Antioxidant Strategies in the Treatment of Bronchial Asthma

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1. Introduction

The oxidant-antioxidant hypothesis and asthma: The pathogenesis of asthma is unknown but imbalances between oxidants and antioxidants are believed to play a fundamental role. One key component of the oxidant-antioxidant hypothesis centers on the huge burden of oxidants derived from inflammatory cell infiltration into the lung. The eosinophil, in particular, is implicated as a major source of oxidative injury, including protein nitration. Dysfunctional mitochondria in lung cells are another potential source of oxidants. Mitochondrial injury to airway epithelium occurs in murine models of allergic asthma.

There is evidence to support its role in human asthma as well including increased oxidative injury to mitochondrial epithelial cell superoxide dismutase (SOD), enhanced mitochondrial proliferation in bronchial smooth muscle, and mutations in mitochondrial DNA. Overall, this oxidative burden, generated by both inflammatory and lung cells, can overwhelm antioxidant defense to cause oxidant stress during asthma. This stress can alter or inactivate the function of essential proteins, lipids and nucleic acids culminating in severe cell injury, dysfunction and death.

An accumulating body of literature suggests that oxidant stress is an important factor in asthma pathogenesis. Oxidant stress can impact the function of a number of different cell types in the lung, and new research has drawn attention to immune cells and airway epithelial cells for the following reasons. First, immune cells are located within the lung and are directly exposed to inhaled allergens so that the local antioxidant milieu of the lung may impact the magnitude of oxidant stress in these cells. Second, antioxidant supplements, including glutathione precursors, have been shown to alter the cellular redox milieu of immune cells and effect pro-inflammatory cytokine production and inflammatory load in the lung (Figure 1). Third, as described above, the airway epithelium appears to be one cellular target that is subject to mitochondrial injury in asthma and in murine asthma models. Fourth, studies from the author’s laboratory suggest that extracellular glutathione within the lung lining fluid has a robust impact on airway epithelial cell responses to inflammation and the development of airway hyperreactivity (AHR). AHR may be related to airway epithelial cell integrity and maintenance of barrier function. These data suggest that the source and the location of oxidative stress, as well as the nature of the oxidant(s) to be targeted, are likely to impact the success of an antioxidant intervention. Nonetheless, broader based interventions have also shown some success in animal models, as discussed below.
Ovalbumin Asthma Model

Fig. 1. Murine Models of Allergic Asthma. Two general models are driven by ovalbumin as allergen, or IL13 as pro-inflammatory cytokine. Cellular antioxidants, such as glutathione, can affect the redox milieu of immune cells to attenuate pro-inflammatory cytokine induction (12). Extracellular antioxidants, such as lung lining fluid (LLF) glutathione, can buffer reactive oxygen species (ROS) from inflammatory cells, protect airway epithelial cells against oxidant stress and prevent airway hyperreactivity (14).

Oxidant stress, transcription factor NF-E2 related factor 2 (Nrf2) and asthma: Cellular antioxidants effectively buffer oxidants generated by metabolism or inhaled during ventilation in the normal lung. Oxidant stress results when the oxidant burden exceeds antioxidant defense and this elicits a cellular response to increase antioxidant capacity and restore balance. Recent studies have identified a central component of this endogenous antioxidant response pathway as transcription factor NF-E2 related factor 2, also known as Nrf2. Nrf2 is a basic leucine zipper transcription factor and a member of the cap-n-collar family of transcription factors. It recognizes a core promoter DNA sequence known as the “antioxidant responsive element” (ARE) and up-regulates several antioxidant and phase 2 detoxifying genes in cells. Targeted deletion of Nrf2 in mice produces no obvious phenotype under normal conditions. But Nrf2 null mice exhibit increased susceptibility to oxidant stress from pro-oxidant agents such as acetaminophen, which causes liver failure, and butylated hydroxytoluene, which causes respiratory failure. Nrf2 deficient mice are also sensitive to several oxidant-mediated injuries in the lung, including exposure to hyperoxia and bleomycin. A common theme in this susceptibility centers on uncompensated oxidant stress which causes excess inflammation along with extensive cell injury leading to cell death and organ failure. An expanding literature now supports Nrf2 as a general regulator of the ARE-mediated cellular antioxidant defense system that enables cell to survive under oxidant stress. The biological relevance of the Nrf2 pathway continues to expand with recent descriptions of its interaction with the notch1 signaling pathway during tissue...
regeneration and the p53/p21 pathway during cell cycle control in response to oxidant-mediated DNA damage. In fact, the known susceptibility of the p21 deficient lung to oxidant stress may result from lack of the p21 protein-protein interaction that liberates Nrf2 from its cytoplasmic inhibitor Keap1. Previous studies have documented induction of p21 protein in airway epithelial cells with asthma. This novel interaction with Nrf2 suggests a biological couple between cell cycle arrest and antioxidant activation that enables cell survival under oxidant stress.

The relevance of Nrf2 to oxidant stress and asthma stems from the fact that Nrf2 null mice are more susceptible to asthma than normal mice using ovalbumin to model experimental allergic airway disease. Oxidant stress, inflammation, airway hyperreactivity and mucus induction are magnified in the lungs of Nrf2 null mice compared to normal mice. Oxidant stress was quantified by total lung glutathione which rose in the normal lung, largely as reduced glutathione (GSH), but not in the Nrf2 null lung. The genes for glutathione synthesis were identified as Nrf2-targets in asthma, as well as in a variety of other oxidant-stress related murine models of lung injury in these mice. In addition, glutathione signaling was shown to be differentially utilized as an effector to regulate gene expression in Nrf2 dependent and independent pathways. These studies added further support to the central biologic role of the glutathione tripeptide in cellular redox homeostasis.

These studies in the Nrf2 null mouse models of increased susceptibility to oxidant stress suggested that oxidant stress is causal in various forms of lung injury, including asthma. They supported epidemiologic studies that linked antioxidant intake with decreased risk of asthma severity, and reinvigorated a search for antioxidant therapeutics to treat asthma despite the fact that single antioxidant agents were largely ineffective in clinical trials. In addition, studies using a mouse model of impaired glutathione metabolism together with those using glutathione precursors to manipulate glutathione homeostasis raised the possibility that antioxidants from separate intracellular or extracellular pools may be relevant for different cell types during asthma pathogenesis, such as immune cells during sensitization and epithelial cells in response to inflammation.

Taken altogether, these studies suggest different strategies that could be explored to develop novel antioxidant therapeutics for asthma. The first is a broad-based approach using activators of the Nrf2 pathway to induce an array of antioxidant genes to widely augment cellular antioxidant defense. One caveat, however, is that the therapeutic benefits of this broad-based approach cannot exclusively be attributed to an "antioxidant" mechanism of action. Nrf2 controls many cytoprotective genes in addition to known antioxidants, and these genes are also expressed at much lower levels in Nrf2 null versus normal mice. In addition, the more severe asthmatic phenotype in Nrf2 null mice is associated not only with increased oxidative stress, but also with increased inflammation. Since loss of Nrf2 does not appear to control production of Th2 cytokines directly, the increased inflammation is attributable to an oxidative stress-mediated activation of pro-inflammatory transcription factors, such as NF-κB. Nonetheless, such observations make it difficult to dissociate antioxidant from anti-inflammatory effects, or from effects on cytoprotective pathways other than those involving antioxidant enzymes, in strategies involving Nrf2 modulation.

A second and more specific therapeutic approach could be designed around more localized, or ROS-specific, interventions using synthetic antioxidant compounds, or agents that otherwise modulate levels of downstream effects of oxidants. Examples of this include...
glutathione selective approaches to augment content in extracellular pools by targeting glutathione metabolism in lung lining fluid. Other approaches that have been suggested include mitochondria-targeted antioxidants or synthetic catalytic ROS scavengers that can gain intracellular access, in some cases mitochondrial access.

2. Therapeutic approaches

**Broad-based strategy based on Nrf2 pathway activation.** Characterization and design of compounds that can activate the Nrf2 pathway are an active focus of research for inflammatory disease and cancer chemoprevention (also www.reatapharma.com). A group of synthetic triterpenoids are now known to exhibit cytoprotective, antioxidant and anti-inflammatory activity largely thru activation of the Nrf2 pathway and are under intense characterization and development as potent Nrf2 activators. CDDO-Im is a well characterized compound that can be delivered enterally and has shown therapeutic benefits in mouse models of hyperoxic acute lung injury, cystic fibrosis-like lung disease and lung cancer. There are no reports, as of yet, on the usage of an Nrf2 activator in allergic asthma. But the synthetic triterpenoid CDDO-Im has been shown to induce Nrf2-mediated activity and protection through its action in normal mice exposed to cigarette smoke as a model of chronic obstructive pulmonary disease, COPD, as compared to Nrf2 null mice. These results are instructive with regard to oxidant stress and airway function. The oxidant burden in COPD results not only from infiltration of the lung with inflammatory cells (which are mainly neutrophils in contrast to eosinophils in allergic asthma), but also from cigarette smoke itself and markers of oxidant stress have been consistently demonstrated in the lung and the blood of smoke-exposed mammals. Certain COPD phenotypes include lung cell injury and death, enlargement of alveoli and eventually right heart failure. All of these changes were modeled in normal mice exposed to cigarette smoke and all were attenuated by concomitant delivery of CDDO-Im as measured by decreased levels of oxidant stress, cellular apoptosis, alveolar destruction and pulmonary hypertension. Furthermore, when Nrf2 null mice were exposed to cigarette smoke, these changes were all magnified, compared to normal mice, and protection by CDDO-Im was absent, supporting the notion that this compound requires Nrf2 for much of its activity.

Interestingly, oxidant stress was assessed by total glutathione content of the lung which decreased acutely with exposure to cigarette smoke and increased over time in normal mice but not in Nrf2 null mice. Treatment with CDDO-Im increased lung glutathione even in normal mice exposed to air as a control, given that this compound is an electrophile itself, but again not in Nrf2 null mice. The genes for glutathione synthesis, γ-glutamyl cysteine ligase and glutathione synthetase, are known Nrf2 targets. The former is the rate limiting enzyme for glutathione synthesis, and its activity is regulated by glutathione levels thru feedback inhibition. Hence increasing content of this synthetic enzyme is permissive to an increase in glutathione content to reset feedback inhibition anew. This stimulation has the potential to be developed for increased protection of an “at risk” population exposed to primary or second-hand smoke. Even though single candidate association studies have not implicated these glutathione synthetic genes in asthma or COPD, they have implicated the glutathione-S-transferase genes GSTM1 and GSTP1, suggesting a role for glutathione derivatives with airway inflammation. Lastly, treatment with CDDO-Im did increase lung glutathione weakly in Nrf2 null mice exposed to cigarette smoke. This suggests an Nrf2-
independent mediator for some CDDO-Im activity that may be fulfilled by an Nrf2-related gene, such as Nrf1 or an Nrf2-independent pathway.

Regarding lung inflammation in this mouse model of COPD, the inflammatory load, assessed thru broncho-alveolar lavage, was similar in cigarette smoke-exposed normal mice regardless of treatment with CDDO-Im. Hence induction of Nrf2-regulated genes was sufficient to protect against cell injury and death in the cigarette smoke exposed lung despite a similar degree of inflammation. The array of antioxidant and detoxifying genes may have provided a much broader level of protection than that afforded by any single antioxidant therapy. The findings in COPD models suggest that CDDO-Im and similar agents should also be investigated as potential asthma treatments. Since inflammation is a prominent feature of established asthma, even in remission, it is possible that this treatment may have to be continued on a chronic basis to prevent future exacerbations. In this regard, CDDO-Im can attenuate cytokine and chemokine expression in LPS-stimulated neutrophils and thereby decrease the inflammatory response. If CDDO-Im can produce similar results in models of allergic inflammation, it could be used to prevent severe exacerbations of asthma. Such an approach is warranted as it has recently been reported that Nrf2 protein itself is susceptible to suppression and inactivation in children with severe asthma when oxidant stress is intense. In adult atopic asthmatics, allergen-provoked airway inflammation also suppresses Nrf2 protein function and this can be attenuated by larger than usual dosing of Vitamin E. The ultimate ability of Vitamin E to rescue Nrf2 function under intense oxidant stress is not yet known.

Selective strategies based on ROS-scavenging or other antioxidant-modulating compounds. These strategies would, in contrast to the very broad Nrf2-modulating approach described above, administer compounds with their own antioxidant properties, or others that specifically modulate endogenous antioxidants. As an example of the latter approach, genetic or pharmacological modulation of endogenous pools of glutathione (GSH) has beneficial effects in asthma models.

Glutathione Modulating Reagents: The central role of glutathione in antioxidant defense and signal transduction, was described previously in the literature and largely reinforced by studies with Nrf2. Studies with the Nrf2 null mice demonstrated that loss of the Nrf2 pathway perturbed lung glutathione homeostasis in the ovalbumin model of asthma. And recent literature demonstrated that glutathione alone can serve a direct role in asthma. In one example from the author’s laboratory, genetic loss of glutathione metabolism in lung lining fluid was shown to augment the concentration of the extracellular glutathione pool and prevent EGF receptor activation, airway epithelial cell mucin gene induction and airway hyperreactivity in a cytokine-driven model of asthma (Figure 1). Loss of glutathione metabolism resulted from the genetic absence of the regulatory enzyme γ-glutamyltrnaferase (GGT). Furthermore, asthma could be limited in normal mice by inhibiting their lung lining fluid GGT pharmacologically with the compound acivicin. A second example of pharmacologically modulating GSH pools involved the glutathione precursor γ-glutamylcysteinylethyl ester (γ-GCE) which was shown to effectively augment reduced cellular glutathione content (GSH) and redox ratio (GSH/GSSG) in antigen presenting cells to limit pro-inflammatory gene induction and attenuate lung inflammation in the ovalbumin model of asthma. Previous studies with cysteine precursors produced similar results but difference in cell permeability were hypothesized to limit overall effectiveness. A potential advantage of these two strategies is that their therapeutic
targets are more selective and focused on glutathione homeostasis itself as compared to the broad array of antioxidant and other cytoprotective genes activated by Nrf2.

Our finding that loss of glutathione metabolism in lung lining fluid could actually attenuate asthma was rather unexpected. Lung lining fluid (LLF) is a continuous but very thin layer of fluid that bathes the epithelial surface of the lung and shields alveolar cells against environmental and endogenous toxins, including oxidants. LLF contains an abundance of antioxidants, including reduced glutathione. This extracellular pool of glutathione buffers hypohalous acid, a potent oxidant from inflammatory cells and inhaled chlorine gas, limits hydrogen peroxides and lipid peroxide accumulation in conjunction with extracellular glutathione peroxidase, and maintains bioavailability of other small antioxidant molecules, such as nitric oxide, ascorbic acid, and alpha-tocopherol. In humans with asthma, the abundance of LLF glutathione content is increased beyond the normal level and the magnitude of this increase is inversely related to asthma severity.

Metabolism of LLF glutathione is regulated by a single extracellular enzyme, GGT, that is associated with surfactant phospholipid. Glutathione metabolism supplies cells with cysteine, the rate-limiting amino acid for glutathione biosynthesis. In the presence of oxidant stress, cells in the lung induce GGT via Nrf2 signaling to maintain cysteine availability for enhanced glutathione synthesis. In the absence of GGT, cells becomes starved for cysteine and glutathione deficiency results. Indeed in the GGTenu1 mouse model of GGT deficiency, lung cells are glutathione deficient and under oxidant stress even in normoxia, and this is magnified in hyperoxia. The presence of oxidant stress at baseline suggested that the GGTenu1 mouse would be more susceptible to asthma, which could then be attenuated by restoring cellular glutathione with a cysteine precursor. However, in a cytokine-driven model of allergic inflammation, cellular glutathione deficiency did not predispose the GGTenu1 mouse to asthma. Rather, in the absence of metabolism, LLF glutathione content in the GGTenu1 mouse increased well beyond its mildly elevated baseline level, buffered oxidant stress and shielded the GGTenu1 mouse lung against asthma, even though the level of inflammation matched that of the asthma-susceptible normal mouse lung. Moreover, asthma susceptibility in the normal mouse lung could be attenuated by inhibiting normal LLF GGT activity with the irreversible GGT inhibitor acivicin. To do this effectively, however, acivicin had to be delivered thru the airway (inhaled), as opposed to the systemic circulation.

These studies provided several insights about asthma and oxidant stress. First, the extracellular LLF glutathione pool can shield lung epithelial cells against oxidant-mediated induction of mucin gene expression and preserve barrier function despite cellular glutathione deficiency. Second, not all cellular sites of oxidant stress are directly casual in asthma. Endothelial, bronchial epithelial and alveolar macrophages of GGTenu1 lung exhibit oxidant stress at baseline, but methacholine-induced airway hyperreactivity is absent. Third, the LLF glutathione pool serves a dual role in antioxidant defense and cysteine supply with glutathione metabolism regulating the balance. As the key regulator of this metabolism, GGT is a novel target to treat asthma as it is accessible to inhibition thru the airway via its presence in lung surfactant and its modulation can augment the antioxidant capacity within LLF. Although acivicin can irreversibly inhibit GGT, there is a critical problem associated with its usage from a pharmaceutical point of view and that is CNS toxicity in vivo and inhibition of several glutamine-dependent biosynthetic enzymes. The recent design and
synthesis of a series of γ-phosphono diester analogues of glutamate as GGT inhibitors helped overcome this concern. The lead compound in this class of compounds is currently the most promising candidate for pharmaceuticals to chemically inactivate GGT activity in vivo. This compound does inhibit lung GGT activity and its advantages include greater specificity, potency, and lack of toxicity. Lastly, cellular glutathione deficiency can be averted by providing a cysteine precursor or the glutathione precursor γ-glutamylcysteinylester (γ-GCE). Esterification of glutathione as a means to increase its membrane permeability was described by Alton Meister. γ-glutamylcysteinyl ester uptake appears to be even more efficient than glutathione and it is directly converted to glutathione by glutathione synthetase which bypasses the rate-limiting enzyme γ-GCS. Hence it is feasible to augment both cellular and extracellular glutathione content using a combination of these reagents.

**Synthetic catalytic antioxidant mimetic compounds:** Superoxide dismutases (SOD) are key endogenous antioxidant defense enzymes, converting superoxide to hydrogen peroxide. There are three forms of SOD, cytosolic (SOD1), extracellular (ECSOD or SOD3) and mitochondrial (SOD2) and various studies have implicated one or more of the SOD enzymes in lung disease. Compared to other tissues, the lung has very high levels of ECSOD, localized in the vasculature and airways. Its localization, as well as its upregulation during inflammation and the increased SOD activity detected in BAL from asthma patients, makes it attractive to speculate that ECSOD plays a role in asthma. However, the relatively mild phenotype shown by mice lacking ECSOD in asthma models leaves the involvement of ECSOD unclear. The mitochondrial form of SOD (MnSOD or SOD2) is oxidatively inactivated in asthmatic airway samples, suggesting that impairment of mitochondrial oxidative defenses might contribute to the asthmatic phenotype. Evidence for mitochondrial injury in murine asthma models, discussed earlier, is consistent with this hypothesis, though the mechanism(s) of mitochondrial damage have not been elucidated. SOD2 polymorphisms are also associated with bronchial hyperresponsiveness in humans. The product of SOD, hydrogen peroxide, is neutralized by several different enzymes, including not only catalase but also various peroxidases including glutathione peroxidase, using glutathione as a substrate. Along with SOD, hydrogen peroxide scavenging enzymes have also been detected in the lung lining fluid, and may also contribute to defense against asthmatic responses. Such findings, overall, do imply that supplementation of the right antioxidant enzyme(s) at the right location(s) could be a viable therapeutic approach for asthma. To avoid the many pharmaceutical challenges, including stability, intracellular accessibility, and expense, associated with therapeutic use of proteins, some investigators have developed low molecular weight synthetic compounds with antioxidant activities. In particular three classes of Mn complex have been studied as catalytic antioxidant enzyme mimetics with efficacy in various disease models, including those involving the lung. Porphyrin Mn complexes and salen Mn complexes are multifunctional catalytic antioxidant compounds, acting on superoxide, hydrogen peroxide, and certain reactive nitrogen species. Macrocyclic Mn complexes, such as M40403, are a class of compounds reported to have SOD activity, with no hydrogen peroxide scavenging properties. Chang and Crapo reported that the Mn porphyrin AEOL-10150 suppressed inflammation and improved airway physiology in a murine allergic asthma model. M40403, a lead macrocyclic complex, was shown to be similarly effective in a guinea pig ovalbumin-induced asthma model. While there have not yet been reports of their effects in asthma models, salen Mn...
complexes, exemplified by compounds such as EUK-189 and a newer cyclized analog EUK-207, are also of potential interest. These compounds have efficacy in other lung injury models, such as a porcine ARDS and pulmonary radiation injury models. As compared to several other agents tested, salen Mn complexes were effective at preventing severe oxidative pathologies in mice lacking SOD2, implying that these compounds have the ability to protect the mitochondria. Certain Mn porphyrin compounds have also shown efficacy in mitochondrial injury models, while M40403 did not rescue mice lacking SOD2. If, indeed, mitochondrial injury is important in asthma, then the effects of such multifunctional ROS/RNS scavenging compounds deserve further study as potential asthma therapeutics. Unlike these Mn complexes, which have broader effects, certain other antioxidant compounds were designed to specifically target the mitochondria. While there has been no report yet testing such agents in asthma models, it seems likely that, because of the multiple potential sites of oxidative injury in asthma, an approach targeted only at the mitochondrial would not be optimally effective. It is worth noting, as well, that both Mn complexes that improved airway physiology in asthma models also suppressed inflammation. As was the case for the Nrf2 null mouse, this makes it difficult to sort out whether their therapeutic benefit is due primarily to their anti-oxidant properties, or is secondary to their anti-inflammatory effects. This is in contrast to the approaches aimed specifically at lung lining fluid GSH, where airway physiology and oxidative stress were improved in the absence of any suppression of inflammation. Certainly, a better understanding of the mechanism(s) and site(s) of action of a given agent will help to facilitate its successful use as an asthma drug. And potentially, for a disease as complex as asthma, combination therapies consisting of both anti-inflammatory and selected antioxidant compounds would be more effective than any agent given alone.

3. Summary

Oxidant stress induced by the accumulation of oxidants in excess of antioxidant defense plays a causal role in asthma. Recent studies in mouse models of asthma have drawn attention to the roles of oxidant stress and antioxidant defense in cellular and extracellular sites of the lung. Cellular sites of oxidant stress during immune cell activation and extracellular sites of oxidant stress in lung lining fluid may play distinct roles during the early phase of sensitization to allergens and the late phase of lung response to inflammation, respectively. It also appears that not all sites of oxidant stress are necessarily directly related to the development of AHR. Novel strategies to treat asthma may involve activation of the Nrf2 pathway and its array of antioxidant and cytoprotective genes, although the necessity of all of the genes is not yet clear, nor are the long term effects of deactivation of this pathway on normal cell function and asthma progression. Alternative strategies designed to modulate lung cell or lung lining fluid glutathione or to administer synthetic antioxidants with more specific ROS targets or other properties may (as compared to the broad panel of Nrf2-regulated antioxidants) provide a more focused approach to control pro-inflammatory stimuli and lung antioxidant defense. Of further interest would be whether the strategy, while acting against oxidative stress, is also anti-inflammatory (e.g. Nrf2 activation) or whether it appears to act downstream of inflammation (e.g. GGT inhibition to increase extracellular GSH). Communication of epithelial cell injury to the adaptive immune system and activation of airway inflammation are common themes identified in human genome-
wide association studies (GWAS) to date, although genes with known antioxidant functions are not readily apparent in susceptibility loci. GWAS studies have also confirmed the genetic heterogeneity of asthma. The causal mechanisms underlying any of these gene associations, however, are yet to be defined. Overall these data suggest that combinations of multiple agents are likely to be more effective than any agent alone. These might be agents that combat oxidative stress, through the various mechanisms discussed here, in combination with other treatments acting by distinct mechanisms to modulate anti-cytokine or anti-inflammatory pathways.

**Abbreviations:** SOD, superoxide dismutase; Nrf2, NF-E2 related factor 2; ARE, antioxidant response element; GSH, glutathione; GSSG, glutathione disulfide; GGT, gamma-glutamyl transferase; ROS, reactive oxygen species; LLF, lung lining fluid; BAL, bronch-alveolar lavage; CDDO-Im, 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole; GWAS, genome-wide association study.

### 4. Acknowledgement

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Asthma remains a serious health concern for millions of people globally. Despite continuing research interest, there have been few advancements that impact clinically on patient care, potentially because asthma has been treated as a homogeneous entity, rather than the heterogeneous condition it is. This book introduces cutting-edge research, which targets specific phenotypes of asthma, highlighting the differences that are present within this disease, and the varying approaches that are utilized to understand it.

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