Università degli Studi Guglielmo Marconi

WHA
WORLD HEALTH ACADEMY
DERMATOLOGY

Low Dose Cytokines & Growth Factors in the Treatment of Skin Diseases

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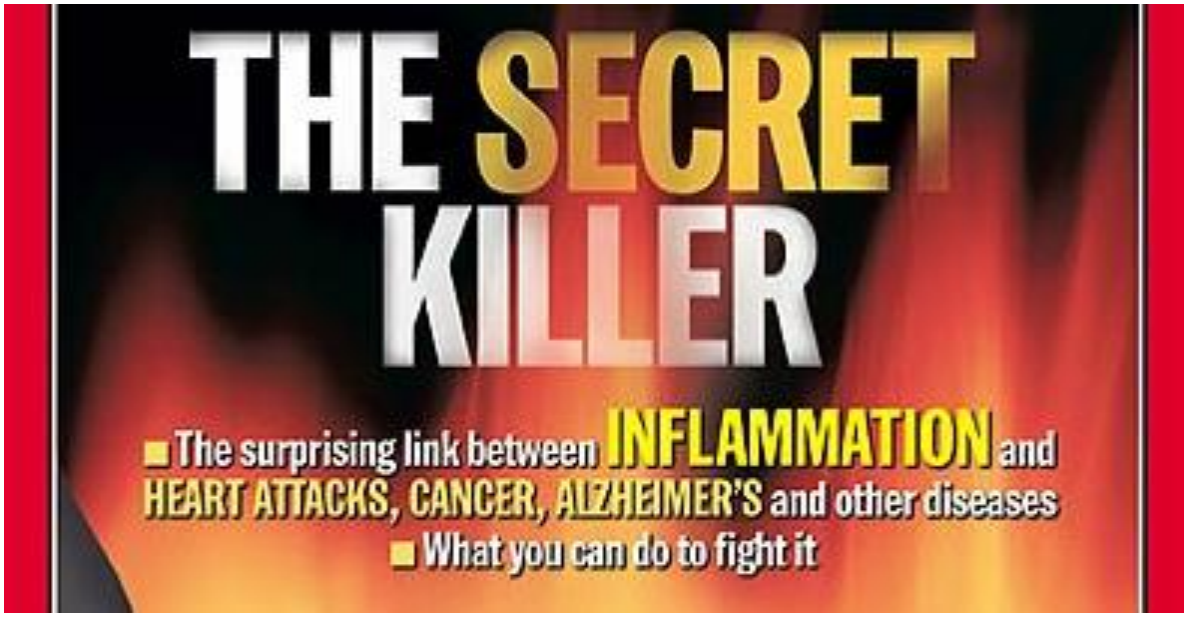
Presented in ICoMI 2017

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY 2017

- - President World Health Academy Publishing House, Zurich, CH
- - Editor, Dermatologic Therapy, Wiley-Blackwell
- - Chief Medical Officer, BIOSKIN EVOLUTION ®
- - Consultant, SIGMA Shanghai, China - 2013
- - 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 – London, UK , 2016



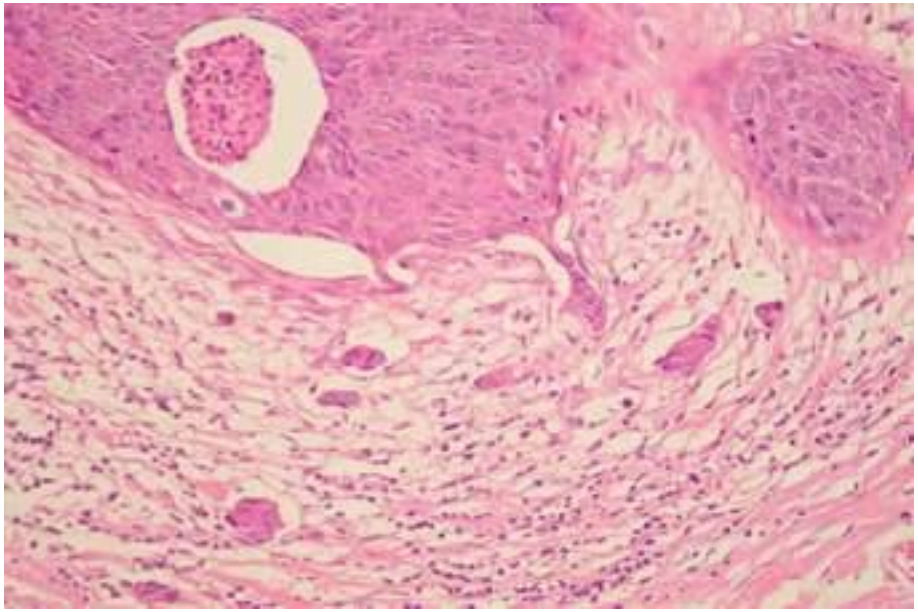
The surprising link between **INFLAMMATION** and HEART ATTACKS, CANCER, SKIN DISEASES, ALZHEIMER'S and all other diseases is under investigation.

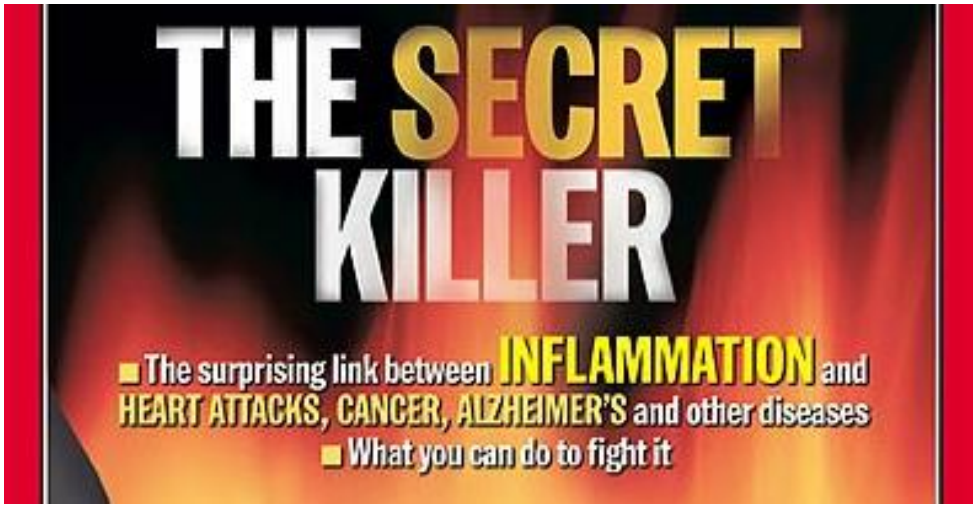
Low Dose Cytokines & Growth Factors deserve a special place in the fight against the **SECRET KILLER**

INFLAMMATION

SECRET KILLER

Inflammation (from Latin *inflammatio*) is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants, and is a protective response involving immune cells, blood vessels, and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair.

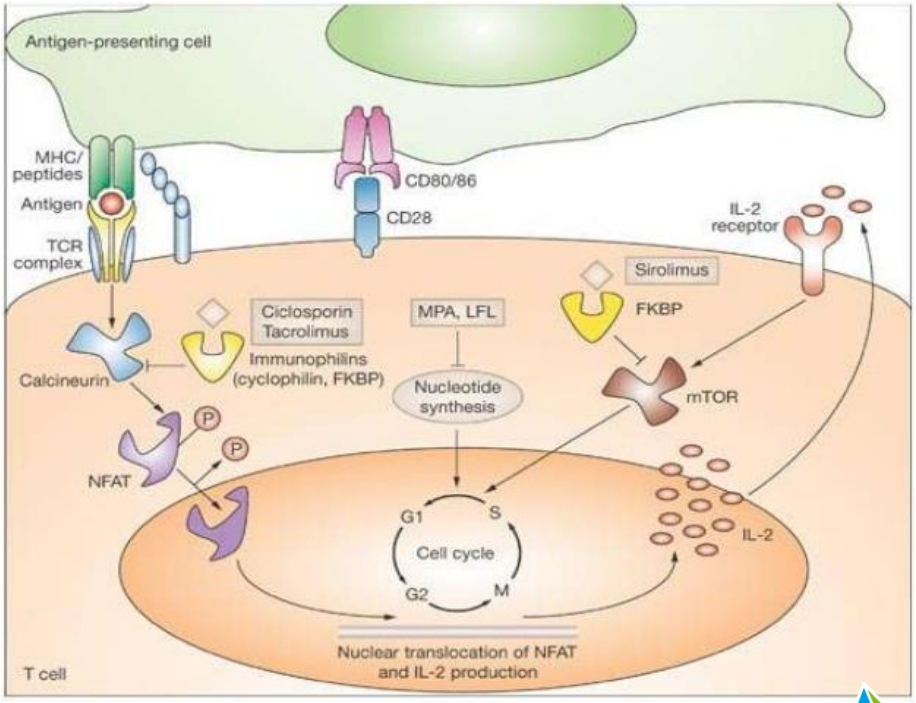




The classical signs of inflammation are heat, pain, redness, swelling, and loss of function. Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.Too little inflammation could lead to progressive tissue destruction by the harmful stimulus (e.g. bacteria) and compromise the survival of the organism. In contrast, **chronic inflammation may lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g., gallbladder carcinoma). Inflammation is therefore normally closely regulated by the body.**

Inflammation can be classified as either **acute or chronic**. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue.

Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation, such as mononuclear cells, and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

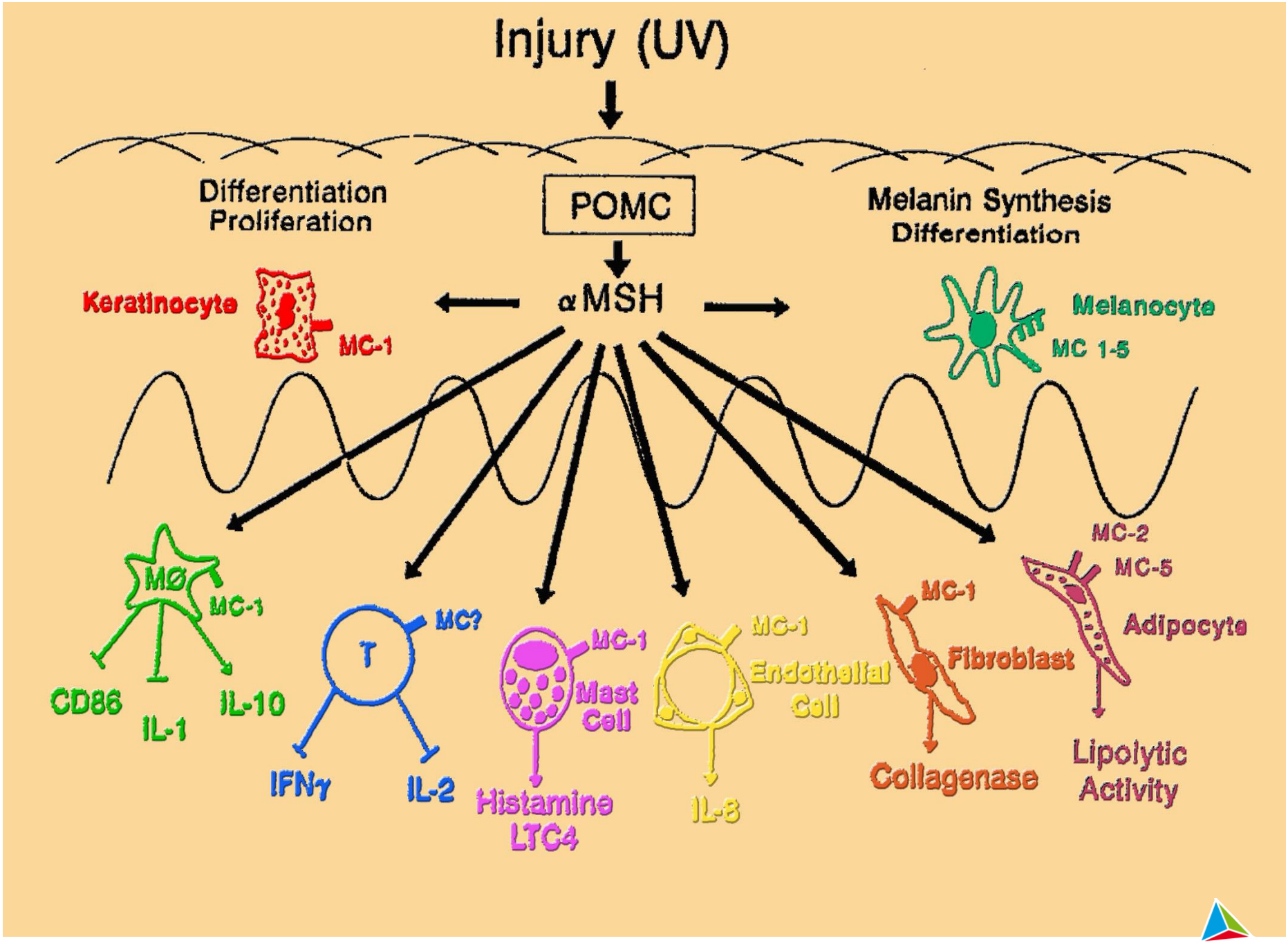


Can the brain inhibit inflammation generated in the skin? The lesson of gamma-melanocyte-stimulating hormone.

Lotti T, et al. Int J Dermatol. 2002.

Abstract

The neuro-immuno-cutaneous-endocrine network is not a simple construct featuring organ systems intimately involved in the bridge between body and mind**. Mind-body influences are bi-directional and the skin should be considered an active neuroimmunoendocrine interface, where effector molecules of neuropeptides act as common words used in a dynamic dialogue between brain, immune system and skin. Gamma-melanocyte stimulating hormone (gamma-MSH), one of the principal** neuroimmunomodulating peptides, seems to exercise some control on the cutaneous inflammatory process, through a central action mediated by descending anti-inflammatory neural pathways and via local direct influence on inflammatory cells infiltrating the dermis, such as monocytes, macrophages and neutrophils. Gamma-MSH down-regulates the production of proinflammatory cytokines, while the production of the anti-inflammatory cytokine IL-10 is stimulated by gamma-MSH. Finally, gamma-MSH seems to regulate the expression of surface molecules in immunocompetent cells. Thus, further studies may lead to the use of **gamma-MSH as an important anti-inflammatory agent in clinical dermatology.**



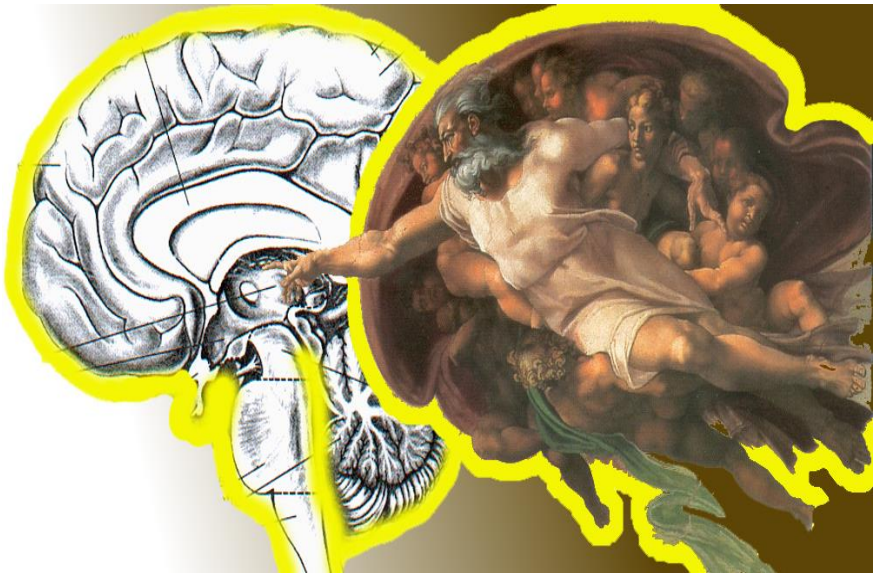
International Journal of Dermatology

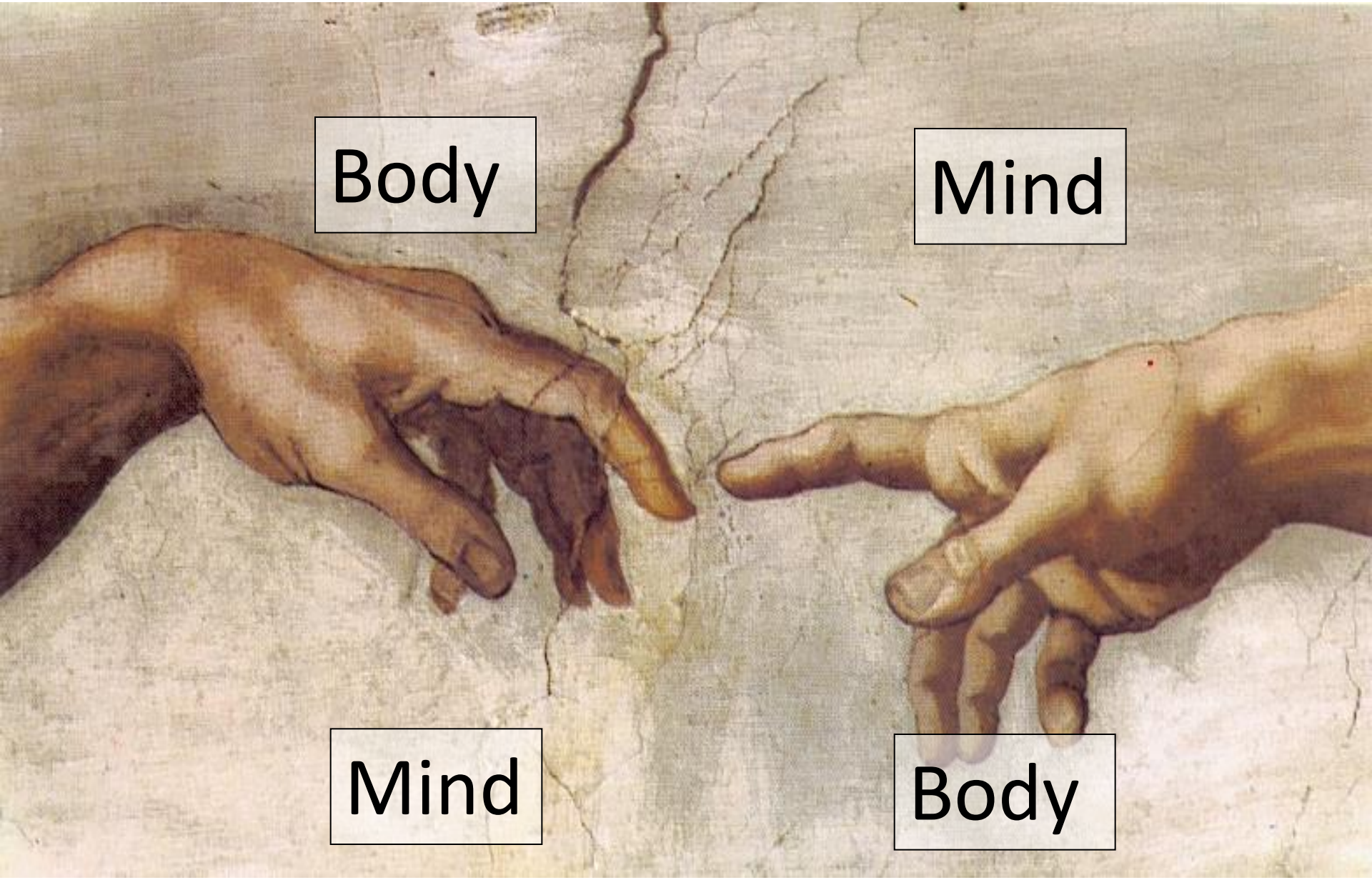
International Journal of Dermatology 2002, **41**, 311–318

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

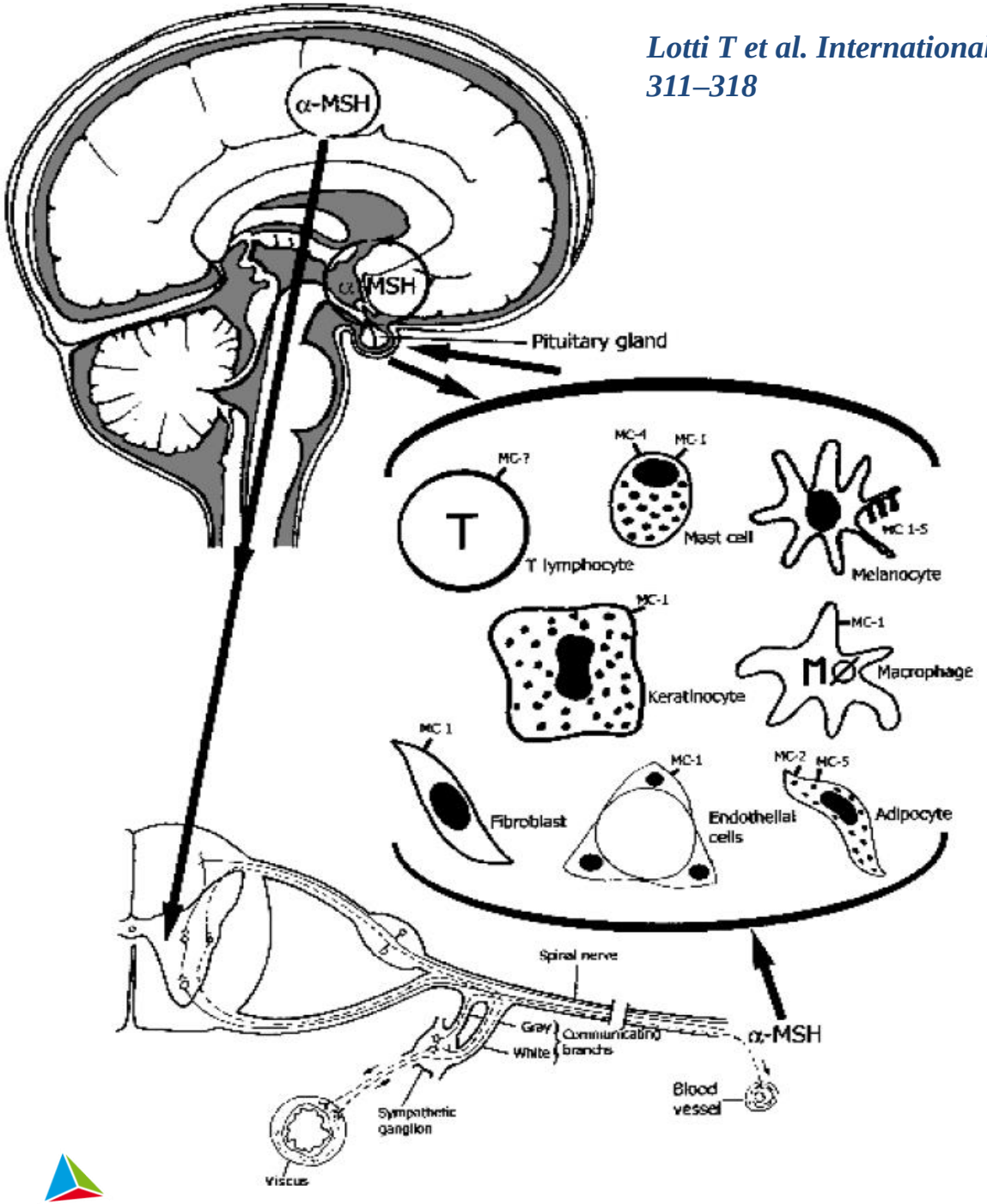


Figure 1 In the brain α-melanocyte stimulating hormone is synthetized predominantly in the pituitary gland. When administered into the cerebral ventriculi (in mice) α-MSH inhibits the cutaneous inflammation induced by application of topical irritants and intradermal injection of cytokines. This action 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 JEADV 2015

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

[†]Department of Critical Care Medicine and Surgery, Division of Dermatology, University of Florence, Florence, Italy
[‡]Department of Psychiatry, University of Florence, Florence, Italy
[§]Department of Emergency Medicine Research, Carolinas Medical Center, Charlotte, NC, USA

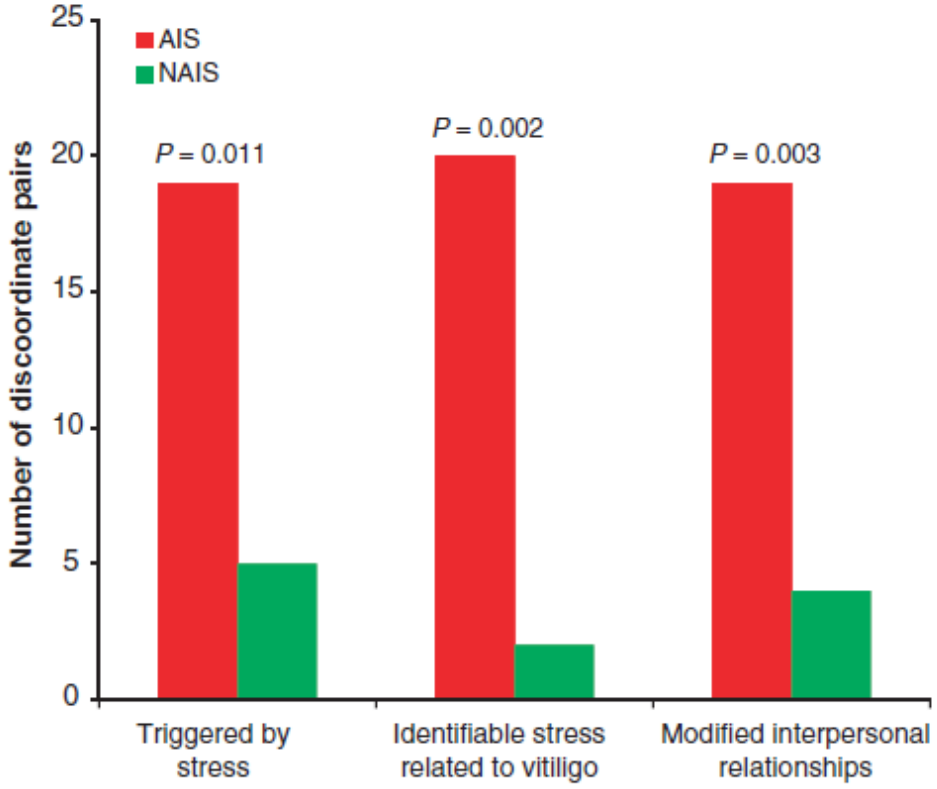
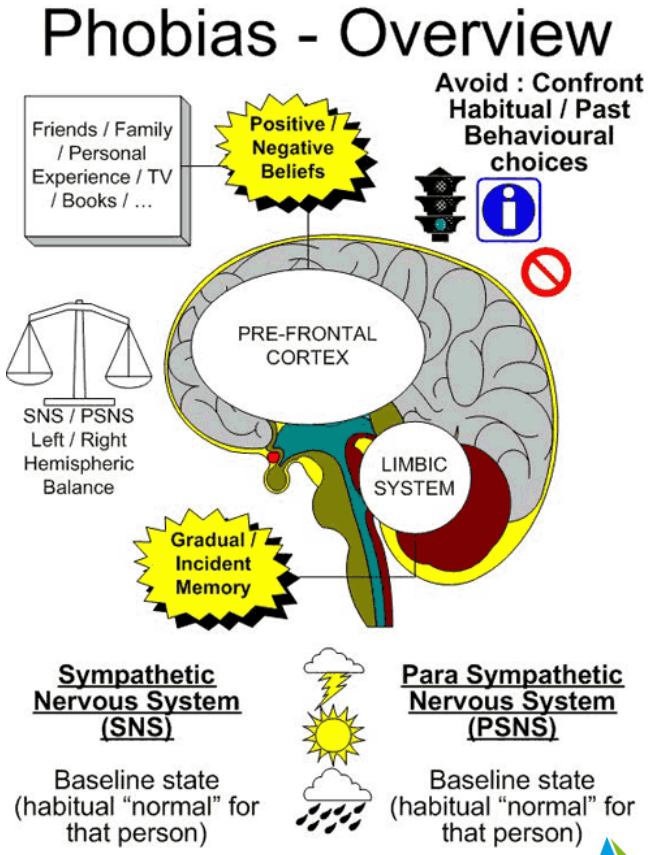


Figure 1 Psychological discomfort factors and social aspects shown in the graph are significantly higher in autoimmune markers vs. negative autoimmune markers vitiligo patients.



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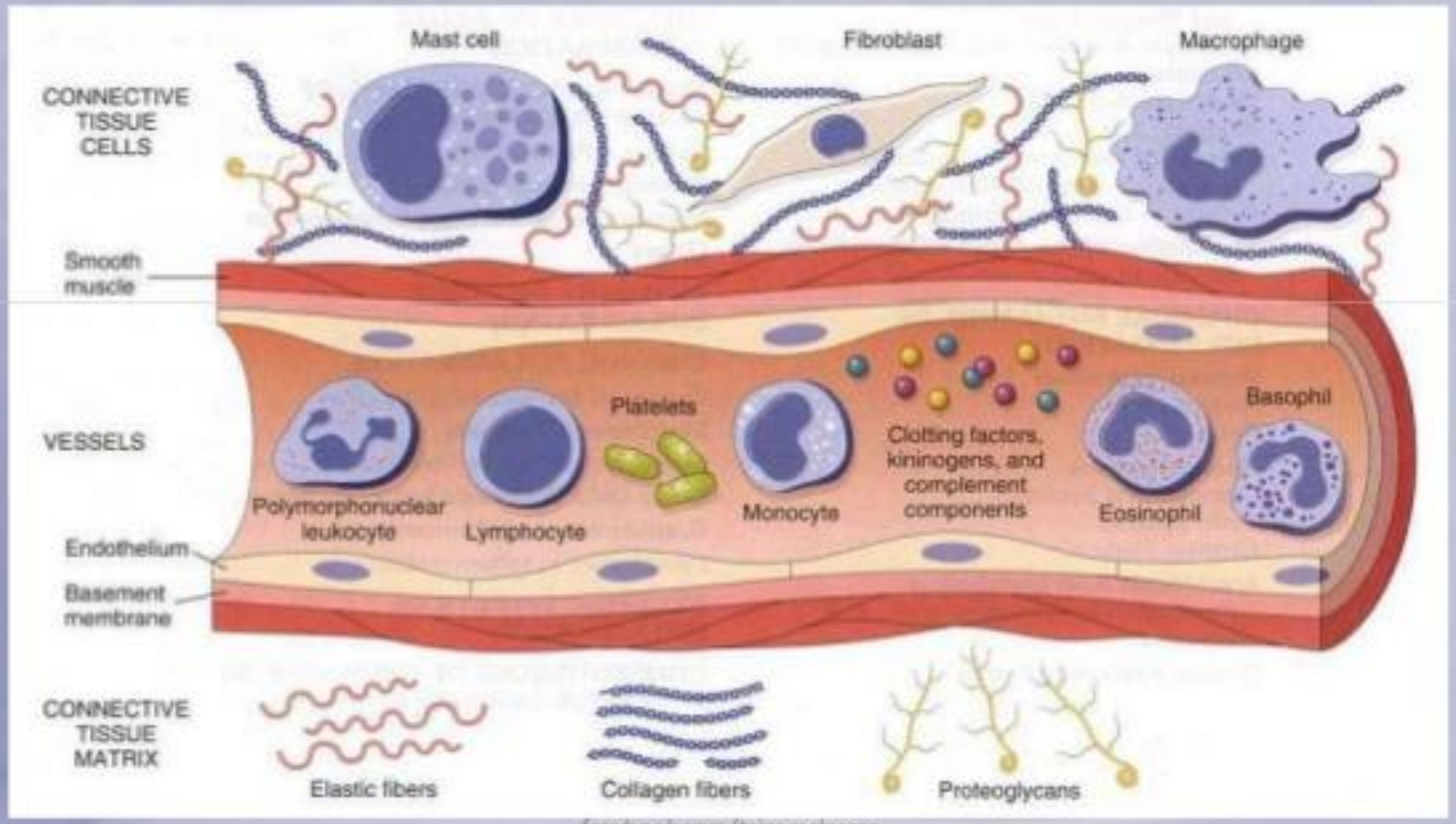
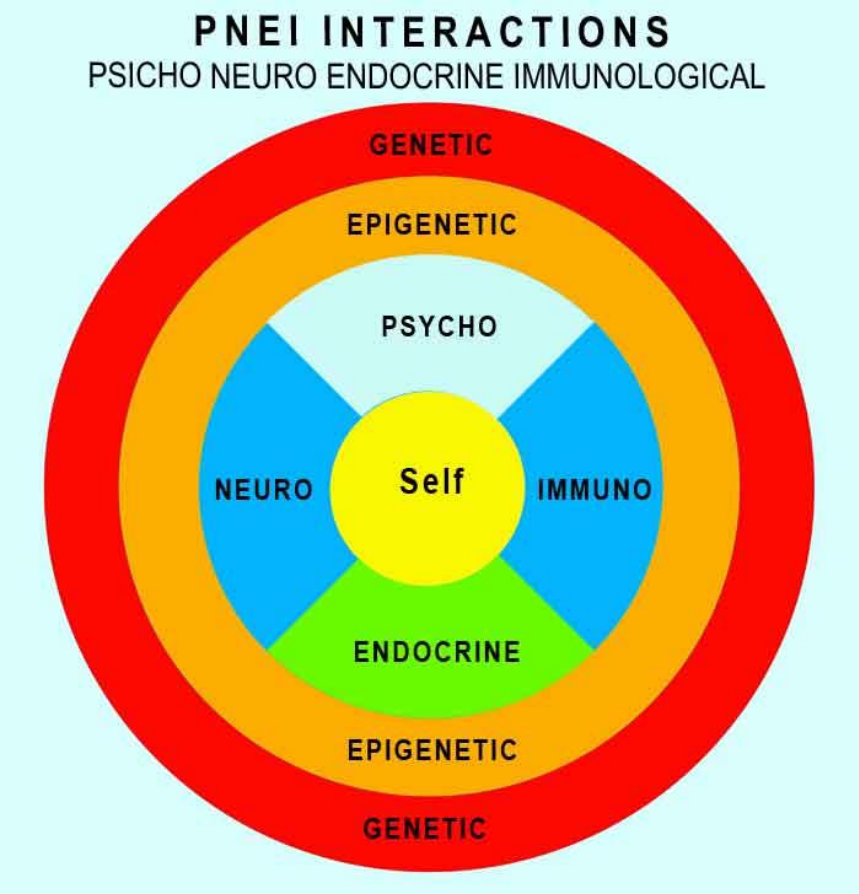
Components of Acute and Chronic Inflammatory responses



Chronic Inflammation is always entangled with Growth Factors, Cytokines, Neuropeptides, Hormones and Neuro-hormones



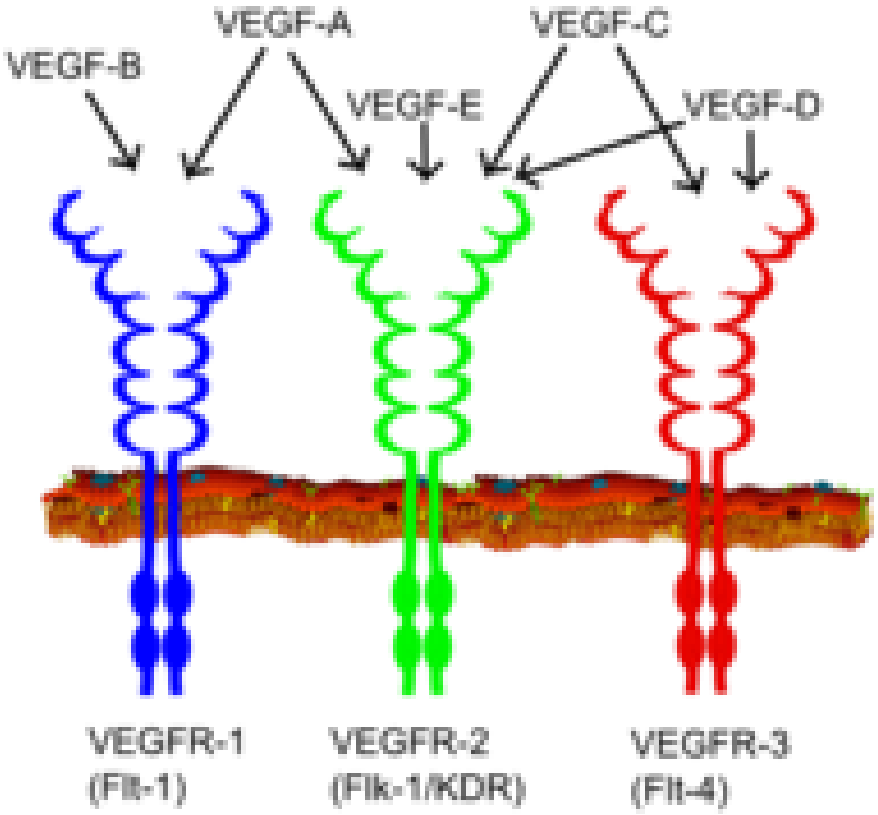
P.N.E.I.: life and death of skin cells. A new paradigm in the treatment & the low dose cytokines therapy.

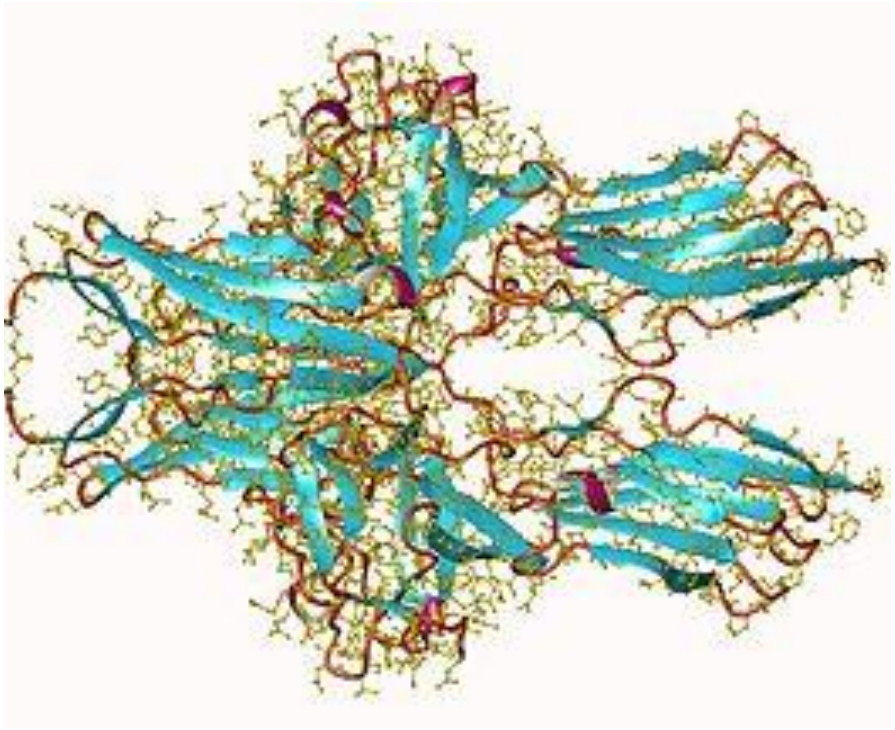
Rivkina T, Hercogova J, **Lotti T.**
Dermatol Ther. 2016 Mar-Apr.

What is a Growth Factor ?

- A **growth factor** is a naturally occurring substance capable of stimulating cellular growth, proliferation, healing, and cellular differentiation. Usually it is a protein or a steroid hormone. Growth factors are important for regulating a variety of cellular processes.
- Growth factors typically act as signaling molecules between cells. Examples are cytokines and hormones that bind to specific receptors on the surface of their target cells.
- They often promote cell differentiation and maturation, which varies between growth factors. For example, bone morphogenetic proteins stimulate bone cell differentiation, while fibroblast growth factors and vascular endothelial growth factors stimulate blood vessel differentiation (angiogenesis).

Growth Factors are signalling molecules: Cytokines and Hormones

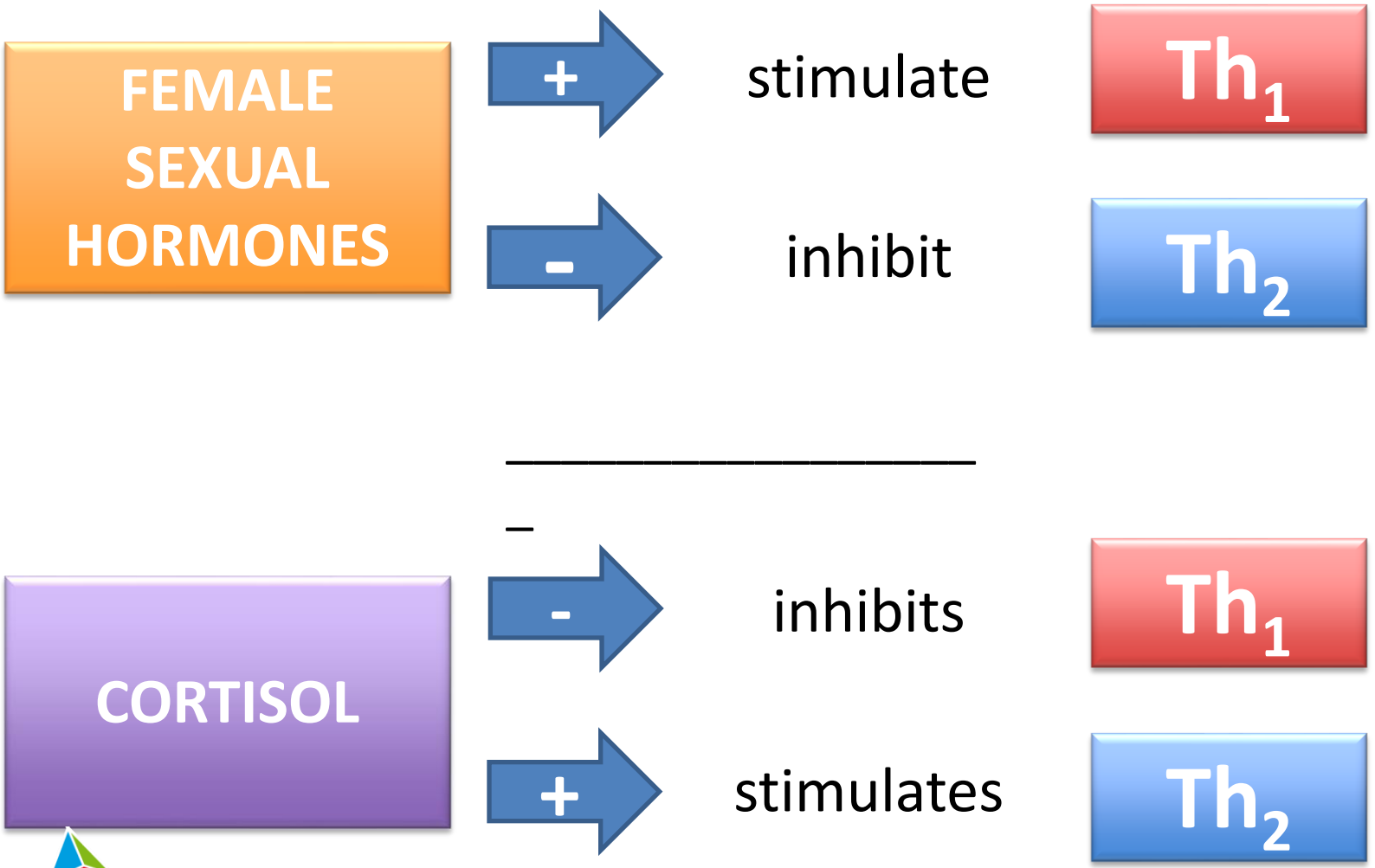




What is a Cytokine?

- **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.

Relationship between hormones and cytokines



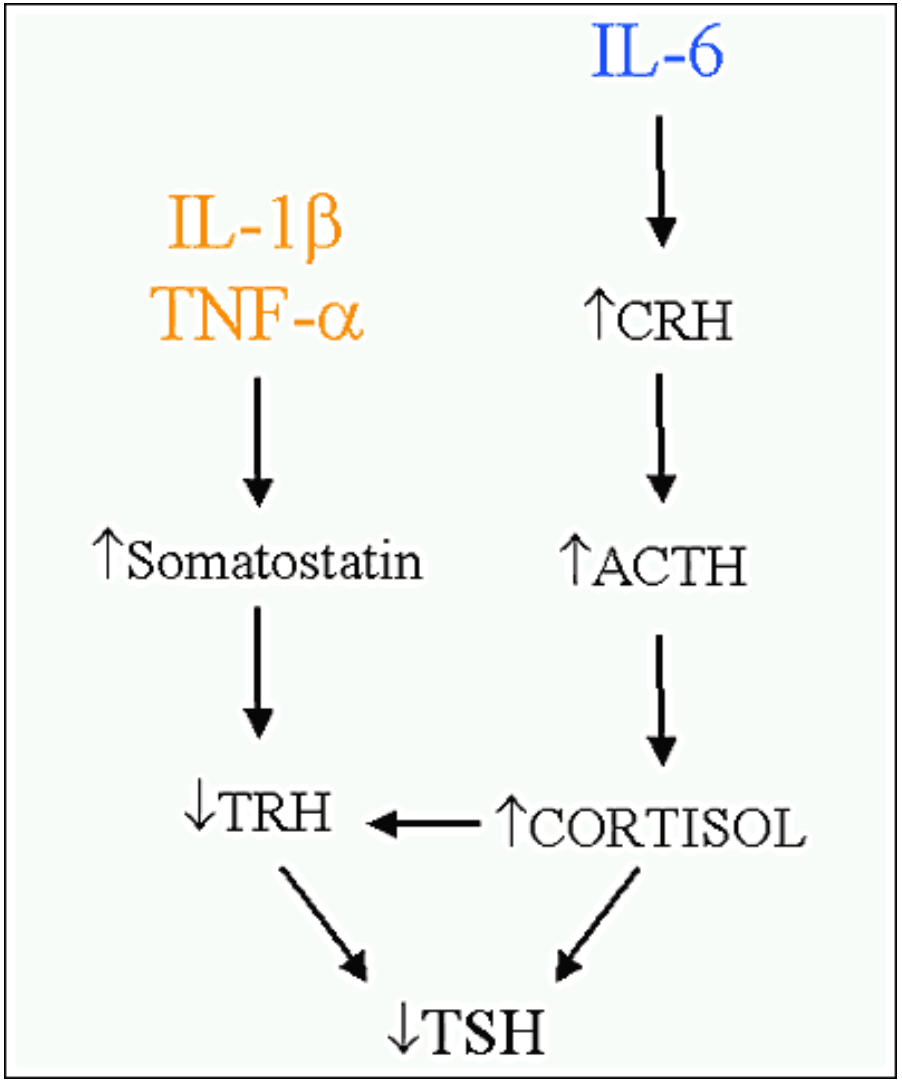
17β-estradiol protects human skin fibroblasts and keratinocytes against oxidative damage.

Bottai G & Lotti T.

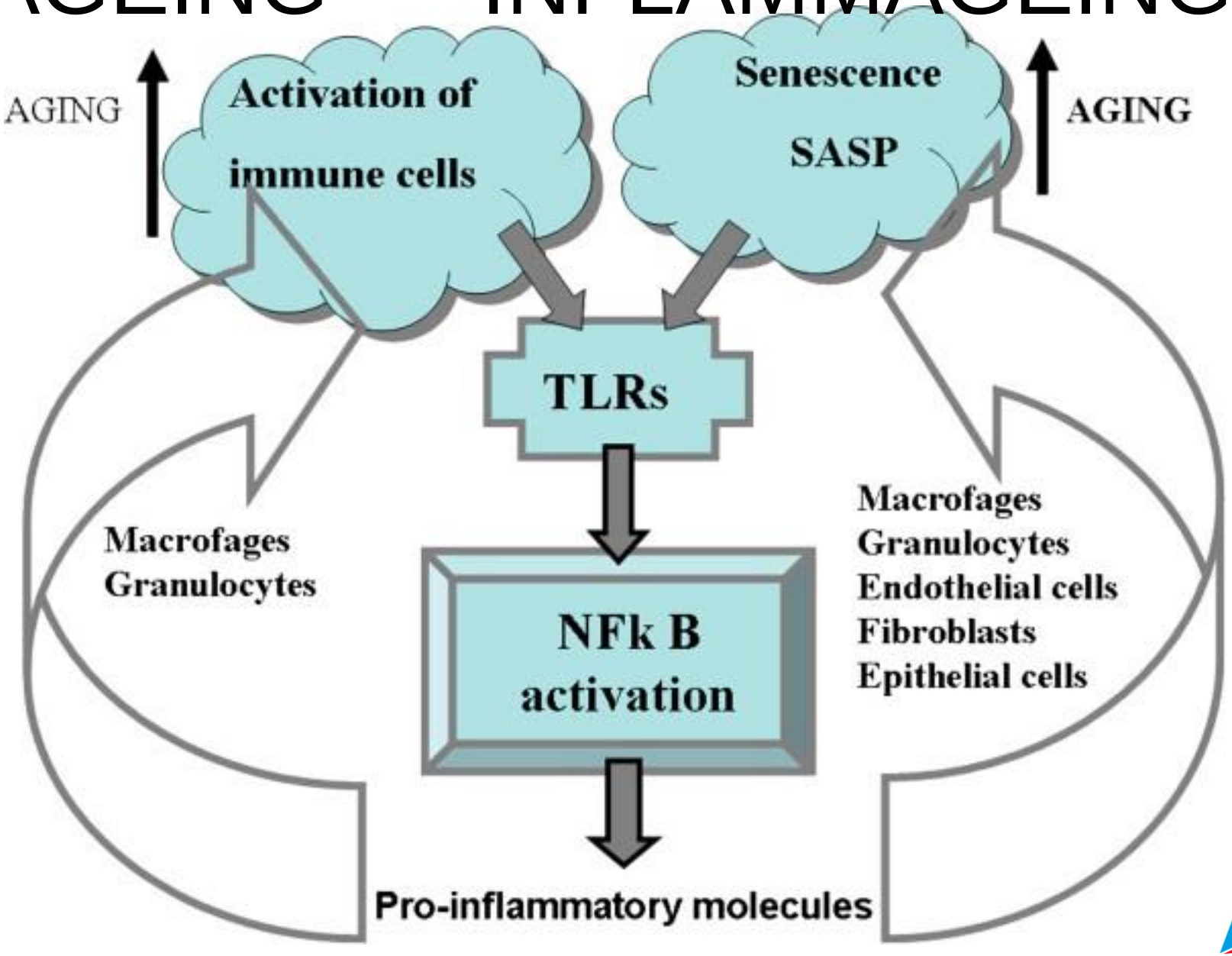
J Eur Acad Dermatol Venereol. 2013.

Our experimental data show that the presence of 17β-estradiol may protect skin cells against oxidative damage and that the dramatic lowering of oestrogen levels during menopause, could render skin more susceptible to oxidative damage.

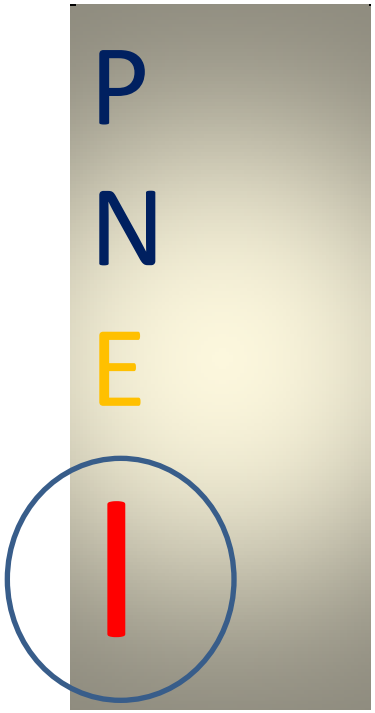
Relationship between cytokines and hormones



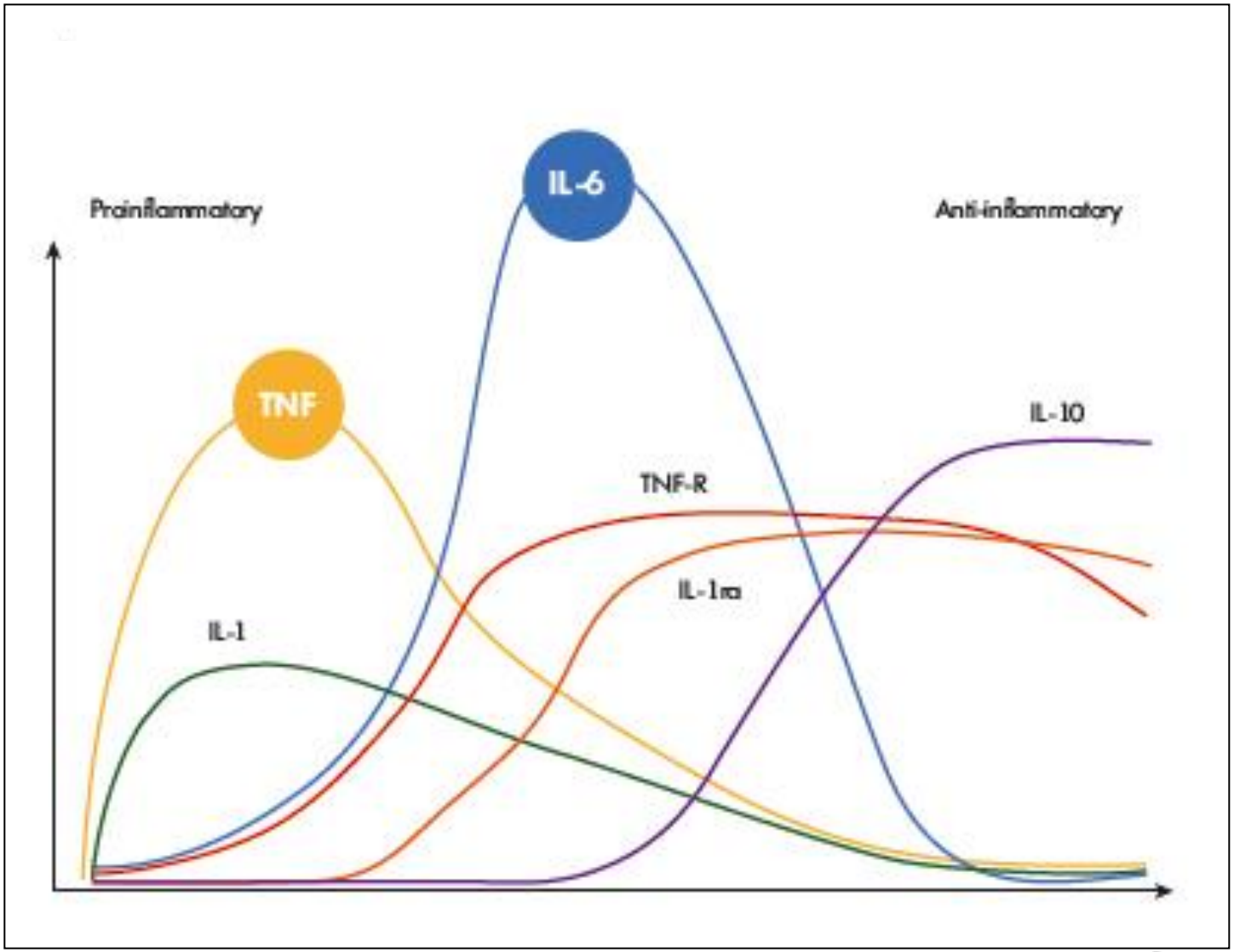
AGEING = INFLAMMAGEING



Single cytokines and INFLAMMAGEING

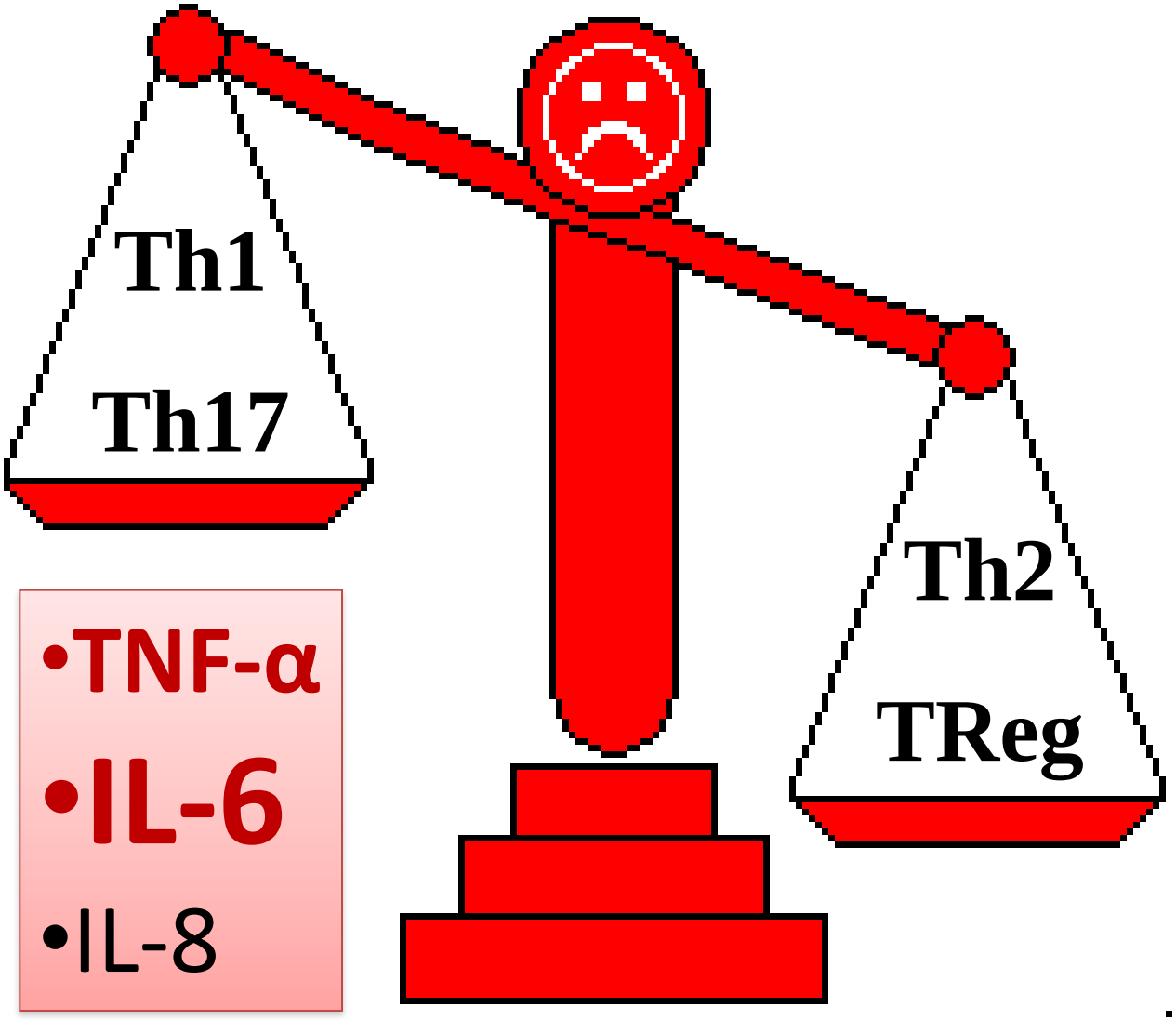


CHRONOBIOLOGY OF MOST IMPORTANT CYTOKINES INVOLVED IN INFLAMMATION - PHYSIOLOGICAL TREND

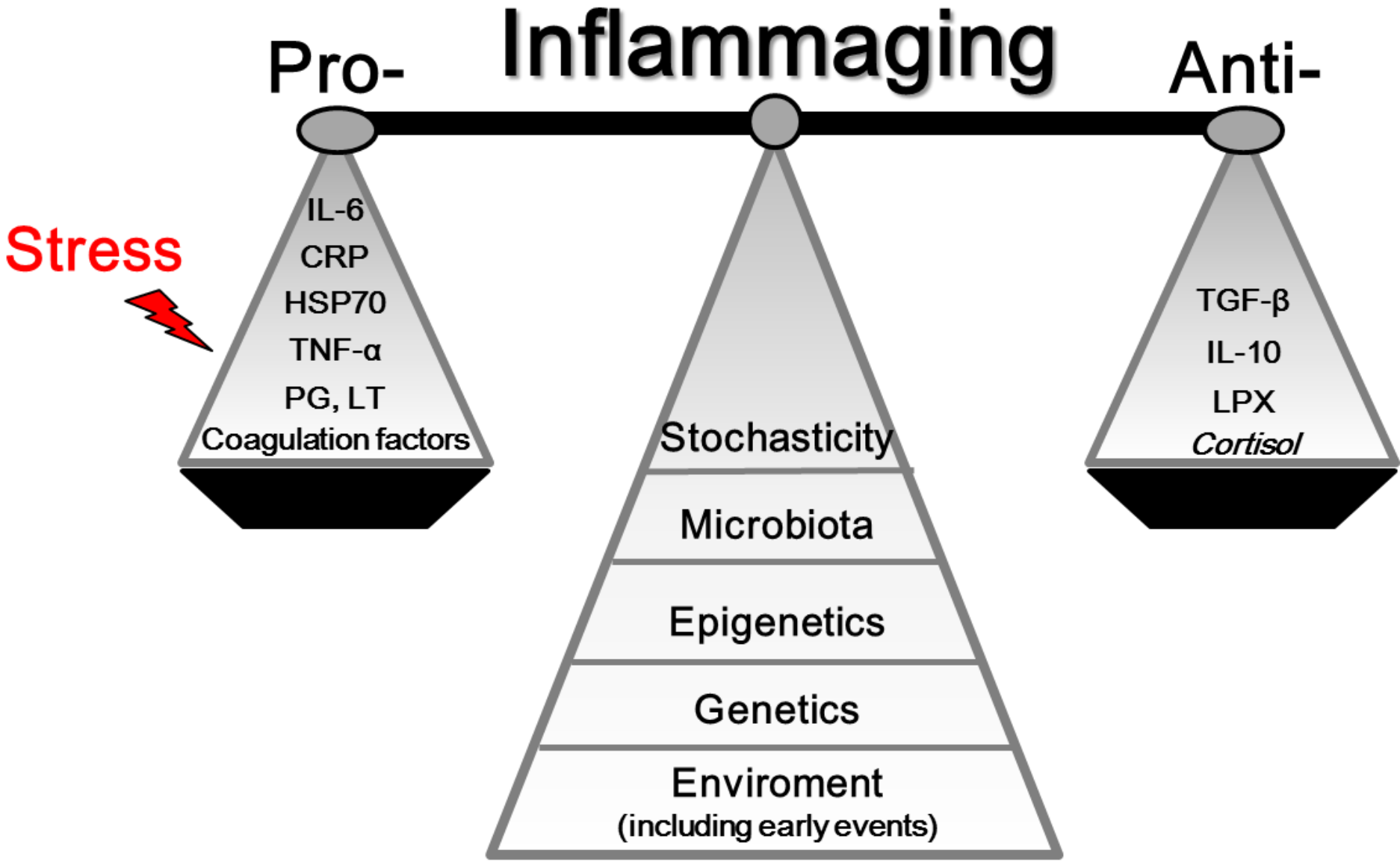


Petersen AM[1], Pedersen BK. The anti-Inflammatory effect of exercise. J Appl Physiol (1985). 2005 Apr;98(4):1154-62.

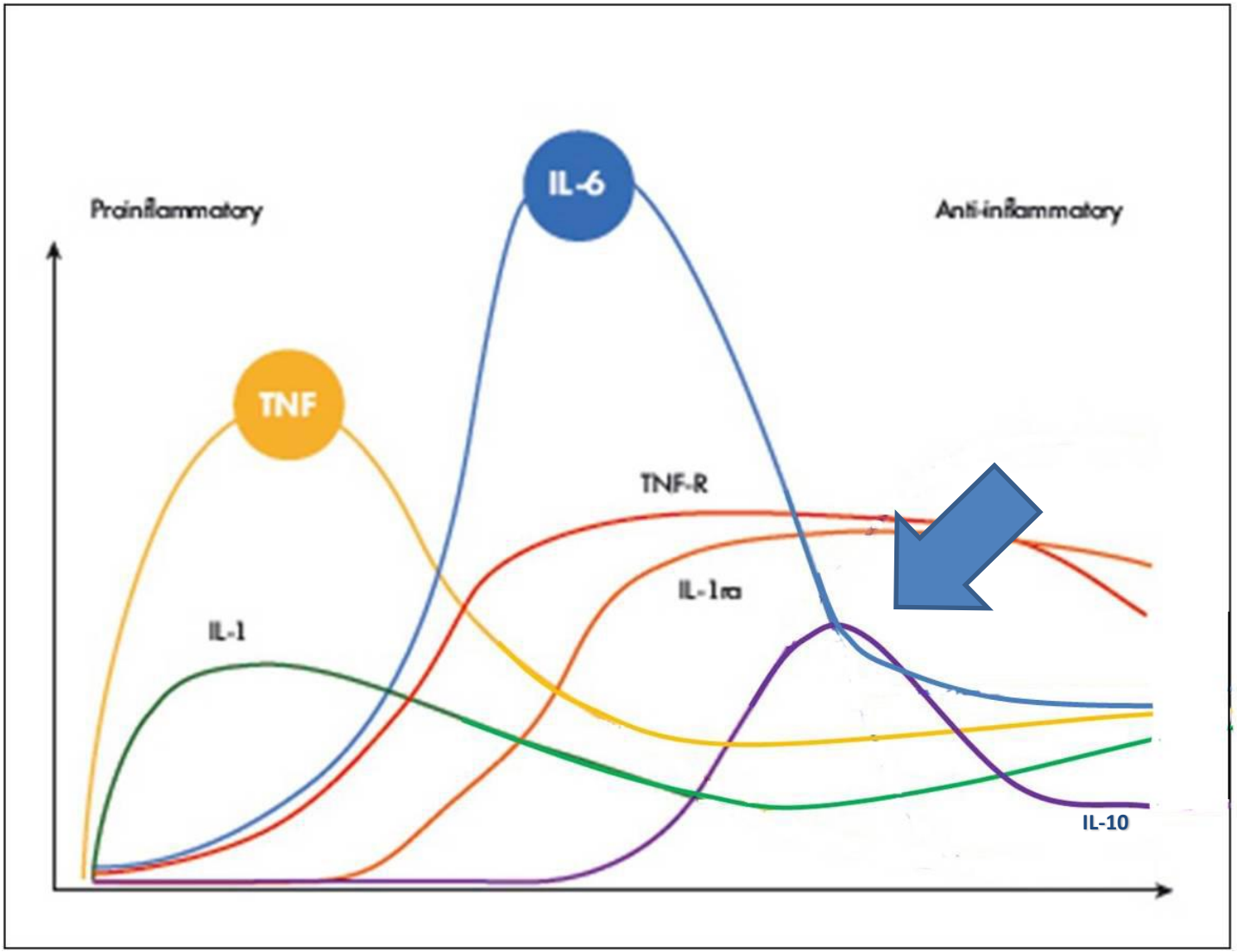
…in low grade chronic INFLAMMATION



- TNF-α
- IL-6
- IL-8



CHRONOBIOLOGY OF MOST IMPORTANT CYTOKINES INVOLVED IN INFLAMMATION IN PRESENCE OF LOW GRADE CHRONIC INFLAMMATION



Petersen AM[1], Pedersen BK. The anti-Inflammatory effect of exercise. J Appl Physiol (1985). 2005 Apr;98(4):1154-62

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How to down-regulate IL-6?

DERMATOLOGY

PubMed Search Search

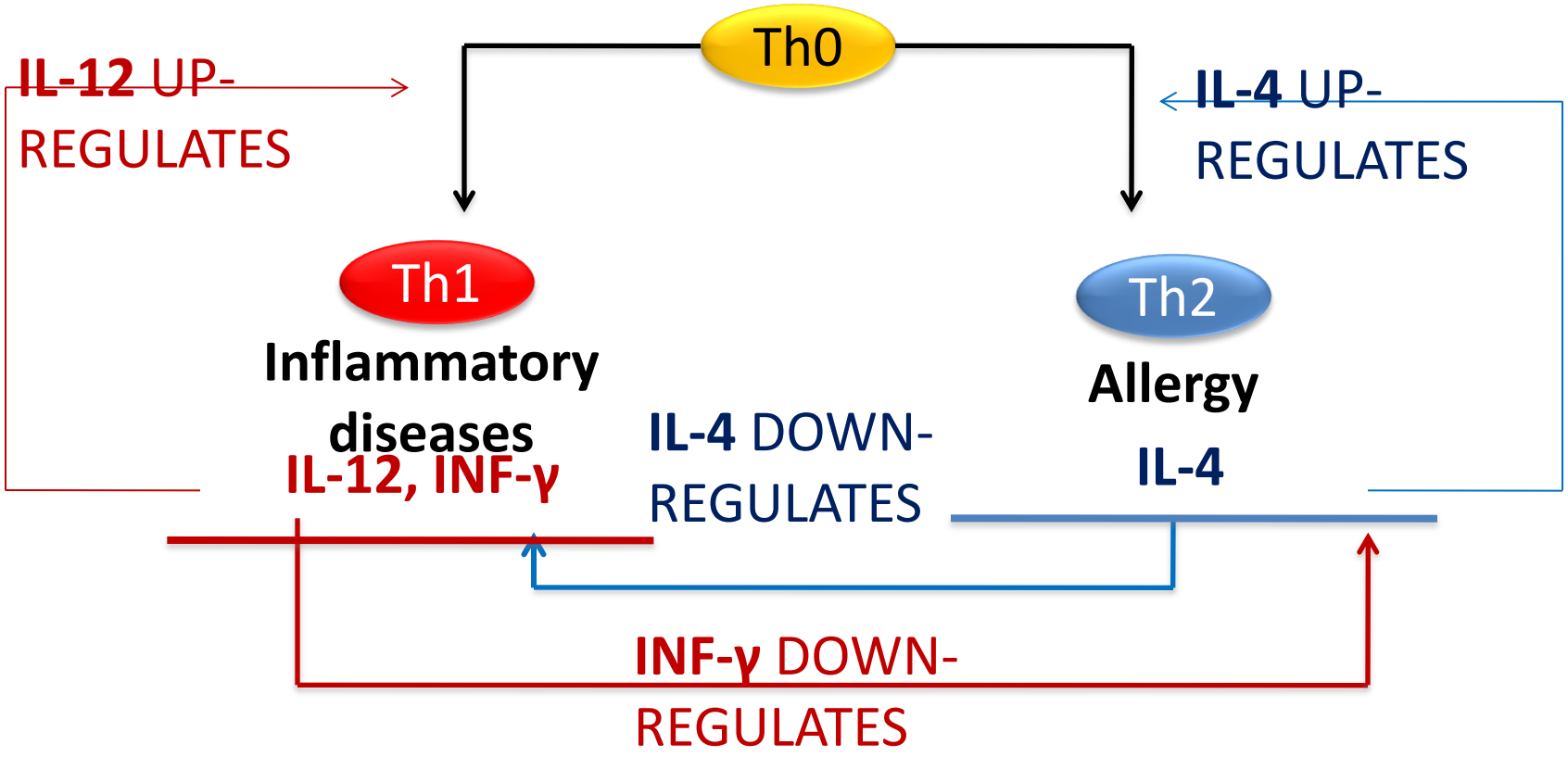
Psycho-neuro-endocrine-immunology and low dose cytokines therapy: principles and evidences for an innovative medical approach in acute and chronic inflammatory diseases.

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

Abstract

The development of the Psycho-Neuro-Endocrine-Immunology (P.N.E.I.), induced a fundamental paradigm shift in the interpretation of the biological functions of the body; from a separatist point of view to an unifying one, centered on the recognized importance of the cross-talk between cells, organs and systems. This interplay is regulated by a great number of messenger molecules and their circulating levels are key parameters for the definition of both physiological and pathological conditions; indeed, the pathological phenomenon can be described as an imbalance in intercellular signaling. The restoration of the impaired signalling molecules balance is the goal of Low Dose Medicine (LDM), a new medical approach based on the administration of low physiological doses of messenger molecules (which act as homeostatic modulating agents). The validity of the Low Dose Medicine conceptual approach in terms of efficacy and safety is assessed by five years of scientific research in this field. In particular the role of low dose Sequential Kinetic Activation (SKA) signalling molecules oral administration in inflammatory status management is demonstrated.

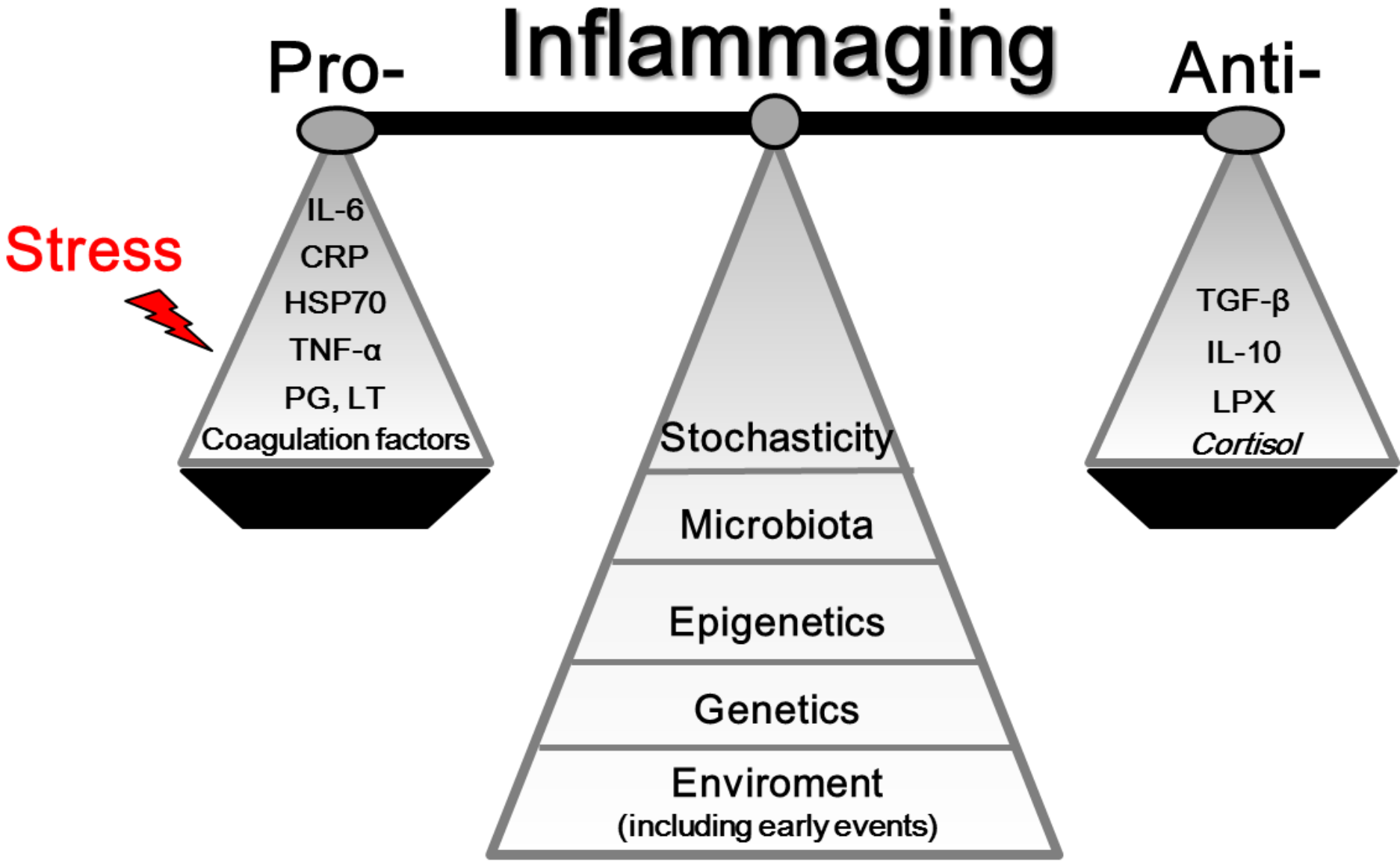
THE CONCEPT OF BALANCE



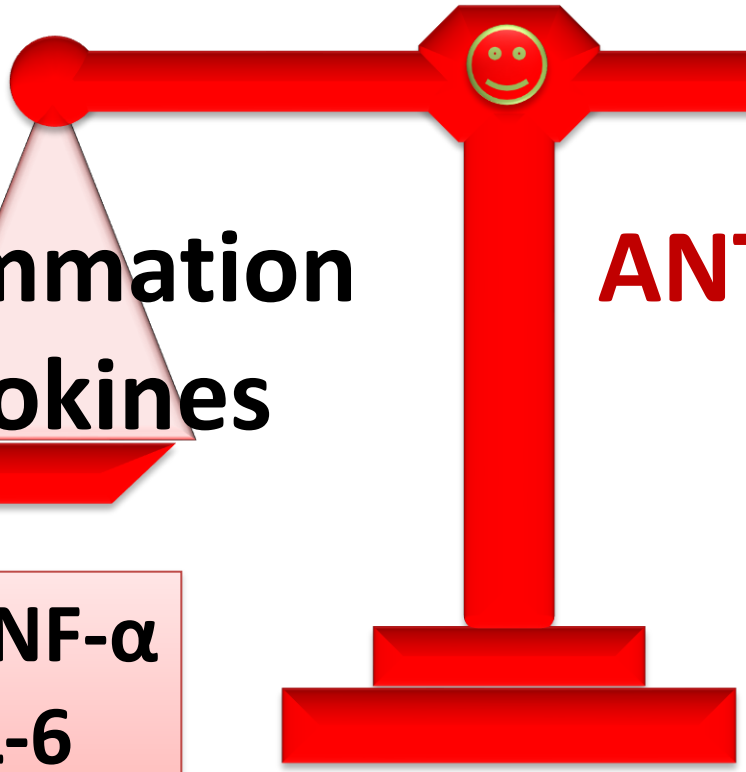
Developing Th subsets cross-regulate expansion and functions each other.

Cooke , A. Th17 in Inflammatory Conditions. ***2006, Rev Diabetic Stud 3: 72-7***

- Bettelli E. et al. Th17: the third member of the effector T cell trilogy. ***Current Opinion in Immunology 2007, 19: 652-657***



RECOVERING THE BALANCE IN SKIN INFLAMMAGEING



Inflammation Cytokines

- TNF-α
- IL-6
- IL-8

ANTI-Inflammation Cytokines

- IL-4
- **IL-10**
- TGF-β

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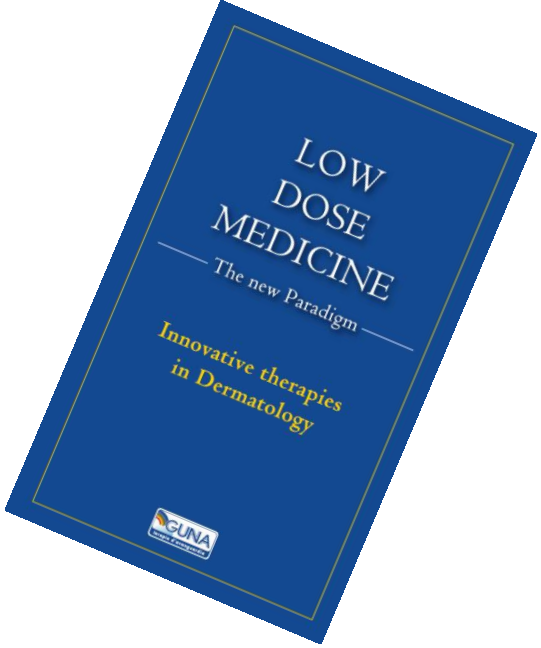
DERMATOLOGIC THERAPY
ISSN 1396-0296

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

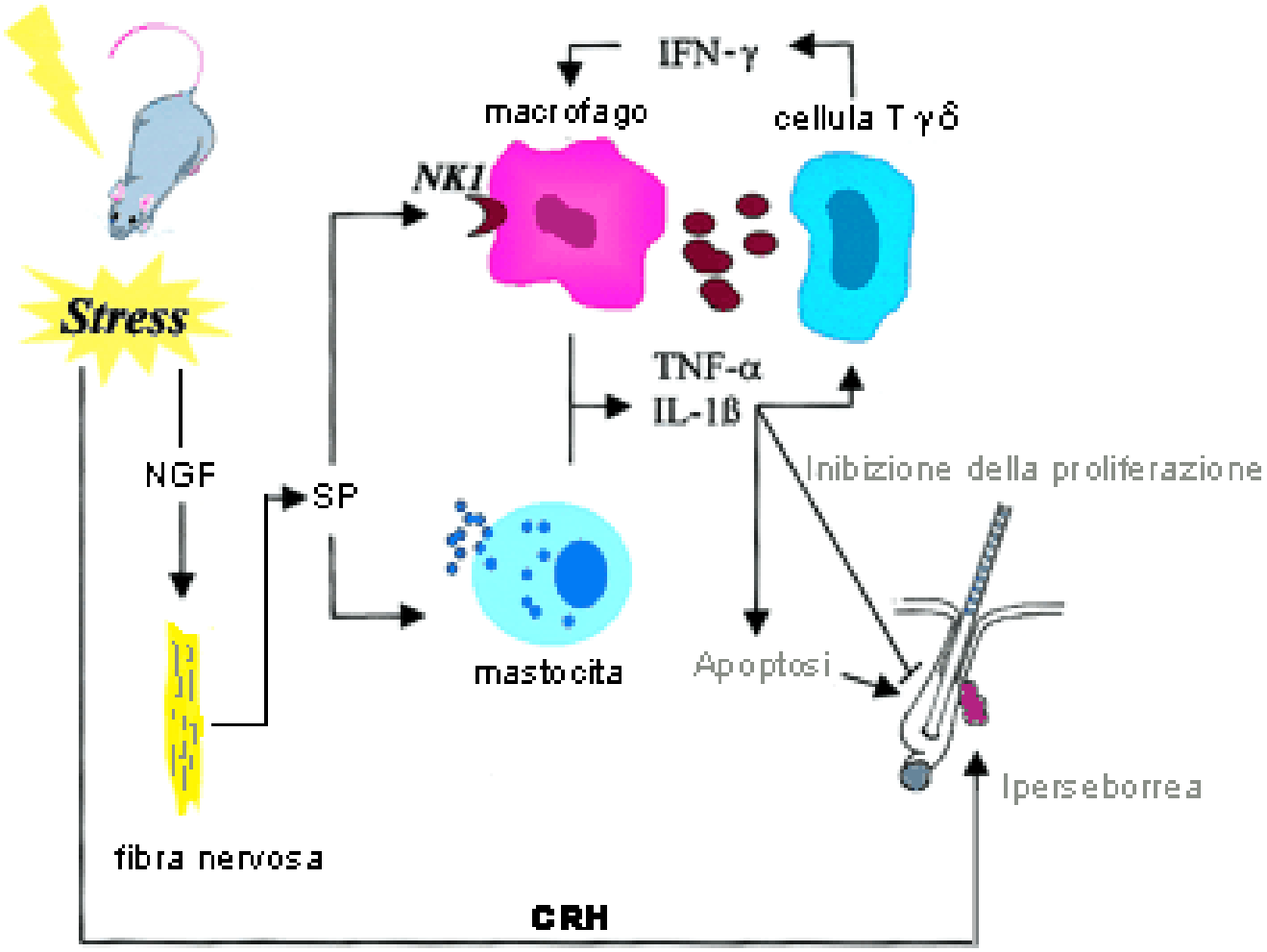
BENEDETTA BRAZZINI,* ILARIA GHERSETICH,* JANA HERCOGOVA,† & TORELLO LOTTI*
**Department of Dermoscience, University of Florence, Florence, Italy, and*
†*Department of Dermatology, Charles University, Prague, Czech Republic*



LOW DOSE MEDICINE
FROM ITALIAN RESEARCH AN INNOVATIVE IMMUNOTHERAPEUTIC APPROACH FOR SKIN DISORDERS

P.N.E.I. and Low Dose Cytokines and Growth Factors Therapy

Torello Lotti
Professor & Chair of Dermatology and Venereology;
Director of the Center for Interdisciplinary Studies of Regenerative Sciences. University of Rome "Guglielmo Marconi" Rome, Italy; Director Institute of Dermatology *LifeCronos*, Florence, Italy;
President *World Health Academy Foundation*, Zurich, Switzerland.



DERMATOLOGY

PubMed Search Search

Treating skin diseases according to the low dose medicine principles. Data and hypotheses.

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

Cytokines, hormones and growth factors, also defined with the collective name of "signaling molecules" are key regulating agents of physiological (and also pathological) functions according to the principles of Psycho-Neuro-Endocrine-Immunology (P.N.E.I.). From the latest evidences in the fields of Molecular Biology, P.N.E.I. and nano-concentration, a new medical approach surfaces: the Low Dose Medicine (LDM), a new tool for the study and the design of therapeutic strategies based on immune rebalance interventions. LDM suggest the use of low-doses of activated signaling molecules in order to restore P.N.E.I. homeostatic conditions and an increasing number of scientific evidences of LDM approach efficacy and safety support LDM-based therapeutic approach for the treatment of many dermatological diseases such as Psoriasis Vulgaris, Vitiligo and Atopic Dermatitis.

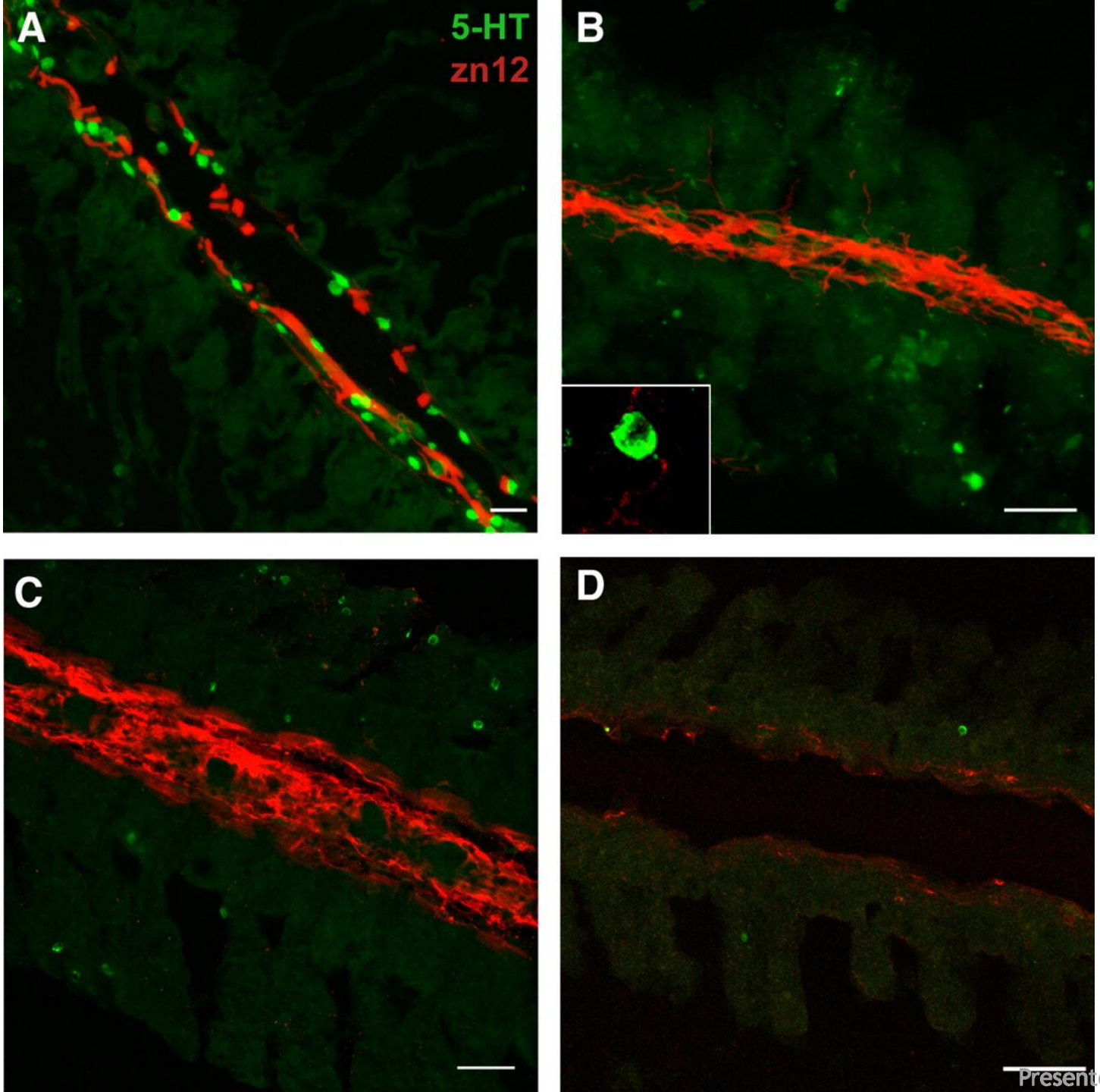
Microinflammation and Neurogenic Inflammation : a clou in anti-ageing treatments

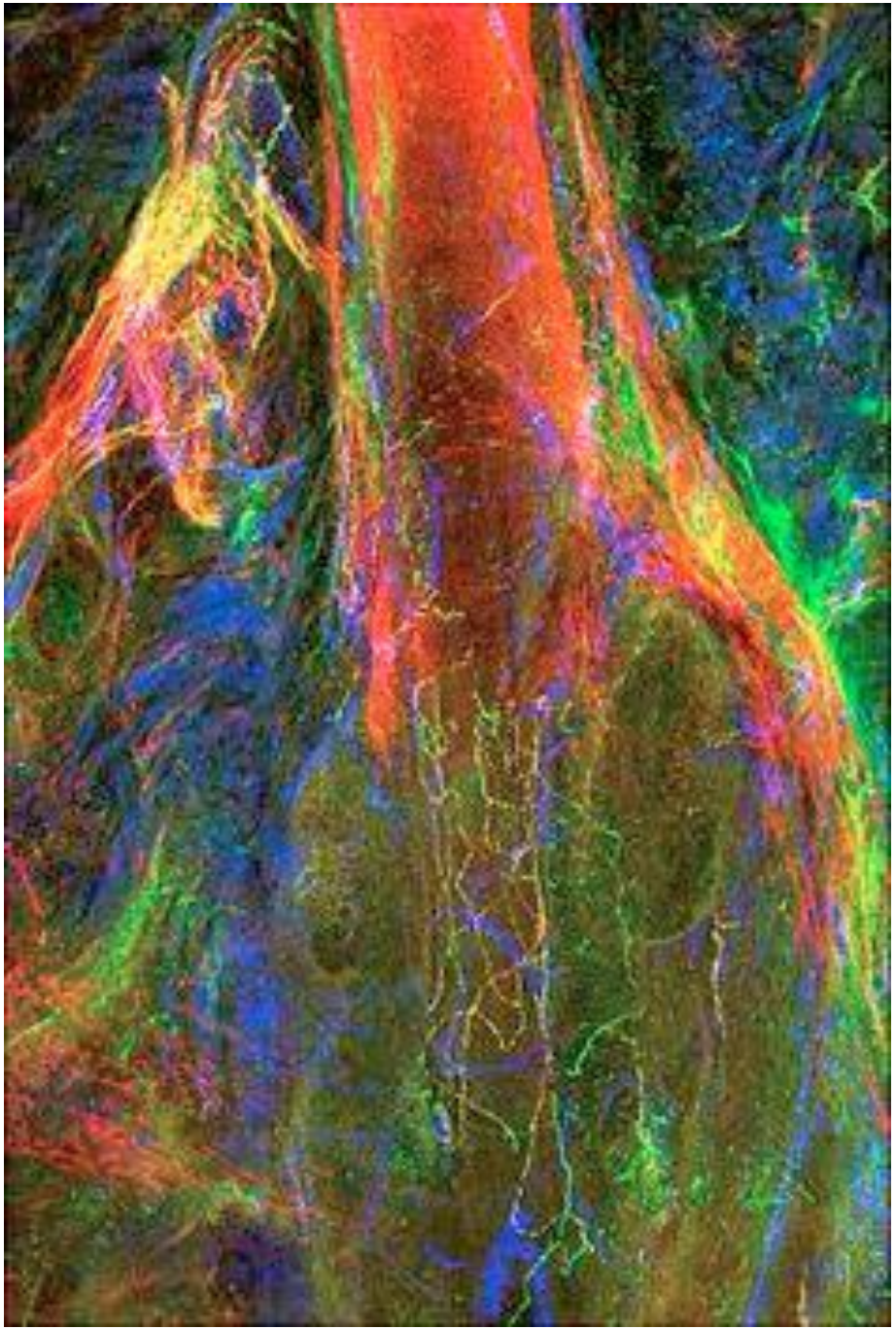
Neuropeptides in skin.
Lotti T, Hautmann G, Panconesi E.
J Am Acad Dermatol. 1995 Sep;33(3):482-96.

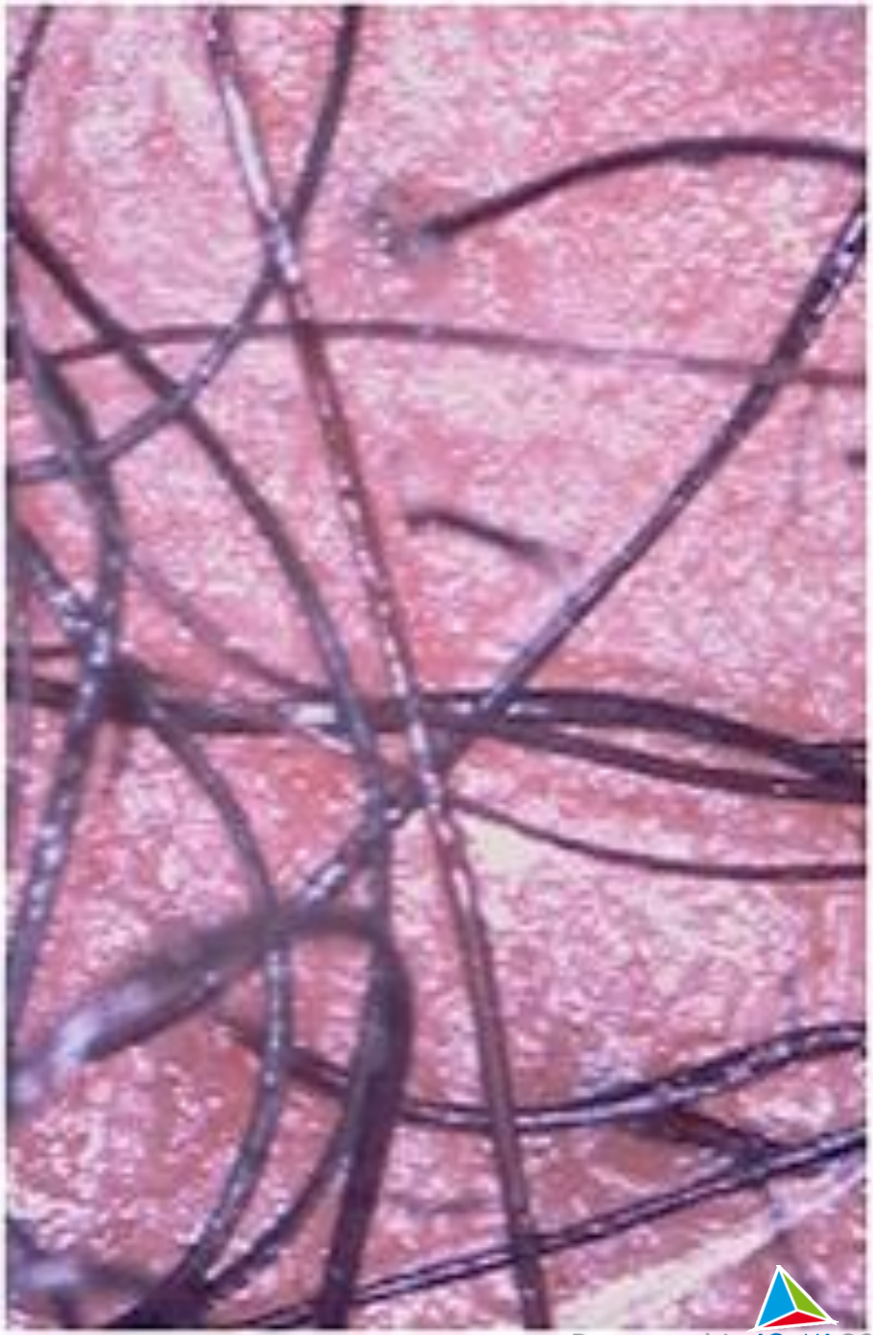
Neuropeptides: role in inflammatory skin diseases.
Luger TA, Lotti T.
J Eur Acad Dermatol Venereol. 1998 May;10(3):207-11.

Neuropeptides and skin disorders. The new frontiers of neuro-endocrine-cutaneous immunology.
Lotti T, Bianchi B, Panconesi E.
Int J Dermatol. 1999 Sep;38(9):673-5.

The role of neuropeptides in the control of regional immunity.
Lotti T, D'Erme AM, Hercogová J.
Clin Dermatol. 2014 Sep-Oct;32(5):633-45. doi: 10.1016/j.clindermatol.2014.04.011.



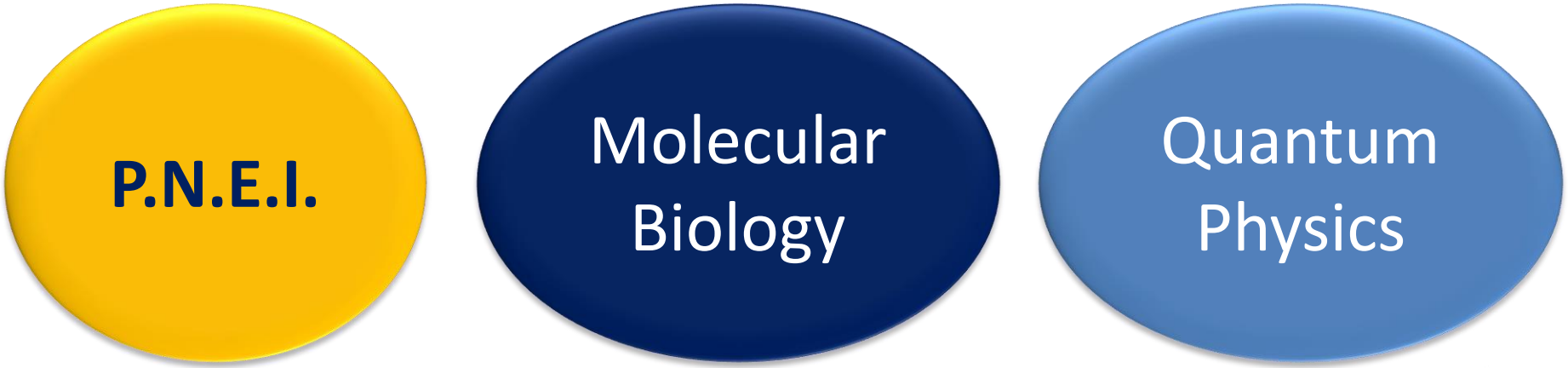


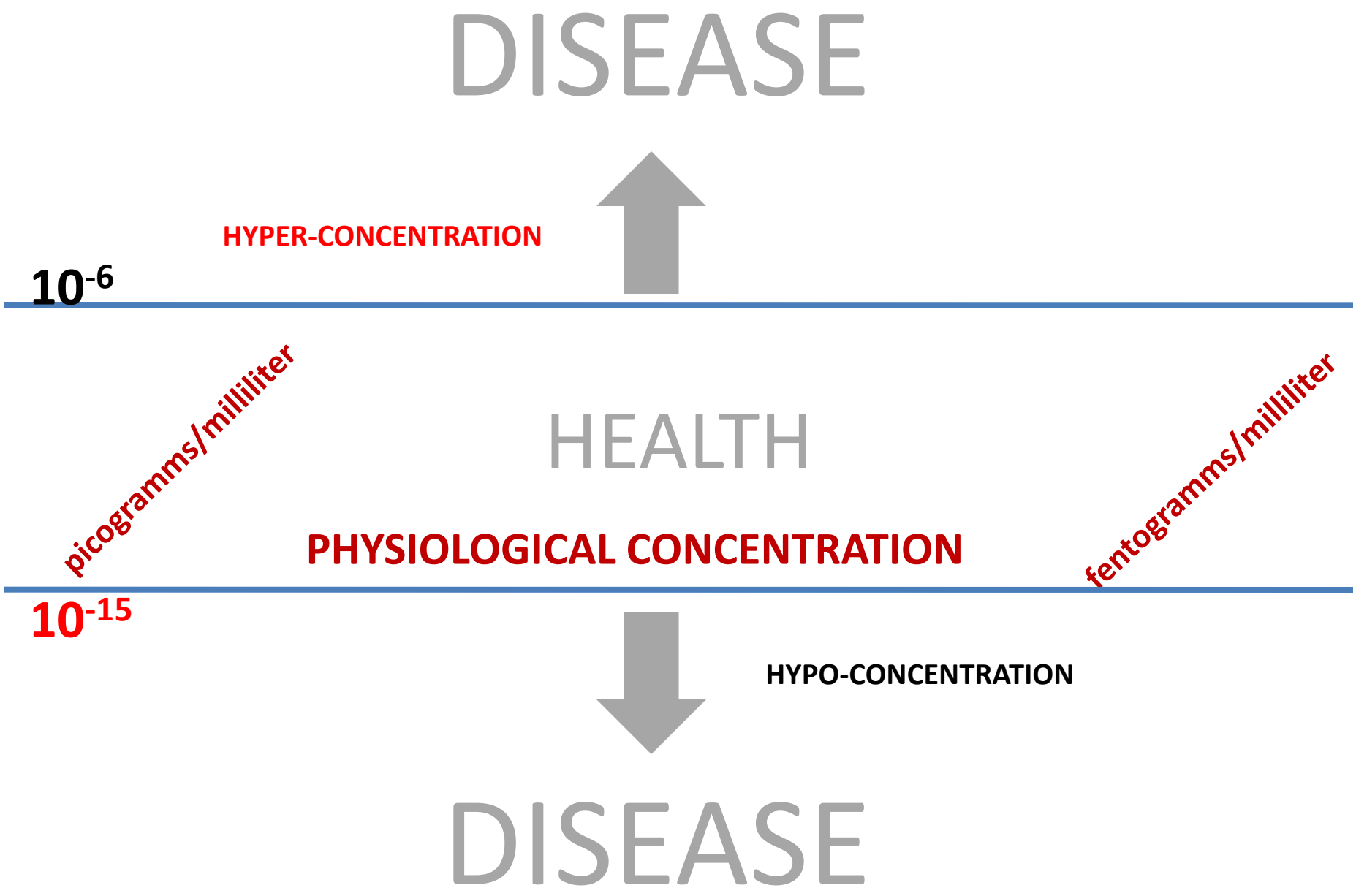


LOW DOSE MEDICINE

Low Dose Medicine integrates state of the art scientific advances in:

- **Psycho-Neuro-Endocrine-Immunology (PNEI)**
- **Molecular Biology**
- **Quantum Physics**





C O P E
Cytokines & Cells Online Pathfinder Encyclopedia
Version 26.7 (Spring 2011 Edition)

LOW DOSE MEDICINE

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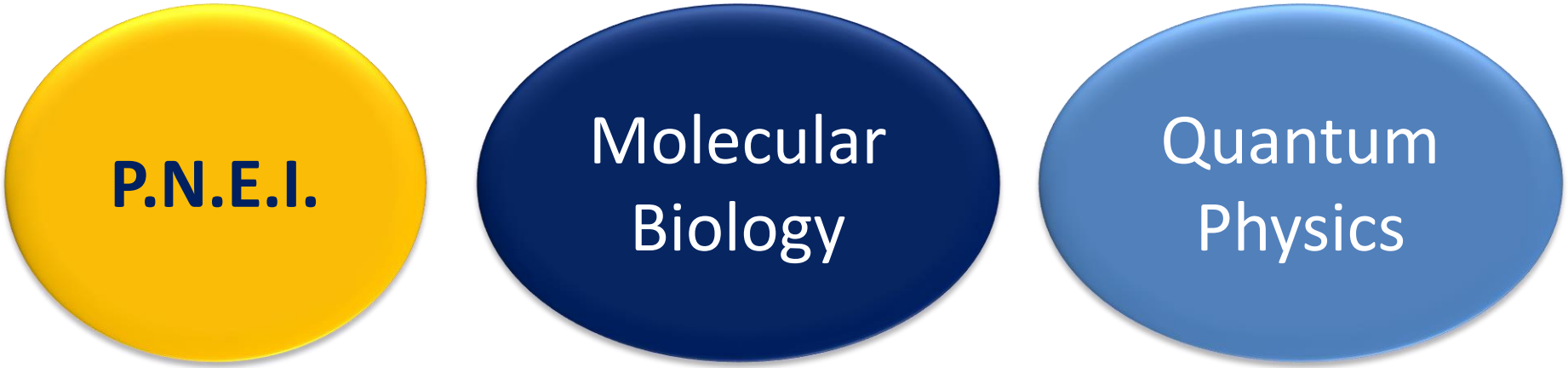
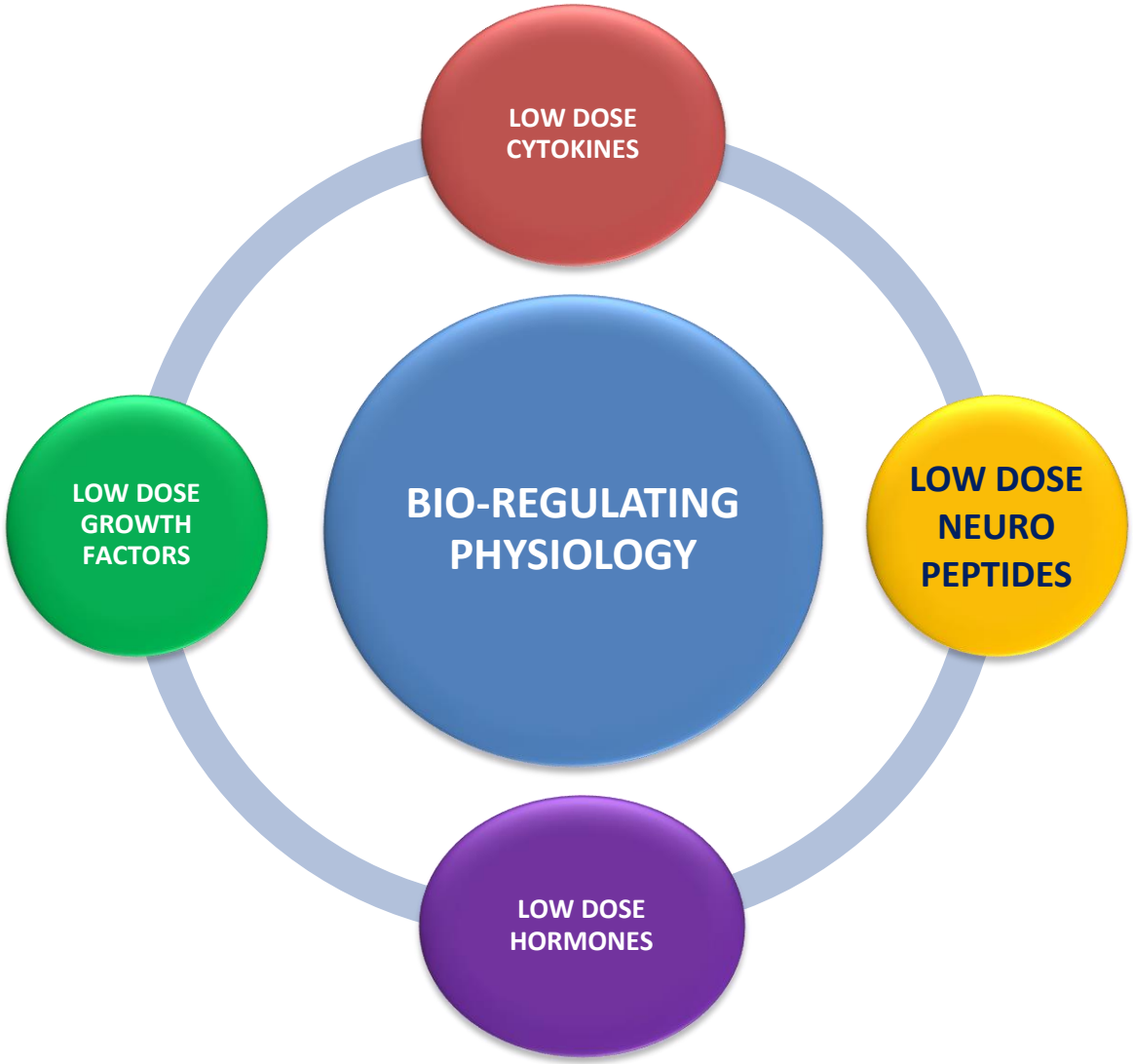


LOW DOSE MEDICINE

A NOVEL, INTEGRATED, SYSTEMIC APPROACH TO DISEASES



HOMEOSTATIC Control Systems and bi-directional cross-talk

P
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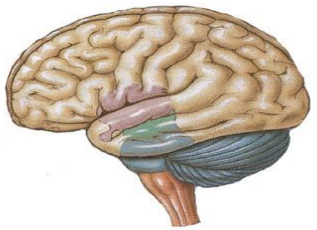
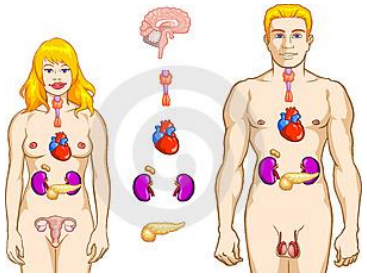
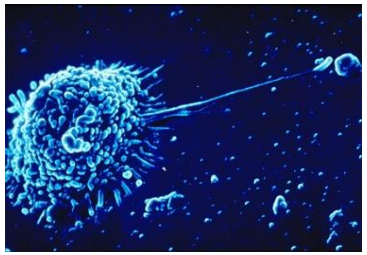
CENTRAL NERVOUS SYSTEM
&
AUTONOMIC SYSTEM



ENDOCRINE SYSTEM



IMMUNE SYSTEM



Ader, R., Psychoneuroimmunology, IV edition, vol. 1 e 2, Academic Press, Amsterdam 2007.
It is the classical text on the matter, pubblished for the first time in 1981.

DEFINITIONS

g (gram)= 1

10^{-1} = 0.1

10^{-2} = 0.01

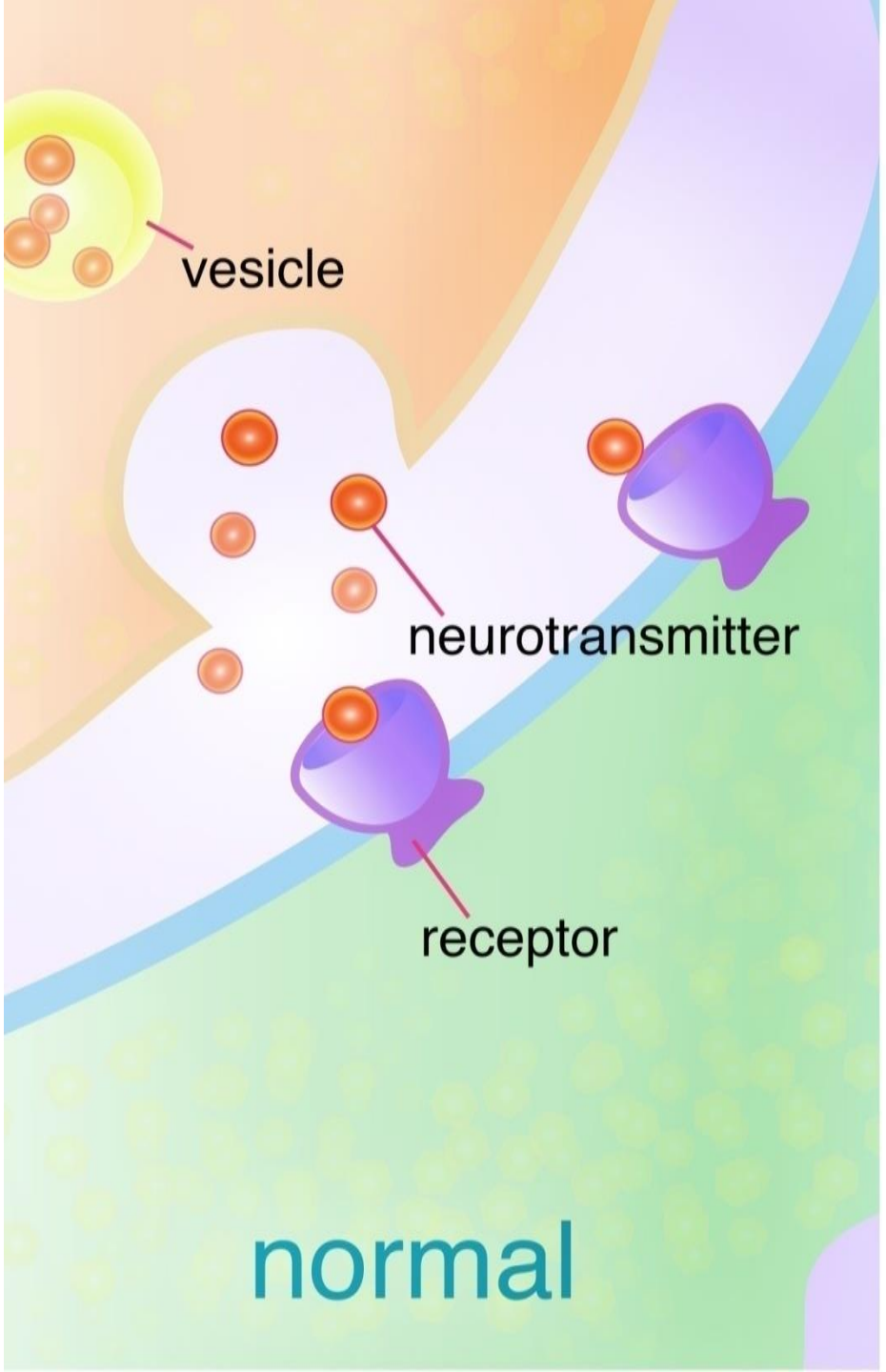
mg (milligram)= 10^{-3} = 0.001

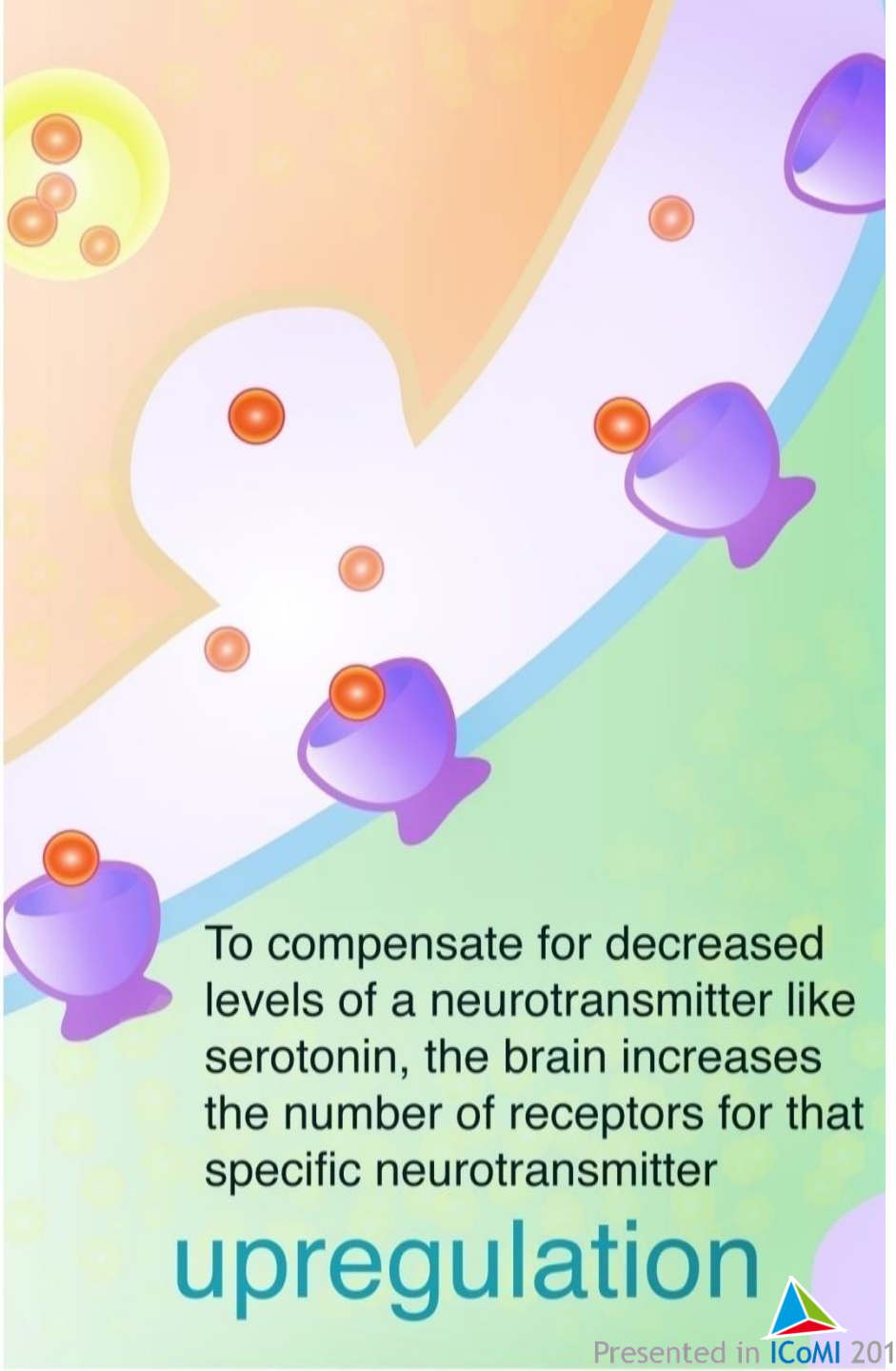
µg (microgram)= 10^{-6} = 0.000001

ng (nanogram)= 10^{-9} = 0.000000001

pcg (picogram)= 10^{-12} = 0.000000000001

fg (femtogram)= 10^{-15} = 0.000000000000001





UP- AND DOWN-REGULATION

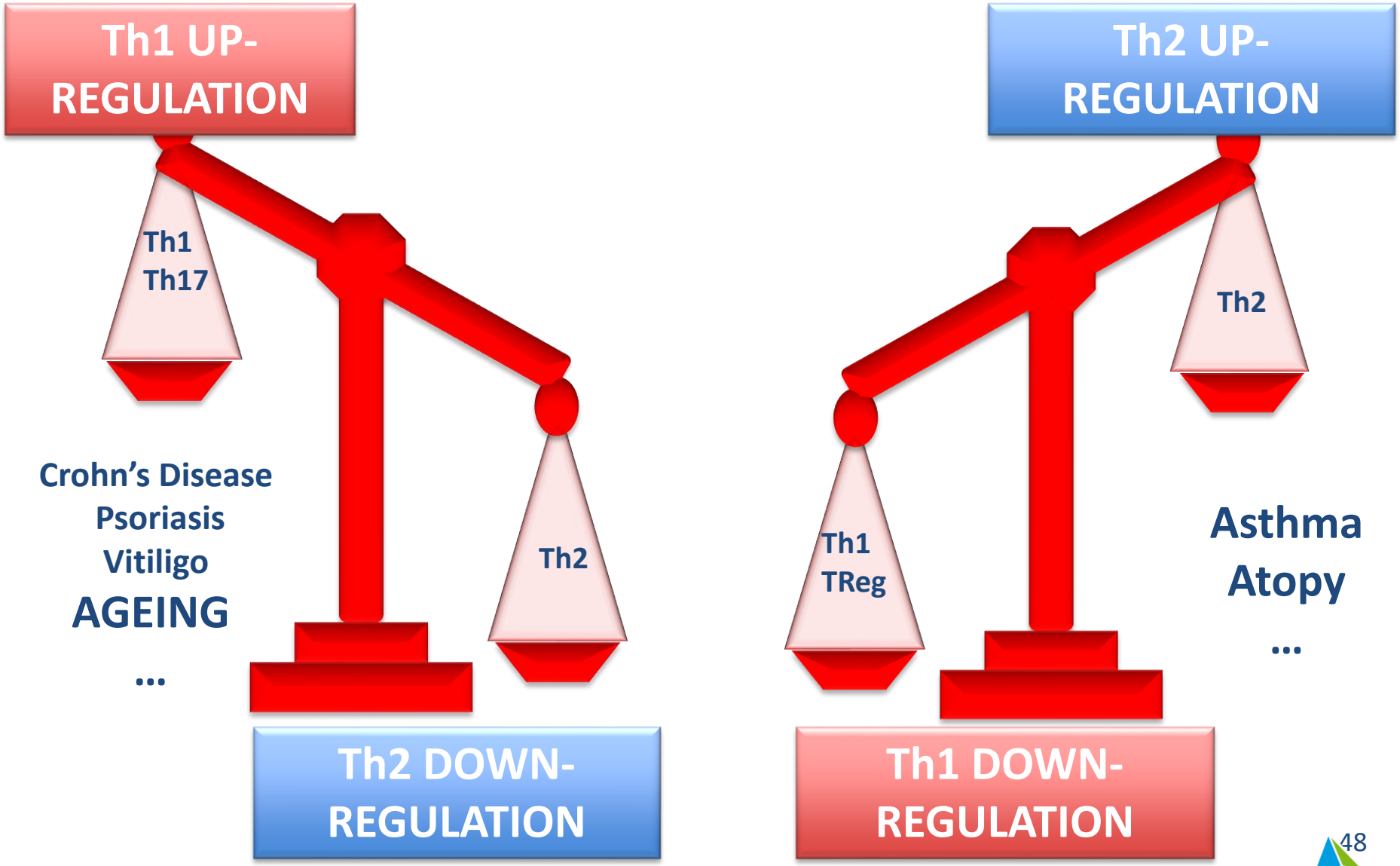
The membrane receptor plays a KEY role.

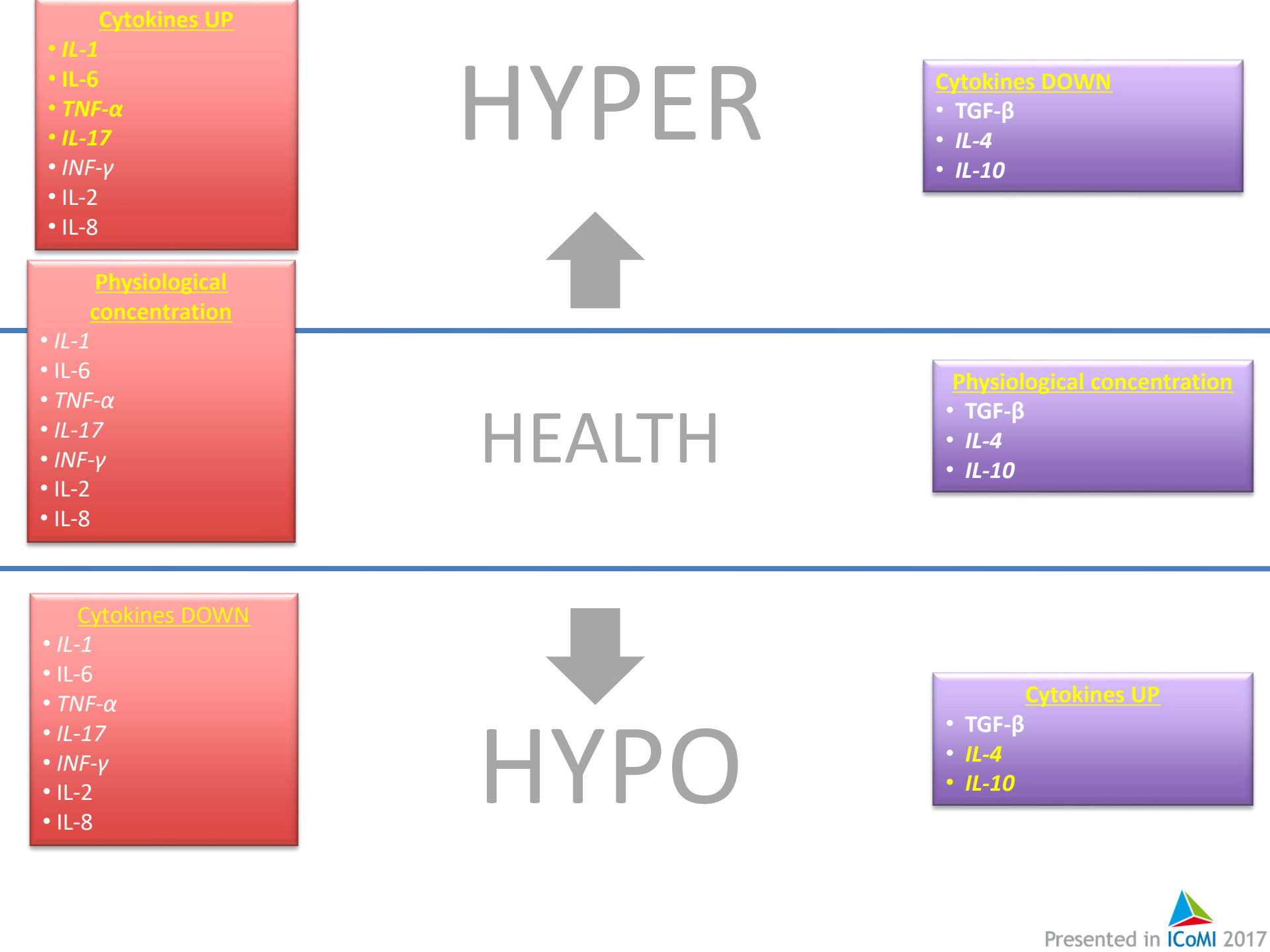
ONLY physiological concentrations are able to activate or reactivate the membrane receptors and consequently, stimulate the physiological function of a target cell.

- Akahoshi T et al. Interleukin 1 stimulates its own receptor expression on human fibroblasts through the endogenous production of prostaglandin(s). J Clin Invest. 1988 Oct;82(4):1219-24

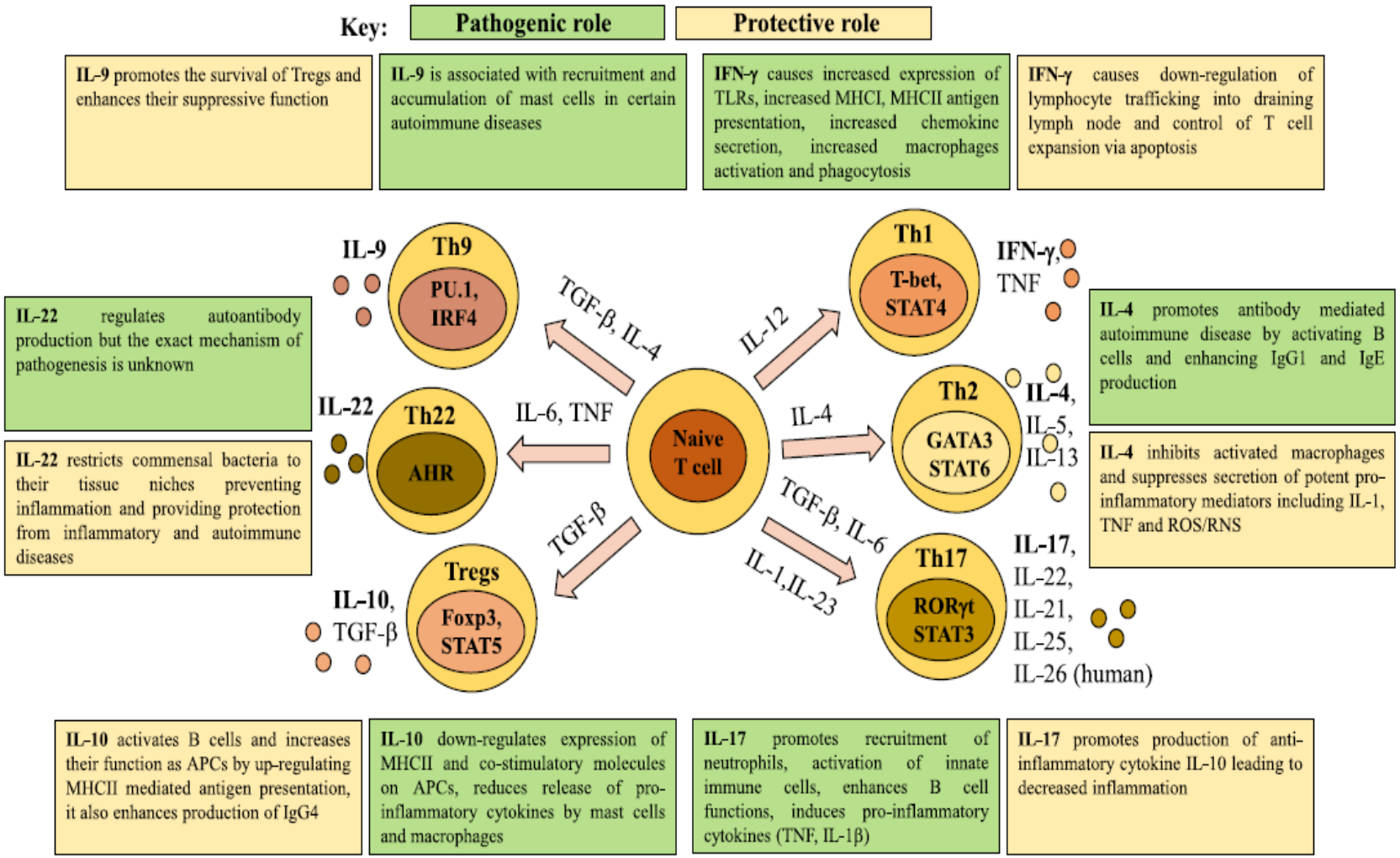
- Samanta AK et al. Interleukin 8 (monocyte-derived neutrophil chemotactic factor) dynamically regulates its own receptor expression on human neutrophils. J Biol Chem. 1990 Jan 5;265(1):183-9.

Th-1/Th-2 BALANCE





Neither good nor bad in Nature



Raphael I et al. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine (2014), http://dx.doi.org/10.1016/j.cyto.2014.09.011

IF DISEASES ARE EXPRESSIONS, CONSEQUENCES OF CHANGED CONCENTRATION OF *MESSENGER MOLECULES…*

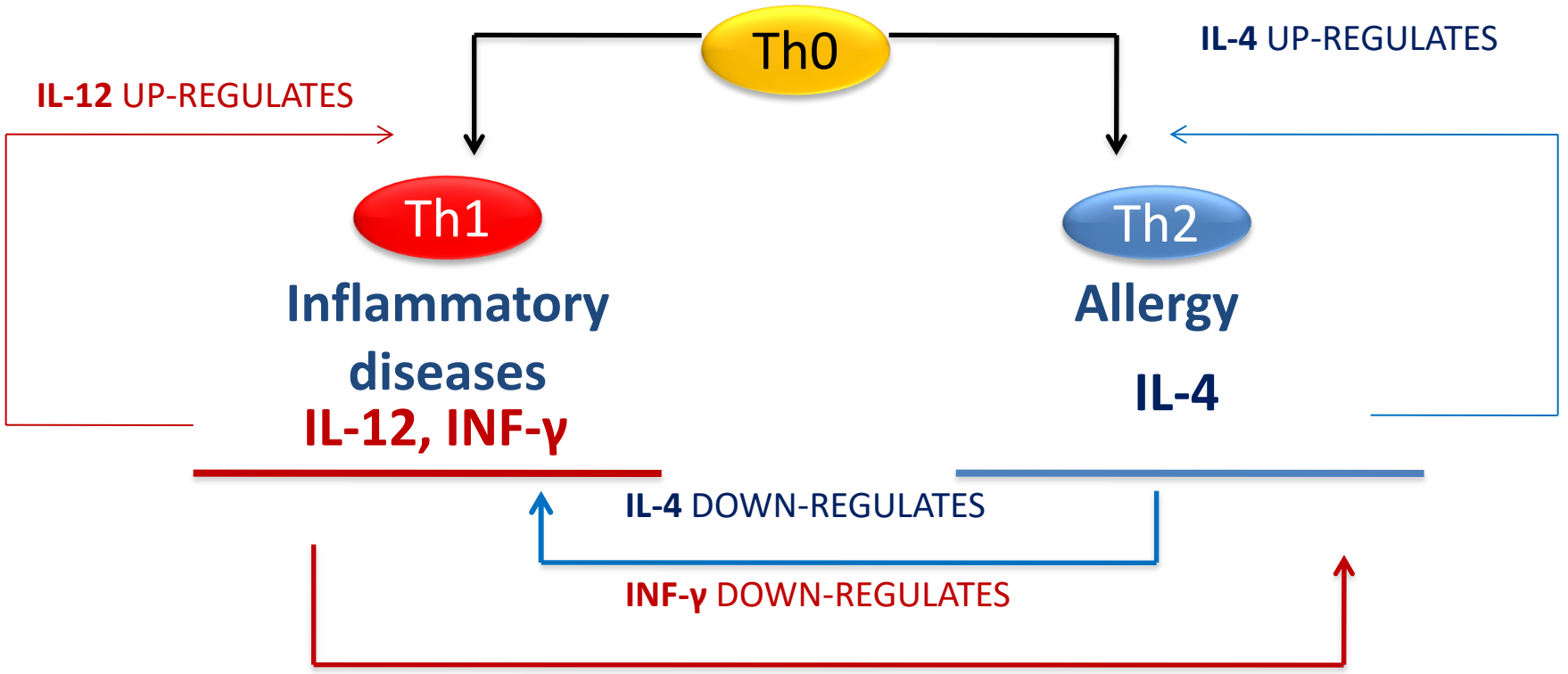
PROBLEM

Is it possible to modulate the action of cytokines and other signaling molecules in Low Grade Chronic Inflammation treatments ?

The concept of BALANCE and the use of SKA low dose cytokines

Antagonistic cytokines are utilized in order to slow down a biological effect; Same cytokines in order to enhance a biological function.

THE CONCEPT OF BALANCE – RECIPROCITY of TH CELLS



Th subsets cross-regulate expansion and functions each other.

- *Cooke , A. Th17 in Inflammatory Conditions.* ***2006, Rev Diabetic Stud 3: 72-7***
- *Bettelli E. et al. Th17: the third member of the effector T cell trilogy.* ***Current Opinion in Immunology 2007, 19: 652-657***

PRESCRIPTION ACCORDING TO THE AETIOLOGICAL DECISIONAL PROCESS

CYTOKINE	STRENGTHENING same cytokine	MODULATION opposing cytokine
GCSF	GCSF 4C	IL-10 4C/IL-4 4C
INF alpha/gamma	INF alpha/gamma 4C	IL-4 4C
IL-1	IL-1 4C	Guna Anti IL-1 4C/IL-10 4C
IL-2	IL-2 4C	IL-11 4C
IL-3	IL-3 4C	IL-10 4C
IL-4	IL-4 4C	INF-gamma 4C/IL-12 4C
IL-5	IL-5 4C	TGF-beta 4C
IL-6	IL-6 4C	IL-10 4C *Chronic inflammation:* IL-6 4C
IL-7	IL-7 4C	IL-10 4C/TGF-β1 4C
IL-8	IL-8 4C	IL-10 4C/TGF-β1 4C
IL-9	IL-9 4C	IL-10 4C
IL-10	IL-10 4C	IL-1 4C/TNF 4C/IL-6 4C
IL-11	IL-11 4C	IL-2 4C
IL-12	IL-12 4C	IL-4 4C/IL-10 4C
TGF-beta 1	TGF-beta 4C	IL-12 4C
TNF	TNF-alpha 4C	Guna Anti IL-1 4C+IL-10 4C

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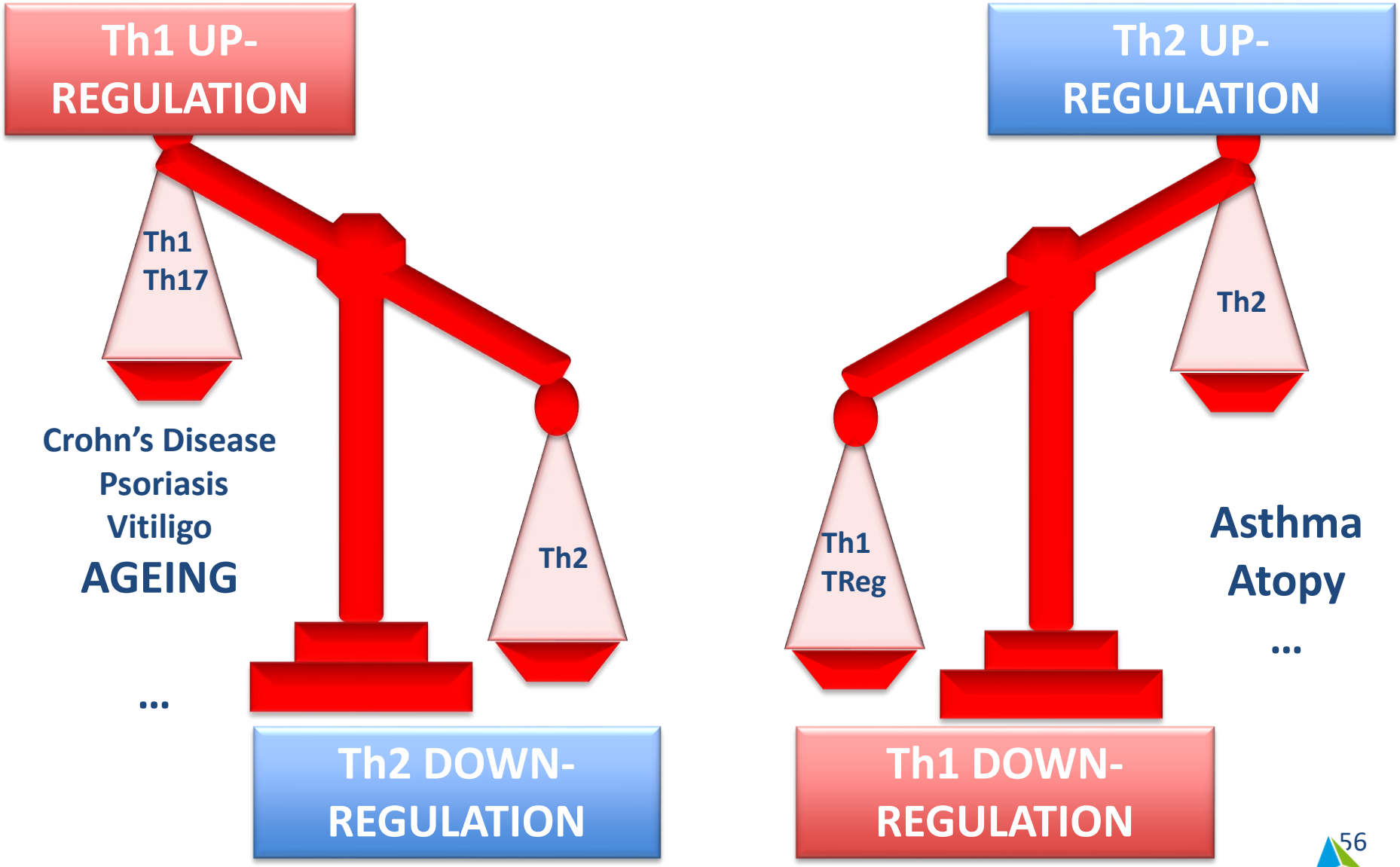
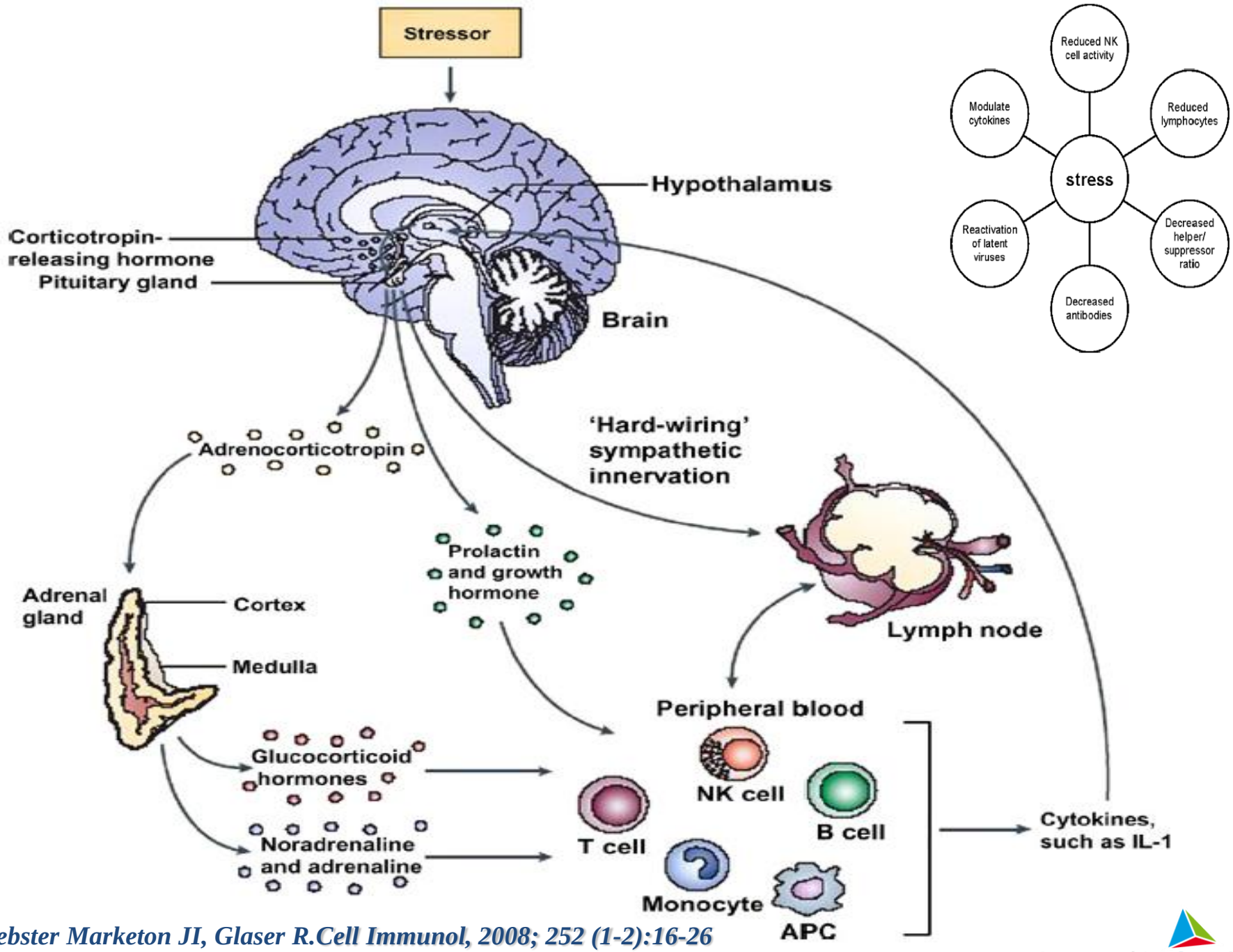
Th-1/Th-2 BALANCE





Webster Marketon JI, Glaser R.Cell Immunol, 2008; 252 (1-2):16-26

Heterologous bio-mimetic growth factors in anti-aging treatments: biological selectivity, indications, side effects and complication

Daily Treatment

- **GUNA ANTI IL/-1 (4CH, 20+20 Drops)**
- **GUNA INTERLEUKIN 10 (4CH, 20+20 Drops)**
- **GUNA Platelet derived Growth Factor (4CH, 20+20 Drops)**
- **GUNA FGF (4CH, 20+20 Drops)**
- **GUNA IGF (4CH, 20+20 Drops)**

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IL-1 family is a group of 11 cytokines, which induces a complex network of proinflammatory cytokines and via expression of integrins on leukocytes and endothelial cells, regulates and initiates inflammatory responses.

IL-1α and IL-1β are the most studied members, because they were discovered first and because they possess strongly proinflammatory effect. They have a natural antagonist IL-1Ra (IL-1 receptor antagonist). All three of them include a beta trefoil fold and bind IL-1 receptor (IL-1R) and activate signaling via MyD88 adaptor, which is described in the Signaling section of this page**. IL-1Ra regulates IL-1α and IL-1β proinflammatory activity by competing with them for binding sites of the receptor.**

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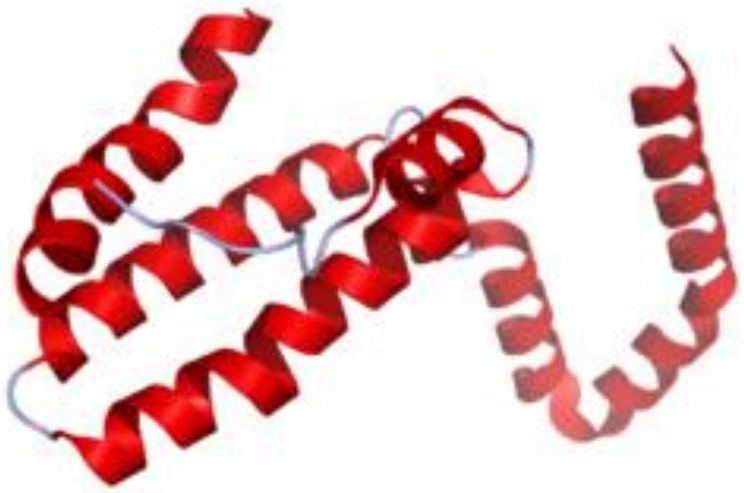
- **GUNA IGF (4CH, 20+20 Drops)**

Interleukin 10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), **is an anti-inflammatory cytokine**. In humans, interleukin 10 is encoded by the IL10 gene. IL-10 signals through a receptor complex consisting of two IL-10 receptor-1 and two IL-10 receptor 2 proteins. Consequently, the functional receptor consists of four IL-10 receptor molecules. IL-10 binding induces STAT3 signaling via the phosphorylation of the cytoplasmic tails of IL-10 receptor 1 + IL-10 receptor 2 by JAK1 and Tyk2 respectively.



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Platelet-derived growth factor (PDGF) is one of the numerous growth factors, or proteins that regulate cell growth and division. In particular, it plays a significant role in blood vessel formation (angiogenesis), the growth of blood vessels from already-existing blood vessel tissue. Uncontrolled angiogenesis is a characteristic of cancer. In chemical terms, platelet-derived growth factor is a dimeric glycoprotein composed of two A (-AA) or two B (-BB) chains or a combination of the two (-AB).

PDGF is a potent mitogen for cells of mesenchymal origin, including fibroblasts, smooth muscle cells and glial cells. In both mouse and human, the PDGF signalling network consists of four ligands, PDGFA-D, and two receptors, PDGFRalpha and PDGFRbeta. All PDGFs function as secreted, disulphide-linked homodimers, but only PDGFA and B can form functional heterodimers.

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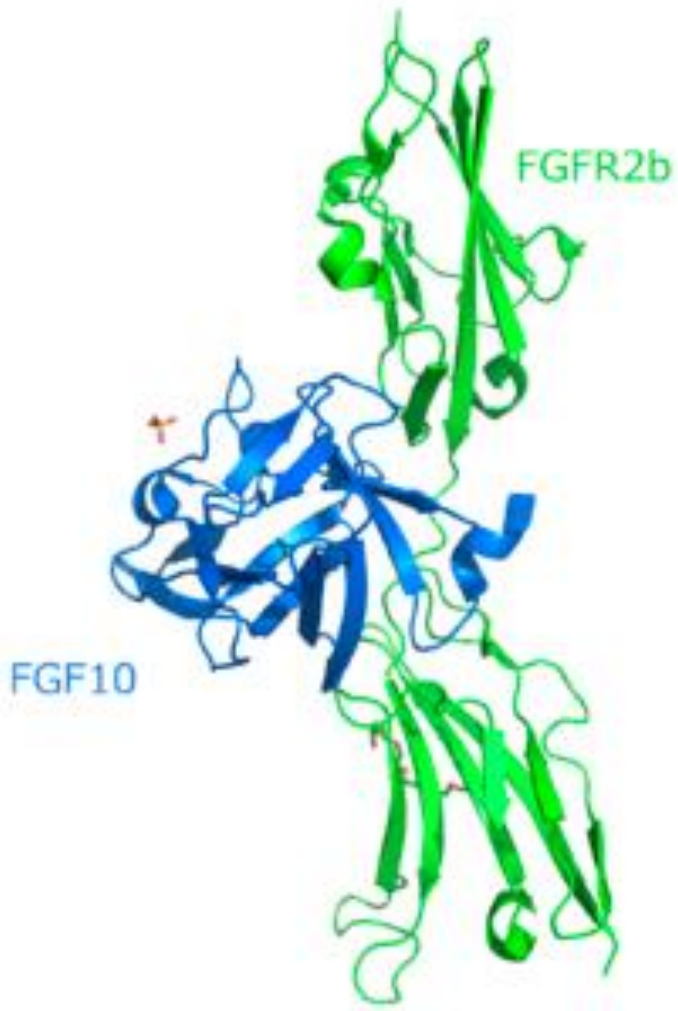
- **GUNA IGF (4CH, 20+20 Drops)**

Fibroblast growth factors, or FGFs, are a family of growth factors, with members involved in angiogenesis, wound healing, embryonic development and various endocrine signaling pathways. The FGFs are heparin-binding proteins and interactions with cell-surface-associated heparan sulfate proteoglycans have been shown to be essential for FGF signal transduction.

FGFs are key players in the processes of proliferation and differentiation of wide variety of cells and tissues.



Heterologous bio-mimetic growth factors in anti-aging treatments: biological selectivity, indications, side effects and complication

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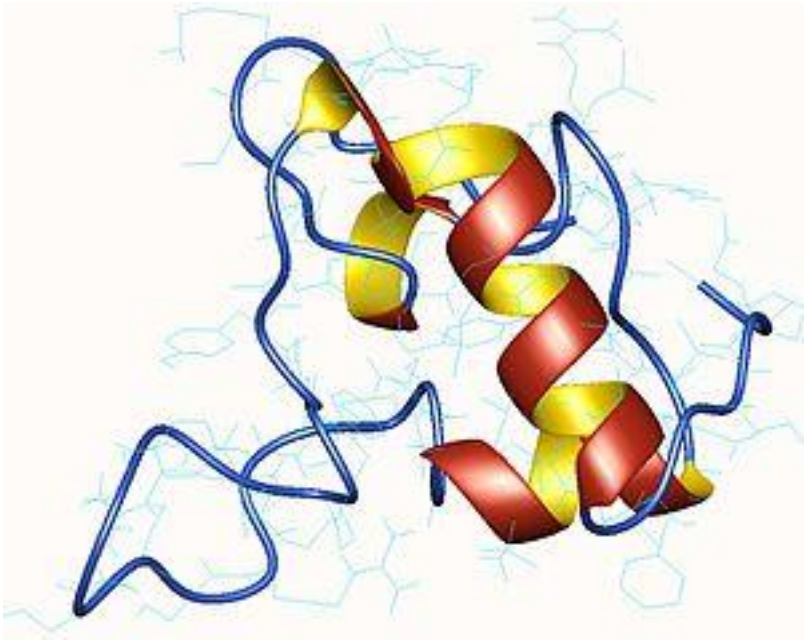
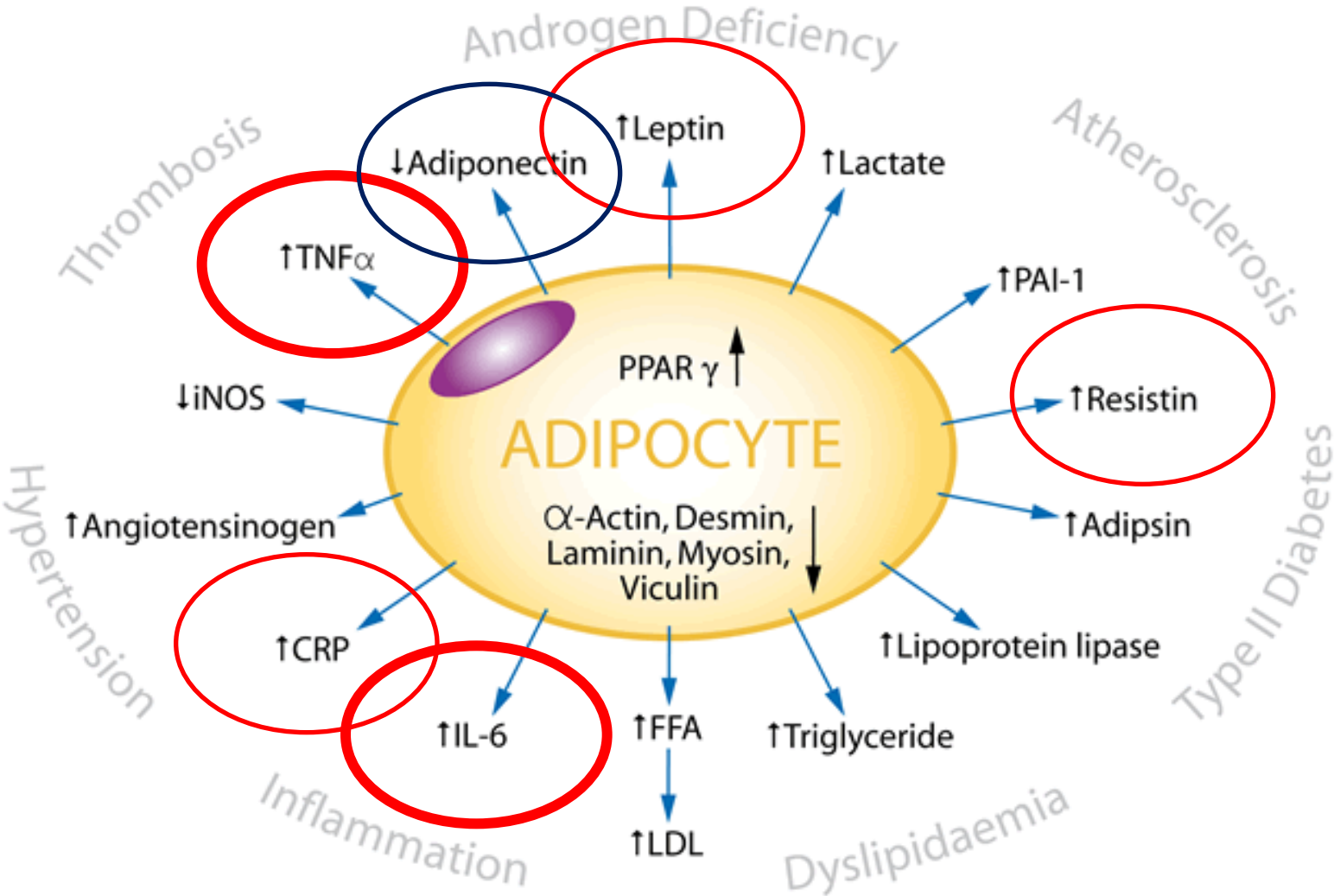
Somatomedins are produced, predominantly by the liver, when **growth hormones** act on target tissue. Somatomedins inhibit the release of growth hormones by acting directly on anterior pituitary and by stimulating the secretion of somatostatin from the hypothalamus.



Somatomedins are a group of hormones that **promote cell growth and division in response to stimulation by growth hormone (GH) also known as somatotropin (STH).**

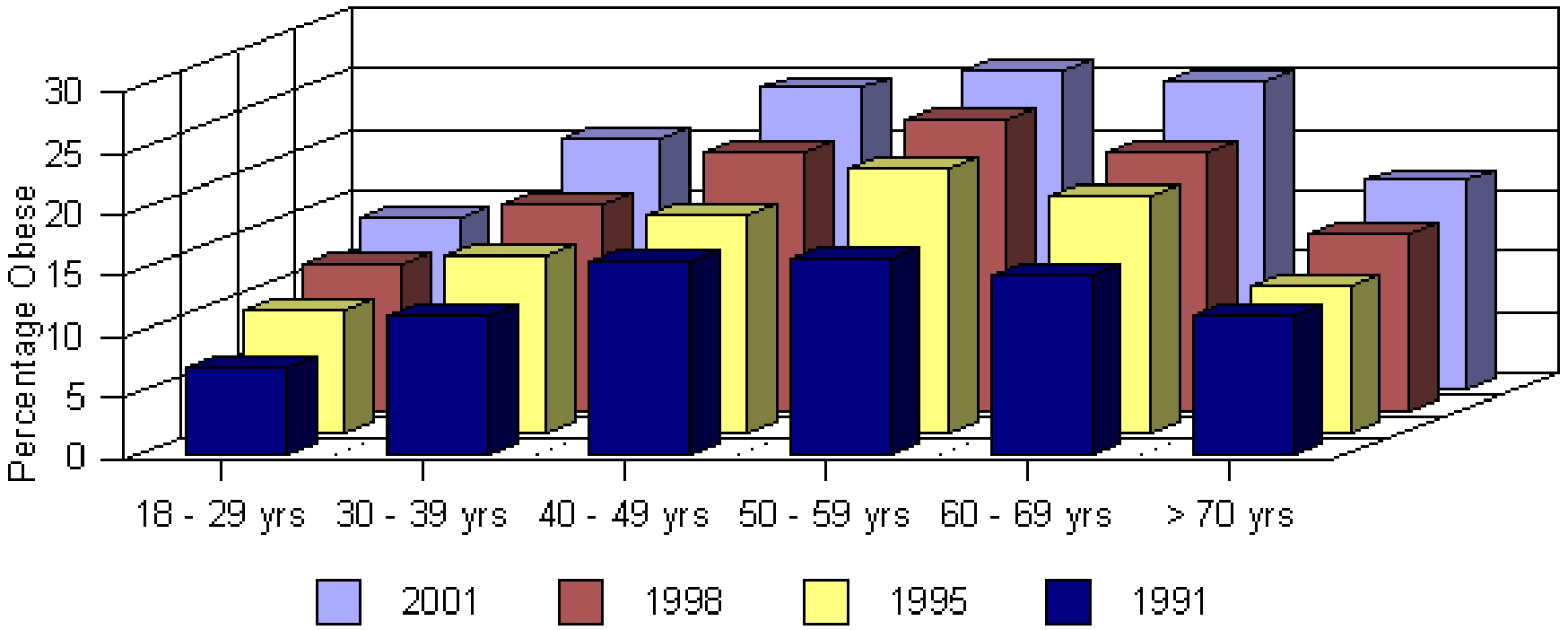
Heterologous bio-mimetic growth factors in anti-aging treatments: biological selectivity, HIGH indications, microinflammation, side effects, NONE, and complication , NONE

OBESITY INDUCED INFLAMMATION



http://www.my-personaltrainer.it/dimagrire/adipochine.html

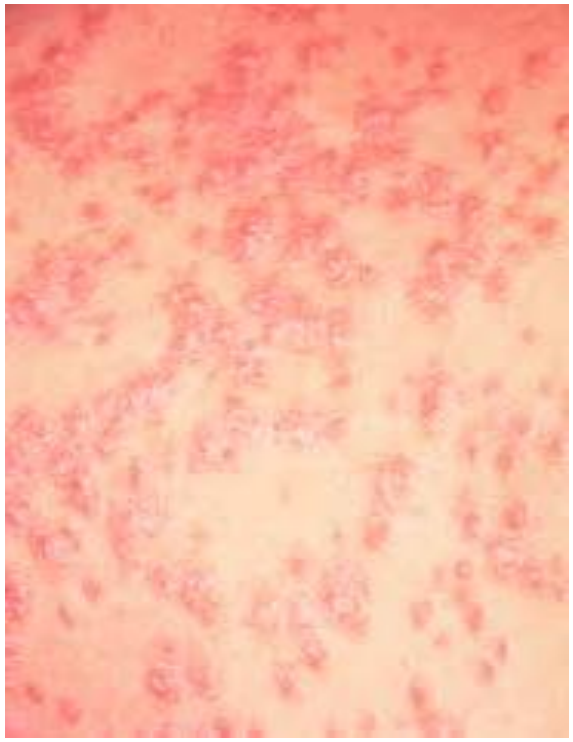
Prevalence of Obesity by Age

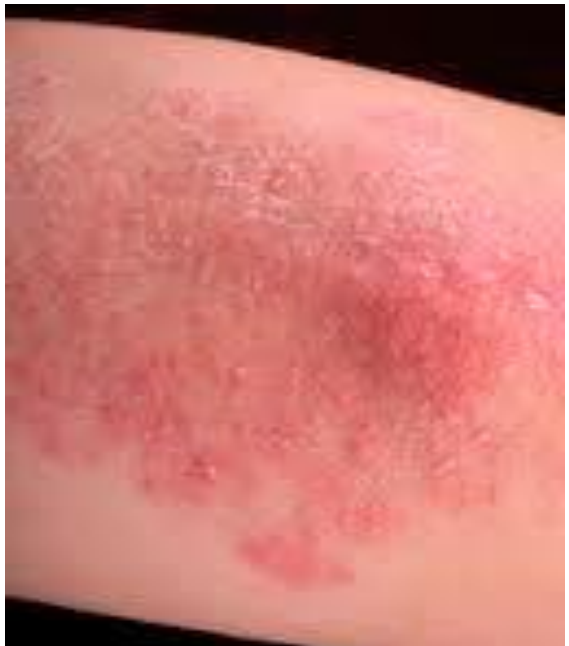


Obesity, psoriasis, and microbiota: an unexplored dangerous connection?

Dermatol Ther. 2015 May-Jun.

Roccia MG, Fioranelli M, Lotti T.





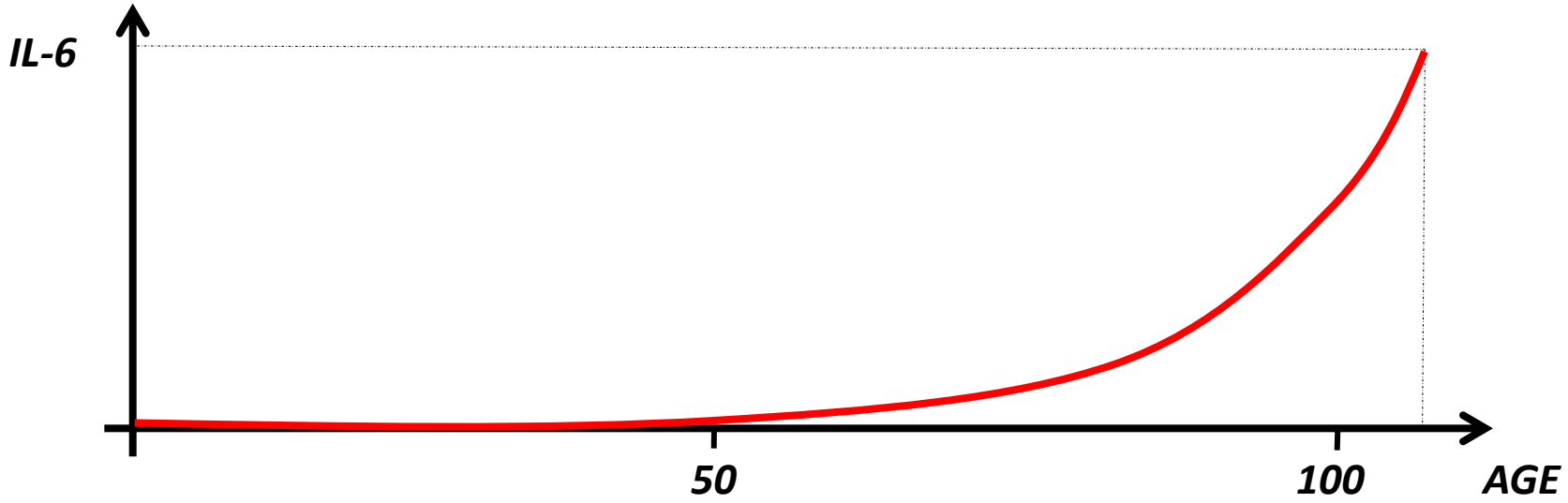
IL-6 and INFLAMM-AGING

INCREASING OF:

- Coagulation factors
- Homocysteine
- IL6
- Proinflammatory cytokines
- Acute Phase Proteins
- Stress hormones
- ROS
- Lp(a)

A PROINFLAMMATORY STATUS OF HEALTHY ELDERLY AND CENTENARIANS

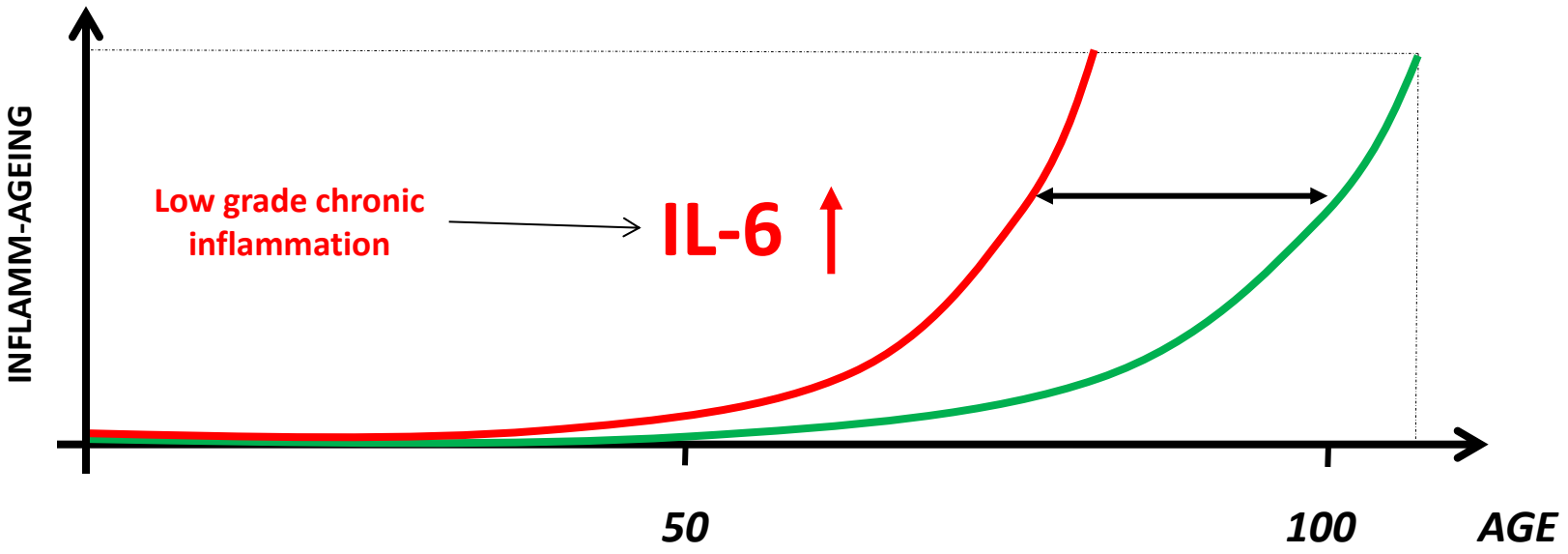
IL-6 increases in healthy subjects after 50 years of life and reaches high levels in advanced old age. The physiological increase of IL-6 is a consequence of an effective adaptation to stressors.

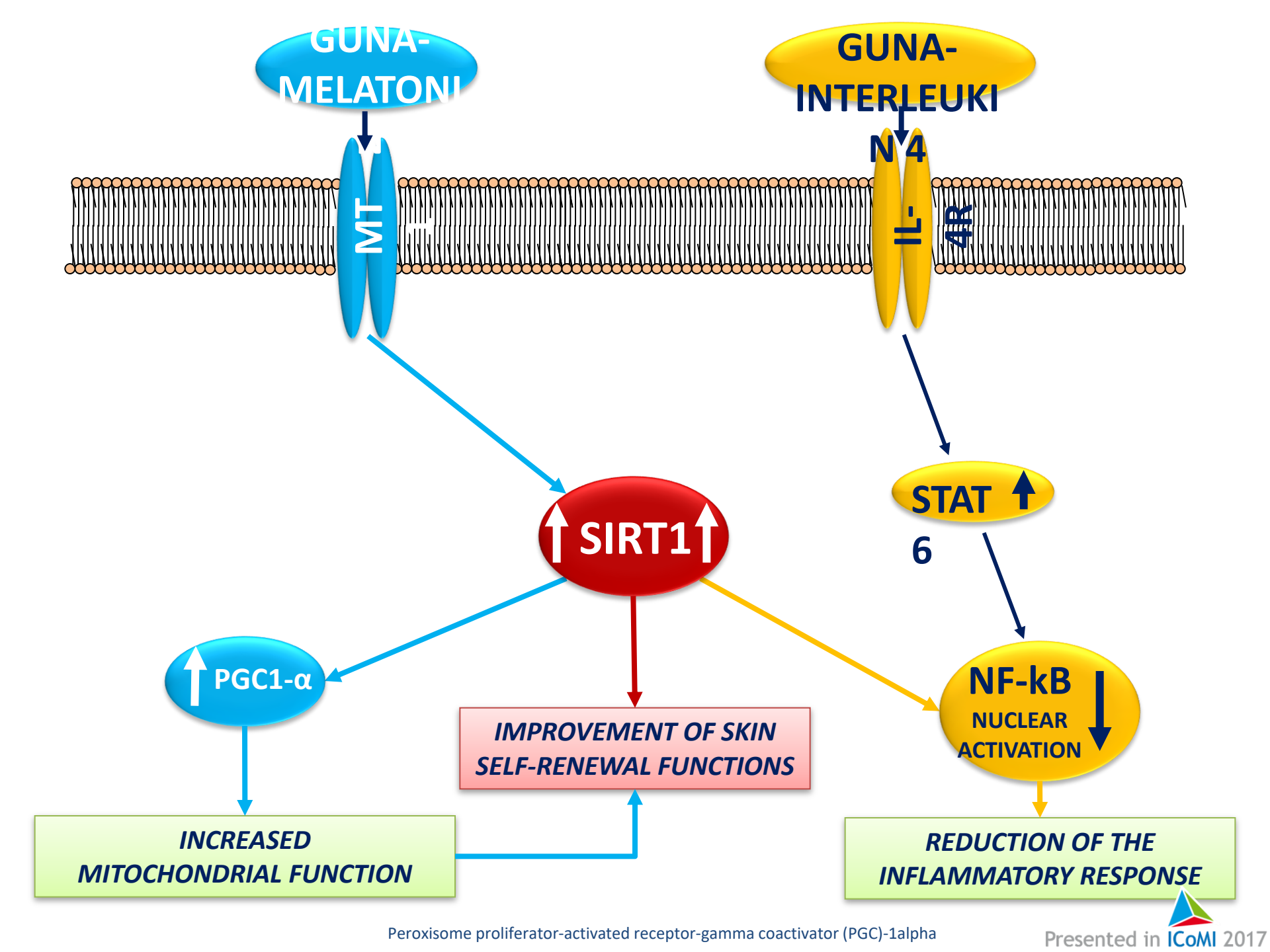


Franceschi *et al.*: Inflamm-aging An evolutionary perspective on immunosenescence. Annals New York Academy of Sciences. 2000

LOW-GRADE CHRONIC INFLAMMATION AND INFLAMM-AGING

***Low Grade Chronic Inflammation** correlated to metabolic syndrome and/or other pathologies induces a **shift** in the curve of aging with a reduction of life span.*





Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha

SIRT1 regulates MAPK pathways in the skin: insight into the molecular pathways of cell survival.

J Cell Mol Med. 2014.

Becatti M1, Fiorillo C, Barygina V, Cecchi C, Lotti T

Thanks for your attention!

Università degli Studi Guglielmo Marconi

www.torellolotti.it