# VITILIGINE: dagli antiossidanti alla Cytokine Theraphy

## 26 Maggio 2018

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WORLD HEALTH ACADEMY
DERMATOLOGY

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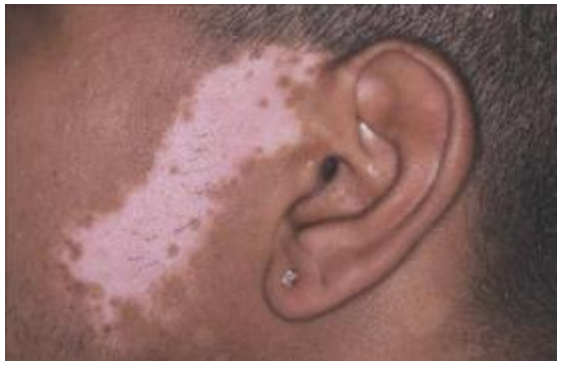
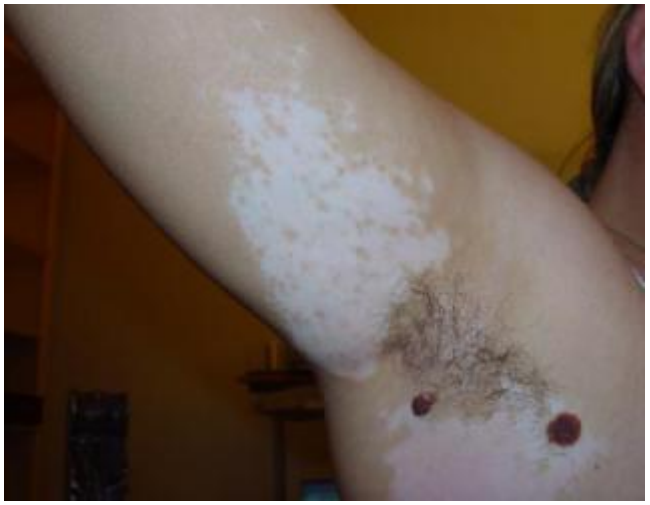
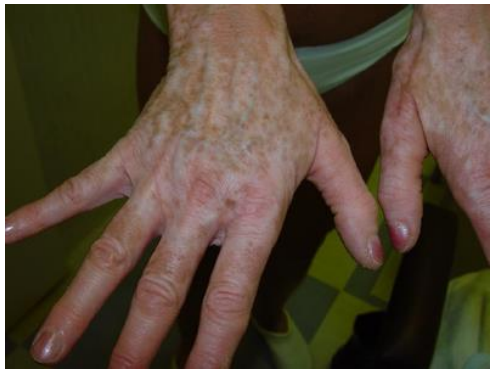
# DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY at 2017

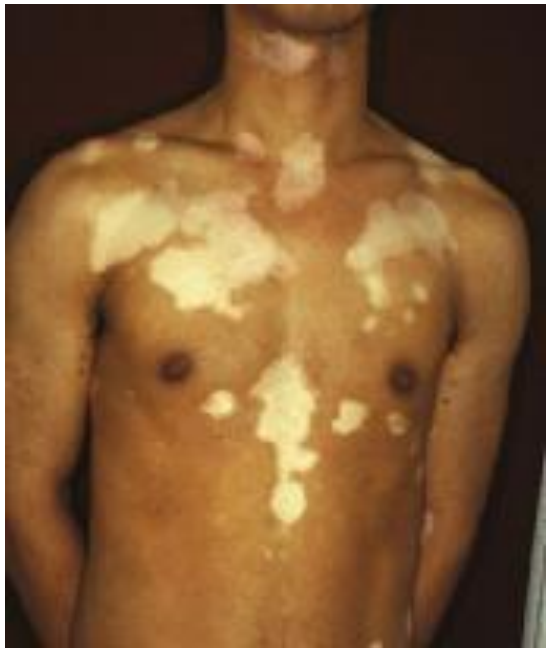
- - President World Health Academy Publishing House, Zurich, CH
- - Editor, Dermatologic Therapy, Wiley-Blackwell
- - Chief Medical Officer, BIOSKIN EVOLUTION ®
- - Consultant, EVLaser
- - Consultant, GLG, USA
- - Consultant, Advance Medical, USA
- - Consultant GUNA International, Italy & USA
- - Scientific Director, Dolce Aqua® , Italy
- - Consultant, CLINUVEL , Australia
- - Chief Medical Officer, Applied Biology, Inc , Irvine, CA , USA
- - Executive, Vitiligo Research Foundation, USA
- - Editor in Chief, Journal of Pigmentary Disorders, 2014
- - Consultant, Frankl Pharma Global Ltd- UK - 2015
- - Consultant, Cell Vital Co. Munich, Germany 2016

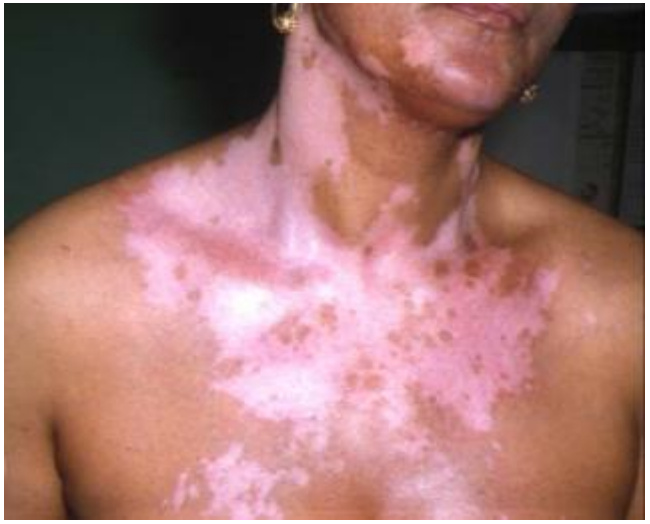
# Vitiligo or Vitiligos ? Need for molecular diagnosis and personalized treatment

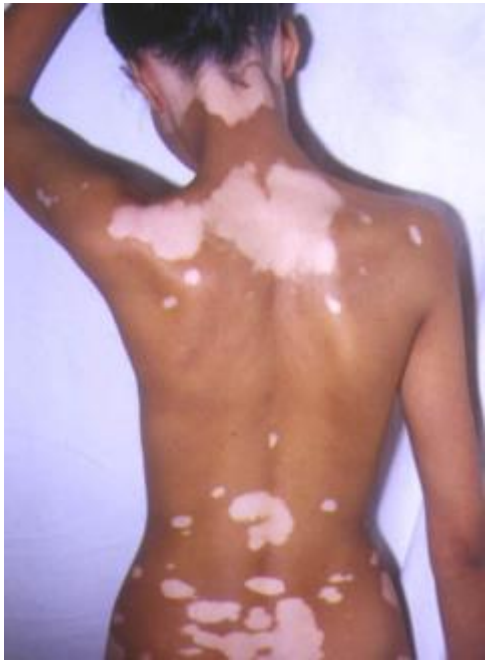










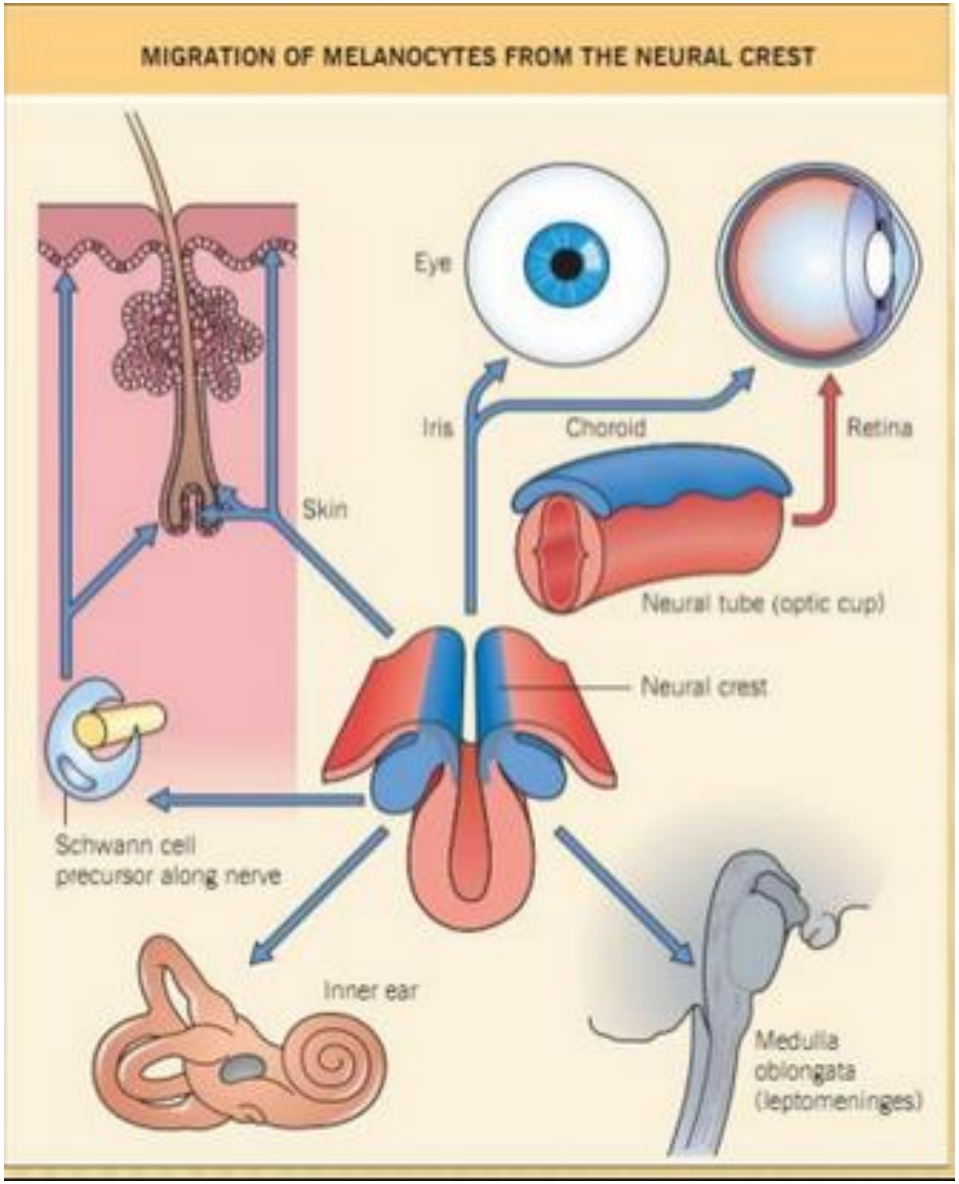


## Vitiligo is a systemic disease.

## Lotti T, D'Erme AM.

Clin Dermatol. 2014 May-Jun;32(3):430-4. doi: 10.1016/j.clindermatol.2013.11.011

**Vitiligo needs systemic treatment because it IS a systemic disease**



TITLE

High prevalence of circulating autoantibodies against thyroid hormones in vitiligo and correlation with clinical and historical parameters of patients.

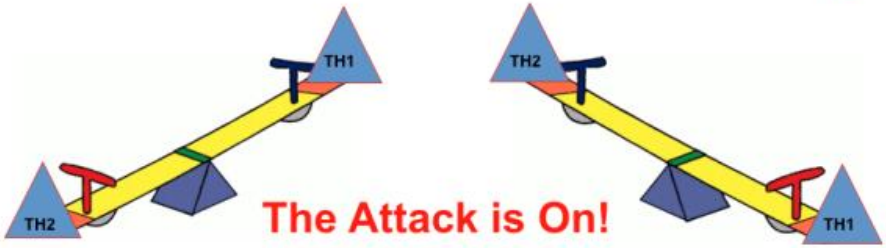
Colucci R, Lotti F, Dragoni F, Arunachalam M, Lotti T.

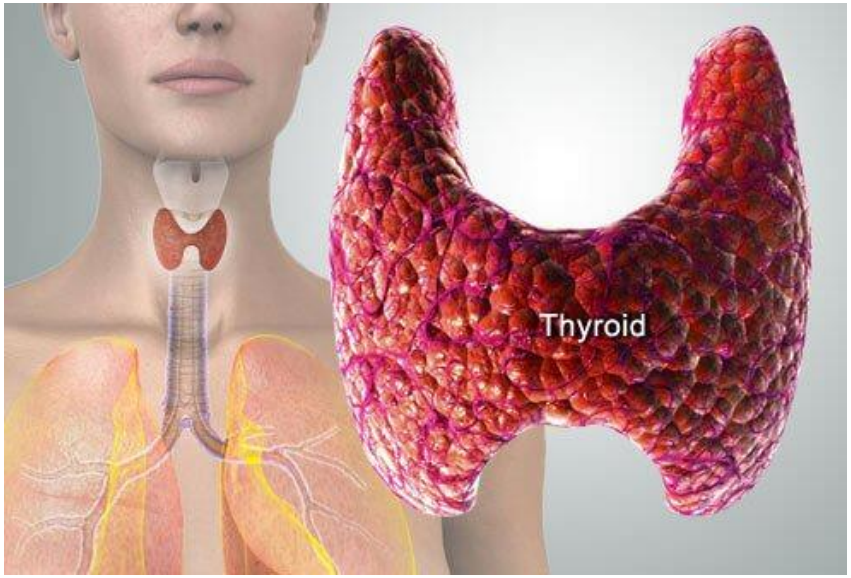
Br J Dermatol. 2014 Oct;171(4):786-98

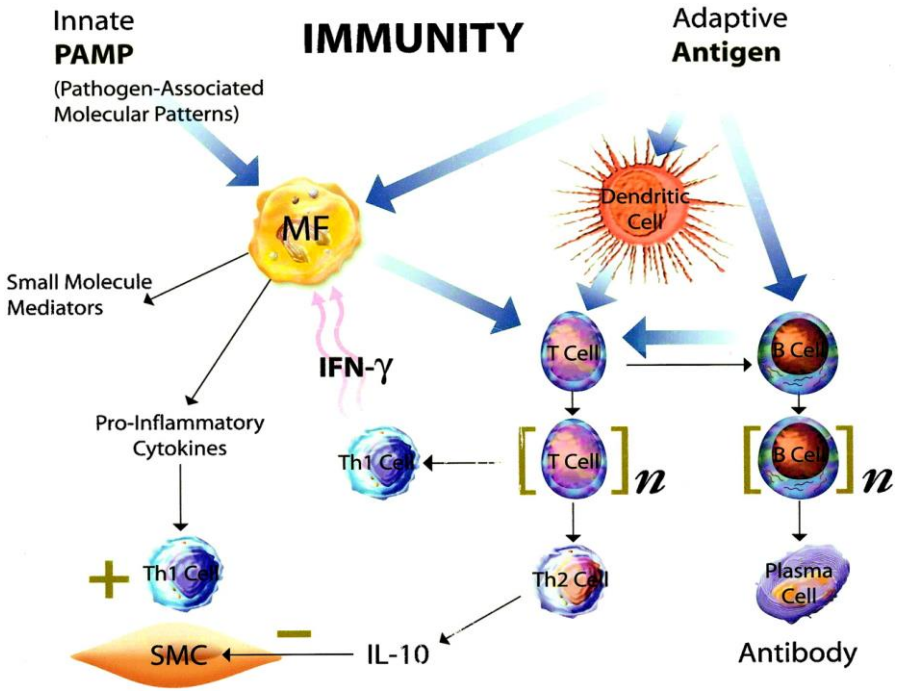
ABSTRACT

Overall 77 of 79 patients (97%) had at least one type of THAb (11 T3-Ab, 10 T4-Ab, 56 both). In the control group, only one person (1%) had THAbs. In patients with vitiligo, T3-Abs were significantly associated with leucotrichia (IgM+IgG, P = 0.033; IgG, P = 0.039; IgM, P = 0.005) and thyroglobulin autoantibodies (IgM+IgG, P = 0.031; IgG, P = 0.058), while the absence of T3-Ab was related to personal history of cancer (IgM+IgG, P = 0.021; IgG, P = 0.039). T4-Abs were significantly associated with vitiligo activity (IgM+IgG, P < 0.001; IgM, P = 0.037) and duration (IgG, P = 0.013).

# Autoimmune Progression

# *On pubmed… **Torello Lotti** and coworkers*

## Vitiligo in Children: What's New in Treatment?

**Review article**

Gianfaldoni S, et al. Open Access Maced J Med Sci. 2018.


**Authors**

Gianfaldoni S[1], Tchernev G[2,3], Wollina U[4], Lotti J[5], Rovesti M[6], Satolli F[6], França K[7], Lotti T[1].

**Author information**

1 University G. Marconi of Rome, Dermatology and Venereology, Rome, Italy.
2 Medical Institute of Ministry of Interior Department of General, Vascular and Abdominal Surgery, Sofia, Bulgaria.
3 Onkoderma - Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria.
4 Städtisches Klinikum Dresden, Department of Dermatology and Allergology, 01067 Dresden, Germany.
5 University G. Marconi of Rome - Dept. of Nuclear, Subnuclear and Radiation Physics, Rome, Italy.
6 Department of Dermatology, University of Parma, Parma, Italy.
7 University of Miami School of Medicine, Miami, Florida, United States and Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy.



**Citation**

Open Access Maced J Med Sci. 2018 Jan 21;6(1):221-225. doi: 10.3889/oamjms.2018.060. eCollection 2018 Jan 25.



**Abstract**

Vitiligo is an acquired chronic hypopigmentary disorder, which usually stars in childhood. The Authors discuss a short review of the more innovative therapies for childhood vitiligo.



PMID: 29484028 [] PMCID: PMC5816304

# *On pubmed… **Torello Lotti** and coworkers*

## Vitiligo in Children: A Review of Conventional Treatments.

**Review article**

Gianfaldoni S, et al. Open Access Maced J Med Sci. 2018.

**Authors**

Gianfaldoni S[1], Wollina U[2], Tchernev G[3], Lotti J[4], França K[5], Lotti T[1].

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5 University of Miami School of Medicine Ringgold standard institution, Miami, Florida, United States and Centro Studi per la Ricerca Multidisciplinare e Rigenerativa, Università Degli Studi "G. Marconi", Rome, Italy.

**Citation**

Open Access Maced J Med Sci. 2018 Jan 21;6(1):213-217. doi: 10.3889/oamjms.2018.054. eCollection 2018 Jan 25.

**Abstract**

Vitiligo is an important skin disease of childhood, which may lead to deep psychological trauma, resulting in a poor quality of life and low self-esteem. The Authors discuss a short review of the more conventional therapies available for the treatment of vitiligo in children.

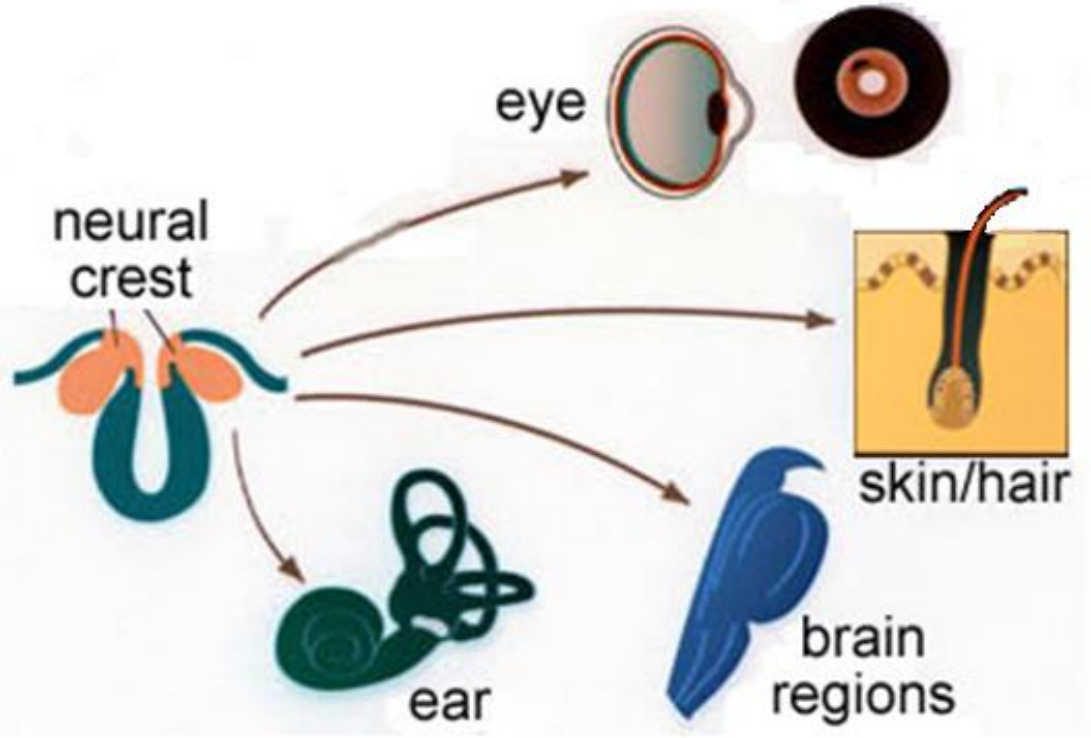
PMID: 29484026 [] PMCID: PMC5816302

# - Melanocytes migration -

Melanocytes precursors, knew as melanoblasts, are formed in the the neural crest: in the 11th week of fetal life, they migrate to various sites, where they proliferate and then differentiate into mature melanocyte.

Melanocytes reside in:

- **skin** (epidermis and hair follicle)
- **inner ear**
- **eye** (choroid and retina)
- **brain** and leptomeninges



# Locations and functions of melanocytes

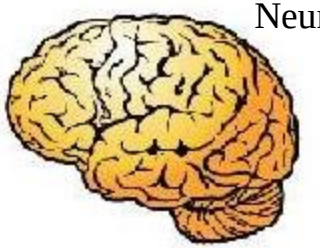
**EYE**

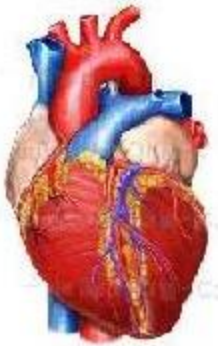
**Choroid**: Constitutive eye pigmentation, protection against UV

**Retinal pigment epithelium**: vision, metabolism of rod outer segments and retinoids

**BRAIN**

Neuroendocrine function and detoxification





**HEART**

unknown

**EAR**

**Inner ear**: balance

**Cochlea**: hearing

**ADIPOSE TISSUE**

Anti-inflammation, reduction/binding of ROS

**HAIR FOLLICLE**

Melanocyte stem cell reservoir for skin. Hair pigmentation, Removal of toxic byproducts

**EPIDERMIS**

Constitutive skin pigmentation.

Responses to and protection against the environment (primarily UV)

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**Review article**

Gianfaldoni S, et al. Open Access Maced J Med Sci. 2018.


**Authors**

Gianfaldoni S[1], Tchernev G[2,3], Wollina U[4], Lotti J[5], Satolli F[6], França K[7], Rovesti M[6], Lotti T[1].

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5 University G. Marconi of Rome, Dept. of Nuclear, Subnuclear and Radiation Physics, Via Plinio 44, Rome 00193, Italy.
6 Department of Dermatology, University of Parma, Via Gramsci 14, Parma, Parma 43126, Italy.
7 University of Miami School of Medicine, 1400 NW 10th Avenue, Miami, Florida 33136-1015, United States.



**Citation**

Open Access Maced J Med Sci. 2018 Jan 20;6(1):181-184. doi: 10.3889/oamjms.2018.040. eCollection 2018 Jan 25.



**Abstract**

Vitiligo is an important skin disease of childhood. The authors briefly discuss the etiopathobiology, clinics and comorbidities of the disease.



PMID: 29484022 [] PMCID: PMC5816297

# *On pubmed… **Torello Lotti** and coworkers*

## Metabolic syndrome in vitiligo.

Pietrzak A, et al. Dermatol Ther. 2012 Nov-Dec.
Show full citation

**Abstract**

Vitiligo is an acquired, depigmenting skin disease with still unclear, multifactorial etiopathogenesis. However, there is growing evidence that vitiligo affects not only the skin but it may also be connected with metabolic abnormalities, including glucose intolerance and lipid abnormalities, all of which confirms the systemic nature of the disease. Recently, it has been shown that melanocytes, especially those found in the adipose tissue, due to their ability to decrease inflammation and oxidative damage, are capable of preventing the metabolic syndrome. The article presents updated knowledge on potential metabolic disturbances in vitiligo.

PMID: 23237037 [Indexed for MEDLINE]

# Vitiligo: correct pragmatic approach

- Repigmentation first
- Stop progression – spreading
- Avoid recurrencies
- Support  Patients
- Educate Patients and Scientific Community

# Systemic treatment for Vitiligo 2016 – 2018

- JAK Inhibitors
- EdnrB – Wnt Signaling
- CD20 Mab
- Afamelanotide
- Statins
- Minocycline
- Low Dose Cytokines and Growth Factors
- ……

# Systemic treatment for Vitiligo 2016 – 2018

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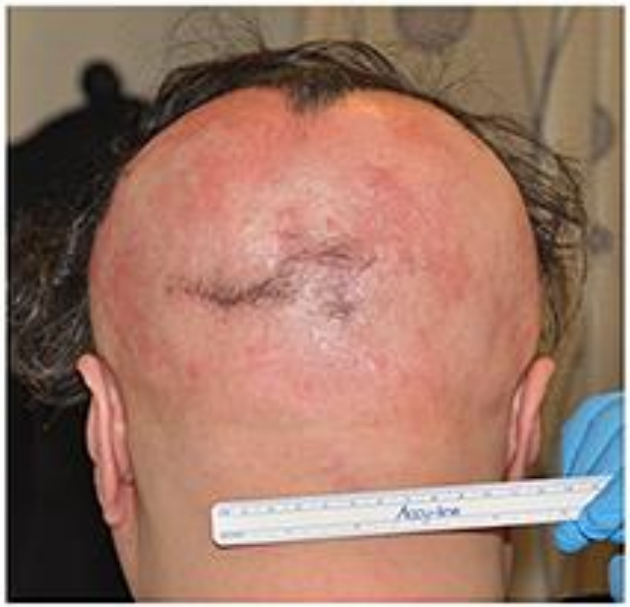
- EdnrB – Wnt Signaling
- CD20 Mab
- Afamelanotide
- Statins
- Minocycline
- Low Dose Cytokines and Growth Factors
- ……

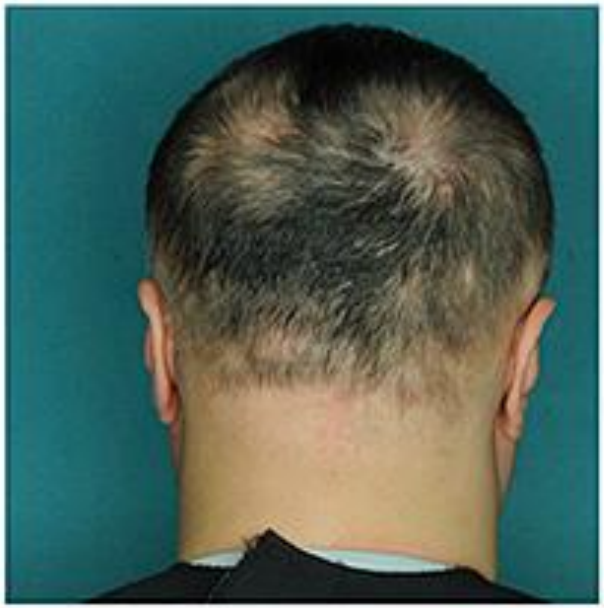
- **Janus kinase inhibitors**, also known as

**JAK inhibitors** or **jakinibs**,are a type of medication that functions by inhibiting the activity of one or more of the Janus kinase family of enzymes (JAK1, JAK2, JAK3, TYK2), thereby interfering with the JAK-STAT signaling pathway. These inhibitors have therapeutic application in the treatment of cancer and inflammatory diseases such as rheumatoid arthritis

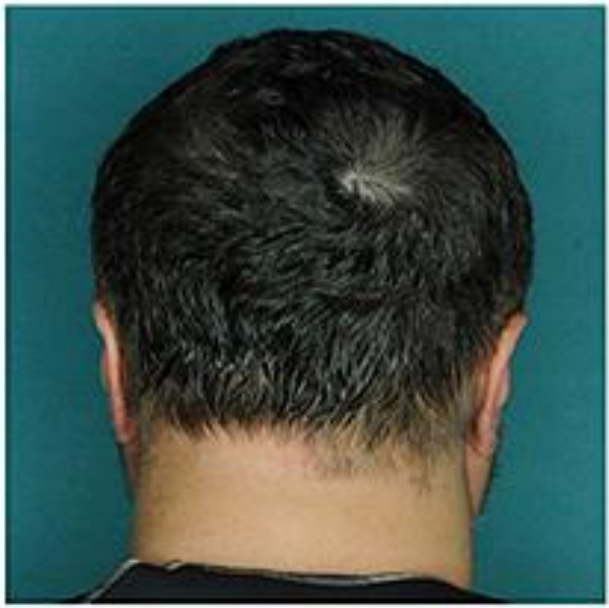
- JAK Inhibitors – Janus kinases inhibitors
- TOFACITINIB
- RUXOLITINIB
- …



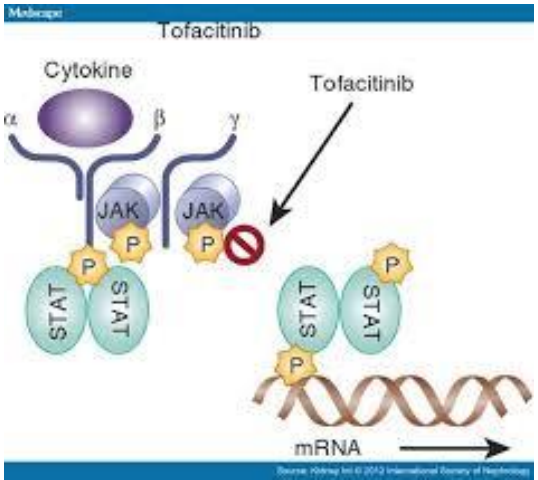
baseline



3 months treatment



4 months treatment

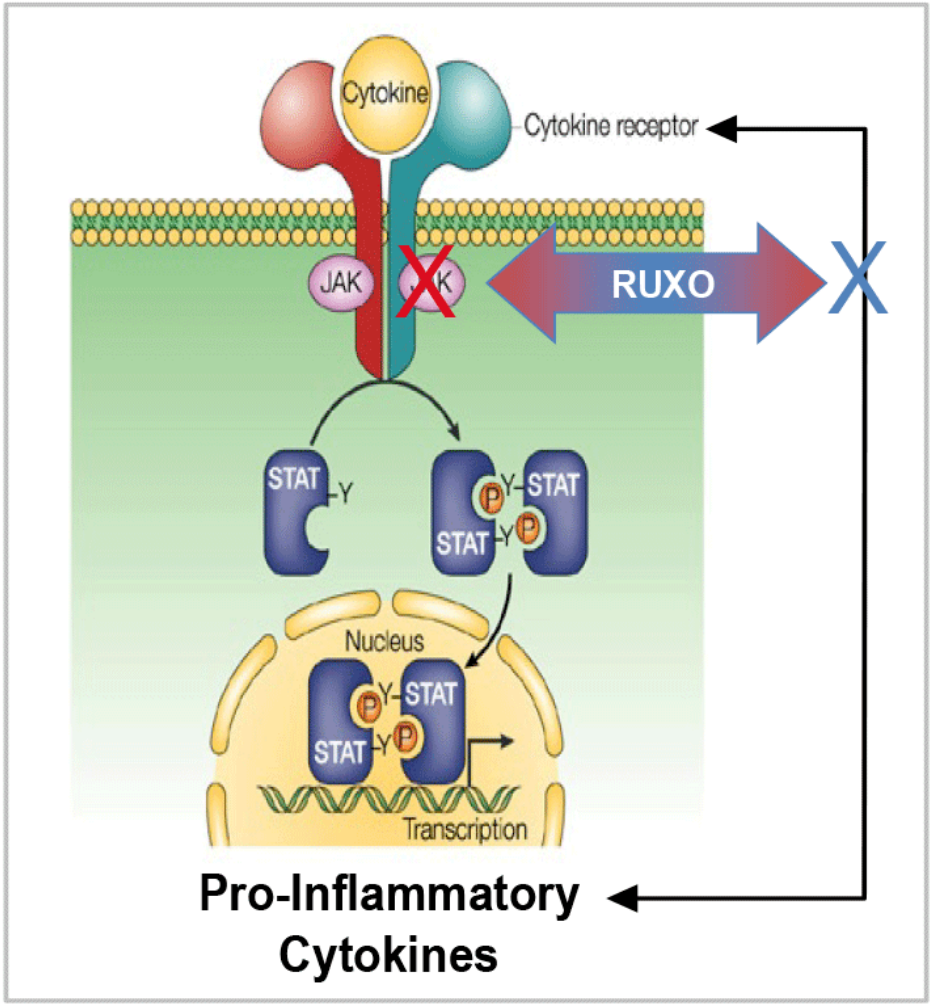



# TOFACITINIB

tablets 5-15 mg/ die

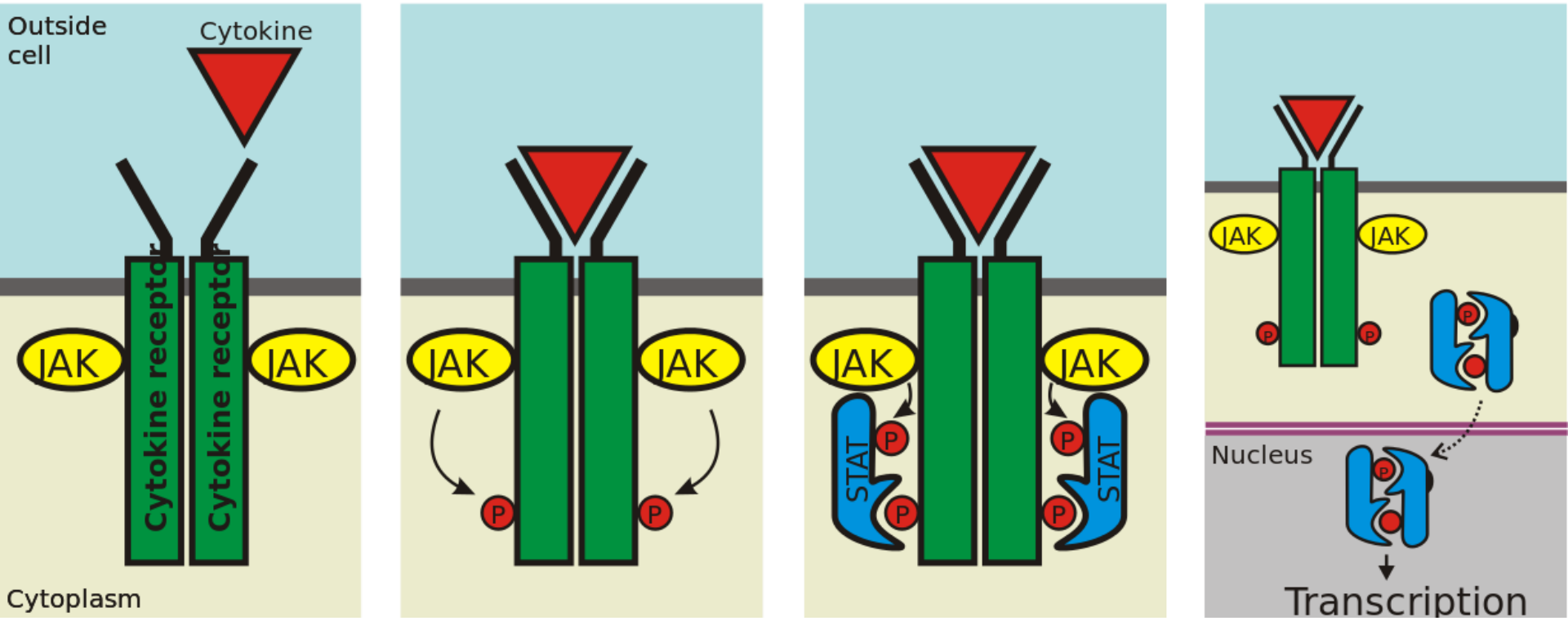
# Ruxolitinib is a JAK1 and JAK2 Inhibitor

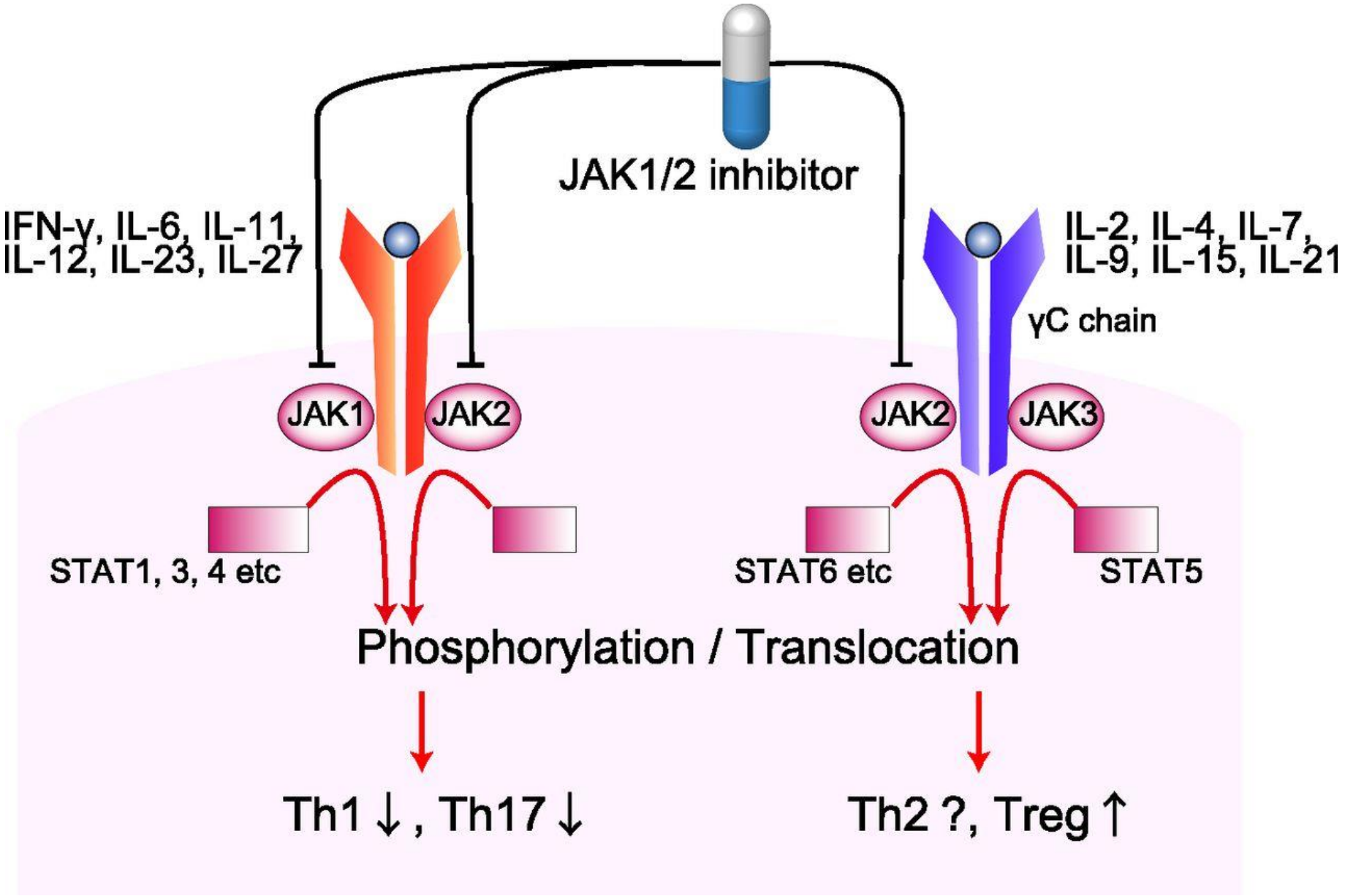
- Potential mechanism of action:
  - Inhibits signaling of cytokine and growth factor receptors that use JAK1 and JAK2 for signaling
  - Suppresses the growth (JAK2 inhibition) of malignant cells
  - Down-regulates the cytokines (JAK1 and JAK2 inhibition) that contribute to hypermetabolic state
- Not selective for JAK2V617F (patients with and without JAK2 mutation benefit)




Pesu M, et al. *Immunol Rev.* 2008;223:132-142.

# JAK Inhibitors




JAK1/2 inhibitor
IFN-γ, IL-6, IL-11,
IL-12, IL-23, IL-27
IL-2, IL-4, IL-7,
IL-9, IL-15, IL-21
γC chain
JAK1
JAK2
JAK2
JAK3
STAT1, 3, 4 etc
STAT6 etc
STAT5
Phosphorylation / Translocation
Th1 ↓, Th17 ↓
Th2 ?, Treg ↑

# *On pubmed… **Torello Lotti** and coworkers*

## Vitiligo in Children: A Better Understanding of the Disease.

**Review article**

Gianfaldoni S, et al. Open Access Maced J Med Sci. 2018.


**Authors**

Gianfaldoni S[1], Tchernev G[2,3], Wollina U[4], Lotti J[5], Satolli F[6], França K[7], Rovesti M[6], Lotti T[1].

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PMID: 29484022 [] PMCID: PMC5816297

# *On pubmed… **Torello Lotti** and coworkers*

## Micro - Focused Phototherapy Associated To Janus Kinase Inhibitor: A Promising Valid Therapeutic Option for Patients with Localized Vitiligo.

Gianfaldoni S, et al. Open Access Maced J Med Sci. 2018.

**Authors**

Gianfaldoni S[1], Tchernev G[2], Wollina U[3], Roccia MG[4], Fioranelli M[5], Lotti J[5], Rovesti M[6], Satolli F[6], Valle Y[7], Goren A[8], Tirant M[9], Situm M[10], Kovacevic M[8,10], França K[11], Lotti T[8].

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1 University G. Marconi of Rome - Dermatology and Venereology, University G. Marconi of Rome, Rome, Italy.
2 Medical Institute of Ministry of Interior (MVR), Department of Dermatology, Venereology and Dermatologic Surgery, Sofia, Bulgaria.
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4 University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India.
5 G. Marconi University - Department of Nuclear Physics, Subnuclear and Radiation, Rome, Italy.
6 Department of Dermatology, University of Parma, Parma, Italy.
7 Vitiligo Research Foundation, New York, United States.
8 University G. Marconi of Rome, Dermatology

**Abstract**

BACKGROUND: Vitiligo is an acquired pigmentary cutaneous disease, characterised by the progressive loss of melanocytes, resulting in hypopigmented skin areas which progressively become amelanotic. Classically, vitiligo treatments are unsatisfactory and challenging. Despite the continuous introduction of new therapies, phototherapy is still the mainstay for vitiligo repigmentation.

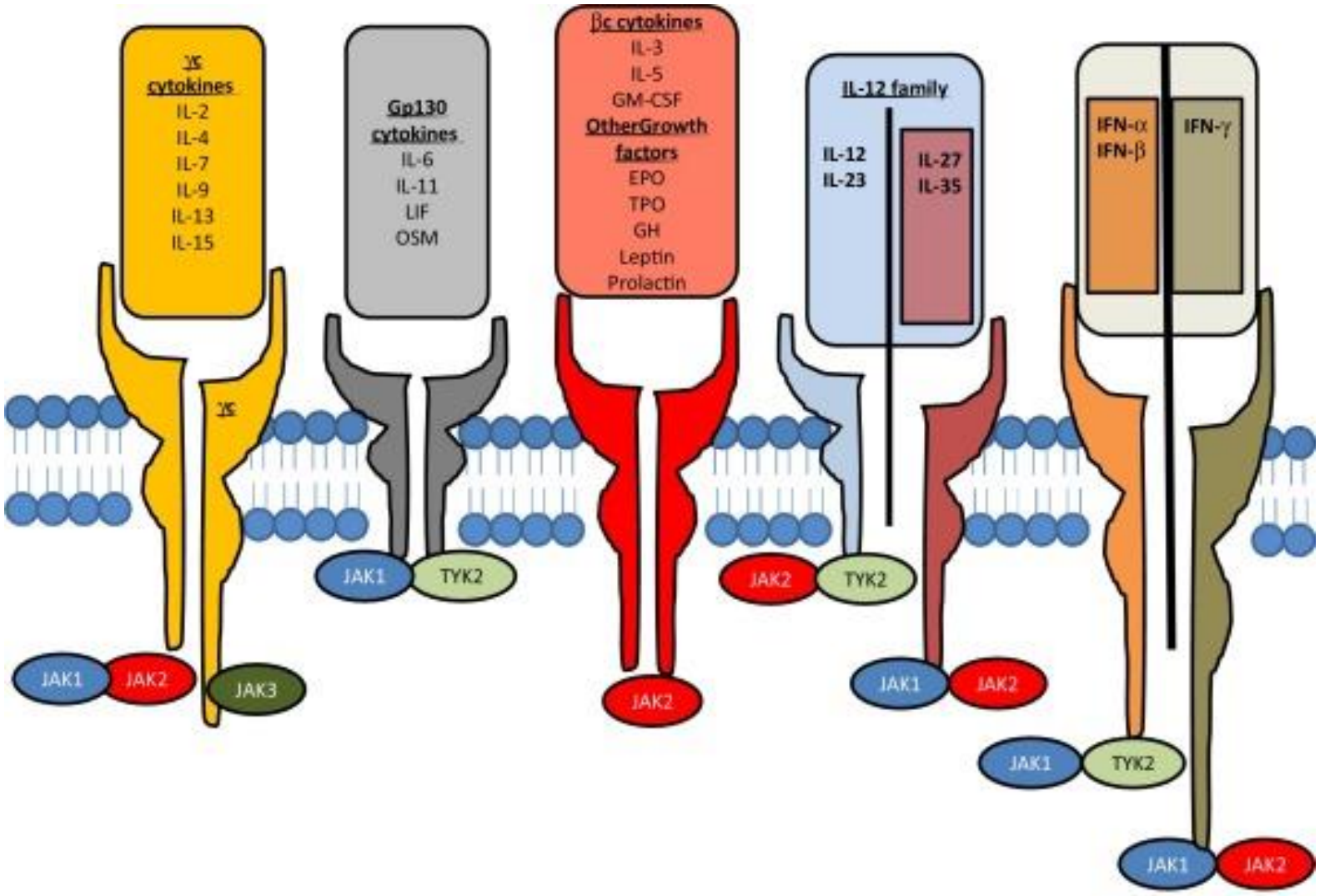
AIM: The aim of this multicenter observational retrospective study was to evaluate the efficacy and safety of the nb - UVB micro - phototherapy (BIOSKIN EVOLUTION®), used alone or in associations with an oral Janus kinase inhibitor (Tofacitinib citrate), in the treatment of stable or active forms of localised vitiligo.

MATERIAL AND METHODS: Fifty eight patients had been treated with n-UVB micro-photootherapy (Group A); 9 patients had been treated with phototherapy plus Tofacitinb citrate (Group B).

RESULTS: Among Group A, 42 patients (72%) obtained a re-pigmentation rate higher than 75%, with a medium value of 77%. 11 patients (19%) achieved a marked improvement of the clinical findings with a repigmentation rate between 50-75%; 4 patients (8%) showed a moderate response with a lesional repigmentation of 25-50%. Only one patient (1%) had a poor response to the phototherapeutic treatment.

CONCLUSION: Nb - UVB micro-focused phototherapy is one of the most effective therapeutic options for vitiligo treatment. The association of micro-focused phototherapy to Tofacitinib citrate seems to provide better clinical results in term of repigmentation rate.

PMID: 29483979 []  PMCID: PMC5816312



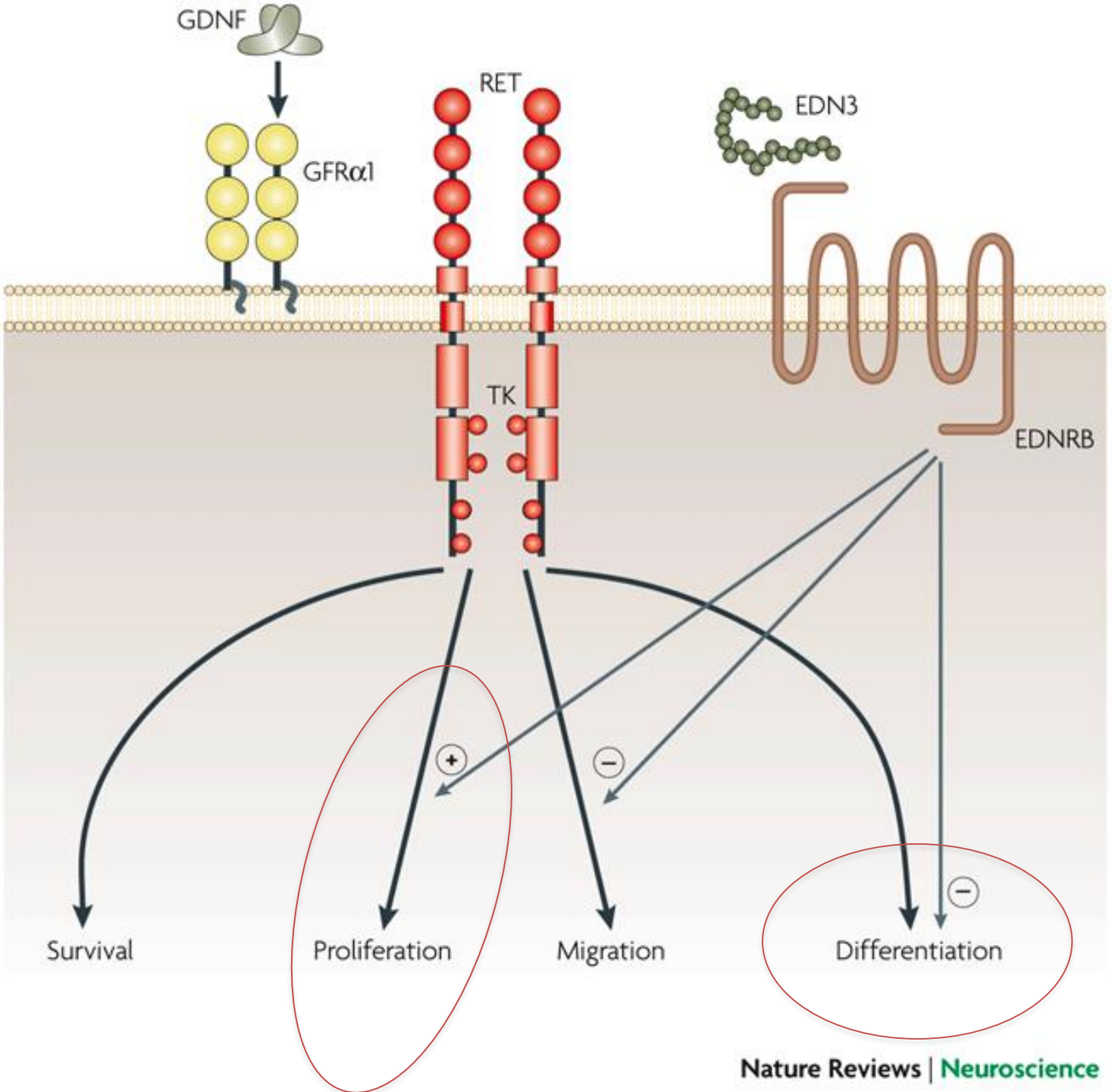

Trends in Molecular Medicine

# Systemic treatment for Vitiligo 2016 – 2017

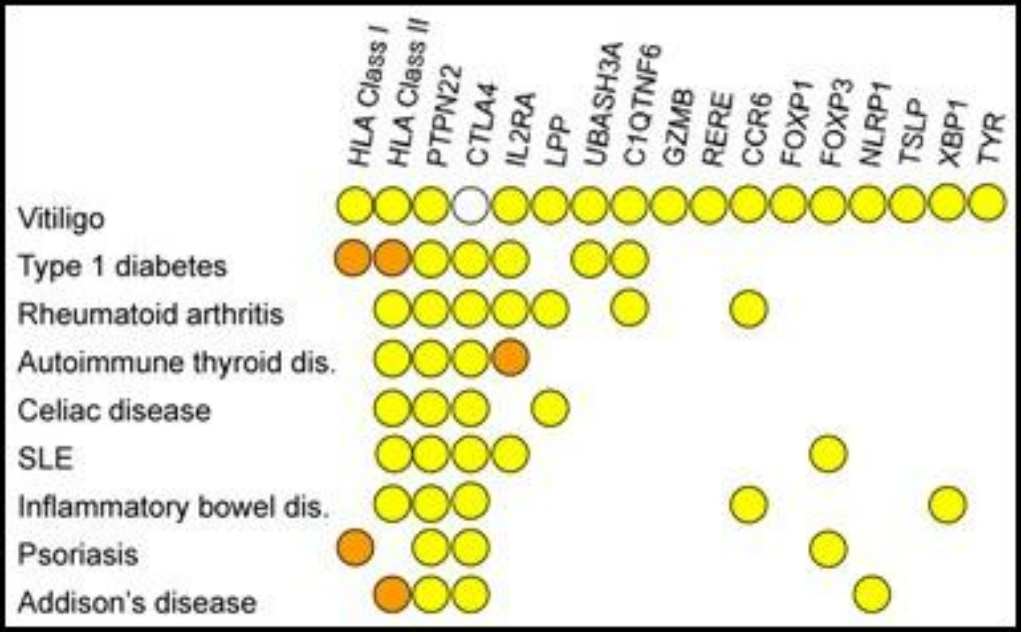
- JAK Inhibitors
- **EdnrB – Wnt Signaling**
- CD20 Mab
- Afamelanotide
- Statins
- Minocycline
- Low Dose Cytokines and Growth Factors
- ……

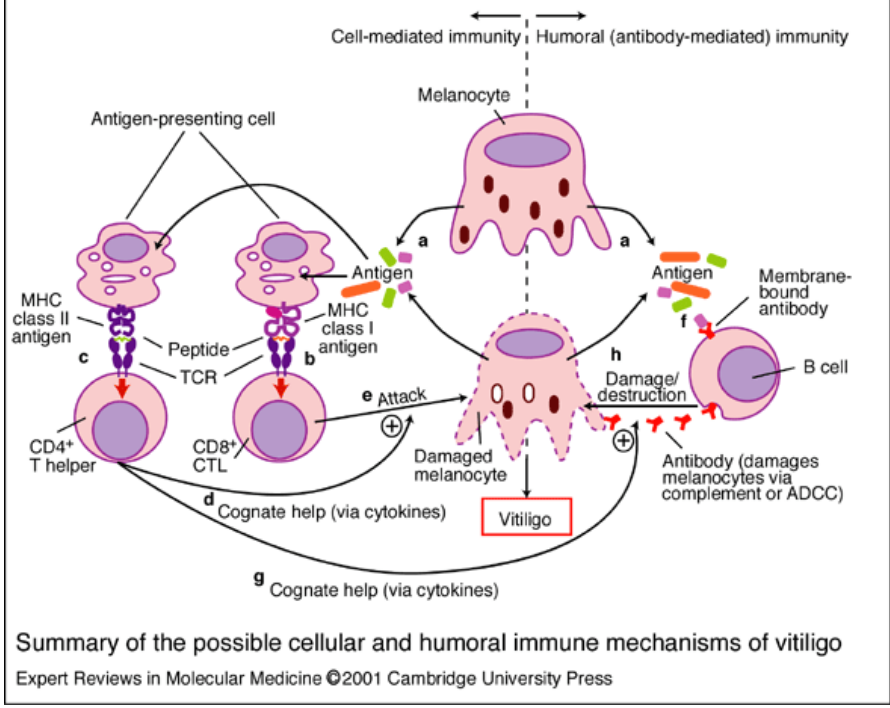
# EdnrB – Wnt Signaling

- Endothelin receptor type B is a G protein-coupled receptor which activates a phosphatidylinositol-calcium second messenger system.
- Regulation In melanocytic cells the EDNRB gene is regulated by the microphthalmia-associated transcription factor. Mutations in either gene are links to Waardenburg syndrome.


GDNF
RET
EDN3
GFRα1
TK
EDNRB
Survival
Proliferation
Migration
Differentiation
Nature Reviews | Neuroscience

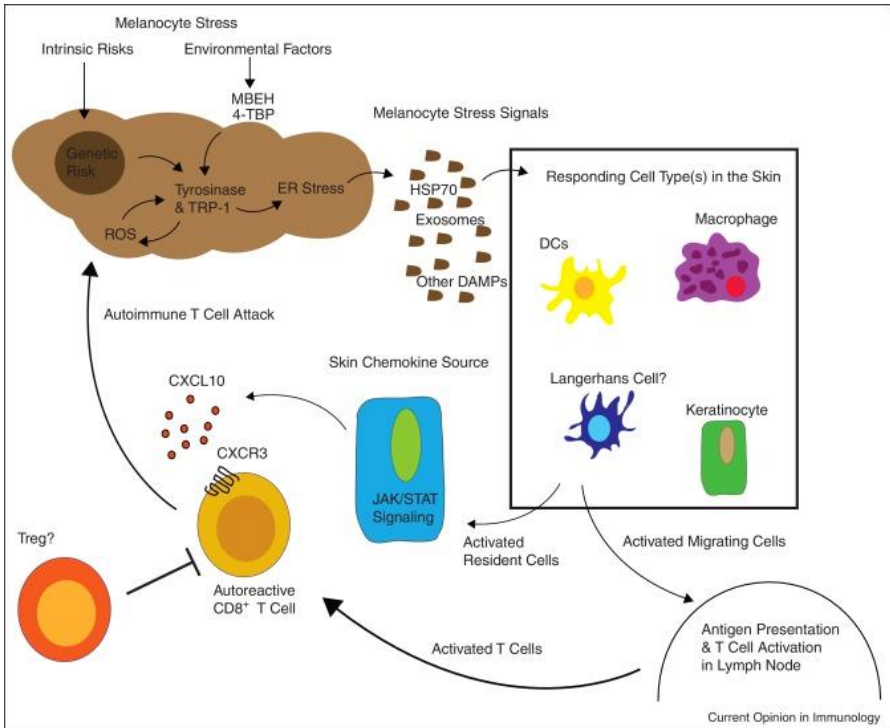
DANGEROUS




Summary of the possible cellular and humoral immune mechanisms of vitiligo

Expert Reviews in Molecular Medicine ©2001 Cambridge University Press



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## Unconventional Treatments for Vitiligo: Are They (Un) Satisfactory?

**Review article**

Gianfaldoni S, et al. Open Access Maced J Med Sci. 2018.


**Authors**

Gianfaldoni S[1], Tchernev G[2,3], Lotti J[4], Wollina U[5], Satolli F[6], Rovesti M[6], França K[7], Lotti T[1].

**Author information**

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**Citation**

Open Access Maced J Med Sci. 2018 Jan 21;6(1):170-175. doi: 10.3889/oamjms.2018.038. eCollection 2018 Jan 25.



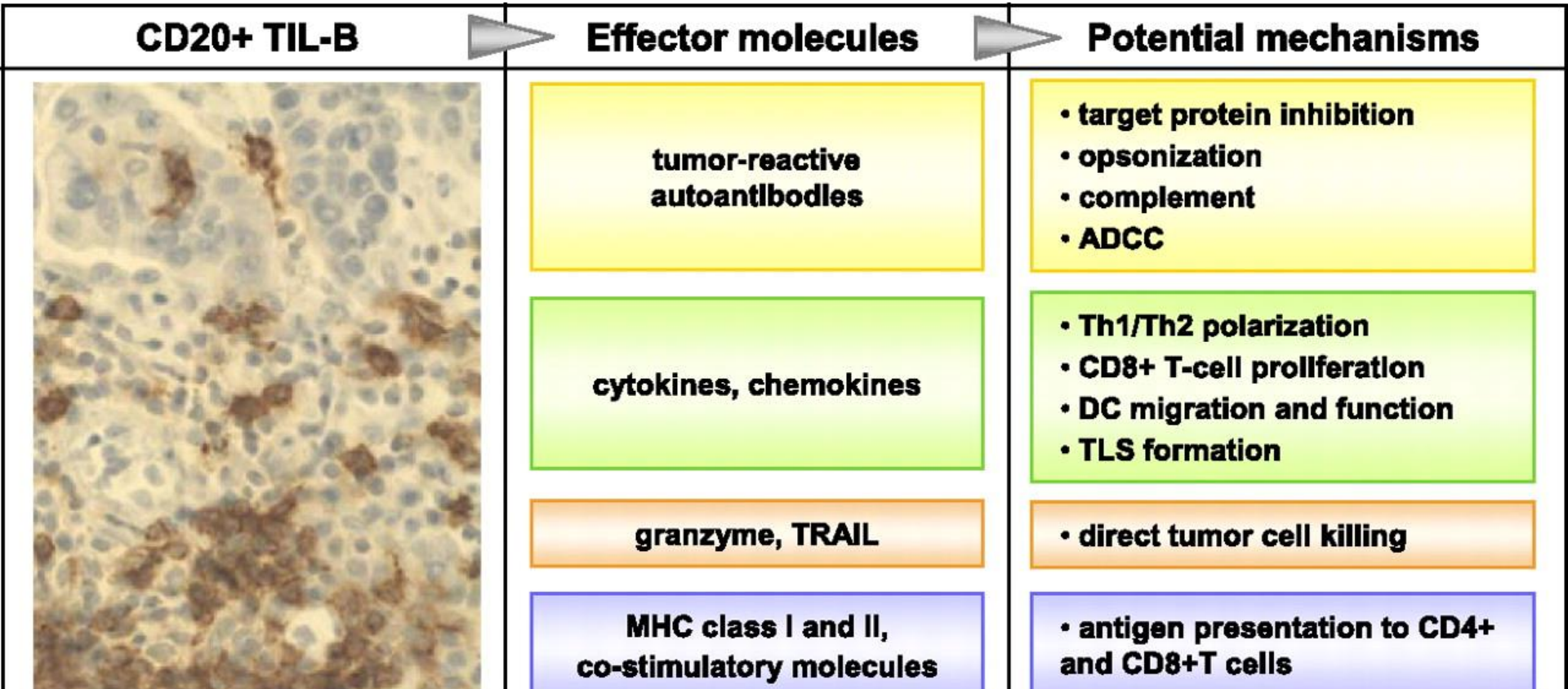
**Abstract**

The authors show a brief overview of the vitiligo's unconventional therapies. A part for well-documented effectiveness of L-phenylalanine, PGE2 and antioxidant agents in the treatment of vitiligo, for the other therapeutical approaches more investigations are needed.



PMID: 29484020 [] PMCID: PMC5816295

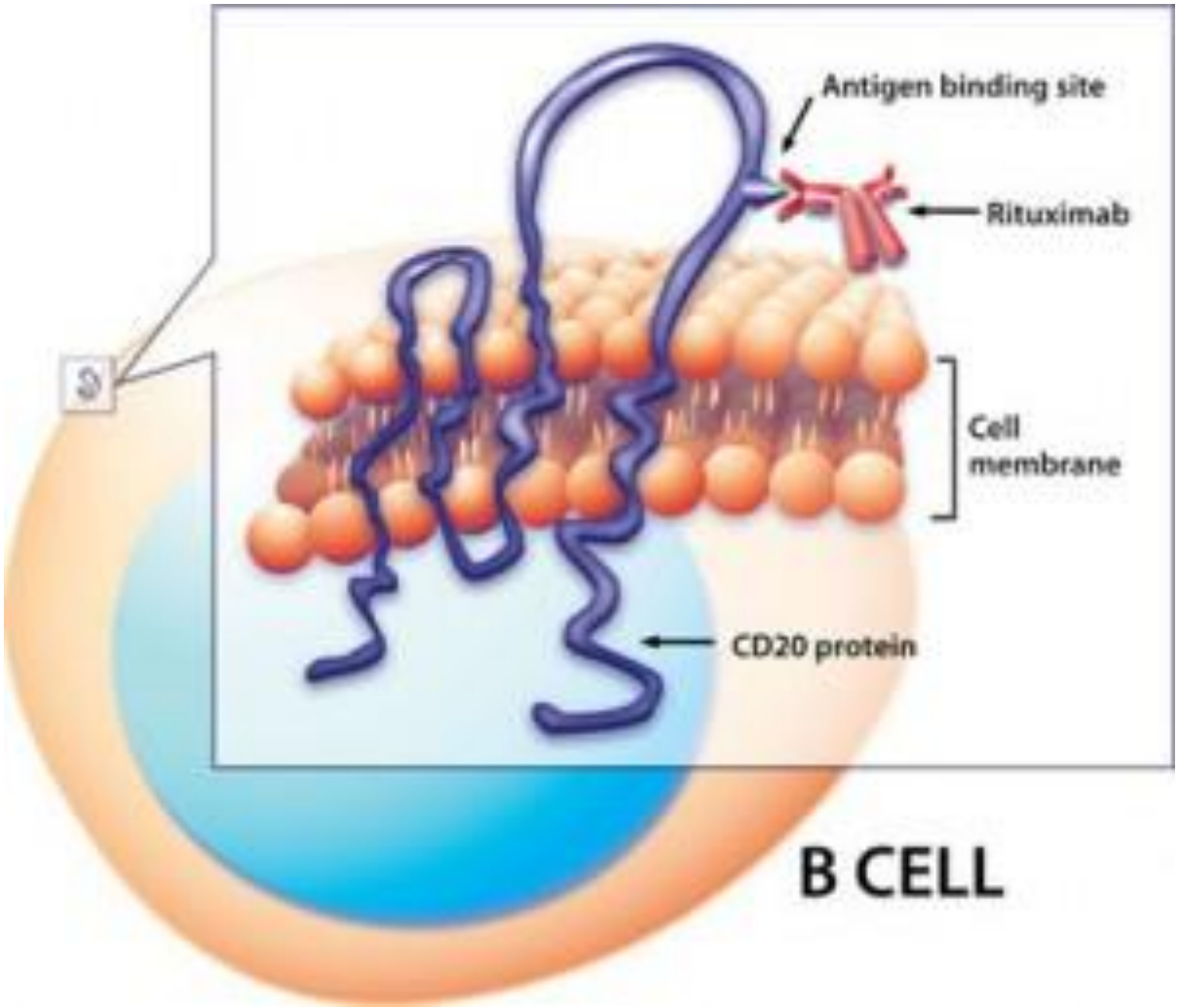
- **B-lymphocyte antigen CD20** or **CD20** is an activated-glycosylated phosphoprotein expressed on the surface of all B-cells beginning at the pro-B phase (CD45R+, CD117+) and progressively increasing in concentration until maturity.
- In humans CD20 is encoded by the *MS4A1* gene.

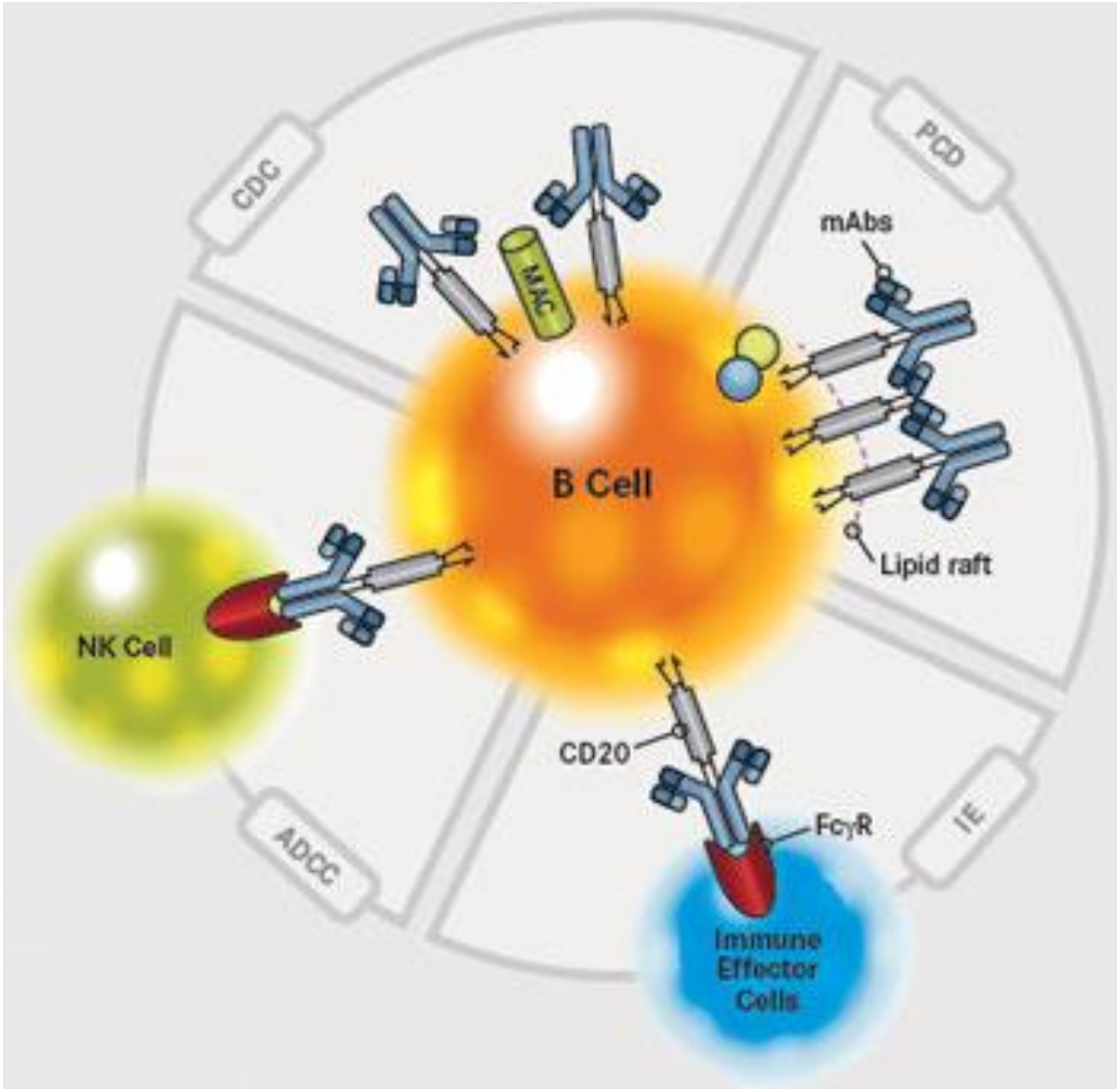


**Advances in the treatment options for vitiligo: activated low-dose cytokines-based therapy.**

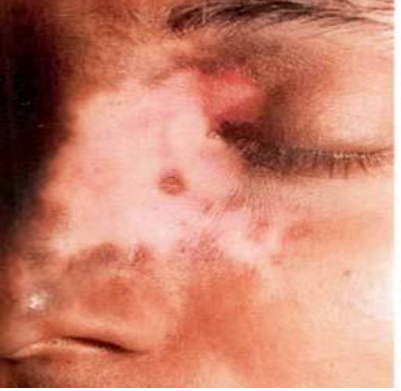
Lotti T, Hercogova J, Fabrizi G.

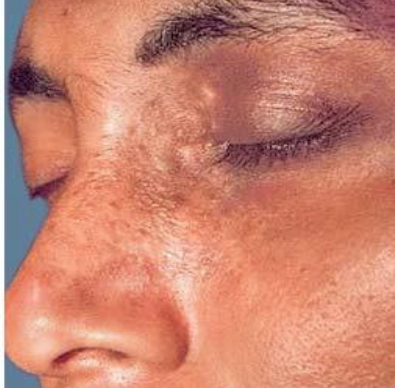
Expert Opin Pharmacother. 2015;16(16):2485-96. doi: 10.1517/14656566.2015.1087508


Antigen binding site
Rituximab
Cell membrane
CD20 protein
B CELL


CDC
PCD
MAC
mAbs
B Cell
Lipid raft
NK Cell
CD20
FcγR
ADCC
IE
Immune
Effector
Cells

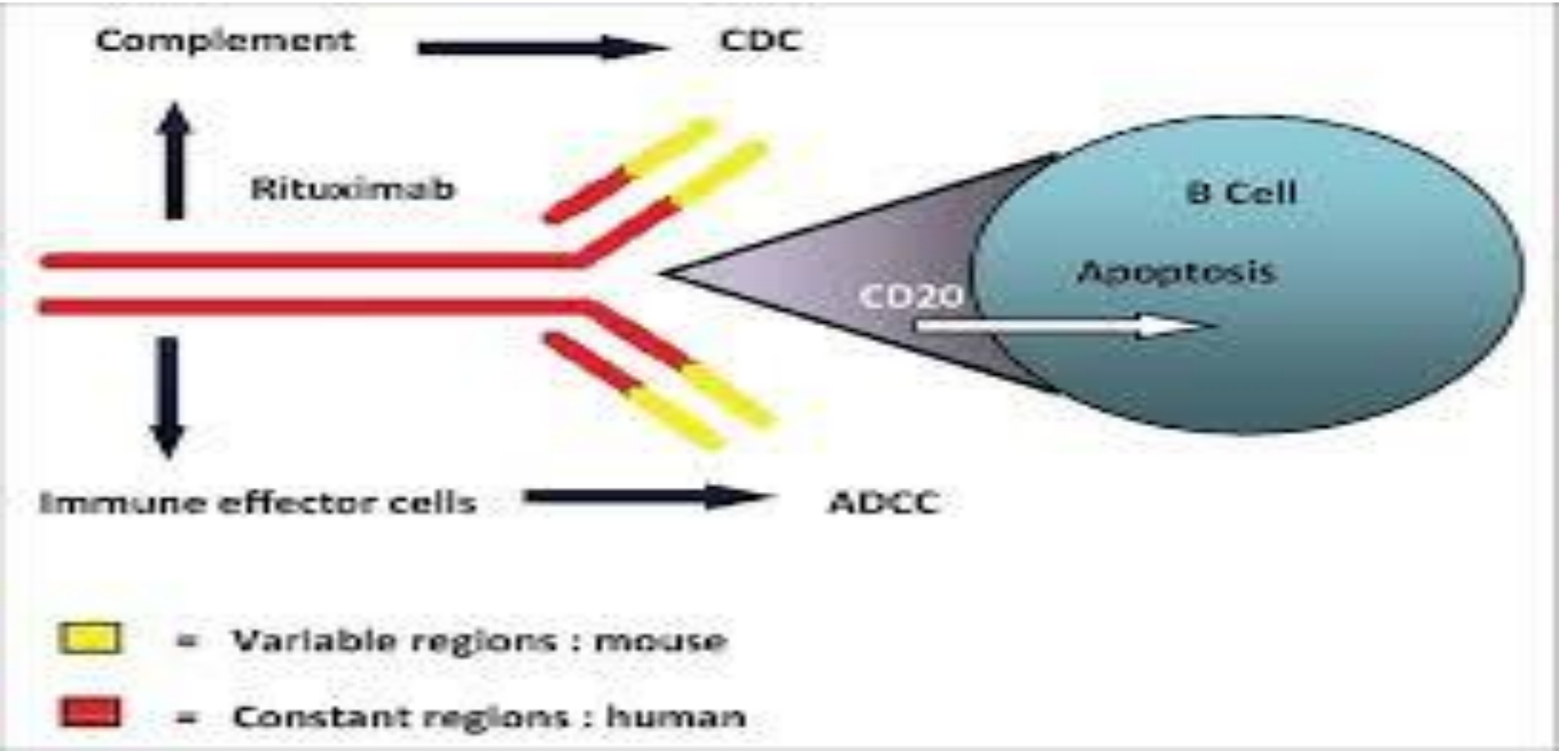

One 500 mg vial
50 mL vial (10 mg/mL)
Rituximab
RITUXAN™
500 mg
Rituximab
RITUXAN



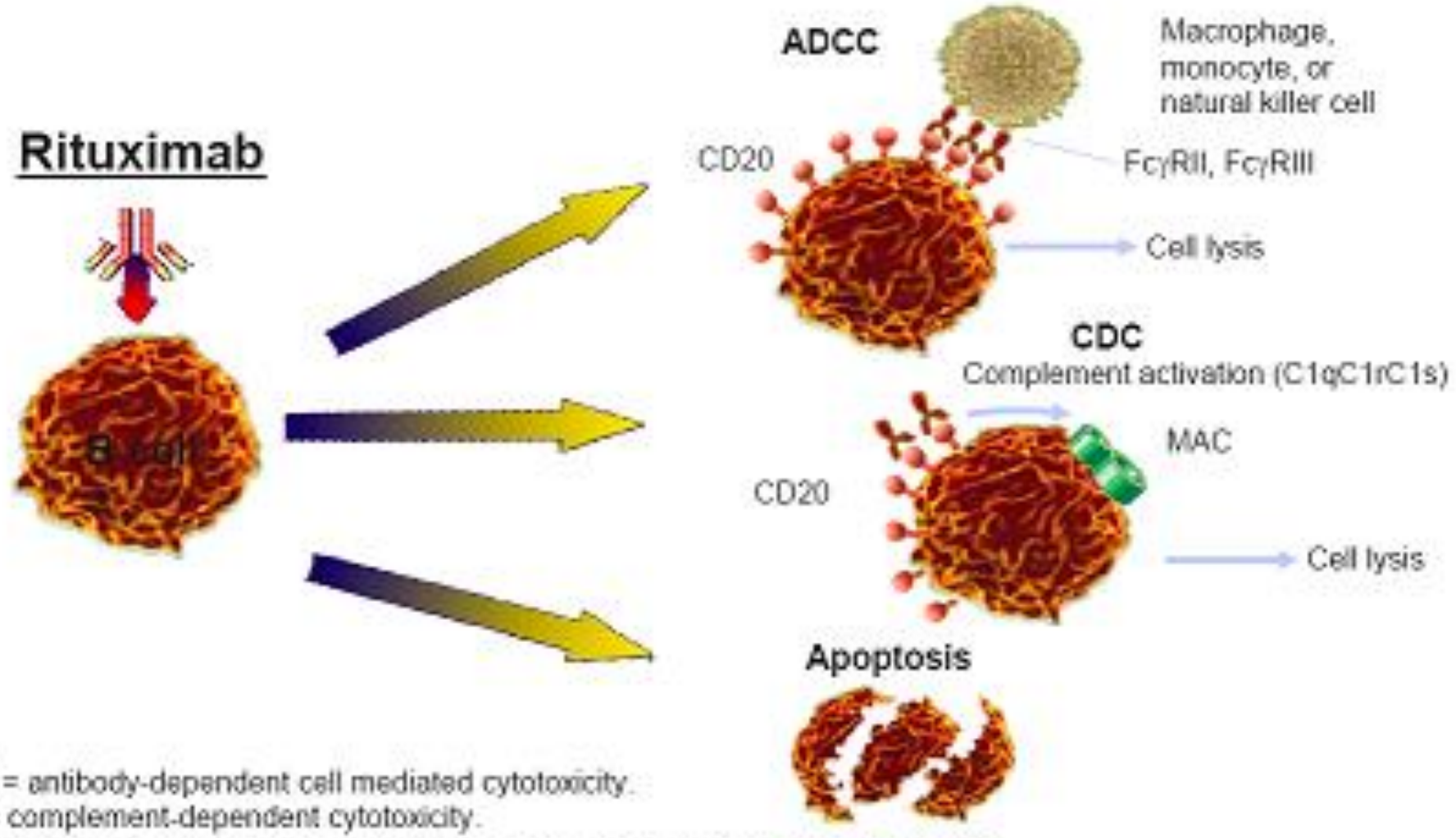


# Systemic treatment for Vitiligo 2016 – 2018

- Monoclonal antibody anti CD20
- RITUXIMAB

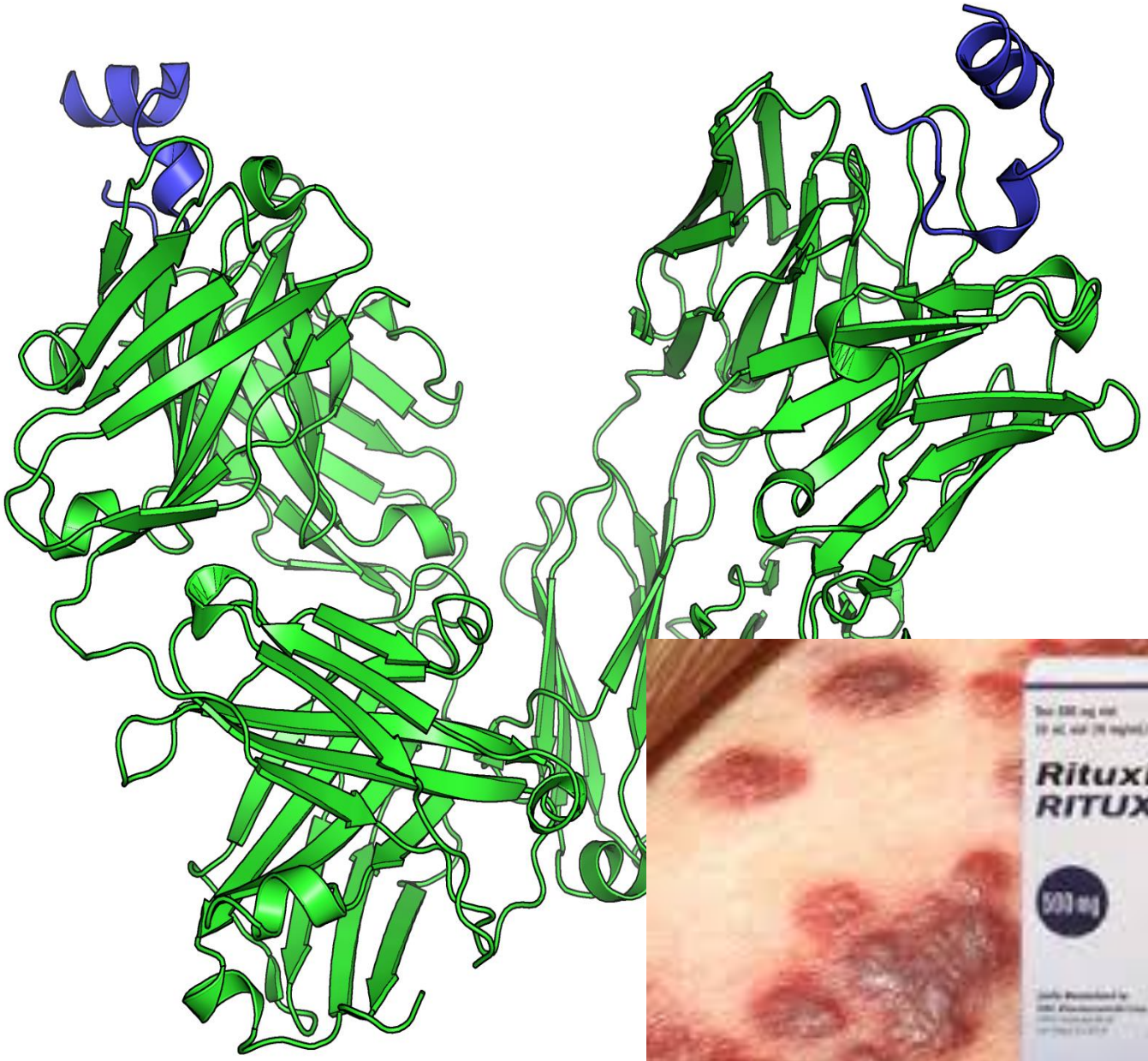


# Rituximab
# Mechanisms of Action

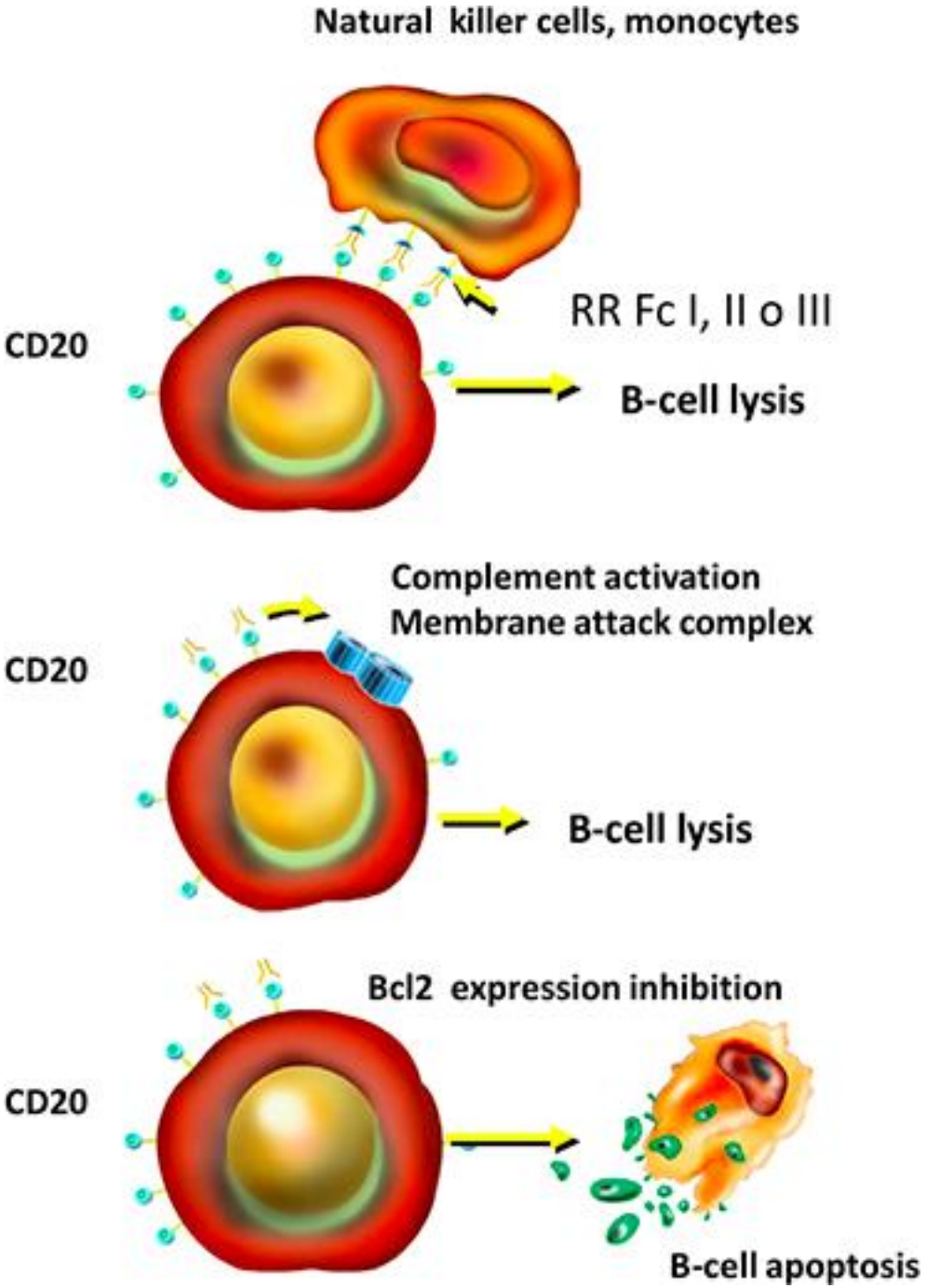


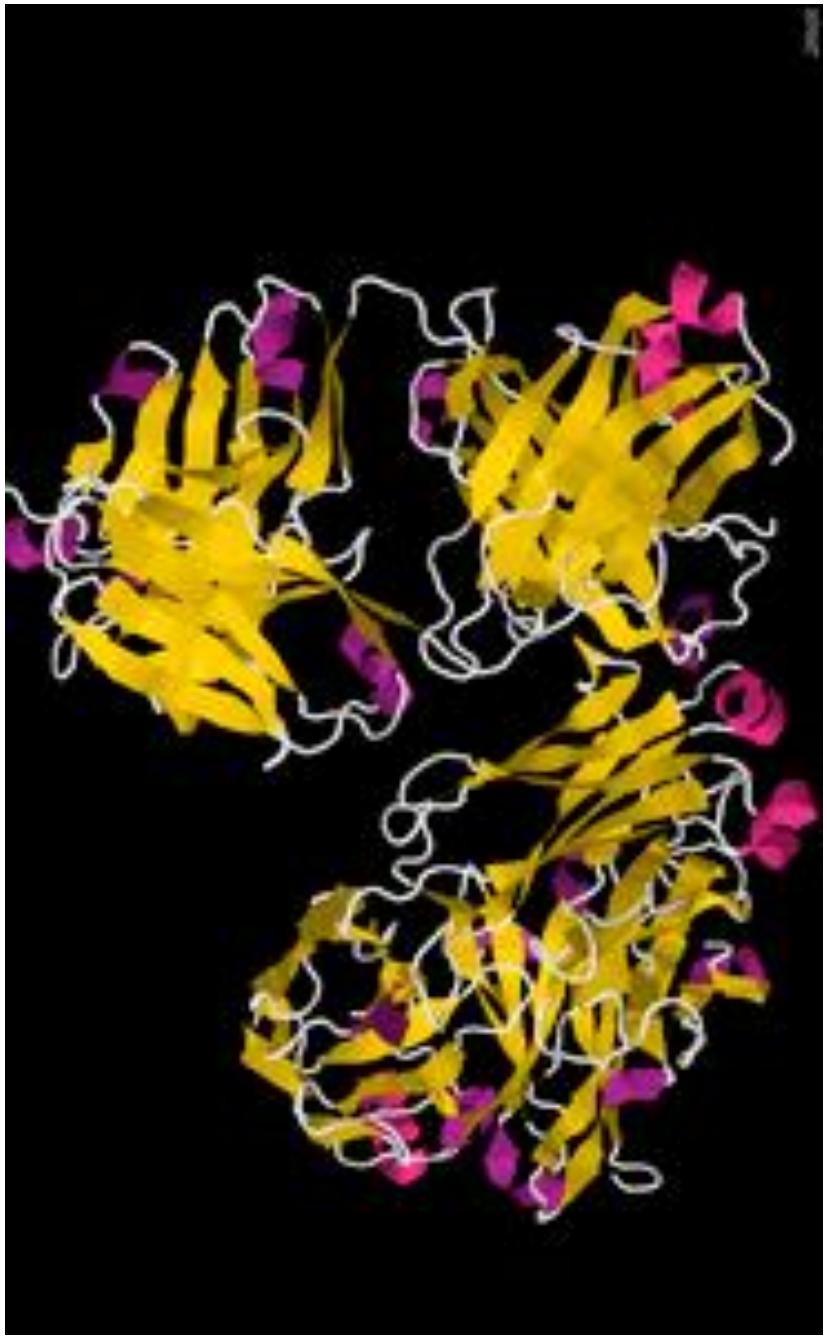

ADCC = antibody-dependent cell mediated cytotoxicity.
CDC = complement-dependent cytotoxicity.

Golay et al. *Blood*. 2000;95:3900; Reff et al. *Blood*. 1994;83:435; Byrd et al. *Blood*. 2002;99:1038.




Rituximab
RITUXAN™
500 mg
Rituximab
RITUXAN


Natural killer cells, monocytes
RR Fc I, II o III
CD20
B-cell lysis
Complement activation
Membrane attack complex
CD20
B-cell lysis
Bcl2 expression inhibition
CD20
B-cell apoptosis



# P.N.E.I.: life and death of skin cells. A new paradigm in the treatment of vitiligo: the low dose cytokines therapy.

Rivkina T, Hercogova J, Lotti T.

Dermatol Ther. 2016 Mar-Apr;29(2):134-5. doi: 10.1111/dth.12268.

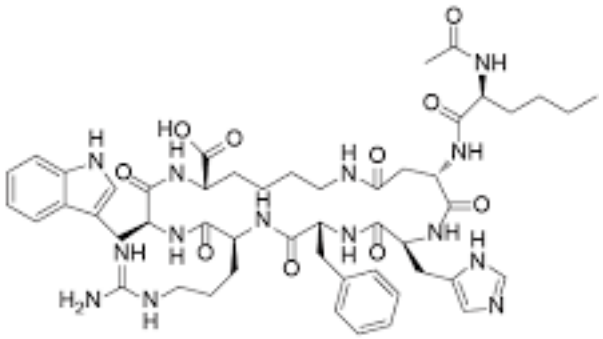
# Systemic treatment for Vitiligo 2016 – 2017

- JAK Inhibitors
- EdnrB – Wnt Signaling
- CD20 Mab
- **Afamelanotide**
- Statins
- Minocycline
- Low Dose Cytokines and Growth Factors
- ……

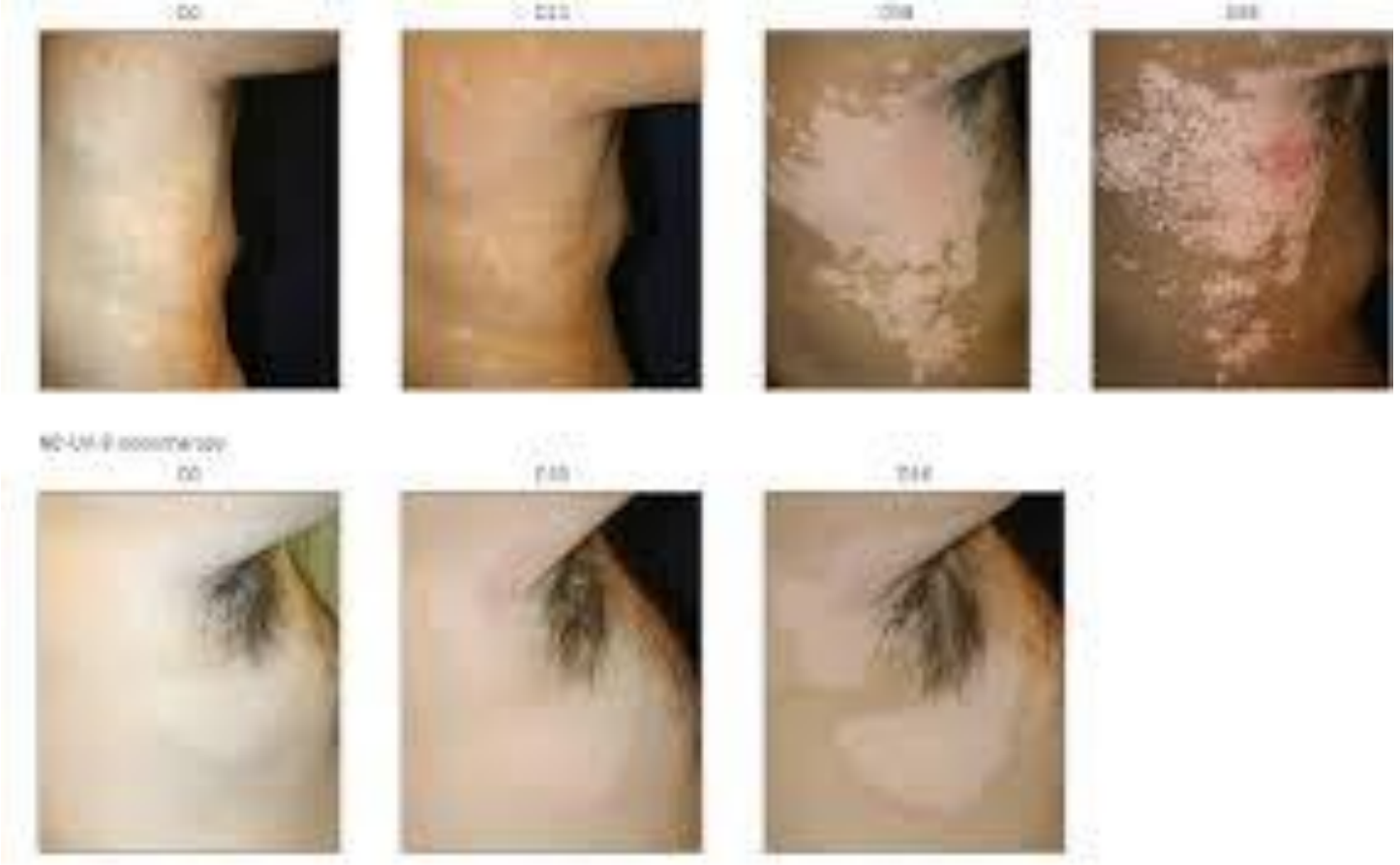
- **Afamelanotide** (ⁱ/ˌæfəmɛˈlænoʊtaɪd/ (INN) (brand name **Scenesse**), also known as **melanotan I** (or **melanotan-1**), originally developed at the University of Arizona and now by Clinuvel Pharmaceuticals, is a synthetic peptide and analogue of the naturally occurring melanocortin peptide hormone α-melanocyte stimulating
- hormone (α-MSH).

- It has been shown to induce the production of darkening dermal pigmentation through melanogenesis and thereby subsequently reduce sun (UV) damage to UV light-exposed skin in preliminary research and human clinical trials. Its amino acid sequence is Ac-Ser-Tyr-Ser-Nle-Glu-His-D-Phe-Arg-Trp-Gly-Lys-Pro-Val-$NH_2$, and it is additionally known as **[Nle$^4$,D-Phe$^7$]-α-MSH**, which is sometimes abbreviated as **NDP-MSH** or **NDP-α-MSH** (especially in the scientific literature).

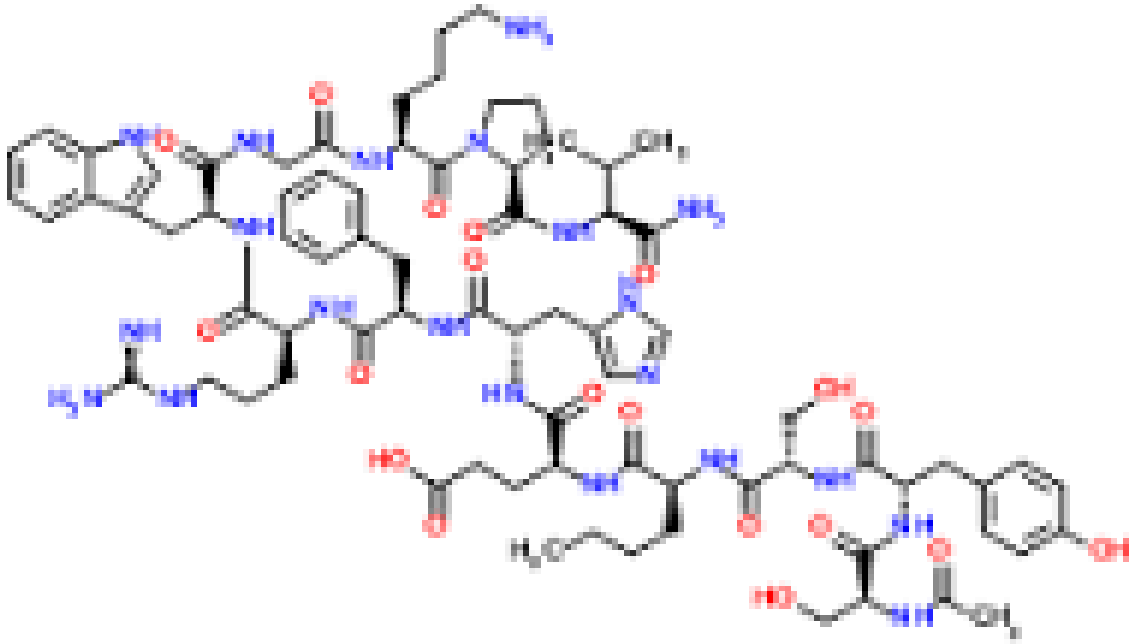
- Afamelanotide

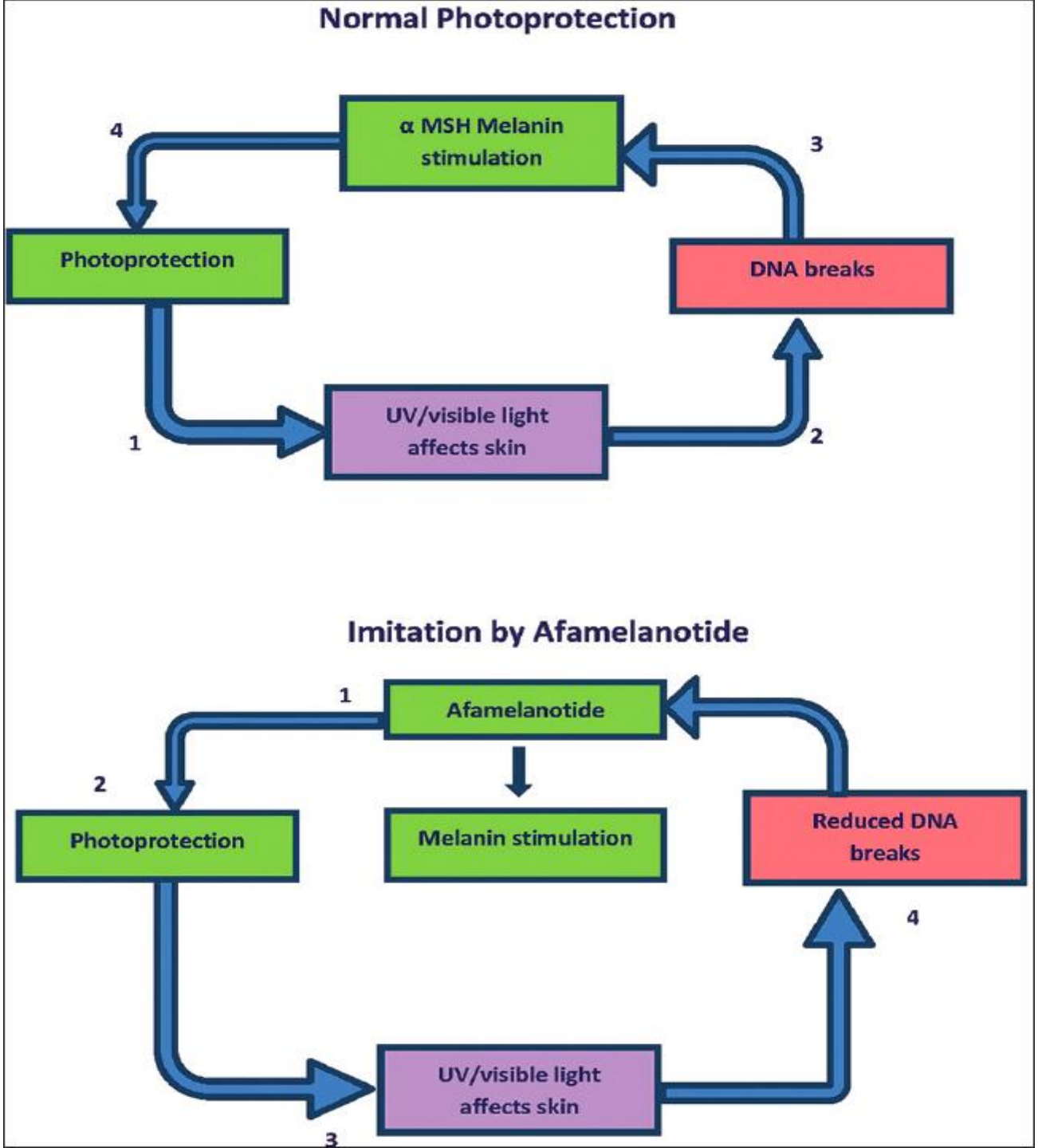


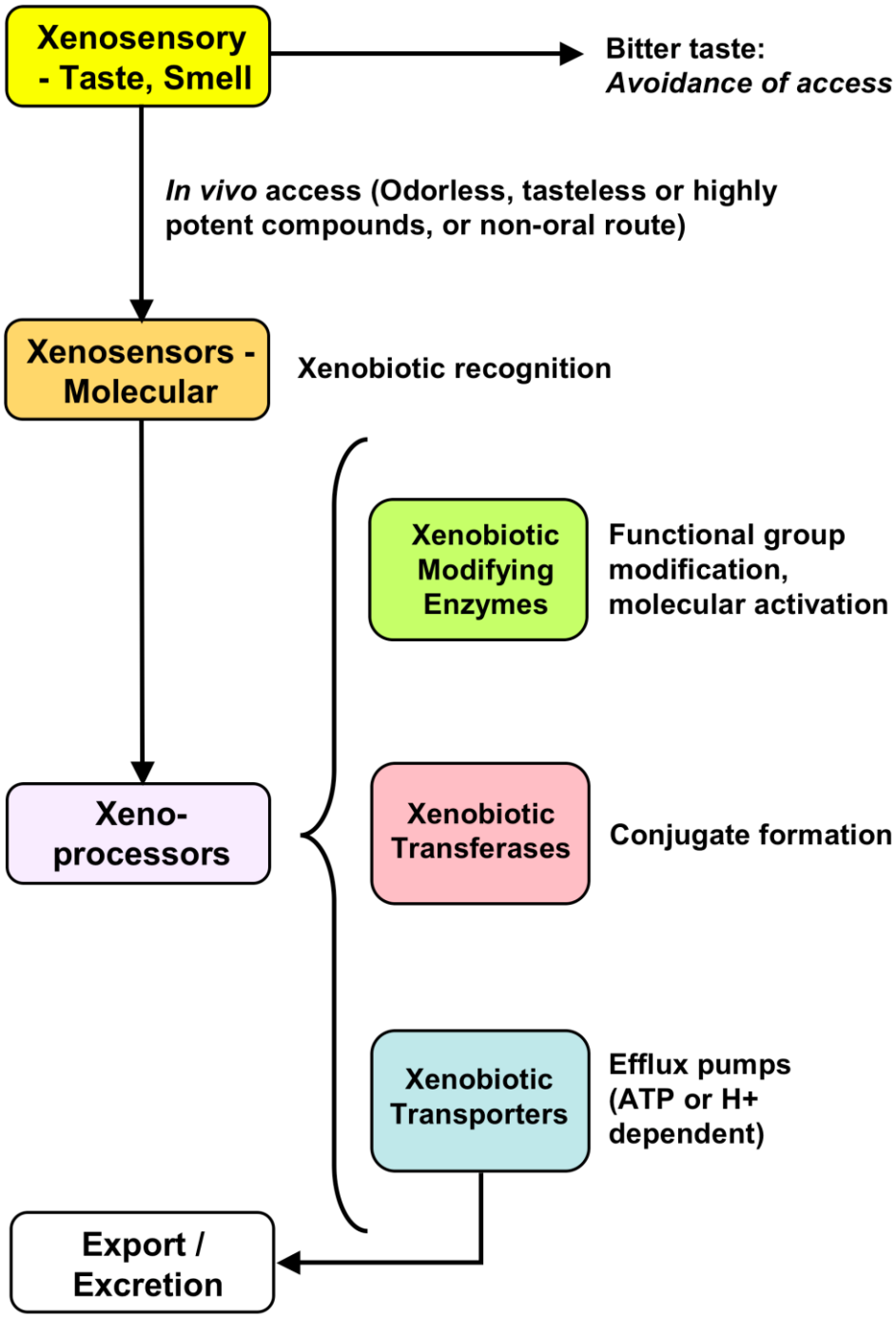
- Afamelanotide is the International Nonproprietary Name for the molecule [Nle$^4$,D-Phe$^7$]α-MSH[3] initially researched and developed as melanotan-1 ⁱ/mɛˈlænoʊtæn/ and later, CUV1647 (by Clinuvel)



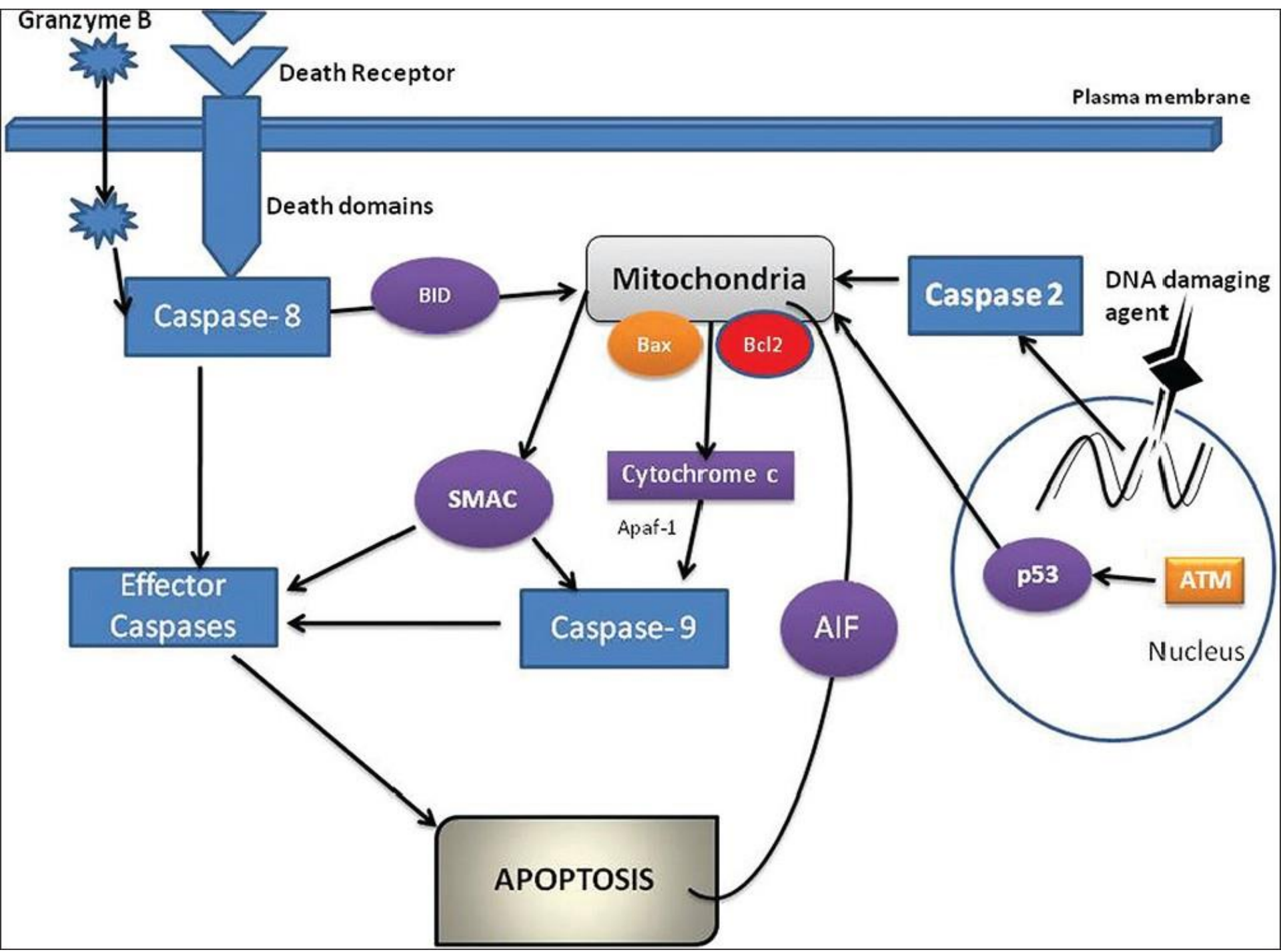
# Afamelanotide

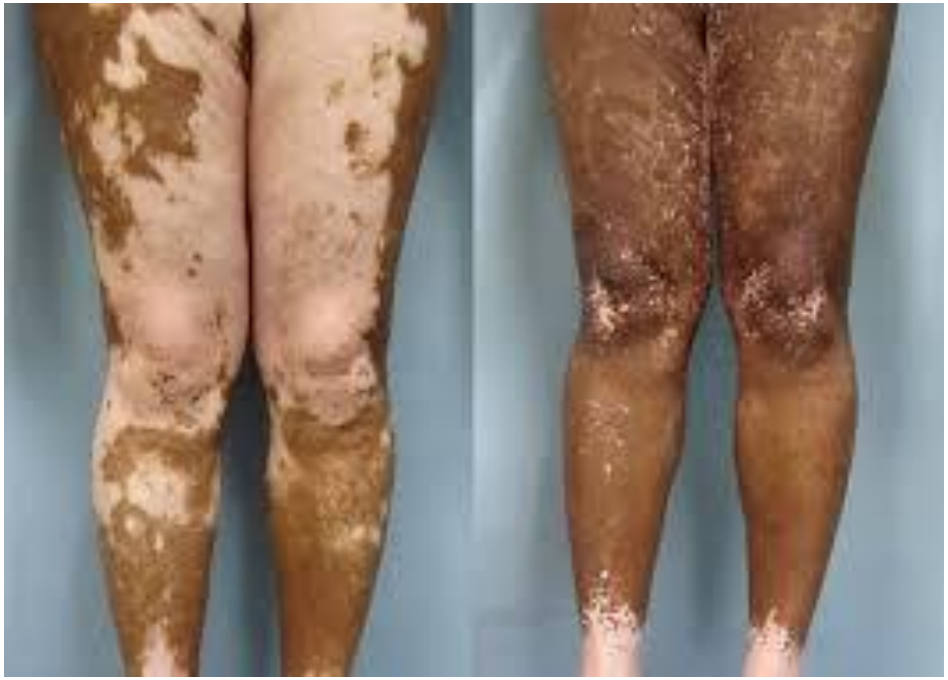

Normal Photoprotection
α MSH Melanin stimulation
4
3
Photoprotection
DNA breaks
UV/visible light affects skin
1
2
Imitation by Afamelanotide
1
Afamelanotide
2
Photoprotection
Melanin stimulation
Reduced DNA breaks
4
UV/visible light affects skin
3

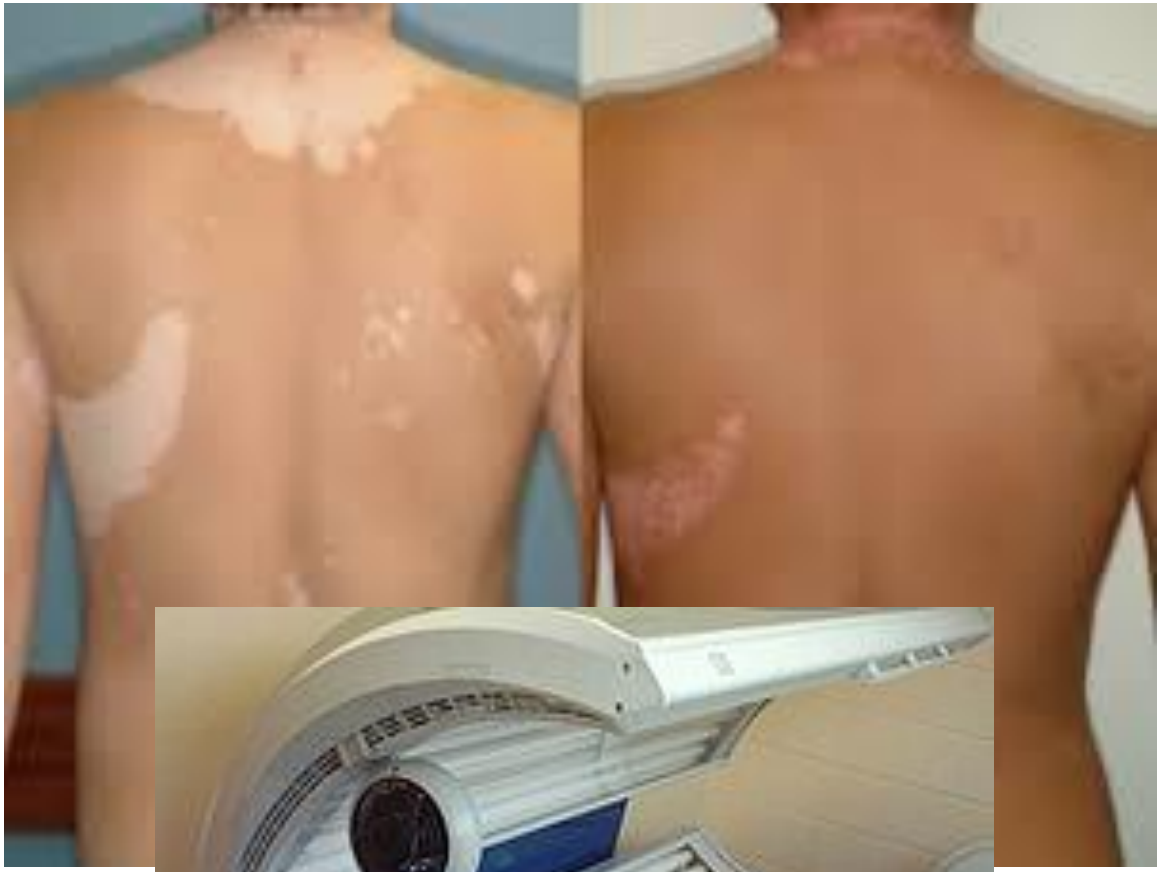

Xenosensory
- Taste, Smell
Bitter taste:
*Avoidance of access*
*In vivo* access (Odorless, tasteless or highly potent compounds, or non-oral route)
Xenosensors - Molecular
Xenobiotic recognition
Xenobiotic Modifying Enzymes
Functional group modification, molecular activation
Xeno-processors
Xenobiotic Transferases
Conjugate formation
Xenobiotic Transporters
Efflux pumps (ATP or H+ dependent)
Export / Excretion


Melanotan
10.0mg
98.00%
www.synprotech.com


Granzyme B
Death Receptor
Plasma membrane
Death domains
Caspase-8
BID
Mitochondria
Bax
Bcl2
Caspase 2
DNA damaging agent
SMAC
Cytochrome c
Apaf-1
Effector Caspases
Caspase-9
AIF
p53
ATM
Nucleus
APOPTOSIS

# Afamelanotide



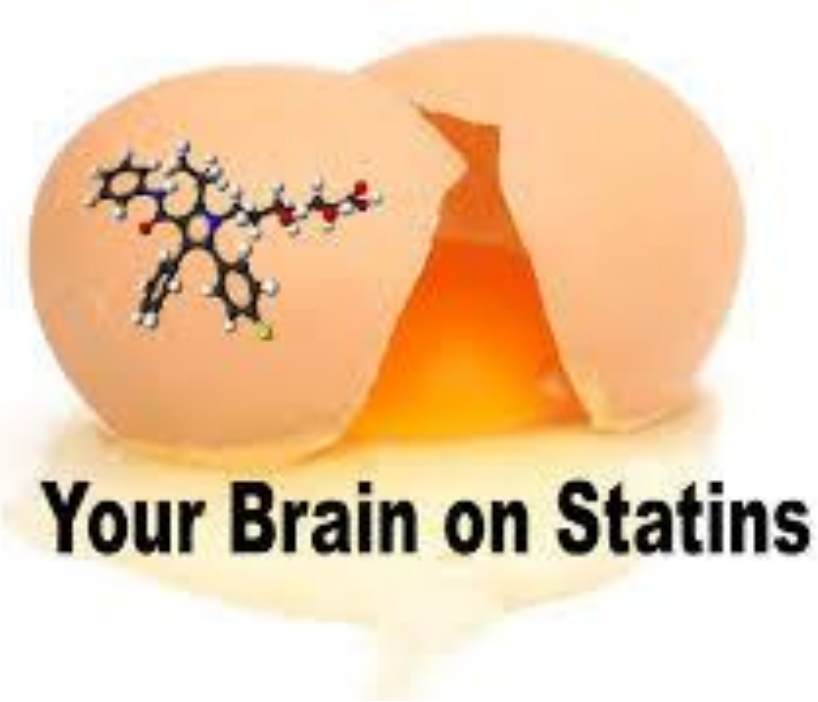


# Systemic treatment for Vitiligo 2016 – 2017

- JAK Inhibitors
- EdnrB – Wnt Signaling
- CD20 Mab
- Afamelanotide
- **Statins**
- Minocycline
- Low Dose Cytokines and Growth Factors
- ……

- Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications.
- Statins have been found to reduce cardiovascular disease and mortality in those who are at high risk. The evidence is strong that statins are effective for treating CVD in the early stages of a disease (secondary prevention) and in those at elevated risk but without CVD (primary prevention)

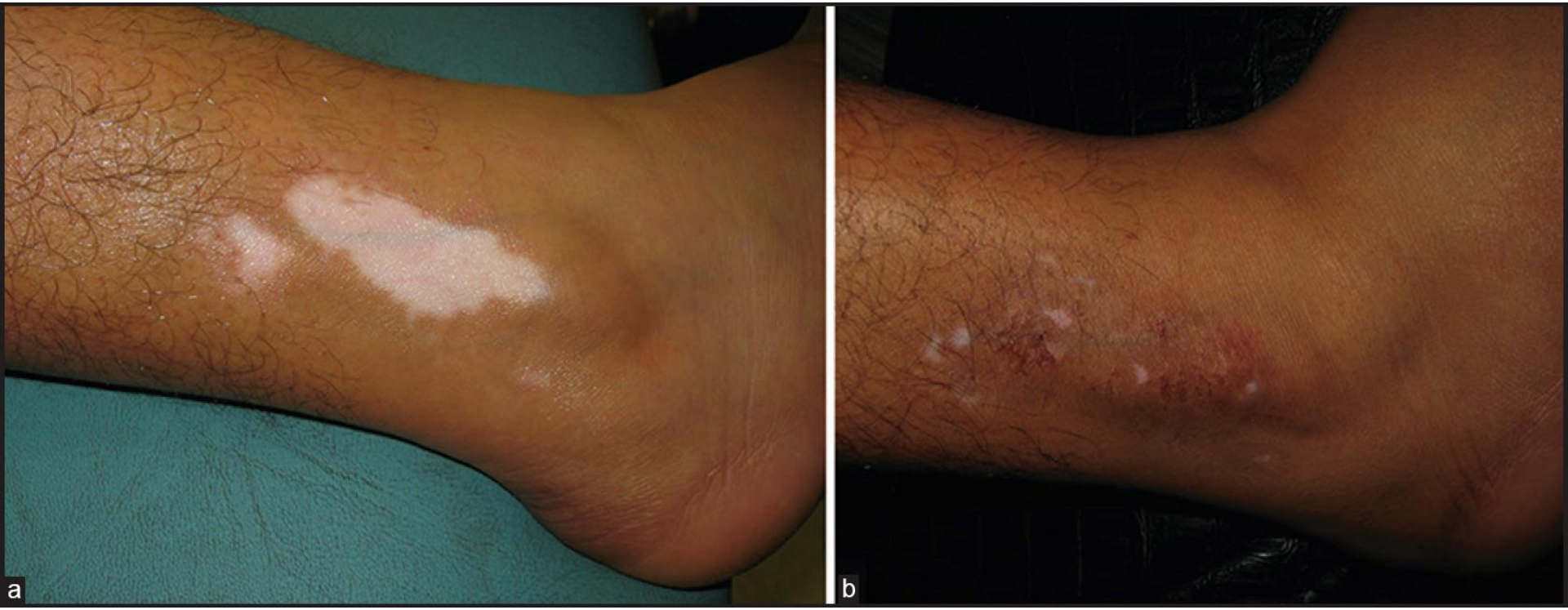
- They inhibit the enzyme HMG-CoA reductase which plays a central role in the production of cholesterol. High cholesterol levels have been associated with cardiovascular disease (CVD).



Lipids Health Dis. 2004; 3: 7.
Published online 2004 May 10. doi: 10.1186/1476-511X-3-7
PMCID: PMC425594

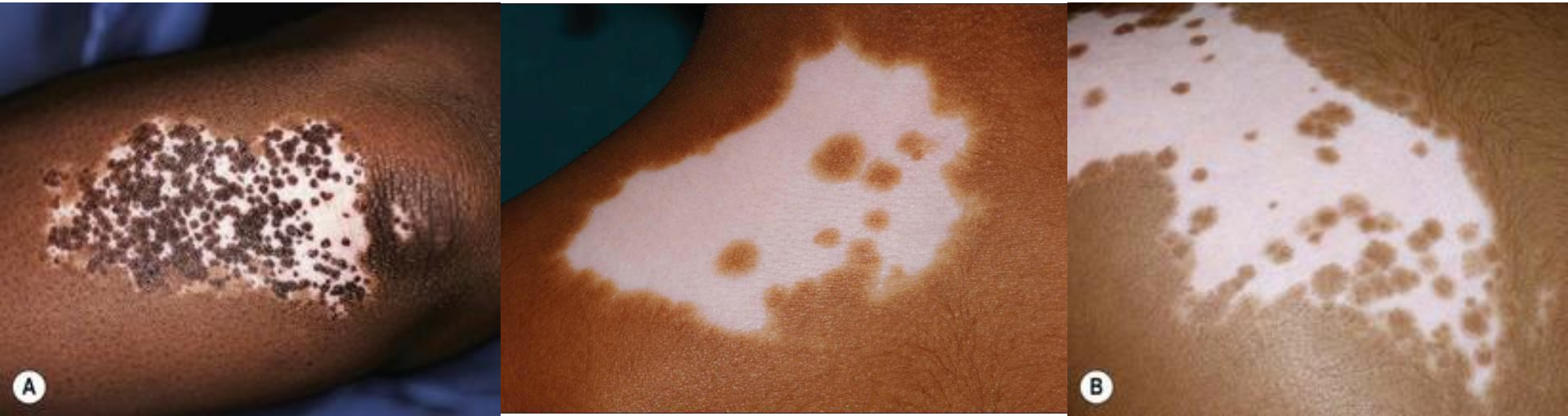
# Positive pleiotropic effects of HMG-CoA reductase inhibitor on vitiligo

Martin Noël,1 Claude Gagné,2 Jean Bergeron,2 Jean Jobin,1 and Paul Poirier

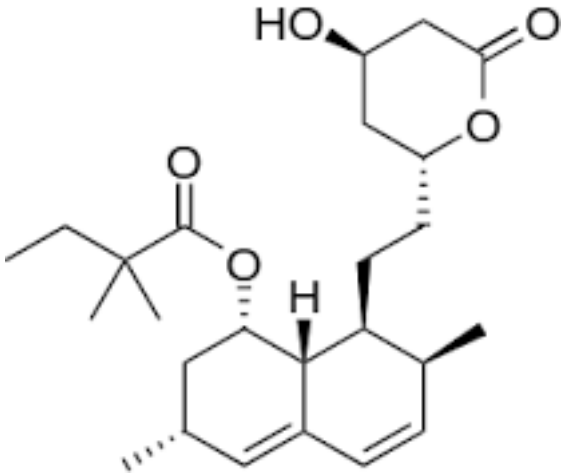


# Background

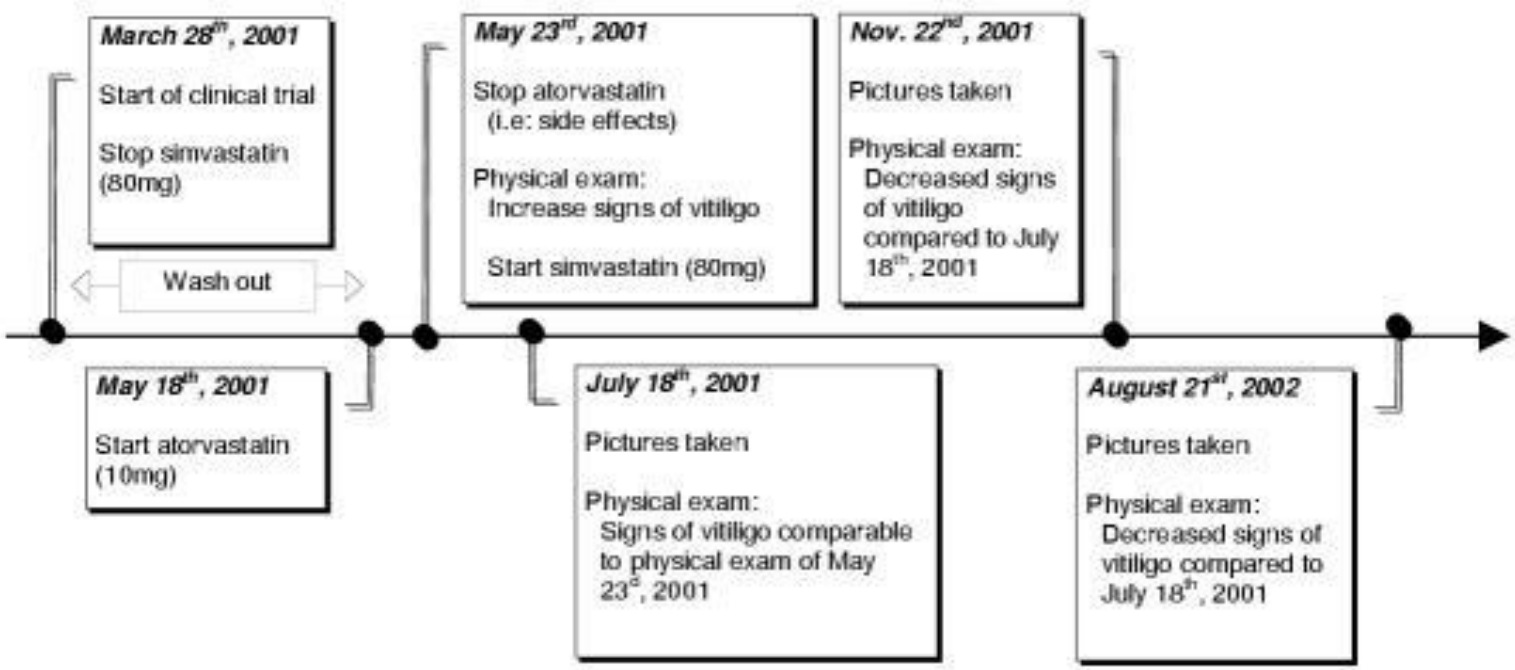
•HMG-CoA reductase inhibitors (statins) are commonly used in medicine to control blood lipid disorder. Large clinical trials have demonstrated that statins greatly reduces cardiovascular-related morbidity and mortality in patients with and without coronary artery disease. Also, the use of HMG-CoA reductase inhibitors has been reported to have immunosuppressive effects.

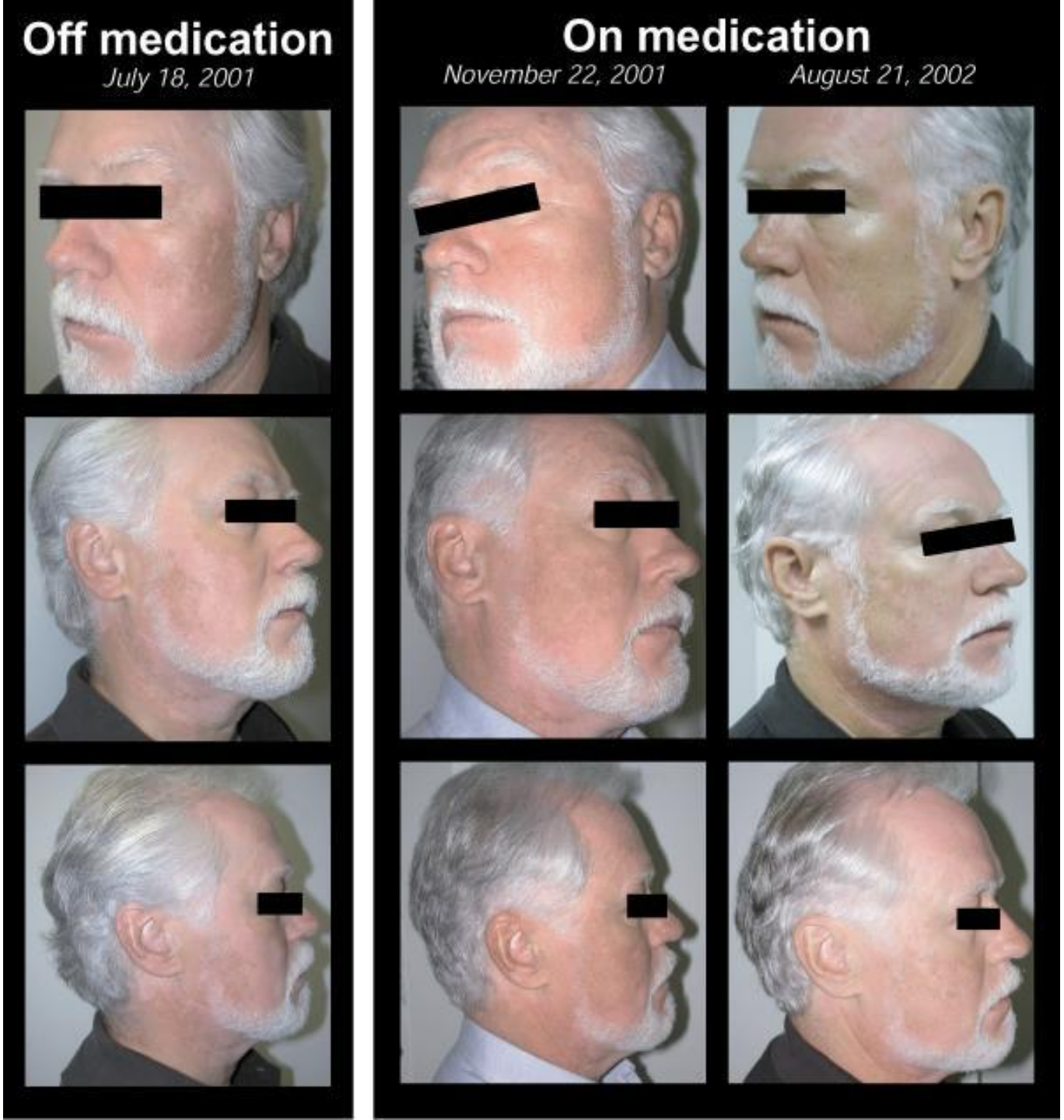


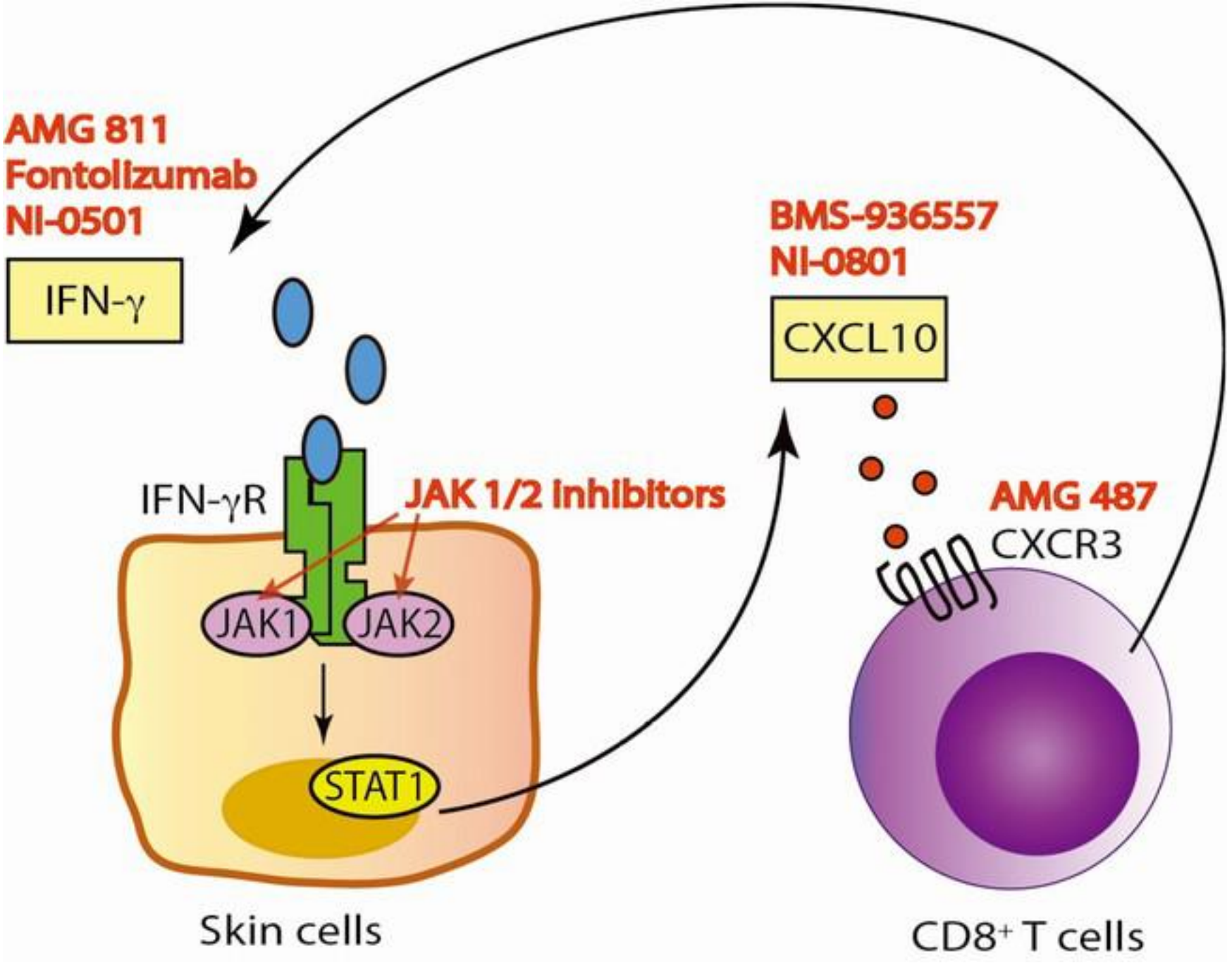
- **Case presentation**
- We describe an unusual case of regression of vitiligo in a patient treated with high dose simvastatin. The relation between simvastatin and regression of vitiligo in this case report may be related to the autoimmune pathophysiology of the disease.

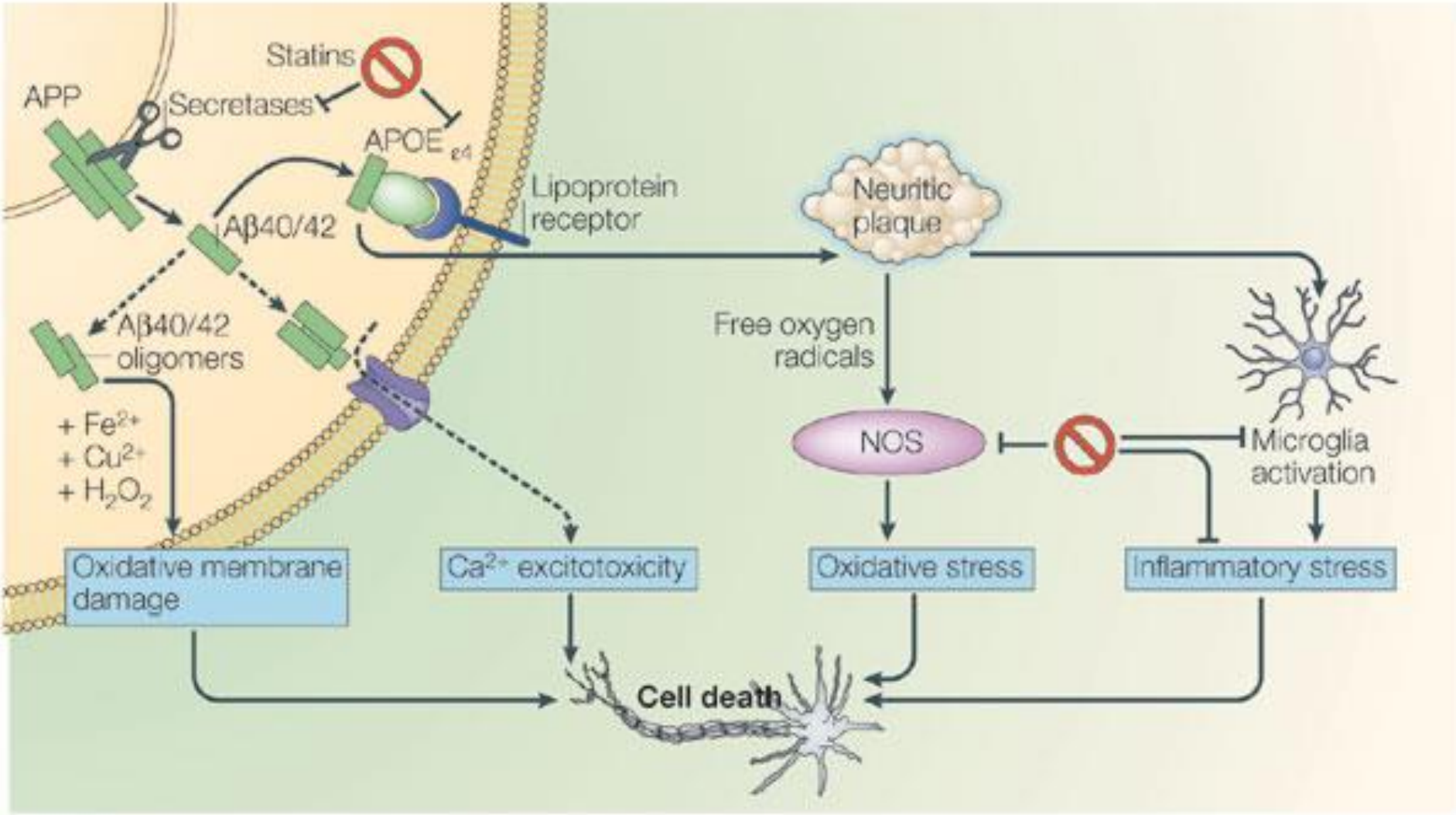
# Figure 1
# Timeline progression of the vitiligo




Off medication
July 18, 2001
On medication
November 22, 2001
August 21, 2002


AMG 811
Fontolizumab
NI-0501
IFN-γ
IFN-γR
JAK 1/2 Inhibitors
JAK1
JAK2
STAT1
Skin cells
BMS-936557
NI-0801
CXCL10
AMG 487
CXCR3
CD8+ T cells

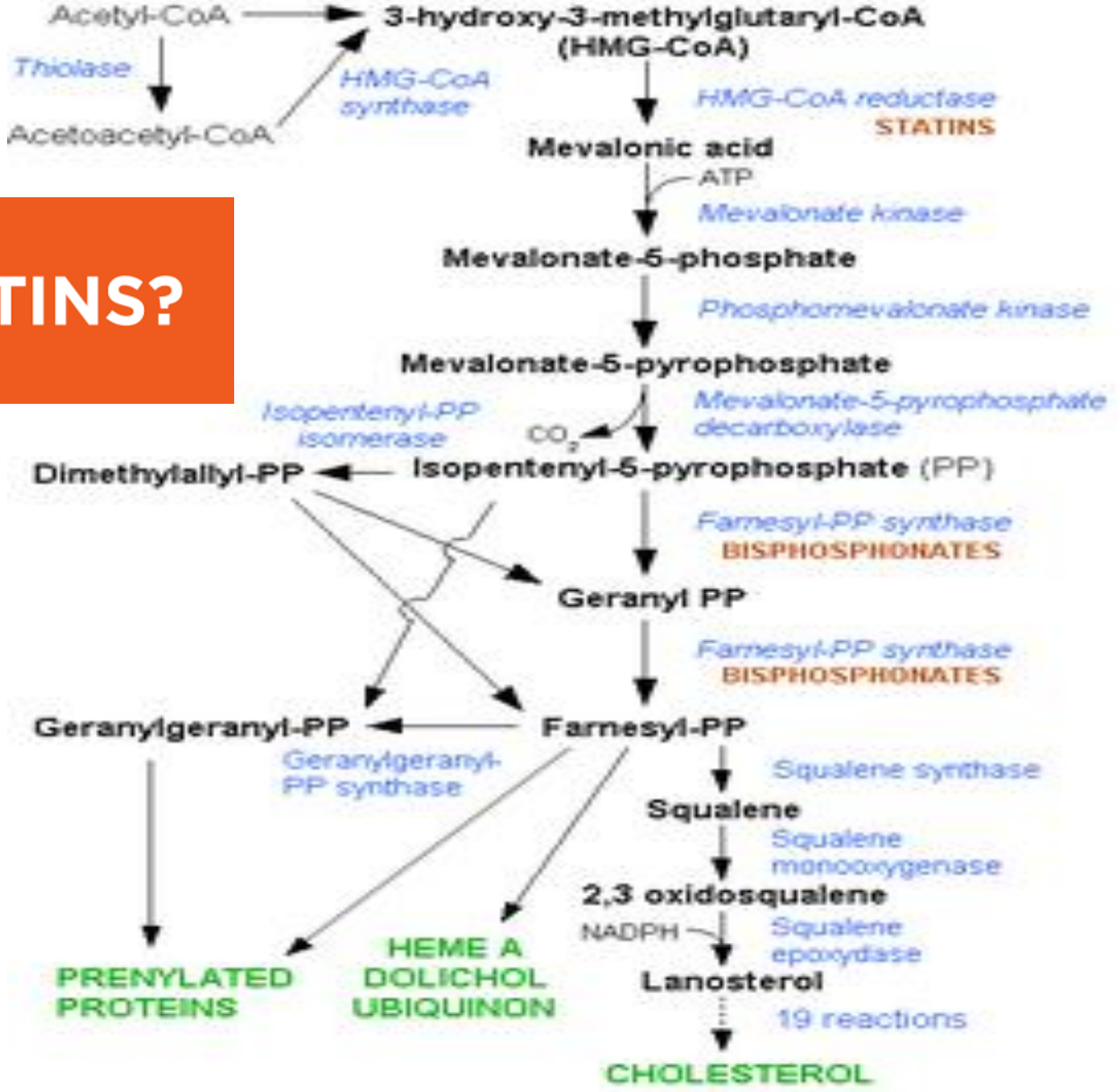
# HOW STATINS REALLY WORK




Nature Reviews | Neuroscience

# STATINS DOSAGE !?

# STATINS?

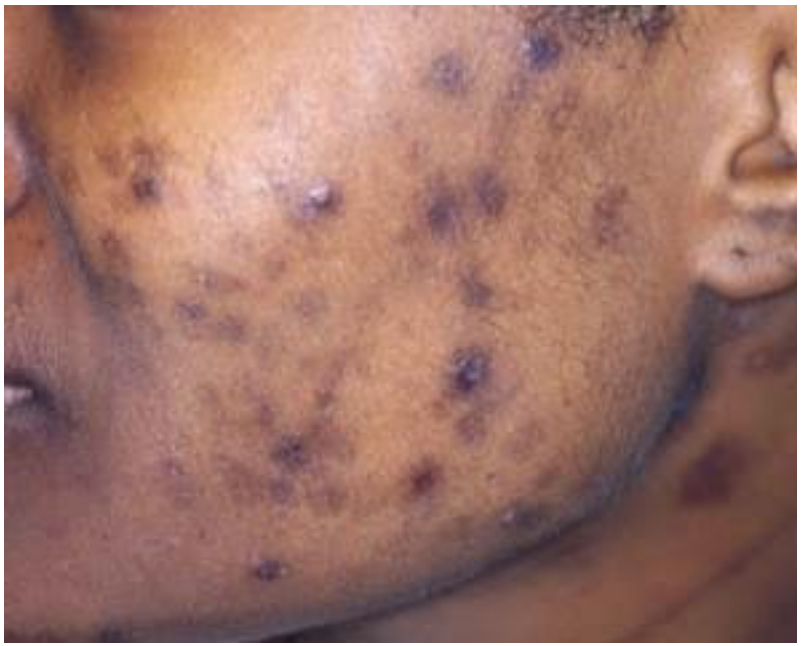

Acetyl-CoA
3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)
Thiolase
HMG-CoA synthase
Acetoacetyl-CoA
HMG-CoA reductase
STATINS
Mevalonic acid
ATP
Mevalonate kinase
Mevalonate-5-phosphate
Phosphomevalonate kinase
Mevalonate-5-pyrophosphate
Isopentenyl-PP isomerase
$CO_2$
Mevalonate-5-pyrophosphate decarboxylase
Dimethylallyl-PP
Isopentenyl-5-pyrophosphate (PP)
Farnesyl-PP synthase
BISPHOSPHONATES
Geranyl PP
Farnesyl-PP synthase
BISPHOSPHONATES
Geranylgeranyl-PP
Farnesyl-PP
Geranylgeranyl-PP synthase
Squalene synthase
Squalene
Squalene monooxygenase
2,3 oxidosqualene
NADPH
Squalene epoxydase
Lanosterol
19 reactions
CHOLESTEROL
PRENYLATED PROTEINS
HEME A
DOLICHOL
UBIQUINON

# Systemic treatment for Vitiligo 2016 – 2018

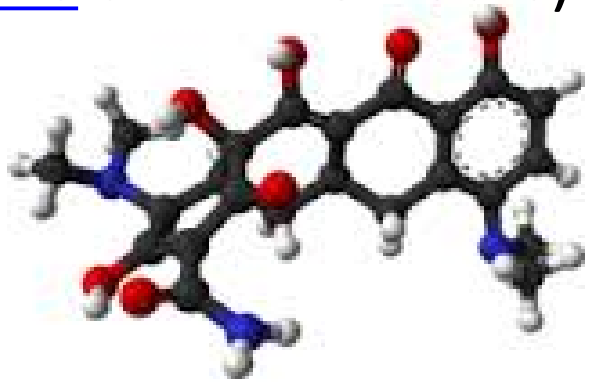
- JAK Inhibitors
- EdnrB – Wnt Signaling
- CD20 Mab
- **Afamelanotide**
- Statins
- Minocycline
- Low Dose Cytokines and Growth Factors
- ……

# Systemic treatment for Vitiligo 2016 – 2018

- Minocycline
- has a wide repertoire of anti inflammatory , immune regulatory and free radicals scavenging effects
- 100mg/die

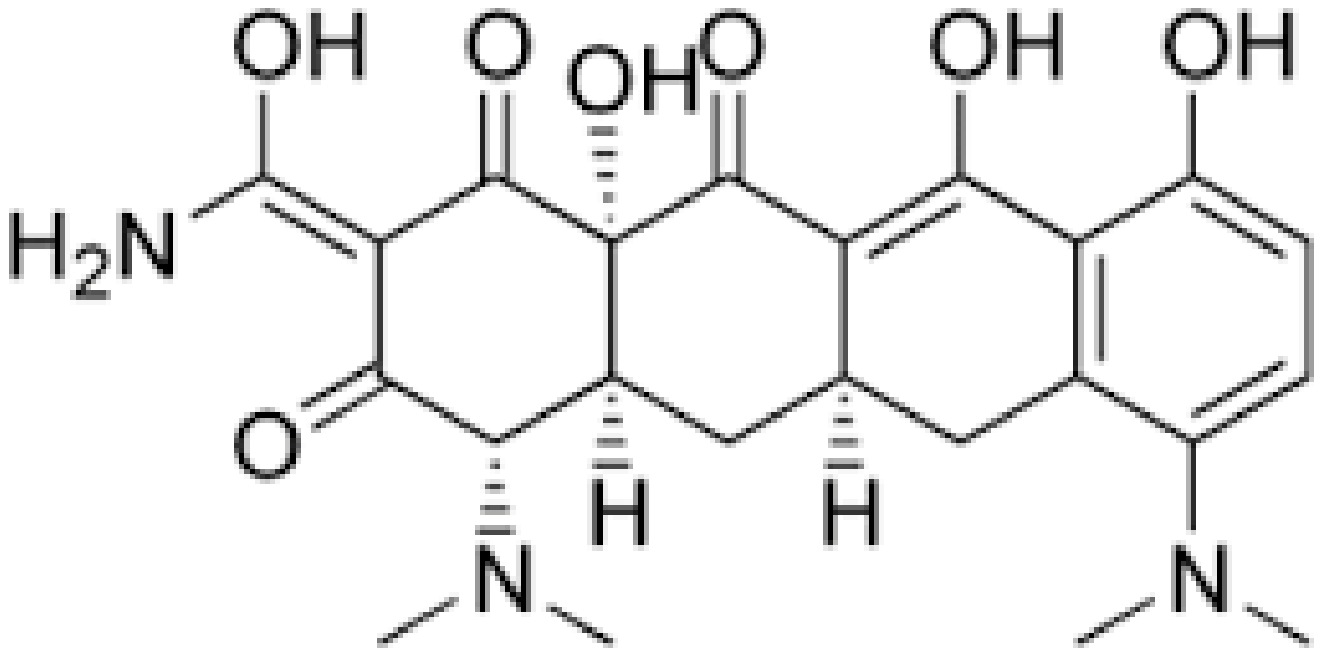




- **Minocycline** (INN) is a broad-spectrum tetracycline antibiotic, and has a broader spectrum than the other members of the group. It is a bacteriostatic antibiotic, classified as a long-acting type. As a result of its long half-life it generally has serum levels 2–4 times that of the simple water-soluble tetracyclines (150 mg giving 16 times the activity levels compared with 250 mg of tetracycline at 24–48 hours).



- Minocycline is the most lipid-soluble of the tetracycline-class antibiotics, giving it the greatest penetration into the prostate and brain, but also the greatest amount of central nervous system (CNS)-related side effects, such as vertigo.
- A common side effect is diarrhea. Uncommon side effects (with prolonged therapy) include skin discolouration and autoimmune disorders that are not seen with other drugs in the class.

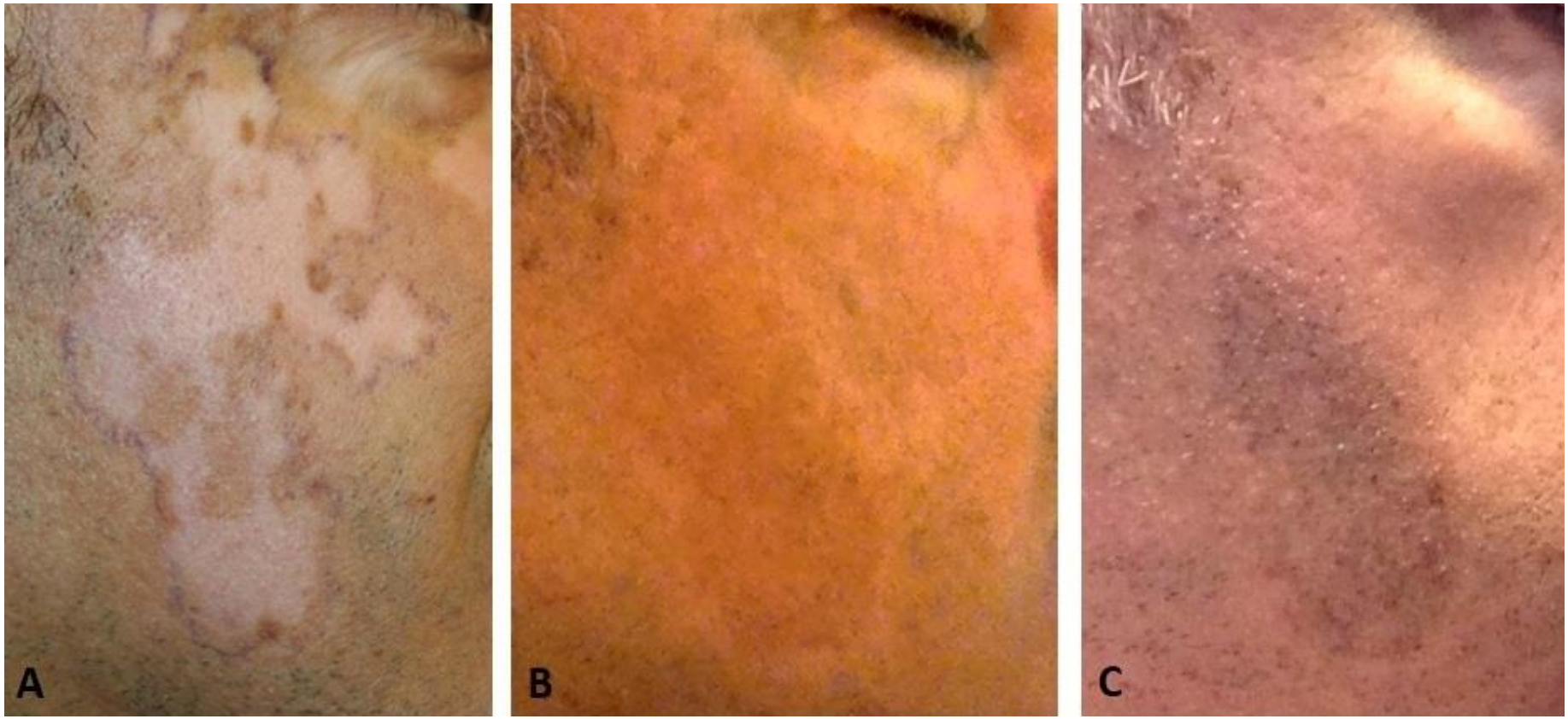

Minocyclin-ratiopharm®
100 mg Hartkapseln
Wirkstoff: Minocyclin
50 Hartkapseln
ratiopharm


OH
O
OH
O
OH
OH
H2N
O
H
H
N
N

Dermatol Ther. 2010 May-Jun;23(3):305-7.

# Oral minocycline in the treatment of vitiligo--a preliminary study.

Parsad D1, Kanwar A.



# Systemic treatment for Vitiligo 2016 – 2018

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- Statins
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- Low Dose Cytokines and Growth Factors
- ……

- **Cytokines** (*cyto*, from Greek "κύτταρο" *kyttaro* "cell" + *kines*, from Greek "κίνηση" *kinisi* "movement") are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling.
- Their release has an effect on the behavior of cells around them. It can be said that cytokines are involved in autocrine signalling, paracrine signalling and endocrine signalling as immunomodulating agents.

# *On pubmed… **Torello Lotti** and coworkers*

## Advances in the treatment options for vitiligo: activated low-dose cytokines-based therapy.

Review article

Lotti T, et al. Expert Opin Pharmacother. 2015.

**Authors**

Lotti T[1], Hercogova J[2], Fabrizi G[3].

**Author information**

1 a 1 University of Rome "G.Marconi" , Rome, Italy professor@torellolotti.it.
2 b 2 Dermatology Clinic Bulovka - Dermatology Bulovka Hospital , Prague Czech Republic.
3 c 3 University of Parma - Clinica Dermatologica , Parma, Italy.

**Citation**

Expert Opin Pharmacother. 2015;16(16):2485-96. doi: 10.1517/14656566.2015.1087508. Epub 2015 Sep 15.

**Abstract**

INTRODUCTION: Vitiligo is a skin disorder characterized by a progressive depigmentation, which is caused by the loss of melanocytes at the cutaneous level. A shift of the immune system with a prevalence of T helper (Th)1/Th17 response instead of a Tregs/Th2 one and may be part of etiology of 10 vitiligo.

AREAS COVERED: This review describes the major points of vitiligo onset and shows the cutting-edge results in the field of low-dose medicine in the treatment of dermatologic diseases and, in particular. in vitiligo. In this review on advances in vitiligo pharmacotherapy, the most pertinent recent publications are reported. Electronic databases such as PubMed were searched for terms 'low-dose medicine' or 'low dose and vitiligo' or 'low dose and psoriasis.'

psoriasis.

EXPERT OPINION: The availability of a systemic treatment for vitiligo, based on the oral administration of low-dose activated signaling molecules represents an opportunity for the dermatologists to overcome some specific pitfalls of currently available therapeutic protocols.

PMID: 26372794 [Indexed for MEDLINE]

# *On pubmed… **Torello Lotti** and coworkers*

## Treatment with low-dose cytokines reduces oxidative-mediated injury in perilesional keratinocytes from vitiligo skin.

Barygina V, et al. J Dermatol Sci. 2015.

**Authors**

Barygina V[1], Becatti M[2], Lotti T[3], Moretti S[4], Taddei N[5], Fiorillo C[6].

**Author information**

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3 Dermatology and Venereology Division, Guglielmo Marconi University, Via Plinio, 44, 00193 Roma, Italy. Electronic address: professor@torellolotti.it.

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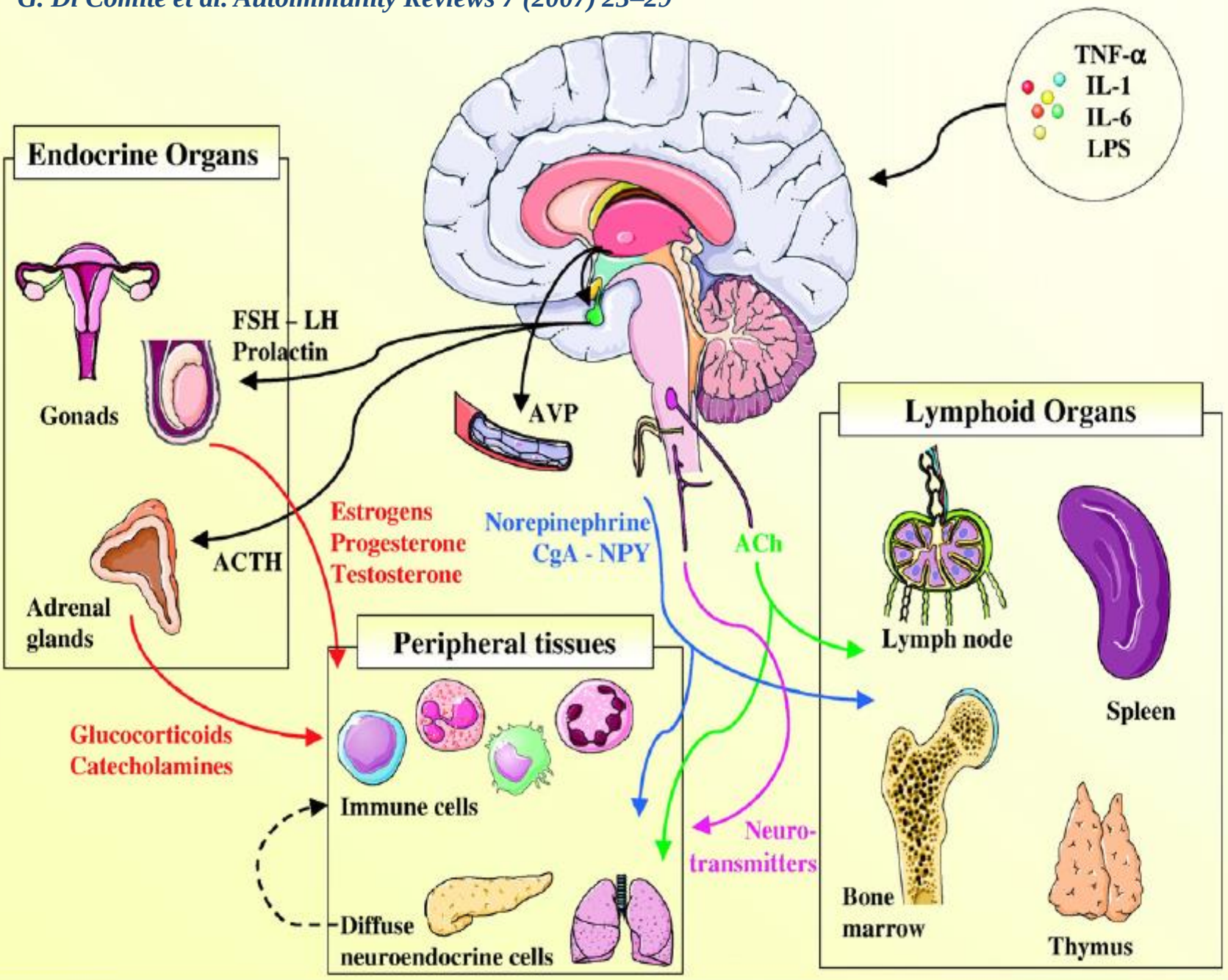
**Abstract**

BACKGROUND: Vitiligo is a systemic dermatological disorder characterized by the loss of skin pigmentation due to melanocyte injury or aberrant functioning. Recent data underline its multifactorial etiology with significant involvement of autoimmune and redox alterations. The major role in vitiligo cellular immunity is displayed by augmented Th1 and Th17 and suppressed TREGs and Th2 lymphocyte populations. Our previous studies indicate a marked redox imbalance in perilesional ("PL", i.e. obtained from visibly unaffected skin surrounding the depigmented area in vitiligo patients) keratinocytes where the massive infiltration of inflammatory cells takes place. No defined therapy exists for vitiligo. Although a number of approaches have been used for the induction of TREGs and Th2 cells, they may be associated with significant off-target effects.

OBJECTIVE: In order to identify a targeted approach for vitiligo treatment we, first, aimed to investigate the possible source of ROS overproduction in PL keratinocytes. Second, we tested the effect of low-dose selected cytokines,

*G. Di Comite et al. Autoimmunity Reviews 7 (2007) 23–29*



*Dermatologic Therapy, Vol. 16, 2003, 123–131*
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DERMATOLOGIC THERAPY
*ISSN 1396-0296*

# The neuro-immuno-cutaneous-endocrine network: relationship between mind and skin

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†*Department of Dermatology, Charles University, Prague, Czech Republic*

International Journal of Dermatology

*International Journal of Dermatology* 2002, **41**, 311–318

Review

# Can the brain inhibit inflammation generated in the skin? The lesson of α-melanocyte-stimulating hormone

Torello Lotti, MD, Beatrice Bianchi, PhD, Ilaria Ghersetich, MD, Benedetta Brazzini, MD, and Jana Hercogova, MD

*Lotti T et al. International Journal of Dermatology 2002, 41, 311–318*

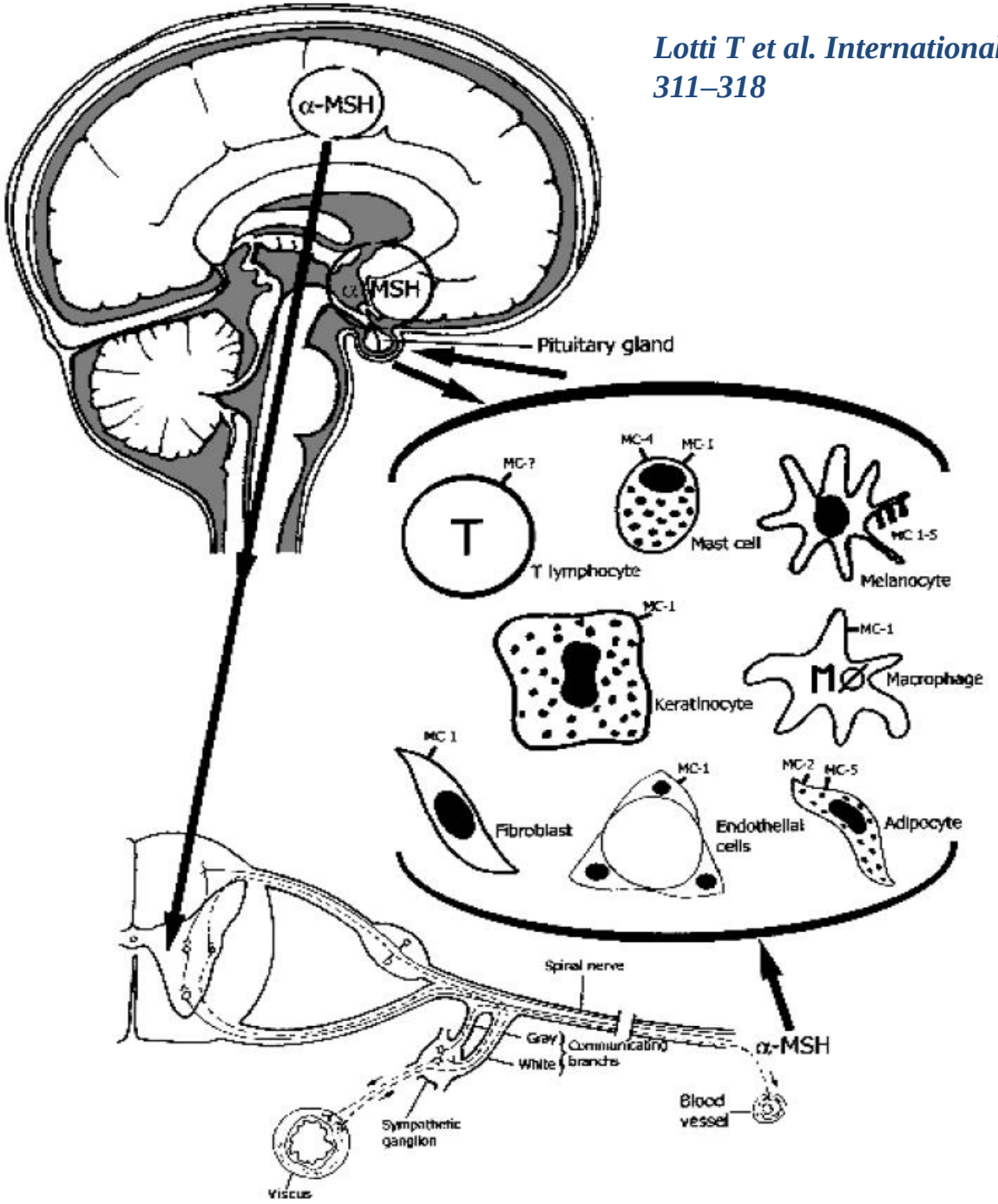


**Figure 1** In the brain α-melanocyte stimulating hormone is synthetized predominantly in the pituitary gland. When administered into the cerebral ventriculi (in mice) α-MSH inhibits the cutaneous inflammation induced by application of topical irritants and intradermal injection of cytokines. This action is related to the integrity of the spinal cord descending neurogenic pathways and of β2 receptors in the periphery. α-melanocyte stimulating hormone is also released in the plasma by the pituitary gland and by different cells, including keratinocytes, melanocytes, monocytes, macrophages, endothelial cells, adipocytes, fibroblasts and mast cells. Membrane receptors for α-MSH are present both in the brain and on nearly all the cells that produce and release α-MSH and participate in cutaneous inflammation mainly by reducing and terminating the same flogistic reactions

# Autoimmune markers in vitiligo patients appear correlated with obsession and phobia

S. Moretti,[†] M. Arunachalam,[†,*] R. Colucci,[†] S. Pallanti,[‡] J.A. Kline,[§] S. Berti,[†] F. Lotti,[†] T. Lotti[†]

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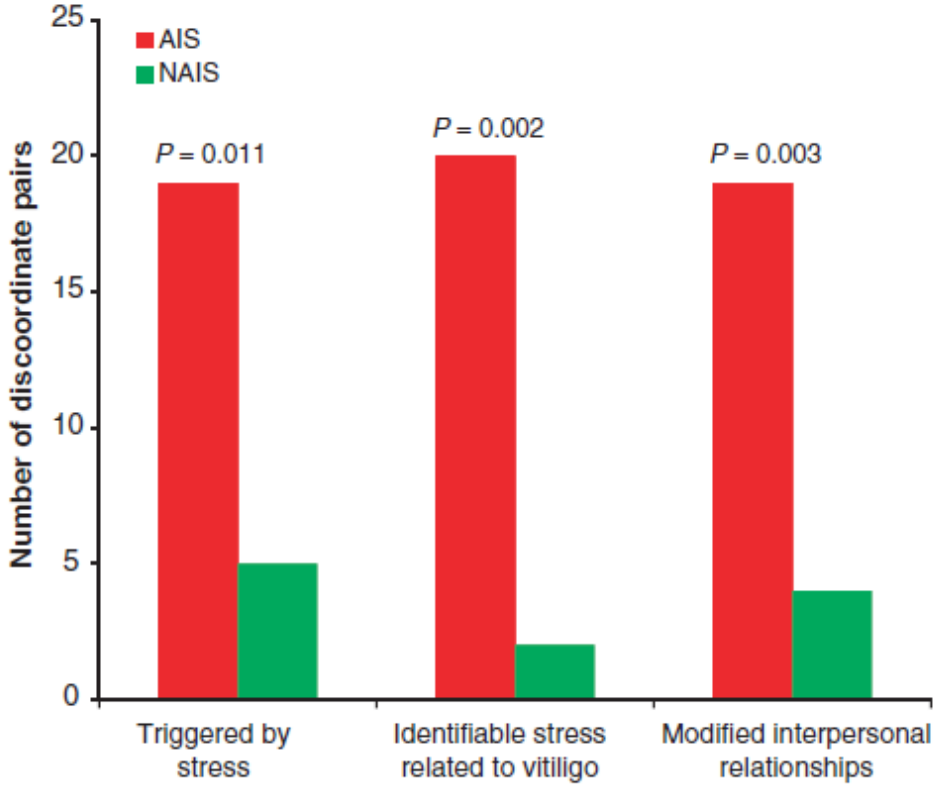
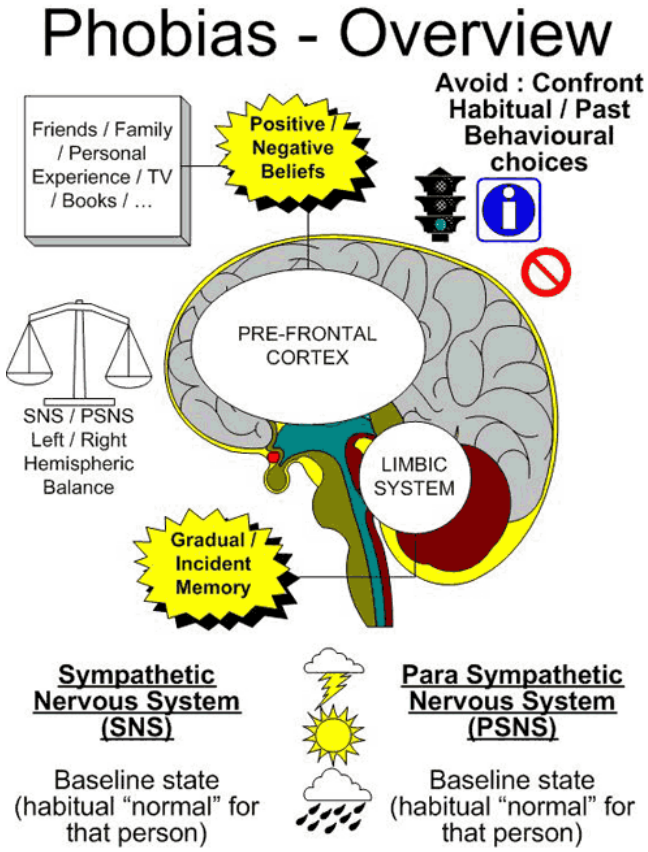
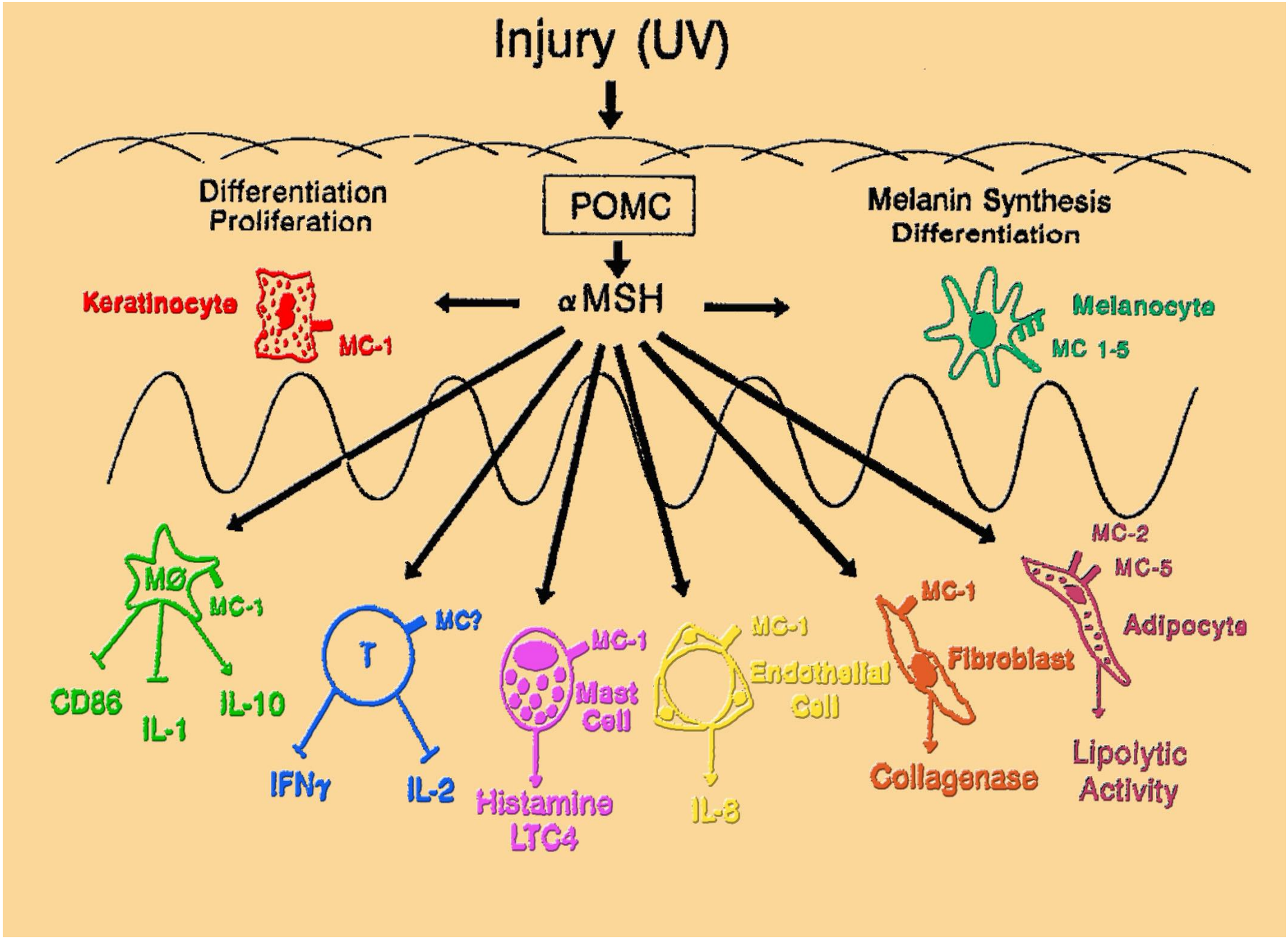



**Figure 1** Psychological discomfort factors and social aspects shown in the graph are significantly higher in autoimmune markers vs. negative autoimmune markers vitiligo patients.




Injury (UV)
Differentiation
Proliferation
POMC
Melanin Synthesis
Differentiation
Keratinocyte
MC-1
αMSH
Melanocyte
MC 1-5
MØ
MC-1
CD86
IL-1
IL-10
T
MC?
IFNγ
IL-2
MC-1
Mast
Cell
Histamine
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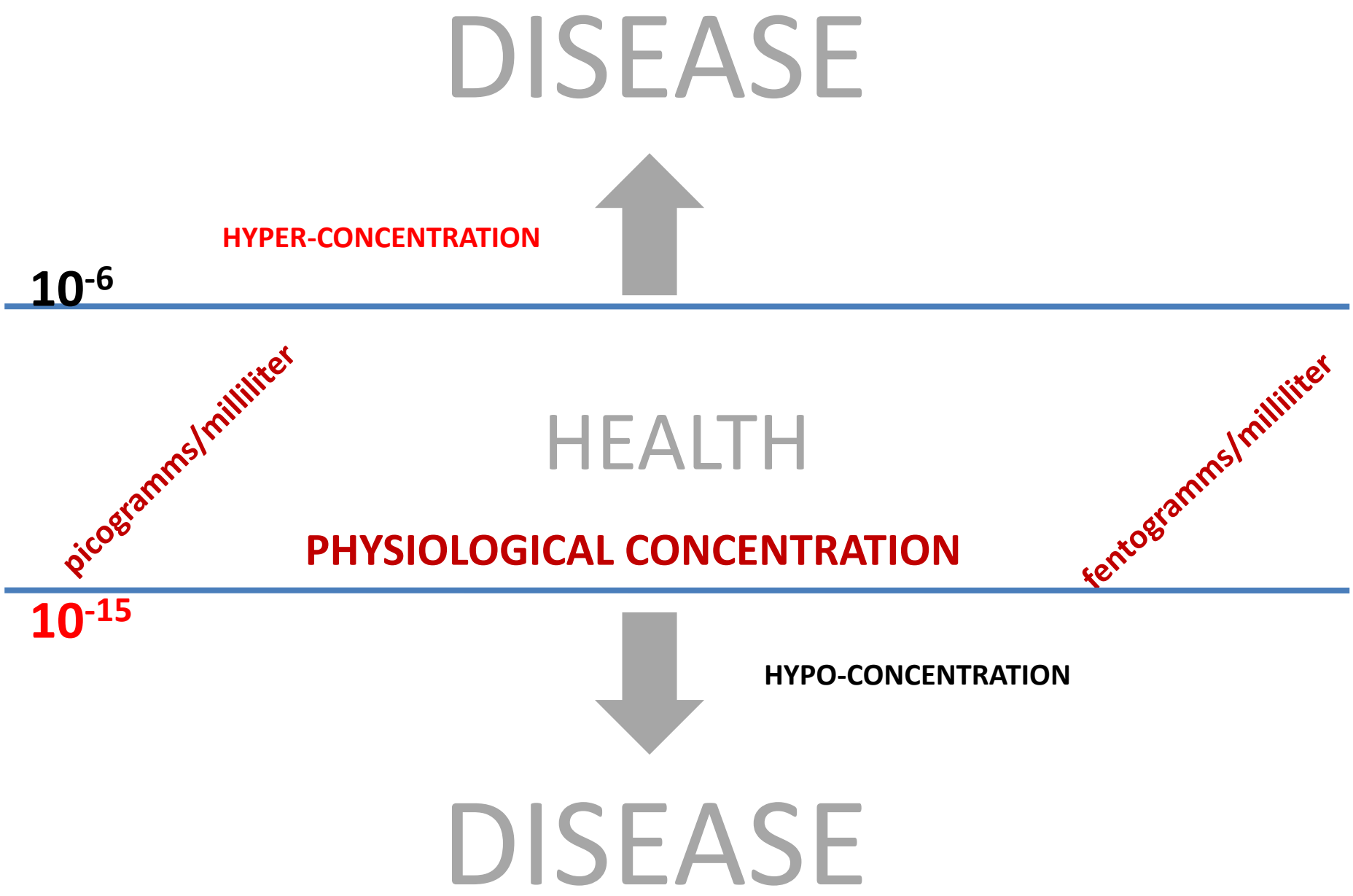
Cell
IL-8
MC-1
Fibroblast
Collagenase
MC-2
MC-5
Adipocyte
Lipolytic
Activity


DISEASE
HYPER-CONCENTRATION
10-6
picogramms/milliliter
HEALTH
PHYSIOLOGICAL CONCENTRATION
fentogramms/milliliter
10-15
HYPO-CONCENTRATION
DISEASE

PubMed Search Search

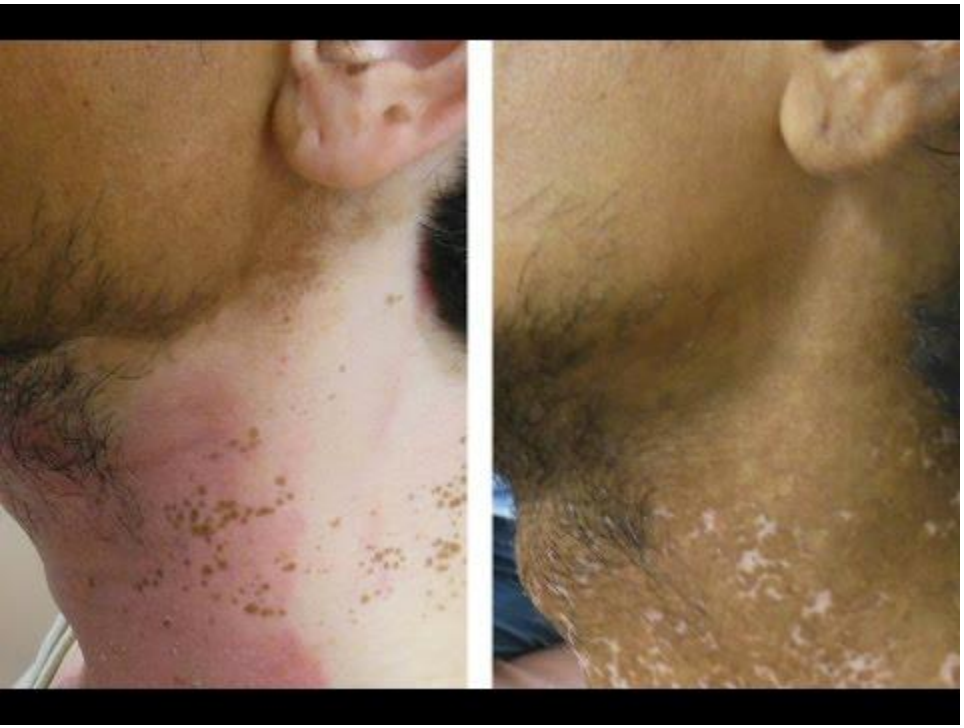
# Vitiligo: successful combination treatment based on oral low dose cytokines and different topical treatments.

Lotti T, et al. J Biol Regul Homeost Agents. 2015 Jan-Mar.

**Authors**
Lotti T[1], Hercogova J[2], Wollina U[3], Chokoeva AA[4], Zarrab Z[5], Gianfaldoni S[6], Roccia MG[7], Fioranelli M[8], Tchernev G[4].

**Abstract**

The current treatments for Vitiligo are not completely satisfactory in terms of clinical, aesthetic and compliance results for patients. Recently, combination therapies had been introduced with positive results. In this paper the combination between systemic oral treatment with Low Dose Cytokines in association with other topical treatments was evaluated. Positive results were obtained both with Low Dose Cytokines alone or in association with microphototherapy with positive percentage of skin repigmentation varying between 74% and 90%. Collected data allow the authors to affirm that the treatment with oral low dose SKA drugs is efficacious per se and highly efficacious in association with targeted phototherapy.



Novel topical cream delivers safe and effective sunlight therapy for vitiligo by selectively filtering damaging ultraviolet radiation.

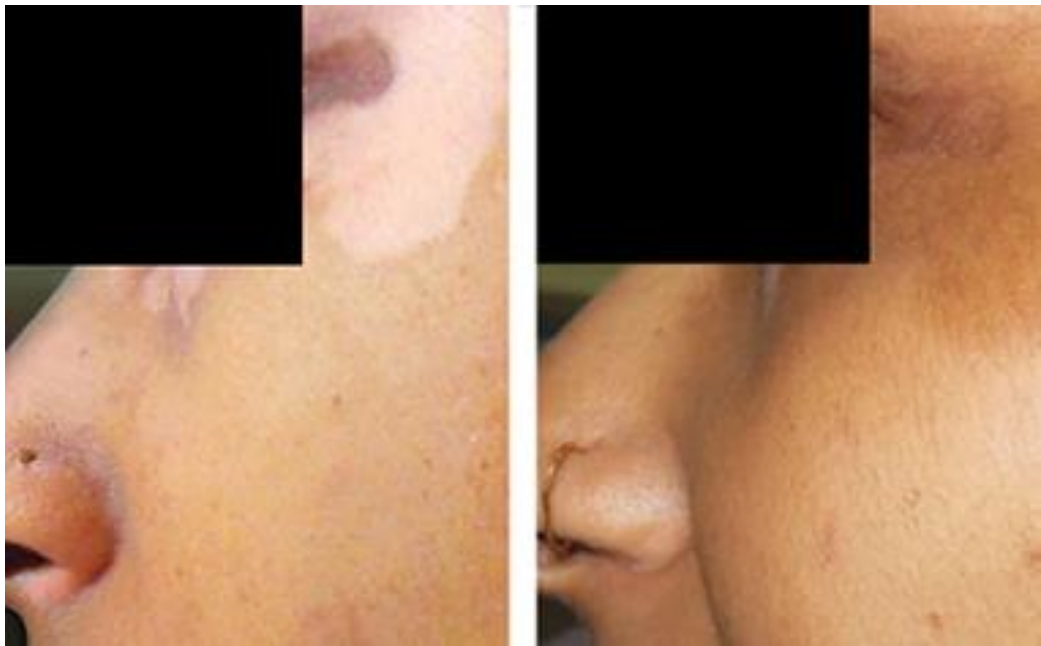
Goren A[1], Salafia A, McCoy J, Keene S, Lotti T.

Dermatol Ther. 2014 Jul-Aug;27(4):195-7.

In vitro evaluation of a novel topical cream for vitiligo and psoriasis that selectively delivers NB-UVB therapy when exposed to sunlight.

McCoy J[1], Goren A, Lotti T.

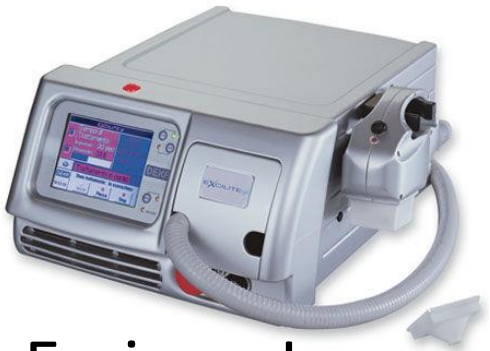
Dermatol Ther. 2014 Mar-Apr;27(2):117-20.



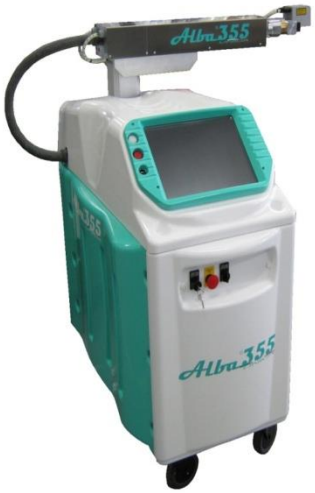
Excimer Light

Bioskin Evolution

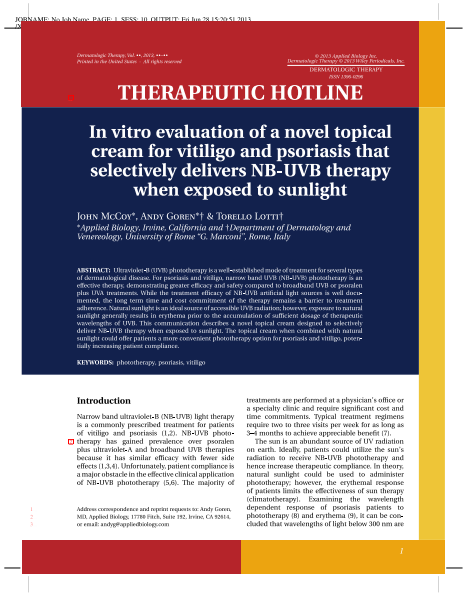
PUVA



Excimer Lasers




UVA-1 355 nm Alba Laser



THERAPEUTIC HOTLINE

In vitro evaluation of a novel topical cream for vitiligo and psoriasis that selectively delivers NB-UVB therapy when exposed to sunlight

John McCoy*, Andy Goren*† & Torello Lotti†
*Applied Biology, Irvine, California and †Department of Dermatology and Venereology, University of Rome "G. Marconi", Rome, Italy

ABSTRACT: Ultraviolet-B (UVB) phototherapy is a well-established mode of treatment for several types of dermatological disease. For psoriasis and vitiligo, narrow band UVB (NB-UVB) phototherapy is an effective therapy, demonstrating greater efficacy and safety compared to broadband UVB or psoralen plus UVA treatments. While the treatment efficacy of NB-UVB artificial light sources is well documented, the long term time and cost commitment of the therapy remains a barrier to treatment adherence. Natural sunlight is an ideal source of accessible UVB radiation; however, exposure to natural sunlight generally results in erythema prior to the accumulation of sufficient dosage of therapeutic wavelengths of UVB. This communication describes a novel topical cream designed to selectively deliver NB-UVB therapy when exposed to sunlight. The topical cream when combined with natural sunlight could offer patients a more convenient phototherapy option for psoriasis and vitiligo, potentially increasing patient compliance.

KEYWORDS: phototherapy, psoriasis, vitiligo

Introduction

Narrow band ultraviolet-B (NB-UVB) light therapy is a commonly prescribed treatment for patients of vitiligo and psoriasis [1,2]. NB-UVB phototherapy has gained prevalence over psoralen plus ultraviolet-A and broadband UVB therapies because it has similar efficacy with fewer side effects [1,3,4]. Unfortunately, patient compliance is a major obstacle in the effective clinical application of NB-UVB phototherapy [5,6]. The majority of treatments are performed at a physician's office or a specialty clinic and require significant cost and time commitments. Typical treatment regimens require two to three visits per week for as long as 3–4 months to achieve appreciable benefit [7].

The sun is an abundant source of UV radiation on earth. Ideally, patients could utilize the sun's radiation to receive NB-UVB phototherapy and hence increase therapeutic compliance. In theory, natural sunlight could be used to administer phototherapy; however, the erythemal response of patients limits the effectiveness of sun therapy (climatotherapy). Examining the wavelength dependent response of psoriasis patients to phototherapy (B) and erythema (9), it can be concluded that wavelengths of light below 300 nm are

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# World Vitiligo Day

www.25June.org

**Petition to UN in favour of vitiligo sufferers**

***Thank you for your attention***