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Perspective

Targeting type 2 immune activation beyond atopic dermatitis

Donald Y.M. Leung, MD, PhD*; Paola Facheris, MD†; Karen A. Veverka, PhD‡; Ferda Cevikbas, PhD‡; Emma Guttman-Yassky, MD, PhD§

* Pediatric Allergy and Clinical Immunology, Department of Pediatrics, National Jewish Health, Denver, Colorado
† Department of Dermatology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Humanitas Rozzano, Milan, Italy
‡ ASLAN Pharmaceuticals, San Mateo, California
§ Dermatology and Clinical Immunology, Icahn School of Medicine at Mount Sinai, New York, New York

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Type 2 immune responses are central in the pathogenesis of allergic diseases, and targeted therapies that act as type 2 immune antagonists lead to marked clinical improvement in allergic diseases such as atopic dermatitis (AD), asthma, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyps.[1] The effectiveness of these agents stems from their blockade of key effector cytokines such as interleukin (IL)–4, IL-5, IL-13, and IL-31.[1] Type 2 inflammation has a pathogenic role in many nonallergic diseases as well, such as alopecia areata, fibrosis, chronic hand dermatitis, keloids, and prurigo nodularis. The clinical use of targeting T helper 2 (T_H2) cytokines in these conditions has been investigated, but there remain relatively few approved therapies for these patient populations compared with a large number of T_H2-targeted biologics and small molecules available for the treatment of AD and asthma (Fig 1).

Among the systemic biologic treatments approved for AD, dupilumab (anti–IL-4Rα) is the only one also currently indicated for the treatment of any nonallergic disorders, but others have exhibited efficacy in clinical trials; notably, a phase 3 trial of nemolizumab (anti–IL-31RA) in prurigo nodularis recently reported positive results. Biologics directed to the IL-13 ligand, such as tralokinumab and lebrikizumab, have exhibited efficacy in AD but their effectiveness in non-AD type 2 inflammatory disorders is still uncertain or unknown.[2] Agents in development include additional antagonists of these established targets such as CBP-201 (anti–IL-4Rα) and cendakimab (anti–IL-13), and eblasakimab, which introduces a novel strategy to target the T_H2-immune pathogenesis by targeting IL-13Rα1. The patient populations in which these investigational drugs may be effective have yet to be established. There is an urgent need to accelerate the development of treatments for T_H2-driven diseases beyond AD, given that these patients have few therapeutic options at present. Fortunately, there are many clinical tools emerging or already available that can be applied to address the unmet needs of these patients.

The specific role of any given cytokine in T_H2-driven diseases is complex and involves interactions with other immune cells and cytokines.[3] In addition, the specific cytokine profile and immune mechanisms vary among individuals and at different stages of the disease. As a result, T_H2 inhibition is not always satisfactory, given the fact that a substantial subset of patients treated with dupilumab are nonresponders. JAK inhibitors, as small molecules with less specificity than monoclonal antibodies, could potentially be useful in situations in which type 2 inflammation is strong but not “predominant” and in which the activation of other inflammatory pathways can lead to the “failure” of pure type 2 targeted drugs. Achieving clinically meaningful efficacy may require more than solely blocking a single cytokine; it may involve targeting multiple components within a pathway. Ideally, we would be able to understand precisely how these interdependent signaling pathways are disrupted in each patient, how treatments alter those pathways as a whole (beyond the expected effects on a specific molecular target), and how these molecular effects relate to clinical responses over time. To this end, established cytokine profiling technologies and emerging techniques for identifying genomic, metabolomic, lipidomic, and proteomic biomarkers offer a myriad of opportunities for personalized medicine in the future. Through patient profiling and the identification of predictive biomarkers, we will be able to address scientific uncertainties, achieve earlier diagnosis, and increase the success rate of treatments by selecting therapies on the basis of an individual’s endotype. For instance, the minimally-invasive technique of skin tape strip analysis was used to assess molecular response to dupilumab in patients with moderate-to-severe AD.[4] Furthermore, analysis of lesional skin samples collected with skin tape strips from individuals with AD identified distinct cytokine profiles and found certain markers correlated with disease severity.[5] Refining and expanding the use of molecular profiling technologies in both research and clinical settings will

Address correspondence to: Donald Y.M. Leung, MD, PhD, Department of Pediatrics, National Jewish Health, 1400 Jackson Street, Denver, CO 80206, USA. E-mail: leungd@njhealth.org.

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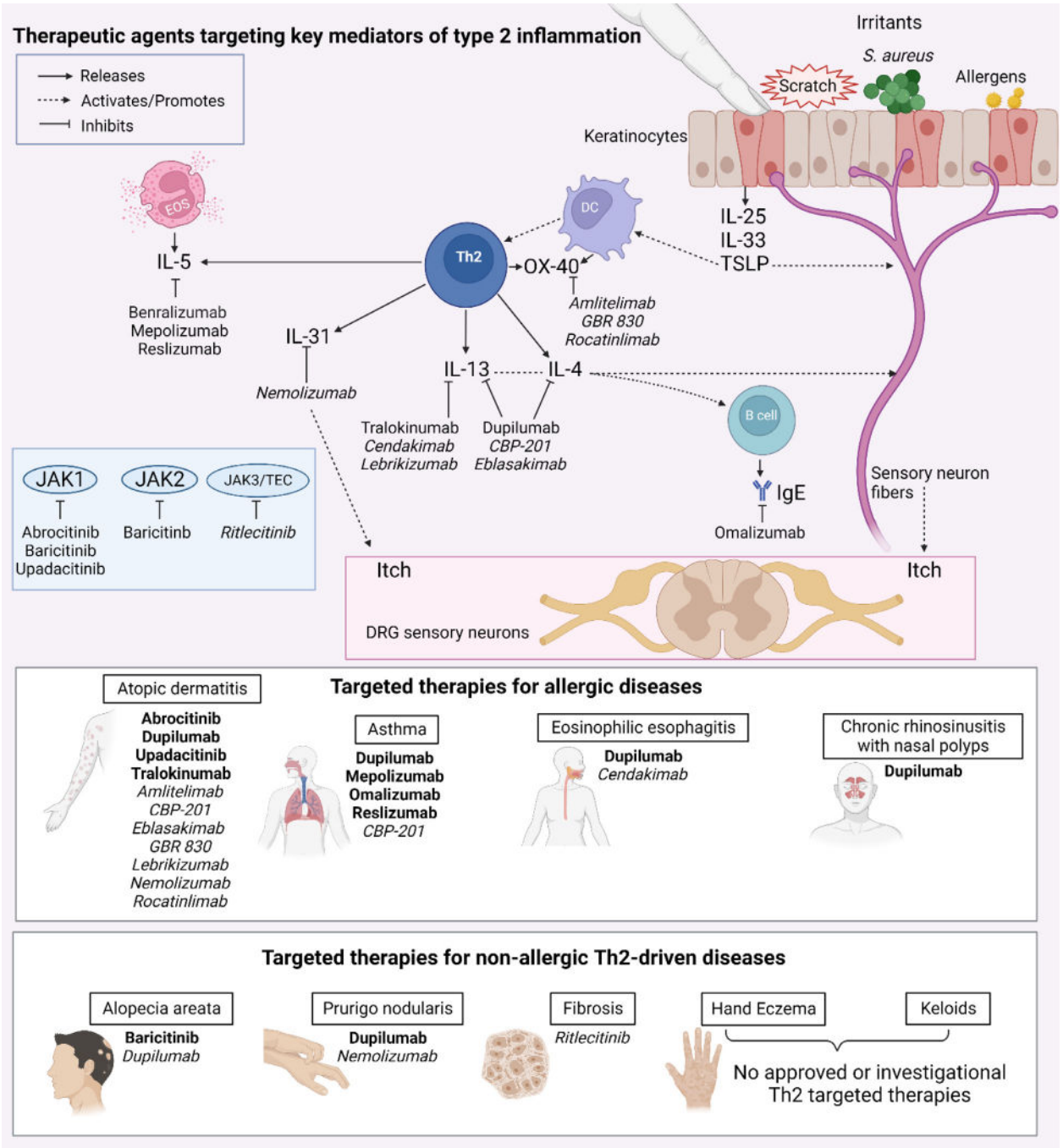

Figure 1. Targeted therapies for T_H2-driven diseases. Agents that inhibit type 2 inflammation are presented with a simplified notation of the pathway(s) they target, not specifying ligand(s), receptor(s), or all known actions of these cytokines. For each disease, bolded agents are US FDA-approved for this indication, whereas italicized agents are under investigation. DC, dendritic cell; DRG, dorsal root ganglion; FDA, Food and Drug Administration; IgE, immunoglobulin E; IL, interleukin; S. aureus, staphylococcus aureus; T_H2, T helper 2; TLSP, thymic stromal lymphopoietin.

accelerate the development of new and more personalized therapies to fill current gaps in patient care for AD and other conditions.

Future innovation is needed to develop tools that will allow us to investigate these complex pathways, elucidate the cause and mechanisms of disease progression, and, ultimately, alleviate symptoms and slow disease progression in T_H2 diseases beyond AD. To advance precision medicine, it is crucial to move beyond phenotype and to focus on characterizing endotypes or cytokine profiles to identify appropriate therapeutic biologics for each patient. Using techniques such as skin tape strip sampling at the point of diagnosis could enable diagnosis on the basis of an individual's specific polarized immune pathway, rather than relying solely on clinical phenotype. This would enable rational treatment selection for patients with conditions such as AD for which multiple targeted therapies are available, and it could support earlier intervention, such as the use of biologics, in earlier stages of disease rather than reserving them for patients who have progressed to moderate-to-severe disease. Endotyping could also identify opportunities to use the same biologic treatment for both skin and systemic diseases that are mediated by T_H2 inflammation. Similarly, this principle may apply to autoimmune diseases driven by T_H1, T_H17, or T_H22 responses.

The future may bring a paradigm shift toward earlier screening and diagnosis, earlier intervention, and potentially even adopting a "treat-to-prevent" approach for atopic disease. For example, emerging data reveal that T_H2 or skin barrier alterations precede the clinical diagnosis of AD or food allergy, and that conducting skin tape strip analysis on asymptomatic infants at the age of 2 months can identify children at high risk of developing AD[6]; this could potentially allow for early use of biologics or other therapeutics to prevent the development of disease entirely, or at least substantially modify its course. With the US Food and Drug Administration now allowing claims regarding disease modification in package inserts for certain drugs approved for AD, it becomes crucial to establish consensus on clinically meaningful outcome measures and to generate data to support such claims, which may not be straightforward in diseases such as eosinophilic esophagitis that are far more heterogenous than AD. Whereas so many patients still await effective therapies, untold scientific discoveries lie in the frontiers of type 2 inflammation beyond AD.

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