



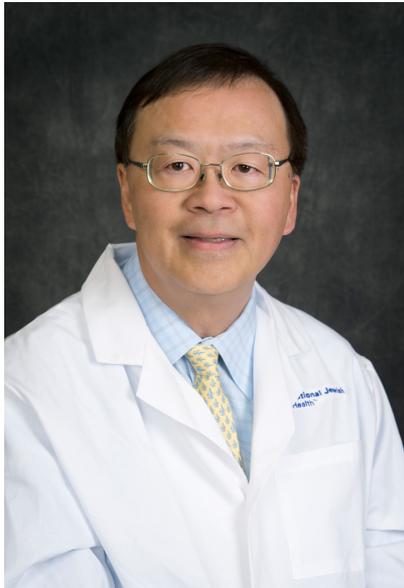
present

LEADERS *in* ECZEMA

ONE-DAY FORUMS

**Why do patients get eczema?
Factors that contribute
to severity**

Why do patients get eczema?



Presented by:

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National Jewish Health

- **Research Grants/Contracts**

 - NIH/NIAID ADRN

 - NIH/NIAMS

 - Pfizer

 - MedImmune

- **Consultant/Advisory Board**

 - Aimmune Therapeutics

 - AbbVie

 - Incyte

 - Regeneron Pharmaceuticals

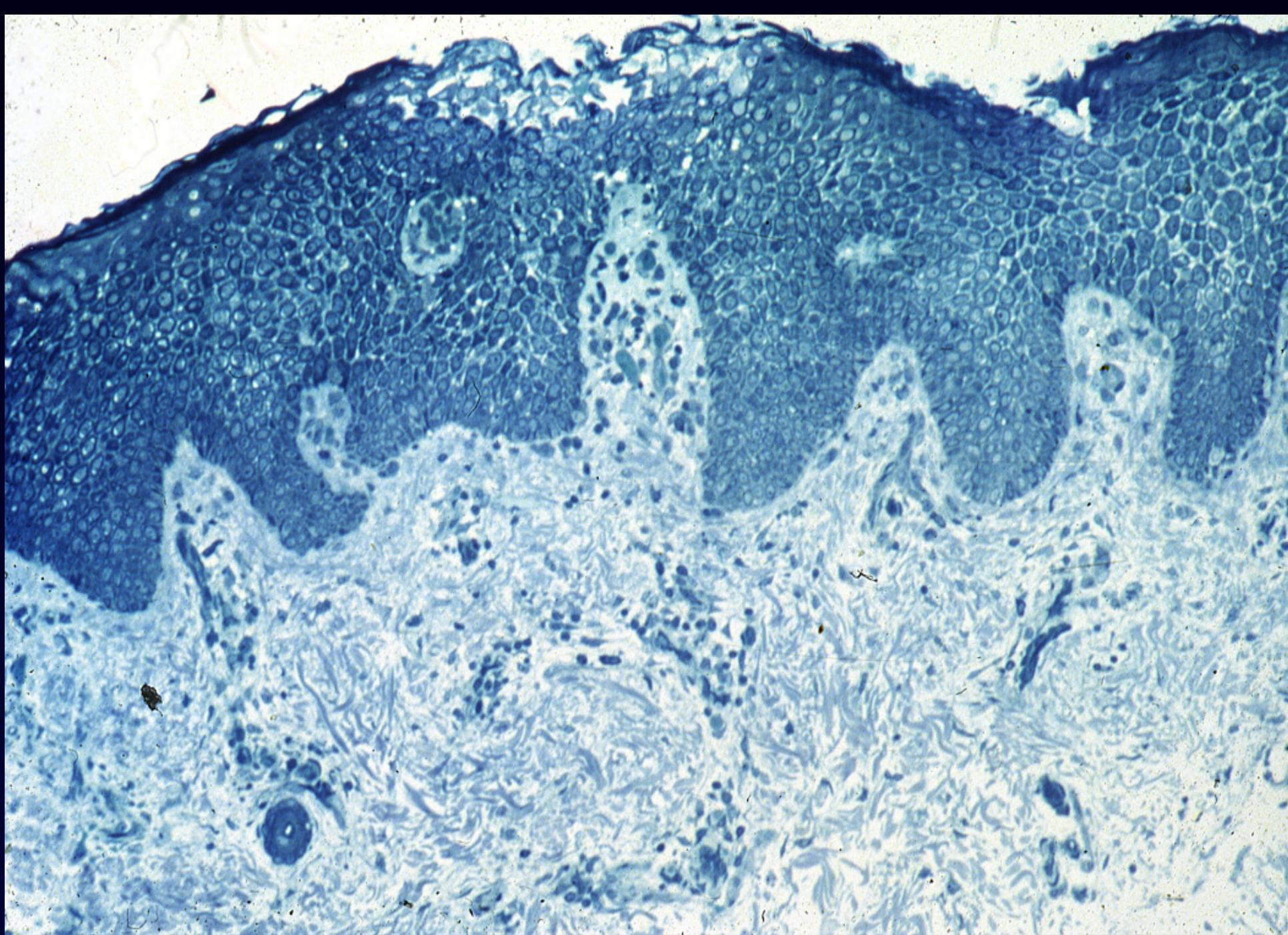
 - Sanofi-Aventis Pharma

What is Eczema?

- “Eczema”, first coined in 1753, derived from the Greek word meaning to “boil over”
- Eczema and dermatitis are used interchangeably
- Atopic Dermatitis – a specific type of eczema
- A chronic skin condition that causes dry, itchy, scaly red (inflamed) skin occurring in infants, children and adults
- Often occurs in families with allergies

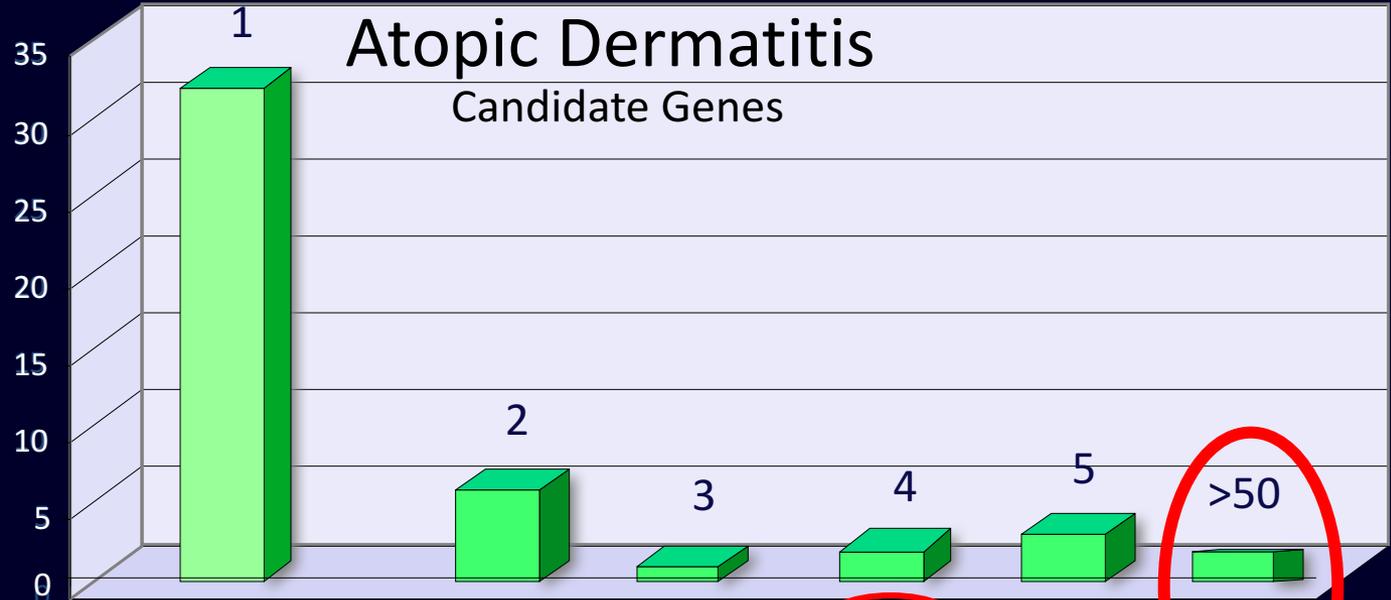
Pathway to Discover Causes of Disease and New Treatments (Leung, JACI 2000)

- **Clinical observations and associations**
- **Understanding mechanisms of disease**
- **Developing treatment interventions**



Atopic Dermatitis

Candidate Genes



- ADAM33 → IL12B
- BDNF → IL12RB1
- BFL1 → IL33
- CARD12 → IRF2
- CARD15 → NAT2
- COL29A1 → PHE11
- CSF2 → SCCE
- CSTA → SMPD2
- CTLA4 → SOCS3
- CYSLTR1 → ST2
- EOTAXIN → TAP2
- FCER1B → TGFB1
- GATA3 → TIM4
- GSTT1 → TLR2
- HNMT → TLR9
- IL10 → TOLLIP
- C11ORF30 → ZGPAT
- ZNF365 → VEGF

- CD14 → RANTES
- DEFB1
- GSTP1
- IL18
- NOD1
- TIM1

- CMA1
- IL13

- IL4
- IL4RA
- SPINK5

- FLG

Skin barrier genes

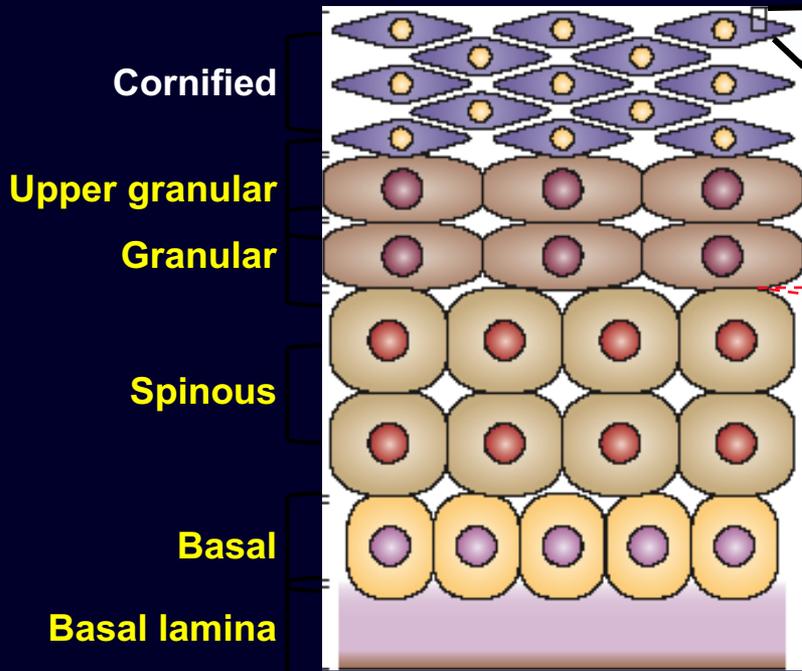
Adaptive Immunity genes

Innate Immunity genes

IBD & AD epithelial genes

Modified from: Barnes K. J Allergy Clin Immunol 2010.

Terminal Differentiation in the Epidermis

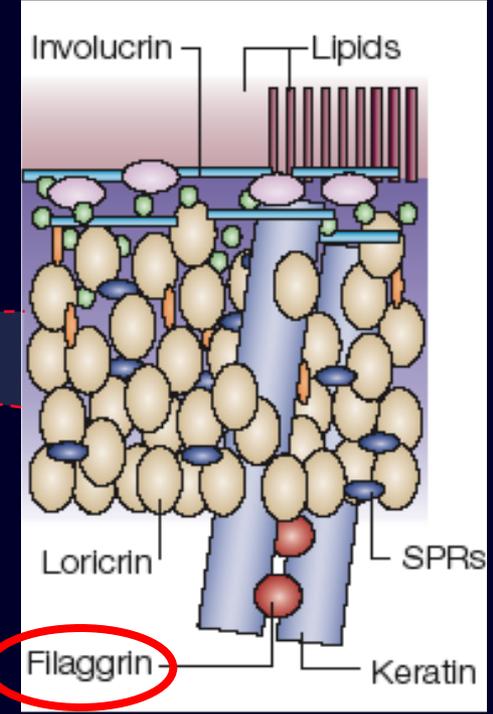


Loricrin, **filaggrin**, involucrin, SPRs, S100A proteins

TG3, keratin-1, -2e, -9, -10, desmoglein-1, desmocollin-1

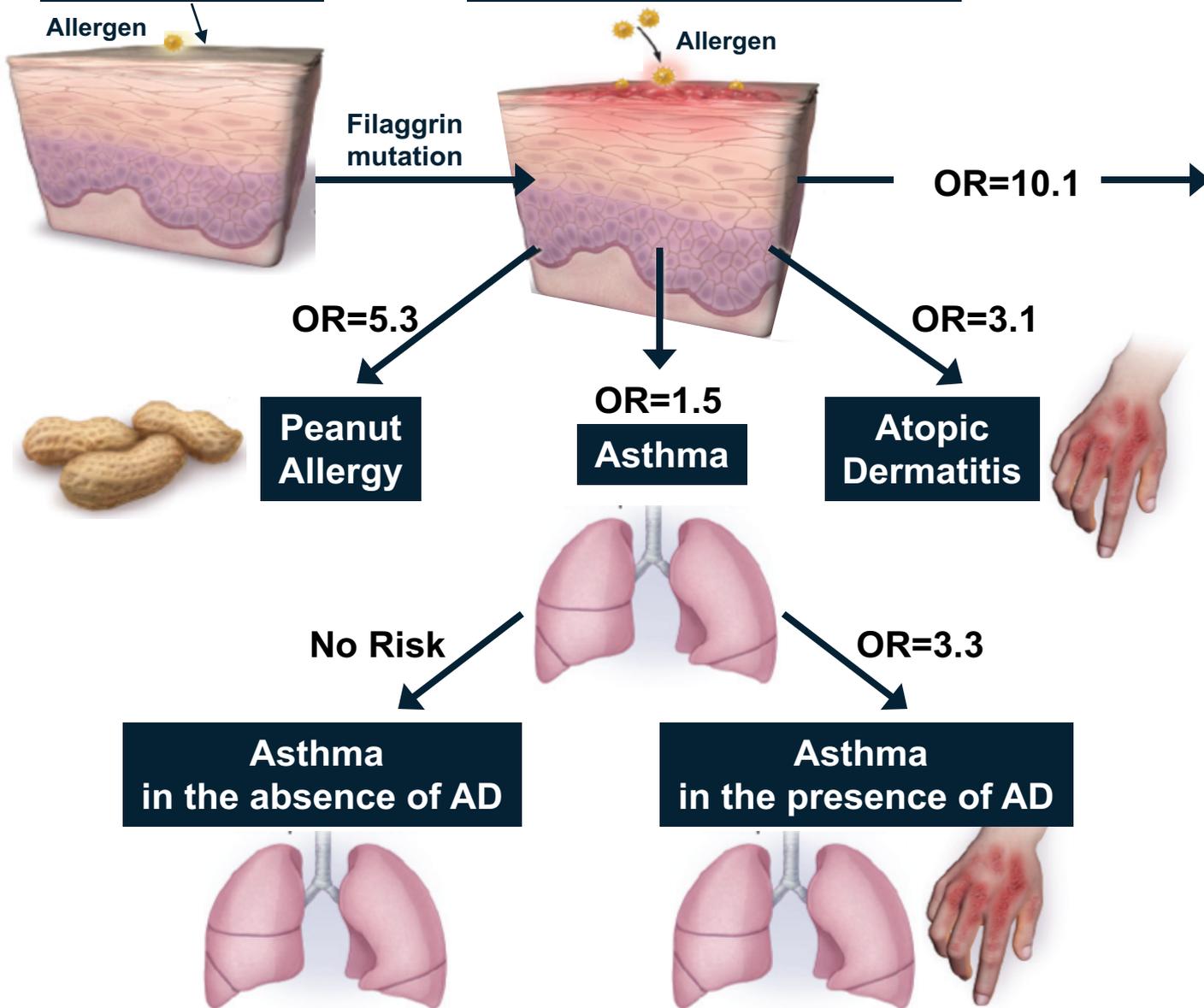
TG2, TG5, desmoglein-1, desmocollin-1

Keratin-5, -14, TG2, BPAG1
BPAG2/collagen-17
✓ 6 ~~3~~ 4 integrin, laminin-5



Healthy Skin

Filaggrin-deficient Skin



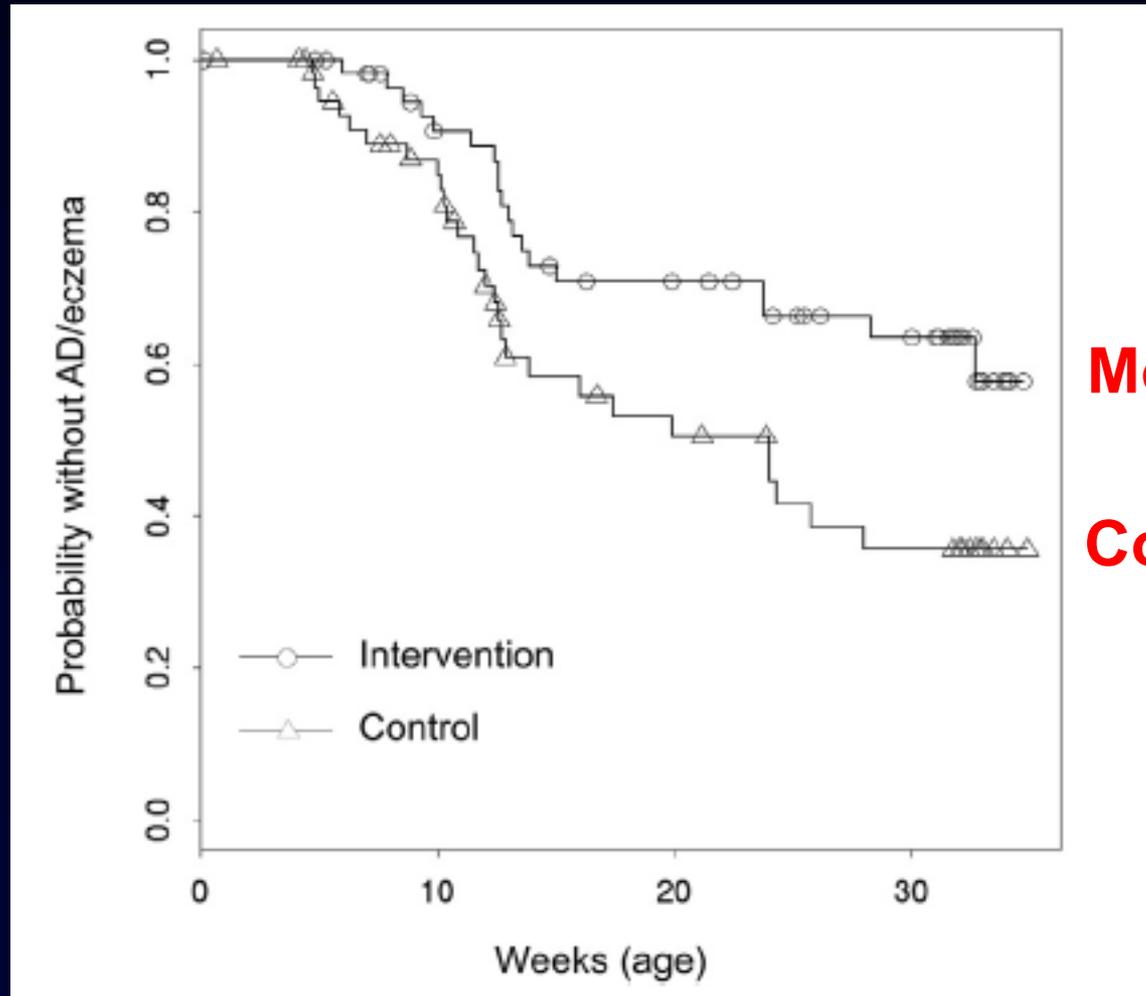
From Irvine, McLean, Leung. N Engl J Med 2011.

Skin Barrier Dysfunction Measured by Transepidermal Water Loss at 2 Days and 2 Months Predates and Predicts Atopic Dermatitis at 1 Year

**Kelleher M, Dunn-Galvin A,
Hourihane JO, Murray D,
Campbell LE, McLean WHI,
Irvin AD**

J Allergy Clin Immunol 2015;135:930-935

Application of Moisturizer to Neonates Prevents Development of Atopic Dermatitis



Moisturizer

Control

Ichthyosis Vulgaris is Often Not Associated with AD

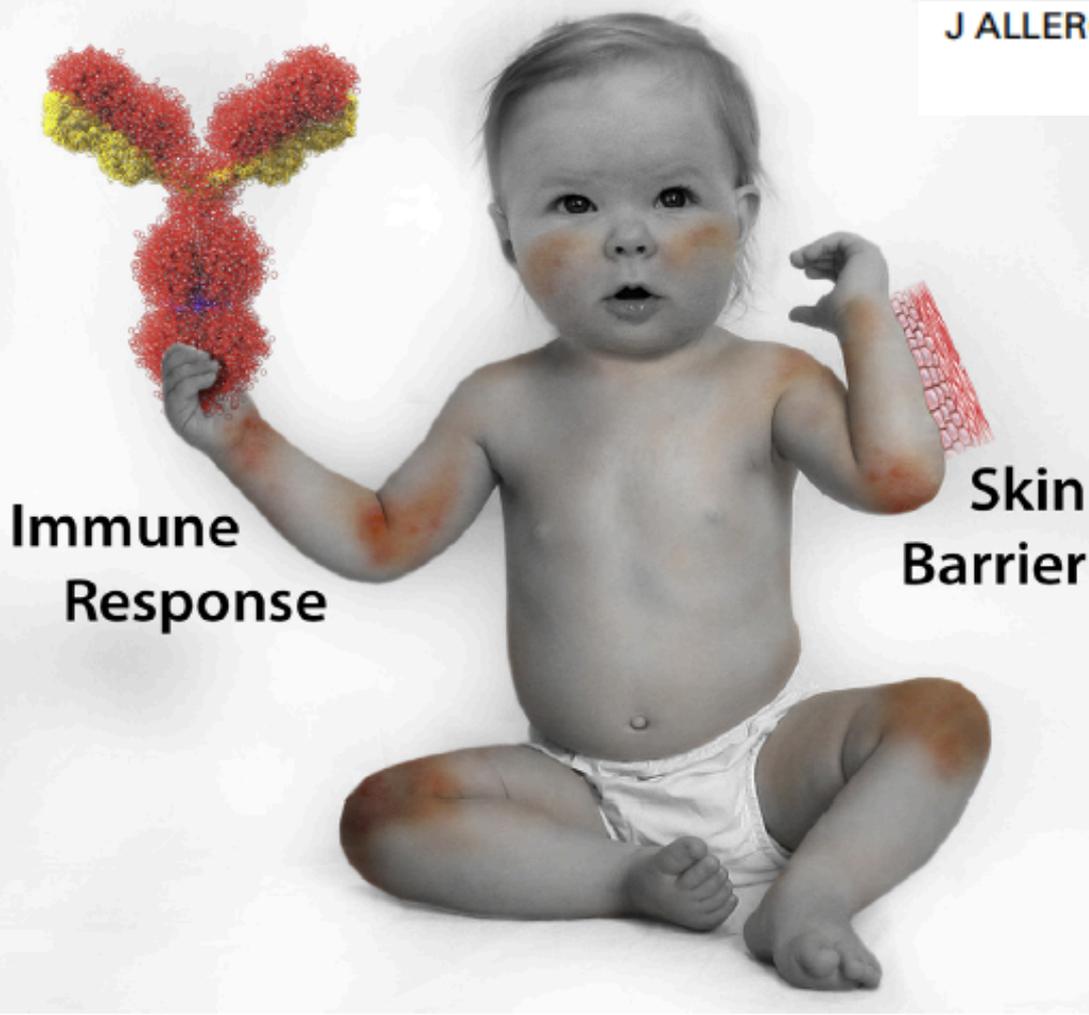


(*Nature Genetics* 38, 337 - 342 (2006))

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

Donald Y. M. Leung, MD, PhD,^a and Emma Guttman-Yassky, MD, PhD^b *Denver, Colo, and New York, NY*

J ALLERGY CLIN IMMUNOL
OCTOBER 2014

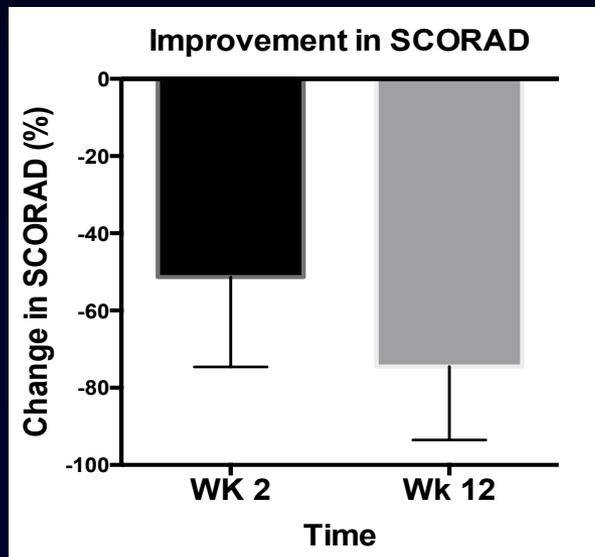


Clinical Disease Reversal with CsA

Baseline

Week 2

Week 12

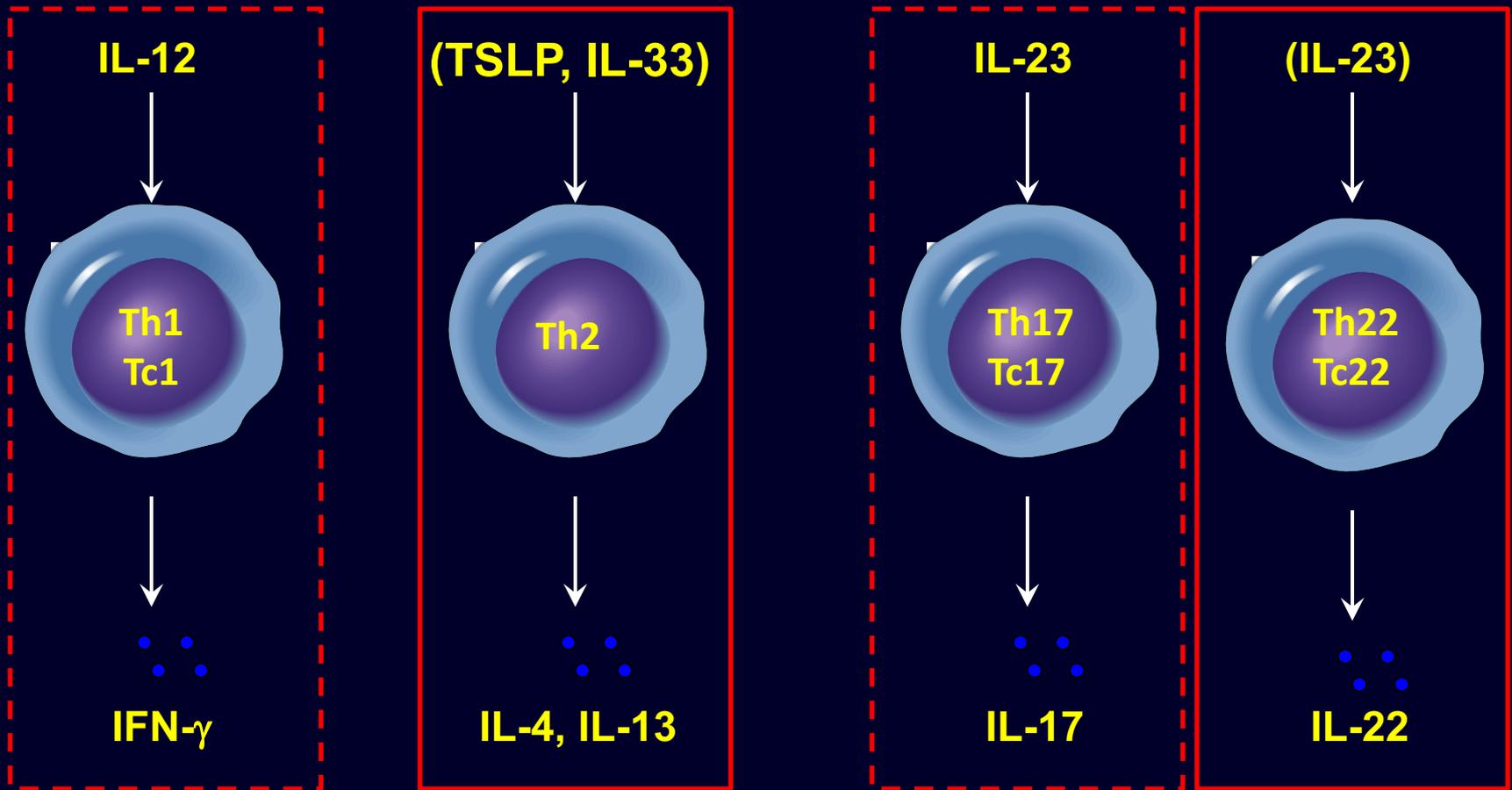


17/19 patients were responders
(achieved SCORAD 50)

Mean reduction
in SCORAD
51% at week 2
72% at week 12

Khattri S, et al. J Allergy Clin Immunol 2014;134:764

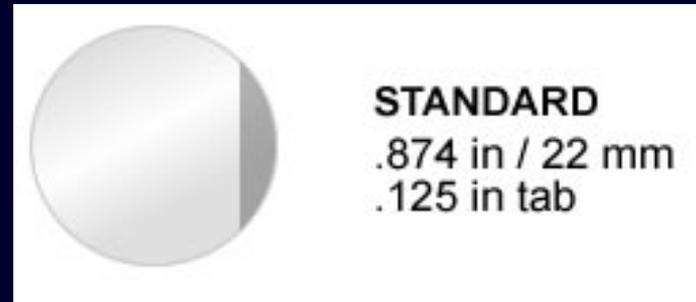
Major Subsets of Effector T-cells in Humans



Atopic Dermatitis

Epidermal Profiling by Skin Tape Stripping

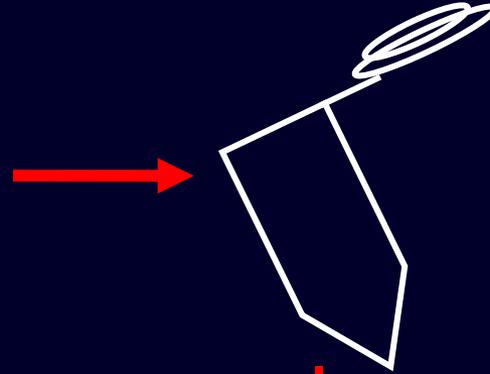
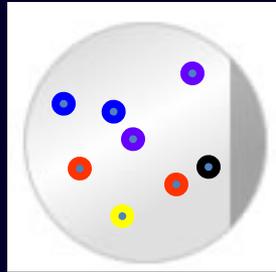
- Removes upper layers of the epidermis
- Noninvasive skin sampling method
- Scarless, pain free method: children



**Forearm
after
20 tapings
at adjacent
sites**

Workflow for Protein Identification

Proteins on
skin tape



↓
Peptides

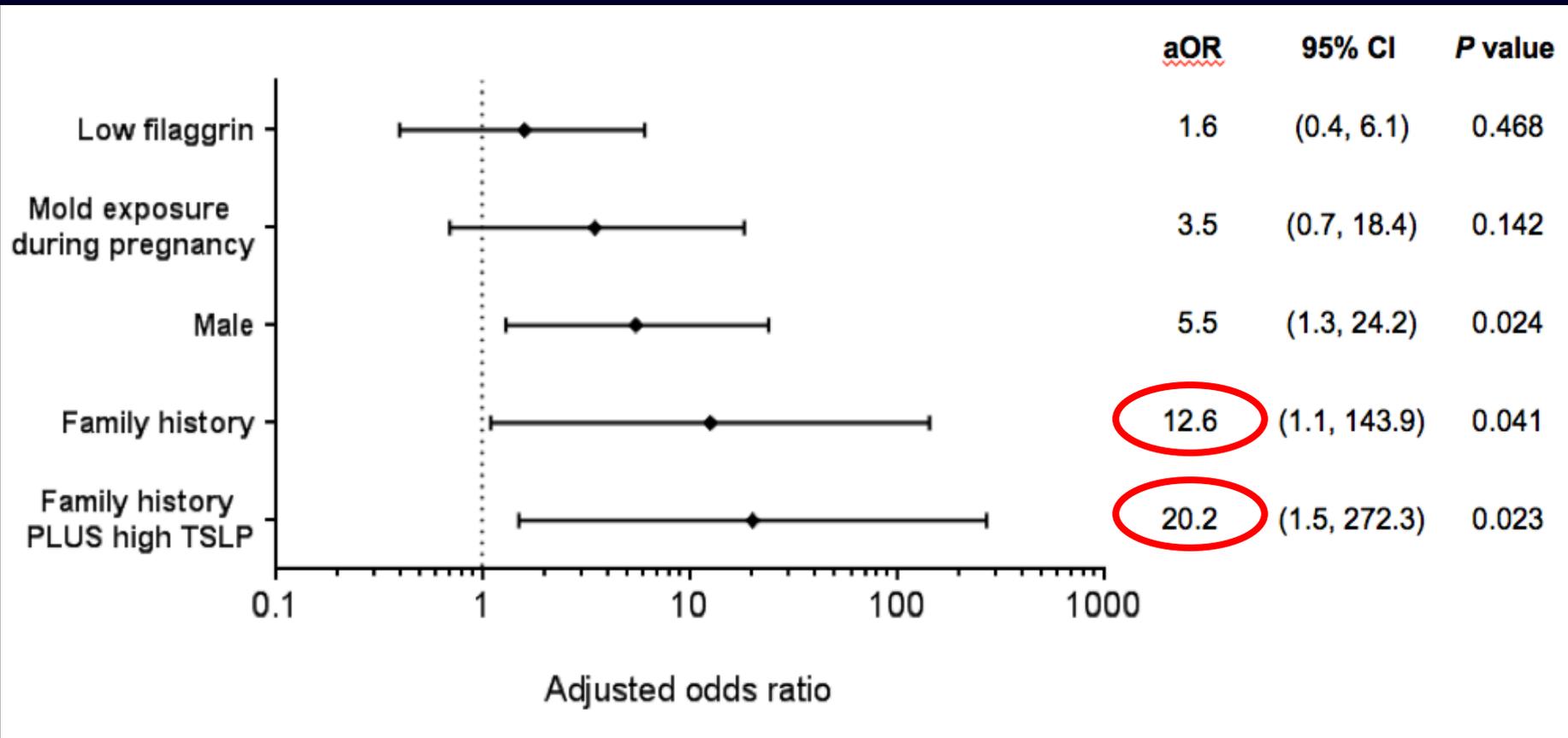
↓
Mass Spectrometry Spectra

↓
Search Engine

↓
153 Proteins Identified

↓
Data Analysis

Increased TSLP Increases Odds Ratio (OR) of Developing Atopic Dermatitis*



*Ahn K, et al. J Allergy Clin Immunol 2016.

Control

K5-TSLP

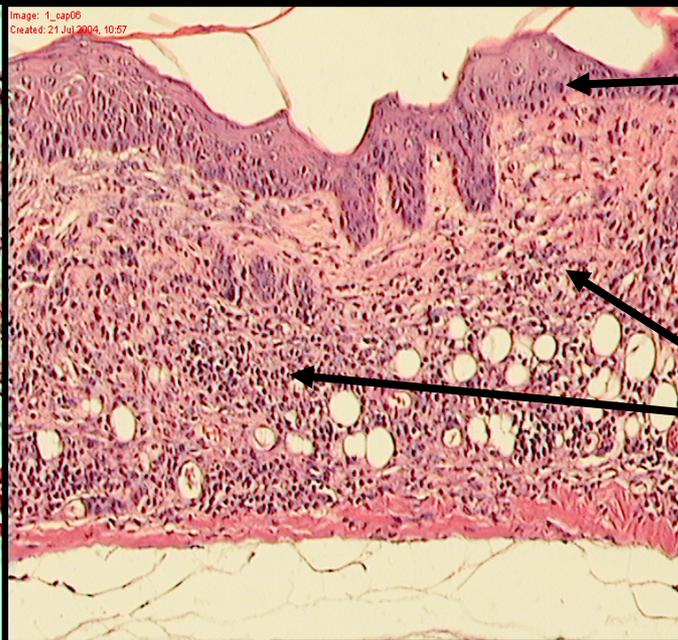
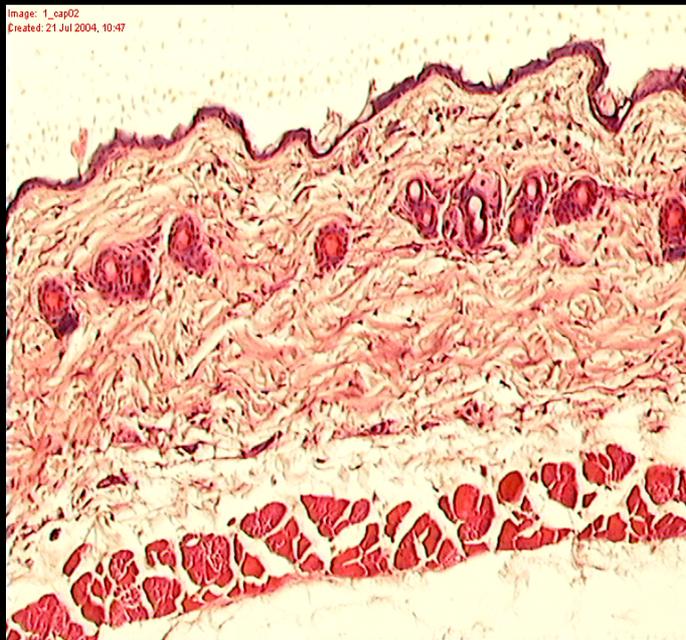


K5-TSLP Mice

Yoo J, et al. J Exp Med 2005;202:541-9

Control

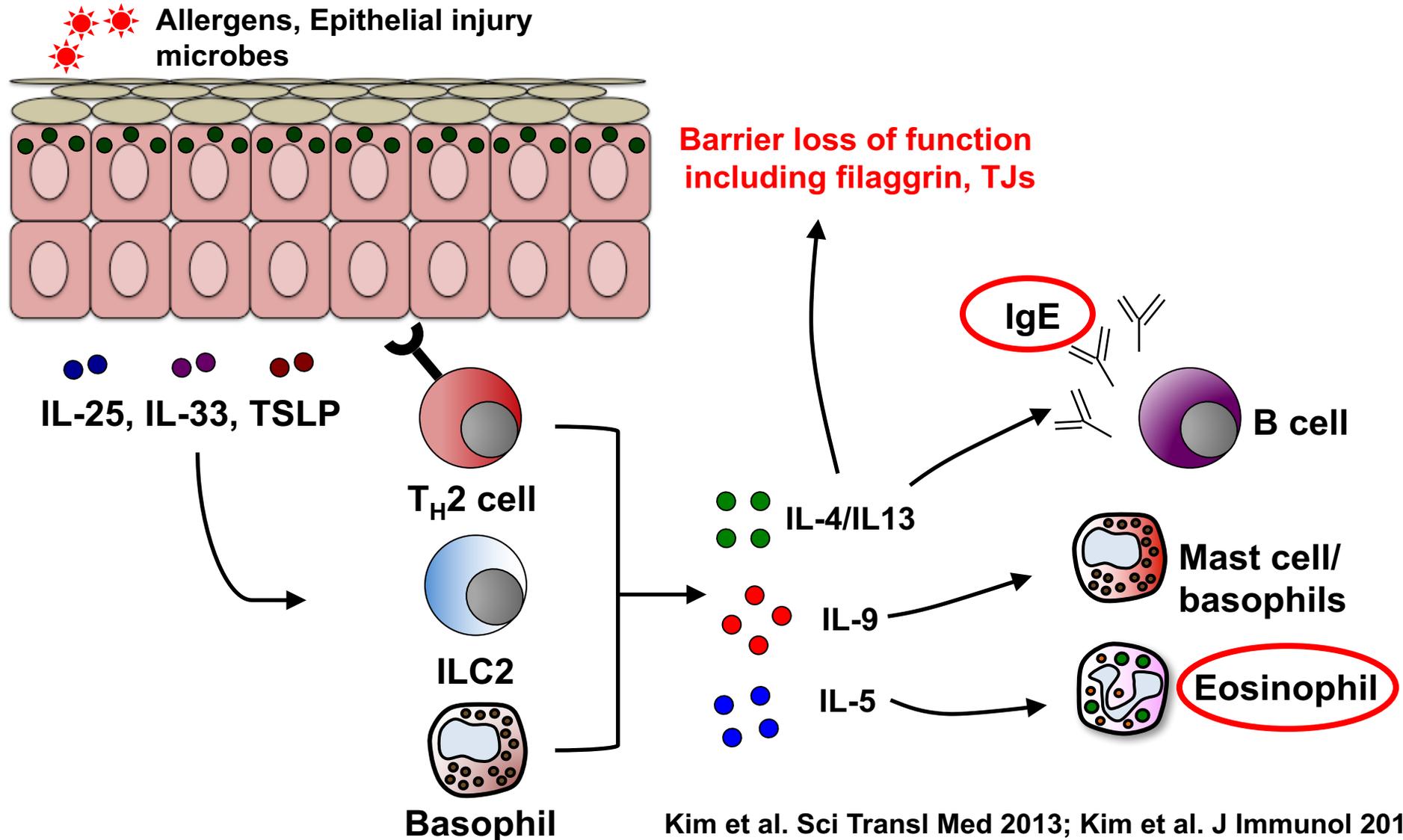
K5-TSLP



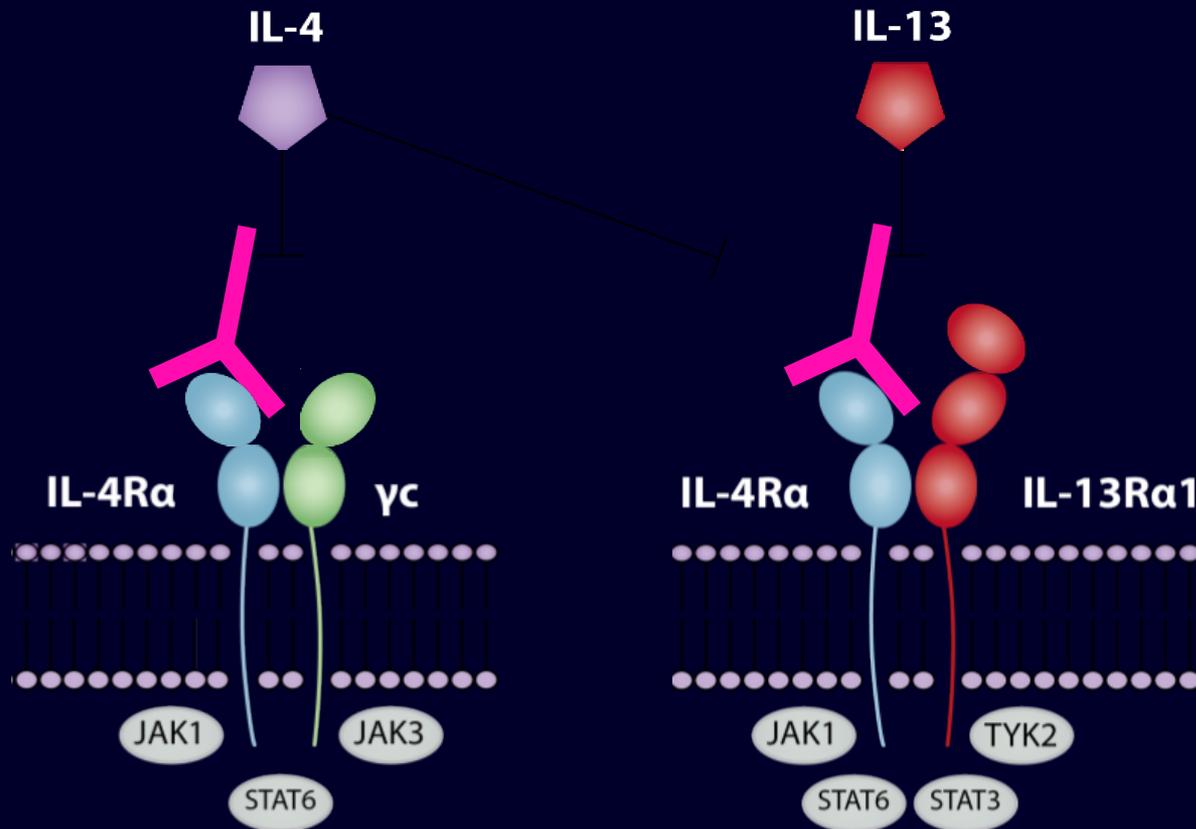
Acanthosis

Dermal infiltrate

The Current Paradigm of Allergic Disease Pathogenesis



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



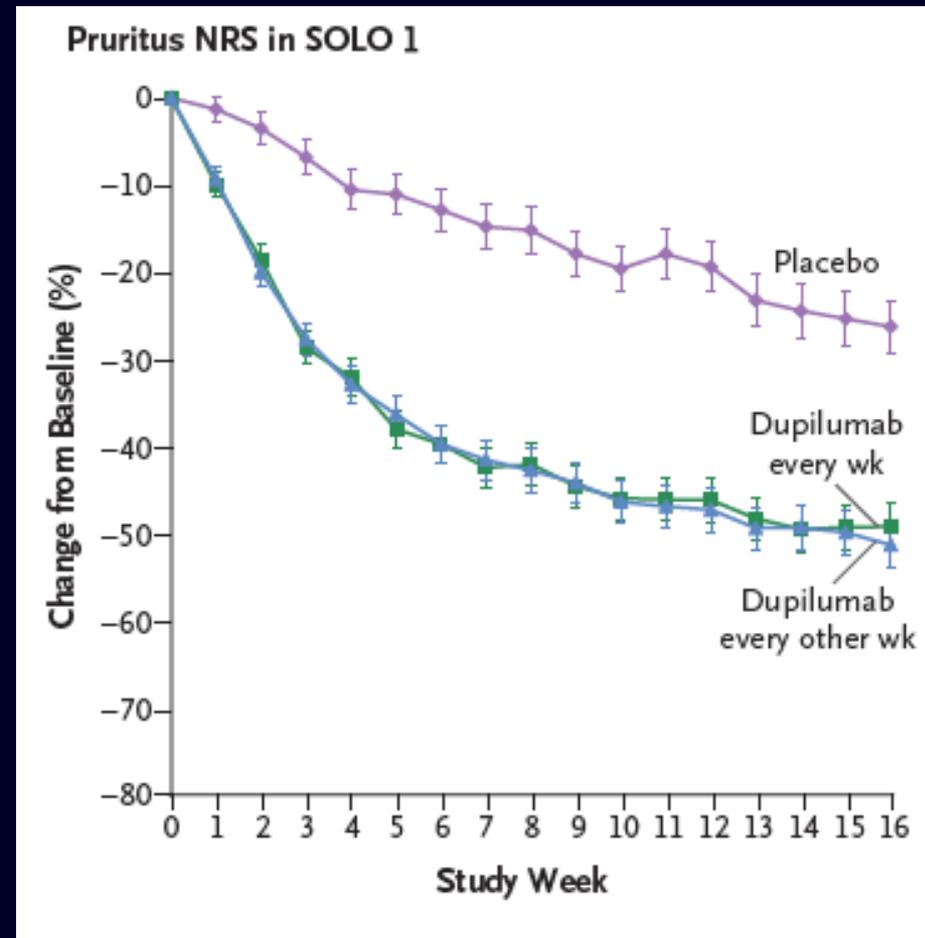
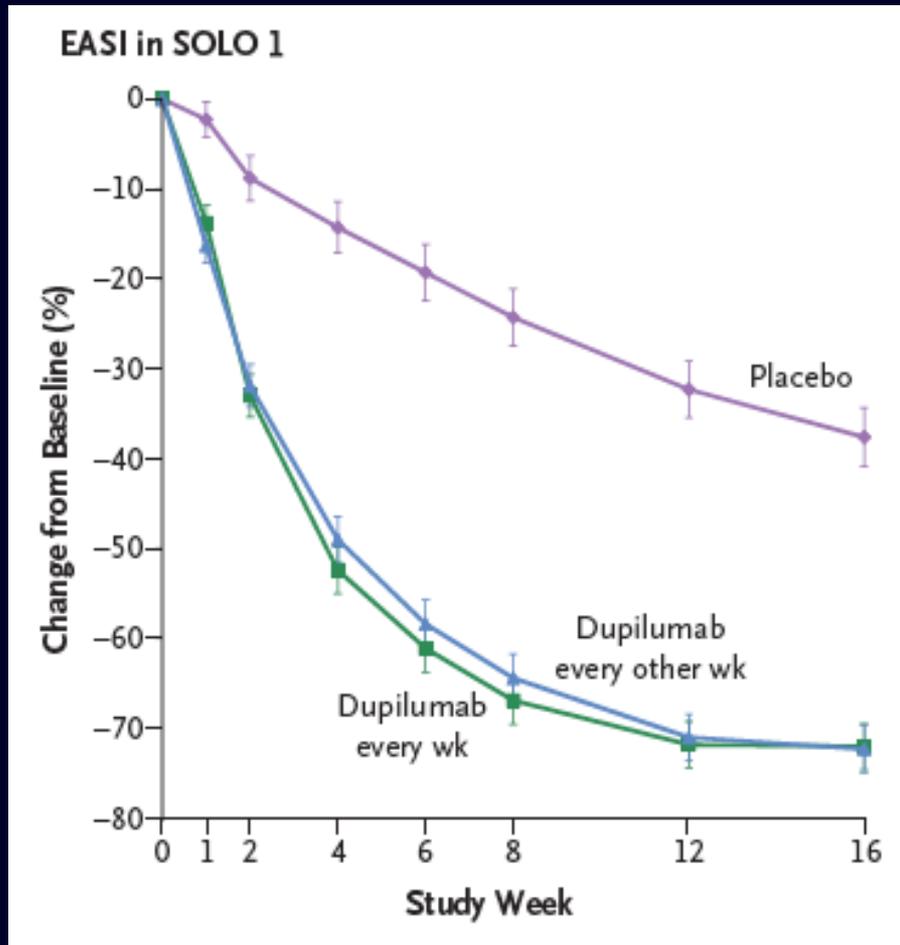
Type I Receptor

IgE responses, Th2 –mediated inflammation, reduced antimicrobial peptides

Type II Receptor

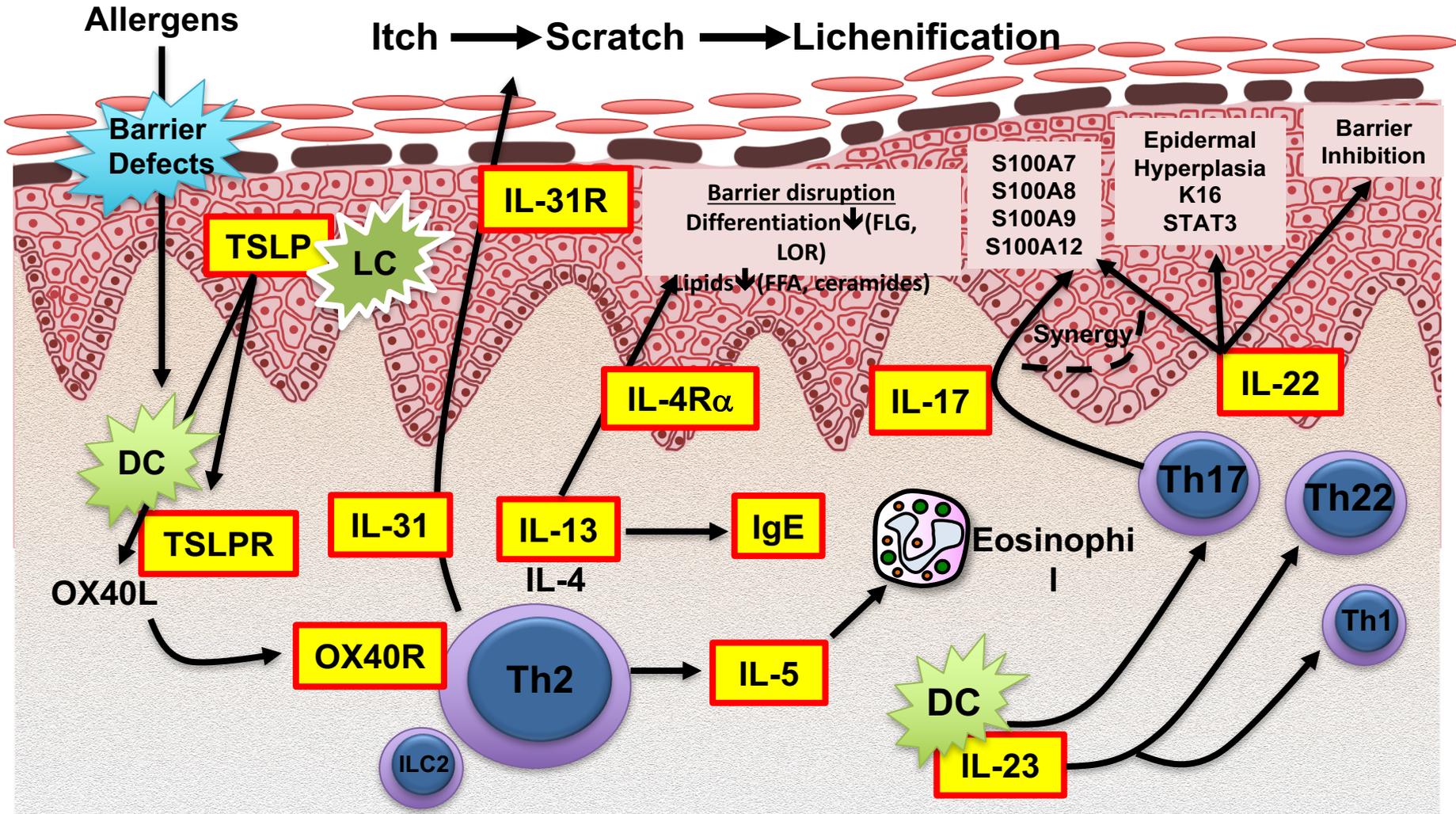
Reduced skin barrier function, increased Th2 responses

Dupilumab Treatment (IL-4/IL-13 blockade) in Moderate-To-Severe AD



Simpson EL, et al. N Engl J Med. October 1, 2016.

Immune Pathways in Atopic Dermatitis

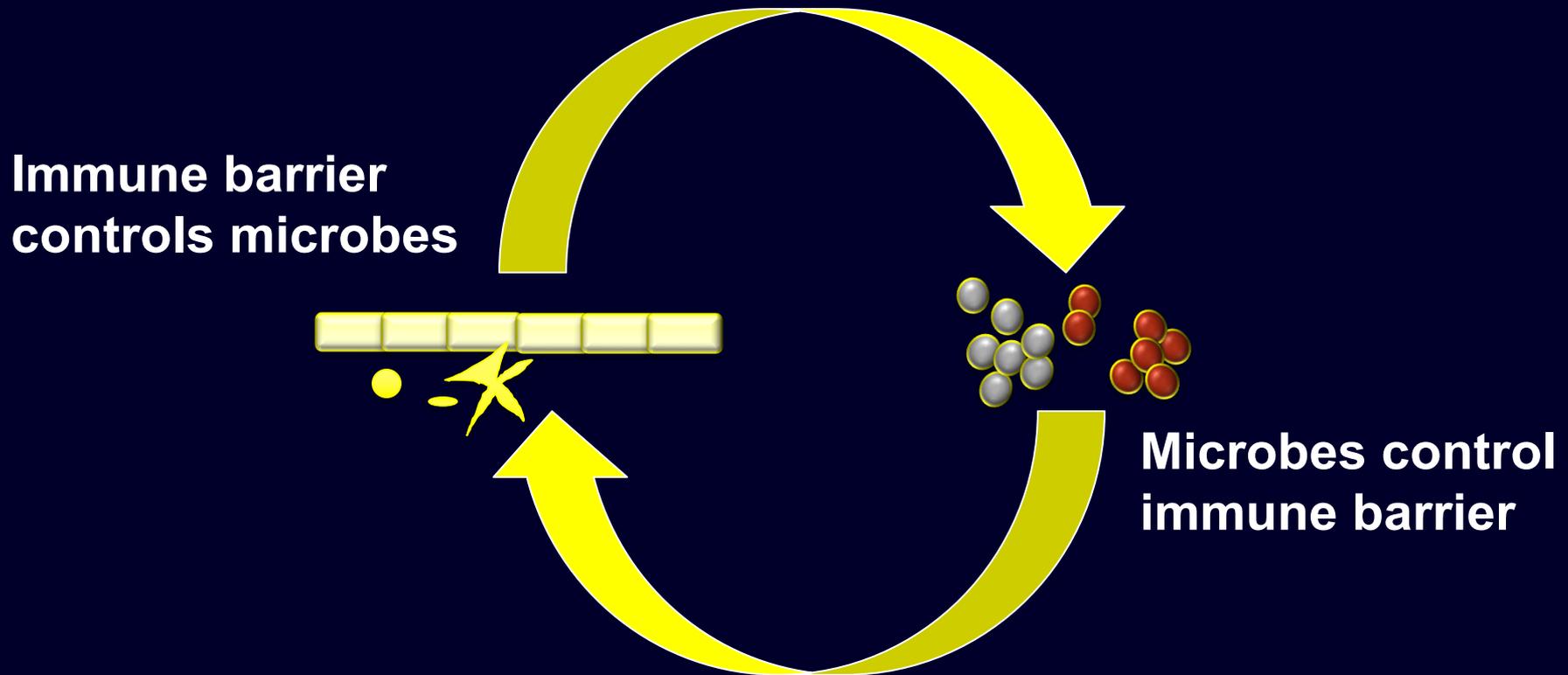


Type 2 cytokines including IL-33

Skin Barrier Abnormalities: BEYOND FILAGGRIN MUTATIONS

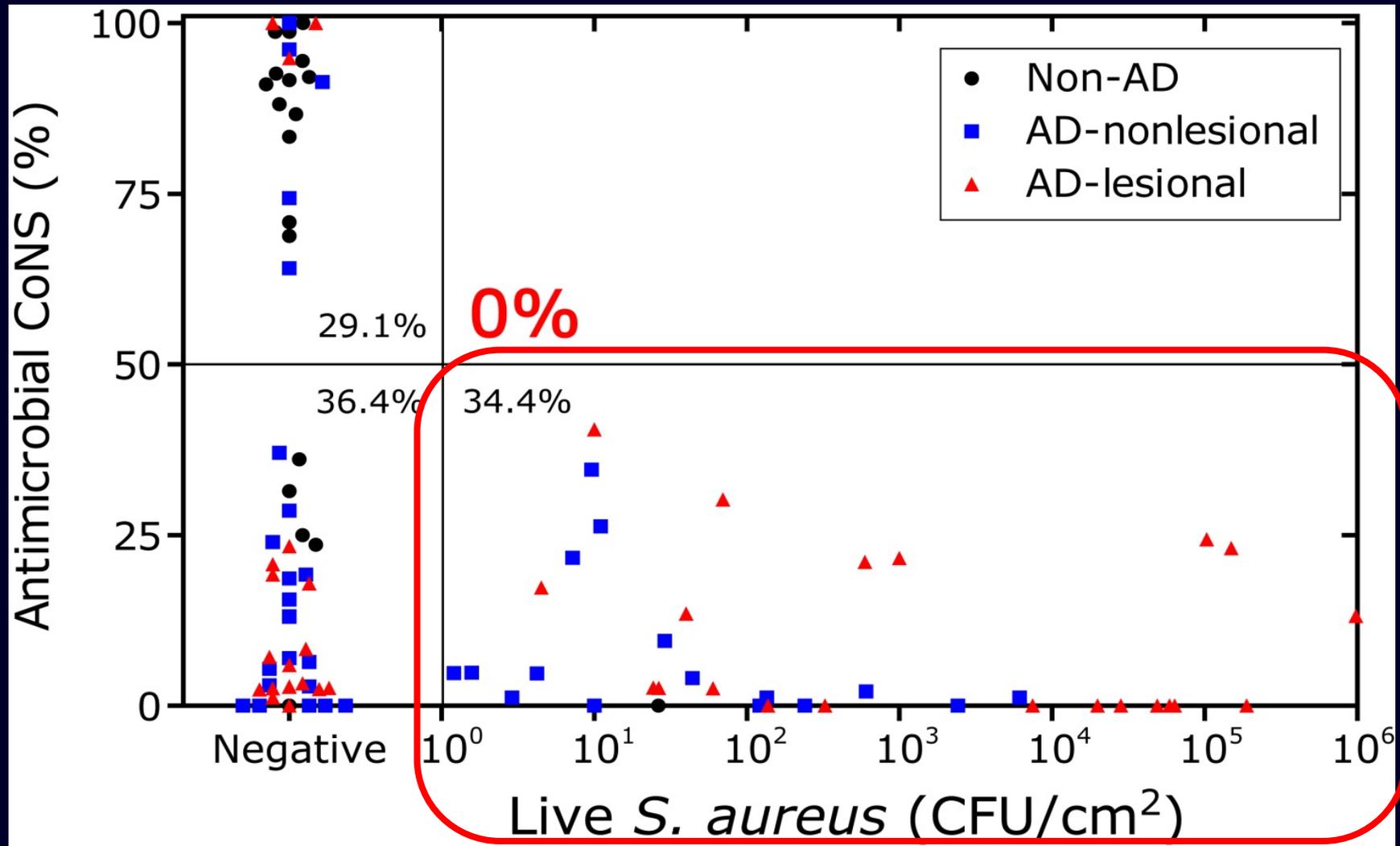
- **Immune activation and inflammation, especially type 2 (IL-4, IL-13) responses reduce epidermal differentiation**
- **Abnormalities in lipid synthesis and metabolism**
- **Microbial dysbiosis, e.g. *S. aureus* colonization and reduced commensal *staphylococci***

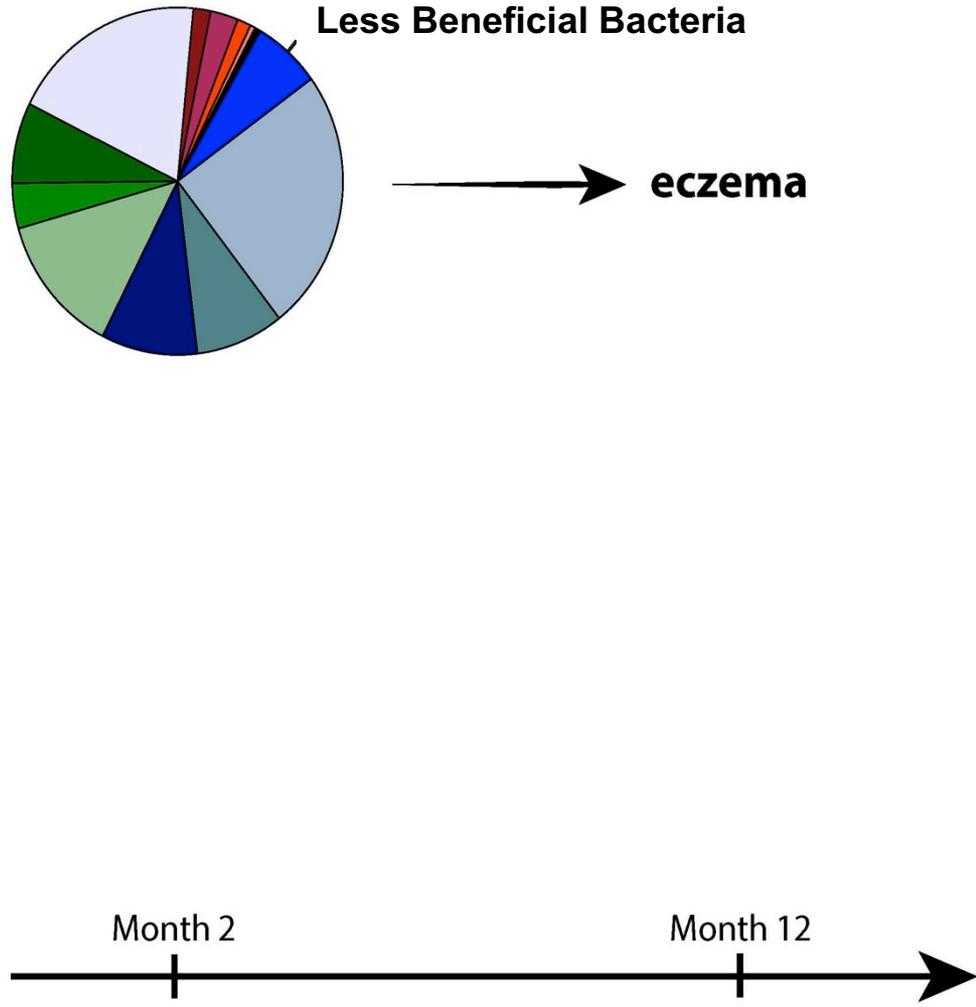
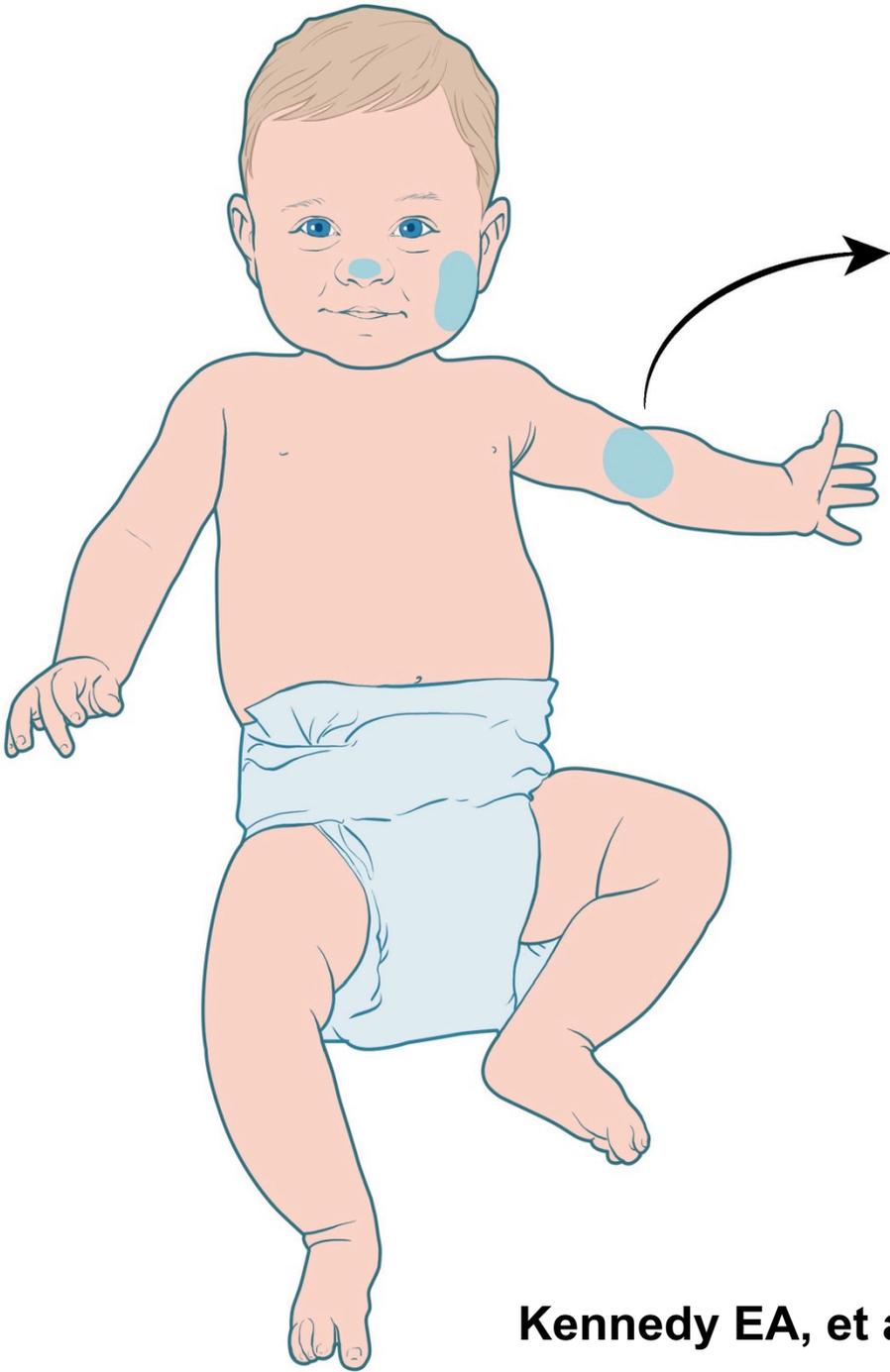
The Skin Immune and Physical Barriers Closely Interact with Surface Microbes



Hypothesis: Restoring this relationship to normal will improve Atopic Dermatitis

Coagulase-negative *Staphylococcus* (CoNS) are Protective against *S. aureus* Colonization





Kennedy EA, et al. J Allergy Clin Immunol 2017;139:166-72

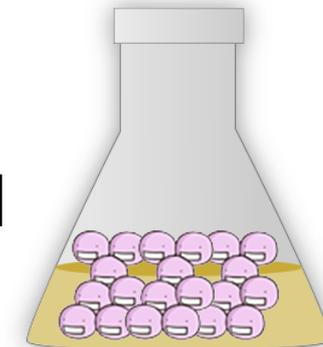
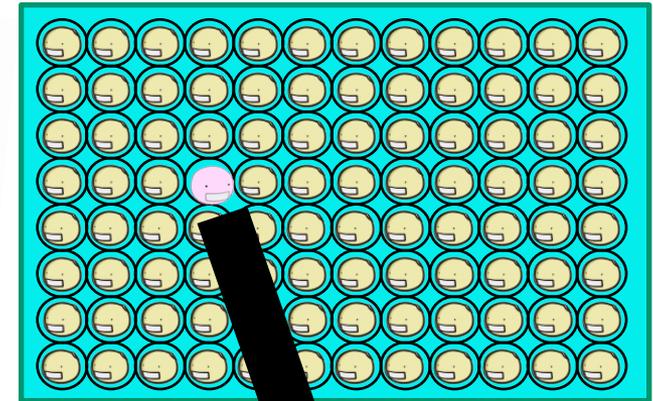
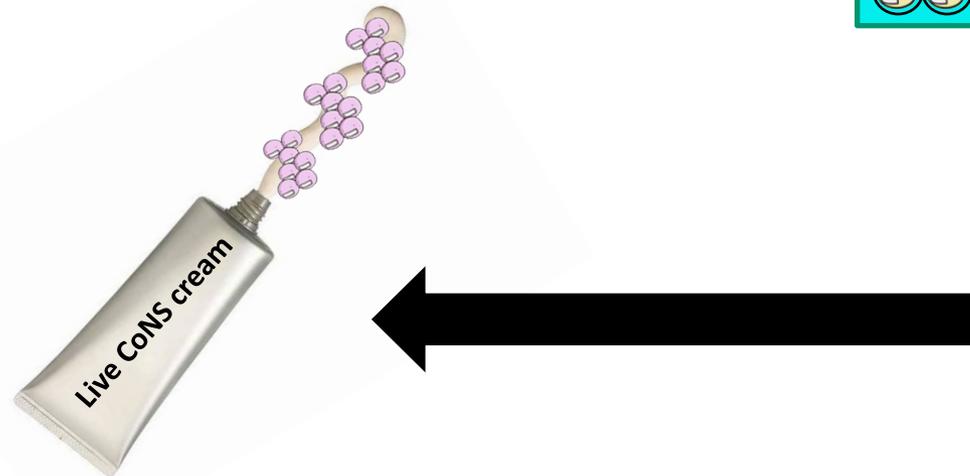
Autologous Microbiome Transplant (AMT)

AD Patients
(*S. aureus* positive)

Nonlesional

Screening for *anti-S. aureus*
CoNS

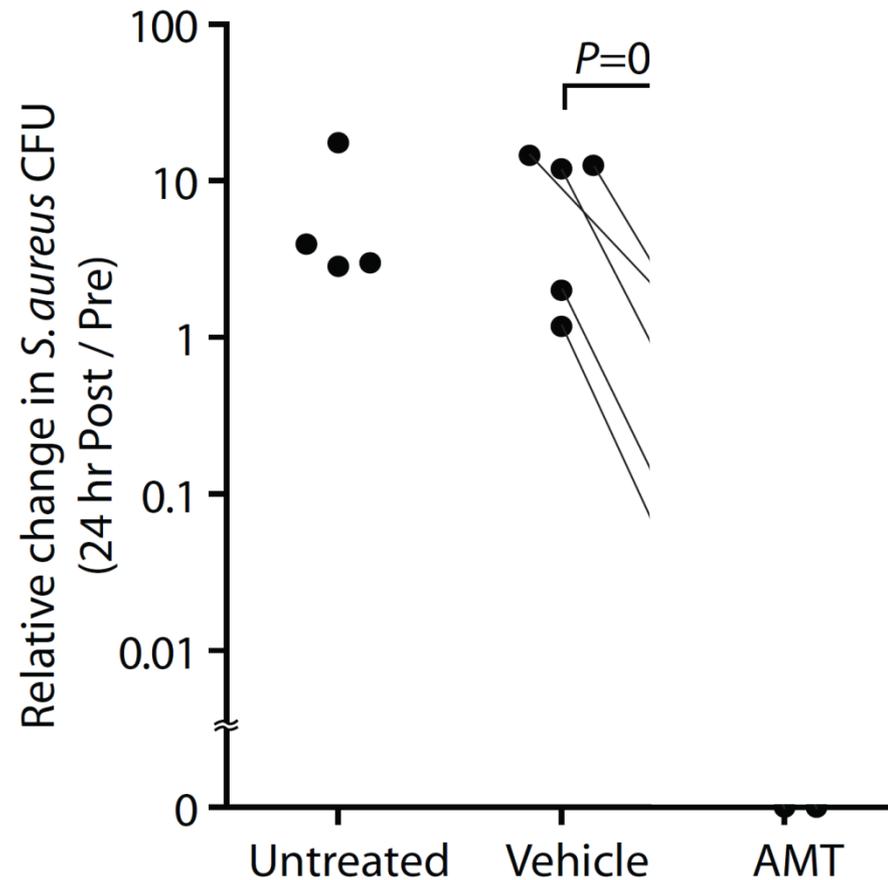
Live *S. aureus* count
Before and after transplant
(AMT vs Placebo)



Expand active
CoNS

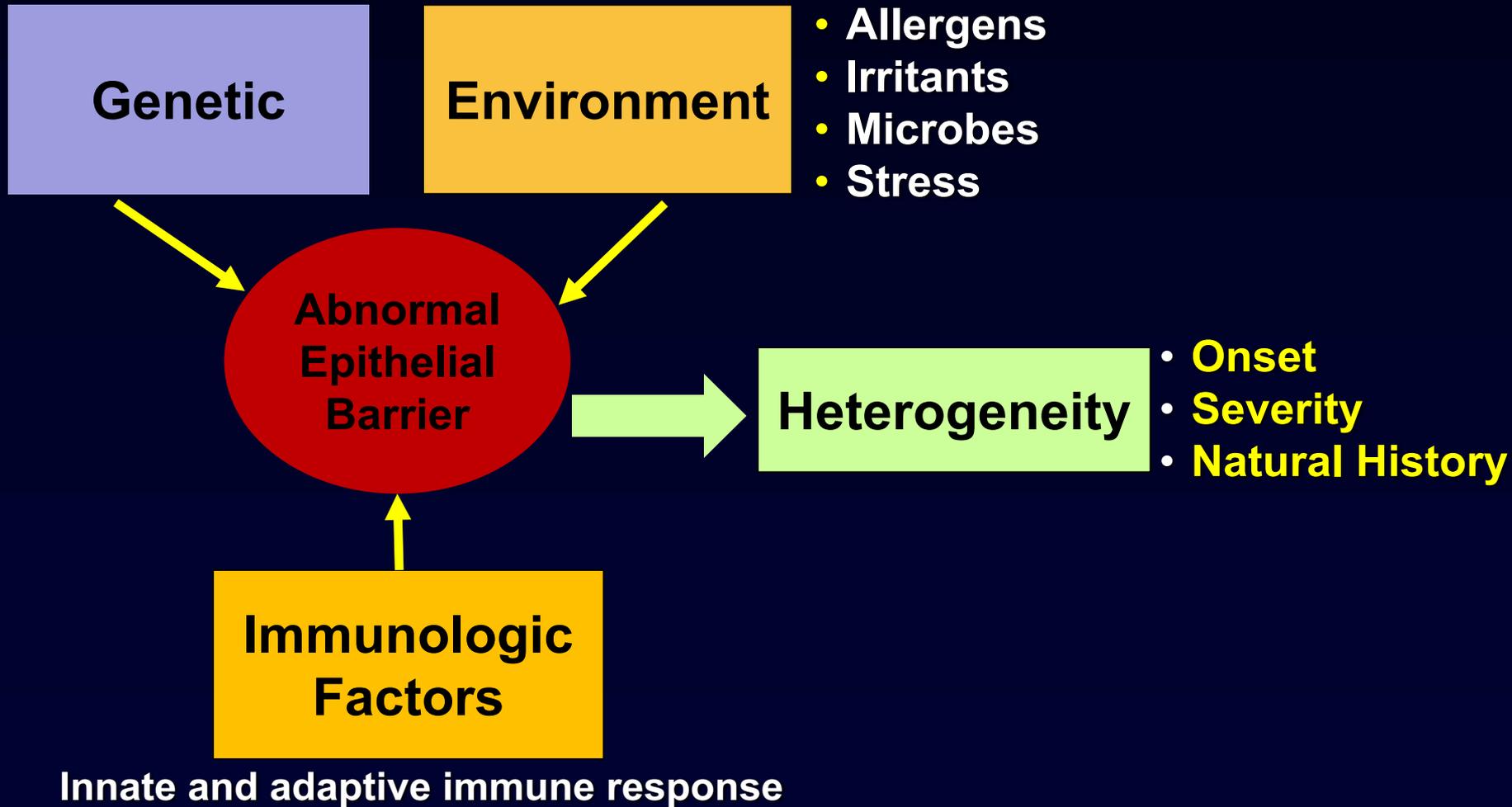
AMT Treatment Decreased *S. aureus* Survival in AD Skin

AD Lesional Skin



Nakatsuji and Gallo, et al. *Sci Transl Med* 2017.

Why do people get Atopic Dermatitis?



Future Directions in Atopic Dermatitis

- **Prevention of AD via skin barrier protection and early use of topical anti-inflammatories**
- **Targeted microbiome transplantation**
- **Intervention in polarized immune pathways (including IL-4/IL-13, IL-22, IL-17, IL-23, IL-33)**
- **Develop non-invasive techniques to assess skin immune response, protein, and lipid content for Precision Medicine approach**

Acknowledgements

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