

Atopic Dermatitis Treatment: A Shifting Paradigm

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Atopic Dermatitis Treatment: a Shifting Paradigm

Atopic dermatitis (AD) occurs when an itchy, irritated rash appears on some areas of the skin. Depending on how severe a rash is, there are several different options for how to treat. There have recently been significant advances and innovations.

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Immunopathogenesis History— Two Paradigms

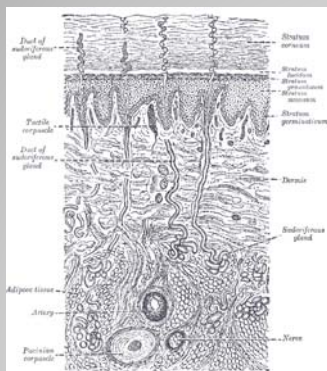
- We have gone from an immune theory for (AD) to a period when the skin barrier function was thought to be predominant.
- Now we are moving back to an immunocentric theory.
- We can treat AD both with emollients and other agents that work on the outside of the skin; and with powerful systemic immunosuppressants such as cyclosporine, azathioprine and methotrexate that are of tremendous benefit, without clearly affecting the skin barrier.

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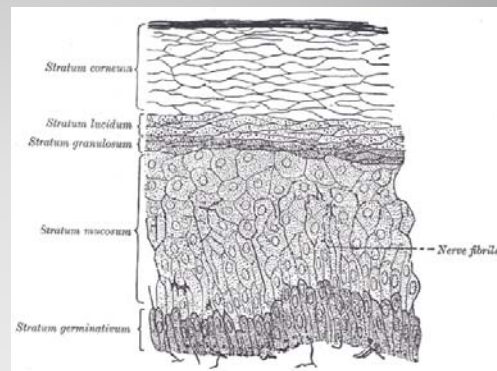
Two paradigms of AD: the outside in and the inside out. We are marrying both paradigms with some of the new data—both the scientific data about therapeutic target and genetic data focusing on genes like filaggrin.

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Histopath of skin



Histopath of epidermis



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Lamellar Bodies: The Key to Cutaneous Barrier Function

The primary barrier functions of the skin (permeability control and microbial protection) are provided by lipids and proteins being delivered to the stratum corneum intercellular space almost simultaneously by the secretion of lamellar bodies into the spaces between the corneocytes.

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Stratum Corneum & Lamellar Body

- The outermost layer of the skin, the (SC), primarily mediates this permeability barrier function. The SC is composed of two different structural components: the corneocytes and the inter-corneocyte lipids.
- Both components are derived from keratinocytes through the terminal differentiation process. The SC is composed of flat cells surrounded by lipid matrix.
- The corneocytes, as terminal differentiation forms of keratinocytes, provide structural supports for the SC and act as hydrating reservoirs for adequate enzymatic processes in the SC. The lipid monolayer provides hydrophobic interfaces between the hydrophilic surface of the cornified envelope and the highly hydrophobic lipid lamellae.

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Lamellar Bodies

- In cell biology, lamellar bodies (LB) (otherwise known as lamellar granules, membrane-coating granules, keratinosomes or Odland bodies) are secretory organelles found in type I alveolar cells in the lungs and in keratinocytes in skin.
- Recent studies have demonstrated that genetic deficiencies in filaggrin lead to defects in cutaneous permeability barrier function and predispose to the development of atopic dermatitis.
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- The two most important barrier properties are creating a barrier against the movement of water and electrolytes out of the skin and creating a barrier against the entry of microorganisms into the skin. Both of these barriers are localized primarily to the stratum corneum (SC) layer.

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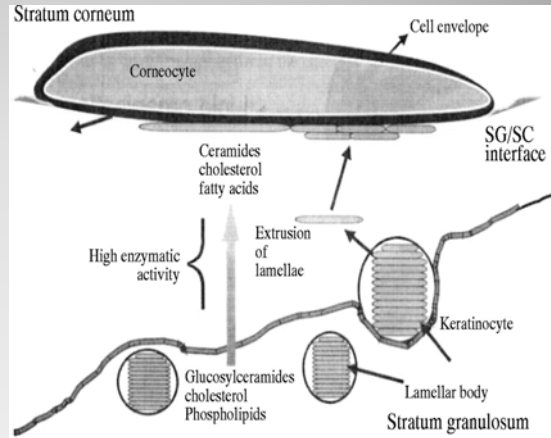
Lamellar Bodies (2)

- The cutaneous permeability barrier is mediated by extracellular lipids, cholesterol, free fatty acids and ceramides, which form extracellular lipid-enriched lamellar membranes between the corneocytes that block the movement of water and electrolytes. The antimicrobial barrier is mediated by both lipids, particularly free fatty acids, and antimicrobial peptides, such as the beta-defensins and cathelicidins, which are also localized to the extracellular spaces of the SC.
- Both the lipids that form the permeability barrier and the antimicrobial peptides are delivered to the extracellular spaces of the stratum corneum by the secretion of lamellar bodies.

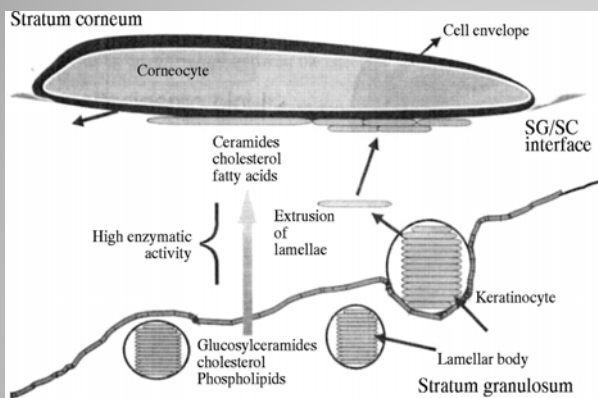
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Lamellar Bodies (2)

- LBs are ovoid secretory organelles that are first observed in the upper stratum spinosum layer of the epidermis, with increasing numbers found in the stratum granulosum layer. Numerous enzymes, including lipid hydrolases such as β glucocerebrosidase, acidic sphingomyelinase, secretory phospholipase A2, and neutral lipases, and proteases such as chemotryptic enzymes (kallikreins) and cathepsins, are present in LBs



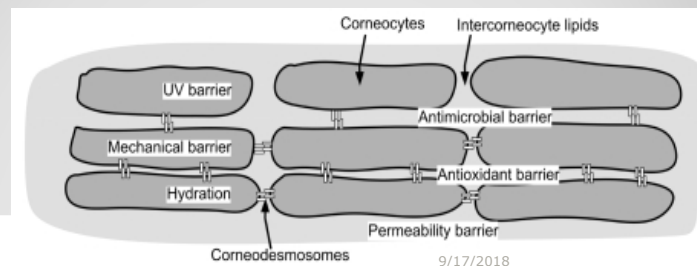
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- Antimicrobial peptides, such as human β -defensin 2 and the cathelicidin LL-37, are also present in LBs
- After acute permeability barrier disruption, LBs are rapidly secreted by stratum granulosum cells and new LBs quickly form. The appearance of lipids and enzymes in these new LB occurs simultaneously. Inhibiting lipid synthesis prevents the delivery of lipids to LBs and also prevents the incorporation of enzymes in the LBs.
- Providing exogenous lipids restore the delivery of lipid to LBs and also leads to the incorporation of enzymes in LBs.

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- While the corneocytes (bricks) serve as UV and mechanical barriers as well as playing a hydrating role in the SC, the intercellular lipids perform the functions of antimicrobial barrier, anti-oxidant barrier and permeability barrier.
- It should be noted, however, that regulation of these protective functions are closely related and modulation of one function can affect other functions.



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- In addition to these major structural domains, the corneodesmosome (CD), which corresponds to desmosomes in the epidermis, is another important component in the SC. Generally, the integrity of the SC is maintained by these intercellular proteins which connect to adjacent corneocytes, both in the plane of the SC layer and in adjacent layers.
- The CD structures represent the primary cohesive force and they are directly related to the desquamation process. These structures are composed of certain proteins, including desmocollins and desmoglein, and special protein-degrading enzymes which are presented in the SC.

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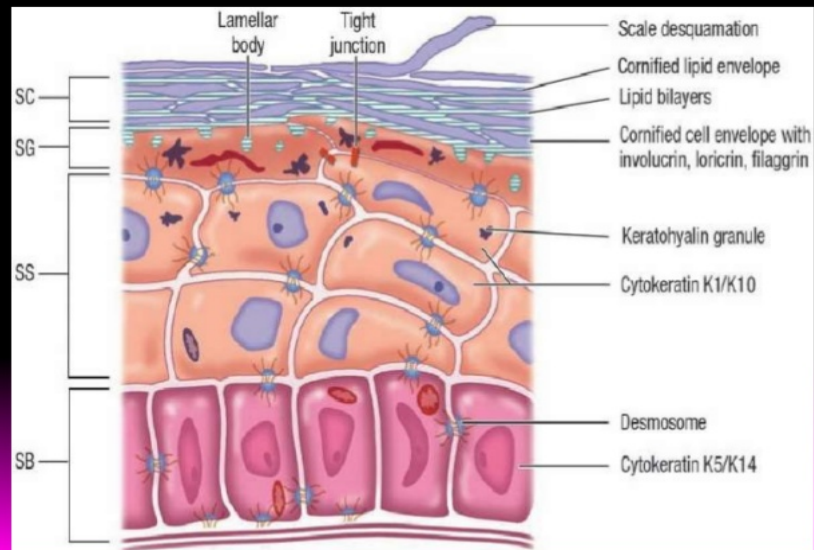
- Previous studies have shown that the barrier disrupted dry skin of AD patients is mainly attributable to significantly decreased levels of ceramides in the SC.
- Ceramide acts as a water modulator and a permeability barrier by forming multi-layered lamellar structures with other lipids between cells in the SC layers.
- In adults with AD, there is a ceramide deficiency even in the non-lesional SC, which is highly associated with the abnormal barrier function, and predisposing the skin to inflammatory processes evoked by irritants and allergens.

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A mechanistic connection between filaggrin (FLG) loss-of-function mutations and barrier disruption has not been resolved and remains controversial. The FLG mutation mechanism as a predisposing factor of AD is a very complex issue, and there is no clear relationship between ceramide levels in the SC and FLG mutations in AD patients



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- Even in patients who make normal filaggrin, inflammatory cytokines can decrease filaggrin expression so patients become functionally deficient in filaggrin. Psychological stress and sleep deprivation can also functionally damage the skin barrier.
- It is interesting to see AD as a holistic process—the mind, the body, the immune system, the skin, all coming together, all playing off each other.

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Atopic dermatitis in Adults

- The International Study of Life with Atopic Eczema (ISOLATE) confirmed the profound effect that AD has on quality of life in adults.
 - 38% said their disease affected their choice of occupations; adults with AD took more sick days from work and were likely to retire early.
 - AD also has effects on sexual and social life: 43 % felt awkward having a partner see or touch their body, and 58% reported avoiding social activities because of their disease.

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- Figuring this out has been the task of the last 40 years. Now we start using longer-term steroid application and even tri-fluorinated steroids and other disease modifying drugs such prednisone, azothiaprime, cyclosporin, mycophenolate, methotrexate. They are a benefit; but at what price in terms of money and risk to our patients health?
- Dermatologists were faced with treating a life-ruining disease without any truly effective therapies and even more disheartening, the patients also know that none of these agents work well enough and that they are not going to have normal lives

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Lets Talk about Barrier Protection

- Since I started Dermatology (40 years ago) we have gone through issues of too much bathing or too little bathing, or bathing with applying grease afterward.
- We have gone through a myriad of lotions and potions from Lubriderm that was too thin to Vaseline petroleum jelly that was too thick and Caucasians didn't want to use that anyway.
- Now we find that they all work to some extent, by supplying lipid to the lamellar body so it can re-establish tissue fluid barriers. What are we doing here?

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- Many patients find it crazy that we can treat AD by rubbing on some moisturizer or by using targeted, high-powered immunosuppressive therapy. Both sides help us elucidate the disease and help us educate patients

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Moisturizers

- Moisturizers the barrier protectors. An embarrassment of riches.
- Newer, available over-the-counter moisturizers and anti-itch preparations contain ceramides, lanolin, hypochlorous acids which can significantly change the colony counts of *Staphylococcus*; also very inexpensive.
- Barrier repair agents may have some advantages. For example, advantages of applying moisturizers to neonates in eczema prone families delays and can prevent the development of atopic dermatitis.
- Petrolatum is cheap and effective. If money is really tight, Crisco will work.

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Drugs Available to Treat Severe AD



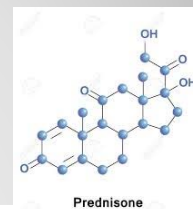
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- Now we start using longer-term steroid administration and even tri-fluorinated and other disease modifying drugs such prednisone, azothiaprime, cyclosporin, mycophenolate, methotrexate. They are a benefit, but not curative. Dermatologists were faced with treating a life-ruining disease without any truly effective therapies and even more disheartening, the patients also knew that none of these agents worked well enough and that they were not going to have normal lives.

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Systemic Prednisone

- Dose: 1-2 mg/kg. Short term only or use in pulse dosing like every 3 or 4 days to cut down and reduce side effects.
- Side effects: weight gain, diabetes, cataracts, dependency, depressed immune system, osteoporosis, acne, delayed growth, etc.
- Financial cost: cheap



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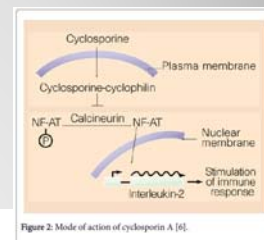
Methotrexate

- Dose: varies, usually up to 6-8 tablets of 2.5mg per week. Also available in solution.
- Side effects: 147 listed side-effects in PDR; generalized immunologic suppression, liver damage, kidney damage, platelet and bone marrow suppression.
- Monitoring/safety: regular blood monitoring for potential side effects.
- Financial cost: cheap

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Gengraf (cyclosporine)

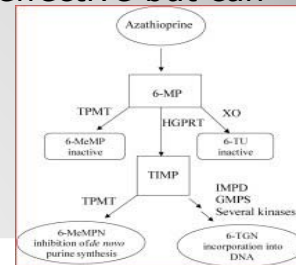
- Dose 3-5 mg/kg daily-- generally it takes 5mg/kg, but only for short term use, no more than 18 months is advised
- Precautions: test frequently for renal effects, hypertension, immunosuppression, severe infection, nephropathy, hepatotoxicity, DM, depression, GI bleeding, hirsutism, electrolyte disturbance. Exact mechanism of action of each is not known.
- Financial cost: cheap



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Imuran (azathioprine)

- Dose: 50mg-100mg daily.
- Side Effects: 0.3% population no TPMT leads to more active metabolite bone marrow suppression. Loss of appetite, nausea, vomiting or diarrhea. Less effective than cyclosporine with an average improvement of 35%. Less effective but can be used long term in those that tolerate it.
- Financial cost: cheap



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Cellcept (mycophenolate)

- Dose: Adults- up to 3 grams per day.
- Side Effects: diarrhea, vomiting, pain, stomach area pain, swelling of the lower legs, ankles/feet, and high blood pressure, increased risk for bacterial and viral infections, lymphoma.
- Financial cost: cheap

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Adding topical therapy and an occasional short course of systemic steroids increases the efficacy of all of the above drugs—but by how much.

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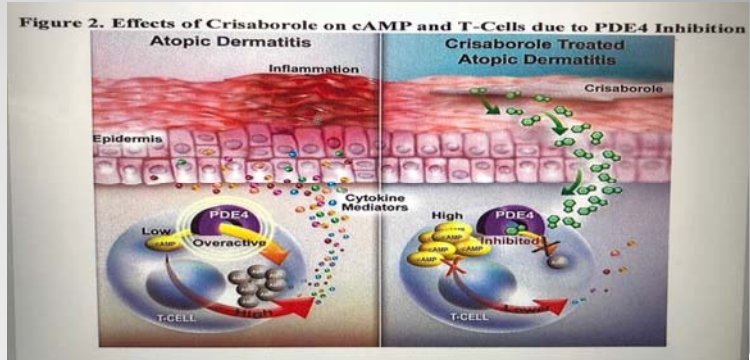
Eucrisa (crisaborole) Ointment 2%

- Crisaborole is a non-steroidal drug released in December of 2016. It is a topical 3-phosphodiesterase 4 (PDE-4) inhibitor in an ointment base indicated for the treatment of mild to moderate AD in patients two years of age and older. It is important because it is not a corticosteroid and it is not a calcineurin inhibitor
- (The black box warning on the calcineurin inhibitors made these drugs more difficult to prescribe even though they were quite safe when used appropriately and the malignancy risk described in the boxed warning is theoretical.)
- Crisaborole fills a niche that topical calcineurin inhibitors filled because they were not steroids, so you can use them on the face and in the groin. There is some application site burning and pain because of the propylene glycol in the base.
- I'm not overly impressed by them because they burn and they just don't work that well. The real advancement here, over their "new class" of mechanism, is that they are approved down to the age of two. Cost about \$616 per tube if you have insurance. \$35 if you don't have insurance

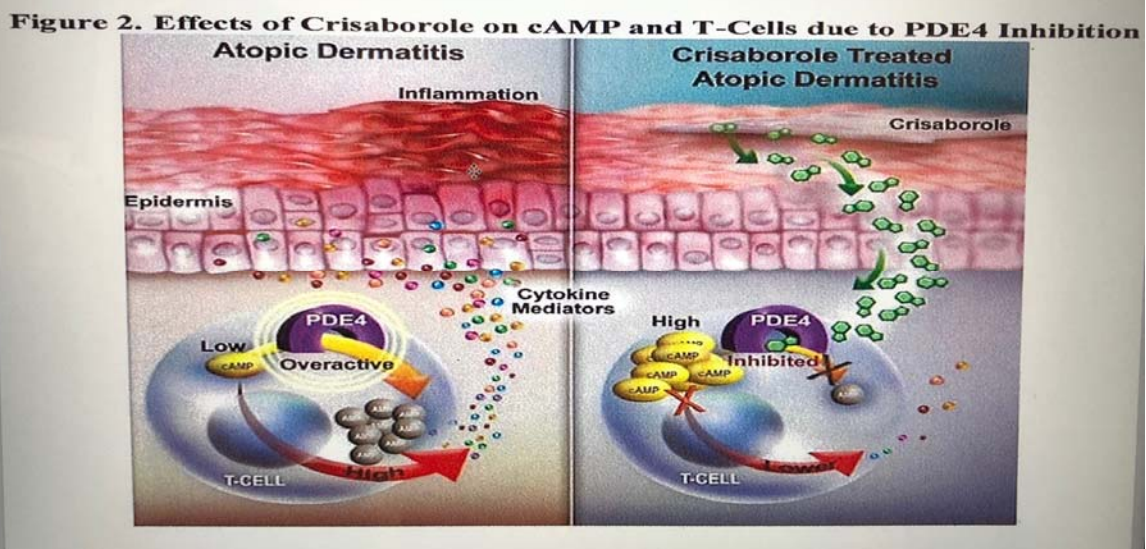
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Eucrisa (crisaborole) continued

- Side effects: Allergic reactions near the application site including- hives, itching, swelling and burning. Takes about 28 days to see improvement.



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Dupixent (dupilumab) Injection 300mg

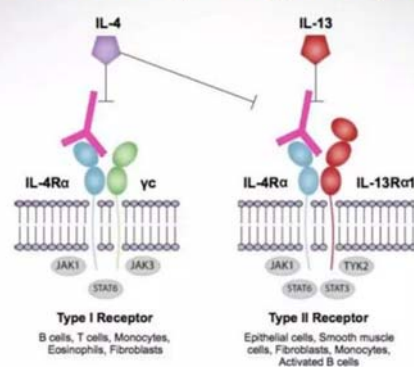
- Launched in 2017 for treatment of adults with moderate to severe disease whose disease is not adequately controlled with topical prescription therapies or when those therapies are not available.
- Dupilumab is a fully human monoclonal antibody directed against the shared alpha subunit of the interleukin-4 (anti-IL-4ra) receptors that blocks signaling from both IL-4 and IL-13. It is not an immunosuppressant.
- We have immune responses for a reason. They help us stay healthy and fight infection. If you use cyclosporine or other immunosuppressants that are nonspecific, you'll get not only the potential benefit but a much greater risk for adverse effects.

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Dupilumab (2)

- We are not seeing opportunistic infections with Dupilumab. This drug targets IL-4 and IL-13 which play a role in the immune system but blocking these doesn't seem to predispose to opportunistic infections.
- This drug is going to help us get patients off more broad-spectrum immunosuppressants

Dupilumab (anti-IL-4Rα) blocks the IL-4/IL-13 receptor/ligand system



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Dupilumab (3)

- When you transition to a drug that's more specific, like dupilumab, you are targeting a specific molecule.
- You might logically expect a cleaner side-effect profile. In adult trials, other than injection site reactions, conjunctivitis was the most frequent treatment-related adverse event with dupilumab.

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- Emma Guttman-Yassky has looked at the cytokine profiles of different groups of patients and there do appear to be differences. For example,
- Asians with AD have more of an IL-17/IL-23 cytokine profile. In comparison, white patients have less of an IL-17/IL23 profile
- Diet plays very little role in AD. Focus on care of the skin.
- Lubricate!!
- Probiotics probably are of no benefit

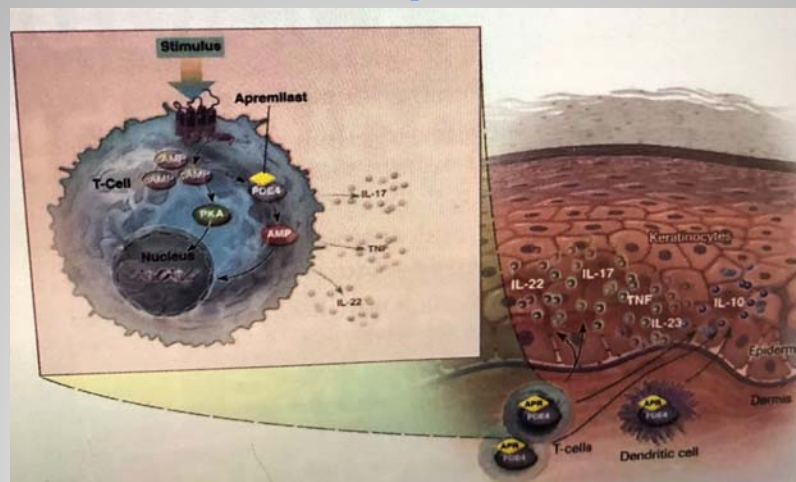
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Drugs in Clinical Trials for AD

- Ustekinumab-Used frequently as Stelara for psoriasis and off-label severe AD.
- A phase 2b dose-ranging and efficacy study of tralokinumab, a monoclonal antibody that targets IL-13 has been completed in adults with moderate to severe AD.
- Also Lebrikizumab, another IL-13 blocker, is being investigated. All possible new drugs for the future.
- Otezla (apremilast)- is in phase 2 trials for AD.

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Otezla (apremilast)



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JAK Inhibitors in Dermatology: The Promise of a new Drug Class

- The Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway is utilized by cytokines, including interleukins (ILs), interferons (IFNs), and other molecules to transmit signals from the cell membrane to the nucleus.
- Upon engagement of extracellular ligands, intracellular JAK proteins, which associate with cytokine receptors, become activated and phosphorylated STAT proteins which dimerize and then translocate into the nucleus to directly regulate gene expression

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JAK-STAT Signaling Pathway

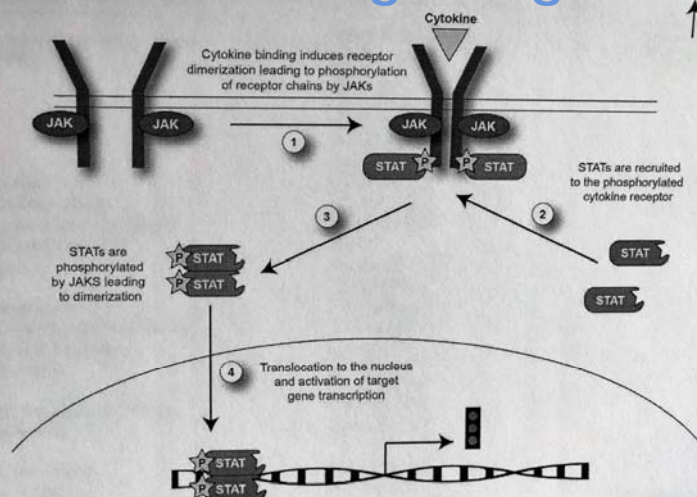


Fig 1. Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. JAK inhibitors antagonize JAK protein function and prevent activation of the pathway.

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- The JAK family of kinases includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2)
- Individual JAKs selectively associate with different receptors but because only 4 JAKs exist, each member is used by multiple different receptors.
- The same is true of STATs, of which there are 7 family members (STAT 1, STAT 2, STAT 3, STAT 4, STAT 5a, STAT 5b and STAT6)

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- A variety of disease-causing cytokines rely on JAK-STAT signaling to elicit their pathogenic effect. Together these observations have led to the development of JAK inhibitors for the treatment of human disease.
- First generation JAK inhibitors include tofacitinib, ruxolitinib, baricitinib and oclacitinib. Ruxolitinib is FDA approved to treat myelodysplastic disorders. Baricitinib is not yet FDA approved but is being tested for rheumatoid arthritis, psoriasis and atopic dermatitis. The FDA approved JAK inhibitor for autoimmune disease is tofacitinib, first studied as an anti-rejection agent in organ transplants. Oclacitinib has been used for atopic dermatitis in dogs.

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- Many inflammatory cytokines and other signaling molecules rely on JAK-STAT signaling, which is indispensable for immune and hematopoietic functions
- For example, loss-of-function mutations in JAK 3 cause severe combined immunodeficiency syndrome.
- Gain of function mutations in JAKs act as oncogenes in lymphoproliferative disorders and some malignancies
- STAT genes are also essential for proper immune function and loss-of-function mutations in these proteins have been associated with immuno-deficiency syndromes

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JAK inhibitors

- JAK inhibitors, especially tofacitinib, is an oral drug approved for treatment of moderate to severe rheumatoid arthritis. A Yale study reported successful tofacitinib treatment of six patients with moderate to severe AD who had failed standard treatments
- JAK inhibitors are broadly immunosuppressive, unlike dupilumab. The holy grail would be a small molecule medication, like JAK inhibitor, that does not have a high frequency of immunosuppression-related side-effects.
- Tofacitinib for psoriasis may not have been approved because we have many other drugs available for psoriasis that are targeted immunosuppressives. Also in some cases of herpes zoster and lymphomas these drugs have been used.

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Many of the dermatologically relevant cytokines rely on the JAK-STAT pathway

- In some instances JAK inhibitors can indirectly suppress certain cytokines (i.e. IL-17) by inhibition of other STAT-dependent cytokines (i.e. IL-23). To date, JAK inhibitors have shown efficacy in the treatment of dermatologic conditions such as AD, alopecia areata, psoriasis and vitiligo.
- Smaller case series and case reports suggest efficacy in dermatomyositis, chronic actinic dermatitis, EM, hypereosinophilic syndrome, GvH disease and lupus.

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JAK Inhibitors in Atopic Dermatitis

- The pathogenesis of AD is complex but in part involves increased helper T cell type 2 (Th2) immunity driven by JAK-STAT signaling downstream of cytokines such as IL-4, IL-5 and IL-13. In experimental models, tofacitinib inhibits IL-4 and IL-13 dependent Th2 differentiation. In a mouse model of AD, a topical JAK inhibitor JTE-053, resulted in decreased IL-4 and IL-13 signaling and improved skin barrier function.
- Tofacitinib has shown marked improvement with a 66% reduction in Severity Scoring Index and a 69% reduction in sleep loss and pruritus. Another study with tofacitinib of 69 adults with mild-to-moderate AD resulted in an 81.7% reduction in Eczema Area and Severity Index.
- They have not yet been approved for unrestricted therapy

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Topical JAK inhibitors

- Leflunomide is a JAK inhibitor that has been studied in AD phase 2 trial of IL-31. It is often referred to as the itch cytokine. Targeting that would be very helpful.
- Leflunomide has properties of some targeted agents that inhibit DNA synthesis. It is a JAK inhibitor; it decreases IL-4 and IL-13 production and has some antibacterial effects. It is relatively safe for long term use.

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Staph Participation

- Staph is not just an innocent bystander. It plays an active role in encouraging the inflammatory response by acting as a superantigen stimulating T cells. Staph produces the delta toxin, which is directly damaging to the skin barrier.

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Vitiligo

- Vitiligo is mediated by targeted destruction of melanocytes by CD8+ cells, with IFN gamma playing a role in disease pathogenesis. Because IFN gamma signaling utilizes the JAK-STAT pathway, vitiligo might be susceptible to treatment with JAK inhibitors.
- Treatment of a patient with generalized vitiligo with Tofacitinib resulted in near complete repigmentation of affected areas of the face, forearms, and hands over 5 months; however, depigmentation reoccurred after discontinuing tofacitinib

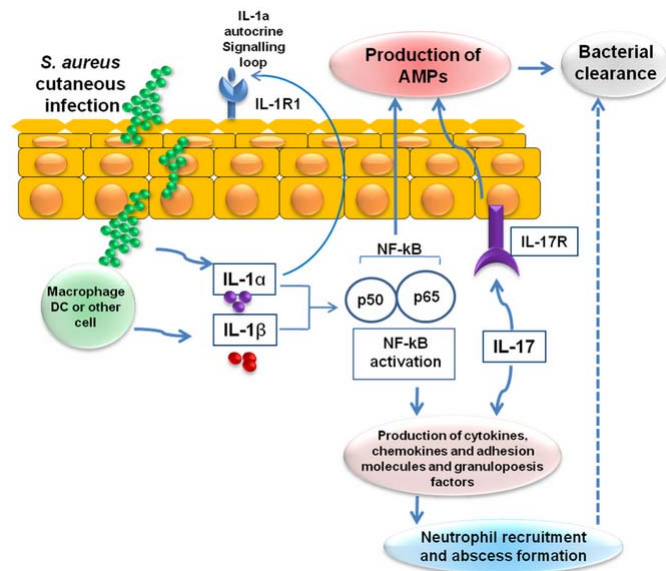
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- Gallo's lab showed that coagulase-negative staph strains produce antimicrobial peptides, and when you look at atopic skin, those Coagulase negative staph that produce antimicrobial peptides are either diminished or absent.
- Ergo, you get *S. aureus* colonization. If you reintroduce those constraints to atopic skin *S. aureus* colonization is diminished.

Bleach baths!



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