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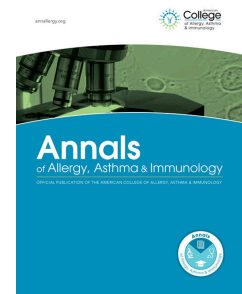
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Title: New treatments for atopic dermatitis targeting beyond IL-4/IL-13 cytokines

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Introduction

The hallmark of atopic dermatitis (AD), the most common inflammatory skin disease, is chronic eczematous rash and itch. These result in significant impact on patients' quality of life, including depression, sleep disturbances and even suicidal ideation.¹ Traditional AD treatments include topical emollients, corticosteroids and calcineurin inhibitors. These, in various regimens and combinations, considerably improve mild to moderate AD patients, and remain the mainstay of treatment. However, for approximately 20% of patients considered to have moderate-to-severe disease, topical treatments are often not satisfactory, due to high disease burden and background systemic inflammation.²⁻⁴ Until recently, treatment options for moderate-to-severe patient populations were limited to phototherapy, systemic immune-modulators such as cyclosporine, methotrexate, mycophenolate mofetil, and systemic corticosteroids.⁵ While phototherapy is not always available and could be substantially time consuming, and systemic immunosuppressants are often associated with significant adverse effects, these treatment modalities cannot provide the much-needed convenient, safe, long-term solution for AD patients requiring systemic therapy. The advances seen in recent years in the research and management of AD are influenced by the interesting path of another common inflammatory skin disease, psoriasis. Psoriasis represents the best immune-characterized skin disease, largely due to results of trials of cytokine-specific inhibitors, which shed light on disease pathogenesis.⁶ ⁷ Dupilumab, a fully human monoclonal antibody blocking two Th2 cytokines, IL-4 and IL-13 (Fig 1), by binding the shared IL-4 receptor α (IL-4R α), was the first AD-specific

therapeutic to be approved in both adults and adolescents.⁸⁻¹⁰ Dupilumab therapy has not only provided another treatment option for moderate-to-severe AD, it has also provided insight into AD pathogenesis. The experience with dupilumab has confirmed that AD can be effectively treated by selectively antagonizing Th2 cytokines.^{11, 12} While two anti-IL-13 monoclonal antibodies are also being tested for AD in advanced studies with favorable outcomes,¹³⁻¹⁶ herein, we focus on novel therapeutics for AD beyond IL-4/IL-13 inhibitors.

AD is heterogeneous with various subtypes

New data demonstrate the complicated immunological/molecular dysregulations underlying clinical features characteristic of AD; and as clinical phenotypes vary, these dysregulations also show wide heterogeneity. While AD is characterized by Th2 skewing across all disease subsets, it shows variable activation of additional immune axes in different disease phenotypes.¹⁷⁻²³ Factors differing among distinct AD subtypes/phenotypes include IgE levels, age, disease chronicity, ethnicity, and barrier proteins dysfunction, such as filaggrin (*FLG*) mutations.

Increased total and allergen-specific IgE levels, eosinophilia, and personal and family history of atopic diseases characterize patients with extrinsic AD that affects ~80% of patients, whereas intrinsic AD patients (~20%) have normal IgE levels and usually lack familial or personal atopy.²⁴ The clinical presentations of extrinsic and intrinsic AD are similar despite these differences. In addition to differing in atopy, intrinsic AD compared to extrinsic AD has greater cutaneous cellular infiltration and increased Th1-, Th17- and

Th22-related cytokines and chemokines. As stated previously, both subtypes exhibit similar Th2 activation.²²

When phenotypes are characterized by age groups, variations are noted in pediatric, adult and elderly (age 61 years and older) patients. Compared to adults, children lack over-expression of Th1-related markers in the skin, but Th2-related cytokines and chemokines show either similar or even greater levels in pediatric AD skin in comparison with adult AD. Th17/Th22-related markers, including IL-17-related anti-microbial peptides (AMPs), are up-regulated in pediatric compared to adult AD, to levels often comparable with those in adults with psoriasis (Fig 1).²⁵⁻²⁷ In elderly AD patients, as compared to younger adult AD patients, Th2/Th22 axes are attenuated, and barrier disruption is less prominent. On the other hand, with increased disease chronicity among adults, there are gradual increases with increasing age in markers of Th1/Th17 pathways.¹⁹ Ethnicity is another variable affecting AD, and phenotypes of European-Americans (EA), various Asians, and African-Americans have been compared. Compared with EA patients, Asian patients show increased Th17 and Th22 activity, while African American patients showed relative decrease in Th1 and Th17-related markers. Th2 skewing was largely consistent among different ethnicities (Fig 1).^{20, 21, 28, 29}

In sum, contrary to the traditional concept of AD as a solely type 2 immune activated disease, new findings highlight AD as a multi-faceted disease, as the disease can be subdivided into variable phenotypes, based on clinical/epidemiological or molecular parameters. These different AD variants may also necessitate different therapeutic approaches, depending on the dominant immune skewing in each patient group.

Why treatments antagonizing IL-4/IL-13 are insufficient?

Given the numerous effects of IL-4 and IL-13 in AD pathophysiology,^{13, 30} including disruption of skin barrier, induction of bacterial binding and colonization, and recruitment of inflammatory cells, these cytokines and cytokine receptors are attractive candidates for therapeutic targeting. Indeed, several therapeutic approaches aimed at inhibiting these cytokines have been explored, and dupilumab is the first biologic treatment licensed for the treatment of moderate-to-severe AD. Clinical studies showed robust clinical efficacy for dupilumab over placebo,^{8, 9} and tissue investigations proved clinical improvements correlated with reversal of molecular and epidermal changes in treated patients.^{11, 31, 32} Although dupilumab directly down-regulates Th2-related markers, it also resulted in down-regulations of some Th17/Th22-related markers, proving its effects beyond narrow IL-4/IL-13 inhibition.¹¹ These “disseminated” effects of dupilumab may contribute to its efficacy in different ethnicities. Nevertheless, despite being a truly significant milestone in AD management as well as other atopic conditions for which it is approved or in clinical trials,^{33, 34} the fact that only 35%-40% of patients on dupilumab achieve clear or almost clear skin, reinforces the need for additional treatment options,^{8, 9, 35} as well as the need for development of a personalized medicine approach tailored to better treat various AD subsets. In order for new treatments to address the unique fingerprint of each AD subtype, targeting of other immune axes beyond IL-4/IL-13 is needed. It likely will be necessary to target a combination of cytokines to fully control AD, regardless of disease phenotype.

Other Th2-targeted therapeutics

The Th2 pathway includes other cytokines and chemokines, some of which are candidates for anti-AD drugs. IL-31, also known as the itch cytokine, has an important role in the resistant itch-scratch cycle of AD. In addition, studies suggest the cytokine has other roles in AD pathogenesis, including inhibition of epidermal terminal differentiation.³⁶⁻³⁸ Several large phase 2 studies of nemolizumab, an IL-31 antibody, highlight the major impact of targeting this cytokine to alleviate the persistent AD-associated itch, with significant improvements in pruritus and sleep loss (percentage change of pruritus score from baseline at 64 week of 70%-80%).³⁹⁻⁴¹ These results are also associated with improvements in clinical disease scores, with significance over placebo as early as week 4 of therapy in a recent trial.⁴² Sustained efficacy was found in a long term follow up trial.³⁹ Interestingly, the 30mg dose outperformed the 90mg dose in both studies, a phenomenon which is unexplained. Phase III studies are underway and will hopefully shed light on the role of IL-31 in the disease, beyond its profound effects on the characteristic itch of AD (NCT03989349, NCT03985943, NCT03989206).

Another interesting target in the Th2 pathway is the thymic stromal lymphopoietin (TSLP), an epithelial cell derived cytokine, which, in conjunction with OX40 and OX40 ligand, strongly drives allergic inflammation with up-regulation of Th2 activation in asthma and AD.⁴³ IL-33, another epidermal derived cytokine, also participates in this process as an amplifier of TSLP-OX40 axis. In addition, IL-33 has a direct negative effect on the integrity of skin barrier in AD.^{44, 45}

In AD lesional skin, TSLP, TSLP receptor, OX40, OX40L, and IL-33, were significantly upregulated, reinforcing the rationale for developing targeted therapeutics antagonizing these factors.^{44, 46} Recently, ST2 (IL1RL1), the IL-33 receptor, was upregulated and

correlated with early AD severity in the pediatric population, suggesting anti-IL-33 strategies may have a role in these young patients as well.⁴⁷

A TSLP inhibitor, tezepelumab, a human monoclonal antibody, showed somewhat disappointing results in a phase II clinical trial for AD in combination with topical corticosteroids.⁴⁸ Nevertheless, a monotherapy clinical trial of tezepelumab for AD is being conducted (NCT03809663), and will hopefully be able to shed light on its role in the disease. In addition, advanced clinical trials of tezepelumab for asthma have shown favorable results.⁴⁹

A phase II proof-of-concept clinical trial of a monoclonal antibody antagonizing OX40, GBR 830, showed that only two intravenous doses of the drug, administered 4 weeks apart, induced significant improvement of tissue and clinical measurements until day 71 (42 days after the last dose).⁵⁰ Although this study was primarily designed as a safety and mechanistic biomarker study, clinical efficacy was observed, as more patients achieved EASI-50 in the GBR 830-treated group vs the placebo group. GBR 830 was well tolerated, and tissue analysis showed significant reductions of Th1, Th2, and Th17/Th22-related markers, as well as significant reduction of epidermal hyperplasia. This study provides first evidence for the pathogenic role of OX40 in AD, and highlights the potential benefits of OX40 antagonism for the disease.⁵⁰ A small Japanese study with another OX40 antagonist, KHK4083, also shows encouraging data in a small study of 22 severe AD patients receiving only three IV doses, with sustained reductions in EASI scores and CCL17 in the circulation until week 22.⁵¹

As for the IL-33 component, anti-IL-33 agents showed favorable results in murine models for AD and acute allergic airway inflammation.^{52, 53} In humans, a small, single

arm, proof-of-concept, phase IIa clinical trial of an anti-IL-33 monoclonal antibody, ANB020 (etokimab), was presented in 2018.⁵⁴ Twelve moderate-to-severe AD patients were enrolled and treated with a single intravenous dose of placebo followed by a single intravenous dose of the drug. All patients achieved at least EASI-50 response and the drug was well tolerated. A phase II clinical trial is ongoing (NCT03533751). In addition, a different agent targeting IL-33 (REGN3500) is also being investigated, as a monotherapy and in combination with dupilumab in another phase II, placebo controlled, clinical trial (NCT03736967). Nevertheless, results of these clinical trials were not yet published in a peer-reviewed journal.

In summary, Th2 pathway includes important immune factors other than IL-4 and IL-13, such as IL-31 and the TSLP-OX40 axis, and agents targeting these cytokines have shown variable efficacy for AD. Further clinical investigations of such targeted drugs (with special attention to younger populations in these trials) may dissect the pathogenic role of each component of the TSLP-OX40 pathway, and its therapeutic potential.

Th22 as a therapeutic target

The Th22 pathway is as consistently activated as the Th2 pathway in AD, and both are considered key immune drivers of AD.⁵⁵ IL-22, the lead Th22 cytokine, was suggested to have a major pathogenic role in epidermal pathology. By attenuating keratinocyte terminal differentiation and inhibiting tight-junction formation, IL-22 over-expression results in barrier dysfunction and epidermal hyperplasia.⁵⁶⁻⁵⁸ There is strong rationale for anti-IL-22 therapeutics in AD, as cytokine levels are significantly elevated in lesional AD skin and correlates with disease severity. IL-22 also correlates with clinical responses to

different AD treatments, including topical corticosteroids, cyclosporine A, phototherapy by NB-UVB, dupilumab, and ustekinumab.^{11, 59-64}

A phase IIa clinical trial investigating fezakinumab, an IL-22–blocking monoclonal antibody, showed significant clinical improvements vs placebo, particularly in patients with severe AD (SCORAD>50), but fezakinumab did not show significant efficacy for moderate patients.⁶⁵ The monoclonal antibody was well tolerated, and the most common adverse events were viral upper respiratory tract infections.⁶⁵ Another study of fezakinumab, focusing on the mechanistic responses to the drug in skin biopsies, revealed reversal of multiple pathologic features of AD skin, as well as reduced overall inflammatory burden, including Th1, Th2, and Th17-related markers, in addition to the Th22 pathway.⁶⁶ In this study, treatment effects were primarily seen in patients with high levels of IL-22 at baseline. Surprisingly, participants with low baseline levels of IL- even had a tendency toward AD exacerbation.⁶⁶

These findings again emphasize the need for a personalized approach in AD patients, as for severe patients, preferably with high baseline levels of IL-22, the drug show significant clinical and molecular benefit.⁹

Agents antagonizing Th17/IL-23

One of the main immune components showing variable over- and under-expression in different AD subtypes, is the Th17/IL-23 pathway. Cytokines related to this pathway, specifically IL-17 and IL-23, play a pivotal role in the pathogenesis of psoriasis, and multiple highly efficacious monoclonal antibodies in psoriasis target these cytokines.^{67, 68}

In AD, greater Th17/IL-23 up-regulations occurs in Asians vs. European Americans,

intrinsic vs. extrinsic, and pediatric vs. adult AD patients.^{21, 22, 29, 69} In these groups, in addition to the common Th2/Th22 over-expression, higher Th17-related markers are detected. Especially in Asian AD, histologic features that are characteristic to psoriasis, such as significant acanthosis and focal parakeratosis, are also more frequent.^{70, 71} In addition, regardless of the AD subtype, both IL-17 and IL-23 decreases are coupled with improvement of AD following various treatments.^{11, 59-61, 63, 66} IL-23 regulates induction of IL-17 and IL-22 cytokines, which synergistically stimulate tissue inflammation and skin barrier disruption.⁷² IL-17 includes six family members, IL-17A-F.⁷³ IL-17A, produced by activated lymphocytes, is perhaps the most known cytokine of this family due to an IL-17A inhibitor, secukinumab, a monoclonal antibody with great efficacy in psoriasis.⁷⁴ Bimekizumab, another monoclonal specific for both IL-17A and IL-17F, is also very effective in psoriasis.⁷⁵ Ustekinumab, a human monoclonal antibody inhibiting the shared p40 subunit of IL-12 and IL-23, is an effective drug for psoriasis due to its IL-23 antagonism.^{76, 77} For AD, despite mechanistic response in skin biopsies, ustekinumab, in conjunction with topical corticosteroids, failed to achieve statistically significant improvement in a phase II, placebo-controlled clinical trial.⁶² The inconclusive results were attributed to insufficient dosing of ustekinumab and to the unlimited use of background topical corticosteroids.⁶² The results of the clinical trial treating AD with secukinumab are not available (NCT02594098, NCT03568136).

Thus, several Th17/IL-23 pathway members might serve as potential targets for AD treatments, particularly in certain AD phenotypes, such as Asians with AD. The efficacy of such approach in AD is yet to be determined.

The unsatisfactory results of both fezakizumab (targeting Th22) and ustekinumab (targeting primarily Th17) in AD reinforce the potential need for a combined therapeutic approach, that will target more than one cytokine/immune axis in AD.

Targeting Other Epidermal Cytokines

Unlike the above-mentioned IL-17 cytokines, which are produced by Th17 T-cells, IL-17C is produced by epidermal keratinocytes and other non-immune cells.⁷⁸ It shares with IL-17A similar effects on keratinocytes, as well as a reciprocal effect in which IL-17A induces IL-17C in keratinocytes, and IL-17C in turn, induces T lymphocytes to produce more IL-17A, a process known as the “feed-forward” mechanism of the skin.^{78, 79} In addition, IL-17C also has autocrine effects on neighboring keratinocytes, as the cytokine influences innate epithelial immune reactions, with synergistic effects with IL-1 and IL-22.⁷⁹ In AD murine models, IL-17C neutralization reduces skin inflammation.^{79, 80} A recent phase I, proof-of-concept, dose ranging clinical trial of a selective IL-17C inhibitor, MOR106, was presented in 2018.⁸¹ In this small preliminary trial of 25 patients, three different doses (1, 4, and 10 mg/kg) of the monoclonal antibody were investigated. Approximately 80% of patients treated with higher doses of MOR106 achieved EASI-50, compared with less than 20% in the placebo group. MOR106 was well tolerated. Phase I data have not been published in a peer-reviewed journal; but due to these promising results, phase II clinical trials are recruiting (NCT03864627, NCT03568071).⁸¹

Broad acting agents

AD is characterized by activation of more than one immune pathway, presenting variable activation of various axes in different disease subsets. Therefore, treatments inhibiting

several immune pathways may be appealing in order to provide therapeutic benefit across all patient populations. Broad acting agents are currently being investigated in large-scale AD clinical trials. It is important to point out that some broad-acting systemic agents were ineffective in AD, such as anti-tumor necrosis factor (TNFs), which are effective for psoriasis, but failed in AD clinical trials.⁸²⁻⁸⁴ Systemic targeting of phosphodiesterase 4 with apremilast, also efficacious in psoriasis, but did not show significant benefit in AD in the 30mg dose.⁸⁴

Janus kinase inhibitors

The Janus kinase (JAK) inhibitors, which are developed both as oral small molecules and topical formulations, are promising agents that target multiple downstream cytokines involved in AD. The JAKs are a family of tyrosine kinases, including JAK1, JAK2, JAK3 and TYK2 (Fig 2).⁸⁵ The JAK/signal transducer and activator of transcription (STAT) pathway is considered a master regulator of immune function, as it mediates a range of intra-cellular immune responses, including polar cytokines involved in the pathogenesis of AD, such as Th2 (IL-4, IL-5, IL-13, TSLP), Th22 (IL-22), and Th1 pathways (IFN- γ , IL-12, IL-23).^{86, 87}

Baricitinib, a JAK 1/2 antagonist, was recently approved by the FDA for rheumatoid arthritis (RA) and was the first oral JAK inhibitor to progress to phase III clinical trials for AD (NCT03435081).⁸⁸ In the phase II trial, significantly more baricitinib-treated patients, compared with placebo, achieved 50% or more reduction of Eczema Area and Severity Index (EASI-50) at 16 weeks (61% vs 37%). Baricitinib efficacy over placebo was apparent after 4 weeks of treatment.⁸⁸ While being mostly well tolerated, more

adverse events were documented in the baricitinib-treated group, including headache, nasopharyngitis, and increased blood creatine phosphokinase (CPK). More adverse events were found in the 4 mg group, which also showed better efficacy, in comparison with the 2 mg dose group and with placebo. On the other hand, baricitinb-related adverse events which were previously reported in RA patients, were not reported in AD patients.⁸⁹

Another JAK inhibitor tested for AD is upadacitinib, a selective JAK1 inhibitor. Upadacitinib showed efficacy in phase III trials for RA,⁹⁰ and was recently FDA approved for this indication, with a boxed warning due to risk of thrombosis and embolisms. Results of a phase II trial of upadacitinib for AD showed impressive clinical outcomes, as approximately 50% of drug-treated patients achieved EASI-90 and clear or almost clear status (IGA 0/1). Upadacitinib was generally well tolerated, with some adverse events such as acne, CPK elevation, and nasopharyngitis.⁹¹ Currently, multiple phase III clinical trials of upadacitinib for AD are recruiting in both adults and adolescents patients (NCT03607422, NCT03569293), including a phase IIIb, randomized, multi-center study that will evaluate upadacitinib vs dupilumab in adults (NCT03738397).

Abrocitinib (formerly PF-04965842), is another specific JAK1 inhibitor tested for AD. The drug showed some efficacy for psoriasis in a phase II clinical trial, but more adverse effects were found in the higher-dose group (where greater efficacy was demonstrated), and the drug did not proceed for further psoriasis trials.⁹² For AD, on the other hand, promising results were found in a phase II clinical trial that showed that up to 45% of abrocitinib-treated patients clinically improved, as assessed by the IGA score, as

276 compared with only 6% of patients treated with placebo.⁹³ Phase III clinical trials of
277 abrocitinib in adults and adolescents with moderate-to-severe AD are being completed
278 (NCT03575871, NCT03422822).

279 In addition to these three JAK inhibitors currently tested for AD, favorable data were
280 recently published on a new dual JAK-Spleen Tyrosine Kinase (SYK) inhibitor
281 (ASN002), following a phase Ib clinical trial for AD.⁹⁴ SYK is a non-receptor tyrosine
282 kinase (Fig 2), and the SYK pathway is involved in several cytokine signaling immune
283 pathways, with subsequent regulation on Th17, B-cell and dendritic cells activation, as
284 well as inhibition on keratinocyte terminal differentiation.⁹⁵⁻¹⁰⁴ Concomitant JAK and
285 SYK inhibition had synergistic, beneficial anti-inflammatory effects,^{100, 105} providing the
286 rationale to add SYK inhibition to JAK antagonism as a potential added therapeutic value
287 to AD.

288 The dual JAK/SYK inhibitor ASN002 was studied in a dose-escalation protocol, with
289 thirty-six adults with moderate-to-severe AD randomized to placebo or 20, 40, or 80 mg
290 of ASN002 for 4 weeks (NCT03139981).⁹⁴ The drug showed rapid therapeutic onset,
291 with improvement in pruritus starting at day 8 in the highest dose-group, in addition to
292 statistically significant decreases in EASI scores in comparison with placebo, with 83%
293 to 100% of patients achieving EASI-50 in the 40mg and 80 mg groups. There were no
294 serious adverse events. Mechanistic investigations of serum markers showed significant
295 down-regulations in Th1, Th2 and Th17/Th22 activation, as well as decreased levels of
296 the atherosclerosis-associated biomarker E selectin/SELE, suggesting improvement in
297 systemic inflammation.⁹⁴ In addition, skin biopsies revealed ASN002 reversed the
298 molecular dysregulations in lesional skin towards a non-lesional phenotype, by rapidly

and significantly suppressing key inflammatory pathways implicated in AD pathogenesis.¹⁰⁶

Some JAK inhibitors are being tested as topical treatments with favorable clinical results in AD trials so far, including tofacitinib,¹⁰⁷ JTE-032,¹⁰⁸ and ruxolitinib (NCT03257644, NCT03011892, NCT03920852).

It may be important to bear in mind that despite disseminating use of JAK inhibitors in dermatology, safety profiles differ among different agents, and long term safety is yet to be determined.¹⁰⁹

Histamine 4 receptor antihistamines

Another class of broad-targeting inhibitors for AD has an entirely different mechanism of action. The histamine 4 receptor (H4R) antihistamines are drugs antagonizing the most recently discovered histamine receptor subtype, H4R, which plays a role in Th2 and Th17 inflammation and pruritus.¹¹⁰⁻¹¹² In contrast to H₁R-blocking antihistamines, which are widely used as anti-pruritic agents, yet their effects in AD patients are mainly sedative,⁵ an oral H₄R antihistamine, ZPL-3893787, showed clinical efficacy on inflammatory skin lesions in an AD phase II clinical trial.¹¹³ In this 8-week trial, 78 moderate-to-severe AD patients were included, and significantly more ZPL-3893787-treated patients achieved EASI-75 score compared with placebo (35% vs 15%). Improvements of pruritus were non significant compared with placebo. ZPL-3893787 was safe and well tolerated.¹¹³ This represents the first investigation of H4R antihistamine in AD patients and suggests the potential of this drug as novel therapeutic option for the disease. A long-term study assessing ZPL-3893787 safety and efficacy in AD is underway (NCT03948334).

Conclusion

Mechanistic studies of AD using information from skin and blood analysis as well as results of clinical trials have highlighted the heterogeneity of this common disease. Patient characteristics such as age, ethnicity, atopic status, and genetic mutations of filaggrin independently affect the clinical phenotype. The variable clinical phenotype and, perhaps more importantly, the variable immunological/molecular fingerprint of AD, may necessitate different therapeutic approaches in different patients subsets, including potentially a personalized medicine approach or dual cytokine targeting, depending on AD subset. Due to this variability, agents with broader, general activity, such as JAK inhibitors, may have more generalized response. Three JAK inhibitors: baricitinib, upadacitinib, and abrocitinib, a dual JAK-SYK inhibitor, ASN002, and a histamine H₄R antagonist, ZPL-3893787, are being investigated with promising results so far as broad-acting, systemic, small molecules in AD clinical trials.^{88, 94, 113} Nevertheless, large long-term studies in AD patients are needed to assess the safety of these treatments for chronic use in AD. Dupilumab, the first FDA-approved targeted monoclonal antibody approved for AD, shows durable efficacy in longer studies and excellent safety for chronic use in both adults and adolescents. Dupilumab is currently considered a mainstay of treatment for moderate-to-severe AD patients, where it revolutionized the treatment armamentarium.^{6, 13, 114, 115} Many other specific agents that are being investigated for moderate-to-severe patients, show favorable results in early or late clinical trials. These include targeted treatments antagonizing other Th2-pathway immune components (i.e OX40/GBR 830, KHK4083, IL-33/etokinumab), Th22/IL-22 (fezakinumab), and

epidermal cytokines (i.e IL-17C/MOR106), which are also anticipated to progress to advanced clinical trial phases.^{50, 65} IL-31, originally considered the itch cytokine, shows significant clinical benefit, in addition to impressive improvement in pruritus, and is advancing to phase III. Anti-IL-13 monoclonal antibodies, tralokinumab and lebrikizumab, are also being investigated with favorable data in late stage trials for AD, but these are beyond the scope of this review.^{14, 15} Various agents differ not only by efficacy, as determined by clinical scoring systems, but also by other aspects. For example, several agents show profound benefits rapidly (e.g some JAK inhibitors), and other agents show later response, yet longevity of effect (e.g TSLP-OX40 antagonists). Parallel investigations of both broad and narrow acting drugs, in multiple ongoing clinical trials, will eventually transform the therapeutic paradigm of moderate-to-severe AD, as was the case for psoriasis. Mechanistic investigations of these various treatments will help dissect the complex contribution of various cytokines to AD, to ultimately improve long-term disease management and prevention of flares.

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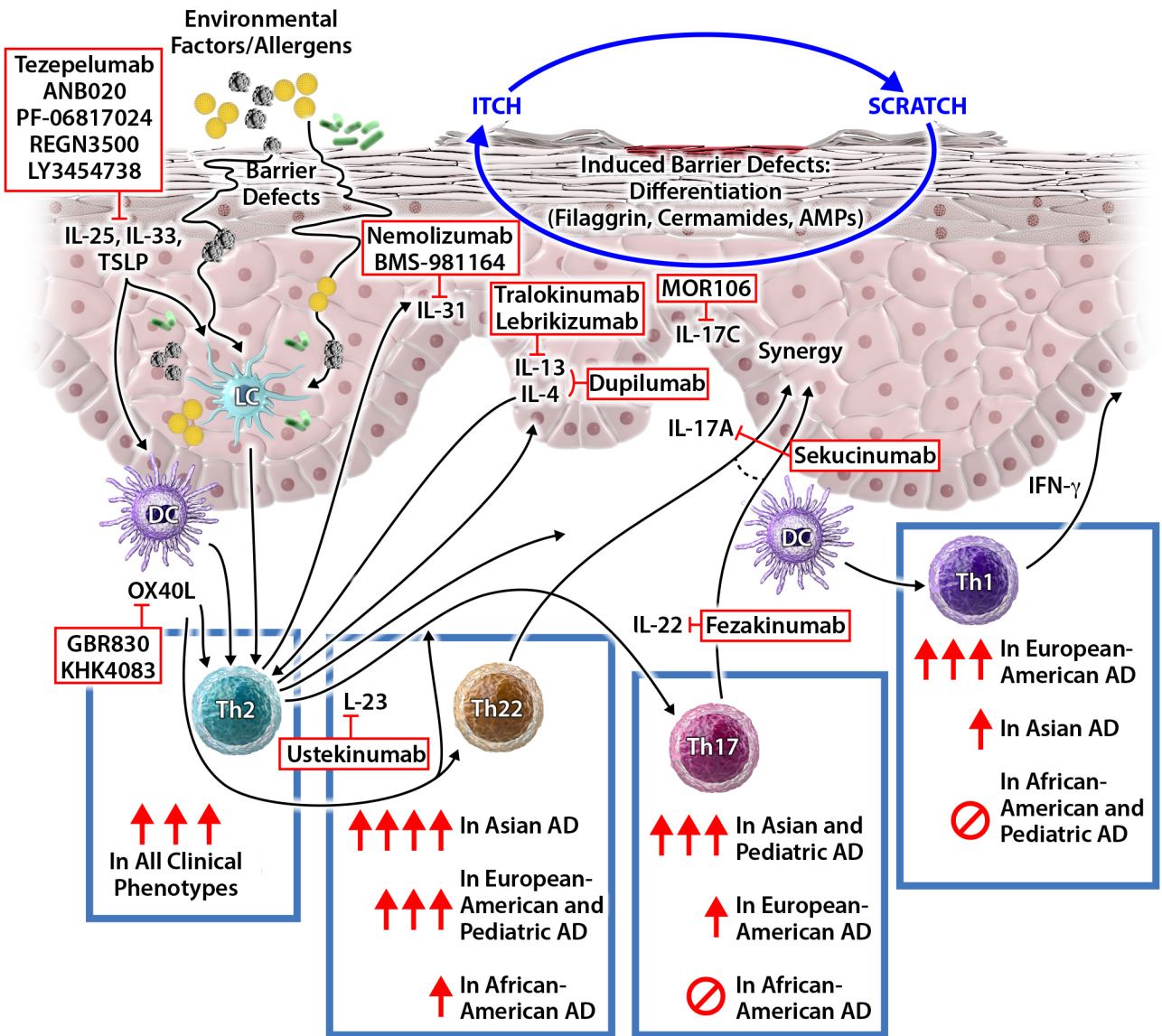
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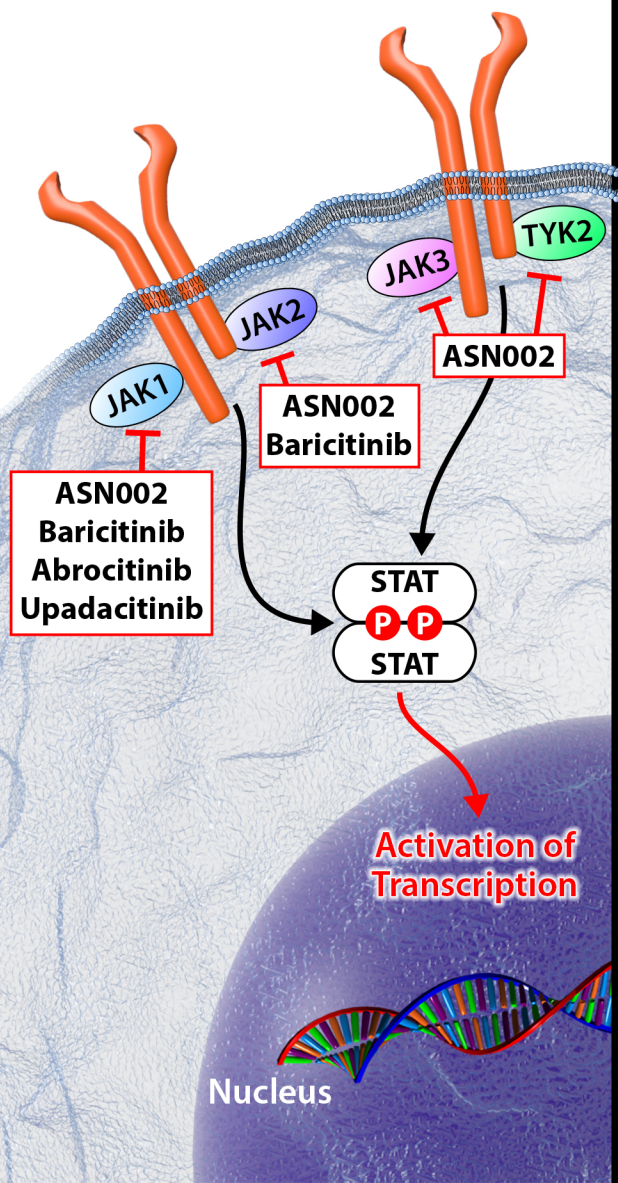
Figure legend

Figure 1. The immune dysregulations of AD, with corresponding targeted agents (red boxes). Under each Th pathway, in black boxes, are AD subtypes that were molecularly characterized, with arrows indicating the degree of over-expression of this specific Th axis in each clinical phenotype.

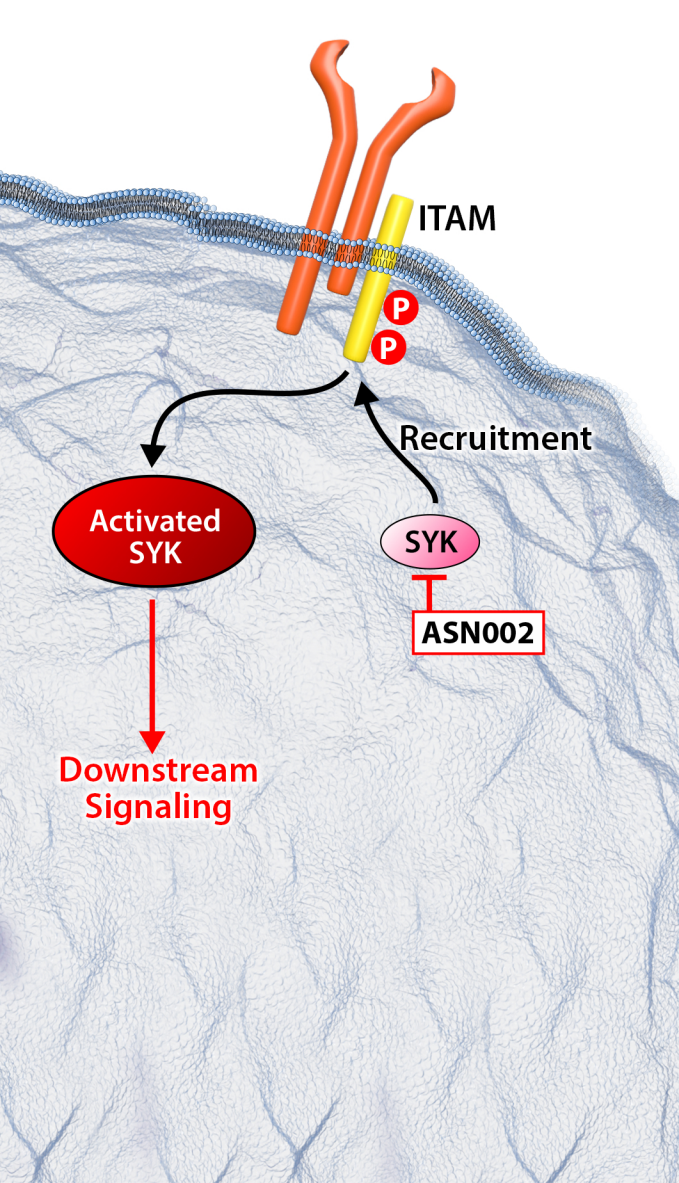
Figure 2. Mechanism of action of JAK and SYK inhibitors. A, JAK inhibitors interfere with cytokine signaling by blocking signal transmission in various immune cells as well as keratinocytes, by preventing JAKs from phosphorylating substrates such as STATS, and therefore cytokine-dependent gene regulation is inhibited. B, SYK inhibition suppresses the activation of down-stream kinases, eventually resulting an anti-inflammatory effect.



A



B



1 **Key messages**

- 2 • Atopic dermatitis (AD) is a common and heterogeneous inflammatory skin
3 disease, with various subtypes differing by clinical, demographic, and molecular
4 characteristics
- 5 • Most patients can be managed by conventional interventions, but for those who
6 require systemic immunosuppressive therapies, safe and effective alternative
7 treatment options are limited
- 8 • Some of the emerging broad- and narrow-targeting agents have shown significant
9 benefit in clinical trials of patients with moderate-to-severe AD, paving the way
10 for novel therapeutic paradigm
- 11 • Beyond IL-4/IL-13 inhibitors, recent favorable outcomes were seen in clinical
12 trials of JAK inhibitors (baricitinib, upadacitinib, and abrocitinib), a dual JAK-
13 SYK inhibitor (ASN002), a histamine H₄R antagonist (ZPL-3893787),
14 antagonists of the TSLP-OX40L axis (GBR 830, etokinumab), an IL-22 inhibitor
15 (fezakinumab), and an IL-17C antagonist (MOR106)
- 16 • These trials, with special attention to the variability among AD sub-populations,
17 will also help to expand the current knowledge on AD pathogenesis, and to
18 dissect the contribution of different molecular factors, to ultimately portray the
19 full immunologic fingerprint of each AD subtype