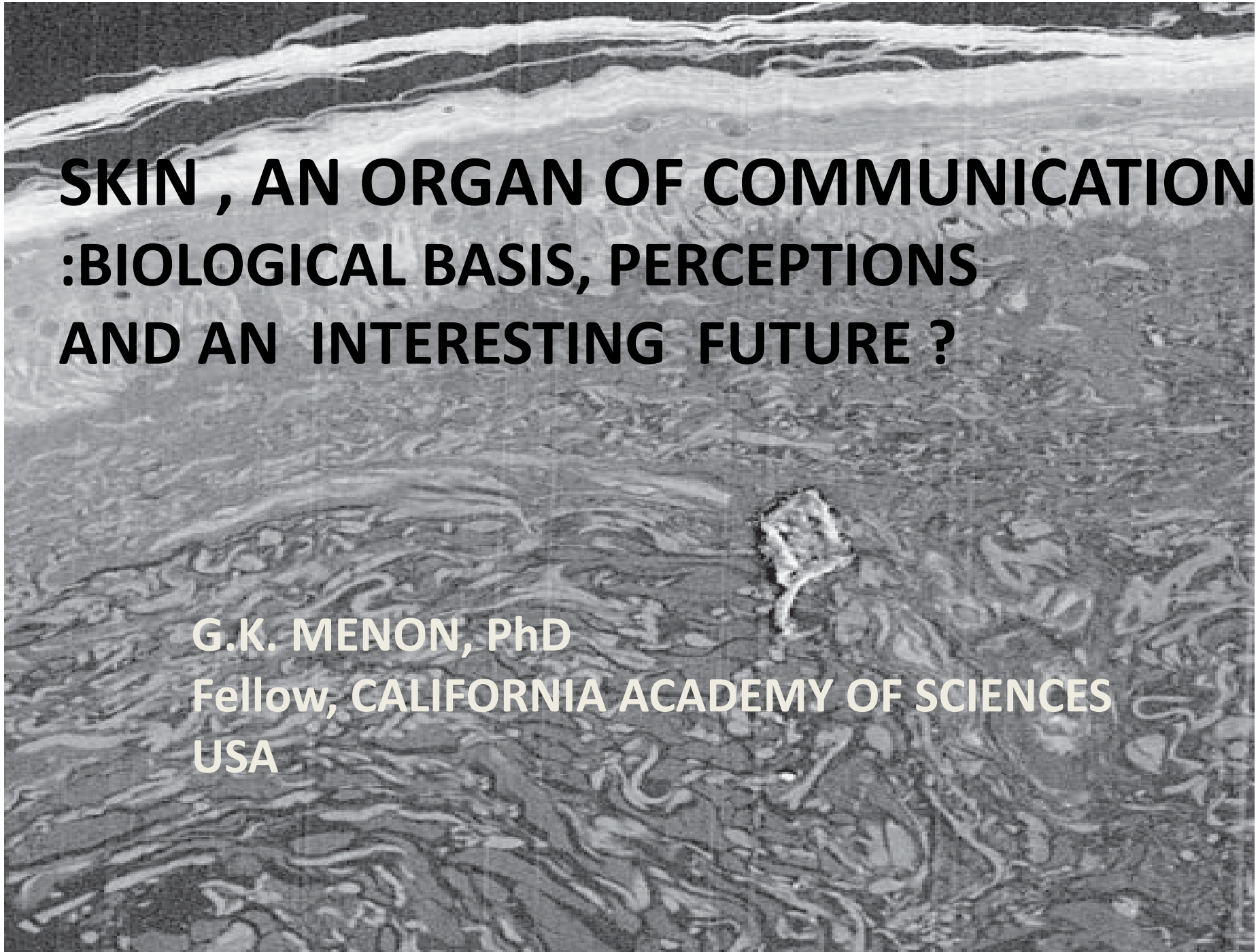

SKIN , AN ORGAN OF COMMUNICATION :BIOLOGICAL BASIS, PERCEPTIONS AND AN INTERESTING FUTURE ?

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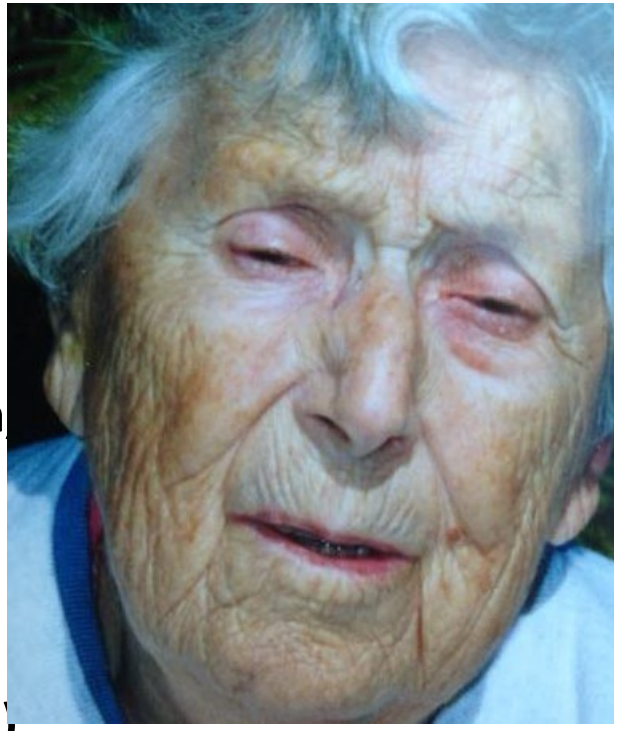
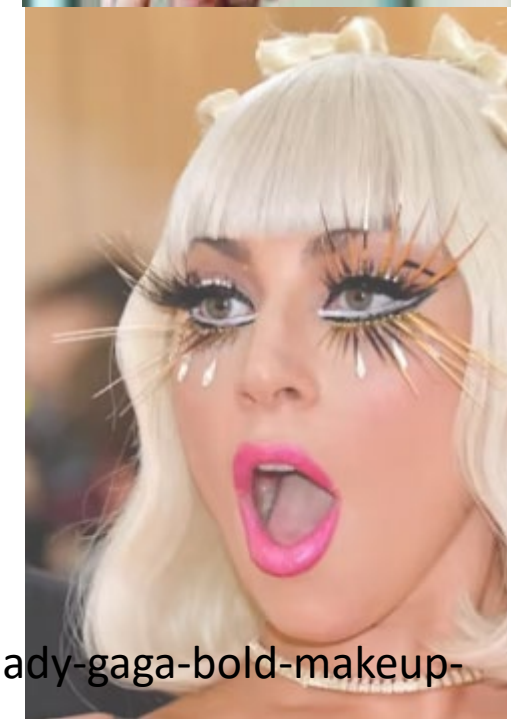
USA

Skin at two extremes of human life: invokes different emotions.

Life Happens in this space.
And A lot happens to skin:
Playing significant roles in
Communication,self esteem,
Sexual attraction.
Reproduction
And Xenophobia (which
Shaped the world we live in).



SKIN, Used as a Canvass : Conveys Tribal Fidelity, Threat, extreme Beauty…



https://www.hellomagazine.com/celebrities/20220707144790/lady-gaga-bold-makeup-transformation

EVERY living OBJECT HAS A SKIN…..

- Thick or thin, porous or impermeable, smooth or rough….
- **It** hides our interior (not always our feelings) but **allows us to experience the external world**…..
- It is the basis of individual identity.
- **It may not be the " largest organ" (Sontheimer, 2013) but is possibly the most important** *

* **My organ is more important than your organ**. Bernhard JD. *Comment in* Arch Dermatol. 1990 126: 301-2..

- Sontheimer, RD, 2013. DOI. 10.1038/jid.2013.335

Dominates our Interpersonal , social life.

- Visual signals from skin : evokes emotional responses. Infant skin; wrinkles , Body art, Makeup, skin color.
- **Subtle signals** such as Blushing, Blanching, Sweating play major roles in human communication.

- Response to **Touch:** enhances bonding, reinforces trust: A hand shake

- Skin is our " Touch screen" –literally and figuratively.
- In health care, it is the surface for diagnostics: (the electrodes attach here) .

Epidermis : sensing & feeling environment

Sensing temperature : Heat and cold by TRP Channels.
(Denda et.al. 2012. *Exp. Dermatol.*, **21**, 535-537 ;Caterina & Peng, Pharmaceuticals. 9: E77); Touch (mechano TRP).

Sensing Light: By Opsins in Keratinocytes and Melanocytes.
Pellicena et.al., 2017. JID 137: s212.

Sensing Oxygen levels: HIF(Hypoxia inducible factor)
Rezvani et.al.2011. JID 131: 1793 -1805

Sensing Xenobiotics: By Aryl hydrocarbon Receptor, and other orphan receptors
Haas. et.al., 2016. JID. 136: 2260-2269.

Microbial factors: By Toll like receptors

.

Allergens: Langerhans cells

Less studied factors:
Olfactory receptors (Denda,M. 2014. JID. 134: 2677-2679).,Endorphins (Bigliardi-Qi et al. 2004. Dermatol. 209: 183-189).Oxytocin secretion (Denda et.al.,2012. Exp. Dermatol. 7: 535-537)

TRP Channels.

- Transient receptor potential (TRP) ion channels - large group of nonselective cation-ion channels.
- Expressed **on neurons as well as various skin cells.**
- **Key role in skin functions**: epidermal barrier regulation, thermo-sensation, immune defense, melanocyte control.
- **Involved in pathophysiology** of many skin diseases, Itch, **Photoaging** etc.

Skin TRPV channels & agonists

- **TRPV 1** (Heat) **Capsaicin**,

- **TRPA 1:** (Noxious cold) **Cinnamon oil, Mustard oil, Wintergreen oil, Bradykinin**
- **TRPA1 orthologues** in Drosophila & Pit Vipers detect **Heat.**

- **TRPV 3**: (warm sensation) **Oregano, Thymol,Eugenol**

.

- **TRPV 4**. Either **mechanical forces** ("mechanoTRPV4") or by **pathogens** ("immunoTRPV4")- explain massage effects ?.

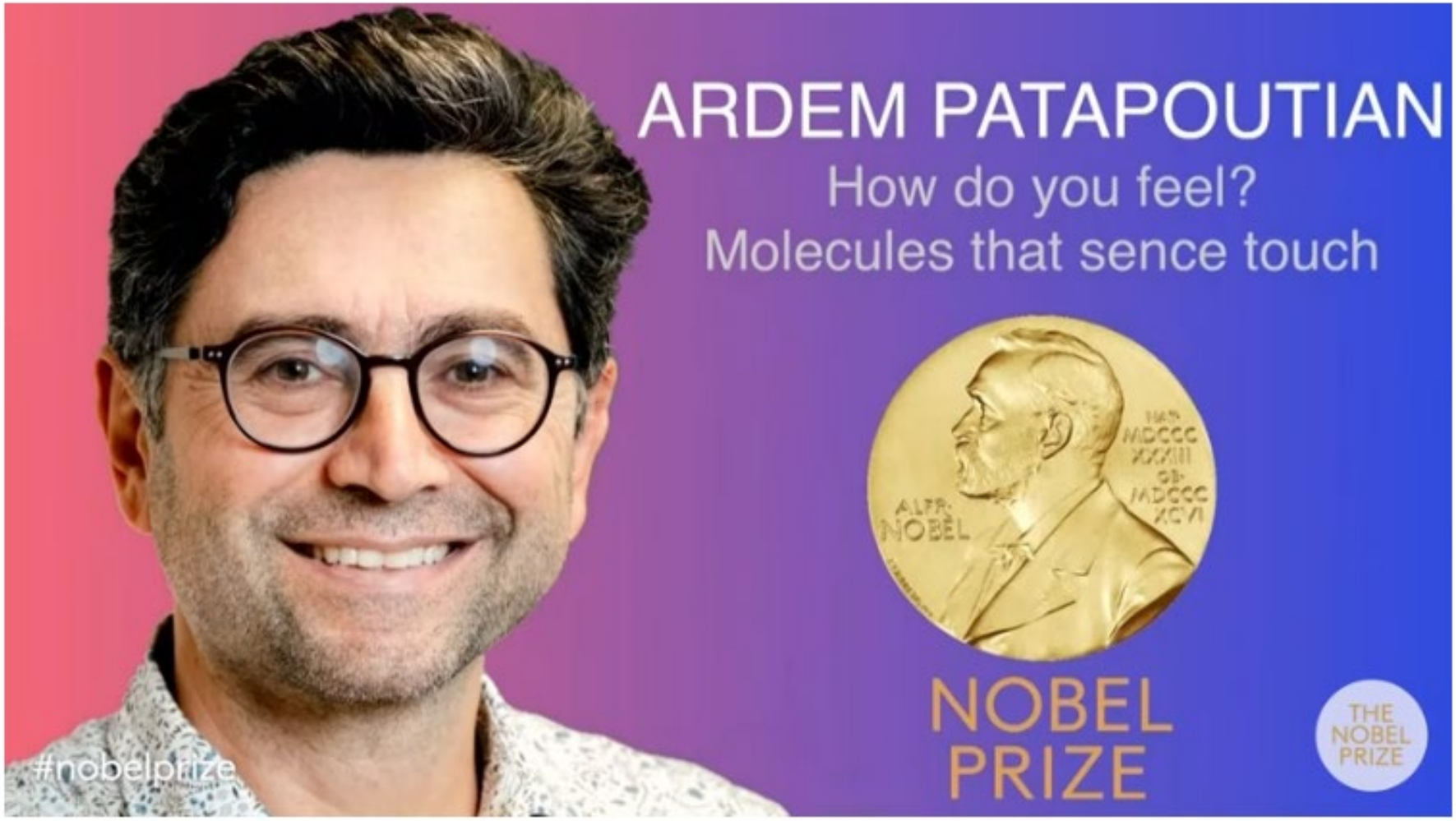
- **TRPM 8. (**Cold sensation) **Menthol.**

Bandel,M. et.al., 2004. Neuron. 41: 849-857

Michalick & Kuebler, 2020, https://doi.org/10.3389/fimmu.2020.00413

Bagood &Isseroff RR. 2021. TRPV1:. Int J Mol Sci. 2021 Jun 7;22(11):6135.

How do you feel? The molecules that sense touch



TRPV needed for skin barrier

- **TRPV3** is required for the **formation of the skin barrier** by regulating the activities of transglutaminases, essential for keratinocyte cornification (Cheng et.al. 2010.Cell 141: 331)

  TRPV4 also crucial for barrier (Kida et.al. 2012. *Eur. J. Physiol.* 463 :715)

Role in Calcium influx into keratinocytes.

TRP Channels and skin aging

- In **sun-exposed skin of elderly, TRP1 expression is increased**: possibly correlated with senile **pruritus, and increased MMP** expression. (Lee,et.al.2012. J. Derm..Sci. 65: 81
- **Photoprotected skin of elderly had more TRPV1 than similar skin from younger** persons.
- Any Role in Menopausal skin?
- **TRP and ORAI may functionally interact** to guide cellular functions. (Saul et.al.2014. Eur J Pharmacol. 739:49-59.

Opsins in Epidermis: Skin sees the light

- Multiple opsin receptors **: Opsins1 , 2, 3; 4, and 5 are expressed in human epidermal cells**. Indicate their function as epidermal photoreceptors.

- **OPN1-SW, a cone opsin activated by blue-violet light, is expressed in Epidermis.**

- **OPN3 mRNA and protein is expressed at higher levels than others: senses blue light, induces skin melanization.**

- **Opsins are now considered not just light sensors—they are 'moonlighting proteins," w**ith various functions.

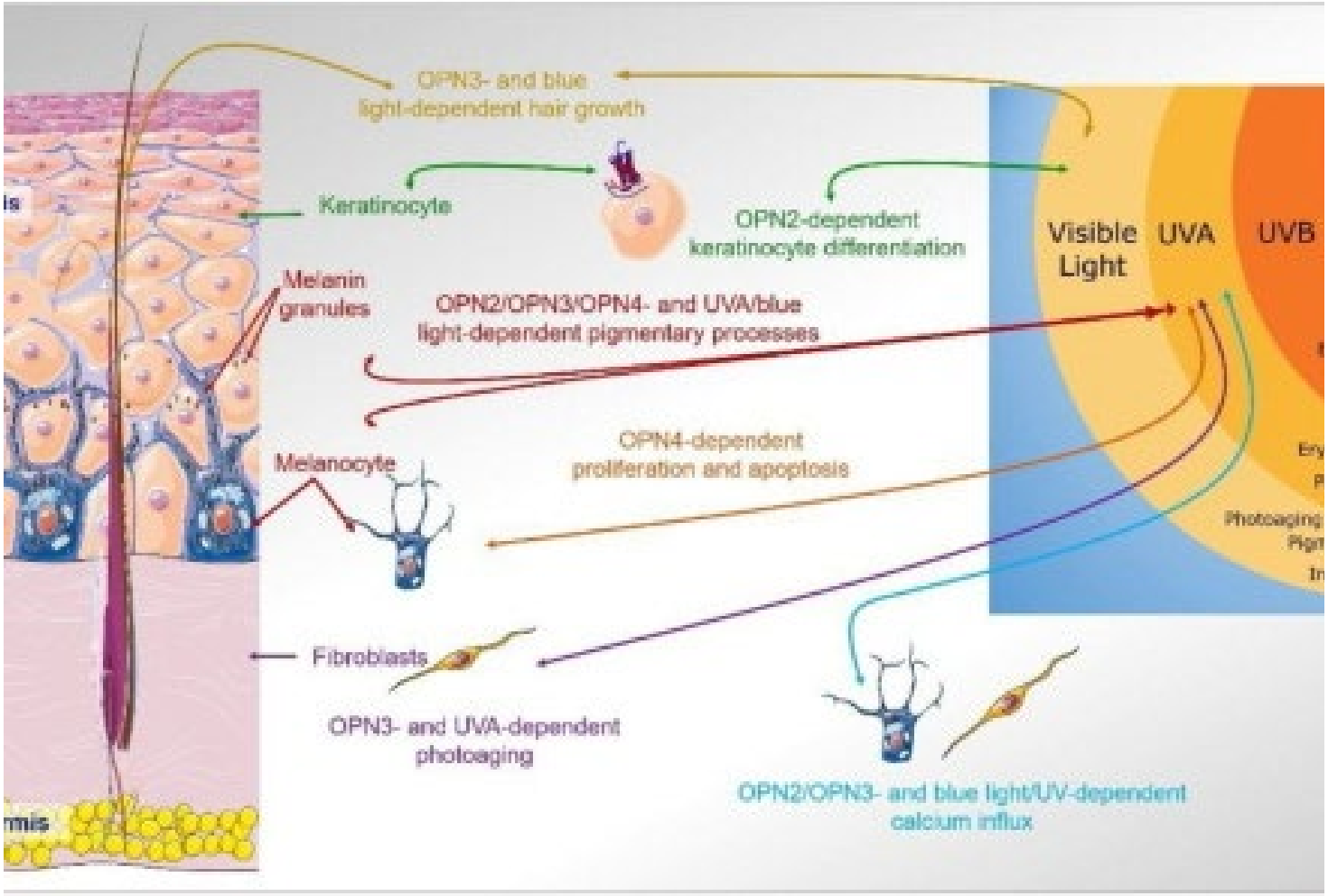
Tsutsumi. et.al.2009; Exptl.dermatol. 18: 567-570

Haltaufderhyde,K. et.al., 2015. Photochem.Photobiol. 91: 117-123.

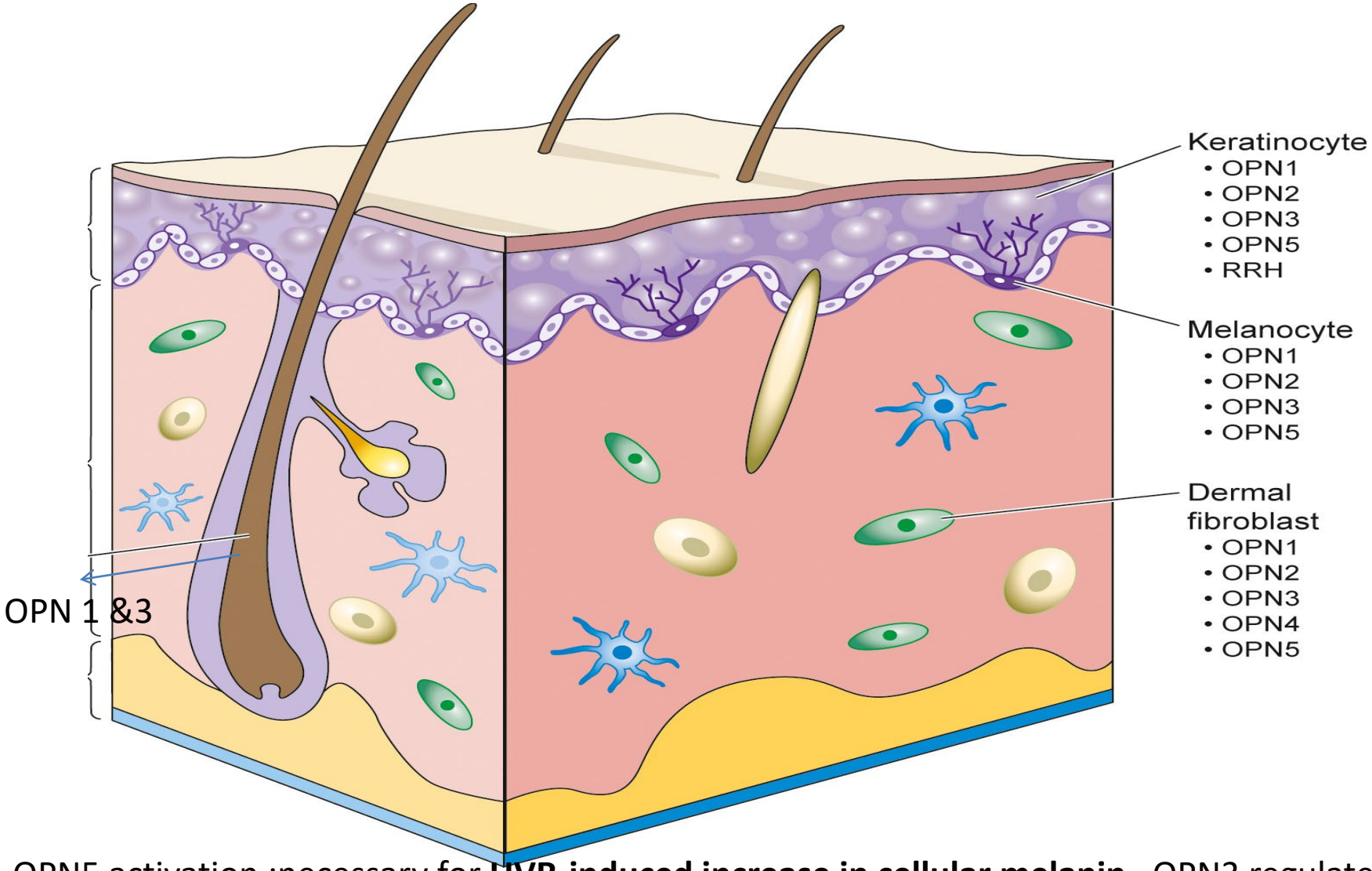
Feuda, R, et.al.2022. Rethinking opsins. *Mol.Biol and evolution. 39: msac033.*

How does the skin sense sun light? An integrative view of light sensing molecules,

de Assis. Et.al., 2021 J, Photochem. Photobiol. 47: 100403.

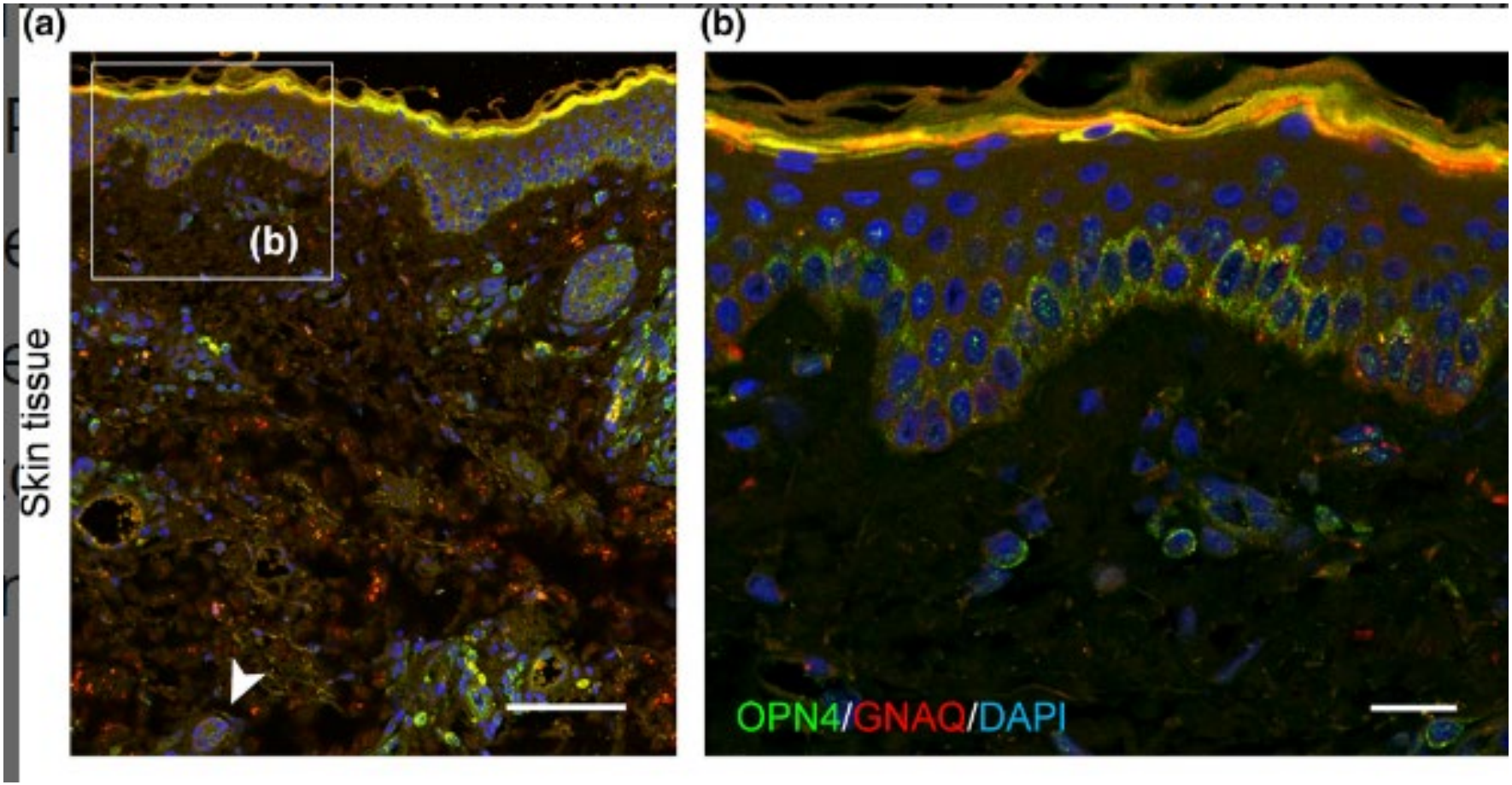


OPSINS IN SKIN



OPN5 activation :necessary for **UVR-induced increase in cellular melanin** , OPN3 regulates . **UV A-induced photo aging via MMP** production. OPN5 involved in **Biological clock.**

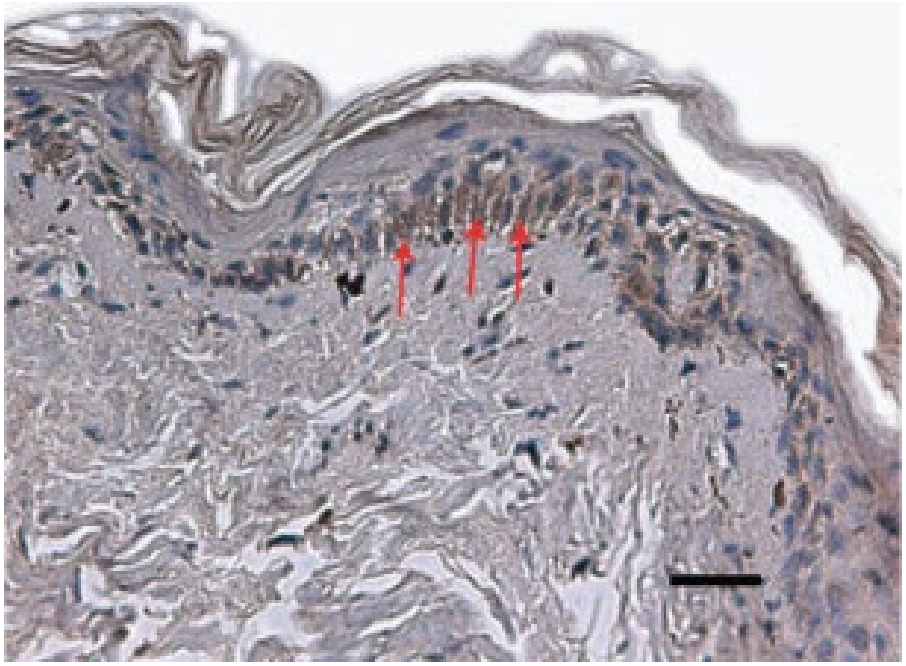
OPN4 belongs to the photosensitive system of the human skin.



Gq family of signal transduction

Kusumoto et.al. 2020. Genes to Cells, *25*(3), pp.215-225.

Skin senses Oxygen levels.



Via Hypoxia Inducible Factors(HIF 1 Alpha).
Sensing of O_2 by keratinocytes leads to NO signals , changing cutaneous blood flow that affect production of the hormone erythropoietin.

It is claimed that **human epidermis** does not obtain its oxygen from the dermal circulation but rather **utilizes oxygen directly from the atmosphere** (Stucker et al., 2002).

Immunostaining of HIF 1 Alpha : Rezvani.et.al. 2011. JID. 131: 1793-1805

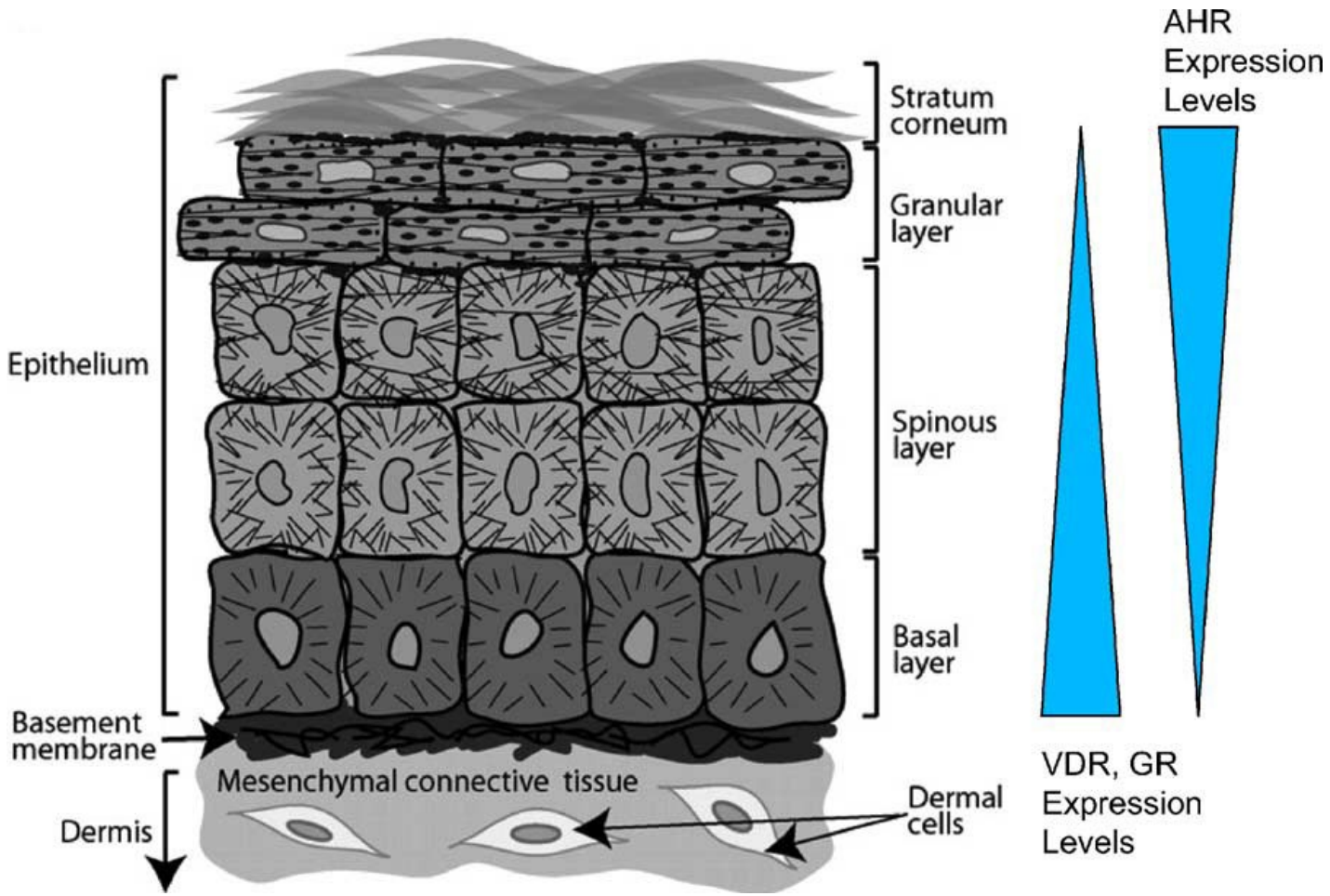
Oblong's lab has recently reported age-related changes in Oxygen sensing
https://doi.org/10.1111/exd.14654

Skin senses air pollution via AhR.

- AhR target gene **Artn** in epidermis lead to production of neurotrophic factor **artemin.**
- Artemin **causes epidermal hyper-innervation and inflammation** that lead to hypersensitivity to pruritus..
- AhR activation and ARTN expression in epidermis **correlated with atopic dermatitis**.

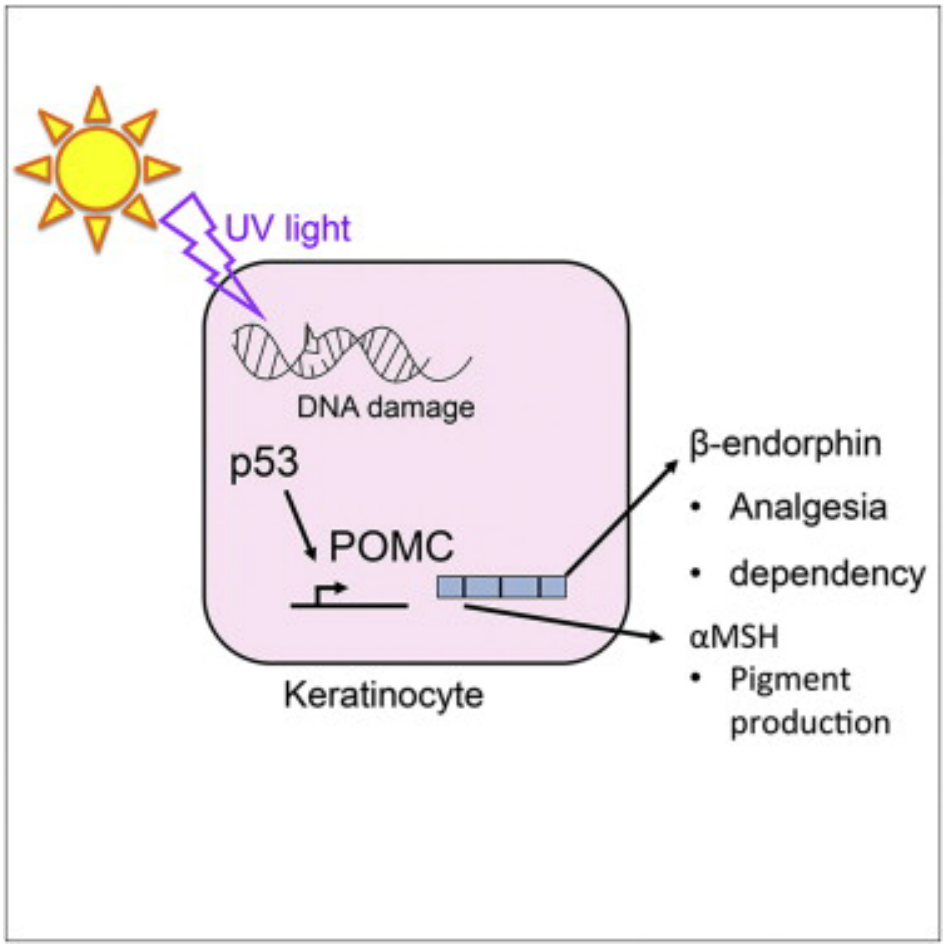
Hidaka.et.al., 2016.The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin. Nature Immunology 18: 64-73.

Aryl Hydrocarbon Receptor & its gradient.



AHR has an evolutionary history of 600 Million Years, gaining new ligands……..

Skin β-Endorphin Mediates Addiction to UV Light



UV elevates blood Endorphin levels

•UV **causes systemic analgesia** (reversible with opioid receptor blockade)

Chronic UV **causes dependency and "addiction"**-like behavior (Tanning booth addiction)

Did Evolution originally favor this for enhanced Vitamin D synthesis?

Fell et.al. 2014. Cell; 157: 1527–1534.

Can skin perceive SMELL too ?

- **Several OLFACTORY RECEPTORS are expressed in Keratinocytes.**
- **OR2AT4, OR2A4/OR2A7, and OR51B5** expressed in keratinocytes **promote wound-healing**-
- **OR10G7** over **expressed in AD,** -involved in allergy to perfumes?
- **OR51E2 activated by β-ionone increased melanogenesis**
- **OR2AT4 (**Sandalore- or brahmanol-activated **) retards catagen; maintain anagen in hair follicle.**

Seo J, et.al. Association between Olfactory Receptors and Skin Physiology. Ann Dermatol. 2022 Apr;34(2):87-94..

Skin tells everything !

- Our skin gives away **information on how we feel** (watching emotionally loaded images, or positive or negative stimuli).
- **Emotions** : Cause subtle changes in electrical conductivity of skin
- Galvanic Skin Response **(GSR)**, or **Skin Conductance is a sensitive measure for emotional arousal.**

Epidermis & Brain Volume

Loss of body hair exposed epidermis as a new boundary layer -- receives and responds to multiple external sensations as well as social /emotional cues.

These peripheral stimuli could have placed additional stress on the CNS, **leading to further encephalization.**

A concept supported by several analogous examples of " brainy" vertebrates.

Denda M, Menon GK, Elias PM (2018) Did Hairlessness Stimulate an Increase in Hominin Brain Size? Insights from the Cutaneous Neurosensory Interface and Comparative Vertebrate Morphology. Anthropol 6: 199.

Today: is it Brain's Turn to modify skin?

- **Human creativity led to digital revolution** that changed the way we perceive skin – Virtually.
- **New norm is conceal the natural; morph our images** (filters / photoshop) to get the most " Likes', for fake images.
- The " Instagram face" or the **Cyborg image** is the virtual reality for many Netizens.

The “Instagram Face”

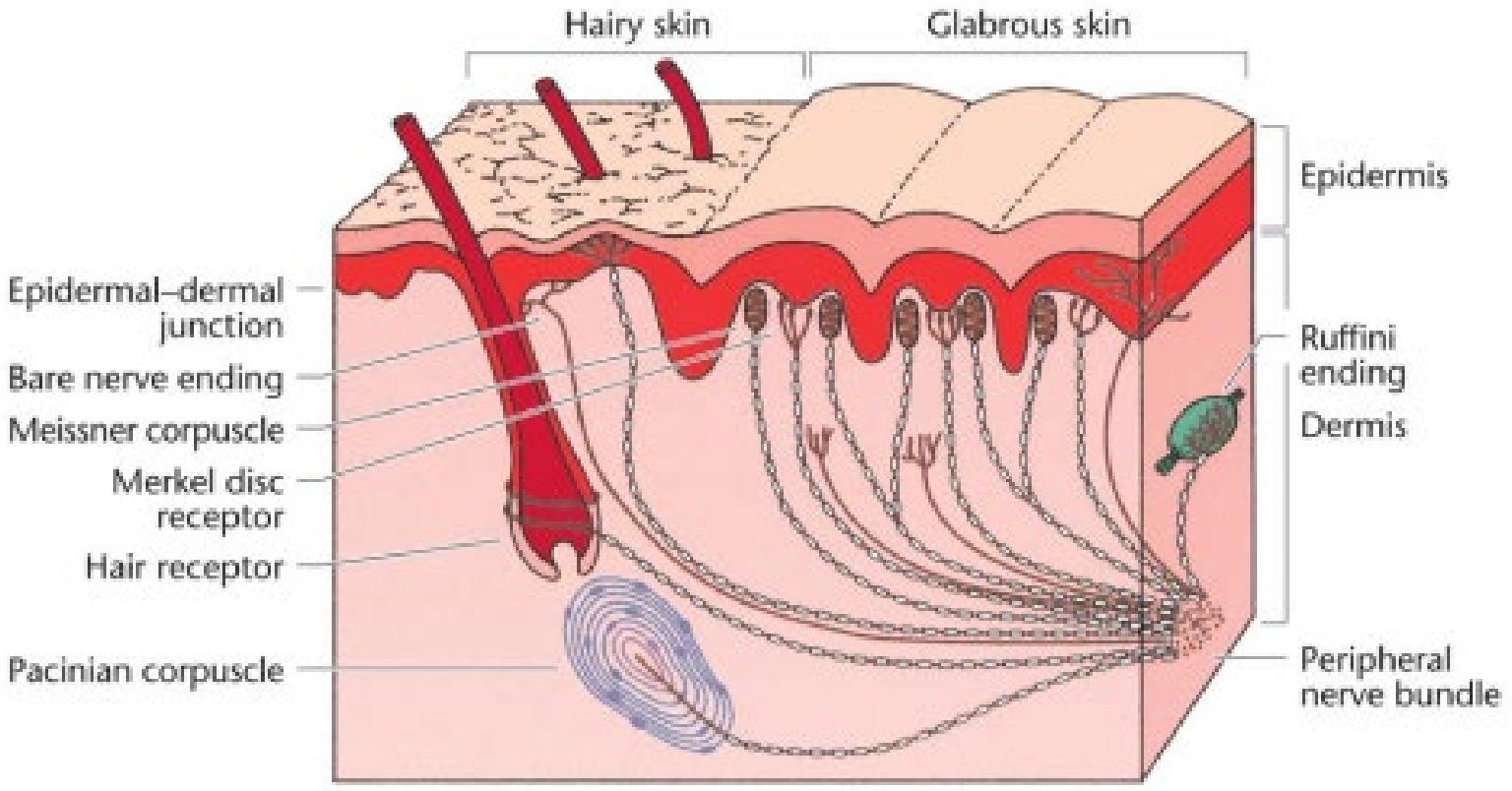
How social media, FaceTune, and plastic surgery created a single, cyborgian look’
J. Talentino, The Newyorker. Dec 2019.

Technology is—rearranging our faces according to whatever increases engagement and “likes.”

….. effectively putting us **out of touch with the professed “*Homo connectus*”?**

Gardner, Esther P (May 2010) Touch. In: Encyclopedia of Life Sciences (ELS). 10.1002/9780470015902.a0000219.pub2

- **TOUCH RECEPTORS : MORE IN THE GLABROUS SKIN.**



Touch and Physical contact lead to release of Oxytocin : the Bonding Hormone.

Oxytocin in skin

- **Oxytocin and its receptor are expressed in Keratinocytes & Fibroblasts**..

- **KO of its receptor** lead to elevated ROS levels, and release of Pro inflammatory cytokines by Keratinocytes.

- **Reduced expression of the OXT** system in **atopic skin** suggest a clinical relevance for the hormone in skin homeostasis.

(Deing V; et.al., 2013 Brain, Behavior, and Immunity. Vol 29; supplement. P.S11.)

- **Good life rests in the simplest of actions: human touch.**

This evolutionarily conserved peptide makes skin a Social Organ.

- Highly conserved evolutionarily, an important modulator of social and emotional processes across species.
- **Impacts** : social stress and anxiety, social memory, parent-child bonding, emotion recognition, empathy, and interpersonal trust.
- Oxytocin-induced norm compliance **reduces Xenophobic Outgroup rejection** (Marsh et.al. PNAS.114:9314)

What next ?
"Second SKIN" in the making……

Electronic materials are now being actively investigated to construct "second skin."

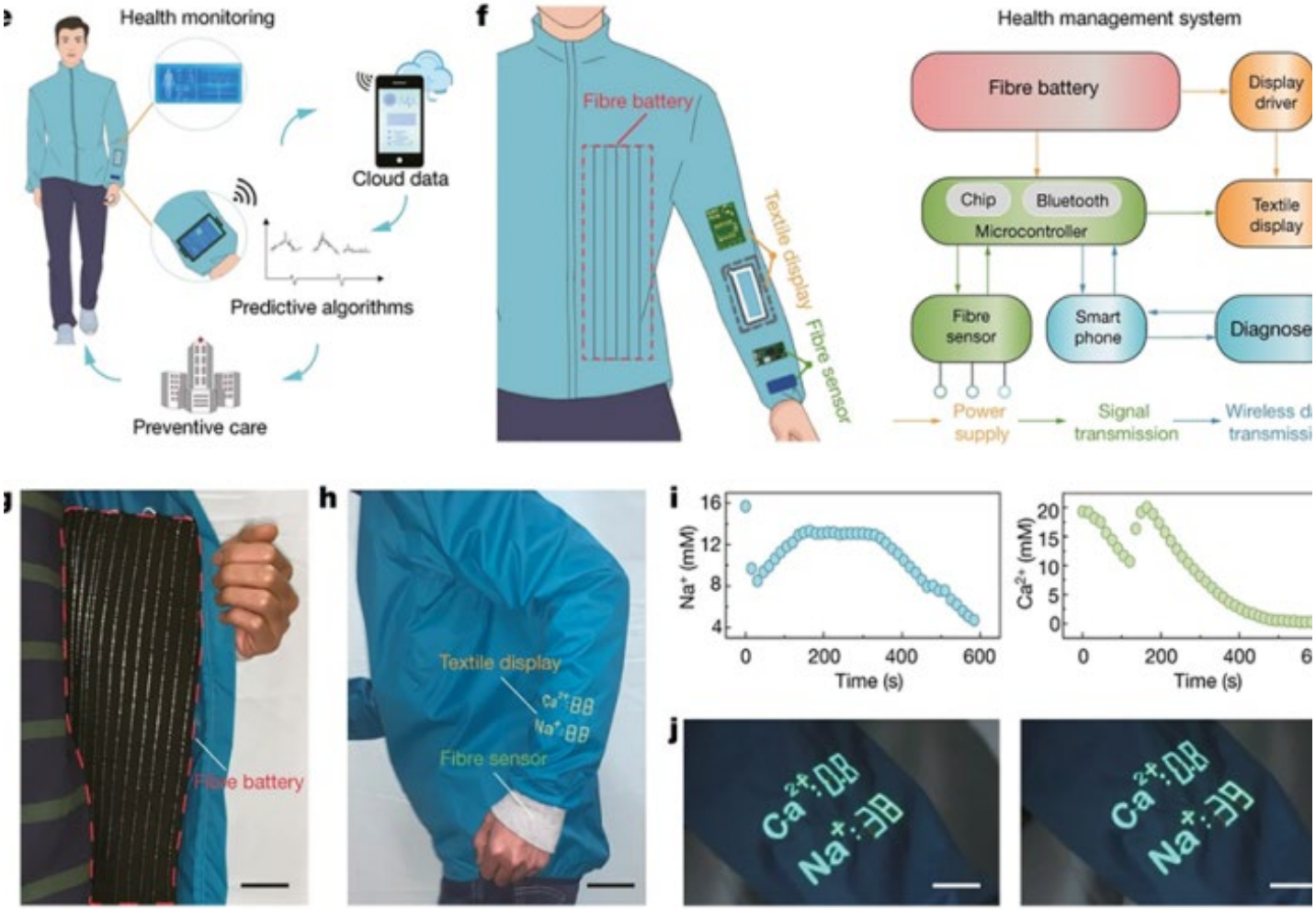
Electronic second skin is touted as the next interface to expand applications of electronics for natural and seamless interactions with humans .

To enable smart health care, the Internet of Things, and **even amplify human sensory abilities.**

Oh, J. Y., & Bao, Z. (2019). Second skin enabled by advanced electronics. *Advanced Science*, *6*(11), 1900186.

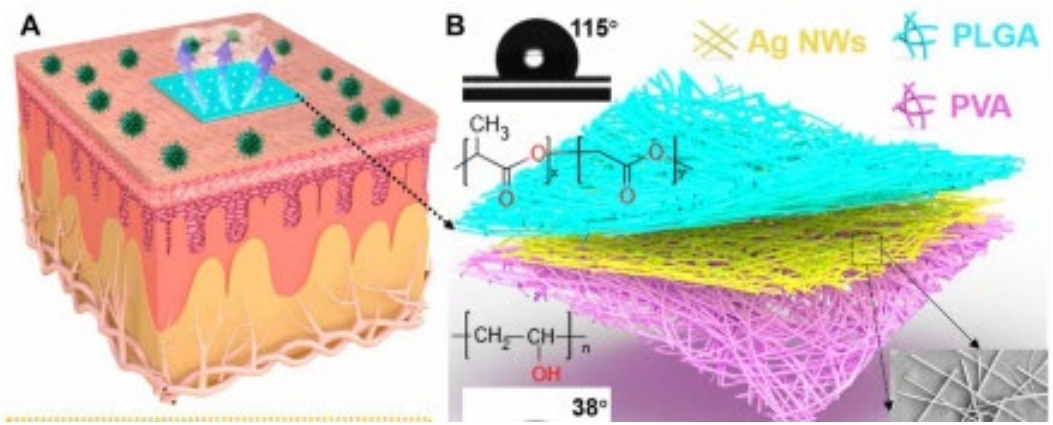
Acutis, A. D., & Rossi, D. D. (2017). e-Garments: Future as "Second Skin"?. In *Smart Textiles* (pp. 383-396). Springer, Cham.

Future Designer Jackets : How will the skin respond & adapt?



Anti-Microbial second skin: Logical, but is it Biological ?

- Peng et al., Sci. Adv. 2020; 6 : eaba9624



Kim, J.J et al., 2022. Antimicrobial second skin using copper nanomesh. *PNAS. 119*(24), p.e2200830119.

Copper nanomesh composed of copper coating and interconnected polymer nanofibers **kills 99.99% of bacteria and viruses within 1 and 10 min and prevents bacterial cross-infection.**

RETHINK MICROBIOME !!

Magnetism in Skin's future?

- Adding a novel information channel—an **electronic sixth sense**—allows humans to utilize the surrounding magnetic fields as **stimuli for touchless interactions**.

Canon Bermudez ,GS &. Makarov, D.“ Magnetosensitive e-skins for interactive devices,” Adv. Funct. Mater. (published online 2021). https://doi.org/10.1002/adfm.202007788

How would it all affect epidermal biology ?

An inert mask causes Maskne, an occlusive bandage retards barrier repair. How would the electronic signals affect epidermal biology?

Quo Vadis…?

- Human skin evolved by adapting (*via* receptors, signaling network , Cytokines) through large scale changes in environment.
- But the **e- revolution** may **be too fast for biological adaptations (an evolutionary Trap ?).**
- Future adaptations may neither be bright nor bleak; but definitely interesting.
- **Impact of " second skins" on skin health & aging (and cosmetic science) should stimulate biological research , rather than speculations.**