New Frontiers and Pivotal Clinical Advances in the PATHOIMMUNOBIOLGY of ATOPIC DERMATITIS

A YEAR 2016 SCIENCE-TO-PRACTICE UPDATE FOR THE DERMATOLOGY, IMMUNOLOGY, AND PEDIATRIC SPECIALIST

The Translational Path in Atopic Dermatitis and Implications for Dermatology Practice

EVIDENCE-BASED ROADMAPS FOR CLINICAL SUCCESS

ADDRESSING NOVEL TARGETS, IMMUNE MECHANISMS, AND ENDURING DISEASE BURDEN IN ATOPIC DERMATITIS

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The Translational Path in Atopic Dermatitis and the Implications for Dermatology Practice

PROFESSOR EMMA GUTTMAN, MD, PhD – Program Chair
Professor and Vice Chair, Dermatology
Director, Center for Excellence in Eczema and Laboratory for Inflammatory Skin Diseases
Icahn School of Medicine at Mount Sinai Medical Center
Welcome and Program Overview

CME-certified symposium jointly provided by Advancing Knowledge in Healthcare (AKH) and CMEducation Resources, LLC

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Enduring Materials from This Symposium

• This entire program will be available as a CME Clinical Excellence WebCAST on multiple clinical websites, including www.BiologicsCAST.com

• PowerPoint slides from today’s program will be available for download

• Clinical questions about atopic dermatitis management may be submitted to www.iQandA-CME.com

Distinguished Program Faculty

PROFESSOR EMMA GUTTMAN, MD, PhD
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PROFESSOR LISA A. BECK, MD
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University of Rochester Medical Center
School of Medicine and Dentistry
Rochester, NY
Welcome to this SCIENCE-to-STRATEGY SUMMIT

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Translational Revolution in AD

- In the last decade there is a real revolution in atopic dermatitis research with rapid therapeutic development, further amplifying our current disease understanding.

- These therapeutic developments are giving our AD patients hope for a better future and quality of life.

Translational Revolution in AD

- This symposium will present current data on disease pathogenesis, the unmet need and the emerging systemic nature of AD, suggesting the need for systemic treatments for patients with severe AD.

- It will also present data on disease control using systemic treatments.
Overview

- Overview of Therapeutic Advances in AD (Dr. Mark Lebwohl)
- Evolving Pathogenic Concepts On Atopic Dermatitis (AD) and Its Systemic Nature with Implications for Targeted Therapeutics (Dr. Emma Guttman-Yassky)
- Review of Published Clinical Trials and How This is Likely to Change Our Approach to the Treatment of AD (Dr. Lisa Beck)
- Summary, future directions, questions (all)
Therapeutic Advances in Atopic Dermatitis

Professor Mark Lebwohl, MD
Sol and Clara Kest Professor and Chairman
Kimberly and Eric J. Waldman Department of Dermatology
Icahn School of Medicine at Mount Sinai

Mount Sinai Gets Dollars From:

- Amgen
- Anacor
- Boehringer Ingleheim
- Celgene
- Lilly
- Janssen Biotech
- Kadmon

- LEO Pharmaceuticals
- Medimmune
- Novartis
- Pfizer
- Sun Pharmaceuticals
- Valeant
Optimist: Glass is half full
Pessimist: Glass is half empty
Realist: Glass is half full and half empty

The Clinical Dilemma in AD

- No universally accepted biomarker to define disease stages, severity or clinical success

- >20 instruments to assess disease severity in clinical trials that differ in items and domains they include and most have not been sufficiently validated
  - Treatment effects cannot be readily compared and meta-analyses are difficult
  - Impacts evidence-based management

- Unmet need for effective therapy of moderate and severe atopic dermatitis
Pathogenesis of Psoriasis
Mechanism of Alefacept

Innate immunity
- Keratinocyte
  - IL-1β
  - TNF-α
  - INF-γ

- Natural killer T cell
  - INF-γ

- Myeloid dendritic cell
  - IL-12

- Plasmacytoid dendritic cell
  - IL-23

- Macrophage


Activation

Adaptive immunity
- IL-17A
- IL-17F
- IL-17R

- Th1 cell
  - TNF-α
  - INF-γ

- Th22 cell
  - IL-22

- Th17 cell
  - IL-17A

Antimicrobial peptides
- IL-1β
- IL-6
- TNF-α
- S100
- CXCL8
- CXCL9
- CXCL10
- CXCL11
- CCL20

Mechanism of Cyclosporine

Innate immunity
- Keratinocyte
  - IL-1β
  - IL-6
  - TNF-α

- Natural killer T cell
  - INF-γ

- Myeloid dendritic cell
  - IL-12

- Plasmacytoid dendritic cell
  - IL-23

- Macrophage

Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis.

Immunity to infection in IL-17-deficient mice and humans.
Cypowyj S, Picard C, Maródi L, et al
*Eur J Immunol.* 2012;42:2246-2254

Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity.
Puel A, Cypowyj S, Bustamante J, et al.
*Science.* 2011;332(6025):65-68.
Mechanism of cyclosporine

Gittler JK...and Guttman-Yassky E. J Allergy Clin Immunol Sep 2012
Cyclosporine

- Nephrotoxicity
- Hypertension
- Hypomagnesemia, Hyperkalemia
- Hyperlipidemia
- Drug interactions
- Hypertrichosis
- Lymphoproliferative disease
- “Sexual Frenzy”

Mechanism of Dupilumab

Gittler JK...and Guttmann-Yassky E. J Allergy Clin Immunol Sep 2012
Th2 Cytokine (IL-4/IL-13) Effects on the Epidermis in AD

- Inhibit terminal differentiation of KCs (IL-4, IL-13, IL-31/Th2)
- Inhibit lipid synthesis (Th2 cytokines/IL-4, IL-13, IL-31)
- Inhibit synthesis of antimicrobial peptides (Th2/IL-4, IL-13, IL-33 cytokines)
- Promote staph aureus binding and colonization (IL-4, IL-13)
- Augment TSLP secretion by KCs (Th2 cytokines/IL-4, IL-13)

Th2 cytokines could link the barrier and immune defects in AD

Nograles KE. Br J Dermatol 2008
Guttman-Yassky E. J Immunol 2008
Howell MD et al. J Invest Dermatol 2008;129:2244-58
Danso MO. JID July 2014

IL-4 Transgenic Mice Demonstrate Atopic Inflammatory Skin Disease Spontaneously

Dupilumab Blocks Signaling Through the IL-4/IL-13 Receptor/Ligand System

Type I Receptor
- IgE responses, Th2-mediated inflammation, reduced antimicrobial peptides

Type II Receptor
- Reduced skin barrier function, increased Th2 responses

Dupilumab in persistent asthma with elevated eosinophil levels.

Dupilumab **treatment in adults with moderate-to-severe atopic dermatitis.**


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Evolving Pathogenic Concepts On Atopic Dermatitis (AD) and Its Systemic Nature with Implications for Targeted Therapeutics

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Speaker Disclosures

- Research support, consulting or lecture fees on atopic dermatitis from Regeneron, Sanofi, Merck, Stiefel/GSK, Pfizer, Genentech, Bristol-Myers Squibb, Galderma, Celgene, Leo Pharma, Janssen, Medimmune, Dermira, Anacor, AnaptysBio, Glenmark, Novartis, Celsus, Abbvie, Sun Pharma, Mitsubishi Tanabe, Vitae, Almirall

- No patents, ownership, or financial gain from any atopic dermatitis drug
Atopic Dermatitis

- Most common inflammatory skin disease (3-7% of adults and 15-25% of children)
- ~ 1/3 of AD patients have moderate-to-severe disease
- Large unmet need for safe and effective therapeutics in both adults and children

Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches

Donald Y. M. Leung, MD, PhD, and Emma Guttmann-Yassky, MD, PhD

J ALLERGY CLIN IMMUNOL
OCTOBER 2014
Barrier Defects in AD (and Clinical Correlations)

**Lichenification:** Epidermal hyperplasia characterizes chronic lesional AD skin

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**Terminal Differentiation, Tight Junction, and Lipid Defects**

- **Stratum Corneum:** ↓FLG, ↓LOR, ↓INV: Lipid defects; ↑proteases, ↓protease inhibitors; trauma from itch-scratch cycle

- **Tight Junction:** ↓CLDN1. Cleavage of TJ proteins by proteases (endogenous, allergen-associated, microbe-associated)

---


De Benedetto A et al. JACI 2011; 127: 773-786
AD Skin Lesions are Invariably Characterized by Immune Activation

- Acute and even more chronic AD are associated with large T cell and dendritic cell infiltrates

AD Lesions are Accompanied by Th2/Th22 Cytokine Activation

Two Proposed Mechanistic Hypotheses for AD

▶ “Outside-in” - AD is a disease of fixed (genetic) epidermal barrier defects, that may trigger abnormal keratinocyte hyperplasia and secondary immune activation

Supported by the FLG gene mutation in 10-40% of AD patients

▶ “Inside-out” - The abnormal epidermal phenotype in lesional AD skin is driven by increased expression of cytokines produced by distinct T-cell subsets

The Th2 Cytokines IL-4 and IL-13 Downregulate Epidermal Differentiation Proteins In Vitro

Pediatric vs Adult AD

- Paradigm-shifting AD discoveries have been based on adult biomarkers, reflecting decades of disease activity
- But, 85% of AD cases begin before 5yo
- We thus (collaboratively with Amy Paller’s group) aimed to:
- Determine differences and similarities between early onset AD in children and chronic AD in adults with similar disease activity
- We assessed blood and skin samples from 20 AD children<5yrs, within 6 month of disease onset, as well as 14 age-matched controls
Early AD Already Shows Strong Th2 Skewing in Blood

- Comparable Th2 activation in both pediatric and adult AD
- In pediatric AD, Th2 imbalance is confined to skin homing/CLA+ T-cells and does not extend to CD8+ T-cells
- In adults, Th2 activation extends into systemic/CLA- T-cells and CD8+ T-cells

No Th1, Th22, Th17 or Th9 subset expansion was seen in blood of AD children

Pediatric AD Exhibits Profound Epidermal Hyperplasia

Th2 Cytokines are Greatly Increased in Skin at Disease Initiation

Continuous Filaggrin Expression Characterizes Pediatric AD
Conclusions

- There is early and potent Th2 activation in blood and skin of AD children, establishing the systemic nature of new onset disease.
- Pediatric non-lesional skin is already hyperplastic, accompanied by significant inflammation and activated cytokines to levels often higher than in adults, possibly reflecting “true” AD initiation.
- FLG deficiency of adult AD is missing in early AD challenging the notion of filaggrin as central for disease elicitation and instigator of the atopic march.

**The Allergic March**

Can the Atopic March can be prevented by appropriate immune manipulations (using broad or specific T-cell targeting) once the skin phenotype has developed?
Testing the Immune Hypothesis of AD

- A prediction of the immune model is that immune suppression will reverse the epidermal pathology.
- The hypothesis can be rejected if immune suppression is achieved but the epidermal phenotype persists.
- Test of this hypothesis is our study with dupilumab, a specific immune antagonist.

Dupilumab, a Fully Human IL-4Rα mAb, Potently Inhibits Both IL-4 and IL-13 Signaling

- Type I Receptor
  - B cells, T cells, Monocytes, Eosinophils, Fibroblasts

- Type II Receptor
  - Epithelial cells, Smooth muscle cells, Fibroblasts, Monocytes, Activated B cells

- 4 week study with weekly injections of dupilumab 75mg, 150 mg, 300 mg and placebo
- A total of 67 patients, 18 participated in the biopsy study
**Dupilumab Response Rates**

No differences in responses were seen between AD patients based on IgE or FLG mutation status

![Graph showing response rates over study weeks for Placebo (n=16), Dupilumab 75 mg (n=8), Dupilumab 150 mg (n=22), and Dupilumab 300 mg (n=21).]

* p<0.05; † p=0.003

Beck L....Guttman-Yassky E et al, NEJM 2014

**Dupilumab Significantly Reduced Epidermal Hyperplasia After Only Four Weeks of Treatment**

![Graph showing significant decreases in expression of genes related to hyperplasia (K16, Mki67) with Dupilumab compared to Placebo.](image)

Significant decreases in the expression of genes related to hyperplasia also by arrays (K16, Mki67)

*Hamilton J.....and Guttman-Yassly E. JACI Dec 2014*
Dupilumab Suppressed Inflammatory Pathways Beyond Th2

Marked reductions in expression of:
- Th2 chemokines (CCL17, CCL18, CCL13, CCL22, CCL26)
- S100 As (S100A8/9/12)
- IL-23/IL-17 genes (elafin, IL-23p19 and p40, IL-17A)
- Hyperplasia related genes (K16, Mki67)

One possibility is through the inhibition of IL-4 induced differentiation of dendritic cells

In vitro studies in KCs suggest that the Th2 cytokines (IL-4, IL-13, and IL-31) inhibit differentiation genes

In vivo, IL-4R blockade increases expression of LOR and FLG mRNAs, but the magnitude of the effect is small at 4 weeks; may also be confounded by reversal of epidermal hyperplasia
Dupilumab Improved the AD Transcriptome in a Dose-Dependent Manner

- Drug Effect = Transcriptome-specific changes with p<0.05 and FCH>2

Dupilumab Impacts Both the Inflammation and the Barrier Dysfunction of AD

This establishes IL-4 and IL-13 as pathogenic cytokines in AD and cements AD as a reversible, immune-driven disease, like psoriasis.

EASI-75 Response in Phase III: Change from Baseline

Week

0 1 2 4 6 8 12 16

Patients (%)

Week

0 1 2 4 6 8 12 16

Patients (%)

Placebo qw (censored)
Θ Placebo qw (uncensored)
Dupilumab 300 mg q2w (censored)
Θ Dupilumab 300 mg q2w (uncensored)
Dupilumab 300 mg qw (censored)
Θ Dupilumab 300 mg qw (uncensored)

* Censored analysis.

Pre-Treatment Pictures (My Own Patient in Phase 2B)
Post-Treatment Pictures

Pre Treatment Pictures (My Own Patient in Phase 3)
What Features of AD May be Explained by Other Cytokines Effects (IL-22, and IL-23/IL-17)?
IL-22 Promotes Hyperplasia and Impairs Terminal Differentiation

Genes up/down-regulated by IL-22 in keratinocytes

<table>
<thead>
<tr>
<th>Genes</th>
<th>S100A7</th>
<th>FCH</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S100A7 psoriasin</em></td>
<td></td>
<td>458.87</td>
</tr>
<tr>
<td>Terminal Differentiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOR Loricrin</td>
<td>0.084</td>
<td></td>
</tr>
<tr>
<td>FLG Filagrin</td>
<td>0.032</td>
<td></td>
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<tr>
<td>CALML5 Calmodulin 5</td>
<td>0.326</td>
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<tr>
<td>KRT1 keratin 1</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>KRT10 keratin 10</td>
<td>0.499</td>
<td></td>
</tr>
</tbody>
</table>


Targeting Th22/IL-22 in AD

- Since IL-22 is involved in the epidermal hyperplasia and barrier defects in AD, we hypothesized that anti IL-22 treatment might prove to be effective in chronic AD patients

- We are conducting an NIH/NIAMS-funded trial with an anti IL-22 antibody (ILV-094) in 60 moderate-to-severe AD patients (study completed, analyses in process)
What is the Potential Significance of IL-23/IL-17 to AD Lesions?

**IL-23**

- **Induction of S100As & Epidermal Hyperplasia**
- **IL-17 induces S100As and impairs differentiation in KCs**

**Antimicrobials and S100as**

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>S100as</th>
<th>FCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEF/4 defensin, beta 4</td>
<td>S100A7 psoriasin</td>
<td>238.549</td>
</tr>
<tr>
<td>S100A12 S100 calcium binding protein A12</td>
<td>189.381</td>
<td></td>
</tr>
<tr>
<td>Cytokines and Chemokines</td>
<td>IL-17</td>
<td>30.707</td>
</tr>
<tr>
<td>IL-8 interleukin 8</td>
<td>CCL20 chemokine (C-C motif) ligand 20</td>
<td>14.529</td>
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<tr>
<td>S100A7 psoriasin</td>
<td>CXCL1 chemokine (C-X-C motif) ligand 1</td>
<td>28.306</td>
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<td>IL-17 IL-22 dependent</td>
<td>CXCL2 chemokine (C-X-C motif) ligand 2</td>
<td>7.688</td>
</tr>
<tr>
<td>IL-17 IL-22 dependent</td>
<td>CXCL3 chemokine (C-X-C motif) ligand 3</td>
<td>6.006</td>
</tr>
<tr>
<td>Terminal Differentiation</td>
<td>LGR loricrin</td>
<td>3.812</td>
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<tr>
<td>Definitive</td>
<td>LGR loricrin</td>
<td>0.163</td>
</tr>
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</table>

**Th22**

**Th17**

Pre ILV-094/anti IL-22

3 months Post ILV-094
A Case Report of Successful Treatment of Refractory AD with High Dose Ustekinumab

Shroff A, and Guttman-Yassky E. JAAD case reports January 2015

Other Pathways/Targets Under Investigation

The AD phenotype cannot be explained by a single cytokine pathway like psoriasis.

It is currently unclear how many immune axes need to be targeted and to what extent to fully reverse the pathogenic disease phenotype.

Clinical trials with IL-17/IL-23, IL-22, and IL-4/IL-13 antagonists (coupled with mechanistic studies) are needed to determine the relative contribution of each axis to AD in different AD phenotypes and in different parts of the world.
What is the Level of Systemic Immune Activation in AD vs Psoriasis (and Controls)?

- Both atopic dermatitis (AD) and psoriasis are characterized by T-cell activation in skin, but their comparable systemic T-cell activation has been unclear.

- We recently evaluated T-cell activation markers (ICOS and HLA-DR) in central (Tcm/CCR7+CD45RO+) and effector memory (CCR7-CD45RO+) skin homing (cutaneous lymphocyte antigen/CLA+) and CLA- subsets from psoriasis, AD and controls.

Compared with psoriasis, AD is characterized by increased levels of T-cell activation (ICOS/HLA-DR) among central and effector CD4+ and CD8+ CLA+ and CLA- memory subsets (p<0.01).
Systemic Cytokine Activation in AD

Serum cytokines levels were shown to be increased in AD patients compared to controls and correlated with disease activity (SCORAD).

Ungar B...Guttman-Yassky E. J Invest Dermatol Nov 2016 (Epub ahead of print)

...post CsA treatment ...

Modifiable risk factors?

Ungar B...Guttman-Yassky E. J Invest Dermatol Nov 2016 (Epub ahead of print)
AD and Cardiovascular Risk Factors

Higher odds of:
- Smoking at least 100 cigarettes
- Current smoker
- Started smoking at younger age
- Drinking >12 alcoholic beverages/yr
- Greater odds of drinking
- Higher BMI, esp. ≥35
- Hypertension
- Pre-diabetes, high cholesterol
- Especially with increased fatigue, sleep issues

Silverberg and Greenland. JACI 2015;135:721

Atopic Dermatitis and Cardiac Disease

National Health Interview Survey 2010 and 2012
- 1 year history of AD associated with:
  - Coronary artery disease -- Stroke
  - Angina -- Myocardial infarction
  - Congestive heart failure -- Peripheral vascular disease

Silverberg J. Allergy 2015
Increased Coronary Calcifications in Severe Psoriasis and AD

Cardiac computed tomography angiography (CCTA) showed plaques in 48.1% of AD patients vs. 38.3% in psoriasis and 21.2% in controls)

Systemic inflammation and CVD

► Chronic inflammation accelerates atherosclerosis due to repetitive vascular injury/endothelial cell activation
  – impaired vascular relaxation
  – increased leukocyte adhesion
  – increased endothelial permeability
  – generation of a pro-thrombotic state

Abnormal Cytokine Profile Already Exists in Non-Lesional AD Skin (Unlike Psoriasis)

**Th2**

- IL-13 (Th2) expression shows a decrease in non-lesional AD compared to normal skin.
- CCL11 (Th22) expression is upregulated in AD lesional skin.
- CCL17 (Th22) expression shows a significant increase in AD lesional skin.
- CCL18 expression is not significantly changed.

**Th22**

- IL-22 (Th22) expression is increased in both non-lesional and lesional AD skin.
- NOS2A7 (Terminal Differentiation) expression is decreased in AD lesional skin.

The Nonlesional Phenotype is Influenced by Disease Severity (SCORAD)

- Nonlesional skin expression of Th2 and Th22 markers IL-13, IL-22, CCL22, and CCL18 showed high correlation with disease activity.
- Expression of terminal differentiation genes (EREG, PPL, and LOR) in nonlesional skin showed an inverse correlation with SCORAD.

Integrated Disease Severity Biomarker Models Highlight Systemic Immune Activation

**LS**
- MX1, S100A12, S100A9, -PPL, IL17A

**NL**
- PPL, CD11c, CD3, IL13, E. Thickness

**LS + NL + Serum**
- EOS (serum), CCL11 (serum), S100A12 (LS), IL13 (NL), E. Thickness (NL)

Ungar B...Guttman-Yassky E.: J Invest Dermatol Nov 2016 (Epub ahead of print)

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**AD Emerges as a Systemic Disease**


2) Allergy, Asthma, and the Atopic March

3) Cardiovascular and other co-morbidities

While Asthma and other comorbidities involve ~30% of AD patients, ALL moderate to severe AD patients are associated with systemic immune abnormalities (might be the common denominator that drives 2-3)
Therapeutic Implications

- The high level systemic immune activation in AD is reflected in the wide immune abnormalities seen in the NL AD skin (compared to psoriasis in which NL is closer to normal skin)

- This emphasizes the need for systemic treatment approaches for patients with moderate-to-severe AD
A Review of Landmark Clinical Trials in Atopic Dermatitis

How Will the Data Change Our Approach to Treating Atopic Dermatitis?

LISA A. BECK, MD
Professor, Department of Dermatology and Medicine (Allergy/Immunology and Rheumatology)
University of Rochester Medical Center
School of Medicine and Dentistry
Rochester, NY

Speaker Disclosures

• Abbvie – AD clinical trials / Consultant
• Array Biopharma - Consultant
• Celgene, Inc. – Consultant
• Hoffman- LaRoche - Consultant
• Genentech, Inc. - Urticaria clinical trials / consultant
• Janssen – Consultant
• Novartis – Consultant
• Regeneron, Inc. - AD Clinical trials / consultant
• Unilever - Consultant
• Pfizer & Medtronics - Stock
AD Pathogenesis

- Itch
- General Inflammation
- Skin Barrier Defects
- Dysbiosis
- Th2 Adaptive Immunity

AD is the Most Type 2 Polarized Allergic Disease

Serum IgE Values

- Hay fever
- Perennial rhinitis
- Asthma
- Atopic Dermatitis
AD is the Most Type 2 Polarized Allergic Disease

Serum TARC (CCL17)

(J Allergy Clin Immunol. 2004;113:334.)

Th2-Mediated Effects

Systemic Th2 Targeted Therapies in ≥ Ph 2 Development

Dupilumab (anti-IL-4Rα) Blocks the IL-4/IL-13 Receptor/Ligand System

- **Dupilumab**: a fully human mAb directed against IL-4Rα subunit
- Blocks IL-4 and IL-13 intracellular signaling
- Efficacy in patients with moderate-to-severe asthma and increased IgE

(Wenzel et al. NEJM 2013;268:2455)
Five DBPC Trials of Dupilumab for Atopic Dermatitis in US, Europe, and Japan

Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis

Lisa A. Beck, M.D., Dussions Hui, M.D., Jennifer D. Hamilton, Ph.D., Neil M. Graham, M.D., Thomas Bieber, M.D., Ph.D., M.D., Ross Rodin, M.D., Jeffrey E. Ming, M.D., Ph.D., Haobo Ren, Ph.D., Richard Kao, Ph.D., Eric Simpson, M.D., Marius Ardelianu, M.D., Steven P. Weinstein, M.D., Ph.D., Giannluca Rizzoli, M.D., Ph.D., Emma Guttman-Yassky, M.D., Ph.D., Maike Gisantes-Fernandez, Ph.D., Melissa D. Hager, M.A., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Allen R. Radin, M.D.

ABSTRACT

BACKGROUND

Dupilumab, a fully human monoclonal antibody that blocks interleukin-4 and interleukin-13, has shown efficacy in patients with asthma and elevated eosinophil levels. The blockade by dupilumab of these key drivers of type 2 helper T-cell (Th2)-mediated inflammation could help in the treatment of related diseases, including atopic dermatitis.

METHODS

We performed randomised, double-blind, placebo-controlled trials involving adults who had moderate-to-severe atopic dermatitis despite treatment with topical glucocorticoids and calcineurin inhibitors. Dupilumab was evaluated as monotherapy in two 4-week trials and in one 12-week trial and in combination with topical glucocorticoids in another 4-week study. End points included the Eczema Area and Severity Index (EASI) score, the investigator’s global assessment score, pruritus, safety assessments, serum biomarker levels, and disease transcriptome.
## Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>4-Wk Monotherapy</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (n=16)</td>
<td>Dupilumab (n=51)</td>
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<tr>
<td>Age – yr</td>
<td>37.4±4.3</td>
<td>42.6±1.9</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>11 (69)</td>
<td>28 (55)</td>
</tr>
<tr>
<td>White race – no. (%)</td>
<td>13 (81)</td>
<td>39 (76)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.7±1.5</td>
<td>26.6±0.9</td>
</tr>
<tr>
<td>EASI score</td>
<td>22.8±3.0</td>
<td>30.0±2.0</td>
</tr>
<tr>
<td>Investigator’s global assessment score</td>
<td>3.6±0.2</td>
<td>2.8±0.1</td>
</tr>
<tr>
<td>Body-surface area affected - %</td>
<td>40.3±6.5</td>
<td>51.4±3.5</td>
</tr>
<tr>
<td>5-D pruritus score</td>
<td>16.9±1.0</td>
<td>19.3±0.5</td>
</tr>
<tr>
<td>Pruritus numerical rating scale</td>
<td>5.98±0.5</td>
<td>6.0±0.2</td>
</tr>
</tbody>
</table>


## Molecular Changes in the Atopic Dermatitis Transcriptome in Studies M4A and M4B

Dupilumab Might have Barrier Repair Effects
Is this a direct or indirect effect?
Five DBPC Trials of Dupilumab for Atopic Dermatitis in US, Europe, and Japan

- Two 4-week monotherapy placebo-controlled dose-finding studies (Europe and US)
- 4-week trial monotherapy vs. placebo + topical steroids allowed ad lib C4
- 16-week monotherapy placebo-controlled (US, Europe, Japan)
- 12-week monotherapy placebo-controlled (Europe)

### Efficacy Endpoints

<table>
<thead>
<tr>
<th>Characteristic (Day 29)</th>
<th>4-Wk Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo and Topical Glucocorticoids (n=10)</td>
</tr>
<tr>
<td>EASI-50 - no. of patients (%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>EASI-75 - no. of patients (%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Change in Pruritus NRS - %</td>
<td>-24.7 ± 15.0</td>
</tr>
<tr>
<td>IGA 0-1 - no. of patients (%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Change in IGA - %</td>
<td>-30.6 ± 12.3</td>
</tr>
<tr>
<td>Change in EASI -%</td>
<td>-52.5 ± 12.5</td>
</tr>
</tbody>
</table>

TCS Use Was About Half in Dupilumab Group


Five DBPC Trials of Dupilumab for Atopic Dermatitis in US, Europe, and Japan

- Two 4-week monotherapy placebo-controlled dose-finding studies (Europe and US)
- 4-week trial monotherapy vs. placebo + topical steroids allowed ad lib
- 16-week monotherapy placebo-controlled (US, Europe, Japan) M16
- 12-week monotherapy placebo-controlled (Europe)
Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial

Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial

Summary
Background Data from early-stage studies suggested that interleukin (IL)-4 and IL-13 are key drivers of atopic dermatitis, evidenced by marked improvement after treatment with dupilumab, a fully-human monoclonal antibody that blocks both pathways. We aimed to assess the efficacy and safety of several dose regimens of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments.

Methods
In this randomised, placebo-controlled, double-blind study, we enrolled patients aged 18 years or older who had an Eczema Area and Severity Index (EASI) score of 12 or higher at screening (≥16 at baseline) and inadequate response to topical treatments from 91 study centres, including hospitals, clinics, and academic institutions, in Canada, Czech Republic, Germany, Hungary, Japan, Poland, and the USA. Patients were randomly assigned (1:1:1:1:1), stratified by severity (moderate or severe, as assessed by an investigator’s Global Assessment) and region (Japan in east of world) to receive subcutaneous dupilumab: 300 mg once a week, 300 mg every 2 weeks, 300 mg every 4 weeks, 300 mg every 4 weeks, or placebo once a week. We used a central randomisation scheme, provided by an interactive voice response system. Drug kits were coded, providing masking to treatment assignment, and allocation was concealed. Patients on treatment every 2 weeks and every 4 weeks received volume-matched placebo every week when dupilumab was not given to ensure double blinding. The primary outcome was efficacy of dupilumab dose regimens based on EASI score least-square mean percentage change (LSMPC) from baseline to week 16. Analyses included all randomly-assigned patients who received one or more doses of study drug. This trial is registered with ClinicalTrials.gov, number NCT01559989.

International Dose-Ranging, Phase 2b Study

- SC dupilumab × 16 weeks in adult patients with moderate-to-severe AD inadequately controlled by topical medications
- Primary endpoint: % change in EASI - baseline to Week 16
- Secondary endpoints: Changes from baseline to Week 16 in: Pruritus score; SCORAD; Proportion of patients achieving EASI-50/75/90; Proportion of patients achieving IGA 0–1; Safety

Lancet. 2016 Jan 2;387(10013):40-52
Study Design and Objective

**Screening**

**Study treatment**
(weekly SC injection for 16 weeks after a loading dose*)

- Dupilumab 100 mg q4w (n = 65)
- Dupilumab 300 mg q4w (n = 65)
- Dupilumab 200 mg q2w (n = 62)
- Dupilumab 300 mg q2w (n = 64)
- Dupilumab 300 mg weekly (n = 63)
- Placebo (n = 61)

*Loading doses:
  - 600 mg for 300 mg dose regimens
  - 400 mg for the 200 mg and 100 mg dose regimens

**Safety follow-up** (16 weeks)

- q4w, every 4 weeks; q2w, every 2 weeks; SC, subcutaneous.

Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics and Clinical Symptoms</th>
<th>Placebo</th>
<th>Dupilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 61</td>
<td>n = 65</td>
</tr>
<tr>
<td>Age (years), mean</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>66</td>
<td>52</td>
</tr>
<tr>
<td>AD duration (years), mean</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>BSA %, mean (SD)</td>
<td>51 (23.5)</td>
<td>49 (23.9)</td>
</tr>
<tr>
<td>SCORAD [range 0–103], mean (SD)</td>
<td>67 (13.6)</td>
<td>68 (15.0)</td>
</tr>
<tr>
<td>EASI [range 0–72], mean (SD)</td>
<td>33 (13.8)</td>
<td>32 (13.5)</td>
</tr>
<tr>
<td>Peak pruritus NRS [0–10 scale], mean (SD)</td>
<td>6.3 (1.8)</td>
<td>6.7 (1.9)</td>
</tr>
<tr>
<td>Patients with IGA score, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGA score = 3</td>
<td>52.5</td>
<td>52.3</td>
</tr>
<tr>
<td>IGA score = 4</td>
<td>47.5</td>
<td>47.7</td>
</tr>
</tbody>
</table>

Moderate AD, IGA = 3; Severe AD, IGA = 4; NRS, Numeric Rating Scale; SCORAD, SCORing in Atopic Dermatitis; SD, standard deviation.
Proportion of Patients Achieving EASI-50/75/90 over 16 Weeks

EASI-50, 50% improvement in EASI score; EASI-75, 75% improvement in EASI score; EASI-90, 90% improvement in EASI score.

Mean % Change in EASI to Week 32
(All Observed Values with Censoring After Rescue Medication Use)

*Week 16, P < 0.001 vs placebo; †Week 16, P < 0.0001 vs placebo; ‡Week 32, P < 0.05 vs placebo.
Dupilumab Summary

- Dupilumab (anti-IL-4Rα) 300 mg dosing schedules provides rapid, marked and sustained improvement in EASI, SCORAD, IGA, and BSA%, and pruritus

- Dupilumab lead to statistically superior clinical outcomes compared to the placebo group in all measures of disease activity and pruritus

- The most common TEAEs were nasopharyngitis, headache, conjunctivitis and possibly Herpes infections.
**Objective:** Demonstrate efficacy and assess safety of dupilumab monotherapy vs placebo in adults with moderate-to-severe AD inadequately controlled with or medically inadvisable for topical therapy

- **671** patients in SOLO 1 and **708** patients in SOLO 2
Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Event</th>
<th>SOLO 1</th>
<th>SOLO 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo qw (n = 224)</td>
<td>Placebo qw (n = 236)</td>
</tr>
<tr>
<td>Duration of AD, median, years</td>
<td>28.0</td>
<td>26.0</td>
</tr>
<tr>
<td>BSA affected, median, %</td>
<td>57.0</td>
<td>53.3</td>
</tr>
<tr>
<td>EASI score, median</td>
<td>31.8</td>
<td>30.5</td>
</tr>
<tr>
<td>IGA score (range 0–4), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (moderate)</td>
<td>50.4</td>
<td>51.3</td>
</tr>
<tr>
<td>4 (severe)</td>
<td>49.1</td>
<td>48.7</td>
</tr>
<tr>
<td>Peak pruritus NRS, median</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Total SCORAD score, median</td>
<td>67.0</td>
<td>68.9</td>
</tr>
<tr>
<td>DLQI score, median</td>
<td>14.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

BSA, body surface area; DLQI, Dermatology Life Quality Index; NRS, numerical rating scale; SCORAD, SCORing Atopic Dermatitis.

IGA 0 or 1 and EASI-75 Response

IGA = 0 or 1 and ≥ 2 points reduction from baseline at Week 16

**P < 0.0001 vs placebo**

EASI-75† at Week 16

**P < 0.0001 vs placebo**

† Co-primary endpoint in EU and Japan; key secondary endpoint in other regions.
EASI: % Change from Baseline

**SOLO 1**

**SOLO 2**

*LS mean percent change in EASI from baseline (± SE)*

- Placebo qw (censored)
- Dupilumab 300 mg q2w (censored)
- Dupilumab 300 mg qw (censored)

LS, least squares; SE, standard error.

Peak Pruritus NRS: % Change from Baseline

**SOLO 1**

**SOLO 2**

*LS mean percent change in peak pruritus NRS from baseline (± SE)*

- Placebo qw (censored)
- Dupilumab 300 mg q2w (censored)
- Dupilumab 300 mg qw (censored)

NRS, numerical rating scale.
DLQI and POEM: Proportions of Patients Achieving Improvement ≥ 4 (MCID) from Baseline at Week 16

HADS-A (Anxiety) and HADS-D (Depression): Proportions of Patients Achieving Score < 8 at Week 16

Analysis conducted in patients with clinical symptoms of anxiety or depression at baseline (i.e., HADS-A or HADS-D ≥ 8)
In the pivotal phase 3 studies the primary endpoints were met

Both dose regimens of dupilumab showed clinically meaningful improvement and statistical significance versus placebo in:
- AD signs and symptoms (including itch/pruritus and sleep)
- Health-related quality of life
- Symptoms of anxiety/depression

Significant improvement in itch was observed as early as Week 2

Most AEs were mild or moderate
- Injection site reactions and conjunctivitis were more frequent with dupilumab
- Overall, there were no observed increases in infections with dupilumab
**T<sub>H</sub> Subsets in Atopic Dermatitis**

Non-lesional

- Dermal DC
- TH17

Acute stage

- Langerhans Cell
- TH2
- TH22
- IL-22
- IL-31
- IL-13
- Disrupted barrier
- Scratching
- Onset of Hyperplasia/Regenerative Epidermal Growth
- AMPs (HBD3, LL-37)

Chronic stage

- Lichenification
- TH22
- TH1

**Systemic Anti-Cytokine Therapies in Development for AD**

<table>
<thead>
<tr>
<th>Name of Agent</th>
<th>Route</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Clinical Trials ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab</td>
<td>SC</td>
<td>Anti-IL-4/IL-13 mAb</td>
<td>3</td>
<td>NCT02260986</td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>SC</td>
<td>Anti-IL-13 mAb</td>
<td>2</td>
<td>NCT02340234</td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>SC</td>
<td>Anti-IL-13 mAb</td>
<td>2</td>
<td>NCT02347176</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>SC</td>
<td>Anti-IL-17A mAb</td>
<td>2</td>
<td>NCT02594098</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>SC</td>
<td>Anti-IL-12/IL-23 (small molecule)</td>
<td>2</td>
<td>NCT01806662</td>
</tr>
<tr>
<td>Fetzakinumab (ILV-094)</td>
<td>SC</td>
<td>Anti-IL-22 mAb</td>
<td>2</td>
<td>NCT01941537</td>
</tr>
<tr>
<td>Nemolizumab (CIM-331)</td>
<td>SC</td>
<td>Anti-IL-31R mAb</td>
<td>2</td>
<td>NCT01986933</td>
</tr>
<tr>
<td>BMS-981164</td>
<td>SC</td>
<td>Anti-IL-31 mAb</td>
<td>1</td>
<td>NCT01617556</td>
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<tr>
<td>MEDI 9929</td>
<td>SC</td>
<td>Anti-TSLP mAb</td>
<td>2</td>
<td>NCT02525094</td>
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<tr>
<td>QA003876</td>
<td>PO</td>
<td>CROT2-R antagonist (small molecule)</td>
<td>2</td>
<td>NCT01785602</td>
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<tr>
<td>QCA0350</td>
<td>PO</td>
<td>CROT2-R antagonist (small molecule)</td>
<td>2</td>
<td>NCT02002208</td>
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<tr>
<td>BB5000</td>
<td>PO</td>
<td>CROT2-R antagonist (small molecule)</td>
<td>1</td>
<td>NCT02550283</td>
</tr>
</tbody>
</table>

- Blocking Th2 pathway
- Blocking Th22 pathway
- Blocking Th17 or Th1/Th17 pathways
- Blocking a pruritogen


DC=dendritic cell; AMPs= Antimicrobial peptides.

Update on Phase 2 clinical trial with OC459 in patients with moderate to severe atopic dermatitis


Efficacy results from the Phase 2 study in patients with moderate to severe atopic dermatitis showed there was no benefit from OC459 compared to placebo. Overall OC459 was generally well tolerated with a similar safety profile to previous studies.
### Other Systemic Rxs

<table>
<thead>
<tr>
<th>Name of Agent</th>
<th>Route</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Clinical Trials ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>SC</td>
<td>Anti-IgE mAb</td>
<td>2</td>
<td>NCT02300701</td>
</tr>
<tr>
<td>Ligelizumab</td>
<td>SC</td>
<td>Anti-IgE mAb</td>
<td>2</td>
<td>NCT01552629</td>
</tr>
<tr>
<td>MEDI4212</td>
<td>SC/IV</td>
<td>Anti-IgE mAb</td>
<td>1</td>
<td>NCT01544348</td>
</tr>
<tr>
<td>XmAb7195</td>
<td>IV</td>
<td>Anti-IgE mAb</td>
<td>1b</td>
<td>NCT02148744</td>
</tr>
<tr>
<td>Apremilast</td>
<td>Oral</td>
<td>PDE-4 inhibitor</td>
<td>2</td>
<td>NCT02087943</td>
</tr>
<tr>
<td>AQ-1125</td>
<td>PO</td>
<td>SHIP1 activator (small molecule)</td>
<td>2</td>
<td>NCT02324972</td>
</tr>
<tr>
<td>DS106/DS107</td>
<td>PO/Topical</td>
<td>DGLA-bioactive lipid</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>


---

Paller et al., JAAD. 2016;75:494

- Two Phase III, RDBPC study (>1400) mild-to-moderate AD (> 2yrs of age) randomized 2:1 to **crisaborole** or vehicle
- **Primary endpoint:** SGA score at day 29 of clear (0)/almost clear (1) with 2-grade or greater improvement from baseline
- Improvement in Itch was earlier in crisaborole-treated pts.
- TEAE were infrequent and mild
JAK Kinase Inhibitors

ABT-494 PO JAK 1 inhibitor (small molecule)

Oral JAK 1 and 3 inhibitor

• 4 wk, Phase IIa, RDBPC study 69 adults with mild-to-moderate AD
• randomized 1:1 to 2% tofacitinib or vehicle ointment twice daily
• Primary endpoint: % change of EASI from baseline (LS Means 81.7% Tofa vs 28.9% Veh)
• Improvement in Itch
• No safety signals
AD Pathogenesis

Skin Barrier Defects

General Inflammation

Dysbiosis

Itch

Th2 Adaptive Immunity

Systemic & Topical Anti-Itch Rxs

<table>
<thead>
<tr>
<th>Name of agent</th>
<th>Route</th>
<th>Mechanism</th>
<th>Phase</th>
<th>NCT ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT327</td>
<td>Topical</td>
<td>TkiA antagonist</td>
<td>II</td>
<td>NCT01808157</td>
</tr>
<tr>
<td>VLY-666</td>
<td>PO</td>
<td>NKI-R antagonist</td>
<td>II</td>
<td>NCT02049414</td>
</tr>
<tr>
<td>DKN333</td>
<td>PO</td>
<td>NK1/NK2-R antagonist</td>
<td>II</td>
<td>NCT01035097</td>
</tr>
<tr>
<td>TS-022</td>
<td>Topical</td>
<td>DPK-R antagonist</td>
<td>II</td>
<td>NCT0014186</td>
</tr>
<tr>
<td>PAC-1401</td>
<td>Topical</td>
<td>TRPV1 channel antagonist</td>
<td>II</td>
<td>NCT020238022</td>
</tr>
<tr>
<td>ZPL-58262</td>
<td>Topical</td>
<td>H2R antagonist</td>
<td>II</td>
<td>NCT02424253</td>
</tr>
<tr>
<td>Asimadoline (EMD-6175)</td>
<td>PO</td>
<td>μ-Opioid-R agonist</td>
<td>II</td>
<td>NCT02475447</td>
</tr>
<tr>
<td>W0L071-001</td>
<td>Topical</td>
<td>μ-Opioid-R agonist</td>
<td>I</td>
<td>NCT02570093</td>
</tr>
<tr>
<td>Clonidine + melatonin</td>
<td>PO</td>
<td>Reduction of sympathetic outflow</td>
<td>I</td>
<td>NCT02268448</td>
</tr>
</tbody>
</table>

AD: atopic dermatitis, DPK-R prostaglandin D2 receptor, H2R histamine H2 receptor, NK neuropeptide, PO oral, R receptor, TRPV1 transient receptor potential cation channel subfamily V member 1, H2R histaminergic receptor kinase A.

Notes:
- All of these agents are in clinical trials for AD. However, many are also in clinical trials for other conditions.
- This drug is only being tested for atopic dermatitis per ClinicalTrials.gov.
AD Pathogenesis

- Itch
- Skin Barrier Defects
- Dysbiosis
- Th2 Adaptive Immunity

Systemic & Topical Barrier Repair Rxs

Table 3: Barrier repair therapies

<table>
<thead>
<tr>
<th>Name of agent</th>
<th>Route</th>
<th>Mechanism</th>
<th>Phase</th>
<th>NCT ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFR277</td>
<td>Topical (ointment)</td>
<td>Kallikrein-related peptidase inhibitor</td>
<td>I</td>
<td>NCT01428397</td>
</tr>
<tr>
<td>BRT-1C-8C</td>
<td>Topical (cream)</td>
<td>Unknown</td>
<td>II</td>
<td>NCT0083311</td>
</tr>
<tr>
<td>Oregano ointment</td>
<td>Topical (ointment)</td>
<td>Antimicrobial and anti-inflammatory properties</td>
<td>NA</td>
<td>NCT02289089</td>
</tr>
<tr>
<td>Holistic fragrance shower gel</td>
<td>Topical (shower gel)</td>
<td>Unknown</td>
<td>III</td>
<td>NCT02172515</td>
</tr>
<tr>
<td>DS107G</td>
<td>Topical (ointment)</td>
<td>Omega-6 fatty acid derivative</td>
<td>II</td>
<td>NCT0214411</td>
</tr>
<tr>
<td>Chloromeric acid</td>
<td>Topical (cream)</td>
<td>Restoration of acidic pH in atopic skin</td>
<td>II</td>
<td>NCT01321879</td>
</tr>
<tr>
<td>EHK02-01 cream</td>
<td>Topical (cream)</td>
<td>Ectoine is a natural product produced by some bacteria and functions as an osmolyte</td>
<td>NA</td>
<td>NCT01075997</td>
</tr>
<tr>
<td>HL-009 (liposomal gel)</td>
<td>Topical (gel)</td>
<td>Anti-inflammatory properties</td>
<td>II</td>
<td>NCT01568489</td>
</tr>
</tbody>
</table>

*All not applicable

* Natural products that do not require FDA approval before marketing and are exempt from the phases of drug development
Conclusions

► Last FDA-approved therapy for AD was 15 yrs ago.
► Many new topical and systemic Rx's are in the pipeline for AD treatment.
  The only ones that have reported Phase 3 data are:
  ✓ Dupilumab – biologic targeting IL-4R alpha chain (moderate-severe AD)
  ✓ Crisaborole – topical PDE4 inhibitor
  • A major focus is on inhibiting components of the Type 2 (Th2) pathway:
    • DPL is effective at reducing the signs, symptoms and S. aureus levels (?barrier)
  • Whether there are AD endotypes that might respond better to Th17 or Th22 antagonists is currently being explored.
  • A number of more general anti-inflammatory therapies show great promise (PDE4 inhibitors, JAK inhibitors, H4R inhibitors)