

Knowledge gaps and future opportunities for biologics in childhood allergic and immunologic disorders



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Key words: Asthma, exacerbation, immune deficiency, inborn errors of immunity, biologic therapy, biomarker

Biologic therapies can improve health outcomes for children with allergic and immunologic disorders when conventional management is lacking, as elaborated in this special edition of the *Journal of Allergy and Clinical Immunology*. Although these biologics can transform the lives of patients, they can also be powerful tools to address knowledge gaps and advance scientific understanding that will improve future care. In this Paradigms and Perspectives article, we will provide some examples in which the use of biologics to treat pediatric allergic and immunologic disorders has provided foundational and sometimes transformational insights, and even paradigmatic shifts in our approach to disease management.

BIOLOGICS CAN DEMONSTRATE FOUNDATIONAL MECHANISMS OF ALLERGIC DISEASE IN CHILDREN

Inhalant allergen sensitization interacts with respiratory virus susceptibility (especially rhinovirus), leading to asthma exacerbations in children, but their interactive causal mechanisms are not clear. In a randomized clinical trial with omalizumab (anti-IgE) to prevent asthma exacerbations in vulnerable children with allergic asthma (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations Study, Inner-City Asthma Consortium-3 [ICAC-3]), IgE cross-linking on plasmacytoid dendritic cells inhibited antiviral IFN- α responses to rhinovirus, omalizumab treatment improved this antiviral response, and

greater IFN- α responses were associated with fewer exacerbations.¹ Omalizumab had sequential effects on rhinovirus: (1) decreased duration of rhinovirus infection, (2) reduced rhinovirus shedding, (3) decreased rhinovirus illness frequency, and (4) decreased rhinovirus exacerbations.² This omalizumab clinical trial provided a great opportunity to fill a knowledge gap and thus help us explain to our colleagues and patients how allergic sensitization can impair antiviral responses, leading to asthma exacerbations.

LEARNING EXPERIENCES FROM BIOLOGICS

Biologic therapies targeting promising molecular mediators of disease can inform knowledge gaps when they are ineffective or cause adverse effects in the human condition. For example, scientific and preclinical evidence implicated the type 2 (T2) cytokine IL-9 in asthma; however, an anti-IL-9 humanized mAb (MEDI-528) was ineffective in treating asthma in randomized, controlled trials.³ Anti-IL-4/IL-13 receptor- α (dupilumab) is effective and US Food and Drug Administration–approved for treating children with T2 inflammatory conditions, including atopic dermatitis, asthma, and eosinophilic esophagitis. Unexpectedly, it was shown that dupilumab can cause a diffuse, inflammatory conjunctivitis in 3.6% to 31% of patients with atopic dermatitis (less common when other conditions are treated).⁴ The anti-IL-13 mAb tralokinumab, which is indicated for adults with atopic dermatitis, is similarly associated with conjunctivitis. This conjunctivitis is typically mild to moderate in severity (rarely severe), reversible with discontinuation of biologic treatment, and treatable with ocular anti-inflammatory treatments. The mechanism by which these selective T2 anti-inflammatory biologics can cause an inflammatory conjunctivitis in some treated patients is a current knowledge gap and an opportunity to understand the interrelatedness of inflammatory mechanisms.

T2 BIOLOGICS CAN REVEAL NON-T2 PATHWAYS OF DISEASE

Like all anti-inflammatory asthma treatments, T2 biologics can prevent asthma exacerbations in some to most, but not all, treated patients, indicating the underlying heterogeneity of disease. What mechanisms of disease distinguish treatment nonresponders from responders? In our current therapeutic landscape of 6 US Food and Drug Administration–approved biologic therapies for treating difficult-to-control, exacerbation-prone asthma by targeting selective aspects of T2 inflammation, the non-T2 pathways are less understood. In a National Institute of Allergy and Infectious Diseases–sponsored randomized controlled clinical trial with an anti-IL-5/eosinophil therapy (mepolizumab) in exacerbation-prone children with asthma who are living in urban, low-income communities (the Mechanisms Underlying Asthma

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Supported in part by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (grants UM1 AI114271 [Inner-City Asthma Consortium-3], UM1 AI160040 [CAUSE], U01 AI160033 [CAUSE]), and R01 AI098077 [Gill] [to C.M.D. and A.H.L.]); the National Heart, Lung, and Blood Institute (grant P01 HL132821 [PPG]); and the National Center for Advancing Translational Sciences (grant UL1 TR002535 [Colorado CTSA]).

Disclosure of potential conflict of interest: C. M. Dutmer reports personal fees from Enzyvant Therapeutics and Horizon Therapeutics outside the submitted work. A. H. Liu reports grants and nonfinancial support from ResMed Propeller Health, nonfinancial support from Revenio, grants and personal fees from Avillion, and personal fees from Phadia ThermoFisher and LabCorp, outside the submitted work.

Received for publication September 29, 2022; revised December 29, 2022; accepted for publication January 3, 2023.

Available online January 10, 2023.

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J Allergy Clin Immunol 2023;151:691-3.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2023.01.003>

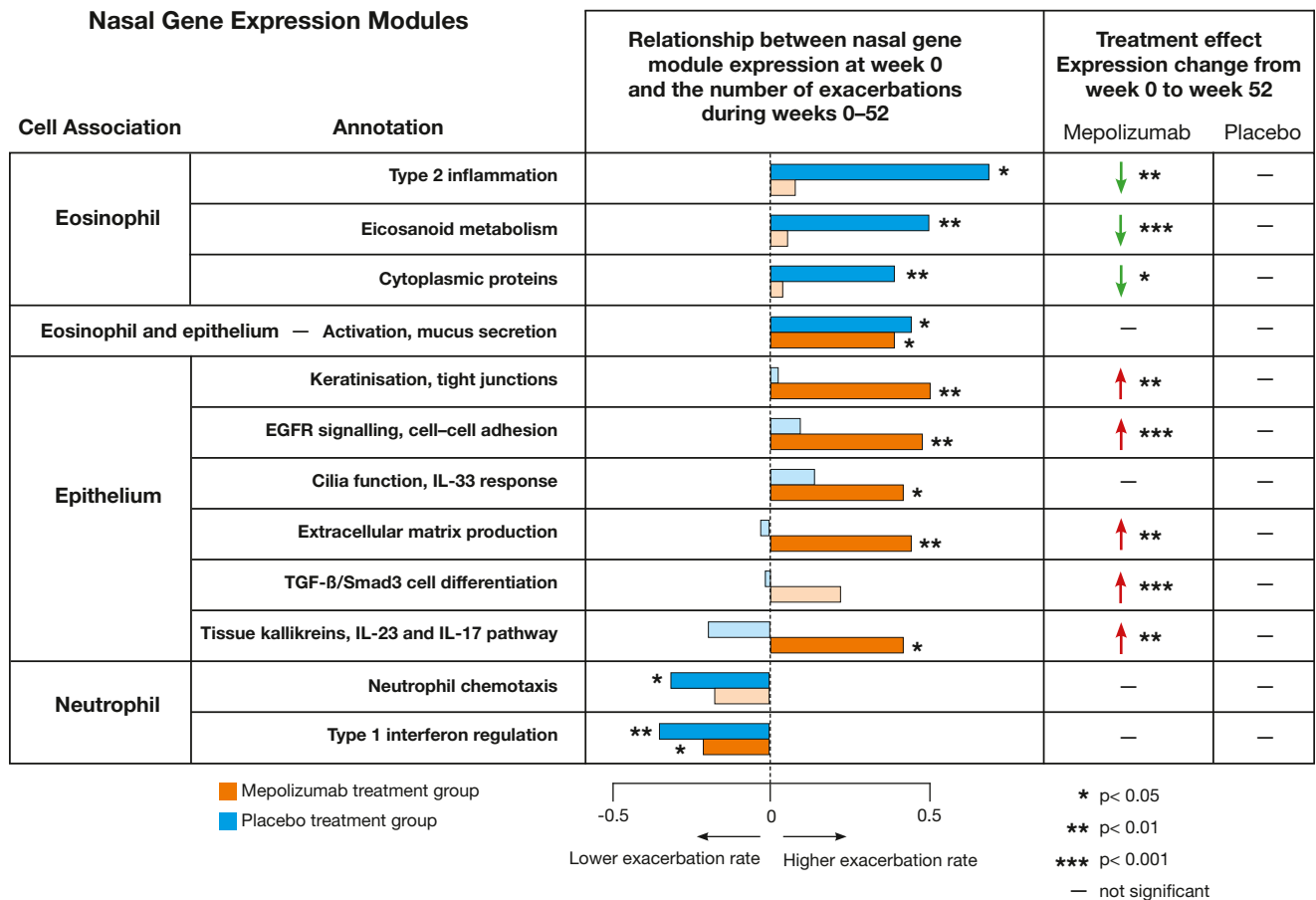


FIG 1. Nasal gene expression and exacerbation rates in exacerbation-prone children with asthma treated with anti-IL-5 (mepolizumab) or placebo: the MUPPITS-2 study (ICAC-3),⁵ a randomized controlled clinical trial for 12 months to reduce exacerbation risk. *Middle column*, The 12 highly coexpressed gene clusters (“modules”) in nasal lavage samples obtained from participants at baseline showed significant relationships to exacerbations during the 12-month treatment period in the placebo and/or mepolizumab groups (multivariate partial least squares regression). The weights for each of the 12 modules for each treatment group indicate these associations: bars to the right of center indicate a positive association with the number of exacerbations versus bars to the left indicate an inverse association. Weight values ranging from 0 to 1 reflect the relative importance of each module in the exacerbation modeling. Significant changes in exacerbation risk with doubling increases in each module are indicated: * $P < .05$; ** $P < .01$; *** $P < .001$; lighter shaded bars are insignificant. *Right column*, Of the 12 modules, 8 showed significant differential expression from weeks 0 to 52 in the mepolizumab treatment group; no modules were differentially expressed in the placebo group. Downward arrows indicate a decrease in expression, whereas upward arrows indicate an increase. * $P < .05$; ** $P < .01$; *** $P < .001$. Dash indicates that change in expression is not significant.

Exacerbations Prevented and Persistent with Immune-Based Therapy: A Systems Approach-2 [MUPPITS-2] study,⁵ ICAC-3), a powerful analytical tool called weighted gene coexpression network analysis was used to reveal airway mechanisms of disease. In a prior study (the Mechanisms Underlying Asthma Exacerbations Prevented and Persistent with Immune-Based Therapy: A Systems Approach-1 [MUPPITS-1] study,⁶ ICAC-3), weighted gene coexpression network analysis of nasal lavage samples identified cell-associated clusters of highly coexpressed genes (“modules”). The 52 nasal modules ranged in size from 36 to 1041 genes.⁵ In MUPPITS-2, 12 of these nasal modules that largely differed by treatment group were associated with exacerbations during the treatment year (Fig 1): (1) in the placebo-treated children, as expected, increased baseline nasal expression of 3 eosinophil gene modules was associated with exacerbations during the subsequent treatment year; (2) in the mepolizumab-treated

children, these eosinophilic modules were not associated with exacerbations, and their expression was significantly reduced by treatment (also as expected); (3) in mepolizumab-treated children, however, increased baseline expression of 6 epithelial gene modules was associated with exacerbations during the treatment year, and the expression of 5 of 6 modules was significantly increased by treatment; (4) in both groups, increased baseline expression of a mucous secretion module was associated with subsequent exacerbations and was unaffected by treatment; (5) in the placebo group, reduced baseline expression of type 1 interferon regulation and neutrophil chemotaxis modules were associated with exacerbations; and (6) in the placebo group, the expression of gene modules did not change during the year-long study.

This investigation of biologic therapies yielded a trove of nasal airway gene expression findings, providing insights to the

molecular mechanisms underlying exacerbations and especially non-T2 epithelial mechanisms in need of better understanding. Building on these insights, directions for future investigations to improve care include (1) refining selection of treatment options based on predictive nasal gene expression biomarkers; (2) identifying new epithelial and immune targets for intervention; and (3) mechanistically seeking to understand, in treated non-responders, the paradoxical increased expression of non-T2 epithelial pathways associated with exacerbation risk.

MULTIPLE PATHWAY APPROACHES IN NONALLERGIC CONDITIONS

Since the recognition of T-cell phenotypes, careful characterization of T_H1, T_H2, and T_H17 lineages and their respective functions has led to novel therapeutic approaches, but often with a compartmentalized focus; in reality, T-cell subpopulations can interact in disease pathogenesis. Hindering the activity of the T2 axis with dupilumab (anti-IL-4 receptor- α) has, as expected, proved beneficial in the management of atopic conditions; however, dysregulated T2 immunity extends beyond atopy alone. Tsai et al explored concurrent immunomodulation of both T1 and T2 axes to manage disseminated coccidioidomycosis in a child by administering dupilumab alongside IFN- γ and antifungal therapies, resulting in improved disease control and highlighting the potential of using multidirectional immune manipulation to direct a desired response.⁷ Arguably less obvious opportunities for targeted therapy have also surfaced. Inflammatory, noninfectious features of leukocyte adhesion deficiency type 1 (LAD1) can be severe, but elucidation of increased IL-17 and IL-23 signatures has paved a path to consider treatment with ustekinumab (anti-IL-12/23p40).⁸ Continual exploration in immunologic pathways of expected and unexpected importance such as these will enhance our understanding of disease pathophysiology and, optimistically, improve outcomes in treatment-refractory conditions.

EXPLORING TREATMENT OPTIONS FOR IEIs

The numbers of known, genetically distinct, inborn errors of immunity (IEIs) continue to increase exponentially. Although outpaced by the speed at which novel disorders are defined, the identification of multiple molecular targets is shifting therapeutic strategies by promoting strategic approaches to capitalize on existing agents while also fostering development of new medications, of which there are many examples. With an expanded understanding of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) biology, abatacept (CTLA-4 fusion protein) is uniquely positioned to serve as a theoretical and, in practice, efficacious intervention for CTLA-4 deficiency, “lipopolysaccharide-responsive and beige-like anchor protein” (LRBA) deficiency, and “differentially expressed in FDCP6 homolog” (DEF6) deficiency.⁹ Broader utility of proinflammatory cytokine (IL-1 β , IL-6, and TNF- α) blockade has also proved effective in

numerous monogenic autoinflammatory disorders. Blocking the T1 axis in familial hemophagocytic lymphohistiocytosis with emapalumab (anti-IFN- γ) may improve survival in this lethal disease.¹⁰ Inhibition of interferon responses with anifrolumab (anti-IFN- α receptor 1) may complement ongoing therapeutic efforts with Janus kinase inhibitors in the management of type I interferonopathies. Beyond treatment strategies alone, use of biologics in the management of IEIs can be leveraged to explore and characterize regulation of key signaling pathways with approaches similar to those of the asthma studies discussed herein. Notably, for most biologics used in IEIs, treatment is off-label and incompletely studied. However, as evidenced earlier in this article, clear and impactful advancements in treating IEIs with biologics have occurred. Future treatment advances for the numerous and growing number of IEIs will continue to depend on strategic, theoretical targeting of specific pathways published as case reports and series because their rarity can make conventional clinical trials relatively infeasible.

In conclusion, the elegance of using biologics to precisely target disease pathways is bringing the power of personalized genomic medicine into view. In complex allergic and immunologic diseases, clinician-researchers are combining genomics with biologics to optimize treatments.

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