The 73rd General Assembly and International Scientific Congress

Low Dose Cytokine Therapy for healthy longevity. A novel Pharmacology for a systemic and multi-level approach to aging

Saturday, November 5th, 2022

Alessandro Perra – Scientific Director GUNA S.p.a.

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Low Dose Cytokine Therapy

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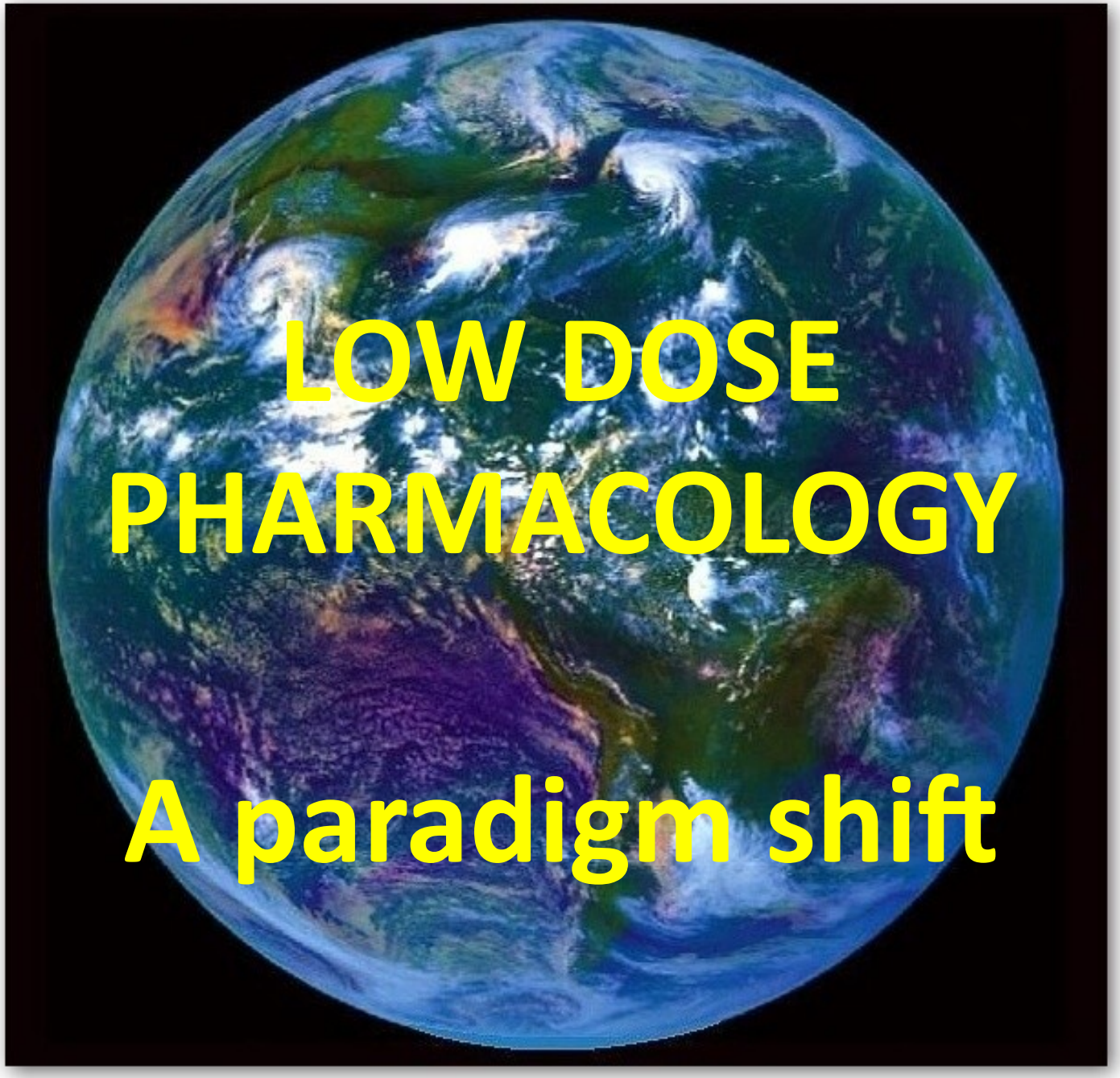

…not only us. A world trend

CMAJ

ANALYSIS

Is bigger better? An argument for very low starting doses

James P. McCormack PharmD, G. Michael Allan MD, Adil S. Virani PharmD

VIEWPOINT

Low drug doses may improve outcomes in chronic disease

Simon B Dimmitt and Hans G Stampfer

Chronic diseases are creating a growing burden of ill health as populations age[1] and become more obese,[2] and as survival from many conditions improves. Long-term pharmacotherapy is used increasingly to control symptoms and slow disease progression. Unfortunately, there is a dearth of reliable information about drug dosages for, and outcomes of, long-term treatment of physical and mental illness. Dosages recommended in clinical practice guidelines are usually derived from studies of acute and severe cases of disease. There is little research to support the application of these guidelines to long-term treatment regimens and to the large number of patients with mild cases of disease who are managed in primary care. In addition, few studies specifically address dosage.

carries the risk of adverse drug

ABSTRACT

- The relationship between drug dose and clinical outcome has not been established for many medications used to treat chronic disease. Evidence is emerging that chronic diseases can be treated effectively with low doses.
- Adverse drug reactions account for significant morbidity and mortality and are generally dose related.
- Optimal drug dose — the best balance of benefit and risk — varies between individuals and may change over time. When treating chronic disease it is important to establish and maintain the optimal dose for each patient by close clinical monitoring.

MJA 2009; 191: 511–513

BMJ Journals | BETA VERSION

Annals of the Rheumatic Diseases

Home / Archive / Volume 74, Issue 4

Letter

Rapid induction of clinical remission by low-dose interleukin-2 in a patient with refractory SLE

Jens Y Humrich1, Caroline von Spee-Mayer1, Elise Siegert1, Tobias Alexander1, Falk Hiepe1, Andreas Radbruch2, Gerd-Rüdiger Burmester1, Gabriela Riemekasten1

frontiers in Immunology

MINI REVIEW
published: 01 April 2021
doi: 10.3389/fimmu.2021.648408

Low-Dose IL-2 Therapy in Autoimmune and Rheumatic Diseases

*Hanna Graßhoff, Sara Comdühr, Luisa R. Monne, Antje Müller, Peter Lamprecht, Gabriela Riemekasten and Jens Y. Humrich**

Department of Rheumatology and Clinical Immunology, University Hospital Schleswig-Holstein Lübeck, Lübeck, Germany

The Journal of Immunology

This information is current as of October 17, 2022.

Low-Dose IL-2 Therapy in Transplantation, Autoimmunity, and Inflammatory Diseases

Maryam Tahvildari and Reza Dana

J Immunol 2019; 203:2749-2755; ;
doi: 10.4049/jimmunol.1900733
http://www.jimmunol.org/content/203/11/2749

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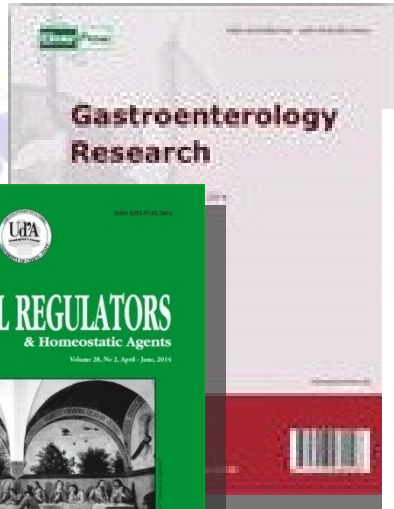
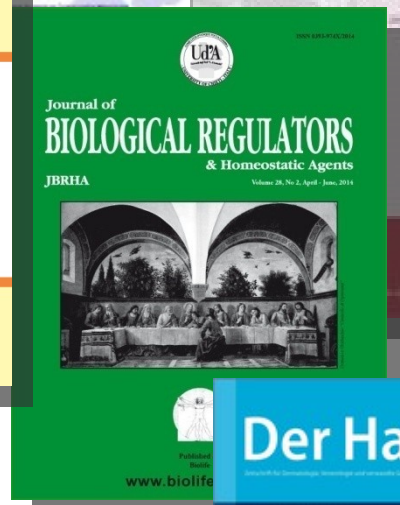
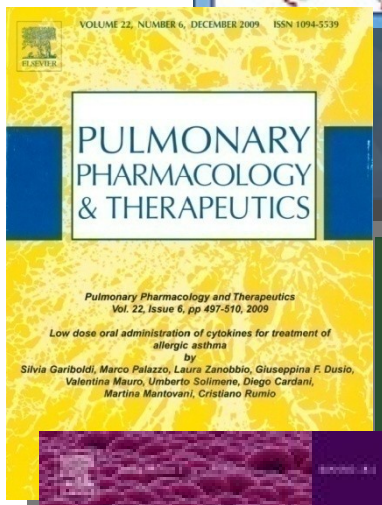
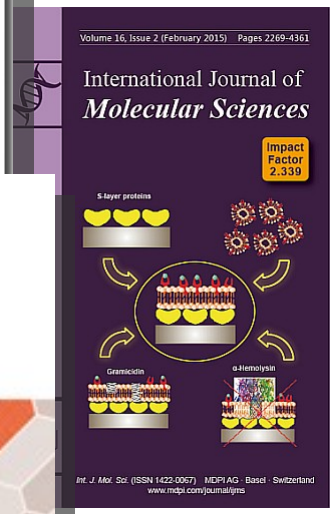
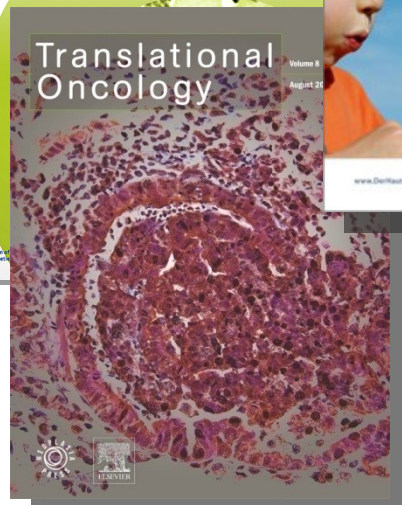
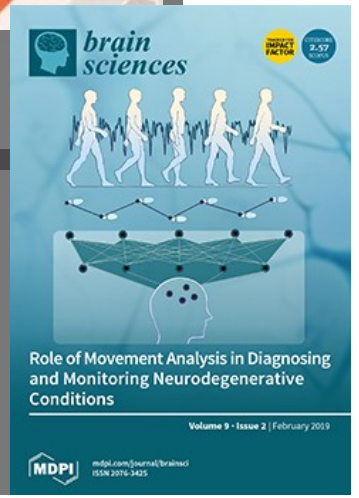






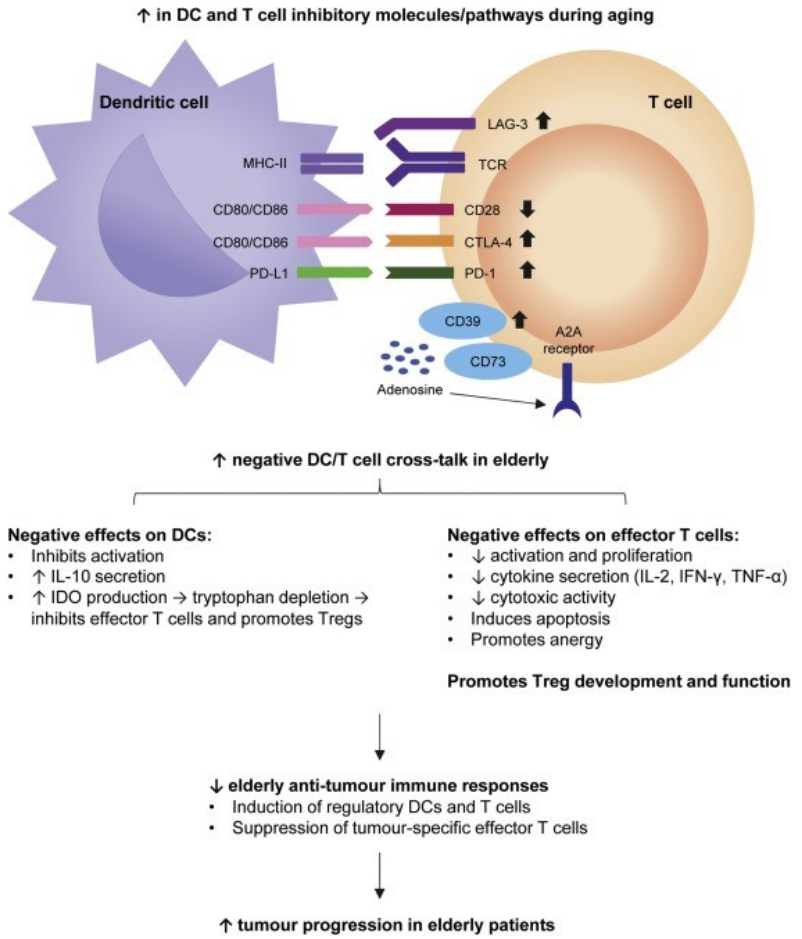






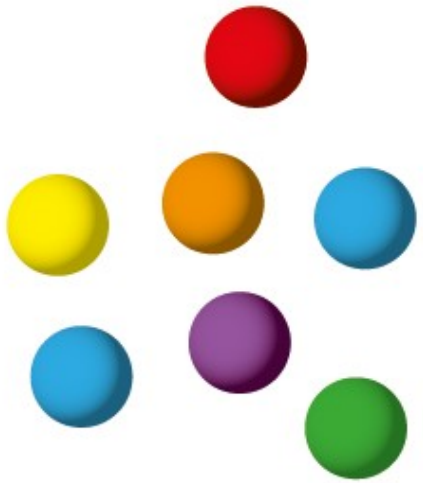
Why *Low Dose Cytokine Therapy* for a healthy longevity?

In a **complex system**
an impairment in the **cross-talk between cells** can be at the origin of the aging process as well as the disease onset.



Wagner JUG, Dimmeler S. Cellular cross-talks in the diseased and aging heart. J Mol Cell Cardiol. 2020 Jan;138:136-146.

Reductionistic approach vs Systemic approach



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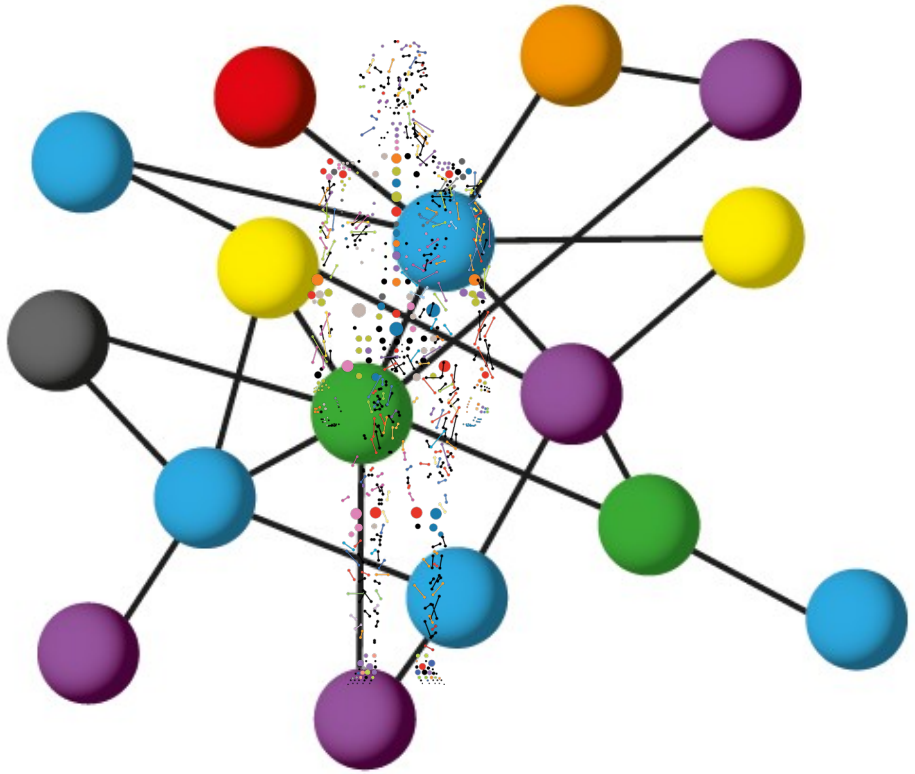
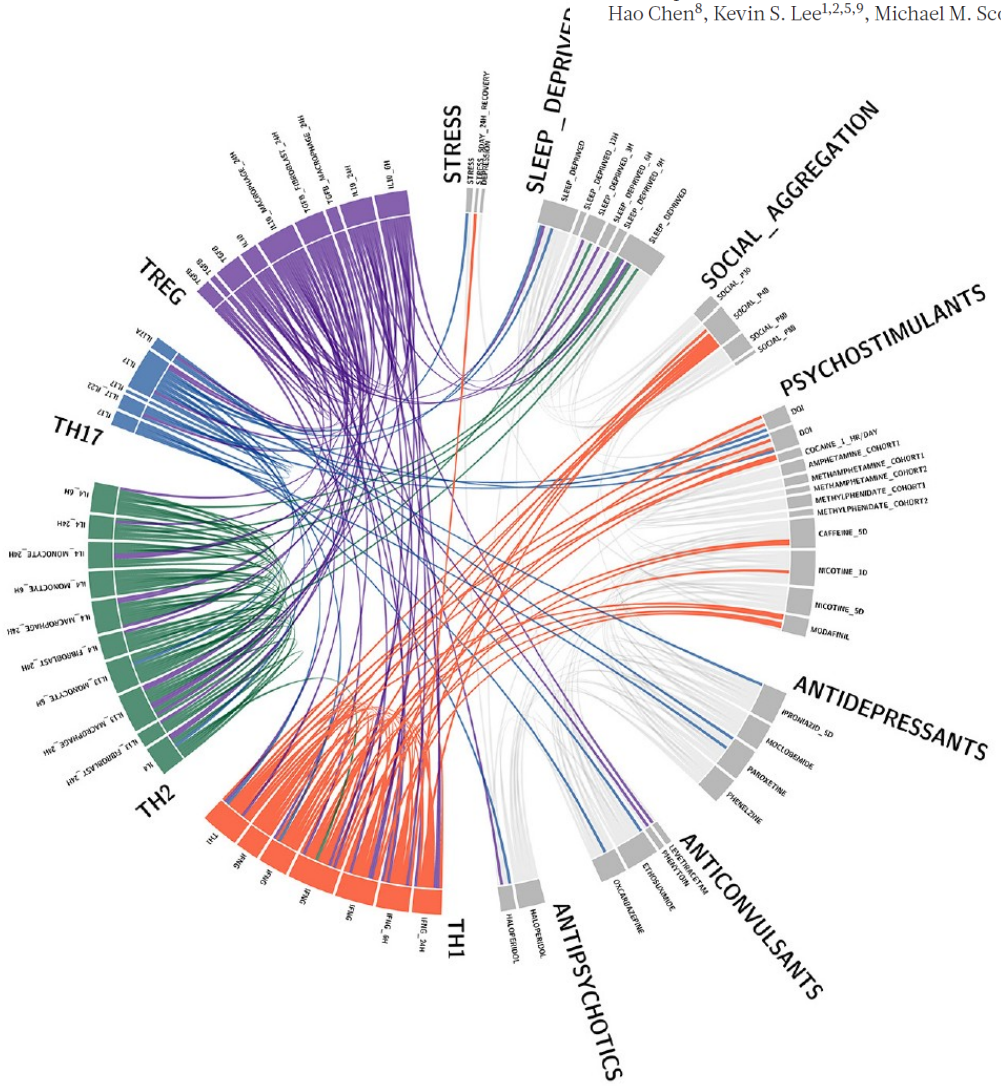


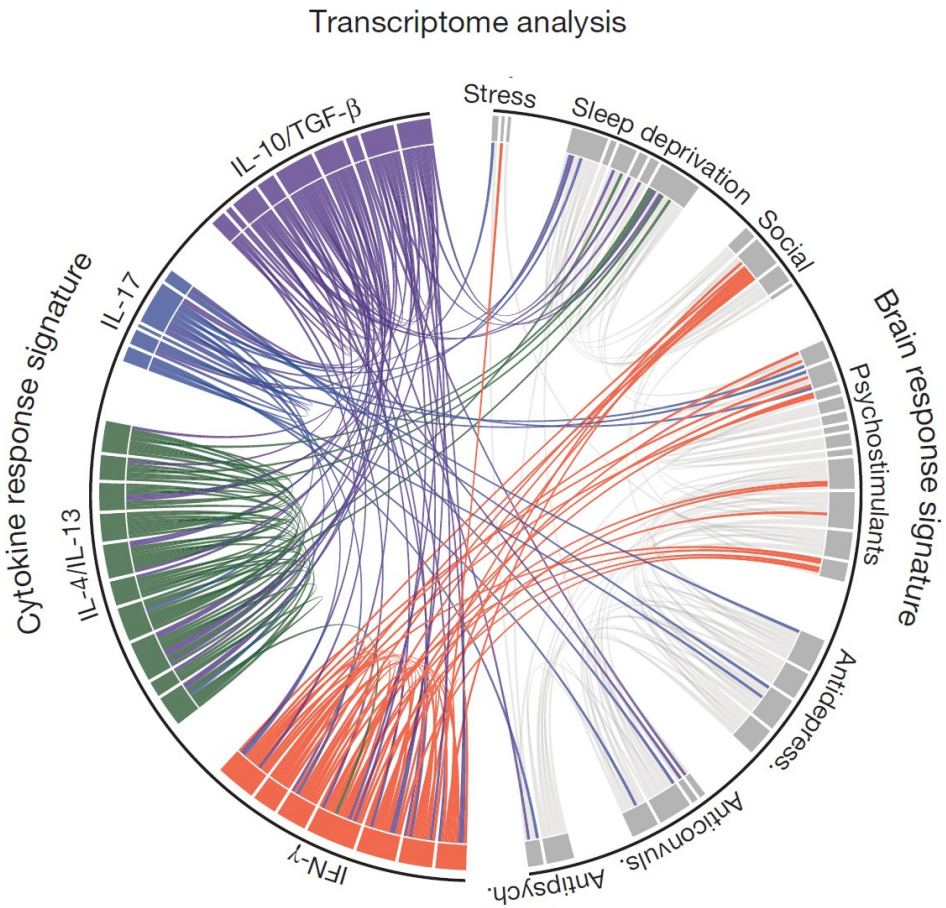
Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet*. 2011;12(1):56-68. doi:10.1038/nrg2918

doi:10.1038/nature18626

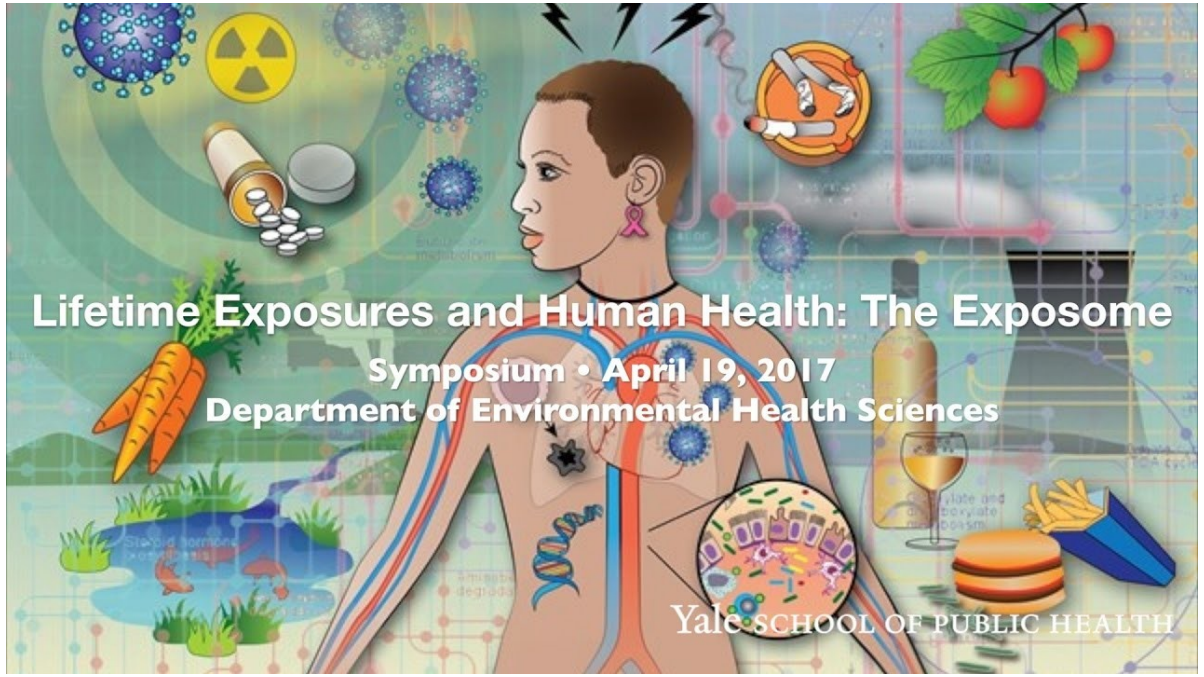
Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour

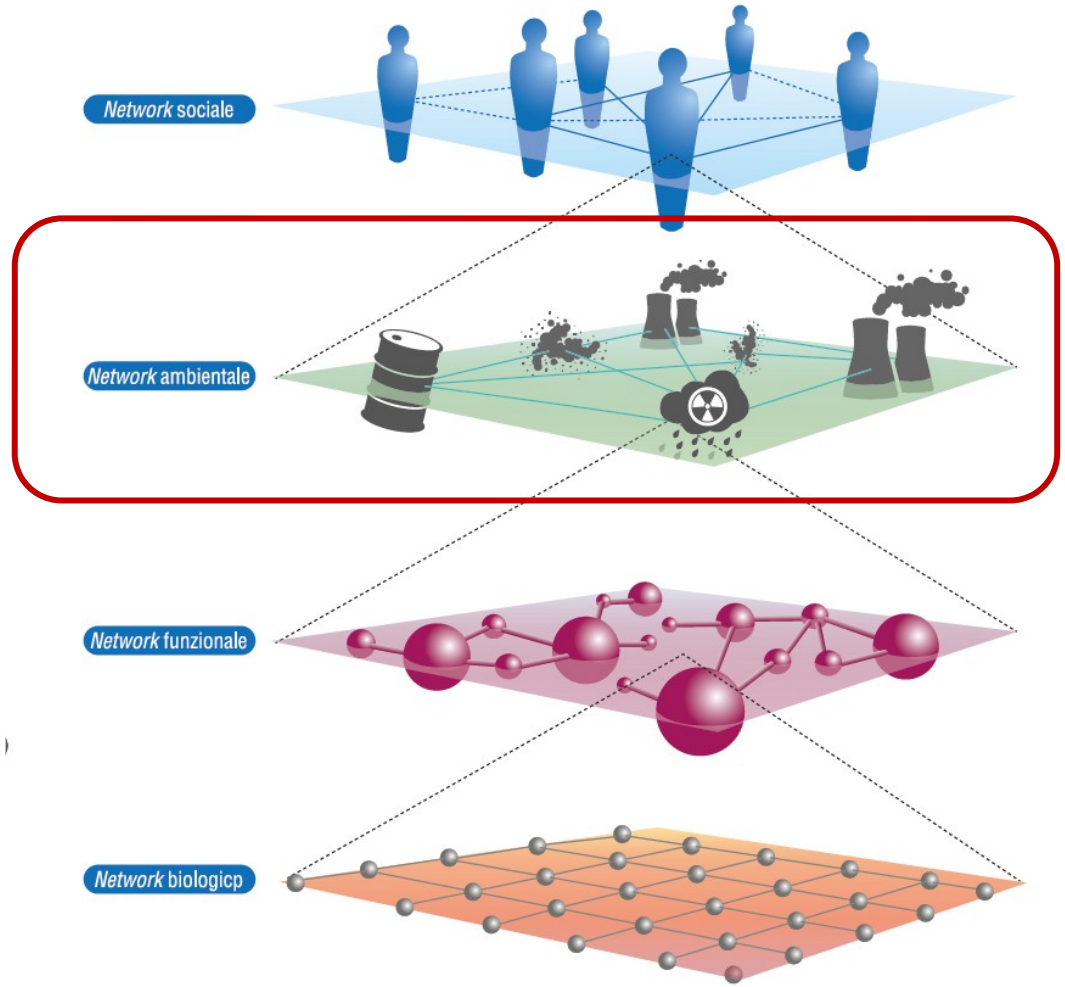
Anthony J. Filiano[1,2], Yang Xu[3], Nicholas J. Tustison[4], Rachel L. Marsh[1,2], Wendy Baker[1,2], Igor Smirnov[1,2], Christopher C. Overall[1,2], Sachin P. Gadani[1,2,5,6], Stephen D. Turner[7], Zhiping Weng[8], Sayeda Najamussahar Peerzade[3], Hao Chen[8], Kevin S. Lee[1,2,5,9], Michael M. Scott[5,10], Mark P. Beenhakker[5,10], Vladimir Litvak[3]* & Jonathan Kipnis[1,2,5,6]*





Systems Medicine (Network Medicine)





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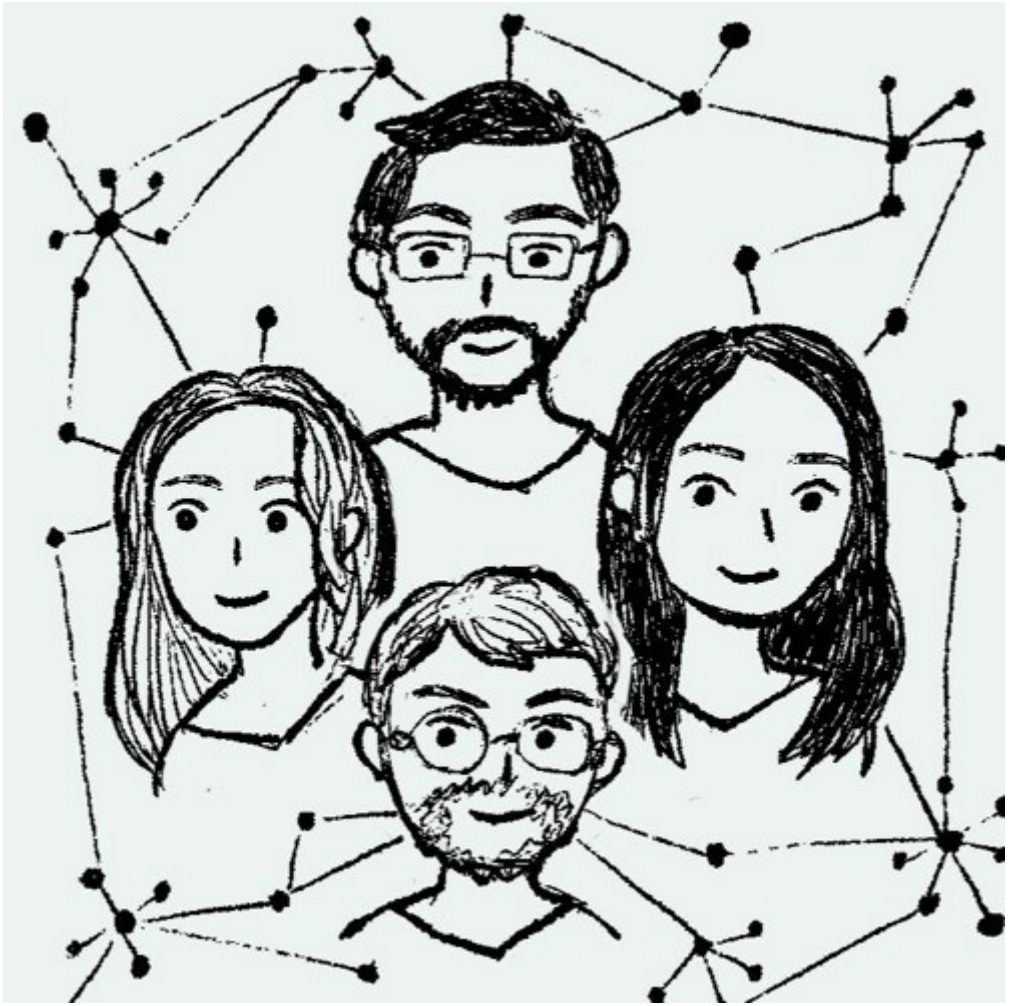

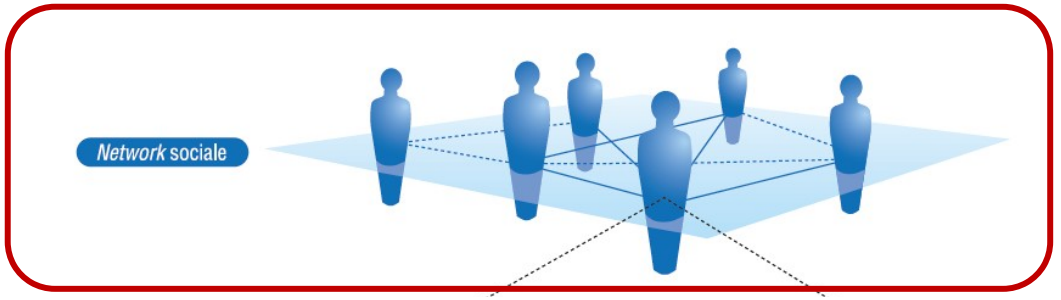

According to the Systems Theory, the mind is not an entity but a process, the process of life.

The living beings' activity of organization, at all the levels where life shows itself, is mental activity.

The interactions of a living being (vegetal, animal, human) with its enviroment are cognitive interactions, i.e. mental.

(F. Capra, La rete della vita 1996)

Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet*. 2011;12(1):56-68. doi:10.1038/nrg2918

«NEGATIVE THOUGHTS» AND LOW-GRADE CHRONIC INFLAMMATION

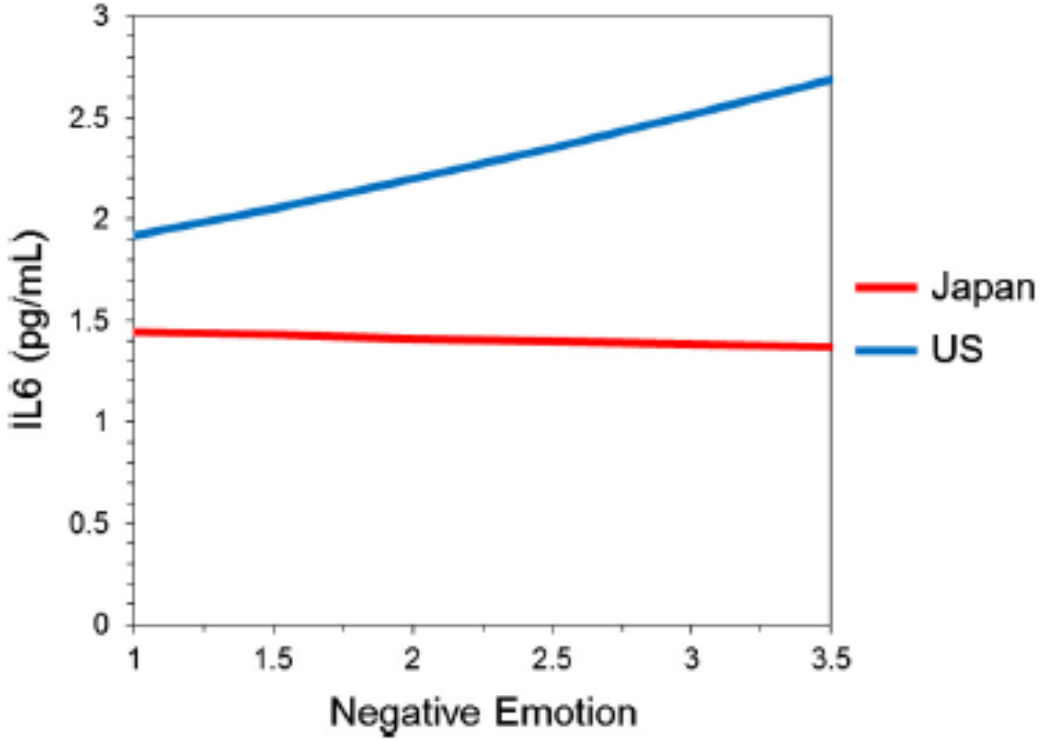

Fig. 1. Cultural moderation of the association between negative emotions and IL-6 after controlling for gender, age, and years of education, positive emotions, neuroticism, extraversion, smoking status, alcohol consumption, the number of chronic conditions linked to inflammation, and log-transformed BMI (Model 5). Negative emotions were rated on a 5-point rating scale: *none of the time* (1), *a little of the time* (2), *some of the time* (3), *most of the time* (4), and *all the time* (5). Negative emotions predicted IL-6 in the United States, $b = 0.06$, S.E. = 0.02, $t(1363) = 2.68$, $p = .001$, but not in Japan, $b = -0.01$, S.E. = 0.03, $t(1363) = 0.35$, $p = .73$.

Miyamoto Y. et al. Negative emotions predict elevated interleukin-6 in the United States but not in Japan. Brain, Behavior, and Immunity 2013

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Symposium
SYSTEMS MEDICINE
Integration models in clinical practice and new therapeutic solutions

Held in Milan, at the University of Milan, on 5 May 2022

under the auspices of:

World Health Organization (WHO) Collaborating Center for Integrative Medicine
P.R.M. (International Academy of Physiological Regulating Medicine)
FEMTEC (Worldwide Federation of Hydrotherapy and Climatotherapy)

under the patronage of:

Italian Ministry of Health
FNOMCeO (National Federation of the Associations of Surgeons and Dentists)

THE SPEAKERS

PROF. GIUSEPPE BELLELLI
Full Professor of Geriatrics-Internal Medicine, Milan-Bicocca University

PROF. SERGIO BERNASCONI
Full Professor of Paediatrics, Former Director of Paediatric Clinics at the Universities of Modena and Parma

PROF. GIANNI BONA
Full Professor of Paediatric Clinic, Former Director of the Paediatric Clinic, University of Eastern Piedmont

PROF. MARIO CLERICI
Full Professor of Immunology and Immunopathology, University of Milan

PROF. GIUSEPPE DE BENEDITTIS
Associate Professor of Neurosurgery, University of Milan

DR. MARCO DEL PRETE
President P.R.M. Academy
(International Academy of Physiological Regulating Medicine)

PROF. FABIO ESPOSITO
Full Professor of Physical Exercise Sciences and Sport, University of Milan

PROF. VASSILIOS FANOS
Full Professor of Paediatrics, University of Cagliari

PROF. ALESSANDRO GENAZZANI
Associate Professor of Obstetrics and Gynaecology, University of Modena-Reggio Emilia

PROF. PAOLO INGHILLERI
Full Professor of Social Psychology, University of Milan

PROF. DAVIDE LAURO
Full Professor of Endocrinology, University of Rome "Tor Vergata"

PROF.SSA JEANETTE MAIER
Full Professor of General and Clinical Pathology, University of Milan

PROF. STEFANO MASIERO
Full Professor of Physical and Rehabilitation Medicine, University of Padua

PROF. MARCO MATUCCI CERINIC
Full Professor of Rheumatology, University of Florence

PROF. ALBERTO MIGLIORE
Director of the UOS (Simple Operative Unit) of Rheumatology, San Pietro Fatebenefratelli Hospital, Rome

PROF. EMILIO MINELLI
WHO *(World Health Organization)* Expert Advisory, Panel Member Clin. Research on Integrative Medicine

PROF. ANDREA MODESTI
Full Professor of General Pathology, University of Rome "Tor Vergata"

PROF. CLAUDIO MOLINARI
Associate Professor of Human Physiology, University of Eastern Piedmont, Vercelli

PROF. VALTER SANTILLI
Full Professor of Physical and Rehabilitative Medicine, University of Rome "La Sapienza"

PROF. UMBERTO SOLIMENE
Direttore *WHO (World Health Organization) Collaborating Center for Integrative Medicine - State University of Milan*

HAVE APPROVED *THE MILAN DECLARATION 2022 – NEW GOALS FOR MEDICINE*
WHICH OUTLINES THE CURRENT AND FUTURE SOCIAL AND HEALTH SCENARIOS THAT MAKE NECESSARY TO DEFINE A NEW PARADIGM OF MEDICINE.

E cellula ad hominem

DICHIARAZIONE DI MILANO 2022
NUOVI OBIETTIVI DELLA MEDICINA

Talking about a Complex System

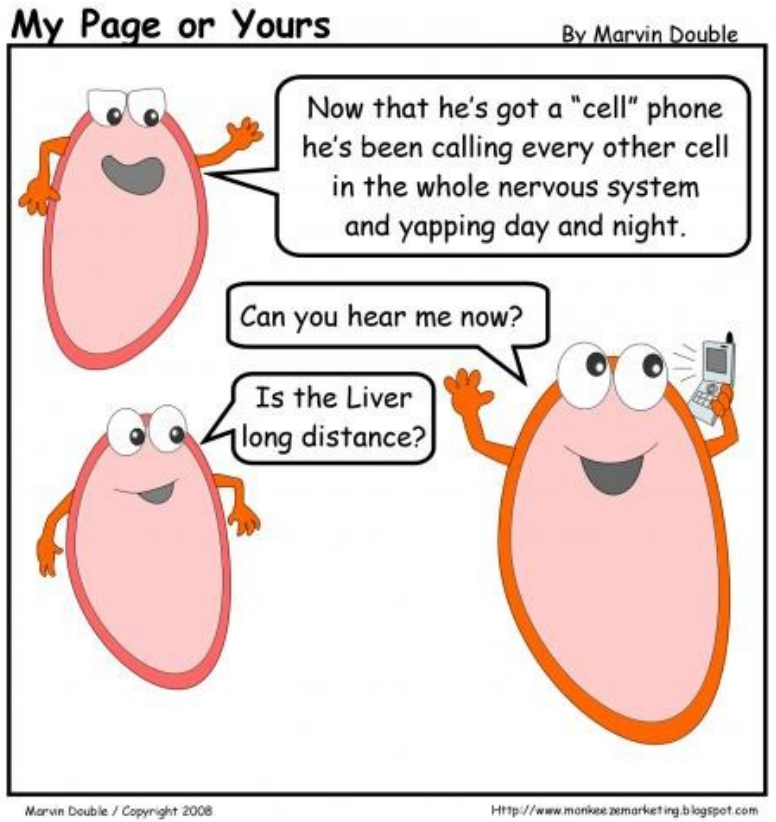
THE HUMAN BODY
IS A NETWORK
OF NETWORKS

40.000 billion cells

Bianconi E, Piovesan A, Facchin F, Beraudi A, Casadei R, Frabetti F, Vitale L, et al. An estimation of the number of cells in the human body. Ann Hum Biol. 2013;40(6):463-71.

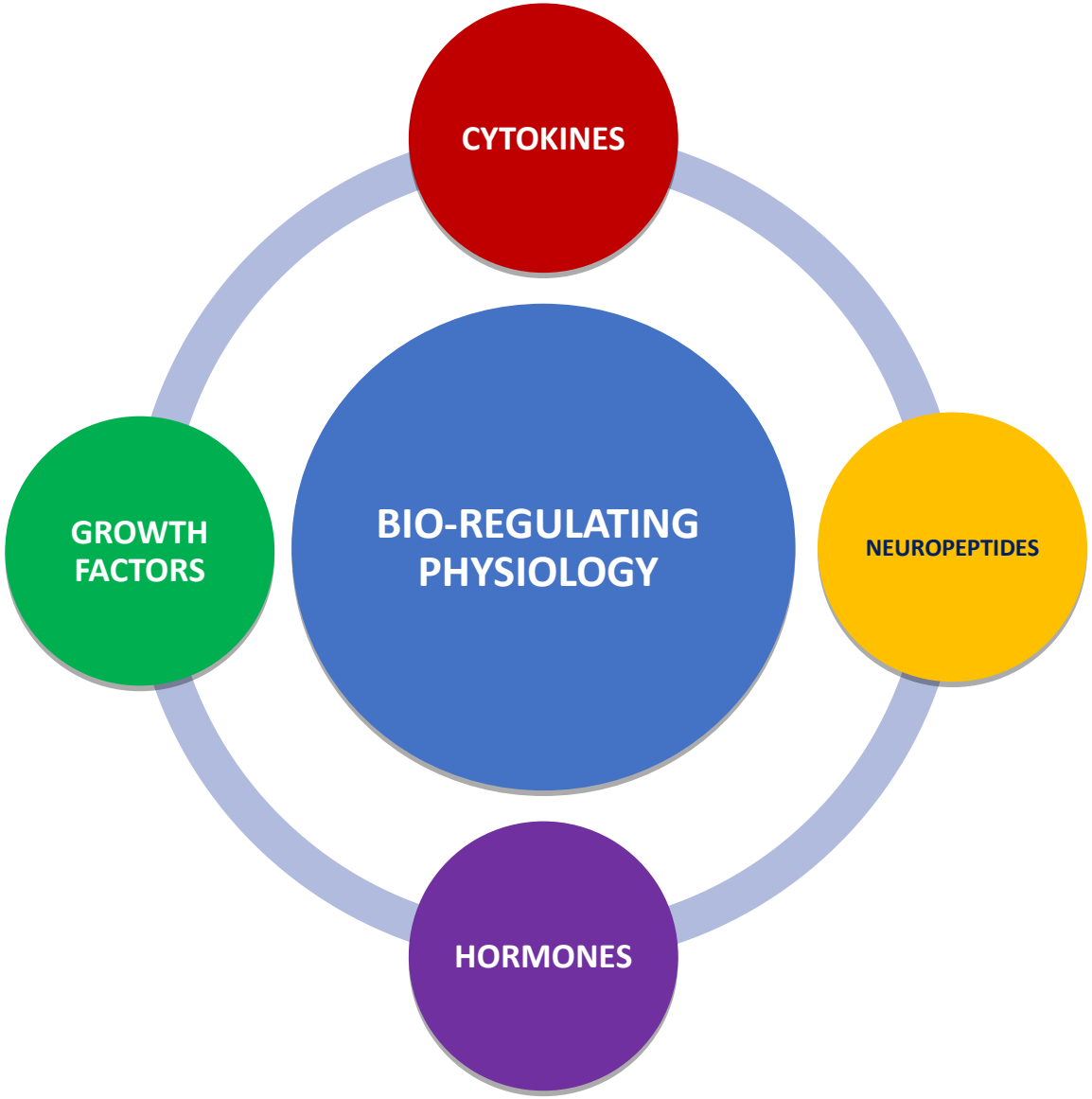
A Complex System

1. How do they talk?
2. Where do they talk?



SIGNALING MOLECULES-BASED LOW DOSE PHARMACOLOGY

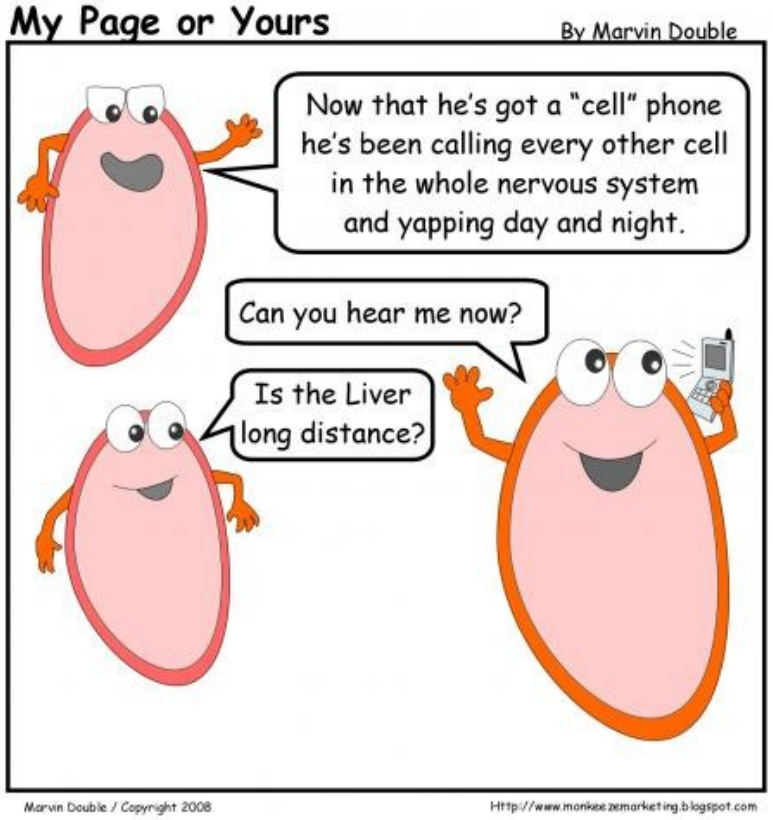
THE GREAT INNOVATION



Signaling Molecules

The Fundation for LDM

CYTYOKINES are MESSENGERS, THE WORDS used by the 3 homeostatic control systems (or functional networks) and BY THE CELLS to speak each other … and to lead the body physiology.

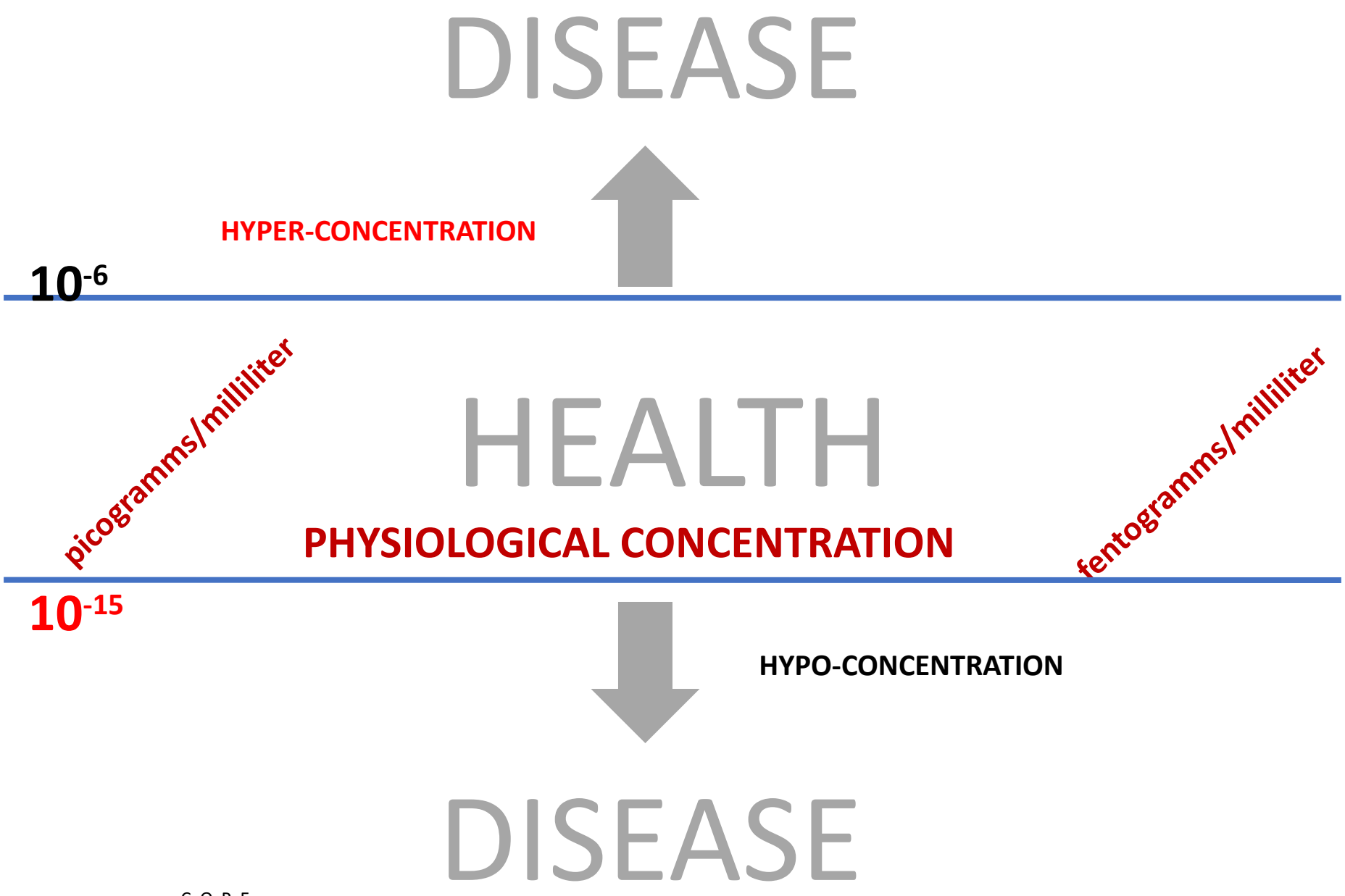


Signaling (Messenger) Molecules

The Foundation for Low Dose Pharmacology

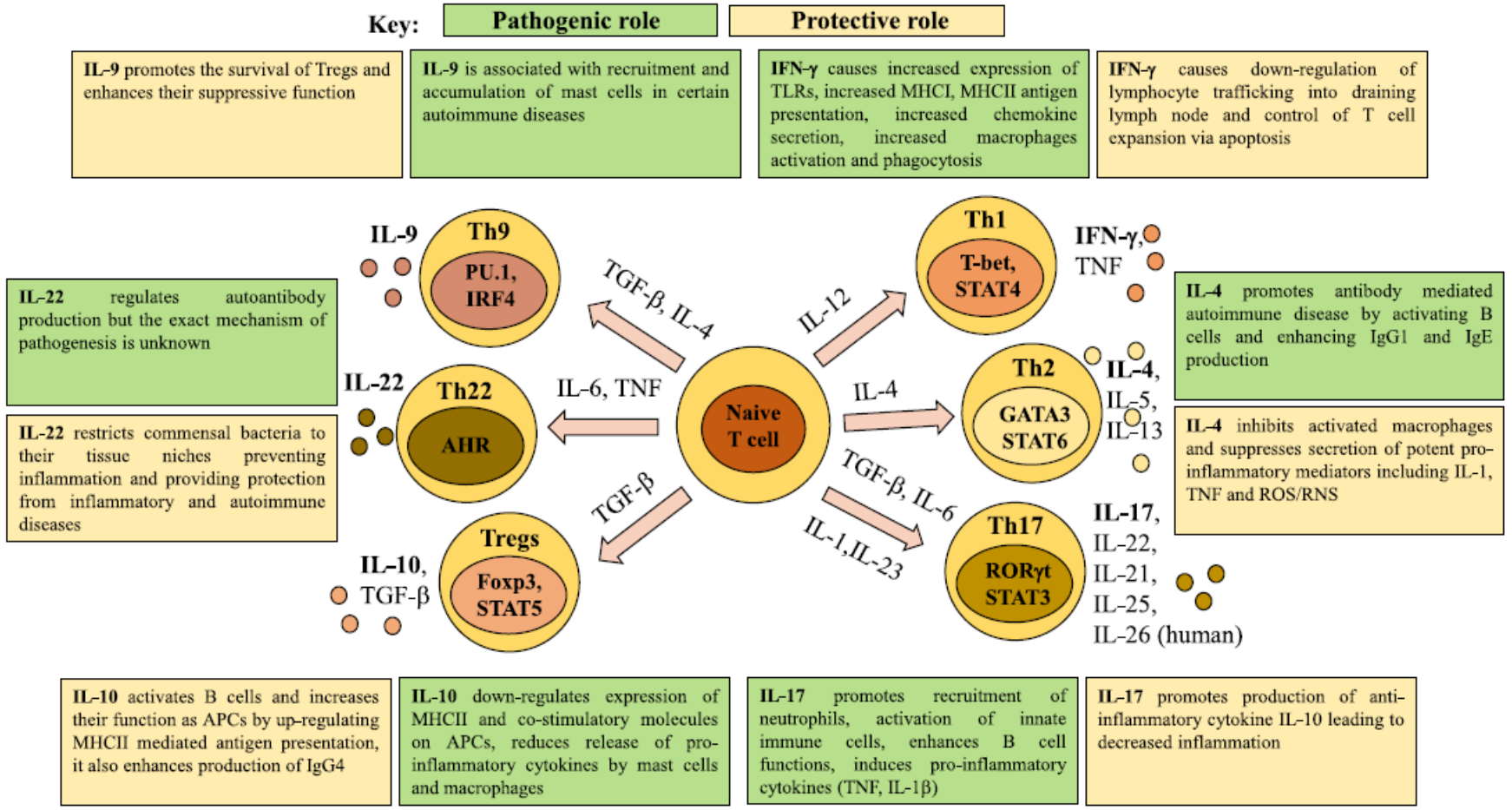
Cells  ***r at a very*** *sub-*

nanc *tion)*



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

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

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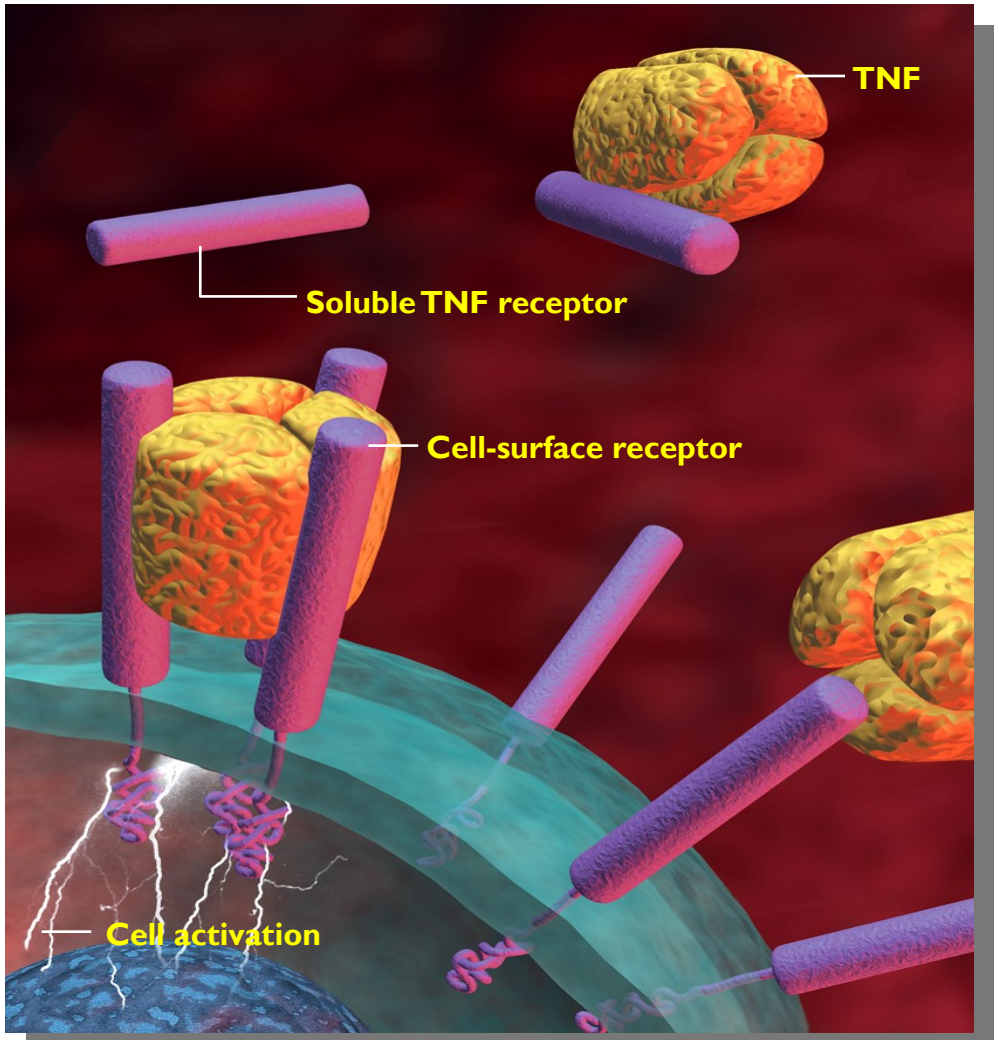
TRANS-MEMBRANE RECEPTORS
Up- and Down-Regulation



Jak-1: Tyrosine kinasis
STAT-1: Signal transducer and activator of transcription 1
SOCS-1:Suppressor of cytokin signaling 1

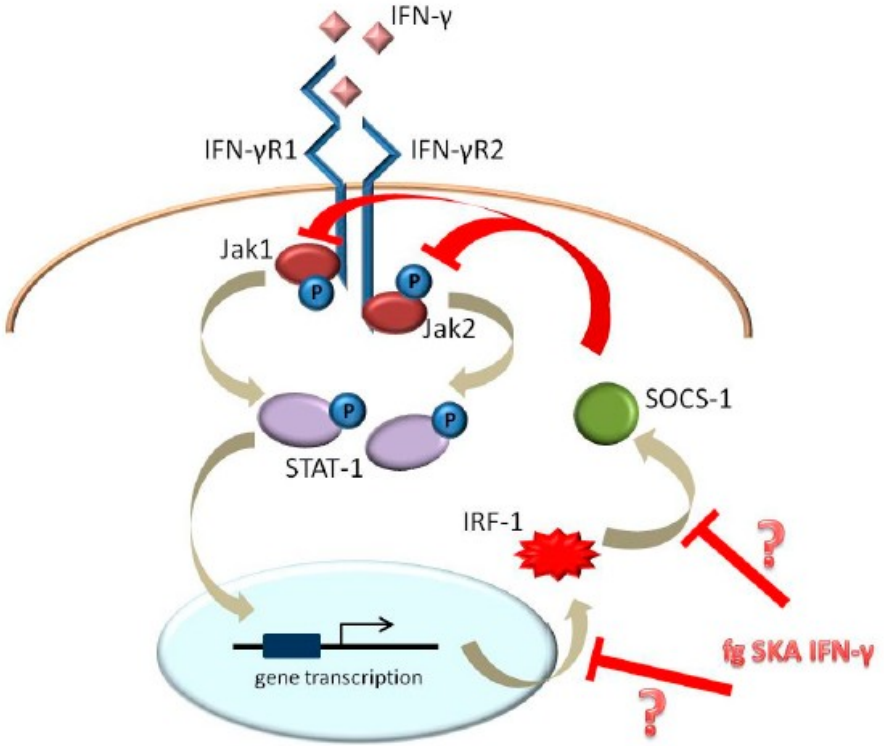
International Journal of *Molecular Sciences*

MDPI

Article

Femtograms of Interferon-γ Suffice to Modulate the Behavior of Jurkat Cells: A New Light in Immunomodulation

Sara Castiglioni [1,*], Vincenzo Miranda [2], Alessandra Cazzaniga [1], Marilena Campanella [2], Michele Nichelatti [3], Marco Andena [1] and Jeanette A. M. Maier [1]



GUNA Signaling Molecules

Drugs: Bio-Tech

Concentration: low dose (sub-nanomolar)

Preparation mode: SKA

- Bio-Tech – human recombinant in *E. Coli or in SF21 (Spodoptera frugiperda).*

The biological EFFECTS of LOW DOSES

brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy; claudio.molinari@med.uniupo.it (C.M.); vera.morsanuto@med.uniupo.it (V.M.); sara.ruga@uniupo.it (S.R.); felice.notte@uniupo.it (F.N.); mahitab.farghali@uniupo.it (M.F.); rebecca.galla@uniupo.it (R.G.)

* Correspondence: francesca.uberti@med.uniupo.it; Tel.: +39-0321-660653

Received: 26 February 2020; Accepted: 4 May 2020; Published: 9 May 2020

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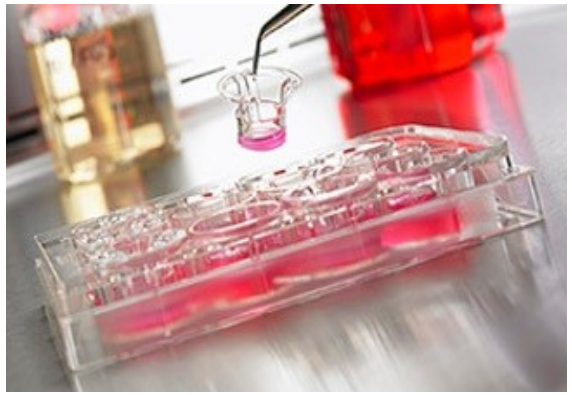

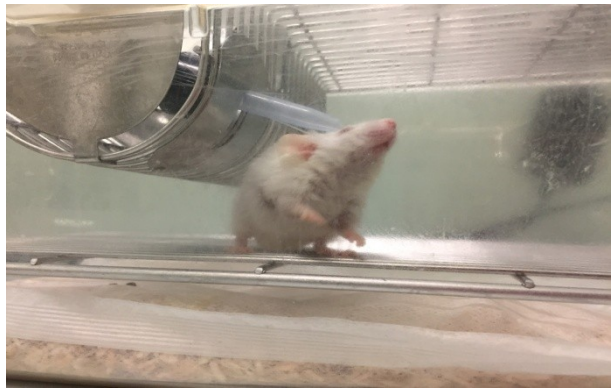

brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy; claudio.molinari@med.uniupo.it (C.M.); vera.morsanuto@med.uniupo.it (V.M.); sara.ruga@uniupo.it (S.R.); felice.notte@uniupo.it (F.N.); mahitab.farghali@uniupo.it (M.F.); rebecca.galla@uniupo.it (R.G.)
* Correspondence: francesca.uberti@med.uniupo.it; Tel.: +39-0321-660653

Received: 26 February 2020; Accepted: 4 May 2020; Published: 9 May 2020

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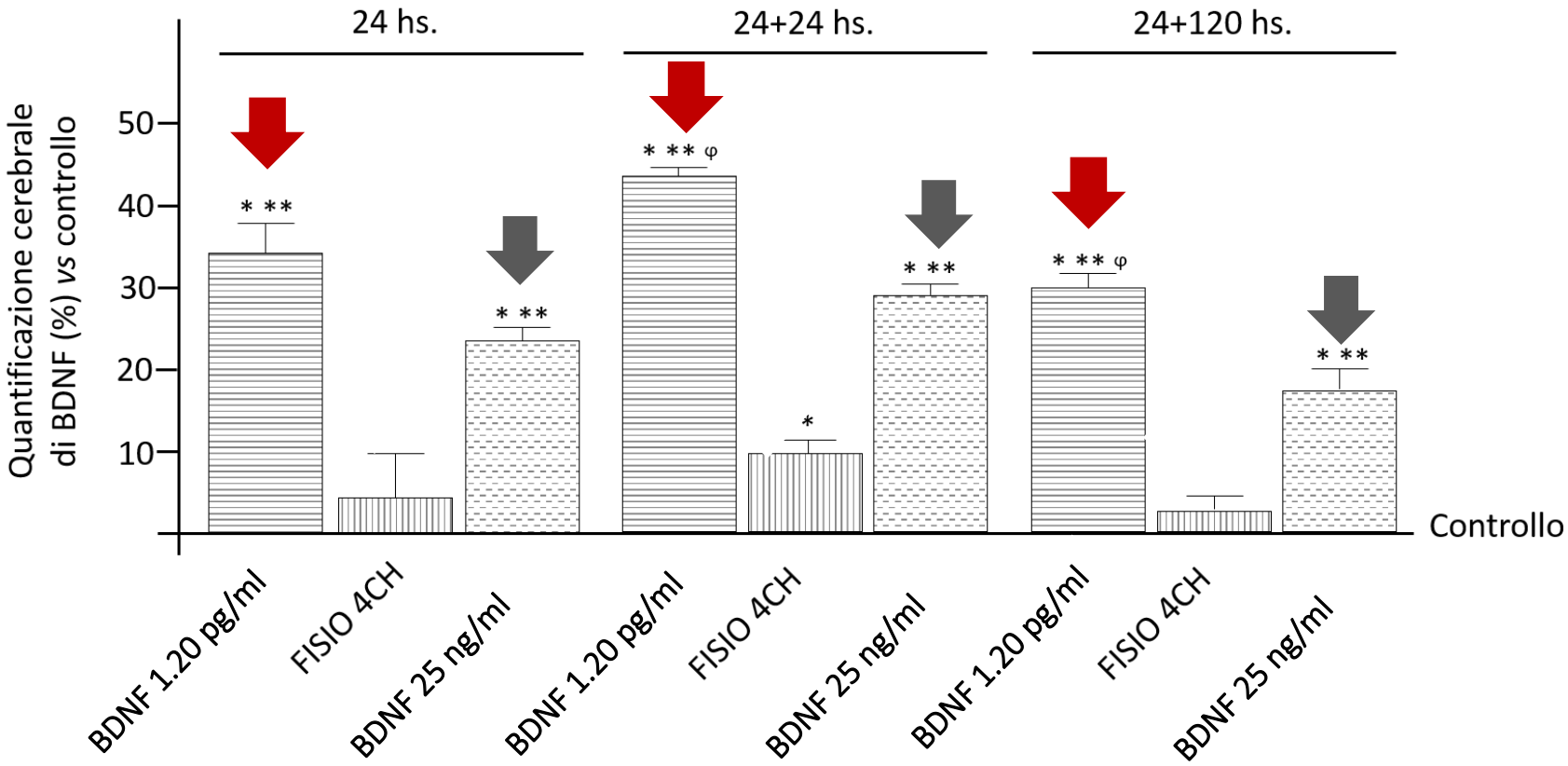
In vivo BRAIN BDNF QUANTIFICATION



12 monthh old mice type C57BL

brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy; claudio.molinari@med.uniupo.it (C.M.); vera.morsanuto@med.uniupo.it (V.M.); sara.ruga@uniupo.it (S.R.); felice.notte@uniupo.it (F.N.); mahitab.farghali@uniupo.it (M.F.); rebecca.galla@uniupo.it (R.G.)
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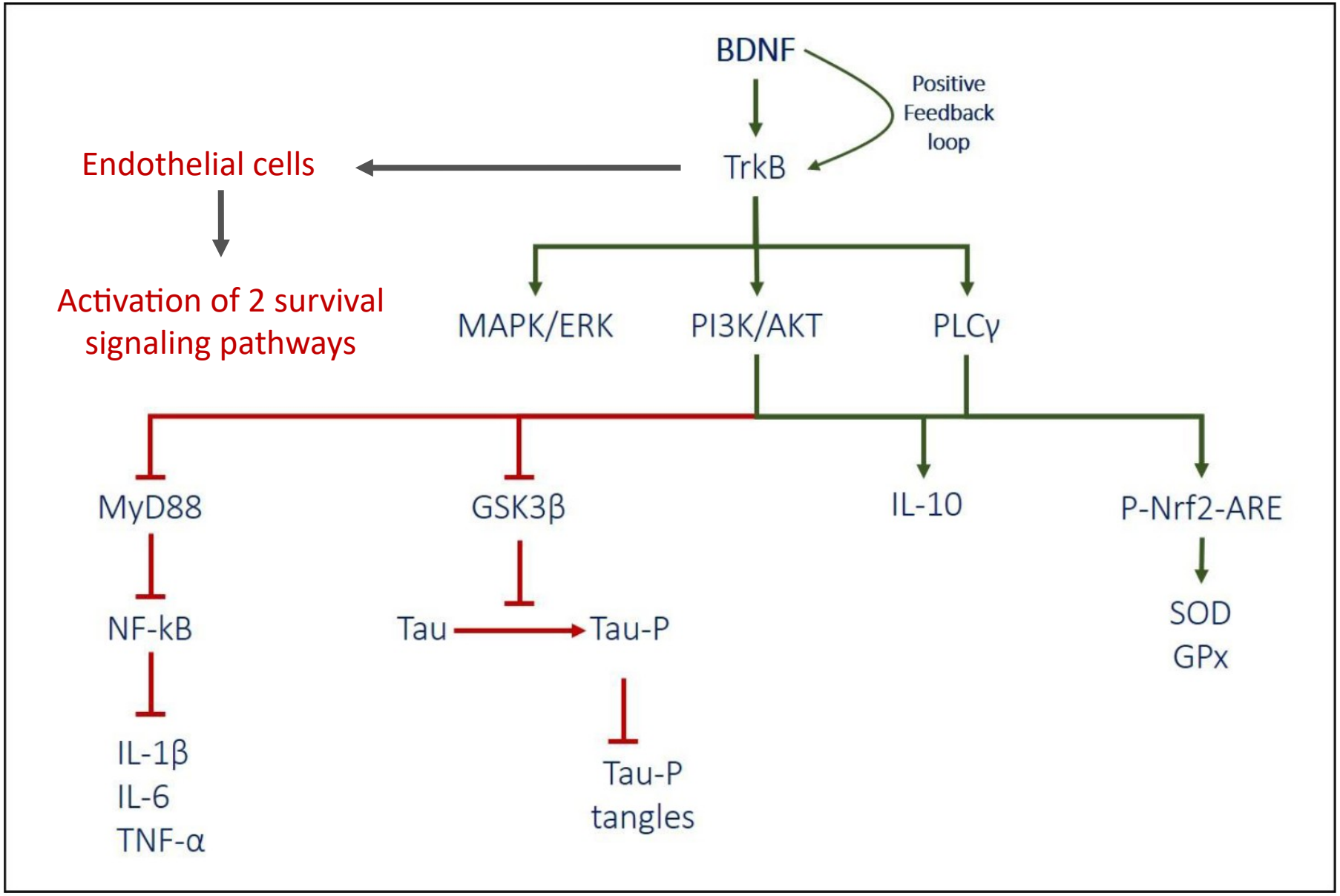
To verify whether the mechanism activated by BDNF solutions is the same as the one observed in cells during in vitro experiments, the effects of 1.2 pg/mL BDNF SKA and 25 ng/mL BDNF on some main markers were investigated by Western blot. Since BDNF is necessary for survival of neurons in the brain, after encoding by this gene its expression was investigated, as reported in Figure 9A. 1.2 pg/mL BDNF SKA and 25 ng/mL BDNF both at 24 h and 24 h plus 24 h were able to induce the expression of BDNF compared to control ($p < 0.05$), indicating a better influence of stimulations. Moreover, 1.2 pg/mL BDNF SKA at 24 h and 24 h plus 24 h caused a significant increase compared to and 25 ng/mL BDNF (about 50% and about 62%, respectively), indicating the induction of endogenous production of BDNF by physiological mechanism, as shown by the significant increase induced by 1.2 pg/mL BDNF SKA at 24 h plus 24 h with respect to at 24 h ($p < 0.05$, about 24%).



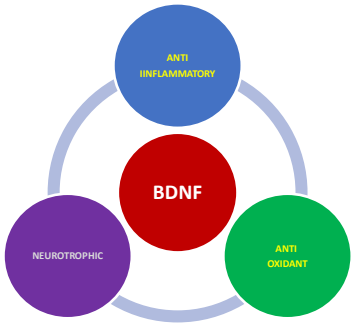
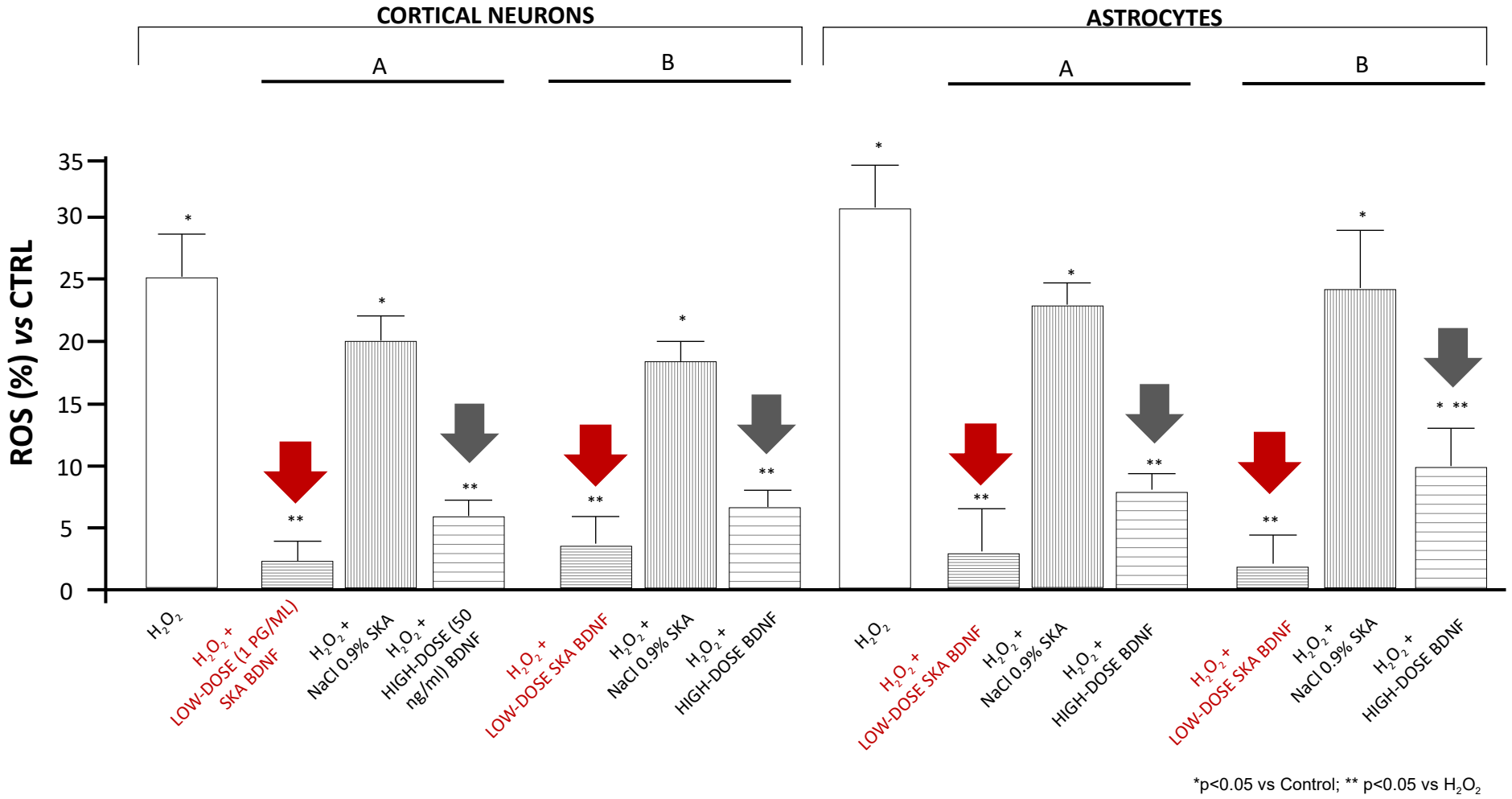


Figure 1 – Simplified synoptic scheme of the main pathways of BDNF's mediated cellular responses.

Amadio P, Baldassarre D, Sandrini L, Weksler BB, Tremoli E, Barbieri SS. Effect of cigarette smoke on monocyte procoagulant activity: Focus on platelet-derived brain-derived neurotrophic factor (BDNF). Platelets. 2016 Aug 5:1-6.

ROS REDUCTION

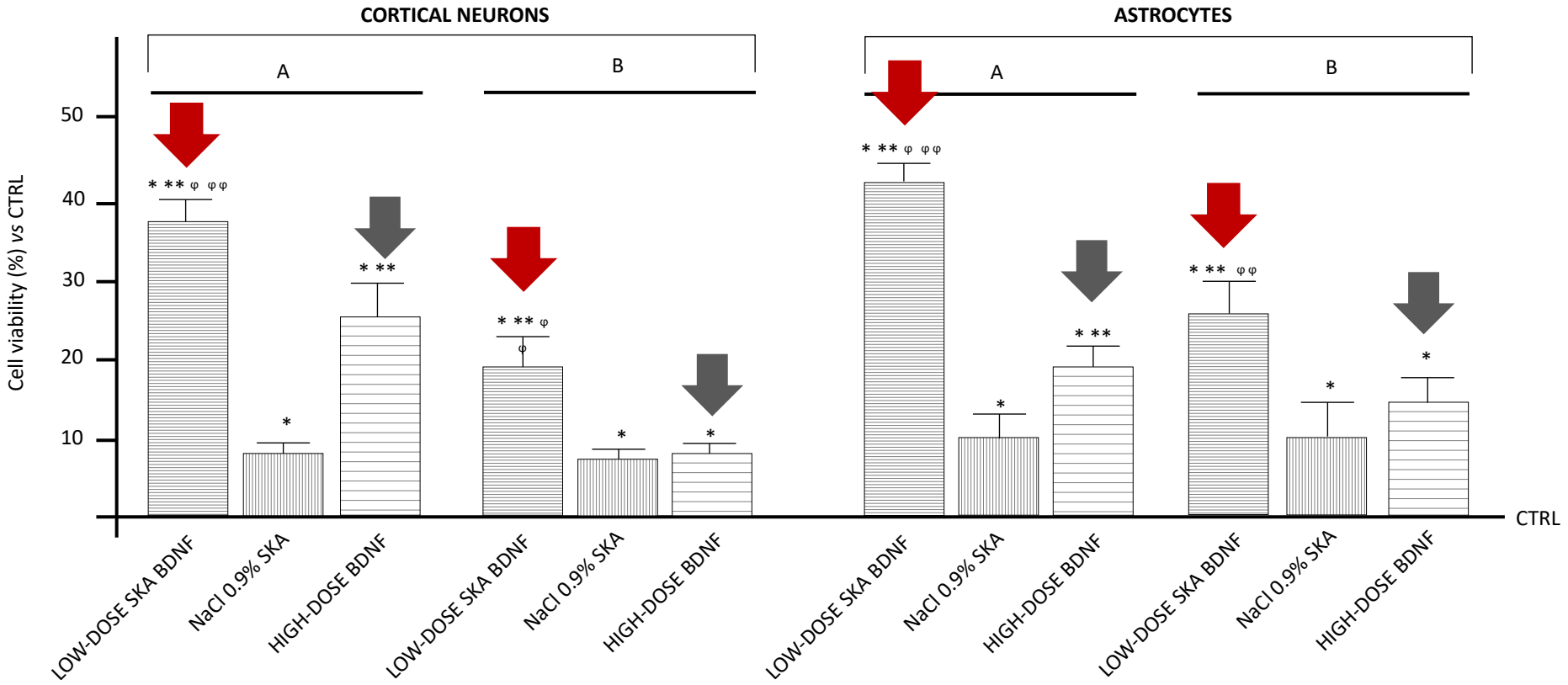


*p<0.05 vs Control; ** p<0.05 vs H_2O_2

Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

CELL VIABILITY

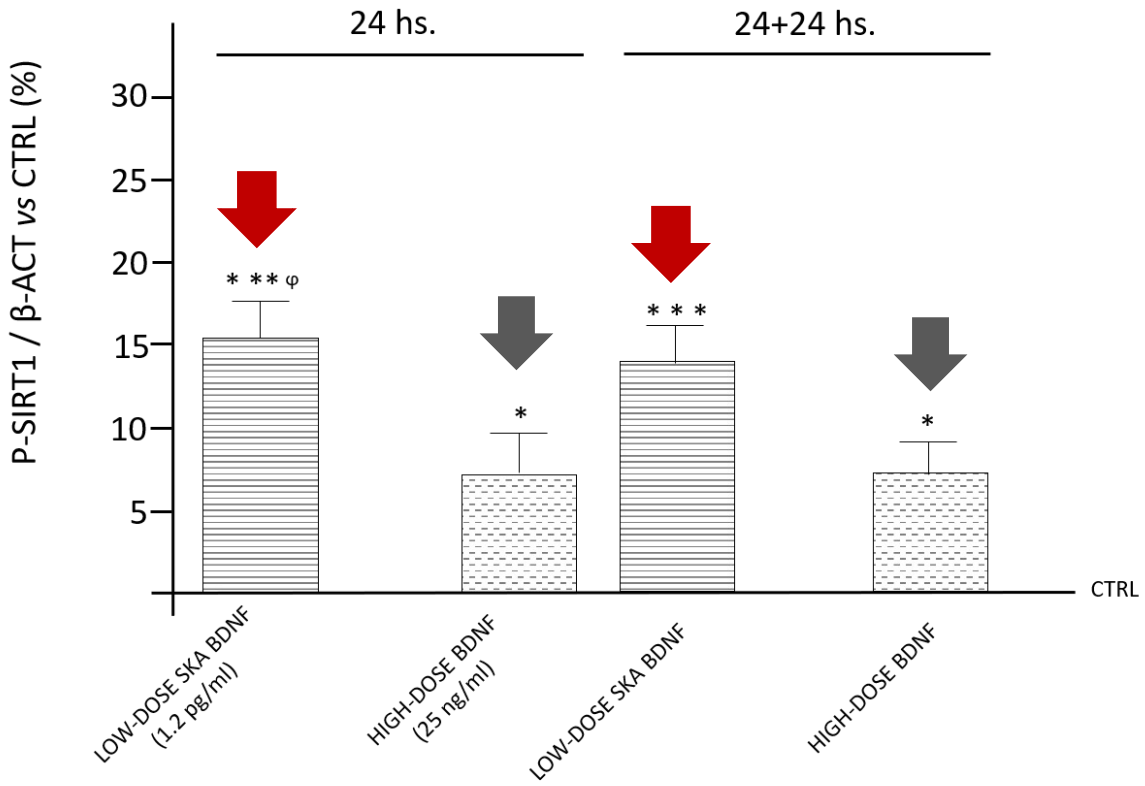


Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

*p<0.05 vs CTRL; ** p<0.05 vs NaCl 0.9% SKA ; $^{\varphi}$p<0.05 vs the same treatment in the two protocols; $^{\varphi\varphi}$ p<0.05 vs BDNF within the same protocol

P-SIRT1


24 hs.
24+24 hs.
P-SIRT1 / β-ACT vs CTRL (%)
30
25
20
15
10
5
* ** φ
*
* * *
*
CTRL
LOW-DOSE SKA BDNF (1.2 pg/ml)
HIGH-DOSE BDNF (25 ng/ml)
LOW-DOSE SKA BDNF
HIGH-DOSE BDNF

MIOKINES PRODUCED AND RELEASED BY THE MUSCLE DURING MUSCLE CONTRACTION

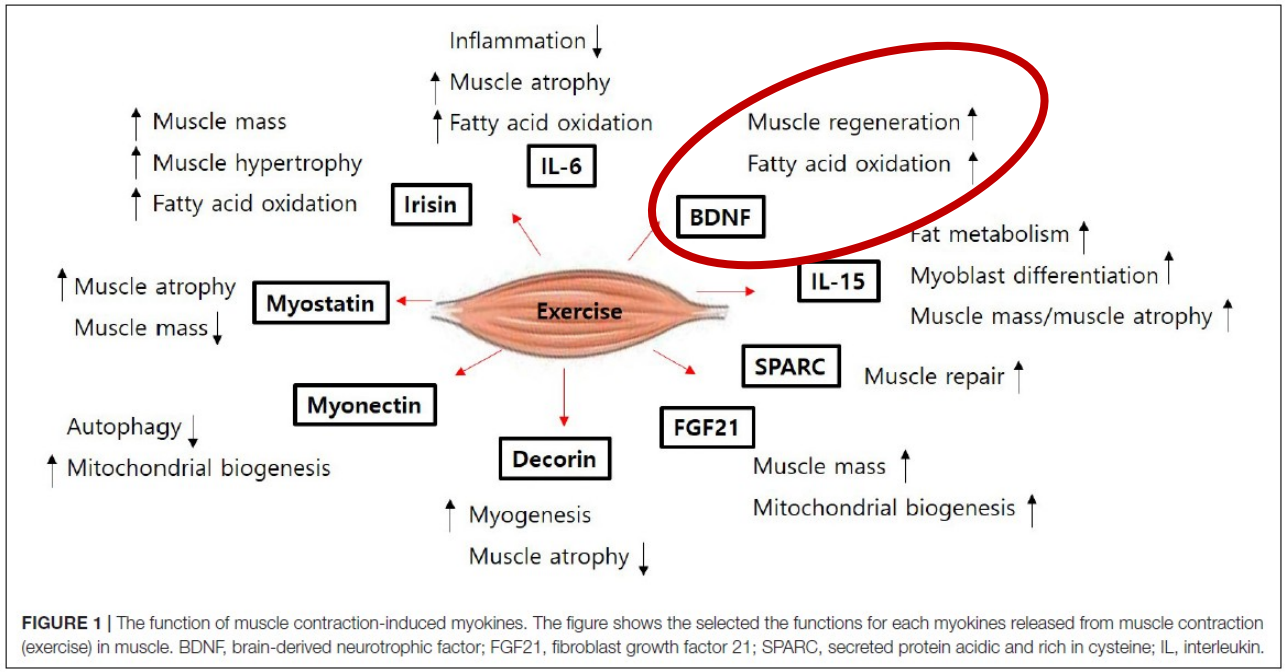


FIGURE 1 | The function of muscle contraction-induced myokines. The figure shows the selected the functions for each myokines released from muscle contraction (exercise) in muscle. BDNF, brain-derived neurotrophic factor; FGF21, fibroblast growth factor 21; SPARC, secreted protein acidic and rich in cysteine; IL, interleukin.

REVIEW ARTICLE

MCBS
Mol Cell Biomed Sci. 2018; 2(2): 38-47
DOI: 10.21705/mcbs.v2i2.32

Myokine Regulation as Marker of Sarcopenia in Elderly

I Gusti Putu Suka Aryana, Anak Agung Ayu Ratih Hapsari, Raden Ayu Tuty Kuswardhani

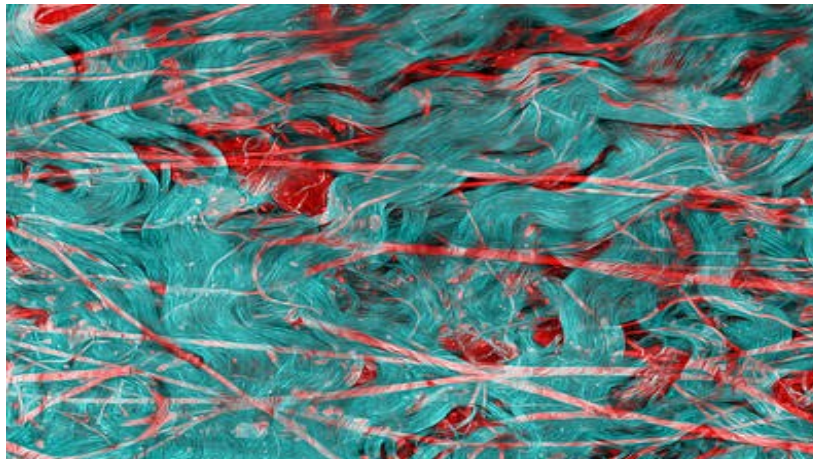
Geriatric Division, Internal Medicine Department, Faculty of Medicine, Udayana University, Sanglah Teaching Hospital, Denpasar, Indonesia

Lee JH, Jun HS. Role of Myokines in Regulating Skeletal Muscle Mass and Function. Front Physiol. 2019;10:42. Published 2019 Jan 30. doi:10.3389/fphys.2019.00042

A Complex System

1. How do they talk?

2. Where do they talk?



ECM and pathological inflammation

LOW GRADE CHRONIC INFLAMMATION (IL-6)

FIBROSIS

ECM RIGIDITY

AGING

TOXIC CONDITIONS

- UP-REGULATION OF PRO-INFLAMMATORY CYTOKINES
- OVEREXPRESSION OF ROS
- REDUCTION OF pH

EXPERIMENTAL AND THERAPEUTIC MEDICINE

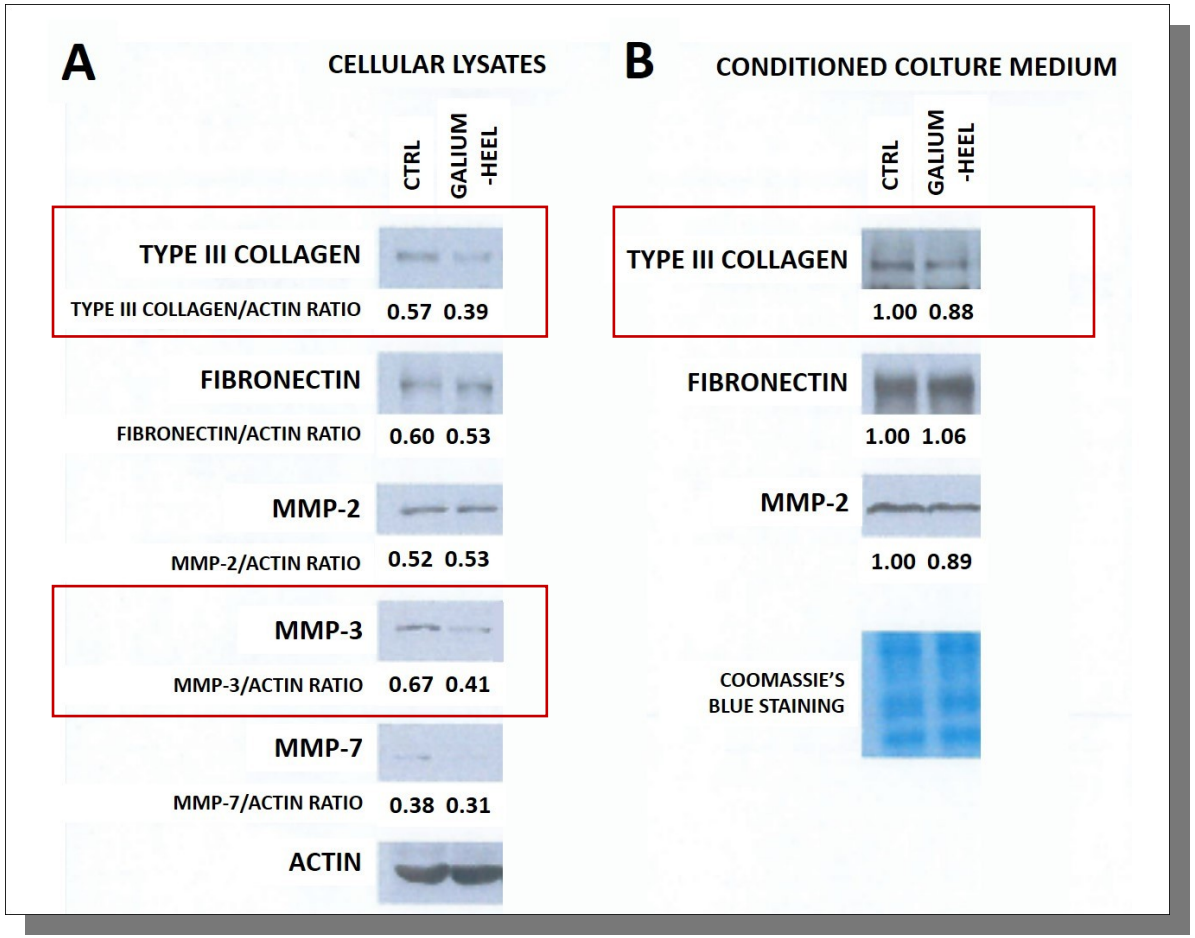
Effects of a natural multi-component compound formulation on the growth, morphology and extracellular matrix production of human adult dermal fibroblasts

MONICA BENVENUTO[1], ROSANNA MATTERA[1], MARTINO TONY MIELE[2], MARIA GABRIELLA GIGANTI[1], ILARIA TRESOLDI[1], LOREDANA ALBONICI[1], VITTORIO MANZARI[1], ANDREA MODESTI[1], LAURA MASUELLI[3*] and ROBERTO BEI[1*]

Departments of [1]Clinical Sciences and Translational Medicine and [2]Experimental Medicine, University of Rome 'Tor Vergata', I-00133 Rome; [3]Department of Experimental Medicine, University of Rome 'Sapienza', I-00161 Rome, Italy

Received January 30, 2019; Accepted July 16, 2019

DOI: 10.3892/etm.2019.7872



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AGING

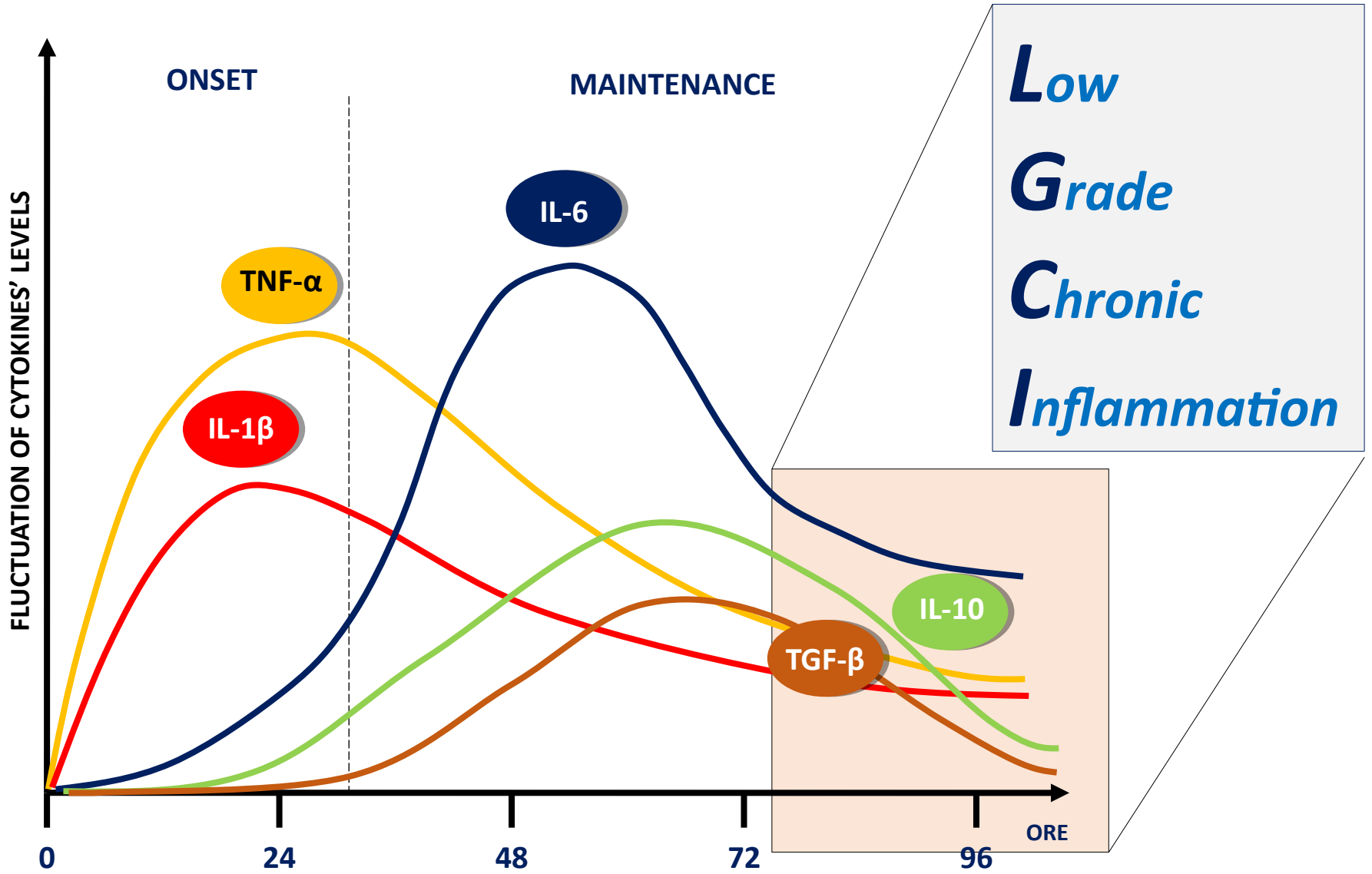
- **HIGH** LEVEL OF INFLAMMATION
- **HIGH** LEVEL OF OXIDATION
- **HIGH** LEVEL OF INTOXICATION

HOMEOSTASIS

- **HISTOLOGICAL DECLINE**
- **HORMONAL DECLINE**
- **IMMUNE DECLINE**

AGING

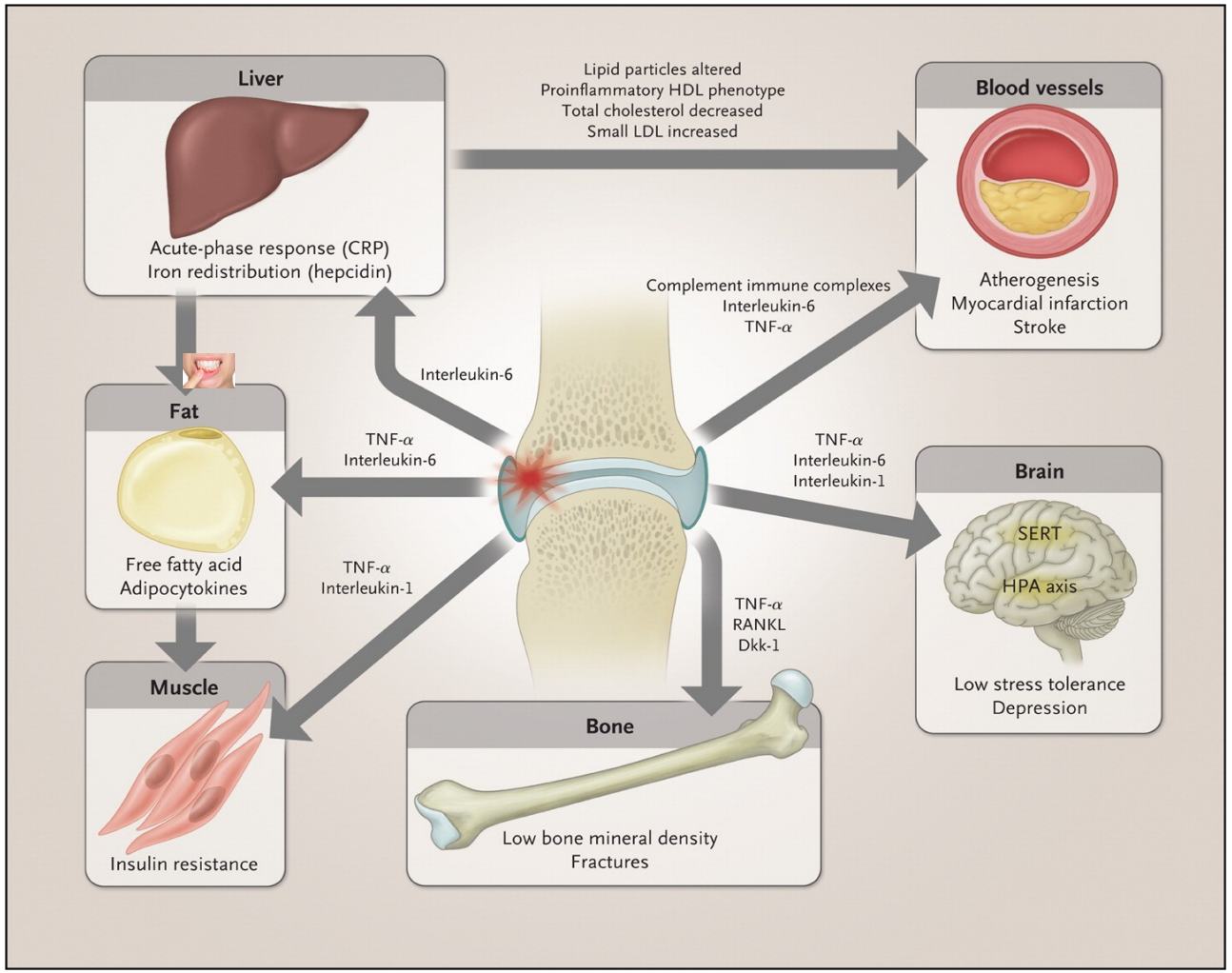
(LOW GRADE) CHRONIC Inflammatory Diseases



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

Modificata a fini didattici.

Mechanisms that contribute to the onset of long term complications in patients suffering from Rheumatoid Arthritis.



McInnes IB, Schett G. N Engl J Med 2011;365:2205-2219.

Immagine modificata a fini didattici

IL-2/IL-6 RATIO AND AGING

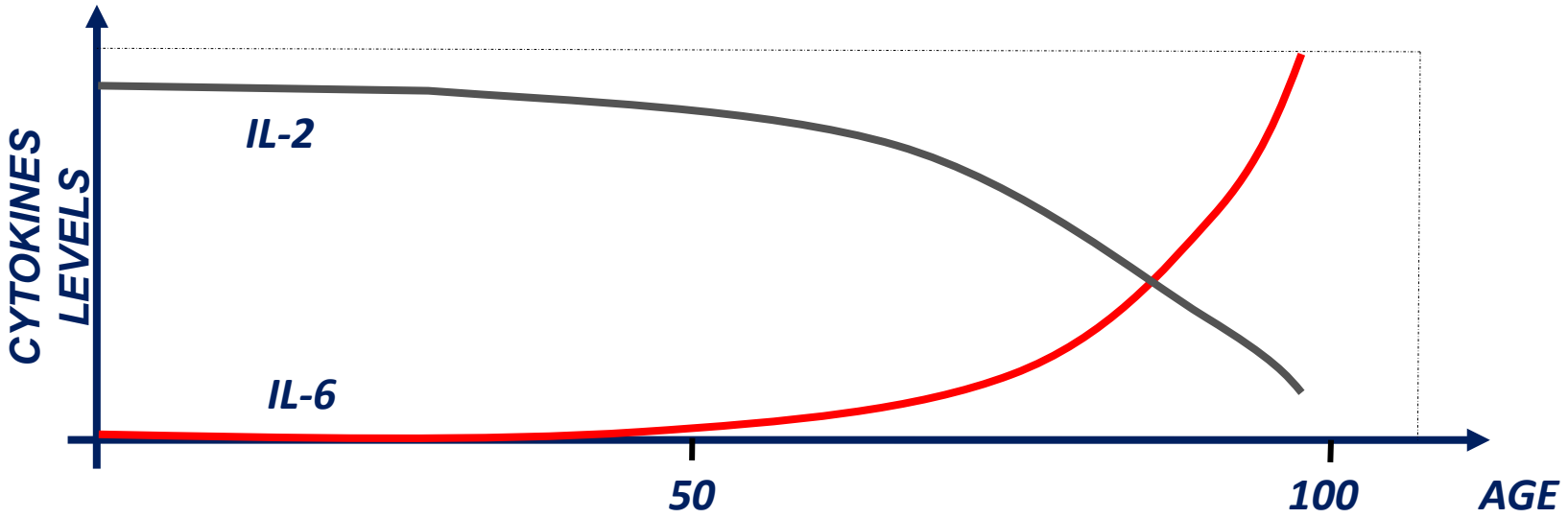
ELSEVIER

Mechanisms of Ageing and Development
100 (1998) 313–328

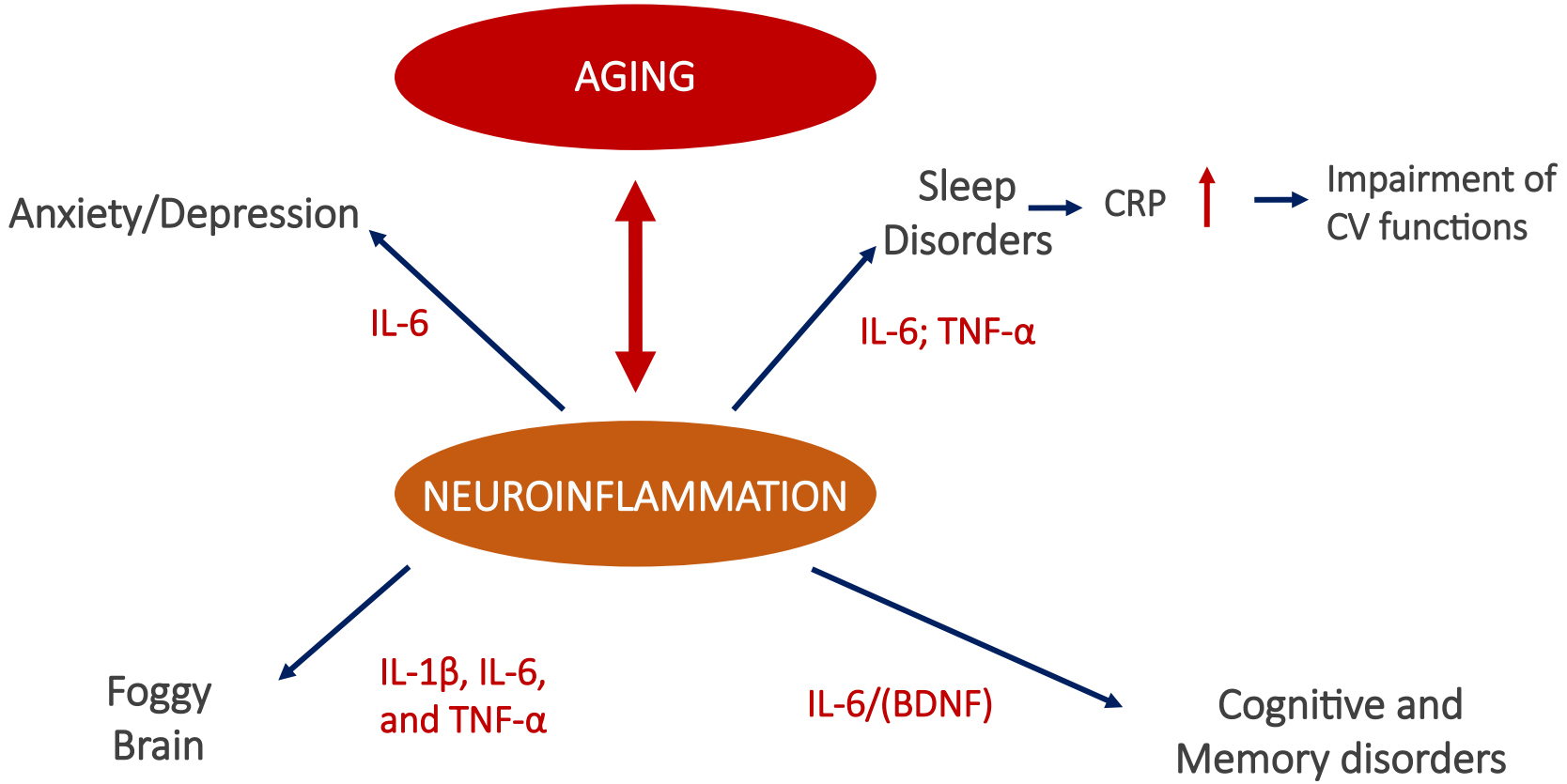
mechanisms of ageing and development

Increase of interleukin 6 and decrease of interleukin 2 production during the ageing process are influenced by the health status

Jolanta Myśliwska [a,*], Ewa Bryl [a], Jerzy Foerster [b], Andrzej Myśliwski [a]



Neuroinflammatory-related disorders associated with aging



- *Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, Ho RC. IL-1β, IL-6, TNF- α and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. Sci Rep. 2018 Aug 13;8(1):12050.*
- *Michal M, Wiltink J, Kirschner Y, Schneider A, Wild PS, Münzel T, Blettner M, Schulz A, Lackner K, Pfeiffer N, Blankenberg S, Tschan R, Tuin I, Beutel ME. Complaints of sleep disturbances are associated with cardiovascular disease: results from the Gutenberg Health Study. PLoS One. 2014 Aug 5;9(8):e104324.*

Neurobiology of Stress 4 (2016) 15–22

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Integrating Interleukin-6 into depression diagnosis and treatment

Georgia E. Hodes*, Caroline Ménard, Scott J. Russo

Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form
24 March 2016
Accepted 25 March 2016
Available online 29 March 2016

ABSTRACT

There is growing evidence of a relationship between inflammation and psychiatric illness. In particular, the cytokine Interleukin-6 (IL-6) has been linked to stress-related disorders such as depression and anxiety. Here we discuss evidence from preclinical and clinical studies examining the role of IL-6 in mood disorders. We focus on the functional role of peripheral and central release of IL-6 on the development of stress susceptibility and depression-associated behavior. By examining the contribution of both peripheral and central IL-6 to manifestations of stress-related symptomatology, we hope to broaden the way the field thinks about diagnosing and treating mood disorders.

frontiers in Neuroscience

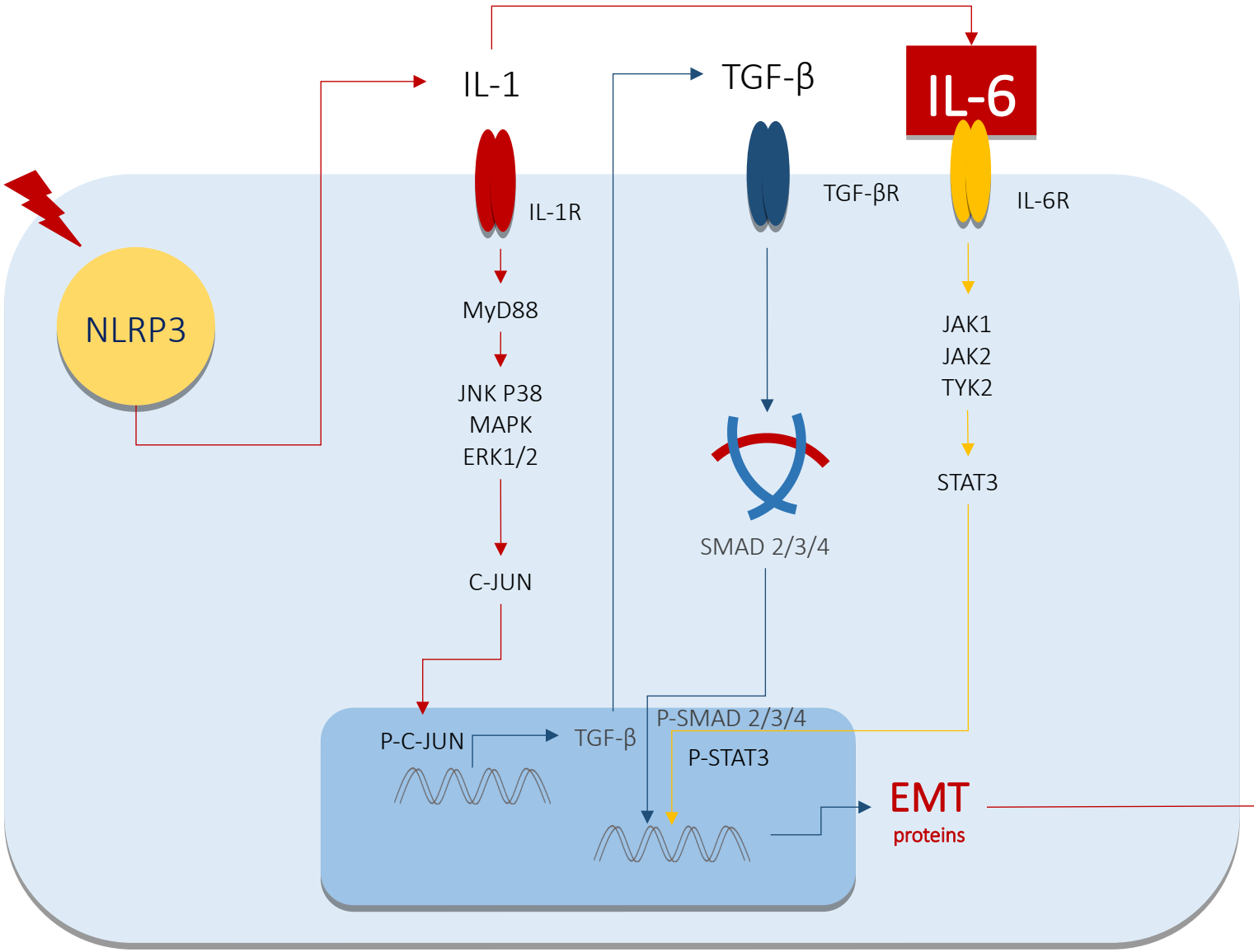
REVIEW
published: 24 July 2018
doi: 10.3389/fnins.2018.00499

Brain Kynurenine and BH4 Pathways: Relevance to the Pathophysiology and Treatment of Inflammation-Driven Depressive Symptoms

*Sylvie Vancassel[1,2], Lucile Capuron[1,2] and Nathalie Castanon[1,2]**

[1] UMR 1286, Laboratory of Nutrition and Integrative Neurobiology (NutriNeuro), INRA, Bordeaux, France, [2] UMR 1286, Laboratory of Nutrition and Integrative Neurobiology (NutriNeuro), Bordeaux University, Bordeaux, France

*THE PIVOT OF FIBROTIC PHENOMENON IS THE **EPITHELIAL MESENCHIMAL TRANSITION MECHANISM (EMT)***



Alyaseer AAA, de Lima MHS, Braga TT. The Role of NLRP3 Inflammasome Activation in the Epithelial to Mesenchymal Transition Process During the Fibrosis. Front Immunol. 2020 May 20;11:883.

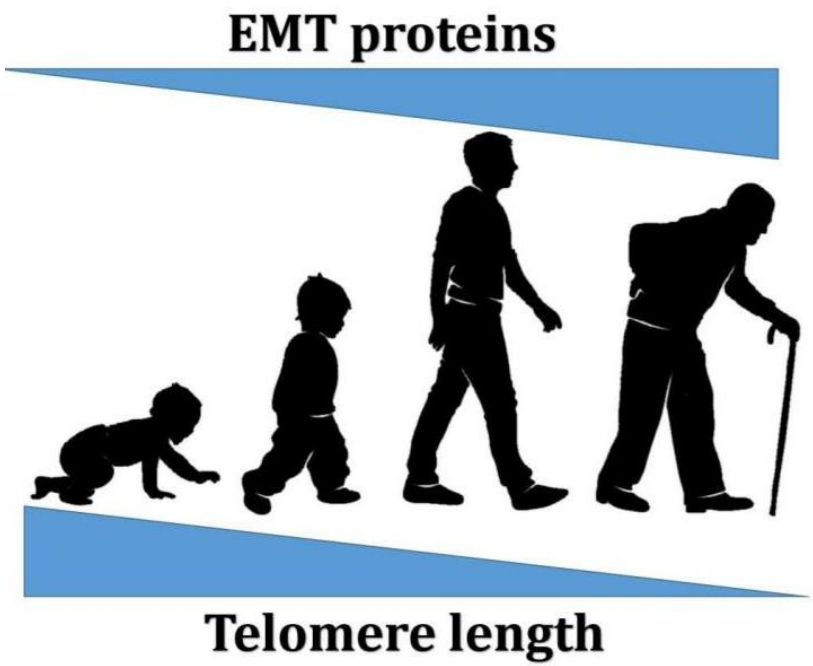
International Journal of
Molecular Sciences

MDPI

Review

Is There an Interconnection between Epithelial–Mesenchymal Transition (EMT) and Telomere Shortening in Aging?

Siti A. M. Imran [1], Muhammad Dain Yazid [1], Ruszymah Bt Hj Idrus [1,2], Manira Maarof [1], Abid Nordin [1,2], Rabiatul Adawiyah Razali [1,2] and Yogeswaran Lokanathan [1,*]



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

PROBLEM

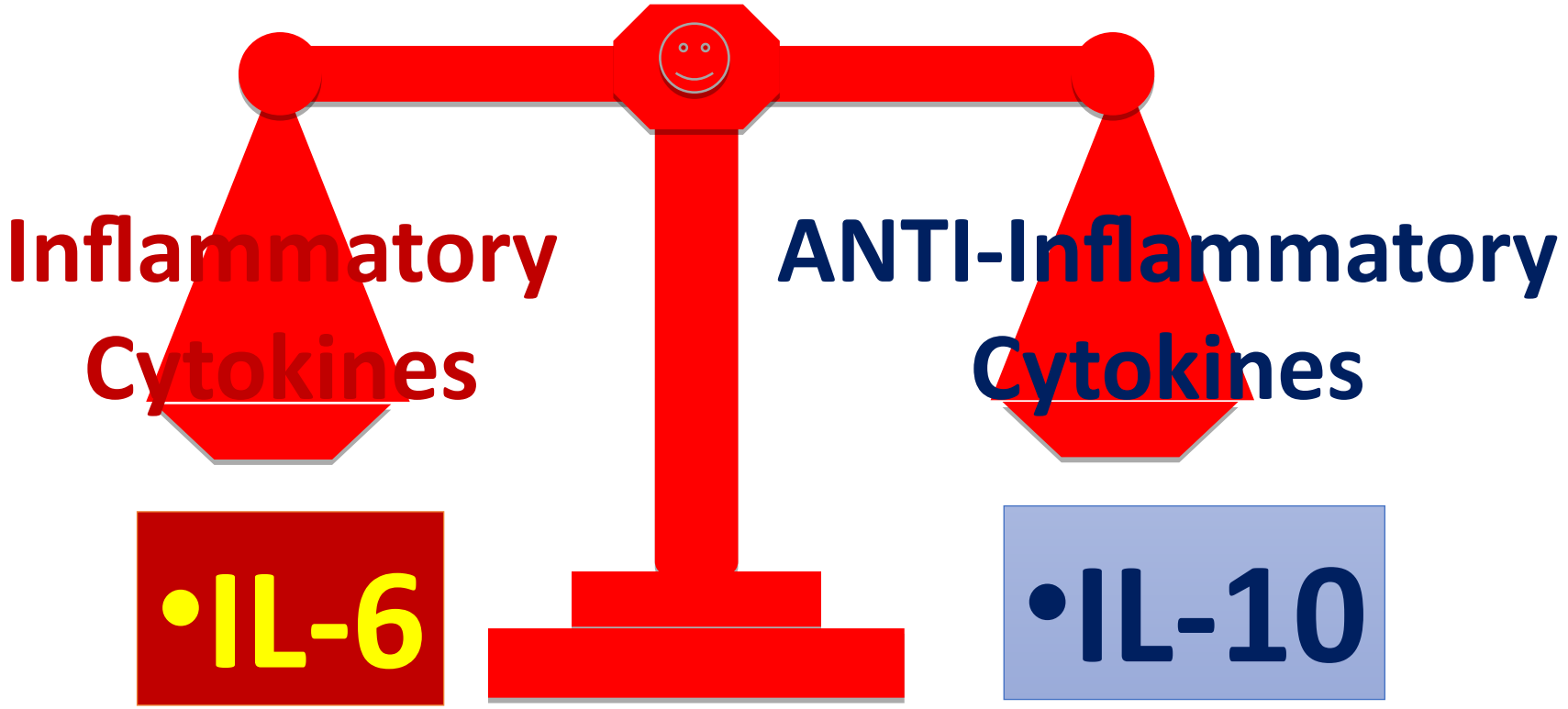
Is it possible to modulate the action of cytokines and other signaling molecules?

Clinical application of low dose cytokines

1. *antagonistic cytokines* are used in order to slow down the biological effect of another specific cytokine

- *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 CHRONIC INFLAMMATORY DISEASES



JEM Journal of Experimental Medicine

REVIEW

Cytokines Focus

Biology and therapeutic potential of interleukin-10

Margarida Saraiva[1,2], Paulo Vieira[3,4,5], and Anne O'Garra[6,7]

The cytokine IL-10 is a key anti-inflammatory mediator ensuring protection of a host from over-exuberant responses to pathogens and microbiota, while playing important roles in other settings as sterile wound healing, autoimmunity, cancer, and homeostasis. Here we discuss our current understanding of the regulation of IL-10 production and of the molecular pathways associated with IL-10 responses. In addition to IL-10's classic inhibitory effects on myeloid cells, we also describe the nonclassic roles attributed to this pleiotropic cytokine, including how IL-10 regulates basic processes of neural and adipose cells and how it promotes CD8 T cell activation, as well as epithelial repair. We further discuss its therapeutic potential in the context of different diseases and the outstanding questions that may help develop an effective a

Cold Spring Harbor Perspectives in Biology
www.cshperspectives.org

Targeting IL-10 Family Cytokines for the Treatment of Human Diseases

Xiaoting Wang,[1] Kit Wong,[2] Wenjun Ouyang,[3] and Sascha Rutz[4]

[1]Department of Comparative Biology and Safety Sciences, Amgen, South San Francisco, California 94080
[2]Department of Biomarker Development, Genentech, South San Francisco, California 94080
[3]Department of Inflammation and Oncology, Amgen, South San Francisco, California 94080
[4]Department of Cancer Immunology, Genentech, South San Francisco, California 94080
Correspondence: wouyang@amgen.com; saschar@gene.com

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Journal of Integrative Cardiology

oat open access text

Research Article

Twenty-five years of studies and trials for the therapeutic application of IL-10 immunomodulating properties. From high doses administration to low dose medicine new paradigm

Massimo Fioranelli[1]* and Roccia Maria Grazia[2]

[1]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India

[2]G.Marconi University, Rome, Italy

Original Article

Elmer Press

Gastroenterology Research • 2013;6(4):124-133

Oral Administration of Interleukin-10 and Anti-IL-1 Antibody Ameliorates Experimental Intestinal Inflammation

Diego Cardani[a], Giuseppina F Dusio[b], Patrizia Luchini[c], Michele Sciarabba[d], Umberto Solimene[e, f], Cristiano Rumio[a, f, g]

Drug Design, Development and Therapy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

An open randomized active-controlled clinical trial with low-dose SKA cytokines versus DMARDs evaluating low disease activity maintenance in patients with rheumatoid arthritis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
29 March 2017
Number of times this article has been viewed

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 28, no. 1, 133-139 (2014)

IMMUNOMODULATING TREATMENT WITH LOW DOSE INTERLEUKIN-4, INTERLEUKIN-10 AND INTERLEUKIN-11 IN PSORIASIS VULGARIS

M.L. ROBERTI[1], L. RICOTTINI[2], A. CAPPONI[3], E. SCLAUZERO[4], P. VICENTI[5], E. FIORENTINI[6], C. SAVOIA[7], G. SCORNAVACCA[8], D. BRAZIOLI[9], L. GAIO[10], R. GIANNETTI[11], C. IGNAZZI[12], G. MELONI[13] and L.M. CHINNI[14]

[1]Private Practice, Rome, Italy; [2]"Sinergheia" Medical Center, Rome, Italy; [3]Private Practice, Latina, Italy; [4]OSTEMDA, Therapeutic Strategies Empowerment and Advanced Diagnostic Methods Organization, Udine, Italy; [5]Private Practice, Altamura, Bari, Italy; [6]Dermatological Health Clinic, Aversa, Caserta, Italy; [7]Private Practice, Fino Mornasco, Como, Italy; [8]Private Practice, Catania, Italy; [9]Private Practice, Turin, Italy; [10]Private Practice, Caserta, Italy; [11]"Aurelia" Medical Center, Rome, Italy; [12]Local Health Unit (ASL), Putignano, Bari, Italy; [13]"GEA Medica" Medical Center, Montebelluna, Treviso, Italy; [14]Istituto Dermopatico dell'Immacolata (IDI), Rome, Italy

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 29, no. 1 (S), 53-58 (2015)

VITILIGO: SUCCESSFUL COMBINATION TREATMENT BASED ON ORAL LOW DOSE CYTOKINES AND DIFFERENT TOPICAL TREATMENTS

T. LOTTI[1], J HERCOGOVA[4], U. WOLLINA[5], A.A. CHOKOEVA[6], Z. ZARRAB[7], S. GIANFALDONI[8], M.G. ROCCIA[9], M. FIORANELLI[10] and G. TCHERNEV[6]

LOW DOSE PHARMACOLOGY
Conclusions

Why take it under consideration?

1) Highest clinical safety
2) Long term treatments
3) Effectiveness
4) Allows an overlapping approach
5) Fills the therapeutic *vacuum(s)*
6) Affordable cost

SHORT VERSION

These slides are based on the presenter's studies on Low Dose Medicine.

The information presented here is not to be considered a prescription and no medical or legal responsibility for misuse of the information presented will be accepted.
This information is for educational purposes for licensed health care professionals within their scope of practice.

The 73rd General Assembly and International Scientific Congress

Low Dose Cytokine Therapy for healthy longevity. A novel Pharmacology for a systemic and multi-level approach to aging

Saturday, November 5th, 2022

Alessandro Perra – Scientific Director GUNA S.p.a.

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Low Dose Cytokine Therapy

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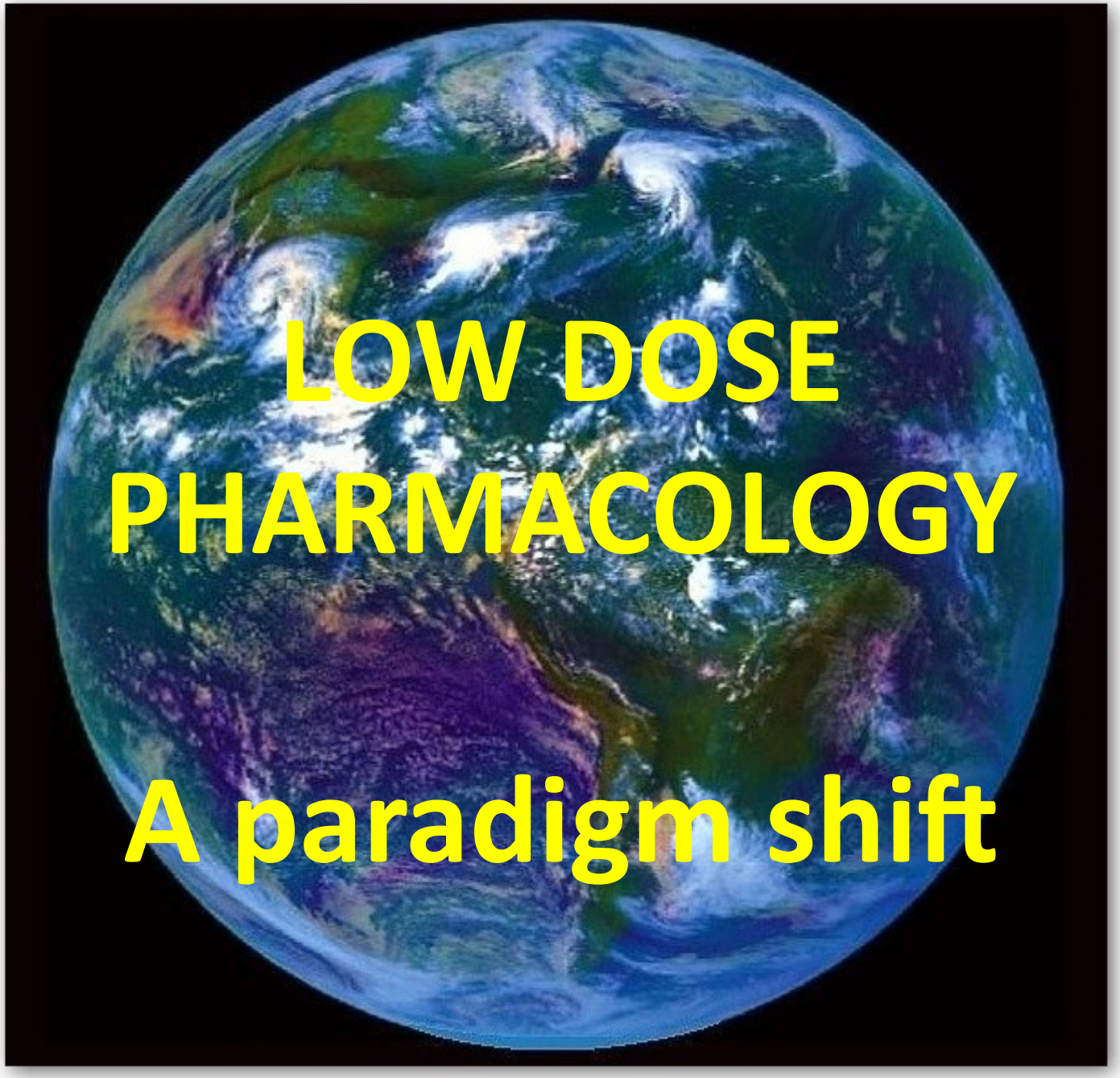

…not only us. A world trend

CMAJ

ANALYSIS

Is bigger better? An argument for very low starting doses

James P. McCormack PharmD, G. Michael Allan MD, Adil S. Virani PharmD

VIEWPOINT

Low drug doses may improve outcomes in chronic disease

Simon B Dimmitt and Hans G Stampfer

Chronic diseases are creating a growing burden of ill health as populations age[1] and become more obese,[2] and as survival from many conditions improves. Long-term pharmacotherapy is used increasingly to control symptoms and slow disease progression. Unfortunately, there is a dearth of reliable information about drug dosages for, and outcomes of, long-term treatment of physical and mental illness. Dosages recommended in clinical practice guidelines are usually derived from studies of acute and severe cases of disease. There is little research to support the application of these guidelines to long-term treatment regimens and to the large number of patients with mild cases of disease who are managed in primary care. In addition, few studies specifically address dosage.

carries the risk of adverse drug

ABSTRACT

- The relationship between drug dose and clinical outcome has not been established for many medications used to treat chronic disease. Evidence is emerging that chronic diseases can be treated effectively with low doses.
- Adverse drug reactions account for significant morbidity and mortality and are generally dose related.
- Optimal drug dose — the best balance of benefit and risk — varies between individuals and may change over time. When treating chronic disease it is important to establish and maintain the optimal dose for each patient by close clinical monitoring.

MJA 2009; 191: 511–513

BMJ Journals | BETA VERSION

Annals of the Rheumatic Diseases

Home / Archive / Volume 74, Issue 4

Letter

Rapid induction of clinical remission by low-dose interleukin-2 in a patient with refractory SLE

Jens Y Humrich1, Caroline von Spee-Mayer1, Elise Siegert1, Tobias Alexander1, Falk Hiepe1, Andreas Radbruch2, Gerd-Rüdiger Burmester1, Gabriela Riemekasten1

frontiers in Immunology

MINI REVIEW
published: 01 April 2021
doi: 10.3389/fimmu.2021.648408

Low-Dose IL-2 Therapy in Autoimmune and Rheumatic Diseases

*Hanna Graßhoff, Sara Comdühr, Luisa R. Monne, Antje Müller, Peter Lamprecht, Gabriela Riemekasten and Jens Y. Humrich**

Department of Rheumatology and Clinical Immunology, University Hospital Schleswig-Holstein Lübeck, Lübeck, Germany

The Journal of Immunology

This information is current as of October 17, 2022.

Low-Dose IL-2 Therapy in Transplantation, Autoimmunity, and Inflammatory Diseases

Maryam Tahvildari and Reza Dana

J Immunol 2019; 203:2749-2755; ;
doi: 10.4049/jimmunol.1900733
http://www.jimmunol.org/content/203/11/2749

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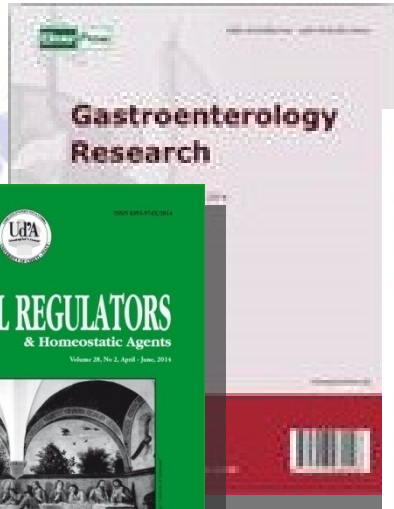
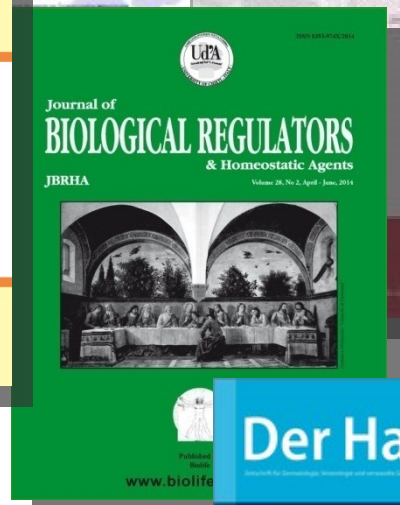
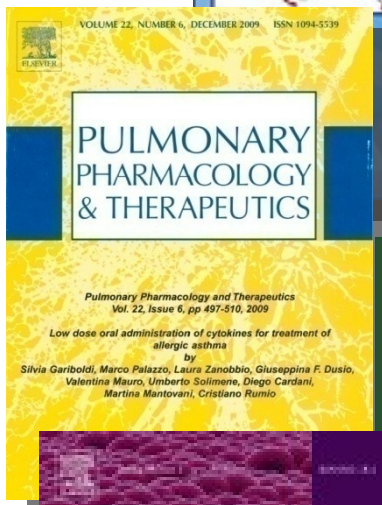
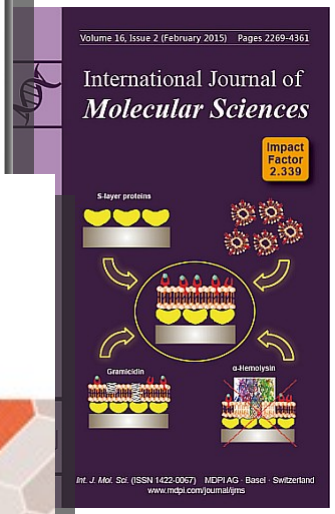
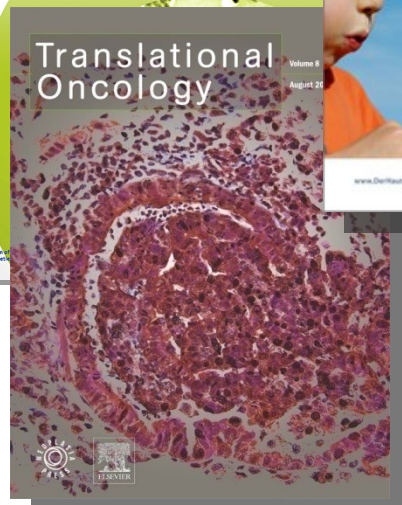
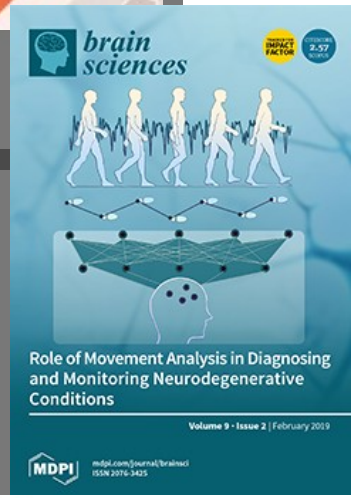






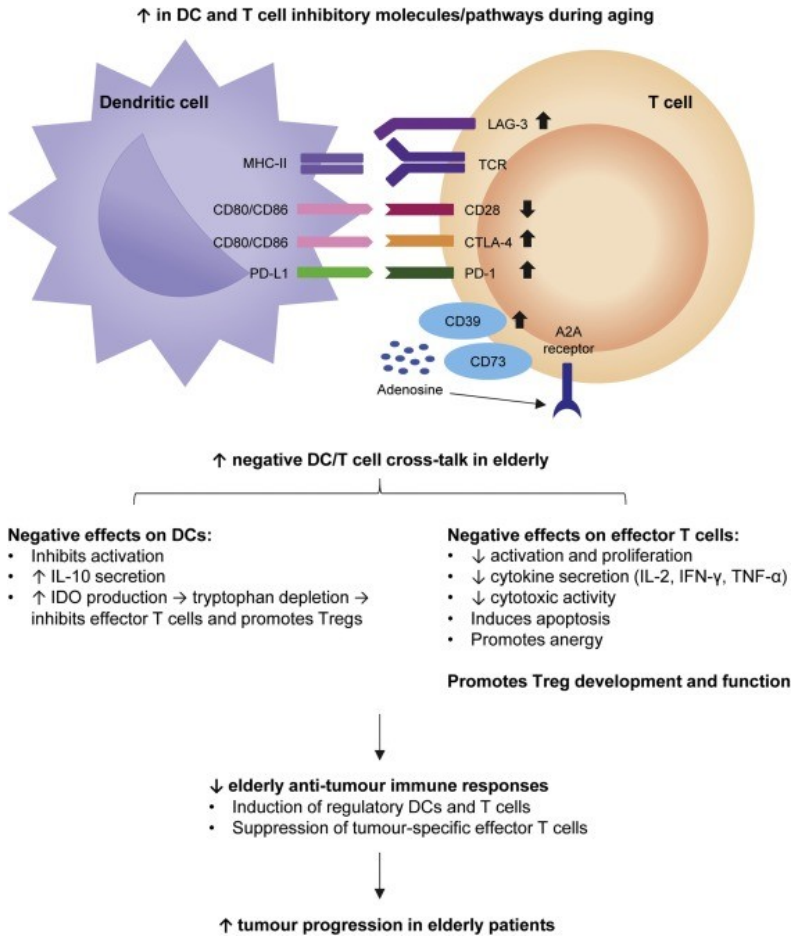






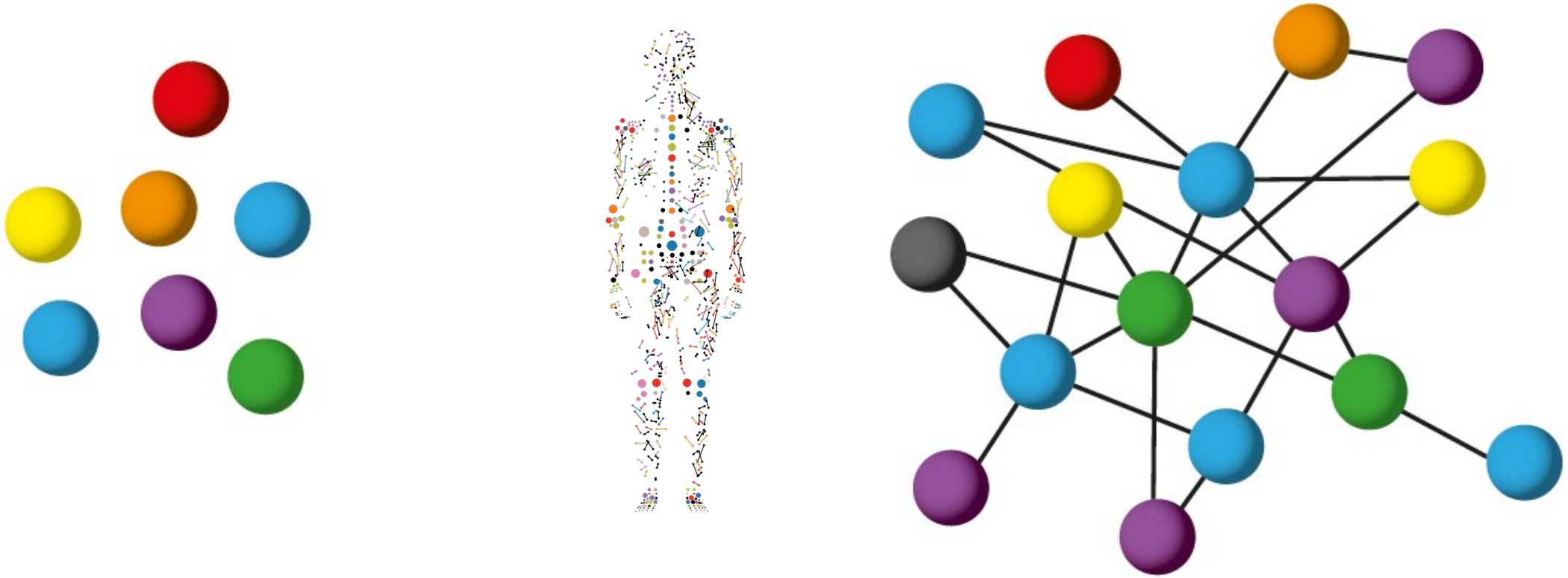
Why *Low Dose Cytokine Therapy* for a healthy longevity?

In a **complex system**
an impairment in the **cross-talk between cells** can be at the origin of the aging process as well as the disease onset.



Wagner JUG, Dimmeler S. Cellular cross-talks in the diseased and aging heart. J Mol Cell Cardiol. 2020 Jan;138:136-146.

Reductionistic approach vs Systemic approach

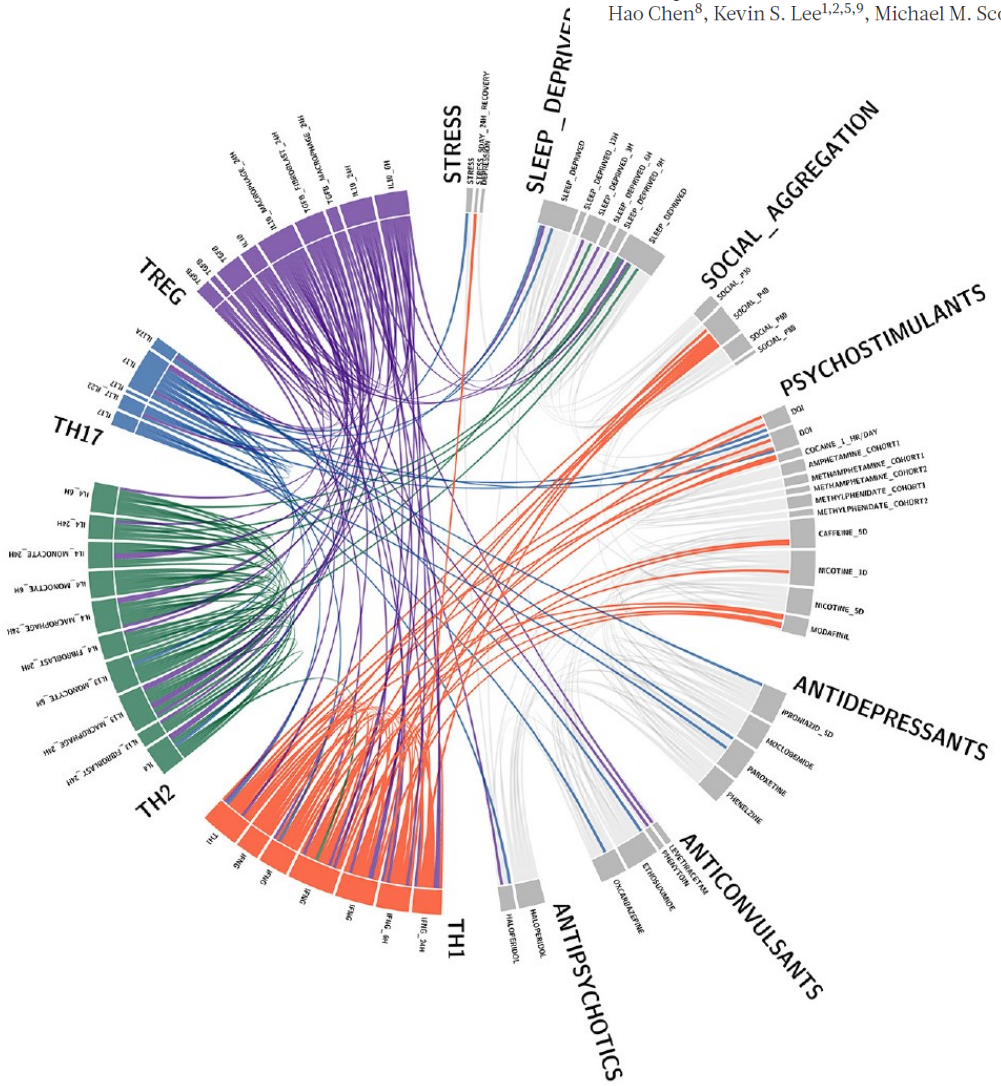


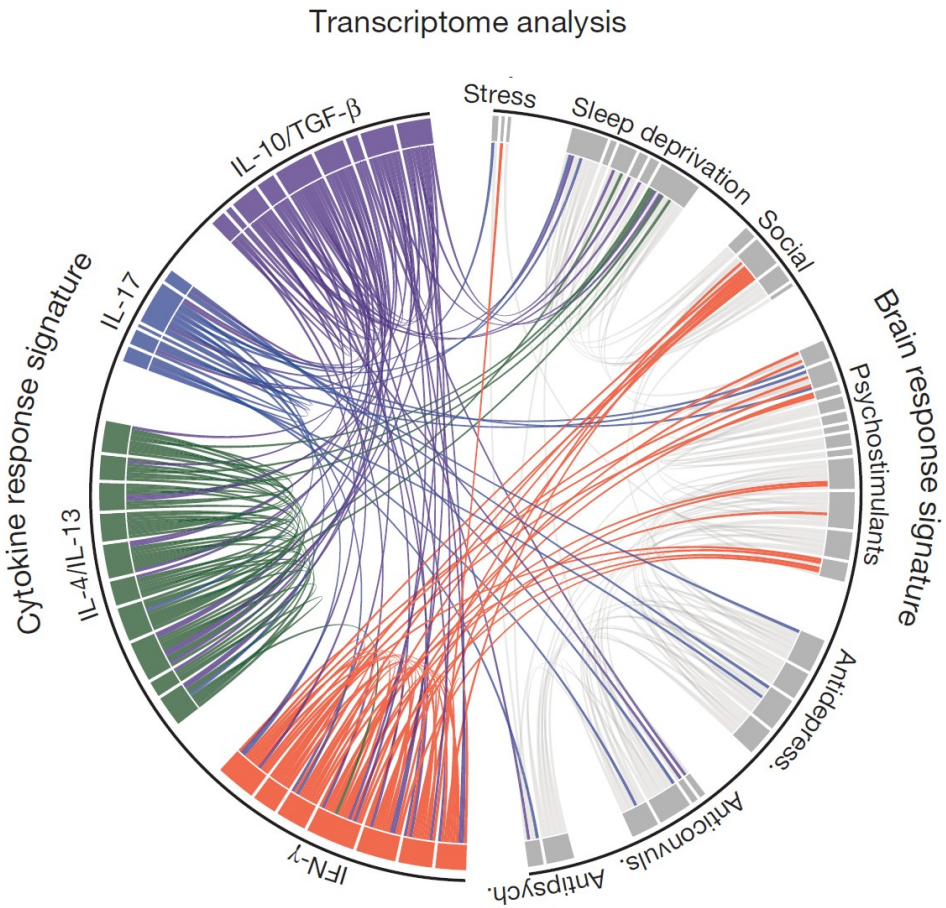
Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet*. 2011;12(1):56-68. doi:10.1038/nrg2918

doi:10.1038/nature18626

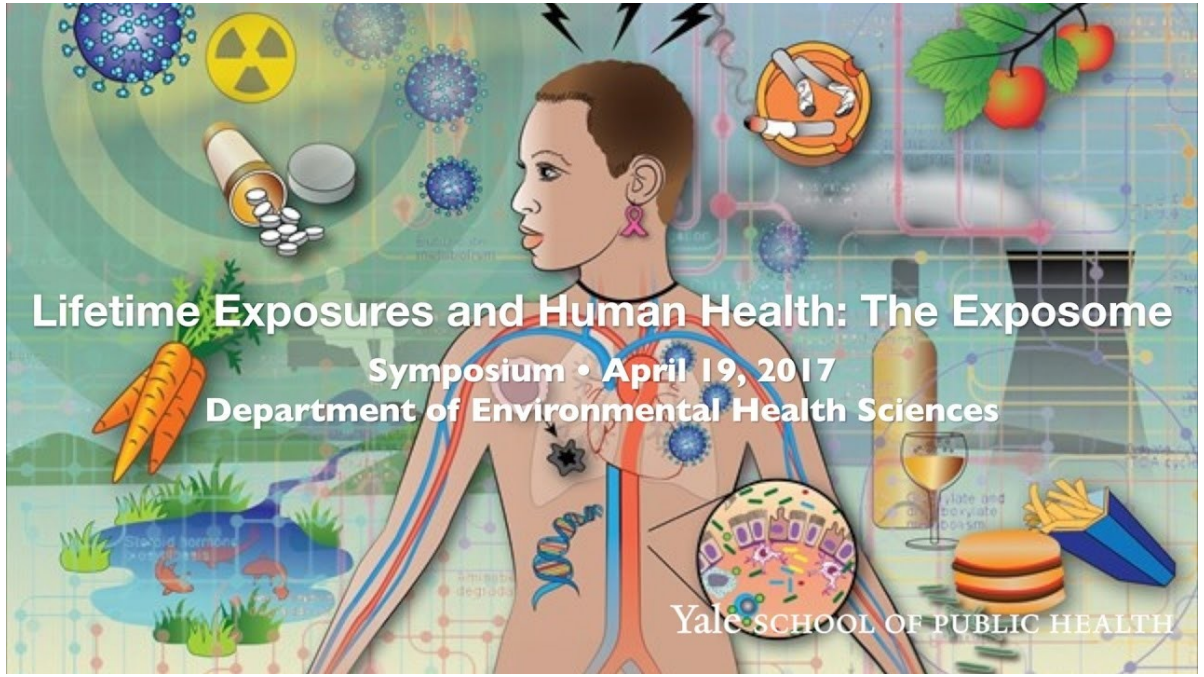
Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour

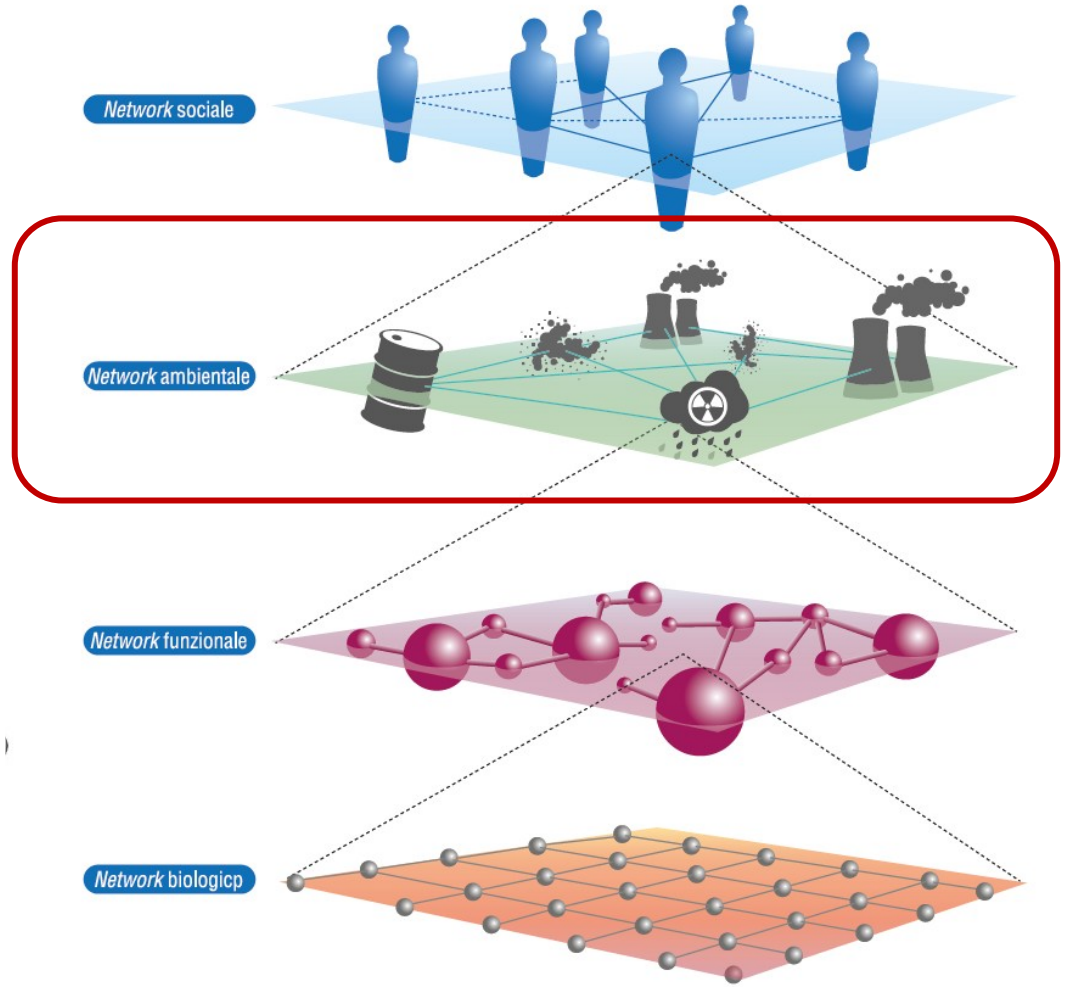
Anthony J. Filiano[1,2], Yang Xu[3], Nicholas J. Tustison[4], Rachel L. Marsh[1,2], Wendy Baker[1,2], Igor Smirnov[1,2], Christopher C. Overall[1,2], Sachin P. Gadani[1,2,5,6], Stephen D. Turner[7], Zhiping Weng[8], Sayeda Najamussahar Peerzade[3], Hao Chen[8], Kevin S. Lee[1,2,5,9], Michael M. Scott[5,10], Mark P. Beenhakker[5,10], Vladimir Litvak[3]* & Jonathan Kipnis[1,2,5,6]*





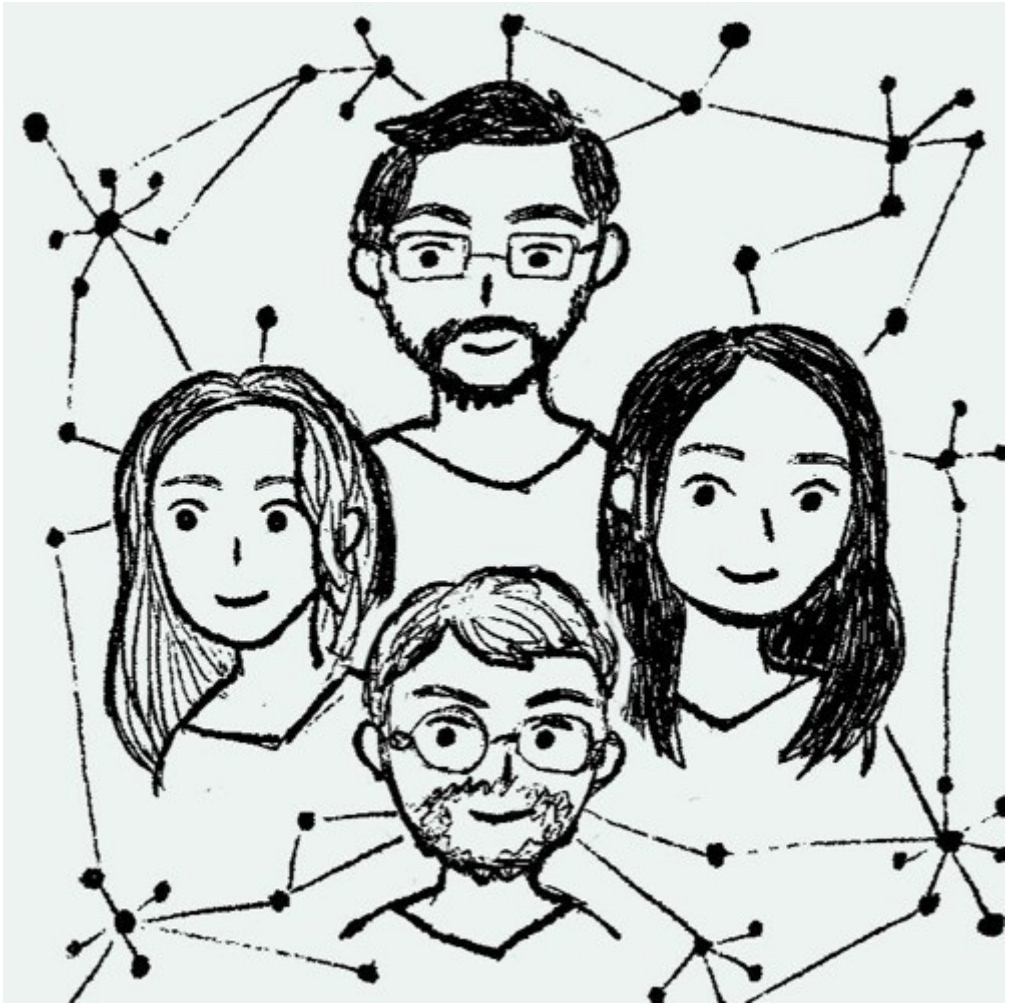
Systems Medicine (Network Medicine)

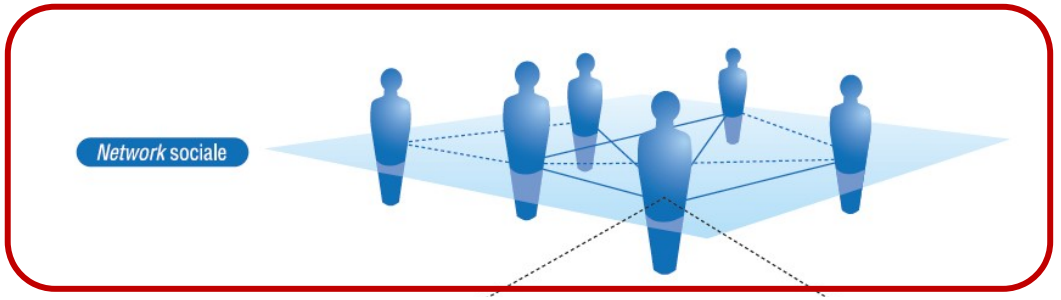




Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet*. 2011;12(1):56-68. doi:10.1038/nrg2918

Systems Medicine (Network Medicine)





According to the Systems Theory, the mind is not an entity but a process, the process of life.

The living beings' activity of organization, at all the levels where life shows itself, is mental activity.
The interactions of a living being (vegetal, animal, human) with its enviroment are cognitive interactions, i.e. mental.

(F. Capra, La rete della vita 1996)

Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet*. 2011;12(1):56-68. doi:10.1038/nrg2918

«NEGATIVE THOUGHTS» AND LOW-GRADE CHRONIC INFLAMMATION

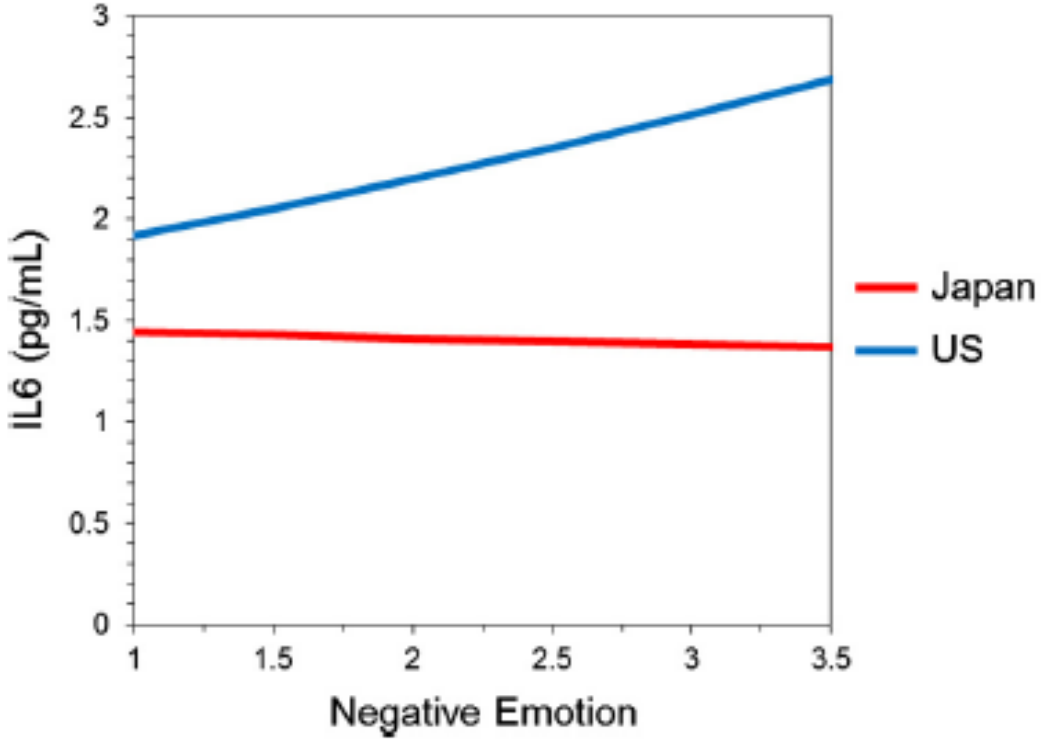


Fig. 1. Cultural moderation of the association between negative emotions and IL-6 after controlling for gender, age, and years of education, positive emotions, neuroticism, extraversion, smoking status, alcohol consumption, the number of chronic conditions linked to inflammation, and log-transformed BMI (Model 5). Negative emotions were rated on a 5-point rating scale: *none of the time* (1), *a little of the time* (2), *some of the time* (3), *most of the time* (4), and *all the time* (5). Negative emotions predicted IL-6 in the United States, $b = 0.06$, S.E. = 0.02, $t(1363) = 2.68$, $p = .001$, but not in Japan, $b = -0.01$, S.E. = 0.03, $t(1363) = 0.35$, $p = .73$.

Miyamoto Y. et al. Negative emotions predict elevated interleukin-6 in the United States but not in Japan. Brain, Behavior, and Immunity 2013

Neurobiology of Stress 4 (2016) 15–22

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Integrating Interleukin-6 into depression diagnosis and treatment

Georgia E. Hodes*, Caroline Ménard, Scott J. Russo

Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form
24 March 2016
Accepted 25 March 2016
Available online 29 March 2016

ABSTRACT

There is growing evidence of a relationship between inflammation and psychiatric illness. In particular, the cytokine Interleukin-6 (IL-6) has been linked to stress-related disorders such as depression and anxiety. Here we discuss evidence from preclinical and clinical studies examining the role of IL-6 in mood disorders. We focus on the functional role of peripheral and central release of IL-6 on the development of stress susceptibility and depression-associated behavior. By examining the contribution of both peripheral and central IL-6 to manifestations of stress-related symptomatology, we hope to broaden the way the field thinks about diagnosing and treating mood disorders.

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Symposium
SYSTEMS MEDICINE
Integration models in clinical practice and new therapeutic solutions

Held in Milan, at the University of Milan, on 5 May 2022

under the auspices of:

World Health Organization (WHO) Collaborating Center for Integrative Medicine
P.R.M. (International Academy of Physiological Regulating Medicine)
FEMTEC (Worldwide Federation of Hydrotherapy and Climatotherapy)

under the patronage of:

Italian Ministry of Health
FNOMCeO (National Federation of the Associations of Surgeons and Dentists)

THE SPEAKERS

PROF. GIUSEPPE BELLELLI
Full Professor of Geriatrics-Internal Medicine, Milan-Bicocca University

PROF. SERGIO BERNASCONI
Full Professor of Paediatrics, Former Director of Paediatric Clinics at the Universities of Modena and Parma

PROF. GIANNI BONA
Full Professor of Paediatric Clinic, Former Director of the Paediatric Clinic, University of Eastern Piedmont

PROF. MARIO CLERICI
Full Professor of Immunology and Immunopathology, University of Milan

PROF. GIUSEPPE DE BENEDITTIS
Associate Professor of Neurosurgery, University of Milan

DR. MARCO DEL PRETE
President P.R.M. Academy
(International Academy of Physiological Regulating Medicine)

PROF. FABIO ESPOSITO
Full Professor of Physical Exercise Sciences and Sport, University of Milan

PROF. VASSILIOS FANOS
Full Professor of Paediatrics, University of Cagliari

PROF. ALESSANDRO GENAZZANI
Associate Professor of Obstetrics and Gynaecology, University of Modena-Reggio Emilia

PROF. PAOLO INGHILLERI
Full Professor of Social Psychology, University of Milan

PROF. DAVIDE LAURO
Full Professor of Endocrinology, University of Rome "Tor Vergata"

PROF.SSA JEANETTE MAIER
Full Professor of General and Clinical Pathology, University of Milan

PROF. STEFANO MASIERO
Full Professor of Physical and Rehabilitation Medicine, University of Padua

PROF. MARCO MATUCCI CERINIC
Full Professor of Rheumatology, University of Florence

PROF. ALBERTO MIGLIORE
Director of the UOS (Simple Operative Unit) of Rheumatology, San Pietro Fatebenefratelli Hospital, Rome

PROF. EMILIO MINELLI
WHO *(World Health Organization)* Expert Advisory, Panel Member Clin. Research on Integrative Medicine

PROF. ANDREA MODESTI
Full Professor of General Pathology, University of Rome "Tor Vergata"

PROF. CLAUDIO MOLINARI
Associate Professor of Human Physiology, University of Eastern Piedmont, Vercelli

PROF. VALTER SANTILLI
Full Professor of Physical and Rehabilitative Medicine, University of Rome "La Sapienza"

PROF. UMBERTO SOLIMENE
Direttore *WHO (World Health Organization) Collaborating Center for Integrative Medicine - State University of Milan*

HAVE APPROVED *THE MILAN DECLARATION 2022 – NEW GOALS FOR MEDICINE*
WHICH OUTLINES THE CURRENT AND FUTURE SOCIAL AND HEALTH SCENARIOS THAT MAKE NECESSARY TO DEFINE A NEW PARADIGM OF MEDICINE.

E cellula ad hominem

DICHIARAZIONE DI MILANO 2022
NUOVI OBIETTIVI DELLA MEDICINA

Talking about a Complex System

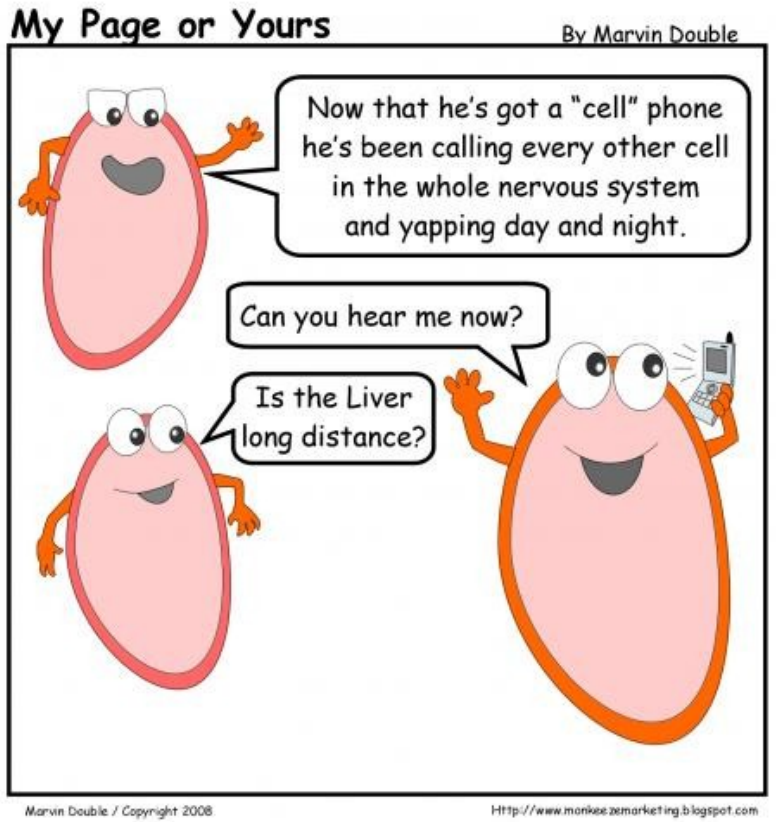
THE HUMAN BODY
IS A NETWORK
OF NETWORKS

40.000 billion cells

Bianconi E, Piovesan A, Facchin F, Beraudi A, Casadei R, Frabetti F, Vitale L, et al. An estimation of the number of cells in the human body. Ann Hum Biol. 2013;40(6):463-71.

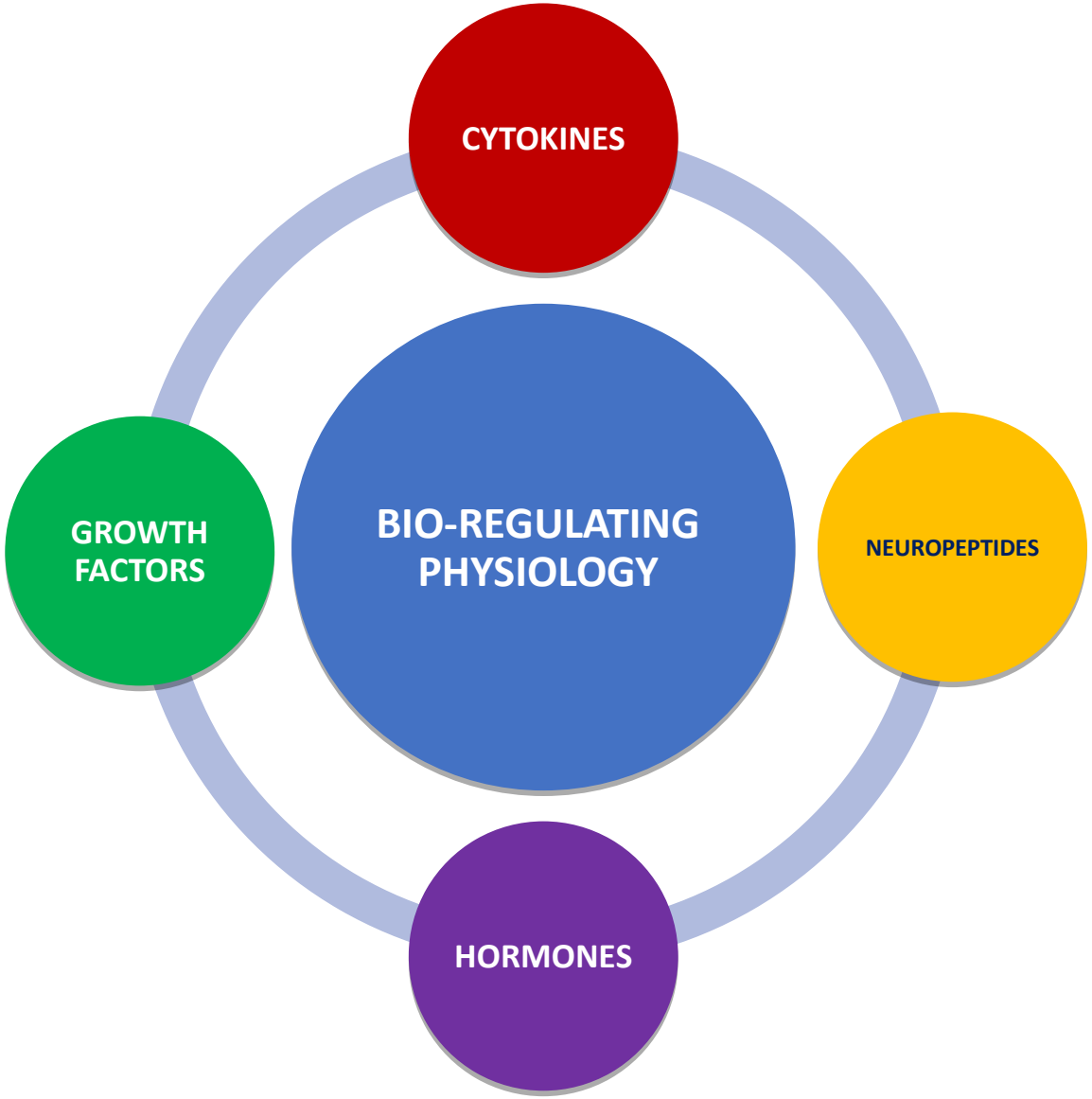
A Complex System

1. How do they talk?
2. Where do they talk?



SIGNALING MOLECULES-BASED LOW DOSE PHARMACOLOGY

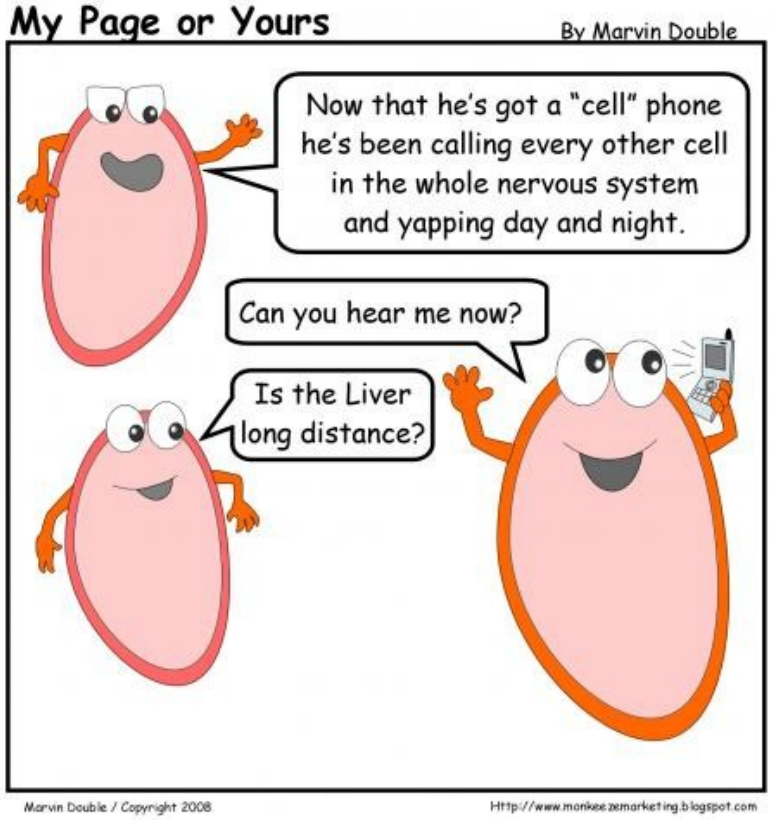
THE GREAT INNOVATION



Signaling Molecules

The Fundation for LDM

CYTYOKINES are MESSENGERS, THE WORDS used by the 3 homeostatic control systems (or functional networks) and BY THE CELLS to speak each other … and to lead the body physiology.

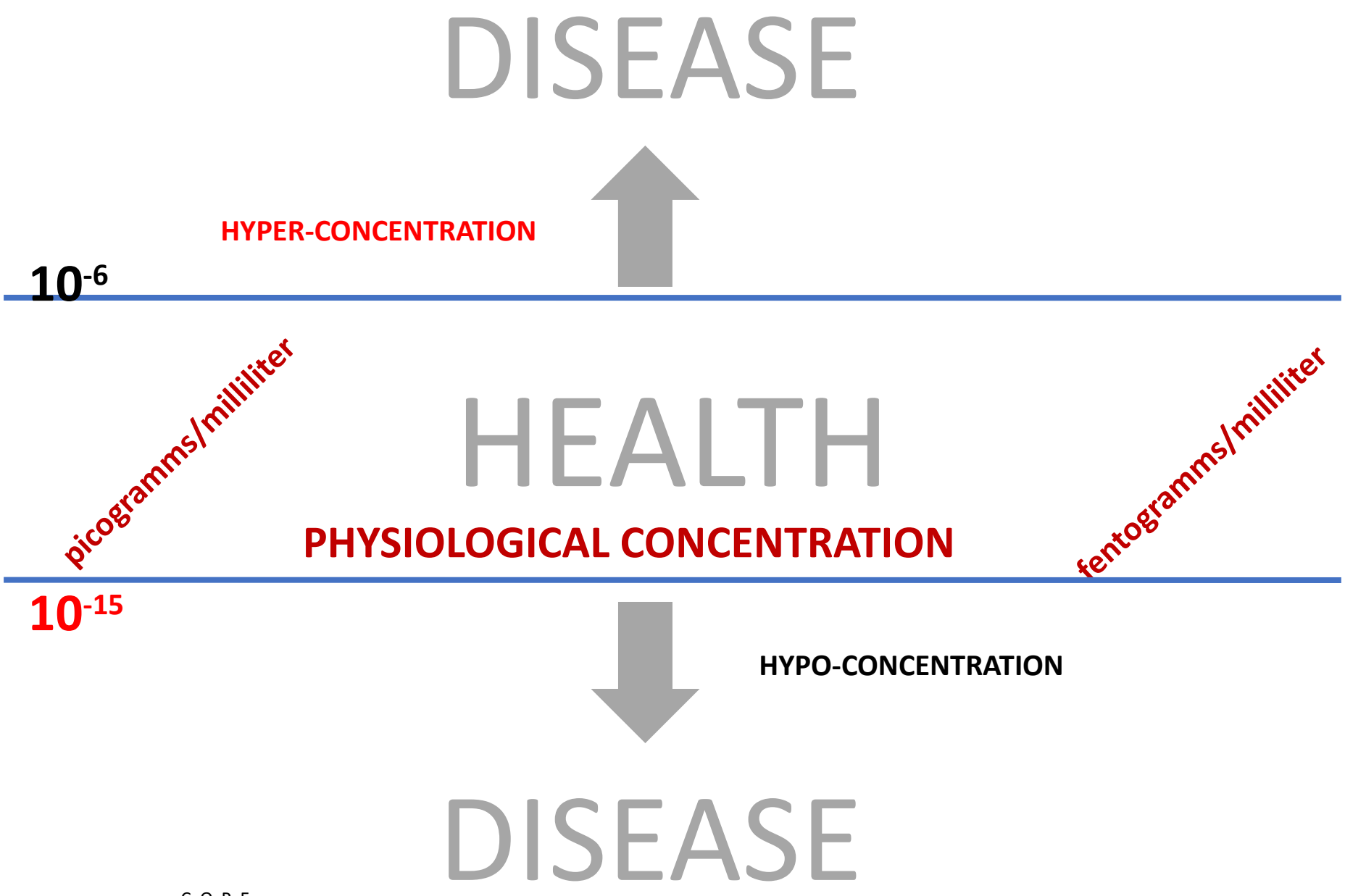


Signaling (Messenger) Molecules

The Foundation for Low Dose Pharmacology

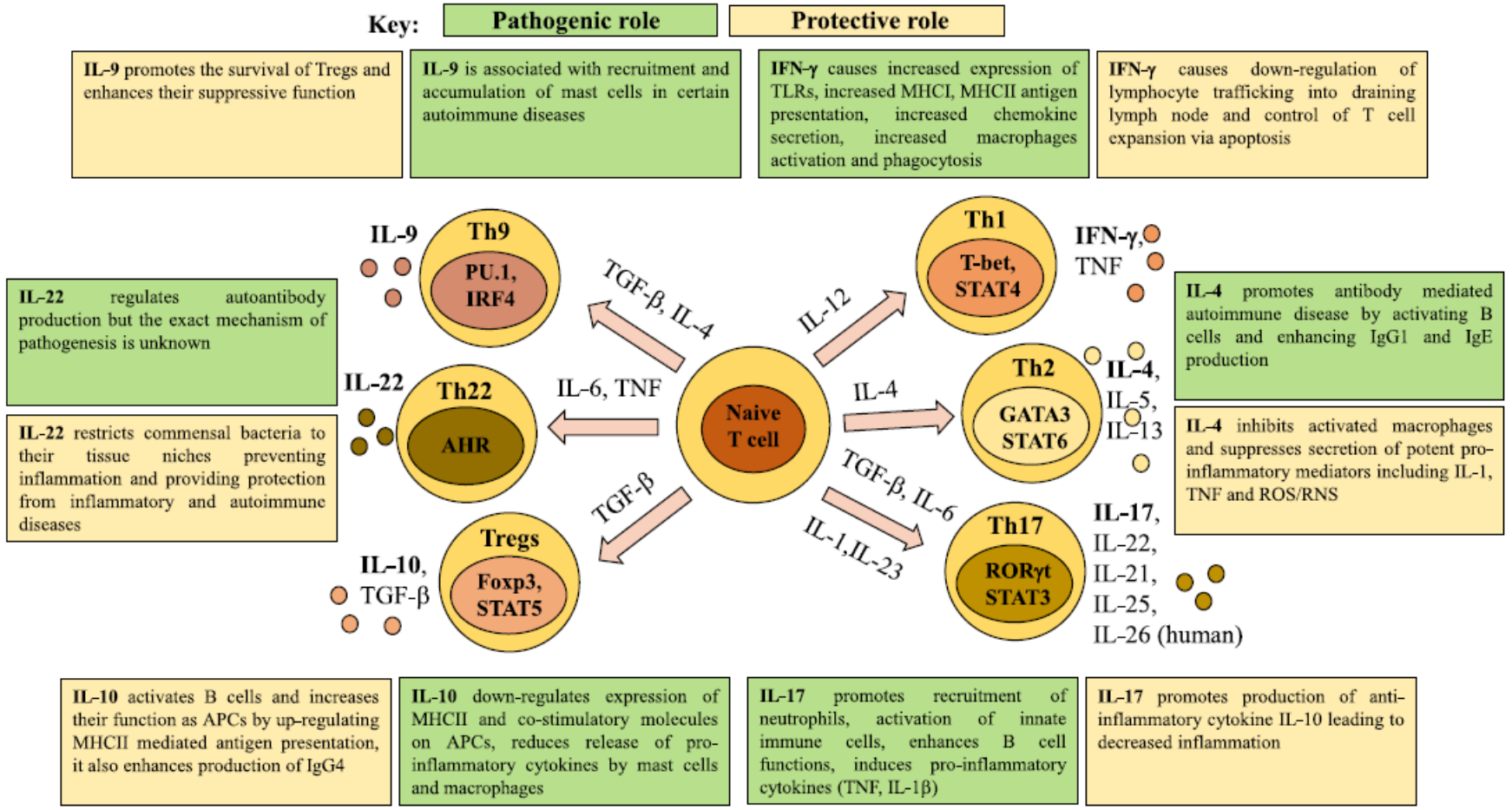
Cells  ***r at a very*** *sub-*

nanc *tion)*



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

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

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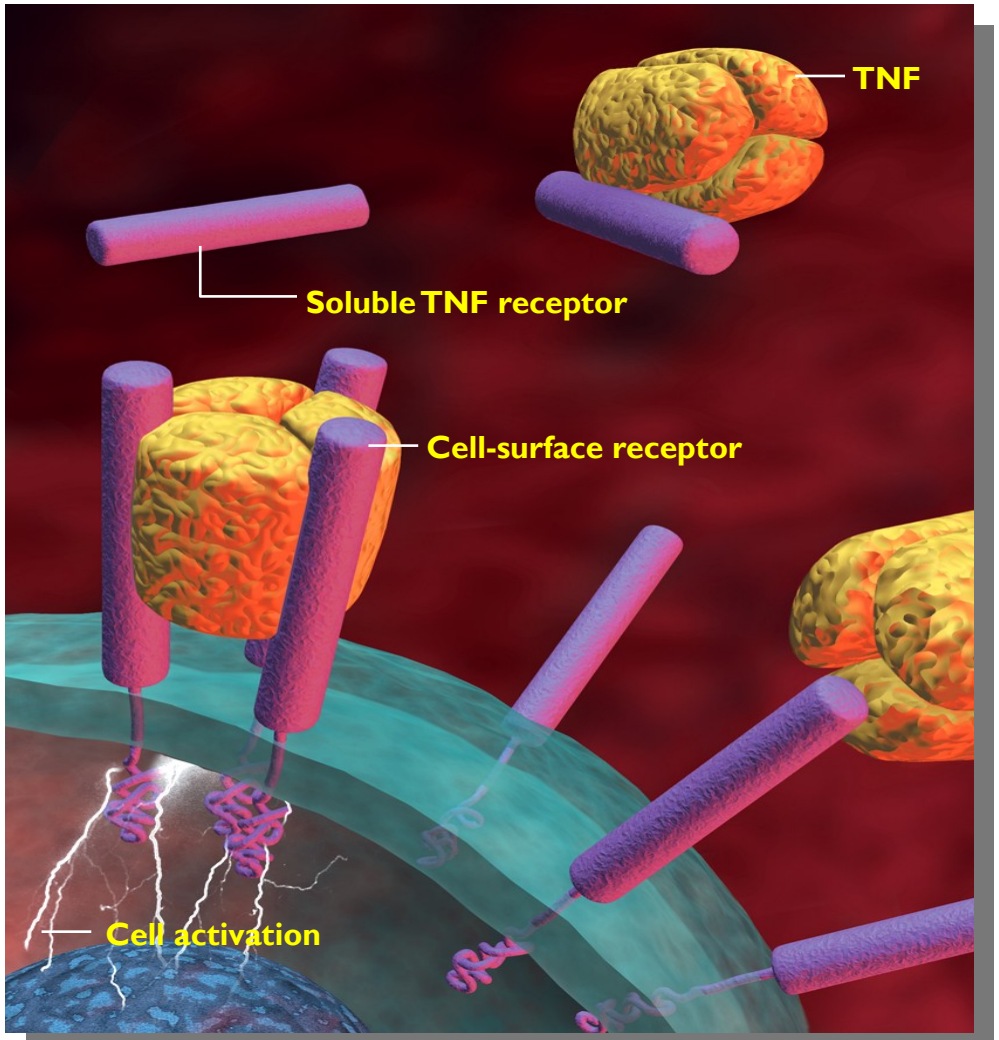
TRANS-MEMBRANE RECEPTORS
Up- and Down-Regulation



Jak-1: Tyrosine kinasis
STAT-1: Signal transducer and activator of transcription 1
SOCS-1:Suppressor of cytokin signaling 1

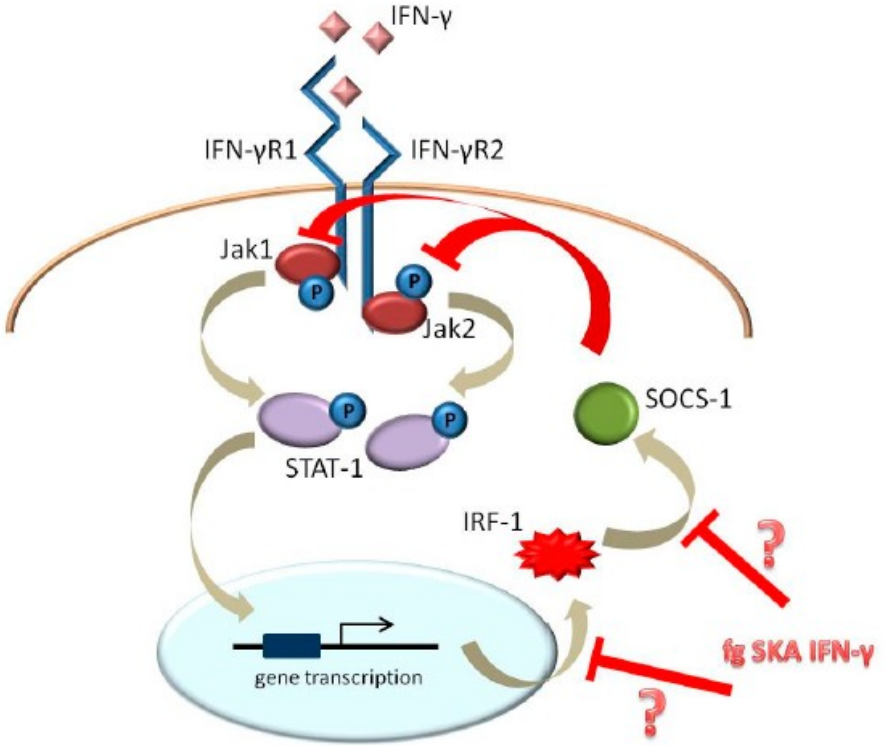
International Journal of *Molecular Sciences*

MDPI

Article

Femtograms of Interferon-γ Suffice to Modulate the Behavior of Jurkat Cells: A New Light in Immunomodulation

Sara Castiglioni [1,*], Vincenzo Miranda [2], Alessandra Cazzaniga [1], Marilena Campanella [2], Michele Nichelatti [3], Marco Andena [1] and Jeanette A. M. Maier [1]



GUNA Signaling Molecules

Drugs: Bio-Tech

Concentration: low dose (sub-nanomolar)

Preparation mode: SKA

- Bio-Tech – human recombinant in *E. Coli or in SF21 (Spodoptera frugiperda).*

The biological EFFECTS of LOW DOSES

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Low dose oral administration of cytokines for treatment of allergic asthma

Silvia Gariboldi [1], Marco Palazzo [1], Laura Zanobbio, Giuseppina F. Dusio, Valentina Mauro, Umberto Solimene, Diego Cardani, Martina Mantovani, Cristiano Rumio*

iMIL – Italian Mucosal Immunity Laboratory, Department of Human Morphology and Biomedical Sciences "Città Studi", Università degli Studi di Milano, via Mangiagalli 31, 20133 Milano, Italy

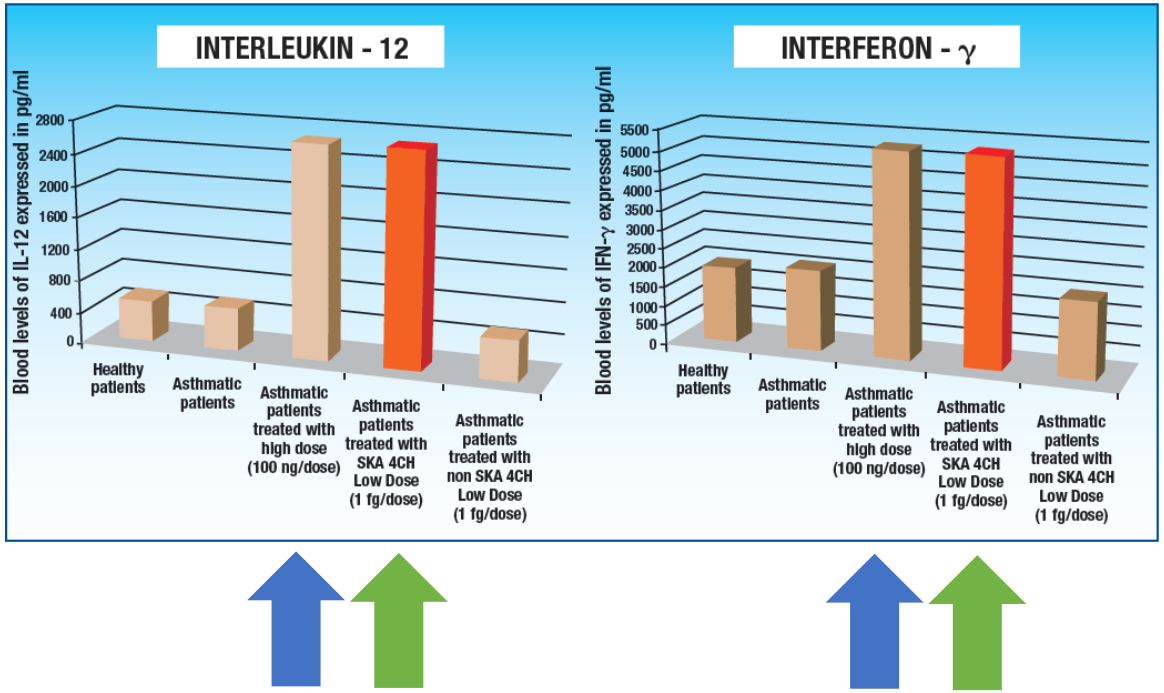
About BIO-STIMULATION activity of physiological low doses

The mystery …which is not a mistery

HIGH DOSE TREATMENT GROUP
100 ng/dose (10^{-9})

Broncho Alveolar
Fluid
Picogramms (10^{-12})

LOW DOSE (HOMEOPATHIC)
TREATMENT GROUP
1 fg/dose (10^{-15})



brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

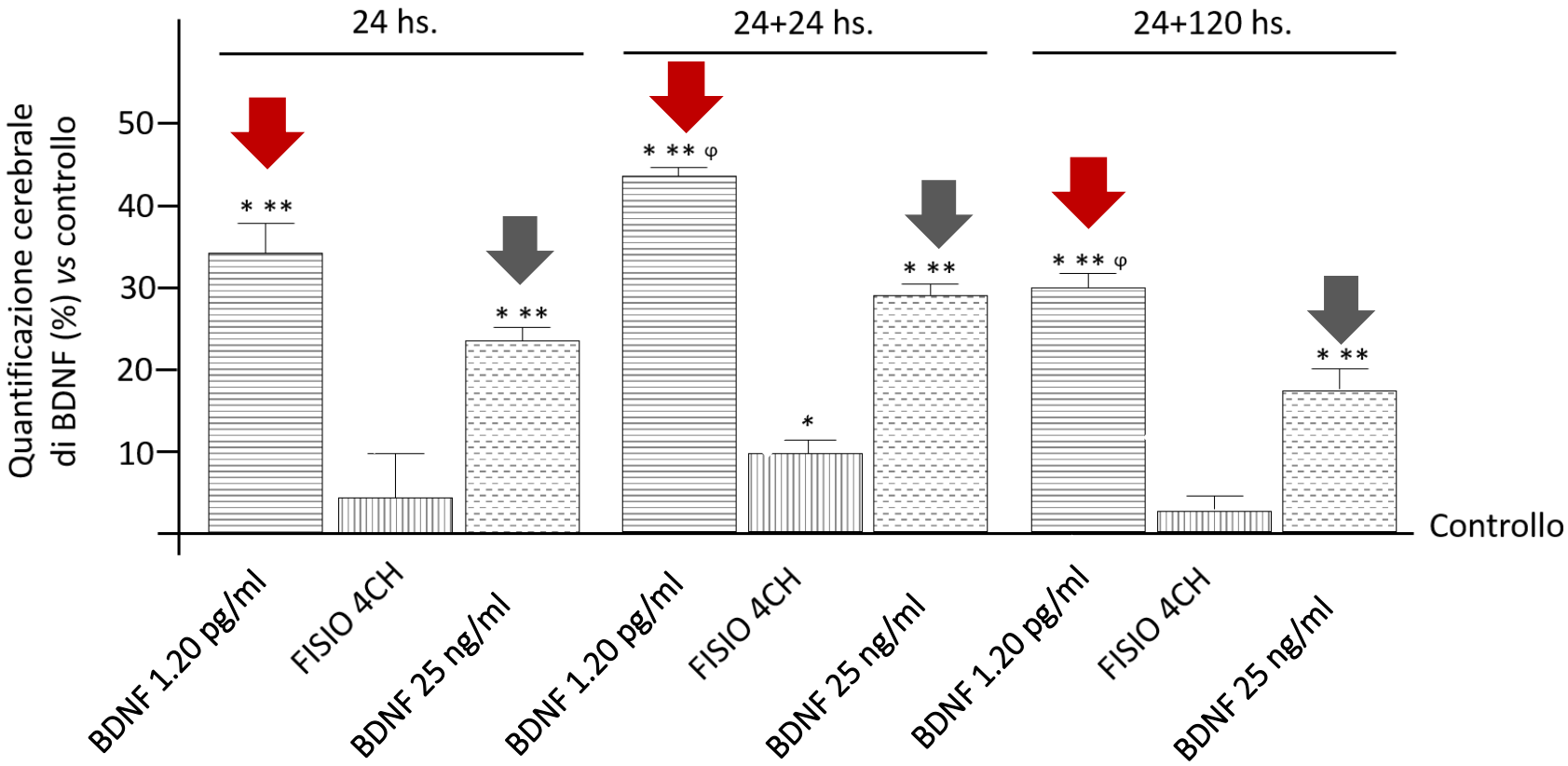
Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy; claudio.molinari@med.uniupo.it (C.M.); vera.morsanuto@med.uniupo.it (V.M.); sara.ruga@uniupo.it (S.R.); felice.notte@uniupo.it (F.N.); mahitab.farghali@uniupo.it (M.F.); rebecca.galla@uniupo.it (R.G.)
* Correspondence: francesca.uberti@med.uniupo.it; Tel.: +39-0321-660653

Received: 26 February 2020; Accepted: 4 May 2020; Published: 9 May 2020

check for updates

In vivo BRAIN BDNF QUANTIFICATION



12 monthh old mice type C57BL

brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

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check for updates

To verify whether the mechanism activated by BDNF solutions is the same as the one observed in cells during in vitro experiments, the effects of 1.2 pg/mL BDNF SKA and 25 ng/mL BDNF on some main markers were investigated by Western blot. Since BDNF is necessary for survival of neurons in the brain, after encoding by this gene its expression was investigated, as reported in Figure 9A. 1.2 pg/mL BDNF SKA and 25 ng/mL BDNF both at 24 h and 24 h plus 24 h were able to induce the expression of BDNF compared to control ($p < 0.05$), indicating a better influence of stimulations. Moreover, 1.2 pg/mL BDNF SKA at 24 h and 24 h plus 24 h caused a significant increase compared to and 25 ng/mL BDNF (about 50% and about 62%, respectively), indicating the induction of endogenous production of BDNF by physiological mechanism, as shown by the significant increase induced by 1.2 pg/mL BDNF SKA at 24 h plus 24 h with respect to at 24 h ($p < 0.05$, about 24%).

brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy; claudio.molinari@med.uniupo.it (C.M.); vera.morsanuto@med.uniupo.it (V.M.); sara.ruga@uniupo.it (S.R.); felice.notte@uniupo.it (F.N.); mahitab.farghali@uniupo.it (M.F.); rebecca.galla@uniupo.it (R.G.)

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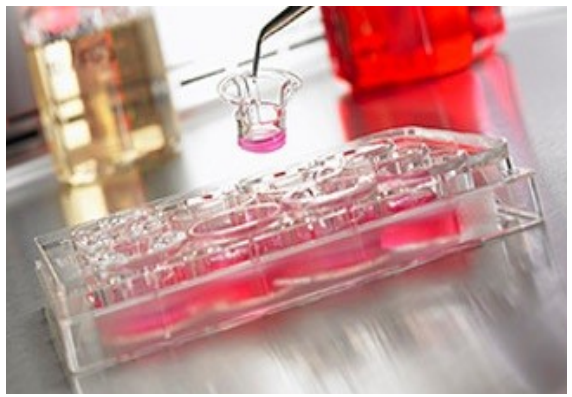
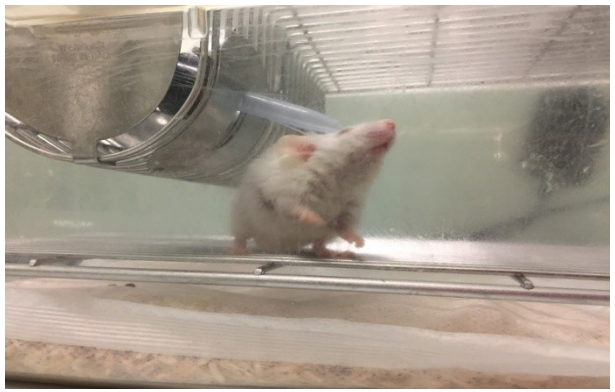
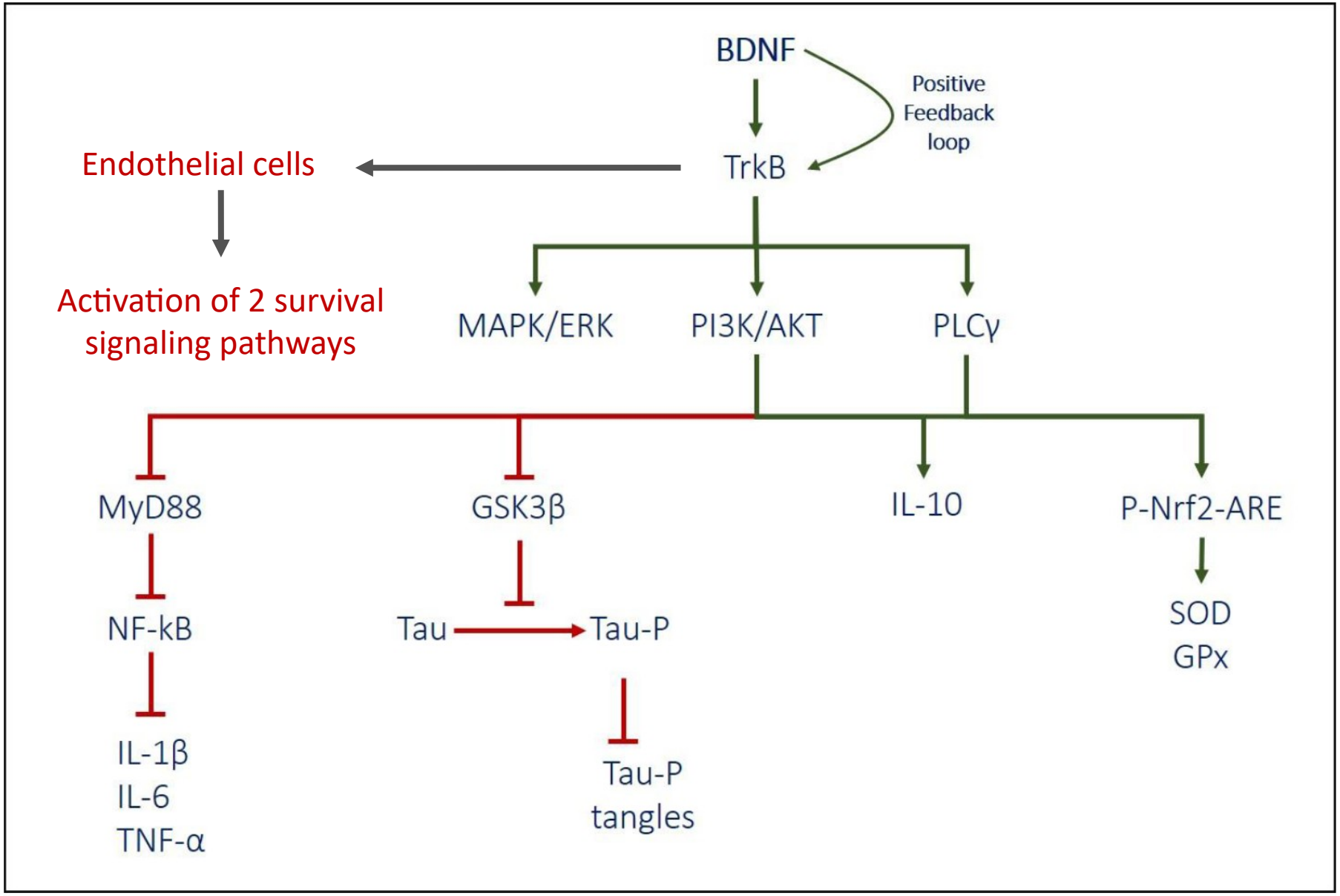
brain sciences







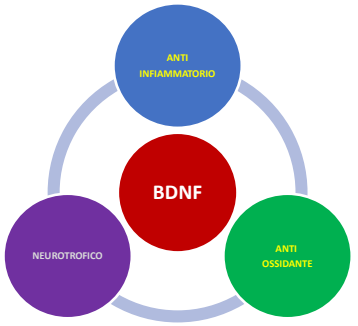
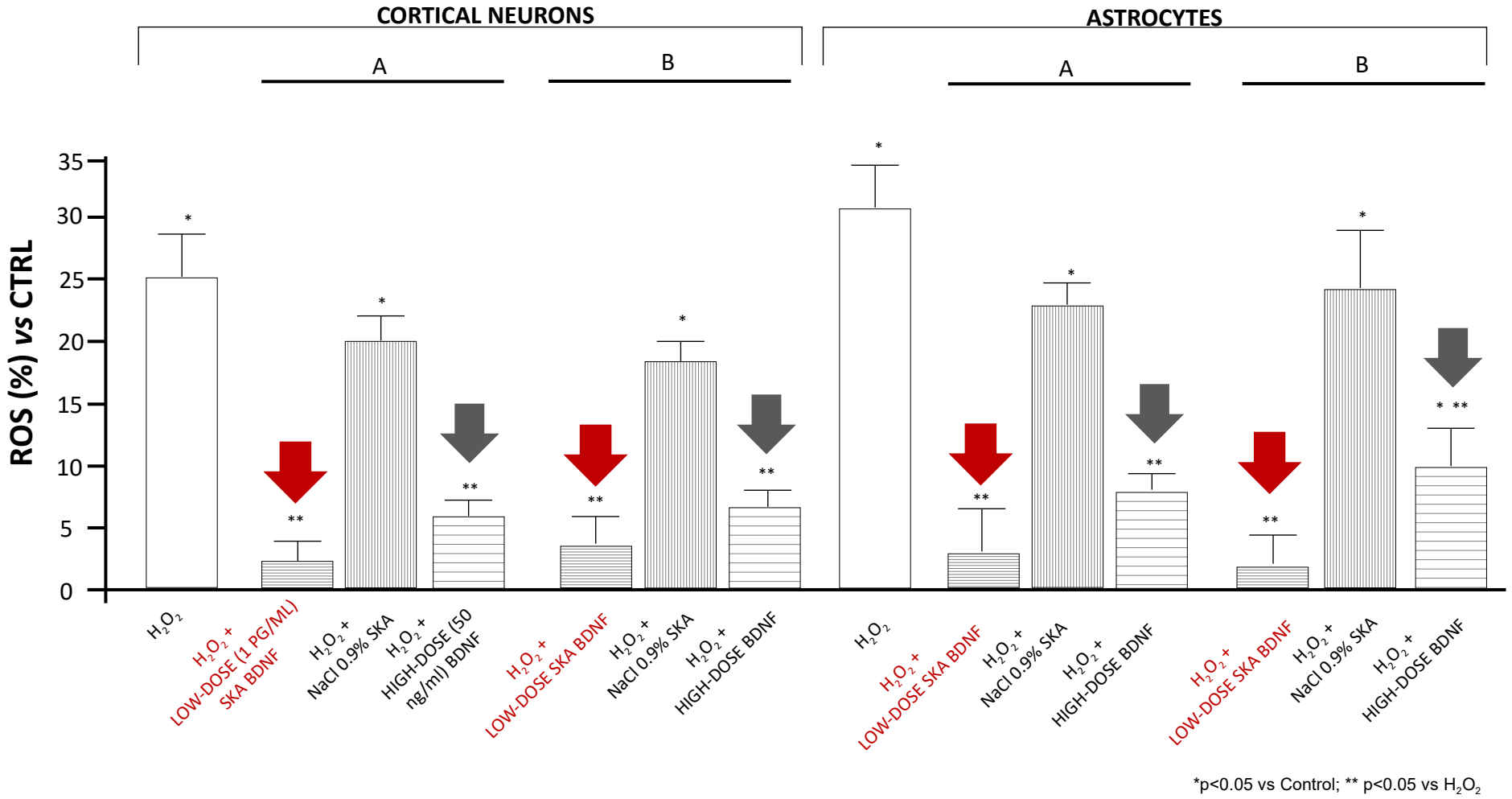


Figure 1 – Simplified synoptic scheme of the main pathways of BDNF's mediated cellular responses.

Amadio P, Baldassarre D, Sandrini L, Weksler BB, Tremoli E, Barbieri SS. Effect of cigarette smoke on monocyte procoagulant activity: Focus on platelet-derived brain-derived neurotrophic factor (BDNF). Platelets. 2016 Aug 5:1-6.

ROS REDUCTION

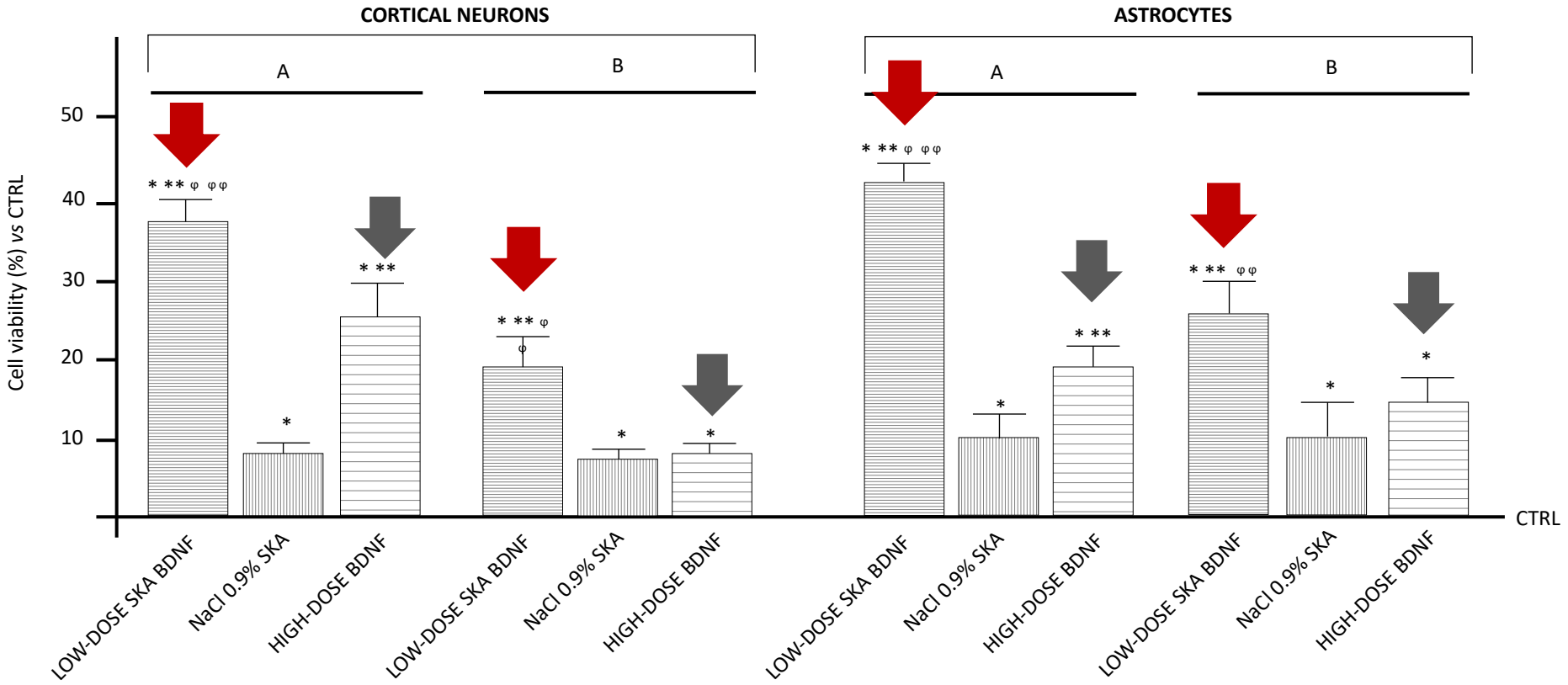


*p<0.05 vs Control; ** p<0.05 vs H_2O_2

Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

CELL VIABILITY

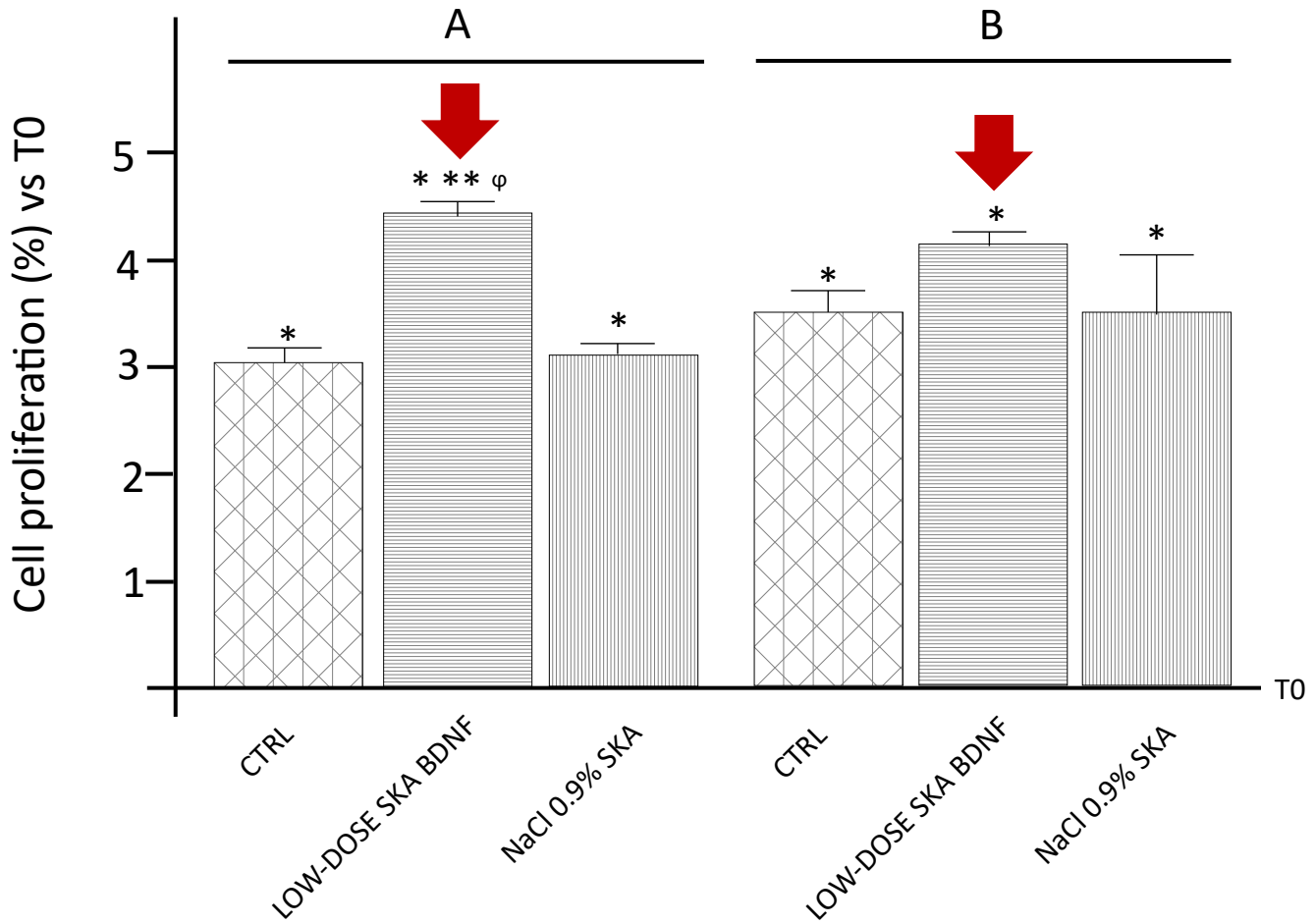


Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

*p<0.05 vs CTRL; ** p<0.05 vs NaCl 0.9% SKA ; $^{\varphi}$p<0.05 vs the same treatment in the two protocols; $^{\varphi\varphi}$ p<0.05 vs BDNF within the same protocol

CELL PROLIFERATION
(Astrocytes*)



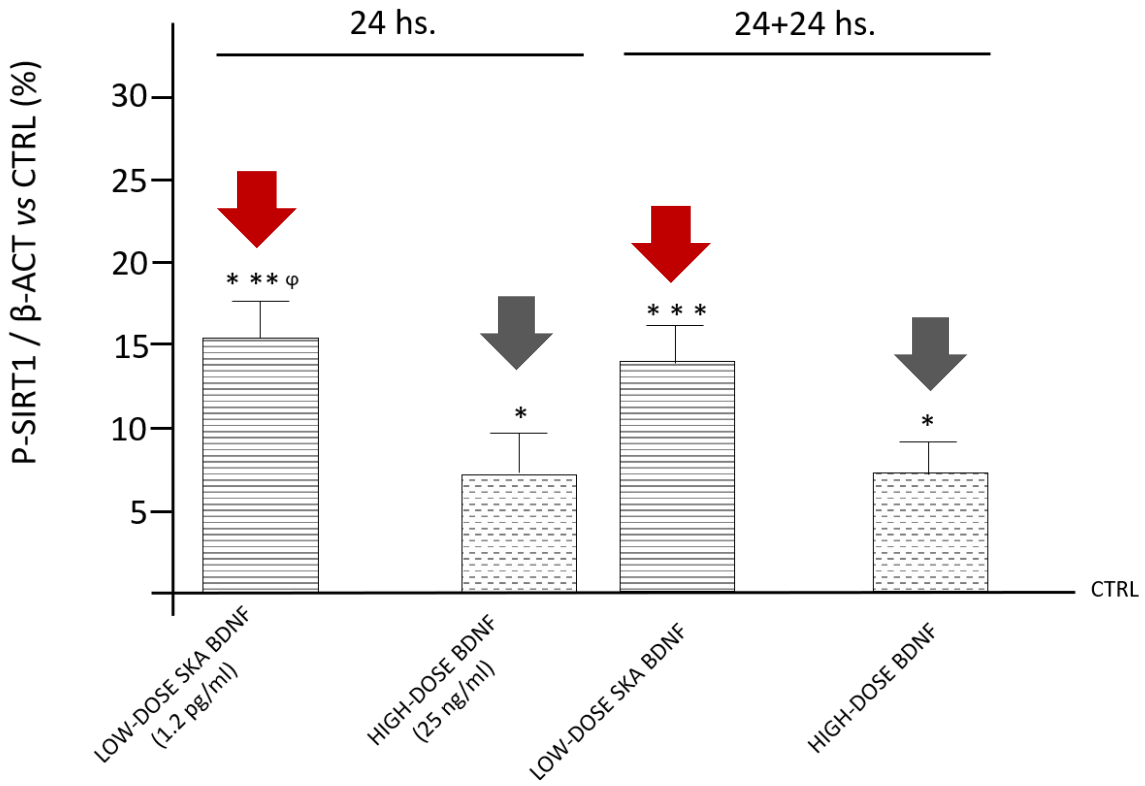
Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

*p<0.05 vs T0; ** p<0.05 vs CTRL; φp<0.05 vs NaCl 0.9% SKA

*Astrocytes are the only brain proliferative cells,
which intervene during development and reparation processes

P-SIRT1


24 hs.
24+24 hs.
P-SIRT1 / β-ACT vs CTRL (%)
30
25
20
15
10
5
* ** φ
*
* * *
*
CTRL
LOW-DOSE SKA BDNF (1.2 pg/ml)
HIGH-DOSE BDNF (25 ng/ml)
LOW-DOSE SKA BDNF
HIGH-DOSE BDNF

guna.it

Guna-BDNF

DIRECTIONS AND ADMINISTRATION WAYS
20 drops twice a day for 4-6 months.
Children under 6 years: 10 drops twice a day for 4-6 months.

Sublingual absorption: directly under the tongue or in a little water, preferably far from the meals.

LOW DOSE BDNF
in Paroxysmal Atrial Fibrillation
Preliminary data

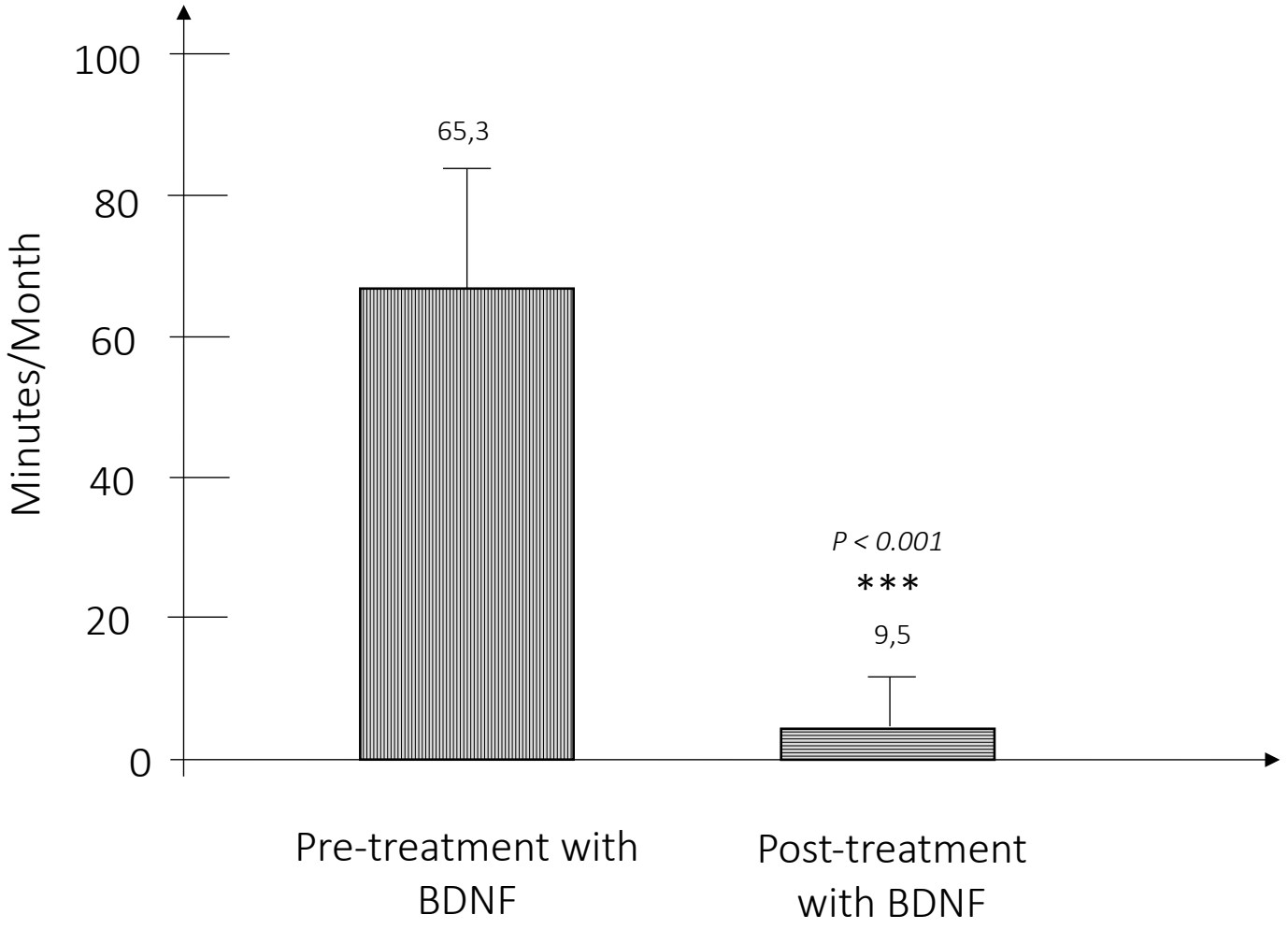
Paroxysmal Atrial Fibrillation

- No structural signs of heart disease
- Not pharmacological treatments suspended

Evaluation of:

- Minutes per month
- Symptoms
- Dynamic ECG (sec. Holter)
- Loop recorder
- PM ICD implanted

Minutes per month



	MINUTES PER MONTH	
	Pre-treatment with BDNF	Post-treatment with BDNF
S1	10	0
S2	45	0
S3	120	2
S4	12	2
S5	10	2
S6	8	3
S7	50	0
S8	20	2
S9	12	2
S10	26	3
S11	260	10
S12	120	2
S13	38	3
S14	14	0
S15	20	0
S16	12	0
S17	250	25
S18	60	3
S19	110	80
S20	60	50
S21	80	20
S22	100	0

Les liaisons dangereous

Published in final edited form as:
Neuropharmacology. 2016 March ; 102: 72–79. doi:10.1016/j.neuropharm.2015.10.034.

BDNF — a key transducer of antidepressant effects

Carl Björkholm[a] and **Lisa M. Monteggia**[b,*]

[a] Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

[b] Department of Neuroscience, University of Texas Southwestern Medical Center, Dallas, TX, USA

Neuroscience and Biobehavioral Reviews 43 (2014) 35–47

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

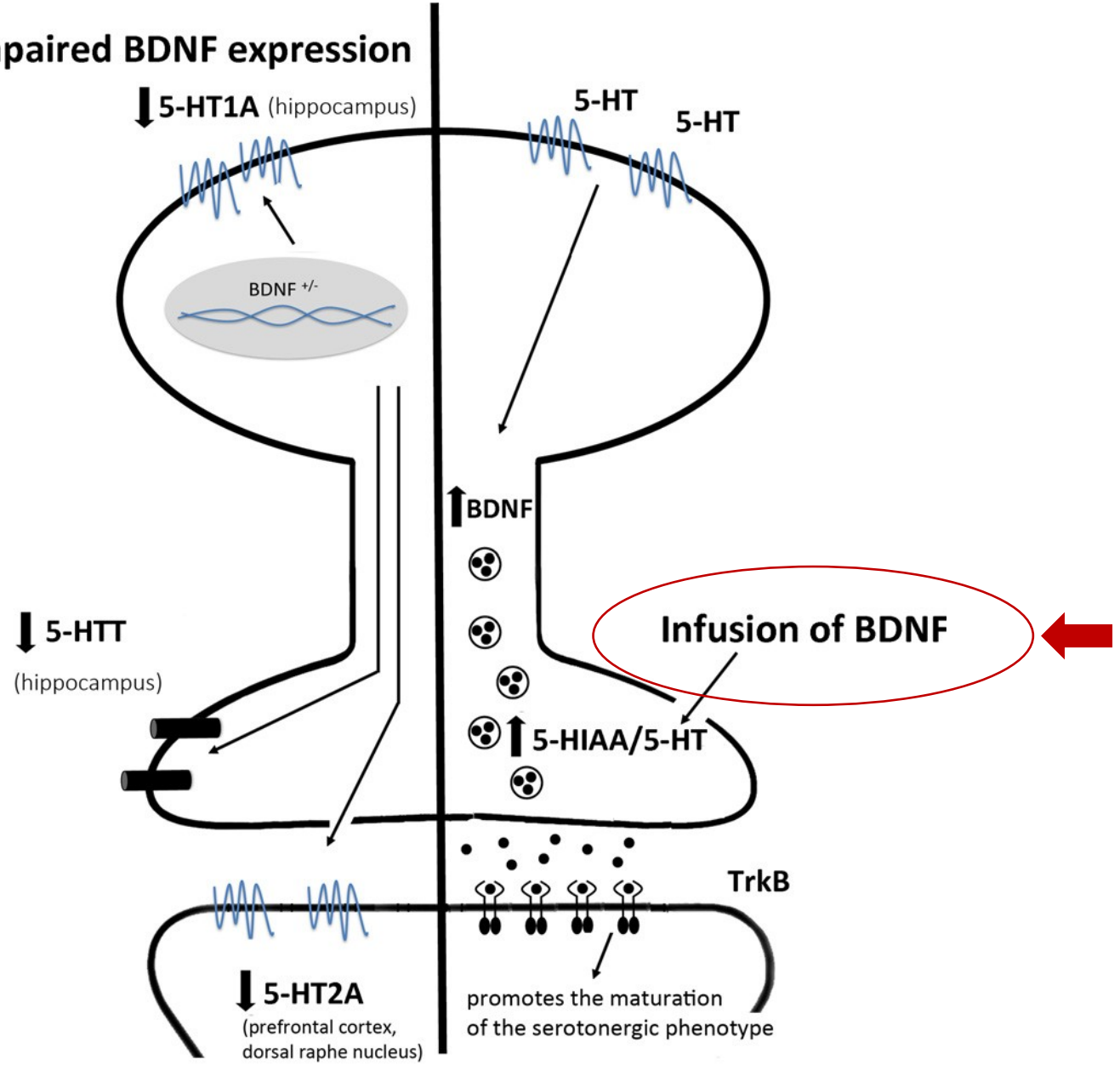
journal homepage: www.elsevier.com/locate/neubiorev

Review

The serotonin–BDNF duo: Developmental implications for the vulnerability to psychopathology

Judith Regina Homberg[a], Raffaella Molteni[b], Francesca Calabrese[b], Marco A. Riva[b,*]

[a] *Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Nijmegen Medical Centre, Geert Grooteplein 21, 6525 EZ Nijmegen, The Netherlands*
[b] *Department of Pharmacological and Biomolecular Sciences, University of Milan, Via Balzaretti 9, 20133 Milan, Italy*



Schematic representation of BDNF effects on the serotonergic system. As shown in the left side of the figure, impaired expression of the neurotrophin, as occurring in BDNF transgenic mice, results in reduced hippocampal function of 5-HT1A and 5-HTT as well as in 5-HT2A receptor defects within the prefrontal cortex and the dorsal raphe nucleus.

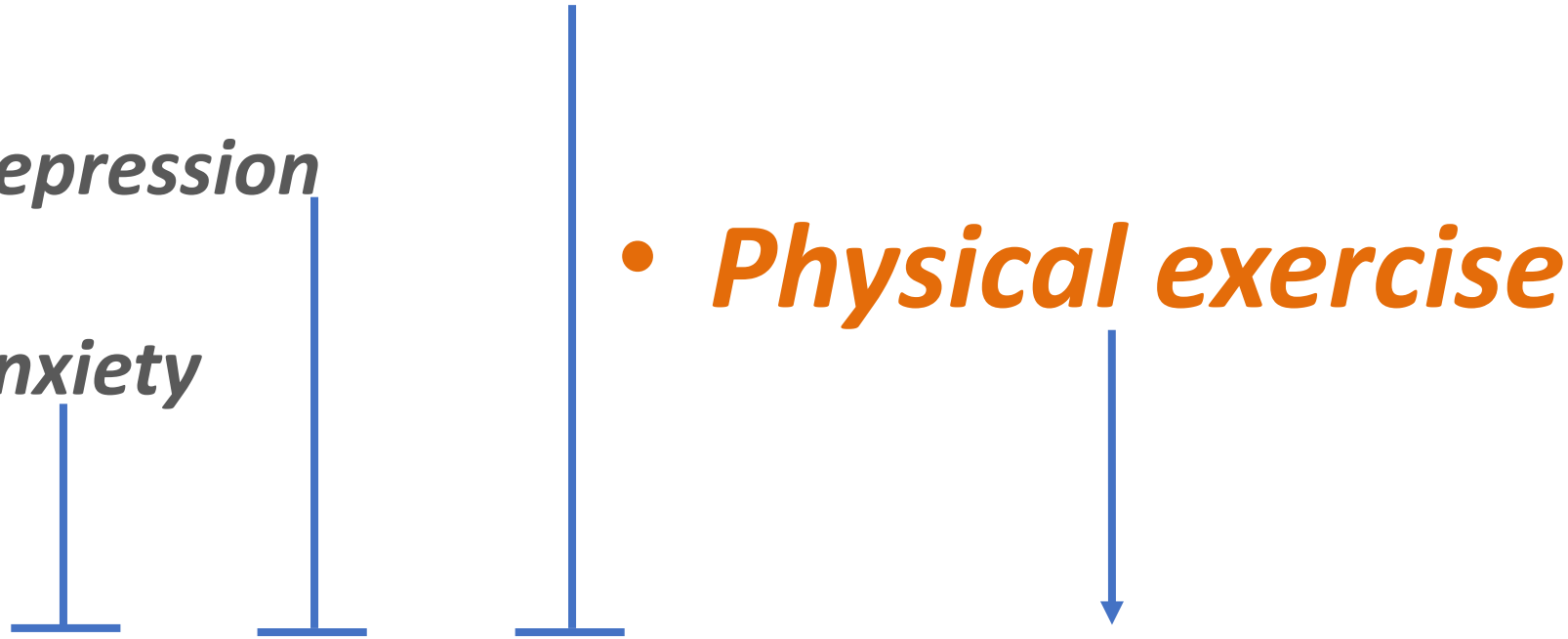
Conversely, as depicted in right side of the figure, **infusion of BDNF leads to enhanced 5HIAA/5-HT ratio and stimulates the maturation of the serotonergic phenotype.**

Homberg JR, Molteni R, Calabrese F, Riva MA. The serotonin-BDNF duo: developmental implications for the vulnerability to psychopathology. Neurosci Biobehav Rev. 2014 Jun;43:35-47. doi: 10.1016/j.neubiorev.2014.03.012. Epub 2014 Apr 3. PMID: 24704572

5-HTT: 5-HT transporter; 5-HIAA: 5-hydroxyindoleacetic acid – catabolita urinario della serotonina; TrkB: tropomyosin related kinase B.

- *Acute intermittent stress*
- *Depression*
- *Anxiety*

- ***Physical exercise***



BDNF codifying mRNA

BDNF 1-7 transcription factors

MIOKINES PRODUCTED AND RELEASED BY THE MUSCLE DURING MUSCLE CONTRACTION

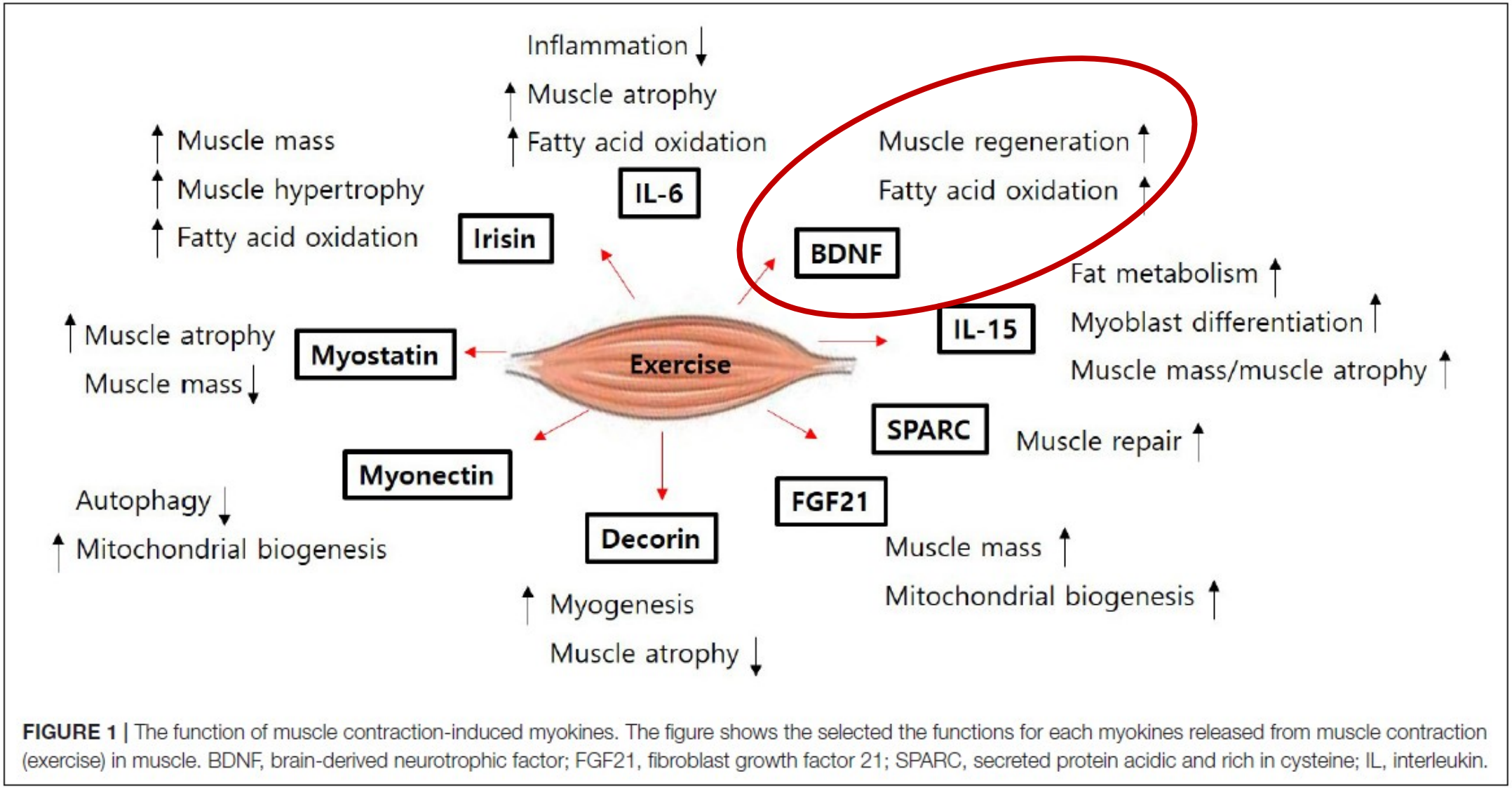


FIGURE 1 | The function of muscle contraction-induced myokines. The figure shows the selected the functions for each myokines released from muscle contraction (exercise) in muscle. BDNF, brain-derived neurotrophic factor; FGF21, fibroblast growth factor 21; SPARC, secreted protein acidic and rich in cysteine; IL, interleukin.

Lee JH, Jun HS. Role of Myokines in Regulating Skeletal Muscle Mass and Function. Front Physiol. 2019;10:42. Published 2019 Jan 30. doi:10.3389/fphys.2019.00042

Muscle BDNF loss or gain of function is sufficient to decrease or increase, respectively, the proportion of type IIB muscle fibers along with a broad range of oxidative and glycolytic marker genes.

REVIEW ARTICLE

MCBS
Mol Cell Biomed Sci. 2018; 2(2): 38-47
DOI: 10.21705/mcbs.v2i2.32

Myokine Regulation as Marker of Sarcopenia in Elderly

I Gusti Putu Suka Aryana, Anak Agung Ayu Ratih Hapsari, Raden Ayu Tuty Kuswardhani

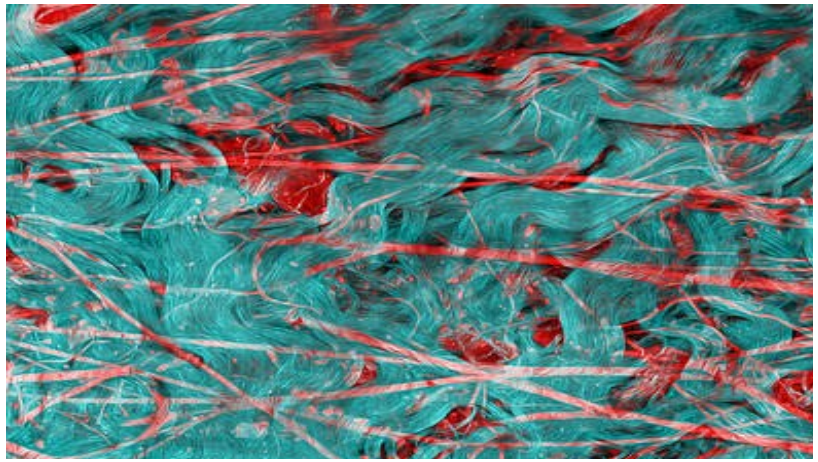
Geriatric Division, Internal Medicine Department, Faculty of Medicine, Udayana University, Sanglah Teaching Hospital, Denpasar, Indonesia

Delezie J, Weihrauch M, Maier G, et al. BDNF is a mediator of glycolytic fiber-type specification in mouse skeletal muscle. Proc Natl Acad Sci U S A. 2019;116(32):16111-16120. doi:10.1073/pnas.1900544116

A Complex System

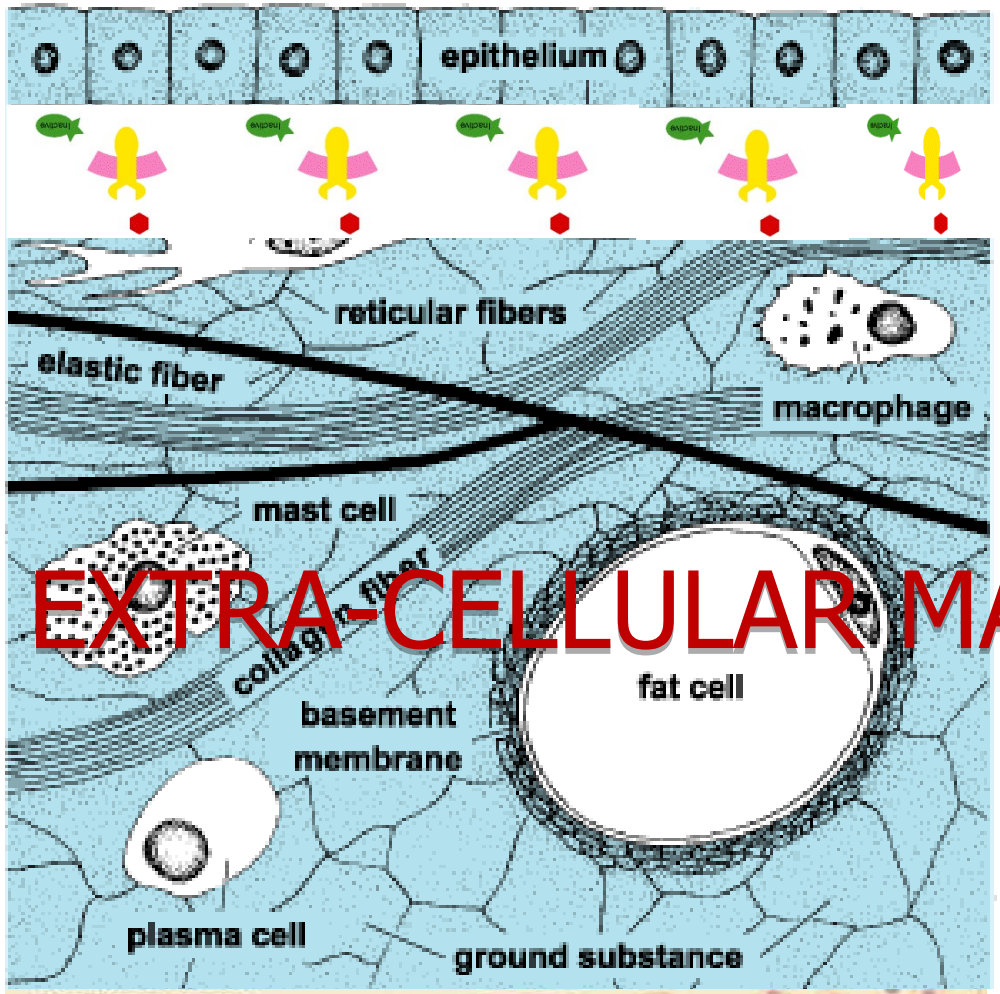
1. How do they talk?

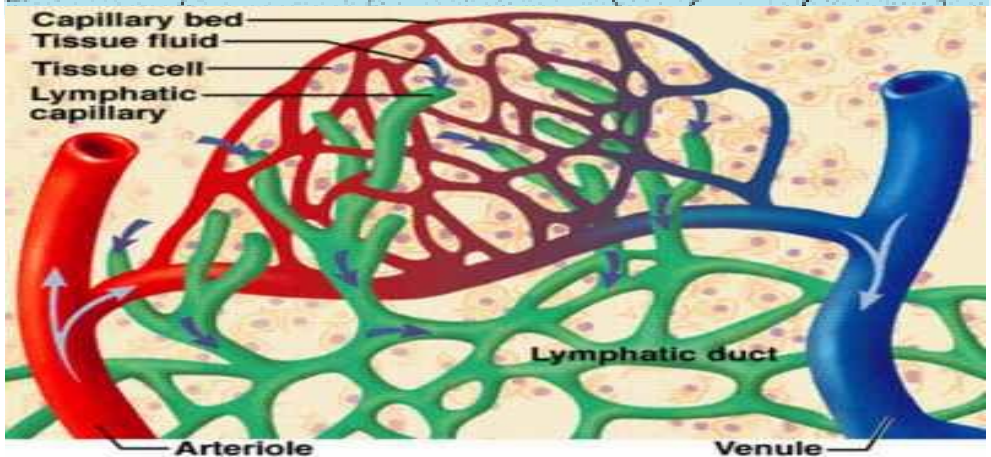
2. Where do they talk?

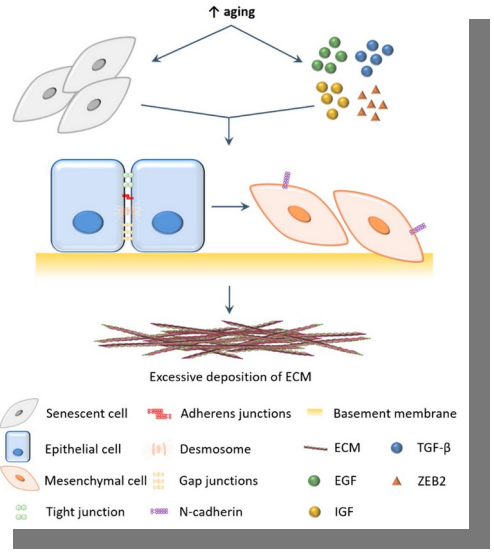


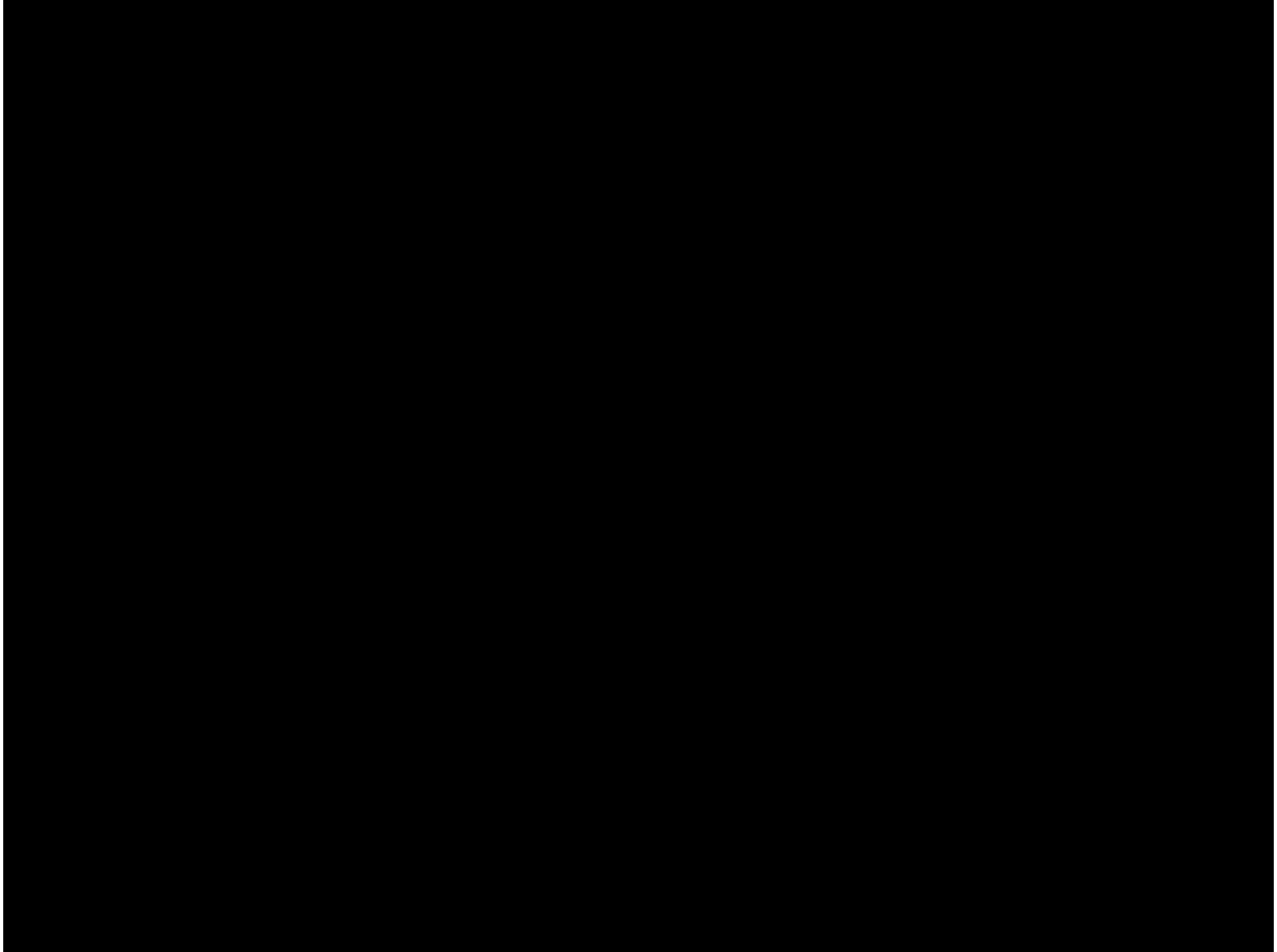
guna.it

THE EXTRA-CELLULAR MATRIX









ECM and pathological inflammation

FIBROSIS

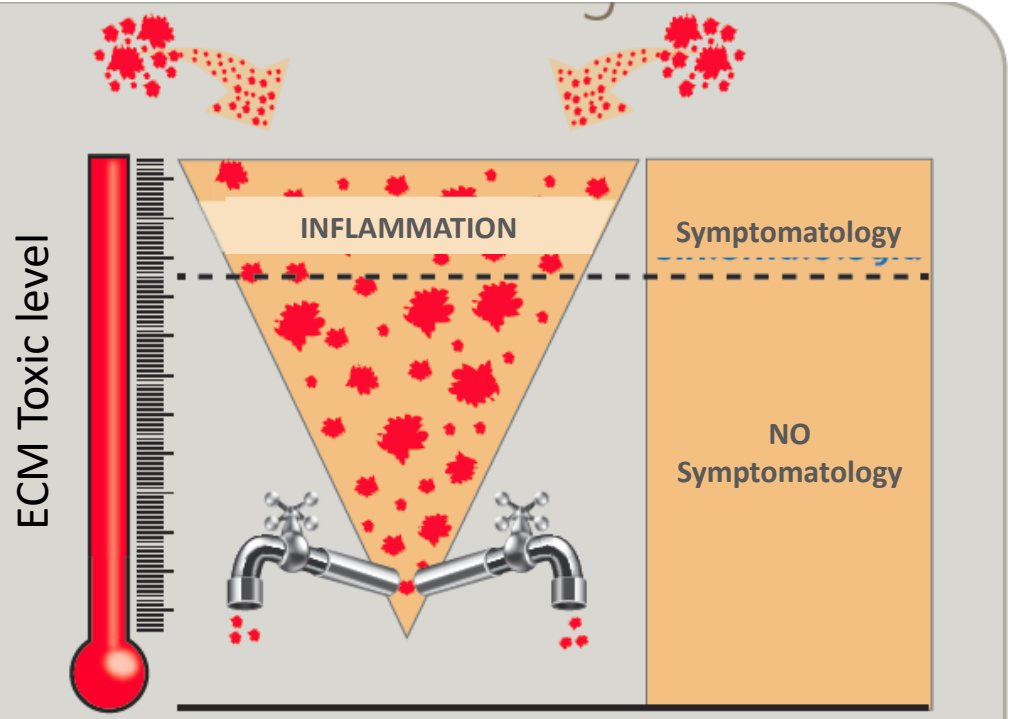
ECM RIGIDITY

AGING

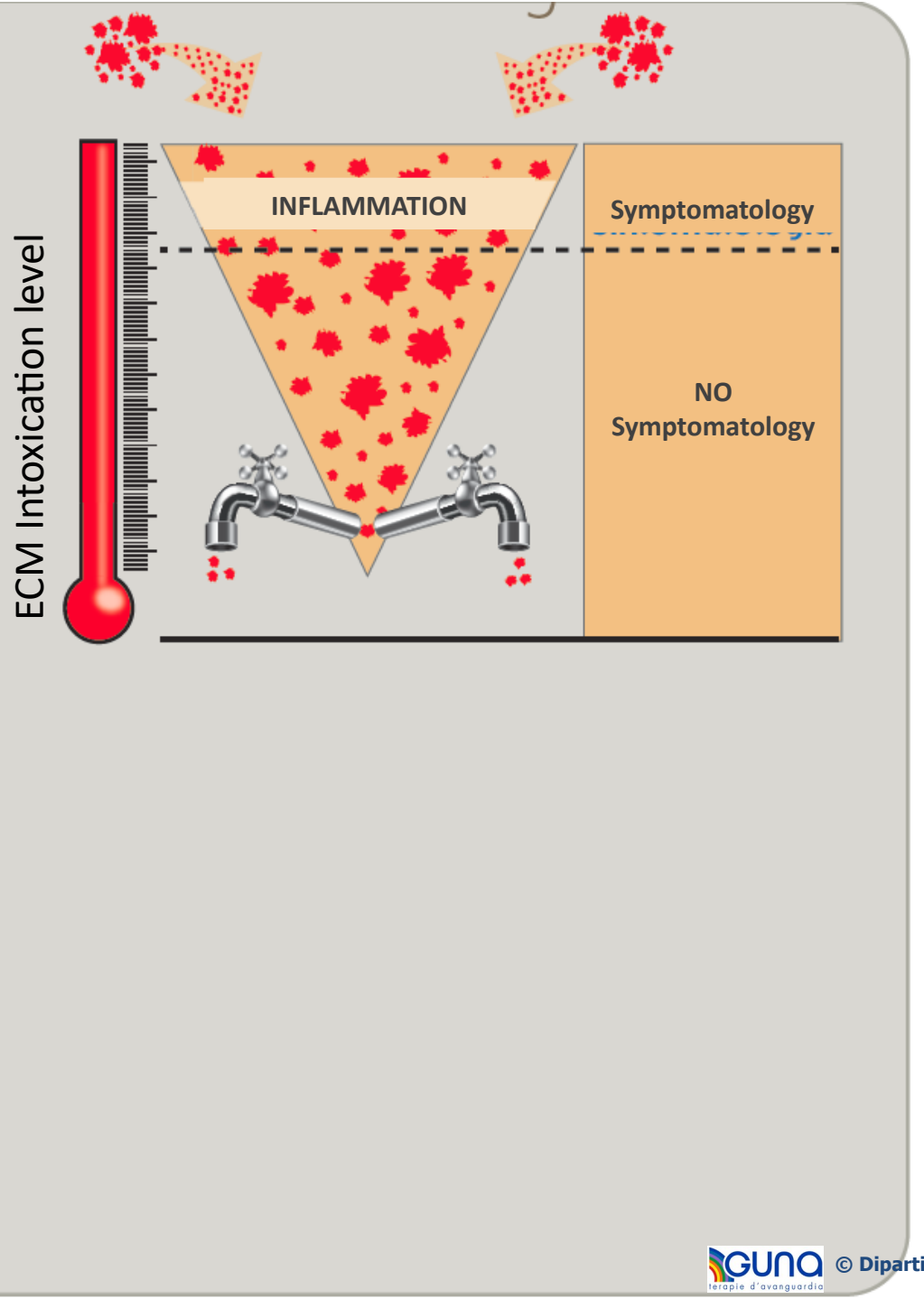
LOW GRADE CHRONIC INFLAMMATION (IL-6)

TOXIC CONDITIONS

- UP-REGULATION OF PRO-INFLAMMATORY CYTOKINES
- OVEREXPRESSION OF ROS
- REDUCTION OF pH



- HIGH LEVEL OF INFLAMMATION
- HIGH LEVEL OF OXIDATION
- **HIGH LEVEL OF INTOXICATION**



- HIGH LEVEL OF INFLAMMATION
- HIGH LEVEL OF OXIDATION
- **HIGH LEVEL OF INTOXICATION**

EXPERIMENTAL AND THERAPEUTIC MEDICINE

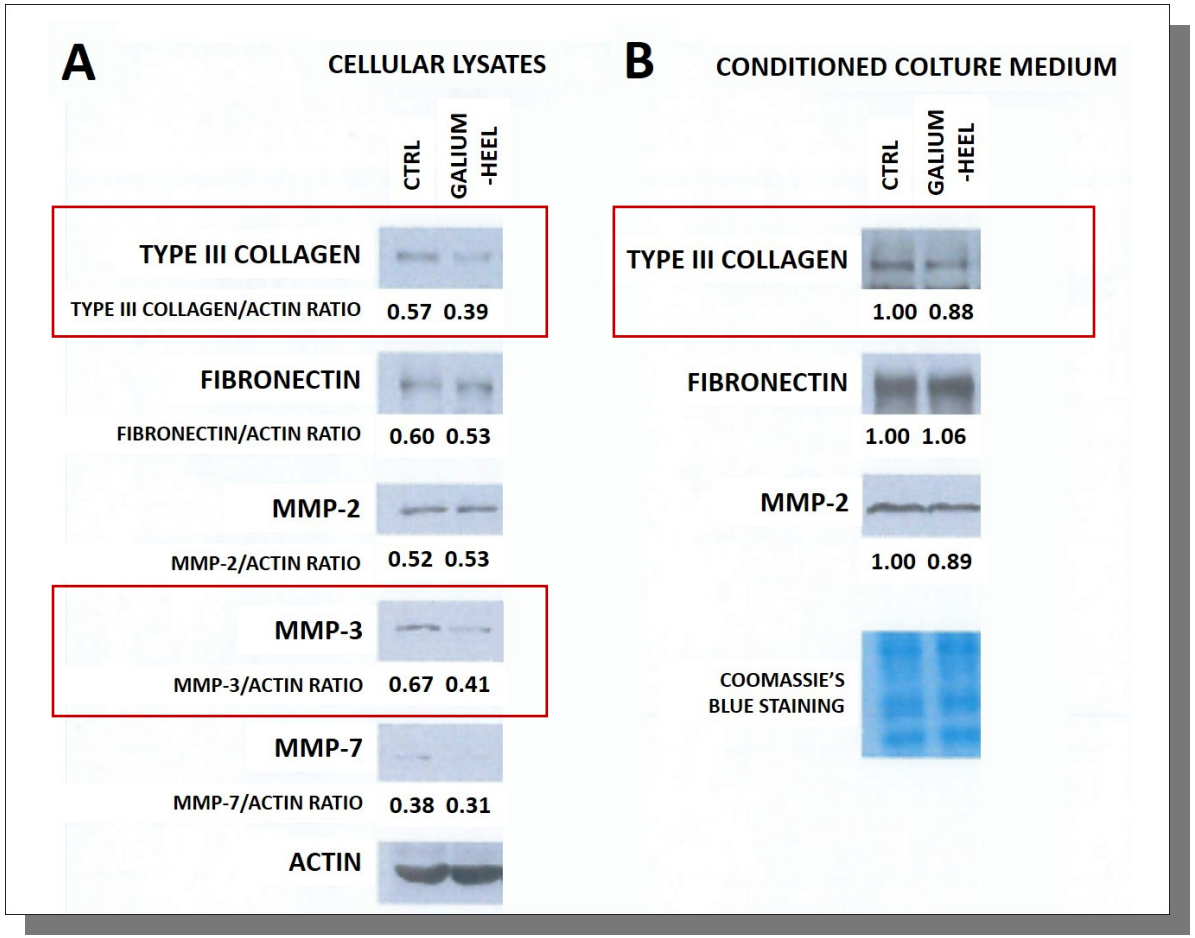
Effects of a natural multi-component compound formulation on the growth, morphology and extracellular matrix production of human adult dermal fibroblasts

MONICA BENVENUTO[1], ROSANNA MATTERA[1], MARTINO TONY MIELE[2], MARIA GABRIELLA GIGANTI[1], ILARIA TRESOLDI[1], LOREDANA ALBONICI[1], VITTORIO MANZARI[1], ANDREA MODESTI[1], LAURA MASUELLI[3*] and ROBERTO BEI[1*]

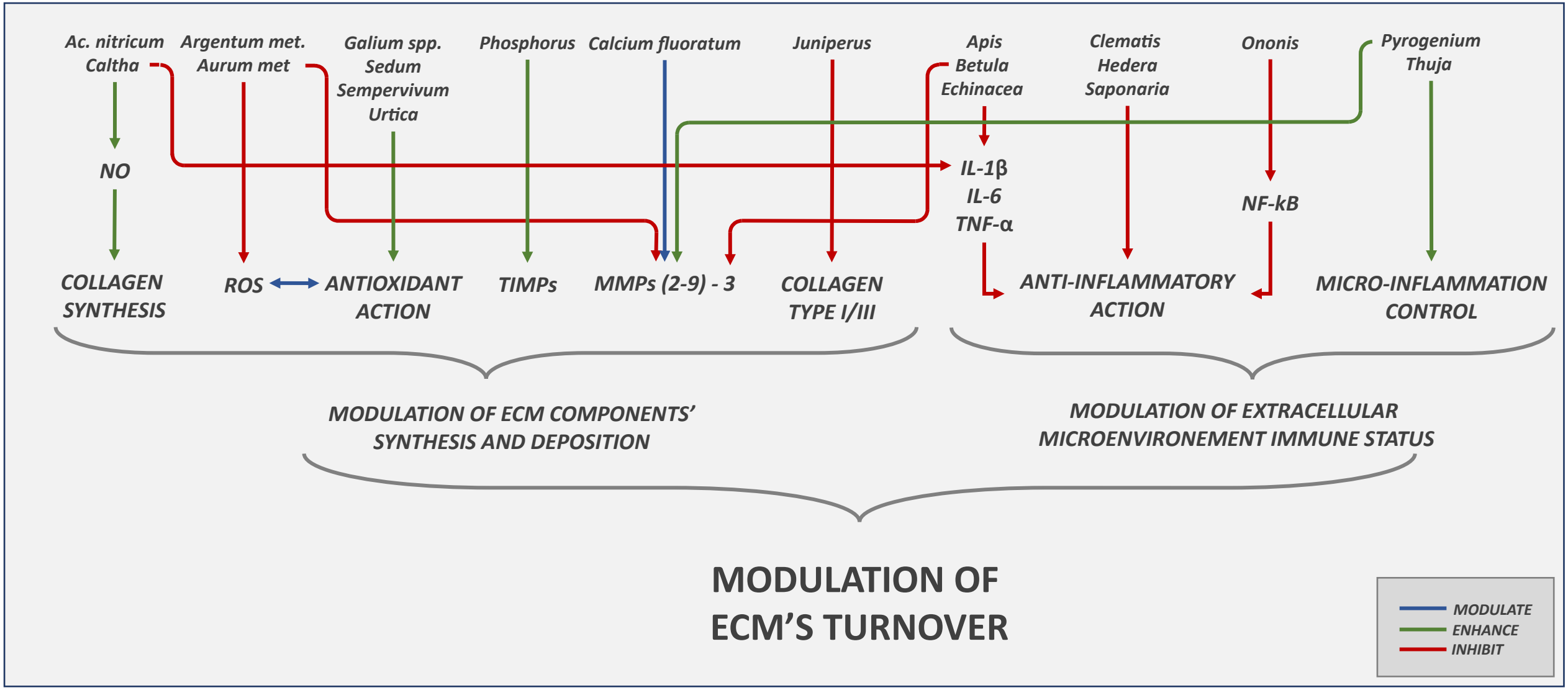
Departments of [1]Clinical Sciences and Translational Medicine and [2]Experimental Medicine, University of Rome 'Tor Vergata', I-00133 Rome; [3]Department of Experimental Medicine, University of Rome 'Sapienza', I-00161 Rome, Italy

Received January 30, 2019; Accepted July 16, 2019

DOI: 10.3892/etm.2019.7872



Galium-Heel


Ac. nitricum
Caltha
Argentum met.
Aurum met
Galium spp.
Sedum
Sempervivum
Urtica
Phosphorus
Calcium fluoratum
Juniperus
Apis
Betula
Echinacea
Clematis
Hedera
Saponaria
Ononis
Pyrogenium
Thuja
NO
IL-1β
IL-6
TNF-α
NF-kB
COLLAGEN SYNTHESIS
ROS
ANTIOXIDANT ACTION
TIMPs
MMPs (2-9) - 3
COLLAGEN TYPE I/III
ANTI-INFLAMMATORY ACTION
MICRO-INFLAMMATION CONTROL
MODULATION OF ECM COMPONENTS' SYNTHESIS AND DEPOSITION
MODULATION OF EXTRACELLULAR MICROENVIRONEMENT IMMUNE STATUS
MODULATION OF ECM'S TURNOVER
MODULATE
ENHANCE
INHIBIT

VAGUE AND INDEFINITIVE SYMPTOMS

- Overweight and obesity
- Skin Rashes
- Itchy skin
- Anxiety and depression
- Sleepness
- Insomnia
- Headche
- Lack of focusing
- Irritability
- Low libido
- Fybromialgia
- IBS
- CFS
- MCS
- …

intoxicated

inflammed

aged

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P
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AGING

- **HIGH** LEVEL OF INFLAMMATION
- **HIGH** LEVEL OF OXIDATION
- **HIGH** LEVEL OF INTOXICATION

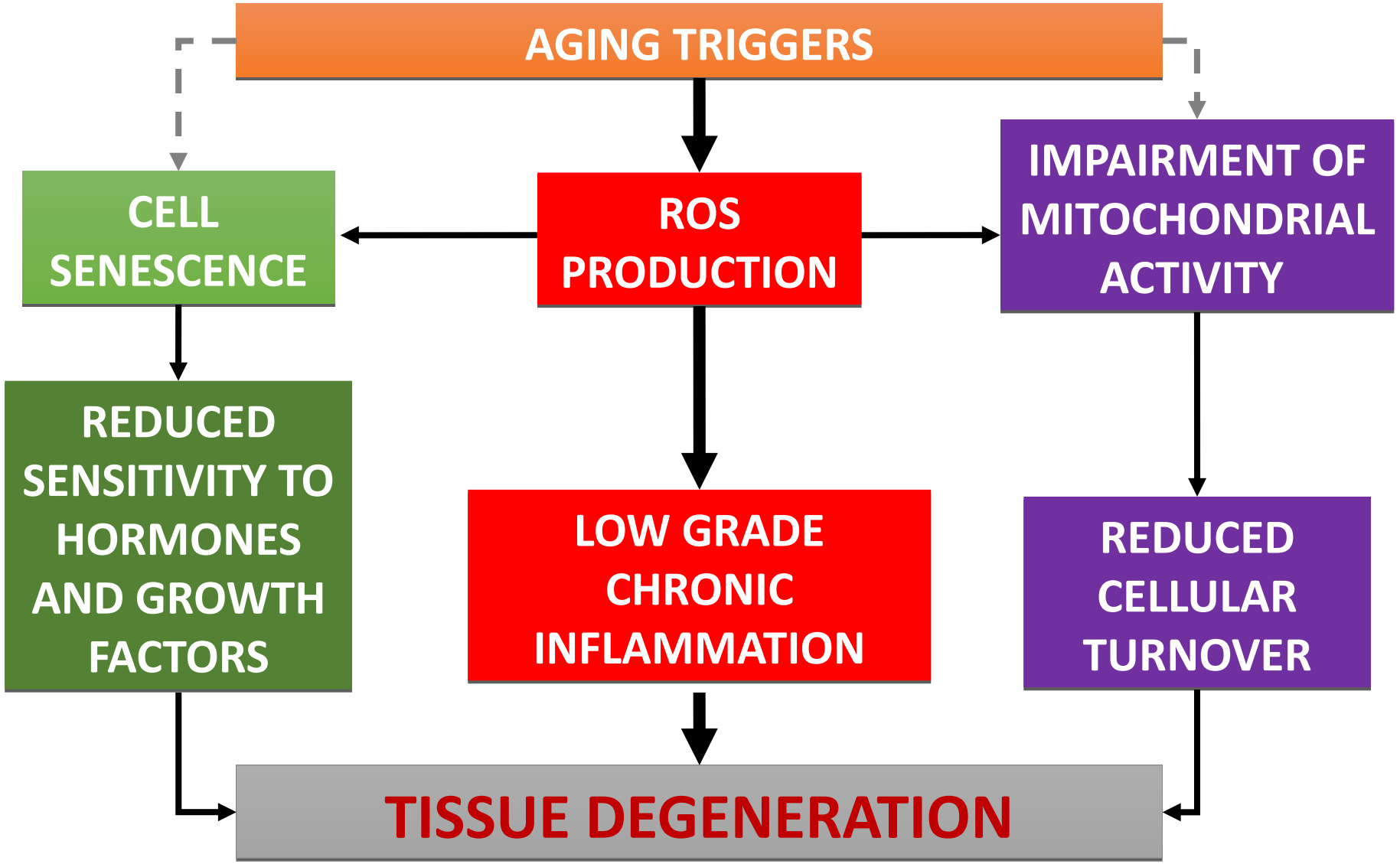
HOMEOSTASIS

- **HISTOLOGICAL DECLINE**
- **HORMONAL DECLINE**
- **IMMUNE DECLINE**

AGING

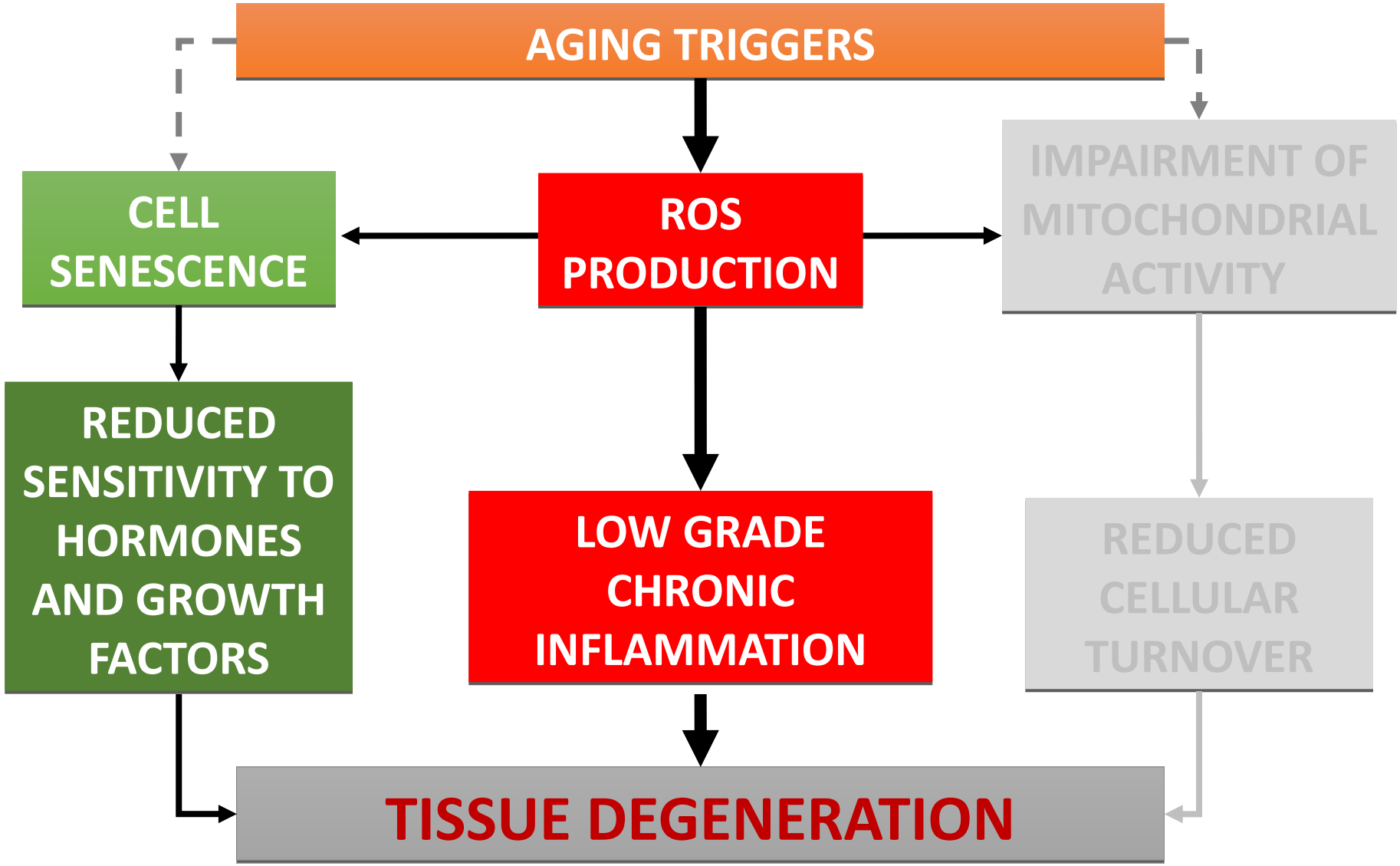
AGING - key factors -

- HIGH LEVEL OF INFLAMMATION
- HIGH LEVEL OF OXIDATION
- HIGH LEVEL OF INTOXICATION

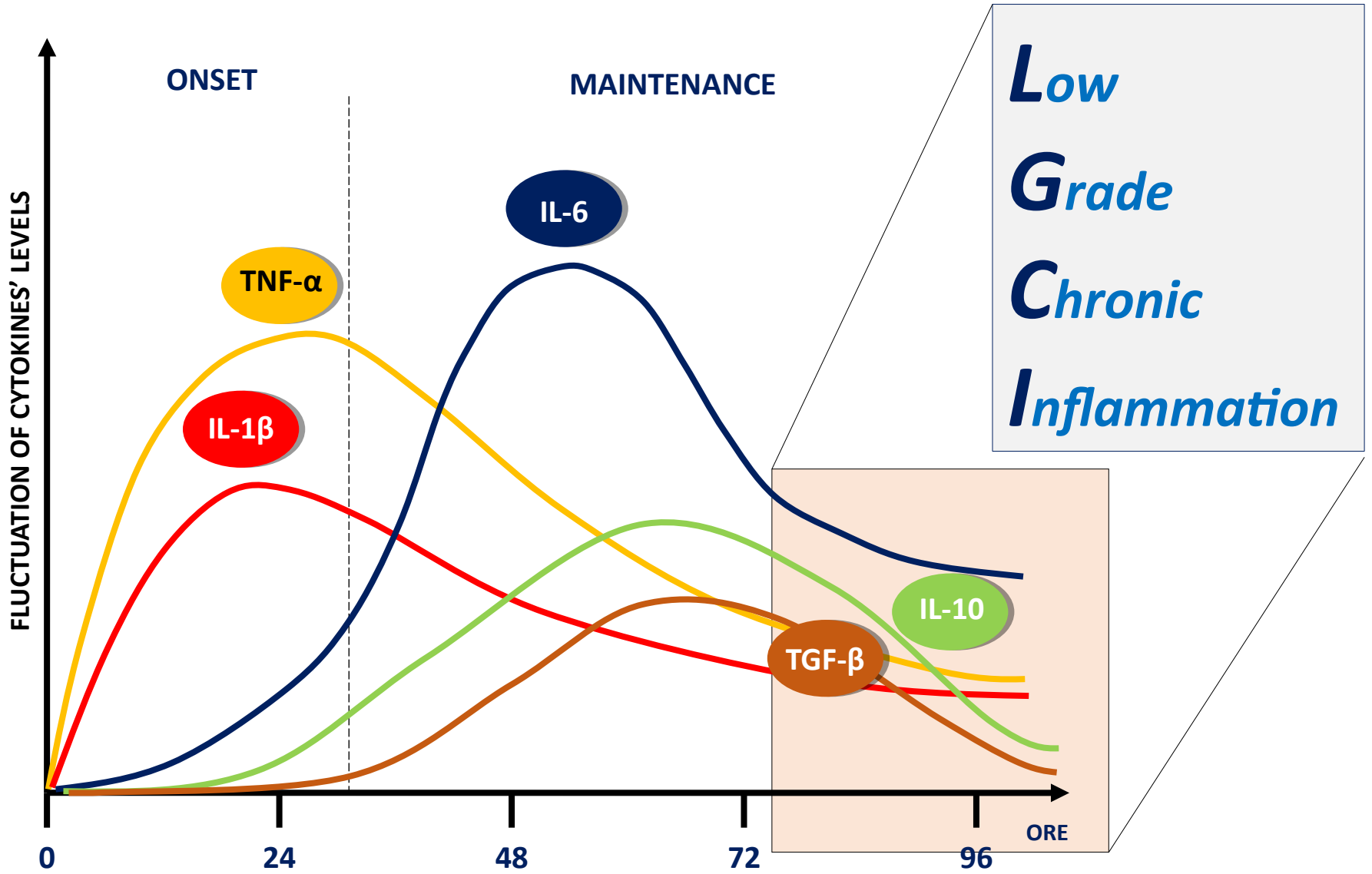


AGING - key factors -

- HIGH LEVEL OF INFLAMMATION
- HIGH LEVEL OF OXIDATION
- HIGH LEVEL OF INTOXICATION



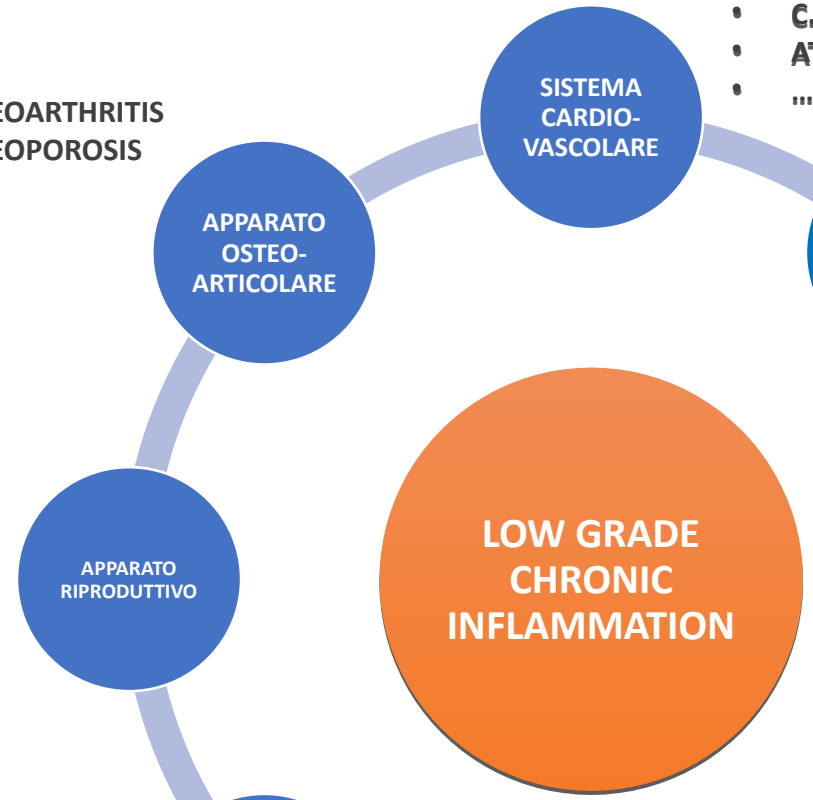
(LOW GRADE) CHRONIC Inflammatory Diseases



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

Modificata a fini didattici.

LOW-GRADE CHRONIC INFLAMMATION: THE MOTHER OF ALL DISEASES



- C.A.D.
- C.V.D.
- ATEROSCLEROSIS
- …

- IBDs/IBS
- GLUTEN SENSITIVITY
- CELIAC DISEASE
- …

- DEPRESSION
- ALZHEIMER'S
- AUTISM
- NEURODEGENERATIVE DISEASES
- …

- CANCER
- AUTOIMMUNE DISEASES
- C.F.S.
- …

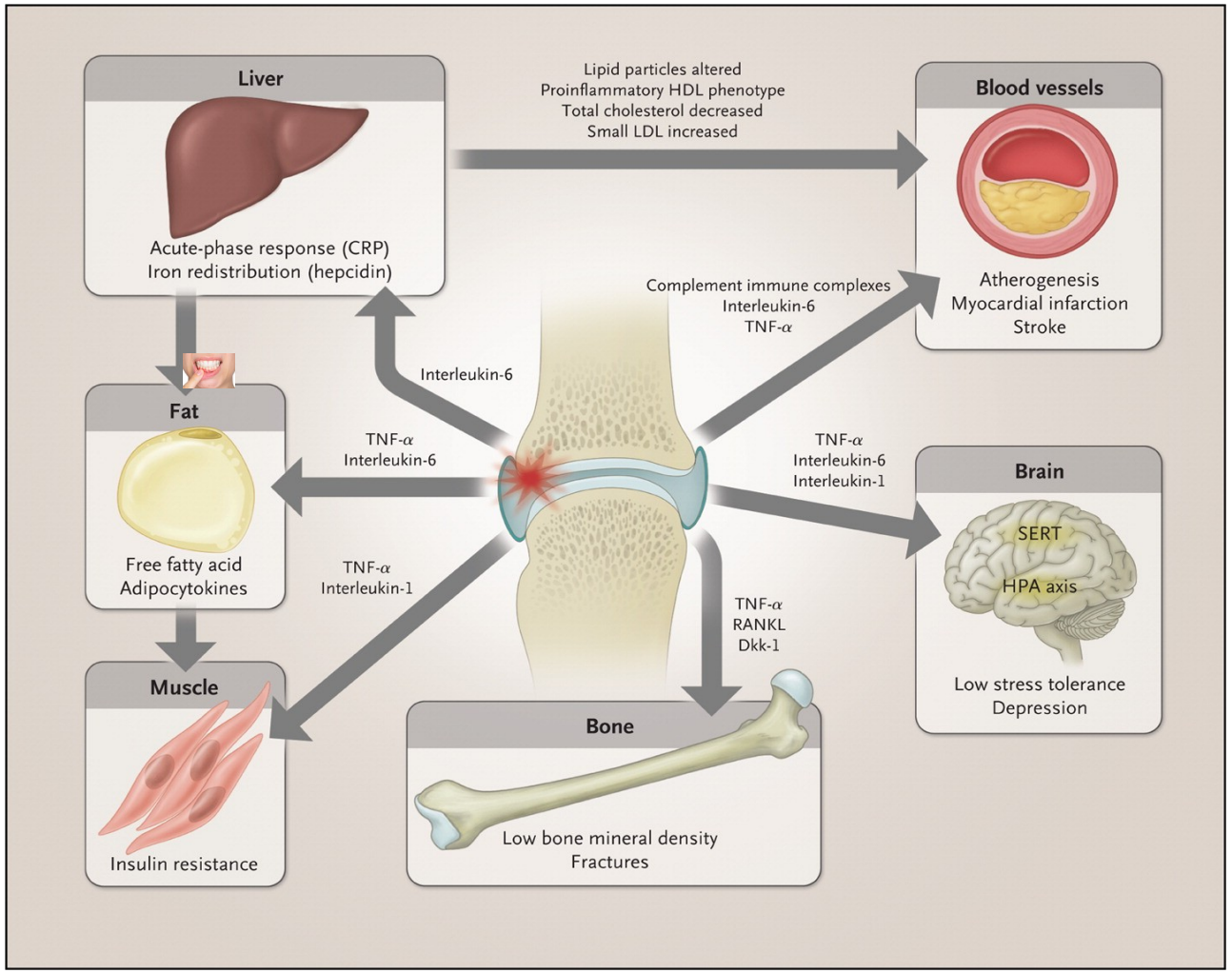
- OBESITY
- TYPE II DIABETES
- METABOLIC SYNDROME
- …

- UV RAYS DAMAGES
- SKIN AGING
- …

- IMPOTENCY
- PCOs
- …

- OSTEOARTHRITIS
- OSTEOPOROSIS
- …

Mechanisms that contribute to the onset of long term complications in patients suffering from Rheumatoid Arthritis.



McInnes IB, Schett G. N Engl J Med 2011;365:2205-2219.

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IL-2/IL-6 RATIO AND AGING

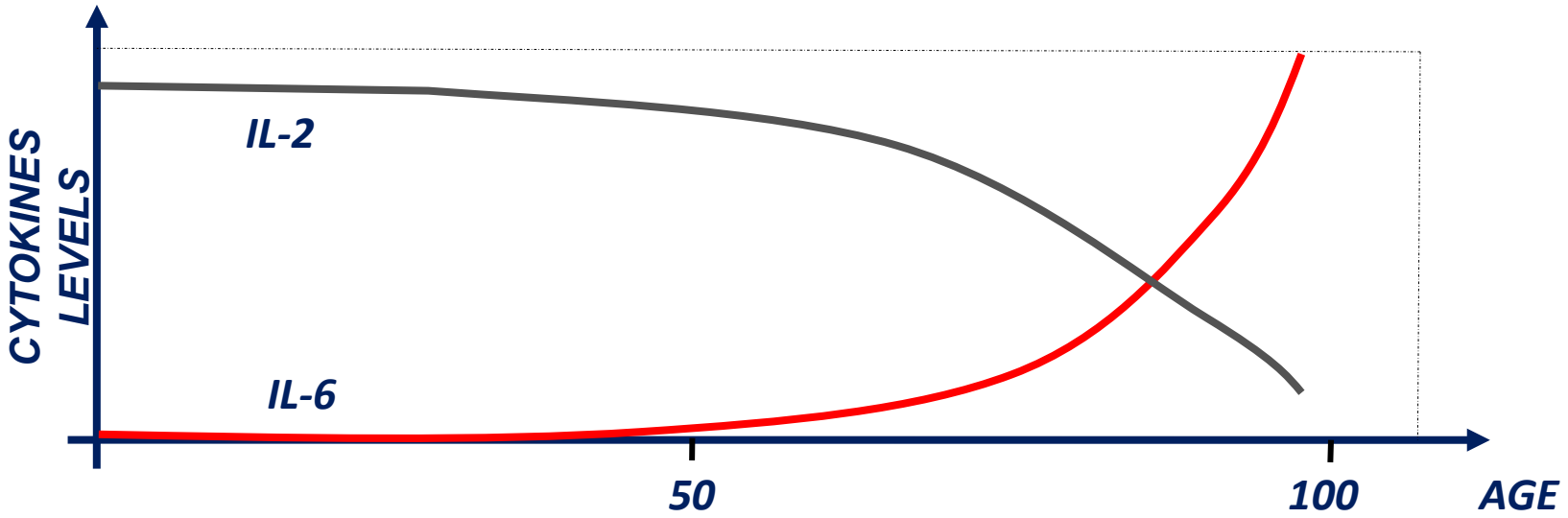
ELSEVIER

Mechanisms of Ageing and Development
100 (1998) 313–328

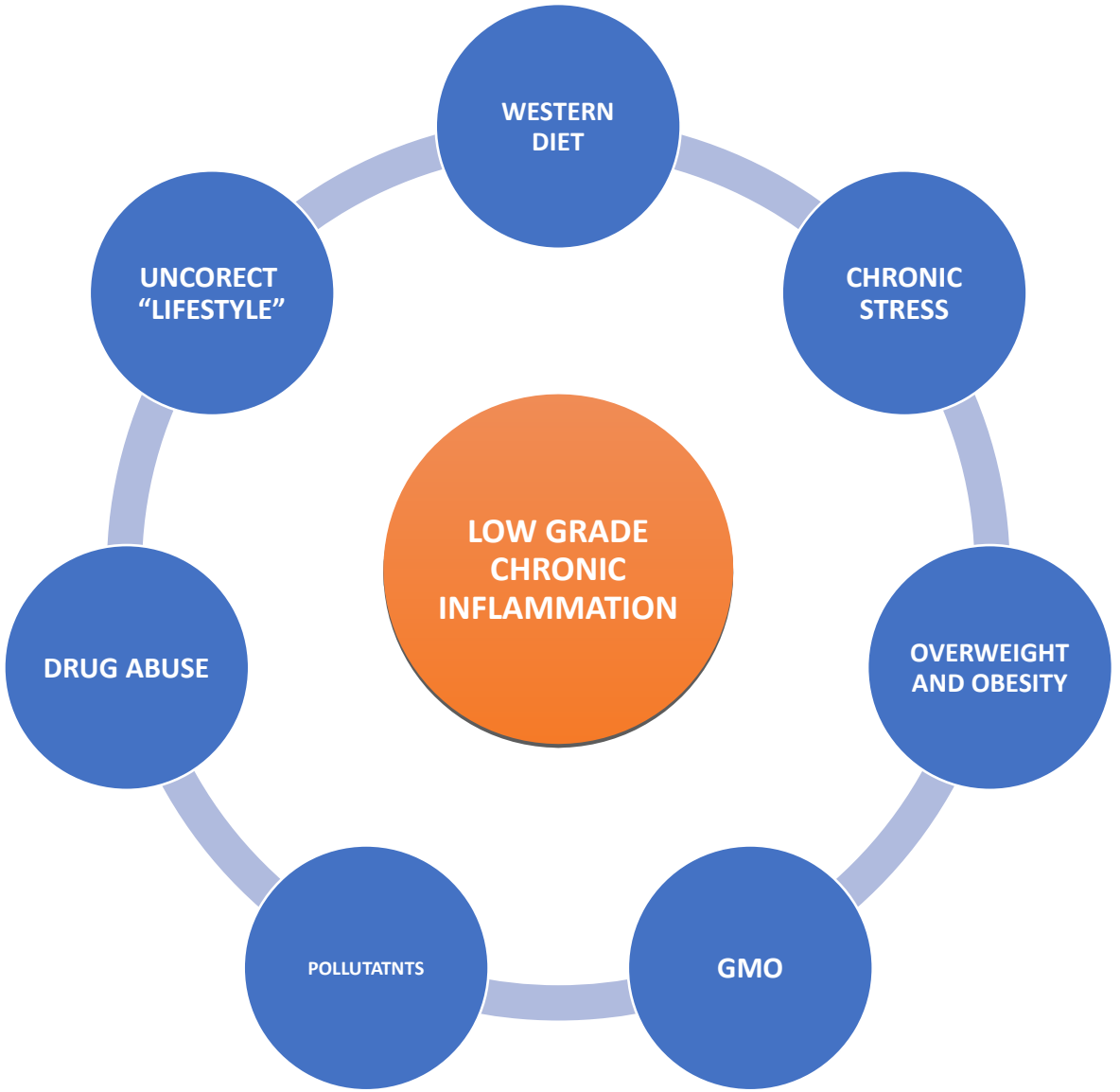
mechanisms of ageing and development

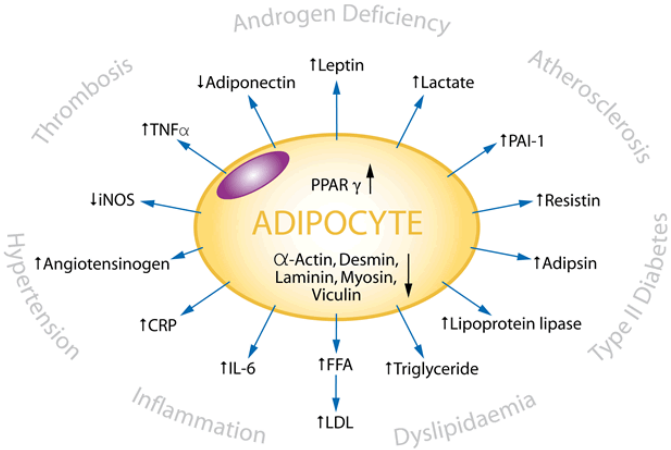
Increase of interleukin 6 and decrease of interleukin 2 production during the ageing process are influenced by the health status

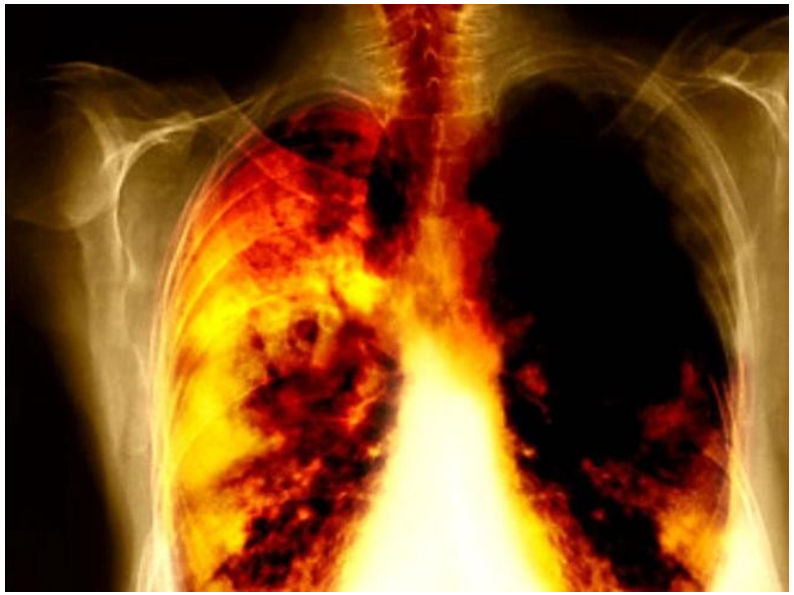
Jolanta Myśliwska [a,*], Ewa Bryl [a], Jerzy Foerster [b], Andrzej Myśliwski [a]



LOW-GRADE CHRONIC INFLAMMATION TRIGGERS







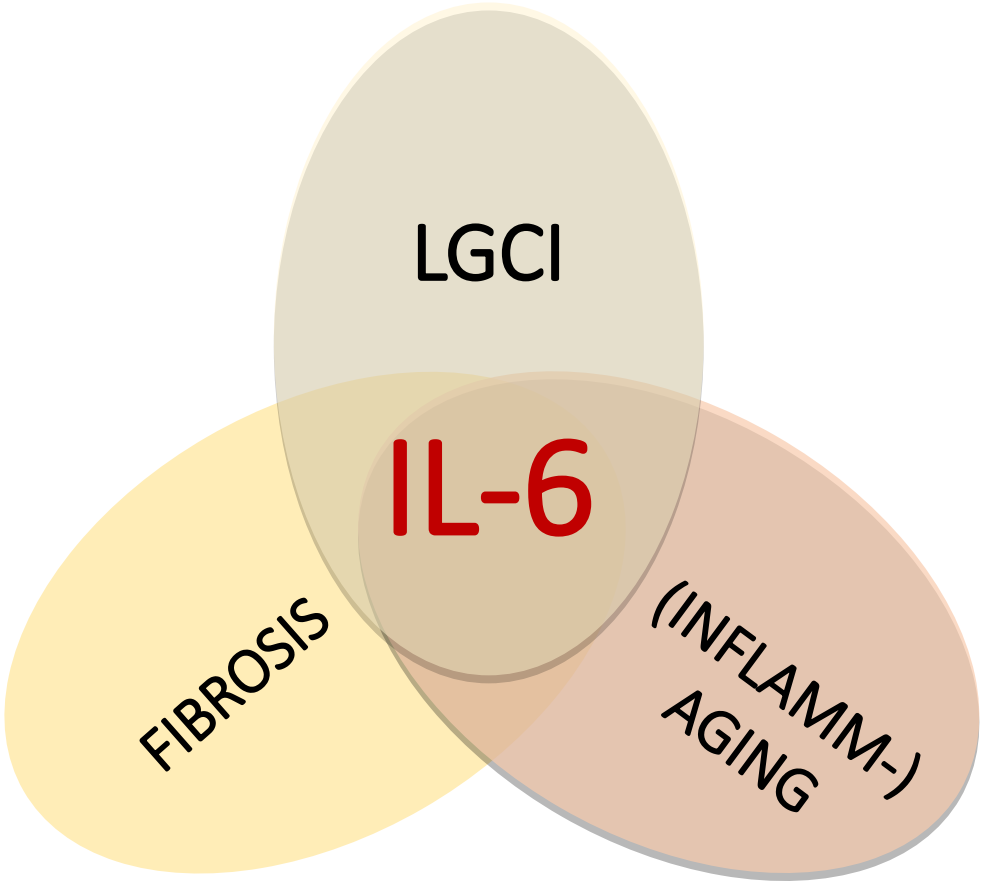
INTERLEUKIN-6

LGCI

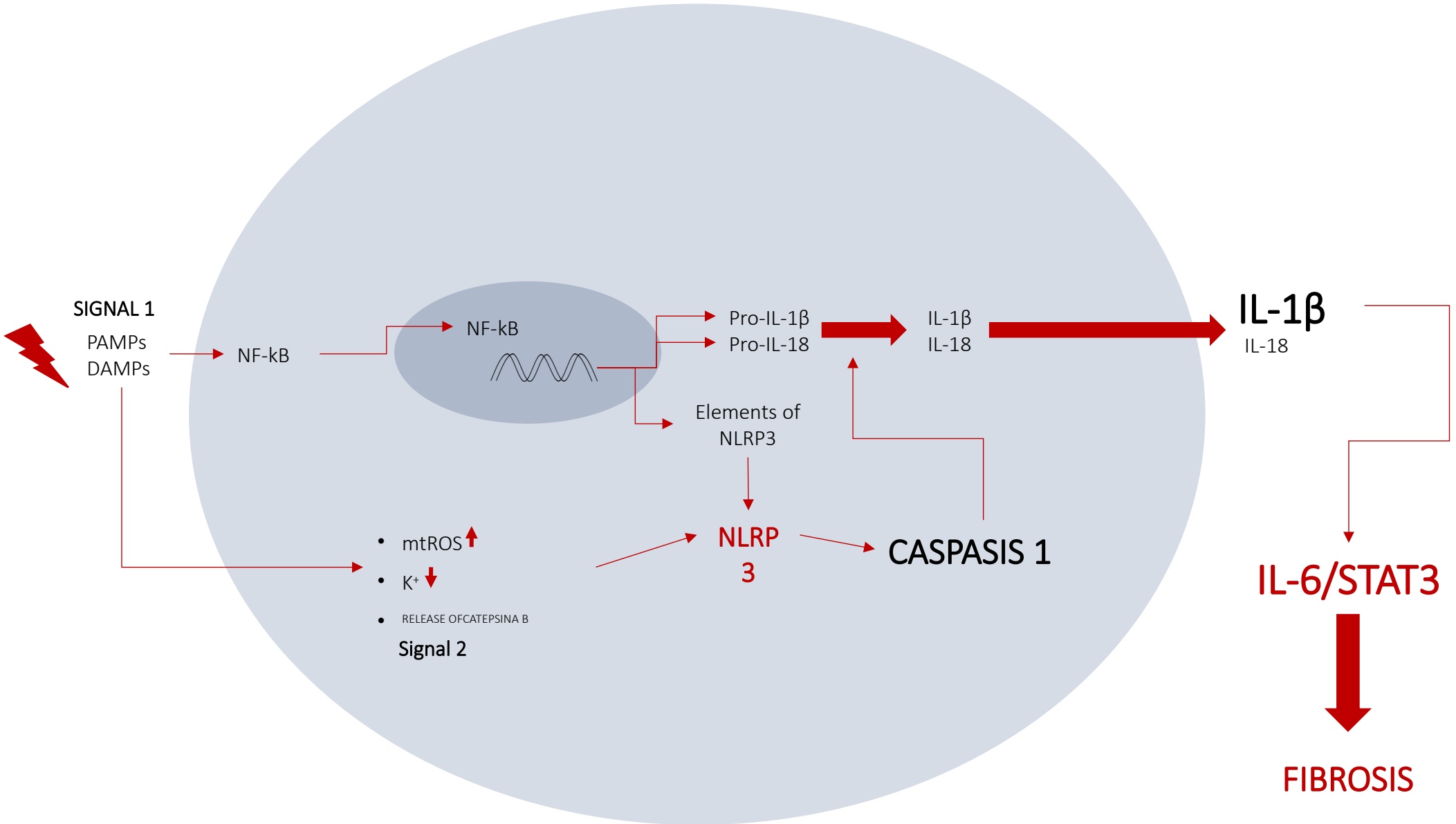
AND

FIBROSIS

The main marker of chronic inflammation, aging, and fibrotic phenomena

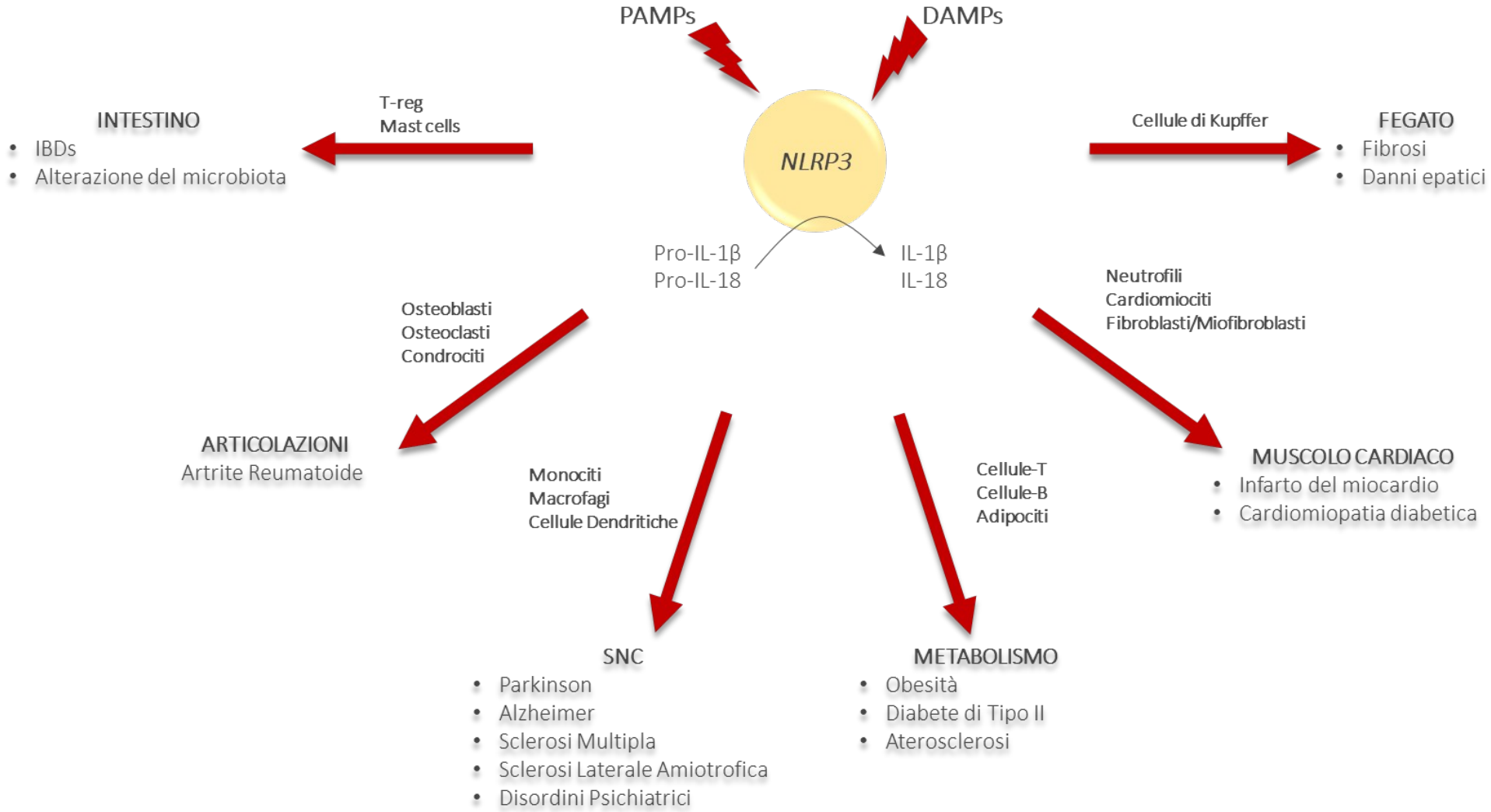


INFLAMMASOME (NLRP3), IL-6 and Fibrosis

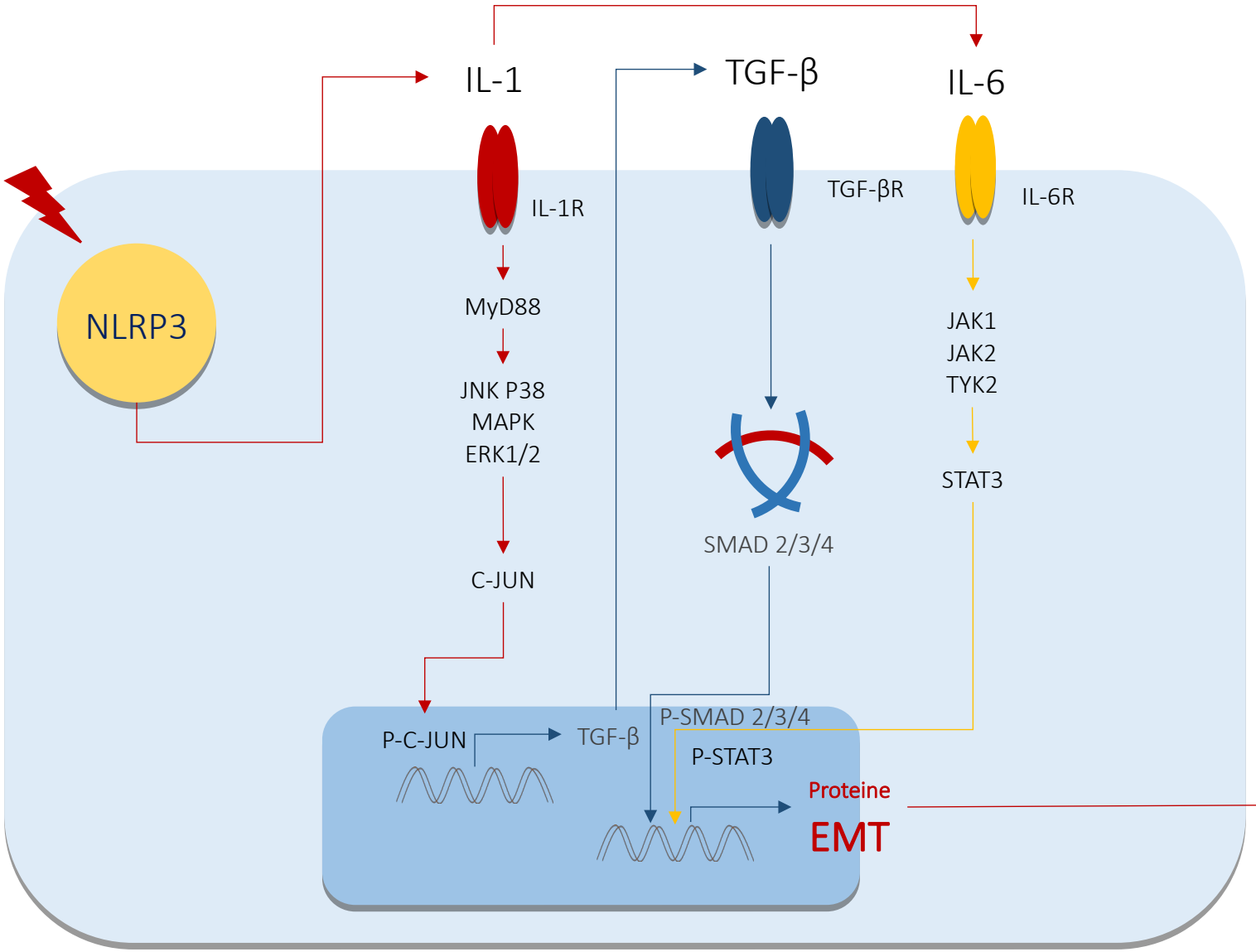


signal transducer of activation

INFLAMMASOME AND RELATED DISEASES



*THE PIVOT OF FIBROTIC PHENOMENON IS THE **EPITHELIAL MESENCHIMAL TRANSITION MECHANISM (EMT)***



Alyaseer AAA, de Lima MHS, Braga TT. The Role of NLRP3 Inflammasome Activation in the Epithelial to Mesenchymal Transition Process During the Fibrosis. Front Immunol. 2020 May 20;11:883.

Review
Inflammation and EMT: organ fibrosis and cancer

EMBO Molecular Medicine

Inflammation and EMT: an alliance towards organ fibrosis and cancer progression

Jose Miguel López-Novoa[1] *& M. Angela Nieto*[2]*

Nephrol Dial Transplant (2012): Editorial Reviews 21

Nephrol Dial Transplant (2012) 27: 21–27
doi: 10.1093/ndt/gfr567
Advance Access publication 18 November 2011

Fibrosis, regeneration and cancer: what is the link?

Valeria Cernaro, Antonio Lacquaniti, Valentina Donato, Maria Rosaria Fazio, Antoine Buemi and Michele Buemi

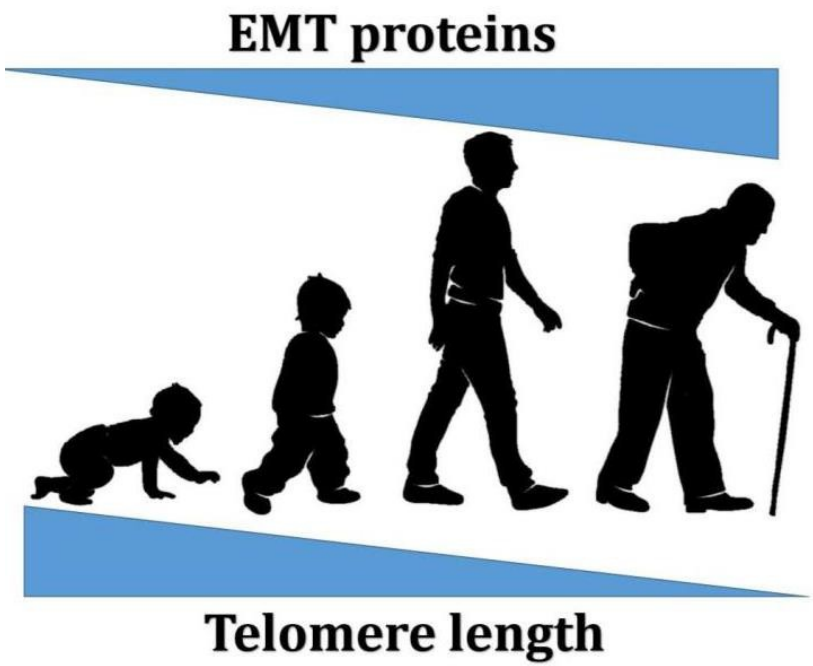
International Journal of
Molecular Sciences

MDPI

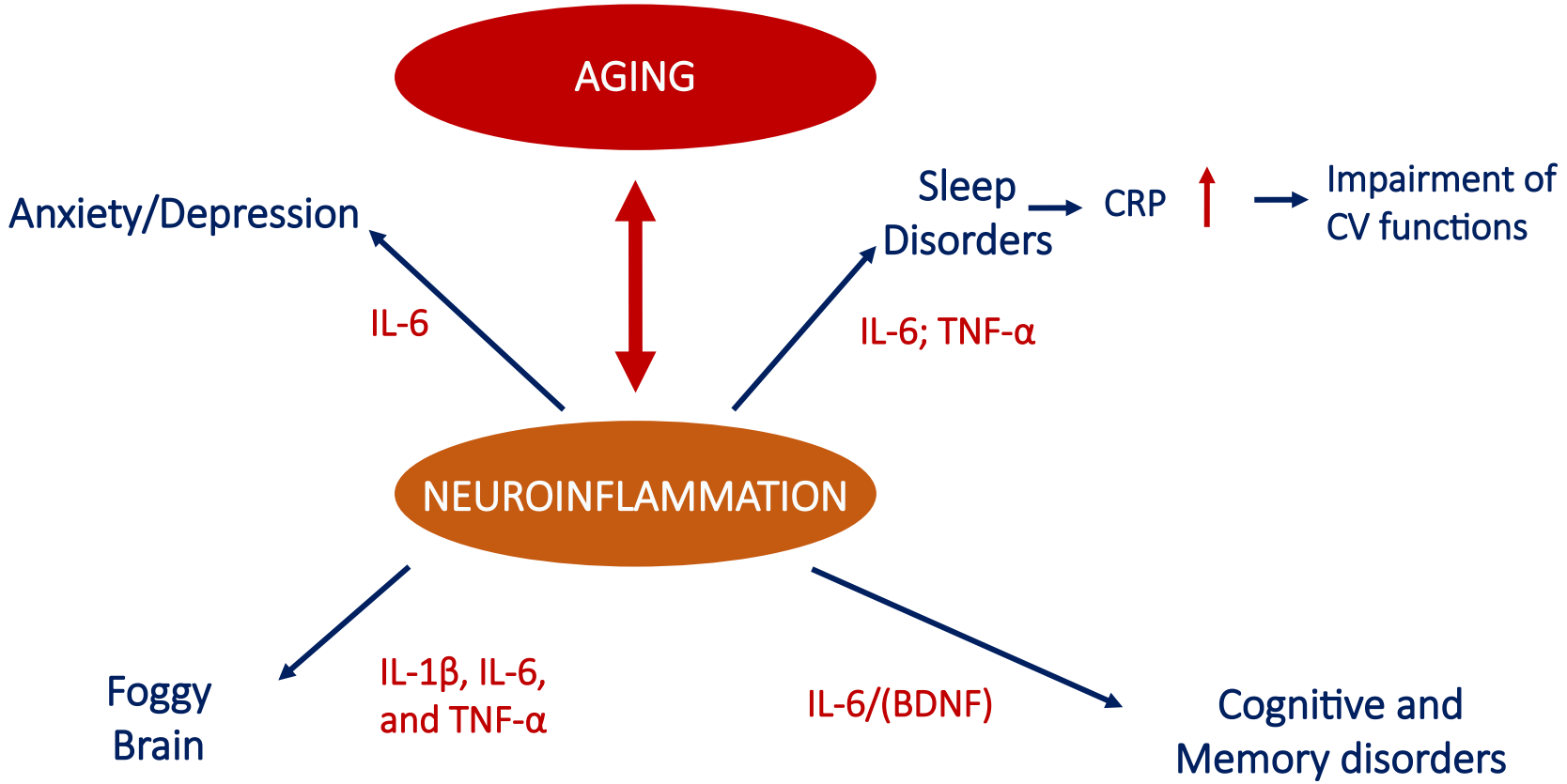
Review

Is There an Interconnection between Epithelial–Mesenchymal Transition (EMT) and Telomere Shortening in Aging?

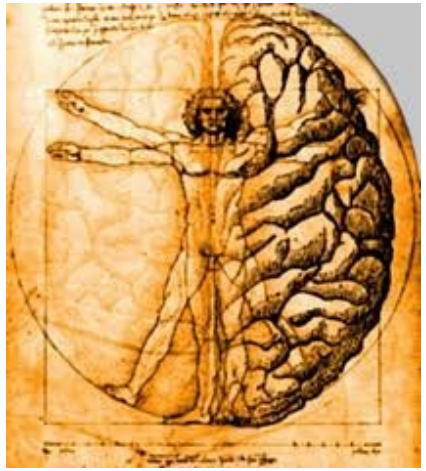
Siti A. M. Imran [1], Muhammad Dain Yazid [1], Ruszymah Bt Hj Idrus [1,2], Manira Maarof [1], Abid Nordin [1,2], Rabiatul Adawiyah Razali [1,2] and Yogeswaran Lokanathan [1,*]



Neuroinflammatory-related disorders associated with aging



- *Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, Ho RC. IL-1β, IL-6, TNF- α and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. Sci Rep. 2018 Aug 13;8(1):12050.*
- *Michal M, Wiltink J, Kirschner Y, Schneider A, Wild PS, Münzel T, Blettner M, Schulz A, Lackner K, Pfeiffer N, Blankenberg S, Tschan R, Tuin I, Beutel ME. Complaints of sleep disturbances are associated with cardiovascular disease: results from the Gutenberg Health Study. PLoS One. 2014 Aug 5;9(8):e104324.*



STRESS – INTERLEUKIN-6

NEURO (-DEGENERATIVE) DISEASES AND DEPRESSION

The psycho-endocrine-neuro connection…

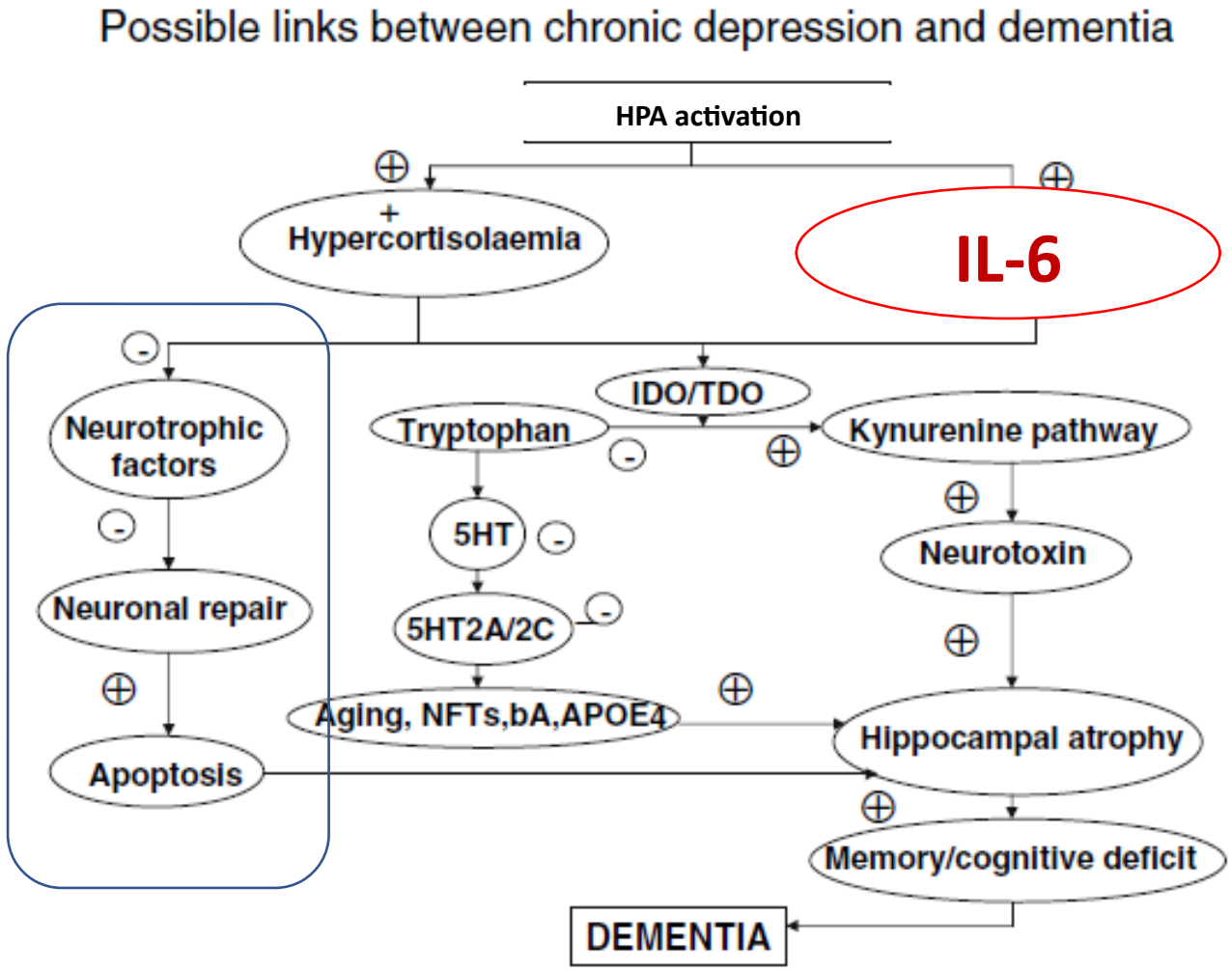


Fig. 1 Possible links between chronic depression and dementia.NFT's = neurofibrillary tangles, bA = beta amyloid, APOE 4 = apolipoprotein E4 (+) = increase; (–) = decrease

Leonard BE. Inflammation, Depression and Dementia: Are they Connected? Neurochem Res 2007

Possible links between chronic depression and dementia

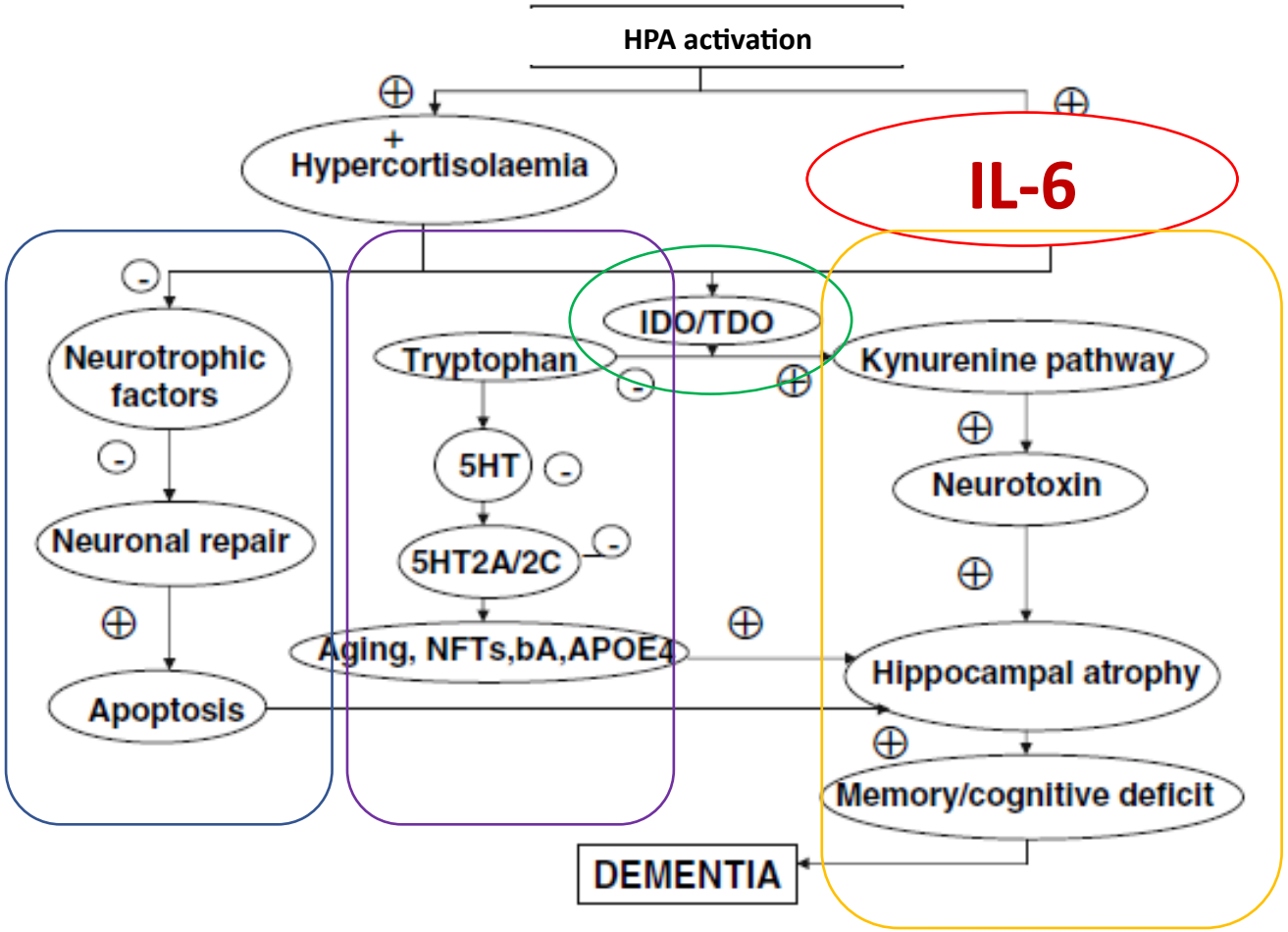


Fig. 1 Possible links between chronic depression and dementia.NFT's = neurofibrillary tangles, bA = beta amyloid, APOE 4 = apolipoprotein E4 (+) = increase; (–) = decrease

Leonard BE. Inflammation, Depression and Dementia: Are they Connected? Neurochem Res 2007

Tryptophan dioxygenase (*TDO*) and indoleamine 2,3-dioxygenase (*IDO*)

Neurobiology of Stress 4 (2016) 15–22

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Integrating Interleukin-6 into depression diagnosis and treatment

Georgia E. Hodes*, Caroline Ménard, Scott J. Russo

Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form
24 March 2016
Accepted 25 March 2016
Available online 29 March 2016

ABSTRACT

There is growing evidence of a relationship between inflammation and psychiatric illness. In particular, the cytokine Interleukin-6 (IL-6) has been linked to stress-related disorders such as depression and anxiety. Here we discuss evidence from preclinical and clinical studies examining the role of IL-6 in mood disorders. We focus on the functional role of peripheral and central release of IL-6 on the development of stress susceptibility and depression-associated behavior. By examining the contribution of both peripheral and central IL-6 to manifestations of stress-related symptomatology, we hope to broaden the way the field thinks about diagnosing and treating mood disorders.

frontiers in Neuroscience

REVIEW
published: 24 July 2018
doi: 10.3389/fnins.2018.00499

Brain Kynurenine and BH4 Pathways: Relevance to the Pathophysiology and Treatment of Inflammation-Driven Depressive Symptoms

*Sylvie Vancassel[1,2], Lucile Capuron[1,2] and Nathalie Castanon[1,2]**

[1] UMR 1286, Laboratory of Nutrition and Integrative Neurobiology (NutriNeuro), INRA, Bordeaux, France, [2] UMR 1286, Laboratory of Nutrition and Integrative Neurobiology (NutriNeuro), Bordeaux University, Bordeaux, France

IF DISEASES ARE EXPRESSIONS, CONSEQUENCES OF

CHANGED CONCENTRATION OF *MESSENGER MOLECULES…*

PROBLEM

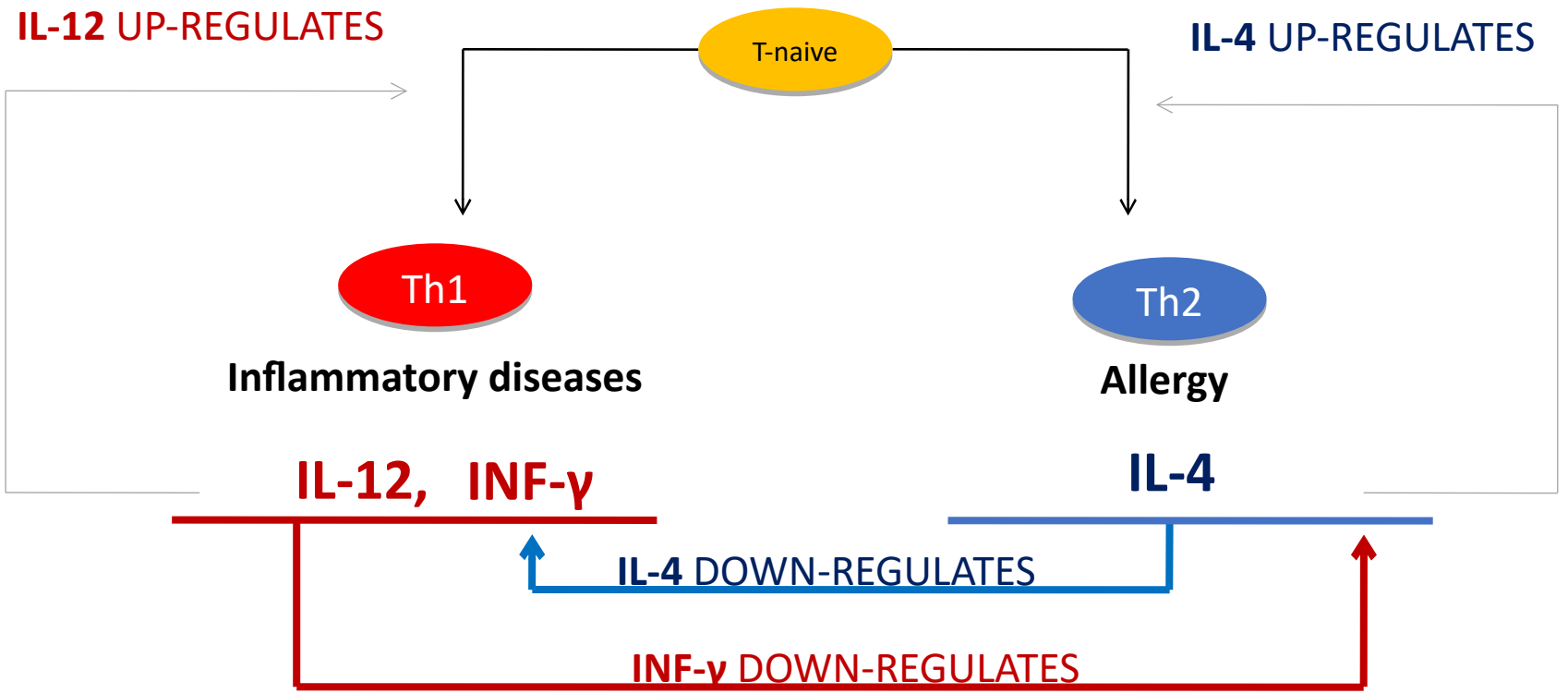
Is it possible to modulate the action of cytokines and other signaling molecules?

Clinical application of low dose cytokines

1. *same cytokines* are used in order to enhance the biological activity of the homologue cytokine

2. *antagonistic cytokines* are used in order to slow down the biological effect of another specific cytokine

THE CONCEPT OF BALANCE – RECIPROCITY of TH CELLS

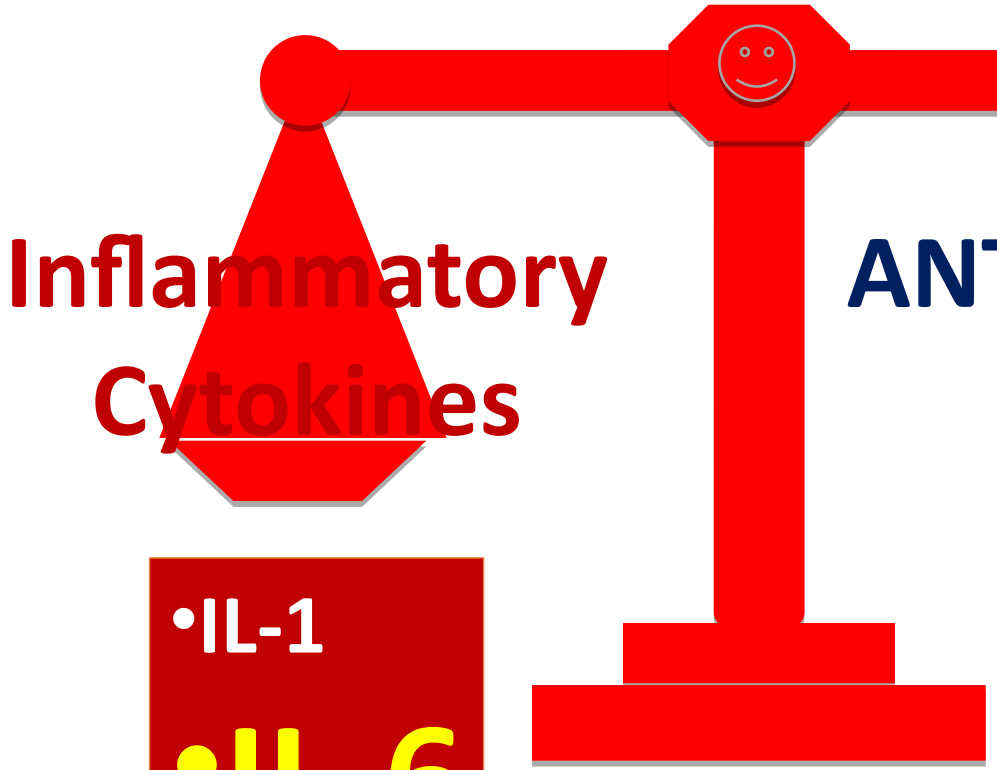


Th subsets cross-regulate expansion and functions each other.

- 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***

RECOVERING THE BALANCE IN CHRONIC INFLAMMATORY DISEASES



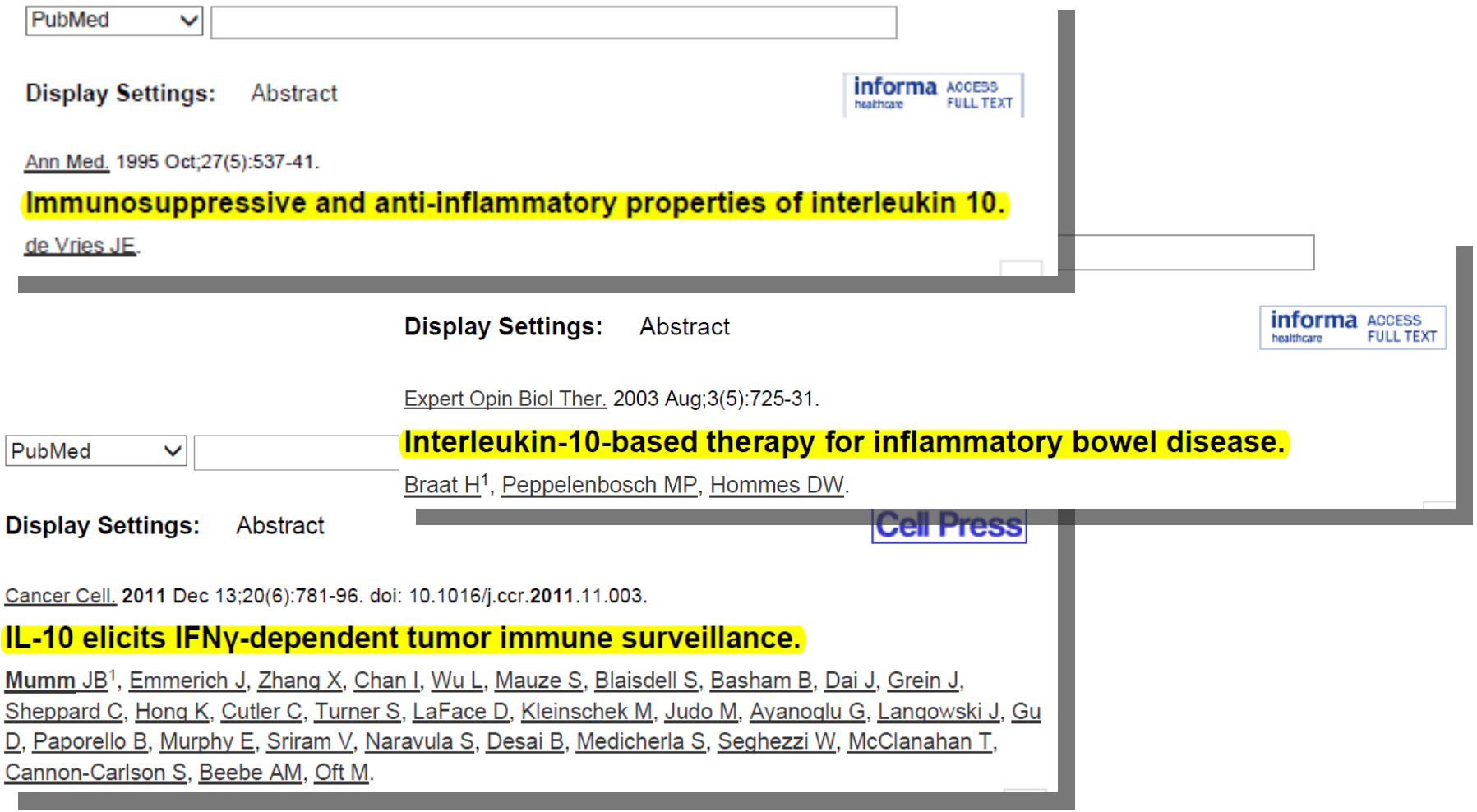
Inflammatory Cytokines

- IL-1
- **IL-6**
- TNF-α

ANTI-Inflammatory Cytokines

- Anti IL-1
- **IL-10**
- IL-4

IL-10 AS AN ANTINFLAMMATORY IN CHRONIC DISEASES



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JEM Journal of Experimental Medicine

REVIEW

Cytokines Focus

Biology and therapeutic potential of interleukin-10

Margarida Saraiva[1,2], Paulo Vieira[3,4,5], and Anne O'Garra[6,7]

The cytokine IL-10 is a key anti-inflammatory mediator ensuring protection of a host from over-exuberant responses to pathogens and microbiota, while playing important roles in other settings as sterile wound healing, autoimmunity, cancer, and homeostasis. Here we discuss our current understanding of the regulation of IL-10 production and of the molecular pathways associated with IL-10 responses. In addition to IL-10's classic inhibitory effects on myeloid cells, we also describe the nonclassic roles attributed to this pleiotropic cytokine, including how IL-10 regulates basic processes of neural and adipose cells and how it promotes CD8 T cell activation, as well as epithelial repair. We further discuss its therapeutic potential in the context of different diseases and the outstanding questions that may help develop an effective a

Cold Spring Harbor Perspectives in Biology
www.cshperspectives.org

Targeting IL-10 Family Cytokines for the Treatment of Human Diseases

Xiaoting Wang,[1] Kit Wong,[2] Wenjun Ouyang,[3] and Sascha Rutz[4]

[1]Department of Comparative Biology and Safety Sciences, Amgen, South San Francisco, California 94080
[2]Department of Biomarker Development, Genentech, South San Francisco, California 94080
[3]Department of Inflammation and Oncology, Amgen, South San Francisco, California 94080
[4]Department of Cancer Immunology, Genentech, South San Francisco, California 94080
Correspondence: wouyang@amgen.com; saschar@gene.com

Guna Interleukin-10

DIRECTIONS AND ADMINISTRATION WAYS

20 drops twice a day for 4-6 months.

Sublingual absorption: directly under the tongue or in a little water, preferably far from the meals.

guna.it

Journal of Integrative Cardiology

oat open access text

Research Article

Twenty-five years of studies and trials for the therapeutic application of IL-10 immunomodulating properties. From high doses administration to low dose medicine new paradigm

Massimo Fioranelli[1]* and Roccia Maria Grazia[2]

[1]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India

[2]G.Marconi University, Rome, Italy

Elmer Press

Original Article

Gastroenterology Research • 2013;6(4):124-133

Oral Administration of Interleukin-10 and Anti-IL-1 Antibody Ameliorates Experimental Intestinal Inflammation

Diego Cardani[a], Giuseppina F Dusio[b], Patrizia Luchini[c], Michele Sciarabba[d], Umberto Solimene[e, f], Cristiano Rumio[a, f, g]

Drug Design, Development and Therapy

Dovepress

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ORIGINAL RESEARCH

An open randomized active-controlled clinical trial with low-dose SKA cytokines versus DMARDs evaluating low disease activity maintenance in patients with rheumatoid arthritis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
29 March 2017
Number of times this article has been viewed

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 28, no. 1, 133-139 (2014)

IMMUNOMODULATING TREATMENT WITH LOW DOSE INTERLEUKIN-4, INTERLEUKIN-10 AND INTERLEUKIN-11 IN PSORIASIS VULGARIS

M.L. ROBERTI[1], L. RICOTTINI[2], A. CAPPONI[3], E. SCLAUZERO[4], P. VICENTI[5], E. FIORENTINI[6], C. SAVOIA[7], G. SCORNAVACCA[8], D. BRAZIOLI[9], L. GAIO[10], R. GIANNETTI[11], C. IGNAZZI[12], G. MELONI[13] and L.M. CHINNI[14]

[1]Private Practice, Rome, Italy; [2]"Sinergheia" Medical Center, Rome, Italy; [3]Private Practice, Latina, Italy; [4]OSTEMDA, Therapeutic Strategies Empowerment and Advanced Diagnostic Methods Organization, Udine, Italy; [5]Private Practice, Altamura, Bari, Italy; [6]Dermatological Health Clinic, Aversa, Caserta, Italy; [7]Private Practice, Fino Mornasco, Como, Italy; [8]Private Practice, Catania, Italy; [9]Private Practice, Turin, Italy; [10]Private Practice, Caserta, Italy; [11]"Aurelia" Medical Center, Rome, Italy; [12]Local Health Unit (ASL), Putignano, Bari, Italy; [13]"GEA Medica" Medical Center, Montebelluna, Treviso, Italy; [14]Istituto Dermopatico dell'Immacolata (IDI), Rome, Italy

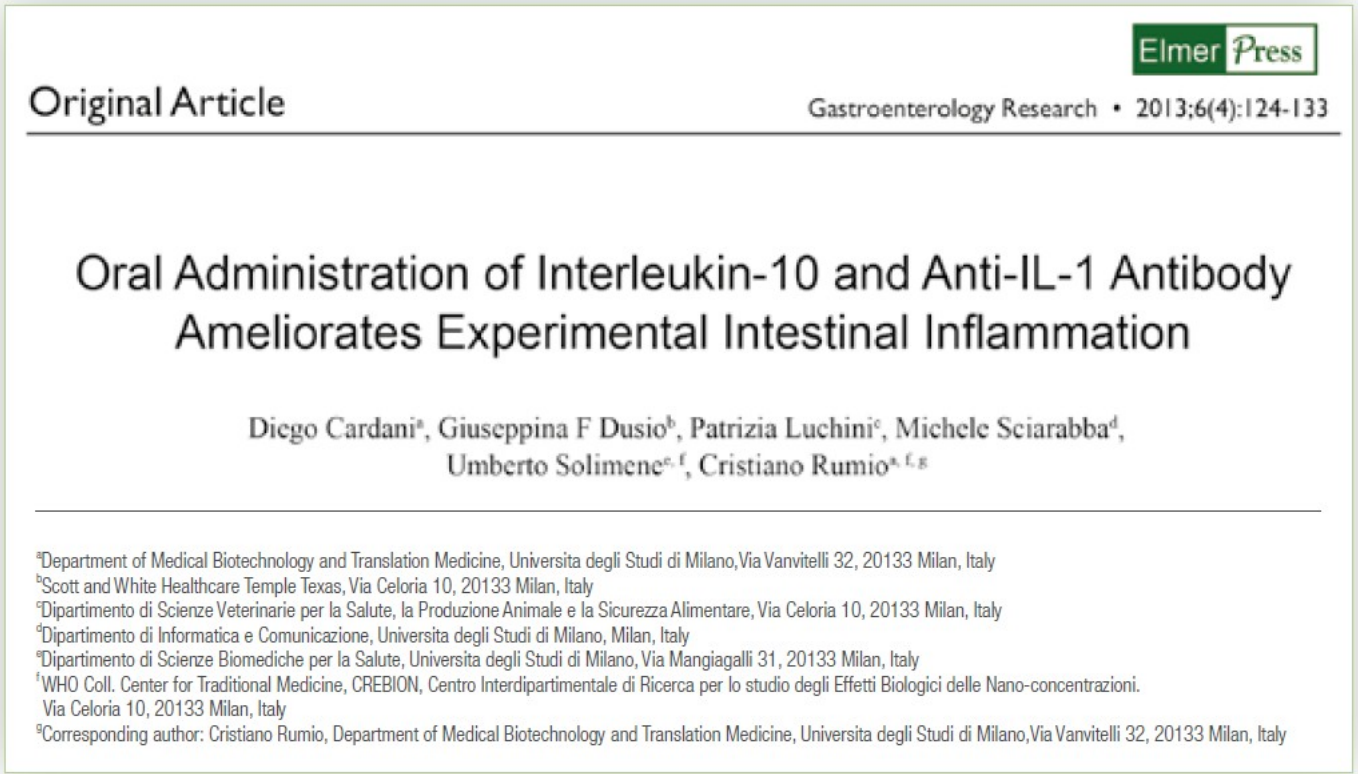
JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 29, no. 1 (S), 53-58 (2015)

VITILIGO: SUCCESSFUL COMBINATION TREATMENT BASED ON ORAL LOW DOSE CYTOKINES AND DIFFERENT TOPICAL TREATMENTS

T. LOTTI[1], J HERCOGOVA[4], U. WOLLINA[5], A.A. CHOKOEVA[6], Z. ZARRAB[7], S. GIANFALDONI[8], M.G. ROCCIA[9], M. FIORANELLI[10] and G. TCHERNEV[6]

Evidence from the Research

ORAL ADMINISTRATION OF INTERLEUKIN-10 AND ANTI-IL-1 ANTIBODY AMELIORATES EXPERIMENTAL INTESTINAL INFLAMMATION



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Oral Administration of Interleukin-10 and Anti-IL-1 Antibody Ameliorates Experimental Intestinal Inflammation

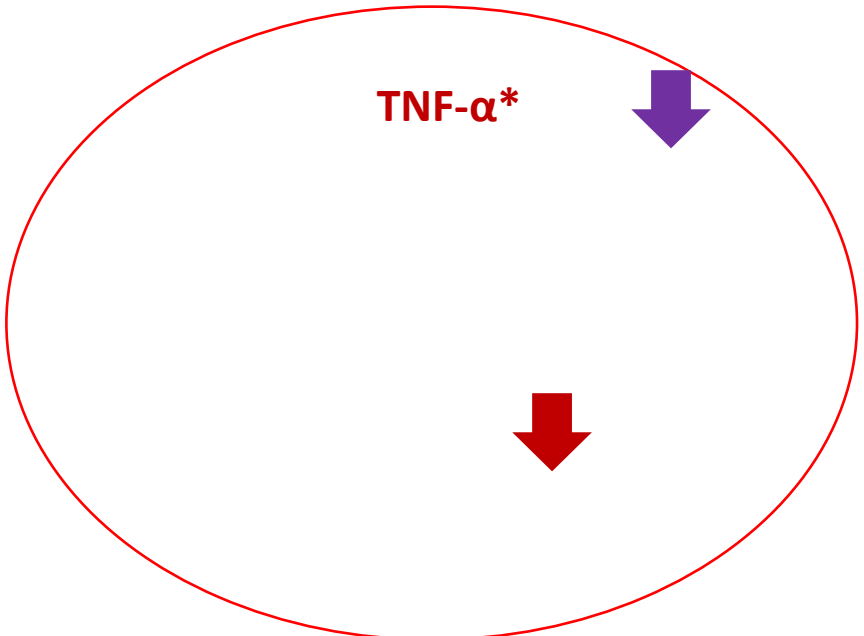
Diego Cardani[a], Giuseppina F Dusio[b], Patrizia Luchini[c], Michele Sciarabba[d], Umberto Solimene[e, f], Cristiano Rumio[a, f, g]

[a]Department of Medical Biotechnology and Translation Medicine, Universita degli Studi di Milano, Via Vanvitelli 32, 20133 Milan, Italy
[b]Scott and White Healthcare Temple Texas, Via Celoria 10, 20133 Milan, Italy
[c]Dipartimento di Scienze Veterinarie per la Salute, la Produzione Animale e la Sicurezza Alimentare, Via Celoria 10, 20133 Milan, Italy
[d]Dipartimento di Informatica e Comunicazione, Universita degli Studi di Milano, Milan, Italy
[e]Dipartimento di Scienze Biomediche per la Salute, Universita degli Studi di Milano, Via Mangiagalli 31, 20133 Milan, Italy
[f]WHO Coll. Center for Traditional Medicine, CREBION, Centro Interdipartimentale di Ricerca per lo studio degli Effetti Biologici delle Nano-concentrazioni. Via Celoria 10, 20133 Milan, Italy
[g]Corresponding author: Cristiano Rumio, Department of Medical Biotechnology and Translation Medicine, Universita degli Studi di Milano, Via Vanvitelli 32, 20133 Milan, Italy

Cytokines levels

IL-12*

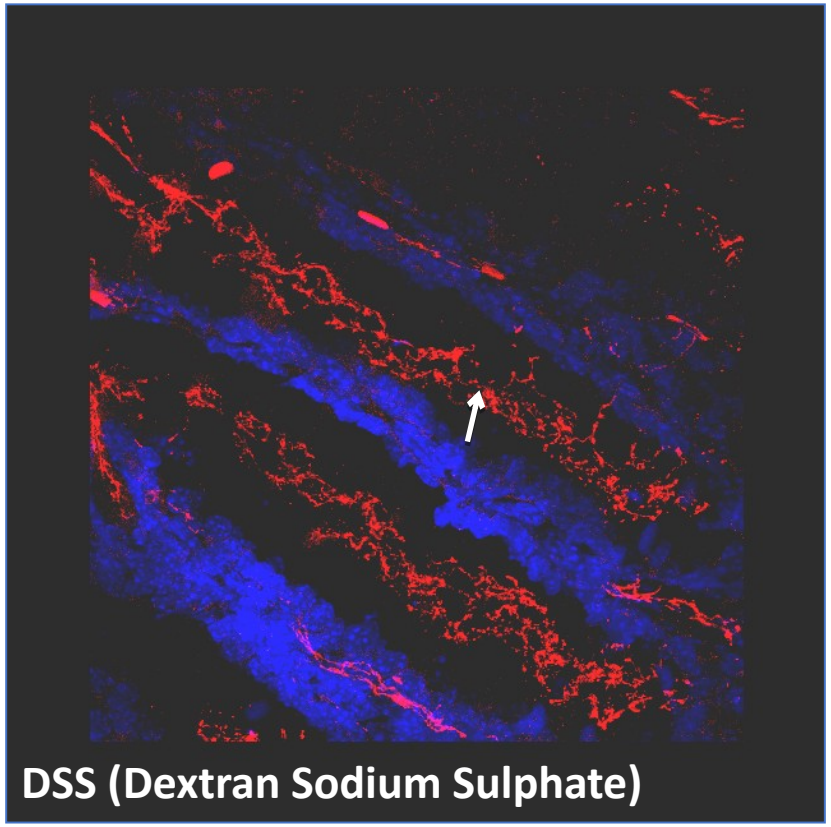
IFN-γ



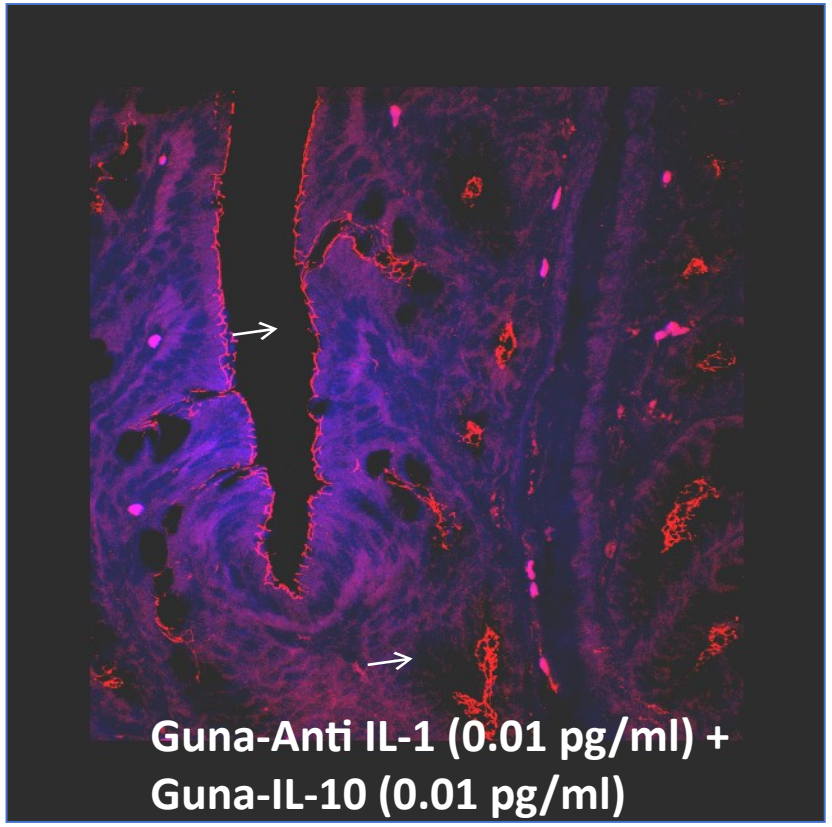
IL-8

Legenda:
1: levels in healthy mouse
2: levels in the mouse with Crohn's
3: levels in the mouse with Crohn's after 7 days treatment with Anti IL-1+IL-10 at pharmacological doses (ng/ml)
4: levels in the mouse with Crohn's after 7 days treatment with Anti IL-1+IL-10 at a concentration of 0.01 pg/ml SKA
5: levels in the mouse with Crohn's after 7 days treatment with Anti IL-1+IL-10 at a concentration of 0.01 pg/ml non-SKA

Immunofluorescence



BEFORE TREATMENT



AFTER TREATMENT

AN OPEN RANDOMIZED ACTIVE-CONTROLLED CLINICAL TRIAL WITH LOW-DOSE SKA CYTOKINES VERSUS DMARDs EVALUATING LOW DISEASE ACTIVITY MAINTENANCE IN PATIENTS WITH RHEUMATOID ARTHRITIS

Drug Design, Development and Therapy

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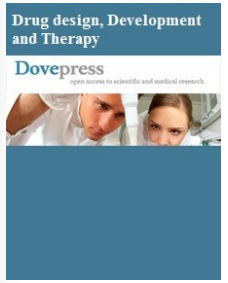
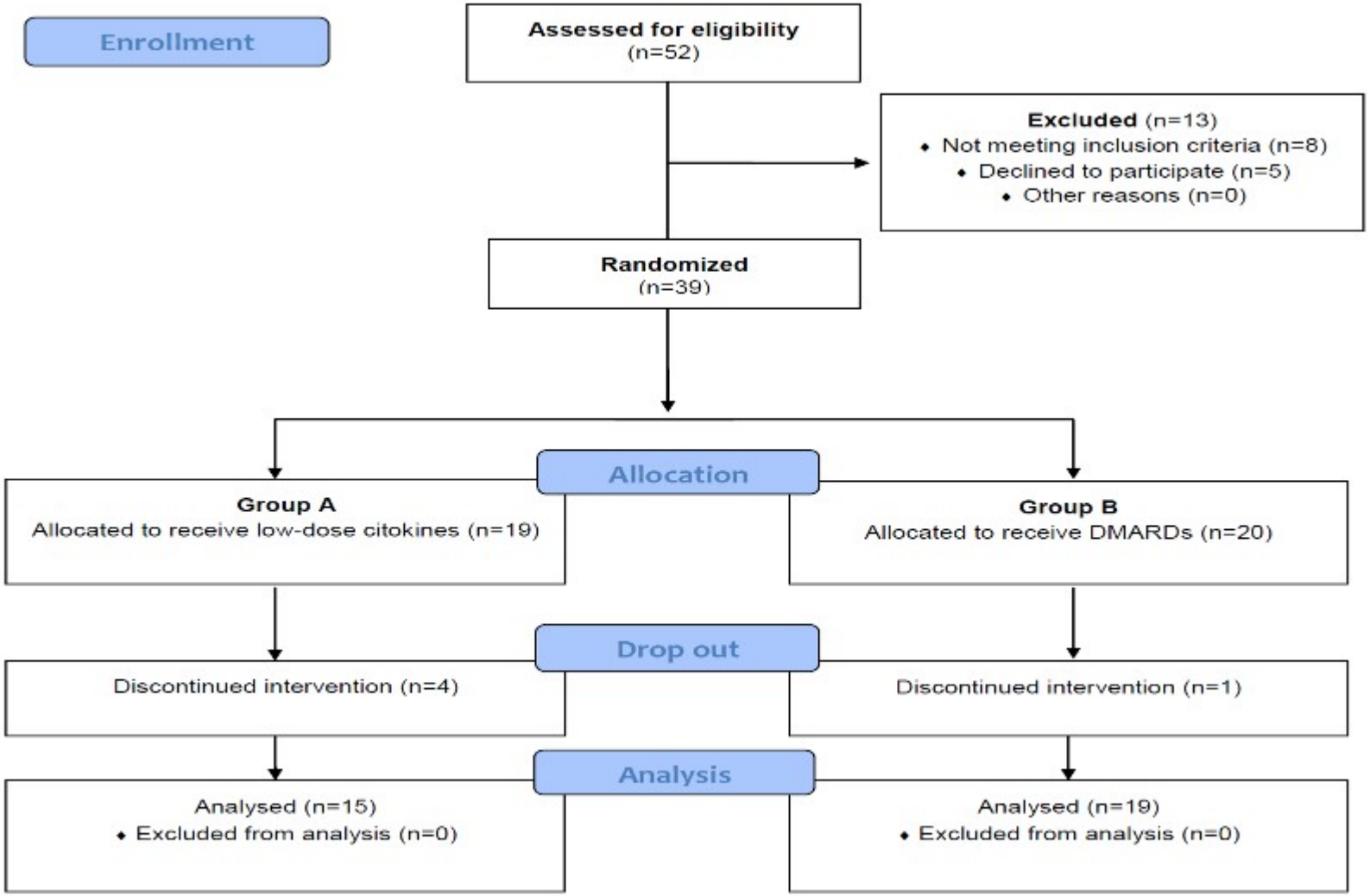
Open access to scientific and medical research

An open randomized active-controlled clinical trial with low-dose SKA cytokines *versus* DMARDs evaluating low disease activity maintenance in patients with rheumatoid arthritis.

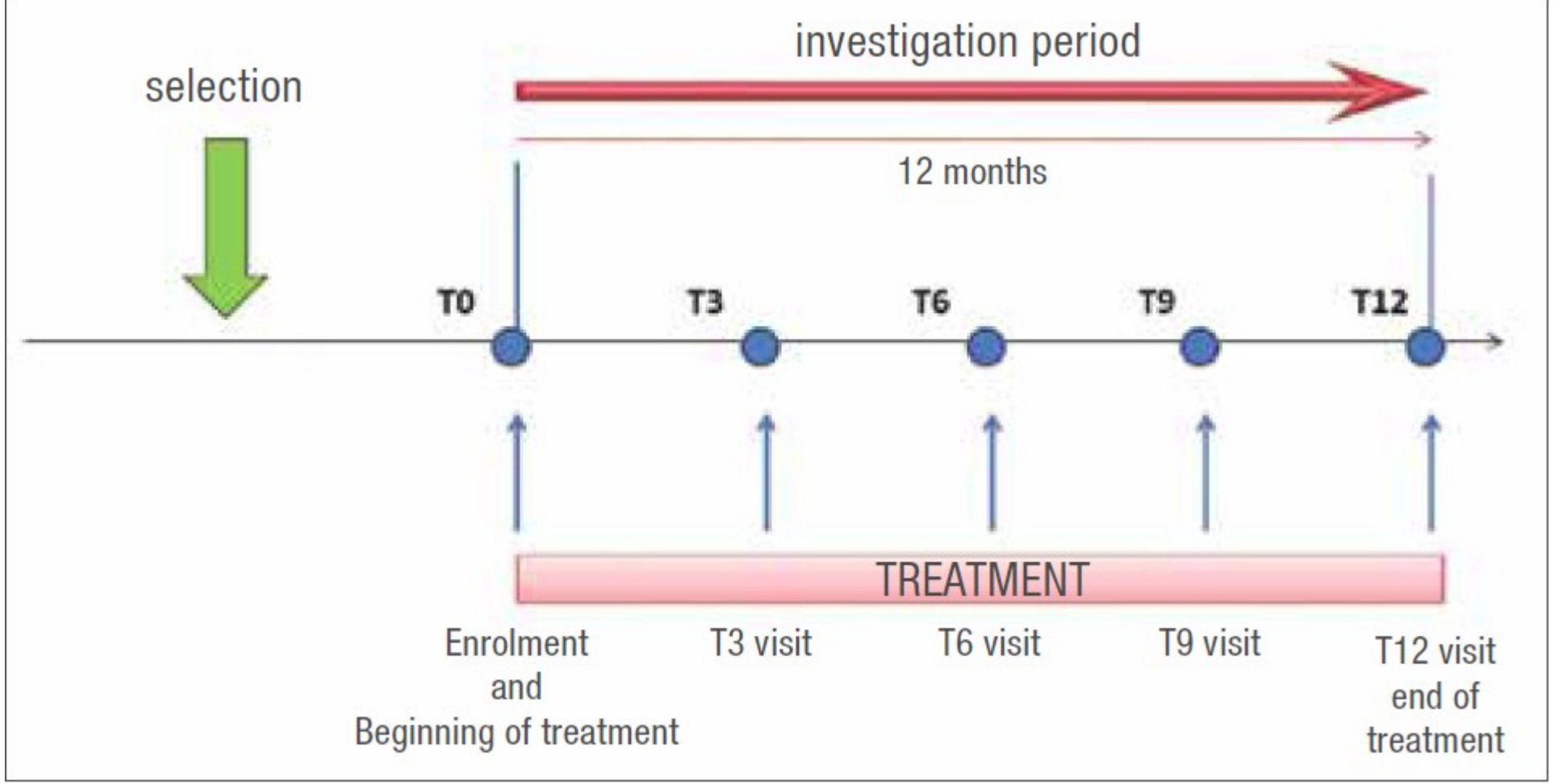
Martin Martin S.[1], Giovannangeli F.[2], Bizzi E.[2], Massafra U.[2], Ballanti E.[2], Cassol M.[3], Migliore A.[2]

[1]Department of Internal Medicine, Regina Apostolorum Hospital, Rome, Italy
[2]Operative Unit of Rheumatology, San Pietro Fatebenefratelli Hospital, Rome, Italy
[3]Department of Internal Medicine, San Pietro Fatebenefratelli Hospital, Rome, Italy





52 Subjects underwent the screening. 39 of these were enrolled. 5 patients did not complete the study



After randomisation, subjects were split into two study groups:

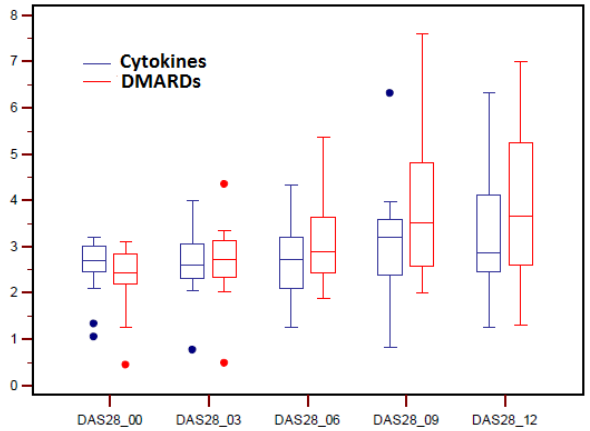
- **Group A started taking GUNA®-IL 4, GUNA®-IL 10 and GUNA®-Anti IL 1 in 10 fg/mL SKA formulations, administered at a dose of 20 drops per day for 12 consecutive months.**
- **Group B started or continued taking DMARD therapy (FIG. 2).**

RESULTS

Primary endpoint

The maintenance of LDA at 12 months is obtained respectively in 66.7% of subjects treated with low-dose cytokines (Group A) (n=10) and in 42.1% of patients treated with DMARDs (Group B) (n=8); the difference between the groups is not statistically significant (Fisher exact test: p = 0.185)

In Group A 2 subject have been treated at the same time with DMARDs (MTX) and low-dose cytokines.

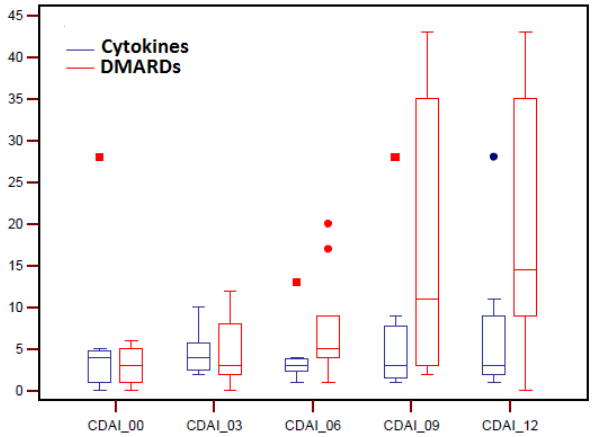


Disease Activity Score DAS28

DAS28 values are similar in the two groups at baseline (Mann-Whitney U test: p = 0.3991) as well as at 12 months (Mann-Whitney U test: p = 0.1030). Group A maintains constant values of DAS 28 (Friedman test: p = 0.41604), while in the Group B DAS 28 values are on the rise (Friedman test: p = 0.00198), with significant difference (test according Conover: p <0.05) between T0 and T9, T0 and T12, T3 and T9, T3 and T12

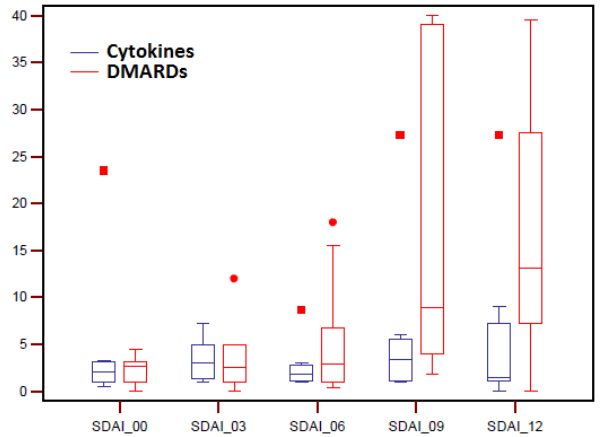
RESULTS

Primary endpoint



Clinical Disease Activity Index CDAI

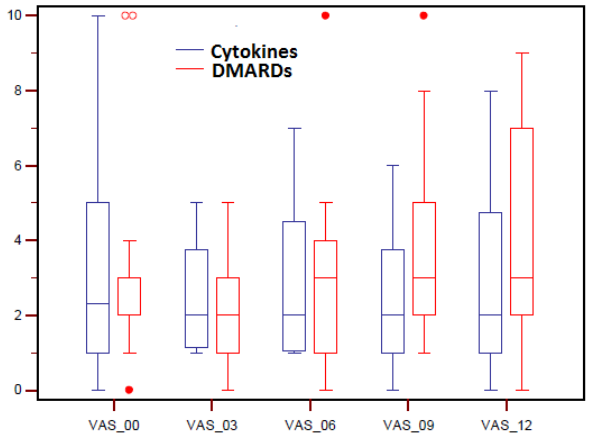
CDAI score are similar in the two groups at baseline (Mann-Whitney U test: p = 0.7317) as well as at 12 months (Mann-Whitney U test: p = 0.0510). The Group A show a constant sealing over time (Friedman test: p = 0.84645), while values are on the rise in the Group B (Friedman test: p = 0.00004), with significant difference (test according Conover: p <0.05) between T0 and T6, T0 and T9, T0 and T12, T3 and T9, T3 and T12, T6 and T9, T6 and T12



Simplified Disease Activity Index SDAI

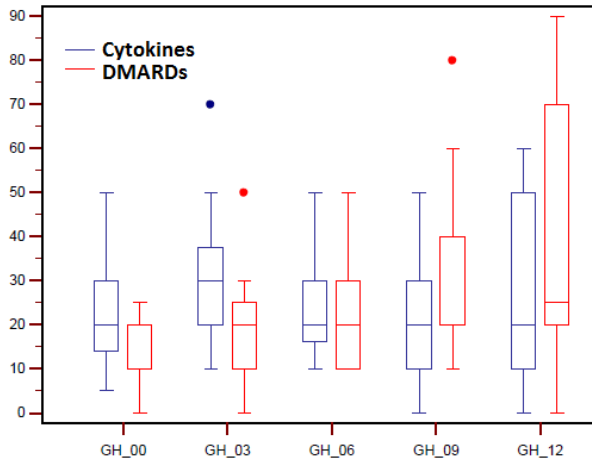
The SDAI showed no statistical difference between the two groups at baseline (Mann-Whitney U test: p = 0.9223) as well as at 12 months (Mann-Whitney U test: p = 0.0790). Group A showed a constant intra-group sealing (Friedman test: p = 0.56774), while a significant intra-group difference was shown in the Group B (Friedman test: p <0.00001 and test according Conover: p <0.05) between the following time points:T0 and T6, T9 and T0, T0 and T12, T3 and T9, T12 and T3, T6 and T9, T6 and T12

Secondary endpoints



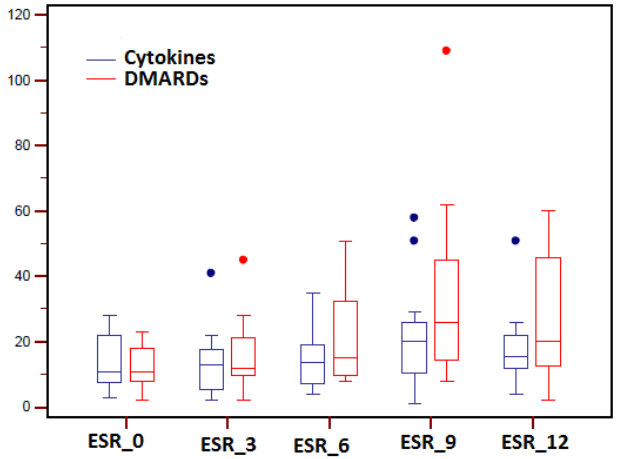
Pain Visual Analog Scale

The Pain VAS values are similar between the two groups at both baseline visit (Mann-Whitney U test: p = 0.7336) and 12 months follow up (Mann-Whitney U test: p = 0.1772). Patients maintain constant levels without any intra-group difference as show by the Friedman test, p values were respectively 0.79490 in the Group A and 0.12474 in the Group B



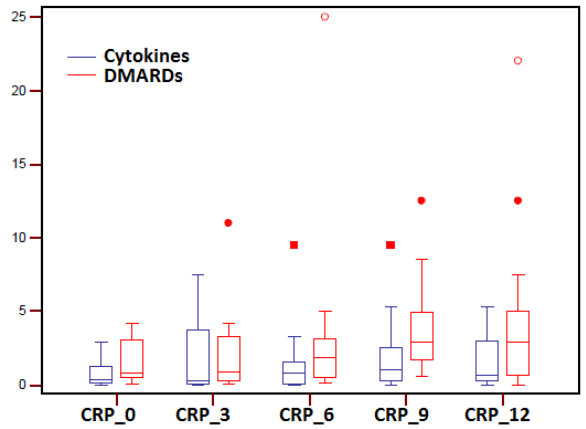
Global Health Assessment GH

GH values didn't show any statistical difference between the two groups at baseline (Mann-Whitney U test: p = 0.4998) and at 12 months (Mann-Whitney U test: p = 0.3269). Patients maintain constant values in both groups; Friedman test: p = 0.19770 in the Group A and Friedman test: p = 0.05608 in the Group B



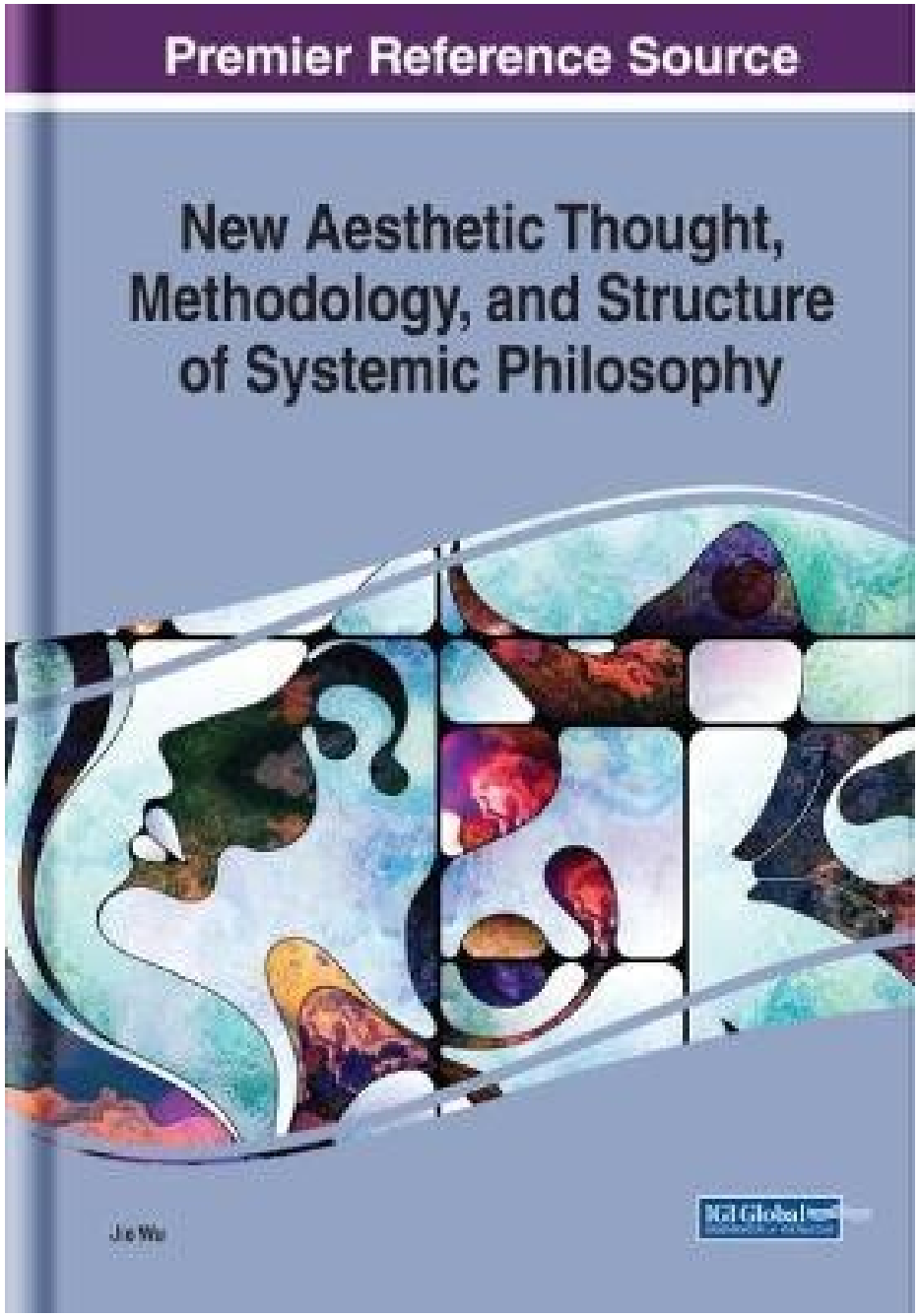
Erythrocyte Sedimentation Rate ESR

ESR mean values didn't show any significant intergroup difference at baseline (Mann-Whitney U test: p = 0.7153) as well as at 12 months (Mann-Whitney U test: p = 0.0699). Similarly no intra-group significant differences were reported, Friedman test p values were respectively 0.53603 in the Group A and 0.08022 in the Group B



C-Reactive Protein CRP

The PCR mean values are lower in the Group A at baseline (Mann-Whitney U test: p = 0.0078), but similar at 12 months without any significant statistical difference (Mann-Whitney U test: p = 0.0966). Patients show intra-group constant levels, Friedman test was respectively p = 0.69002 in the Group A and p = 0.22356 in the Group B



Growth Factors and SKIN AGING

- *EGF is involved in the regulation of the growth and differentiation of bulge cells.*
- *PDGFs manages the interaction arising between the bulge and associated tissue during follicle morphogenesis.*

*Location of **hair bulge**, which is a stem cell reserve involved in hair regeneration phase.*

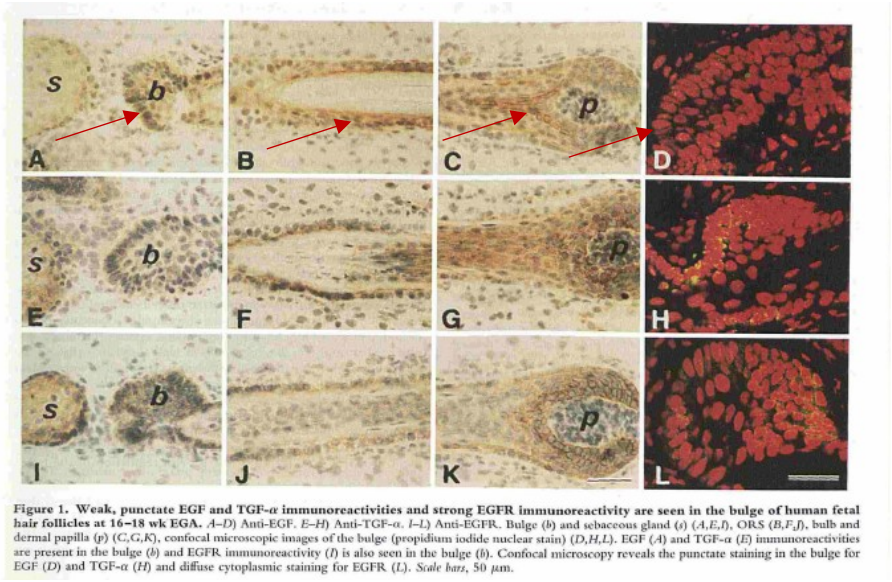


Figure 1. Weak, punctate EGF and TGF-α immunoreactivities and strong EGFR immunoreactivity are seen in the bulge of human fetal hair follicles at 16–18 wk EGA. *A–D*) Anti-EGF. *E–H*) Anti-TGF-α. *I–L*) Anti-EGFR. Bulge (*b*) and sebaceous gland (*s*) (*A,E,I*), ORS (*B,F,J*), bulb and dermal papilla (*p*) (*C,G,K*), confocal microscopic images of the bulge (propidium iodide nuclear stain) (*D,H,L*). EGF (*A*) and TGF-α (*E*) immunoreactivities are present in the bulge (*b*) and EGFR immunoreactivity (*I*) is also seen in the bulge (*b*). Confocal microscopy reveals the punctate staining in the bulge for EGF (*D*) and TGF-α (*H*) and diffuse cytoplasmic staining for EGFR (*L*). *Scale bars*, 50 μm.

EGFR expression at hair bulge level (red arrows)

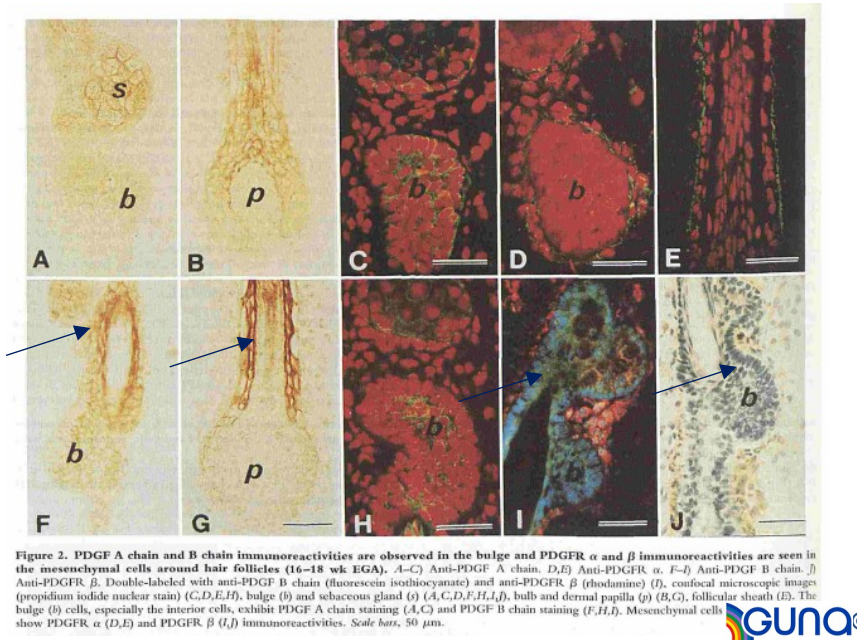


Figure 2. PDGF A chain and B chain immunoreactivities are observed in the bulge and PDGFR α and β immunoreactivities are seen in the mesenchymal cells around hair follicles (16–18 wk EGA). *A–C*) Anti-PDGF A chain. *D,E*) Anti-PDGFR α. *F–I*) Anti-PDGF B chain. *J*) Anti-PDGFR β. Double-labeled with anti-PDGF B chain (fluorescein isothiocyanate) and anti-PDGFR β (rhodamine) (*I*), confocal microscopic images (propidium iodide nuclear stain) (*C,D,E,H*), bulge (*b*) and sebaceous gland (*s*) (*A,C,D,F,H,I,J*), bulb and dermal papilla (*p*) (*B,G*), follicular sheath (*E*). The bulge (*b*) cells, especially the interior cells, exhibit PDGF A chain staining (*A,C*) and PDGF B chain staining (*F,H,I*). Mesenchymal cells show PDGFR α (*D,E*) and PDGFR β (*I,J*) immunoreactivities. *Scale bars*, 50 μm.

PDGFR expression at hair bulge level (blue arrows)

- *Akiyama M, Smith LT, Holbrook KA. Growth factor and growth factor receptor localization in the hair follicle bulge and associated tissue in human fetus. J Invest Dermatol. 1996 Mar;106(3):391-6.*
- *González R, Moffatt G, Hagner A, Sinha S, Shin W, Rahmani W, Chojnacki A, Biernaskie J. Platelet-derived growth factor signaling modulates adult hair follicle dermal stem cell maintenance and self-renewal. NPJ Regen Med. 2017 Apr 14;2:11.*

Directions

- **<u>For 4 consecutive months (or more):</u>**

20 drops twice a day

Sublingual administration directly under the tongue or in a little water, preferibly far from meals.

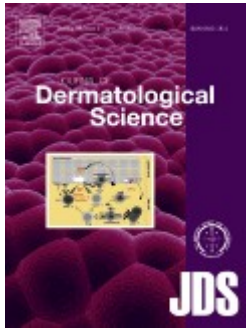
<u>For 4 months (or more):</u>

40 drops (of one or more products) directly in a bottle a water. Drink with little sips during the day.

PRE-CLINICAL STUDY

Ex vivo

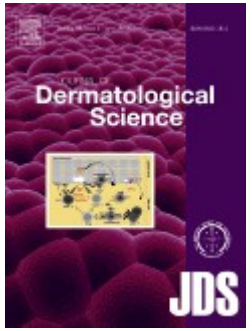
Treatment with low-dose cytokines (**IL-4, IL-10, b-FGF and β-Endorphin)** reduces oxidative-mediated injury in perilesional keratinocytes from vitiligo skin



Journal Of Dermatological Science

Reference: JDS-15-256

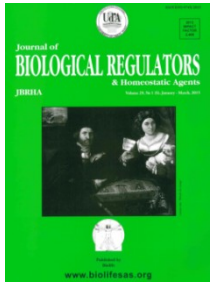
Barygina V, Becatti M, Lotti T, Moretti S, Taddei N, Fiorillo C, TREATMENT WITH LOW-DOSE CYTOKINES REDUCES OXIDATIVE-MEDIATED INJURY IN PERILESIONAL KERATINOCYTES FROM VITILIGO SKIN, *Journal of Dermatological Science (2015),* http://dx.doi.org/10.1016/j.jdermsci.2015.05.003



Victoria Barygina [1], Matteo Becatti [1], Niccolo Taddei [1], Claudia Fiorillo [1], Torello Lotti [2].

[1] Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Florence, Italy. [2] Dermatology and Venereology Division, University of Rome "G.Marconi", Rome, Italy.

VITILIGO: SUCCESSFUL COMBINATION TREATMENT BASED ON ORAL LOW DOSE CYTOKINES AND DIFFERENT TOPICAL TREATMENTS



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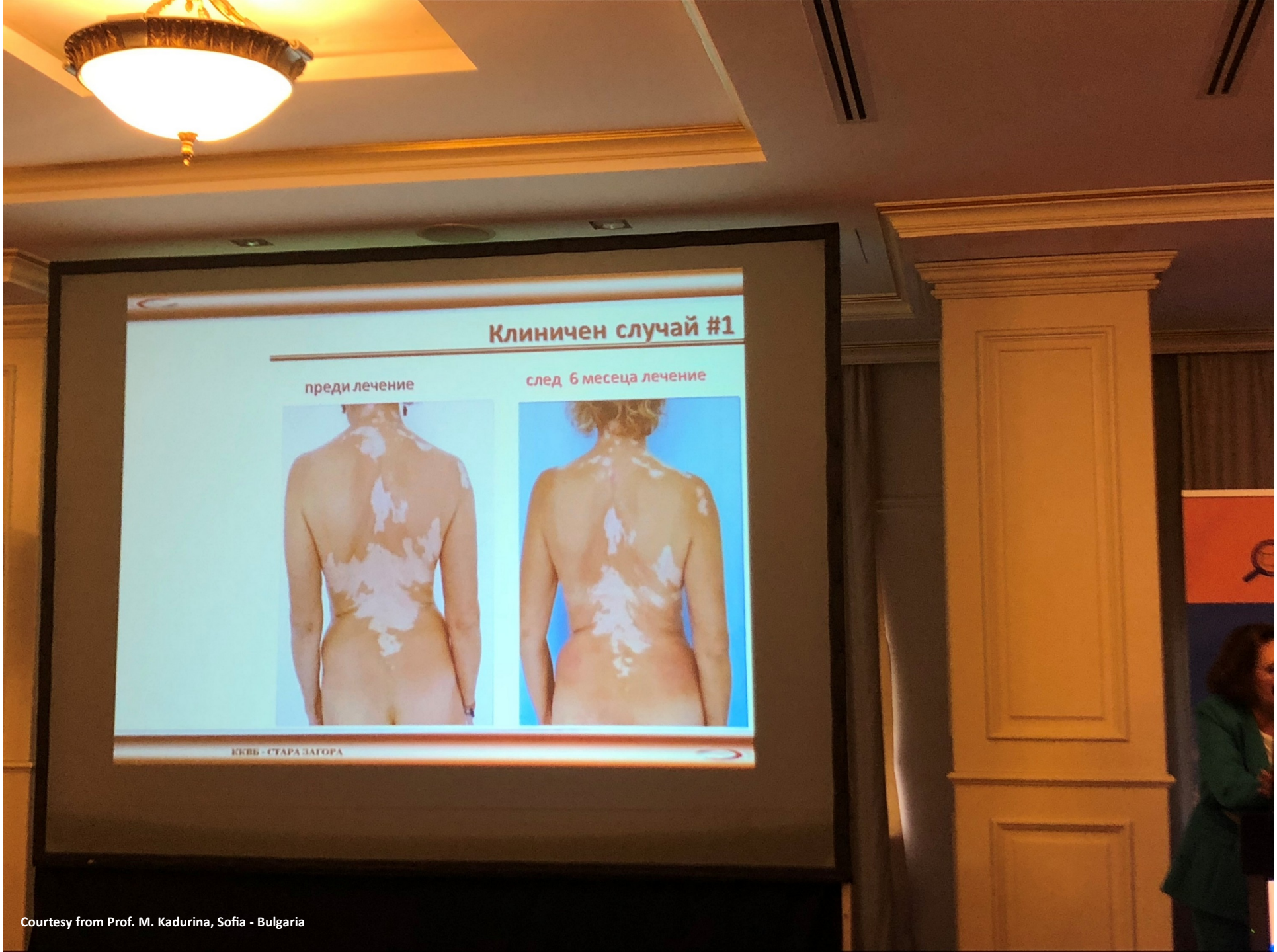
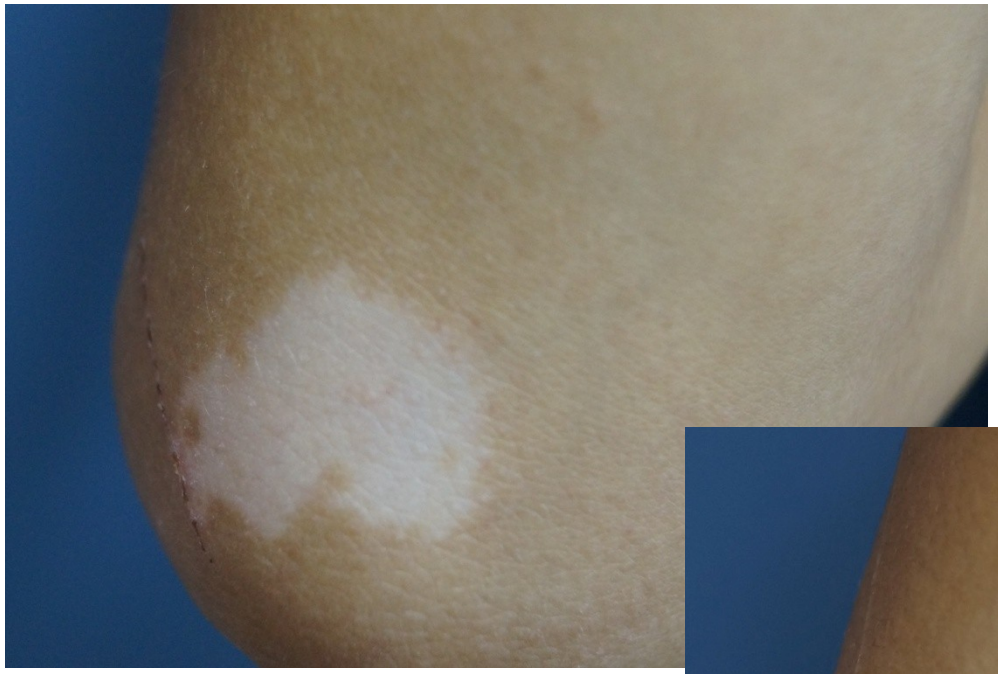
[1]Professor & Chair of Dermatology, University of Rome "G. Marconi" Rome, Italy; [2]Director Institute of Dermatology Life Cronos, Florence, Italy; [3]President World Health Academy Foundation, Zurich, Switzerland; [4]Dept. Dermatology, 2nd Medical School, Charles University, Prague, Czech Republic; [5]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [6]"Onkoderma"-Policlinic for Dermatology, Venereology and Dermatologic surgery, Sofia, Bulgaria; [7]University of Rome "G. Marconi", Rome, Italy; [8]Department of dermatologic Sciences, University of Florence, Florence, Italy; [9]Chandigarh University, Punjab, India; [10]Associate Professor of Physiology, University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India



Courtesy from Prof. M. Kadurina, Sofia - Bulgaria

CLINICAL RESULTS



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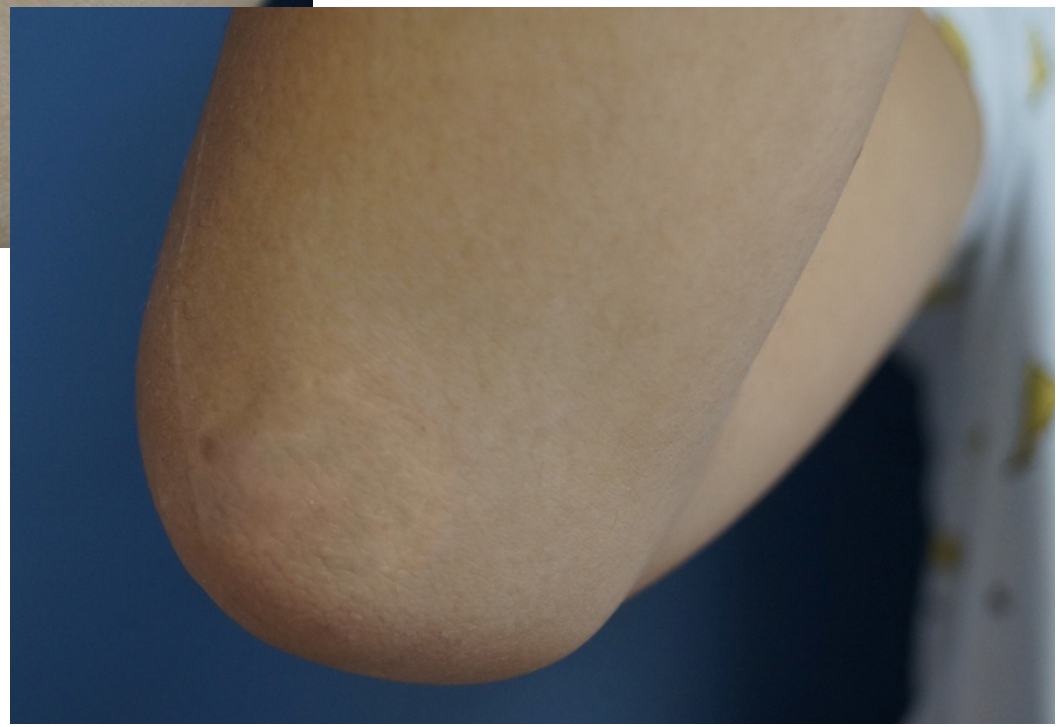
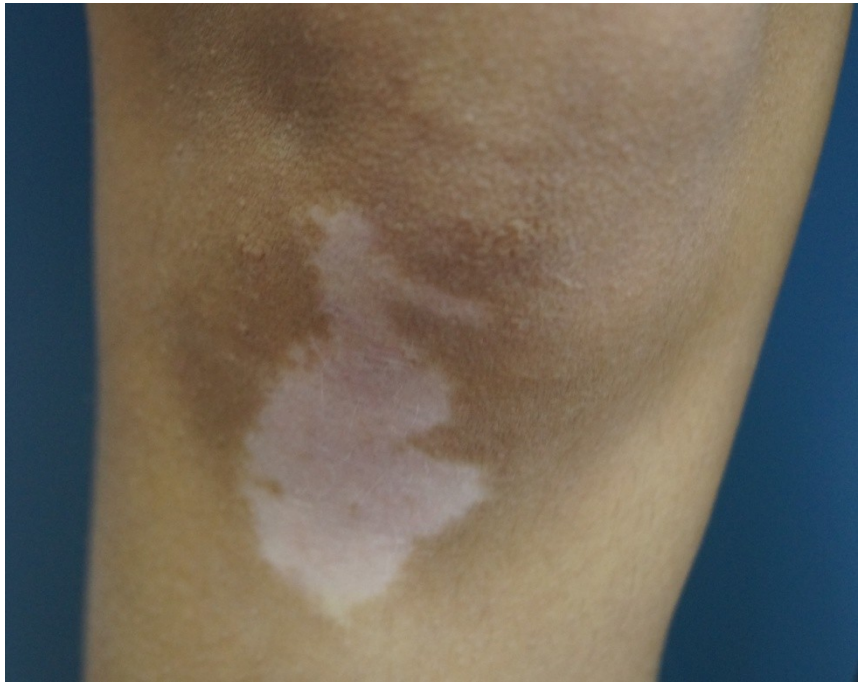


after

Courtesy from Prof. M. Kadurina, Sofia - Bulgaria

CLINICAL RESULTS



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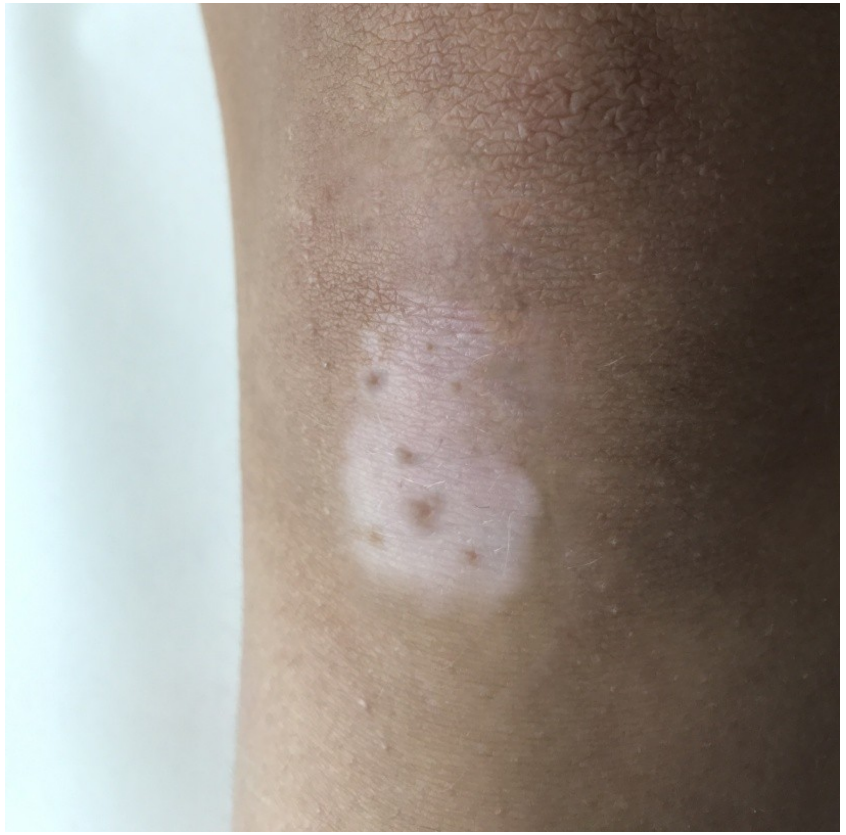

after

Courtesy from Prof. M. Kadurina, Sofia - Bulgaria

LOW DOSE PHARMACOLOGY
Conclusions

Why take it under consideration?

1) Highest clinical safety
2) Long term treatments
3) Effectiveness
4) Allows an overlapping approach
5) Fills the therapeutic *vacuum(s)*
6) Affordable cost

EXTENDED VERSION

The 73rd General Assembly and International Scientific Congress

Low Dose Cytokine Therapy for healthy longevity. A novel Pharmacology for a systemic and multi-level approach to aging

Saturday, November 5th, 2022

Alessandro Perra – Direttore Scientifico GUNA S.p.a.

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Low Dose Cytokine Therapy

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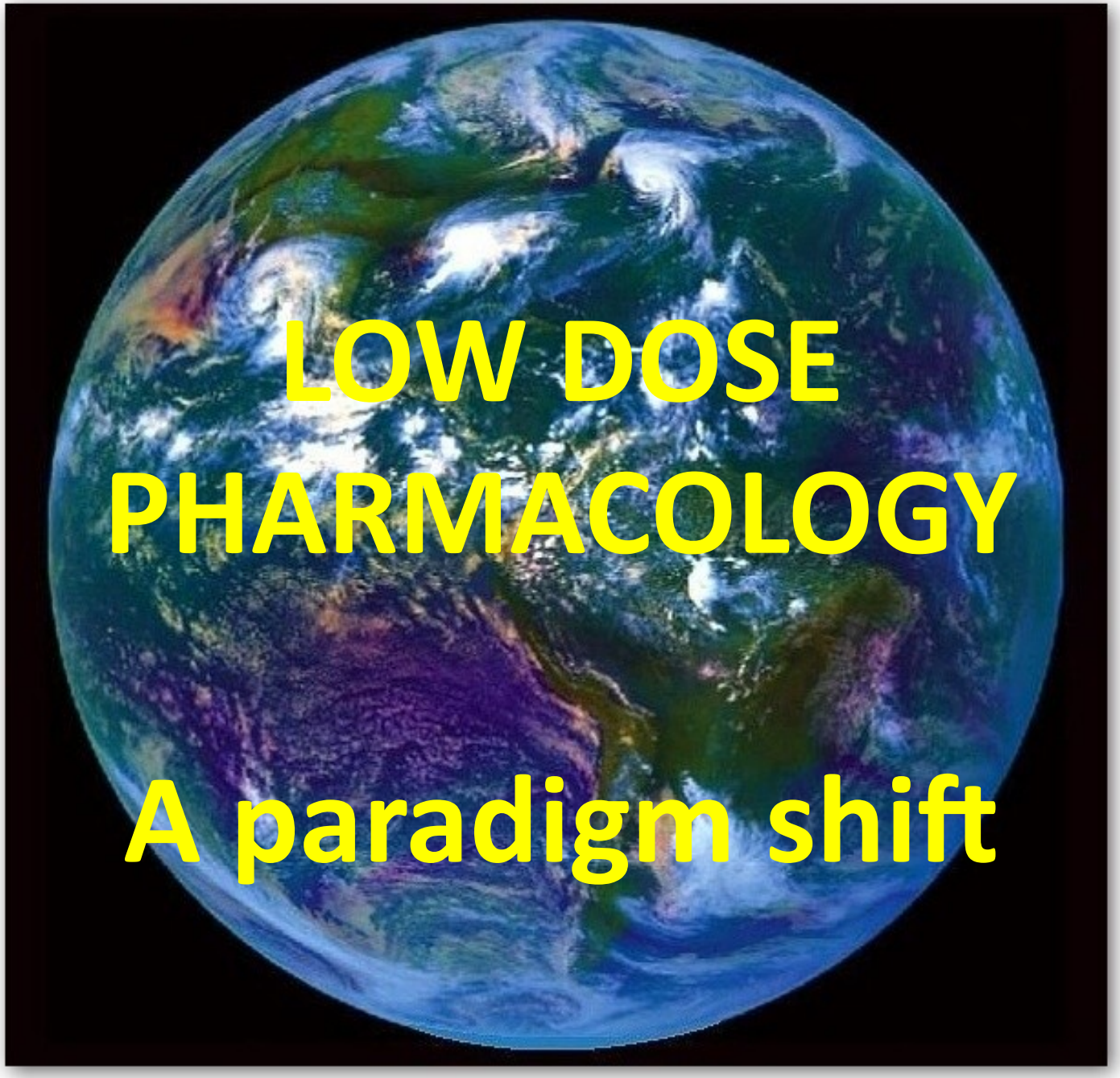

…not only us. A world trend

CMAJ

ANALYSIS

Is bigger better? An argument for very low starting doses

James P. McCormack PharmD, G. Michael Allan MD, Adil S. Virani PharmD

VIEWPOINT

Low drug doses may improve outcomes in chronic disease

Simon B Dimmitt and Hans G Stampfer

Chronic diseases are creating a growing burden of ill health as populations age[1] and become more obese,[2] and as survival from many conditions improves. Long-term pharmacotherapy is used increasingly to control symptoms and slow disease progression. Unfortunately, there is a dearth of reliable information about drug dosages for, and outcomes of, long-term treatment of physical and mental illness. Dosages recommended in clinical practice guidelines are usually derived from studies of acute and severe cases of disease. There is little research to support the application of these guidelines to long-term treatment regimens and to the large number of patients with mild cases of disease who are managed in primary care. In addition, few studies specifically address dosage.

Long-term pharmacotherapy carries the risk of adverse drug

ABSTRACT

- The relationship between drug dose and clinical outcome has not been established for many medications used to treat chronic disease. Evidence is emerging that chronic diseases can be treated effectively with low doses.
- Adverse drug reactions account for significant morbidity and mortality and are generally dose related.
- Optimal drug dose — the best balance of benefit and risk — varies between individuals and may change over time. When treating chronic disease it is important to establish and maintain the optimal dose for each patient by close clinical monitoring.

MJA 2009; 191: 511–513

frontiers in Immunology

MINI REVIEW
published: 01 April 2021
doi: 10.3389/fimmu.2021.648408

Low-Dose IL-2 Therapy in Autoimmune and Rheumatic Diseases

*Hanna Graßhoff, Sara Comdühr, Luisa R. Monne, Antje Müller, Peter Lamprecht, Gabriela Riemekasten and Jens Y. Humrich**

Department of Rheumatology and Clinical Immunology, University Hospital Schleswig-Holstein Lübeck, Lübeck, Germany

The Journal of Immunology

This information is current as of October 17, 2022.

Low-Dose IL-2 Therapy in Transplantation, Autoimmunity, and Inflammatory Diseases

Maryam Tahvildari and Reza Dana

J Immunol 2019; 203:2749-2755; ;
doi: 10.4049/jimmunol.1900733
http://www.jimmunol.org/content/203/11/2749

BMJ Journals | BETA VERSION

Annals of the
Rheumatic Diseases

Home / Archive / Volume 74, Issue 4

Letter

Rapid induction of clinical remission by low-dose interleukin-2 in a patient with refractory SLE

Jens Y Humrich[1], Caroline von Spee-Mayer[1], Elise Siegert[1], Tobias Alexander[1], Falk Hiepe[1], Andreas Radbruch[2], Gerd-Rüdiger Burmester[1], Gabriela Riemekasten[1]

Low Dose IL-2 Increase Regulatory T Cells and Elevate Platelets in a Patient with Immune Thrombocytopenia

Jiakui Zhang,[1] Yanjie Ruan,[1] Yuanyuan Shen,[1] Qianshan Tao,[1] Huiping Wang,[1] Lili Tao,[1] Yin Pan,[1] Huizi Fang,[1] Yiping Wang,[2] and Zhimin Zhai[1]*

Cytometry Part B (Clinical Cytometry) 00:00–00 (2016)

Table 2
Results of the Patient's Blood Routine Examination During Treatment

Patient characteristics	Day 0	Day 6	Day 13	Day 20	Day 25	Day 29
White blood cell($\times 10^9$/L)	4.78	3.74	3.84	9.63	5.97	6.88
Lymphocyte($\times 10^9$/L)	1.47	0.73	1.05	1.55	1.01	1.26
Neutrophils($\times 10^9$/L)	2.87	2.49	2.16	7.12	4.01	4.75
Monocyte($\times 10^9$/L)	0.38	0.39	0.48	0.62	0.57	0.70
Hemoglobin(g/L)	136	137	123	130	119	127
Platelet($\times 10^9$/L)	**36**	**40**	**43**	**73**	**66**	**85**
Tregs	3.50	ND	10.2	13.0	ND	9.0
CD4/CD8 ratio	1.39	ND	ND	1.64	ND	1.16

Day 1 was considered as the first day treating with low dose IL-2.

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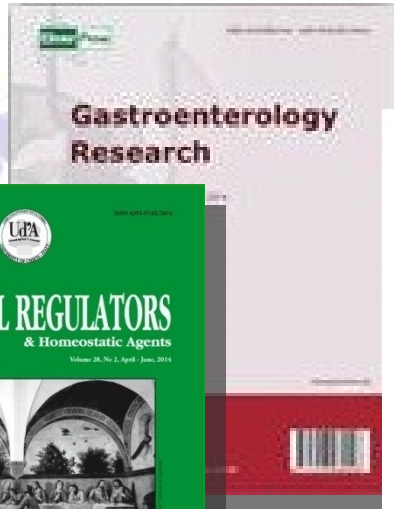
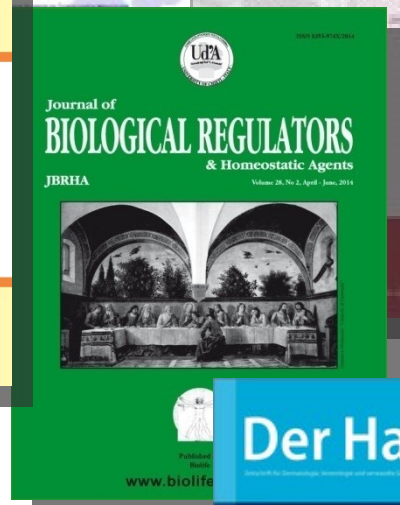
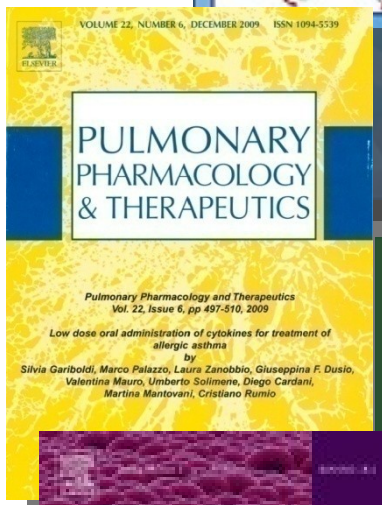
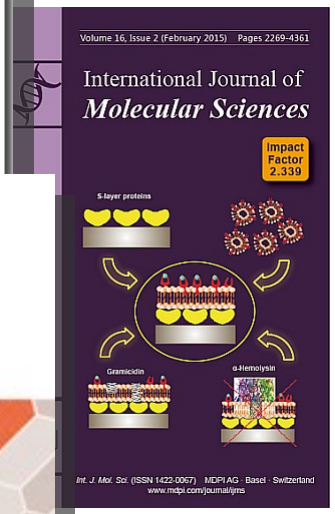
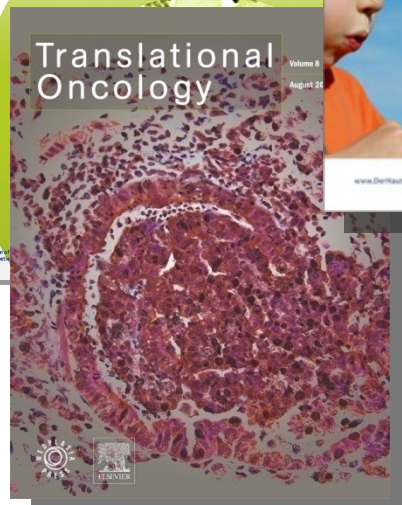
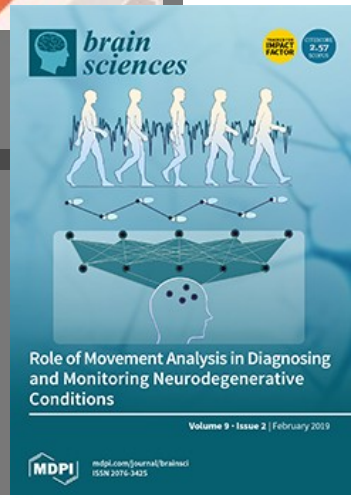






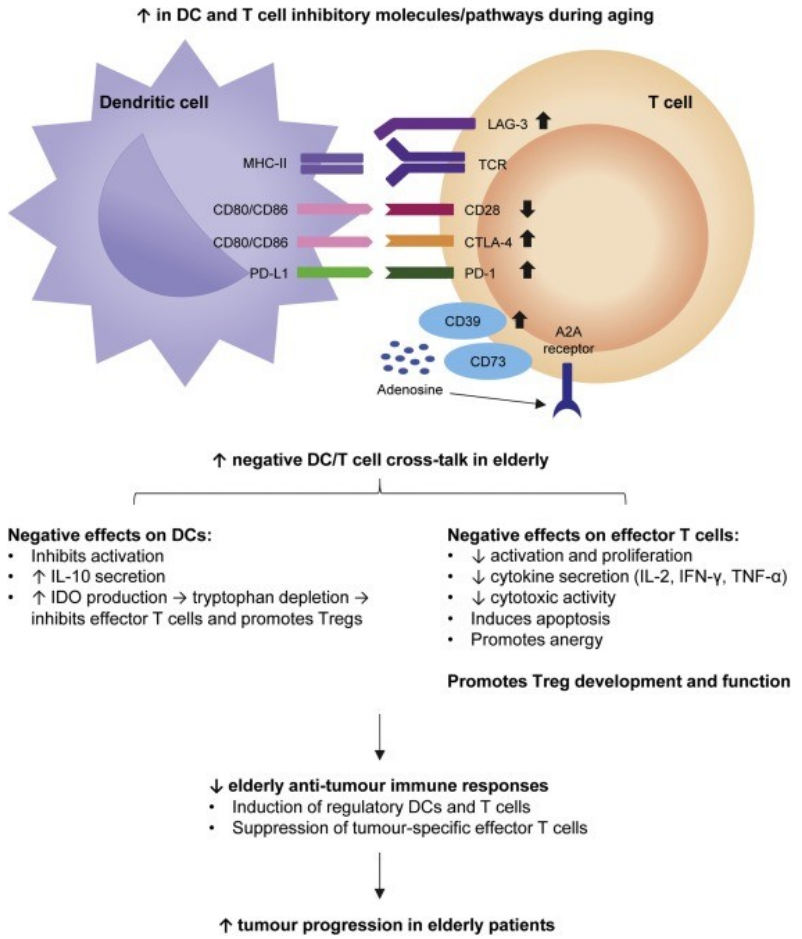






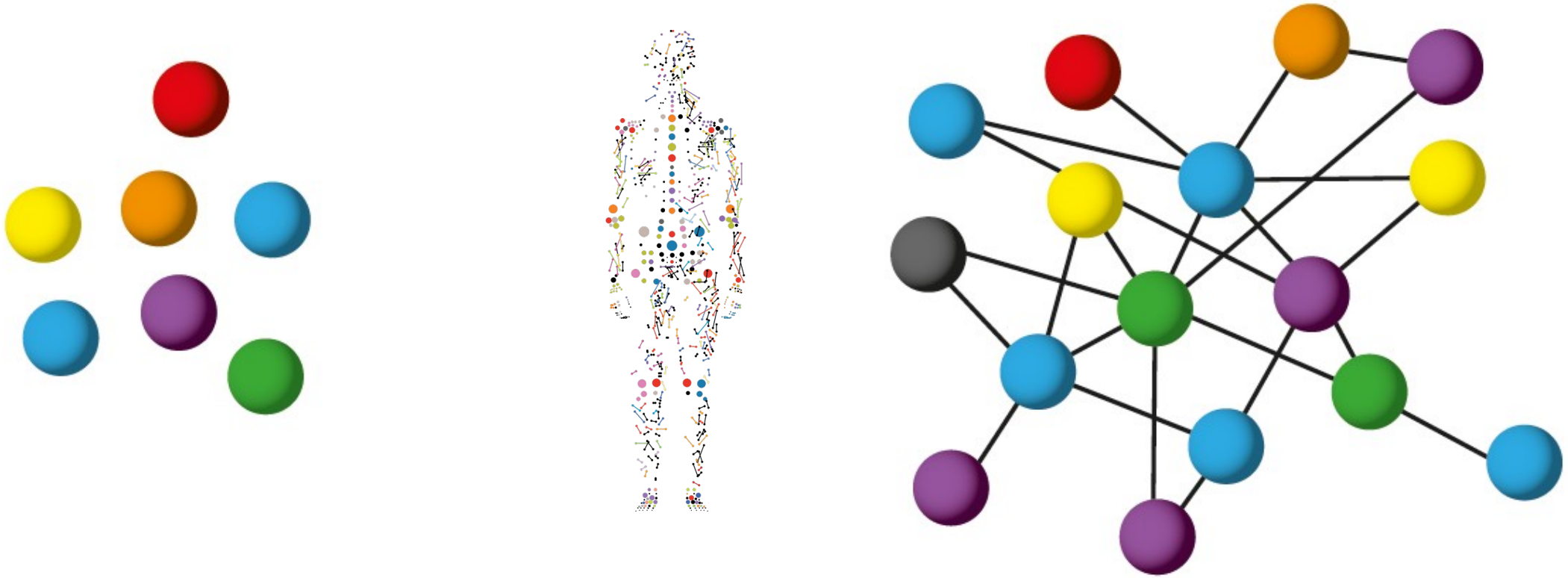
Why *Low Dose Cytokine Therapy* for a healthy longevity?

In a complex system
an impairment in the cross-talk between cells can be at the origin of the aging process as well as the disease onset.



Wagner JUG, Dimmeler S. Cellular cross-talks in the diseased and aging heart. J Mol Cell Cardiol. 2020 Jan;138:136-146.

Reductionistic approach vs Systemic approach



Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet*. 2011;12(1):56-68. doi:10.1038/nrg2918

Systems Medicine (Network Medicine)

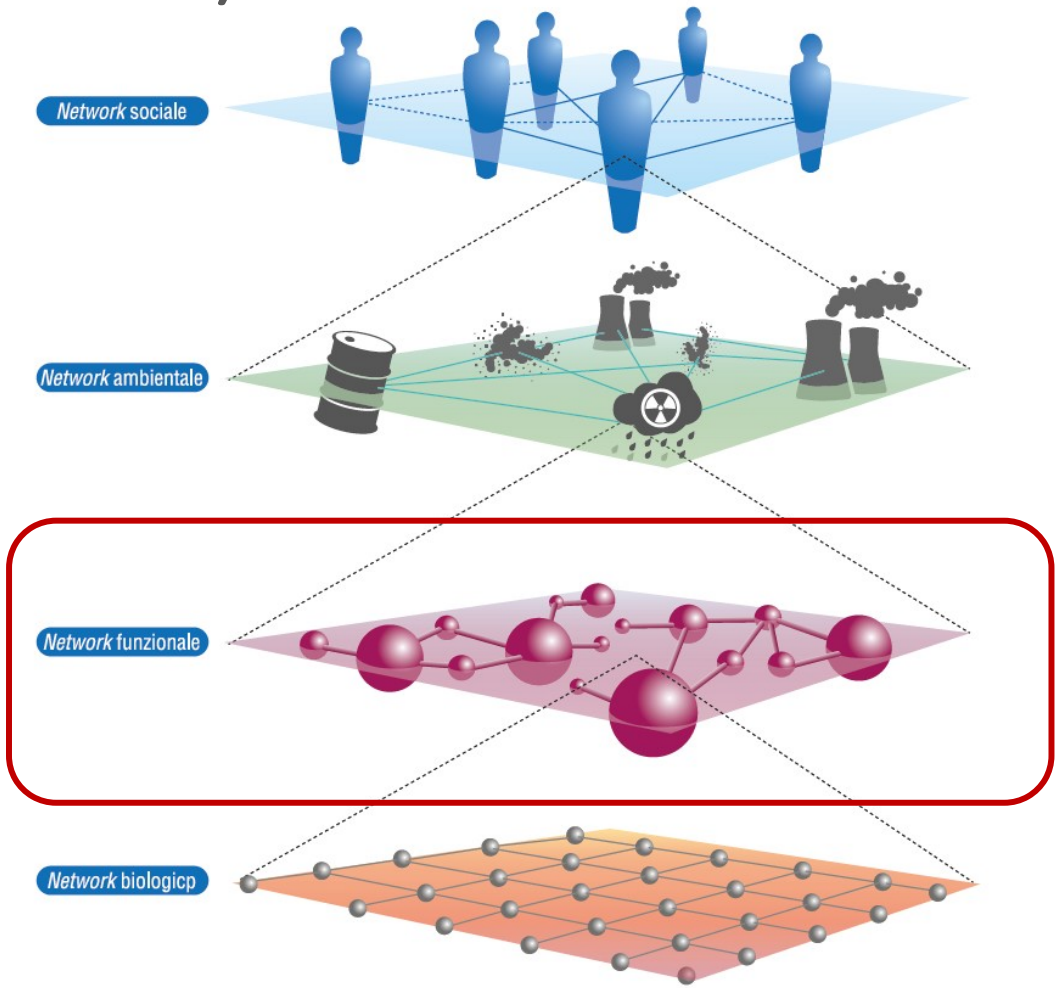
SISTEMA NERVOSO CENTRALE & SISTEMA NEUROVEGETATIVO

SISTEMA ENDOCRINO

SISTEMA IMMUNITARIO

P N E I

- Neuroendocrine network
- Immunological network
- Metabolic network
- Cell-Energy network



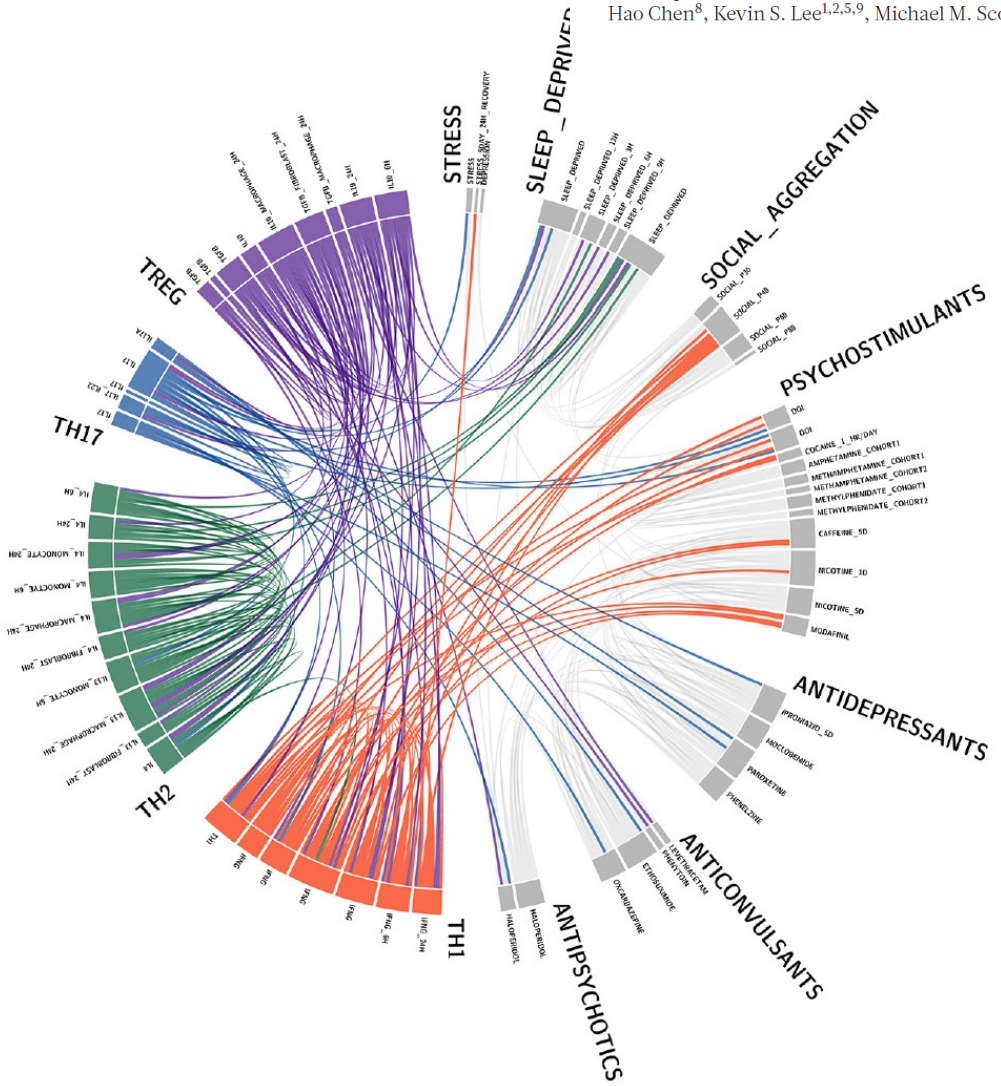
Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12(1):56-68. doi:10.1038/nrg2918

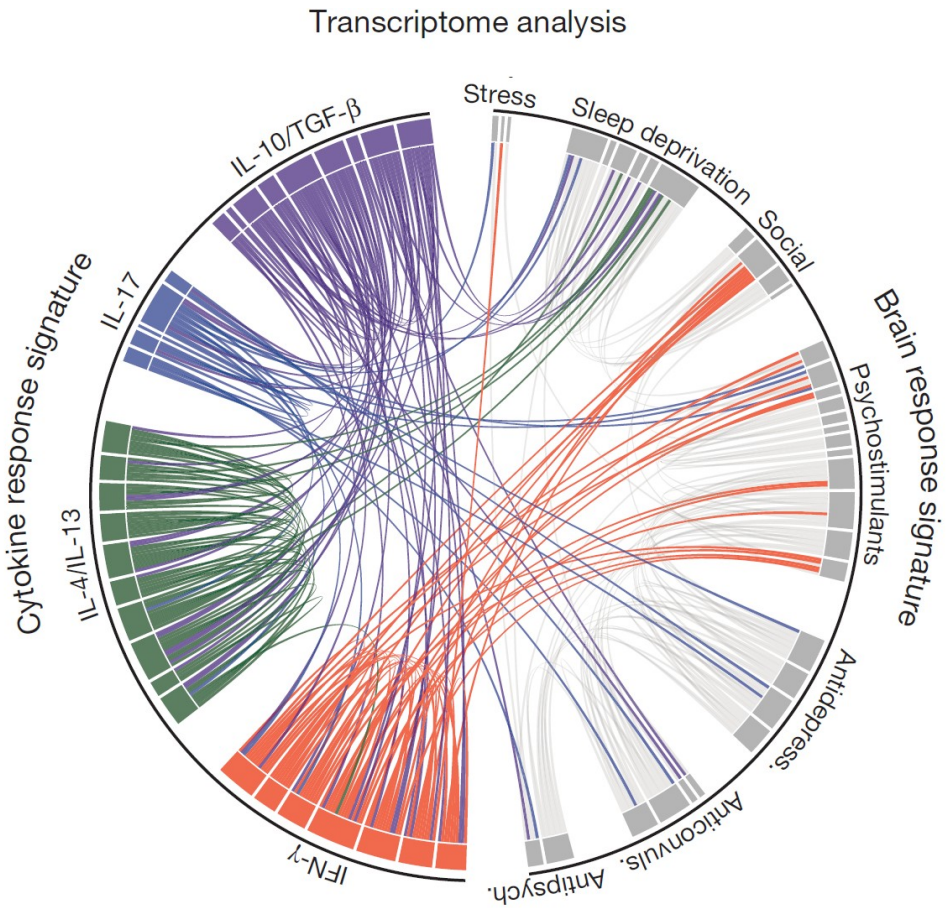
Ader, R., Psychoneuroimmunology, IV edition, vol. 1 e 2, Academic Press, Amsterdam 2007. (It is the classical text on the matter, pubblished for the first time in 1981)

doi:10.1038/nature18626

Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour

Anthony J. Filiano[1,2], Yang Xu[3], Nicholas J. Tustison[4], Rachel L. Marsh[1,2], Wendy Baker[1,2], Igor Smirnov[1,2], Christopher C. Overall[1,2], Sachin P. Gadani[1,2,5,6], Stephen D. Turner[7], Zhiping Weng[8], Sayeda Najamussahar Peerzade[3], Hao Chen[8], Kevin S. Lee[1,2,5,9], Michael M. Scott[5,10], Mark P. Beenhakker[5,10], Vladimir Litvak[3]* & Jonathan Kipnis[1,2,5,6]*





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

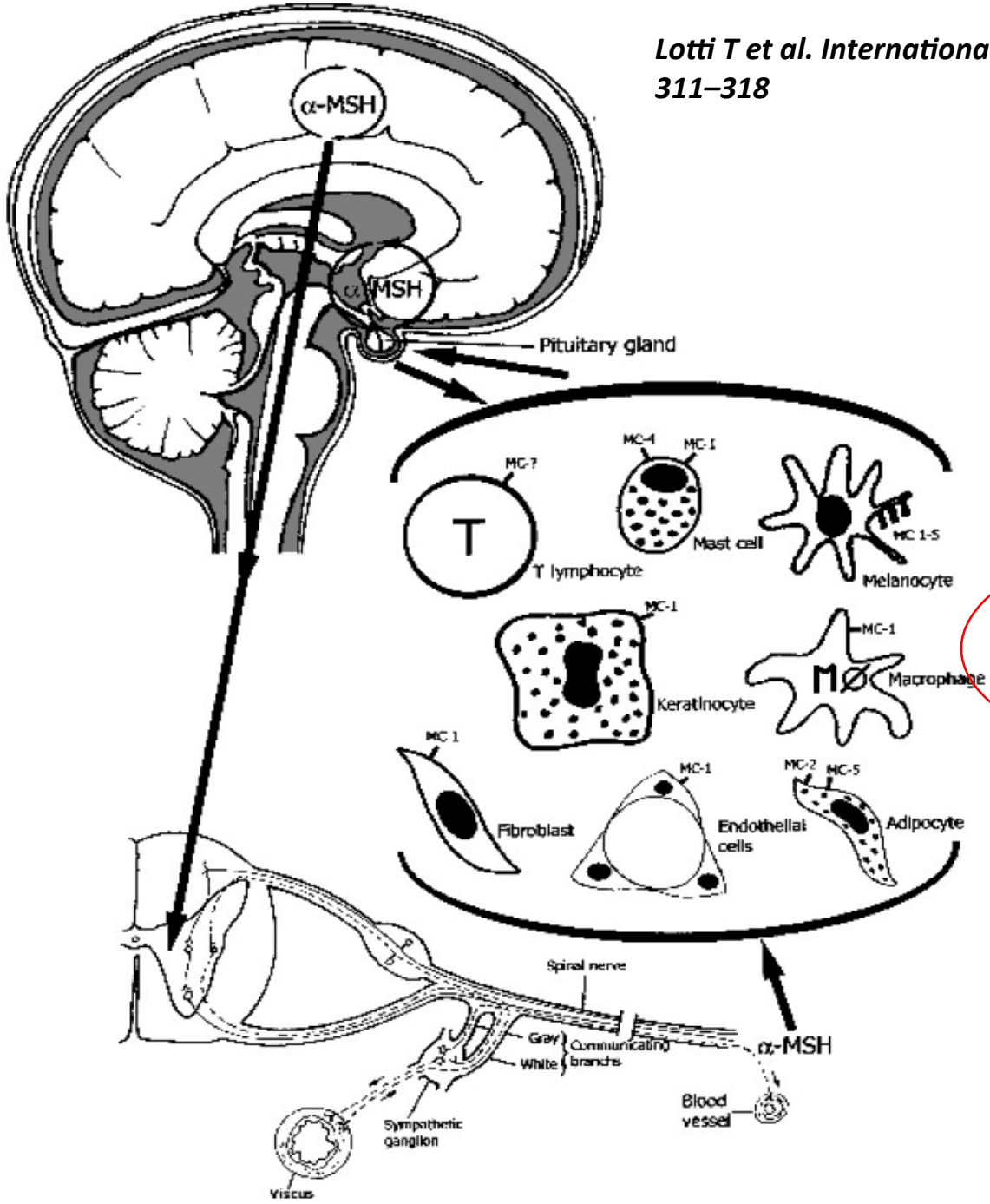
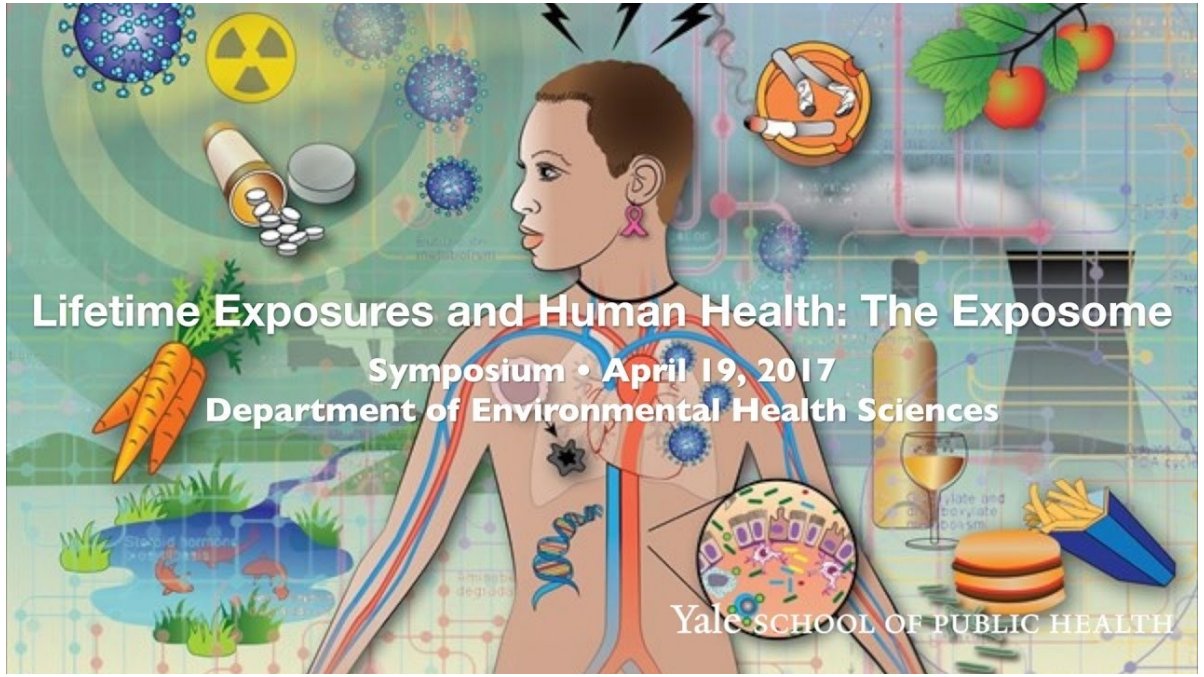
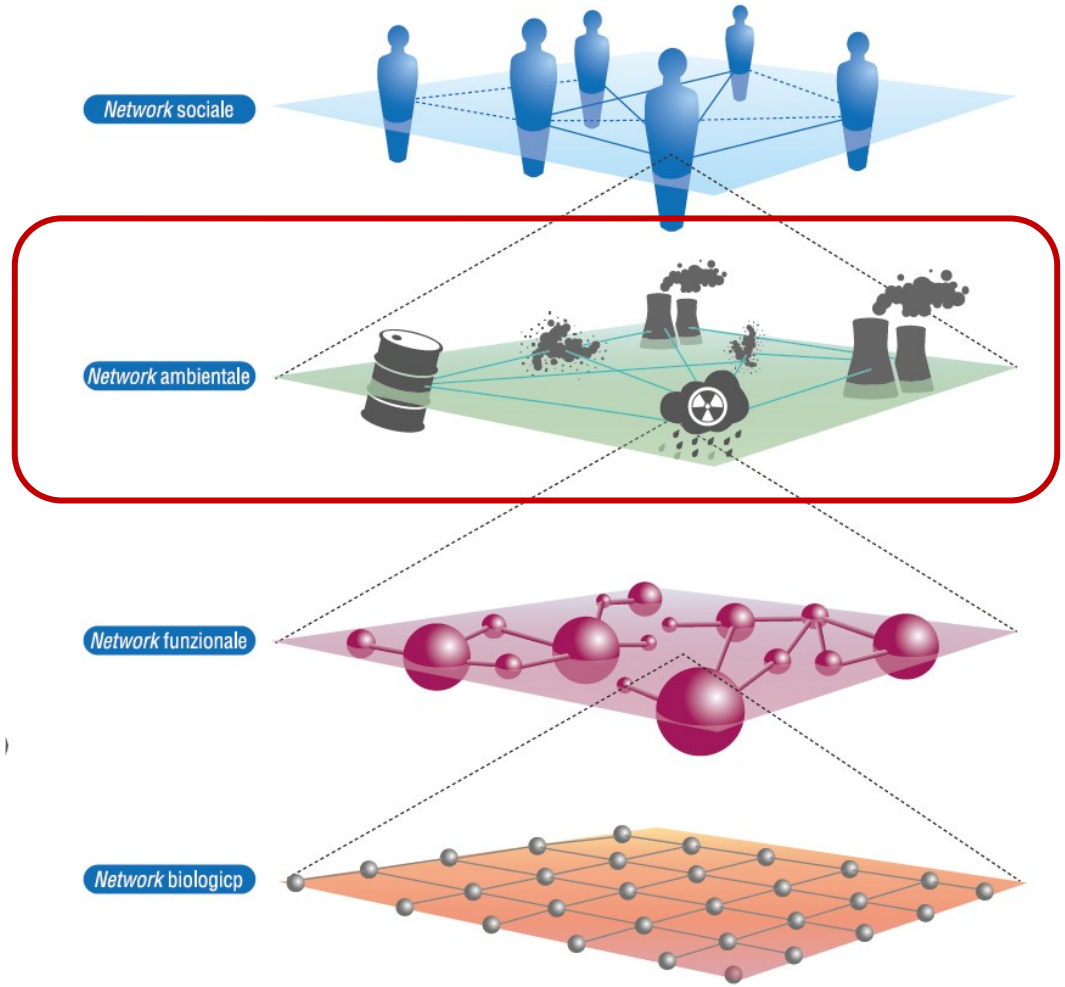


Figure 1 In the brain α-melanocyte stimulating hormone is synthetized predominantly in the pituitary gland. When administered into the cerebral ventriculi (in mice) α-MSH inhibits the cutaneous inflammation induced by application of topical irritants and intradermal injection of cytokines. This action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

Systems Medicine (Network Medicine)





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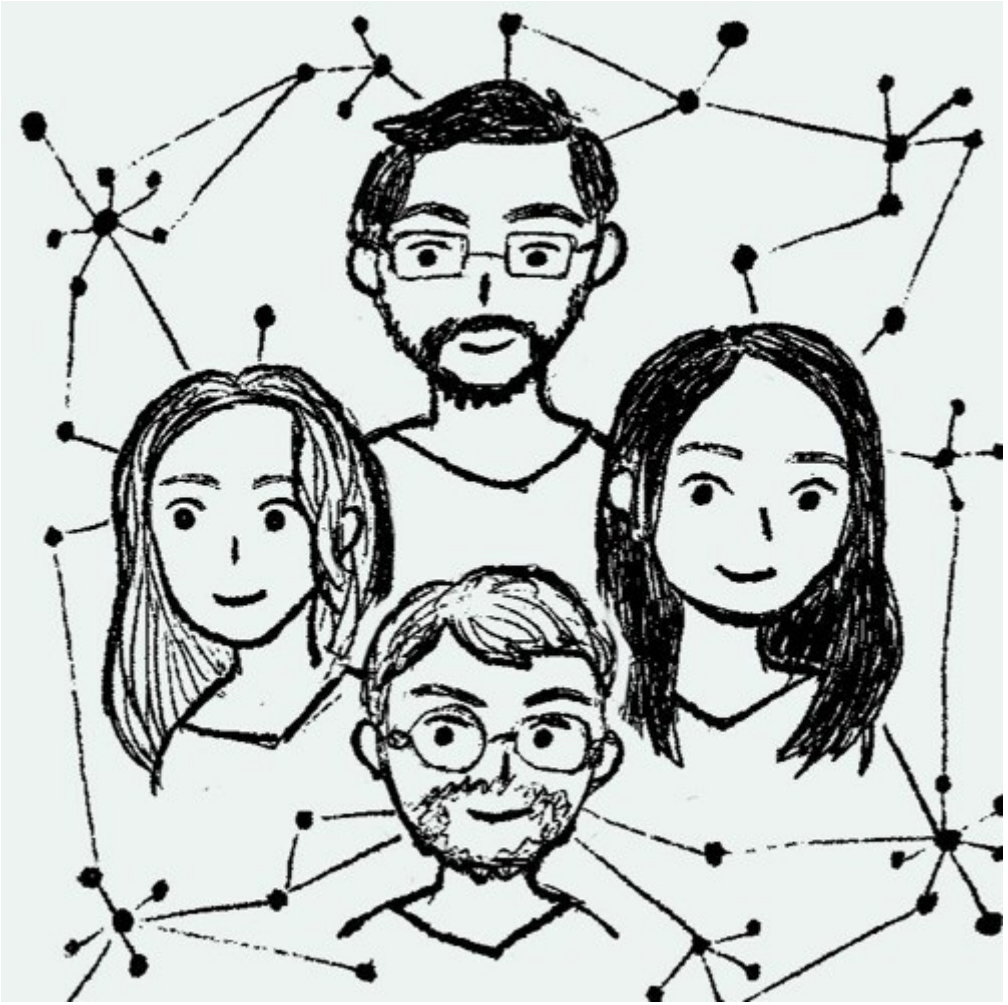
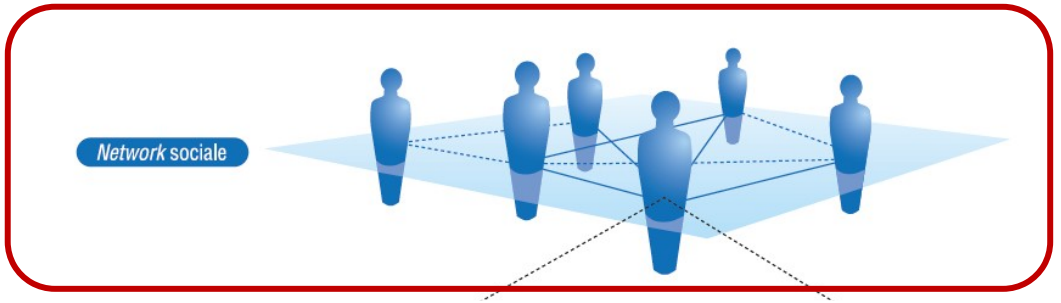
Systems Medicine (Network Medicine)





Secondo la teoria dei sistemi viventi, la mente non è un'entità ma un processo, il processo stesso della vita.
In altre parole, l'attività di organizzazione dei sistemi viventi, ad ogni livello a cui si manifesta la vita, è attività mentale.
Le interazioni di un organismo vivente (vegetale, animale, umano) con il suo ambiente sono interazioni cognitive, ossia mentali.
Dunque, vita e cognizione risultano connesse in modo inseparabile. La mente, o per essere più precisi, il processo mentale, è insita nella materia ad ogni livello a cui si manifesta la vita.

(F. Capra, La rete della vita 1996)

Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet*. 2011;12(1):56-68. doi:10.1038/nrg2918

«NEGATIVE THOUGHTS» AND LOW-GRADE CHRONIC INFLAMMATION

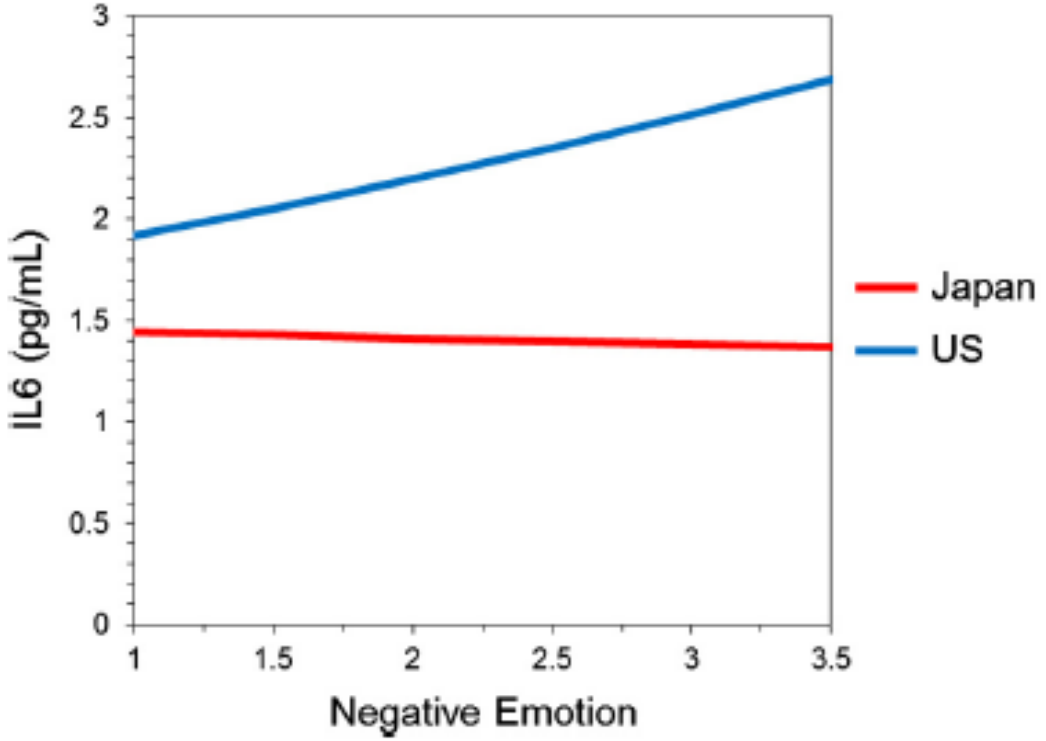


Fig. 1. Cultural moderation of the association between negative emotions and IL-6 after controlling for gender, age, and years of education, positive emotions, neuroticism, extraversion, smoking status, alcohol consumption, the number of chronic conditions linked to inflammation, and log-transformed BMI (Model 5). Negative emotions were rated on a 5-point rating scale: *none of the time* (1), *a little of the time* (2), *some of the time* (3), *most of the time* (4), and *all the time* (5). Negative emotions predicted IL-6 in the United States, $b = 0.06$, S.E. = 0.02, $t(1363) = 2.68$, $p = .001$, but not in Japan, $b = -0.01$, S.E. = 0.03, $t(1363) = 0.35$, $p = .73$.

Miyamoto Y. et al. Negative emotions predict elevated interleukin-6 in the United States but not in Japan. Brain, Behavior, and Immunity 2013

Neurobiology of Stress 4 (2016) 15–22

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Integrating Interleukin-6 into depression diagnosis and treatment

Georgia E. Hodes*, Caroline Ménard, Scott J. Russo

Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form
24 March 2016
Accepted 25 March 2016
Available online 29 March 2016

ABSTRACT

There is growing evidence of a relationship between inflammation and psychiatric illness. In particular, the cytokine Interleukin-6 (IL-6) has been linked to stress-related disorders such as depression and anxiety. Here we discuss evidence from preclinical and clinical studies examining the role of IL-6 in mood disorders. We focus on the functional role of peripheral and central release of IL-6 on the development of stress susceptibility and depression-associated behavior. By examining the contribution of both peripheral and central IL-6 to manifestations of stress-related symptomatology, we hope to broaden the way the field thinks about diagnosing and treating mood disorders.

Psychoneuroendocrinology (2006) 31, 288–294

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www.elsevier.com/locate/psyneuen

Raised plasma nerve growth factor levels associated with early-stage romantic love

Enzo Emanuele[a,*], Pierluigi Politi[b], Marika Bianchi[a], Piercarlo Minoretti[a], Marco Bertona[a], Diego Geroldi[a]

[a]*Interdepartmental Center for Research in Molecular Medicine (CIRMC), University of Pavia, Viale Taramelli 24, I-27100 Pavia, Italy*
[b]*Department of Health Sciences, Section of Psychiatry, University of Pavia, Pavia, Italy*

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Symposium
SYSTEMS MEDICINE
Integration models in clinical practice and new therapeutic solutions

Held in Milan, at the University of Milan, on 5 May 2022

under the auspices of:

World Health Organization (WHO) Collaborating Center for Integrative Medicine
P.R.M. (International Academy of Physiological Regulating Medicine)
FEMTEC (Worldwide Federation of Hydrotherapy and Climatotherapy)

under the patronage of:

Italian Ministry of Health
FNOMCeO (National Federation of the Associations of Surgeons and Dentists)

THE SPEAKERS

PROF. GIUSEPPE BELLELLI
Full Professor of Geriatrics-Internal Medicine, Milan-Bicocca University

PROF. SERGIO BERNASCONI
Full Professor of Paediatrics, Former Director of Paediatric Clinics at the Universities of Modena and Parma

PROF. GIANNI BONA
Full Professor of Paediatric Clinic, Former Director of the Paediatric Clinic, University of Eastern Piedmont

PROF. MARIO CLERICI
Full Professor of Immunology and Immunopathology, University of Milan

PROF. GIUSEPPE DE BENEDITTIS
Associate Professor of Neurosurgery, University of Milan

DR. MARCO DEL PRETE
President P.R.M. Academy
(International Academy of Physiological Regulating Medicine)

PROF. FABIO ESPOSITO
Full Professor of Physical Exercise Sciences and Sport, University of Milan

PROF. VASSILIOS FANOS
Full Professor of Paediatrics, University of Cagliari

PROF. ALESSANDRO GENAZZANI
Associate Professor of Obstetrics and Gynaecology, University of Modena-Reggio Emilia

PROF. PAOLO INGHILLERI
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Full Professor of Endocrinology, University of Rome "Tor Vergata"

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PROF. ALBERTO MIGLIORE
Director of the UOS (Simple Operative Unit) of Rheumatology, San Pietro Fatebenefratelli Hospital, Rome

PROF. EMILIO MINELLI
WHO *(World Health Organization)* Expert Advisory, Panel Member Clin. Research on Integrative Medicine

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Full Professor of General Pathology, University of Rome "Tor Vergata"

PROF. CLAUDIO MOLINARI
Associate Professor of Human Physiology, University of Eastern Piedmont, Vercelli

PROF. VALTER SANTILLI
Full Professor of Physical and Rehabilitative Medicine, University of Rome "La Sapienza"

PROF. UMBERTO SOLIMENE
Direttore *WHO (World Health Organization) Collaborating Center for Integrative Medicine - State University of Milan*

HAVE APPROVED *THE MILAN DECLARATION 2022 – NEW GOALS FOR MEDICINE*
WHICH OUTLINES THE CURRENT AND FUTURE SOCIAL AND HEALTH SCENARIOS THAT MAKE NECESSARY TO DEFINE A NEW PARADIGM OF MEDICINE.

E cellula ad hominem

DICHIARAZIONE DI MILANO 2022
NUOVI OBIETTIVI DELLA MEDICINA

A Complex System

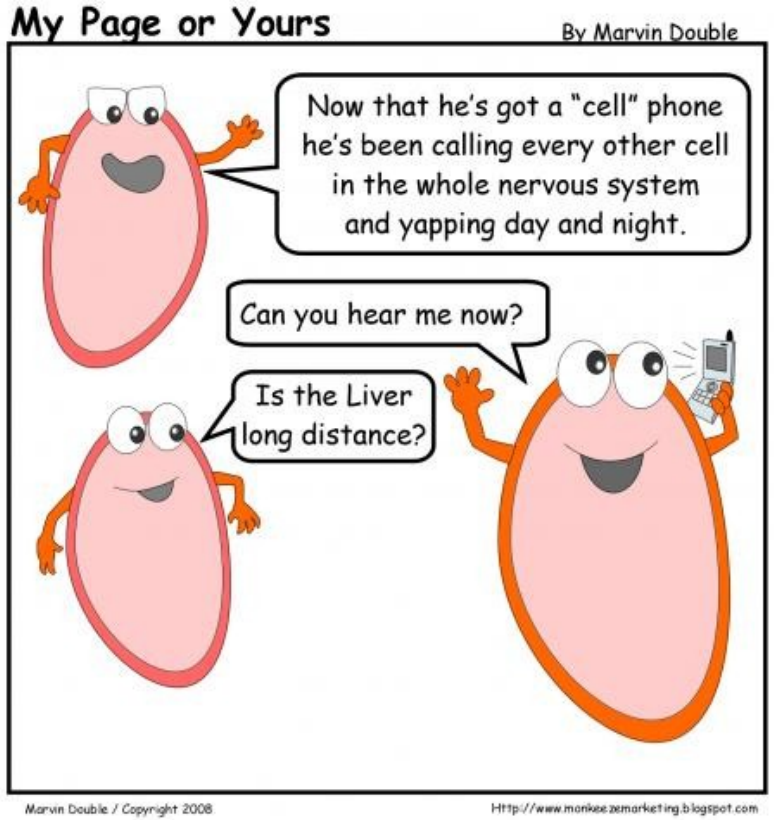
THE HUMAN BODY
IS A NETWORK
OF NETWORKS

40.000 billion cells

Bianconi E, Piovesan A, Facchin F, Beraudi A, Casadei R, Frabetti F, Vitale L, et al. An estimation of the number of cells in the human body. Ann Hum Biol. 2013;40(6):463-71.

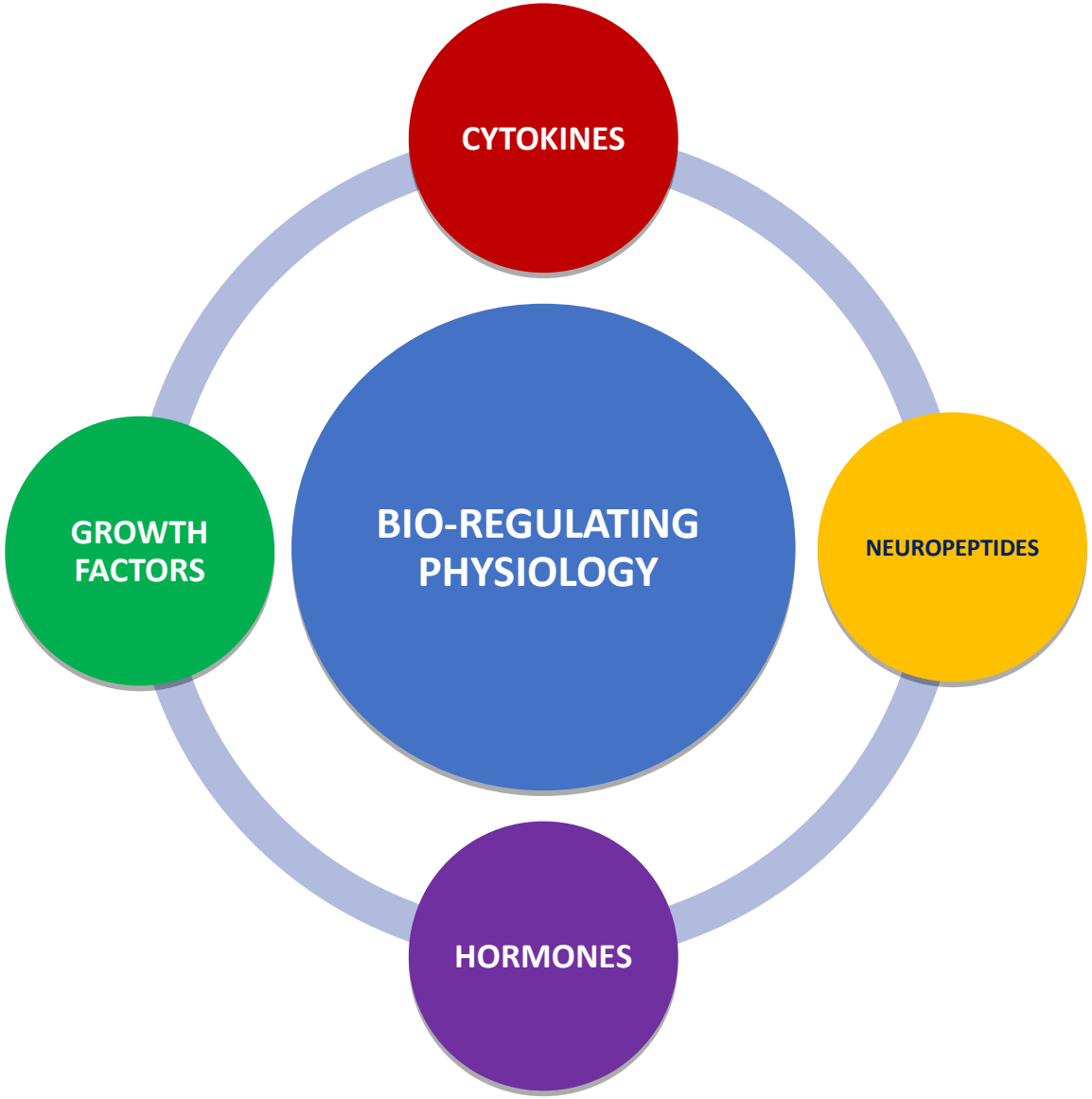
A Complex System

1. How do they talk?
2. Where do they talk?



SIGNALING MOLECULES-BASED LOW DOSE PHARMACOLOGY

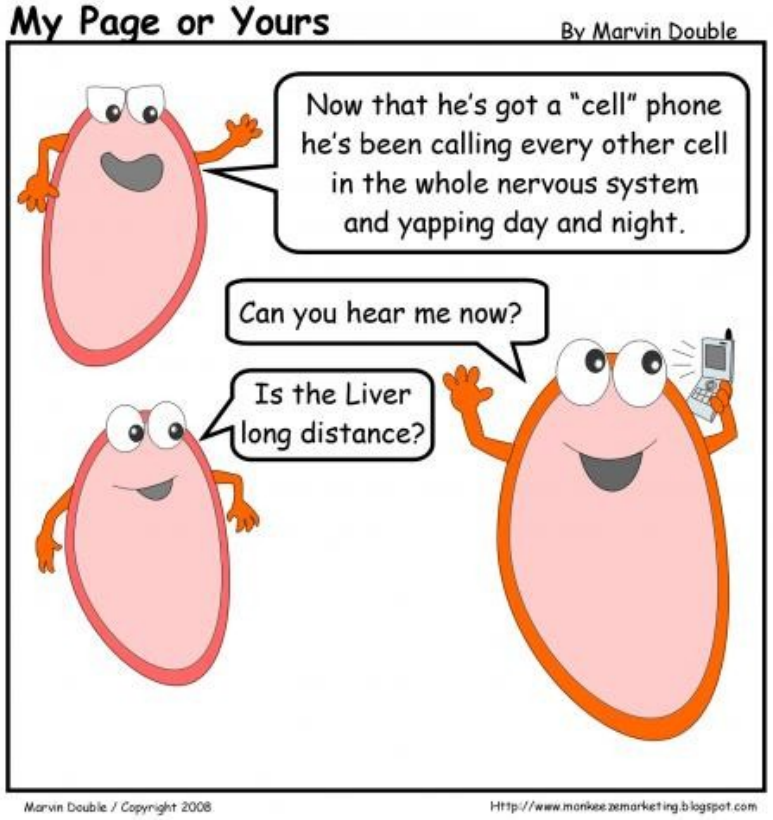
THE GREAT INNOVATION



Signaling Molecules

The Fundation for LDM

CYTYOKINES are MESSENGERS, THE WORDS used by the 3 homeostatic control systems (or functional networks) and BY THE CELLS to speak each other … and to lead the body physiology.



Signaling (Messenger) Molecules

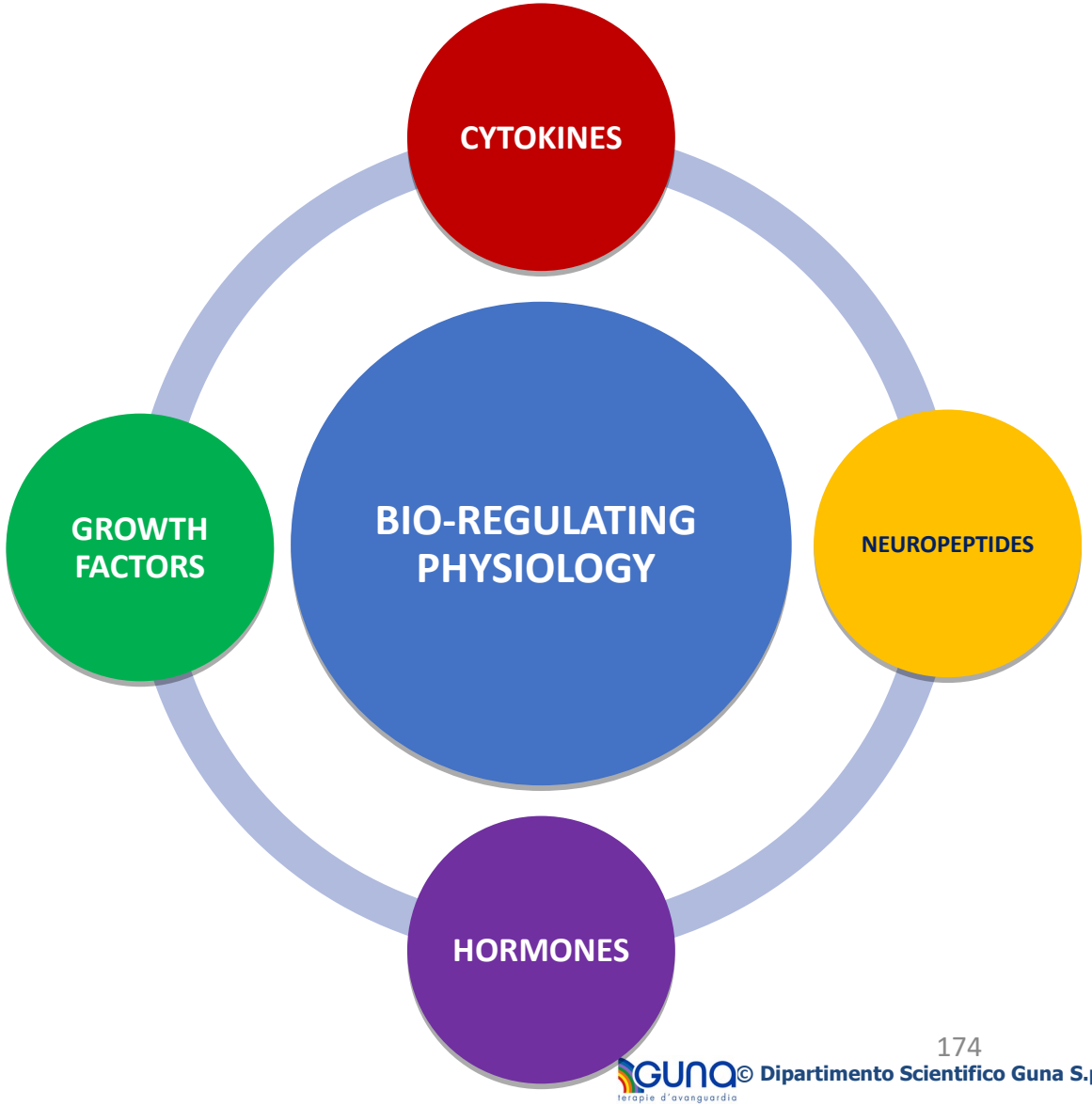
The Foundation for Low Dose Pharmacology

Cells  ***r at a very*** *sub-*

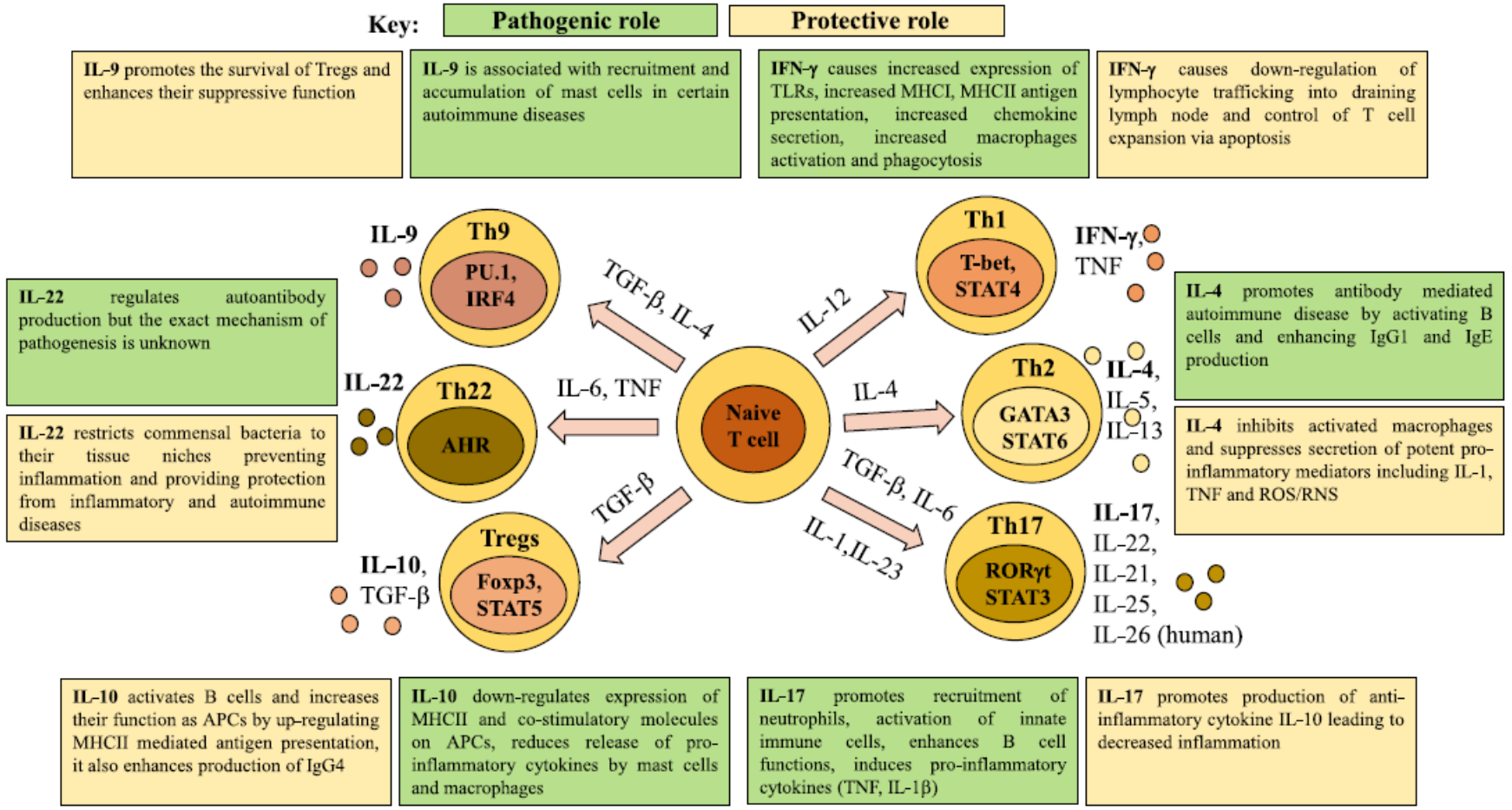
nanc *tion)*

SIGNALING MOLECULES
Quality and Quantity

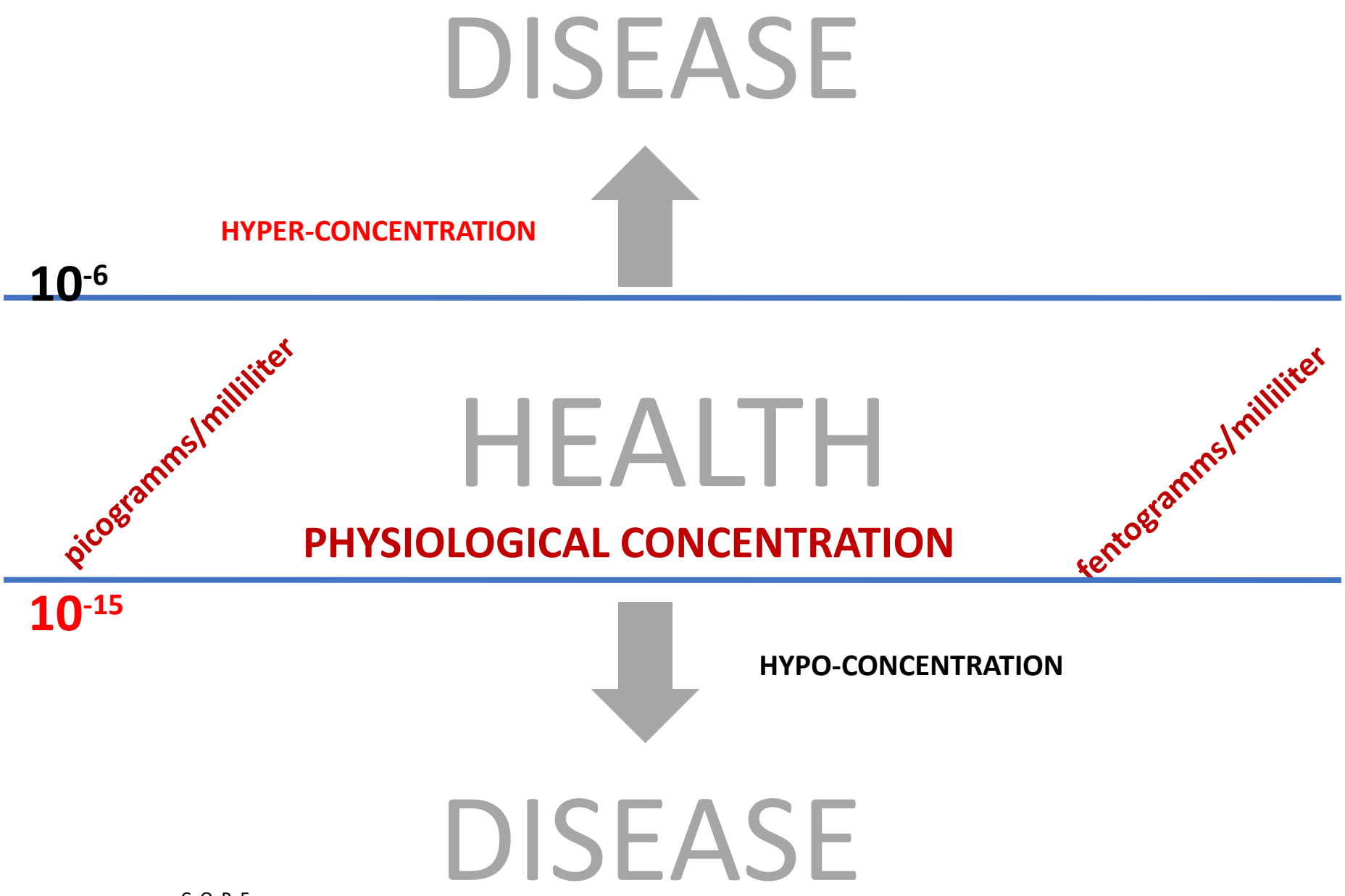
Not just the right **MESSAGE** but the right «**VOLUME**» too.



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



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

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

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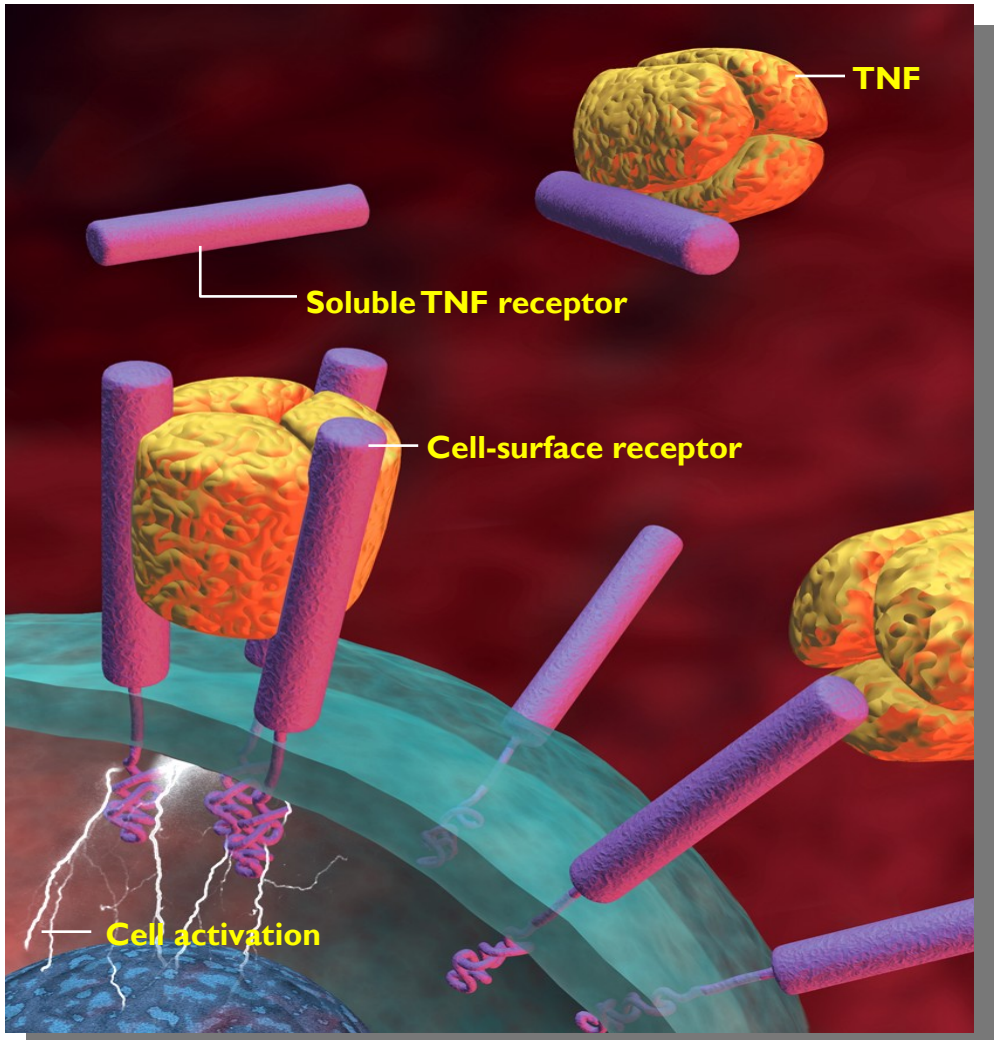
TRANS-MEMBRANE RECEPTORS
Up- and Down-Regulation



Jak-1: Tyrosine kinasis
STAT-1: Signal transducer and activator of transcription 1
SOCS-1:Suppressor of cytokin signaling 1

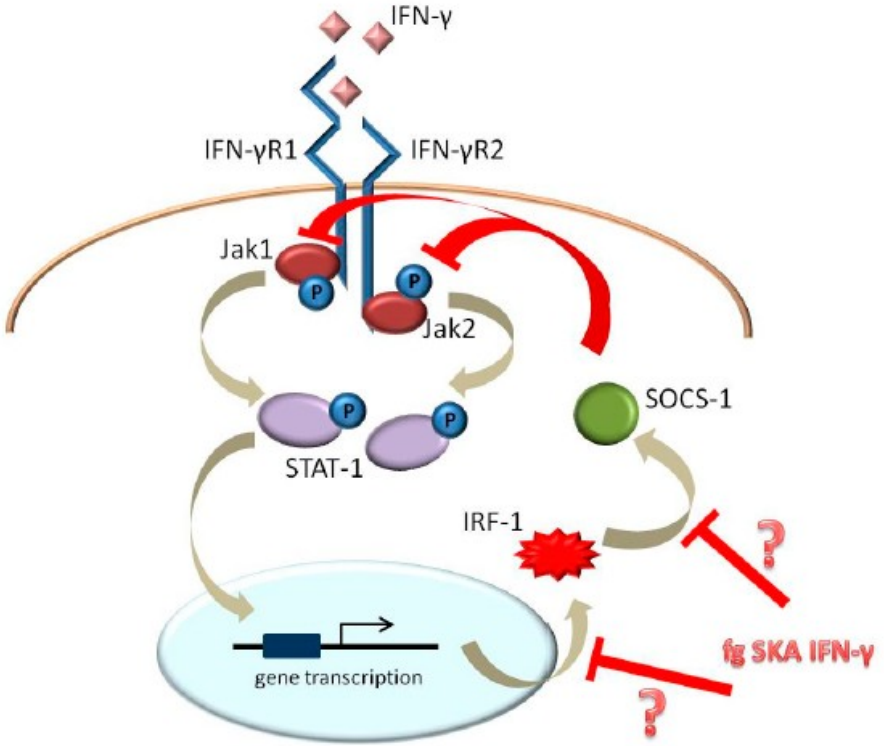
International Journal of *Molecular Sciences*

MDPI

Article

Femtograms of Interferon-γ Suffice to Modulate the Behavior of Jurkat Cells: A New Light in Immunomodulation

Sara Castiglioni [1,*], Vincenzo Miranda [2], Alessandra Cazzaniga [1], Marilena Campanella [2], Michele Nichelatti [3], Marco Andena [1] and Jeanette A. M. Maier [1]



GUNA Signaling Molecules

Drugs: Bio-Tech

Concentration: low dose (sub-nanomolar)

Preparation mode: SKA

- Bio-Tech – human recombinant in *E. Coli or in SF21 (Spodoptera frugiperda).*

The biological "INTELLIGENCE" of LOW DOSES

Journal of Cancer Therapy, 2012, 3, ***-***
Published Online September 2012 (http://www.SciRP.org/journal/jct)

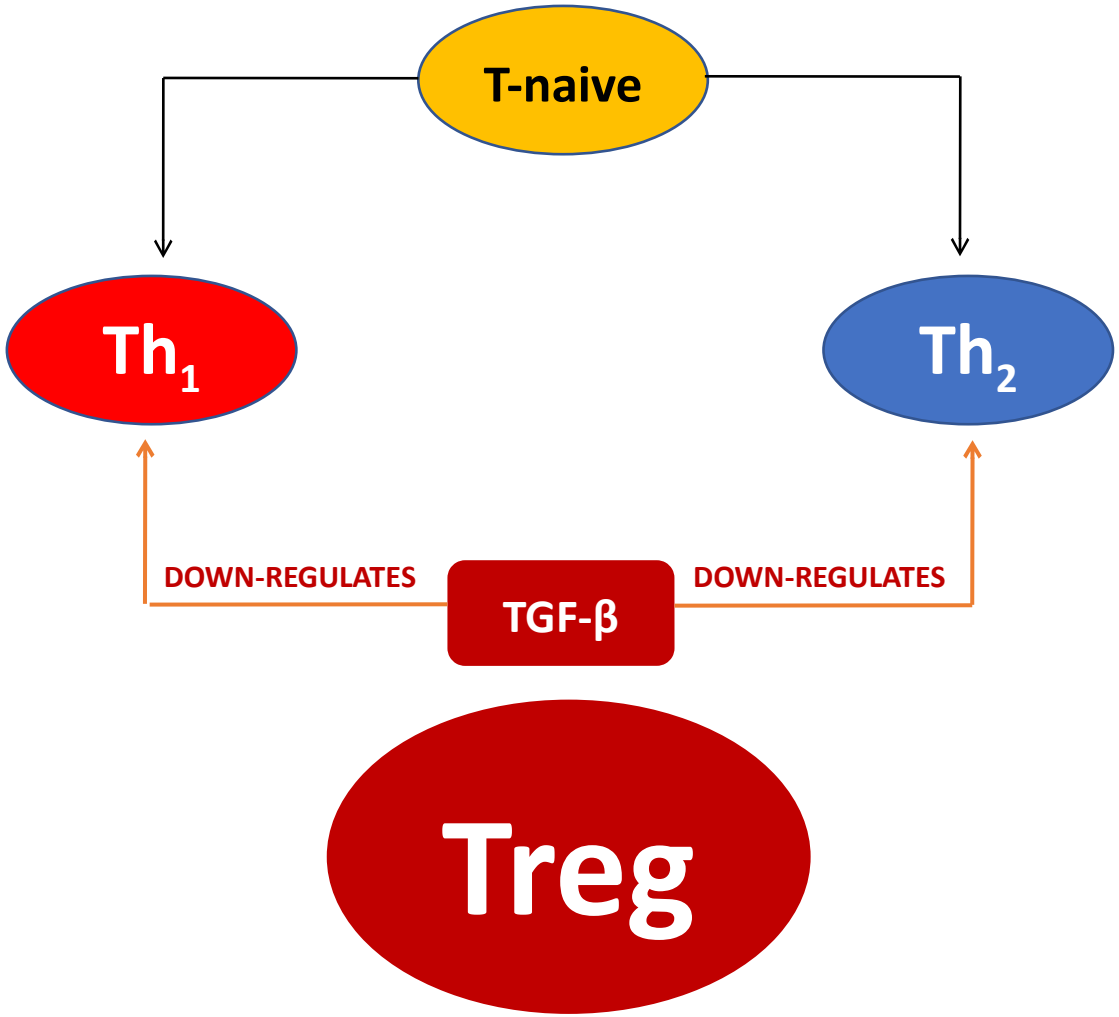
Low Dose of IL-12 Stimulates T Cell Response in Cultures of PBMCs Derived from Non Small Cell Lung Cancer Patients*

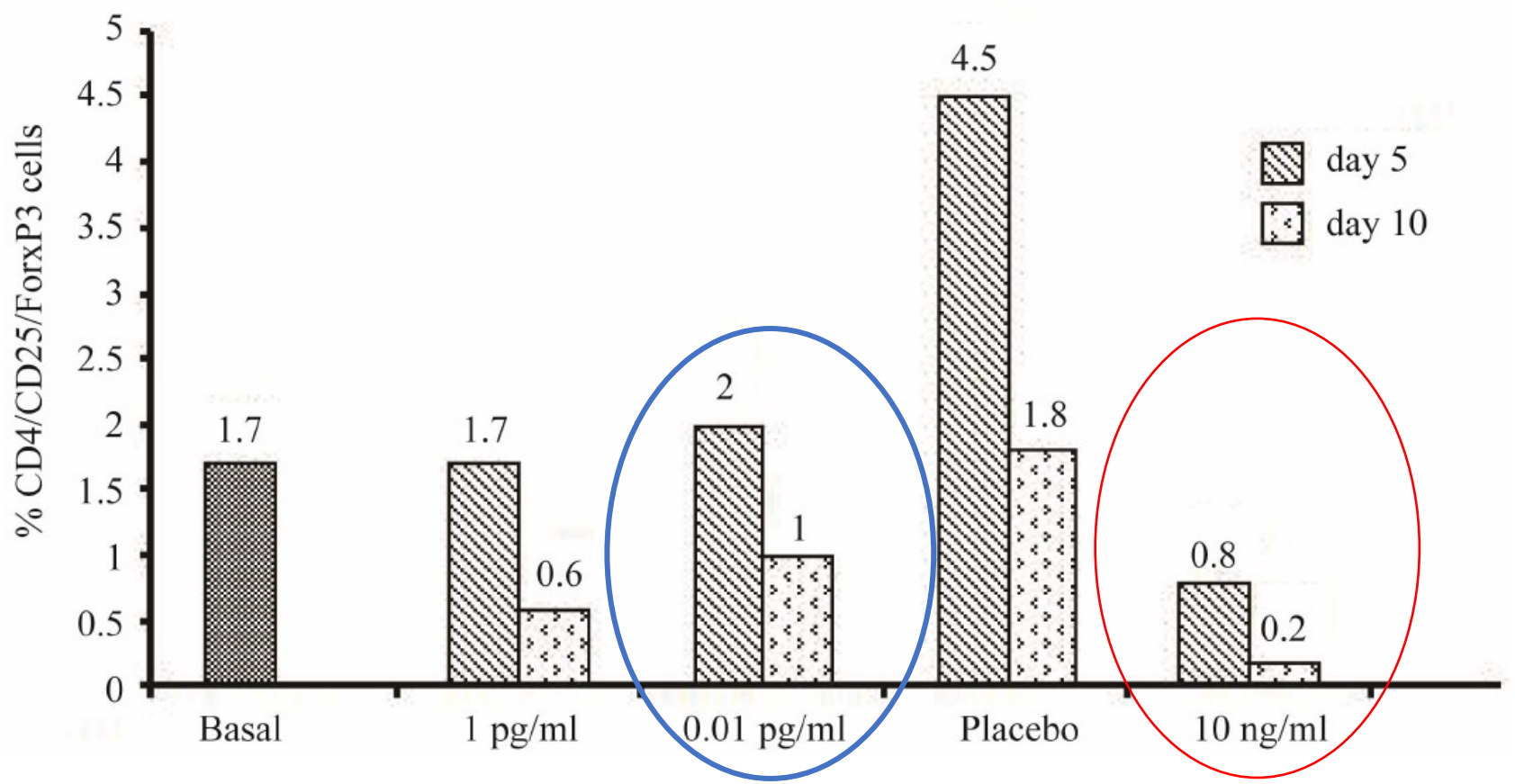
Lucia D'Amico[1], Enrico Ruffini[2], Riccardo Ferracini[3], Ilaria Roato[1#]

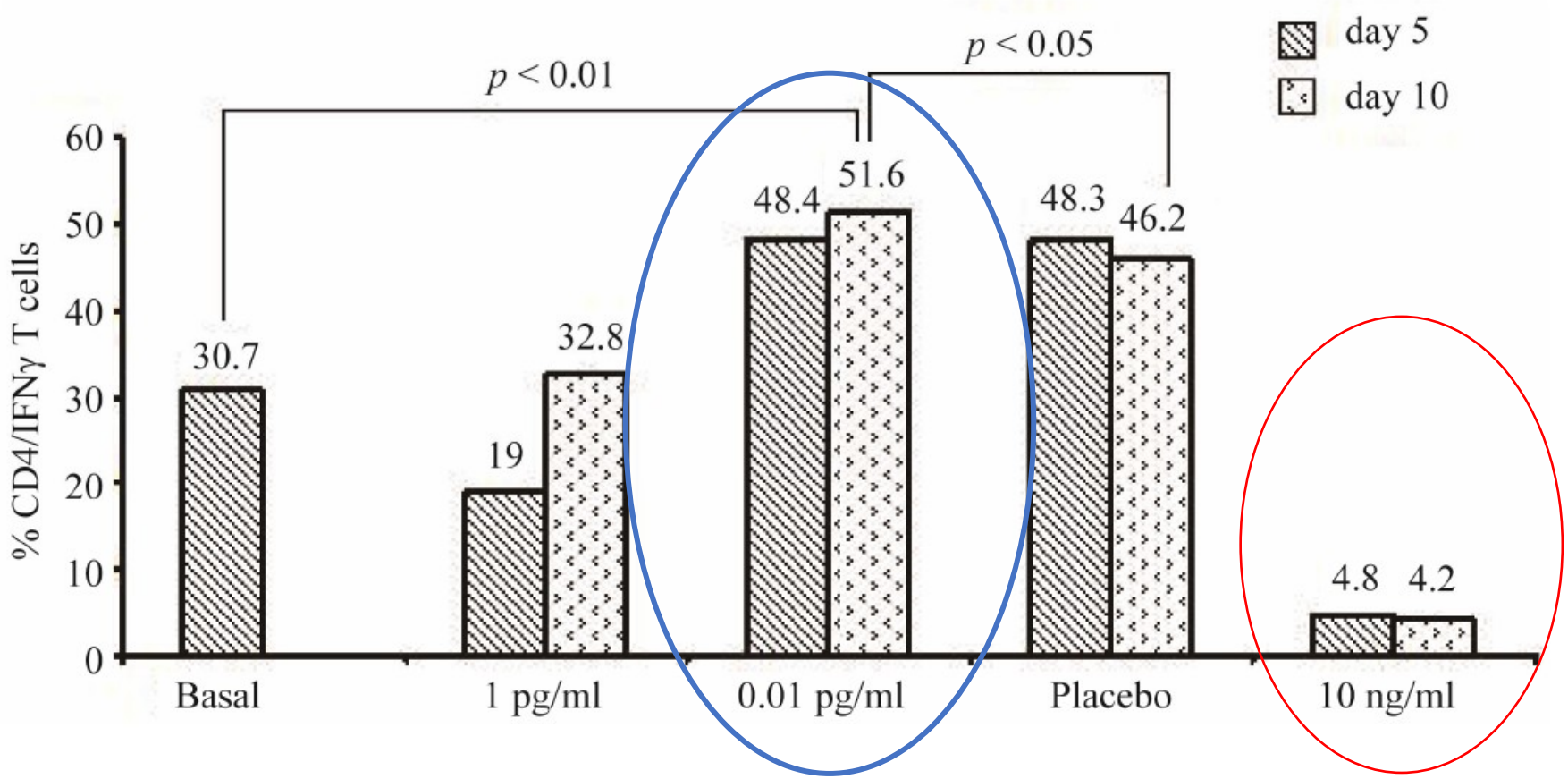
[1]CeRMS (Center for Research and Medical Studies), A.O. della Salute e della Scienza di Torino, Torino, Italy; [2]Department of Toracic Surgery, A.O. della Salute e della Scienza di Torino, Torino, Italy; [3]Department of Orthopaedics, A.O. della Salute e della Scienza di Torino, Torino, Italy.
Email: #roato78@libero.it

Received 2012

Relationship among Th1-Th2-Treg







The biological EFFECTS of LOW DOSES

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Low dose oral administration of cytokines for treatment of allergic asthma

Silvia Gariboldi [1], Marco Palazzo [1], Laura Zanobbio, Giuseppina F. Dusio, Valentina Mauro, Umberto Solimene, Diego Cardani, Martina Mantovani, Cristiano Rumio*

iMIL – Italian Mucosal Immunity Laboratory, Department of Human Morphology and Biomedical Sciences "Città Studi", Università degli Studi di Milano, via Mangiagalli 31, 20133 Milano, Italy

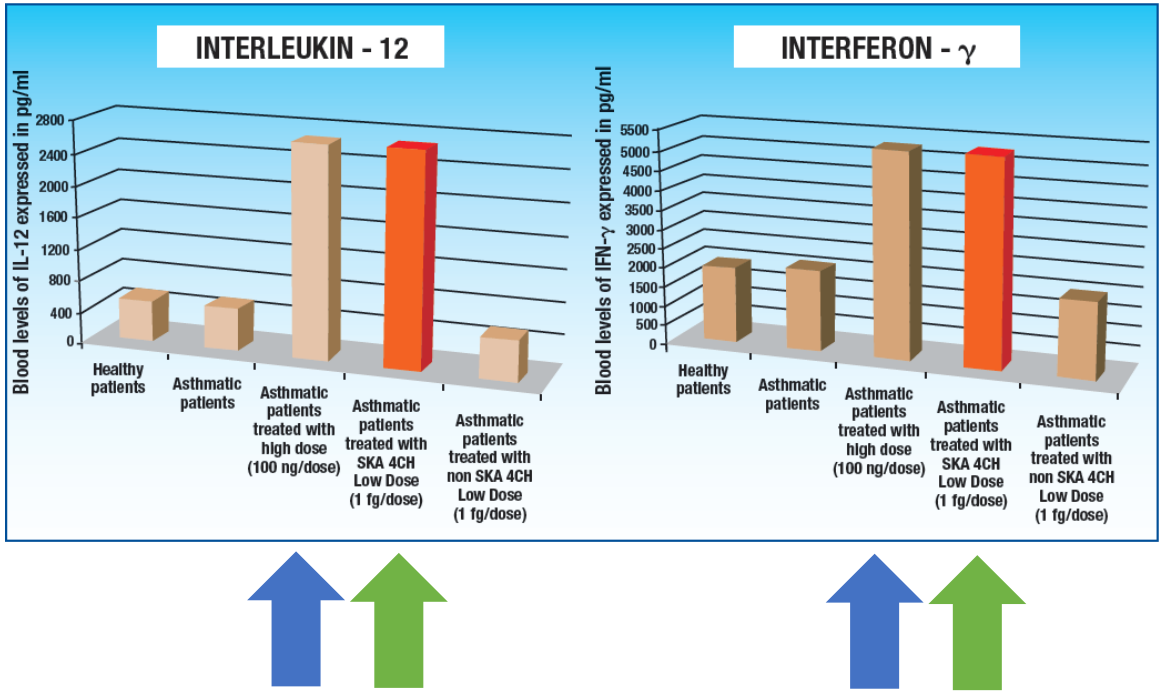
About BIO-STIMULATION activity of physiological low doses

The mystery …which is not a mistery

HIGH DOSE TREATMENT GROUP
100 ng/dose (10^{-9})

Broncho Alveolar
Fluid
Picogramms (10^{-12})

LOW DOSE (HOMEOPATHIC)
TREATMENT GROUP
1 fg/dose (10^{-15})



brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

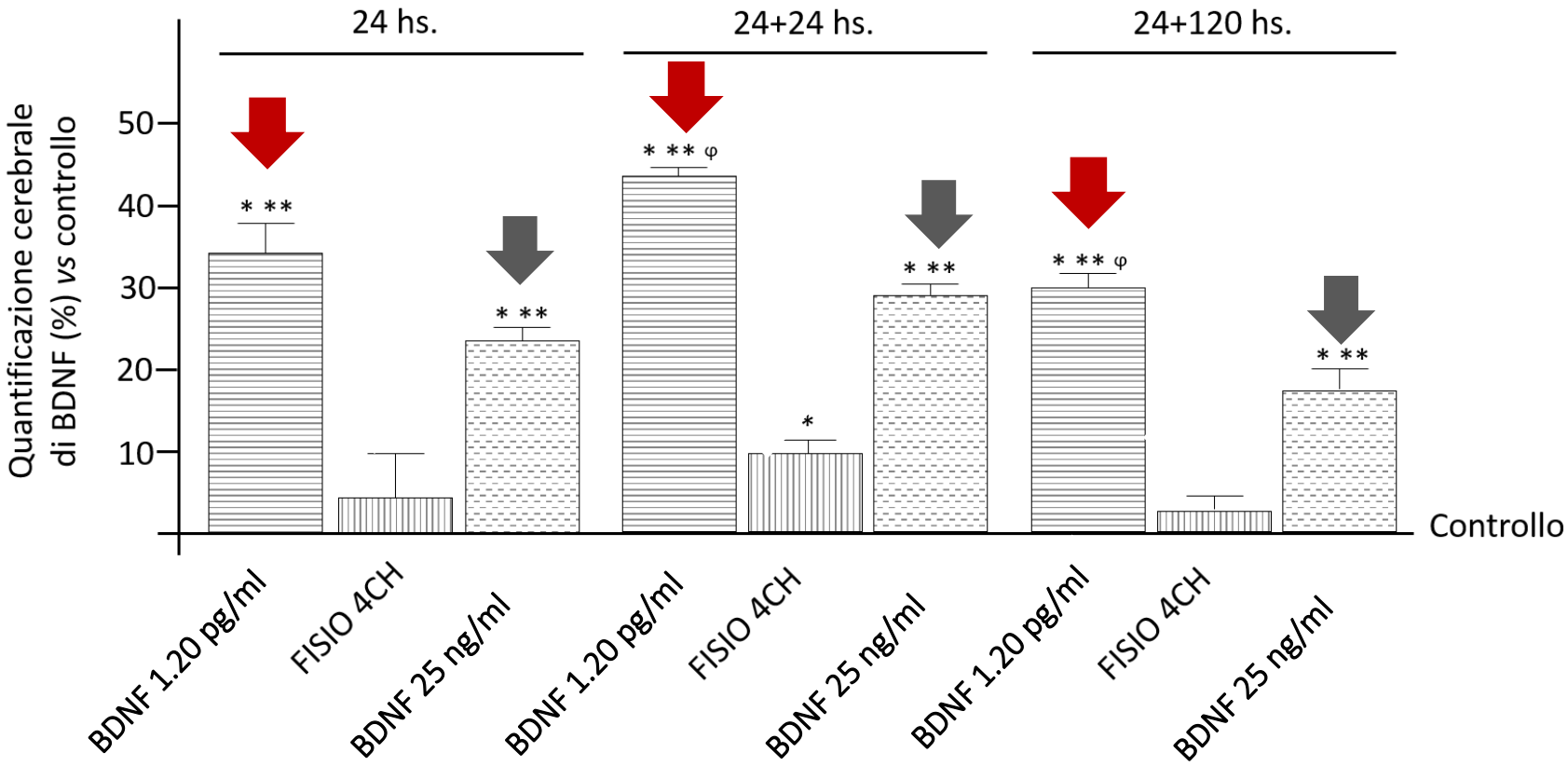
Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy; claudio.molinari@med.uniupo.it (C.M.); vera.morsanuto@med.uniupo.it (V.M.); sara.ruga@uniupo.it (S.R.); felice.notte@uniupo.it (F.N.); mahitab.farghali@uniupo.it (M.F.); rebecca.galla@uniupo.it (R.G.)
* Correspondence: francesca.uberti@med.uniupo.it; Tel.: +39-0321-660653

Received: 26 February 2020; Accepted: 4 May 2020; Published: 9 May 2020

check for updates

In vivo BRAIN BDNF QUANTIFICATION



12 monthh old mice type C57BL

brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy; claudio.molinari@med.uniupo.it (C.M.); vera.morsanuto@med.uniupo.it (V.M.); sara.ruga@uniupo.it (S.R.); felice.notte@uniupo.it (F.N.); mahitab.farghali@uniupo.it (M.F.); rebecca.galla@uniupo.it (R.G.)
* Correspondence: francesca.uberti@med.uniupo.it; Tel.: +39-0321-660653

Received: 26 February 2020; Accepted: 4 May 2020; Published: 9 May 2020

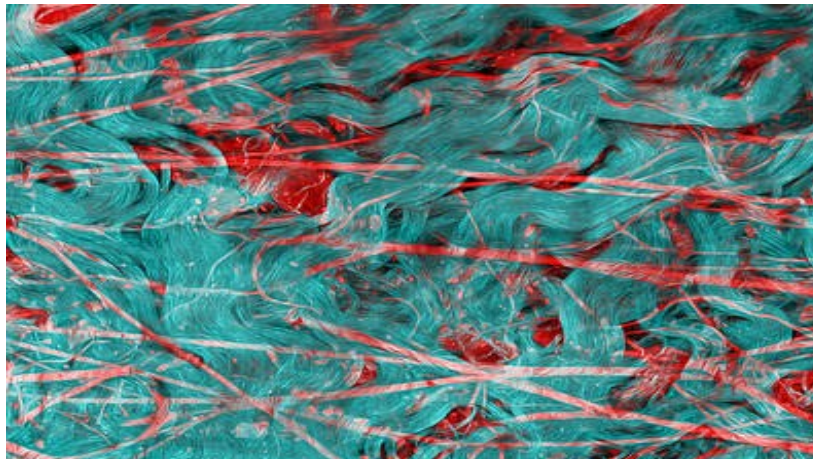
check for updates

To verify whether the mechanism activated by BDNF solutions is the same as the one observed in cells during in vitro experiments, the effects of 1.2 pg/mL BDNF SKA and 25 ng/mL BDNF on some main markers were investigated by Western blot. Since BDNF is necessary for survival of neurons in the brain, after encoding by this gene its expression was investigated, as reported in Figure 9A. 1.2 pg/mL BDNF SKA and 25 ng/mL BDNF both at 24 h and 24 h plus 24 h were able to induce the expression of BDNF compared to control ($p < 0.05$), indicating a better influence of stimulations. Moreover, 1.2 pg/mL BDNF SKA at 24 h and 24 h plus 24 h caused a significant increase compared to and 25 ng/mL BDNF (about 50% and about 62%, respectively), indicating the induction of endogenous production of BDNF by physiological mechanism, as shown by the significant increase induced by 1.2 pg/mL BDNF SKA at 24 h plus 24 h with respect to at 24 h ($p < 0.05$, about 24%).

A Complex System

1. How do they talk?

2. Where do they talk?



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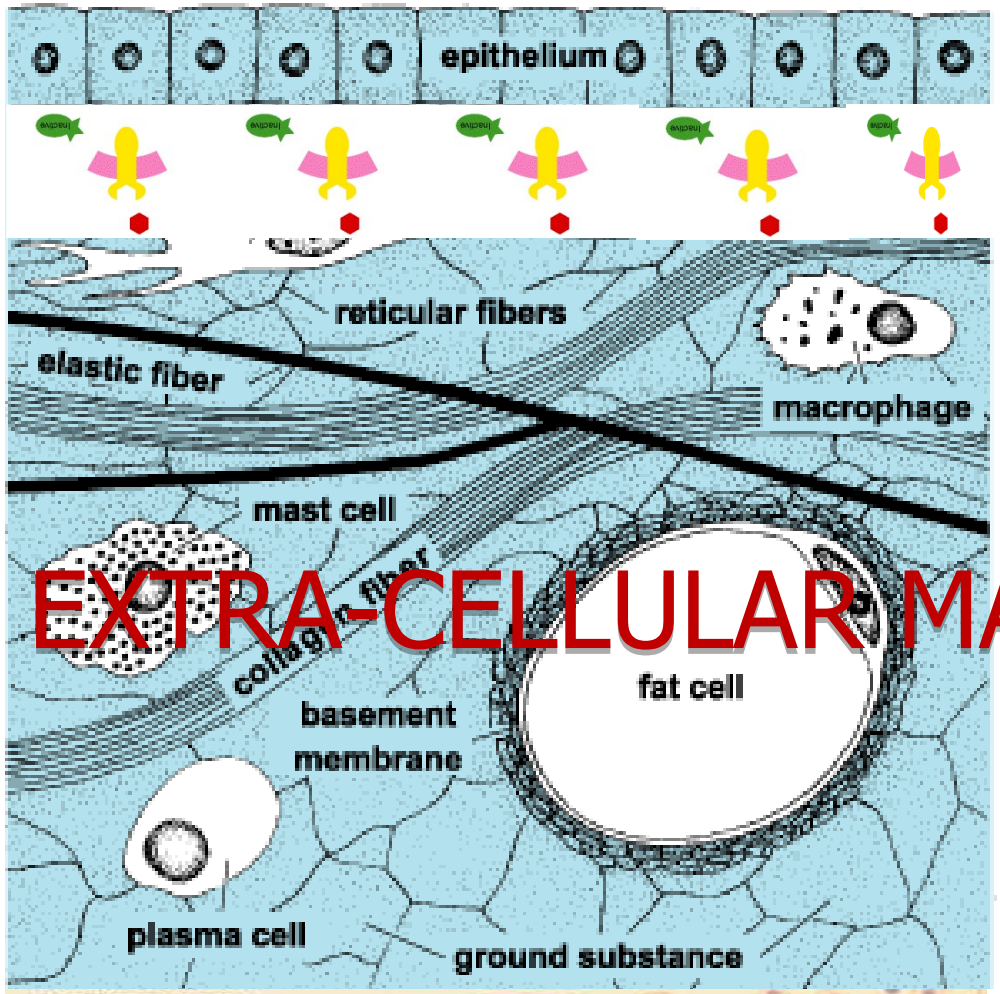
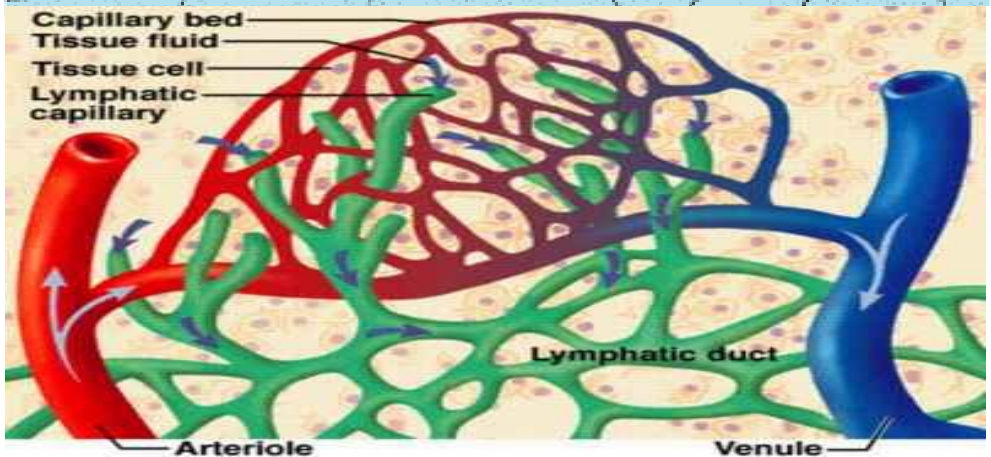
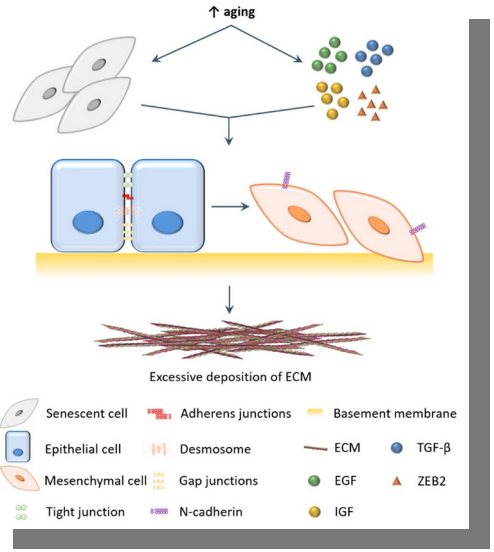
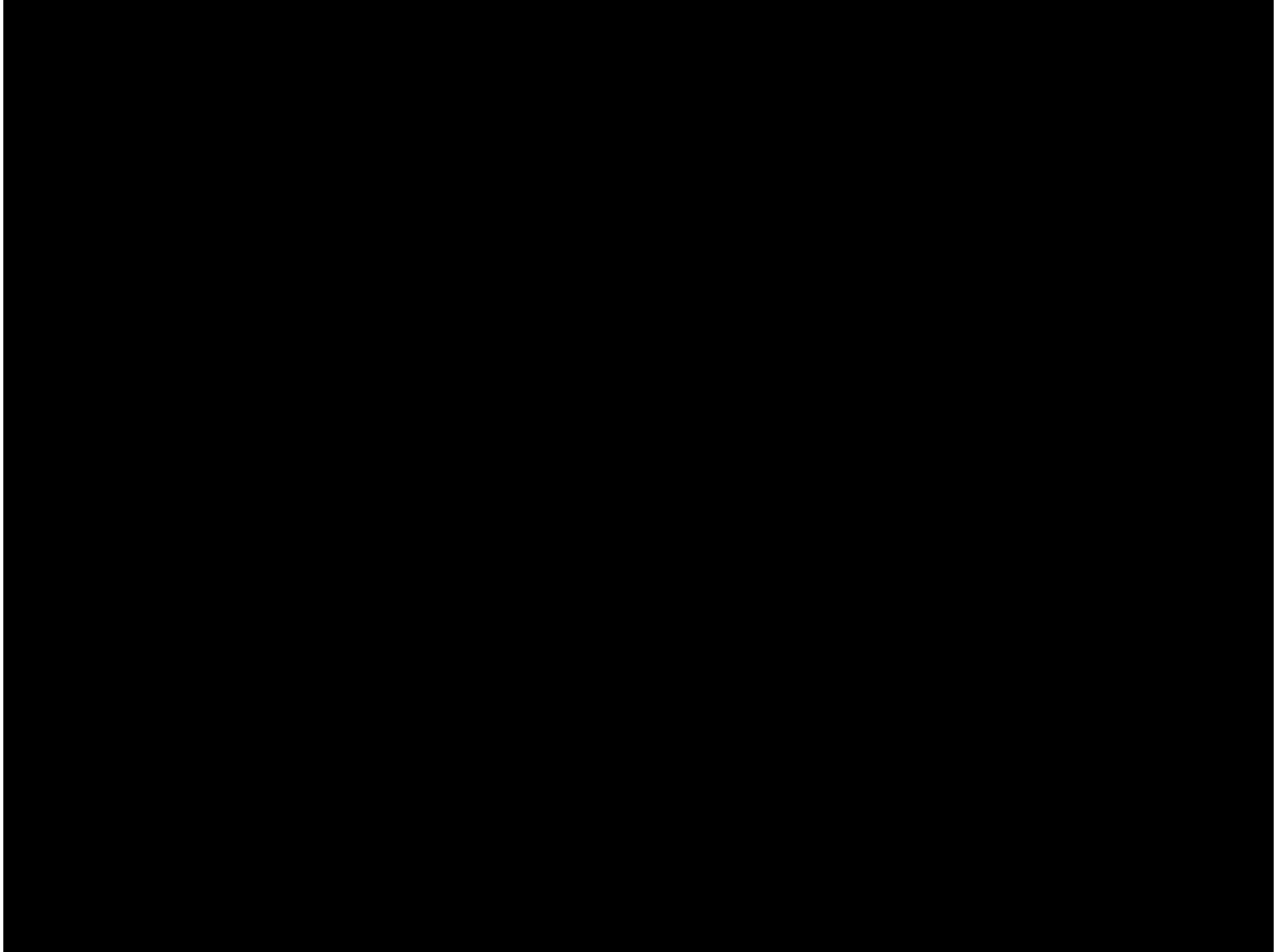
THE EXTRA-CELLULAR MATRIX









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P
N
E
I

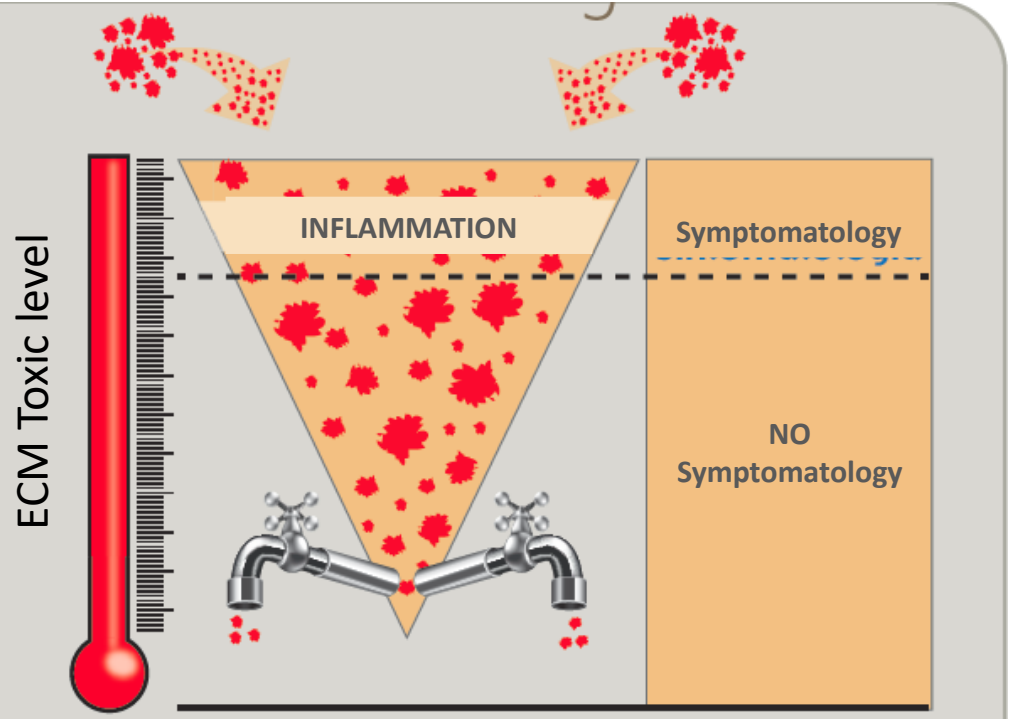
AGING

- **HIGH** LEVEL OF INFLAMMATION
- **HIGH** LEVEL OF OXIDATION
- **HIGH** LEVEL OF INTOXICATION

HOMEOSTASIS

- **HISTOLOGICAL DECLINE**
- **HORMONAL DECLINE**
- **IMMUNE DECLINE**

AGING



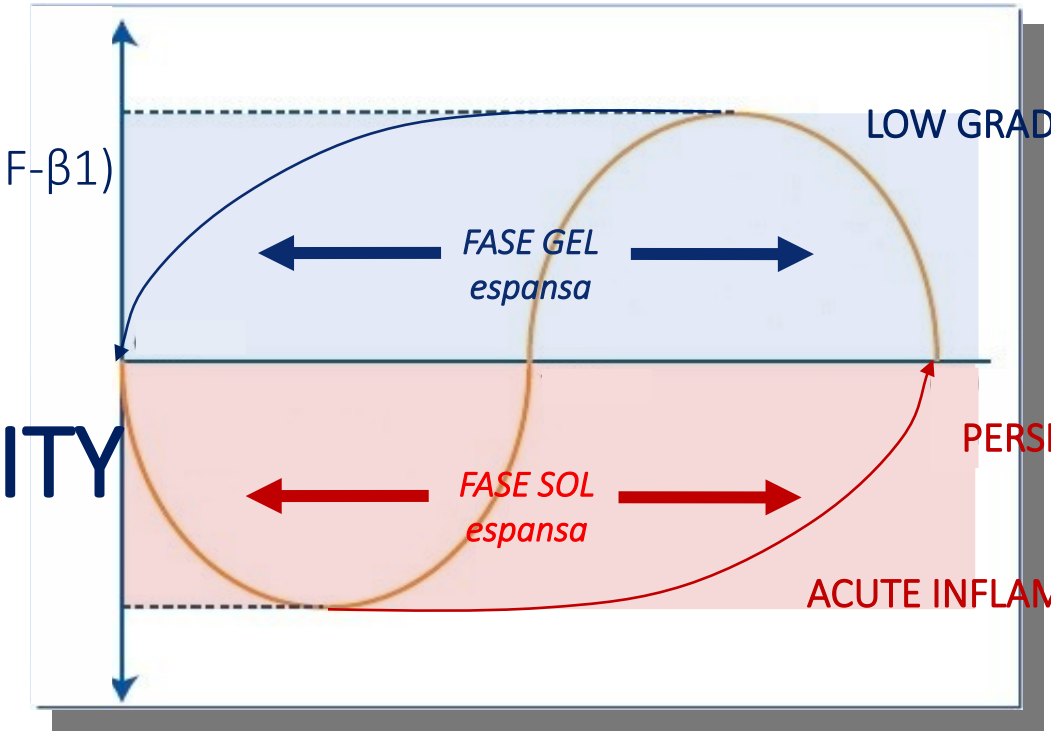
- HIGH LEVEL OF INFLAMMATION
- HIGH LEVEL OF OXIDATION
- **HIGH LEVEL OF INTOXICATION**

ECM and pathological inflammation

FIBROSIS (TGF-β1)

ECM RIGIDITY

AGING



LOW GRADE CHRONIC INFLAMMATION (IL-6)

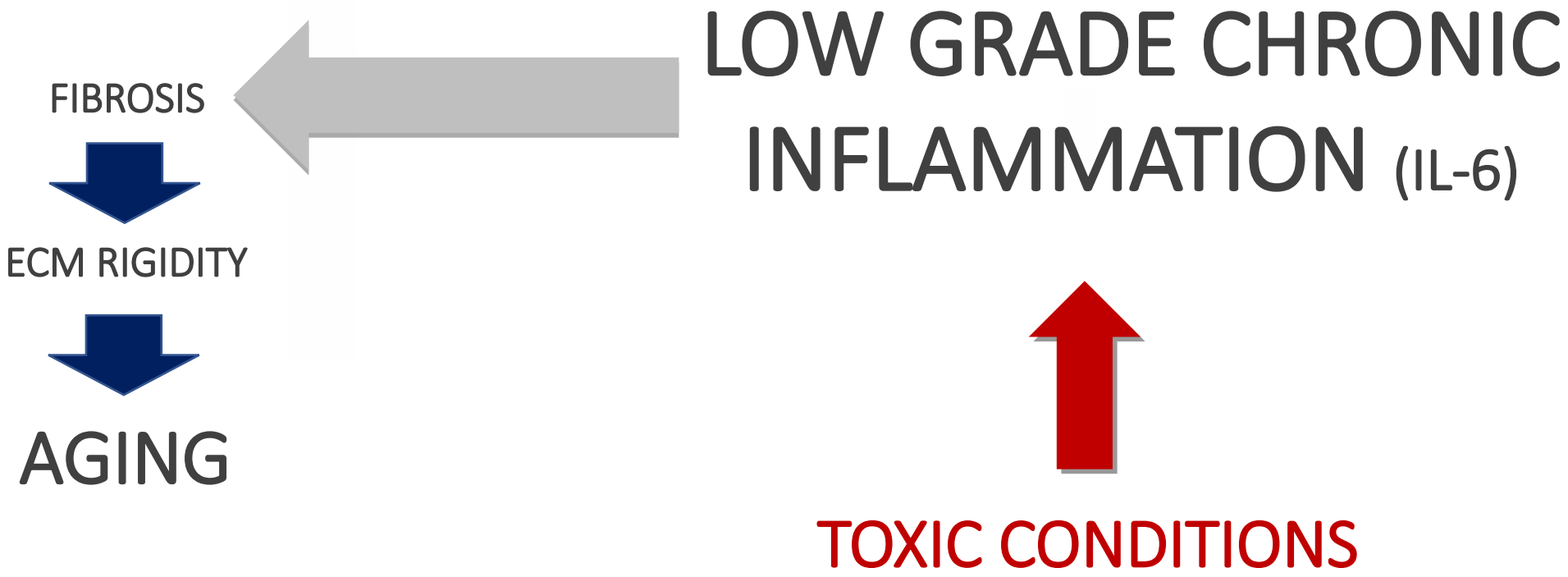
PERSISTENT ACUTE INFLAMMATION (IL-1)

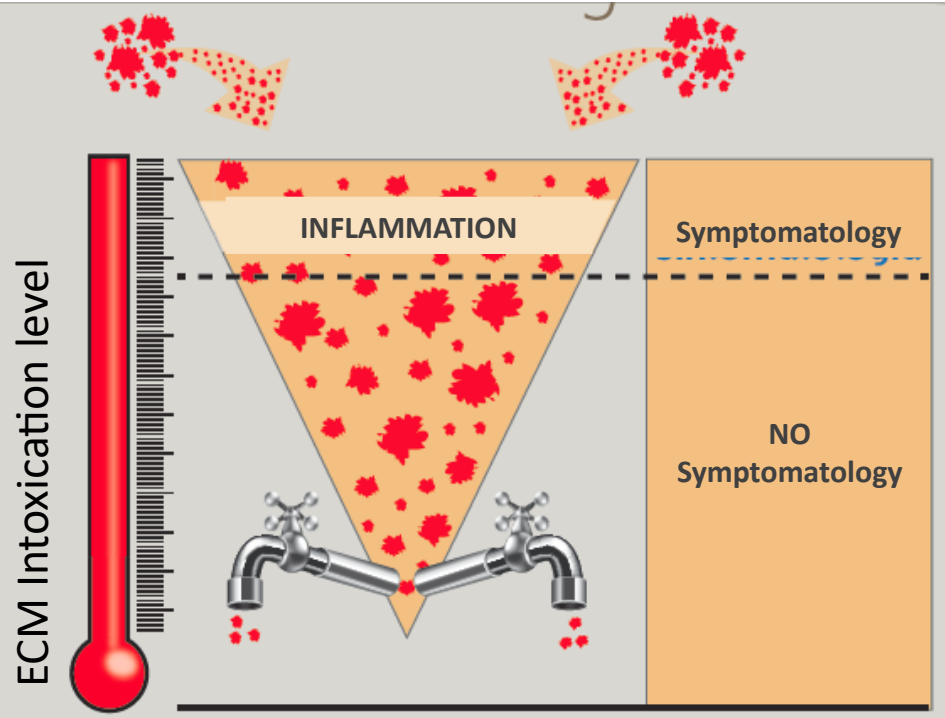
ACUTE INFLAMMATION (IL-1)

TOXIC CONDITIONS

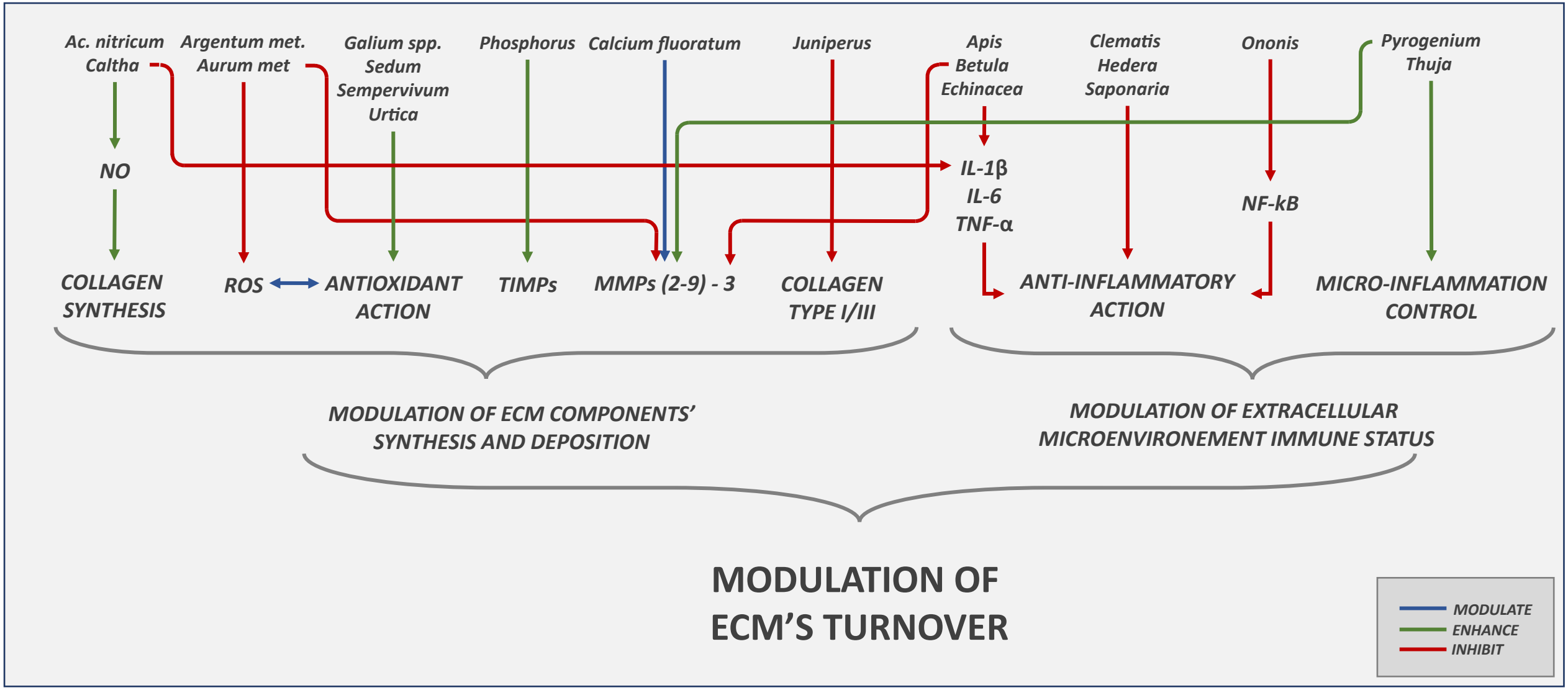
- UP-REGULATION OF PRO-INFLAMMATORY CYTOKINES
- OVEREXPRESSION OF ROS
- REDUCTION OF pH

ECM and pathological inflammation





Galium-Heel


Ac. nitricum
Caltha
Argentum met.
Aurum met
Galium spp.
Sedum
Sempervivum
Urtica
Phosphorus
Calcium fluoratum
Juniperus
Apis
Betula
Echinacea
Clematis
Hedera
Saponaria
Ononis
Pyrogenium
Thuja
NO
IL-1β
IL-6
TNF-α
NF-kB
COLLAGEN SYNTHESIS
ROS
ANTIOXIDANT ACTION
TIMPs
MMPs (2-9) - 3
COLLAGEN TYPE I/III
ANTI-INFLAMMATORY ACTION
MICRO-INFLAMMATION CONTROL
MODULATION OF ECM COMPONENTS' SYNTHESIS AND DEPOSITION
MODULATION OF EXTRACELLULAR MICROENVIRONEMENT IMMUNE STATUS
MODULATION OF ECM'S TURNOVER
MODULATE
ENHANCE
INHIBIT

VAGUE AND INDEFINITIVE SYMPTOMS

- Overweight and obesity
- Skin Rashes
- Itchy skin
- Anxiety and depression
- Sleepness
- Insomnia
- Headche
- Lack of focusing
- Irritability
- Low libido
- Fybromialgia
- IBS
- CFS
- MCS
- …

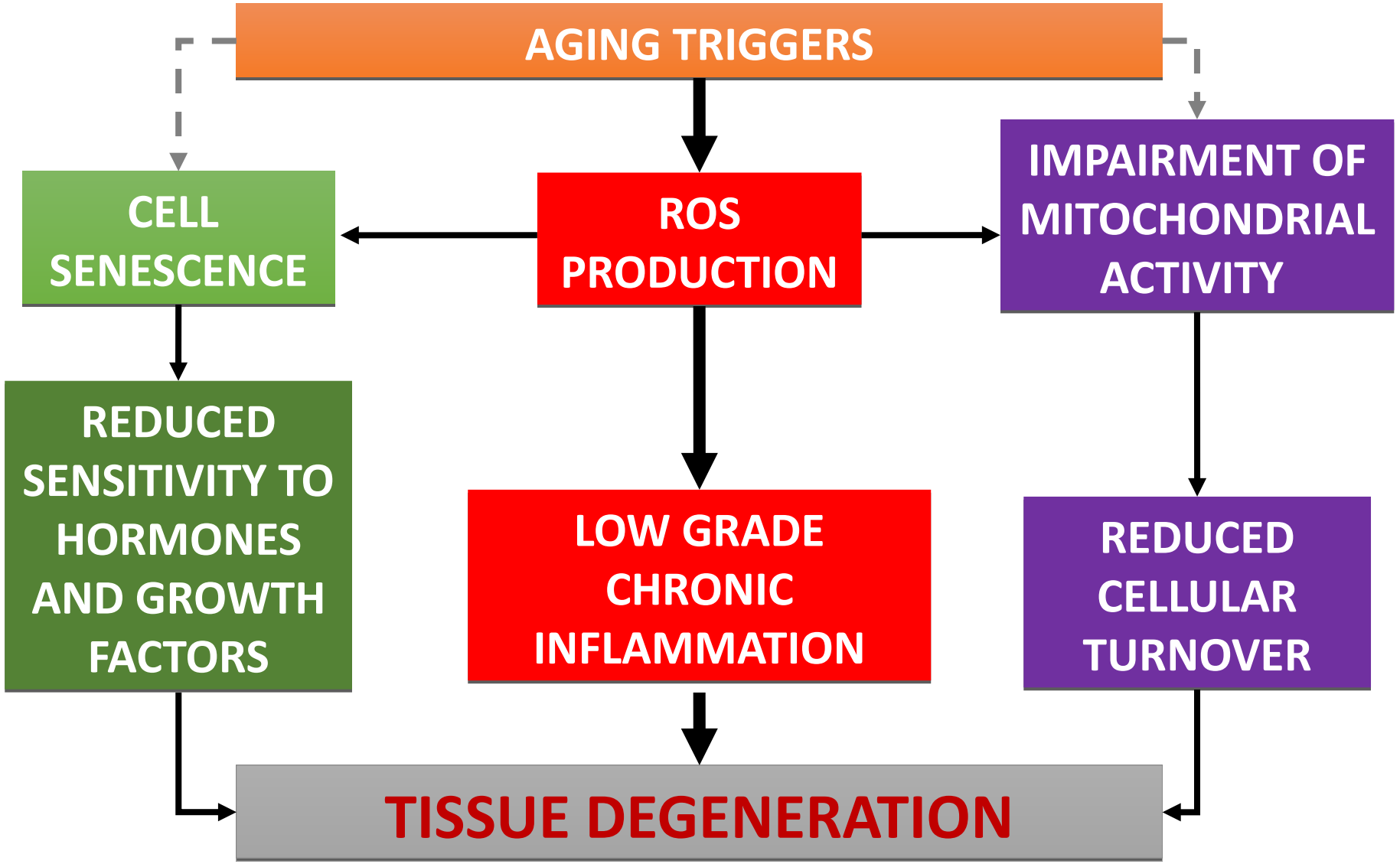
intoxicated

inflammed

aged

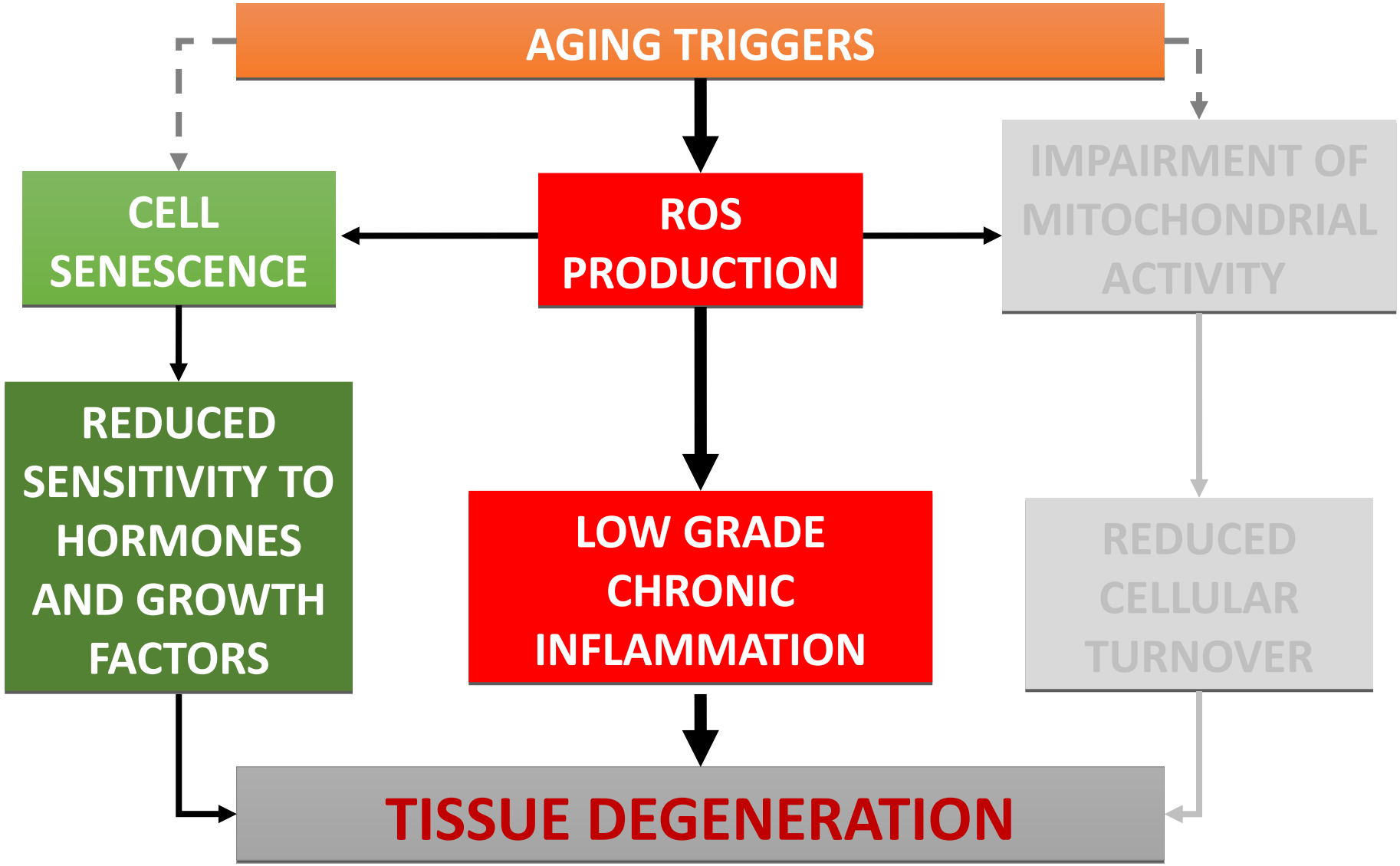
AGING - key factors -

- HIGH LEVEL OF INFLAMMATION
- HIGH LEVEL OF OXIDATION
- HIGH LEVEL OF INTOXICATION



AGING - key factors -

- HIGH LEVEL OF INFLAMMATION
- HIGH LEVEL OF OXIDATION
- HIGH LEVEL OF INTOXICATION



A premise for the clinical use of low dose cytokines

DISEASES ARE EXPRESSIONS,

CONSEQUENCES OF CHANGED

CONCENTRATION OF

SIGNALING MOLECULES.

In healthy conditions

GOOD

IMMUNOSTIMULATING CYTOKINES
Physiological concentration

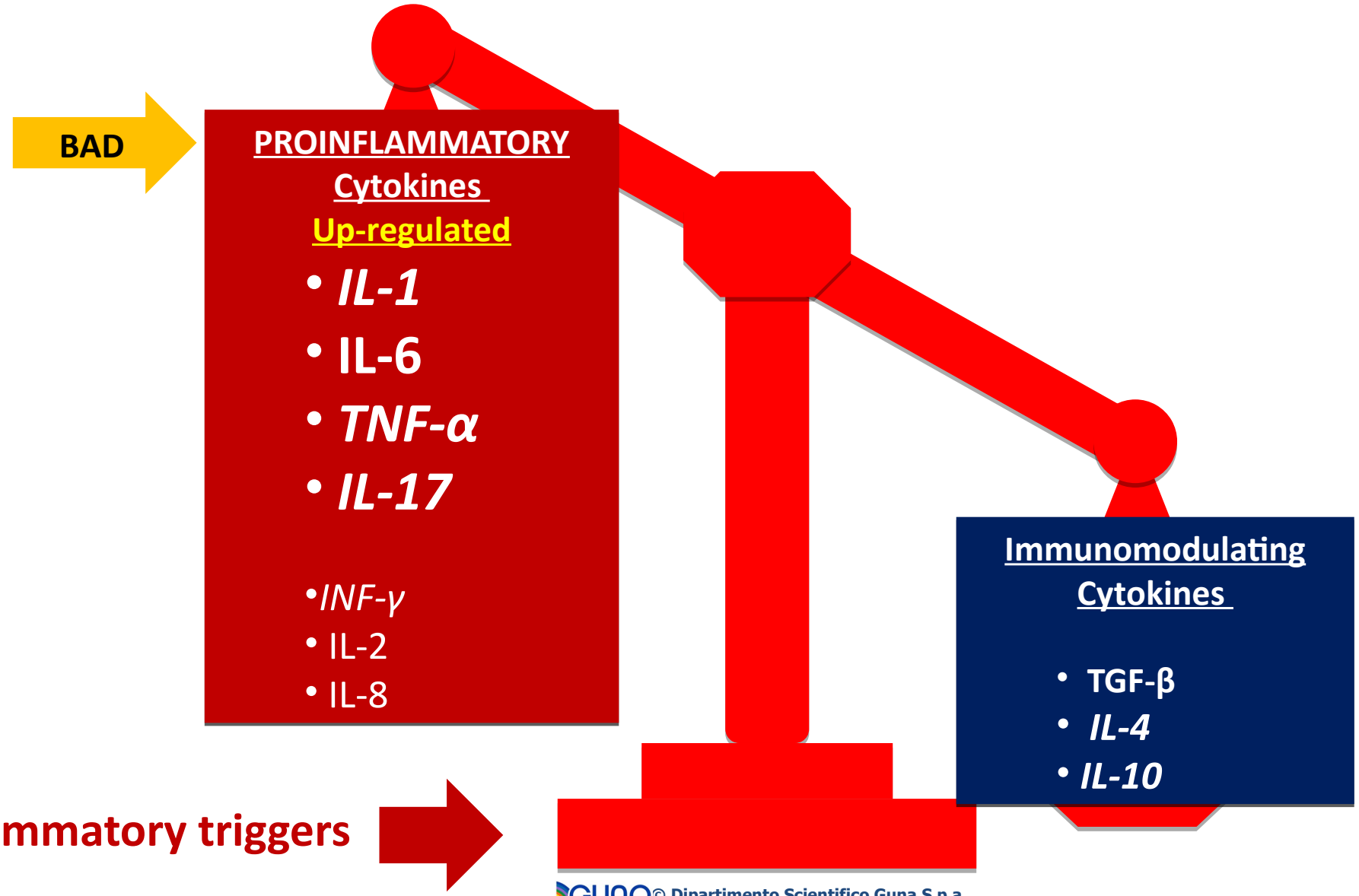
- IL-1
- IL-6
- TNF-α
- IL-17
- INF-γ
- IL-2
- IL-8

IMMUNOMODULATING CYTOKINES
Physiological concentration

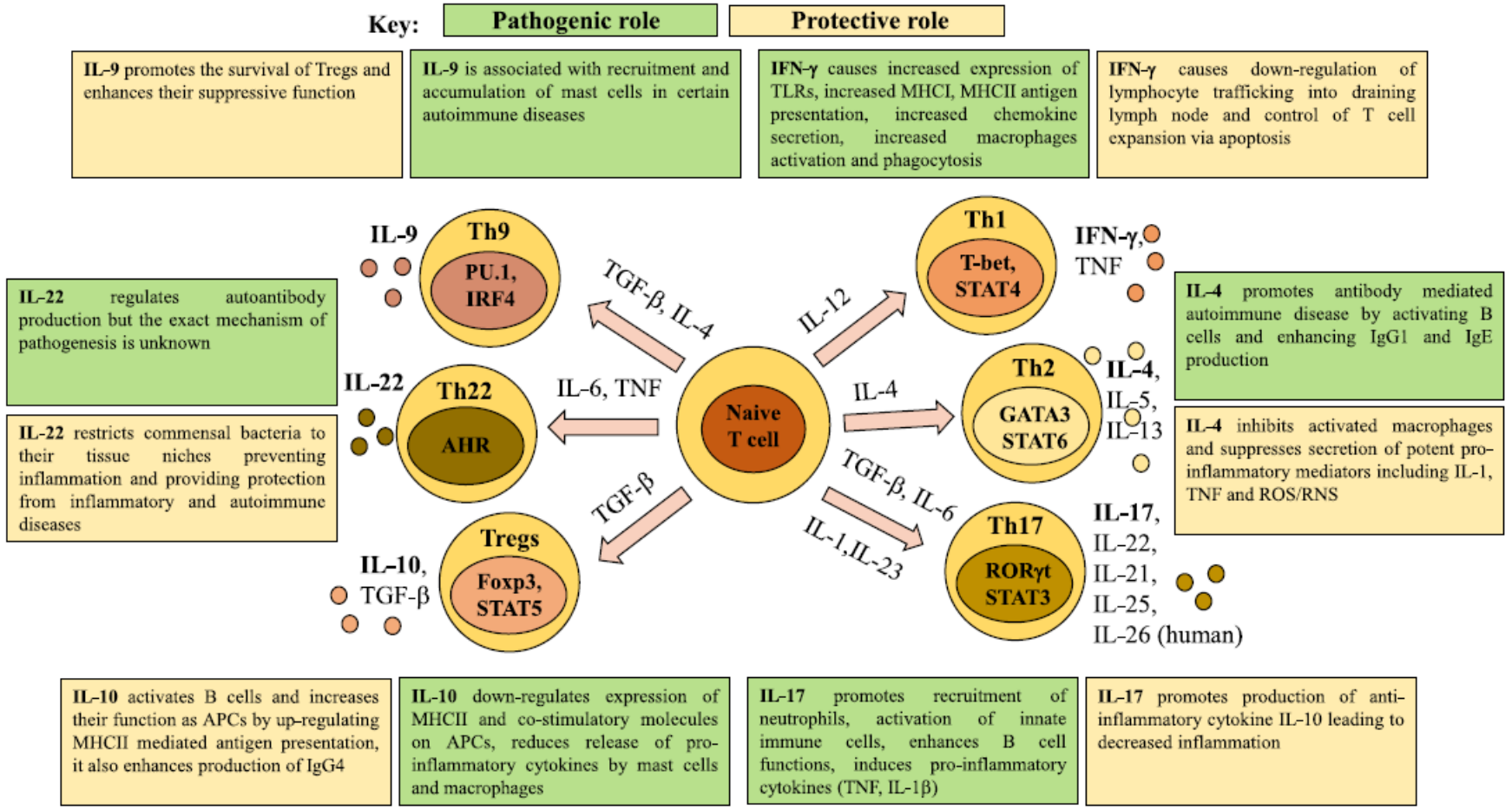
- TGF-β
- IL-4
- IL-10

GOOD

...in inflammation

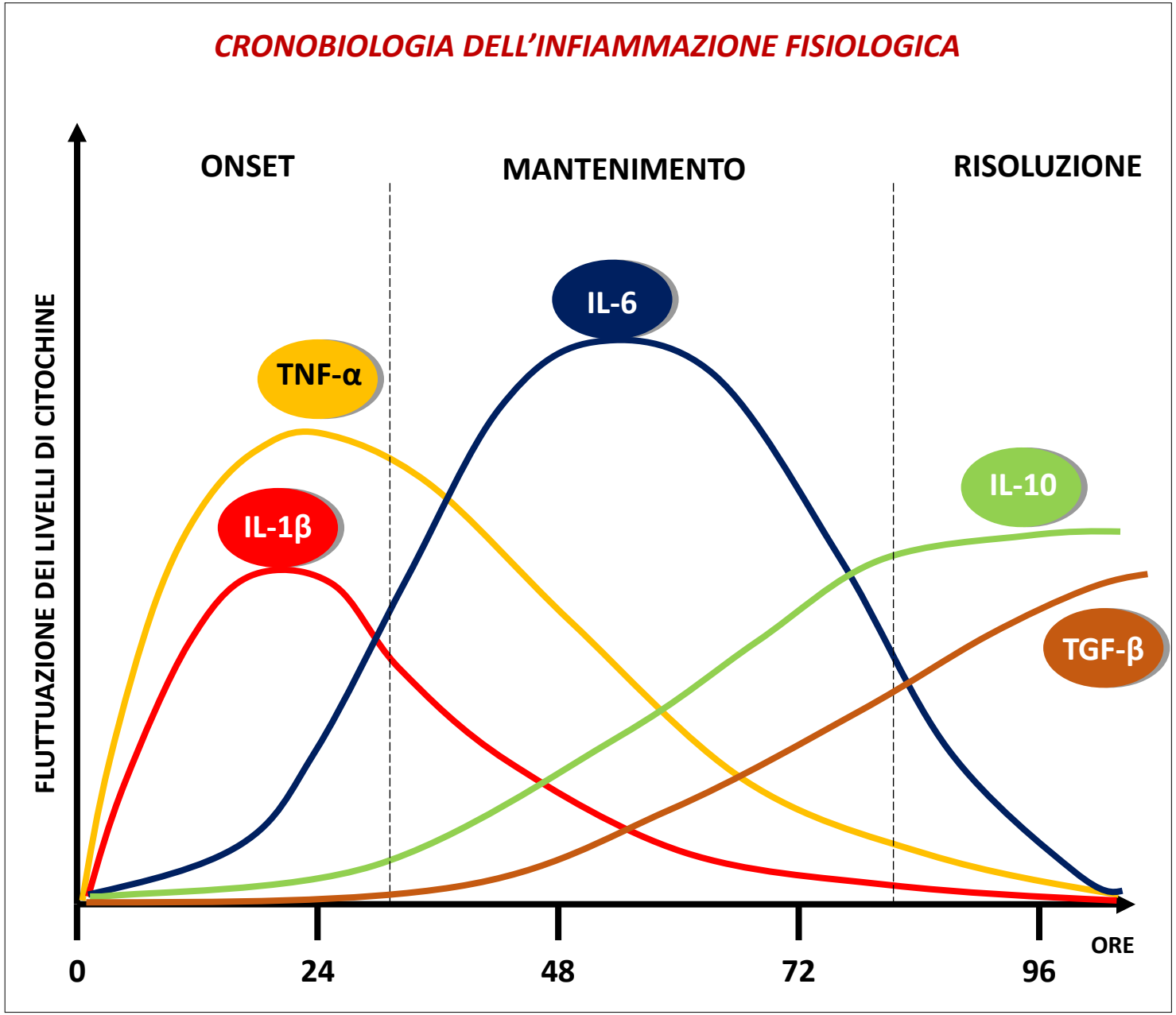


Neither good nor bad in Nature



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

CRONOBIOLOGIA DELL'INFIAMMAZIONE FISIOLOGICA

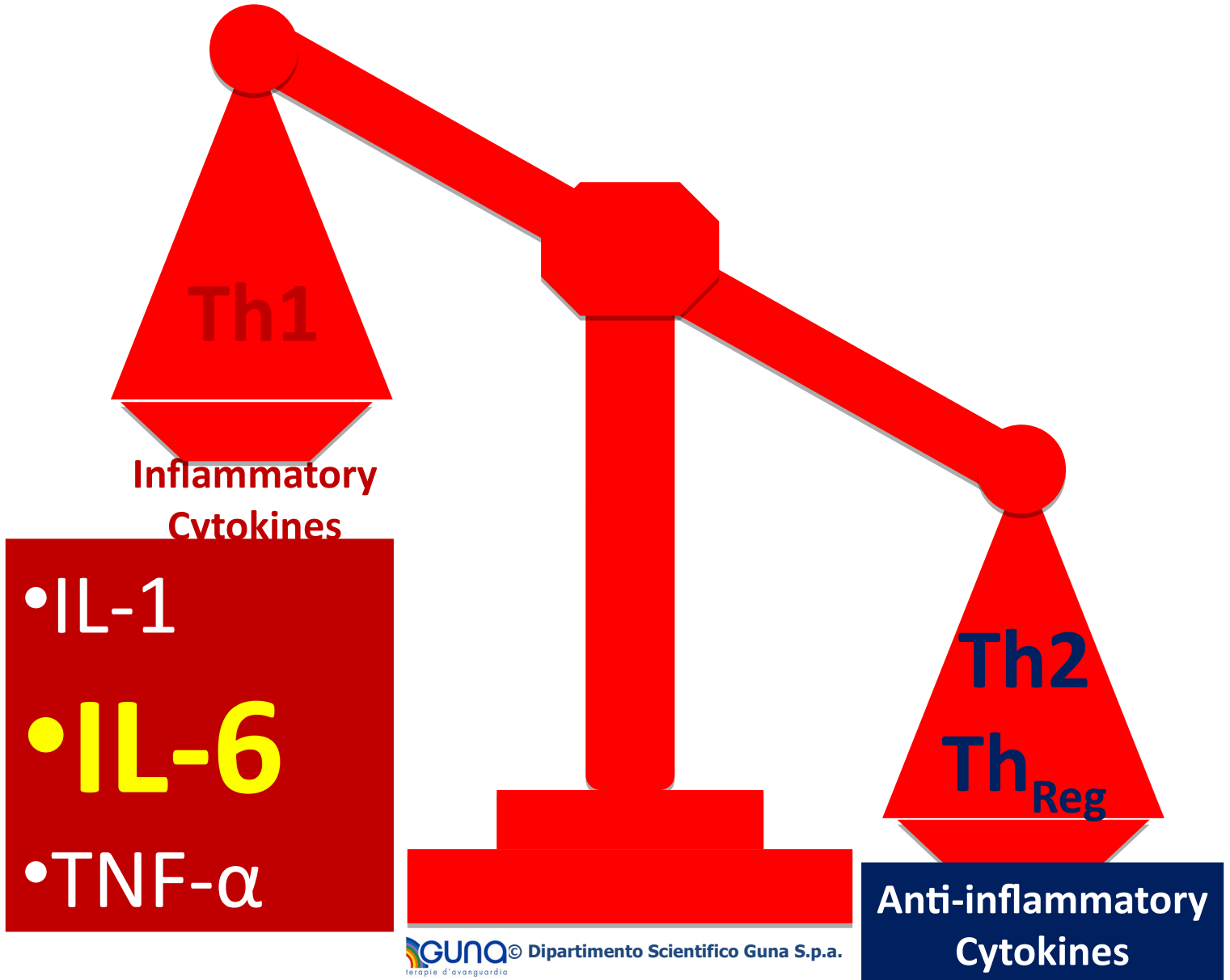


Petersen AM[1], Pedersen BK. The anti-Inflammatory effect of exercise. J Appl Physiol (1985). 2005 Apr;98(4):1154-62

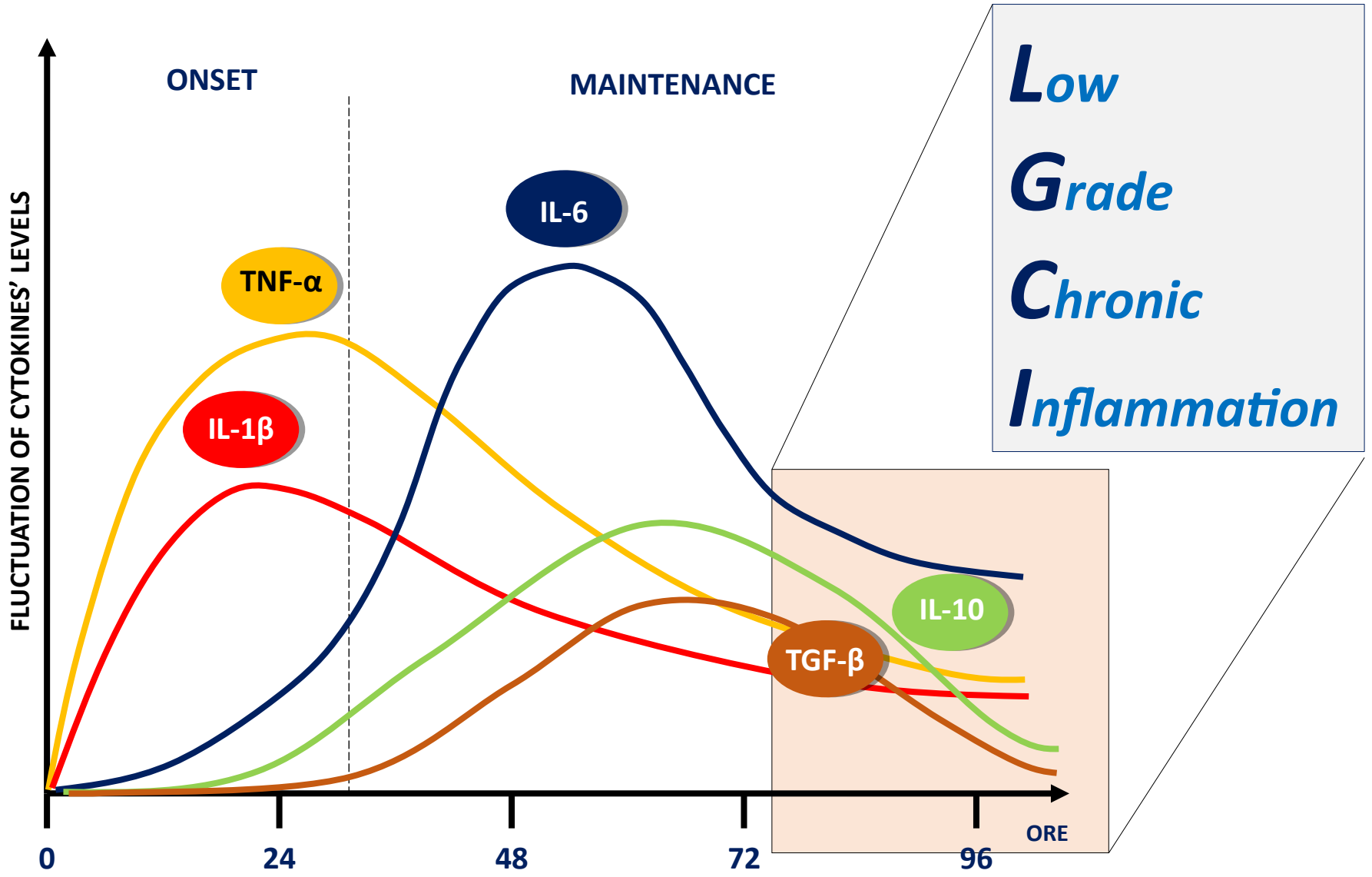
Modificata a fini didattici.

Chronic Inflammation

…in (LOW GRADE) CHRONIC inflammatory diseases



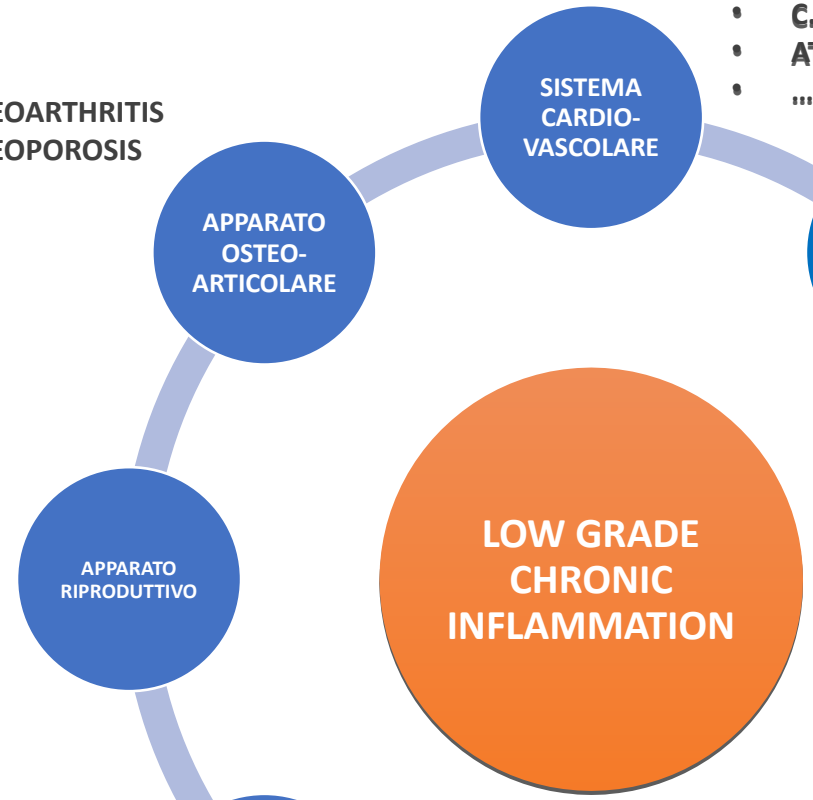
LOW GRADE CHRONIC (SYSTEMIC) INFLAMMATION



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

Modificata a fini didattici.

LOW-GRADE CHRONIC INFLAMMATION: THE MOTHER OF ALL DISEASES



- C.A.D.
- C.V.D.
- ATEROSCLEROSIS
- …

- IBDs/IBS
- GLUTEN SENSITIVITY
- CELIAC DISEASE
- …

- DEPRESSION
- ALZHEIMER'S
- AUTISM
- NEURODEGENERATIVE DISEASES
- …

- CANCER
- AUTOIMMUNE DISEASES
- C.F.S.
- …

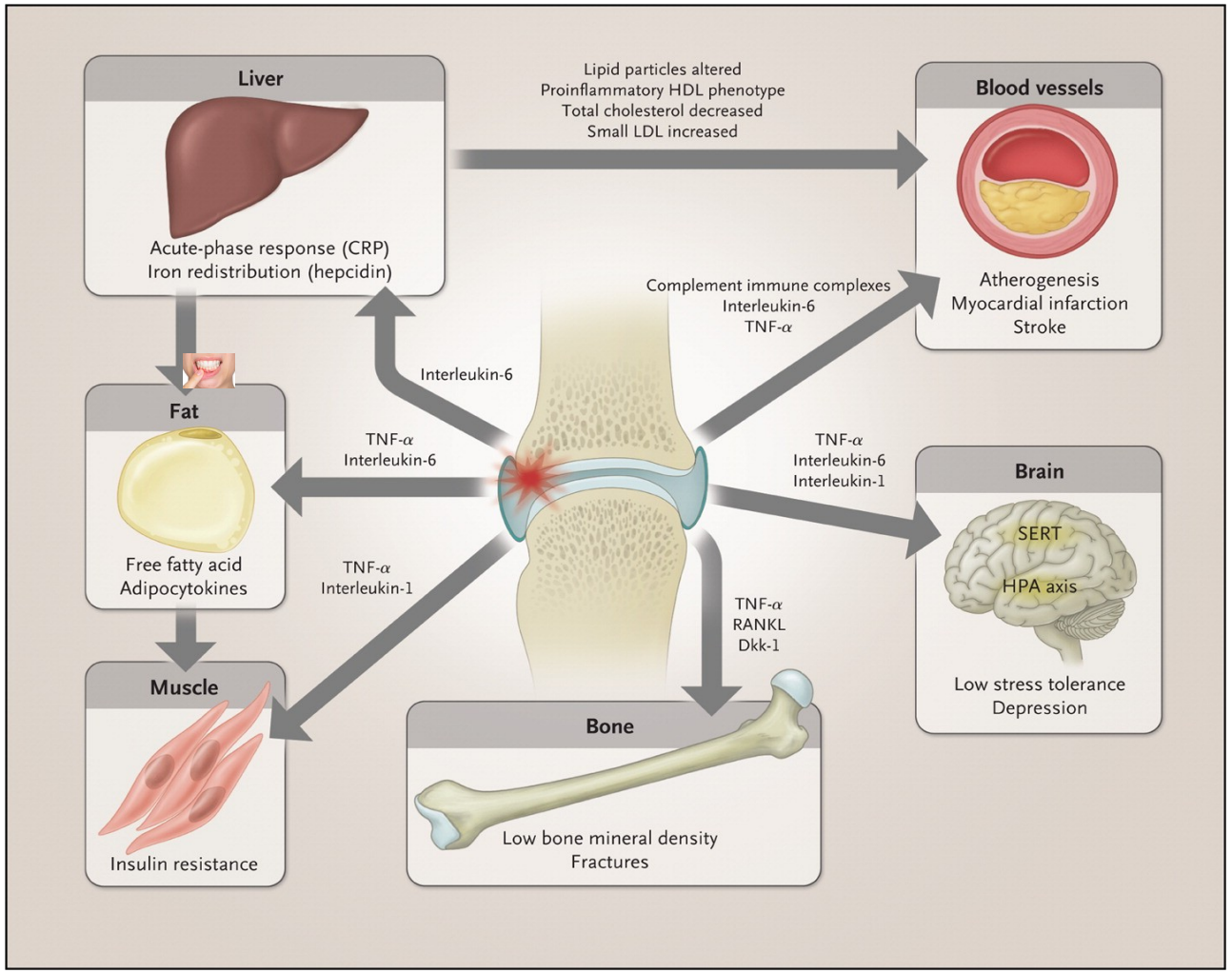
- OBESITY
- TYPE II DIABETES
- METABOLIC SYNDROME
- …

- UV RAYS DAMAGES
- SKIN AGING
- …

- IMPOTENCY
- PCOs
- …

- OSTEOARTHRITIS
- OSTEOPOROSIS
- …

Mechanisms that contribute to the onset of long term complications in patients suffering from Rheumatoid Arthritis.



McInnes IB, Schett G. N Engl J Med 2011;365:2205-2219.

Immagine modificata a fini didattici

IL-2/IL-6 RATIO AND AGING

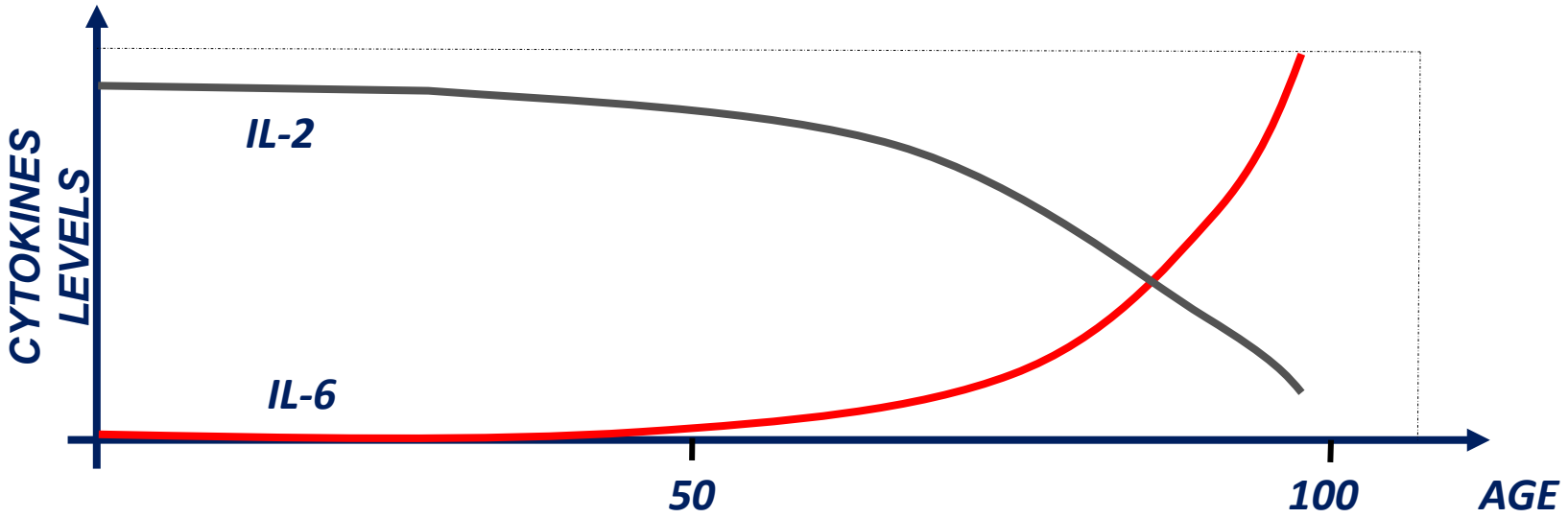
ELSEVIER

Mechanisms of Ageing and Development
100 (1998) 313–328

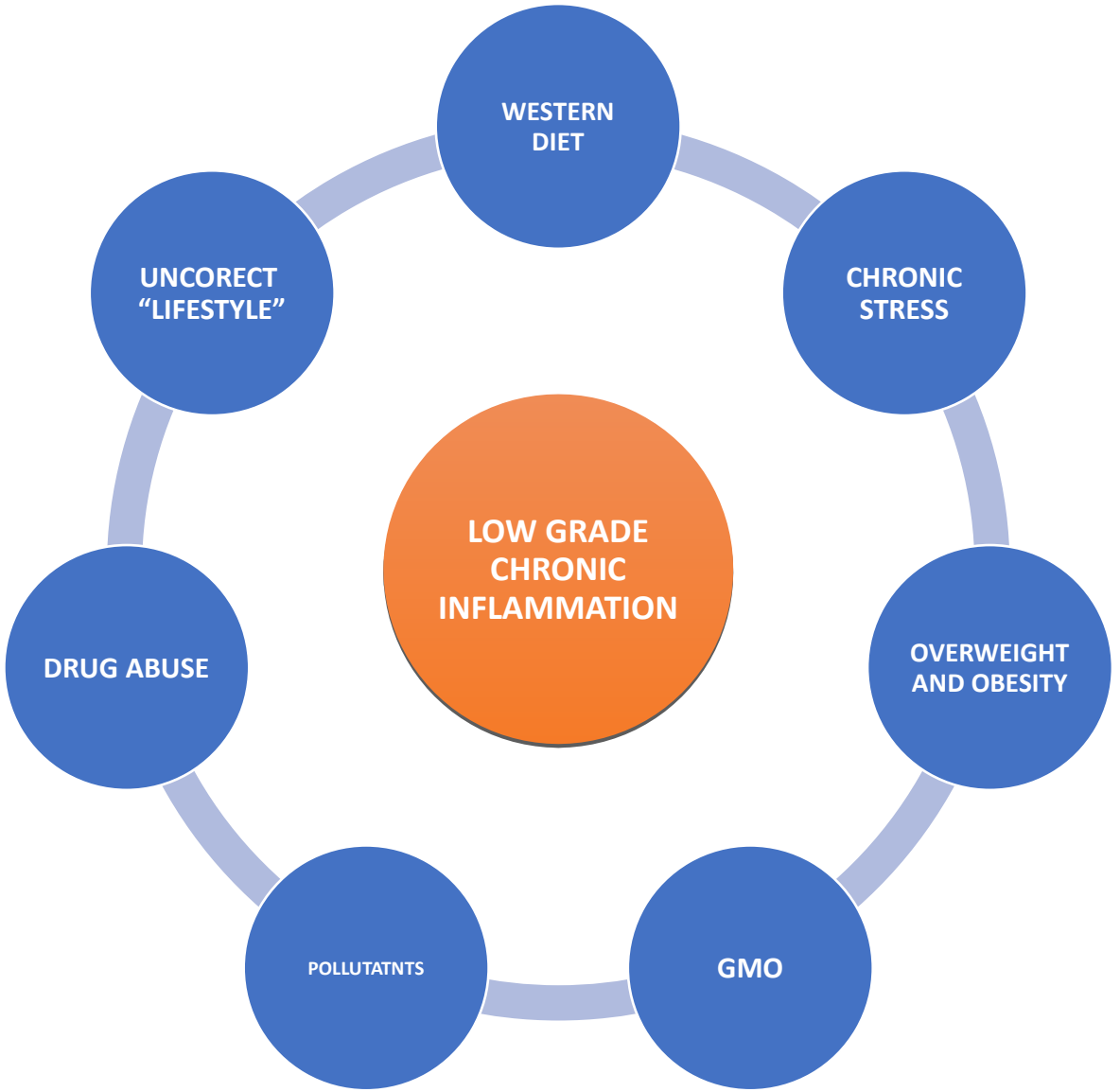
mechanisms of ageing and development

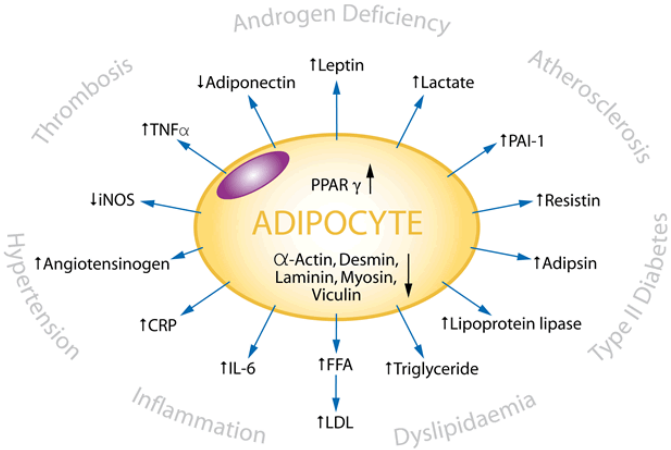
Increase of interleukin 6 and decrease of interleukin 2 production during the ageing process are influenced by the health status

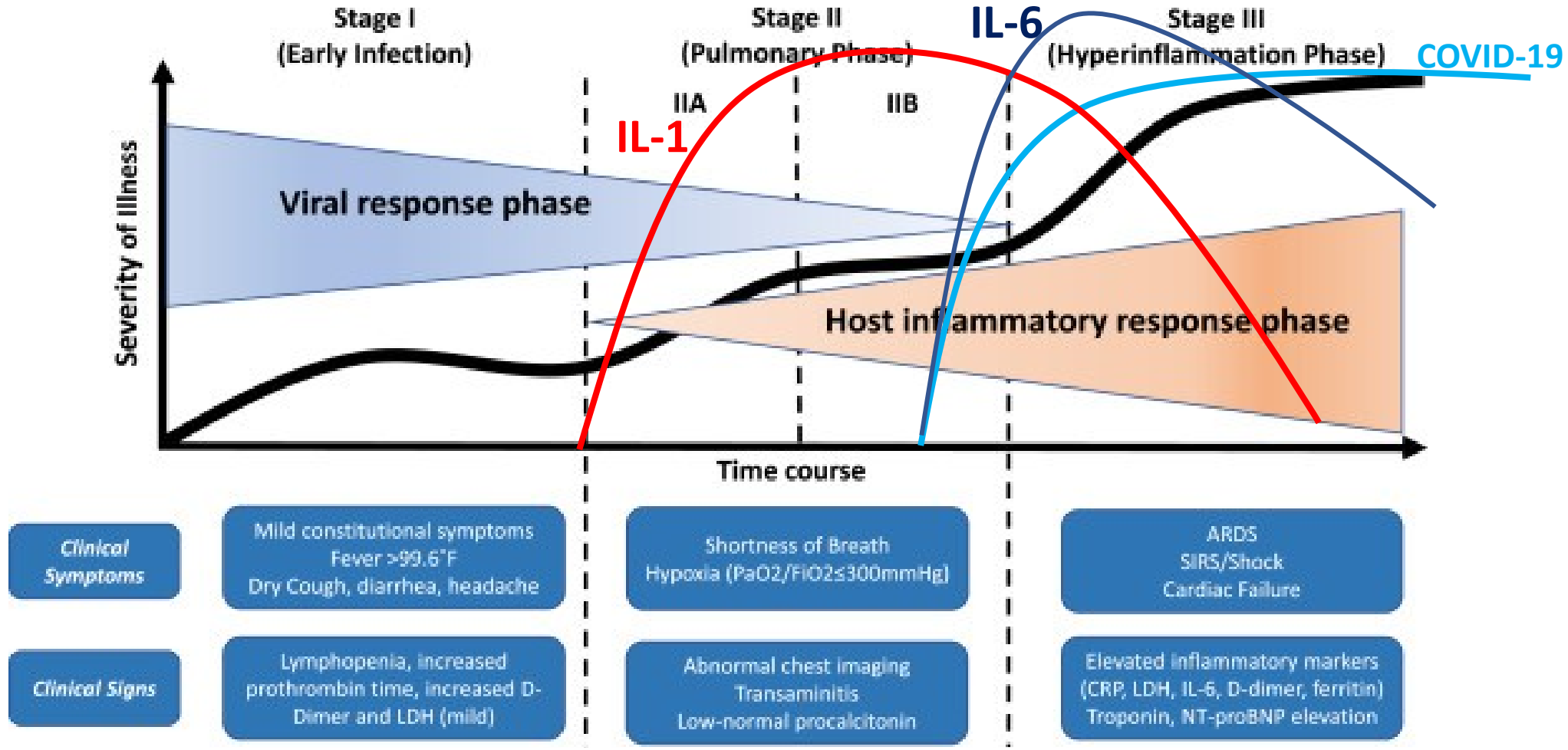
Jolanta Myśliwska [a,*], Ewa Bryl [a], Jerzy Foerster [b], Andrzej Myśliwski [a]

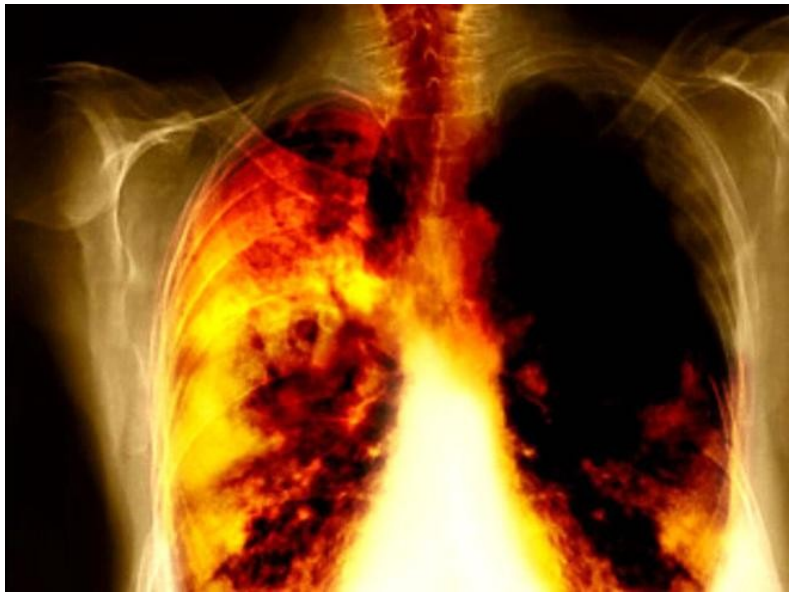


LOW-GRADE CHRONIC INFLAMMATION TRIGGERS









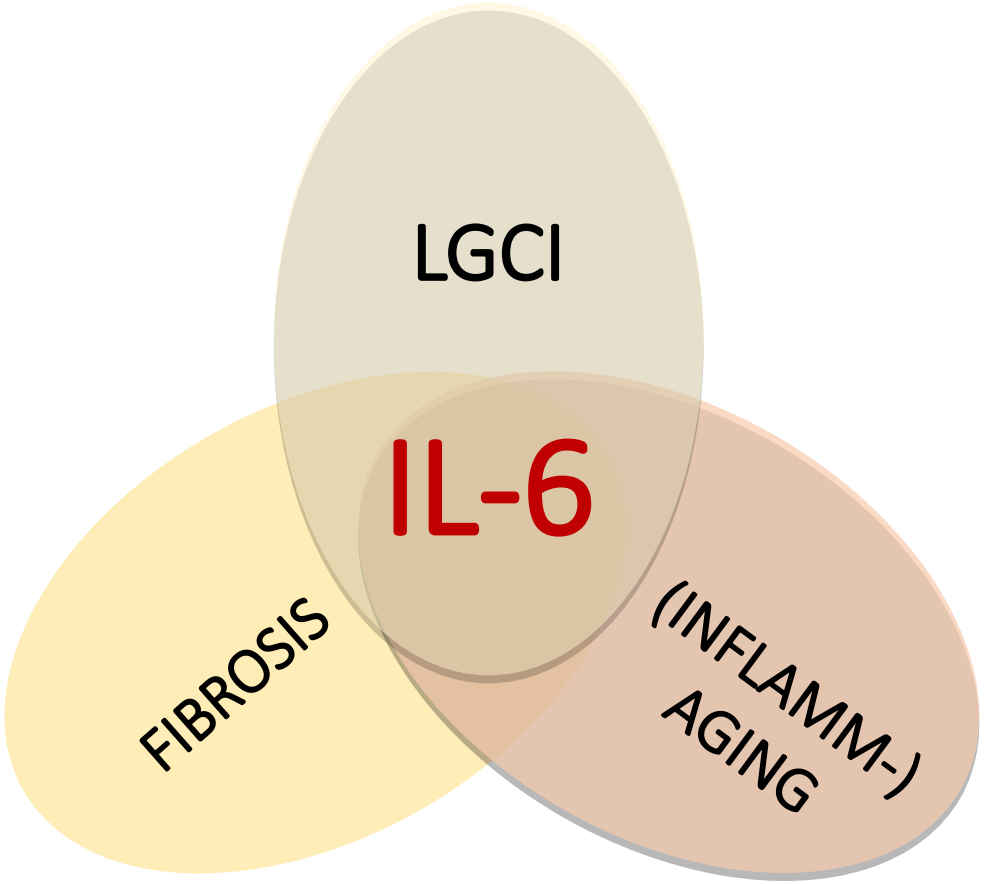
INTERLEUKIN-6

LGCI

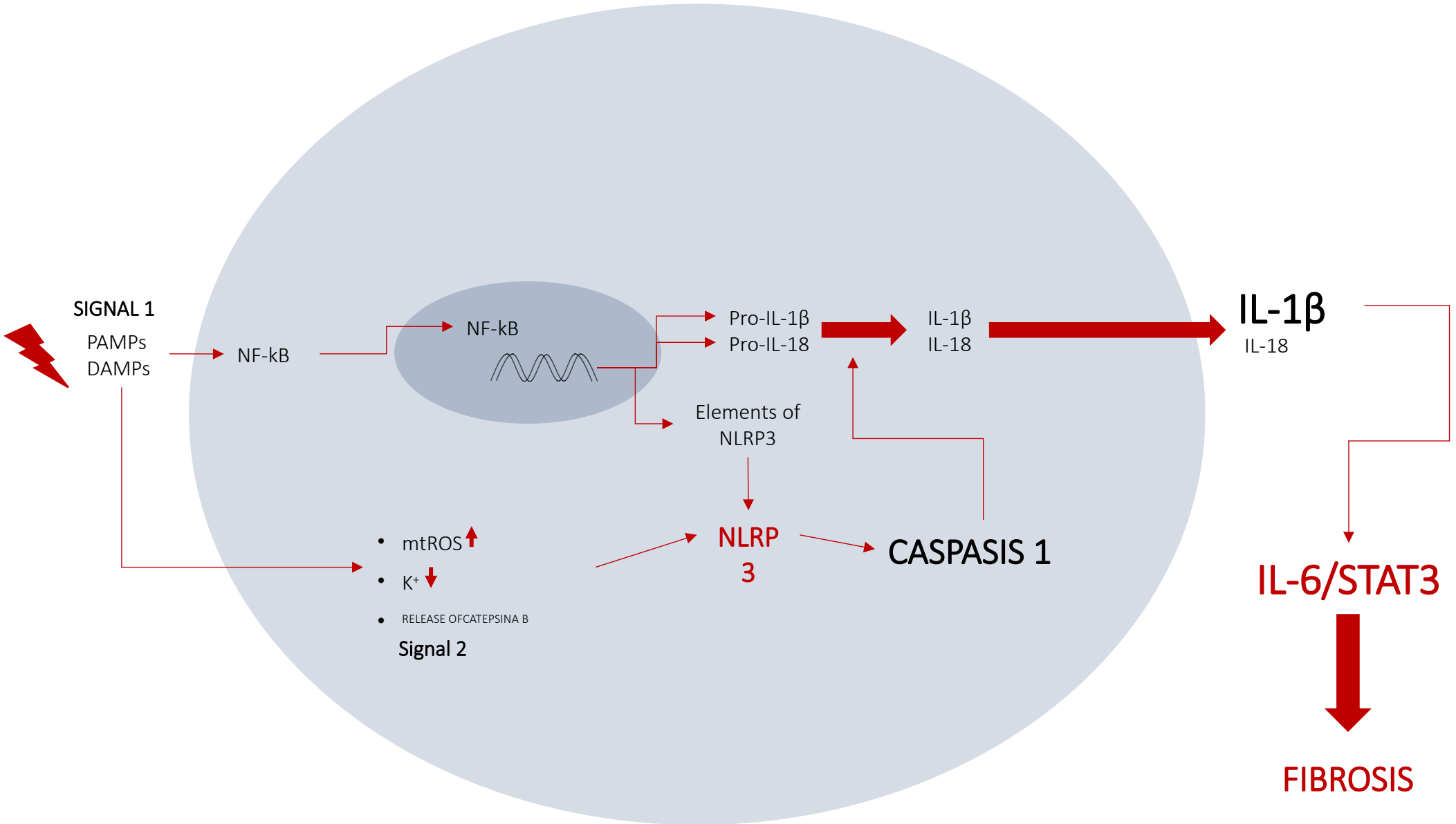
AND

FIBROSIS

The main marker of chronic inflammation, aging, and fibrotic phenomena



INFLAMMASOME (NLRP3), IL-6 and Fibrosis



signal transducer of activation

guna.it

Cell PRESS

Immunity

Article

Interleukin-6 Signaling Drives Fibrosis in Unresolved Inflammation

Ceri A. Fielding,[1,6] Gareth W. Jones,[1,6] Rachel M. McLoughlin,[1,8] Louise McLeod,[2] Victoria J. Hammond,[1] Javier Uceda,[1] Anwen S. Williams,[1] Mark Lambie,[3] Thomas L. Foster,[1] Chia-Te Liao,[1] Christopher M. Rice,[1] Claire J. Greenhill,[1] Chantal S. Colmont,[1] Emily Hams,[1,9] Barbara Coles,[1] Ann Kift-Morgan,[1] Zarabeth Newton,[1] Katherine J. Craig,[4] John D. Williams,[4] Geraint T. Williams,[5] Simon J. Davies,[3] Ian R. Humphreys,[1] Valerie B. O'Donnell,[1] Philip R. Taylor,[1] Brendan J. Jenkins,[2] Nicholas Topley,[1,7,*] and Simon A. Jones[1,7,*]


frontiers in Molecular Biosciences

Deep Sequencing Transcriptome Analysis of Murine Wound Healing: Effects of a Multicomponent, Multitarget Natural Product Therapy-Tr14

nature COMMUNICATIONS

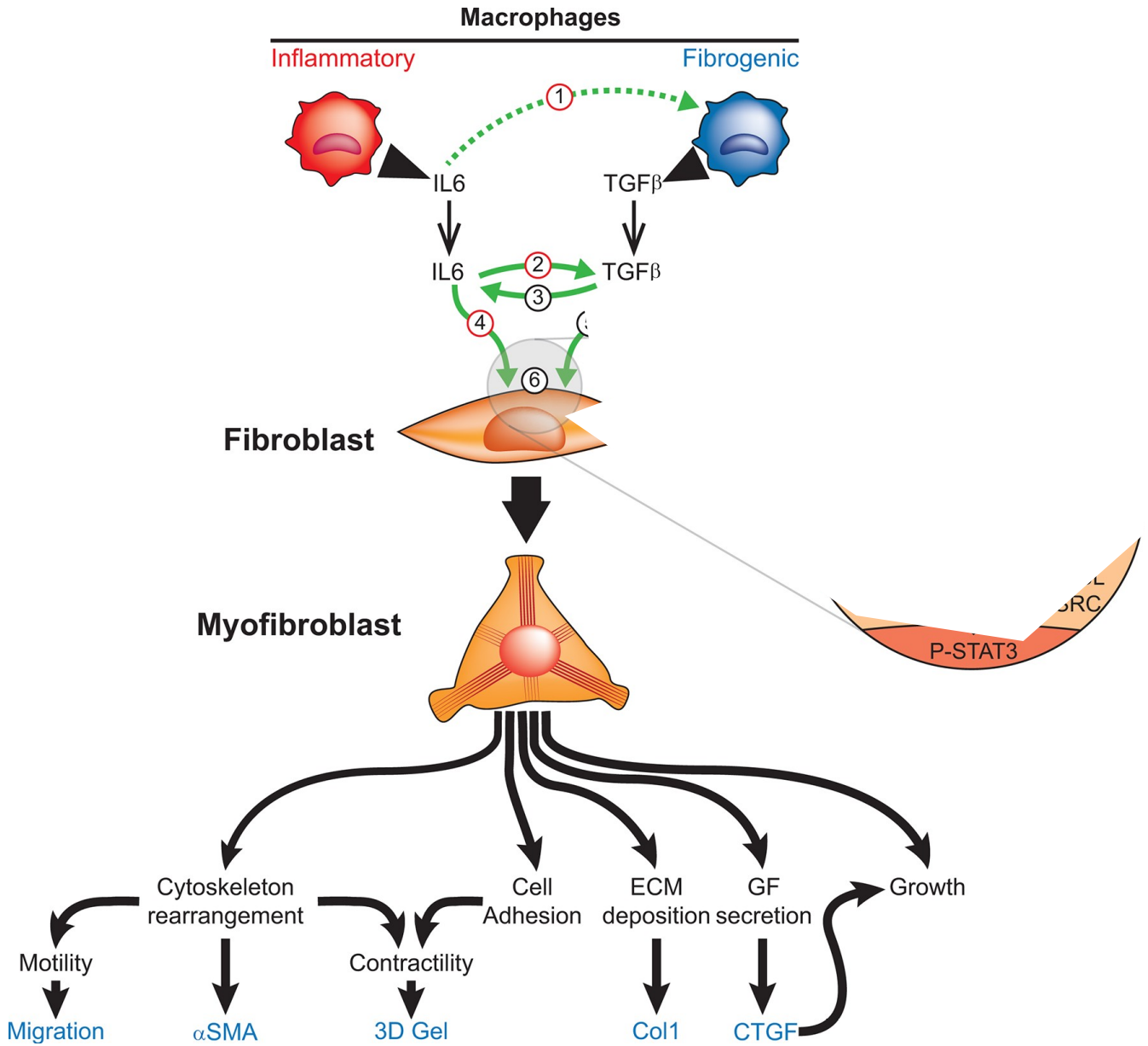
ARTICLE

DOI: 10.1038/s41467-017-01236-6 OPEN

Activation of STAT3 integrates common profibrotic pathways to promote fibroblast activation and tissue fibrosis

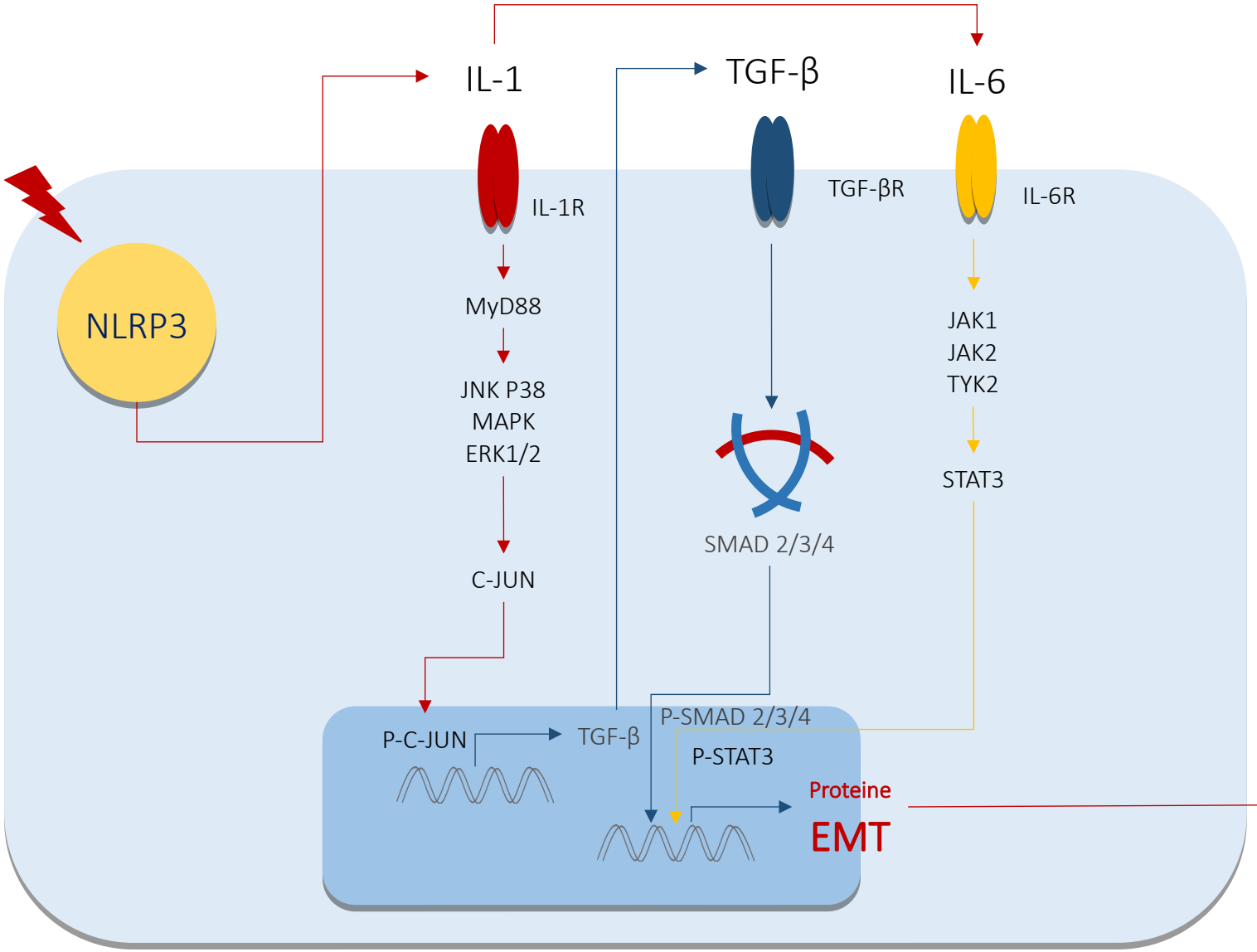
Debomita Chakraborty[1], Barbora Šumová[1,2], Tatjana Mallano[1], Chih-Wei Chen[1], Alfiya Distler[1], Christina Bergmann[1], Ingo Ludolph[3], Raymund E. Horch[3], Kolja Gelse[4], Andreas Ramming[1], Oliver Distler[5], Georg Schett[1], Ladislav Šenolt[2] & Jörg H.W. Distler[1]

IL-6 compromises tissue repair shifting the inflammation process from acute to chronic, and triggering the pro-fibrotic process



Col1, collagen alpha 1
CTGF, connective tissue growth factor
ECM, extracellular matrix
GF, growth factor;
IL-6, interleukin-6
JAK, Janus-activated kinase
JNK, Jun N-terminal kinase
P-STAT, phosphorylated STAT
STAT, signal transducer and activator of Transcription
TGFβ, transforming growth factor beta
TGFβR, transforming growth factor beta receptor
TYK, tyrosine kinase.

*IL FULCRO DEL FENOMENO FIBROTICO È IL **MECCANISMO DI TRANSIZIONE EPITELIALE-MESENCHIMALE (EMT)***



Alyaseer AAA, de Lima MHS, Braga TT. The Role of NLRP3 Inflammasome Activation in the Epithelial to Mesenchymal Transition Process During the Fibrosis. Front Immunol. 2020 May 20;11:883.

Review
Inflammation and EMT: organ fibrosis and cancer

EMBO Molecular Medicine

Inflammation and EMT: an alliance towards organ fibrosis and cancer progression

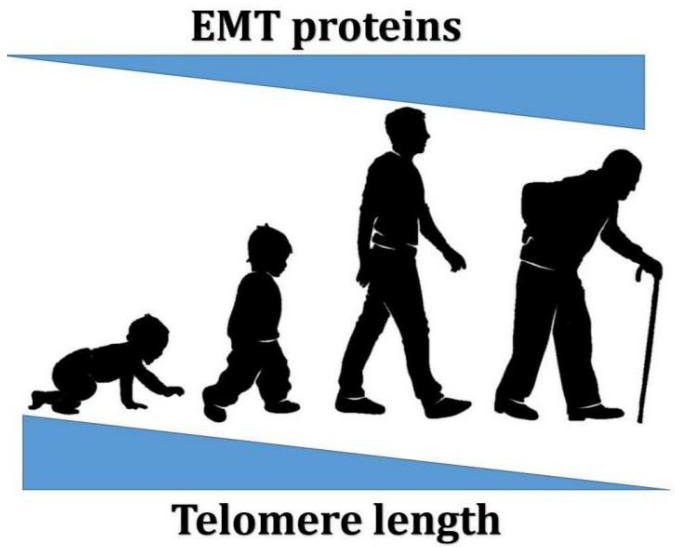
Jose Miguel López-Novoa[1] *& M. Angela Nieto*[2]*

Nephrol Dial Transplant (2012): Editorial Reviews 21

Nephrol Dial Transplant (2012) 27: 21–27
doi: 10.1093/ndt/gfr567
Advance Access publication 18 November 2011

Fibrosis, regeneration and cancer: what is the link?

Valeria Cernaro, Antonio Lacquaniti, Valentina Donato, Maria Rosaria Fazio, Antoine Buemi and Michele Buemi



International Journal of
Molecular Sciences

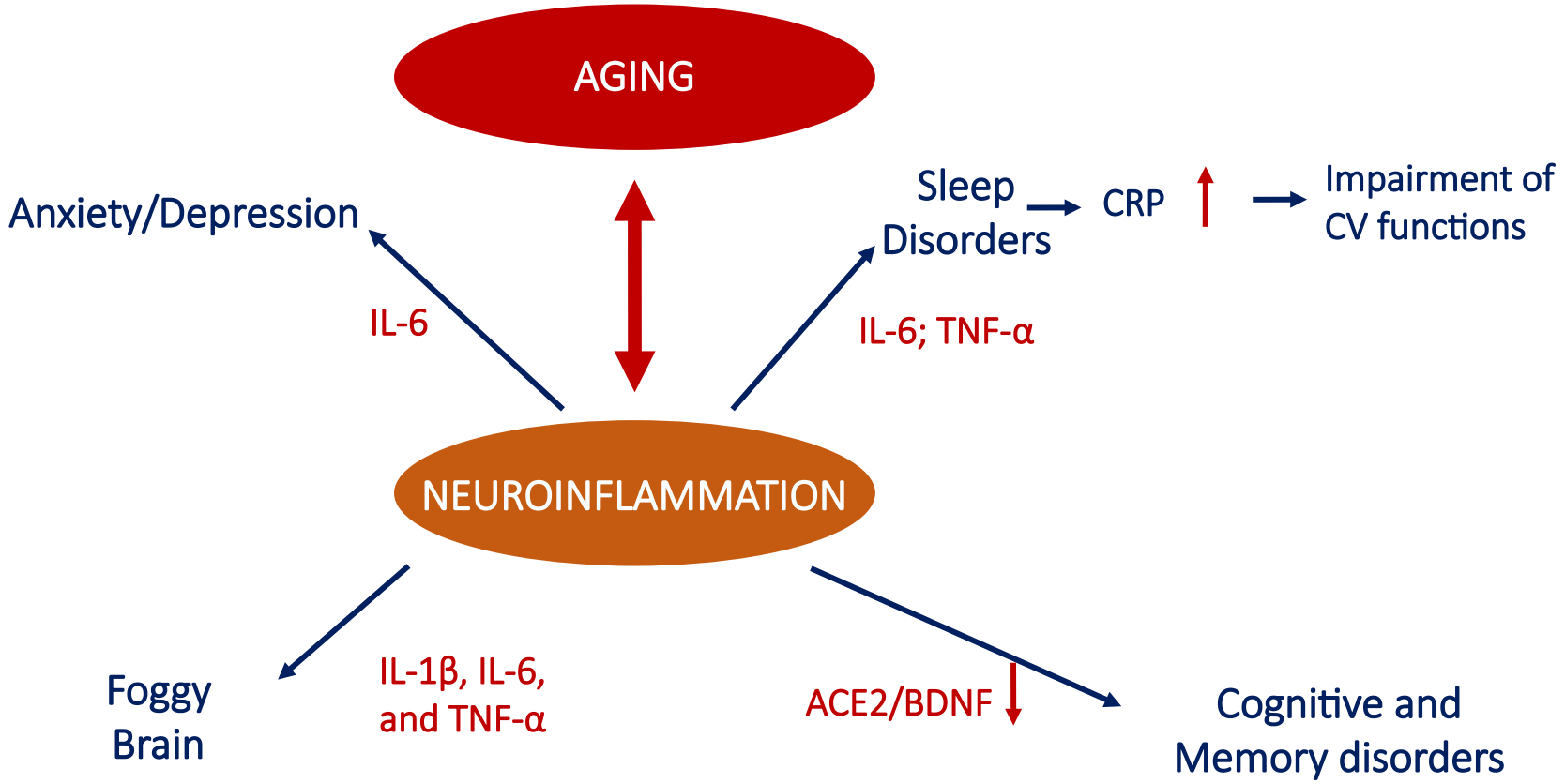
MDPI

Review

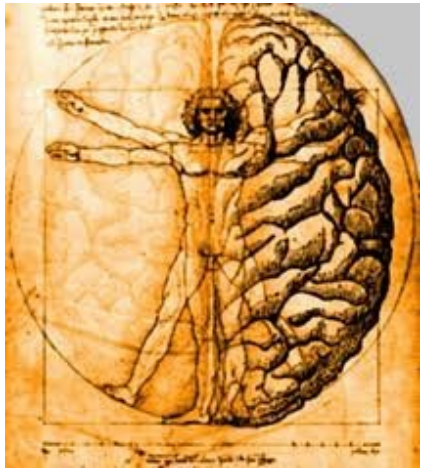
Is There an Interconnection between Epithelial–Mesenchymal Transition (EMT) and Telomere Shortening in Aging?

Siti A. M. Imran [1], Muhammad Dain Yazid [1], Ruszymah Bt Hj Idrus [1,2], Manira Maarof [1], Abid Nordin [1,2], Rabiatul Adawiyah Razali [1,2] and Yogeswaran Lokanathan [1,*]

Neuroinflammatory-related disorders associated with aging



- *Ng A, Tam WW, Zhang MW, Ho CS, Husain SF, McIntyre RS, Ho RC. IL-1β, IL-6, TNF- α and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. Sci Rep. 2018 Aug 13;8(1):12050.*
- *Michal M, Wiltink J, Kirschner Y, Schneider A, Wild PS, Münzel T, Blettner M, Schulz A, Lackner K, Pfeiffer N, Blankenberg S, Tschan R, Tuin I, Beutel ME. Complaints of sleep disturbances are associated with cardiovascular disease: results from the Gutenberg Health Study. PLoS One. 2014 Aug 5;9(8):e104324.*



STRESS – INTERLEUKIN-6 AND NEURO (-DEGENERATIVE) DISEASES

The psycho-endocrine-neuro connection…

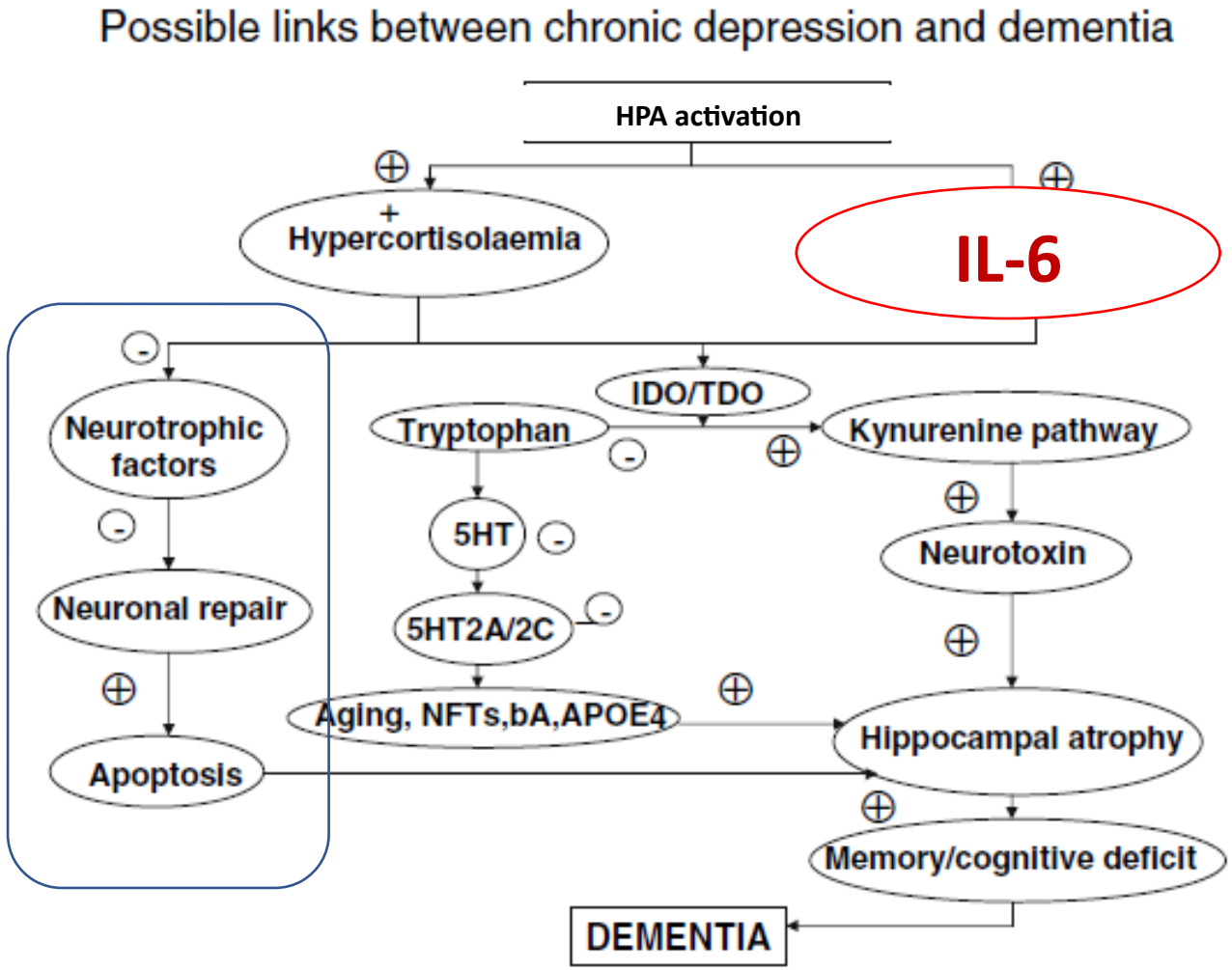


Fig. 1 Possible links between chronic depression and dementia.NFT's = neurofibrillary tangles, bA = beta amyloid, APOE 4 = apolipoprotein E4 (+) = increase; (–) = decrease

Leonard BE. Inflammation, Depression and Dementia: Are they Connected? Neurochem Res 2007

Possible links between chronic depression and dementia

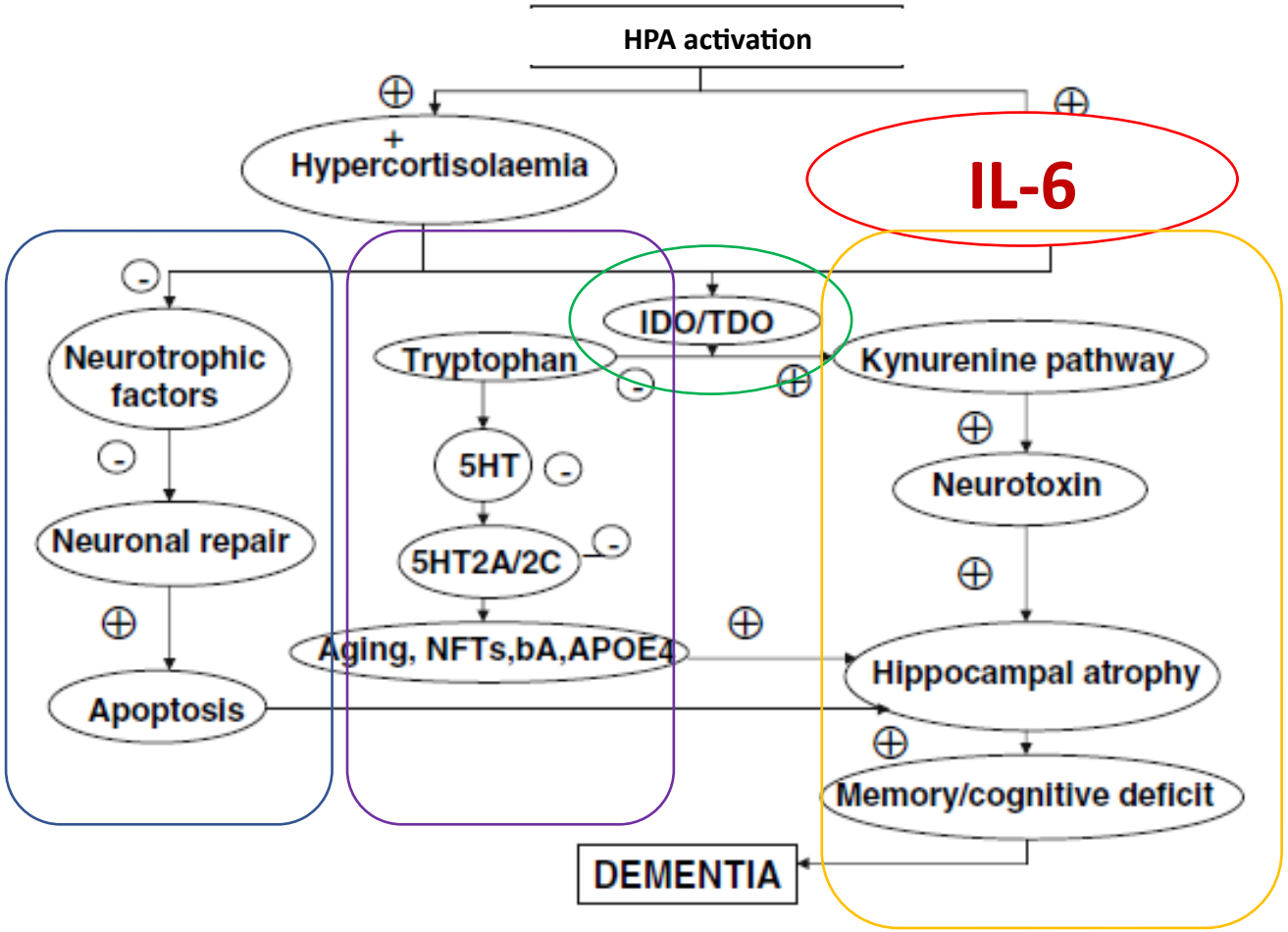


Fig. 1 Possible links between chronic depression and dementia.NFT's = neurofibrillary tangles, bA = beta amyloid, APOE 4 = apolipoprotein E4 (+) = increase; (–) = decrease

Leonard BE. Inflammation, Depression and Dementia: Are they Connected? Neurochem Res 2007

Tryptophan dioxygenase (*TDO*) and indoleamine 2,3-dioxygenase (*IDO*)

frontiers in Neuroscience

REVIEW
published: 24 July 2018
doi: 10.3389/fnins.2018.00499

Brain Kynurenine and BH4 Pathways: Relevance to the Pathophysiology and Treatment of Inflammation-Driven Depressive Symptoms

*Sylvie Vancassel[1,2], Lucile Capuron[1,2] and Nathalie Castanon[1,2]**

[1] UMR 1286, Laboratory of Nutrition and Integrative Neurobiology (NutriNeuro), INRA, Bordeaux, France, [2] UMR 1286, Laboratory of Nutrition and Integrative Neurobiology (NutriNeuro), Bordeaux University, Bordeaux, France

tetrahydrobiopterin (BH4

Neurobiology of Stress 4 (2016) 15–22

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Integrating Interleukin-6 into depression diagnosis and treatment

Georgia E. Hodes*, Caroline Ménard, Scott J. Russo

Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

ARTICLE INFO

Article history:
Received 16 December 2015
Received in revised form
24 March 2016
Accepted 25 March 2016
Available online 29 March 2016

ABSTRACT

There is growing evidence of a relationship between inflammation and psychiatric illness. In particular, the cytokine Interleukin-6 (IL-6) has been linked to stress-related disorders such as depression and anxiety. Here we discuss evidence from preclinical and clinical studies examining the role of IL-6 in mood disorders. We focus on the functional role of peripheral and central release of IL-6 on the development of stress susceptibility and depression-associated behavior. By examining the contribution of both peripheral and central IL-6 to manifestations of stress-related symptomatology, we hope to broaden the way the field thinks about diagnosing and treating mood disorders.

IF DISEASES ARE EXPRESSIONS, CONSEQUENCES OF

CHANGED CONCENTRATION OF *MESSENGER MOLECULES…*

PROBLEM

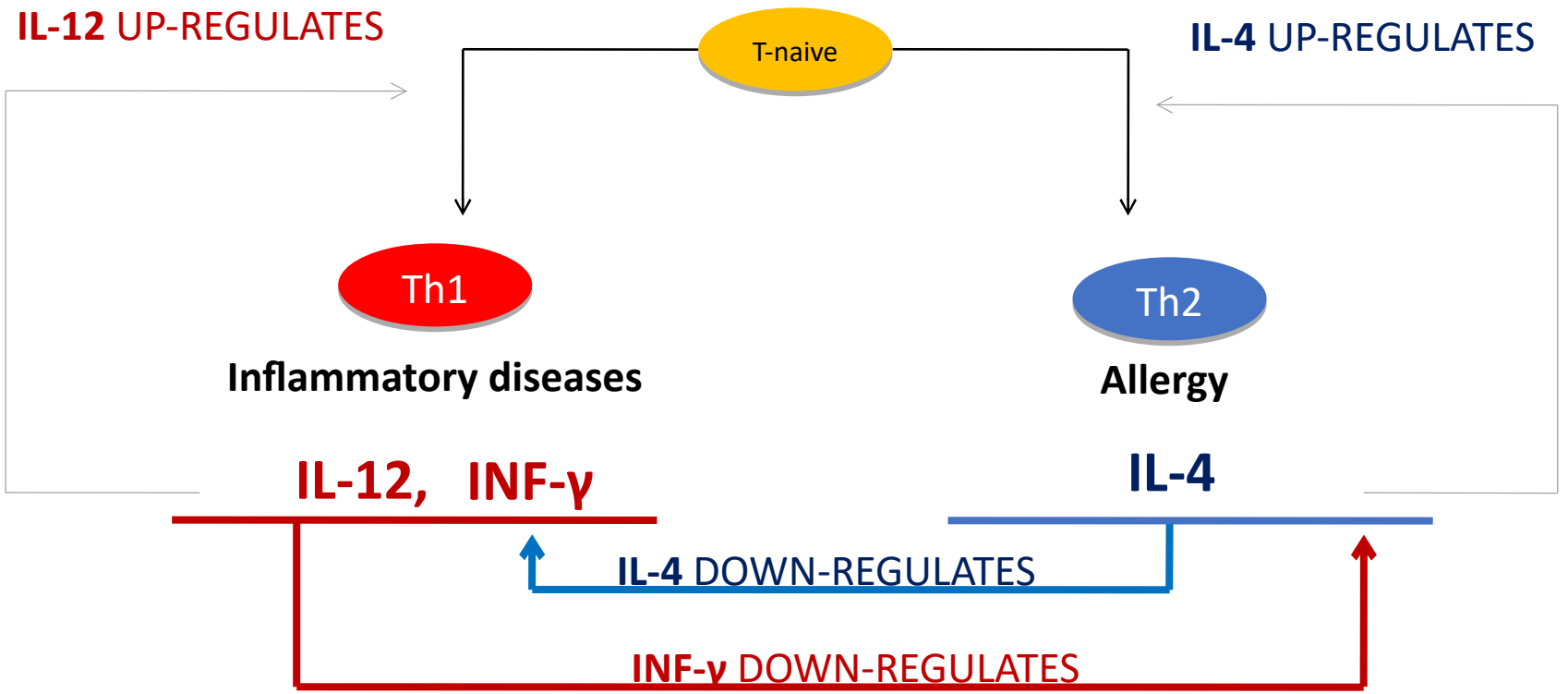
Is it possible to modulate the action of cytokines and other signaling molecules?

Clinical application of low dose cytokines

1. *same cytokines* are used in order to enhance the biological activity of the homologue cytokine

2. *antagonistic cytokines* are used in order to slow down the biological effect of another specific cytokine

THE CONCEPT OF BALANCE – RECIPROCITY of TH CELLS



Th subsets cross-regulate expansion and functions each other.

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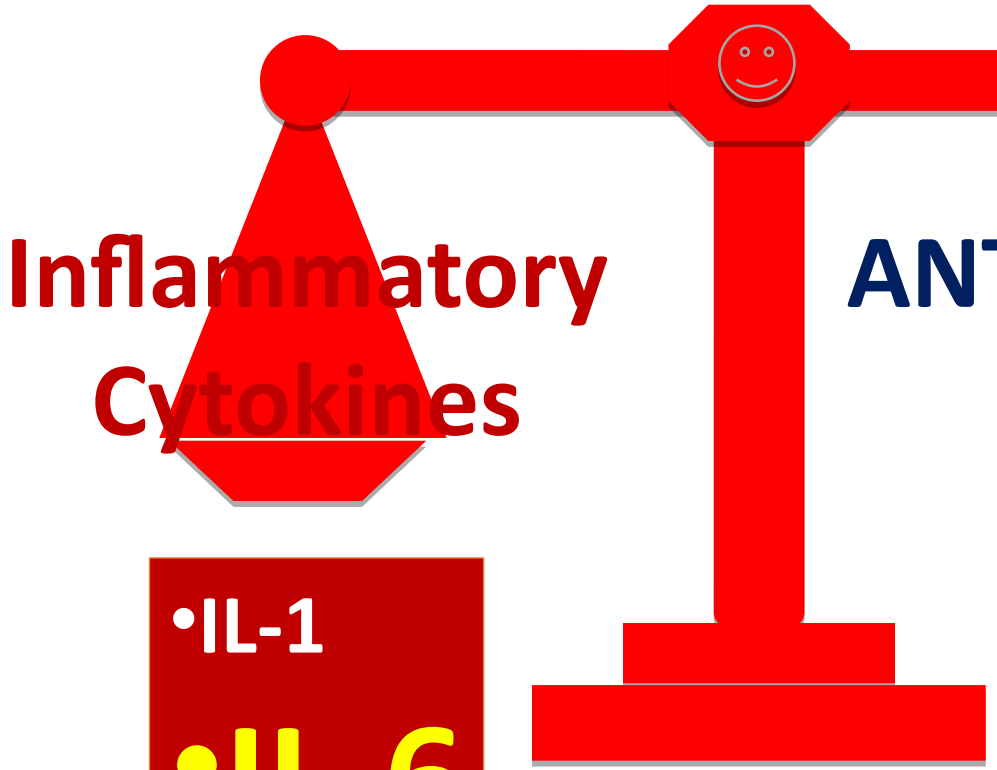
RECOVERING THE BALANCE IN CHRONIC INFLAMMATORY DISEASES



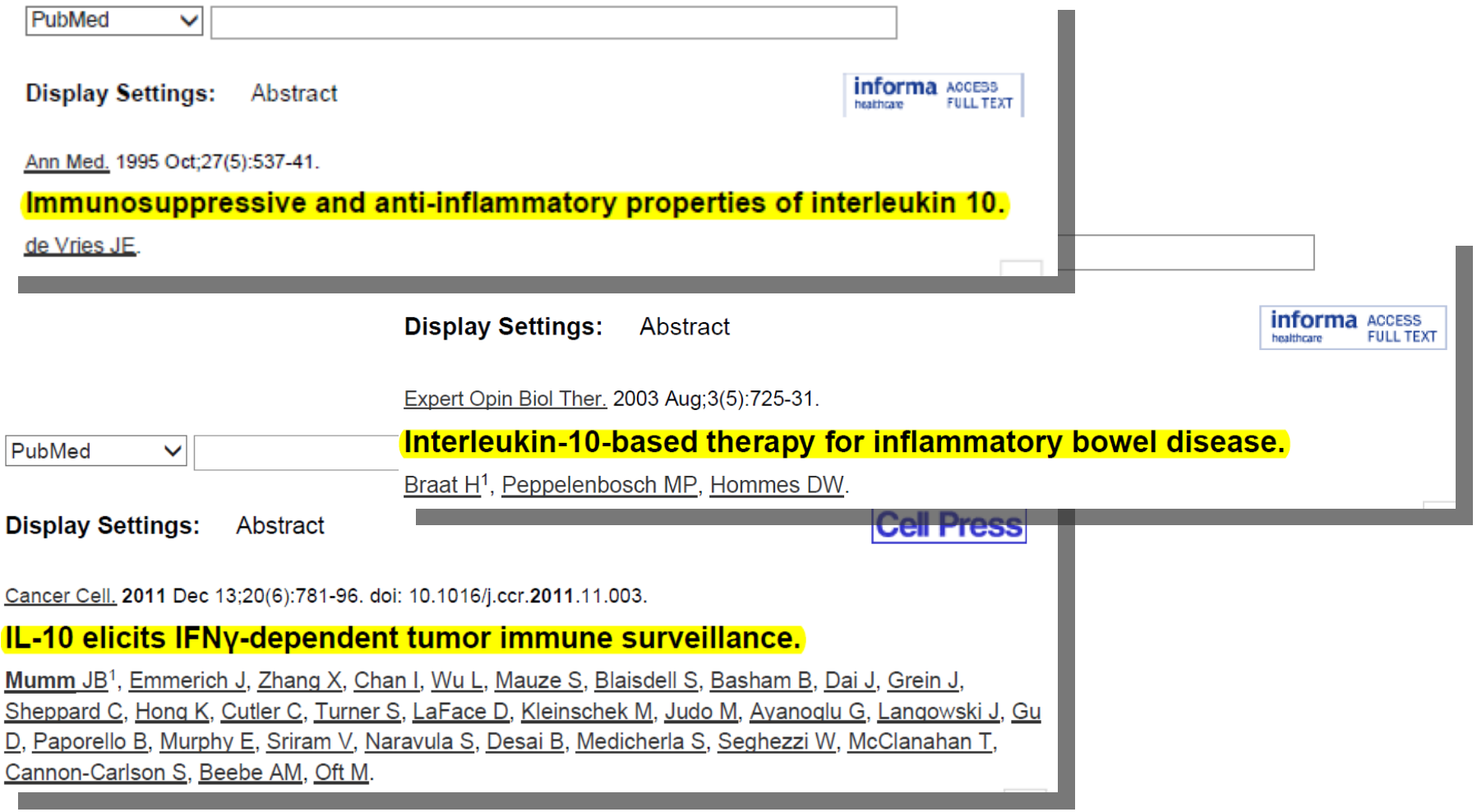
Inflammatory Cytokines

- IL-1
- **IL-6**
- TNF-α

ANTI-Inflammatory Cytokines

- Anti IL-1
- **IL-10**
- IL-4

IL-10 AS AN ANTINFLAMMATORY IN CHRONIC DISEASES



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JEM Journal of Experimental Medicine

REVIEW

Cytokines Focus

Biology and therapeutic potential of interleukin-10

Margarida Saraiva[1,2], Paulo Vieira[3,4,5], and Anne O'Garra[6,7]

The cytokine IL-10 is a key anti-inflammatory mediator ensuring protection of a host from over-exuberant responses to pathogens and microbiota, while playing important roles in other settings as sterile wound healing, autoimmunity, cancer, and homeostasis. Here we discuss our current understanding of the regulation of IL-10 production and of the molecular pathways associated with IL-10 responses. In addition to IL-10's classic inhibitory effects on myeloid cells, we also describe the nonclassic roles attributed to this pleiotropic cytokine, including how IL-10 regulates basic processes of neural and adipose cells and how it promotes CD8 T cell activation, as well as epithelial repair. We further discuss its therapeutic potential in the context of different diseases and the outstanding questions that may help develop an effective a

Cold Spring Harbor Perspectives in Biology
www.cshperspectives.org

Targeting IL-10 Family Cytokines for the Treatment of Human Diseases

Xiaoting Wang,[1] Kit Wong,[2] Wenjun Ouyang,[3] and Sascha Rutz[4]

[1]Department of Comparative Biology and Safety Sciences, Amgen, South San Francisco, California 94080
[2]Department of Biomarker Development, Genentech, South San Francisco, California 94080
[3]Department of Inflammation and Oncology, Amgen, South San Francisco, California 94080
[4]Department of Cancer Immunology, Genentech, South San Francisco, California 94080
Correspondence: wouyang@amgen.com; saschar@gene.com

Guna Interleukin-10

DIRECTIONS AND ADMINISTRATION WAYS

20 drops twice a day for 4-6 months.

Sublingual absorption: directly under the tongue or in a little water, preferably far from the meals.

guna.it

Journal of Integrative Cardiology

oat open access text

Research Article

Twenty-five years of studies and trials for the therapeutic application of IL-10 immunomodulating properties. From high doses administration to low dose medicine new paradigm

Massimo Fioranelli[1]* and Roccia Maria Grazia[2]

[1]University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India

[2]G.Marconi University, Rome, Italy

Elmer Press

Original Article

Gastroenterology Research • 2013;6(4):124-133

Oral Administration of Interleukin-10 and Anti-IL-1 Antibody Ameliorates Experimental Intestinal Inflammation

Diego Cardani[a], Giuseppina F Dusio[b], Patrizia Luchini[c], Michele Sciarabba[d], Umberto Solimene[e, f], Cristiano Rumio[a, f, g]

Drug Design, Development and Therapy

Dovepress

open access to scientific and medical research

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ORIGINAL RESEARCH

An open randomized active-controlled clinical trial with low-dose SKA cytokines versus DMARDs evaluating low disease activity maintenance in patients with rheumatoid arthritis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
29 March 2017
Number of times this article has been viewed

JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 28, no. 1, 133-139 (2014)

IMMUNOMODULATING TREATMENT WITH LOW DOSE INTERLEUKIN-4, INTERLEUKIN-10 AND INTERLEUKIN-11 IN PSORIASIS VULGARIS

M.L. ROBERTI[1], L. RICOTTINI[2], A. CAPPONI[3], E. SCLAUZERO[4], P. VICENTI[5], E. FIORENTINI[6], C. SAVOIA[7], G. SCORNAVACCA[8], D. BRAZIOLI[9], L. GAIO[10], R. GIANNETTI[11], C. IGNAZZI[12], G. MELONI[13] and L.M. CHINNI[14]

[1]Private Practice, Rome, Italy; [2]"Sinergheia" Medical Center, Rome, Italy; [3]Private Practice, Latina, Italy; [4]OSTEMDA, Therapeutic Strategies Empowerment and Advanced Diagnostic Methods Organization, Udine, Italy; [5]Private Practice, Altamura, Bari, Italy; [6]Dermatological Health Clinic, Aversa, Caserta, Italy; [7]Private Practice, Fino Mornasco, Como, Italy; [8]Private Practice, Catania, Italy; [9]Private Practice, Turin, Italy; [10]Private Practice, Caserta, Italy; [11]"Aurelia" Medical Center, Rome, Italy; [12]Local Health Unit (ASL), Putignano, Bari, Italy; [13]"GEA Medica" Medical Center, Montebelluna, Treviso, Italy; [14]Istituto Dermopatico dell'Immacolata (IDI), Rome, Italy

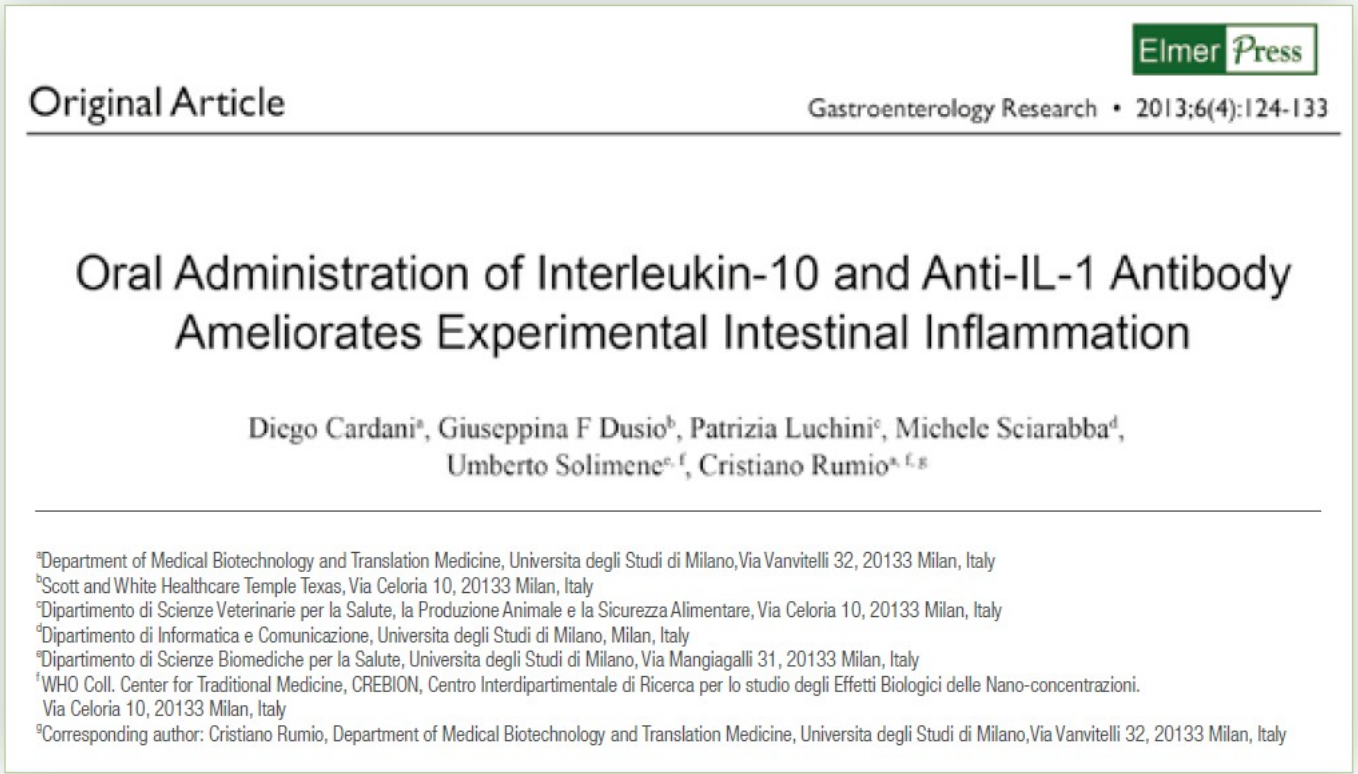
JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 29, no. 1 (S), 53-58 (2015)

VITILIGO: SUCCESSFUL COMBINATION TREATMENT BASED ON ORAL LOW DOSE CYTOKINES AND DIFFERENT TOPICAL TREATMENTS

T. LOTTI[1], J HERCOGOVA[4], U. WOLLINA[5], A.A. CHOKOEVA[6], Z. ZARRAB[7], S. GIANFALDONI[8], M.G. ROCCIA[9], M. FIORANELLI[10] and G. TCHERNEV[6]

Evidence from the Research

ORAL ADMINISTRATION OF INTERLEUKIN-10 AND ANTI-IL-1 ANTIBODY AMELIORATES EXPERIMENTAL INTESTINAL INFLAMMATION



Elmer Press

Original Article

Gastroenterology Research • 2013;6(4):124-133

Oral Administration of Interleukin-10 and Anti-IL-1 Antibody Ameliorates Experimental Intestinal Inflammation

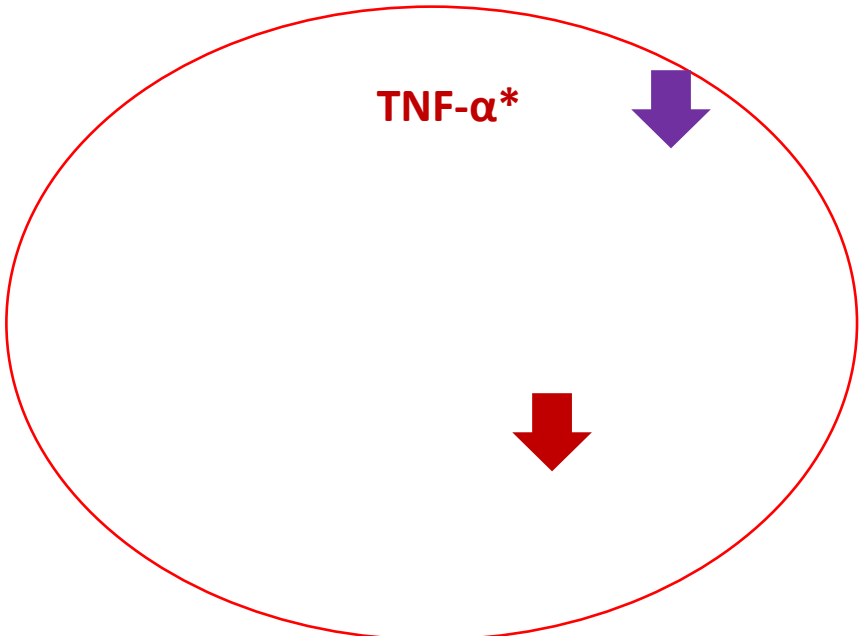
Diego Cardani[a], Giuseppina F Dusio[b], Patrizia Luchini[c], Michele Sciarabba[d], Umberto Solimene[e, f], Cristiano Rumio[a, f, g]

[a]Department of Medical Biotechnology and Translation Medicine, Universita degli Studi di Milano, Via Vanvitelli 32, 20133 Milan, Italy
[b]Scott and White Healthcare Temple Texas, Via Celoria 10, 20133 Milan, Italy
[c]Dipartimento di Scienze Veterinarie per la Salute, la Produzione Animale e la Sicurezza Alimentare, Via Celoria 10, 20133 Milan, Italy
[d]Dipartimento di Informatica e Comunicazione, Universita degli Studi di Milano, Milan, Italy
[e]Dipartimento di Scienze Biomediche per la Salute, Universita degli Studi di Milano, Via Mangiagalli 31, 20133 Milan, Italy
[f]WHO Coll. Center for Traditional Medicine, CREBION, Centro Interdipartimentale di Ricerca per lo studio degli Effetti Biologici delle Nano-concentrazioni. Via Celoria 10, 20133 Milan, Italy
[g]Corresponding author: Cristiano Rumio, Department of Medical Biotechnology and Translation Medicine, Universita degli Studi di Milano, Via Vanvitelli 32, 20133 Milan, Italy

Cytokines levels

IL-12*

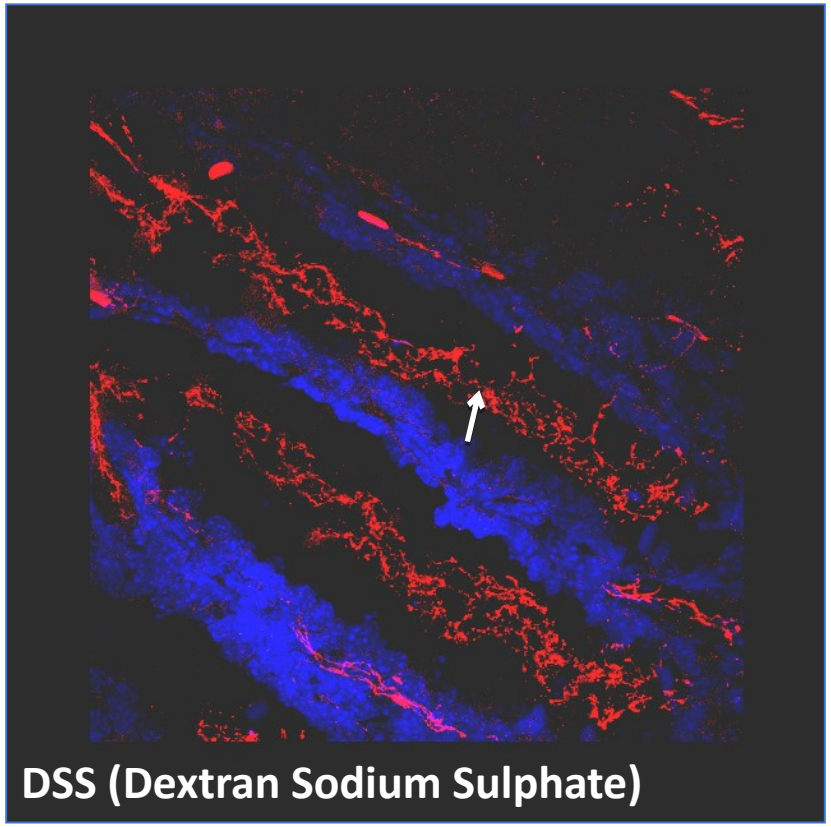
IFN-γ



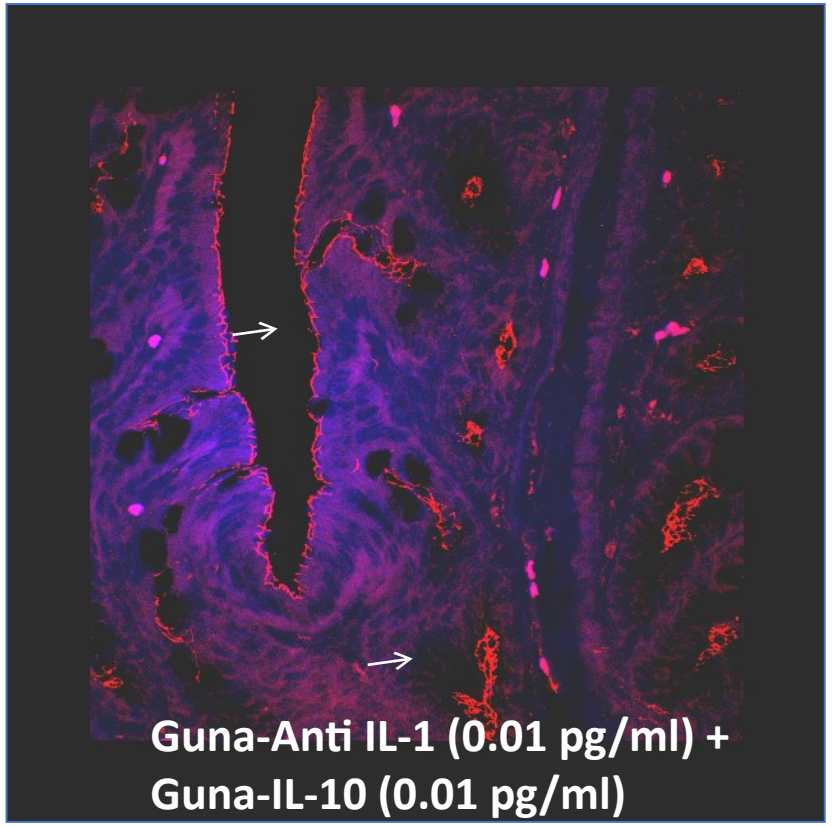
IL-8

Legenda:
1: levels in healthy mouse
2: levels in the mouse with Crohn's
3: levels in the mouse with Crohn's after 7 days treatment with Anti IL-1+IL-10 at pharmacological doses (ng/ml)
4: levels in the mouse with Crohn's after 7 days treatment with Anti IL-1+IL-10 at a concentration of 0.01 pg/ml SKA
5: levels in the mouse with Crohn's after 7 days treatment with Anti IL-1+IL-10 at a concentration of 0.01 pg/ml non-SKA

Immunofluorescence



BEFORE TREATMENT



AFTER TREATMENT

AN OPEN RANDOMIZED ACTIVE-CONTROLLED CLINICAL TRIAL WITH LOW-DOSE SKA CYTOKINES VERSUS DMARDs EVALUATING LOW DISEASE ACTIVITY MAINTENANCE IN PATIENTS WITH RHEUMATOID ARTHRITIS

Drug Design, Development and Therapy

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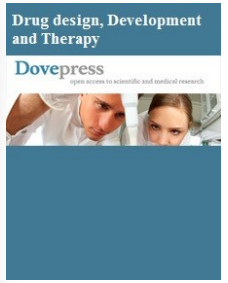
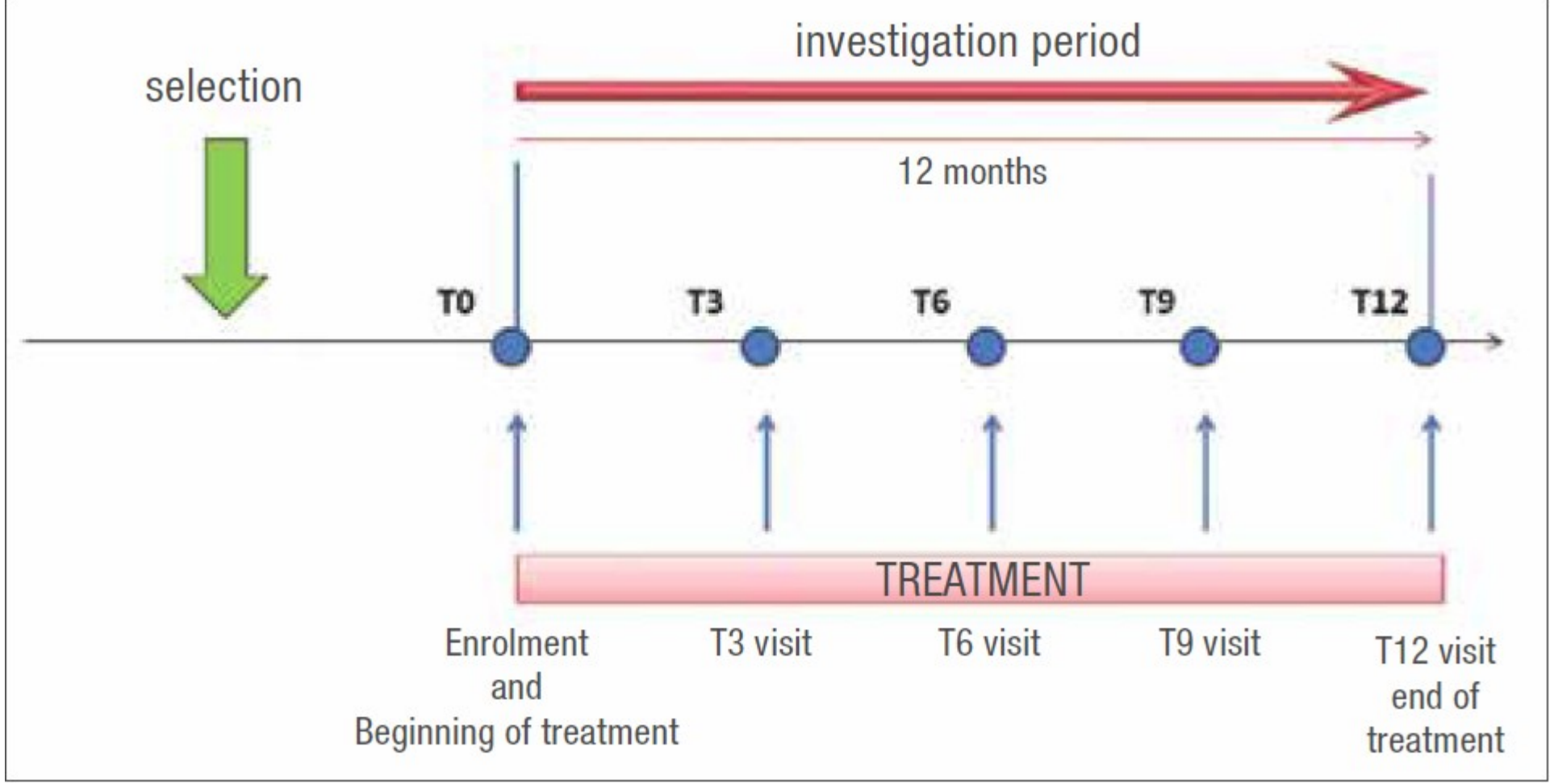
An open randomized active-controlled clinical trial with low-dose SKA cytokines *versus* DMARDs evaluating low disease activity maintenance in patients with rheumatoid arthritis.

Martin Martin S.[1], Giovannangeli F.[2], Bizzi E.[2], Massafra U.[2], Ballanti E.[2], Cassol M.[3], Migliore A.[2]

[1]Department of Internal Medicine, Regina Apostolorum Hospital, Rome, Italy
[2]Operative Unit of Rheumatology, San Pietro Fatebenefratelli Hospital, Rome, Italy
[3]Department of Internal Medicine, San Pietro Fatebenefratelli Hospital, Rome, Italy





After randomisation, subjects were split into two study groups:

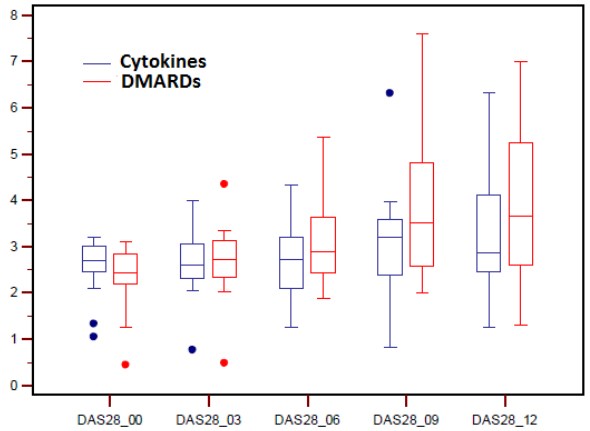
- **Group A started taking GUNA®-IL 4, GUNA®-IL 10 and GUNA®-Anti IL 1 in 10 fg/mL SKA formulations, administered at a dose of 20 drops per day for 12 consecutive months.**
- **Group B started or continued taking DMARD therapy (FIG. 2).**

RESULTS

Primary endpoint

The maintenance of LDA at 12 months is obtained respectively in 66.7% of subjects treated with low-dose cytokines (Group A) (n=10) and in 42.1% of patients treated with DMARDs (Group B) (n=8); the difference between the groups is not statistically significant (Fisher exact test: p = 0.185)

In Group A 2 subject have been treated at the same time with DMARDs (MTX) and low-dose cytokines.

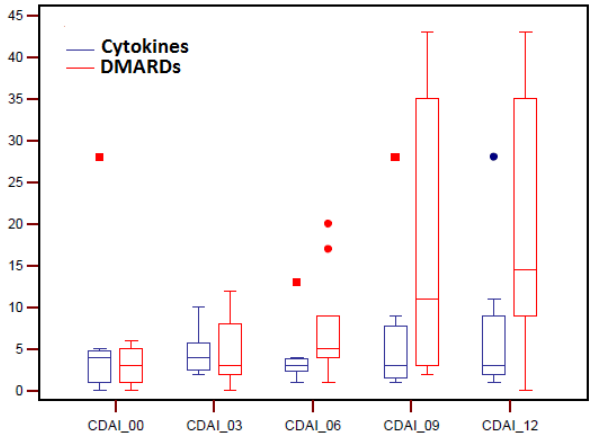


Disease Activity Score DAS28

DAS28 values are similar in the two groups at baseline (Mann-Whitney U test: p = 0.3991) as well as at 12 months (Mann-Whitney U test: p = 0.1030). Group A maintains constant values of DAS 28 (Friedman test: p = 0.41604), while in the Group B DAS 28 values are on the rise (Friedman test: p = 0.00198), with significant difference (test according Conover: p <0.05) between T0 and T9, T0 and T12, T3 and T9, T3 and T12

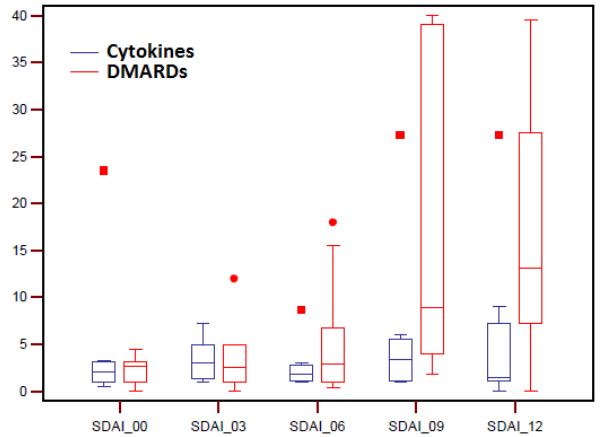
RESULTS

Primary endpoint



Clinical Disease Activity Index CDAI

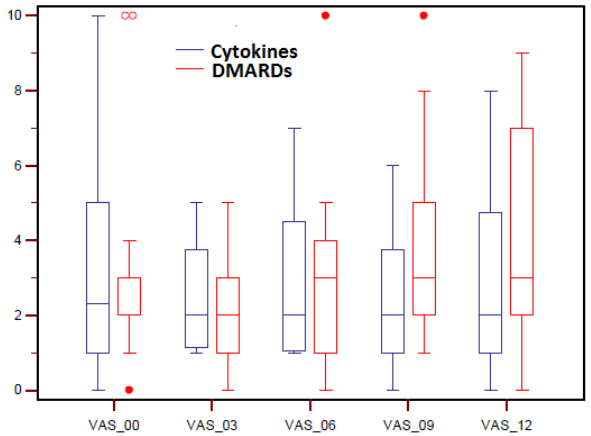
CDAI score are similar in the two groups at baseline (Mann-Whitney U test: p = 0.7317) as well as at 12 months (Mann-Whitney U test: p = 0.0510). The Group A show a constant sealing over time (Friedman test: p = 0.84645), while values are on the rise in the Group B (Friedman test: p = 0.00004), with significant difference (test according Conover: p <0.05) between T0 and T6, T0 and T9, T0 and T12, T3 and T9, T3 and T12, T6 and T9, T6 and T12



Simplified Disease Activity Index SDAI

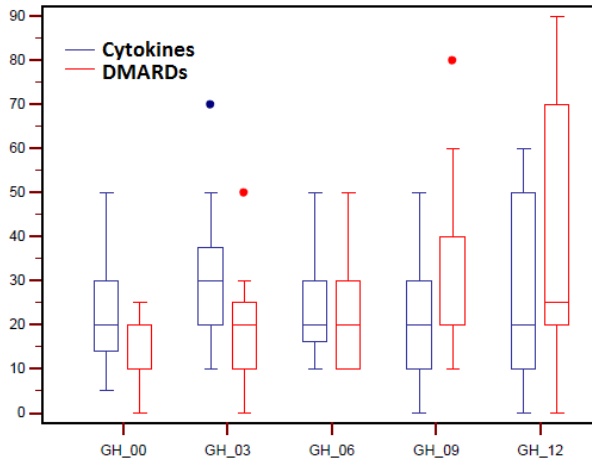
The SDAI showed no statistical difference between the two groups at baseline (Mann-Whitney U test: p = 0.9223) as well as at 12 months (Mann-Whitney U test: p = 0.0790). Group A showed a constant intra-group sealing (Friedman test: p = 0.56774), while a significant intra-group difference was shown in the Group B (Friedman test: p <0.00001 and test according Conover: p <0.05) between the following time points:T0 and T6, T9 and T0, T0 and T12, T3 and T9, T12 and T3, T6 and T9, T6 and T12

Secondary endpoints



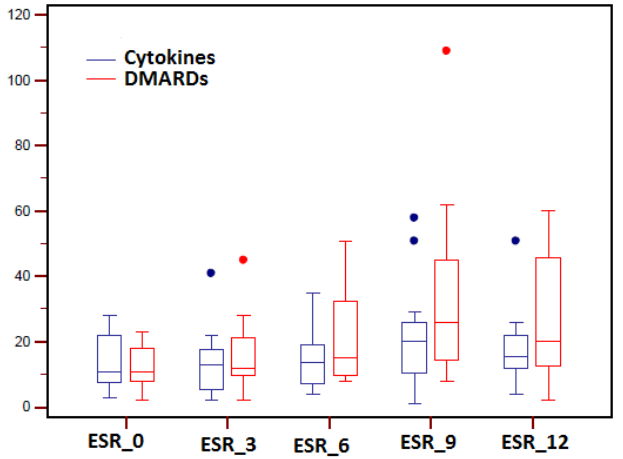
Pain Visual Analog Scale

The Pain VAS values are similar between the two groups at both baseline visit (Mann-Whitney U test: p = 0.7336) and 12 months follow up (Mann-Whitney U test: p = 0.1772). Patients maintain constant levels without any intra-group difference as show by the Friedman test, p values were respectively 0.79490 in the Group A and 0.12474 in the Group B



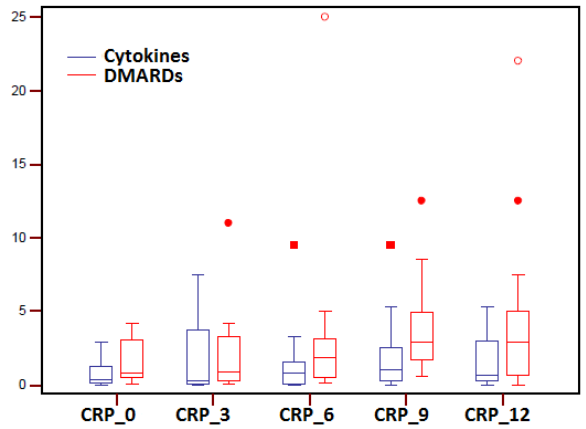
Global Health Assessment GH

GH values didn't show any statistical difference between the two groups at baseline (Mann-Whitney U test: p = 0.4998) and at 12 months (Mann-Whitney U test: p = 0.3269). Patients maintain constant values in both groups; Friedman test: p = 0.19770 in the Group A and Friedman test: p = 0.05608 in the Group B



Erythrocyte Sedimentation Rate ESR

ESR mean values didn't show any significant intergroup difference at baseline (Mann-Whitney U test: p = 0.7153) as well as at 12 months (Mann-Whitney U test: p = 0.0699). Similarly no intra-group significant differences were reported, Friedman test p values were respectively 0.53603 in the Group A and 0.08022 in the Group B



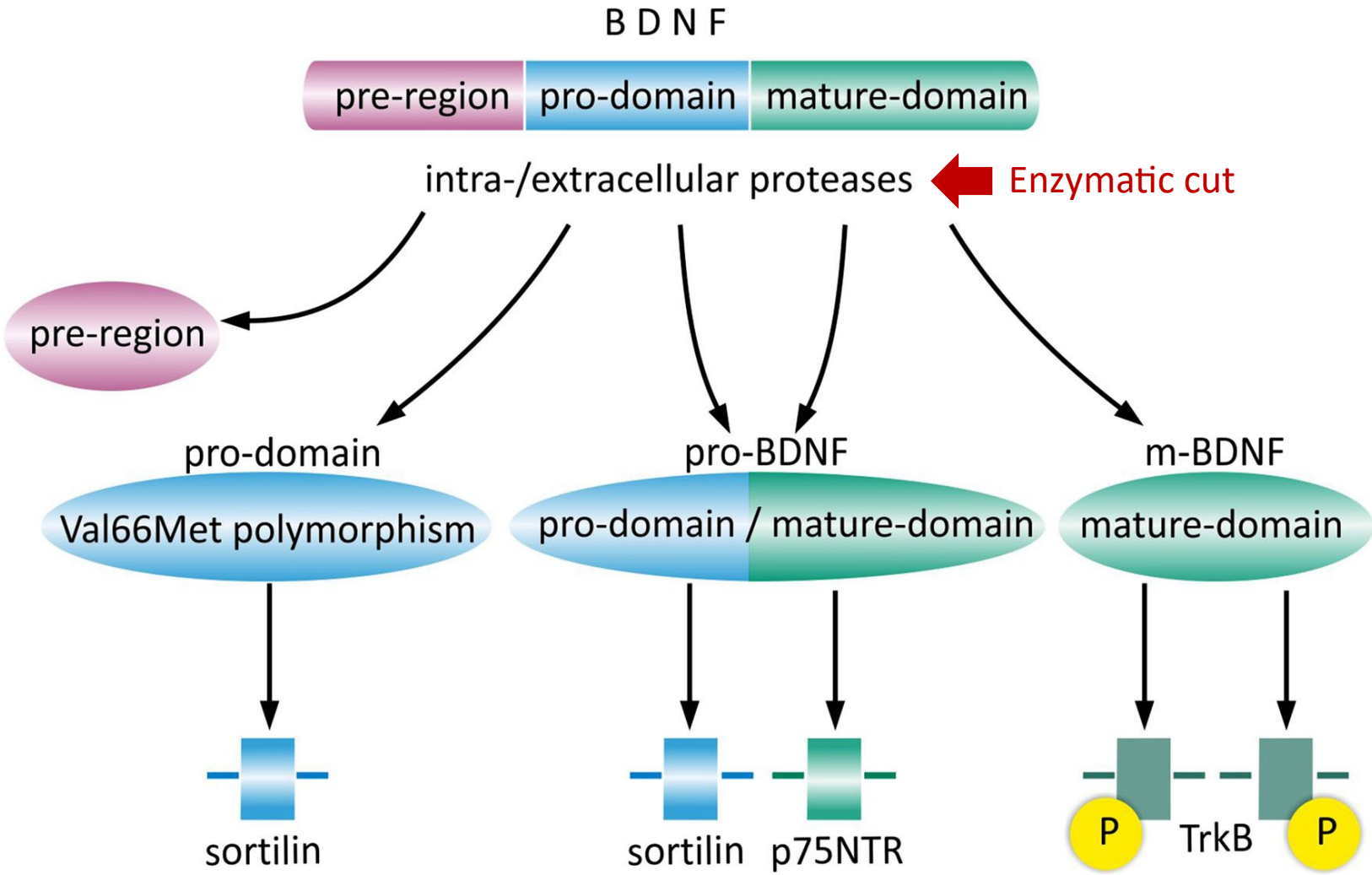
C-Reactive Protein CRP

The PCR mean values are lower in the Group A at baseline (Mann-Whitney U test: p = 0.0078), but similar at 12 months without any significant statistical difference (Mann-Whitney U test: p = 0.0966). Patients show intra-group constant levels, Friedman test was respectively p = 0.69002 in the Group A and p = 0.22356 in the Group B

Clinical application of low dose cytokines

1. *same cytokines* are used in order to enhance the biological activity of the homologue cytokine
2. *antagonistic cytokines* are used in order to slow down the biological effect of another specific cytokine

BDNF maturation processes



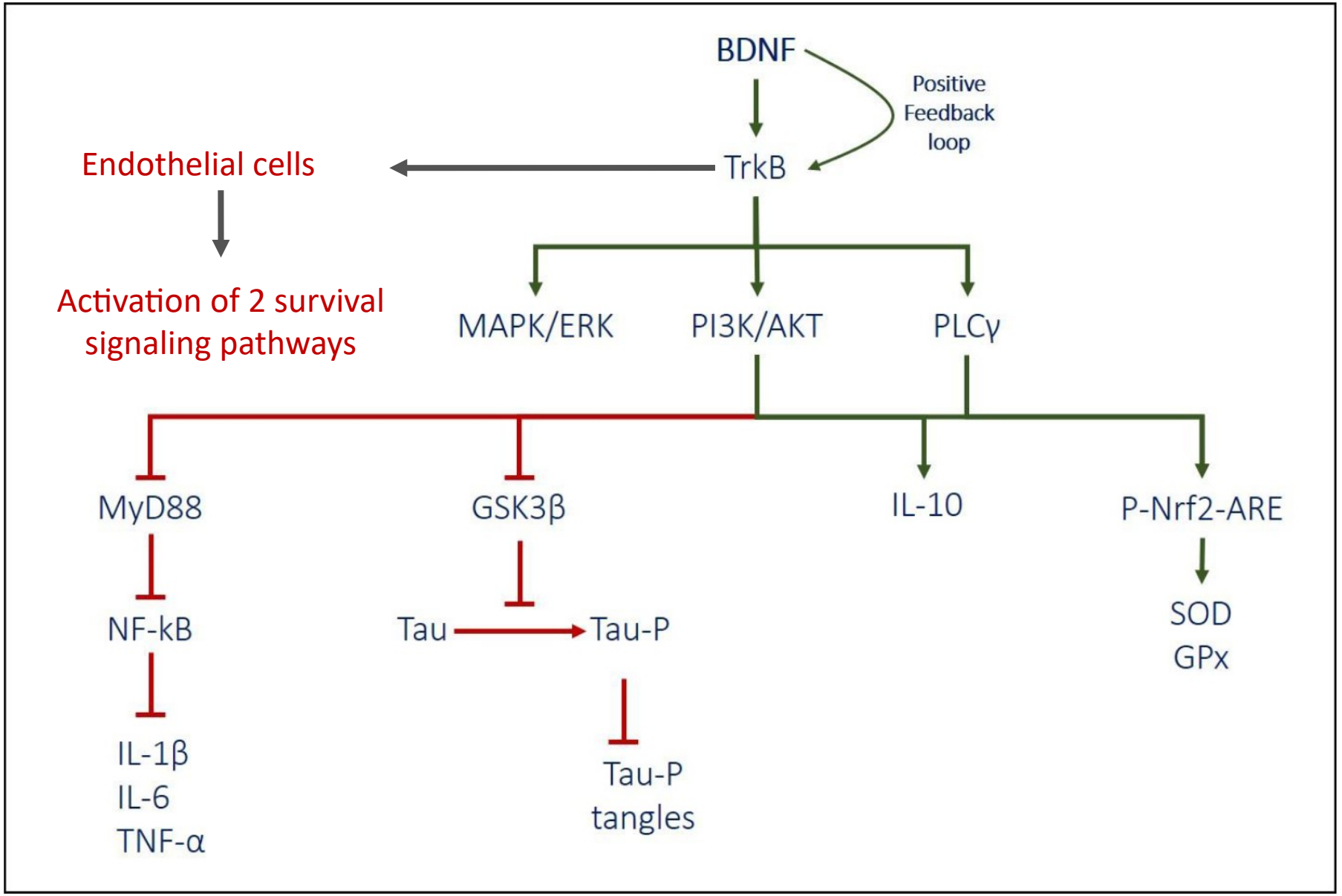
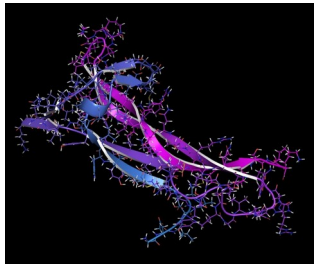


Figure 1 – Simplified synoptic scheme of the main pathways of BDNF's mediated cellular responses.

Amadio P, Baldassarre D, Sandrini L, Weksler BB, Tremoli E, Barbieri SS. Effect of cigarette smoke on monocyte procoagulant activity: Focus on platelet-derived brain-derived neurotrophic factor (BDNF). Platelets. 2016 Aug 5:1-6.

BDNF – main functions involved in cognitive and memory mechanisms



- Neuronal surviving
- Neuronal growth and differentiation
- Snaptogenesis
- Synaptic transmission
- Neuronal plasticity

- Stimulation and control of neurogenesis through its proper action on neuronal brain pluripotent stem cells.

- *A BDNF autocrine loop in adult sensory neurons prevents cell death*, in *Nature*, vol. 374, n. 6521, March 1995, pp. 450-53, Bibcode:1995Natur.374..450A, DOI:10.1038/374450a0, PMID 7700353.
- *Neurotrophins: roles in neuronal development and function*, in *Annual Review of Neuroscience*, vol. 24, 2001, pp. 677-736, DOI:10.1146/annurev.neuro.24.1.677, PMID 11520916.
- *Brain-derived neurotrophic factor/TrkB signaling in memory processes*, in *Journal of Pharmacological Sciences*, vol. 91, n. 4, April 2003, pp. 267-70, DOI:10.1254/jphs.91.267, PMID 12719654.
- *Identification of pro- and mature brain-derived neurotrophic factor in human saliva*, in *Archives of Oral Biology*, vol. 54, n. 7, July 2009, pp. 689-95, DOI:10.1016/j.archoralbio.2009.04.005, PMID 19467646.

brain sciences

MDPI

Article

The Role of BDNF on Aging-Modulation Markers

Claudio Molinari, Vera Morsanuto, Sara Ruga, Felice Notte, Mahitab Farghali, Rebecca Galla and Francesca Uberti *

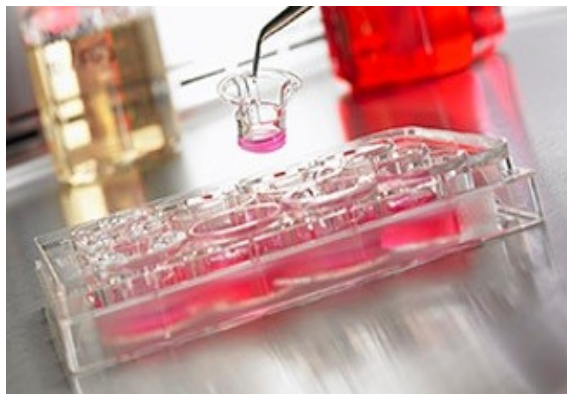
Laboratory of Physiology, Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy; claudio.molinari@med.uniupo.it (C.M.); vera.morsanuto@med.uniupo.it (V.M.); sara.ruga@uniupo.it (S.R.); felice.notte@uniupo.it (F.N.); mahitab.farghali@uniupo.it (M.F.); rebecca.galla@uniupo.it (R.G.)

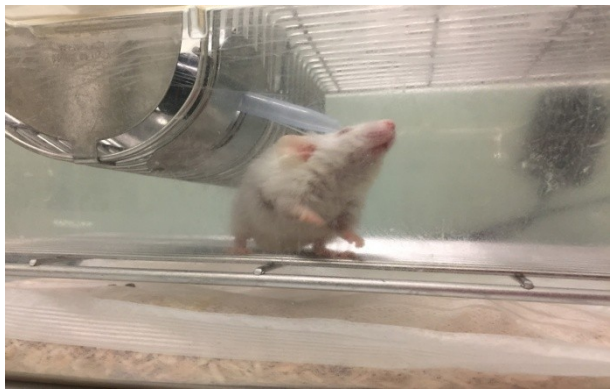
* Correspondence: francesca.uberti@med.uniupo.it; Tel.: +39-0321-660653

Received: 26 February 2020; Accepted: 4 May 2020; Published: 9 May 2020

check for updates

brain sciences

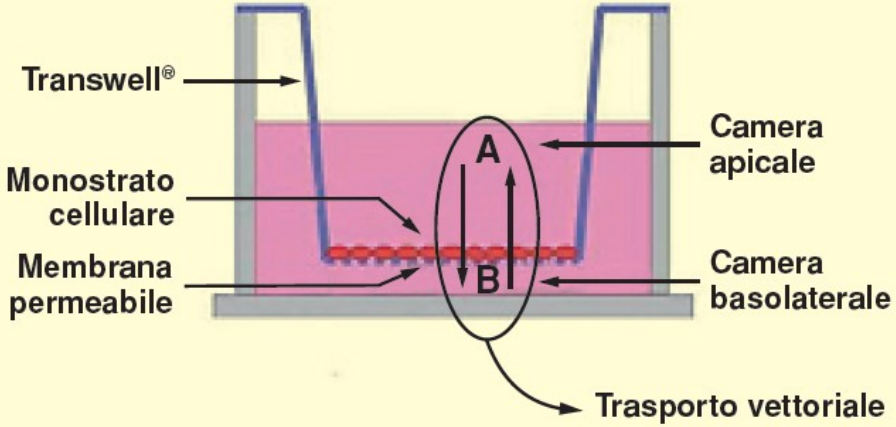




In vitro BBB model

FIG. 2

Immagine e schema di funzionamento del Transwell®. Sn: Transwell® impiegato; dx: principio di funzionamento (32).



HUVEC cells

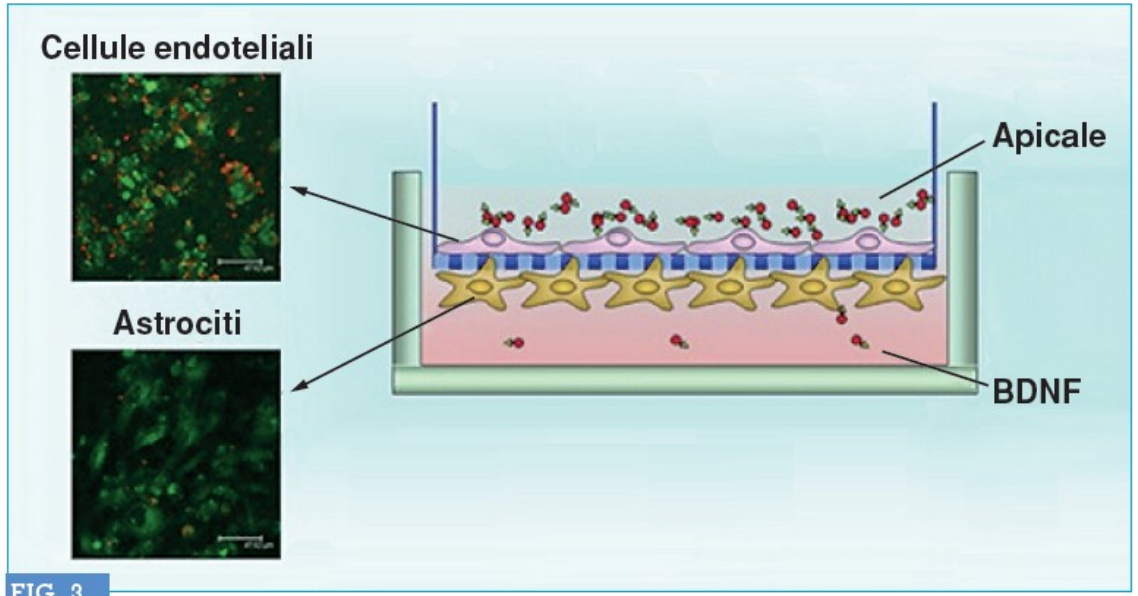
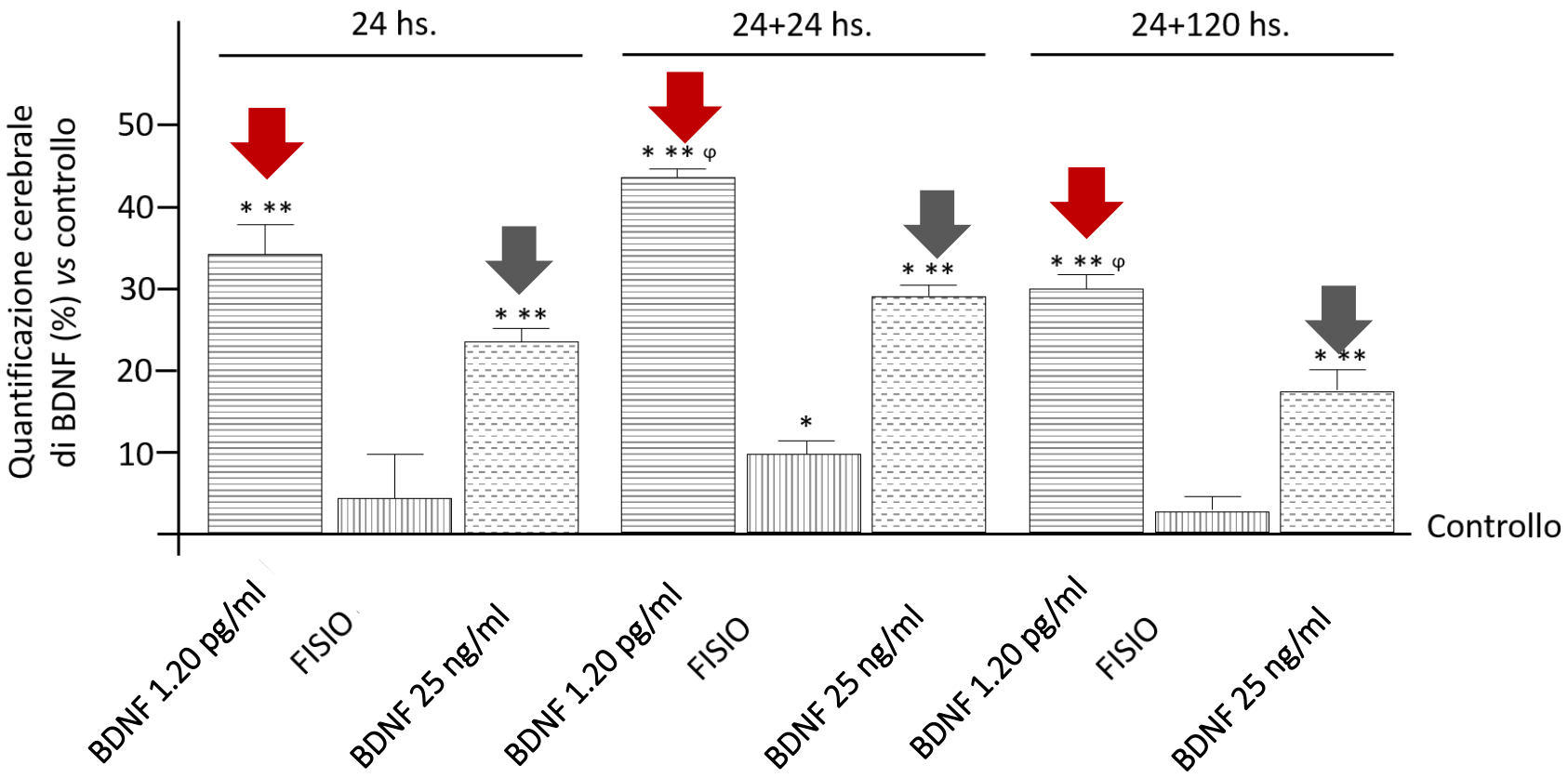


FIG. 3

human umbilical vein endothelial cells (HUVEC)

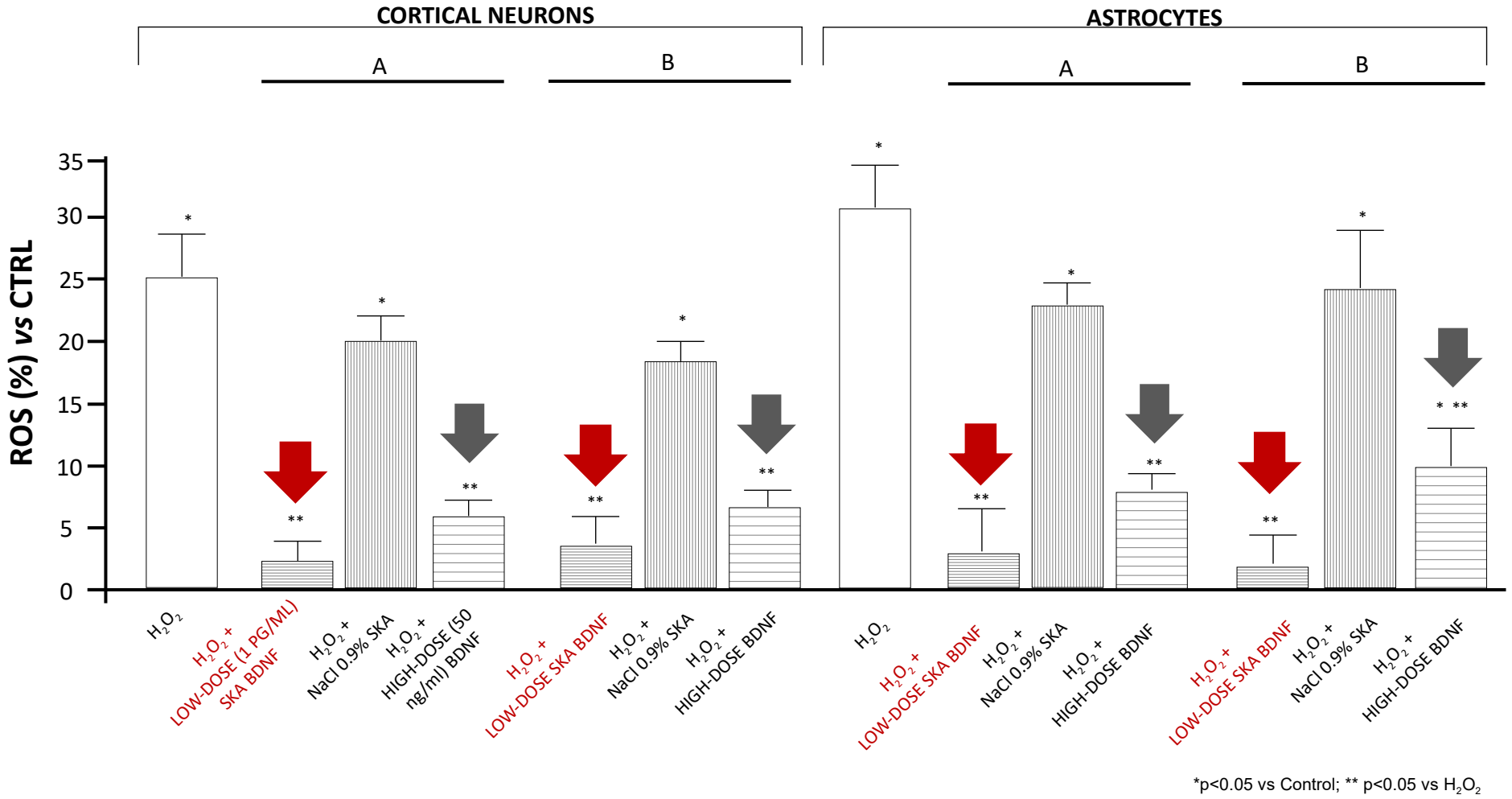
Rappresentazione schematica del metodo usato.
– Immagine adattata dalla letteratura (Xu G. *et* al., 2013) (33).

In vivo BRAIN BDNF QUANTIFICATION



12 monthh old mice type C57BL

ROS REDUCTION

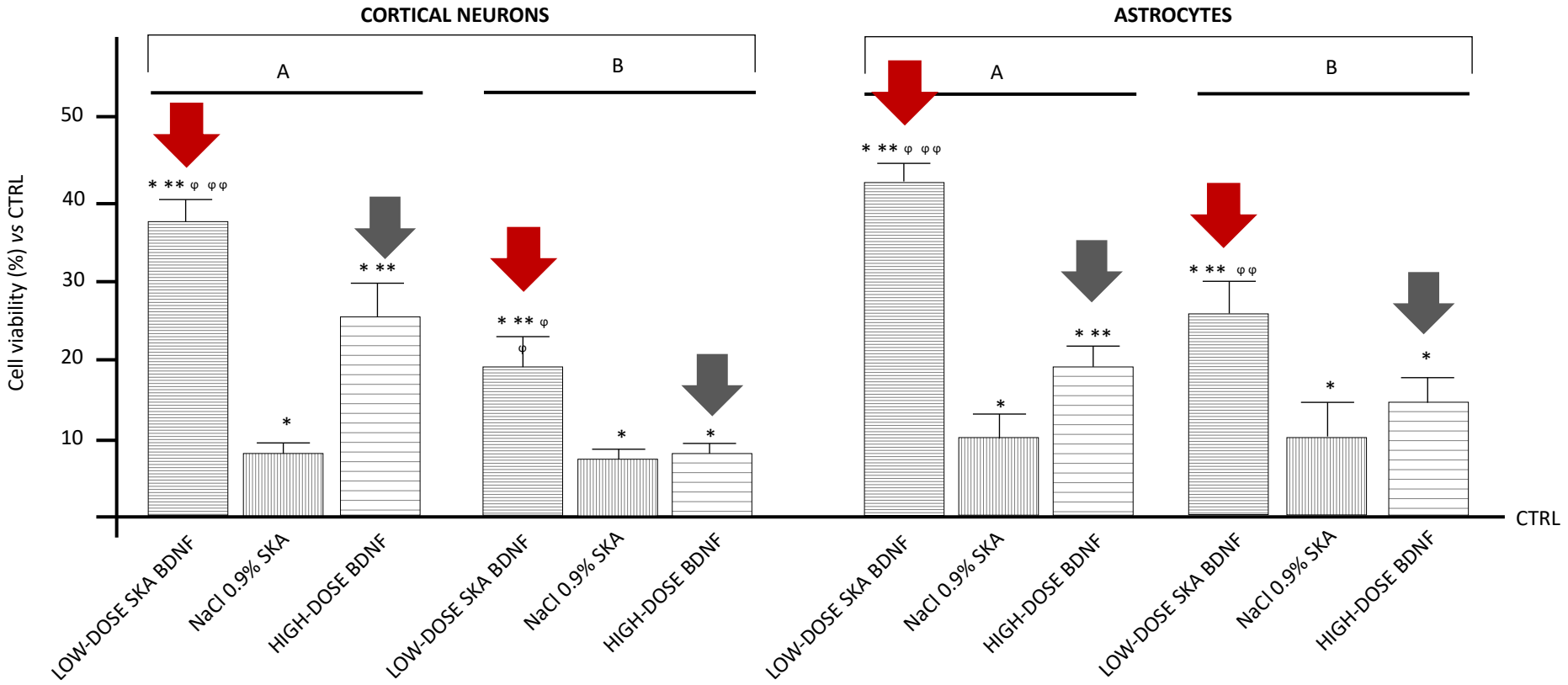


*p<0.05 vs Control; ** p<0.05 vs H_2O_2

Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

CELL VIABILITY

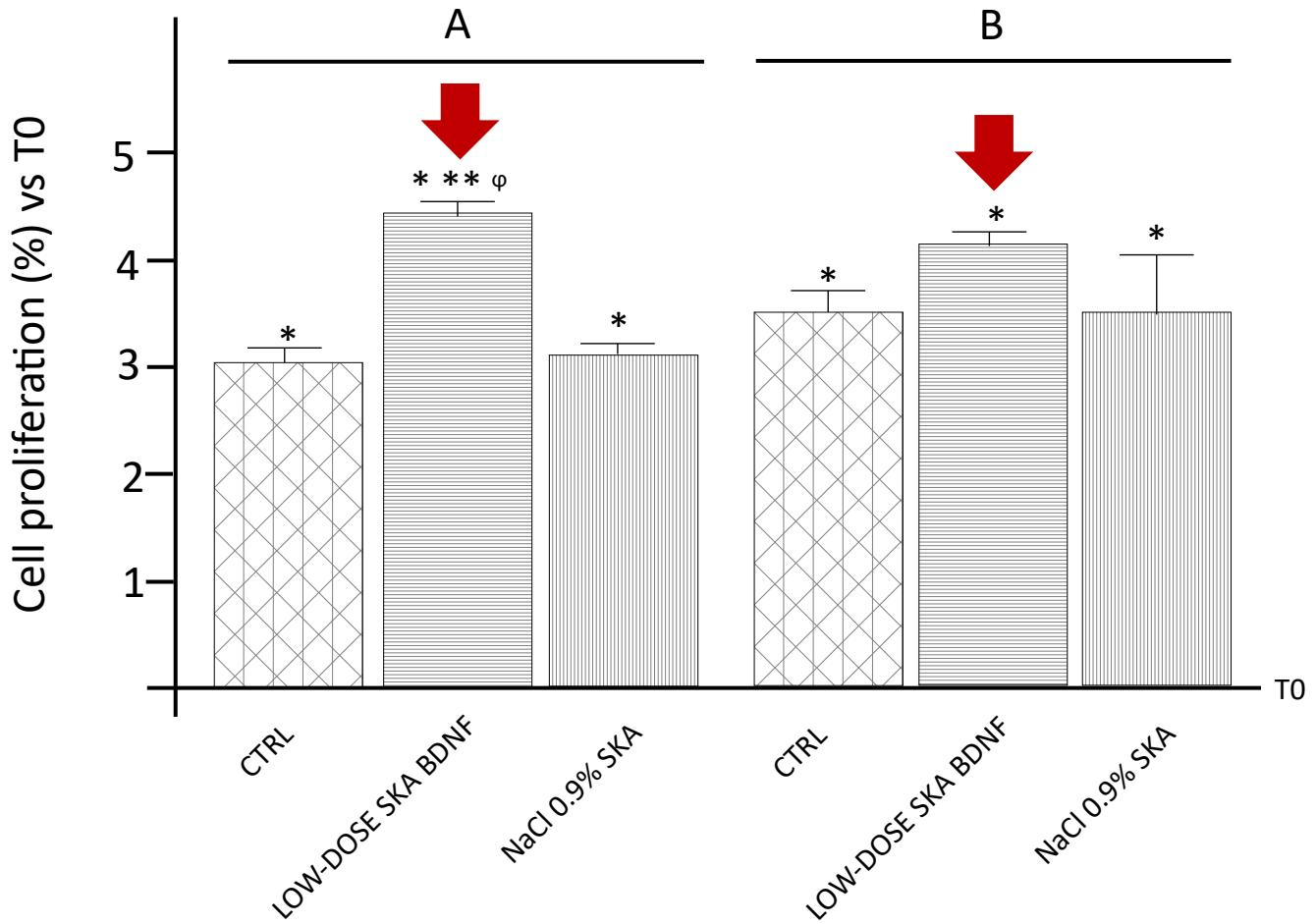


Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

*p<0.05 vs CTRL; ** p<0.05 vs NaCl 0.9% SKA ; $^{\varphi}$p<0.05 vs the same treatment in the two protocols; $^{\varphi\varphi}$ p<0.05 vs BDNF within the same protocol

CELL PROLIFERATION
(Astrocytes*)



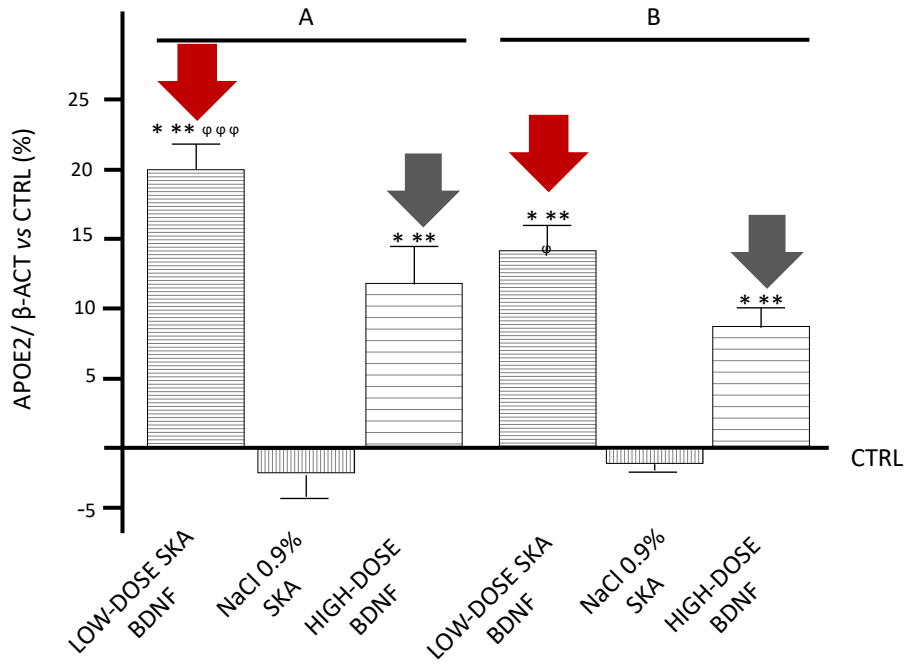
Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

*p<0.05 vs T0; ** p<0.05 vs CTRL; φp<0.05 vs NaCl 0.9% SKA

*Astrocytes are the only brain proliferative cells,
which intervene during development and reparation processes

APOE2



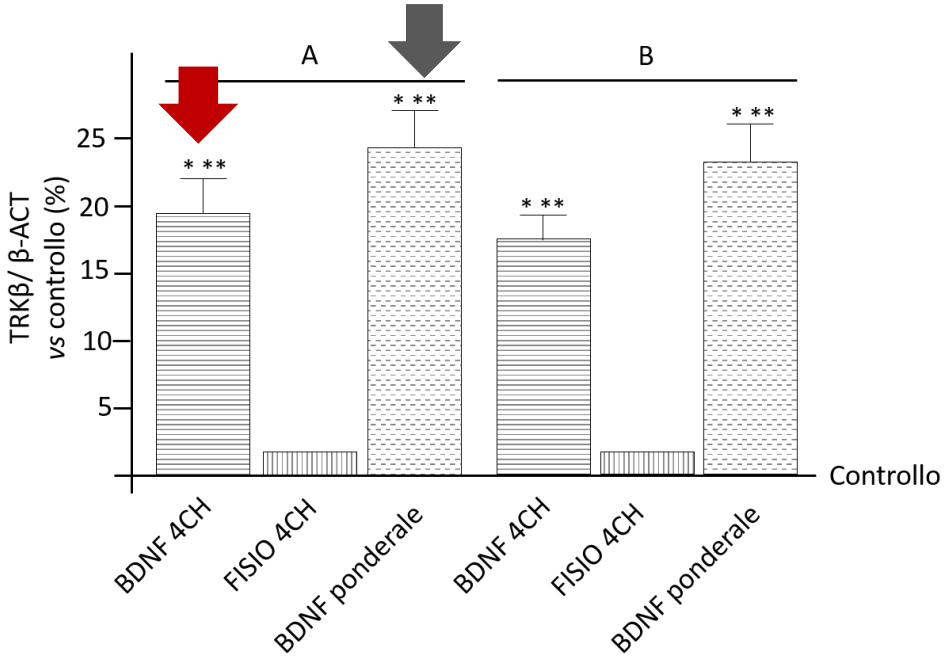
Protocol A

a single cell treatment in 6 days

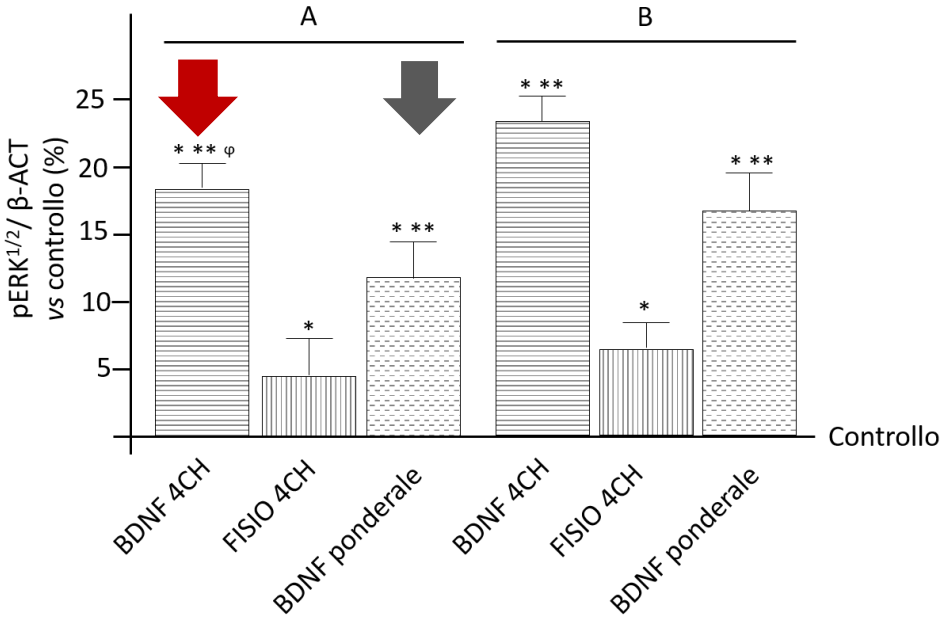
Protocol B

1 cell treatment a day for 6 days

TRkβ



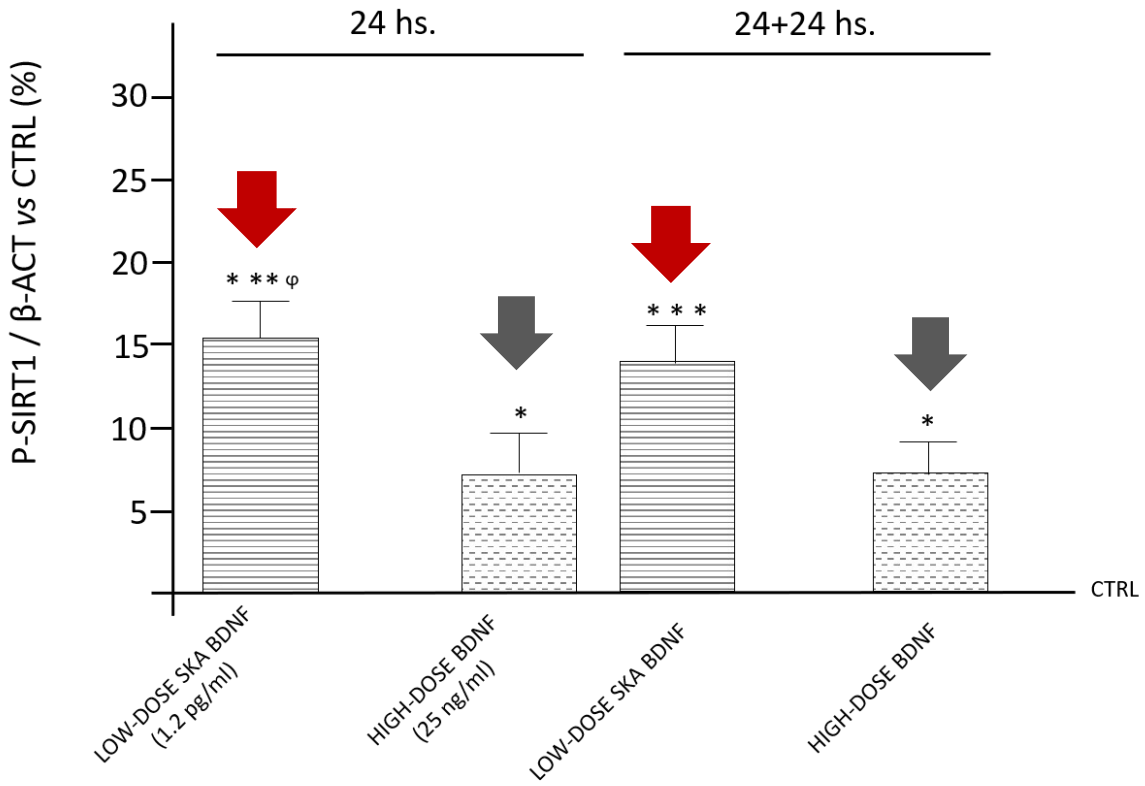
pERK



Protocol A
a single cell treatment in 6 days

Protocol B
1 cell treatment a day for 6 days

P-SIRT1


24 hs.
24+24 hs.
P-SIRT1 / β-ACT vs CTRL (%)
30
25
20
15
10
5
* ** φ
*
* * *
*
CTRL
LOW-DOSE SKA BDNF (1.2 pg/ml)
HIGH-DOSE BDNF (25 ng/ml)
LOW-DOSE SKA BDNF
HIGH-DOSE BDNF

guna.it

Guna-BDNF

DIRECTIONS AND ADMINISTRATION WAYS
20 drops twice a day for 4-6 months.
Children under 6 years: 10 drops twice a day for 4-6 months.

Sublingual absorption: directly under the tongue or in a little water, preferably far from the meals.

Brain Fog

+

POSOLOGIA E MODALITÀ DI ASSUNZIONE

20 gocce due volte al giorno di entrambi per 4-6 mesi.

Assorbimento sublinguale: direttamente sotto la lingua o in poca acqua, preferibilmente lontano dai pasti.

BDNF LOW DOSE
in Paroxysmal Atrial Fibrillation
Preliminary data

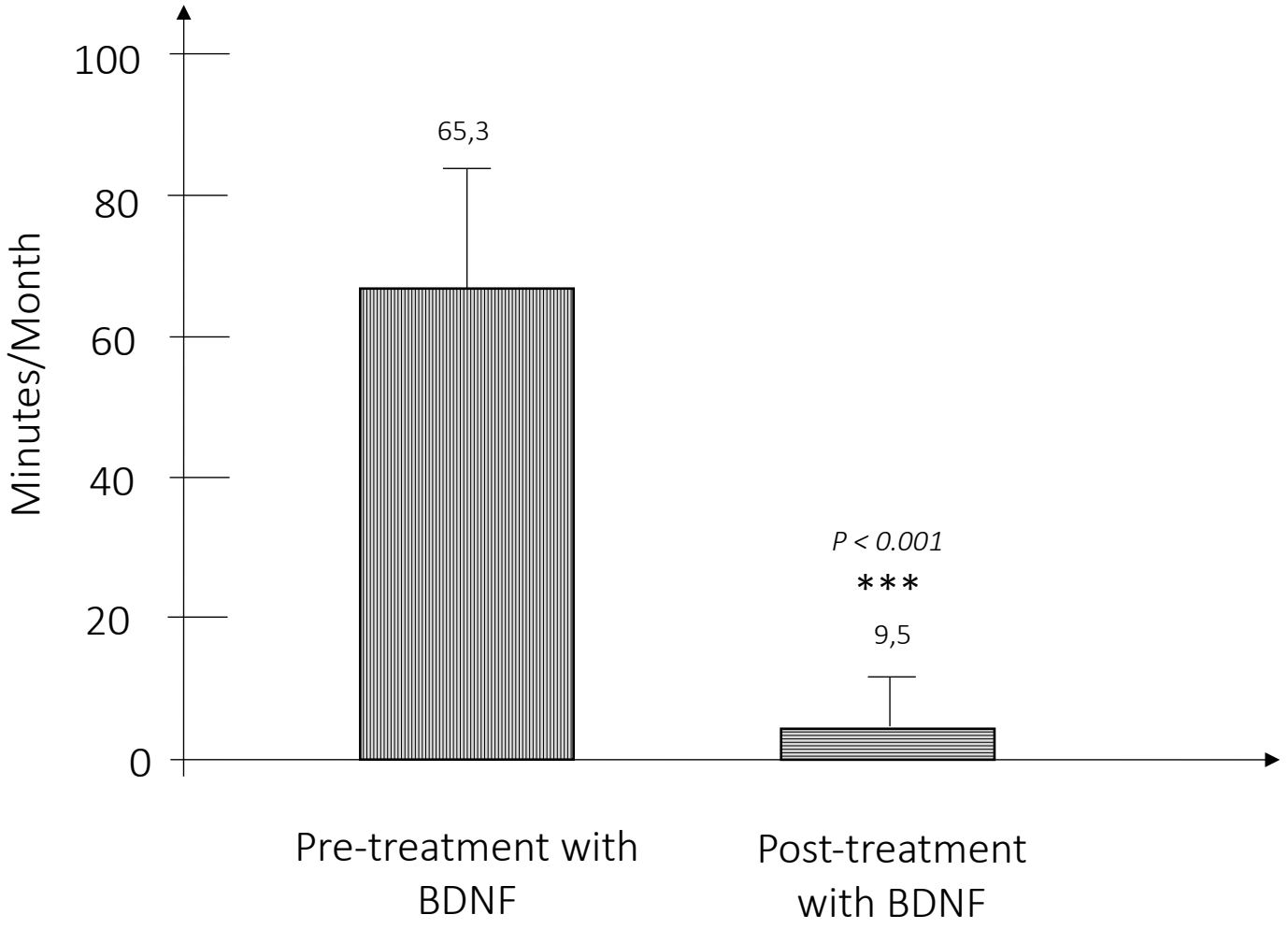
Paroxysmal Atrial Fibrillation

- No structural signs of heart disease
- Not pharmacological treatments suspended

Evaluation of:

- Minutes per month
- Symptoms
- Dynamic ECG (sec. Holter)
- Loop recorder
- PM ICD implanted

Minutes per month



	MINUTES PER MONTH	
	Pre-treatment with BDNF	Post-treatment with BDNF
S1	10	0
S2	45	0
S3	120	2
S4	12	2
S5	10	2
S6	8	3
S7	50	0
S8	20	2
S9	12	2
S10	26	3
S11	260	10
S12	120	2
S13	38	3
S14	14	0
S15	20	0
S16	12	0
S17	250	25
S18	60	3
S19	110	80
S20	60	50
S21	80	20
S22	100	0

Les liaisons dangereous

Published in final edited form as:
Neuropharmacology. 2016 March ; 102: 72–79. doi:10.1016/j.neuropharm.2015.10.034.

BDNF — a key transducer of antidepressant effects

Carl Björkholm[a] and **Lisa M. Monteggia**[b,*]

[a] Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

[b] Department of Neuroscience, University of Texas Southwestern Medical Center, Dallas, TX, USA

Neuroscience and Biobehavioral Reviews 43 (2014) 35–47

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

The serotonin–BDNF duo: Developmental implications for the vulnerability to psychopathology

Judith Regina Homberg[a], Raffaella Molteni[b], Francesca Calabrese[b], Marco A. Riva[b,*]

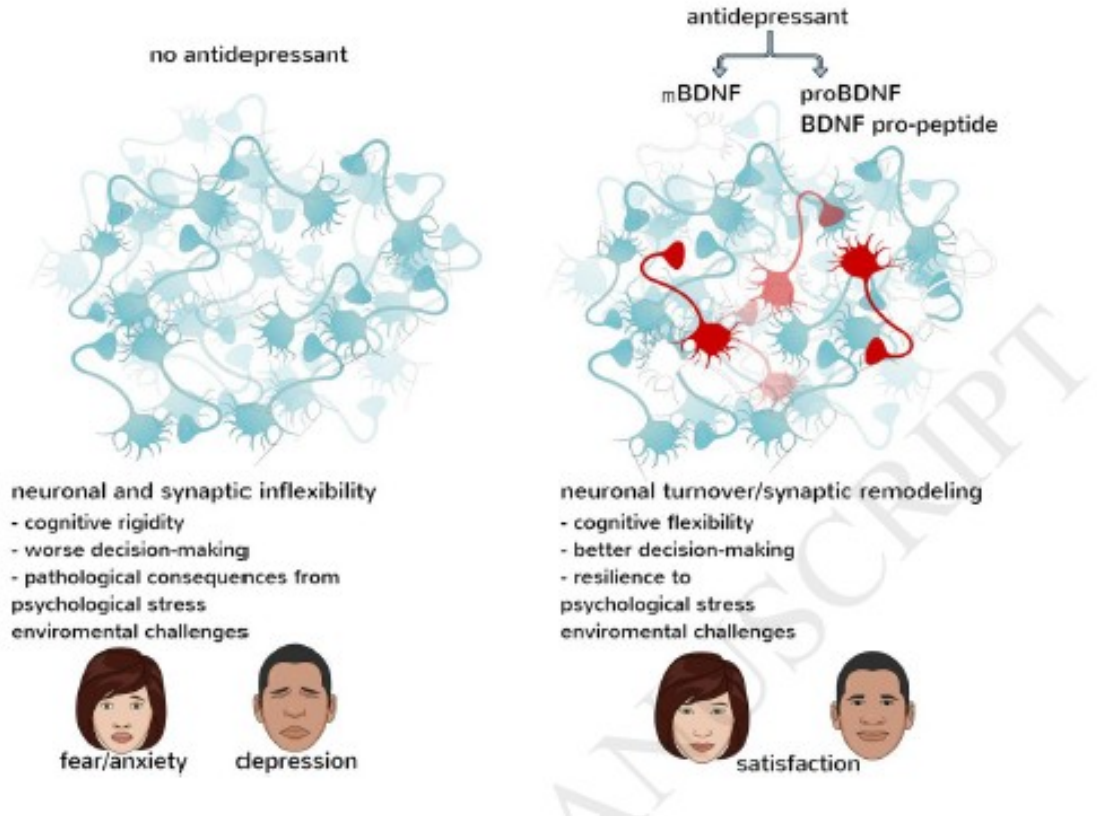
[a] *Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Nijmegen Medical Centre, Geert Grooteplein 21, 6525 EZ Nijmegen, The Netherlands*
[b] *Department of Pharmacological and Biomolecular Sciences, University of Milan, Via Balzaretti 9, 20133 Milan, Italy*

BDNF is a key transducer of antidepressant effects

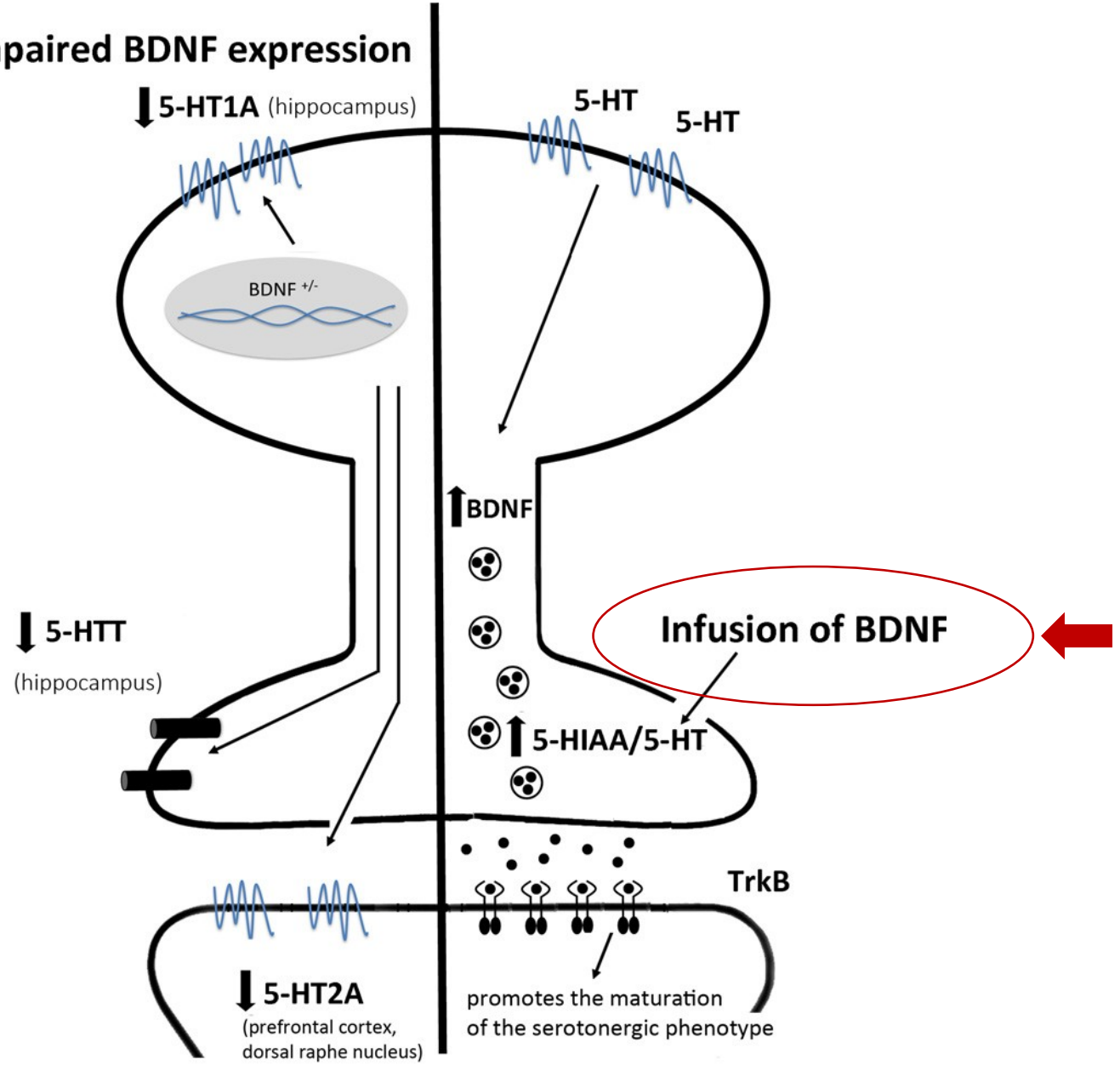
SSRIs

Ketamine

→ BDNF mRNA ↑ → BDNF ↑ → BDNF/TrkB interaction ↑ → Improved neuronal and astrocytes plasticity



- *Arumugam V, John VS, Augustine N, Jacob T, Joy SM, Sen S, Sen T. The impact of antidepressant treatment on brain-derived neurotrophic factor level: An evidence-based approach through systematic review and meta-analysis. Indian J Pharmacol. 2017 May-Jun;49(3):236-242. doi: 10.4103/ijp.IJP_700_16. PMID: 29033483; PMCID: PMC5637134.*
- *Diniz CRAF, Casarotto PC, Resstel L, Joca SRL. Beyond good and evil: A putative continuum-sorting hypothesis for the functional role of proBDNF/BDNF-propeptide/mBDNF in antidepressant treatment. Neurosci Biobehav Rev. 2018 Jul;90:70-83. doi: 10.1016/j.neubiorev.2018.04.001. Epub 2018 Apr 4. PMID: 29626490*
- *Björkholm C, Monteggia LM. BDNF - a key transducer of antidepressant effects. Neuropharmacology. 2016 Mar;102:72-9. doi: 10.1016/j.neuropharm.2015.10.034. Epub 2015 Nov 11. PMID: 26519901; PMCID: PMC4763983*



Schematic representation of BDNF effects on the serotonergic system. As shown in the left side of the figure, impaired expression of the neurotrophin, as occurring in BDNF transgenic mice, results in reduced hippocampal function of 5-HT1A and 5-HTT as well as in 5-HT2A receptor defects within the prefrontal cortex and the dorsal raphe nucleus.

Conversely, as depicted in right side of the figure, **infusion of BDNF leads to enhanced 5HIAA/5-HT ratio and stimulates the maturation of the serotonergic phenotype.**

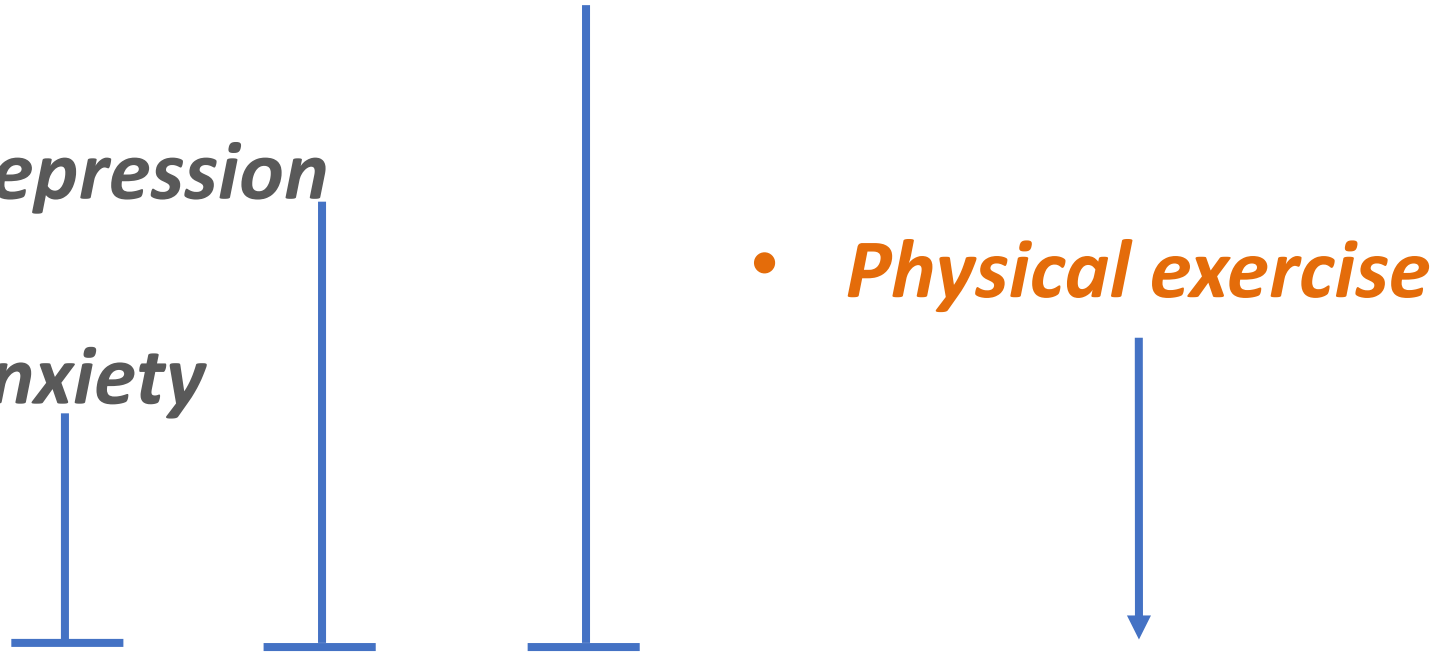
Homberg JR, Molteni R, Calabrese F, Riva MA. The serotonin-BDNF duo: developmental implications for the vulnerability to psychopathology. Neurosci Biobehav Rev. 2014 Jun;43:35-47. doi: 10.1016/j.neubiorev.2014.03.012. Epub 2014 Apr 3. PMID: 24704572

5-HTT: 5-HT transporter; 5-HIAA: 5-hydroxyindoleacetic acid – catabolite urinario della serotonina; TrkB: tropomyosin related kinase B.

BDNF nella muscolatura scheletrica

funzioni biologiche
e
potenziali campi di applicazione in
Odontoiatria Geriatrica

- *Acute intermittent stress*
- *Depression*
- *Anxiety*
- *Physical exercise*



BDNF codifying mRNA

BDNF 1-7 transcription factors

Miochine: citochine prodotte dal muscolo, la cui concentrazione varia in rapporto all'intensità della contrazione muscolare (esercizio).

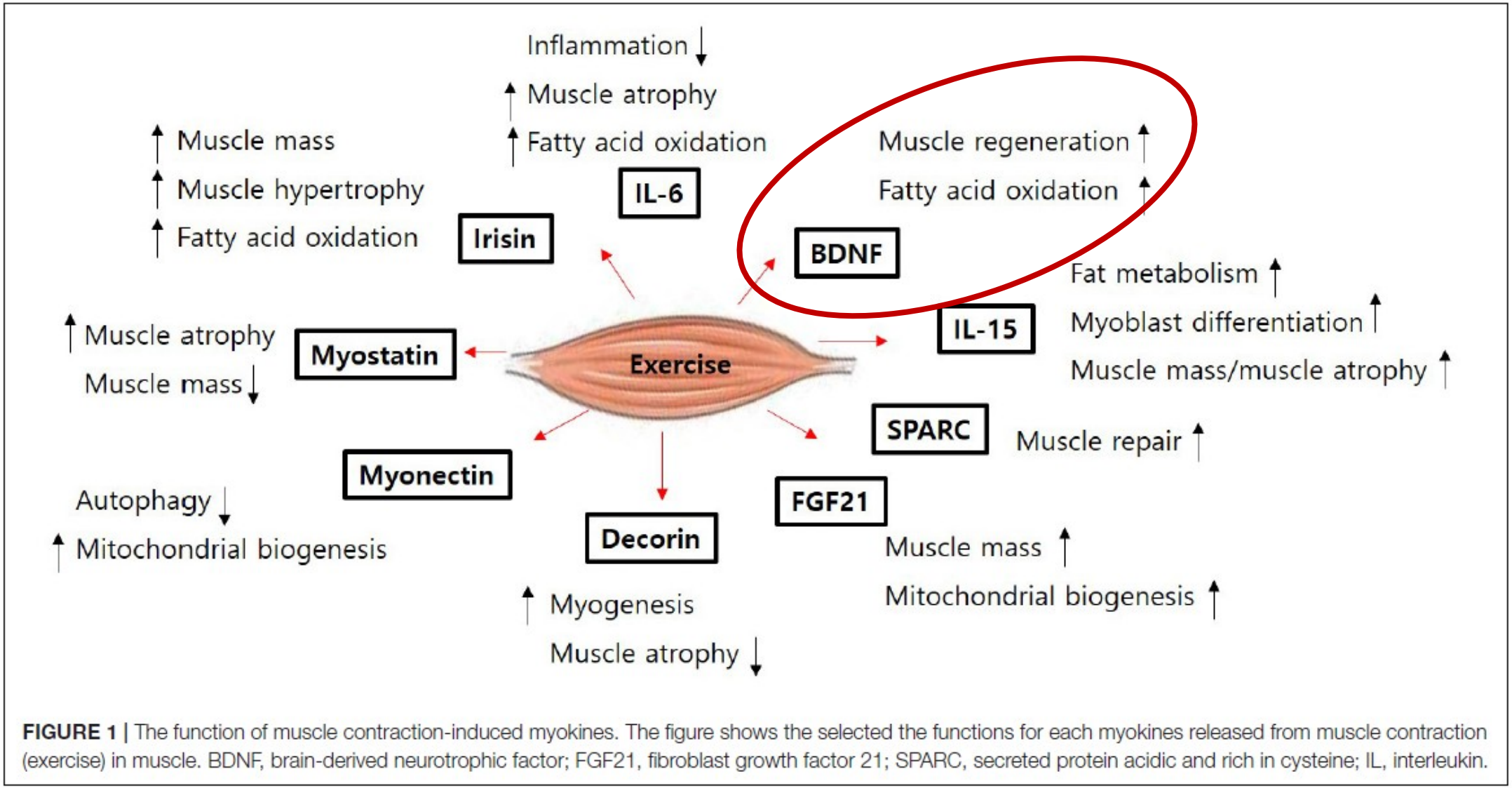
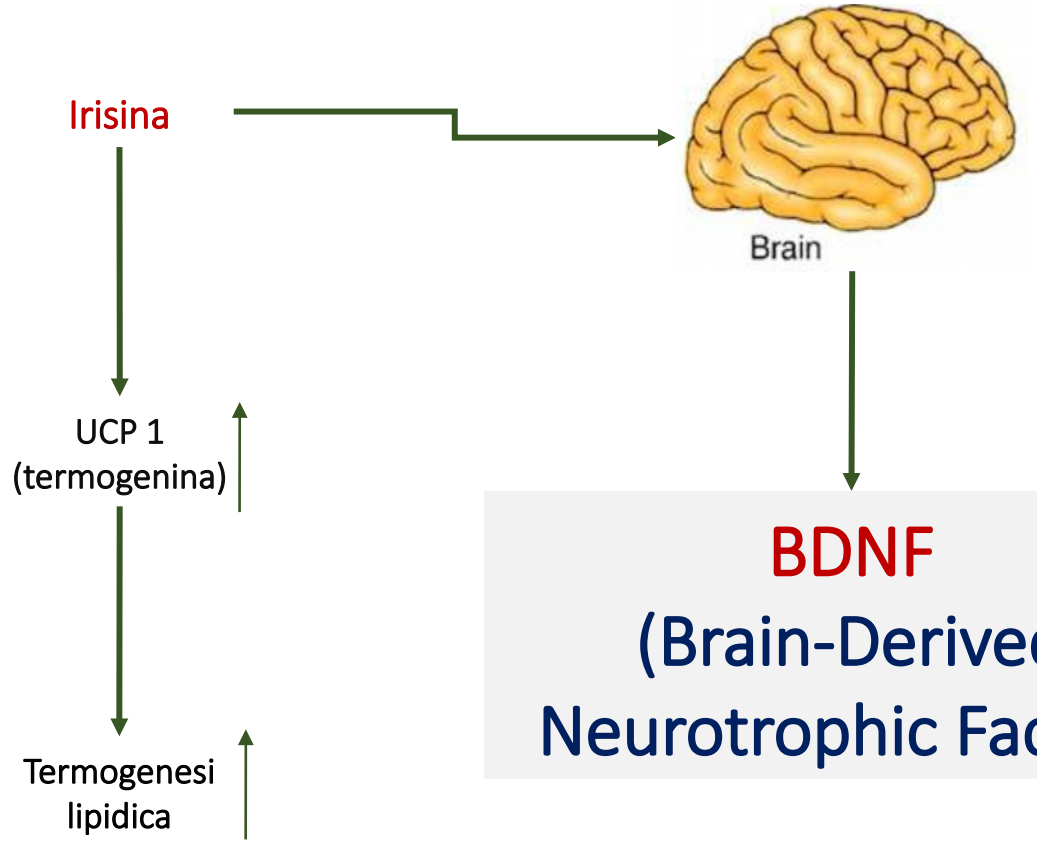


FIGURE 1 | The function of muscle contraction-induced myokines. The figure shows the selected the functions for each myokines released from muscle contraction (exercise) in muscle. BDNF, brain-derived neurotrophic factor; FGF21, fibroblast growth factor 21; SPARC, secreted protein acidic and rich in cysteine; IL, interleukin.

Lee JH, Jun HS. Role of Myokines in Regulating Skeletal Muscle Mass and Function. Front Physiol. 2019;10:42. Published 2019 Jan 30. doi:10.3389/fphys.2019.00042

Miochine ed esercizio muscolare



L'**irisina** è un ormone, identificato dai ricercatori della Harvard Medical School, che può replicare alcuni degli effetti positivi dell'attività fisica e della dieta[1][2][3]. Prodotta in grande quantità dal tessuto muscolare umano durante le attività sportive, la molecola è in grado di operare il meccanismo molecolare detto "browning", ovvero di conversione della cellula adiposa bianca in cellula adiposa bruna

- *Pedersen BK. Physical activity and muscle-brain crosstalk. Nat Rev Endocrinol. 2019;15(7):383-392. doi:10.1038/s41574-019-0174-x*
- *Jang C, Obeyesekere VR, Dilley RJ, Alford FP, Inder WJ. 11Beta hydroxysteroid dehydrogenase type 1 is expressed and is biologically active in human skeletal muscle. Clin Endocrinol (Oxf). 2006;65(6):800-805. doi:10.1111/j.1365-2265.2006.02669.x*

BDNF, differenziazione delle fibre muscolari e la sarcopenia nell'anziano

Muscle BDNF loss or gain of function is sufficient to decrease or increase, respectively, the proportion of type IIB muscle fibers along with a broad range of oxidative and glycolytic marker genes.

REVIEW ARTICLE

MCBS
Mol Cell Biomed Sci. 2018; 2(2): 38-47
DOI: 10.21705/mcbs.v2i2.32

Myokine Regulation as Marker of Sarcopenia in Elderly

I Gusti Putu Suka Aryana, Anak Agung Ayu Ratih Hapsari, Raden Ayu Tuty Kuswardhani

Geriatric Division, Internal Medicine Department, Faculty of Medicine, Udayana University, Sanglah Teaching Hospital, Denpasar, Indonesia

Delezie J, Weihrauch M, Maier G, et al. BDNF is a mediator of glycolytic fiber-type specification in mouse skeletal muscle. Proc Natl Acad Sci U S A. 2019;116(32):16111-16120. doi:10.1073/pnas.1900544116

Growth Factors and SKIN AGING

- *EGF is involved in the regulation of the growth and differentiation of bulge cells.*
- *PDGFs manages the interaction arising between the bulge and associated tissue during follicle morphogenesis.*

*Location of **hair bulge**, which is a stem cell reserve involved in hair regeneration phase.*

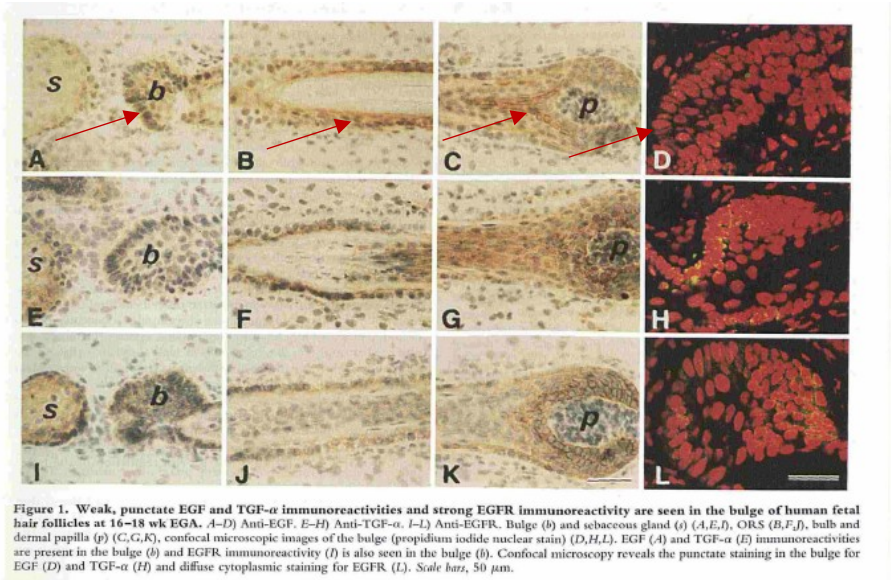


Figure 1. Weak, punctate EGF and TGF-α immunoreactivities and strong EGFR immunoreactivity are seen in the bulge of human fetal hair follicles at 16–18 wk EGA. *A–D*) Anti-EGF. *E–H*) Anti-TGF-α. *I–L*) Anti-EGFR. Bulge (*b*) and sebaceous gland (*s*) (*A,E,I*), ORS (*B,F,J*), bulb and dermal papilla (*p*) (*C,G,K*), confocal microscopic images of the bulge (propidium iodide nuclear stain) (*D,H,L*). EGF (*A*) and TGF-α (*E*) immunoreactivities are present in the bulge (*b*) and EGFR immunoreactivity (*I*) is also seen in the bulge (*b*). Confocal microscopy reveals the punctate staining in the bulge for EGF (*D*) and TGF-α (*H*) and diffuse cytoplasmic staining for EGFR (*L*). *Scale bars*, 50 μm.

EGFR expression at hair bulge level (red arrows)

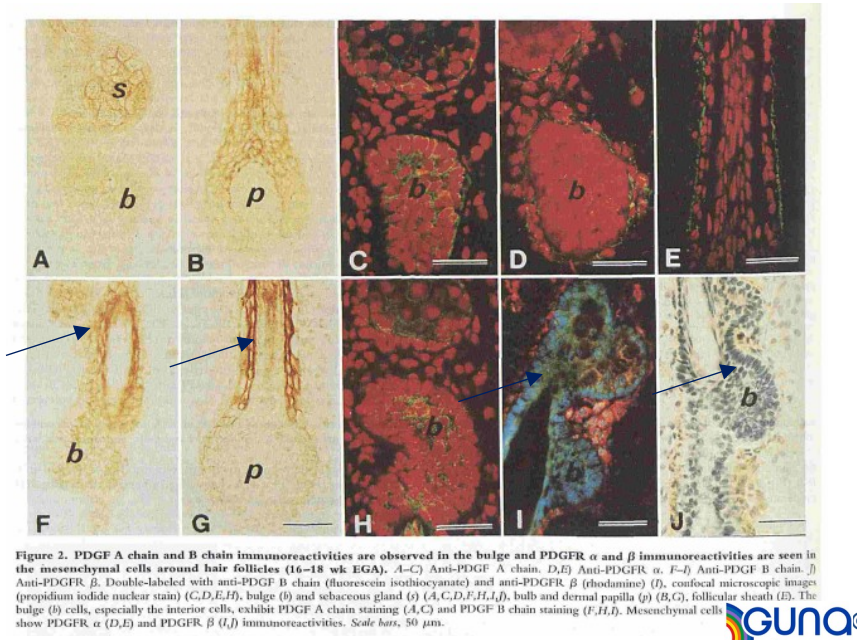


Figure 2. PDGF A chain and B chain immunoreactivities are observed in the bulge and PDGFR α and β immunoreactivities are seen in the mesenchymal cells around hair follicles (16–18 wk EGA). *A–C*) Anti-PDGF A chain. *D,E*) Anti-PDGFR α. *F–I*) Anti-PDGF B chain. *J*) Anti-PDGFR β. Double-labeled with anti-PDGF B chain (fluorescein isothiocyanate) and anti-PDGFR β (rhodamine) (*I*), confocal microscopic images (propidium iodide nuclear stain) (*C,D,E,H*), bulge (*b*) and sebaceous gland (*s*) (*A,C,D,F,H,I,J*), bulb and dermal papilla (*p*) (*B,G*), follicular sheath (*E*). The bulge (*b*) cells, especially the interior cells, exhibit PDGF A chain staining (*A,C*) and PDGF B chain staining (*F,H,I*). Mesenchymal cells show PDGFR α (*D,E*) and PDGFR β (*I,J*) immunoreactivities. *Scale bars*, 50 μm.

PDGFR expression at hair bulge level (blue arrows)

- *Akiyama M, Smith LT, Holbrook KA. Growth factor and growth factor receptor localization in the hair follicle bulge and associated tissue in human fetus. J Invest Dermatol. 1996 Mar;106(3):391-6.*
- *González R, Moffatt G, Hagner A, Sinha S, Shin W, Rahmani W, Chojnacki A, Biernaskie J. Platelet-derived growth factor signaling modulates adult hair follicle dermal stem cell maintenance and self-renewal. NPJ Regen Med. 2017 Apr 14;2:11.*

Directions

- **<u>For 4 consecutive months (or more):</u>**

20 drops twice a day

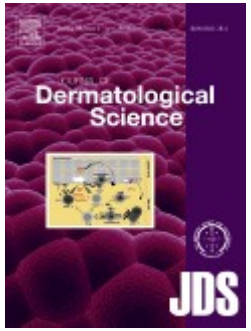
Sublingual administration directly under the tongue or in a little water, preferibly far from meals.

<u>For 4 months (or more):</u>
40 drops (of one or more products) directly in a bottle a water. Drink with little sips during the day.

PRE-CLINICAL STUDY

Ex vivo

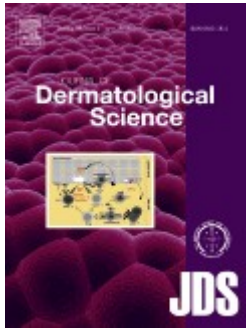
Treatment with low-dose cytokines (**IL-4, IL-10, b-FGF and β-Endorphin)** reduces oxidative-mediated injury in perilesional keratinocytes from vitiligo skin



Journal Of Dermatological Science

Reference: JDS-15-256

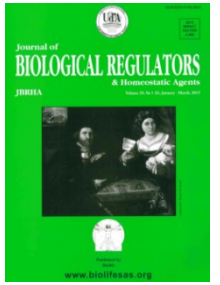
Barygina V, Becatti M, Lotti T, Moretti S, Taddei N, Fiorillo C, TREATMENT WITH LOW-DOSE CYTOKINES REDUCES OXIDATIVE-MEDIATED INJURY IN PERILESIONAL KERATINOCYTES FROM VITILIGO SKIN, *Journal of Dermatological Science (2015),* http://dx.doi.org/10.1016/j.jdermsci.2015.05.003



Victoria Barygina [1], Matteo Becatti [1], Niccolo Taddei [1], Claudia Fiorillo [1], Torello Lotti [2].

[1] Department of Biomedical, Experimental and Clinical Sciences, University of Florence, Florence, Italy. [2] Dermatology and Venereology Division, University of Rome "G.Marconi", Rome, Italy.

VITILIGO: SUCCESSFUL COMBINATION TREATMENT BASED ON ORAL LOW DOSE CYTOKINES AND DIFFERENT TOPICAL TREATMENTS

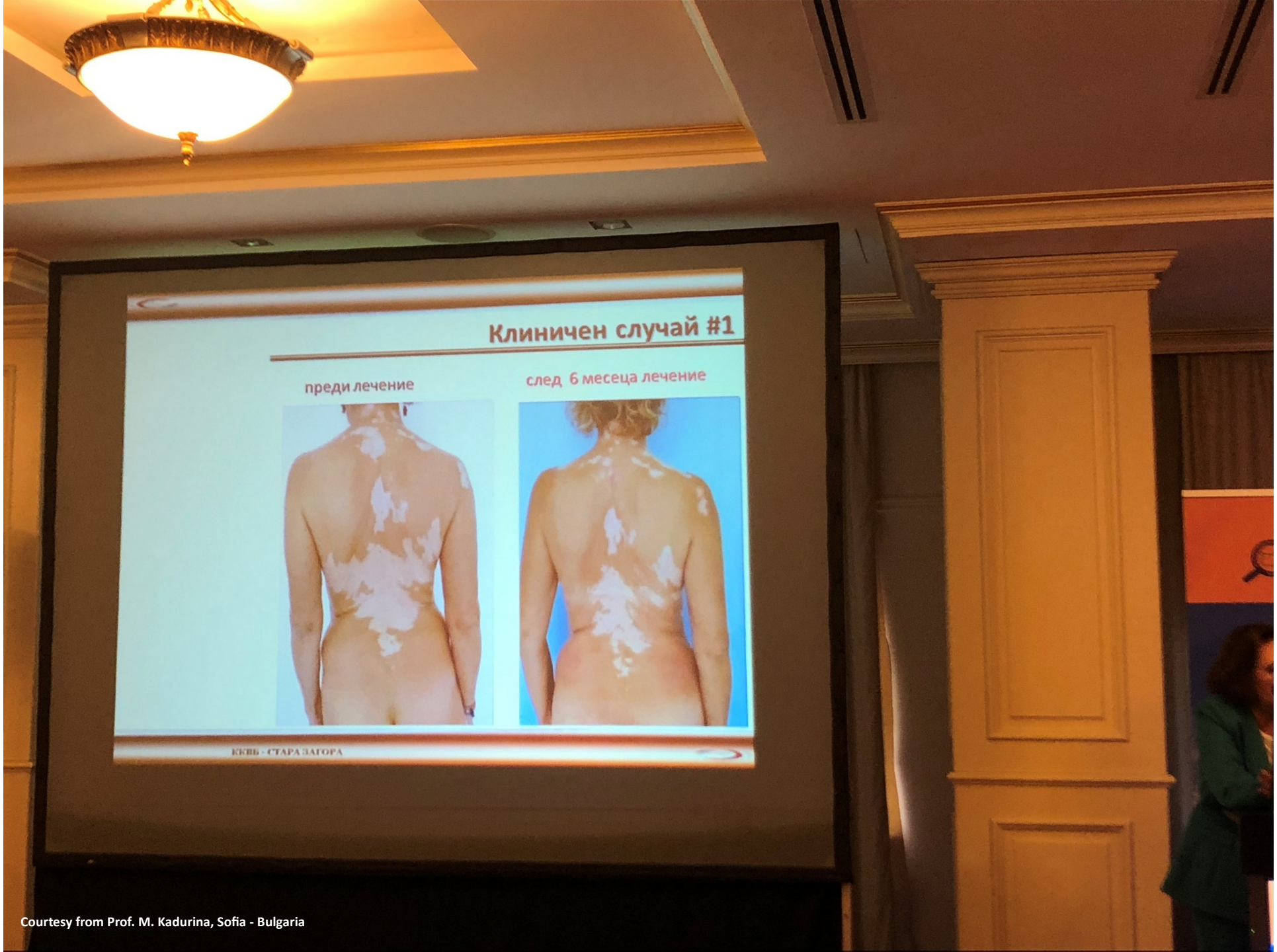


JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 29, no. 1 (S), 53-58 (2015)

VITILIGO: SUCCESSFUL COMBINATION TREATMENT BASED ON ORAL LOW DOSE CYTOKINES AND DIFFERENT TOPICAL TREATMENTS

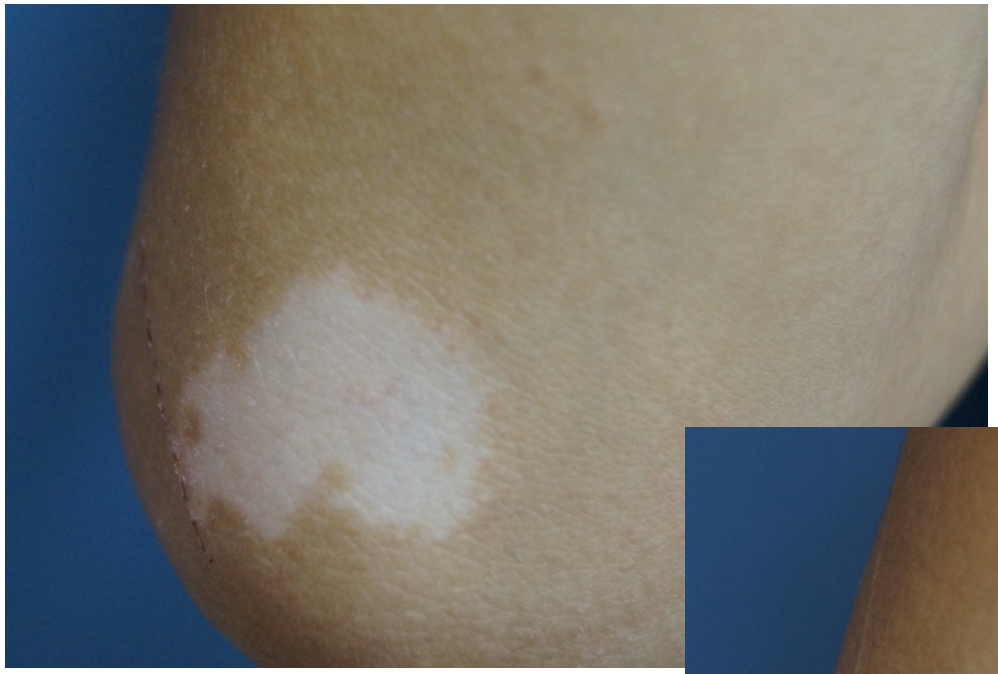
T. LOTTI[1], J HERCOGOVA[4], U. WOLLINA[5], A.A. CHOKOEVA[6], Z.ZARRAB[7], S. GIANFALDONI[8], M.G. ROCCIA[9], M. FIORANELLI[10] and G. TCHERNEV[6]

[1]Professor & Chair of Dermatology, University of Rome "G. Marconi" Rome, Italy; [2]Director Institute of Dermatology Life Cronos, Florence, Italy; [3]President World Health Academy Foundation, Zurich, Switzerland; [4]Dept. Dermatology, 2nd Medical School, Charles University, Prague, Czech Republic; [5]Department of Dermatology and Allergology, Academic Teaching Hospital Dresden-Friedrichstadt, Dresden, Germany; [6]"Onkoderma"-Policlinic for Dermatology, Venereology and Dermatologic surgery, Sofia, Bulgaria; [7]University of Rome "G. Marconi", Rome, Italy; [8]Department of dermatologic Sciences, University of Florence, Florence, Italy; [9]Chandigarh University, Punjab, India; [10]Associate Professor of Physiology, University B.I.S. Group of Institutions, Punjab Technical University, Punjab, India



Courtesy from Prof. M. Kadurina, Sofia - Bulgaria

CLINICAL RESULTS



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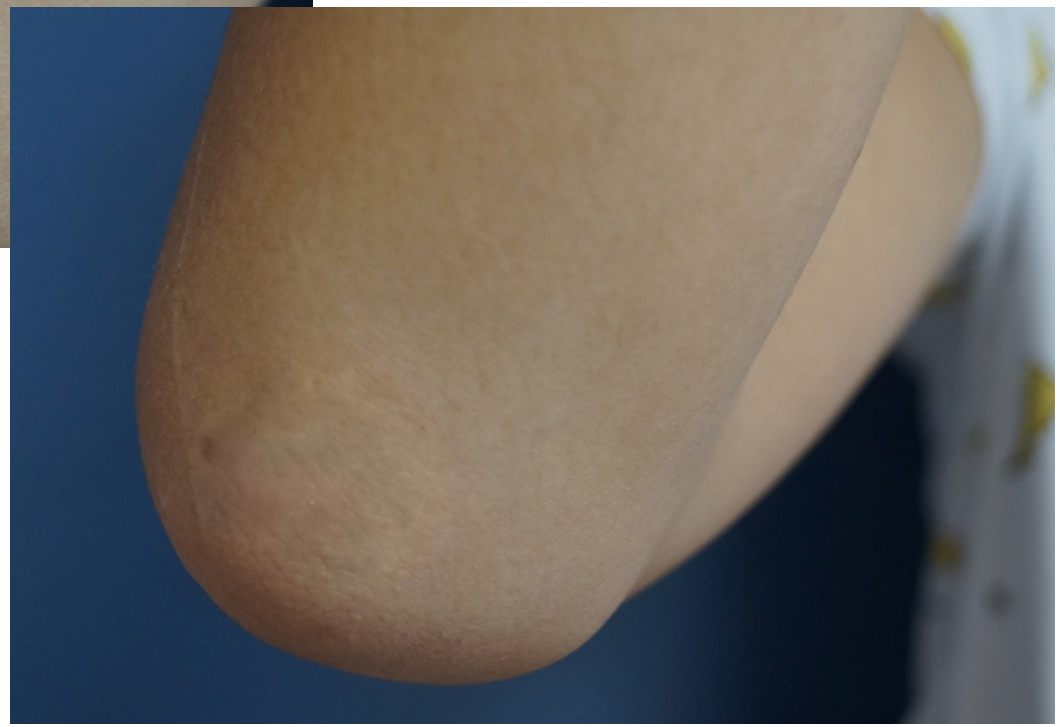

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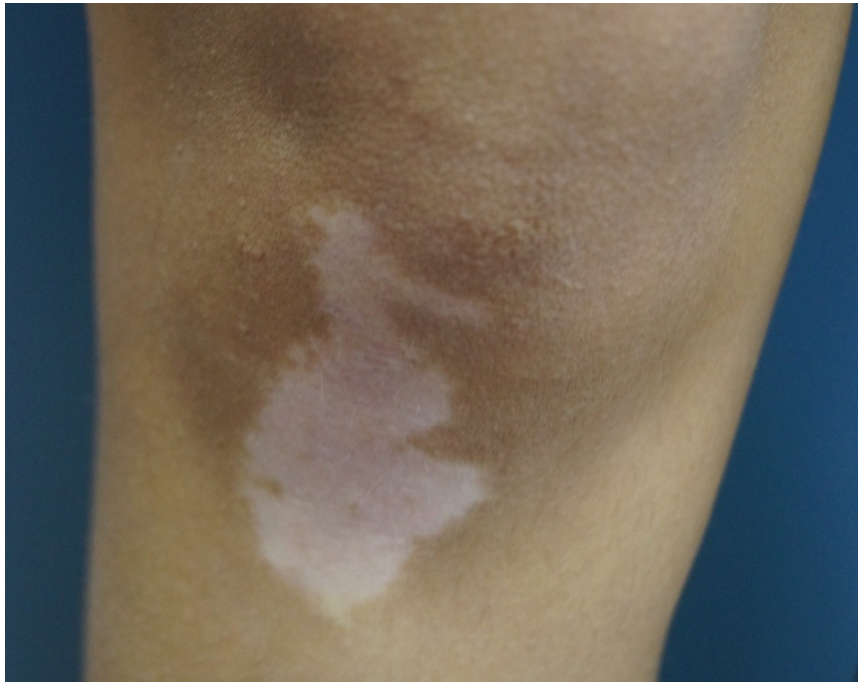
CLINICAL RESULTS



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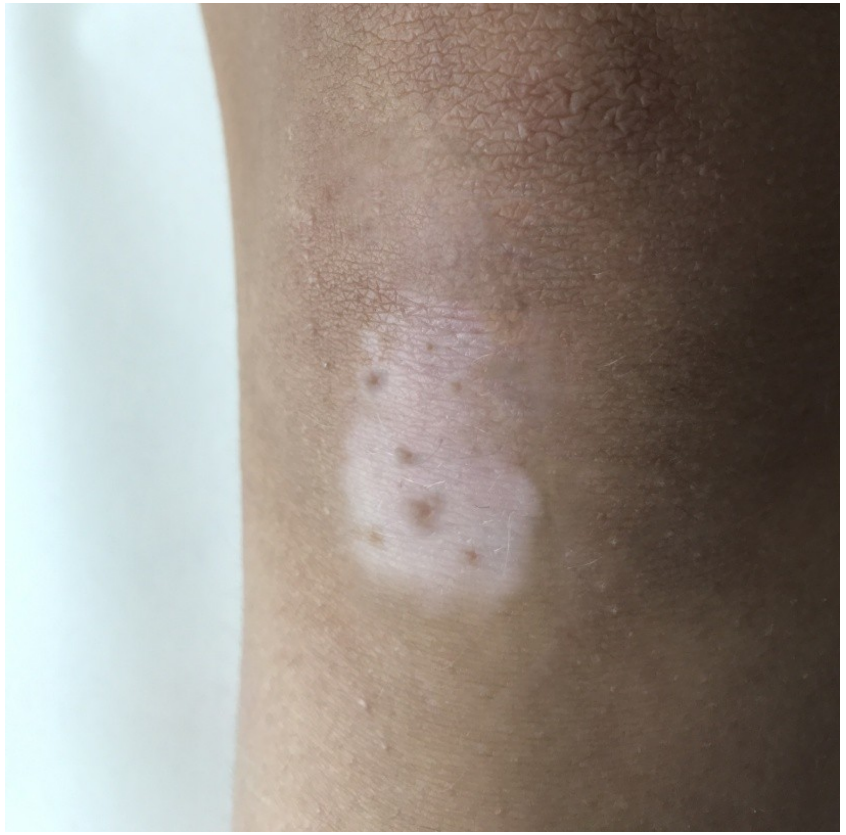

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IL-2/IL-6 RATIO AND AGING

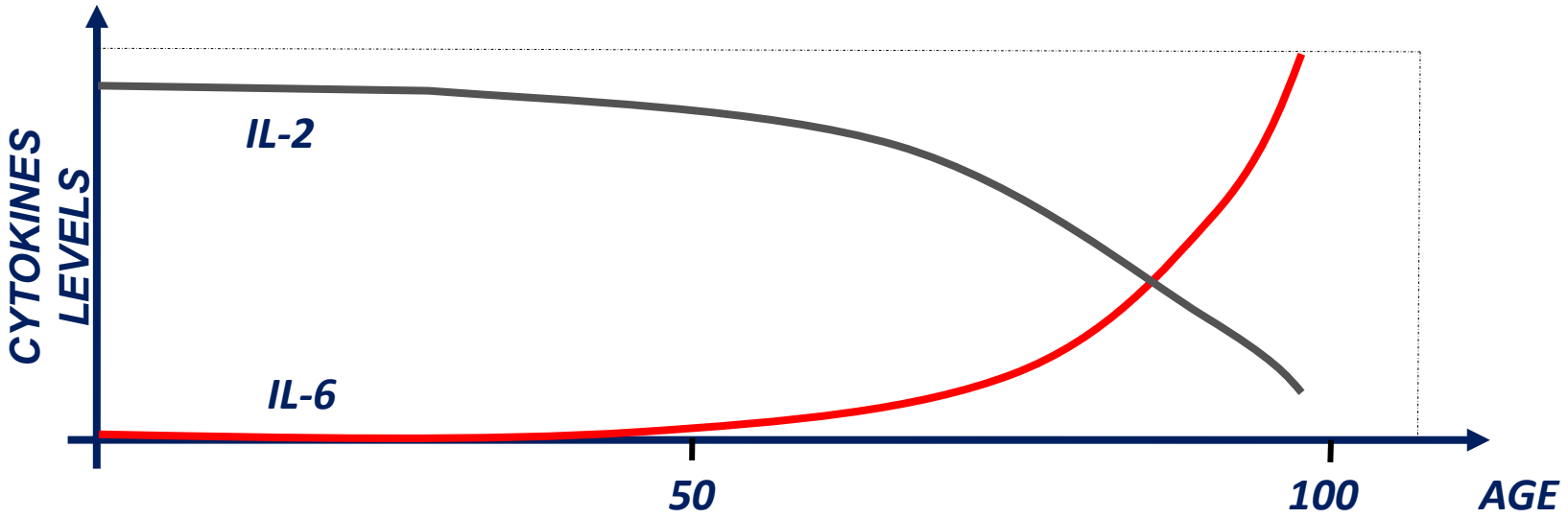
ELSEVIER

Mechanisms of Ageing and Development
100 (1998) 313–328

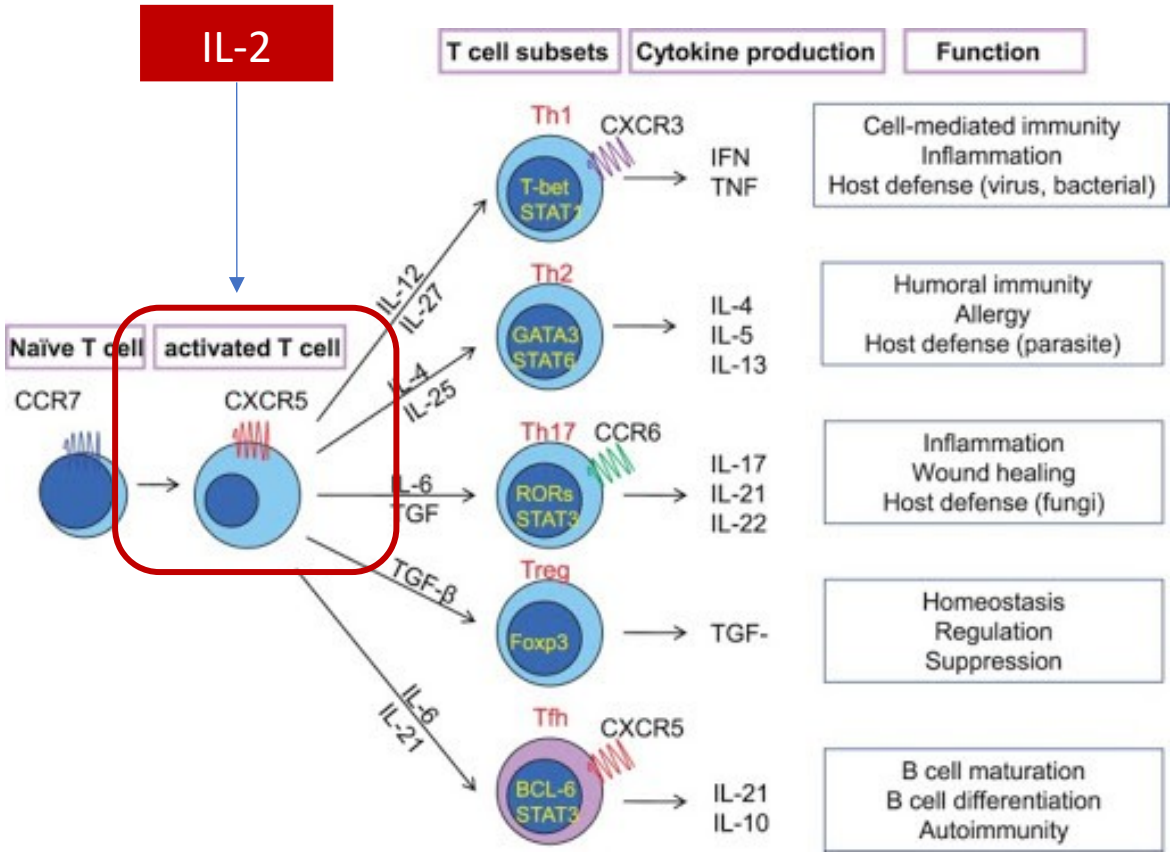
mechanisms of ageing and development

Increase of interleukin 6 and decrease of interleukin 2 production during the ageing process are influenced by the health status

Jolanta Myśliwska [a,*], Ewa Bryl [a], Jerzy Foerster [b], Andrzej Myśliwski [a]



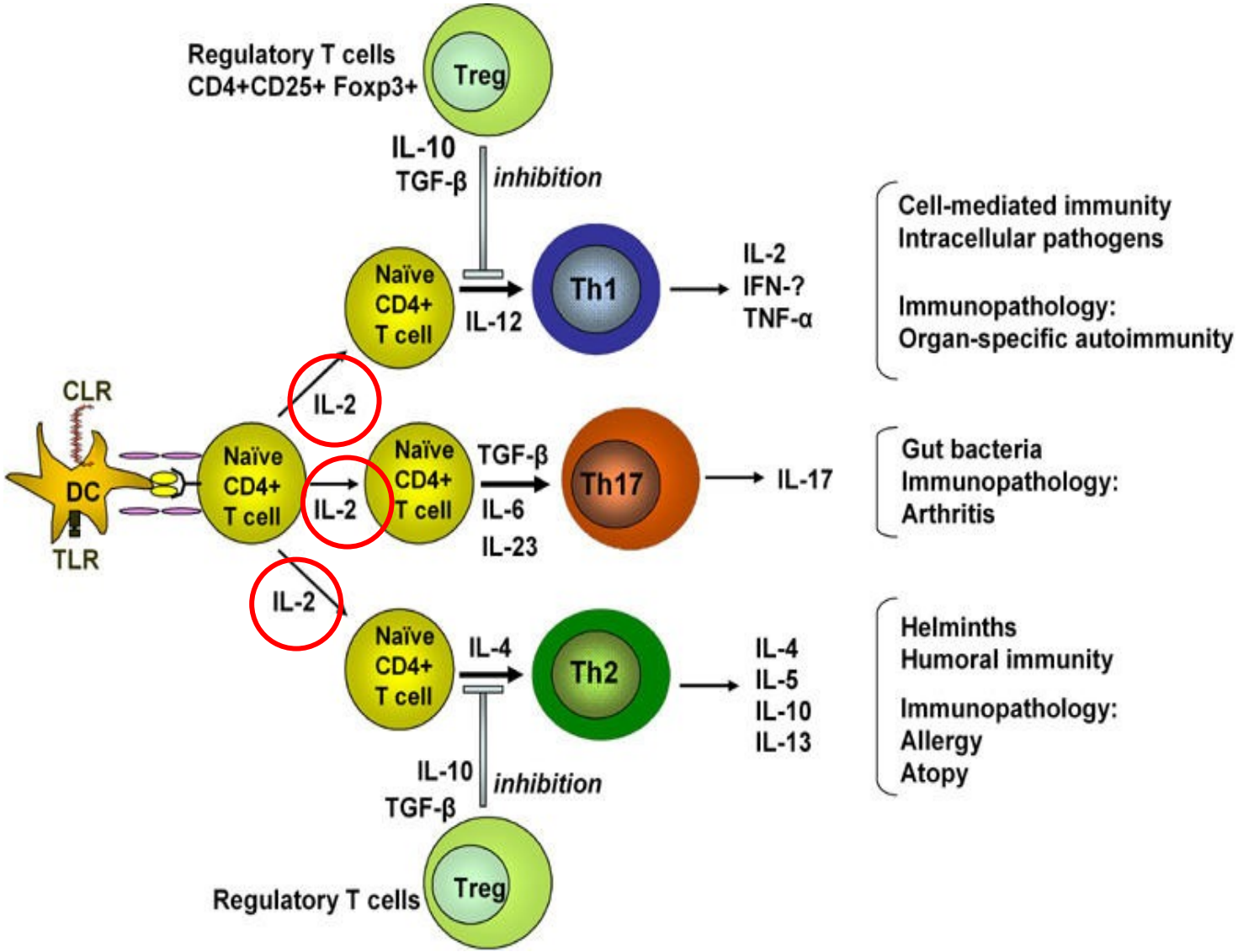
INTERLEUKIN-2 INDUCES THE CLONAL EXPANSION OF T CELLS



INTERLEUKIN-2 INDUCES THE CLONAL EXPANSION OF T CELLS

- **Interleukin-2 (IL-2)**, identified more than 40 years ago, **was initially called T Cell Growth Factor**; it induces the T cells to enter the S phase of the cell cycle, favoring their **expansion**. From the outset, its fundamental role in the management of the immune response and the pharmacological potential associated with it was evident.

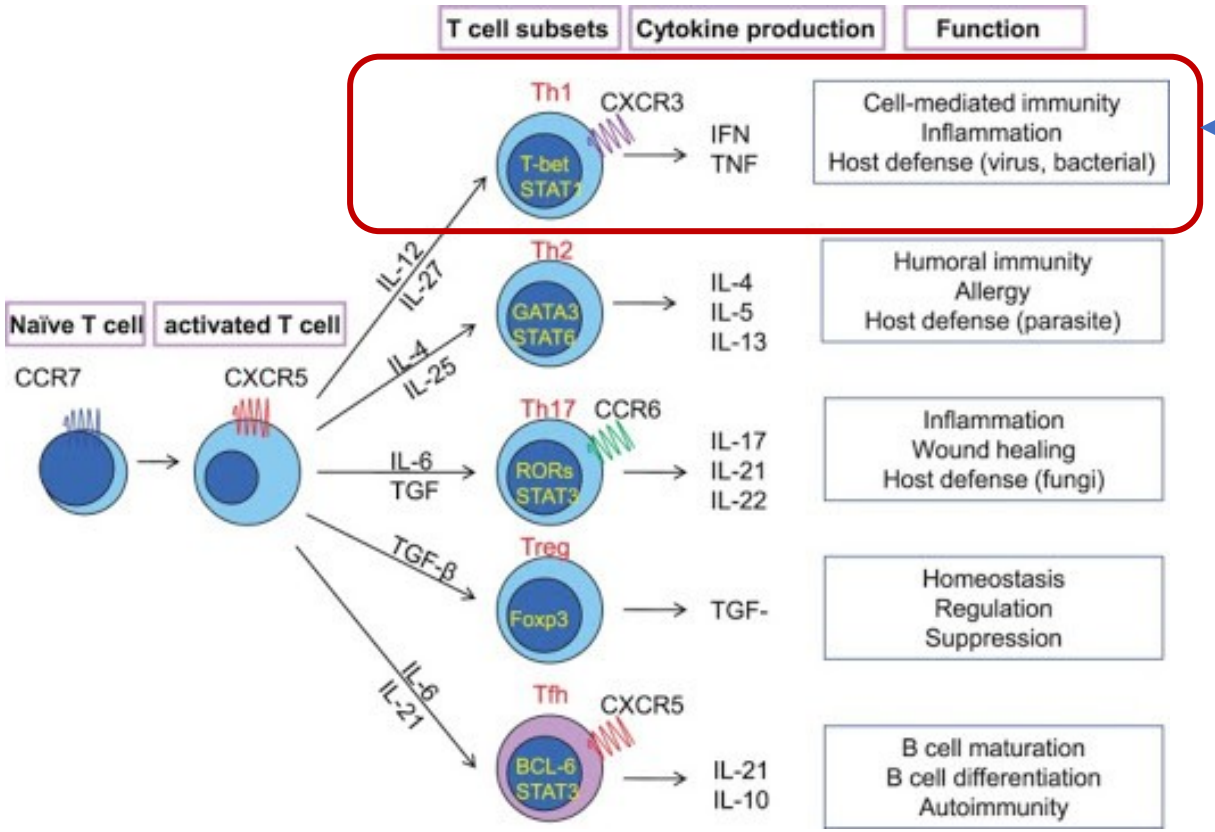
- **IL-2** is produced by activated T cells and has a key role in triggering immune responses. **The main effect of IL-2 is to induce the clonal expansion of T cells after antigen recognition; moreover, IL-2 induces the proliferation of activated B cells, increases the levels of Natural Killer (NK) cells, supports cytotoxicity mediated by T cells (CTL - Cytotoxic T-lymphocytes), stimulates the production of other cytokines including TNF, IFN-γ and GM-CSF.**



Antigen presentation to naïve T cells results in the development of Th1, Th2 or Th17 cells depending on the cytokine milieu.

From: **The Review of Diabetic Studies (2006) 3:72-75**

INTERFERON-γ ACTIVATES CD8+ IN T CYTOTOXIC CELLS



IFN-γ

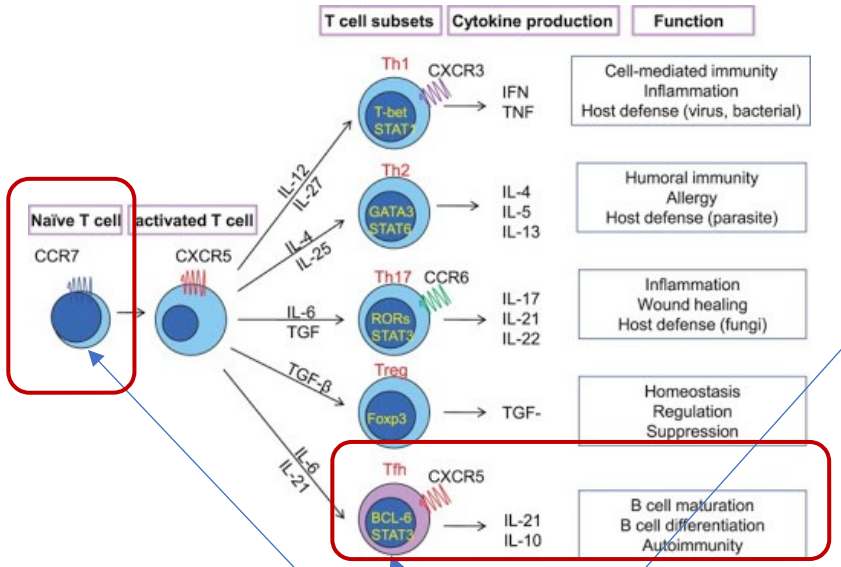
INTERFERON-γ AND α ARE PARTICULARLY ACTIVE IN THE ONSET OF THE CYTOLITIC RESPONS

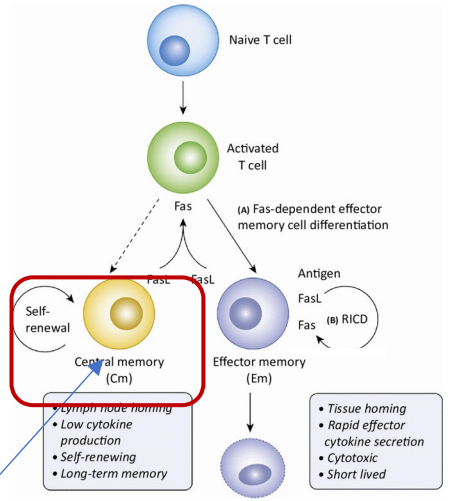
- IFN-γ can activate a cell-mediated immune response (IFN-γ stimulates CD8 + to differentiate into cytotoxic T effector cells) ideal against viruses. The Tc, in fact, operate the non-specific cytolysis of the cell infected with the virus (the Natural Killer- NK cells- instead, operate the specific cytolysis).

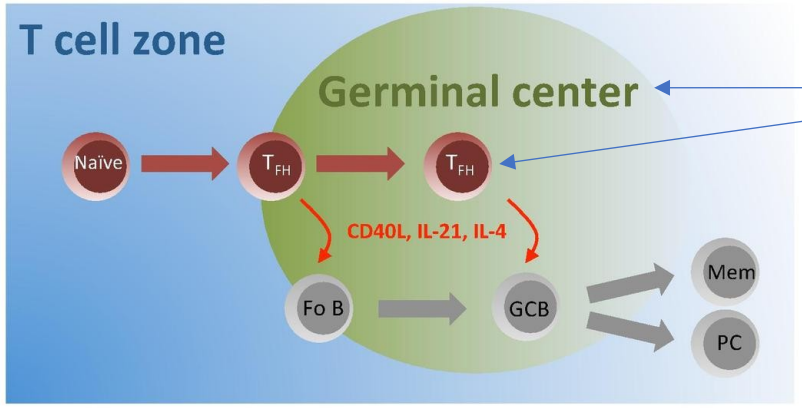
- Interferon-α (in some papers alpha seems to be favored over gamma; it is interesting how Interferon-α prevents the virus from penetrating through the viropexy mechanism, used by many viruses, into the cells not yet infected

[IFN-γ is also used by the body for the synthesis (conversion) into IFN-α (it is a bit like the mechanism of reciprocity between hormone T4 and T3, where T4 is the precursor of the hormone T3, true effector of the activity thyroid]

INTERLEUKIN-7 PLAYS IN SEVERAL T CELLS LIFE STAGES







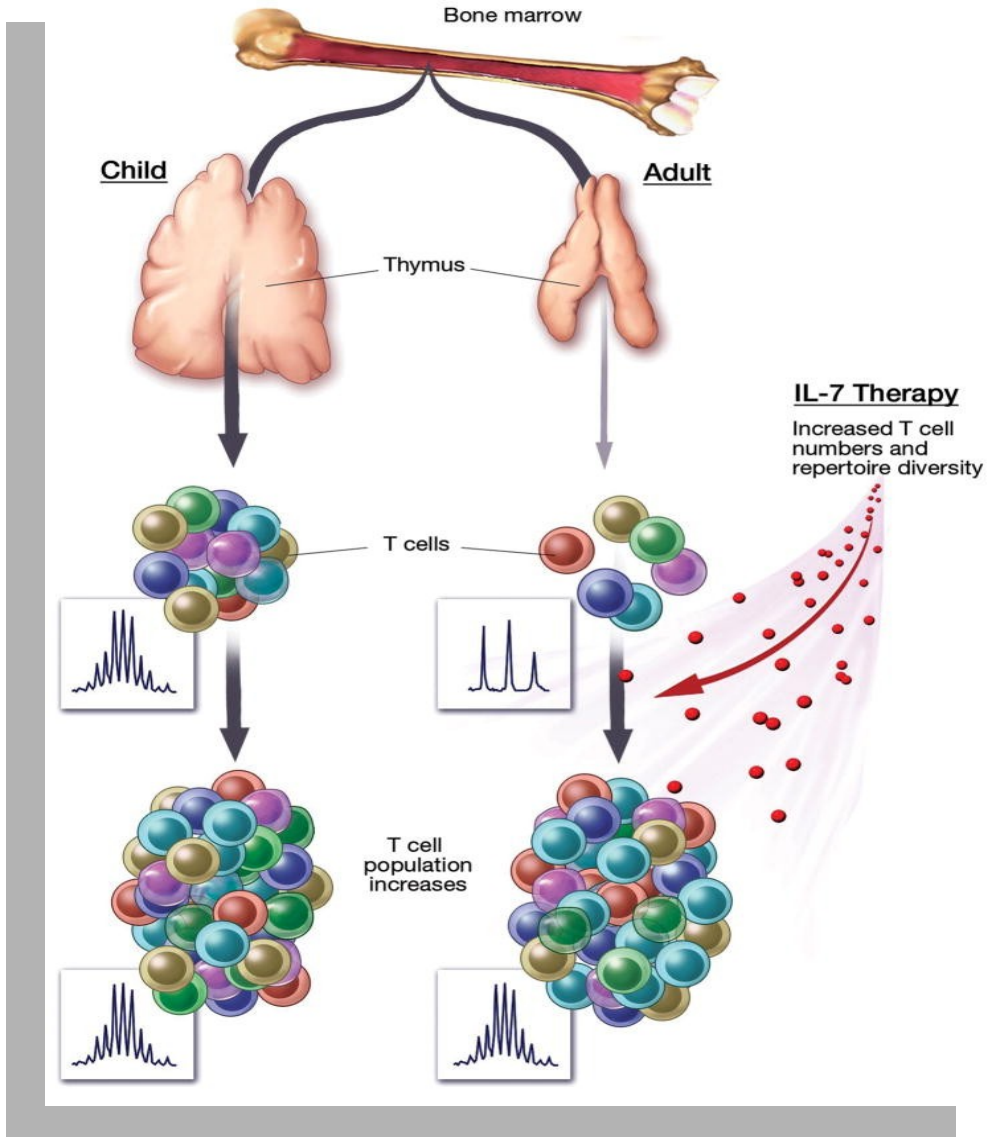
IL-7

IL-7: PLAYS IN SEVERAL T CELLS LIFE STAGES

- Induces **CD4+ naïve T cells proliferation** before activation (T cells ready for antigen presentation by dendritic cells).
- Induces **Thf cells proliferation**, critical for B cells activation in the lymph nodes.
- **Induces T memory cells (main players in infections driven by antigen representation).**

TO NOTE – In the adults, the Thymus is partially atrophic (immune-decline), thus T cells production is slower than that of babies-teenagers, because it needs different extra-thymic production systems (HPE - *Homeostatic Peripheral Expansion*).

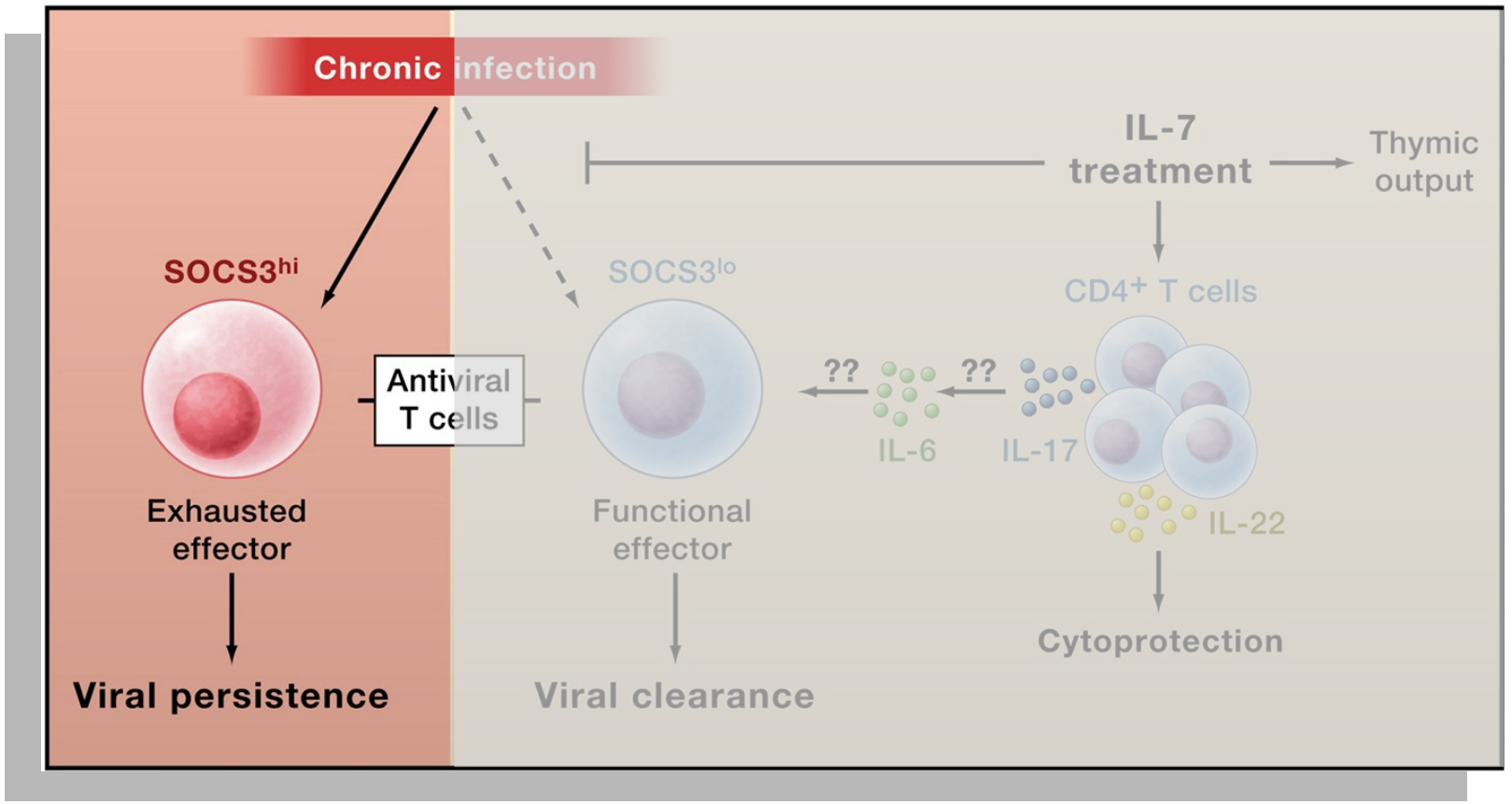
INTERLEUKIN-7 INCREASES THE NUMBER OF T LYMPHOCYTES



A THYMUS-INDIPENDENT MECHANISM
(which is active in adult and elderly subjects)

Homeostatic Peripheral Expansion

INTERLEUKIN-7 INCREASES THE NUMBER OF T LYMPHOCYTES



- Socs3 is upregulated in T cells during chronic active viral infection in mice
- Deletion of socs3 in T cells prevents immune failure and promotes viral clearance
- In vivo IL-7 therapy represses Socs3 in T cells and clears chronic infection
- IL-7 promotes IL-22 production to mitigate immunopathology in chronic infection

Parish IA, Kaech SM. IL-7 knocks the socs off chronic viral infection. *Cell*. 2011;144(4):467-468. doi:10.1016/j.cell.2011.01.038

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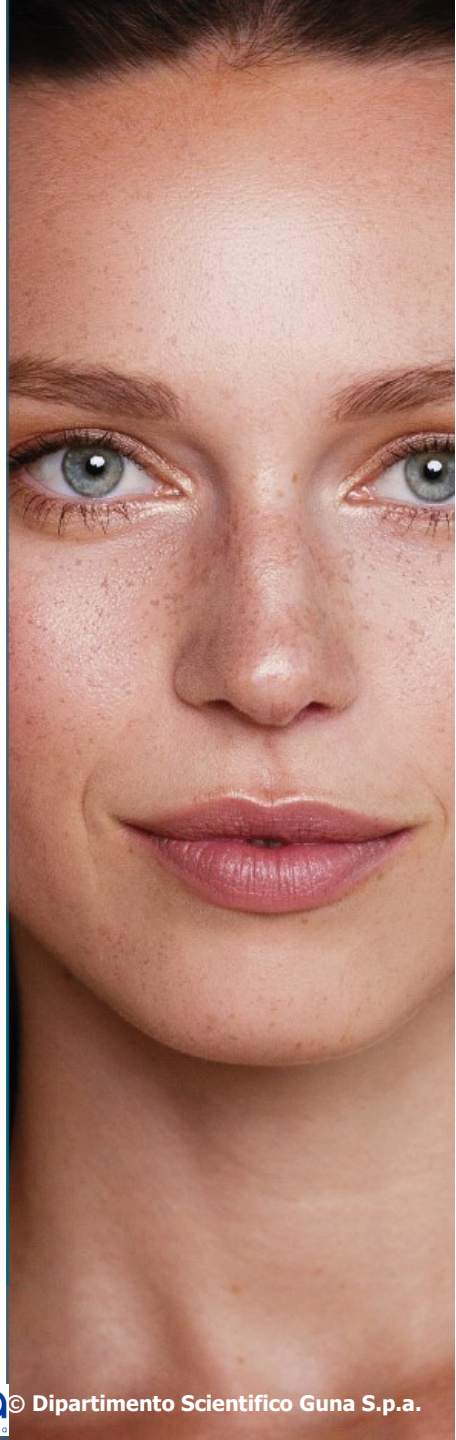

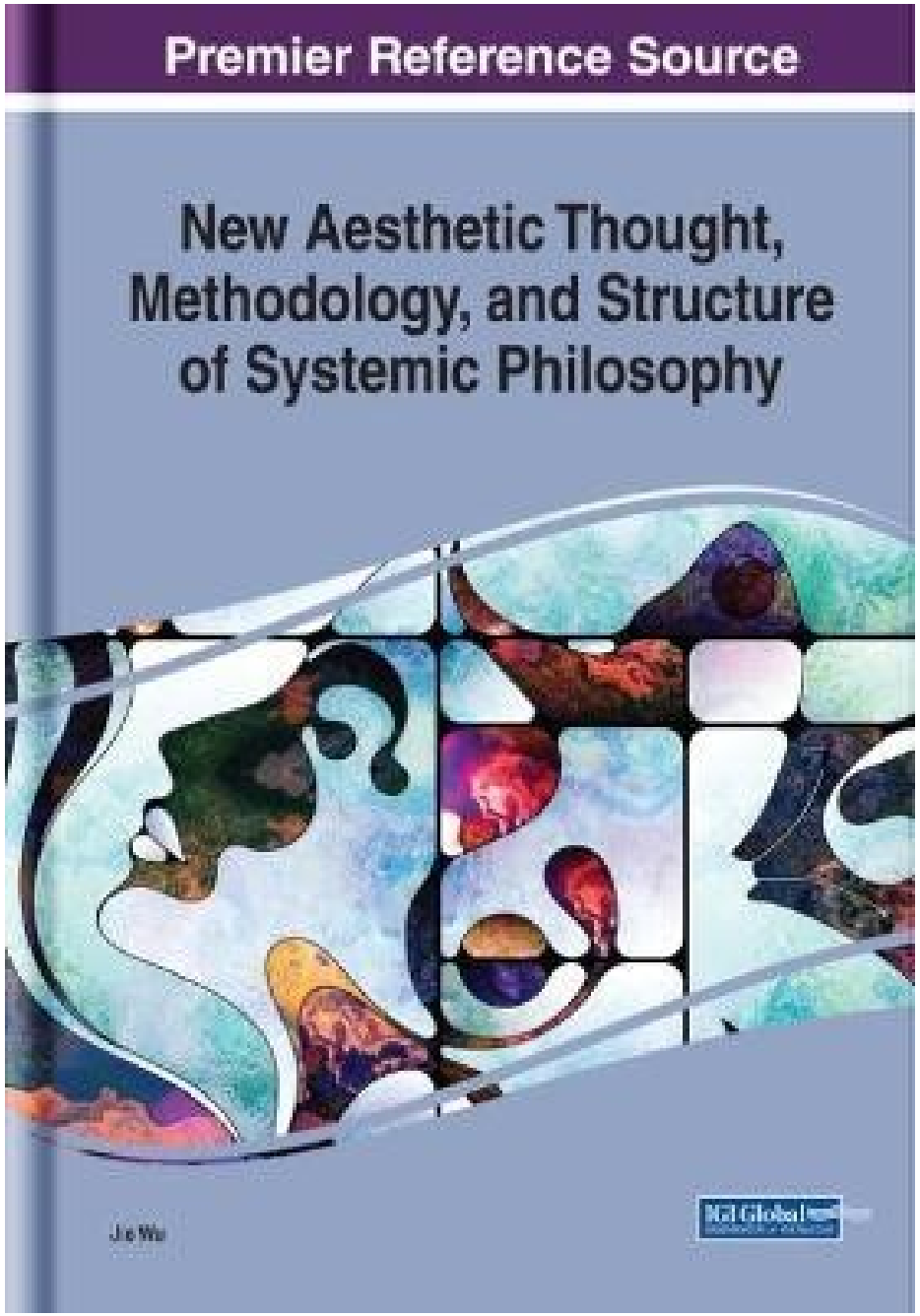

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