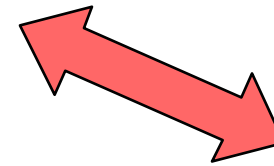
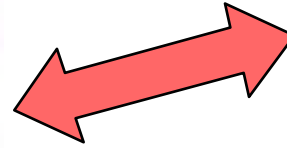
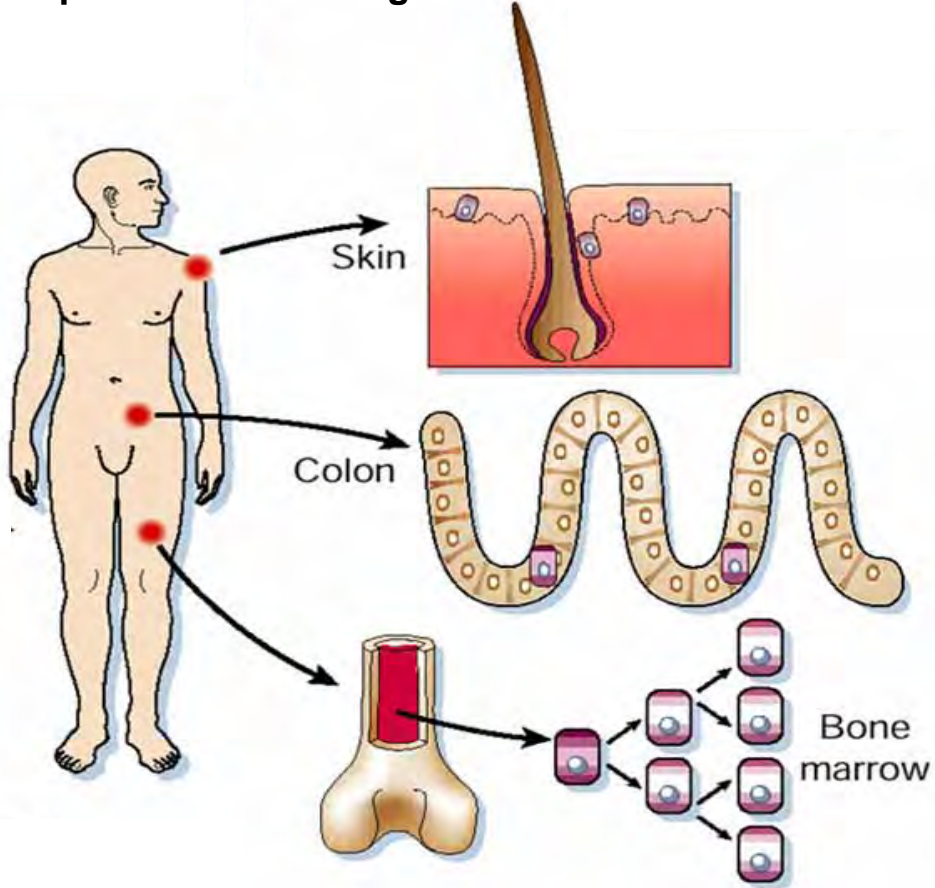


Unexpected consequences of loss of Notch signaling in the skin

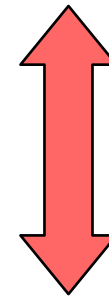


Swiss-Japanese workshop 2008

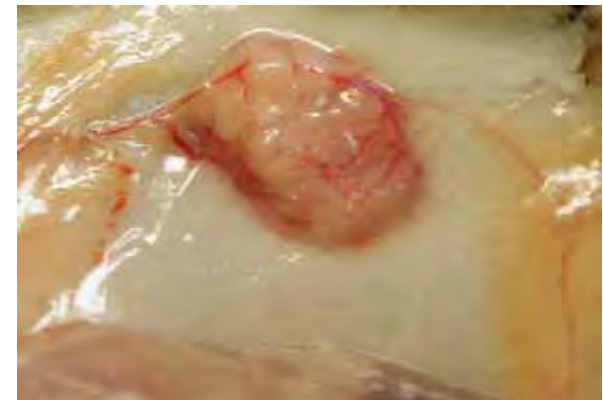
Undergo replenishment or repair from SC throughout life



QuickTime™ et un décompresseur TIFF (LZW) sont requis pour visionner cette image.



Tumorigenesis

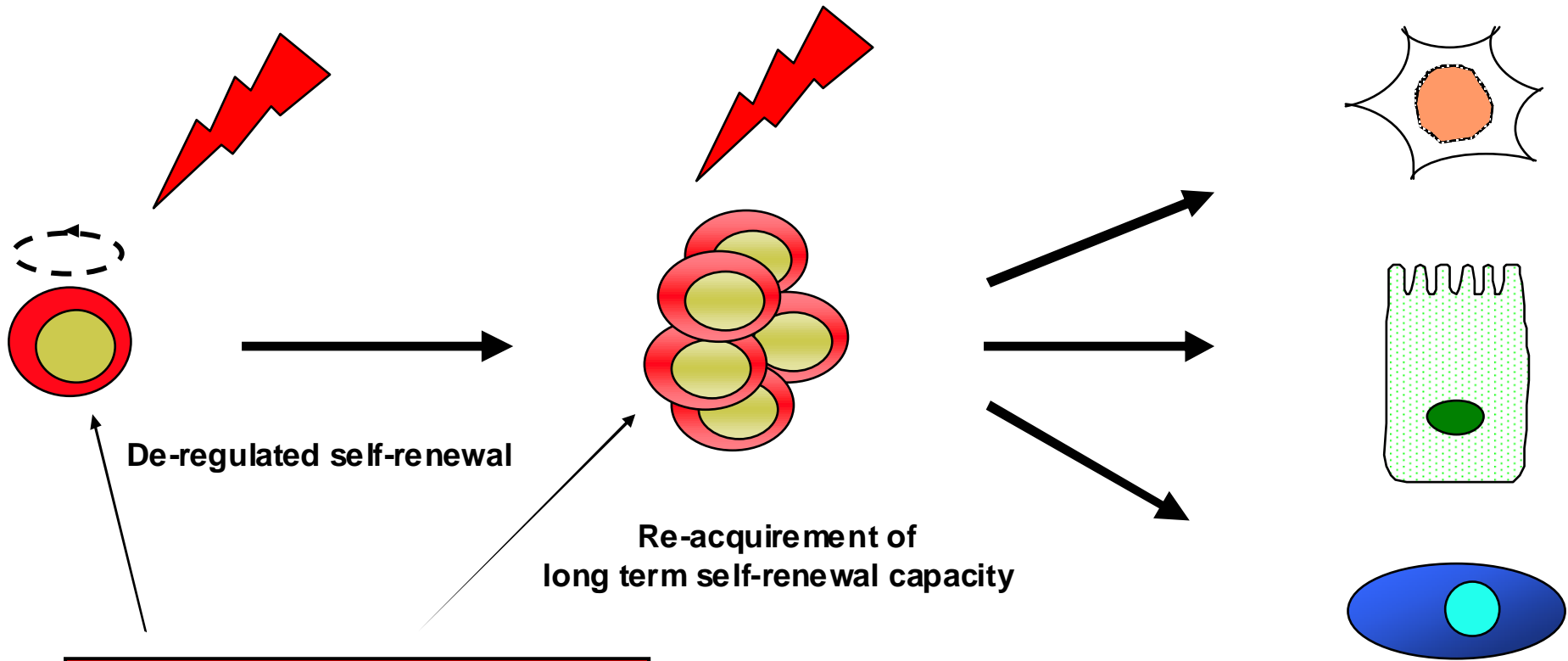


Cancer is a disease of uncontrolled self-renewal

Stem cells

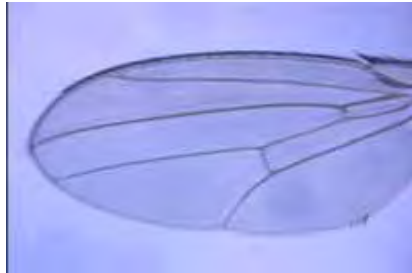
Transient amplifying cells

Diff. cells

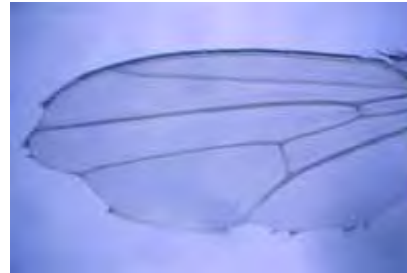


**Cancer Initiating Cell
or
Cancer Stem Cells**

**no division
« work »**

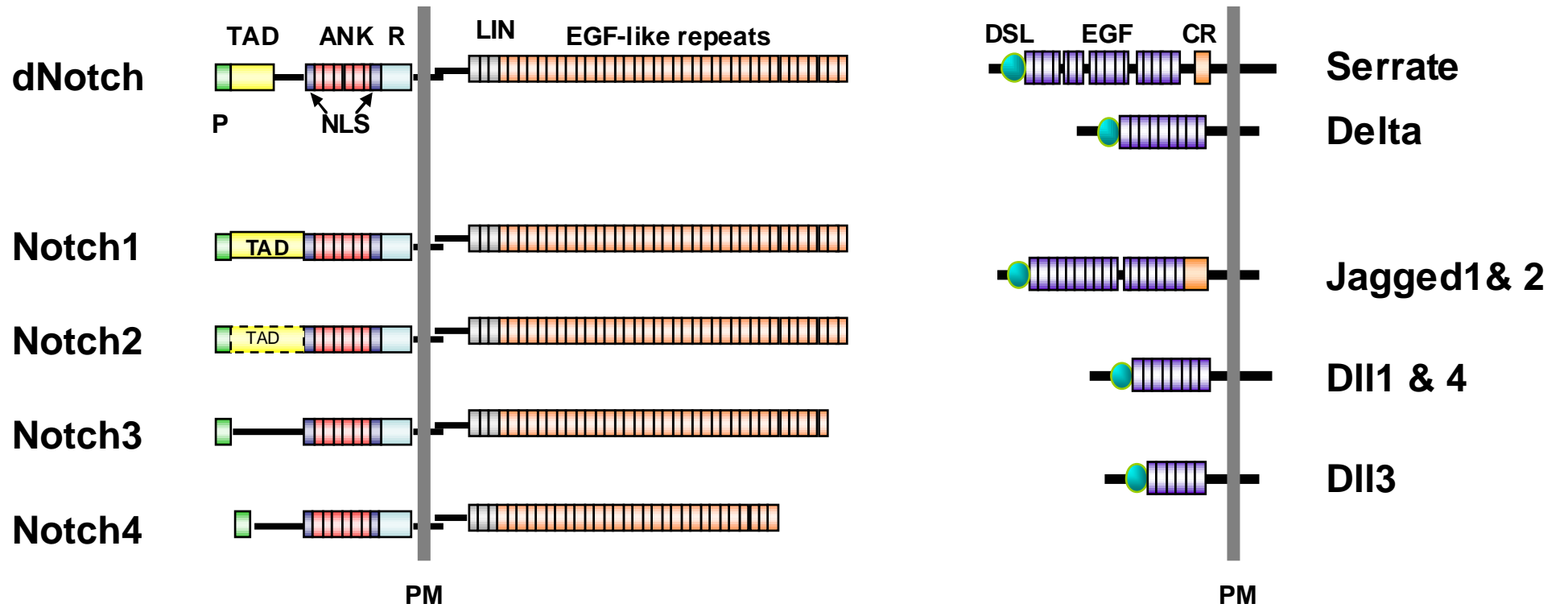


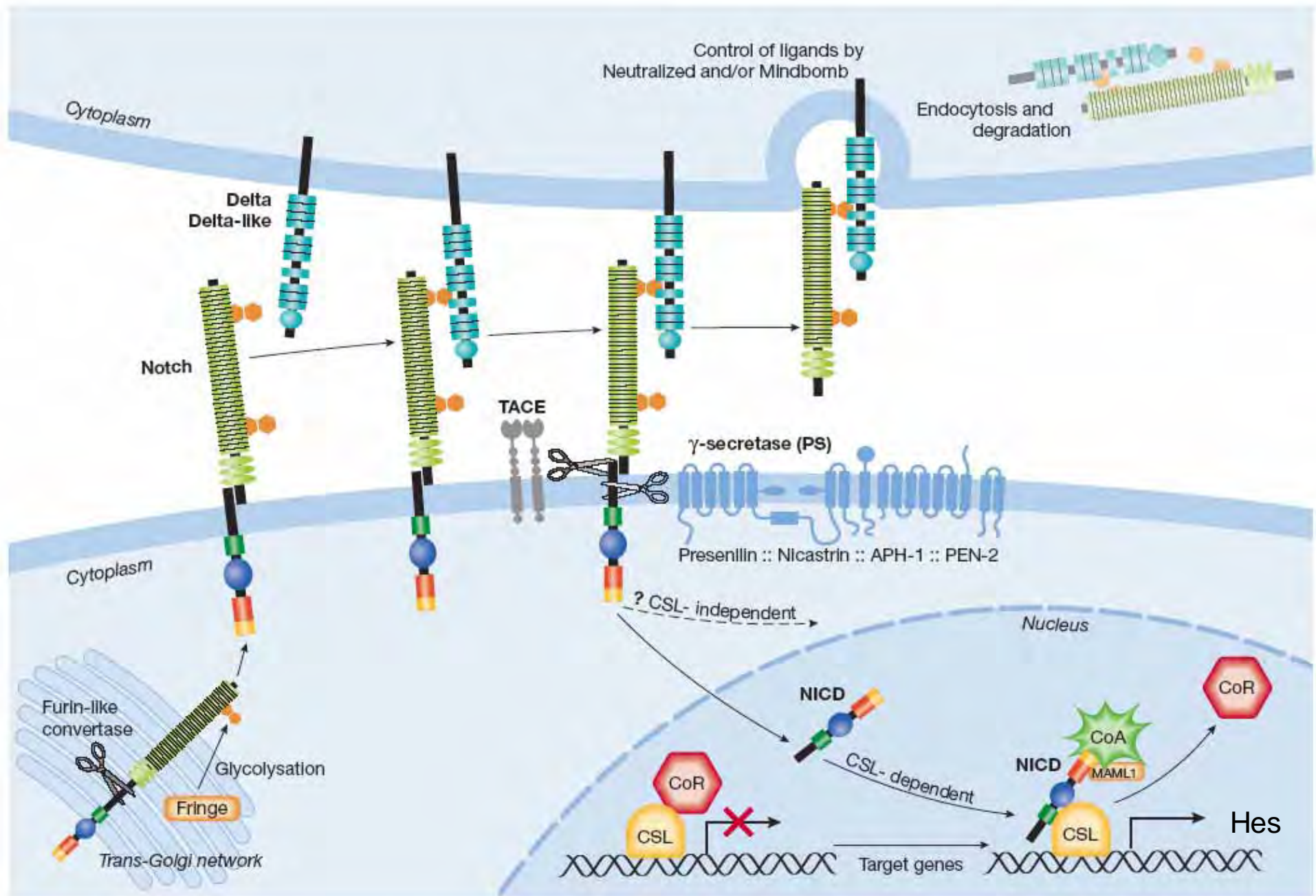
Normal wing



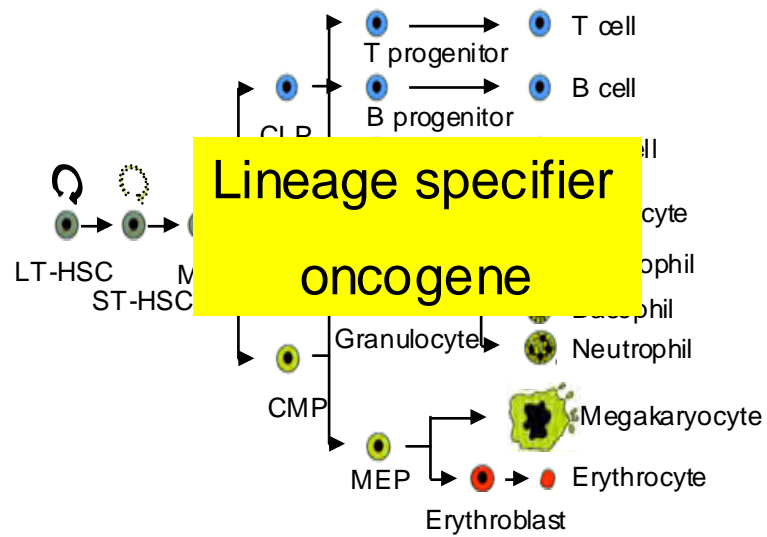
"Notched" Wing

Thomas Hunt Morgan 1917

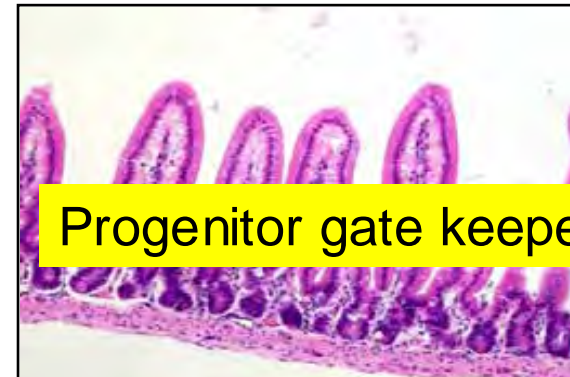




Hematopoiesis

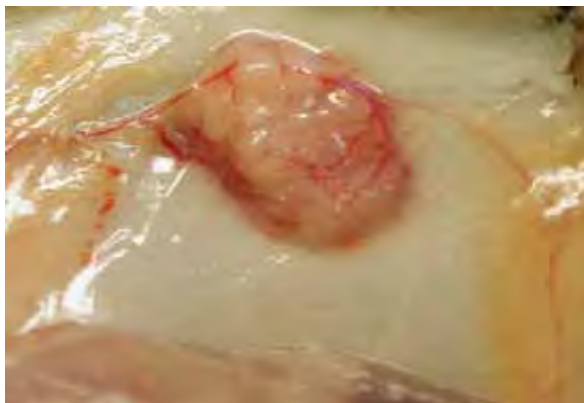


Intestine

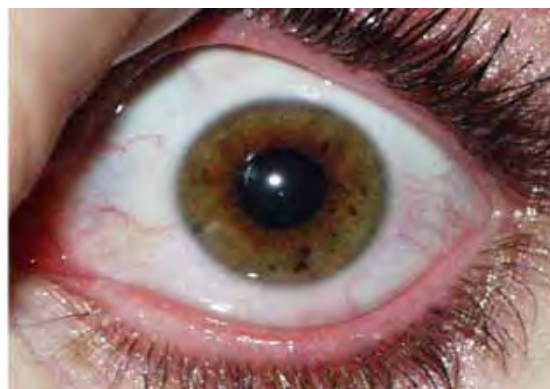


Progenitor gate keeper

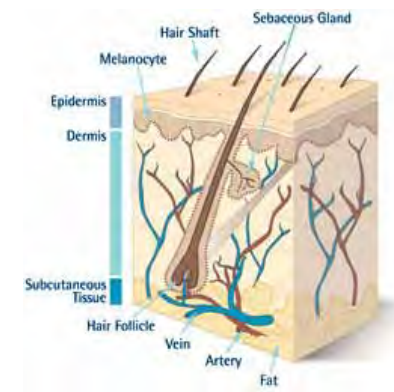
Tumorigenesis



Cornea

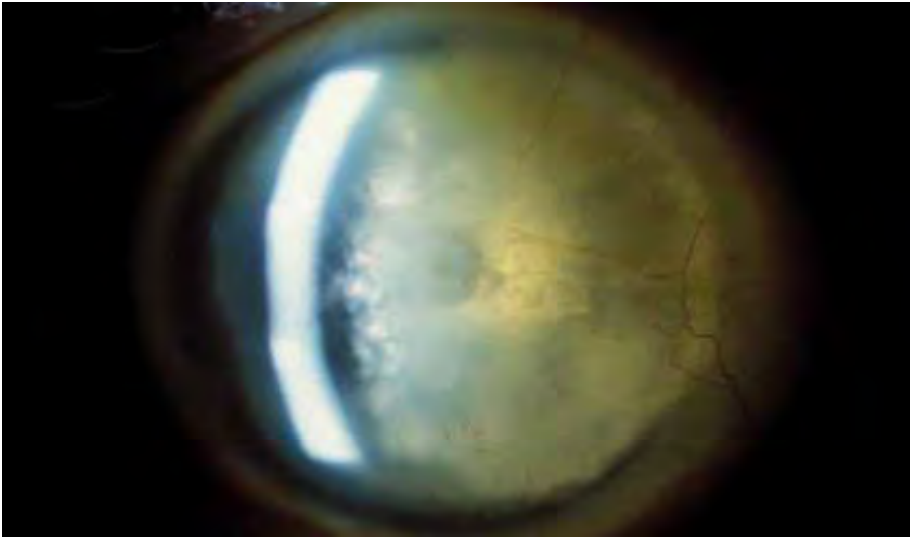


Skin and hair follicle homeostasis



The corneal phenotype can change!

Aniridia and Bitot's spots.

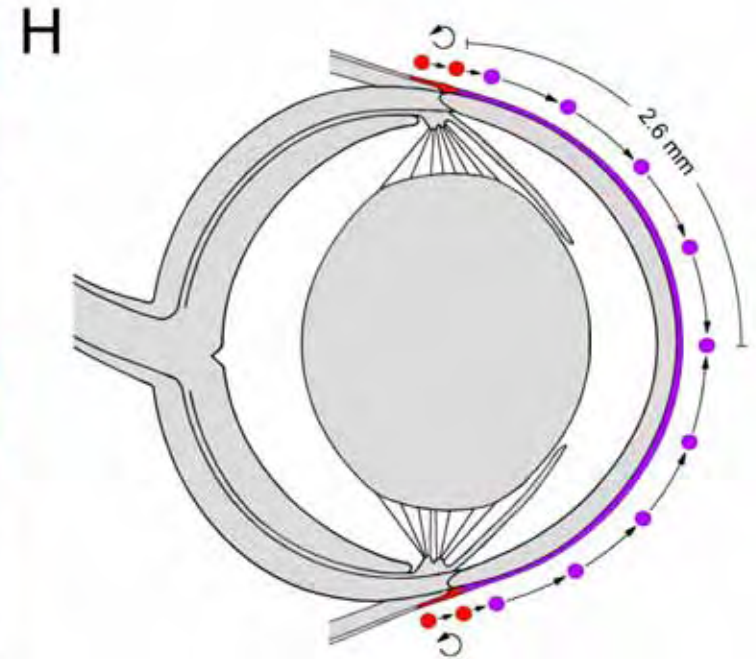
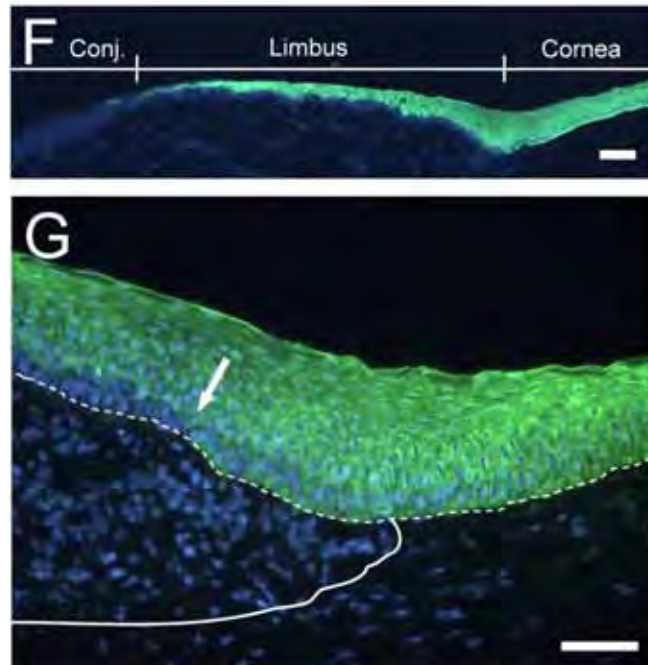
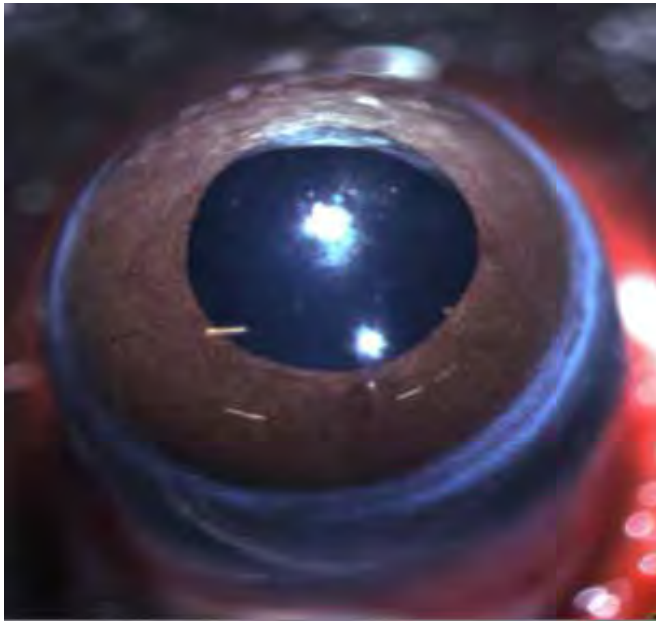


Corneal conjunctivalization



Limbal dermoide

Corneal stem cells in the limbus are responsible for renewal of the cornea and wound healing



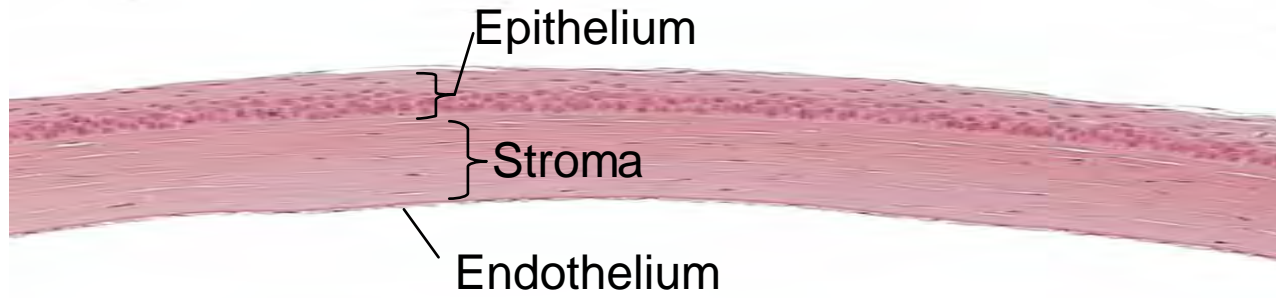
1. Do not express Keratin 3/12
2. Limbus cells are LRC
3. After severe injuries cells of the limbus migrate towards the wound to repair the injury
4. Cells can be cultured and transplanted to improve vision.

QuickTime™ and a
Photo - JPEG decompressor
are needed to see this picture.

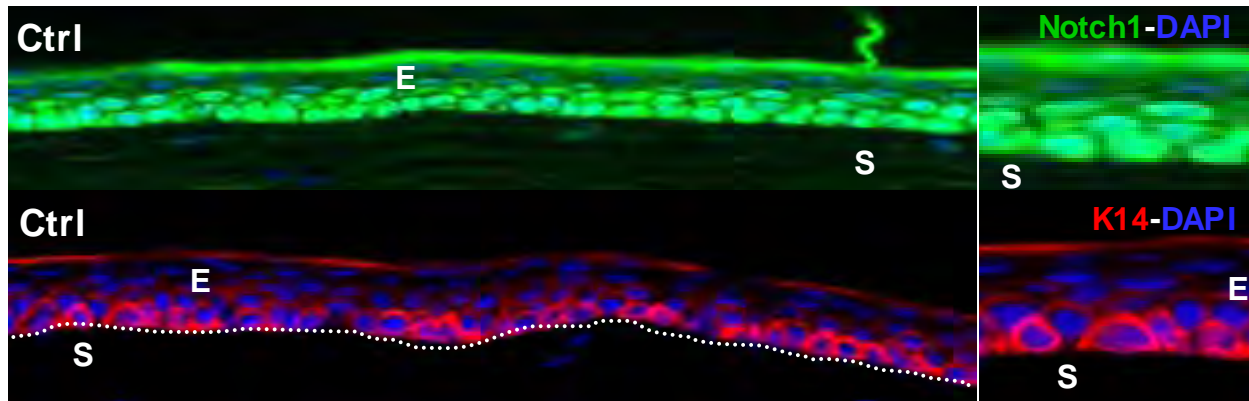
Sophie Vauclair



Francois Majo



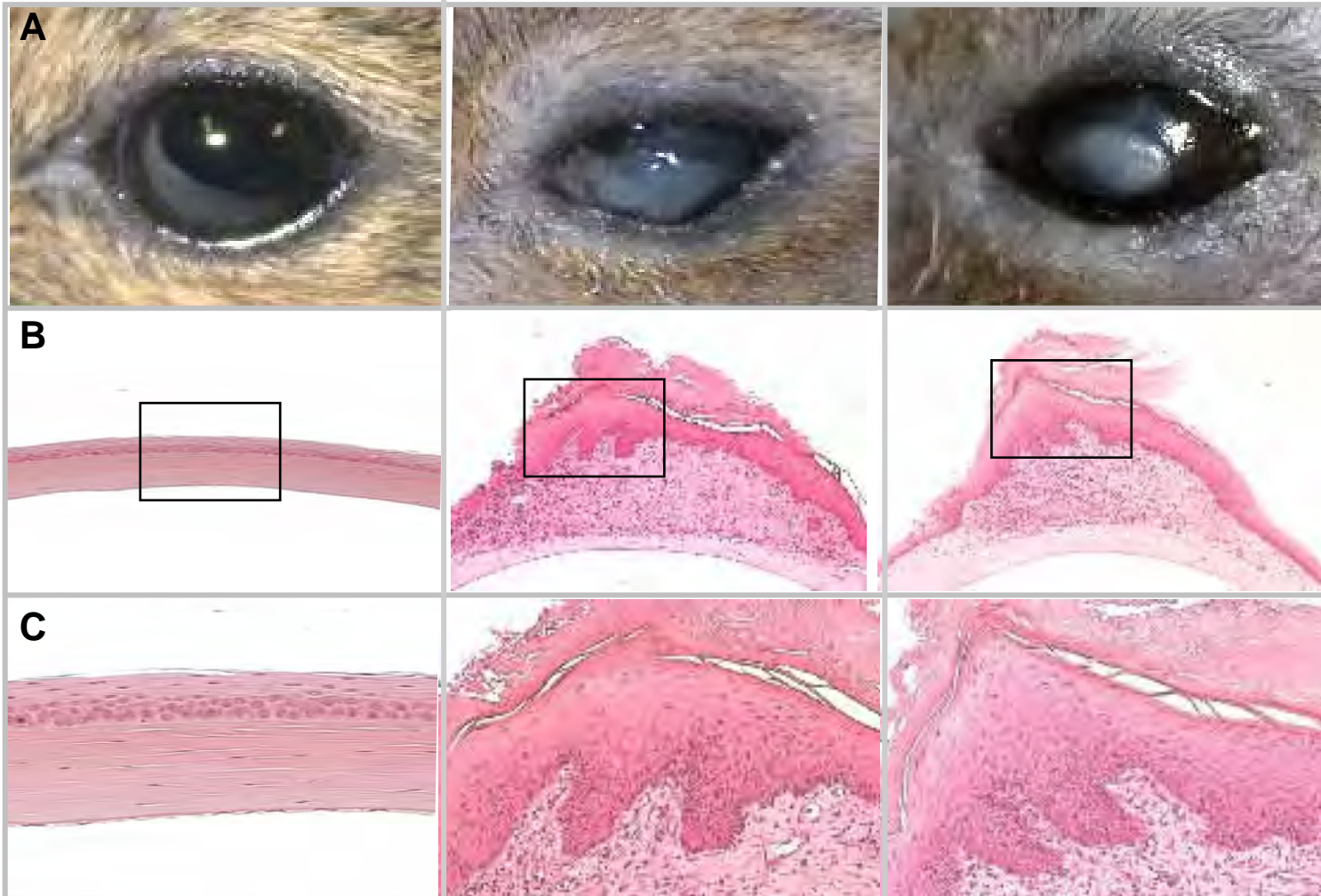
Yann Barrandon



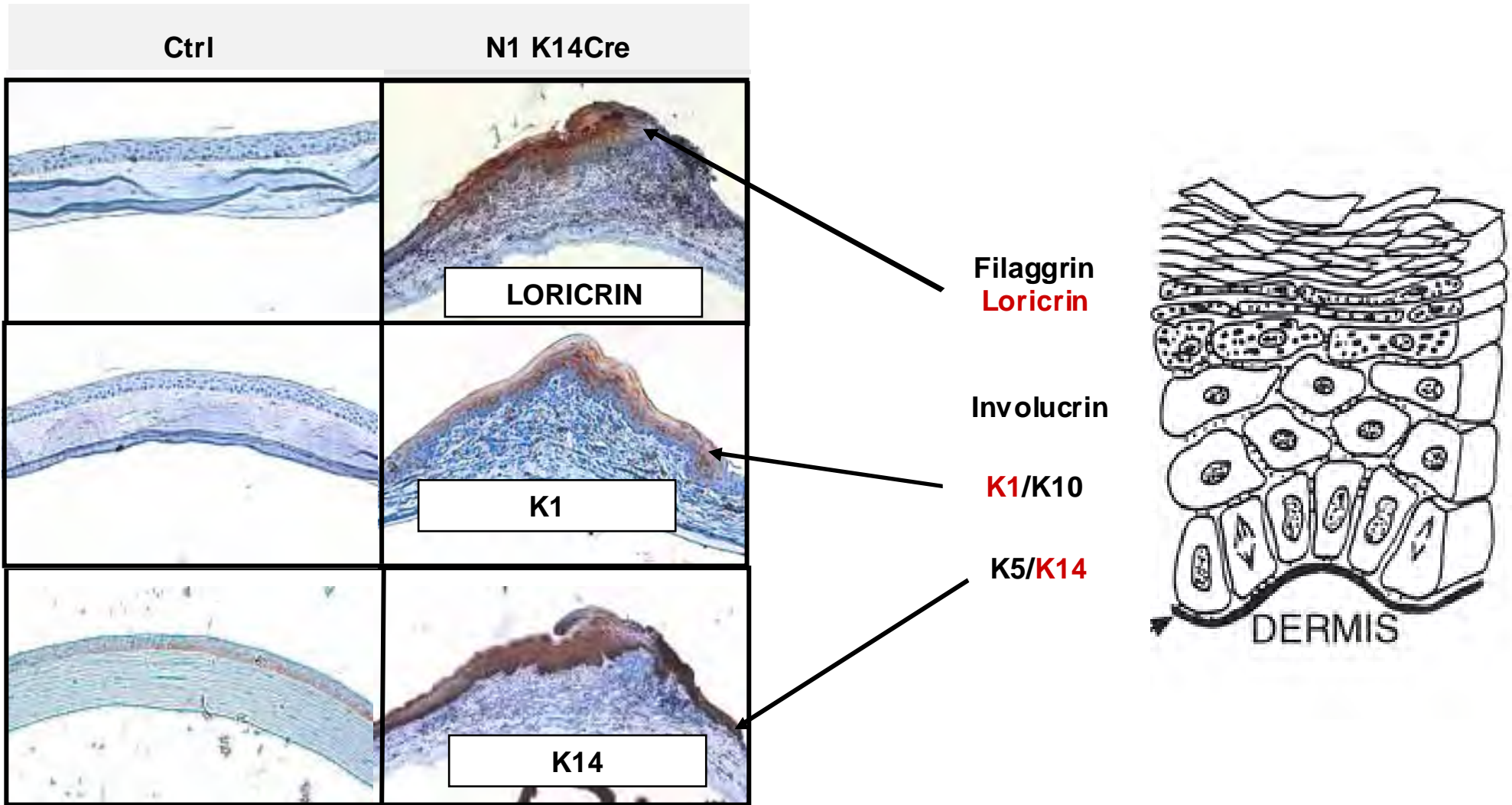
Ctrl

N1 K5Cre^{ERT}

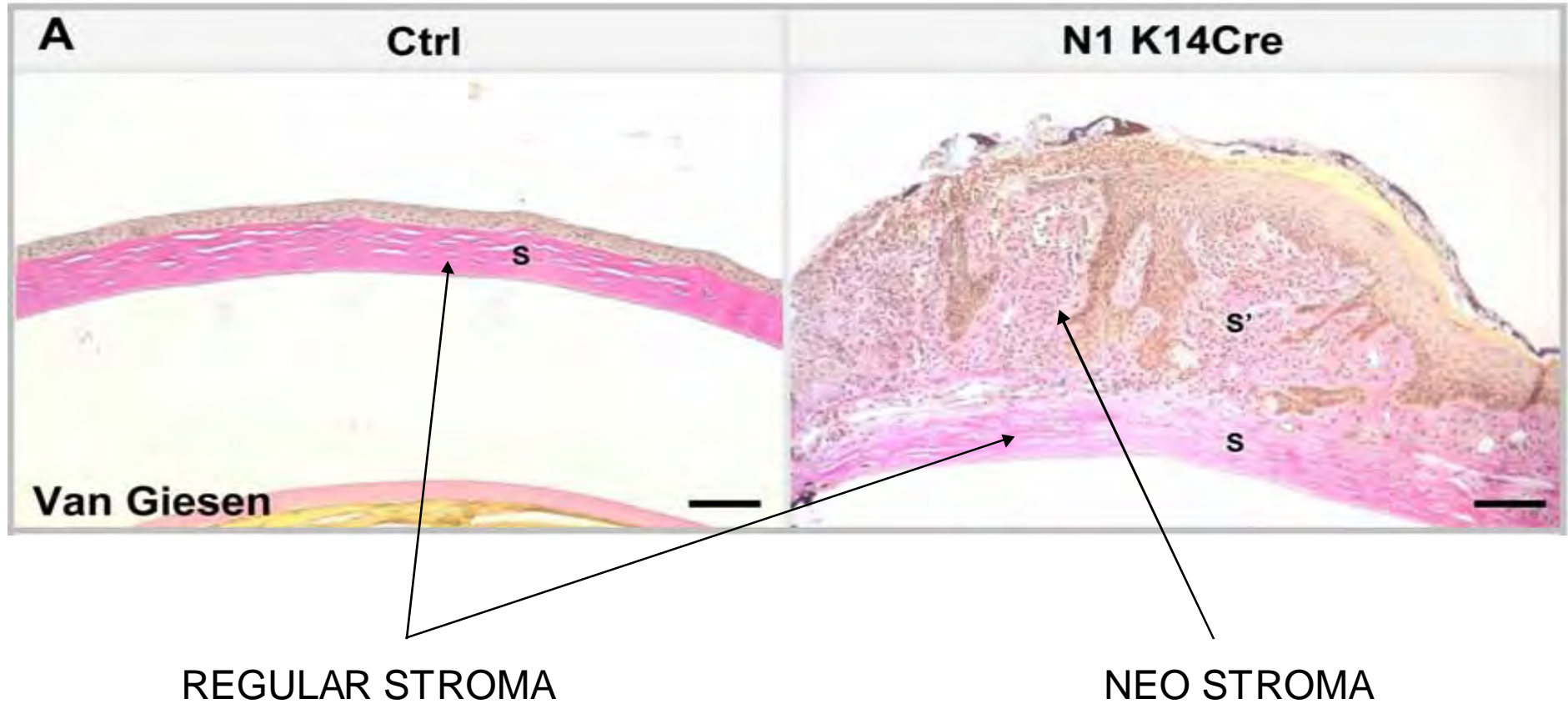
N1 K14Cre



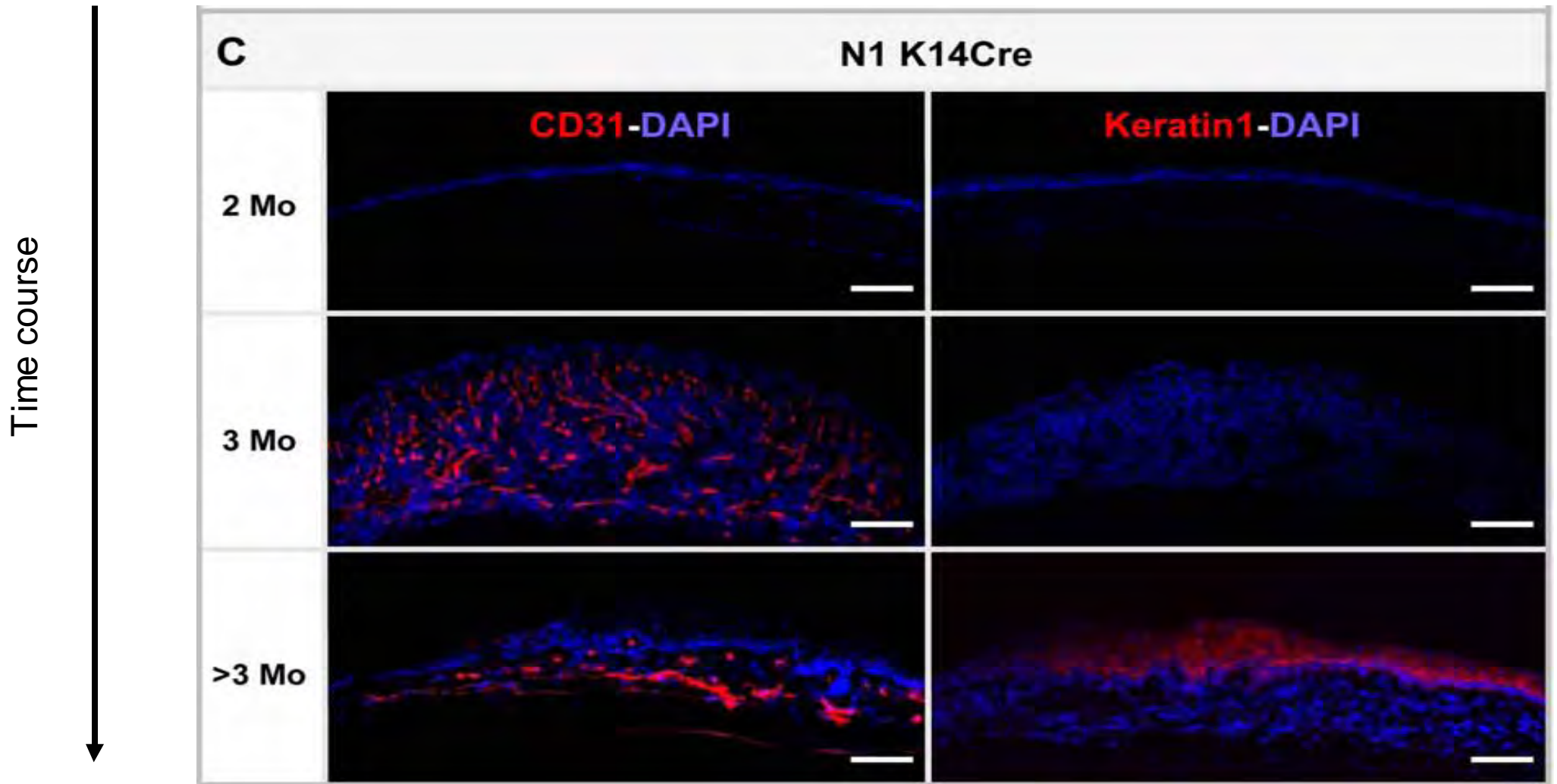
(2) Inactivation of Notch1 in the corneal epithelium induces its differentiation into epidermis.



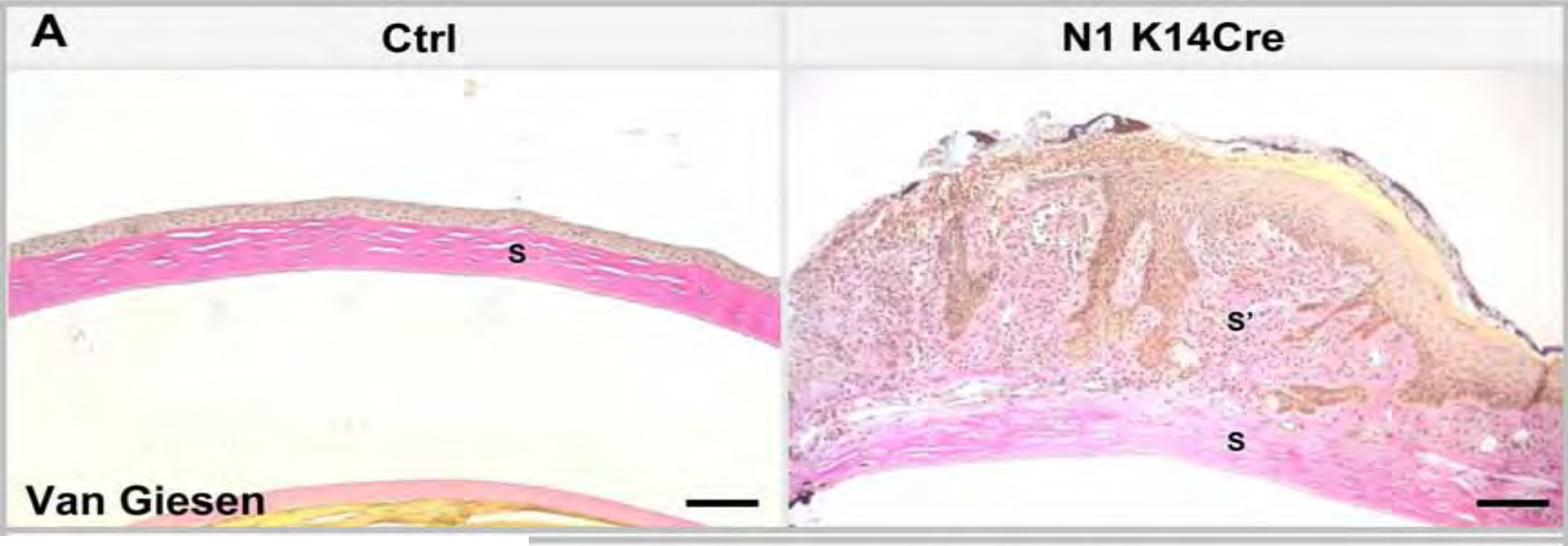
**(1) Notch 1 inactivation in the epithelium
modifies the corneal stroma.**



Notch1 deficiency in the corneal epithelium leads first to changes in the stroma before the epithelium changes its fate



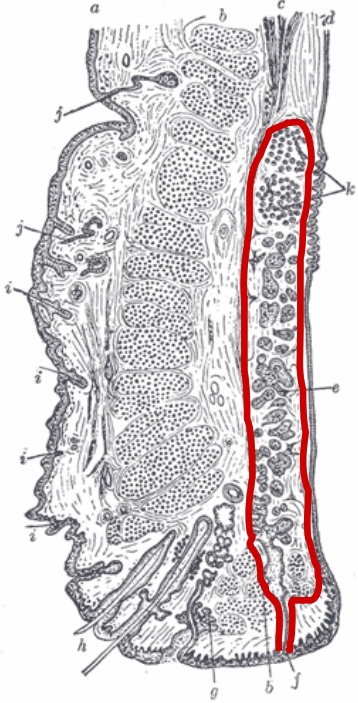
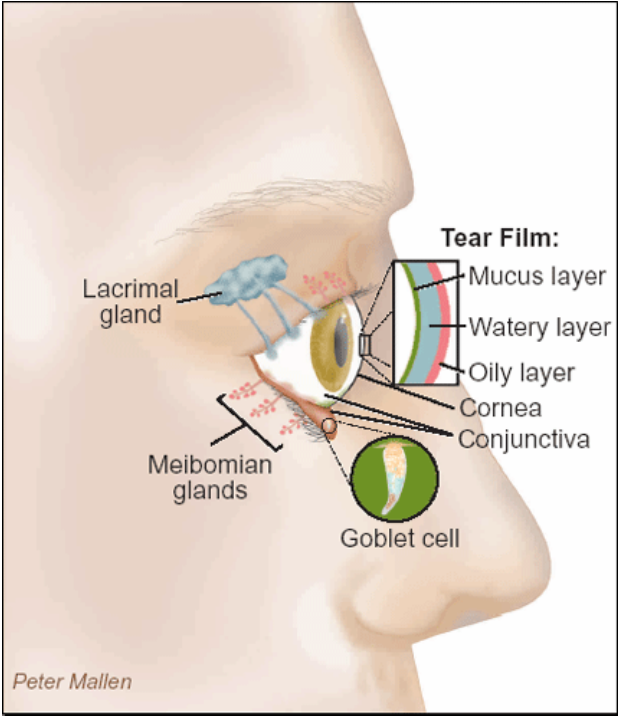
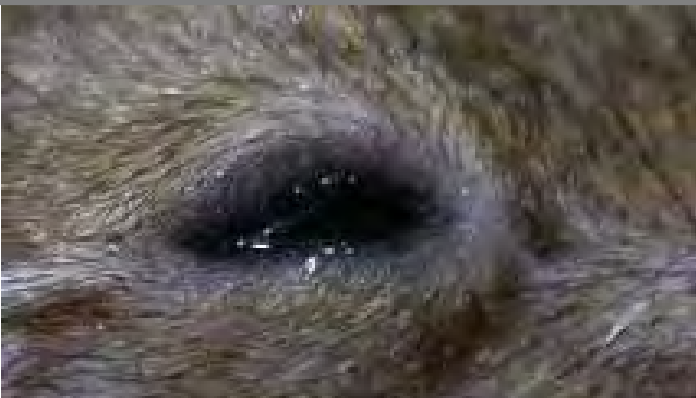
Which growth factors induce neovascularization of the dermis?



Notch1^{loxlox}

Notch1^{loxlox&K5CreERT}

Notch1^{loxlox&K14Cre}



eye

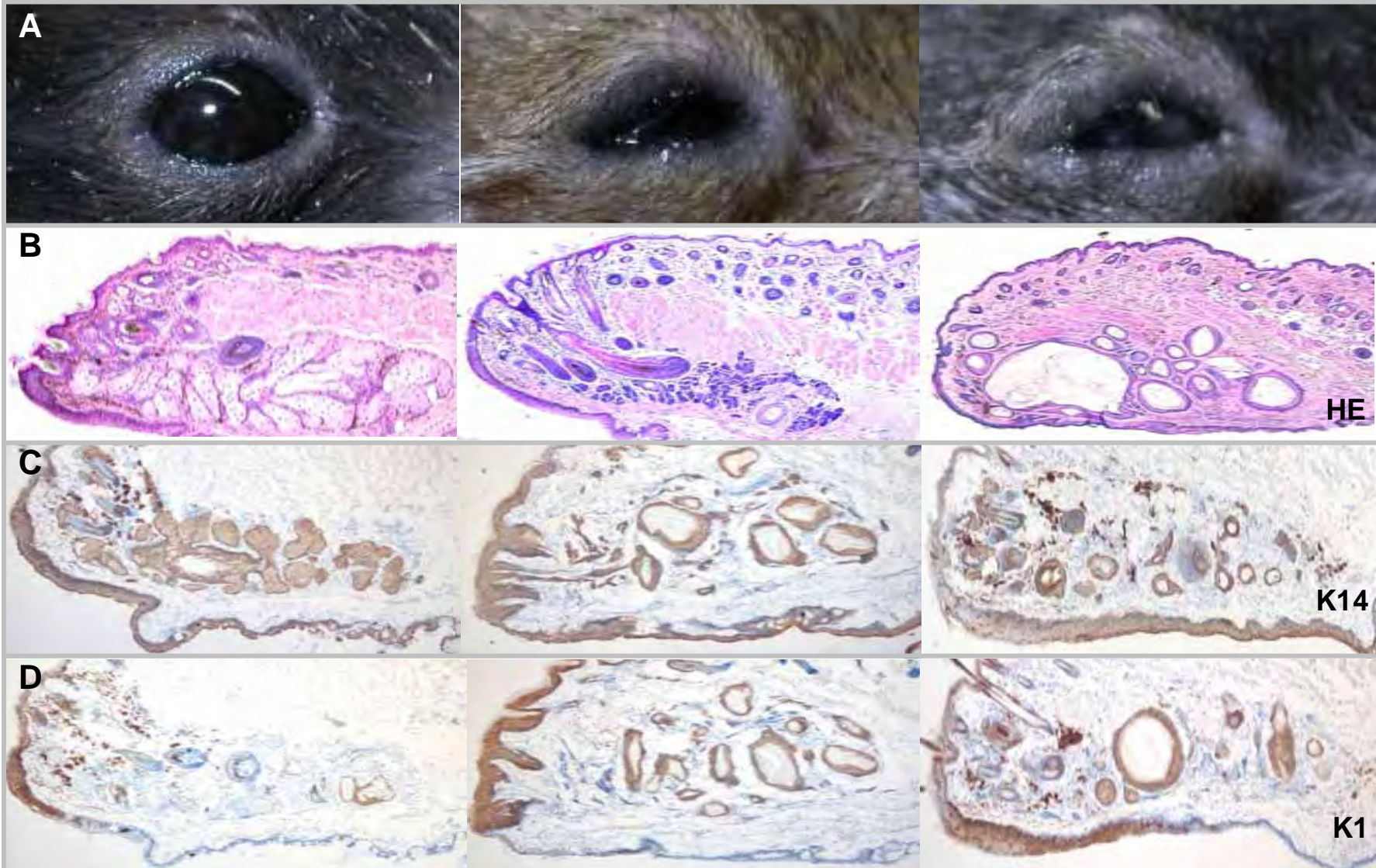
Meibomian gland

Notch1^{-/-} Meibomian glands form cysts

Ctrl

N1 K5Cre^{ERT}

N1 K14Cre

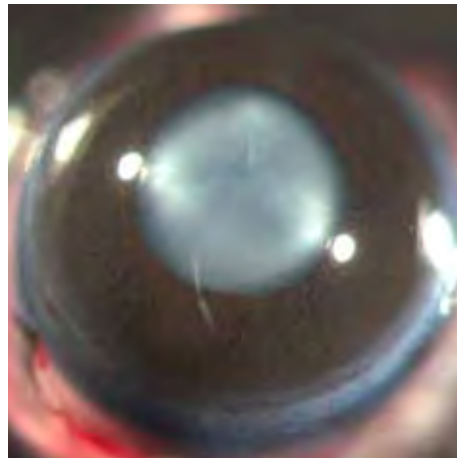
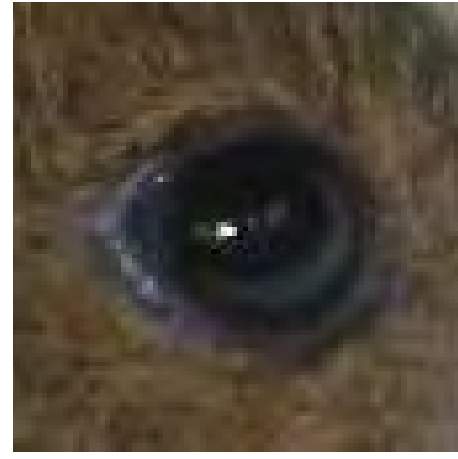


Only chronic irritation of the cornea results in differentiation of the Notch1-/- cornea into skin

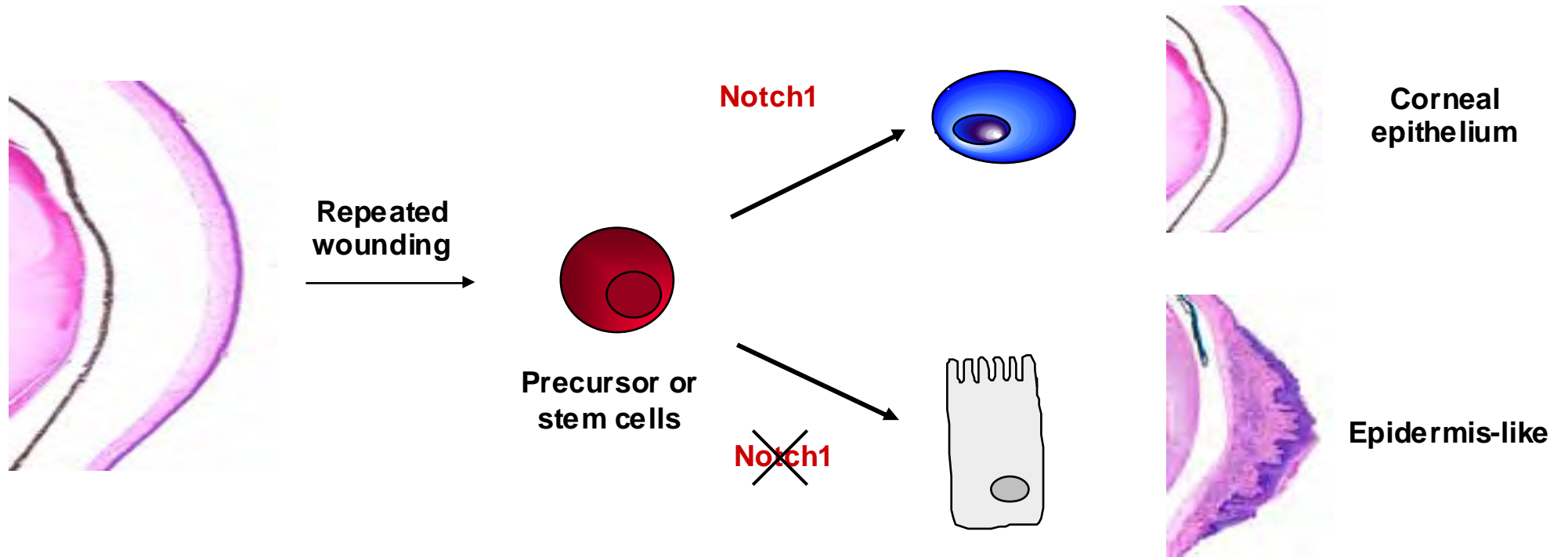
closed eye



open eye



Hypothesis

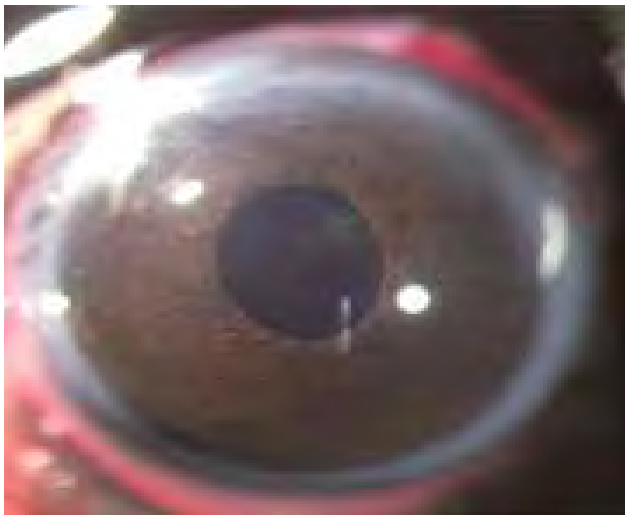
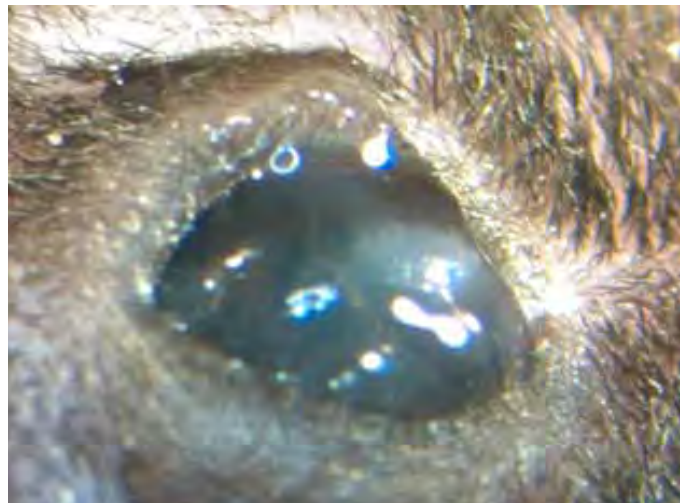


Notch1 deficient mice develop a vascularised corneal plaque after 3 consecutive woundingings

Control wounded



N1 lox/lox K14 Cre wounded (<2month)



Differentiation of the cornea into an epidermis-like structure after 3 surgical woundingings

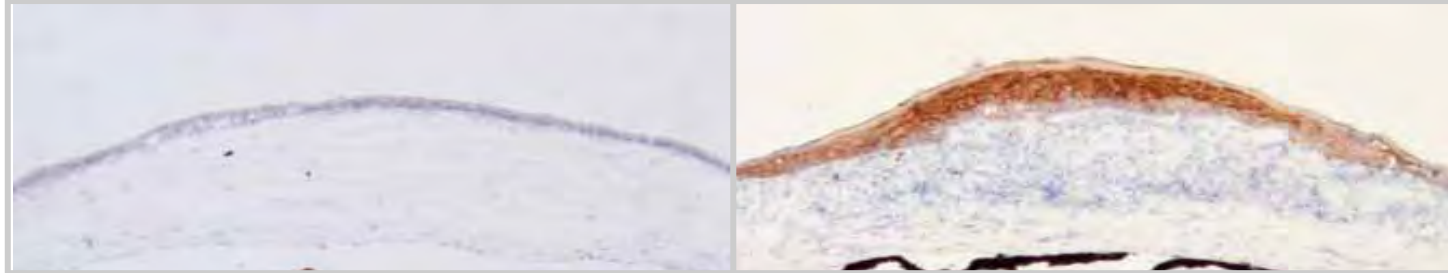
Control (wounded)

N1 lox/lox K14 Cre (wounded)

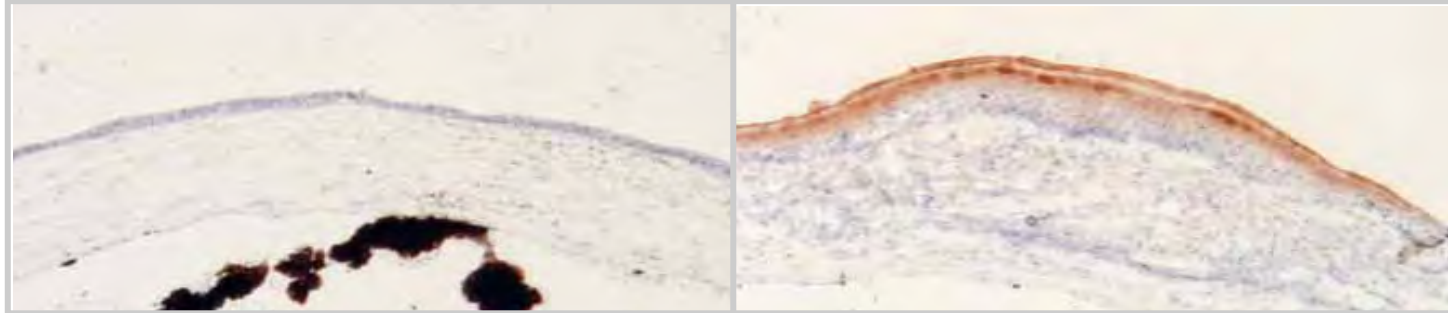
K14



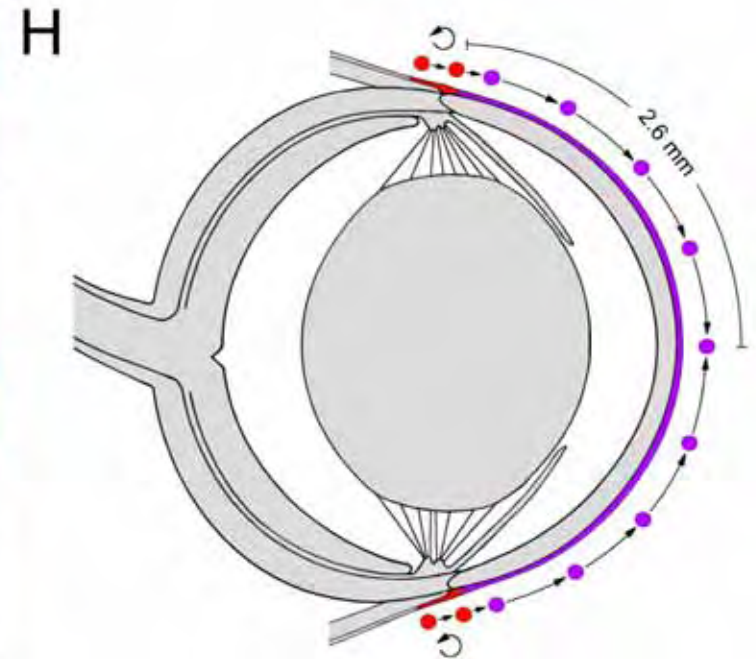
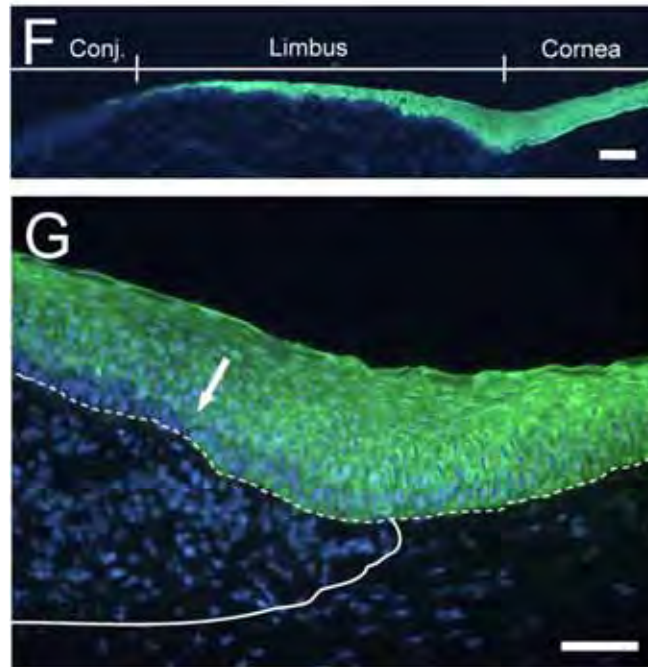
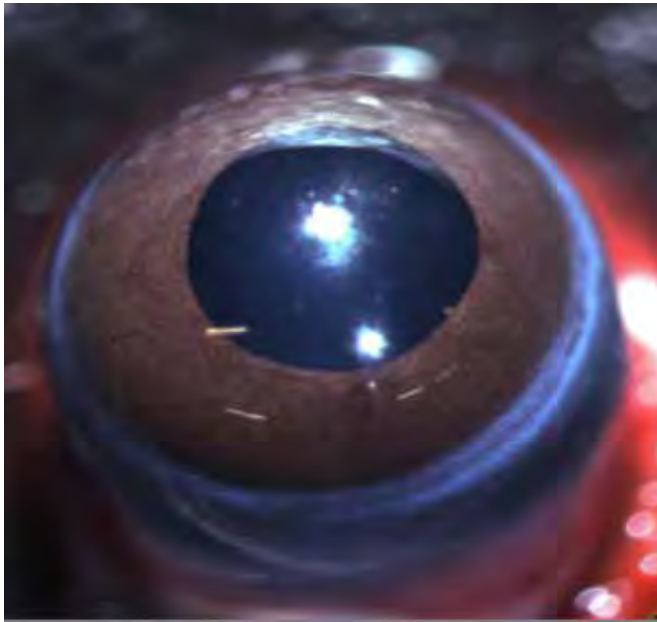
K1



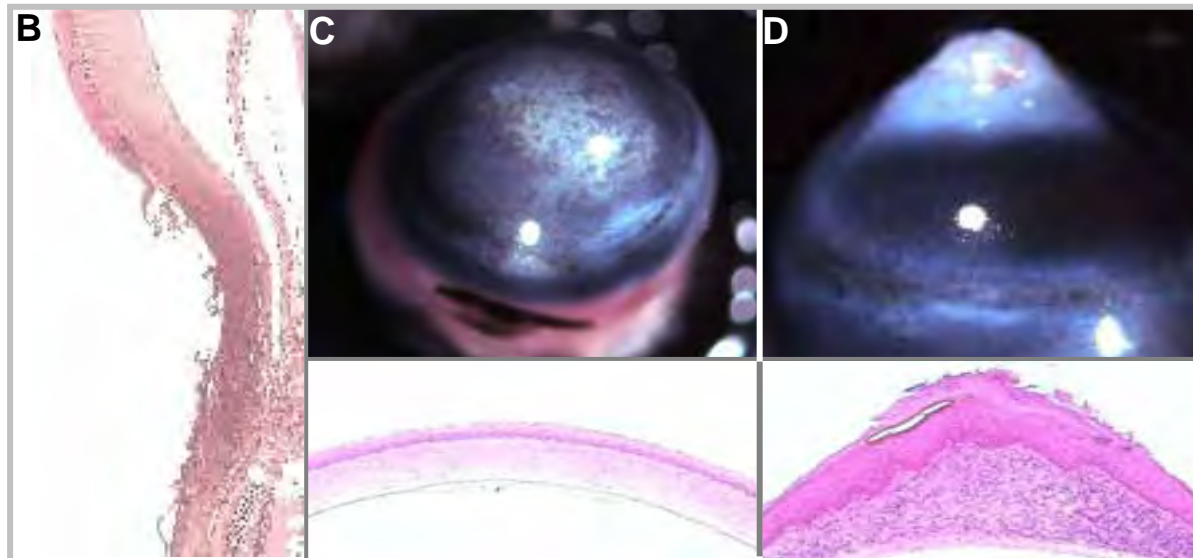
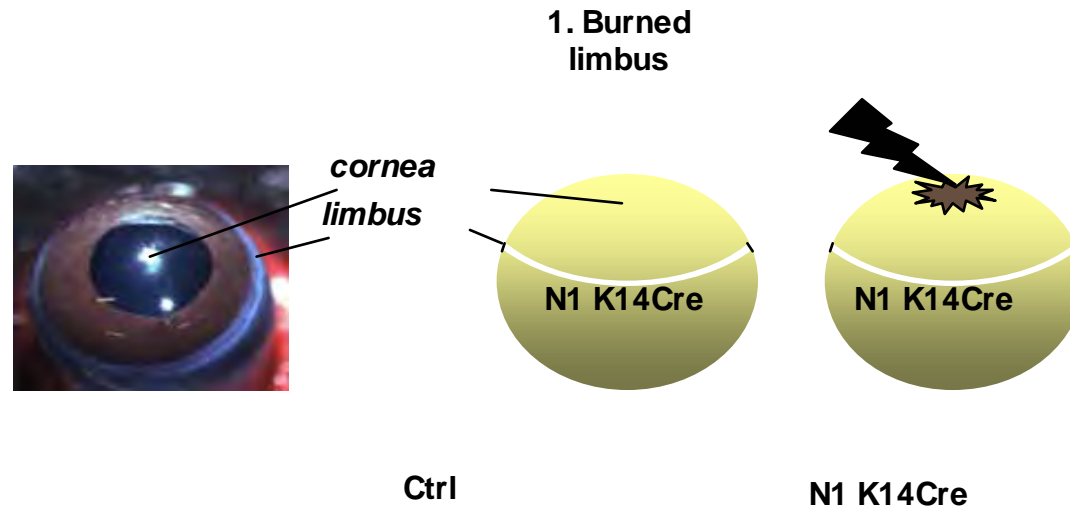
Loricrin



Corneal stem cells in the limbus are responsible for renewal of the cornea and wound healing



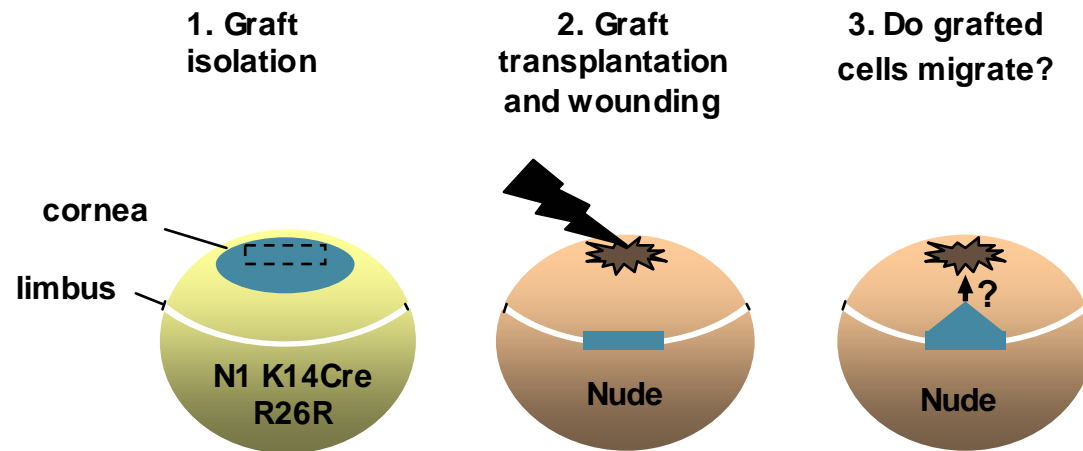
Notch1^{-/-} corneal stem cells within the central cornea can repair a wounded cornea only into skin-like epidermis



Notch1^{-/-} corneal stem cells are still migration competent



E



F

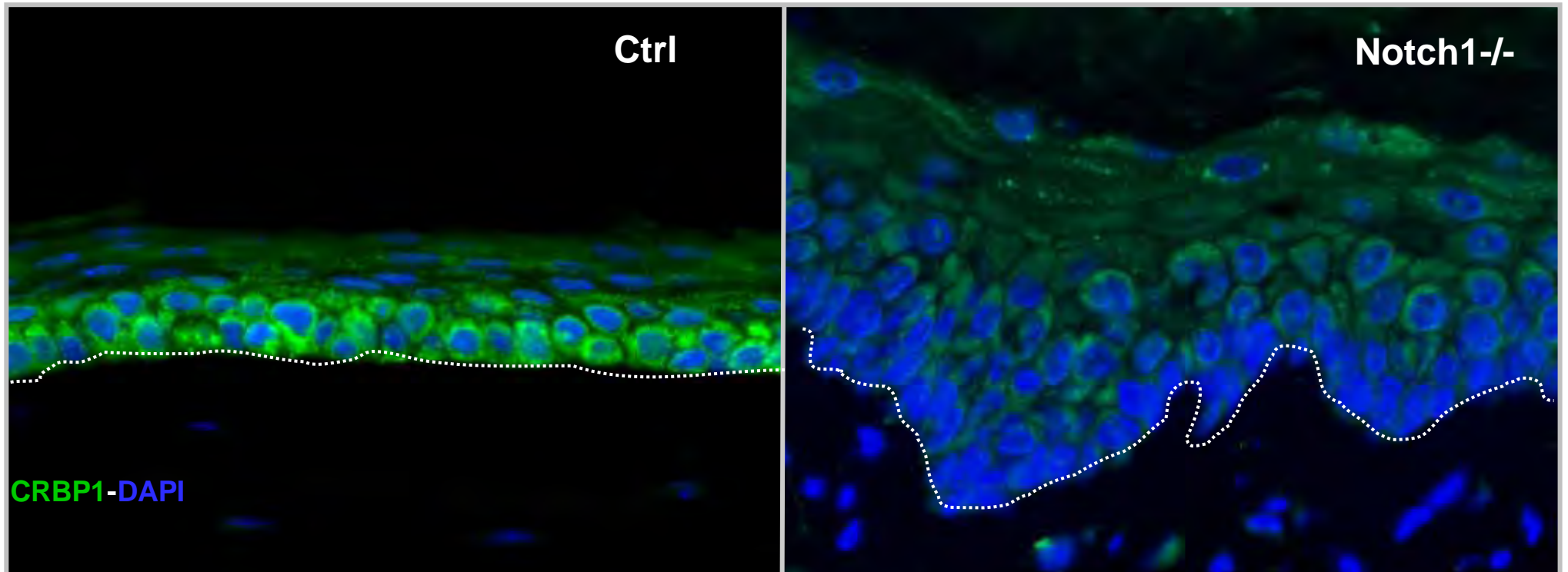


Xerophthalmia

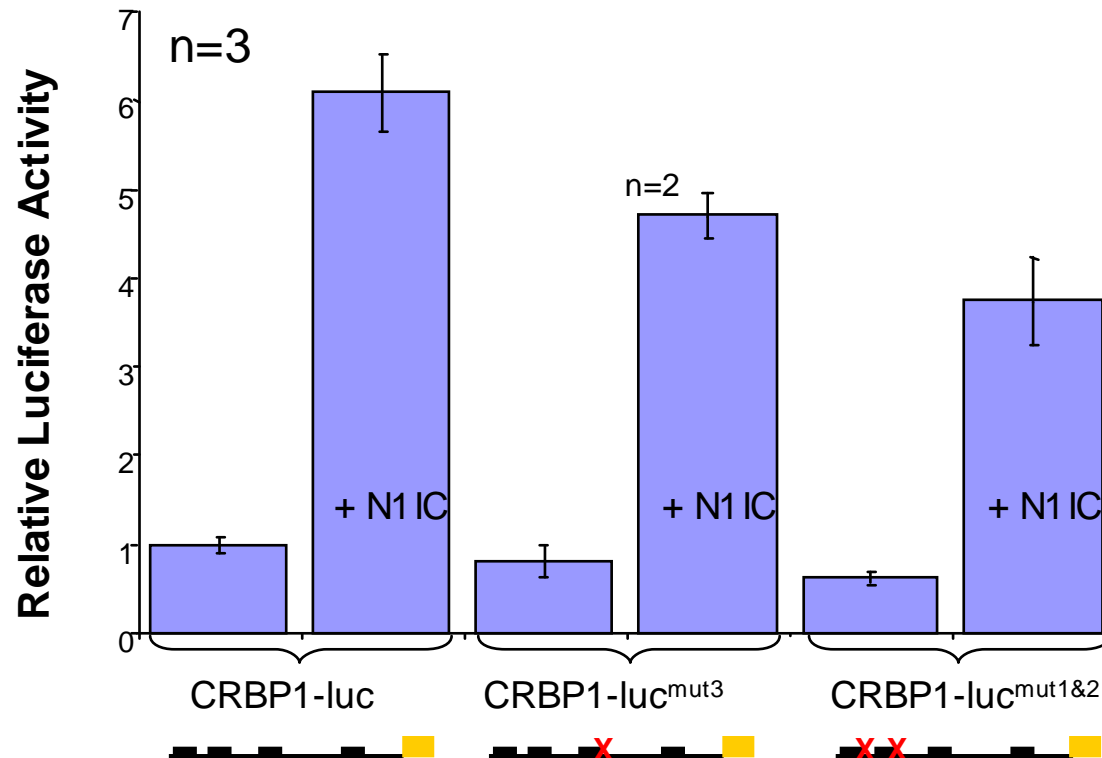
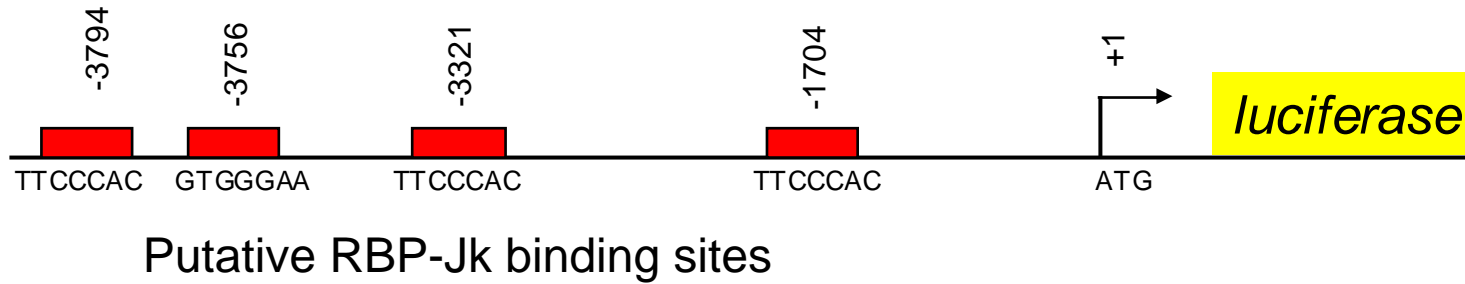


Due to vitamin A deficiency!

Loss of CRBP1 expression in the Notch1 deficient corneal epithelium



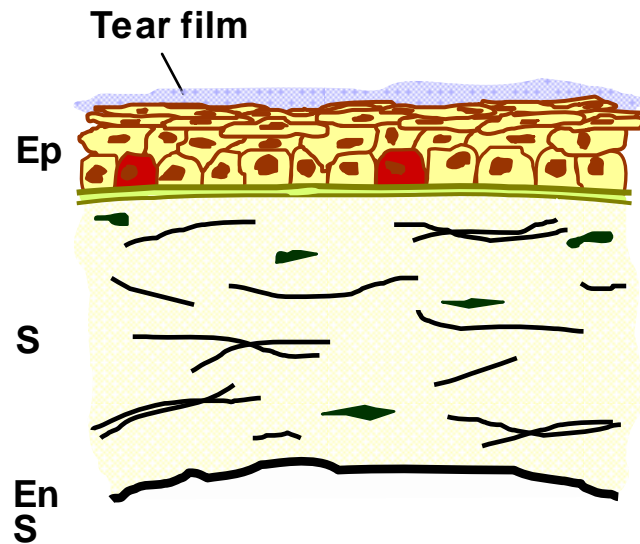
Notch1 IC activates the CRBP1 promoter



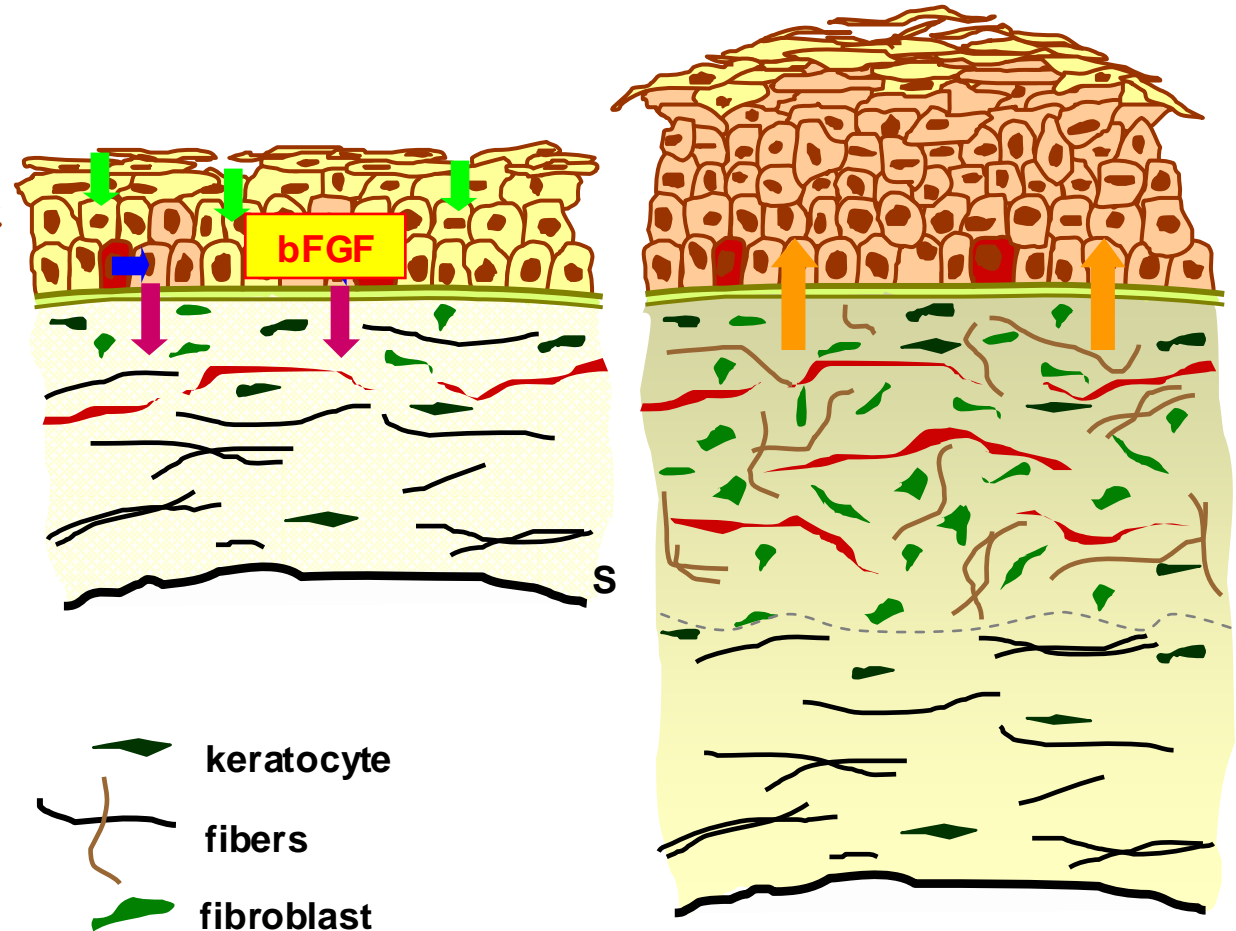
Andre Durham



Corneal cell fate is maintained during repair by Notch1 signaling via regulation of Vitamin A metabolism




A. With Notch1



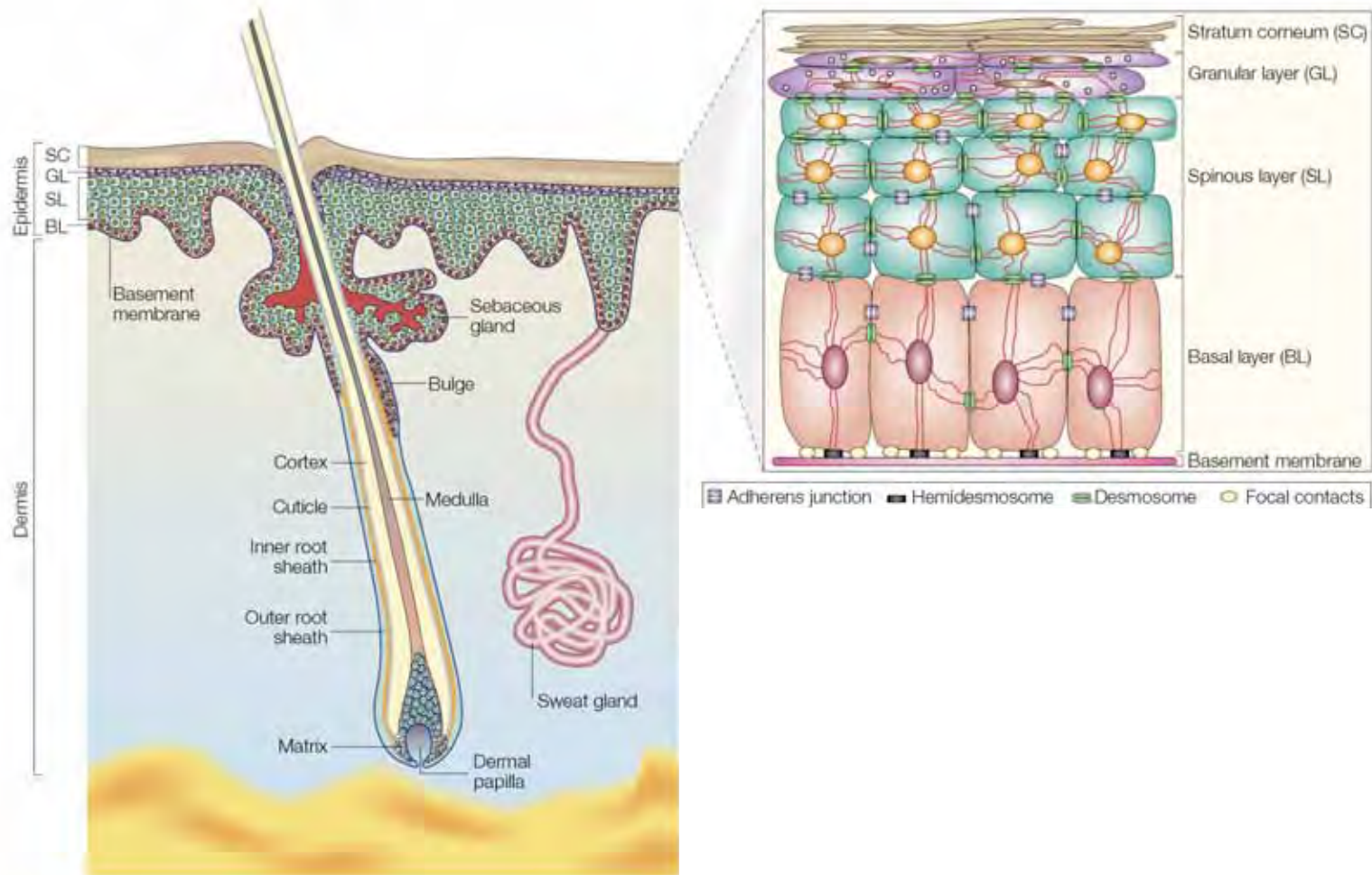
B. Without Notch1



-  stem cell
-  corneal keratinocyte

-  keratocyte
-  fibers
-  fibroblast

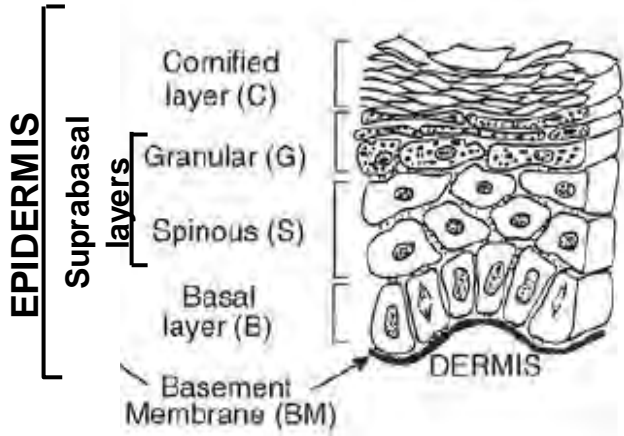
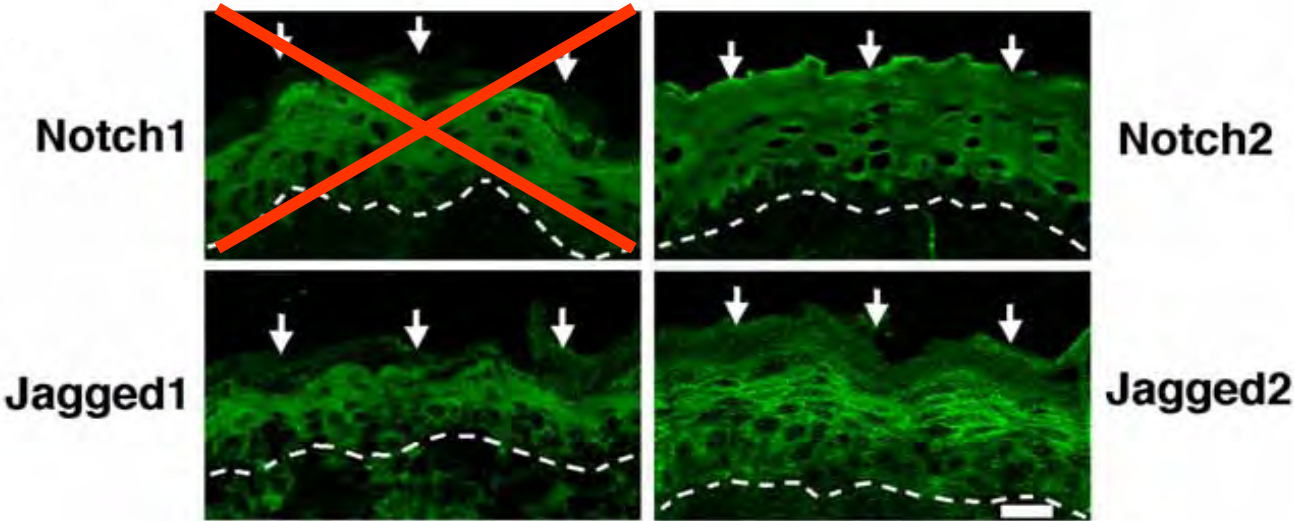
The skin and its appendages



Fuchs & Raghavan

Nature Reviews Genetics Vol. 8 March 2002

Notch in the skin



Notch1 is necessary for the maintenance of skin appendage: eg. hair, sweat and Meibomian glands

Notch1 deficient mice develop BCC-like tumors

Notch1^{lox/lox}



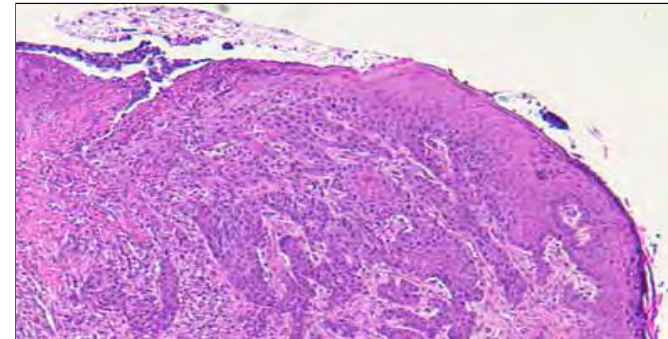
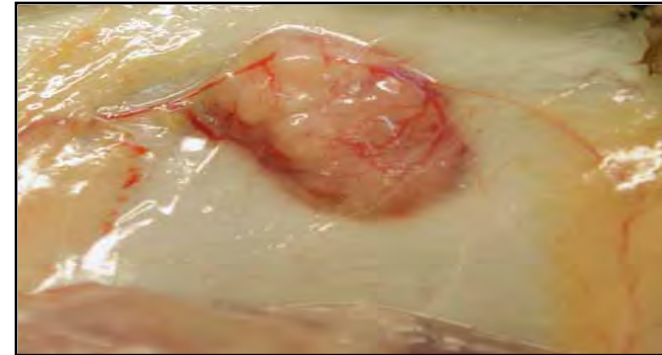
Notch1^{lox/lo}K14 Cre



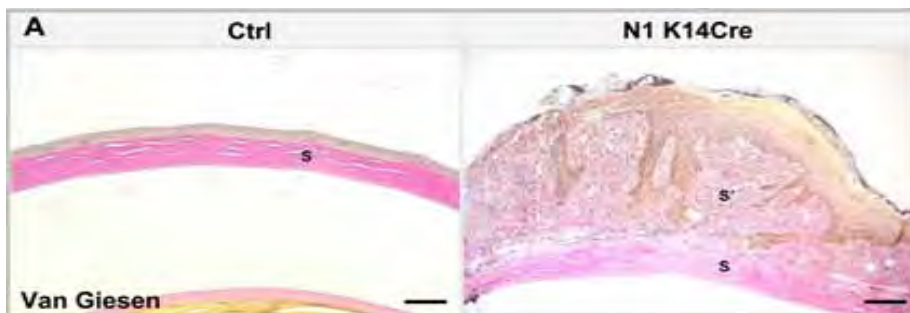
Notch1^{lox/lo}K5 CreERT



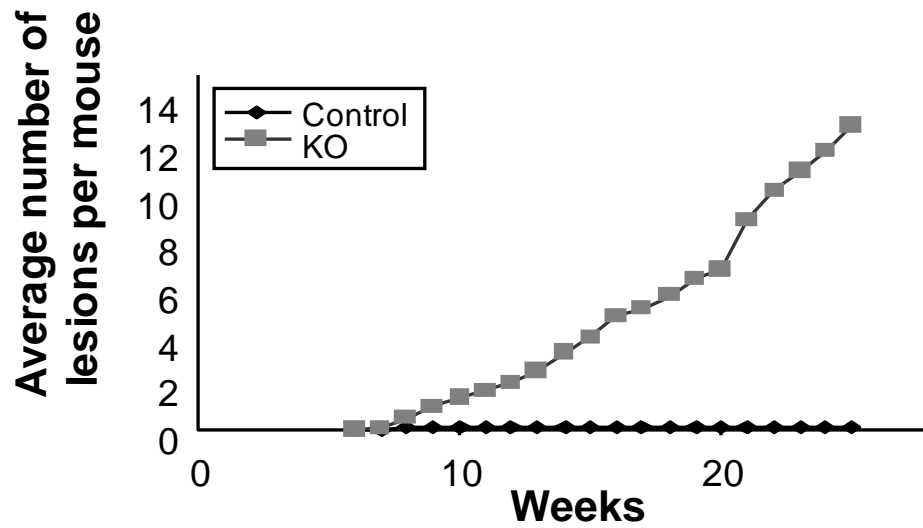
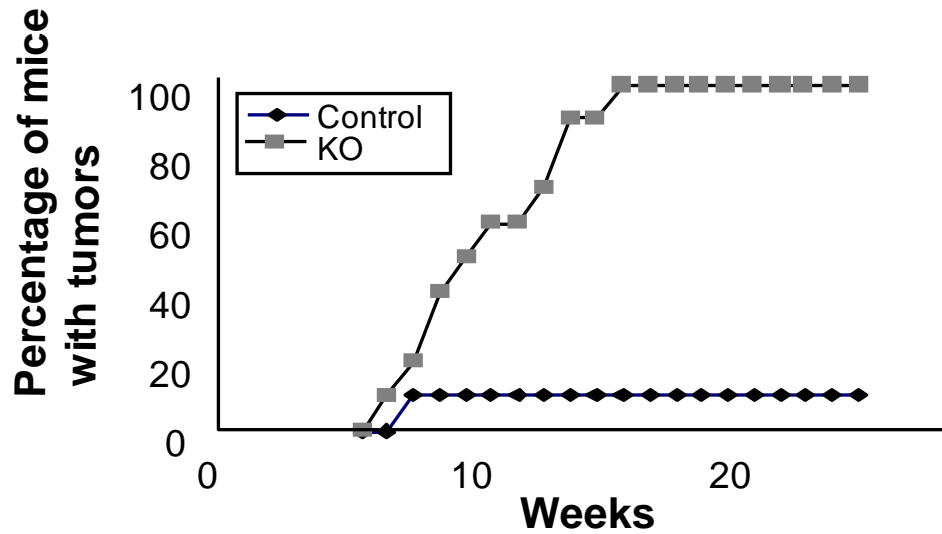
Notch1^{fl/fl} K5Cre^{ERT}



Notch1 deficient cornea adopts an epidermal cell fate upon repair



Loss of Notch1 facilitates chemically induced carcinogenesis



Tumor suppressor function of Notch1 in the mouse skin

Notch1 lox/lox K5 CreERT

