

**HIGHLIGHTS**



**SINGAPORE**

3-8 / july / 2023

Con el patrocinio de:



Iniciativa científica de:





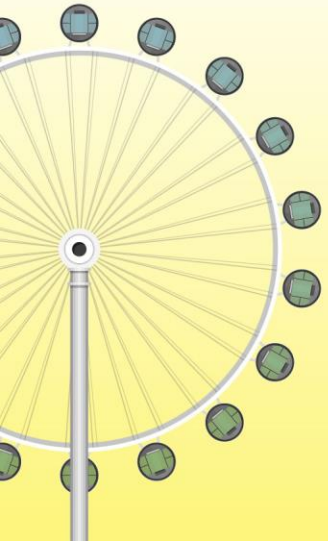
# DERMATOLOGÍA ESTÉTICA Y LÁSER

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**@almuderma**

**almudena@imda.es**





## SKIN AGING

Con el patrocinio de:



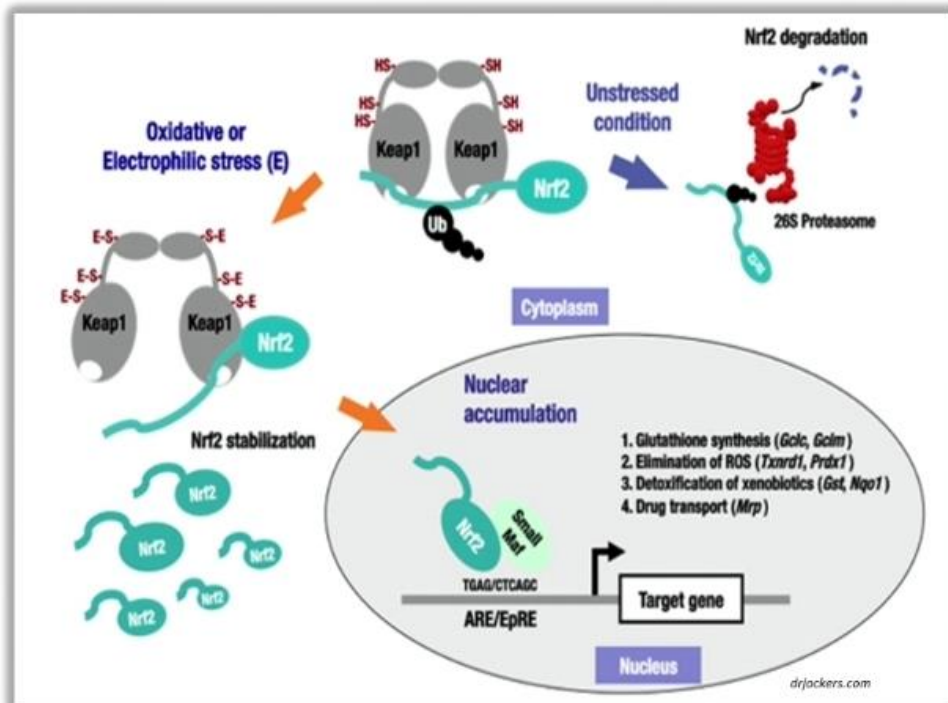
Almudena Nuño González

Iniciativa científica de:





## NRF2 Signaling: Cellular Stress Pathway



## Nuclear factor erythroid 2-related factor 2 (Nrf2)

- A transcription factor
- Initially found to be important in erythropoiesis & platelet development
- DNA binding domain sequence is *antioxidant response element* (ARE)
- Orchestrates transcriptional programs that facilitate adaptation & survival in the setting of oxidative stress
- Constitutively expressed in all skin cell types

# Sulforaphane

HIGHLIGHTS

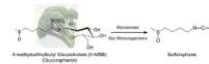


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## Sulforaphane

- Dr. Paul Talalay = “father of sulforaphane” & former Chairman of Pharmacology Dept. at Johns Hopkins
- Sulforaphane (SF) is a broccoli sprout extract, and is a potent inducer of NRF2
- When topically applied, SF prevents UVR induced erythema in human skin
- SF prevents UVB-induced inflammation in mouse skin



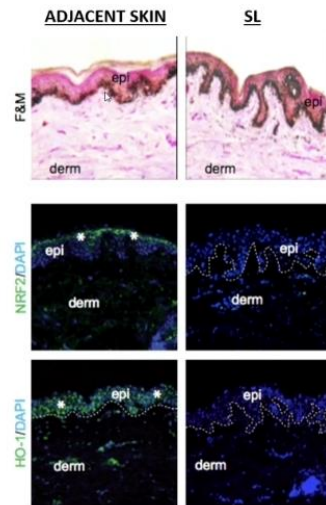
References:  
Talalay et al., *PNAS* 2005  
Saw et al., *Mol Carcinog* 2011  
Arowojolu et al., *Exp Derm* 2017

## Topical SF impacts UV-induced hyperpigmentation in an NRF2 dependent manner.

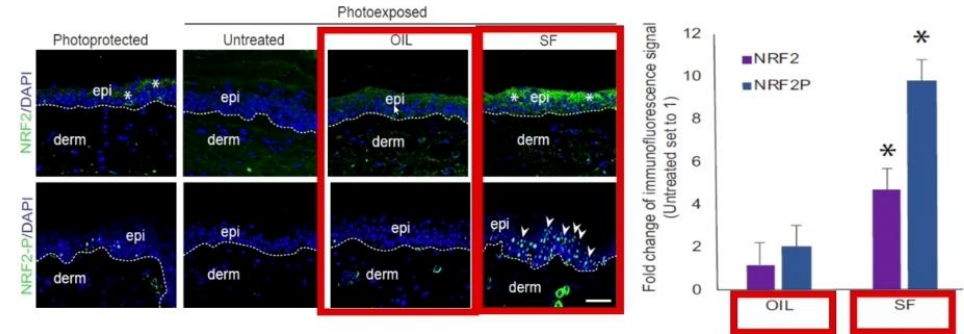


*JCI Insight* 2020; Oct 15; 5(20): e139342

**NRF2 AND ITS TARGET  
 HO-1 ARE ATTENUATED IN  
 SOLAR LENTIGO (SL),  
 COMPARED TO ADJACENT  
 PHOTOEXPOSED SKIN**

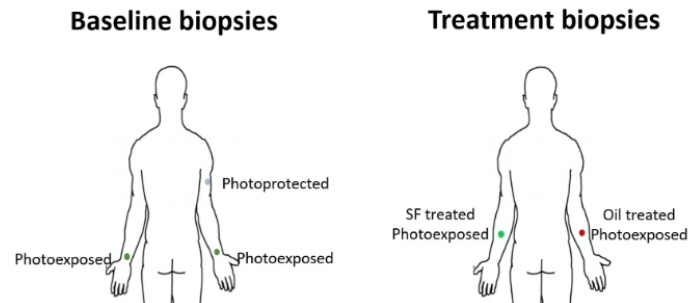


**Topical SF activates NRF2 in 6 subjects.**



*JCI Insight 2020; Oct 15; 5(20): e139342*

## A PILOT STUDY WITH TOPICAL SULFORAPHANE: RANDOMIZED, BLINDED, SPLIT-BODY DESIGN



Applied SF or Jojoba oil (vehicle) to 4 cm<sup>2</sup> of clinically similar areas of photodamaged skin on either forearm for 7 nights

## Pilot Study: Subject Demographics

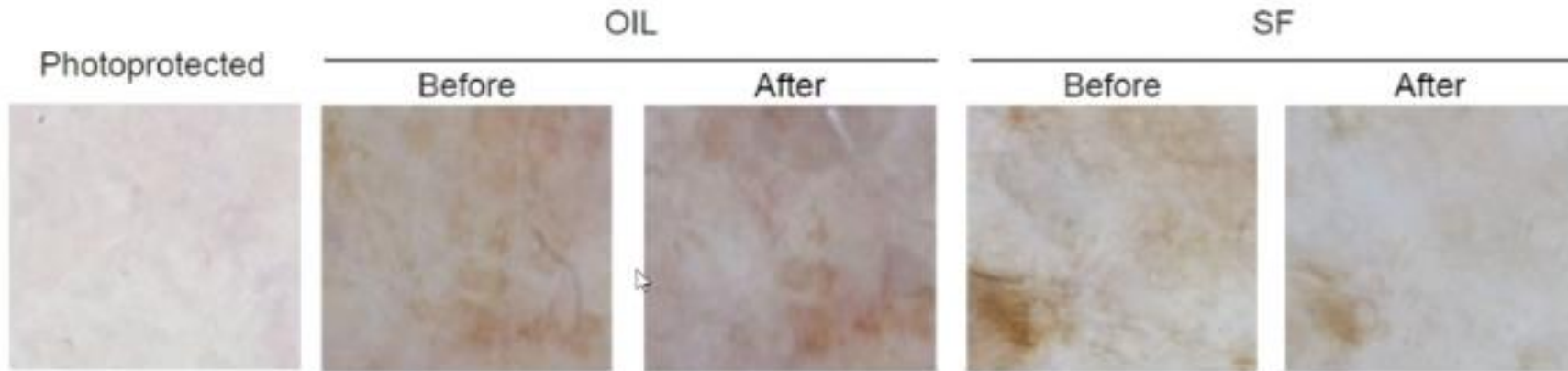
- Single center: Johns Hopkins
- N = 8
- 52-77 years old (mean = 60)
- 6 females & 2 males



# Topical SF improves hyperpigmentation in subjects who activate NRF2

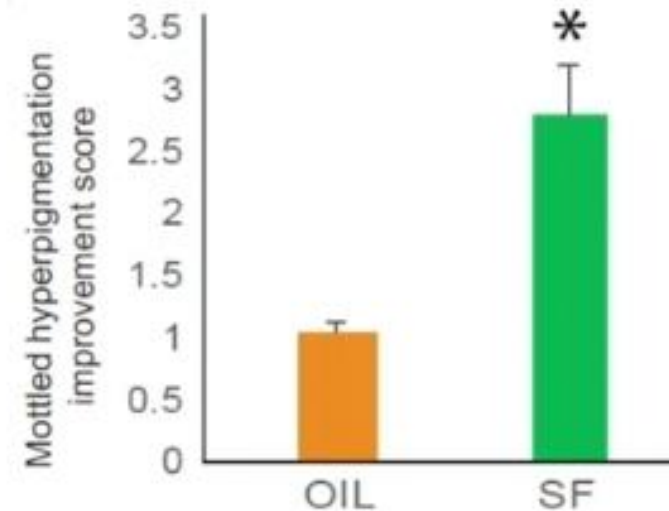
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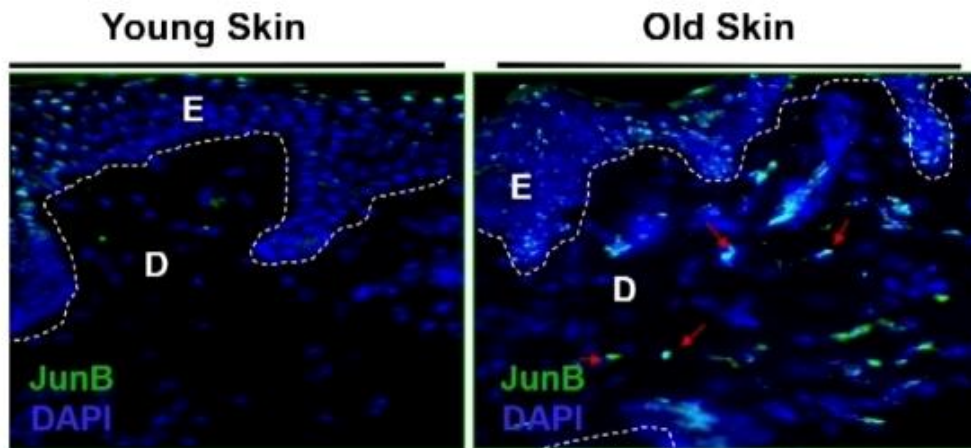
Score	%	Improvement
0	< 25	Minimal
1	26-50	Fair
2	51-75	Good
3	76-90	Excellent
4	91-100	Clear

Lee et al., 2006





## JunB Expression is Enhanced in Skin of Old Adults



Maity P, Singh K et al., Cell Reports 2021

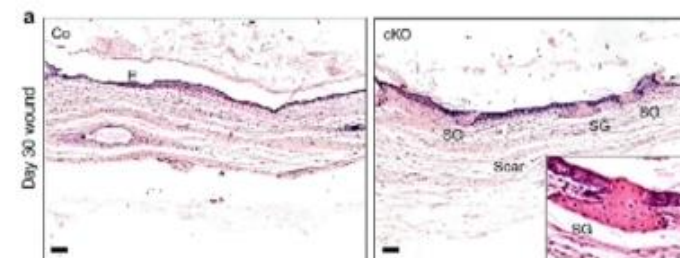


### ARTICLE

DOI: 10.1038/s41467-021-02161-0 OPEN

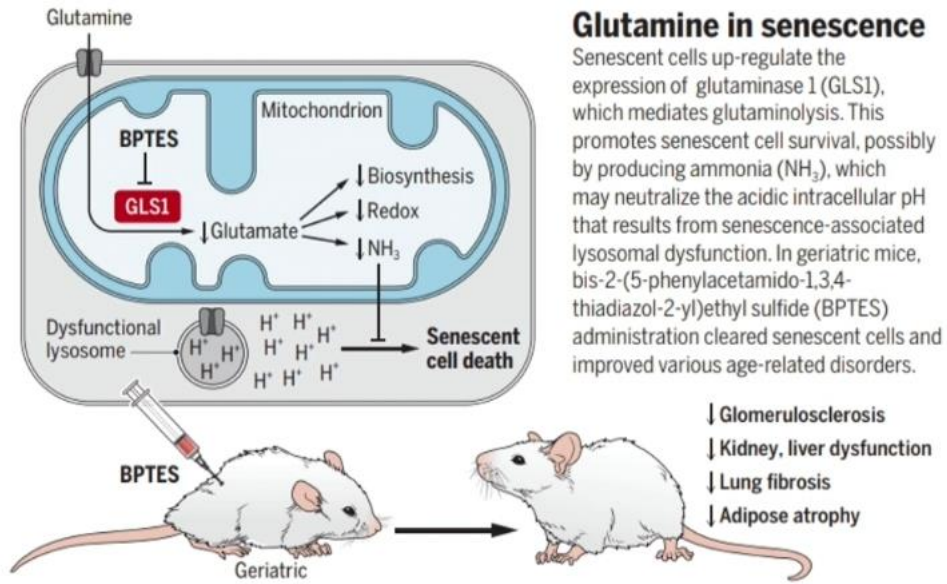
### JunB defines functional and structural integrity of the epidermo-pilosebaceous unit in the skin

Karmveer Singh<sup>1,2</sup>, Emanuela Camera<sup>1,2</sup>, Linda Krug<sup>1,2</sup>, Abhijit Basu<sup>1</sup>, Rajeev Kumar Pandey<sup>1</sup>, Saira Munir<sup>1</sup>, Meinhard Wlaschek<sup>1,2</sup>, Stefan Kochanek<sup>1</sup>, Marina Schorpp-Kistner<sup>1</sup>, Mauro Picardo<sup>1</sup>, Peter Angele<sup>1</sup>, Catharin Nisamann<sup>1,2</sup>, Pallab Maity<sup>1,2</sup> & Karin Scharfetter-Kochanek<sup>1,2</sup>



Development of a specific JunB inhibitor for senescent fibroblasts

# Glutaminase-Inhibitors Rejuvenate



Johmura et al. Senolysis by glutaminolysis inhibition ameliorates various age-associated disorders. *Science* 371(6526), 235- 243, 2021



## Substances with Senotherapeutic Effects



- Navitoclax
- Dasatinib
- Quercetin
- Others...

Zhu Y et al., Identification of novel senolytic agents, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. *Aging Cell* 15: 428-435, 2016  
 Raffaele M, Vinciguerra M. *Lancet Healthy Longv* 3: e67-77, 2022

## Genetic Depletion of Senescent Cells Results in Rejuvenation

**Old Mouse**



**Rejuvenated Mouse**

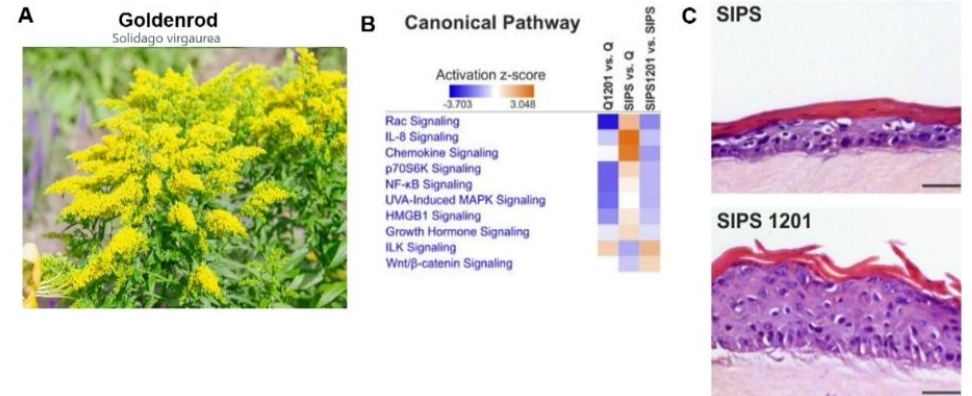


Baker DJ, Wijshake T, Tchkonja T, LeBrasseur NK, Childs BG, van de Sluis B, Kirkland JL, van Deursen JM. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* 479:232-236, 2011

Childs BG, Baker DJ, Wijshake T, Conover CH, Campisi J, van Deursen JM. Senescent intimal foam cells are deleterious at all stages of atherosclerosis. *Science* 354: 472-477, 2016

Farr J, Weivoda MM, Monroe DG, Fraser DG, Onken JL, Negley BA... Kirkland JL, Khosla S. Targeting senescence prevents age-related bone loss in mice. *Nature Medicine*. 2017; Doi10.1038/nm.4385

## Plant Extract (Goldenrod) Reduces the Senescence Associated Secretory Phenotype in Senescent Fibroblasts



Lämmermann I et al., *Aging Mech Dis* 11(4), 2018



# Papel del fibroblasto en el envejecimiento

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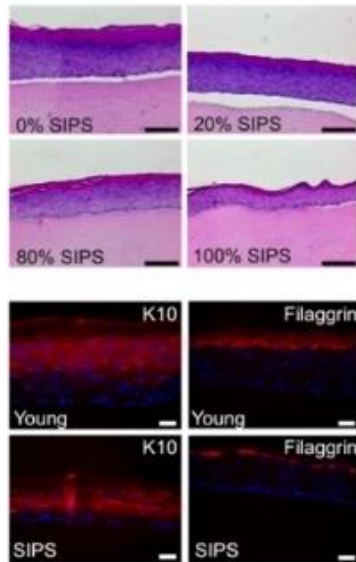
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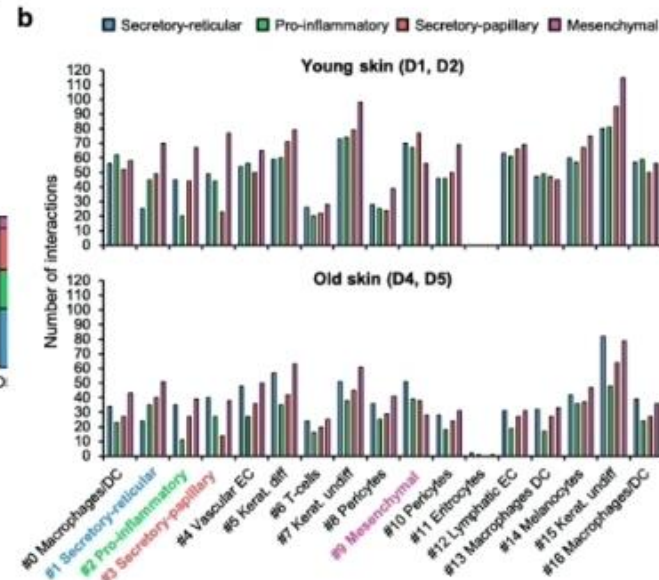
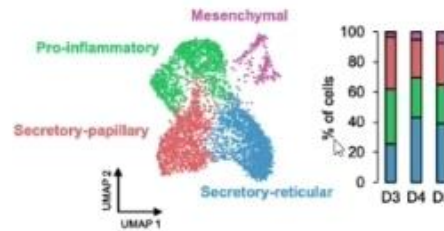


## Role of fibroblast senescence in skin aging

- Transplantation of human senescent fibroblasts into the skin of young immunodeficient mice resulted in the spreading of senescence.



Stress-induced premature senescent (SIPS) fibroblasts



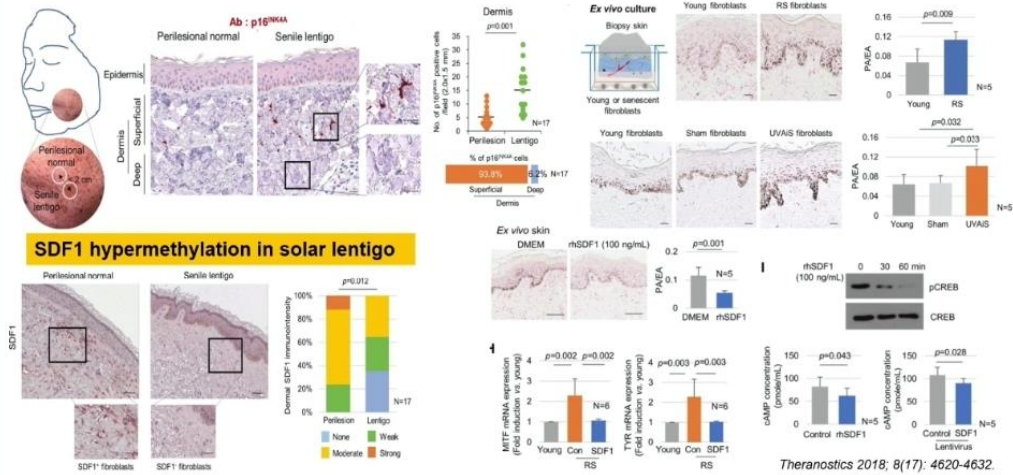
*J Invest Dermatol* 2021, 141, 985–992.  
*Aging Cell*.2019;18:e12848

*NPJ Aging Mech Dis* 2020;6:4  
*Commun Biol* 2020;3(1):188.





## Senescent fibroblasts in solar lentigo



## Cellular senescence in idiopathic guttate hypomelanosis



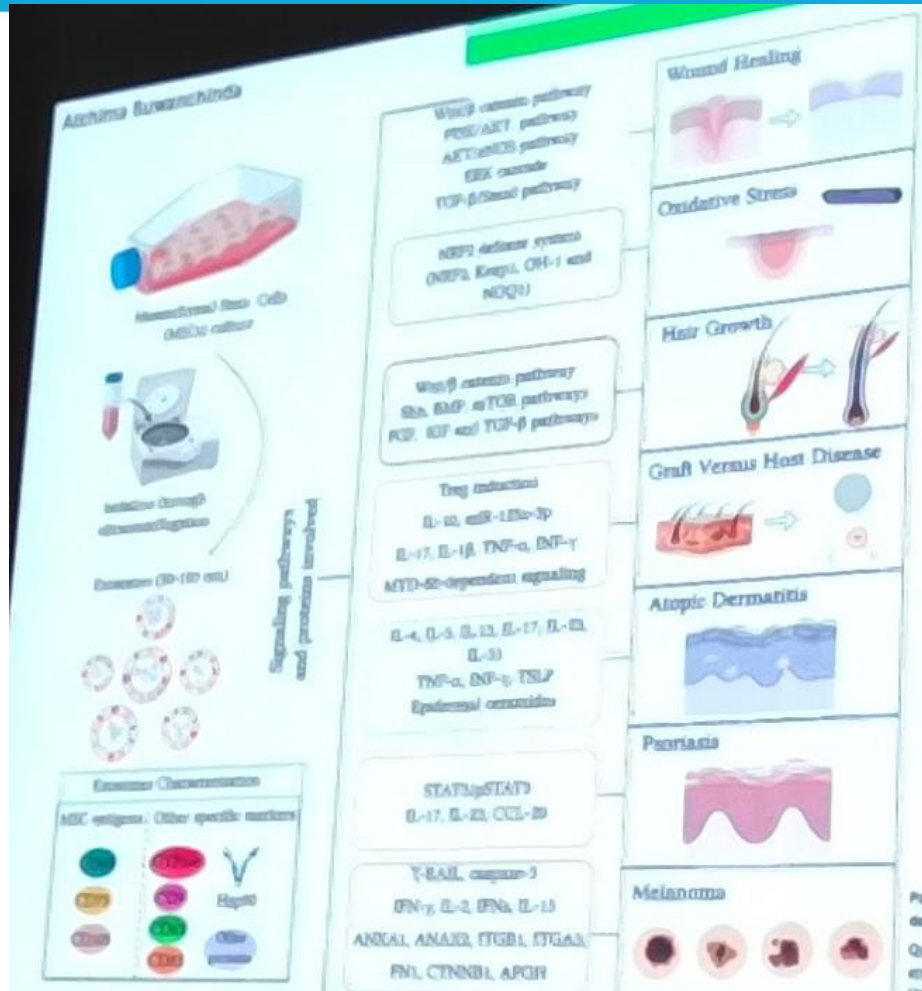


Derivan de las células madre

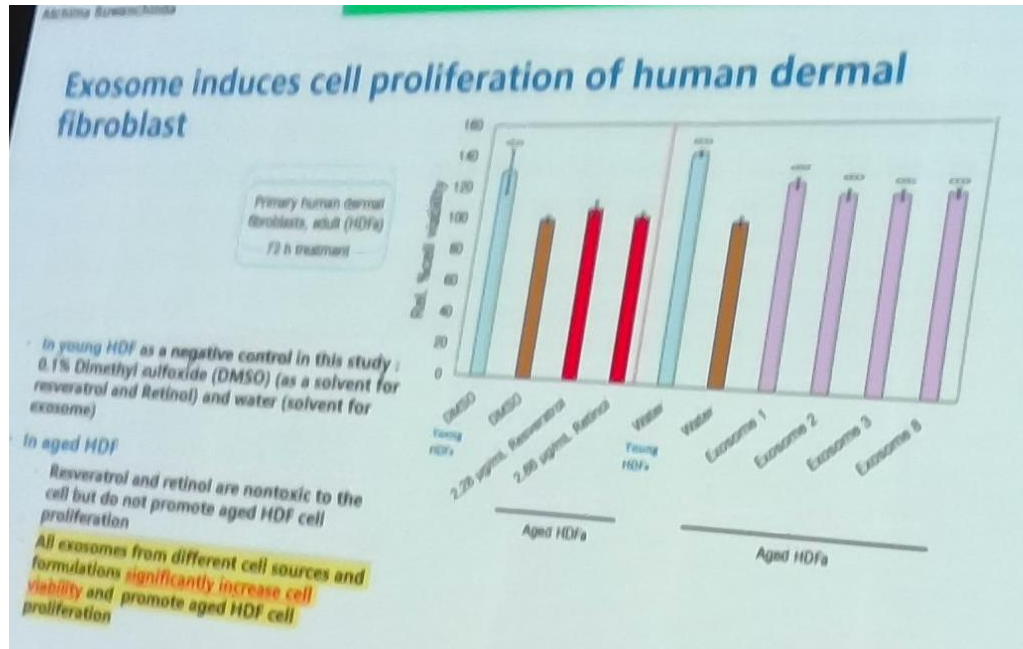
- Efecto paracrino

Funciones

# Exosomas



- Regeneración de úlceras y heridas
- Tratamiento estrés oxidativo
- Crecimiento del pelo
- Enfermedad injerto contra huésped
- Dermatitis atópica
- Psoriasis
- Melanoma



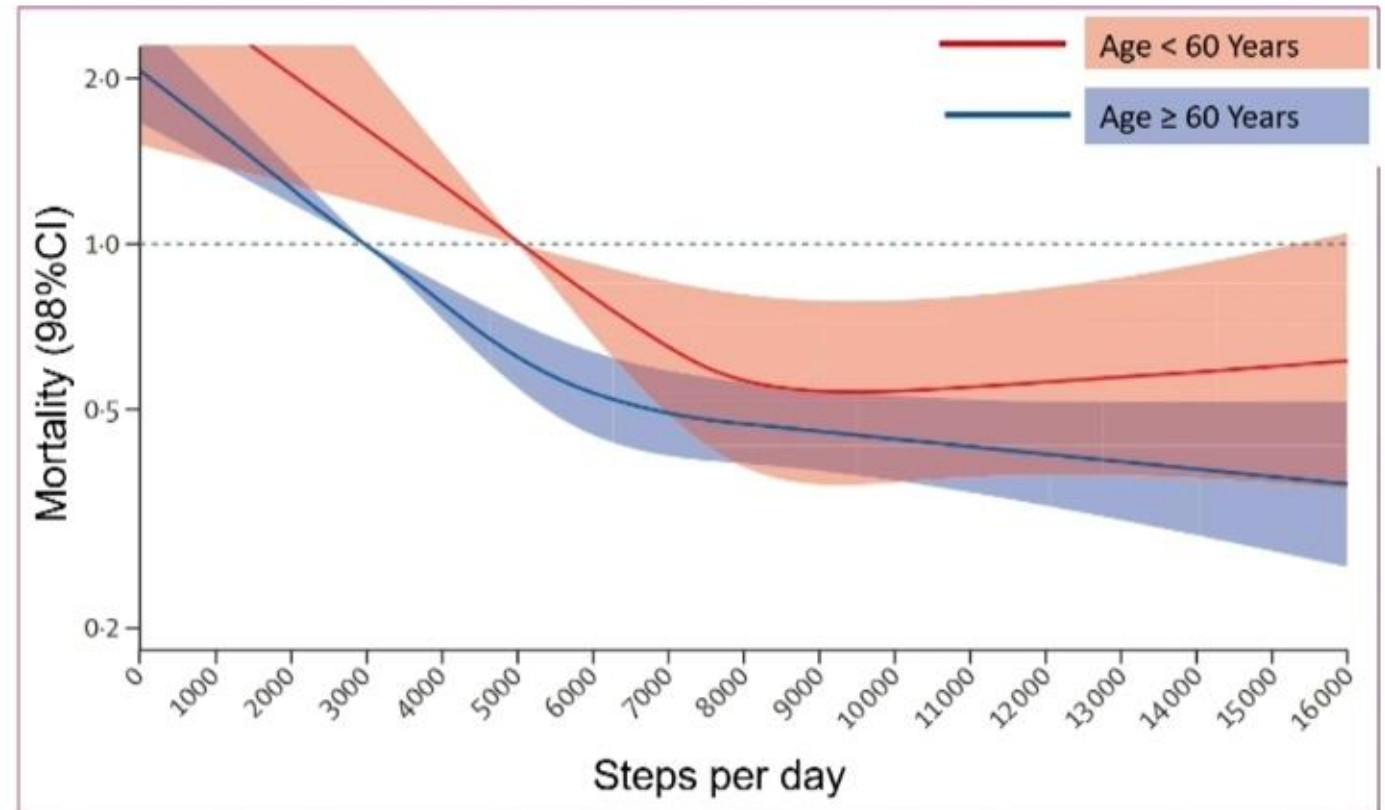
- Exosomas:
  - Inducen la proliferación celular de fibroblastos humanos
  - Inhiben la inflamación
  - Inhiben la generación de pigmento
  - Inhiben la senescencia
- RESULTADOS PROMETEDORES PERO HACEN FALTA MÁS ESTUDIOS Y ENSAYOS CLÍNICOS



# 6000 pasos al día disminuyen mortalidad



## Reduced Mortality with only 6000 Steps per Day



Palluch AE et al. Lancet Public Health 7:e219-228, 2022

# El ejercicio disminuye el número de células envejecidas

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## Exercise Reduce the Numbers of Senescent Cells

After exercise	Mononuclear cells	p16 reduced	Werner et al., 2009
After exercise	Endothelial cells	p16 reduced	Rossmann et al., 2017
After exercise	Endothelial progenitor cells	p16 reduced	Yang et al., 2018
After exercise	T-lymphocytes	p16 reduced	Liu et al., 2009
After exercise	T-lymphocytes	p16, p21 and SASP reduced	Englund et al., 2021

Chen XK et al.: Is exercise a senolytic medicine? A systematic review. Aging Cell 20e13294, 2021

## Future Directions and Perspectives



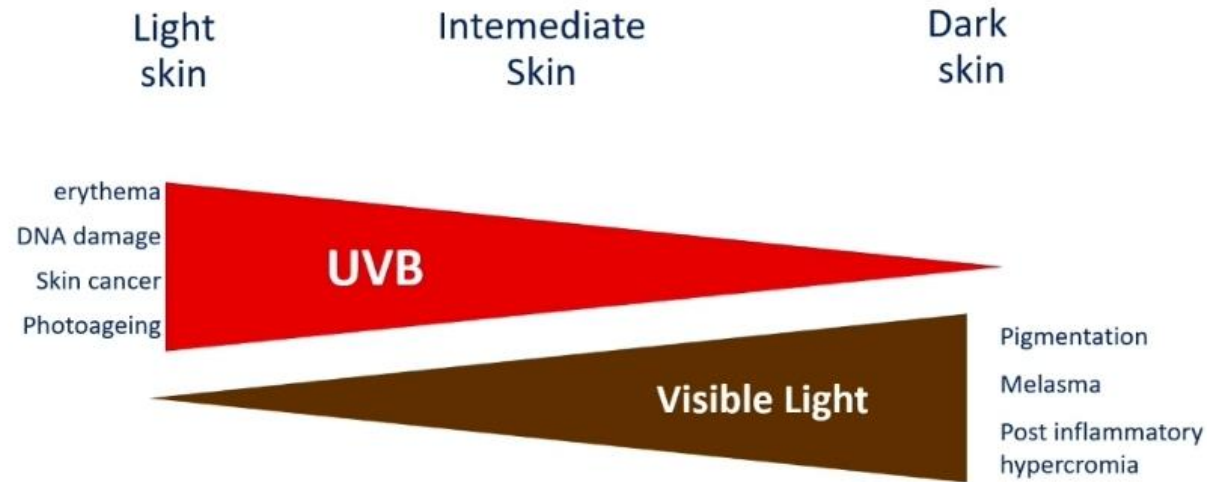
- The safety profile and efficacy of senotherapeutics and MSC based therapies in patients are yet to be fully investigated in clinical trials
- Cell specific delivery of senotherapeutics is essential to avoid side effects
- Clinically proven as anti-aging is exercise and in part caloric restriction
- The TAME\* Study with Metformin is still ongoing

\* Target of Aging with Metformin

- El ejercicio y la restricción calórica han demostrado disminuir el envejecimiento
- La seguridad de los senoterapéuticos aún deben investigarse adecuadamente en los ensayos clínicos
- Deben garantizar que actúan sólo en la célula diana para evitar efectos secundarios
- El estudio TAME (Target of Aging with Metformin) sigue en desarrollo.



## In Summary....



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of Dermatology  
SINGAPORE 2023

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www.wcd2023.org

## And in the Skin Of Colour?

- Mizuno (2016)
  - Daily use of sunscreen in Japanese volunteers reduce photoaging signs after 18 months
- Sarkar (2019)
  - 216 east Indians subjects with skin phototype IV and V and with pigmentation irregularities
  - 2 groups
    - SPF 50 / High UVA protection
    - SPF 19 / High UVA protection
  - 12 weeks
    - Significant ( $P < .001$ ) improvement in pigmented spots and skin radiance in both groups
    - No significant differences between the two groups

There is enough evidence that regular use of sunscreens is effective in preventing the development of wrinkles and uneven pigmentation in different ethnic groups.

Krutmann J, Schalka S, Watson REB, Wei L, Morita A. Daily photoprotection to prevent photoaging. Photodermatol Photoimmunol Photomed. 2021 Nov;37(6):482-489.

25<sup>th</sup> World Congress  
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# ¿Protección solar para todos los fototipos?



REVIEW ARTICLE

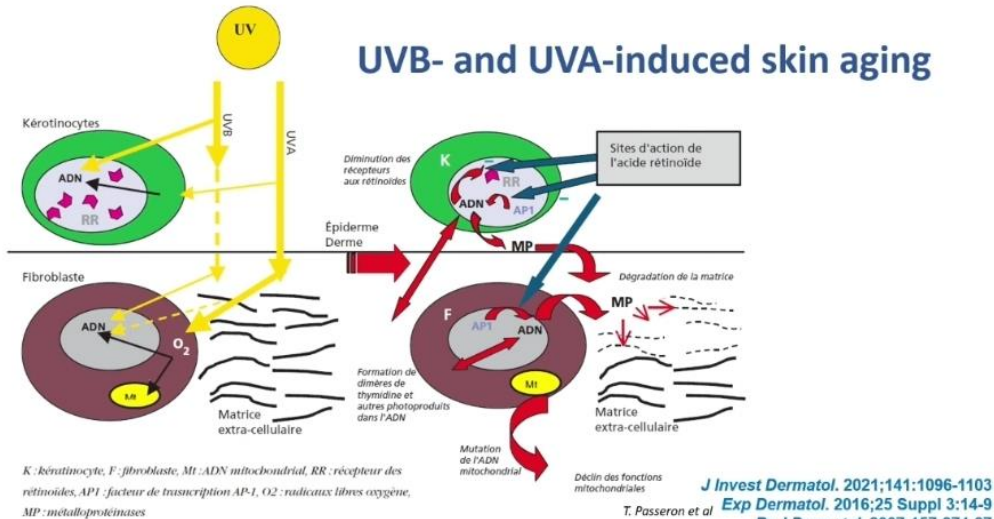
## Photoprotection according to skin phototype and dermatoses: practical recommendations from an expert panel

T. Passeron,<sup>1,2,\*</sup> H.W. Lim,<sup>3</sup> C.-L. Goh,<sup>4</sup> H.Y. Kang,<sup>5</sup> F. Ly,<sup>6</sup> A. Morita,<sup>7</sup> J. Ocampo Candiani,<sup>8</sup> S. Puig,<sup>9</sup> S. Schalka,<sup>10</sup> L. Wei,<sup>11</sup> B. Dréno,<sup>12†</sup> J. Krutmann<sup>13,14,†</sup>

Fitzpatrick phototype	Description	Individual Typology Angle (ITA)	Skin color (ITA classification)	UVB protection (SPF)	UVA protection (UVA-PF)	High energy visible light protection (VL-PF)
I	Always burns, never tans	ITA° >55°	Very light	SPF50+	UVA-PF +++ (>1/3 labelled SPF)	VL-PF+++
II	Burns easily, sometimes tans	41° <ITA° <55°	Light			
III	Sometimes burns, always tans	28° <ITA° <41°	Intermediate			
IV	Rarely burns, tans easily	10° <ITA° <28°	Tan			
V	Rarely burns tans easily; moderately pigmented	-30° <ITA° <10°	Brown			
VI	Rarely burns, tans promptly and intensely; highly pigmented	ITA° <-30°	Dark			

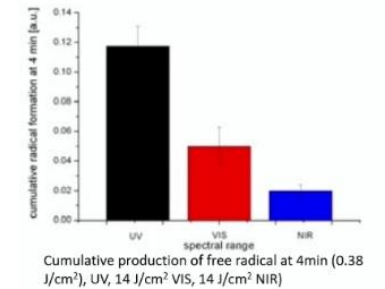
Passeron T, Lim HW, Goh CL, Kang HY, Ly F, Morita A, Ocampo Candiani J, Puig S, Schalka S, Wei L, Dréno B, Krutmann J. Photoprotection according to skin phototype and dermatoses: practical recommendations from an expert panel. *J Eur Acad Dermatol Venereol.* 2021 Jul;35(7):1460-1469.

# La luz visible también causa fotoenvejecimiento



## Visible light induces oxidative stress *in vivo*

- VL induces oxidative stress on fibroblasts *in vitro*  
*Photodermatol Photoimmunol Photomed.* 2020;36:135-144
- VL induces oxidative stress in human reconstructed skin models  
*J Invest Dermatol.* 2012;132:1901-7
- Free radical are measured *in vivo* using spectrophotometry  
*Exp Dermatol.* 2016;25:380-5
- UV (325-380nm) vs VL vs IR  
*Free Radic Biol Med.* 2017;108:300-10



# ¿Por qué nos hace más felices tomar el sol?

HIGHLIGHTS



## Looks more “attractive” and “in better health”

- In many Western countries a tanned skin is considered attractive and a sign of good health and wealth



*Adolesc Health* 2013;52:S52e9

## UV exposure is important for Vitamin D synthesis

- UVB convert 7-dehydrocholesterol (7DHC) into pre-vitamin D3,
- Pre-vitamin D3 is then thermally converted into cholecalciferol (vitamin D3)
- Pre-vitamin D3 increases linearly as a function of time of exposure to UV dose over a period of 30 min
- Importance of vitamin D in musculo-skeletal disease
- Role in immunity and cancers is still under debate
- BUT there are other sources of vitamin D than sun exposure

*N Engl J Med* 1977; 297: 974-83  
*Br J Dermatol.* 2019;181:916-931

## Sun exposure decreases blood pressure

- Sun exposure can rapidly decrease blood pressure
- UVA mediated
- Keratinocytes and microvascular endothelial cells release nitric oxide that induce vasodilation and further decrease the blood pressure

*J Invest Dermatol.* 2014;134:1839-1846  
*Eur J Appl Physiol.* 2018;118:1043-1052  
*J Am Heart Assoc.* 2020;9:e013837

## Sun exposure warms skin and joints



- The sun rays (mainly the short infrared radiations) warm the skin and can sometimes be appreciated by some individuals, mostly in cold season
- The impact of the warm provided by sun exposure on joint pain is debated
- A large survey on 16,000 individuals suffering from arthritis and fibromyalgia using an App monitoring weather condition and their joint pain:
  - High barometric pressure with warm and dry weather is associated with 20% decrease of joint pain

*Plos Digital Health* 2023;2:e0000204



# ¿Realmente nos hace más felices tomar el sol?

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## Sun exposure release endorphins

- Keratinocytes secrete beta-endorphins after UV exposure
- Systemic levels of beta-endorphins are NOT increase after sunk in human volunteers
- In mice:
  - UVR induce beta-endorphin production by keratinocytes that are detected in the plasma and increase their tolerance to pain
  - Knock-out of beta-endorphin gene in keratinocytes prevent this UVR-induced tolerance
- 5 consecutive days of UVB exposure increase the mood of healthy volunteers along with vitamin D and basal cortisol levels but not endorphin

*Photodermatol Photoimmunol Photobiol  
Br J Dermatol  
Cell  
Chronobiol Int*

## Some people are genetically predisposed to sun addiction!

- 265,000 Individuals of European Ancestry
- Allelic variations associated with sun addiction
  - TMEM182, CADM2, MIR2113, MTMR2/CEP57/FAM76B, and PLCL1/LINC01923/SATB2
  - All the five genetic loci have previously been identified in GWAS for behavioral traits and addiction
  - **Genetic predisposition for sun addiction**
  - **Must be taken into consideration for preventive campaign information against the deleterious effects of excessive sun exposure**



# MUCHAS GRACIAS

Con el patrocinio de:



Almudena Nuño González

@almuderma

Iniciativa científica de:



La Academia Española de Dermatología y Venereología expresa su agradecimiento al patrocinador UCB, por su especial apoyo y contribución con la actividad formativa Highlights 2023.



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