# CONSIDERATIONS FOR FUTURE TREATMENT OF INFLAMMATORY SKIN DISEASES

## *Immune Regulation, Cutaneous Tolerance, and T-cell Plasticity*

Supported by educational grants from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC. and Novartis Pharmaceuticals Corporation.

**NOVEMBER 18, 2016**

**4:00PM – 5:30PM**

New York Academy of Medicine
NYC – Hosack Hall

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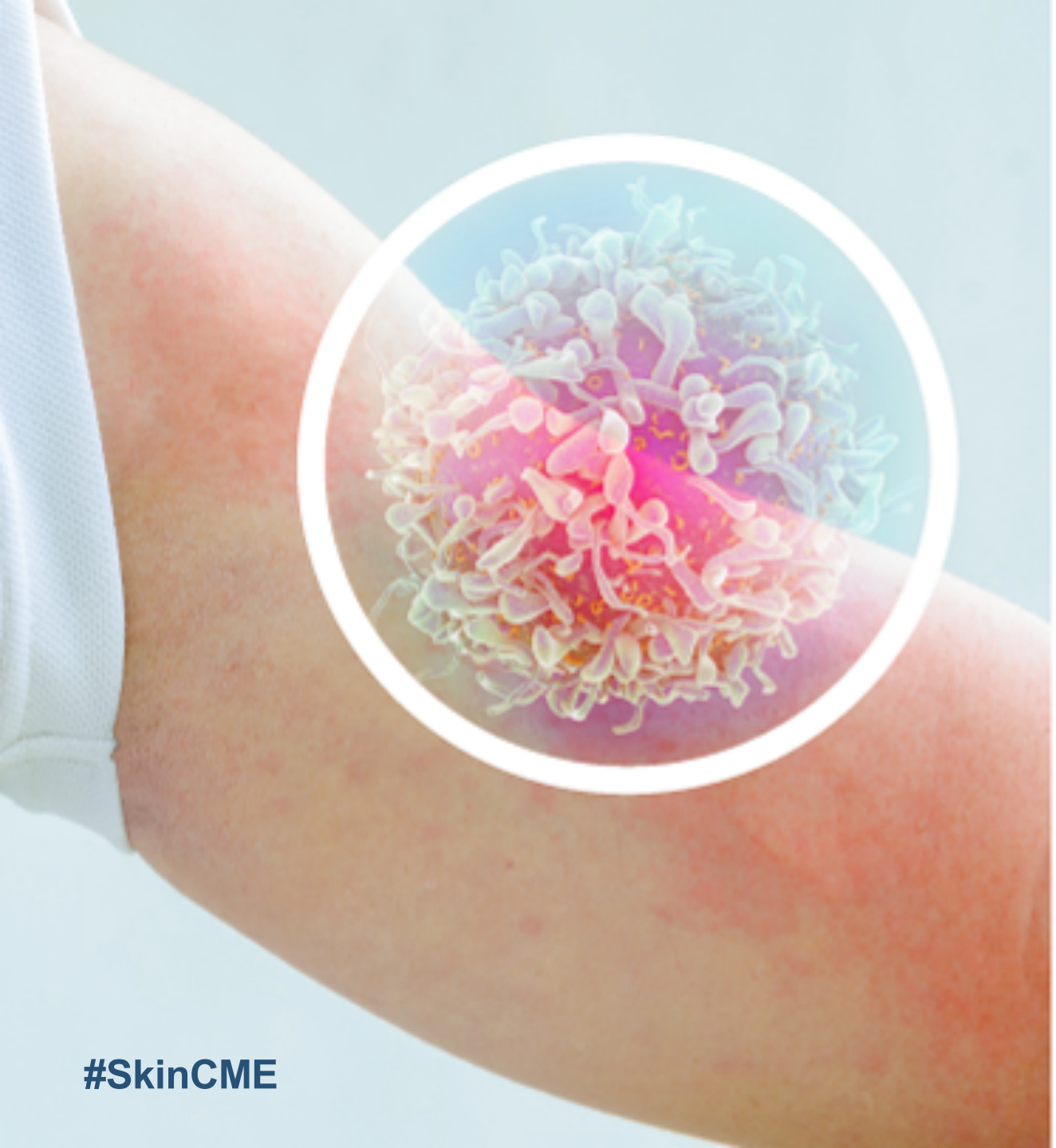


# James G. Krueger, MD, PhD

D. Martin Carter Professor in Clinical Investigation
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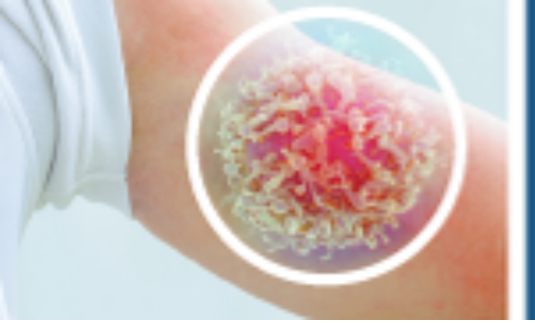
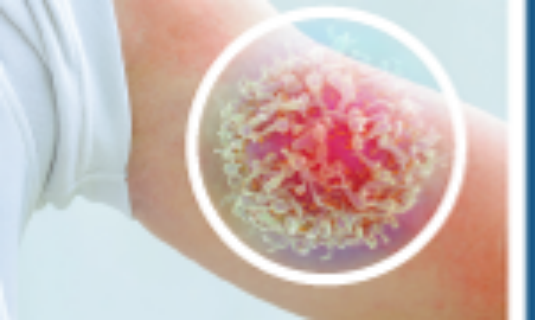
New York, NY



# James G. Krueger, MD, PhD
## Disclosures

- ***Research/Grants:*** Amgen Inc.; Boehringer Ingelheim; Bristol-Myers Squibb Company; Dermira, Inc.; Innovaderm Research Inc.; Janssen Pharmaceuticals, Inc.; Kadmon Corporation, LLC; Kyowa Hakko Kirini Co., Ltd.; LEO Pharma Inc.; Novartis; PAREXEL International Corporation; Pfizer Inc.; Regeneron Pharmaceuticals, Inc.; Vitae Pharmaceuticals, Inc.
- ***Consultant:*** AbbVie Inc.; Baxter; Biogen Idec; Boehringer Ingelheim; Bristol-Myers Squibb Company; Demira, Inc.; Janssen Pharmaceuticals, Inc.; Kadman Corporation, LLC; Kineta, Inc.; Eli Lilly and Company, Merck & Co., Inc.; Novartis; Pfizer Inc.; sanofi-aventis U.S. LLC; EMD Serono, Inc.; and XenoPort, Inc.



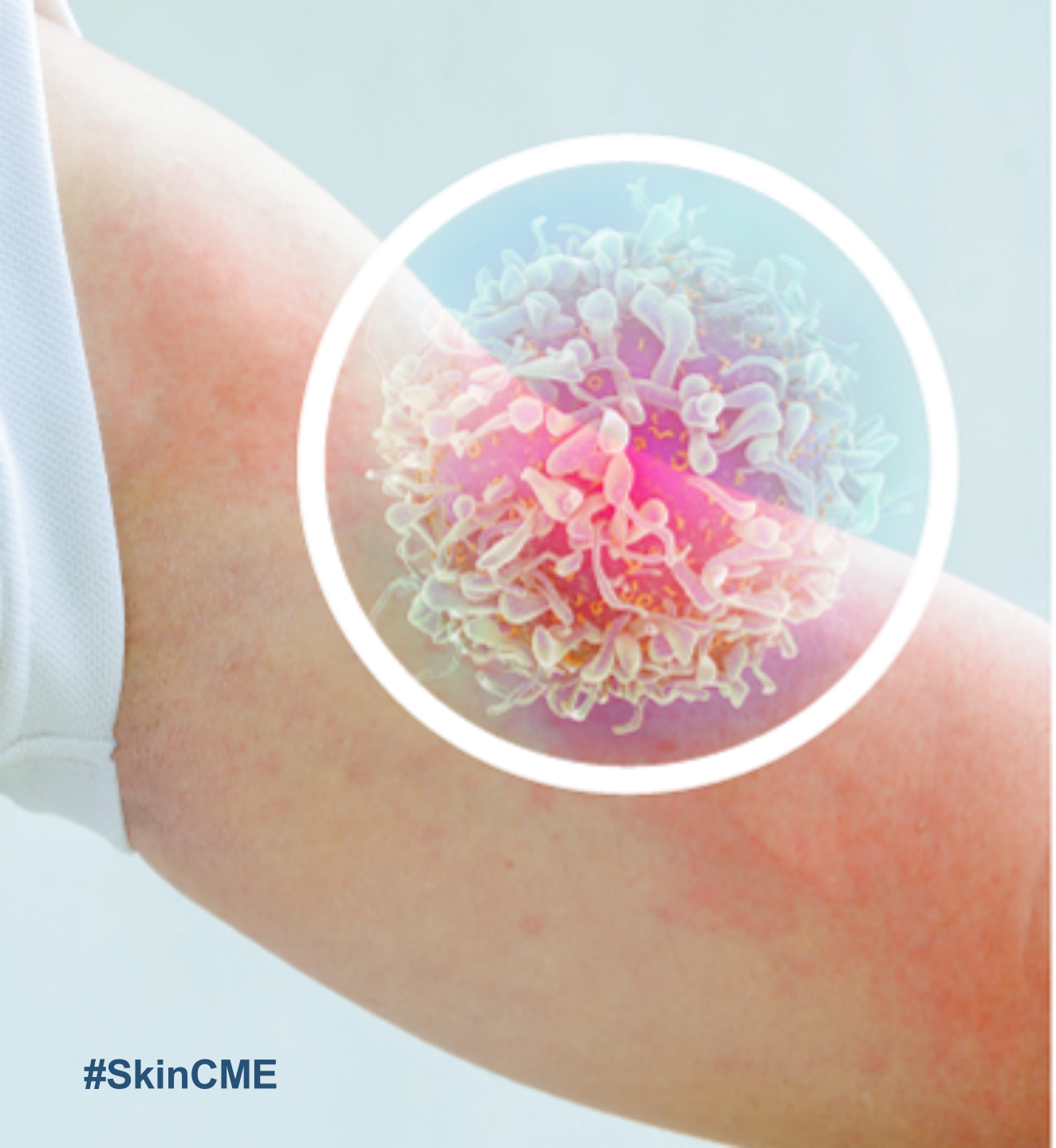
# Agenda

**4:00PM:** Introduction: Tolerance, Immune Regulation, and Disease Interception

**4:10PM:** Tregs, Immune Regulation in the Skin, and Tolerance

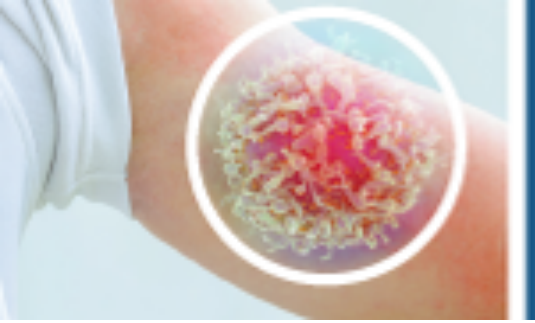
**4:40PM:** T-cell Plasticity: A Focus on Th-17 T-cells

**5:10PM:** Q&A




# Regulating Immune Responses in Skin

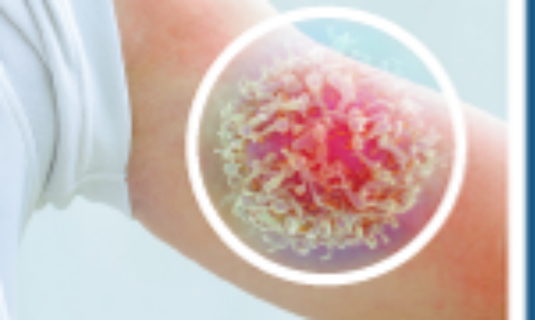
**Michael D. Rosenblum, MD, PhD**
Assistant Professor
Department of Dermatology
University of California
San Francisco
San Francisco, CA



# Michael D. Rosenblum, MD, PhD

## Disclosures

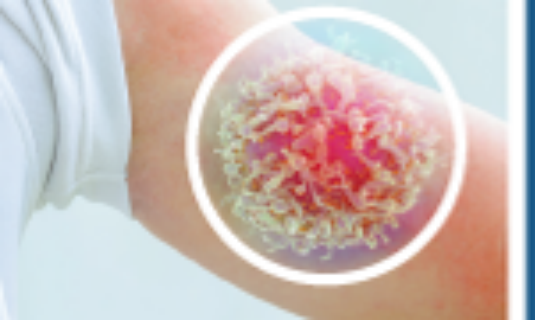
- ***Consultant:*** AbbVie Inc.
- ***Stock Shareholder (directly purchased):*** Delinia, Inc.



# Audience Response

**When compared to normal skin, Tregs in psoriatic skin are:**

A. Increased
B. Decreased
C. No change



# Audience Response

**Tregs in psoriatic skin produce increased amounts of:**

A. IFN-gamma
B. IL-22
C. IL-17
D. IL-2

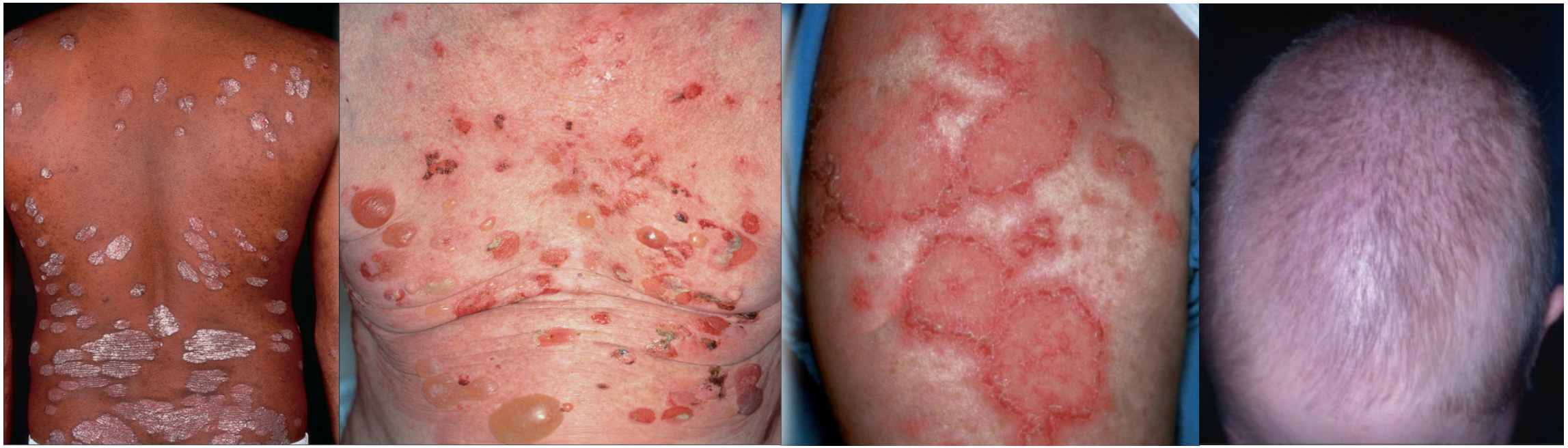
# Autoimmune and Chronic Inflammatory Diseases of the Skin

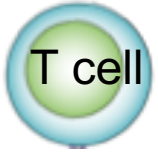
Psoriasis

Pemphigus & Pemphigoid

Cutaneous Lupus

Alopecia Areata



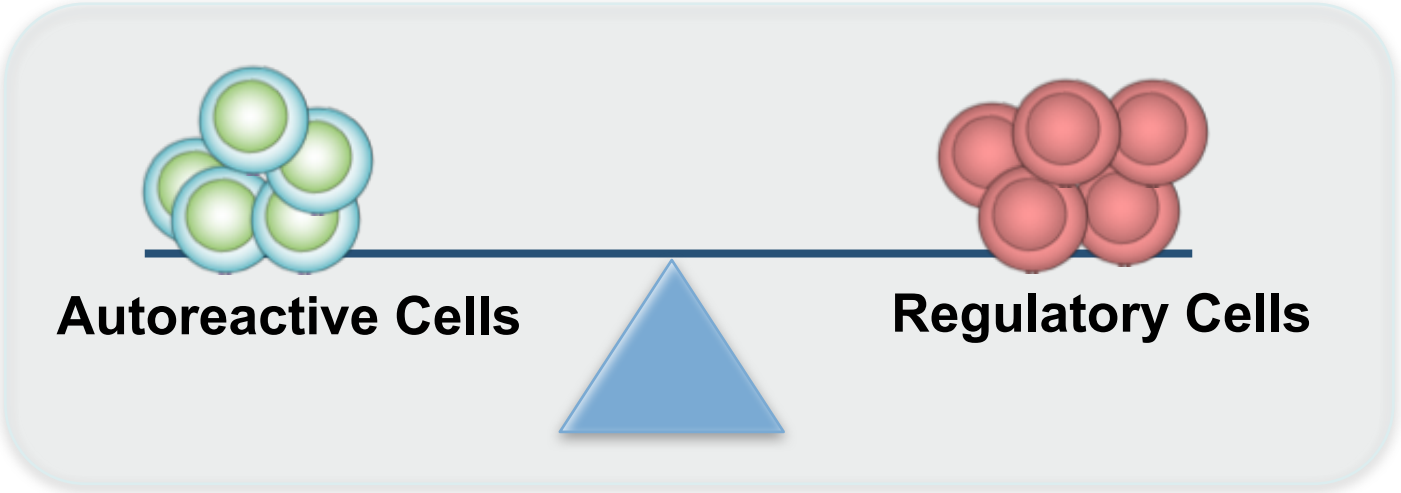



Autoreactive T cell

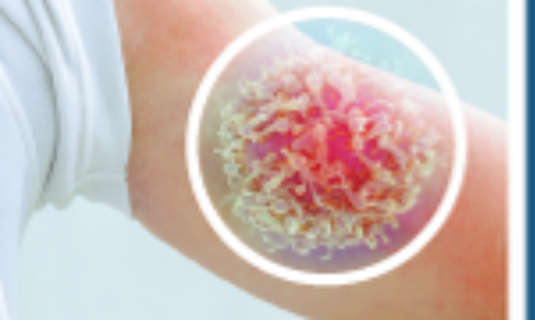
Self Antigen

Skin Inflammation

# Regulatory Cells Maintain Immune Homeostasis in Skin




- Disruption in this balance results in autoimmunity and/or chronic inflammation
- Understanding regulatory cells in the skin will:
  - Help us elucidate the pathogenesis of autoimmune and inflammatory skin diseases
  - Help us develop better treatment strategies



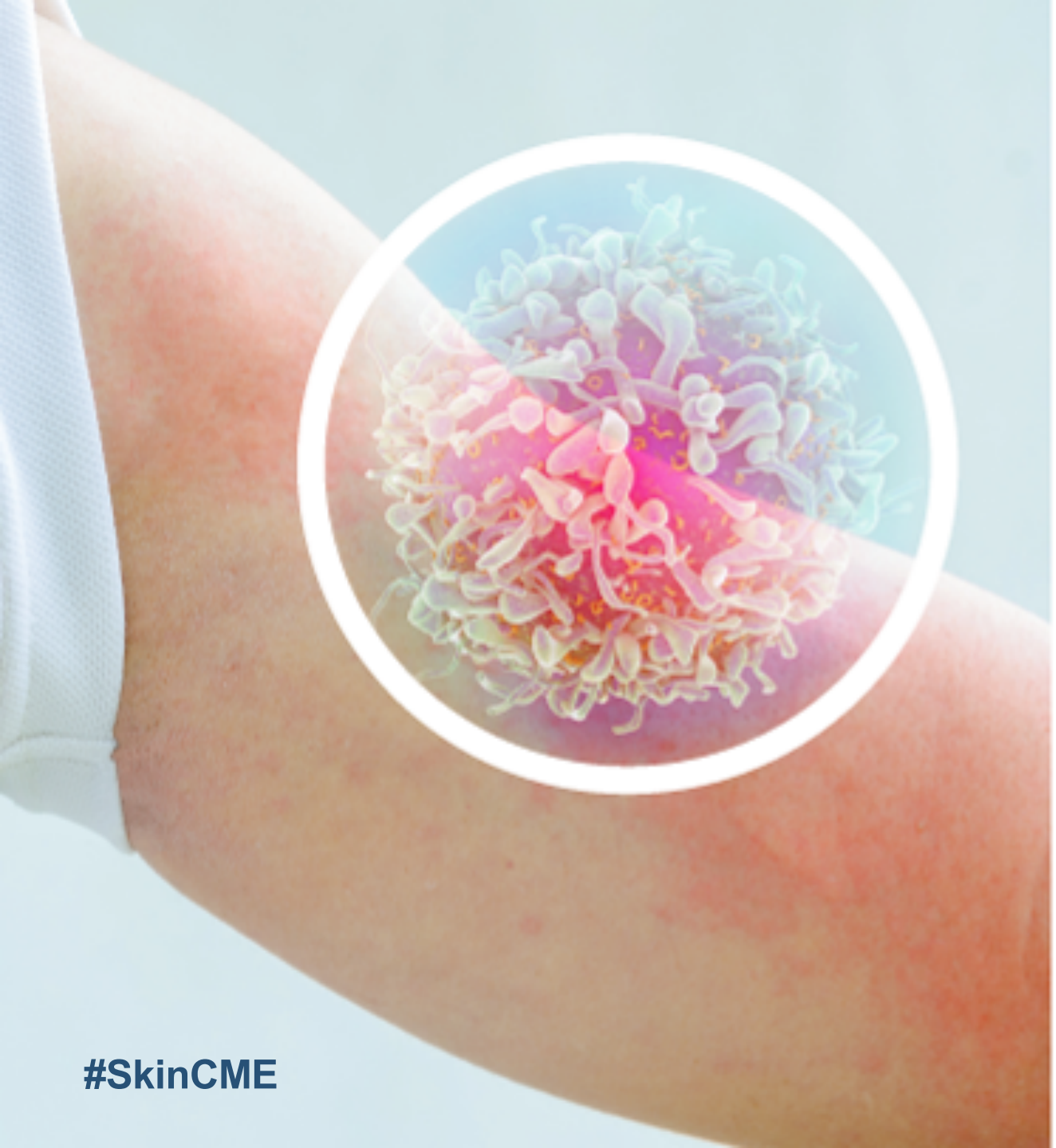
# Regulatory T cells (Tregs)


$CD4^{+}Foxp3^{+}$ T cell

- Play an indispensable role in suppressing inflammation
- Differentiation is driven by the transcription factor Foxp3
- Derived in the thymus and in peripheral tissues
- Play a major role in attenuating skin inflammation

CD4 = cluster of differentiation 4; Foxp3= Forkhead Box P3.

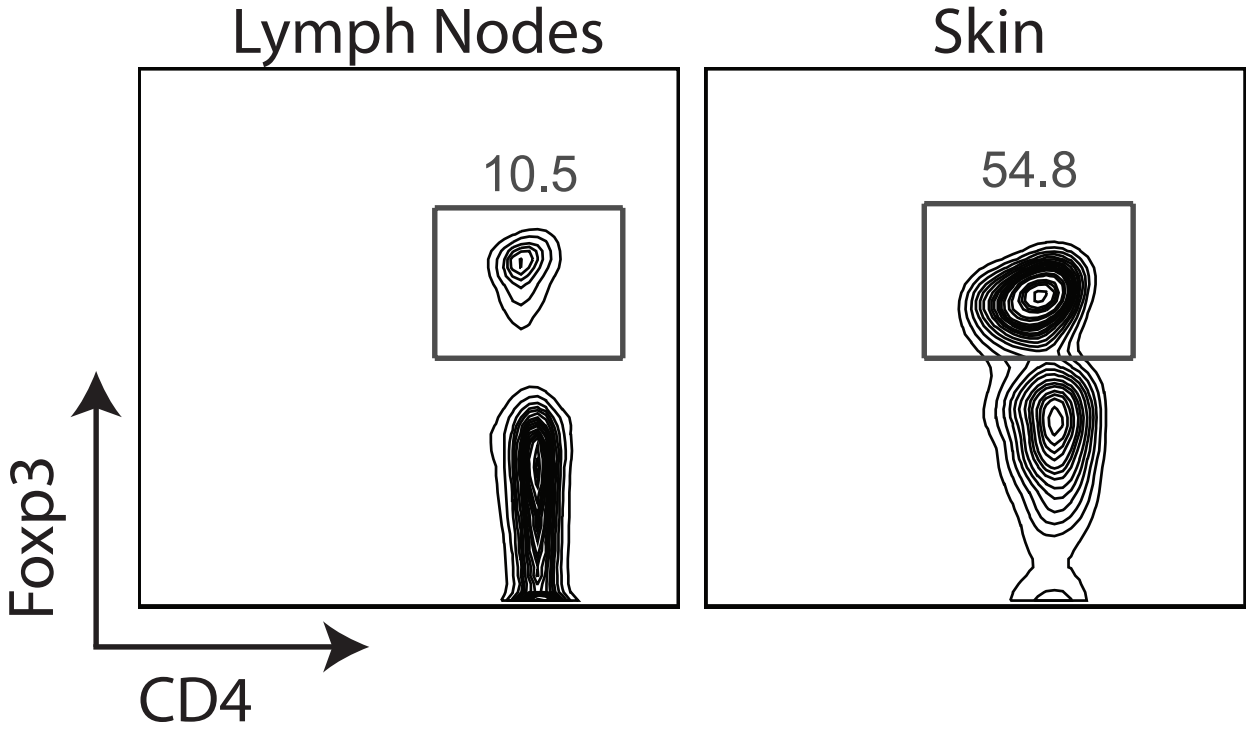
Rudra D, et al. *Nature Immunol*. 2012;13:1010-1019; Attridge K, et al. *Immunological Reviews*. 2014;259:23-29.

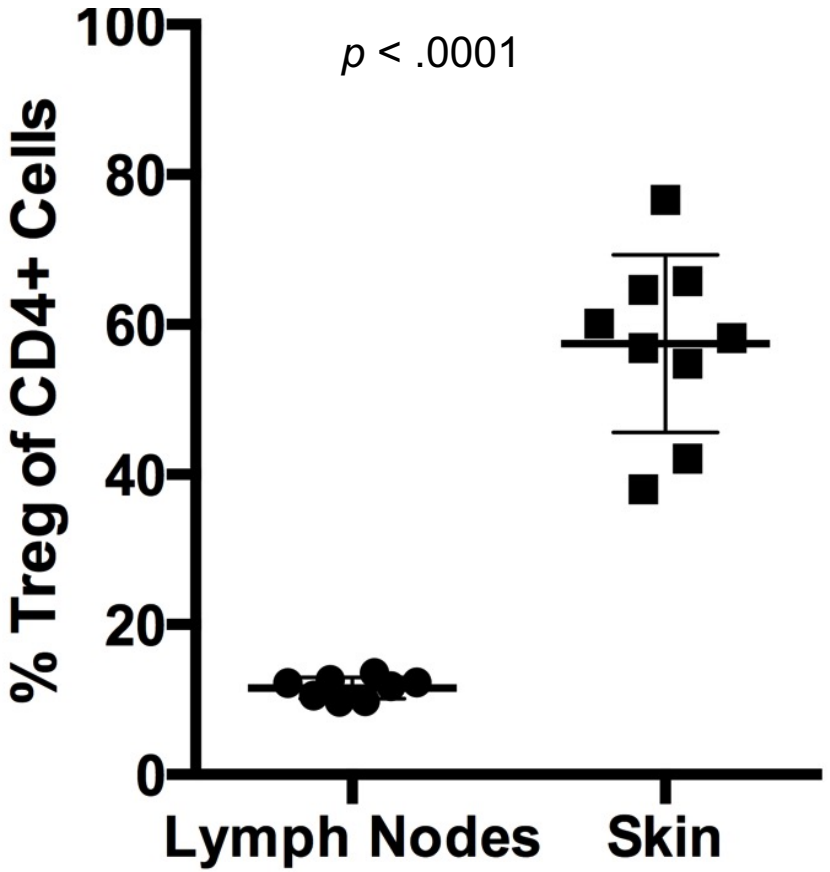


# Tregs in Mouse Skin

#SkinCME

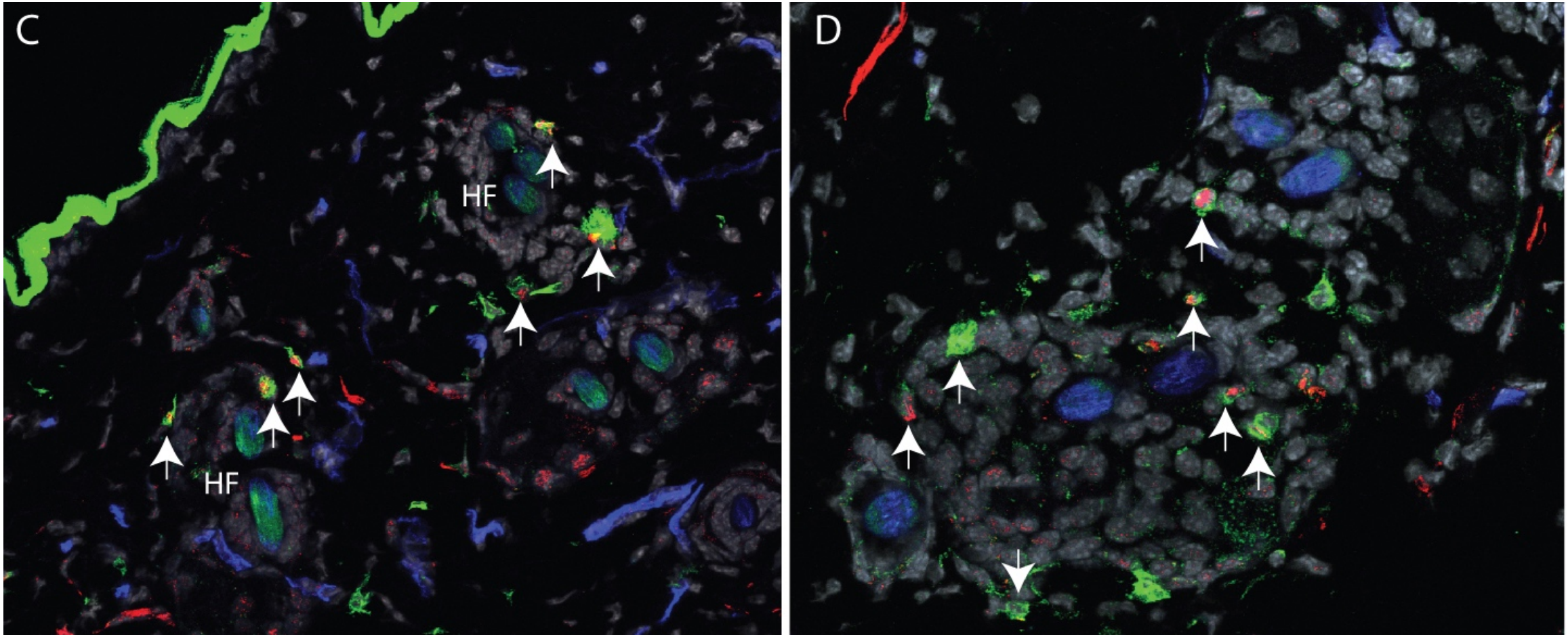
# Tregs Are Abundant in Murine Skin



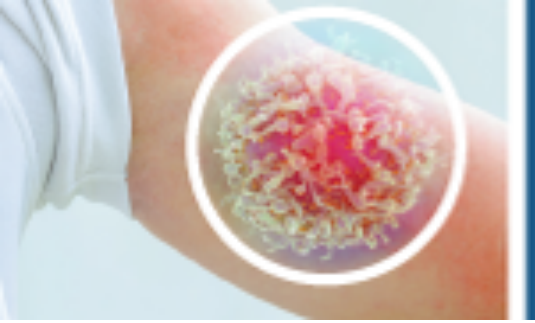




Schwarzschild TC, et al. *Immunity*. 2015;43(5):1011-1021.

# Tregs Localize to Hair Follicles in Murine Skin




Gratz JK, et al. *J Immunol*. 2013;190(9):4483-4487.

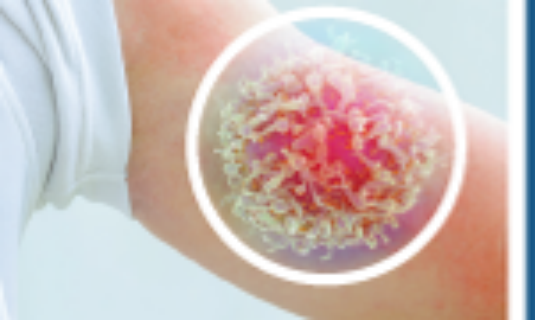


# Real Time Imaging of Tregs in Skin

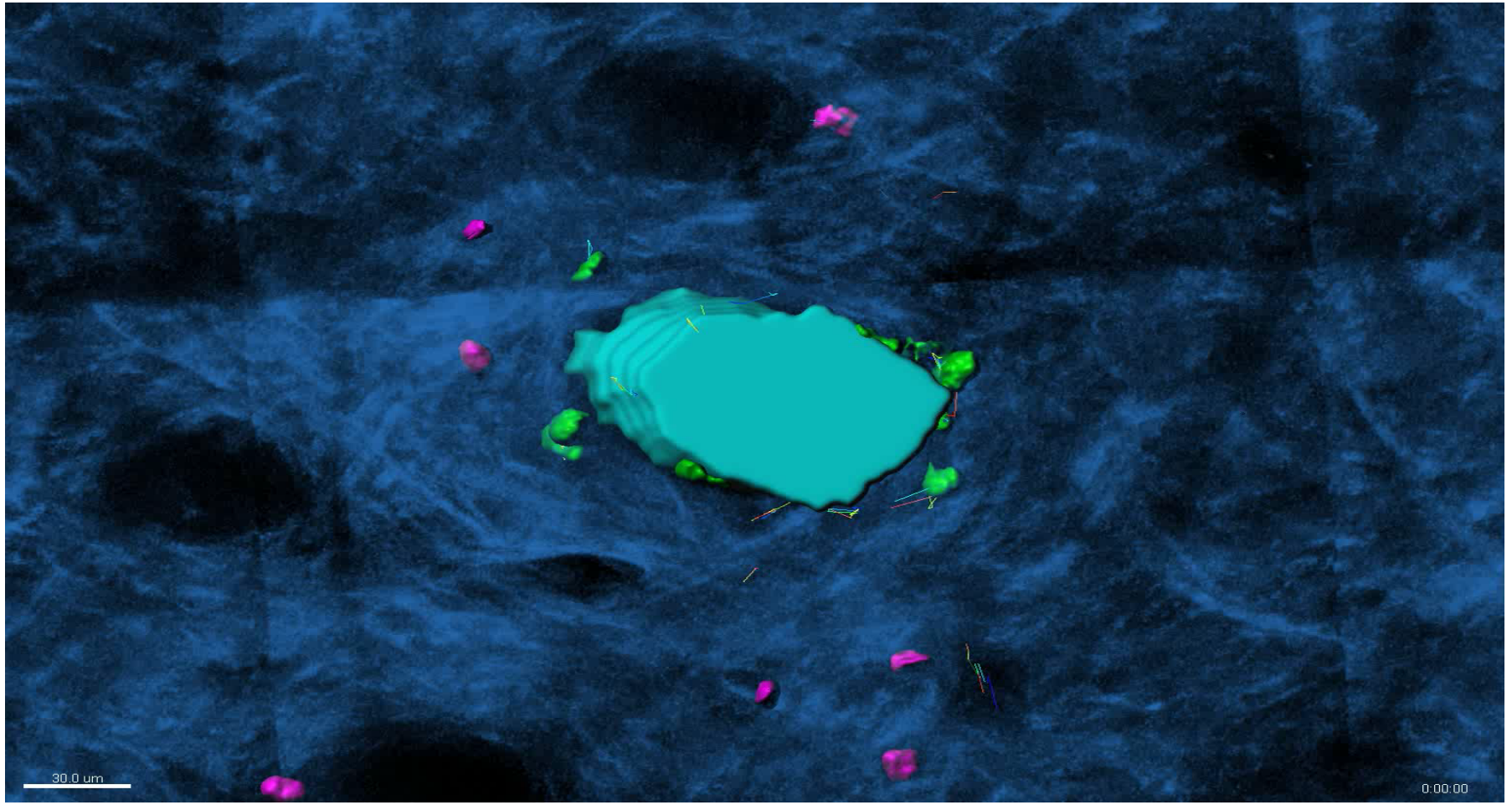

Foxp3-GFP mice

**Trunk Skin Vacuum Imaging**

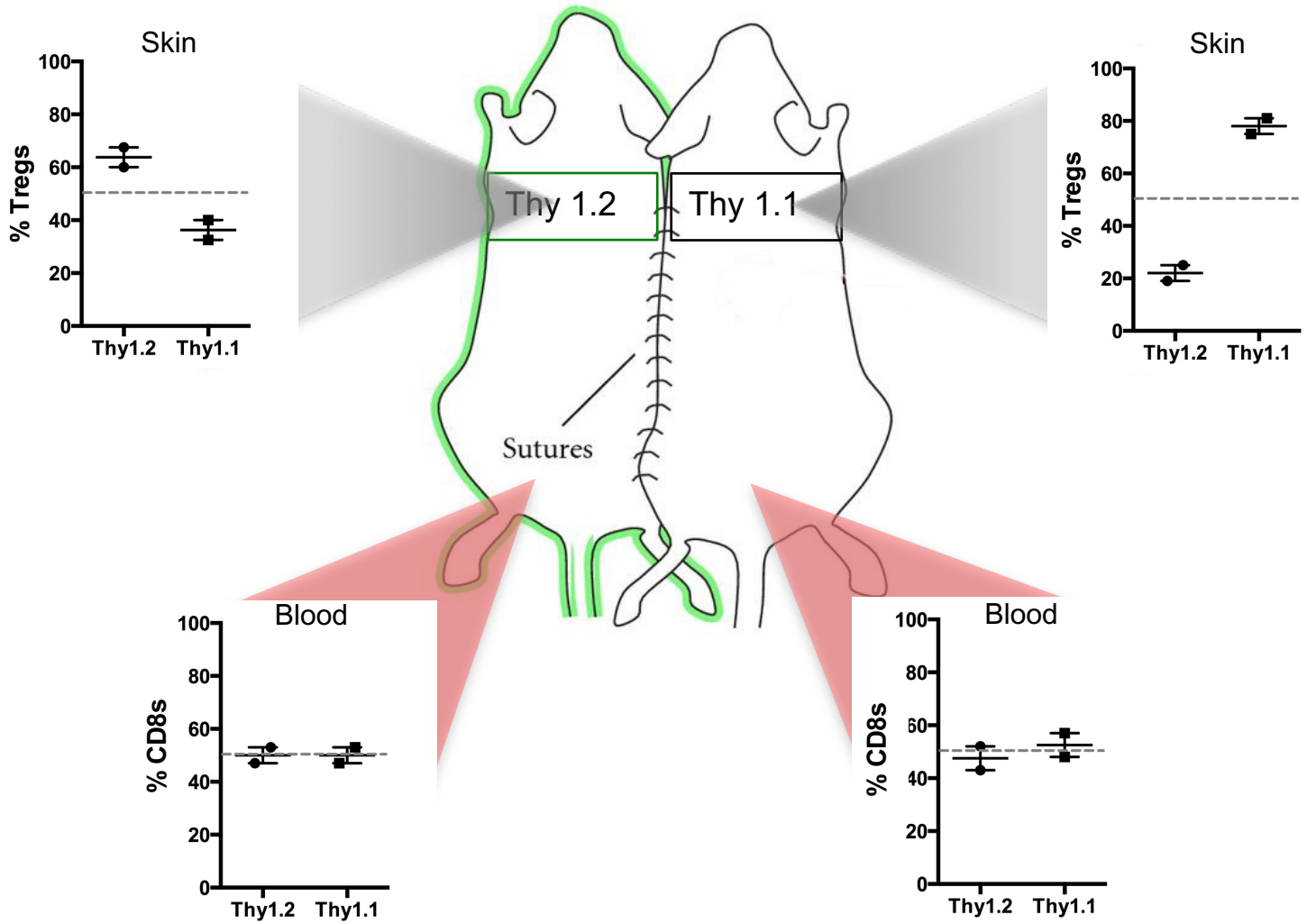
*3 hour time-lapse, images acquired every 10 minutes*

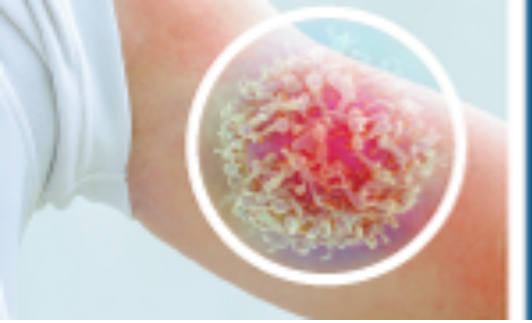


# Tregs Are Highly Active Around Hair Follicles

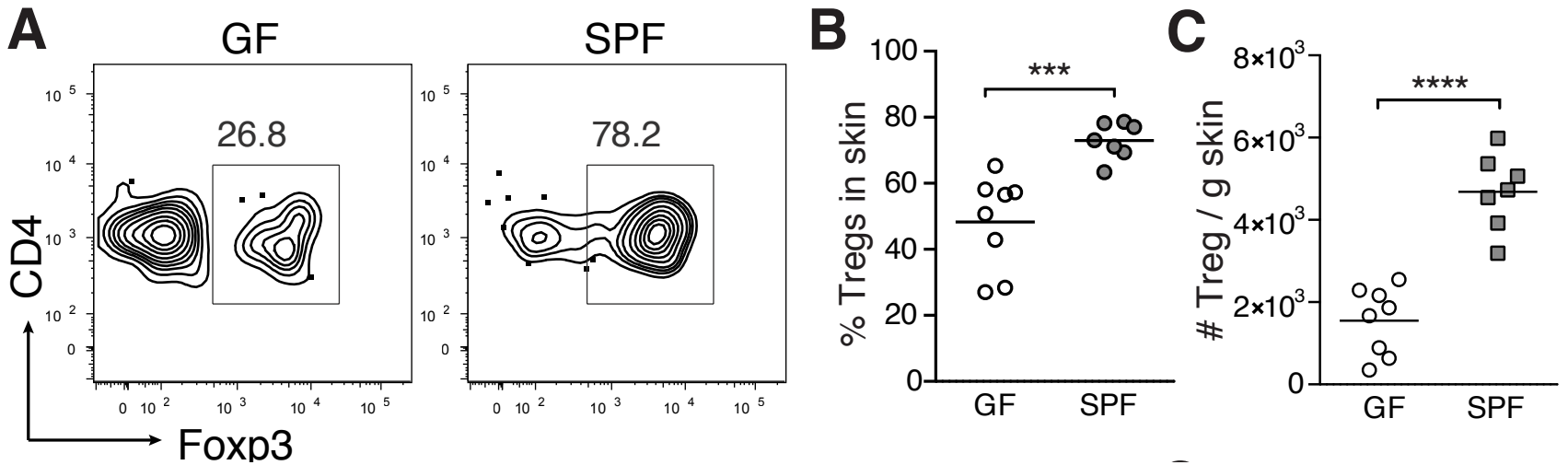


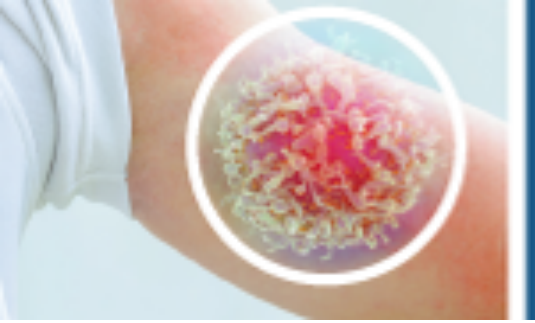
# Tregs Are a Relatively Stable Resident Population in Mouse Skin





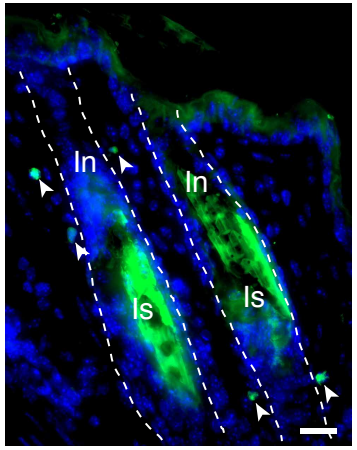
# Commensal Microbes Facilitate Treg Accumulation in Neonatal Skin





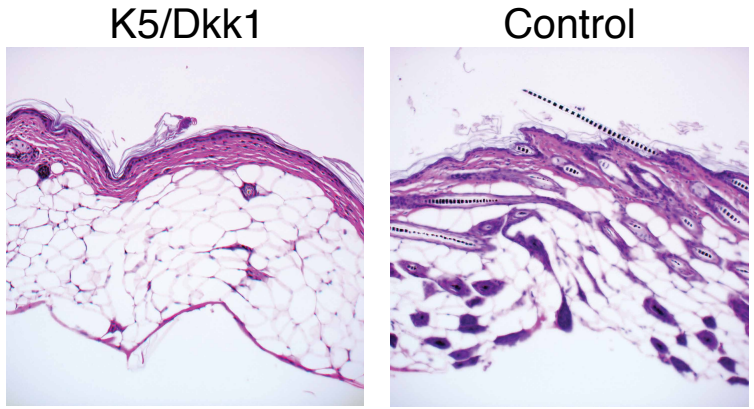
# HF Development Facilitates Treg Accumulation in Neonatal Skin

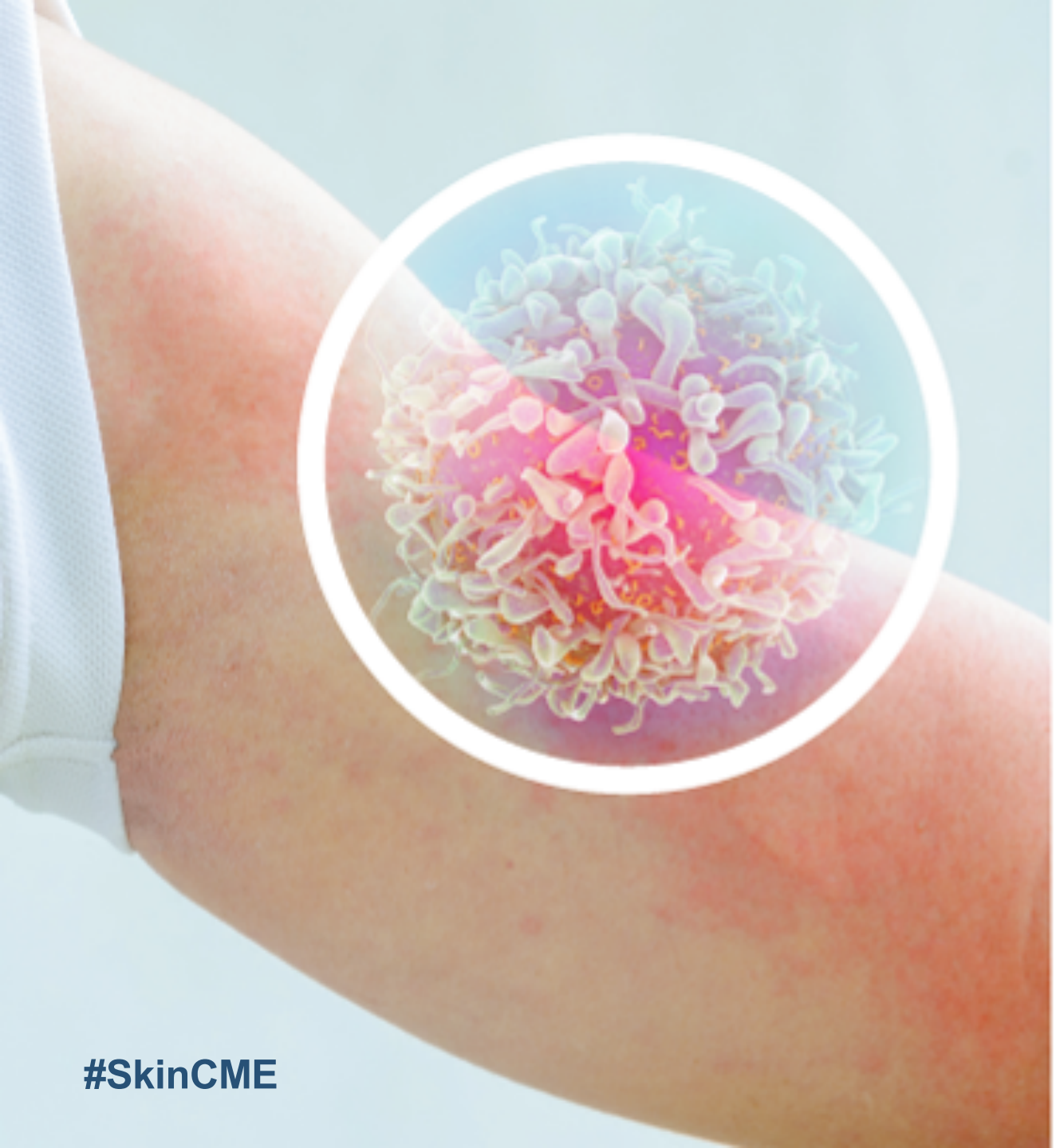
A




B


C

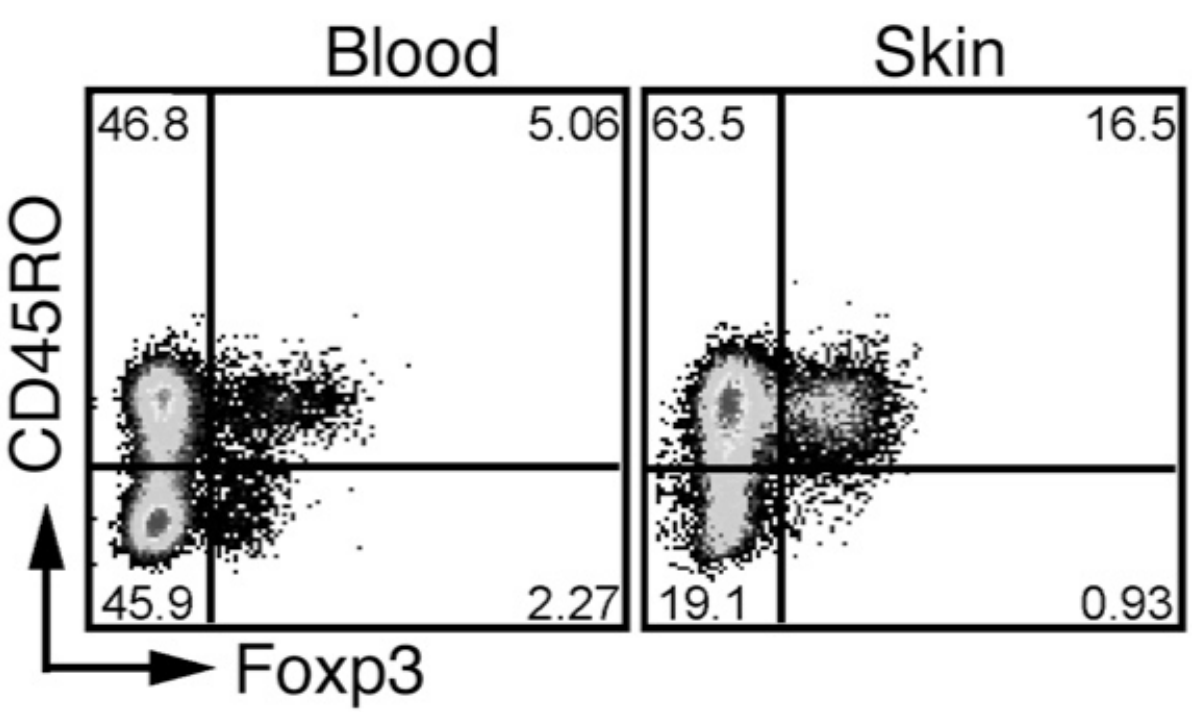


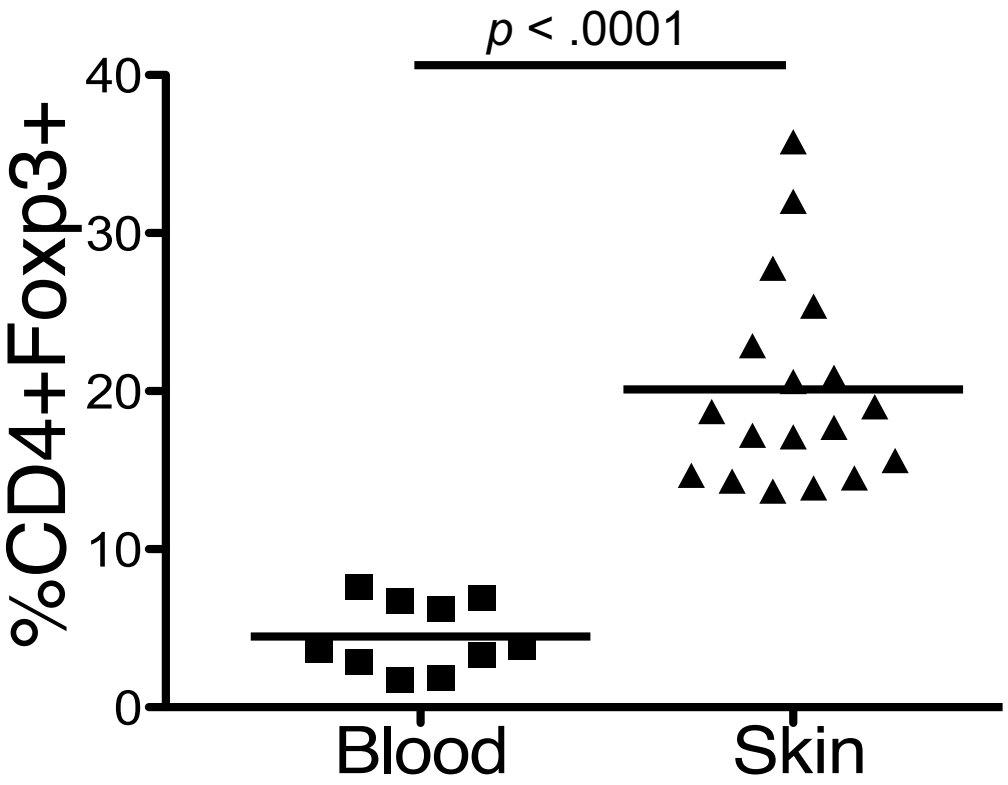


# Tregs in Human Skin

#SkinCME

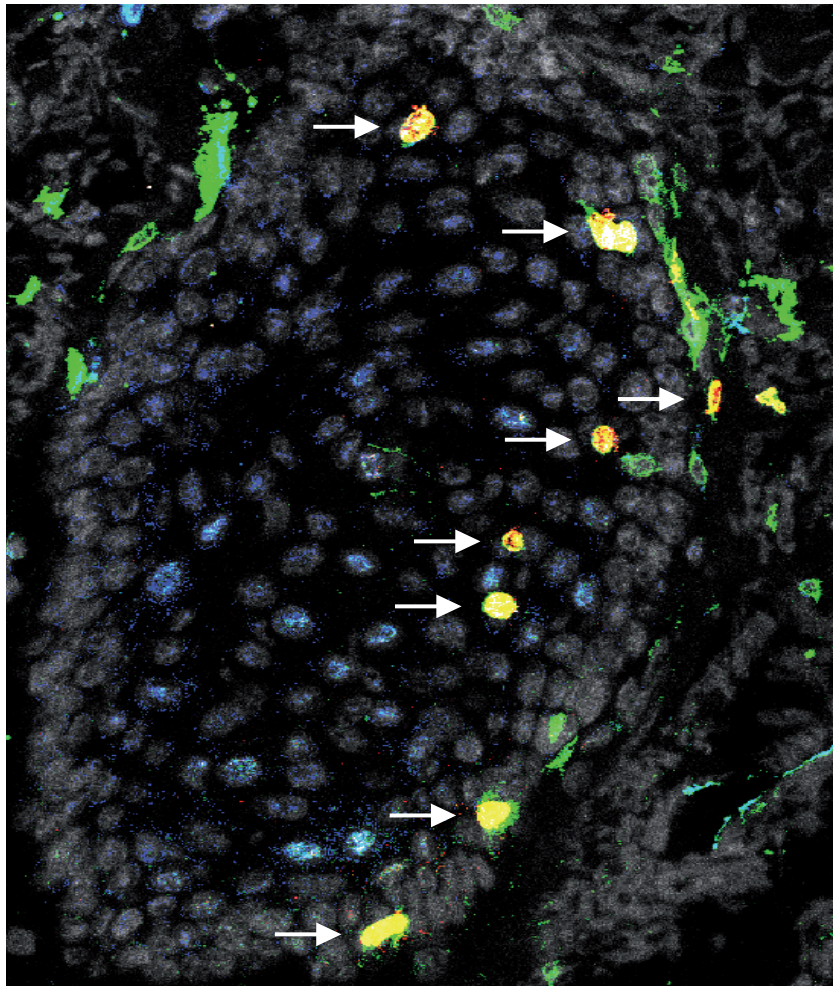
# Tregs Are Abundant in Human Skin

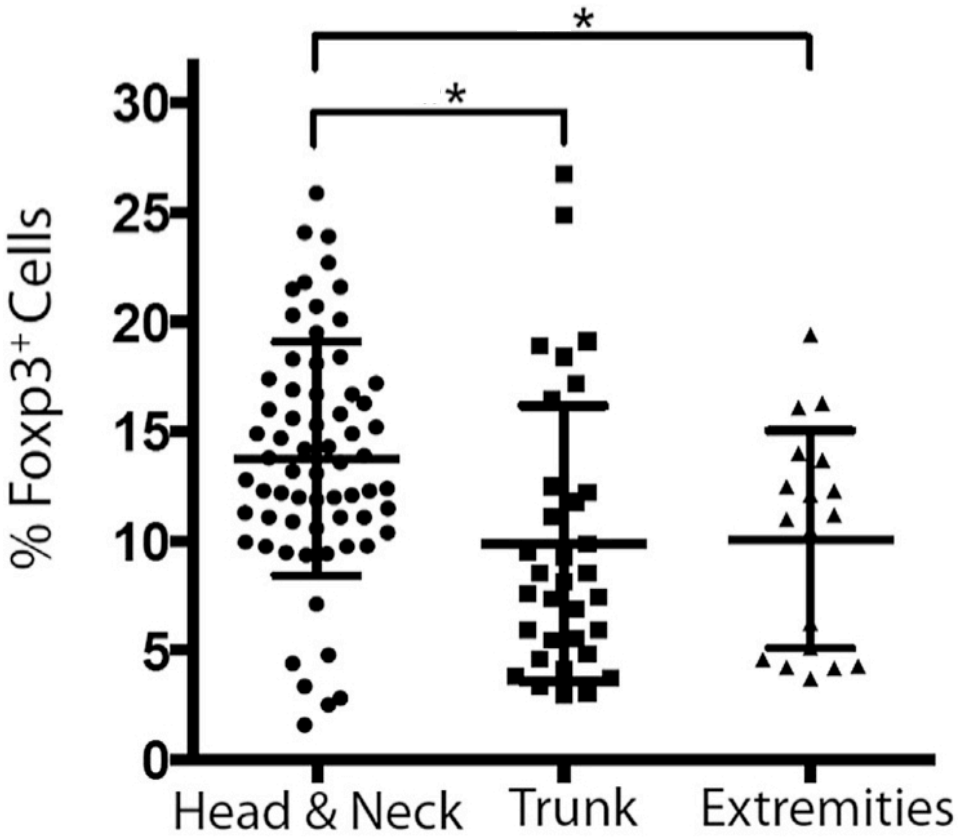



Sanchez Rodriguez R, et al. *J Clin Invest.* 2014;124:1027-1036.

# Tregs Localize to Hair Follicles in Human Skin

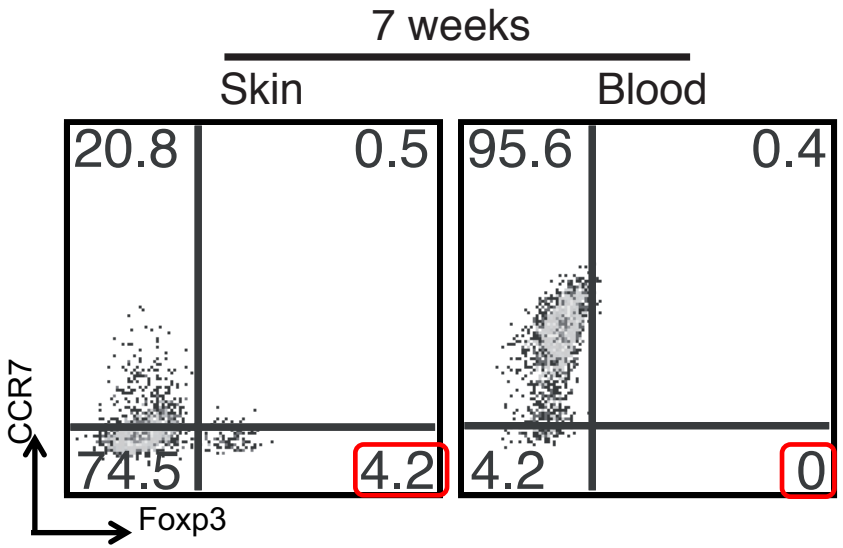


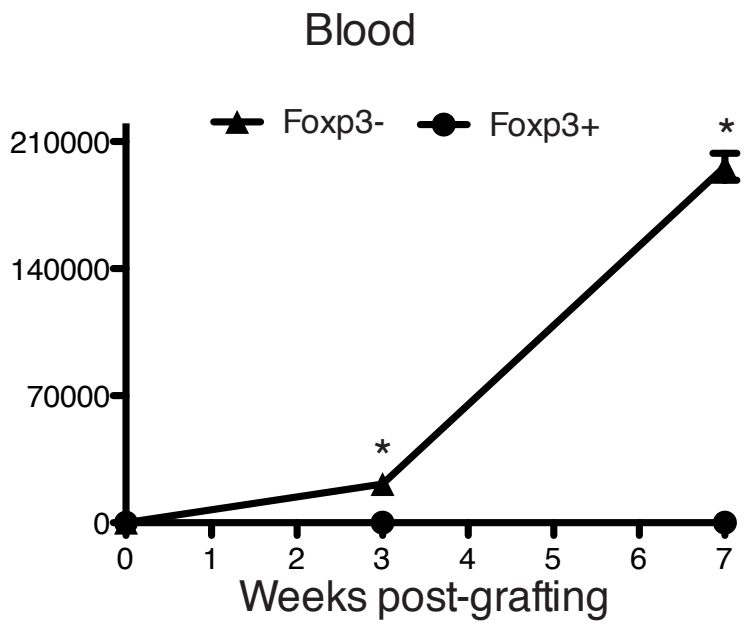



*$p \leq .05$.

Sanchez Rodriguez R, et al. *J Clin Invest.* 2014;124:1027-1036; Schulman JM, et al. *J Am Acad Dermatol.* 2016;74(3):470-476.

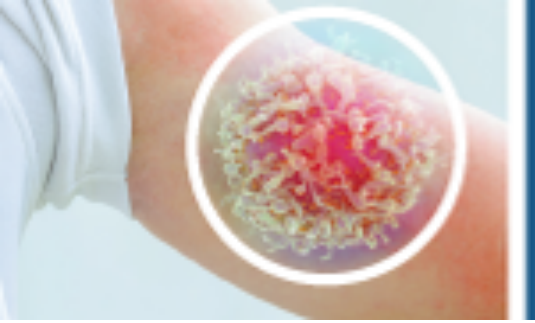
# Tregs Are a Relatively Stable Resident Population in Human Skin


*$p < .05$

Sanchez Rodriguez R, et al. *J Clin Invest*. 2014;124:1027-1036.



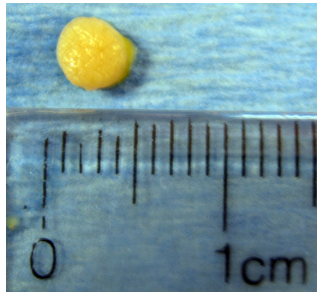
# Summary #1

- Tregs comprise a large percentage of CD4+ T cells in both mouse and human skin.
- In the steady-state, Tregs are a relatively stable resident population in both mouse and human skin.
- Tregs localize to hair follicles in both mice and humans.

**Are Tregs functioning properly in the skin of patients with inflammatory disease?**

# How can we study the function of immune cell populations in human skin?

# Multi-Parameter Flow Cytometry of Human Skin

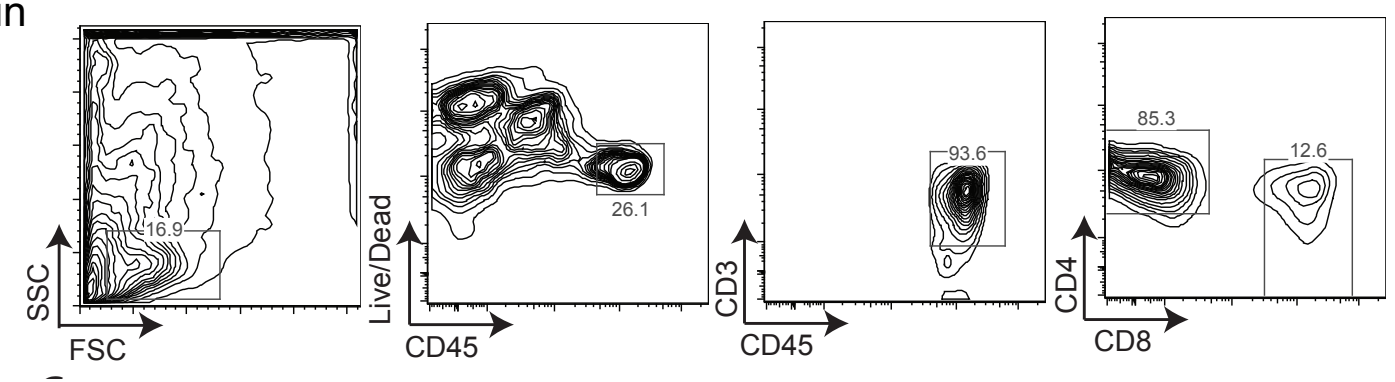


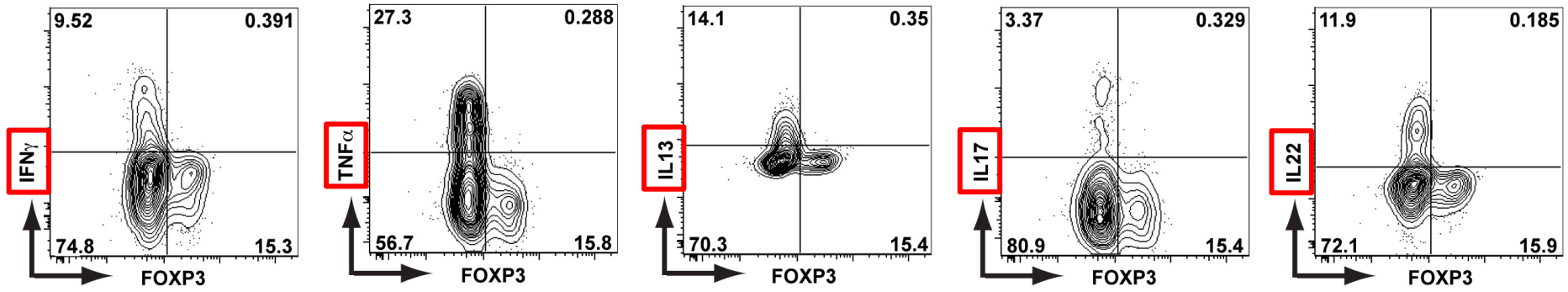

4mm Punch Biopsy from Human Skin

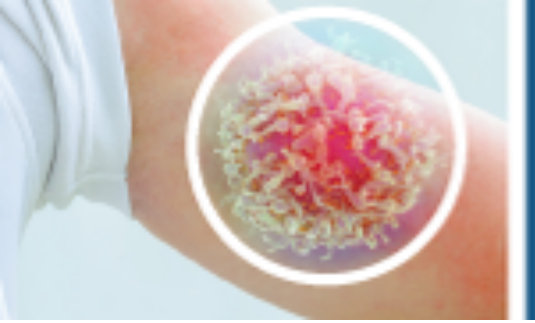
Short digestion

PMA/ionomycin (cytokines)

Multi-parameter flow cytometry





# Technological Advances

1) Performed on relatively small tissue samples

2) No culture time (overnight digestion only)

3) Growth factors not required

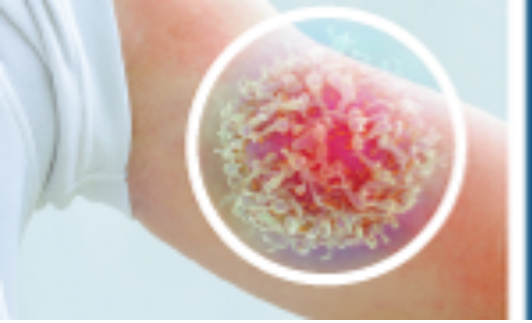
Compared to Previous Approaches

4) Objective and quantitative

5) Multi-parameter analysis

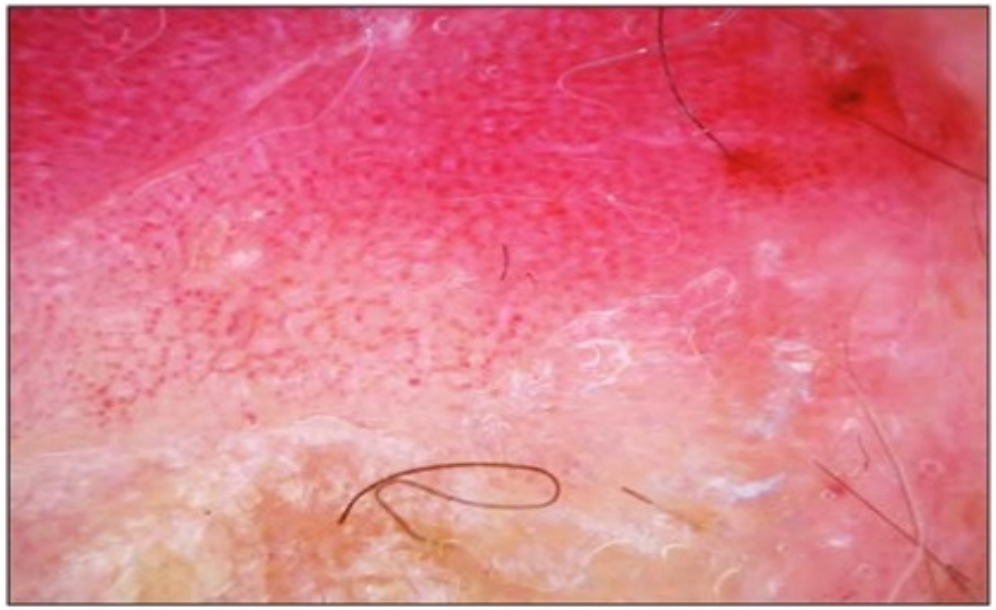
6) Examination of the entire tissue specimen

Compared to IHC

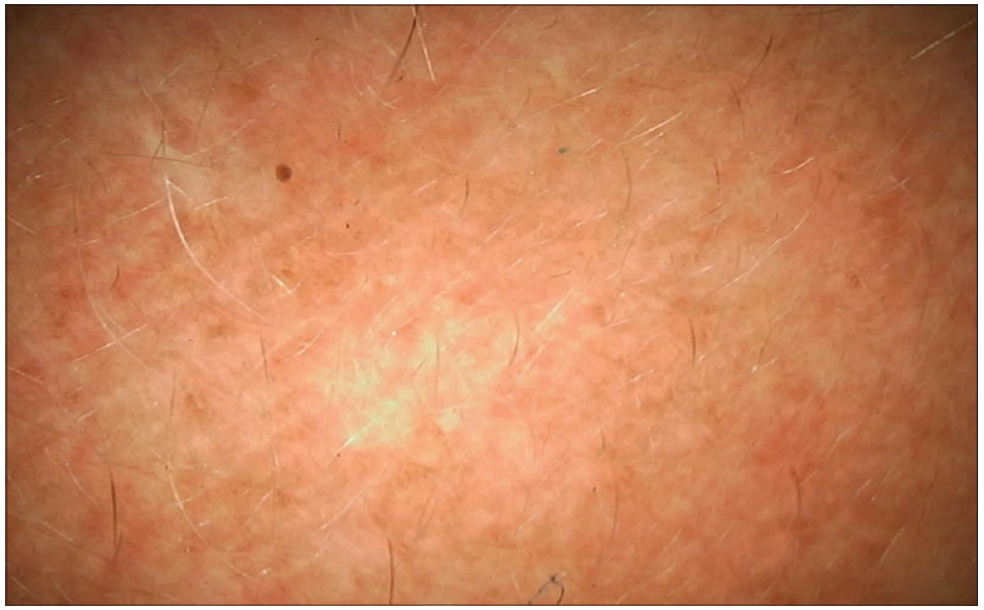


# Are Tregs Abnormal in the Skin of Psoriasis Patients?

**Lesional**



**Non-Lesional**



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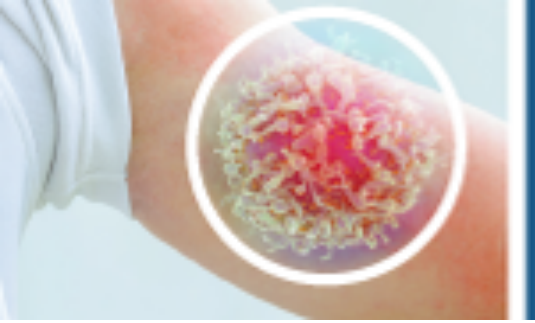
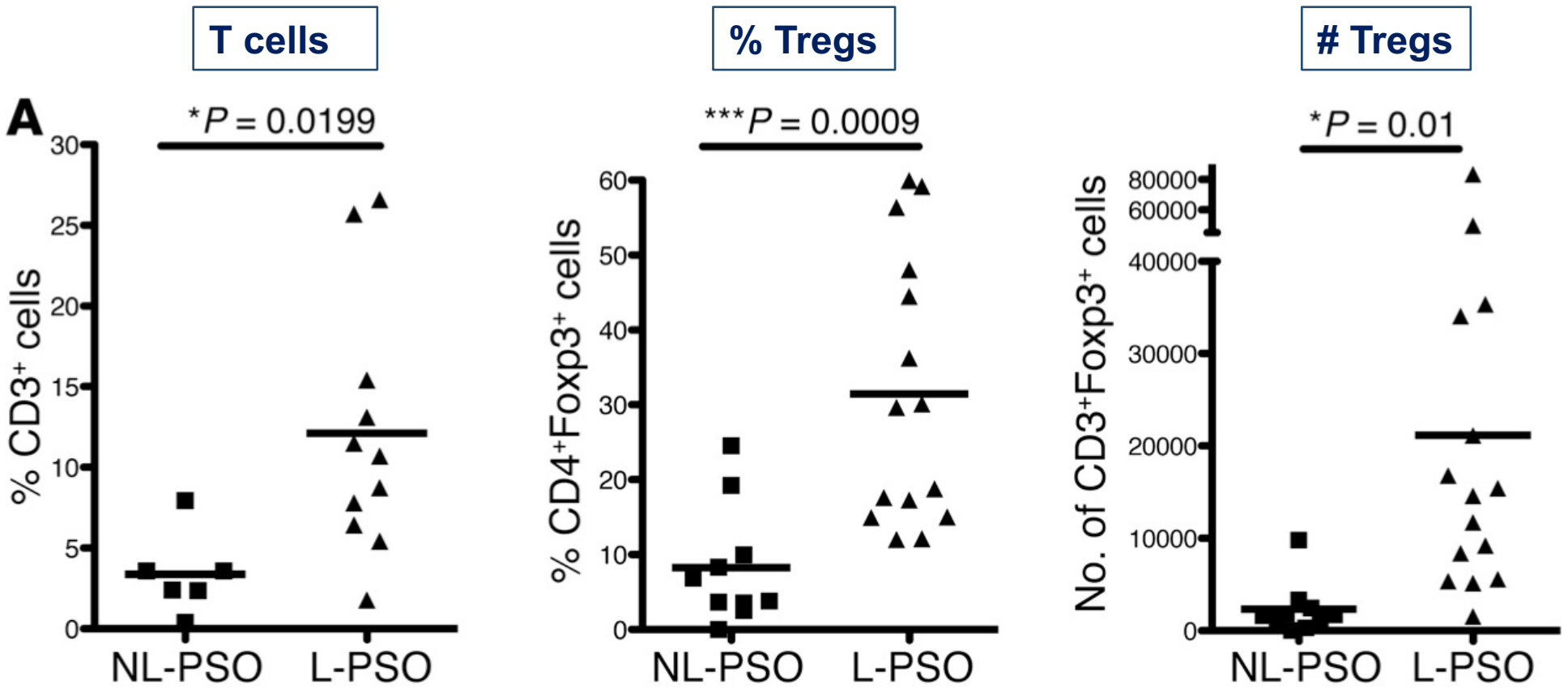


# Tregs Are Increased in Lesional Skin of Psoriasis Patients

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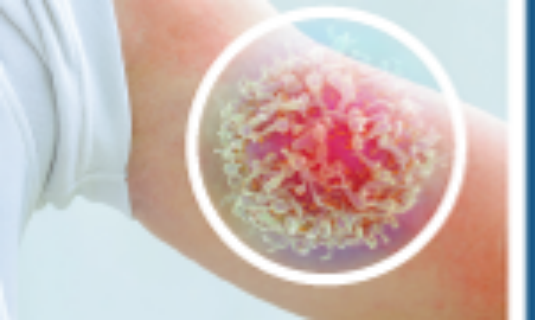
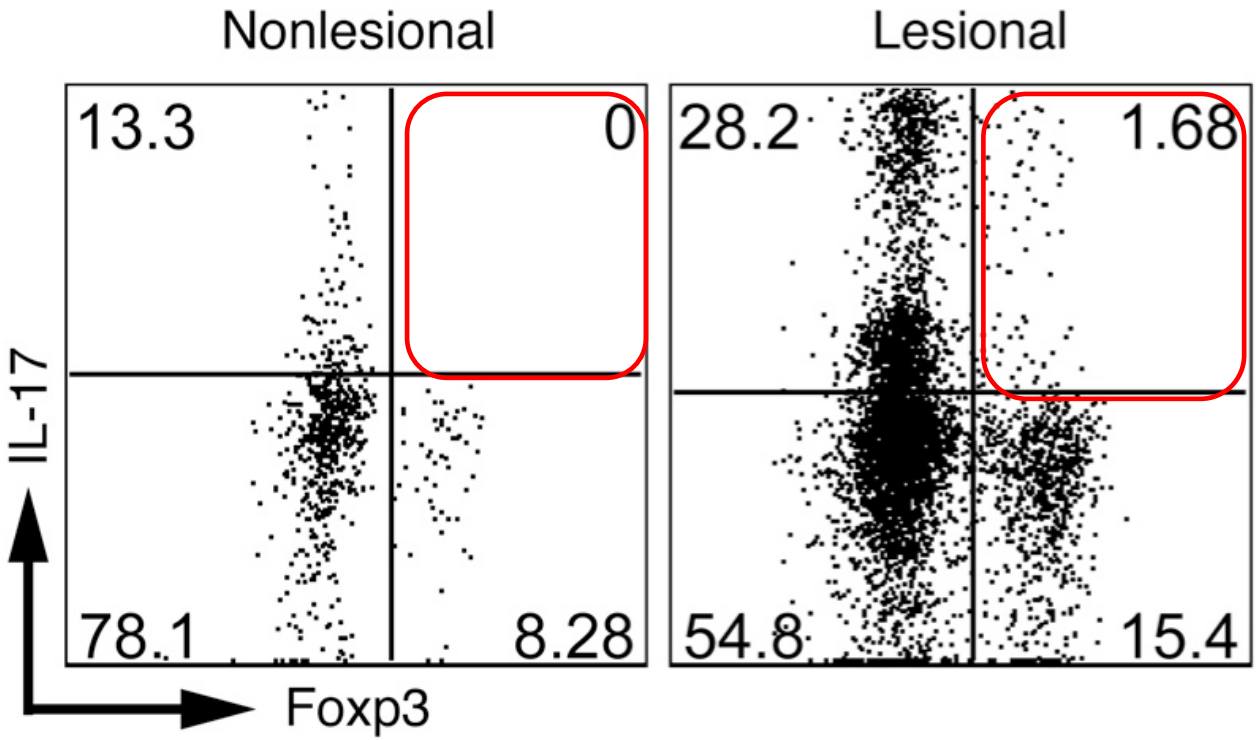
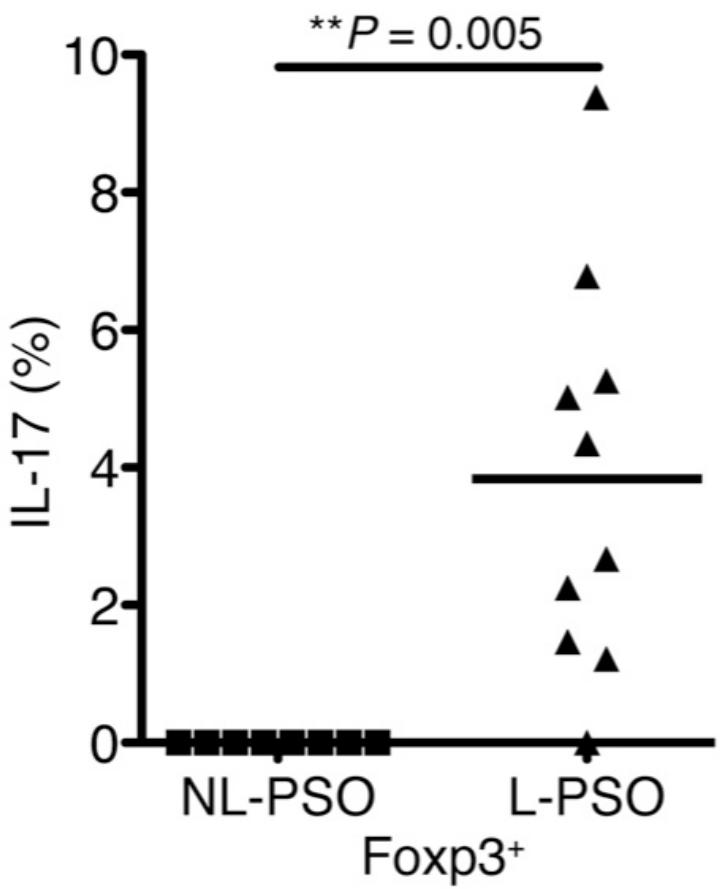


# Tregs Produce More IL-17 in Lesional Skin of Psoriasis Patients

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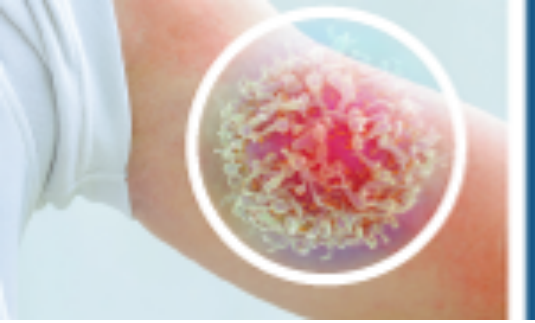

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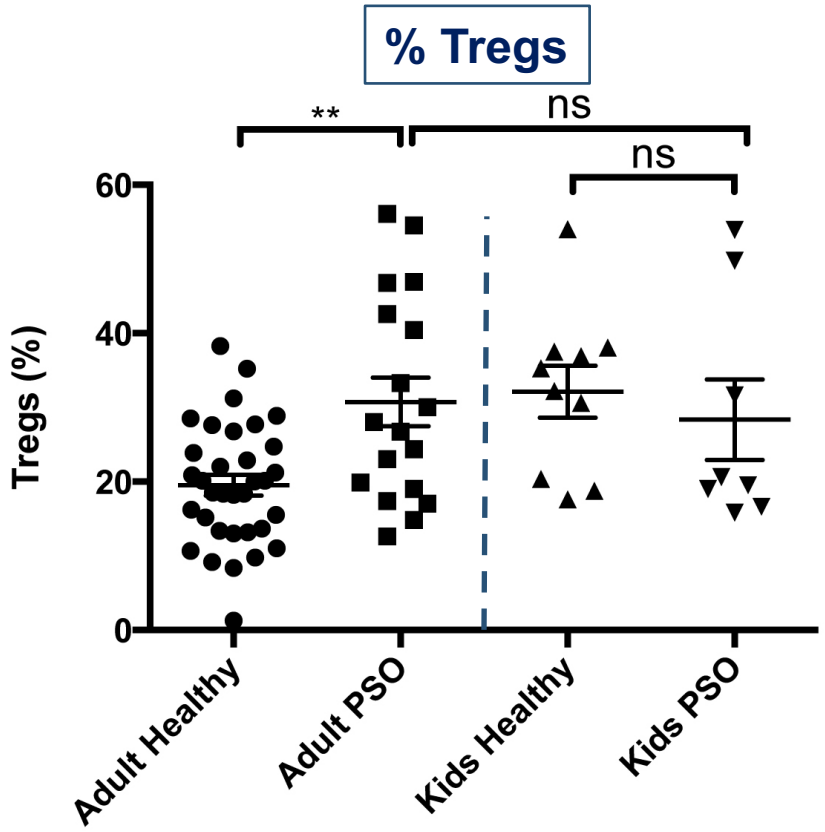
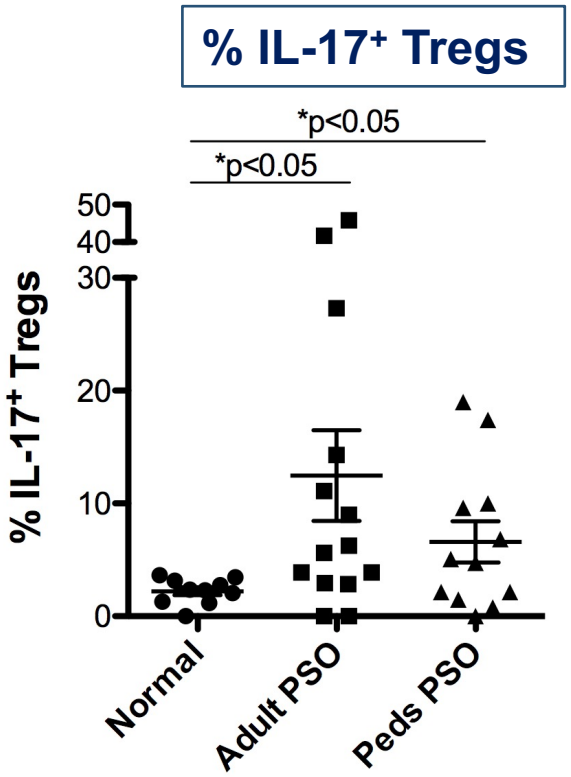
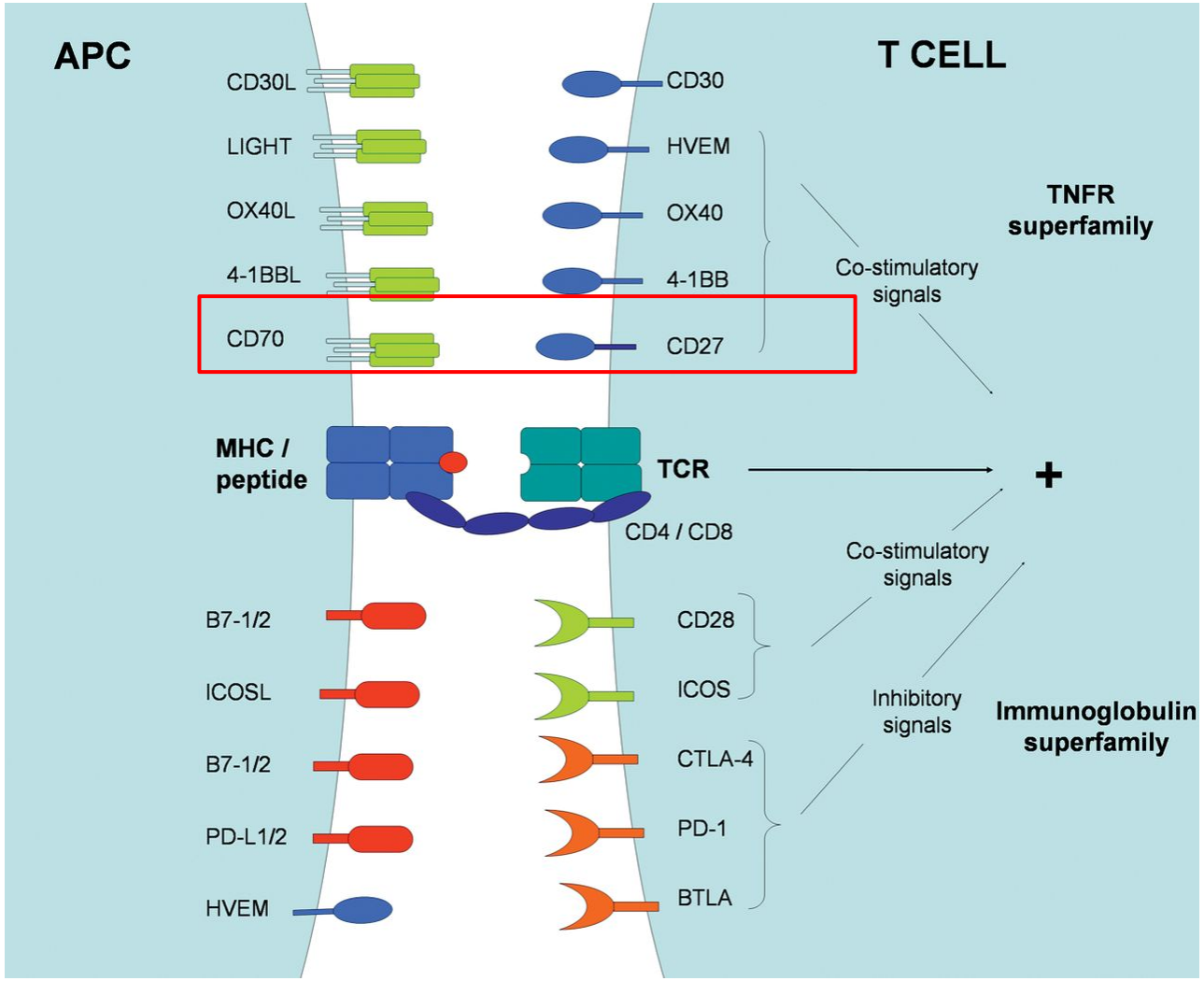


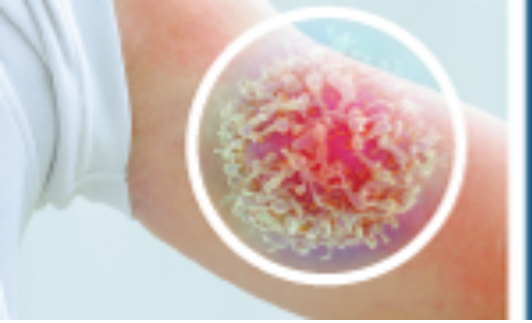



# Why do Tregs in psoriatic skin make IL-17?

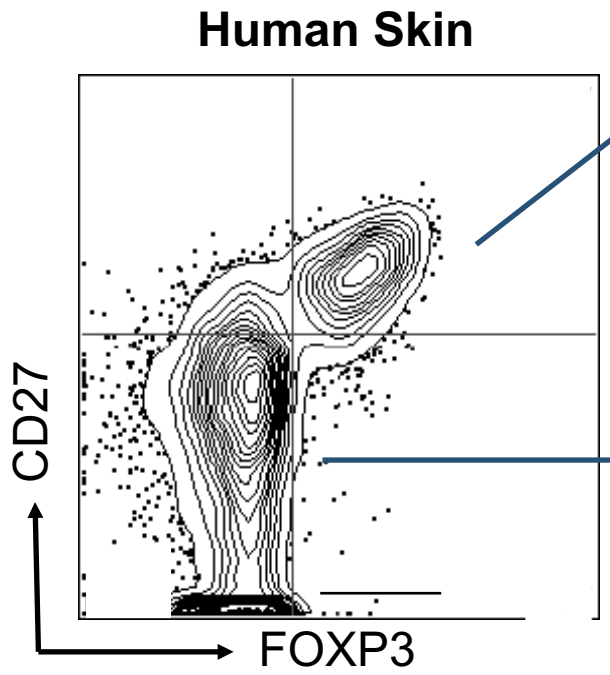
# CD27 Is a Costimulatory Receptor That Inhibits Th17 Differentiation




Gray JC, et al. *Clin Sci*. 2006;111:93-106.



# CD27 is Highly Expressed on Tregs in Normal Human Skin




**CD27 expression on Tregs is unknown?**

**CD27 expression on Teff cells:**

- Inhibits Th17 differentiation
- Promotes Th1 differentiation

# Susceptibility Loci for Psoriasis

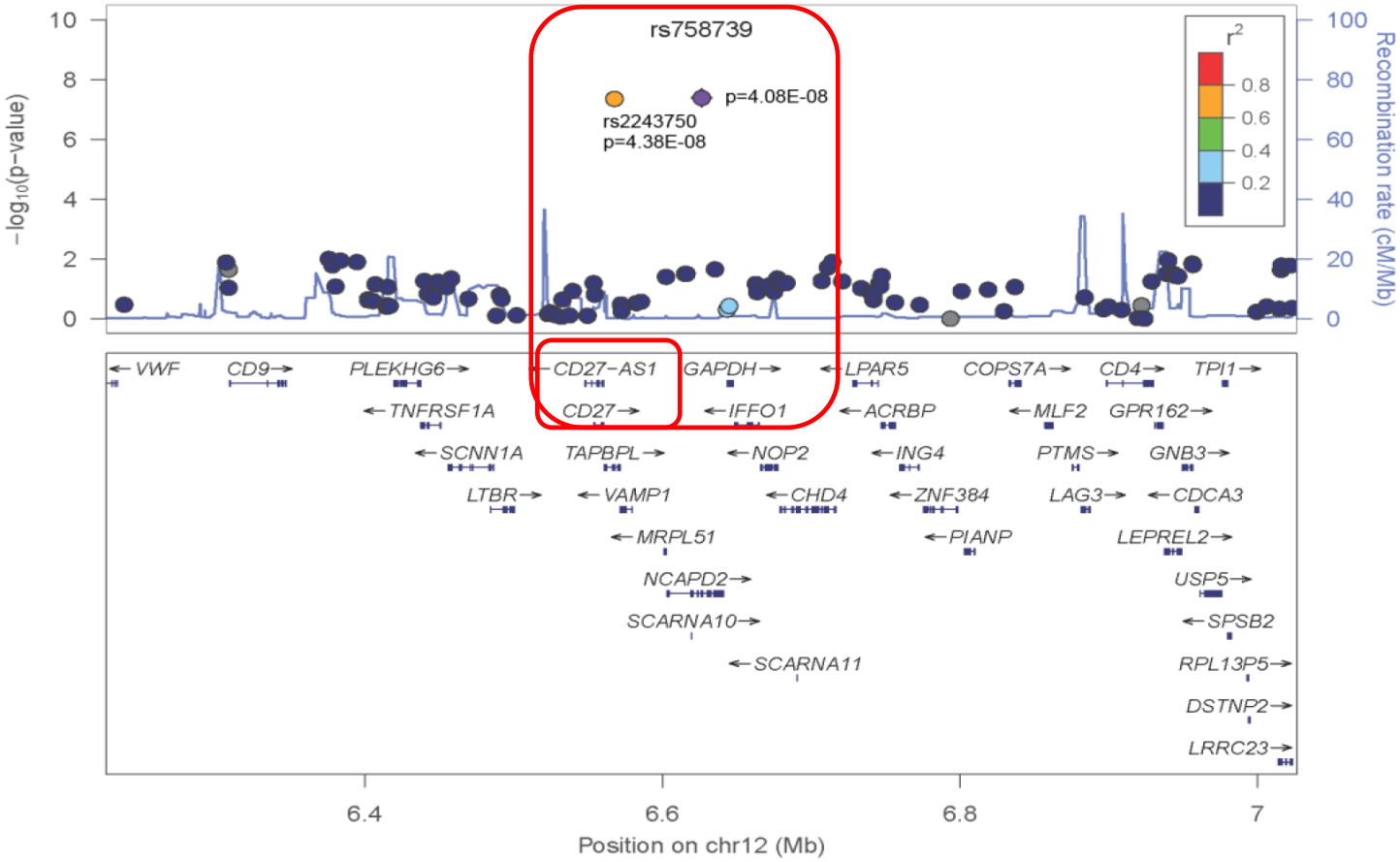
nature COMMUNICATIONS

ARTICLE

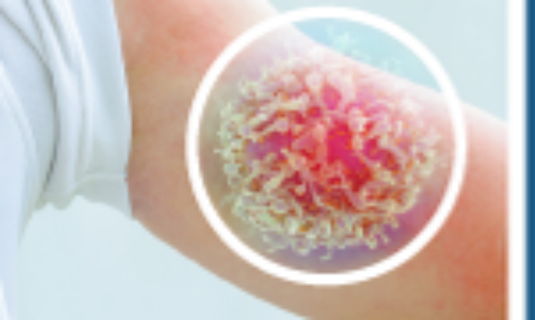
Received 11 Nov 2013 | Accepted 9 Jun 2014 | Published 9 Jul 2014

DOI: 10.1038/ncomms5331

Sequencing-based approach identified three new susceptibility loci for psoriasis



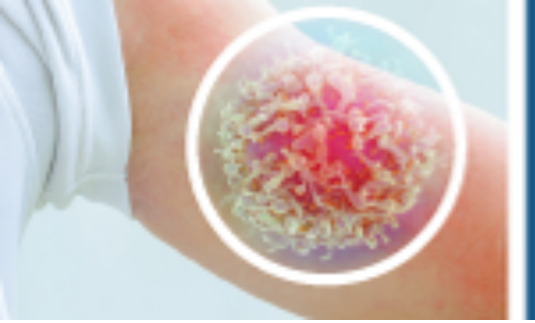

Sheng Y, et al. *Nat Commun*. 2014;5:4331.



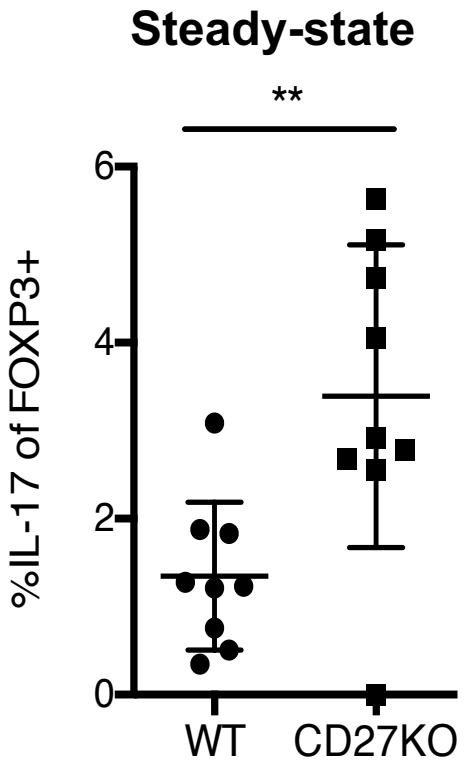
# Hypotheses

1. CD27 expression on Tregs inhibits IL-17 production.

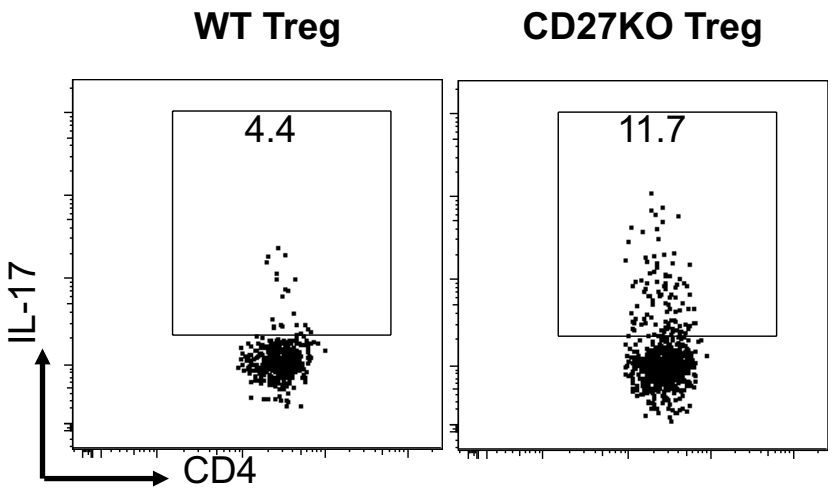
2. This pathway is disrupted in patients with psoriasis.

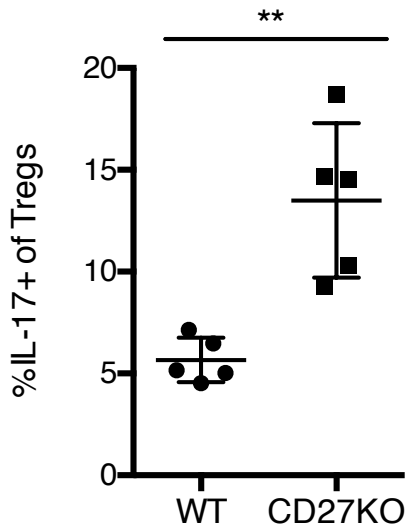


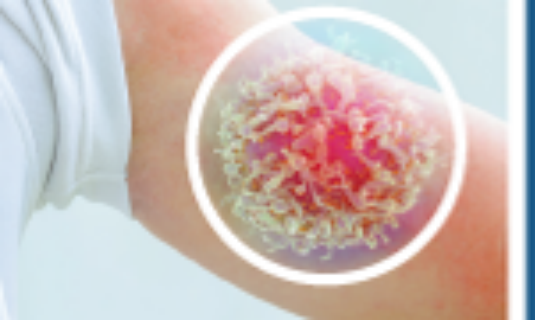
# CD27 Attenuates IL-17 Production From Tregs



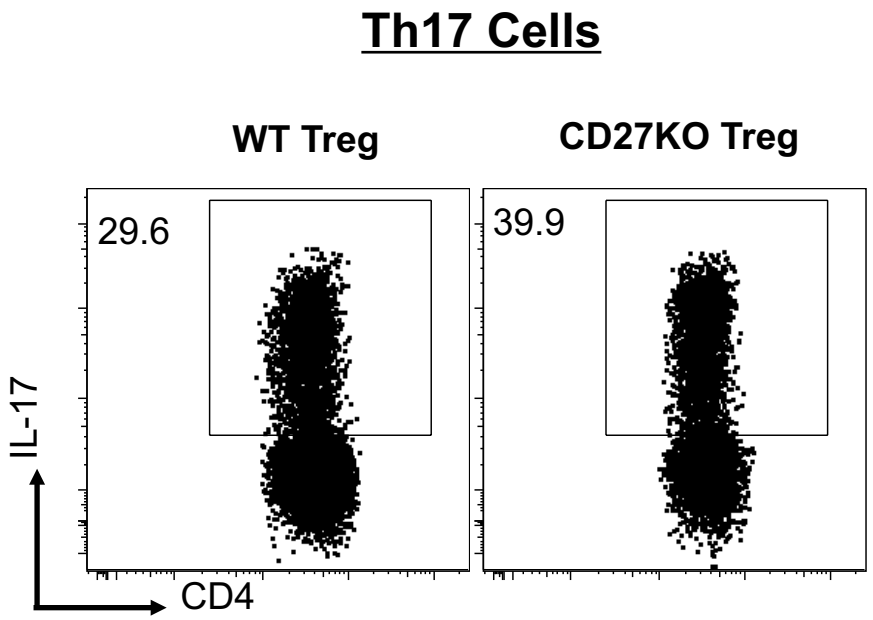

Candida Infection

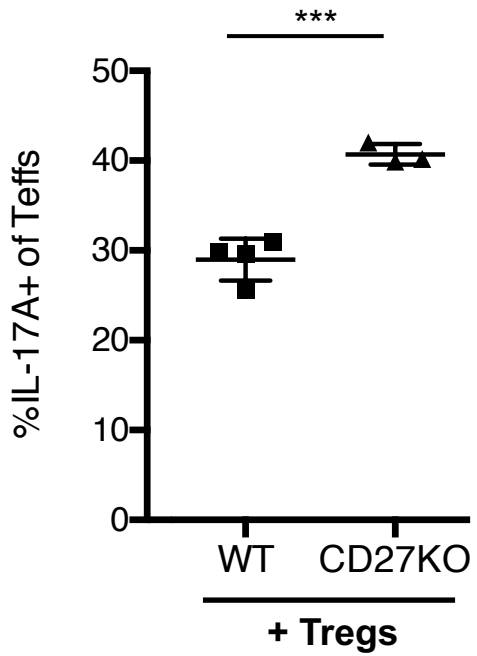




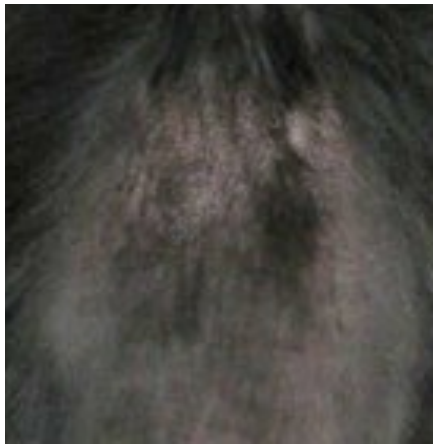
# CD27 on Tregs Attenuates IL-17 Production From Th17 Cells



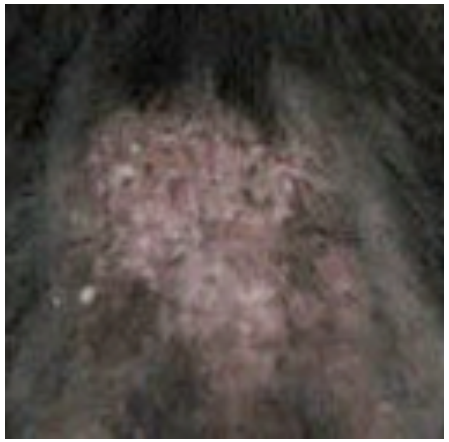



# CD27 Attenuates Imiquimod-Induced Skin Inflammation

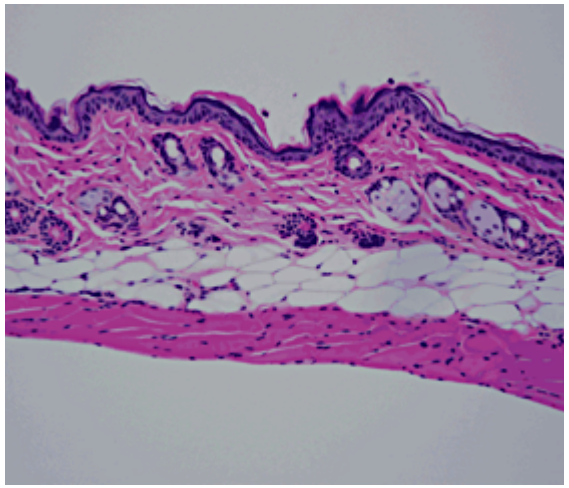
WT + IMQ



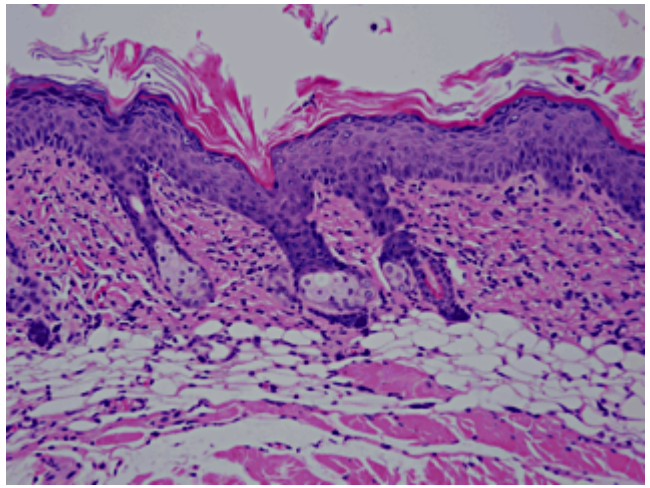
CD27KO + IMQ



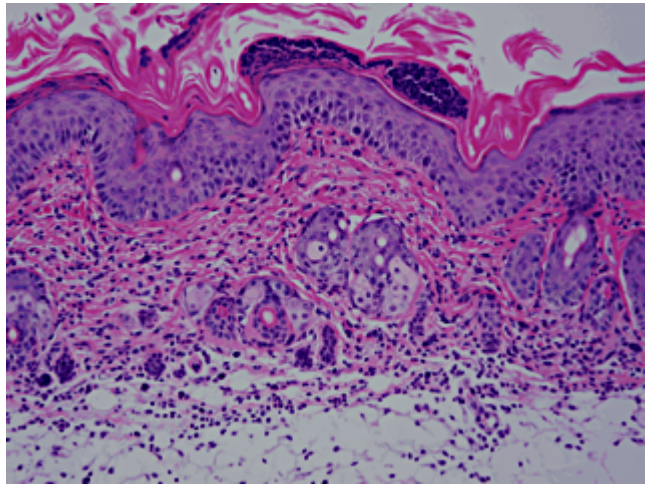
Untreated

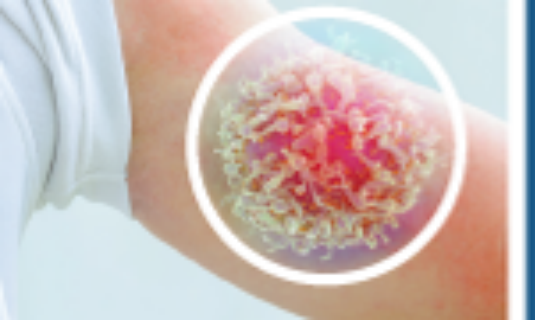


WT + IMQ



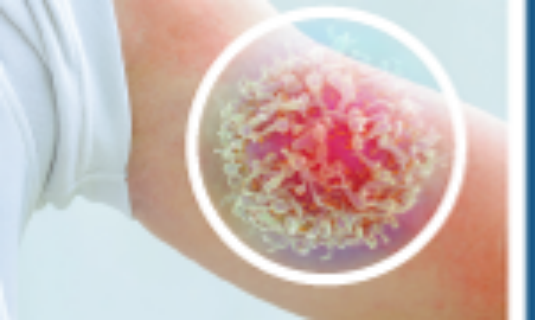
CD27KO + IMQ





# Summary #2

- Tregs are increased in psoriatic skin
- Tregs in psoriatic skin produce increased amounts of IL-17
- Polymorphisms in the CD27 gene are associated with psoriasis
- CD27 expression on Tregs inhibits IL-17 production from Tregs and TH17 cells



# Conclusions

- Tregs are an abundant tissue-resident cell population in both murine and human skin
- Tregs play a major role in suppressing skin inflammation
- Tregs are dysfunctional in the skin of patients with psoriasis
- The CD27 pathway plays a role in inhibiting IL-17 production from Tregs and Teff cells in skin

# Acknowledgments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Priscila Munoz-Sandoval
Shrishti Bhattarai

**Mentorship**

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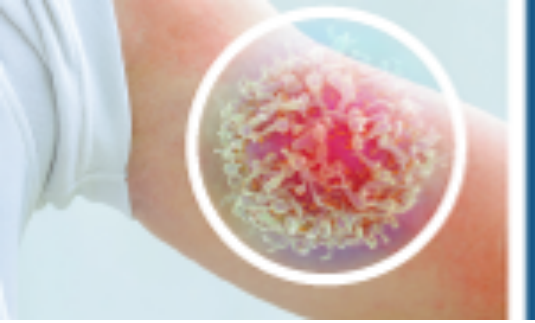
Kelly Cordoro, MD
Hobart Harris, MD
Qizhi Tang, PhD
Jeff Bluestone, PhD
Thea Mauro, MD
Max Krummel, PhD

**Outside Collaborators**

Iris Gratz (U. Salzburg)



# Funding


- NIH K08 (NIAMS)
- NIH DP2 (DPCPSI)
- NIH R21 (NIAMS)
- NIH R03 (NIAMS)
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- Scleroderma Research Foundation
- National Psoriasis Foundation
- Abbvie Inc.
- Dermatology Foundation
- UCSF Dermatology
- Kawaja Family
- Charles and Daneen Stiefel

# CONSIDERATIONS FOR FUTURE TREATMENT OF INFLAMMATORY SKIN DISEASES

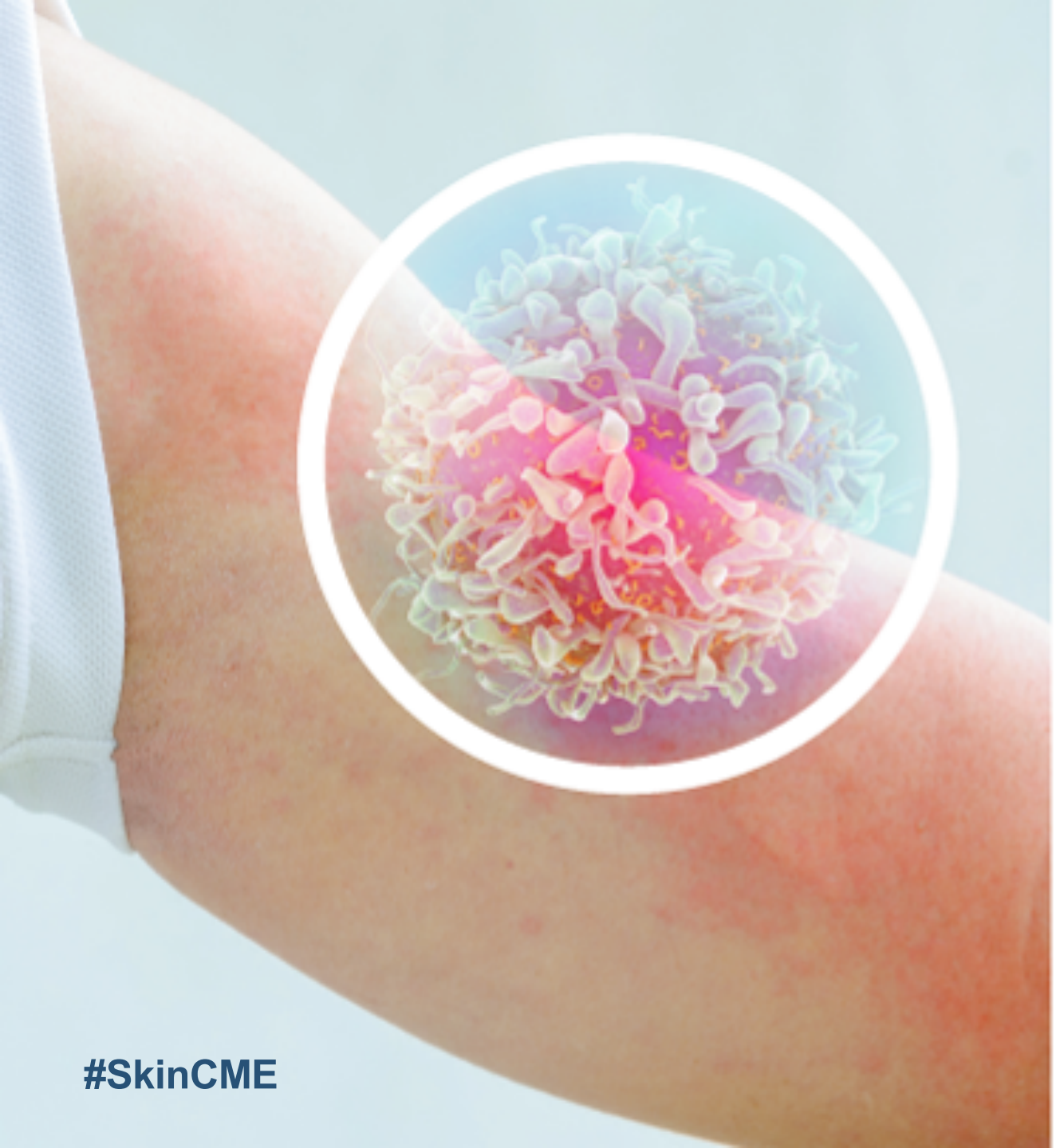
## *Immune Regulation, Cutaneous Tolerance, and T-cell Plasticity*

**NOVEMBER 18, 2016**

**4:00PM – 5:30PM**

New York Academy of Medicine
NYC – Hosack Hall

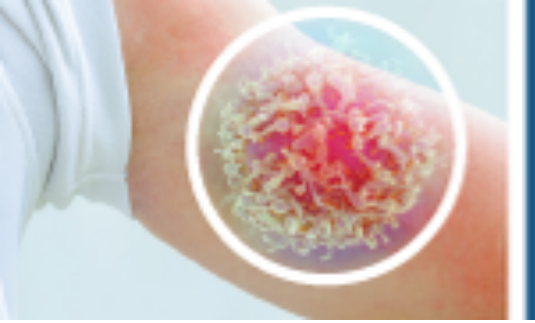
*Co-provided by* USF HEALTH | CME Outfitters



#SkinCME

# Vijay K. Kuchroo, DVM, PhD

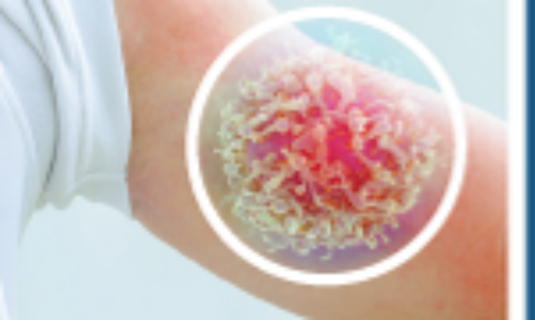
Samuel L. Wasserstrom Professor of Neurology
Harvard Medical School
Director, Evergrande Center for Immunologic Diseases
Harvard Medical School and Brigham and Women's Hospital
Boston, MA



# Vijay K. Kuchroo, DVM, PhD

## Disclosures

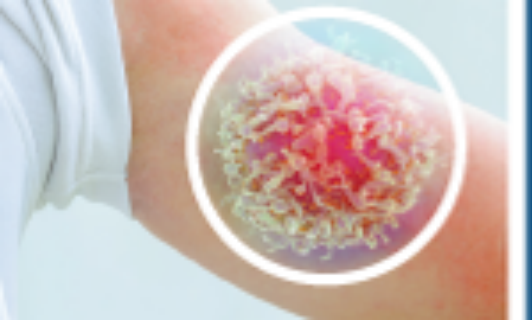
- ***Research/Grants:*** NIH/National Institute of Neurological Disorders and Stroke (NINDS); NIH/National Institute of Diabetes and Digestive and Kidney Disease (NIDDK); NIH/National Institute of Allergy and Infectious Diseases; Crohn's and Colitis Foundation of America; Guthy Jackson Charitable Foundation; Sanofi/Genzyme Corporation



# Audience Response

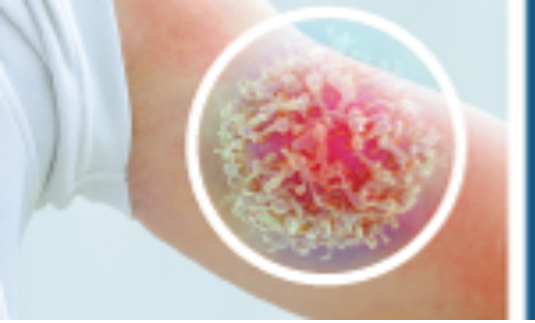
**Why do patients treated with anti-IL-17 develop fungal infections?**

A. IL-17 induces neutrophil infiltration critical for clearing fungal infections;
B. IL-17 is the cytokine that induces tissue inflammation;
C. IL-17 is induced by fungal products and therefore initiates an anti-fungal response;
D. IL-17 directly kills fungal spores.



**Why do the IBD patients treated with anti-IL-17 and anti-IL-17R antibody have increased disease severity?**

A. IL-17 and Th17 cells are not critical for induction of IBD
B. Antibody binds to the IL-17 receptor on the gut epithelial cells and kills them;
C. Antibody inhibits growth of protective FoxP3+ Treg cells;
D. Antibody may be inhibiting function of protective Th17 cells in the gut



# Functional Plasticity of Pathogenic and Nonpathogenic Th17 Cells

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Yasuhiro Kishi
Takaaki Kondo
Youjin Lee
Anneli Jager
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Lionel Apetoh
**Ana C. Anderson**

**Broad Institute**
Meromit Singer
Nir Yosef
Orit Rozenblatt-Rosen
**Aviv Regev**

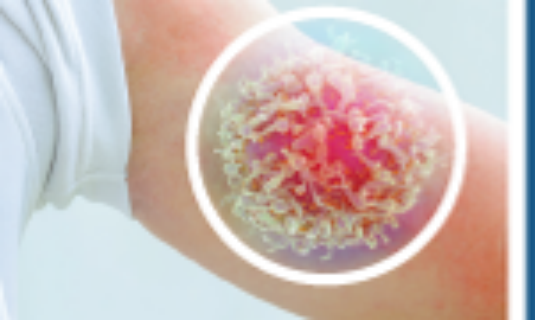
**Arlene Sharpe**
Harvard Medical School

**Jellert Gaublomme**
Hongkun Park

**Alex Shalek**
Harvard college

**Markus Kleinewietfeld**
**David Hafler**
Yale Medical School

**Raymond Sobel**
Stanford



# Functional Plasticity of Pathogenic and Nonpathogenic Th17 Cells

- Introduction and Th17 differentiation
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  - Single cell RNA-seq
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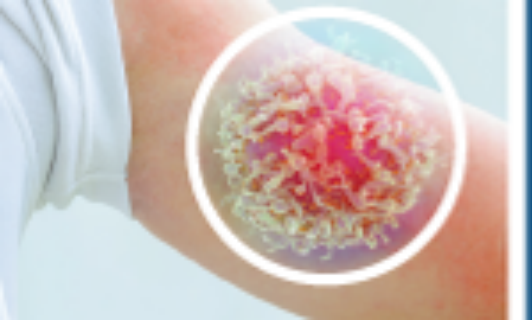
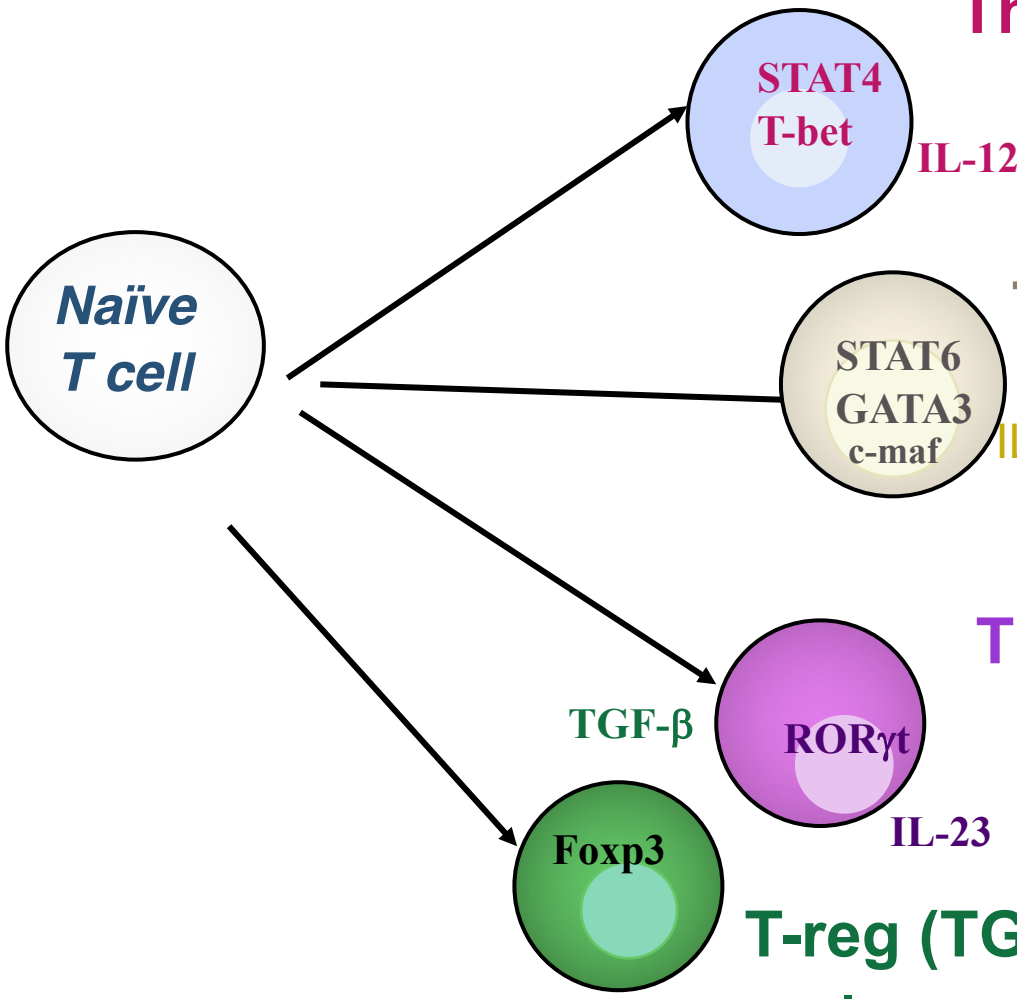


# Fates of CD4 T Cells



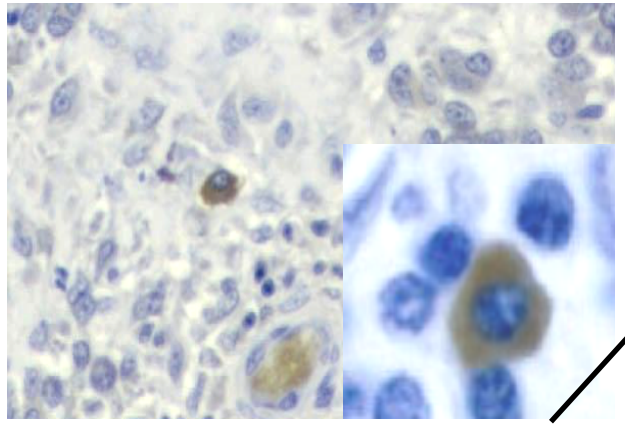

**Th1 (IFN-γ):Host defense**
**(IC pathogens)**
**autoimmunity**

**Th2 (IL-4, IL-5,IL-13):**
**Host defense (parasites), Allergy, asthma**

**Th17 (IL-17): Host defense**
**(EC pathogens)**
**Inflammation**
**Autoimmunity**

**T-reg (TGF-β, IL-10, IL-35)**
**Immunosuppression**

# Th17 Cells are Highly Pathogenic and Induce Autoimmune Tissue Inflammation



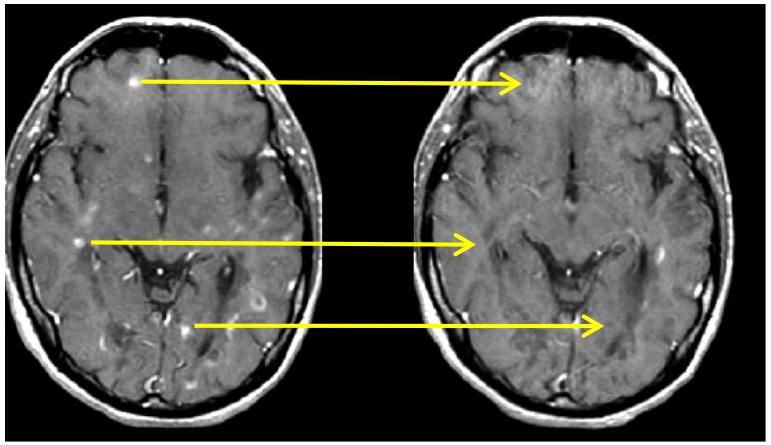



Miossec P, Korn T, Kuchroo V. *N Engl J Med*. 2009;361(9):888-898.

# Anti-IL-17 Antibody (Secukinumab) Reduces MRI-Lesions in Multiple Sclerosis

**MRI lesions in MS**

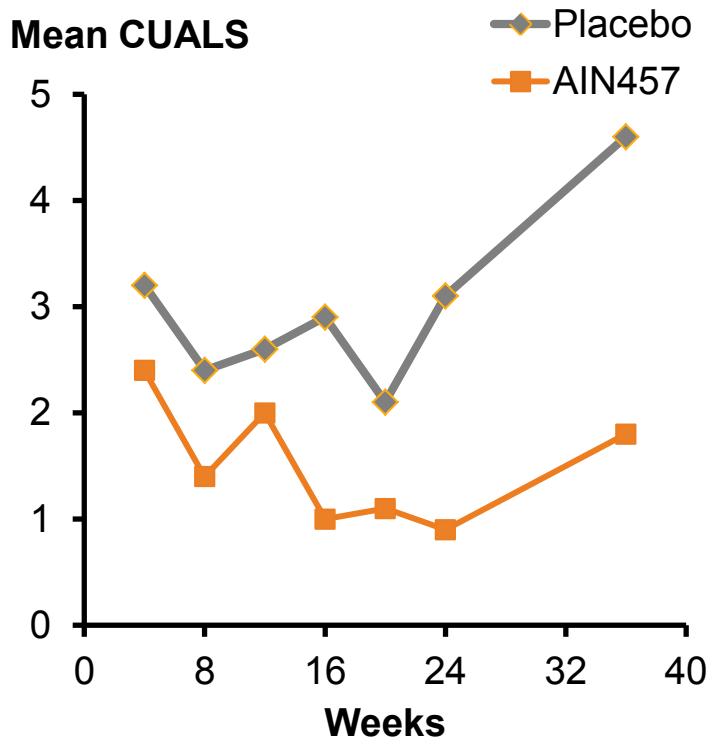
T1 magnetic resonance imaging (T1 MRI) with contrast agent (Gadolinium).



Baseline

Week 24
AIN457

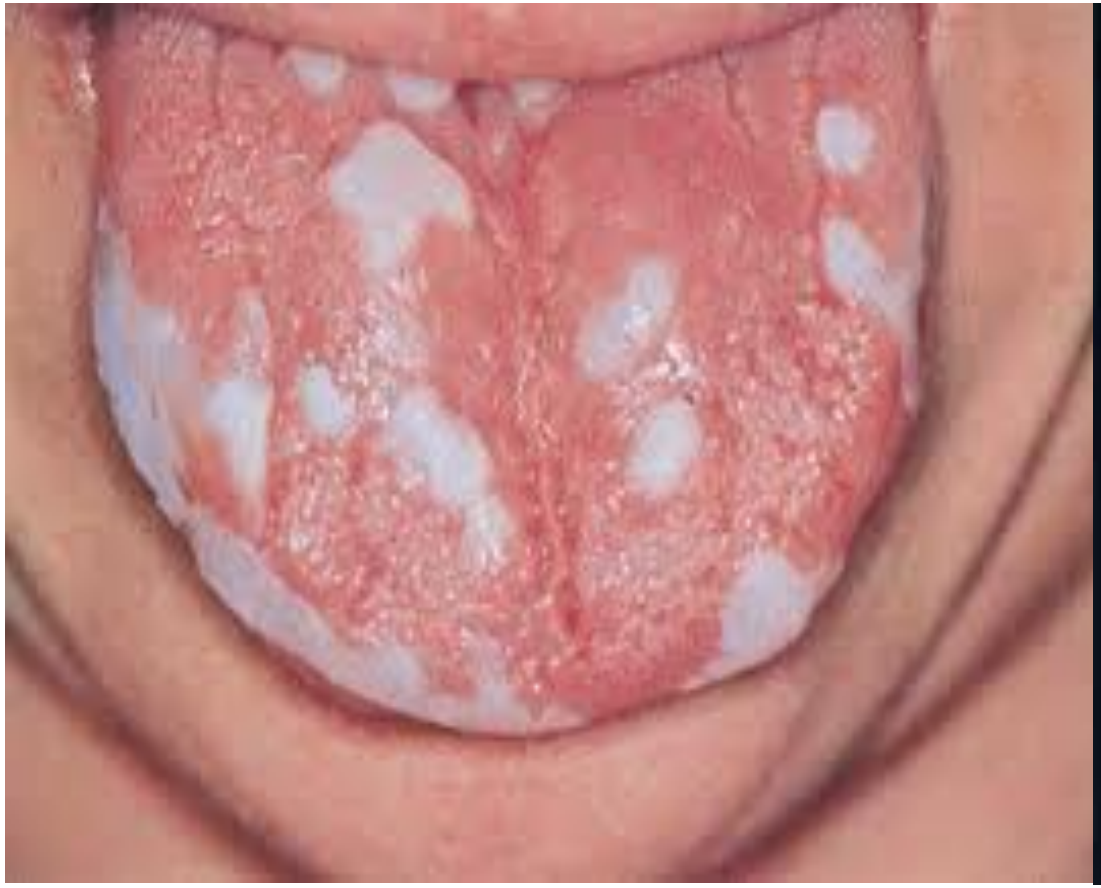
**C**ombined **U**nique **A**ctive **L**esions (**CUALS**[1])

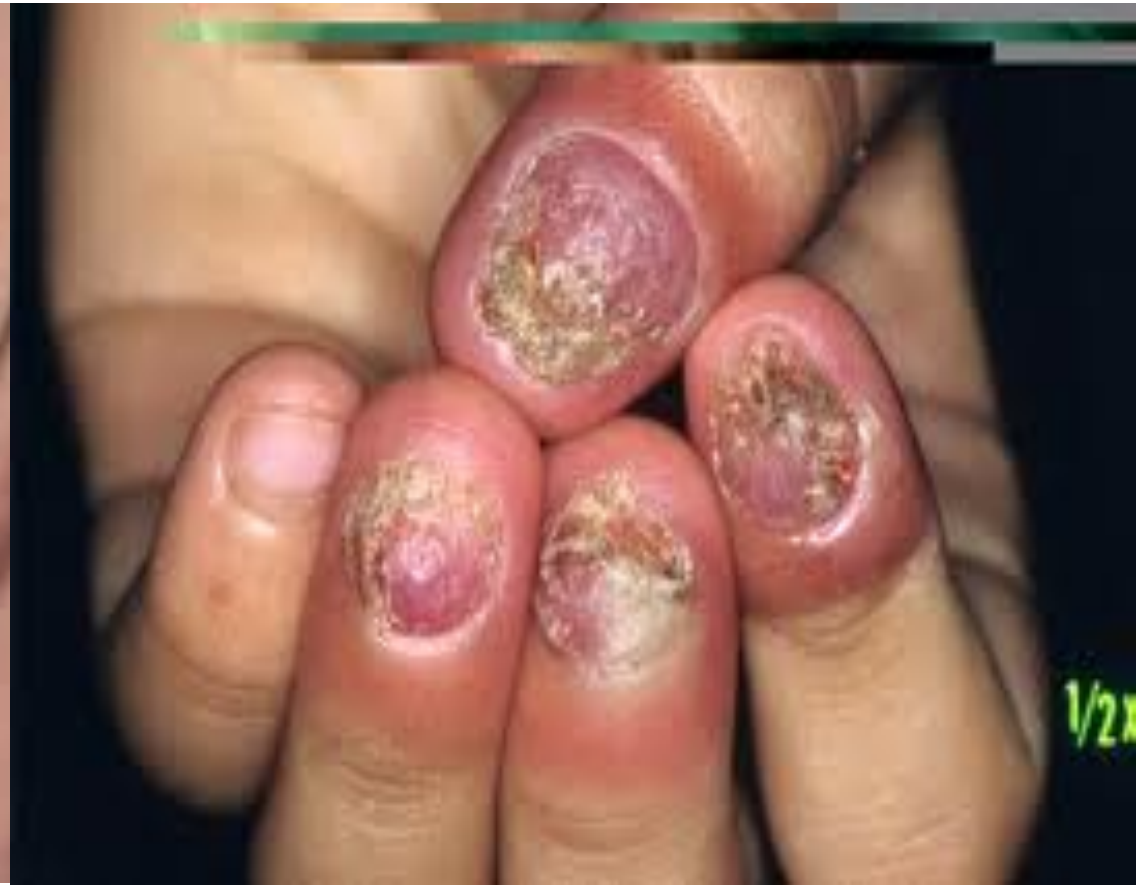



[1] *CUALS = new T1 Gd-enhancing lesions or new/enlarging T2 lesions*
*Data presented at ECTRIMS, Oct. 13, 2012: Study performed in 73 Relapsing-remitting MS patients (38 AIN457, 35 Placebo)*

Havrdová E, et al. *ECTRIMS* October 13, 2012. Abstract 168.

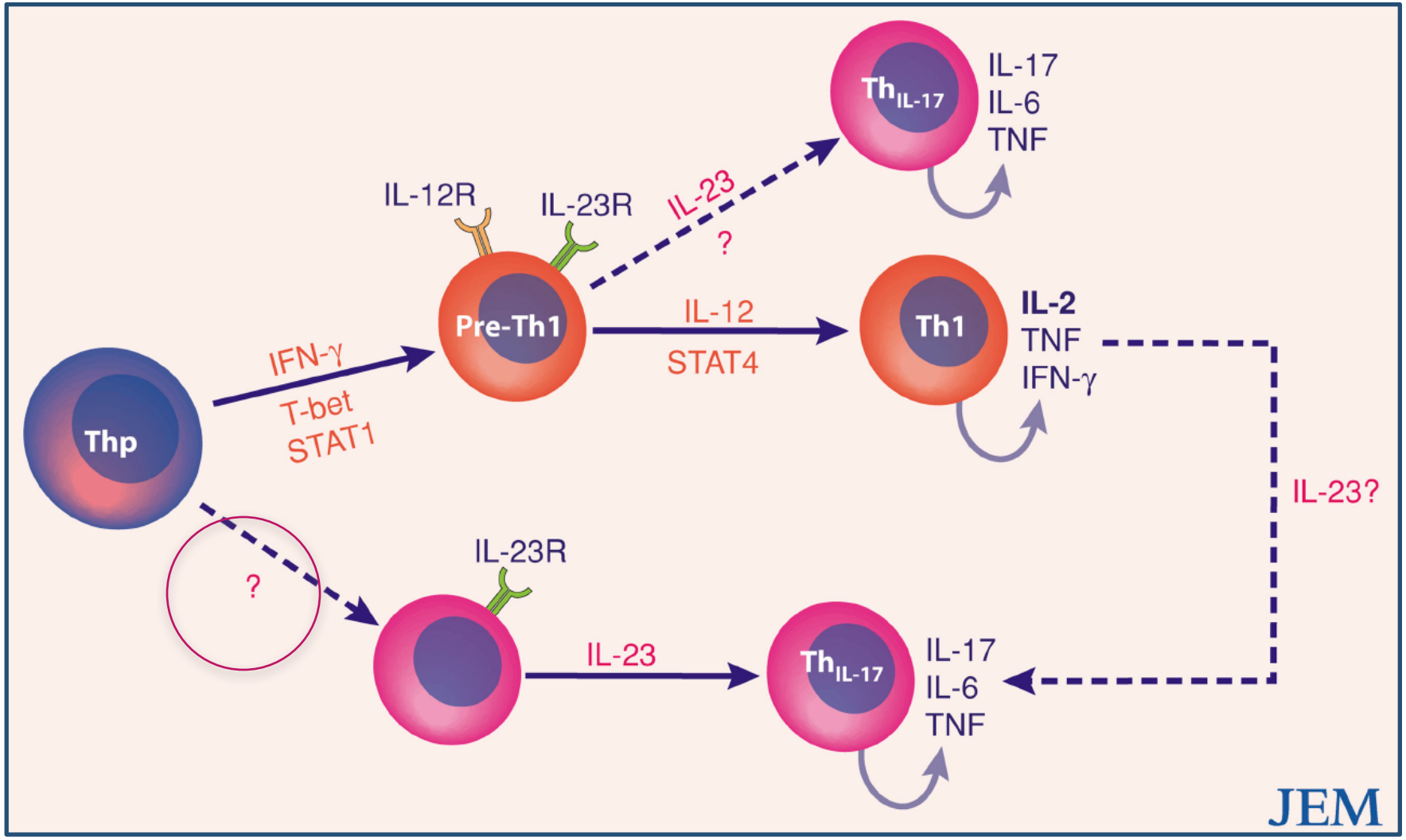
# Defects in IL-17/TH17 Pathway in Chronic Mucocutaneous Candidiasis





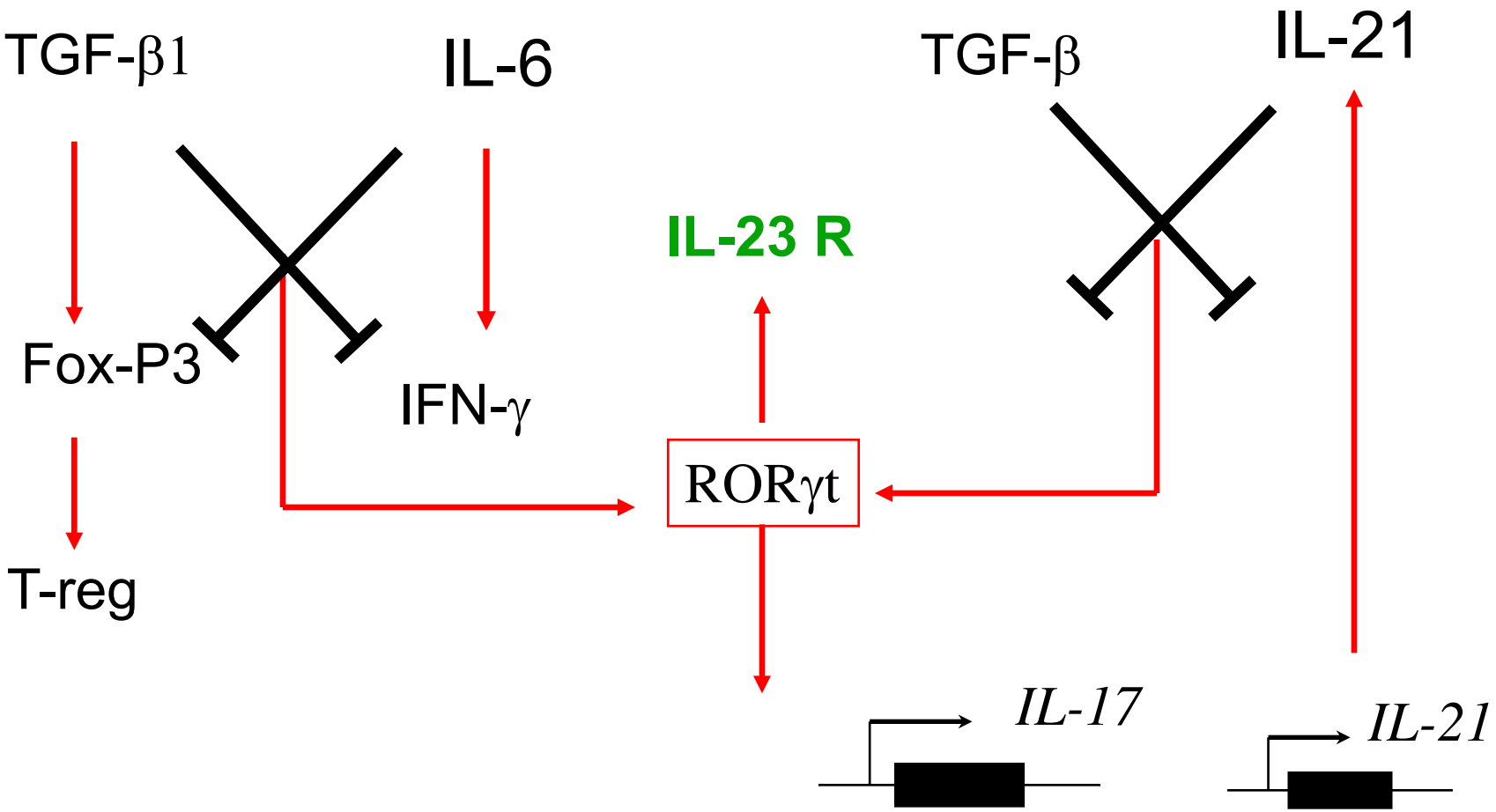
Puel A, et al. *Curr Opin Immunol*. 2010;22(4)467-474.

# IL-12 and IL-23-Induced T Helper Cell Subsets: Birds of the Same Feather Flock Together




Bettelli E, et al. *J Exp Med.* 2005;201(2):169-171.

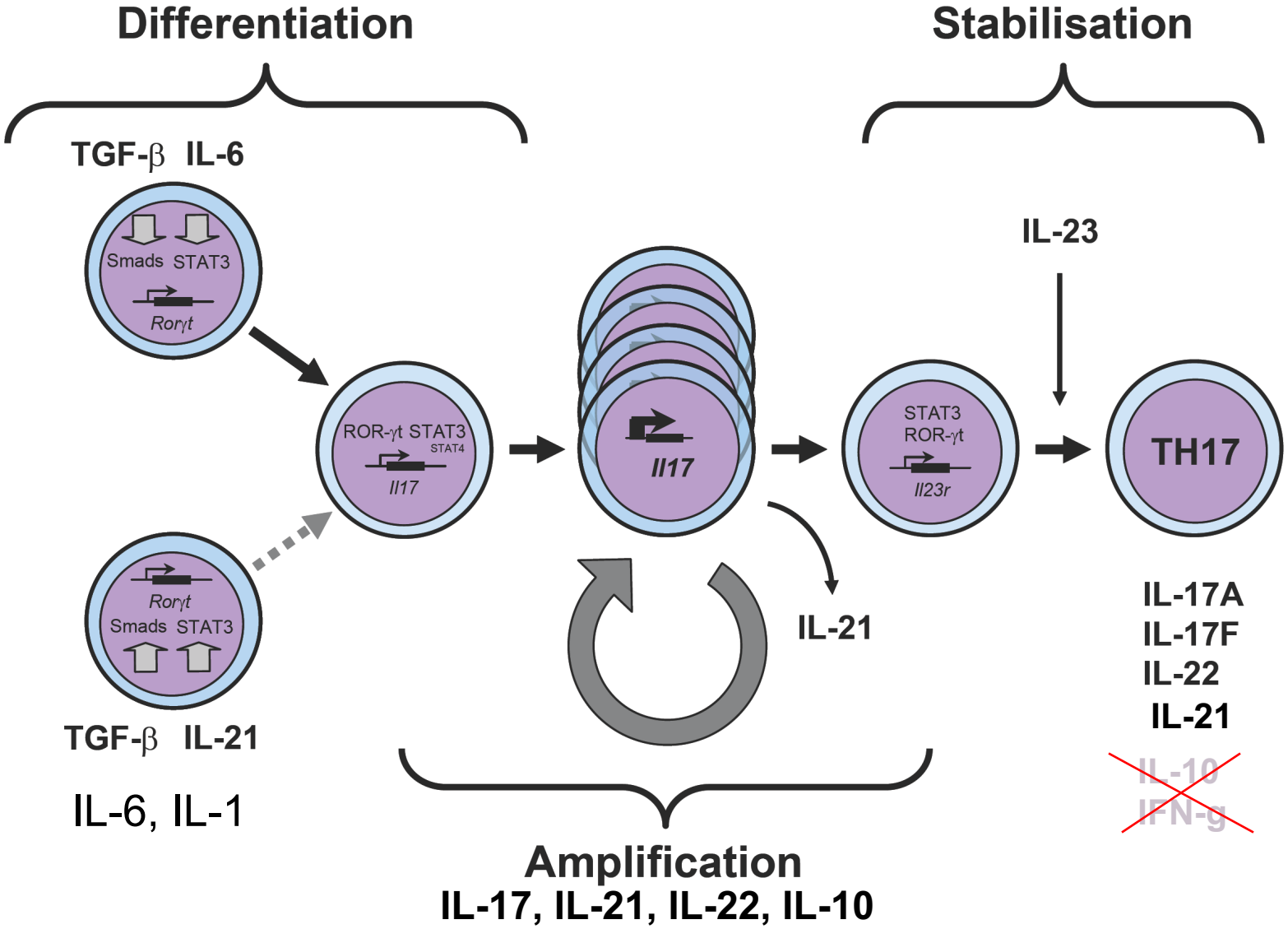
# Induction of Th17 cells




| Induction | Amplification | Stabilization |
|---|---|---|
| TGFβ + IL-6 | TGF-β + IL-21 | IL-23 |

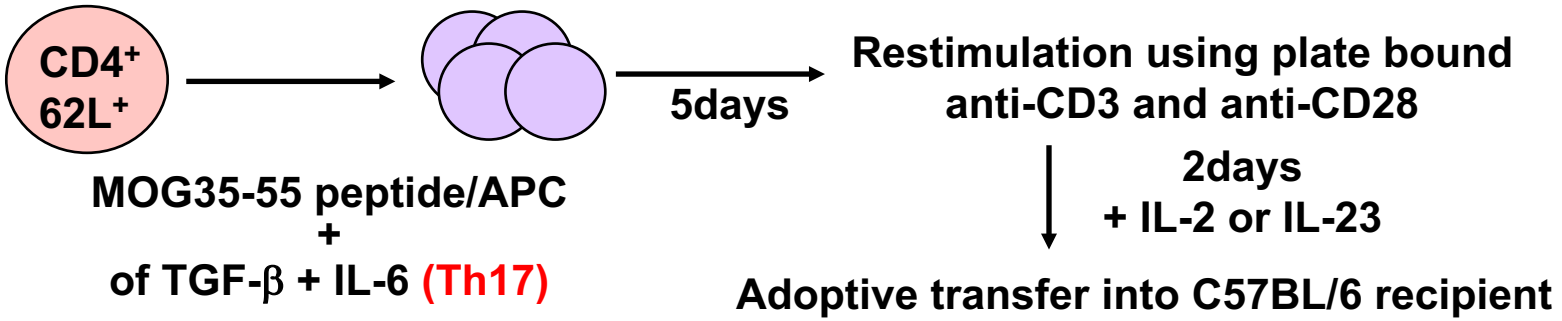
Korn T, et al. *Nature.* 2007;448(7152):484-487. Bettelli E, et al. *Nature.* 2006;441(7090):235-238.; Awasthi A, et al. *J Immunol.* 2009;10(2):167-175. Bauquet AT, et al. *Nat Immunol*. 2009;10(2):167-175.

# Hypothesis for the Generation of Th17 Cells (Three Step Model)

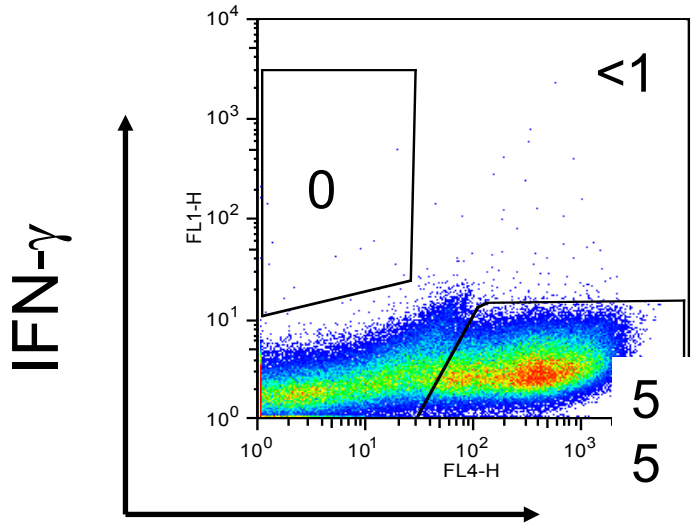


# IL-23 Promotes Pathogenicity in Th17 Cells

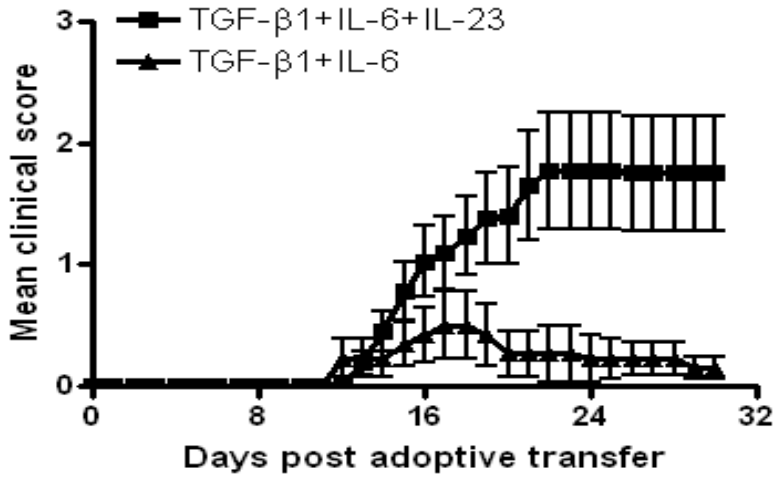
## 2D2 TcR transgenic




## Cytokine profile

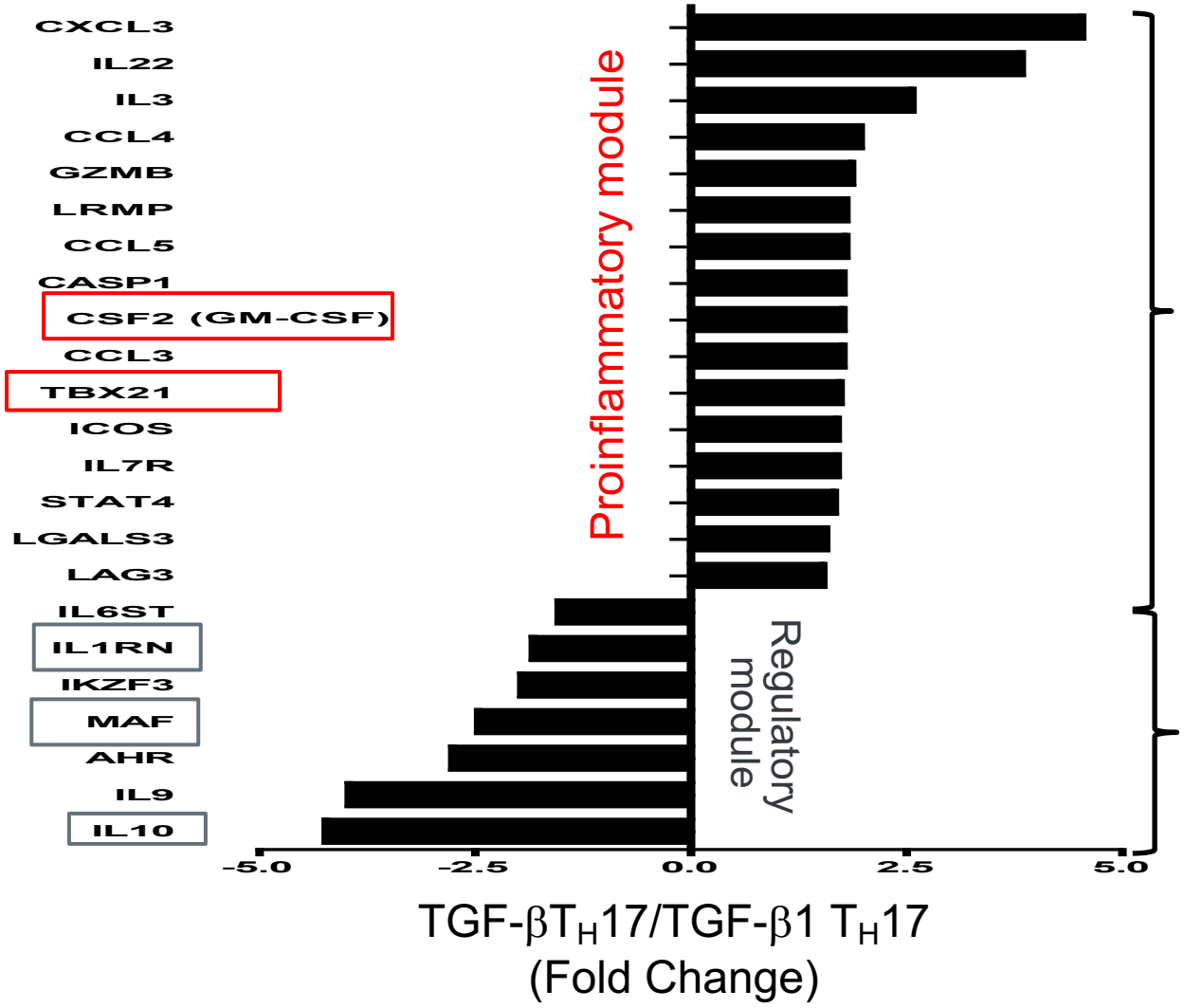



## EAE induction




Anneli Jaeger, Youjin Lee

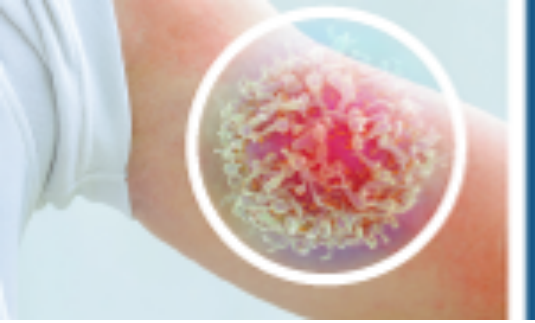
# Signature of Pathogenic Th17 cells




**Up-regulated in pathogenic $T_H17$ "Pathogenic cells"**
**IL-1β+IL-6+IL-23**
**TGFβ3+IL-6+IL-23**

**Up-regulated in TGF-β1-$T_H17$ "nonpathogenic cells"**
**TGF-β+IL-6**

Lee Y, et al. *Nature Immunology*. 2012;13(10):991-999.



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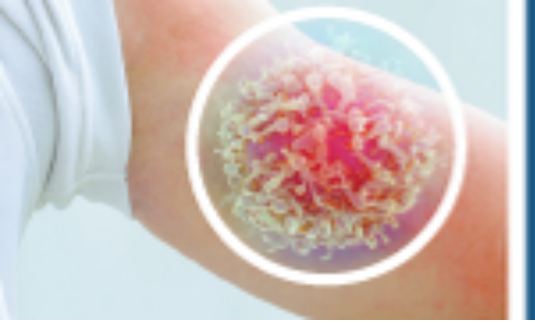


# Single-Cell Expression Profiling Pipeline

1. Cell Harvest

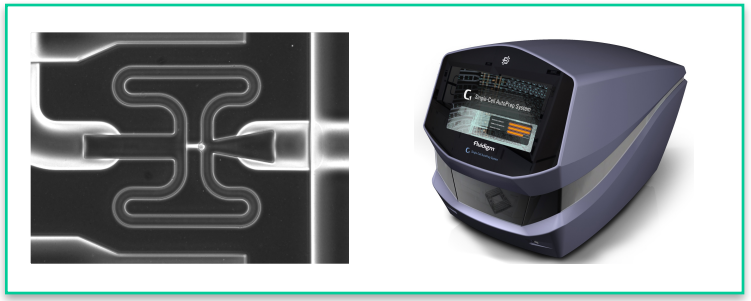
2. Single Cell Preparation
   (a) C1: Cells → Whole Transcriptome Amplification
   (b) Multiwell Plates

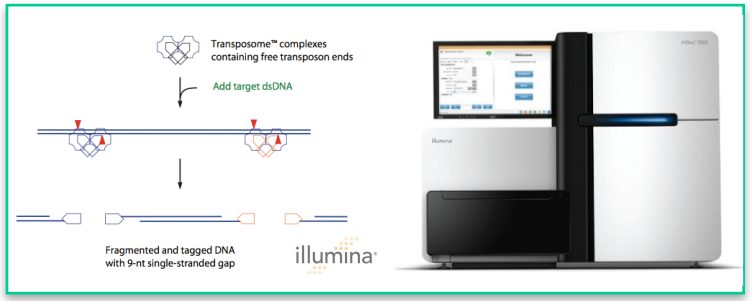
3. Expression Profiling

Cell work

Single cell processing

Library construction, validation, HiSeq





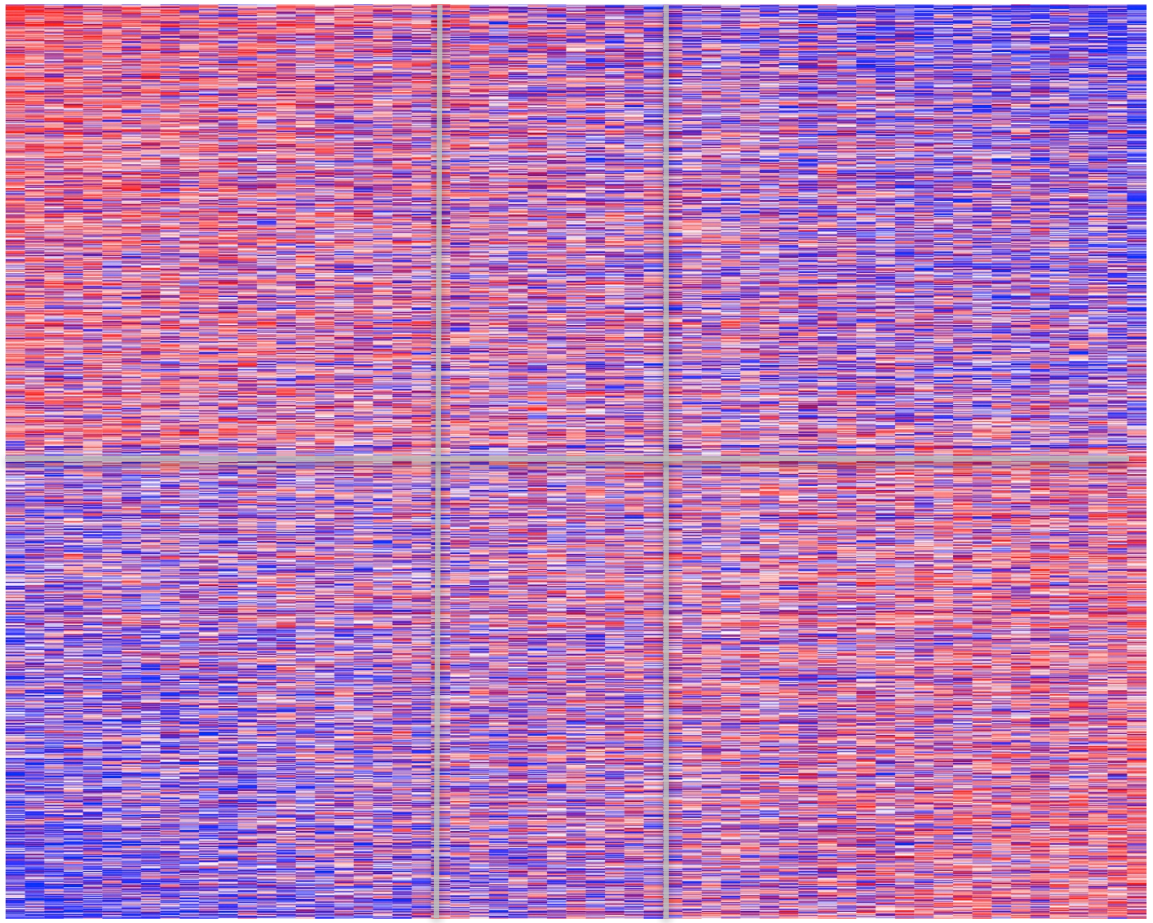
# Th17 Cell Heterogeneity Shows a Spectrum

Cells (n = 74)

Pathogenic Th17 signature

Pro-inflammatory Genes (IL-17, IFN-g, GMCSF, MInA)

Genes

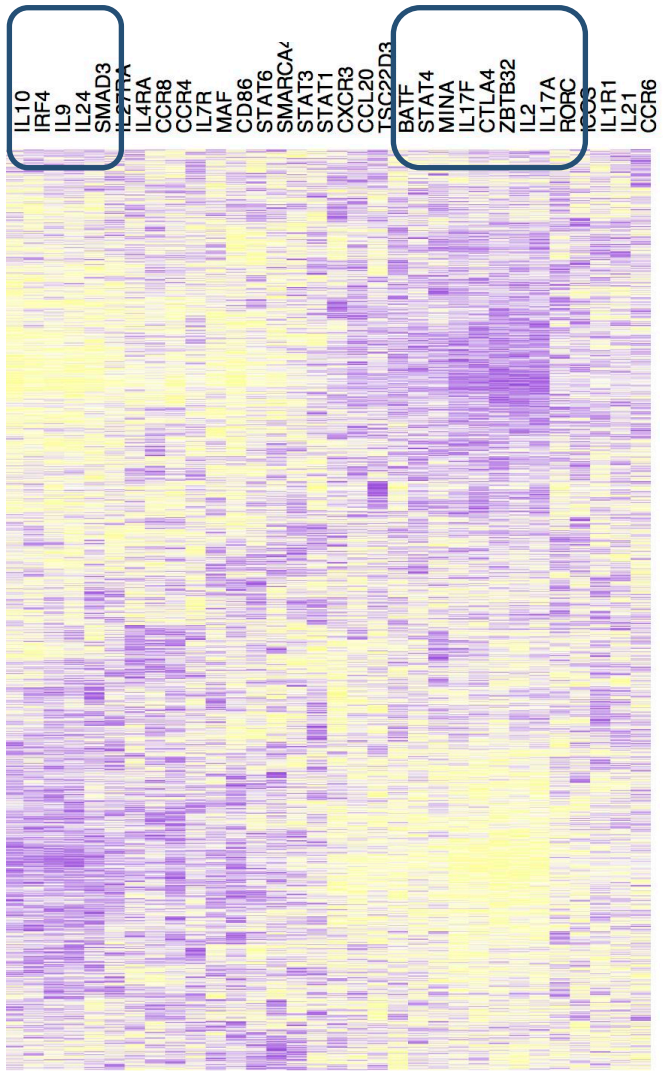


Nonpathogenic Th17 signature

Regulatory Genes (IL-10, IL-9, cMaf, IL-24, FoxP3, Trp53)

Jellert Gaublomme, Aviv Regev, Hongkun Park, unpublished

# Co-Variation Identifies Novel Regulators of Pathogenic and Nonpathogenic Th17 State




**Positive correlation with proinflammatory *Th17* module:**

*IL-17a, IL-23R, GM-CSF, Mina*

**and the novel regulators: i.e.**

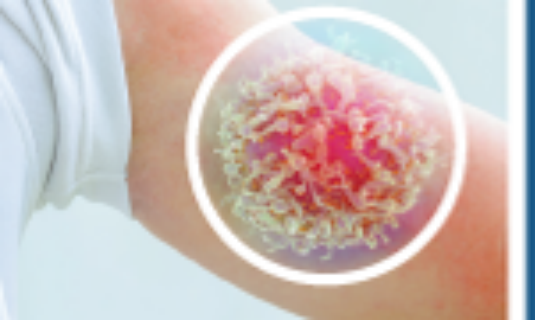
***GPR65***
***TOSO***
***Dec1***
***Zbtb32***
***Gimap5***
***Ilf2***

**Correlation with regulatory Th17 module:**

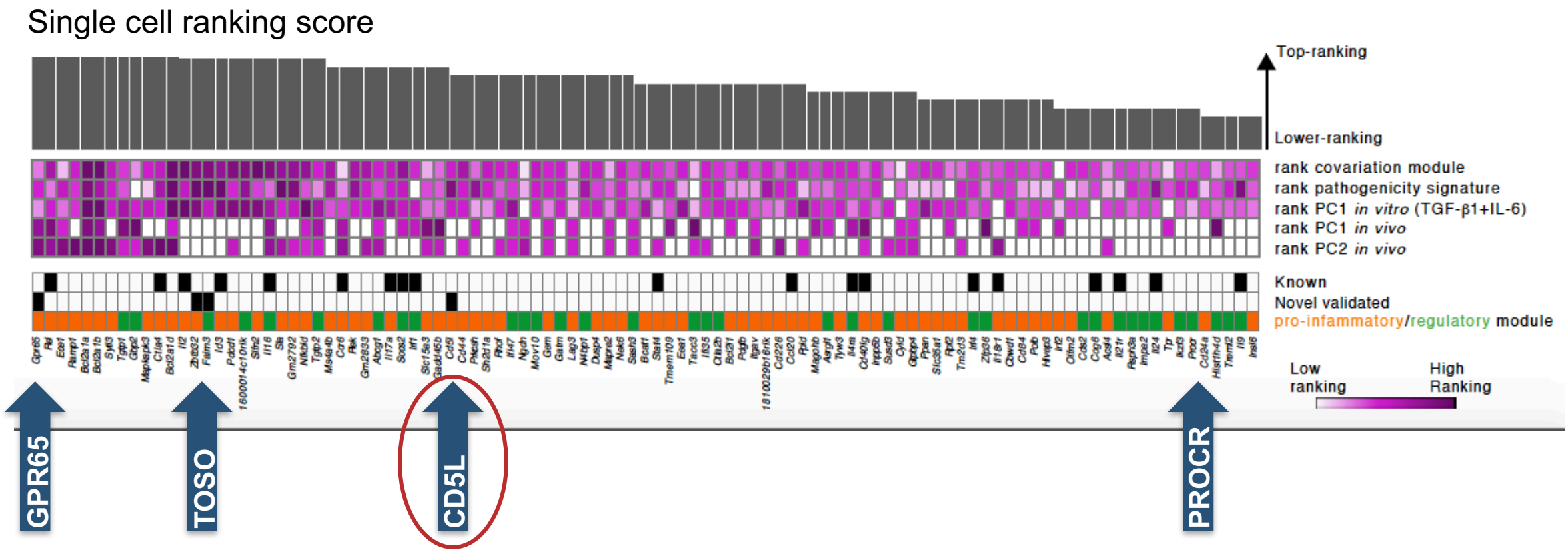
*IL-10, Ahr, Ikzf3, IL24, IL9*

**and novel regulators: i.e.**

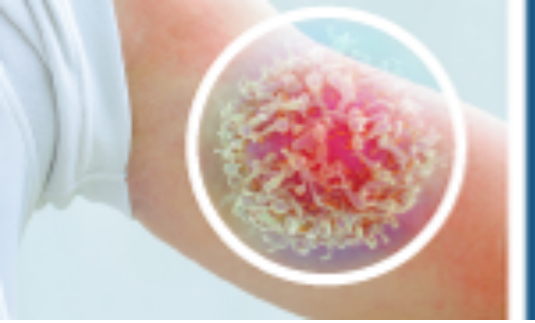
***PROCR***
***Nfe2l2***
***Sash3***
***Tgfbr3***



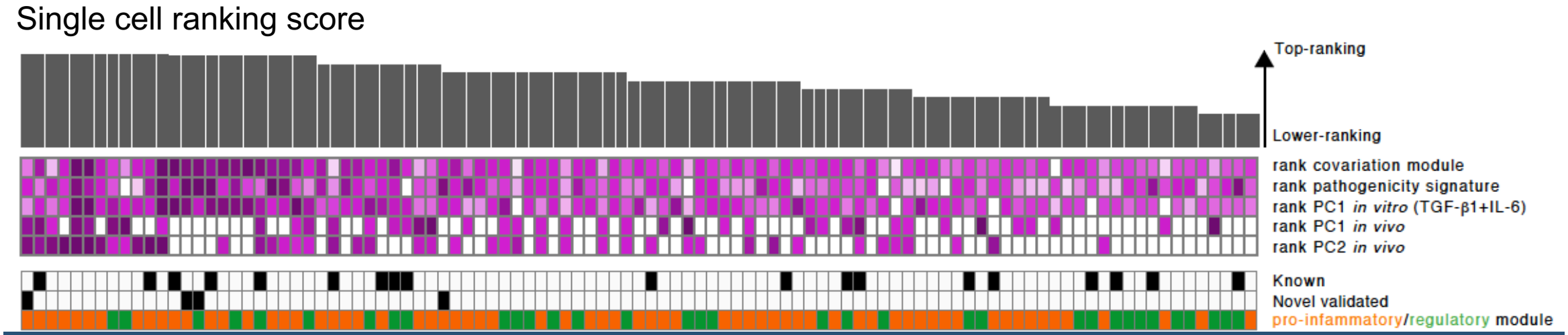
# Genes Ranked and Selected for Functional Validation




Gaublomme JT, et al. *Cell*. 2015; 163(6):1400-1412; Wang C, et al. *Cell.* 2015;163(6):1413-1427.



# Genes Ranked and Selected for Functional Validation

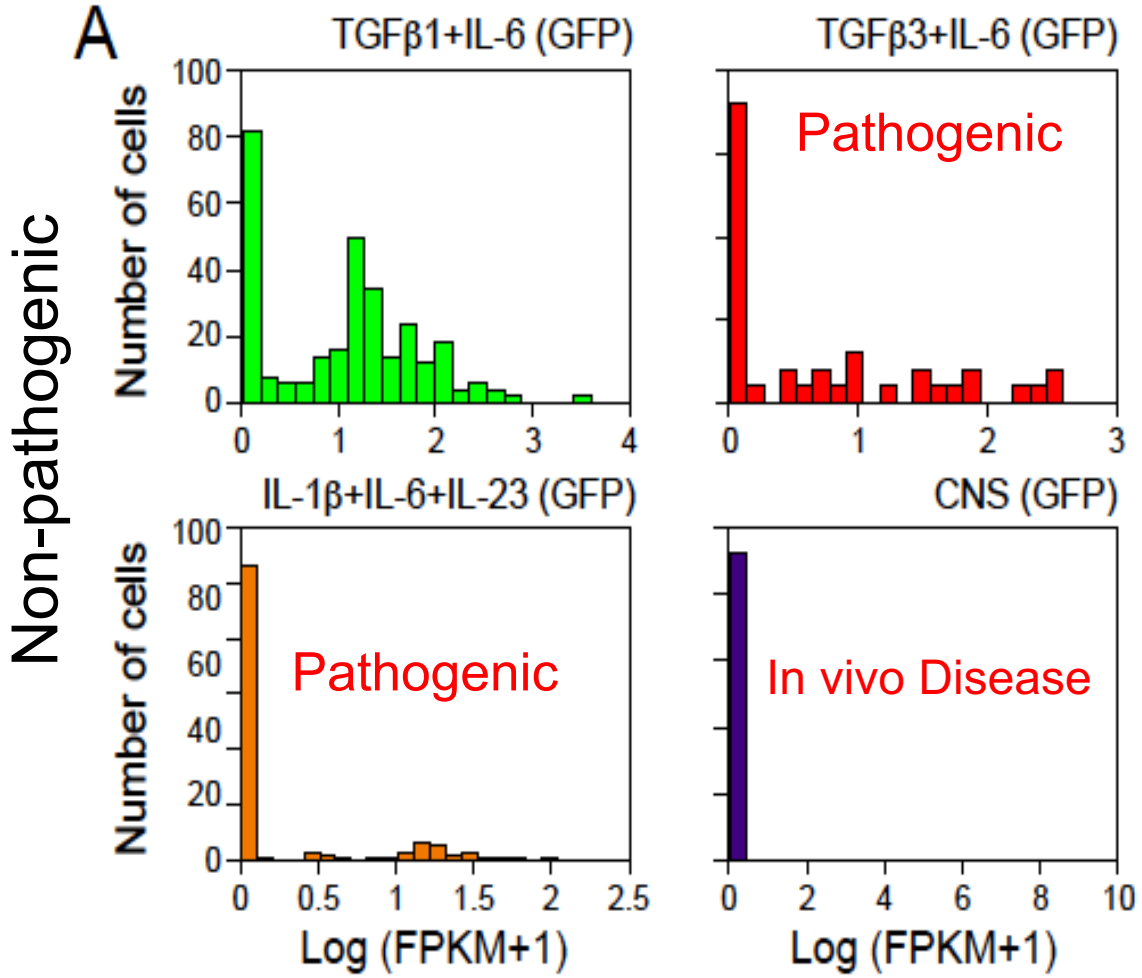


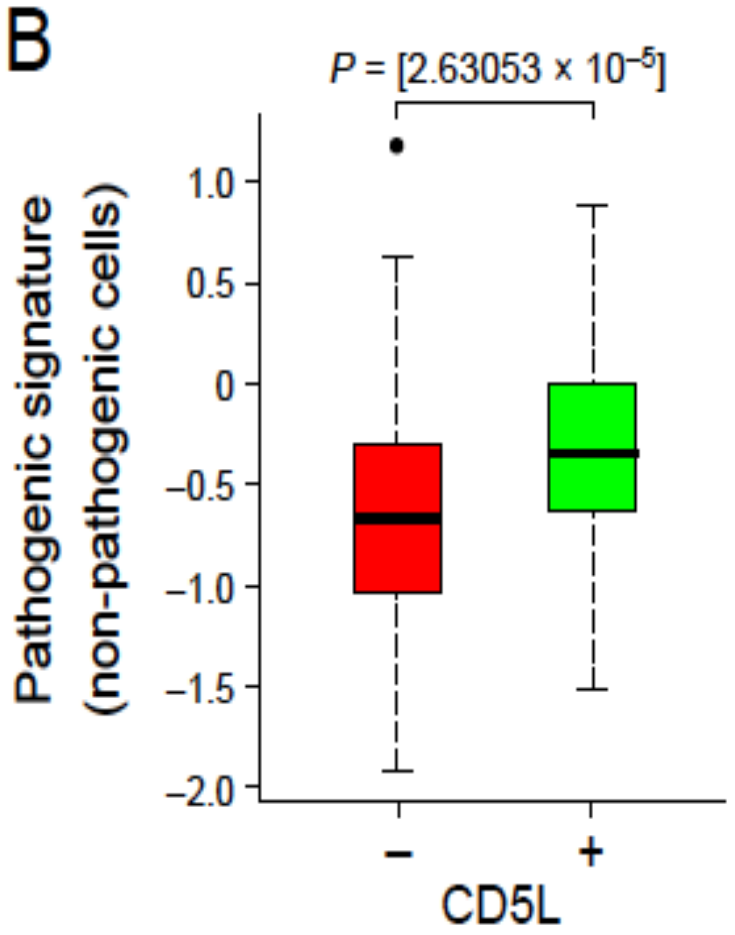

## CD5L, a novel regulator of pathogenic Th17 state

Expressed at a higher frequency in non-pathogenic but not in pathogenic Th17 cells

Gaublomme JT, et al. *Cell*. 2015; 163(6):1400-1412; Wang C, et al. *Cell.* 2015;163(6):1413-1427.

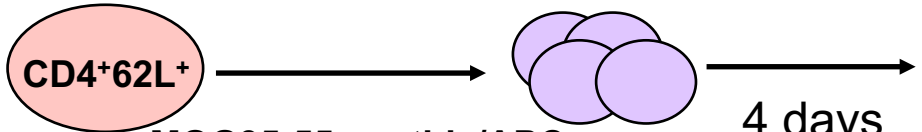
# CD5L is Highly Expressed on Nonpathogenic Th17 Cells



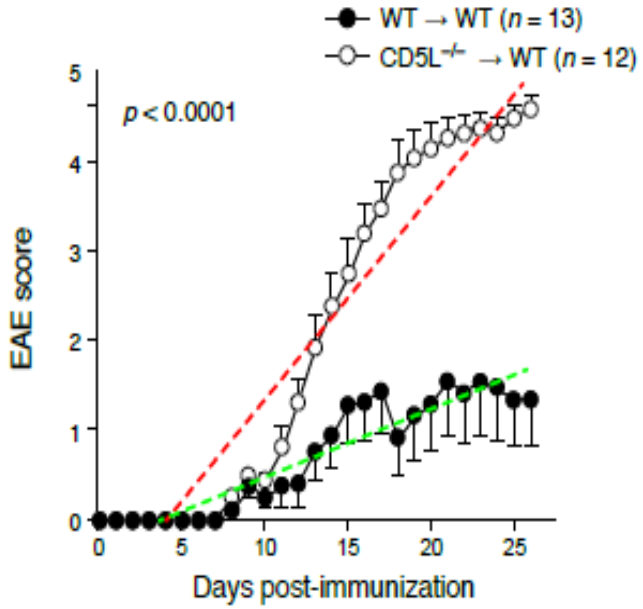



# Loss of CD5L Converts Non-Pathogenic Th17 cells Into Pathogenic Effector Th17 Cells

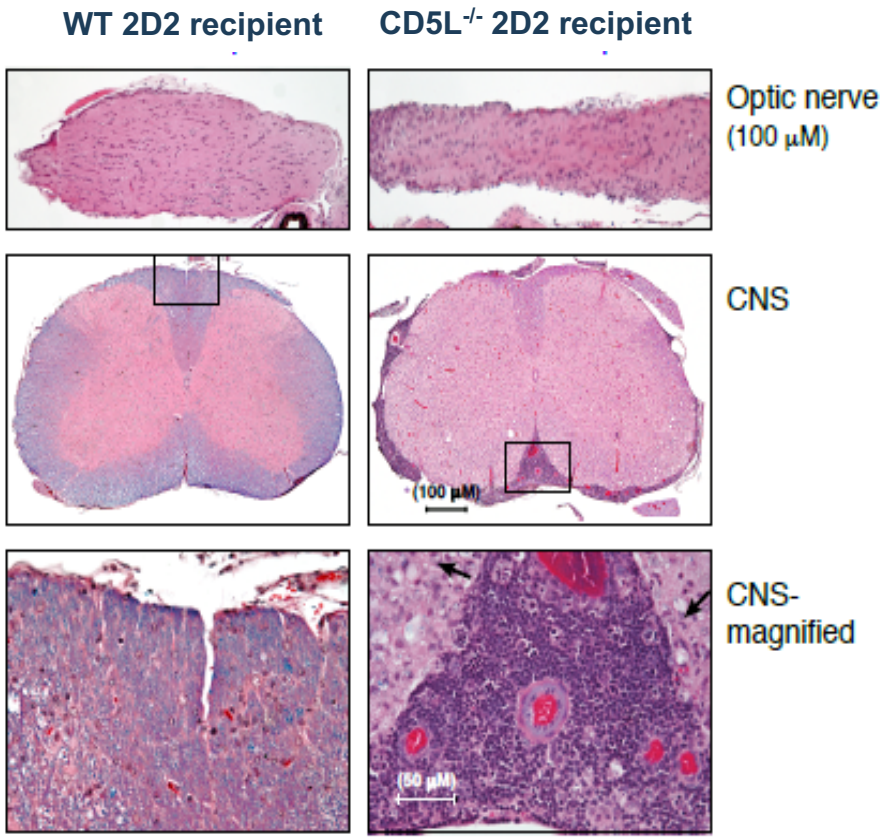
2D2 TcR transgenic
Naïve T cells
WT or CD5L$^{-/-}$



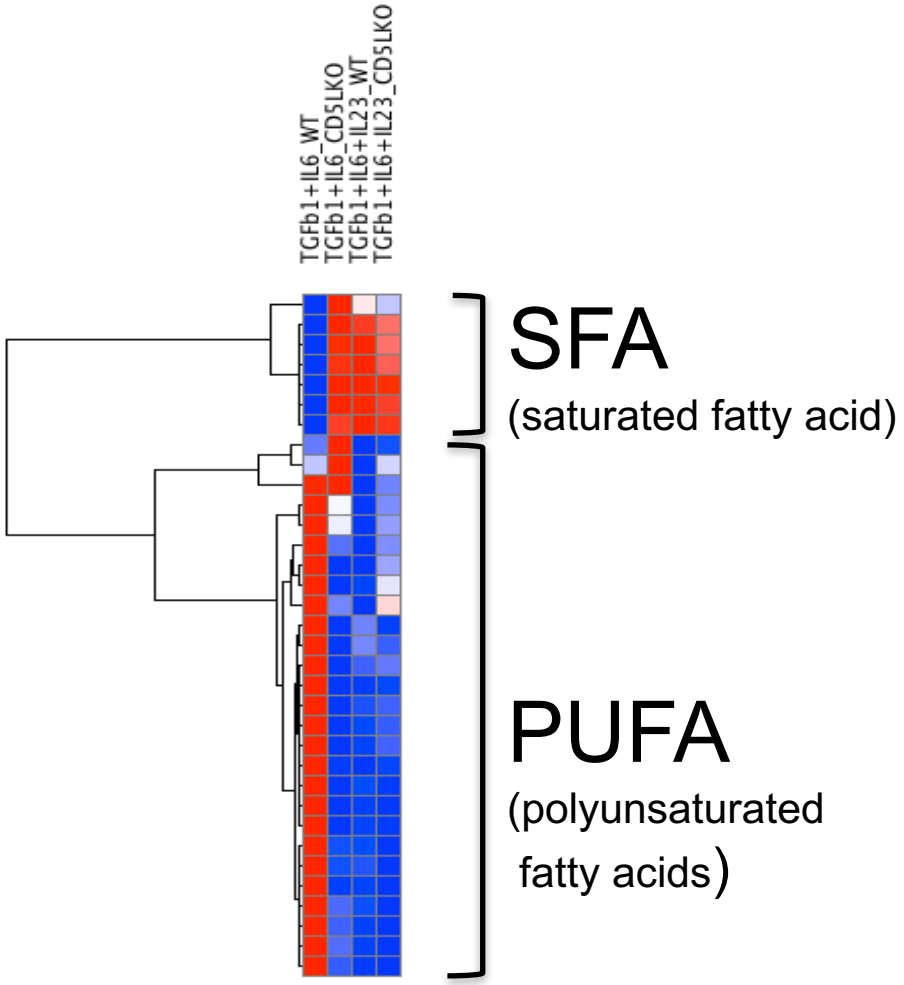

**Adoptive transfer into WT mice**
**EAE**
**T cell response**

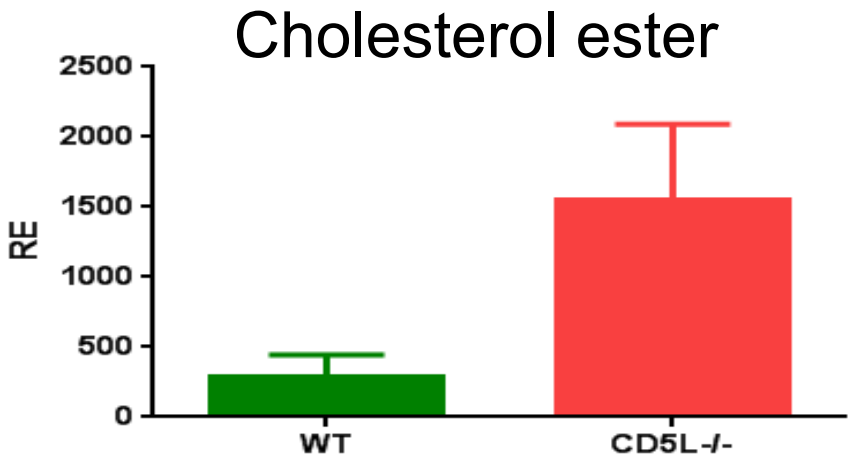


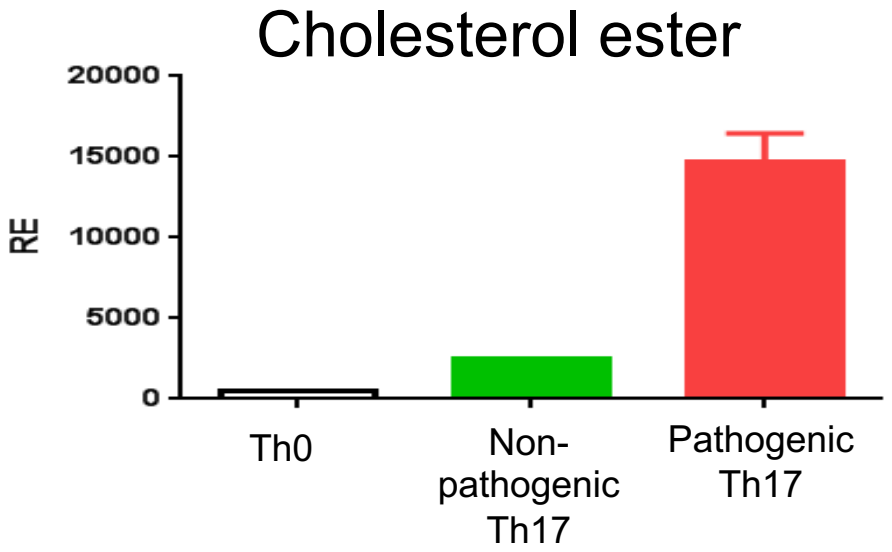

| | Incidence rate | Day of onset | Mean max score |
|---|---|---|---|
| WT | 7/13 | 13.4±1.3 | 1.7±0.6 |
| CD5L-/- | 12/12 | 11.0±0.4 | 4.7±0.1 |

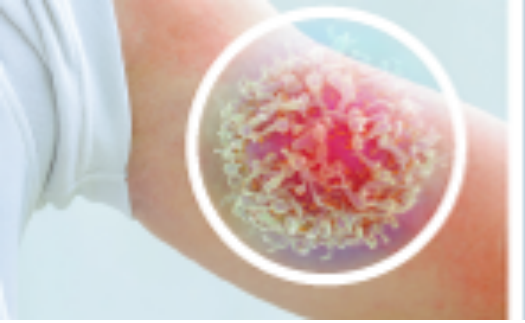


# LIPIDOMICS: CD5L Regulates Balance Between Saturated vs. Polyunsaturated Fatty Acids by Binding to Fatty Acid Synthase

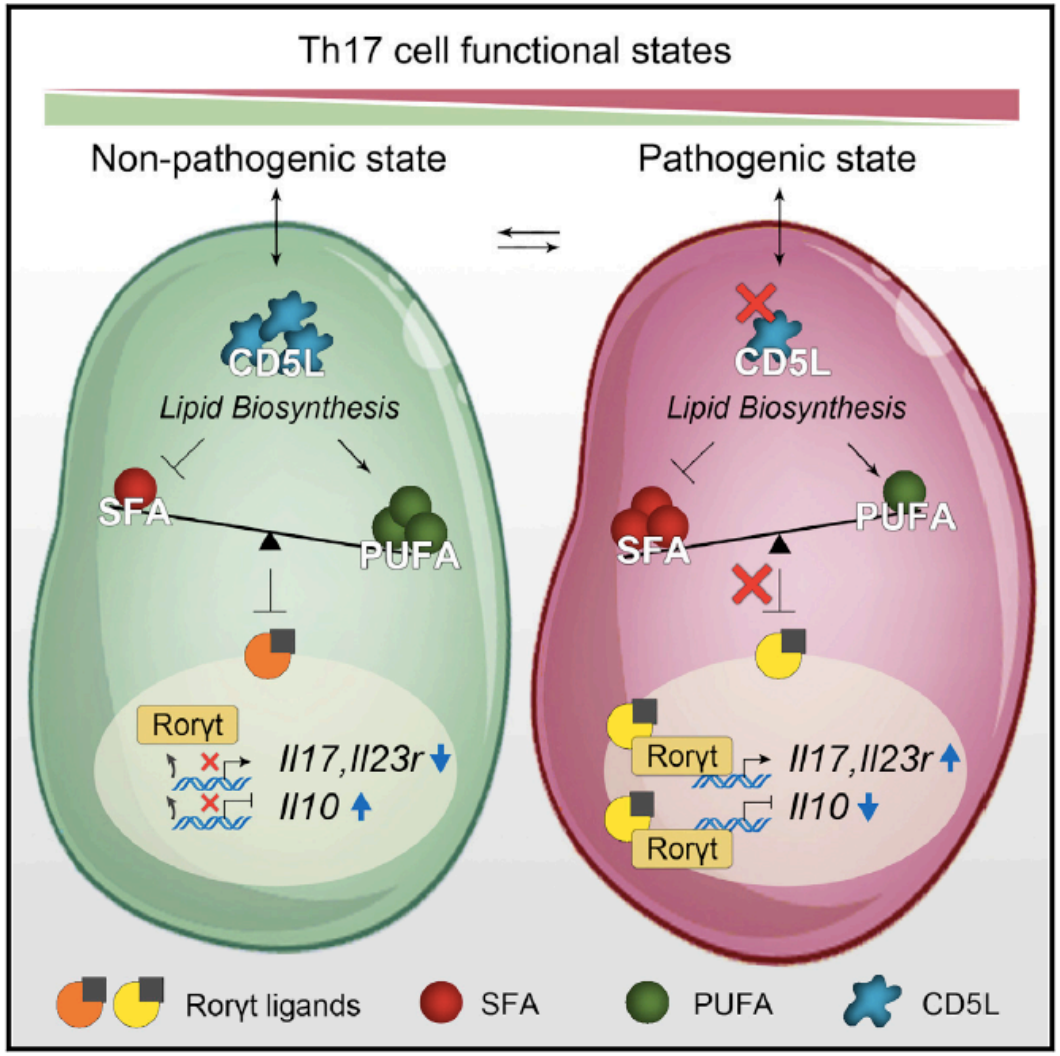


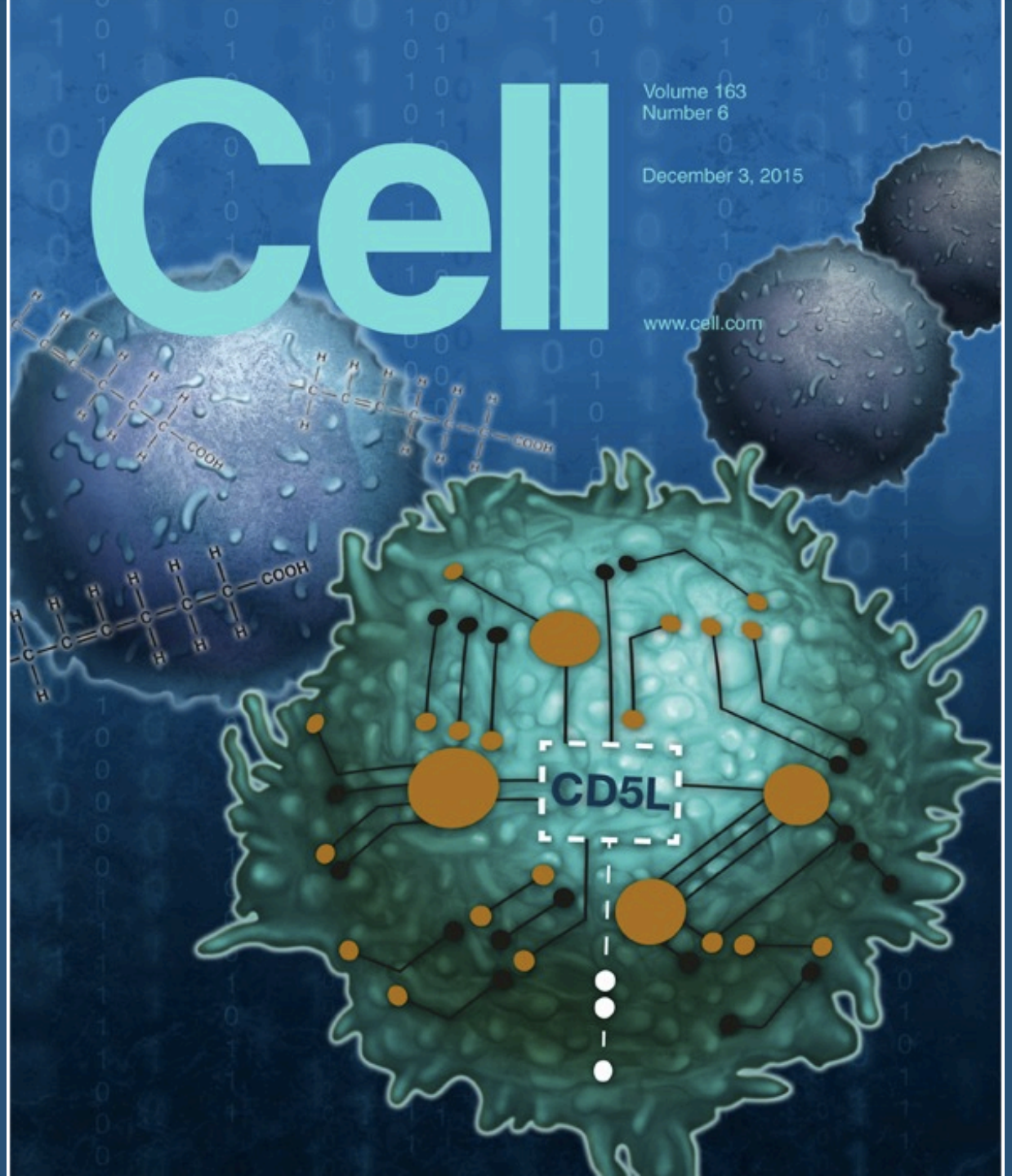



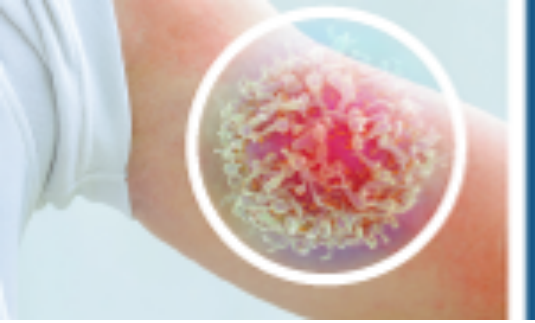


# CD5L Regulates Lipid Biosynthesis by Binding to Fatty Acid Synthase



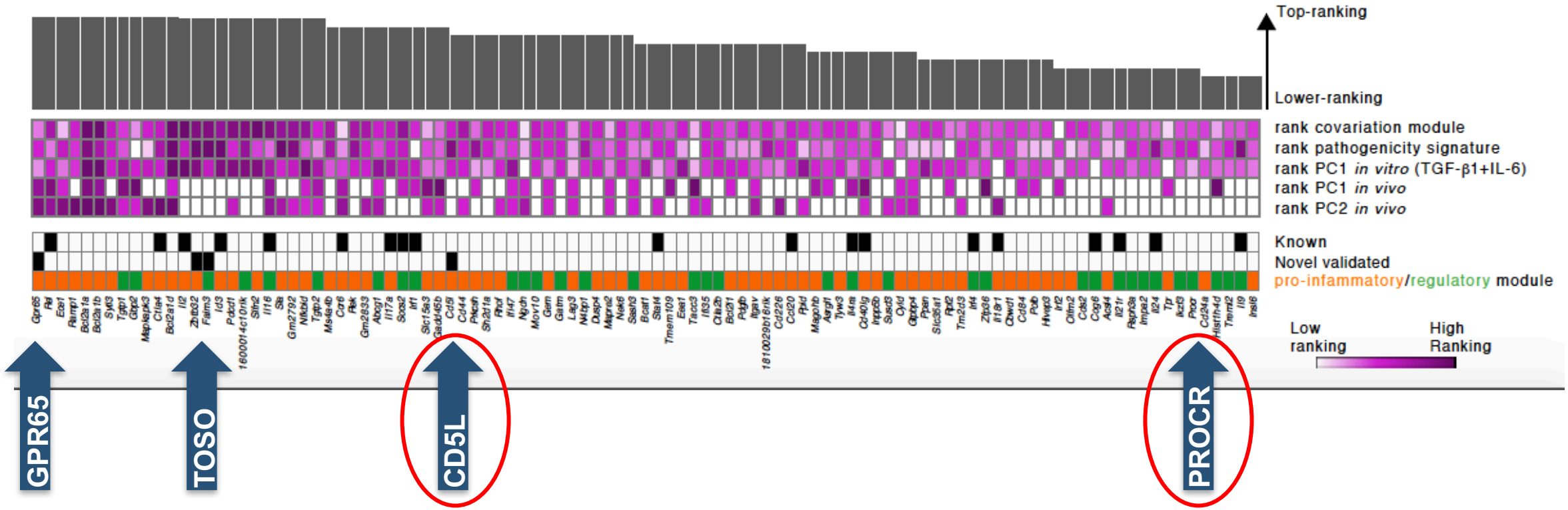

Wang C, et al. *Cell.* 2015;163:1-15.


Cell
Volume 163
Number 6
December 3, 2015
www.cell.com
CD5L



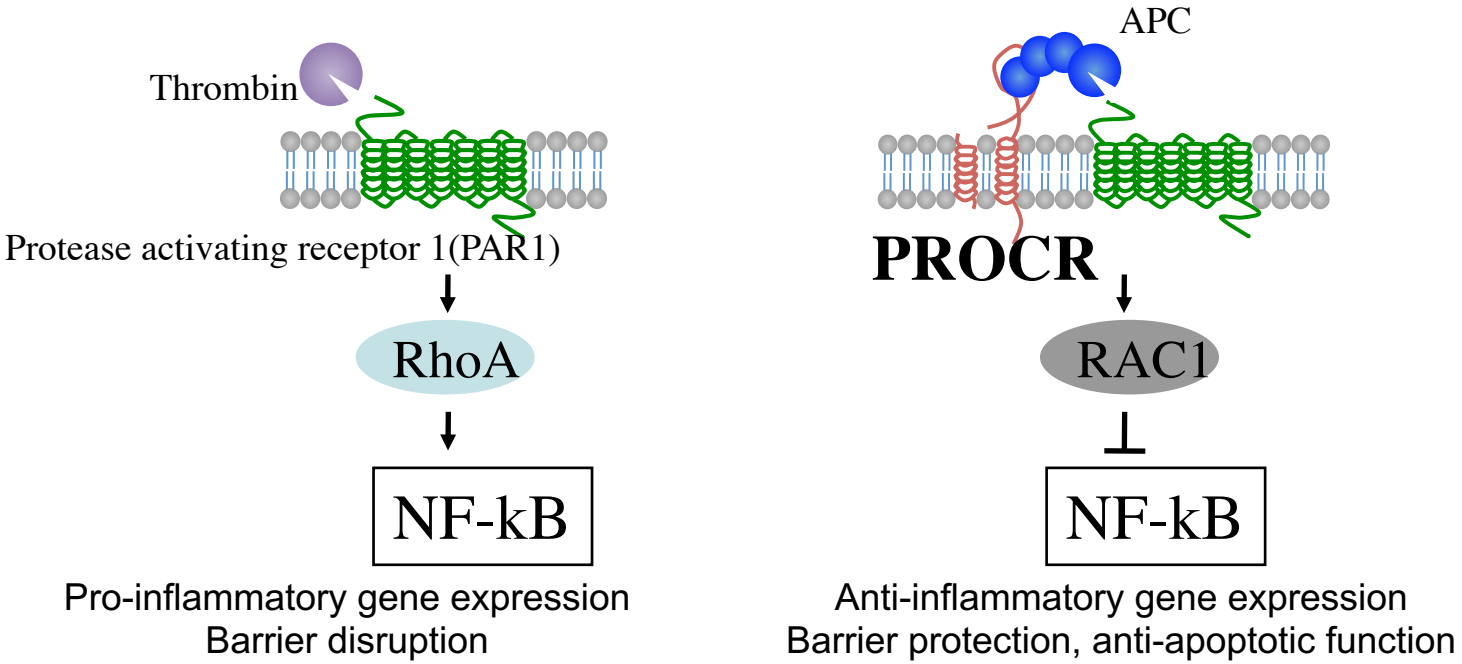
# Genes Ranked and Selected for Functional Validation

Single cell ranking score

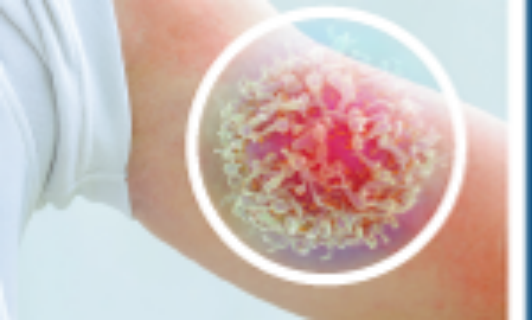


# PROCR (Protein C Receptor)

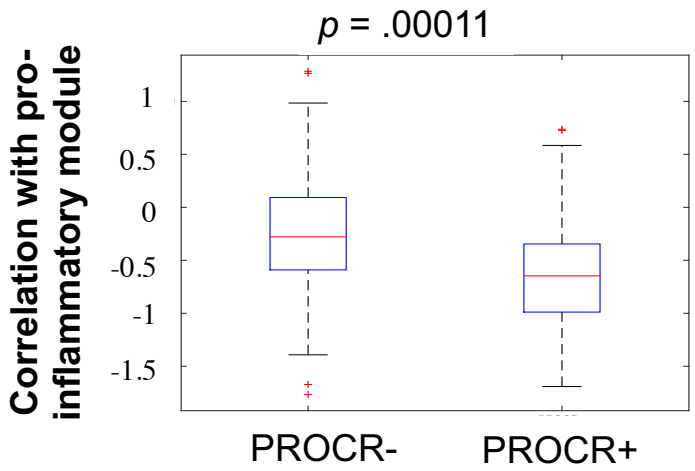
- Protein C receptor (PROCR) was originally identified as a type1 transmembrane glycoprotein that binds to protein C and activated protein C (APC).
- PROCR is expressed on many type of cells including endothelial cells, monocytes, neutrophils, muscle cells, neuronal cells, and cancer cells.
- PROCR plays a crucial role in the protein C anticoagulant pathway by promoting protein C activation.
- PROCR signaling provides multiple cyto-protective effects (anti-inflammatory activities, anti-apoptotic activity, and protection of endothelial barrier integrity).
- The role of PROCR on T cells is not known.

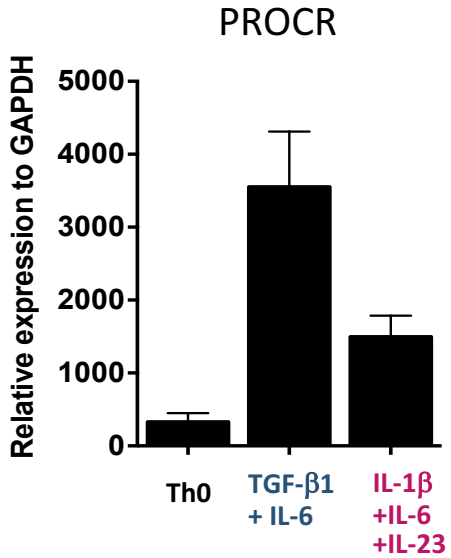


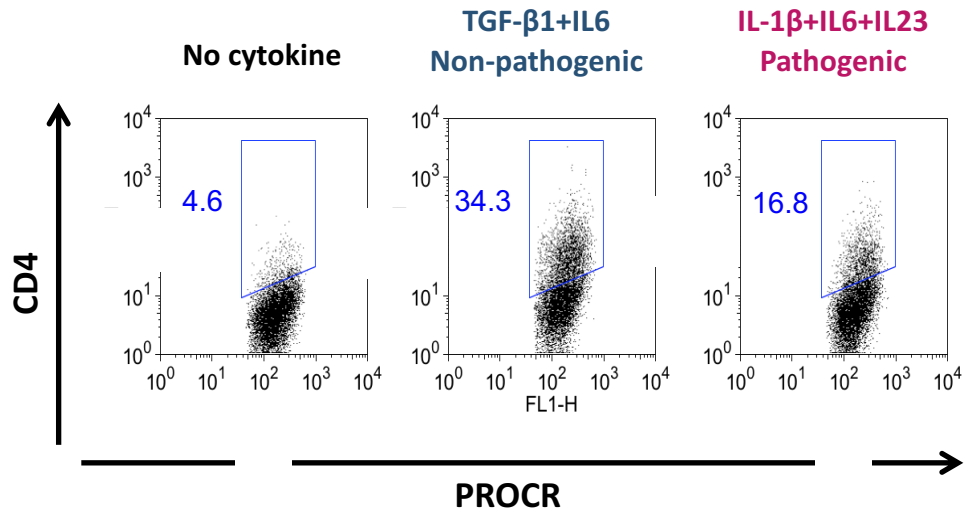

Rao LVM, et al. *Blood*. 2014;124(10):1553-1562.

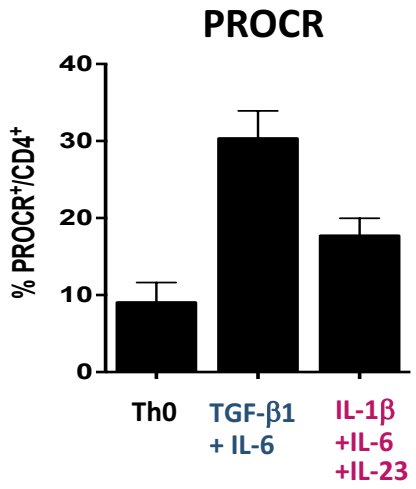


# PROCR Expression on Th17 Cells Inversely Correlates With Their Pathogenicity



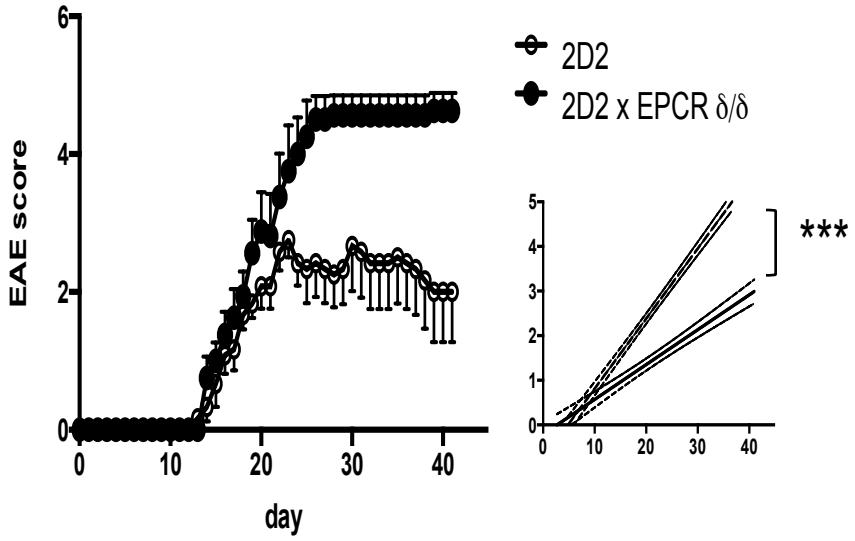
# Loss of PROCR Enhances Pathogenicity of Th17 cells

2D2 TcR transgenic
Naïve T cells
WT or CD5L$^{-/-}$

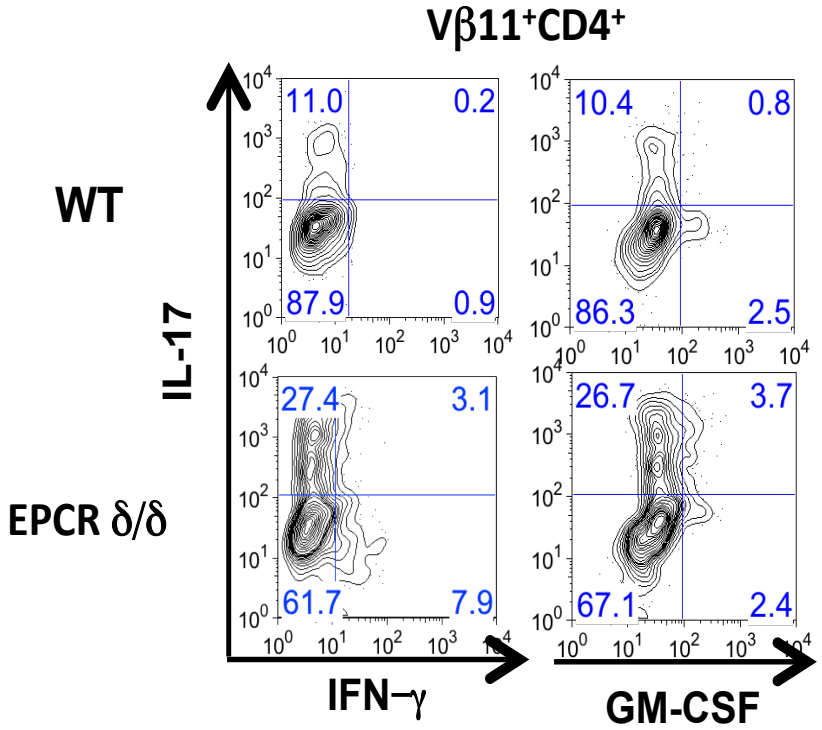

MOG35-55 peptide/APC
+
of TGF-β + IL-6 (Th17)

4 days

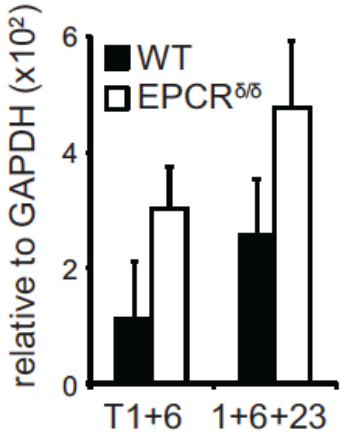
**Adoptive transfer into WT mice**
**EAE**
**T cell response**



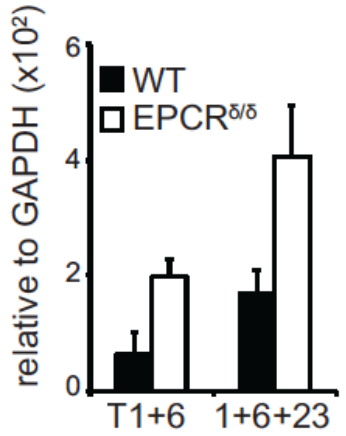

| Group | Disease Incident | Day of Onset | Mean Max Score |
|---|---|---|---|
| 202 | 6/6 | 15.8 ± .7 | 3.5 ± .4 |
| 2D2 x EPCR$\delta/\delta$ | 8/8 | 15.3 ± .8 | 4.6 ± .3 |



E *Il23r*

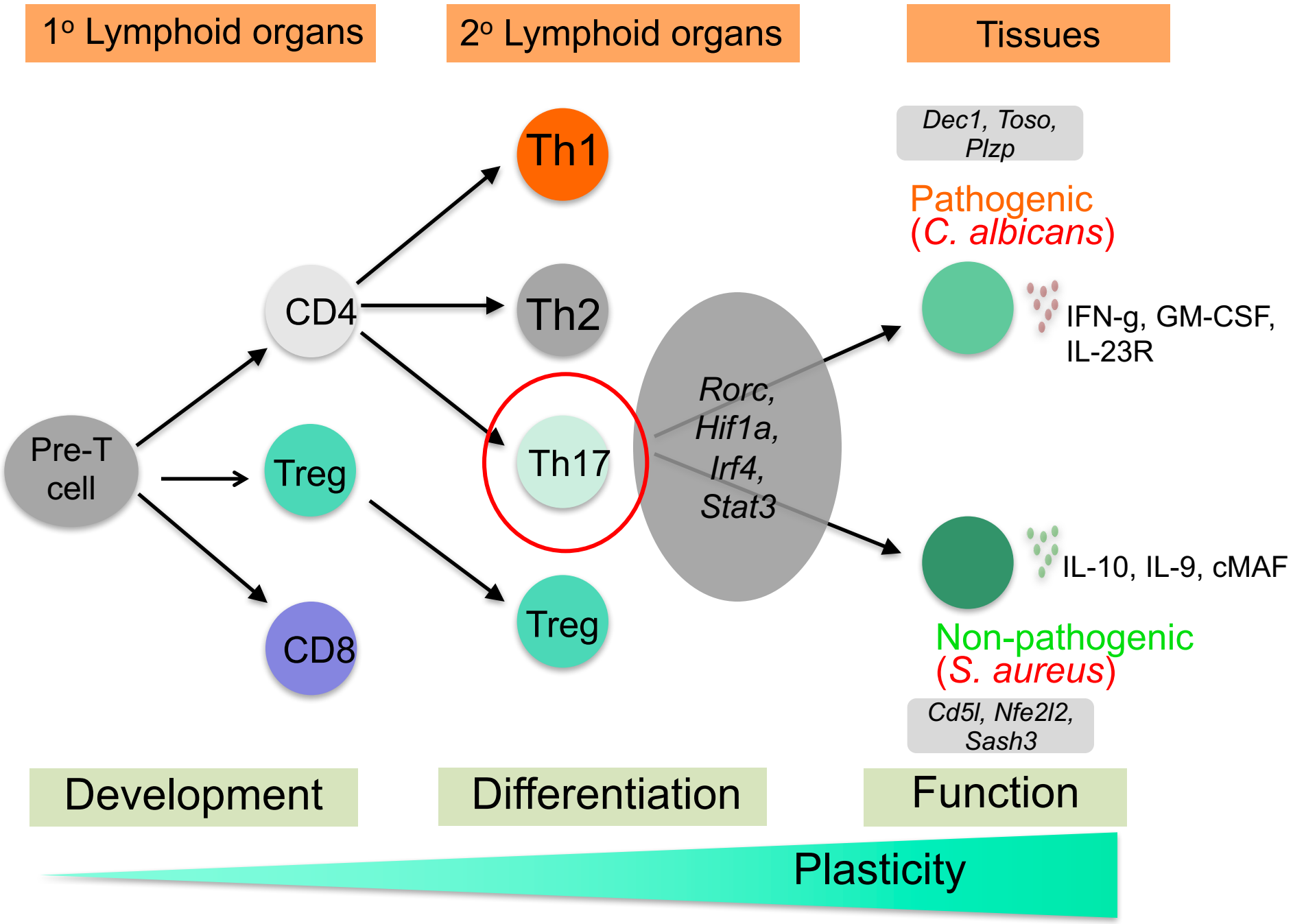


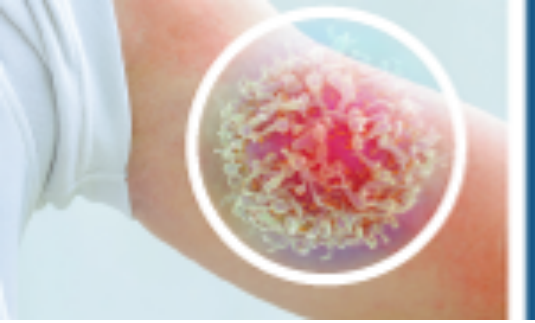

G *Il1r1*




# Activated Protein C Receptor Regulates IL-23R and IL-1R Expression on Developing Th17 Cells

Kishi Y, et al. *J Exp Med*. 2016;213(11):2489-2501.

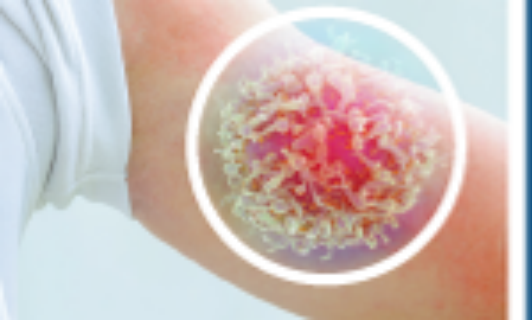

1º Lymphoid organs
2º Lymphoid organs
Tissues
Th1
Th2
Th17
Treg
Treg
CD4
CD8
Pre-T cell
Rorc, Hif1a, Irf4, Stat3
Dec1, Toso, Plzp
Pathogenic (C. albicans)
IFN-g, GM-CSF, IL-23R
IL-10, IL-9, cMAF
Non-pathogenic (S. aureus)
Cd5l, Nfe2l2, Sash3
Development
Differentiation
Function
Plasticity



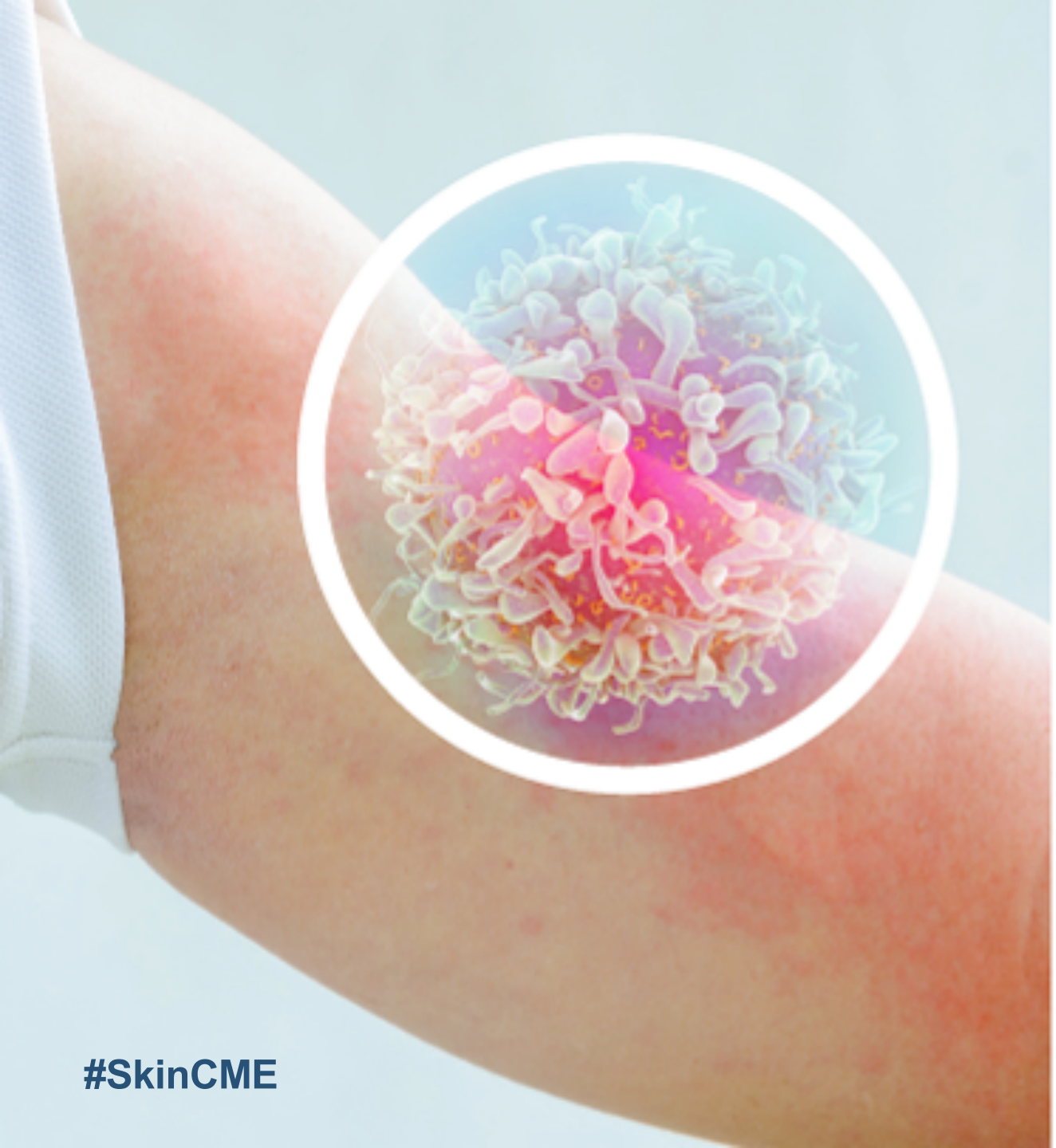
# Conclusions

- IL-6 plus TGF-b induces Th17 cells and IL-21 amplifies them.
- IL-23 acts on differentiated Th17 cells to induce expansion and full expression of pathogenic Th17 phenotype.
- By undertaking whole genome transcriptional analysis we have constructed a transcriptional network for the development of Th17 cells.
- Not all Th17 cells are pathogenic, infact both pathogenic and nonpathogneic Th17 cells exist defining different functional states of Th17 cells.
- By undertaking single cell expression analysis, we have identified novel regulators of pathogenic and nonpathogenic Th17 state.
- PROCR, an inhibitory receptor expressed in a subset of Th17 cells which restrains their pathogenicity by regulating IL-1R and IL-23R expression on Th17 cells.
- PROCR is also expressed on exhausted T cells in cancer and chronic viral infection.

Gaublomme JT, et al. *Cell*. 2015; 163(6):1400-1412; Wang C, et al. *Cell*. 2015; 163(6):1413-1427; Wu C, et al. *Nature*. 2013;496(7446):513-517. Yosef N, et al. *Nature*. 213;486(7446):461-468.



# The Kuchroo Laboratory, 2015



#SkinCME

# Thank You!

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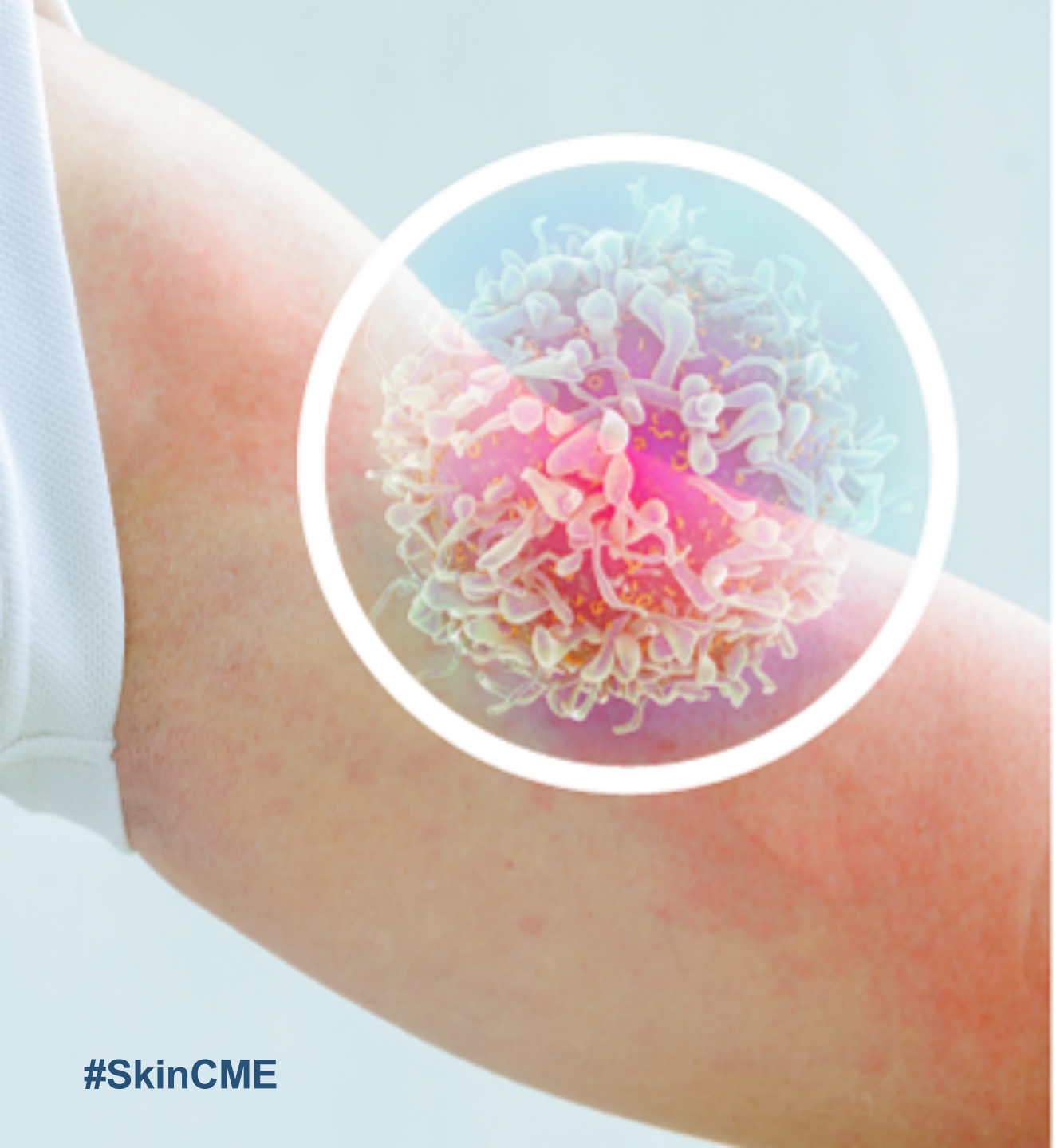

# Questions & Answers

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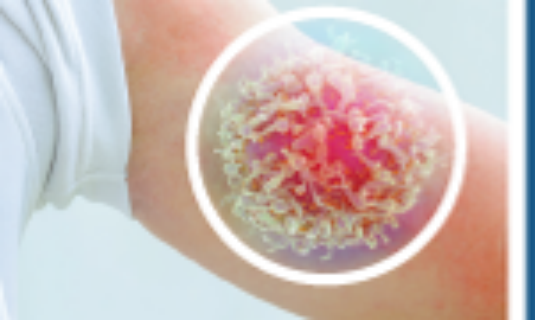
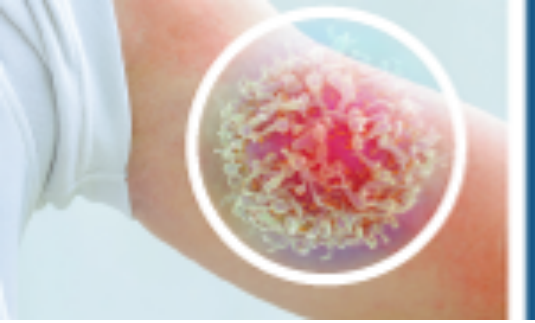


# Downloadable Resources

Presentation slides, the course guide booklet, and the credit request/evaluation form will be available for download at:

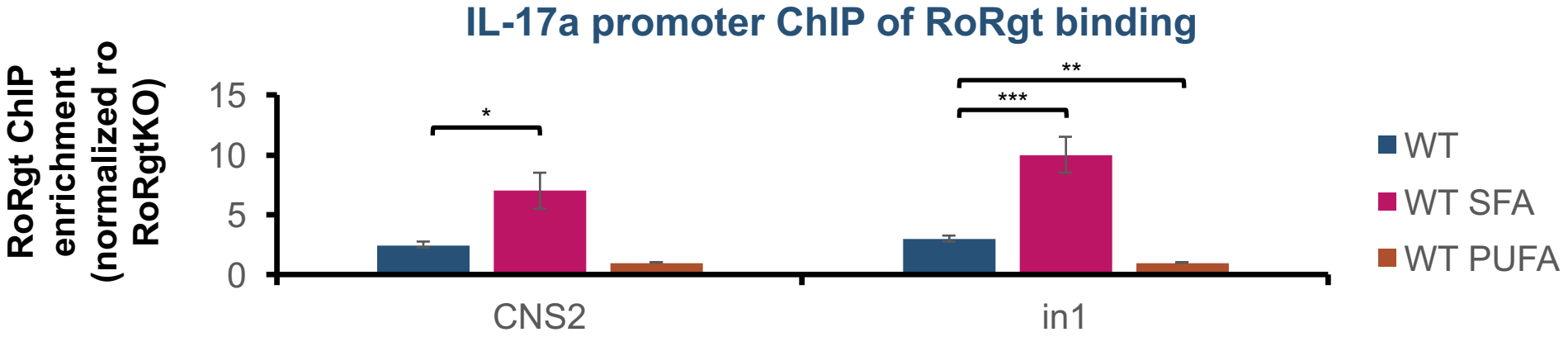
**www.CMEOutfitters.com/SkinResources**

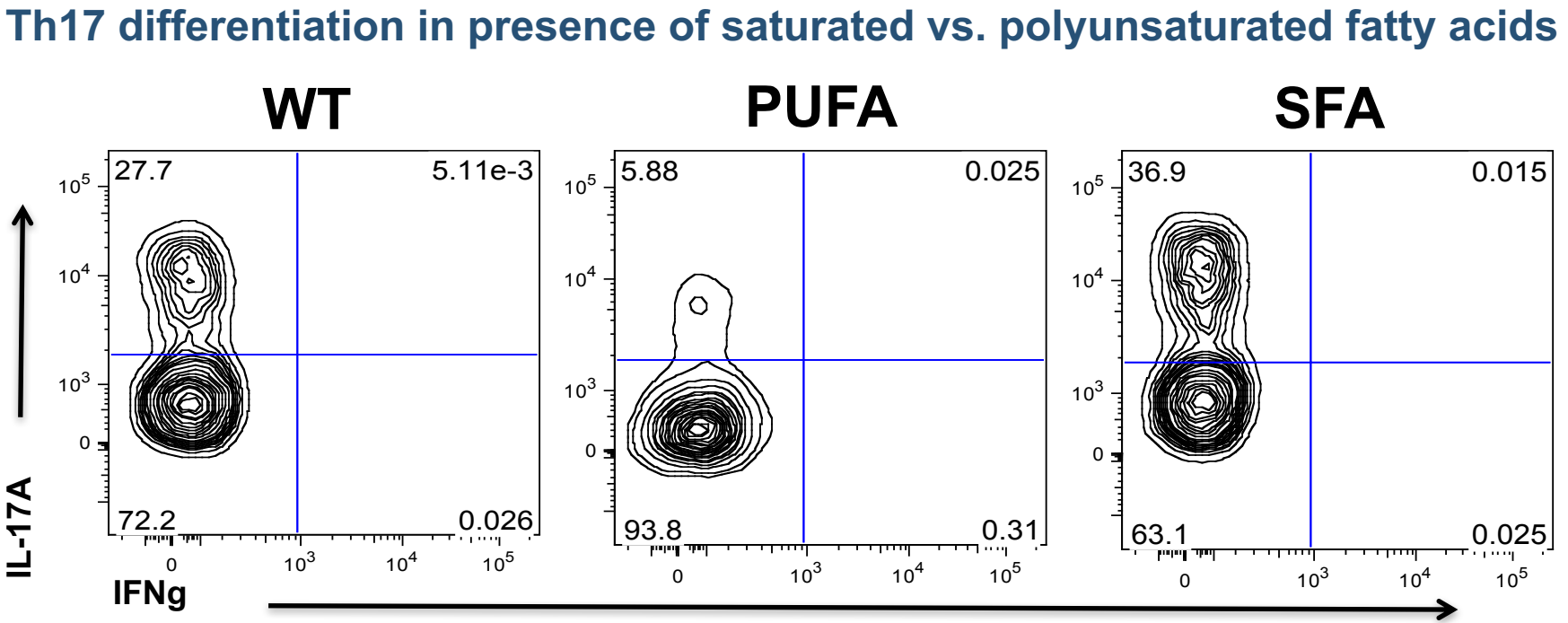


# Obtaining Credit

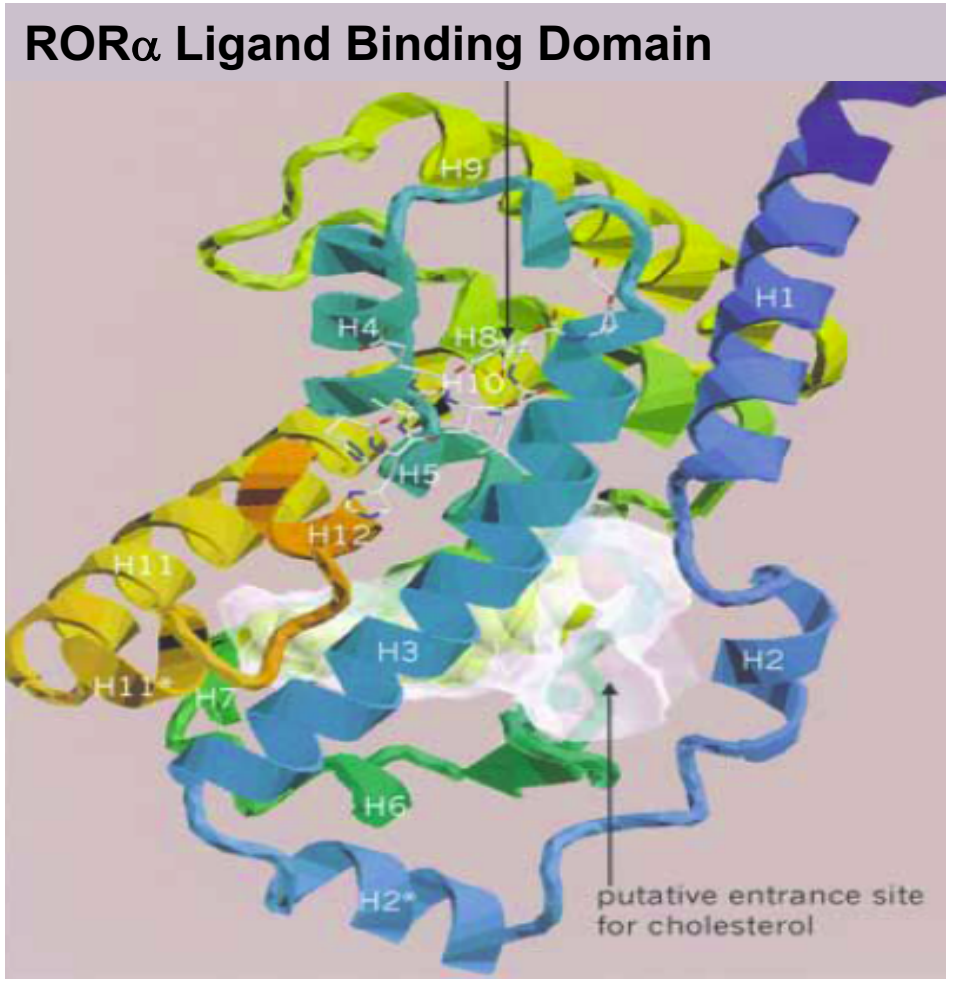
**In order to receive credit, please complete the evaluation/credit request form found on your table and turn them in to the CME Outfitters staff on your way out.**

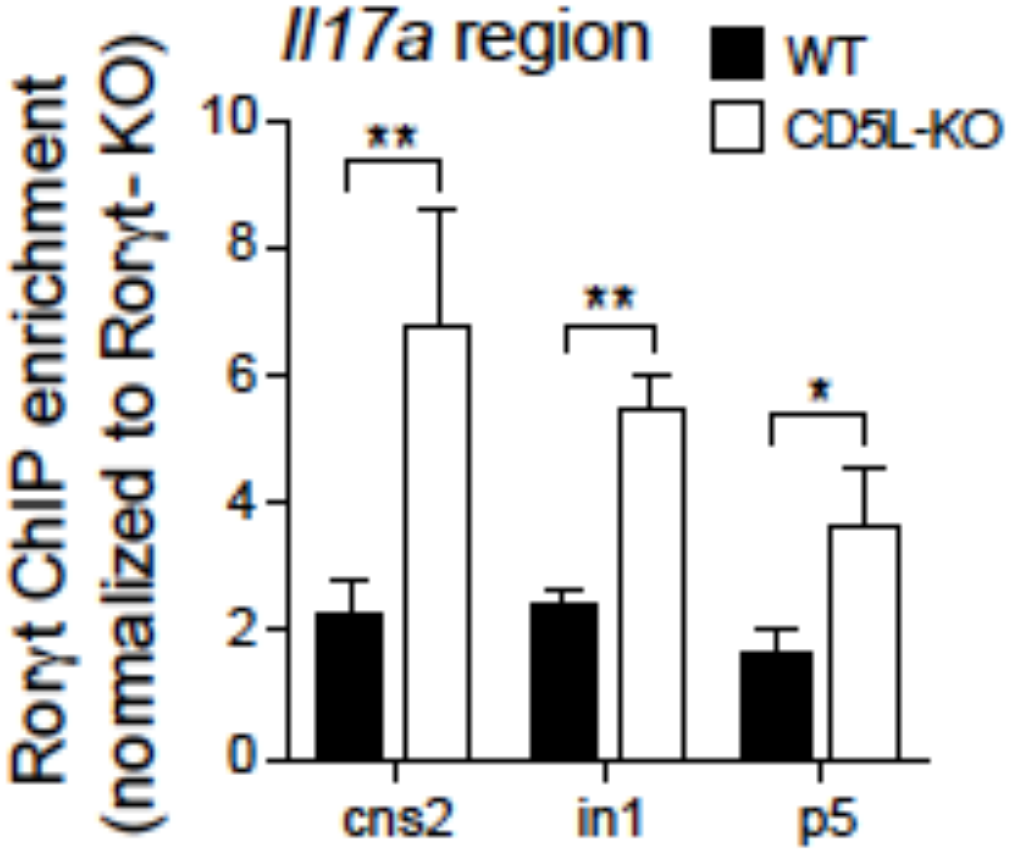
# Saturated Fatty Acids (SFA) Enhance While Unsaturated Fatty Acids (PUFA) Inhibit RORɣt Binding and Activity



# Oxysterols are Agonist Ligands of RORγt and Drive Th17 Cell Differentiation




Ciofani M, et al. *Cell*. 2012;151(2):289-303; Xiao S, et al. *Immunity*. 2014;40(4):477-489; Soroosh P, et al. *Proc Natl Acad Sci USA*. 2014;111(33):12163-12168.