Published in final edited form as:

J Allergy Clin Immunol. 2017 April ; 139(4 Suppl): S65–S76. doi:10.1016/j.jaci.2017.01.011.

The Immunology of AD and its Reversibility with Broad Spectrum and Targeted Therapies

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Abstract

Atopic dermatitis (AD), the most common chronic inflammatory skin disease, is driven by both terminal keratinocyte differentiation defects and strong type 2 immune responses. In contrast to chronic plaque-type psoriasis, AD is now understood to be a much more heterogeneous disease, with additional activation of Th22, Th17/IL-23 and Th1 cytokine pathways, depending on the subtype of the disease. In this review, we discuss our current understanding of the AD immune map in both early-onset as well as chronic disease. Clinical studies using broad and targeted therapeutics have helped to elucidate the contribution of various immune axes to the disease phenotype. Importantly, immune activation extends well beyond lesional AD, as non-lesional skin and the blood component harbor AD-specific inflammatory changes. For this reason, future therapeutics will need to focus on a systemic treatment approach, especially in patients suffering from moderate-to-severe disease.

Keywords

Atopic dermatitis; eczema; keratinocyte; immune; T helper cell; skin immune map; targeted therapy

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, with a prevalence of up to 7% in adults and up to 25% among children.[1–5] Characteristically,

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Disclosures: EGY is a board member for Sanofi Aventis, Regeneron, Stiefel/GlaxoSmithKline, MedImmune, Celgene, Anacor, AnaptysBio, Celsus, Dermira, Galderma, Glenmark, Novartis, Pfizer, Vitae and Leo Pharma; has received consultancy fees from Regeneron, Sanofi, MedImmune, Celgene, Stiefel/GlaxoSmithKline, Celsus, BMS, Amgen, Drais, AbbVie, Anacor, AnaptysBio, Dermira, Galderma, Glenmark, LEO Pharma, Novartis, Pfizer, Vitae, Mitsubishi Tanabe and Eli Lilly; and has received research support from Janssen, Regeneron, Celgene, BMS, Novartis, Merck, LEO Pharma and Dermira. DYML has received research support from Pfizer, AstraZeneca and MedImmune, is on the advisory board for Celgene and Anacor; and has received consultancy fees from Aimmune Therapeutics and Novartis. PMB declares not to have a relevant conflict of interest.

symptoms start within the first 5 years of life, and in adult patients, the disease has generally been present for decades. Similar to psoriasis,[6,7] AD is now considered a primarily T-cell driven disease,[8,9] as proven by the clinical efficacy of broad T-cell targeting therapeutics such as cyclosporine, efalizumab, and alefacept.[10,11,12] While the latter two are no longer available due to safety concerns, cyclosporine, oral glucocorticosteroids (GCS) and phototherapy (NB-UVB) are often used to treat moderate-to-severe disease.[13–15] However, cyclosporine and even more so GCS are not suitable for long term use due to multiple side effects. Phototherapy is very time consuming and not feasible for most patients.[16] Therefore, AD presents a large unmet need for both effective and safe therapeutics.[2] While animal models have been instrumental in deciphering general components of cutaneous biology in health and disease, the complex interplay between immune mechanisms, skin barrier and potential intrinsic and extrinsic triggers of disease are not well represented in a single animal model, and thus need to be addressed and characterized in humans.[17,18]

One strategy that was instrumental in psoriasis to educate on disease pathogenesis and activated cytokines is through clinical trials with broad and specific immune antagonists coupled with tissue biomarkers.[19] Such an approach is also being successfully implemented in AD.[20] Broad therapeutics such as GCS, cyclosporine, topical calcineurin inhibitors and NB-UVB have suggested the immune nature of AD, and indicated possible involvement of more than one cytokine pathway.[13,14,21,22] These studies not only provided the final proof of the immune nature of AD, but also of the pathogenic role of the Th2 axis in this disease. Although increased IL-4 and IL-13 in lesional and non-lesional AD was first described in 1994, it was not until recent that studies demonstrated the clinical efficacy of dupilumab, an IL4R antagonist, and that conclusive clinical proof became available supporting the importance of the type 2 immune pathway in AD.[23–26]

The emerging immune map of AD

Similar to psoriasis, that is centered around a Th17/IL-23 axis, AD has been associated with activation of T-cell subsets.[27] Although AD seems to be unanimously characterized by a strong activation of Th2 immune responses in lesions and even in non-lesional skin,[20] Th22, Th17/IL-23 and Th1 cytokine pathways likely play a role in the disease, particularly in some AD subtypes.[8]

In acute lesions, AD onset is characterized by profound increases of Th2 (IL-4, IL-5, IL-13, IL-31, CCL18) and Th22 (IL-22, S100A proteins) responses.[28,29] These mediators have been demonstrated to down-regulate terminal differentiation genes and tight junction products such as claudins, contributing to the barrier defect in AD.[30–40] Recently, it has been demonstrated that group 2 innate lymphoid cells (ILC) can also produce Th2 cytokines. While present at much lower frequencies than T cells, type 2 ILC have been found at increased levels in AD lesions compared to healthy control skin,[41–43] thereby possibly promoting Th2 responses.[41,44]

Among Th2 immune mediators, IL-4 and IL-13 have been demonstrated to play a key role in AD pathogenesis. Genetically, AD has been shown to be associated with IL-4 and IL-13 polymorphisms,[45–48] and eczema-like features can be induced in transgenic mice

overexpressing these cytokines.[49–52] In humans, mRNA in situ hybridization studies by Hamid et al. demonstrated increased levels of IL-4 and IL-13 in both acute and chronic AD, to a higher degree than IFN-γ.[26,53] IL-4 decreases the expression of multiple genes in the epidermal differentiation complex (EDC) that regulate epidermal barrier function.[54] Keratinocytes differentiated in the presence of IL-4 and IL-13 exhibited significantly reduced filaggrin gene expression, even in patients without filaggrin mutations.[38] Aside from filaggrin, loricrin and involucrin are also downregulated in lesional and nonl-lesional AD skin by IL-4 and IL-13, contributing to a defective skin barrier in AD.[31] A compromised barrier allows penetration of bacteria and allergens in to the skin, leading to infections and allergen sensitization, both being highly characteristic of AD.[31]

Th2 polarization facilitates *Staphylococcus aureus* binding and colonization,[55,56] and IL-4 and IL-13 inhibit skin production of antimicrobial peptides (AMP),[56] predisposing AD skin to *S. aureus* infections,[57] which, in turn, further exacerbates skin inflammation and barrier defects.[58–62] Also, eczema vaccinatum, a disseminated viral skin infection that occurs in AD following inoculation with vaccinia virus, has been demonstrated to depend on IL-4/IL-13 expression via AMP downregulation.[63] Mechanistically, it has been shown that IL-4 and IL-13 inhibit TNF-α and IFN-γ-induced human beta-defensin(HBD)-3 via activation of STAT-6 production in keratinocytes,[64,65] as well as TNF-α-induced cathelicidin production.[57] Despite the fact that IL-17 can be found in AD lesions, its antimicrobial effects (via the up-regulation of antimicrobial peptides such as HBD-2 in keratinocytes) are inhibited when IL-4 and/or IL-13 are present.[62] The fact that IL-4/IL-13-driven inflammation can truncate these key Th1 (IFN-γ) and Th17 (IL-17) dependent skin defense mechanisms in AD, as well as the successful treatment of AD with dupilumab, which blocks receptor binding of both IL-4 and IL-13,[23–25] proves their central role in disease pathogenesis.

Th17-associated molecules (IL-17A, PI3/elafin, CCL20) are consistently up-regulated in both acute and chronic AD, but at lower levels than in psoriasis (as compared to normal skin).[66,67] IL-17A could possibly contribute to the immune dysregulation in AD by synergistically upregulating S100A7/8/9 together with IL-22.[68] The S100A proteins, which are highly upregulated in AD, can act as both antimicrobials and inflammatory molecules.[69] There is also evidence that IL-17 can contribute to barrier abnormalities by down-regulating filaggrin, and by affecting keratinocyte expression of genes associated with cellular adhesion.[34]

Th2 and Th22 responses are intensified in chronic AD lesions, with parallel activation of the Th1 axis (IFN-γ, CXCL9, CXCL10), rather than a “switch” to a Th1-only signature.[66,70] IL-22 has also been identified as a key mediator of epidermal hyperplasia.[68] IL-31, a cytokine associated with itch,[71,72] shows large increases in acute lesions, correlating with disease severity in some studies.[29,66,73,74]

AD shows phenotypic variations

Several AD subtypes have been described, with considerable variations (Figure 1).[8,75] These are based on IgE levels (intrinsic versus extrinsic AD),[76] filaggrin mutations status, race, and age.[3,29,77–79]

Mutations in the *FLG* gene, leading to a deficiency in filaggrin, have been associated with AD that is more severe and persistent than its wild type counterpart. This includes a higher degree of immune dysregulation with type 1 interferon-mediated stress responses and higher IL-1 cytokine levels, and higher rates of skin infections and allergies.[28,29,34,35,80–84] However, *FLG* mutations are only detected in up to 30% of individuals (and rarely occurs in African-American populations with AD),[84] and patients with *FLG* mutations have been shown to outgrow their disease.[35] Consistently, dupilumab treatment was demonstrated to work equally well independent of filaggrin status.[24]

Extrinsic AD is characterized by an increase in total and allergen-specific IgE levels, higher rates of eosinophils, and a family history of atopic diseases. In contrast, intrinsic AD shows normal IgE levels, and patients usually lack a personal or familial history of atopy.[85] Both intrinsic and extrinsic subtypes show strong Th2 activation,[79] consistent with similar treatment efficacy of dupilumab in both conditions.[25] However, intrinsic AD shows a stronger activation of Th17 and Th22 responses, with levels of some Th17-related mediators (i.e. CCL20) correlating with AD disease severity.[79]

Ethnic differences have also been demonstrated to contribute to AD disease heterogeneity.[86–90] In Asian AD patients, the Th17 axis was significantly increased compared to European American patients, and its overall cytokine profile, together with features atypical for AD such as parakeratosis, suggest that Asian AD is likely a blend between AD and psoriasis.[78] Future studies will show whether this effect is genetic or environmental, and whether Asian AD can be successfully targeted with the IL-17-targeting drugs originally developed for psoriasis.[91–93]

Pediatric versus adult AD – Different immune phenotypes on a common Th2 background

Despite the fact that AD usually starts early in childhood, most AD studies have only investigated adult patients. However, there are some clinical clues for differences between early pediatric and adult AD, such as lesions on extensor surfaces in infants, whereas adults typically show flexor involvement.[3] Furthermore, the skin microbiome differs in pediatric vs. adult AD.[94] Most studies in AD children are limited to studies of peripheral blood,[80,95–107] demonstrating that disease activity correlates with several serum biomarkers (i.e. IL-31, CCL17, CCL22, CCL27, eosinophils, IgE), and a limited array of Th2/Th1 markers using mRNA expression.[108–112] Recently, the peripheral blood phenotype of early pediatric AD has been characterized only by Th2 expansion, without other polar T-cell subsets in blood.[113] In contrast, adult AD blood also shows increases in Th22 polarization, possibly reflecting continuous immune stimulation over time.[113] Remarkable differences also have been detected in a recent study between the skin profiles of infants and adults.[114]

While both early-onset pediatric as well as adult AD show a strong Th2 activation, there is increased innate and IL-17-related inflammation in early AD lesions of infants. This dual upregulation of both Th2 and Th17 responses might be explained by profoundly increased levels of IL-19, a cytokine that can be induced by both IL-17 and IL-4/IL-13, and which has been shown to amplify the effects of IL-17 on keratinocytes.[115] Besides Th17 responses, early-onset pediatric AD showed increased levels of antimicrobial peptides (AMP),[114] comparable to levels in adult psoriasis. This increase in AMP might serve as a danger signal triggering disease, as demonstrated in psoriasis, where complexes of AMP with either self-DNA or RNA can stimulate dendritic cell activation.[116,117] However, control skin from healthy infants also showed elevated levels of Th17 and Th22 associated mediators, including AMPs,[114,118,119] possibly rooted in the necessity of newborn skin to combat infections when the skin immune system is not yet fully developed. Thus, the pathogenic role of these immune axes in children need to ultimately be evaluated through clinical trials.

Strikingly, the filaggrin deficiency of adult AD was missing in early AD,[114] perhaps challenging the notion of defective filaggrin as primary factor for disease elicitation and an instigator of the atopic march. Future studies will need to further characterize epidermal barrier features in early-onset AD.

Surprisingly, the non-lesional skin of infants and young children also showed significant hyperplasia, and activated cytokines to levels as high or even higher than in adult non-lesional skin.[114] Thus, the non-lesional skin of children with early AD can be viewed as a true state of disease initiation. Interestingly, at 2 months of age prior to onset of AD, infant non-lesional skin contain increased TSLP, a cytokine that drives differentiation of Th2 cells.[120] In sum, the Th2 axis seems to be pathogenic across all AD phenotypes. But, other cytokine axes may have a pathogenic role is some AD subtypes. Clinical trials with specific Th2, Th17/IL-23 and Th22 antagonists are needed in different parts of the world and in different phenotypes to be able to dissect the pathogenic contribution of each axis to the disease.

AD as a systemic disease

Often AD begins during early infancy or childhood, and adult patients usually have longstanding disease for decades.[121,122] Circulating skin homing T-cells, marked by cutaneous lymphocyte antigen/CLA, in severe AD patients show significant increases in activation markers, and polar cytokines, even compared to those seen in psoriasis, as compared to healthy individuals.[123] Significant increases in B-cells in blood are also seen in AD, but not in psoriasis, perhaps reflecting the atopic or allergic associations characterizing the disease,[124] and the atopic march.[4,125] The systemic nature of AD is also reflected in the wide abnormalities seen in the non-lesional skin of adult patients with severe, chronic disease, since even non-lesional skin harbors considerable immune activation and terminal differentiation defects.[114,126] Non-lesional AD shows increased expressions levels of Th2 (CCL22, CCL18, and IL-13), Th22 (L-22), and Th1 (MX-1) cytokines, significantly correlating with disease severity.[126] In addition, it is characterized by profound decreases in terminal differentiation genes, and their expression is inversely correlation to disease activity

as defined by SCORAD.[126] These non-lesional abnormalities have therapeutic implications, suggesting the need for systemic treatments for patients with severe AD.

AD is increasingly recognized to also be associated with other, non-allergic conditions.[127,128] Similar to psoriasis, adult AD patients harbor an increased risk of cardiovascular disease.[129] So far, people suffering from AD were shown to have higher odds of heavy smoking, increased alcohol intake, and decreased rates of vigorous physical activity compared to non-AD individuals.[130] In line, adult AD patients were identified to have increased cardiovascular risk factors such as a higher BMI, higher odds of arterial hypertension and lifetime pre-diabetes, and a sedentary lifestyle.[131–134] Recently, an increased prevalence of coronary artery disease has been reported in severe AD patients without known cardiovascular disease, showing the presence of coronary plaques in 48.1% of AD patients, being significantly increased compared to healthy controls which showed a rate of 21.2%, as assessed by coronary computed tomography angiography.[135]

It is now well established that chronic inflammation accelerates atherosclerosis due to repetitive vascular injury.[136] Mechanistically, elevated levels of TNF-α, IL-17 and IL-22 are currently thought to contribute to the increased cardiovascular risk in chronic plaque-type psoriasis, another chronic inflammatory skin disease.[137,138] These cytokines are also activated in skin of AD patients, and circulating T cells skewed towards the production of several of these markers are also increased in AD,[79,139–142] possibly mediating endothelial damage in this patient population. In vitro data suggest that IL-17 can indeed contribute to pro-inflammatory changes in endothelial cells, and the inhibition of IL-17 in a mouse model of atherosclerosis significantly decreased disease.[143,144]

It will be important to characterize serum markers of cardiovascular risk (and associated inflammatory markers) to better estimate disease risk, and to monitor therapeutics on their effect of cardiovascular risk factors.

Targeted therapies as milestones in understanding pathogenesis

Due to the advent of new, targeted therapeutics (Figure 2A), our knowledge in key disease pathways is rapidly expanding. Ongoing or recently published controlled trials are summarized in Table 1.

IgE, which is profoundly increased in 80% of patients suffering from extrinsic disease, has long been regarded as key in the development of eczema.[145] So far, two randomized-controlled studies failed to show clinical effects of the IgE-blocker omalizumab,[146,147] suggesting that increased IgE levels are an epiphenomenon of AD, mediating comorbidities such as food allergy, asthma and rhinoconjunctivitis, but not AD itself. However, results from a current trial with a higher affinity anti-IgE antibody (QGE031) are currently pending. Eosinophils, which can be found at increased levels in AD patients both in blood and skin, are also likely not central to disease development. In this regard, IL-5 which specifically acts on eosinophils resulting in accelerated eosinophilopoiesis, chemotaxis, cell activation, and delayed apoptosis,[148] may not play a key role in AD as mepolizumab, a monoclonal IL-5 antagonist did not show efficacy in early trials.[149] However, more definitive longer trials are

needed to define the role of IL-5 in AD, since the initial studies were of only two-week duration, which may be potentially too short a time frame to judge treatment effect in this disease.[149,150]

On the other hand, dupilumab, a monoclonal antibody that specifically targets IL-4Rα, thereby blocking the two key mediators of the Th2 pathway, IL-4 and IL-13 is highly efficacious for controlling skin disease in moderate-to-severe AD patients (Figure 3).[23–25] Dupilumab has shown excellent safety and efficacy in phase II trials, with Eczema Area and Severity Index (EASI)50, EASI75 and EASI90 responses of 82.5%, 60.3% and 36.5%, respectively, after 16 weeks of treatment (300mg once a week), compared to 29.5%, 11.5%, and 3.3% of respective responses in the placebo group.[23] These results have also been confirmed in two large phase III studies with dupilumab (SOLO1 and SOLO2) in 671 and 708 moderate-to-severe AD patients, respectively (Table 2). Weekly doses of 300mg dupilumab (without concomitant topical glucocorticosteroids or calcineurin inhibitors) elicited a 72% and 69% improvement of baseline EASI, and 37% and 36% of patients achieved clearing or near-clearing of skin lesions, compared to only 10% and 8% in the placebo group ($p<0.001$).[151]

Current trials with monoclonal antibodies that exclusively target IL-13 (tralokinumab - NCT02347176, lebrikizumab - NCT02340234) will shed further light on the question whether IL-4 and IL-13 are redundant, or complementary, in the pathogenesis of AD. Blockade of IL-31 (BMS-981164), the Th2-associated itch cytokine,[71] is also currently being investigated (NCT01614756).[8] A single subcutaneous dose of CIM331 (nemolizumab), a monoclonal antibody blocking IL-31 receptor A, was well tolerated in a phase I study in healthy volunteers and patients with AD, decreasing pruritus, sleep disturbance and topical use of glucocorticosteroids in the latter.[152] Future studies should clarify the role of anti IL-31 treatment for AD disease activity, versus control of the itch associated with the disease.

The thymic stromal lymphopoietin (TSLP)-OX40 ligand (OX40L) pathway has recently been suggested to be an initiation factor for exacerbated Th2 immune activation.[153,154] Keratinocytes and Langerhans cells in lesional skin of AD patients were shown to highly express TSLP,[155] triggering the expression of OX40L on dendritic cells. TSLP blockade is currently assessed in a phase I clinical trial (AMG-157, NCT00757042; MK-8226 NCT01732510). OX40L and OX40 (a co-stimulatory receptor expressed on activated T cells) are important in generating and maintaining Th2 responses as well as in the development of adaptive and innate allergic inflammation.[156] OX40-OX40L interaction has also been demonstrated in a variety of inflammatory conditions associated with allergy, including allergic asthma, rhinitis, and conjunctivitis.[153,154] Blocking this Th2 biased costimulation might be a therapeutic target in the future, and is currently assessed in a clinical trial (NCT02683928).

The prostaglandin DP2 receptor CRTH2 (CD294), a G protein-coupled receptor expressed by CLA^+ Th2 cells,[157] has been shown to be important for allergic skin inflammation after epicutaneous antigen challenge.[158,159] Polymorphisms in CRTH2 have been associated with allergic sensitization.[160] CRTH2 blockade (Figure 2B) via the small molecules fevipiprant

(QAW039, NCT01785602) and OC000459 (NCT02002208) are currently being assessed in clinical trials.

While the efficacy of dupilumab proves the pathogenic role of type 2 immune responses in AD, the role of other cytokine pathways remains to be elucidated, as dupilumab not only reduces Th2 associated molecules such as CCL17, CCL18 and CCL26, but also strongly decreased mediators associated with Th17 and Th22 responses, such as S100A proteins, PI3/elafin and IL-23p19 (Figure 4).[24] Th17/IL-23 axis is up-regulated in AD patients and might have a role in AD development, in line with recent findings in a flaky tail mouse model showing that IL-4 signaling can be regulated by the IL-17 pathway,[161] and the up-regulated Th17 responses in early-onset AD in children.[114]

Ustekinumab is an IL-12/IL-23p40 blocker inhibiting Th1 and Th17/Th22 responses, successfully used for the treatment of moderate-to-severe psoriasis.[162] In a small phase II study[163] using the FDA-approved psoriasis dosing, ustekinumab had clear and sustained clinical and molecular effects,[163] but outcomes (as compared to the “placebo” arm) were likely obscured by the allowed background topical glucocorticosteroid use,[21] and waning treatment effects after 8–10 weeks from each ustekinumab administration, suggesting under-dosing of the drug. Interestingly, ustekinumab treatment in AD[163] and alopecia areata patients[164] induced significant reductions in Th2 axis, in addition to the expected reductions in Th1, Th17 and Th22 axes.

Since Th22 and Tc22 T-cells have been correlated with AD disease severity,[32] and the Th22 cytokine, IL-22, is involved in epidermal hyperplasia and barrier defects in AD,[32,68] an anti IL-22 treatment might prove to be effective in chronic AD patients. This approach is currently being investigated using the IL22 blocking antibody ILV-094 (NCT01941537). Anti-IL-17 (secukinumab - NCT02594098) treatment is also being explored for AD in both intrinsic and extrinsic AD patients.[68]

Broader treatment approaches (Figure 2B) that show first, promising results, but need to be verified in larger, controlled studies, include apremilast (anti-phosphodiesterase (PDE)-4),[165,166] JAK inhibition,[167,168] and H4R antagonists.[169]

Apremilast, which showed treatment effects in psoriasis[170] and is currently being evaluated in a controlled trial in AD (NCT02087943), inhibits PDE-4, thereby increasing the intracellular cAMP levels, which in turn results in a reduction in inflammatory mediators (e.g. IFN-γ, TNF-α, IL-12, IL-17, IL-23), and an increase in anti-inflammatory effects.[15] Crisaborole, a topical PDE-4 inhibitor, demonstrated a favorable safety profile and improvement in clinical disease severity in phase III studies, both in children and adults with AD.[171]

In AD, the JAK-STAT signaling pathway is thought to have multiple effects, including the induction of Th2 polarization and skin barrier disruption,[172] the activation of eosinophils and B cell maturation, the upregulation of epidermal chemokines, and the downregulation of AMPs.[173] Topical tofacitinib, a JAK1/3-inhibitor, showed promising results in a placebo controlled phase II trial.[167] Several oral JAK 1 and 2 inhibitors are now in phase II trials in

moderate-to-severe AD patients (baricitinib - NCT02576938; PF-04965842 - NCT02780167).

The histamine H4 receptor has recently been identified to be involved in keratinocyte proliferation[174] in patients with AD. ZPL389, a small molecule blocking this receptor, is currently evaluated in clinical trials for psoriasis (NCT02618616) and AD (NCT02424253). In AD, significant improvement of EASI and SCORAD over placebo have been announced in a congress report.[8]

Outlook

Currently, clinical trials with targeted therapeutics have become key in the advancement of understanding the pathophysiology of this debilitating skin disease. Both successful treatment approaches, as well as failing therapies, have profoundly increased our understanding of AD, and will help to shape future therapies, hopefully at a similar successful pace as seen for psoriasis in the last 15 years.

Acknowledgments

Funding: PMB was supported in part by grant # UL1TR001866 from the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program.

Abbreviations

AD	Atopic dermatitis
AMP	Antimicrobial peptide
CLA	Cutaneous lymphocyte antigen
CRTH2	Prostaglandin DP2 receptor
EASI	Eczema Area and Severity Index
EDC	Epidermal differentiation complex
FLG	Filaggrin
GCS	Glucocorticosteroid
HBD	Human beta-defensin
H4R	Histamine H4 receptor
ILC	Innate lymphoid cells
IL4R	Interleukin 4 receptor
JAK	Janus kinase
NB-UVB	Narrow-band ultraviolet B

OX40L	OX40 ligand
PDE	Phosphodiesterase
PGD_2	Prostaglandin D_2
PI3	Peptidase inhibitor 3
SCORAD	SCORing Atopic Dermatitis
STAT	Signal Transducer and Activator of Transcription
TSLP	Thymic stromal lymphopoietin
TSLPR	Thymic stromal lymphopoietin receptor

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Figure 1A

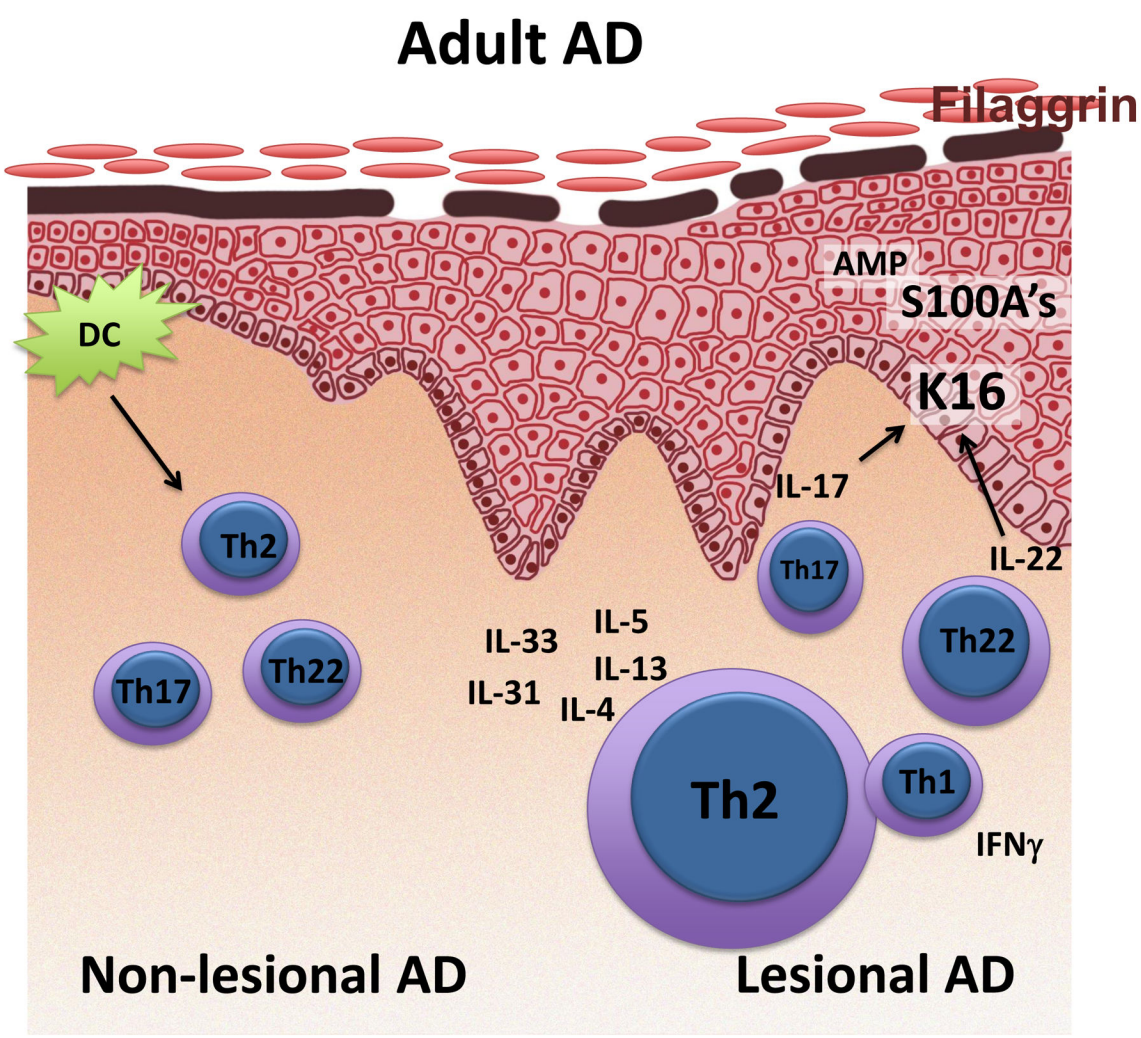
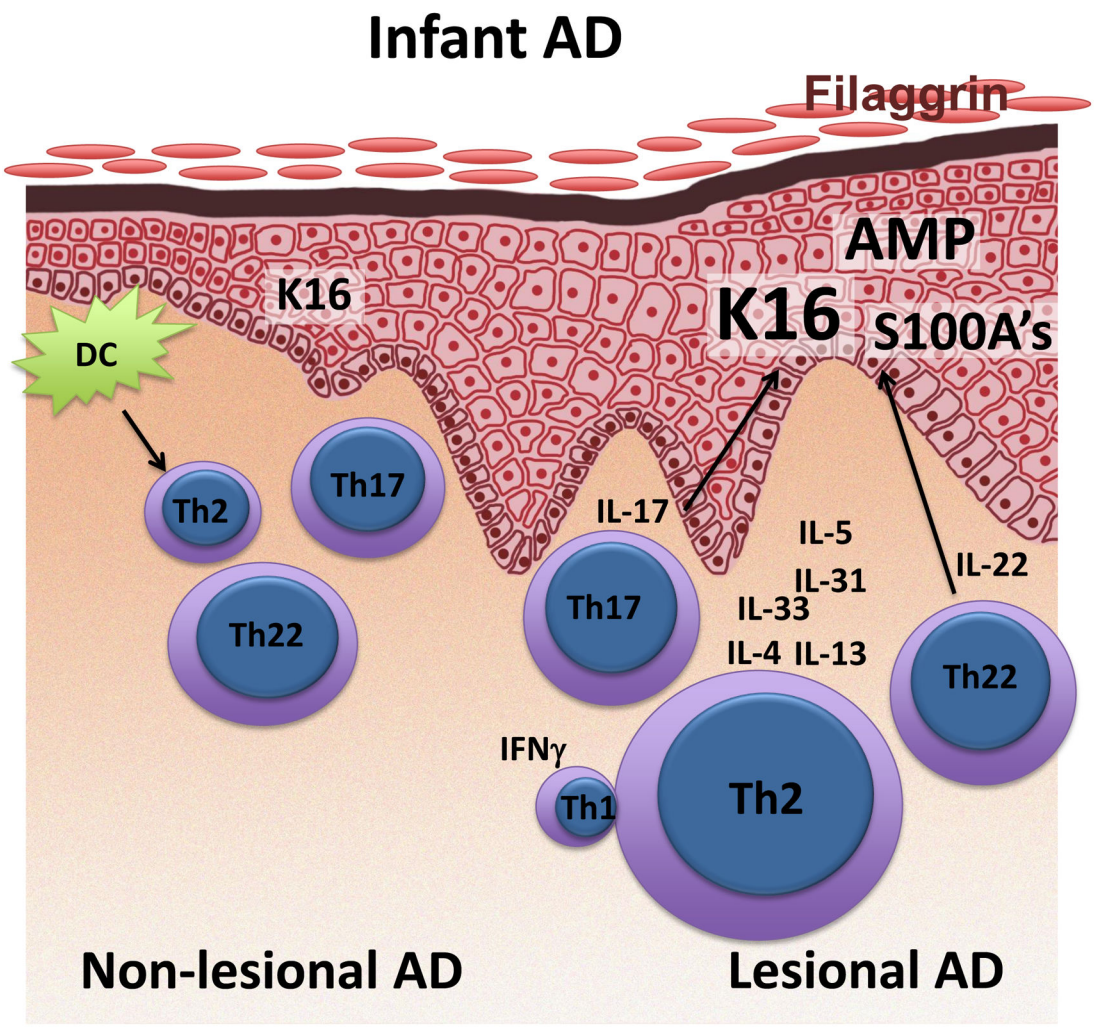


Figure 1B



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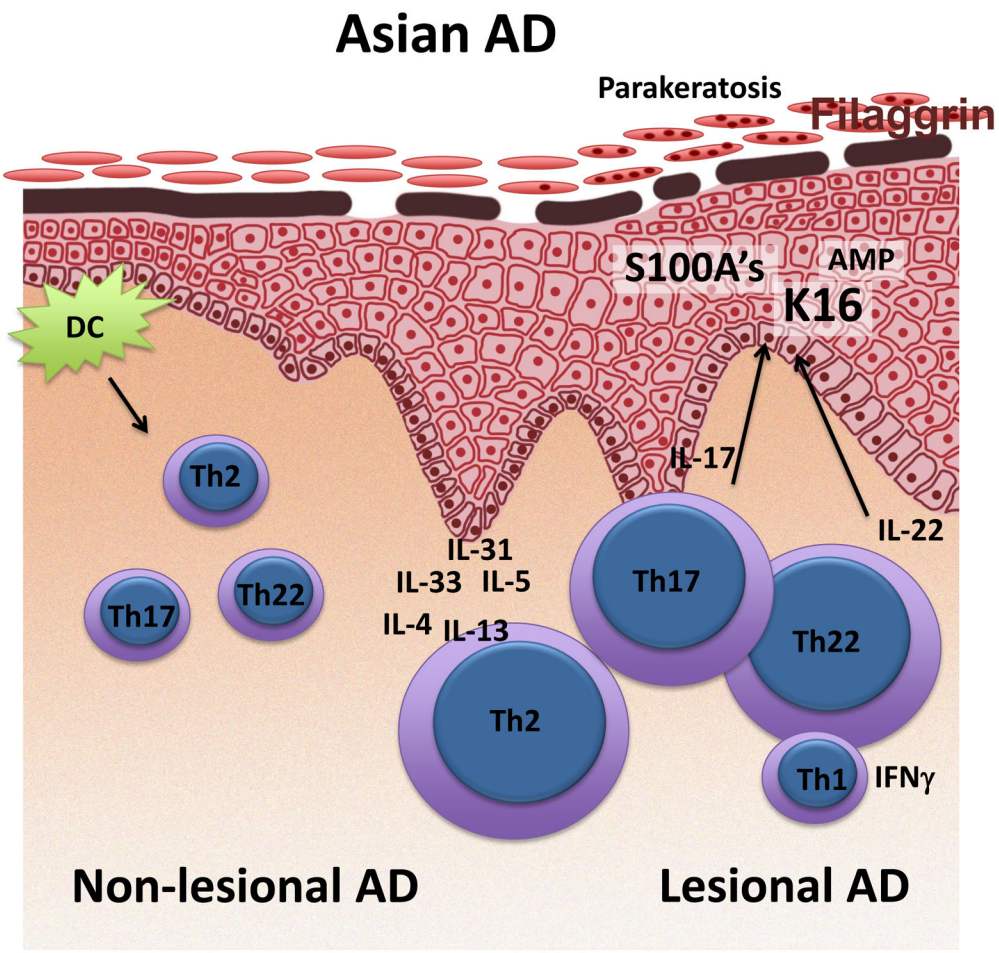

Figure 1.

Schematic representation/activation levels of selected immune pathways and epidermal responses in lesional and non-lesional skin in **(A)** infant, **(B)** early-onset AD and **(C)** Asian AD, **(D)** compared to psoriasis. *AMP* Antimicrobial peptide. *K16* Keratin 16.

Figure 2A

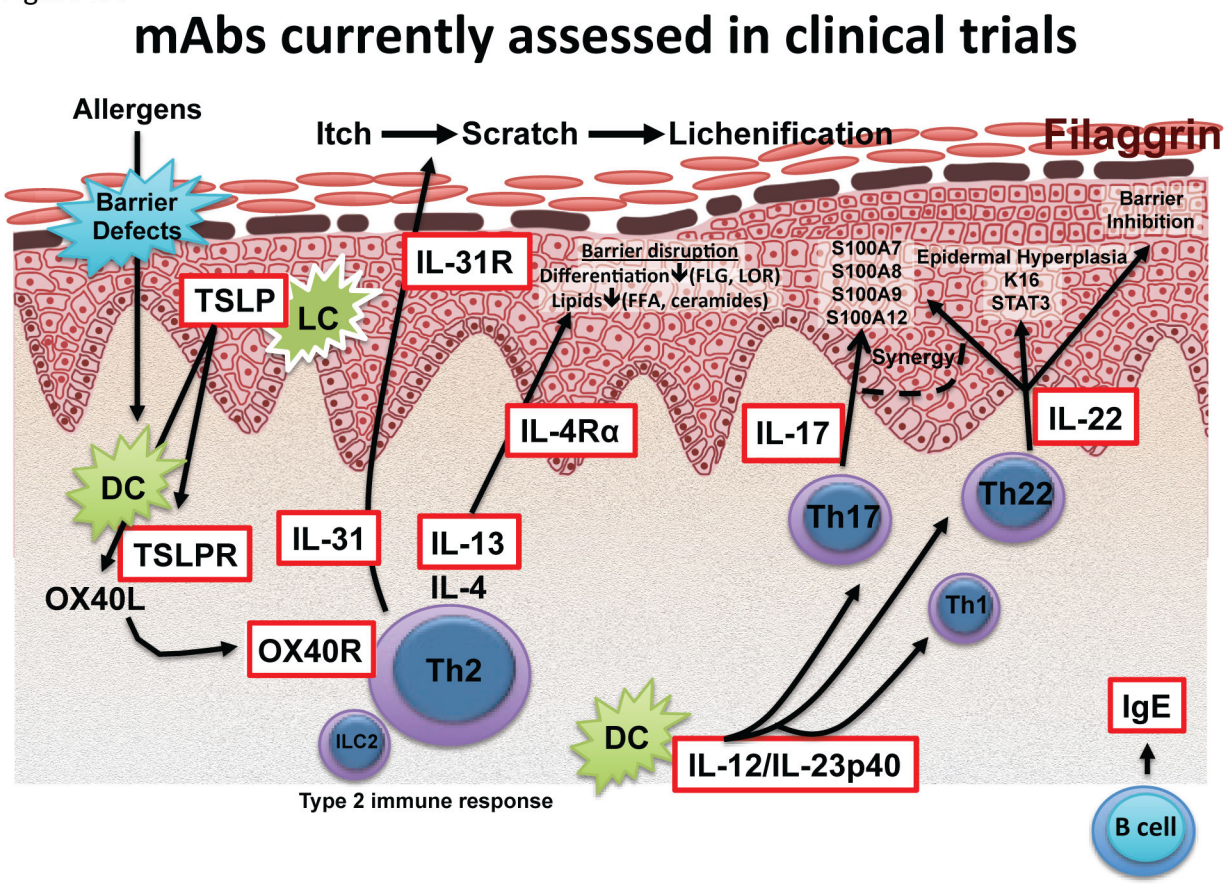

Figure 2B

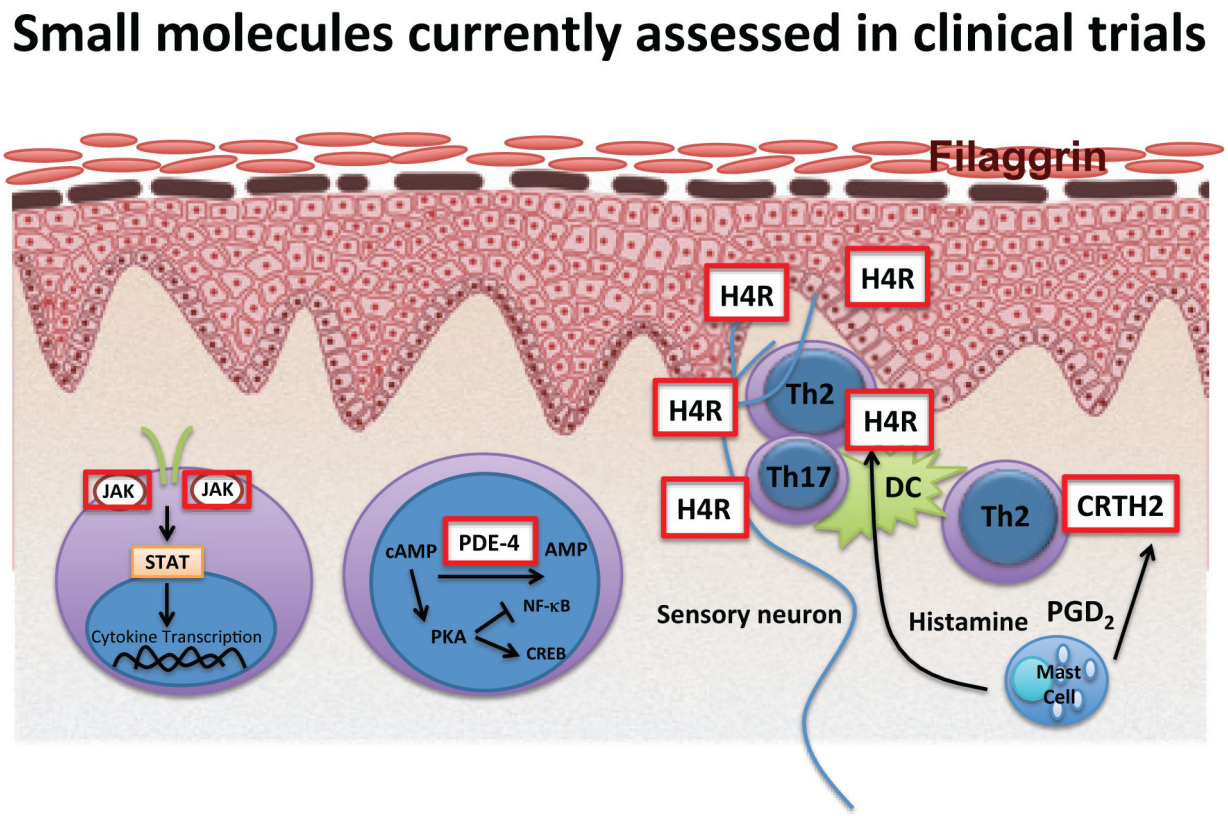

Figure 2.

Targets of **(A)** biologics and **(B)** small molecules recently published or currently being assessed in clinical trials. *AMP adenosine monophosphate; cAMP* cyclic adenosine monophosphate; *CREB* cAMP response element-binding protein; *CRTH2* Prostaglandin DP2 receptor*; FFA* Free fatty acids; *H4R* Histamine H4 receptor*; JAK* Janus kinase; *NF-kB* Nuclear factor kappa-light-chain-enhancer of activated B cells; *PGD_2* Prostaglandin D_2; *PKA* Protein kinase A; *STAT* signal transducer and activator of transcription.

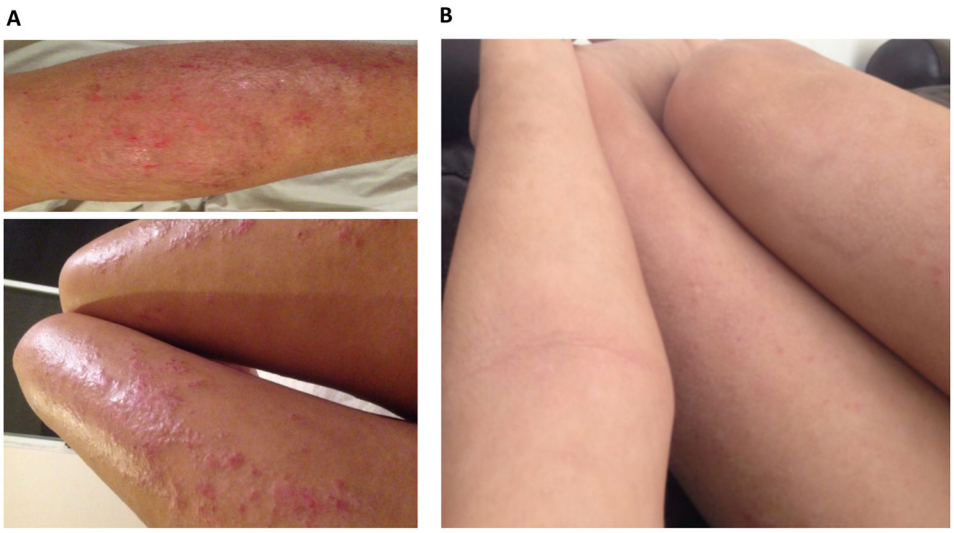

Figure 3.

Clinical responses in an AD patient before **(A)** and after **(B)** treatment with dupilumab 300mg eow. Hallmarks of AD such as widely distributed erythema and excoriations are largely relieved after 16 weeks of treatment.

Figure 4A

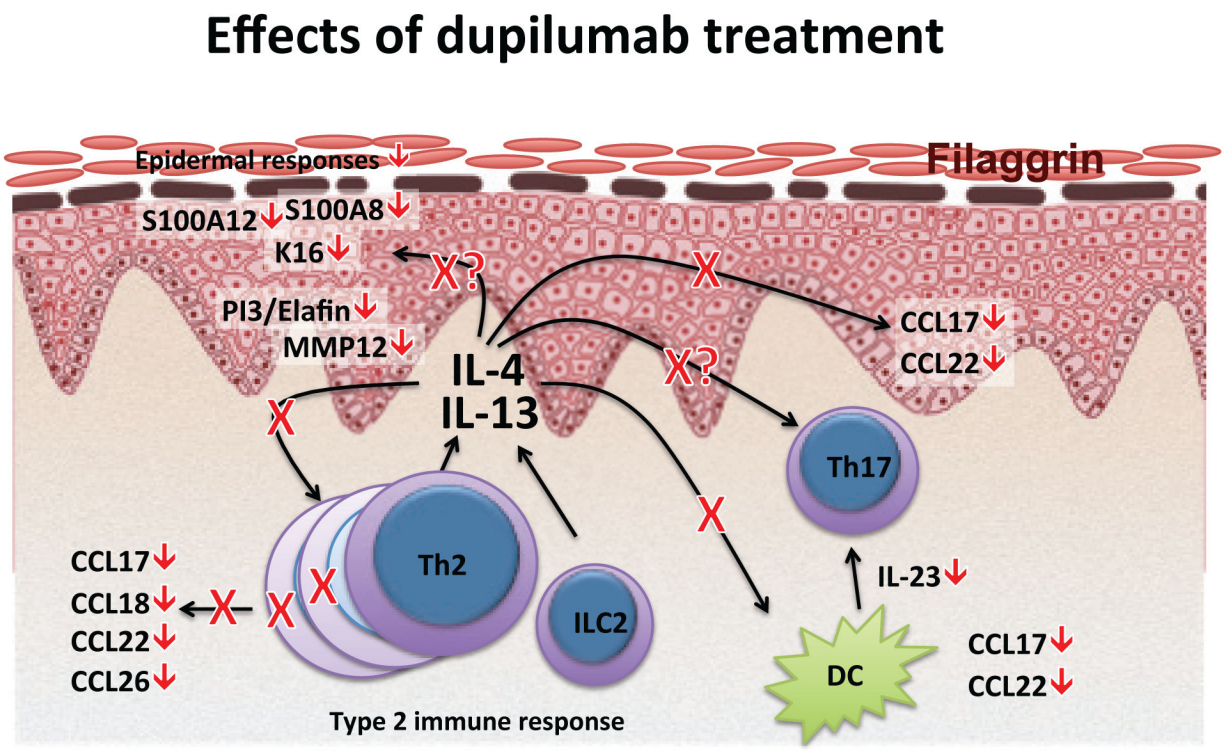

Figure 4B

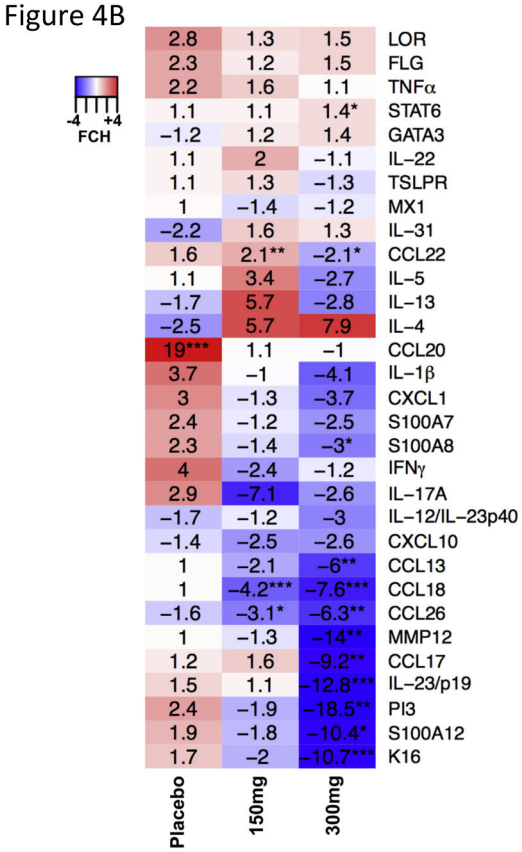

Figure 4.

Effects of dupilumab on lesional AD skin. **(A)** Schematic representation of pathways influenced by dupilumab treatment. **(B)** Summary heat map of quantitative RT-PCR mRNA expression changes in placebo, 150mg and 300mg dupilumab after 4 weeks of treatment. Values represent mean fold change (FCH) +/− SEM. *p<0.1, **p<0.05, ***p<0.01. Figure reproduced with permission of publisher from Hamilton et al.[24] *FLG* Filaggrin; *K16* Keratin 16; *LOR* Loricrin; *MMP12* Matrix metalloproteinase-12; *PI3* Peptidase inhibitor 3; *TSLPR*: Thymic stromal lymphopoietin receptor.

J Allergy Clin Immunol. Author manuscript; available in PMC 2018 April 01.

Table 1

Recent controlled trials in AD

CRTH2 Prostaglandin D2 receptor 2; *H4R* Histamine H4 receptor; *JAK* Janus kinase; *PDE4* Phosphodiesterase 4; *TSLP* thymic stromal lymphopoietin; *TSLPR* thymic stromal lymphopoietin receptor;

Agent	Trade name	Target	Drug	Phase	Manufacturer	ClinicalTrials.gov
Dupilumab		IL-4Rα	Anti-IL-4Rα mAb	Phase III published	Regeneron	NCT01949311
Crisaborole		PDE4	Topical PDE4 Inhibitor	Phase III published	Pfizer	NCT02118766 NCT02118792
Ustekinumab	Stelara	IL-12/23p40	Anti-p40 mAb	Phase II published	Janssen	NCT01806662
Tralokinumab		IL-13	Anti-IL-13 mAb	Phase II completed	MedImmune	NCT02347176
Tofacitinib		JAK1/3	Topical JAK1/3 Inhibitor	Phase II published	Innovaderm	NCT02001181
Lebrikizumab		IL-13	Anti-IL-13 mAb	Phase II completed	Hoffmann-La Roche	NCT02340234
CIM331/Nemolizumab		IL-31R	Anti-IL-31R mAb	Phase II completed	Chugai	NCT01986933
QGE031		IgE	Anti-IgE mAb	Phase II completed	Novartis	NCT01552629
Apremilast	Otezla	PDE4	PDE4 Inhibitor - Oral small molecule	Phase II completed	Celgene	NCT02087943
QAW039/Fevipiprant		CRTH2	CRTH2 Inhibitor - Oral small molecule	Phase II completed	Novartis	NCT01785602
ILV-094		IL-22	Anti-IL-22 mAb	In Phase II	Pfizer	NCT01941537
GBR830		OX40	Anti-OX40 mAb	In Phase II	Glenmark	NCT02683928
Secukinumab	Cosentyx	IL-17	Anti-IL-17 mAb	In Phase II	Novartis	NCT02594098
OC000459		CRTH2	CRTH2 Inhibitor - Oral small molecule	In phase II	Atopix	NCT02002208
Baricitinib		JAK1/2	Jak1/2 inhibitor – Oral small molecule	In Phase II	Eli Lilly	NCT02576938
PF-04965842		JAK1/2	Jak1/2 inhibitor – Oral small molecule	In Phase II	Pfizer	NCT02780167
ZPL389		H4R	Histamine H4 receptor inhibitor – Oral small molecule	Phase II completed	Ziarco Pharma	NCT02424253
BMS-981164		IL-31	Anti-IL-31 mAb	Phase I completed	BMS	NCT01614756
AMG157/Tezepelumab		TSLP	Anti-TSLP mAb	Phase I completed	Amgen	NCT00757042
MK-8226		TSLPR	Anti-TSLPR mAb	In Phase I	Merck	NCT01732510

Table 2

Study results from two independent, randomized, placebo-controlled, phase 3 trials of identical design (SOLO1 and SOLO 2)

16 weeks treatment, randomized 1:1:1 to subcutaneous dupilumab 300mg weekly (QW), every other week (Q2W), or placebo. In addition, each patient randomized to dupilumab received a single loading dose of 600mg on day 1. *EASI* Eczema Area and Severity Index; *EASI-75* Proportion of patients with an EASI improvement from baseline at week 16 of at least 75%; *IGA* Investigator's Global Assessment; *LS* least-squares; *NRS* numerical rating scale; *wks* weeks;

		SOLO 1	SOLO 2	All comparisons
Patients enrolled		671	708	
Primary end point (16wks): IGA of 0/1 – clear/almost clear	Dupilumab Q2W	85 (38%)	84 (36%)	P<0.001
	Dupilumab QW	83 (37%)	87 (36%)	
	Placebo	23 (10%)	20 (8%)	
Key secondary/coprimary end point (16wks): EASI-75	Dupilumab Q2W	115 (51%)	103 (44%)	P<0.001
	Dupilumab QW	117 (52%)	115 (48%)	
	Placebo	33 (15%)	28 (12%)	
LS mean % change (±SE) in EASI from baseline (16wks)	Dupilumab Q2W	−72.3±2.6	−67.1±2.5	P<0.001
	Dupilumab QW	−72.0±2.6	−69.1±2.5	
	Placebo	−37.6±3.3	−30.9±3.0	
LS mean % change from baseline in peak score on NRS for pruritus (16wks)	Dupilumab Q2W	−51.0±2.5	−44.3±2.3	P<0.001
	Dupilumab QW	−48.9±2.6	−48.3±2.4	
	Placebo	−26.1±3.0	−15.4±3.0	