Normal skin pigmentation and its regeneration

Vitiligo perspective

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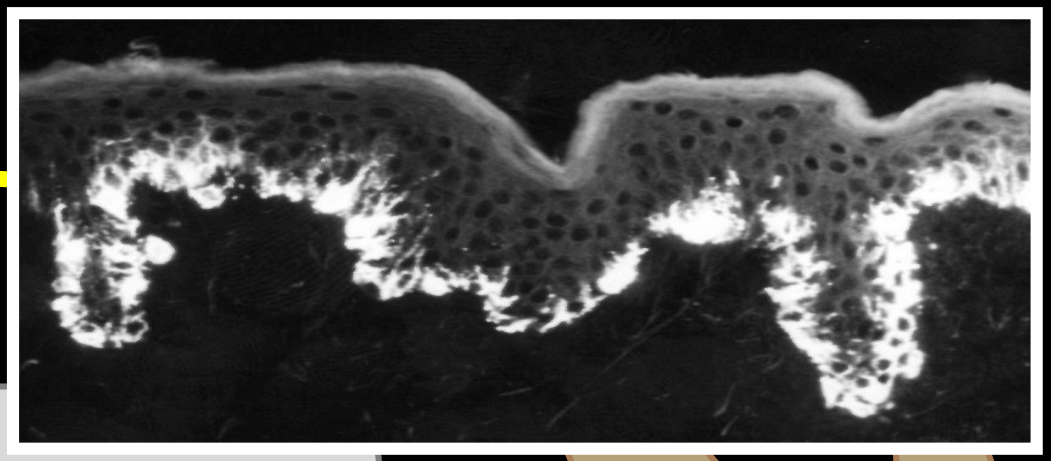
The color of the skin

1. **Melanins+++** → **Eumelanins**, **Pheomelanins**
2. **Hemoglobin**
3. **Carotenoids**

MORE THAN 170 GENES ARE INVOLVED IN THE CONTROL OF HUMAN SKIN PIGMENTATION

SKIN TANNING

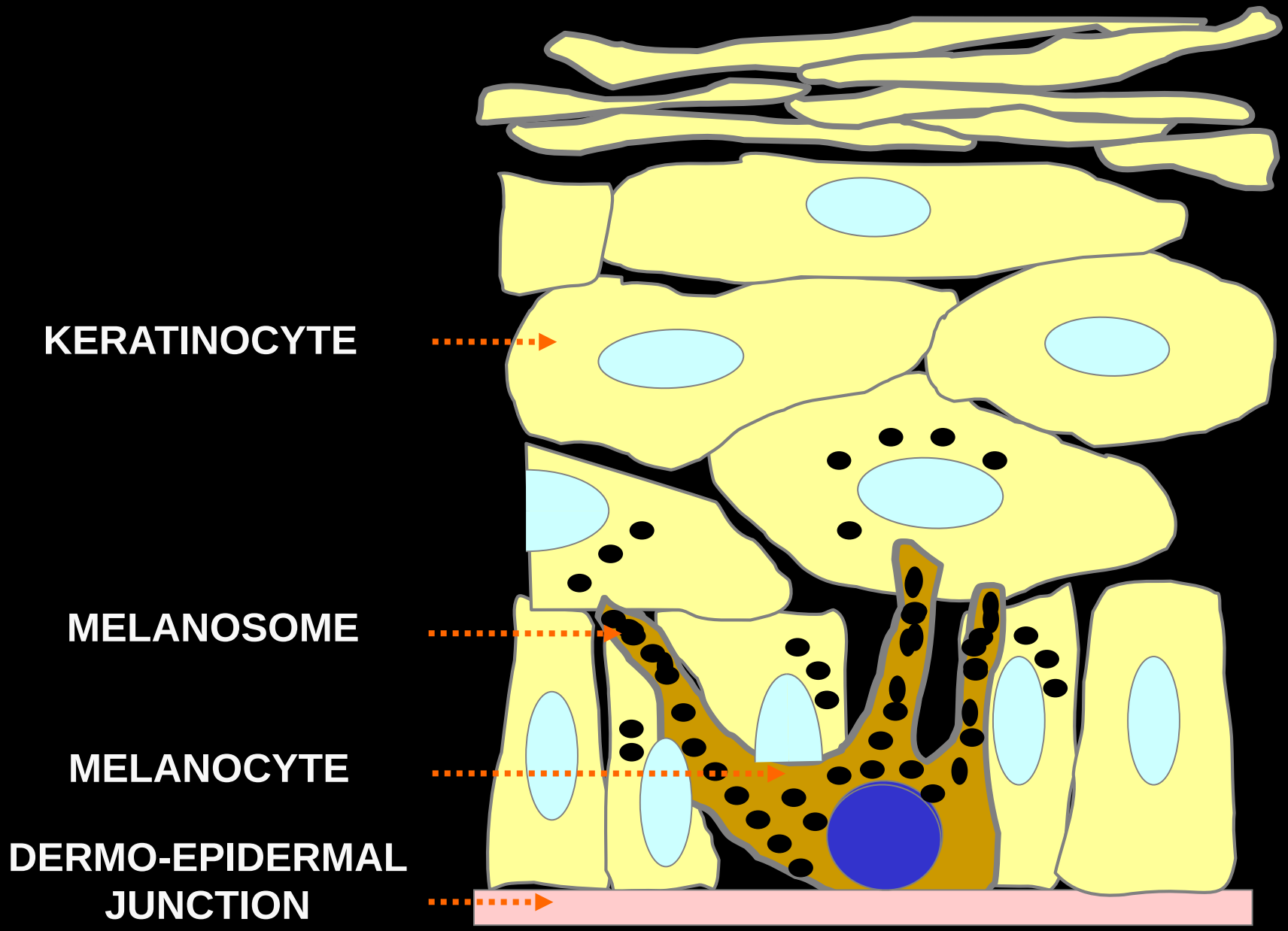
Schematization of Human Skin Pigmentation



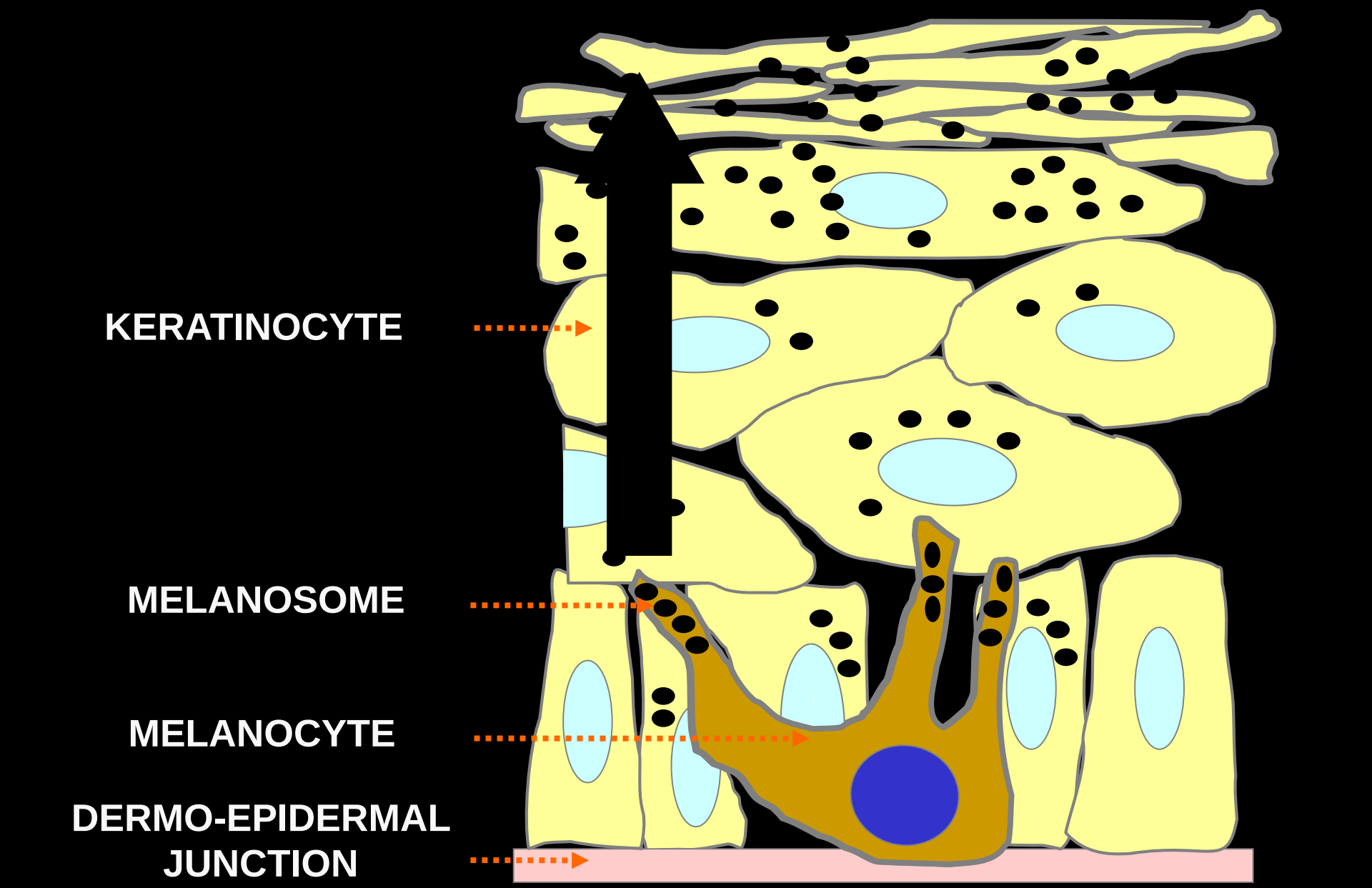
Keratinocytes

Melanocytes

Skin pigmentation



Skin pigmentation

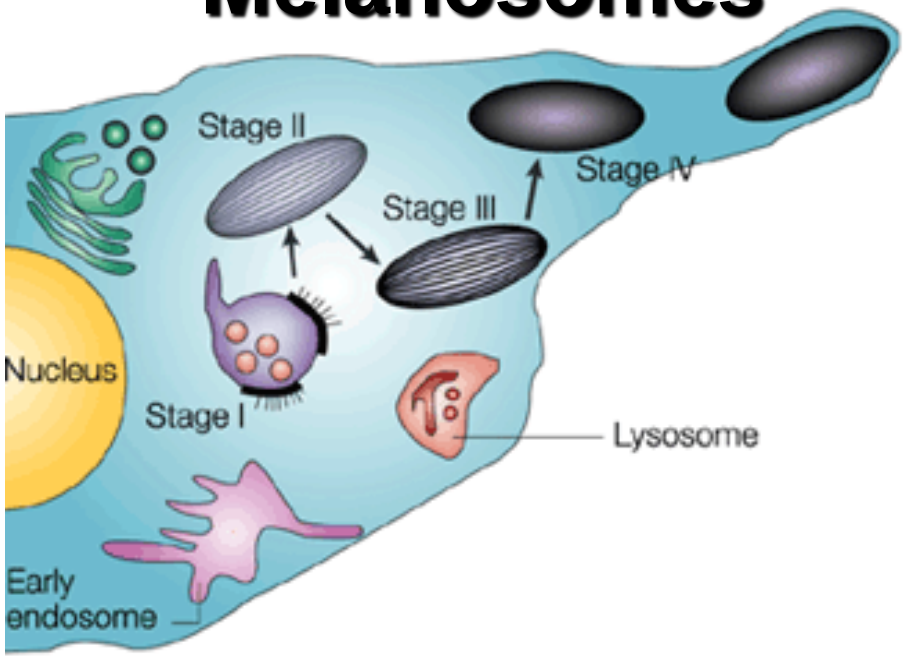


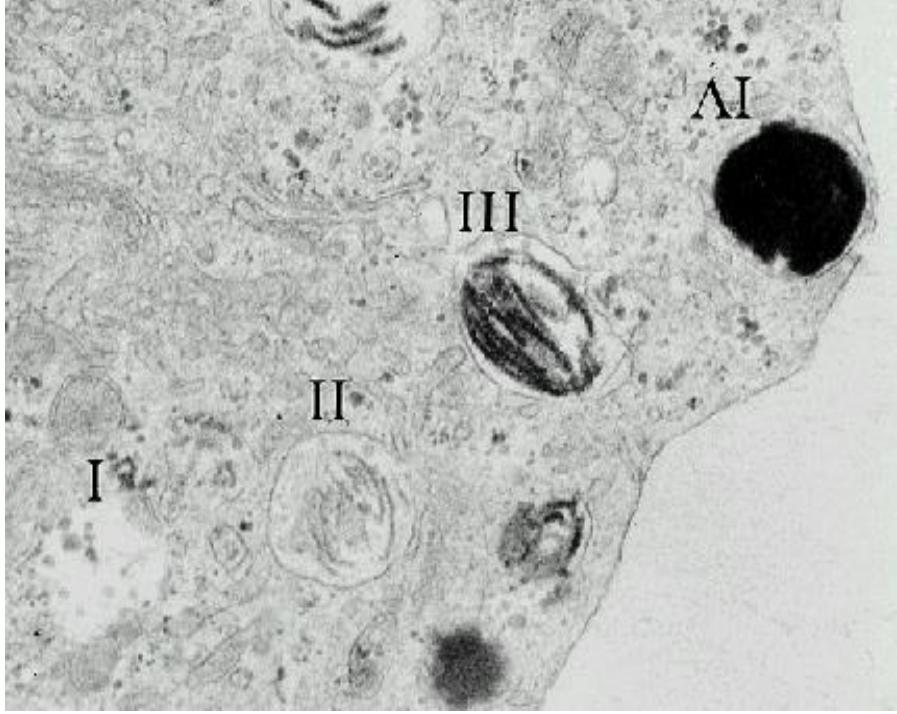
Key factors of the skin pigmentation

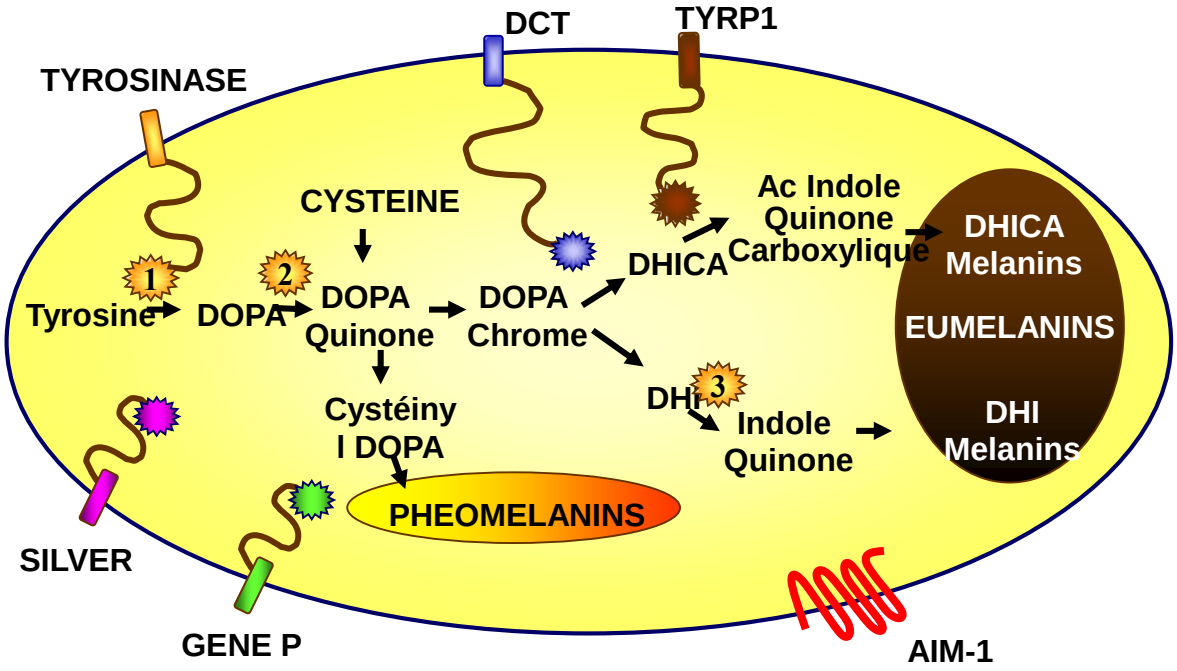
1. Number of melanocytes
2. Quantity and quality of produced melanins
3. Dendricity
4. Transport and transfer of melanosomes

5. Localization of the pigments within the skin
6. Elimination rate and/or degradation of melanins
7. Melanosome pH

Melanosomes

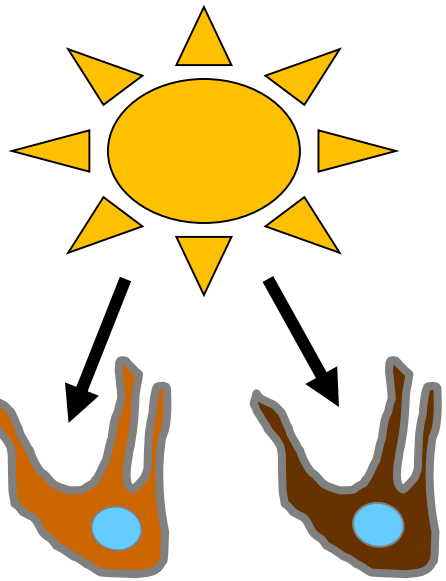




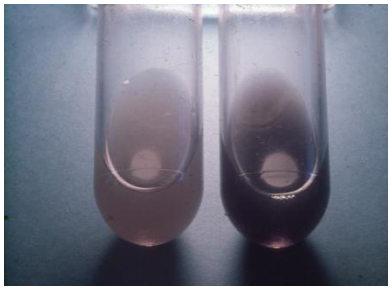


Tyrosinase, DCT, TYRP1

- Key enzymes of melanogenesis
- Main targets of depigmenting agents



PHEOMELANINS



EUMELANINS

Production of free radicals

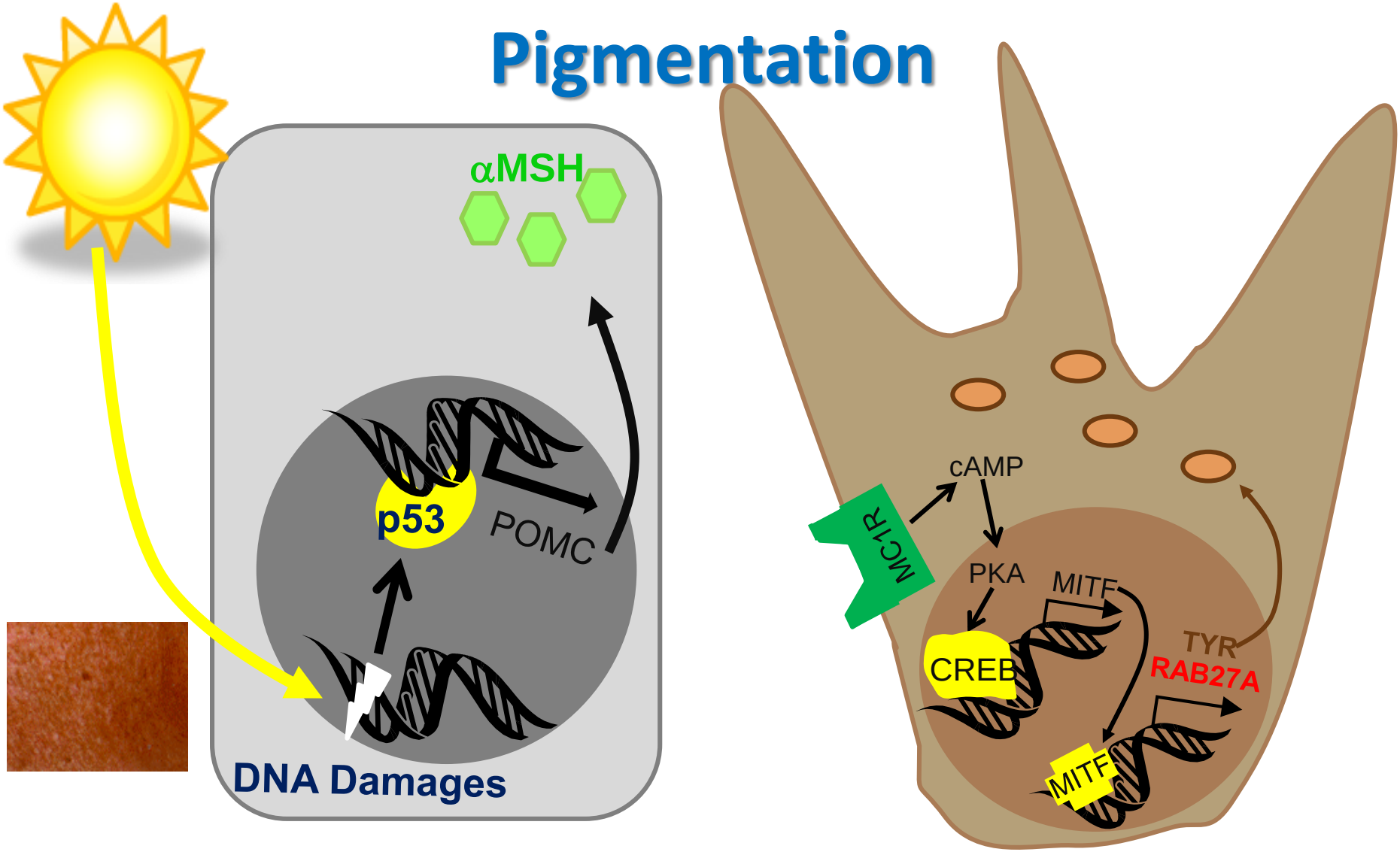
Decrease of free radicals

DNA damages

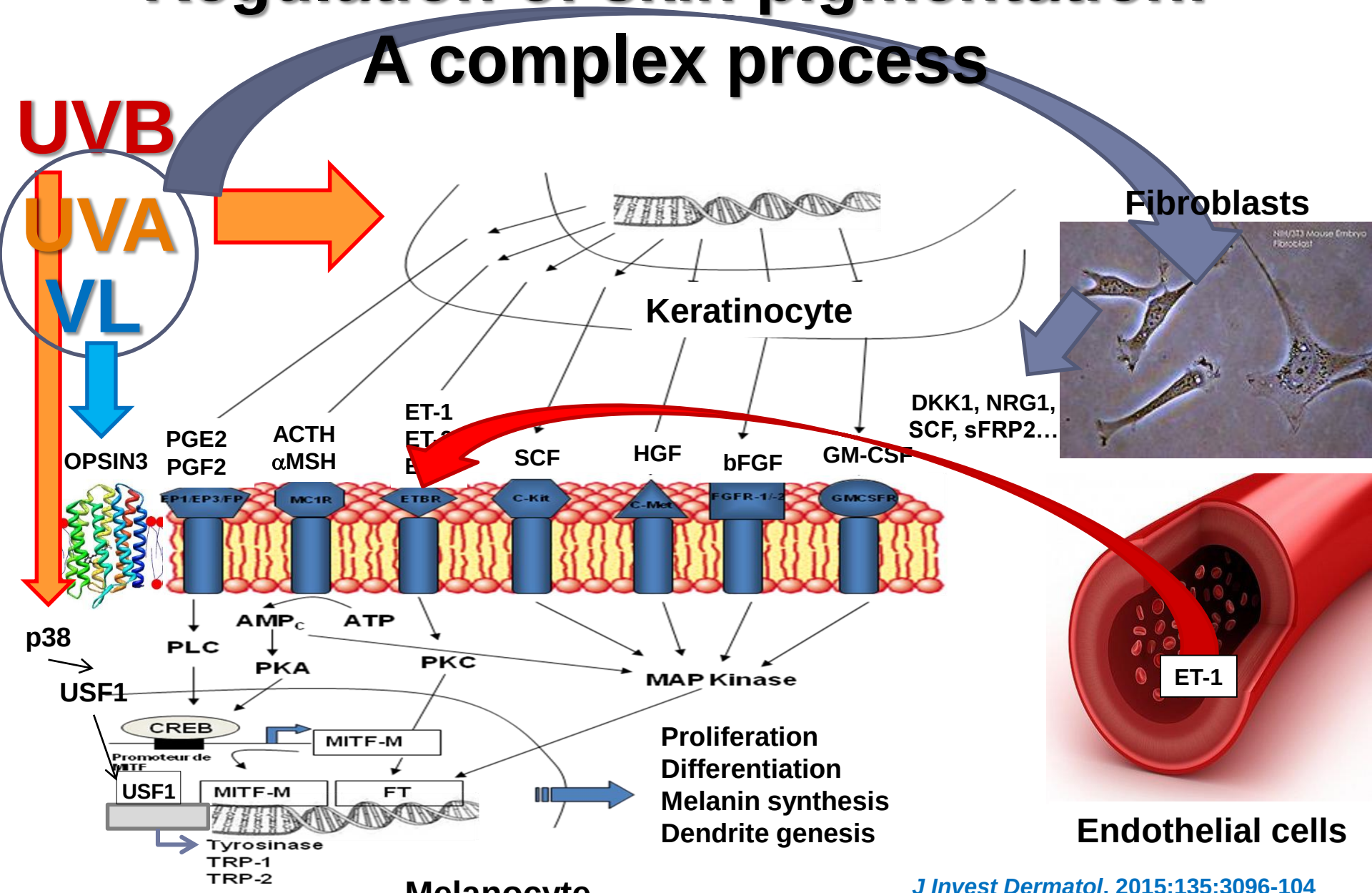
Photodamages

Photoprotection

Overview of the Molecular Mechanisms Involved in UVB-induced Skin Pigmentation



Regulation of skin pigmentation: A complex process

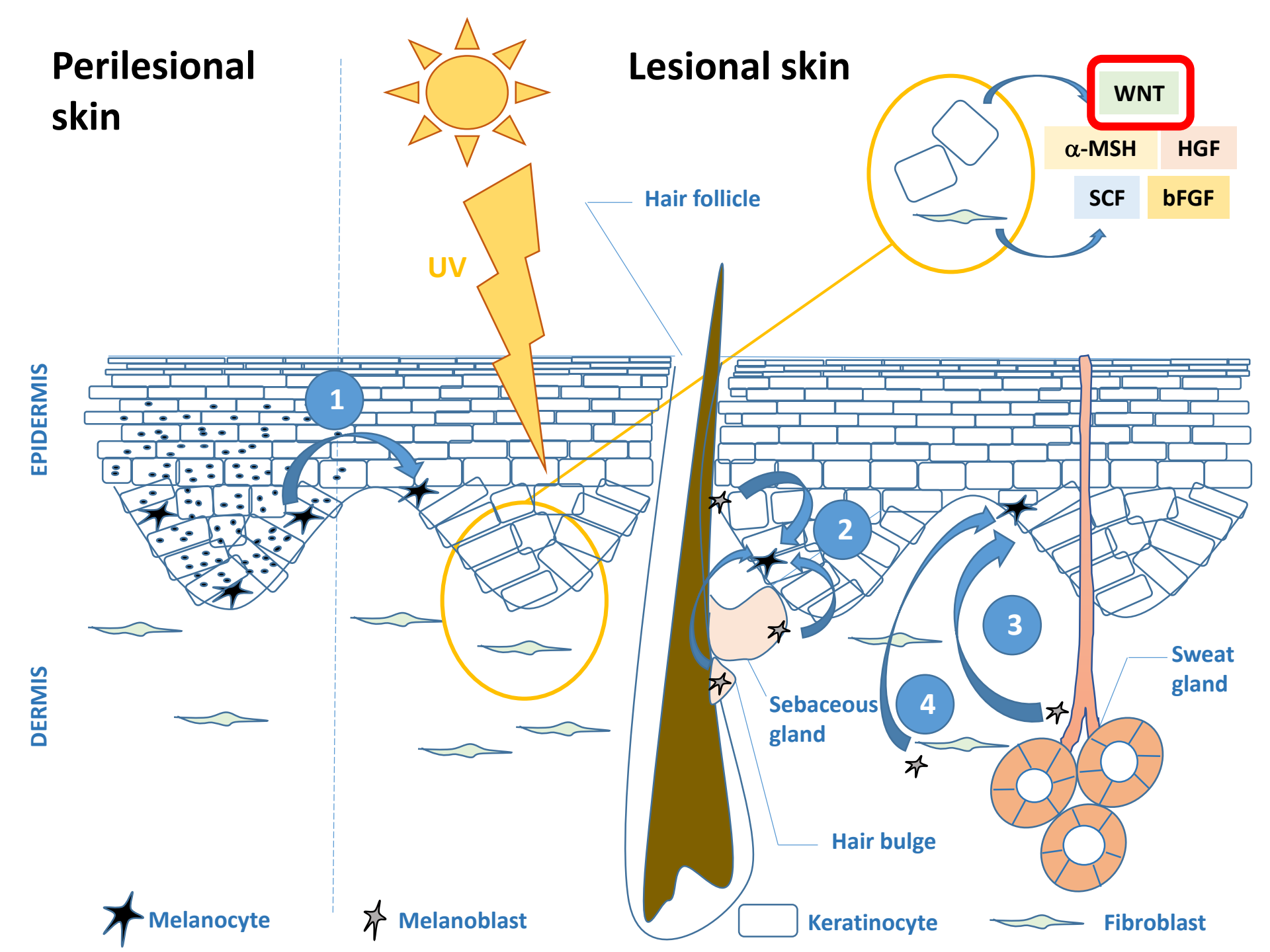


J Invest Dermatol. 2015;135:3096-104
J Invest Dermatol. 2018;138:171-178

Differentiation of the melanocytes stem cells

A key factor to induce the repigmentation of lesional skin

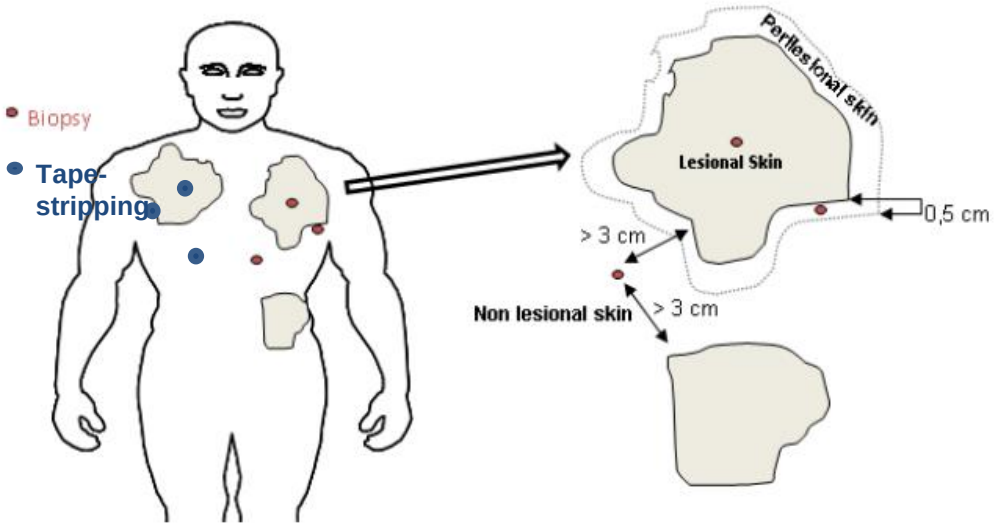
- Melanocyte stem cells in the bulge of hair follicles
  - The most well know source for repigmenting vitiligo lesion
  - Actual treatments mostly stimulate this source
  - BUT it is not the only one

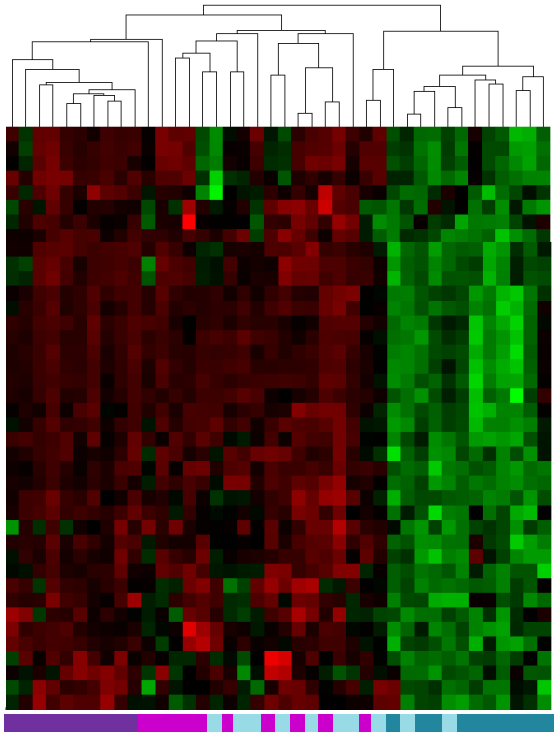

Perilesional skin
Lesional skin
WNT
α-MSH
HGF
SCF
bFGF
Hair follicle
UV
EPIDERMIS
DERMIS
1
2
3
4
Sebaceous gland
Sweat gland
Hair bulge
Melanocyte
Melanoblast
Keratinocyte
Fibroblast

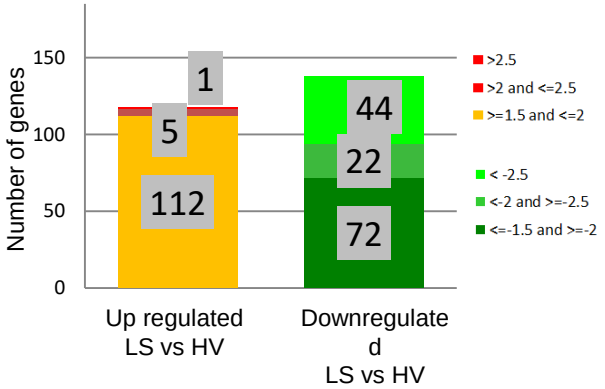
Transcriptome analysis

10 patients with active vitiligo
10 matched controls

- Transcriptome
- Cytokine and chemokine protein expression profiling

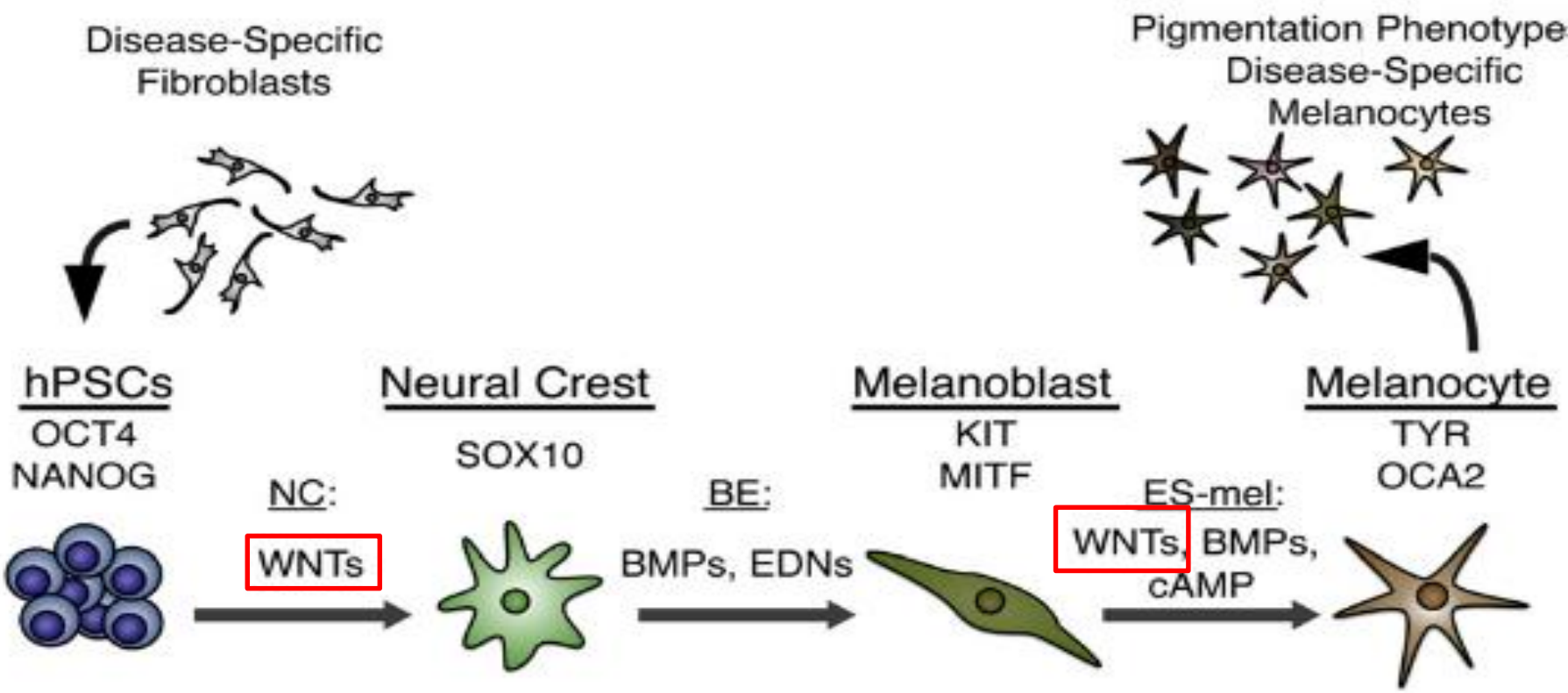






Ingenuity Canonical Pathways	P value	Count	Genes
Melanocyte Development and Pigmentation Signaling	4,5E-07	9	*TYRP1*, *ADCY2*, *MITF*, *TYR*, *SOX10*, *PAX3*,*KIT*, *DCT*, *MC1R*
Circadian Rhythm Signaling	1,7E-06	6	*PER3, PER1*, **ARNTL**, *NR1D1, BHLHE41*, **CLOCK**
Wnt/β-catenin Signaling	3,2E-03	7	**TP53**, *CDH2*, *CDH3, SOX10*, **DVL1, TLE4**, *LEF1*

WNT pathway is involved in melanocyte differentiation



Development of an *ex vivo* model

Difficulties for studying vitiligo:

- Absence of melanocytes
- Many cellular interactions (keratinocytes, fibroblasts, stem cells)
- Animal models very interesting but mostly useful for studying the melanocyte loss

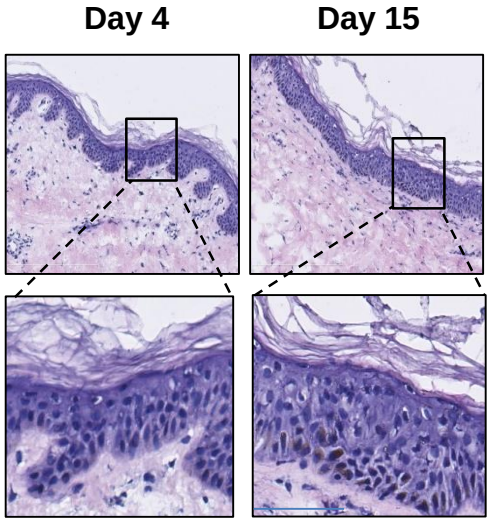
***Ex vivo* skin model:** dermis + epidermis functional long enough for studying the differentiation of melanocyte stem cells

Skin from abdominoplasties

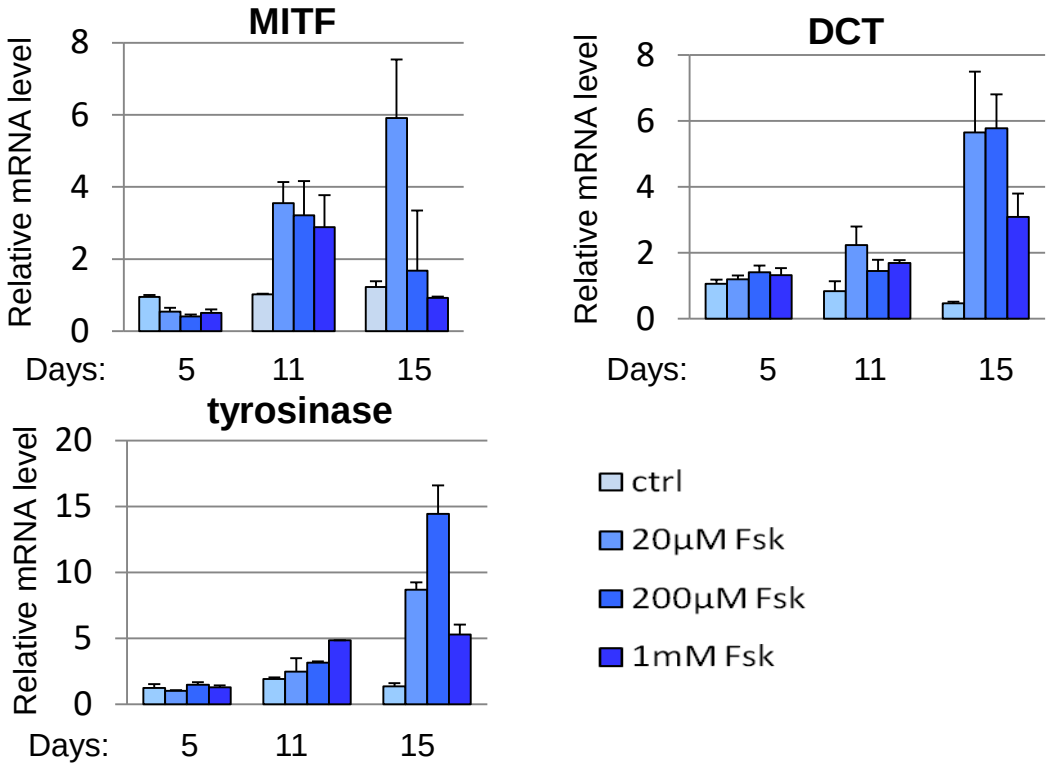
- 6 mm punch biopsies
- Culture in semi liquid condition

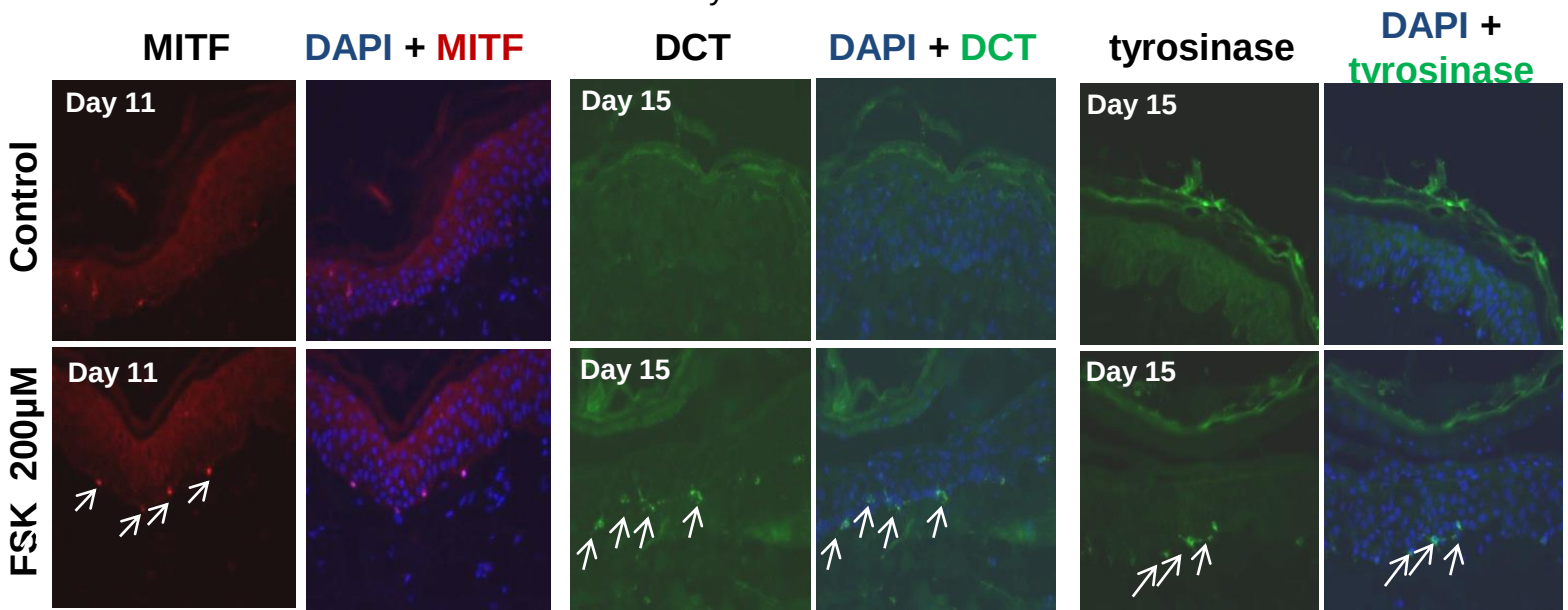
Objective: 15 days

Morphology

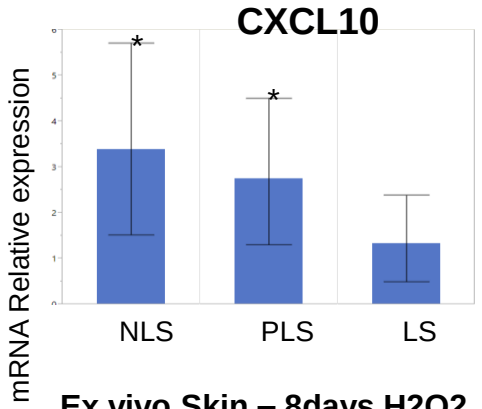


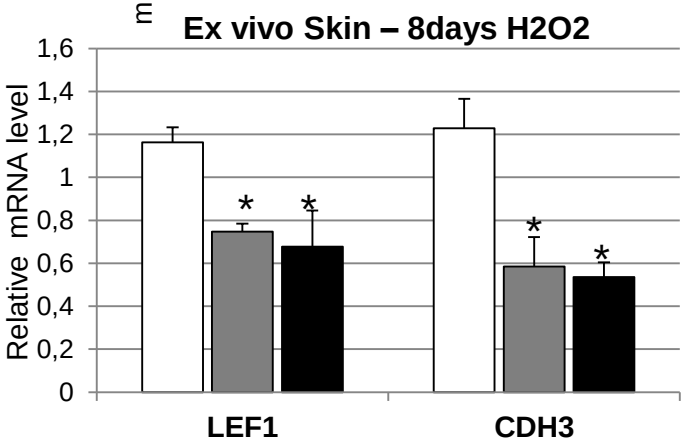
Functional (forskolin)

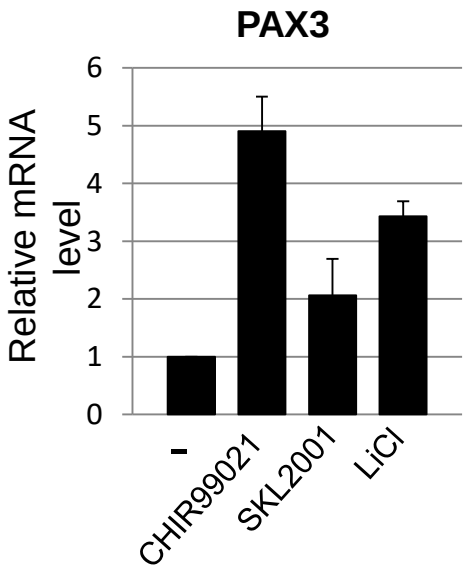


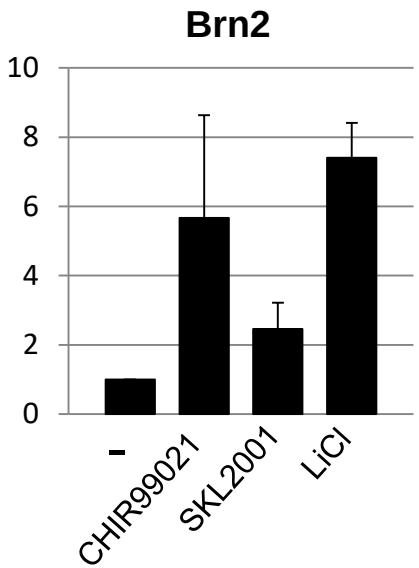


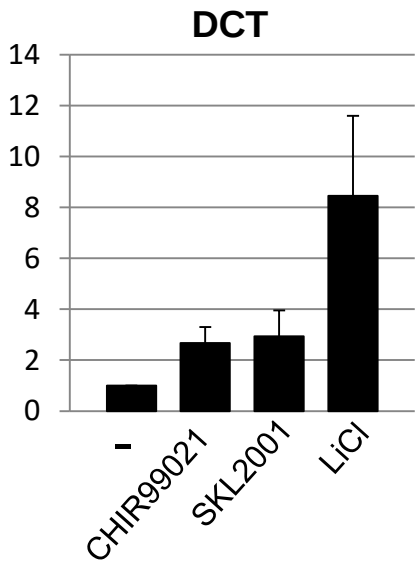
- Confirmation of the increase of CXCL10 (but no increase in depigmented lesions)
- Oxidative stress decrease the activation of WNT pathway
- Treatment with WNT agonist (or inhibitors of GSK3b) induce the differentiation of melanocyte stem cells into pre-melanocytes

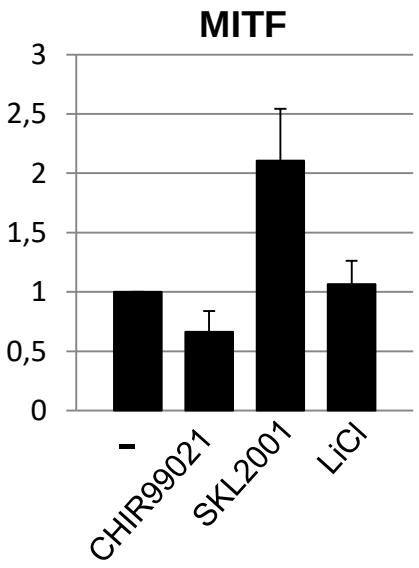




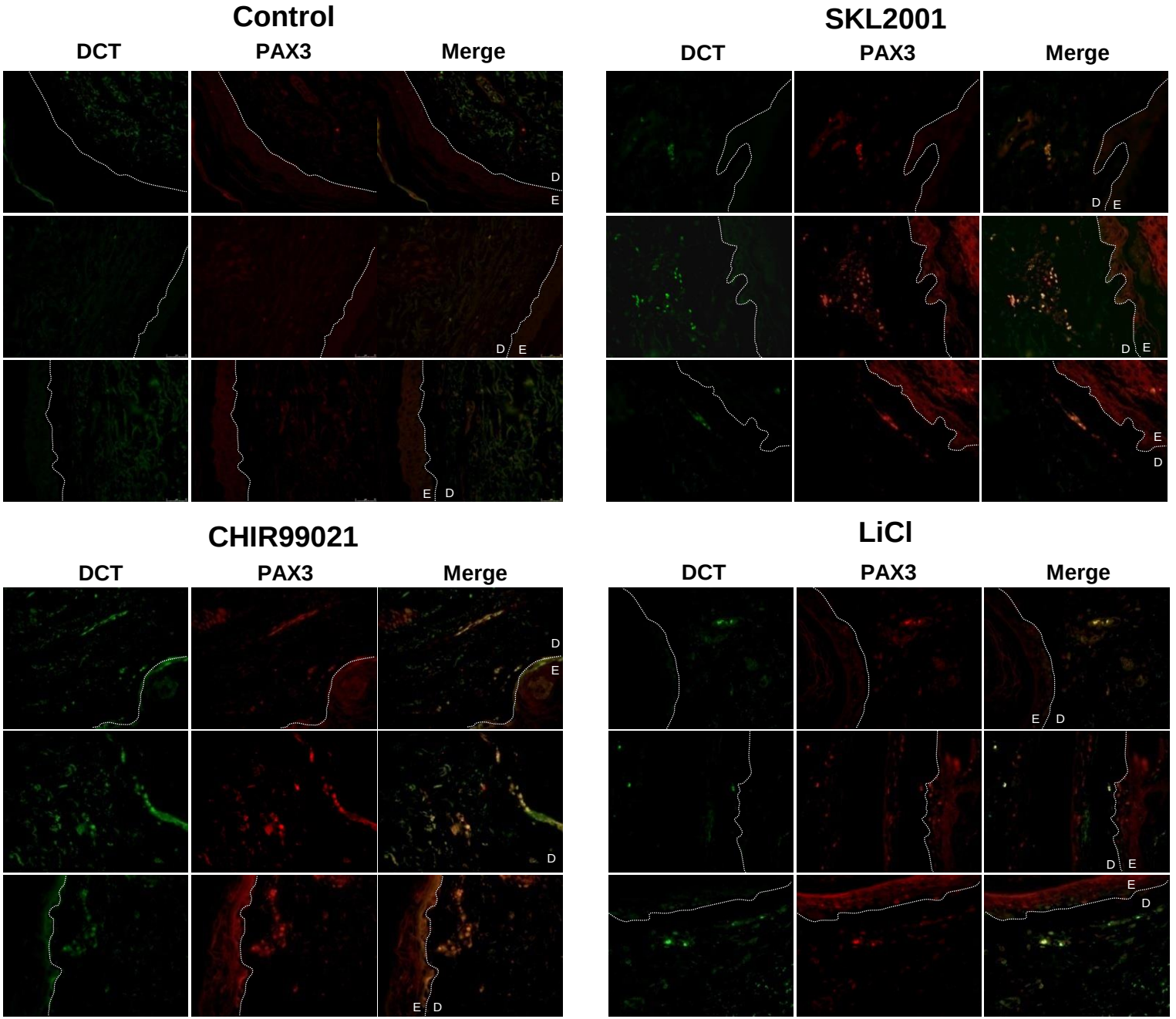








Differentiation of dermal stem cells into pre-melanocytes



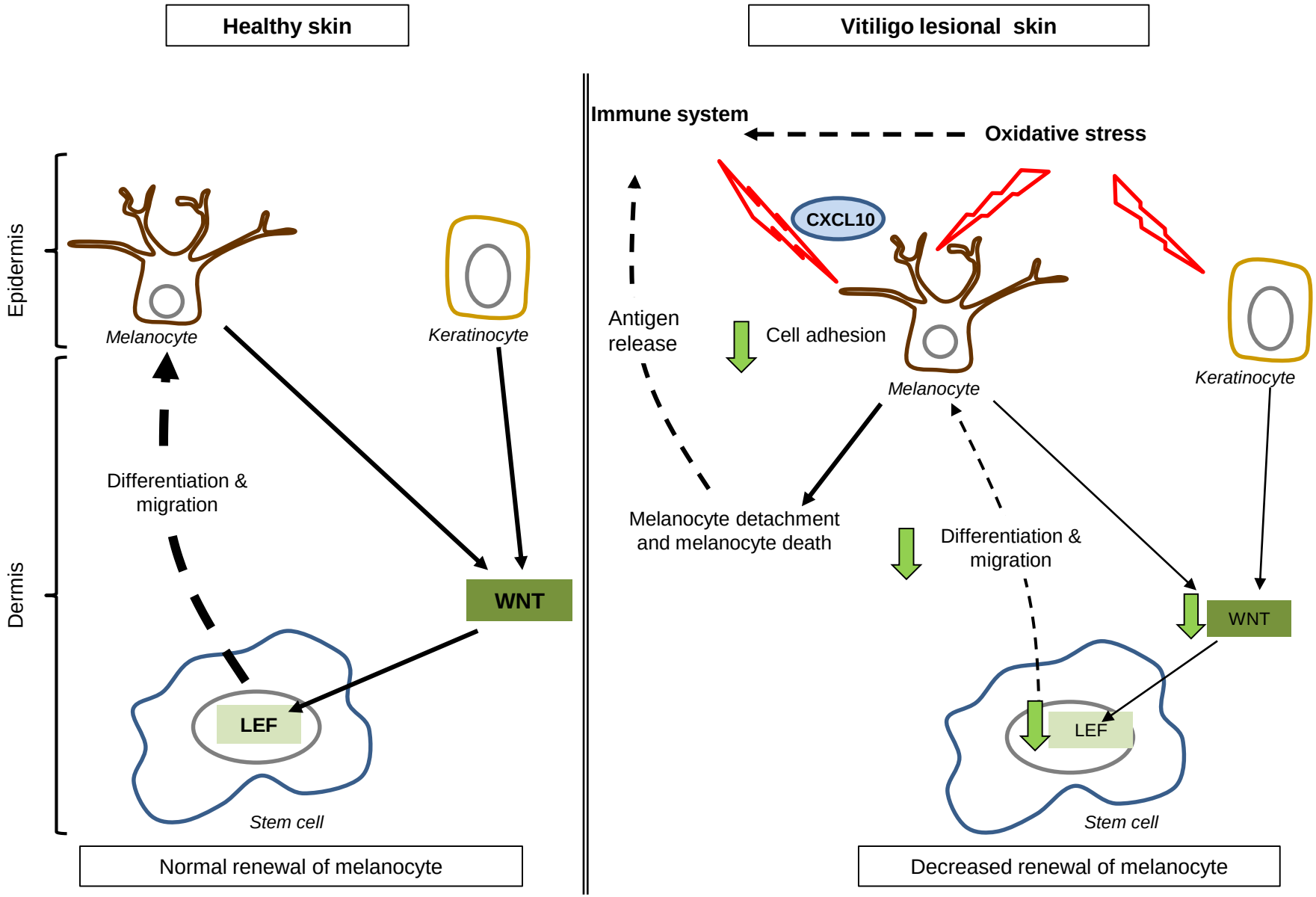
Conclusions

- First evidence of defect in WNT pathway in vitiligo skin
- The decrease of WNT activity is trigger by oxidative stress that reduce the ability of the skin to differentiate stem cells into melanocytes

➢ **Interest of WNT activators for repigmenting vitiligo lesions**

➢ **First clinical trial with topical GSK3b antagonist will start in 2018**

J Invest Dermatol. 2015;135:3105-14



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Thank you for your attention!