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ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

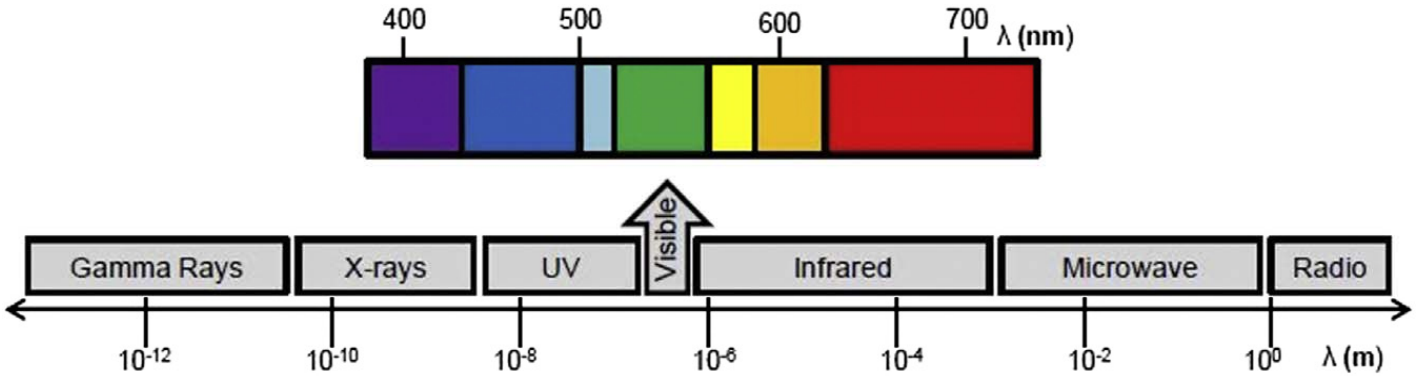
SCUOLA DERMATOLOGICA SERGIO CHIMENTI

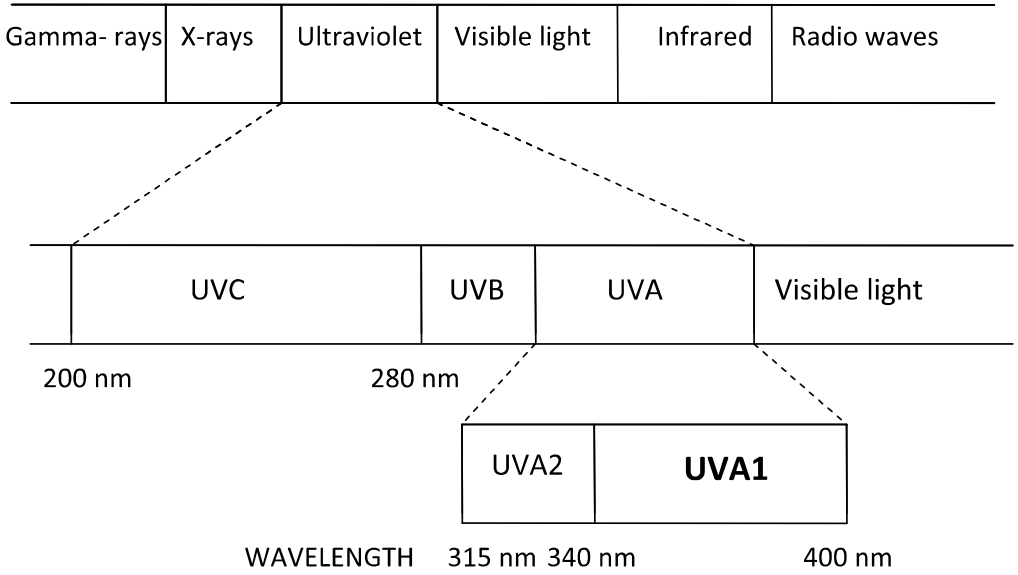
Principi ed Aggiornamenti in Dermatologia
Roma, 10-11 Febbraio 2017

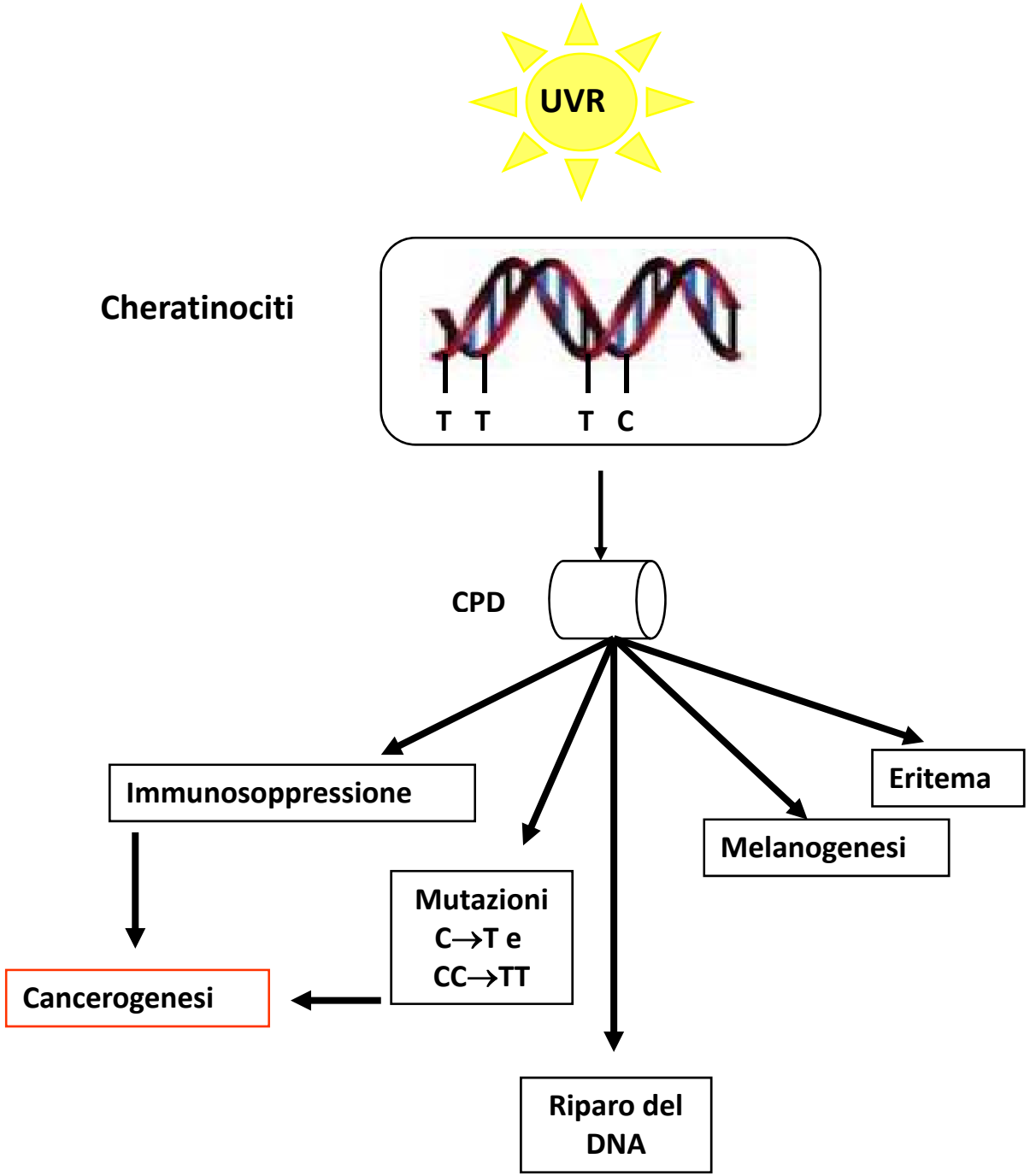
Gli effetti biologici degli ultravioletti da sorgenti artificiali

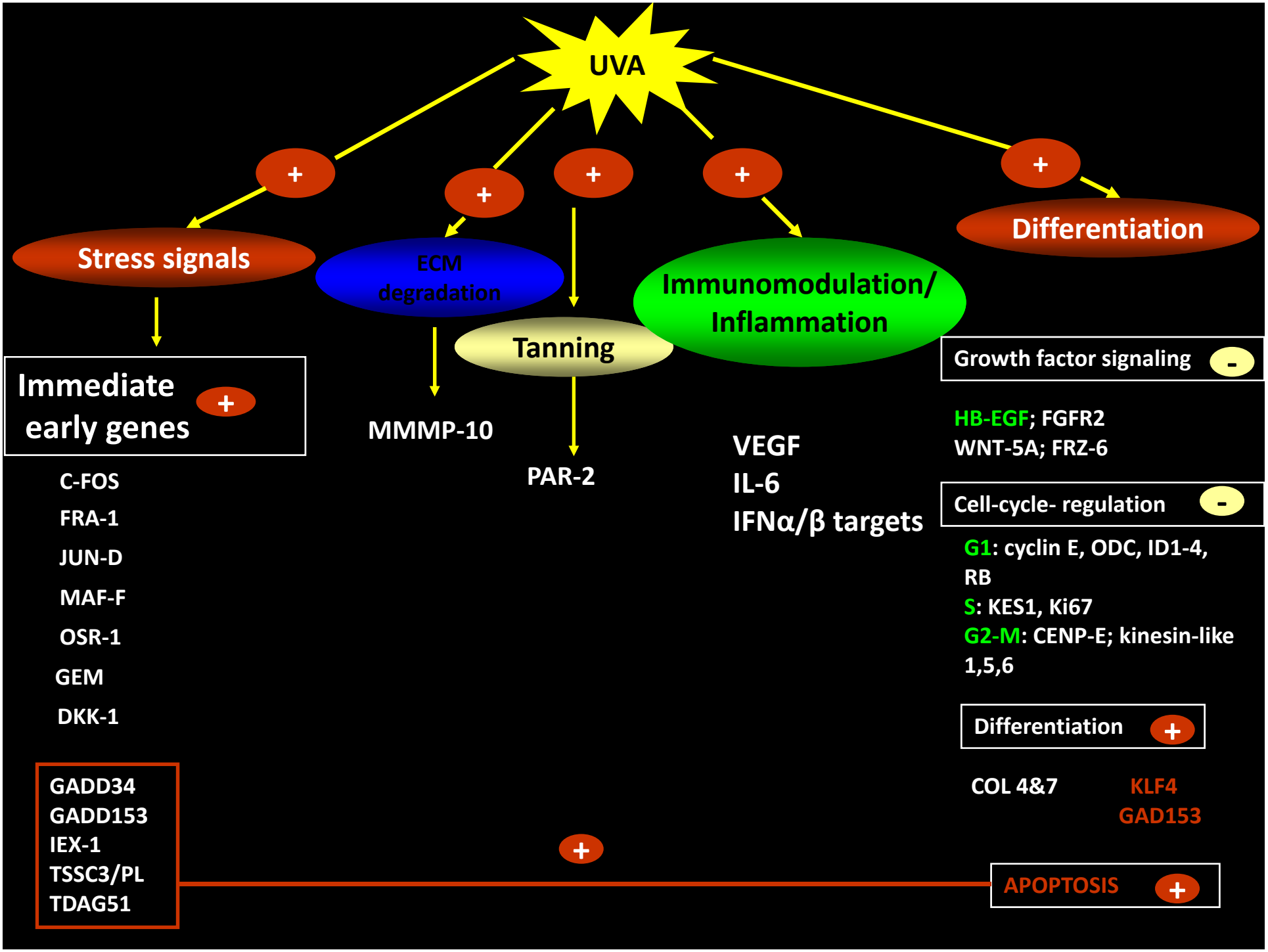
Alessia Pacifico
Servizio di Fototerapia – UOC Dermatologia Clinica
Istituto Dermatologico San Gallicano, IRCCS, Roma

Spettro elettromagnetico






UVR
Cheratinociti
T T T C
CPD
Immunosoppressione
Eritema
Melanogenesi
Mutazioni
C→T e
CC→TT
Cancerogenesi
Riparo del
DNA


UVA
+
+
+
+
+
Stress signals
ECM degradation
Tanning
Immunomodulation/ Inflammation
Differentiation
Immediate early genes
+
C-FOS
FRA-1
JUN-D
MAF-F
OSR-1
GEM
DKK-1
MMMP-10
PAR-2
VEGF
IL-6
IFNα/β targets
Growth factor signaling
-
HB-EGF; FGFR2
WNT-5A; FRZ-6
Cell-cycle- regulation
-
G1: cyclin E, ODC, ID1-4, RB
S: KES1, Ki67
G2-M: CENP-E; kinesin-like 1,5,6
Differentiation
+
COL 4&7
KLF4
GAD153
GADD34
GADD153
IEX-1
TSSC3/PL
TDAG51
+
APOPTOSIS
+

The effect of ultraviolet (UV) A1, UVB and solar-simulated radiation on p53 activation and p21$^{Waf1/Cip1}$

P.E. Beattie, L.E. Finlan,*† N.M. Kernohan,* G. Thomson,* T.R. Hupp*† and S.H. Ibbotson

British Journal of Dermatology 2005 **152**, pp1001–1008

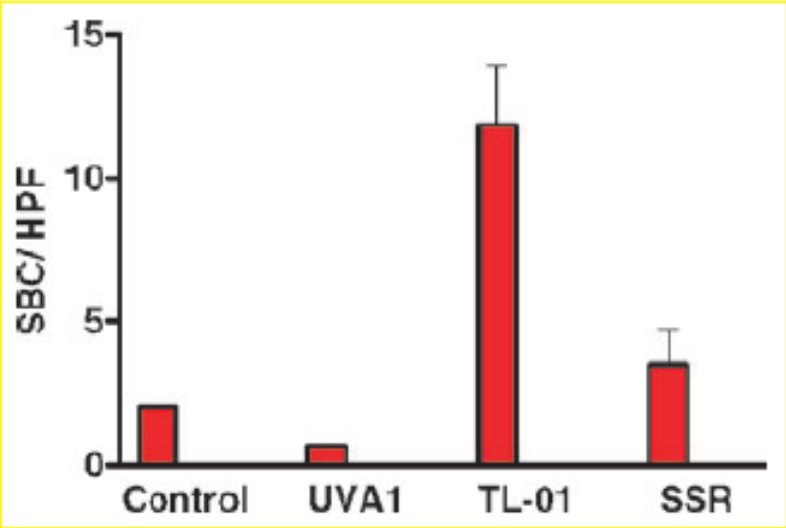


Fig 1. Mean ± SD sunburn cell (SBC) counts per high-power field (HPF) in unirradiated skin and 24 h after irradiation with 3 minimal erythema doses of ultraviolet (UV) A1, narrowband UVB (TL-01) and solar-simulated radiation (SSR) (n = 5).

Table 1 The skin type and minimal erythema dose (MED) for each radiation source for each of the volunteers

		MED		
Patient	Skin type	TL-01 (mJ cm^{-2})	SSR (J cm^{-2})	UVA1 (J cm^{-2})
1	II	390	6·8	20
2	II	200	6·8	40
3	III	280	12	60
4	III	550	5·6	60
5	IV	280	5·6	30

UV, ultraviolet; TL-01, narrowband UVB; SSR, solar-simulated radiation.

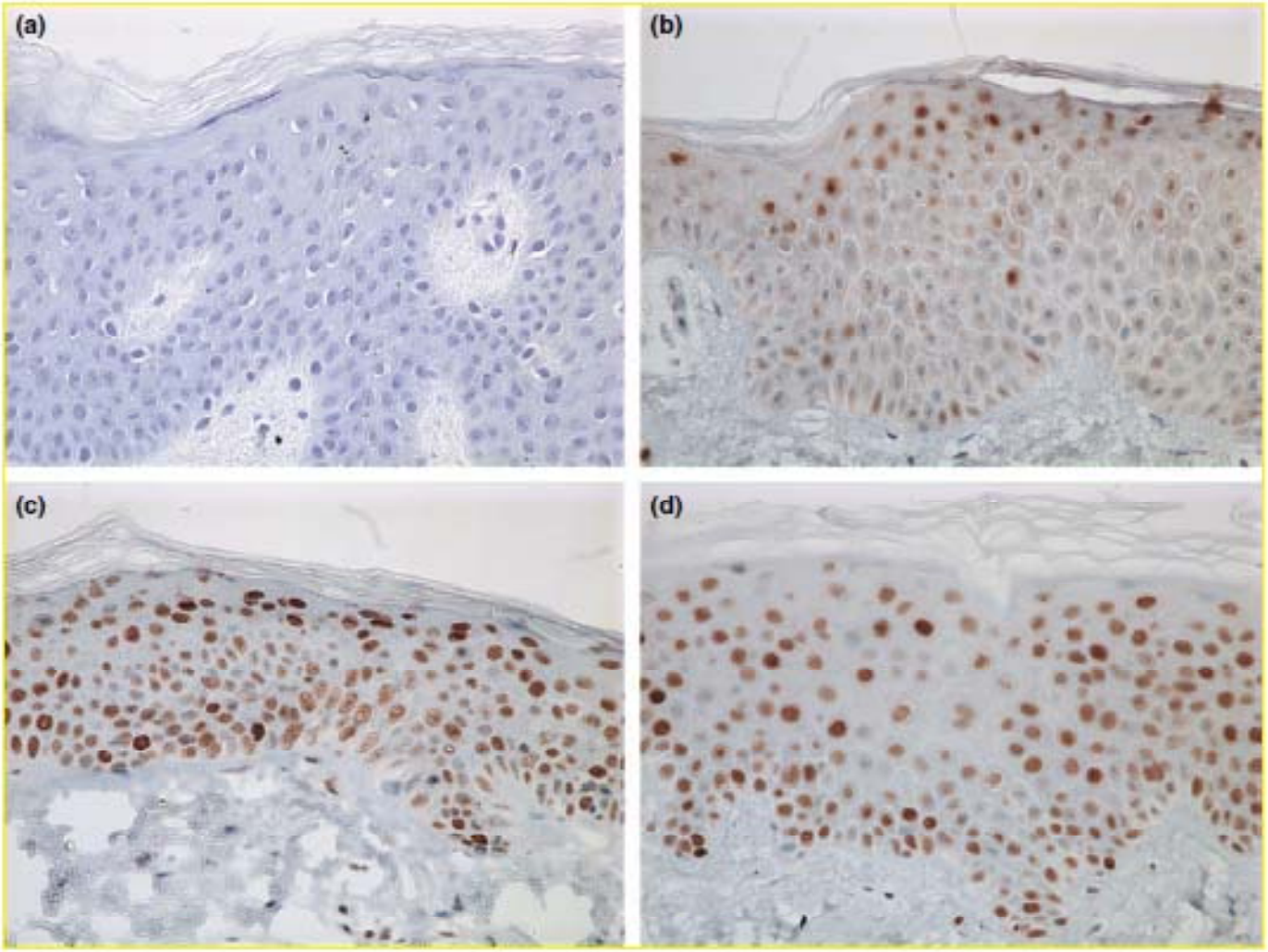


Fig 3. Immunostaining with pan-p53 antibody, Do-1, which recognizes wild-type and mutated p53, at an unirradiated control site (a) and 24 h after irradiation with 3 minimal erythema doses of ultraviolet (UV) A1 (b), narrowband UVB (TL-01) (c) and solar-simulated radiation (SSR) (d), showing little p53 accumulation after UVA1 in comparison with TL-01 and SSR.

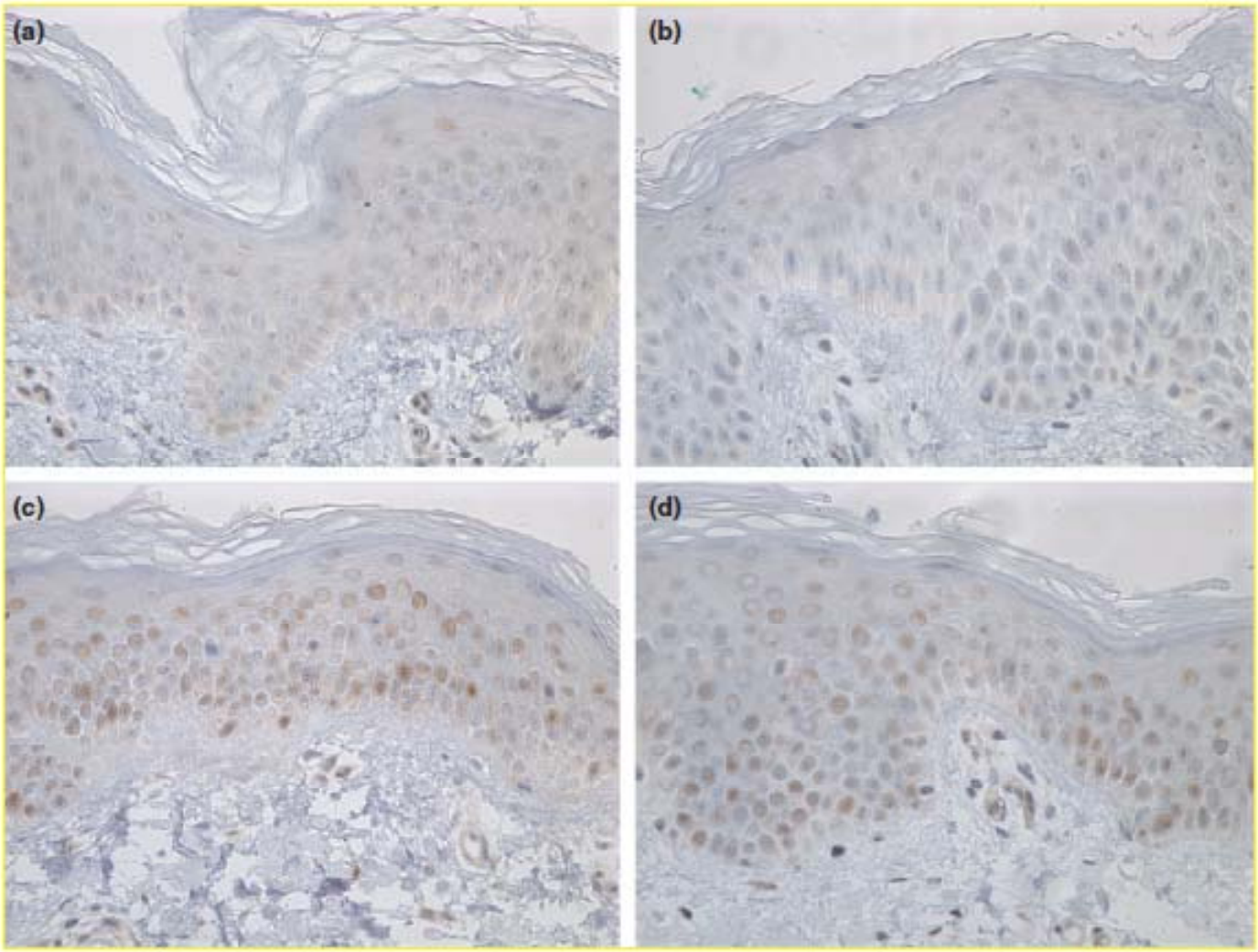


Fig 4. Immunostaining of the p53 AT (serine 15) phosphorylation site at an unirradiated control site (a) and 24 h after irradiation with 3 minimal erythema doses of ultraviolet (UV) A1 (b), narrowband UVB (TL-01) (c) and solar-simulated radiation (SSR) (d), showing no p53 phosphorylation at this site after UVA1 in comparison with TL-01 and SSR.

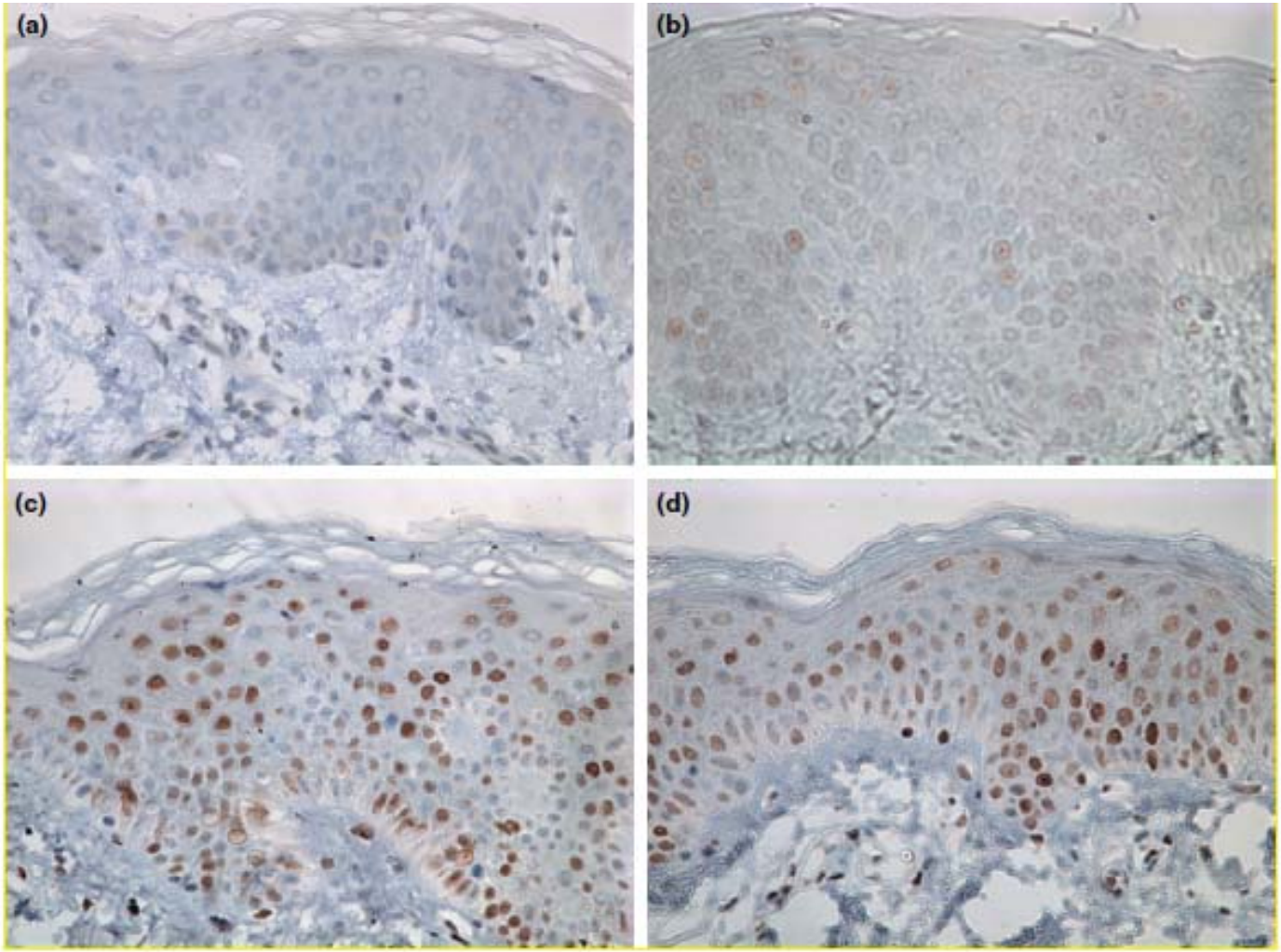
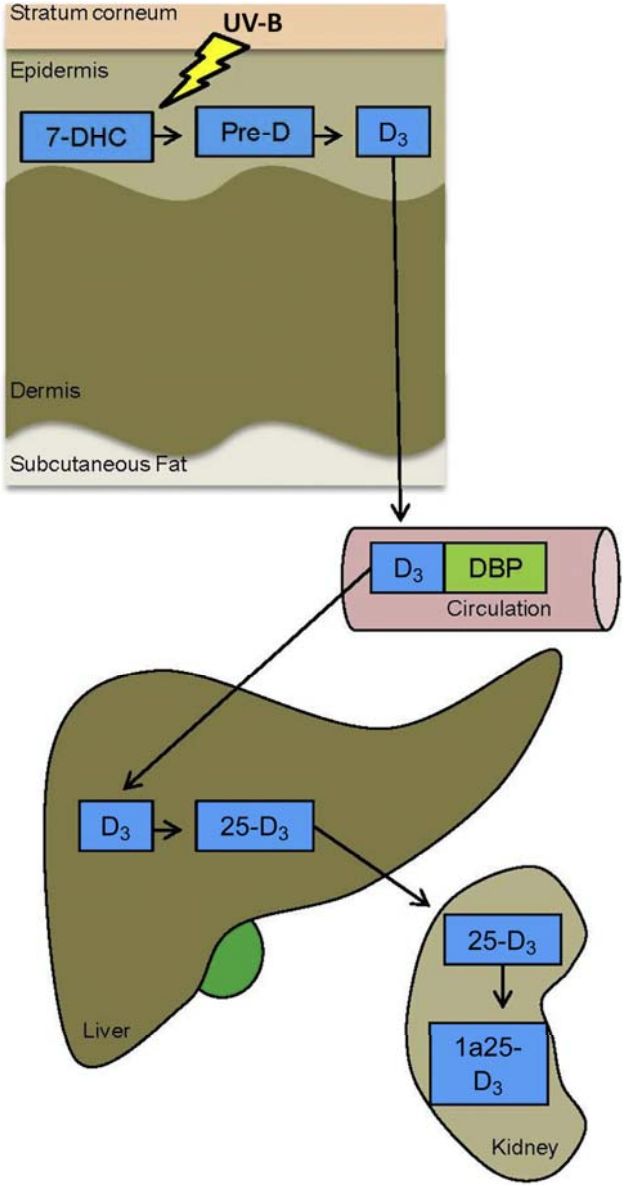


Fig 5. Immunostaining of the p53 CK2 (serine 392) phosphorylation site at an unirradiated control site (a) and 24 h after irradiation with 3 minimal erythema doses of ultraviolet (UV) A1 (b), narrowband UVB (TL-01) (c) and solar-simulated radiation (SSR) (d), showing no p53 phosphorylation at this site after UVA1 in comparison with TL-01 and SSR.

Introduction to Photobiology

Dermatol Clin 32 (2014) 255–266

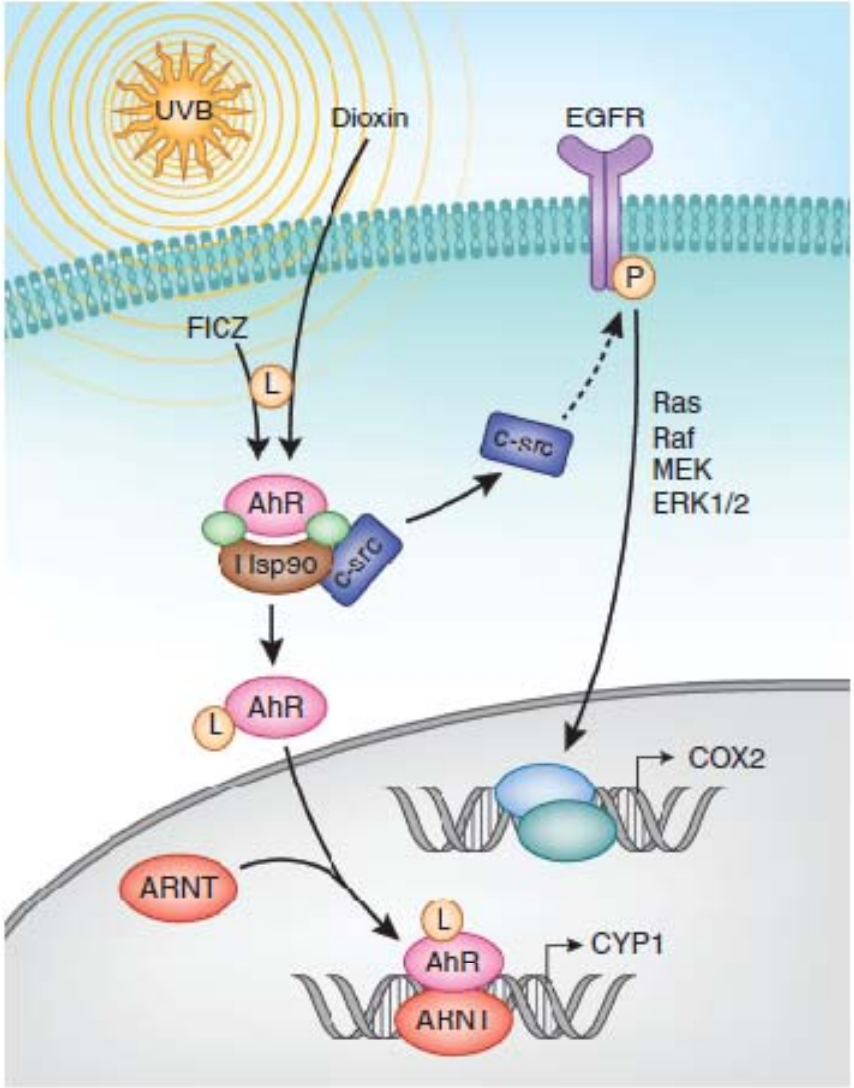
Elma D. Baron, MD[a,*], Amanda K. Suggs, MD[b]



Sun Exposure: What Molecular Photodermatology Tells Us About Its Good and Bad Sides

Jean Krutmann[1], Akimichi Morita[2] and Jin Ho Chung[3]

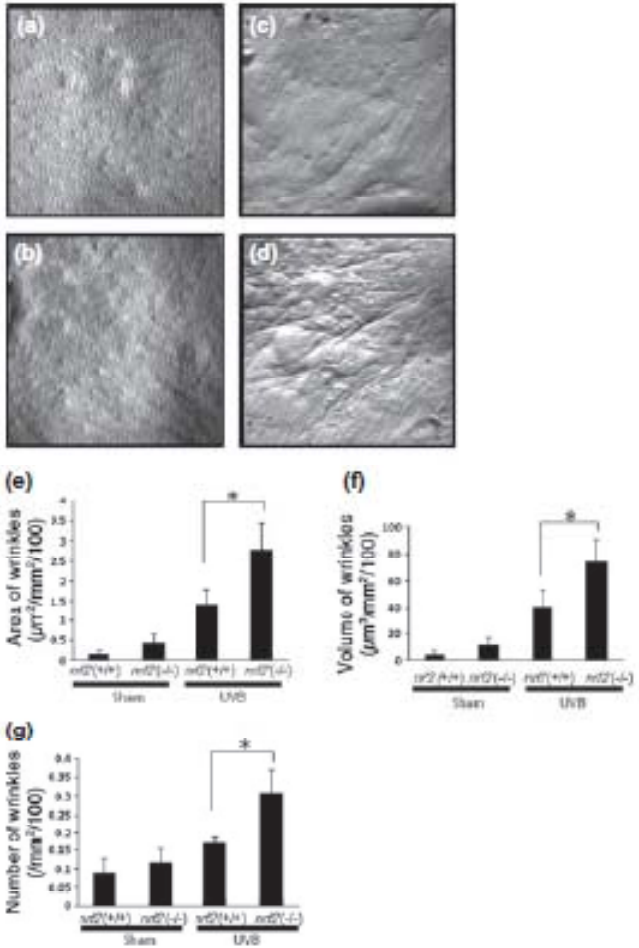
Journal of Investigative Dermatology (2012) **132,** 976–984;

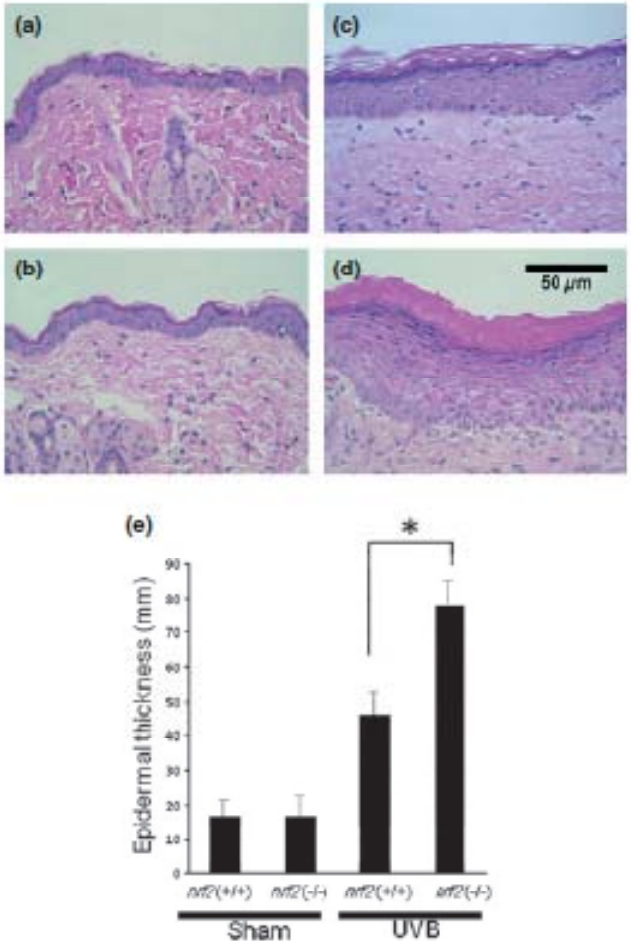


Acceleration of UVB-induced photoageing in *nrf2* gene-deficient mice

Ayako Hirota[1,2], Yasuhiro Kawachi[1], Masayuki Yamamoto[3], Tsutomu Koga[2], Kazuhiko Hamada[2] and Fujio Otsuka[1]

2011 John Wiley & Sons A/S, *Experimental Dermatology*, **20**, 664–668

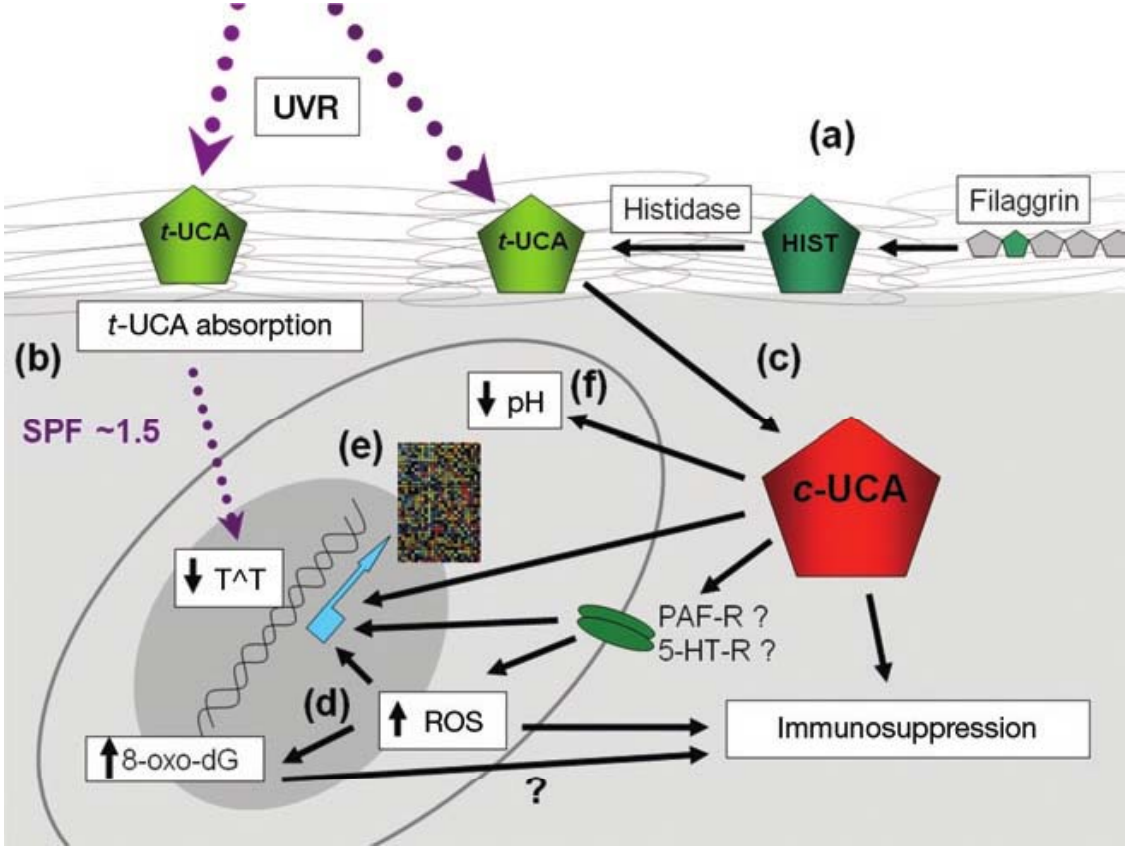




Urocanic Acid in the Skin: A Mixed Blessing?

Neil K. Gibbs[1] and Mary Norval[2]

Journal of Investigative Dermatology (2011) **131**, 14–17



UV-A Fingerprint Mutations in Human Skin Cancer[†]

Gary M. Halliday[1,*], Nita S. Agar[1], Ross St.C. Barnetson[1], Honnavara N. Ananthaswamy[2], Alexandra M. Jones[1]

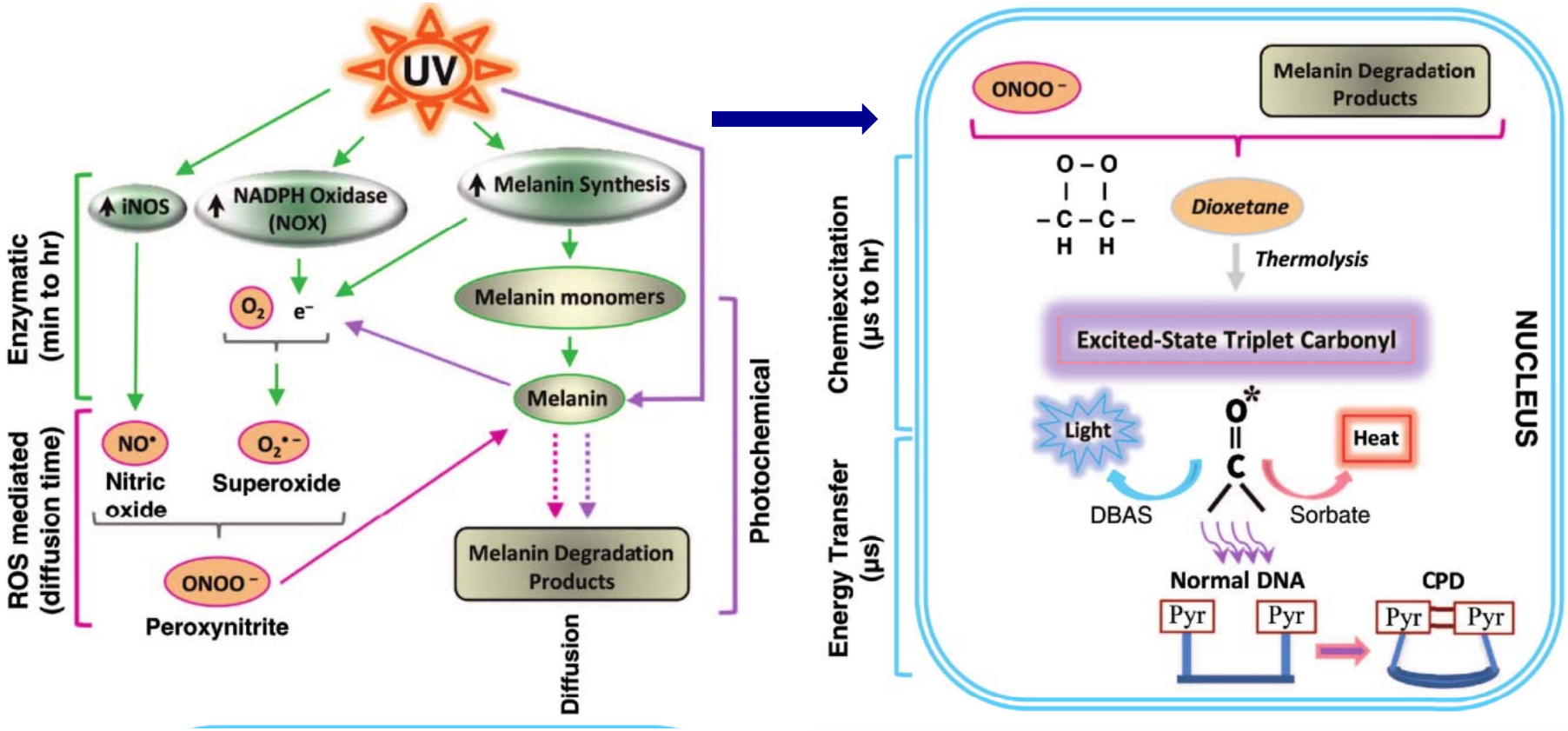
Photochemistry and Photobiology, 3–8, January 2005

PHOTOCHEMISTRY

Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure

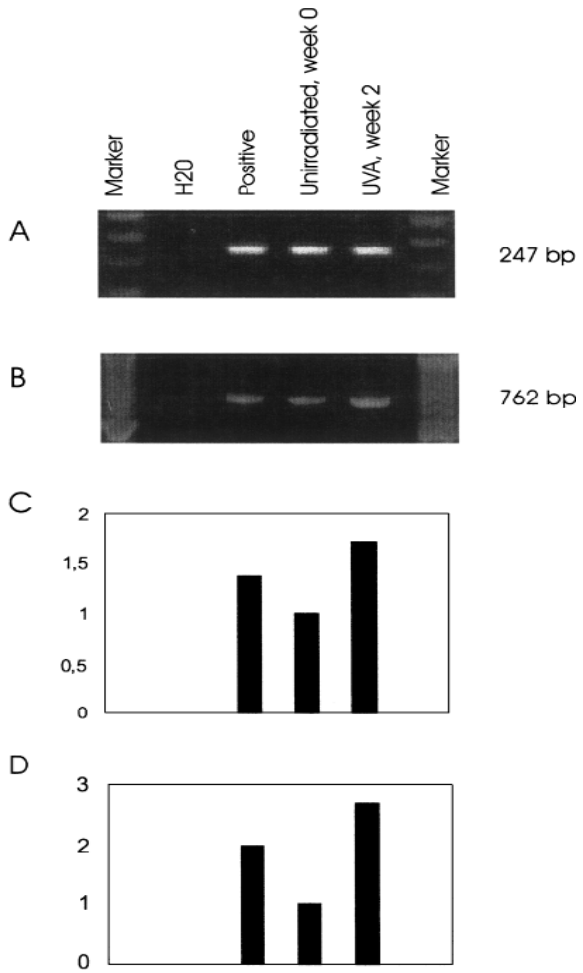
Sanjay Premi,[1] Silvia Wallisch,[1] Camila M. Mano,[1,2] Adam B. Weiner,[1*] Antonella Bacchiocchi,[3] Kazumasa Wakamatsu,[4] Etelvino J. H. Bechara,[2,5†] Ruth Halaban,[3,6] Thierry Douki,[7†] Douglas E. Brash[1,6‡]

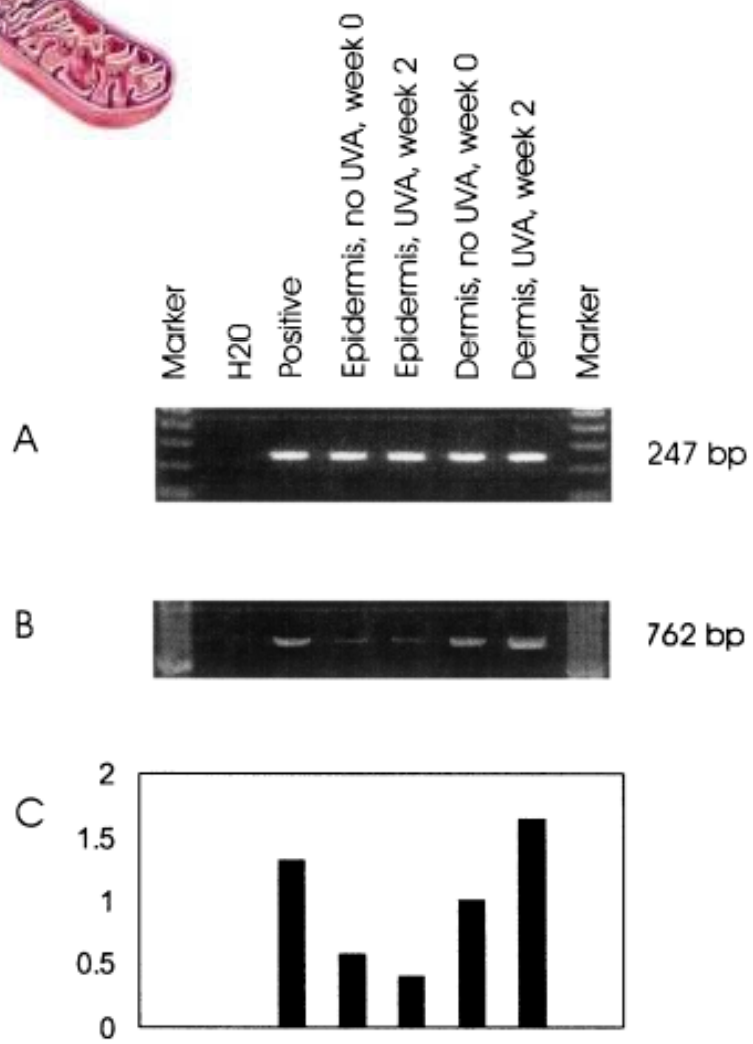
SCIENCE 20 FEBRUARY 2015 • VOL 347 ISSUE 6224

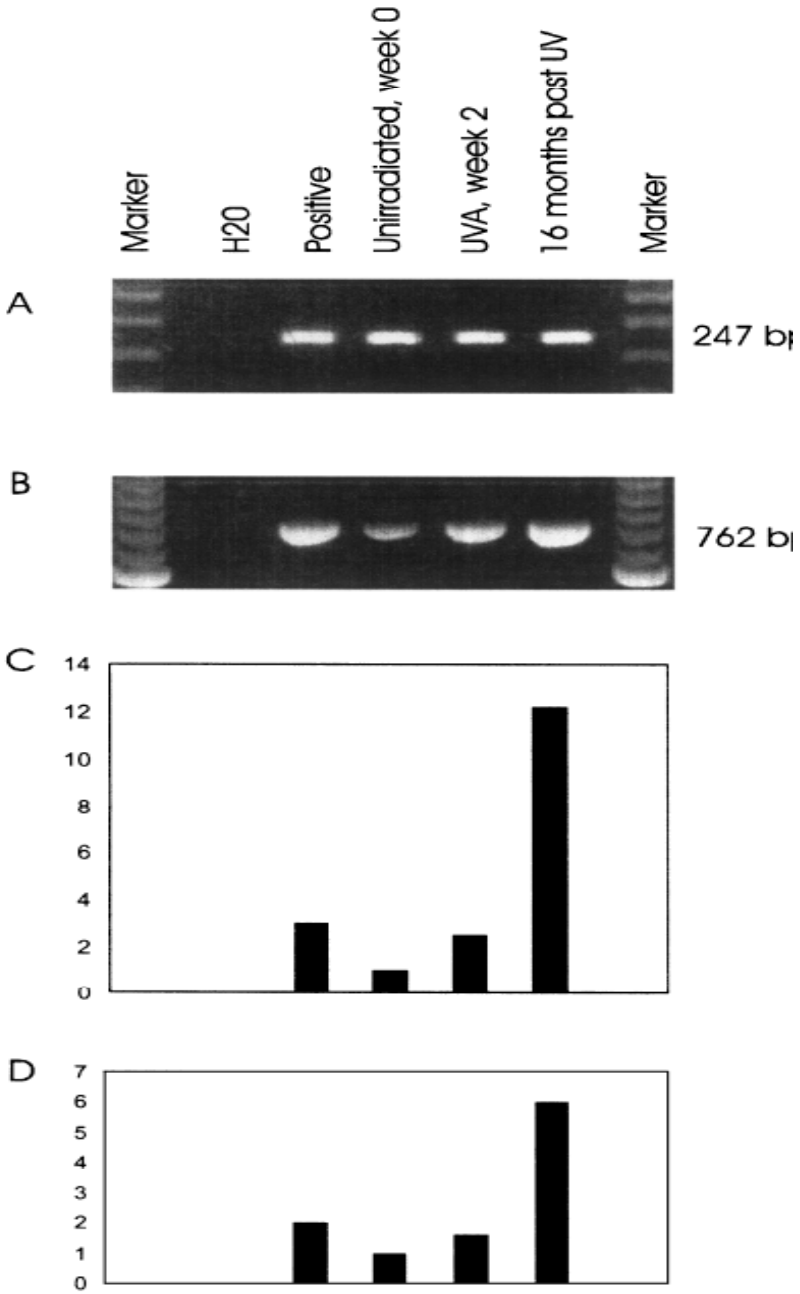


Induction of the photoaging associated mitochondrial common deletion in vivo in normal human skin.

Berneburg M et al. *J Invest Dermatol* 2004; 122: 1277-83




Marker
H20
Positive
Epidermis, no UVA, week 0
Epidermis, UVA, week 2
Dermis, no UVA, week 0
Dermis, UVA, week 2
Marker
A
247 bp
B
762 bp
C
2
1.5
1
0.5
0


Marker
H20
Positive
Unirradiated, week 0
UVA, week 2
16 months past UV
Marker
A
247 bp
B
762 bp
C
14
12
10
8
6
4
2
0
D
7
6
5
4
3
2
1
0

Molecular aspects of skin ageing

Elizabeth C. Naylor[a,b], Rachel E.B. Watson[a,b], Michael J. Sherratt[a,c,*]

[a] Manchester Academic Health Sciences Centre, The University of Manchester, Manchester M13 9PT, UK
[b] School of Translational Medicine, Faculty of Medical and Human Sciences, The University of Manchester, Manchester, M13 9PT UK
[c] School of Biomedicine, The University of Manchester, Manchester, M13 9PT UK

Maturitas 2011; 69: 249-256

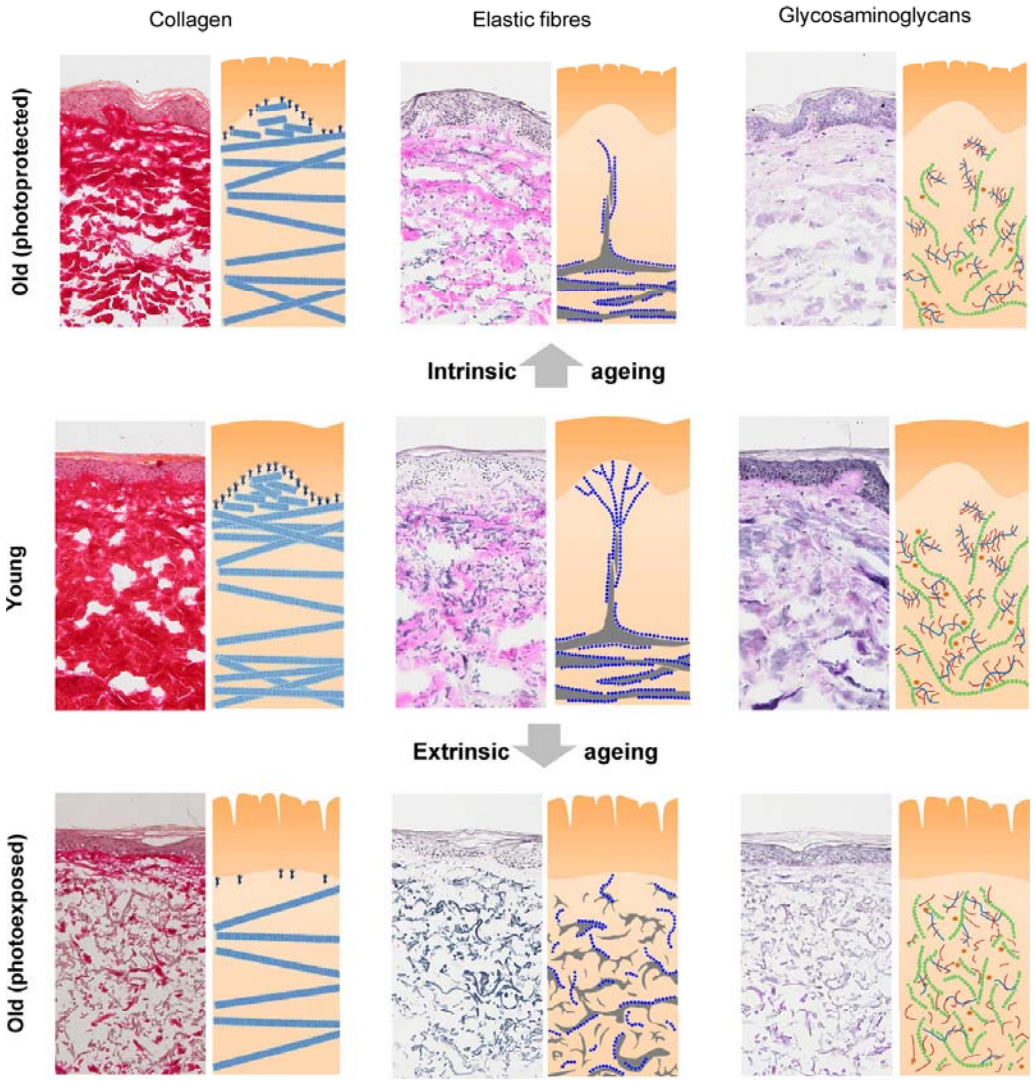


Fig. 2. ECM remodeling in intrinsically and extrinsically aged skin. Dermal collagens, elastic fibres and glycosaminoglycans (visualised with picrosirrius red, Miller's ela and periodic acid staining respectively) all undergo significant, yet differential, remodeling in photoprotected and photoexposed aged skin (young: 23 year old upper ir arm, old photoprotected: 75 year old buttock, old photoexposed: 75 year old forearm). Specifically, whilst atrophy of dermal collagens (particularly in the reticular der is evident in intrinsically aged skin, extrinsically aged skin is characterised both by a profound reduction in fibrillar collagen staining and by the specific loss of collager

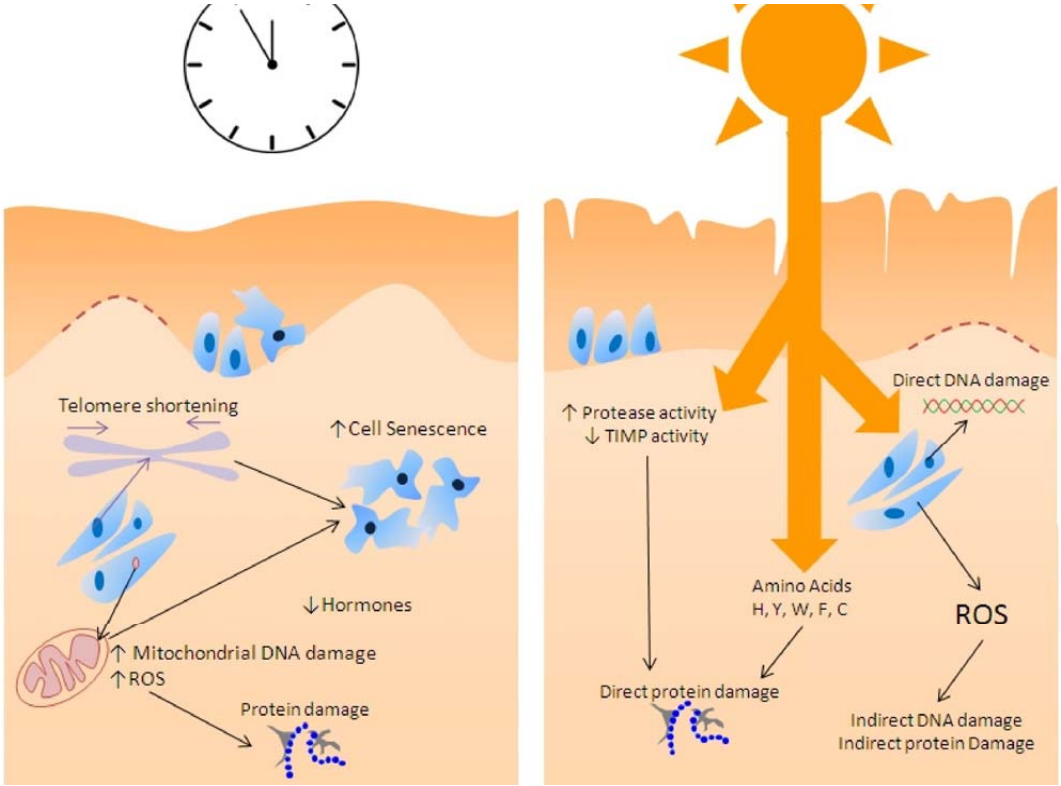


Fig. 5. Potential mechanisms of skin ageing. Skin is subject to both an intrinsic ageing process (due to the passage of time-left hand panel) and to an extrinsic ageing processes (principally as a result of exposure to ultraviolet radiation [UVR]-right hand panel). Mitochondrial DNA damage, increased ROS production and telomere shortening are thought to play a role in the intrinsic ageing process where an accumulation of senescent cells not only proves incapable of proliferation but exhibits an altered synthetic phenotype and hence may play a role in pathologically remodeling the ECM. In contrast, the mechanisms leading to photoageing of skin are caused mainly by the repetitive adsorption of UVR which can upregulate the expression of ECM proteases via AP-1 signaling. In addition, UVR can directly damage cutaneous biomolecules which are rich in chromophores and may induce the production of ROS which in turn can act on both cells and matrix components to mediate further turnover.

GUIDELINES

An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report

2004 British Association of Dermatologists, *British Journal of Dermatology*, **151**, 283–297

Table 4. Other diseases that have been treated with TL-01

Condition	References	Best study evidence	Strength of recommendation/ quality of evidence[a]	Comparators (in controlled studies)
Atopic dermatitis	30,31,34,35	RCT	A I	UVA1 Visible light (placebo); BB-UVA;
Seborrhoeic dermatitis	38	Open, uncontrolled study	B III	NA
Nodular prurigo	122	Case report	C III	NA
Vitiligo	41,43,44,122,123	Controlled trial without randomization	B III	PUVA
Mycosis fungoides	47–49,122	Open, uncontrolled study	B III	NA
Lichen planus	124,125	Case series	C III	NA
Subcorneal pustular dermatosis	126,127	Case reports	C III	NA
Alopecia areata	128,129	Case reports	C IV	NA
Granuloma annulare	128	Case report	C IV	NA
Acquired perforating dermatosis	130	Case report	C IV	
Pityriasis rubra pilaris[b]	122	Case report	D IV	NA
Photodermatoses				
Polymorphic light eruption	39	RCT	A I	PUVA
Erythropoietic protoporphyria	40,131	Case reports	B III	NA
Actinic prurigo	40	Case reports	B III	NA
Hydroa vacciniforme	40	Case reports	C IV	NA
Drug-induced photosensitivity	40	Case reports	C III	NA
Pruritus				
of polycythaemia vera	132	Open, uncontrolled study	B III	NA
of infiltrating breast cancer	133	Case report	C III	NA
Other generalized itch	122	Case series	C III	NA

BB-UVA, broadband ultraviolet (UV) A; RCT, randomized controlled trial; NA, not applicable. [a]See Appendix 1. [b]Other reports suggest that narrowband UVB may be contraindicated in adult pityriasis rubra pilaris; it should certainly be used with caution.

Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy

R.M.R. Hearn, A.C. Kerr, K.F. Rahim, J. Ferguson and R.S. Dawe
British Journal of Dermatology 2008 **159**, pp931–935

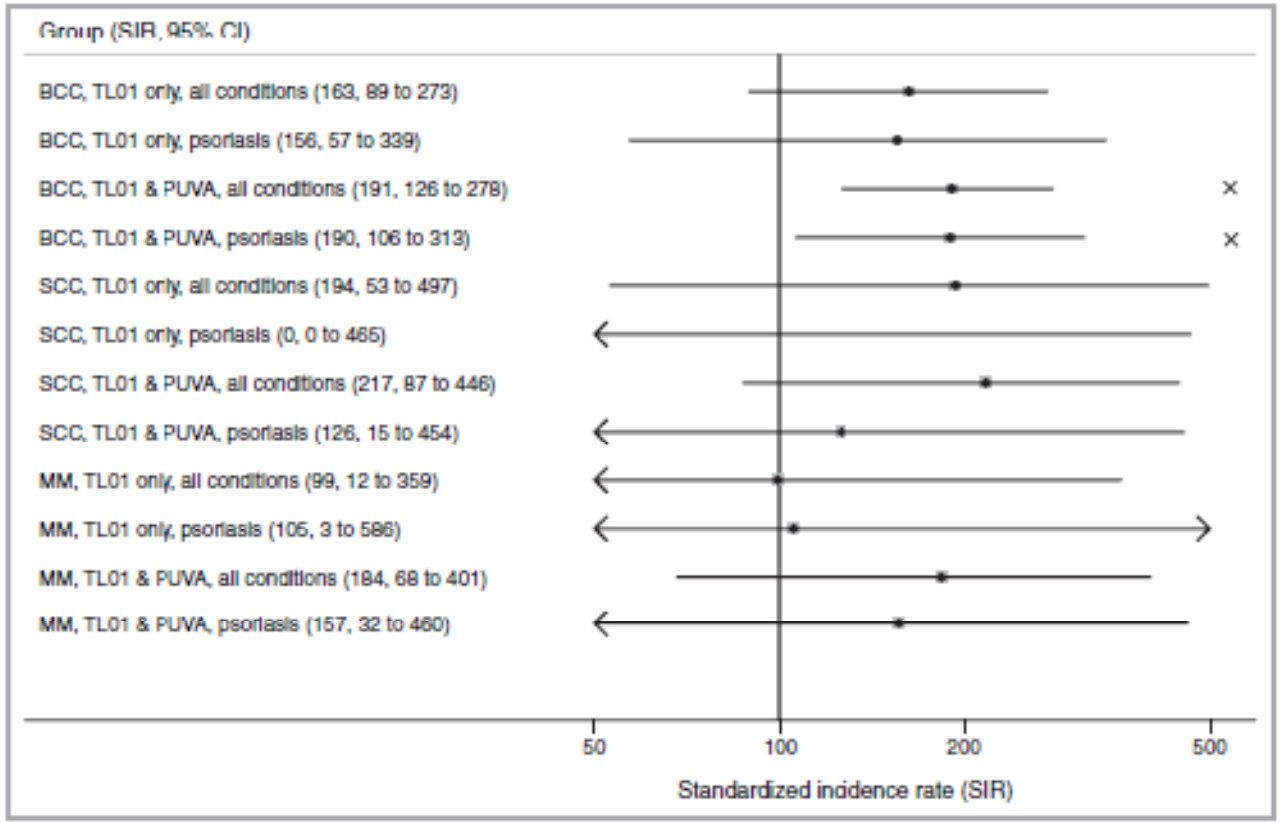


Table 1 Incidence rate ratios (IRR, comparing number of new cancers per person-year of follow-up) for skin cancers amongst patients treated with ≥ 100 NB-UVB treatments compared with those treated with ≤ 25 NB-UVB treatments

	IRR	95% confidence interval
BCC	1·22	0·28–4·25
SCC	2·04	0·17–17·82
Melanoma	1·02	0·019–12·73

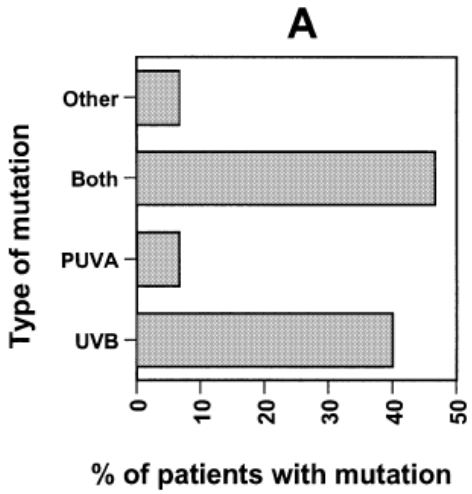
Table 2 Incidence rate ratios (IRR, comparing number of new cancers per person-year of follow-up) for skin cancers amongst patients treated with ≥ 100 PUVA treatments compared with those treated with no PUVA treatments

	IRR	95% confidence interval
BCC	2·06	0·89–4·73
SCC	1·66	0·24–9·80
Melanoma	4·43	0·64–48·99

p53 Mutation in Nonmelanoma Skin Cancers Occurring in Psoralen Ultraviolet A-Treated Patients: Evidence for Heterogeneity and Field Cancerization

Robert S. Stern, Svetlana Bolshakov*, Arun J. Nataraj,† and Honnavara N. Ananthaswamy*

VOL. 119, NO. 2 AUGUST 2002



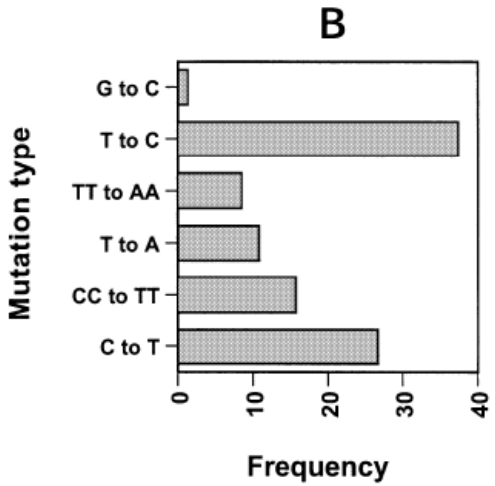


Table III. Frequency of PUVA and UV type *p53* mutations in skin cancers from PUVA-treated patients

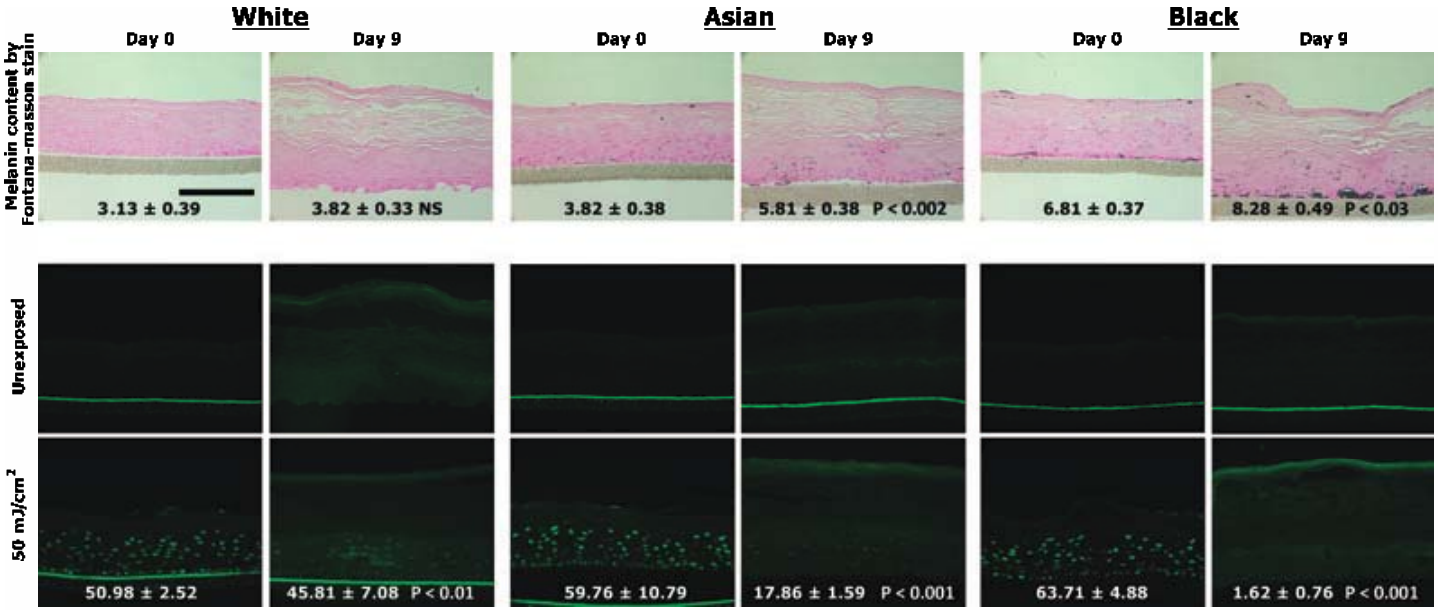
Mutation type[a]	Number of specific mutations/ total number of mutations	Mutation frequency
PUVA	34/83	41%
UV	36/83	44%
Other	13/83	15%

[a]Mutations arising at 5′-TpA and 5′-TpT sites are considered as PUVA type, whereas C to T, T to C, and CC to TT mutations occurring at dipyrimidine sites are considered as UV type.

The deceptive nature of UVA tanning versus the modest protective effects of UVB tanning on human skin

Yoshinori Miyamura[1], Sergio G. Coelho[1], Kathrin Schlenz[2], Jan Batzer[2], Christoph Smuda[2], Wonseon Choi[1], Michaela Brenner[1], Thierry Passeron[1], Guofeng Zhang[3], Ludger Kolbe[2], Rainer Wolber[2] and Vincent J. Hearing[1]

Pigment Cell Melanoma Res. **24**; 136–147 2010



Ultraviolet A1 phototherapy: a British Photodermatology Group workshop report

A. C. Kerr, J. Ferguson, S. K. Attili, P. E. Beattie,* A. J. Coleman,† R. S. Dawe, B. Eberlein,‡ V. Goulden,§ S. H. Ibbotson, H. du P. Menage,¶ H. Moseley, L. Novakovic,¶ S. L. Walker,¶ J. A. Woods, A. R. Young¶ and R. P. E. Sarkany¶

2012 British Association of Dermatologists • *Clinical and Experimental Dermatology*, **37**, 219–226

Chronic adverse effects of UVA1

Studies of chronic UVA1 effects in humans are limited. Three retrospective studies involving 423 patients, who received between 4 and 116 treatments in total,[26–28] reported no chronic effects. A case report of melanoma after UVA1 and PUVA treatment has been published.[29] There is some limited information on UVA1 from animal models, showing that it can induce squamous cell carcinomas and melanomas.

The role of near infrared radiation in photoaging of the skin

Peter Schroeder *, Judith Haendeler, Jean Krutmann

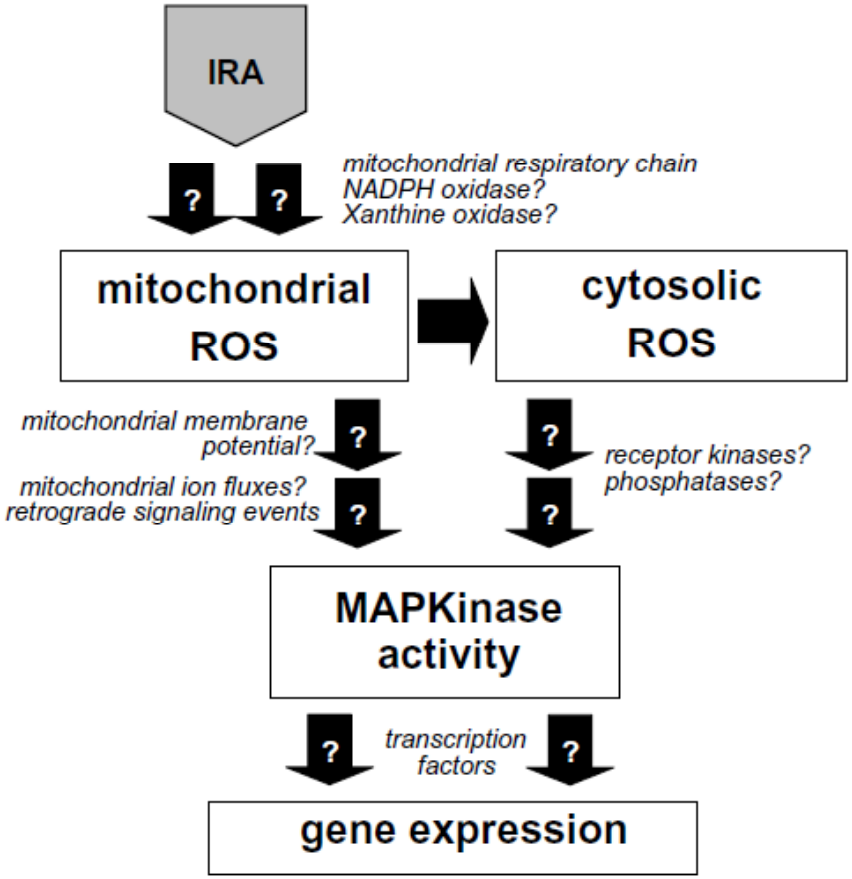
Experimental Gerontology 43 (2008) 629–632

Relevant sources:

-Natural solar radiation

-Artificial IRA sources used for therapeutic or wellness purpose

-Artificial UV sources contaminated with IRA



Conclusioni

Le sorgenti fototerapiche risultano essere molto efficaci nel trattamento di numerose patologie della cute presentando dei costi contenuti. Tuttavia occorre uno stretto controllo del dosaggio cumulativo e del numero di sedute al fine di limitare i danni a lungo termine (fotocancerogenesi e fotoinvecchiamento)

Studi epidemiologici hanno dimostrato che il maggior utilizzo dei lettini abbronzanti ha portato ad un'aumentata incidenza di tumori cutanei

Gli UVB a banda stretta possono contribuire al photoaging e in via teorica possono aumentare il rischio di insorgenza di tumori cutanei potenziando l'azione degli UVA

E' importante comprendere meglio l'azione molecolare di porzioni di spettro fino a poco tempo fa inesplorate quali l'IRA