

# UV and Children's Skin

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## Epidemiological studies indicate that sunburns in childhood are associated with an enhanced risk of malignant melanoma later in life

e.g. Oliveria SA, Saraiya M, Geller AC, Heneghan MK, Jorgensen C. Sun exposure and risk of melanoma. Arch Dis Child. 2006 Feb;91(2):131-8

## Migration studies indicate that prepubertal high UV-exposure is associated with an enhanced risk of malignant melanoma and BCC later in life

e.g. Kricker A, Armstrong BK, English DR, Heenan PJ. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer--a case-control study. Int J Cancer. 1991 Jul 9;48(5):650-62

# UV-Exposure and number of Nevi in Childhood (The Hamburg School Children Study, n= 13,500)



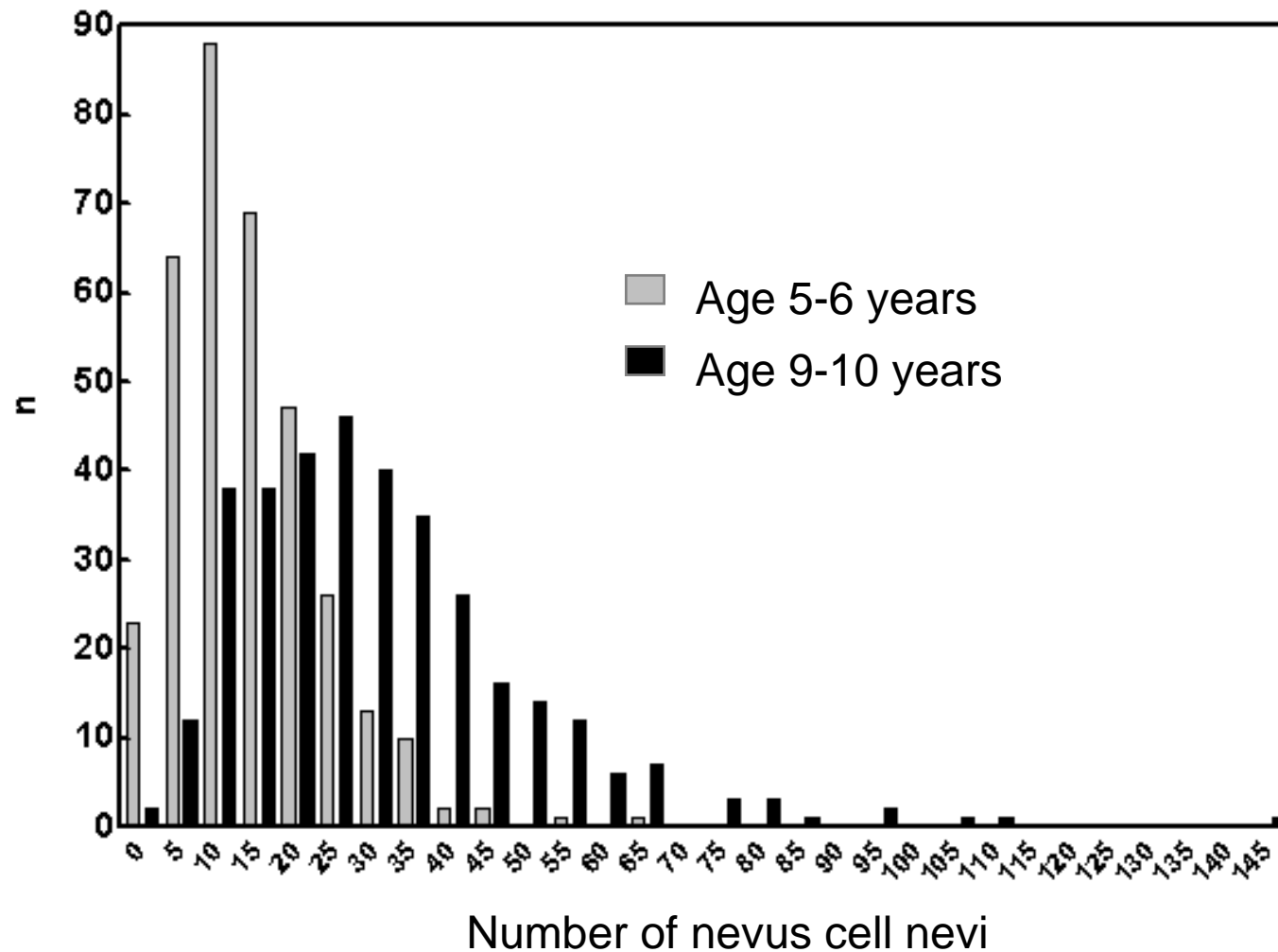
Number of severe sunburns	Number of Holidays in the South (<48°)					
	0	1	2	3	4	5+
<b>0</b>	9,79	11,11	11,70	12,84	13,53	<b>16,95</b>
<b>1</b>	11,12	11,92	14,24	13,67	12,80	13,80
<b>2+</b>	11,39	12,70	12,68	19,57	<b>30,48</b>	20,21

Dulon M, Weichenthal M, Blettner M, Breitbart M, Hetzer M, Greinert R, Baumgardt-Elms C, Breitbart EW. Sun exposure and number of nevi in 5- to 6-year-old European children. J Clin Epidemiol. 2002 Nov;55(11):1075-81

# UV-Exposure and number of Nevi in Childhood (The Hamburg School Children Study, Follow up)



Frequency distribution of nevus cell nevi



**Animal study: In contrast to adult mice neonatal mice do not show an immune-response after UVB-radiation. This might reduce the possibility to recognize and remove damaged cells.**

Wolnicka-Glubisz A, Damsker J, Constant S, Corn S, De Fabo E, Noonan F. Deficient inflammatory response to UV radiation in neonatal mice. *J Leukoc Biol.* 2007 Jun;81(6):1352-61

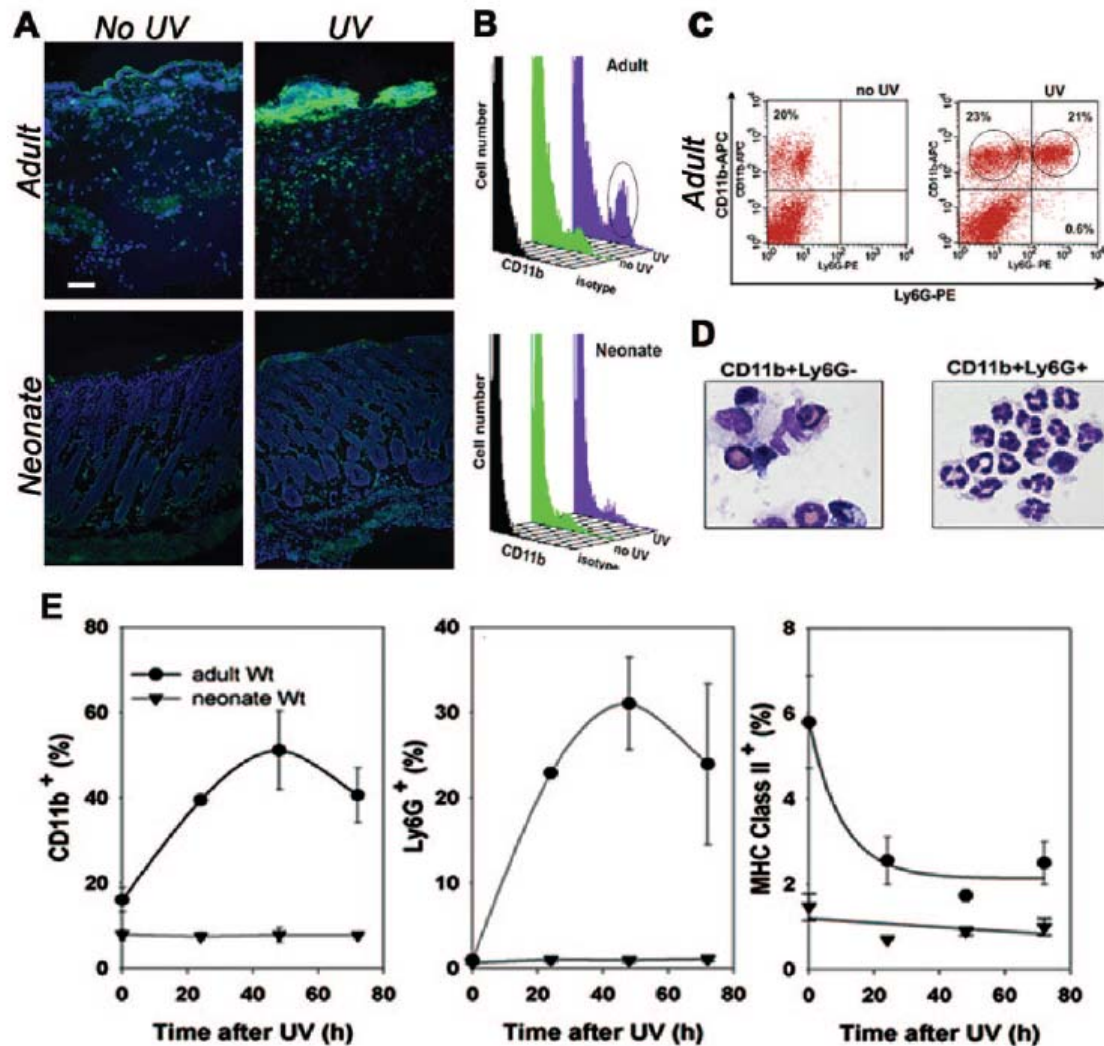


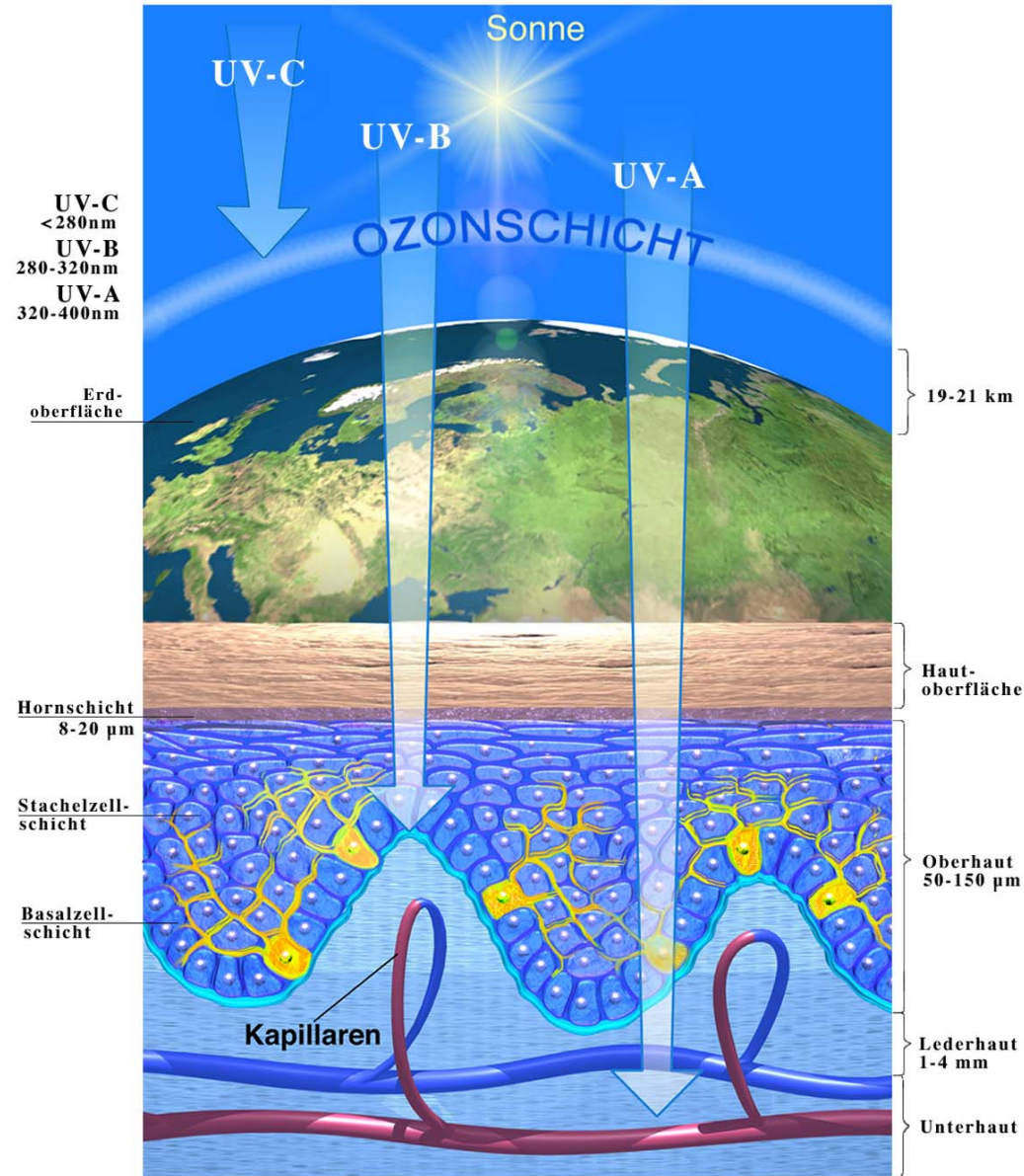
Fig. 2. UV irradiation induces infiltration of CD11b<sup>+</sup>Ly6C<sup>+</sup> cells in adult but not in neonatal mouse skin. (A) CD11b<sup>+</sup> cells (green, upper right panel) infiltrate adult but not neonatal FVB mouse skin 48 h after UV irradiation with F40 sunlamps as for Figure 1. Original bar represents 0.1 mm. (B) FACS analysis of disaggregated skin cells from adults and neonates confirms adult CD11b<sup>+</sup> infiltrate (circled). (C) FACS analysis of unirradiated (left panel) and UV-irradiated (right panel) adult skin double-stained for CD11b and Ly6G. In unirradiated skin, all CD11b<sup>+</sup> cells were Ly6G<sup>-</sup> (left panel), but after UV, CD11b<sup>+</sup>Ly6G<sup>-</sup> and CD11b<sup>+</sup>Ly6G<sup>+</sup> cells were detected (right panel). (D) Cytopsin of FACS-sorted cells from UV-irradiated, adult animals. CD11b<sup>+</sup>Ly6G<sup>-</sup> cells (left panel) were a mixed population including lymphocytes, eosinophils, and large mononuclear cells, whereas CD11b<sup>+</sup>Ly6G<sup>+</sup> cells (right panel) were neutrophils. (E) Time course, quantitated by FACS analysis, of infiltrating CD11b<sup>+</sup> and Ly6G<sup>+</sup> cells and loss of MHC Class II cells after UV. In adults, significant influx of CD11b<sup>+</sup> and Ly6G<sup>+</sup> cells was observed ( $P < 0.001$  compared with unirradiated control) and was maximal 48 h after UV, whereas loss of MHC Class II ( $P < 0.01$ ) reached a plateau by 24 h. In neonates, no significant changes in CD11b<sup>+</sup>, Ly6G<sup>+</sup>, or MHC Class II cells were detected. The data represent the mean of three to five independent experiments  $\pm$  SEM.

# Is there any difference between children's skin and adult skin?

- There is no difference in sunburn sensitivity MED\*
- There is a difference in thickness due to structure of the rete ridges
- There is a difference in contribution of vellus, intermediate and terminal hair type

\*Cox NH, Diffey BL, Farr PM. The relationship between chronological age and the erythematous response to ultraviolet B radiation. Br J Dermatol. 1992 Apr;126(4):315-9



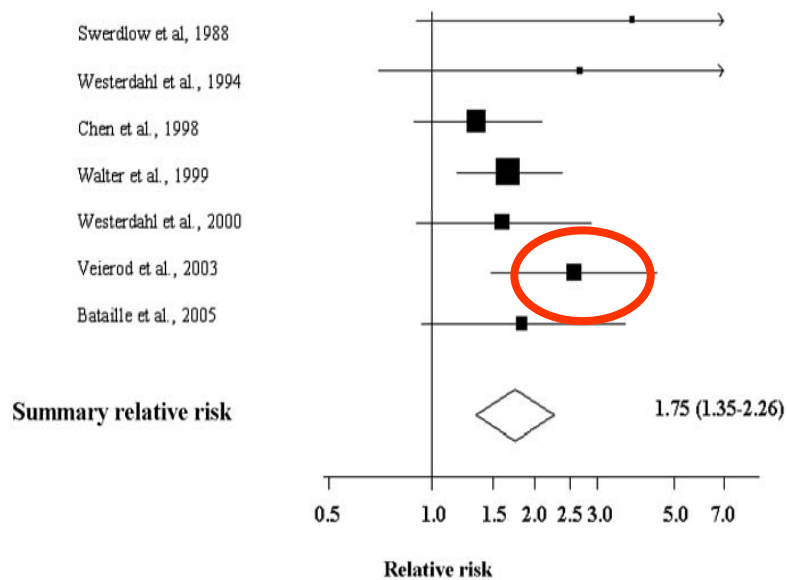




# The sunbed problem

# Sunbed use and melanoma risk

## Studies



Start of use of sunbeds  
Before the age of 35  
Increase risk of melanoma  
Later in life by

75 %

# Some numbers from Germany 2008

SUN study (Sunbed-Use: Needs for Action-Study 2008)

Diehl et al., Int. J. Public Health (2010)

Schneider et al. Acta Derm. Venerol. (2009)

Börner, F. et al. Gesundheitswesen, (2009)

User prevalence* (18-45 years)	time
46.7 %	ever
18.1 %	Last 6 month
17.4 %	Last 3 month
12.5 %	Last month (1-10 times)

Average current user (last 12 month)

**Extrapolation for whole Germany: 14 Mio of about 30 Mio of 18-45 years old have ever been exposed to sunbed UV. About 3 Mio started (first time) ≤ 18 years of age !**

Exposer time (mean): 13.6 min ± 4.3

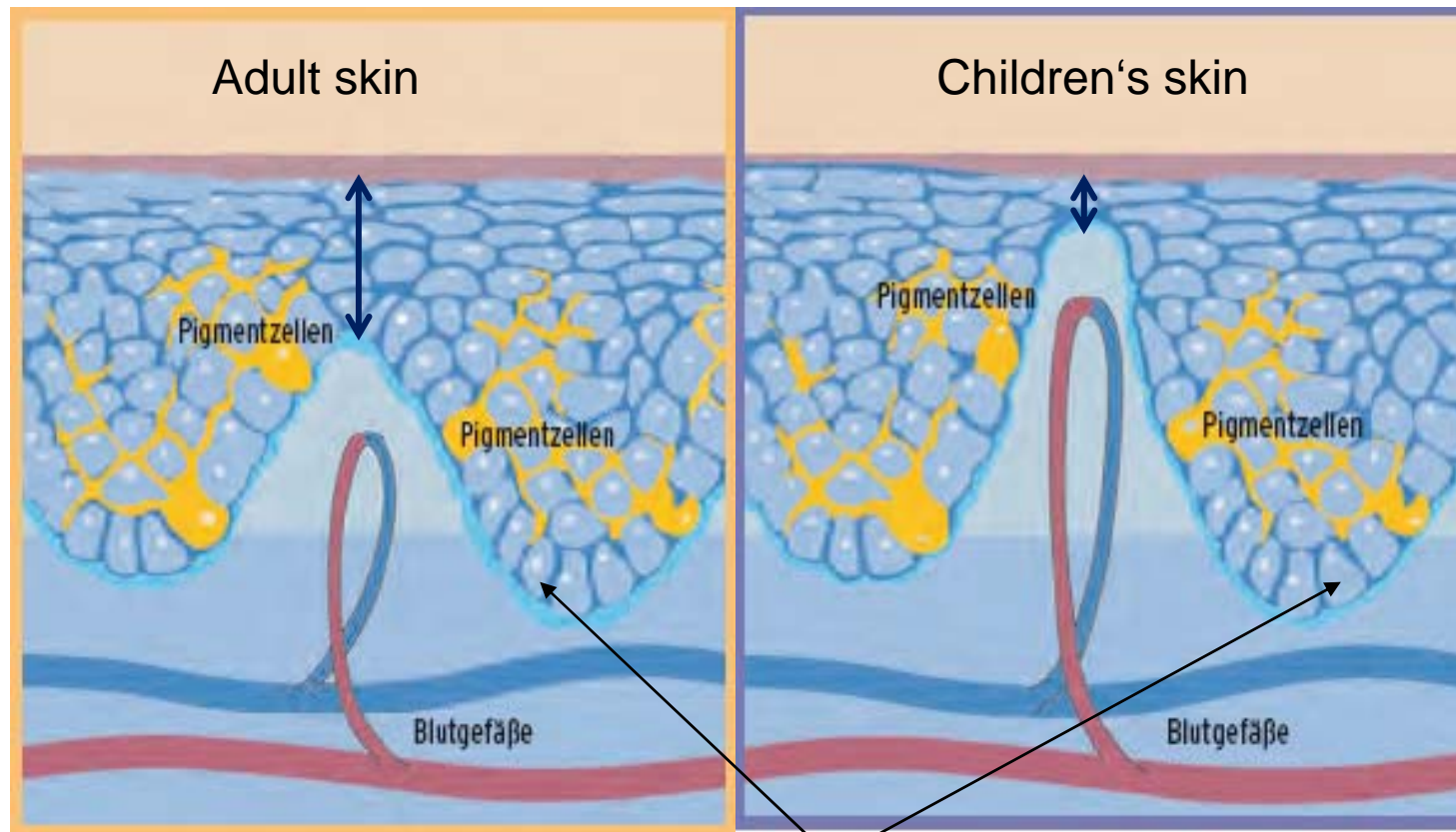
\* City of Mannheim (327.000 Inh.), southern Germany, according to telefon interviews

# Some numbers from UK

Thompson C.S. et al. , BMJ (2010): Sunbed use in children aged 11-17 in England: face to face quota sampling surveys in National Prevalence Study and Six Cit Study

- Already 6% of those aged 11-17 had used a sunbed (8% in girls, 3.5 % in boys)
- Sunbed use gradient from „north“ to „south“  
(11% vs 4.2 %)
- In six cities Liverpool and Sunderland (20% and 15.6 %) showed the highest use (with rates especially high in girls (15-17 years or from lower social grades
- 23 % of children used a sunbed at home

# Different structure of the rete ridges



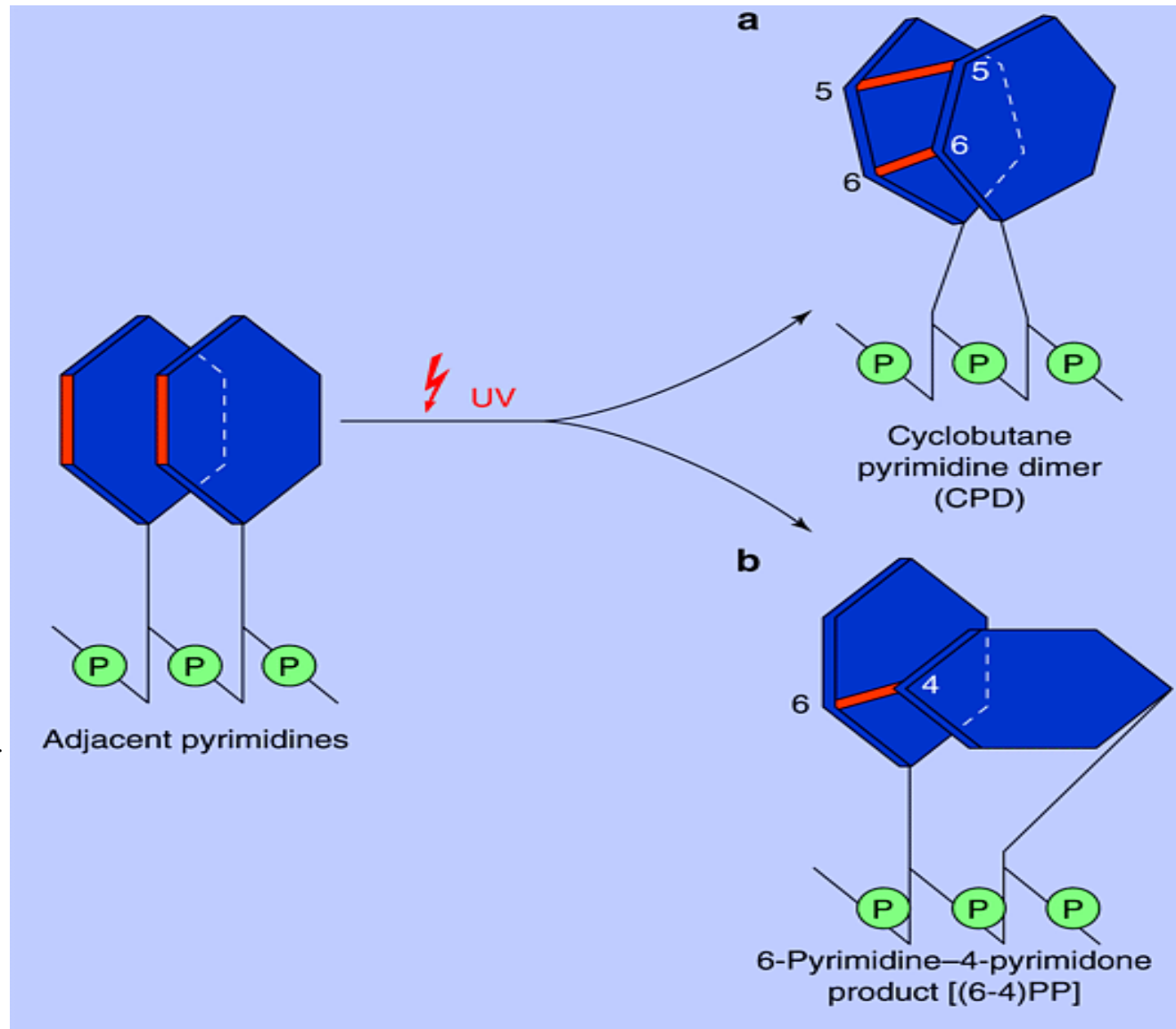
Basal layer containing epidermal stem cells and melanocytes

# Consequences?

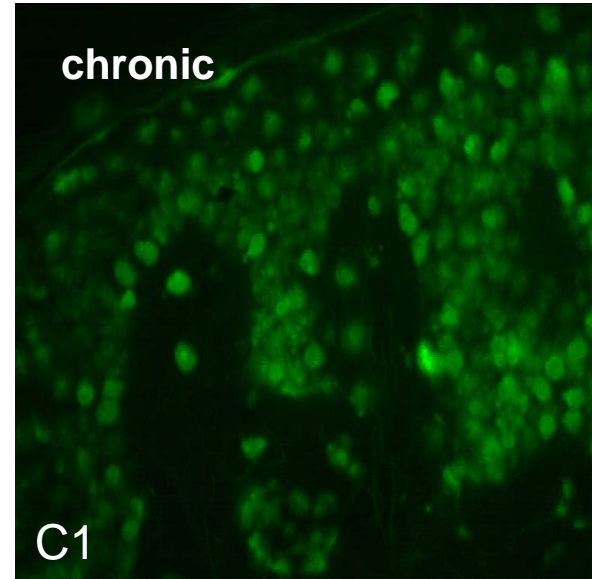
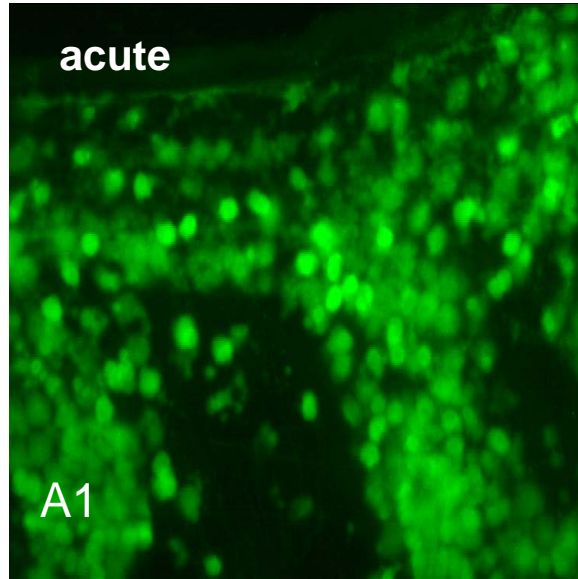
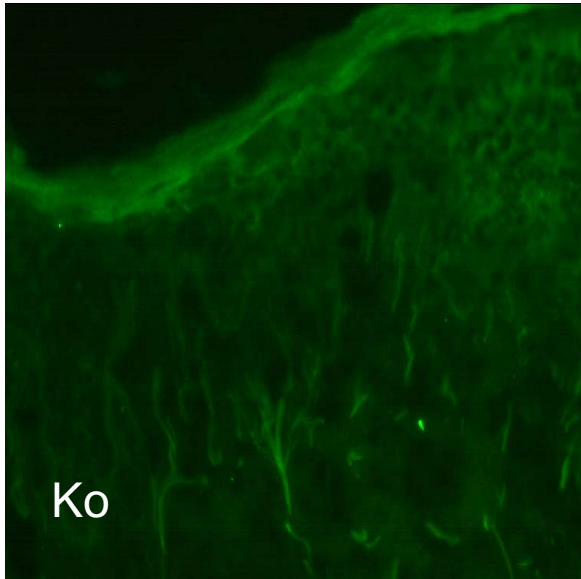
- The basal layer of the epidermis is more exposed to UV-irradiation on the base of the rete ridges in children's skin as compared to adult skin.
- Interfollicular epidermal stem cells as well as melanocytes are located in the basal layer of the epidermis
- Epidermal stem cells are supposed to be the most important target for the carcinogenic effect of UV-irradiation related to non-melanocytic skin cancer



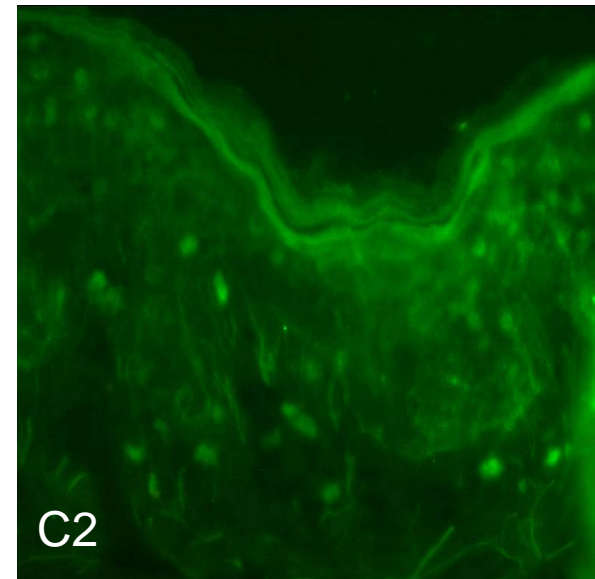
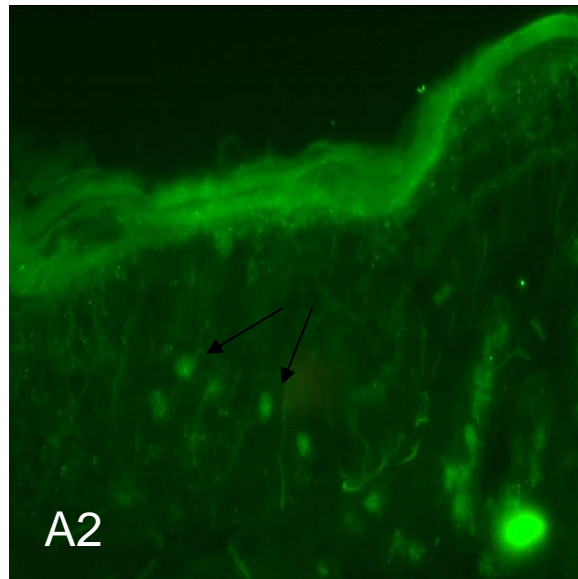
# UV-induced specific DNA lesions



Trends in Molecular  
Medicine, 5, 86-94,  
1998

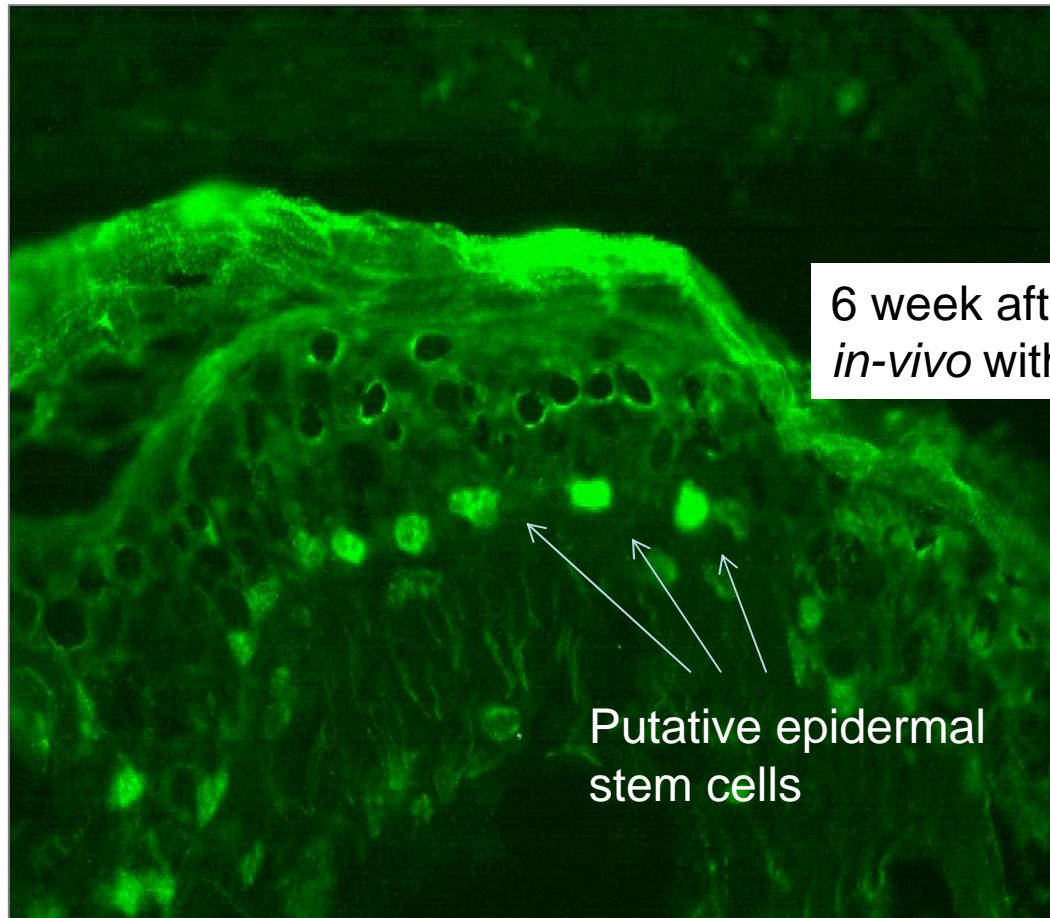


Proband 3\_03  
Skin type I-II  
IMED = 350 J/m<sup>2</sup>



After 6 weeks

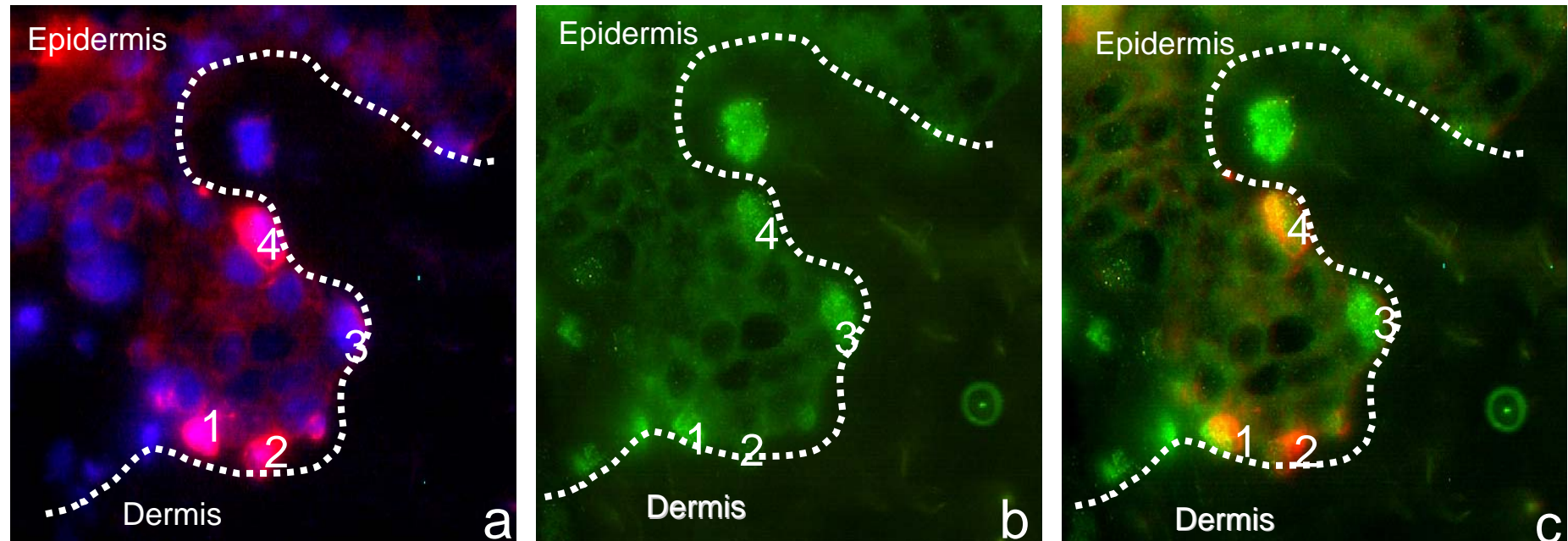
# Cyclobutane-Pyrimidine-Dimer retaining basal cells (CRBC) are induced by UV-irradiation



6 week after irradiation human skin  
*in-vivo* with SSR, 1.5 MED

Putative epidermal  
stem cells

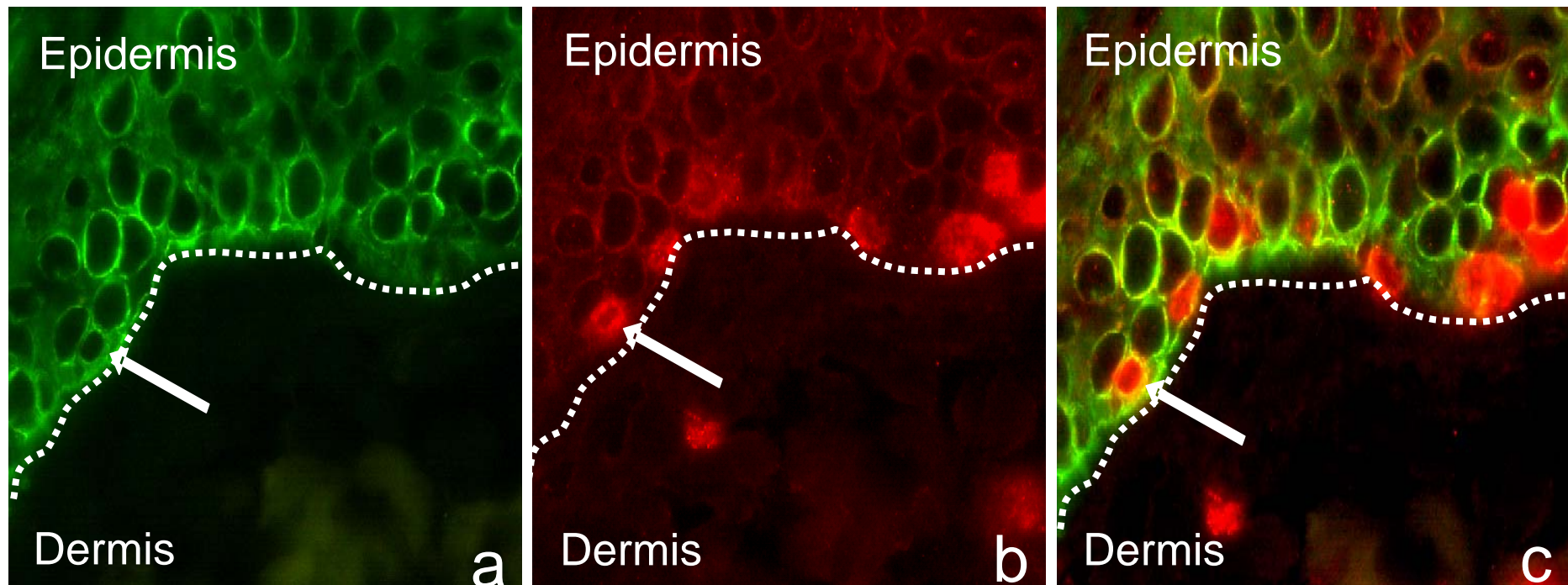
## About 80% of CRBCs are melanocytes



Skin section with CRBCs: a) melanocyte-marker (Melan-A)(red);nuclei are labelled with Dapi, b) anti-CPD-antibody (green) c) merge of a) and b). (1) and (4): melanocytic CRBC, (2) undamaged melanocyte, (3) non-melanocytic



## About 20% of CRBCs are keratinocytes



Skin section with CRBCs stained with a) an anti-cytokeratin-antibody (red), b) an anti-CPD-antibody (green) c) merge of a) and b).

# Consequences?

- The special structure of the rete ridges in children's skin can lead to enhanced induction of melanocytic and keratinocytic CRBC at the base of the rete ridges
  
- Due to the special structure of the rete ridges in children's skin melanocytic precursor cells that are supposed to be located in the dermis\* are at higher risk to be exposed to UV-radiation

\* Li L, Fukunaga-Kalabis M, Yu H, Xu X, Kong J, Lee JT, Herlyn M. Human dermal stem cells differentiate into functional epidermal melanocytes. J Cell Sci. 2010 Mar 15;123(Pt 6):853-60

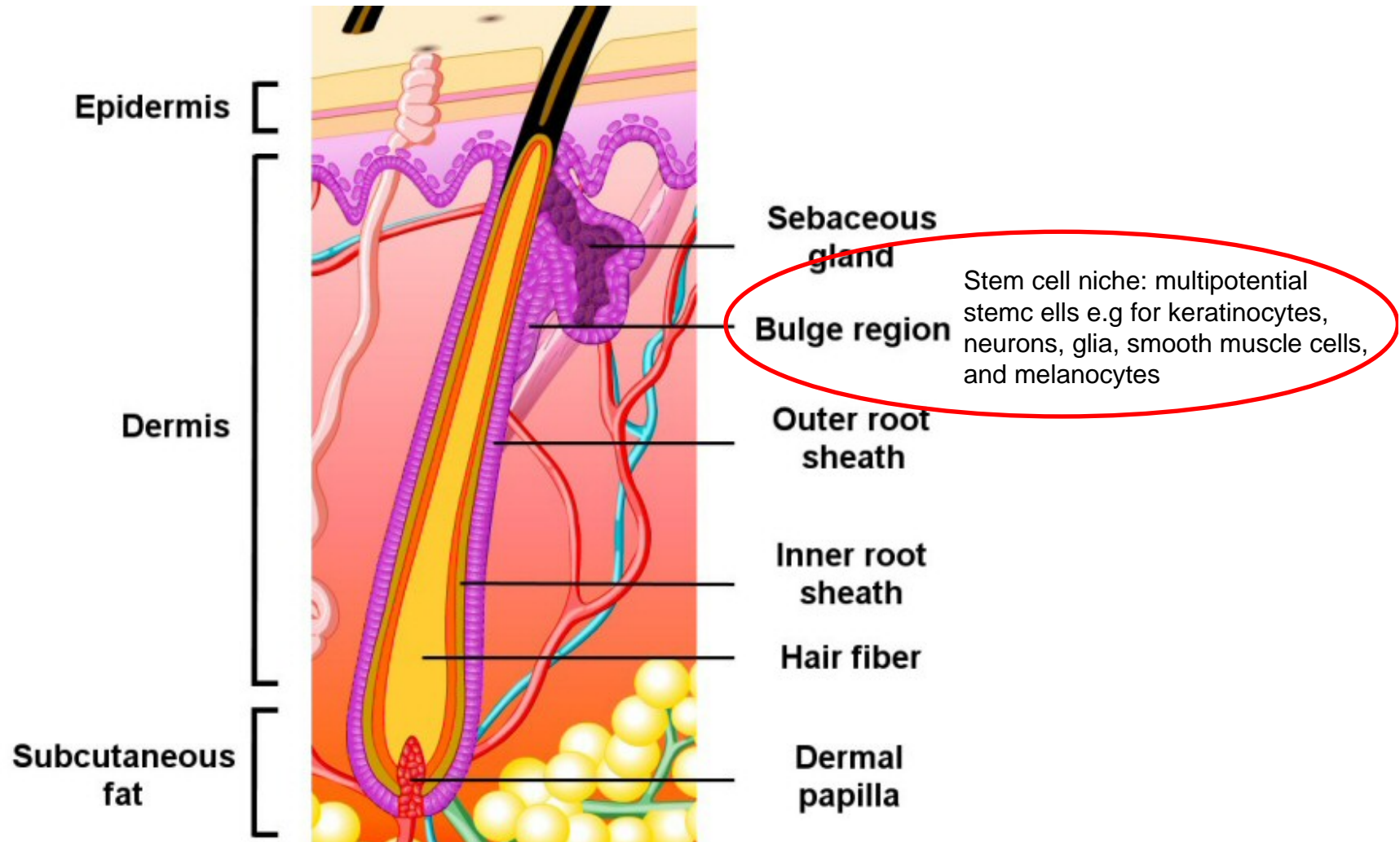


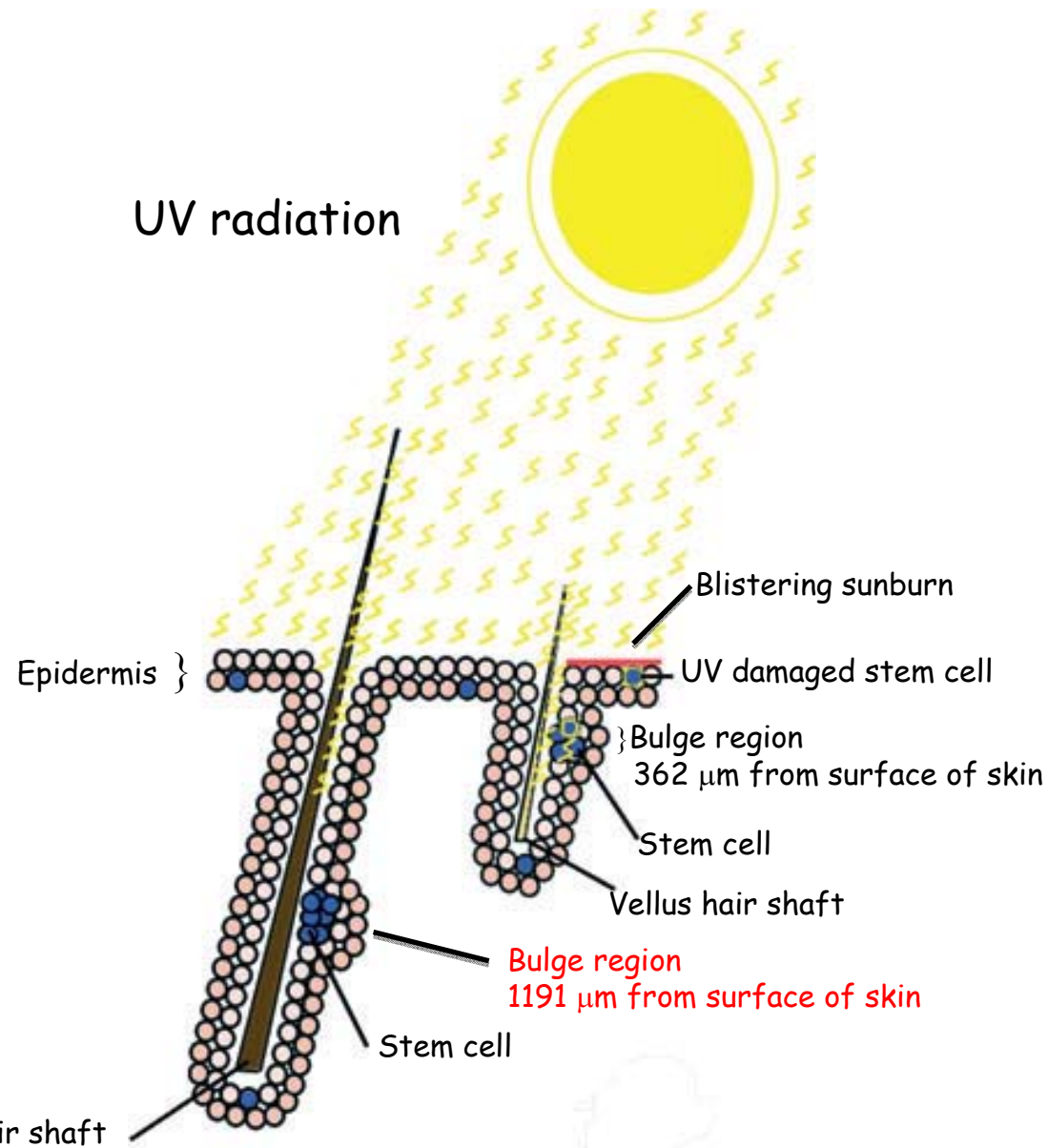
# Difference in contribution of vellus, intermediate and terminal hair type

- At birth all hair follicles are present, no further follicles will develop throughout life
- Prepubertal children have a much higher proportion of vellus hair compared to adults
- During puberty in some areas of the body vellus hair develop into terminal hair with follicles relocated deeper within the skin

*Garcia, A.M.G. et al.: Melanoma: is hair the root of the problem? Pigment Cell Melanoma Res., 24, 110-118 (2011)*

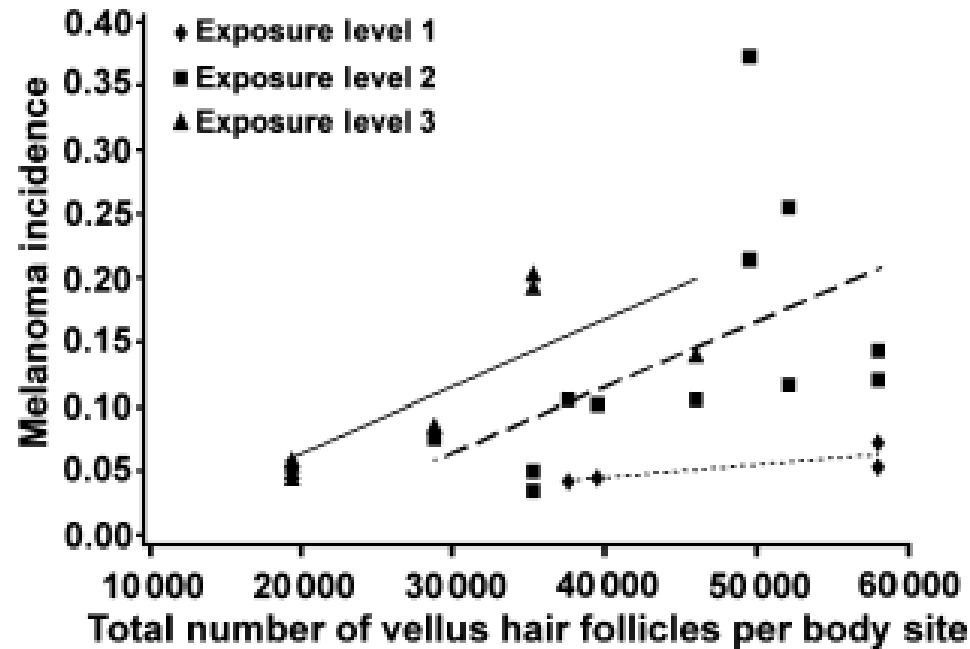
# Consequences?





Garcia, A.M.G. et al.: Melanoma: is hair the root of the problem? *Pigment Cell Melanoma Res.*, 24, 110-118 (2011)

A positive correlation between number of vellus hair follicles and melanoma incidence is described by Garcia et al.



**Figure 3.** Scatter plot of melanoma incidence versus total number of vellus hair follicles per body site. Linear regression lines are superimposed on the scatter plot and correspond to regression results for sun exposure level 1 (minimum lifetime), level 2 (low lifetime, mainly intermittent), and level 3 (high lifetime, mainly intermittent).

Garcia, A.M.G. et al.: *Melanoma: is hair the root of the problem?* *Pigment Cell Melanoma Res.*, 24, 110-118 (2011)

# Conclusion

- There is no difference in UV-sensitivity between children's and adult skin in relation to sunburn
- Structural differences can lead to higher UV-exposure of epidermal stem cells and melanocytic precursor cells, potentially enhancing the skin cancer risk in later life
- In children vellus hair is the primary hair type with a probable higher UV-exposure of multipotential stem cells in the bulge region of the hair follicle
- Since during puberty the vellus hair develop into terminal hair with follicles located deeper and thus more protected in the skin these data for the first time can explain the data of migration studies.

# Future aspects

- Comprehensive data related to the UV-sensitivity of children's skin are still lacking
- In vitro models for children's skin have to be developed to get more basal data like e.g. DNA-repair capacity
- The involvement of interfollicular and follicular epidermal stem cells as well dermal stem cells in the development of malignant melanoma and non-melanocytic skin cancer has to be investigated



Thank you