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

The information presented here is not to be considered as 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 it is intended as scholastic information only. Only the Doctor can decide if the information can be considered for their patient alongside with all the other necessary treatments and therapies.

The Presenter declares his conflict of interests with GUNA Pharmaceuticals

INTERNATIONAL ACADEMY OF PHYSIOLOGICAL REGULATING MEDICINE

CITOMIX UPDATES

Pharmacology Insights

Webinar

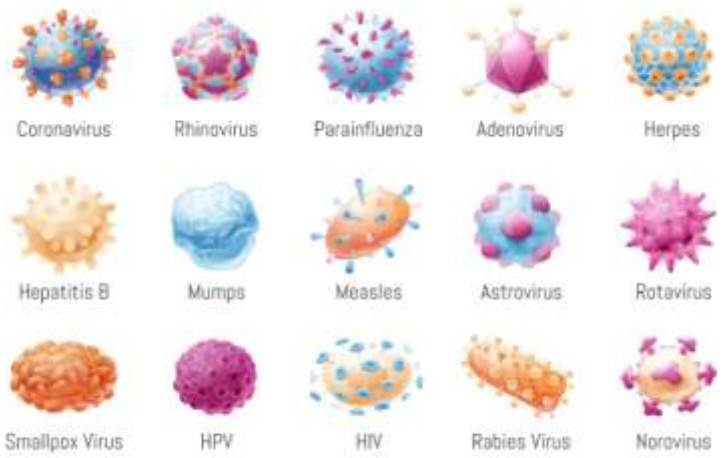
Wednesday, October 17th, 2024

Alessandro Perra – Scientific Director of Guna Pharmaceuticals

guna
terapie d'avanguardia

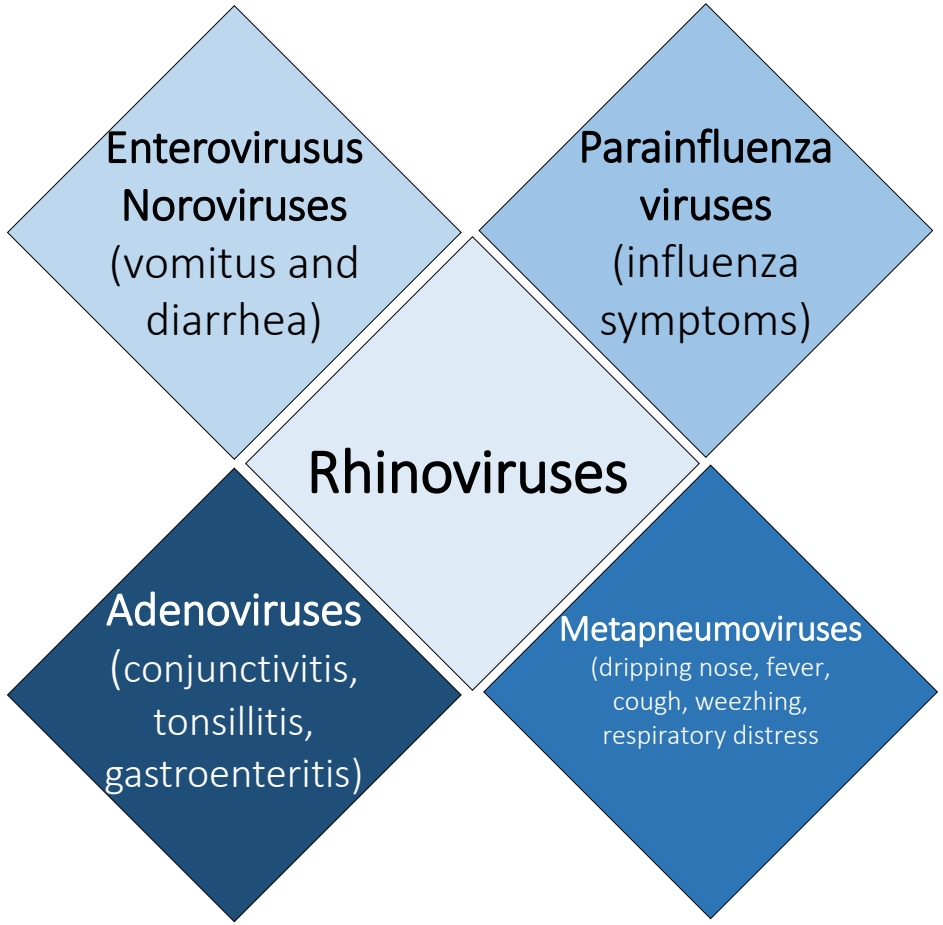
guna.it

The big challenge of winter season 2024-2025



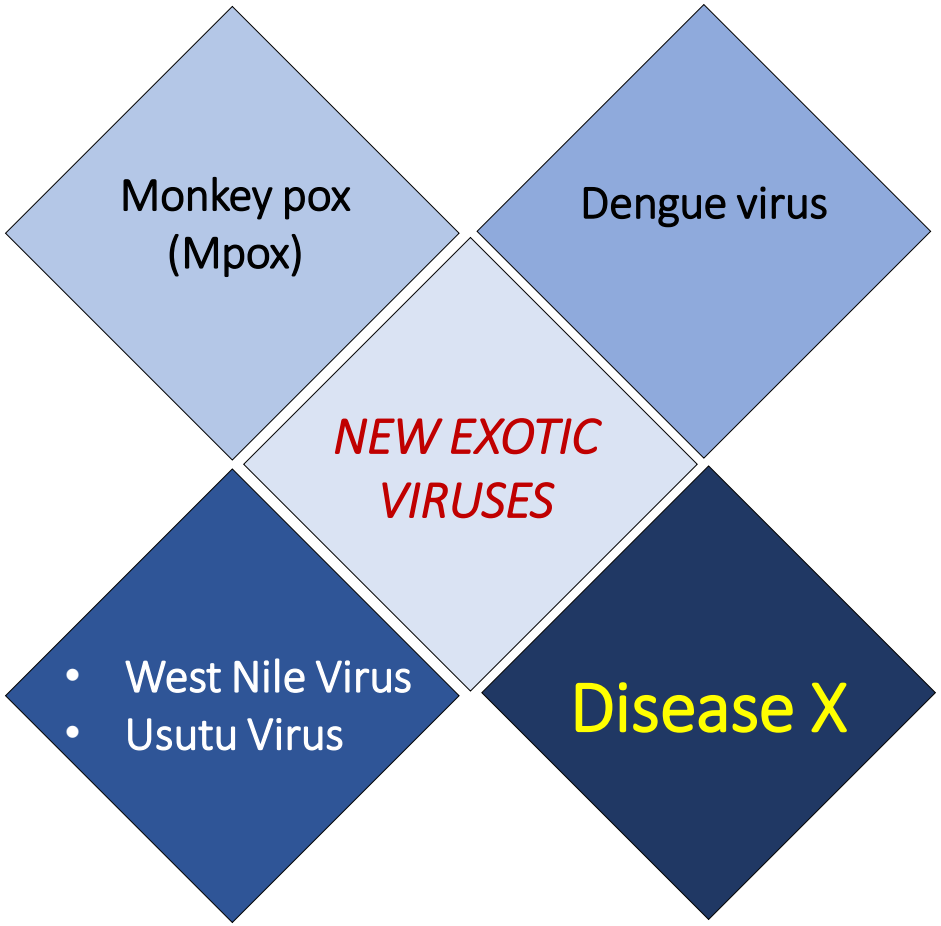
The co-circulation of several, different viral species

Virus actually in circulation, …and a little out of season

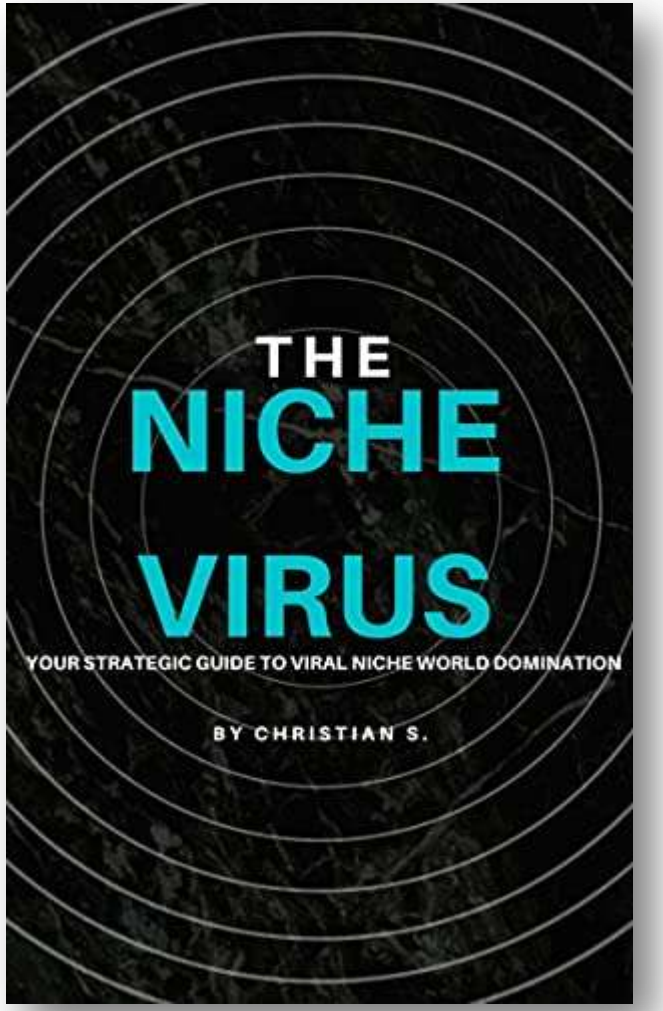


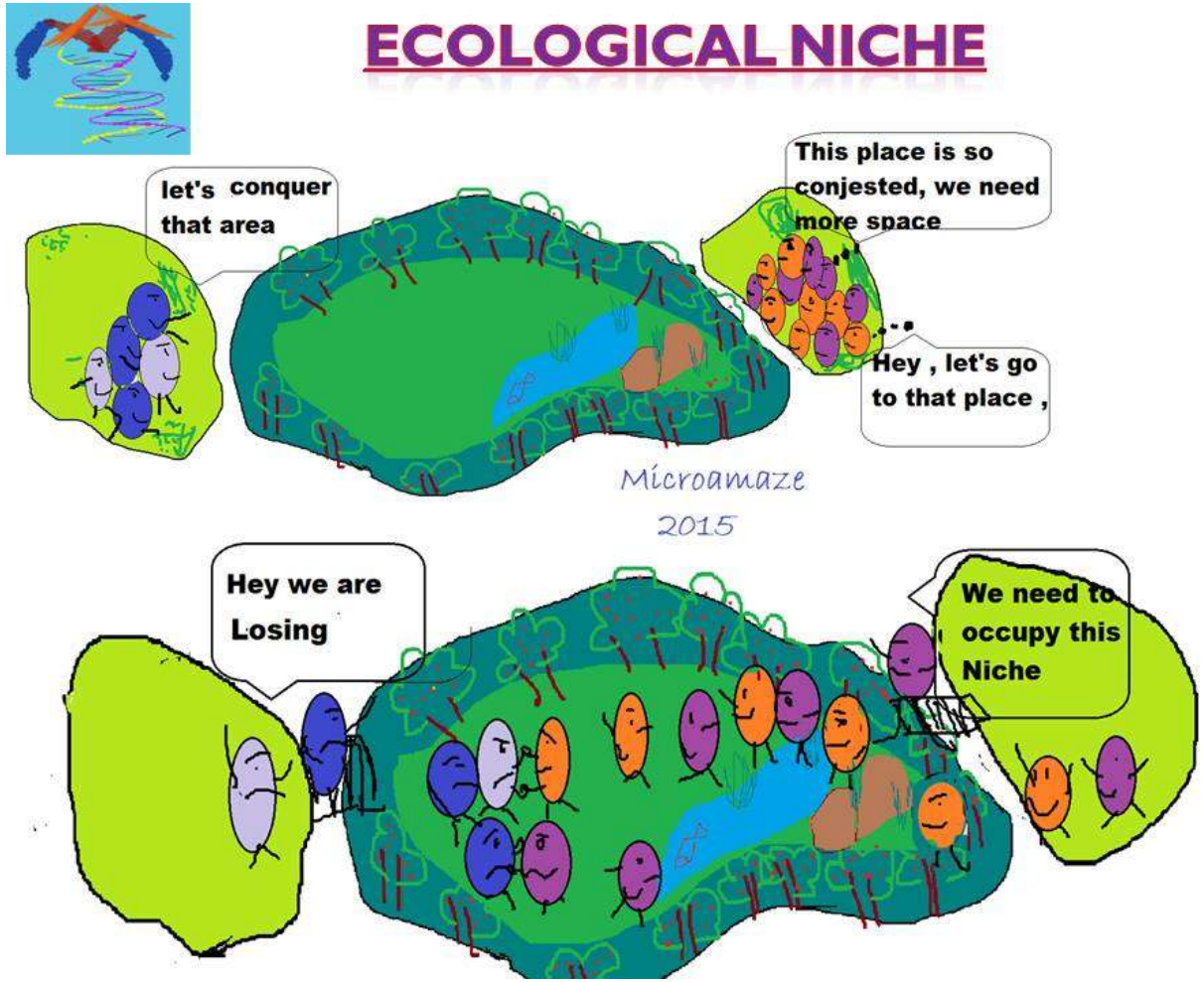
https://tg24.sky.it/salute-e-benessere/2024/06/04/influenza-giugno-virus-fuori-stagione

…and new «exotic» viruses



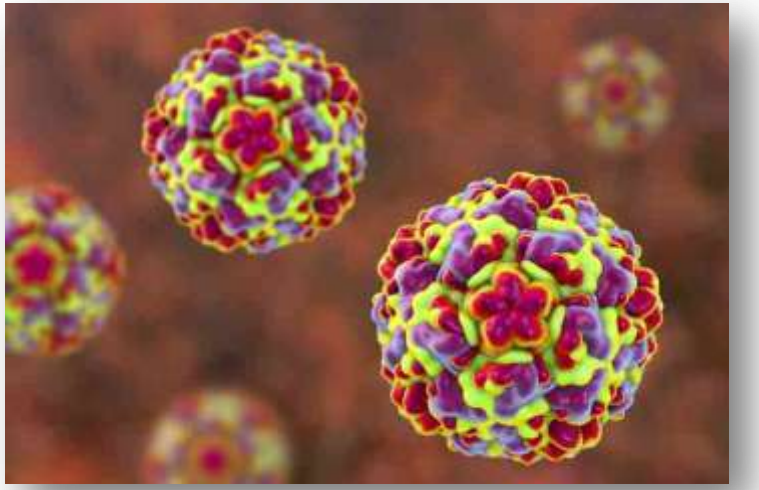
Winter season 2024-2025: the concept of ECOLOGICAL NICHE



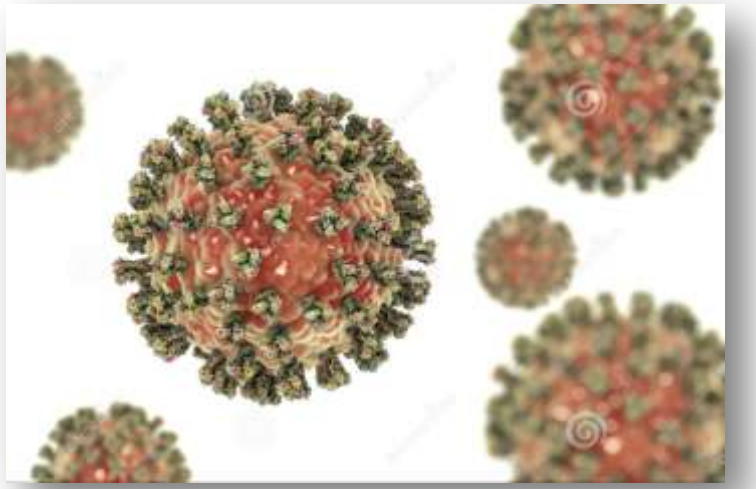


Winter season 2024-2025

Be careful with these 2 guys

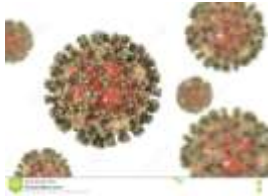


RHINO



PARA-

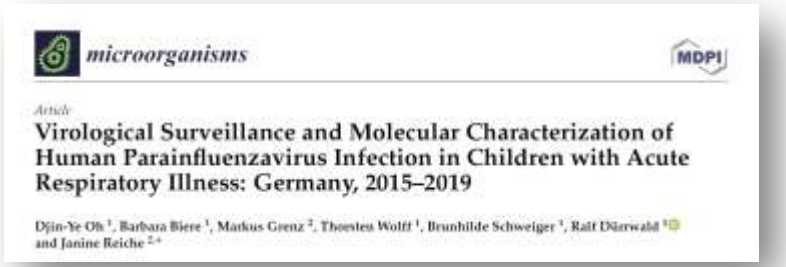
Human Parainfluenza Virus



Parainfluenza viruses are paramyxoviruses and are classified as types 1, 2, 3 e 4. They share an antigenic cross-reactivity but tend to cause different diseases of different severity

They are interested in both children and adults

- Types 1 e 2 normally cause fall epidemics, with recurrency of different siero types every other year *(2024 should show the prevalence of Type 2)*



microorganisms MDPI

Article

Virological Surveillance and Molecular Characterization of Human Parainfluenzavirus Infection in Children with Acute Respiratory Illness: Germany, 2015–2019

Djin-Ye Oh [1], Barbara Biere [1], Markus Grenz [2], Thorsten Wolff [1], Brunhilde Schweiger [1], Ralf Dürrwald [1] and Janine Reiche [2,*]

Oh DY, Biere B, Grenz M, Wolff T, Schweiger B, Dürrwald R, Reiche J. Virological Surveillance and Molecular Characterization of Human Parainfluenzavirus Infection in Children with Acute Respiratory Illness: Germany, 2015-2019. Microorganisms. 2021 Jul 14;9(7):1508.

https://www.msdmanuals.com/it-it/professionale/malattie-infettive/virus-respiratori/infezioni-da-virus-parainfluenzali

Articles

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

Mutual assistence between viruses

Hui KPY, Cheung MC, Perera RAPM, et al. 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 [published online ahead of print, 2020 May 7]. Lancet Respir Med. 2020;S2213-2600(20)30193-4. doi:10.1016/S2213-2600(20)30193-4

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Yale Medicine 1-877-YALEMDS

Specialists Fact Sheets Departments Clinical Trials News Patient Tools

‘Tripledemic:’ What Happens When Flu, RSV, and COVID-19 Cases Collide?

WHAT HAPPENS WHEN THE IMMUNE SYSTEM HAS TO FACE SEVERAL VIRUSES SIMUOLTANEOUSLY OR SEQUENTIALLY?

“The innate immune system takes up arms”


REVIEW

nature immunology

Innate immune recognition of viral infection

Taro Kawai[1] & Shizuo Akira[1,2]

Induction of the antiviral innate immune response depends on recognition of viral components by host pattern-recognition receptors. Members of the Toll-like receptor family have emerged as key sensors that recognize viral components such as nucleic acids. Toll-like receptor signaling results in the production of type I interferon and inflammatory cytokines and leads to dendritic cell maturation and establishment of antiviral immunity. Cells also express cytoplasmic RNA helicases that function as alternative pattern-recognition receptors through recognition of double-stranded RNA produced during virus replication. These two classes of pattern-recognition receptor molecules are expressed in different intracellular compartments and induce type I interferon responses via distinct signaling pathways.


Karolinska Institutet

Department of Laboratory Medicine

/ About KI / Laboratory Medicine / Divisions / Division of Clinical Microbiology / Team Innate immune responses during viral infections

Navigate on the page

Team Innate immune responses during viral infections

Team leader

Publications

Team Innate immune responses during viral infections

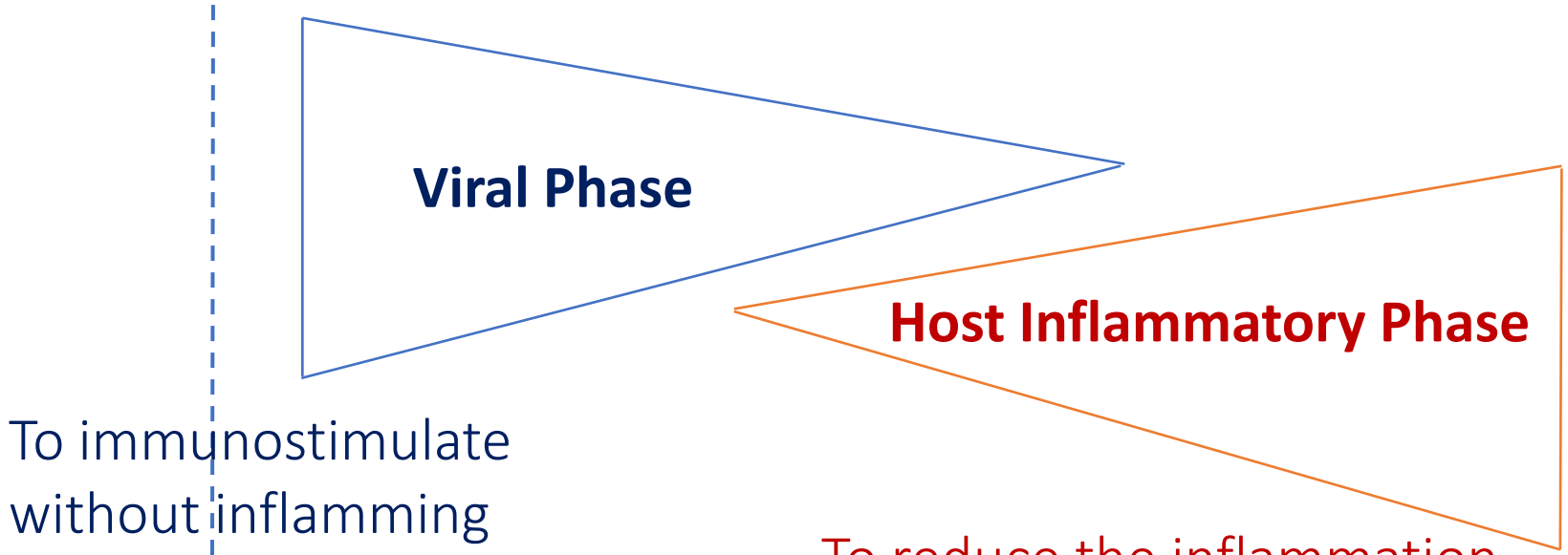
We aim to understand common global interferon-stimulated gene (ISG) responses against different viruses can provide a novel avenue for viral antagonism.

- https://www.the-scientist.com/what-happens-when-you-catch-more-than-one-virus-70817
- https://ki.se/en/labmed/divisions/division-of-clinical-microbiology/team-innate-immune-responses-during-viral-infections
- Kawai, T., Akira, S. Innate immune recognition of viral infection. Nat Immunol 7, 131–137 (2006). https://doi.org/10.1038/ni1303

EDUCATIONAL AGREEMENT

- PREMISE: A **SYSTEMIC** AND **SYNTHETIC** VIEW OF THE IMMUNE SYSTEM
- FOCUSING THE ATTENTION ON INNATE IMMUNITY AND CELL-MEDIATED IMMUNE RESPONSE
- SINGLE LOW DOSE CYTOKINES AND A MULTICOMPONENT MEDICATION **(CITOMIX)** TO DRIVE THE IMMUNE RESPONSE
- **EVIDENCE FROM THE RESEARCH… AND A NEWS**

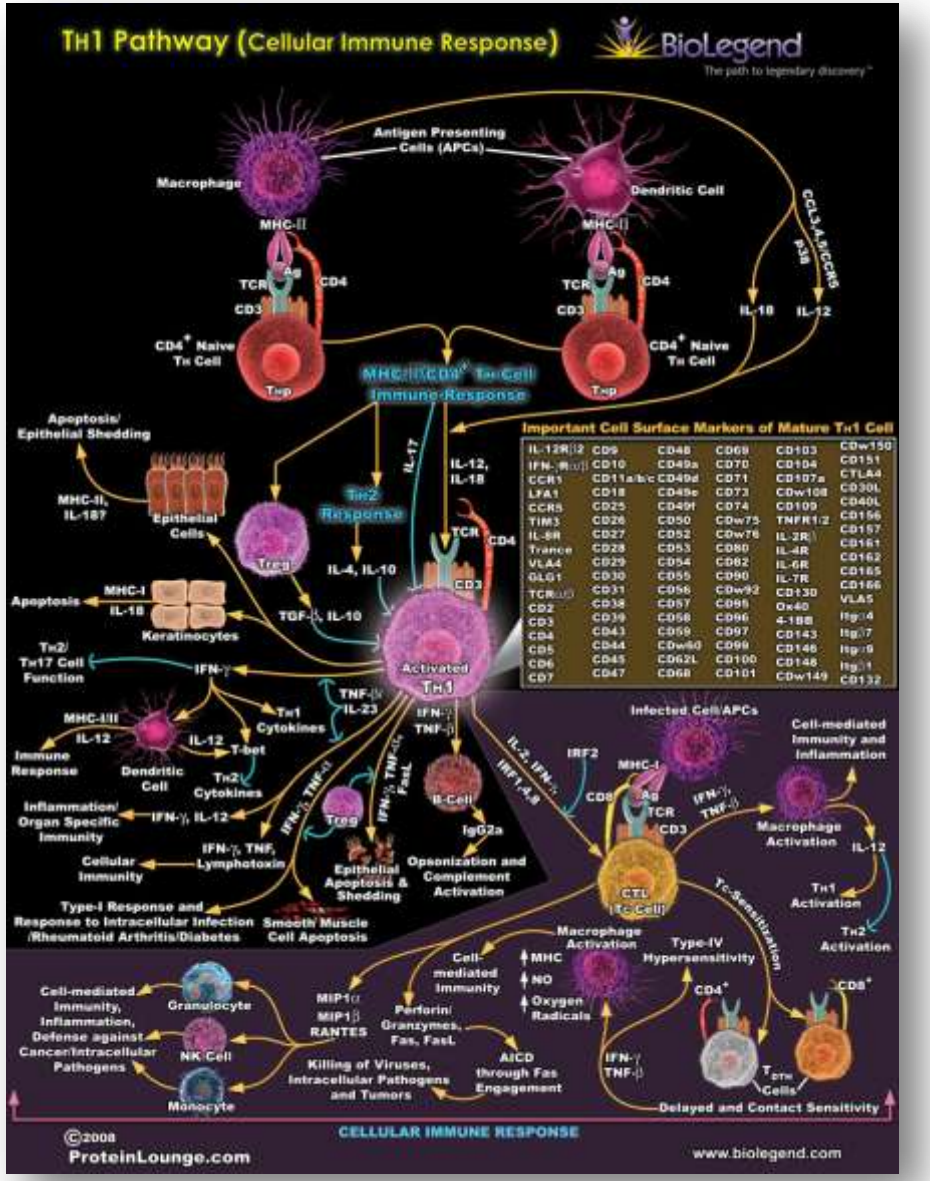
Our (unique) goal in infectious diseases

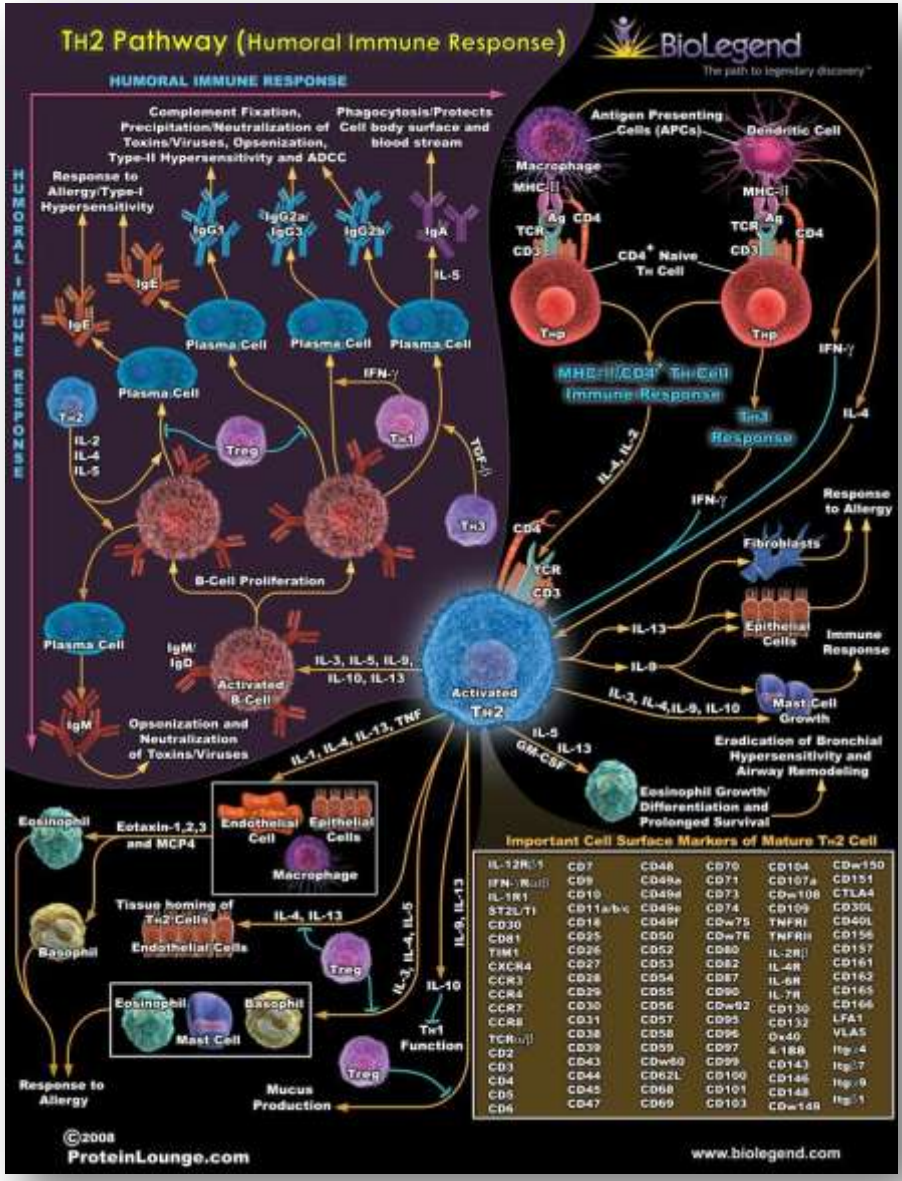


A SHORT BUT FUNDAMENTAL PREMISE

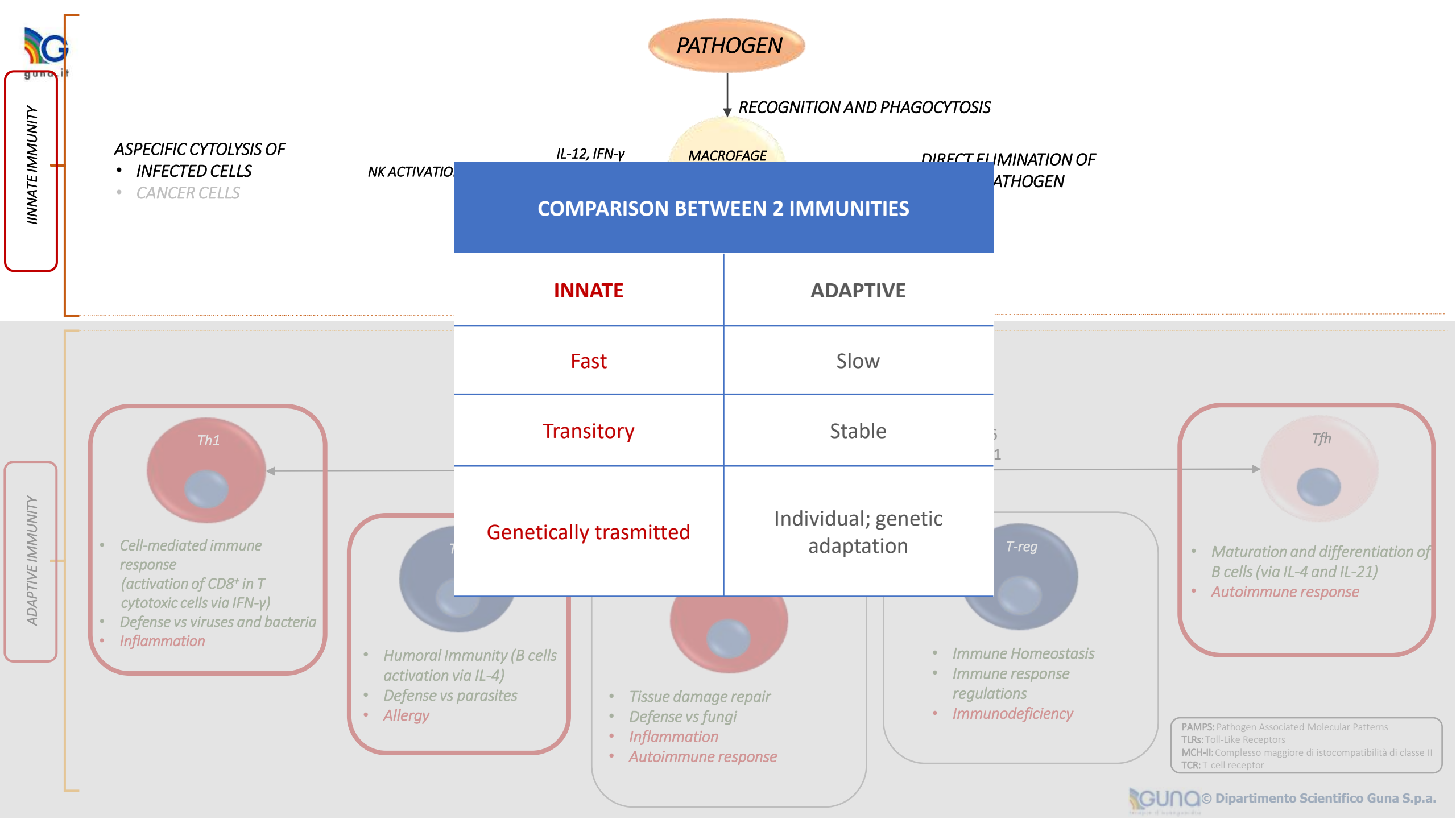
Essential bases of Immunology

The Complexity of the Immune System

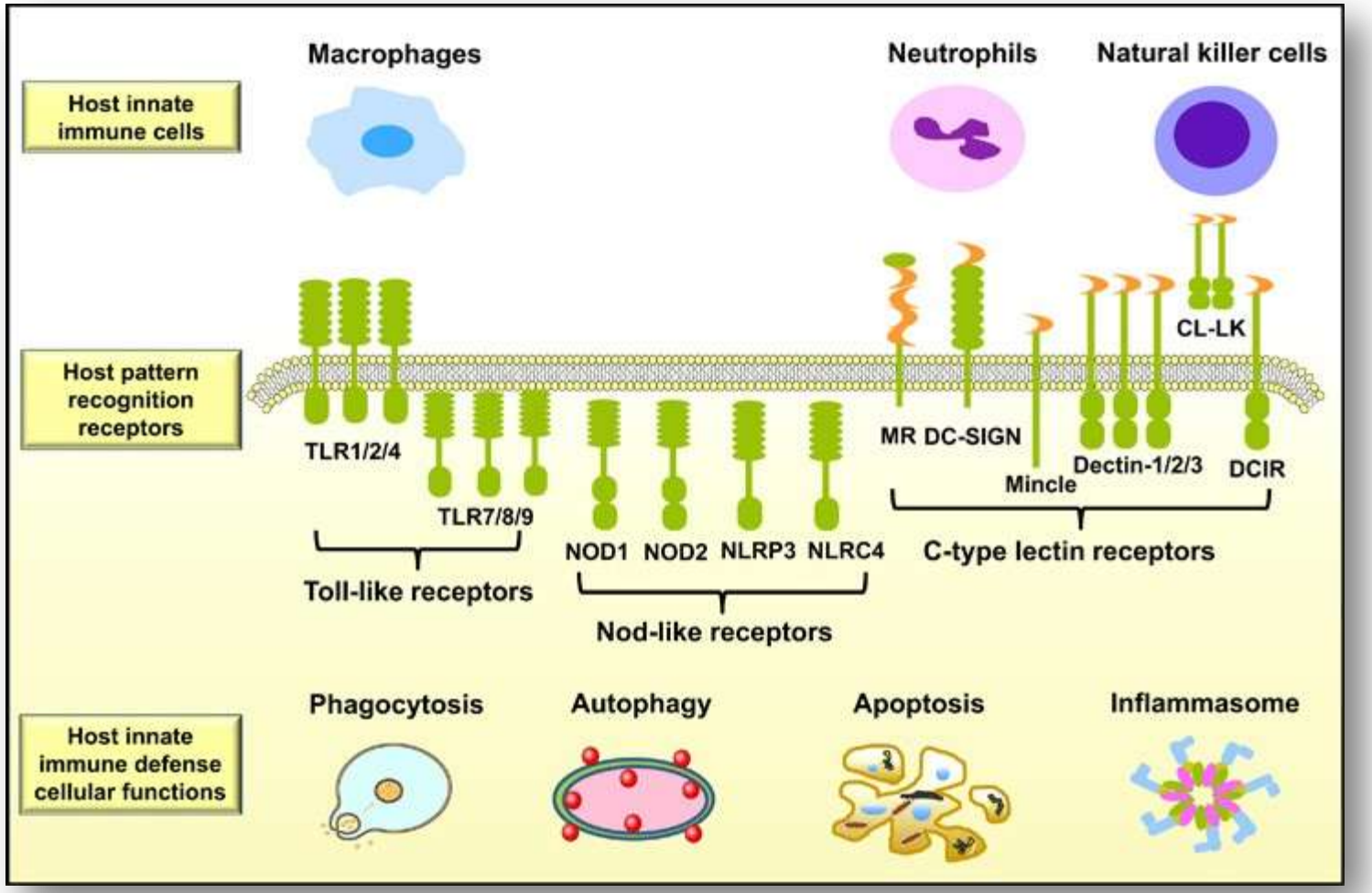




The Immune System Orchestra

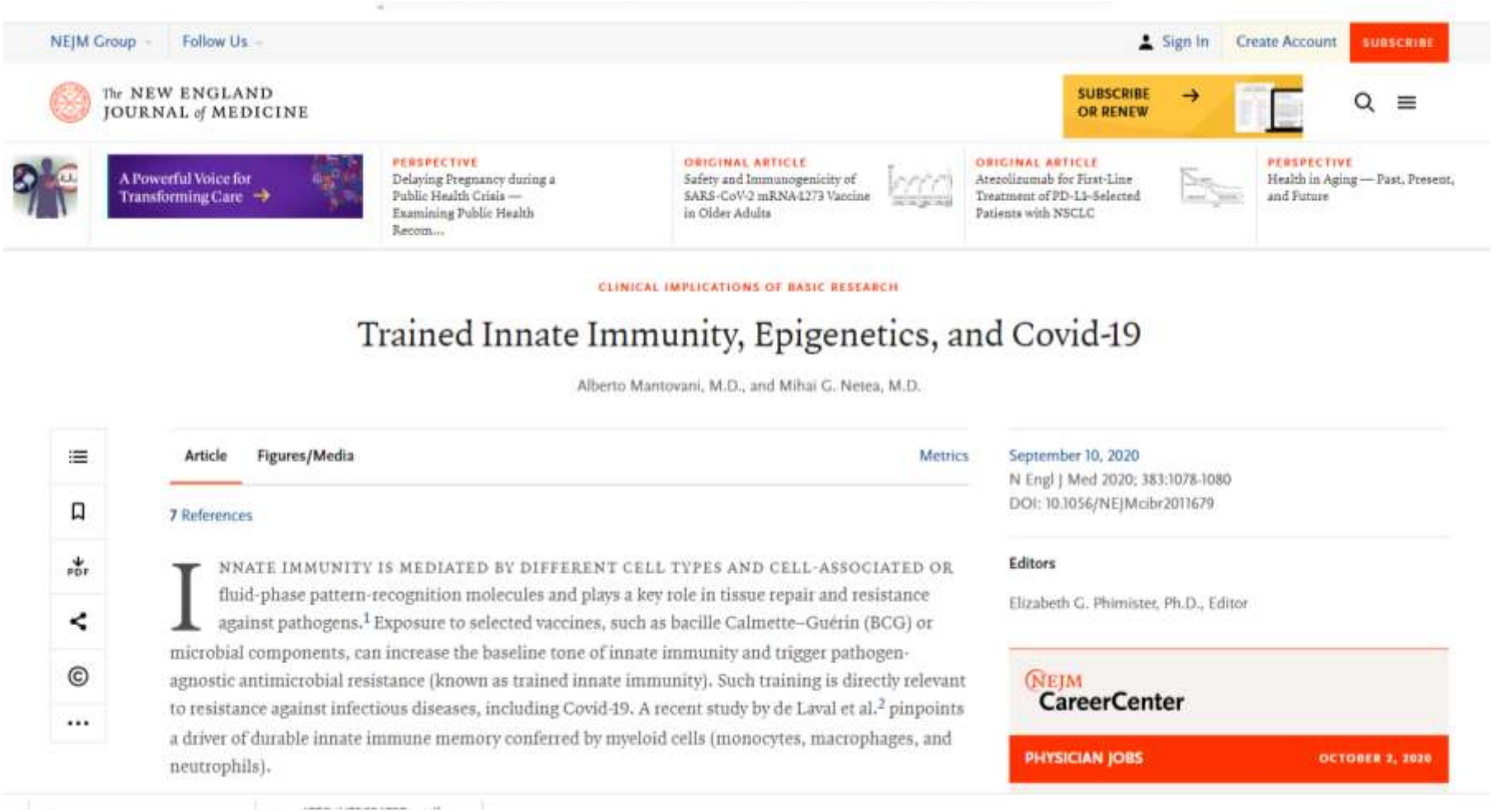


INNATE IMMUNITY

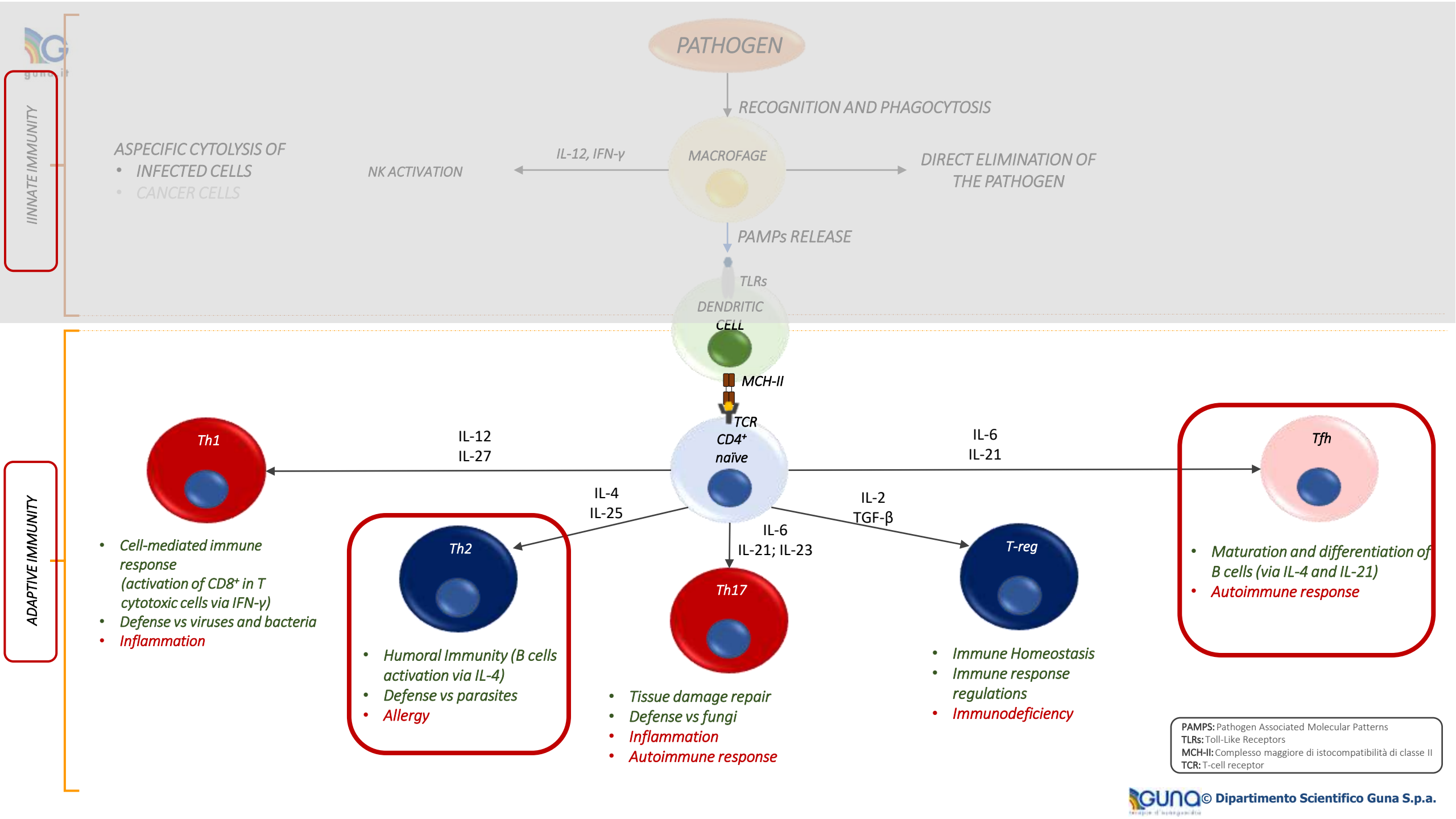


Players of Innate Immunity:

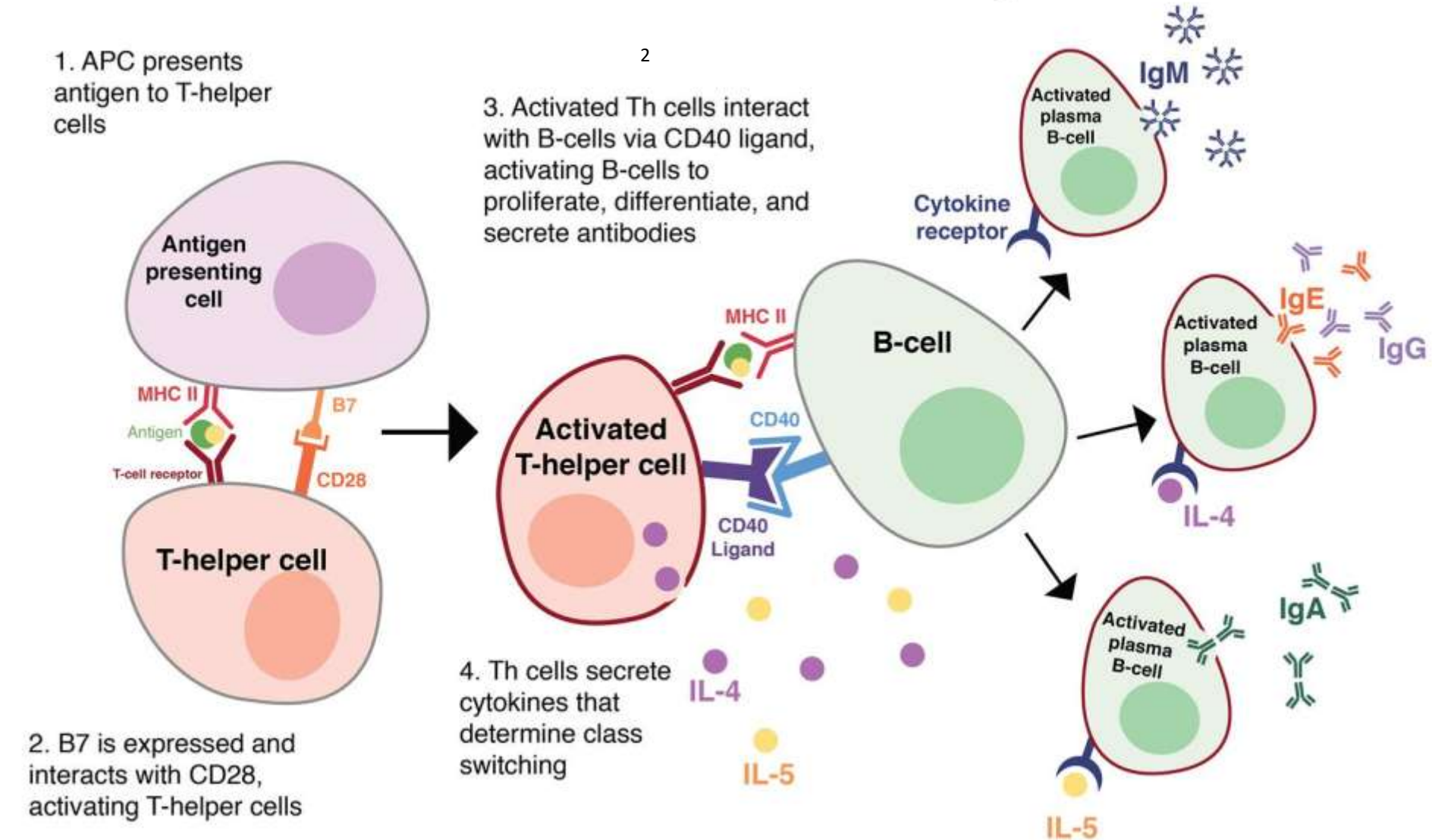
- **Anatomic barriers**
- **Physiological barriers** (lisozima, interferons, and complement complex)
- **Inflammatory barriers**
- **Endocytosis/Phagocytosis**



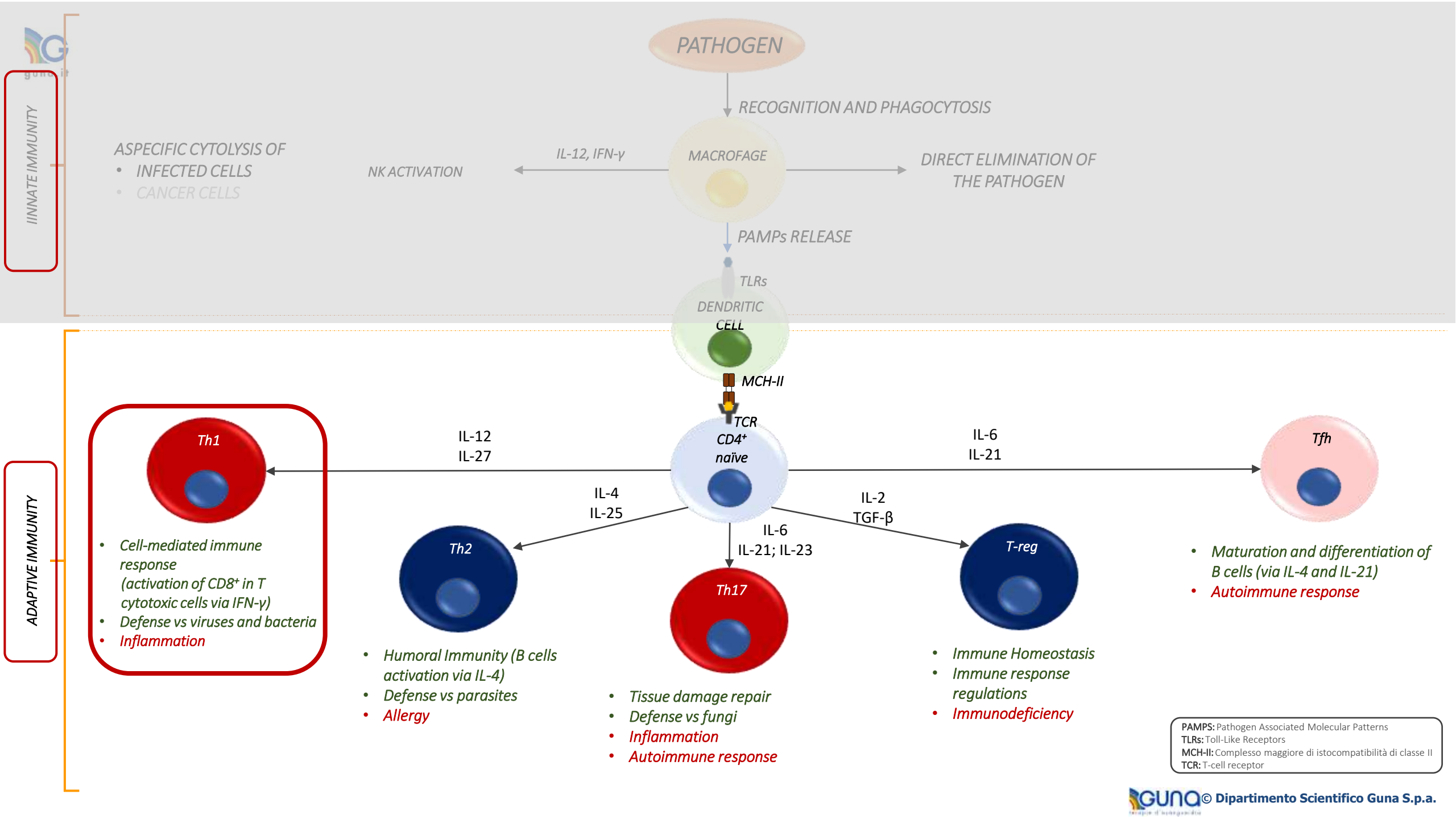
INNATE IMMUNITY REPRESENTS 90% OF OUR DEFENSIVE IMMUNOLOGICAL POTENTIAL.

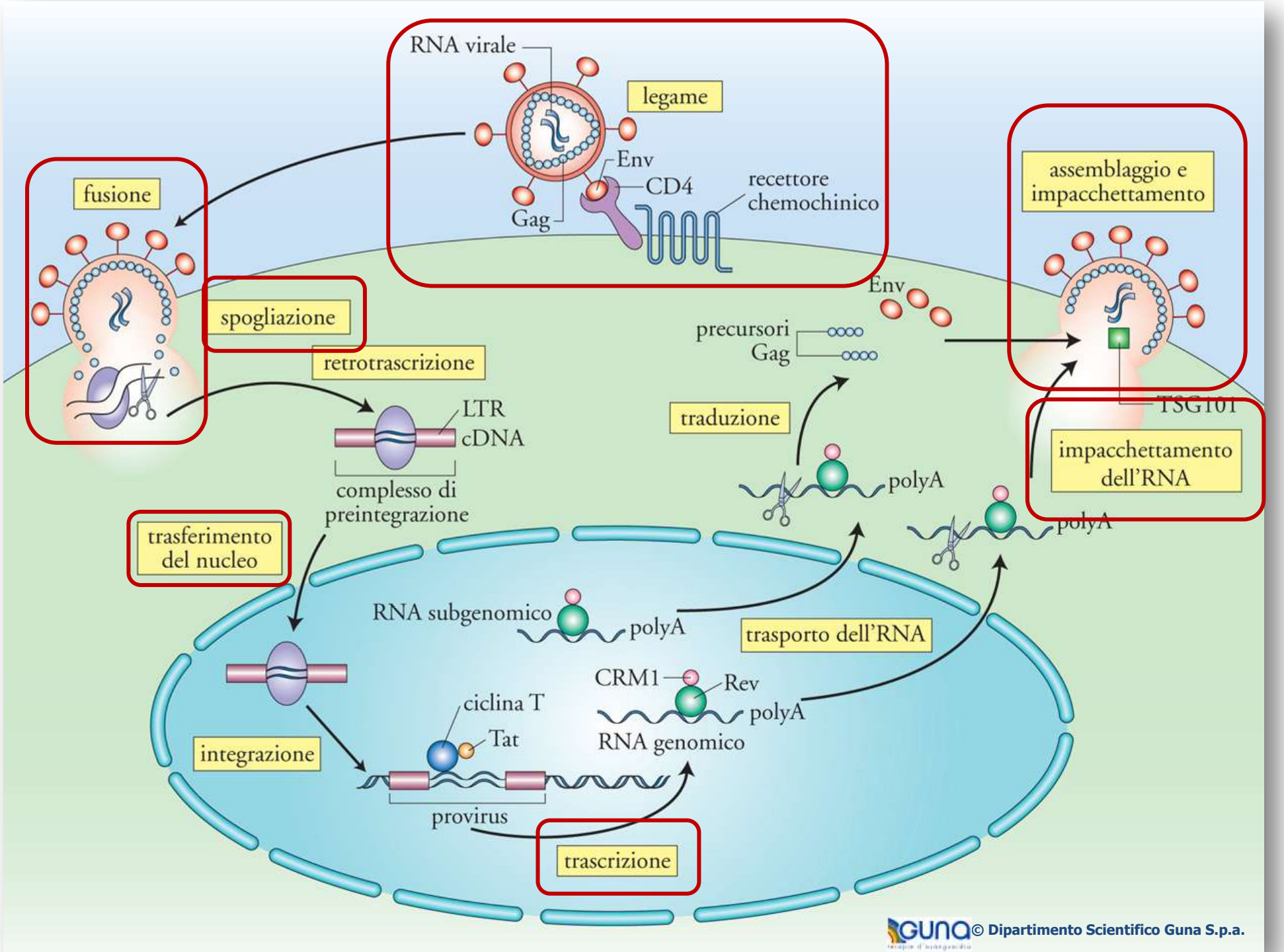


Activation and Class-switching of B-cells



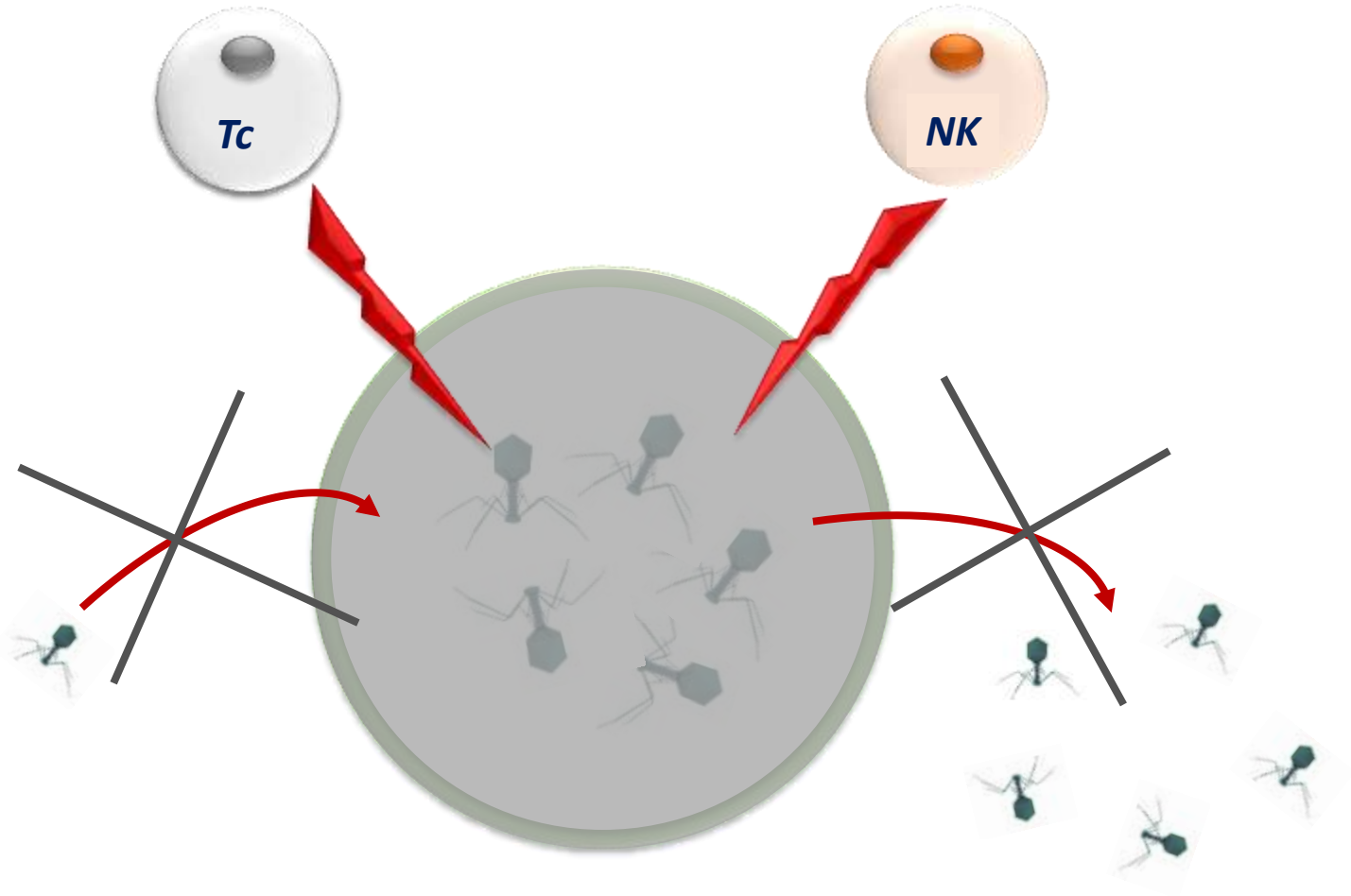
Lucy Liu

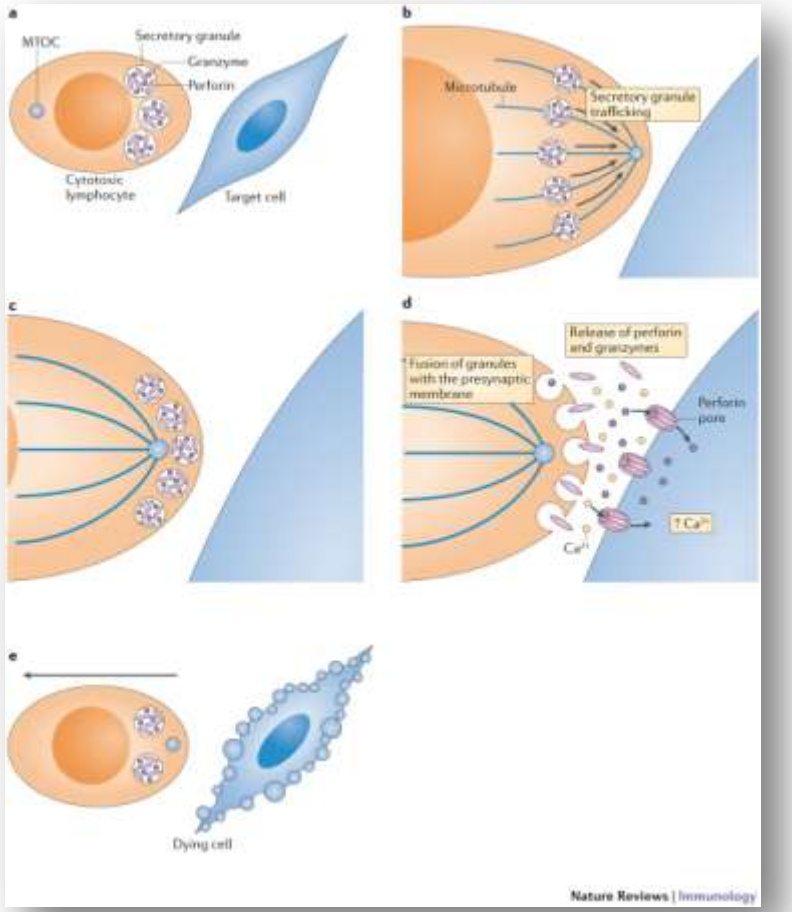




Viral Infections and the *Cell-Mediated Immune Response*

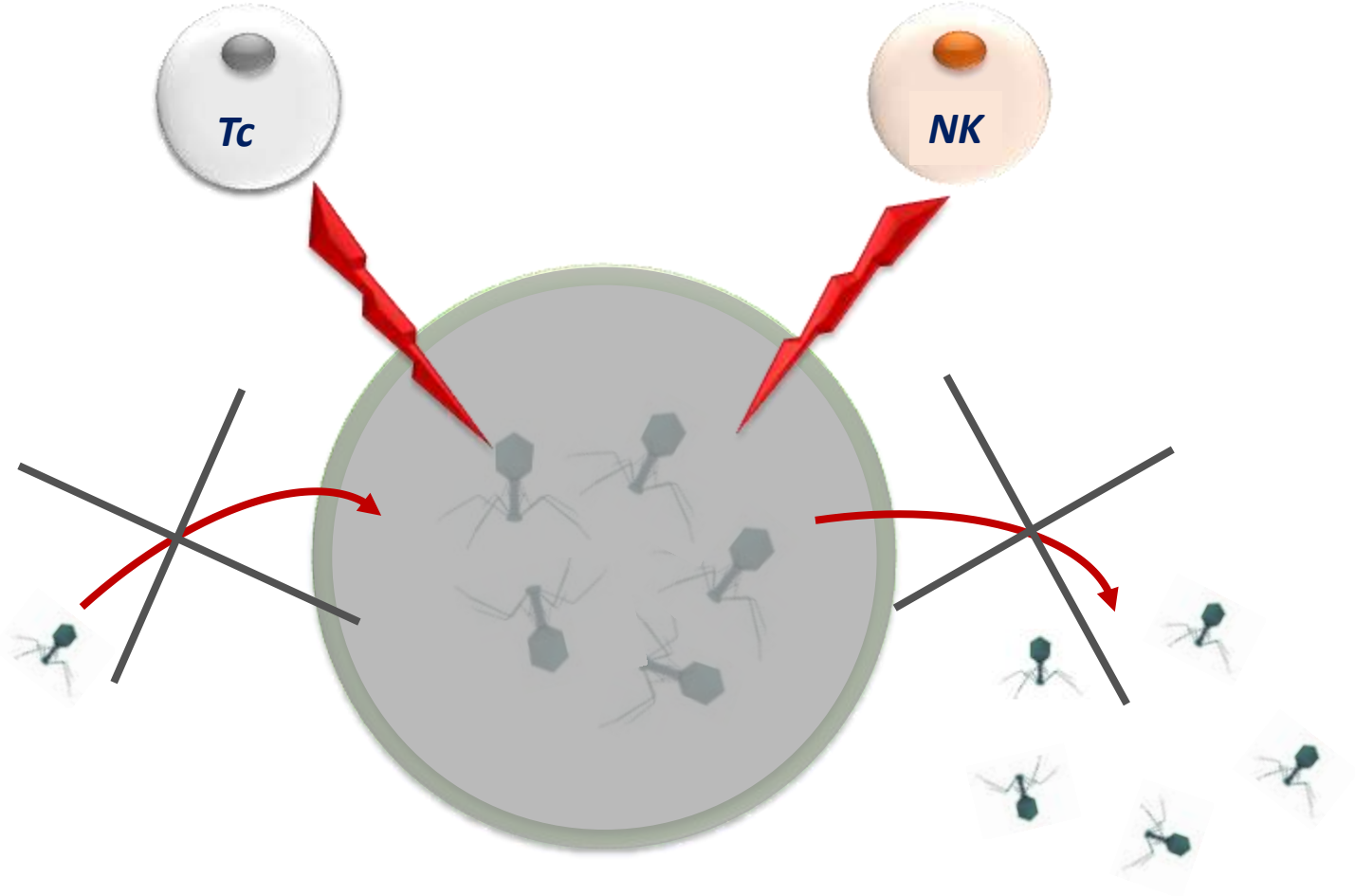
Viral Infections and CYTOTOXIC ACTIVITY OF Tc and NK-cells





How to support the activity of T-cytotoxic cells and NK cells?

2 important CYTOKINES



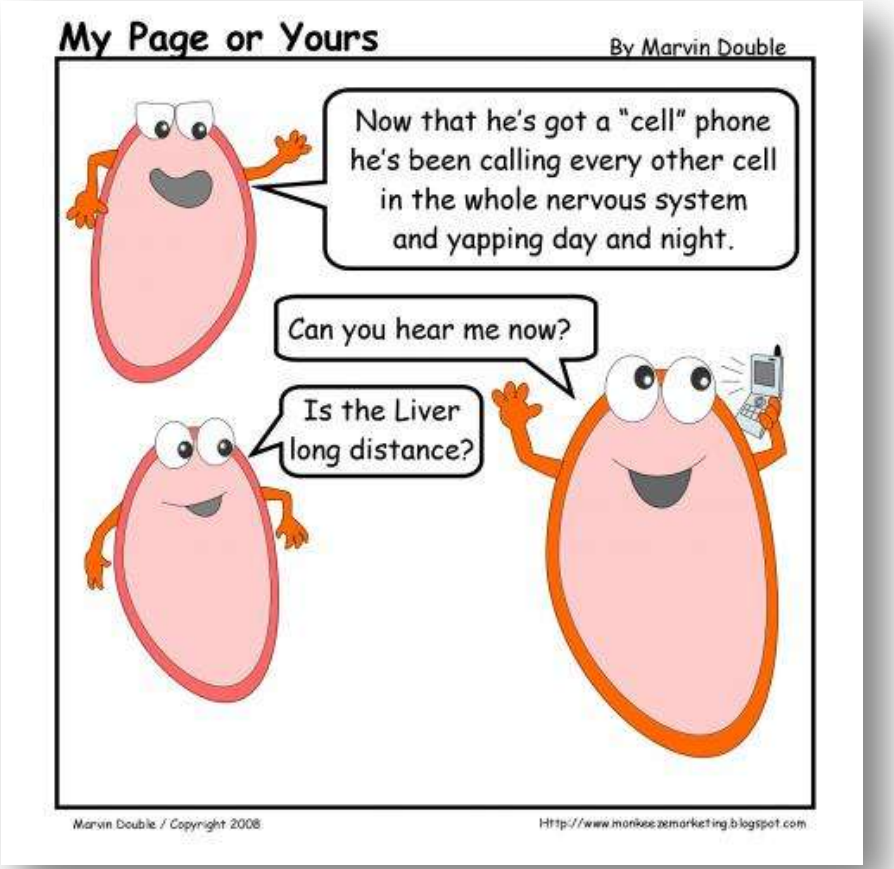
IL-2

IFN-γ

Signaling Molecules

The Fundation for LDM

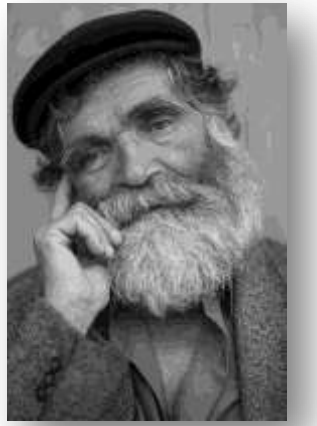
CYTYOKINES are MESSENGERS, THE WORDS used by the 3 homeostatic control systems and BY THE CELLS to speak each other ...and to lead the Immune System physiology.



T cytotoxic

CD8+

IL-2



IFN-γ

NK cells

Pathways of Lymphocytes maturation and circulation

THYMUS (T precursor)

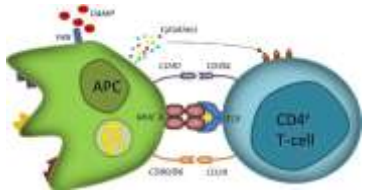
T Lymphocytes are released from the Thymus as CD4+ naive

Tissues

CD4+ naive get into the lymphatic circulation

Through the lymph, CD4+ naive reach the lymph nodes

Activated T cytotoxic lymphocytes attack the infected cells



BONE MARROW (B precursor)

B cells are released from the bone marrow

Tissues

Through the lymph B cells reach the lymph nodes

LYMPH NODE

Activated T cytotoxic lymphocytes reach the tissues

CD4+ naive

After the Ag presentation **CD4+ naive** undergo the differentiation in the T helper subsets

T cytotoxic activated

CD8+ → T cytotoxic memory

activation (via IFN-gamma)

Th2 Tfh Treg Th1

activation (via IL-4)

maturation (via IL-6)

B Lymphocyte → B lymphocytes memory

Plasma cells

antibodies

Abs reach the tissues

Abs attack the viruses

Central role of cytokines in the modulation of the Immune System

- Cytokines are the great performers of the immune response, the real regulators

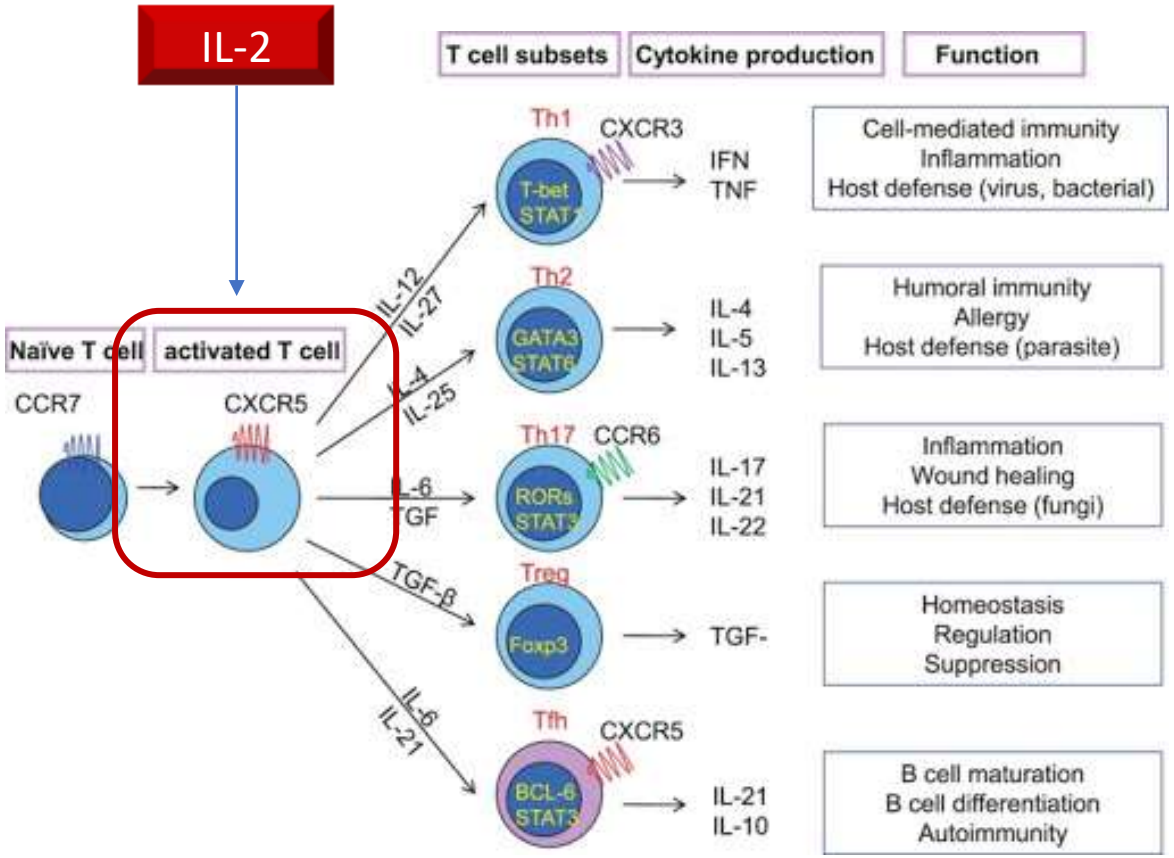
- The chance to have them under the form of low dose medications is an extraordinary therapeutic opportunity

- In Guna pharmacological range stand out, for immunoregulation purposes:

- IL-1
- IL-2
- IL-4
- IL-6
- (IFN-alpha)/IFN- gamma
- GCSF

?

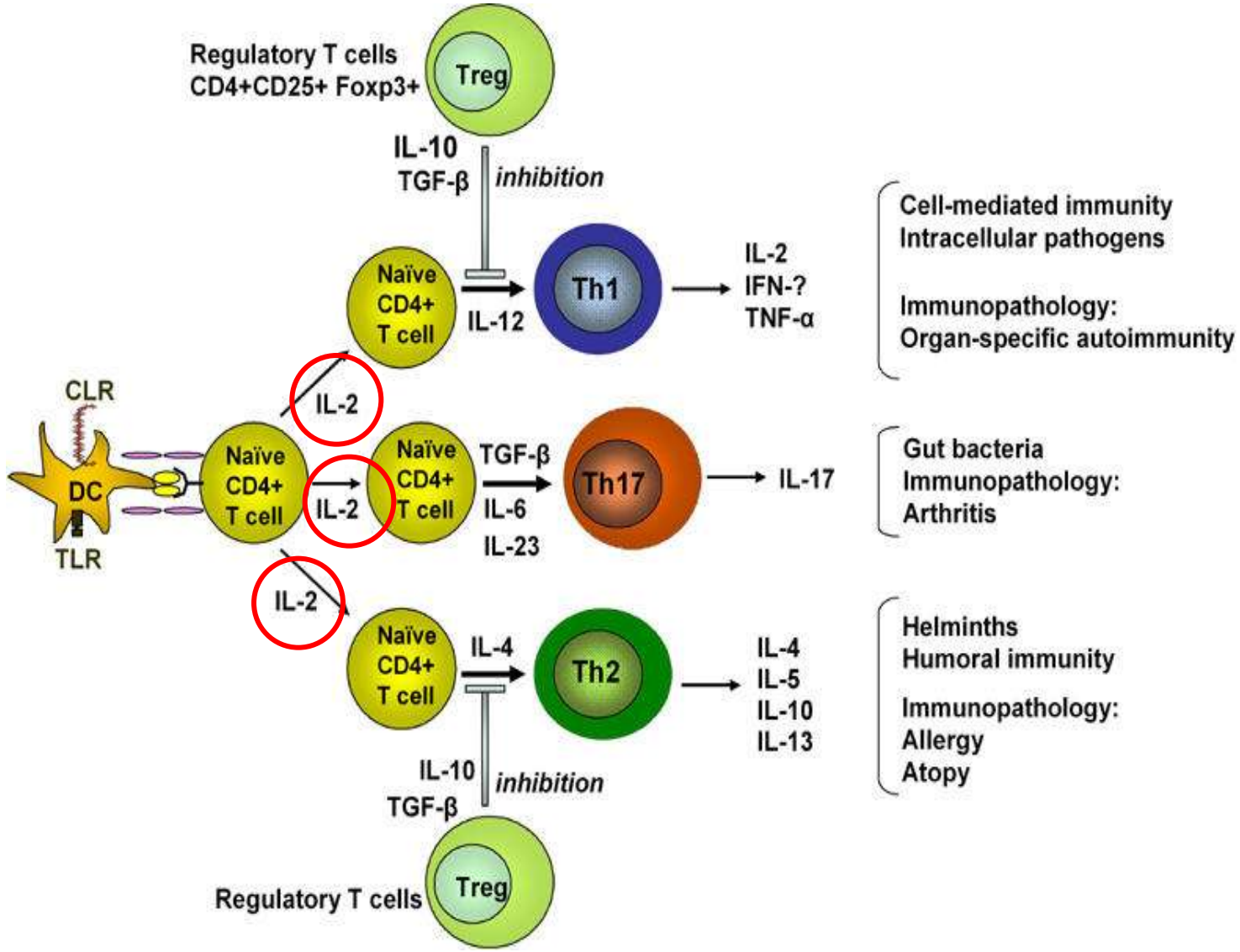
INTERLEUKIN-2 INDUCES THE CLONAL EXPANSION OF T CELLS



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.

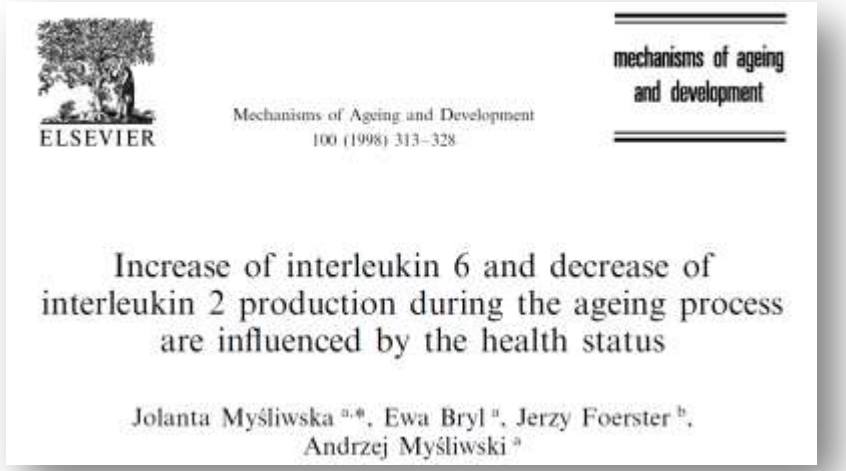
- **IL-2** is produced by activated T cells and has a key role in triggering immune responses. **The main effect of IL-2 is to induce the clonal expansion of T cells after antigen recognition; moreover, IL-2 induces the proliferation of activated B cells, increases the levels of Natural Killer (NK) cells, 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**

IL-2/IL-6 RATIO AND AGING



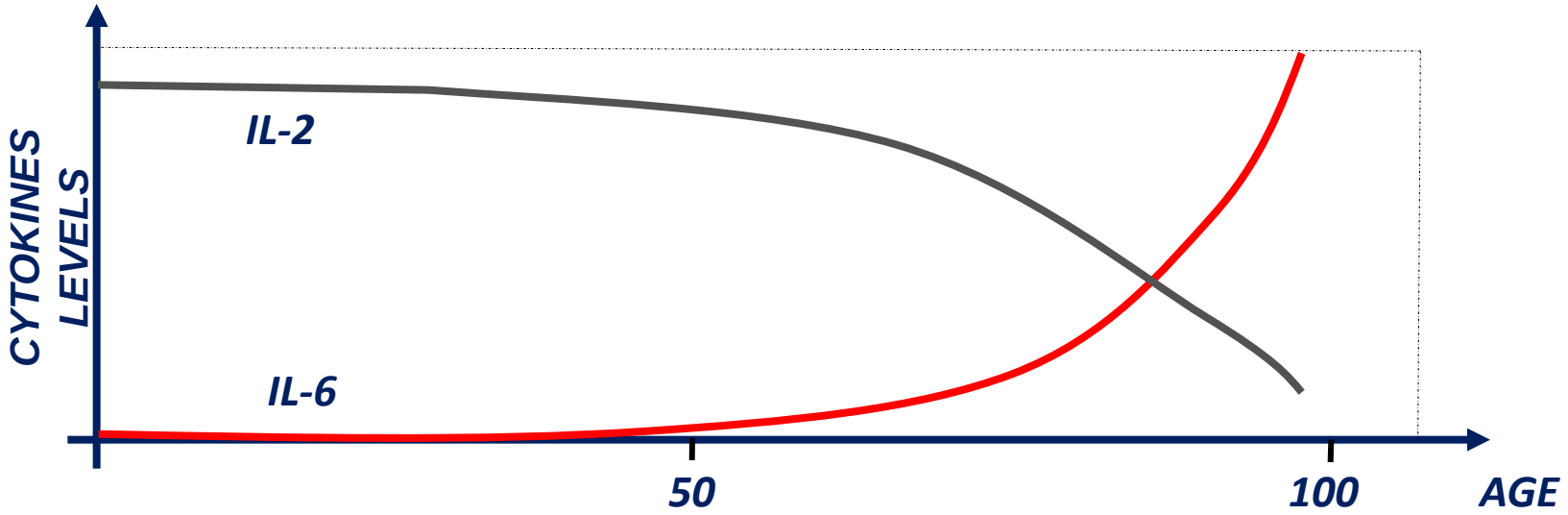
ELSEVIER

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]



IL-2 AND ANTIVIRAL IMMUNE RESPONSE

IL-2 LOW DOSE regulates espression and function of:

- NK cells
- $CD8^+$ cells
- T-reg cells
- Follicular T-helper cells (Tfh)
- Follicular T-reg cells (Tfr)

REGULATORY EFFECT OF IL-2 UPON IMMUNOLOGICAL HOMEOSTASIS IN PRESENCE OF VIRAL INFECTIONS

IL-2 *low dose* supports the host antiviral response and counteracts the tendency towards the infection chronicization

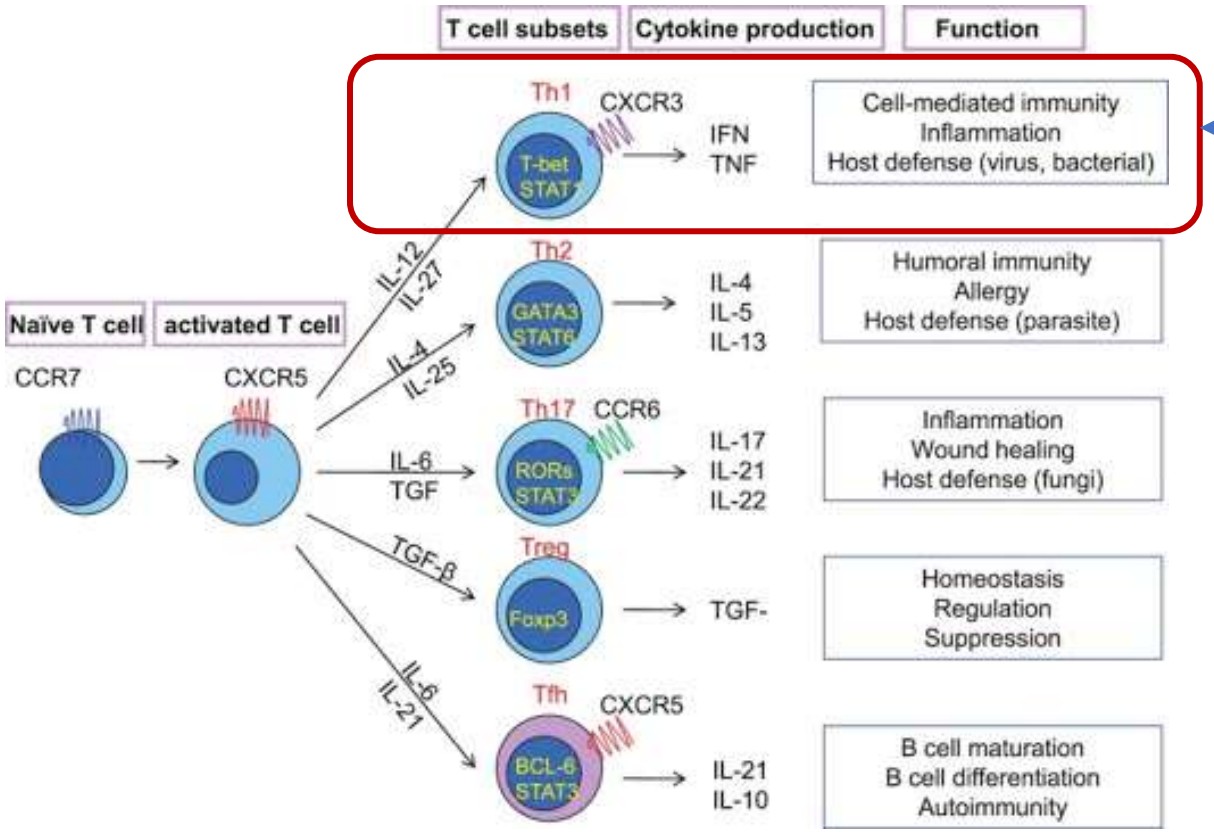
IL-2 *low dose* modulates the inflammatory response, when overexpressed, and contains the pathological damage

IL-2 *low dose* counteracts the onset of autoimmune diseases and neoplastic diseases secondary to viral infections

IL-2 LOW DOSE CONTRIBUTES TO THE ANTIVIRAL RESPONS VERSUS

- Influenzavirus
- Epstein-Barr Virus and Cytomegalovirus
- Herpes simplex virus
- Respiratory Syncizitial Virus (RSV)
- SARS-CoV-2

INTERFERON-γ ACTIVATES CD8+ IN T CYTOTOXIC CELLS



IFN-γ

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

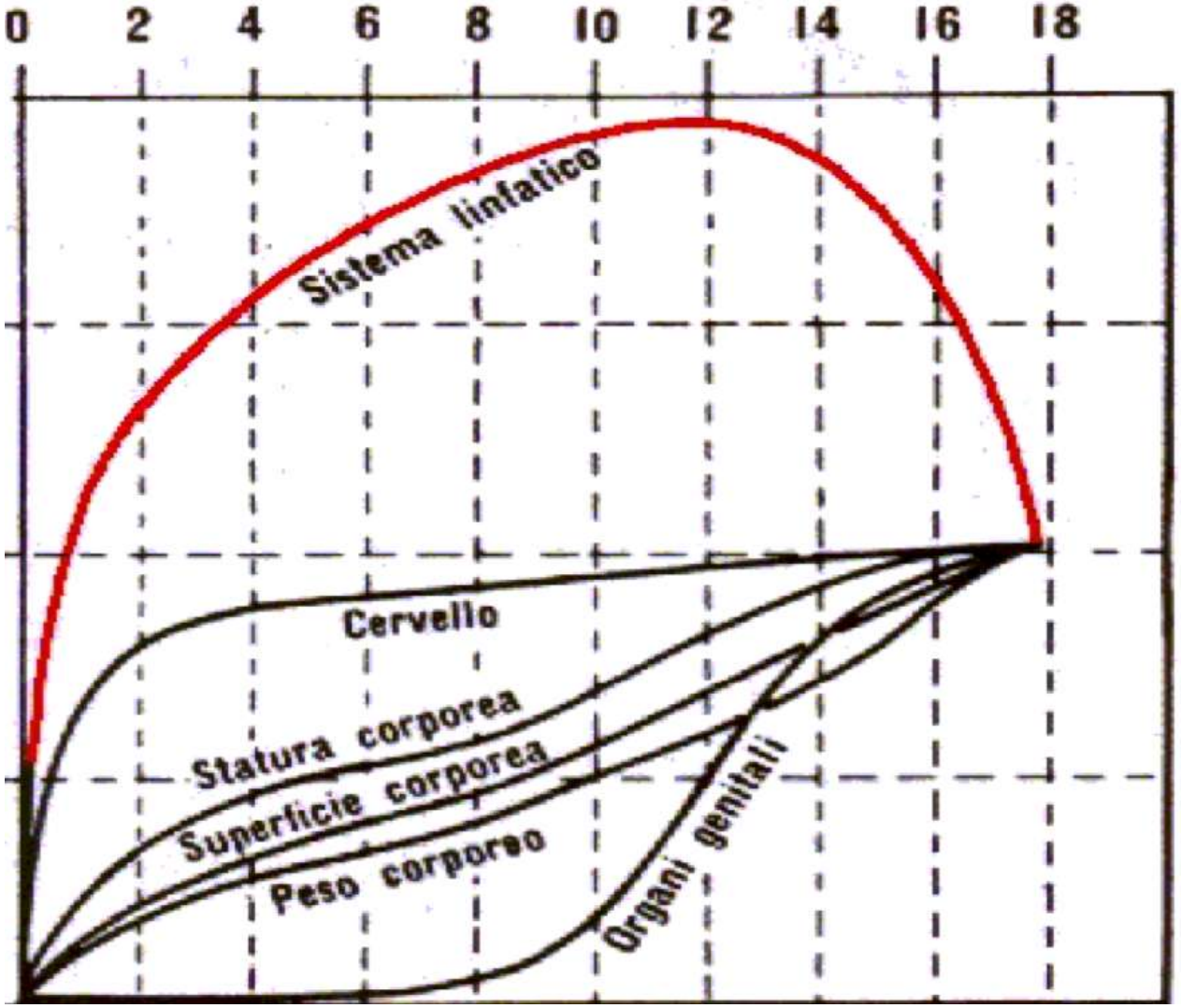
- IFN-γ can activate a cell-mediated immune response (IFN-γ stimulates CD8 + to differentiate into cytotoxic T effector cells) ideal against viruses. The Tc, in fact, operate the non-specific cytolysis of the cell infected with the virus (the Natural Killer - NK cells - instead, operate the specific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

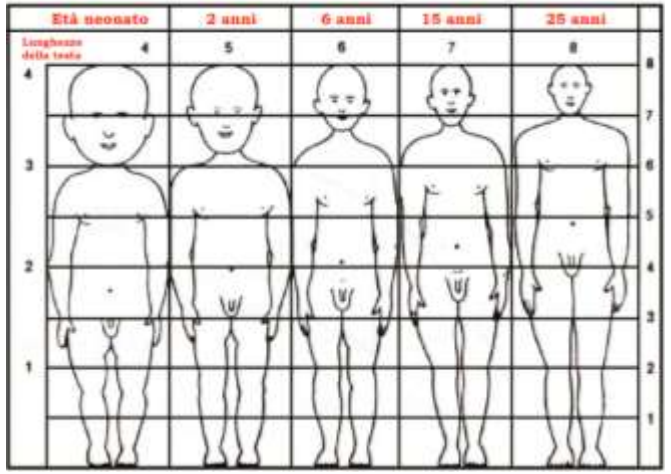
- Interferon-α (in some papers alpha seems to be favored over gamma; it is interesting how Interferon-α prevents the virus from penetrating through the viropexy mechanism, used by many viruses, into the cells not yet infected

/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/

LOW IMMUNOCOMPETENCE IN CHILDREN

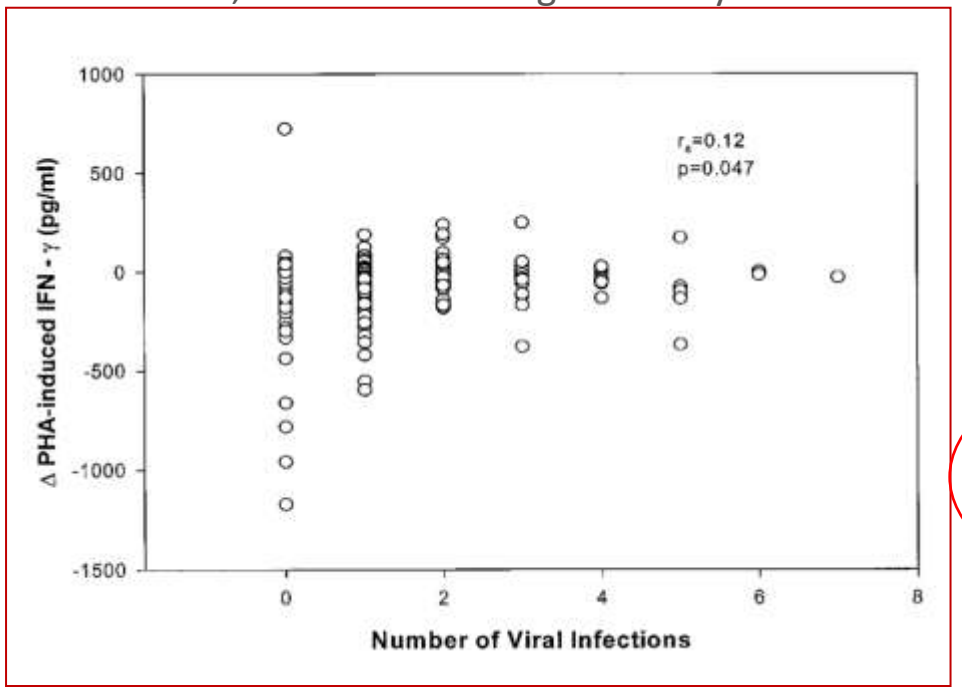
Immune System Development Timeline in Children





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-γ in the first year of life (57–26 pg/ml, p 0.001)

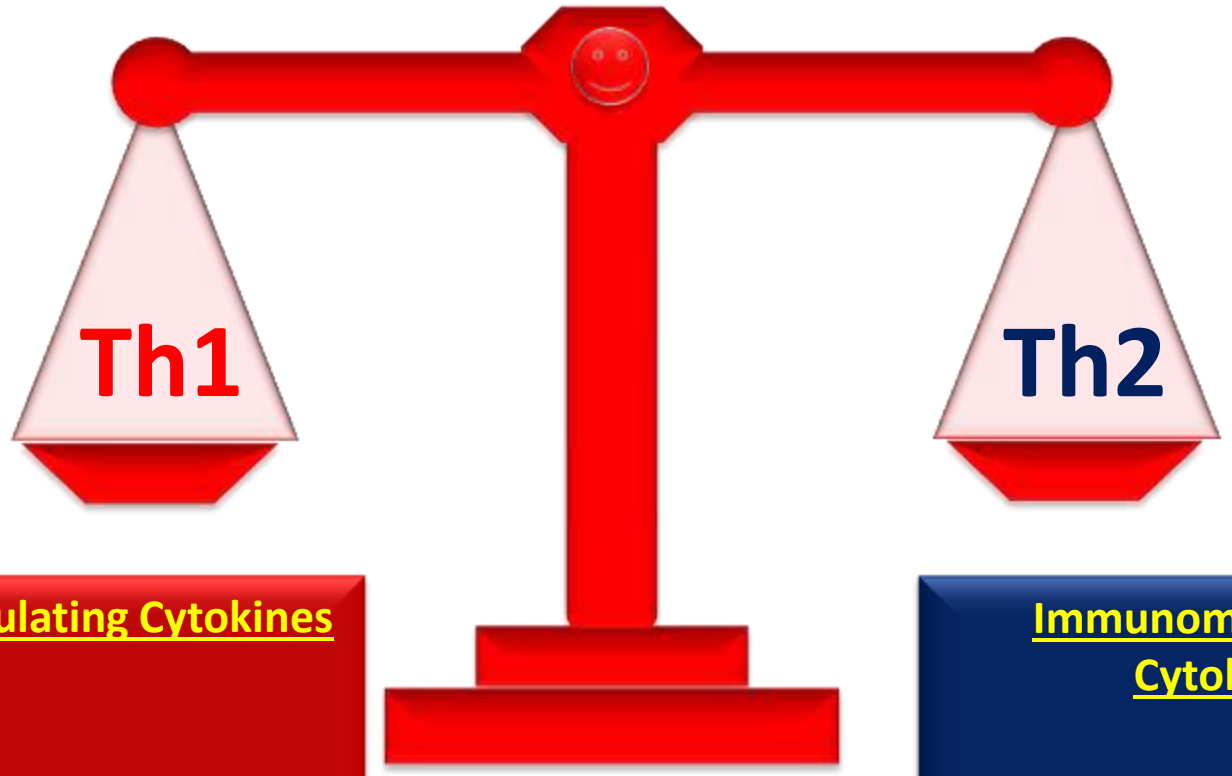
Significant positive correlation between number of respiratory infections and reduced production of **IFN-γ** (rs 0.12, p 0.047)

Am J Respir Crit Care Med Vol 170. pp 175–180, 2004

Courtesy from Prof. G. Marseglia - Pavia

When do viruses have a party?

Immunological homeostasis



GOOD

Immunostimulating Cytokines

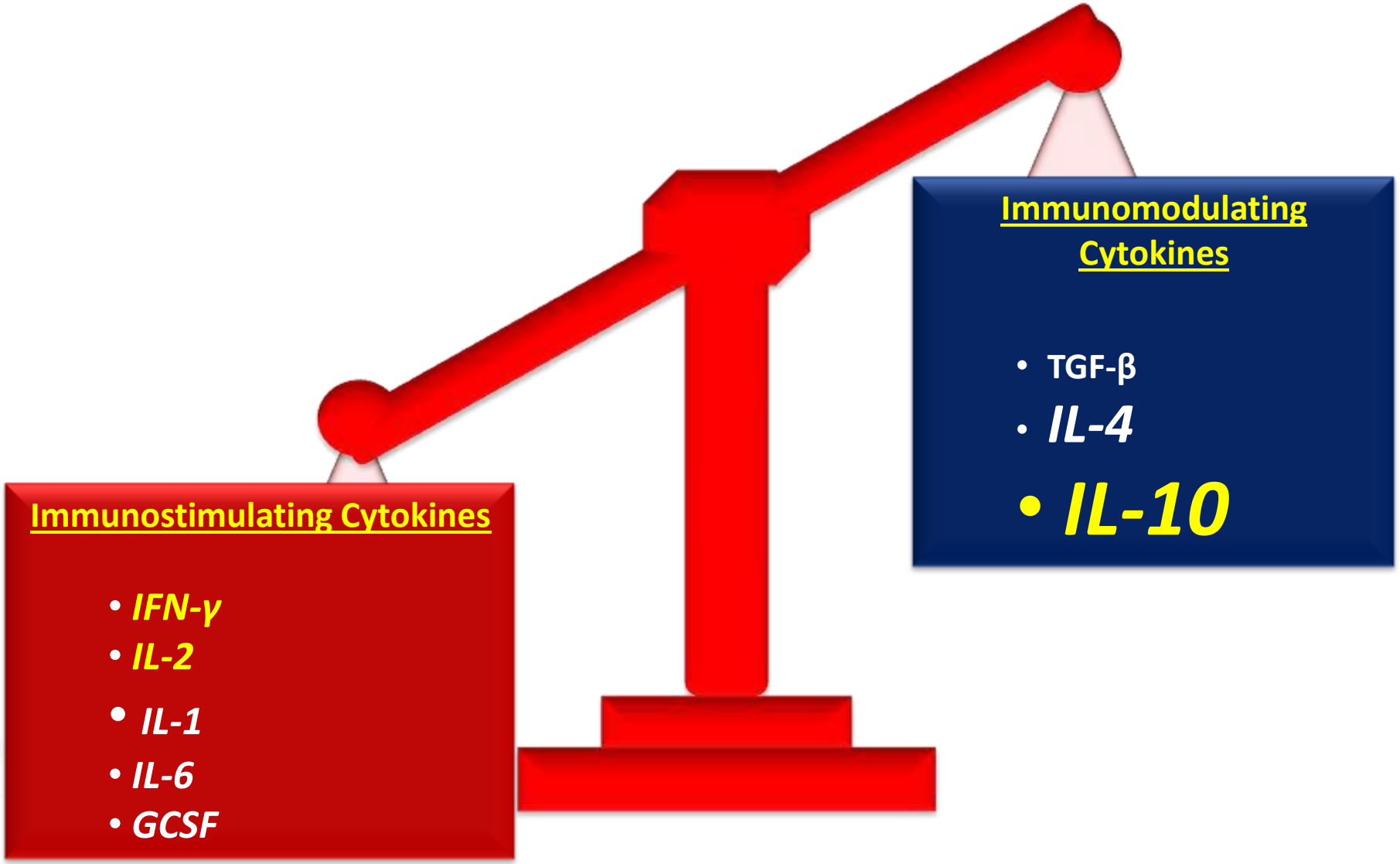
- *IFN-γ*
- *IL-2*
- *IL-1*
- *IL-6*
- *GCSF*

Immunomodulating Cytokines

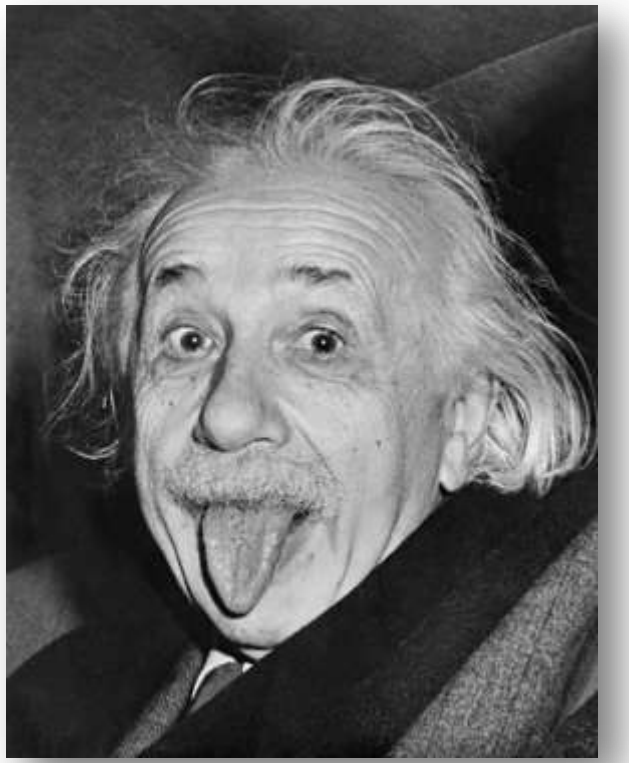
- TGF-β
- *IL-4*
- *IL-10*

GOOD

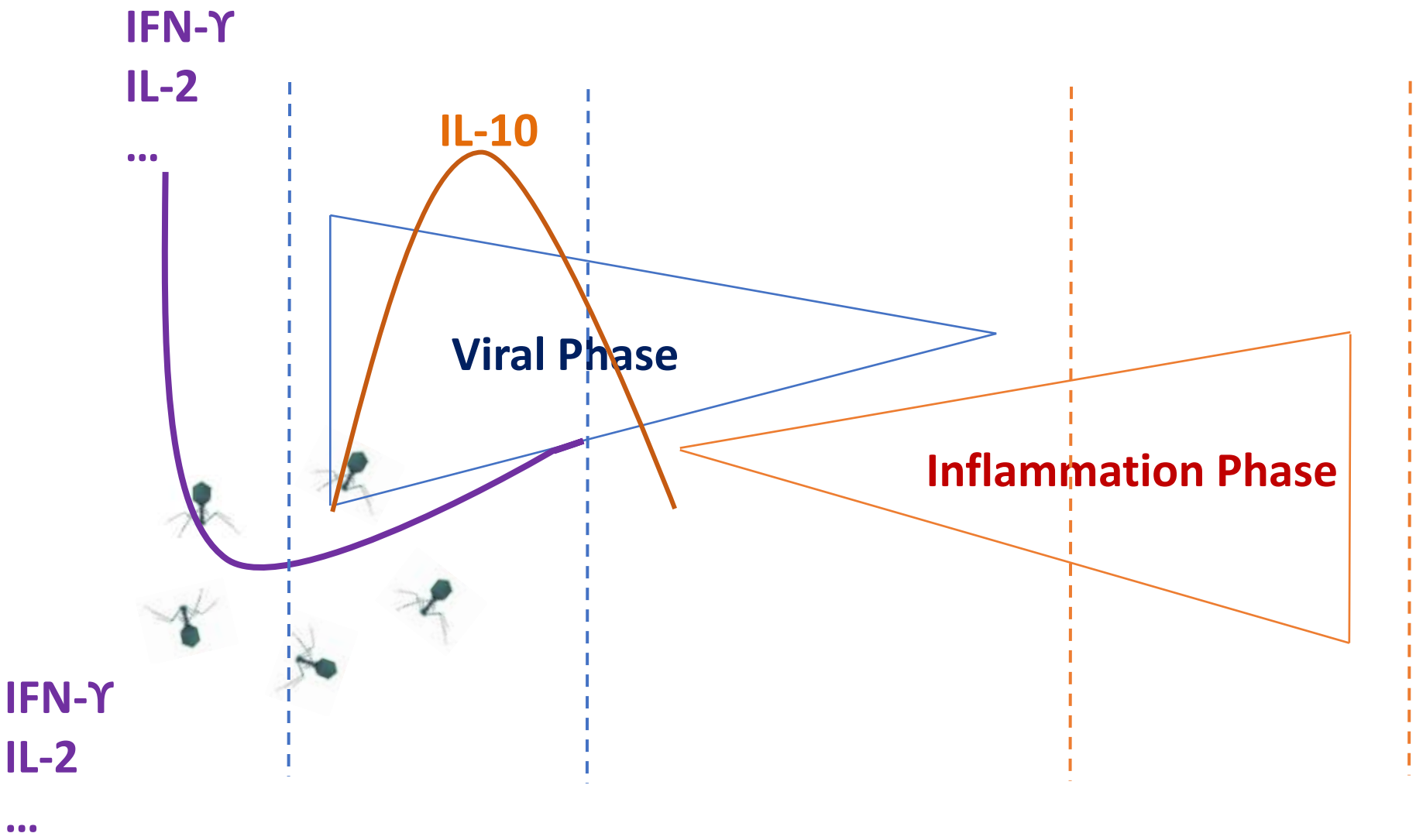
…susceptibility to viral attacks

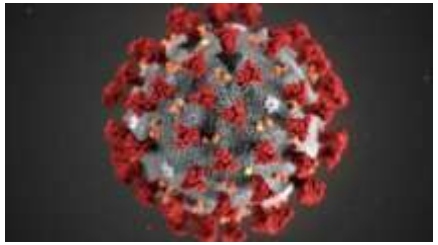


Unavoidable necessity of IFN-γ in the antiviral immuno-protection
(…also because virus are SUPER SMART)



Space-Time Immunomodulation





Under viral attack

Cytokines UP

IL-10

Concentrazione Fisiologica

- *IL-1*
- IL-6
- *IL-2*
- *IL-8*
- *INF-ϒ*

HEALTH

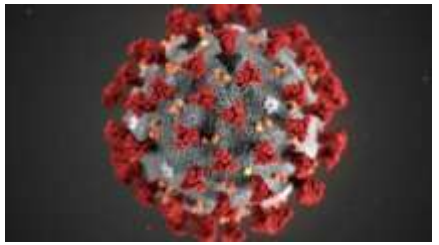
Concentrazione Fisiologica

- **TGF-β**
- ***IL-4***
- ***IL-10***

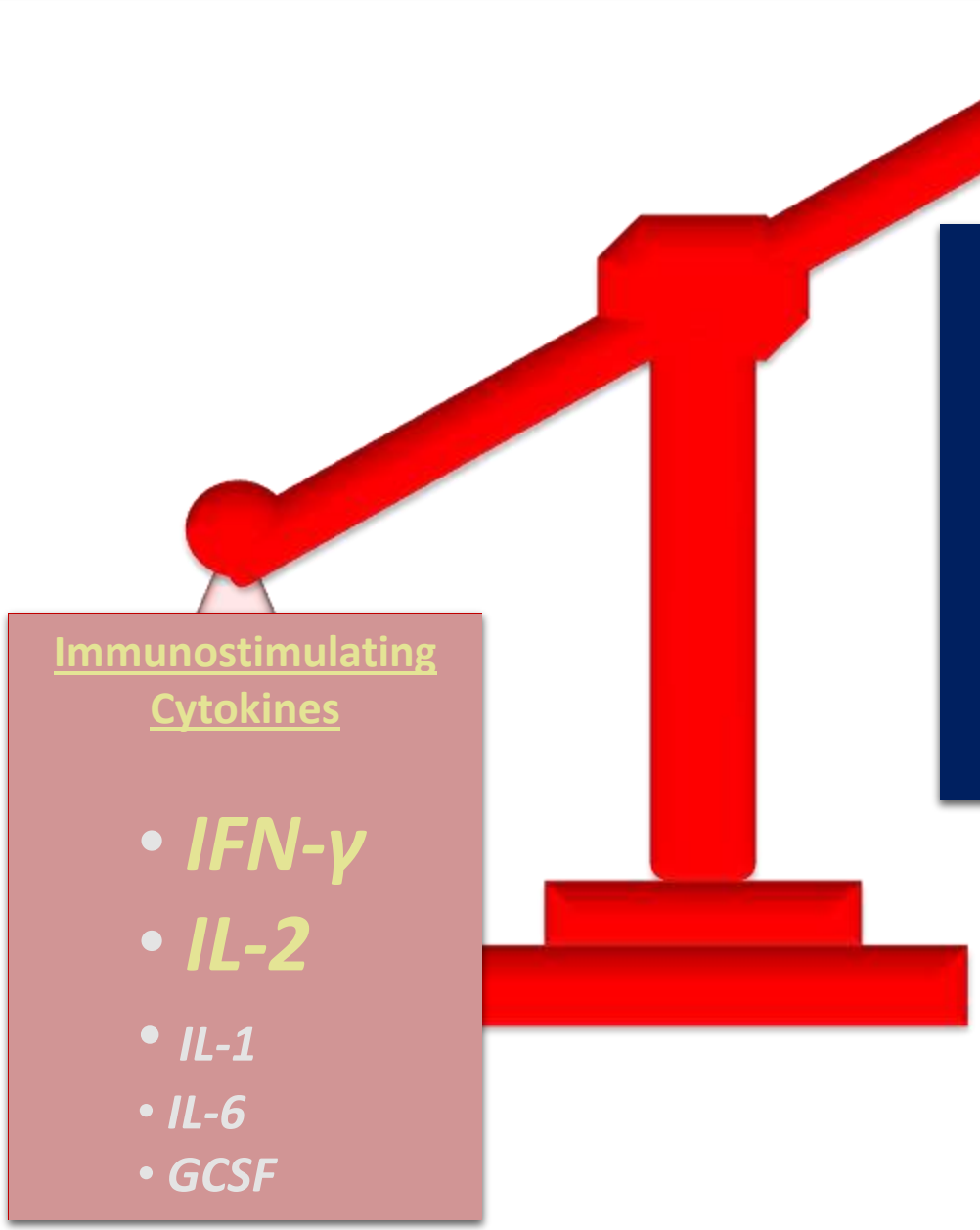
Cytokines DOWN

- ***IFNs***

Under viral attack



…under viral attack



Immunostimulating Cytokines

- *IFN-γ*
- *IL-2*
- *IL-1*
- *IL-6*
- *GCSF*

Immunomodulating Cytokines

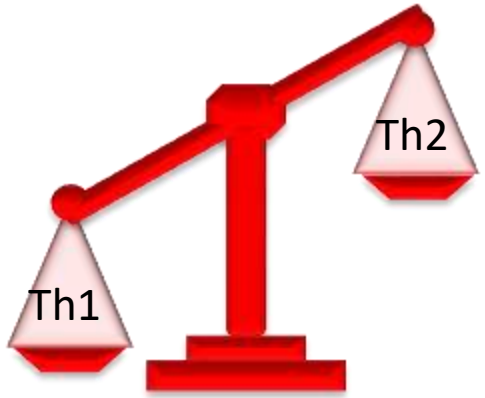
- TGF-β
- *IL-4*
- ***IL-10***

Virus immune-escape mechanisms

IMMUNE-ESCAPE MECHANISMS

Viral infection and inhibition of cell-mediated immune response

IL-10
Up-regulation



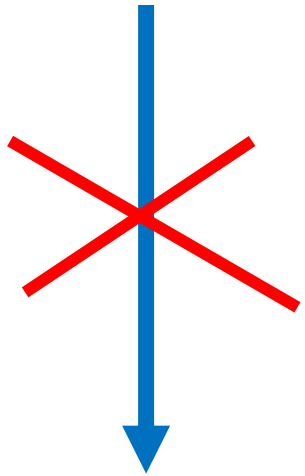
IMMUNE-ESCAPE MECHANISMS

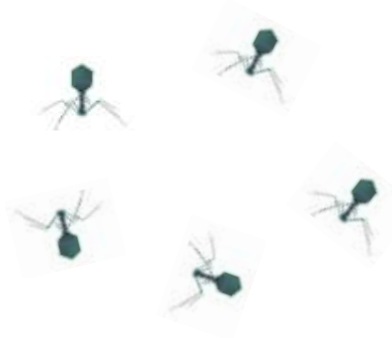
Virale infection and IFNs inhibition

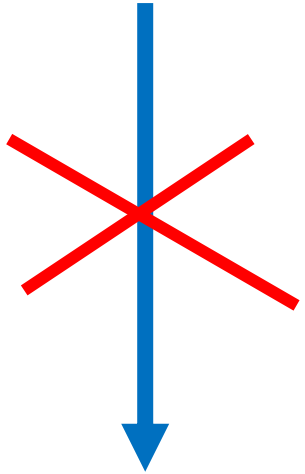
IFN-alpha

IFN-beta

IFN-gamma







NK activation

Tc activation

We need to increase the expression of IFN-γ…

Cite as: Q. Zhang *et al.*, *Science* 10.1126/science.abd4570 (2020).

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Qian Zhang[1], Paul Bastard[2,3]*, Zhiyong Liu[1]*, Jérémie Le Pen[1]*, Marcela Moncada-Velez[1]*, Jie Chen[1]*, Masato Ogishi[1]*, Ira K. D. Sabli[5]*, Stephanie Hodeib[5]*, Cecilia Korol[2]*, Jérémie Rosain[2,3]*, Kaya Bilguvar[6]*, Junqiang Ye[7]*, Alexandre Bolze[8]*, Benedetta Bigio[1]*, Rui Yang[1]*, Andrés Augusto Arias[1,9,10]*, Qinhua Zhou[1]*, Yu Zhang[11,12]*, Fanny Onodi[13], Sarantis Korniotis[13], Léa Karpf[13], Quentin Philippot[2,3], Marwa Chbihi[2,3], Lucie Bonnet-Madin[14], Karim Dorgham[15], Nikaïa Smith[16], William M. Schneider[1], Brandon S. Razooky[1], Hans-Heinrich Hoffmann[1], Eleftherios Michailidis[1], Leen Moens[17], Ji Eun Han[1], Lazaro Lorenzo[2,3], Lucy Bizien[2,3], Philip Meade[18], Anna-Lena Neehus[2,3], Aileen Camille Ugurbil[1], Aurélien Corneau[19], Gaspard Kerner[2,3], Peng Zhang[1], Franck Rapaport[1], Yoann Seeleuthner[2,3], Jeremy Manry[2,3], Cecile Masson[20], Yohann Schmitt[20], Agatha Schlüter[21], Tom Le Voyer[2,3], Taushif Khan[22], Juan Li[1], Jacques Fellay[23,24,25], Lucie Rousseł[26], Mohammad Shahrooei[27,28], Mohammed F. Alosaimi[29], Davood Mansouri[30,31,32], Haya Al-Saud[33], Fahd Al-Mulla[34], Feras Almourfi[33], Saleh Zaid Al-Muhsen[35], Fahad Alsohime[29], Saeed Al Turki[36,37], Rana Hasanato[29], Diederik van de Beek[38], Andrea Biondi[39], Laura Rachele Bettini[39], Mariella D'Angio[39], Paolo Bonfanti[40], Luisa Imberti[41], Alessandra Sottini[41], Simone Paghera[41], Eugenia Quiros-Roldan[42], Camillo Rossi[43], Andrew J. Oler[44], Miranda F. Tompkins[45], Camille Alba[45], Isabelle Vandernoot[46], Jean-Christophe Goffard[47], Guillaume Smits[46], Isabelle Migeotte[48], Filomeen Haerynck[49], Pere Soler-Palacin[50], Andrea Martin-Nalda[50], Roger Colobran[51], Pierre-Emmanuel Morange[52], Sevgi Keles[53], Fatma Çölkesen[54], Tayfun Ozcelik[55], Kadriye Kart Yasar[56], Sevtap Senoglu[56], Şemsi Nur Karabela[56], Carlos Rodríguez Gallego[57,58], Giuseppe Novelli[59], Sami Hraiech[60], Yacine Tandjaoui-Lambiotte[61,62], Xavier Duval[63,64], Cédric Laouénan[63,64,65], COVID-STORM Clinicians†, COVID Clinicians†, Imagine COVID Group†, French COVID Cohort Study Group†, CoV-Contact Cohort†, Amsterdam UMC Covid-19 Biobank†, COVID Human Genetic Effort†, NIAID-USUHS/TAGC COVID Immunity Group†, Andrew L. Snow[66], Clifton L. Dalgard[15,67], Joshua Milner[68], Donald C. Vinh[26], Trine H. Mogensen[69,70], Nico Marr[22,71], András N. Spaan[1,72], Bertrand Boisson[1,2,3], Stéphanie Boisson-Dupuis[1,2,3], Jacinta Bustamante[1,2,3,73], Anne Puel[1,2,3], Michael Ciancanelli[1,74], Isabelle Meyts[17,75], Tom Maniatis[7,76], Vassili Soumelis[13,77], Ali Amara[14], Michel Nussenzweig[78,79], Adolfo García-Sastre[18,80,81,82], Florian Krammer[18], Aurora Pujol[21], Darragh Duffy[16], Richard Lifton[83,84,85]‡, Shen-Ying Zhang[1,2,3]‡, Guy Gorochov[15]‡, Vivien Béziat[1,2,3]‡, Emmanuelle Jouanguy[1,2,3]‡, Vanessa Sancho-Shimizu[5]‡, Charles M. Rice[4]‡, Laurent Abel[1,2,3]‡, Luigi D. Notarangelo[11,12]§, Aurélie Cobat[1,2,3]§, Helen C. Su[11,12]§, Jean-Laurent Casanova[1,2,3,79,86]§

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Clinical outcome upon infection with SARS-CoV-2 ranges from silent infection to lethal COVID-19. We have found an enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern TLR3- and IRF7-dependent type I interferon (IFN) immunity to influenza virus, in 659 patients with life-threatening COVID-19 pneumonia, relative to 534 subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, we experimentally define LOF variants in 23 patients (3.5%), aged 17 to 77 years, underlying autosomal recessive or dominant deficiencies. We show that human fibroblasts with mutations affecting this pathway are vulnerable to SARS-CoV-2. Inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection.

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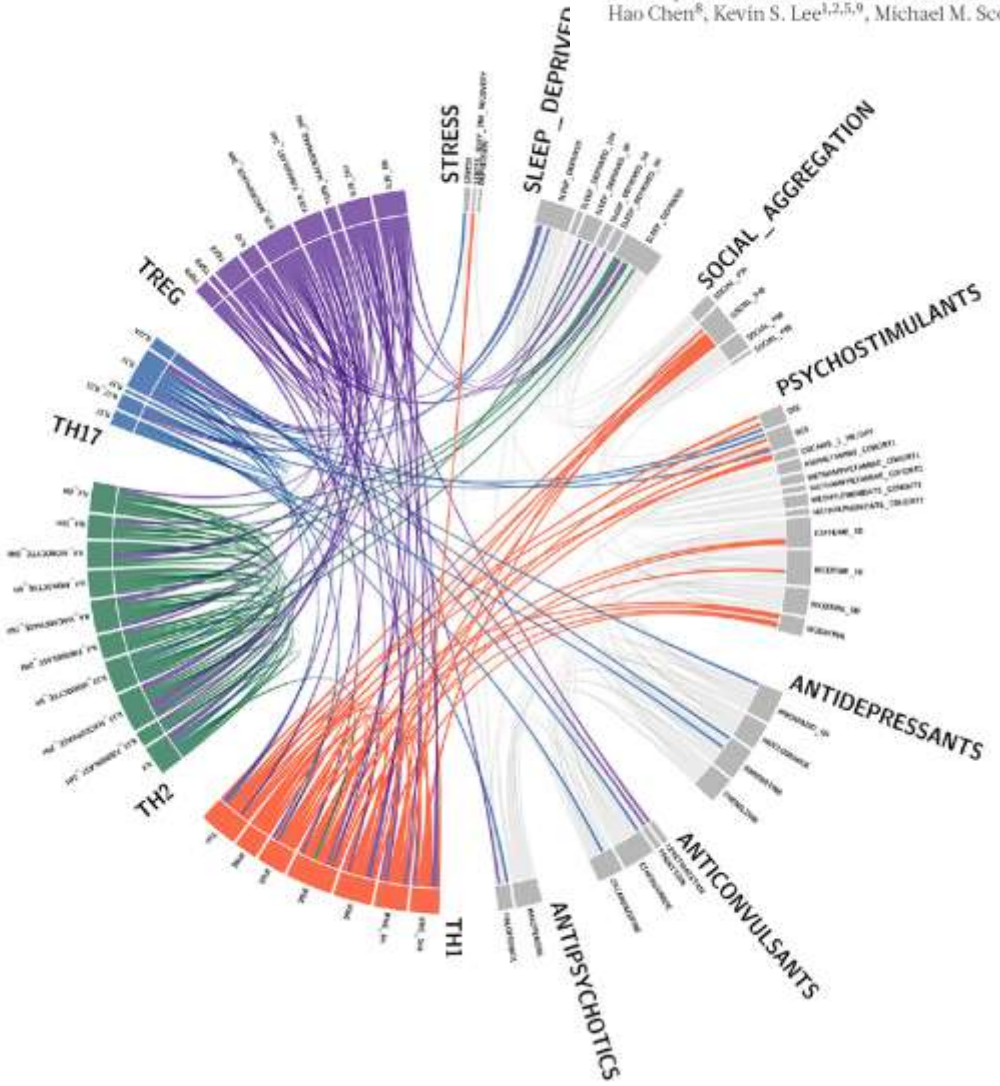
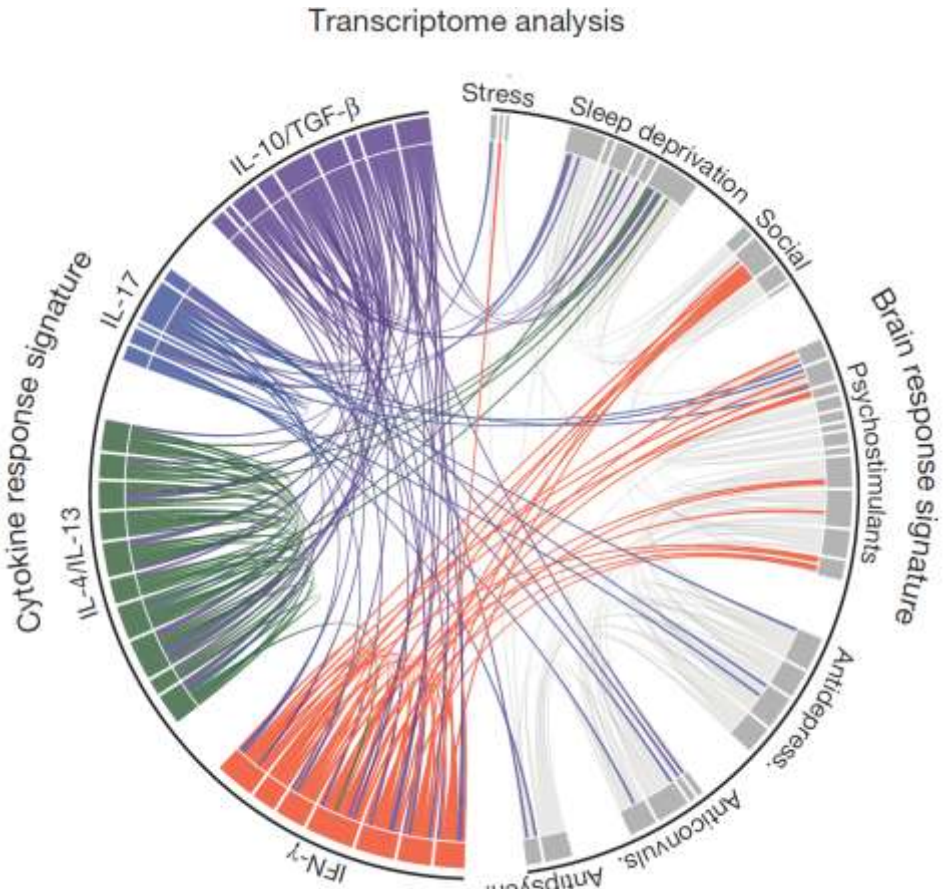
LETTER

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]*





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

Since the Immune System is an orchestra…

…do we have to think in terms of **single soloyst** or in terms of **many musicians**? …

CITOMIX

Our (and only our) goal:

- *To immunostimulate withot inflamming*
- *To control the inflammation without immunosupression*

CITOMIX

- *Vaccinium vitis*
- *Ananassa sativa*
- *Hydrocotyle asiatica 4X*

- *Vasa lymphatica suis*
- *Medulla ossis suis*
- *Thymuline*

- *IL-1 beta*
- *IL-2*
- *IL-4*
- *IL-6*
- *IFN-gamma*
- *GCSF*

To immunostimulate
without inflamming

Controllo
dell'Infiamma
organospeci

Controllo
fiammazione *non*
ganospecifica

CITOMIX – KEYNOTES FOR SIGNALING MOLECULES

G-CSF

Keynotes

- Pleiotropic hematopoietic growth factor
- Priming of immune response
- Control of secondary neutropenia

IL-1 beta

Keynotes

- *Onset of both innate and cell-mediated immune response*
- *Support for antiviral response*
- *"Immunological" adjuvant in vaccine therapies*

IFN-γ

Keynotes

- T-naïve to Th1 cell differentiation
- CD8⁺ cells maturation
- Macrophage activation
- NK cells cytotoxicity

IL-2

Keynotes

- *Pleiotropic action*
- *Clonal expansion of T, B and NK lymphocytes*
- *Antiviral response homeostatic regulation*

IL-6

Keynotes

- T follicular helper cells differentiation
- Response to infections; synthesis of acute phase proteins
- B lymphocytes maturation
- Support of antibody response
- Control of viral immune escape mechanism

IL-4

Keynotes

- T-naïve to Th2 cell differentiation
- B Lymphocyte activation
- Macrophage response activation


International Journal of Molecular Sciences

MDPI

Brief Report

Rethinking IL-1 Antagonism in Respiratory Viral Infections: A Role for IL-1 Signaling in the Development of Antiviral T Cell Immunity

Bram Van Den Eeckhout [1,2,3], Matties Ballegeer [4,5], Jozefien De Clercq [1,2], Elianne Burg [1,2], Xavier Saelens [4,5], Linos Vandekerckhove [1,2] and Sarah Gerlo [1,2,*]


npj | Vaccines

www.nature.com/npjvaccines

ARTICLE OPEN

Check for updates

Specific targeting of IL-1β activity to CD8$^+$ T cells allows for safe use as a vaccine adjuvant

Bram Van Den Eeckhout[1,2], Lien Van Hoecke[1,3], Elianne Burg[1,2], Sandra Van Lint[1,2], Frank Peelman[1,2], Niko Kley[4], Gilles Uzé[5], Xavier Saelens[1,3,6], Jan Tavernier[1,2,4,7✉] and Sarah Gerlo[1,2,7✉]

IL-1 beta

In prevention, and therapy:
Supports the antiviral response, also in case of re-infection

As adjuvant during vaccine therapies
Increases the Immune System sensitivity to the immunizing agent

- Van Den Eeckhout B, Ballegeer M, De Clercq J, Burg E, Saelens X, Vandekerckhove L, Gerlo S. Rethinking IL-1 Antagonism in Respiratory Viral Infections: A Role for IL-1 Signaling in the Development of Antiviral T Cell Immunity. Int J Mol Sci. 2023 Oct 30;24(21):15770..
- Van Den Eeckhout B, Van Hoecke L, Burg E, Van Lint S, Peelman F, Kley N, Uzé G, Saelens X, Tavernier J, Gerlo S. Specific targeting of IL-1β activity to CD8+ T cells allows for safe use as a vaccine adjuvant. NPJ Vaccines. 2020 Jul 23;5(1):64.

INTERLEUCHINA 1 CON FUNZIONE DI ADIUVANTE

Vaccine. 1993;11(5):594-5.

Cytokines as vaccine adjuvants: interleukin 1 and its synthetic peptide 163-171.

Tagliabue A[1], Boraschi D.

Author information

Abstract

The possibility of preventing infectious diseases by employing efficacious vaccine is rapidly growing as a consequence of the new technologies in recombinant DNA and protein chemistry. However, the increasing number of synthetic and recombinant antigens further stresses the role of appropriate adjuvants to ensure maximal vaccine activity and the protection of all vaccinees. Several approaches can be applied to develop safe and effective agents capable of enhancing specific immune responses which can then protect the host from the pathogen. Among others, the direct use as adjuvant of those cytokines which are induced in animals by the classical Freund's adjuvants has recently become a matter of investigation. In particular, interleukin 1 (IL-1) has been shown to possess adjuvant activity for a variety of infectious and tumour antigens. However, the numerous side effects associated with the proinflammatory action of IL-1 represent a serious disadvantage for its use as a vaccine adjuvant. It was therefore of great interest that a nonpeptide contained in the IL-1 beta sequence (residues 163-171 corresponding to the sequence VQGEESNDK) is devoid of all proinflammatory activities but maintains the immunostimulating activity of the whole IL-1 beta. Thus, peptide 163-171 was successfully employed in animals to potentiate the specific immune response against T-helper-dependent cellular antigens, T helper-independent polysaccharidic antigens and recombinant as well as synthetic antigenic preparations derived from human pathogens. Furthermore, IL-1 and peptide 163-171 have been successfully used in tumour vaccines in experimental systems. It can therefore be concluded that peptide 163-171 is potentially a good candidate as vaccine adjuvant for human use.

PMID: 8488719

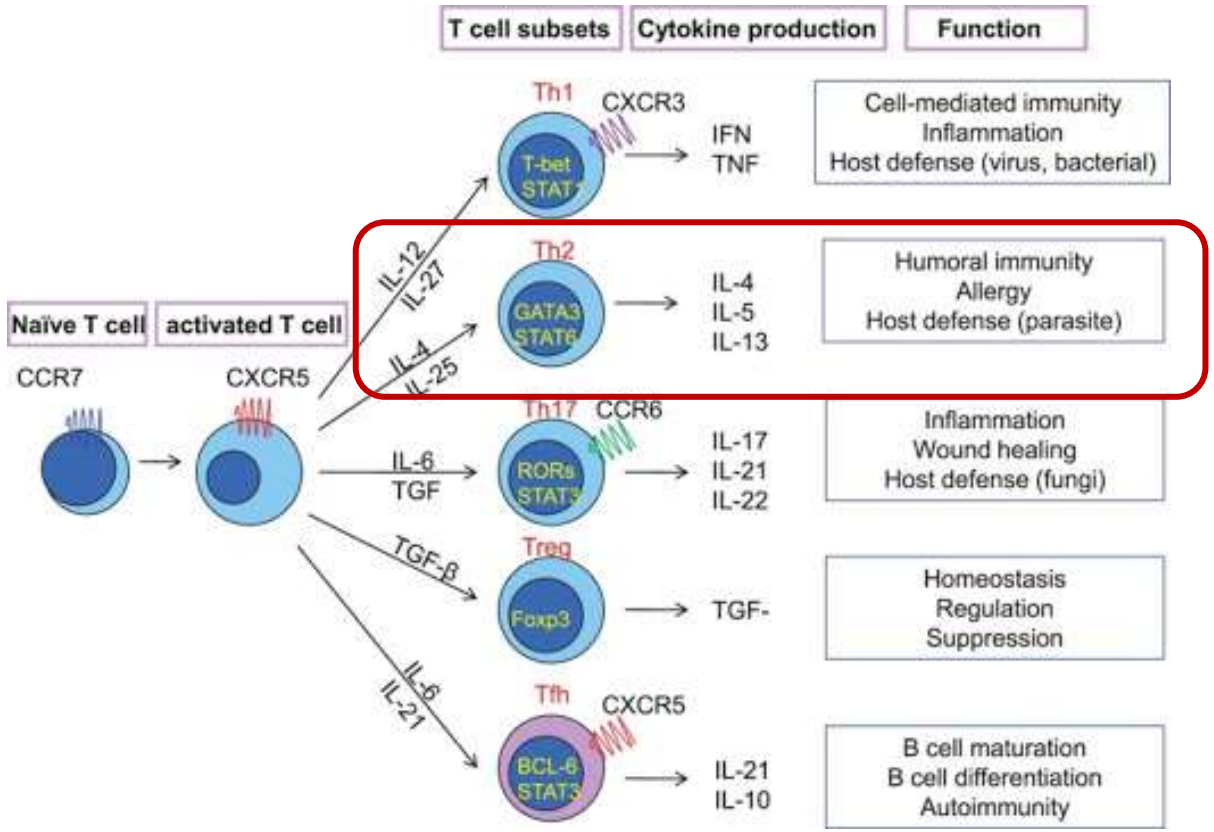
[Indexed for MEDLINE]

JOURNAL OF VIROLOGY, Dec. 2010, p. 12703–12712 Vol. 84, No. 24
0022-538X/10/$12.00 doi:10.1128/JVI.01182-10

Interleukin-1 Family Cytokines as Mucosal Vaccine Adjuvants for Induction of Protective Immunity against Influenza Virus[▽]

Hiroyuki Kayamuro,[1,2]† Yasuo Yoshioka,[1,3]† Yasuhiro Abe,[1]† Shuhei Arita,[1,2] Kazufumi Katayama,[4] Tetsuya Nomura,[1] Tomoaki Yoshikawa,[1,2] Ritsuko Kubota-Koketsu,[5] Kazuyoshi Ikuta,[5] Shigefumi Okamoto,[6] Yasuko Mori,[6] Jun Kunisawa,[7] Hiroshi Kiyono,[7] Norio Itoh,[2] Kazuya Nagano,[1] Haruhiko Kamada,[1,3] Yasuo Tsutsumi,[1,2,3] and Shin-Ichi Tsunoda[1,3]*

INTERLEUKIN-4 ACTIVATES B LYMPHOCYTES

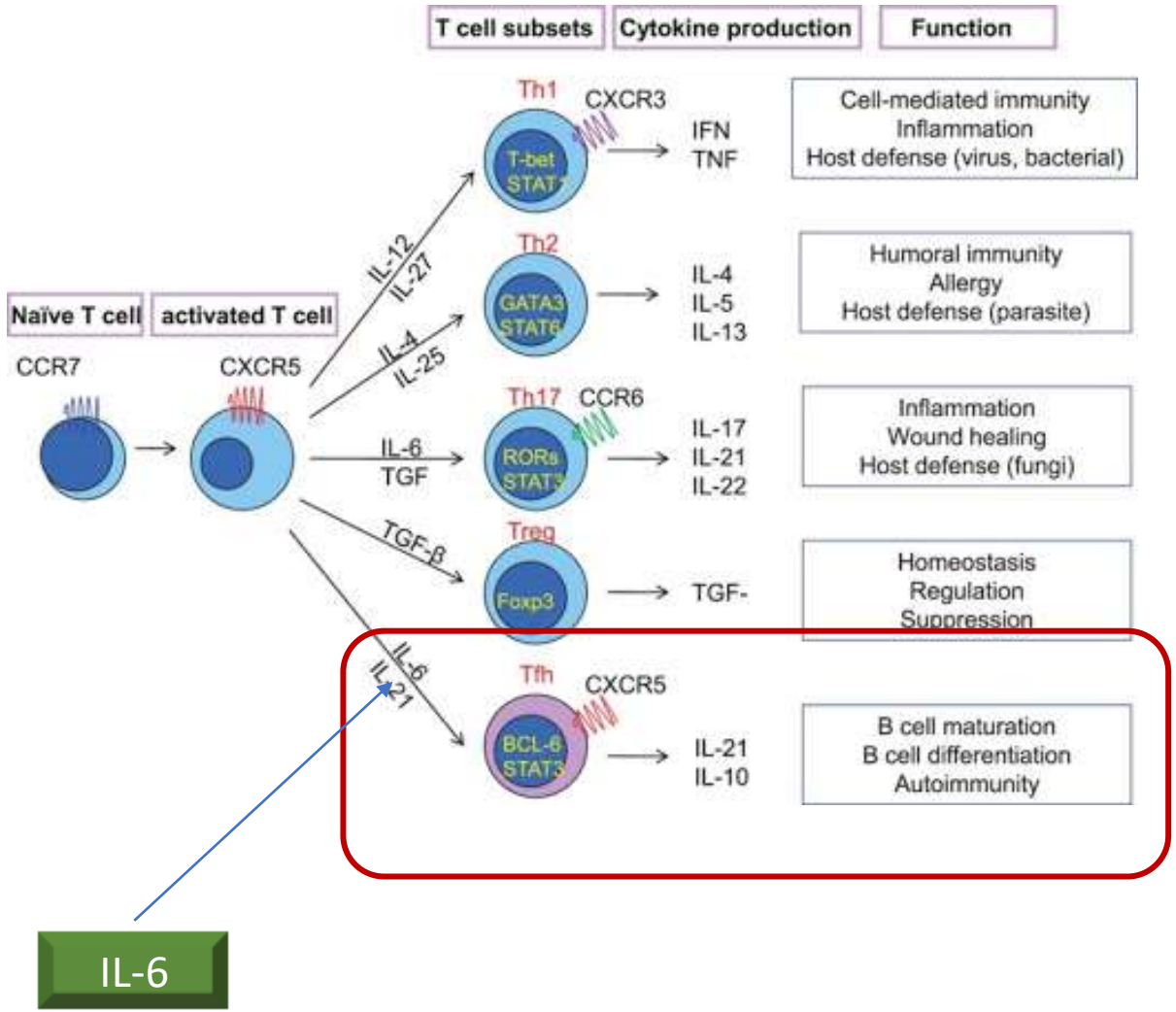


IL-4

INTERLEUKIN-4 (IL-4)

- Induces CD4+ naive T cells differentiation into Th2 cells, key players of humoral immunity.
- Activates B cells in lymph nodes.
- Helps in stimulating B cells to turn into plasma cells, and to secrete antibodies (particularly IgG).

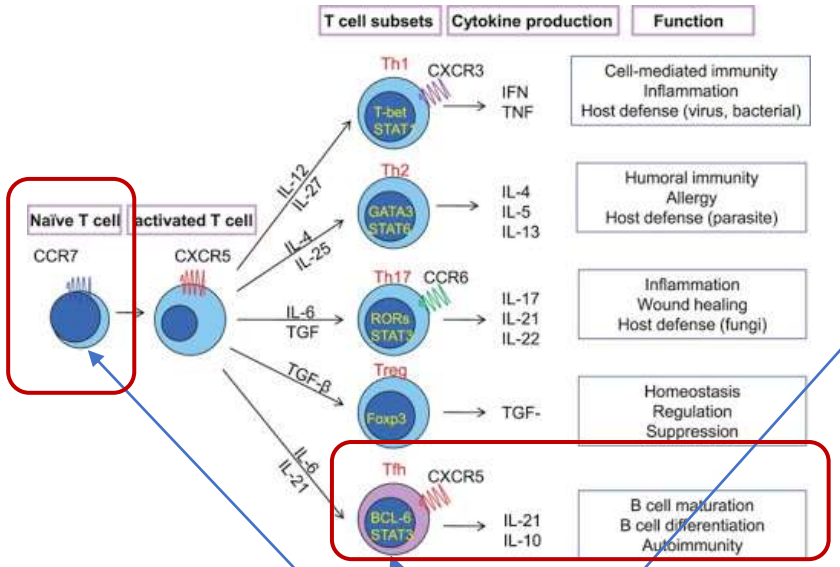
INTERLEUKIN-6 INDUCES THE DIFFERENTIATION OF CD4+ IN Tfh, WHICH ARE CRUCIAL FOR THE MATURATION OF B CELLS INTO PLASMA CELLS

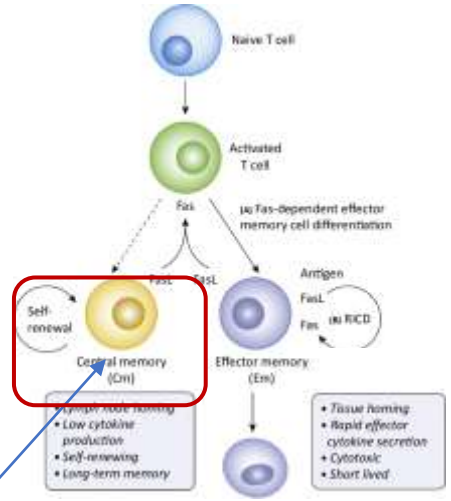


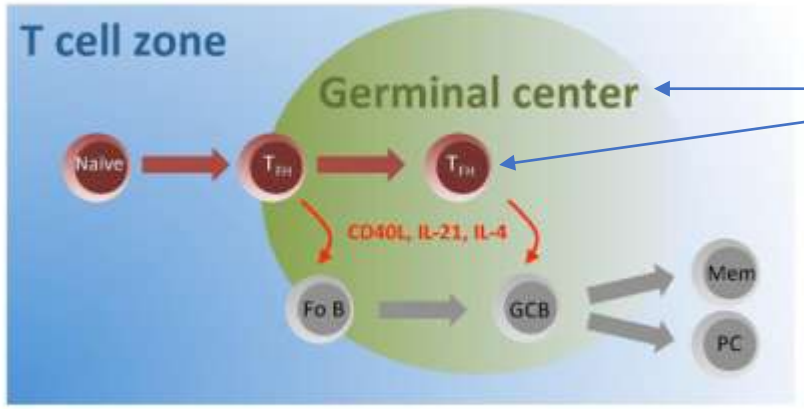
INTRLEUKIN-6 (IL-6)

- Down-regulates IL-10, immunosuppressive cytokine used by viruses to do immune-escape and to survive.
- Induces IgA production (critical antibody for its mucosal-based localisation).
- Induces **CD4+ naive T cells differentiation into Tfh (follicular) cells**, main players in B cells maturation into plasma cells.

INTERLEUKIN-7 PLAYS IN SEVERAL T CELLS LIFE STAGES







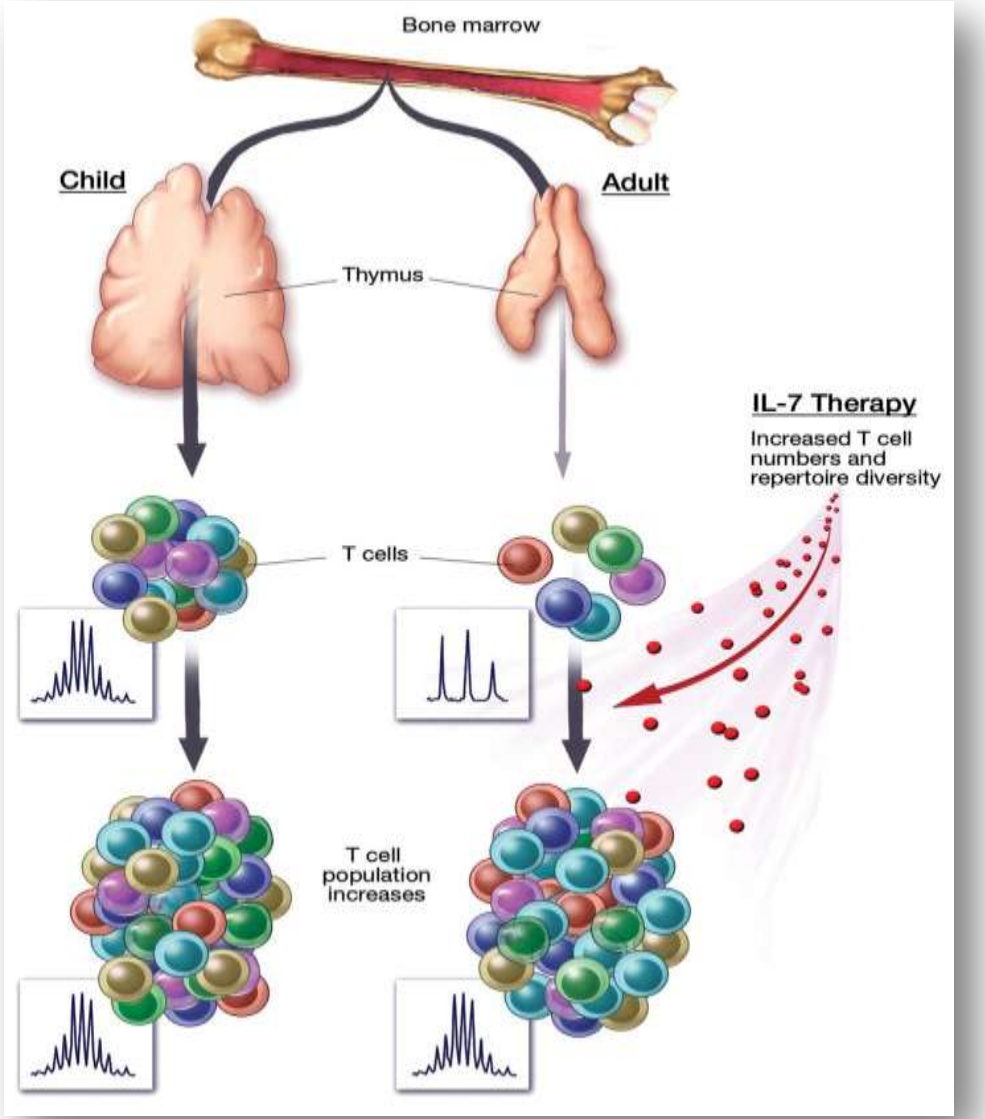
IL-7

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 NOTICE – 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*).

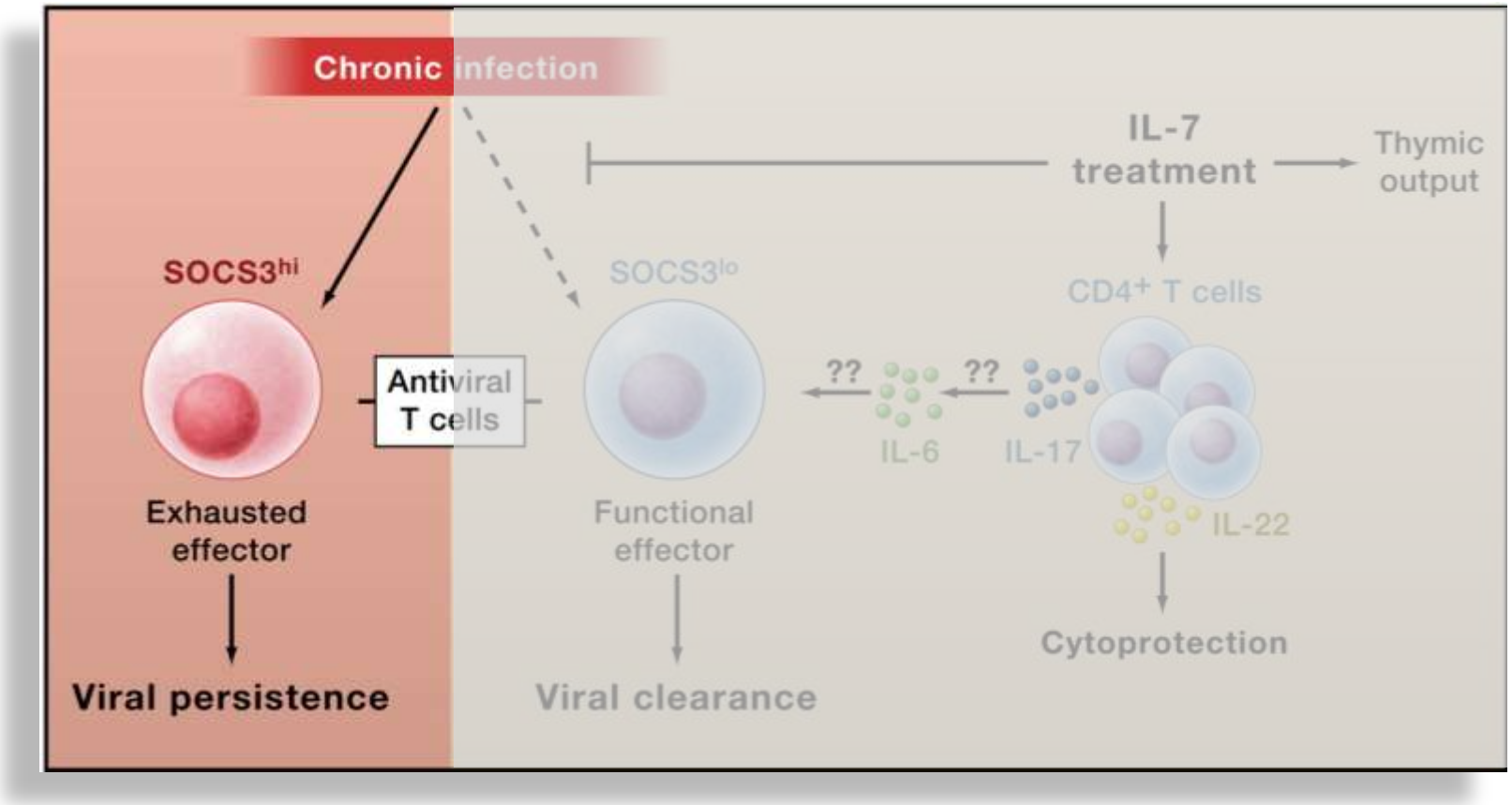
INTERLEUKIN-7 INCREASES THE NUMBER OF T LYMPHOCYTES



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

Homeostatic Peripheral Expansion

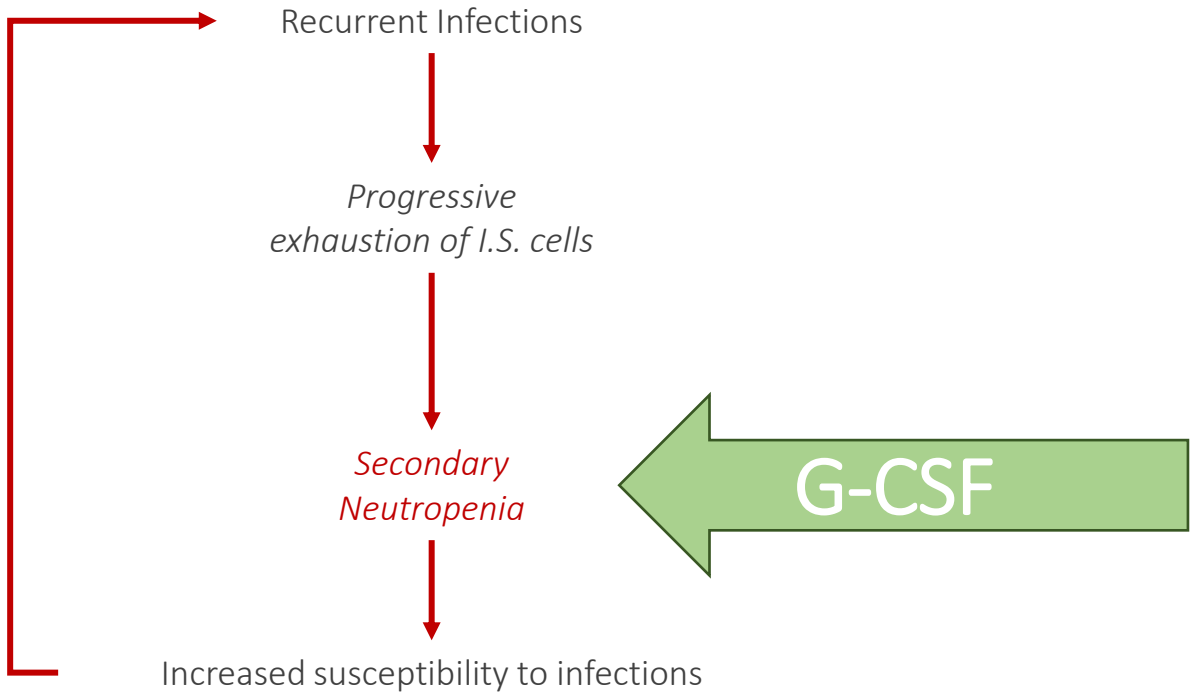
INTERLEUKIN-7 INCREASES THE NUMBER OF T LYMPHOCYTES



- 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

CITOMIX and NEUTROPENIA DUE TO CHRONIC-RECURRENT VIRAL INFECTIONS
- THE ROLE of G-CSF -



G-CSF: cytokine produced by activated T lymphocytes, macrophages, and endothelial cells; it acts on bone marrow increasing productions and trafficking of neutrophils in order to replace the granulocytes during the inflammation process

Mehta HM, Malandra M, Corey SJ. G-CSF and GM-CSF in Neutropenia. J Immunol. 2015 Aug 15;195(4):1341-9.

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Translating Immunology

The Journal of Immunology

G-CSF and GM-CSF in Neutropenia

Hrishikesh M. Mehta,* Michael Malandra,† and Seth J. Corey*,‡

OPEN ACCESS Freely available online

PLoS one

Granulocyte Colony-Stimulating Factor Protects Mice during Respiratory Virus Infections

Tamar Hermesh[1¤], Thomas M. Moran[1], Deepika Jain[2], Carolina B. López[1,2]*

1 Department of Microbiology and Immunology Institute, Mount Sinai School of Medicine, New York, New York, United States of America, **2** Department of Pathobiology School of Veterinary Medicine and Institute for Immunology, University of Pennsylvania, Philadelphia, Pennsylvania, United States of America

Immunity, Vol. 17, 413–423, October, 2002, Copyright ©2002 by Cell Press

G-CSF Is an Essential Regulator of Neutrophil Trafficking from the Bone Marrow to the Blood

Craig L. Semerad, Fulu Liu, Alyssa D. Gregory, Katherine Stumpf, and Daniel C. Link[1]
Division of Oncology
Department of Internal Medicine
Washington University School of Medicine
St. Louis, Missouri 63110

blood barrier) that separates the hematopoietic compartment from the circulation (Petrides and Dittmann, 1990). Bone marrow venous sinuses are the sites of neutrophil egress from the hematopoietic compartment and represent the only complete barrier to the intravascular space. The sinus wall is a trilaminar structure composed of endothelial cells, a basement membrane, and

THE IMMUNE SYSTEM IN ONE MEDICATION

CITOMIX IS THE PACE MAKER OF THE IMMUNE RESPONSE

The co-presence of IL-2 e IFN-gamma makes CITOMIX a medication for all the lifetimes

CITOMIX

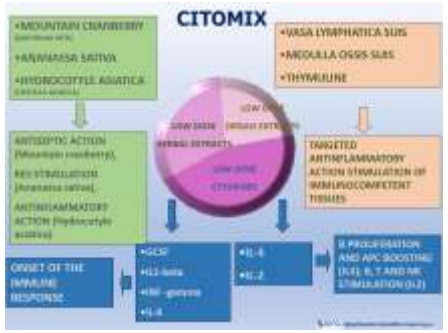
- *Vaccinium vitis*
- *Ananassa sativa*
- *Hydrocotyle asiatica 4X*

- *Vasa lymphatica suis*
- *Medulla ossis suis*
- *Thymuline*

To reduce the inflammation
without immunosuppressing

- *IL-1 beta*
- *IL-2*
- *IL-4*
- *IL-6*
- *IFN-gamma*
- *GCSF*

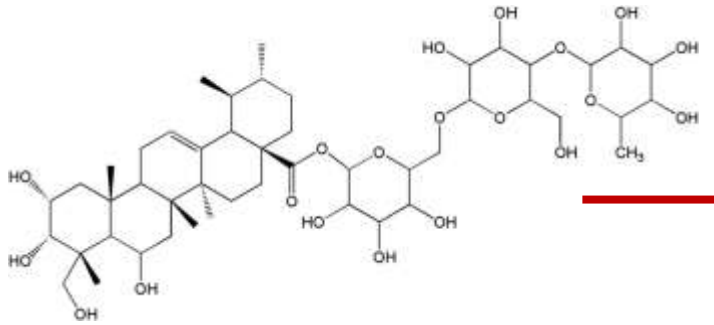
To immunostimulate
without inflamming



Hydrocotyle asiatica L. 3X
Centella asiatica

EFFECTS
- *Anti-oxidant*
- *Anti-inflammatory*

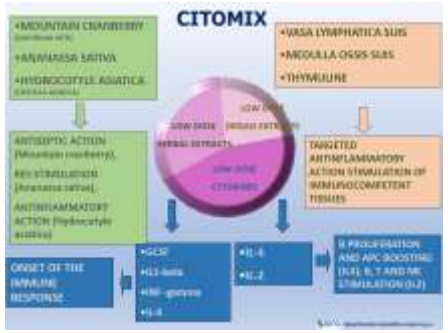
MADECASSOSIDE



- Nitric Oxide (NO)
- Prostaglandin E2 (PGE2)
- TNF-α
- Interleukin-1β (IL-1β)

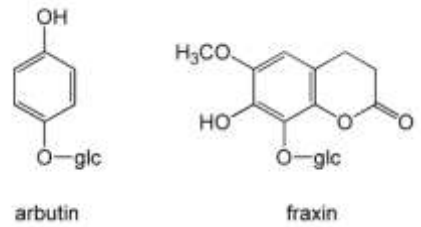
Madecassoside (MA), major triterpenoid component of *Centella asiatica*

Cao W, Li XQ, Zhang XN, Hou Y, Zeng AG, Xie YH, Wang SW. Madecassoside suppresses LPS-induced TNF-alpha production in cardiomyocytes through inhibition of ERK, p38, and NF-kappaB activity. Int Immunopharmacol. 2010;10(7):723-9.



Vaccinium vitis-idaea L. 3X
Lingonberry

EFFECTS
- *Anti-oxidant*
- *Anti-inflammatory*

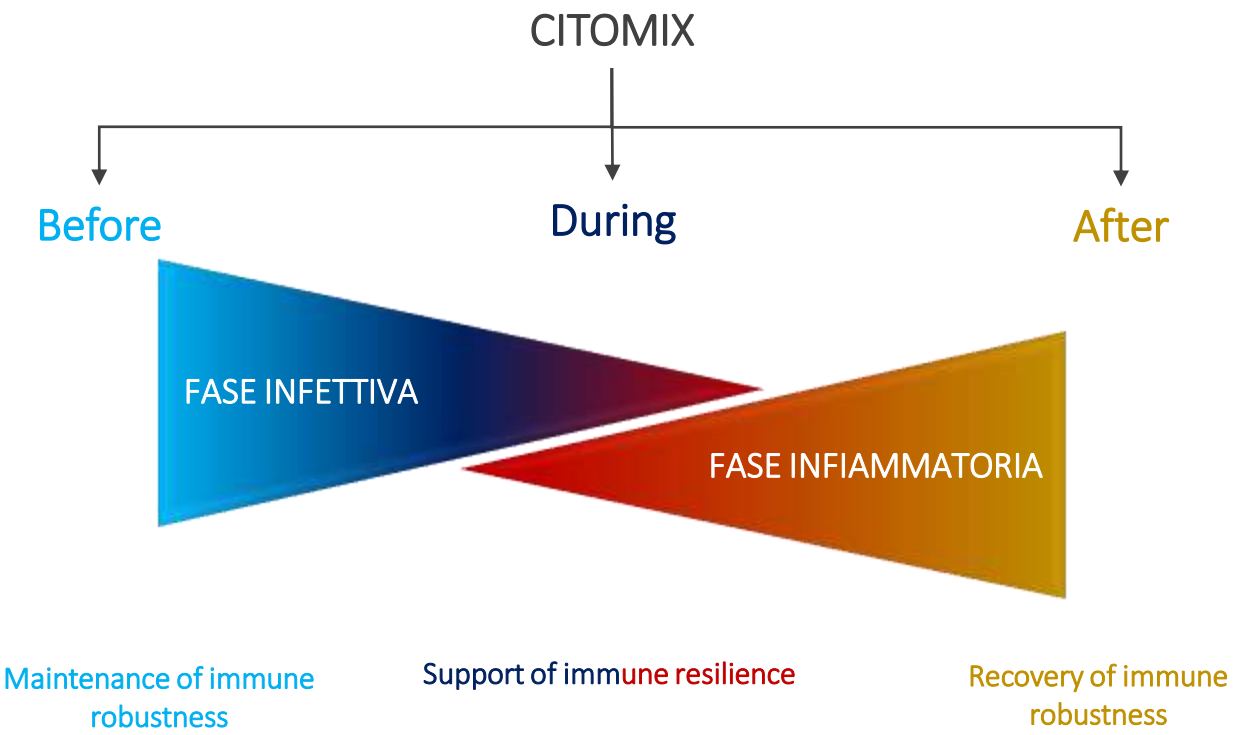


Lingonberry fruit extract (LGBE)

- TNF-α
- IL-1β
- MCP-1
- COX-2
- iNOS
- NADPH oxidase 4

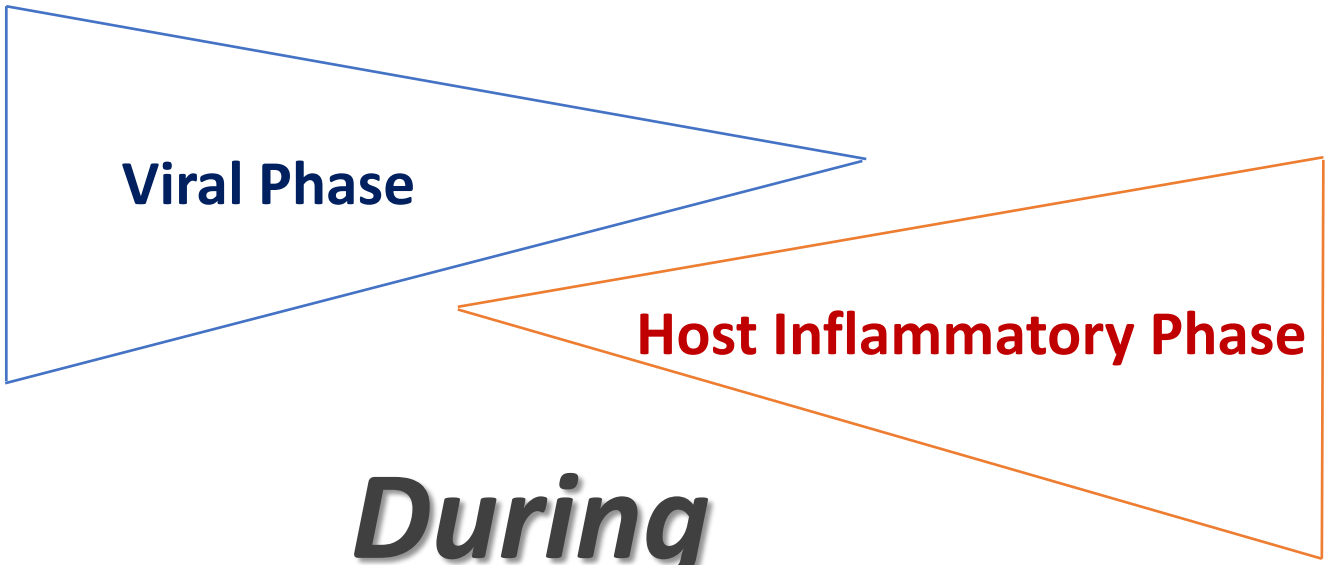
- SOD
- Catalase,

Wang SY, Feng R, Bowman L, Penhallegon R, Ding M, Lu Y. Antioxidant activity in lingonberries (Vaccinium vitis-idaea L.) and its inhibitory effect on activator protein-1, nuclear factor-kappaB, and mitogen-activated protein kinases activation. J Agric Food Chem. 2005;53(8):3156-66.
Kowalska K, Olejnik A, Zielińska-Wasielica J, Olkowicz M. Inhibitory effects of lingonberry (Vaccinium vitis-idaea L.) fruit extract on obesity-induced inflammation in 3T3-L1 adipocytes and RAW 264.7 macrophages. Journal of Functional Foods 54 (2019) 371–380.
Wang X, Sun H, Fan Y, Li L, Makino T, Kano Y. Analysis and bioactive evaluation of the compounds absorbed into blood after oral administration of the extracts of Vaccinium vitis-idaea in rat. Biol Pharm Bull. 2005;28(6):1106-8.



Our goal in prevention

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



Before

IMMUNOSTIMULATION

During

IMMUNOSTIMULATION
ANTINFLAMMATORY THER.

After

CONVALESCENCE AND
PREVENTION OF RELAPSES

Our goal in immunostimulation during the early stage of the host ionflammatory phase

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 days; continue with 5 pellets twice a day per 5-7 days.

Viral Phase

Host Inflammatory Phase

Before

IMMUNOSTIMULATION

During

IMMUNOSTIMULATION
ANTINFLAMMATORY THER.

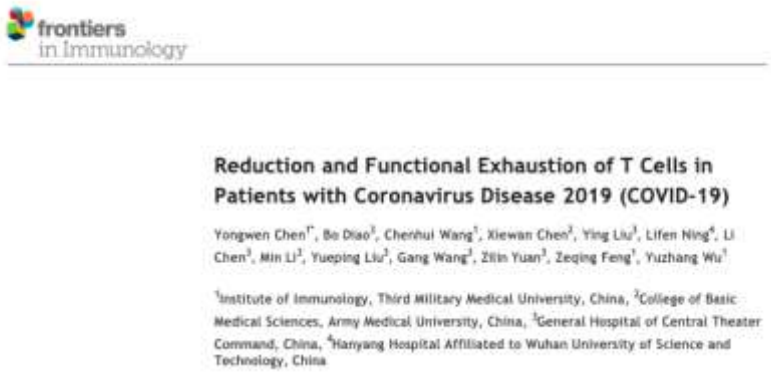
After

CONVALESCENCE AND PREVENTION OF RELAPSE

AFTER AN INFECTIOUS DISEASE A (MORE OR LESS PERSISTENT) *SUBVERSION* OF THE IMMUNE SYSTEM VERY OFTEN PERSISTS

- *Increased IL-10* *(insufficient to suppress the inflammation)*

- *T (naïve) and B (naïve) cells depletion*



frontiers in Immunology

Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19)

Yongwen Chen[†], Bo Diao[†], Chenhui Wang[†], Xiewan Chen[2], Ying Liu[1], Lifen Ning[4], Li Chen[3], Min Li[1], Yueping Liu[1], Gang Wang[3], Zilin Yuan[3], Zeqing Feng[1], Yuzhang Wu[1]

[1]Institute of Immunology, Third Military Medical University, China, [2]College of Basic Medical Sciences, Army Medical University, China, [3]General Hospital of Central Theater Command, China, [4]Hanyang Hospital Affiliated to Wuhan University of Science and Technology, China

- *Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, Juno JA, Burrell LM, Kent SJ, Dore GJ, Kelleher AD, Matthews GV. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol. 2022 Feb;23(2):210-216.*
- *Ryan FJ, Hope CM, Masavuli MG, Lynn MA, Mekonnen ZA, Yeow AEL, Garcia-Valtanen P, Al-Delfi Z, Gummow J, Ferguson C, O'Connor S, Reddi BAJ, Hissaria P, Shaw D, Kok-Lim C, Gleadle JM, Beard MR, Barry SC, Grubor-Bauk B, Lynn DJ. Long-term perturbation of the peripheral immune system months after SARS-CoV-2 infection. BMC Med. 2022 Jan 14;20(1):26.*

Our goal after the infectious disease

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

Before

IMMUNOSTIMULATION

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

Viral Phase

Host Inflammatory Phase

During

IMMUNOSTIMULATION
ANTINFLAMMATORY THER.

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

After

CONVALESCENCE AND
PREVENTION OF RELAPSES

PHYSIOLOGICAL REGULATING MEDICINE 1/2009

A. Arrighi

CITOMIX™ *VS* IMMUCYTAL® IN THE PREVENTION AND THERAPY OF ACUTE RESPIRATORY INFECTIONS IN PEDIATRIC AGE.

- A CONTROLLED PROSPECTIVE CLINICAL TRIAL

M. Colombo

ABSTRACT

CITOMIX NELLA PREVENZIONE DELLE COMPLICANZE PIU' FREQUENTI DELLA VARICELLA IN ETA' PEDIATRICA

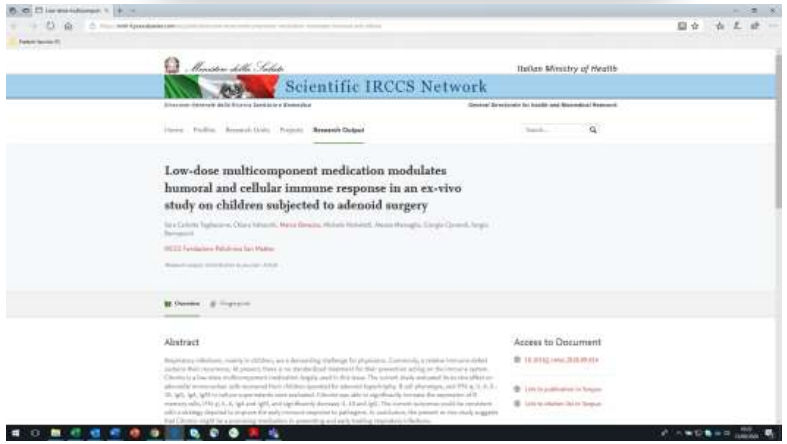
CITOMIX IN THE PREVENTION OF THE MOST WIDESPREAD VARICELLA COMPLICATIONS IN PAEDIATRIC AGE

A low-dose multicomponent medication as a new approach in prevention and early add-on treatment of recurrent respiratory infections in children: a Delphi Consensus

M. AGOSTI[1], A. ARRIGHI[2], S. BERNASCONI[3], G. BONA[4], G. CIPRANDI[5], S. LEONARDI[6], G.L. MARSEGLIA[7,8]

[1]Pediatric Department, Hospital 'F. Del Ponte', University of Insubria, Varese, Italy
[2]Pediatric Primary Care, ASL 8, Arezzo, Italy
[3]Secretary of the "Complementary Medicines and Integrated Therapies" Study Group of the Italian Pediatric Society (SIP), Parma, Italy
[4]Department of Health Sciences, University of Piemonte Orientale, Novara, Italy
[5]Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy
[6]Pediatric Respiratory Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[7]Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[8]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy

Risultati



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

CITOMIX INDUCES A SIGNIFICANT INCREASE OF IFN-γ AFTER 3 AND 10 DAYS OF TREATMENT

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

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

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

CITOMIX – AIM OF THE STUDY

To evaulate the immunomodulation activity "in vitro" of CITOMIX

Adenoidal Mononuclear Cells) from pediatric patients

Immunological p

phocytes subsets prolifera

ines and Immunoglobulin

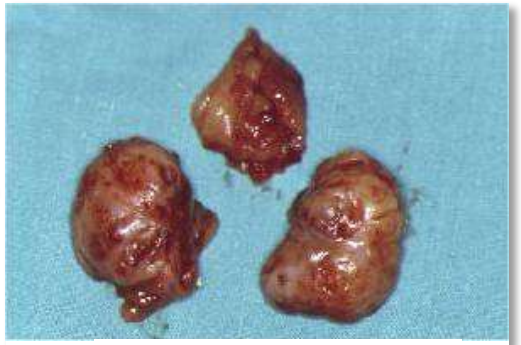
RITERIA:

omy

- Autoimmunity pathologies
- Obesity
- Chronic use of steroideal drugs
- Presensce of disability (physical or psychic)

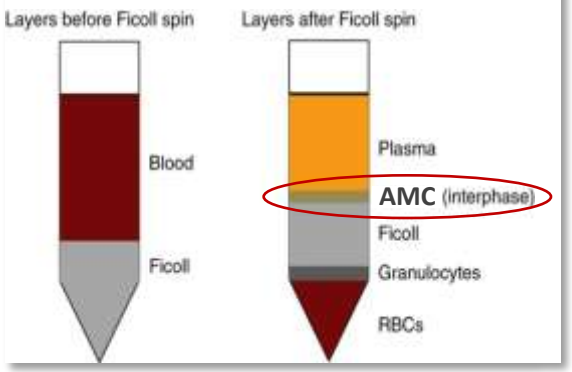
IMMUNOMODULATING ACTIVITY OF CITOMIX – *STUDY DESIGN*

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



Schiacciamento meccanico

Cell iosolation



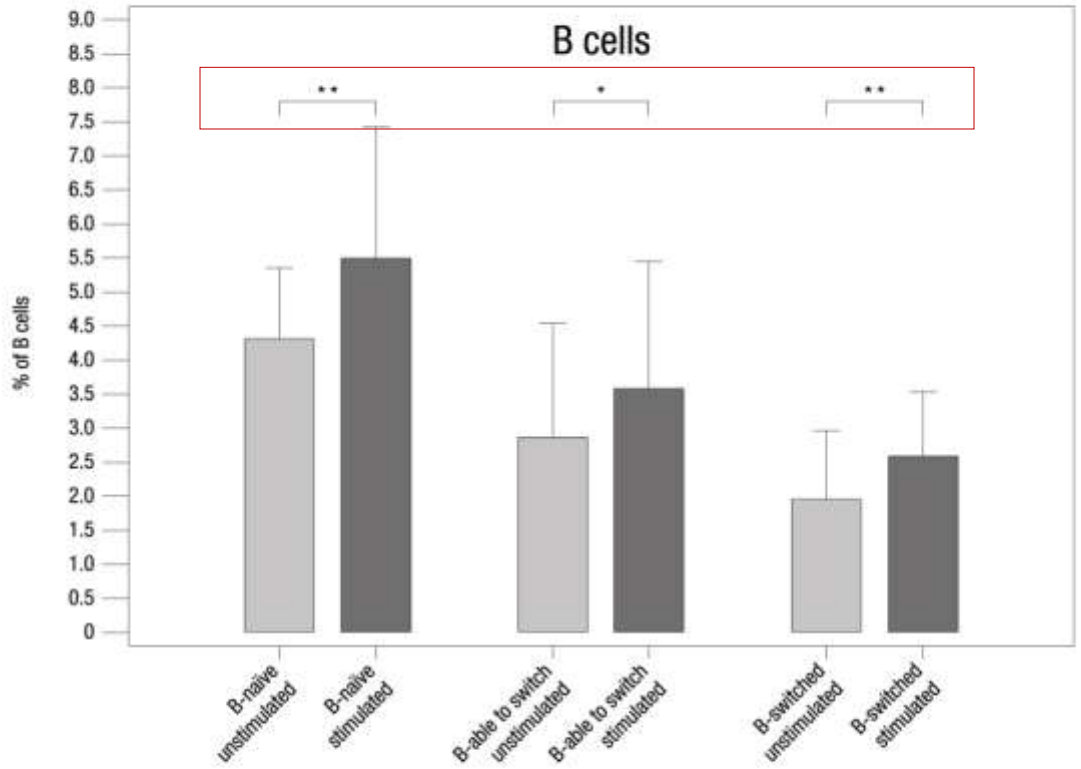
AMC expansion *in vitro*

Cytokines quantification
- **IL-6**
- **IL-10**
- **IFN-γ**

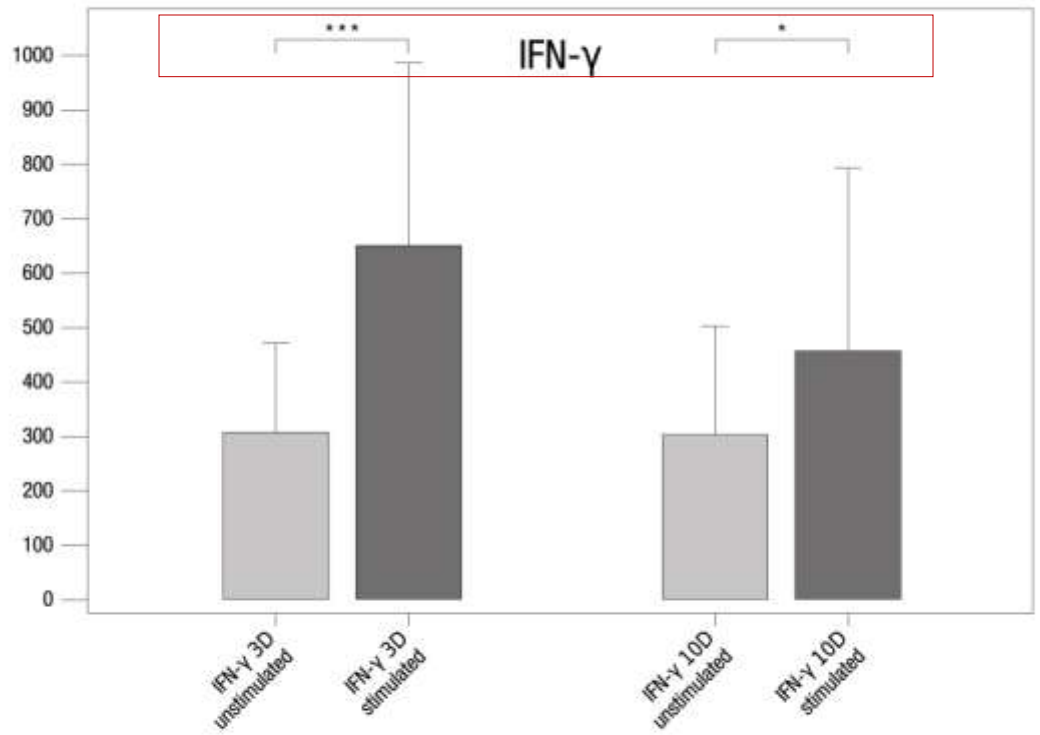
Igs quantification
- **IgA**
- **IgG**
- **IgM**

B-cells sub-clones characterization

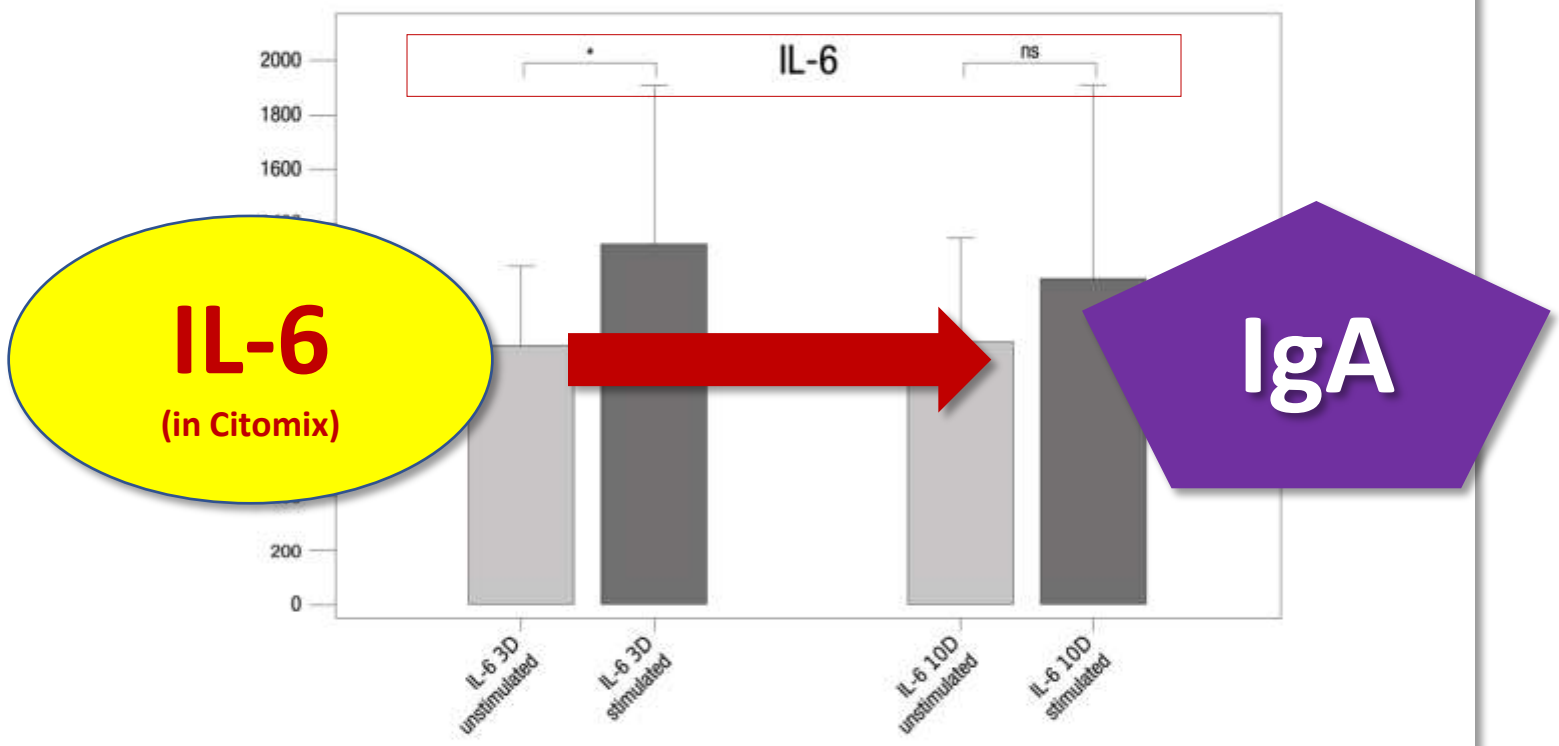
CITOMIX INDUCES A SIGNIFICANT INCREASE OF B *NAÏVE*, B *ABLE TO SWITCH,* AND B *SWITCHED CELLS*



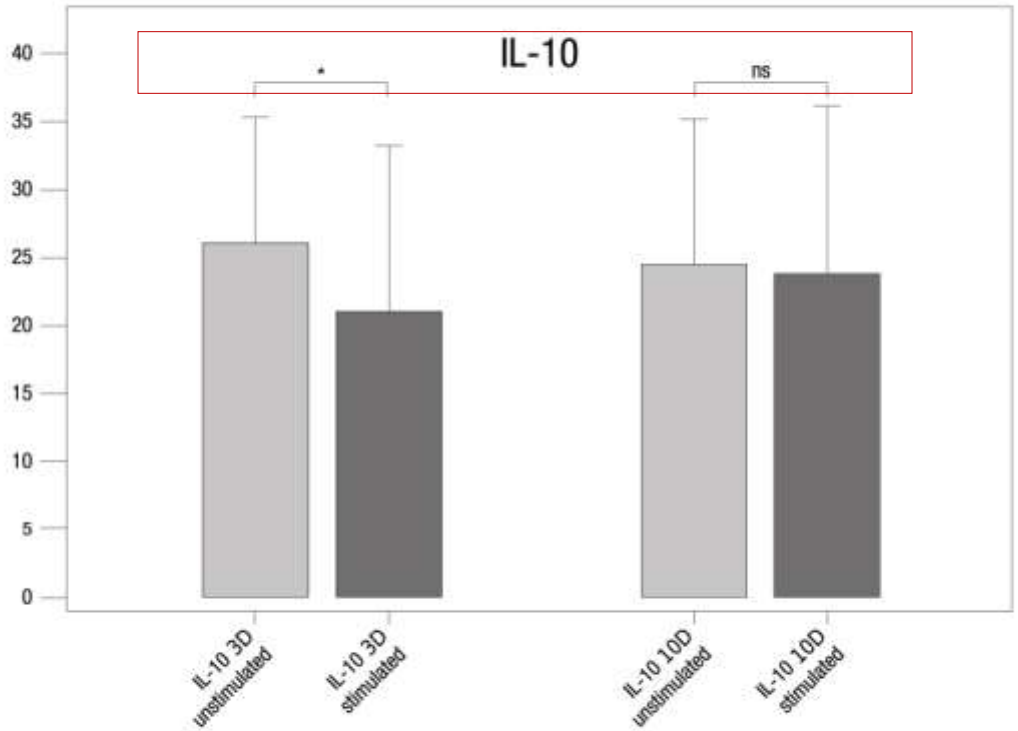
CITOMIX INDUCES A SIGNIFICANT INCREASE OF IFN-γ AFTER 3 AND 10 DAYS OF TREATMENT



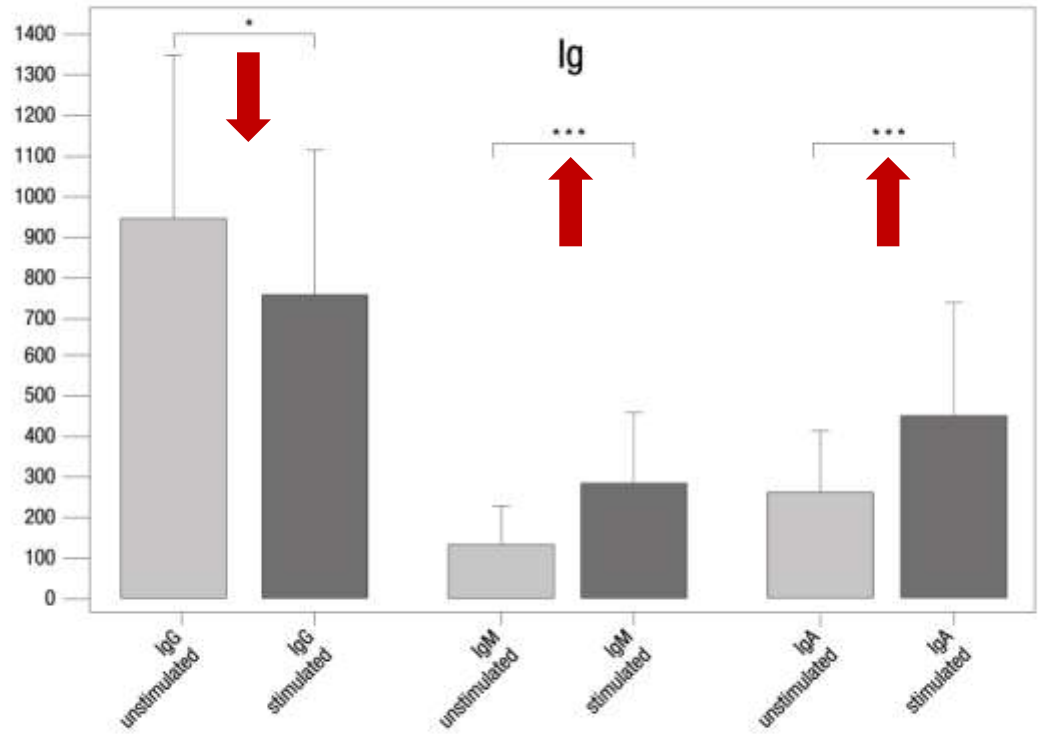
CITOMIX INDUCES A SIGNIFICANT INCREASE OF IL-6 AFTER 3 AND 10 DAYS OF TREATMENT



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



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



Pediatric Immune Disorders

CITOMIX

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1

Clinical Immunology 209 (2019) 108293

Contents lists available at ScienceDirect

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

Review Article

Immunoglobulin A deficiency in children, an undervalued clinical issue

M.H. (Mischa) Koenen[a,**], L.M. (Joris) van Montfrans[a], E.A.M. (Elisabeth) Sanders[a,b], D. (Debby) Bogaert[a,c], L.M. (Lilly) Verhagen[a,*]

[a] Department of Pediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, Lundlaan 6, 3508 AB Utrecht, the Netherlands
[b] Centre for Infectious Disease Control (Cib), National Institute of Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, 3720 BA Bilthoven, the Netherlands
[c] Center for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Little France Crescent 47, EH16 4TJ Edinburgh, United Kingdom

2

Hindawi Publishing Corporation
Clinical and Developmental Immunology
Volume 2008, Article ID 624850, 10 pages
doi:10.1155/2008/624850

Review Article

Pediatric Selective IgM Immunodeficiency

Marc F. Goldstein,[1] Alex L. Goldstein,[2] Eliot H. Dunsky,[1] Donald J. Dvorin,[1] George A. Belecanech,[1] and Kfir Shamir[3]

4

Published in final edited form as:
Curr Top Microbiol Immunol. 2011 ; 350: 39–65. doi:10.1007/82_2010_96.

The role of IL-10 in regulating immunity to persistent viral infections

Elizabeth B. Wilson and **David G. Brooks**
Department of Microbiology, Immunology and Molecular Genetics and the UCLA AIDS Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California 90095

3

0031-3998/01/5001-0008
PEDIATRIC RESEARCH

Vol. 50, No. 1, [illegible]
Printed in U.S.A.

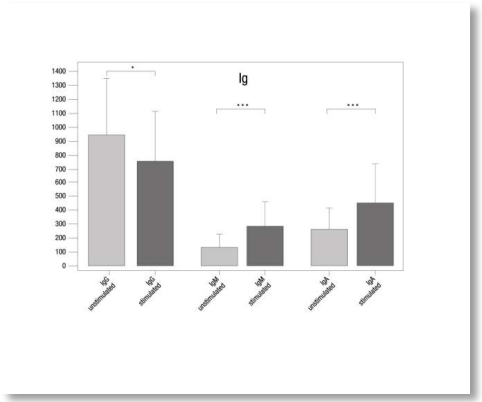
REVIEW ARTICLE

Impaired Interferon Gamma-Mediated Immunity and Susceptibility to Mycobacterial Infection in Childhood

NATASCHA REMUS, JANINE REICHENBACH, CAPUCINE PICARD, CHRISTOPH RIETSCHEL, PHILIP WOOD, DAVID LAMMAS, DINAKANTHA S. KUMARARATNE, AND JEAN-LAURENT CASANOVA

guna.it

CITOMIX in pediatric immune disorders



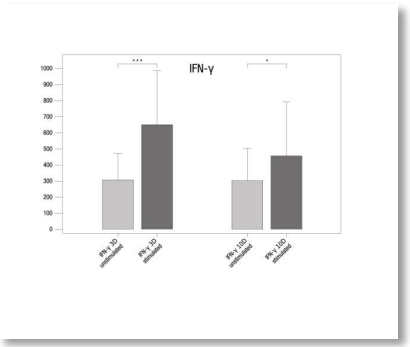
IMPROVES IgA AND IgM EXPRESSION

Non genetic transient IgA and IgM production defects

- *RECURRENT ACUTE BACTERIAL INFECTIONS*
- *ALLERGIC MANIFESTATIONS*

1 2

IMPROVES IFN-γ EXPRESSION

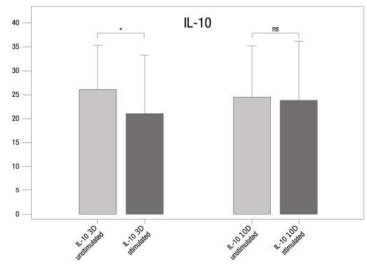


IFN-γ production defects

VIRAL INFECTIONS

3

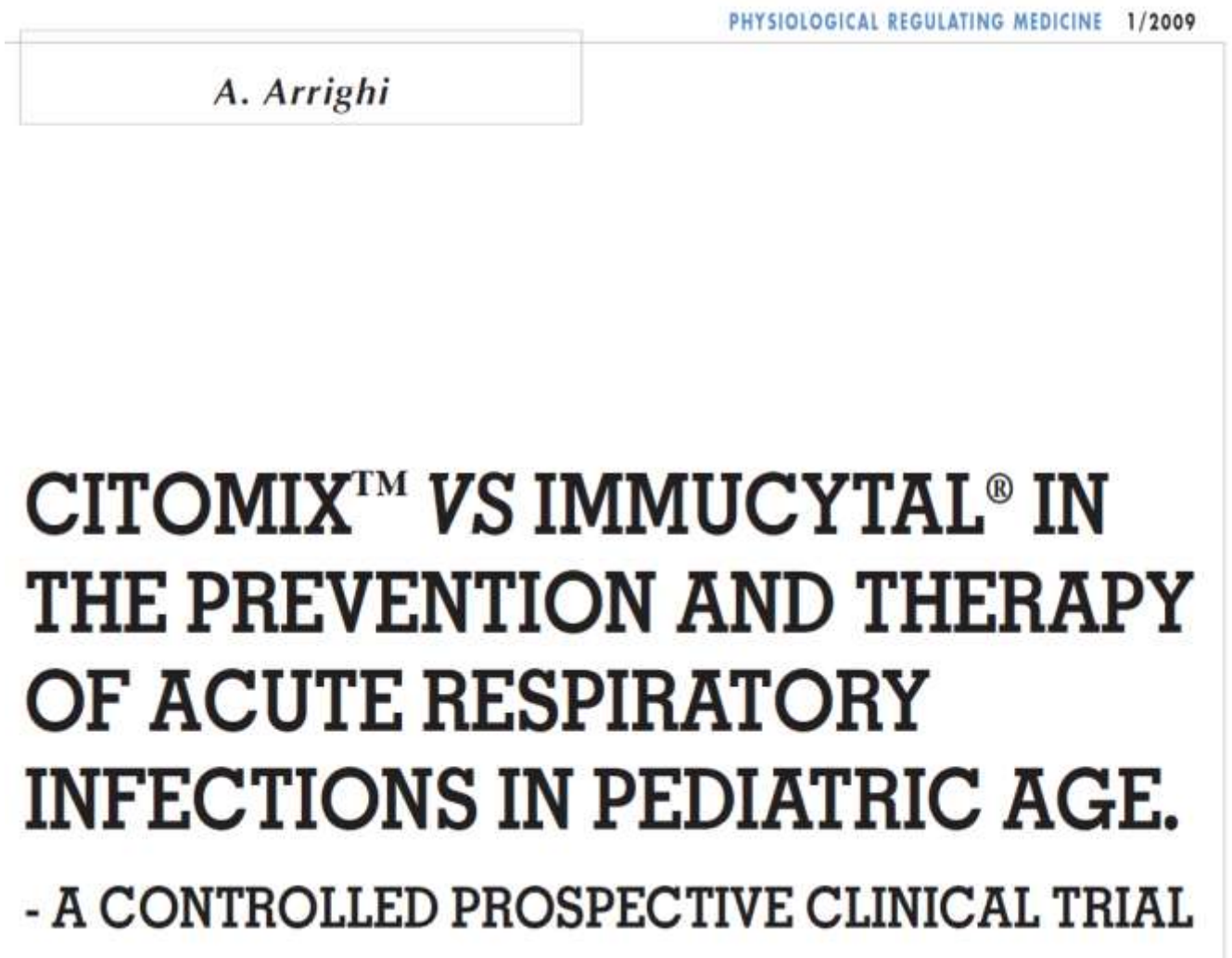
REDUCES EARLY IL-10 EXPRESSION



hIL-10 overexpression

VIRAL RE-INFECTIONS AND CHRONIC VIRAL INFECTIONS

4



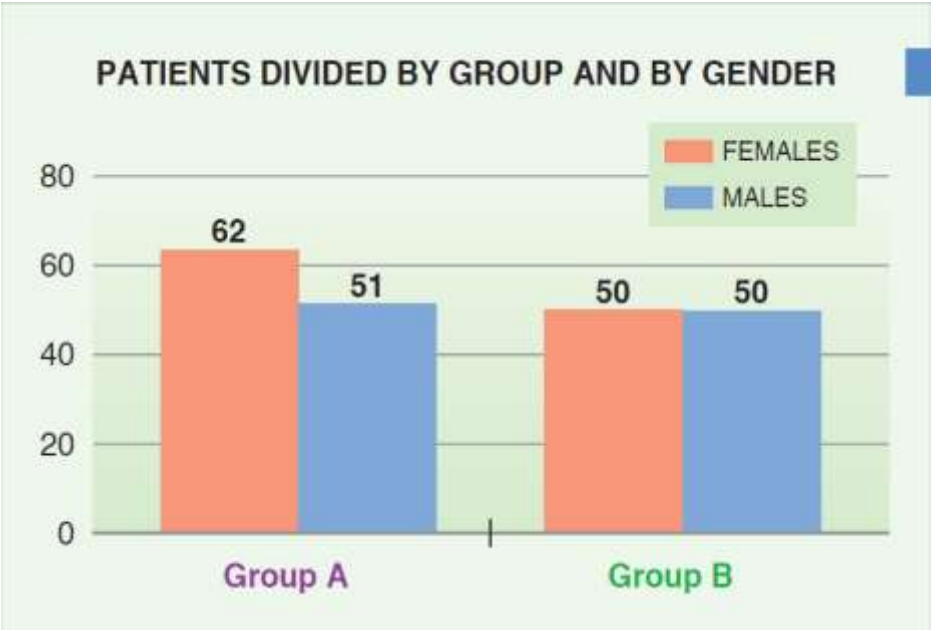
- Positive Delta on URTI episodes
- Positive Delta on days of fever
- Positive Delta on minor use of antibiotics
- Positive Delta on days of absence from school
- Positive Delta on IgA parameter

A. Arrighi

CITOMIX™ *VS* IMMUCYTAL® IN THE PREVENTION AND THERAPY OF ACUTE RESPIRATORY INFECTIONS IN PEDIATRIC AGE.

- A CONTROLLED PROSPECTIVE CLINICAL TRIAL

PATIENTS DIVIDED BY TYPE OF TREATMENT	
Type of treatment	**No. of patients**
Group A CITOMIX	**113** (51 M, 62 F)
Group B BACTYERIAL LYSATES	**100** (50 M, 50 F)



RESULTS

TAB.6		Total		Group A		Group B	
		Mean	SEM	Mean	SEM	Mean	SEM
Total	N° ARTI episodes	2,79	,06	2,37	,06	3,26	,09
F	N° ARTI episodes	2,72	,09	2,37	,09	3,16	,13
M	N° ARTI episodes	2,86	,09	2,37	,09	3,36	,13

ARTI: Acute Respiratory Tract Infections

Δ

0.89

TAB.7 DAYS OF FEVER

Δ=3.58

		Total		Group A		Group B	
		Mean	SEM	Mean	SEM	Mean	SEM
Total	Days of fever	6,64	,22	4,96	,16	8,54	,35
F	Days of fever	6,39	,26	4,97	,20	8,16	,42
M	Days of fever	6,92	,36	4,96	,24	8,92	,56

TAB.8 CYCLES OF ANTIBIOTICS

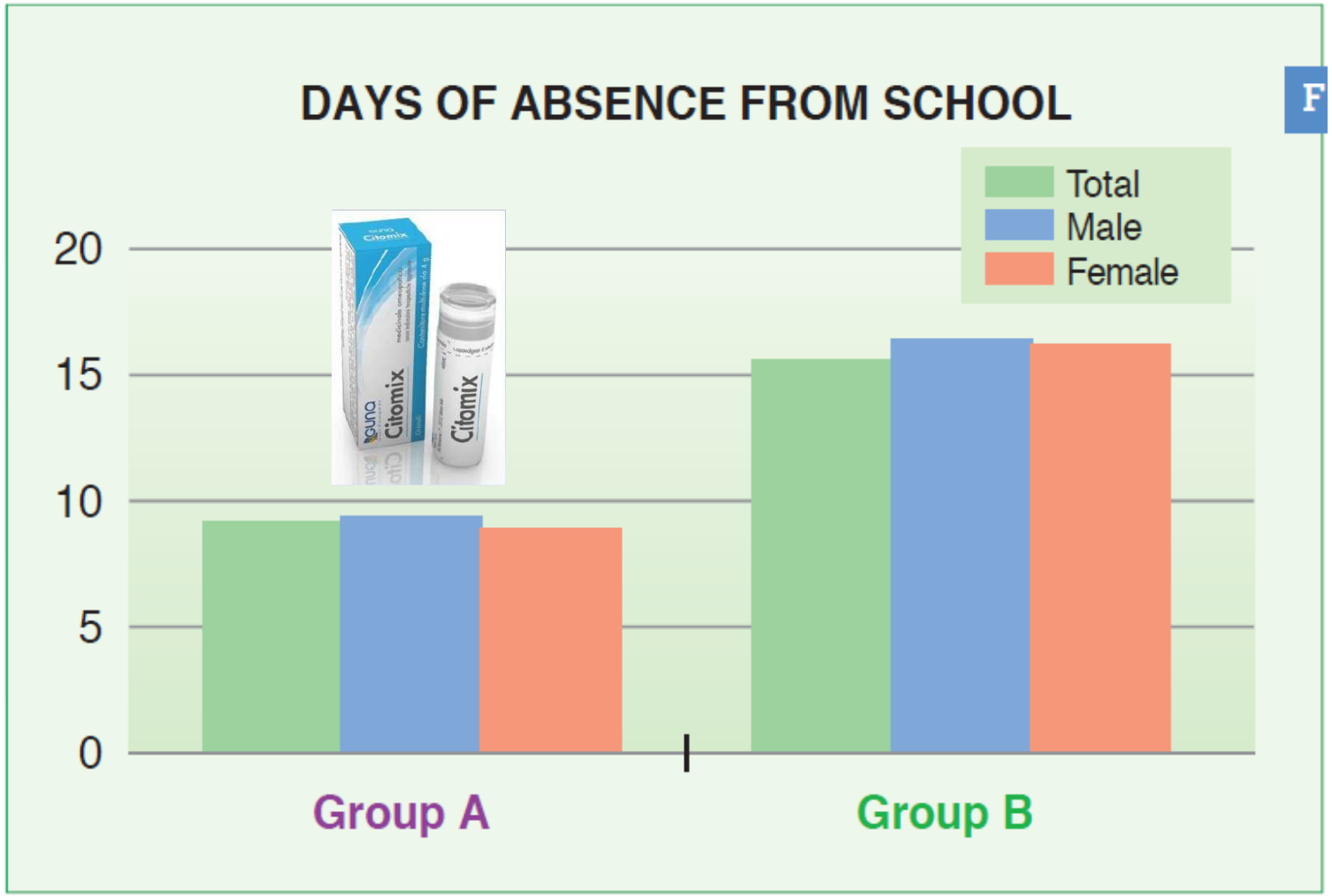
Δ=1.04

		Total		Group A		Group B	
		Mean	SEM	Mean	SEM	Mean	SEM
Total	Cycles of antibiotics	,88	,06	,39	,05	1,43	,09
F	Cycles of antibiotics	,82	,09	,37	,07	1,38	,13
M	Cycles of antibiotics	,94	,09	,41	,08	1,48	,13

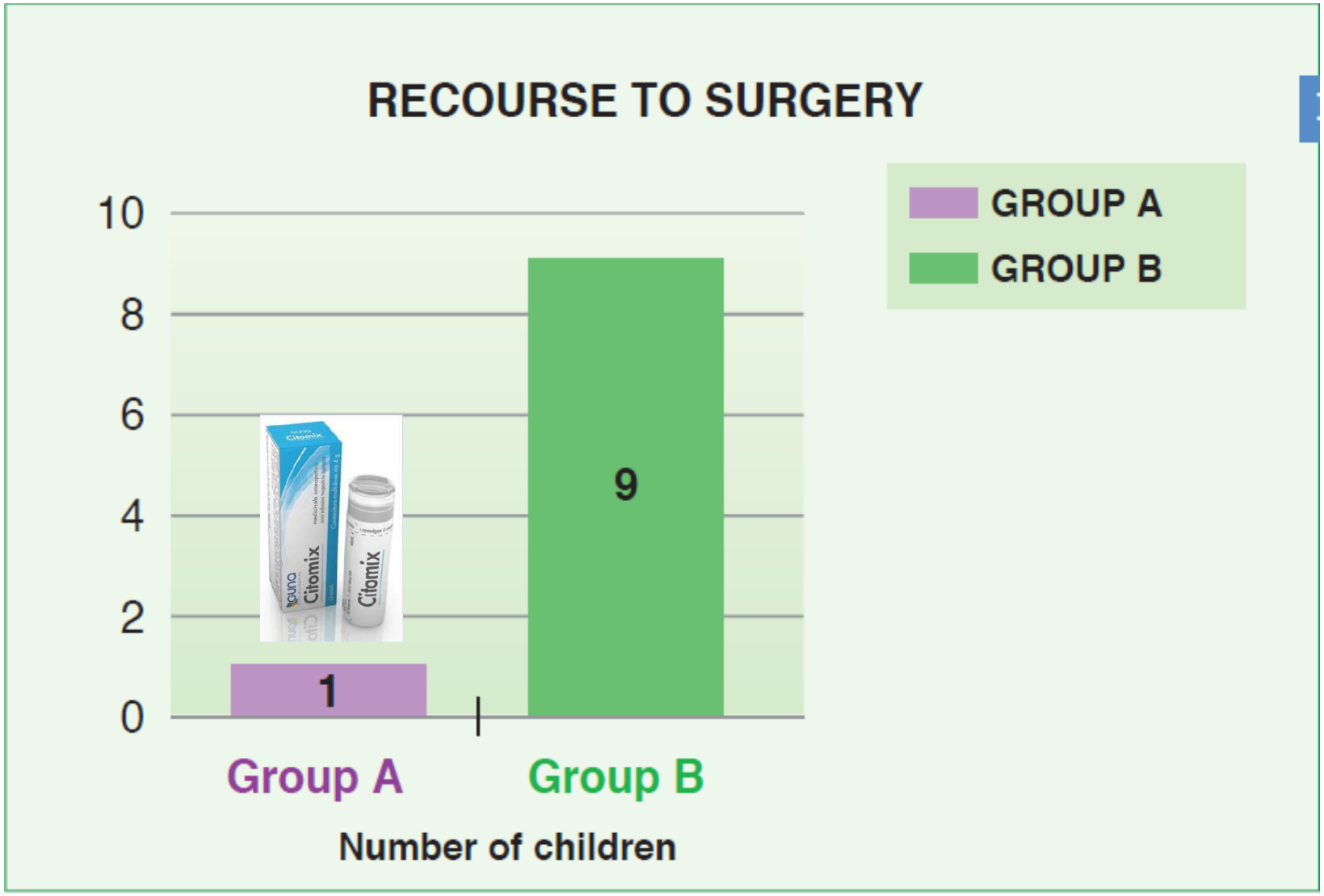
TAB.13

IGA CHANGES AFTER 4 MONTHS OF TREATMENT: percentage differences

		Total		Group A		Group B	
		Mean	SEM	Mean	SEM	Mean	SEM
Total	**difference %**	21,24	,88	25,17	1,51	16,80	,45
F	**difference %**	22,88	1,56	28,40	2,56	16,03	,74
M	**difference %**	19,42	,61	21,25	1,04	17,56	,51


DAYS OF ABSENCE FROM SCHOOL
Total
Male
Female
20
15
10
5
0
Group A
Group B
Citomix
Citomix

Δ=5.49

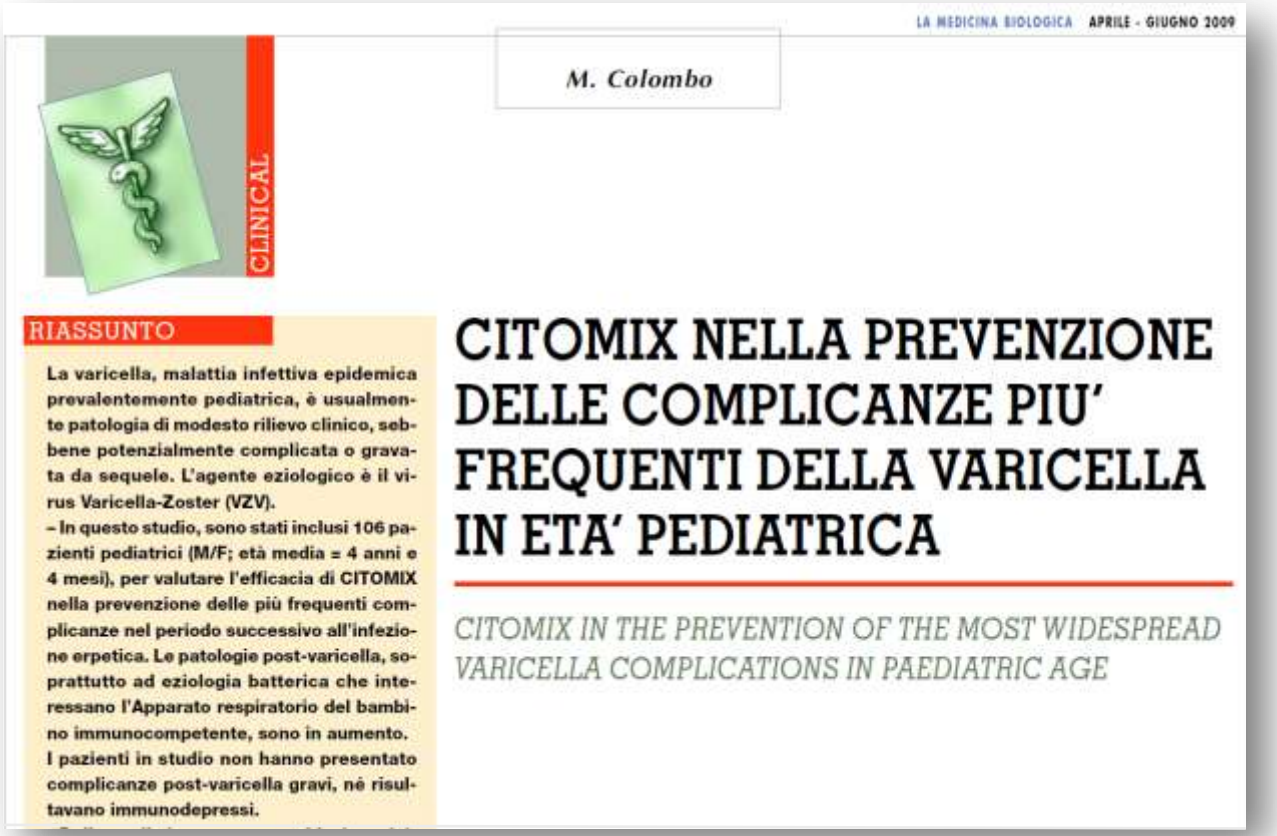

RECOURSE TO SURGERY
10
8
6
4
2
0
GROUP A
GROUP B
9
1
Group A
Group B
Number of children

Δ=8.00

DIRECTIONS (URTI – RRI)

- **<u>Prevention:</u>** 5 granules a day, every day, for 3 consecutive months.

- **<u>Treatment of acute symptomatology:</u>** 10 granules 2-3 times a day for 2-3 days.



LA MEDICINA BIOLOGICA APRILE - GIUGNO 2009

M. Colombo

CLINICAL

RIASSUNTO

La varicella, malattia infettiva epidemica prevalentemente pediatrica, è usualmente patologia di modesto rilievo clinico, sebbene potenzialmente complicata o gravata da sequele. L'agente eziologico è il virus Varicella-Zoster (VZV).
– In questo studio, sono stati inclusi 106 pazienti pediatrici (M/F; età media = 4 anni e 4 mesi), per valutare l'efficacia di CITOMIX nella prevenzione delle più frequenti complicanze nel periodo successivo all'infezione erpetica. Le patologie post-varicella, soprattutto ad eziologia batterica che interessano l'Apparato respiratorio del bambino immunocompetente, sono in aumento.
I pazienti in studio non hanno presentato complicanze post-varicella gravi, né risultavano immunodepressi.

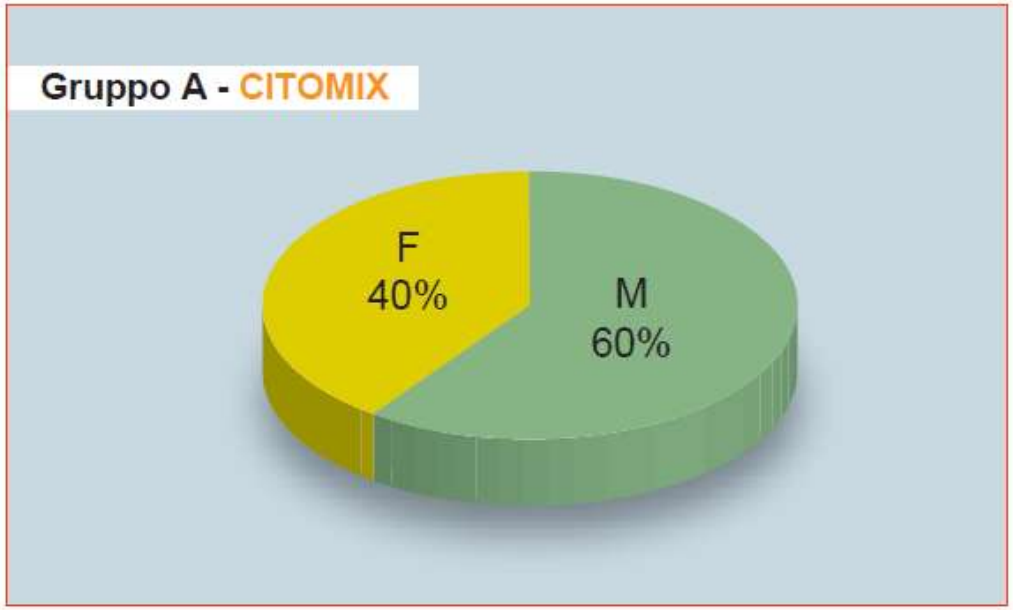
CITOMIX NELLA PREVENZIONE DELLE COMPLICANZE PIU' FREQUENTI DELLA VARICELLA IN ETA' PEDIATRICA

CITOMIX IN THE PREVENTION OF THE MOST WIDESPREAD VARICELLA COMPLICATIONS IN PAEDIATRIC AGE

- Reduction of respiratory complications in the following 30 days after the blister phase
- Reduction of respiratory symptoms in the following 30 days after the blister phase

53 patients

- 32 boys (8 months-10 years and 7 months)
- 21 girls (2 years and 6 months- 9 years and 1 month)

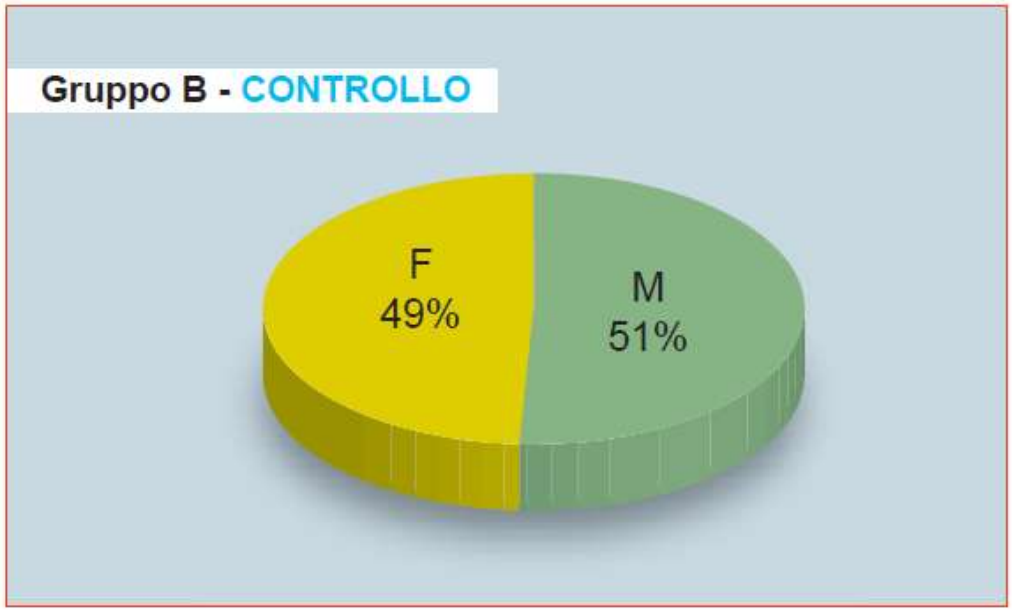


TAB. 3

Suddivisione percentuale secondo il sesso dei pz. inclusi nel Gruppo A.

TAB. 4

Suddivisione percentuale secondo il sesso dei pz. inclusi nel Gruppo B.

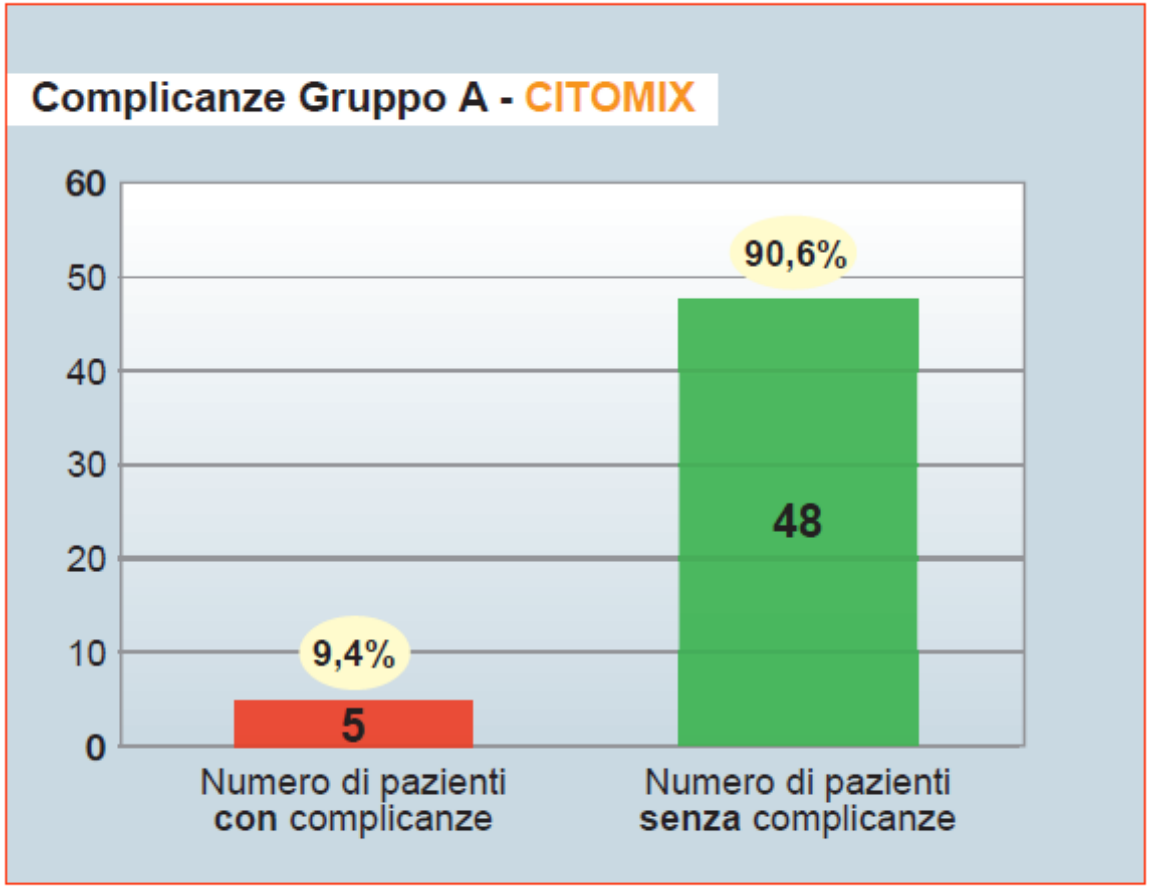


53 patients

- 27 boys (1 year and 2 months – 10 years and 2 months)
- 26 girls (1 year and a 9 years)

Presence of respiratory symptomatology in the 30 days after the scab phase:

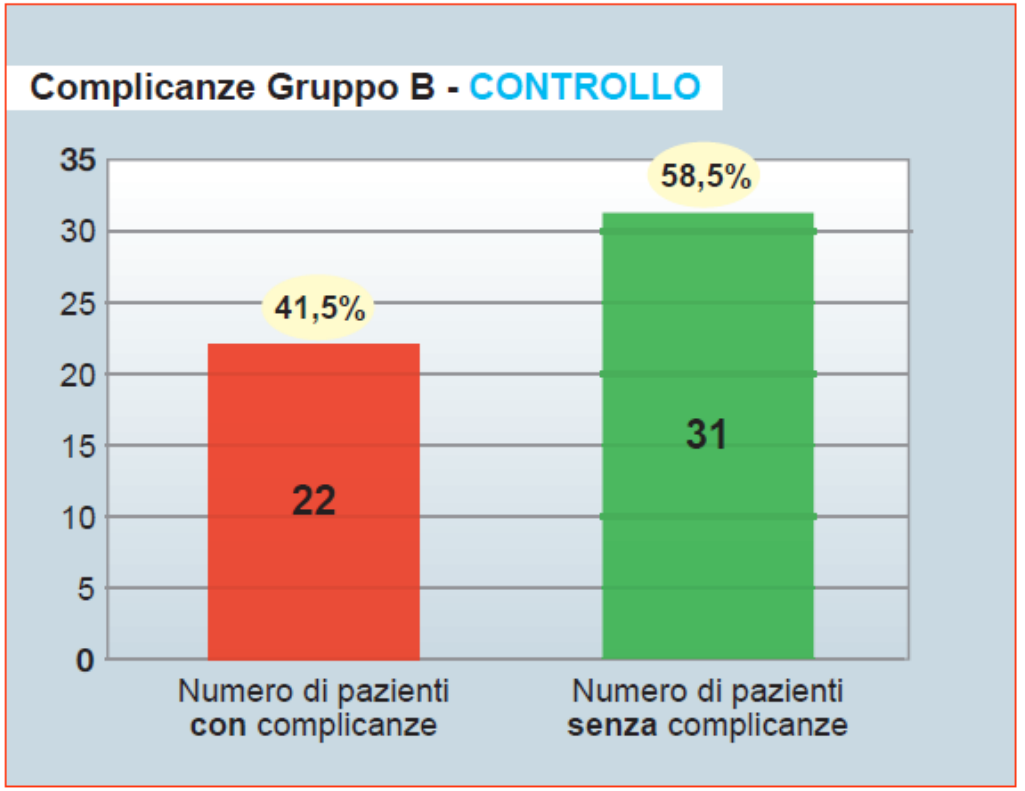
9.4%



Dettaglio delle complicanze nel Gruppo A - CITOMIX	
Otite media acuta	2
Infezione da Streptococco beta-emolitico di Gruppo A	1
Bronchite	2
Totale	**5**

Presence of respiratory symptomatology in the 30 days after the scab phase:

41.5%



Dettaglio delle complicanze nel Gruppo B - CONTROLLO	
Otite media acuta	5
Infezione da Streptococco beta-emolitico di Gruppo A	1
Bronchite	7
Tracheite	2
Laringite	1
Tonsillite	1
Adenoidite	1
Bronchite asmatiforme	1
Otite media acuta + Bronchite	3
Totale	**22**

DIRECTIONS (CHICKEN POX COMPLICATIONS)

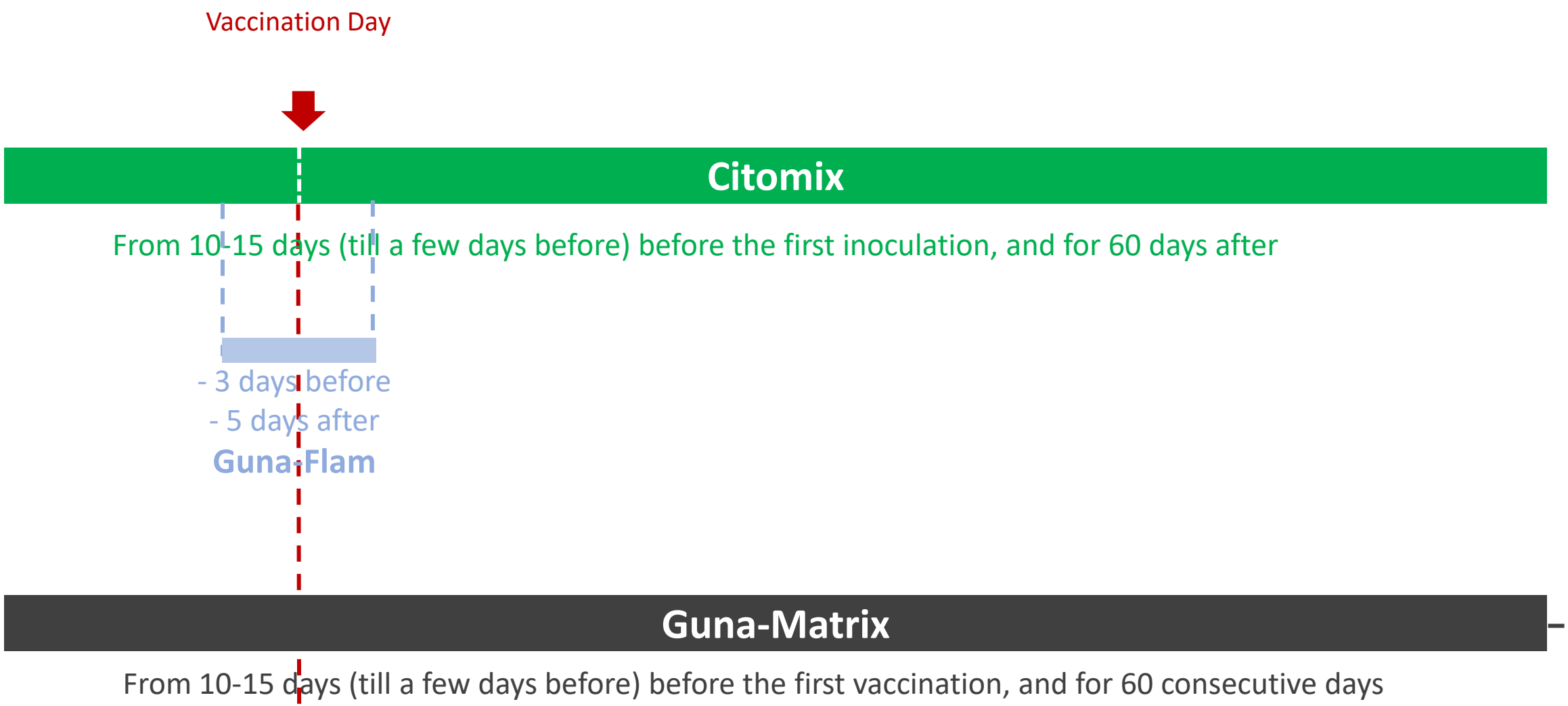
- **<u>Under 3 years of age:</u> 3** granules twice a day, for 30 consecutive days from the scab phase.

- **<u>Over 3 years of age:</u> 5** granules twice a day, for 30 consecutive days from the scab phase.

Operation OVERLAPPING

LDM Therapy as an adjuvant support to all vaccines

SPATIO-TEMPORAL algorithm of admnistration of LDM in overlapping with vaccines



SPATIO-TEMPORAL algorithm of admnistration of LDM in overlapping with vaccines

Directions

Citomix
5 pellets per day from 10-15 days (till a few days before) before the first inoculation and for 60 days after

Guna-Matrix
20 drops twice a day from 10-15 days (till a few days before) before the first vaccination and continuing for 60 consecutive days

Guna-Lympho
20 drops twice a day from the day of the first vaccination and for 60 consecutive days after

Guna-Flam
- 3 days before the first and second inoculation: 20 drops twice a day

- 5 days after the first and second inoculation: 20 drops 4 times a day

guna.it

CITOMIX CONSENSUS
DELPHI PROJECT

Delphi Consensus Survey
su **CITOMIX** nella prevenzione e nel trattamento precoce
delle infezioni respiratorie ricorrenti in età pediatrica.

L'*European Review for Medical and Pharmacological Sciences* is indexed on: Current Contents, EMBASE, Index Medicus, MEDLINE, Science Citation Index e Scopus. The **impact factor** is **3,507**

A low-dose multicomponent medication as a new approach in prevention and early add-on treatment of recurrent respiratory infections in children: a Delphi Consensus

M. AGOSTI[1], A. ARRIGHI[2], S. BERNASCONI[3], G. BONA[4], G. CIPRANDI[5], S. LEONARDI[6], G.L. MARSEGLIA[7,8]

[1]Pediatric Department, Hospital 'F. Del Ponte', University of Insubria, Varese, Italy
[2]Pediatric Primary Care, ASL 8, Arezzo, Italy
[3]Secretary of the "Complementary Medicines and Integrated Therapies" Study Group of the Italian Pediatric Society (SIP), Parma, Italy
[4]Department of Health Sciences, University of Piemonte Orientale, Novara, Italy
[5]Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy
[6]Pediatric Respiratory Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[7]Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[8]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy

Table 1 Panel definition of RRIs

The criteria for defining a child with Recurrent Respiratory Infections (RRIs) in paediatric age [a,b] are:

- **1–3 years[c]:**

➢ 6 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or

➢ 2 mild cases[d] of pneumonia confirmed by clinical criteria and/or x-ray in a year

- **3–6 years[c]:**

➢ 5 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or

➢ 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year

- **6–12 years:**

➢ 3 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or

➢ 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year

[a] Children with recurrent infections in one area only (e.g., recurrent rhinosinusitis, recurrent otitis media, recurrent wheezing or recurrent pharyngotonsillitis), with known primary or secondary immunodeficiencies (including IgA deficiency), cystic fibrosis and/or CFTR-pathies, primary ciliary dyskinesia, non-cystic fibrosis-related bronchiectasis, genetic disorders, known cardio-respiratory malformations, neuromuscular disorders and other pre-existing chronic lung diseases were excluded from this definition

[b] This definition does not apply to children under 1 year of age

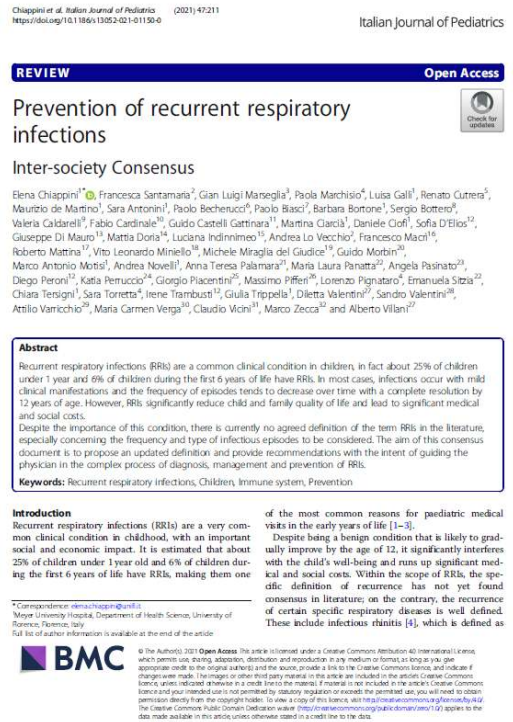
[c] **1–3 years** = from 1 year to 2 years and 11 months; **3–6 years** = from 3 years to 5 years and 11 months; **6–12 years** = from 6 years to 11 years and 11 months

[d] In accordance with the definition of the *British Thoracic Society*, partially modified

PREVALENCE URTI

- 25% of children under 1 year
- 6% of children during firts 6 months of life

de Martino et al. 2007; Fiore et al. 2010; Toivonen et al. 2016; De Benedictis et al. 2018).



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Italian Journal of Pediatrics

REVIEW Open Access

Prevention of recurrent respiratory infections

Inter-society Consensus

Elena Chiappini[1*], Francesca Santamaria[2], Gian Luigi Marseglia[3], Paola Marchisio[4], Luisa Galli[1], Renato Cutrera[5], Maurizio de Martino[1], Sara Antonini[1], Paolo Becherucci[6], Paolo Biasci[7], Barbara Bortone[1], Sergio Bottero[8], Valeria Caldarelli[9], Fabio Cardinale[10], Guido Castelli Gattinara[11], Martina Ciarcià[1], Daniele Ciofi[1], Sofia D'Elios[12], Giuseppe Di Mauro[13], Mattia Doria[14], Luciana Indinnimeo[15], Andrea Lo Vecchio[2], Francesco Macrì[16], Roberto Mattina[17], Vito Leonardo Miniello[18], Michele Miraglia del Giudice[19], Guido Morbin[20], Marco Antonio Motisi[1], Andrea Novelli[1], Anna Teresa Palamara[21], Maria Laura Panatta[22], Angela Pasinato[23], Diego Peroni[12], Katia Perruccio[24], Giorgio Piacentini[25], Massimo Pifferi[26], Lorenzo Pignataro[4], Emanuela Sitzia[22], Chiara Tersigni[1], Sara Torretta[4], Irene Trambusti[12], Giulia Trippella[1], Diletta Valentini[27], Sandro Valentini[28], Attilio Varricchio[29], Maria Carmen Verga[30], Claudio Vicini[31], Marco Zecca[32] and Alberto Villani[27]

Abstract

Recurrent respiratory infections (RRIs) are a common clinical condition in children, in fact about 25% of children under 1 year and 6% of children during the first 6 years of life have RRIs. In most cases, infections occur with mild clinical manifestations and the frequency of episodes tends to decrease over time with a complete resolution by 12 years of age. However, RRIs significantly reduce child and family quality of life and lead to significant medical and social costs.

Despite the importance of this condition, there is currently no agreed definition of the term RRIs in the literature, especially concerning the frequency and type of infectious episodes to be considered. The aim of this consensus document is to propose an updated definition and provide recommendations with the intent of guiding the physician in the complex process of diagnosis, management and prevention of RRIs.

Keywords: Recurrent respiratory infections, Children, Immune system, Prevention

Introduction

Recurrent respiratory infections (RRIs) are a very common clinical condition in childhood, with an important social and economic impact. It is estimated that about 25% of children under 1 year old and 6% of children during the first 6 years of life have RRIs, making them one of the most common reasons for paediatric medical visits in the early years of life [1–3].

Despite being a benign condition that is likely to gradually improve by the age of 12, it significantly interferes with the child's well-being and runs up significant medical and social costs. Within the scope of RRIs, the specific definition of recurrence has not yet found consensus in literature; on the contrary, the recurrence of certain specific respiratory diseases is well defined. These include infectious rhinitis [4], which is defined as

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Introduction

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Table 2 Recommendations

Synthetic Molecules	**The evidence available to date does not allow recommendation of the routine use of synthetic molecules for the prevention of RRIs (weak negative recommendation).** **Pidotimod has demonstrated a consistent likelihood of efficacy and can be recommended in selected populations of children, always considering the cost-benefit ratio (weak positive recommendation).**
Probiotics, Prebiotics, Symbiotics, Postbiotics	In the absence of proof of efficacy, the use of oral probiotic formulations should not be recommended for the prevention of RRIs (**weak negative recommendation**). Given the scarcity of supporting evidence, the use of nasal spray formulations containing *Streptococcus salivarius* 24SMB should not be recommended for the prevention of RRIs (**weak negative recommendation**). In the absence of proof of efficacy and safety, the use of prebiotics and symbiotics should not be recommended for the prevention of RRIs (**weak negative recommendation**). In the absence of proof of efficacy and safety, the use of postbiotics should not be recommended for the prevention of RRIs (**weak negative recommendation**).
Lysates and bacterial extracts	The evidence available to date does not allow recommendation of the routine use of bacterial lysates for the prevention of RRIs (**weak negative recommendation**). Among the lysates, OM-85 has demonstrated a consistent likelihood of efficacy and can be recommended in selected populations of children, always considering the cost-benefit ratio (**weak positive recommendation**).
Vitamins and trace elements	Due to the lack of studies conducted, the heterogeneity of the populations studied, the diversity of dosages, formulations and duration of treatments, zinc and other trace elements should not be used in the prophylaxis of RRIs **(weak negative recommendation).** There is no evidence that low levels of vitamin A and vitamin E create a predisposition to respiratory infections in children. There is more evidence that reduced levels of vitamin D are associated with an increased incidence of respiratory infections, particularly viral infections, in the first years of life. The heterogeneity of the populations studied, and the diversity of the outcomes considered mean that it is not possible to recommend the use of vitamin D in the prevention of RRIs. In populations with low socioeconomic status and clearly insufficient levels of vitamin D, and in patients with recurrent acute otitis, there may be a greater likelihood of efficacy in the prevention of RRIs (**weak negative recommendation**). Due to the lack of studies conducted, the heterogeneity and small size of the study populations, and the diversity of dosages and duration of treatment, routine vitamin C supplementation should not be used in the prevention of RRIs (**strong negative recommendation**).
Complementary/alternative medicines	The studies currently available on the efficacy of homoeopathy, natural substances and phytotherapy, do not allow recommendations on the use of these products in the prevention of RRIs at this time. This is due, in some cases, to the small number of studies, and, in others, to methodological shortcomings or the fact that they do not include patients of exclusively paediatric age.
Vaccinations	There is little evidence regarding the role of influenza and anti-pneumococcal vaccinations specifically for the prevention of RRIs. However, in view of the safety, efficacy and cost-benefit data on the use of these vaccinations, they are still recommended in paediatric age groups (**weak positive recommendation).**
Nasal therapies with hyaluronic acid, thermal waters and resveratrol	Based on the limited evidence on nasal therapies with hyaluronic acid, thermal waters and resveratrol for the prevention of RRIs currently available, it is not possible to make a recommendation, but their use is not discouraged.
Modification of risk factors	There is little literature on modifying risk factors for the prevention of RRIs, so the evidence currently available does not allow recommendation in this sense. However, limiting exposure to environmental and household pollutants is recommended and exposure to second-hand smoke is strongly discouraged.
Adeno/Tonsillectomy	Adeno/Tonsillectomy is not recommended for the reduction of RRIs (**strong negative recommendation**). Adeno/Tonsillectomy is not recommended for the reduction of the number of visits to the doctor for RRIs (**strong negative recommendation**). Adeno/Tonsillectomy is not recommended for the reduction of the number of days of illness (**strong negative recommendation**). As regards the impact of Adeno/Tonsillectomy in reducing the use of respiratory tract medications (including bronchodilators, mucolytics, antihistamines, steroids), no recommendation can be made.
Antibiotic prophylaxis	No studies are available on the efficacy of antibiotic prophylaxis in preventing RRIs, so no recommendations can be made. However, in view of the need to promote rational use of antibiotics in order to contain the selection of resistant bacterial strains, reduce costs and reduce adverse events, the panel suggests that antibiotic prophylaxis for the prevention of RRIs should be discouraged.

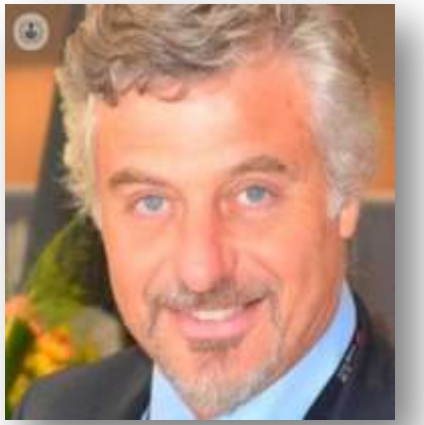
Scientific Board

Prof. Massimo Agosti - Dipartimento di Pediatria, Ospedale F. Del Ponte, Università dell'Insubria, Varese.

Prof. Gian Luigi Marseglia – Clinica Pediatrica, Fondazione IRCCS Policlinico San Matteo, Pavia. Dipartimento di Scienze Cliniche, Chirurgiche, Diagnostiche e Pediatriche, Università di Pavia.

Prof. Sergio Bernasconi - Segretario del gruppo di studio "Medicine Complementari e Terapie Integrate" della Società Italiana di Pediatria (SIP).

Prof. Gianni Bona - Dipartimento di Scienze della Salute, Università del Piemonte Orientale, Novara.



Prof. Salvatore Leonardi- Unità di Pneumologia Pediatrica, Dipartimento di Medicina Clinica e Sperimentale, Università di Catania.

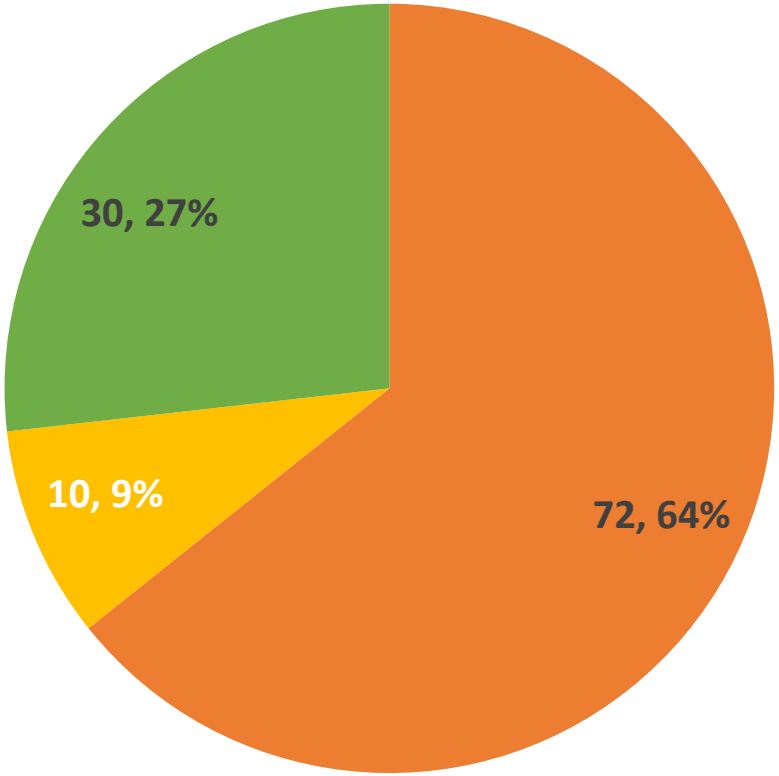
Dr. Antonello Arrighi – Pediatra di Base, ASL 8, Arezzo.

Prof. Giorgio Ciprandi - Clinica Allergologica, Casa di Cura Villa Montallegro, Genova.

The Panel – 112 Pediatricians

National Health System Pediatric Primary Care Pediatricians

Hospital or University Pediatricinas



Private Practice Pediatricians

The Statements

18 statements in total:

- 6 aboput RRIs definitions
- 12 about RRIs Treatment and Prophylaxis

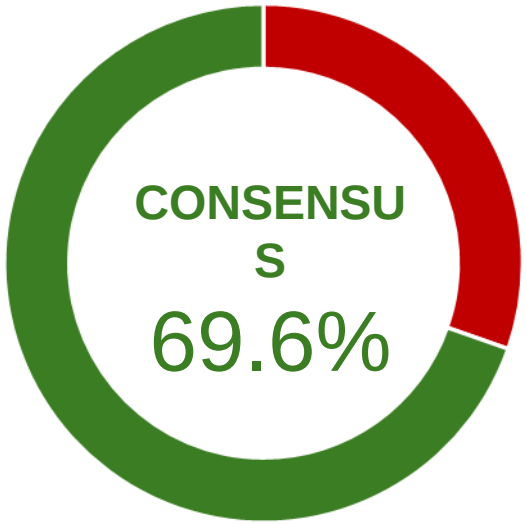
Citomix consensus - Rationale

- Upper Respiratory Tract Infections (URTI) are a common problem during childhood
- Social and economic impact is global
- For what it concerns the possible **preventive treatment of URTI, the Inter Italian Pediatric Societies Consensus stated that practically all proposed therapeutic solutions had weak or negative reccomandations.** Only a bacterial lysate (Poditimod) had weak positive reccomandations but in few selectyed casespostive.
- Many pediatricians normally use immunomodulants in their clinical practice in order **to offer a possible solution to the parents who need help for their children's helath problems.**

Low Dose Phramacology can reppresent a new possible solution

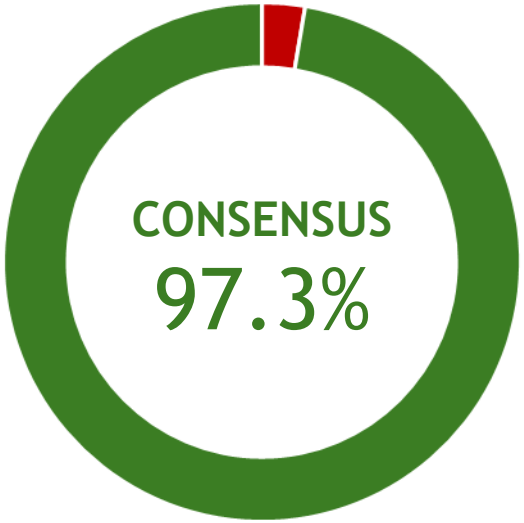
STATEMENT 9

A recent Inter-Society Consensus recognized as weakly effective the RRIs prophylaxis based on the use of: Biological Response Modifiers (BRMs), Probiotics, prebiotics, symbiotics, postbiotics, Lysates and bacterial extracts, Vitamins and trace elements, Vaccination against flu and pneumococcus, Nasal lavages with hyaluronic acid, thermal waters, resveratrol, Reduction of risk factors, Adeno/tonsillectomy, Antibiotic prophylaxis



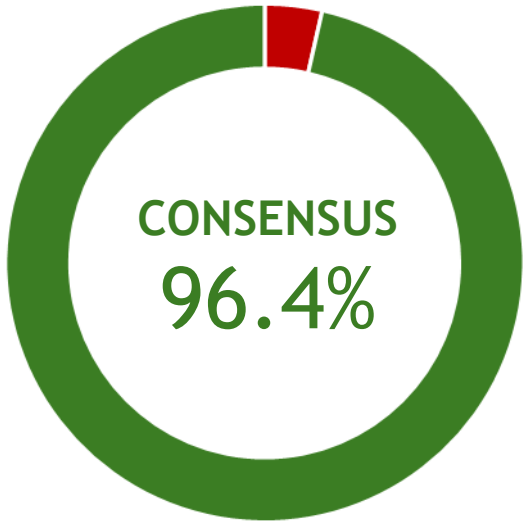
STATEMENT 10

Complementary or alternative immunomodulation interventions for RRIs prophylaxis might be instead an option.



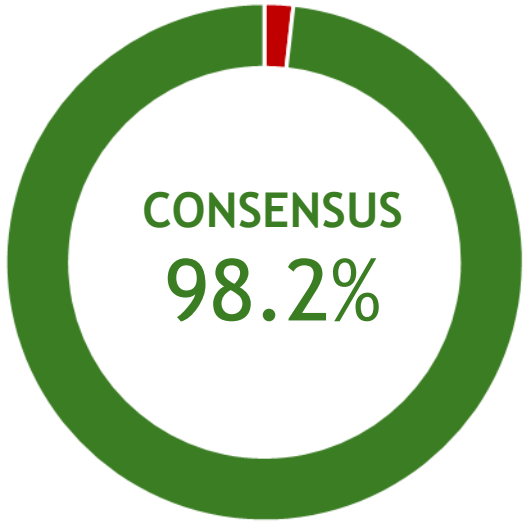
STATEMENT 11

Oral administration of cytokines has been shown to be effective in modulating the immune response.



STATEMENT 12

Citomix is a low-dose multicomponent product based on cytokines and components of natural origin that can **modulate the immune response** by acting on both innate and adaptive immunity.



STATEMENT 13

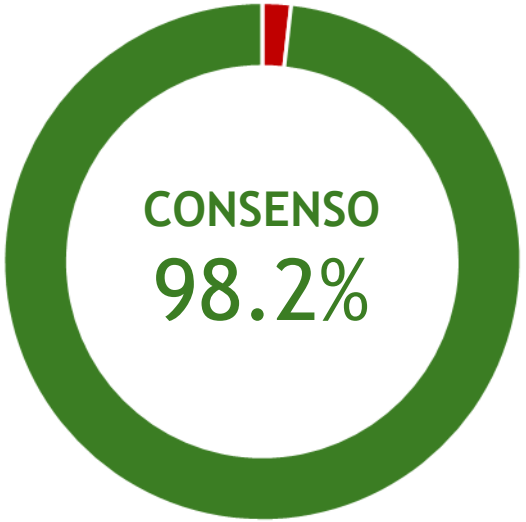
Citomix has a good safety and tolerability profile.

STATEMENT 14

Citomix could improve the early response to pathogens.

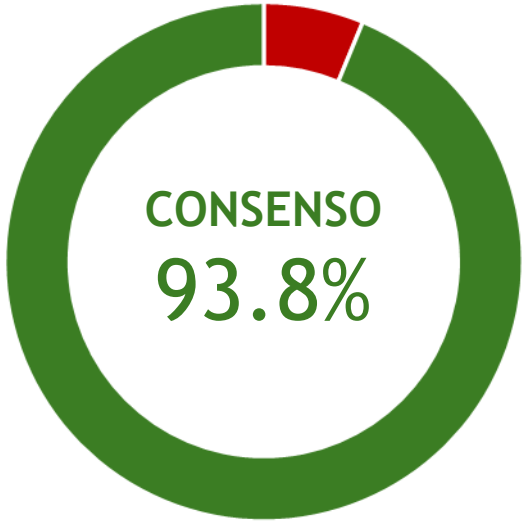
STATEMENT #15

Citomix could be considered in RRIs management.



STATEMENT #16

In RRIs prophylaxis, the recommended dosage of Citomix is 5 granules per day for 12 weeks.

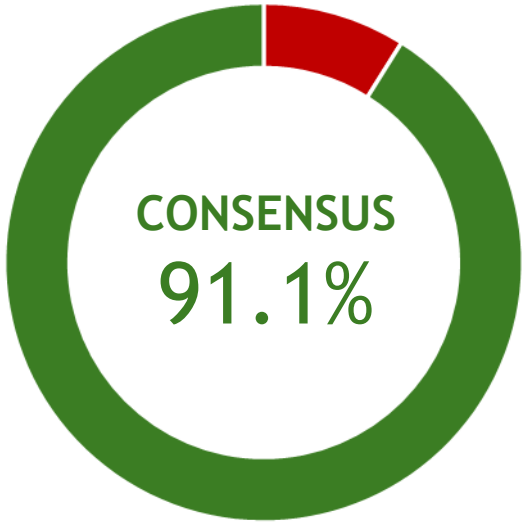


COMMENT FROM PROF. G. L. MARSEGLIA

«In immunology, the dosage is secondary; what matters is the continuity over time with which the stimulus is administered»

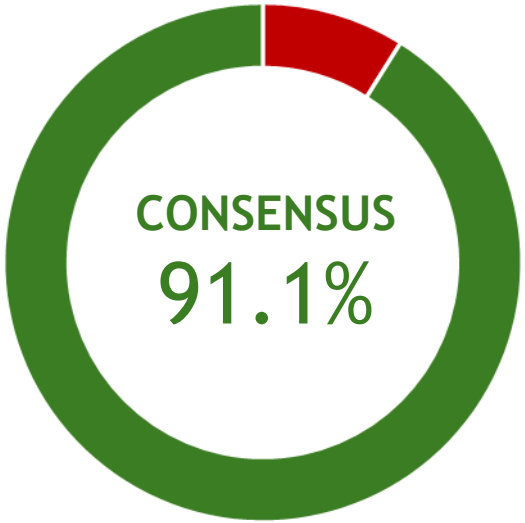
STATEMENT #17

Citomix could be added in the early treatment of acute RRIs



STATEMENT #18

In the early treatment of the acute episode of RRIs, the **recommended dosage of Citomix is 10 granules per day 2 times per day for 2-3 days, continuing with 5 granules 2 times per day for 5-7 days.**



PROF. S. BERNASCONI - PROF. G. L. MARSEGLIA

«The use of Citomix in the early phase is still little known with respect to prevention but should be encouraged and is supported by studies in order to highlight the medication's activity on both innate and acquired immunity.»

The present Delphi consensus collected the agreement grade expressed by a large panel of primary care, private practice, and hospital/university pediatricians who have developed robust experience using Citomix to manage children with RRIs. The high level of agreement could endorse the use of Citomix in clinical practice for prevention and early add-on treatment of RRIs. It is opportune to highlight that the opinions expressed by the panelists are derived both from their experience, acquired by daily practice and from the evidence derived from preclinical studies and an observational study. In conclusion, according to the present Delphi consensus, Citomix appears to be a valid opportunity for the prevention and early add-on treatment of RRIs. Nevertheless, there is a need to endorse these opinions by conducting further studies that should be performed according to robust evidence-based methodology.

Citomix may represent a valuable option for preventive therapy, acute event add-on treatment, and relapse prevention. The absence of side effects, good compliance, and the results obtained justify the large-scale use of the product as initially demonstrated by a clinical trial[48].

CITOMIX STUDIES

Take home

1) Modulation of the immune response
2) Slowing down of the virulence
3) Reduction of the symptomatology
4) Reduction in the antiobiotics use