



**VITILIGO**  
CLINIC & RESEARCH CENTER

Department of Dermatology  
University of Massachusetts  
Medical School



# New Research Discoveries in Vitiligo

Website:  
[Umassmed.edu/vitiligo](http://Umassmed.edu/vitiligo)



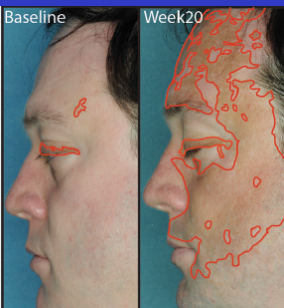
Twitter:  
[@HarrisVitiligo](https://twitter.com/HarrisVitiligo)



John E. Harris, MD, PhD

Associate Professor

University of Massachusetts Medical School





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## DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

John E. Harris, MD, PhD

Investigator – Pfizer, Genzyme/Sanofi, Stiefel/GSK, Celgene, Aclaris Therapeutics, Dermira, Incyte, Rheos Medicines, Sun Pharmaceuticals

Consultant – Pfizer, Abbvie, Genzyme/Sanofi, Aclaris Therapeutics, The Expert Institute, BiologicsMD, Janssen, TeVido BioDevices, EMD Serono, 3<sup>rd</sup> Rock Ventures, Rheos Medicines, Sun Pharmaceuticals

Equity – TeVido Biodevices, Rheos Medicines, Villaris Therapeutics, Inc

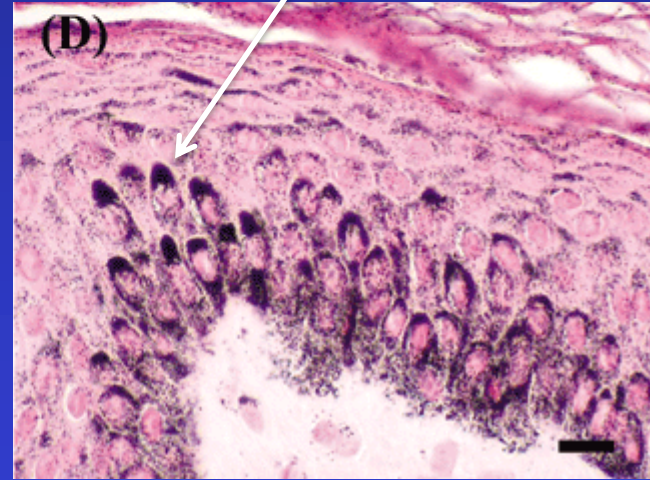
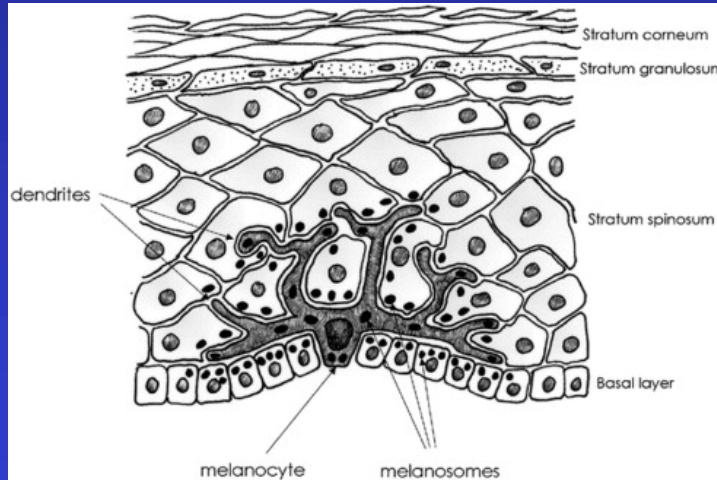
Founder – Villaris Therapeutics, Inc



# Vitiligo: What causes it?

# Skin color comes from melanosomes created in melanocytes and passed to keratinocytes

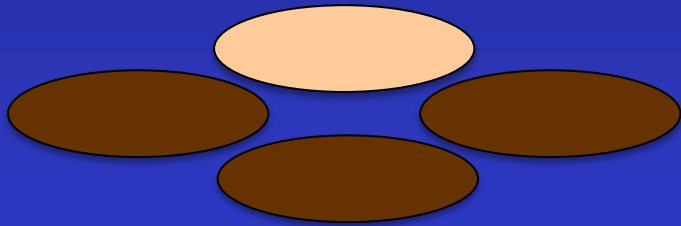
“parasol” of melanosomes protect the cell’s DNA in the nucleus



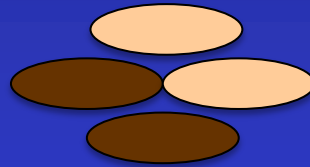
1:36

# What determines skin color?

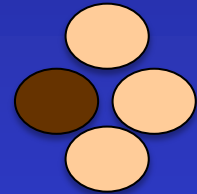
Melanosome type, size, and shape – NOT melanocyte number



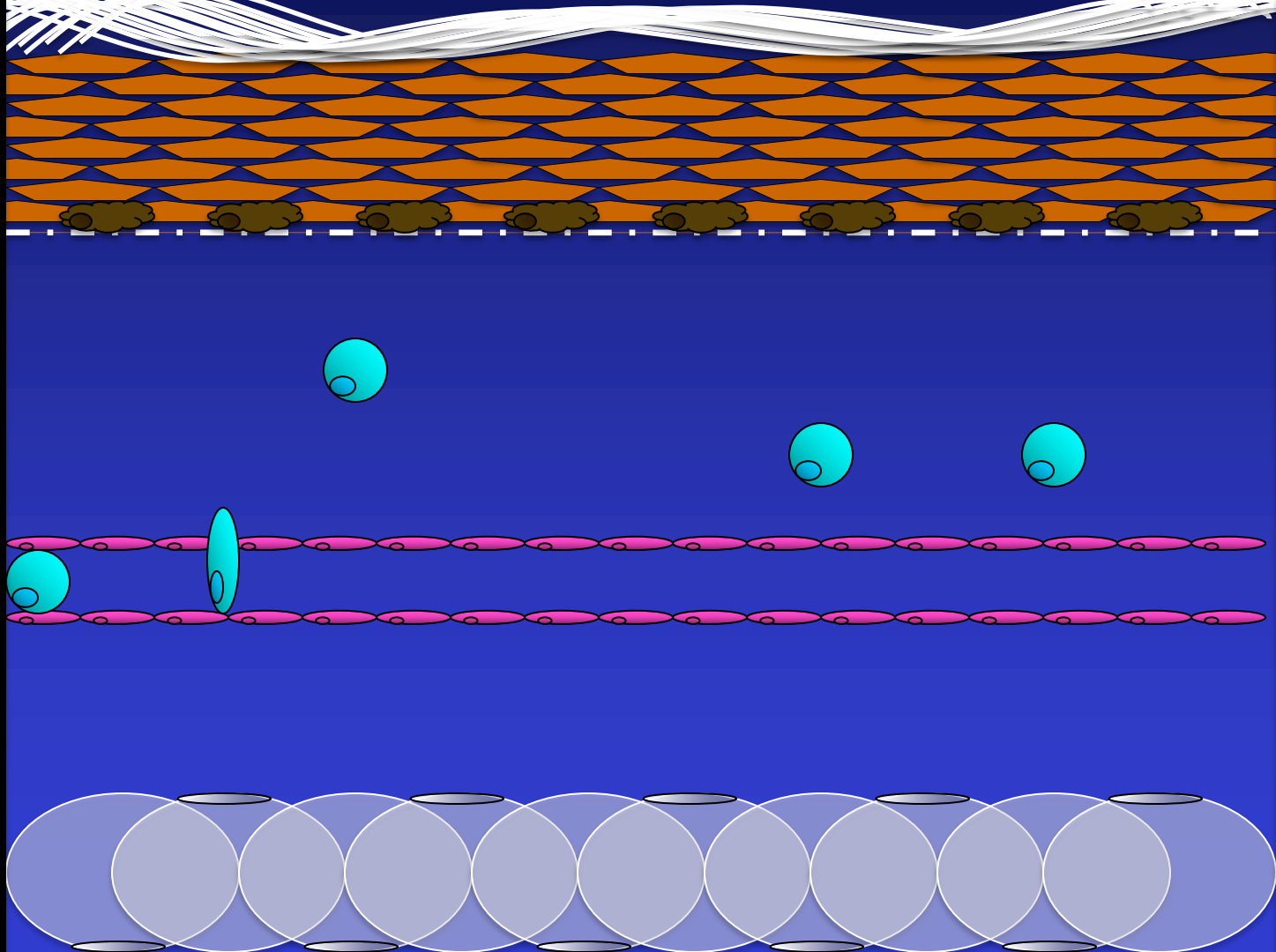
African

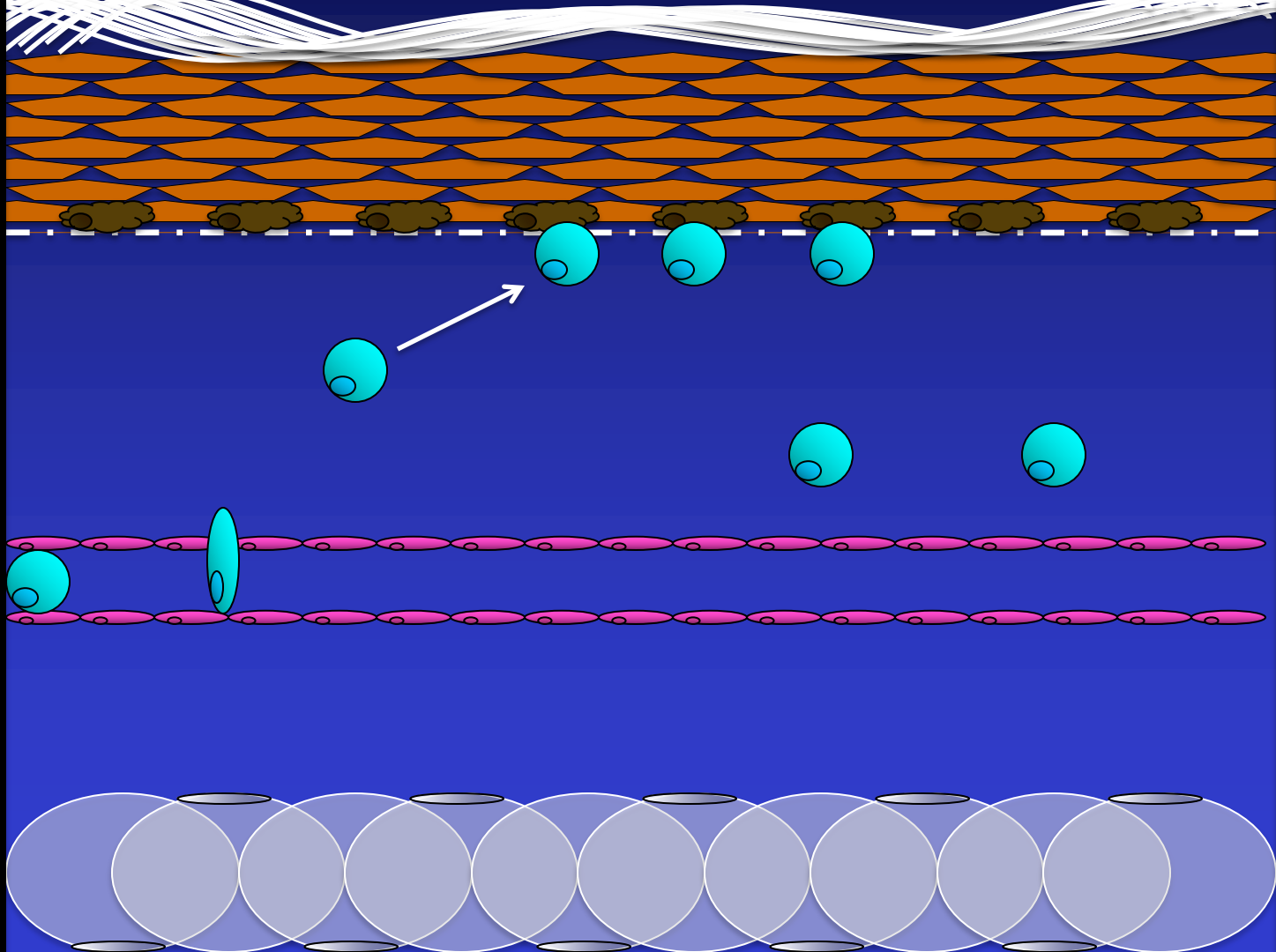


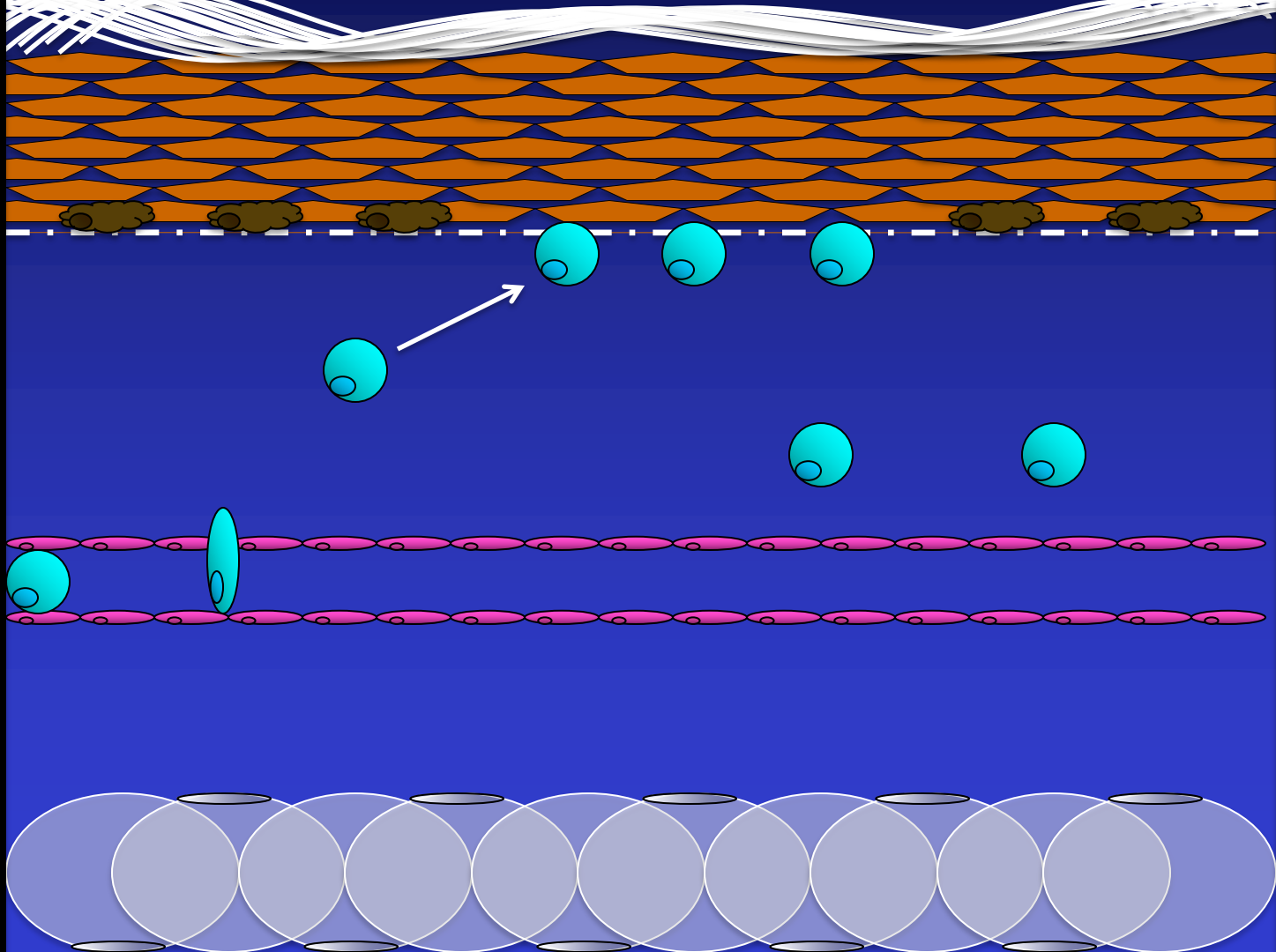
Asian



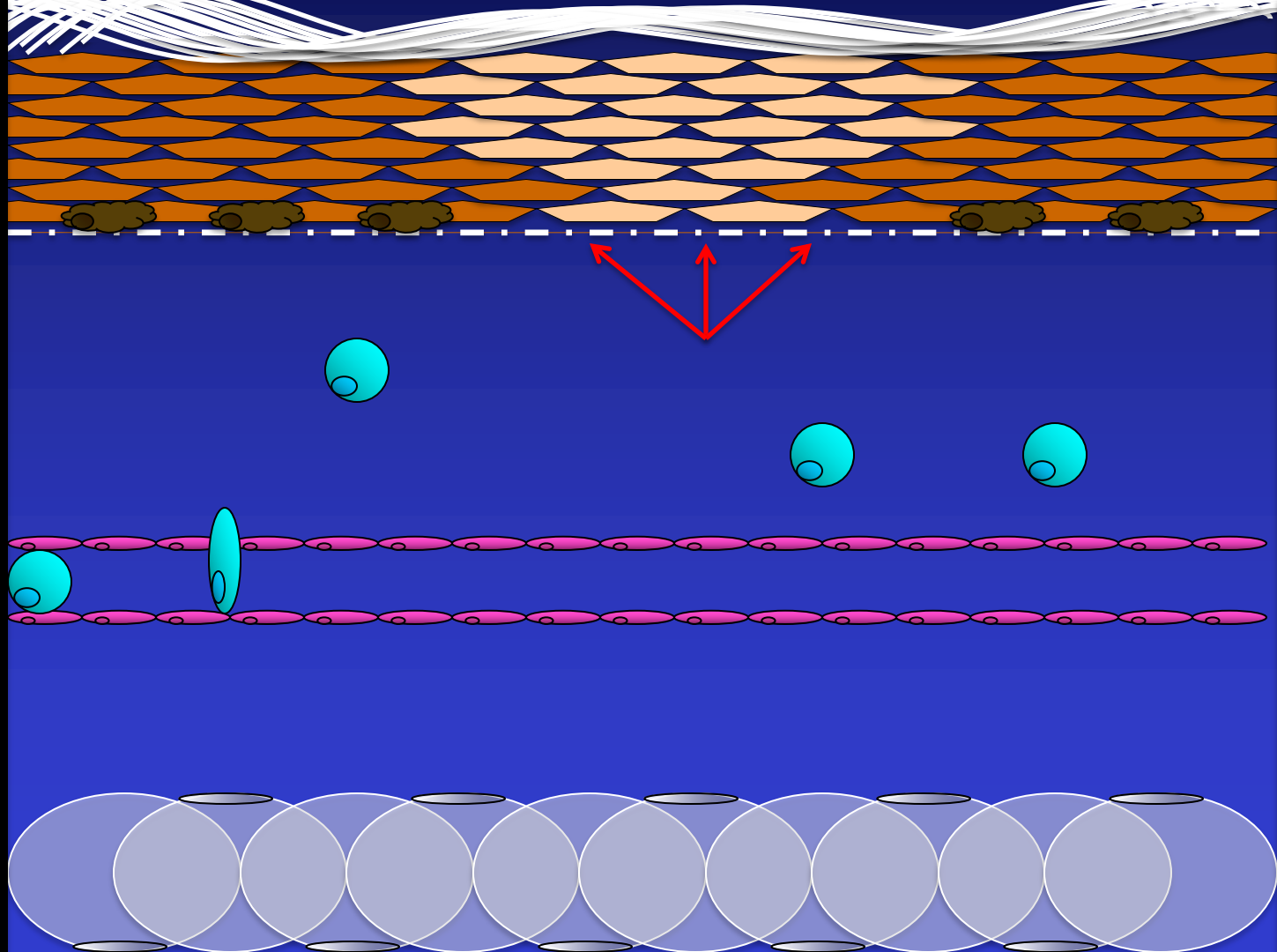
Caucasian

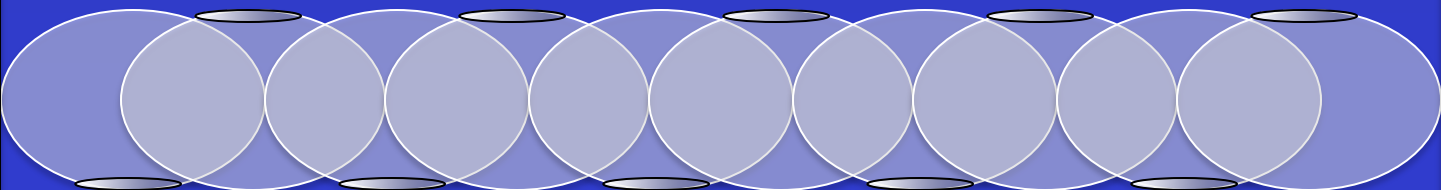
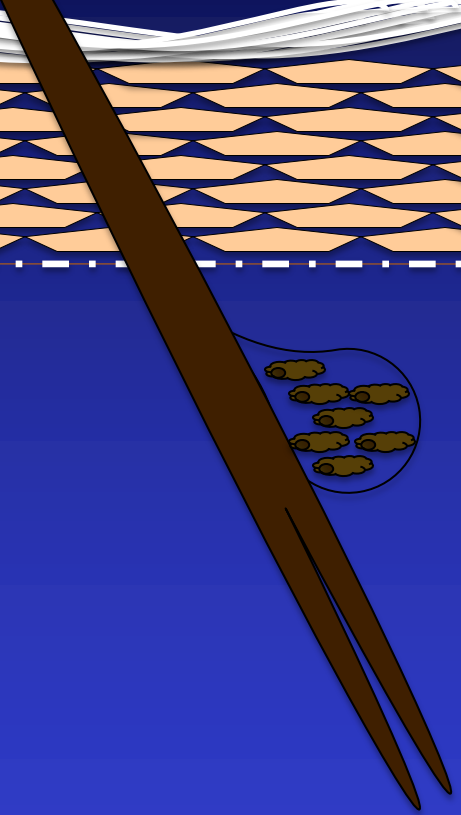
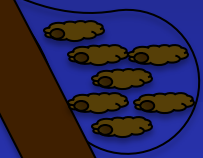
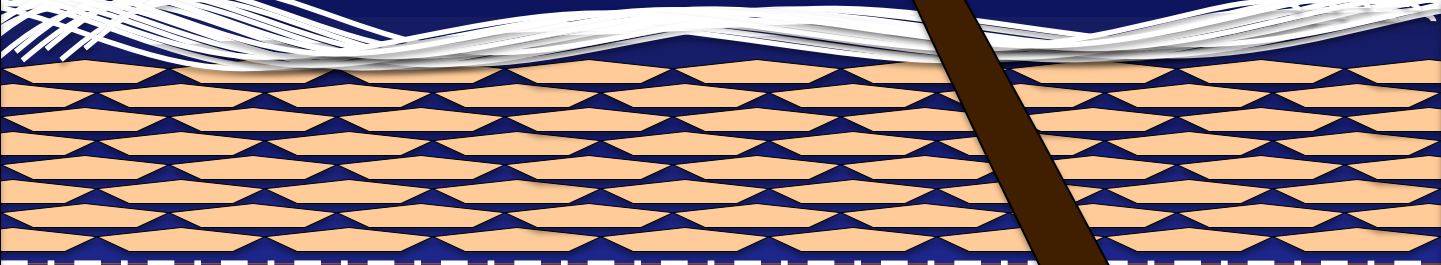


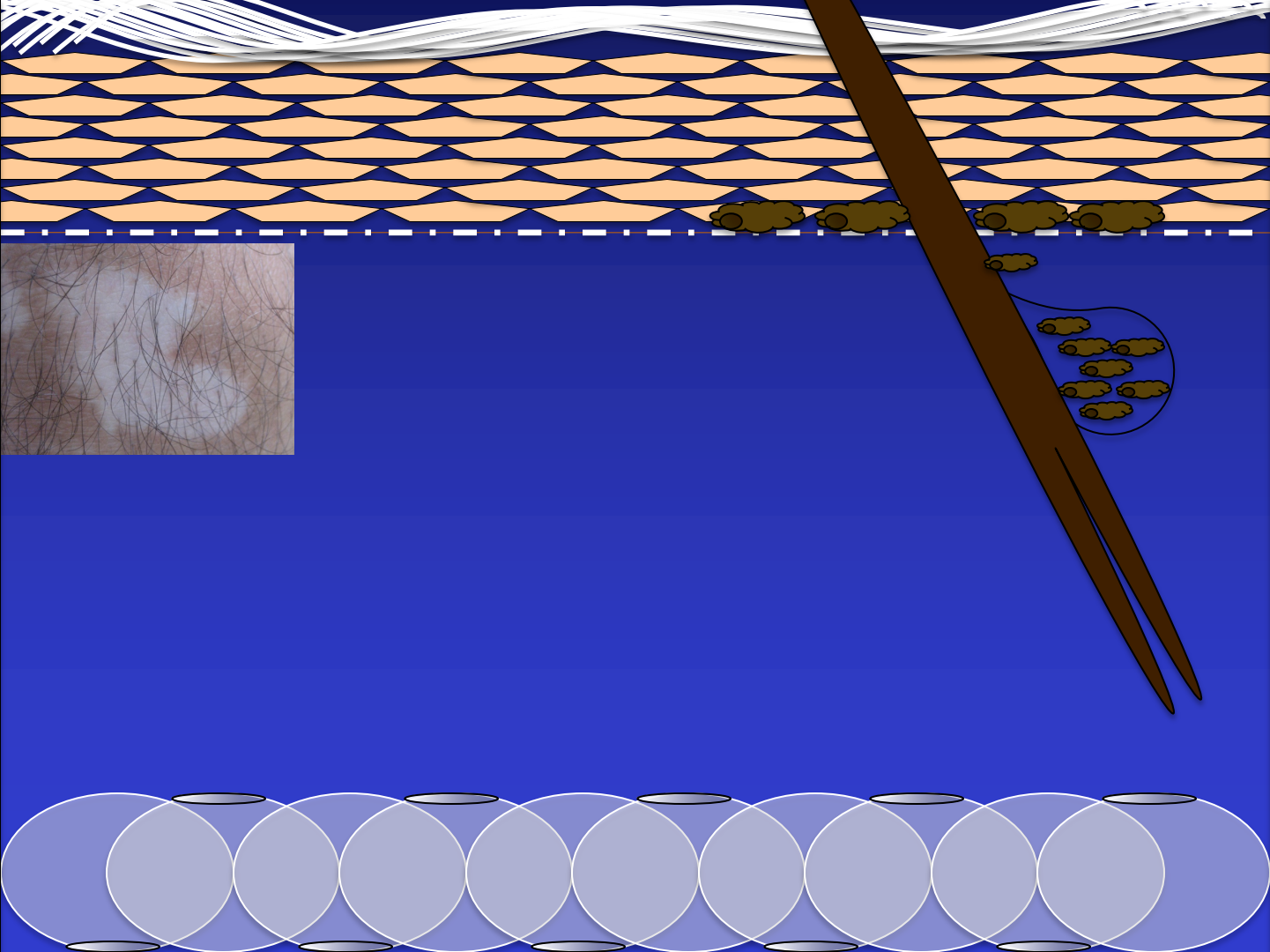


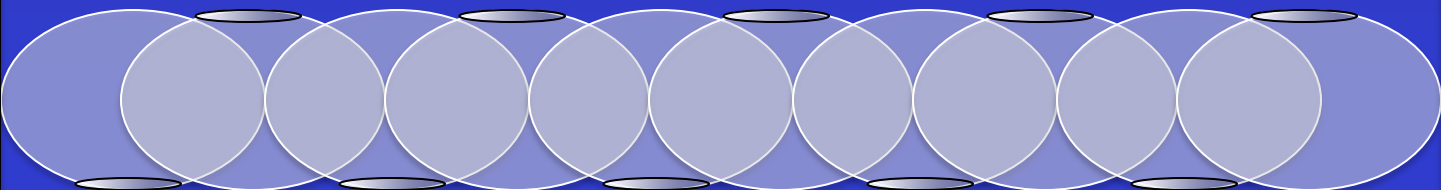
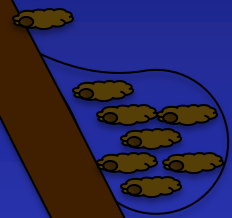
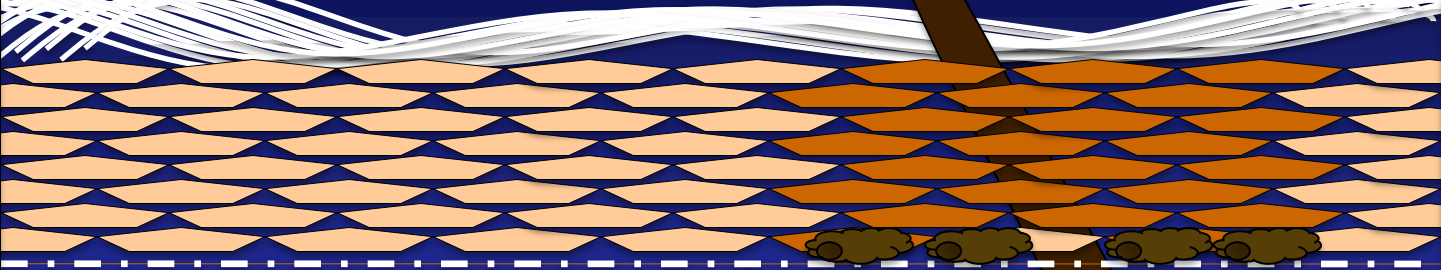














# Vitiligo:

## My research questions

Systemic immunosuppression + nbUVB

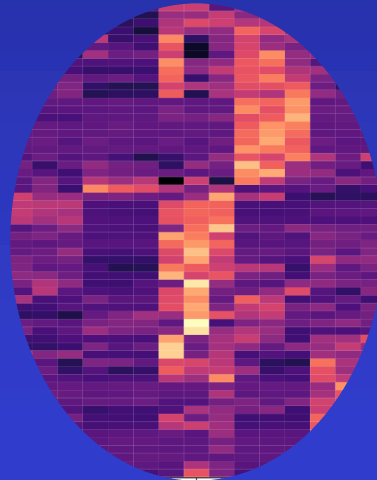
**Can a focused treatment work better and be safer?**

Clinical

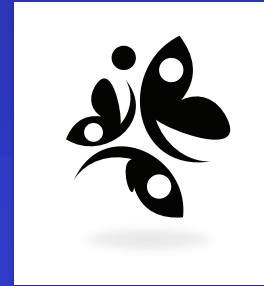


## Our Research Strategy:

Seamless integration of  
clinical, translational,  
and basic research



Translational



Basic

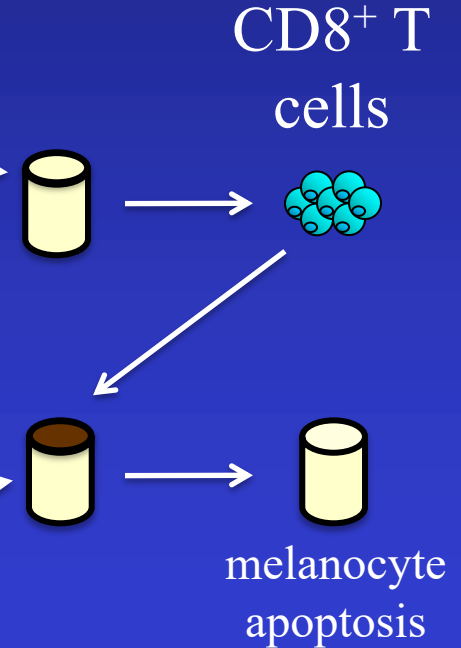
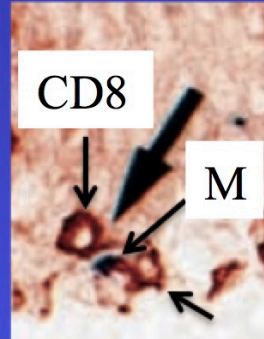
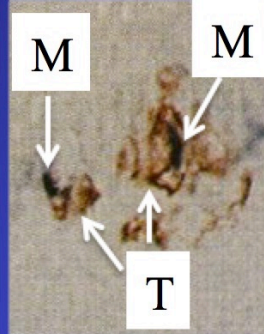
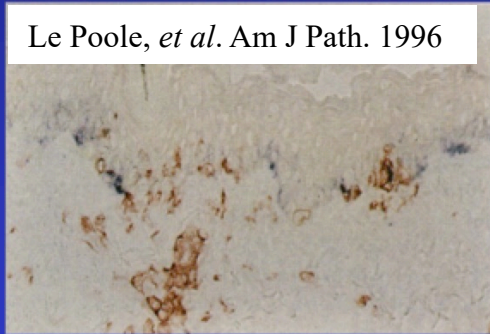
# T cells kill melanocytes



1990's  
Biopsies



2009  
Cell culture



van den Boorn JG, *et al.* JID. 2009



# A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN- $\gamma$ for Autoreactive CD8<sup>+</sup> T-Cell Accumulation in the Skin

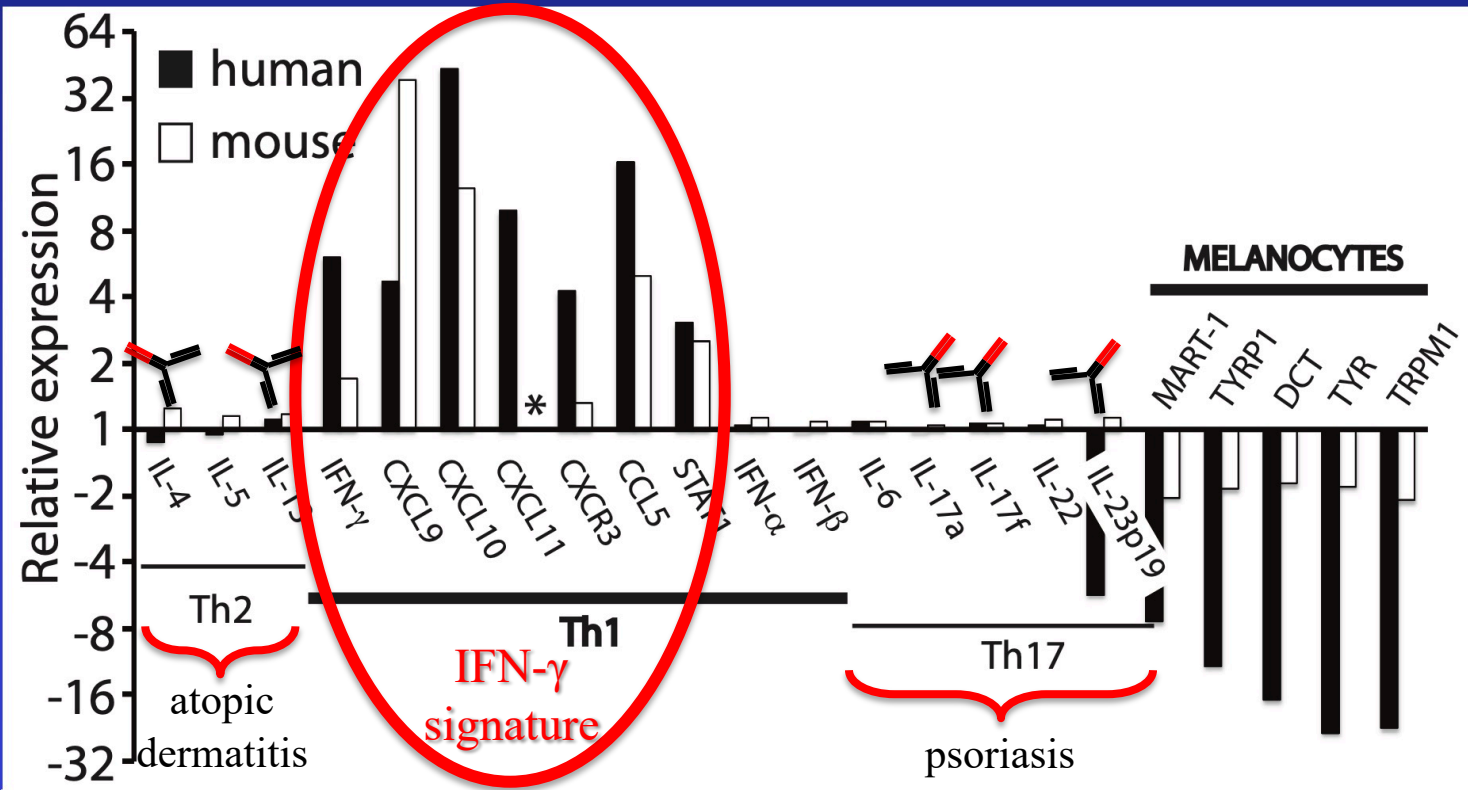
John E. Harris<sup>1</sup>, Tajie H. Harris<sup>2</sup>, Wolfgang Weninger<sup>3,4</sup>, E. John Wherry<sup>5</sup>, Christopher A. Hunter<sup>2</sup> and Laurence A. Turka<sup>6</sup>

*Journal of Investigative Dermatology* advance online publication, 2 February 2012; doi:10.1038/jid.2011.463

Melanocyte-specific  
CD8<sup>+</sup> T cells



# Gene expression is similar in mouse and human vitiligo



# Vitiligo - Hypothesis

We thought that IFN- $\gamma$  is a cause of vitiligo

# A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN- $\gamma$ for Autoreactive CD8<sup>+</sup> T-Cell Accumulation in the Skin

John E. Harris<sup>1</sup>, Tajie H. Harris<sup>2</sup>, Wolfgang Weninger<sup>3,4</sup>, E. John Wherry<sup>5</sup>, Christopher A. Hunter<sup>2</sup> and Laurence A. Turka<sup>6</sup>

*Journal of Investigative Dermatology* advance online publication, 2 February 2012; doi:10.1038/jid.2011.463

Science  
Translational  
Medicine



RESEARCH ARTICLE

VITILIGO

## CXCL10 Is Critical for the Progression and Maintenance of Depigmentation in a Mouse Model of Vitiligo

Mehdi Rashighi,<sup>1</sup> Priti Agarwal,<sup>1</sup> Jillian M. Richmond,<sup>1</sup> Tajie H. Harris,<sup>2\*</sup> Karen Dresser,<sup>3</sup> Ming-Wan Su,<sup>4</sup> Youwen Zhou,<sup>4</sup> April Deng,<sup>3</sup> Christopher A. Hunter,<sup>2</sup> Andrew D. Luster,<sup>5</sup> John E. Harris<sup>1†</sup>

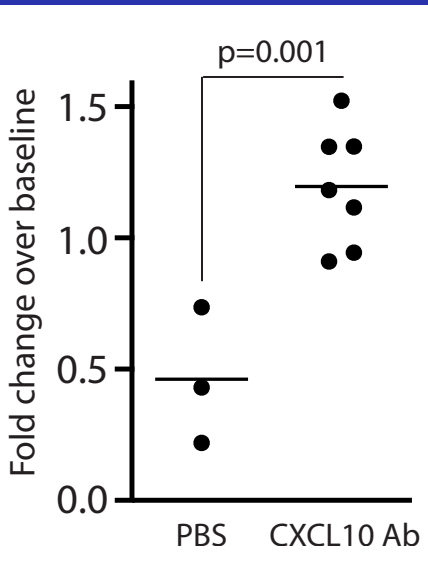




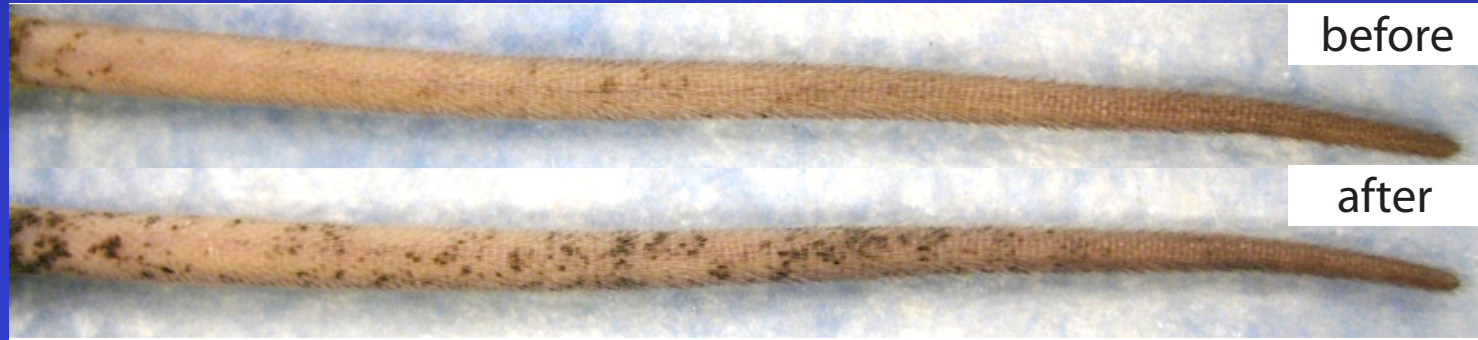
VITILIGO

## CXCL10 Is Critical for the Progression and Maintenance of Depigmentation in a Mouse Model of Vitiligo

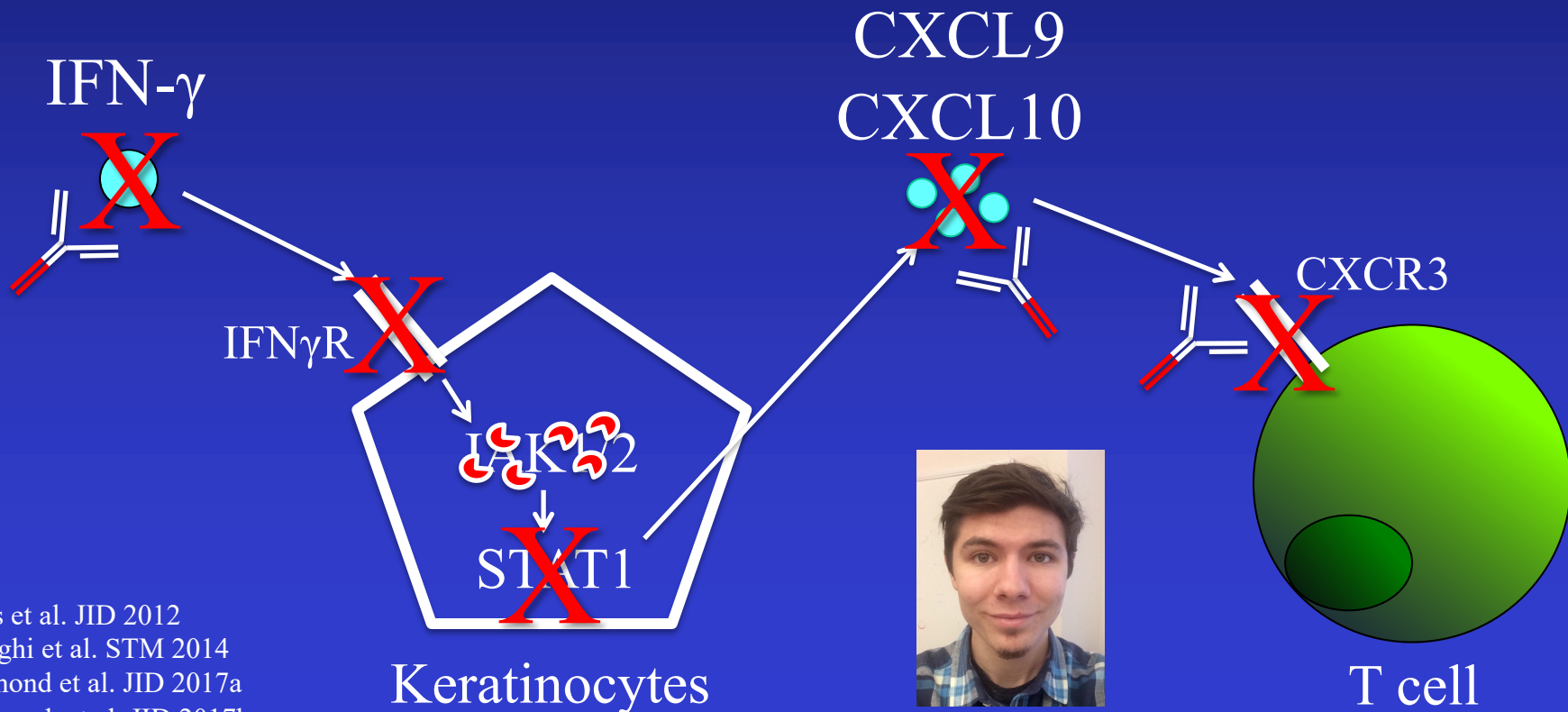
Mehdi Rashighi,<sup>1</sup> Priti Agarwal,<sup>1</sup> Jillian M. Richmond,<sup>1</sup> Tajie H. Harris,<sup>2\*</sup> Karen Dresser,<sup>3</sup> Ming-Wan Su,<sup>4</sup> Youwen Zhou,<sup>4</sup> April Deng,<sup>3</sup> Christopher A. Hunter,<sup>2</sup> Andrew D. Luster,<sup>5</sup> John E. Harris<sup>1†</sup>



## CXCL10 antibody reverses vitiligo



# Emerging Treatments



Harris et al. JID 2012  
Rashighi et al. STM 2014  
Richmond et al. JID 2017a  
Richmond, et al. JID 2017b

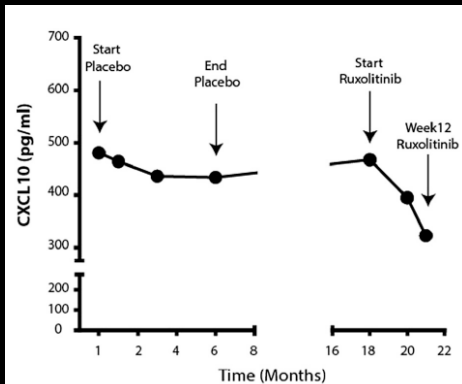
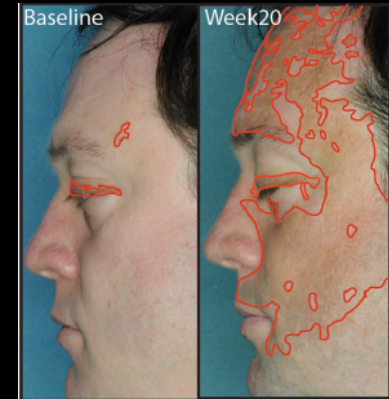
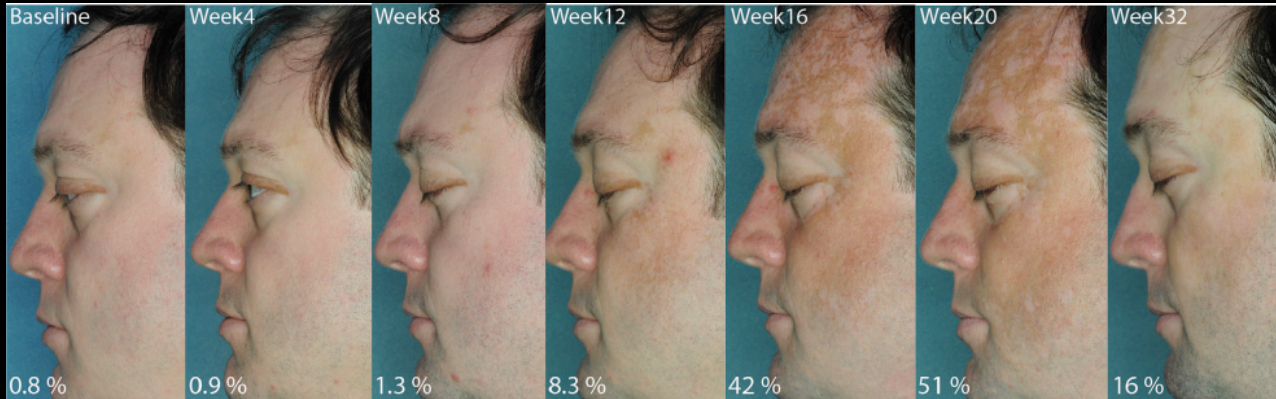
# Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA)

RESEARCH LETTER

John E. Harris, MD, PhD,<sup>a</sup> Mehdi Rasbighi, MD,<sup>a</sup>  
 Nban Nguyen, MD,<sup>b</sup> Ali Jabbari, MD, PhD,<sup>b</sup>  
 Grace Ulerio, BA,<sup>b</sup> Raphael Clynes, MD, PhD,<sup>b</sup>  
 Angela M. Christiano, PhD,<sup>b,c</sup> and Julian  
 Mackay-Wiggan, MD, MS<sup>b</sup>

370 FEBRUARY 2016

J AM ACAD DERMATOL  
 VOLUME 74, NUMBER 2



Ongoing Trials:  
**Aclaris**  
**Incyte**  
**Pfizer**



Presented at the 24th World Congress of Dermatology  
June 10–15, 2019; Milan, Italy

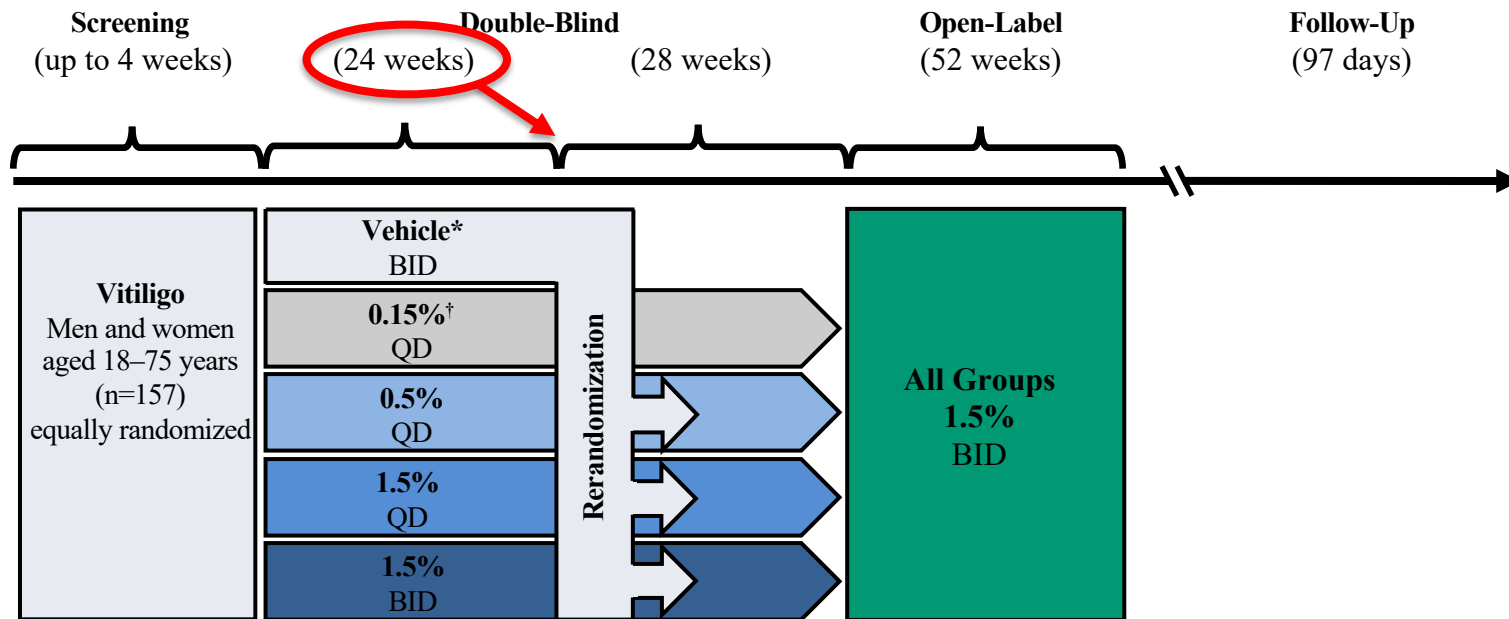
# **Efficacy and Safety of Ruxolitinib Cream for the Treatment of Vitiligo: Results of a 24-Week, Randomized, Double-Blind, Dose-Ranging, Vehicle-Controlled Study**

David Rosmarin, MD,<sup>1</sup> Amit G. Pandya, MD,<sup>2</sup> Mark Lebwohl, MD,<sup>3</sup> Pearl Grimes, MD,<sup>4</sup>  
Iltefat Hamzavi, MD,<sup>5</sup> Alice B. Gottlieb, MD, PhD,<sup>6</sup> Kathleen Butler, MD,<sup>7</sup> Fiona Kuo, PhD,<sup>7</sup>  
Michael D. Howell, PhD,<sup>7</sup> Kang Sun, PhD,<sup>7</sup> John E. Harris, MD, PhD<sup>8</sup>

**First release of results!**



# Study Design

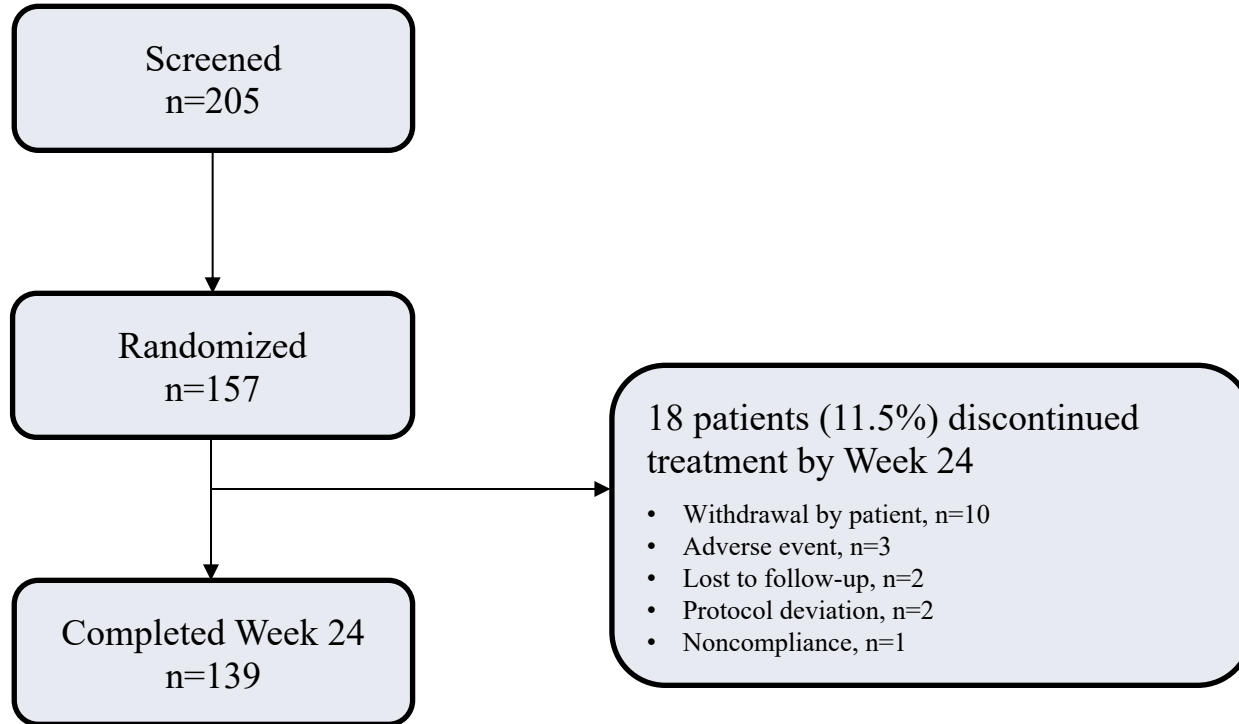


\* Rerandomization to 0.5% QD, 1.5% QD, or 1.5% BID at Week 24 for vehicle group.

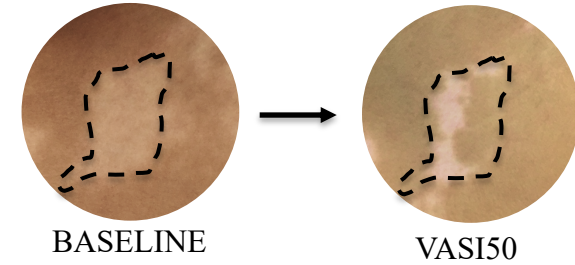
† Rerandomization to 0.5% QD, 1.5% QD, or 1.5% BID if <25% improvement in F-VASI at Week 24.

# Patient Disposition

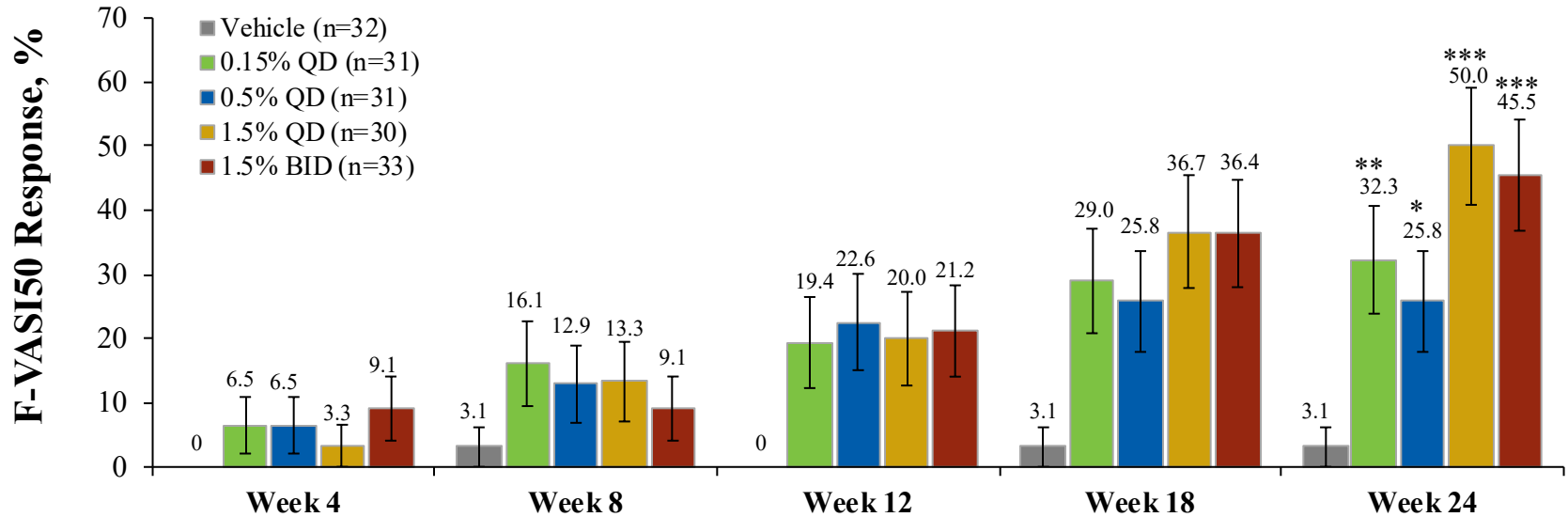
*Double-Blind (Day 1 to Week 24)*



# F-VASI50 Response



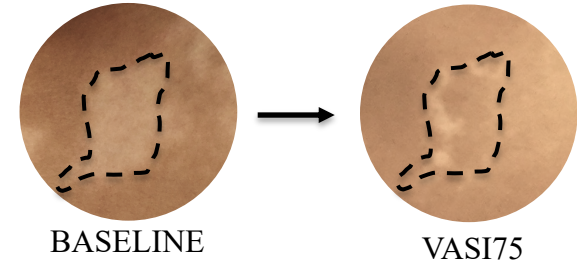
- At Week 24, the highest F-VASI50 response was achieved with the ruxolitinib cream 1.5% QD and BID regimens



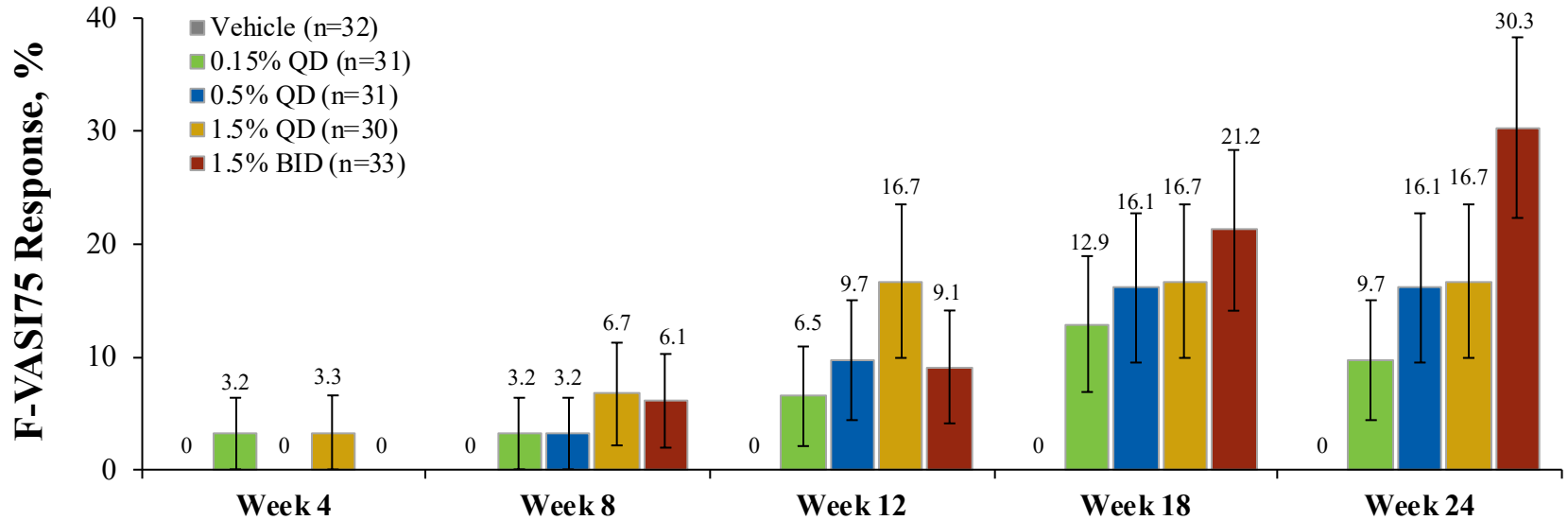
Error bars indicate standard error.

\*\*\*  $P < 0.001$  vs vehicle at Week 24; \*\*  $P < 0.01$  vs vehicle at Week 24; \*  $P < 0.05$  vs vehicle at Week 24.

# F-VASI75 Response



- At Week 24, the highest F-VASI75 response was achieved with the ruxolitinib cream 1.5% BID regimen



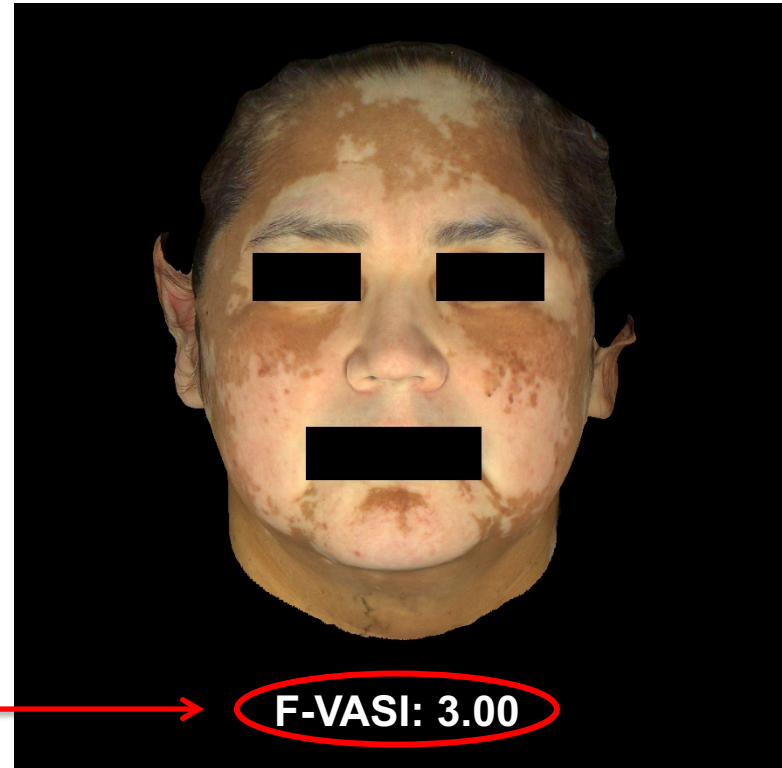
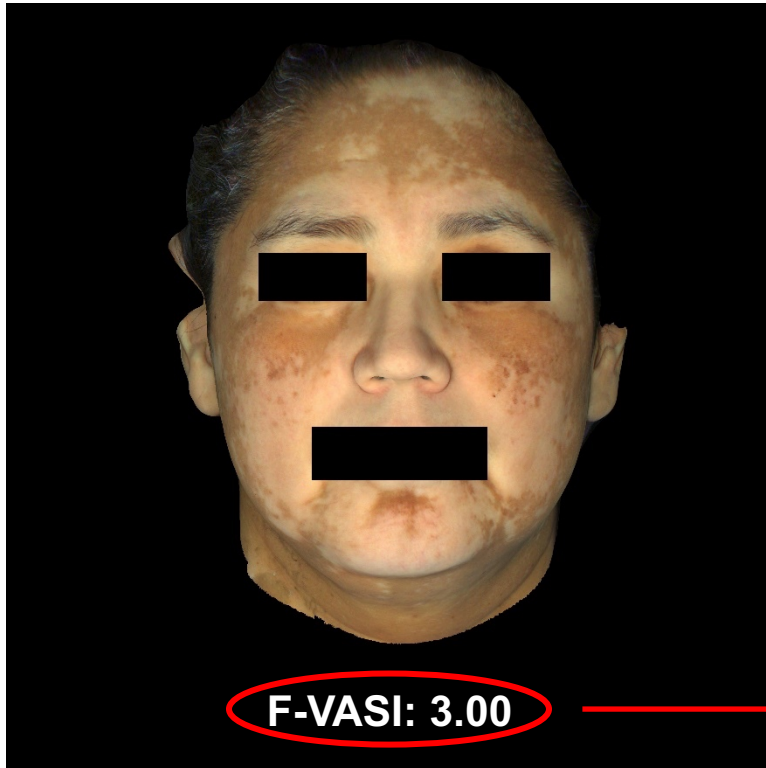
Error bars indicate standard error.

# Clinical Images Showing F-VASI Response

*Vehicle*

Day 1

Week 24

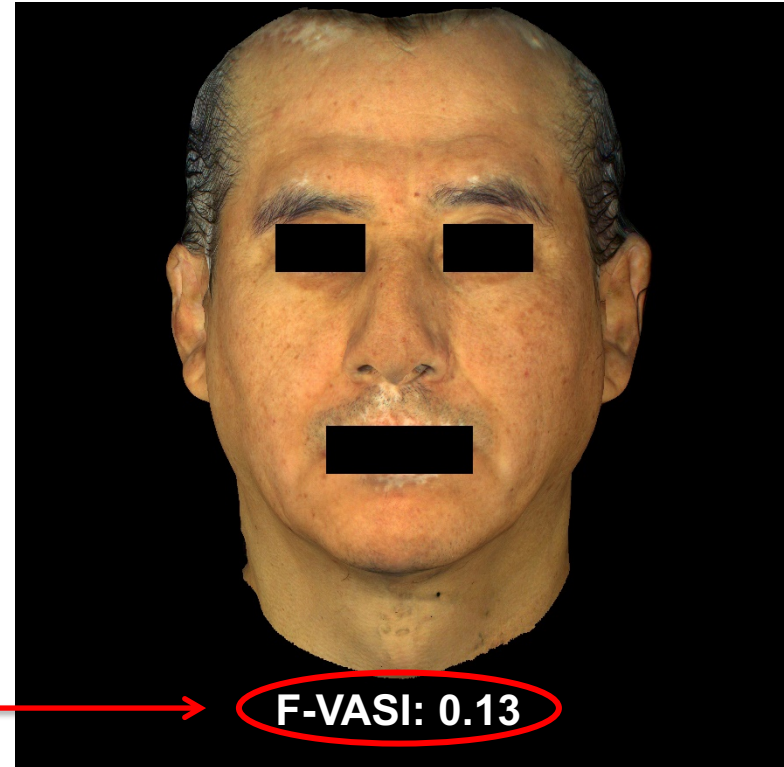
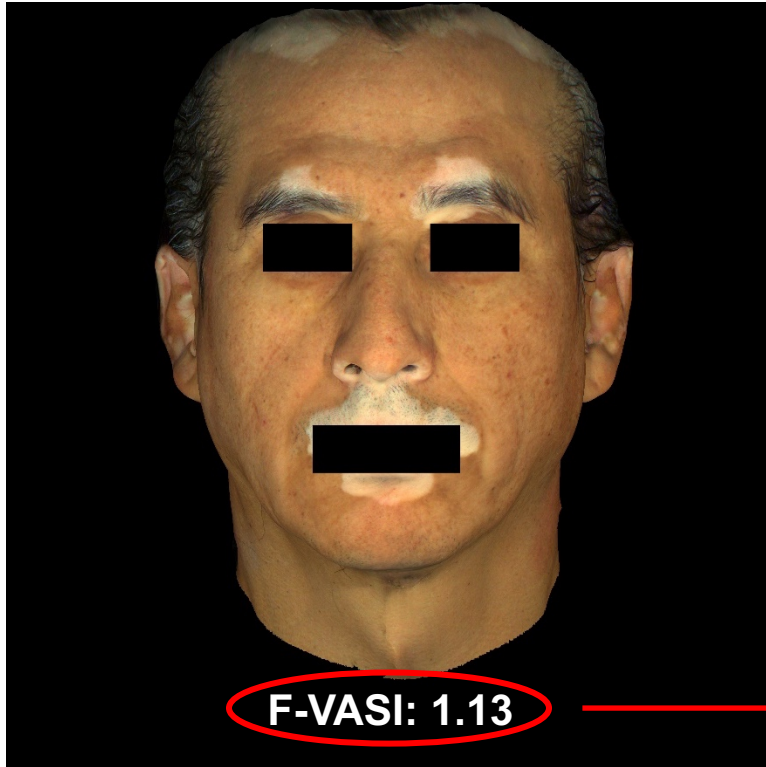


# Clinical Images Showing F-VASI Response

*Ruxolitinib Cream 1.5% BID*

Day 1

Week 24

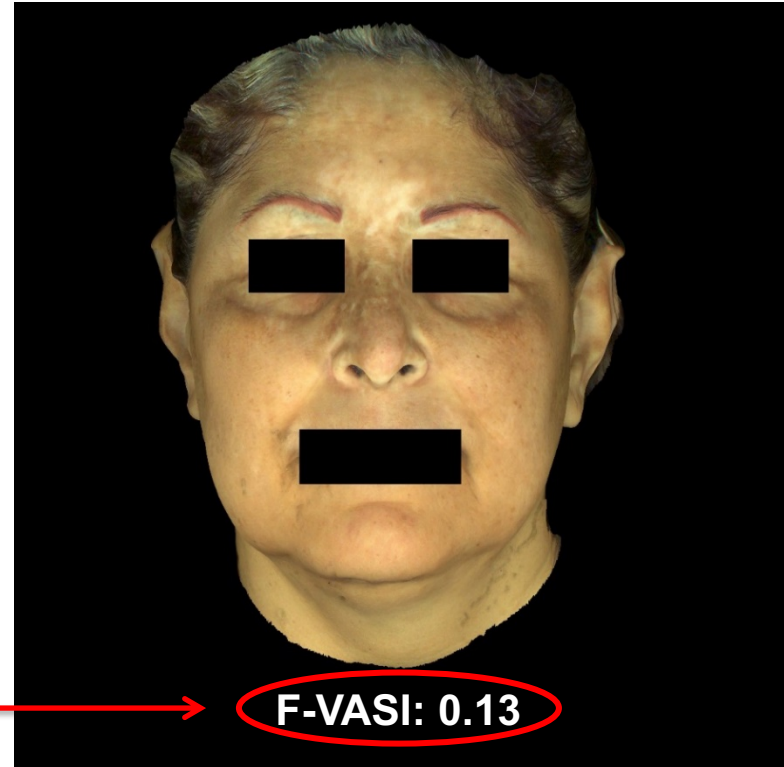


# Clinical Images Showing F-VASI Response

*Ruxolitinib Cream 1.5% BID*

Day 1

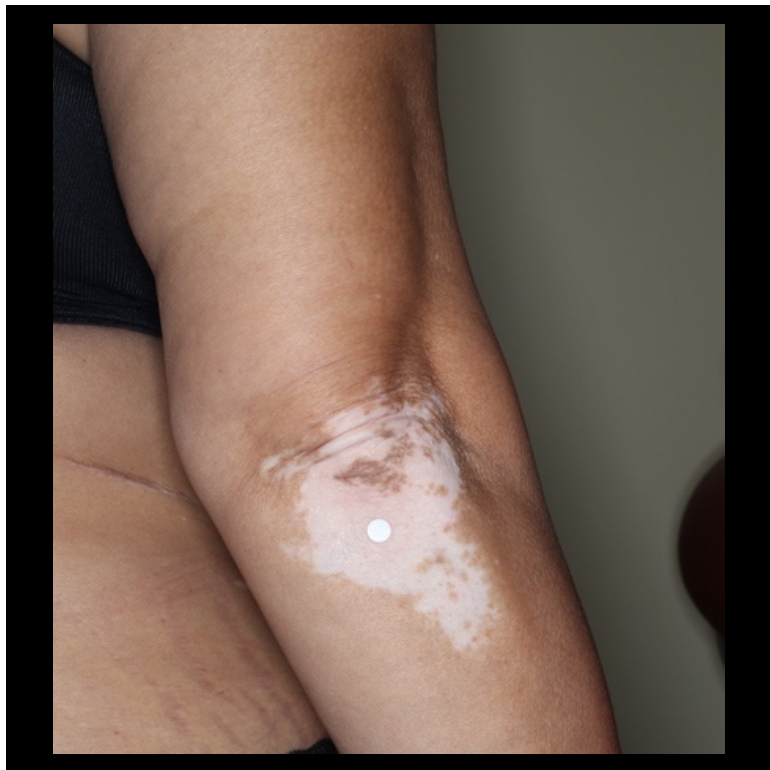
Week 24



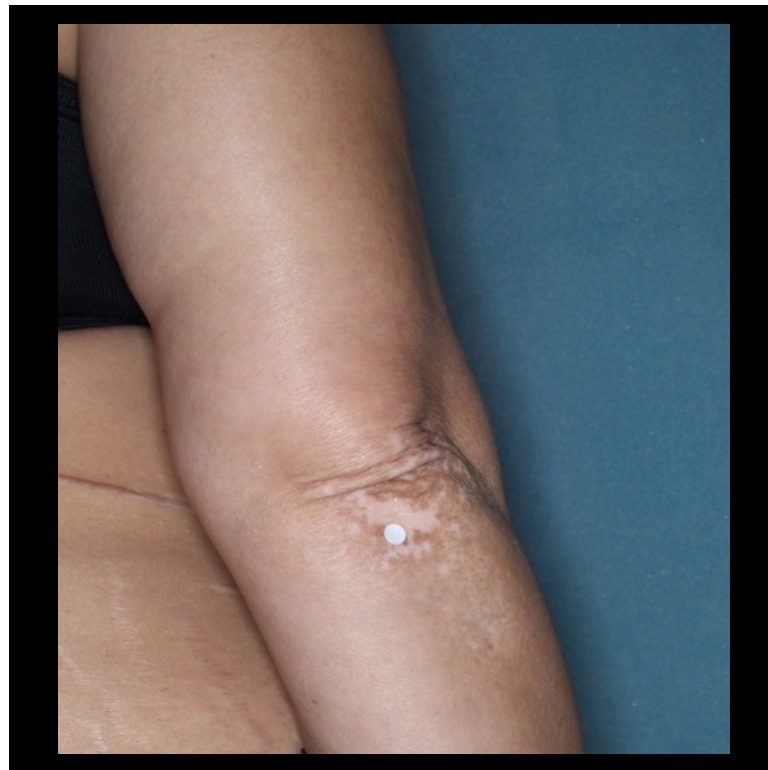
# Clinical Images Showing T-VASI Response

*Ruxolitinib Cream 1.5% BID*

**Day 1**



**Week 24**





# Safety

## *Treatment-Emergent Adverse Events Through 24 Weeks*

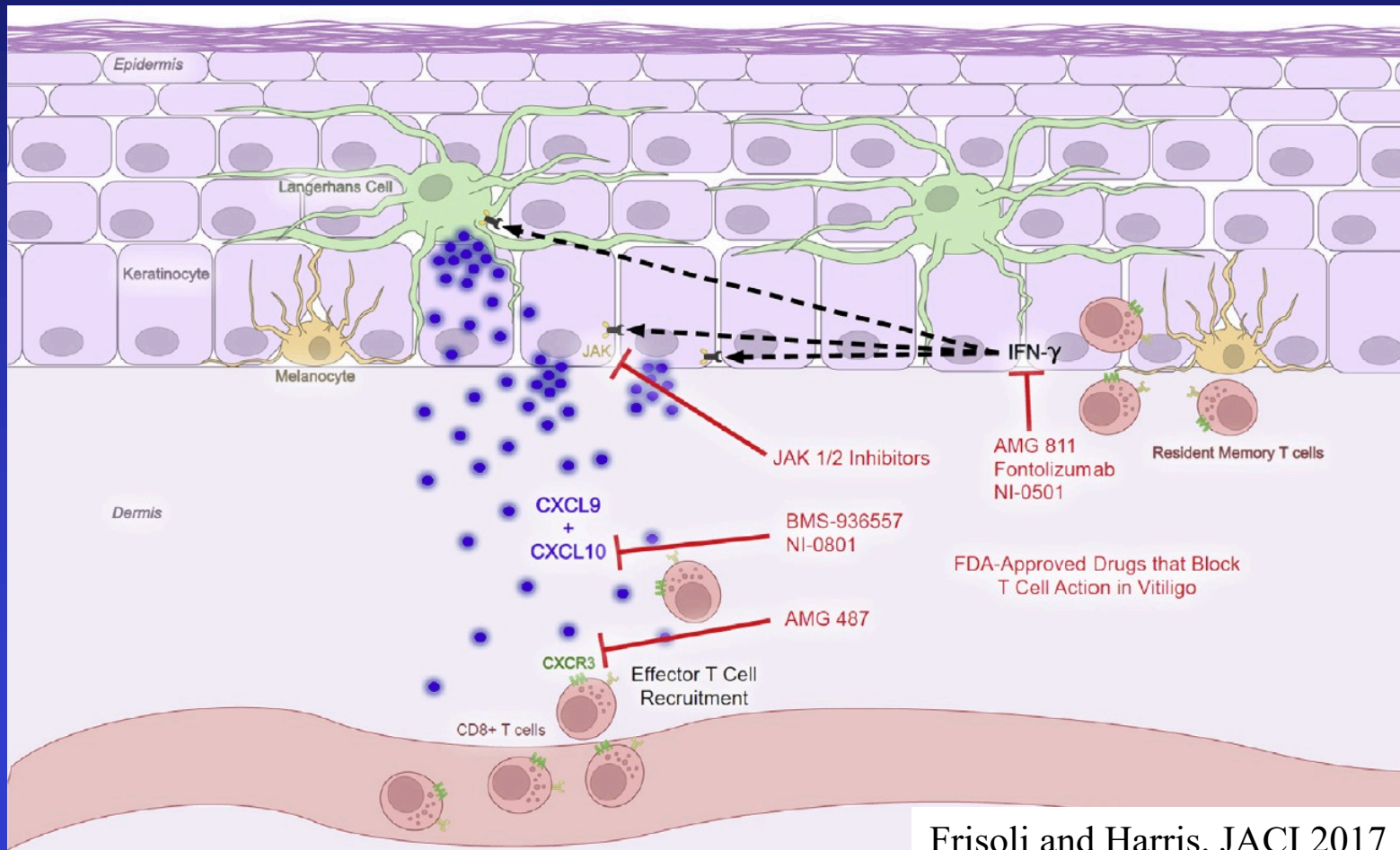
- Ruxolitinib cream was not associated with clinically significant application site reactions or serious treatment-related adverse events

	Ruxolitinib Cream					Total (n=157)
	Vehicle (n=32)	0.15% QD (n=31)	0.5% QD (n=31)	1.5% QD (n=30)	1.5% BID (n=33)	
Patients with TEAE, n (%)	20 (62.5)	20 (64.5)	22 (71.0)	22 (73.3)	20 (60.6)	104 (66.2)
Most common TEAEs,* n (%)						
Acne	1 (3.1)	4 (12.9)	3 (9.7)	3 (10.0)	5 (15.2)	16 (10.2)
Application site pruritus	3 (9.4)	6 (19.4)	3 (9.7)	3 (10.0)	1 (3.0)	16 (10.2)
Pruritus	3 (9.4)	1 (3.2)	4 (12.9)	4 (13.3)	2 (6.1)	14 (8.9)
Viral upper respiratory tract infection	5 (15.6)	3 (9.7)	2 (6.5)	2 (6.7)	1 (3.0)	13 (8.3)
Headache	3 (9.4)	1 (3.2)	0	3 (10.0)	2 (6.1)	9 (5.7)
Treatment-related TEAE, n (%)	12 (37.5)	11 (35.5)	11 (35.5)	10 (33.3)	10 (30.3)	54 (34.4)
TEAE leading to discontinuation, n (%)	1 (3.1)	1 (3.2) <sup>†</sup>	0	0	0	2 (1.3)
Serious TEAE, n (%)	0	0	0	0	1 (3.0) <sup>‡</sup>	1 (0.6)

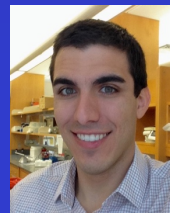
TEAE, treatment-emergent adverse event.

\* Occurring in  $\geq 5\%$  of the total patient population; <sup>†</sup> Headache related to treatment; <sup>‡</sup> Subdural hematoma not related to treatment.

# Emerging Treatments



Frisoli and Harris. JACI 2017



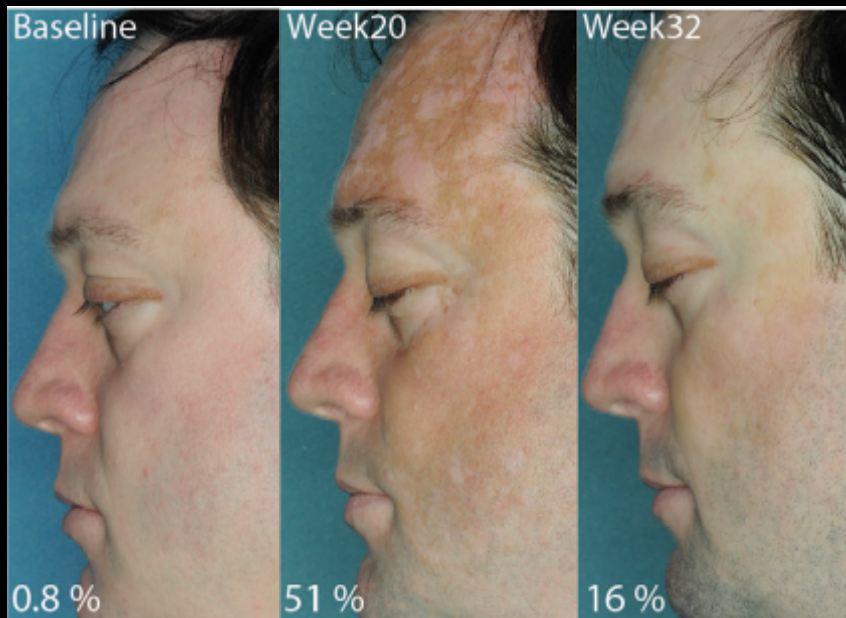
# Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA)

RESEARCH LETTER

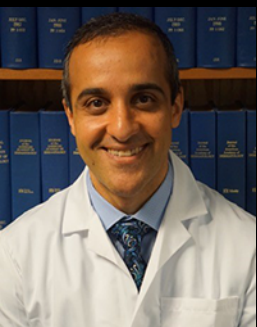
*John E. Harris, MD, PhD,<sup>a</sup> Mehdi Rasbighi, MD,<sup>a</sup>  
Nhan Nguyen, MD,<sup>b</sup> Ali Jabbari, MD, PhD,<sup>b</sup>  
Grace Ulerio, BA,<sup>b</sup> Raphael Clynes, MD, PhD,<sup>b</sup>  
Angela M. Christiano, PhD,<sup>b,c</sup> and Julian  
Mackay-Wiggan, MD, MS<sup>b</sup>*

370 FEBRUARY 2016

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VOLUME 74, NUMBER 2



Not durable





# Maintenance Therapy of Adult Vitiligo with 0.1% Tacrolimus Ointment: A Randomized, Double Blind, Placebo–Controlled Study

Marine Cavalié<sup>1</sup>, Khaled Ezzedine<sup>2</sup>, Eric Fontas<sup>3</sup>, Henri Montaudie<sup>1</sup>, Emeline Castela<sup>1</sup>, Philippe Bahadoran<sup>1,4</sup>, Alain Taïeb<sup>2</sup>, Jean-Philippe Lacour<sup>1</sup> and Thierry Passeron<sup>1,5</sup>

**\*Spots recur\***

Relapse rate is 40% within 1<sup>st</sup> year of stopping treatment

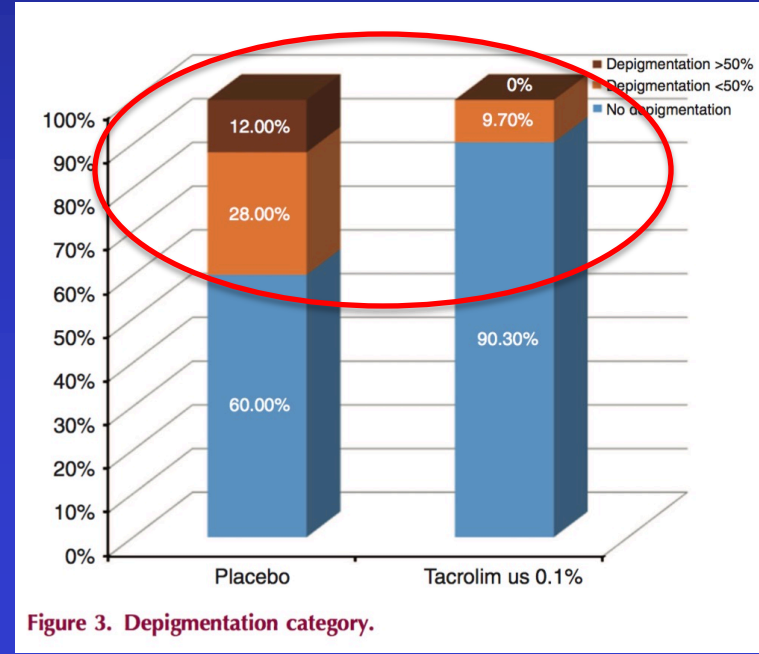
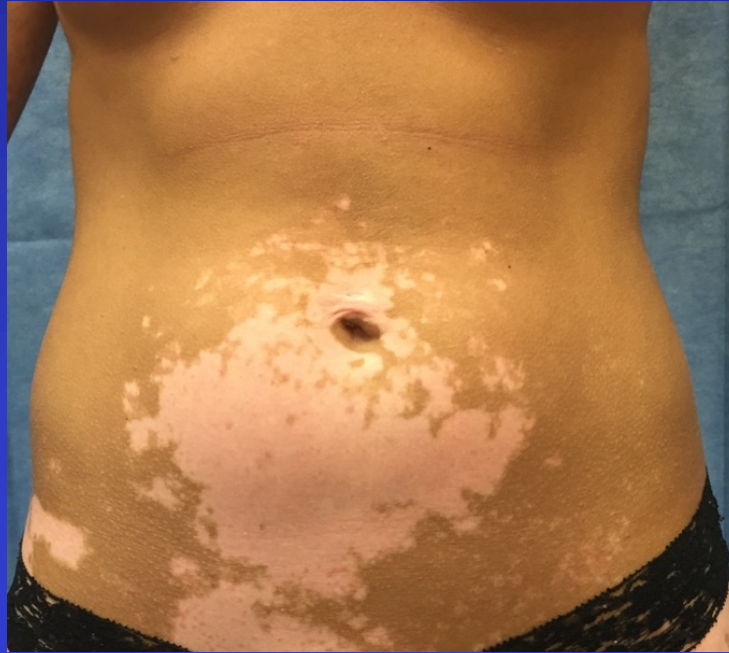


Figure 3. Depigmentation category.

## CD49a Expression Defines Tissue-Resident CD8<sup>+</sup> T Cells Poised for Cytotoxic Function in Human Skin

Stanley Cheuk,<sup>1</sup> Heinrich Schlums,<sup>2</sup> Irène Gallais Séroizat,<sup>1,3</sup> Elisa Martini,<sup>1</sup> Samuel C. Chiang,<sup>2</sup> Nicole Marquardt,<sup>3</sup> Anna Gibbs,<sup>1</sup> Ebba Detlofsson,<sup>1</sup> Andrea Introini,<sup>1</sup> Marianne Forkel,<sup>3</sup> Charlotte Höög,<sup>4</sup> Annelie Tjernlund,<sup>1</sup> Jakob Michaëlsson,<sup>3</sup> Lasse Folkersen,<sup>5</sup> Jenny Mjösberg,<sup>3</sup> Lennart Blomqvist,<sup>6</sup> Marcus Ehrström,<sup>7</sup> Mona Ståhle,<sup>1,3</sup> Yanan T. Bryceson,<sup>2,6,\*</sup> and Liv Eidsmo<sup>1,3,5,\*</sup>



# Four teams discover “resident memory T cells” in vitiligo

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

CANCER

## Resident memory T cells in the skin mediate durable immunity to melanoma

Brian T. Malik,<sup>1</sup> Katelyn T. Byrne,<sup>1,2</sup> Jennifer L. Vella,<sup>1</sup> Peisheng Zhang,<sup>1</sup> Tamer B. Shabaneh,<sup>1</sup> Shannon M. Steinberg,<sup>1</sup> Aleksey K. Molodtsov,<sup>1</sup> Jacob S. Bowers,<sup>3</sup> Christina V. Angeles,<sup>4,5</sup> Chrystal M. Paulos,<sup>3</sup> Yina H. Huang,<sup>1,5</sup> Mary Jo Turk<sup>1,5\*</sup>



Journal of Investigative Dermatology (2018) 138, 355–364;

ORIGINAL ARTICLE

## Vitiligo Skin Is Imprinted with Resident Memory CD8 T Cells Expressing CXCR3



Katia Boniface<sup>1</sup>, Clément Jacquemin<sup>1</sup>, Anne-Sophie Darrigade<sup>2</sup>, Benoît Dessarthe<sup>1</sup>, Christina Martins<sup>1</sup>, Nesrine Boukhedouni<sup>1</sup>, Charlotte Vernisse<sup>1</sup>, Alexis Grasseau<sup>1</sup>, Denis Thiolat<sup>1</sup>, Jérôme Rambert<sup>3</sup>, Fabienne Lucchese<sup>1</sup>, Antoine Bertolotti<sup>2</sup>, Khaled Ezzedine<sup>4</sup>, Alain Taieb<sup>1,2</sup> and Julien Seneschal<sup>1,2</sup>



SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

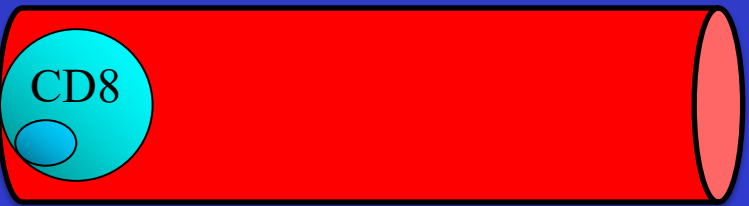
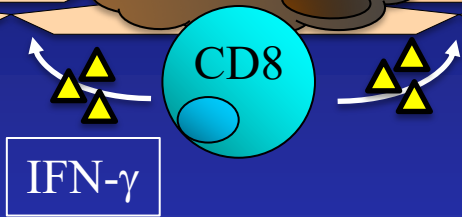
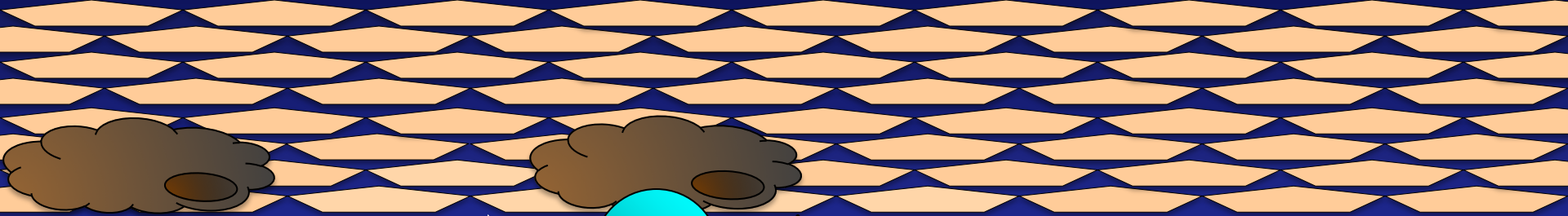
AUTOIMMUNITY

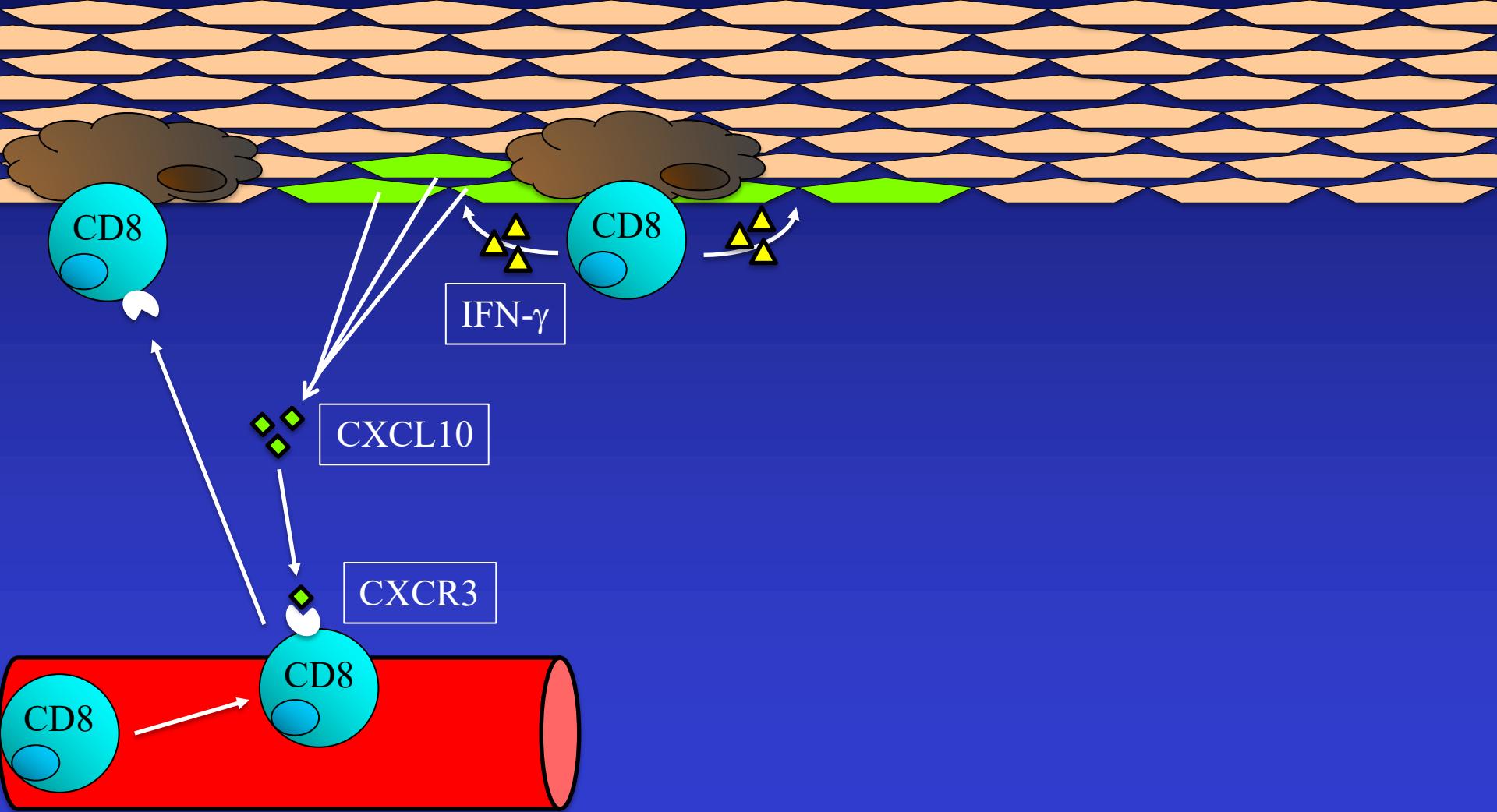
Richmond et al., *Sci. Transl. Med.* 10, eaam7710 (2018) 18 July 2018

## Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo

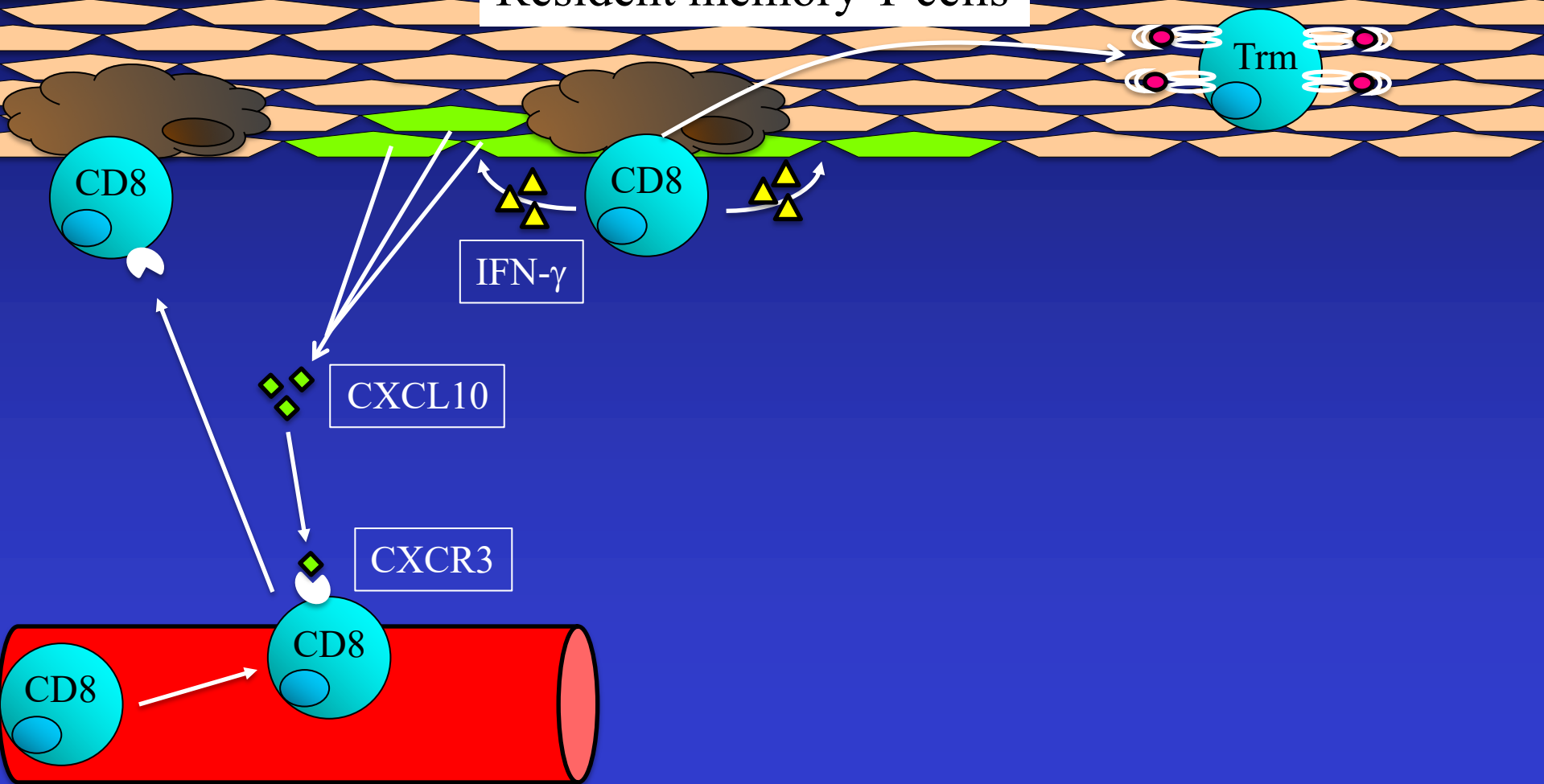
Jillian M. Richmond<sup>1</sup>, James P. Strassner<sup>1</sup>, Lucio Zapata Jr.<sup>1</sup>, Madhuri Garg<sup>1</sup>, Rebecca L. Riding<sup>1</sup>, Maggi A. Refat<sup>1</sup>, Xueli Fan<sup>1</sup>, Vincent Azzolino<sup>1</sup>, Andrea Tovar-Garza<sup>2</sup>, Naoya Tsurushita<sup>3</sup>, Amit G. Pandya<sup>2</sup>, J. Yun Tso<sup>3</sup>, John E. Harris<sup>1\*</sup>







# Resident memory T cells



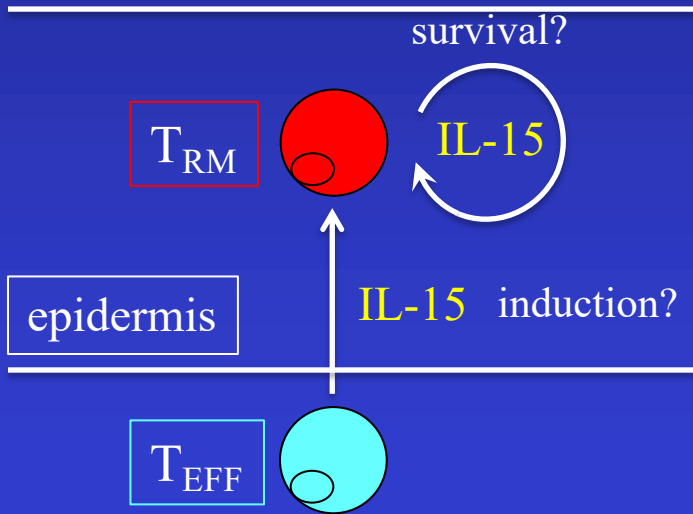
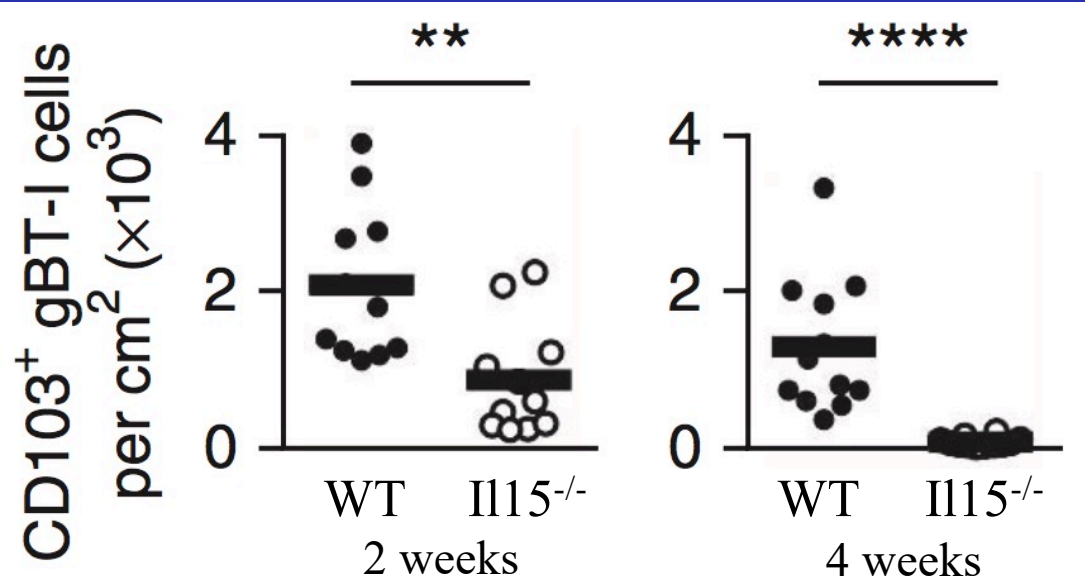




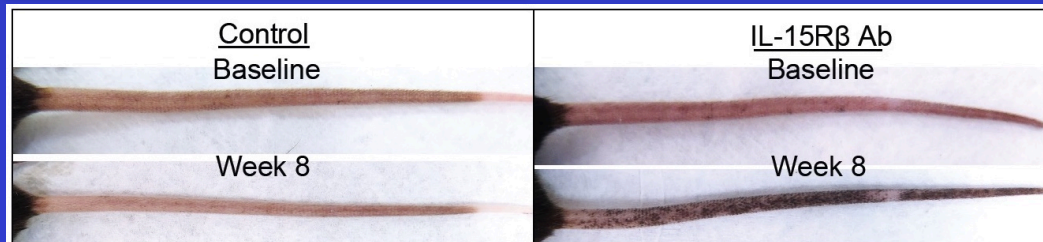
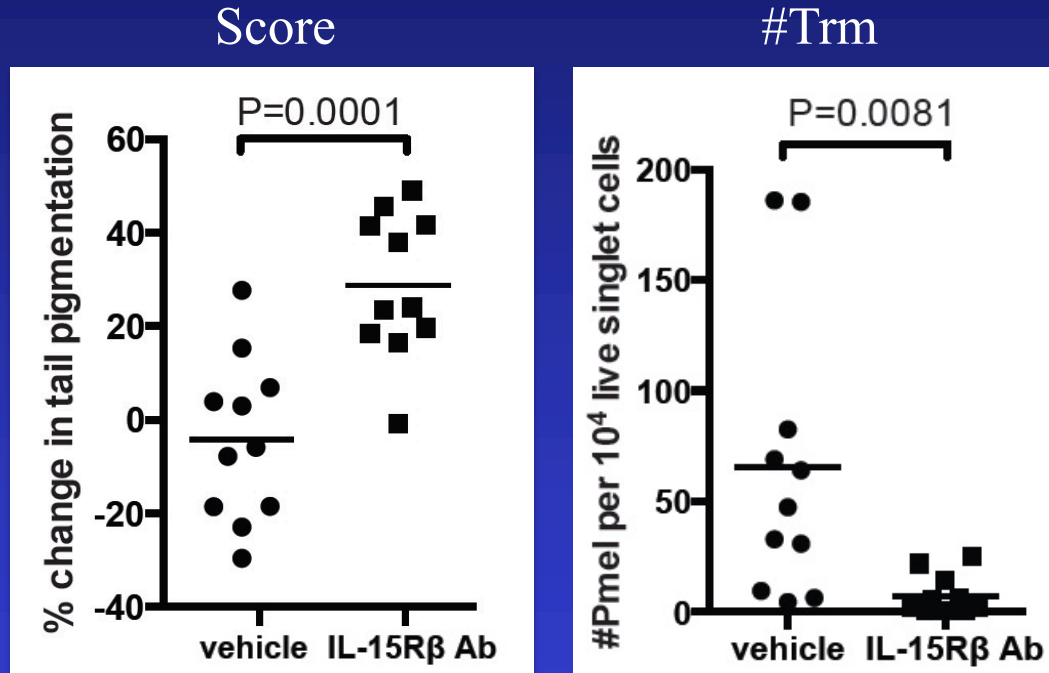
# The developmental pathway for CD103<sup>+</sup>CD8<sup>+</sup> tissue-resident memory T cells of skin

Laura K Mackay<sup>1,5</sup>, Azad Rahimpour<sup>1,5</sup>, Joel Z Ma<sup>1,5</sup>, Nicholas Collins<sup>1</sup>, Angus T Stock<sup>1</sup>, Ming-Li Hafon<sup>1</sup>, Javier Vega-Ramos<sup>1</sup>, Pilar Lauzurica<sup>2</sup>, Scott N Mueller<sup>1</sup>, Tijana Stefanovic<sup>3</sup>, David C Tschärke<sup>3</sup>, William R Heath<sup>1</sup>, Michael Inouye<sup>1,4</sup>, Francis R Carbone<sup>1,6</sup> & Thomas Gebhardt<sup>1,6</sup>

VOLUME 14 NUMBER 12 DECEMBER 2013 NATURE IMMUNOLOGY



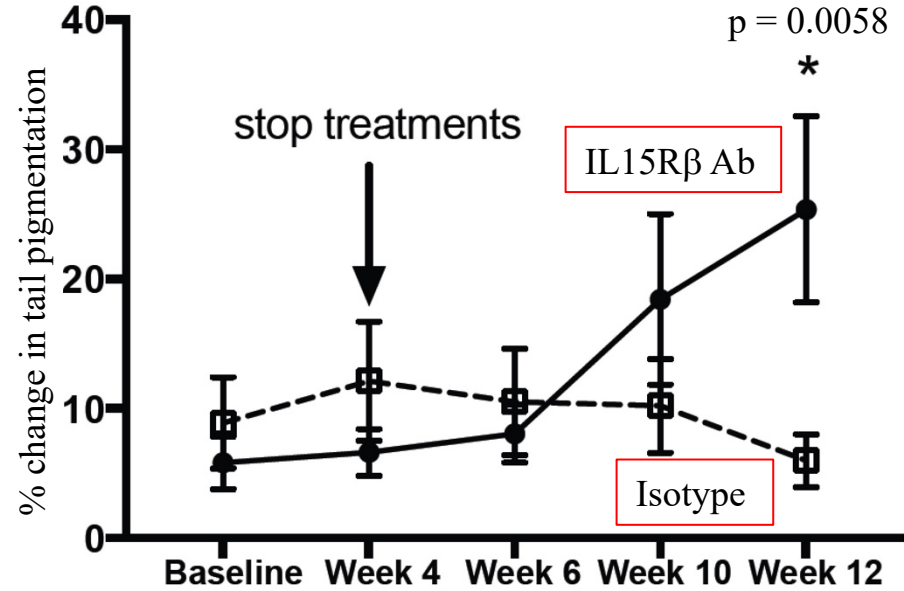
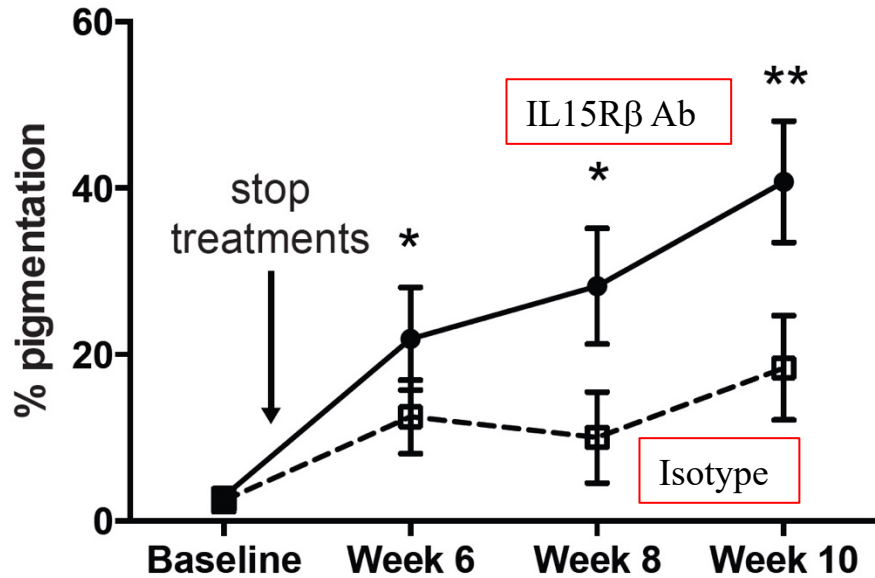
# IL15R $\beta$ Ab removes Trm and reverses vitiligo



# IL15R $\beta$ Ab treatment is long-lasting

Systemic

Intradermal





# Future Studies

Developing  
Clinical Trial:

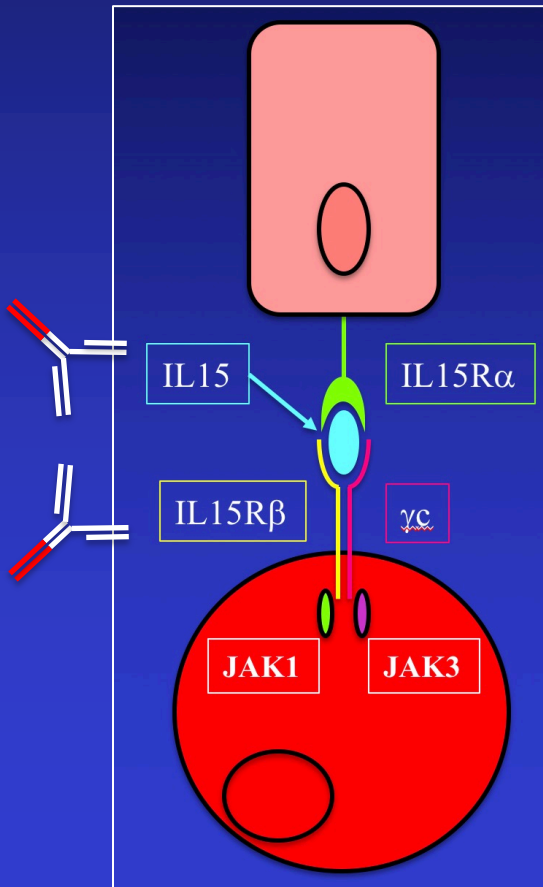
**Amgen**



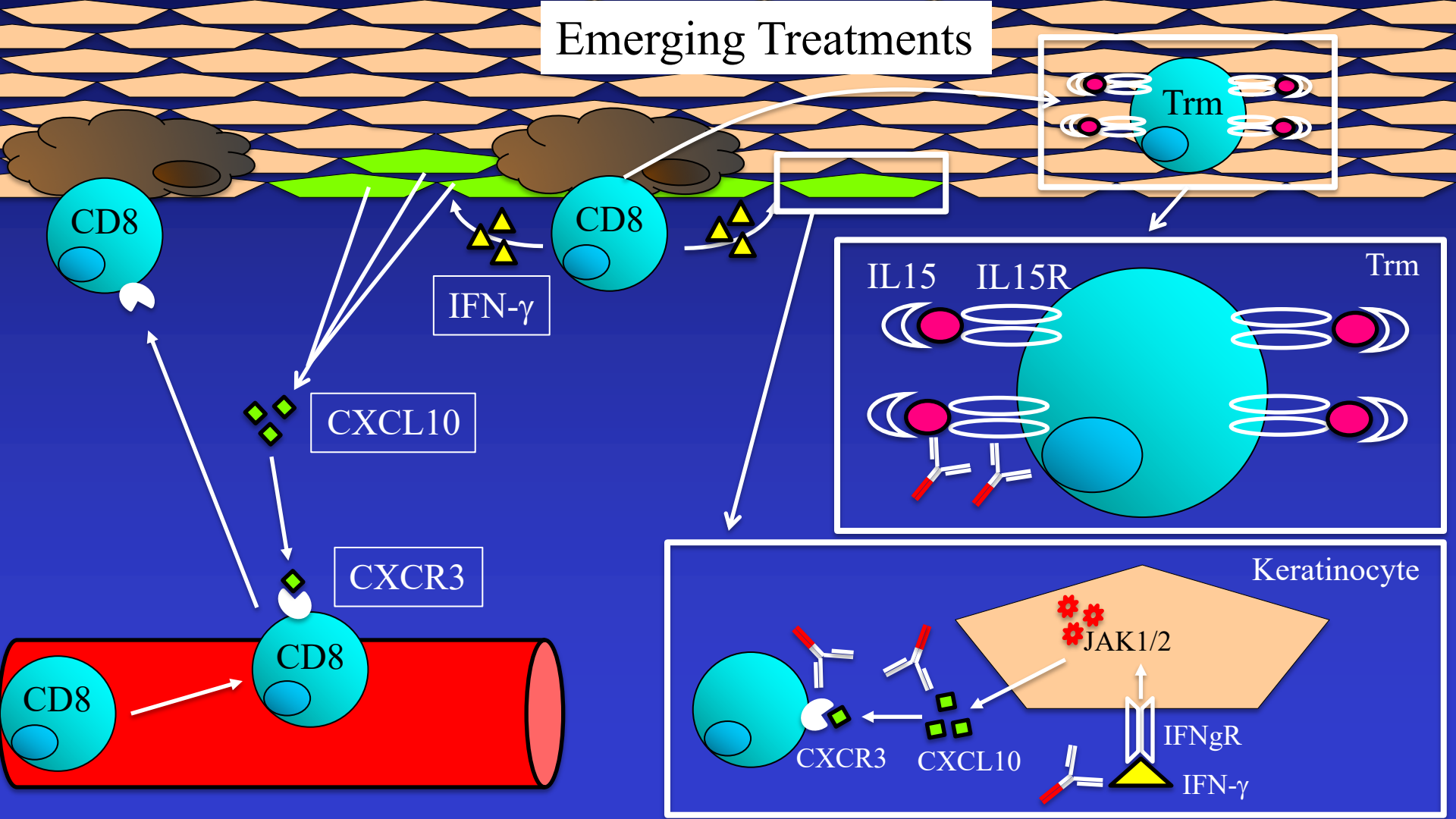
Immune  
Tolerance  
Network



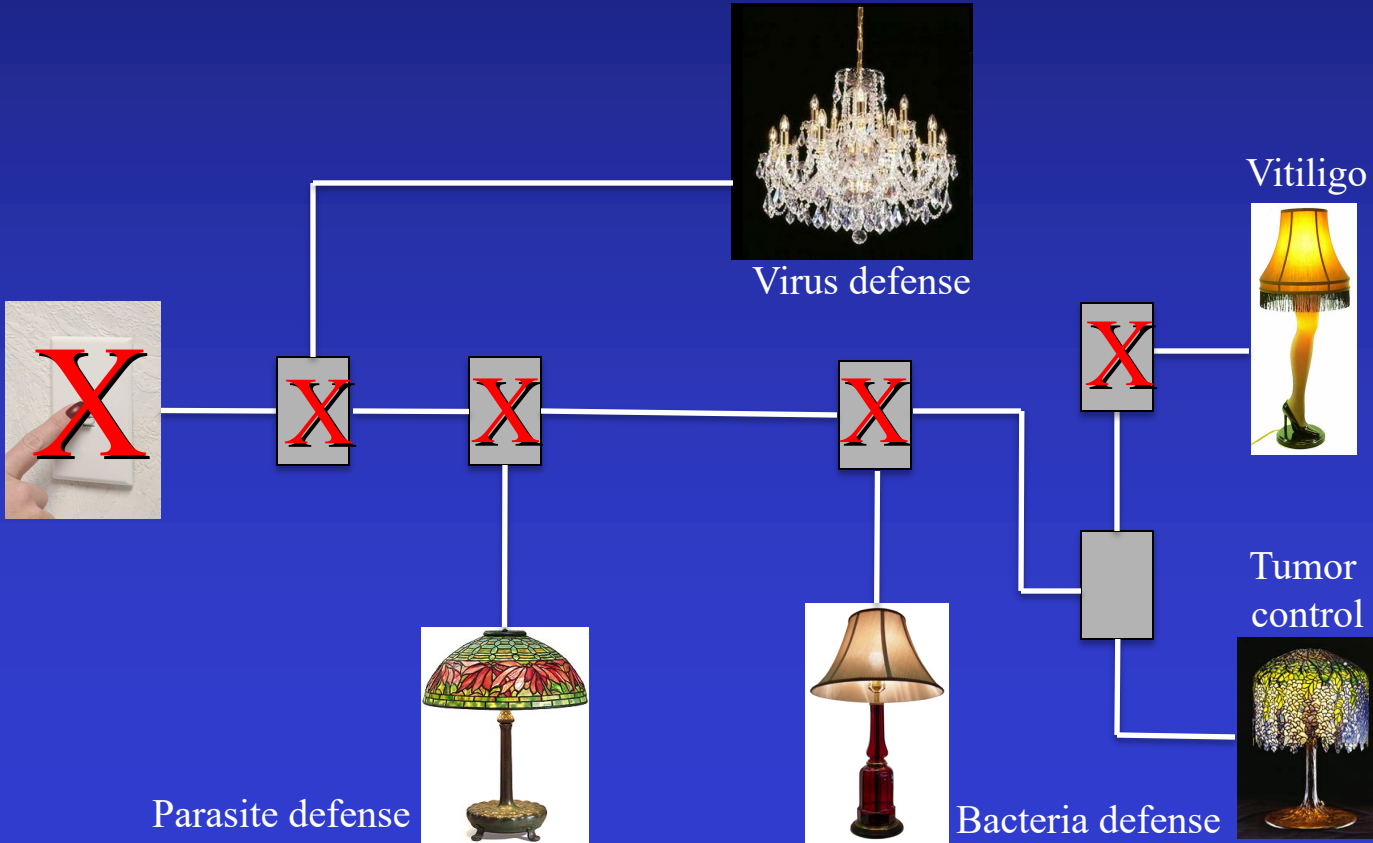
VILLARIS  
therapeutics



# Emerging Treatments



# Shutting off the power with new treatments



# The Dermatology Foundation

has supported & advanced my career.

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Research Grant

Career Development  
Award



Research Fellowship

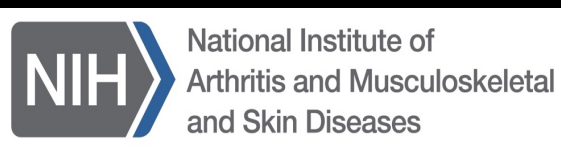
Stiefel Scholar  
Award



Website:  
[Umassmed.edu/vitiligo](http://Umassmed.edu/vitiligo)



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R01  
R61/R33

