Despite heroic leaps in scientific understanding of the disease, the fundamental cause of atopic dermatitis (AD) remains obscure. That said, we finally have some new ideas about what causes it and have probably learned more in the past decade than in all the years that preceded it. Beyond a better understanding of the type of inflammation and immune system dysfunction, we have discovered a great deal about the role of the skin barrier. In particular, a protein called “filaggrin” explains a lot about why patients might develop AD in the first place, but also—possibly—why they develop other types of allergies, including food allergies. Here we review updates in the pathophysiology of AD, including structural and immunologic contributors, as well as new therapeutic developments with an eye toward breakthroughs on the horizon.

PATHOPHYSIOLOGY

Filaggrin story. AD is a complex disease with multifaceted etiology that includes disruption of skin barrier, Th2 predominant inflammatory response to environmental allergens, and skin colonization with Staphylococcus aureus. Filaggrin, a critical structural protein in the stratum corneum of the epidermis, helps to maintain skin hydration and barrier function. A breakthrough in our understanding of AD took place with the discovery that loss-of-function mutations in the filaggrin gene (FLG) are associated with eczema. FLG is located on chromosome 1q21 within the epidermal differentiation complex (EDC), which codes for many key proteins involved in cornification. Cornification is the process of forming the cornified envelope, a tough, insoluble protein structure that replaces the plasma membrane in corneocytes and forms a crucial component of the skin barrier. Filaggrin plays a broad and critical role in this process by providing stratum corneum structural integrity as well as the precursors to natural moisturizing factor, a substance that further contributes to epidermal hydration and barrier function. The breakdown products of filaggrin also promote an acidic pH of the epidermis, essential for antimicrobial effect, ceramide synthesis, and modulation of enzymes required for differentiation.

The initial discovery of filaggrin dysfunction was made in ichthyosis vulgaris, but many studies have since confirmed the role of decreased filaggrin in AD pathogenesis. Loss-of-function genetic variants in FLG are common in people of European origin, carried by approximately nine percent of this population, and their penetrance is high, with 63 percent of FLG-null carriers demonstrating AD by age three in one study. Two meta-analyses found FLG-null mutations to be a significant risk factor for AD, estimating the odds ratio of developing AD at 4.786 and 3.12. Studies have also confirmed the disruptive effects of absent filaggrin on the epidermal barrier. Compared to AD patients without FLG-null mutations, those with loss-of-function variants are at significantly increased risk of recurrent bacterial skin infections with an odds ratio of 6.74, hinting at loss of antimicrobial activity. Interestingly, even AD patients with normal FLG genotypes are functionally deficient in filaggrin, as Th2 signaling decreases filaggrin expression in keratinocytes. Thus, whether the causative factor is a genetic mutation or local cytokine milieu, filaggrin deficiency is a critical step in AD pathogenesis and an invaluable therapeutic target for improving skin barrier function.

LEAP Study. With the prevalence of peanut allergy having doubled in Western countries over the last decade, the Learning Early About Peanut Allergy (LEAP) study sought to evaluate the efficacy of early peanut consumption as primary and secondary prevention for peanut allergy. Patients had a
history of severe eczema, egg allergy, or both, and were stratified according to preexisting sensitivity to peanut extract, then randomized to consume or avoid peanuts until five years of age. Prevalence of peanut allergy at five years was significantly lower in patients exposed to peanuts, both those with preexisting sensitivity and those without. Peanut-specific IgG4 was elevated in the consumption group, while peanut-specific IgE levels were increased in the avoidance group; a lower ratio of peanut-specific IgG4:IgE was associated with peanut allergy. In a follow-up study, Persistence of Oral Tolerance to Peanut (LEAP-On), all participants in the original study were asked to avoid peanuts for one year and prevalence of peanut allergy was reassessed at age six. The protective effect of early peanut exposure against development of peanut allergy persisted after 12 months of peanut avoidance.

To determine whether early peanut introduction influences the development of allergic disease, asthma, eczema, and rhinoconjunctivitis were diagnosed by clinical assessment and reported for study participants. In this high-risk population, the burden of allergic disease increased across study time points, with 76 percent of participants diagnosed with at least one allergic disease by five years of age. Notably, the early consumption of peanuts did not prevent development of atopic disease or hasten resolution of preexisting AD. Thus, while early allergen exposure holds significant potential to modulate immune response and prevent the development of allergy, this effect is allergen-specific and does not generalize to unrelated antigens. Further studies of common allergens in AD are needed to assess whether early exposure holds potential to mitigate the development of eczema in children.

**Immune Advancements.** Our understanding of the immunologic underpinnings of AD has seen great strides in recent years, presenting a more nuanced picture of T-cell polarization and downstream cytokine signaling. The acute phase of AD is characterized by overactivation of Th2, Th22, and Th17 cells. In response to allergens that have breached the skin barrier, epidermal keratinocytes release IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). These cytokines activate dendritic cells, which then stimulate Th2 cells to produce IL-4, IL-13, and IL-31. A positive feedback loop is formed wherein IL-4 and IL-13 induce keratinocytes to release additional TSLP, and TSLP drives Th2 polarization, resulting in more IL-4 and IL-13. Th2 activation also leads to reduction of barrier integrity proteins, such as filaggrin, as well as decreased free fatty acids and ceramides. In parallel, Th22 cells promote hyperplasia, downregulate terminal differentiation, and together with IL-17 induce expression of EDC genes, which regulate keratinocyte differentiation and stratum corneum development. Rather than marking a shift in inflammatory pattern, chronic AD reflects intensification of the immune pathways already upregulated in acute disease. In the chronic state, Th1 cells are recruited and Th2 and Th22 subsets continue to be mobilized. In keeping with the precedent of the acute phase, the epidermis is infiltrated by additional T-cells and dendritic cells; EDC gene expression is further upregulated, altering keratinocyte differentiation; and epidermal proliferation continues to increase, leading to epidermal thickening. Interestingly, underlying immune activation is also present in non-diseased skin of AD patients, as evidenced by elevated Th2 and Th22 cytokines as well as epidermal thickening and aberrant epidermal differentiation. That these alterations are clinically relevant is suggested by their correlation with increased disease activity as assessed by Scoring Atopic Dermatitis (SCORAD) index.

Elucidation of these immunologic pathways has yielded a trove of potential therapeutic targets, which are only beginning to be explored. This work also spurred the development and approval of the first biologic drug for AD, dupilumab, a monoclonal antibody that inhibits IL-4 and IL-13 signaling. A number of other promising immunomodulating therapies inspired by these advances are in the therapeutic pipeline.

**CORNERSTONES OF AD THERAPY**

**Patient education**

**Barrier restoring therapy**

**Topical anti-inflammatory therapy**

*Phototherapy and systemic therapies, reserved for severe or refractory cases*
wool clothing, unfamiliar pets, dust, shampoo, and sweating to be associated with AD flares, particularly when several of these exposures occurred in combination. However, these factors are individualized and should be assessed based on a definite history of disease worsening after exposure. Allergy testing, for both type I allergies (via blood or skin prick testing) and type IV allergies (via patch testing), may also be performed to help sort out triggering allergens and eczematous contact dermatitis. Many treatment failures can be attributed to nonadherence due to concerns about topical corticosteroid use, inconvenience of regimens, and lack of education. Taking time to explain the disease and its treatment, simplify regimens, and assess patient concerns is essential to improving treatment success. Many psychological and educational interventions are being assessed in this population, and models such as multidisciplinary eczema interventions and nurse-...
Emollients to repair epidermal barrier function supply exogenous lipids to soften the skin and form an occlusive layer to protect against water loss. Emollients should be used two or more times per day, including after bathing, and generously applied over the whole body, which equates to application of roughly 250-500g of emollient each week.

Topical corticosteroids are first-line therapy for acute exacerbations of AD, and their efficacy has been demonstrated in multiple randomized controlled trials (RCTs). When used appropriately and intermittently, the risk of adverse effects is low. Topical calcineurin inhibitors, including tacrolimus and pimecrolimus, are second-line for man-

Small Molecules. Targets of small molecule therapies in the pipeline include chemoattractant receptor-homologous molecules expressed on Th2 lymphocytes (CRTH2), PDE4, histamine receptor type 4 (H4R), JAK 1 and 2, and neurokinin 1 receptor (NK1R). CRTH2 is a prostaglandin D2 receptor found on Th2 lymphocytes that promotes Th2 cell migration into the skin. Proof-of-concept studies have been carried out for two CRTH2 antagonists, QAW039 (NCT01785602) and OC000459 (NCT02002208), but were without compelling results. The systemic PDE4 inhibitor apremilast, which has been approved for treatment of psoriasis, showed promising results in an AD pilot study, but a double-blind, placebo-controlled trial failed to meet its primary endpoint of reduction in EASI score at 12 weeks (NCT02087943).

H4R antagonists including JNJ-39758979 and ZPL-389 have been evaluated in patients with AD. Though histamine is commonly thought of as a mediator of pruritus, recent studies suggest an even more significant role for this molecule in AD pathogenesis. H4R is expressed on human Th2 cells, and activation of these receptors leads to IL-31 synthesis. Thus, histamine may partly mediate the inflammation underlying AD as well as act as a pruritogen. A Phase 2a trial of JNJ-39758979 showed improvement of pruritus without significant reduction in EASI score, but the study was terminated early due to two cases of agranulocytosis in patients receiving the study drug.

In contrast, a proof-of-concept trial of ZPL-389 demonstrated significant improvement in EASI and SCORAD indices, with comparable reduction in pruritus to placebo.

Small molecule JAK inhibitors, which modulate the downstream signaling of inflammatory cytokines, are another topic of research interest. Upadacitinib (NCT02925117) and PF-04965842 (NCT02780167), both JAK 1 inhibitors, are in Phase 2 clinical trials. A recently completed Phase 2 trial of baricitinib, a JAK1/2 antagonist, showed promising results, with significant improvement in EASI-50 score, pruritus, and sleep loss compared to placebo. In addition, NK1R, a receptor for substance P, is under investigation as a therapeutic target. Substance P is a known plasma biomarker for AD disease activity. NK1R antagonists tradipitant (NCT02651714) and serlopitant (NCT02975206) are in Phase 2 clinical trials for AD.

When used properly, emollients can serve as adjuvant therapy to decrease the need for topical corticosteroids.
management of AD. They are safe, effective, and comparable to their corticosteroid counterparts, with the extrapolated potencies of tacrolimus 0.1% ointment and pimecrolimus 1% cream similar to that of mild to moderate potency corticosteroids. Topical calcineurin inhibitors do not cause thinning of the skin and therefore afford an advantage in treating sensitive areas. Long-term safety data for tacrolimus and pimecrolimus are favorable and support their use as maintenance therapy with intermittent topical corticosteroids reserved for flares.

Once a disease exacerbation has been stabilized, emollients should be employed as maintenance therapy. Proactive therapy with twice weekly application of topical corticosteroids or calcineurin inhibitors has also been shown to be effective, particularly in patients with frequent flares in the same location. If a patient fails topical therapy, a four to eight week course of phototherapy may be considered. Of note, phototherapy should not be combined with calcineurin inhibitors or cyclosporine due to cumulative increased risk of skin cancer. Lastly, once the options of topical therapy and phototherapy have been exhausted, systemic treatment with immunosuppressants such as cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil may be required, despite their off-label status for AD. These medications may be used for induction or maintenance therapy in severe refractory AD and will be further described below.

Moisturizers: State of the Art. Topical moisturizers have long served as pillars of AD therapy, and exciting new advances suggest they are here to stay, with even more therapeutic potential than before. While recommendations for specific moisturizers according to disease severity have been put forth, practical considerations and patient preference necessitate flexibility. Emollients have demonstrated merit both as prophylactic and therapeutic measures in AD. Recent studies of moisturizers for prevention of atopic disease found that full-body application for six to eight months starting in the first few weeks of life reduced the incidence of AD in infants with a first-degree relative with the disease. Further, a cost-effectiveness analysis of prophylactic moisturization for high-risk infants demonstrated favorable cost-benefit ratios for multiple common moisturizers, most favorably petroleum jelly at $353 per quality-adjusted life year (QALY), satisfying the standard of the National Institute for Health and Care Excellence of the United Kingdom for cost-effectiveness. Even assuming the lowest incremental QALYs for the most expensive moisturizer, the cost of the intervention still fell below $45,000/QALY. This simple intervention could have tremendous impact in reducing the burden of AD.

One novel approach to topical therapy is the concept of a compounded antibacterial, steroid, and moisturizer (CASM). This treatment combines several therapeutic cornerstones, an emollient and a steroid, with antibiotics, the role of which in AD is hotly debated. The idea behind CASM is to target multiple facets of AD in patients refractory to standard therapy. In addition to potentially increasing efficacy by uniting multiple treatment modalities, it may improve compliance due to a simpler regimen. A retrospective study that assessed the efficacy of CASM demonstrated a decrease in mean AD severity and mean percent body surface area affected. Notably, CASM therapy was also effective in patients previously receiving medium potency or stronger topical corticosteroids, though the compounded steroid was of lower potency. It is possible that this therapy could therefore reduce the risk of side effects from corticosteroids by eliciting response at lower potency.

In a recent development, prescription emollient devices (PED) have been developed, and a number have been FDA approved (in a far less rigorous manner than for drugs) for a variety of dry skin conditions. PED are intended to improve skin barrier function by replacing physiologic lipids deficient in these conditions. Studies have shown PED products to be superior to vehicle and comparable to a low-potency corticosteroid cream in improving SCORAD index and patient-reported outcomes. However, comparison of an over-the-counter petroleum-based moisturizer to two barrier repair creams found similar efficacy across groups, though the petroleum product was at least 47-times more cost effective than the other products. Given the expense of these new products and absence of evidence for superior efficacy, recommending their use may be premature.

Crisaborole: A Novel Topical Anti-inflammatory. Though topical corticosteroids are a mainstay of AD therapy, they are associated with a number of adverse effects with short- and long-term use. Crisaborole (Eucrisa, Pfizer), a novel nonsteroidal topical medication, holds potential to supplement or supplant steroids for both acute and chronic management of AD due to its favorable efficacy and safety profiles. Crisaborole is a phosphodiesterase (PDE) 4 inhibitor that acts to increase concentrations of cyclic adenosine monophosphate (cAMP) and thereby suppress proinflammatory cytokine production. It was FDA approved in December 2016 for treatment of mild to moderate AD in patients two years of age and older. Initial evidence came from an early vehicle-controlled proof of concept study, in which greater improvement was seen in crisaborole-treated lesions than vehicle-treated lesions after four weeks. This early evidence for crisaborole was confirmed by two identi-
Systemic Agents. Systemic therapies, both biologic and non-biologic, may be appropriate for patients with more severe, chronic AD refractory to topical medications. Though systemic treatments are less commonly used in children due to their potential for adverse effects, as many as 10 percent of adults with AD will be treated systemically in their lifetime. For best results, topical and systemic therapies are often used in combination.

Systemic immunosuppressants used for AD include cyclosporine, azathioprine, mycophenolate, methotrexate, and corticosteroids; of these, only systemic corticosteroids are labeled for use in AD, yet cyclosporine is the most frequently prescribed. Cyclosporine is a potent immunosuppressant that inhibits calcineurin, thereby inhibiting cytokine production and T-cell activation, and it has multiple trials to support its use in AD. RCTs have demonstrated significant improvement in disease control, pruritus, and quality of life with cyclosporine treatment in both pediatric and adult patients. Further, a meta-analysis of 15 studies of cyclosporine reported 55 percent improvement in AD severity after six to eight weeks of treatment. Initial recommended dosing of cyclosporine is 3-5mg/kg/day, which can be tapered once disease improvement has been achieved. Interval therapy in patients with recurrent flares may be appropriate, and in more severe cases, long-term therapy with lowest possible maintenance dose may be used. Interestingly, a case series examining “weekend cyclosporine”—or cyclosporine at a dose of 5mg/kg on Saturdays and Sundays only—suggests that this may be a viable option for patients with severe AD to prevent relapse while avoiding toxicity. Potential adverse effects of cyclosporine include renal toxicity, hypertension, gastrointestinal symptoms and headache; adverse effects are dose-dependent.

Azathioprine, another immunosuppressive medication utilized in AD, is an antimetabolite that inhibits purine synthesis and consequently lymphocyte synthesis. It has been shown to reduce skin symptoms, pruritus, sleep loss, and Staphylococcus colonization in children and adults with AD. Side effects, including gastrointestinal symptoms, liver dysfunction, and leukopenia, are more common at higher doses and in patients with thiopurine methyltransferase (TPMT) polymorphism conferring reduced enzyme activity. Genetic testing prior to initiating therapy can circumvent severe toxicity. In pediatric patients without TPMT polymorphism, treatment with 2.5-3.5mg/kg azathioprine did not result in myelosuppression. Additionally, dose adjusting for patients with reduced TPMT activity does not decrease therapeutic efficacy. Patients with AD treated with TPMT-appropriate doses showed similar improvement to patients without the polymorphism receiving a standard dose of 2.5mg/kg.

Mycophenolate mofetil (MMF), another antimetabolite, selectively hinders lymphocyte DNA replication via potent inhibition of an enzyme essential to de novo purine synthesis. It is less well studied than other systemic agents in AD, with evidence limited to case reports and small trials. Several small pilot studies in AD demonstrated improvement in SCORAD index with 1-2g/day MMF over four to 12 weeks, without evidence of relapse during 20-week follow up. Further, MMF at doses of 1,440mg daily has proven to be equivalent to cyclosporine for maintenance therapy in AD, following induction of remission with high-dose cyclosporine. Adverse events reported with MMF therapy include flu-like symptoms, liver enzyme abnormalities, and infections.

Methotrexate is a folic acid analogue that interferes with purine and pyrimidine synthesis. While RCTs on its use in AD are lacking, several small trials lend support to its efficacy. Non-controlled studies demonstrated reduction in disease activity from baseline, improved quality of life, and decreased pruritus with doses ranging from 7.5-15mg/week; improvements in disease activity seemed to persist after the medication had been stopped. Notably, methotrexate 7.5mg weekly has proven to be as effective and safe as cyclosporine 2.5mg/day in children age seven to 14 years with severe AD. Side effects of methotrexate range from gastrointestinal disturbance to liver toxicity and teratogenicity, though at doses below 15mg and with folate supplementation, it appears to be well tolerated.

Oral corticosteroids are rarely used for long-term management of AD due to their extensive side effect profile, but a brief course is occasionally used to interrupt a disease flare. Despite broad clinical experience with steroids, however, formal trials assessing their efficacy in AD are sparse. A multicenter RCT comparing prednisolone to cyclosporine...
in adults with severe AD demonstrated stable remission in significantly more patients treated with cyclosporine than with prednisolone, and the study was terminated early due to severe rebound flares precipitated by the steroid taper.  

Biologic therapies are being developed at a rapid pace and hold great potential for improving management of AD. More convenient dosing schedules, less frequent lab monitoring, and improved safety profiles compared to traditional systemic therapies are among the many potential benefits of biologics. The only biologic agent currently approved for treatment of AD is dupilumab (Dupixent, Sanofi/Regeneron), a human monoclonal antibody that blocks IL-4 and IL-13 signaling. Additional biologics and small molecules in the therapeutic pipeline, including omalizumab, ustekinumab and baricitinib, are discussed in the sidebar on the preceding pages.  

**Dupilumab: A Novel Biologic Therapy.** Dupilumab (Dupixent, Sanofi Genzyme, Regeneron), a human monoclonal antibody against IL-4 receptor α, is a new AD therapy that inhibits IL-4 and IL-13 signaling and thereby mitigates Th2-mediated inflammation. It has been FDA approved since March 2017 for treatment of moderate to severe AD in adults, particularly those with disease refractory to or who cannot tolerate topical therapy. A number of studies have demonstrated its efficacy both as monotherapy and in combination with topical steroids. Two identical phase 3 RCTs compared dupilumab to placebo in adults with moderate to severe AD inadequately controlled with topical therapy. Significantly more patients in the dupilumab arm than placebo reached the primary endpoint of Investigator’s Global Assessment (IGA) score of 0 or 1 and reduction of two or more points in IGA score from baseline; reduction in pruritus and improved Eczeema Area and Severity Index (EASI) score was also reported. Further, the long-term safety and efficacy of dupilumab in conjunction with topical corticosteroids were examined in the LIBERTY AD CHRONOS study. At 16 weeks, significantly more patients in the dupilumab group than placebo attained the primary endpoints of EASI 75 percent improvement from baseline and IGA score of 0 or 1 and reduction of two or more points in IGA score from baseline; the results at 52 weeks were comparable. Adverse events were similar to those reported in previous studies.  

Effect on quality of life has also been studied in several trials. An RCT comparing multiple dupilumab regimens to placebo demonstrated significant improvement in patient-reported sleep, mental health, and health-related quality of life, with greatest benefits in the patients receiving the 300mg dose. In a subsequent phase 2a placebo-controlled study, the dupilumab arm experienced significant improvement in quality of life as assessed by the Quality of Life Index of Atopic Dermatitis (QoLIAD), and QoLIAD scores significantly correlated with changes in efficacy outcomes.  

Adverse events commonly reported in clinical trials of dupilumab include exacerbations of AD, injection-site reactions, nasopharyngitis and conjunctivitis. Injection site reactions and conjunctivitis were more common with dupilumab than placebo. Conversely, skin infections were shown in a meta-analysis of eight randomized controlled trials to be decreased in adults with moderate to severe AD treated with dupilumab compared to placebo. Decreased incidence of skin infections and eczema herpetiformum may be related to restoration of skin barrier function due to improvement of AD.

**A BRIGHT FUTURE**  
After many decades of stagnation, exciting new advances in our understanding of AD hold the potential to revolutionize the way we conceptualize and treat this disease. Breakthroughs in our knowledge of skin barrier function and the immunologic underpinnings of AD have advanced the forefront of pathophysiology, and optimization of traditional AD therapies as well as evolution of novel ones promise to improve disease management. The future is finally looking bright for AD, with many impressive developments sure to come.


