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# New targets for resolution of airway remodeling in obstructive lung diseases.

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REVIEW

# New targets for resolution of airway remodeling in obstructive lung diseases [version 1; referees: 2 approved]

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**Abstract**



Airway remodeling (AR) is a progressive pathological feature of the obstructive lung diseases, including asthma and chronic obstructive pulmonary disease (COPD). The pathology manifests itself in the form of significant, progressive, and (to date) seemingly irreversible changes to distinct respiratory structural compartments. Consequently, AR correlates with disease severity and the gradual decline in pulmonary function associated with asthma and COPD. Although current asthma/COPD drugs manage airway contraction and inflammation, none of these effectively prevent or reverse features of AR. In this review, we provide a brief overview of the features and putative mechanisms affecting AR. We further discuss recently proposed strategies with promise for deterring or treating AR.

**Keywords**

airway remodeling, asthma, GPCR, smooth muscle

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## Airway remodeling in obstructive lung diseases

Airway remodeling (AR) can be defined as a progressive pathological reorganization of the cellular and molecular constitution of the airway wall. While the onset and rate of progression of structural changes in the airways have been subjects of immense debate, AR has been associated with each of the asthmatic phenotypes<sup>1</sup>. Furthermore, the gradual deleterious transformation in lungs can affect airways of all sizes along the bronchial tree. Although the strategies for reversing airway contraction and mitigating airway inflammation have been mainstays of asthma therapy, AR has been clinically intractable. Consequently, a pressing need exists for defining the fundamental pathways contributing to AR pathology and for empowering both basic and clinical research to address this problem. For a comprehensive understanding of the conceptual and practical challenges in AR research, readers are encouraged to review the official research statement of the American Thoracic Society<sup>2</sup>. In this current report, we provide an overview of the limitations of currently approved anti-asthma/chronic obstructive pulmonary disease (COPD) drugs in addressing AR and further describe the therapeutic potential of recently proposed approaches for targeting AR.

AR was first described in 1922 in patients whose death was attributed to asthma. Necropsy specimens from these patients revealed extensive bronchial mucus plugs and thickening of the airway wall<sup>3</sup>. Numerous subsequent clinical investigations have revealed that AR encompasses broad structural changes in the airway that includes thickening of the airway wall, airway smooth muscle (ASM) hyperplasia and hypertrophy, edema, subepithelial fibrosis, increased extracellular matrix (ECM) deposition, immune cell and fibroblast accumulation, angiogenesis,

altered matrix composition, goblet cell metaplasia, and mucus hypersecretion<sup>2</sup>. A consensus has emerged that multiple cell types (including epithelium, ASM, fibroblasts, and immune cells) contribute to the development of AR in asthma and COPD<sup>4,5</sup> (Table 1).

The role of the airway epithelium in triggering initial responses and sustaining architectural changes in asthmatic lungs is evident<sup>6,7</sup>. In asthma, repetitive damage to the epithelium from exposure to noxious environmental agents and immune modulators promotes shedding of the epithelium. Consequently, the underlying epithelial-mesenchymal trophic unit may be persistently active and in a reparative state, thus promoting chronic and progressive remodeling of the airway<sup>8</sup>. Remodeling manifests in the form of thickening of the epithelial layer, loss of cilia, compromised barrier function, mucus hypersecretion, and ECM remodeling of the subepithelial space<sup>6,7,9-17</sup>. Moreover, the number of mucus-secreting goblet cells also increases in asthmatics<sup>18,19</sup>. These features collectively contribute to anatomical changes that cause airway narrowing, increased fixed resistance, and mucus plugging of the bronchial lumen.

Physiological ASM function is crucial for maintaining adequate airflow. Changes in both ASM responsiveness and morphology occur with asthma, which affects airway resistance and airflow. A critical feature of AR is an increase in ASM mass that contributes significantly to asthma pathology<sup>20,21</sup>. Furthermore, the increased ASM mass and increased airway wall thickness reduce airway lumen area, resulting in increased dynamic and fixed resistance<sup>21-26</sup>. Asthmatic ASM can also acquire a synthetic phenotype, which is characterized by increased secretion of ECM, cytokines, and growth factors. Clinical outcomes

**Table 1. Contribution by distinct cell types to the overall pathology of airway remodeling in obstructive lung diseases.**

Lung cell type	Contribution to the pathophysiology of airway remodeling
Epithelial cells	Epithelial shedding
	Mucus secretion
	Subepithelial fibrosis
	Goblet cell hyperplasia
	Stimulating airway smooth muscle (ASM) proliferation through release of growth factors
	Recruitment of pro-inflammatory cells
	Promoting extracellular matrix (ECM) deposition
	Promoting angiogenesis
ASM cells	Increased ASM mass
	ASM migration and invasion of the epithelium
	Adoption of synthetic phenotype (for example, secretion of transforming growth factor-beta, chemokines, and ECM components)
	Interaction with immune cells through cell adhesion molecules
Fibroblasts	Differentiation into myofibroblasts and secretion of ECM components
	Accumulation in subepithelial regions

associated with bronchial thermoplasty intervention (application of controlled radiofrequency energy to the airway wall) suggest that reducing ASM area is sufficient to improve outcomes in asthmatics<sup>27</sup>.

Fibroblasts can contribute to AR through increased secretion of ECM<sup>28,29</sup>. Beyond contributing to increased airway wall thickness, ECM components can modulate cellular proliferation and migration. However, the role of fibroblast and ECM components in AR in the context of obstructive lung diseases is not fully understood.

The structural changes may contribute toward a gradual decline in lung function and potentially in loss of pulmonary elasticity, leading to hyperinflation and air trapping in lungs. Moreover, remodeling reduces effectiveness of bronchodilatory treatments<sup>3,30-32</sup>. A correlation between AR and disease severity has been established, but the clinical consequences of AR are yet to be fully understood<sup>33-38</sup>. This lack of knowledge also impacts drug discovery efforts. In the subsequent sections, we review the efficacy of current therapeutics in blunting or reversing AR and discuss novel therapeutic approaches to regulate progression of AR.

**Overview of current therapeutics and their limitations**

Current management of asthma focuses on reversing ASM contraction and mitigating airway inflammation. None of these approaches directly addresses the progressive pathology that causes remodeling in the lung (Table 2).

As noted earlier, bronchial thermoplasty has been shown to reduce ASM mass in conducting airways of some, but not all, severe asthmatics undergoing the procedure<sup>27,39,40</sup>. This procedure has been shown to significantly reduce collagen deposition in the basement membrane. Although bronchial thermoplasty has been shown to improve quality of life for severe asthmatics in the short term, the cost of the procedure, post-procedure exacerbations, and questions regarding long-term efficacy have limited its application<sup>41</sup>.

Among pharmacological options,  $\beta$ -agonists are the drug of choice for evoking bronchorelaxation in attempting to reverse an acute

asthma attack or for providing bronchoprotection when used in combination with an inhaled corticosteroid as a maintenance therapy. However, there is no compelling evidence that  $\beta$ -agonists deter or reverse AR<sup>5</sup>. Signaling through cysteinyl leukotriene receptors (CysLTRs) and muscarinic acetylcholine receptors (mAChRs) has been established to promote outcomes that contribute to AR<sup>42-44</sup>. Antagonists of both receptors have shown some utility in preventing AR. Treatment with the CysLTR antagonist montelukast reversed ovalbumin-induced AR by decreasing goblet cell metaplasia, ASM mass, and subepithelial collagen deposition<sup>45,46</sup>. In a cohort of mild asthmatics, montelukast treatment showed reduced accumulation of myofibroblasts in the airway wall, suggesting some potential to mitigate AR<sup>47</sup>. Similarly, the long-acting mAChR antagonist, tiotropium, has demonstrated a robust ability in preventing AR in rodent (guinea pig and mouse) models of ovalbumin-induced asthma and lipopolysaccharide-induced COPD<sup>48-52</sup>. Overall, although some evidence suggests that mAChR and CysLTR antagonists may have utility in deterring AR, additional studies in humans are necessary to establish the true effectiveness of these drugs in preventing or reversing AR<sup>5</sup>.

Persistent asthma is commonly treated with inhaled corticosteroids either as a monotherapy or in combination with a  $\beta$ -agonist or mAChR antagonist. In epithelial cells, corticosteroids limit the inflammatory response and induce apoptosis<sup>53,54</sup>. *In vitro*, multiple corticosteroids have been shown to significantly inhibit fibroblast proliferation either alone or in combination with  $\beta$ -agonists<sup>55,56</sup>. Similar anti-proliferative effects have also been reported with corticosteroids in ASM cells stimulated with distinct mitogenic agents<sup>57,58</sup>. However, others have shown that corticosteroids have no effect on ASM proliferation<sup>59,60</sup>. While corticosteroids inhibit growth factor-stimulated proliferation of ASM cells sourced from healthy controls, this effect was lacking on ASM cells from asthmatics<sup>59</sup>. In animal models, dexamethasone has been shown to reduce goblet cell metaplasia; however, this treatment showed no effect on ASM mass and subepithelial fibrosis<sup>45</sup>. In humans, in conjunction with limiting inflammation and airway hyperresponsiveness, corticosteroid treatment can also reduce mucin secretion and limit ECM deposition and AR<sup>61-64</sup>. However, others have shown that corticosteroids have a mixed effect on the resolution of subepithelial fibrosis<sup>65-70</sup>.

**Table 2. Current therapeutic targets for asthma management and their effect on airway remodeling.**

Class of therapeutic drugs	Target	Effect on airway remodeling
$\beta$ -agonists	$\beta_2$ -AR (beta 2 adrenergic receptor)	Limited effect on airway remodeling <sup>5</sup> . Combination therapy with inhaled corticosteroid limits angiogenesis and fibroblast proliferation <sup>55,56,71</sup> .
Inhaled corticosteroids	Glucocorticoid receptor	Combination therapy with $\beta$ -agonists limits angiogenesis <sup>71</sup> . Mixed anti-proliferative actions on airway smooth muscle cells and human fibroblasts <sup>55,56</sup> . Reduced mucin secretion and limited extracellular matrix deposition <sup>61-64</sup> .
Anti-leukotrienes	CysLTR (cysteinyl leukotriene receptor)	Moderate effect on airway smooth muscle mass, goblet cell metaplasia, and subepithelial collagen deposition <sup>45,46,62</sup> . Decreased accumulation of fibroblasts in lungs <sup>47</sup> .

Collectively, studies to date indicate a need for developing better therapeutic drugs for targeting AR pathology in obstructive lung diseases.

**New targets and approaches for airway remodeling**

In recent years, basic science research has begun to provide insight into the mechanisms, mediated by multiple cell types, that promote AR and these studies help to inform potential strategies for managing AR. Certain approaches that show promise in mitigating features of AR have recently been proposed (Table 3).

**(Other) G protein-coupled receptor ligands**

G protein-coupled receptors (GPCRs) play a substantial role in numerous normal physiological functions. Unsurprisingly, they can contribute towards the pathophysiology of various diseases. As noted earlier, GPCR agonists (of the  $\beta$ 2-adrenergic receptor) and antagonists (of the mAChRs and CysLTR) are principal drugs in the management of asthma and COPD. In this section, we provide a brief overview of novel targets, the drugs that modulate them, and the potential of such drugs to address AR pathology.

**E-prostanoid receptor agonists.** The role of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and E-prostanoid (EP) receptor subtypes in mitigating AR has been a subject of recent research. Early studies demonstrated that autocrine PGE<sub>2</sub>, generated as a consequence of cytokine-induced cyclooxygenase-2 induction, significantly suppresses mitogen-induced ASM proliferation *in vitro*<sup>72</sup>. Furthermore, studies of cultured human ASM in our laboratory have demonstrated that exogenous PGE<sub>2</sub> shows relatively superior anti-mitogenic activity in comparison to multiple  $\beta$ -agonists with anti-mitogenic effects corresponding to drug efficacy in activating the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) axis<sup>73,74</sup>. Application of PGE<sub>2</sub> in humans has been hindered by the ability of PGE<sub>2</sub> to signal through multiple receptor subtypes (EP1–4)<sup>75–79</sup>, which contributes to undesirable side effects. It is now known that the cough response is mediated by PGE<sub>2</sub> activation of the EP3 receptor on vagal sensory nerves<sup>80</sup>. Additionally, studies in our lab have shown that EP3 receptor signaling has a pro-mitogenic role in ASM<sup>74</sup>. To overcome the heterogeneity of PGE<sub>2</sub> signaling, the development of EP receptor subtype-specific modulators that specifically promote Gs-cAMP-PKA axis activity (via EP2 and EP4 subtypes) has been

**Table 3. Anti-remodeling effects of novel therapeutic approaches (*in vitro*, animal, and human studies).**

Class of therapeutic drugs	Target	Potential effect on airway remodeling (AR)
G protein-coupled receptor modulators	E-prostanoid receptors	Suppression of airway smooth muscle (ASM) proliferation <sup>72-74</sup> .
	Bitter taste receptors (TAS2Rs)	Regulation of ASM proliferation <sup>81,82</sup> . Reversal of allergen-induced AR features, including ASM mass <sup>83</sup> . Alteration of mitochondrial function and induction of autophagy <sup>84</sup> .
Biologics	Interleukin-5 (IL-5) cytokine	Reduced subepithelial fibrosis and extracellular matrix (ECM) deposition <sup>85,86</sup> .
	Immunoglobulin E	Reduced thickening of reticular lamina <sup>87</sup> .
Mitogen-activated protein kinase (MAPK) inhibitors	MEK1 (MAPK kinase)	Regulation of mucus secretion <sup>88,89</sup> .
	p38	Reduced ASM mass and goblet cell metaplasia <sup>90</sup> .
	c-Jun N-terminal kinases (JNKs)	Reduced mucus secretion and expansion of goblet cells <sup>91,92</sup> . Reduced proliferation of ASM and epithelial cells <sup>93</sup> .
	Transforming growth factor-beta-activated kinase 1 (TAK1)	Reduced synthesis of IL-8 in ASM cells and reduced proliferation <sup>94,95</sup> .
Receptor tyrosine kinase inhibitors	Epidermal growth factor receptor	Reduced proliferation of ASM and epithelial cells <sup>96-98</sup> .
		Regulation of mucus secretion <sup>99-102</sup> .
		Reduced ASM thickening and goblet cell metaplasia <sup>103</sup> .
	Platelet-derived growth factor receptor	Reduced ASM proliferation <sup>104</sup> .
Stem cell growth factor receptor (c-kit)	Attenuated collagen accumulation in lungs <sup>105</sup> .	
Non-receptor tyrosine kinase inhibitors	Spleen tyrosine kinase (Syk)	Reduced bronchial edema <sup>106</sup> .
	Janus kinase (JAK)	Reduced expression of Gob-5 <sup>107</sup> .
Other kinase inhibitors	TGF- $\beta$ receptor type I (T- $\beta$ RI) kinase	Diminished collagen deposition and reduced proliferation of ASM and epithelial cells in lungs <sup>108</sup> .
	Rho-associated protein kinase (ROCK)	Curtailed ECM remodeling process <sup>109</sup> .
Phosphodiesterase (PDE) inhibitors	PDEs	Marked reduction in subepithelial fibrosis and epithelial layer thickening <sup>110</sup> . Reduced proliferation of ASM <sup>111</sup> .

purposed<sup>84,112–114</sup>. Currently, our lab is evaluating various strategies of targeting specific EP receptor subtypes in pre-clinical models of allergen-induced asthma<sup>84</sup>.

**Bitter taste receptors.** Recently, our laboratory showed that bitter taste receptor (TAS2R) agonists can limit proliferation of ASM cells *in vitro*<sup>81,82</sup>. Mechanistically, TAS2R agonists restrict ASM proliferation by inhibiting (1) the growth factor-activated protein kinase B (Akt) phosphorylation; (2) transcription factors AP-1, STAT3, E2 factor, and NFAT; and (3) genes associated with cell cycle progression.

The anti-mitogenic effects of TAS2R agonists further translate to pre-clinical asthma models as well. In a chronic allergen (ovalbumin or house dust mite) challenge model, treatment with bitter taste compounds (chloroquine and quinine) significantly reversed remodeling features<sup>83</sup>. Specifically, treatment with bitter compounds inhibited the expression of calponin, smooth muscle alpha-actin, and smooth muscle myosin heavy chain in lungs. Furthermore, levels of matrix metalloproteinase-8 (MMP-8) (neutrophil collagenase), pro-MMP-9 (gelatinase), and MMP-12 (macrophage metalloelastase) were significantly reduced in lungs following treatment with TAS2R agonists. Finally, allergen-induced expression of pro-fibrotic cytokine transforming growth factor-beta (TGF- $\beta$ ) as well as phospho-mothers against decapentaplegic homolog 2 (pSmad2) and fibronectin in the lung tissue was also curtailed by TAS2R agonists. Collectively, these studies indicate that TAS2R agonists, unlike current GPCR ligands used to treat asthma, address multiple features of asthma pathology, including AR. Advancements in the development of selective ligands for TAS2R subtypes will allow for a refined therapeutic approach in the near future.

Bitter tastants have also been shown to modulate function of ciliated epithelial cells<sup>115</sup>. Specifically, the motile cilia on human airway epithelia express TAS2Rs (T2R4, T2R43, T2R38, and T2R46). The organization of TAS2Rs on cilia with the distribution of the signaling machinery along the ciliary shaft and within the attached epithelial cell presents an interesting mechanical apparatus for signal transduction. Stimulation of TAS2Rs with bitter tastants induces transient Ca<sup>2+</sup> flux within the epithelial cells and increases ciliary beat frequency. Functionally, promoting increased ciliary movement could be beneficial in the removal of excess mucus from the airways.

In recent years, the role of mitochondrial dysfunction in disease states, including obstructive lung diseases, has become increasingly clear<sup>116,117</sup>. Specifically, a role for autophagy/mitophagy in regulating mitochondrial function in pathophysiology of obstructive lung diseases is emerging. As noted earlier, our studies show that activation of TAS2Rs can promote anti-mitogenic activities. Further explorations into the mechanisms that underlie the anti-mitogenic effects of TAS2R agonists have uncovered an interesting role for bitter tastants in altering mitochondrial function and inducing autophagy<sup>82</sup>. TAS2R agonists can induce changes in mitochondrial membrane potential, increase reactive oxygen species generation, and promote mitochondrial fragmentation. These observations provide insight into the broader therapeutic potential of targeting mitochondrial function and promoting autophagy to restrict cellular proliferation.

## Biologics

Asthma pathology is orchestrated by multiple immunologic mediators (cellular and secreted)<sup>118</sup>. Consequently, in recent years, therapies that target specific cytokines or immune cells to disrupt immune networks responsible for asthma pathology have gained significant interest. Targeting key cytokines with specific antibodies—biologics, including antibodies targeting interleukin-4 (IL-4), IL-5, and IL-13—can significantly limit recruitment of inflammatory cells to the lungs or blunt their pleiotropic effects. For instance, anti-IL-5 treatment can significantly reduce the number of circulating eosinophils in asthmatics and improve lung function<sup>119–121</sup>. Anti-IL-5 treatment has been shown to prevent the development of subepithelial fibrosis in a murine model of asthma and reduce incorporation of proteoglycans in the human airway wall<sup>85,86</sup>. However, antibodies targeting other cytokines or their receptors have not been studied in the context of AR<sup>122</sup>. Collectively, the data on the effects of biologics on AR are lacking and this is possibly due to the relatively recent development of these drugs. Future longitudinal studies that evaluate biologics in the context of remediation of AR features are needed to address the utility of these drugs as anti-AR agents.

Allergen-specific immunoglobulin E (IgE) isotype antibodies can cross-link on mast cells and basophils, causing degranulation and release of histamine, cytokines, and growth factors<sup>123</sup>. Biologics that block the interactions of IgE antibodies to the high-affinity Fc $\epsilon$ RI receptors on mast cells and antigen presenting cells can curtail the sensitization profile in asthmatics and reduce exacerbations. In severe asthmatics evaluated for 36 months, blocking IgE activity was sufficient to reduce the thickening of the reticular lamina, thereby having an impact on AR<sup>87</sup>.

Although biologics have become an increasingly important tool in the management of severe asthma, their application in the clinic has some drawbacks<sup>124–126</sup>. Application of cytokine-specific antibody therapy is limited by the heterogeneity of asthma phenotypes<sup>127</sup>. Non-atopic asthmatics are also not suitable for certain therapy (for example, anti-IgE). Biologics can also cause side effects such as hypersensitivity reactions, although the underlying mechanisms are unclear. Finally, there is also significant cost associated with the use of biologics.

## Kinase inhibitors

Kinase enzymes modulate multiple cellular functions by regulating various signaling networks, including those regulating cellular proliferation and growth. Consequently, inhibitors that target various kinases have received increasing attention. Modulators of kinase functions account for one third of drugs in the development pipeline, and the majority of these represent cancer therapeutics<sup>128</sup>. In this section, we provide a brief overview of drugs that target distinct kinases. For a more comprehensive discussion of targeting kinases in the context of obstructive lung diseases, the reader is referred to<sup>129</sup>.

**Mitogen-activated protein kinase inhibitors.** Mitogen-activated protein kinases (MAPKs) have been studied extensively for their contribution to inflammatory gene expression and activation of multiple networks that contribute to the pathophysiology of obstructive lung diseases<sup>130</sup>. Extracellular signal-regulated

kinases (ERK1/2) are particularly interesting given that they are activated in multiple cell types that contribute to asthma and COPD pathology<sup>88,131,132</sup>. Inhibition of ERK kinase (MAPK1, or MEK1) which is upstream of ERK1/2 can significantly reduce mucin 5AC, oligomeric mucus/gel-forming (*MUC5AC*) expression in cultured human bronchial epithelial cells subjected to chronic mechanical stress at the air-liquid interface<sup>88,89</sup>. Other MAPKs, such as p38, c-Jun N-terminal kinase (JNK), and transforming growth factor beta-activated kinase 1 (TAK1), are activated in asthma and COPD<sup>129</sup>, and inhibitors of these targets can mitigate various features of AR in both cell and animal asthma models<sup>90–95</sup>. However, to date, no studies in humans have evaluated these inhibitors. Another limitation of kinase inhibitors is that these compounds are predominantly inhibitors of ATP-competitive and catalytic sites and block all enzymatic activity, including MAPK functions important for normal physiological activity in cells. Given the ubiquitous functions of the MAPK signaling pathway, development of substrate-selective MAPK inhibitors with the goal of targeting specific kinase functions associated with disease, while preserving kinase functions in normal cells, appears necessary to overcome limitations of off-target effects.

**Receptor tyrosine kinase inhibitors.** Receptor tyrosine kinases (RTKs) occupy a central role in critical signaling networks that promote asthma pathology, including remodeling<sup>133</sup>. With inflammation, distinct RTKs and their ligands (for example, epidermal growth factor) are upregulated in human asthmatic airways and show a strong correlation with disease severity<sup>134–143</sup>. RTKs can stimulate pathophysiological functions in ASM and epithelial cells. Thus, significant interest in advancing tyrosine kinase inhibitors for targeting RTKs has developed.

Activation of epidermal growth factor receptor (EGFR) is essential for mucus secretion and goblet cell metaplasia<sup>144</sup>. It is also responsible for sustaining oxidative damage in the epithelial compartment through recruitment of neutrophils in a TGF- $\beta$ -dependent manner<sup>145–148</sup>. EGFR inhibitors tyrphostin AG1478 and BIBX1522 have been evaluated *in vitro* and in animal models of lung inflammation<sup>99–101</sup>. Collectively, these studies report significant reductions in expression of mucus-associated *MUC5AC* gene and mucin secretion. More importantly, there is a concomitant reduction in collagen deposition and ASM proliferation<sup>96–98</sup>. Although these observations are encouraging, some inhibitors of EGFR have failed to produce similar outcomes in clinical studies<sup>149</sup>. Activation of platelet-derived growth factor receptor (PDGFR) has been shown to stimulate ASM proliferation *in vitro* and *in vivo*<sup>138,150,151</sup>. Multiple drugs targeting PDGFR can mitigate ASM proliferation *in vitro*, although animal and human studies that address AR are lacking<sup>104</sup>. In severe corticosteroid-dependent asthmatics, treatment with the tyrosine kinase inhibitor mastinib has shown improved outcomes; however, some adverse effects, including skin rash and edema, have also been reported<sup>152</sup>. During airway inflammation, multiple cell types (immune and resident) can be stimulated to secrete angiogenic factors, including vascular endothelial growth factor (VEGF)<sup>153–159</sup>. These angiogenic factors can further stimulate increase in formation of new blood vessels from endothelial cells in the sub-epithelial mucosa<sup>160–162</sup>. Although the contribution of neovascularization in AR is unclear, it has been suggested that newly formed

vasculature is permeable, thus contributing to edema and limiting airflow<sup>71,161,163,164</sup>. An antagonist of VEGFR-1 and VEGFR-2 (SU5416) has been shown to limit inflammatory responses in animals<sup>165</sup>, although its impact on AR is unknown and studies in humans are lacking.

Because multiple RTKs contribute to pathology of AR, a novel strategy that targets multiple RTKs has gained momentum. In a pre-clinical murine model of ovalbumin-induced asthma, treatment with nintedanib—a small-molecule inhibitor that targets multiple RTKs (VEGFR, fibroblast growth factor receptor, and PDGFR)—significantly improved indices of remodeling and airway inflammation<sup>166</sup>. This approach could be useful in targeting multiple redundant RTK networks that contribute to AR. Finally, inhibitors of non-RTKs, such as stem cell growth factor receptor (c-kit), spleen tyrosine kinase (SYK), the proto-oncogene tyrosine-protein kinase Src, and Janus kinase (JAK), have also been investigated in rodent models of asthma but have not yet progressed to studies in humans<sup>105,106,167–171</sup>.

**Other kinase inhibitors.** Diverse stimuli (cytokines, viruses, growth factors, free radicals, and so on) can activate the transcription factor nuclear factor-kappa B (NF- $\kappa$ B) in multiple airway cell types. This transcription factor plays a key role in orchestrating immune responses and thus multiple intra- and inter-cell inflammatory signals<sup>129</sup>. Although inhibitors that target activation of NF- $\kappa$ B have been shown to suppress certain synthetic functions of ASM<sup>172</sup> and modulate pro-inflammatory outcomes in epithelial cells<sup>173</sup>, specific NF- $\kappa$ B inhibitors have not translated into clinical trials for asthma and this is due to their multiple side effects<sup>129</sup>. Inhibitors of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI-3K) that regulate cellular lipids and coordinate inflammatory pathways have undergone extensive investigation in asthma and COPD<sup>174,175</sup>. However, data assessing AR indices are lacking. TGF- $\beta$  plays an important role in cellular proliferation and differentiation and its expression increases in asthmatic airways, especially in the submucosal compartment<sup>176–178</sup>. TGF- $\beta$  has also been implicated in AR and can promote proliferation in ASM<sup>179,180</sup>. TGF- $\beta$  activates TGF- $\beta$  receptor type I (T- $\beta$ RI) kinase, which in turn activates Smad-dependent signaling that regulates expression of various genes. Small-molecule inhibitors of (T- $\beta$ RI) kinase have yielded mixed results in studies assessing their effects on mechanisms mediating AR. T- $\beta$ RI kinase inhibitors have been shown to diminish collagen deposition in lungs of rats challenged repeatedly with an allergen<sup>108</sup>. *In vitro*, T- $\beta$ RI inhibitors have demonstrated the ability to limit ASM proliferation, although their use in animal studies failed to inhibit TGF- $\beta$ -induced increases in ASM mass<sup>108,181</sup>. Clinical application of these inhibitors has been limited due to adverse effects, including cardiotoxicity in clinical trials for cancer therapy<sup>182</sup>. Protein kinase C (PKC) is another target of interest given its ability to promote contractile signaling in ASM following activation of Gq-coupled GPCRs. PKC is also relevant to AR because of its role in ASM proliferation<sup>183</sup> and mucus secretion in epithelium<sup>148</sup>. Owing to severe toxicity, non-selective inhibitors of PKC have not progressed to clinical trials<sup>129,184</sup>. Selective inhibitors of PKC isoforms have been developed for clinical studies for treatment of cancer, metabolic diseases, and psychiatric disorders, although adverse effects have been problematic and no clinical trials have been



conducted for treatment of obstructive lung diseases in humans<sup>129,184</sup>. Finally, Rho-associated protein kinase (ROCK) inhibitors have been shown to mitigate multiple features of asthma, including AR in guinea pig and murine models<sup>109,185</sup>. Although ROCK inhibitors have been approved for certain indications, clinical trials in asthma or COPD are lacking<sup>129</sup> as issues regarding selectivity and toxicity have limited progression of these inhibitors to clinical application in airway diseases<sup>129</sup>.

In summary, *in vitro* studies of pharmacological inhibition of multiple kinases that contribute to dysfunction in ASM and epithelium have yielded promising results<sup>181,186</sup>. However, certain limitations have stalled progression of many drugs for clinical use. Specificity, efficacy, solubility issues, and poor pharmacokinetic profiles plague drug development<sup>187</sup>. With chronic inhibitor treatment, compensatory signaling by other kinases may limit drug efficacy; this appears to be the case with p38 isoform inhibitors<sup>129,188</sup>. Inhibition of any widely expressed kinase runs the risk of adverse effects. For example, given that NF- $\kappa$ B is crucial for mounting an immune response to microbial pathogens, blocking its activation could render patients susceptible to life-threatening infections<sup>129</sup>. Current challenges in developing effective and safe kinase inhibitors hinge on improving the poor solubility, selectivity, and targeting of the current versions of these drugs<sup>129</sup>.

#### Other small-molecule inhibitors

Phosphodiesterase (PDE) inhibitors have a beneficial effect of promoting ASM relaxation by increasing intracellular cAMP resulting in PKA-mediated ASM relaxation. In murine models of asthma, PDE inhibitors have also been shown to curtail inflammation and reduce AR<sup>110</sup>. Inhibition of PDE3 (but not PDE4) has anti-proliferative action on mitogen-activated human ASM cells *in vitro*, but as with most potential anti-AR drugs, useful *in vivo* data are lacking<sup>111</sup>. More recently, an inhibitor of PDE8 (PF-04957325) has been shown to regulate proliferation of ASM cells by enhancing cAMP accumulation generated specifically from the  $\beta$ 2-AR/AC6 pathway<sup>189</sup>.

The rapamycin derivative SAR-943 has been shown to limit the mitogen-induced proliferation of human ASM cells (but not human epithelial cells) *in vitro* and mitigate inflammation and AR *in vivo* in ovalbumin-challenged mice<sup>190</sup>, yet no clinical studies for asthma or COPD have been reported.

#### Conclusions

The correlation between AR and obstructive lung disease severity suggests a strong pathogenic role of AR in these diseases. Thus, remediation of AR appears critical for improving the severity and progression of these diseases. A growing arsenal of small-molecule

inhibitors and biologics in conjunction with non-pharmacological interventions such as bronchial thermoplasty has shown promise in addressing this unmet clinical need. As our understanding of mechanisms underlying AR improves, so will the drug development approaches as well as the phenotyping capabilities that accurately assess AR in humans. These advances will undoubtedly fulfill our need for more refined, efficacious, and safer drugs that enable us to finally control the entire spectrum of asthma pathology.

#### Abbreviations

AR, airway remodeling;  $\beta$ <sub>2</sub>-AR, beta 2 adrenergic receptor; ASM, airway smooth muscle; cAMP, cyclic adenosine monophosphate; c-kit, Stem cell growth factor receptor; COPD, chronic obstructive pulmonary disease; CysLTR, cysteinyl leukotriene receptor; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EP, E prostanoid; ERK1/2, extracellular signal-regulated kinases 1/2; GPCR, G protein-coupled receptor; FGFR, fibroblast growth factor receptor; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; mAChR, muscarinic acetylcholine receptor; MAPK, mitogen-activated protein kinase; MEK1, mitogen-activated protein kinase kinase 1; MMP, matrix metalloproteinase; MUC5AC: mucin 5AC, oligomeric mucus/gel-forming; NF- $\kappa$ B, nuclear factor-kappa B; PDE, phosphodiesterase; PDGFR, platelet-derived growth factor receptor; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; PI-3K, phosphatidylinositol-4,5 biphosphate 3-kinase; PKA, protein kinase A; PKC, protein kinase C; ROCK, Rho-associated proteinase kinase; RTK, receptor tyrosine kinase; Smad2: Mothers against decapentaplegic homolog 2; Syk, spleen tyrosine kinase; TAK1, Transforming growth factor- $\beta$ -activated kinase 1; TAS2R, bitter taste receptor; TGF- $\beta$ , transforming growth factor-beta; T- $\beta$ RI, transforming growth factor-beta receptor type I kinase; VEGFR; vascular endothelial growth factor receptor

#### Competing interests

The authors declare that they have no competing interests.

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#### References

1. James AL, Maxwell PS, Pearce-Pinto G, *et al.*: **The relationship of reticular basement membrane thickness to airway wall remodeling in asthma.** *Am J Respir Crit Care Med.* 2002; **166**(12 Pt 1): 1590–5. [PubMed Abstract](#) | [Publisher Full Text](#)
2. Prakash YS, Halayko AJ, Gosens R, *et al.*: **An Official American Thoracic Society Research Statement: Current Challenges Facing Research and Therapeutic Advances in Airway Remodeling.** *Am J Respir Crit Care Med.* 2017; **195**(2): e4–e19. [PubMed Abstract](#) | [Publisher Full Text](#)



3. HUBER HL, KOESSLER KK: **THE PATHOLOGY OF BRONCHIAL ASTHMA.** *Arch Intern Med.* 1922; **30**: 689.  
[Publisher Full Text](#)
4. Kuwano K, Bosken CH, Paré PD, *et al.*: **Small airways dimensions in asthma and in chronic obstructive pulmonary disease.** *Am Rev Respir Dis.* 1993; **148**(5): 1220–5.  
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Halwani R, Al-Muhsen S, Hamid Q: **Airway remodeling in asthma.** *Curr Opin Pharmacol.* 2010; **10**(3): 236–45.  
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Fahy JV: **Remodeling of the airway epithelium in asthma.** *Am J Respir Crit Care Med.* 2001; **164**(10 Pt 2): S46–51.  
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Davies DE: **The bronchial epithelium in chronic and severe asthma.** *Curr Allergy Asthma Rep.* 2001; **1**(2): 127–33.  
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Holgate ST, Arshad HS, Roberts GC, *et al.*: **A new look at the pathogenesis of asthma.** *Clin Sci (Lond).* 2009; **118**(7): 439–50.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Loxham M, Davies DE, Blume C: **Epithelial function and dysfunction in asthma.** *Clin Exp Allergy.* 2014; **44**(11): 1299–313.  
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Lambrecht BN, Hammad H: **The airway epithelium in asthma.** *Nat Med.* 2012; **18**(5): 684–92.  
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Erle DJ, Sheppard D: **The cell biology of asthma.** *J Cell Biol.* 2014; **205**(5): 621–31.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. Holgate ST: **The airway epithelium is central to the pathogenesis of asthma.** *Allergol Int.* 2008; **57**(1): 1–10.  
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Holgate ST: **Pathogenesis of asthma.** *Clin Exp Allergy.* 2008; **38**(6): 872–97.  
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Sumi Y, Hamid Q: **Airway remodeling in asthma.** *Allergol Int.* 2007; **56**(4): 341–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
15. Hirota JA, Hackett TL, Inman MD, *et al.*: **Modeling asthma in mice: what have we learned about the airway epithelium?** *Am J Respir Cell Mol Biol.* 2011; **44**(4): 431–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Bossé Y, Paré PD, Seow CY: **Airway wall remodeling in asthma: from the epithelial layer to the adventitia.** *Curr Allergy Asthma Rep.* 2008; **8**(4): 357–66.  
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Proud D, Leigh R: **Epithelial cells and airway diseases.** *Immunol Rev.* 2011; **242**(1): 186–204.  
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Aikawa T, Shimura S, Sasaki H, *et al.*: **Marked goblet cell hyperplasia with mucus accumulation in the airways of patients who died of severe acute asthma attack.** *Chest.* 1992; **101**(4): 916–21.  
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Kim KC, McCracken K, Lee BC, *et al.*: **Airway goblet cell mucin: its structure and regulation of secretion.** *Eur Respir J.* 1997; **10**(11): 2644–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
20. **F** Pascoe CD, Seow CY, Hackett TL, *et al.*: **Heterogeneity of airway wall dimensions in humans: a critical determinant of lung function in asthmatics and nonasthmatics.** *Am J Physiol Lung Cell Mol Physiol.* 2017; **312**(3): L425–L431.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
21. Prakash YS: **Airway smooth muscle in airway reactivity and remodeling: what have we learned?** *Am J Physiol Lung Cell Mol Physiol.* 2013; **305**(12): L912–33.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Gosens R, Grainge C: **Bronchoconstriction and airway biology: potential impact and therapeutic opportunities.** *Chest.* 2015; **147**(3): 798–803.  
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Noble PB, Pascoe CD, Lan B, *et al.*: **Airway smooth muscle in asthma: linking contraction and mechanotransduction to disease pathogenesis and remodelling.** *Pulm Pharmacol Ther.* 2014; **29**(2): 96–107.  
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Johnson PR: **Role of human airway smooth muscle in altered extracellular matrix production in asthma.** *Clin Exp Pharmacol Physiol.* 2001; **28**(3): 233–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Johnson PR, Burgess JK: **Airway smooth muscle and fibroblasts in the pathogenesis of asthma.** *Curr Allergy Asthma Rep.* 2004; **4**(2): 102–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
26. Panettieri RA Jr: **Airway smooth muscle: an immunomodulatory cell.** *J Allergy Clin Immunol.* 2002; **110**(6 Suppl): S269–74.  
[PubMed Abstract](#) | [Publisher Full Text](#)
27. Chakir J, Haj-Salem I, Gras D, *et al.*: **Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Collagen Deposition in Asthma.** *Ann Am Thorac Soc.* 2015; **12**(11): 1612–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Pain M, Bermudez O, Lacombe P, *et al.*: **Tissue remodelling in chronic bronchial diseases: from the epithelial to mesenchymal phenotype.** *Eur Respir Rev.* 2014; **23**(131): 118–30.  
[PubMed Abstract](#) | [Publisher Full Text](#)
29. **F** Ball SL, Mann DA, Wilson JA, *et al.*: **The Role of the Fibroblast in Inflammatory Upper Airway Conditions.** *Am J Pathol.* 2016; **186**(2): 225–33.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
30. Bonacci JV, Stewart AG: **Regulation of human airway mesenchymal cell proliferation by glucocorticoids and beta<sub>2</sub>-adrenoceptor agonists.** *Pulm Pharmacol Ther.* 2006; **19**(1): 32–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Girodet PO, Ozier A, Bara I, *et al.*: **Airway remodeling in asthma: new mechanisms and potential for pharmacological intervention.** *Pharmacol Ther.* 2011; **130**(3): 325–37.  
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Hassan M, Jo T, Risse PA, *et al.*: **Airway smooth muscle remodeling is a dynamic process in severe long-standing asthma.** *J Allergy Clin Immunol.* 2010; **125**(5): 1037–1045.e3.  
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Mitsunobu F, Tanizaki Y: **The use of computed tomography to assess asthma severity.** *Curr Opin Allergy Clin Immunol.* 2005; **5**(1): 85–90.  
[PubMed Abstract](#) | [Publisher Full Text](#)
34. Bai TR: **Evidence for airway remodeling in chronic asthma.** *Curr Opin Allergy Clin Immunol.* 2010; **10**(1): 82–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
35. Yamauchi K: **Airway remodeling in asthma and its influence on clinical pathophysiology.** *Tohoku J Exp Med.* 2006; **209**(2): 75–87.  
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Niimi A, Matsumoto H, Takemura M, *et al.*: **Clinical assessment of airway remodeling in asthma: utility of computed tomography.** *Clin Rev Allergy Immunol.* 2004; **27**(1): 45–58.  
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Aysola R, de Lange EE, Castro M, *et al.*: **Demonstration of the heterogeneous distribution of asthma in the lungs using CT and hyperpolarized helium-3 MRI.** *J Magn Reson Imaging.* 2010; **32**(6): 1379–87.  
[PubMed Abstract](#) | [Publisher Full Text](#)
38. Montaudon M, Lederlin M, Reich S, *et al.*: **Bronchial measurements in patients with asthma: comparison of quantitative thin-section CT findings with those in healthy subjects and correlation with pathologic findings.** *Radiology.* 2009; **253**(3): 844–53.  
[PubMed Abstract](#) | [Publisher Full Text](#)
39. **F** Cox G, Thomson NC, Rubin AS, *et al.*: **Asthma control during the year after bronchial thermoplasty.** *N Engl J Med.* 2007; **356**(13): 1327–37.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
40. Pavord ID, Cox G, Thomson NC, *et al.*: **Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma.** *Am J Respir Crit Care Med.* 2007; **176**(12): 1185–91.  
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Wahidi MM, Kraft M: **Bronchial thermoplasty for severe asthma.** *Am J Respir Crit Care Med.* 2012; **185**(7): 709–14.  
[PubMed Abstract](#) | [Publisher Full Text](#)
42. **F** Trian T, Allard B, Dupin I, *et al.*: **House dust mites induce proliferation of severe asthmatic smooth muscle cells via an epithelium-dependent pathway.** *Am J Respir Crit Care Med.* 2015; **191**(5): 538–46.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
43. **F** Grainge CL, Lau LC, Ward JA, *et al.*: **Effect of bronchoconstriction on airway remodeling in asthma.** *N Engl J Med.* 2011; **364**(21): 2006–15.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
44. Kistemaker LE, Oenema TA, Meurs H, *et al.*: **Regulation of airway inflammation and remodeling by muscarinic receptors: perspectives on anticholinergic therapy in asthma and COPD.** *Life Sci.* 2012; **91**(21–22): 1126–33.  
[PubMed Abstract](#) | [Publisher Full Text](#)
45. **F** Henderson WR Jr, Chiang GK, Tien YT, *et al.*: **Reversal of allergen-induced airway remodeling by CysLT<sub>2</sub> receptor blockade.** *Am J Respir Crit Care Med.* 2006; **173**(7): 718–28.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
46. Muz MH, Deveci F, Bulut Y, *et al.*: **The effects of low dose leukotriene receptor antagonist therapy on airway remodeling and cysteinyl leukotriene expression in a mouse asthma model.** *Exp Mol Med.* 2006; **38**(2): 109–18.  
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Kelly MM, Chakir J, Vethanayagam D, *et al.*: **Montelukast treatment attenuates the increase in myofibroblasts following low-dose allergen challenge.** *Chest.* 2006; **130**(3): 741–53.  
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Gosens R, Bos IS, Zaagsma J, *et al.*: **Protective effects of tiotropium bromide in the progression of airway smooth muscle remodeling.** *Am J Respir Crit Care Med.* 2005; **171**(10): 1096–102.  
[PubMed Abstract](#) | [Publisher Full Text](#)
49. Pera T, Zuidhof A, Valadas J, *et al.*: **Tiotropium inhibits pulmonary inflammation and remodelling in a guinea pig model of COPD.** *Eur Respir J.* 2011; **38**(4): 789–96.  
[PubMed Abstract](#) | [Publisher Full Text](#)
50. Ohta S, Oda N, Yokoe T, *et al.*: **Effect of tiotropium bromide on airway inflammation and remodelling in a mouse model of asthma.** *Clin Exp Allergy.* 2010; **40**(8): 1266–75.  
[PubMed Abstract](#) | [Publisher Full Text](#)
51. Kang JY, Rhee CK, Kim JS, *et al.*: **Effect of tiotropium bromide on airway remodeling in a chronic asthma model.** *Ann Allergy Asthma Immunol.* 2012;

- 109(1): 29–35.  
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Bos IS, Gossens R, Zuidhof AB, *et al.*: Inhibition of allergen-induced airway remodelling by tiotropium and budesonide: a comparison. *Eur Respir J*. 2007; 30(4): 653–61.  
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Levine SJ, Larivée P, Logun C, *et al.*: Corticosteroids differentially regulate secretion of IL-6, IL-8, and G-CSF by a human bronchial epithelial cell line. *Am J Physiol*. 1993; 265(4 Pt 1): L360–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Dorscheid DR, Wojcik KR, Sun S, *et al.*: Apoptosis of airway epithelial cells induced by corticosteroids. *Am J Respir Crit Care Med*. 2001; 164(10 Pt 1): 1939–47.  
[PubMed Abstract](#) | [Publisher Full Text](#)
55. Sabatini F, Silvestri M, Sale R, *et al.*: Concentration-dependent effects of mometasone furoate and dexamethasone on foetal lung fibroblast functions involved in airway inflammation and remodeling. *Pulm Pharmacol Ther*. 2003; 16(5): 287–97.  
[PubMed Abstract](#) | [Publisher Full Text](#)
56. Descalzi D, Folli C, Nicolini G, *et al.*: Anti-proliferative and anti-remodelling effect of beclomethasone dipropionate, formoterol and salbutamol alone or in combination in primary human bronchial fibroblasts. *Allergy*. 2008; 63(4): 432–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Young PG, Skinner SJ, Black PN: Effects of glucocorticoids and beta-adrenoceptor agonists on the proliferation of airway smooth muscle. *Eur J Pharmacol*. 1995; 273(1–2): 137–43.  
[PubMed Abstract](#) | [Publisher Full Text](#)
58. Stewart AG, Fernandes D, Tomlinson PR: The effect of glucocorticoids on proliferation of human cultured airway smooth muscle. *Br J Pharmacol*. 1995; 116(8): 3219–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Damera G, Fogle HW, Lim P, *et al.*: Vitamin D inhibits growth of human airway smooth muscle cells through growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase 1. *Br J Pharmacol*. 2009; 158(6): 1429–41.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. Perry MM, Baker JE, Gibbon DS, *et al.*: Airway smooth muscle hyperproliferation is regulated by microRNA-221 in severe asthma. *Am J Respir Cell Mol Biol*. 2014; 50(1): 7–17.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
61. Ward C, Reid DW, Orsida BE, *et al.*: Inter-relationships between airway inflammation, reticular basement membrane thickening and bronchial hyper-reactivity to methacholine in asthma; a systematic bronchoalveolar lavage and airway biopsy analysis. *Clin Exp Allergy*. 2005; 35(12): 1565–71.  
[PubMed Abstract](#) | [Publisher Full Text](#)
62. Bergeron C, Tulic MK, Hamid Q: Airway remodelling in asthma: from benchside to clinical practice. *Can Respir J*. 2010; 17(4): e85–93.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. Laitinen A, Altraja A, Kämpe M, *et al.*: Tenascin is increased in airway basement membrane of asthmatics and decreased by an inhaled steroid. *Am J Respir Crit Care Med*. 1997; 156(3 Pt 1): 951–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Laitinen LA, Laitinen A: Inhaled corticosteroid treatment for asthma. *Allergy Proc*. 1995; 16(2): 63–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Boulet LP, Turcotte H, Lavolette M, *et al.*: Airway hyperresponsiveness, inflammation, and subepithelial collagen deposition in recently diagnosed versus long-standing mild asthma. Influence of inhaled corticosteroids. *Am J Respir Crit Care Med*. 2000; 162(4 Pt 1): 1308–13.  
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Olivieri D, Chetta A, Del Donno M, *et al.*: Effect of short-term treatment with low-dose inhaled fluticasone propionate on airway inflammation and remodeling in mild asthma: a placebo-controlled study. *Am J Respir Crit Care Med*. 1997; 155(6): 1864–71.  
[PubMed Abstract](#) | [Publisher Full Text](#)
67. Trigg CJ, Manolitsas ND, Wang J, *et al.*: Placebo-controlled immunopathologic study of four months of inhaled corticosteroids in asthma. *Am J Respir Crit Care Med*. 1994; 150(1): 17–22.  
[PubMed Abstract](#) | [Publisher Full Text](#)
68. Hoshino M, Takahashi M, Takai Y, *et al.*: Inhaled corticosteroids decrease subepithelial collagen deposition by modulation of the balance between matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 expression in asthma. *J Allergy Clin Immunol*. 1999; 104(2 Pt 1): 356–63.  
[PubMed Abstract](#) | [Publisher Full Text](#)
69. Sont JK, Willems LN, Bel EH, *et al.*: Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. *Am J Respir Crit Care Med*. 1999; 159(4 Pt 1): 1043–51.  
[PubMed Abstract](#) | [Publisher Full Text](#)
70. Chakir J, Shannon J, Molet S, *et al.*: Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression. *J Allergy Clin Immunol*. 2003; 111(6): 1293–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
71. Orsida BE, Li X, Hickey B, *et al.*: Vascularity in asthmatic airways: relation to inhaled steroid dose. *Thorax*. 1999; 54(4): 289–95.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
72. Belvisi MG, Saunders M, Yacoub M, *et al.*: Expression of cyclo-oxygenase-2 in human airway smooth muscle is associated with profound reductions in cell growth. *Br J Pharmacol*. 1998; 125(5): 1102–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Misior AM, Yan H, Pascual RM, *et al.*: Mitogenic effects of cytokines on smooth muscle are critically dependent on protein kinase A and are unmasked by steroids and cyclooxygenase inhibitors. *Mol Pharmacol*. 2008; 73(2): 566–74.  
[PubMed Abstract](#) | [Publisher Full Text](#)
74. Yan H, Deshpande DA, Misior AM, *et al.*: Anti-mitogenic effects of  $\beta$ -agonists and PGE<sub>2</sub> on airway smooth muscle are PKA dependent. *FASEB J*. 2011; 25(1): 389–97.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
75. Kawakami Y, Uchiyama K, Irie T, *et al.*: Evaluation of aerosols of prostaglandins E<sub>1</sub> and E<sub>2</sub> as bronchodilators. *Eur J Clin Pharmacol*. 1973; 6(2): 127–32.  
[PubMed Abstract](#) | [Publisher Full Text](#)
76. Walters EH, Davies BH: Dual effect of prostaglandin E<sub>2</sub> on normal airways smooth muscle *in vivo*. *Thorax*. 1982; 37(12): 918–22.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
77. Costello JF, Dunlop LS, Gardiner PJ: Characteristics of prostaglandin induced cough in man. *Br J Clin Pharmacol*. 1985; 20(4): 355–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
78. Coleridge HM, Coleridge JC, Ginzler KH, *et al.*: Stimulation of 'irritant' receptors and afferent C-fibres in the lungs by prostaglandins. *Nature*. 1976; 264(5585): 451–3.  
[PubMed Abstract](#) | [Publisher Full Text](#)
79. Gauvreau GM, Watson RM, O'Byrne PM: Protective effects of inhaled PGE<sub>2</sub> on allergen-induced airway responses and airway inflammation. *Am J Respir Crit Care Med*. 1999; 159(1): 31–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
80. Maher SA, Birrell MA, Belvisi MG: Prostaglandin E<sub>2</sub> mediates cough via the EP<sub>3</sub> receptor: implications for future disease therapy. *Am J Respir Crit Care Med*. 2009; 180(10): 923–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
81. Sharma P, Panebra A, Pera T, *et al.*: Antimitogenic effect of bitter taste receptor agonists on airway smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol*. 2016; 310(4): L365–76.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
82. Pan S, Sharma P, Shah SD, *et al.*: Bitter taste receptor agonists alter mitochondrial function and induce autophagy in airway smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol*. 2017; 313(4): L154–L165.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
83. Sharma P, Yi R, Nayak AP, *et al.*: Bitter Taste Receptor Agonists Mitigate Features of Allergic Asthma in Mice. *Sci Rep*. 2017; 7: 46166.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
84. Pera T, Penn RB: Bronchoprotection and bronchorelaxation in asthma: New targets, and new ways to target the old ones. *Pharmacol Ther*. 2016; 164: 82–96.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. Flood-Page P, Menzies-Gow A, Phipps S, *et al.*: Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest*. 2003; 112(7): 1029–36.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
86. Blythe DI, Wharton TF, Pedrick MS, *et al.*: Airway subepithelial fibrosis in a murine model of atopic asthma: suppression by dexamethasone or anti-interleukin-5 antibody. *Am J Respir Cell Mol Biol*. 2000; 23(2): 241–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
87. Riccio AM, Mauri P, De Ferrari L, *et al.*: Galectin-3: an early predictive biomarker of modulation of airway remodeling in patients with severe asthma treated with omalizumab for 36 months. *Clin Transl Allergy*. 2017; 7: 6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
88. Li N, Li Q, Zhou XD, *et al.*: Chronic mechanical stress induces mucin 5AC expression in human bronchial epithelial cells through ERK dependent pathways. *Mol Biol Rep*. 2012; 39(2): 1019–28.  
[PubMed Abstract](#) | [Publisher Full Text](#)
89. Shinkai M, López-Boado YS, Rubín BK: Clarithromycin has an immunomodulatory effect on ERK-mediated inflammation induced by *Pseudomonas aeruginosa* flagellin. *J Antimicrob Chemother*. 2007; 59(6): 1096–101.  
[PubMed Abstract](#) | [Publisher Full Text](#)
90. Nath P, Leung SY, Williams A, *et al.*: Importance of p38 mitogen-activated protein kinase pathway in allergic airway remodeling and bronchial hyperresponsiveness. *Eur J Pharmacol*. 2006; 544(1–3): 160–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
91. Nath P, Eynott P, Leung SY, *et al.*: Potential role of c-Jun NH<sub>2</sub>-terminal kinase in allergic airway inflammation and remodeling: effects of SP600125. *Eur J Pharmacol*. 2005; 506(3): 273–83.  
[PubMed Abstract](#) | [Publisher Full Text](#)
92. Wu H, Fang L, Shen QY, *et al.*: SP600125 promotes resolution of allergic airway inflammation via TLR9 in an OVA-induced murine acute asthma model. *Mol Immunol*. 2015; 67(2 Pt B): 311–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
93. Eynott PR, Nath P, Leung SY, *et al.*: Allergen-induced inflammation and airway epithelial and smooth muscle cell proliferation: role of Jun N-terminal kinase.

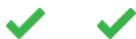
- Br J Pharmacol.* 2003; **140**(8): 1373–80.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
94. Pera T, Atmaj C, van der Vegt M, *et al.*: **Role for TAK1 in cigarette smoke-induced proinflammatory signaling and IL-8 release by human airway smooth muscle cells.** *Am J Physiol Lung Cell Mol Physiol.* 2012; **303**(3): L272–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
95. Pera T, Sami R, Zaagsma J, *et al.*: **TAK1 plays a major role in growth factor-induced phenotypic modulation of airway smooth muscle.** *Am J Physiol Lung Cell Mol Physiol.* 2011; **301**(5): L822–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
96. Krymskaya VP, Orsini MJ, Eszterhas AJ, *et al.*: **Mechanisms of proliferation synergy by receptor tyrosine kinase and G protein-coupled receptor activation in human airway smooth muscle.** *Am J Respir Cell Mol Biol.* 2000; **23**(4): 546–54.  
[PubMed Abstract](#) | [Publisher Full Text](#)
97. Puddicombe SM, Polosa R, Richter A, *et al.*: **Involvement of the epidermal growth factor receptor in epithelial repair in asthma.** *FASEB J.* 2000; **14**(10): 1362–74.  
[PubMed Abstract](#) | [Publisher Full Text](#)
98. Booth BW, Adler KB, Bonner JC, *et al.*: **Interleukin-13 induces proliferation of human airway epithelial cells *in vitro* via a mechanism mediated by transforming growth factor- $\alpha$ .** *Am J Respir Cell Mol Biol.* 2001; **25**(6): 739–43.  
[PubMed Abstract](#) | [Publisher Full Text](#)
99. Hegab AE, Sakamoto T, Nomura A, *et al.*: **Niflumic acid and AG-1478 reduce cigarette smoke-induced mucin synthesis: the role of hCLCA1.** *Chest.* 2007; **131**(4): 1149–56.  
[PubMed Abstract](#) | [Publisher Full Text](#)
100. **F** Takezawa K, Ogawa T, Shimizu S, *et al.*: **Epidermal growth factor receptor inhibitor AG1478 inhibits mucus hypersecretion in airway epithelium.** *Am J Rhinol Allergy.* 2016; **30**(1): 1–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
101. Burchell PR, Lazarus SC, Tam DC, *et al.*: **Human eosinophils induce mucin production in airway epithelial cells via epidermal growth factor receptor activation.** *J Immunol.* 2001; **167**(10): 5948–54.  
[PubMed Abstract](#) | [Publisher Full Text](#)
102. Kim S, Lewis C, Nadel JA: **CCL20/CCR6 feedback exaggerates epidermal growth factor receptor-dependent MUC5AC mucin production in human airway epithelial (NCI-H292) cells.** *J Immunol.* 2011; **186**(6): 3392–400.  
[PubMed Abstract](#) | [Publisher Full Text](#)
103. Le Cras TD, Acciani TH, Mushaben EM, *et al.*: **Epithelial EGF receptor signaling mediates airway hyperreactivity and remodeling in a mouse model of chronic asthma.** *Am J Physiol Lung Cell Mol Physiol.* 2011; **300**(3): L414–21.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
104. Bossé Y, Thompson C, Stankova J, *et al.*: **Fibroblast growth factor 2 and transforming growth factor beta1 synergism in human bronchial smooth muscle cell proliferation.** *Am J Respir Cell Mol Biol.* 2006; **34**(6): 746–53.  
[PubMed Abstract](#) | [Publisher Full Text](#)
105. Berlin AA, Hogaboam CM, Lukacs NW: **Inhibition of SCF attenuates peribronchial remodeling in chronic cockroach allergen-induced asthma.** *Lab Invest.* 2006; **86**(6): 557–65.  
[PubMed Abstract](#) | [Publisher Full Text](#)
106. Yamamoto N, Takeshita K, Shichijo M, *et al.*: **The orally available spleen tyrosine kinase inhibitor 2-[7-(3,4-dimethoxyphenyl)-imidazo[1,2-c]pyrimidin-5-ylamino]nicotinamide dihydrochloride (BAY 61-3606) blocks antigen-induced airway inflammation in rodents.** *J Pharmacol Exp Ther.* 2003; **306**(3): 1174–81.  
[PubMed Abstract](#) | [Publisher Full Text](#)
107. Matsunaga Y, Inoue H, Fukuyama S, *et al.*: **Effects of a Janus kinase inhibitor, pyridone 6, on airway responses in a murine model of asthma.** *Biochem Biophys Res Commun.* 2011; **404**(1): 261–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
108. Leung SY, Niimi A, Noble A, *et al.*: **Effect of transforming growth factor- $\beta$  receptor I kinase inhibitor 2,4-disubstituted pteridine (SD-208) in chronic allergic airway inflammation and remodeling.** *J Pharmacol Exp Ther.* 2006; **319**(2): 586–94.  
[PubMed Abstract](#) | [Publisher Full Text](#)
109. Possa SS, Charafeddine HT, Righetti RF, *et al.*: **Rho-kinase inhibition attenuates airway responsiveness, inflammation, matrix remodeling, and oxidative stress activation induced by chronic inflammation.** *Am J Physiol Lung Cell Mol Physiol.* 2012; **303**(11): L939–52.  
[PubMed Abstract](#) | [Publisher Full Text](#)
110. Kumar RK, Herbert C, Thomas PS, *et al.*: **Inhibition of inflammation and remodeling by roflumilast and dexamethasone in murine chronic asthma.** *J Pharmacol Exp Ther.* 2003; **307**(1): 349–55.  
[PubMed Abstract](#) | [Publisher Full Text](#)
111. Billington CK, Joseph SK, Swan C, *et al.*: **Modulation of human airway smooth muscle proliferation by type 3 phosphodiesterase inhibition.** *Am J Physiol.* 1999; **276**(3 Pt 1): L412–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
112. Buckley J, Birrell MA, Maher SA, *et al.*: **EP<sub>4</sub> receptor as a new target for bronchodilator therapy.** *Thorax.* 2011; **66**(12): 1029–35.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
113. Birrell MA, Maher SA, Dekkak B, *et al.*: **Anti-inflammatory effects of PGE<sub>2</sub> in the lung: role of the EP<sub>4</sub> receptor subtype.** *Thorax.* 2015; **70**(8): 740–7.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
114. Tilley SL, Hartney JM, Erikson CJ, *et al.*: **Receptors and pathways mediating the effects of prostaglandin E<sub>2</sub> on airway tone.** *Am J Physiol Lung Cell Mol Physiol.* 2003; **284**(4): L599–606.  
[PubMed Abstract](#) | [Publisher Full Text](#)
115. **F** Shah AS, Ben-Shahar Y, Moninger TO, *et al.*: **Motile cilia of human airway epithelia are chemosensory.** *Science.* 2009; **325**(5944): 1131–4.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
116. Aravamudan B, Thompson MA, Pabelick CM, *et al.*: **Mitochondria in lung diseases.** *Expert Rev Respir Med.* 2013; **7**(6): 631–46.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
117. **F** Prakash YS, Pabelick CM, Sieck GC: **Mitochondrial Dysfunction in Airway Disease.** *Chest.* 2017; **152**(3): 618–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
118. Lambrecht BN, Hammad H: **The immunology of asthma.** *Nat Immunol.* 2015; **16**(1): 45–56.  
[PubMed Abstract](#) | [Publisher Full Text](#)
119. Nair P: **Anti-interleukin-5 monoclonal antibody to treat severe eosinophilic asthma.** *N Engl J Med.* 2014; **371**(13): 1249–51.  
[PubMed Abstract](#) | [Publisher Full Text](#)
120. **F** Russell R, Brightling C: **Mepolizumab for the reduction of exacerbations in severe eosinophilic asthma.** *Expert Rev Respir Med.* 2016; **10**(6): 607–17.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
121. **F** Russell R, Brightling CE: **Anti-IL-5 for Severe Asthma: Aiming High to Achieve Success.** *Chest.* 2016; **150**(4): 766–8.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
122. Cho JY: **Recent advances in mechanisms and treatments of airway remodeling in asthma: a message from the bench side to the clinic.** *Korean J Intern Med.* 2011; **26**(4): 367–83.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
123. Gould HJ, Sutton BJ: **IgE in allergy and asthma today.** *Nat Rev Immunol.* 2008; **8**(3): 205–17.  
[PubMed Abstract](#) | [Publisher Full Text](#)
124. Bousquet J, Chiron R, Humbert M: **Biologics in asthma: difficulties and drawbacks.** *Expert Opin Biol Ther.* 2008; **8**(12): 1921–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
125. McCracken JL, Tripple JW, Calhoun WJ: **Biologic therapy in the management of asthma.** *Curr Opin Allergy Clin Immunol.* 2016; **16**(4): 375–82.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
126. Darveaux J, Busse WW: **Biologics in asthma—the next step toward personalized treatment.** *J Allergy Clin Immunol Pract.* 2015; **3**(2): 152–60; quiz 161.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
127. Godar M, Blanchet C, de Haard H, *et al.*: **Personalized medicine with biologics for severe type 2 asthma: current status and future prospects.** *MAbs.* 2018; **10**(1): 34–45.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
128. Wu P, Nielsen TE, Clausen MH: **FDA-approved small-molecule kinase inhibitors.** *Trends Pharmacol Sci.* 2015; **36**(7): 422–39.  
[PubMed Abstract](#) | [Publisher Full Text](#)
129. **F** Barnes PJ: **Kinases as Novel Therapeutic Targets in Asthma and Chronic Obstructive Pulmonary Disease.** *Pharmacol Rev.* 2016; **68**(3): 788–815.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
130. **F** Khorasanizadeh M, Eskian M, Gelfand EW, *et al.*: **Mitogen-activated protein kinases as therapeutic targets for asthma.** *Pharmacol Ther.* 2017; **174**: 112–26.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
131. Kim DH, Jung WS, Kim ME, *et al.*: **Genistein inhibits pro-inflammatory cytokines in human mast cell activation through the inhibition of the ERK pathway.** *Int J Mol Med.* 2014; **34**(6): 1669–74.  
[PubMed Abstract](#) | [Publisher Full Text](#)
132. Kono Y, Nishiuma T, Okada T, *et al.*: **Sphingosine kinase 1 regulates mucin production via ERK phosphorylation.** *Pulm Pharmacol Ther.* 2010; **23**(1): 36–42.  
[PubMed Abstract](#) | [Publisher Full Text](#)
133. Guntur VP, Reiner CR: **The potential use of tyrosine kinase inhibitors in severe asthma.** *Curr Opin Allergy Clin Immunol.* 2012; **12**(1): 68–75.  
[PubMed Abstract](#) | [Publisher Full Text](#)
134. Amishima M, Munakata M, Nasuhara Y, *et al.*: **Expression of epidermal growth factor and epidermal growth factor receptor immunoreactivity in the asthmatic human airway.** *Am J Respir Crit Care Med.* 1998; **157**(6 Pt 1): 1907–12.  
[PubMed Abstract](#) | [Publisher Full Text](#)
135. Polosa R, Puddicombe SM, Krishna MT, *et al.*: **Expression of c-erbB receptors and ligands in the bronchial epithelium of asthmatic subjects.** *J Allergy Clin Immunol.* 2002; **109**(1): 75–81.  
[PubMed Abstract](#) | [Publisher Full Text](#)
136. Takeyama K, Dabbagh K, Lee HM, *et al.*: **Epidermal growth factor system regulates mucin production in airways.** *Proc Natl Acad Sci U S A.* 1999; **96**(6): 3081–6.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
137. Takeyama K, Fahy JV, Nadel JA: **Relationship of epidermal growth factor receptors to goblet cell production in human bronchi.** *Am J Respir Crit Care Med.* 2001; **163**(2): 511–6.  
[PubMed Abstract](#) | [Publisher Full Text](#)
138. Wu LS, Tan C, Wang LM, *et al.*: **Variant in promoter region of platelet-derived growth factor receptor- $\alpha$  (PDGFR $\alpha$ ) gene is associated with the severity and allergic status of childhood asthma.** *Int Arch Allergy Immunol.*

- 2006; 141(1): 37–46.  
[PubMed Abstract](#) | [Publisher Full Text](#)
139. Leung TF, Wong GW, Ko FW, *et al.*: Analysis of growth factors and inflammatory cytokines in exhaled breath condensate from asthmatic children. *Int Arch Allergy Immunol.* 2005; 137(1): 66–72.  
[PubMed Abstract](#) | [Publisher Full Text](#)
140. Lee CG, Link H, Baluk P, *et al.*: Vascular endothelial growth factor (VEGF) induces remodeling and enhances TH2-mediated sensitization and inflammation in the lung. *Nat Med.* 2004; 10(10): 1095–103.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
141. Asai K, Kanazawa H, Kamoi H, *et al.*: Increased levels of vascular endothelial growth factor in induced sputum in asthmatic patients. *Clin Exp Allergy.* 2003; 33(5): 595–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
142. Da Silva CA, Blay F, Israel-Biet D, *et al.*: Effect of glucocorticoids on stem cell factor expression in human asthmatic bronchi. *Clin Exp Allergy.* 2006; 36(3): 317–24.  
[PubMed Abstract](#) | [Publisher Full Text](#)
143. Makowska JS, Cieslak M, Kowalski ML: Stem cell factor and its soluble receptor (c-kit) in serum of asthmatic patients- correlation with disease severity. *BMC Pulm Med.* 2009; 9: 27.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
144. Nadel JA, Burgel PR: The role of epidermal growth factor in mucus production. *Curr Opin Pharmacol.* 2001; 1(3): 254–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
145. Hamilton LM, Torres-Lozano C, Puddicombe SM, *et al.*: The role of the epidermal growth factor receptor in sustaining neutrophil inflammation in severe asthma. *Clin Exp Allergy.* 2003; 33(2): 233–40.  
[PubMed Abstract](#) | [Publisher Full Text](#)
146. Takeyama K, Dabbagh K, Jeong Shim J, *et al.*: Oxidative stress causes mucin synthesis via transactivation of epidermal growth factor receptor: role of neutrophils. *J Immunol.* 2000; 164(3): 1546–52.  
[PubMed Abstract](#) | [Publisher Full Text](#)
147. Takeyama K, Jung B, Shim JJ, *et al.*: Activation of epidermal growth factor receptors is responsible for mucin synthesis induced by cigarette smoke. *Am J Physiol Lung Cell Mol Physiol.* 2001; 280(1): L165–72.  
[PubMed Abstract](#) | [Publisher Full Text](#)
148. Shao MX, Nadel JA: Neutrophil elastase induces MUC5AC mucin production in human airway epithelial cells via a cascade involving protein kinase C, reactive oxygen species, and TNF- $\alpha$ -converting enzyme. *J Immunol.* 2005; 175(6): 4009–16.  
[PubMed Abstract](#) | [Publisher Full Text](#)
149. Woodruff PG, Wolff M, Hohlfield JM, *et al.*: Safety and efficacy of an inhaled epidermal growth factor receptor inhibitor (BIBW 2948 BS) in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2010; 181(5): 438–45.  
[PubMed Abstract](#) | [Publisher Full Text](#)
150. Hirst SJ, Barnes PJ, Twort CH: PDGF isoform-induced proliferation and receptor expression in human cultured airway smooth muscle cells. *Am J Physiol.* 1996; 270(3 Pt 1): L415–28.  
[PubMed Abstract](#) | [Publisher Full Text](#)
151. Hirota JA, Ask K, Farkas L, *et al.*: In vivo role of platelet-derived growth factor-BB in airway smooth muscle proliferation in mouse lung. *Am J Respir Cell Mol Biol.* 2011; 45(3): 566–72.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
152. Humbert M, de Blay F, Garcia G, *et al.*: Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics. *Allergy.* 2009; 64(8): 1194–201.  
[PubMed Abstract](#) | [Publisher Full Text](#)
153. Chetta A, Zanini A, Foresi A, *et al.*: Vascular endothelial growth factor up-regulation and bronchial wall remodelling in asthma. *Clin Exp Allergy.* 2005; 35(11): 1437–42.  
[PubMed Abstract](#) | [Publisher Full Text](#)
154. Zanini A, Chetta A, Saetta M, *et al.*: Chymase-positive mast cells play a role in the vascular component of airway remodeling in asthma. *J Allergy Clin Immunol.* 2007; 120(2): 329–33.  
[PubMed Abstract](#) | [Publisher Full Text](#)
155. Hoshino M, Nakamura Y, Hamid QA: Gene expression of vascular endothelial growth factor and its receptors and angiogenesis in bronchial asthma. *J Allergy Clin Immunol.* 2001; 107(6): 1034–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
156. Hoshino M, Takahashi M, Aoike N: Expression of vascular endothelial growth factor, basic fibroblast growth factor, and angiogenin immunoreactivity in asthmatic airways and its relationship to angiogenesis. *J Allergy Clin Immunol.* 2001; 107(2): 295–301.  
[PubMed Abstract](#) | [Publisher Full Text](#)
157. Simcock DE, Kanabar V, Clarke GW, *et al.*: Induction of angiogenesis by airway smooth muscle from patients with asthma. *Am J Respir Crit Care Med.* 2008; 178(5): 460–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)
158. Simcock DE, Kanabar V, Clarke GW, *et al.*: Proangiogenic activity in bronchoalveolar lavage fluid from patients with asthma. *Am J Respir Crit Care Med.* 2007; 176(2): 146–53.  
[PubMed Abstract](#) | [Publisher Full Text](#)
159. Keglowlch L, Roth M, Philippova M, *et al.*: Bronchial smooth muscle cells of asthmatics promote angiogenesis through elevated secretion of CXCL-chemokines (ENA-78, GRO- $\alpha$ , and IL-8). *PLoS One.* 2013; 8(12): e81494.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
160. Barbato A, Turato G, Baraldo S, *et al.*: Epithelial damage and angiogenesis in the airways of children with asthma. *Am J Respir Crit Care Med.* 2006; 174(9): 975–81.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
161. Vrugt B, Wilson S, Bron A, *et al.*: Bronchial angiogenesis in severe glucocorticoid-dependent asthma. *Eur Respir J.* 2000; 15(6): 1014–21.  
[PubMed Abstract](#) | [Publisher Full Text](#)
162. Tanaka H, Yamada G, Saikai T, *et al.*: Increased airway vascularity in newly diagnosed asthma using a high-magnification bronchovideoscope. *Am J Respir Crit Care Med.* 2003; 168(12): 1495–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
163. Nagy JA, Benjamin L, Zeng H, *et al.*: Vascular permeability, vascular hyperpermeability and angiogenesis. *Angiogenesis.* 2008; 11(2): 109–19.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
164. Li X, Wilson JW: Increased vascularity of the bronchial mucosa in mild asthma. *Am J Respir Crit Care Med.* 1997; 156(1): 229–33.  
[PubMed Abstract](#) | [Publisher Full Text](#)
165. Kim YS, Hong SW, Choi JP, *et al.*: Vascular endothelial growth factor is a key mediator in the development of T cell priming and its polarization to type 1 and type 17 T helper cells in the airways. *J Immunol.* 2009; 183(8): 5113–20.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
166. Lee HY, Hur J, Kim IK, *et al.*: Effect of nintedanib on airway inflammation and remodeling in a murine chronic asthma model. *Exp Lung Res.* 2017; 43(4–5): 187–96.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
167. Berlin AA, Lukacs NW: Treatment of cockroach allergen asthma model with imatinib attenuates airway responses. *Am J Respir Crit Care Med.* 2005; 171(1): 35–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
168. Seow CJ, Chue SC, Wong WS: Piceatannol, a Syk-selective tyrosine kinase inhibitor, attenuated antigen challenge of guinea pig airways in vitro. *Eur J Pharmacol.* 2002; 443(1–3): 189–96.  
[PubMed Abstract](#) | [Publisher Full Text](#)
169. Sakai H, Nishimura A, Watanabe Y, *et al.*: Involvement of Src family kinase activation in angiotensin II-induced hyperresponsiveness of rat bronchial smooth muscle. *Peptides.* 2010; 31(12): 2216–21.  
[PubMed Abstract](#) | [Publisher Full Text](#)
170. Kudlacz E, Conklyn M, Andresen C, *et al.*: The JAK-3 inhibitor CP-690550 is a potent anti-inflammatory agent in a murine model of pulmonary eosinophilia. *Eur J Pharmacol.* 2008; 582(1–3): 154–61.  
[PubMed Abstract](#) | [Publisher Full Text](#)
171. Ghoreschi K, Jesson MI, Li X, *et al.*: Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J Immunol.* 2011; 186(7): 4234–43.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
172. Catley MC, Sukkar MB, Chung KF, *et al.*: Validation of the anti-inflammatory properties of small-molecule I $\kappa$ B Kinase (IKK)-2 inhibitors by comparison with adenoviral-mediated delivery of dominant-negative IKK1 and IKK2 in human airways smooth muscle. *Mol Pharmacol.* 2006; 70(2): 697–705.  
[PubMed Abstract](#) | [Publisher Full Text](#)
173. Newton R, Holden NS, Catley MC, *et al.*: Repression of inflammatory gene expression in human pulmonary epithelial cells by small-molecule I $\kappa$ B kinase inhibitors. *J Pharmacol Exp Ther.* 2007; 321(2): 734–42.  
[PubMed Abstract](#) | [Publisher Full Text](#)
174. Doukas J, Eide L, Stebbins K, *et al.*: Aerosolized phosphoinositide 3-kinase gamma/delta inhibitor TG100-115 [3-[2,4-diamino-6-(3-hydroxyphenyl)pteridin-7-yl]phenol] as a therapeutic candidate for asthma and chronic obstructive pulmonary disease. *J Pharmacol Exp Ther.* 2009; 328(3): 758–65.  
[PubMed Abstract](#) | [Publisher Full Text](#)
175. Wilson R, Cahn A, Deans A, *et al.*: Safety, tolerability and pharmacokinetics (PK) of single and repeat nebulised doses of a novel phosphoinositide 3-kinase  $\delta$  inhibitor (PI3K $\delta$ ), GSK2269557, administered to healthy male subjects in a phase I study. *Eur Respir J.* 2013; 42: 729.  
[Reference Source](#)
176. Massagué J: TGF $\beta$  signalling in context. *Nat Rev Mol Cell Biol.* 2012; 13(10): 616–30.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
177. Kokturk N, Tatlicioglu T, Memis L, *et al.*: Expression of transforming growth factor beta1 in bronchial biopsies in asthma and COPD. *J Asthma.* 2003; 40(8): 887–93.  
[PubMed Abstract](#) | [Publisher Full Text](#)
178. Balzar S, Chu HW, Silkoff P, *et al.*: Increased TGF-beta2 in severe asthma with eosinophilia. *J Allergy Clin Immunol.* 2005; 115(1): 110–7.  
[PubMed Abstract](#) | [Publisher Full Text](#)
179. Aschner Y, Downey GP: Transforming Growth Factor- $\beta$ : Master Regulator of the Respiratory System in Health and Disease. *Am J Respir Cell Mol Biol.* 2016; 54(5): 647–55.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
180. Goldsmith AM, Bentley JK, Zhou L, *et al.*: Transforming growth factor-beta induces airway smooth muscle hypertrophy. *Am J Respir Cell Mol Biol.* 2006; 34(2): 247–54.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

181. Xie S, Sukkar MB, Issa R, *et al.*: **Mechanisms of induction of airway smooth muscle hyperplasia by transforming growth factor-beta.** *Am J Physiol Lung Cell Mol Physiol.* 2007; **293**(1): L245–53.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
182. Herberitz S, Sawyer JS, Stauber AJ, *et al.*: **Clinical development of galunisertib (LY2157299 monohydrate), a small molecule inhibitor of transforming growth factor-beta signaling pathway.** *Drug Des Devel Ther.* 2015; **9**: 4479–99.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
183. Carlin S, Poronnik P, Cook DI, *et al.*: **An antisense of protein kinase C-zeta inhibits proliferation of human airway smooth muscle cells.** *Am J Respir Cell Mol Biol.* 2000; **23**(4): 555–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
184. Mochly-Rosen D, Das K, Grimes KV: **Protein kinase C, an elusive therapeutic target?** *Nat Rev Drug Discov.* 2012; **11**(12): 937–57.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
185. Schaafsma D, Bos IS, Zuidhof AB, *et al.*: **The inhaled Rho kinase inhibitor Y-27632 protects against allergen-induced acute bronchoconstriction, airway hyperresponsiveness, and inflammation.** *Am J Physiol Lung Cell Mol Physiol.* 2008; **295**(1): L214–9.  
[PubMed Abstract](#) | [Publisher Full Text](#)
186. Lee KY, Ito K, Hayashi R, *et al.*: **NF-kappaB and activator protein 1 response elements and the role of histone modifications in IL-1beta-induced TGF-beta1 gene transcription.** *J Immunol.* 2006; **176**(1): 603–15.  
[PubMed Abstract](#) | [Publisher Full Text](#)
187. Dienstmann R, Rodon J, Serra V, *et al.*: **Picking the point of inhibition: a comparative review of PI3K/AKT/mTOR pathway inhibitors.** *Mol Cancer Ther.* 2014; **13**(15): 1021–31.  
[PubMed Abstract](#) | [Publisher Full Text](#)
188. Norman P: **Investigational p38 inhibitors for the treatment of chronic obstructive pulmonary disease.** *Expert Opin Investig Drugs.* 2015; **24**(3): 383–92.  
[PubMed Abstract](#) | [Publisher Full Text](#)
189. **F** Johnstone TB, Smith KH, Koziol-White CJ, *et al.*: **PDE8 Is Expressed in Human Airway Smooth Muscle and Selectively Regulates cAMP Signaling by  $\beta_2$ -Adrenergic Receptors and Adenylyl Cyclase 6.** *Am J Respir Cell Mol Biol.* 2018; **58**(4): 530–41.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
190. Fujitani Y, Trifilieff A: **In vivo and in vitro effects of SAR 943, a rapamycin analogue, on airway inflammation and remodeling.** *Am J Respir Crit Care Med.* 2003; **167**(2): 193–8.  
[PubMed Abstract](#) | [Publisher Full Text](#)

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## The referees who approved this article are:

### Version 1

- 1 **Omar Tliba** Rutgers Institute for Translational Medicine and Science, Child Health Institute of New Jersey, The State University of New Jersey, New Jersey, USA  
**Competing Interests:** No competing interests were disclosed.
- 1 **Rennolds Ostrom** Department of Biomedical and Pharmaceutical Sciences, Chapman University School of Pharmacy, California, USA  
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