of empirical basis to guide timing and targets for intervention.
- *Economic and regulatory issues*, including perceived economic risk in investing in AR research or potential anti-AR therapeutics and regulatory indicators that are not AR outcomes.

Table 1. Publications Relating to Airway Remodeling (as of April 15, 2016)

Topic	No. of Publications
Thickening of lamina propria	297
Increased extracellular matrix	271
Mucus production	101
Mucous metaplasia	53
Airway smooth muscle	913
Fibroblast	250
Airway remodeling in asthma	2,437

Recommendations for Enhancing AR Research and Therapeutics

- *Promote multiple educational and informational opportunities/forums*, including National Institutes of Health (NIH) workshops and symposia at major national/international meetings to discuss and highlight importance, limitations, and future of AR research (Table 3).
- *Promote multidisciplinary efforts that encourage and enhance establishing a broad and deep collaborative, complementary platform to further AR research* by:
  - Helping resolve fundamental outstanding issues in the definition of AR;
  - Emphasizing the value of "basic" research in AR mechanisms;
  - Identifying key biomarkers of AR induction, maintenance, progression, and responsiveness to therapy;
  - Advancing the development and application of novel imaging technologies in AR research;
  - Establishing a means of obtaining airway samples and relevant clinical data from diverse human populations;
  - Encouraging inclusion of AR phenotyping in clinical research (with appropriate guidelines and policies) and in clinical trials that assess therapeutics for obstructive lung disease, such as asthma and chronic obstructive pulmonary disease (COPD). Here, it would be important to establish a means of associating AR data with lung function and clinical outcomes (e.g., symptoms, exacerbations, inflammatory markers);
  - Enhancing cross-fertilization of bench and clinical research information on remodeling in other organ systems and disease conditions, including, heart, kidney, liver, and skin.
- *Work with leading federal and foundation-based funding agencies, as well as the pharmaceutical industry, to emphasize the need and potential impact of funding* AR-focused research.
- *Improve the design of human studies* of AR, particularly focusing on specific patient populations that will serve as more useful models for clinical research into AR and help identify factors that promote pathology or where potential anti-AR drugs could be tested over shorter, financially viable durations.
- *Leverage long-term funding strategies with international networking/partnerships* to allow sufficient duration and depth to develop strategies and models to observe, characterize, and interfere with specific AR features.
- *Convene an NIH-sponsored workshop involving relevant institutes*, such as the National Institute of Child Health and Human Development, NHLBI, National Institute on Aging (NIA), National Institute of Allergy and Infectious Diseases, and National Institute of Biomedical Imaging and Bioengineering, to identify and address specific scientific, logistical, monetary, and regulatory challenges and consider innovative, multidisciplinary solutions for research and prophylactic/therapeutic targeting of slow-developing diseases.
- *Identify and develop academia-government-industry partnerships* that will help advance funding, science, and

Table 2. Major Issues Hindering Airway Remodeling Research and Its Appeal

Issue	Approach(es) or Solution(s)
Methodologic	
Lack of consensus regarding physiologically or clinically relevant features/aspects of AR	Agreement on definitions and indices for AR
Difficulties in accessing or measuring critical indices	Assessment of importance of indices in asthma pathophysiology and symptoms (and, conversely, responses to therapy) Identification of biomarkers or indicators of AR that correlate with disease phenotype, severity, responsiveness to therapy, and other relevant factors
Lack of relevant models	Identification of preclinical models that most closely approximate the human condition for both AHR and AR
Costs and logistics given longitudinal and slow-developing nature of AR	Attention to balance between reasonable timeframes for AR development or intervention in preclinical models vs. much slower AR development in humans Exploration of AR prevention/prophylaxis in asthma, thus identifying "at-risk" populations (aided by research using genetic and phenotypic markers), overall reducing timeframe of studies
Fundability	
Perceived limited impact of AR research and associated difficulties and increased competitiveness for funding	Education, education, education, regarding importance of AR and the many limitations that render AR research and advancement of AR therapeutics difficult
Economic/regulatory	
Jaundiced perspective of regulatory bodies (lack of FDA regulatory indicators for asthma medications that include changes in airway histopathology)	Encourage preclinical and clinical studies establishing that AR features cause or exacerbate regulatory indicators of asthma (airflow obstruction, AHR, resolution of inflammation, and inflammatory markers)
Difficulties of proposing deliverables with any anti-AR drug leading to limited interest by pharmaceutical industry (lack of regulatory indications, proof of concept, and unclear commercialization strategy)	Establish regulatory precedent that includes AR features

Definition of abbreviations: AHR = airway hyperresponsiveness; AR = airway remodeling; FDA = Food and Drug Administration.

drug development in AR. Potential examples include the NIH Small Business Innovation Research and Small Business Technology Transfer grants, R33 and other grants for drug repurposing, and larger clinical/translational grants and contracts.

- *Assess drugs targeting AR in the context of current regulator indicators*, given the history of difficulty in establishing a new regulatory indicator for most diseases.
- *Initiate and maintain dialogue* among investigators, funding agencies, and regulatory agencies with frequent informational meetings, preferably at large scientific/clinical gatherings, to provide updates on research and drug

Table 3. Recommendations for Enhancing Visibility and Appeal of Airway Remodeling Research

- Promote educational and informational opportunities at national/international forums for discussing and highlighting the importance, limitations, and future of AR research.
- Promote multidisciplinary, multicenter efforts to enhance cooperative and complementary approaches to AR research. The intent should be:
  - exploring mechanisms and functional role of AR in obstructive lung disease
  - identifying indices (including biomarkers) that encompass genetic, molecular, biochemical, anatomical, and functional aspects of AR
  - identifying therapeutic targets.
- Promote inclusion of AR phenotyping in clinical research and in clinical trials that assess pathological mechanisms as well as therapeutics for obstructive lung disease.
- Improve the design of human studies of AR.
- Convene an NIH workshop with the purpose of publishing a consensus review article summarizing current state of AR research; identifying features of AR that link to asthma pathophysiology, exacerbation, and phenotype; and identifying ways forward for mechanism and therapy-oriented research.
- Work with funding agencies as well as regulatory agencies and pharmaceutical industry to emphasize the need and potential impact of AR-focused research.
  - Leverage long-term funding strategies to allow sufficient duration to develop pathways and models to observe, characterize, and interfere with specific AR features.
  - Develop academia-government-industry partnerships to advance funding, science, and drug development in AR.
- Help establish guidelines for assessment of drugs targeting AR to focus on current regulatory indicators in asthma.

Definition of abbreviations: AR = airway remodeling; NIH = National Institutes of Health.

development breakthroughs and obtain recommendations for further development toward clinical trials and commercialization.

Introduction

AR associated with asthma and other obstructive lung diseases has been a well-appreciated, although loosely defined, feature that has appeared prominently in the literature over the past 25 years. Recognition of AR dates back to 1922, when Huber and Koessler (1) noted thickening of the airway wall as well as mucus plugs in the bronchial lumen in necropsy samples from patients who died from severe asthma. Subsequent studies have helped to better delineate, characterize, and quantify the structural changes that occur in the remodeled airway and of the cell types involved, particularly in the context of diseases such as asthma and COPD (2–23).

Interest in AR research and its clinical relevance, particularly with respect to asthma, increased dramatically in the early 1990s, as evidenced by a significant increase in peer-reviewed publications (680 reviews alone among 2,430 peer-reviewed publications since ~1995) (Table 1). Multiple studies and review articles posit AR as a principal cause of irreversible airway obstruction and the therapy-resistant component of AHR, noting the association of AR and rapid decline in lung function in individuals with severe asthma and modeling that predicts the effect of airway wall remodeling on airflow obstruction (24–28). This interest in AR has been maintained over the last 2 decades, as indicated by relevant publications, particularly in the context of asthma (9–22). However, an important caveat is that a majority of studies have used multiple models and systems (*in vivo*, *ex vivo*, and *in vitro* preclinical models using different species, including human and animal airway tissue- and cell-based studies) to further characterize AR and the mechanisms driving it. Specific to the human condition, the longitudinal and progressive nature of AR contrasts with the largely cross-sectional nature of most AR-focused studies in human asthma, thus severely limiting our understanding of the likely multiple cell types and mechanisms that contribute to AR and allowing only predictions about whether current or emerging therapies can impact AR. Nonetheless, studies to date reflect a general, albeit not unanimous, consensus that AR contributes significantly to the pathology of asthma and other obstructive lung diseases and is an important therapeutic target. However, despite sustained enthusiasm among the research community for this topic, little if any progress has been made in developing therapeutics that inhibit or reverse AR. Here, it is important to emphasize that current therapies targeting asthma that help alleviate other key aspects of asthma, AHR and inflammation, are largely ineffective in addressing AR, whereas therapy-resistant aspects of AHR may further represent AR (16, 29–37).

This Research Statement attempts to examine the underlying barriers to progress in AR research and development of therapeutics. Of note, this Research Statement is not intended to provide any clinical guidelines or recommendations for treatment of AR or any obstructive lung disease but rather to provide direction regarding how to better advance AR research and the development of therapeutic strategies that address it. For practical purposes, this Research Statement will focus on AR that occurs with asthma, although many of the issues raised and recommendations proposed are applicable to AR in other obstructive lung diseases.

Methods

Committee Composition and Meetings

The project organizers invited an international, multidisciplinary group with expertise relevant to the main objectives of the project. Accordingly, the group was composed of bench and clinical researchers with expertise in AR in various diseases in various populations, industry representatives with experience in drug development and regulatory approval of drugs, and program officials from the NIH (lung biology programs of the NIA and NHLBI).

Two separate meetings were held. The first meeting was conducted in March 2015 using the web-based forum "Chatter" (www.salesforce.com/chatter) and facilitated by ATS support staff. In this meeting, participants discussed and refined the objectives of the ATS Project and identified key talking points that were used by the project organizers to generate and disseminate an agenda for a subsequent face-to-face meeting at the 2015 ATS International Conference in Denver, Colorado. Participants at the ATS meeting arrived at a general consensus regarding the issues that currently face the advancement of AR research and therapeutics and discussed various strategies for addressing these issues. The Project Organizers reviewed the discussions from the two meetings, performed a literature search as described below, and collectively wrote the Research Statement. Participants disclosed all potential conflicts of interest, which were vetted and managed in accordance with the policies and procedures of the ATS.

Literature Search and Appraisal of Existing Evidence

Each of the authors performed a PubMed search related to specific topics. The results were shared among all authors and additional references, where appropriate, were identified. The literature search conducted for this Research Statement was not a systematic review of the evidence, given the broad definition of AR, lack of preclinical or clinical/human data on the many factors influencing AR, and limited longitudinal studies in humans.

Document Development

Project organizers identified two leaders who prepared a draft document on the basis of the web and in-person discussion and contributions from the members of the writing group. These leaders collated, organized, and formatted a complete single document that was sent to all participants for review and feedback. After multiple cycles of revision, review, and feedback until all participants agreed on a version of the draft, the document was finalized for submission.

The Problem: Advancing AR as a Mechanistic Focus and Therapeutic Target

AR can be collectively considered as a process encompassing changes in the structural cells and tissues of the obstructive diseased airway (particularly asthmatic airways) (38–46). Although AR studies differ in characteristics of patient population, such as age, disease definition

severity and duration, atopy, smoking history, and the types of tissues analyzed (e.g., whole lung samples from autopsies versus bronchial biopsies), what is most relevant to this report, and part of what makes AR difficult to study, is the many histological features noted in the AR response. These include airway wall thickening, airway edema, subepithelial fibrosis, epithelial hyperplasia with mucus metaplasia, airway smooth muscle (ASM) hyperplasia and hypertrophy, and the increased presence of myofibroblasts and inflammatory cells. The questions then become: (*1*) What mechanisms underlie initiation, maintenance, and progression of these various aspects of AR? (*2*) How do these AR elements contribute to the AHR of asthma, disease progression, and severity? (*3*) How does AR contribute to individual and age-related differences in asthma symptomatology? and (*4*) Are current therapeutic approaches effective in blunting or reversing AR, and, if not, what are the most promising alternative strategies?

All structural components of the airway wall have been reported to be thickened in asthma (47) (Figure 1), with the extent of thickening worsening with disease severity, but importantly, with different contributions of the small (<600 μm) and mid-sized (1–3 mm) airways in nonfatal asthma versus larger membranous airways in fatal asthma (48–53). Here, the role of the airway epithelium as a recipient of asthma triggers, in the initial and sustained immune response of asthma, as well as a key aspect of AR are recognized, the latter involving epithelial layer thickening, mucous metaplasia, and subepithelial fibrosis (54–56). The role of ASM in AR is also being increasingly recognized, with hyperplasia and hypertrophy of this cell type contributing to wall thickness and AHR and, in addition, ASM being a source of extracellular matrix (ECM), and of growth factors and cytokines that promote inflammation and AR itself (22, 32, 57). Certainly, fibroblasts can contribute to AR via increased ECM production, although their role is perhaps less well explored in the context of asthma (18, 58). Conversely, ECM components can influence cellular behavior, such as proliferation and migration. Finally, there is increasing recognition that enhanced airway vascularity is an important aspect of AR, highlighting the potential role of angiogenic factors and, furthermore, interactions between airways and vasculature (59, 60). Downstream, hyperinflation and air trapping occur consequent to these structural changes in the bronchial airway, leading to well-recognized features in radiographic images. The relevance of the different cell types and the consequences of AR lies in the potential for identifying targets for AR therapy and, conversely, alleviation of AR effects as indicators of therapeutic efficacy.

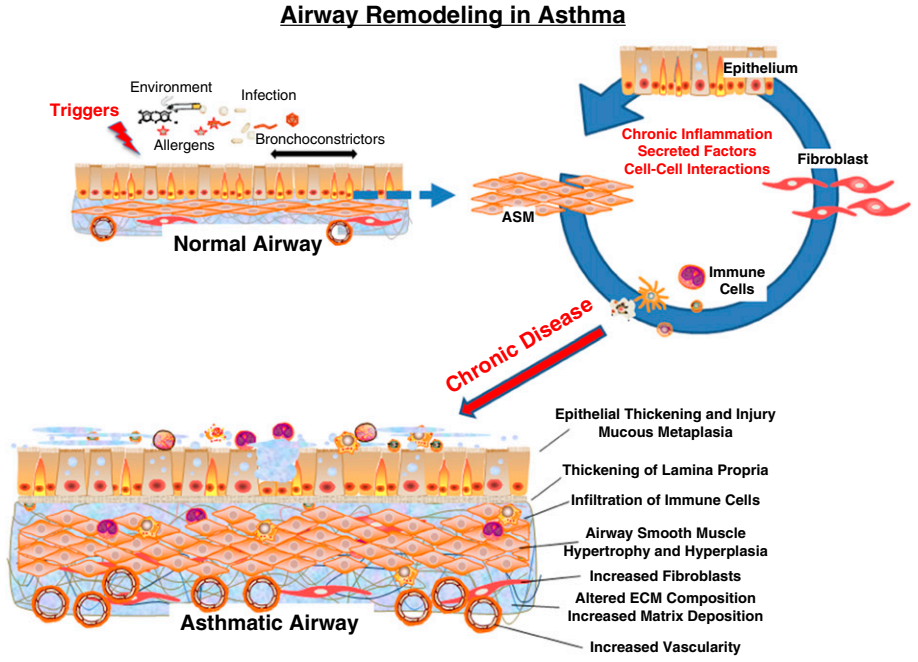

Figure 1. Aspects of airway remodeling (AR) of asthma. Initiation of asthma results from a variety of triggers affecting the normal airway. Here, well-recognized allergic, infectious, and environmental factors can play a role. In addition, there is increasing evidence that agonist-induced bronchoconstriction and the associated mechanical forces acting on the airway can trigger changes to the airway. Asthma induction leads to a sustained cycle of chronic inflammation, cell–cell interactions, and secreted factors (from both immune cells and structural cells of the airway), leading to chronic disease characterized by airway hyperresponsiveness and a multitude of structural changes to the airway that represent AR. Here, AR includes changes to epithelial thickness, composition (greater proportion of mucus-producing cells), thickening and fibrosis of the underlying lamina propria, increased numbers and size of airway smooth muscle cells, increased presence of fibroblasts and altered extracellular matrix (ECM) composition, and increased microvasculature in the asthmatic airway wall. ASM = airway smooth muscle.

However, an important hindrance to AR as a major focus in asthma research is that the physiologic and clinical consequences of wall thickening are not well understood, despite studies suggesting that increased wall thickness correlates with disease severity (61–66). Here, modeling and imaging evaluations are consistent with the intuitive idea that airway thickening enhances the extent of luminal closure for a specific extent of airway contraction, thus contributing to the AHR of asthma. Conversely, outer wall thickening could alter the relationships between tethering forces of the airway and luminal closure, affecting dynamic mechanical properties of the airways that promote their collapse (3, 67). Thus, the link between wall thickening and AHR drives the essential goal of understanding the cell types and mechanisms that contribute to structural changes within the airway and the need to target cells or pathways that contribute to functional changes in asthma.

The role of the epithelium in AR is not in doubt (11, 54, 68–74), with mucus hypersecretion and metaplasia and epithelial hypertrophy leading to mucus plugging of the bronchial lumen. Subepithelial mucus-secreting glands are increased in fatal and nonfatal asthma (75, 76), as is epithelial area within the

asthmatic airways (24), leading to changes in luminal diameter. Furthermore, changes in mucus properties can modulate the effects of airway shortening and surface tension at the air–liquid interface, leading to greater airway narrowing. In terms of subepithelial fibrosis, it appears that increased fibrotic responses within the lamina reticularis are particularly relevant (4, 42, 44, 77–79), characterized by accumulation of ECM elements such as fibronectin, various collagens, and matrix metalloproteinases (38, 80–85). Some studies have associated subepithelial fibrosis with asthma severity and changes in FEV_1 (63, 86–88) as well as sensitivity to methacholine challenge (i.e., AHR) (89), but others do not find a correlation (90). Therefore, fibrosis may promote or act as a marker for AHR, although the link is not well established, given its presence even in mild asthma (79) and conversely lack of correlation with asthma severity in some studies (90, 91). Furthermore, increases in sub–basement membrane fibrosis can occur to comparable levels in subjects with allergic rhinitis and in asthma. Therefore, the physiological relevance of such fibrosis remains unknown. Conversely, basement membrane thickening can occur early in lung development/growth as well as before AHR and symptoms (92–96), suggesting that fibrosis is a biomarker for ongoing biological processes and risk for AR that eventually does affect lung function. Along similar lines, an increase in ASM mass has been demonstrated in some studies (41, 62, 72, 97–101), with evidence for both hyperplasia and hypertrophy, although the contribution of either mechanism to AHR *per se* is not established. Furthermore, the presence of myofibroblasts has been reported in asthma (102–105), although their origin and eventual differentiation are a topic of debate (106–108). Thus, overall, a number of cell types/layers can contribute to AR, with either variable or unclear contributions to AHR. In this regard, the relative roles of these cell types in different age groups and disease-specific contexts (atopy, infections, environmental exposures) are a major topic of ongoing investigation.

AR can appear early in disease, as suggested by airway changes in pediatric asthma (92–96). However, given that such remodeling is already present by the time of patient presentation, and bronchial samples are unlikely to be obtained early for disease diagnosis or in a serial fashion, much of the information regarding AR induction is speculative and generated in studies using animals or reductionist cell-based experiments. Accordingly, what induces AR in the human is not well defined. Certainly, the inflammatory cascade initiated by asthma triggers can influence every cell type that contributes to AR. Thus, a major confounding factor is the concurrent presence of chronic and/or acute inflammation that likely influences remodeling. Indeed, the plethora of inflammatory mediators that influence various aspects of AR is ever increasing (5, 22, 44, 104, 109–112), further compounded by the immunomodulatory capabilities of structural airway cells (40, 102, 113, 114). The importance of understanding mechanisms in early and persistent AR further lies in the recognition that current pharmacological therapies for established asthma, such as corticosteroids, are largely ineffective in alleviating AR (16, 63, 69, 115–118); although emerging interventions such as bronchial thermoplasty appear to locally alleviate AR (119, 120), there continue to be no approaches for global targeting of AR in the obstructed lung. Interestingly, recent studies demonstrate the potential for disease in which airway inflammation is uncoupled from AHR (121–123), underscoring the complexity of this latter phenomenon and highlighting the potential role for AR as a contributory rather than consequent factor in asthma diathesis. Accordingly, it becomes important to define what AR *per se* encompasses, what factors contribute to AR, and how these factors can be therapeutically targeted to alleviate structural and functional changes in airway diseases.

A fundamental feature of AR is its longitudinal and progressive nature (although there is some evidence that ASM thickness may be related more to asthma severity than duration [124]). However, longitudinal studies unfortunately remain limited in scope and number, typically involve only larger airways (where disease manifestation may be variable) (125–131), and are often confounded by ongoing therapy. Thus, studies of asthmatic airway structure have tended to be cross-sectional in nature and may not encompass the disease spectrum. Overall, the question of whether AR is a separate process in asthma, a consequence of the persistent inflammation or of other ongoing insults, remains to be established but is of obvious and considerable relevance to understanding both the pathogenesis and treatment of asthma.

Given the increasing recognition of the importance of AR in asthma pathogenesis and symptoms, a fundamental unmet clinical and research need is therapeutic targeting of remodeling. Although some studies using animal models suggest certain drugs may prevent the development of AR concomitant with allergic lung inflammation and AHR (132–135), there is no clinical evidence that currently prescribed asthma drugs prevent or deter the progression of AR. The preponderance of literature demonstrates that AR is progressive in many individuals with asthma who are otherwise effectively managed with corticosteroids or β-agonists and, importantly, that AR progression parallels the reduced sensitivity of individuals with longstanding asthma to their therapy (16, 63, 69, 115–118). Thus, it is tempting to propose that with long-term disease, the eventual refractoriness to therapy and lack of improvement in lung function in individuals with asthma may reflect fixed airway obstruction resulting from AR. Consequently, if AR is of pathophysiological significance, even patients with "well-controlled" asthma will suffer a progressive loss of lung function and increased fixed airway resistance, and thus even this population is in need of improved therapy. Importantly, AR features render current asthma therapies even less effective in regulating airway resistance and improving airflow. Accordingly, targeting AR represents an opportunity for early intervention in asthma, an approach that would address a major, unmet clinical need.

Despite the importance of AR to asthma pathophysiology, several factors deter the development of therapies that prevent or treat AR. An obvious factor is the longitudinal and ill-defined nature of AR that necessitates long-term investment in AR research that is economically prohibitive in nature (particularly in the current federal funding environment) and furthermore leads to regulatory issues relevant to the development and approval of AR drugs.

Specific Issues That Hinder AR Research

There are intrinsic characteristics of AR research that render it difficult to perform. THERE ARE MULTIPLE FEATURES OF AR AND A LACK OF CONSENSUS REGARDING WHICH ARE IMPORTANT.

As noted above, alterations in the morphology or function of numerous airway cells can contribute to AR, particularly epithelial cells, ASM, fibroblasts, and even infiltrating immune cells, with the additional contribution of ECM components, inflammatory mediators, and even vasculogenesis. A majority of AR studies have focused on changes in ASM mass, thickening of the lamina propria, increased matrix deposition, or mucous metaplasia. Although in one sense these studies have substantially advanced the AR field, most research has simply noted the existence of AR-relevant changes associated with human asthma or murine models of asthma (typically allergic lung inflammation), and some studies have attempted to implicate specific effectors. Moreover, the causative role of various indices of AR in the well-accepted features of asthma, such as AHR, increased airway impedance (independent of AHR), or increased airway inflammation itself, is largely conceptual and based on association/correlation data. The inability to specifically manipulate AR features to demonstrate their requirement/sufficiency in asthma (or other obstructive lung diseases) means definitive proof of their pathogenic roles is lacking. This equivocation and uncertainly over the extent to which different features of AR are functionally important translates into a lack of direction for the AR field and lack of a clear rationale for pursuing and designing translational and clinical research that would help alleviate AR.

There are fundamental methodologic limitations in performing AR research. Fundamental methodological limitations in performing AR research include (*1*) a lack of relevant models, (*2*) the longitudinal and slow-developing nature of AR, (*3*) difficulty in accessing or accurately measuring critical indices, and (*4*) prohibitive expenses relating to its longitudinal nature and the associated costs of sensitive and specific techniques necessary to identify/quantify AR.

Model systems. Although much of preclinical asthma research embraces the murine model (typically of allergic lung inflammation), especially given the ease of manipulating the mouse genome, there are also well-known limitations of the mouse "asthma" model (136–145). The most relevant limitations include an immune response to allergens qualitatively different from that which occurs with most human asthma (leading to an ever-expanding search for the ideal allergic model), species differences in the expression or function of numerous airway genes important in the asthma phenotype, and difficulty in measuring certain features of asthma (including both lung function and AR) due to either size or anatomic differences (141, 143, 145). Although some differences are less important for assessing AHR (regardless of the effect of AR on this feature), the study of AR *per se* is considerably more problematic. Although many features of AR observed in humans can be induced in the mouse, such induction typically occurs much more rapidly in mouse models, coinciding with the short and intense sensitization/challenge to allergen used in most protocols. Although this compressed time frame of AR development is cost saving, it does not replicate the slow-developing nature of AR in humans involving persistent as well as intermittent exacerbating stimuli. Although an attenuated and extended duration protocol in the mouse is possible, the trade-off appears to be more modest AHR. Perhaps most problematic with the mouse model for AR research is airway architecture, where, unlike the more than 20 levels of dichotomous branching of conducting airways in humans leading to respiratory bronchioles, after the large conducting airways, the monopodial branches of the mouse airways quickly transition into terminal bronchioles and alveolar ducts. It is likely that this very different architecture influences the response to both the physical forces and (localized) inflammatory factors that promote AR. Conversely, the effect of localized AR and resultant airway narrowing and AHR on other lung areas also likely differ. And, finally, the lack of murine transgenic or knockout models that regulate specific AR attributes has greatly hindered our ability to link such attributes to physiologically relevant outcomes.

Several studies have successfully examined features of AR using other animal models of asthma, including the rat (146–156), guinea pig (11, 157–165), dog (166–171), horse (172–176), and nonhuman primate (177). Larger animals, by simple virtue of their size, are obviously better models when assessing morphology changes, yet many of the same issues (species differences in genome, lung architecture) remain in these models. Here, the lung architecture of the dog may be closer to the human, but gravitational effects due to postural differences may be limiting. Conversely, the guinea pig is often used as a model of AHR (particularly when examining neural influences) and has evidence for AR. Moreover, the cost of working with larger animals is understandably greater, and given that asthma (and AR) phenotyping does not lend itself to longitudinal analysis, the need for population-based analyses over time to obtain AR data often makes studies with larger animals cost prohibitive.

Given the above limitations of animal models, human studies of AR of course represent the gold standard model of asthma, yet they are difficult to perform due to the numerous methodological, logistical, and economic issues, as discussed below.

Methodological limitations with respect to protocols and techniques in AR research. Beyond those limitations related to species differences in the use of animals, there are numerous other methodological limitations of AR research. These include:

1. A lack of standardization in fundamental experimental and technical design across studies. Although species differences alone can be a challenge, the ability to compare results across studies is further confounded when the means, mode, intensity, and duration of effector for AR (including the age of initiation of the effector, or even the sex of the animal), the techniques of assessing AR, and the features actually examined, all vary widely among studies. For example, in the use of noninvasive imaging of the lung/airway, questions abound with respect to standardization of the lung volume at which measurements are made; whether the animal (or human) is anesthetized, paralyzed, or mechanically ventilated versus spontaneously breathing; and in what position measurements are made. Even with such standardization, differences in the size(s) of airways that are assessed lead to confusion regarding the extent of AR or changes with any intervention. In this regard, the imaging modality has substantial influence in the sensitivity and specificity for assessing AR (50, 61, 65, 66, 178–185), where high-resolution computed tomography, hyperpolarized magnetic resonance imaging, xenon

magnetic resonance imaging, positron emission tomography, ultrasound, and more recently coherence tomography may be used, with the addition of improved probes, tracers, and other enhancers. Furthermore, none of the current whole-organ/full-body imaging modalities has the necessary resolution to identify individual cell types, and they can only assess the presence/absence of wall thickening with varying degrees of quantification and accuracy.

2. As noted above, the slow-developing nature of human AR limits the relevance of short-term protocols in other species (with more rapid AHR and AR development over shorter lifespans). Moreover, any research into a slowly developing, progressive disease, be it in animals or humans, is often expensive, difficult to control, and dependent on insufficiently sensitive analytic tools (most obvious in the inherent limitations of aging research).
3. Related to number 2 above, a desirable longitudinal analysis of AR induction, development, persistence, and progression (or the effect of intervention) lacks feasibility, due primarily to the lack of useful, noninvasive tools in animals and even more so in humans.
4. Most animal models of allergic lung inflammation (or other disease) use prophylactic strategies to prevent or delay the onset of AR pathology. Not only is the relevance of this approach to disease management (which is most often treatment) limited (186) but, at least in asthma research, such an approach cannot effectively distinguish AR pathobiology from asthma pathophysiology independent of AR.
5. Most techniques/tools for characterizing AR suffer from poor accuracy, precision, and sensitivity. Quantifying AR indices from biopsy samples is fraught with these problems, raising questions such as the generation of airway being assessed (typically limited to fifth or sixth generation in humans), access to all relevant cell types within a biopsy, the need for normalizing measurements within and across samples, and the contributions of error from the plane of section, sampling, or Mendelian sorting bias. Moreover, as is the case with human clinical research in general, these approaches combine samples in a manner that normalizes disease phenotype; thus, critical links between AR and clinical subphenotypes of asthma are not extractable. With noninvasive or even invasive imaging approaches, a lack of sensitivity for most modalities leads to data acquisition being limited to airway wall thickness, with no appreciation of specific cellular changes that contribute to AR.
6. The lack of any established biomarkers for or surrogates of AR limits the power of clinical studies and the ability to associate clinical data and disease phenotype data with any AR data.
7. Last, it remains incredibly difficult to design human studies testing a potential anti-AR intervention given the lack of consensus of which AR index is important (or responsive to therapy), the difficulty (including cost) and feasibility of measuring accurately and sensitively any AR index in a large number of subjects, the difficulty in justifying any intervention specific for AR without compromising the Protection of Human Subjects, and the need to preserve the objectives and enrollment of any study testing another intervention where an anti-AR drug might be tested as an adjunct.

It is difficult to propose "deliverables" for research testing any anti-AR drug. This point is explained in part by point 7 immediately above and the fact that much of AR research remains "basic" (i.e., identifying indices of interest, quantification of such indices, establishing upstream and downstream mechanisms, and overall exploring functional outcomes). In contrast, few studies examine strategies to prevent or reverse AR overall. More recently, some studies have identified anti-remodeling effects of certain agents, such as long-acting β_2 agonists (187, 188) or bitter tastants (189), but these studies remain preclinical and have not even started to explore AR in the context of age and disease severity. Bronchial thermoplasty, a relatively new procedure resulting in sustained improvement of asthma symptoms (190, 191), is proposed to reduce the exaggerated amounts of ASM in the asthmatic airway; however, systematic studies to demonstrate blunting of AR are lacking.

The many hurdles limit the peer review assessment of "impact" of AR research and competitiveness for funding. With respect to NIH or other major funding agencies, grant proposals focused on exploring AR mechanisms, or avenues to target AR, carry with them the many limitations discussed above. The lack of relevant human data that causatively tie AR to AHR, inflammation, and other recognized features of asthma limits the ability to successfully argue the "significance" aspect of an AR proposal. The multiple features of AR, and a lack of consensus regarding which are important from mechanistic or therapeutic perspectives, further reduce enthusiasm for the significance of a proposal and frequently lead to lack of enthusiasm of any otherwise coherent, focused, and innovative "approach." Here, the inherent limitations in studying a slow, progressive phenomenon blunt the appeal and feasibility of the "approach," a problem not unique to AR research but nonetheless difficult to circumvent. The lack of methodologies/tools—especially imaging tools—also limits diversity in "approach" and further limits "innovation." As a result, AR research may be seen as less "impactful" due to a limited ability to "translate" fundamental discovery research into preclinical/clinical research in the immediate or short term and ultimately leads to clinical trials and/or approved drugs (discussed further below). In the context of an extremely competitive funding environment, these limitations are difficult to overcome, and, as a consequence, AR grants would be expected to fare poorly in peer review settings where imminent deliverables from grants are expected. Again, although this issue is not unique to AR-focused grants, and indeed not even to remodeling in other organ systems, it is possible that AR research *per se* faces more numerous and significant limitations in terms of definition, methodology, impact, etc., that places this field at a relative disadvantage.

Priorities for AR Research

Certainly, given the broad, multifaceted, longitudinal nature of AR and the many hurdles identified above, it is important to delineate priorities in AR research areas that would most likely lead to logistically feasible and actionable avenues for drug development and therapeutic intervention. We propose the following priorities:

1. Agree on definitions and indices for AR overall and explore the importance of indices in age-, sex-, and etiology-specific contexts of asthma, thus establishing the platform for mechanistic exploration of AR induction, maintenance, and progression.
2. Identify biomarkers, or nonlaborious indicators of AR, to facilitate comparisons to asthma phenotype data. Here, it would be important to identify the appropriate patient populations across the age and etiology spectrum for asthma that would most likely manifest AR, particularly early in disease.
3. Encourage clinical studies that establish what features of AR cause or exacerbate features of asthma that are regulatory indicators (airflow obstruction, AHR, resolution of inflammation, and inflammatory markers), thus enhancing the interest of industry partners toward AR-focused drug development.
4. Given that AR can occur early in disease, perhaps even before overt symptoms, explore whether prophylaxis of AR in asthma is even feasible, thus identifying "at-risk" populations, aided by research using genetic and phenotypic markers.

Specific Issues That Hinder AR Drug Development and Approval

There exists a mutual reinforcing relationship among the difficulties in mechanistic bench AR research, clinical studies focusing on AR aspects of asthma, and AR drug development/approval. Thus, some points below incorporate concepts already articulated above.

Much of AR research is still in the "discovery stage". Indeed, given the broad definition of AR and the cell types involved, both upstream and downstream targets and mechanisms are not clearly established, thus making it somewhat premature and quite difficult to propose and design interventional or prophylactic basic or clinical research. Consequently, human trials of anti-AR drugs are also premature and difficult to justify.

Economic, particularly regulatory, issues thwart the appeal and feasibility of anti-AR drug discovery and trials.

Perspective of drug and therapy regulatory bodies. Current Food and Drug Administration (FDA) regulatory indications for first approval of asthma medications include: (*1*) FEV_1 (a surrogate marker of disease), (*2*) signs and symptoms, and (*3*) decreased exacerbation rate over a clinically meaningful period (e.g., over 1 yr). None of these indications links directly and specifically to a change in histopathology within the airway. What is unfortunate is that any drug that meets current regulatory indications is examined *post hoc* in the research community for relevance to AR, without necessarily a strategic plan toward assessing the anti-AR potential of such therapies. A similar pattern of expectations has been noted by regulatory agencies within the European Union. This makes critical the identification of AR indices or biomarkers that serve as acceptable regulatory indications. Given the recent history of the FDA to deny approval of any new regulatory indication for asthma, such an advance appears unlikely. Accordingly, in the near and possibly extended future, anti-AR drugs will need to be examined for their ability to impact current indications. The hope, of course, is that educational measures, including progress in AR research, prompt regulatory agencies to reconsider and expand regulatory indications.

Perspective of the pharmaceutical industry. Regulatory issues factor into calculation by this industry regarding the value of AR research and the need for industry-supported efforts to develop an anti-AR drug. The impact of absent regulatory indications related to AR and lack of interest of pharma/biotech to invest in anti-AR drugs is suggested by: (*1*) the lack of mention of any potential anti-AR effects of existing asthma/COPD drugs, (*2*) the lack of in-house research by pharma/biotech on anti-AR effects of existing or pipeline drugs, (*3*) minimal industry funding of AR research within academia. In this regard, three elements of an adequate risk-mitigation strategy are a prerequisite for undertaking novel drug development. First, the regulatory indication must be known and agreed on. Second, the intermediate proof of concept should be well defined in terms of duration and endpoint. Third, the commercialization strategy should be agreed on; it will not be possible to commercialize a drug for asthma that requires biopsy proof of efficacy.

To initiate anti-AR focused therapies, there is the need to establish a regulatory precedent that defines the clinical trial program for a new drug candidate. Before initiating drug or biologic development, there is a meeting between representatives of the sponsor and regulatory authority (e.g., FDA), which, even before the first human data are generated, outlines the goals of the program, including the initial indication. FEV_1 improvement has been well defined for decades at 15%. Improved signs and symptoms over 3 months has created a cottage industry of validated diaries to capture cough, wheeze, shortness of breath, sputum, nocturnal awakenings, and home-base measures of rescue medication usage and pulmonary function reporting. Reduction in exacerbations has more recently been accepted for two classes of drugs that failed to meet the accepted criteria. Risk mitigation is critical for pharma and especially so for innovative biotechnology companies. Bronchodilation can typically be demonstrated in a single dose and sustained bronchodilation within a few weeks. For drugs/biologics that do not improve FEV_1 predictably, improvement in signs and symptoms can be shown in clinical trials 4 to 6 weeks (less than 2 mo) in duration, certainly a more expensive path to risk mitigation but now defined. Subsequent longer-term ("chronic") indications, such as cost-effectiveness, or steroid sparing could be developed to extend a profitable franchise. Reduction in exacerbations as a primary indication reflects three products (anti–IL-5 monoclonal antibody, roflumilast, and anti-IgE) with massive expenditure and (unacceptably) long development histories that failed to achieve the accepted endpoints in prior adequate and well-controlled clinical trials. These are substantial barriers for anti-AR drugs, given lack of a regulatory indication; the difficulty of proof of concept in terms of a long, slow process of yet-undefined endpoint; and thus lack of a commercialization strategy that would be appealing to pharma and unlikely to be accepted by regulatory agencies.

Other economic factors. In addition to the confounding regulatory issues noted above, the inherent difficulties in performing human research/trials, their cost, and the reality that more potentially lucrative drugs may be competing for the eligible subject pool represent additional economic factors that hinder anti-AR drug development and approval.

Recommendations for Enhancing AR Research and Therapeutics

1. Promote multiple educational and informational opportunities/forums for discussing and highlighting the importance, limitations, and future of AR research:
   - Convene an NIH workshop with the purpose of publishing a consensus review article that summarizes the current state of AR research and, importantly, links specific features of AR to asthma pathophysiology, exacerbation, and phenotype.
   - Convene symposia at major national/international gatherings of pulmonary researchers and clinicians, such as the ATS, European Respiratory Society, and Canadian Thoracic Society, where published proceedings will review the evidence that specific features of AR cause or exacerbate the asthma phenotype, highlight the importance of AR research toward preventative or therapeutic approaches, and emphasize the need for providing specific recommendations for future research.
2. Promote multidisciplinary efforts to encourage and enhance a cooperative and complementary approach to AR research. Here, it will be important to work toward developing a multicenter initiative to explore the mechanisms and role of AR in obstructive lung disease with a range of direct and indirect indices that encompass genetic, molecular, biochemical, anatomical, and functional aspects of AR. Activities such as programming seminars, establishing cooperative funding mechanisms involving scientists, clinicians, and engineers (especially those with biomedical engineering and imaging expertise) will:
   - Help resolve fundamental outstanding issues in the definition of AR in general and in age-, sex-, and etiology-specific contexts, thus establishing a broad and deep platform for further AR research. Additional need for such a platform lies in the fact that AR genetics, molecular biology, and physiology likely differ among individuals and across populations and thus may benefit from developments in personalized medicine as we go forward in understanding AR mechanisms.
   - Emphasize the value of "basic" research in AR mechanisms toward understanding what causes AR induction, maintenance, and progression. This is important not only to expand and advance AR-focused research but also to educate potential manuscript and grant reviewers, funding agencies, and industry.
   - Help identify key biomarkers of AR induction, maintenance, progression, and responsiveness to any therapy that is developed. Here, engagement with networked studies in asthma (e.g., SARP [Severe Asthma Research Program], AsthmaNet, U-BIOPRED [Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes]) would be critical.
   - Advance development and application of novel imaging technologies in AR research.
   - Help obtain airway samples and descriptive clinical data opportunistically from different populations, especially across the extremes of ages. The importance of such efforts would be to corroborate published and ongoing bench research data in airways of clinically relevant patient populations. In this regard, opportunistic acquisition of airway samples from children undergoing bronchoscopy, aerodigestive procedures, or elective airway surgery procedures under anesthesia would allow leveraging basic data from children (e.g., proteomic or transcriptomic profile from airway epithelia or other cell types) toward generation of novel hypotheses for further AR research. This would be particularly important in understanding the influence of early life insults in maintenance and progression of AR. Conversely, given the increasing focus on asthma in the elderly, and sex differences in asthma pathophysiology, but the near impossibility of decades-long longitudinal sampling of asthmatic airways, opportunistic sampling of well-defined populations with asthma in different adult age groups would be highly appealing.
   - Encourage the inclusion of AR phenotyping in clinical research and in clinical trials that assess therapeutics for obstructive lung disease. These data may represent secondary outcomes of a trial, and be added to the study design assuming: (*1*) acceptable cost, and (*2*) minimal effect on subject recruitment. Here, consistent embedding of imaging and physiology cores in networked studies in asthma (e.g., SARP, AsthmaNet, U-BIOPRED) would greatly enhance multidimensional exploration of AR.
   - Help establish guidelines and policies in clinical research that prioritizes investigation into AR that are addressable in networked asthma or COPD studies. Here, it would be important to establish means of associating AR data with lung function and clinical outcomes (symptoms, exacerbations, inflammatory markers).
   - Enhance cross-fertilization of bench and clinical research information on remodeling in other organ systems and disease conditions, including, heart, kidney, liver, and skin.
3. Work with leading federal and foundation-based funding agencies as well as the pharmaceutical industry to emphasize the need and potential impact of AR-focused research toward development of supportive peer-review strategies that will expand the portfolio of grants and research efforts in this area.
4. Improve the design of human studies of AR. One means for such improvement might be to identify specific patient populations that will serve as more useful models for clinical research into AR. Ideally, the disease status of these patients will make them either prone to or protected from AR and, accordingly, responsive or resistant to any therapy. In this manner, effect sizes for experimental endpoints may be large, thus favoring statistical power. Possibilities include focusing on patient populations with specific Th2 profiles that are more or less likely to have AR, profiling based on steroid sensitivity/insensitivity (severe, persistent asthma), etiology (atopic versus occupational), age, and/or sex. Of particular interest are data suggesting certain elite athletes (particularly those with high ventilatory demands training in noxious environments [192, 193]) are susceptible to rapid development of AR, suggesting that these populations may enable a study design in which the factors that promote pathology or potential anti-AR drugs could be tested over shorter, financially viable durations.

5. Leverage long-term funding strategies (>5 yr), such as those from the Howard Hughes Medical Institute and recent NIH U01 and R35 programs, which may allow sufficient duration to develop strategies and models to observe, characterize, and interfere with specific AR features. Moreover, given the hurdles to AR research, initiatives that link international funding bodies with long-term goals that leverage networks and cross-sector partnerships will be critical to support significant advancement.
6. Convene an NIH-sponsored workshop involving relevant institutes, such as the National Institute of Child Health and Human Development, NHLBI, NIA, National Institute of Allergy and Infectious Diseases, and National Institute of Biomedical Imaging and Bioengineering, to identify and address specific challenges and innovative, multidisciplinary solutions for research and prophylactic or therapeutic targeting of slow-developing diseases, using asthma as an example. In addition to furthering mechanistic exploration, such a workshop should specifically address the issue of approval of drugs that treat/prevent slow-developing pathologies and whose assessment in clinical trials is confounded by design issues or the cost of performing long-term, longitudinal studies. Here, to gain broader knowledge of the process of remodeling, it would be beneficial that the workshop evaluate remodeling in other organs.
7. Identify and develop academia-government-industry partnerships that will help advance funding, science, and drug development in AR. Potential examples include the NIH Small Business Innovation Research/Small Business Technology Transfer grants, R33 and other grants for drug repurposing, and larger clinical/translational grants and contracts.
8. Introduce aspects of AR in regulatory indicators for drugs. Although establishing new regulatory indicators for most diseases is difficult, at least two potential avenues should be pursued, ideally in parallel and in collaboration with the NIH and other funding agencies, to incorporate aspects of AR into regulatory indicators. One is to incorporate AR features in assessment of current drugs, admittedly a tall order but mechanistically relevant and supported by evidence of correlation of diseased lung function with quantitative AR features such as wall thickening. This would be particularly important in the context of recent biologic therapies for asthma that should impact AR and help promote the idea that assessment of AR not only holds mechanistic significance but also could help broaden a product's therapeutic impact. The second is to promote the idea that assessment of drugs targeting AR should focus on effects on current regulator indicators. In asthma, this would be FEV_1, signs, symptoms, and exacerbations. These approaches would help crystallize and highlight the relevance of AR and understanding of the challenges of developing a therapeutic in this area.
9. Initiate and maintain dialogue among investigators, funding agencies (federal or industrial), and regulatory agencies with frequent informational meetings, preferably at large scientific/clinical gatherings to provide updates on research and drug development breakthroughs and obtain recommendations for further development toward clinical trials and commercialization.

Conclusions

A contributory role of AR in asthma pathogenesis and pathobiology is largely accepted, although the specifics of what features of AR are causally important remain the subject of debate. Alterations in multiple cell types occur with AR, and the impact of these alterations likely varies in the context of age, sex, disease severity, etiology, responsiveness to therapy, and other factors. Understanding AR mechanisms and their impact on disease is key to development of anti-AR therapies. However, significant barriers exist due to limitations in our ability to define the AR parameters to study, lack of appropriate tissue samples or longitudinal sampling approaches for a slowly progressing process, lack of biomarkers for AR, technological limitations in noninvasively assessing AR, and overall lack of enthusiasm from funding agencies, regulatory agencies, and the pharmaceutical industry in pursuing a protracted approach for a process with unclear regulatory indications. Nonetheless, given the emerging and increasingly established importance of AR in asthma, there need to be clear educational, research, funding, and regulatory advancements toward enhancing research into AR and development of novel therapies to blunt this process. Via this Research Statement, we have provided specific recommendations to achieve these goals. ■

This official research statement was prepared by a working group of the ATS Assembly on Respiratory Structure and Function.

Members of the committee are as follows:

Raymond B. Penn, Ph.D. (*Chair*)
Blanca Camoretti-Mercado, Ph.D.
Reinoud Gosens, Ph.D.
Andrew J. Halayko, Ph.D.
Reynold A. Panettieri, Jr., M.D.
Y. S. Prakash, M.D., Ph.D.

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