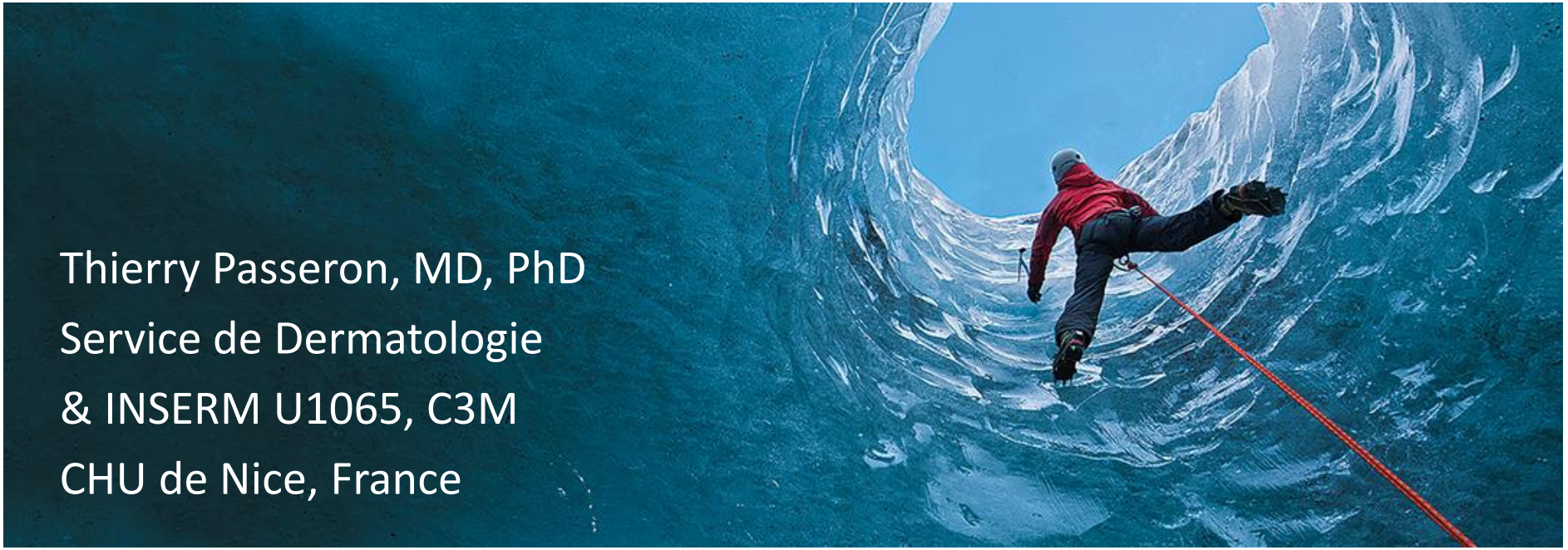
# VITILIGO

## Perspectives and pipeline



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# Conflicts of Interest

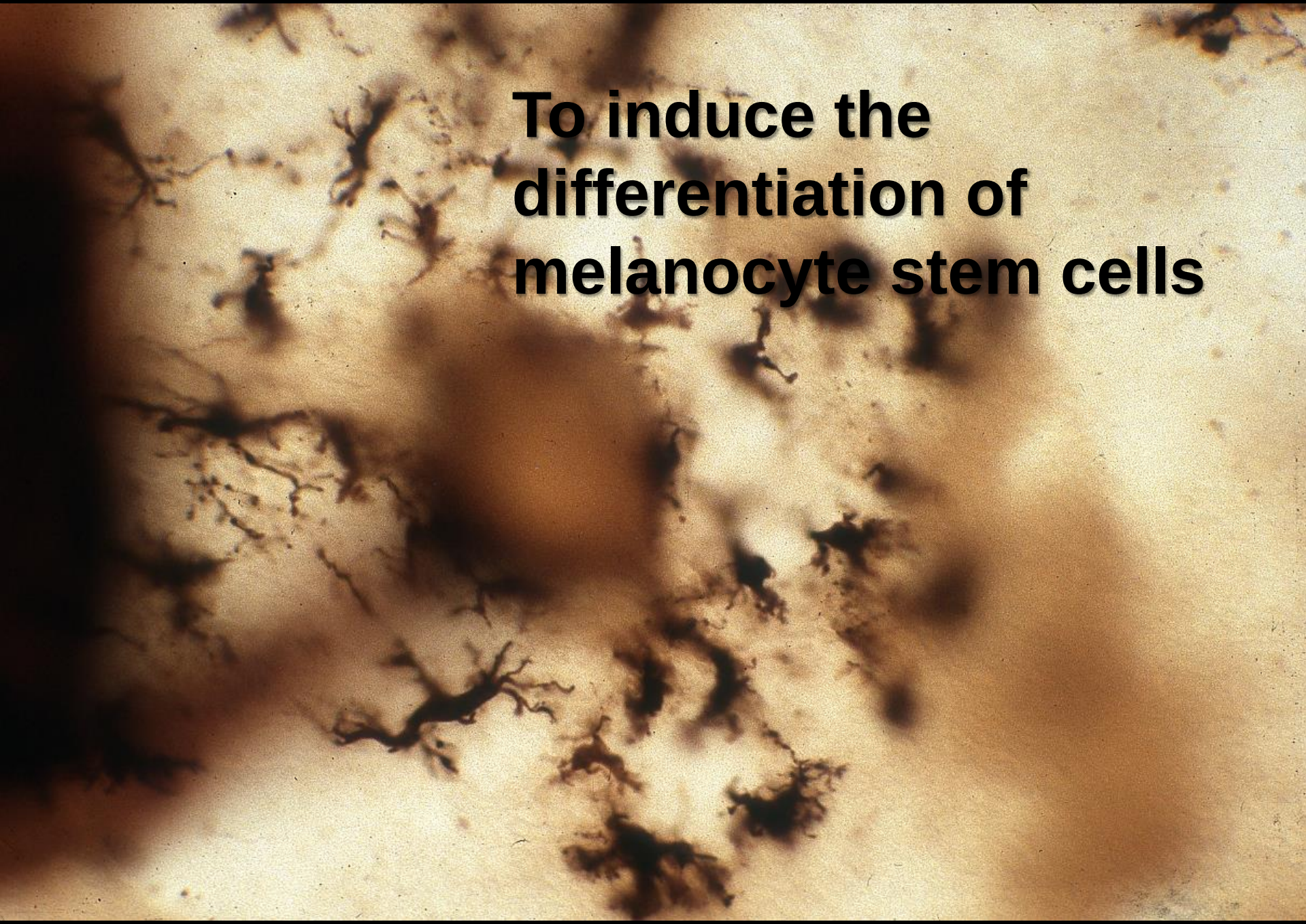
- Abbvie
- ACM Pharma
- Astellas
- BMS
- Celgene
- Galderma
- GSK
- Janssen
- LEO Pharma
- Lilly
- Novartis
- Pfizer
- Sanofi-Genzyme

- 3 objectives in vitiligo treatment:

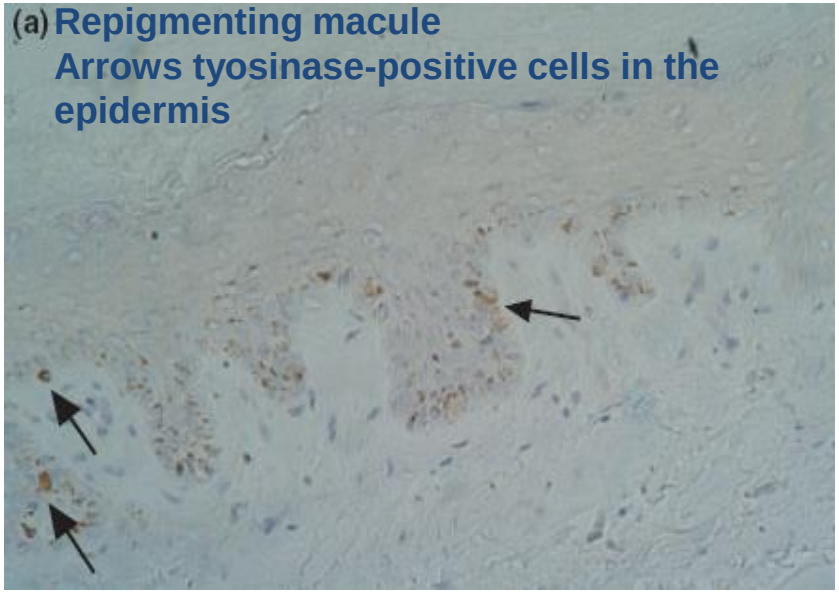
  1. To halt the melanocytic loss

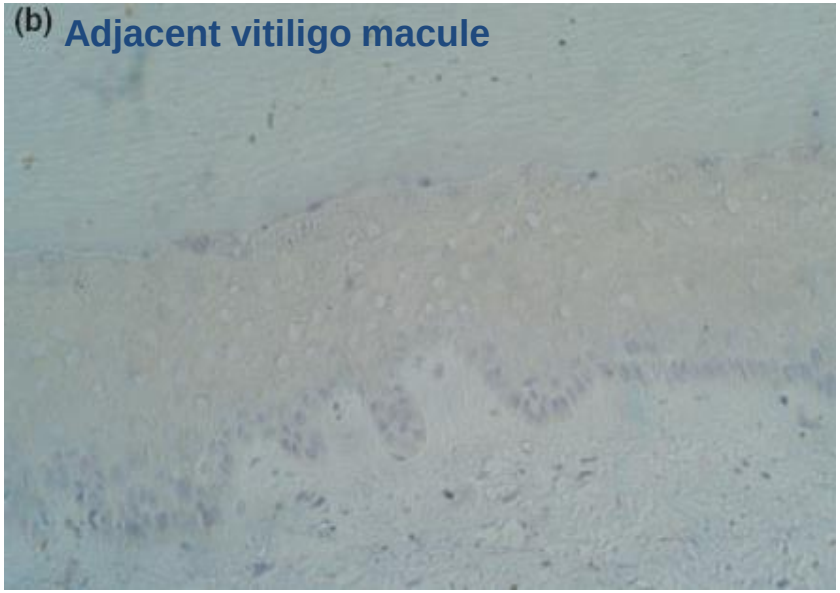
  2. To induce the differentiation and the proliferation of melanocytes (***long process that usually takes 6 to 24 months***)

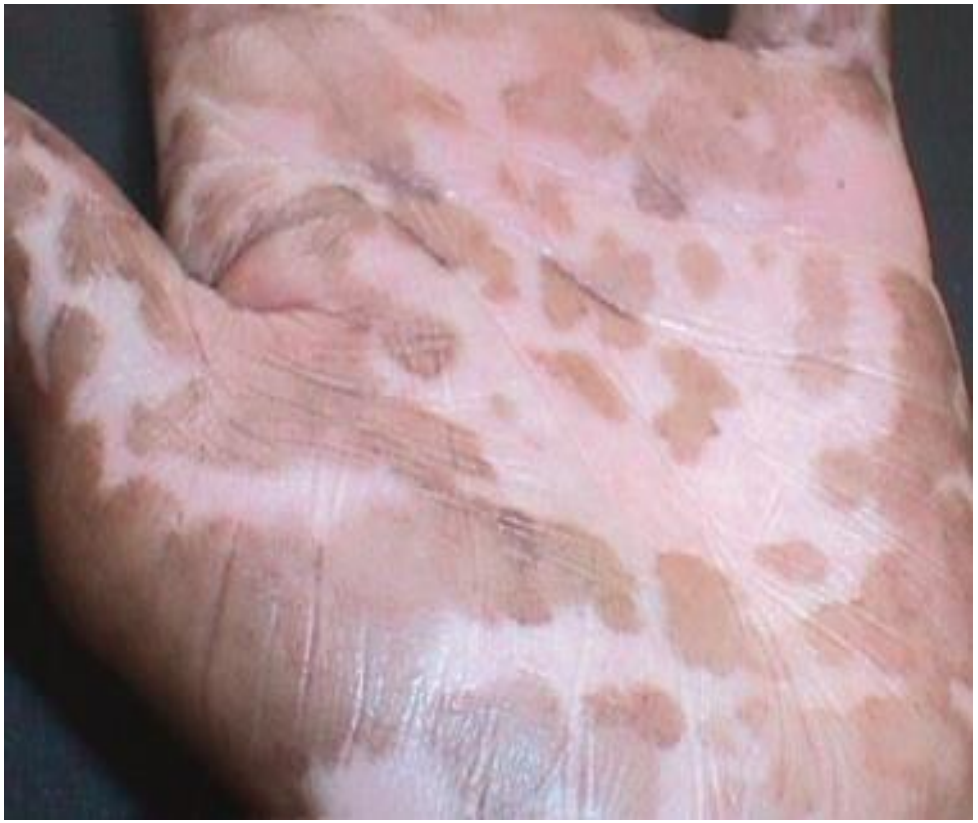
  3. To prevent relapses


To induce the differentiation of melanocyte stem cells

# Are there some melanocyte progenitors in glabrous skin?



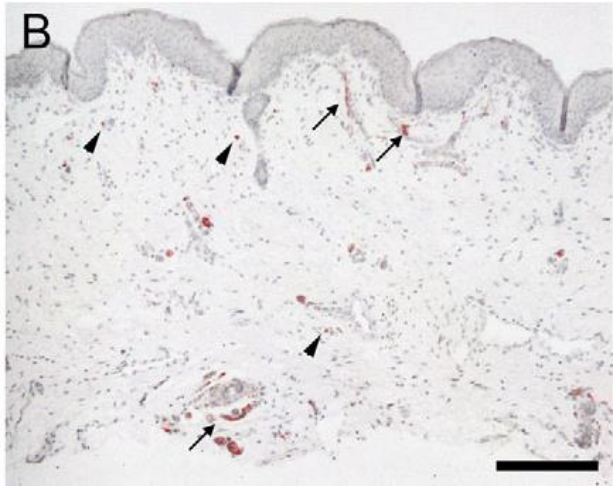
*LM. Davids et al. Clin Exp Dermatol. 2008*

# Human dermal stem cells differentiate into functional epidermal melanocytes

Journal of Cell Science 123, 853-860

Ling Li[1,*], Mizuho Fukunaga-Kalabis[1,*], Hong Yu[2], Xiaowei Xu[2], Jun Kong[1], John T. Lee[1] and Meenhard Herlyn[1,‡]

- Melanocyte progenitors located in the bulge of the hair follicles

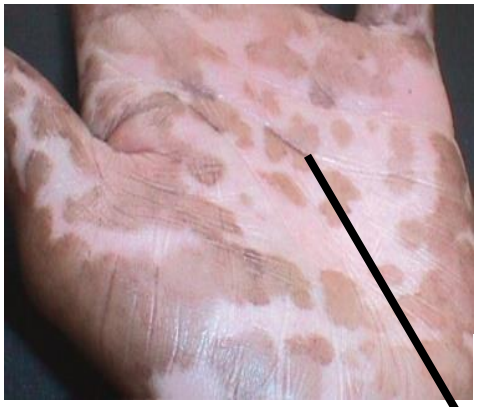



- Dermal stem cells in the glabrous skin
  - With stem cell markers
  - And markers of the neural crest
- Those cells can differentiate in fully differentiated melanocytes and migrate to the epidermis

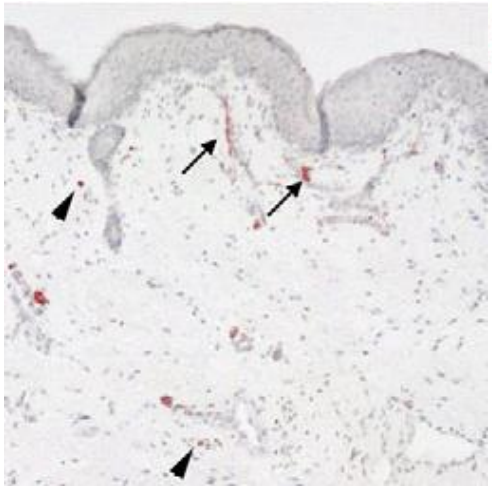
⇒ New reservoir of melanocytes

⇒ **Potential interest in treating vitiligo but how stimulating those cells**

- **Targeting the WNT pathway to induce the differentiation and the proliferation of melanocyte progenitors**

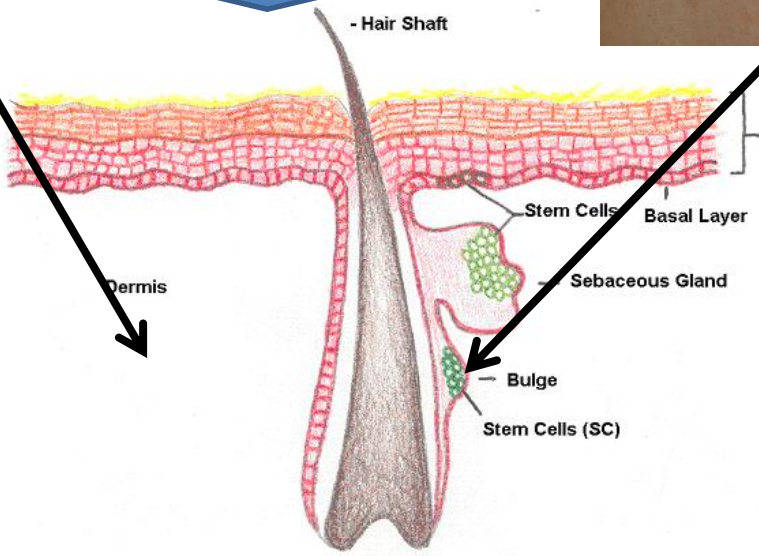


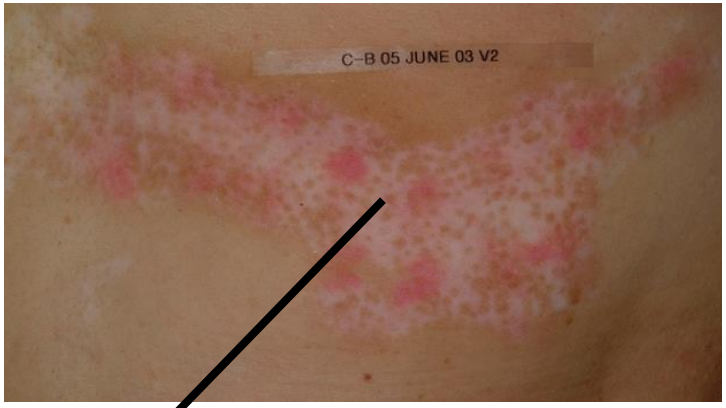
Clin Exp Dermatol. 2008

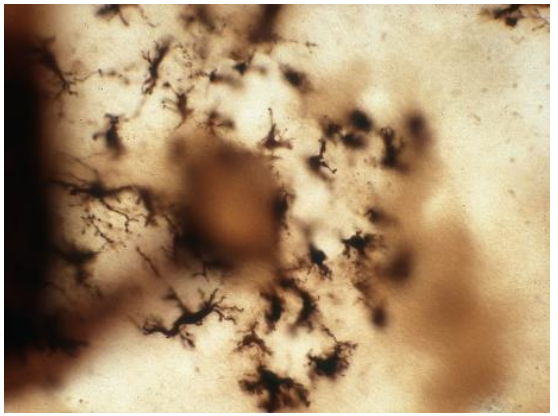


J Cell Science 2009;123:853-60

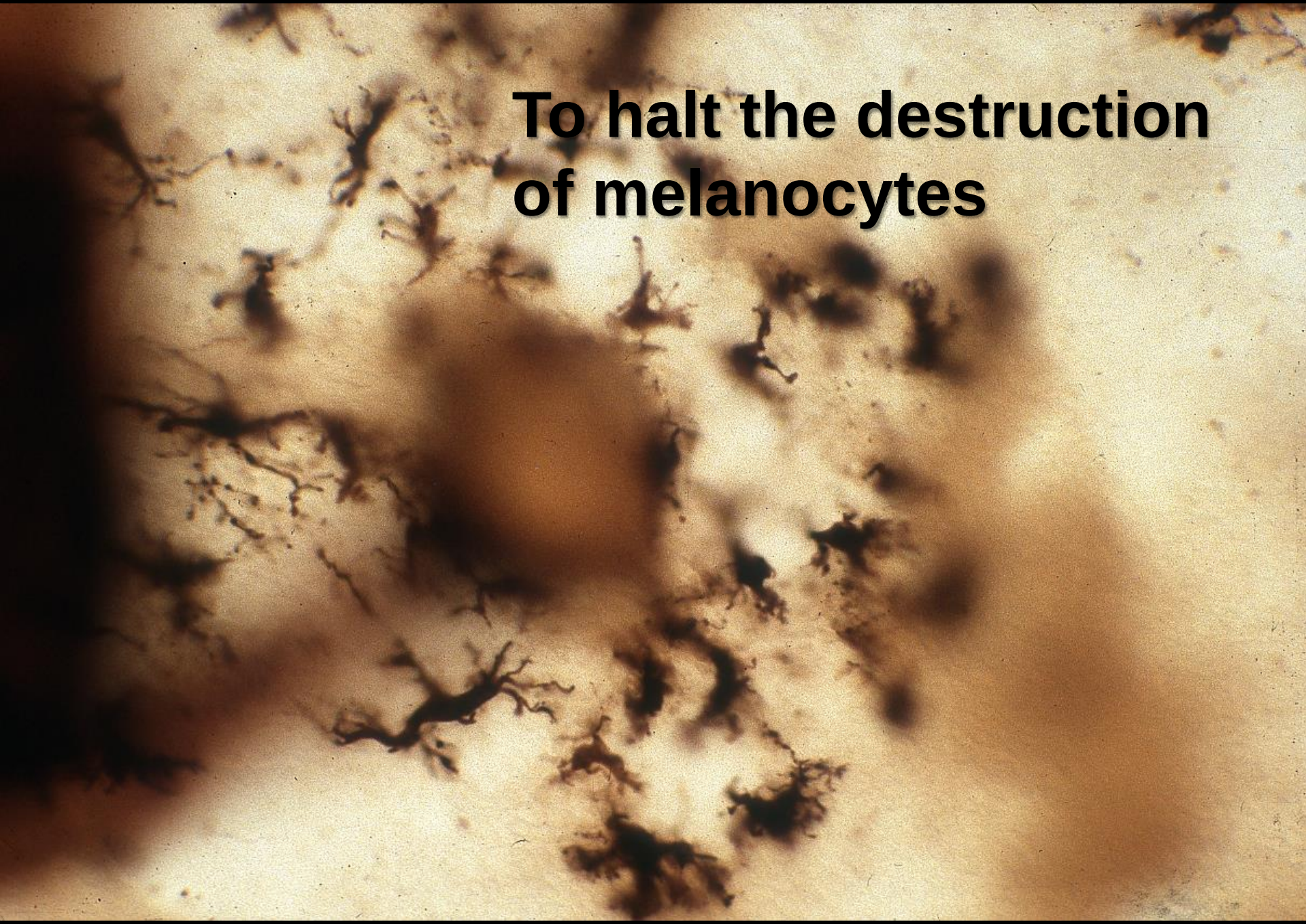
**Topical application of WNT agonists or GSK3b inhibitors**



*J Invest Dermatol*. 2015;135:3105-14

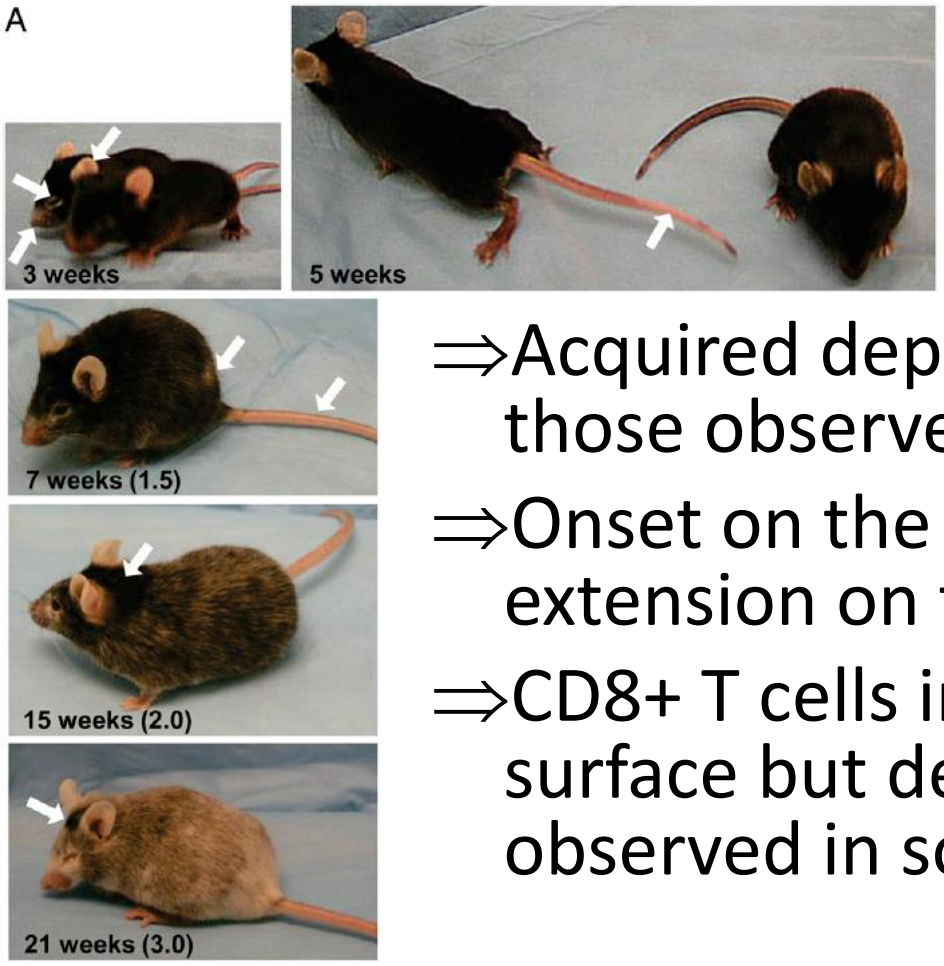

To halt the destruction
of melanocytes

# Mechanisms of Spatial and Temporal Development of Autoimmune Vitiligo in Tyrosinase-Specific TCR Transgenic Mice

The Journal of Immunology

*J. Immunol.* 2010;184;1909-1917;

Randal K. Gregg, Lisa Nichols, Yiming Chen, Bao Lu and Victor H. Engelhard




- Transgenic mice with T cells recognizing a tyrosinase epitope

⇒Acquired depigmented lesions similar to those observed in NSV

⇒Onset on the head than progressive extension on the rest of the body

⇒CD8+ T cells infiltrate in the entire skin surface but depigmentation only observed in some areas

# Decrease of Tregs

- T regulatory lymphocytes (Tregs) (CD3+, FOXP3+)are involved in many inflammatory and auto-immune disorders (ie. Alopecia areata or type 1 diabetes)
- Significant decrease of Tregs in lesional but also peri lesional vitiligo skin compared to controls
- Decrease of the chemokine CCL22

$\Rightarrow$ Potential role of Tregs in the anti-melanocyte reaction?

*Pigment Cell Melanoma Res.* 2010;23:276-86

$\Rightarrow$Activation and recruitment of Tregs when using CCL22

$\Rightarrow$Decrease significantly the depigmentation of a mouse model of vitiligo

$\Rightarrow$Decrease the production of IFN$\gamma$

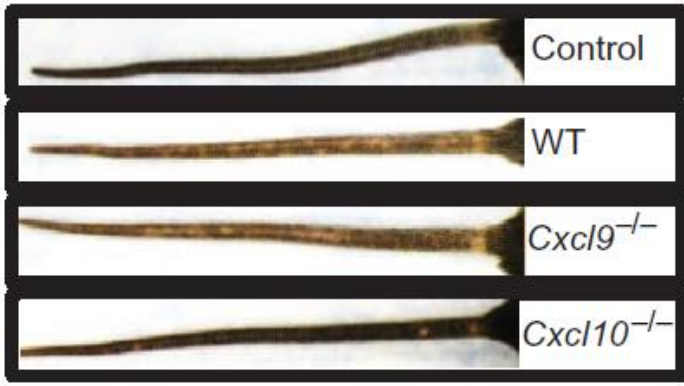
*J Invest Dermatol* 2015; 135: 1574-80

# CXCL10 and vitiligo

- CXCL10: chemokine of IFNγ pathway

➢ CXCL10 is increased in the skin and serum of vitiligo patients

- Mice model of vitiligo:
  - ➢ Mice CXCL10-/- : no depigmentation




  - ➢ Partial repigmentation using anti CXCL10 antibodies


➢ **Development of anti CXCL10 Ab for treating vitiligo**

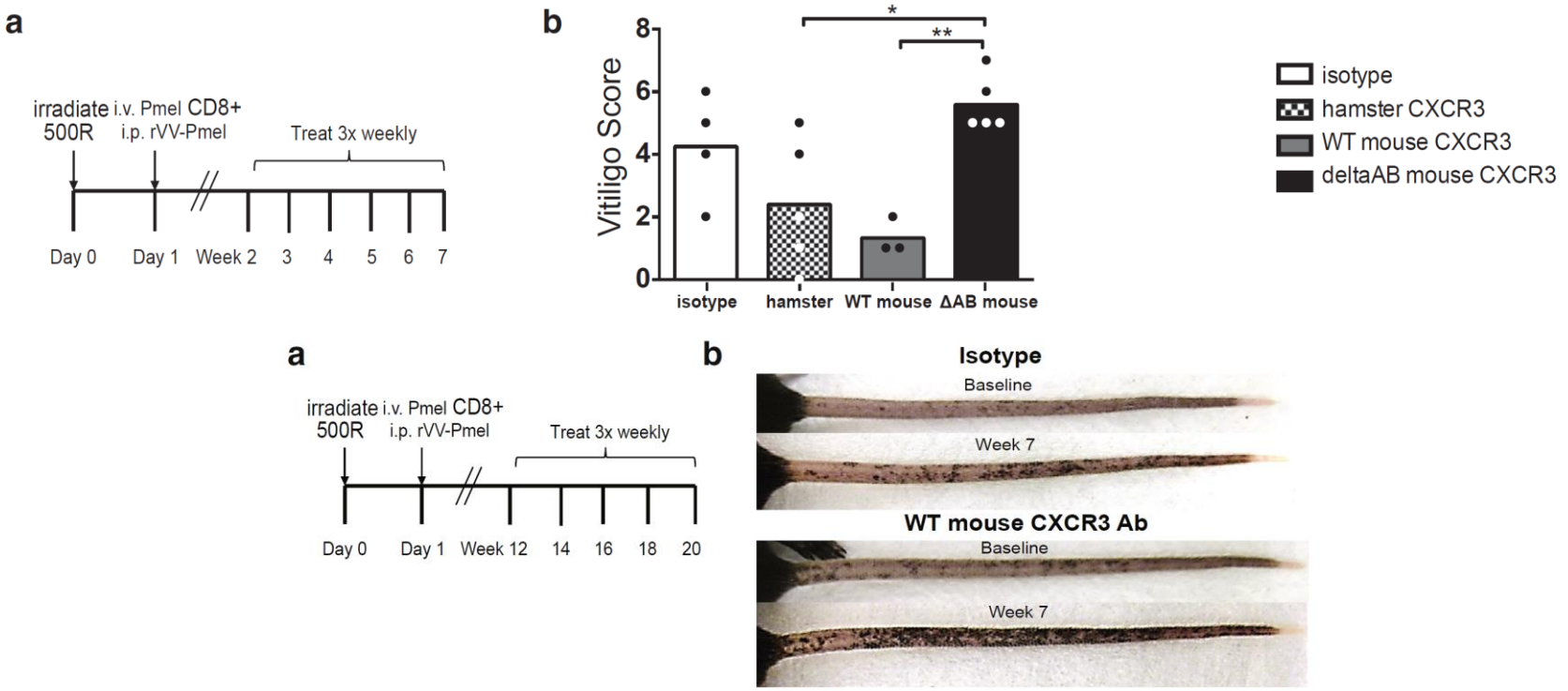
*Sci Transl Med 2014;6:223ra23*

# CXCR3, a potential target

- CXCR3: main receptor on immune cells (T cells) for CXCL9,10,11

- To test 2 types of anti-CXCR3 ab in mouse model:
  - Blocking Ab
  - Depleting Ab

*J Invest Dermatol.* 2017;137:782e985




- Depleting CXCR3 ab provide so far the best response in mouse model
- Efficacy in Man? Safety?

*J Invest Dermatol.* 2017;137:782e985

# Modification in humans?

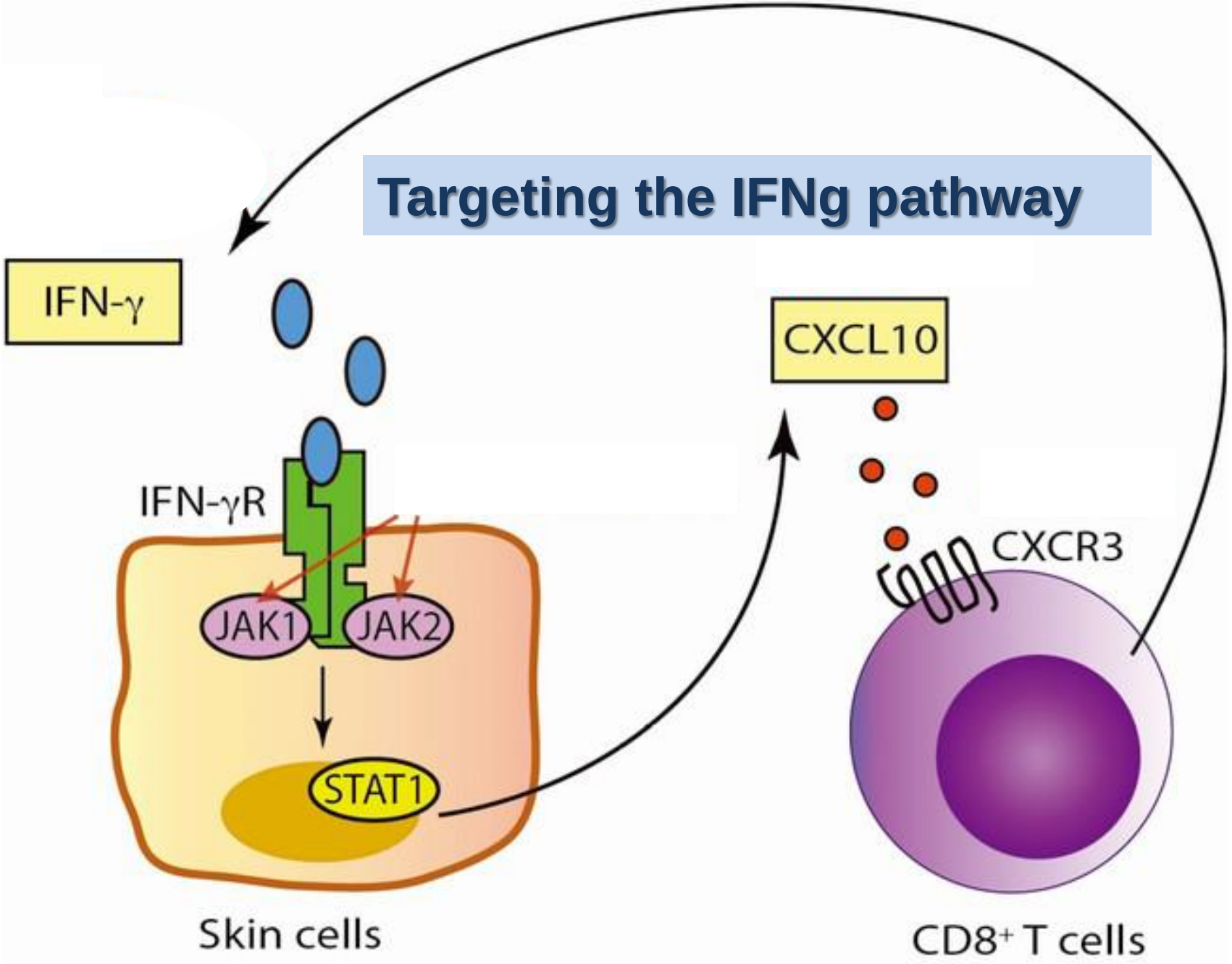
- Significant increase of IFNγ, CXCL9, CXCL10, CXCL11 and their receptor CXCR3 in the sera of vitiligo patients
- Increase correlated to the severity of the disease
- No clear correlation with the activity of the disease

➢ The main source of CXCL10 production in vitiligo skin are the keratinocytes

➢ No increase of CXCL9-10 or IFNγ in completely depigmented vitiligo lesions

***Sci Transl Med 2014*;6:223ra23**
***Brit J Dermatol* 2016; 174: 1318-26**
***J Invest Dermatol* (doi: 10.1016/j.jid.2016.09.016)**
***Pigment Cell Melanoma Research* (doi: 10.1111/pcmr.12559)**

# Targeting the IFNg pathway



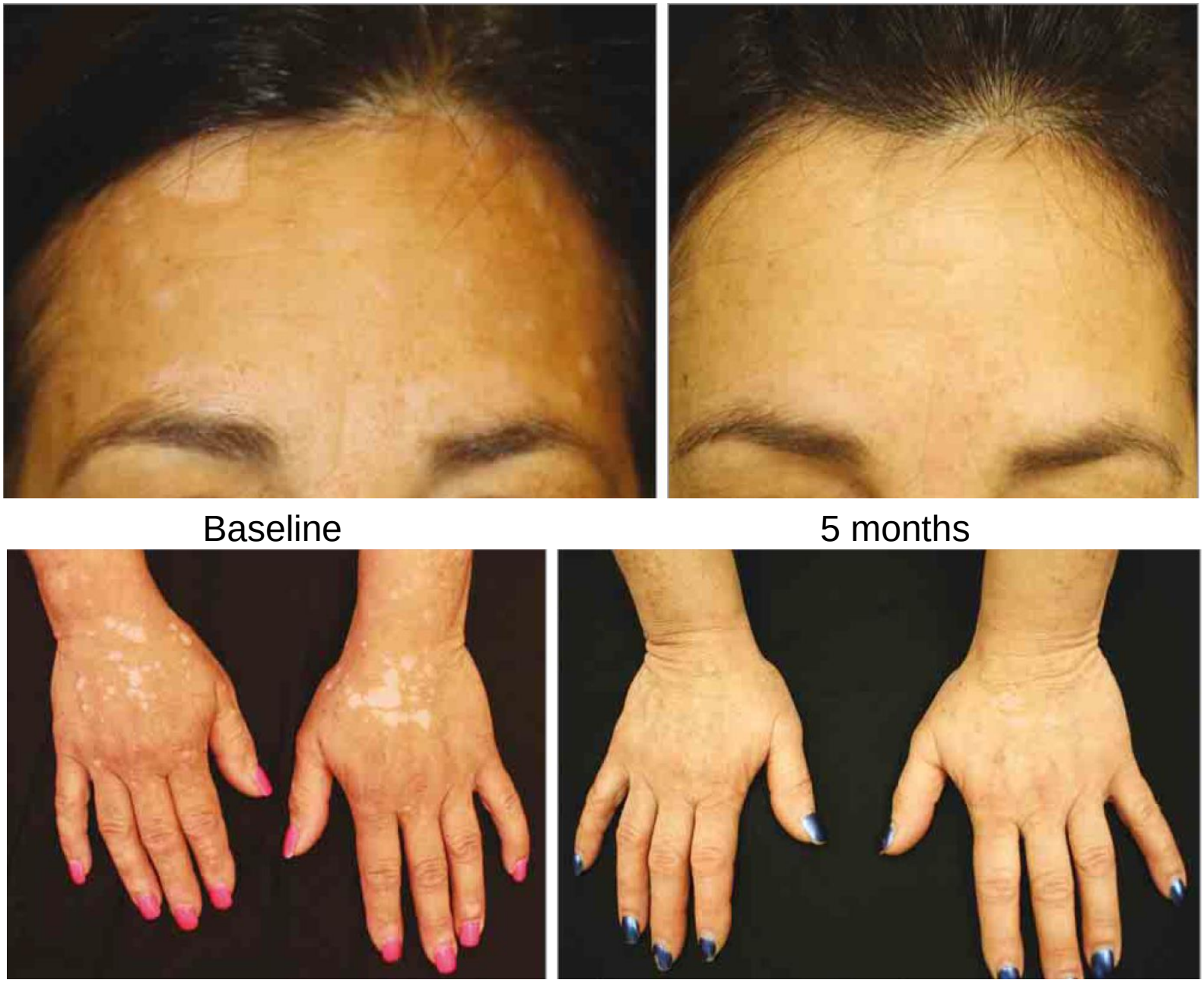

*Ann Transl Med* 2015;3:343

# Tofacitinib citrate for treating vitiligo

- 50 year-old woman
- Rapidly evolving vitiligo since 1 year
- Topical steroid and topical tacrolimus failed to improve the condition
- 3 sessions of Nb-UVB then discontinued by the patient

➢ Oral tofacitinib citrate
  - ➢ 3mg/d for 3 weeks
  - ➢ then 5mg/d
  - ➢ (5mg X2/d for rheumatoid arthritis)

*JAMA Dermatol* 2015;151:1110-2




*JAMA Dermatol* 2015;151:1110-2

- Tofacitinib : JAK 1/3 inhibitor
  - Approved for rheumatoid arthritis
  - Show potential interest in alopecia areata
  - May act downstream CXCL10 on the IFNγ signaling

- Prospective trials required++

➢ **Potentially interesting**

➢ **Supports the interest of targeting the CXCL10 / IFNγ pathway**

*JAMA Dermatol* 2015;151:1110-2

# Ruxolitinib and vitiligo

- 35-year-old man with alopecia areata and vitiligo
- Treatment with ruxolitinib for a phase II open trial for alopecia areata: 20mg x2/d for 20 weeks

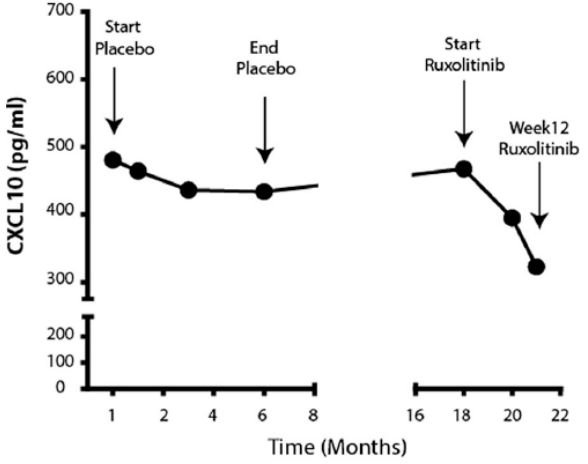
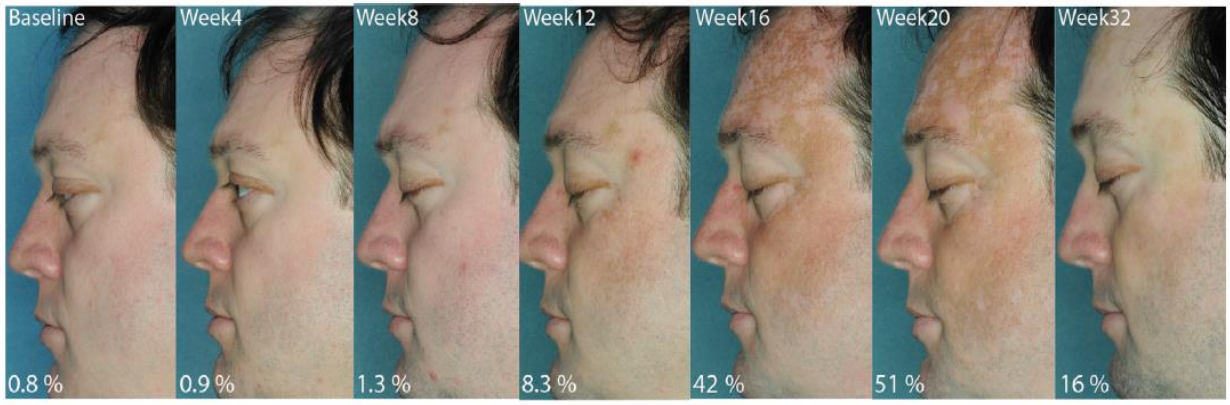



**Fig 2.** Decrease in serum CXCL10 after initiating treatment with ruxolitinib. Serum samples were analyzed by enzyme-linked immunosorbent assay. CXCL10 level was elevated and remained stable while the patient was taking placebo in the first trial, but decreased after initiating treatment with ruxolitinib.



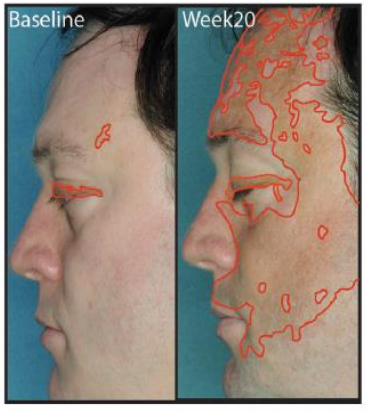




**Fig 1.** Vitiligo repigmentation during treatment with ruxolitinib. Screening skin examination reveals near-complete depigmentation of the patient's face at baseline. The first evidence of skin repigmentation appeared after 12 weeks of therapy, which continued until week 20, when ruxolitinib was discontinued. Follow-up visit 12 weeks after stopping the treatment shows recurrent depigmentation in the majority of previously repigmented areas. Pigmented areas of the face were outlined using the freehand selection tool followed by calculation of the percent selected area using ImageJ software (National Institutes of Health, Bethesda, MD).

Ruxolitinib: anti JAK 1/2
Treatment of intermediate- or high-risk myelofibrosis and polycythemia vera

*J Am Acad Dermatol*. 2016;74:370-1

# Tofacitinib and vitiligo

- Retrospective study on 10 cases
- Partial repigmentation in 5 cases/10

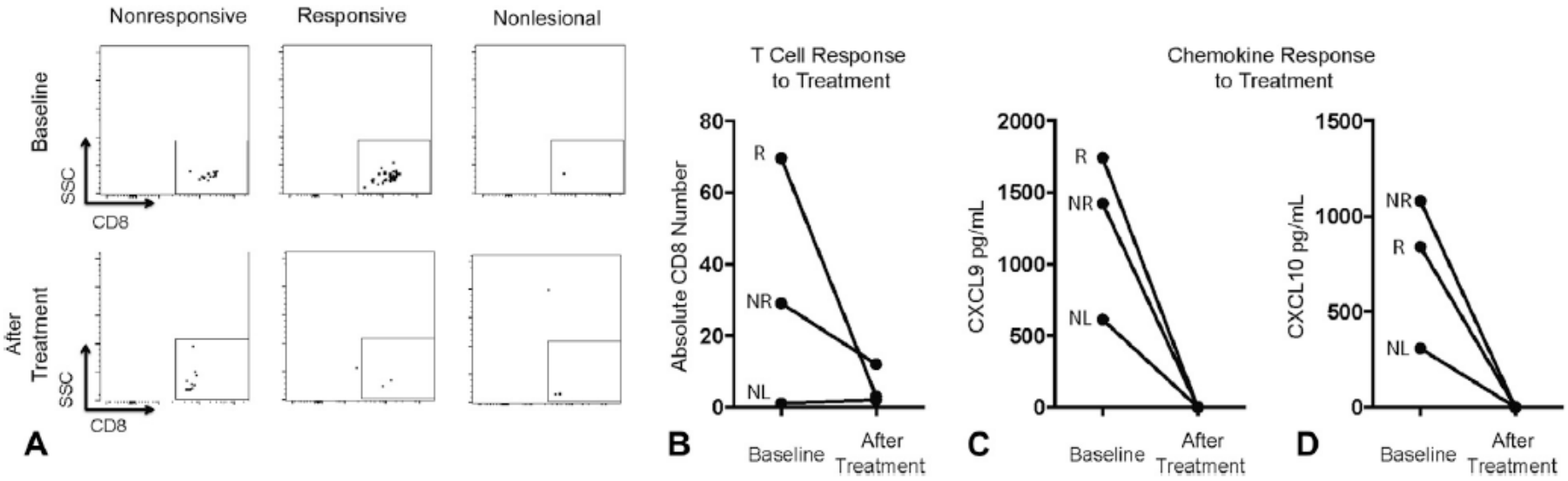
**Table I.** Clinical characteristics of patients with vitiligo

| Patient No. | Age | Sex | Race | BSA before tofacitinib | BSA after tofacitinib treatment | Body site involvement | Tofacitinib treatment duration, mo | Vitiligo disease duration, y | Responder status | Previous treatments |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 54 | F | White | 10% | 4% | Face, torso, arms and hands, legs and feet | 10 | 4 | R | nbUVB, topical tacrolimus |
| 2 | 45 | M | White | 28% | 24% | Face, neck, torso, arms and hands, legs and feet | 8 | 23 | R | Prednisone |
| 3 | 46 | F | White | 39% | 24% | Face, neck, torso, arms and hands, legs and feet | 11 | 16 | R | nbUVB, topical steroids, pseudocatalase cream, blister grafting |
| 4 | 55 | F | White | 10% | 8% | Face, neck, torso, hands, feet | 14 | 24 | R | nbUVB, secukinumab |
| 5 | 45 | M | East Indian | 2% | 2%* | Torso, elbows and hands | 14 | 5 | R | nbUVB, topical tacrolimus |
| 6 | 28 | M | White | 7% | 7% | Face, neck, arms and hands, legs | 3 | 14 | NR | nbUVB, topical steroids, topical tacrolimus |
| 7 | 47 | F | Hispanic | 1% | 1% | Face, neck, arms and hands, legs<br>Hands, feet | 9 | 18 | NR | nbUVB, excimer laser, topical PUVA, topical steroids |
| 8 | 49 | M | White | 4% | 4% | Forehead, torso, arms and hands, legs | 15 | 17 | NR | nbUVB, topical steroids, topical tacrolimus |
| 9 | 32 | M | Hispanic | 6% | 6% | Lower forehead, eyelids, perioral, axillae, elbows and hands, lower back, gluteal cleft, feet | 4 | 12 | NR | nbUVB, fraxel laser, cryotherapy, topical tacrolimus |
| 10 | 73 | F | White | 100% | 100% | Entire body | 11 | 33 | NR | nbUVB, PUVA |

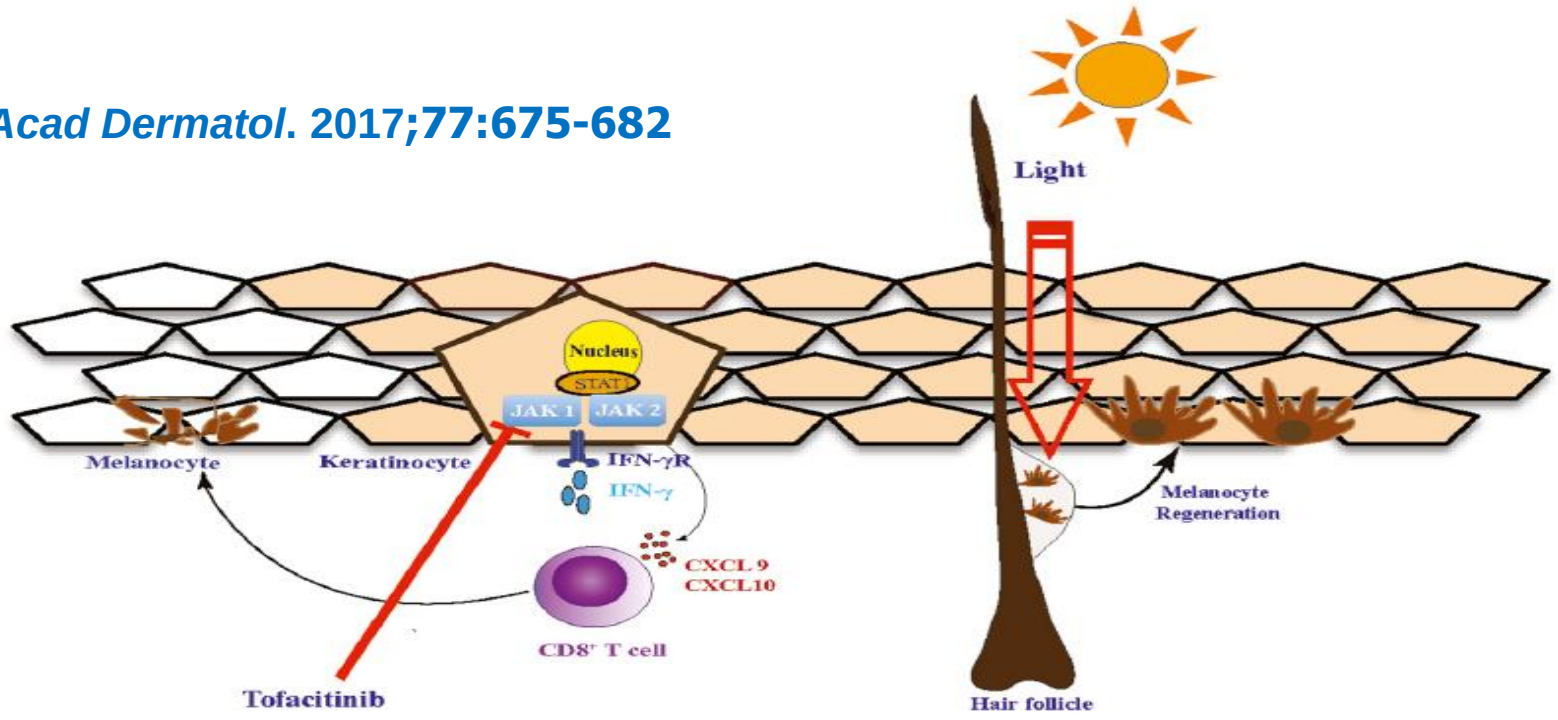
*BSA*, Body surface area; *F*, female; *M*, male; *nbUVB*, narrow band ultraviolet B; *NR*, nonresponder; *PUVA*, psoralen with ultraviolet A; *R*, responder.
*Islands of repigmentation, which were apparent after 12 treatments with nbUVB phototherapy over 4 weeks, did not change the BSA appreciably at this early time point.

➢ **Mild repigmentation and only if sun exposure or combined with UVB**

*J Am Acad Dermatol*. 2017 Aug 17. pii: S0190-9622(17)31799-1




*J Am Acad Dermatol*. 2017;77:675-682




## ➢ Interest for active forms or for maintenance

# Which targets? Which treatments?

| TARGETS | TREATMENT | ACTUAL STAGE OF DEVELOPMENT |
|---|---|---|
| TREGS | Low dose IL2<br>Activation of specific TREGS | 0<br>0 |
| IFNγ | Antibodies | 0 |
| CXCL10 | Antibodies<br><br>Statins | Effective proof of concept in mice<br><br>Negative results |
| CXCR3 | Antibodies | Effective proof of concept in mice |
| JAK | JAKs inhibitors | Encouraging first results in Human<br>Prospective trials ongoing but only topical so far |
| STAT1 | Inhibitors | 0 |
| TH1/TH17 | Apremilast | Prospective randomized trial ongoing (first results summer 2018) |
| STIMULATION OF REPIGMENTATION | WNT agonists or inhibitors of GSK3β | Phase 2 study with topical approach in 2018 |

# Thank you for your attention !

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