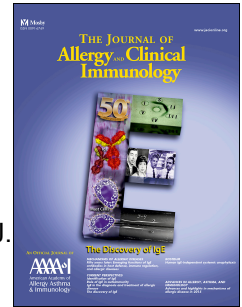


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Advances in asthma in 2017: Mechanism, biologics, and genetics

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Abstract

This review summarizes some of the most significant advances in asthma research over the past year. We first focus on novel discoveries in the mechanism of asthma development and exacerbation. This is followed by a discussion of potential new biomarkers, including the use of radiographic markers of disease. Several new biologics have become available to the clinician in the past year, and we summarize these advances and how they may influence the clinical delivery of asthma care. Following this, important findings in the genetics of asthma and heterogeneity in phenotypes of the disease are explored, as is the role the environment plays in shaping the development and exacerbation of asthma. Finally, we conclude with a discussion of advances in health literacy and how they will impact asthma care.

Introduction

This past year significant achievements have been made in nearly all areas of asthma research. This review highlights many of these important advances. While we focused on publications from the *Journal of Allergy and Clinical Immunology*, we also identified numerous other studies that have helped move the field forward. Studies cited extend our understanding of the mechanisms through which asthma develops and exacerbates (figure 1), as well as newly identified potential biomarkers. We also report several studies exploring new imaging techniques.

We summarize important developments in new therapies and therapeutic targets for asthma (figure 2). This is followed by a discussion on genetics of asthma and the heterogeneity of asthma phenotypes. The role environment plays in shaping development and exacerbation of asthma is examined as well (figure 3). We conclude with a section on health literacy, a critical component for successfully treating asthma, and other related advances.

Our summary is not a comprehensive list of all the novel and important information that has been gleaned about asthma and its treatment, but provides an indication of the direction of research and potential discoveries that remain to be uncovered.

Biomarkers and mechanisms

This past year saw advances in understanding mechanisms that drive development and exacerbation of asthma (figure 1). Using both human and mouse data, these studies assessed cellular and molecular interactions underlying asthma, and identified new biomarkers – both cellular/protein and clinical – that may delineate the risk of developing asthma.

Risk of developing wheeze/asthma

Studies this year continued to examine the influence of respiratory viruses on subsequent wheeze or asthma. Lukkarinen et al. evaluated risk factors for asthma at 7 years of age, based on the first severe wheezing episode (90% hospitalized with their wheezing episode).¹ Examining 127 children, the authors found that wheezing with rhinovirus, having allergic sensitization at the time of wheezing illness, and eczema were all risk factors for having atopic asthma at 7 years. Interestingly, non-atopic asthma at 7 years of age associated with parental smoking or RSV infection (without evidence of rhinovirus) as the cause of initial wheeze, and was associated with wheezing before 1 year of age. In addition to providing predictive

biomarkers for atopic versus non-atopic asthma, this study suggests mechanisms of viral-induced disease differ between rhinovirus and RSV. The Childhood Origins of ASThma (COAST) study found a similar risk for atopic asthma at 13 years of age with sensitization and rhinovirus induced wheezing; however, RSV and wheezing in the first 3 years of life was not associated with asthma at 13 years.² Whether RSV wheezing in the first year of life correlates with subsequent asthma was not determined. While not specifically looking at viral infections, another group examined cellular signatures in the lower airways of children with severe asthma.³ Regardless of atopic status, researchers found a strong Th1 signature in the airways and hypothesized that respiratory pathogens might be the prime candidates for driving this Th1 response in these children.

Rosas-Salazar et al. identified a link connecting early life RSV infection/wheeze and the infant nasal microbiome. Of 118 infants with confirmed RSV acute respiratory infections, those who had an increased abundance of *Lactobacillus* in their nasopharyngeal microbiome were significantly less likely to have wheeze at 2 years of age.⁴ In adults, the nasal microbiome significantly differentiated between healthy controls and subjects with asthma, as well as asthma exacerbation status. Increasing abundance of four species of bacteria (*Prevotella buccalis*, *Dialister invisus*, *Gardnerella vaginalis*, and *Alkanindiges hongkongensis*) associated with the presence of asthma, and their abundance was higher in those with an exacerbation.⁵ Another study found the level of airway inflammation correlated with bacterial composition in bronchoalveolar lavage (BAL) fluid.⁶ Subjects with high levels of eosinophils or low levels of neutrophils had BAL microbiomes most similar to non-asthmatic subjects. Meanwhile, low levels of eosinophils or high levels of neutrophils were both associated with the most significant reduction in microbial diversity. Another interesting study this year demonstrated higher IL-33 levels in the nasal pharyngeal fluid of children with asthma that were colonized with gram negative bacteria.⁷ These children further had decreased FEV1 and an increased frequency of antibiotic use. Together, these studies demonstrate that mechanisms of asthma (or wheeze) development likely contribute to differences in the microbiome and/or vice versa. Further studies are needed to determine the mechanistic implications of these works.

Cellular mechanisms in asthma

The role of neutrophils in asthma was explored in 2017. Alam et al. broadly characterized subjects with asthma who were or were not responsive to controller medications and compared them to healthy subjects.⁸ Those with non-responsive asthma had increased neutrophils and

pro-neutrophil factors (Lipocalin-2, CXCL7, IL-8, IL-1 β , and IL-6, amongst others) in their airways. Up to 40% of these patients had a subclinical infection, raising a question of whether these patients have an impairment in clearing infection. While this study was of adults, another considered the association of intraepithelial neutrophils and lung function in children with therapy-resistant asthma.⁹ Unlike adults, where neutrophil presence was associated with increasing inflammation, in children increased intraepithelial neutrophils correlated with better lung function. Whether the role of the neutrophil differs in adults versus children, or whether these findings all relate to neutrophil location (intraepithelial versus bronchoalveolar) must be further examined. Finally, there may be a link between neutrophils and viral-induced disease, as neutrophils expressing the cysteinyl leukotriene receptor 1 were found in nasal secretions during symptoms of a viral infection; using a mouse model, the authors demonstrated the murine equivalent of these CD49d-expressing neutrophils were critical for post-viral airway disease.¹⁰

Neutrophil recruitment can involve IL-17, and IL-17-related cytokines were elevated in the airway mucosa of subjects with neutrophilic asthma who were prone to exacerbation.¹¹ Exposure to fungal cell wall β -glucans also increased IL-17 related cytokines and contributed to severe steroid-resistant asthma.¹² However, not all studies demonstrated a role for IL-17 in neutrophilic asthma. Characterizing subjects on the presence of Th2 and Th17 cells, Liu et al. found that neutrophilic asthma was associated with those with Th2/Th17 low phenotype. This group also had increased IL-8 in their airways (and decreased IL-4), while in the Th2/Th17 high group (with low neutrophils), the IL-1 β pathway seemed to be of great importance.¹³

In 2017 several papers dissected the importance of B cells in asthma. Lymph node B cells were noted to present antigen – independent of the B cell receptor – and to skew developing T cells towards a Th1/Th17 phenotype with an initial antigen exposure. However, upon a secondary immune response, B cells appeared to drive Th2 proliferation.¹⁴ Some B cells can express FoxP3 and demonstrate a regulatory phenotype. Oliveria et al. demonstrated that these so-called Breg cells are found in much lower frequency in peripheral blood of allergic asthmatic patients compared to allergic non-asthmatic patients (or normal controls). Allergen challenge resulted in decreased Breg in bone marrow and a concomitant increase in the peripheral blood. The authors suggest that one component of continued inflammation in asthma might be reduced Breg-mediated regulation of the immune response.¹⁵ The same authors demonstrated that IgE-bearing B cells, memory B cells, and plasma cells were elevated in the sputum of allergic

asthma. Interestingly, this finding was limited to sputum, as there was no difference in the blood.¹⁶ These studies all suggest the importance of the B cell in asthma development and/or exacerbation.

Dendritic cells gained attention in asthma in the past year. Considering that Th17-mediated neutrophilic inflammation is often seen in severe asthma, while Th2-mediated eosinophilic inflammation tends to be found in milder-to-moderate disease, Vroman et al. examined what might control dendritic cell skewing of T cell development.¹⁷ In a mouse model of asthma, they demonstrated that TNF α -induced protein 3 (also known as A20) was critical in deciding the effect of dendritic cell T cell skewing. In the absence of A20, dendritic cells drove a Th17 response, while in its presence they skewed toward Th2. Importantly, the authors note that the gene for A20 (*TNFAIP3*) has been associated with the risk of asthma and allergies in humans. Another animal study exploring dendritic cell skewing, found genetic deletion of mechanistic target of Rapamycin (mTOR) promoted Th17-dependent neutrophilic airway inflammation.¹⁸ In the context of allergic inflammation, mTOR was found to control catabolism in dendritic cells, which prevented excessive inflammation.

Using both animal models and human samples, Chairakaki et al. explored the role of plasmacytoid dendritic cells (pDC) in allergen and viral induced asthma exacerbations.¹⁹ They found IL-25, released as a result of a viral or allergen challenge, "conditioned" murine pDC to become proinflammatory; depleting pDC prevented disease. The authors noted that human pDC numbers correlated with disease severity, exacerbations, and risk of asthma attacks. Another study using both animal models and human samples demonstrated that the low-density lipoprotein receptor-related protein 1 (LRP-1), a scavenger receptor not previously associated with asthma, was expressed on human peripheral blood myeloid dendritic cells (mDC).²⁰ The level of expression of LRP-1 was reduced on mDC from subjects with eosinophilic asthma compared to healthy controls. Using a mouse model, the authors demonstrated a genetic lack of LRP-1 on mDC associated with increased house dust mite induced airway disease, suggesting the reduced expression might be mechanistically important for the development of asthma. Another mouse model study identified a potential pathway linking protease allergen exposure to airway PD-L2 expressing Th2 skewing dendritic cells.²¹ This novel pathway was based upon protease induced fibrinogen cleavage products acting on mast cells leading to release of IL-13, which skewed the dendritic cells become "Th2 favorable PD-L2⁺" cells. Whether this pathway is operative in humans remains to be determined.

174 *Signaling and protein based mechanisms in asthma*

175 The gene encoding orosomucoid-like 3 (*ORMDL3*) has been linked to human asthma, although
176 the mechanism tying this gene product to asthma has not been clear. This year two groups
177 characterized different potential mechanisms for *ORMDL3* using mouse models. Chen et al.
178 built upon their prior work showing that mice over-expressing *ORMDL3* had increased airway
179 smooth muscle cells and airway hyper-reactivity in the absence of inflammation.²² In the current
180 study, the authors demonstrated that *ORMDL3* increases levels of airway smooth muscle
181 sarcoplasmic reticulum Ca^{2+} ATPase 2b (SERCA2b), which in turn leads to increased smooth
182 muscle proliferation and contractility -- providing a mechanism through which *ORMDL3* might
183 drive asthma in the absence of inflammation.²³ In contrast, Löser et al. built upon the
184 observation that *ORMDL3* modulates cellular response to stress (through the unfolded protein
185 response), and examined how mice over-expressing *ORMDL3* or deficient in *Ormdl3* responded
186 to *Alternaria*-induced stress.²⁴ The authors found that *ORMDL3* appeared important for
187 generating the cellular stress response to *Alternaria* in airway epithelium. This study provides
188 initial support for exploring novel asthma therapies focused at reducing cell stress, and gives us
189 an additional mechanism through which *ORMDL3* might induce asthma. Another study explored
190 the importance of the epithelial barrier in asthma. Using cell culture, and human and mouse
191 models, Sweerus et al. demonstrated that claudin-18, the only known lung-specific tight junction
192 protein, was essential to maintaining airway epithelial integrity.²⁵ Epithelial brushings from
193 asthma patients had lower levels of claudin-18 compared to non-asthmatic subjects. Further, IL-
194 13 decreased claudin-18 expression, suggesting that Th2 inflammation could suppress claudin-
195 18 expression and lead to dysfunction of the epithelium and subsequent sensitization and
196 airway hyper-responsiveness. Potentially connecting viral infection with asthma pathogenesis,
197 down-regulation of claudin-18 was also demonstrated in mice infected with RSV, although it is
198 not clear whether this applies to humans.²⁶

200 Another well-studied area in the past year was mechanisms through which calcium flux
201 associated with asthma. Airway smooth muscle cells expressing CD151, a tetraspanin protein
202 associated with laminin binding integrin, were noted to be significantly increased in humans with
203 moderate asthma as compared to healthy subjects.²⁷ Further, using human cell cultures and
204 mouse models, Qiao et al. were able to demonstrate that CD151 is required for optimal G
205 protein-coupled receptor induced intracellular calcium release and translocation of protein
206 kinase C to the cell membrane. Thus CD151 has a functional role in airway smooth muscle

contraction and could be a therapeutic target. Another group examined calcium channels activated by known inflammatory mediators.²⁸ Using mice, these authors found histamine, 5-hydroxytryptamin, and LTD₄, amongst others, induced calcium activated chloride currents in airway smooth muscle cells through transmembrane protein 16A (TMEM16A), a voltage dependent calcium channel. If these findings are verified in humans, then TMEM16A may be a target to inhibit airway bronchoconstriction. Another study, utilizing both animal models and human samples, found that Rac1, a GTPase of the Rho family, regulated intracellular calcium in airway smooth muscle cells through PLC β 2.²⁹ As the authors point out, because Rac1 has been shown to be involved in respiratory inflammation, targeting Rac1 might have the dual ability to block both smooth muscle contraction and inflammation.

Lessons from mouse studies

Several other studies utilized mouse models of asthma to demonstrate importance of components of the immune response. One study found induced Treg cells, but not natural Treg cells, were capable of suppressing ILC2 driven IL-5 and IL-13 production.³⁰ This suppression depended upon a cognate interaction (between inducible T-cell costimulator (ICOS) and ICOS-ligand) and production of TGF β and IL-10. In a separate study a subset of ILC2s were shown to produce vascular endothelial growth factor A (VEGFA), which drove airway hyper-reactivity as well as provided autocrine regulation of IL-13.³¹ Further, ILC2s may represent a significant source of neuro-immune cross-talk. Murine ILC2s express NMUR1, the receptor for the neuropeptide NMU, and signaling by NMU through this receptor amplified ILC2 immune responses (which were further augmented by IL-25).³² Finally, two studies explored the role of sex hormones in controlling ILC2 numbers.^{33, 34} Female asthma patients were noted to have higher levels of ILC2s in their peripheral blood compared to males. In mice, males had fewer lung ILC2s, an apparent result of testosterone metabolite inhibition of ILC2 numbers and activation.

Biomarker discovery in asthma

Periostin, which has been associated with Th2 high eosinophilic asthma in adults, was studied in children. In contrast to adults, periostin levels were up to 2-3 fold higher, and were found to peak at 2 years of age.³⁵ Nonetheless, the level of periostin at 2 years of age was predictive of asthma at 6 years old, although the elevated levels at baseline may blunt the potential clinical utility of periostin in children. In this study the authors found that periostin levels remained stable between 4 and 11 years of age. Another group looked at fluctuations in periostin in adults and

found no evidence of fluctuation in serum levels over an 8-week period, suggesting levels in adults are stable.³⁶ Further, the authors found no evidence of a seasonal effect on periostin levels. Together, these studies support the use of serum periostin as a biomarker for type 2 high asthma in adults and children. In fact, the Airways Disease Endotyping for Personalized Therapeutics (ADEPT) study was able to classify type 2 status in mild, moderate, and severe asthma patients using airway mucosal CCL26, periostin, and a multiple gene signature (so-called "IL-13 *in vitro* signature").³⁷ Interestingly, of all the biomarkers utilized, CCL26 provided the best discriminator for type-2 inflammation. The authors also demonstrated a combination of clinical data (biomarkers, FeNO, serum CCL17 and CCL26, and blood eosinophil count) provided similar clarity in identifying type 2 high asthma patients. While these studies are of biomarkers, it is important to remember that peripheral blood studies often do not reflect airway biology – so peripheral blood biomarkers may not represent physiologic mechanisms in the airways.

Using 266 adult subjects with asthma, the Unbiased Biomarkers for the Prediction of Respiratory Diseases Outcome (U-BIOPRED) cohort was evaluated for asthma age of onset, smoking pack-years, BMI, FEV₁% predicted, FEV₁/FVC, asthma control questionnaire-5, number of exacerbations in past year, and daily oral corticosteroid dose.³⁸ From these data, 4 clusters were identified, which were validated in a second cohort of 152 subjects. The clusters differed in severity of asthma, level of control, level of airflow obstruction, exacerbation rate, history of smoking, sex, and blood eosinophil level. This represents another unbiased approach that has identified similar phenotypes in adult asthma, further supporting the idea that there are specific types of asthma.

As demonstrated above and in figure 1, this past year was a productive one for mechanistic and biomarker studies in asthma. While there have been many significant findings over the past year, we believe several stand out. In particular, the interconnectedness between the microbiome and the risk of development of asthma (and wheeze) was a prominent feature of these studies, as was the identification of cellular stress (and, in particular, ORMDL3) as a mechanism for asthma development.^{4, 5, 21-23} Nonetheless, all of the investigations discussed have greatly expanded our knowledge base, and the future will tell whether these findings lead to novel therapies and/or better targeting of our therapies to specific patient populations.

Chest imaging and other new assessment tools

Although chest radiographs and computed tomography are used frequently in asthma, newer modalities are coming into use to assess lung function and structure. These are described in several reviews and perspectives.³⁹⁻⁴¹ In addition, there are research reports of newer imaging techniques using quantitative computed tomography (QCT). QCT estimates airway wall remodeling by measuring airway wall thickness percentage and wall area percentage. Air trapping is calculated as percent of low attenuation area measured at functional residual capacity from a single coached breath-hold.⁴² Remodeling and air trapping correlate with lung function, asthma severity, and histology. In a study from the Severe Asthma Research Program (SARP), Shim et al. used QCT to examine whether change in lumen area between total lung capacity and functional residual capacity lung volumes correlated with severe asthma, thickness of the wall area, and air trapping.⁴³ The researchers defined delta lumen, a new metric based on percentage change in each generation's airway lumen area between inspiration and expiration. The delta lumen reflects both airway remodeling and/or distal air trapping that is an indicator of severe disease uncontrolled by inhaled corticosteroids.⁴³ Investigators found the delta lumen negatively correlated with both airway remodeling and air trapping and with unstable refractory asthma. In another SARP study, Choi et al. studied 248 nonsmokers, 142 with severe and 106 with non-severe asthma, using QCT and a principal component analysis followed by clustering analysis of 57 imaging variables.⁴² The analyses defined 4 unique structural and clinical clusters: (1) younger patients with reversible airflow obstruction, (2) non-severe and severe asthma with minimal inflammation but persistent abnormality in lung function, (3) obese mostly female patients with severe asthma and reversible lung function, and (4) older predominantly male patients with late onset severe asthma and neutrophilic-dominant inflammation. The researchers hypothesized such techniques would lead to pathophysiologic hypotheses of the clusters motivating future interventions.

Biologics in asthma

Many patients with difficult-to-control asthma rely on frequent courses of oral glucocorticoid therapy, which may lead to adverse events. Recent increases in understandings of the mechanisms of disease and new biomarkers have led to development of potentially more targeted therapy for the management of severe asthma (figure 2), supplanting the use of long-term steroids, and thereby bypassing steroid related adverse events.

Anti-IgE therapy

Omalizumab, a recombinant, humanized, monoclonal antibody directed against IgE, has been shown to reduce asthma exacerbations, decrease ICS use, and improve symptom control and quality of life in patients on maintenance therapy with ICS and long-acting beta agonists.⁴⁴ The EXCELS trial (Epidemiologic Study of Xolair: Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate to Severe Asthma), a post-marketing, observational study, examined long-term safety and efficacy of omalizumab, with the risk of malignancy as primary outcome measure.⁴⁴ The analysis did not find an association with malignancy, but an imbalance in cardiovascular and cerebrovascular events was observed.⁴⁴ A follow-up analysis evaluated the risk of serious cardiovascular and cerebrovascular adverse events, and showed a higher crude incidence of these events in omalizumab-treated patients (13.4 per 1000 person years) compared to non-omalizumab-treated patients (8.1 per 1000 person years).⁴⁵ The omalizumab group had more than half the number of patients with severe asthma compared to the non-omalizumab group, which may have contributed to these findings. Indeed, after adjusting for confounders, the estimated increase in risk was reduced from the crude estimates.

In a pooled analysis of 25 core trials and 2 extension studies, there were few cardiovascular events in either omalizumab (n=5) or placebo groups (n=4) and the rates for arterial thrombotic events were similar between the two groups.⁴⁶ However, confidence intervals were wide, limiting the ability to exclude small differences in risk. Anaphylaxis has also been reported. Lieberman et al. evaluated a larger patient population (N=132) compared to a previous published case control study (N=30) on anaphylactic reactions with omalizumab.^{47, 48} In this larger cohort, investigators found 43% of patients had a prior anaphylactic event unrelated to omalizumab. Most common symptoms of anaphylaxis involved the respiratory tract, but angioedema and cutaneous symptoms also were reported. Most cases of anaphylaxis occurred within 60 minutes of the first 3 doses.⁴⁷ These results may help determine risk factors for developing anaphylaxis and observation time after omalizumab administration.

Anti-IL-5 therapy

Asthma is thought to be an inflammatory disease in which eosinophils play a key role. IL-5 is the primary activator of eosinophils. Mepolizumab, reslizumab and benralizumab target IL-5 or its receptor. According to a Cochrane review, in patients with poorly controlled eosinophilic asthma on at least medium dose ICS, all of the anti-IL5 therapies (mepolizumab, benralizumab and reslizumab) reduced rates of asthma exacerbation by about half with no excess serious adverse

events.⁴⁹ Mepolizumab, a humanized monoclonal antibody directed against IL-5, was shown to have a glucocorticoid-sparing effect.⁵⁰ In a meta-analysis of four placebo-controlled studies ranging from 24-52 weeks in duration, there was a significant reduction of asthma exacerbations requiring hospitalization (45%) or combined hospitalization and emergency room visits (38%) in patients with severe eosinophilic asthma on maximal therapy receiving mepolizumab compared with placebo.⁵¹ In a post-hoc analysis of Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study, reductions in exacerbation rates were seen relative to placebo irrespective of the number and type of controller therapies.⁵²

Nair et al. assessed the role of benralizumab, a monoclonal antibody against the alpha subunit of the IL-5 receptor (IL-5R α), in reducing oral glucocorticoid use.⁵³ Subjects were those with severe asthma and blood eosinophil count of at least 150 cells/mm³, treated with medium-high dose inhaled glucocorticoids, LABA therapy and oral glucocorticoids for at least 6 months before enrollment. Benralizumab administration for 28 weeks significantly reduced oral glucocorticoid dose by 75% compared to placebo, with about half of subjects receiving baseline prednisone doses of ≤ 12.5 mg/day stopping steroids completely. Benralizumab treated patients also had lower annual rates of asthma exacerbations and exacerbation-related hospital visits. A smaller Canadian sub-study showed that benralizumab significantly reduced both circulating and sputum numbers of mature eosinophils, eosinophil lineage-committed progenitor cells and IL-5R α ⁺ ILC2 cells, showing that targeting IL-5R α attenuates IL-5 driven airway eosinophilia in patients with severe asthma on oral glucocorticoid therapy.⁵⁴

Anti IL-4/IL-13

As type 2 cytokines such as IL-4, IL-5 and IL-13 play a role in the pathogenesis of asthma, investigators have targeted the IL-4 receptor alpha (IL-4R α) subunit (thus also inhibiting IL-13 signaling due to a shared IL-4R α chain) through the fully human monoclonal antibody dupilumab. Dupilumab is currently approved for adult patients with moderate to severe atopic dermatitis uncontrolled on topical prescription medications. In a phase 2b study, dupilumab reduced the rate of severe exacerbations, improved lung function and improved quality of life in uncontrolled, persistent asthma patients on medium-high dose ICS and LABA.⁵⁵ A post hoc analysis of this trial studied patients with perennial allergic rhinitis with IgE of 0.35 kU/L or more to *Aspergillus fumigates*, cat dander, dust mite, dog dander, German cockroach or Oriental cockroach.⁵⁶ Patients taking dupilumab 300mg every 2 weeks had significant improvement in

SNOT-22 scores at 24 weeks compared to placebo. Patients taking dupilumab also had improvement in lung function and annualized rate of severe asthma exacerbations compared to placebo. No statistically significant differences in nasal symptom control, lung function, or annualized rate of severe asthma were seen in patients with perennial allergic rhinitis receiving dupilumab 200mg every 2weeks over 24-week period. These data show dupilumab 300mg used as add-on therapy to medium-high dose ICS + LABA for patients with perennial allergic rhinitis may improve nasal symptom control, lung function and exacerbation rates of asthma.

Anti TSLP

An epithelial cell-derived cytokine, thymic stromal lymphopoietin (TSLP), regulates type 2 responses through its activity on innate immune cells, T cells and B cells. Tezepelumab is an investigational human IgG2 monoclonal antibody that binds to TSLP and suppresses type 2 inflammation. In a multicenter, placebo-controlled, double-blind phase 2 trial, patients with uncontrolled asthma despite treatment with medium-high doses of ICS and LABA had significantly lower annualized rates of asthma exacerbation after 52 weeks of tezepelumab treatment, independent of baseline eosinophil count or other Th2 biomarkers.⁵⁷ Furthermore, FEV₁ increased after 52 weeks in low, medium and high dose tezepelumab groups compared to placebo. Tezepelumab reduced FeNO levels, blood eosinophil counts and total serum IgE levels. When looking at the safety profile, the incidence of adverse events was similar in tezepelumab and placebo groups regardless of asthma-related adverse events.

Genetic and environmental factors in asthma

Asthma is a complex disease with both genetic and environmental factors playing roles in its development and manifestation (figure 3). In 2017 a few studies sought to better characterize how these factors lead to phenotypic differences within the disease.

Asthma phenotype heterogeneity

One approach to understanding how genetic variation leads to differences in disease expression is the characterization of gene expression differences between different asthma phenotypes. Hekking et al. examined specific gene expression profiles associated with severe, adult-onset asthma.⁵⁸ The authors performed gene set variation analysis on RNA isolated from induced sputum (n=83), nasal brushings (n=41), and endobronchial brushings (n=65) from baseline visits of a cohort of severe adult asthmatics. Their results showed a differential enrichment of genes between adult-onset (asthma starting at age ≥18 years) and childhood-

onset asthma. Specifically, compared to childhood-onset, adult-onset asthmatics had more gene signatures associated with eosinophilic airway inflammation, mast cells, and group 3 innate lymphoid cells (ILC) and fewer signatures associated with induced lung injury. The authors suggest these pathways may be potential therapeutic targets in patients with adult onset asthma.⁵⁸ Given the known role of IgE in certain asthma phenotypes, another study looked for an association of genome-wide DNA methylation in white blood cells (WBC) and total IgE level among 879 Puerto Rican and Latino American children with asthma.⁵⁹ Using multivariable linear regression, the authors determined that methylation sites within many WBC genes were significantly associated with total IgE -- similar to what was previously reported in non-Hispanic Caucasians. Two of the most significantly associated genes (*ACOT7* and *ZFPM1*) were previously linked to asthma.⁶⁰

Inhaled corticosteroid response

Over the past decade pharmacogenetic studies have identified several candidate genes that may be associated with differences in inhaled corticosteroid (ICS) responses. Recently, several studies attempted to better describe genetic differences that may account for variability in ICS response. Clemmer et al. previously published that a composite ICS response phenotype, which combined 6 different clinical elements known to be modulated by corticosteroids, was better able to measure the steroid responsive asthma phenotype across populations compared to any individual clinical element by itself.⁶¹ This year, the same group applied this composite phenotype approach to 104 asthmatic children from the CAMP cohort being treated with budesonide along with each patient's *in vitro* cellular response to dexamethasone.⁶² By using a systems approach to combine an individual's genomic data with composite ICS response phenotype, they identified 7 different genes associated with variation in clinical asthma steroid responsiveness. The authors further demonstrated that small interfering RNA (siRNA) transfection knockdown of one of these genes (*FAM129A*) in human lung epithelial cells reduced steroid response. Another study utilized a reverse engineering process using independent published databases to predict regulatory relationships among genes, transcription factors, and proteins. Qiu et al. analyzed gene expression data from immortalized B cell lines of 47 good and 48 poor ICS responders from the CAMP cohort and demonstrated differences between the regulatory networks of good ICS responders and poor responders.⁶³ The most striking difference was that good responders supported more "proapoptosis" pathways while poor responders had more "antiapoptosis" pathways.

Although new molecular techniques have led to significant advances in our understanding of associations between certain genetic variants and ICS response among asthmatics, some studies have shown mixed results. In an attempt to replicate previously published findings on a larger scale, Mosteller et al. conducted the largest pharmacogenetic study to date, genotyping 2672 patients with asthma from 7 different randomized, double-blind, placebo-controlled, parallel group, multicenter clinical studies utilizing fluticasone furoate or fluticasone propionate.⁶⁴ Despite analyzing more than 9.8 million common genetic variants, none were found to be significantly associated with a change in FEV₁ after 8-12 weeks of ICS treatment.

Environmental triggers in asthma

Environmental exposures continue to be a significant cofactor in both children and adults with asthma. Chipps et al. performed a follow up analysis of 341 of the original 4756 severe or difficult to treat asthmatic participants from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR I) multicenter study from 2004.⁶⁵ The authors found more than half of the participants evaluated continued to have very poorly controlled asthma. The most common comorbidities were allergic rhinitis and sinusitis (84% and 48% of patients respectively). Environmental stimuli, such as pet and pest exposure, mold, and second hand smoke exposure, also were significant factors contributing to a lower quality of life among patients. One area of interest drawing more attention over the last decade is thunderstorm-related asthma attacks among individuals with pollen or mold sensitization. While a review of the evidence proposed for pathogenesis of this phenomenon can be found elsewhere, one group attempted to utilize Google Trends to determine if a web-based surveillance tool could predict thunderstorm-induced asthma outbreaks in 10 different countries over the last 13 years.^{66, 67} Using 4 search terms ("allergy," "allergic rhinitis," "asthma," and "pollen") the authors identified 2 severe thunderstorm-induced asthma outbreaks in 2016. Although they were not able to identify any other peak in asthma queries, there did appear to be seasonal trends for both allergic disease and asthma.

Environmental triggers can play a significant role in non-sensitized individuals with asthma. Nitrogen dioxide (NO₂) is a known traffic and combustion-associated air pollutant in urban environments and homes. It is linked to asthma exacerbations and decreased lung function, yet little is known about the impact of NO₂ exposure in the classroom. Gaffin et al. characterized classroom NO₂ content and lung function among asthmatic children enrolled in the School Inner-City Asthma Study.⁶⁸ The mean NO₂ level measured in 218 classrooms across 37 schools

was found to be 11.1ppb. Interestingly, NO₂ exposure above 8ppb was highly associated with decreases in FEV₁/FVC ratio and FEF₂₅₋₇₅ even after adjusting for race and season. E-cigarettes have recently proliferated and emerging data point to their deleterious effects on airways, with a recent paper demonstrating that chronic exposure alters the human bronchial epithelial proteome.^{69, 70}

Efficacy of environmental avoidance strategies

In 2017, experts in the field released a workshop report summarizing previously published literature evaluating the evidence for home environmental interventions in the prevention and management of childhood asthma.⁷¹ There have been several novel contributions to the literature over the past year evaluating the utility of various environmental allergen avoidance strategies in decreasing asthma comorbidity.

Three randomized clinical trials tested the effects of environmental interventions targeting a single allergen, focusing on either dust mite, mouse, or cockroach allergens.⁷²⁻⁷⁴ Murray et al. evaluated the use of house dust mite-impermeable bed encasings compared to placebo covers over a 12-month period in 284 dust mite sensitized children in the United Kingdom presenting to the hospital with an asthma exacerbation.⁷³ Children in the active group had 42% lower odds of a severe asthma exacerbation, defined as an emergency department (ED) visit for asthma requiring systemic corticosteroids, compared to children in the placebo group. While there was a 27% decrease in total ED visits among the active group compared to placebo, this did not reach statistical significance. Another study examined efficacy of professionally delivered, integrated pest management (IPM) in 361 mouse sensitized children and adolescents compared to pest management education alone.⁷² Despite a full year of intervention, there were no differences in the primary outcome of maximal asthma symptom days or any of the secondary outcomes studied. Although there was no statistically significant difference between the two groups in mouse allergen levels, both groups had marked reductions in mouse allergen, which associated with improvements across a range of asthma symptom and exacerbation-related outcomes. The authors concluded that mouse IPM interventions may not be superior to pest management education alone, but that larger reductions in mouse allergen are feasible and associated with improvements in asthma that may be similar in magnitude to controller medications. Because IPM is costly and difficult to implement, another study looked at the impact of a single intervention of insecticidal bait placement on reduction of cockroach infestation and asthma morbidity in 102 children and adolescents with moderate to severe asthma.⁷⁴ After a full year,

households receiving the intervention had significantly fewer cockroaches compared to control homes. Furthermore, children in control homes had more asthma symptoms, unscheduled health care utilization, and decreased lung function compared to children living in intervention homes irrespective of cockroach sensitization. The authors conclude that this single intervention may be a cost-effective alternative to IPM to improve asthma morbidity in children living in cockroach infested homes. Together, these three studies suggest that population-level approaches targeting the primary allergen responsible for asthma morbidity in a community are worth studying.

Early life exposures and the development of wheeze/asthma

One area of continued interest is the role environmental exposures play in development of asthma. There is a significant amount of evidence that early life viral exposures, particularly rhinovirus and respiratory syncytial virus (RSV), increase an individual's risk for subsequent wheeze, and various mechanisms by which this might occur were discussed in the section on novel mechanisms. Herein we discuss evidence gained over the last year from studying various high-risk birth cohorts.

The Urban Environment and Childhood Asthma (URECA) birth cohort was established in 2004 to evaluate the influence of early life environmental exposures on immune development and subsequent clinical outcomes in an urban population at high-risk for atopic disease. O'Connor et al. evaluated 442 children within this population to identify specific prenatal and early-life environmental factors associated with the presence of asthma at 7 years of age.⁷⁵ Interestingly, higher house dust concentrations of cockroach, mouse, and cat allergens in the first 3 years of life associated with a lower risk for asthma, which the authors suggest may be secondary to alterations in indoor bacterial microbiome that may occur with pest and pet animals in the home. In contrast, maternal stress during infancy and prenatal maternal smoking associated with an increased asthma risk. Another study utilizing the URECA cohort examined cytokine responses associated with wheezing and allergic sensitization.⁷⁶ Blood mononuclear cells isolated at birth, 1 year, and 3 years of age were incubated with a panel of various stimuli. The authors found cytokine responses generally increased with age, but responses at birth did not predict responses at 1 and 3 years of age. Exposure to cockroach, mouse, and dust mite was significantly associated with enhanced cytokine responses at age 3 years, and children with recurrent wheeze at 3 years of age had reduced LPS induced IL-10 production at birth. The

authors conclude that environmental exposures early in life stimulate development of cytokine responses, and differences in these responses may predispose to recurrent wheezing.

Schoos et al. investigated 398 children from the Copenhagen Prospective Studies on Asthma in Childhood 2000 (COPSAC₂₀₀₀) birth cohort of infants born to mothers with a history of asthma.⁷⁷ Sensitization to various food and environmental allergens at 0.5, 1.5, 4, and 6 years of age was analyzed to determine if specific patterns of sensitization might be more relevant to various atopic diseases. Using an unsupervised data-driven cluster analysis 7 different age- and allergen-specific patterns were found, and then verified in an independent cohort of 3051 children. Early-life sensitization to dog/cat/horse at 1.5 years of age was most associated with a diagnosis of asthma at age 7, whereas other patterns of sensitization were more likely to be associated with allergic rhinitis or eczema. The authors suggest that distinct sensitization patterns during childhood may represent biologically meaningful and clinically relevant sensitization phenotypes.

Gene-by-environment interactions

The interaction between an individual's genetic information and their environment is one possible explanation for why previous studies evaluating associations between environmental exposures and asthma risk have shown conflicting results. Since dust mite exposure is thought to increase the risk of asthma exacerbations, one group looked for specific gene-by-environment interactions between dust mite exposure and lung function. Using the Puerto Rico Genetics of Asthma and Lifestyle (PRGOAL) cohort, they performed a genome-wide interaction analysis on 440 Puerto Rican children, who had not been selected based on dust mite sensitization, and attempted to replicate their findings in two other independent cohorts (CAMP and Genetics of Asthma in Costa Rica Study (GACRS)) of 552 and 549 children, respectively.⁷⁸ Interestingly, a single nucleotide polymorphism (SNP), *rs117902240*, was positively associated with FEV₁ in children exposed to low levels of dust mite, but negatively associated with FEV₁ in children exposed to high dust mite levels. This finding was replicated in the CAMP cohort but not the GACRS cohort and the authors suggest that this SNP may have possible transcription factor regulatory functions altered by dust mite exposure.

Another study examined gene-by-environment interactions between a SNP in the 17q21 locus and cat or dog exposure. Stokholm et al. performed genotyping in 377 children from the high-risk COPSAC₂₀₀₀ birth cohort and found cat and/or dog exposure from birth was associated with

a lower prevalence of asthma by age 12 years among children with the TT genotype, but not the CC or CT genotype of SNP *rs7216389*.⁷⁹ A similar interaction was found within the TT genotype and cat allergen levels at 1 year of age, but not for dog allergen levels. This association between cat ownership and decreased asthma risk within the *rs7216389* TT, but not CC or CT genotype was also replicated in 604 children within the unselected COPSAC₂₀₁₀ birth cohort.

Studies published over the last year have helped expand our knowledge of the role various genetic and environmental differences play in the development and manifestation of asthma. Of these, some stand out demonstrating the important roles that the genetic predisposition and environmental exposure play in manifestation of asthma, and the heterogeneity of asthma phenotypes.^{58, 59, 62, 63, 66-68, 75-77} Importantly, several studies demonstrated how the interaction between the environment and genetics can lead to a differential response.^{78, 79} Further, there were important contributions on environmental avoidance strategies for dust mite, cockroach, and mouse avoidance/management, which suggested that these interventions may be important components of asthma management.⁷²⁻⁷⁴ Although more studies are clearly needed, further understanding of the complex interplay between an individual's genetic background and the influence of environment will hopefully lead to a better, more personalized treatment approach.

Dietary Supplements

Dietary supplements received attention this year. One such supplement, gamma-tocopherol, is the predominant isoform of vitamin E and found in dietary sources. It was studied as an anti-inflammatory compound, but more study is needed. Because previous studies demonstrated gamma-tocopherol could reduce eosinophilia and endotoxin (LPS) -induced neutrophilic responses to inhaled LPS in a mouse model and in healthy volunteers, Burbank et al. examined the effect of gamma-tocopherol on inhaled LPS responses in adults with mild asthma.⁸⁰ Similar to what was shown in the previous studies, gamma-tocopherol reduced eosinophilic airway inflammation and attenuated the neutrophilic airway response to inhaled LPS.

Fish oil, a source of long-chain n-3 polyunsaturated fatty acid, crosses the placenta, and was hypothesized to have anti-inflammatory properties reducing the risk of asthma development in the offspring based on data from a national hospital birth registry.⁸¹ In 2017, with 24 years of follow-up, the investigators extended their observations and found that among the original 533 women in the third trimester of pregnancy randomly assigned to receive fish oil, olive oil, or no oil there was reduced probability of the offspring having had asthma medications in the group

given fish oil (hazard ratio 0.54 (95% CI 0.32-0.90;p=0.02). However, there were no significant differences between the groups in development of allergic rhinitis, lung function, total or specific IgE, or eosinophilic cationic protein.⁸² Finally, in a recent meta-analysis fish oil was not found to reduce risk of fatal or nonfatal coronary heart disease or major vascular events like stroke mortality, although adherence to the supplement was not described in this study.⁸³

Other Potential targets

Several reports in the past year suggest pathways to be explored as promising future therapies for treating or preventing asthma (figure 2). Jo et al. demonstrated plasminogen activator inhibitor type 1 (PAI-1), an inhibitor of urokinase- and tissue-type plasminogen activators, promotes airway inflammation and remodeling in a murine model of asthma.⁸⁴ The investigators found mast cells are an important source of PAI-1, a potential therapeutic target.

The Notch family of receptors has attracted interest in asthma research. These are cell surface proteins on lymphocytes that are proteolytically cleaved upon interaction with ligands of neighboring cells. The cleaved fragment migrates to the nucleus and modulates expression of specific target genes. Notch proteins and their ligands prominently play a role in type 2 immunity. In a mouse model, Notch signals were inhibited by stapled α -helical peptide derived from mastermind-like 1 (SAHM-1).⁸⁵ In another mouse model study, monocyte chemotactic protein-induced protein 1(MCP-IP) 1 was found to inhibit Th2 differentiation and function acting through the Notch pathway and GATA-3.⁸⁶ Thus, if Notch signaling can be similarly inhibited in humans without significant adverse effects, it is a potential therapeutic target.

Targeting inflammatory cells is an important potential mechanism for addressing asthma. Both Th2 and Th17 pathways have been implicated, Th17 for neutrophilic inflammation. Dendritic cells can activate both Th2 and Th17 pathways through nuclear factor kappa B. Thus, Vroman and Mishra suggest targeting dendritic cells as a potential therapeutic benefit (discussed in the section on mechanisms).^{17, 20} Hekking et al. studying adult onset severe asthma note ILC3 cells as potential targets for obesity-associated and neutrophilic asthma.⁵⁸

There is interest in whether environmental exposures lead to epigenetic modifications, like DNA methylation, affecting expression of target genes such as *GSDMB* and *ORMDL3* of the 17q21 locus. In a population-based integrative genomics analysis of the 17q21 asthma-susceptibility locus using two large and racially diverse cohorts, methylation correlated with functional effects

of variants of *GSDMB* and *ORMDL3*.⁸⁷ The investigators proposed that epigenetic manipulation is a potential therapeutic strategy.

Parasites can survive in mammalian hosts without excessive tissue damage and parasite survival may result from anti-inflammatory immune responses by the parasites. The products of this response may have a clinical application. Tanaka et al. examined a peptide secreted by an animal and human parasite, *Fasciola hepatica*.⁸⁸ The peptide, *Fasciola hepatica* helminth defense molecule 1 (FhHDM-1), has potential anti-inflammatory properties. Previously, FhHDM-1 was shown to inhibit lysosomal-associated NLRP3 inflammasome activation in murine and human macrophages *in vitro*. The authors now found FhHDM-1 suppressed both eosinophilic and neutrophilic granulocytic inflammation and airway hyper-reactivity in a mouse model of asthma, providing additional support for potential use of this peptide in asthma therapy.

Health literacy, health disparities and asthma

Although the global asthma mortality rate decreased markedly from 1993 to 2006, there has been no appreciable change since for those between 5-34 years of age.⁸⁹ Health literacy, race/ethnicity, and socioeconomic status all play a role in asthma prevalence, adherence, management, and health-care utilization. One study this past year showed a parent's childhood socioeconomic status could influence their child's asthma control.⁹⁰ Parents with lower socioeconomic status in childhood had children with poorer asthma control and more current family relationship stress, independent of current socioeconomic status. Furthermore, parents with lower socioeconomic status in childhood were more likely to have children whose peripheral blood mononuclear cells produced large Th1 and Th2 cytokine responses when stimulated with phorbol 12-myristate 13-acetate and ionomycin.

In another study of 1.5 million children with asthma enrolled in Medicaid from 2009-2010, those living in inner city (poor-urban) areas were found to have a higher risk of asthma-related ED visits and asthma-related hospitalizations, though asthma prevalence was not increased.⁹¹ To improve asthma control for children living in urban areas, Halterman et al. examined telemedicine clinician visits and supervised administration of preventative asthma medications in school students with asthma.⁹² Urban children with persistent asthma receiving these interventions had fewer asthma ED visits and hospitalizations. These children also had more symptom-free days, less activity limitation, and less airway inflammation.

Racial/ethnic disparities were seen in children with asthma. Among children ages 5-19 years enrolled in Medicaid in 2009-2010, black race was associated with increased rates of asthma outpatient visits, ED visits, and hospitalizations, after adjusting for neighborhood poverty. Some theories for this finding include genetic differences and the contribution of socioeconomic disparities to racial/ethnic disparities.⁹¹ A separate study found African Americans taking ICS were more likely to have eosinophilic airway inflammation after adjusting for confounders (age, sex, atopic status, BMI, FEV₁ percent predicted, and uncontrolled asthma).⁹³ African Americans had lower lung function, higher total serum IgE and worse symptom control compared to white subjects. This study did not adjust for neighborhood poverty.

Older patients with asthma also have a high burden of asthma morbidity and mortality. A study assessed the association of health literacy, health beliefs, and cognition with medication adherence in patients with asthma aged 60 years and older and found patients with limited health literacy had more negative perception of their illness, greater medication concerns and poorer performance on cognitive measures.⁹⁴ Those with poor adherence to medications were more likely to believe that asthma was temporary and present only when they had symptoms. Using a structural equation model, health literacy was found to influence concerns about medications, which in turn influences medication adherence. and limited health literacy may lead to concerns about side effects of controller medications with decreased adherence.

Conclusion

2017 was a year marked with many advances in our understanding of the epidemiology, genetics, environmental exposures, and mechanisms underlying the development and exacerbation of asthma. We saw advancement in novel therapies and identification of new biomarkers and potential therapeutics. While we do not have a crystal ball to know which of these findings will lead to the greatest impact on the development and treatment of asthma, we have highlighted those findings that we think are of most importance in the Key Advances box. Further, in figures 1-3 we have identified those findings that we think are the most important, and most likely to stand the test of time. With each new discovery we move closer to better diagnosing, phenotyping and treating asthma, as well as beginning to elucidate the mechanisms that one day may allow us to prevent the development of asthma.

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Figure Legends.

Figure 1. Mechanistic and biomarker advances in asthma in 2017. Included studies demonstrated differential effects of RSV/RV wheeze and asthma development.^{1, 2} Inducible regulatory T cells and prevention of airway hyper-reactivity development were discussed.^{30, 31} IL-13 reduced Claudin 18 (important for epithelial integrity).²⁵ Viral infection drove increased airway inflammation through IL-25 and plasmacytoid dendritic cells.¹⁹ Fungal wall components associated with increased neutrophilic asthma and lower microbial diversity in airways -- often linked with therapy resistant asthma.^{4-6, 8, 12} Intraepithelial neutrophils associated with improved pediatric lung function.⁹ Elevated periostin levels and a Th1 airway signature regardless of asthma presence were found in children.^{3, 35}

In asthmatics' sputum, IgE⁺ B cells and plasma cells were increased.¹⁶ Regulatory B cells were decreased in asthma patients' circulation.¹⁵ B cells in draining lymph nodes skewed developing Th0 into Th2 and Th17 cells.¹⁴ During an airway secondary immune response B cells induced Th2 cell proliferation, which associated with eosinophilic asthma.¹⁴ Th2 development was driven by A20 exposed dendritic cells, whereas A20 absence led to Th17 cells.¹⁷

Studies examined smooth muscle cell components involved in bronchoconstriction, including CD151, Rac1 and PLC β 2.^{27, 29} Airway epithelial stress increased with asthma through ORMDL3, increasing SERCA2b expression, and airway smooth muscle mass.^{23, 24}

Figure 2. Current and potential targeted therapies. Current upstream to downstream biologic therapies and other therapeutics that were studied in the past year.^{44-48, 50-57, 84-86} Items in parenthesis are not discussed in this review. TSLP, thymic stromal lymphopoietin, PAI-1, plasminogen activator inhibitor type 1. Adapted from reference⁹⁵, figure 1.

Figure 3. Summary of genetic and environmental factors impacting asthma development, phenotype, and exacerbations. (A) The interplay of genetics and environment in development of asthma. Genetics (green) and environmental exposures (yellow) shape the risk of asthma development, while various genetic signatures predispose to differences in asthma phenotype. Previous work identified genetic polymorphisms and allergen exposures associated with asthma risk (including to cat, dog, and dust mite), and this past year several studies expanded our knowledge of the influence of early life allergen exposure on asthma risk and demonstrated interactions between these indoor allergens and genetic polymorphisms.^{71, 75, 76, 78, 79} These

gene*environment interactions could act via epigenetic or non-epigenetic mechanisms. In addition, studies demonstrated links between genetic signatures and asthma phenotypes related to steroid responsiveness, adult-onset asthma, and total IgE.^{58, 59, 61-64} (B) Environmental exposures, specifically nitrogen dioxide in schools and thunderstorms, are associated with markers of asthma morbidity.⁶⁶⁻⁶⁸ Thunderstorms are thought to disrupt pollen and fungal spores, potentially through strong downdrafts or production of ozone, releasing allergen-bearing small particles that can penetrate beyond the upper airway. Home environmental interventions (red) targeting single allergens (dust mite, cockroach, mouse) may improve asthma control and reduce the risk of exacerbations among pediatric populations.⁷¹⁻⁷⁴

Key Advances

-The mechanism of asthma (wheeze) development is interwoven with microbiome differences: early life viral (RSV) infections alter nasal microbiome³ and there are differences in adult nasal microbiome between healthy adults, asthmatic adults, and adults with airway inflammation.^{4, 5}

-Cellular stress, specifically a role for ORMDL3, may prove to be a novel therapeutic target as a mechanistic cause of airway hyperreactivity and asthma development.²¹⁻²³

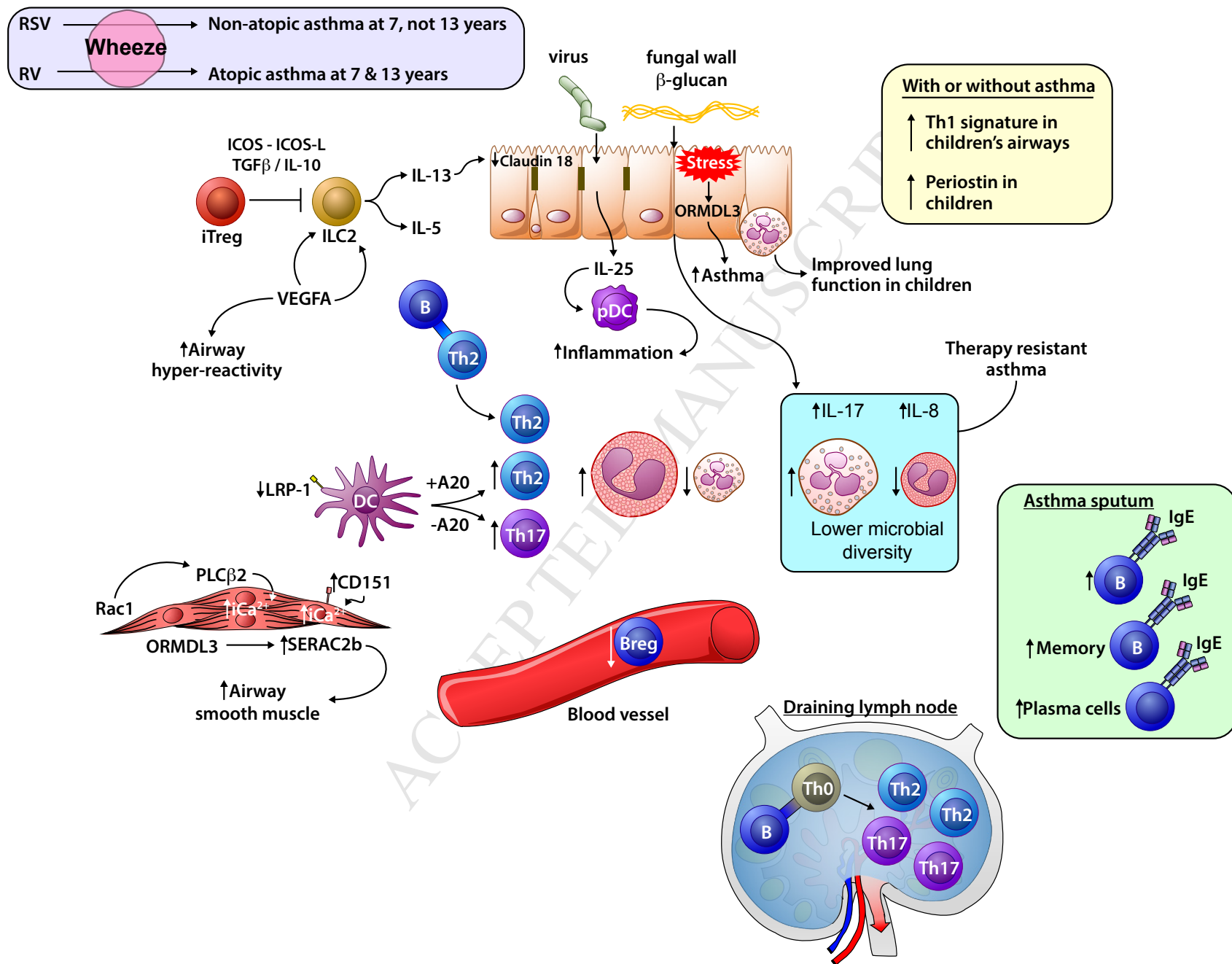
-Newer imaging modalities to assess lung function include quantitated computed tomography, which can help estimate airway wall remodeling and air trapping.^{42, 43}

-Recent biologics in asthma include upstream targets such as anti thymic stromal lymphopoeitin (tezepelumab) and downstream targets such as anti-IgE (omalizumab), anti IL-5 (mepolizumab and benralizumab) and anti-IL4/IL13 (dupilumab) which have all been shown to decrease asthma exacerbations.^{44, 51, 53, 55, 57}

-Genetic predisposition and environmental exposure both play important roles in asthma manifestation^{66-68, 75-77}, and phenotype heterogeneity^{58, 59, 62, 63} and the interaction between these two factors can lead to a differential response.^{78, 79}

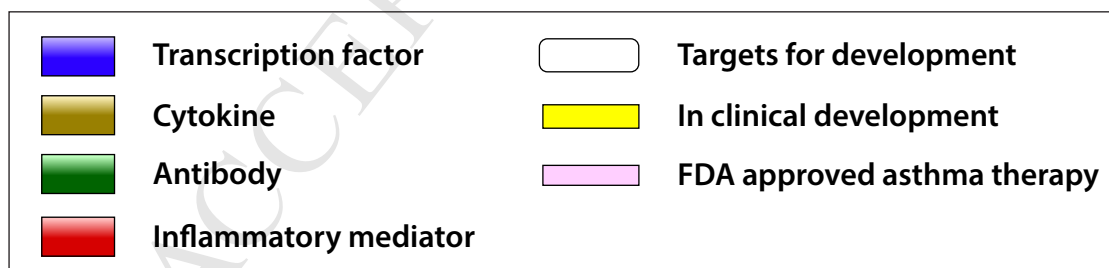
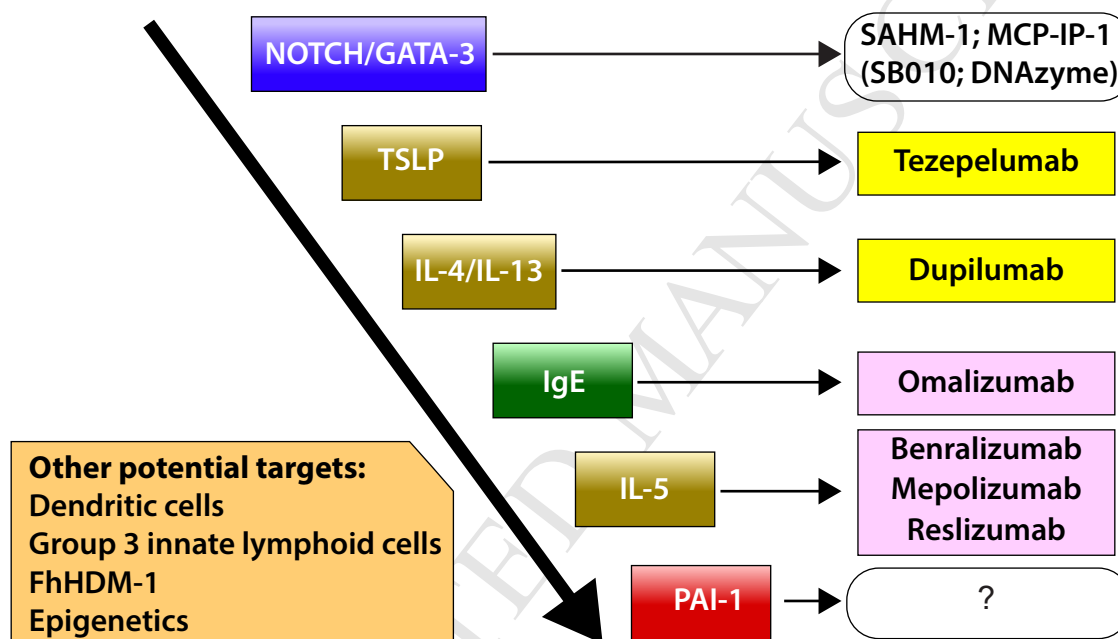
-Environmental avoidance strategies targeting single allergens for dust mite⁷³ and cockroach⁷⁴ are effective interventions in selected pediatric populations and integrated pest management targeting mouse can result in large reductions in the allergen and improvements in asthma in sensitized and highly exposed children with asthma.⁷²

-Race/ethnicity, socioeconomic status, including parent's socioeconomic status, age and living in an urban environment may all play a role in level of asthma control.⁹⁰⁻⁹⁴

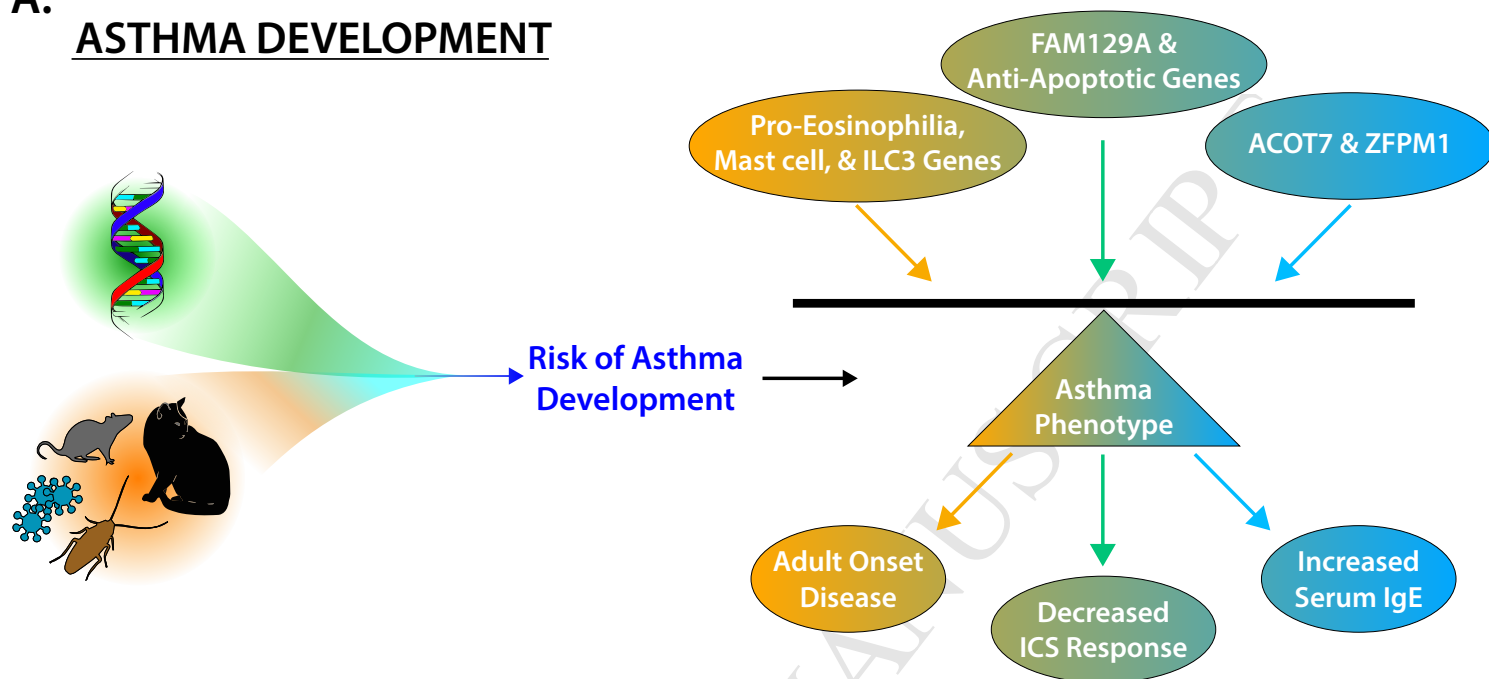


Therapeutic Targets

Therapeutics



A. ASTHMA DEVELOPMENT



B. ASTHMA EXACERBATIONS

