

## 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 we do not accept medical or legal responsibility for misuse of the information presented. This information is for educational purposes for licensed health care professionals within their scope of practice and must be intended as scholastic information and only the Doctor can decide if they can be considered for his/her patient and adapted to him/her, besides all the other necessary treatments and therapies.*

*INTERNATIONAL WEB-CONFERENCE*



The dangerous relationships between stress,  
Immune System, and Central Nervous System.

*The contribution of Low Dose Medicine  
in the times of Pandemic*



Friday November 20, 2020

H. 18.00-20.00 (CET)

**Alessandro Perra** – *Scientific Director of Guna S.p.a.*

**Marco Del Prete** – *Specialist in Nephrology – President of the International Academy of  
Physiological Regulating Medicine*

## TAKE HOME

What will we have learnt at the end of the first part of this webinar?



**THE CONNECTION BETWEEN CNS AND I.S.**



**OUR STRATEGY AGAINST INFECTIONS**



**THE LOW DOSE MEDICINE APPROACH BEFORE, DURING AND AFTER COVID-19**

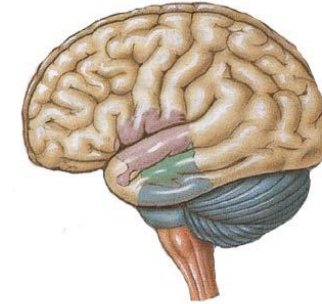


**DURING ALL THE 3 PREVIOUS SESSIONS: DEEPENINGS ON GUNA MEDICATIONS**

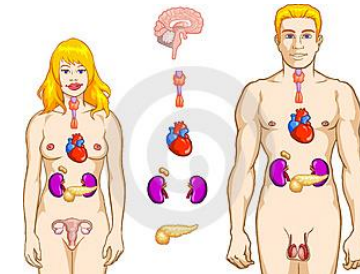
# HOMEOSTATIC Control Systems and bi-directional cross-talk

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N  
E  
I

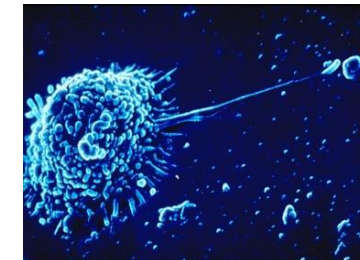
CENTRAL NERVOUS SYSTEM  
&  
AUTONOMIC SYSTEM



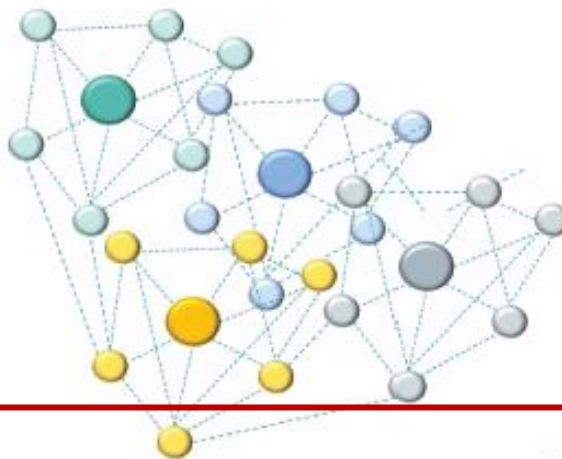
ENDOCRINE SYSTEM



IMMUNE SYSTEM



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



● **SOCIAL LEVEL (INTERATTOMA)**

- Individui nella società

Network sociale



● **ENVIRONMENTAL LEVEL (ESPOSOMA)**

- Tossine ambientali
- Tossine endogene

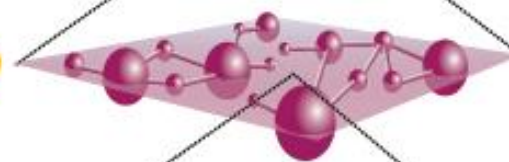
Network ambientale



● **FUNCTIONAL LEVEL (LIVELLO FUZIONALE)**

- Network neuroendocrino
- Network immunitario-infiammatorio
- Network metabolico
- Network energetico-cellulare

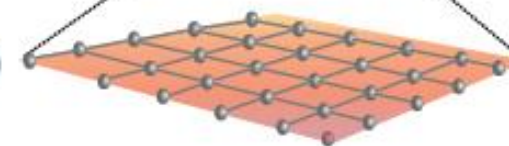
Network funzionale



● **BIOLOGICAL LEVEL (LIVELLO BIOLOGICO)**

- Network genetico
- Network molecolare
- Network cellulare
- Network degli organi

Network biologico





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

**Enzo Emanuele<sup>a,\*</sup>, Pierluigi Politi<sup>b</sup>, Marika Bianchi<sup>a</sup>, Piercarlo Minoretti<sup>a</sup>, Marco Bertona<sup>a</sup>, Diego Geroldi<sup>a</sup>**

<sup>a</sup>*Interdepartmental Center for Research in Molecular Medicine (CIRMC), University of Pavia, Viale Taramelli 24, I-27100 Pavia, Italy*

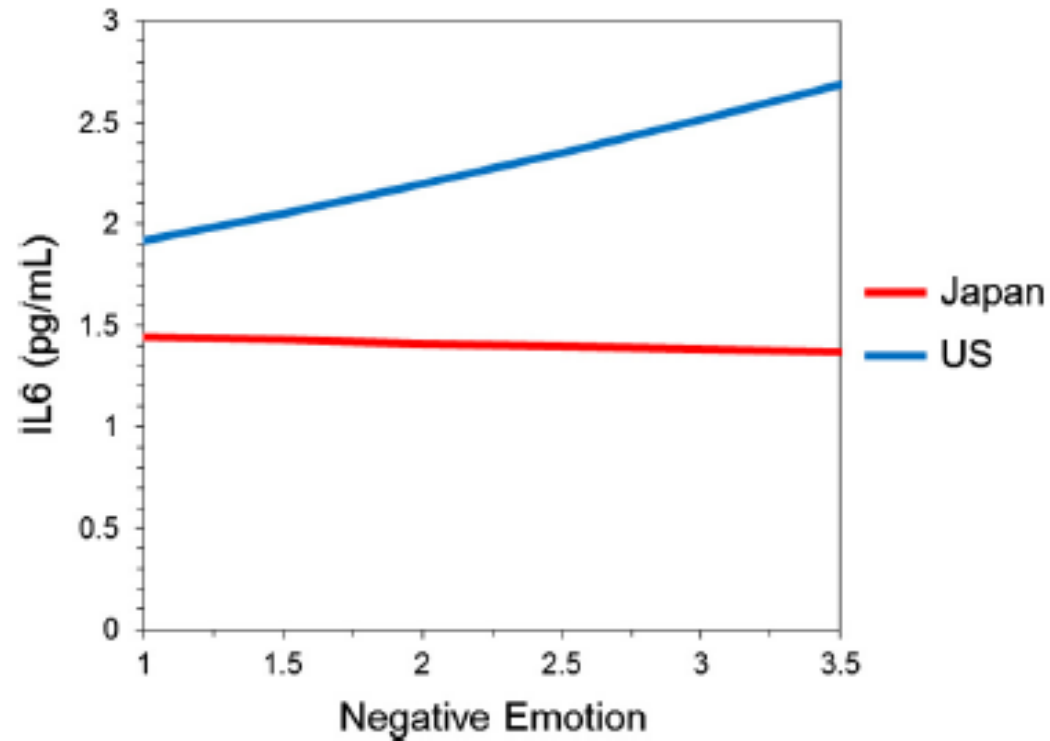
<sup>b</sup>*Department of Health Sciences, Section of Psychiatry, University of Pavia, Pavia, Italy*

Review

# **Can the brain inhibit inflammation generated in the skin? The lesson of $\alpha$ -melanocyte-stimulating hormone**

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



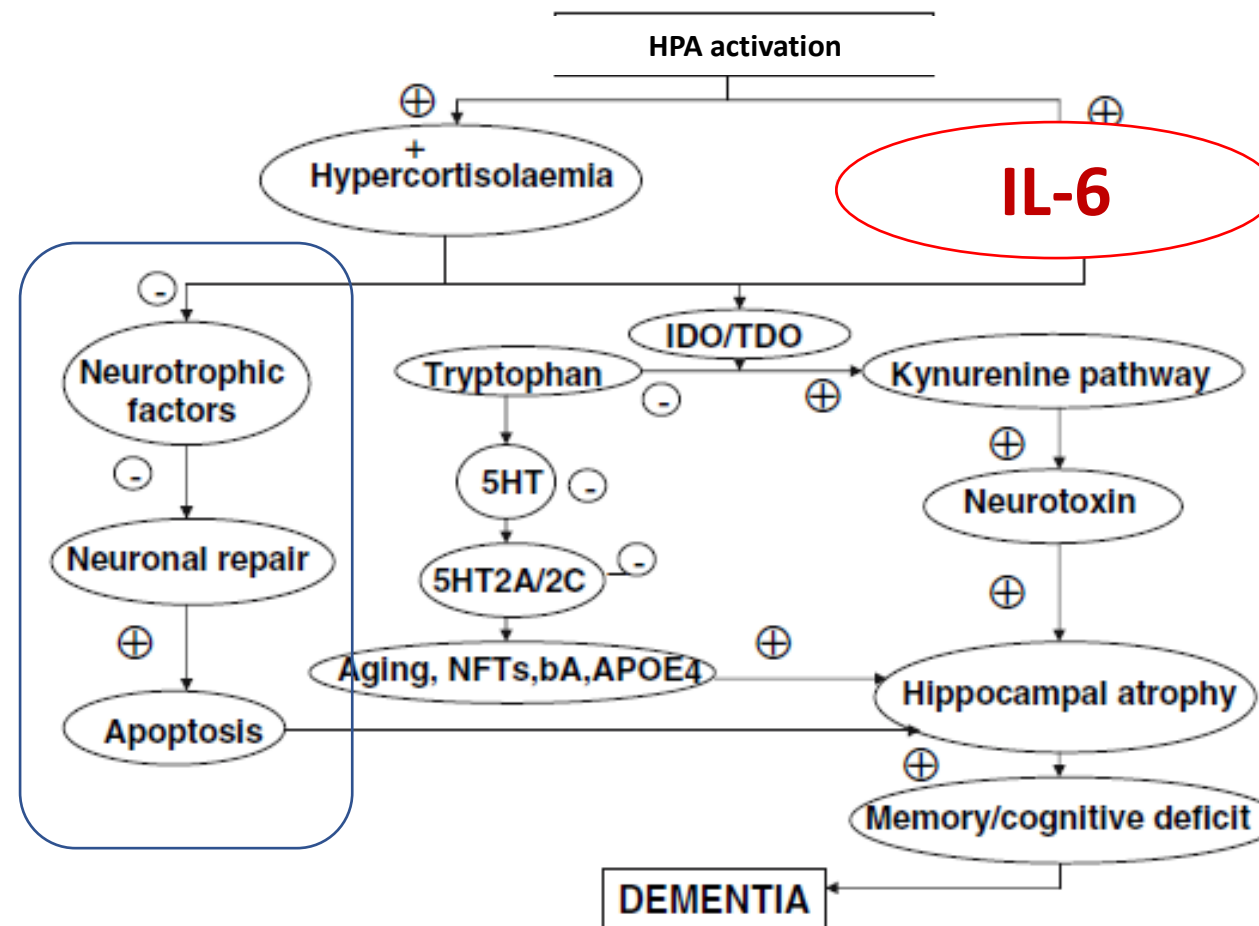


**Fig. 1.** Cultural moderation of the association between negative emotions and IL-6 after controlling for gender, age, and years of education, positive emotions, neuroticism, extraversion, smoking status, alcohol consumption, the number of chronic conditions linked to inflammation, and log-transformed 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,  $t(1363) = 0.35$ ,  $p = .73$ .



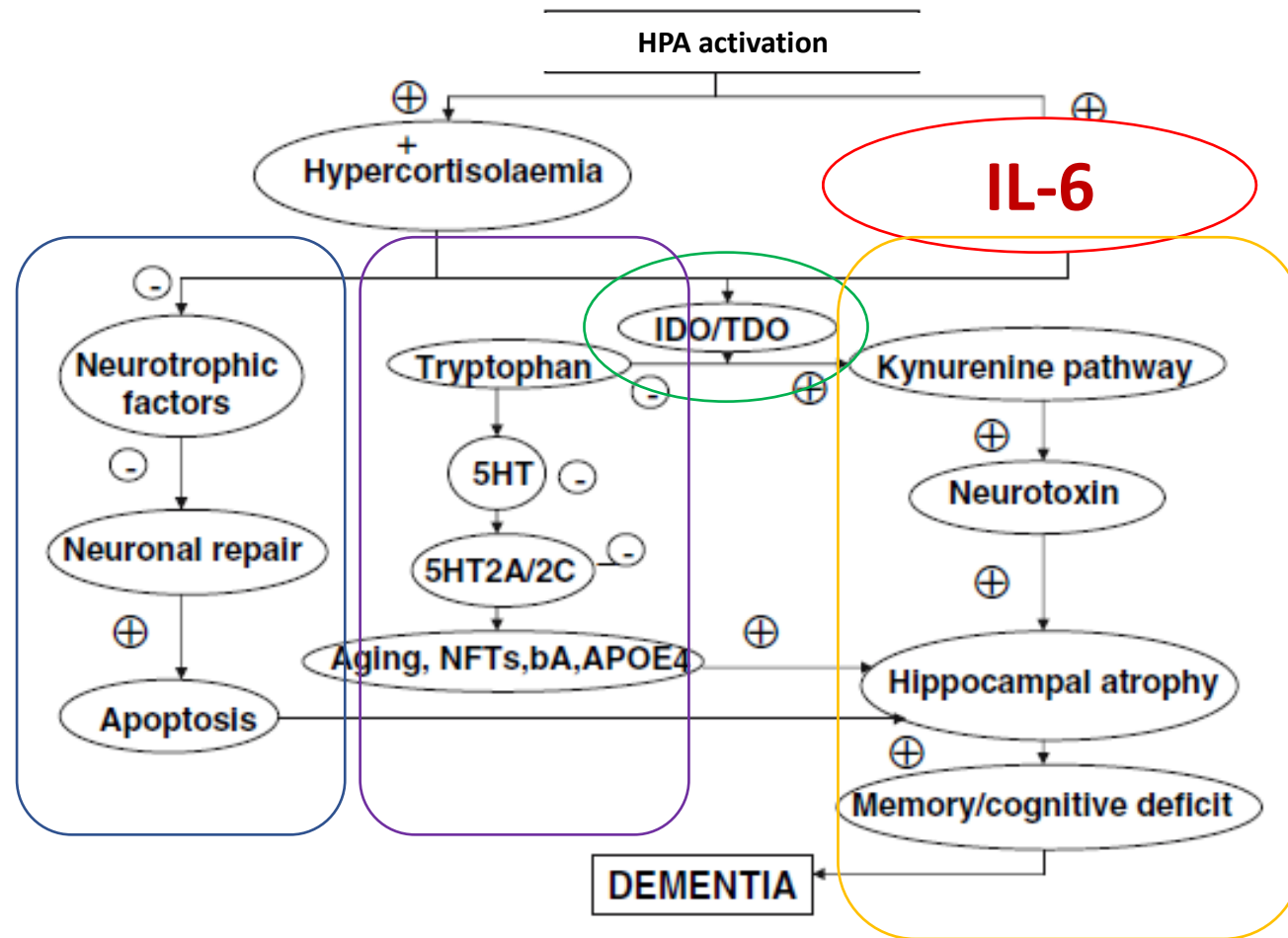
# The psycho-endocrine-neuro connection...

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

## 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

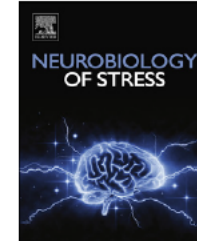
Leonard BE. *Inflammation, Depression and Dementia: Are they Connected?* *Neurochem Res* 2007



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*

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#### *Article history:*

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

*Sylvie Vancassel<sup>1,2</sup>, Lucile Capuron<sup>1,2</sup> and Nathalie Castanon<sup>1,2\*</sup>*

<sup>1</sup> UMR 1286, Laboratory of Nutrition and Integrative Neurobiology (NutriNeuro), INRA, Bordeaux, France, <sup>2</sup> UMR 1286, Laboratory of Nutrition and Integrative Neurobiology (NutriNeuro), Bordeaux University, Bordeaux, France

tetrahydrobiopterin (BH4)

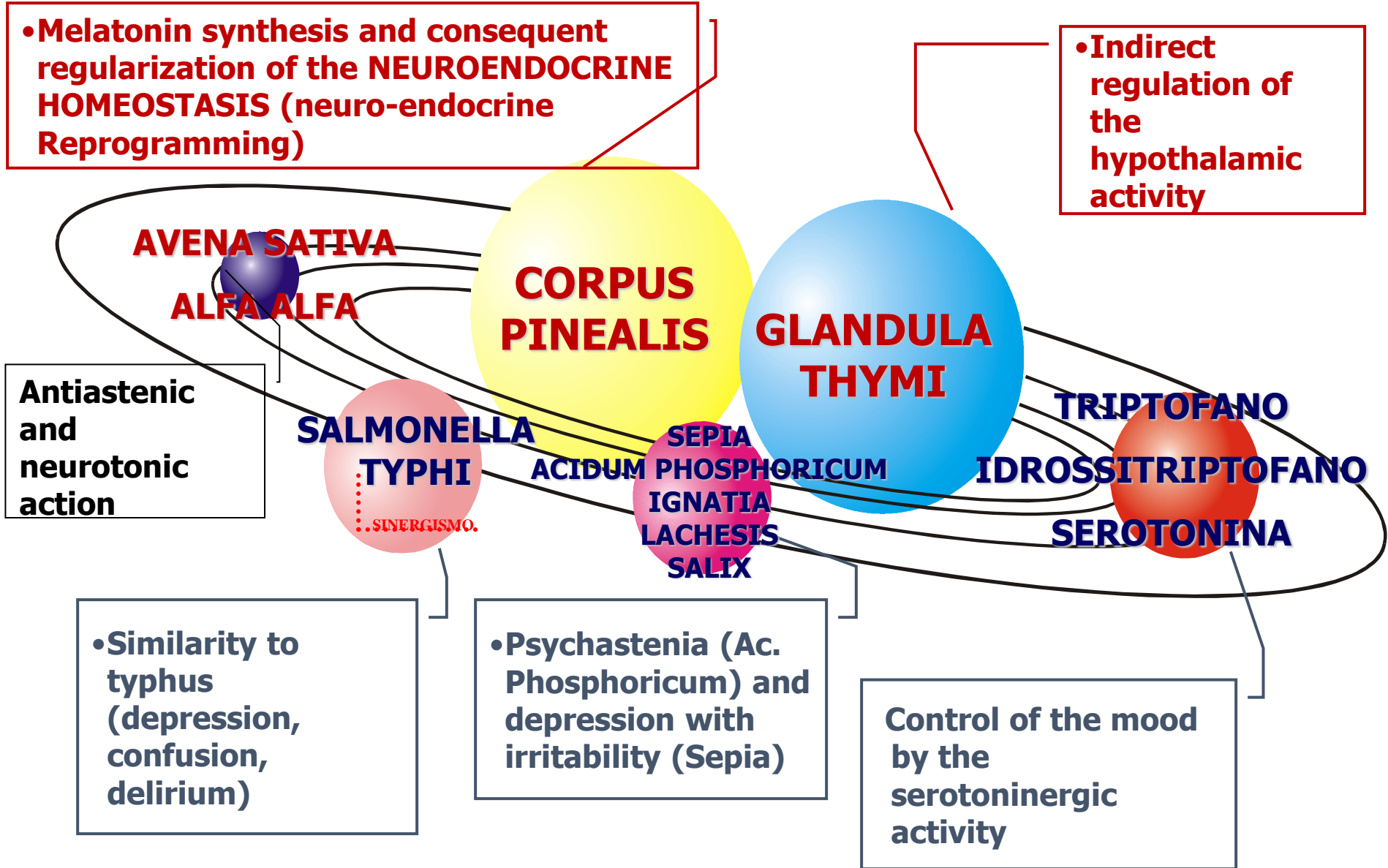


## DIRECTIONS AND ADMINISTRATION

20 drops twice a day for cycles of 2 months or more (to be repeated).

Sub-lingual administration directly under the tongue or in a little quantity of water, preferably far from meals.

# GUNA-MOOD





## 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.

## *Molecules involved in the PTSD*

- Catecolamines: adrenaline-nor-adrenaline                      HIGH
- Serotonin    LOW RESPONSE
- Endorfine (oppiacei)    LOW
- T3 – T4    HIGH
- Melatonina    SWING
-



## The Relationship Between Intestinal Microbiota and the Central Nervous System in Normal Gastrointestinal Function and Disease



Stephen M. Collins



Przemyslaw Borok

The Fanccombe Family Digestive Health Research Institute, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

Although many people are aware of the communication that occurs between the gastrointestinal (GI) tract and the central nervous system, fewer know about the ability of the central nervous system to influence the microbiota or of the microbiota's influence on the brain and behavior. Within the GI tract, the microbiota have a mutually beneficial relationship with their host that maintains normal mucosal immune function, epithelial barrier integrity, motility, and nutrient absorption. Disruption of this relationship alters GI function and disease susceptibility. Animal studies suggest that perturbations of behavior, such as stress, can change the composition of the microbiota; these changes are associated with increased vulnerability to inflammatory stimuli in the GI tract. The mechanisms that underlie these alterations are likely to involve stress-induced changes in GI physiology that alter the habitat of enteric bacteria. Furthermore, experimental perturbation of the microbiota can alter behavior, and the behavior of germ-free mice differs from that of colonized mice. Gaining a better understanding of the relationship between behavior and the microbiota could provide insight into the pathogenesis of functional and inflammatory bowel disorders.

The gut-brain axis (GBA) is a bidirectional neurohumoral communication system that integrates brain and gastrointestinal (GI) functions. The GBA has been implicated in the pathophysiology of functional GI disorders, and evidence is emerging for its role in the pathogenesis of inflammatory disorders of the gut such as inflammatory bowel disease (IBD). It would be a relatively straightforward matter to integrate information about the intestinal microbiota with that of the GBA by simply reviewing literature on interactions between flora and the GI tract. However, the brain is the most influential organ within the axis, and communication is bidirectional. Thus, it is important to

consider the influence of the brain on the microbial content of the gut and, conversely, to examine the evidence showing that the intestinal microbiota influences the brain and behavior. Investigation of the integration of the intestinal microbiota into the GBA could improve the understanding of the pathophysiology of both functional<sup>1</sup> and inflammatory<sup>2</sup> bowel conditions.

The GBA contributes to homeostasis of several systems, including GI function, appetite, and weight control. Because GI motility and epithelial function are critical determinants of the habitat for the microbiota, changes induced by the central nervous system or the GI tract alter the habitat and perturb the intestinal microbiota.<sup>3</sup> The longstanding observation that oral antibiotics and laxatives ameliorate hepatic encephalopathy provides a potent reminder that the intestinal microbiota is capable of influencing behavior, albeit under pathologic conditions.<sup>4</sup> Taken together, these observations provide a framework for considering the integration of the intestinal microbiota into the bidirectional GBA.

### The Intestinal Microbiota

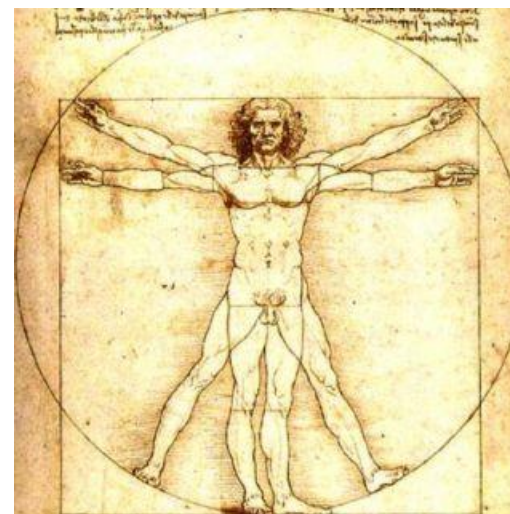
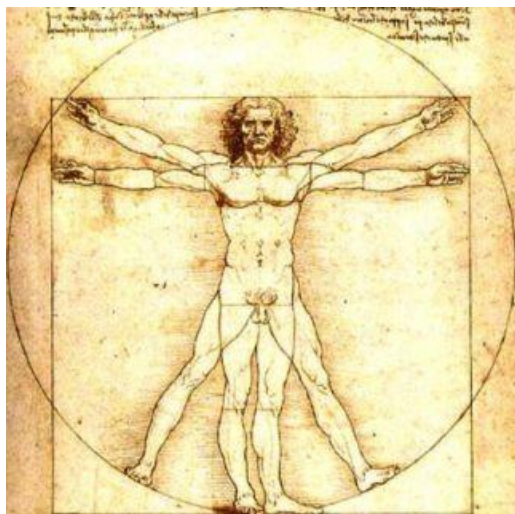
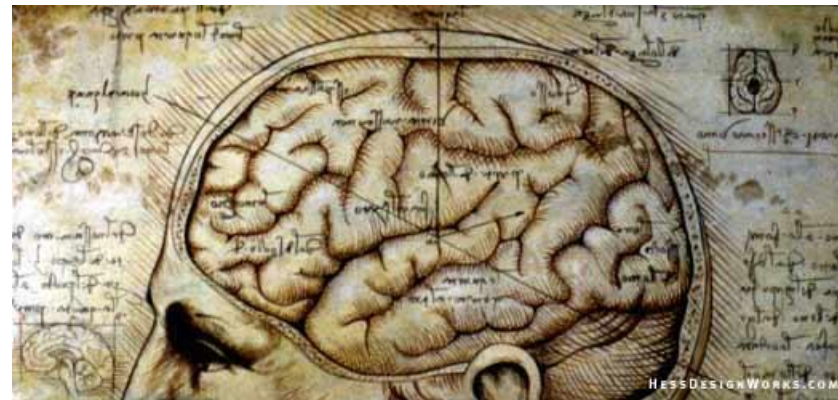
The gut contains a vast and complex microbial ecosystem, comprising mainly bacteria, of which most are strict anaerobes; it also includes fungi and viruses,<sup>5-7</sup> but only bacteria are considered in this review. Commensal bacteria instruct the immune and physiologic systems throughout life and are responsible for the presence of inflammatory and immune cells in the healthy gut: so-called "physiologic" or "controlled" inflammation. The term physiologic inflammation refers to the presence of

**Abbreviations used in this paper:** ACTH, adrenocorticotropic hormone; GBA, gut-brain axis; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; SPF, specific pathogen-free.

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0018-5085/09/\$36.00  
doi:10.1053/j.gast.2009.01.075

# PSYCHO-SOMATIC OR SOMATO-PSYCHIC?



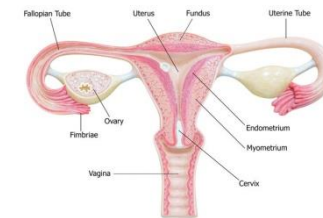
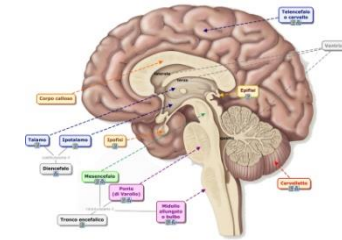


# MOOD SWINGS IN POSTMENOPAUSAL SYNDROME

Decreased serotonin function is associated with numerous cognitive and affective disorders. Women in menopause have the more mood swings than before menopause.

- Menopausal loss of estrogen induces low serotonin (5HT) levels.
- Estrogen-Serotonin signaling is implicated in the pathophysiology of mood disorders including depression.

The ovaries slow the production of estrogen and progesterone during menopause.



- Hiroi R, Weyrich G, Koebele SV, Mennenga SE, Talboom JS, Hewitt LT, Lavery CN, et al. Benefits of Hormone Therapy Estrogens Depend on Estrogen Type: 17 $\beta$ -Estradiol and Conjugated Equine Estrogens Have Differential Effects on Cognitive, Anxiety-Like, and Depressive-Like Behaviors and Increase Tryptophan Hydroxylase-2 mRNA Levels in Dorsal Raphe Nucleus Subregions. *Front Neurosci.* 2016;10:517.
- Chhibber A, Woody SK, Karim Rumi MA, Soares MJ, Zhao L. Estrogen receptor  $\beta$  deficiency impairs BDNF-5-HT2A signaling in the hippocampus of female brain: A possible mechanism for menopausal depression. *Psychoneuroendocrinology.* 2017;82:107-116.
- Heidari M, Ghodusi M, Rafiei H. Sexual Self-concept and Its Relationship to Depression, Stress and Anxiety in Postmenopausal Women. *J Menopausal Med.* 2017;23(1):42-48.

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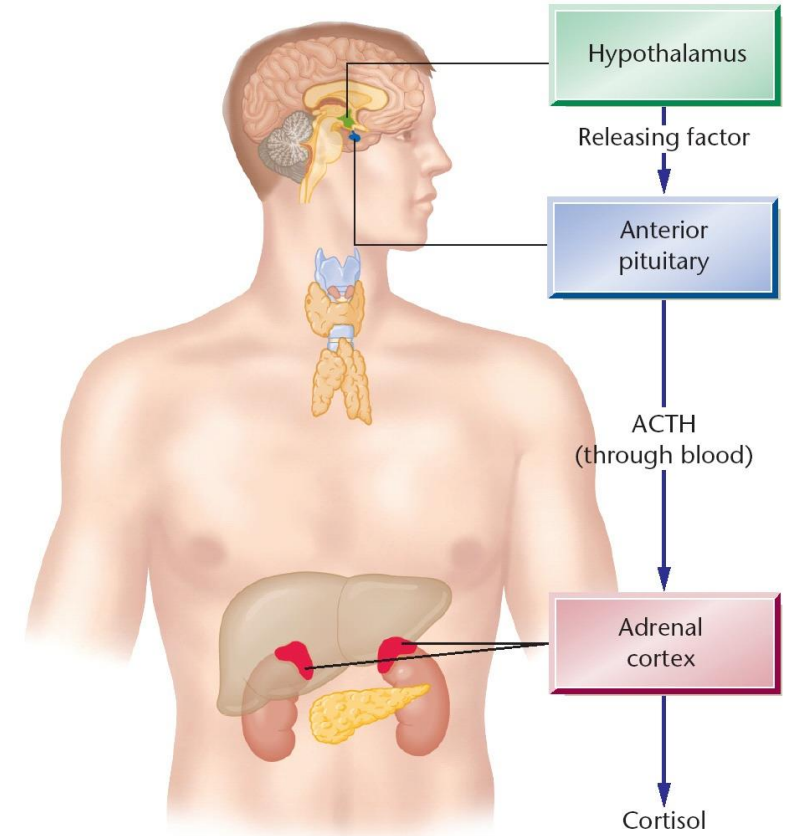
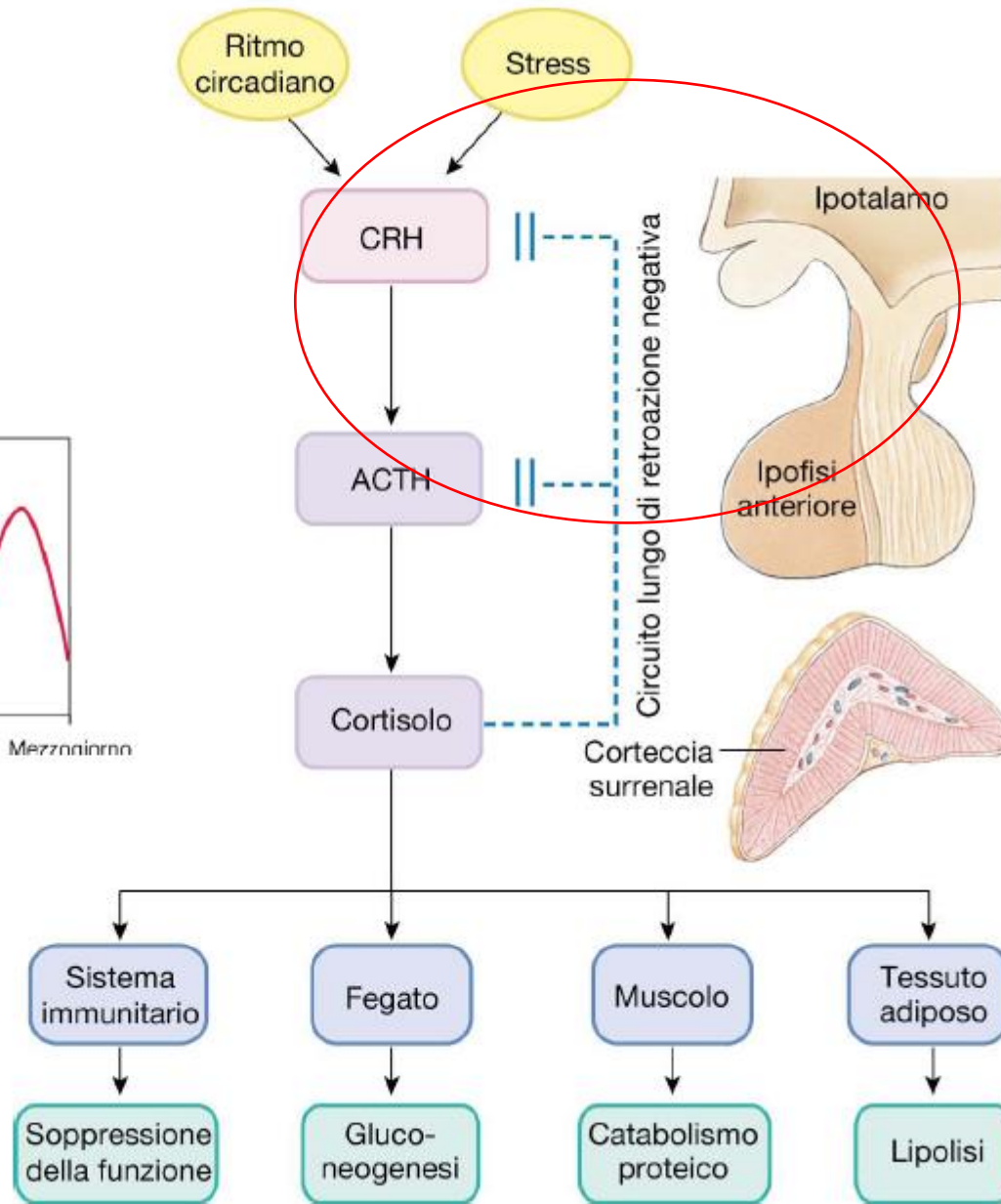
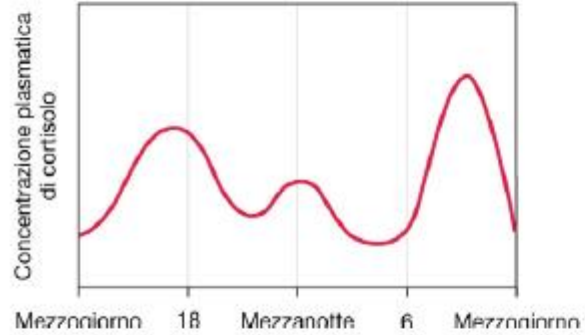
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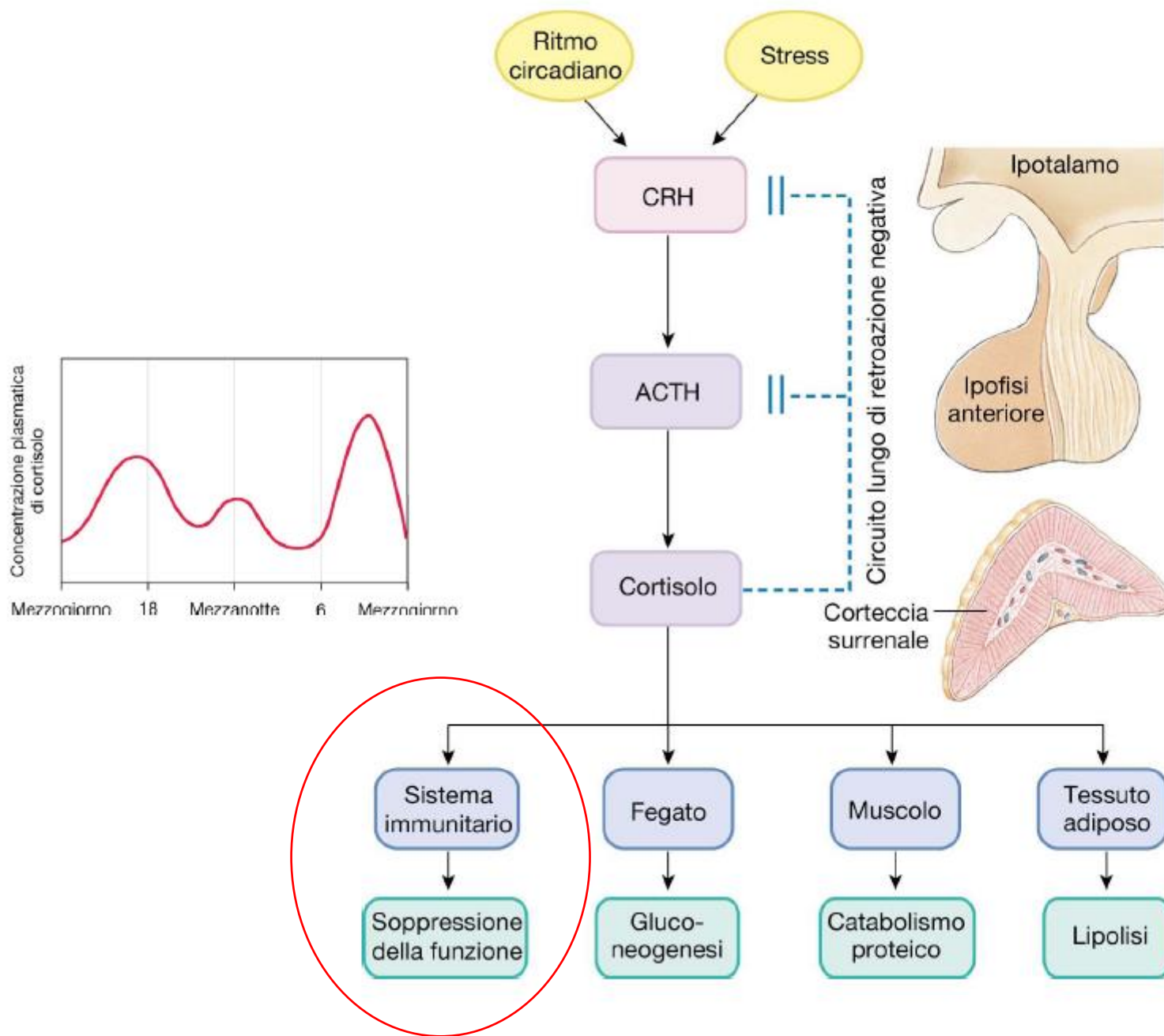
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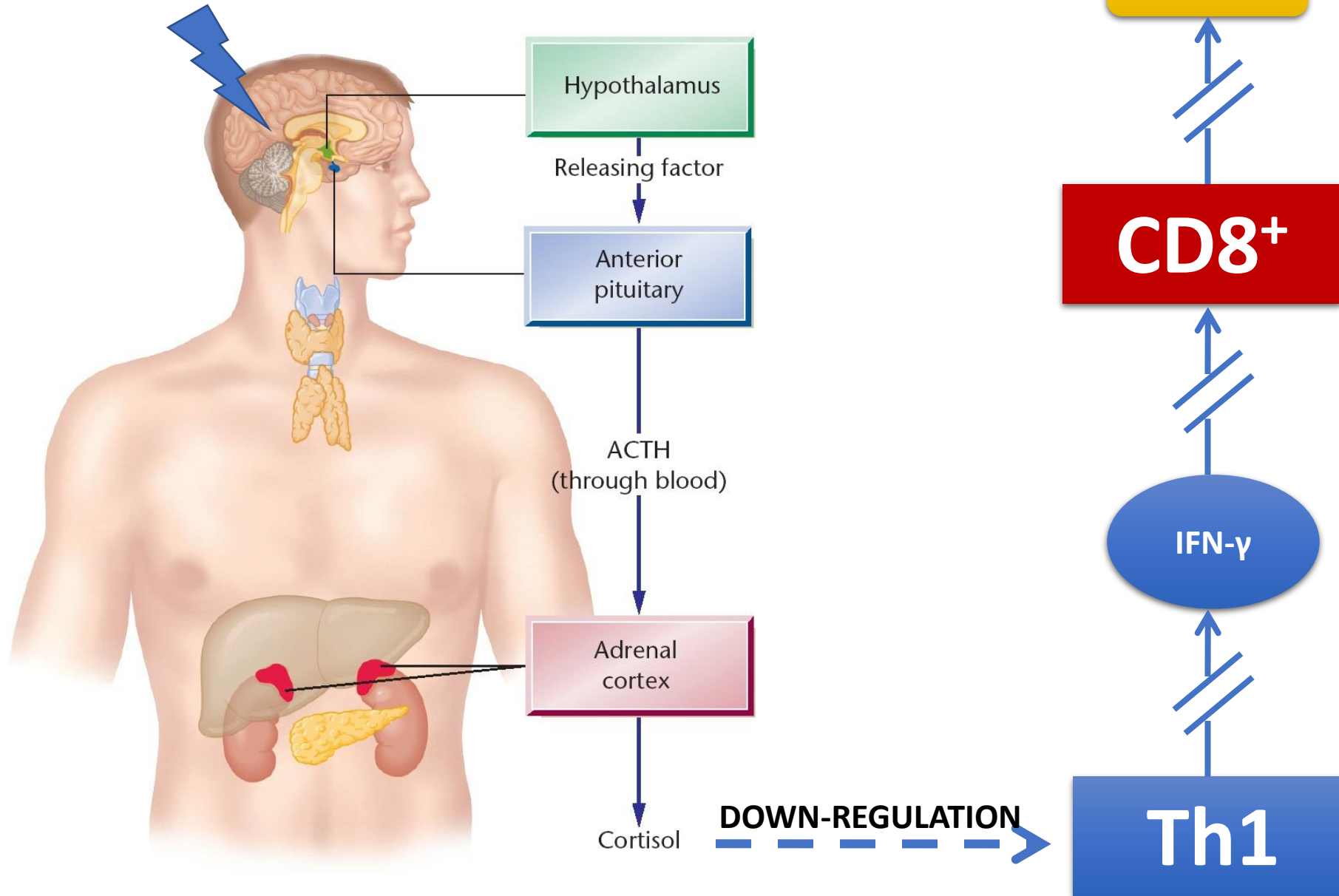
CIRCULARITY



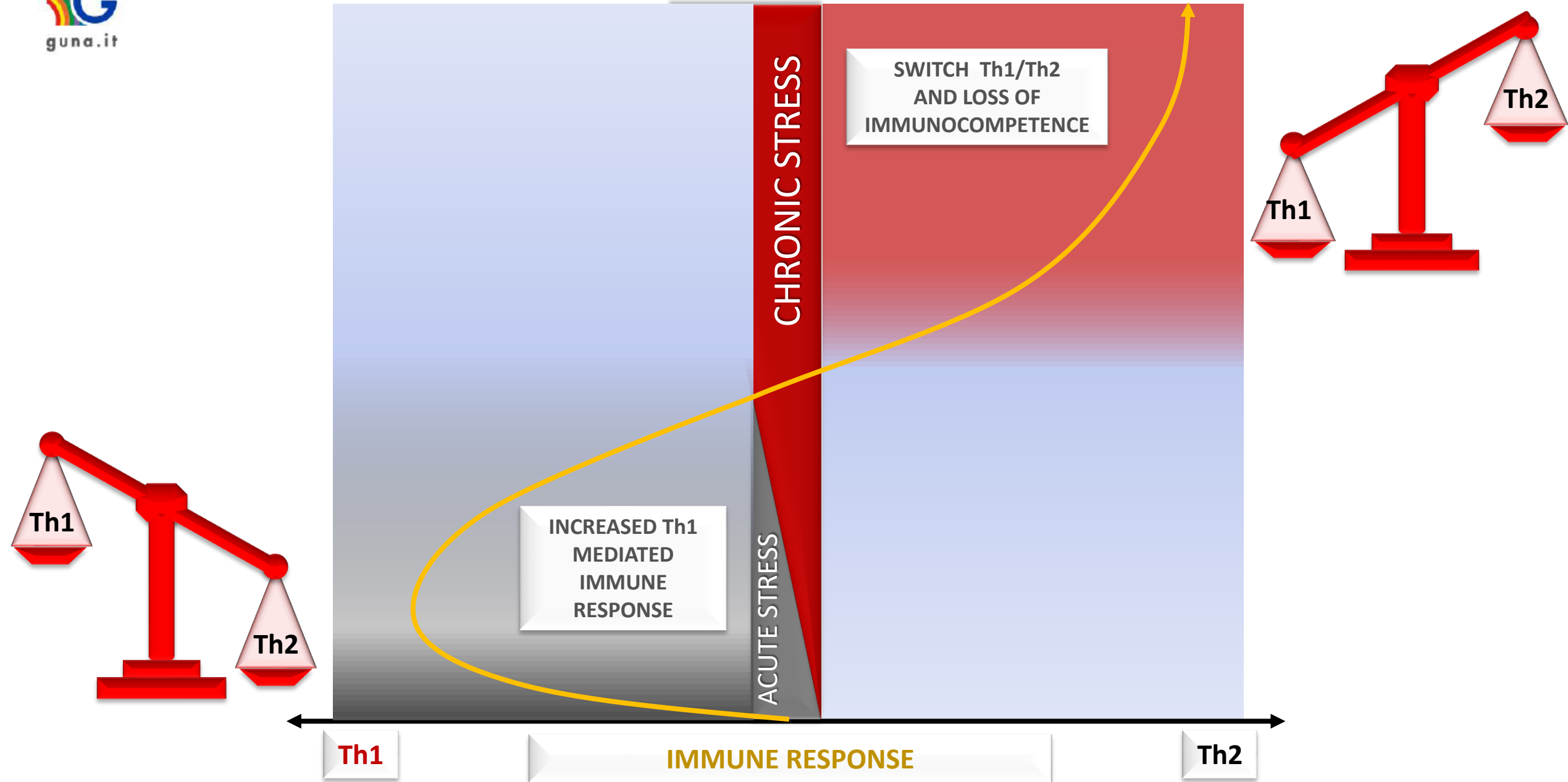


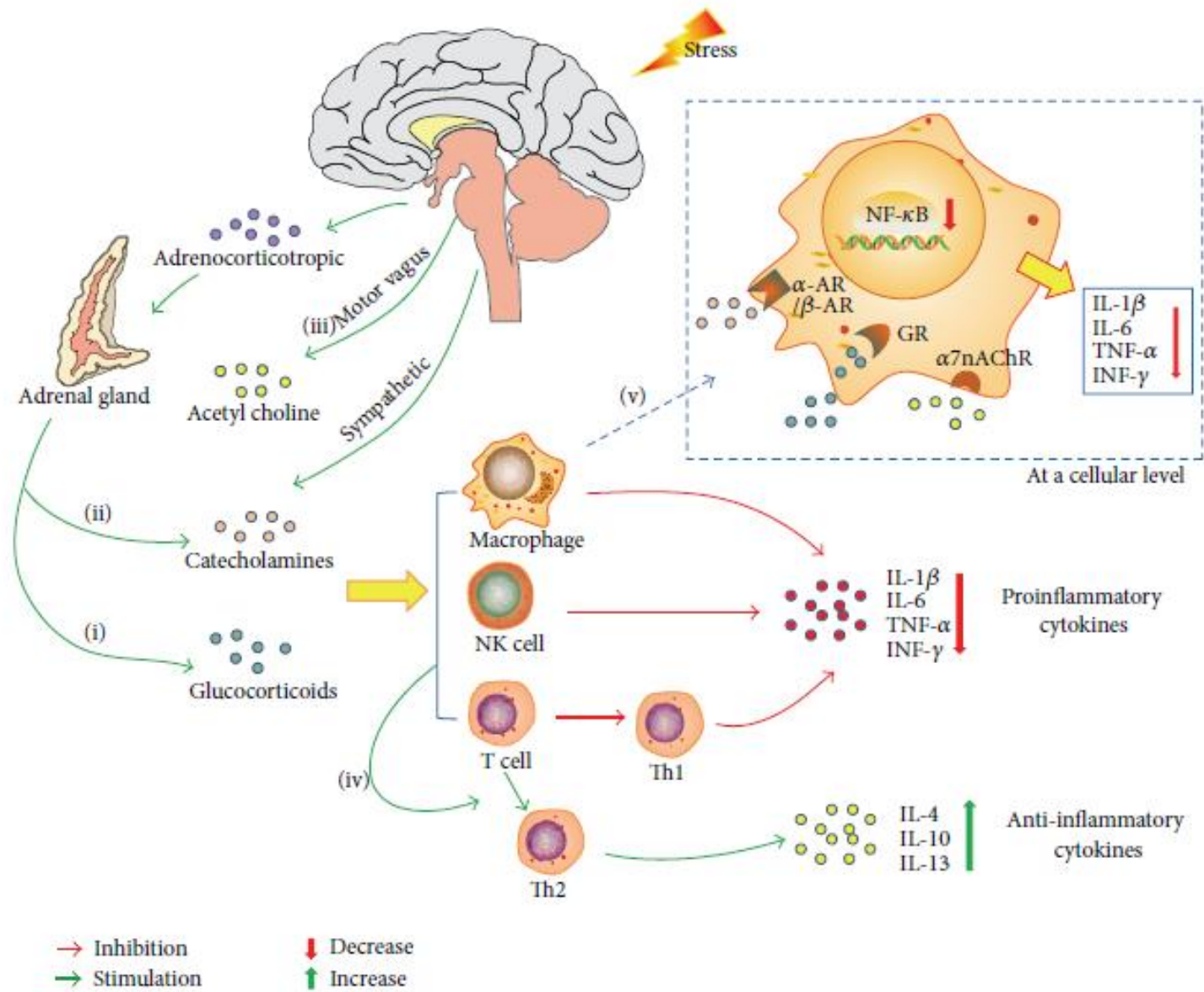


# STRESS



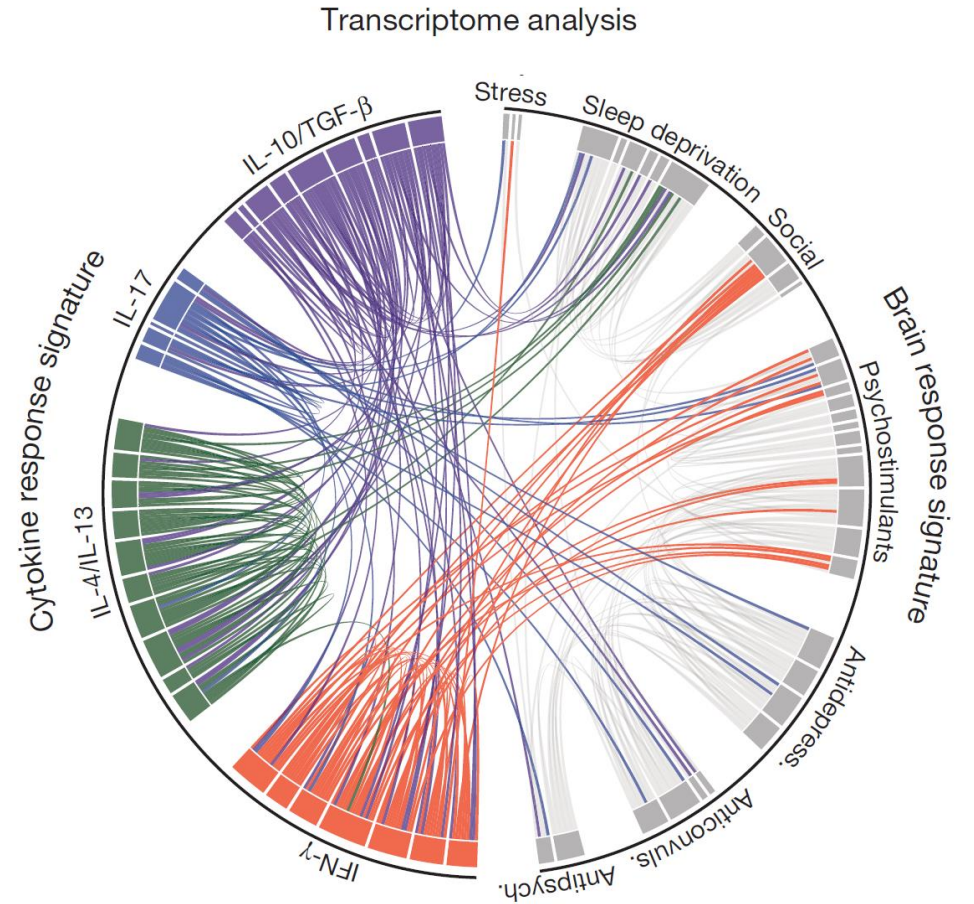
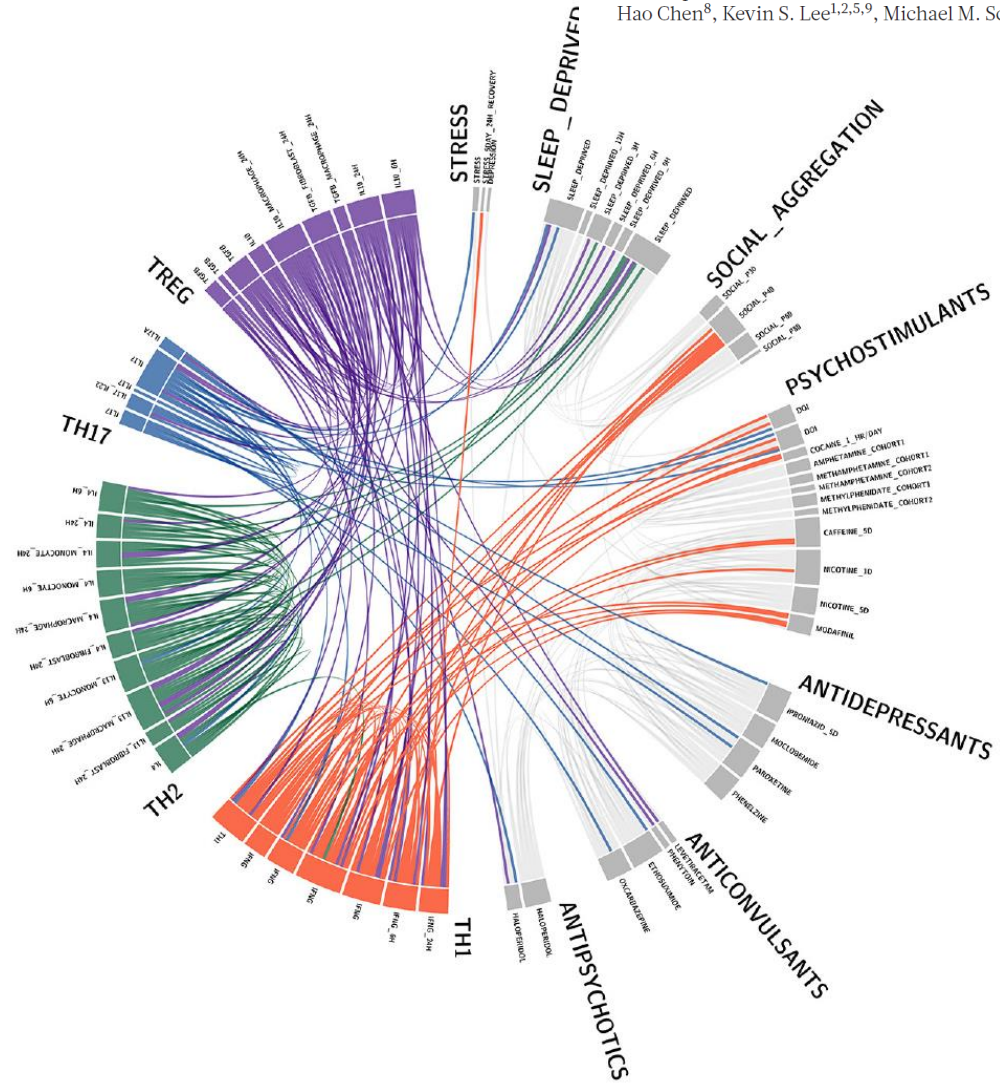






## Unexpected role of interferon- $\gamma$ in regulating neuronal connectivity and social behaviour

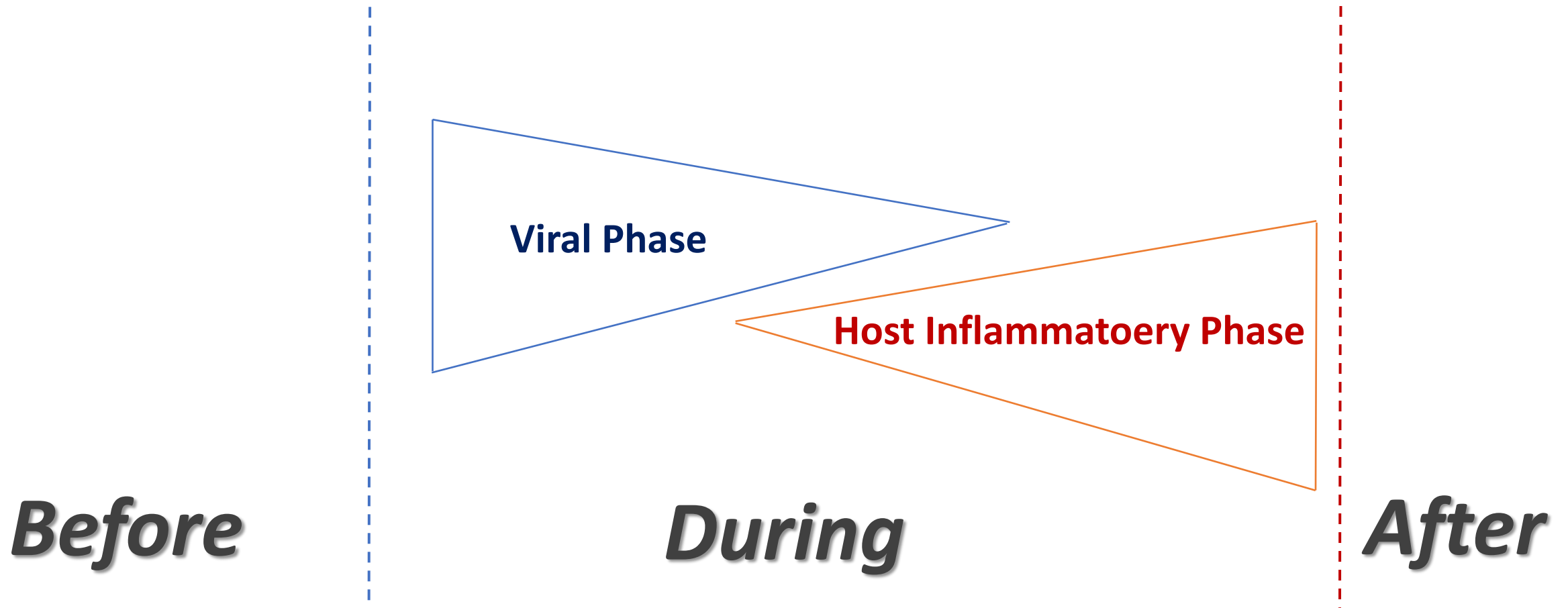
Anthony J. Filiano<sup>1,2</sup>, Yang Xu<sup>3</sup>, Nicholas J. Tustison<sup>4</sup>, Rachel L. Marsh<sup>1,2</sup>, Wendy Baker<sup>1,2</sup>, Igor Smirnov<sup>1,2</sup>, Christopher C. Overall<sup>1,2</sup>, Sachin P. Gadani<sup>1,2,5,6</sup>, Stephen D. Turner<sup>7</sup>, Zhiping Weng<sup>8</sup>,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



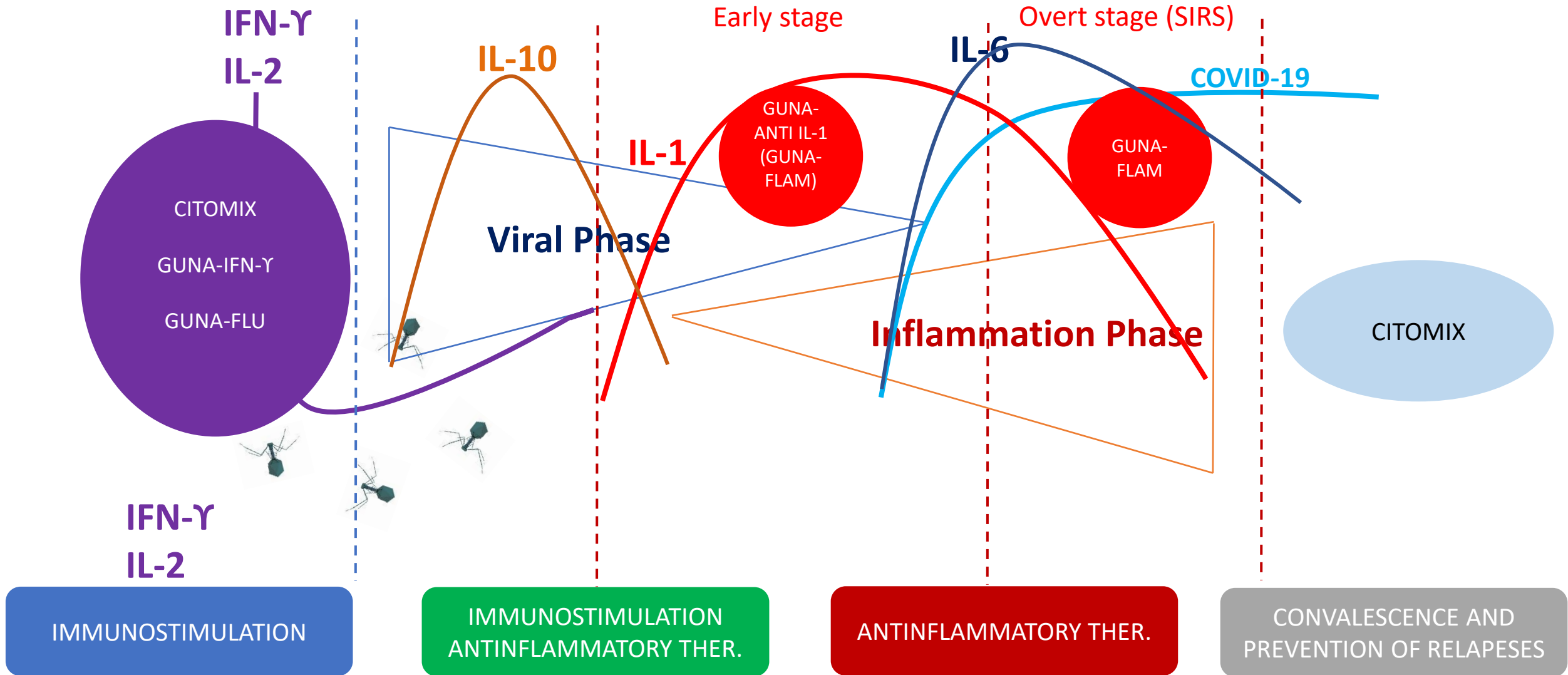
# Our (unique) goal

- *To immunostimulate without inflaming*
- *To reduce the inflammation without immunosuppressing*

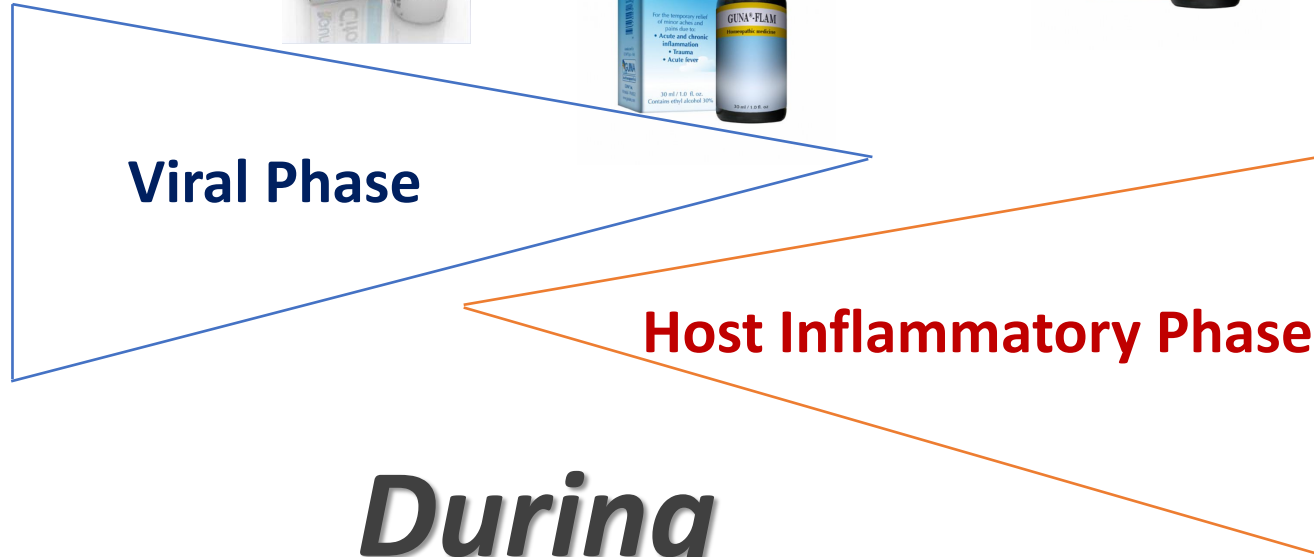
# Our goal in infectious diseases



# Space-Time Immunomodulation



# The bag of tools



**Viral Phase**

**Host Inflammatory Phase**

**Before**

**During**

**After**

IMMUNOSTIMULATION

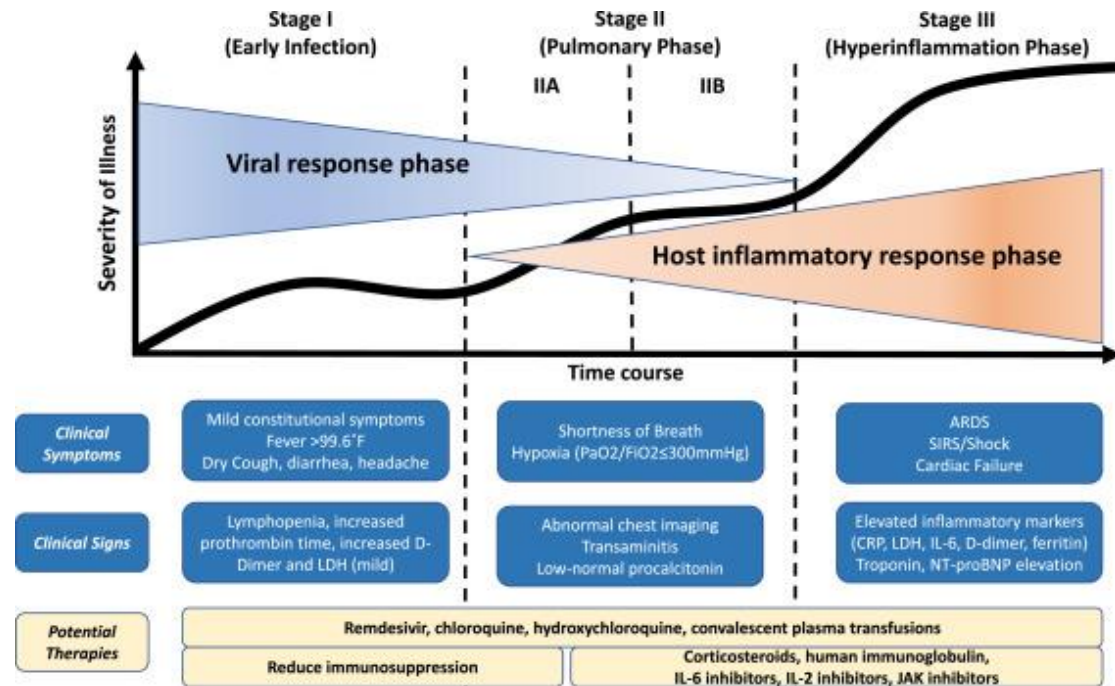
IMMUNOSTIMULATION  
ANTINFLAMMATORY THER.

ANTINFLAMMATORY THER.

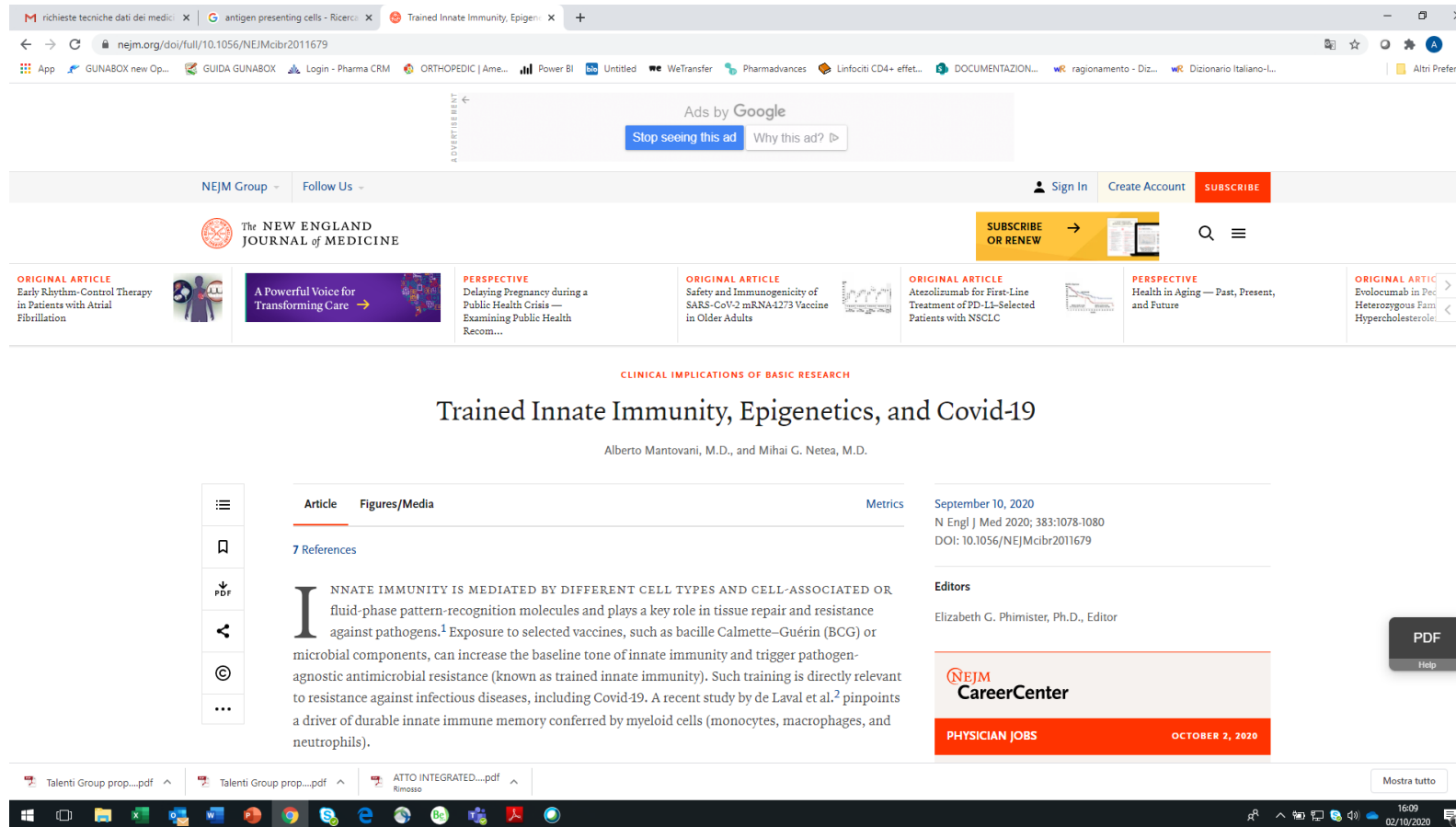
CONVALESCENCE AND  
PREVENTION OF RELAPSES

# Our (unique) goal

- *Before*
- *During*
- *After*





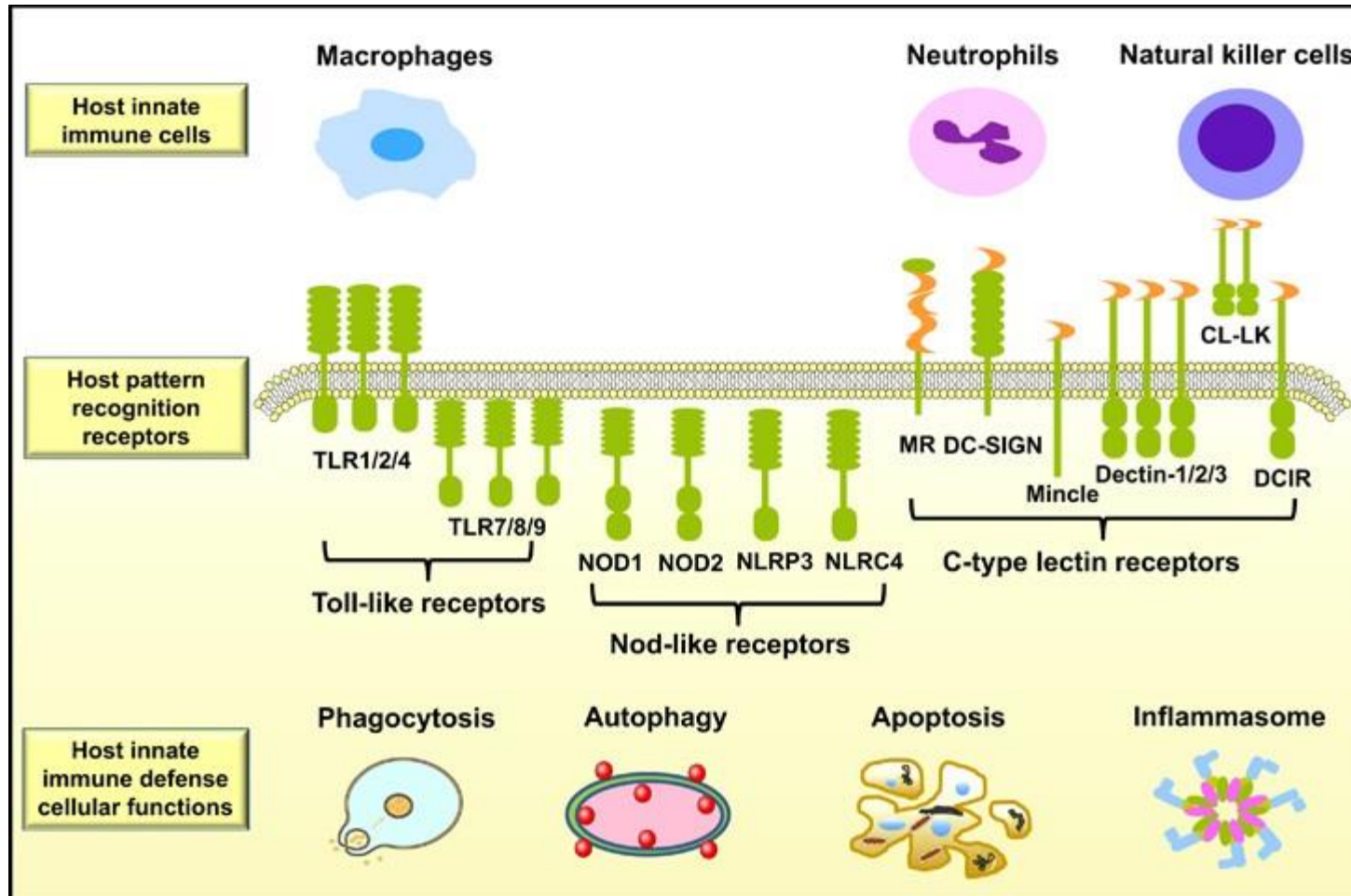


INNATE IMMUNITY REPRESENTS 90% OF PUR DEFENSIVE IMMUNOLOGICAL POTENTIAL.

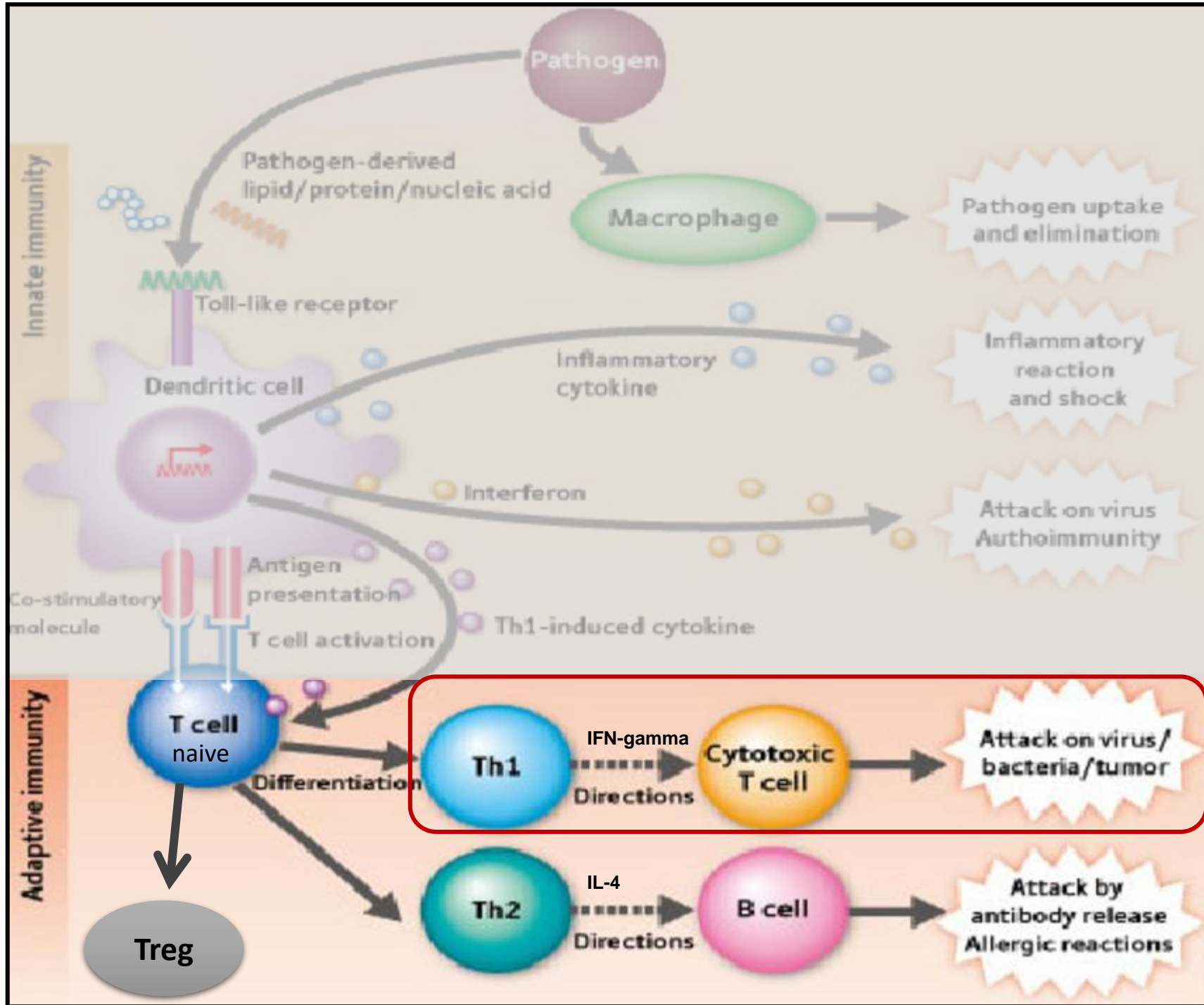
# INNATE IMMUNITY

They are part of Innate Immunity:

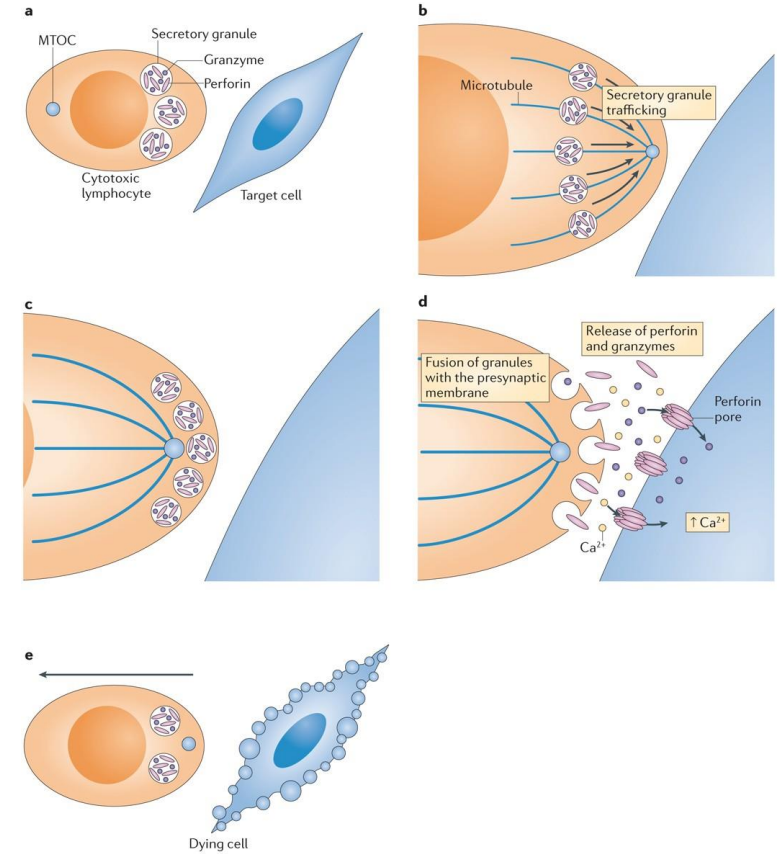
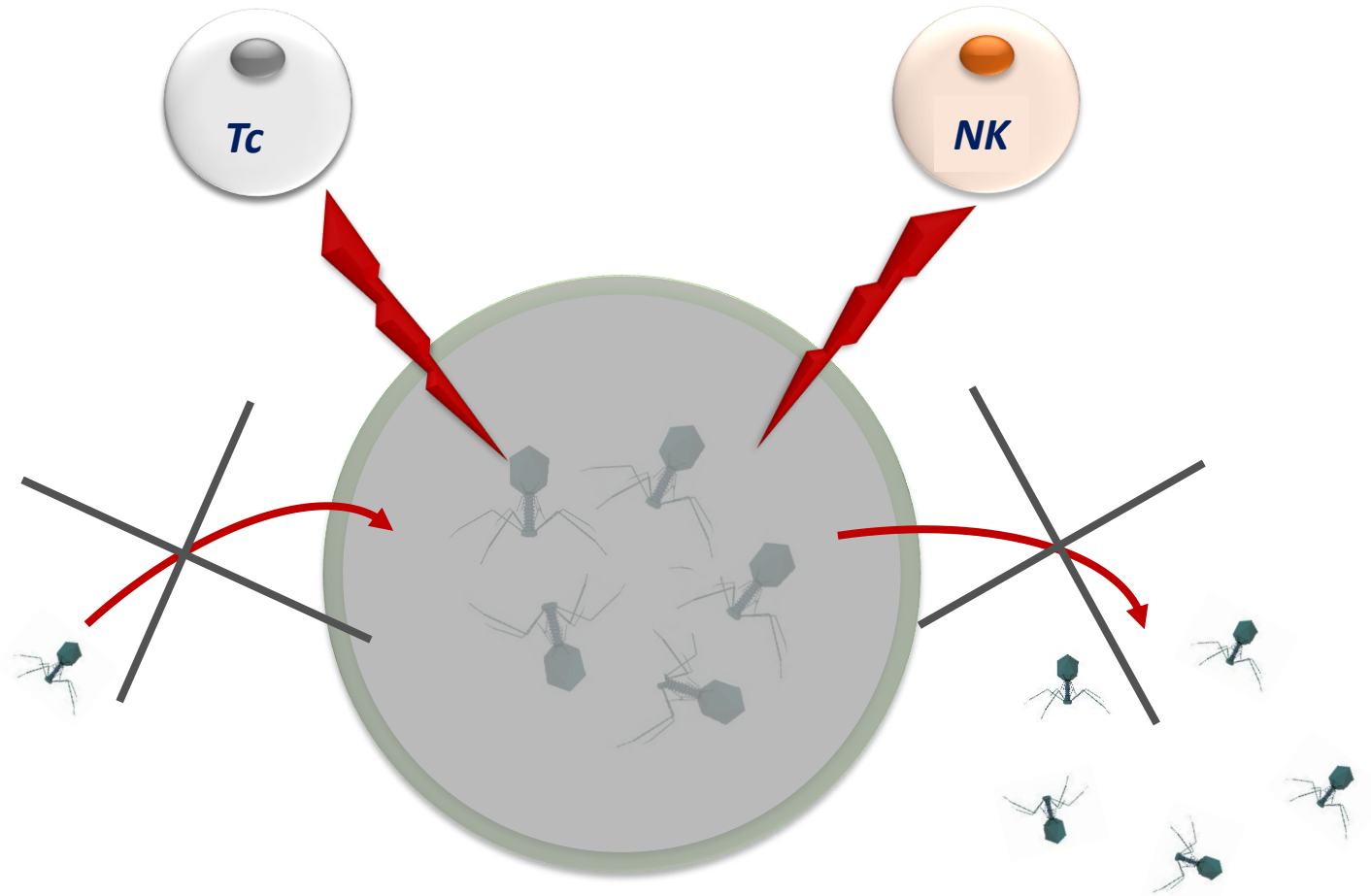
- **Anatomic barriers**
- **Physiological barriers** (lisozima, interferons, and complement)
- **Endocytosis/Phagocytosis**
- **Inflammatory barriers**



# ADAPTIVE IMMUNITY



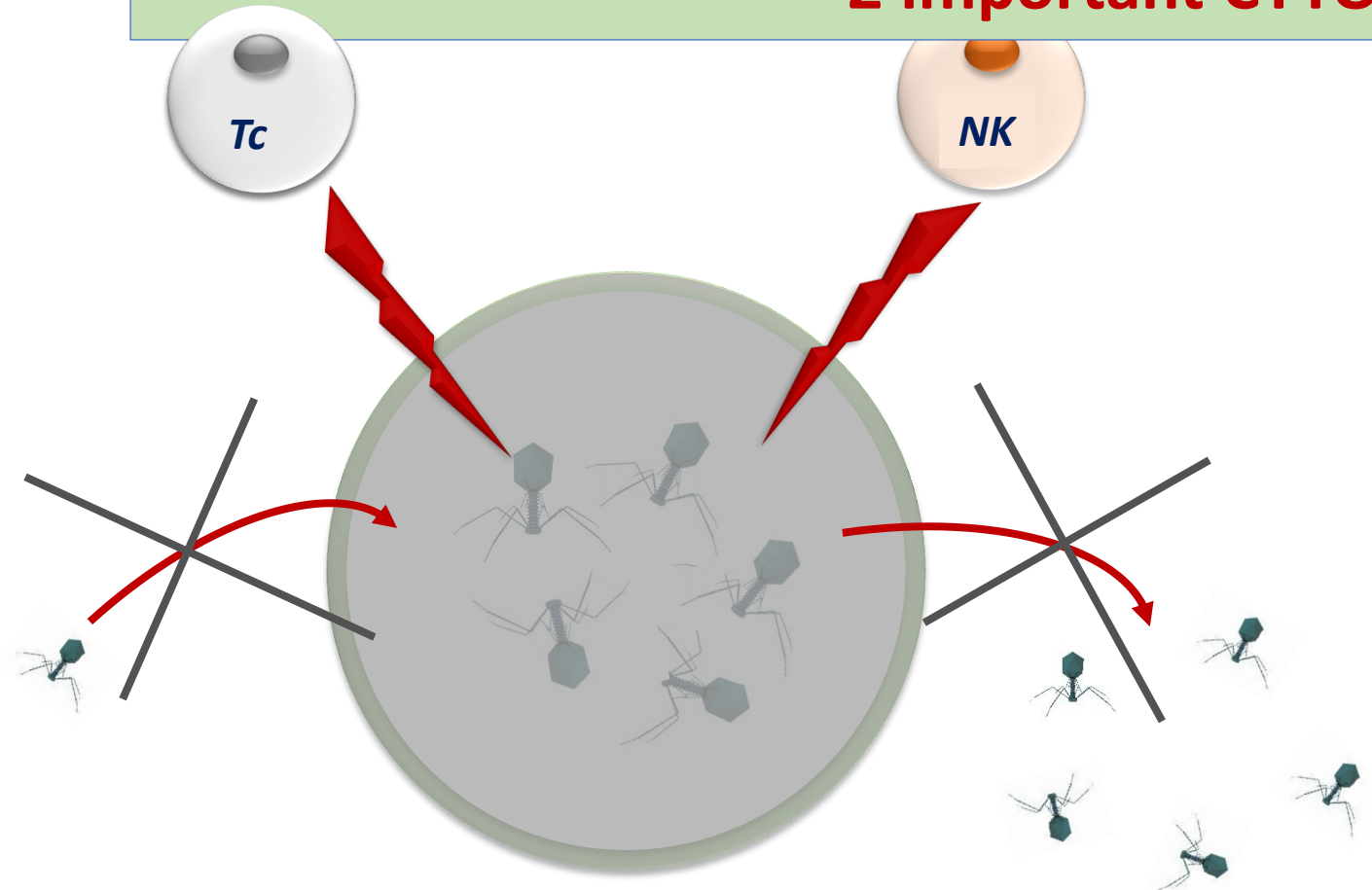
# CYTOTOXIC ACTIVITY OF Tc and NK-cells



Nature Reviews | Immunology

# How to support the activity of T-cytotoxic cells and Natural Killer cells?

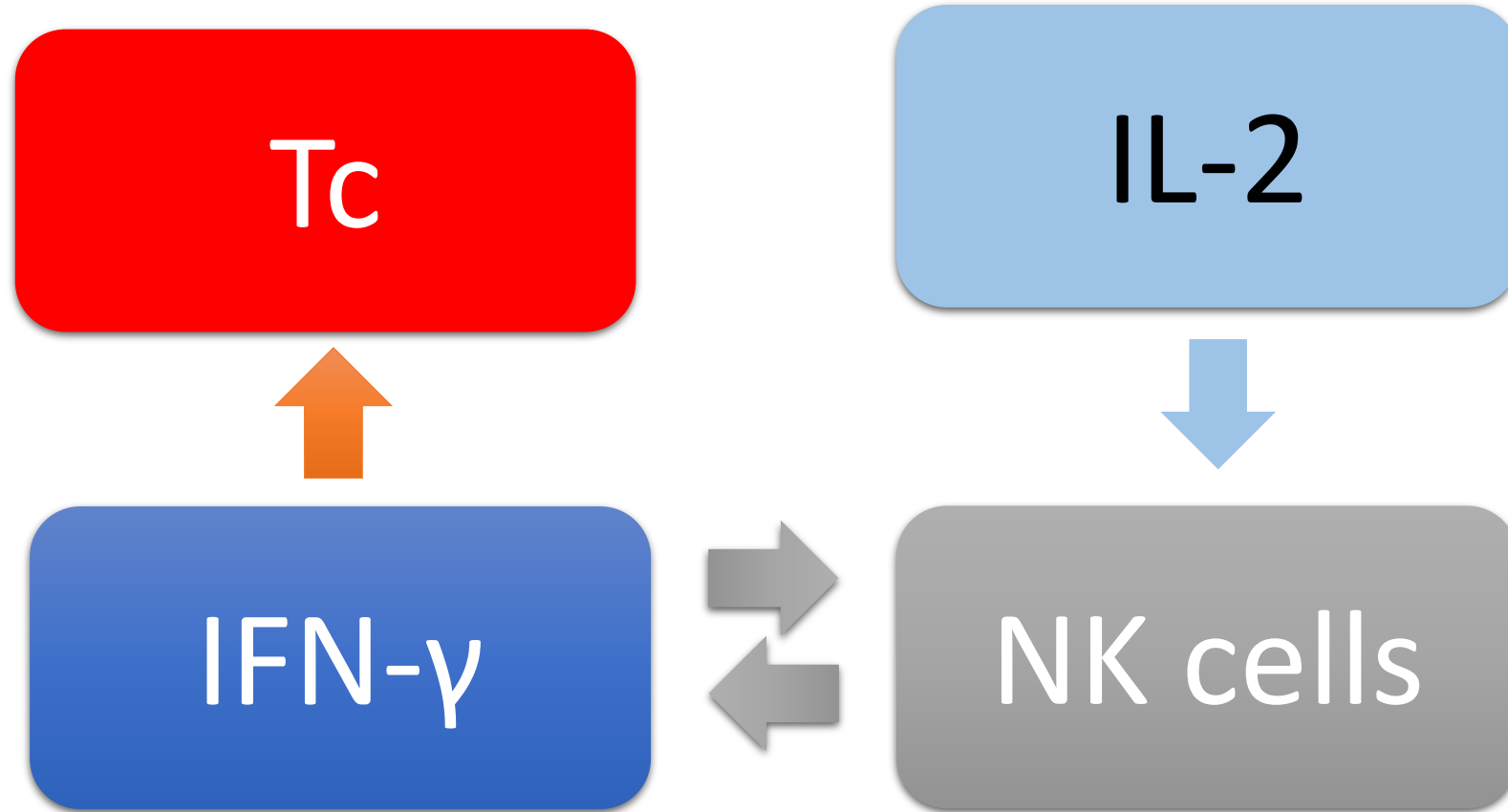
**2 important CYTOKINES**



IL-2

IFN- $\gamma$

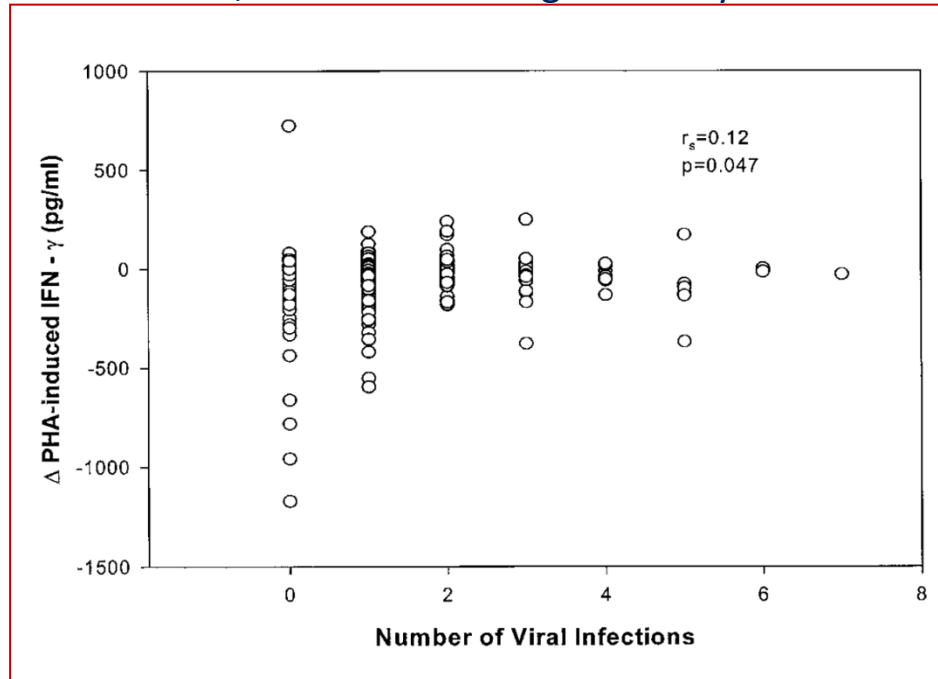
# CYTOTOXIC ACTIVITY OF IFN-gamma



# Cytokines response pattern, viruses exposure and respiratory infections during the first year of life



285 children, monitored during the first year of life



**Reduced production of IFN-gamma**  
in the first year of life (57–26  
pg/ml, p 0.001)

Significant positive correlation  
between number of respiratory  
infections and reduced production  
of **IFN-gamma**  
(rs 0.12, p 0.047)

# IL-2/IL-6 RATIO AND AGING

INCREASING OF:

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



**A**  
**PROINFLAMMATORY**  
**STATUS OF HEALTHY**  
**ELDERLY AND**  
**CENTENARIANS**



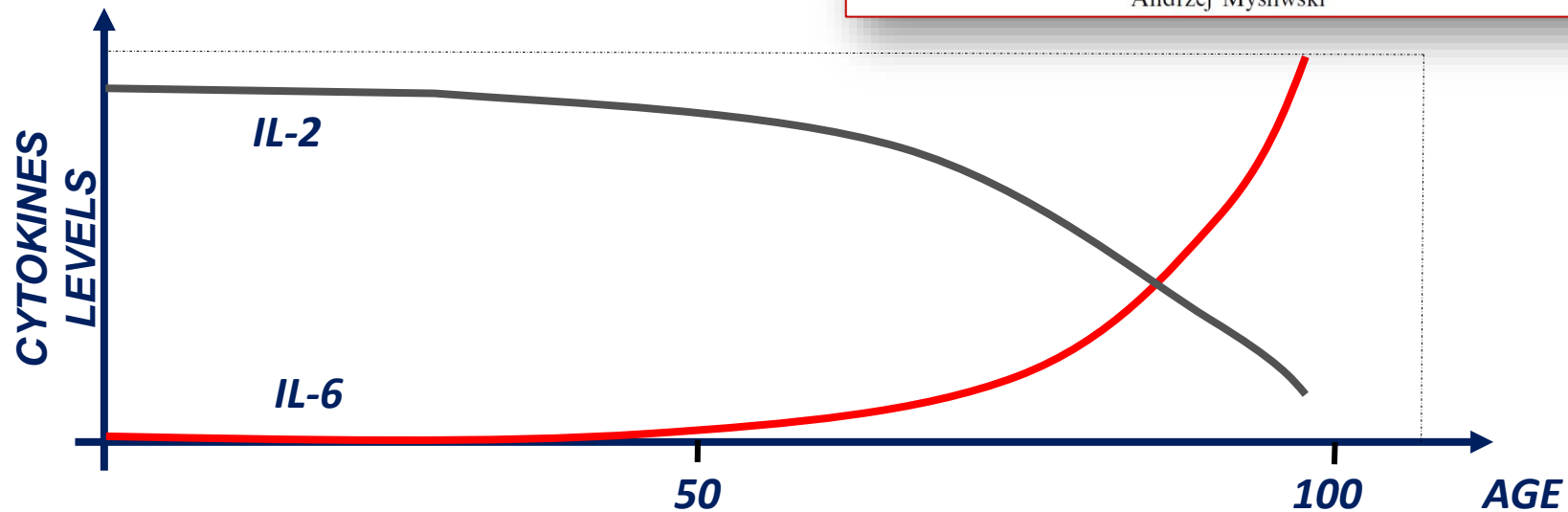
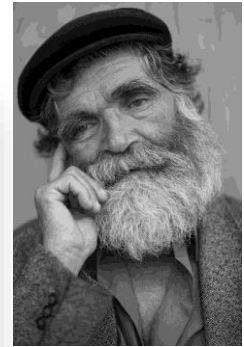
ELSEVIER

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

mechanisms of ageing  
 and development

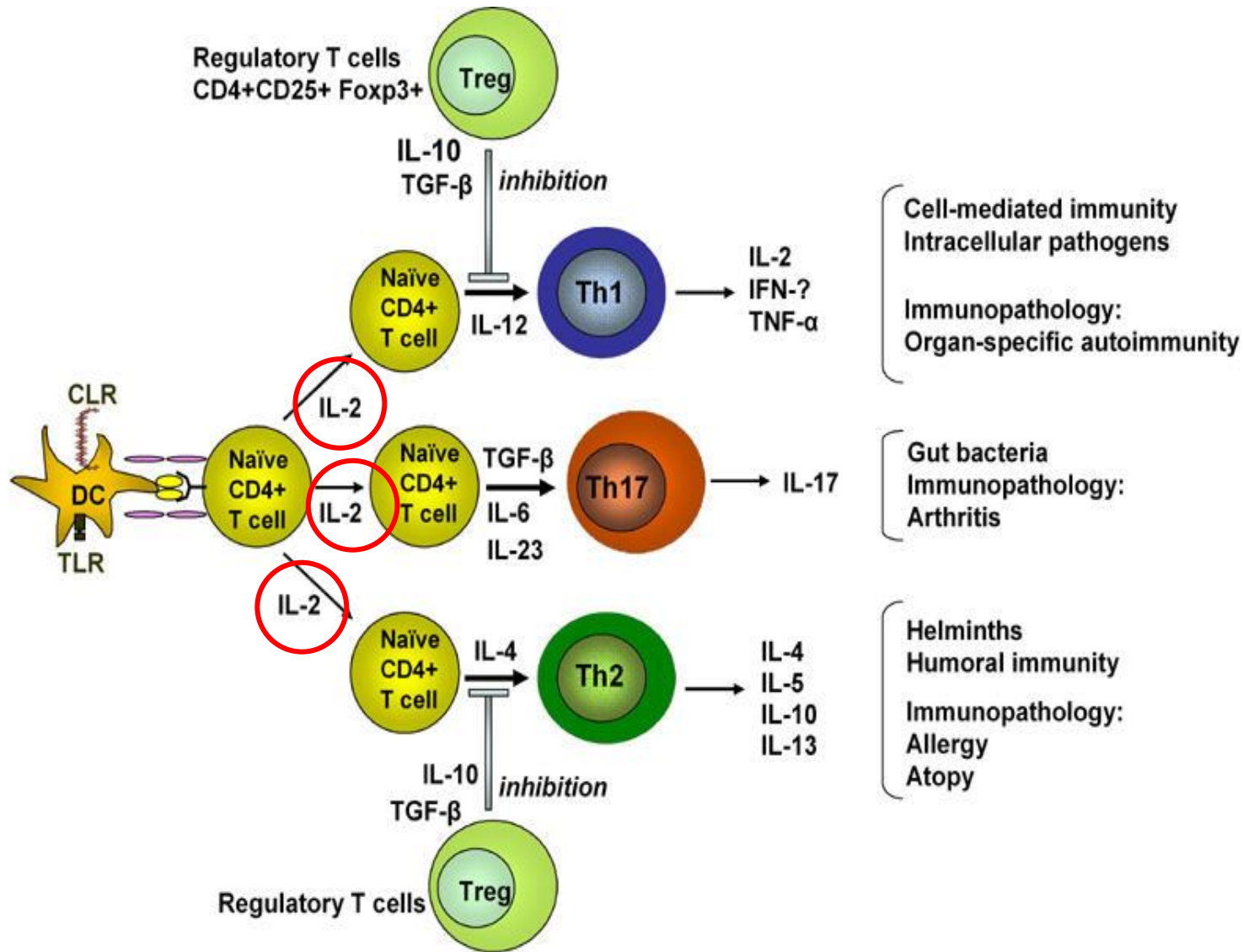
Increase of interleukin 6 and decrease of interleukin 2 production during the ageing process are influenced by the health status

Jolanta Myśliwska <sup>a,\*</sup>, Ewa Bryl <sup>a</sup>, Jerzy Foerster <sup>b</sup>,  
 Andrzej Myśliwski <sup>a</sup>



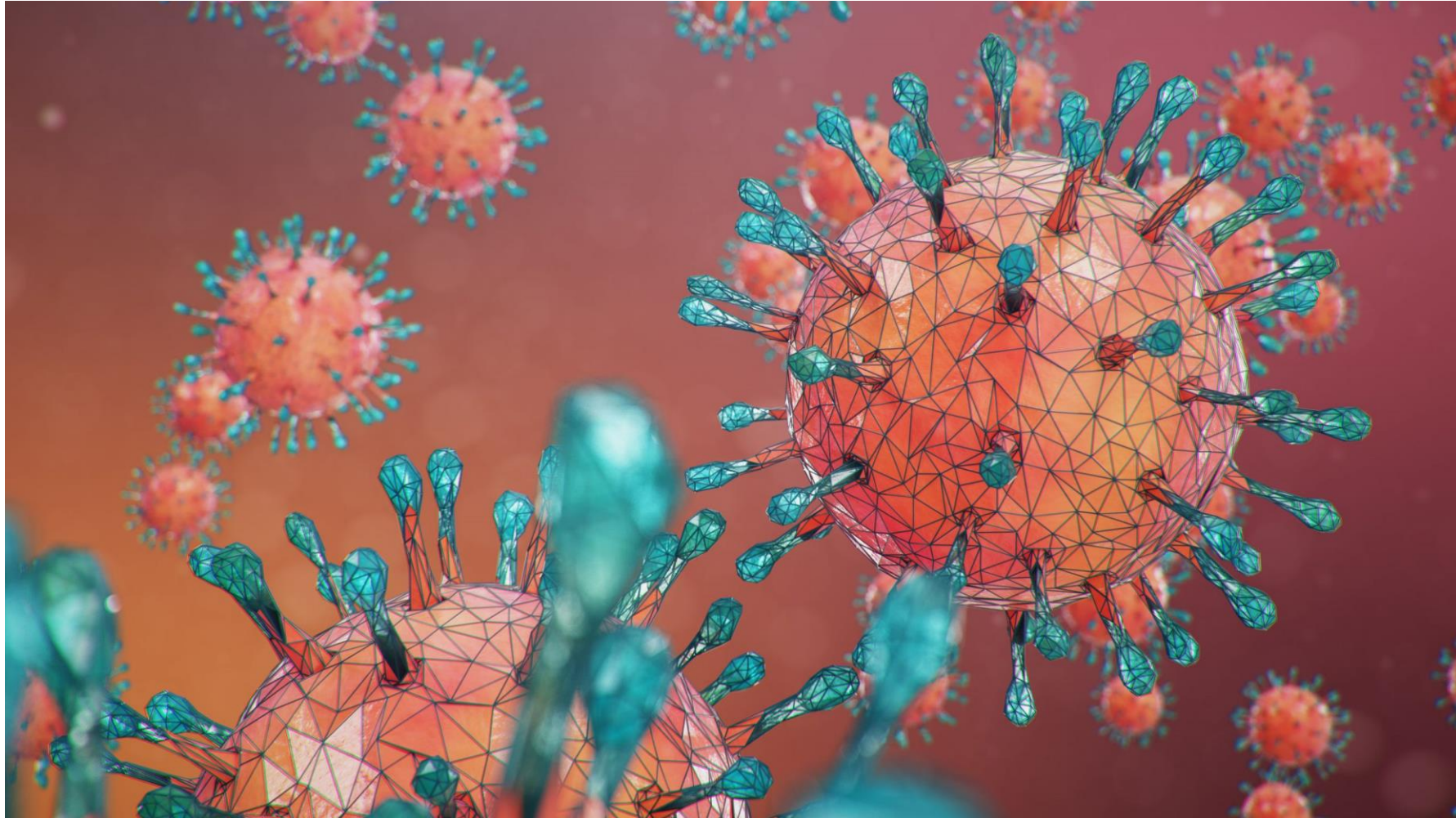
*Much of immune decline may be traceable to a decreased ability of activated T-cells (both helpers and cytotoxic cells) to undergo clonal expansion*

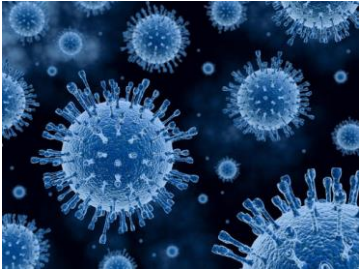




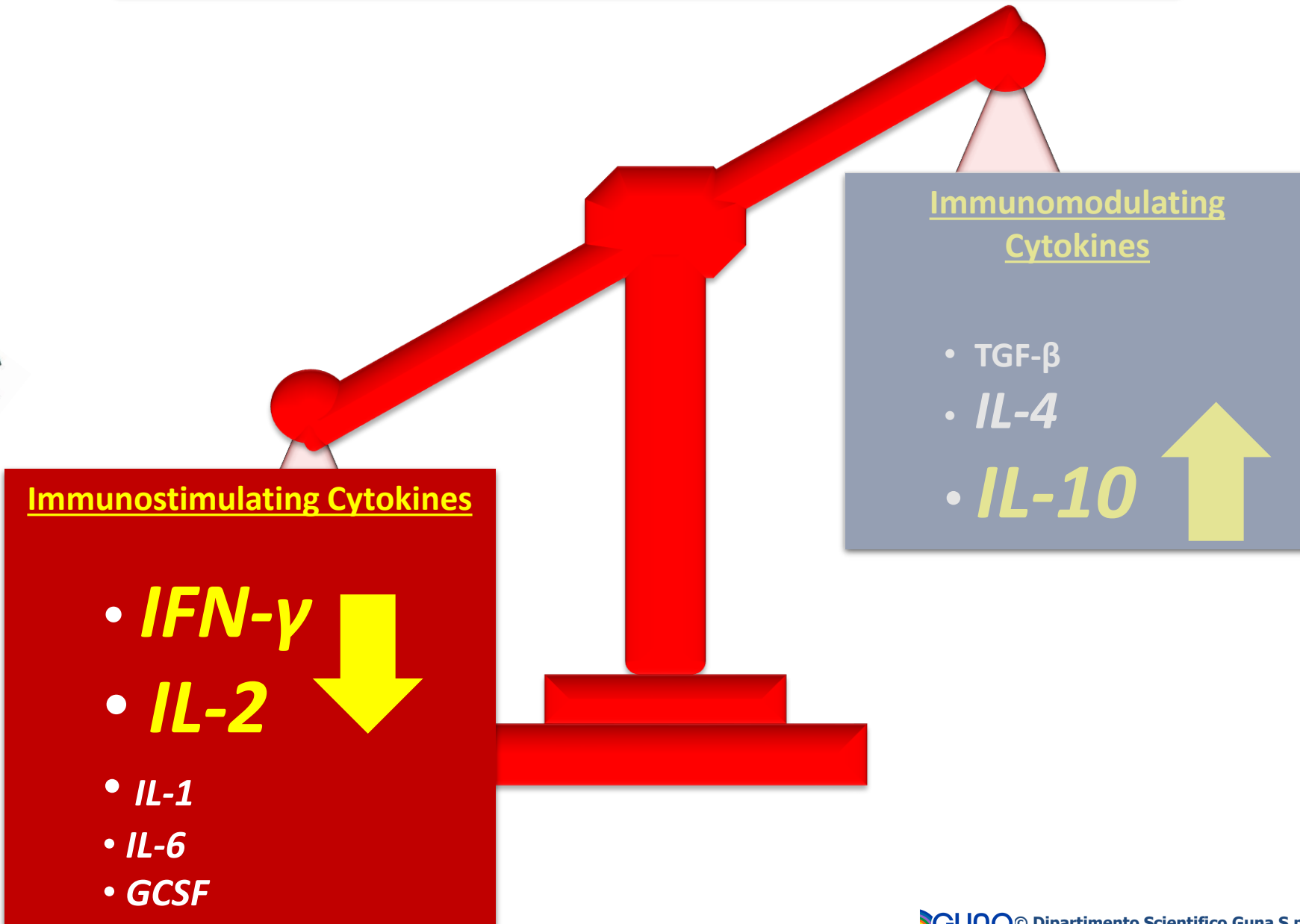
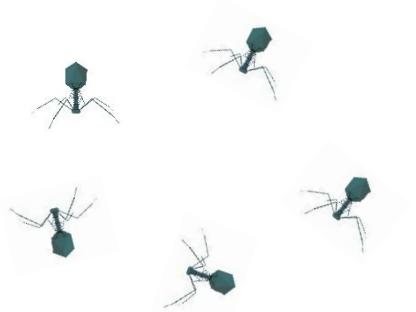
Antigen presentation to naïve T cells results in the development of Th1, Th2 or Th17 cells depending on the cytokine milieu.

# When do viruses have a party?

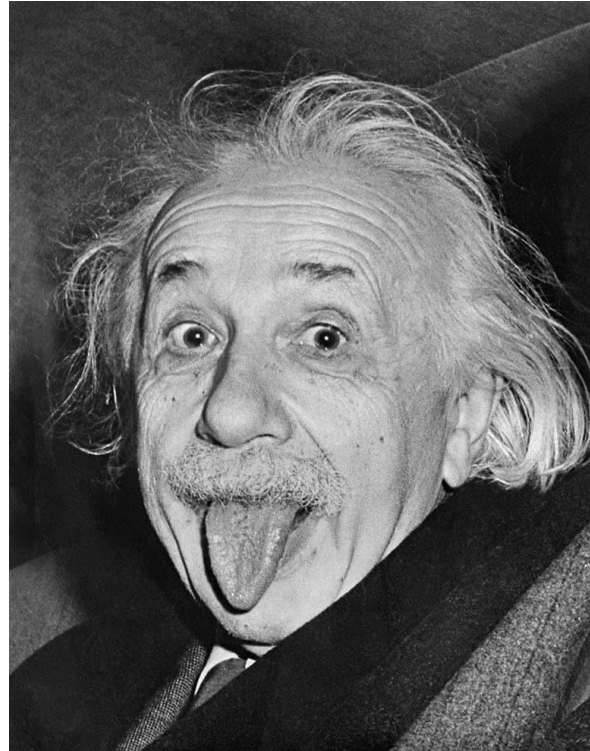




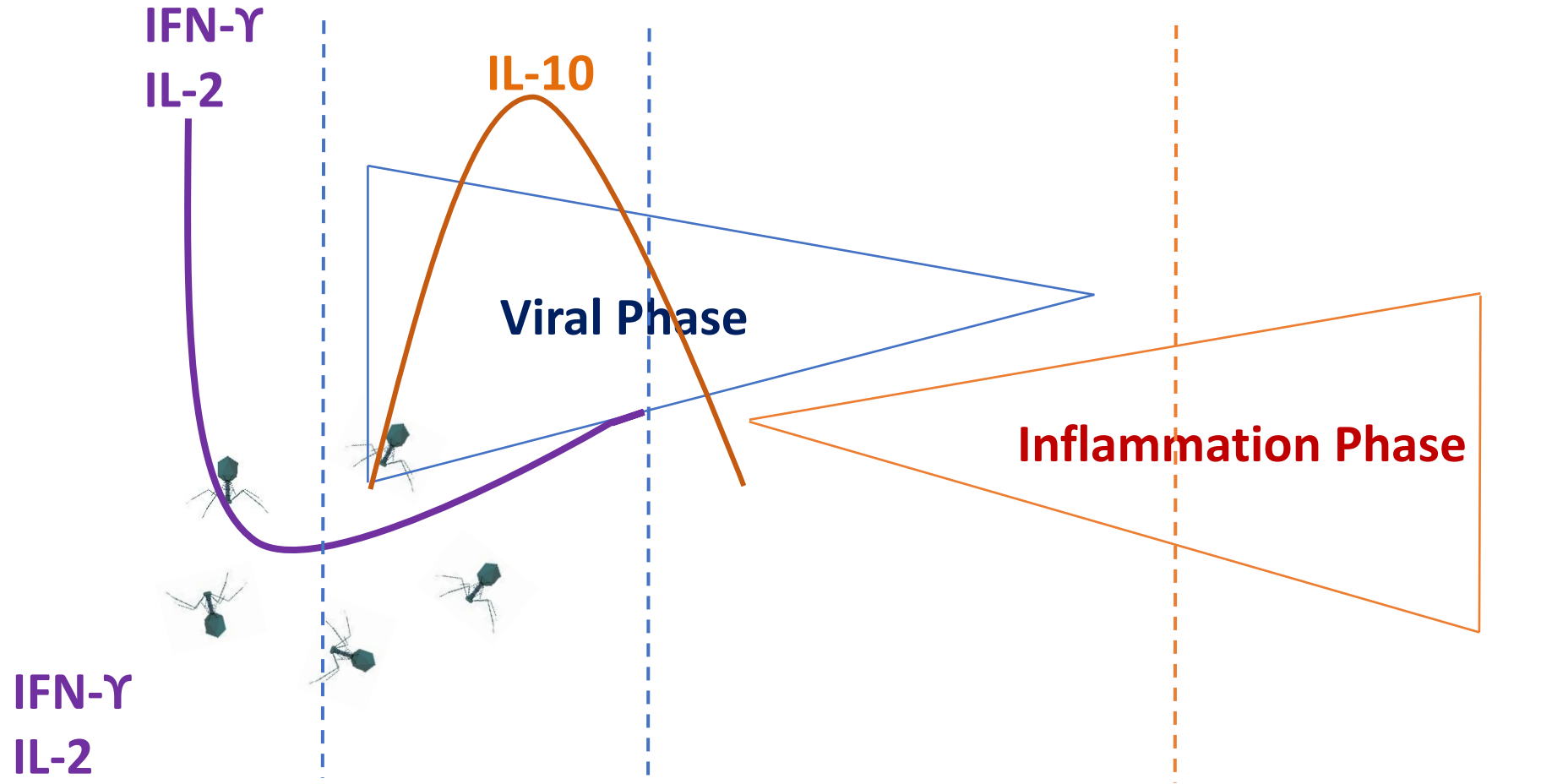
# ...susceptibility to viral attacks



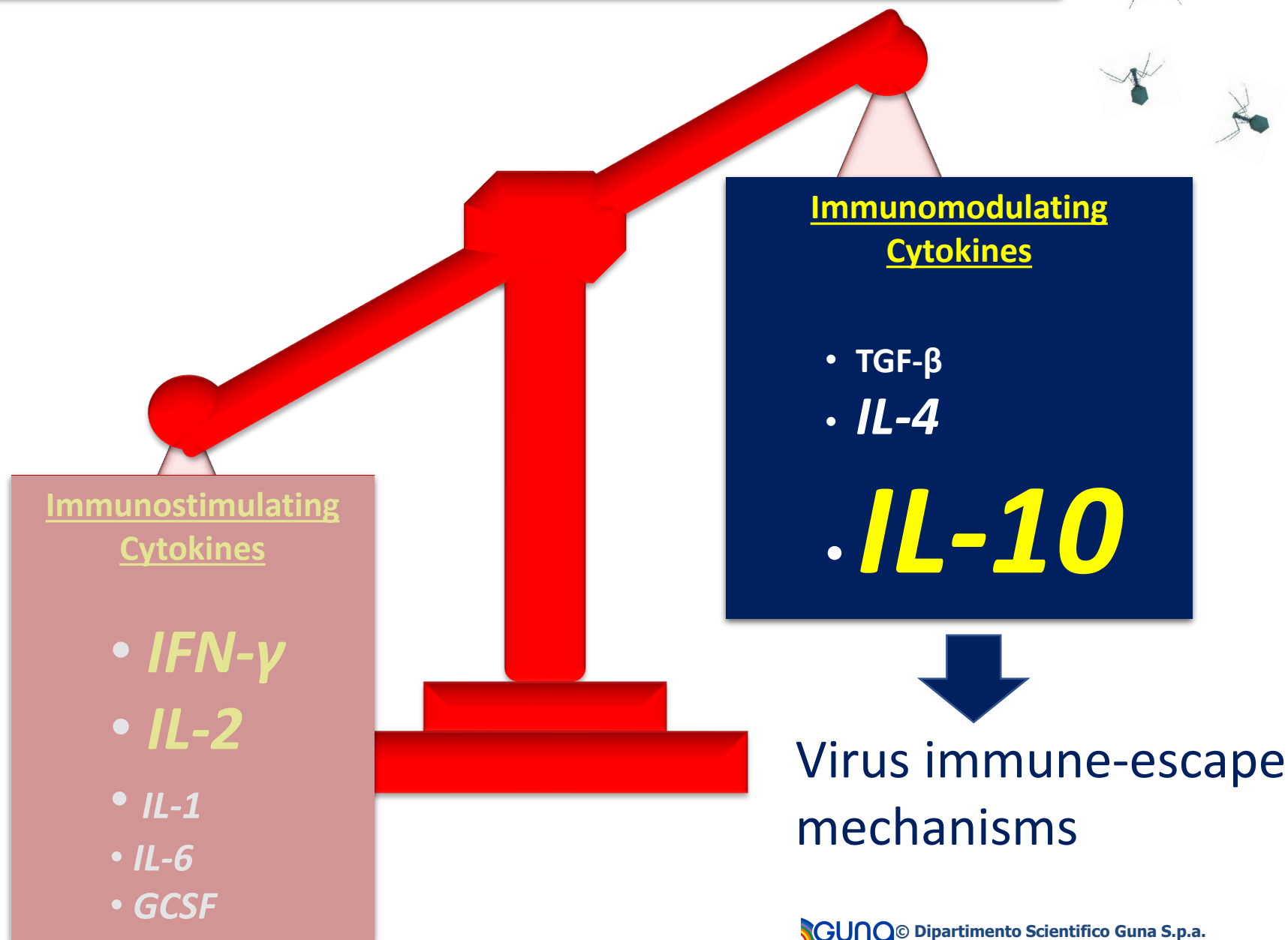
# *Viruses are super smart!*



# Space-Time Immunomodulation

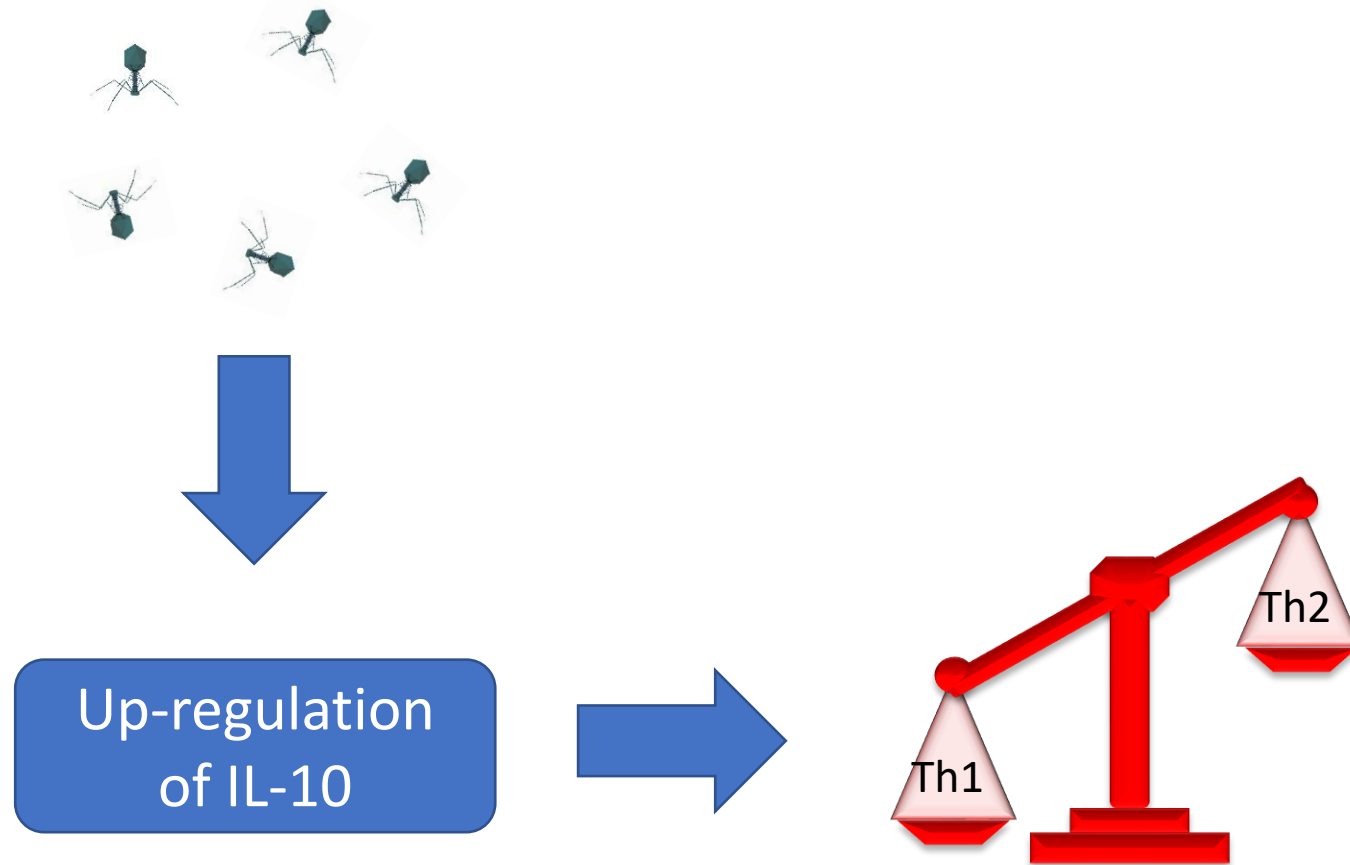


# ...under viral attack



# IMMUNE-ESCAPE MECHANISM

## Viral infection and cell-mediated immune response inhibition



# IMMUNE-ESCAPE MECHANISM

## Viral infection and IFNs inhibition

IFN-alpha

IFN-beta

IFN-gamma

Virus inhibits innate  
immune response by  
IFNs down-regulation

NK activation

Tc activation



A novel, systemic, approach to  
*viral infections protection*



We need to enhance the expression and  
activity of Interferons...

#### DIRECTIONS AND WAY OF ADMINISTRATION

- **Guna-Interferon gamma: 20 drops twice a day for 2 to 4 months (half dosage for children below 6 years)**

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

INTERFERONE GAMMA E ALFA SONO PARTICOLARMENTE  
ATTIVI SULL'INNESCO DELLA RISPOSTA CITOLITICA

- IFN-gamma is able to activate a cell-mediated immune response (IFN-gamma stimulates CD8 + to differentiate into cytotoxic T effector cells) ideal against viruses. The

[IFN-gamma is also used by the body for the synthesis (conversion) into IFN-alpha (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)]

PRESCRIPTION ACCORDING TO  
THE AETIOLOGICAL DECISIONAL PROCESS

CYTOKINE	STRENGTHENING <i>same cytokine</i>	MODULATION <i>opposing cytokine</i>
----------	---------------------------------------	--

...and we need to counteract the overexpression of IL-10

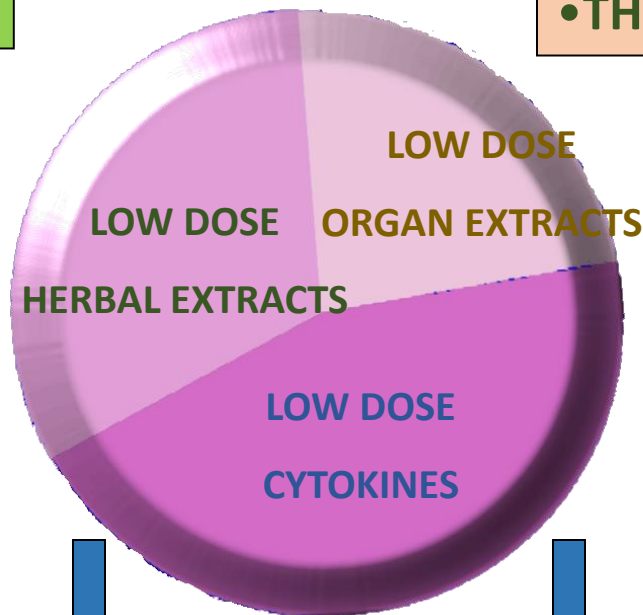
IL-4	IL-4 4C	TNF-gamma 4C/IL-12 4C
IL-5	IL-5 4C	TGF-beta 4C
IL-6	IL-6 4C	IL-10 4C
IL-7	IL-7 4C	IL-10 4C/TGF-β1 4C
IL-8	IL-8 4C	IL-10 4C/TGF-β1 4C
IL-9	IL-9 4C	IL-10 4C
IL-10	IL-10 4C	IL-1 4C/TNF-α 4C/IL-6 4C
IL-11	IL-11 4C	IL-2 4C
IL-12	IL-12 4C	IL-4 4C/IL-10 4C
TGF-beta 1	TGF-beta 4C	IL-12 4C
TNF	TNF-alpha 4C	Guna Anti IL-1 4C+IL-10 4C

# CITOMIX



- VACCINIUM VITIS
- ANANASSA SATIVA
- HYDROCOTYLE ASIATICA  
(CENTELLA ASIATICA)

- VASA LYMPHATICA SUIS
- MEDULLA OSSIS SUIS
- THYMULINE



ANTINFLAMMATORY AND ANTIOXIDANT ACTION (*Vaccinium vitis*),  
RES STIMULATION (*Ananassa sativa*),  
ANTINFIAMMATORY ACTION (*Hydrocotyle asiatica*)

TARGETED ANTINFLAMMATORY ACTION; STIMULATION OF IMMUNOCOMPETENT TISSUES

ONSET OF THE IMMUNE RESPONSE

- GCSF
- IL1-beta
- **INF -gamma**
- **IL-6**

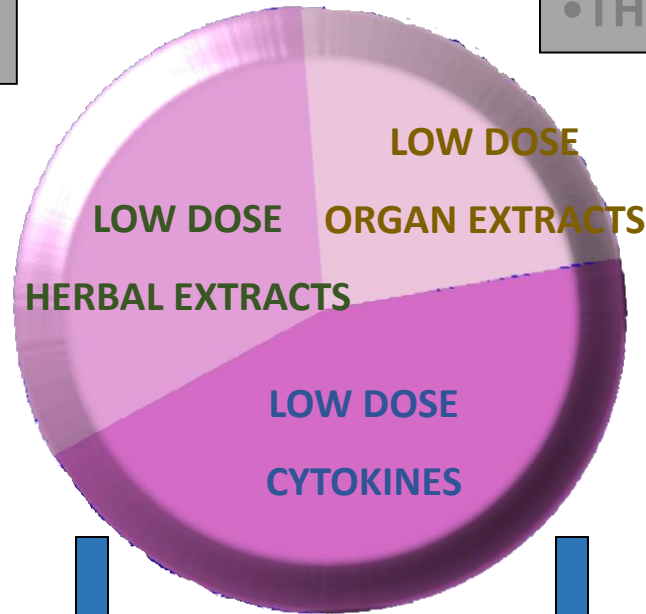
- IL-4
- IL-2

B PROLIFERATION AND APC BOOSTING (IL-4); B, T AND NK STIMULATION (IL-2)

# CITOMIX

- VACCINIUM VITIS (MOUNTAIN CRANBERRY)
- ANANASSA SATIVA
- HYDROCOTYLE ASIATICA (CENTELLA ASIATICA)

- VASA LYMPHATICA SUIS
- MEDULLA OSSIS SUIS
- THYMULINE



ANTINFLAMMATORY AND ANTIOXIDANT ACTION (*Vaccinium vitis*),  
 RES STIMULATION (*Ananassa sativa*),  
 ANTINFIAMMATORY ACTION (*Hydrocotyle asiatica*)

TARGETED ANTINFLAMMATORY ACTION; STIMULATION OF IMMUNOCOMPETENT TISSUES

## IMMUNOLOGIC NETWORK

ONSET OF THE IMMUNE RESPONSE

- GCSF
- IL1-beta
- INF -gamma
- IL-6

- IL-4
- IL-2

B PROLIFERATION AND APC BOOSTING (IL-4); B, T AND NK STIMULATION (IL-2)





ELSEVIER

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

## Immunology Letters

journal homepage: [www.elsevier.com/locate/immllet](http://www.elsevier.com/locate/immllet)



### Low-dose multicomponent medication modulates humoral and cellular immune response in an ex-vivo study on children subjected to adenoid surgery



Sara Carlotta Tagliacarne<sup>a</sup>, Chiara Valsecchi<sup>b</sup>, Marco Benazzo<sup>c</sup>, Michele Nichelatti<sup>d</sup>, Alessia Marseglia<sup>b</sup>, Giorgio Ciprandi<sup>e,\*</sup>, Sergio Bernasconi<sup>f</sup>

<sup>a</sup> Department of Clinical Surgical Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy

<sup>b</sup> Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

<sup>c</sup> Department of Otolaryngology, University of Pavia and Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy

<sup>d</sup> Service of Biostatistics Hematology Department, Niguarda Ca' Granda Hospital, Milan, Italy

<sup>e</sup> Department of Medicine, IRCCS-Ospedale Policlinico San Martino, Genoa, Italy

<sup>f</sup> Department of Pediatrics, University of Parma, Parma, Italy





Italian Ministry of Health

# Scientific IRCCS Network

Direzione Generale della Ricerca Sanitaria e Biomedica

General Directorate for health and Biomedical Research

- Home
- Profiles
- Research Units
- Projects
- Research Output**

## Low-dose multicomponent medication modulates humoral and cellular immune response in an ex-vivo study on children subjected to adenoid surgery

Sara Carlotta Tagliacarne, Chiara Valsecchi, Marco Benazzo, Michele Nichelatti, Alessia Marseglia, Giorgio Ciprandi, Sergio Bernasconi

IRCCS Fondazione Policlinico San Matteo

Research output: Contribution to journal > Article

- Overview**
- Fingerprint

### Abstract

Respiratory infections, mainly in children, are a demanding challenge for physicians. Commonly, a relative immune-defect sustains their recurrence. At present, there is no standardized treatment for their prevention acting on the immune system. Citomix is a low-dose multicomponent medication largely used in this issue. The current study evaluated its ex vivo effect on adenoidal mononuclear cells recovered from children operated for adenoid hypertrophy. B cell phenotype, and IFN- $\gamma$ , IL-6, IL-10, IgG, IgA, IgM in culture supernatants were evaluated. Citomix was able to significantly increase the expression of B memory cells, IFN- $\gamma$ , IL-6, IgA and IgM, and significantly decrease IL-10 and IgG. The current outcomes could be consistent with a strategy deputed to improve the early immune response to pathogens. In conclusion, the present ex vivo study suggests that Citomix might be a promising medication in preventing and early treating respiratory infections.

### Access to Document

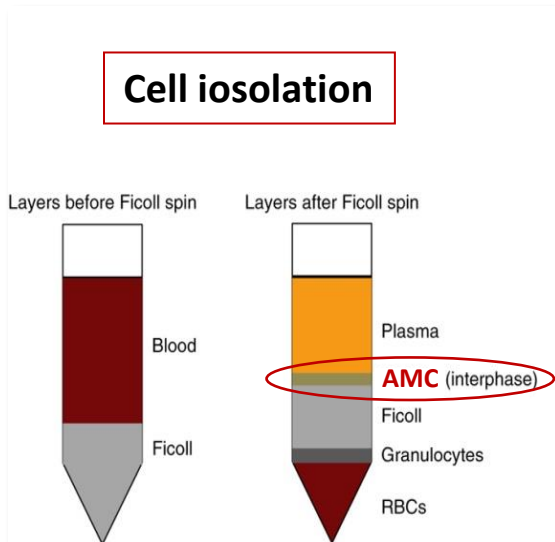
- [10.1016/j.imlet.2018.09.014](https://doi.org/10.1016/j.imlet.2018.09.014)
- [Link to publication in Scopus](#)
- [Link to citation list in Scopus](#)

# IMMUNOMODULATING ACTIVITY OF CITOMIX – STUDY DESIGN

Adenoids from **50 children** (35 males, 15 female, 6 years average age) affected with RRI



Schiacciamento meccanico



AMC expansion *in vitro*

**Cytokines quantification**

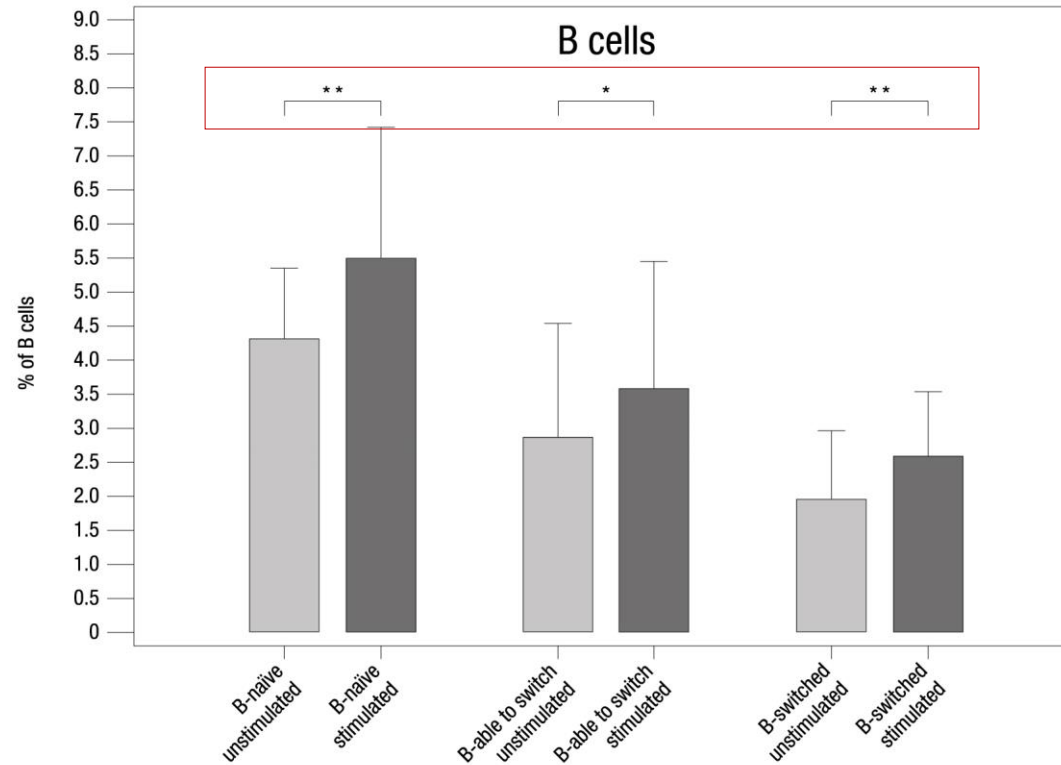
- IL-6
- IL-10
- IFN- $\gamma$

**Ig quantification**

- IgA
- IgG
- IgM

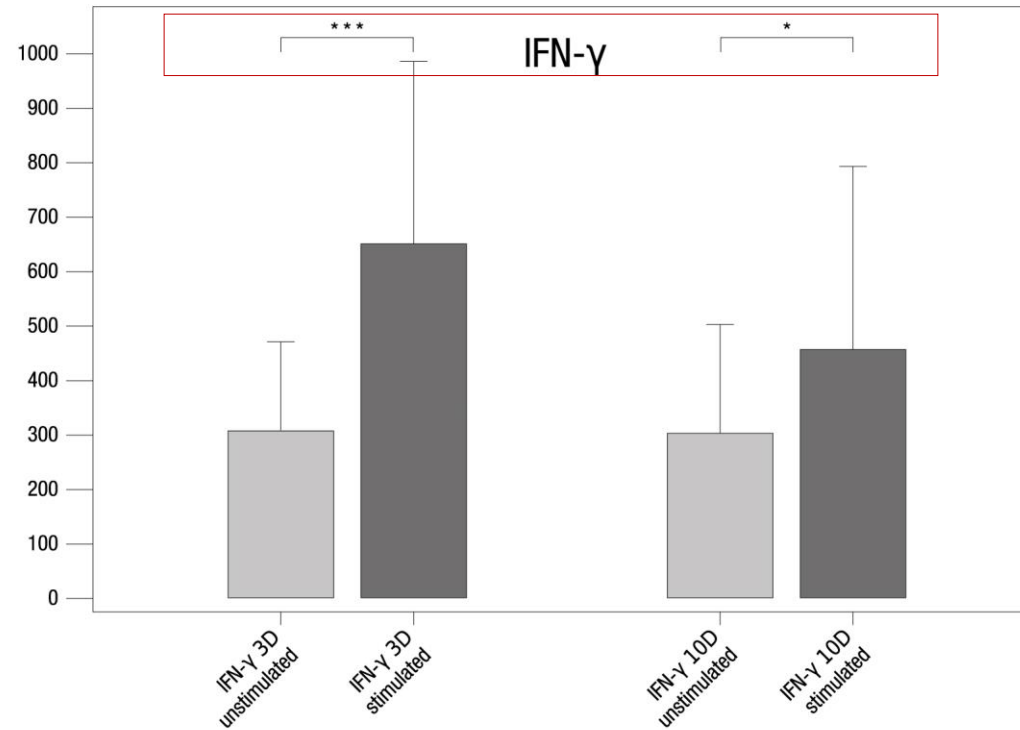
**B-lymphocytes sub-clones characterization**

# CITOMIX INDUCES A SIGNIFICANT INCREASE OF B NAÏVE, B ABLE TO SWITCH AND B SWITCHED

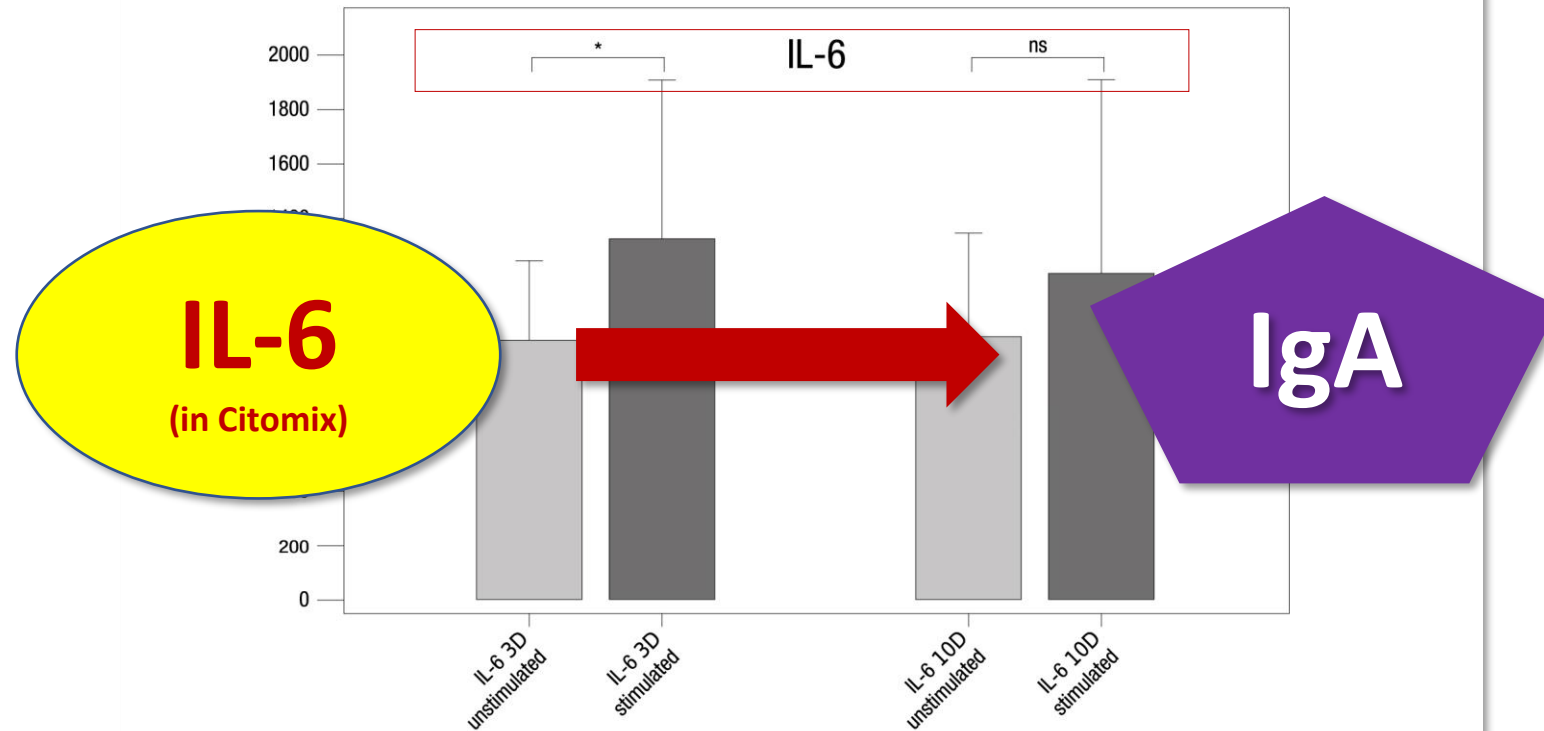




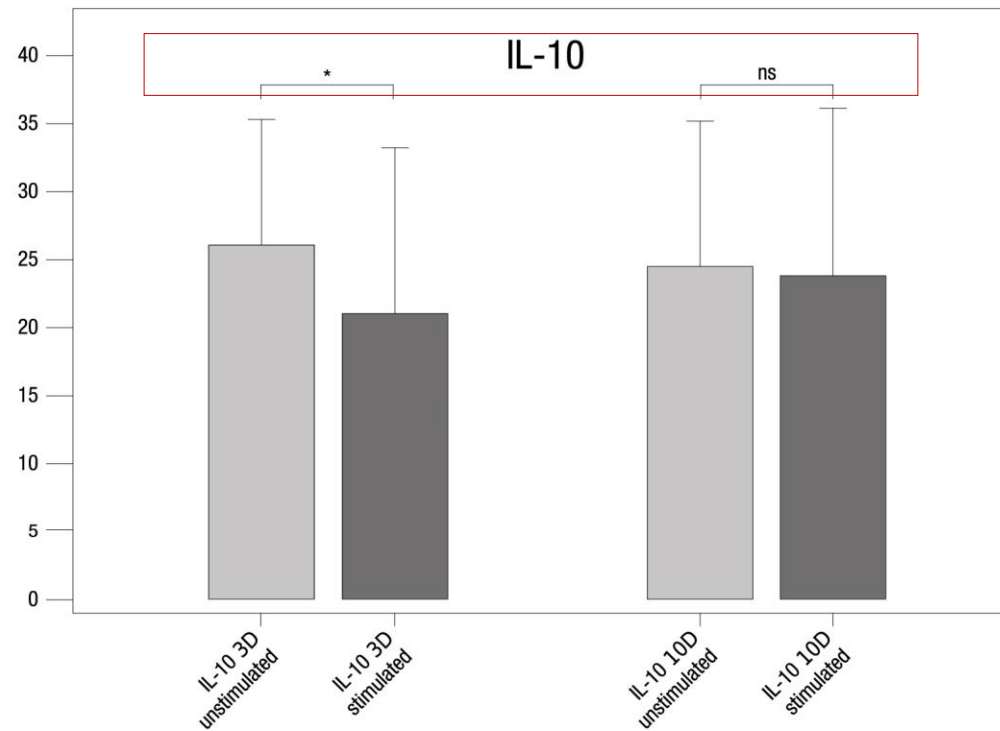
# CITOMIX INDUCES A SIGNIFICANT INCREASE OF IFN- $\gamma$ AFTER 3 AND 10 TREATMENT DAYS



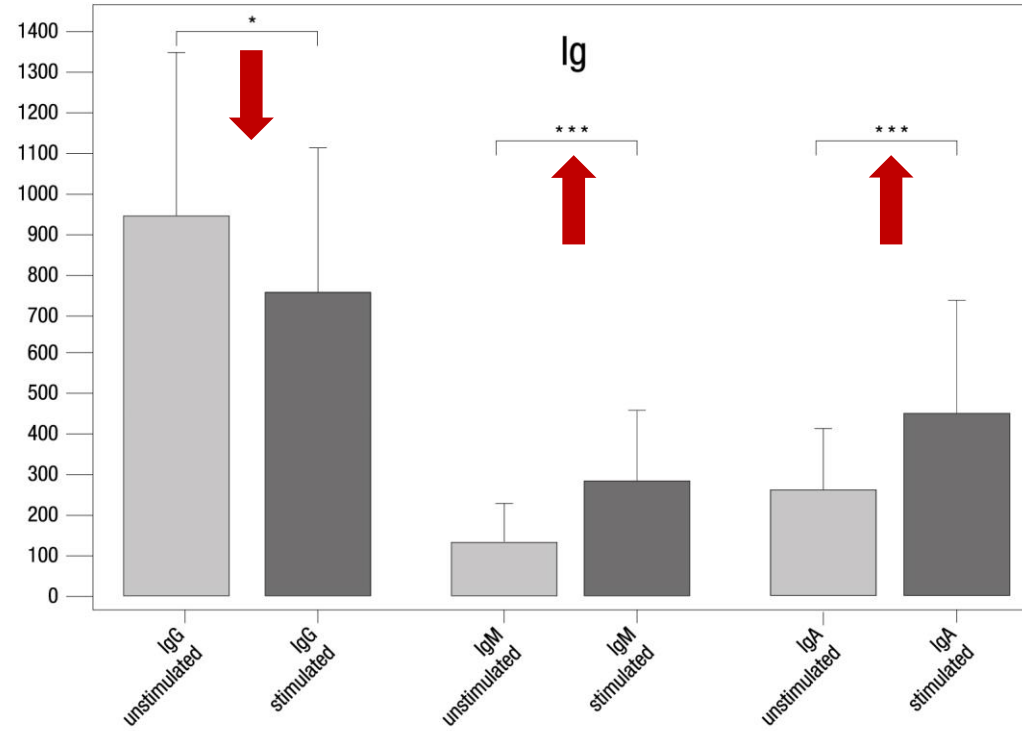
# CITOMIX INDUCES A SIGNIFICANT INCREASE OF IL-6 AFTER 3 AND 10 TREATMENT DAYS



# CITOMIX INDUCES A SIGNIFICANT DECREASE OF IL-10 AFTER 3 AND 10 TREATMENT DAYS



# CITOMIX INDUCES A SIGNIFICANT INCREASE OF IgA AND IgM AFTER 3 AND 10 TREATMENT DAYS



*A. Arrighi*

**CITOMIX VS IMMUCYTAL®  
NELLA PREVENZIONE E  
TERAPIA DELLE INFEZIONI  
RESPIRATORIE ACUTE  
IN ETÀ PEDIATRICA**  
– STUDIO PROSPETTICO CONTROLLATO

*CITOMIX VS IMMUCYTAL® IN THE PREVENTION AND  
THERAPY OF ACUTE RESPIRATORY INFECTIONS IN  
PAEDIATRICS*

*– A CONTROLLED PROSPECTIVE TRIAL*

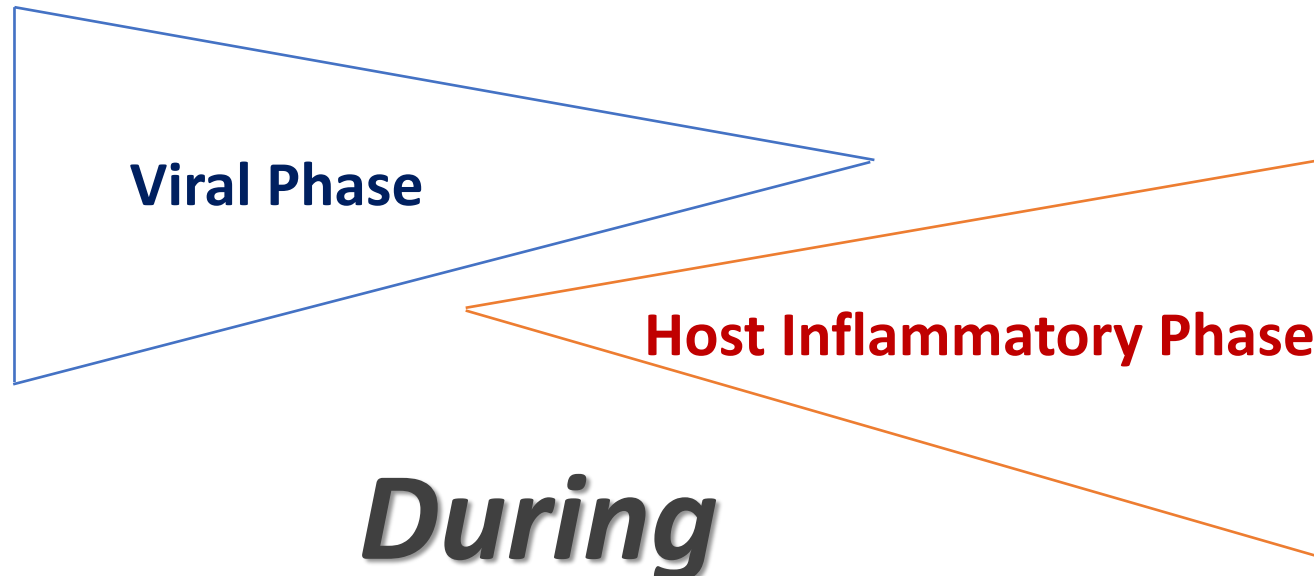
# Our goal in prevention



**Prevention:** 5 pellets a day, every day for 3 consecutive months.

**Before**

IMMUNOSTIMULATION



**During**

IMMUNOSTIMULATION  
ANTINFLAMMATORY THER.

ANTINFLAMMATORY THER.

**After**

CONVALESCENCE AND  
PREVENTION OF RELAPSES

## In fragile patients



### DIRECTIONS AND WAY OF ADMINISTRATION

- **Prevention:** 5 pellets a day, every day for 3 consecutive months.

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

### DIRECTIONS AND WAY OF ADMINISTRATION

- **Guna-Interferon gamma:** 20 drops twice a day for 2 to 4 months (half dosage for children below 6 years)

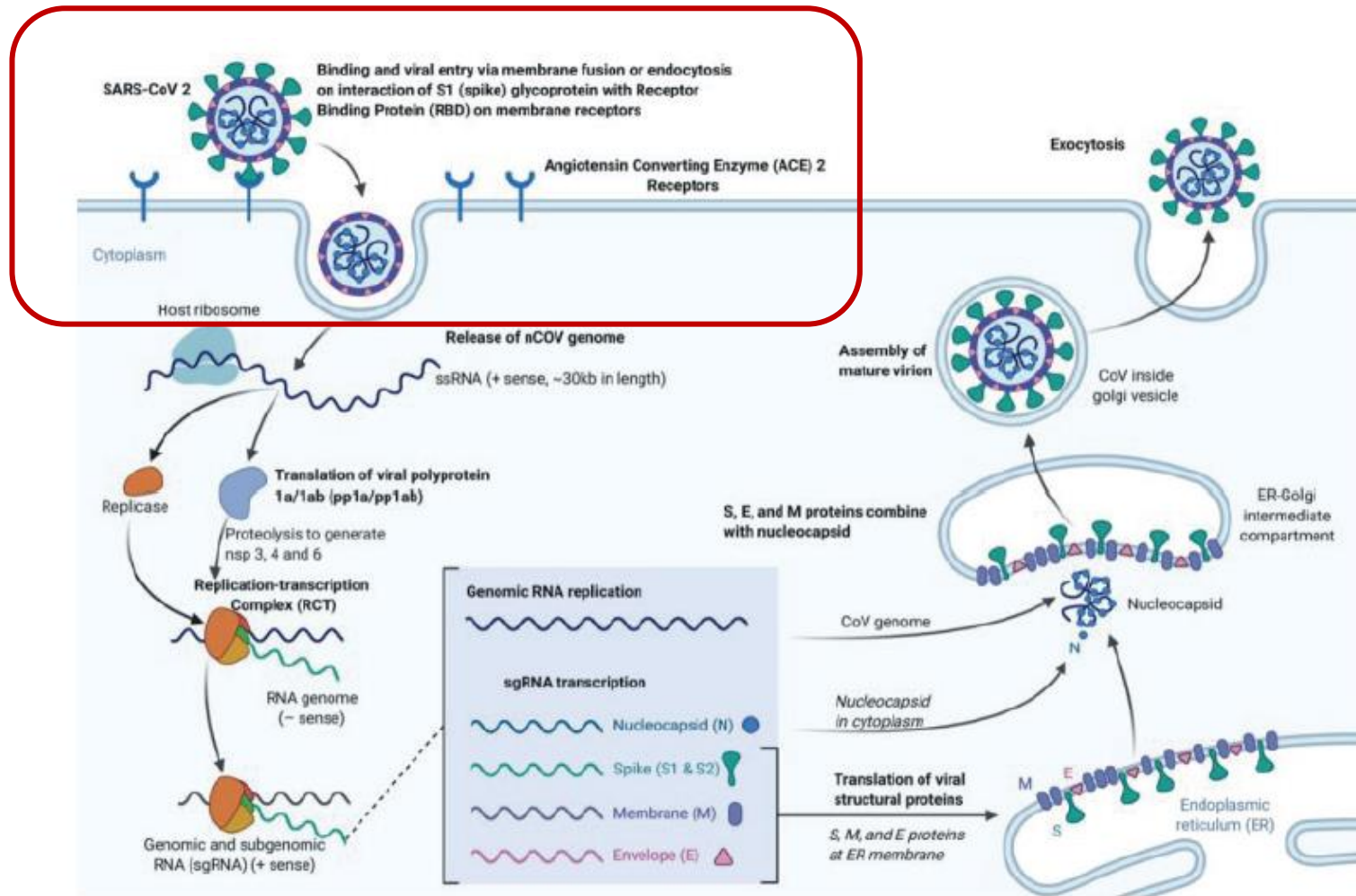
Sublingual administration directly under the tongue or in a little water, preferably far from meals.

# 2020 SARS-Cov-2 Pandemic





# Infection mechanisms of Sars-Cov-2



---

# Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures



*Kenrie P Y Hui, Man-Chun Cheung, Ranawaka A P M Perera, Ka-Chun Ng, Christine H T Bui, John C W Ho, Mandy M T Ng, Denise I T Kuok, Kendrick C Shih, Sai-Wah Tsao, Leo L M Poon, Malik Peiris, John M Nicholls, Michael C W Chan*

[www.thelancet.com/respiratory](http://www.thelancet.com/respiratory) Published online May 7, 2020 [https://doi.org/10.1016/S2213-2600\(20\)30193-4](https://doi.org/10.1016/S2213-2600(20)30193-4)

## Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex-vivo and in-vitro cultures



Kenrie P Y Hui, Man-Chun Cheung, Ranawaka A P M Perera, Ka-Chun Ng, Christine H T Bui, John C W Ho, Mandy M T Ng, Denise I T Kuok, Kendrick C Shih, Sai-Wah Tsao, Leo L M Poon, Malik Peiris, John M Nicholls, Michael C W Chan

*ACE2, flu e SARS-CoV-2: L'ipotesi di Hui e colleghi.*

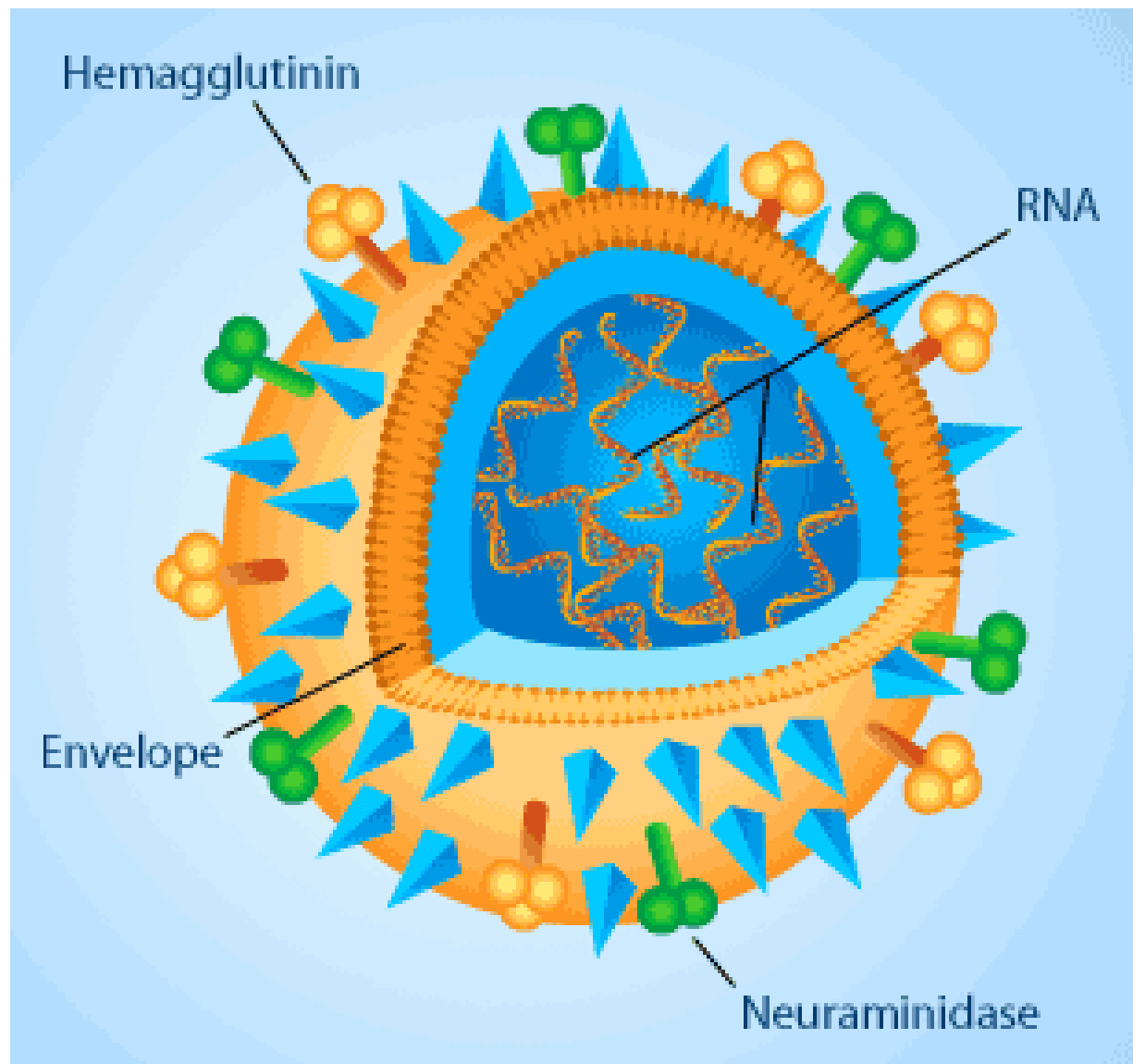
“We showed that ACE2 mRNA expression was significantly upregulated in alveolar epithelial cells after influenza A virus infection, with H5N1 having a more pronounced effect than H1N1pdm in vitro. If replicated in a larger sample, this upregulation could suggest that recent exposure to influenza virus might worsen the outcome of COVID-19 through upregulation of the ACE2 receptor in human respiratory epithelium. By contrast, ACE2 expression might also offer protective effects during acute lung injury as shown for SARS. Therefore, the role of ACE2 expression during influenza infection should be defined, and its implications on susceptibility to and severity of SARS-CoV-2 infection should be investigated.”

***Profilaxis and treatment of  
influenza and  
parainfluenza syndromes  
with LDM***

# Let's better know the Flu Orthomyxovirus

**Lipidic envelope**, with surface glycoproteins such as *Hemagglutinin* (*adesion*) and *Neuraminidase* (*penetration*), that represent the antigenic determinants.

**Genome:**  
8 molecules with single RNA filament (negative polarity).



## *Problem #1*

**HIGHEST antigenic variability of the  
Orthomyxoviruses**

**Facing the antigenic DRIFT problem**

*... but also... Problem #2*

**HIGHEST variability of Influenza and Parainfluenza viruses**

# MORE THAN **263** PARAINFLUENZA VIRUSES (responsible of the *Influenza Like Illness-ILI*)

- **Rhinovirus**
- **Coronavirus**
- **Respiratory syncytial virus**
- **Metapneumo-virus**
- **Para-influenza virus**
- **Adenovirus**
- **Influenza-virus**
- **...**



Literature shows that only **32-55%** of **ILI** cases are due to influenza virus.

Wallace LA, Collins TC, Douglas JD, McIntyre S, Millar J, Carman WF. Virological surveillance of influenza-like illness in the community using PCR and serology. J Clin Virol. 2004 Sep;31(1):40-

Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. Lancet. 2001 Oct 27;358(9291):1410-6.

*The Journal of Infectious Diseases*

MAJOR ARTICLE

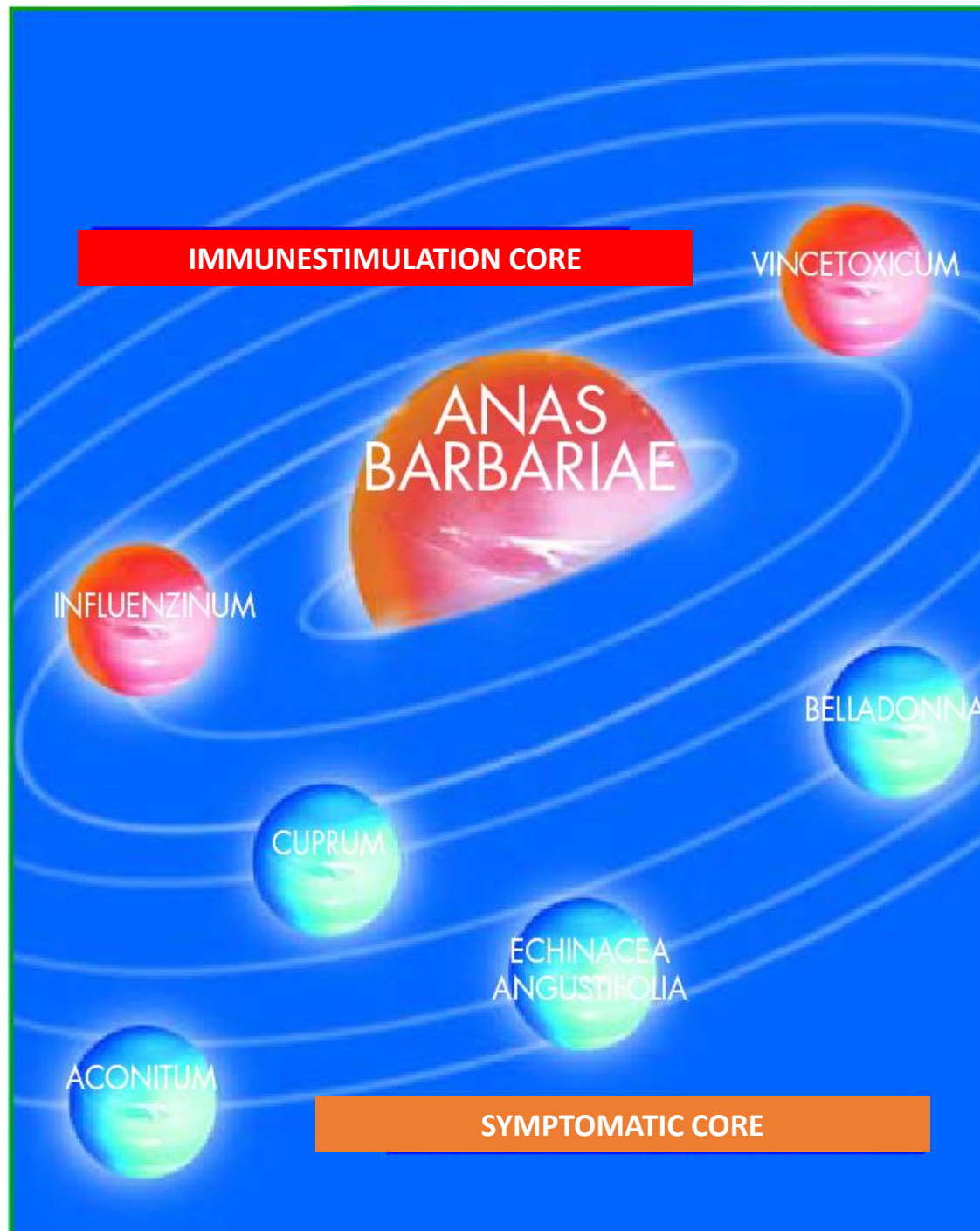


# Influenza-like Illness Incidence Is Not Reduced by Influenza Vaccination in a Cohort of Older Adults, Despite Effectively Reducing Laboratory-Confirmed Influenza Virus Infections

Josine van Beek,<sup>1</sup> Reinier H. Veenhoven,<sup>2,a</sup> Jacob P. Bruin,<sup>3</sup> Renée A. J. van Boxtel,<sup>1</sup> Marit M. A. de Lange,<sup>1</sup> Adam Meijer,<sup>1</sup> Elisabeth A. M. Sanders,<sup>1,4</sup> Nynke Y. Rots,<sup>1</sup> and Willem Luytjes<sup>1</sup>

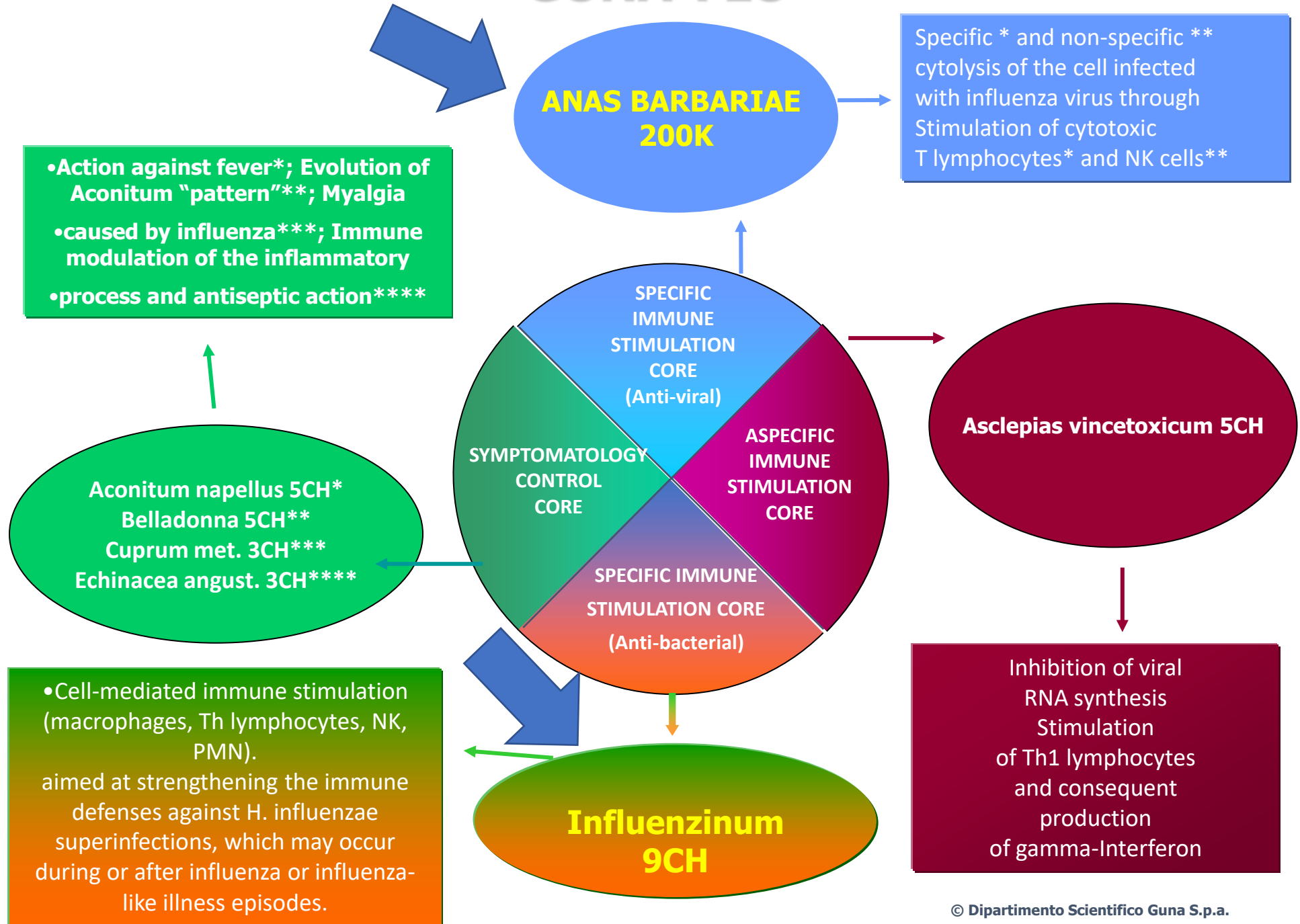
<sup>1</sup>Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven; <sup>2</sup>Spaarne Gasthuis Academy, Hoofddorp; <sup>3</sup>Regional Laboratory for Public Health Kennemerland, Haarlem; and <sup>4</sup>Department of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital/University Medical Center, Utrecht, The Netherlands

# GUNA-FLU<sup>®</sup>



**Prevention and  
treatment of flu  
and cold syndromes**

# GUNA-FLU

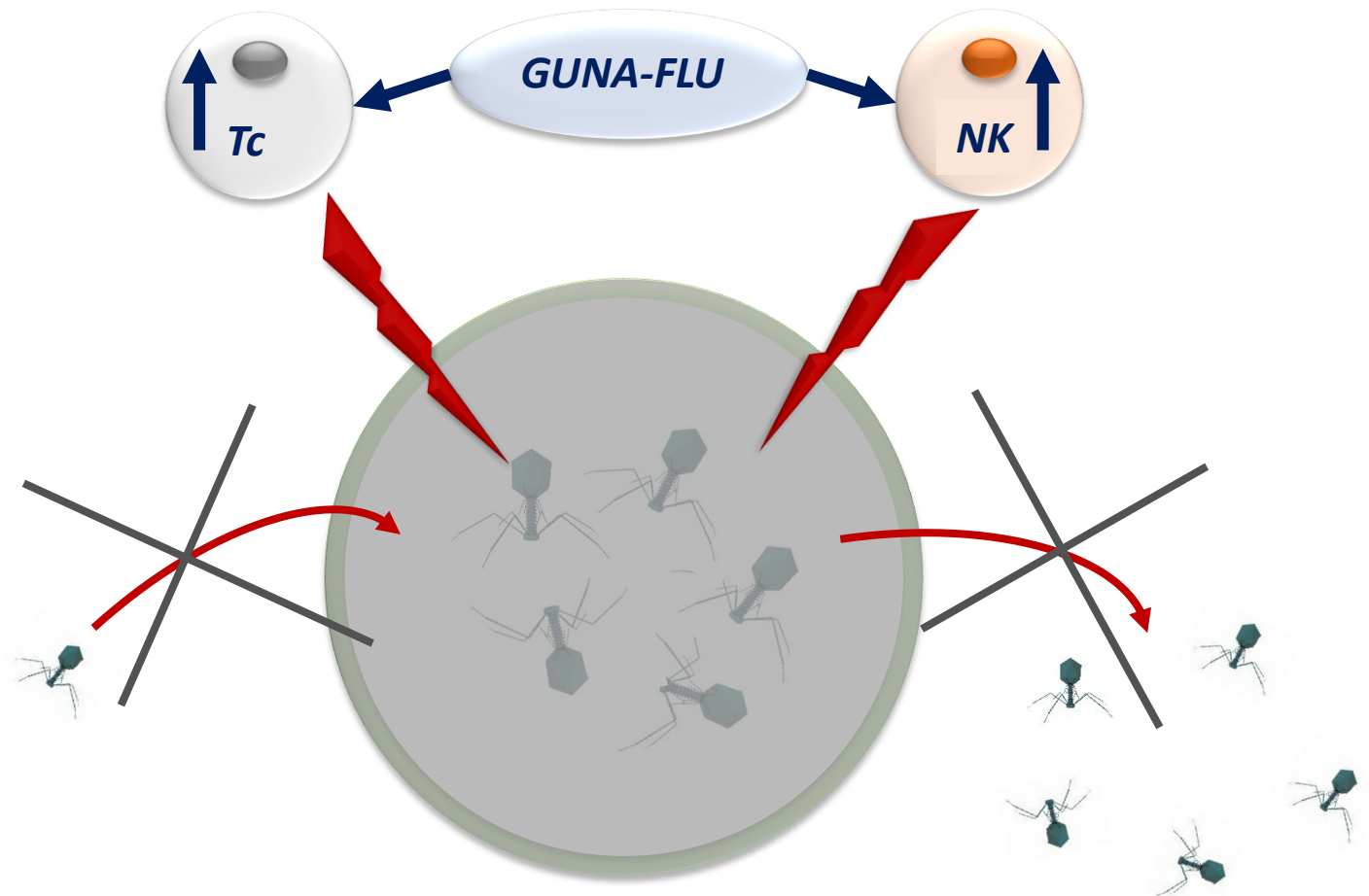




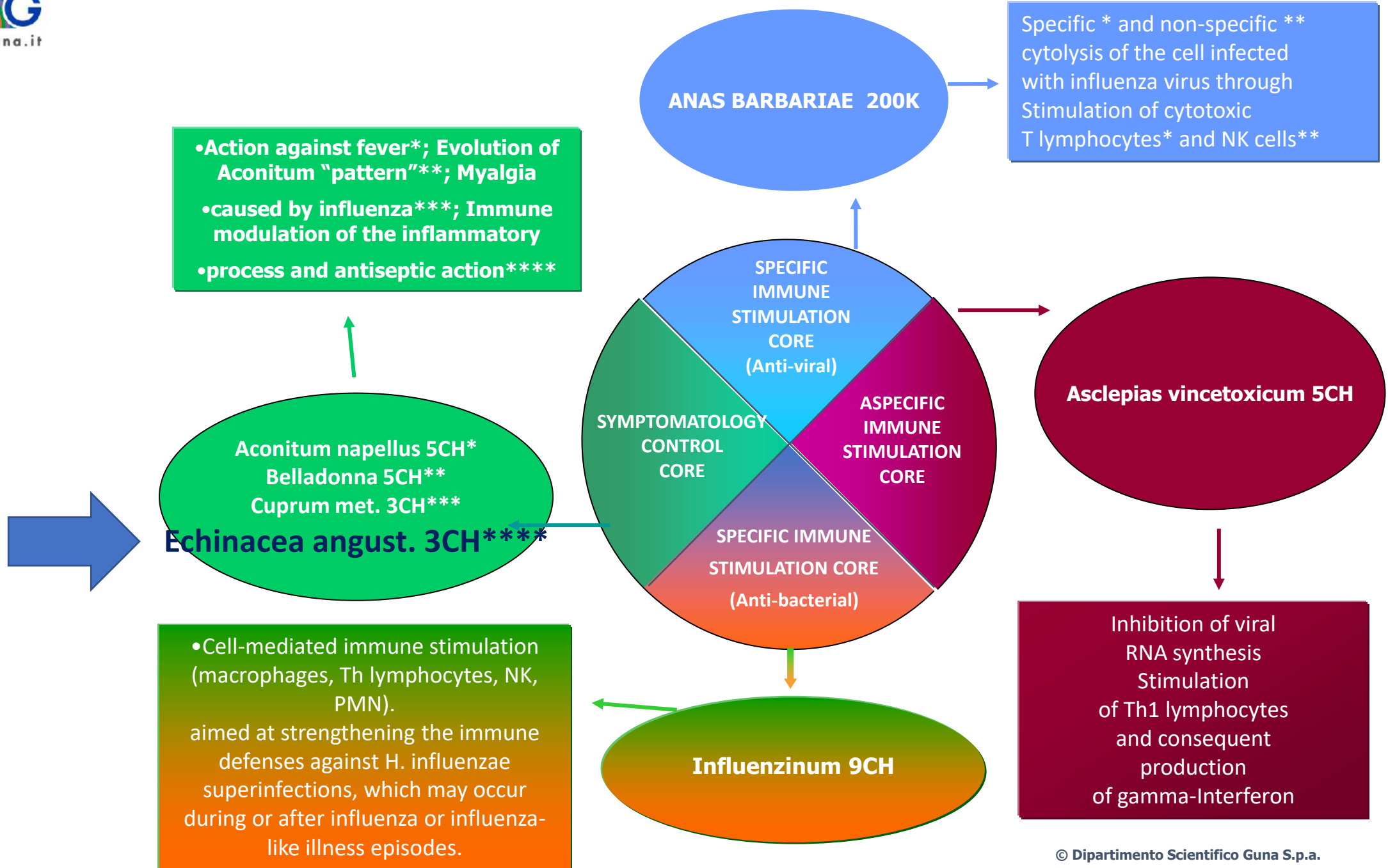
Interesting!!!

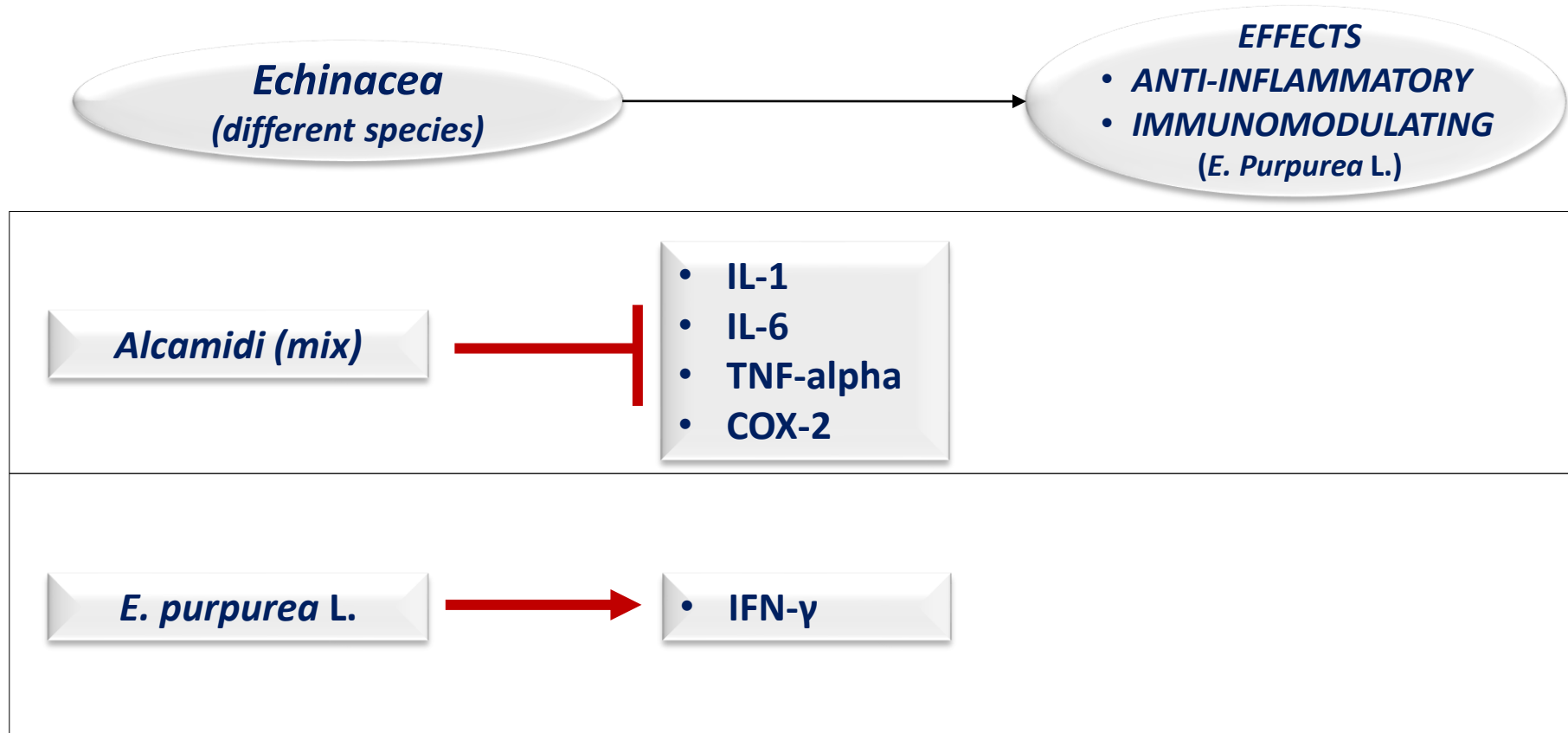
*Influenzinum of GUNA-FLU is obtained from the expectorated of patients infected with influenza and it is particularly rich of Haemophilus influenzae*

# MECHANISM OF ACTION OF GUNA-FLU



# GUNA-FLU

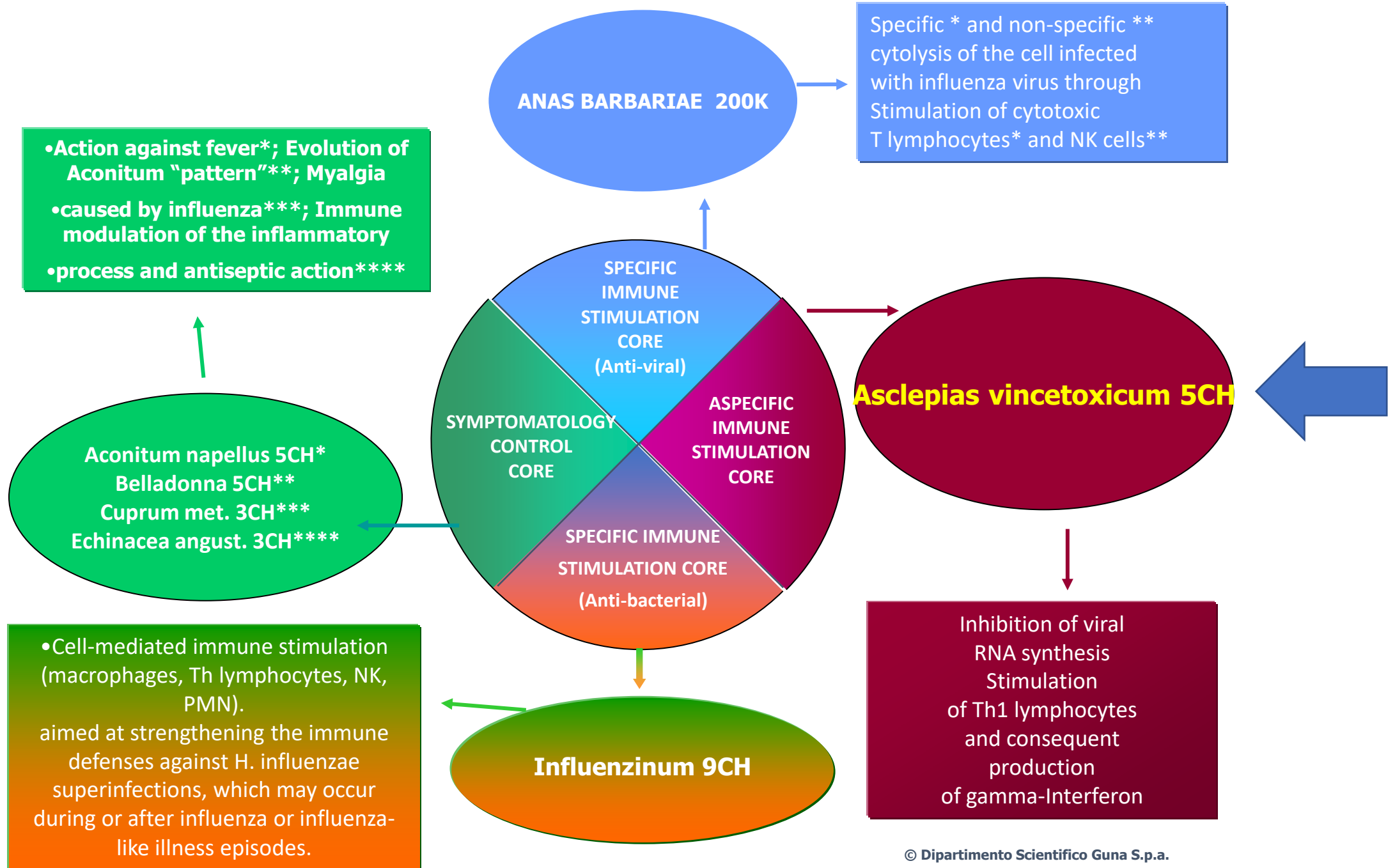


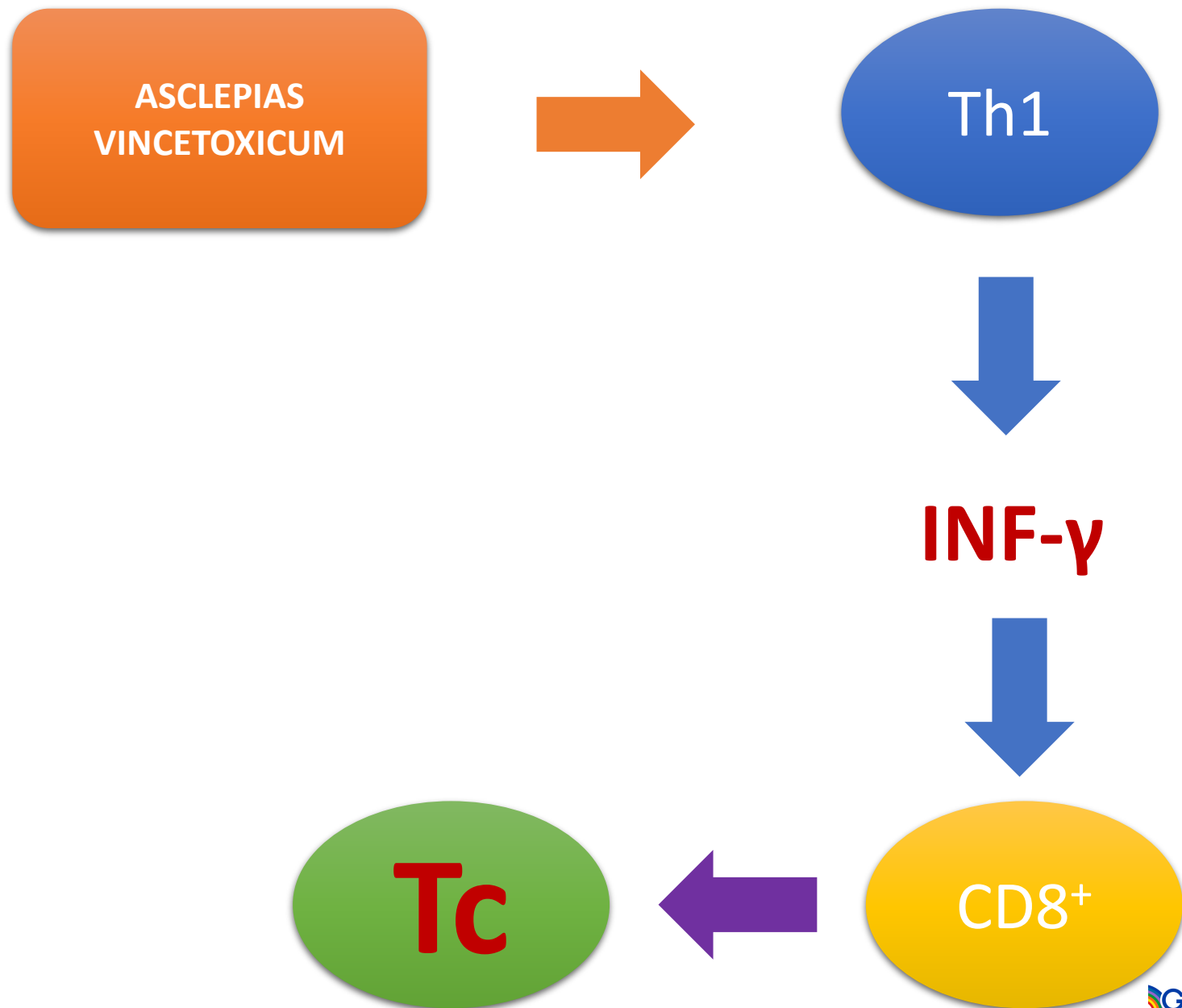


- Hou CC, et al. Comparative metabolomics approach coupled with cell- and gene-based assays for species classification and anti-inflammatory bioactivity validation of Echinacea plants. *J Nutr Biochem.* 2010;21(11):1045-59.
- Bałan BJ, et al. The modulatory influence of some Echinacea-based remedies on antibody production and cellular immunity in mice. *Cent Eur J Immunol.* 2016;41(1):12-8.
- Hayashi I, et al. Effects of oral administration of *Echinacea purpurea* (American herb) on incidence of spontaneous leukemia caused by recombinant leukemia viruses in AKR/J mice. *Nihon Rinsho Meneki Gakkai Kaishi.* 2001;24(1):10-20.



# GUNA-FLU





# GUNA<sup>®</sup>-FLU

## Clinical Studies

1) COMPARATIVE EVALUATION OF GUNA<sup>®</sup>-FLU vs VACCINE FOR THE INFLUENZA SYNDROME PREVENTION IN PEDIATRICS

A prospective, multicentre, randomized, controlled study

M. Colombo, G. Rigamonti, M.L. Danza, A. Bruno

LA MEDICINA BIOLOGICA 2007/3; 3-10

2) EFFICACY OF A COMPLEX HOMOEOPATHIC MEDICINE IN THE RECURRENT RESPIRATORY INFECTIONS PREVENTION IN HIGHLY-SUSCEPTIBLE CHILDREN

A controlled, randomized study

G. Rocca, M. Colombo

ECAM (EVIDENCE BASED COMPLEMENTARY AND ALTERNATIVE MEDICINE)

- in press -

3) UPPER RESPIRATORY INFECTIONS PREVENTION IN CHILDREN WITH GUNA<sup>®</sup>-FLU

A multicentre, controlled, randomized study

C. Supino

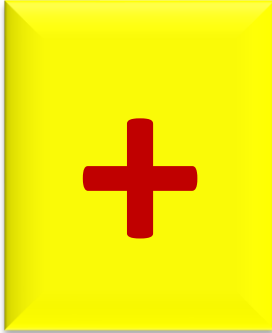
LA MEDICINA BIOLOGICA 2002/3; 19-23

## INTERNATIONAL LITERATURE REVIEW

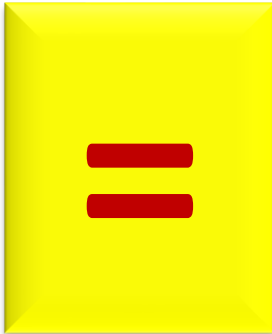


Omeopatia d'avanguardia

**PREVENTION OVERLAP**

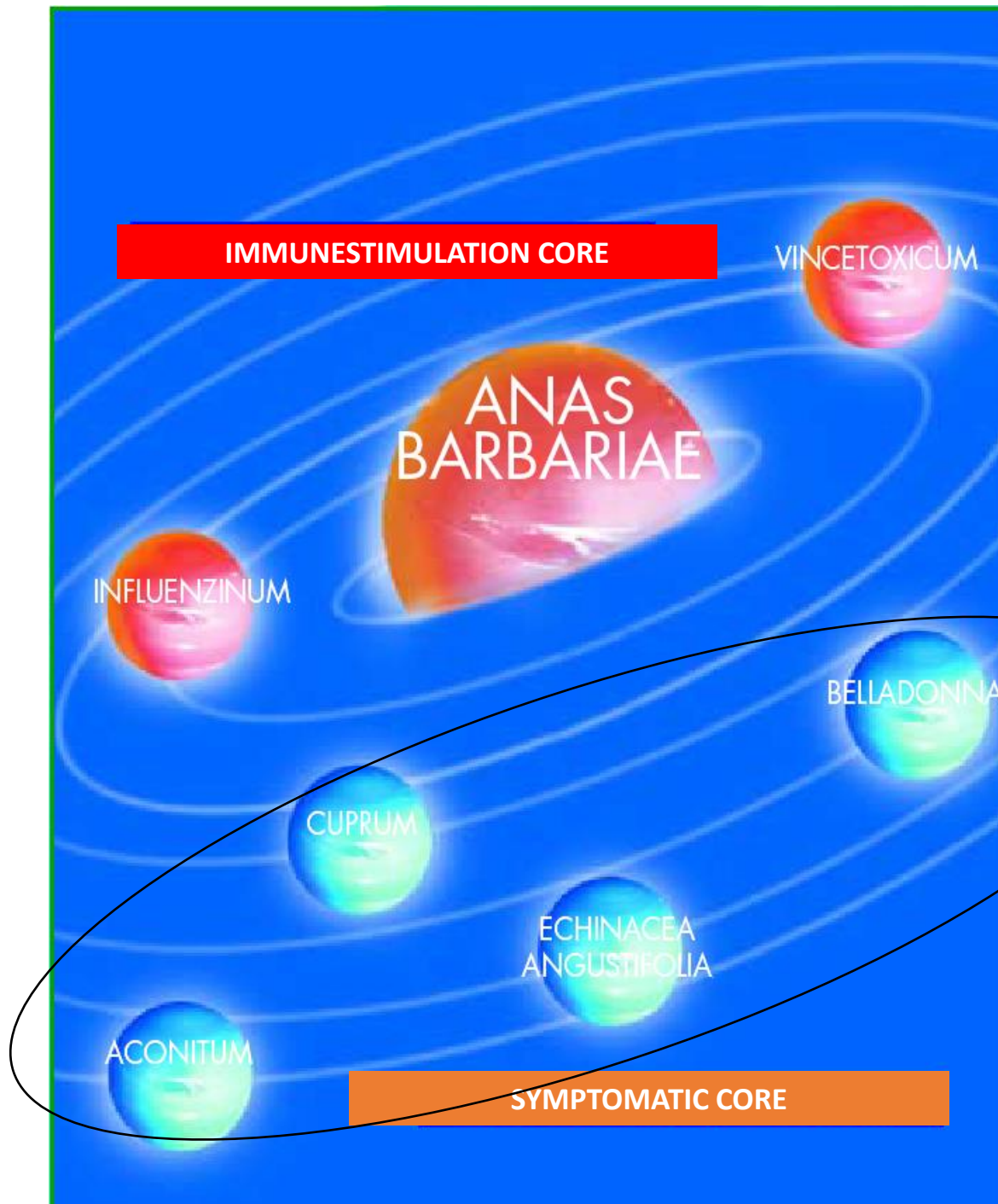


**ANTI-FLU VACCINE**



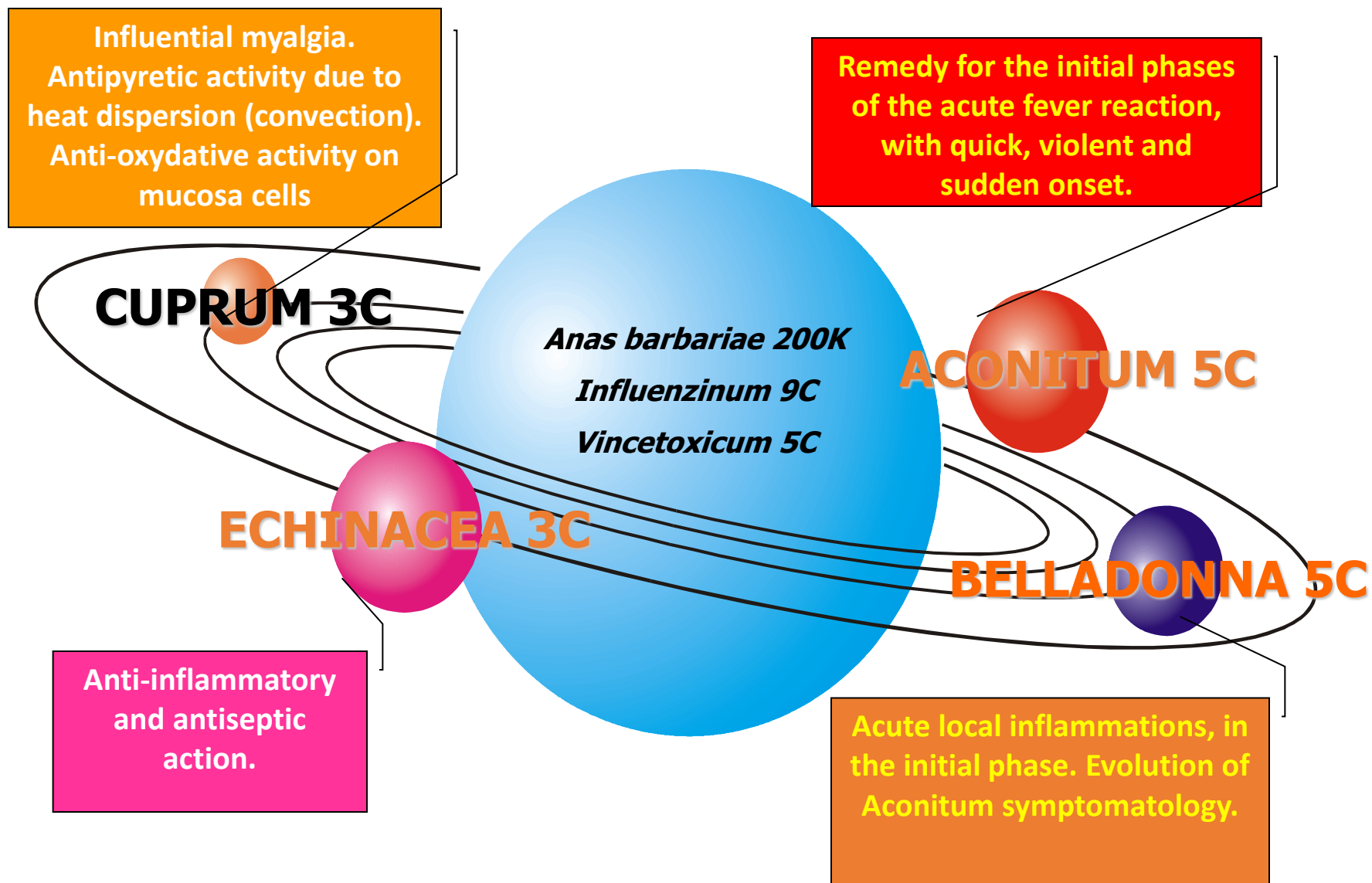
**BY-PASSING THE ANTIGENIC DRIFT OF THE INFLUENZA VIRUS**

# GUNA-FLU<sup>®</sup>



**Prevention and  
treatment of flu  
and cold syndromes**

# SYMPTOMATIC REMEDIES CORE



## RISOLUZIONE DEL SINTOMO FEBBRE dopo 24-48-72 ore

	Dopo 24h (percentuale pazienti)	Dopo 48h (percentuale pazienti)	Dopo 72h (percentuale pazienti)
<b>Gruppo A</b> – OMEOGRIPIHI®	25%	56%	89%
<b>Gruppo B</b> – Paracetamolo	23%	49%	76%

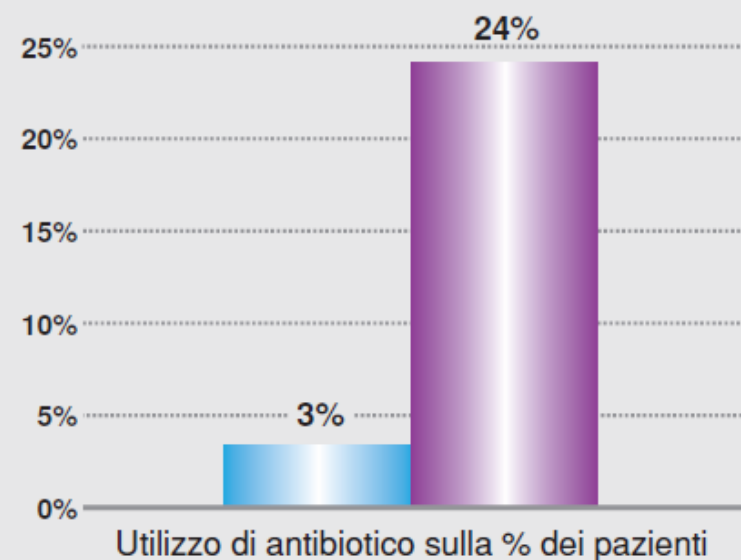
### Riferimento bibliografico

ARRIGHI A. – Omeogriphi® vs paracetamolo nel trattamento della Sindrome influenzale.

– Studio clinico prospettico controllato

La Med. Biol., 2013/4; 3-12.

### UTILIZZO DI ANTIBIOTICO SULLA % DEI PAZIENTI – CONFRONTO TRA I DUE GRUPPI –



# GUNA-FLU

## *Directions*

- **SEASONAL PREVENTION:** one dose once a week for 6-8 weeks to be repeated after 2 weeks

- **TREATMENT OF ACUTE SYMPTOMATOLOGY** (in the first 36 hours from the onset): one dose every 6 hours until acute symptoms disappear



# GUNA-FLU

## *Directions*

• **SEASONAL PREVENTION:** one dose once a week for 6-8 weeks to be repeated after 2 weeks

• **TREATMENT OF ACUTE SYMPTOMATOLOGY** (in the first 36 hours from the onset): one dose every 6 hours until acute symptoms disappear

# Space-Time Immunomodulation

## IMMUNOSTIMULATION IN **PREVENTION**

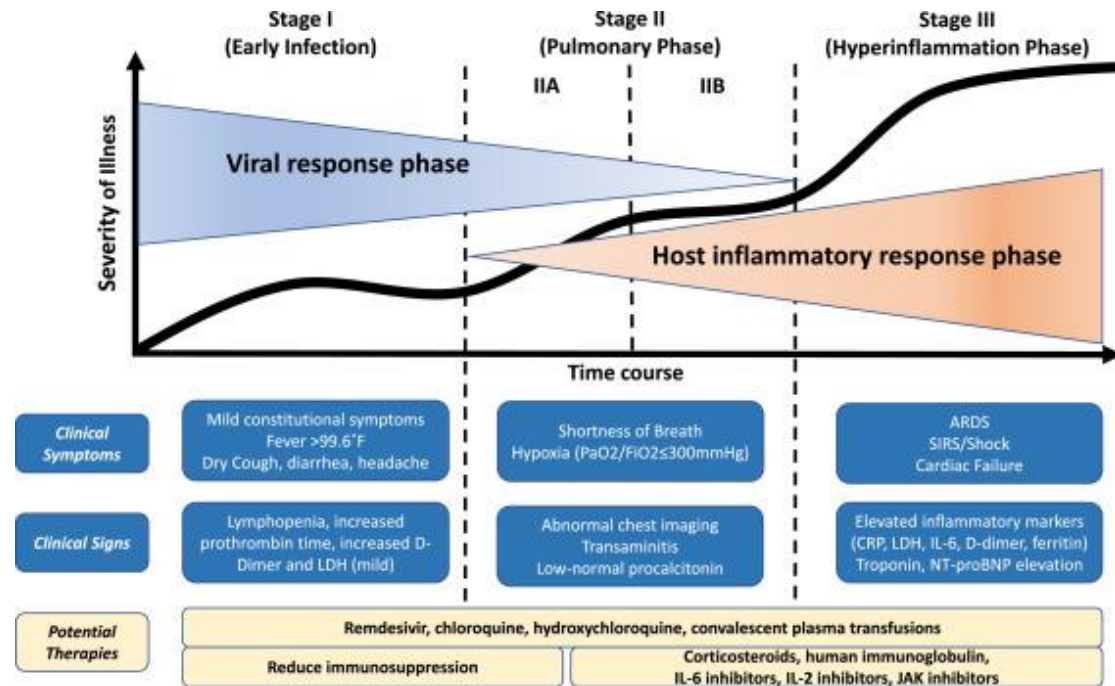
- **CITOMIX** (granuli): 5 pellets once a day
- **GUNA-INTERFERON-GAMMA** (gocce): 20 drops twice a day

## IMMUNOSTIMULATION AND **CO-PREVENTION**

- **GUNA-FLU**: 1 dose a week

# Our (unique) goal

- *Before*
- ***During***
- *After*

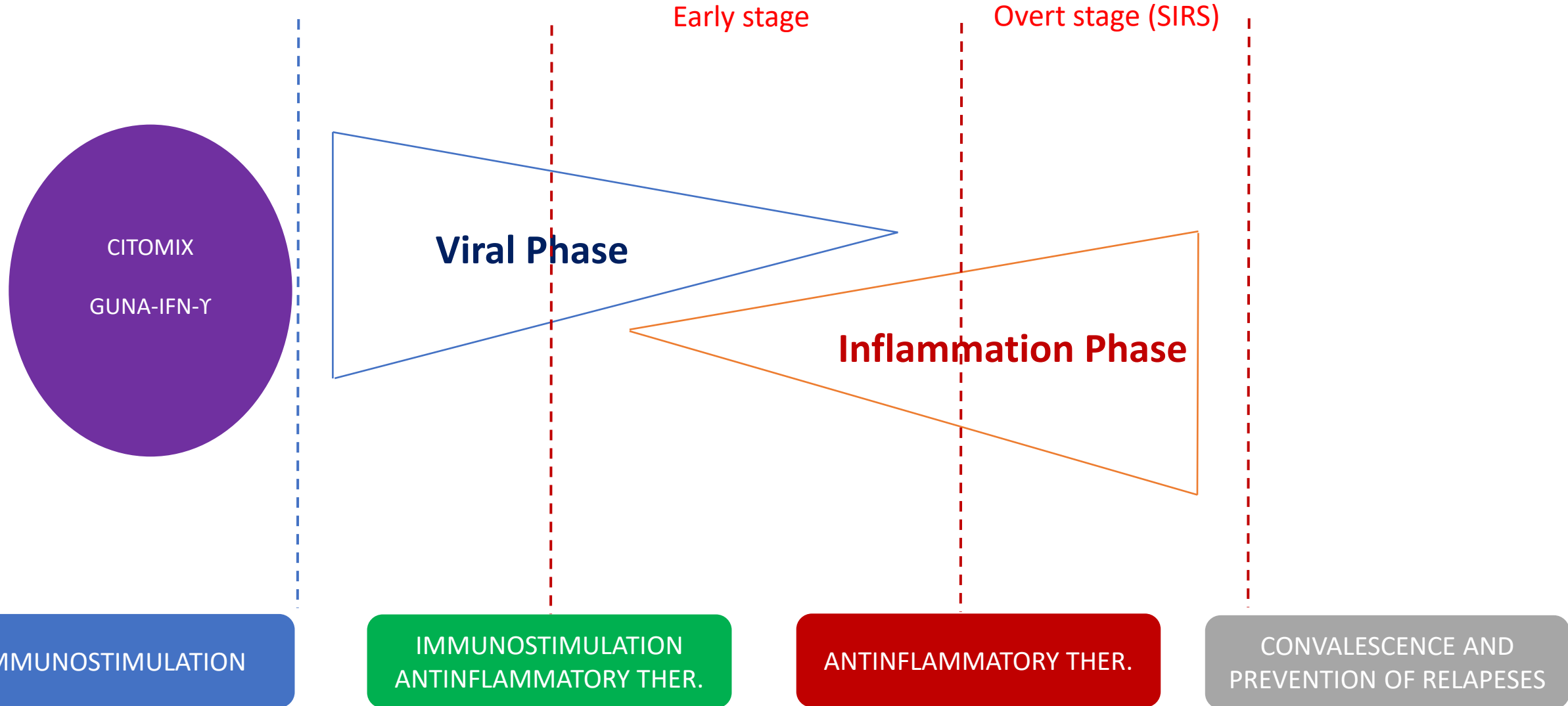


***And what to do during  
an infective disease?  
(in overlapping with other  
treatments)***

The example of [Covid-19] and the management of a pauci-symptomatic *early stage* patient.

*Importance of the correct time –space intervention*

# Space-Time Immunomodulation



# Our goal in prevention



**Prevention:** 5 pellets a day (even twice in fragile patients), every day for 3 consecutive months.



**Treatment of active viral phase and related symptomatology:** 10 pellets 2-3 times a day for 2-3 giorni days; continue with 5 pellets twice a day per 5-7 days.

**Viral Phase**

**Host Inflammatory Phase**

**Before**

IMMUNOSTIMULATION

**During**

IMMUNOSTIMULATION  
ANTINFLAMMATORY THER.

**After**

CONVALESCENCE AND  
PREVENTION OF RELAPSES

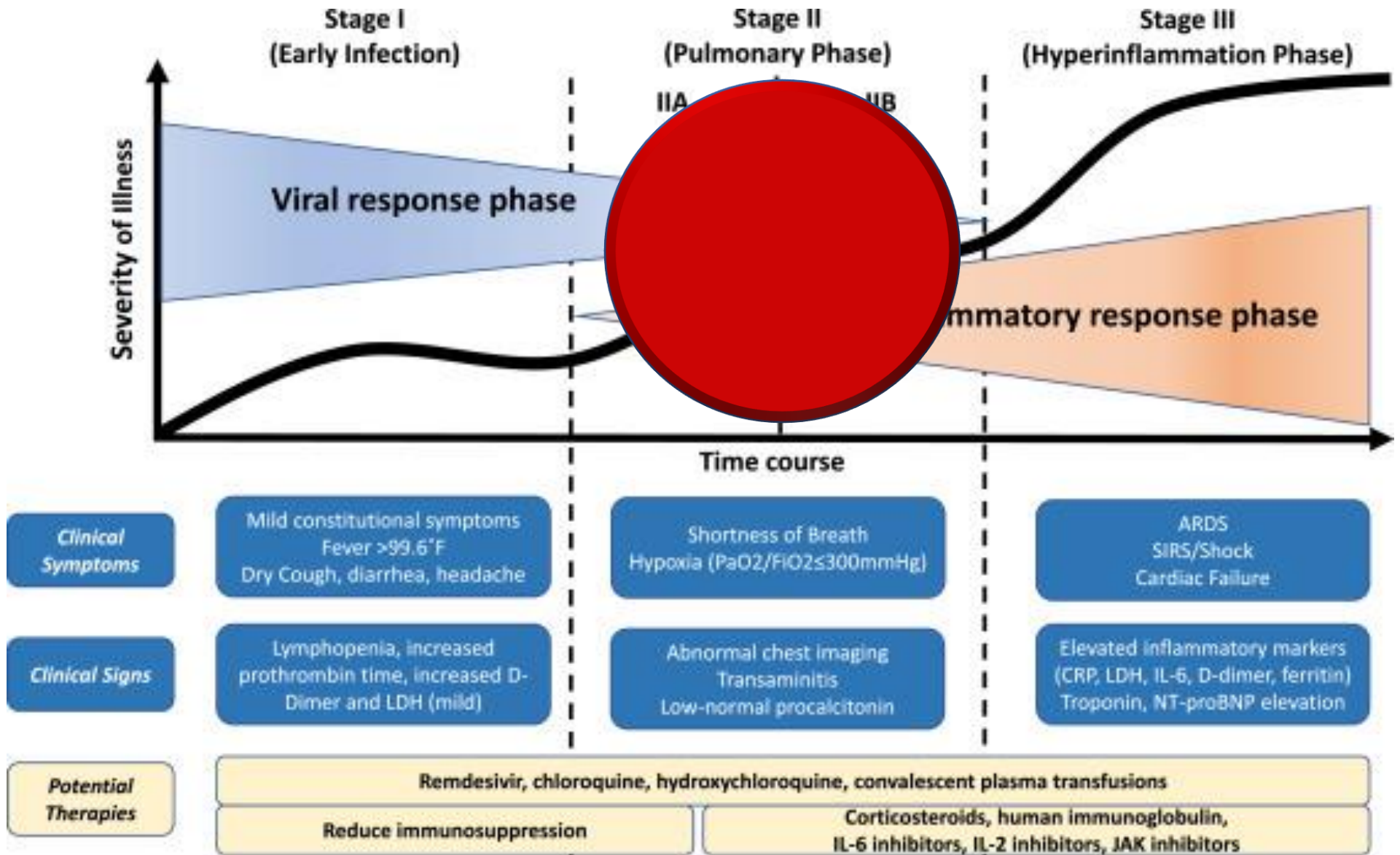
**NATURE NEWS 09 APRIL 2020**

**How does COVID-19 kill? Uncertainty is hampering doctors' ability to choose treatments**

Doctors are reaching for drugs that dampen the immune response — but these also undermine the body's own fight against the coronavirus.



Can Low Dose Pharmacology be supportive during the active phase of a viral disease?



Keep in mind  
these drugs

Emapalumab

IFN- $\alpha$

Anakinra

IL-1RA

Sarilumab

IL-6RA

Tocilizumab

IL-6

--	--

Study Type : Interventional (Clinical Trial)

Estimated Enrollment : 342 participants

Allocation: Randomized

Intervention Model: Factorial Assignment

Masking: None (Open Label)

Primary Purpose: Treatment

Official Title: A Prospective, Randomized, Factorial Design, Interventional Study to Compare the Safety and Efficacy of Combinations of Blockade of Interleukin-6 Pathway and Interleukin-1 Pathway to Best Standard of Care in Improving Oxygenation and Short- and Long-term Outcome of COVID-19 Patients With Acute Hypoxic Respiratory Failure and Systemic Cytokine Release Syndrome

Estimated Study Start Date : April 2020

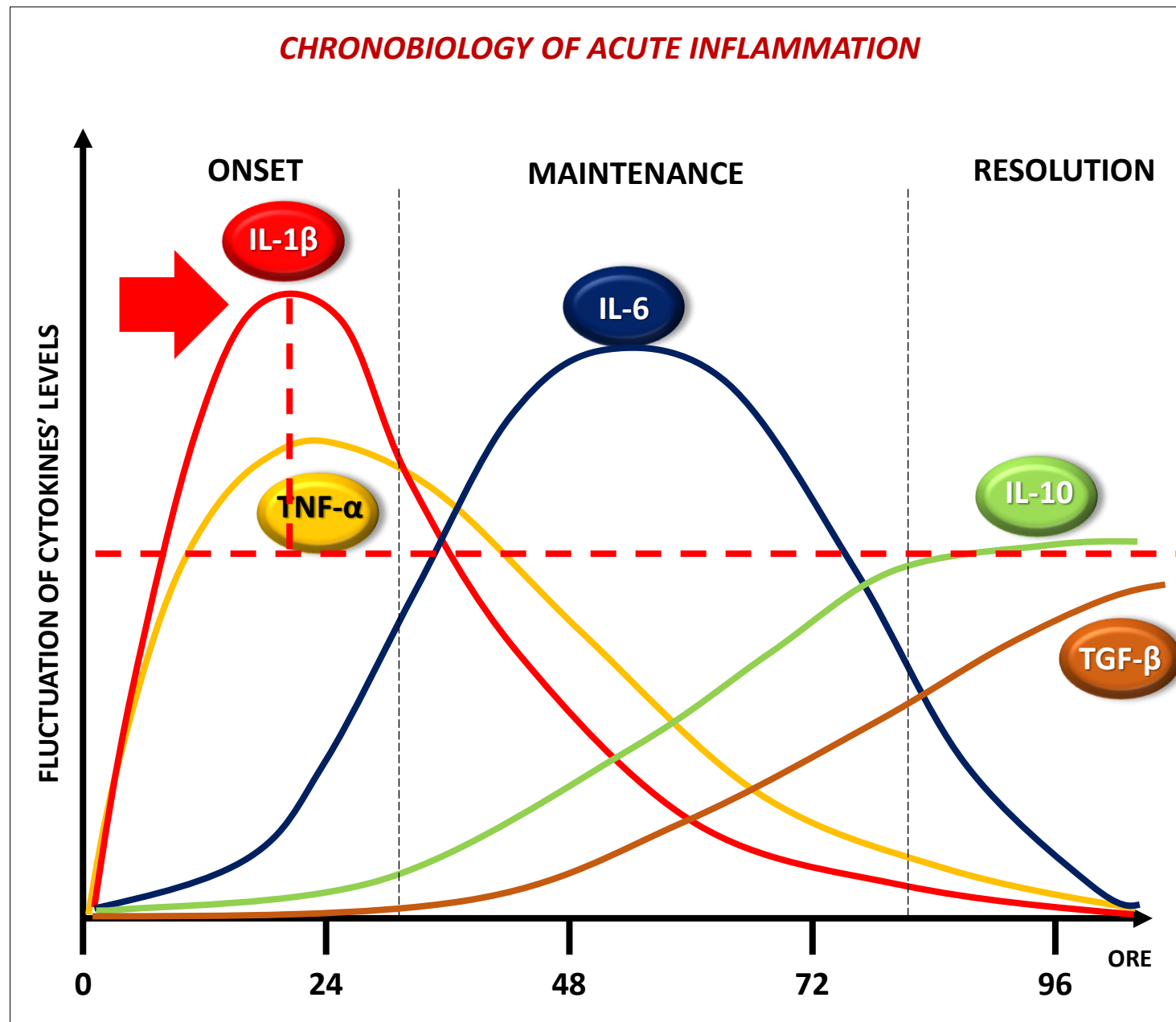
Estimated Primary Completion Date : September 2020

Estimated Study Completion Date : December 2020



*ClinicalTrials.gov*

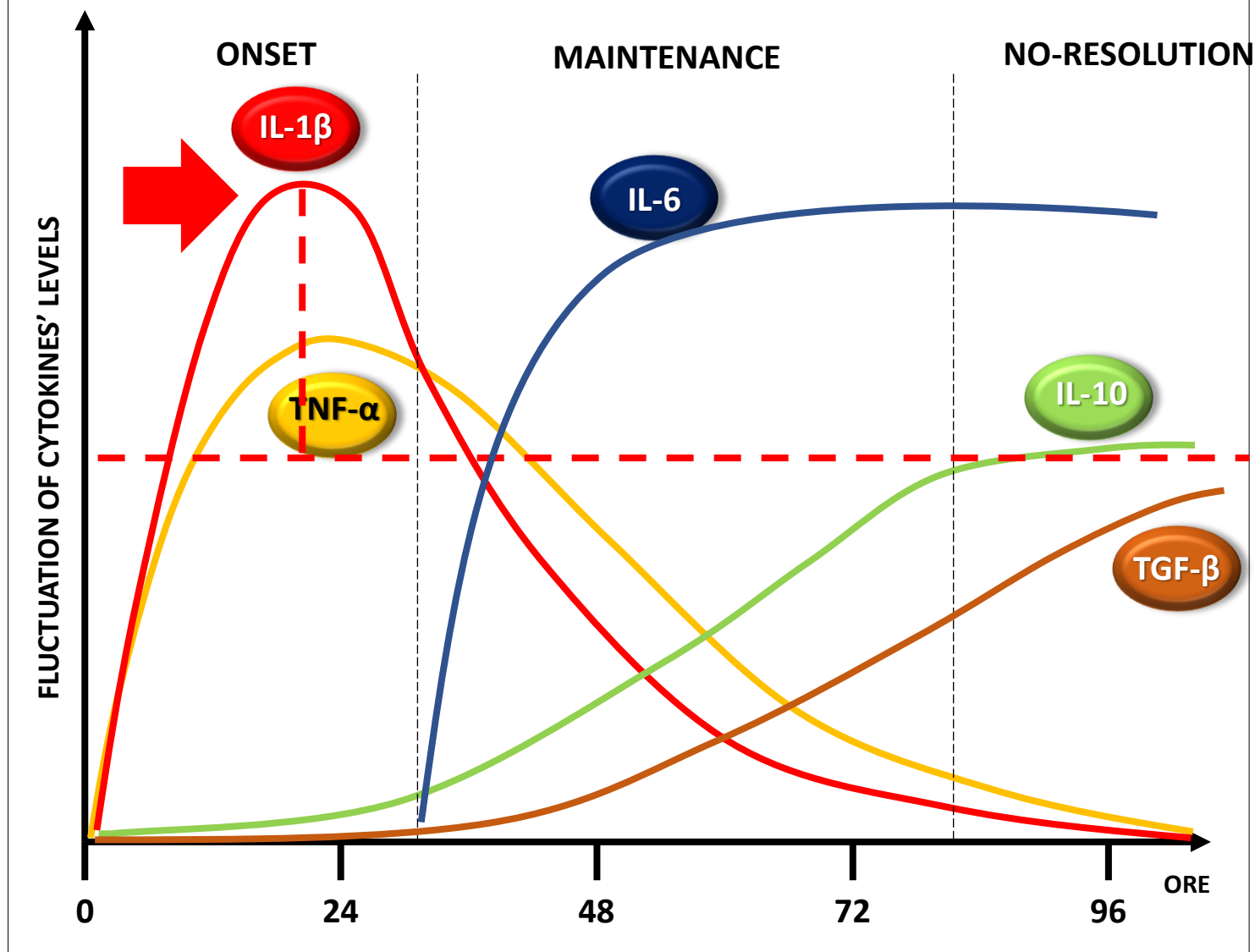
Condition or disease	Intervention/treatment	Phase
COVID-19	Other: Usual Care Drug: <b>Anakinra Drug:</b> Siltuximab Drug: Tocilizumab	Phase 3



Petersen AM<sup>1</sup>, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* (1985). 2005 Apr;98(4):1154-62

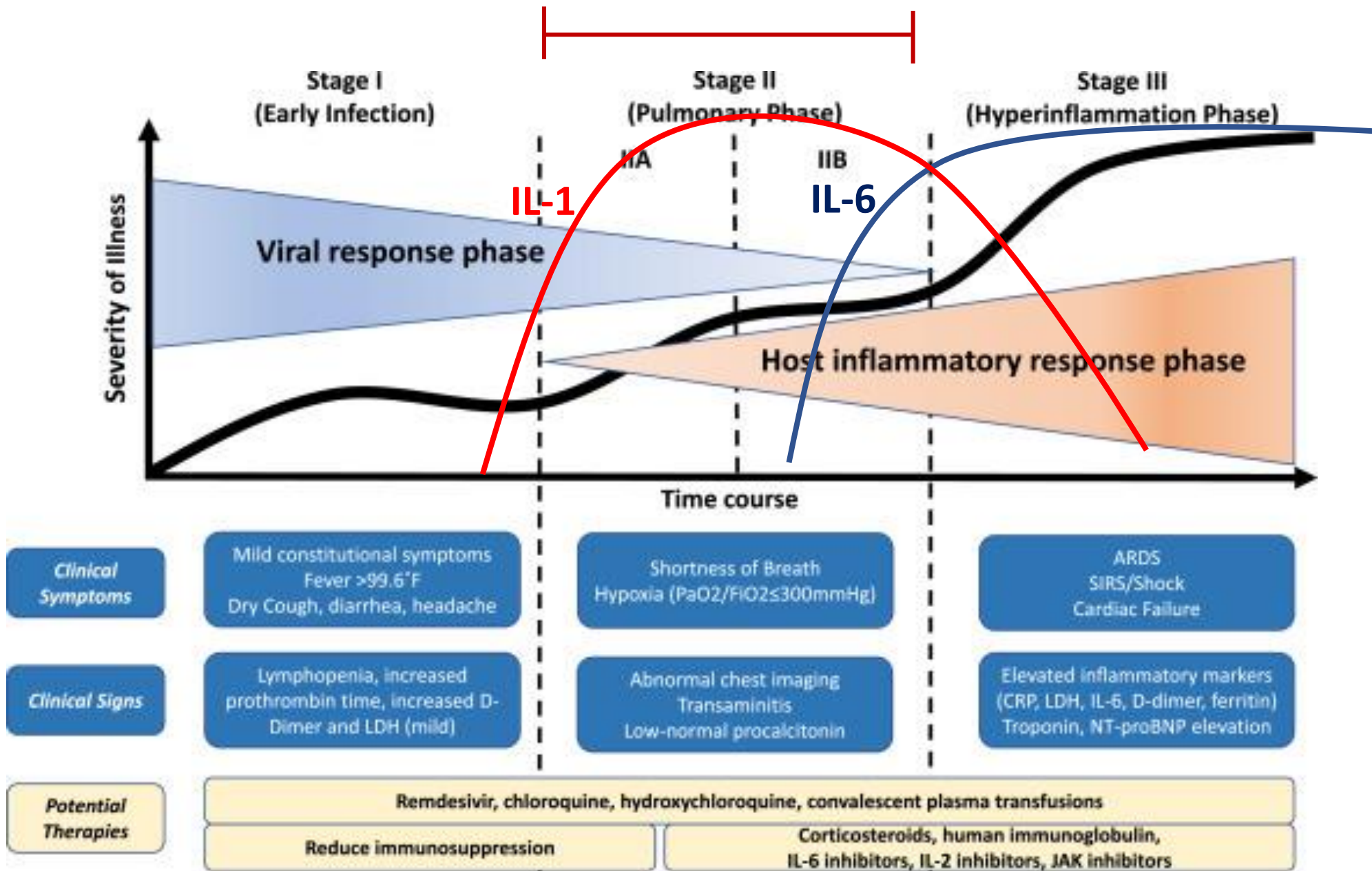
Modificata a fini didattici.

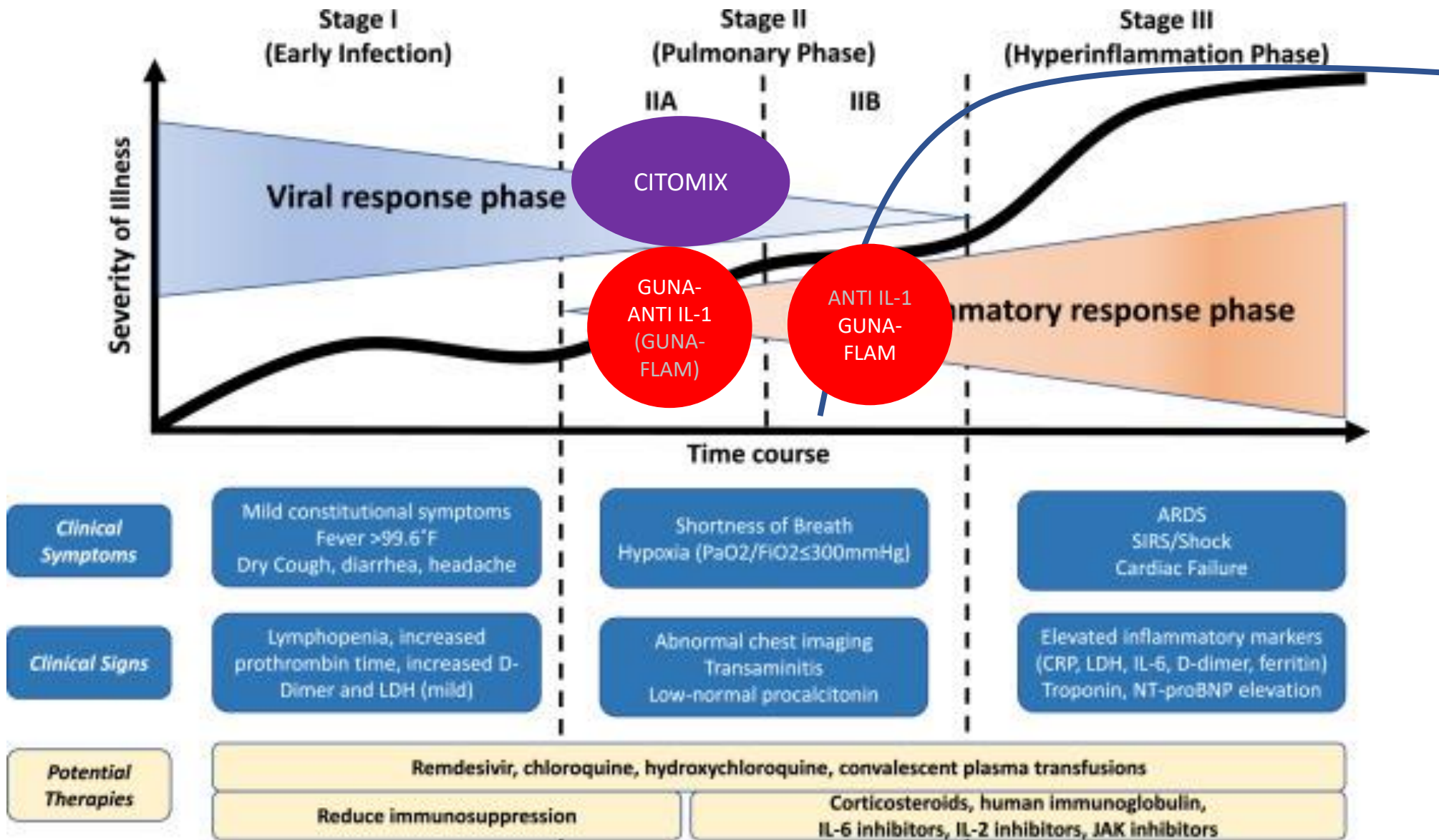
## CHRONOBIOLOGY OF INFLAMMATION IN COVID-19



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

Modificata a fini didattici.







A novel, systemic, approach to  
*The **first** stage of the inflammatory  
phase of an infection*



#### DIRECTIONS AND WAY OF ADMINISTRATION

Guna-Anti IL 1: **20 drops 10-12 times a day** for a short-medium time (half dosage for children below 6 years)

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

**Anti Interleukins-1 ( $\alpha$ ;  $\beta$ ) act as NSAIDs, cortisone and, in part, as salicylates**, without the negative side effects caused by these allopathic medicines.

Anti IL-1 4CH

BLOCK

IL-1

COX<sub>2</sub>

PGE<sub>2</sub>

NO

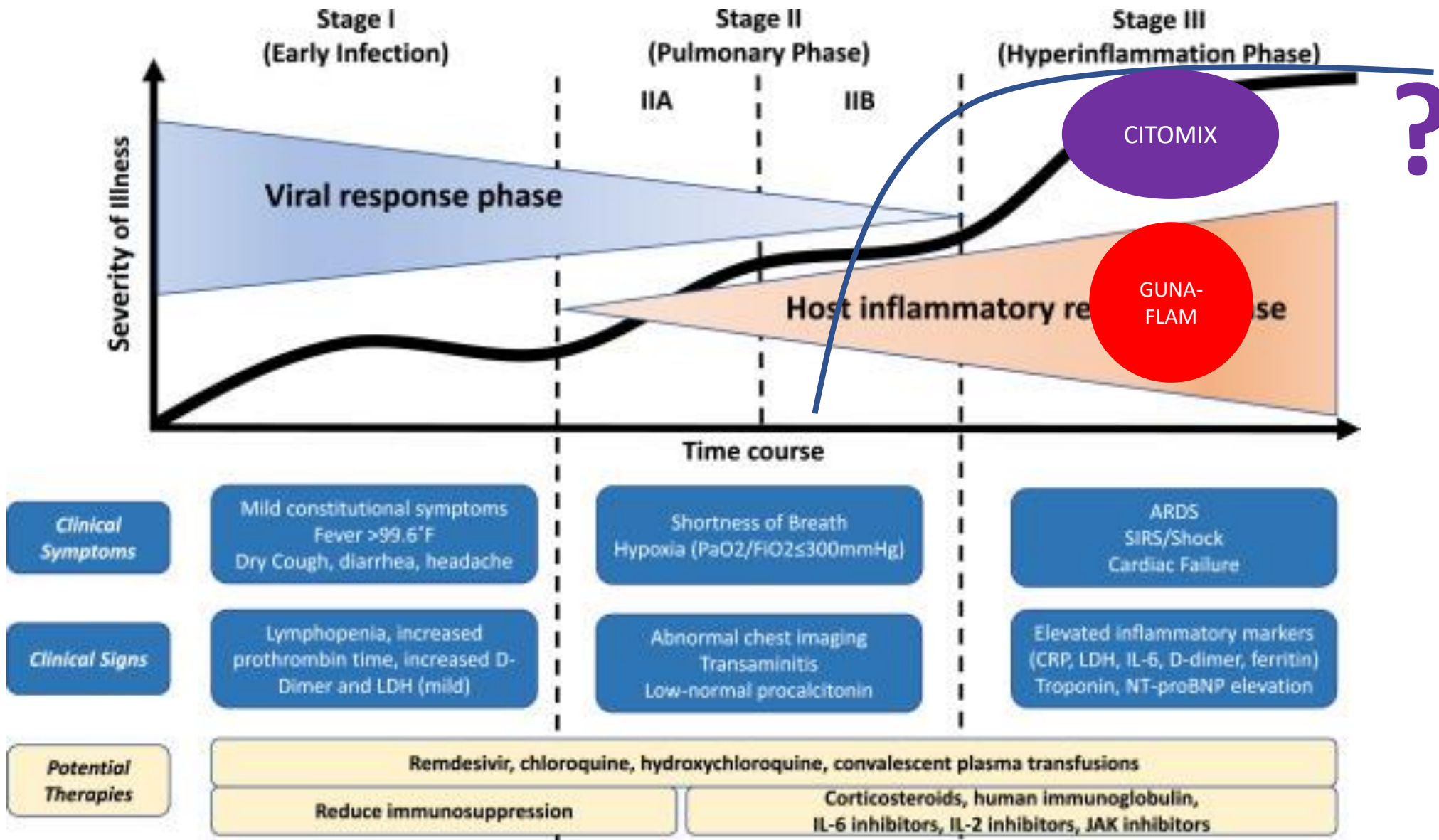
# Space-Time Immunomodulation

## IMMUNOSTIMULATION IN PREVENTION

- CITOMIX (granuli): 5 pellets once a day
- GUNA-INTERFERON-GAMMA (gocce): 20 drops twice a day
- GUNA-FLU: 1 dose a week

## IMMUNOSTIMULATION IN THE **EARLY STAGE OF THE INFECTION** AND **EARLY STAGE ANTINFLAMMATORY THERAPY**

- CITOMIX (granuli): 10 pellets 2-3 days a day
- GUNA-ANTIL IL 1: 20 drops **10-12 times a day** for 2 to 6 days



# Space-Time Immunomodulation

IMMUNOSTIMULATION

- CITOMIX (granuli): 5 pellets once a day
- GUNA-INTERFERON-GAMMA (gocce): 20 drops twice a day
- GUNA-FLU: 1 dose a week

IMMUNOSTIMULATION AND  
ANTINFLAMMATORY THER.

- CITOMIX (granuli): 10 pellets 2-3 days a day
- GUNA-ANTIL IL 1: 20 drops 10-12 times a day for 2 to 6 days

**ANTINFLAMMATORY  
THER.**

- **GUNA-FLAM: 20 drops 10-12 times a day**

A novel, systemic, approach to  
*The **second** stage of the  
inflammatory phase of an infection*



#### DIRECTIONS AND WAY OF ADMINISTRATION

**Guna-Flam: 20 drops 10 to 12 times a day a day  
(half dosage for children below 6 years)**

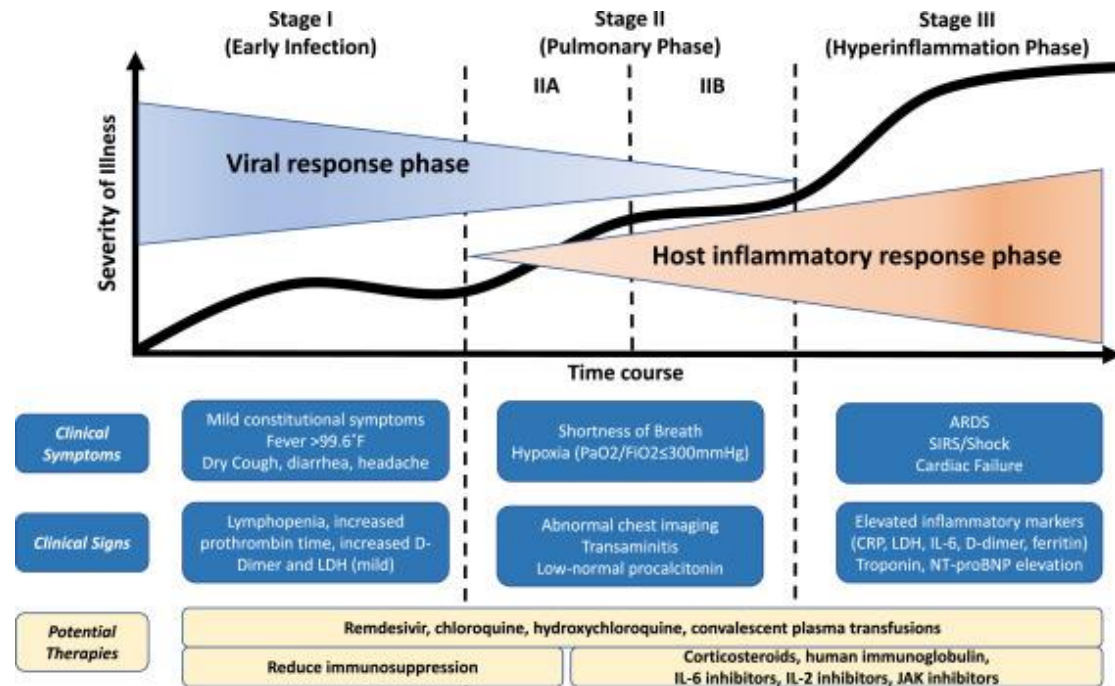
Sublingual administration directly under the tongue or in a little water, preferably far from meals.

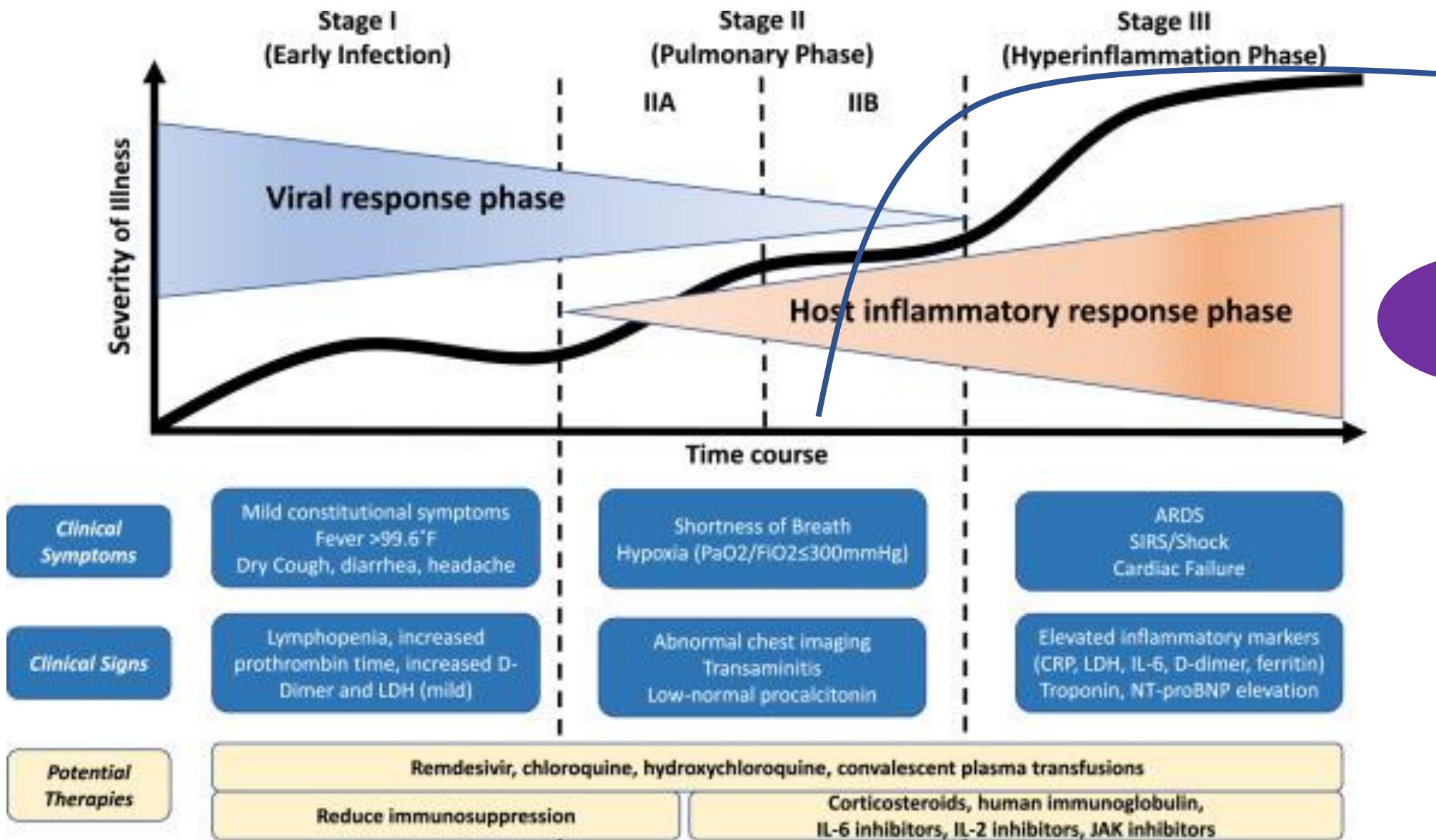
#### Ingredients

→  
Aconitum napellus 6X/12X/30X/200X  
Anti interleukin 1 alpha 4C  
Apis mellifica 6X/12X/30X/200X  
Belladonna 6X/12X/30X/200X  
Beta-Endorphin 6X  
Bryonia alba 6X/12X/30X/200X  
Citricum acidum 3X  
Conjunctiva tissue, Porcine 12X/30X/200X  
Copper gluconate 4X  
Ferrum phosphoricum 6X/12X/30X/200X  
Hepar sulphuris calcareum 6X/12X/30X/200X  
Hypophysis, Porcine 200X  
→  
Interleukin 10 4C  
Melatonin 4C  
Natrum pyruvicum 3X  
Phytolacca decandra 6X/12X/30X/200X  
Pineal gland, Porcine 6X  
Pyrogenium 30X/200X  
Transforming Growth Factor 1 beta 4C

# Our (unique) goal

- *Before*
- *During*
- *After*





CITOMIX

# Our goal in prevention



**Prevention:** 5 pellets a day (even twice in fragile patients), every day for 3 consecutive months.

## Before

IMMUNOSTIMULATION



### Viral Phase

## During

IMMUNOSTIMULATION  
ANTINFLAMMATORY THER.

**Treatment of active viral phase and related symptomatology:** 10 pellets 2-3 times a day for 2-3 giorni days; continue with 5 pellets twice a day per 5-7 days.

### Host Inflammatory Phase

ANTINFLAMMATORY THER.



**Prevention of relapses:** 5 pellets a day, every day for 2 consecutive months.

## After

CONVALESCENCE AND  
PREVENTION OF RELAPSES



# Space-Time Immunomodulation

IMMUNOSTIMULATION

- CITOMIX: 5 pellets once a day
- GUNA-INTERFERON-GAMMA: 20 drops twice a day
- GUNA-FLU: 1 dose a week

IMMUNOSTIMULATION AND  
ANTINFLAMMATORY THER.

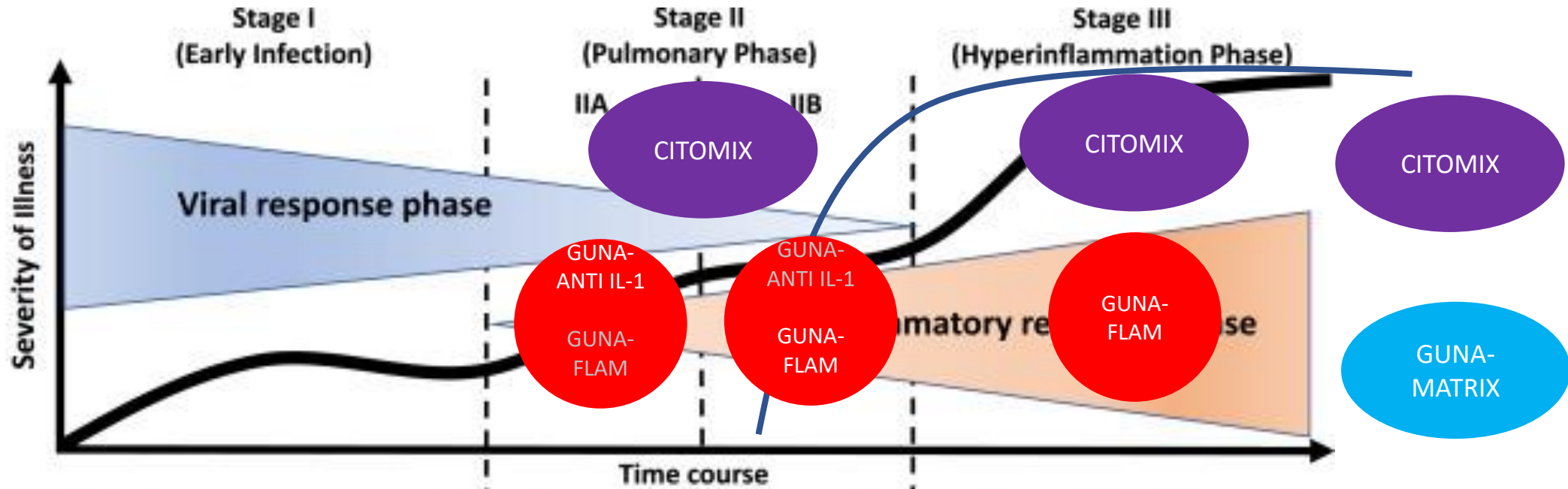
- CITOMIX: 10 pellets 2-3 days a day
- GUNA-ANTIL IL 1: 20 drops 10-12 times a day for 2 to 6 days

ANTINFLAMMATORY THER.

- GUNA-FLAM: 20 drops 10-12 times a day

**CONVALESCENCE AND  
PREVENTION OF  
RELAPSES**

- **CITOMIX: 5 pellets once a day for 2-4 months**



	Stage I (Early Infection)	Stage II (Pulmonary Phase)	Stage III (Hyperinflammation Phase)
<b>Clinical Symptoms</b>	Mild constitutional symptoms Fever >99.6°F Dry Cough, diarrhea, headache	Shortness of Breath Hypoxia (PaO <sub>2</sub> /FIO <sub>2</sub> ≤ 300mmHg)	ARDS SIRS/Shock Cardiac Failure
<b>Clinical Signs</b>	Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation
<b>Potential Therapies</b>	Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions		
	Reduce immunosuppression	Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors	

# Space-Time Immunomodulation

## IMMUNOSTIMULATION IN **PREVENTION**

- CITOMIX: 5 pellets twice a day
- GUNA-INTERFERON-GAMMA: 20 drops twice a day
- GUNA-FLU: 1 dose a week

## IMMUNOSTIMULATION IN THE **EARLY STAGE OF THE INFECTION AND ANTINFLAMMATORY THERAPY**

- CITOMIX: 10 pellets 2-3 days a day
- GUNA-ANTIL IL 1: **20 drops 10-12 times a day for 2 to 6 days**

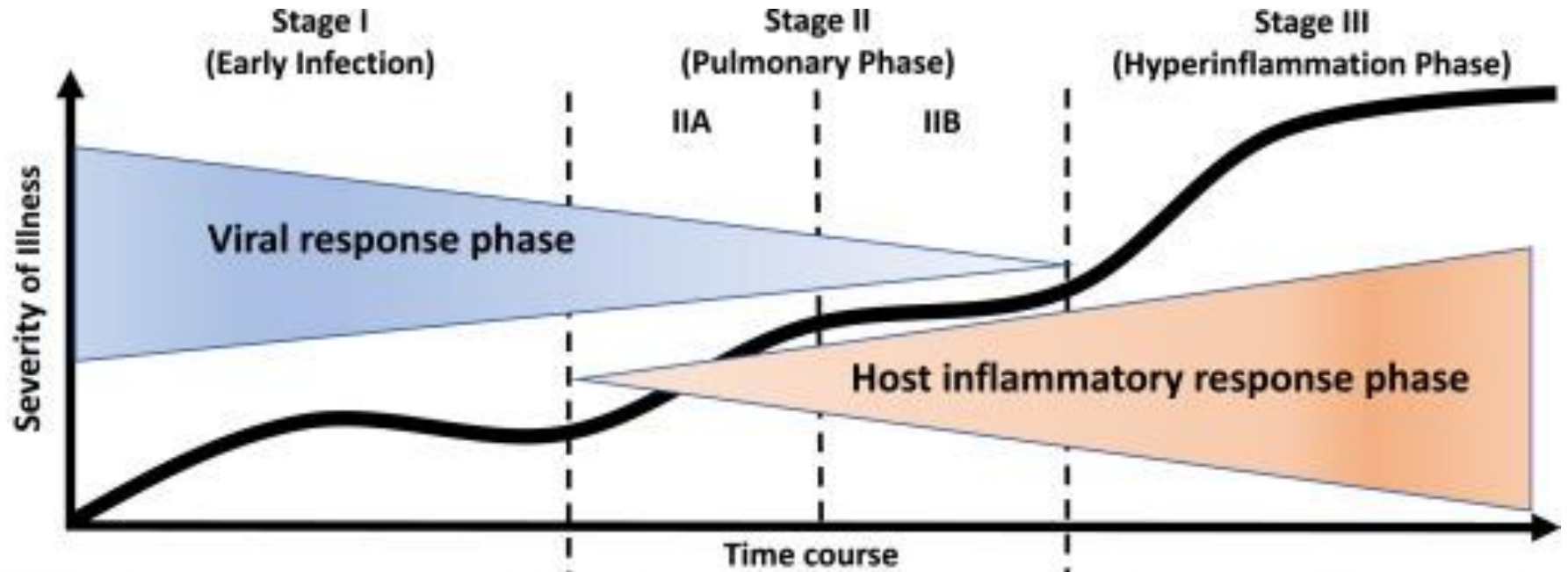
## ANTINFLAMMATORY THERAPY

- GUNA-FLAM: 20 drops 10-12 times a day

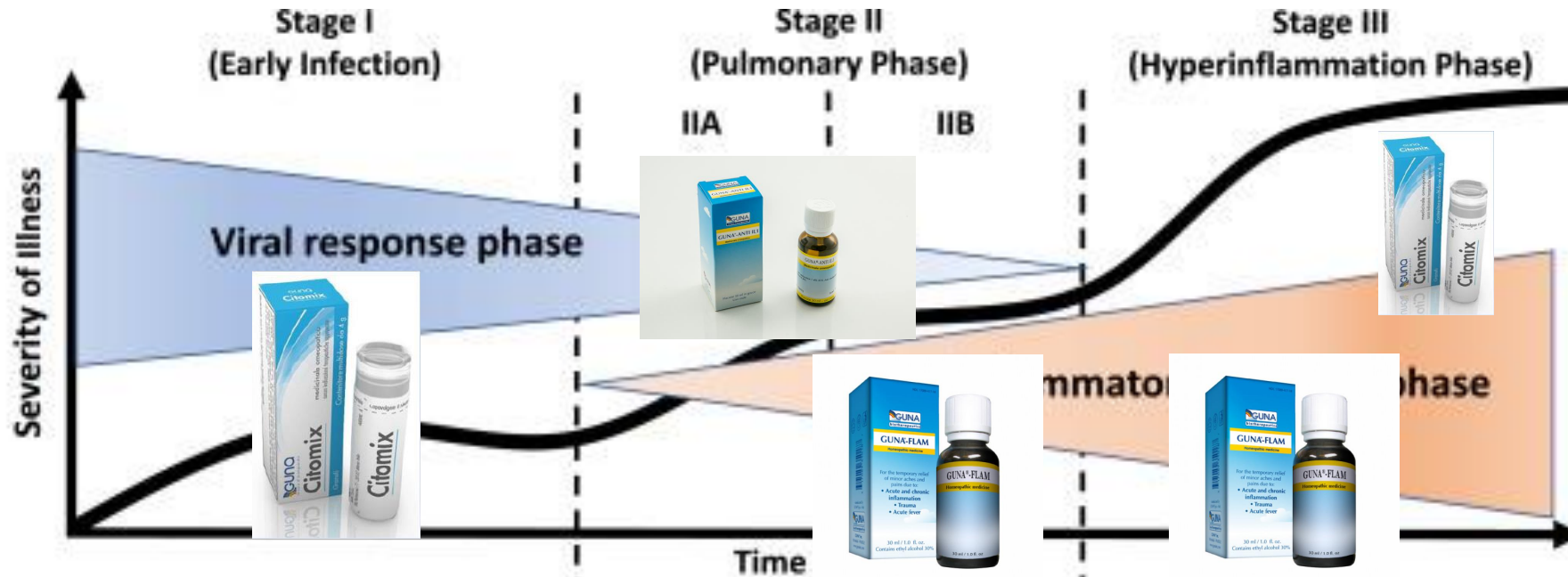
## CONVALESCENCE AND PREVENTION OF RELAPSES

- CITOMIX: 5 pellets one a day for 2-4 months

*And what to do during  
an infective disease?  
(in **OVERLAPPING** with other  
treatments)*



<b>Clinical Symptoms</b>	Mild constitutional symptoms Fever >99.6°F Dry Cough, diarrhea, headache	Shortness of Breath Hypoxia (PaO <sub>2</sub> /FIO <sub>2</sub> ≤ 300mmHg)	ARDS SIRS/Shock Cardiac Failure
<b>Clinical Signs</b>	Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation
<b>Potential Therapies</b>	Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions Reduce immunosuppression Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors		



Clinical Symptoms	Stage I (Early Infection)	Stage II (Pulmonary Phase)	Stage III (Hyperinflammation Phase)
	Mild constitutional symptoms Fever >99.6°F Dry Cough, diarrhea, headache	Shortness of Breath Hypoxia (PaO2/FiO2 ≤ 300 mmHg)	ARDS SIRS/Shock Cardiac Failure
	Lymphopenia, increased D-dimer	Abnormal chest imaging Procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation
Recovery		convalescent plasma transfusions	corticosteroids, human immunoglobulin, 5 inhibitors, IL-2 inhibitors, JAK inhibitors

- **COLOSTRONONI:** 1 sachet 1-2 times a day
- **VITAMIN C:** 1 g a day
- **ZINCO:** 15 mg/die in adults e 7.5 mg/die in children
- **VITAMIN D3:** 1.000-1.500 U.I. /die; in children 600-1.000 U.I./die
- **OMEGA 3:** 500 mg 1 to 3 volte times a day; in children: 400 mg 1-2 times a day

- **COLOSTRONONI:** 1 sachet 2-4 times a day
- **VITAMIN C:** 4 grams per day
- **ZINCO:** 15 mg/die nell'adulto e 7.5 mg/die nei bambini
- **VITAMIN D3:** 10.000-U.I. /die
- **OMEGA 3:** 1 g 3 times a day



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