



THE EFFECTS OF REPEATED SUB-ERYTHEMAL EXPOSURES OF UVR ON HUMAN IMMUNITY

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Photoimmunosuppression

ULTRAVIOLET RADIATION

DNA damage

**Isomerisation of
UCA *trans* to *cis***

Alterations in cutaneous mediators: cytokines, PGE₂, cyclooxygenases, ...

Depletion of Langerhans cells from epidermis

Generation of antigen-specific T regulatory cells and modulation of T cell response

SUPPRESSION OF CONTACT HYPERSENSITIVITY RESPONSE

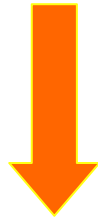


Objectives of the studies

To learn the effect of repeated sub-erythema
irradiation of SSR/UVB on human immunity

- LCs
- Cytokine, PGE2 and cyclooxygenases alterations
- CHS response

Threshold of UV doses which triggers the cascade of immunological changes



Question:
Do photoprotection and photoadaptation exist?

Whole body irradiation

SSR (1,2 SED)

10 days 0.7 MED UVB
(n=30)

2 days
(n=34)

10 days
(n=33)

30 days
(n=34)

Local irradiation (buttock skin)

3 MED UVB (n=30)

4 MED UVB (n=10)

Photoadaptation

10 days 1.2 SED SSR + 3
MED UVB (n=30)

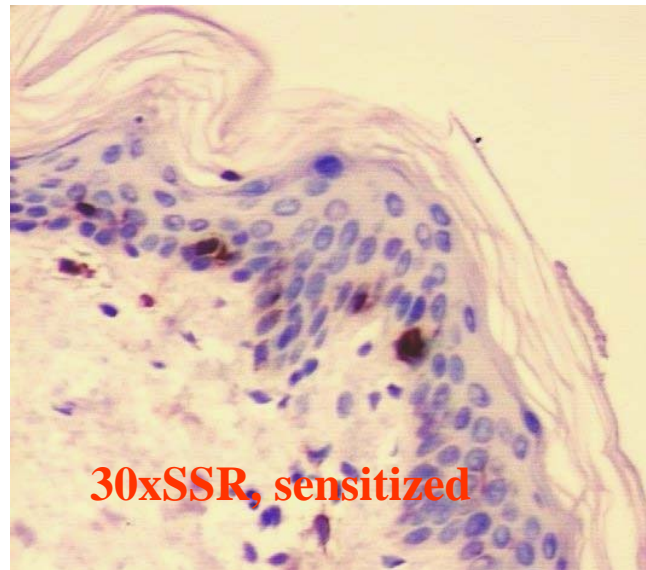
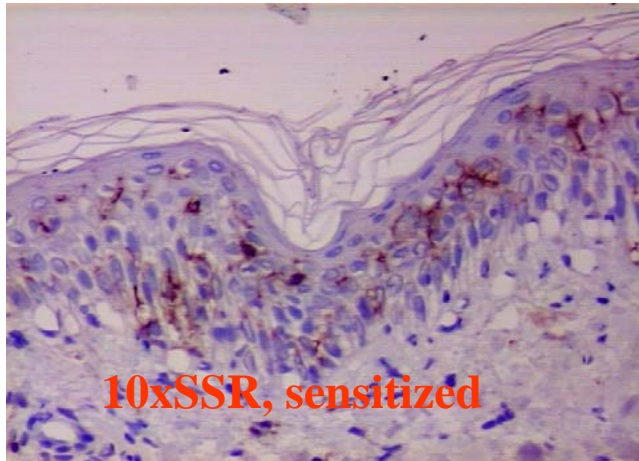
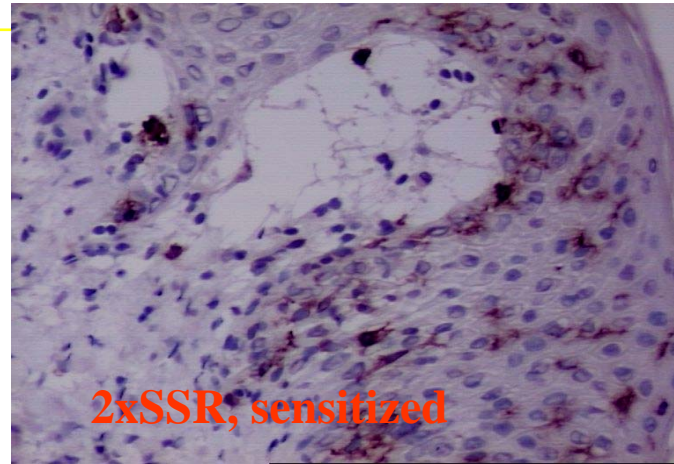
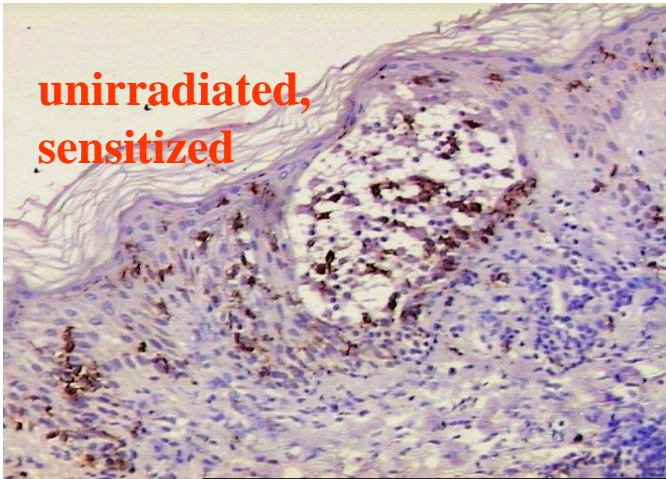
10 days 0.7 MED UVB + 3
MED UVB (n=30)

Controls (unirradiated)
n=40

SSR and LCs

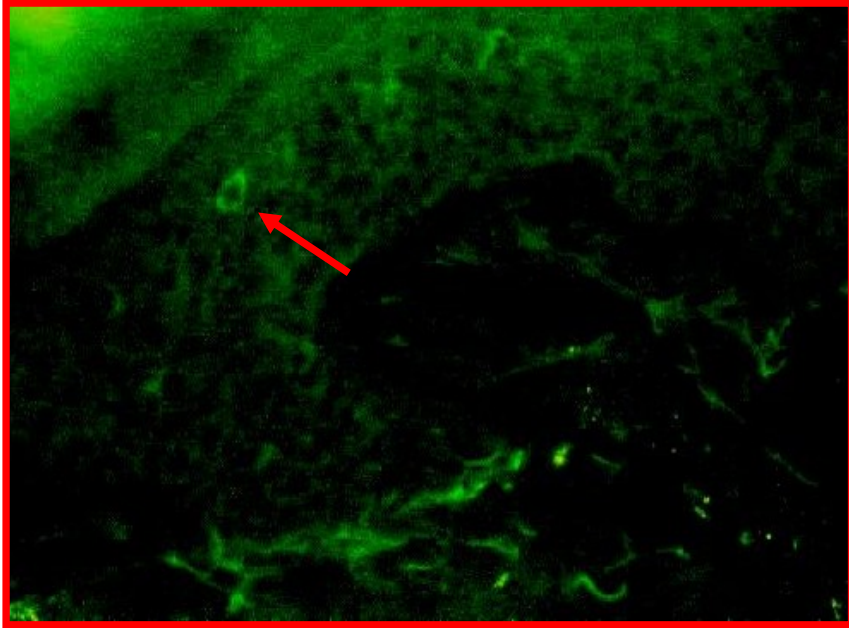
- After repeated SSR exposures CD1a+ cells migrate to lower parts of the epidermis and are less dendritic
- CD1a+ cells number is reduced at CHS elicitation site; it correlates negatively with SSR cumulative dose (*Lesiak et al., Contact dermatitis 2007*)

CD1a+ cells in skin biopsies during the elicitation phase of CHS

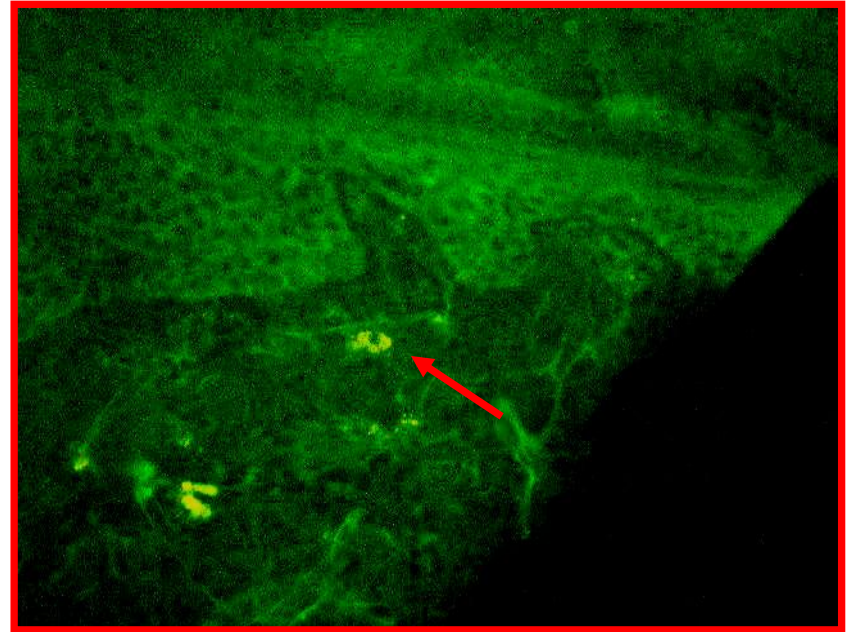


BLOOD DENDRITIC CELLS (Epidermis and dermis)

MDC1



PDC



**No effect of UVB on their number
and distribution (Narbutt et al.,
Folia Histochem 2005)**

SSR and BLOOD DENDRITIC CELLS

- The percentage of total BDCs was elevated in all groups by the SSR (0.3 MED daily) exposure
- The MDC2s showed an increase after 10 days, and a subsequent decrease after 30 days irradiation - photoadaptation (*Narbutt et al., Scand J Immunol 2004*)

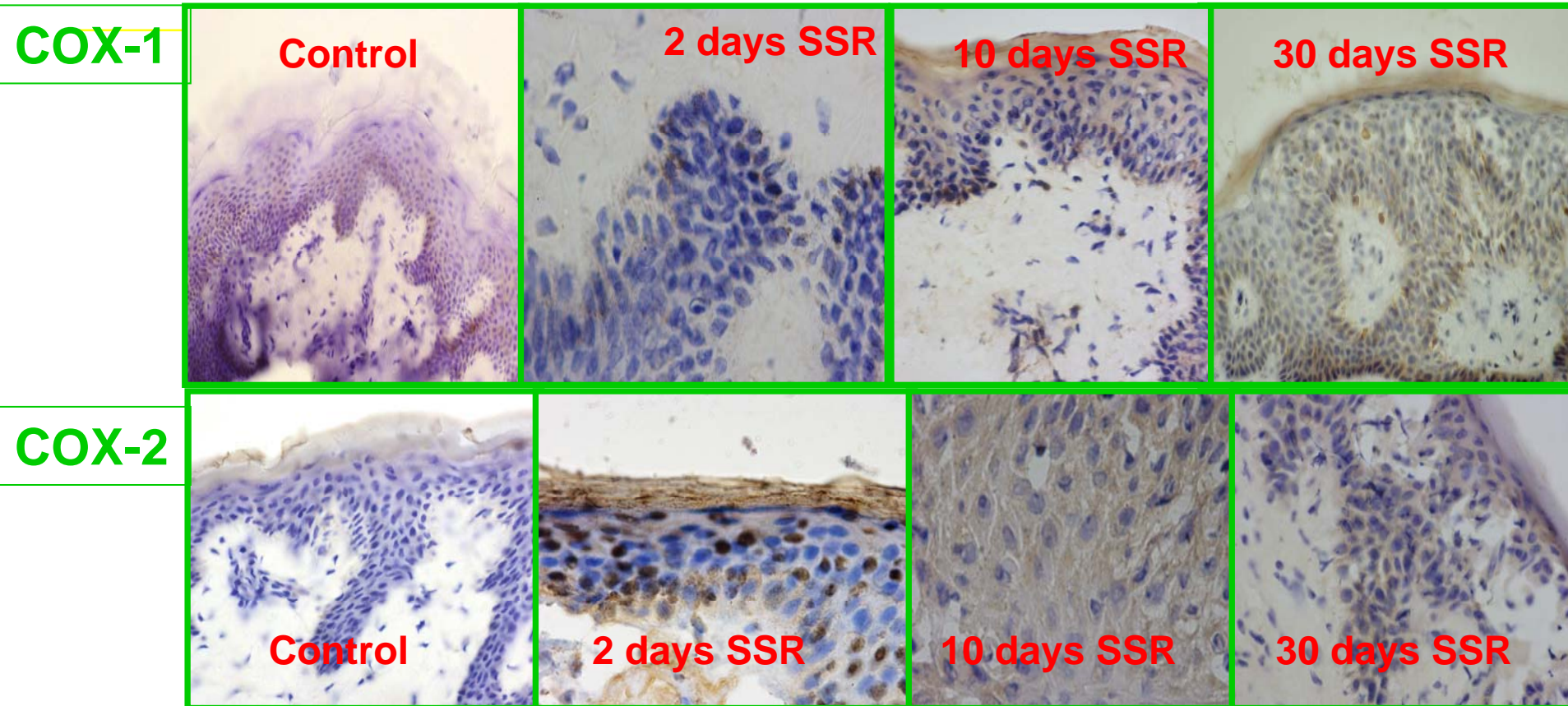
SSR and cytokines mRNAs

- Repeated sub-erythemal SSR exposures increased the expression of IL-1beta, IL-6, IL-10 and TNF-alpha mRNAs in skin biopsies
- After 30 SSR the expression of IL-1beta, IL-6, IL-10 mRNAs showed **a tendency to decrease** – tendency to photoadaptation? (*Narbutt et al. J Dermatol Sci 2007*)

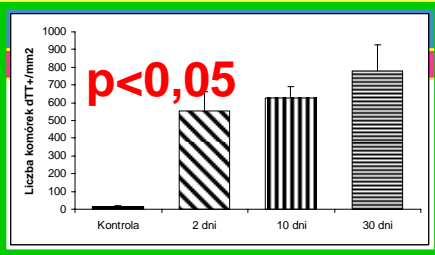
SSR and Cyclooxygenases

- UV exposure of the skin induces the expression of the COX-2 and prostaglandin PGE2
- COX-2 is overexpressed in premalignant lesions and in NMSC in humans
- UV-induced COX-2 expression plays a major role in UV-induced PGE2 production, inflammation, edema, keratinocyte proliferation, epidermal hyperplasia, and generation of oxidative DNA damage.
- Chronic exposure to UV leads to up-regulation of COX-2 expression and chronic inflammation with the accumulation of DNA damage

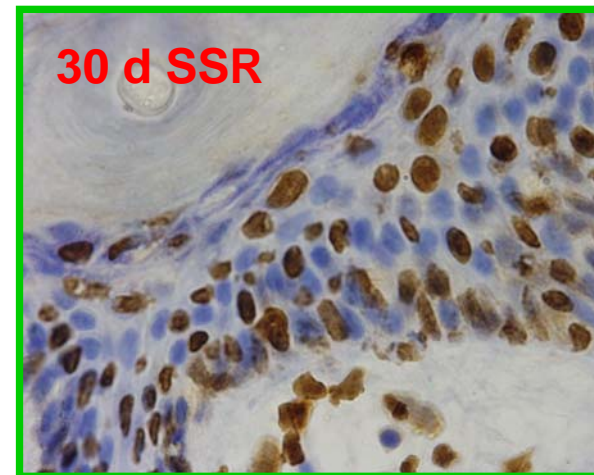
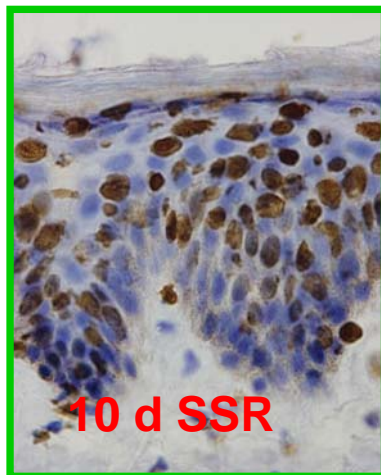
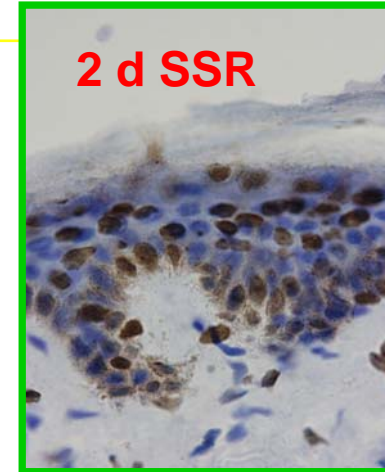
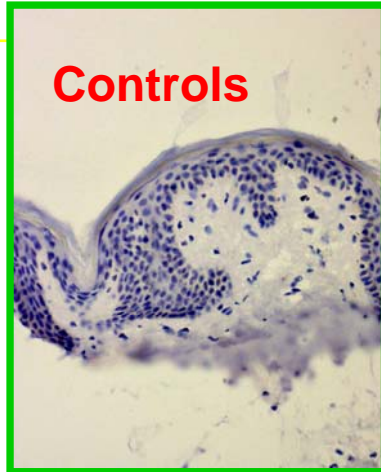
SSR/COX-1 and COX-2

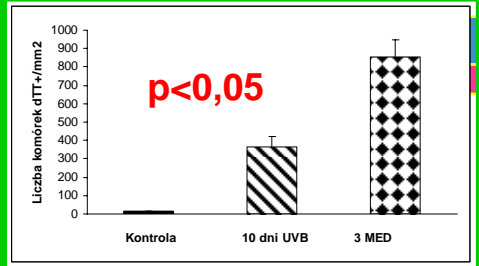


Number of COX-1+ and COX-2+ cells increased significantly after irradiations (*Narbutt et al., Exp Dermatol 2007*)

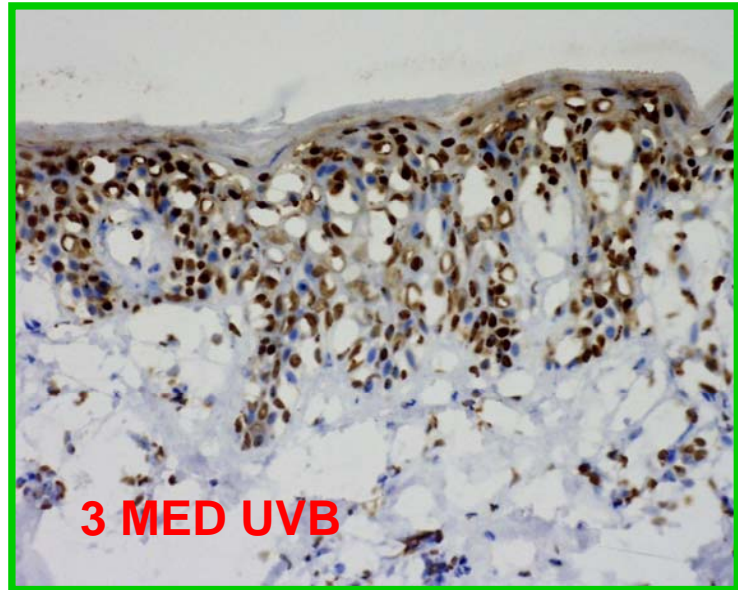
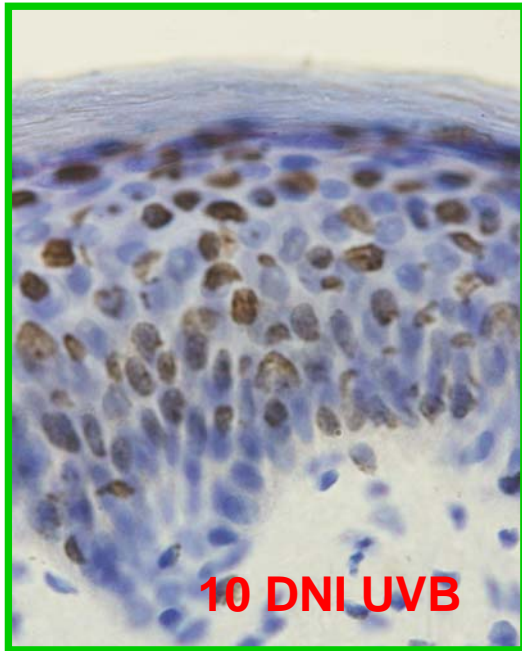


DNA damage (SSR)



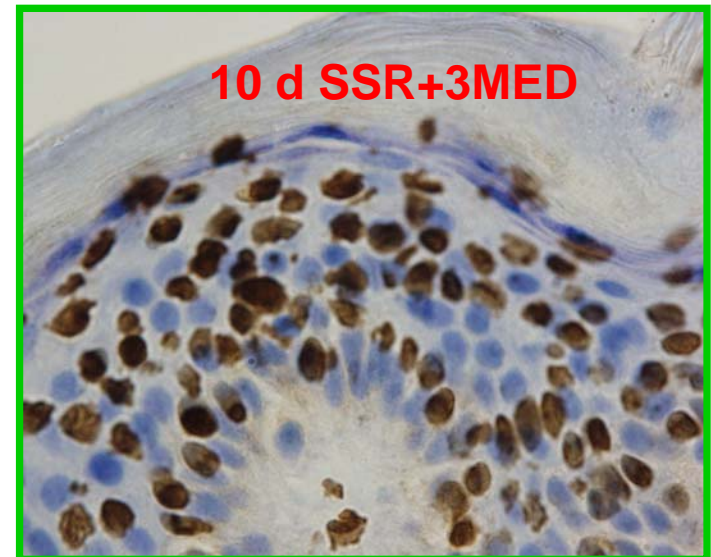
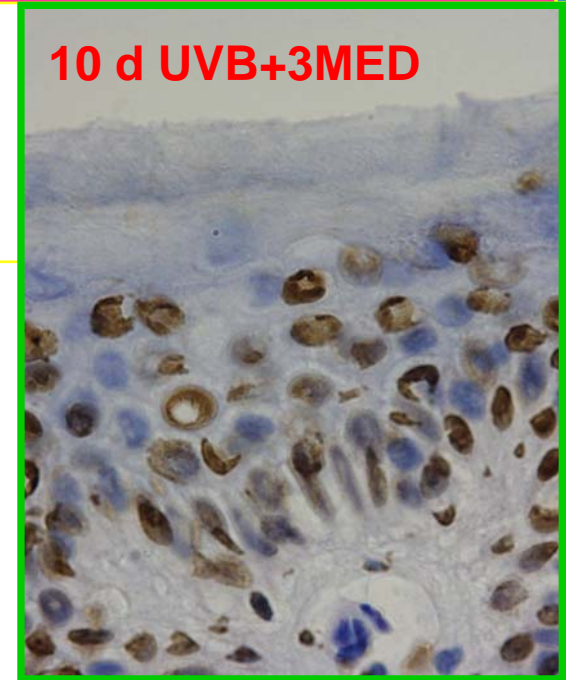
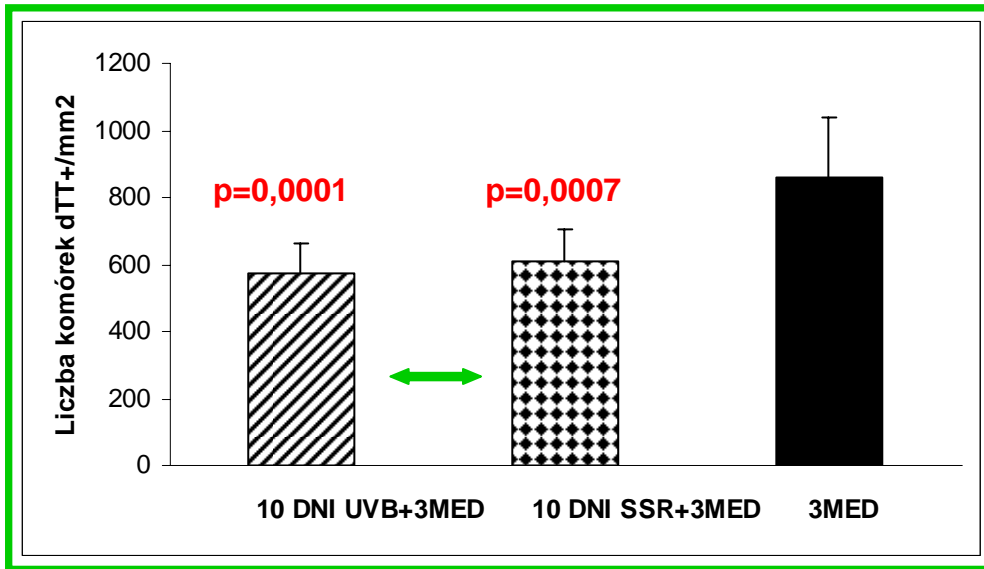


DNA damage (UVB)



Photoadaptation

DNA damage (UVB and SSR)



CHS and repeated SSR

- Assessment of the contact hypersensitivity reaction
 - used to evaluate the immune response following UV exposure
- Few studies
- Most experiments : sources emitting a higher proportion of UVB to UVA (often more than 50% UVB) compared with that found in sunlight (about 3.4% UVB and 96.6% UVA)
- Solar simulated radiation (SSR)

CHS and repeated SSR - results

- Irradiation with suberythemal doses of SSR – suppression of CHS (*Narbutt et al., Photochem Photobiol Sci 2005*)





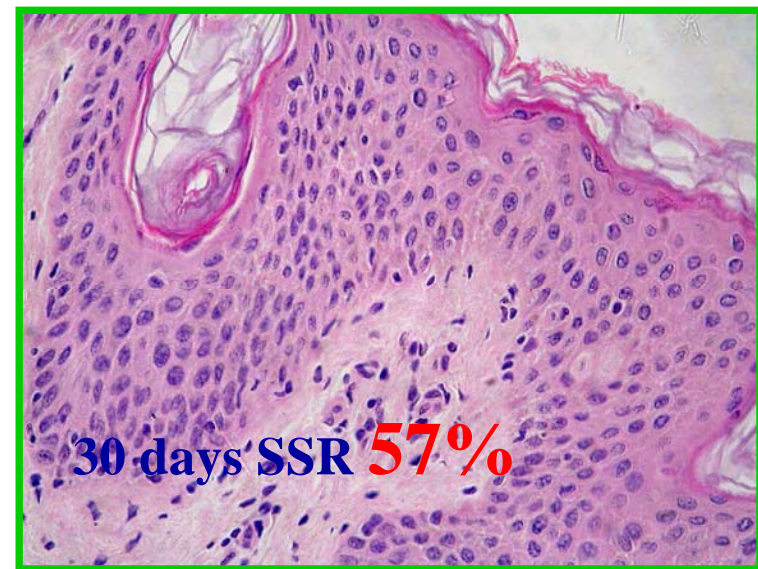
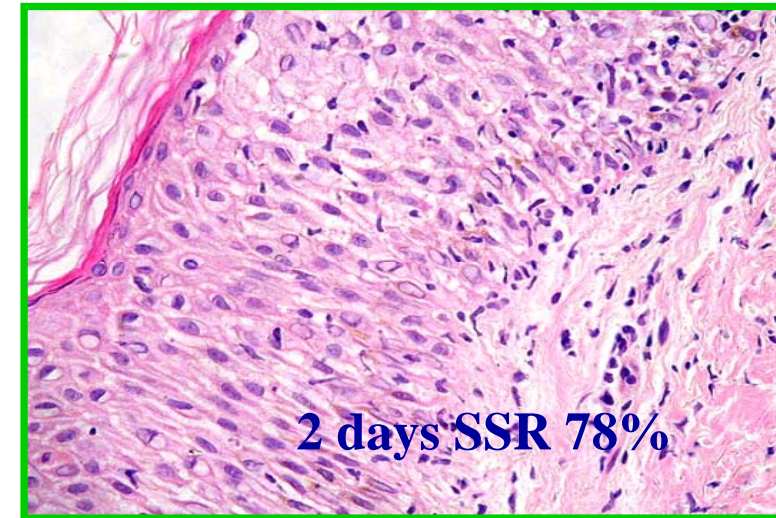
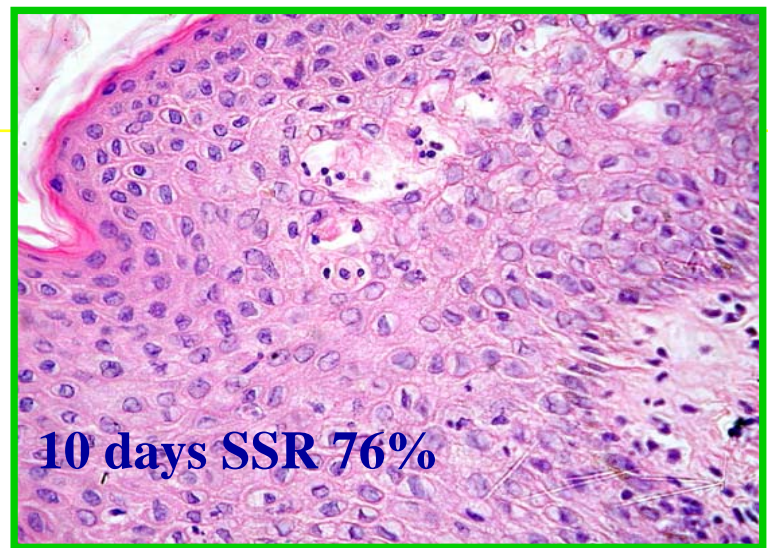
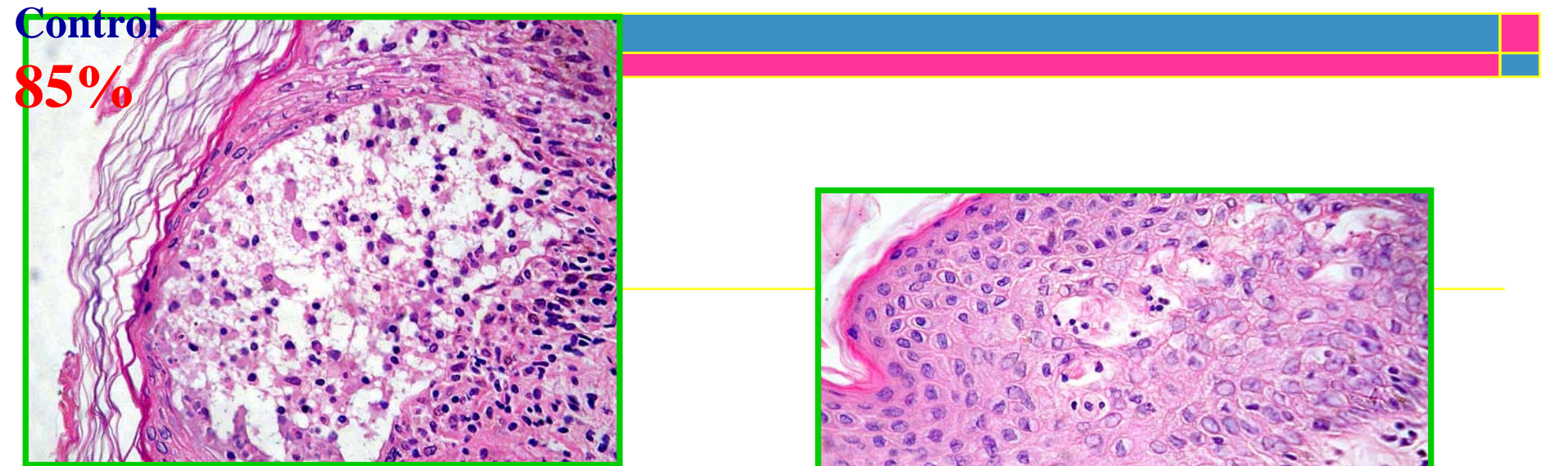
SSR/PAR

Group	1 (n=40) Control	2 (n=33) 2 days SSR	3 (n=34) 10 days SSR	4 (n=33) 30 days SSR
% subjects with PAR	85.0	78.8	76.5	64.0 (p=0.03)
% subjects with bisters	12.5	9.1	2.9	0 (p=0.03)
Mean time of PAR occurrence (days)	9.5	8.5	7.5	11.0




SSR/VISUAL ASSESSMENT OF CHS

CHS	Group 1 n=40 Control	Group 2 n=33 2 days SSR	Group 3 n=34 10 days SSR	Goup 4 n=33 30 days SSR
0	22.5%	24.2%	35.3%	54.5% (p=0.015; R=-0.2)
1	77.5%	75.8%	64.7%	45.5%




Cumulative dose vs. spongiosis

R=-0.2; p=0.01




Daily exposure to a low dose of SSR over a period of 30 days can reduce the PAR and the CHS response to DPCP in human subjects, as assessed by clinical scoring and histology while no adaptation to these effects become evident



The results obtained indicate that repeated sub-erythemal doses of SSR do not cause clinical symptoms of inflammation but are responsible for skin immunity alterations



The results demonstrate the hazardous effects of sub-erythemal doses of UVR

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- Further investigations are required to measure other types of innate and acquired immune responses under low chronic UVR doses, particularly those thought to be important in the control of tumours and infectious diseases