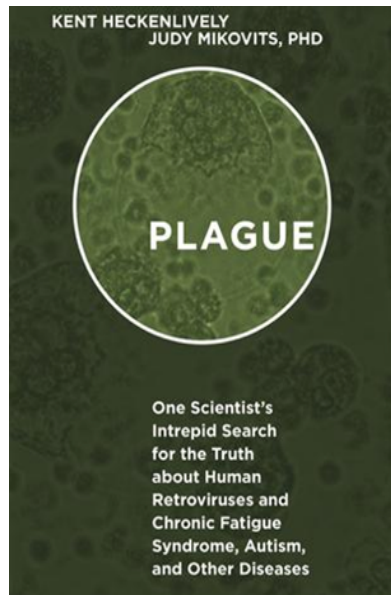
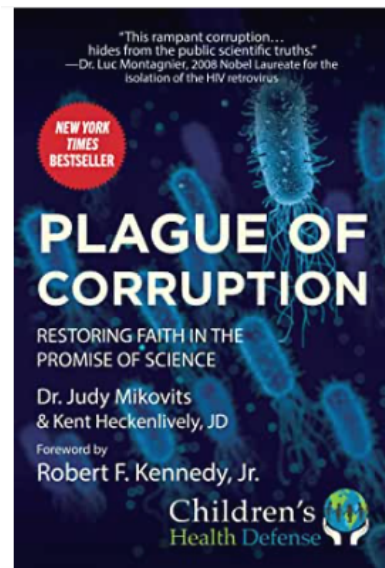
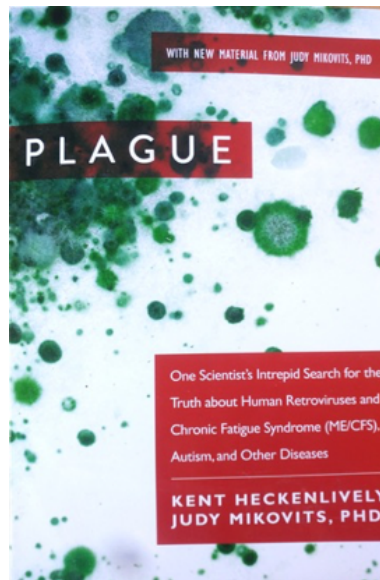


GOD'S People are destroyed from lack of Knowledge (Hosea 4:6)

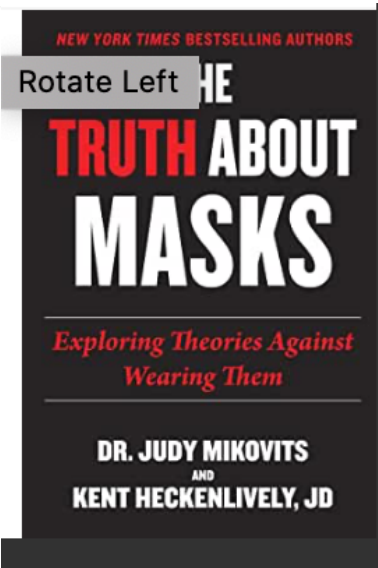
THE FEAR OF THE LORD is the Beginning of Knowledge but Fools Despise Wisdom & Instruction
(PROVERBS 1:7)



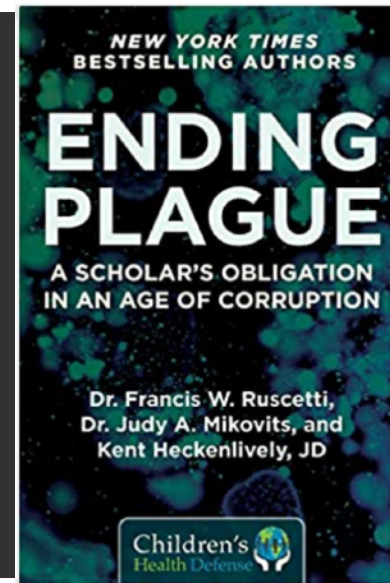
2014 (James 1:19-22) 2017



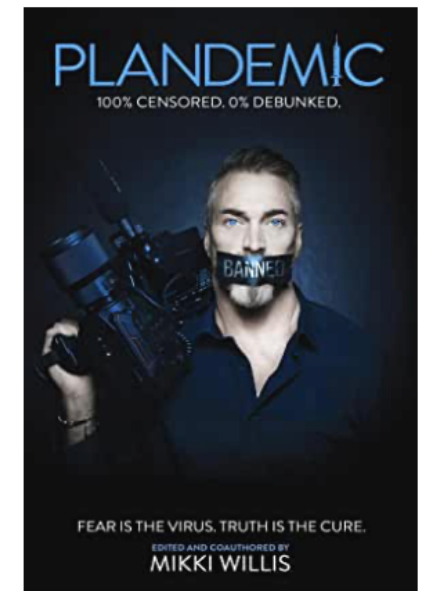
2020 (Psalm 91)



2020 1(Cor 3:18)



2021(Ephesians 5:11)

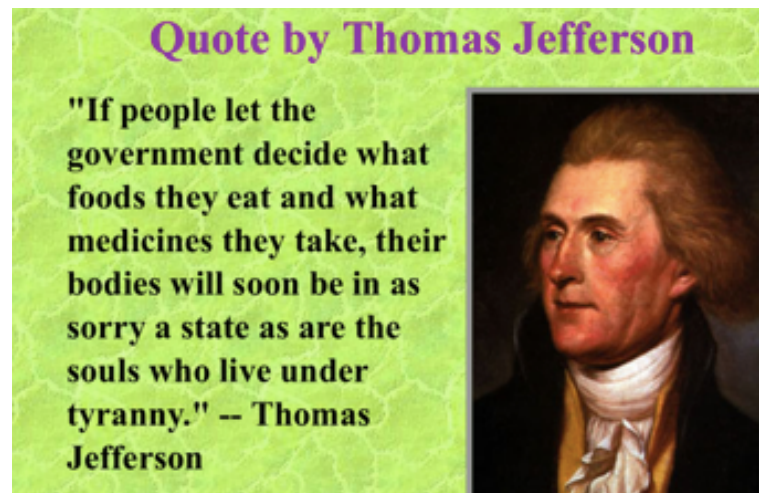


2021(2 Chronicles 7:14)

DrJudy@TheRealDrJudy.com

www.Plaguethebook.com

Shop.therealdrjudy.com



VACCINE AIDS = COVID19: Autoimmune, Autoinflammatory Disease & Cancer *Unintended* Consequences of 3
 DECADES LIABILITY FREE VACCINES

Prostate Cancer*	Crohn's Disease*	Gulf War Syndrome*
Breast Cancer *	Hashimoto's Thyroiditis*	Autism / ASD*
Multiple Myeloma*	Polymyositis*	Multiple Sclerosis*
Non-Hodgkins Lymphoma*	Sjogren's Syndrome *	Parkinson's*
Chronic Lymphocytic Leukemia*	Bechet's Disease*	ALS*
Mantle Cell Lymphoma*	Primary Biliary Cirrhosis*	Fibromyalgia*
Hairy Cell Leukemia*	Inflammatory Bowel Disease*	Chronic Lyme Disease*
Bladder Cancer *	Psoriasis, Dermatitis	OCD*
Colorectal Cancer*	Diabetes*	ADHD*
Kidney Cancer *	Cardiovascular Disease*	PTSD*
Ovarian Cancer*	ME / CFS*	Psychosis*
	Lupus/SLE*	Rheumatoid Arthritis*

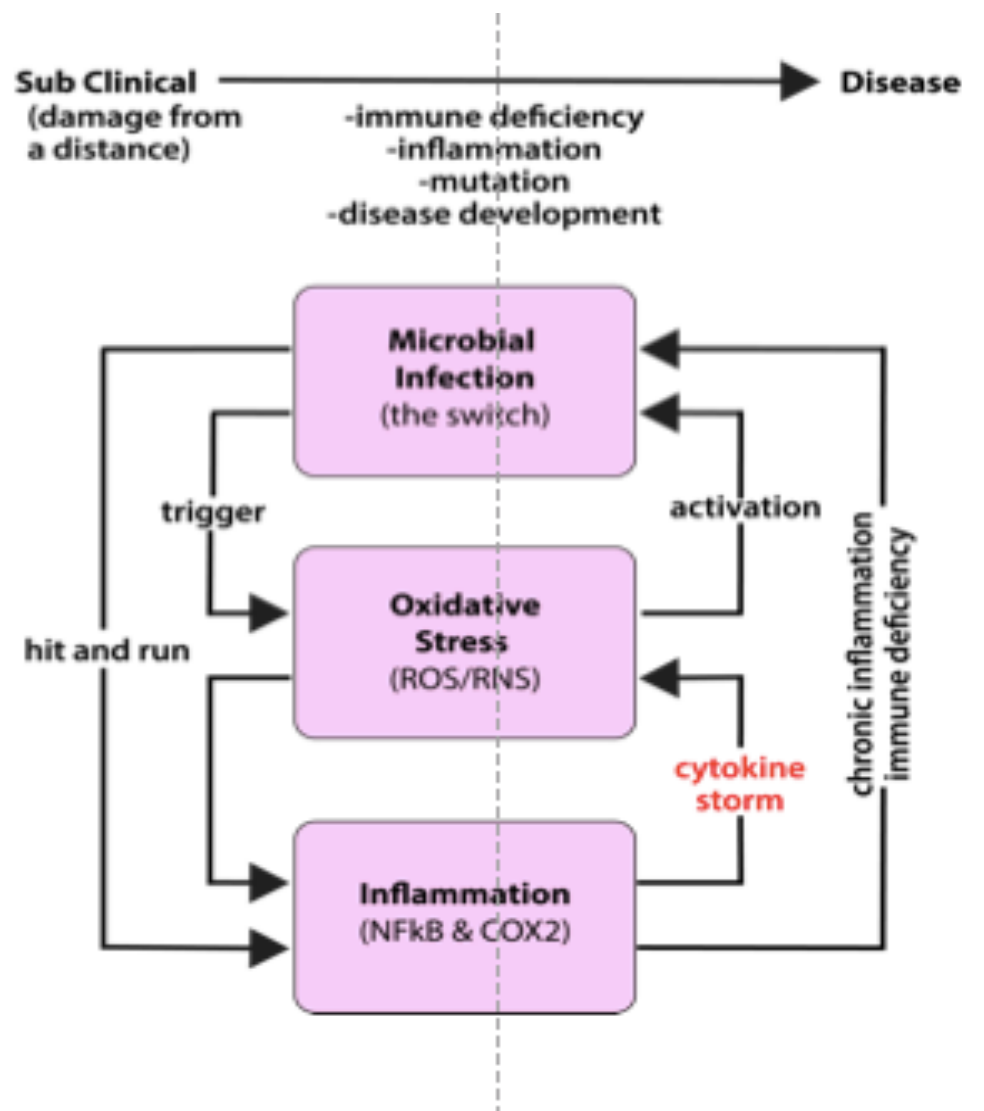
**Neuroendocrine Tumors*

**KEY to IMMUNITY is do not defile the TEMPLE of GOD
 NEVER GET ANOTHER VACCINE**

Effects of environmental change on zoonotic disease risk: an ecological primer

HAZARDS of GMOS: ALL Vaccines are GMO

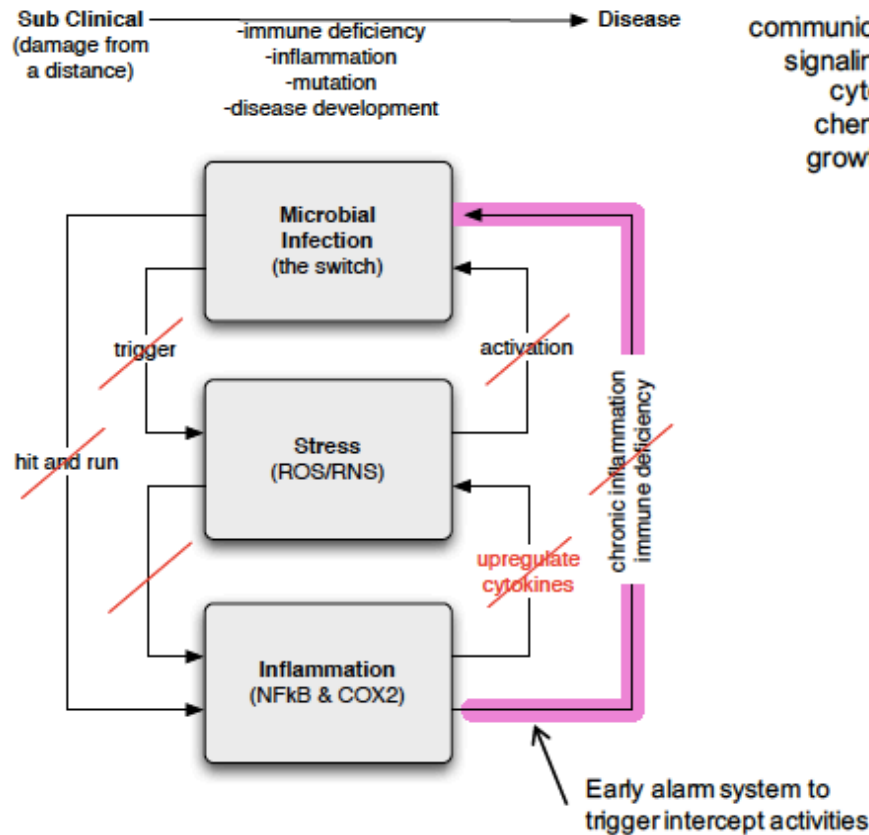
- | |
|--|
| <p>1. Uncontrollable, unpredictable impacts on safety due to the genetic modification process *</p> <ul style="list-style-type: none"> Scrambling the host genome * Widespread mutations * Inactivating genes * Activating genes * Creating new transcripts (RNAs) including those with regulatory functions * Creating new proteins * Creating new metabolites or increasing metabolite to toxic levels * Activating dormant viruses * Creating new viruses by recombination of viral genes in GM insert with those in the host genome * |
| <p>2. Toxicity of transgene protein(s) introduced (intentionally or otherwise)</p> <ul style="list-style-type: none"> Transgene protein toxic * Transgene protein allergenic or immunogenic * Transgenic protein becoming allergenic or immunogenic due to processing * Unintended protein created by sequence inserted may be toxic or immunogenic |
| <p>3. Effects due to the GM insert and its instability *</p> <ul style="list-style-type: none"> Genetic rearrangement with further unpredictable effects * Horizontal gene transfer and recombination * Spreading antibiotic and drug resistance * Creating new viruses and bacteria that cause diseases Creating mutations in genomes of cells to which the GM insert integrate including those associated with cancer * |
| <p>4. Toxicity of herbicides used with herbicide tolerant GM crops *</p> |



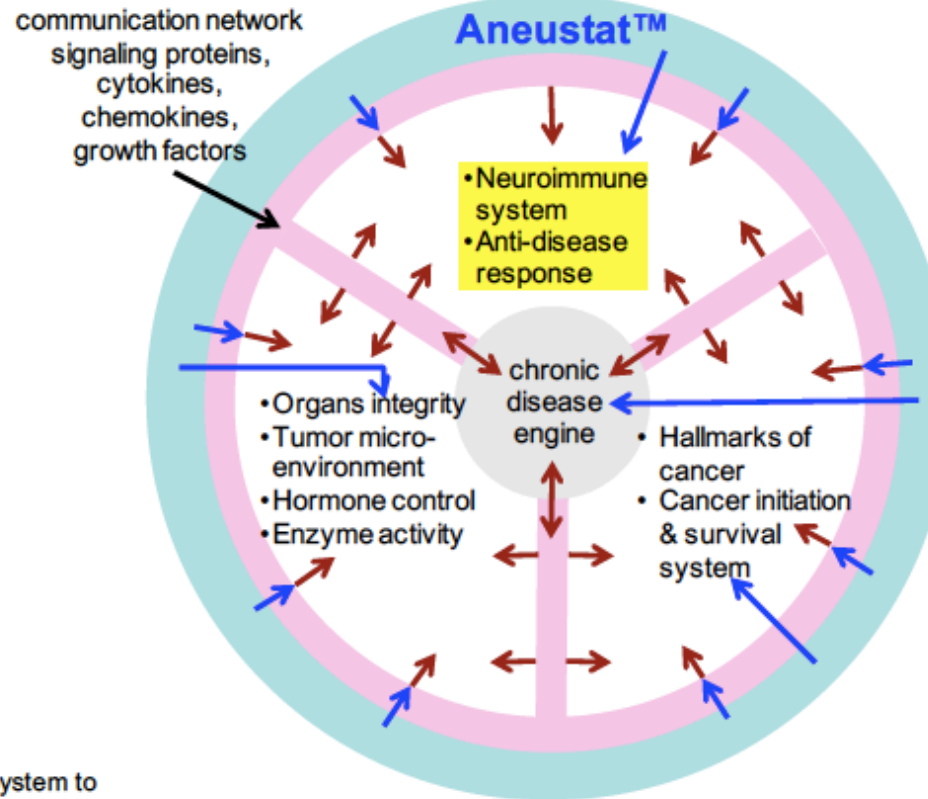
GMOS cause aberrant expression of animal retroviruses, end up in milk, food!

FOOD IS MEDICINE: 1/2 Day Education in Medical School Of God Given Solutions

Inhibiting The Chronic Disease Engine (the interplay of microbial infection, oxidative stress, and inflammation)



Directly and Indirectly Modulates Key Biology Systems And Their Communication to Intercept, Treat and Prevent Cancer Proliferation



Toxic GMO Foods:

- Fats/Oils
- Type 1 Interferons
- Mineral Depleted Soil
- PhytoCannabinoids
- GlyPhosate

Parental Methylomes protect Chromosomes

Beyond DNA: Programming and Inheritance of Parental Methylomes

Jamie A. Hackett^{1,2,3} and M. Azim Surani^{1,2,3,*}

¹Wellcome Trust/Cancer Research UK Gurdon Institute

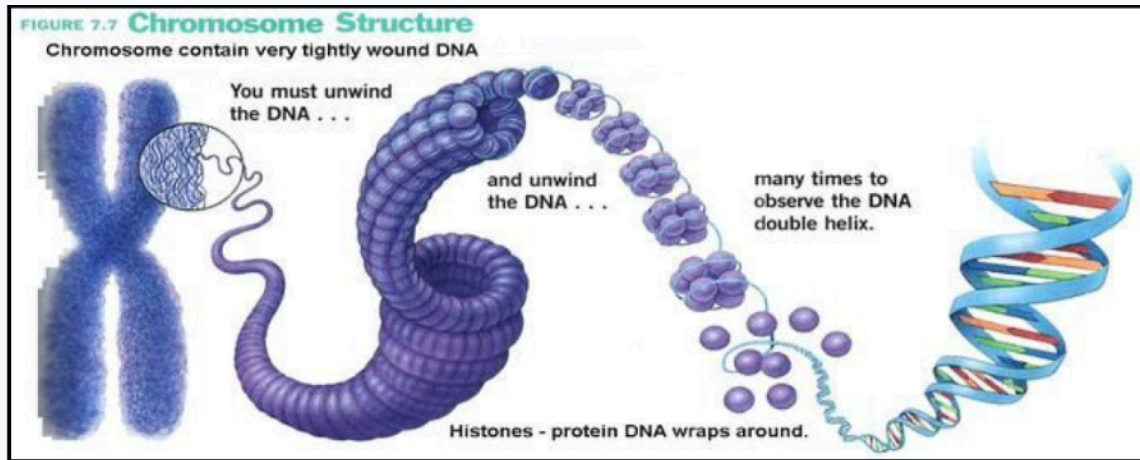
²Wellcome Trust/MRC Stem Cell Institute

³Department of Physiology, Development, and Neuroscience

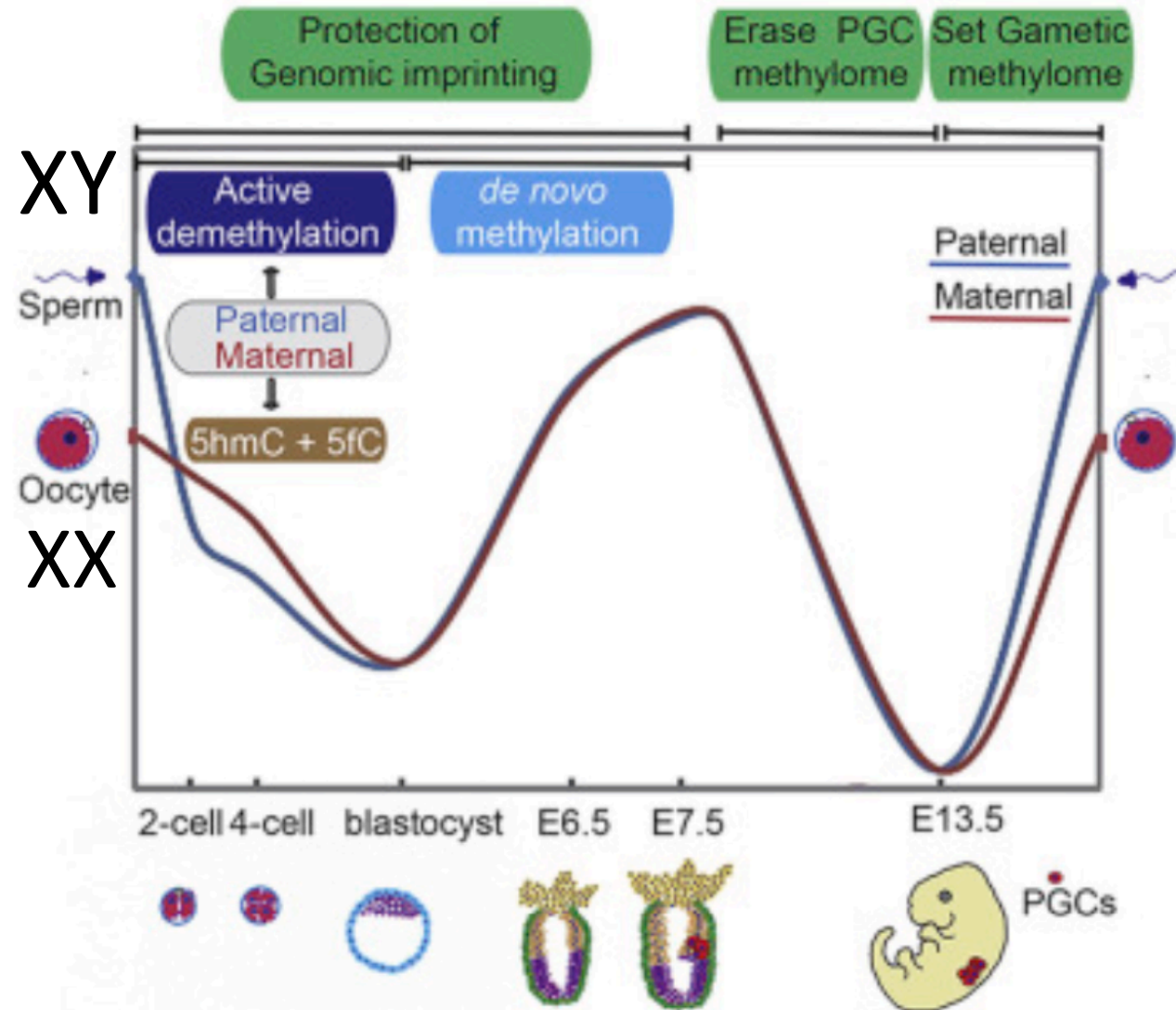
University of Cambridge, Cambridge CB2 1QN, UK

*Correspondence: a.surani@gurdon.cam.ac.uk

<http://dx.doi.org/10.1016/j.cell.2013.04.044>

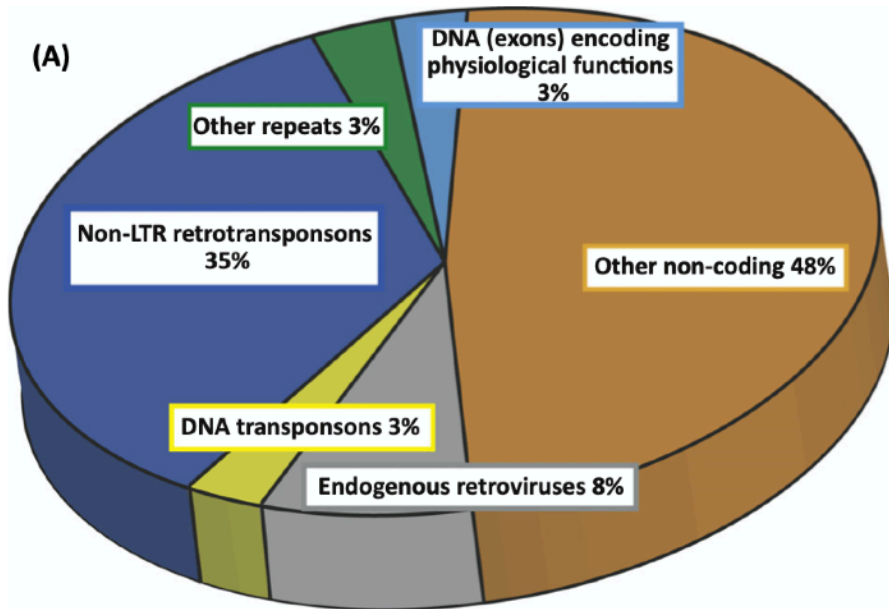


Sperm and oocytes are highly distinct and specialized cell types, yet together they generate the totipotent state following fertilization. Significantly, although they make an equivalent genetic contribution to the zygote, their epigenetic states are highly asymmetric due to their diverse origins and are therefore reset soon after fertilization



Human Endogenous (God GIVEN) VIROME: Protection against Viral Infections

Retroviruses, heavy metals, GMOs, and environmental toxins: Drivers of Accelerated Disease Evolution via altered balance between Endogenous (HERVS) and Exogenous Viruses

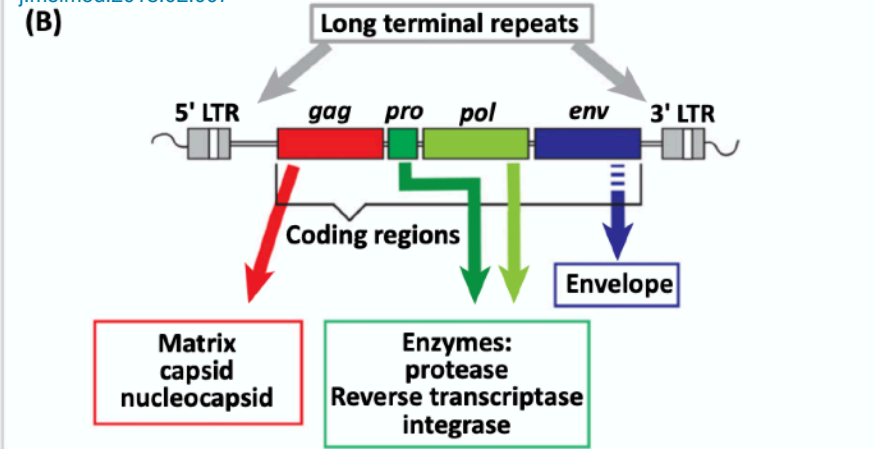


- 8% of our genome composed of sequences of viral origin
- stable elements at the interface between self and foreign DNA.

- HERV envelope Syncytin “Velcro” Fertilized embryo
- LTR participate in the transcriptional regulation of cellular genes

- HERV basal expression in healthy tissues
- HERV RNA, DNA, Proteins shape & expand the interferon network
- HERVs play a central role in the evolution and functioning of human innate immunity

Trends in Molecular Medicine, April 2018, Vol. 24, No. 4 <https://doi.org/10.1016/j.molmed.2018.02.007>





Dr Neu: Autoimmune antibodies From Mom Pass to Fetus: 4 Generations

Review

Do Transgenerational Epigenetic Inheritance and Immune System Development Share Common Epigenetic Processes?

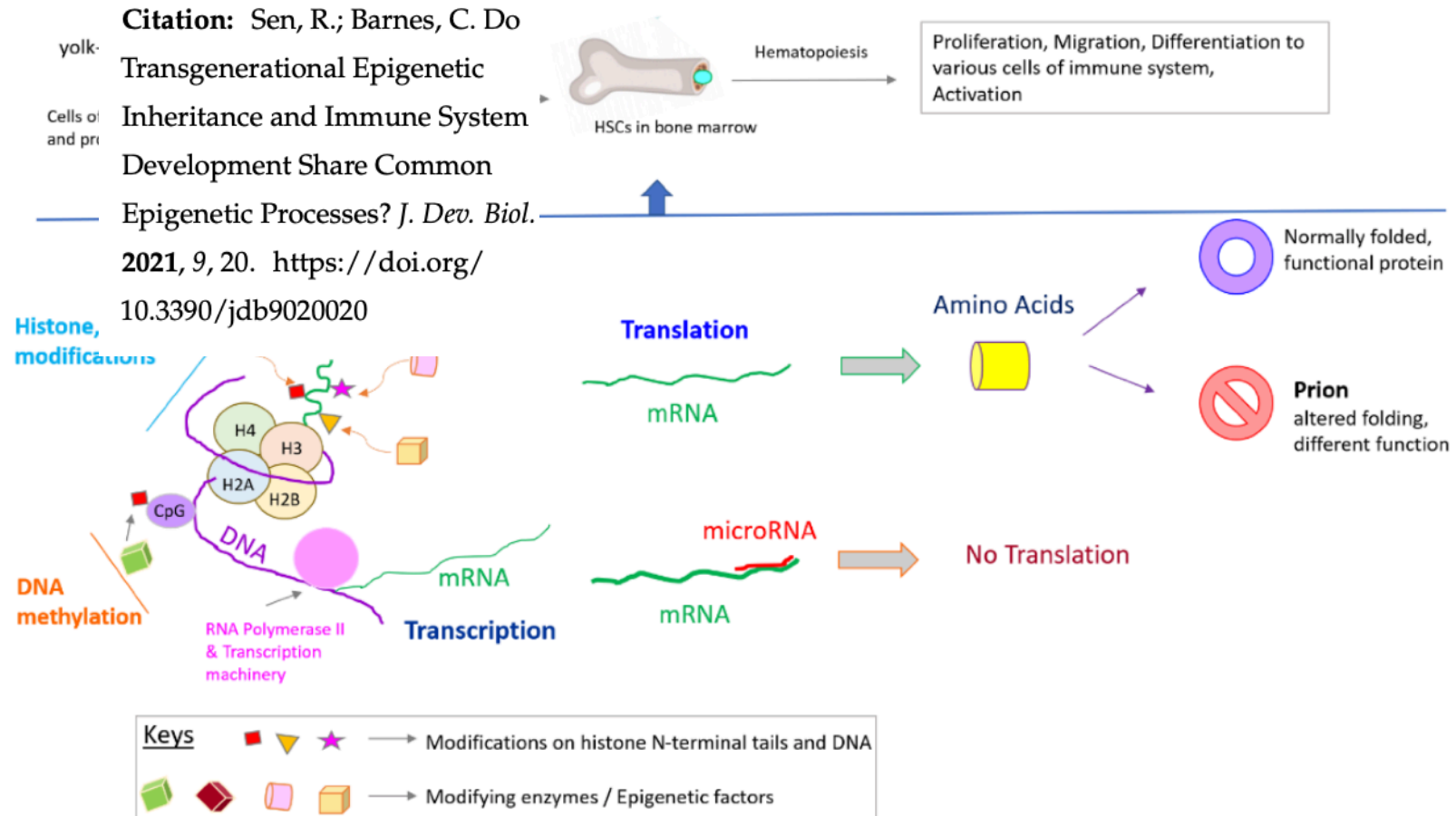
Rwik Sen * and Christopher Barnes

Citation: Sen, R.; Barnes, C. Do Transgenerational Epigenetic Inheritance and Immune System Development Share Common Epigenetic Processes? *J. Dev. Biol.* **2021**, *9*, 20. <https://doi.org/10.3390/jdb9020020>

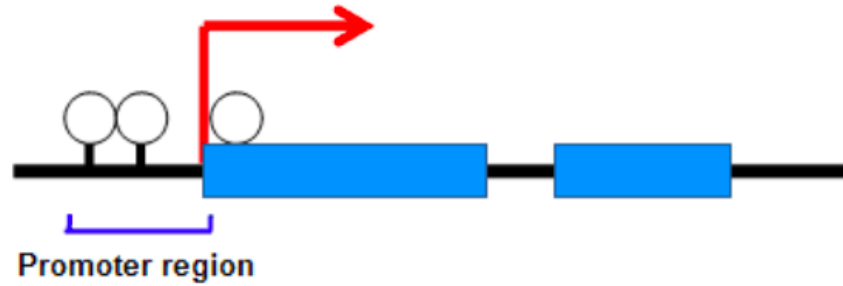
Received: 1 April 2021

Accepted: 6 May 2021

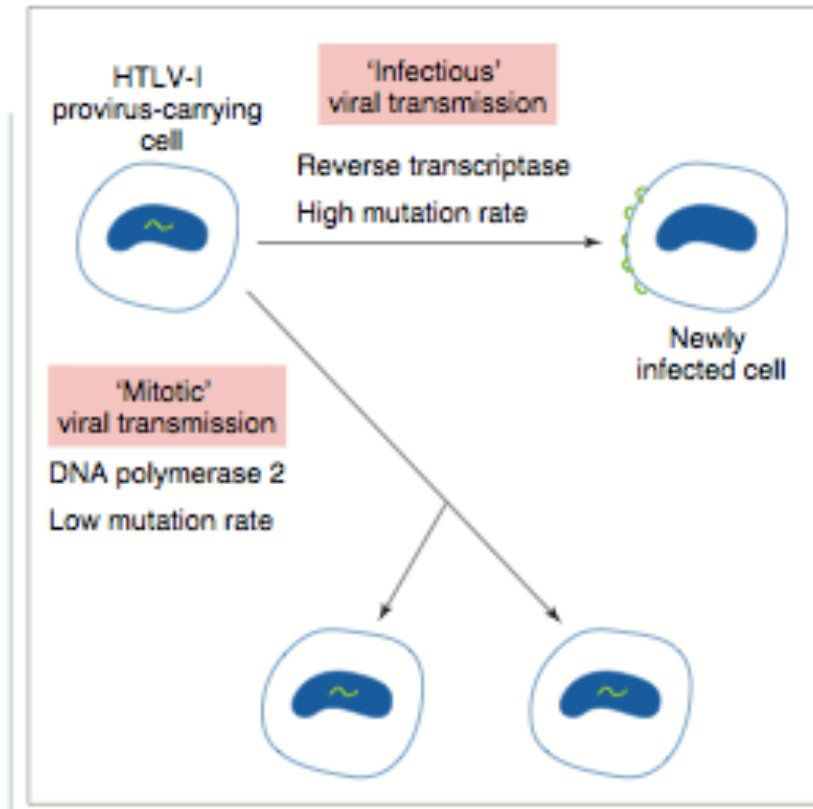
Published: 12 May 2021



Genes that can be expressed



Genes inactivated by DNA methylation



Molecular and Cellular Biology

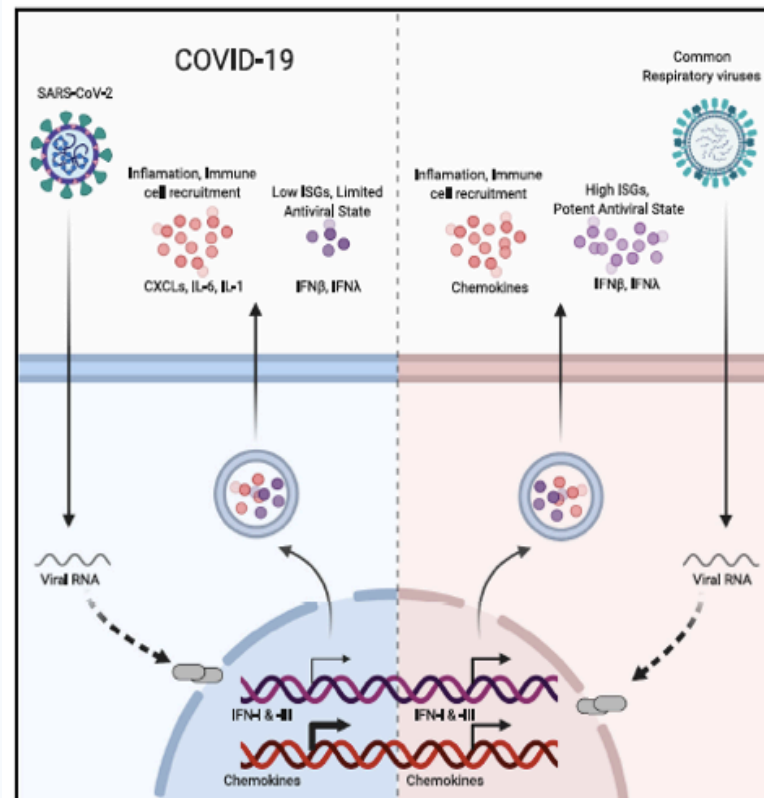
Infection with Human Immunodeficiency Virus Type 1 Upregulates DNA Methyltransferase, Resulting in De Novo Methylation of the Gamma Interferon (IFN- γ) Promoter and Subsequent Downregulation of IFN- γ Production

Judy A. Mikovits, Howard A. Young, Paula Vertino, Jean-Pierre J. Issa, Paula M. Pitha, Susan Turcoski-Corrales, Dennis D. Taub, Cari L. Petrow, Stephen B. Baylin and Francis W. Ruscetti
Mol. Cell. Biol. 1998, 18(9):5166.

Imbalanced IFN Response to RNA Viruses Drives Development of Autoimmune, Autoinflammatory Disease & Cancer



Graphical Abstract



Authors

Daniel Blanco-Melo,
Benjamin E. Nilsson-Payant,
Wen-Chun Liu, ..., Jean K. Lim,
Randy A. Albrecht, Benjamin R. tenOever

Correspondence

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jean.lim@mssm.edu (J.K.L.),
randy.albrecht@mssm.edu (R.A.A.),
benjamin.tenoever@mssm.edu (B.R.t.)

In Brief

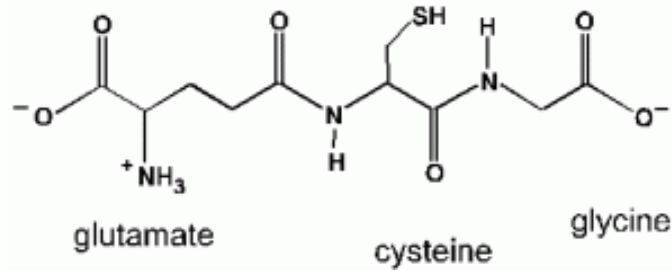
In comparison to other respiratory viruses, SARS-CoV-2 infection drives a lower antiviral transcriptional response that is marked by low IFN-I and IFN-III levels and elevated chemokine expression, which could explain the pro-inflammatory disease state associated with COVID-19.



Glyphosate: Damages Key GOD GIVEN antioxidant Glutathione

Produced by the liver, glutathione is made up of three amino acids: [Lcysteine](#), [glycine](#), and L-glutamate

glutathione (GSH)



[ACS Infect Dis.](#) 2020 May 28 : acsinfecdis.0c00288.

PMCID: PMC7263077

Published online 2020 May 28. doi: [10.1021/acsinfecdis.0c00288](#)

PMID: [32463221](#)

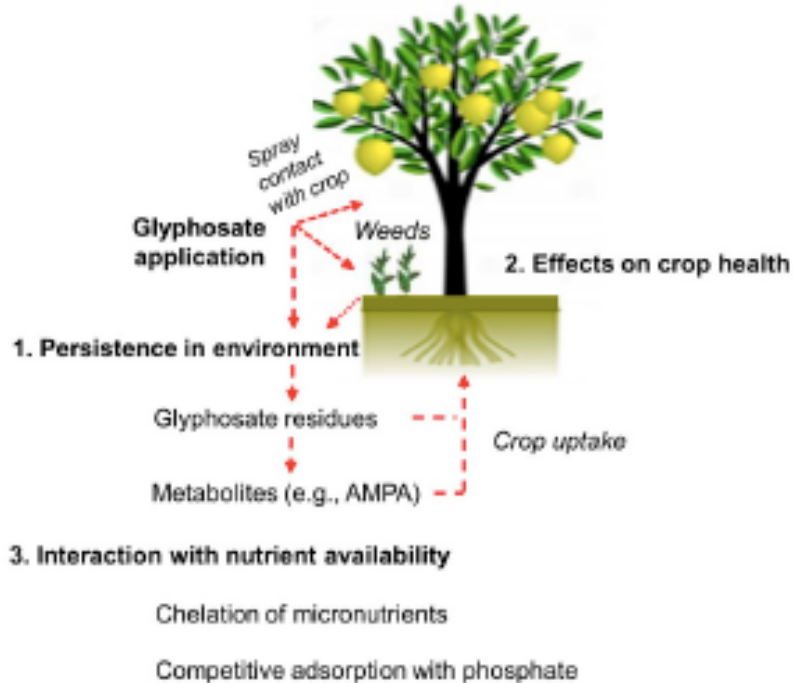
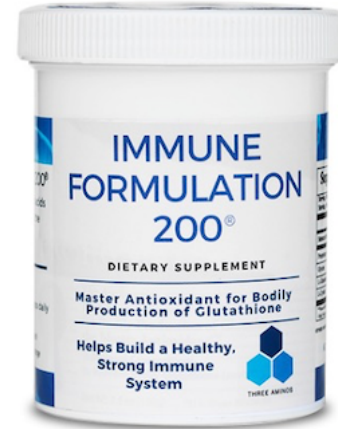
Endogenous Deficiency of Glutathione as the Most Likely Cause of Serious Manifestations and Death in COVID-19 Patients

[Alexey Polonikov^{MD}](#)

▶ [Author information](#) ▶ [Article notes](#) ▶ [Copyright and License information](#) ▶ [Disclaimer](#)



SCAN ME



Endogenous glutathione deficiency appears to be a crucial factor enhancing SARS-CoV-2-induced oxidative damage of the lung and, as a result, leads to serious manifestations, such as acute respiratory distress syndrome, multiorgan failure, and death in COVID-19 patients. When the antiviral activity of GSH is taken into account, individuals with glutathione deficiency seem to have a higher susceptibility for uncontrolled replication of SARS-CoV-2 virus and thereby suffer from an increasing viral load. The severity of clinical manifestations in COVID-19 patients is apparently determined by the degree of impaired redox homeostasis attributable to the deficiency of reduced glutathione and increased ROS production. This assumption can be supported by our findings. In particular, COVID-19 patients with moderate and severe illness had lower levels of glutathione, higher ROS levels, and greater redox status (ROS/GSH ratio) than COVID-19 patients with a mild illness. Long-term and severe manifestations of COVID-19 infection in one of our patients with marked glutathione deficiency suggest that the degree of glutathione decrease correlates negatively with viral replication rate and that an increasing viral load exacerbates oxidative damage of the lung. This finding suggests that the virus cannot actively replicate at higher levels of cellular glutathione, and therefore, milder clinical symptoms are observed with lower viral loads.

SUPPLEMENT FACTS			
Servings Per Container			62
Serving Size			1 Scoop (1.6g)
Amount per serving			
Calories			0
	Standard DV	% Daily Value*	
Selenium (from selenomethionine)	4.5 mcg	75 mcg	6%
Proprietary Amino Acid Blend	1450 mg		
Glycine			
L-Glutamine			
L-Cystine			

Glyphosate in our soil -> our plants are SICK -> Does toxic food cause COVID?

Taking advantage of Synergies: Pathway Crosstalk and DMG

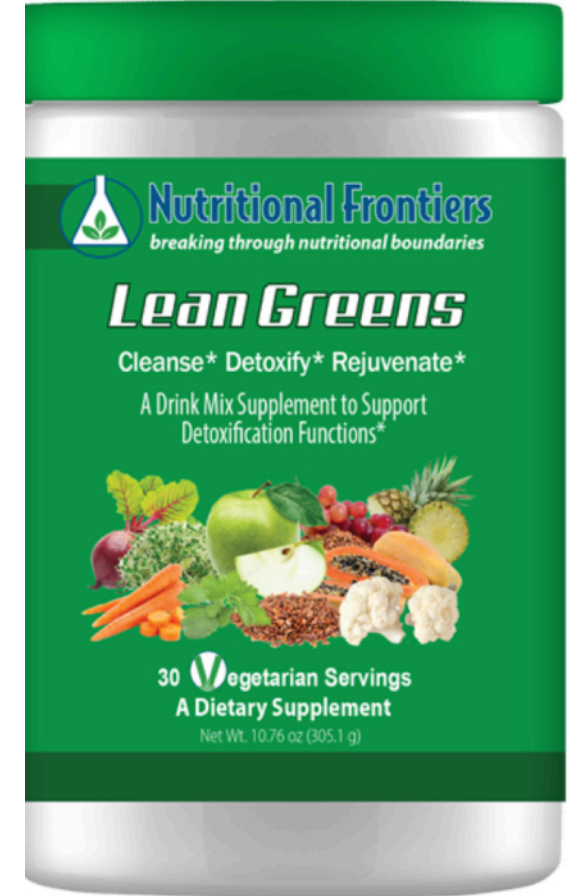
•Detoxification support is provided in **Pro Lean Greens** as N-Acetyl- L-Cysteine, spirulina, chlorella, N,N-Dimethylglycine (DMG), milk thistle, and **Emothion® S-Acetyl-L-Glutathione**. Glutathione is a key part of liver detoxification as it binds toxic chemicals as well as being a free radical scavenger.

•Glutathione is active in Phase II detoxification, helping the body manage carcinogens, toxins, and drugs.

- The **methyl donor DMG** assists in the biosynthesis of vitamins, hormones, neurotransmitters, antibodies & nucleic acids.
- **DMG was patented over three decades ago for treating systemic inflammatory disease**, modulating immune response, and boasts in vitro evidence of antioxidant effects via free radical scavenging activity and enhancement of the endogenous antioxidant defense system.
- Milk thistle (*Silybum marianum*) is used to protect and restore function of the liver with ample research behind its traditional uses.

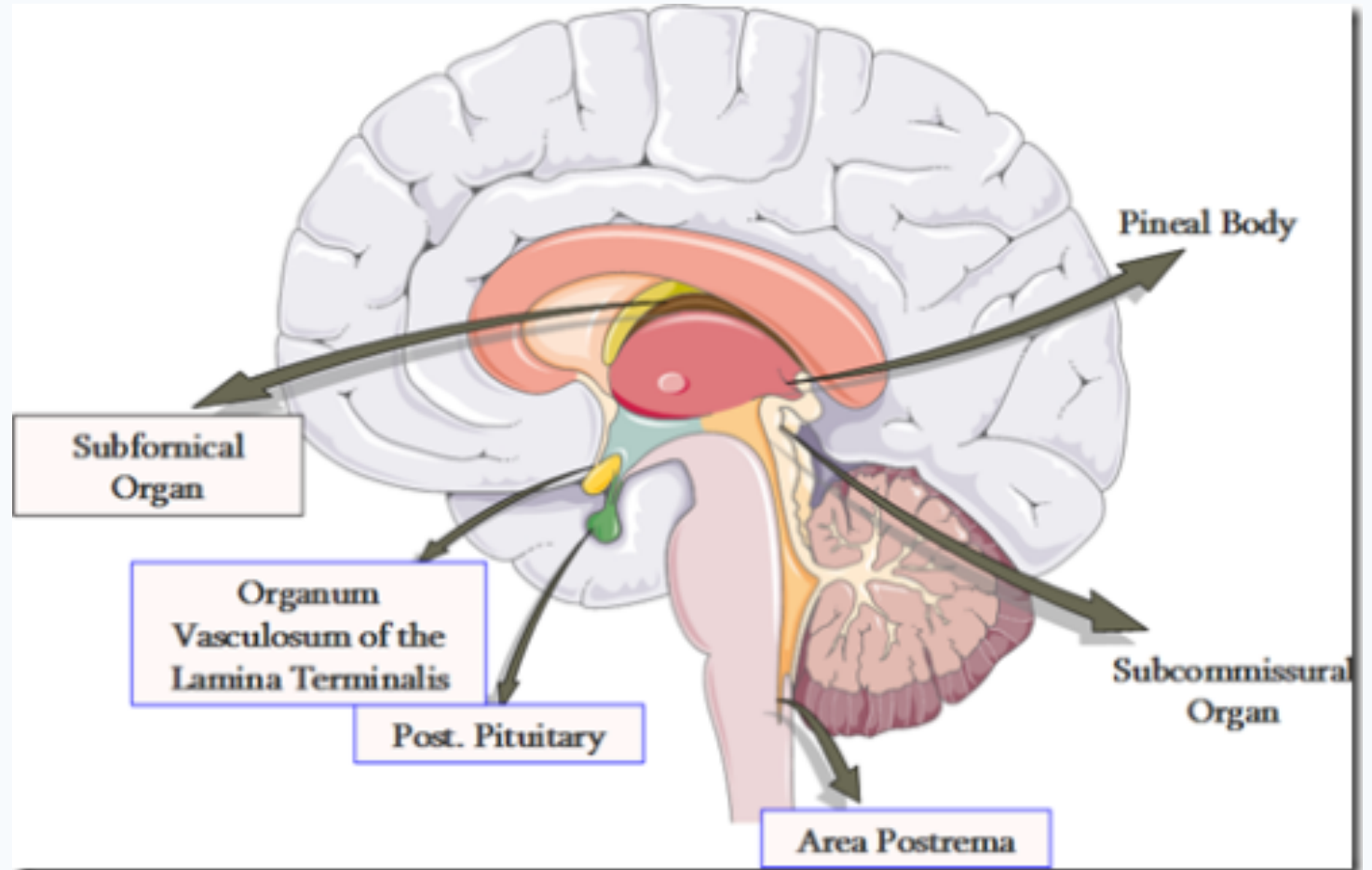


SCAN ME



Circumventricular Organs vulnerable to toxins

Four areas of the brain are not protected by the blood-brain barrier. These areas include the **posterior pituitary gland, pineal gland, the median eminence of the hypothalamus and the area postrema.**



Chronic Disease involves every aspect of Human Biology.

From birth the developing: Brain and Immune system are Inextricably linked

NO/ONOO Ratio Deficiency Common Denominator to Inflammatory Diseases

“We found that a deficiency in bioavailable NO and/or an excess of ONOO- is a common denominator of several diseases:

- Hypertension
- Diabetes
- Stroke
- aging
- heart attack
- Alzheimer's disease
- Parkinson's disease
- epilepsy, and
- migraine

Pharmacogn. Res.

A multidisciplinary peer-reviewed journal in the field of Pharmacognosy and Natural Products
www.phcogres.com | www.phcogres.net

ORIGINAL ARTICLE

Vitamin D₃, L-Arginine, L-Citrulline, and Antioxidant Supplementation Enhances Nitric Oxide Bioavailability and Reduces Oxidative Stress in the Vascular Endothelium – Clinical Implications for Cardiovascular System

Hazem Dawoud, Tadeusz Malinski

Department of Chemistry and Biochemistry, Nanomedical Research Laboratories, Ohio University, Athens, Ohio, USA

ABSTRACT

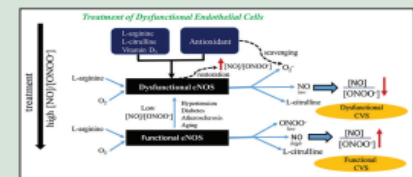
Background: Nitric oxide (NO) is a crucial signaling molecule which regulates the blood flow and prevents the adhesion of blood components to the vascular wall. A deficiency in bioavailable NO concentration is associated with the dysfunction of endothelial NO synthase (eNOS) and/or an increase in oxidative stress. The deficiency of bioavailable NO is a common denominator of several cardiovascular diseases, including diabetes, atherosclerosis, and hypertension. **Materials and Methods:** We used a nanomedical technology to elucidate the balance between bioavailable NO and oxidative stress (peroxynitrite [ONOO⁻]) in human umbilical vein endothelial cells (HUVECs) treated with a supplement containing L-arginine, L-citrulline, Vitamin D₃, and antioxidants. Nanosensors, with a diameter of 200–300 nm, are capable of measuring *in situ* NO and peroxynitrite [ONOO⁻] concentrations produced by single endothelial cells. **Results:** The ratio of the concentration of cytoprotective NO [NO] to the concentration of cytotoxic peroxynitrite [ONOO⁻] was used to estimate the efficiency of eNOS. HUVECs incubated with L-citrulline, L-arginine, and Vitamin D₃ increased the [NO]/[ONOO⁻] ratio by 25%, while in the presence of antioxidants, the increase was 15%. The synergistic effect between the mix of L-arginine, L-citrulline, Vitamin D₃, and antioxidants was a favorable increase of the overall [NO]/[ONOO⁻] ratio by 50%. **Conclusion:** The findings of the study presented here clearly indicate that L-arginine, L-citrulline, and Vitamin D₃ can significantly alter the function of the endothelium and NO production, in a favorable manner, while pointedly reducing ONOO⁻ – the main component of oxidative stress. This effect can be significantly potentiated in the presence of antioxidants.

Key words: Antioxidant, endothelium, L-arginine, L-citrulline, nitric oxide, peroxynitrite, Vitamin D₃

SUMMARY

- Nanomedical studies were used to elucidate the role of a mixture of Vitamin D₃, L-arginine, L-citrulline, and several antioxidants in the improvement of nitric

oxide production and the reduction of oxidative stress in human endothelial cells. It appears that the combination of natural products can effectively improve endothelial function by about 50% and has shown that, on cellular models, it could potentially be used to improve the endothelial function in cardiovascular diseases.



Abbreviations Used: HUVECs: Human umbilical vein endothelial cells; O₂⁻: Superoxide; HBSS: Hank's balanced salt solution; EC: Endothelial cell; Cal: Calcium ionophore; CVD: Cardiovascular disease; eNOS: Endothelial nitric oxide synthase.

Correspondence:

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Nanomedical Research Laboratories, Ohio
University, 350 West State Street, Athens, Ohio,
USA.
E-mail: malinski@ohio.edu
DOI: 10.4103/pr.pr_79_19

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Quick Response Code:



INTRODUCTION

Nitric oxide (NO) is a gaseous molecule that is generated by the NO synthase (NOS) enzyme. NO is synthesized from two substrates: L-arginine (non-essential amino acid) and oxygen.^[1,2] This synthesis occurs through NOS in a five-electron transfer oxidation of L-arginine to L-citrulline. NOS is located in the membrane of endothelial cells, and its synthesis is stimulated by calcium flux.^[3,4] In the cardiovascular system, the calcium flux is triggered by a mechanical process (shear stress)^[5] and chemical stimuli such as acetylcholine, norepinephrine, angiotensin II, and many others.^[6,7]

NO can react rapidly with many biological components, including superoxide (O₂⁻), Fe (III) of hemoglobin, guanylate cyclase, and many others.^[8-11] Therefore, the measurement of reactive “free” NO is a challenging problem. In our laboratories, we are able to perform measurements of bioavailable NO produced by a single endothelial cell in different segments of the cardiovascular system, such as

capillary vessels, aorta, and heart. Maximal NO concentrations vary significantly, depending on the location of the endothelial cells – with the lowest concentrations in the small capillary (about 80 nM) and the highest in the endocardium of the heart (about 2.0 μM).^[11] The level of NO concentration depends largely on the velocity and type of blood flow (laminar vs. turbulent).^[12-14]

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Cite this article as: Dawoud H, Malinski T. Vitamin D₃, L-Arginine, L-Citrulline, and antioxidant supplementation enhances nitric oxide bioavailability and reduces oxidative stress in the vascular endothelium – Clinical implications for cardiovascular system. Phcog Res 2020;12:17-23.

Nutritional Support

provide the building blocks to support nitric oxide formation which may enhance overall circulation, including heart health and erectile dysfunction.

SUPPLEMENT FACTS

Serving Size: 2 Capsules

Servings Per Container: 60

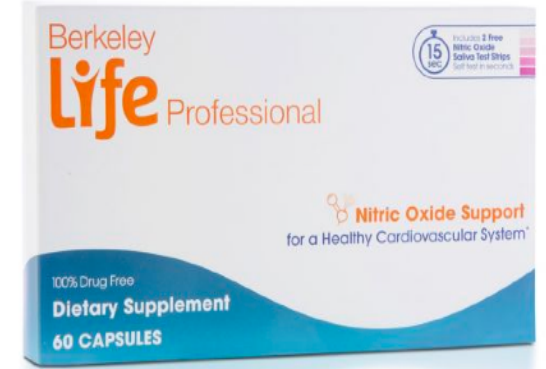
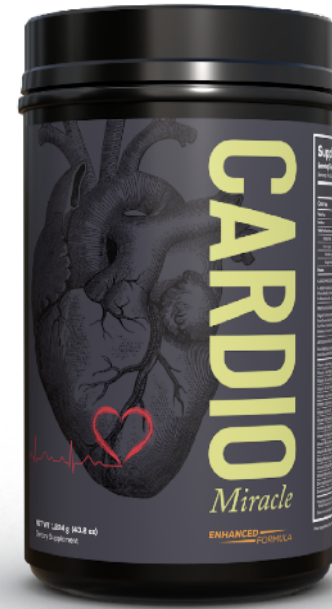
Amount Per Serving

Vitamin C (as Ascorbic Acid)	100 mg
Vitamin B12 (Methylcobalamin)	100 mcg
Folate (as Quatrefolic® (equivalent to 200 mcg of [6S]-5-Methyltetrahydrofolic acid, glucosamine salt))	100 mcg
Beet Root Powder	200 mg
Activin® Grape Seed Extract (vitis vinifera) 100:1	120 mg
Hawthorne	100 mg
L-Citrulline	100 mg
L-Arginine	100 mg

Other Ingredients: Vegetable Cellulose (Capsule), Microcrystalline Cellulose, Silicon Dioxide, Magnesium Stearate

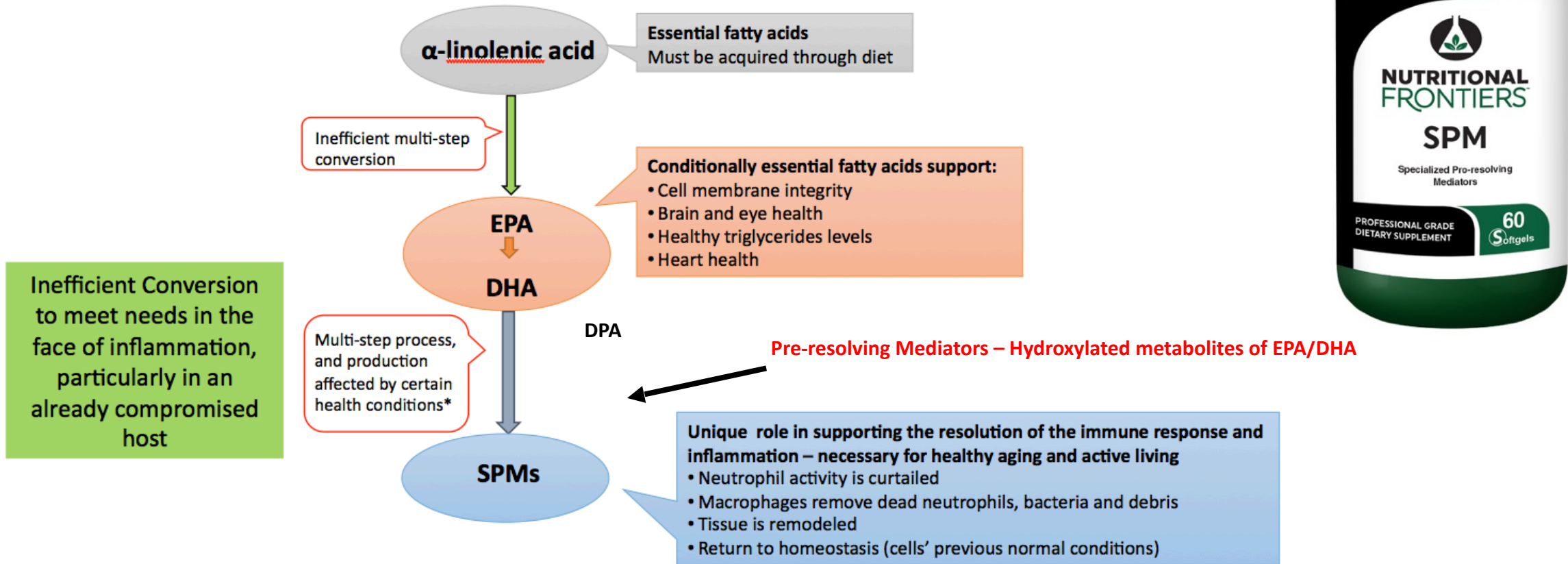
Suggested Use: As a dietary supplement, take two capsules daily, or as directed by your healthcare practitioner.

Warning: If you are pregnant or nursing, consult your health care practitioner before taking this product.



Nitric oxide is a soluble gas that is continually being made from arginine in endothelial cells. Endothelial cells comprise a layer of cells inside the lining of our blood vessels.

Specialized Pro-Resolving Mediators (SPM)



Serhan CN. *Nature*. 2014;510:92-101

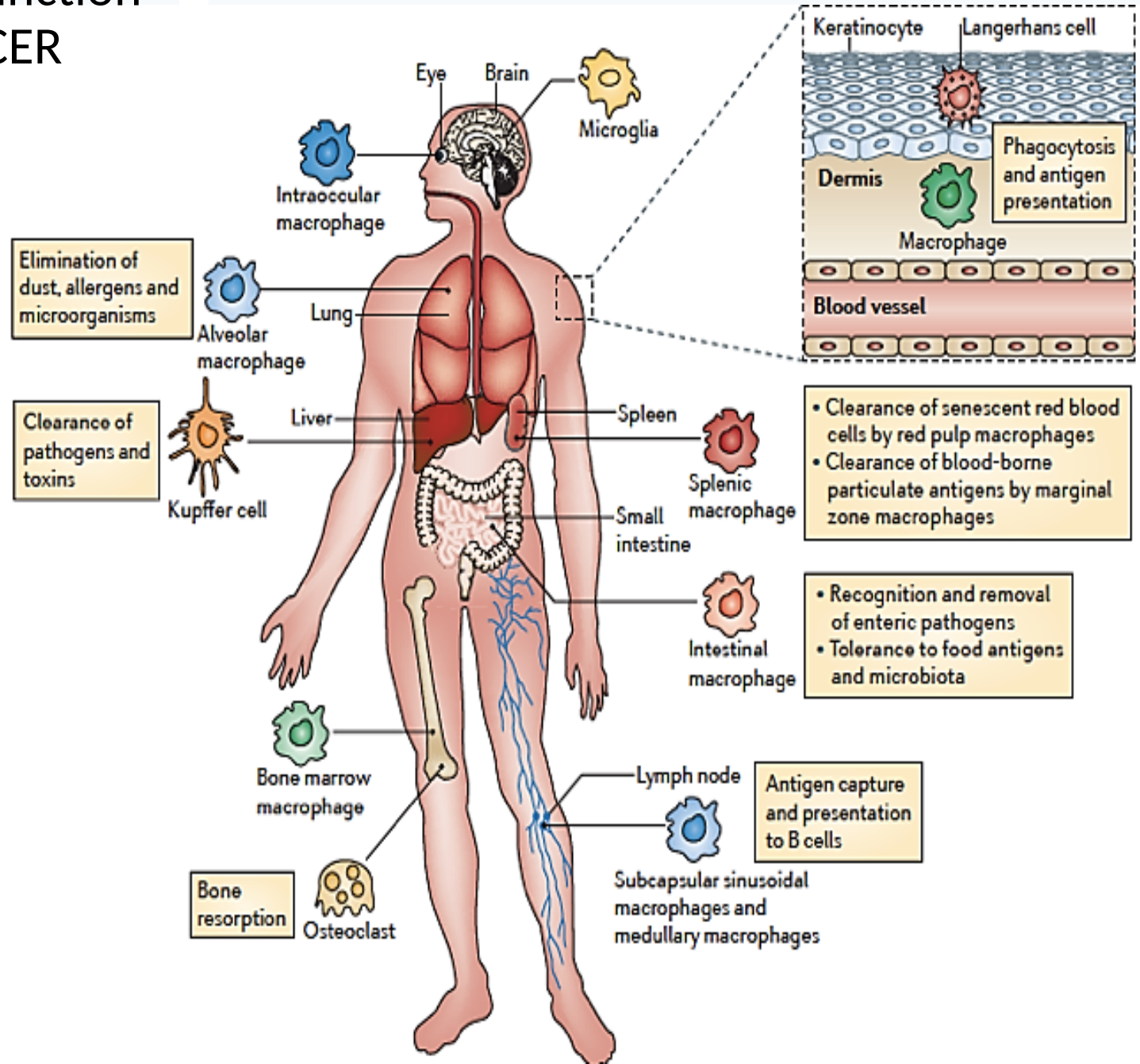
They are called 'resolving mediators' because of their role in facilitating natural resolution of the inflammatory response. Examples of SPMs include resolvins, lipoxins, protectins, and maresins.

Monocyte/Macrophage Dysfunction as a Driver of AEIDS/CANCER

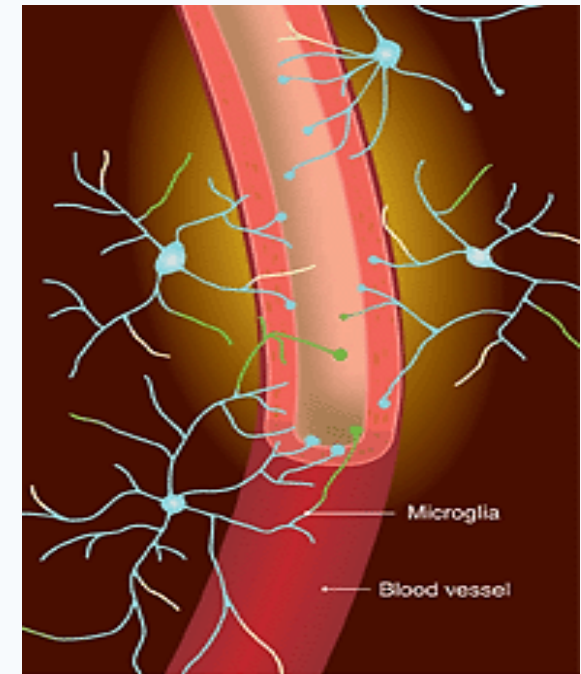
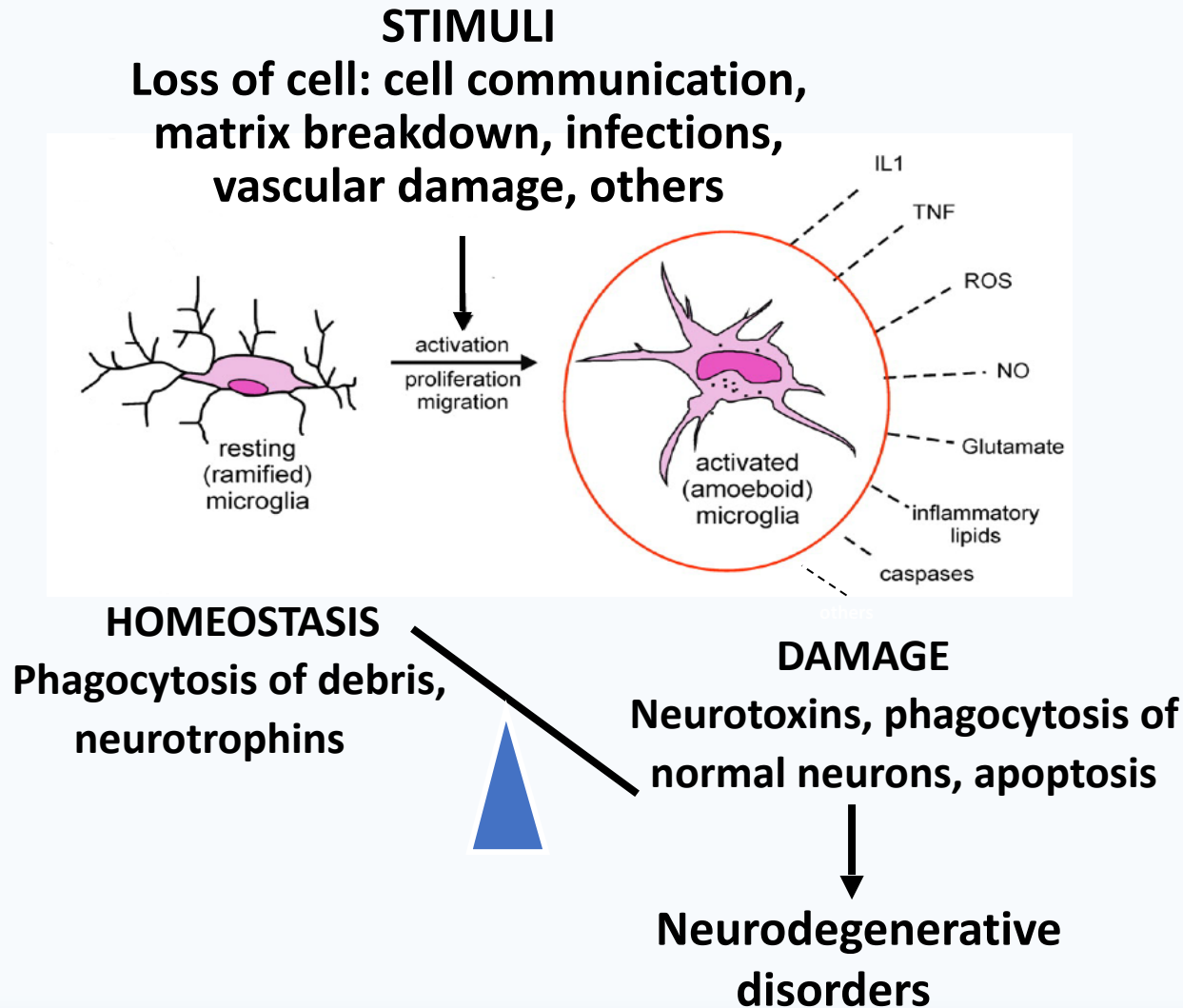
- Express Purinergic Receptors:
- P2XR and P2YR.
- Express Cannabinoid Receptors
- CB1 & CB2

Tissue Macrophages perform Key Homeostatic Functions Modulated by

- Cannabinoids
- GcMAF
- Suramin
- Ivermectin
- Vitamin C
- DMG
- Decitibine (Vidaza)
- Peptide T



Microglia Activation in Neurodegeneration



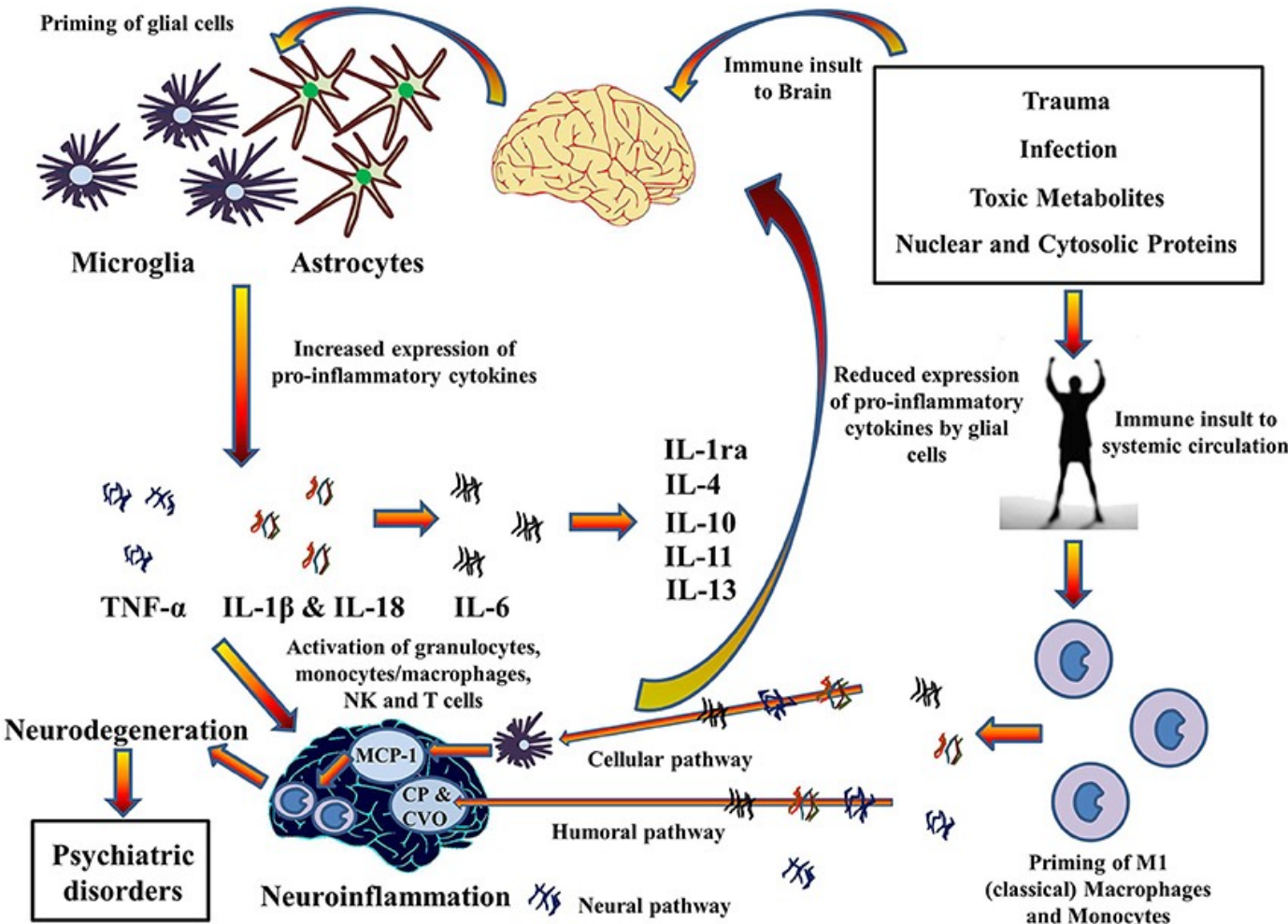
Fetler, L and S Amigorena,
Science 2005, 309:392

- Parkinson's disease
- Alzheimer's disease
- Multiple sclerosis
- Autism
- ME/CFS

Xenotropic Murine Leukemia Virus-related Virus-associated Chronic Fatigue Syndrome Reveals a Distinct Inflammatory Signature

in vivo 25: 307-314 (2011)

VINCENT C. LOMBARDI¹, KATHRYN S. HAGEN¹, KENNETH W. HUNTER⁴,
JOHN W. DIAMOND^{2†}, JULIE SMITH-GAGEN³, WEI YANG³ and JUDY A. MIKOVITS¹



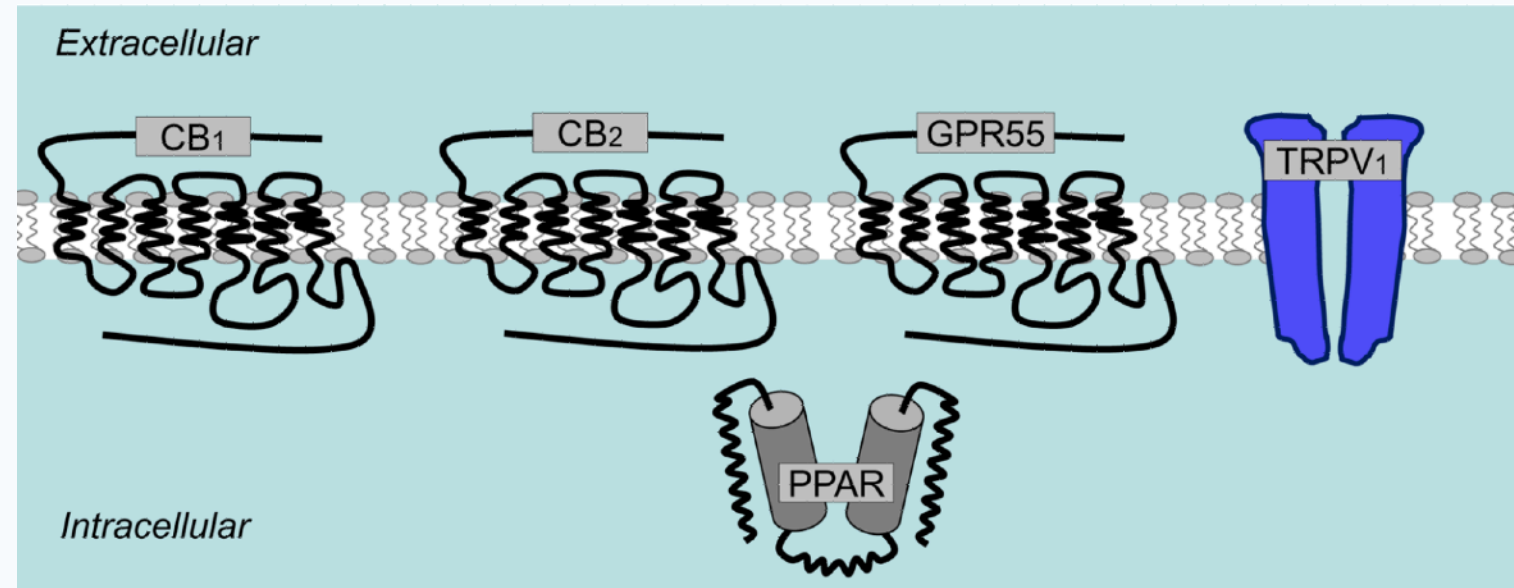
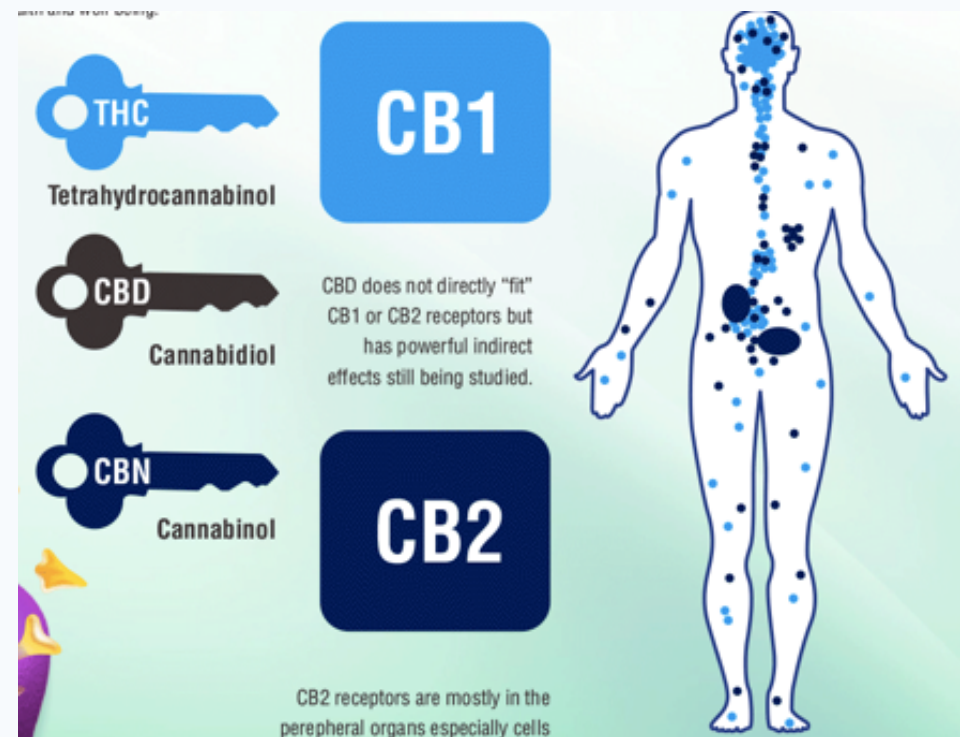
CYTOKINES/ CHEMOKINES	Patient N = 156	Control N=140	P value	FUNCTION IN INFLAMMATION
IL-8	1067	11.1	<0.0001	RNase L and CMV activated
IL-13	28	86	<0.0001	Inhibits inflammatory cytokine production
MIP-1β	1840	157	<0.0001	Elevated in Neurodegenerative disease
TNF-α	109	12.8	<0.0001	Stimulates chronic inflammation
MCP-1	468	421	0.003	Elevated in chronic inflammatory diseases
IL-7	21.1	82	<0.0001	Stimulates proliferation of B and T lymphocytes and NK cells
IFN-α	35	60	<0.0001	Stimulates macrophages and NK cells to elicit an anti-viral response
IL-6	271	29	<0.0001	Stimulates chronic inflammation
MIP-1α	673	91	0.0062	Elevated in Neurodegenerative disease
GM-CSF	108	166	<0.0001	Stimulates proliferation of B and T lymphocytes and NK cells

The Human Endocannabinoid System (eCS)

GOD GIVEN Regulator of stem cells Immune Homeostasis & Neuroimmune Health

A signaling system that helps to modulate all other physiological, behavioral, and energetic processes in the body.

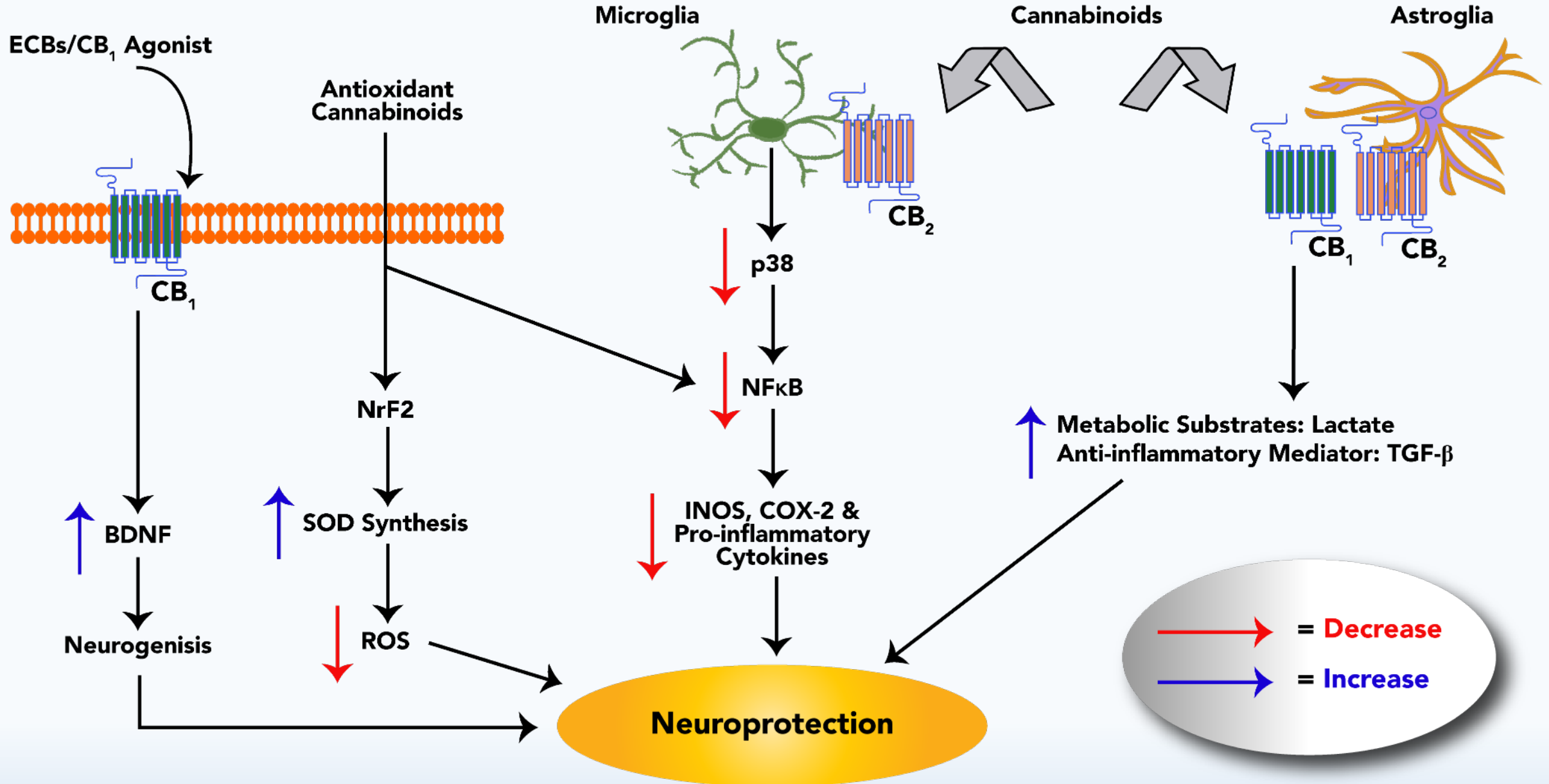
Glia. 2010 July ; 58(9): 1017–1030



- Anxiety
- Depression
- Sleep Disorders
- Pain
- Itch
- Wound healing

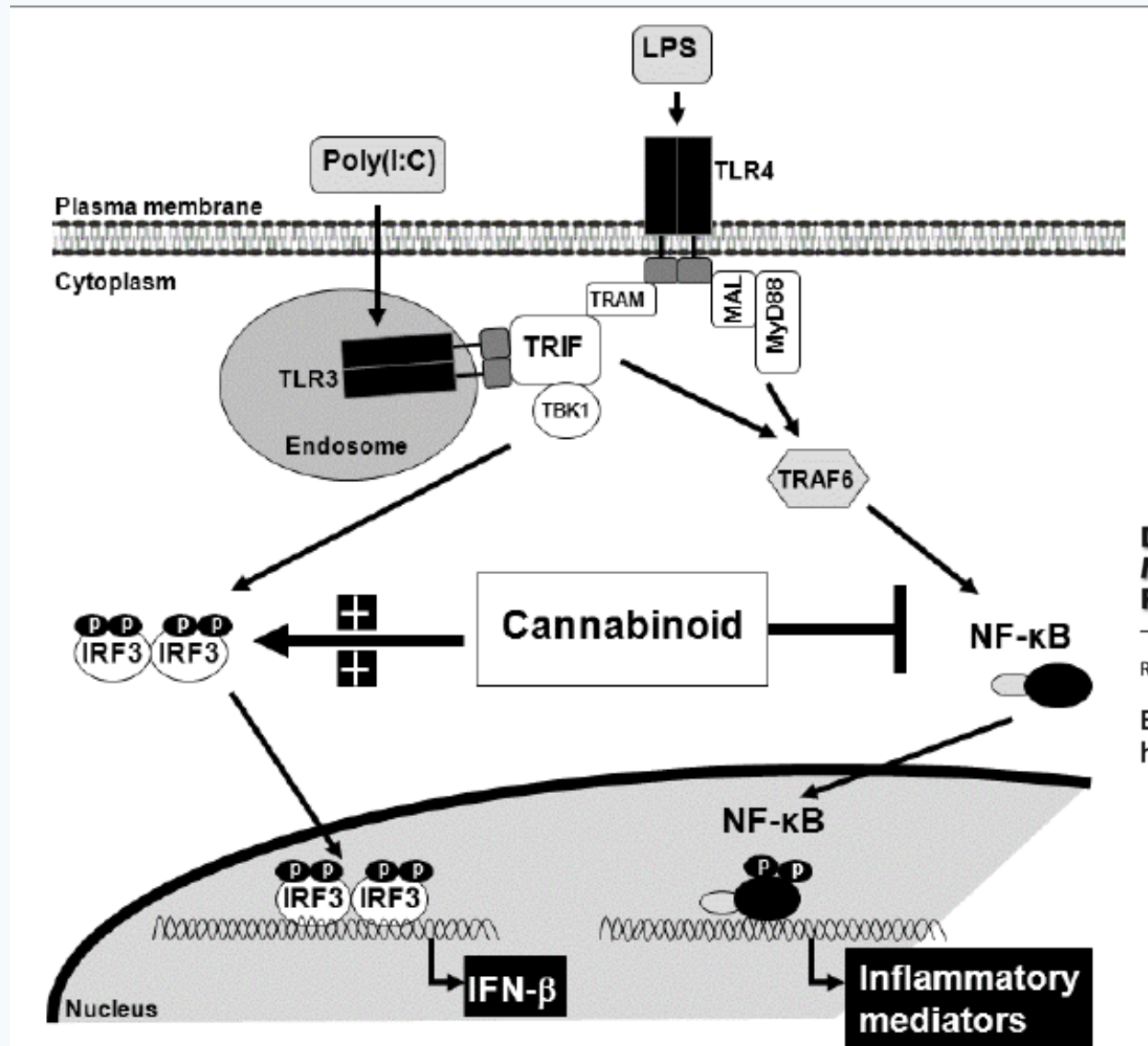
- *neuroprotection & plasticity*
- *immunity & inflammation*
- *apoptosis & carcinogenesis*
- *pain and emotional memory*
- *Supports detoxification:*
 - *repairs Fibrosis*
 - *fatty Liver disease*

Neuroprotection by Endocannabinoid Modulation in Neurodegenerative Disease



Cannabinoids are Anti-Viral and Reduce inflammation

THE DIMMER SWITCH ON THE FLAME



CANNABIS is NOT a DRUG! IT'S Food!! Nourish CELLS ALL Plants (HEMP & CANNABIS) Removed from US 1938!

Drug
Metabolism
Reviews

<http://informahealthcare.com/dmr>
ISSN: 0360-2532 (print), 1097-9883 (electronic)
Drug Metab Rev, 2014; 46(1): 86-95
© 2014 Informa Healthcare USA, Inc. DOI: 10.3109/03602532.2013.849268

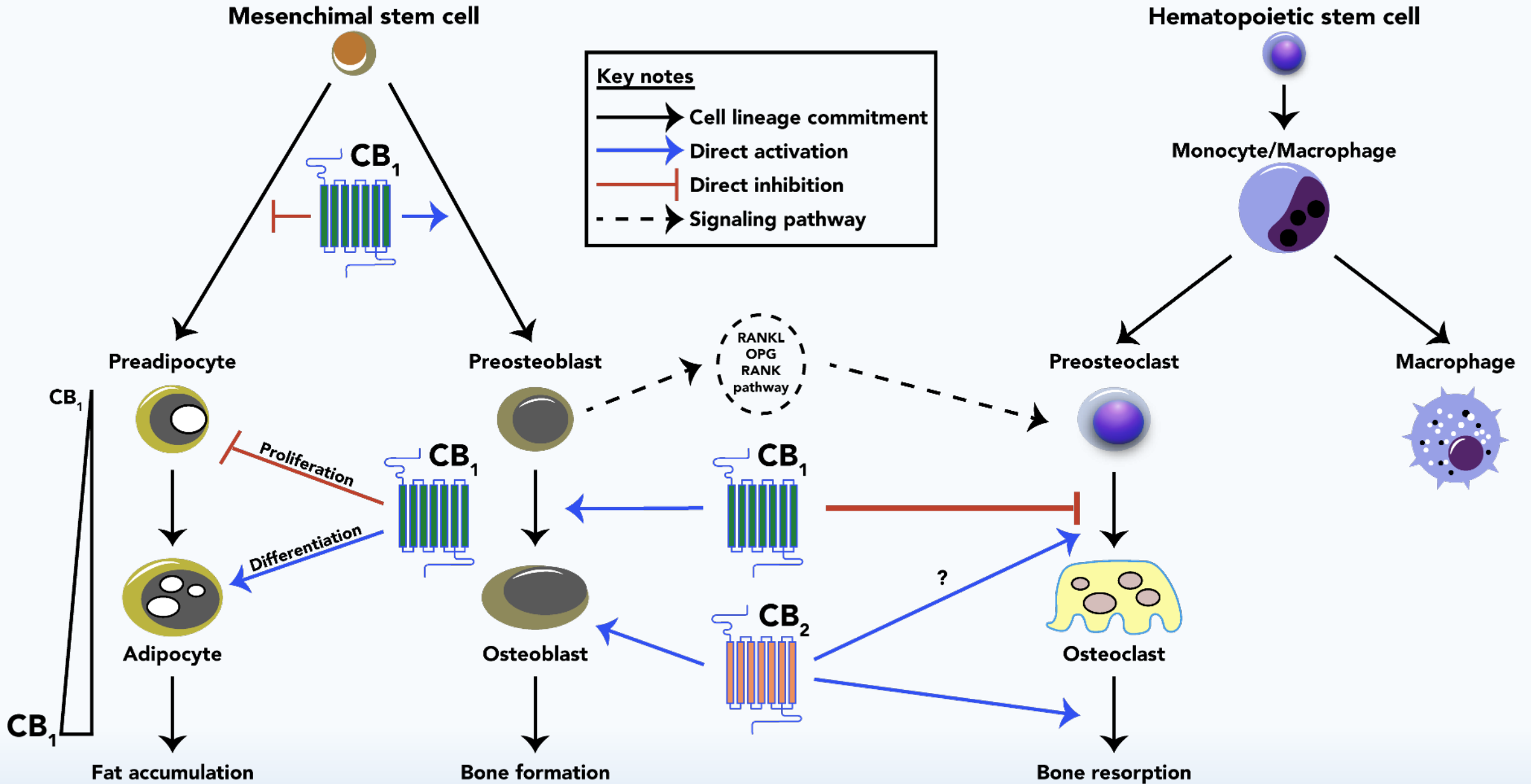
informa
healthcare

REVIEW ARTICLE

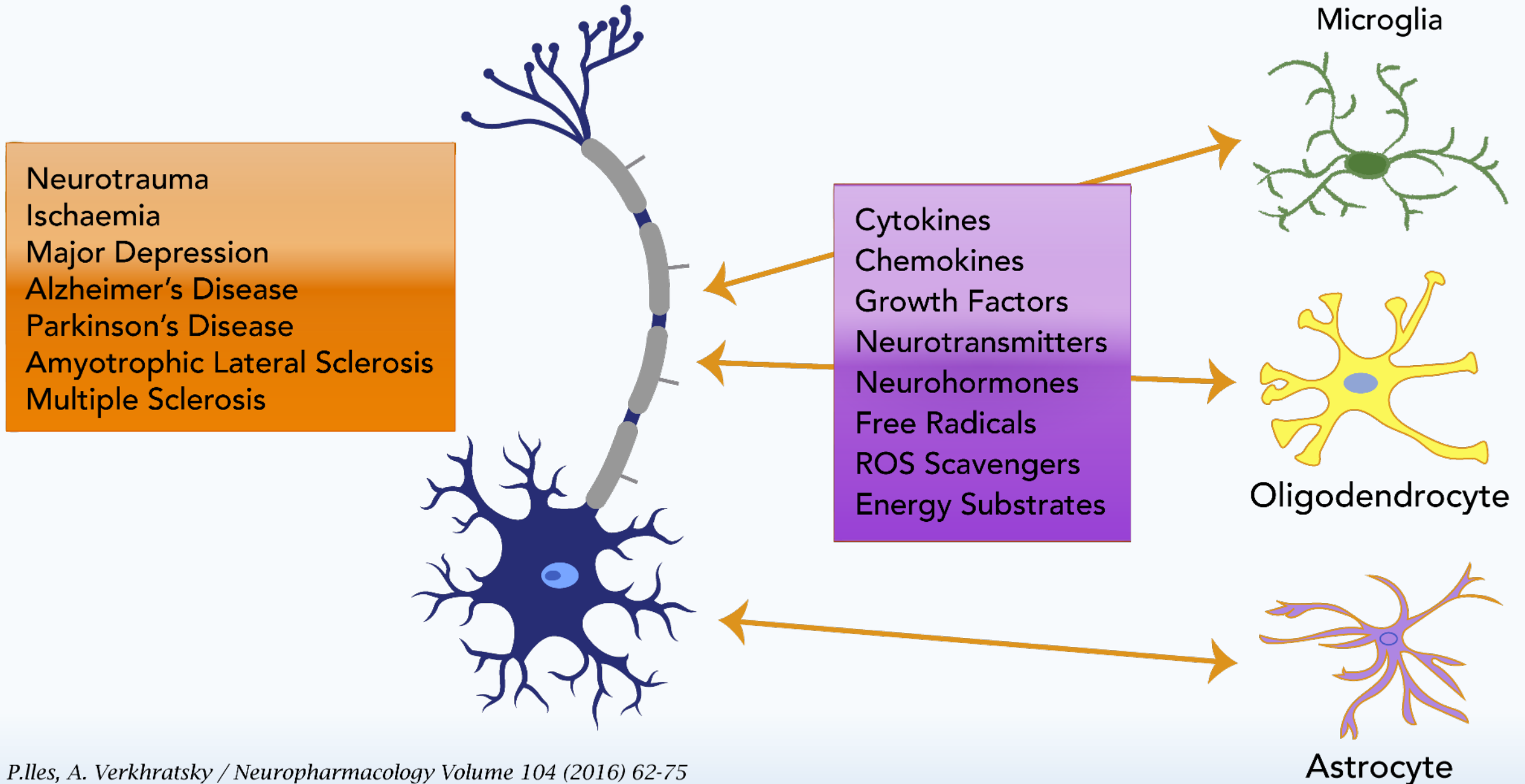
Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review

GOD GIVEN LIPID/FAT SIGNALING SYSTEM in EVERY Cell MEMBRANE

CB2 Is associated with Chronic inflammation of the nervous system, Cardiovascular and Bone Disorders



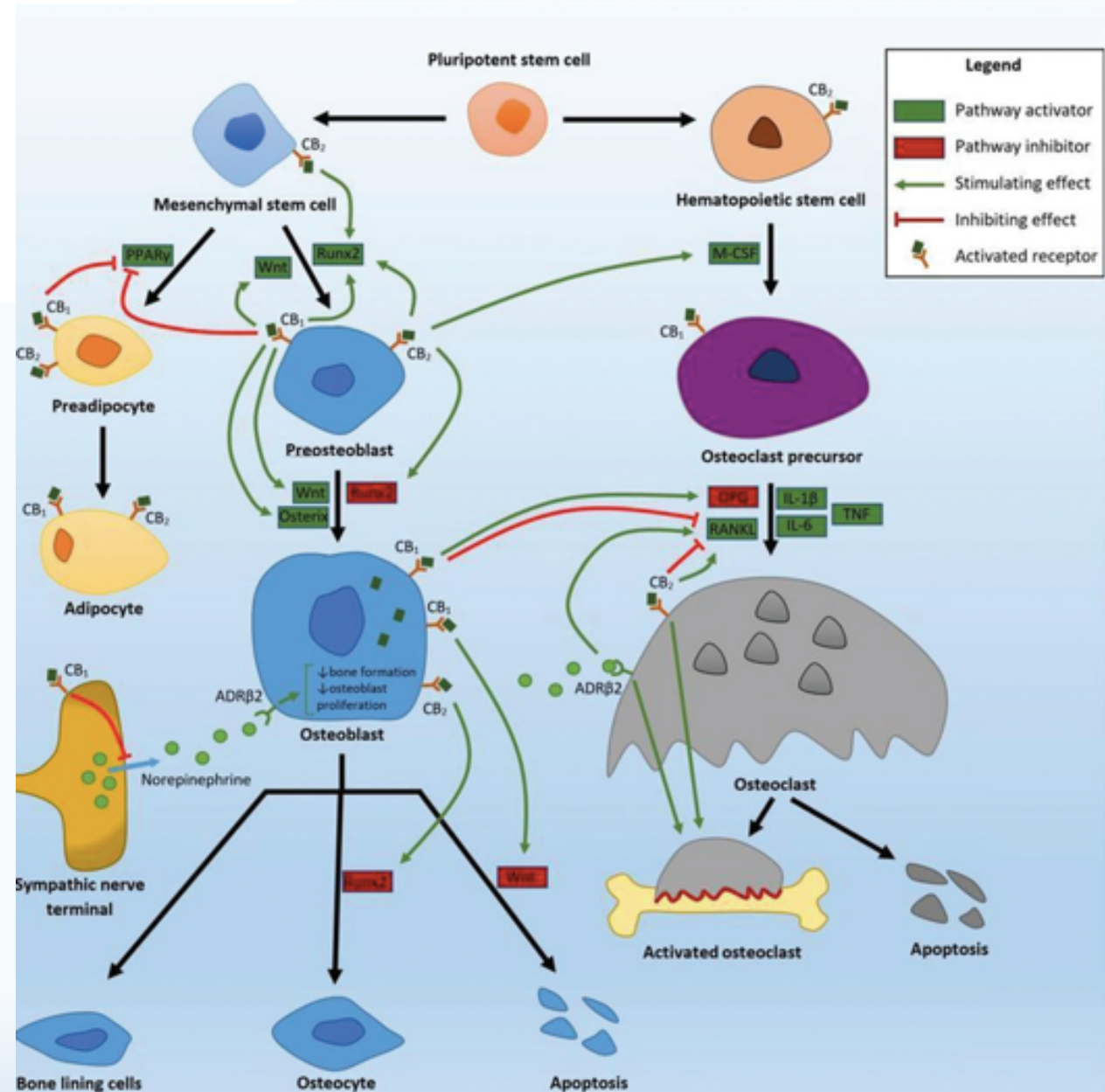
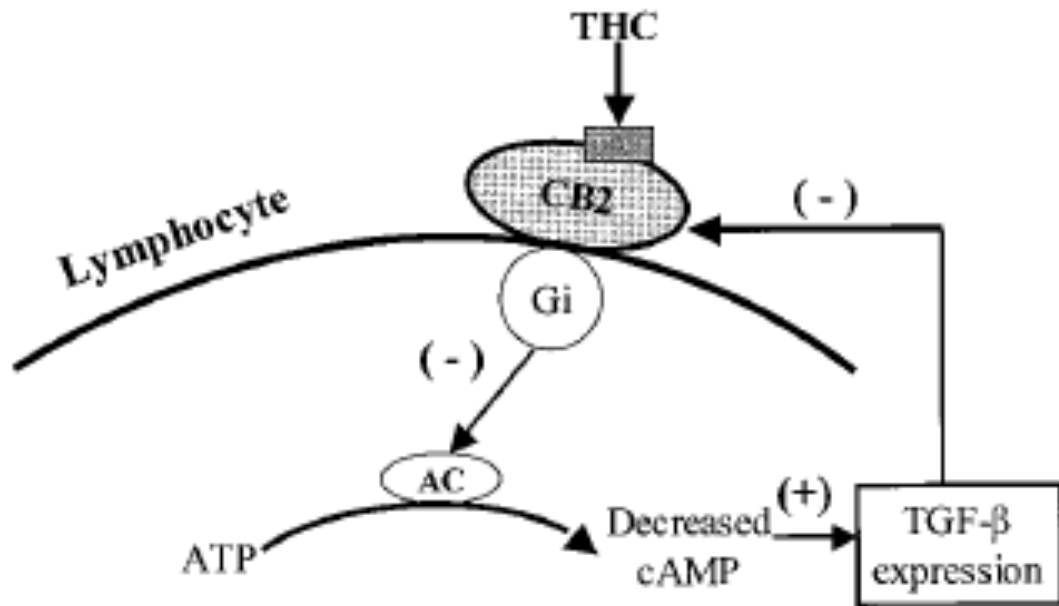
Phyto-cannabinoids Dampen Tissue Injury to Prevent Progression of Neurodegenerative Disease and Cancer



Review

Ion Channel Functions in Early Brain Development

Richard S. Smith^{1,*} and Christopher A. Walsh^{1,*}



Cannabinoids regulate MINERALS in Immune Cells via endocannabinoid System Receptors

- A downside of activation of MINERALS is the dysregulation endogenous microbes
- OUR SOILS ARE DEPLETED OF MINERALS!

TRPV1/2	Ca ²⁺ /Na ⁺	PM	Heat (fever?), low pH, mechanical stress		Mono, macro	Degranulation, phagocytosis, cytokine production
TRPC3/6	Ca ²⁺ /Na ⁺	PM	PLC activation (DAG), PIP ₂		T, B, NK cells, neutro	Chemotaxis, degranulation
TRPM2	Ca ²⁺ /Na ⁺	PM, lys	H ₂ O ₂ , NAADP, cADPR		T, B, neutro, mast cells, DC	Cytokine production, degranulation
Magnesium						
TRPM6	Mg ²⁺ >Ca ²⁺	PM		Inhibited by [Mg ²⁺] _i	Gut, kidney, hematopoietic (not T cells)	Unknown in immune cells
TRPM7	Mg ²⁺ >Ca ²⁺	PM	Unknown (BCR, TCR?) PIP ₂ (?)	Inhibited by [Mg ²⁺] _i	Ubiquitous	T cell development, T and B cell proliferation, cytokine production



Review

CellPress

Divalent cations of two alkaline earth metals Ca²⁺ and Mg²⁺ and the transition metal Zn²⁺ play vital roles in the immune system, and several immune disorders are associated with disturbances of their function. Until re-

Divalent cation signaling in immune cells

Benjamin Chaigne-Delalande and Michael J. Lenardo

Molecular Development of the Immune System Section, Lymphocyte Molecular Genetics Unit, Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA

Trends in Immunology July 2014, Vol. 35, No. 7

Non-selective cationic channels in chemical and physical stress?

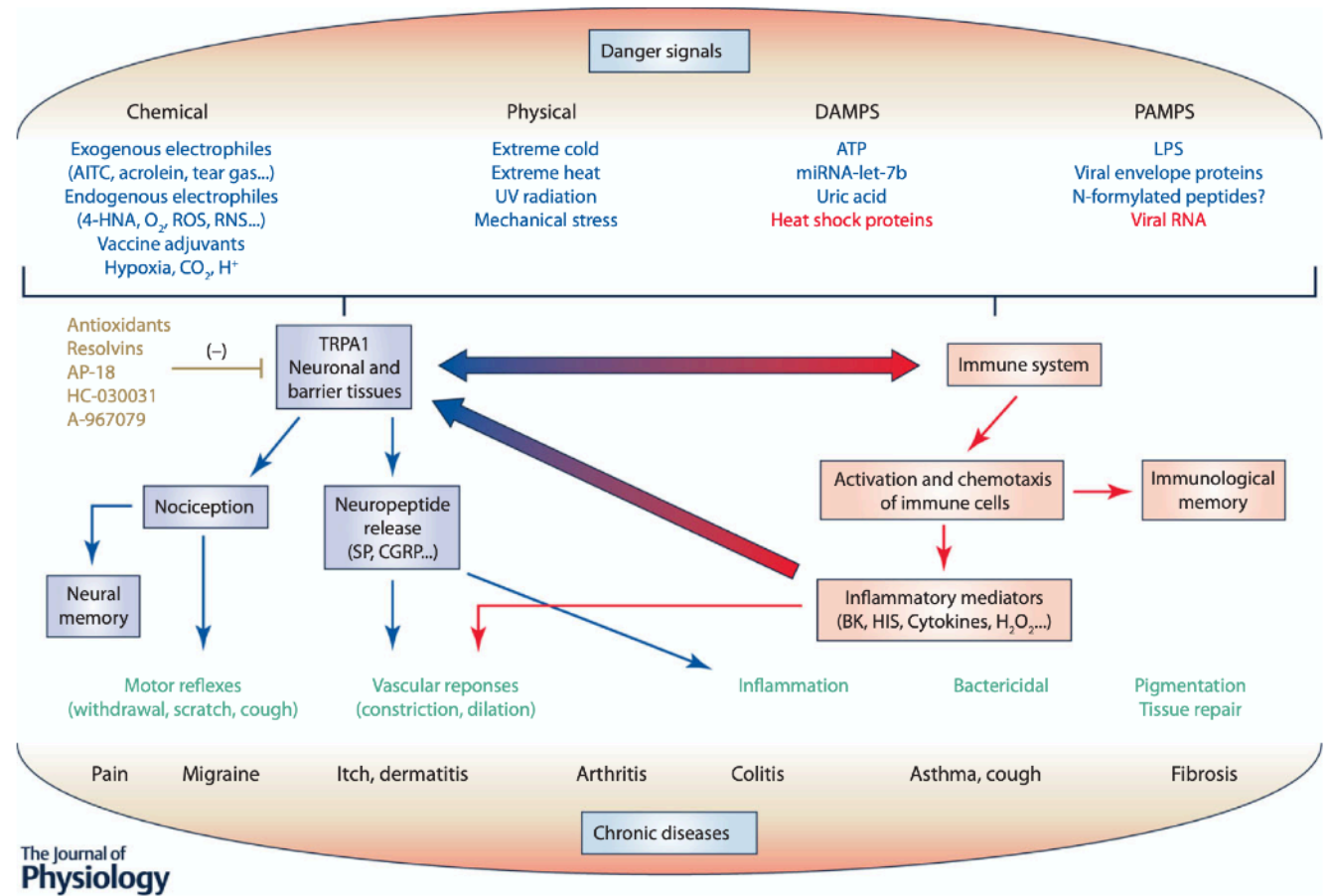
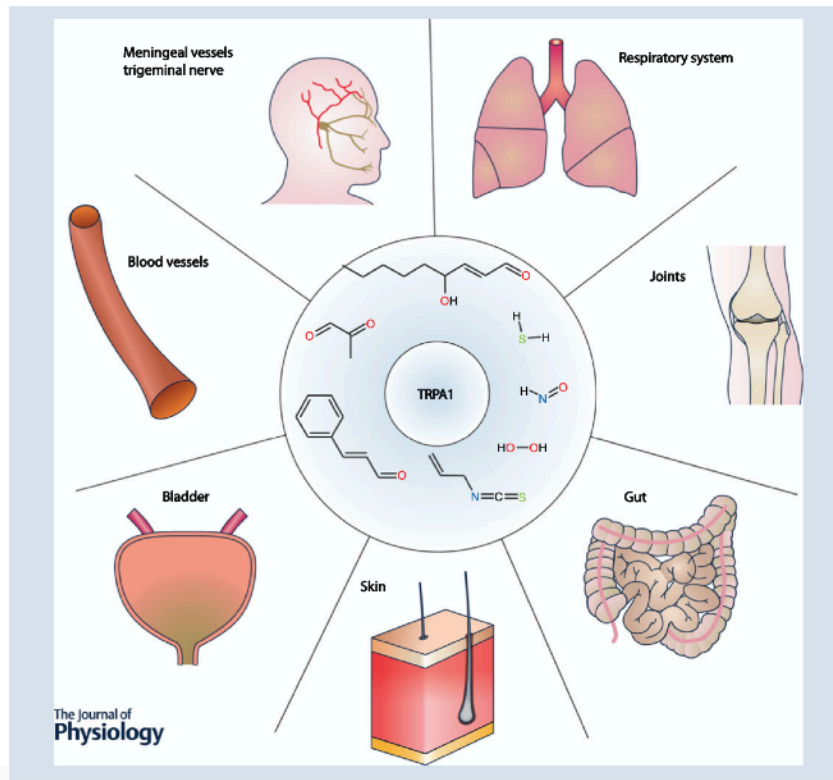
J. Physiol 594.15 (2016) pp 4151–4169

SYMPOSIUM REVIEW

TRPA1 channels: molecular sentinels of cellular stress and tissue damage

Félix Viana

Instituto de Neurociencias de Alicante, Universidad Miguel Hernández-CSIC, Alicante, Spain



REVIEW

Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

Ethan B Russo

GW Pharmaceuticals, Salisbury, Wiltshire, UK

Correspondence

Ethan Russo, MD, 20402 81st Avenue SW, Vashon, WA 98070, USA. E-mail: ethanrusso@comcast.net

Keywords

cannabinoids; terpenoids; essential oils; THC; CBD; limonene; pinene; linalool; caryophyllene; phytotherapy

Received

19 November 2010

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29 December 2010

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12 January 2011

Article



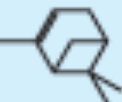




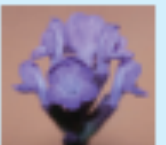
Terpenoids and Phytocannabinoids Co-Produced in *Cannabis Sativa* Strains Show Specific Interaction for Cell Cytotoxic Activity





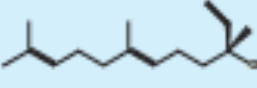

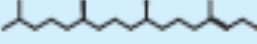

Dvora Namdar^{1,*}, Hillary Voet¹, Vinayaka Ajjampura¹, Stalin Nadarajan¹, Einav Mayzlish-Gati², Moran Mazuz¹, Nurit Shalev¹ and Hinanit Koltai¹

¹ Institute of Plant Sciences, Agricultural Research Organization, Volcani Center, Bet Dagan 7505101, Israel

² Israeli Gene Bank, Volcani Center, Bet Dagan 7505101, Israel

* Correspondence: dvoran@volcani.agri.gov.il

Terpenoid	Structure	Commonly encountered in	Pharmacological activity (Reference)	Synergistic cannabinoid
Limonene		 Lemon	Potent AD/immunostimulant via inhalation (Komori et al., 1995) Acidolytic (Carvalho-Freitas and Costa, 2002; Palfrei Ade et al., 2006) via 5-HT _{1A} (Korniya et al., 2004) Apoptosis of breast cancer cells (Vigushin et al., 1998) Active against acne bacteria (Kim et al., 2008) Dermatophytes (Sanguinetti et al., 2007; Singh et al., 2010) Gastro-oesophageal reflux (Hertz, 2010)	CBD CBD CBD, CBG CBD CBG THC
α -Pinene		 Pine	Anti-inflammatory via PGE-1 (Gil et al., 1989) Bronchodilatory in humans (Falk et al., 1990) Acetylcholinesterase inhibitor, aiding memory (Ferry et al., 2000)	CBD THC THC, CBD
β -Myrcene		 Hops	Blocks inflammation via PGE-2 (Lorenzetti et al., 1991) Analgesic, antagonized by naloxone (Rao et al., 1990) Sedating, muscle relaxant, hypnotic (de Vile et al., 2002) Blocks hepatic carcinogenesis by aflatoxin (de Oliveira et al., 1997)	CBD CBD, THC THC CBD, CBG
Linalool		 Lavender	Anti-anxiety (Russo, 2001) Sedative on inhalation in mice (Buchbauer et al., 1993) Local anesthetic (Re et al., 2000) Analgesic via adenosine A _{2A} (Peters et al., 2004) Anticonvulsant/anti-glutamato (Silabebdy et al., 1995)	CBD, CBG THC THC CBD CBD, THC, CBG, CBDV
			Potent anti-leishmanial (do Socorro et al., 2003)	?

β -Caryophyllene		 Pepper	AI via PGE-1 comparable phenylbutazone (Stalle et al., 1988) Gastric cytoprotective (Tambe et al., 1996) Anti-malarial (Carpbell et al., 1997) Selective CB ₂ agonist (100 nM) (Gerlach et al., 2000) Treatment of pruritus? (Karak et al., 2007) Treatment of addiction? (Xi et al., 2010)	CBD THC ? THC THC CBD
Caryophyllene Oxide		 Lemon balm	Decreases platelet aggregation (Lin et al., 2003) Antifungal in onychomycosis comparable to ciclopiroxolamine and salicylate (Yang et al., 1999) Insecticidal/anti-feedant (Sattarini et al., 1993)	THC CBG, CBG THCA, CBGA
Nerolidol		 Orange	Sedative (Sirel et al., 1972) Skin penetrant (Cornwell and Barry, 1994) Potent antimarial (Lopes et al., 1999, Rodrigues Goulart et al., 2004) Anti-leishmanial activity (Amada et al., 2005)	THC, CBN - ? ?
Phytol		 Green tea	Breakdown product of chlorophyll Prevents Vitamin A isomerization (Arnhold et al., 2002) TGASA via SSADH inhibition (Yang et al., 2002)	- - CBG

VIRUSES/POSIONS

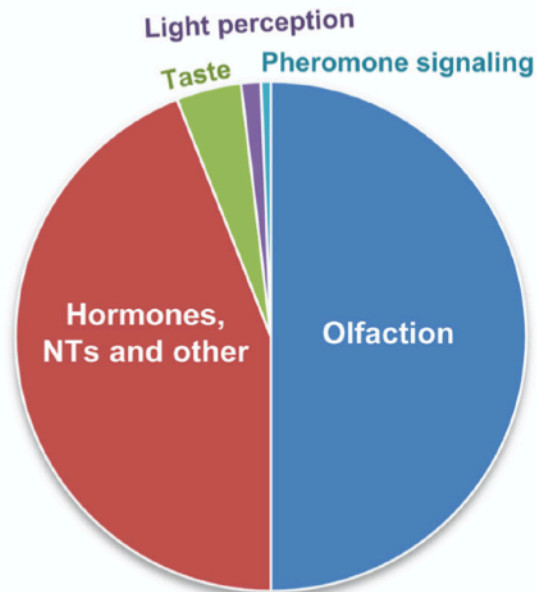
Lack of Minerals, Essential Amino acids, Phytocannabinoids



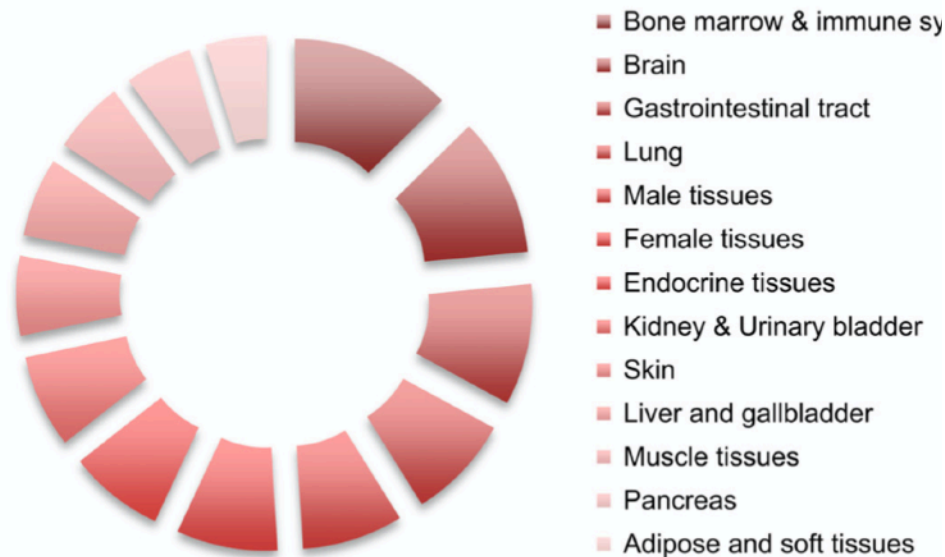
$G_{i/o}$ -Protein Coupled Receptors in the Aging Brain

Patrícia G. de Oliveira^{1†}, Marta L. S. Ramos^{1†}, António J. Amaro², Roberto A. Dias^{1††} and Sandra I. Vieira^{1††}

A GPCRs main functions

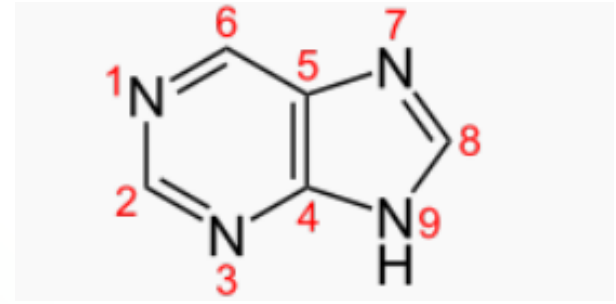


B Tissue distribution of $G_{i/o}$ -coupled GPCRs



Purinergic regulation of the immune system

Caglar Cekic¹ and Joel Linden²



Acute: initiation of inflammation

ATP release:

- Nerves
- Mast cells
- Platelets (ADP)
- Apoptotic cells
- Necrotic cells
- Stressed cells (pannexin channels, connexin channels, maxichannels and P2X₇ pores)

Excitatory P2 receptor activation (chemotaxis and activation):

- Phagocytes
- DCs
- Mast cells
- Platelets
- Lymphocytes (increased T_H17 cells and decreased T_{Reg} cells)

Subacute: resolution of inflammation

- Reduced ATP release and rapid dephosphorylation
- Accumulation of T_{Reg} cells expressing CD39 and CD73 (accelerated ATP dephosphorylation)

Inhibitory G_s-coupled A2AR induction and activation

- Lymphocytes (decreased T_H17 cells and increased T_{Reg} cells)
- Macrophages and/or DCs
- Platelets
- Mast cells
- NK cells
- B cells

Inhibitory G_s-coupled A2BR induction and activation:

- Macrophages
- DCs

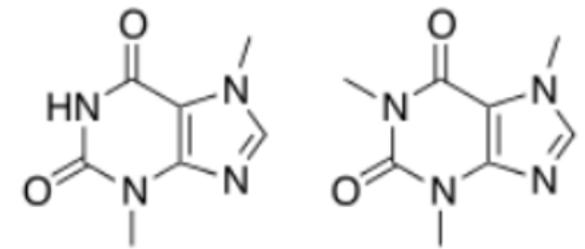
Chronic: fibrosis and angiogenesis

Moderate rates of ATP release and rapid dephosphorylation

Activation of G_s- and G_q-coupled A2BRs:

- Macrophages and/or DCs (wound healing, IL-6 release, fibrosis, T_H17 polarization, VEGF and angiogenesis)
- Pathological responses (fibrosis and heart failure)

- Nitrogenous bases of DNA
- Deoxyadenosine
- Deoxyguanine



theobromine
6

caffeine
7

Time after tissue injury

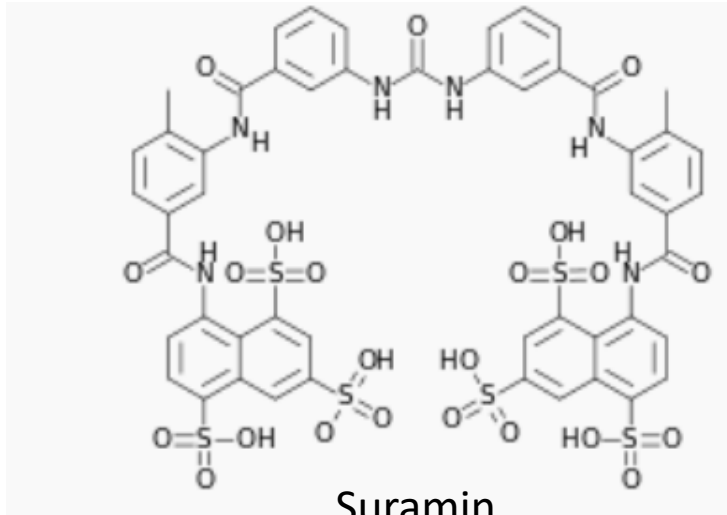
Minutes

Hours

Days

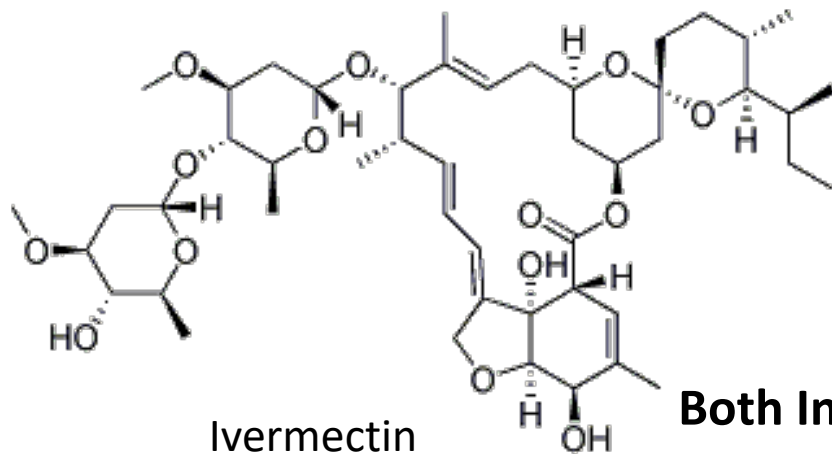
Weeks/
months

Suramin & Ivermectin: Purinergic Modulators important for restoring balance of Innate and adaptive Immunity



Suramin

- Antiparasitic 1920s
- Potent RT inhibitor 1986
- P2Y Purinergic Receptor inhibitor
- Cancer therapy prostate cancer, HTLV-1 cancer Bladder Cancer
- inhibits the binding of growth factors (TGF-beta, EGF, PDGF to their receptors and thus antagonize the ability of these factors to stimulate growth of tumor cells

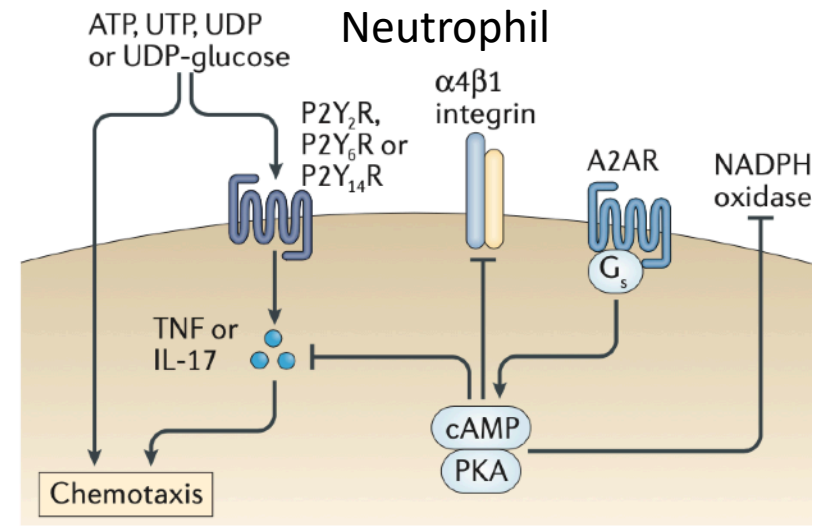
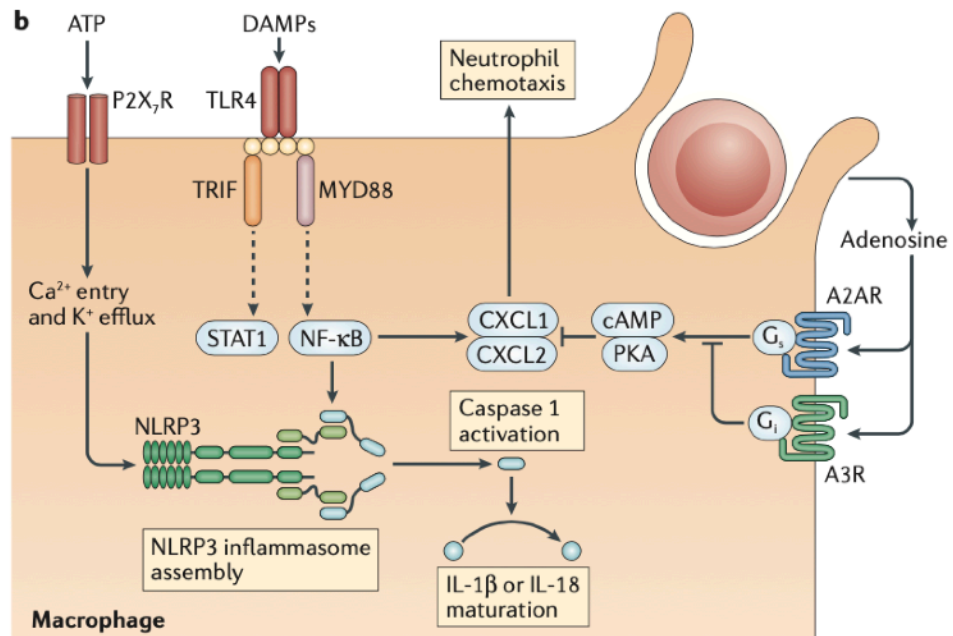
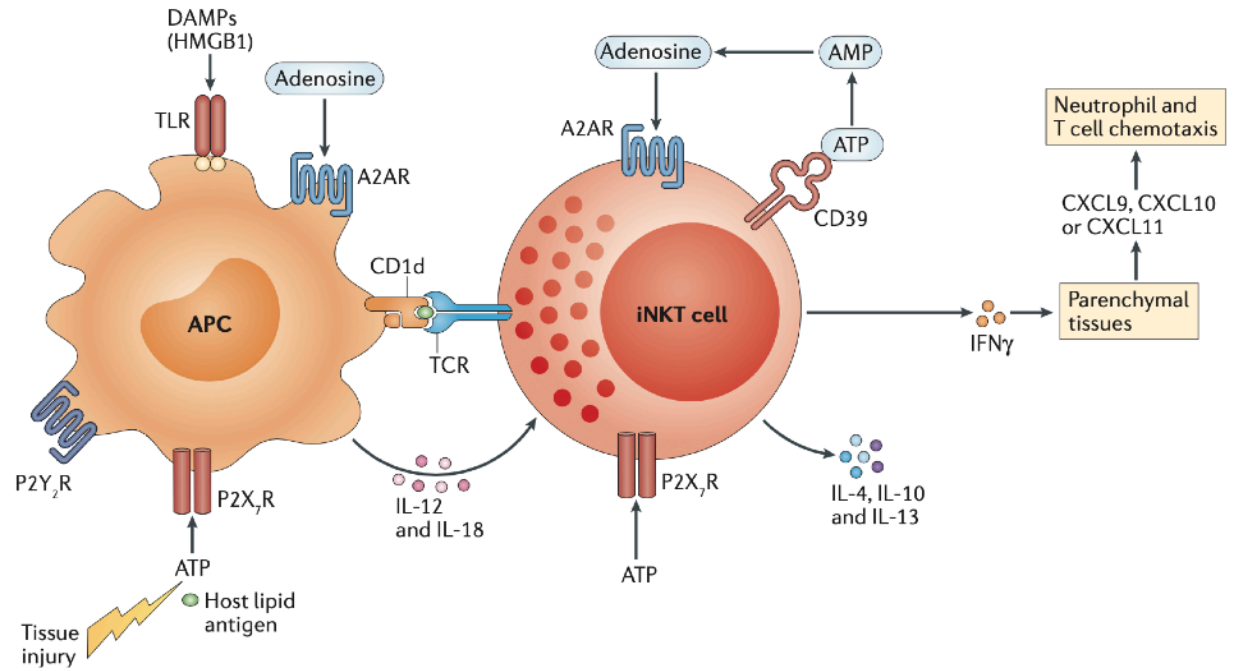
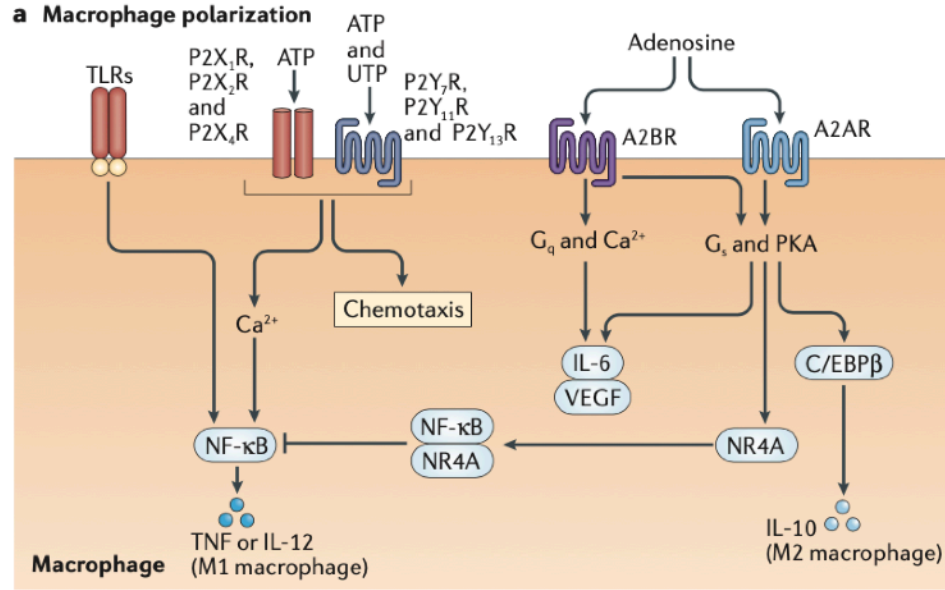


Ivermectin

- modulator of the ATP/P2X4/P2X7 axis
- selectively targets immunosuppressive myeloid cells and Tregs
- functions as an RNA helicase
- an activator of chloride channel receptors
- inducer of mitochondrial dysfunction and oxidative stress

**Both Inhibit Plasmodium parasite of the blood plasma.
a parasite that affects the oxygen carrying capacity of the red blood cells**

Purinergic Signaling in Monocyte/ Macrophages, Natural Killer Cells, Neutrophils





AMERICAN
SOCIETY FOR
MICROBIOLOGY

Antimicrobial Agents
and Chemotherapy®

100 Years of Suramin

Natalie Wiedemar,^{a,b} Dennis A. Hauser,^{a,b}  Pascal Mäser^{a,b}

SURAMIN, THE FRUIT OF EARLY MEDICINAL CHEMISTRY

SURAMIN AS AN ANTIPARASITIC DRUG

SURAMIN AS AN ANTIVIRAL AGENT

SURAMIN AGAINST CANCER

SURAMIN AS AN ANTIDOTE

Three of the many biological activities of suramin support its potential use as a protective agent: the inhibition of thrombin, the inhibition of phospholipase A2, and the inhibition of purinergic signaling

FURTHER POTENTIAL USES OF SURAMIN

Citation Wiedemar N, Hauser DA, Mäser P. 2020. 100 years of suramin. *Antimicrob Agents Chemother* 64:e01168-19. <https://doi.org/10.1128/AAC.01168-19>.

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Address correspondence to Pascal Mäser, pascal.maeser@unibas.ch.

Accepted manuscript posted online 16 December 2019

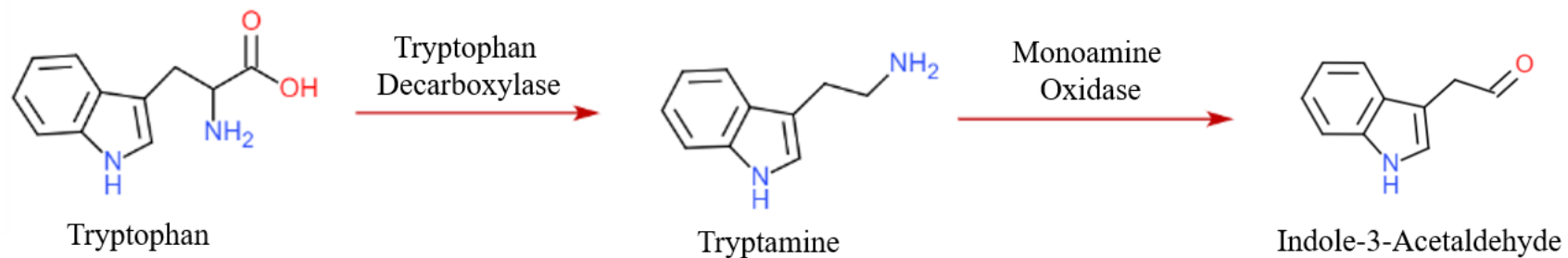
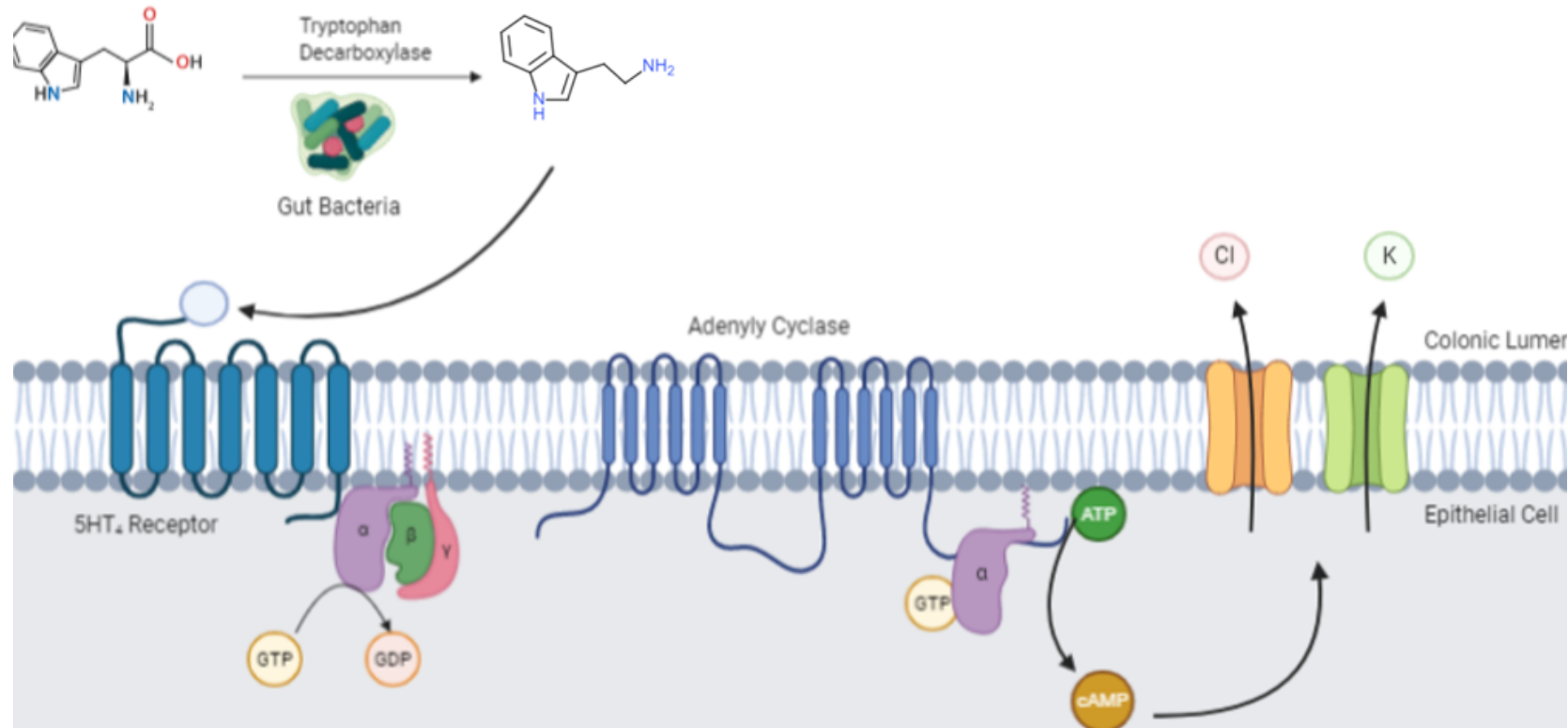
Published 21 February 2020



TABLE 1 Diseases and pathogens susceptible to suramin

Disease and/or pathogen	Activity in ^a :		
	Cell culture	Animal model	Patient
Parasitic infections			
<i>T. b. rhodesiense</i> HAT	X	X	X
<i>T. brucei gambiense</i> HAT	X	X	X
Surra, <i>T. evansi</i>	X	X	NA
River blindness, <i>O. volvulus</i>	X	X	X
<i>T. cruzi</i>	X		
<i>Leishmania</i> spp.	X		
<i>P. falciparum</i>	X		
Viral infections			
Hepatitis virus	X	X	X
AIDS, HIV	X		X
Herpes simplex virus	X	X	
Chikungunya virus	X	X	
Enterovirus 71	X	X	
Dengue virus	X		
Zika virus	X		
Ebola virus	X		
Neoplastic diseases			
Non-small cell lung cancer	X	X	
Breast cancer	X	X	
Bladder cancer	X	X	
Brain tumors	X	X	
Prostate cancer	X	X	X
Other			
Snakebite	X	X	
Arthritis	X	X	
Autism	NA	X	X

GOD GIVEN/Endogenous Microbiome Metabolizes Food



Gut Dysbiosis Promotes M2 Macrophage Polarization and Allergic Airway Inflammation via Fungi-Induced PGE₂

Yun-Gi Kim,^{1,2,5} Kankanam Gamage Sanath Udayanga,^{1,2} Naoya Totsuka,^{1,2} Jason B. Weinberg,⁴ Gabriel Núñez,⁵ and Akira Shibuya^{1,2,3,*}

¹Department of Immunology, Faculty of Medicine

²Japan Science and Technology Agency, Core Research for Evolutional Science and Technology (CREST)

³Life Science Center of Tsukuba Advanced Research Alliance (TARA)

University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan

⁴Department of Pediatrics and Communicable Diseases, Microbiology, and Immunology

⁵Pathology and Comprehensive Cancer Center

University of Michigan Medical School, Ann Arbor, MI 48109, USA

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<http://dx.doi.org/10.1016/j.chom.2013.12.010>

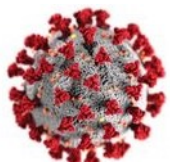
Celebrex

Only certain antibiotics promote fungal overgrowth in the gut, suggesting
Specific commensal bacteria have the ability to prevent colonization of Candida

Kinetics and Intensity of Anti-viral Response with Holistic Intervention

Prophylaxis

Vitamin C
Vitamin D
CBAs
Melatonin
Curcumin



Prophylaxis

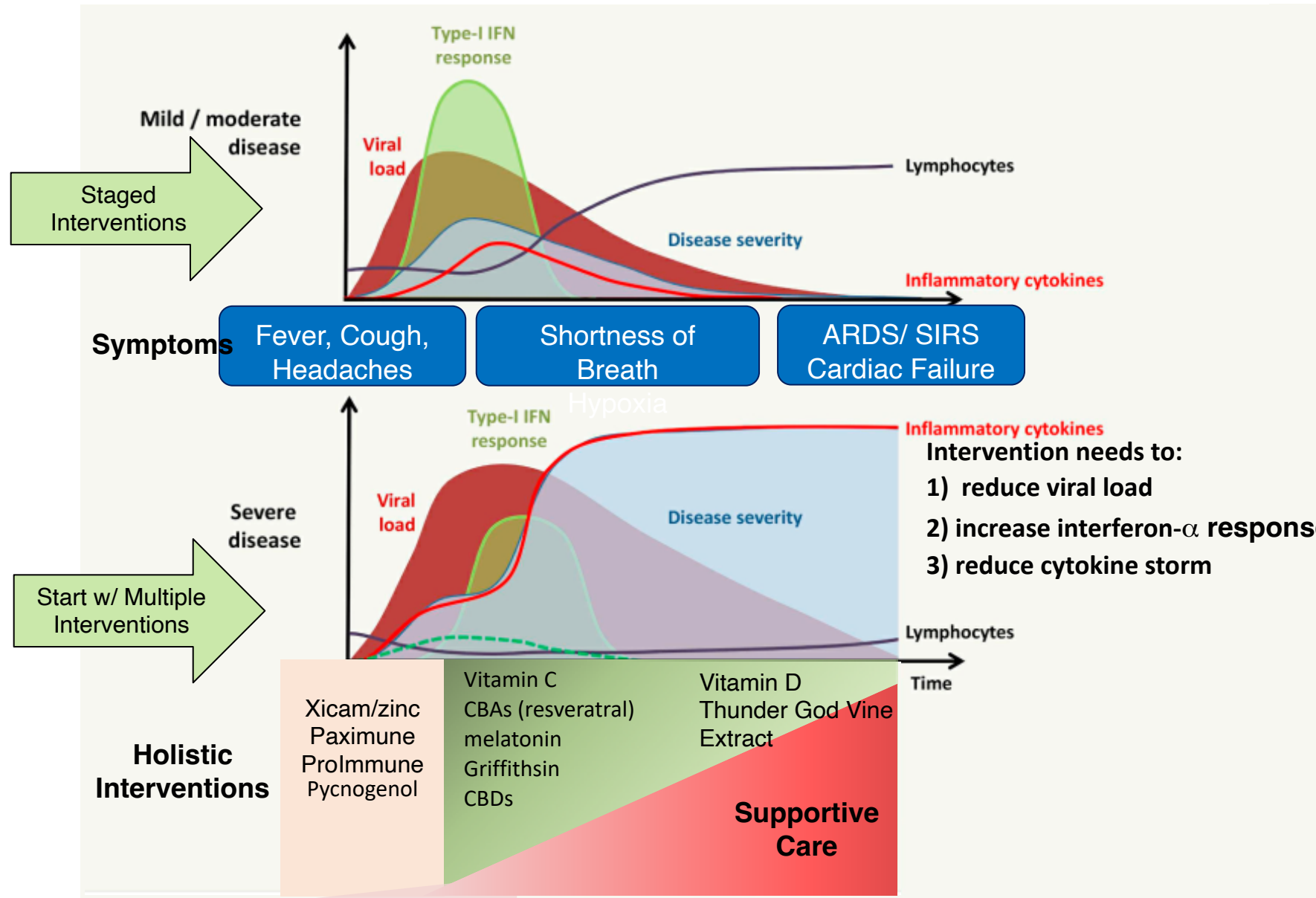
Vitamin C
Vitamin D
Curcumin
CBAs
melatonin
CBDs
Zinc



At risk



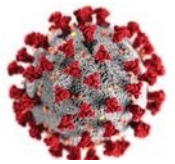
Genetic
susceptibility



Kinetics and Intensity of Anti-viral Response with Pharmaceutical Intervention

Prophylaxis

Vitamin C
Vitamin D
CBAs
Melatonin
Curcumin



Prophylaxis

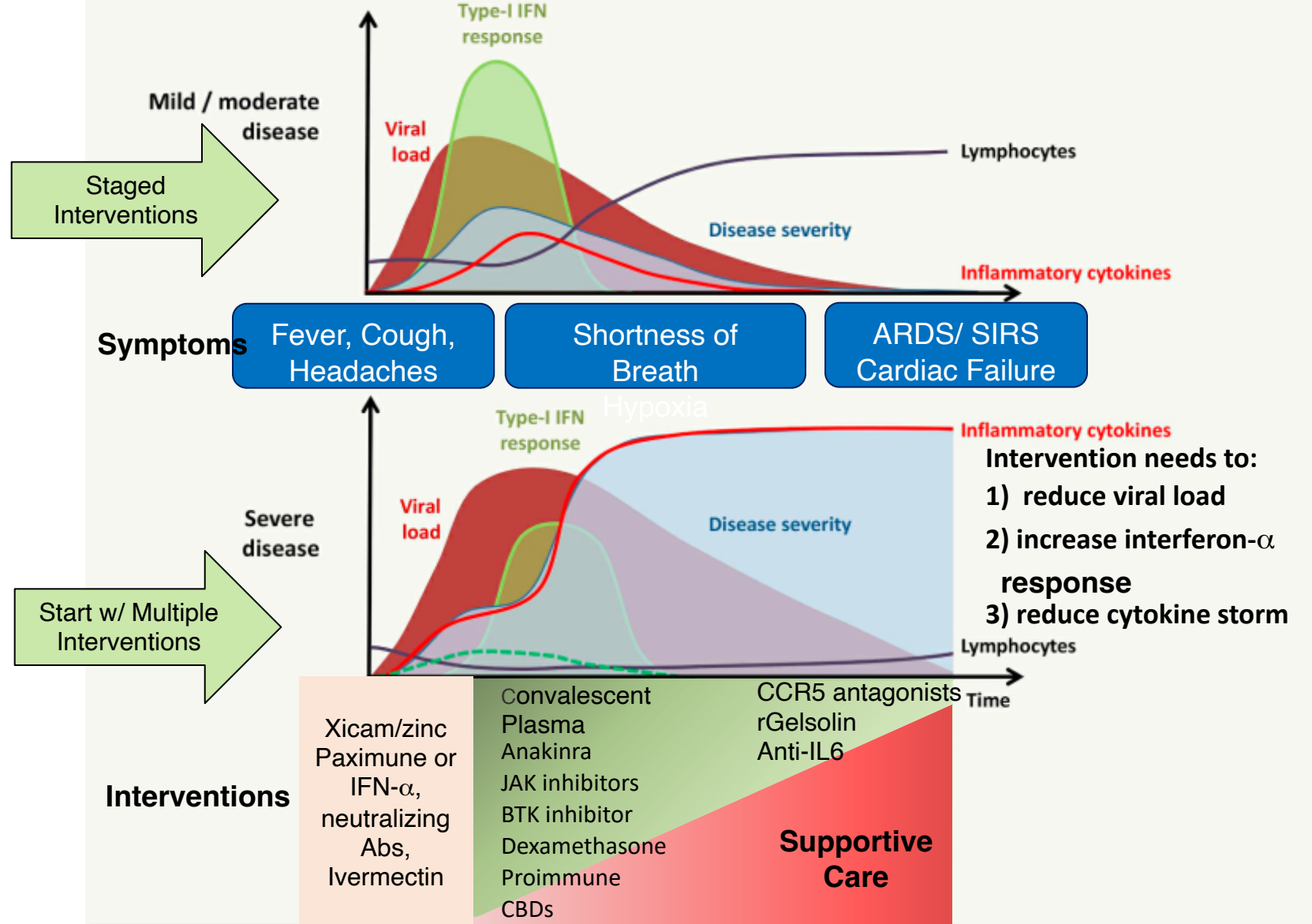
Vitamin C
Vitamin D
Curcumin
CBAs
melatonin
CBDs
Zinc



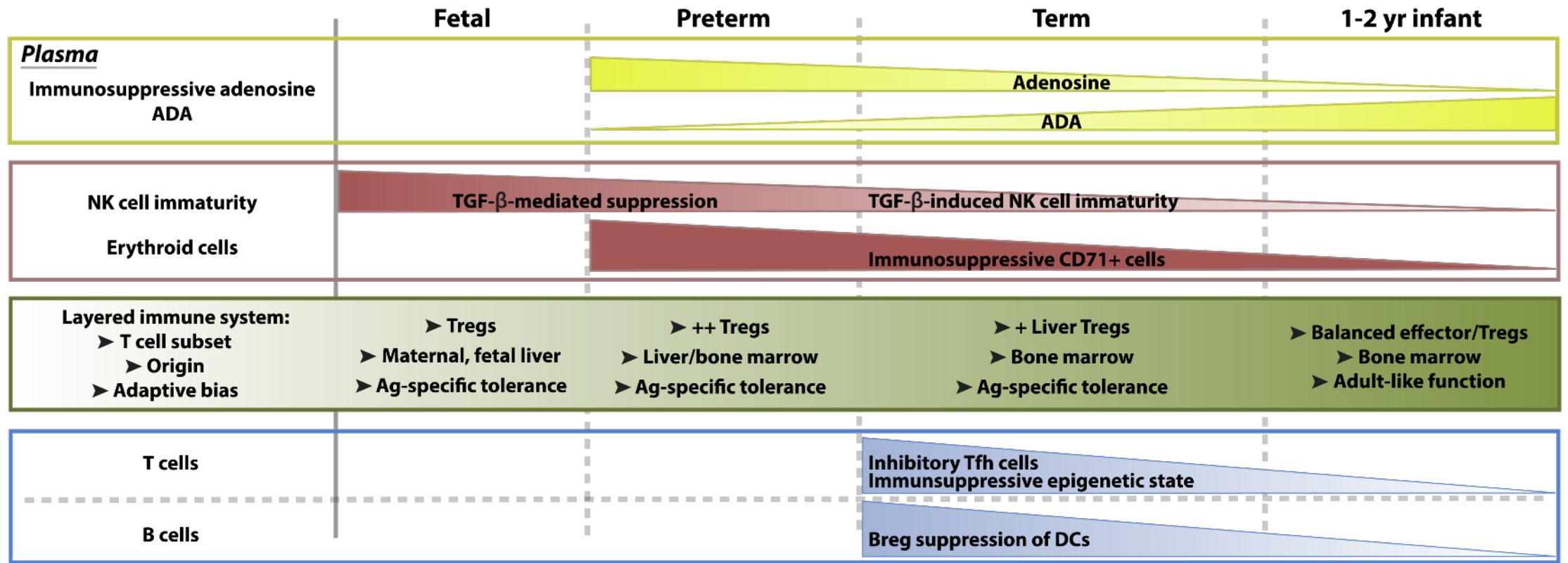
At risk



Genetic susceptibility



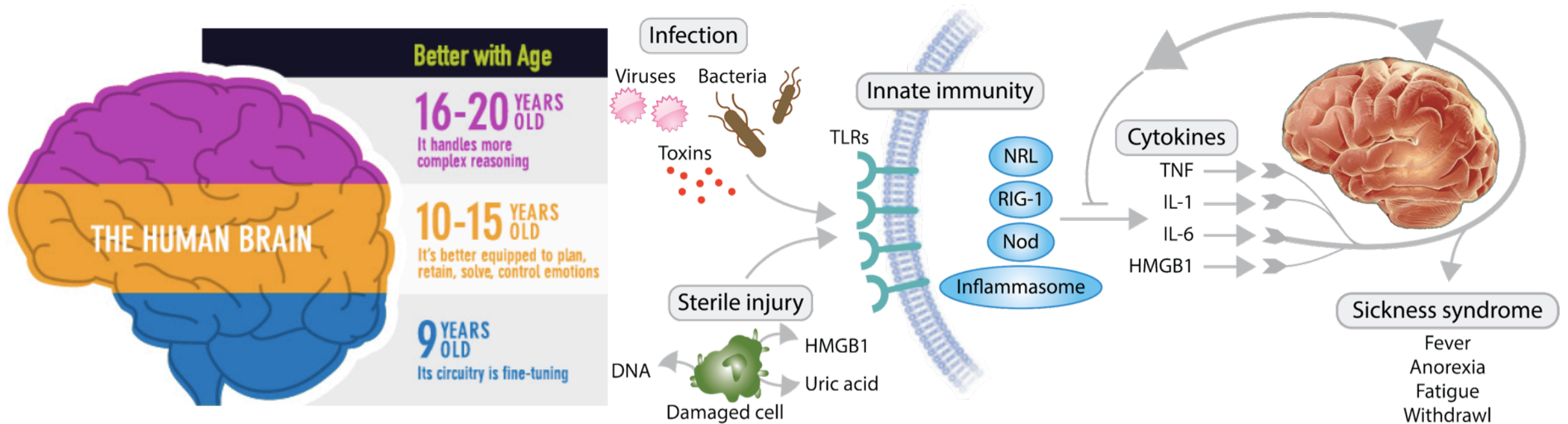
Immunity is not static: it changes with age; many unique features in early life



TRENDS in immunology

The Brain and The Immune System are inextricably linked from Conception

Danger of Inoculation During key Developmental Phases

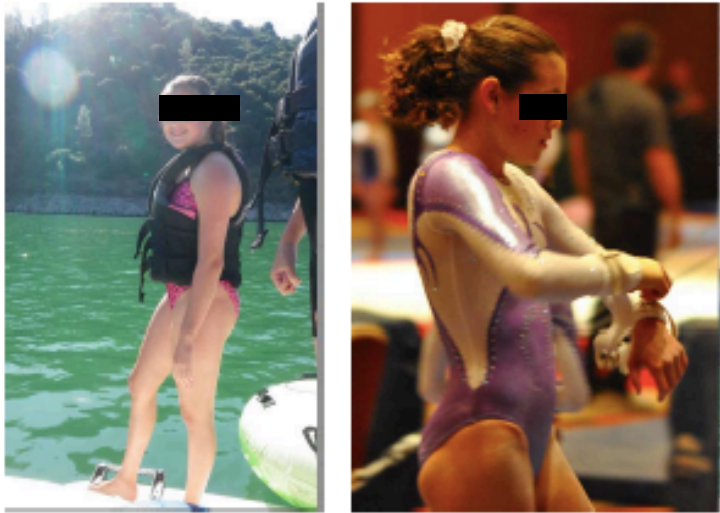


- The Brain cannot tolerate the introduction of antigens without eliciting an inflammatory immune response

GARDASIL INJURY

Death, Leukemia, Psychosis, Cardiac Arrest, Autoimmune Disease, Alopecia, Sterility in 25% of those vaccinated

Jessica – Before Vaccine



Jessica – After Vaccine



**IS IT GARDASIL INJURY
OR NON-HIV AEIDS?**



Lauren After Gardasil

**Is it Gardasil Injury or COVID
Hair loss? Is there a difference?**

Poisons (ADJUVANTS): Aluminum, LPS (ENDOTOXIN), Xenoestrogens, Arsenic in Vaccines food & water target Innate Immune responses

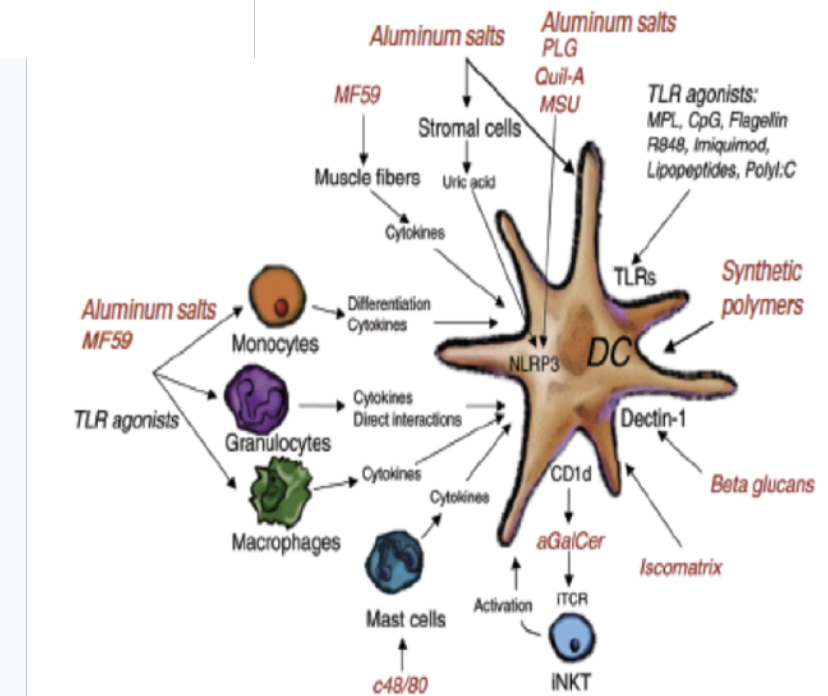
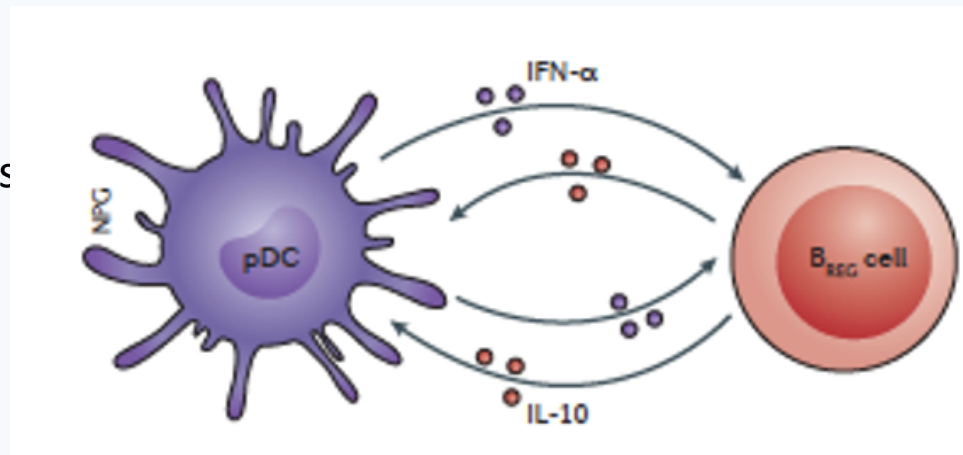
Lupus is an autoimmune inflammatory disease in which the body produces antibodies causing the immune system to affect the skin, joints, blood and kidneys.

Symptoms include:

- Skin rashes/ Inflammation
- Arthritis/ Joint Pain
- Extreme Fatigue
- Anemia/ Blood Disorders
- Kidney Damage
- Immune Disorder
- Antinuclear Antibodies

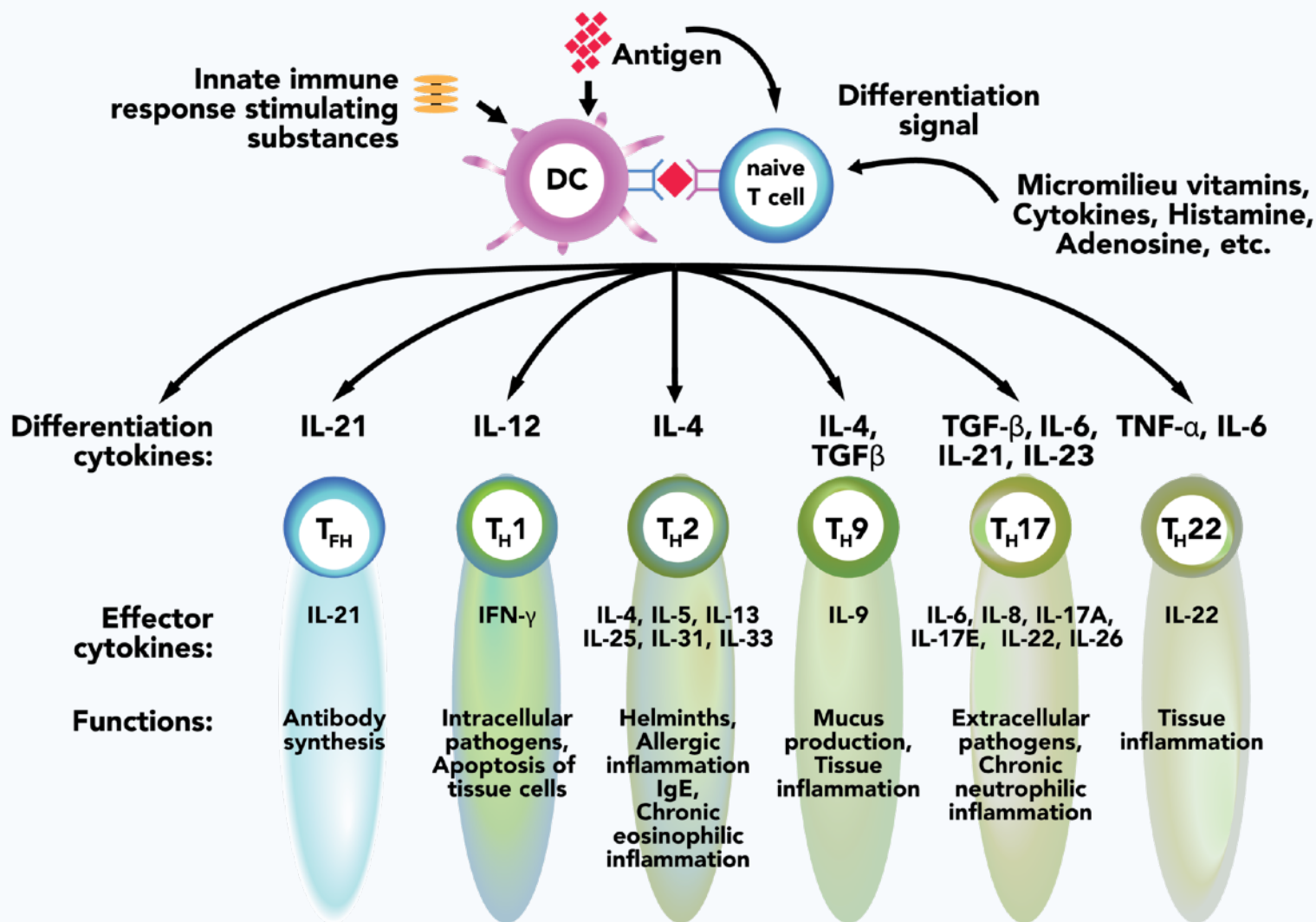
Nature Reviews Rheumatology | Published online 24 Mar 2016; doi:10.1038/nrrheum.2016.43

Compromised pDC-B_{REG} cell crosstalk



Unintended Consequences of Inappropriate Immune Activation?

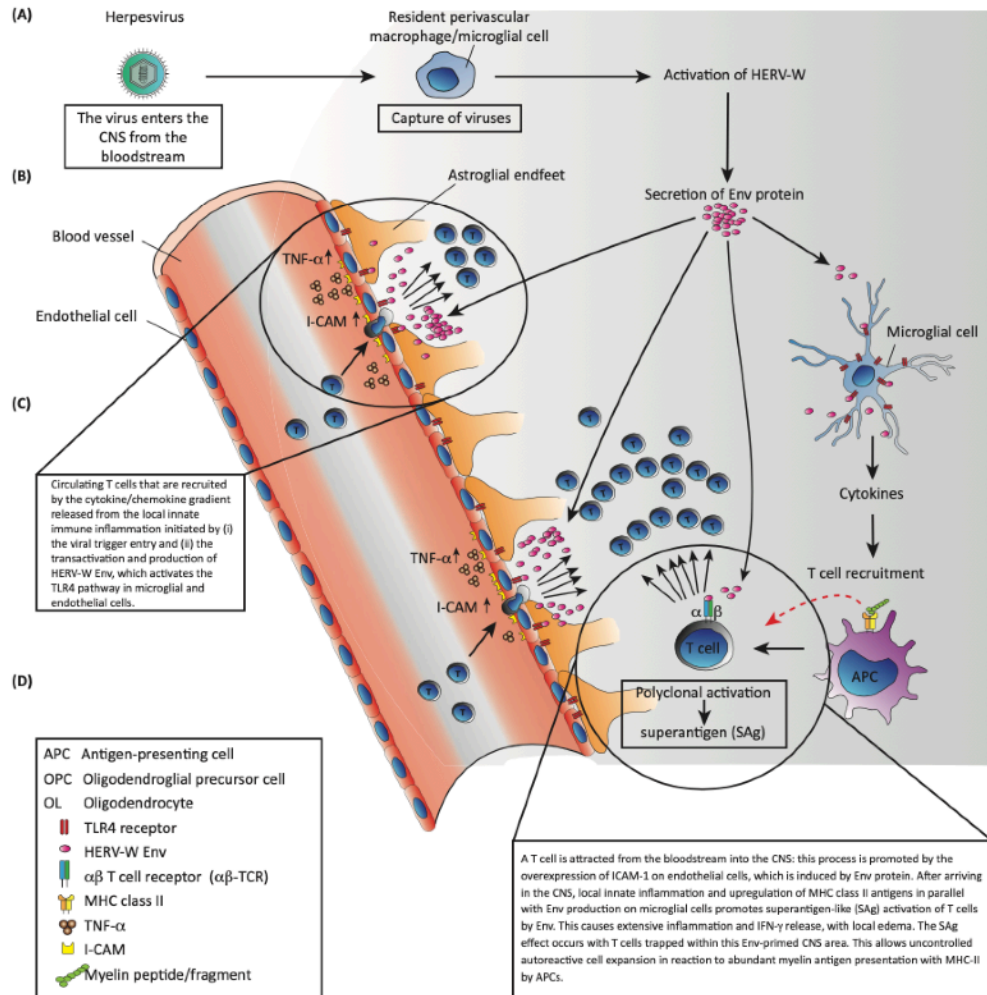
Inappropriate Activation of the cellular Immune system is important in the pathogenesis of human Retrovirus Associated Disease



Every Experimental injection Bypasses The Innate Immune System

“We also introduce chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)”

Moreover, HERVs have also been associated with other diseases such as schizophrenia and bipolar disorder, type 1 diabetes

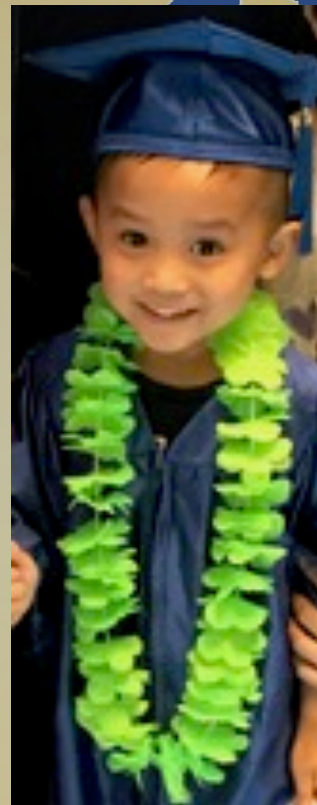


Chronic inflammatory demyelinating polyneuropathy (CIDP): a peripheral nervous system disease and the commonest chronic immune-mediated peripheral neuropathy that takes either a relapsing or progressive course. Clinically it manifests by the development of weakness and sensory disturbance that lead to marked disability. Multifocal inflammation and stripping of myelin sheaths by macrophages are thought to result from aberrant immune responses, mediated by T and/or B lymphocytes, against peripheral nerve antigens.

1986theact.com NVICP Justice Denied: HBV vaccine at birth when DNA Methylation resets



We Can Restore Faith in The Promise of Science



XMRVs: of MICE, Monkey & Manufactured Viruses Human Xenotransplantation - Threats Masquerading as Vaccines.

September 1, 1996

- Dr. John Coffin*, a leading expert on recombination in viruses, concluded "the infection is a virtually inevitable consequence" of xenotransplantation and "This is a very serious worry because the animals that have been chosen for doing this -- the baboon and the pig -- are both known to carry endogenous viruses, replication competent, but very poorly studied, that are capable of infecting human cells."."
- FDA convened lengthy hearings of the National Academy of Sciences' Institute of Medicine and its own Biological Response Modifiers Advisory Committee. Dr. Marion Michaels*, from the University of Pittsburgh, told the committee that despite rigorous screening, "the donor organ, the tissue or the accompanying hematopoietic cells can also be the source of infection. Most often these infections are latent organisms and are often clinically silent in the donor."

Isn't Injecting babies and the elderly with mouse, monkey and manufactured viruses capable of infecting human cells the same thing??

What can we do?

- LivComplete/Pro Lean Greens – Glutathione production – P450
- DMG – Methylation/Super B complete –ATP - Neurotransmitter
- Lean greens – chelator
- Activin (Circucore)/Quercetin – endothelial repair
- CBD/D – lipophilicity
- Reprograming DNA for Tauopathy repair
 - Natural Kinase inhibitors: Quercetin, Resveratrol, Berberine, CBD, Omegas, SPM
- Omegas – Cellular integrity
- Gut Health – GI complete, IgG, Probiotics
- Gut Integrity – KBMO Testing