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.

ALLA RICERCA DEL RESPIRO PERDUTO

Approccio multilaterale e integrato per la prevenzione ed il benessere

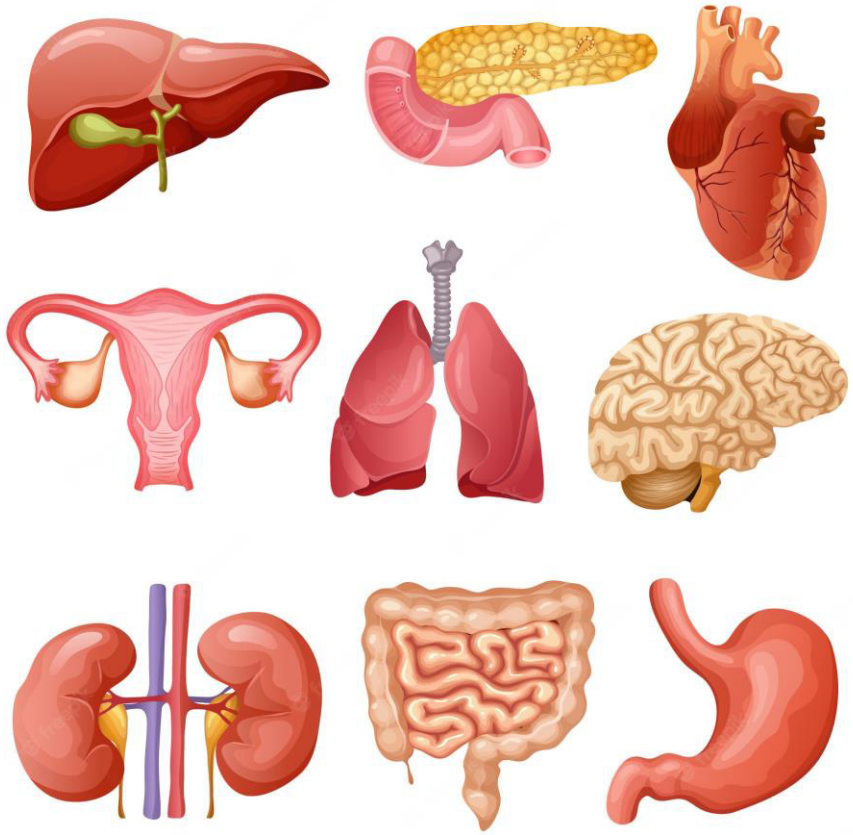
Castel San Pietro Terme

27 Maggio 2023

Rationale farmacologico *low dose* nelle patologie respiratorie allergiche

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

A long journey from Reductionism to SYSTEM MEDICINE



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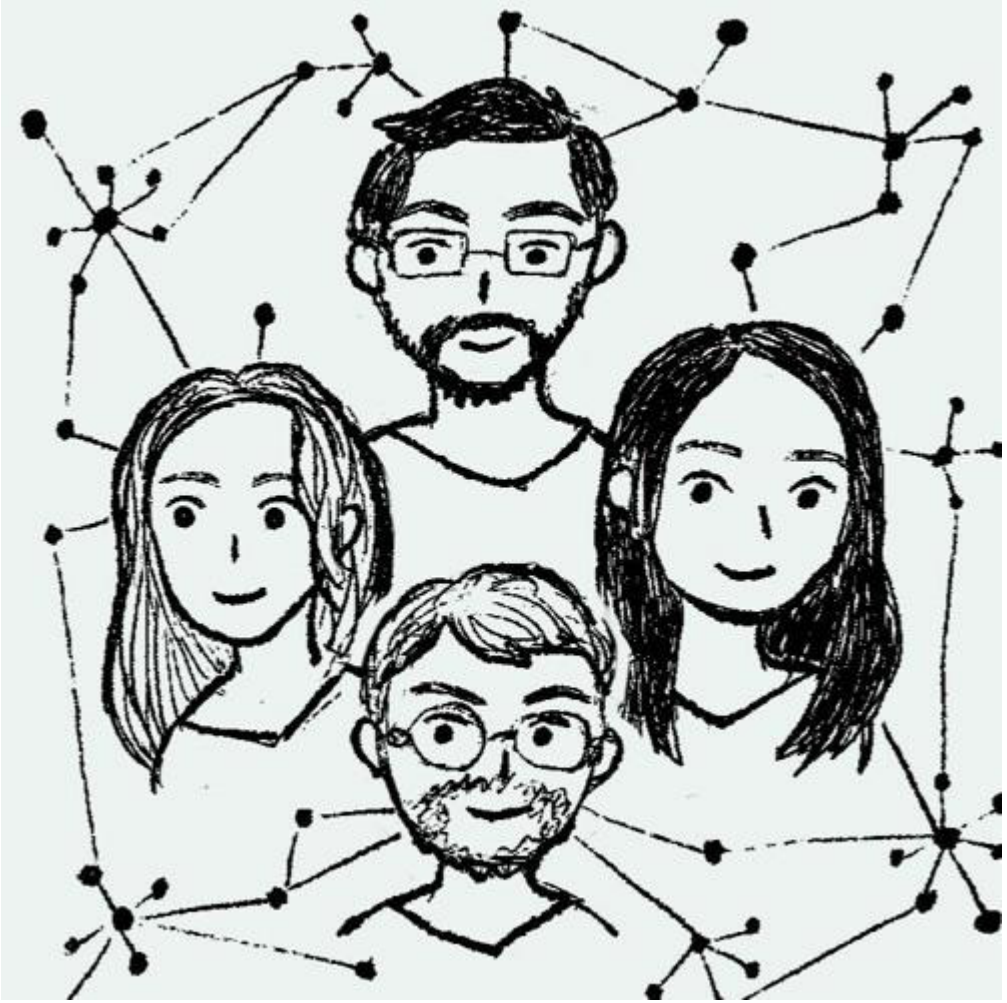
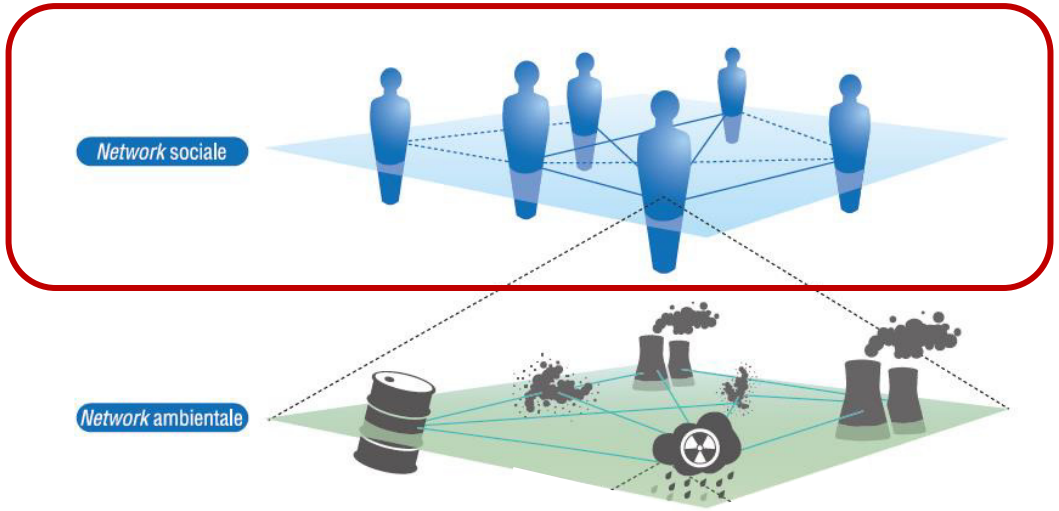
THE HUMAN BODY
IS A NETWORK
OF COMMUNICATING CELLS

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.

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

«NEGATIVE THOUGHTS» AND LOW-GRADE CHRONIC INFLAMMATION

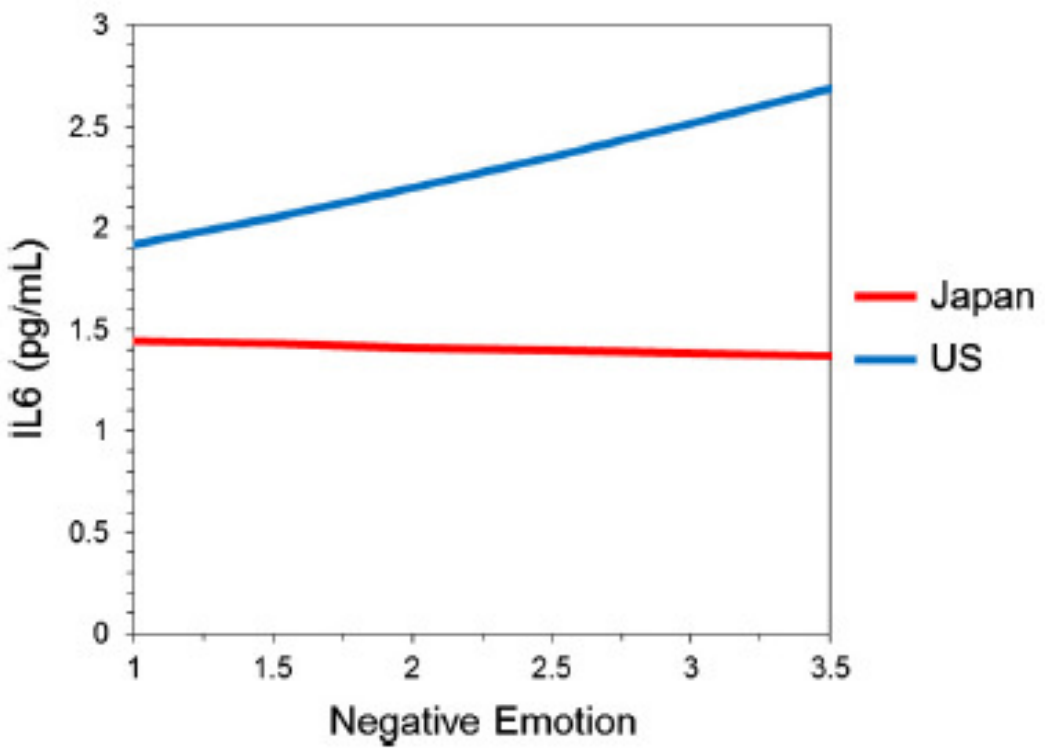


Fig. 1. Cultural moderation of the association between negative emotions and IL-6 after controlling for gender, age, and years of education, positive emotions, neuroticism, extraversion, smoking status, alcohol consumption, the number of chronic conditions linked to inflammation, and log-transformed 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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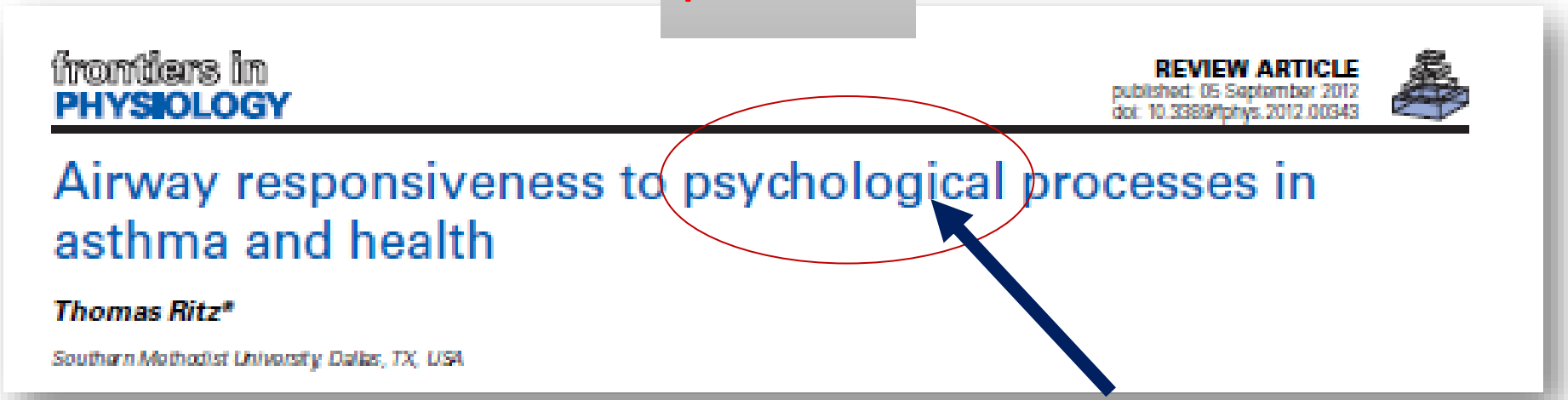


Psychological factors impact airway diseases pathophysiology: i.e. **asthma exacerbation**

Adversity and Resilience Science (2022) 3:1–19
https://doi.org/10.1007/s42844-022-00051-3

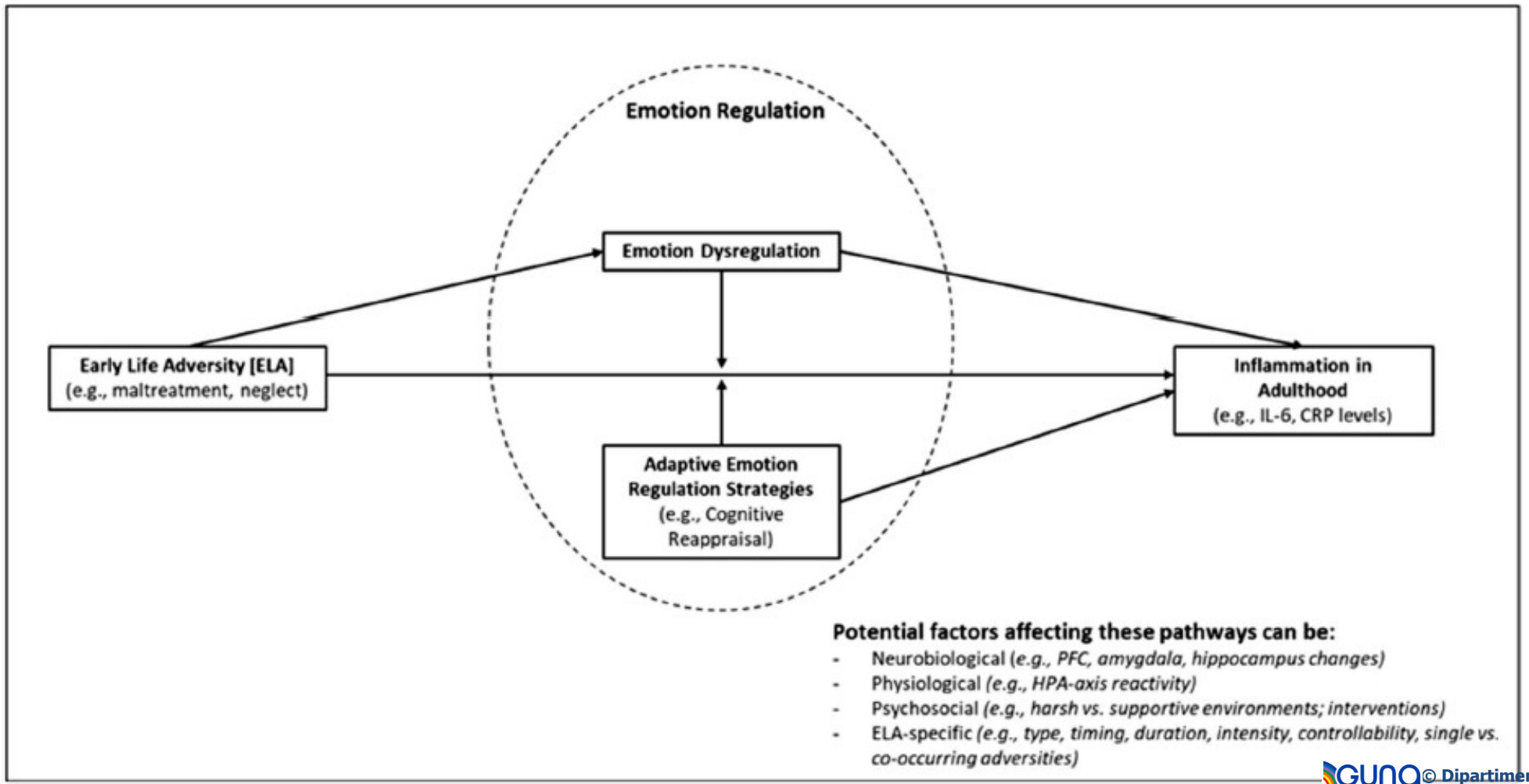
2022

REVIEW ARTICLE

Emotion Regulation as a Pathway Connecting Early Life Adversity and Inflammation in Adulthood: a Conceptual Framework

Ambika Mathur[1] · Jacinda C. Li[2] · Sarah R. Lipitz[1] · Jennifer E. Graham-Engeland[1]

Accepted: 6 January 2022 / Published online: 23 February 2022

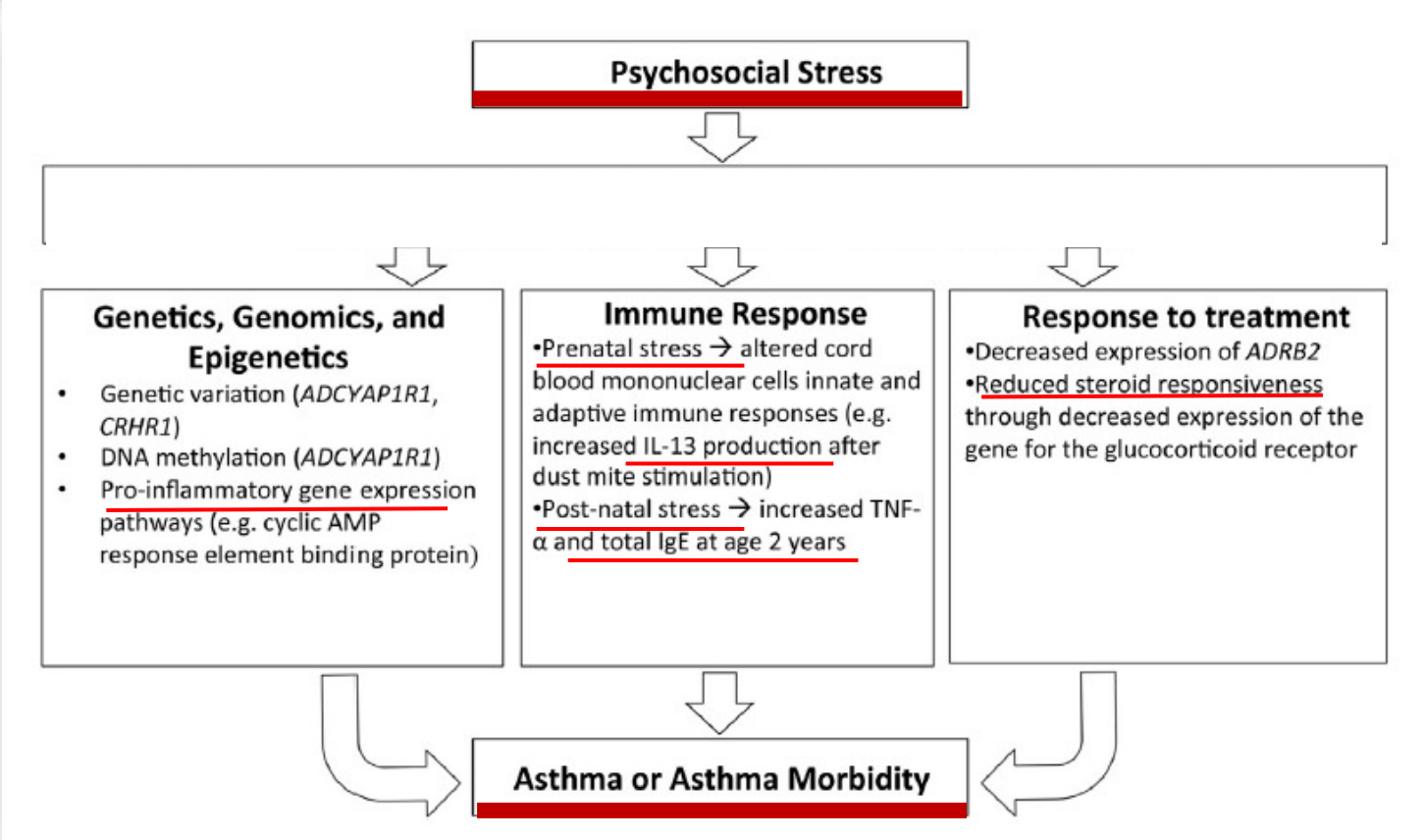


(J Allergy Clin Immunol 2014;134:1009-15.)

Stress and asthma: Novel insights on genetic, epigenetic, and immunologic mechanisms

Stacy L. Rosenberg, MD,[a] Gregory E. Miller, PhD,[b] John M. Brehm, MD, MPH,[a] and Juan C. Celedón, MD, DrPH[a]

Pittsburgh, Pa, and Evanston, Ill



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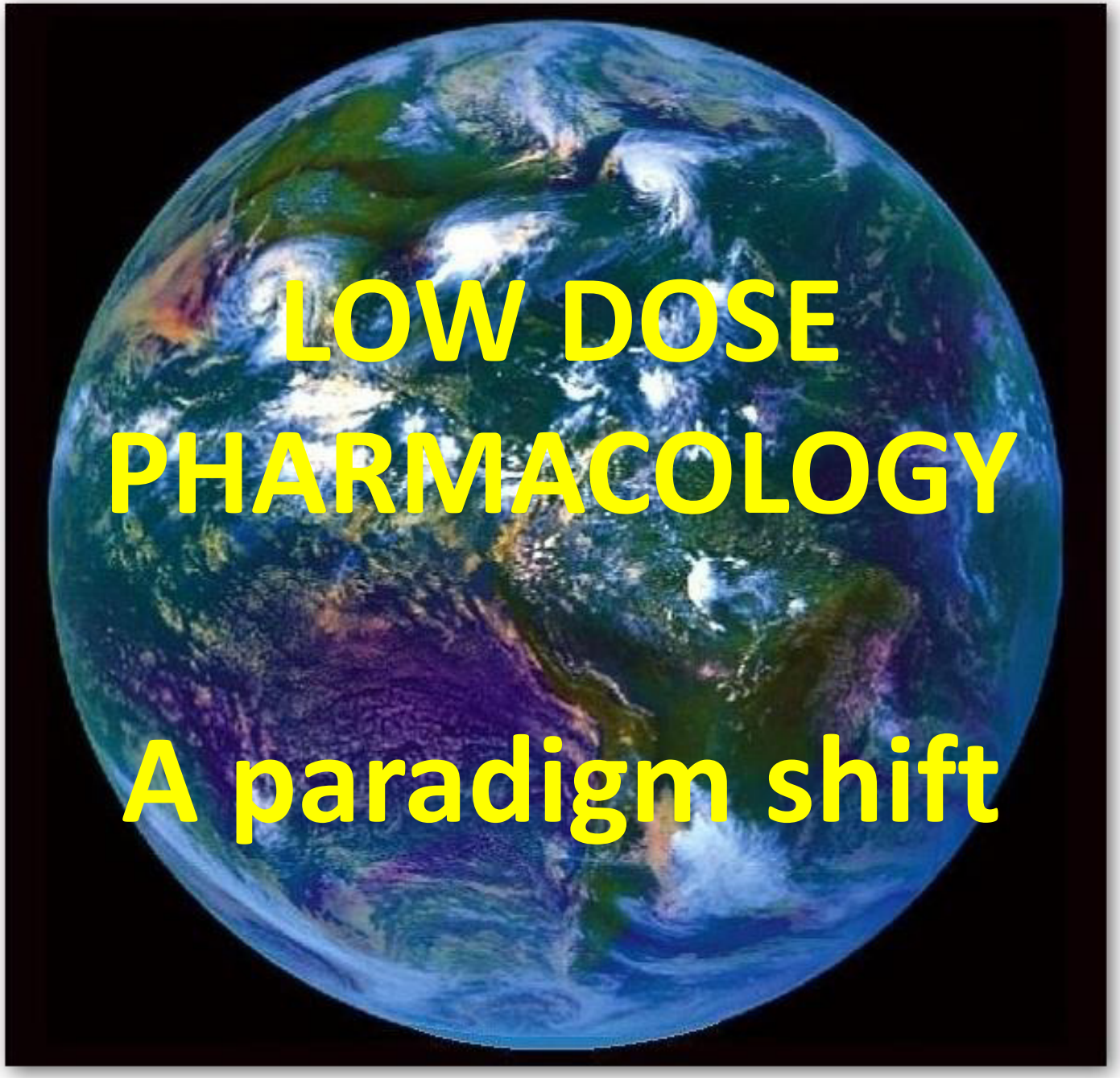


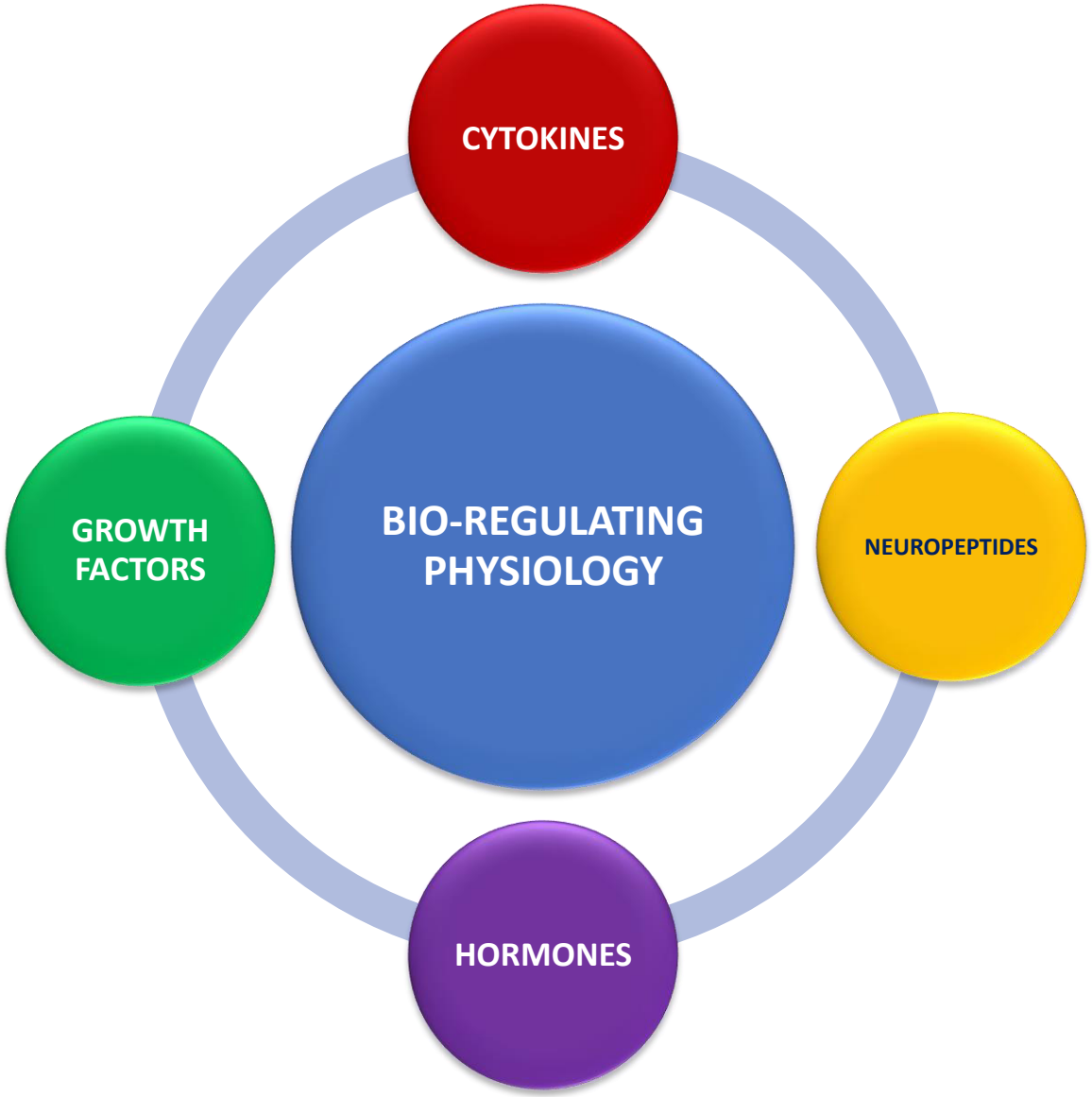
LOW DOSE PHARMACOLOGY

A paradigm shift

guna.it

SIGNALING MOLECULES-BASED LOW DOSE PHARMACOLOGY

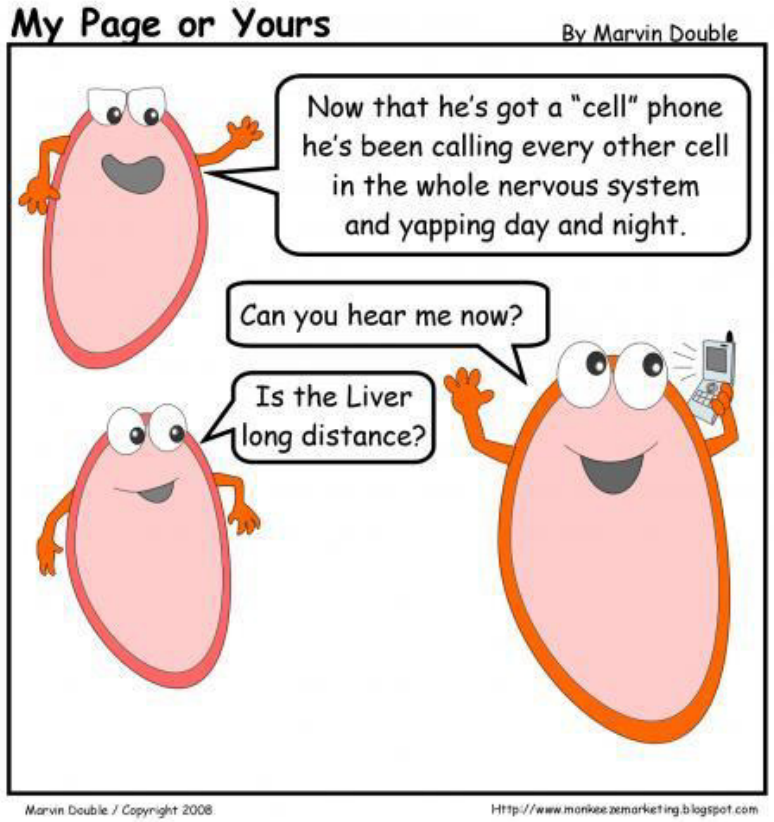
THE GREAT INNOVATION



Signaling Molecules

The Fundation for LDM

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



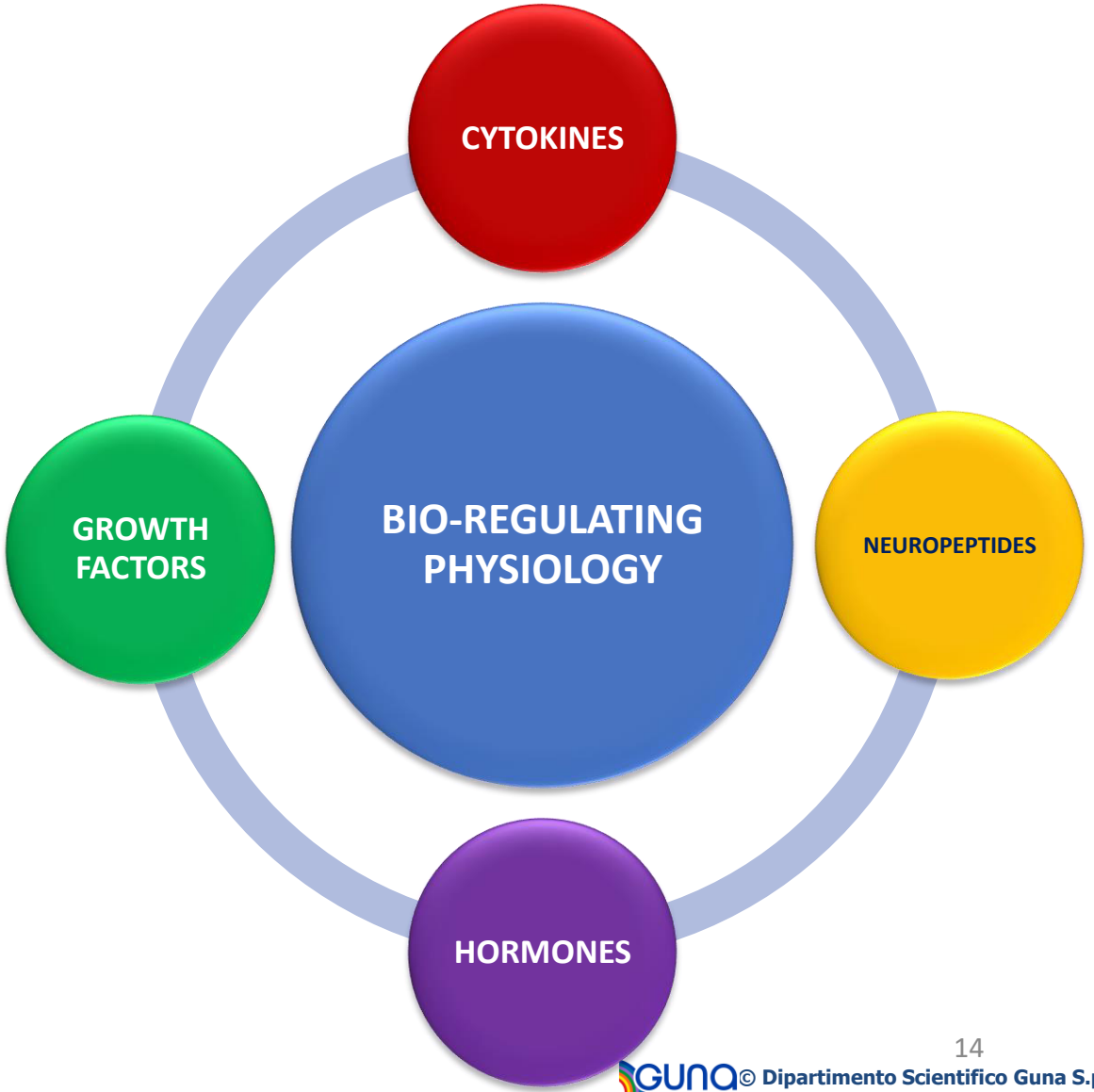
Signaling (Messenger) Molecules

The Foundation for Low Dose Pharmacology

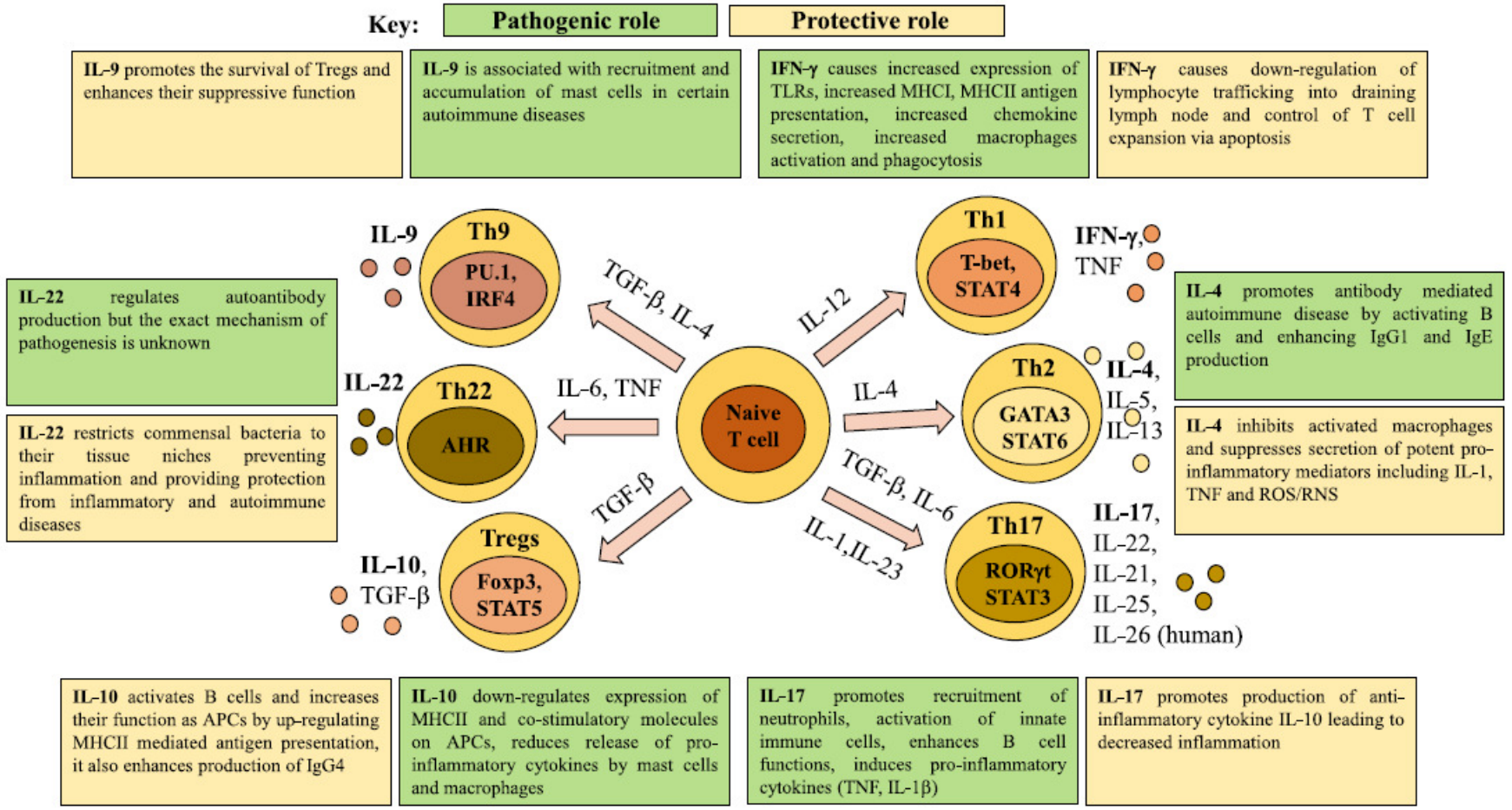
***Cells talk to each other at a very low volume** (i.e. sub-nanomolar concentration)*

SIGNALING MOLECULES
Quality and Quantity

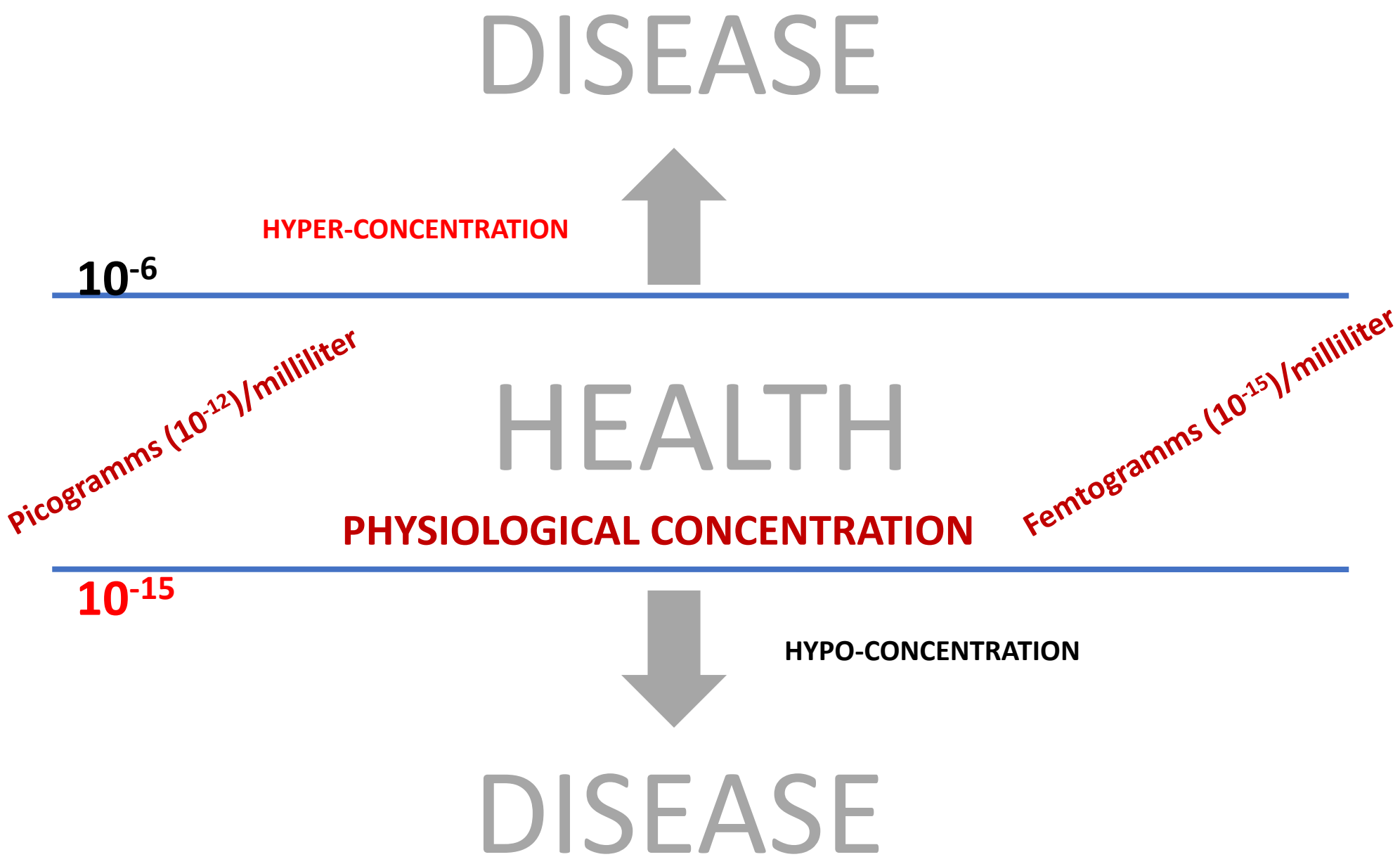
Not just the right **MESSAGE** but the right «**VOLUME**» too.



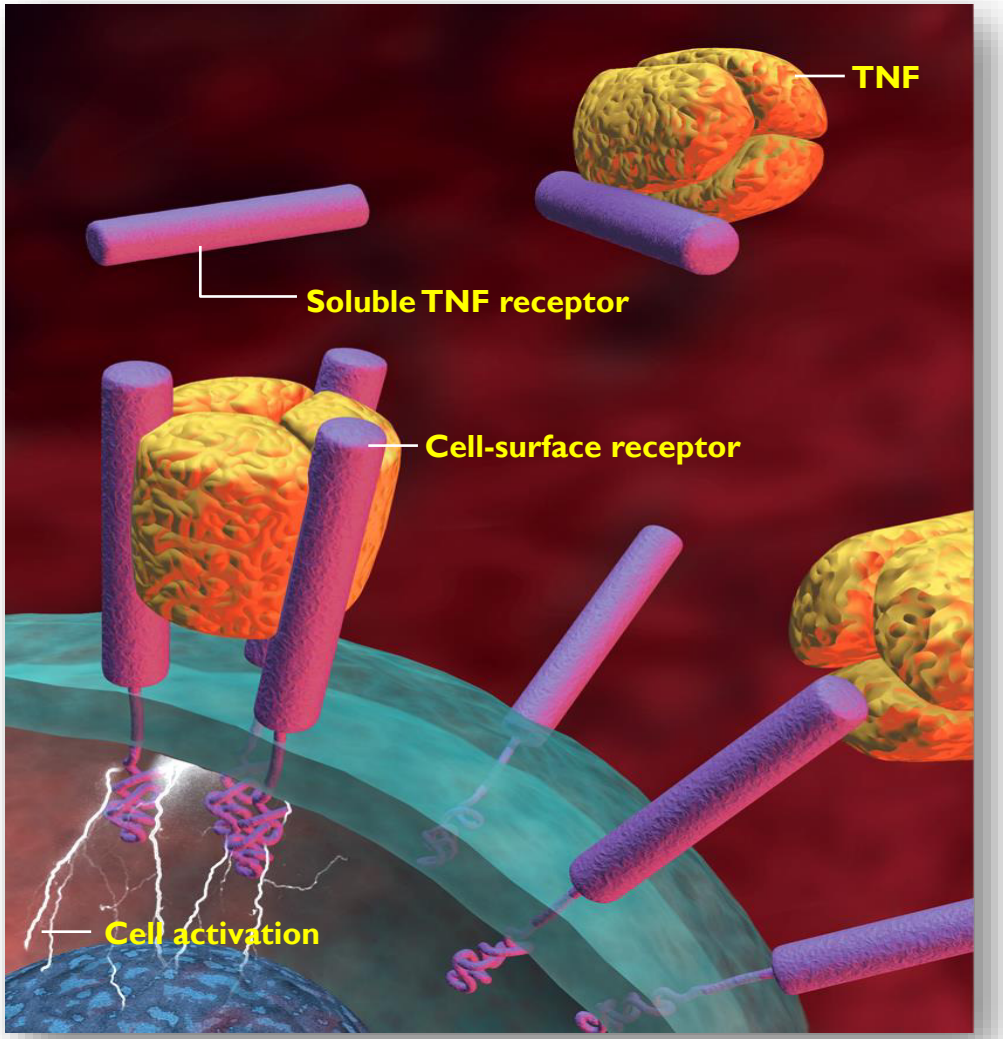
Neither good nor bad in Nature



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



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

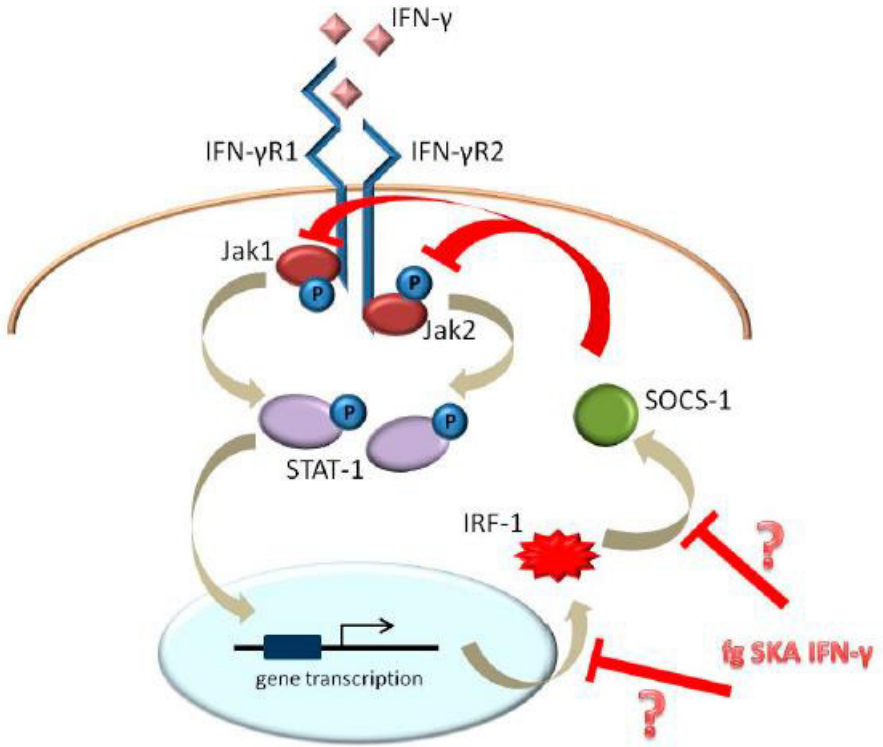
International Journal of *Molecular Sciences*

MDPI

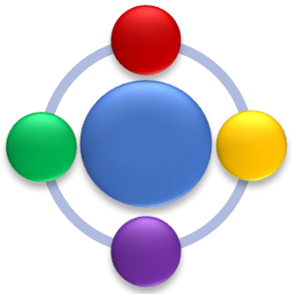
Article

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]

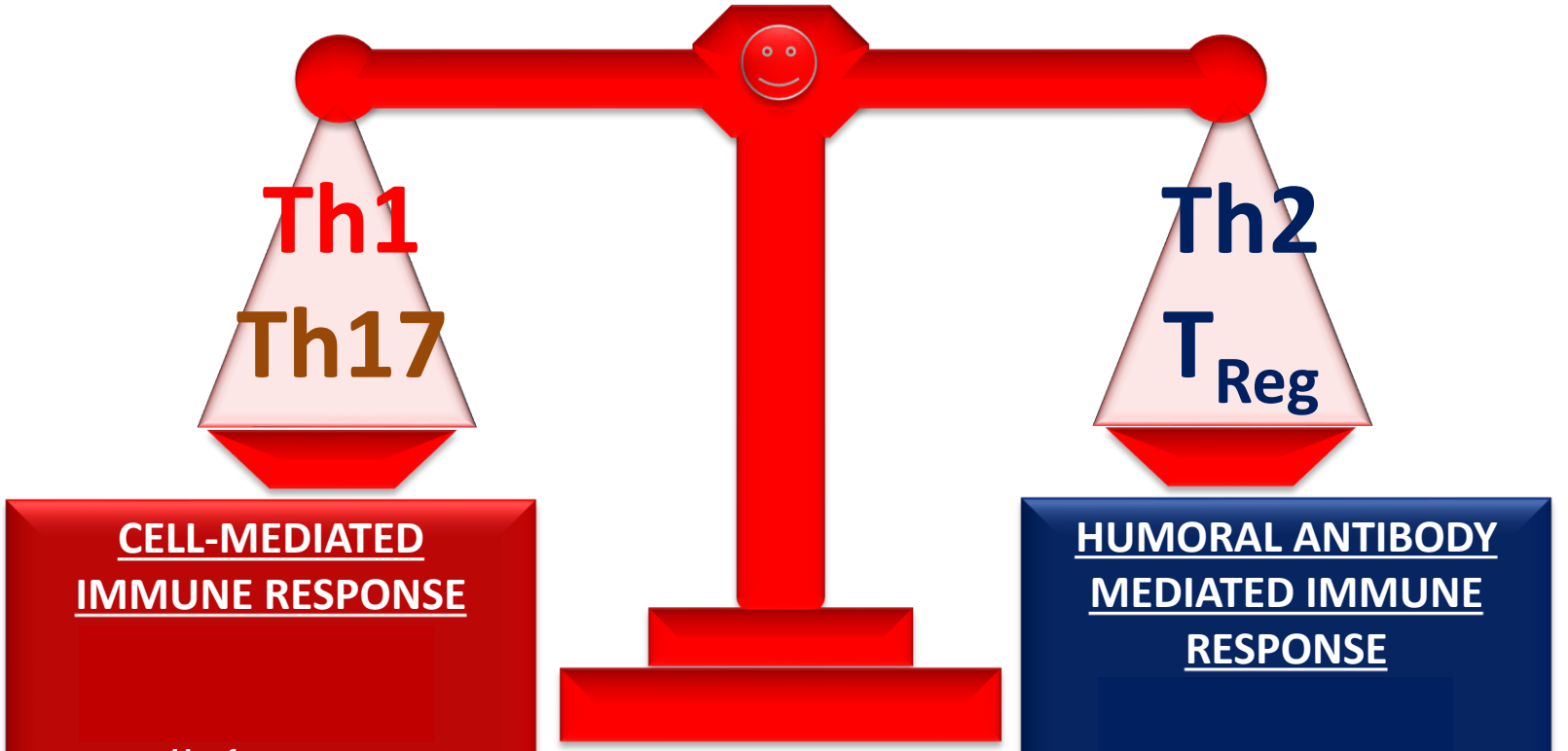


A premise for the clinical use of low dose cytokines in allergic asthma



DISEASES CAN BE CONSIDERED AS AN EXPRESSION, A CONSEQUENCE OF AN **UMBALANCE OF T- HELPER SUBSETS** AND **CHANGED EXPRESSIONS OF RELATED *SIGNALING MOLECULES* CONCENTRATION**

Relationships between Th subsets



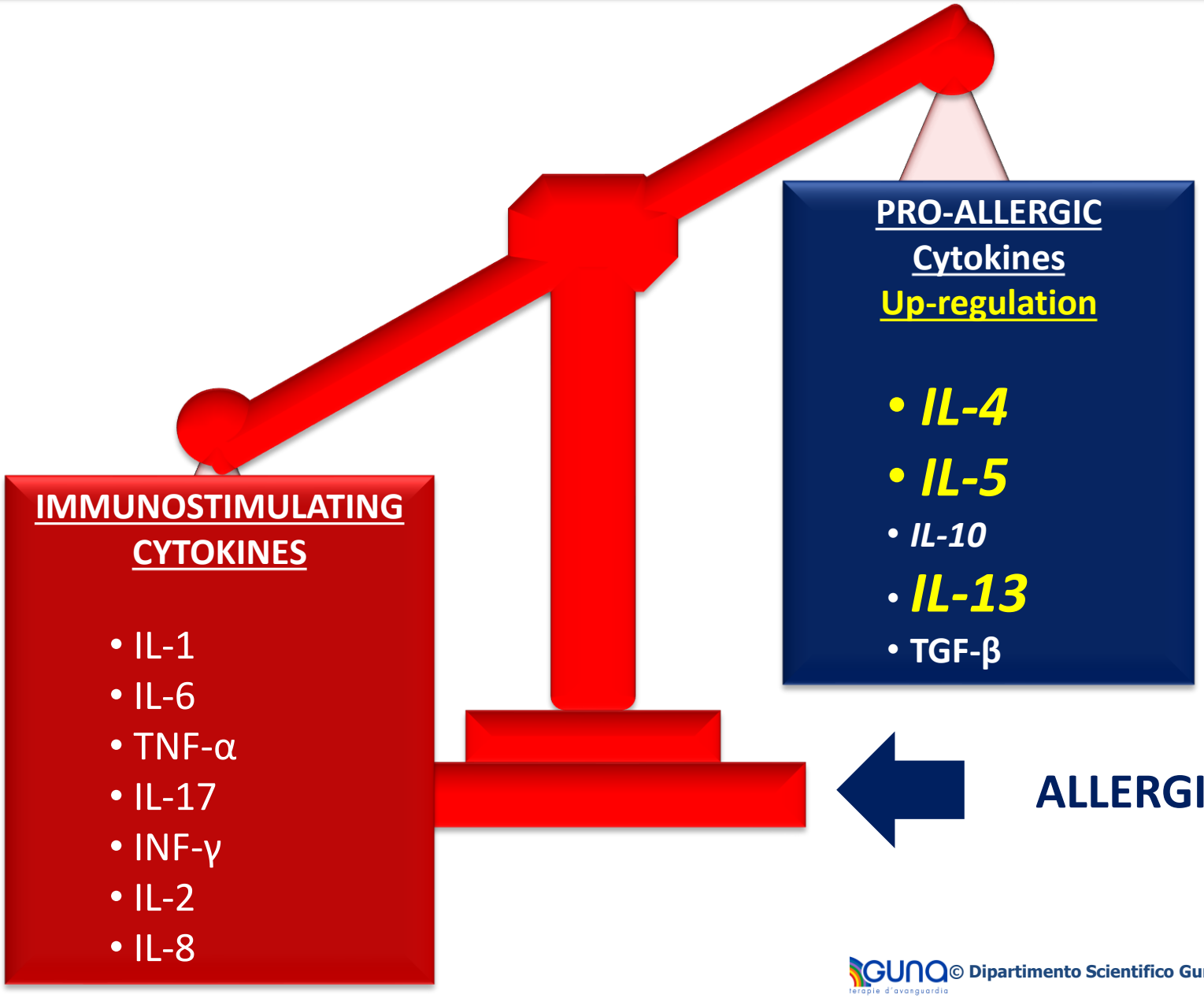
CELL-MEDIATED IMMUNE RESPONSE

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

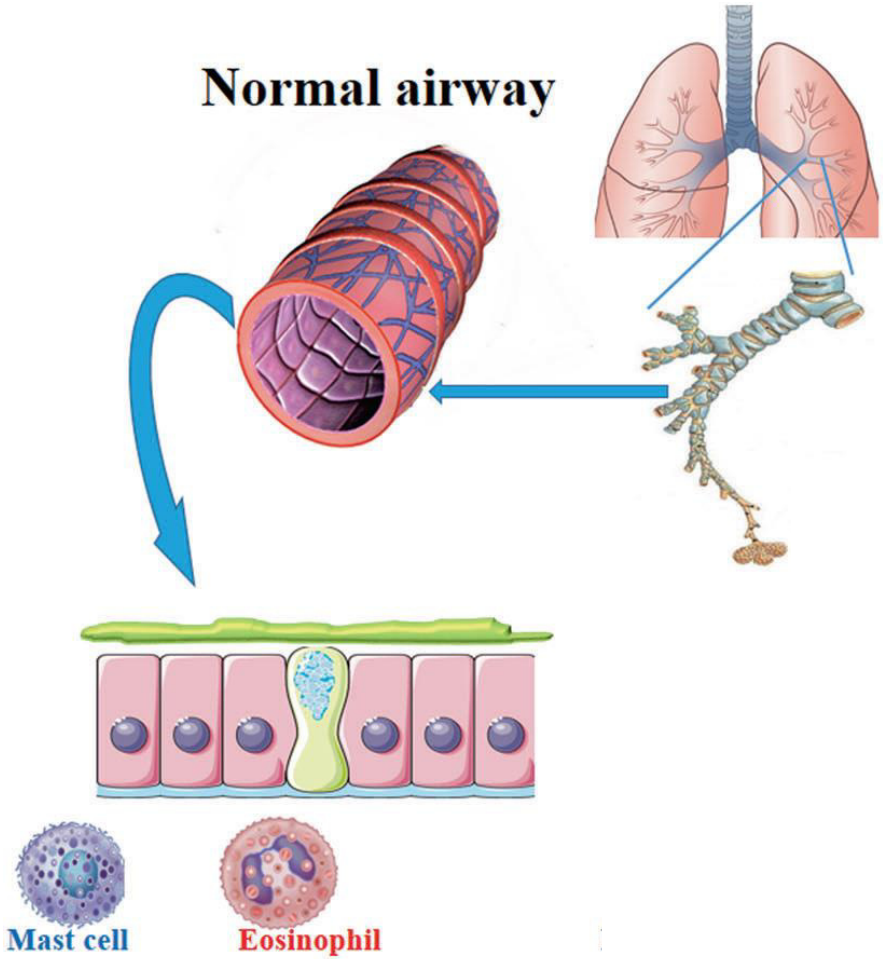
HUMORAL ANTIBODY MEDIATED IMMUNE RESPONSE

- ***IL-4***
- ***IL-5***
- ***IL-10***
- ***IL-13***
- **TGF-β**

By an immunological point of view…in allergic diseases



Cytokines and asthmatic airway



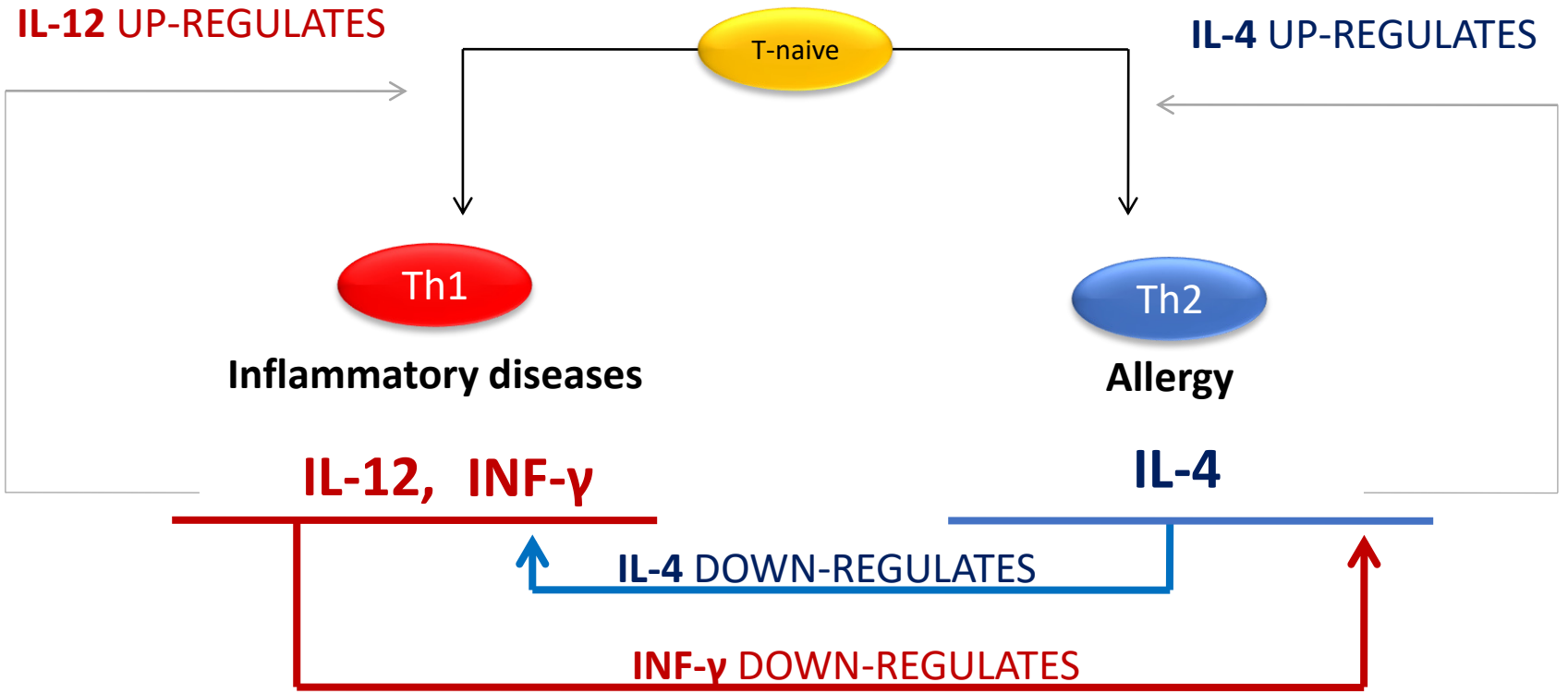
Athari SS. Targeting cell signaling in allergic asthma. Signal Transduct Target Ther. 2019;4:45. doi: 10.1038/s41392-019-0079-0. PMID: 31637021; PMCID: PMC6799822.

IF ALLERGIC ASTHMA IS AN EXPRESSION, A CONSEQUENCE OF CHANGED CONCENTRATION OF *SIGNALING MOLECULES…*

PROBLEM

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

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***

guna.it

Signal Transduction and Targeted Therapy

www.nature.com/sigtrans

REVIEW ARTICLE OPEN

Targeting cell signaling in allergic asthma

Seyyed Shamsadin Athari

International Journal of *Molecular Sciences*

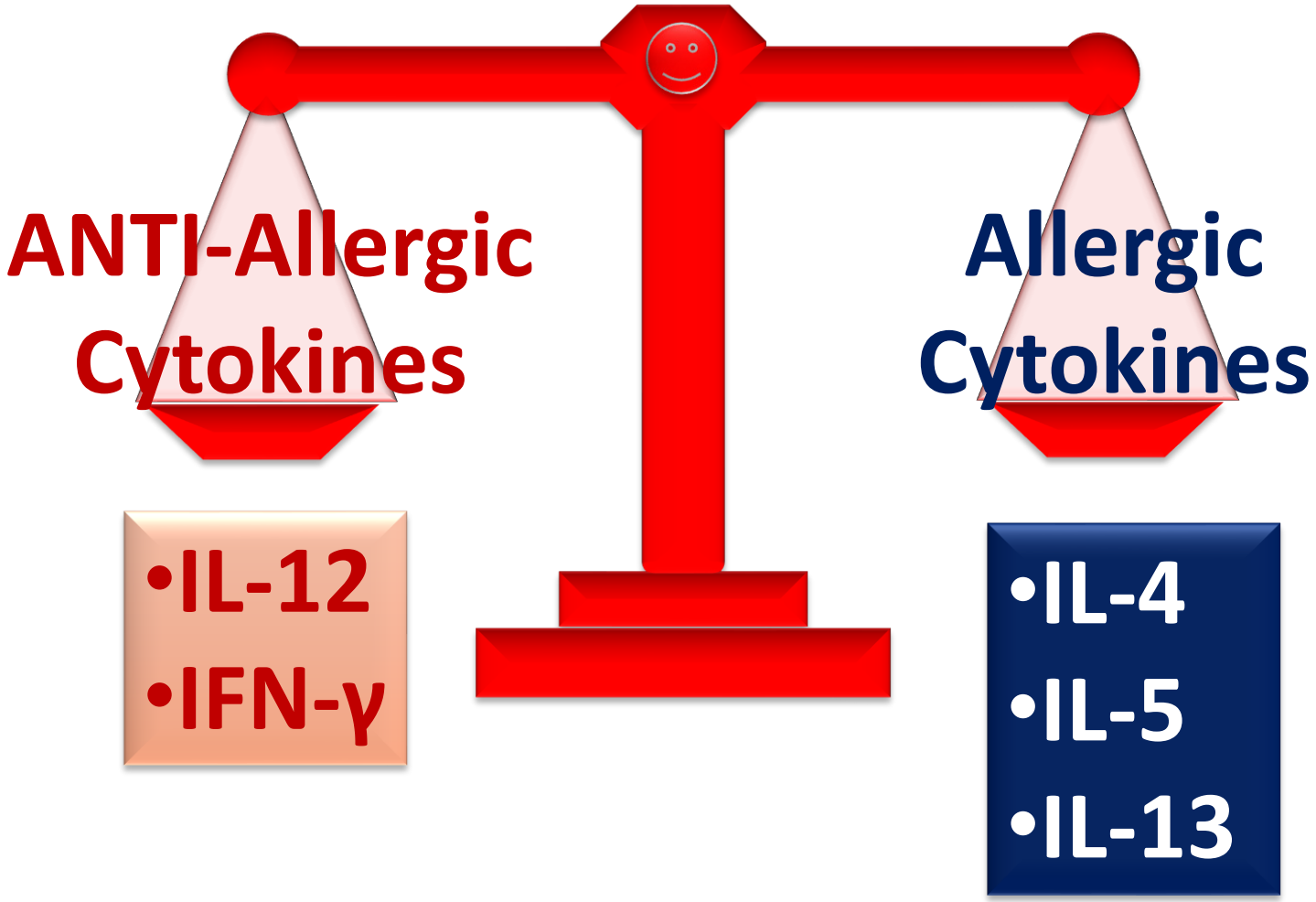
MDPI

Review

Taking a Breather: Advances in Interleukin 5 Inhibition for Asthma Relief

Oliver William Massey [1,2] and Cenk Suphioglu [1,2,*]

RECOVERING THE BALANCE IN ALLERGIC DISEASES



THE ORIGINAL SIN OF THE ALLERGIC PATIENT

The great innovative element brought by LDM is to be able to act on the **Th1/Th2 SWITCH** through mechanisms of immunoregulation operated **signaling molecules** **(IL-12 e IFN-γ)** in physiological *low dose (1pg/ml) SKA*[1] *able to cross-regulate the immune balance*

THAT'S THE DEEP MEANING OF OUR AETIOLOGIC/PREVENTIVE THERAPY FOR ALLERGIES

1. Gariboldi S. et al. – Low dose oral administration of cytokines for treatment of allergic asthma, Pulmonary Pharmacology & Therapeutics 22 (2009) 497-510, doi: 10.1016/j.pupt.2009.05.002

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

1. Gariboldi S. et al. – Low dose oral administration of cytokines for treatment of allergic asthma, Pulmonary Pharmacology & Therapeutics 22 (2009) 497-510, doi: 10.1016/j.pupt.2009.05.002

EXPERIMENTAL PROTOCOL

LUCKY MOUSE

DAY 1 → **DAY 7** → **DAY 13**

Injection of 1 mg of egg-albumin + 5 mg $Al(OH)_3$ in PBS (IP)

Injection of 1 mg of egg-albumin + 5 mg $Al(OH)_3$ in PBS (IP)

Aerosol of 1 mg of egg-albumin + 5 mg $Al(OH)_3$ in PBS

ALLERGIC MOUSE

TREATMENT WITH IL-12+IFN-γ

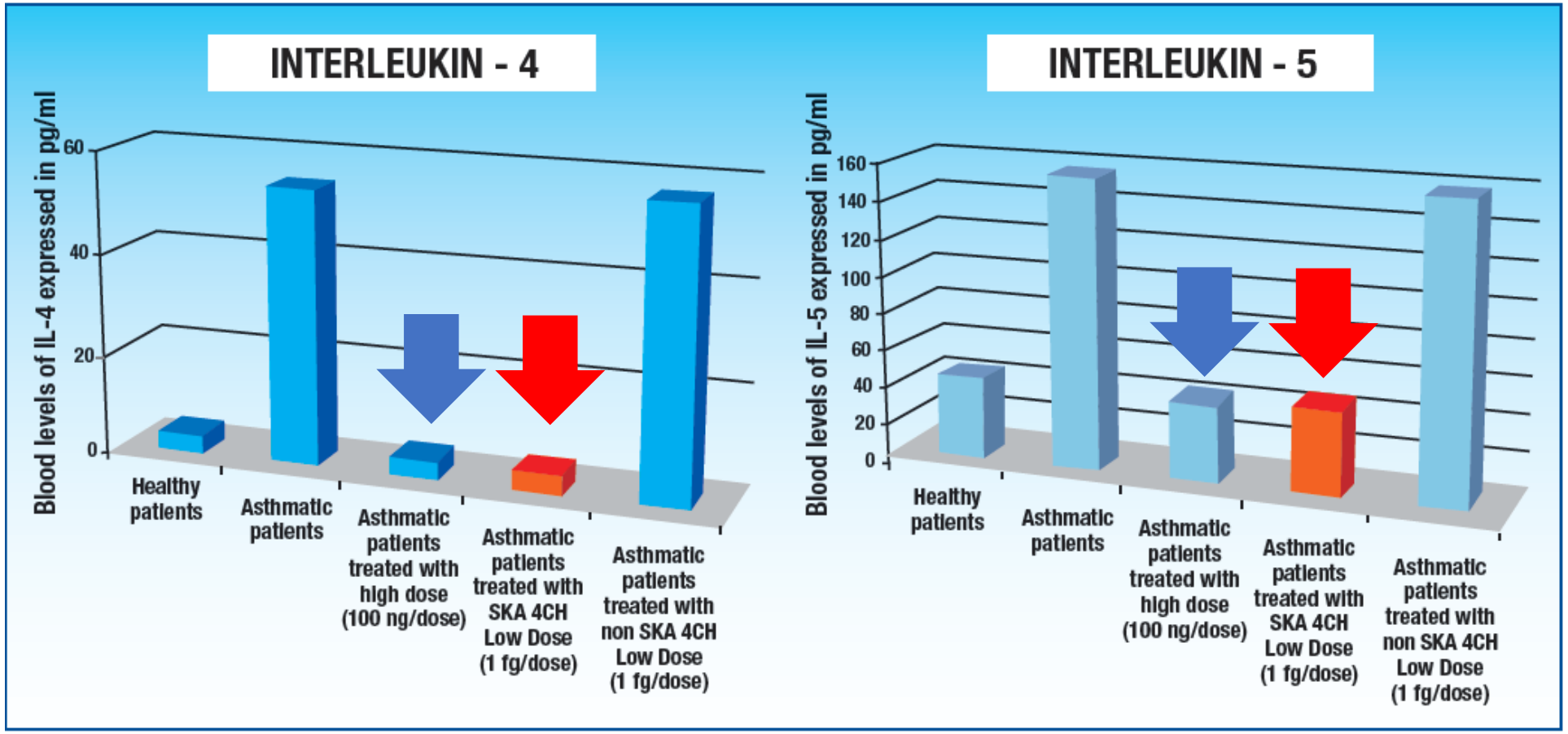
from DAY 18 until DAY 38 Blood drawing

DAY 38 Bronchoalveolar lavage fluid

DAY 30 5% egg-albumin in PBS 0,5. (Aerosol)

DAY 27 Injection of 1 mg of egg-albumin + 5 mg $Al(OH)_3$ in PBS (IP)

Level of IL-4 and IL-5 in mice sera at day 7th of treatment

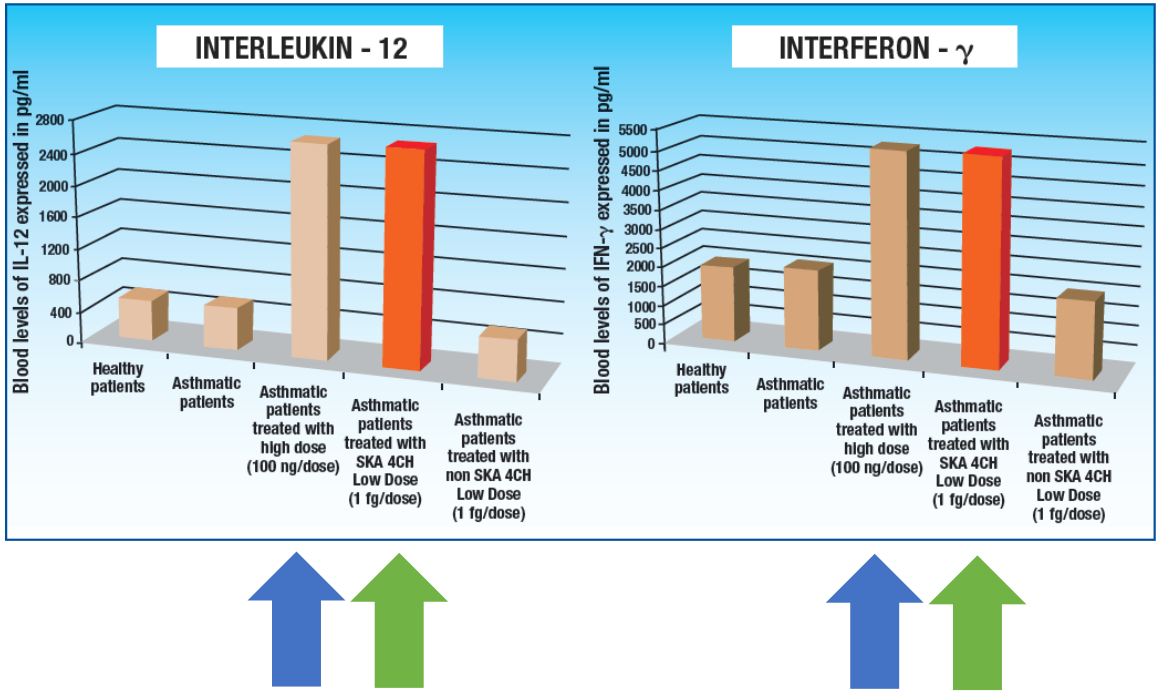


Level of IL-12 and IFN-γ in mice sera at day 7th of treatment

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})

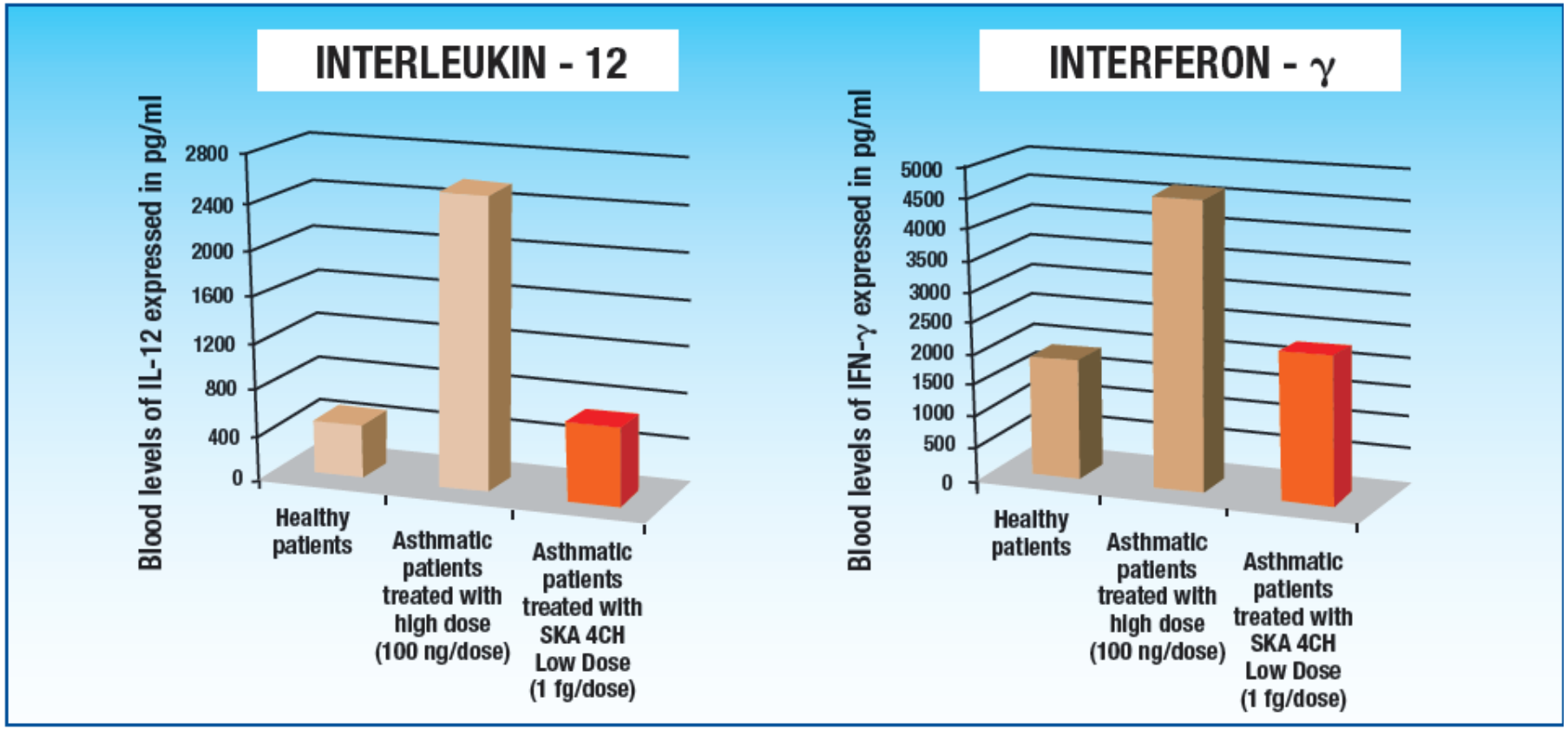


Eosinophils number in mouse BALF *(Bronchoalveolar Lavage Fluid)* at day 20 of treatment

Group	Number of eosinophil granulocytes in the bronchoalveolar lavage fluid (BALF) on day 20th
Healthy patients	0
Asthmatic patients	20,188 ± 0,613
Asthmatic patients treated with high dose (100 ng/dose)	0
Asthmatic patients treated with SKA 4CH Low Dose	**0**
Asthmatic patients treated with non SKA 4CH Low Dose	19,567 ± 0,685

Number of cells expressed in cells/BALF (x10^4)

Blood levels of IL-12 and IFN-γ 13 days after the end of the treatment based on high dose administration of IL-12 and IFN-γ or SKA Low Dose



Carello et al. Italian Journal of Pediatrics (2017) 43:78
DOI 10.1186/s13052-017-0393-5

Italian Journal of Pediatrics

RESEARCH Open Access

Long-term treatment with low-dose medicine in chronic childhood eczema: a double-blind two-stage randomized control trial

R. Carello[1*†], L. Ricottini[2†], V. Miranda[2], P. Panei[3], L. Rocchi[1], R. Arcieri[3] and E. Galli[1]

Coordinating centre
U.O. di Immuno-Allergologia dell'Età Evolutiva
Responsabile Prof.ssa Elena Galli
Centro Ricerca, Ospedale S.Pietro Fatebenefratelli
Via Cassia, 600 - 00189 Roma

U.O. di Bio-Statistica dell'Istituto Superiore di Sanità
Responsabile dr. Pietro Panei
Via Regina Elena, 299 – 00161Roma

Carello et al. Italian Journal of Pediatrics (2017) 43:78
DOI 10.1186/s13052-017-0393-5

Italian Journal of Pediatrics

RESEARCH Open Access

Long-term treatment with low-dose medicine in chronic childhood eczema: a double-blind two-stage randomized control trial

R. Carello[1*†], L. Ricottini[2†], V. Miranda[2], P. Panei[3], L. Rocchi[1], R. Arcieri[3] and E. Galli[1]

- **IFN-gamma low dose (1 pg/ml):** 8/15 drops twice a day for 8 months (discontinued)

+

- **IL-12 low dose (1 pg/ml):** 8/15 drops twice a day for 8 months (discontinued)

+

- **GALIUM (20 components):** 8/15 drops twice a day for 8 months (discontinued)

STUDY OUTCOMES

Primary outcome

- Reduction of the severity of atopic dermatitis evaluated according to the **SCORAD** index with a percentage of predicted improvement of **30%.**

Secondary outcomes

- Elongation of the "disease-free interval".
- Tolerability and compliance of the treatment and management of adverse events.
- Skin Prick Test to major inhalant allergens and food.
- Skin Prick by Prick Test to major food allergens.
- Patch Test to major food allergens, mites and Nickel.
- Total and specific IgE to major inhalant allergens and food.
- Characterization of lymphocyte subpopulations by flow cytometry using battery of monoclonal antibodies.
- Study of cellular and serum pro-and anti-inflammatory cytokines IL-10, IL-13, IL-12 and IFN gamma.

RESULTS

The group treated with **low dose SKA CTK** registered a decrease of SCORAD score between T0 and T8 of **54%**, decrease which continues in the follow-up until it reaches **64%.**

In the same period of observation, the treated group had a significant reduction of the medication to control symptoms (antihistamines and topical corticosteroids).

The study also showed a progressive improvement of the quality of life (itching and nocturnal disturbances) of subjects treated with **low dose SKA CTK** during the entire period of investigation.

Respiratory Research

BioMed Central

Research

Open Access

IL-13 induces a bronchial epithelial phenotype that is profibrotic

Nikita K Malavia[1], Justin D Mih[2], Christopher B Raub[2], Bao T Dinh[2] and Steven C George*[1,2]

Asthmatic Epithelial Cell Proliferation and Stimulation of Collagen Production

Human Asthmatic Epithelial Cells Stimulate Collagen Type III Production by Human Lung Myofibroblasts after Segmental Allergen Challenge

ANNETTE T. HASTIE, WALTER K. KRAFT, KRISTIN B. NYCE, JAMES G. ZANGRILLI, ALI I. MUSANI, JAMES E. FISH, and STEPHEN P. PETERS

Department of Medicine, Division of Critical Care, Pulmonary, Allergic & Immunologic Diseases, and Division of Clinical Pharmacology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

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

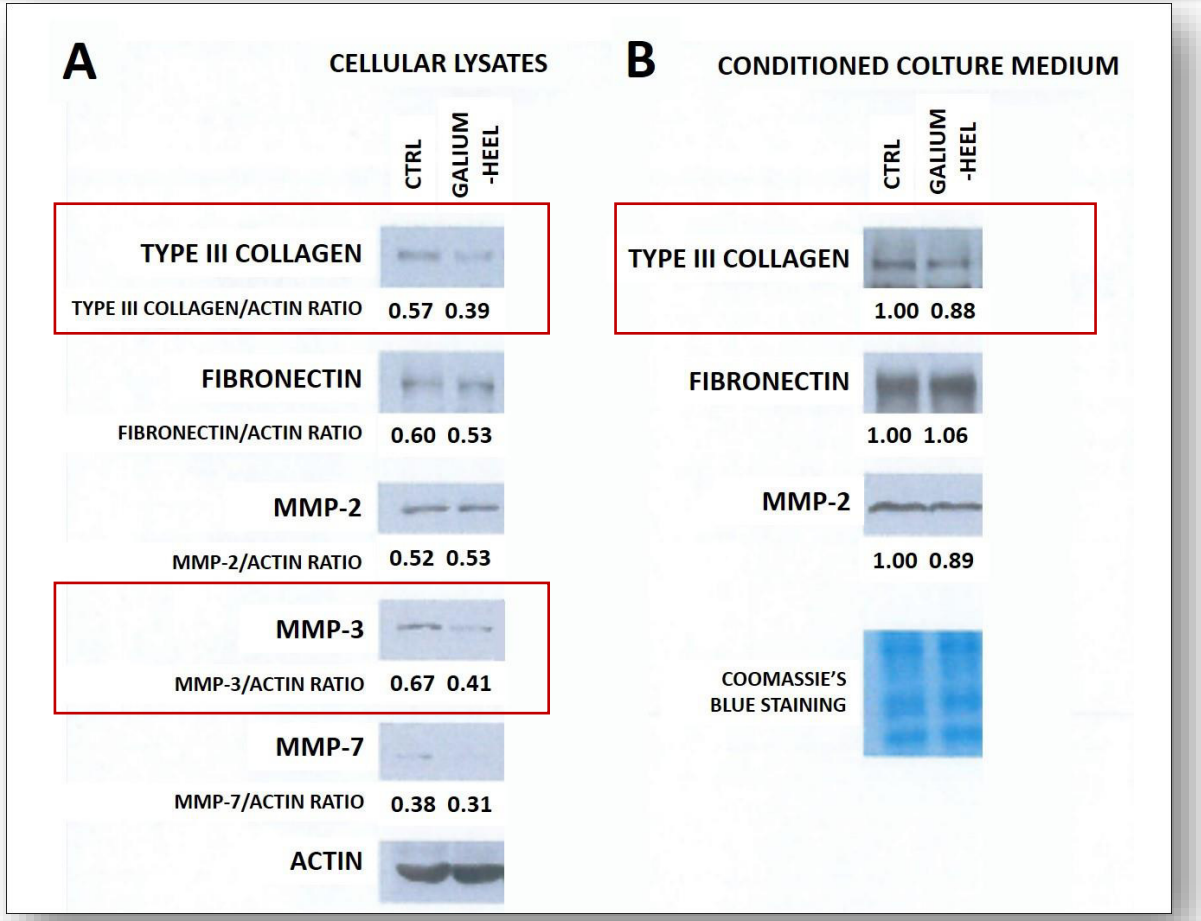
MONICA BENVENUTO[1], ROSANNA MATTERA[1], MARTINO TONY MIELE[2], MARIA GABRIELLA GIGANTI[1], ILARIA TRESOLDI[1], LOREDANA ALBONICI[1], VITTORIO MANZARI[1], ANDREA MODESTI[1], LAURA MASUELLI[3*] and ROBERTO BEI[1*]

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

EFFETTI DI GALIUM-HEEL SULL'ESPRESSIONE DI MOLECOLE DELL'ECM E SULLE METALLOPROTEINASI



Pannello A – L'espressione del collagene di Tipo III, della fibronectina, delle MMP-2, MMP-3 e MMP-7 è stata valutata tramite Western Blotting su lisato cellulare (HDF) trattate per 48 ore con Cloruro di Sodio (CTRL) o GALIUM HEEL alla diluizione l :2 in DMEM 0.2% BSA. L'Actina è stata usata come controllo interno. Vengono riportati i rapporti densitometrici tra ogni proteina e l'actina.
Il trattamento CON GALIUM-HEEL riduce significativamente l'espressione di Collagene di Tipo III (p=0.02) e di MMP-3 (P=0.002)

Panel B. L'espressione del collagene di Tipo III, della fibronectina ed MMP-2 è stata valutata tramite Western Blotting sul medium di coltura condizionato di cellule HDF. Il rapporto densitometrico tra l'espressione delle proteine analizzate è stato valutato tramite colorazione del gel con Blu di Coomassie per confermare il caricamento della medesima quantità di materiale proteico.
Il trattamento con GALIUM-HEEL riduce significativamente l'espressione di Collagene di Tipo III (p<0.001).

guna.it

LA MEDICINA BIOLOGICA APRILE - GIUGNO 2005

CLINICAL

C. Supino, M. Rainone

MIGLIORAMENTO DELLA QUALITA' DI VITA (QDV) IN BAMBINI ASMATICI CON *GALIUM-HEEL®*

– STUDIO CLINICO OSSERVAZIONALE

IMPROVEMENT IN THE QUALITY OF LIFE (QOL) IN ASTHMATIC CHILDREN INDUCED BY GALIUM-HEEL®

– AN OBSERVATIONAL CLINICAL TRIAL

RIASSUNTO

In questo studio clinico aperto, condotto su 81 pazienti pediatrici di età compresa tra 3 e 12 anni, viene valutata l'efficacia di un medicinale omotossicologico nella terapia integrata dell'asma.
L'asma è patologia che penalizza la qualità di vita (QDV) dei pazienti.
– Il protocollo prevede la somministrazione di un medicinale omeopatico complesso (Galium-Heel®) in associazione a farmaci convenzionali inseriti nelle Linee Guida internazionali sec. il protocollo GINA.
I fattori "crisi d'asma" ed "assunzione di farmaci convenzionali" sono considerati parametri di valutazione della QDV per un periodo di osservazione di 36 mesi.
Lo studio evidenzia l'efficacia dell'associazione del medicinale omotossicologico nella diminuzione delle crisi e dell'assunzione di farmaci convenzionali e, conseguentemente, nel miglioramento della QDV.

PAROLE CHIAVE PEDIATRIA, ASMA, GALIUM-HEEL®, OMOTOSSICOLOGIA, QUALITA' DI VITA

SUMMARY: The present open clinical trial, carried out on 81 paediatric patients, aged between 3 and 12 years, has meant to prove the effectiveness of a homotoxicological medicine in chronic pathology such as asthma.
Asthma is a pathology that reduces the patients' quality of life (QOL) for several reasons.
– The protocol consists in the administration of a complex homeopathic remedy (Galium-Heel®) in association with the conventional drugs included in the International Guida Lines according to the GINA protocol. The crisis of asthma and the use of conventional drugs are taken into consideration as evaluation parameters of QOL in a 36 months observational clinical trial.
The study highlights the effectiveness of the association of the homotoxicological remedy in diminishing the asthma crisis and the consumption of allopathic drugs in bettering the QOL.

KEYWORDS: PEDIATRICS, ASTHMA, GALIUM-HEEL®, HOMOTOXICOLOGY, QUALITY OF LIFE

INTRODUZIONE

La peculiare *personalizzazione* della prescrizione omeopatica rappresenta/ha rappresentato il principale ostacolo per l'inserimento dell'Omeopatia all'interno dell'ufficialità della ricerca scientifica, poichè è inevitabile incorrere in inconvenienti legati alle difficoltà di applicare all'Omeopatia i parametri sperimentali imposti dall'EBM *(Evidence-Based Medicine)*, in particolare la randomizzazione dei pazienti e la prescrizione dei rimedi che, in studi clinici controllati *(vs* placebo, farmaco allopatico di riferimento, terapia fisica di riferimento), deve essere univoca per la stessa patologia, in disaccordo con la regola dell'individualizzazione e reperorizzazione del medicinale omeopatico. Attualmente si ritiene che l'unica metodologia accettabile per la verifica clinico-sperimentale negli studi clinici aperti (osservazio-

TAB. 1
Campione dallo studio. Età media = 7 anni, 5 mesi.

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Pazienti totali	Crisi di asma totali 12 mesi precedenti l'introduzione in terapia di Galium-Heel® gocce	Tempo zero Inizio di terapia con Galium-Heel® 10 gtt x 3 volte/die	Crisi di asma totali 1° controllo a 6 mesi 81 pazienti	Crisi di asma totali 2° controllo a 12 mesi 81 pazienti	Crisi di asma totali 3° controllo a 24 mesi 15 pazienti (osservazione iniziata nel 2004)	Crisi di asma totali 4° controllo a 36 mesi 7 pazienti (osservazione iniziata nel 2003)
81	392		364	79	2	0

Farmaci allopatici utilizzati	n. pazienti	Inizio di terapia con Galium-Heel®	1° controllo n. pazienti	2° controllo n. pazienti	3° controllo n. pazienti	4° controllo n. pazienti
Immunoterapia specifica	30		30	30	0	0
Beta2-agonisti *long action*	56		54	0	0	0
Beta2-agonisti *short action*	81		62	45	2	0
Antistaminici	26		7	0	0	0
Antileucotrieni	15		0	0	0	0
Corticosteroidi inalanti	81		73	45	2	0

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