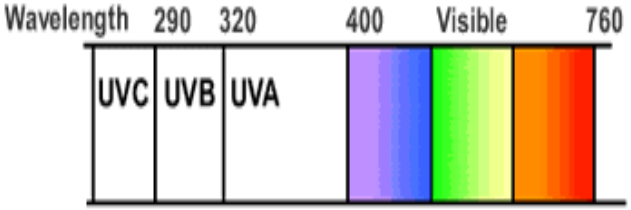
EXPOSURE TO ULTRAVIOLET (UV) LIGHT

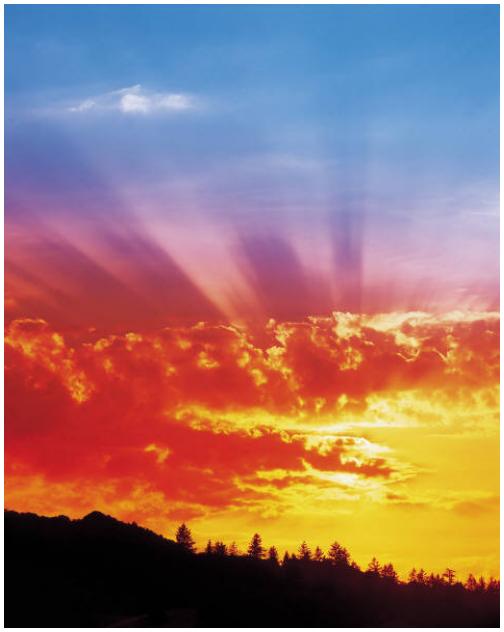
An Introduction To The Health Effects of Radiation

Elena Fridman
Beilinson Medical Center
Tel Aviv University
Israel

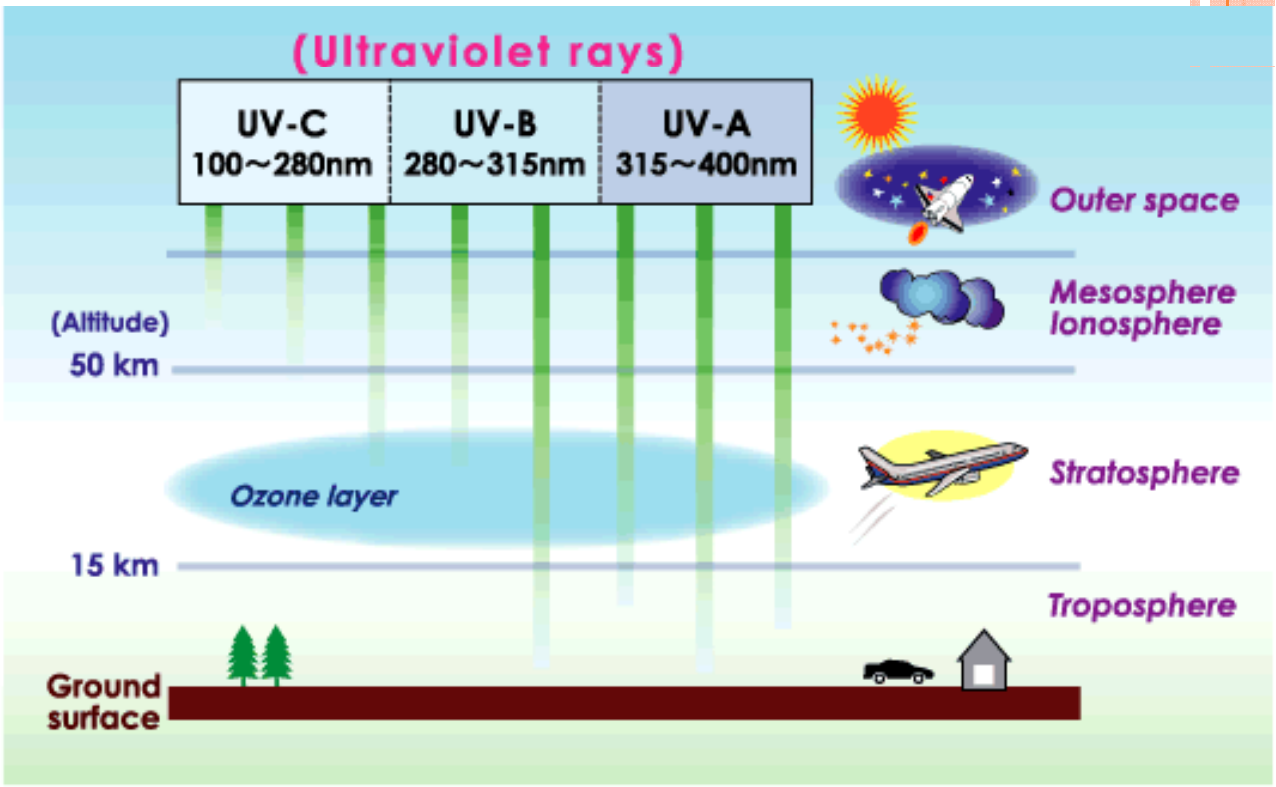
Ultraviolet Radiation

- Most significant source of U.V. is the sun.
- 1801, Johann Wilhelm Ritter
- Electromagnetic radiation
- Wavelength 400nm to below 290nm.
- Divided into three bands, A, B and C band.





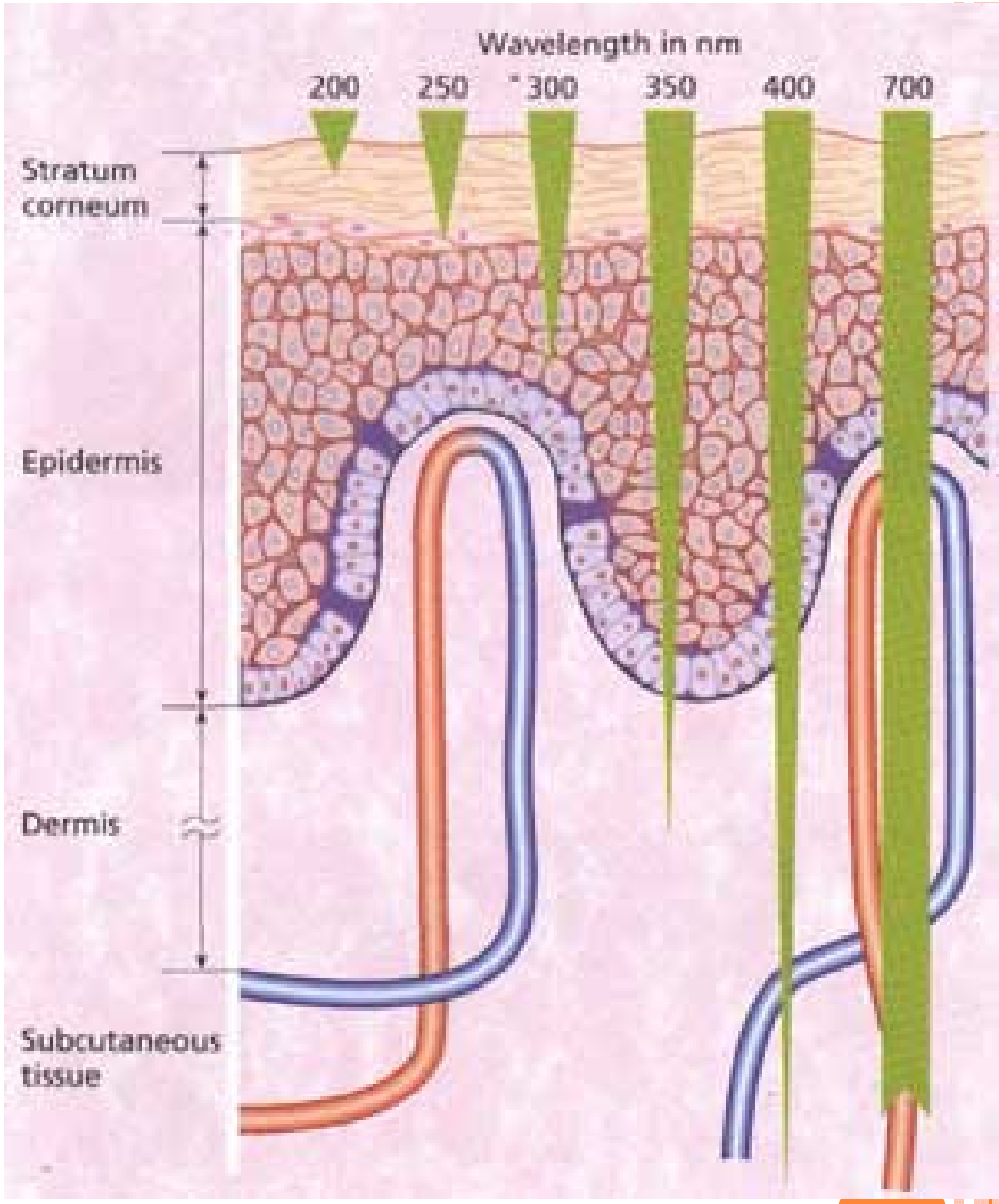
- A and B bands reach the earth, whereas C band is filtered by the ozone layer. U.V.A penetrate farthest
- Produce physiological effect by non thermal mechanism
- Deepest penetration with high intensity, long wavelength and lower frequency.



1.Ultraviolet C (UVC, 100-290 nm) are the shortest and most energetic portion of the UV spectrum. These highly energetic wavelengths The important wavelengths in the UVC are removed within the atmosphere, mainly by absorption in the ozone layer and not reach the earth's surface in any quantity.

2.Ultraviolet B (UVB, 290-320nm) is the most damaging part of UVR that we encounter. UVB are wavelengths mostly blocked by dense clouds, closely woven clothing and glass window panes. Significant amounts are transmitted from blue sky in the middle of the day in summer. It is less dangerous when the sun is low in the sky, at high latitude in winter, and in early mornings and late evenings in summer.

3.Ultraviolet A (UVA, 320-400nm) is about 1000 times less damaging to the skin than UVB as measured by sunburn (Erythema) or damage to cell DNA. On the other hand, 20 times more UVA than UVB reaches the earth in the middle of a summer's day. It is not greatly affected by absorption and scattering in the atmosphere when the sun is low in the sky, and is now known to contribute significantly to the total exposure at moderate levels throughout the whole day and year. UVA penetrates deeper into the skin and leads to deeper damage than UVB does. It penetrates cloud cover, light clothing and untinted glass relatively easily, and may induce a degree of continuing skin damage over long periods, even when UVR exposure is not obvious.



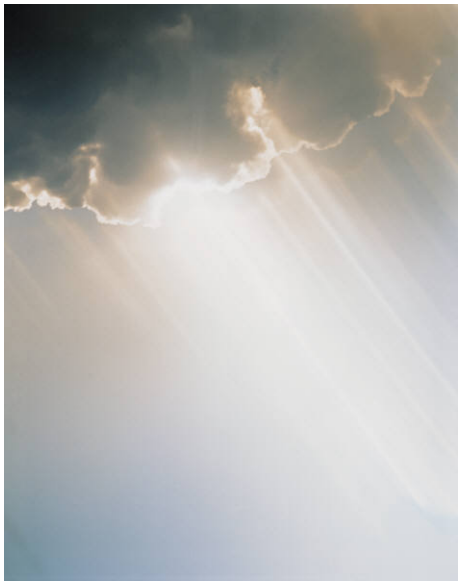
American Cancer Society 2006

PHYSIOLOGICAL EFFECTS OF U.V.R

1- Erythema production:

- Generalized response to UVR exposure culminates in development of an acute inflammatory reaction
- Depends on the amount of U.V.
- High dose → destructive.
- Suberythemal dose SED
  - No change in 24h after exposure.
- Minimal erythema dose MED
  - Smallest dose that produces erythema within 1-6 hr
  - Disappears within 24 hours
- 1st to 3 rd-degree erythema

AAP *Pediatric Environmental Health*, November 2003.

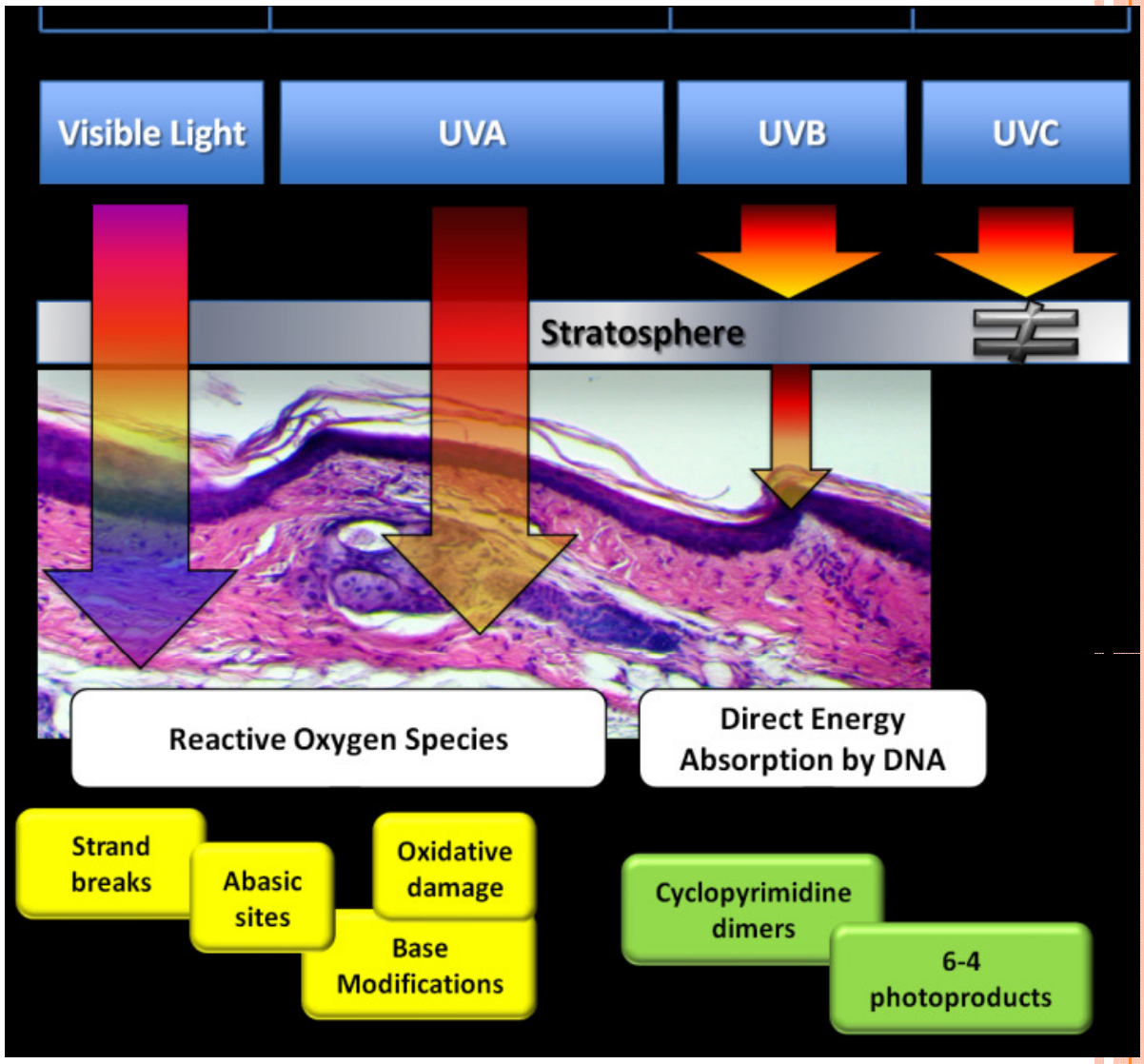


The Invisible Health Risk

Sunlight, Ultraviolet Radiation, and the Skin. NIH Consensus Statement Online 1989 May 8-10;7(8):1-29.

•Human exposure to UVR from natural sunlight and artificial sources is increasing substantially.
•UVR in sunlight is critical for vitamin D synthesis in the skin. However, it produces a variety of pathologic effects, including sunburn, pigmentary change, immunologic alterations, and neoplasia and photodamage.

- Human exposure to ultraviolet radiation. Diffey BL. Semin Dermatol 1990 Mar;9(1):2-10.
- Mouret S, Baudouin C, Charveron M, Favier A, Cadet J, Douki T. Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation. Proc Natl Acad Sci USA 2006; 103: 13765- 13770.
- Jou PC, McCormick TS, Baron ED. UV immunosuppression and cutaneous malignancies. Expert Rev Dermatol 2011; 6:61-74.



Proc. Natl. Acad. Sci. USA
Vol. 74, No. 4, pp. 1688–1692, April 1977
Immunology

Systemic alteration induced in mice by ultraviolet light irradiation and its relationship to ultraviolet carcinogenesis

(immune surveillance/tumor immunology/immunosuppression)

MICHAEL S. FISHER AND MARGARET L. KRIPKE

THE FIRST EVIDENCE OF THE IMPACT OF UVR ON THE IMMUNE SYSTEM IN A RODENT MODEL WAS REPORTED IN 1977 BY FISHER ET AL, WHO NOTICED THAT ANTIGENIC TUMOR CELLS, WHICH ARE REJECTED BY THE IMMUNE SYSTEM OF NON-IRRADIATED MICE, ARE NOT REJECTED WHEN THE ANIMAL HAS UNDERGONE A PERIOD OF UVR PRIOR TO TRANSPLANTATION OF THE TUMOR CELLS

Animal data

J Immunol.1987 Oct 15;139(8):2788-93.
Immunity to herpes simplex virus type 2. Suppression of virus-induced immune responses in ultraviolet B-irradiated mice.
Yasumoto S[1], Hayashi Y, Aurelian L

Eur J Pharmacol.1995 Mar 16;292(3-4):223-31.
A rat cytomegalovirus infection model as a tool for immunotoxicity testing.
Garssen J, Van der Vliet H, De Klerk A, Goettsch W, Dormans JA ,Bruggeman CA, Osterhaus AD, Van Loveren H

Int Immunopharmacol.2002 Feb;2(2-3):263-75.
A review of studies on the effects of ultraviolet irradiation on the resistance to infections: evidence from rodent infection models and verification by experimental and observational human studies.
Termorshuizen F[1], Garssen J, Norval M, Koulu L, Laihia J, Leino L, Jansen CT, De Gruijl F, Gibbs NK, De Simone C, Van Loveren H

Ultraviolet Light (UVR) Effects Immunity

- Sub-erythemal doses of UVR (x5) increased polymorphonuclear chemotaxis in healthy volunteers. Csato M et al., British Journal of Dermatology 1984;111: 567-570.

- 410 athletes who received sub-erythemal doses of UVR (twice a year for three years) had more salivary IgA, IgG and IgM; 50% less respiratory viral infections, 300% fewer absence days and 30% shorter illness than did 446 non-irradiated control athletes. Gigineishvili GR, *et al*. Voprosy Kurortologii, Fizioterapii, i Lechebnoĭ Fizicheskoĭ Kultury 1990 May-Jun;(3):30-3.

- A sub-erythemal dose of UVR for 6-8 weeks doubled phagocytic activity in 21 children with recurrent respiratory tract infections. Krause R, et al. In: Holick MF and Jung EG, eds. Biological Effects of Light. Kluver Academic Publishers, 1998: pp. 49-51.

HIV

Solar ultraviolet radiation exposure does not appear to exacerbate HIV infection in homosexual men. The Multicenter AIDS Cohort Study.
Saah AJ, Horn TD, Hoover DR, Chen C, Whitmore SE, Flynn C, Wesch J, Detels R, Anderson R.
Int J STD AIDS. **1990** Jan;1(1):46-8.

Flegg PJ. Int J STD AIDS.1990 Jan;1(1):46-8.**Potential risks of ultraviolet radiation in HIV infection.**

Med Hypotheses.1996 Jul;47(1):11-4.**Review of the impact on the activation of the human immunodeficiency virus type 1 of ultraviolet light.** Duan Y[1], Kennedy SB 4th

Int J Hyg Environ Health.2002 Jul;205(5):373-7.
Amsterdam Cohort Study on HIV and AIDS: impact of exposure to UVR as estimated by means of a 2-year retrospective questionnaire on immune parameters in HIV positive males.
Maas J[1], Termorshuizen F, Geskus RB, Goettsch W, Coutinho RA, Miedema F Van Loveren H

Int J Hyg Environ Health.2002 Jul;205(5):379-84.
Seasonal influences on immunological parameters in HIV-infected homosexual men: searching for the immunomodulating effects of sunlight.
Termorshuizen F[1], Geskus RB, Roos MT, Coutinho RA, Van Loveren H

HERPES SMPLEX

Lancet.1991 Dec 7;338(8780):1419-22.
Prevention of ultraviolet-light-induced herpes labialis by sunscreen.
Rooney JF[1], Bryson Y, Mannix ML, Dillon M, Wohlenberg CR, Banks S, Wallington CJ Notkins AL, Straus SE

Cutis.2004 Nov;74(5 Suppl):14-8.
Sunlight is an important causative factor of recurrent herpes simplex.
Ichihashi M[1], Nagai H, Matsunaga K

The Effect of Ultraviolet Radiation on Human Viral Infections
Norval, Mary
Photochemistry and Photobiology; Nov/Dec 2006; 82, 6; ProQuest Nursing & Allied Health Source pg. 1495

Visser et al. BMC Infectious Diseases 2014, 14:151
http://www.biomedcentral.com/1471-2334/14/151

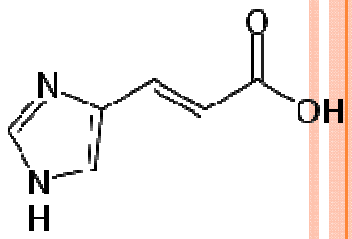
BMC Infectious Diseases

RESEARCH ARTICLE Open Access

The epidemiology of infectious mononucleosis in Northern Scotland: a decreasing incidence and winter peak

Elizabeth Visser[1*], Denis Milne[2], Ian Collacott[3], David McLernon[1], Carl Counsell[4] and Mark Vickers[5]

IMMUNE SUPPRESSION BY UV RAYS



- direct
  - pyrimidin dimers formation – mostly thymin
  - indirect
    - ROS formation (following excitation of „chromophores“ – molecules containing conjugated double bonds and/or aromatic circles)
    - retinoid depletion in skin
- folate degradation – systemic effects
- UCA urocanic acid

Natural sunscreen

Cis-UCA immunosupression

An Action Spectrum for the Production of *cis*-Urocanic Acid in Human Skin *In Vivo*

J Invest Dermatol 124:1071–1074, 2005

Pauline McLoone,*† Eniko Simics,†‡ Alan Barton,† Mary Norval,* and Neil K. Gibbs§

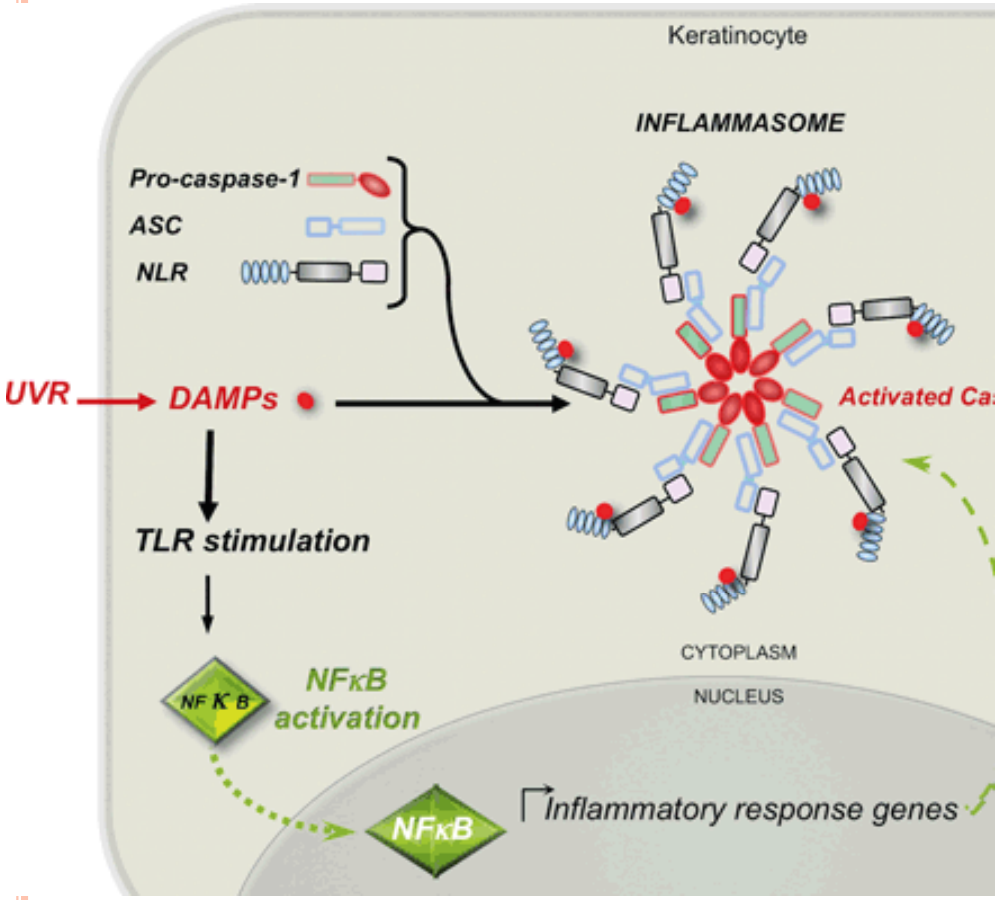
The effect of clinical UVA/B exposures on urinary urocanic acid isomer individuals with caucasian type (II/III) skin types
Chandan M Sastry[1], Susan E Whitmore[2], Patrick N Breysse[1], Warwic T Strickland[1] Dermatology Online Journal 11 (3): 1 2005

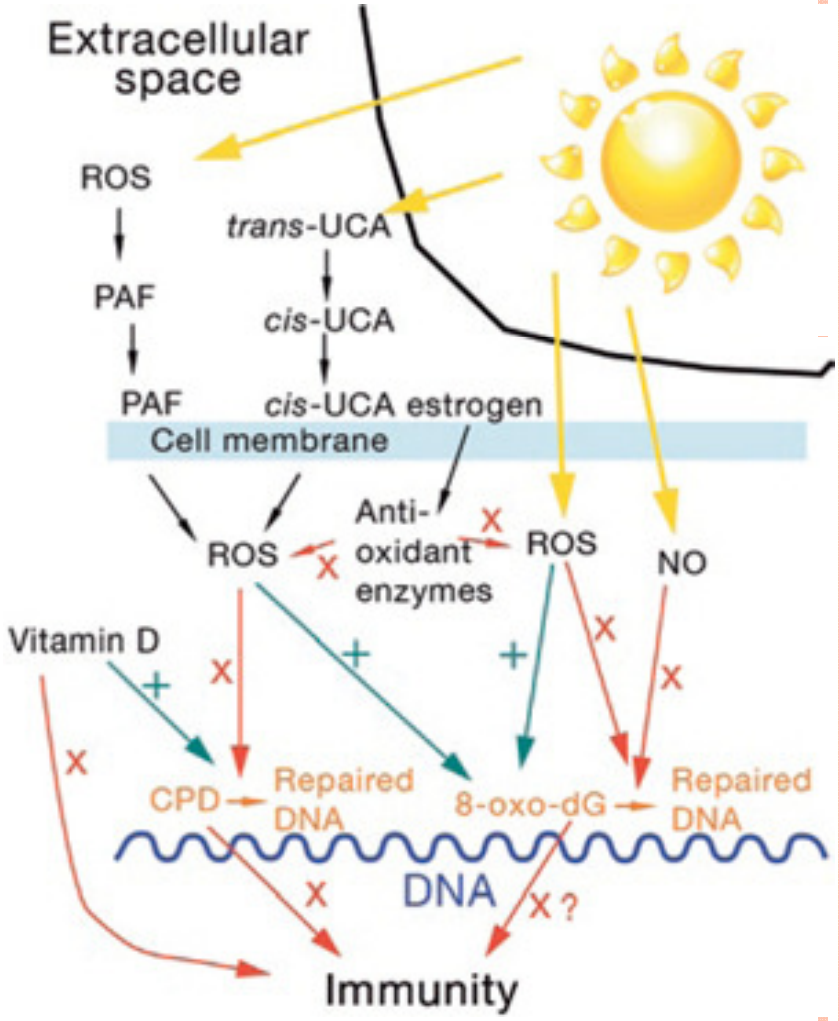
Cole C. Sunscreen protection in the ultraviolet A region: how to measure the effectiveness. *Photodermatol Photoimmunol Photomed* 2001;17(1):2–10

Hebert AA. Photoprotection in children. *Adv Dermatol.* 1993;8:309–324; discussion 325

Marrot L, Meunier JR. Skin DNA photodamage and its biological consequences. *J Am Acad Dermatol.* 2008;58(5 suppl 2): S139–S148

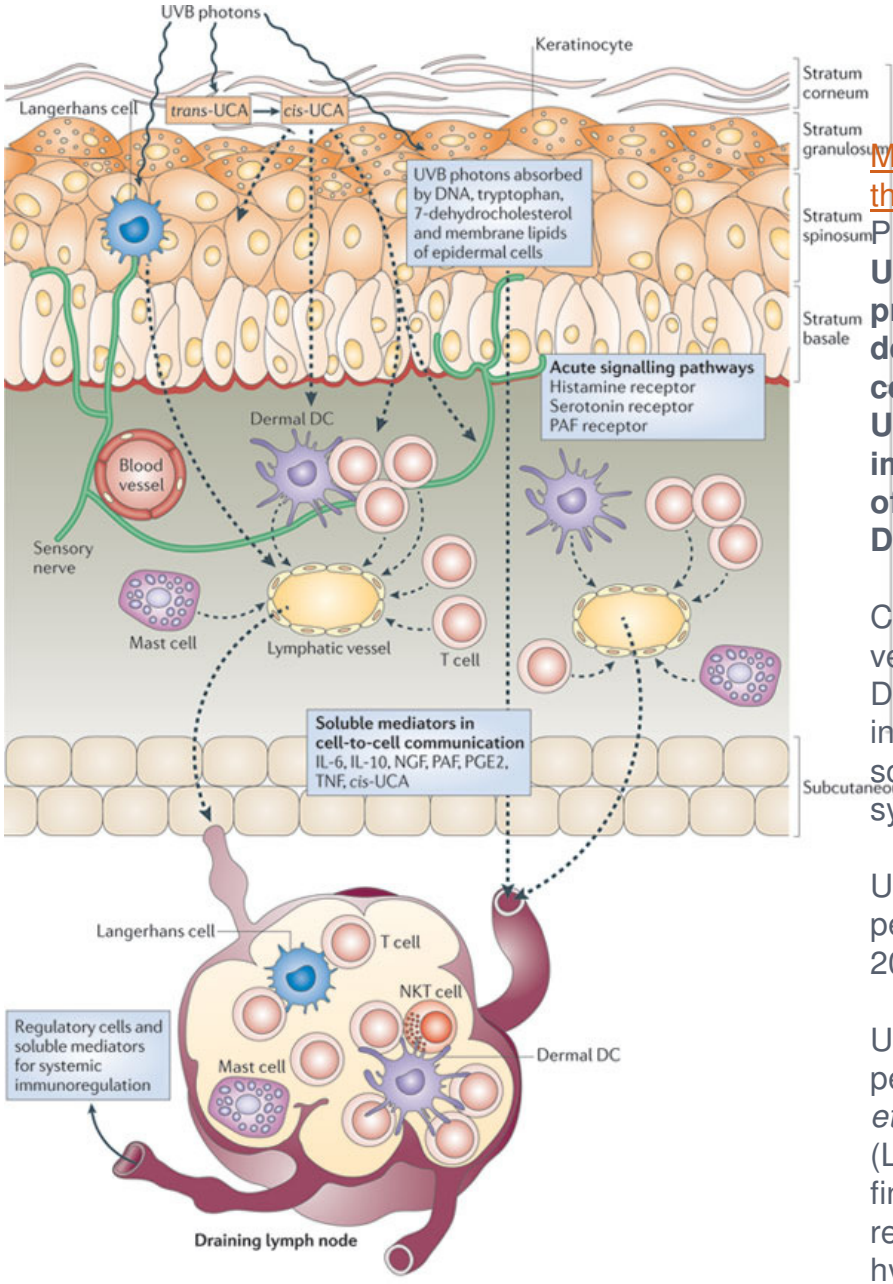
Dahle J, Kvam E. Induction of delayed mutations and chromosomal instability in fibroblasts after UVA-, UVB-, and X-radiation. *Cancer Res.* 2003;63(7):1464–1469





Common Links among the Pathways Leading to UV-Induced Immunosuppression
Gary M. Halliday

UV-induced mechanisms of immunomodulation



[Modulation of the immune system by UV radiation: more than just the effects of vitamin D?](#)

Prue H. Hart, Shelley Gorman & John J. Finlay-Jones

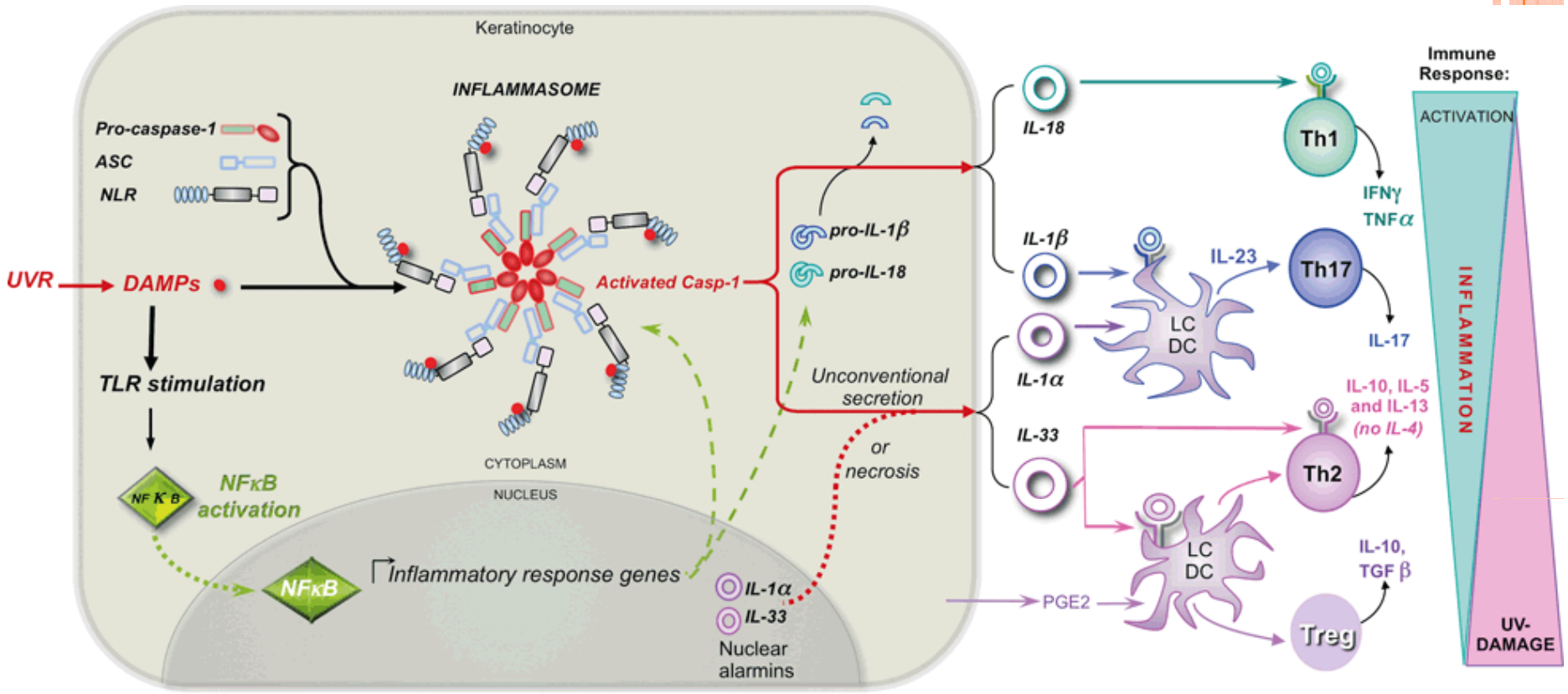
UV radiation causes dysregulation of antigen-presenting cells such as Langerhans cells and dermal dendritic cells, which in turn can activate regulatory T cells to suppress the immune system.

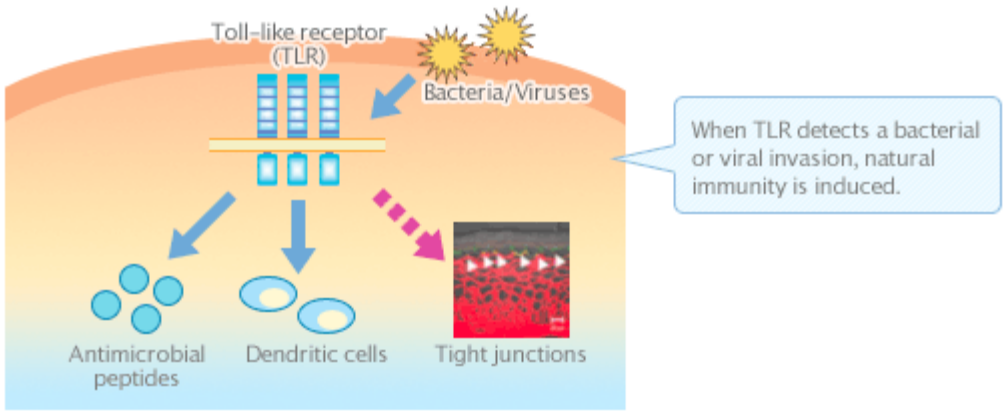
UV radiation can also induce keratiocytes produce immunosppressive cytokines that inhibit the production of a number of " repair cytokines" that fix UV induced DNA damage.

Cellular traffic to the draining lymph nodes via lymphatic vessels increases and includes Langerhans cells, dermal DCs and mast cells. In the draining lymph nodes, cell–cell interactions stimulate the production of regulatory cells and soluble mediators that are responsible for UV-induced systemic immunoregulation.

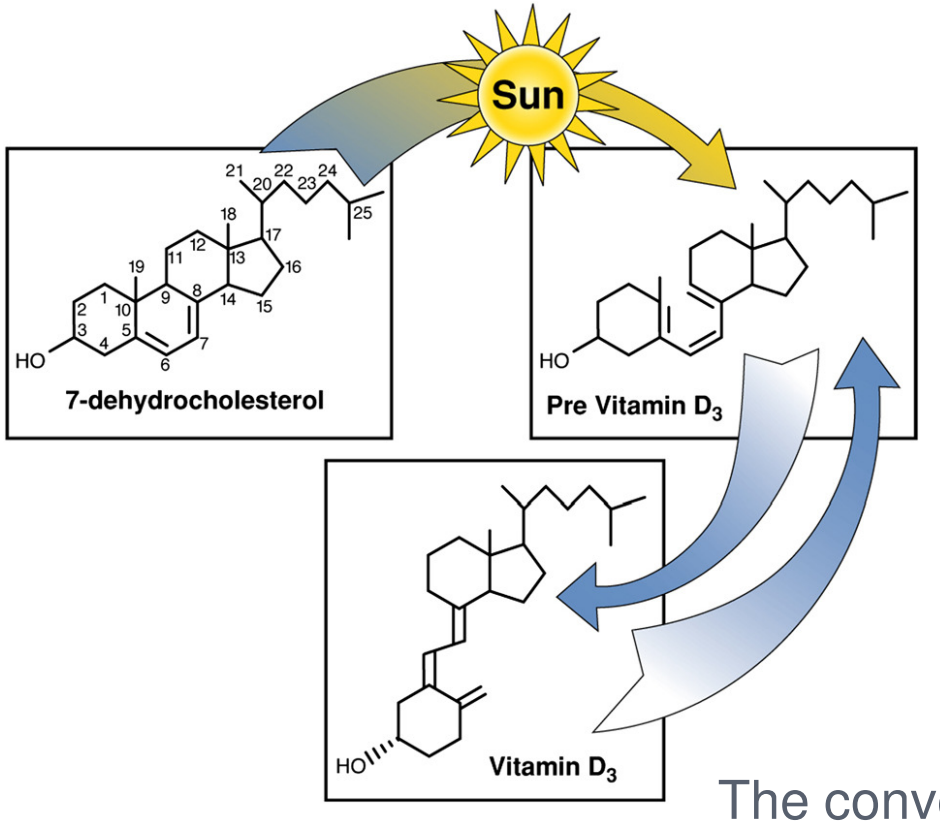
UVR disrupts the corneal layer, which enables the penetration of bacteria and contact allergens (Jiang *et al.*, 2006).

UVR stimulates keratinocytes to release antimicrobial peptides (AMPs), which attack the invading microbes (Gläser *et al.*, 2009). UVR alters the capacity of Langerhans cells (LC) to present antigens including contact allergens. This finally does not result in sensitization but in the induction of regulatory T cells (Treg cells), which suppress the contact hypersensitivity response against these antigens (Schwarz, 2008).


Keratinocyte
INFLAMMASOME
Pro-caspase-1
ASC
NLR
UVR
DAMPs
TLR stimulation
NFκB activation
NFκB
Activated Casp-1
pro-IL-1β
pro-IL-18
Unconventional secretion
or necrosis
CYTOPLASM
NUCLEUS
Inflammatory response genes
IL-1α
IL-33
Nuclear alarmins
IL-18
IL-1β
IL-1α
IL-33
PGE2
LC DC
LC DC
IL-23
Th1
Th17
Th2
Treg
IFNγ
TNFα
IL-17
IL-10, IL-5 and IL-13 (no IL-4)
IL-10, TGF β
Immune Response:
ACTIVATION
INFLAMMATION
UV-DAMAGE


Toll-like receptor (TLR)
Bacteria/Viruses
When TLR detects a bacterial or viral invasion, natural immunity is induced.
Antimicrobial peptides
Dendritic cells
Tight junctions

The Primary Source Of Vitamin D Is UVB Radiation From Sunlight

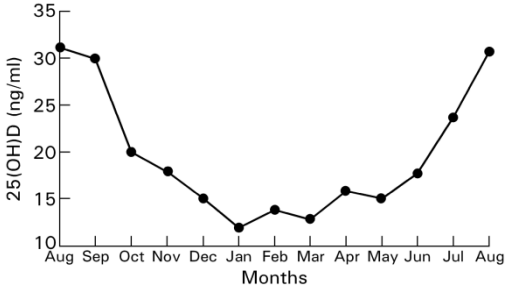


Engelsen, O., M. Brutstad, L. Aksnes and E. Lund (2005) Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover and cloud thickness. *Photochem. Photobiol.* **81**, 1287–1290.

Webb, A. R., L. Kline and M. F. Holick (1988) Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J. Clin. Endocrinol. Metab.* **67**, 373–378.

The conversion of 7-dehydrocholesterol to previtamin D_3 by 282–310 nm UV light and the temperature-dependent equilibrium between previtamin D_3 and vitamin D_3.

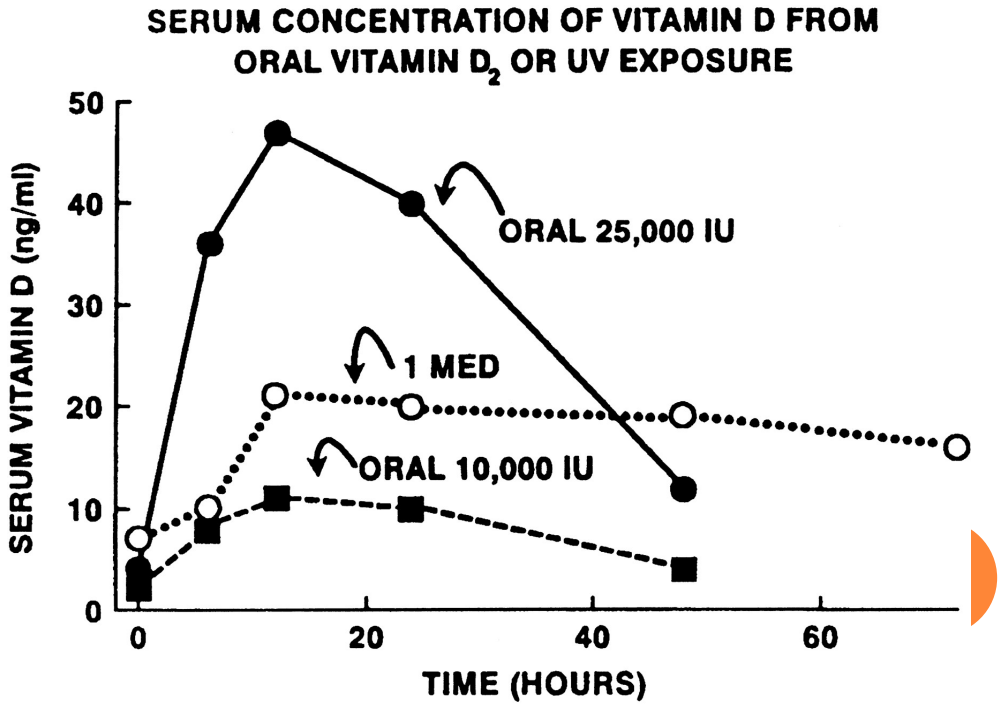
SEASONAL VARIATION OF 25(OH)D LEVELS



Cannell JJ, Vieth R, Umhau JC,et al. Epidemiol Infect. 2006

Serum vitamin D concentrations after a whole-body exposure to 1 MED (of simulated sunlight in a tanning bed and after a single oral dose of either 10,000 or 25,000 IU vitamin D-2.

JN THE JOURNAL OF NUTRITION



Holick M F J. Nutr. 2005;135:2739S-2748S

VITD AND INFLAMMATION

- Vit D injections averaging 547iu/day x 2-5 years – 23% decrease in CRP Timms et al. QJM. 2002;95:787.
- Vit D supp in pts w/ prolonged clinical illness saw decreases in IL-6 and CRP. Van den Berghe et al. J Clin Endocrinol Metab. 2003;88(10):4623
- 1,25(OH)2D3 has opposing effects: it can mimic immunosuppressive effects caused by UV irradiation in some models, or reverse UV-induced DNA damage and immunosuppression in other models.
- 1,25(OH)2D3 exerts effects on Langerhans cells that are characteristic of those associated with UV radiation (UVR)-induced suppression of contact hypersensitivity.
- 1,25(OH)2D3 as either a mediator of UVR-induced immune suppression or as a photoprotective molecule against UVR-induced DNA damage and immune suppression.

- Reichrath J, Rappl G. Ultraviolet light (UV)-induced immunosuppression: is vitamin D the missing link? J Cell Biochem 2003; 89: 6–8.
- Hanneman KK, Scull HM, Cooper KD, Baron ED. Effect of topical vitamin D analogue on in vivo contact sensitization. Arch Dermatol 2006; 142: 1332–4.
- Wong G, Gupta R, Dixon KM et al. 1,25-Dihydroxyvitamin D and three low-calcemic analogs decrease UV-induced DNA damage via the rapid response pathway. J Steroid Biochem Mol Biol 2004; 89–90: 567–70.

VITAMIN D EFFECTS IMMUNITY

- 1,25(OH)2D3 mediates photoprotection in both mouse and human skin. It reduces DNA damage and skin-cell apoptosis after UVR irradiation of human skin cells in vitro,4,5 and in mouse skin in vivo.5–7
- Treatment with 1,25(OH)2D3 or a cis-locked vitamin D analogue of cultured human fibroblasts, keratinocytes and melanocytes protects these cells from UVR-induced apoptosis.4
- In both mouse skin in vivo and human skin cells cultured in vitro, 1,25(OH)2D3 is photoprotective, in that it decreases cell death and DNA damage, and also reverses immunosuppression caused by UVR in a murine CHS model.

- Wong G, Gupta R, Dixon KM et al. 1,25-Dihydroxyvitamin D and three low-calcemic analogs decrease UV-induced DNA damage via the rapid response pathway. J Steroid Biochem Mol Biol 2004; 89–90: 567–70.
- Dixon KM, Deo SS, Wong G et al. Skin cancer prevention. A possible role of 1, 25dihydroxyvitamin D3 and its analogs. J Steroid Biochem Mol Biol 2005; 97: 137–43.
- Vitamin D promotes macrophage production of specific surface antigens, the lysosomal enzyme acid phosphatase, and the secretion of H_2O_2 (which is antimicrobial), but vitamin D deficiency decreases these functions. Abu-Amer Y, Bar-Shavit Z. Cellular Immunology 1993; 151: 356-368. Cohen MS, *et al*. Journal of Immunology 1986; 136: 1049-1053.

- Vitamin D stimulates genetic expression of antimicrobial peptides, which have broad-spectrum antimicrobial activity and inactivate influenza virus. Wang TT, *et al*. Journal of Immunology 2004; 173: 2909-2912. Gombart AF et al, The FASEB Journal 2005; 19: 1067-1077. Liu PT, *et al*. 2006; 311: 1770-1773. Reddy KV et al, International Journal of Antimicrobial Agents 2004; 24: 536-547. Hiemstra PS, *et al*. Current Pharmaceutical Design 2004; 10: 2891-2905. Daher KA et al, Journal of Virology 1986; 60: 1068-1074.

Research associates vitamin D with:

Acne
Acute lower respiratory infection
Alzheimer's disease
Amyotrophic lateral sclerosis
Anaphylaxis
Anemia
Ankylosing spondylitis
Anxiety
Asthma
Athersclerosis
Autism
Bacterial vaginosis
Biliary cirrhosis, primary (PBC)
Birth defects
Bones – fractures
Bones - osteopenia
Bones – osteoporosis
Bones – Paget's disease? Bones – rickets
Brain injury, traumatic
Bronchitis
Cancer – 20 types (Bladder, breast, cervical, colorectal, endometrial, esophageal, gallbladder, gastric, Hodgkin's lymphoma, leukemia, lung, melanoma, multiple myeloma, non-Hodgkin's lymphoma, ovarian, pancreatic, prostate, renal, vulvar)
Cardiovascular disease
Celiac disease
Cerebrovascular disease
Chronic kidney disease
Chronic liver disease
Chronic, non-specific muscle pain
Cognitive impairment
Common cold
Epstein-Barr virus
Congestive heart failure
Chronic obstructive pulmonary disease
Coronary heart disease
Craniotabies
Cystic fibrosis
Dental caries
Depression
Diabetes, type 1
Diabetes, type 2,
Epilepsy
Fertility, regular menses
Fibromyalgia
Hashimoto's thyroiditis (HT)
Headache
Hearing loss
Hepatitis
HIV/AIDS
Hypercalcemia
Hyperparathyroidism
Hypertension
Inflammatory bowel disease
Influenza, type A
Insulin resistance
Ischemic cardiac arrhythmias
Kidney stones
Lupus
Macular degeneration
Meningitis
Metabolic disease
Mononucleosis
Multiple sclerosis
Muscle strength
Osteoarthritis
Pancreatis
Parkinson's disease
Pelvic floor status
Periodontal disease
Peripheral artery disease
Pneumonia
Polycystic ovary syndrome
Post herpetic neuralgia
Preeclampsia
Premature birth and low birth weight
Psoriatic arthritis
Renal failure
Renal osteodystrophy
Rheumatoid arthritis
Respiratory syncytial virus
Schizophrenia
Sepsis/septicemia
Sickle cell disease
Systemic sclerosis
Tonsillitis
Tuberculosis
Thrombosis
Uterine leiomyomas (fibroids)
Vascular dementia
Vitiligo vulgaris

VITAMIN D FROM SUNLIGHT AFFECTS TB

- The 1903 Nobel prize was awarded for the discovery that vitamin D from sunlight could cure cutaneous TB….

- **The Nobel Prize in Physiology or Medicine 1903**
- **Niels Ryberg Finsen**
- "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science"
- He has himself given the following short description of his work. «My disease has played a very great role for my whole development... The disease was responsible for my starting investigations on light

Cytokine. 2011 Aug;55(2):294-300 Khoo AL[1], Chai LY, Koenen HJ, Oosting M, Steinmeyer A, Zuegel U, Joosten I, Netea MG, van der Ven AJ	• Vitamin D(3) downregulates proinflammatory cytokine response t o Mycobacterium tuberculosis through patternrecognition recepto rs while inducing protective cathelicidin production..
Salamon H, Bruiners N, Lakehal K, Shi L, Ravi J, Yamaguchi KD, Pine R, Gennaro ML. J Immunol. 2014 Jul 1;193(1):30-4.	• Cutting edge: Vitamin D regulates lipid metabolism in Mycobacterium tuberculosis infection.
Jo EK. Cell Microbiol. 2010 Aug;12(8):1026-35.	• Innate immunity to mycobacteria: vitamin D and autophagy.
Wu S, Sun J. Discov Med. 2011 Apr;11(59):325-35.	• Vitamin D, vitamin D receptor, and macroautophagy in inflammation and infection.
Proc A. 2012 Dec 18;109(51):E3528; author reply E3529. doi: 10.1073/pnas.1216417109. Epub 2012 No v 6. Grey A, Bolland M	• Vitamin D and tuberculosis.
J Infect Dis.2014 Sep 1;210(5):774-83 Wingfield T[1], Schumacher SG[2], Sandhu G[3], Tovar MA[4], Zevallos K[5], Baldwin MR[6], Montoya R[5], Ramos ES[6], Jongkaewwattana C[7], Lewis JJ[8], Gilman RH[9],Friedland JS[10], Evans CA[11]	• The seasonality of tuberculosis, sunlight, vitamin D, and household crowding.
Chun RF, Adams JS, Hewison M. Expert Rev Clin Pharmacol. 2011 Sep;4(5):583-91.	• Immunomodulation by vitamin D: implications for TB.

HISTORICAL STUDIES: COD LIVER OIL PREVENTS RESPIRATORY INFECTIONS

- In the 1930's, Vitamin A was investigated for its anti-infective properties using Cod liver oil, (which is also abundant in Vitamin D)
- Five studies using cod liver oil, (involving over 7,000 subjects), showed that cod liver oil reduced respiratory infections
- Cod liver oil given to 185 adults for four months reduced colds by 50%; Holmes AD, et al. Journal of Industrial and Engineering Chemistry 1932; 24; 1058-1060.
- In a five year study, cod liver reduced industrial absenteeism caused by colds and respiratory illness; days of missed work was reduced by 30%. (n=3031) Homes AD, et al. Industrial Medicine 1936; 5: 359-361.

Epidemic Influenza

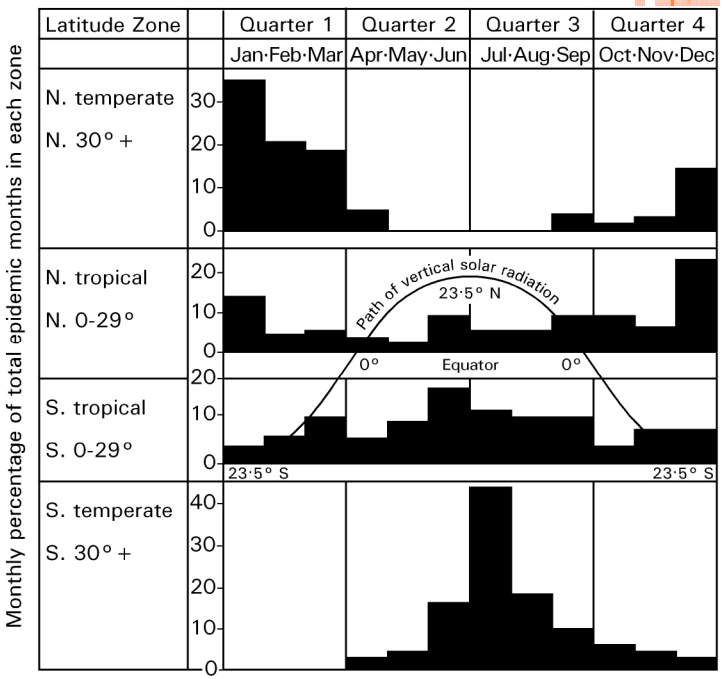
- Edgar Hope-Simpson pointed out that influenza outbreaks were inversely correlated with solar UV.
- Hope-Simpson RE. The role of season in the epidemiology of influenza. J Hyg (Lond). 1981 Feb;86(1):35-47.

The seasonal and latitudinal distribution of outbreaks of type A influenza in the world, 1964-1975

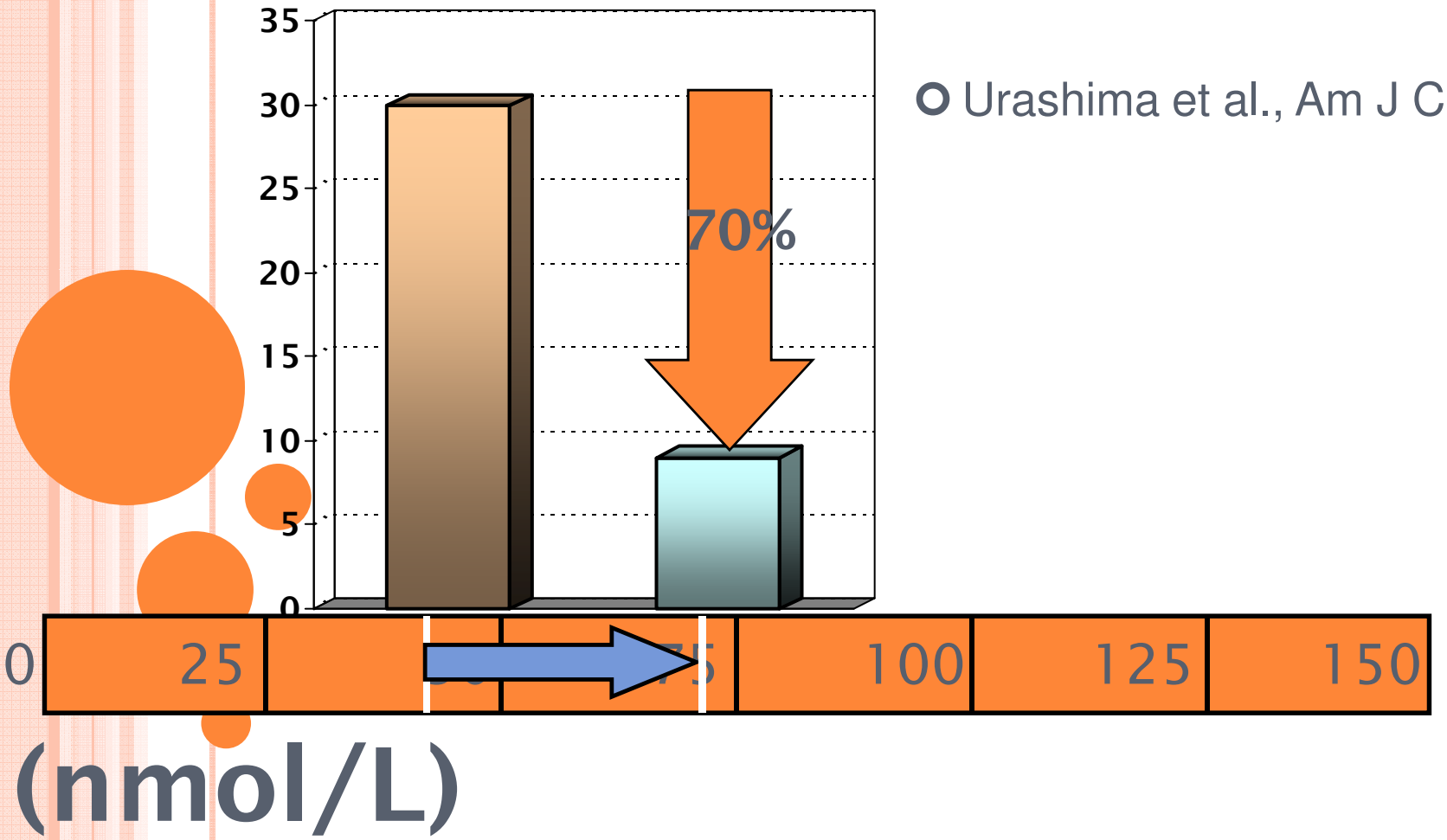
Shadrin AS, Marinich IG, Taros LY. Journal of Hygiene, Epidemiology, Microbiology, and Immunology 1977; 21:155–161.

- Zykov MP, Sosunov AV. Vaccination activity of live influenza vaccine in different seasons of the year. Journal of Hygiene, Epidemiology, Microbiology, and Immunology 1987; 31: 453–459.

(WHO Data)



RCT with Vitamin D for Type A Influenza



- Urashima et al., Am J Clin

VITAMIN D_3 SUPPLEMENTS ELIMINATE THE WINTER EXCESS INCIDENCE OF COLD / FLU

JOHN F. ALOIA AND MELISSA LI-NG, 2007, Epidemiology and Infection

RSV bronchiolitis

Vitamin D receptor (VDR) polymorphisms and severe RSV bronchiolitis: a systematic review and meta-analysis.

McNally JD, Sampson M, Matheson LA, Hutton B, Little J.
Pediatr Pulmonol. 2014 Aug;49(8):790-9.

J Pathol. 2014 Jan;232(1):57-64.

Defective control of vitamin D receptor-mediated epithelial STAT1 signalling predisposes to severe respiratory syncytial virus bronchiolitis.

Stoppelenburg AJ[1], von Hegedus JH, Huis in't Veld R, Bont L, Boes M.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Steroids in Neuroendocrine Immunology and Therapy of Rheumatic Diseases I*

Vitamin D: a new anti-infective agent?

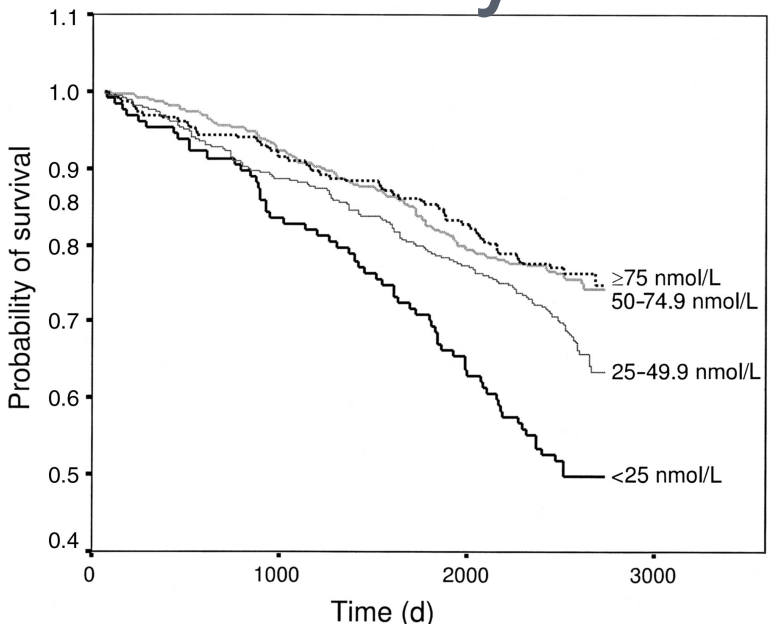
Elisabetta Borella,[1,2] Gideon Nesher,[2,3] Eitan Israeli,[2] and Yehuda Shoenfeld[2]

Table 1. Studies on Vitamin D supplementation in prevention and treatment of infectious diseases

Population studied	Vitamin D dose and duration	Outcome	References
67 patients with TB	0.25 mg/day of vitamin D or placebo during TB treatment	Significantly higher rate of sputum conversion in the vitamin D group (100% vs. 77%, $P = 0.002$)	32
Children 1–5 years old with recurrent episodes of otitis media and 25(OH) vitamin D deficiency	5000 IU/day in addition to conventional therapy	Decreased number of otitis media episodes	40
140 patients with Ig deficiencies or frequent RTIs	4000 IU/day of vitamin D3 or placebo for 1 year	Significantly fewer infections in the vitamin D group ($P = 0.04$)	68
247 children with vitamin D deficiency	Milk fortified with 300 IU of vitamin D3 ($n = 143$), or regular milk for 3 months	Vitamin D significantly reduced the risk of RTIs in winter among children with vitamin D deficiency	69
569 subjects	1111–6800 IU/day of vitamin D ($n = 289$) or placebo ($n = 280$)	No significant difference in the number of RTIs between the two groups	70
164 young men (18–28 years old)	400 IU/day of vitamin D3 ($n = 80$) or placebo for 6 months	Subjects who received vitamin D had fewer days of absence due to RTI during the first 6 weeks of follow-up	71
334 school children	1200 IU vitamin D3/day ($n = 167$) or placebo for 4 months	Influenza A occurred in 11% of children in the vitamin D group compared with 19% in the placebo group ($P = 0.04$)	72
162 adults	Vitamin D3 2000 IU/day or placebo for 12 weeks	No difference in incidence of RTIs or duration and severity of symptoms between the two groups	73
3046 children aged 1–11 months	100,000 IU of vitamin D3 once every 3 months for 18 months ($n = 1524$) or placebo	No significant difference in the incidence of pneumonia between the two groups	74
453 children aged 1–36 months with pneumonia	A single dose of 100,000 IU of vitamin D3 ($n = 224$) or placebo, along with antibiotics	No difference in mean number of days to recovery; risk of recurrent pneumonia within 90 days was lower in the vitamin D group (45% vs. 58%, $P = 0.01$)	75
322 healthy adults	200,000 IU vitamin D3 then 100,000 IU monthly ($n = 161$) or placebo, for 18 months	No reduction in incidence or severity of RTIs	76

Ig, immunoglobulin; RTI, respiratory tract infection; TB, tuberculosis.

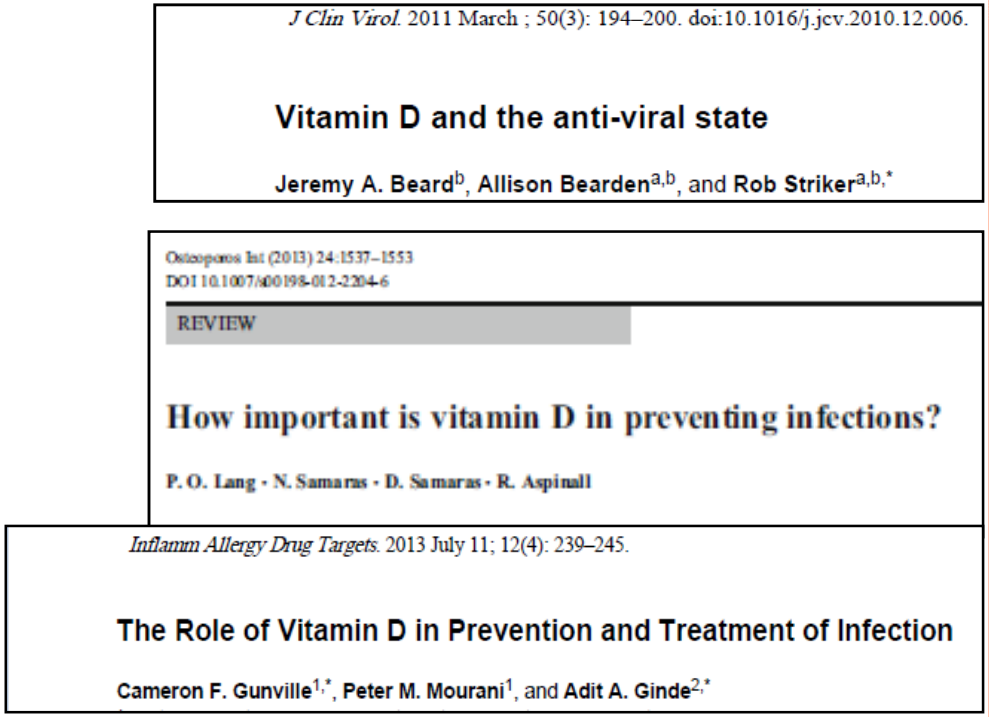
Mortality Rate and Vitamin D



Visser, M. et al
ACJN 2006: 616-622

- Overall, 12 original studies were included in the review and meta-analysis comprising 32,142 mainly elderly study participants with measured 25(OH)D of whom 6921 died during follow-up. An inverse association between 25(OH)D levels and all-cause mortality was found in all but two studies that was statistically significant in several of the individual studies. In meta-analysis, 25(OH)D levels were significantly inversely associated with all-cause mortality with a pooled HR of 0.92 (95% confidence interval: 0.89-0.95) for a 20 nmol/l increase in 25(OH)D levels.
- Schöttker B, Ball D, Gellert C, Brenner H. Serum 25-hydroxyvitamin D levels and overall mortality. A systematic review and meta-analysis of prospective cohort studies. Ageing Res Rev. 2012 Feb 16.
- **Vitamin D** deficiency in critically ill children. Madden K, Feldman HA, Smith EM, Gordon CM, Keisling SM, Sullivan RM, Hollis BW, Agan AA, Randolph AG. **Pediatrics**. **2012** Sep;130(3):421-8.

- HIV- immunological status, outcome, morbidity and mortality as well as the antiretrovial treatment
- Hepatitis B and C infection
- Colonic bacterial load and colitis, enteric infections, clostridium infections
- Bacterial vaginosis
- UTIs
- Sepsis
- Dengue fever



J Clin Virol. 2011 March ; 50(3): 194–200. doi:10.1016/j.jcv.2010.12.006.

Vitamin D and the anti-viral state

Jeremy A. Beard[b], Allison Bearden[a,b], and Rob Striker[a,b,*]

Osteoporos Int (2013) 24:1537–1553
DOI 10.1007/s00198-012-2204-6

REVIEW

How important is vitamin D in preventing infections?

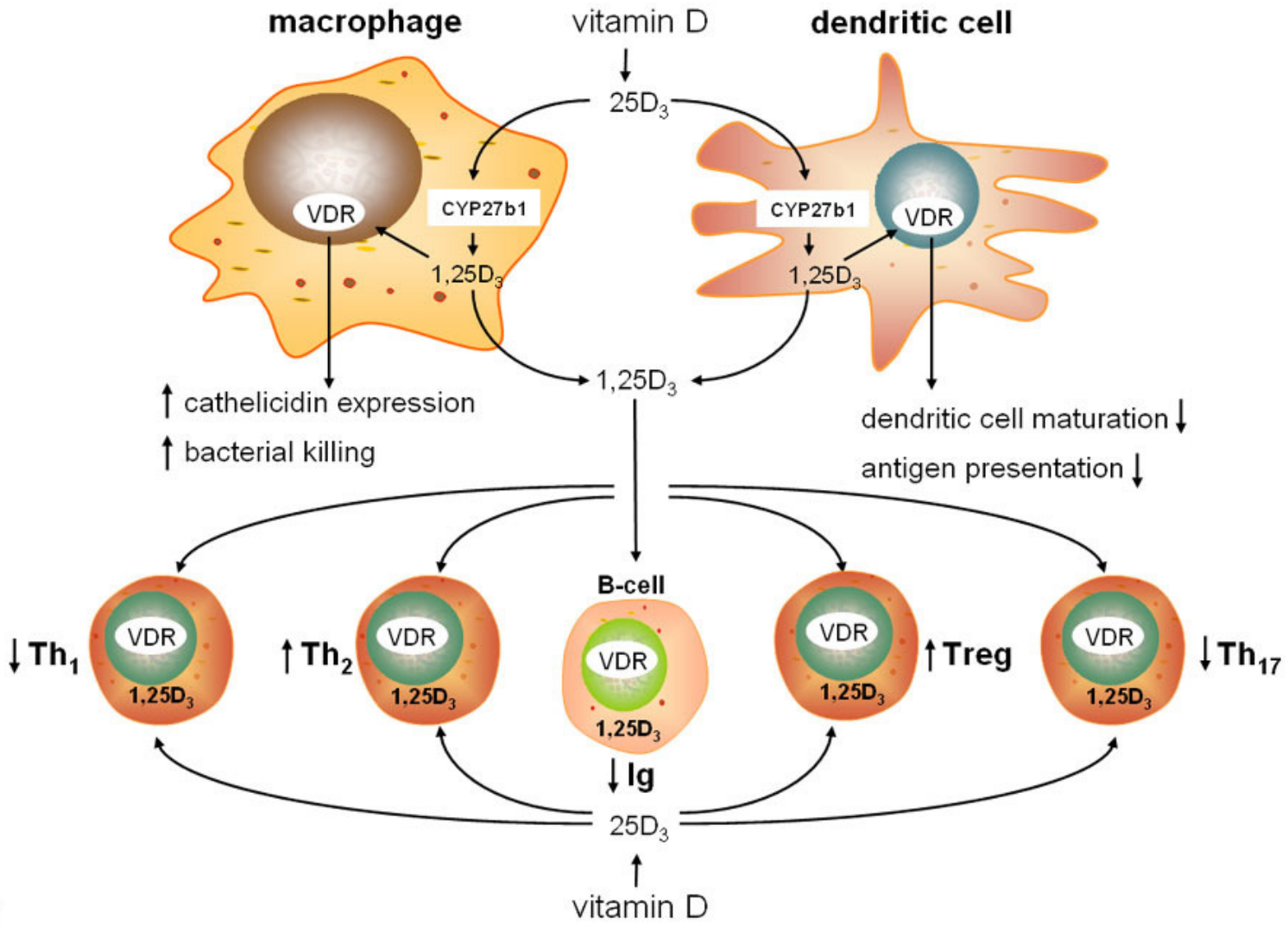
P. O. Lang · N. Samaras · D. Samaras · R. Aspinall

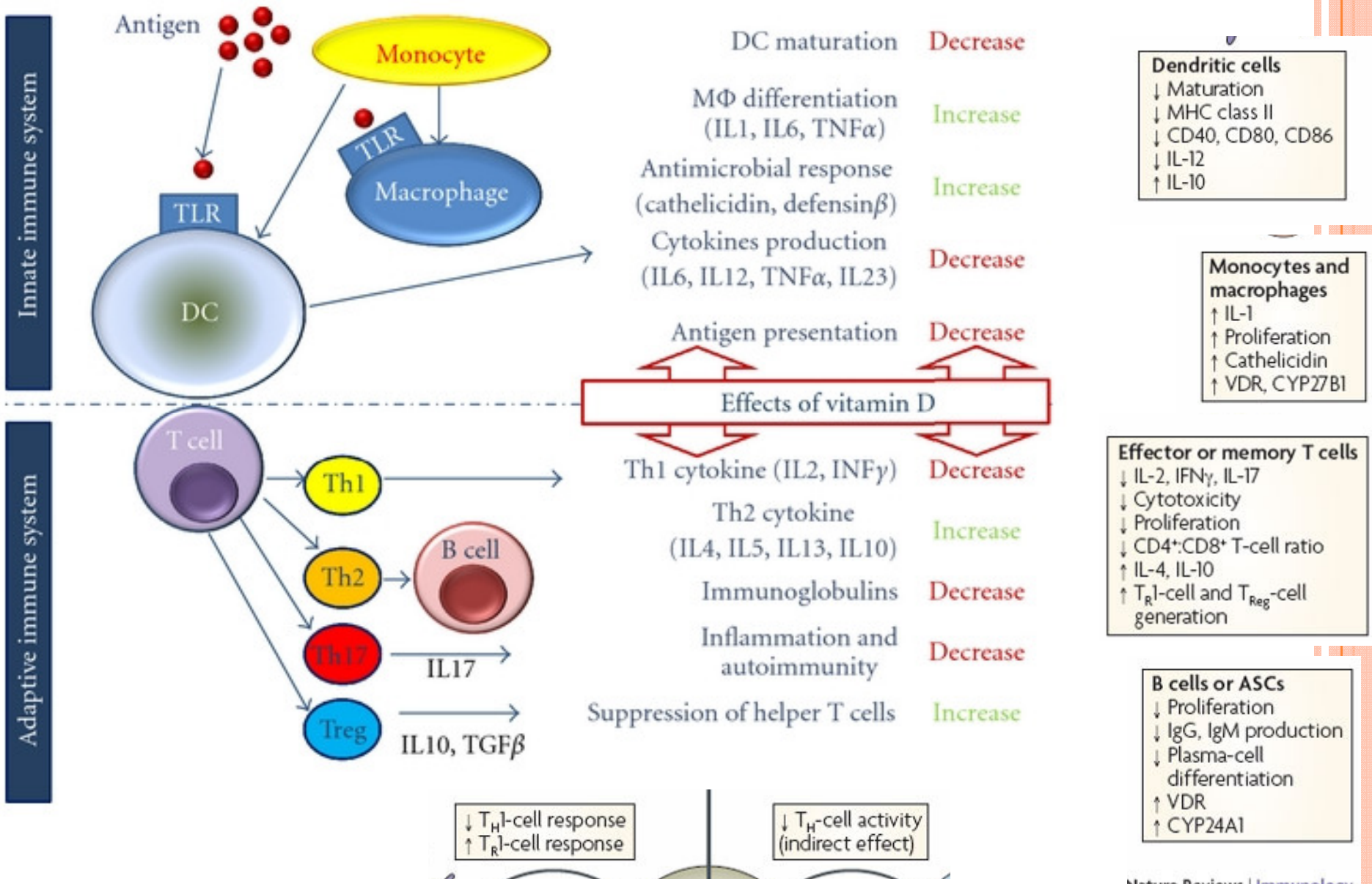
Inflamm Allergy Drug Targets. 2013 July 11; 12(4): 239–245.

The Role of Vitamin D in Prevention and Treatment of Infection

Cameron F. Gunville[1,*], Peter M. Mourani[1], and Adit A. Ginde[2,*]

VITAMIN D AND INNATE AND ADAPTIVE IMMUNITY.




Innate immune system
Adaptive immune system
Antigen
Monocyte
TLR
Macrophage
TLR
DC
T cell
Th1
Th2
B cell
Th17
IL17
Treg
IL10, TGFβ
DC maturation
Decrease
MΦ differentiation (IL1, IL6, TNFα)
Increase
Antimicrobial response (cathelicidin, defensinβ)
Increase
Cytokines production (IL6, IL12, TNFα, IL23)
Decrease
Antigen presentation
Decrease
Effects of vitamin D
Th1 cytokine (IL2, INFγ)
Decrease
Th2 cytokine (IL4, IL5, IL13, IL10)
Increase
Immunoglobulins
Decrease
Inflammation and autoimmunity
Decrease
Suppression of helper T cells
Increase
↓ TH1-cell response
↑ TR1-cell response
↓ TH-cell activity (indirect effect)
Dendritic cells
↓ Maturation
↓ MHC class II
↓ CD40, CD80, CD86
↓ IL-12
↑ IL-10
Monocytes and macrophages
↑ IL-1
↑ Proliferation
↑ Cathelicidin
↑ VDR, CYP27B1
Effector or memory T cells
↓ IL-2, IFNγ, IL-17
↓ Cytotoxicity
↓ Proliferation
↓ CD4+:CD8+ T-cell ratio
↑ IL-4, IL-10
↑ TR1-cell and TReg-cell generation
B cells or ASCs
↓ Proliferation
↓ IgG, IgM production
↓ Plasma-cell differentiation
↑ VDR
↑ CYP24A1
Nature Reviews | Immunology

North American Conference on Vitamin D

"to minimize the health risks associated with UVB radiation exposure while maximizing the potential benefits of optimum vitamin D status, {dietary} supplementation and small amounts of sun exposure are the preferred methods of obtaining vitamin D."

Consensus statement, 2006

Published by Oxford University Press on behalf of the International Epidemiological Association
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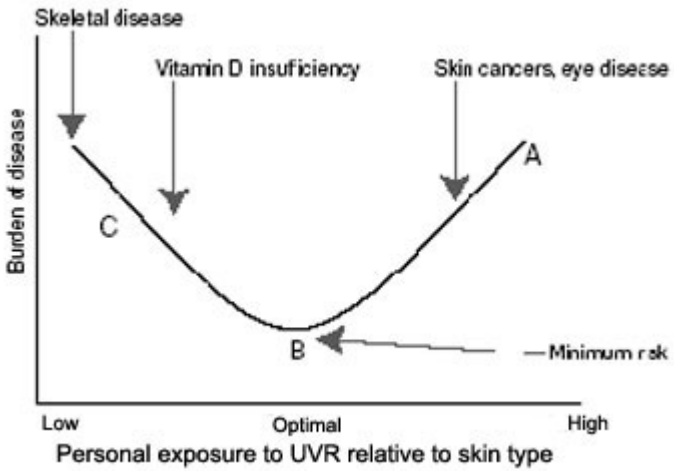
International Journal of Epidemiology 2008;**37**:654–667
doi:10.1093/ije/dyn017

Estimating the global disease burden due to ultraviolet radiation exposure

Robyn M Lucas,[1]* Anthony J McMichael,[1] Bruce K Armstrong[2] and Wayne T Smith[3]



- 1.6 million *Disability Adjusted Life Yrs* due to UVR over exposure
- 3.3 billion *Disability Adjusted Life Yrs* due to UVR under exposure

x 2000

Conclusions Sun protection messages are important to prevent diseases of UVR exposure. However, without high dietary (or supplemental) intake of vitamin D, some sun exposure is essential to avoid diseases of vitamin D insufficiency.

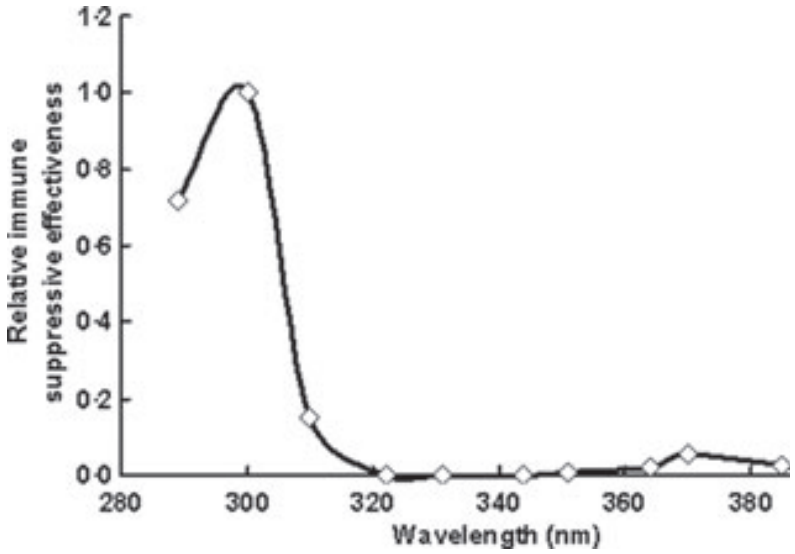
Addressing the health benefits and risks, involving vitamin D or skin cancer, of increased sun exposure

Johan Moan*†‡, Alina Carmen Porojnicu*, Arne Dahlback†, and Richard B. Setlow‡§

Lucas RM
Int J Epidemiology 2008

Effects of ultraviolet radiation reaching the biosphere

- Assess new understanding of relationship between ultraviolet wavelength and key “target processes”, e.g. vitamin D synthesis, suppression of the immune system.



Relationship between UV wavelength and immune suppression

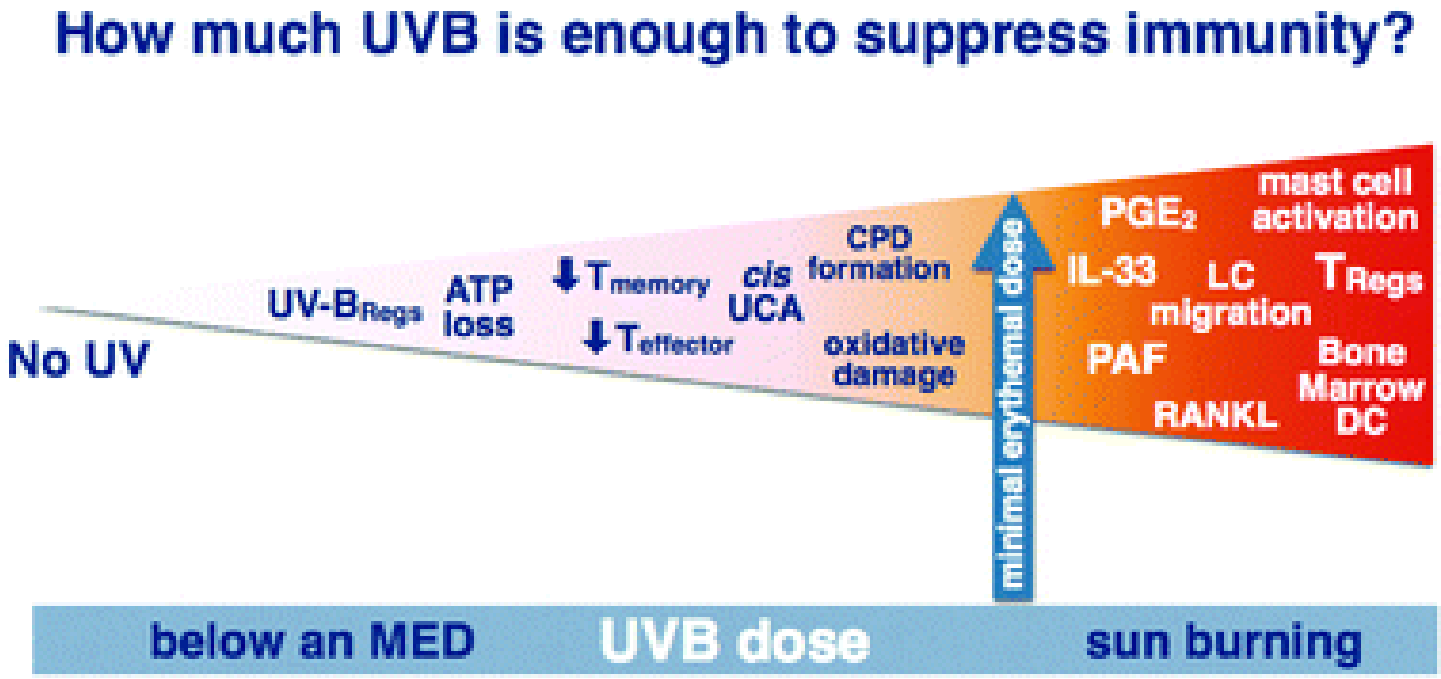
Damian et al 2011

Sunlight-Induced Immunosuppression in Humans Is Initially Because of UVB, Then UVA, Followed by Interactive Effects

Terence S. C. Poon, Ross St. C. Barnetson, and Gary M. Halliday

J Invest Dermatol 125:840–846, 2005

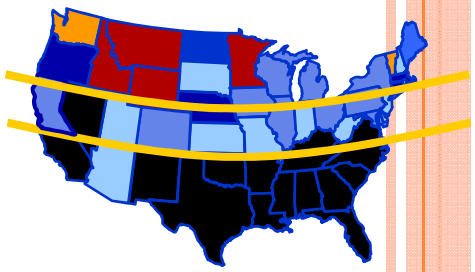
Both UVA and UVB interact o enhance UV induced immunosuppression, and this can occur even at doses that do not cause erythema

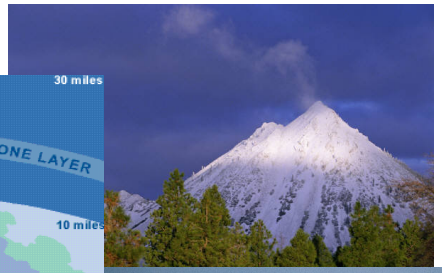


Seite S, Fourtsnier AM. The benefit of daily phtoprotecion. J Am Acad Dermatol 2008; 58 [5 suppl 2]:S160-166

UV RADIATION IS NOT ALWAYS THE SAME IT CHANGES BASED ON…

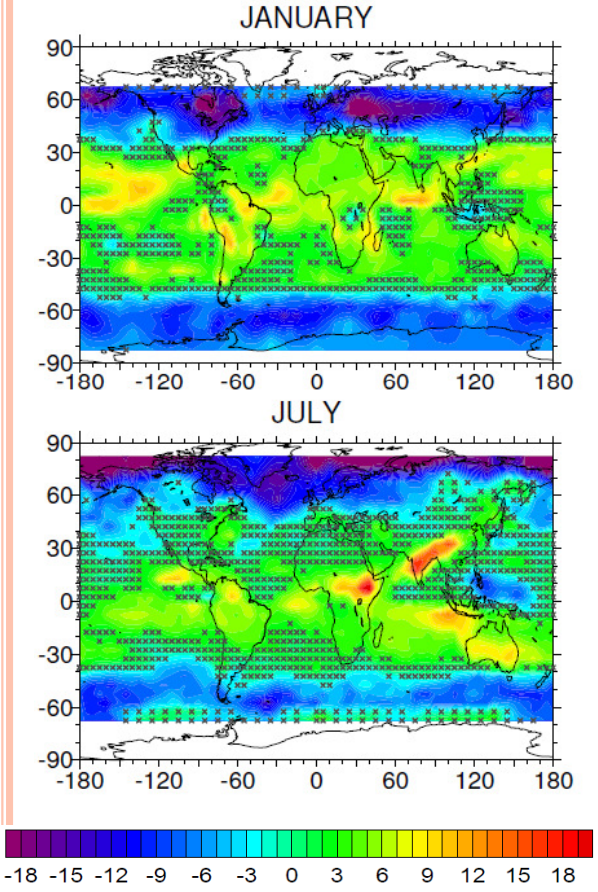
- Time of day
- Time of year
- Location
- Altitude
- Weather
- Reflection
- Ozone Layer





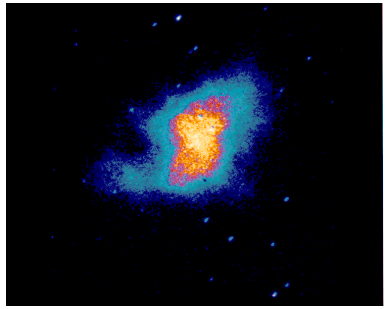
Armas L. et al. 2007
J Am Acad Dermatol 57:588.

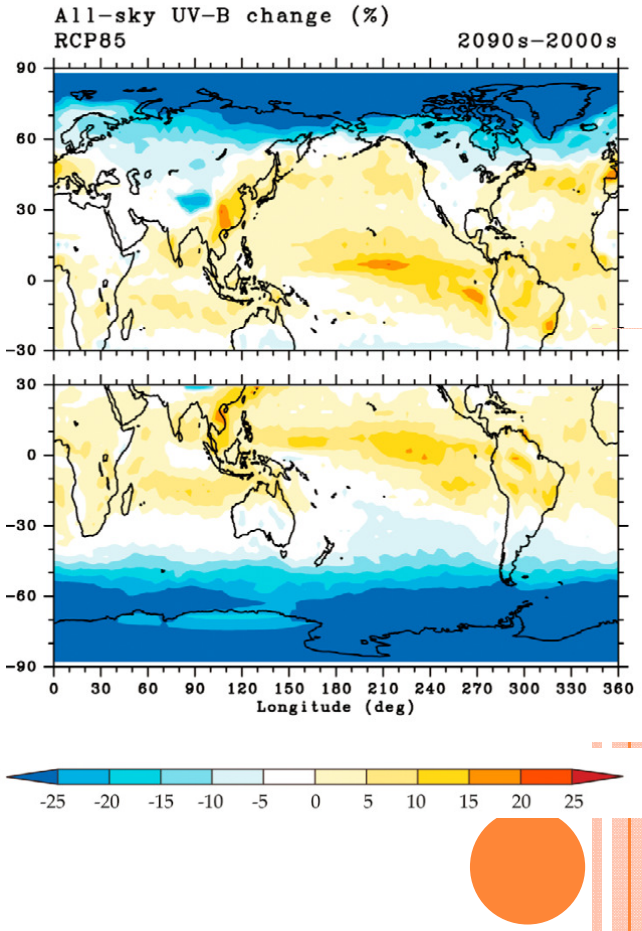
XXIII/13.3 a) Effects of ultraviolet radiation reaching the biosphere and how those effects relate to physical, biological and environmental processes.



Changes in solar UV predicted for this century.

Bais *et al* (2011: left) and Watanabe *et al* (2012: right) independently predict increases in solar UV at low-mid-latitudes but decreases in solar UV at high latitudes.





Minimal erythemal dose (MED) depends on

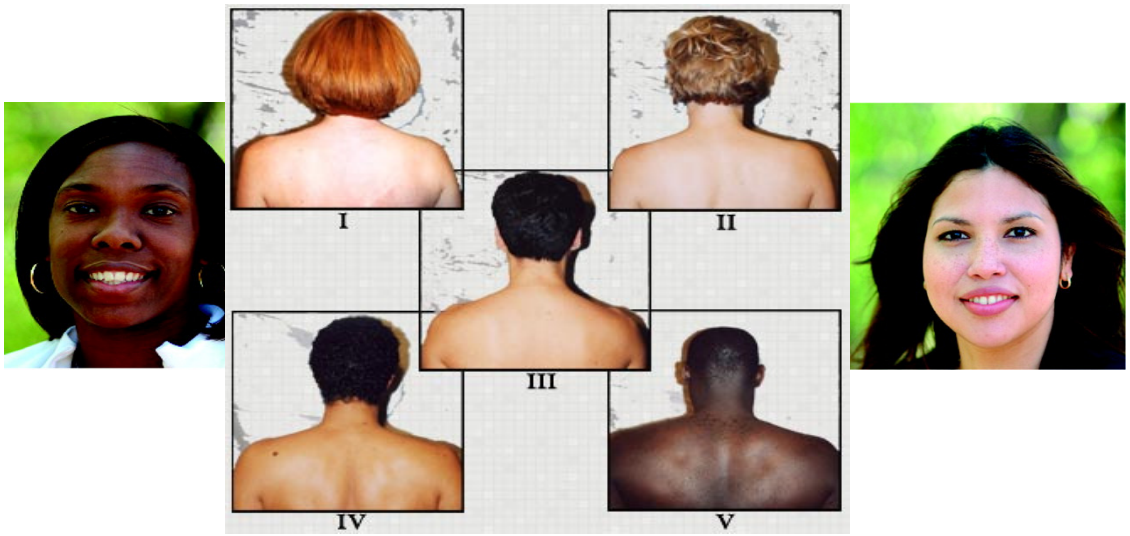
- **Skin type and thickness**
- **Amount of melanin and ability to produce melanin after exposure**
- **Intensity of the radiation**

- **Six sun-reactive skin types**
  - People with dark skin require significantly more sun exposure

  Holick, 2004

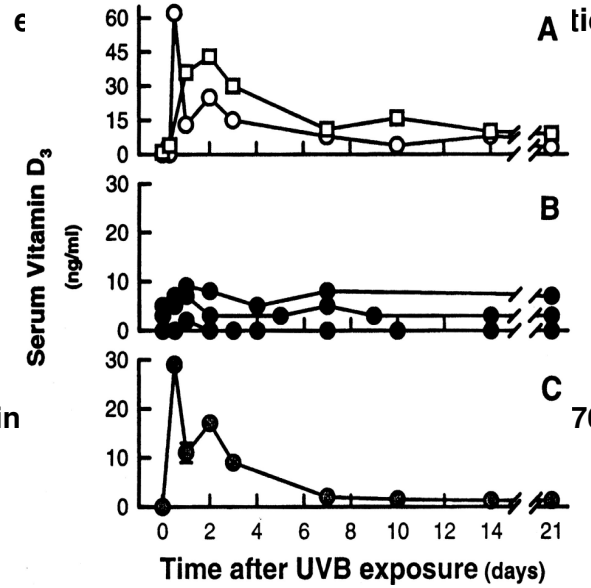
Armas L. et al. 2007
J Am Acad Dermatol 57:588

Human pigmentation—the main skin types: African-American, Asian, Caucasian, and Hispanic (left to right).



Change in serum concentrations of vitamin D-3 in 2 lightly pigmented white (skin type II) (A) and 3 heavily pigmented African American subjects (skin type V) (B) after total-body

ϵ **A** **tion.**



Costin **76-994**

JN THE JOURNAL OF NUTRITION

The FASEB Journal

TANNING

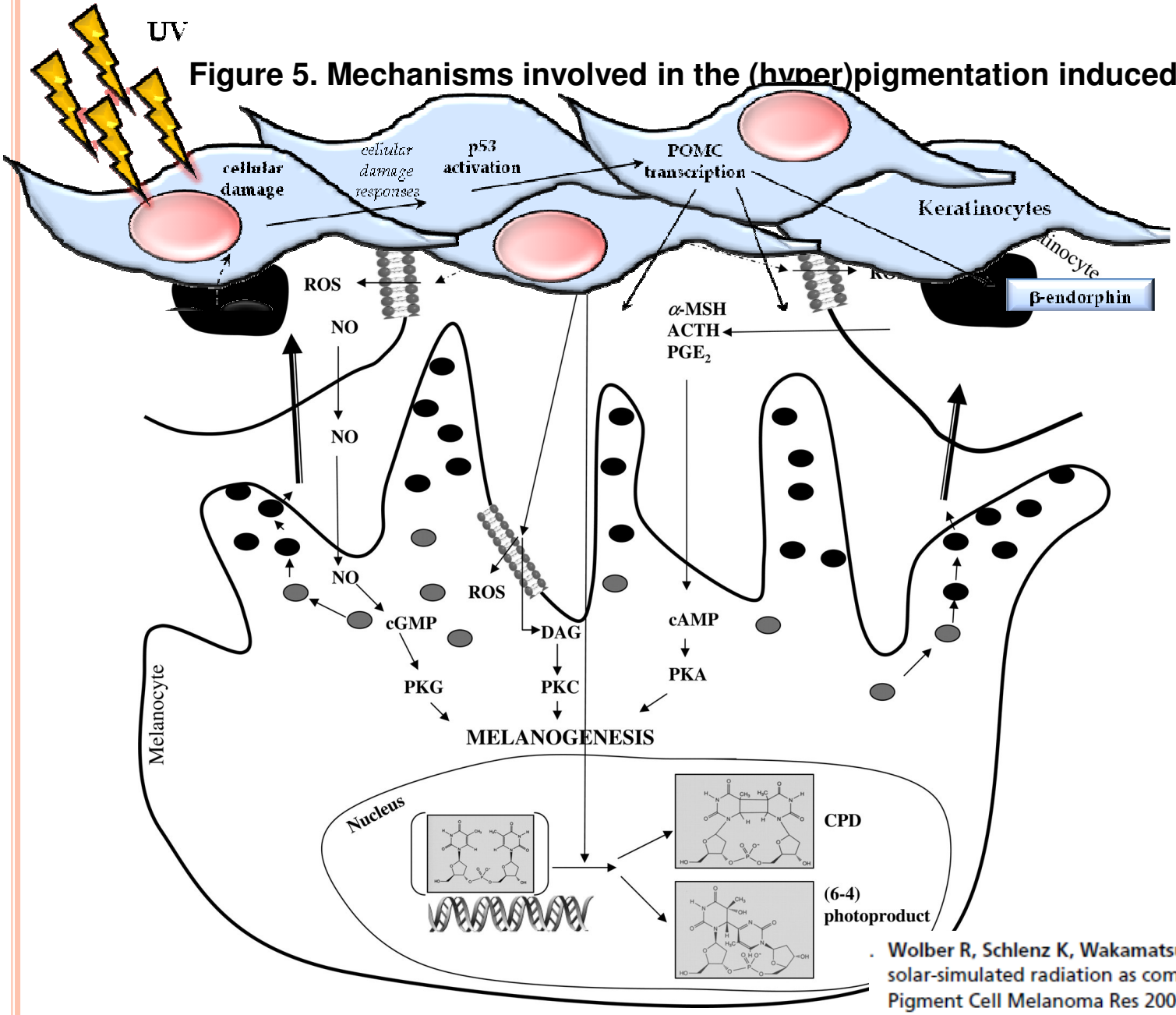
- **Protective response to sun exposure**

UV radiation

Stimulates melanin (dark pigment) that absorbs UV protecting cells

- ***melanin*** (pigment responsible for darkening) within skin causes tan
  - Functions as a biologic filter of UVR
    - By scattering radiation
    - By absorbing UVR
    - By dissipating absorbed energy as heat
- **Immediate tanning: Induced by UV-A, no new melanin**
- **Delayed tanning: Induced by UV-B, begins at 2-3 days, peaks at 7-10 days, new melanin formed**
  - Increase production and upward migration of melanin granules
  - Oxidation of premelanin in the skin
  - Protective response of the body

Figure 5. Mechanisms involved in the (hyper)pigmentation induced by UV-R.



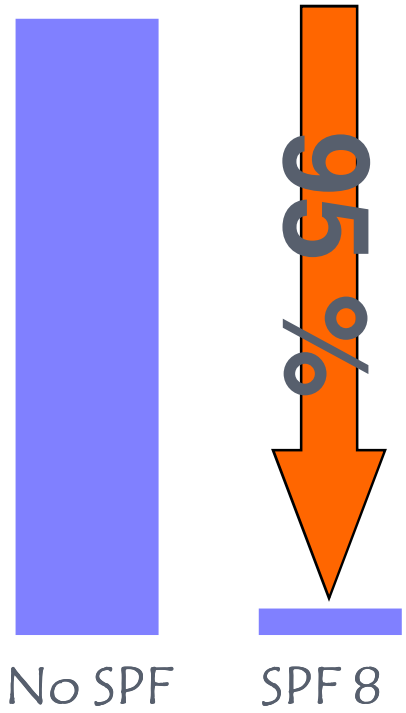
Costin G , and Hearing V J FASEB J 2007;21:976-994

. Wolber R, Schlenz K, Wakamatsu K, et al. Pigmentation effects of solar-simulated radiation as compared with UVA and UVB radiation. Pigment Cell Melanoma Res 2008; 21:487–491.

. Miyamura Y, Coelho SG, Wolber R, et al. Regulation of human skin pigmentation and responses to ultraviolet radiation. Pigment Cell Res 2007; 20:2–13.

Vitamin D and sun-screen

- **SPF 8 reduces Vitamin D production by 95%**
- **SPF 15 reduces Vitamin D production by 99%**



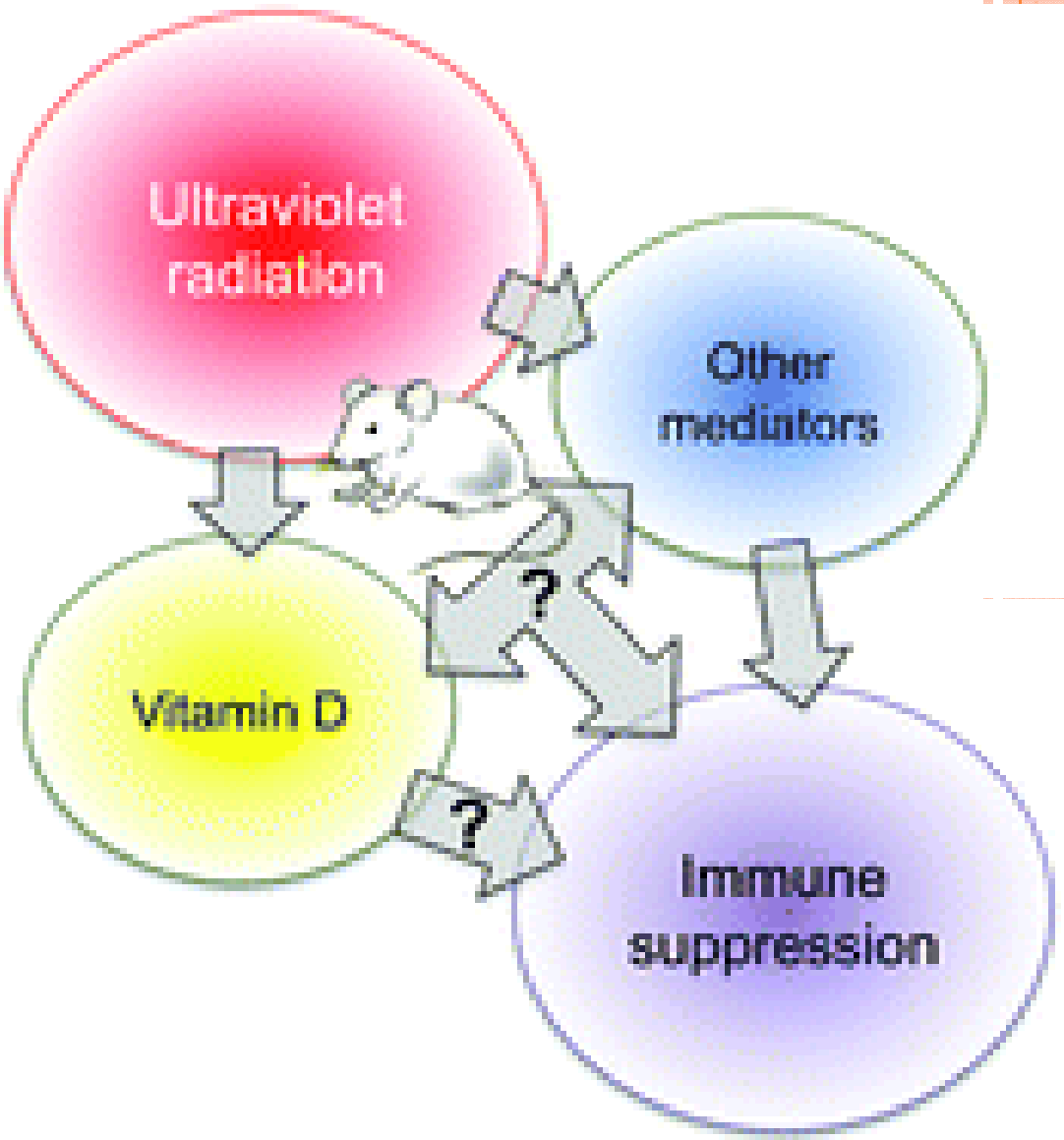
Matsuoka *JCEM* 1987

Norval M, Wulf HC. Does chronic sunscreen use reduce vitamin D production to insufficient levels? *Br J Dermatol* 2009; **161**: 732–736.

Faurschou A, Wulf HC. The relation between sun protection factor and amount of sunscreen applied *in vivo*. *Br J Dermatol* 2007; **156**: 716–719.

- **The current state of play of rodent models to study the role of vitamin D in UV-induced immunomodulation**

- Shelley Gorman*[a] and Prue H. Hart[a] ***Photochem. Photobiol. Sci.***, 2012,**11**, 1788-1796



INFANTS

- Infants and toddlers are at higher risk of uv damage, as structurally, children's skin is thinner- a thinner stratum corneum- than that of adults and has lower melanin concentrations. Thus, UV penetrates more deeply into skin that is less able to absorb UV radiation.
- New insights about infant and toddler skin: implications for sun protection. **Paller** AS, Hawk JL, Honig P, Giam YC, Hoath S, Mack MC, Stamatas GN. Pediatrics. **2011** Jul;128(1):92-102
- Effect of UV radiation on the neonatal skin immune system- implications for **melanoma**.**Muller** HK, Malley RC, McGee HM, Scott DK, Wozniak T, Woods GM.Photochem Photobiol. **2008** Jan-Feb;84(1):47-54.

- Development of solar UVR-related **pigmentation** begins as early as the first summer of life.**Mack** MC, Tierney NK, Ruvolo E Jr, Stamatas GN, Martin KM, Kollias N.J Invest Dermatol. **2010** Sep;130(9):2335-

Vitamin D Receptor Gene – Chr 12q13

- Vitamin D receptors (VDRs) are activated by $1,25(OH)_2D$ and affect expression of over 200 genes, upregulating about two-thirds, downregulating one-third.
- VDRs come in different alleles, with different effects.

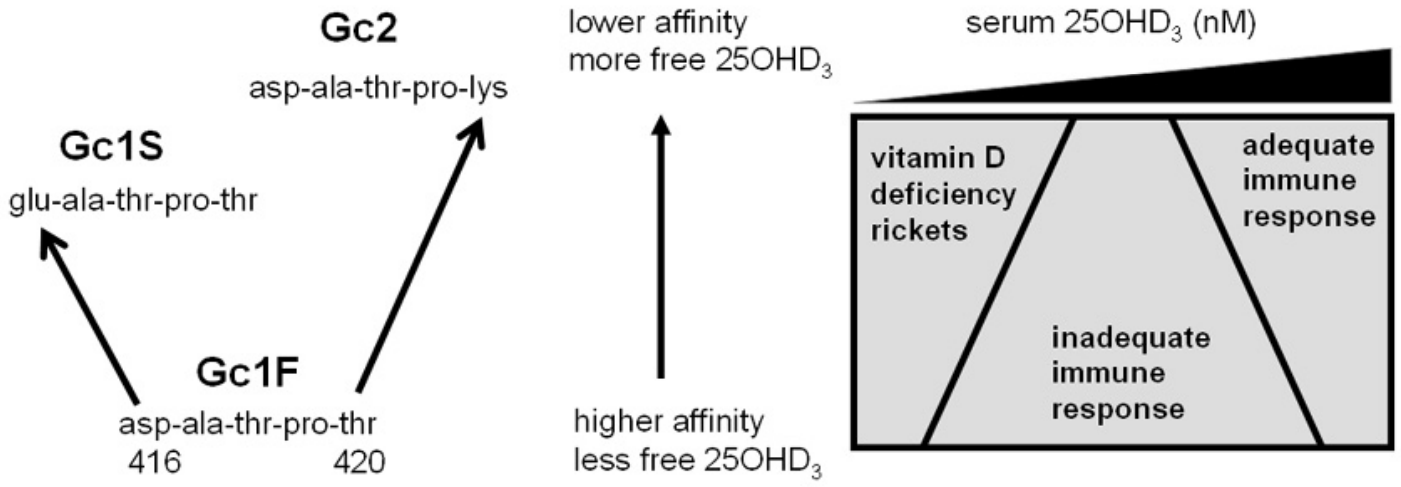
9 exons, alternatively spliced promoter region

Binding domains: DNA binding domain – binds VDRE
Ligand binding domain – $1,25(OH)_2$ Vit D

Human VDR >470 reported SNPs

Many have low allele frequency

Evolution of low affinity forms of DBP enhances monocyte responses to vitamin D.



Journal of Medical Virology 83:1834–1840 (2011)

Confirmation of an Association Between Single Nucleotide Polymorphisms in the *VDR* Gene With Respiratory Syncytial Virus Related Disease in South African Children

T.L. Kresfelder,[1] R. Janssen,[2] L. Bont,[3] and M. Venter[1,4]*

Pediatr Nephrol (2012) 27:417–421
DOI 10.1007/s00467-011-2000-0

ORIGINAL ARTICLE

Vitamin D receptor gene polymorphism in children with urinary tract infection

Sule Aslan · Ipek Akil · Gulcin Aslan · Huseyin Onay · Beyhan Cengiz Ozyurt · Ferda Ozkinay

Journal of Viral Hepatitis, 2014, 21, 297–304 doi: 10.1111/jvh.12139

Tumour necrosis factor-alpha, interleukin-10, interferon-gamma and vitamin D receptor gene polymorphisms in patients with chronic hepatitis delta

S. C. Karatayli,[1,*] Z. E. Ulger,[1,*] A. A. Ergul,[1,*] O. Keskin,[2] E. Karatayli,[1] R. Albayrak,[3] M. Ozkan,[3] R. Idilman,[2] K. Yalcin,[4] H. Bozkaya,[2] O. Uzunalimoğlu,[1,2] C. Yurdaydin[1,2] and A. M. Bozdayi[1,2] [1]Hepatology Institute, Ankara University, Ankara, Turkey; [2]Department of Gastroenterology, Medical School, Ankara

Erythemal UVR does not increase 1,25(OH)2D3 in the skin and serum of vitamin D3-deficient mice.

UVR suppresses immune responses in female and male

Erythemal UVR does not increase 1,25(OH)2D3 in the skin and serum of vitamin D3-deficient mice.

PLOS ONE | www.plosone.org 1 September 2012 | Volume 7 | Issue 9 |

Acute Erythemal Ultraviolet Radiation Causes Systemic Immunosuppression in the Absence of Increased 25-Hydroxyvitamin D_3 Levels in Male Mice

Shelley Gorman[1]*, Naomi M. Scott[1], Daryl H. W. Tan[1], Clare E. Weeden[1], Robert C. Tuckey[2], Jacqueline L. Bisley[1], Michele A. Grimbaldeston[3], Prue H. Hart[1]

UV radiation suppresses experimental autoimmune encephalomyelitis independent of vitamin D production

Bryan R. Becklund, Kyle S. Severson, Souriya V. Vang, and Hector F. DeLuca[1]

PNAS | April 6, 2010 | vol. 107 | no. 14 |

NUTRITION

Randomized controlled trial of oral omega-3 PUFA in solar-simulated radiation-induced suppression of human cutaneous immune responses[1–3]

Suzanne M Pilkington, Karen A Massey, Susan P Bennett, Naser MI Al-Aasswad, Khaled Roshdy, Neil K Gibbs, Peter S Friedmann, Anna Nicolaou, and Lesley E Rhodes

Am J Clin Nutr 2013;97:646–52. Printed in USA. © 2013 American Society for Nutrition

Photodermatology, Photoimmunology & Photomedicine

REVIEW ARTICLE

Nutritional abrogation of photoimmunosuppression: *in vivo* investigations

Suzanne M. Pilkington[1], Neil K. Gibbs[1], Peter S. Friedmann[2] & Lesley E. Rhodes[1]

Photodermatol Photoimmunol Photomed 2014; 30: 112–127

What about vaccines?

WHAT ABOUT VACCINES?

Polio

- Am J Epidemiol.1972 Oct;96(4):263-9.**Oral polio vaccination of children in the tropics. I. The poor seroconversion rates and the absence of viral interference.**John TJ JayabalP

- 1,25-dihydroxyvitamin d3 enhances systemic and mucosal immune responses to inactivated poliovirus **vaccine** in mice. **Ivanov** AP, Dragunsky EM, Chumakov KM. J Infect Dis. **2006** Feb 15;193(4):598-600

Tetanus

- Efficient **tetanus** toxoid immunization on vitamin D supplementation. **Heine** G, Drozdenko G, Lahl A, Unterwalder N, Mei H, Volk HD, Dörner T, Radbruch A, Worm M. Eur J Clin Nutr. 2011 Mar;65(3):329-34

BCG

- **BCG** vaccination: a role for vitamin D? **Lalor** MK, Floyd S, Gorak-Stolinska P, Weir RE, Blitz R, Branson K, Fine PE, Dockrell HM. PLoS One. 2011 Jan 31;6(1):e16709.

INFLUENZA

- J Hyg Epidemiol Microbiol Immunol.1987;31(4):453-9.
- Vaccination activity of live influenza vaccine in different seasons of the year. Zykov MP[1], Sosunov AV
- Vitamin D supplementation does not increase immunogenicity of seasonal influenza vaccine in HIV-infected adults.Cooper C, Thorne A; Canadian Hiv Trials Network Ctn Influenza Vaccine Research Group. HIV Clin Trials. 2011 Sep-Oct;12(5):275-6.
- Vitamin D and influenza vaccination. Principi N, Esposito S. Hum Vaccin Immunother. 2013 May;9(5):97
- Impact of vitamin D administration on immunogenicity of trivalent inactivated influenza vaccine in previously unvaccinated children. Principi N, Marchisio P, Terranova L, Zampiero A, Baggi E, Daleno C, Tirelli S, Pelucchi C, Esposito S. Hum Vaccin Immunother. 2013 May;9(5):969-74.
- **Immunogenicity of inactivated seasonal influenza vaccine in adult and pediatric liver transplant recipients over two seasons.** Suzuki M[1], Torii Y, Kawada J, Kimura H, Kamei H, Onishi Y, Kaneko K, Ando H, Kiuchi T, Ito Y
- Vitamin D is not associated with serologic response to **influenza** vaccine in adults over 50 years old. **Sundaram** ME, Talbot HK, Zhu Y, Griffin MR, Spencer S, Shay DK, Coleman LA. Vaccine. 2013 Apr 12;31(16):2057-61

HEPATITIS B

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Active Immunization

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POLICIE- TIME TO CHANGE?

THANK YOU FOR YOUR ATTENTION