Restoring Immune and Stem Cell Function and Homeostasis Using Natural Remedies and Purinergic Therapy

Judy A. Mikovits, PhD
November 19, 2017
www.marcinc.org

Waking to a New Dawn: The Emergence of 21st Century Acquired Immune Deficiencies & Innovative Solutions

1980 Discovery of HTLV-I

Pathogenesis:

- **Asymptomatic in majority of individuals**
- **5% lifetime risk of developing either type of disease:**

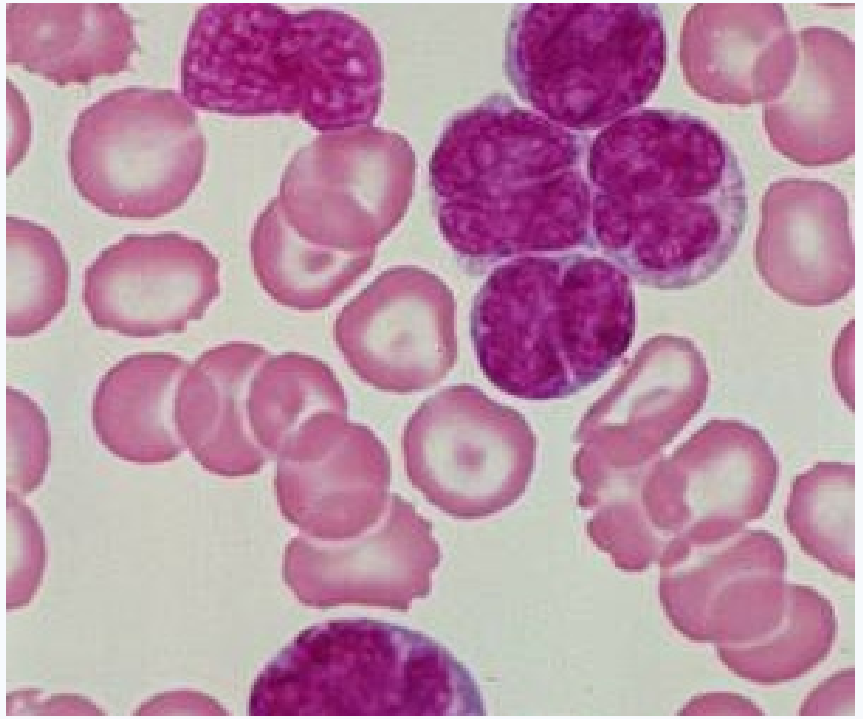
- Adult T cell leukemia

- Clonal malignancy of $CD4^+$ T cells.
- Long latency; Immune deficiency

- Inflammatory syndromes not realized until decades later

HTLV-I associated myelopathy/Tropical spastic paraparesis

- Uveitis
- Arthropathy
- Sjogren's Syndrome

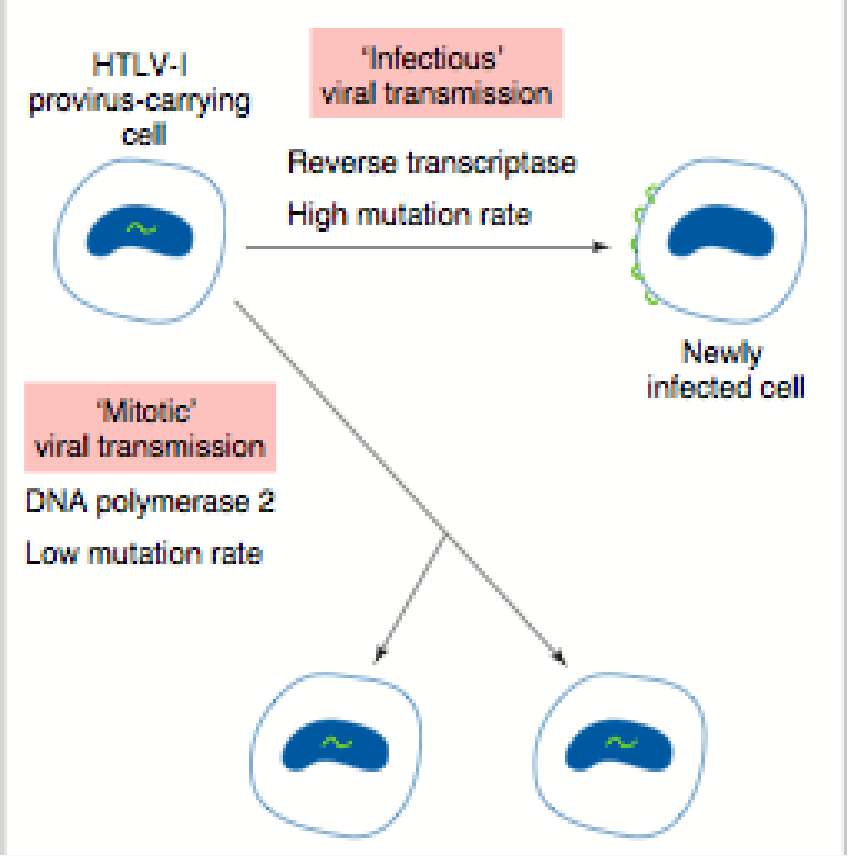


Many Factors important in Development of Chronic Diseases associated with Retroviruses

Subacute progression of human T-lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis

Journal of NeuroVirology
September 2007, Volume 13, Issue 5, pp 468–473

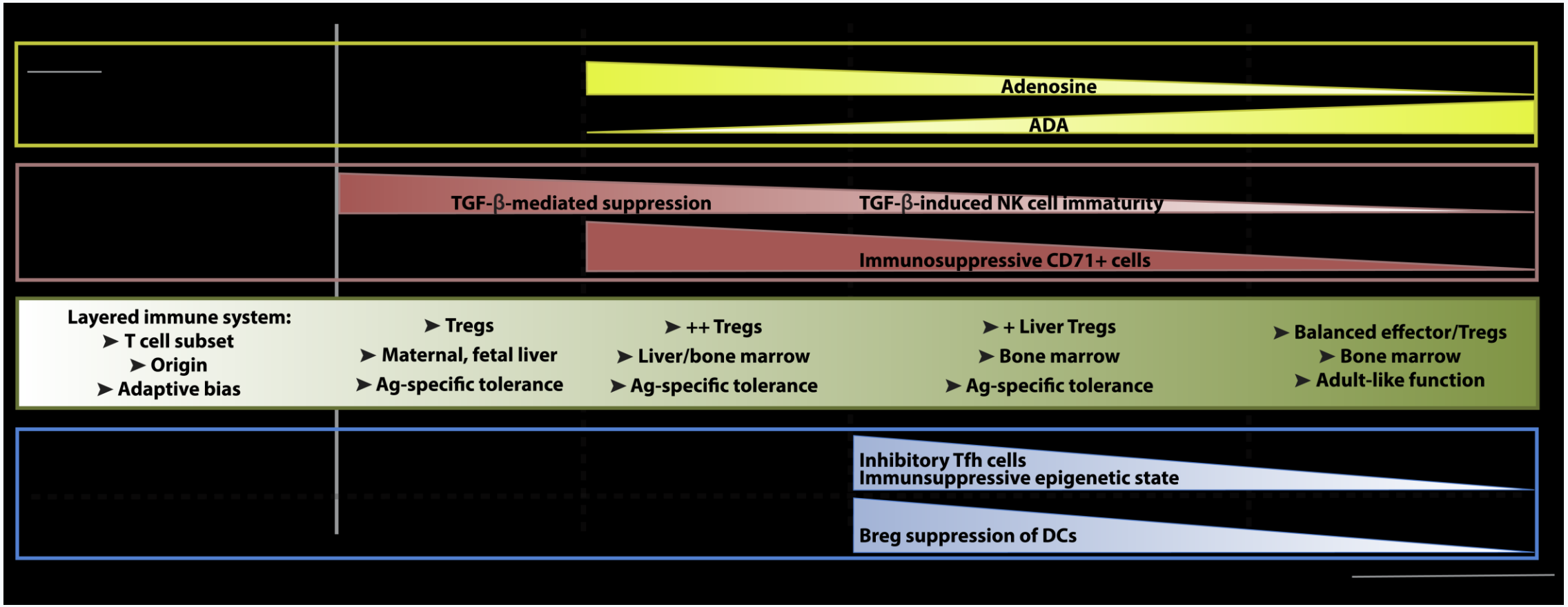
Marco A. Lima, Ramza C. Harab, Doris Schor, Maria J. Andrada-Serpa, Abelardo Q. C. Araújo



HAM/TSP Usually Chronic Slowly progressing

- Northeastern Brazil: rapid progression Necessitating Wheelchair in 2 Years
- 8% had rapid progression: Peru 21% had rapid progression
- No difference in Viral Load
- Early Recognition is critical, immune suppressive therapy BENEFICIAL EARLY

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



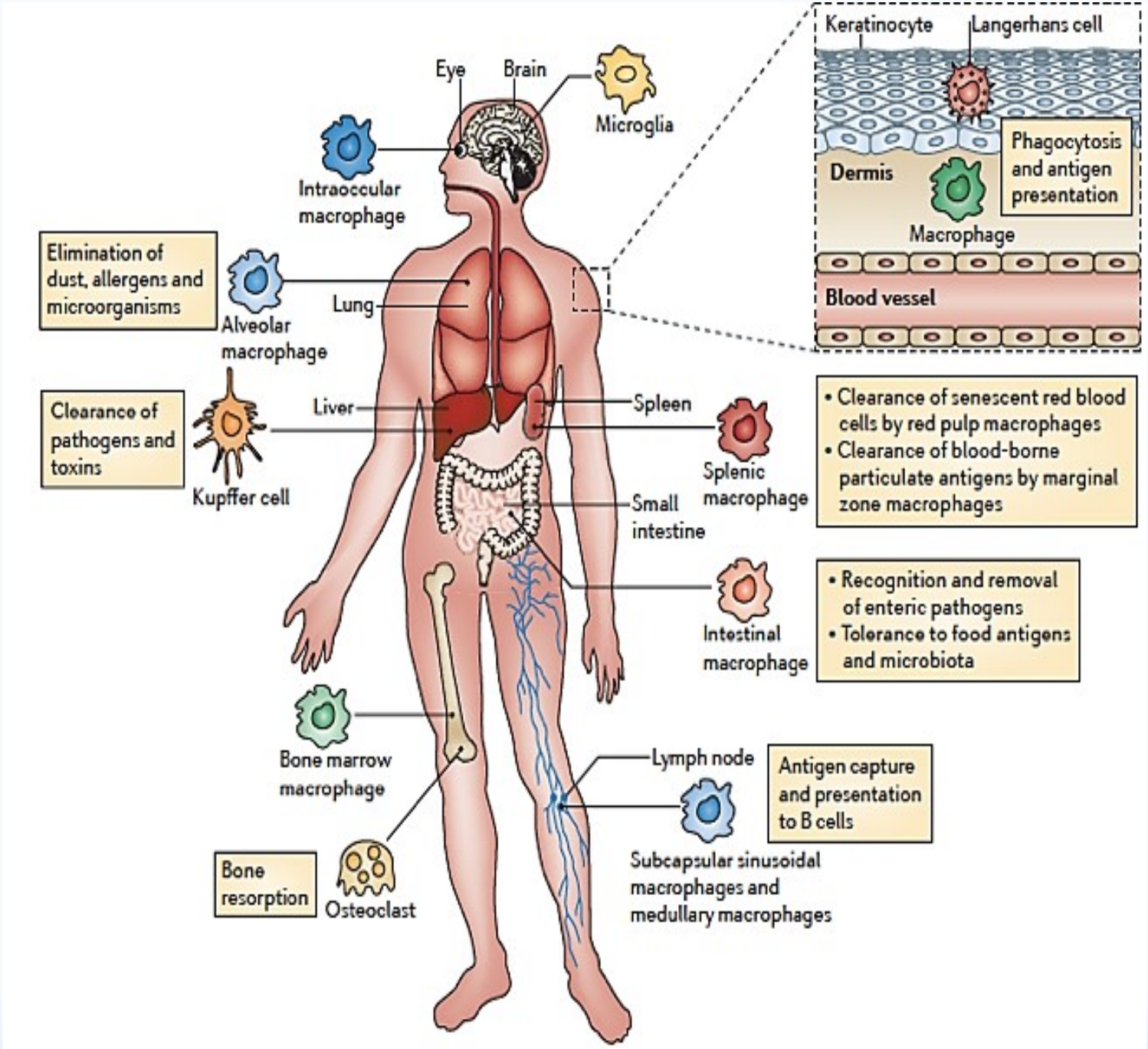
The Brain and The Immune System are inextricably linked from Conception

Monocyte/Macrophage as the Driver of AIDS

- **Express Purinergic Receptors**:
- **P2XR and P2YR**.

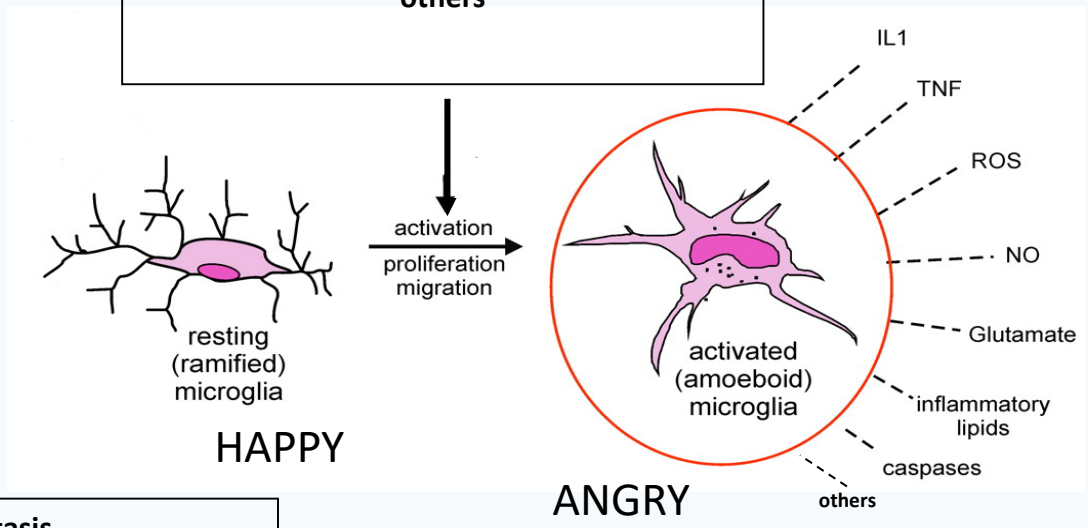
Tissue Macrophages perform Key Homeostatic Functions Modulated by

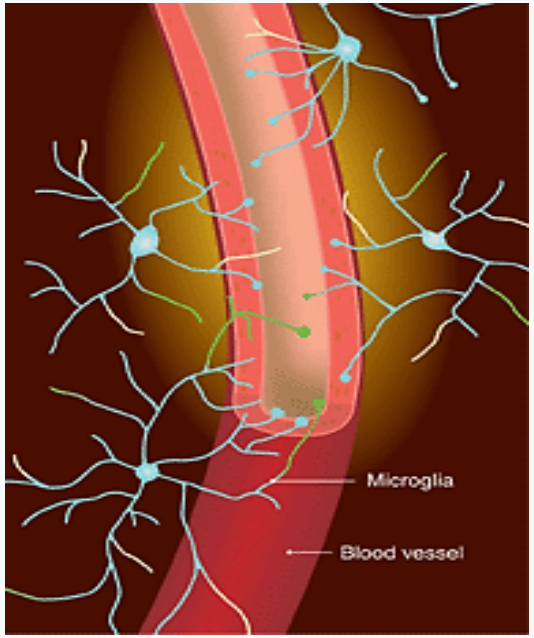
- **Cannabinoids**
- **Suramin**
- **Flavonoids Baicalein, Quercetin**
- **GcMAF(Rerum)**



Microglia Activation in Neurodegeneration

Stimuli
Loss of cell:cell communication, matrix breakdown, infections, vascular damage, others





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

Homeostasis
Phagocytosis of debris, neurotrophins

Damage
Neurotoxins, phagocytosis of normal neurons, apoptosis

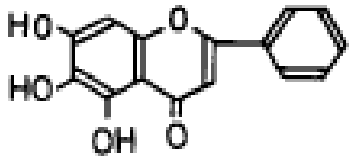
Neurodegenerative disorders

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

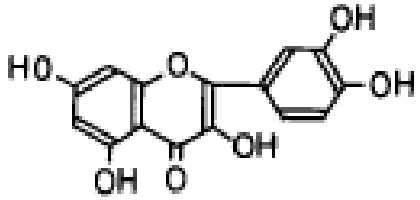
Eur. J. Biochem. *190*, 469–476 (1990)

Differential inhibitory effects of various flavonoids on the activities of reverse transcriptase and cellular DNA and RNA polymerases

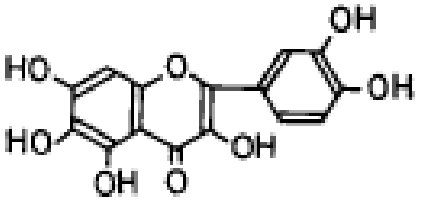
Katsuhiko ONO[1], Hideo NAKANE[1], Masanori FUKUSHIMA[2], Jean-Claude CHERMANN[3] and Françoise BARRÉ-SINOUSSI[4]

A 

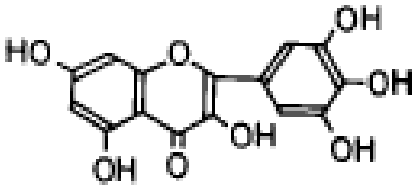
Baicalein

B 

Quercetin

C 

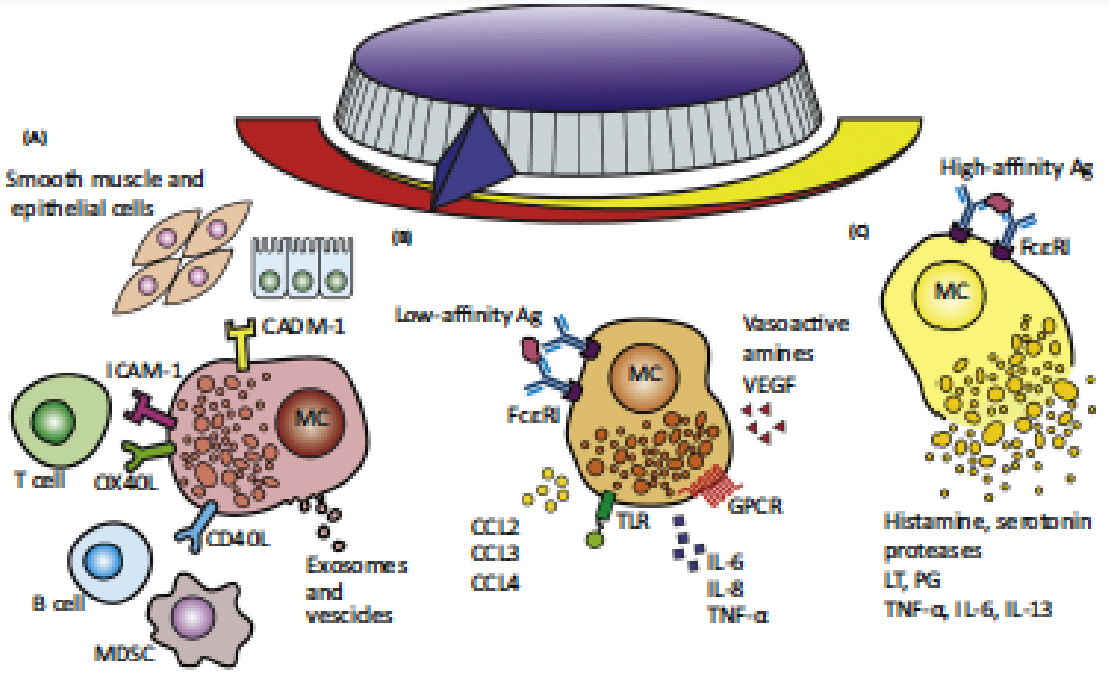
Quercetagetin

D 

Myricetin

MAST cell a Rheostat ?

Modulates Type and amplitude of innate and adaptive Immune



- Homeostatic function
- Cell–cell interactions
- Spontaneous mediator release

- Selective release of 'prestored' inflammatory mediators
- Selective release of 'neosynthesized' cytokines and/or chemokines
- Local reaction

- Massive degranulation and prolonged inflammation
- Systemic reaction
- Tissue 'remodeling'

OPEN ACCESS Freely available online

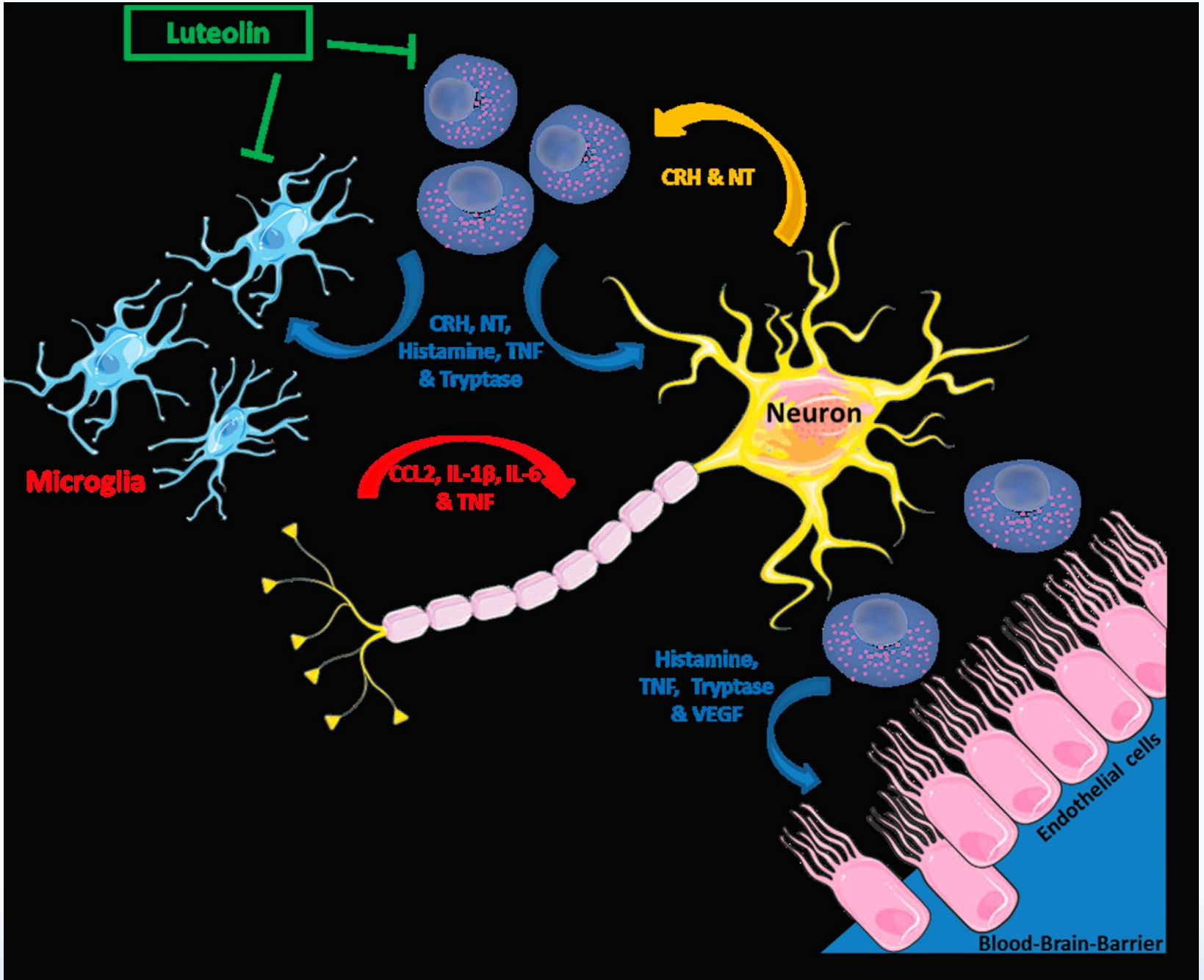
PLoS one

Quercetin Is More Effective than Cromolyn in Blocking Human Mast Cell Cytokine Release and Inhibits Contact Dermatitis and Photosensitivity in Humans

Zuyi Weng[1,2☯], Bodi Zhang[1,2,3☯], Shahrzad Asadi[1,4], Nikolaos Sismanopoulos[1], Alan Butcher[5], Xueyan Fu[6], Alexandra Katsarou-Katsari[7], Christina Antoniou[7], Theoharis C. Theoharides[1,2,3,8*]

March 2012 | Volume 7 | Issue 3 | e33805

Interactions among mast cells–microglia–neurons and the blood–brain barrier



Citation: Transl Psychiatry (2016) 6, e844; doi:10.1038/tp.2016.77

Dendritic Cells vs. Viruses

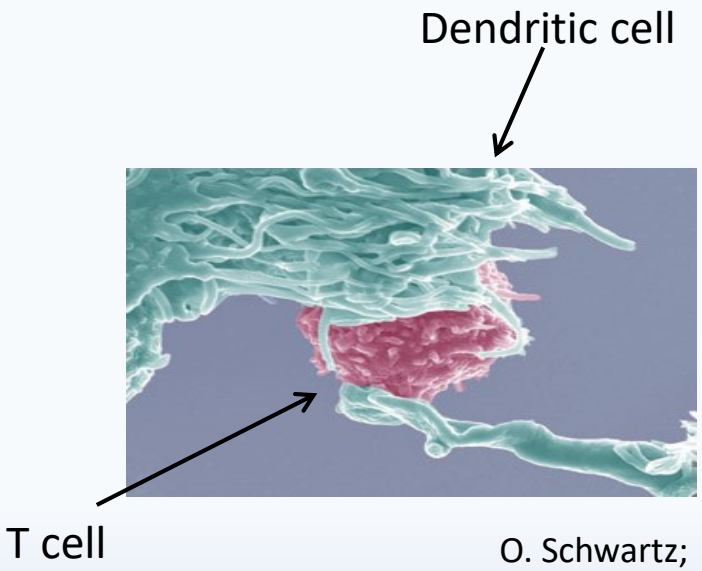
Unintended Consequences of Inappropriate Immune Activation

Many viruses use DC to facilitate spread:

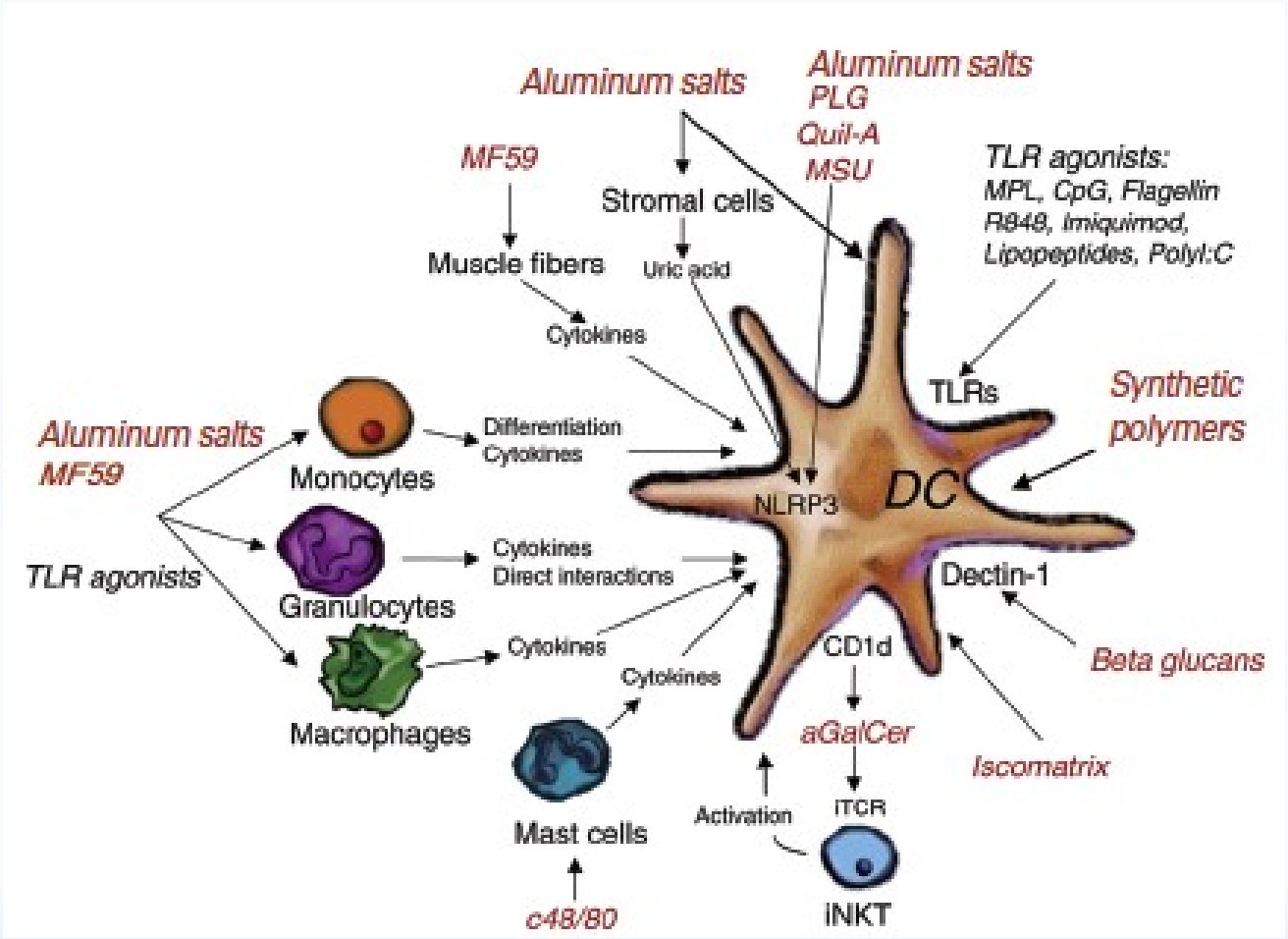
- Some viruses infect DC, then are transmitted to target cells
- Other viruses are transmitted by DC without infection

Viruses can interfere with immune responses:

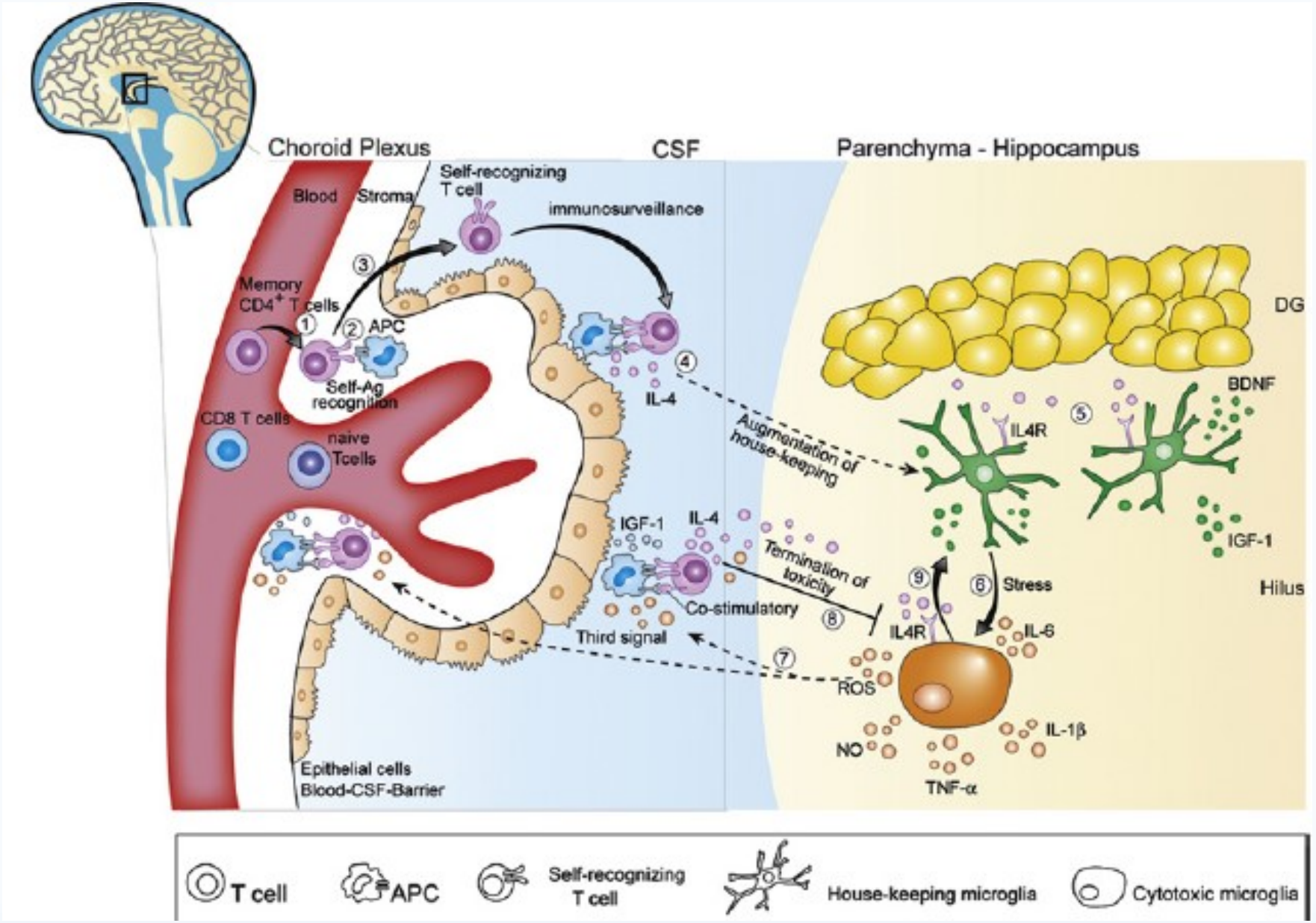
- Inhibit maturation and/or migration of immature DC
- Alter cytokine/chemokine production
- Cause apoptosis
- Impair (or enhance) DC function



O. Schwartz;
Nat Cell Bio



Brain Homeostasis Maintained by Danger Signals

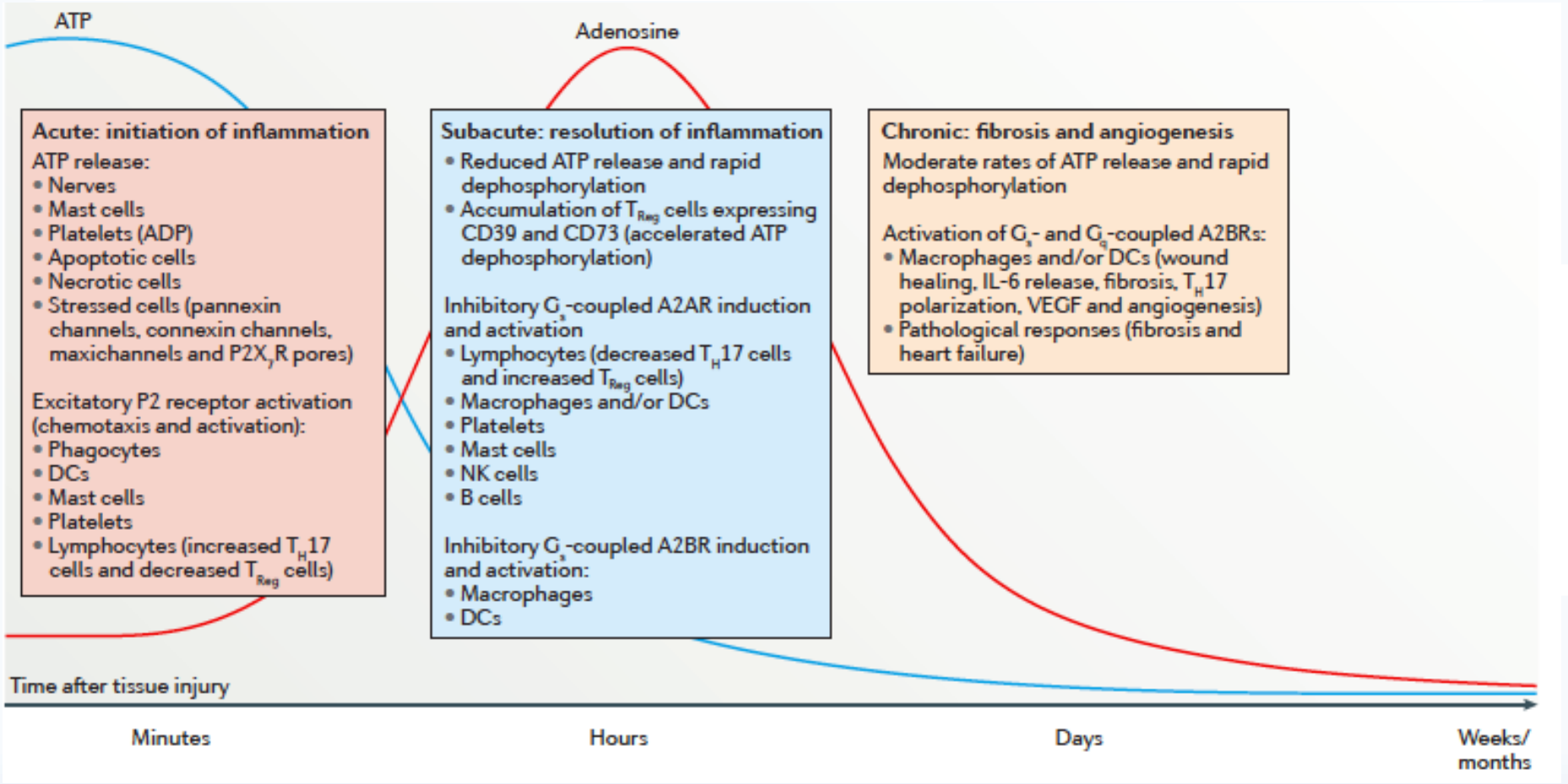


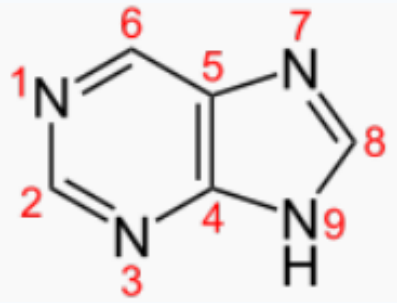
Brain, Behavior, and Immunity 25 (2011) 1036–1043

Purinergic regulation of the immune system

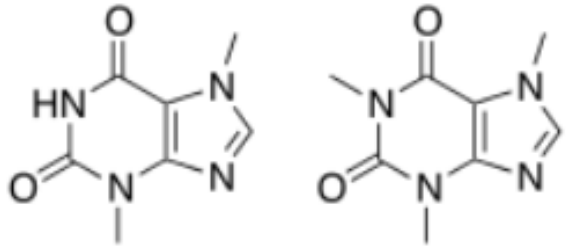
Caglar Cekic[1] and Joel Linden[2]

NATURE REVIEWS | IMMUNOLOGY VOLUME 16 | MARCH 2016 | 177



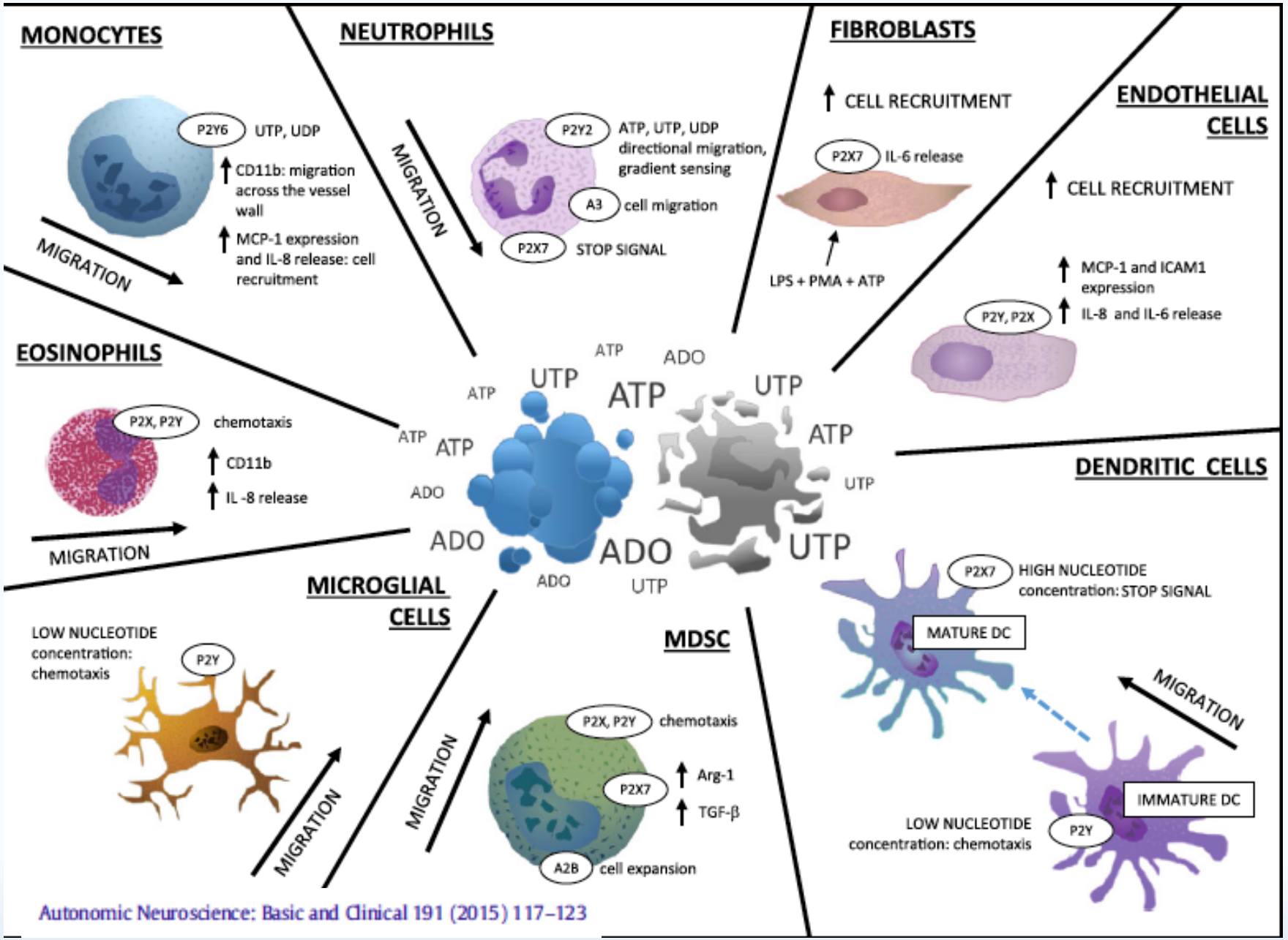


- Nitrogenous bases of DNA
- Deoxyadenosine
- Deoxyguanine



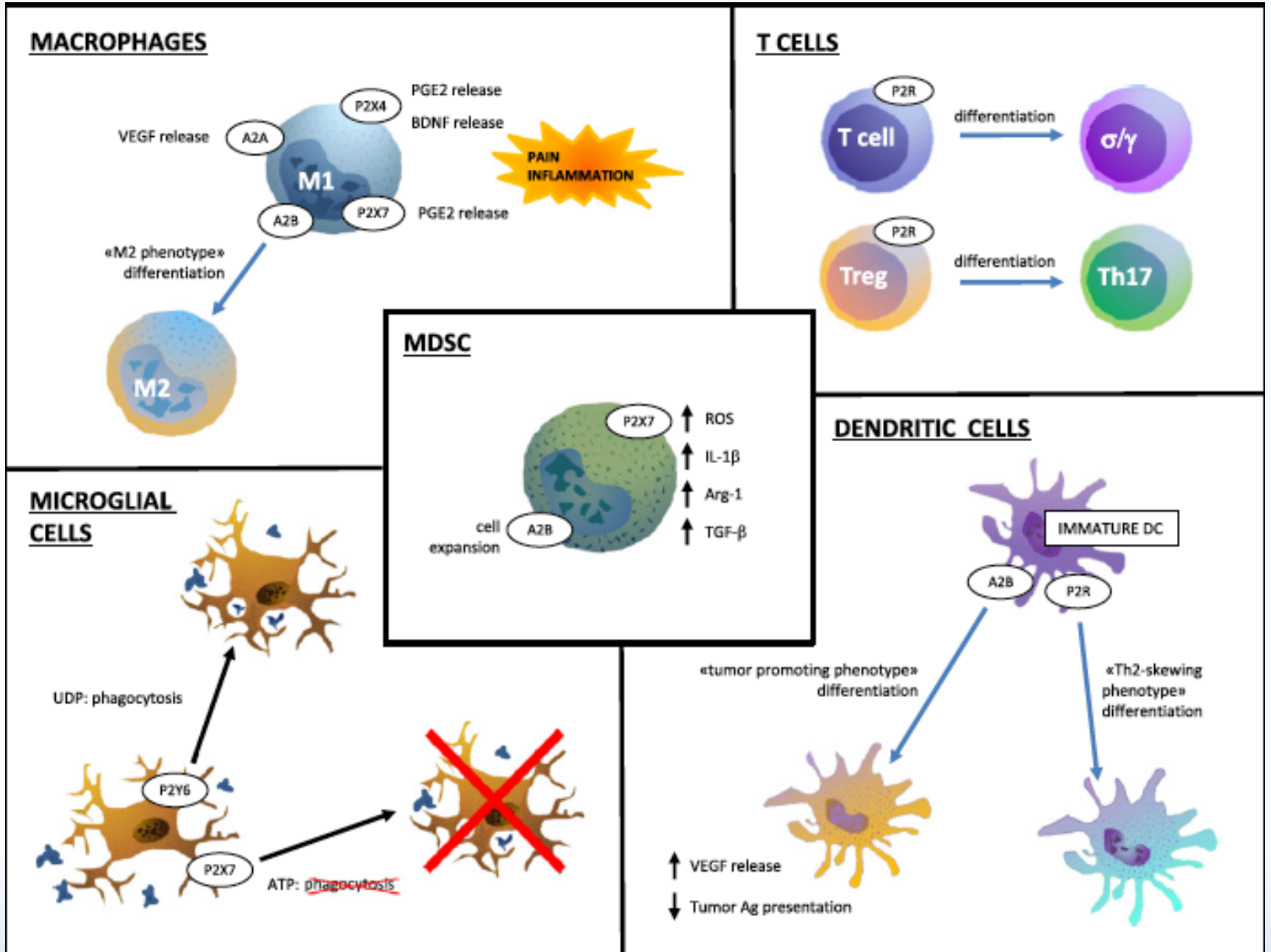
theobromine **6** caffeine **7**

Purinergic Signaling plays a critical Role In Chemotaxis of Multiple Cell Types



Autonomic Neuroscience: Basic and Clinical 191 (2015) 117–123

Pathophysiology of Purinergic Signaling



Trends Mol Med. 2013 June ; 19(6): 355–367. doi:10.1016/j.molmed.2013.03.005.

CD39 and CD73 in immunity and inflammation

Luca Antonioli[1,2], Pál Pacher[3], E. Sylvester Vizi[4,5], and György Haskó[2]
[1]Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy

Trends Mol Med. 2013 June ; 19(6): 355–367. doi:10.1016/j.molmed.2013.03.005.

Highlights

CD39 and CD73 are important for calibrating the duration, magnitude, and composition of the "purinergic halo" surrounding immune cells

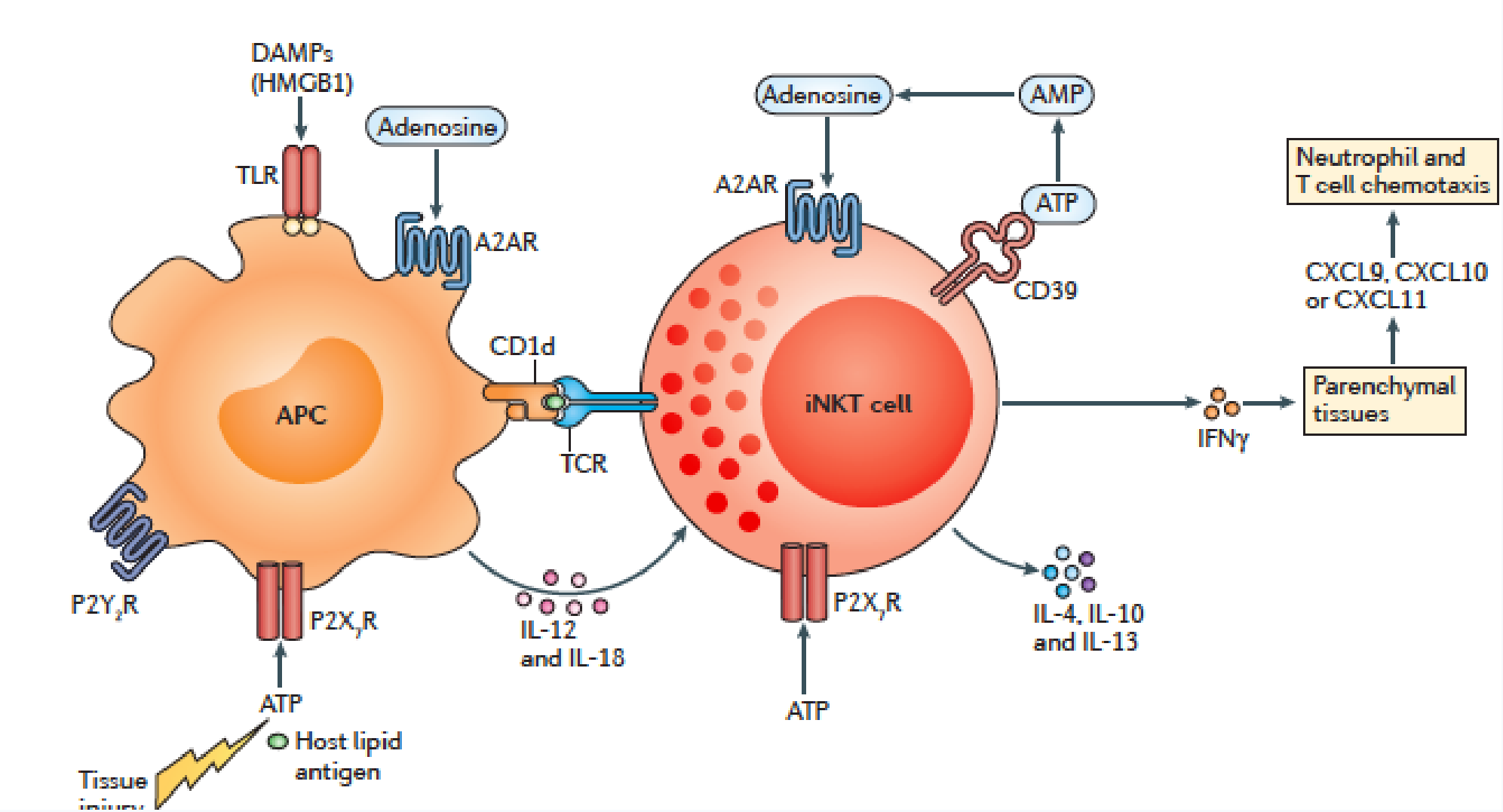
CD39 and CD73 degrade ATP, ADP and AMP to adenosine, they can be viewed as "immunological switches" that shift ATP-driven pro-inflammatory immune cell activity toward an anti-inflammatory state mediated by adenosine

CD39 and CD73 are highly expressed on the surface of Foxp3$^+$ Tregs and have been increasingly used as markers of Tregs

CD39 and CD73 are important for the immunosuppressive activity of Tregs

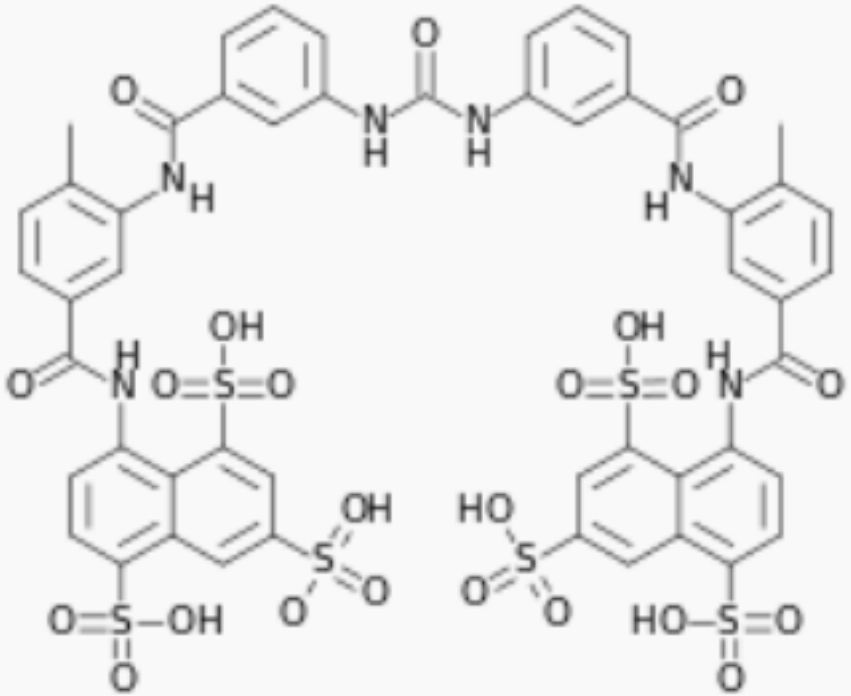
CD39 and CD73 generate an immunosuppressed environment, characterized by increased adenosine levels, which promotes the development and progression of cancer

Adenosine produced by enzymatic Activity of CD39 implicated in progressive immunosuppression HIV/AIDS



P2Y receptor (P2YR) inhibitor (Suramin) critical response to Tissue injury

Suramin: on WHO list of Essential Medicines needed in a Basic Health System



- Antiparasitic 1920s
- Potent RT inhibitor 1986
- P2Y Purinergic Receptor inhibitor
- Cancer therapy prostate cancer, HTLV-1 cancer Bladder Cancer

- inhibit 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

Antiviral Research

Volume 7, Issue 1, January 1987, Pages 1–10

Editorial

Suramin in the treatment of AIDS: Mechanism of action

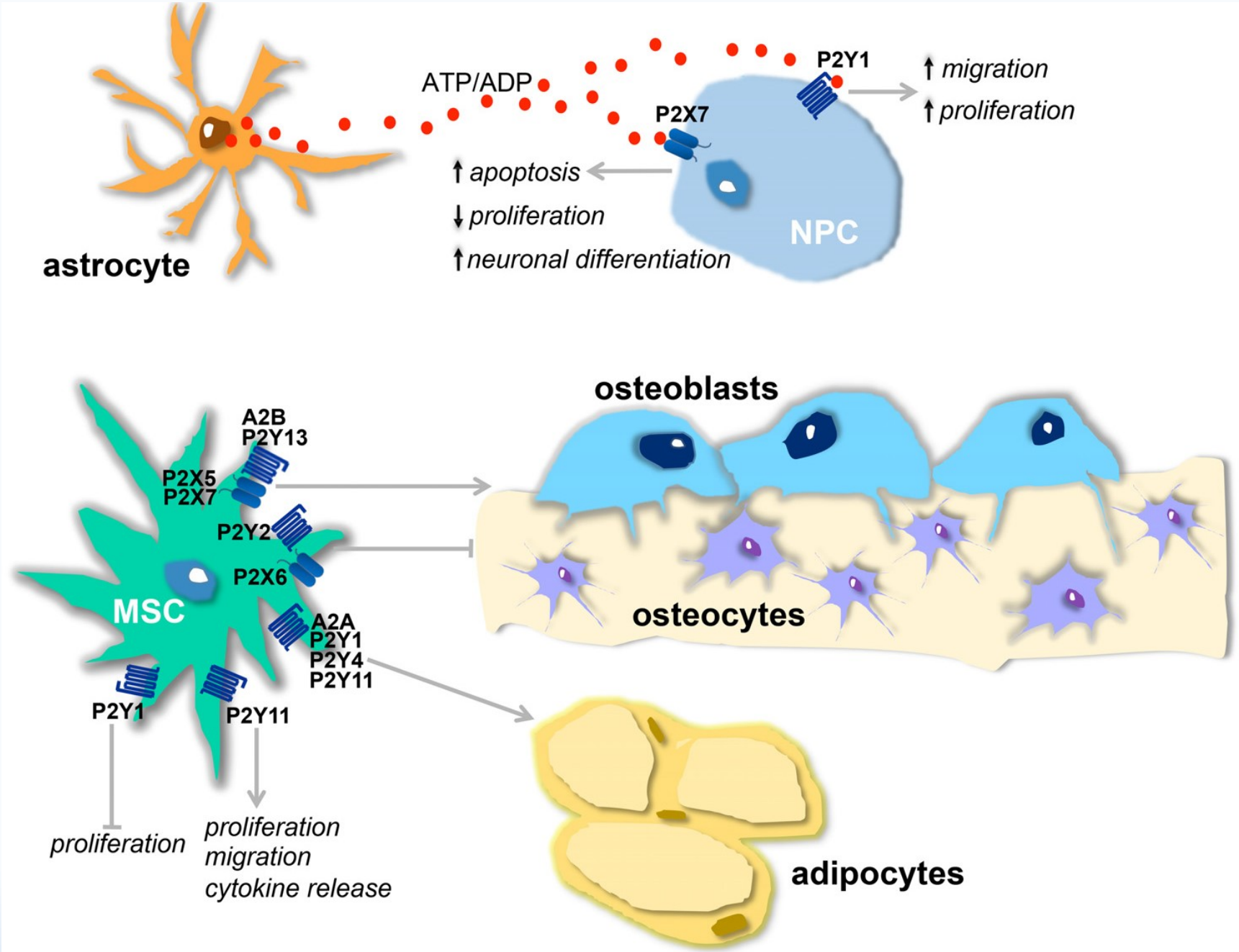
Erik De Clercq

Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

Received 14 April 1986, Accepted 17 April 1986, Available online 12 November 2002

Purinergic signaling neural and Mesenchymal Stem Cell Maintenance and Differentiation

MINI REVIEW
published: 02 June 2015
doi: 10.3389/fncel.2015.00211



Progress in Lipid Research 52 (2013) 633–650

Contents lists available at ScienceDirect

Progress in Lipid Research

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

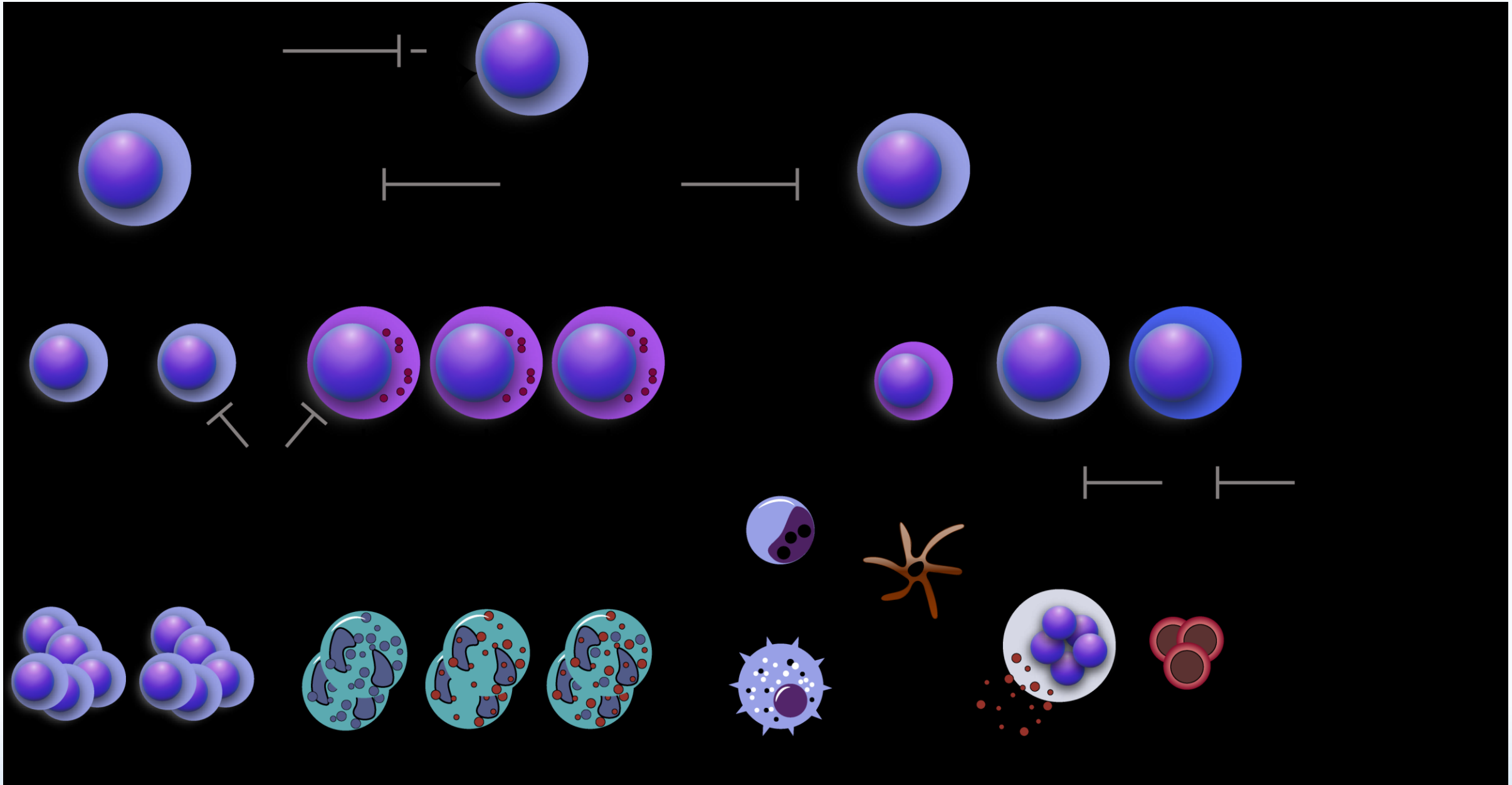
Review

Cannabinoid receptor signaling in progenitor/stem cell proliferation and differentiation

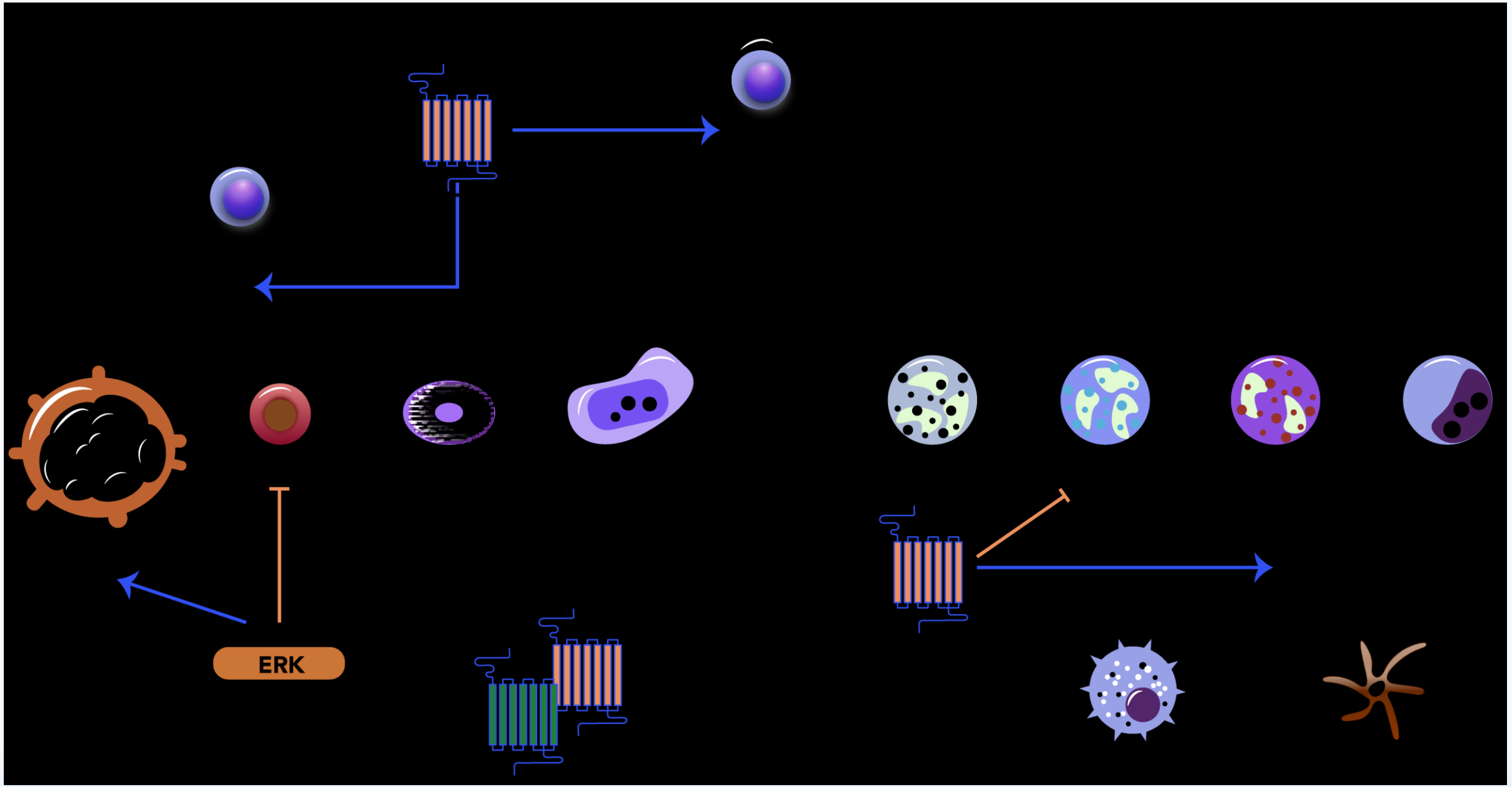
Ismael Galve-Roperh [a,*,1], Valerio Chiurchiù [b,c,1], Javier Díaz-Alonso [a], Monica Bari [d], Manuel Guzmán [a], Mauro Maccarrone [c,e,*]

[a] Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, IUIN, CIBERNED and IRYCIS, 28040 Madrid, Spain
[b] Department of Biomedical Sciences, University of Teramo, 64100 Teramo, Italy
[c] European Center for Brain Research (CERC)/Santa Lucia Foundation, 00143 Rome, Italy
[d] Department of Experimental Medicine & Surgery, Tor Vergata University of Rome, 00133 Rome, Italy
[e] Center of Integrated Research, Campus Bio-Medico University of Rome, 00128 Rome, Italy

TGF-β is a Master Regulator of the Hematopoietic Stem Cell



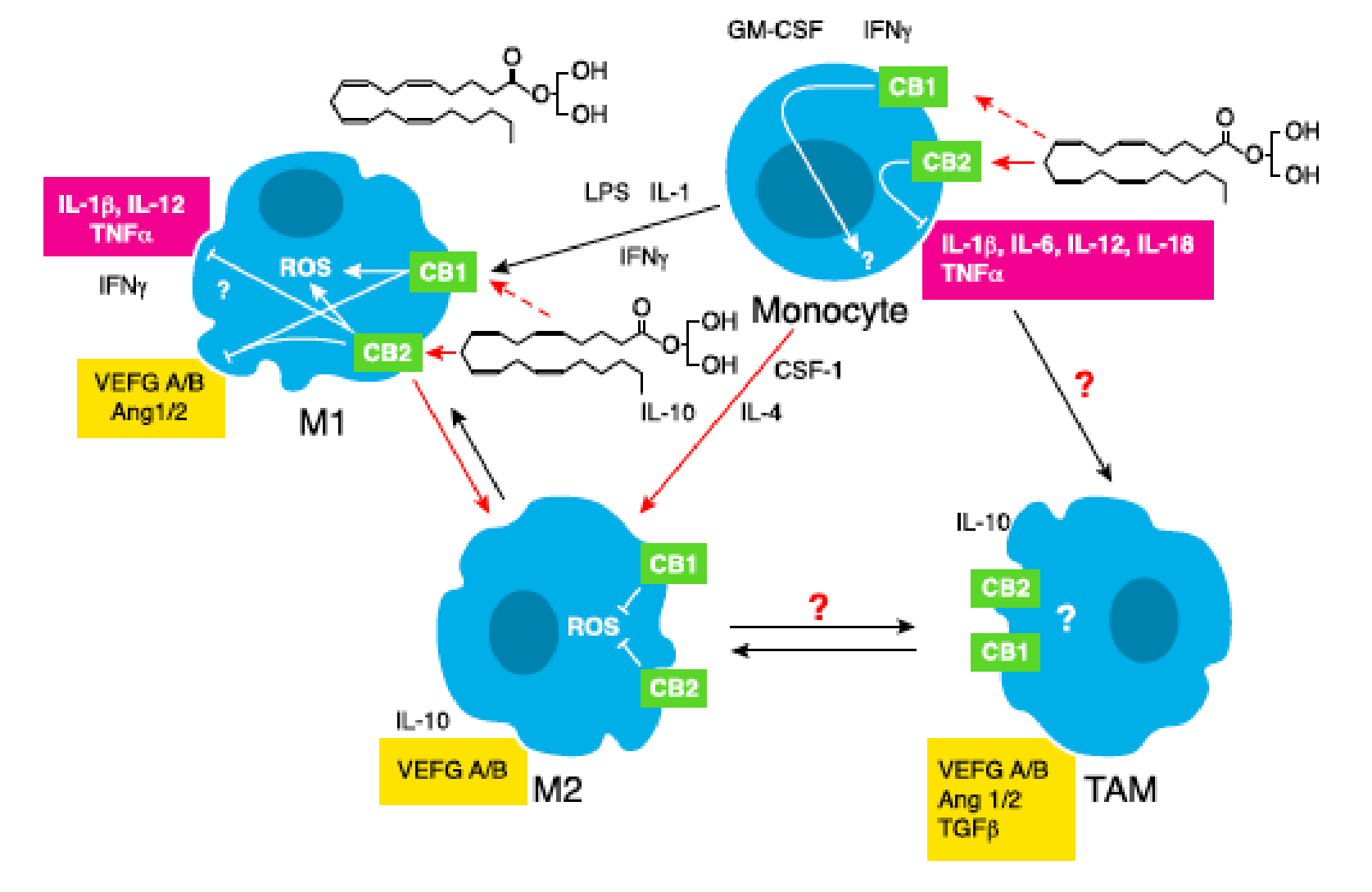
Endocannabinoid System Regulates the Generation of Mononuclear Phagocytes



Progress in Lipid Research 52 (2013) 633–650

Cannabinoid Receptor Activation of Macrophages

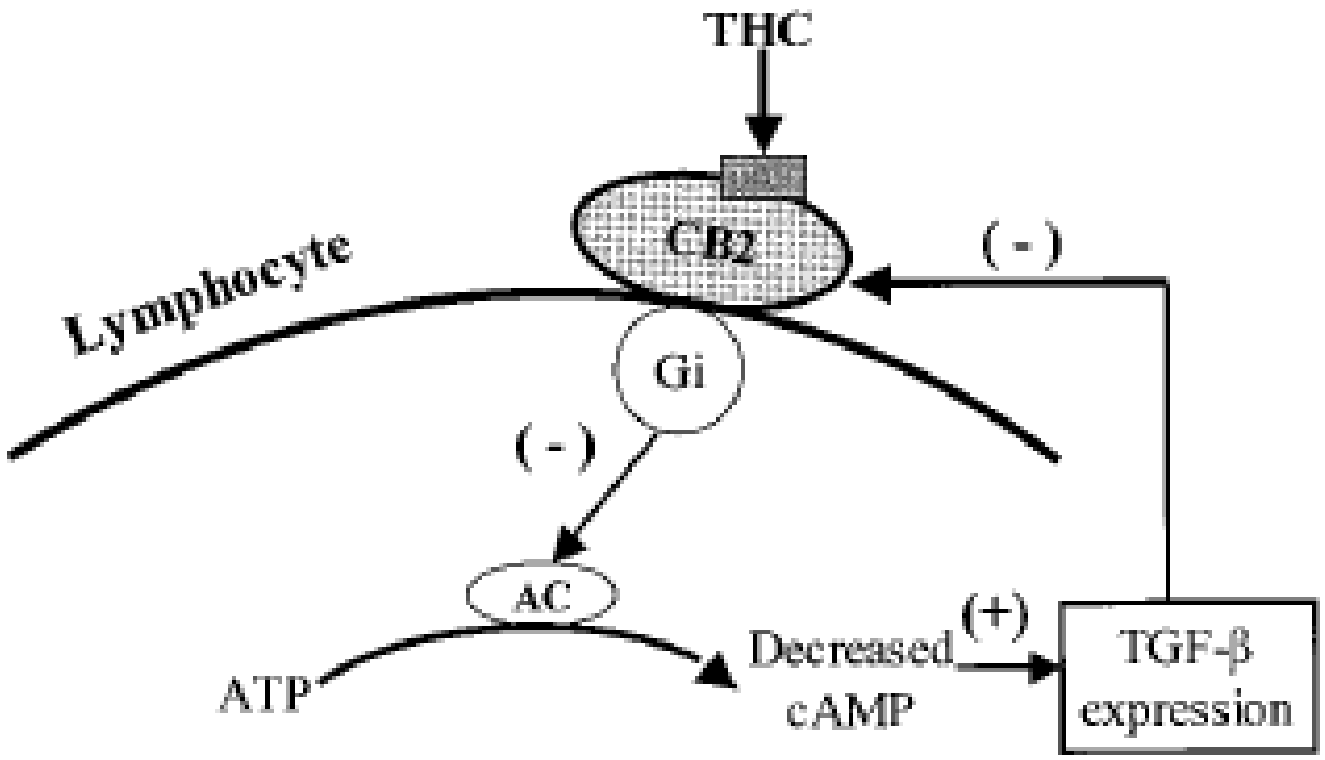
Is Purinergic Signaling the Driver of Development of Myelosuppressive (MDSC)/and Tumor associated Macrophages (TAM)?



Autocrine and Paracrine Regulation of Lymphocyte CB2 Receptor Expression by TGF-β

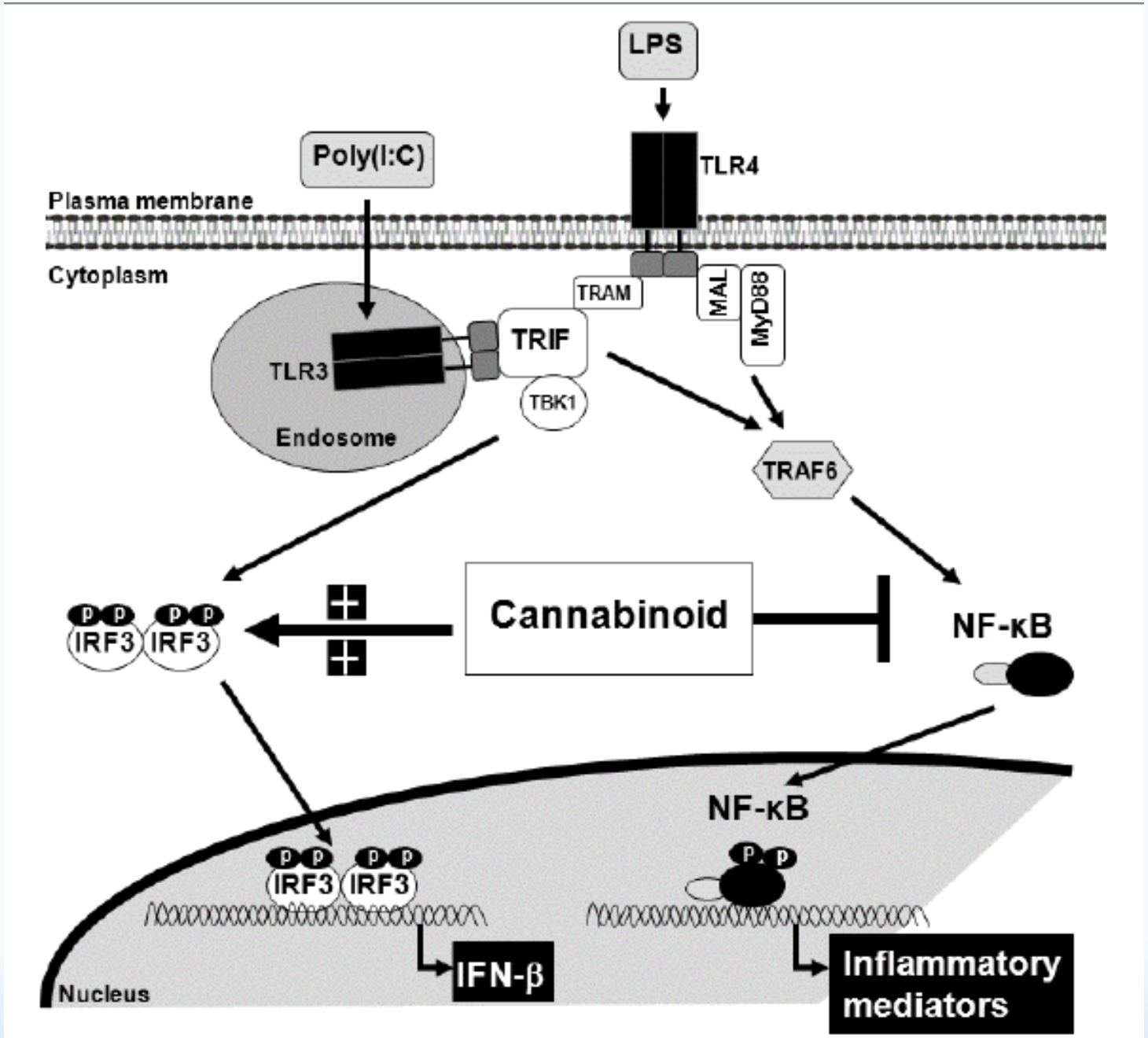
Brian Gardner,*·†·[1] Li X. Zu,*·†·[1] Sherven Sharma,*·†·‡ Qian Liu,§·[¶] Alexandros Makriyannis,§·[¶] Donald P. Tashkin,† and Steven M. Dubinett*·†·‡·[2]

*Pulmonary Immunology Laboratory, †Division of Pulmonary and Critical Care Medicine, UCLA School of Medicine, Los Angeles, California 90073; ‡VA West Los Angeles Healthcare Center, Los Angeles, California 90073; and §Department of Pharmaceutical Sciences and ¶Department of Molecular and Cell Biology, University of Connecticut, Storrs, Connecticut 06269

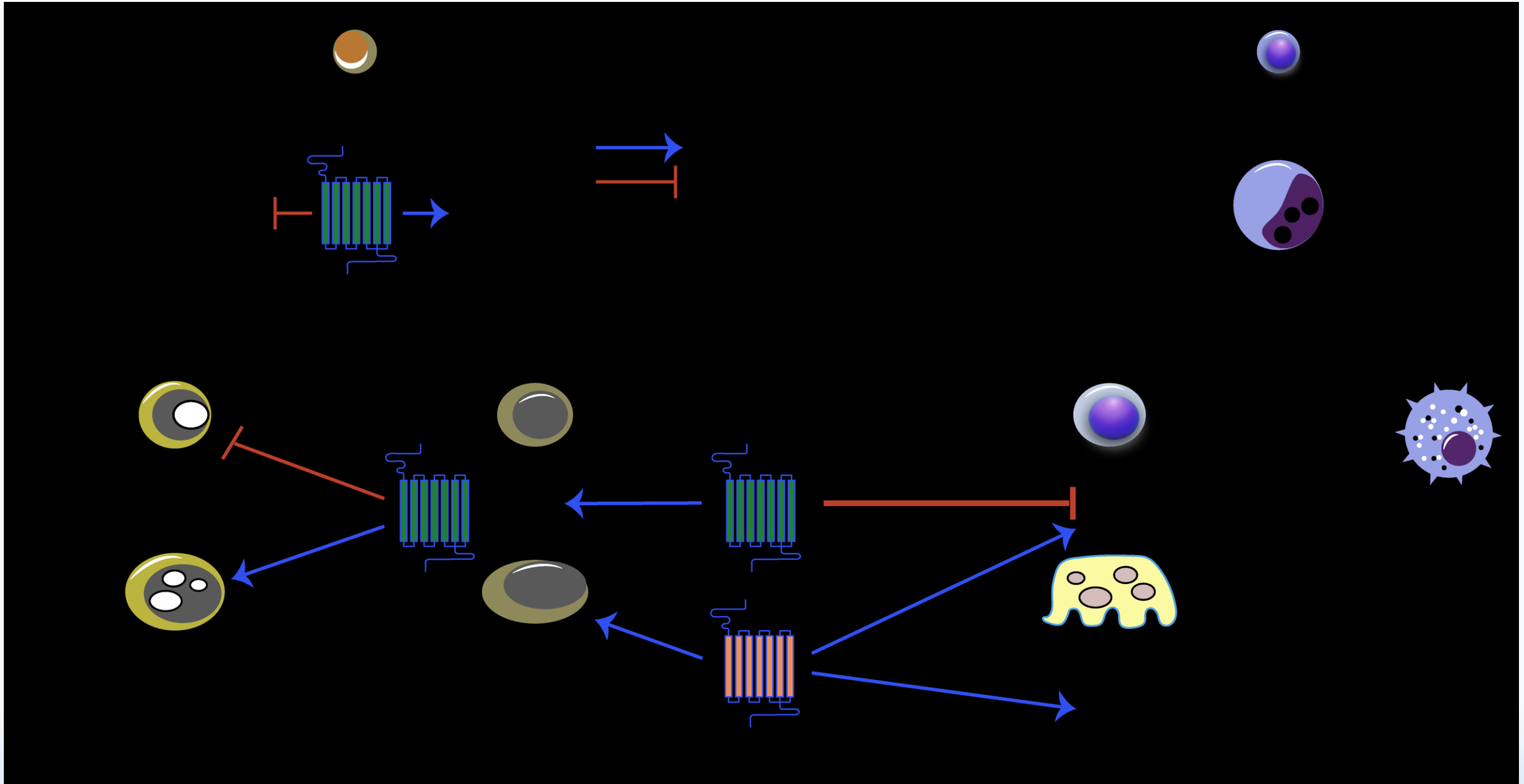


Induction of CB2 on Lymphocytes is THC dependent

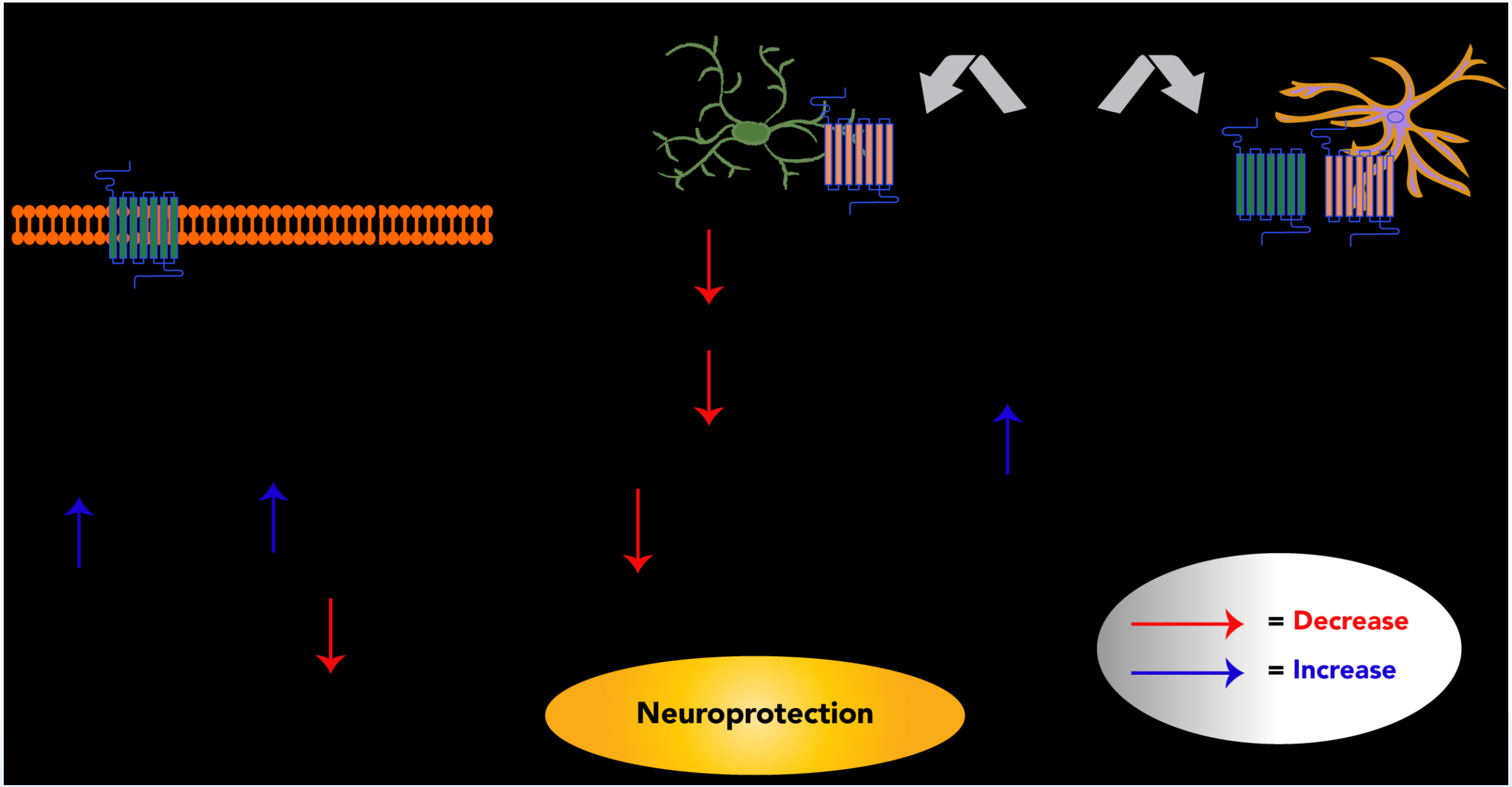
Cannabinoids are Anti-Viral and Reduce Neuroinflammation

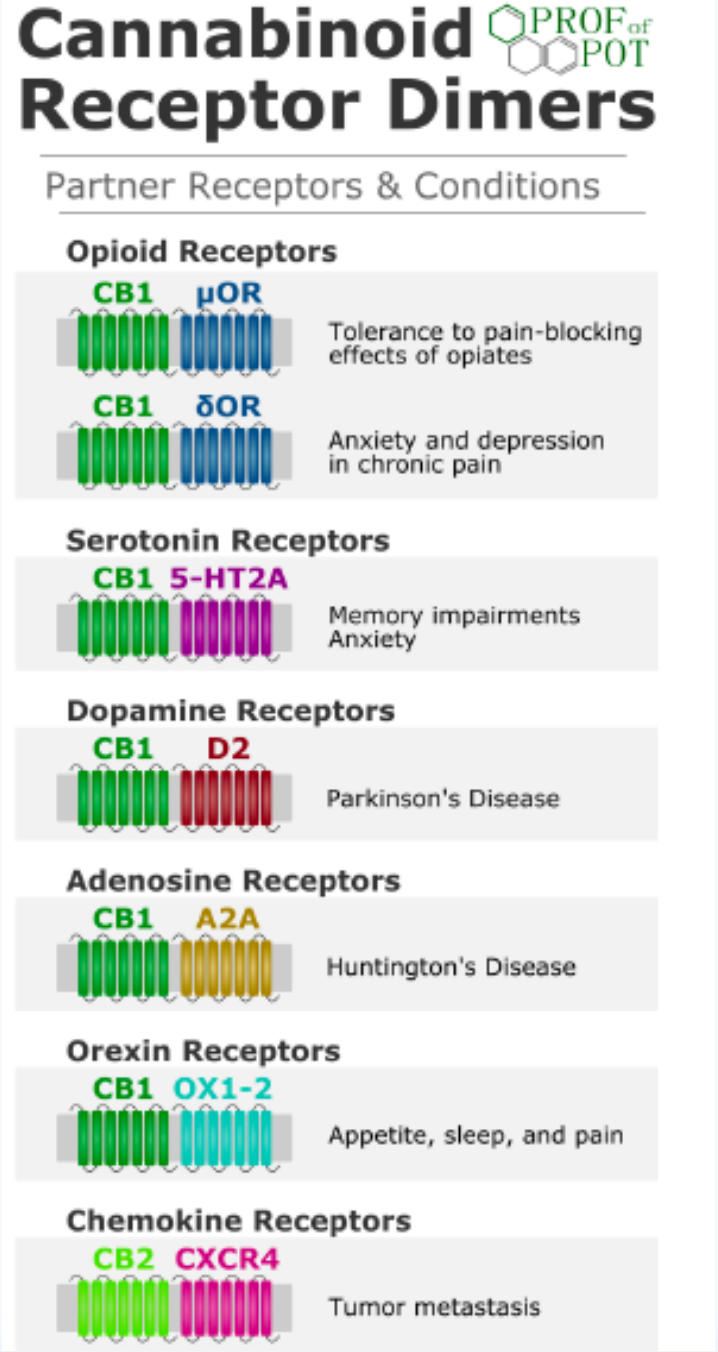


CB2 Is associated with Chronic inflammation of the nervous system, Cardiovascular and Bone Disorders



Neuroprotection by Endocannabinoid Modulation in Neurodegenerative Disease

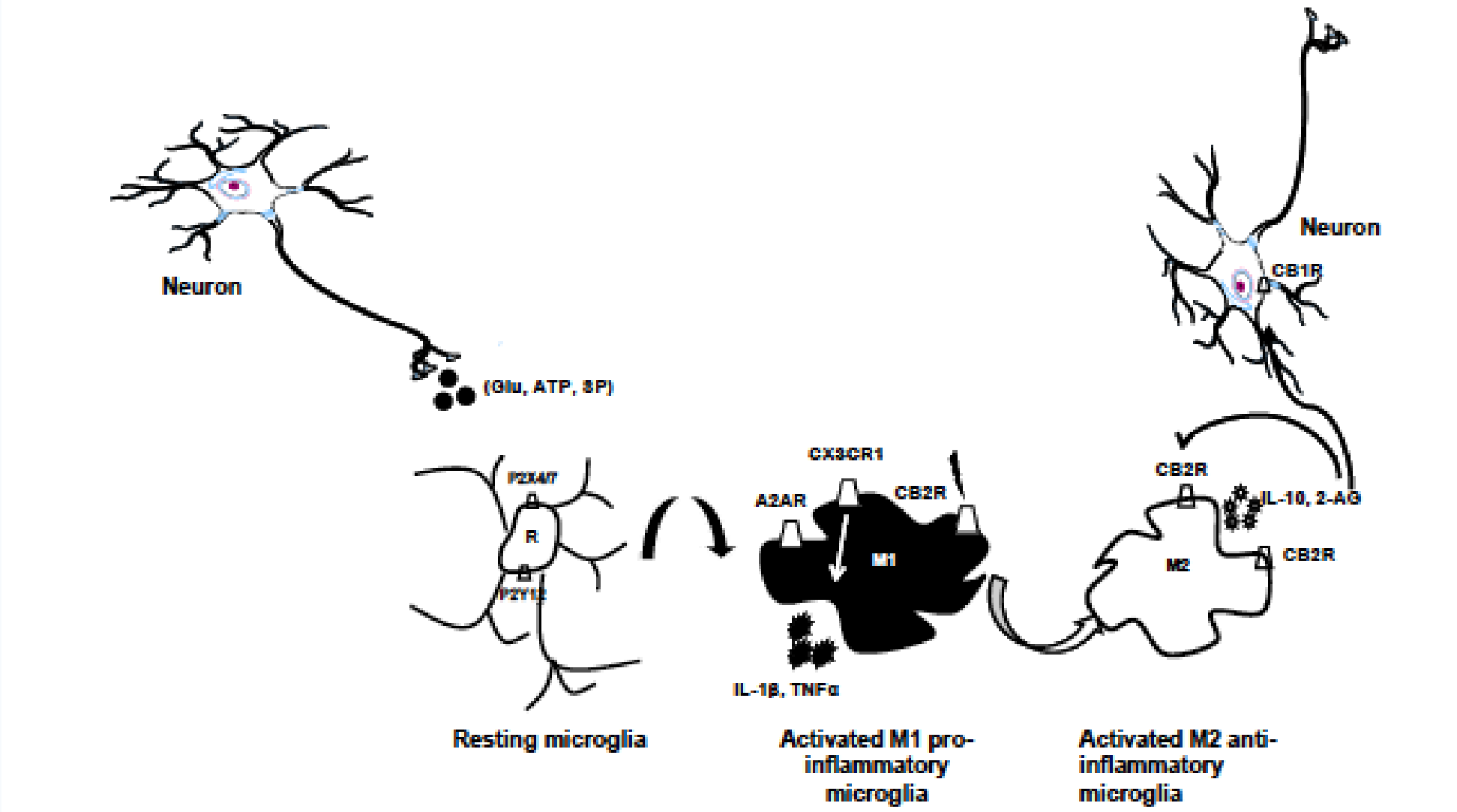




- Tolerance to pain-blocking effects of opiates
- Depression and anxiety in chronic pain
- Negative effects of cannabis on memory
- Parkinson’s and Huntington’s Disease
- Cancer cell metastasis

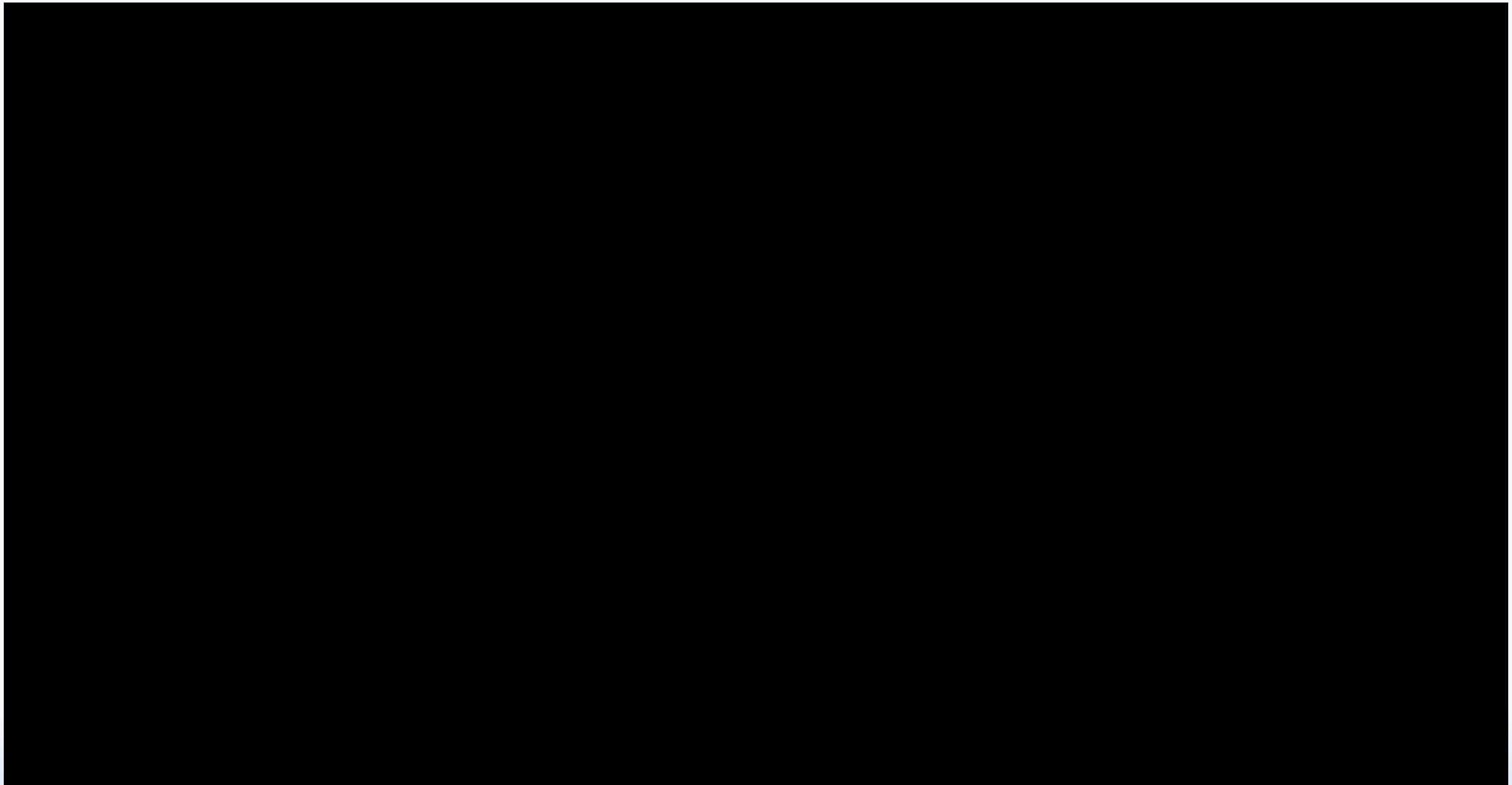
http://profofpot.com

Crosstalk between Purinergic receptors and cannabinoid Receptors regulates Microglia

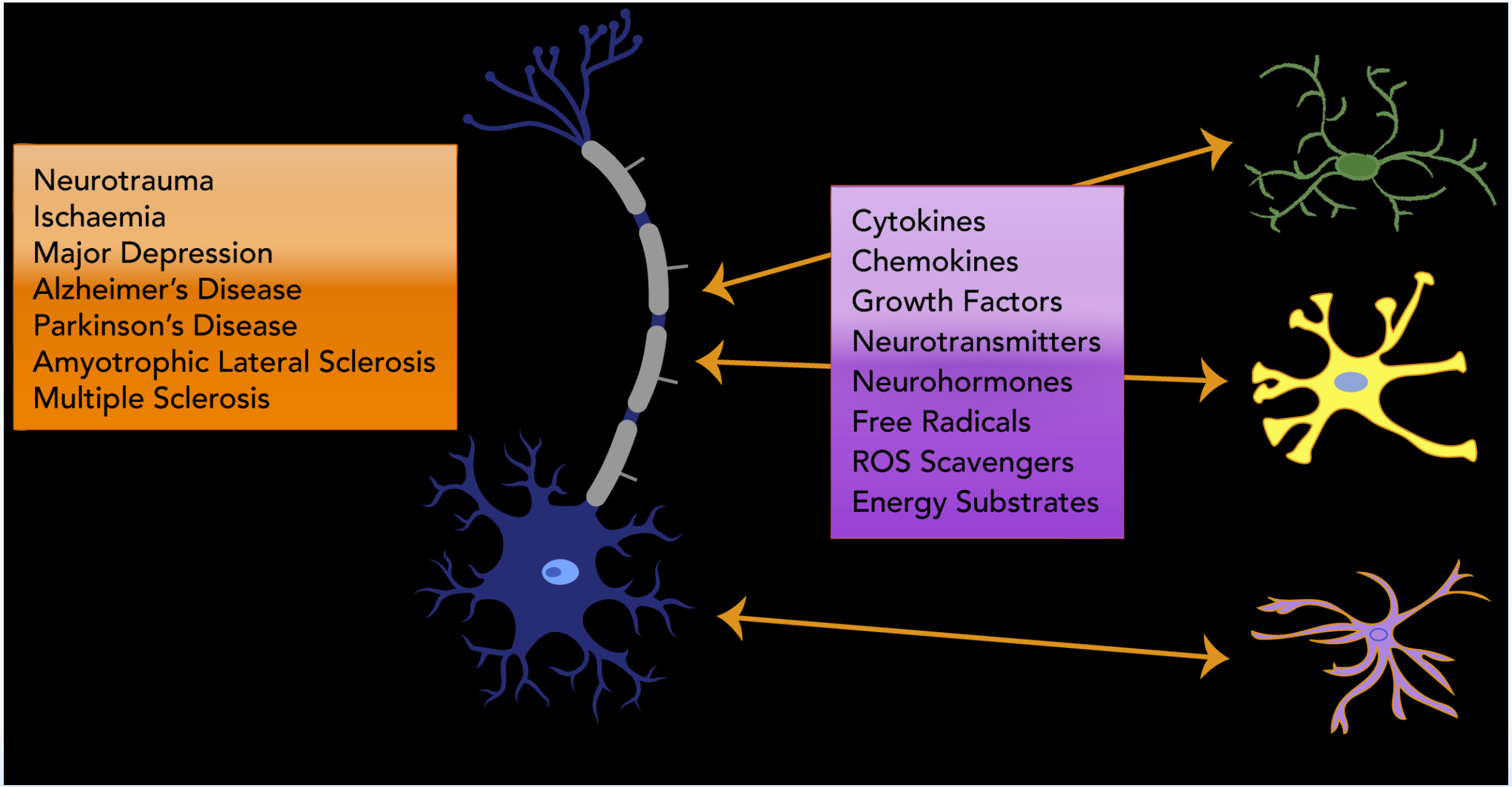


The Open Pain Journal, 2010, Volume 3

Plant Derived- Phytocannabinoids

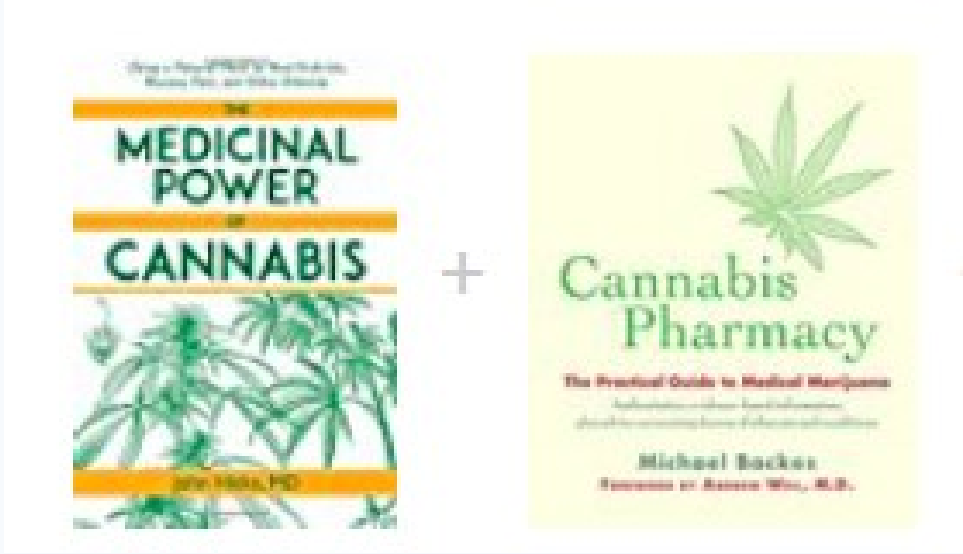


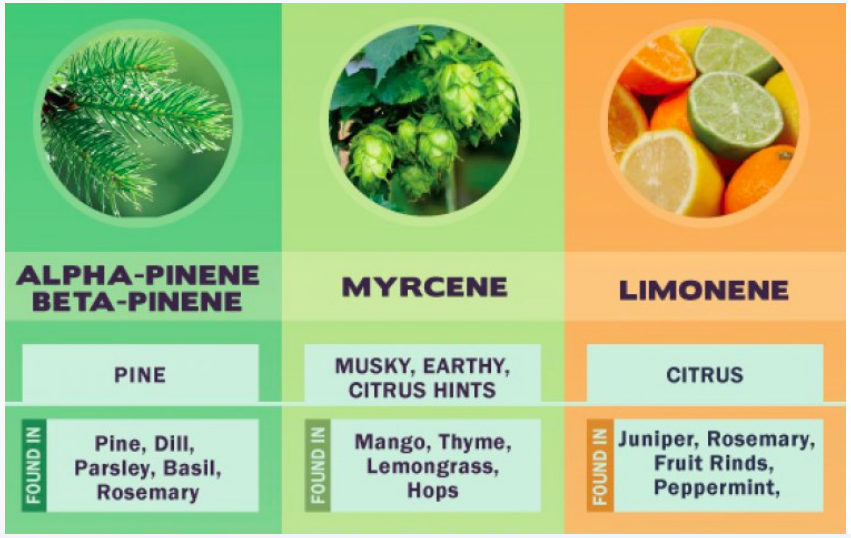
Phyto-cannabinoids Dampen Tissue Injury to Prevent Progression of Neurodegenerative Disease and Cancer

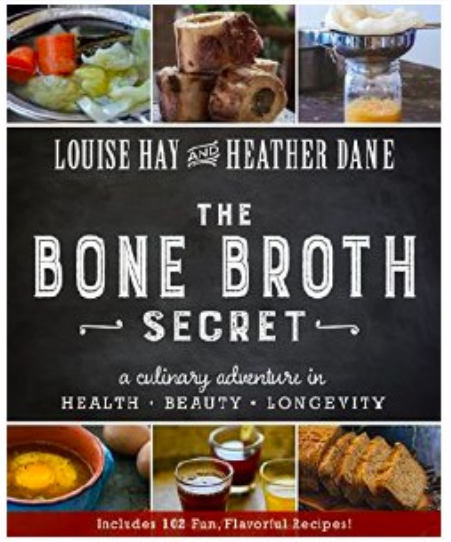


Restoring Gut Homeostasis

- Cannabinoids/EndoCannabinoids
- Bone Broth organixx.com
- Camels Milk
- BRAVO Yogurt Probiotic /Restore
- Essential Oils







Summary /Conclusion

The endocannabinoid system is involved in immunoregulation and neuroprotection.
Cannabinoid receptors crosstalk with Purinergic Receptors

Dysregulation of Endocannabinoid and Purinergic signaling by Overstimulation of Immune system by vaccines containing retroviruses and toxins (AL ,Glyphosate) is causative for cancer Autoimmune neuroimmune diseases

Lipid mediators of the Endocannabinoid System and their receptors exert pleiotropic and complex immunoregulatory effects.

Endocannabinoids are master regulators of the innate adaptive-immune axis.

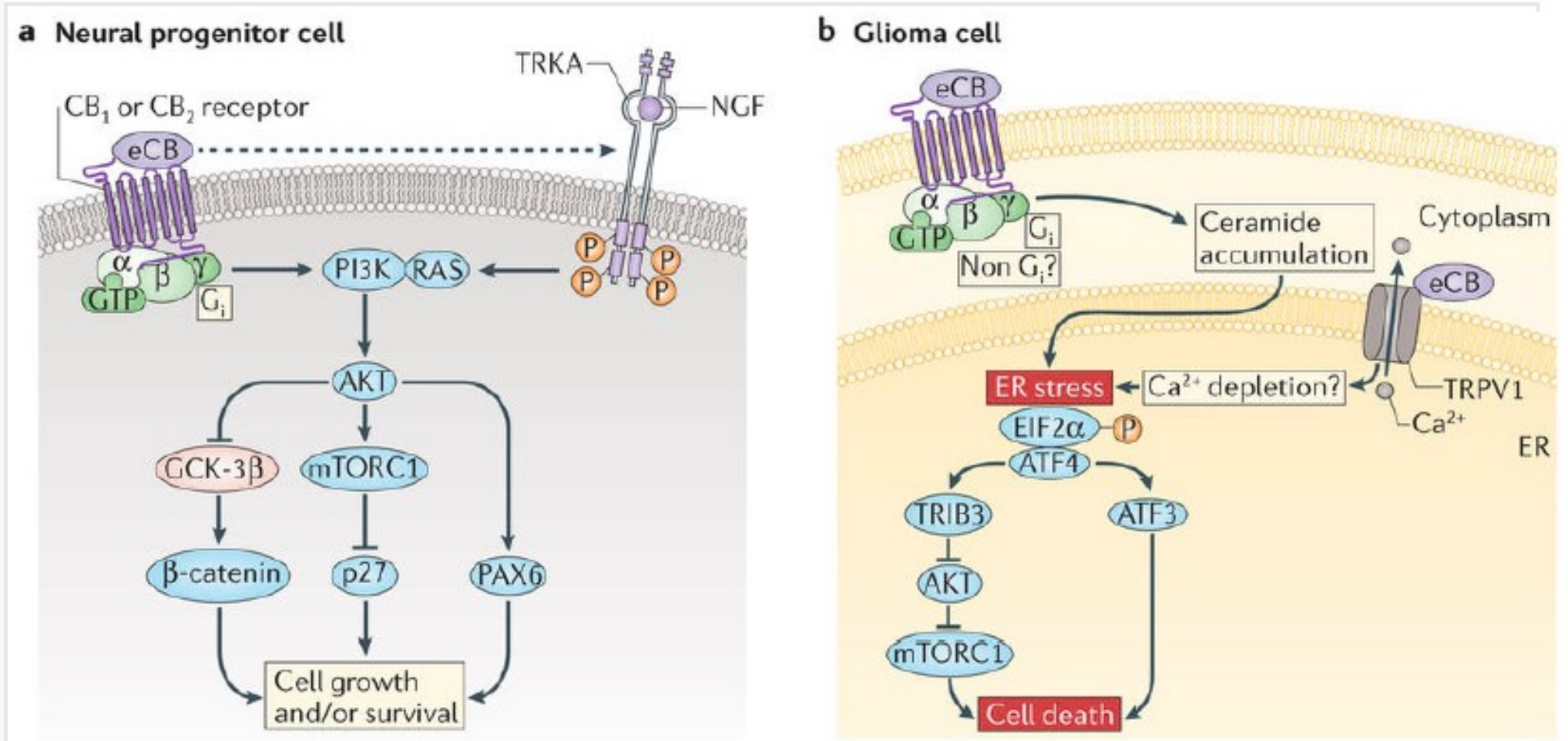
The effect of endocannabinoids on the orchestrators of the immune response, the monocyte/ macrophage, is a key therapeutic target to modulate sterile inflammation and protect tissues from damage from excessive inflammatory mediators.

Combination therapies using Suramin (and other modulators of purinergic signaling) and cannabinoids can be curative therapies for 21st Century AIDS

Toxicity, Efficacy, and Pharmacology of Suramin in Adults With Recurrent High-Grade Gliomas

J Clin Oncol 19:3260-3266. © *2001 by American Society of Clinical Oncology.*

Dysregulation of cannabinoid receptor signalling in glioma cells.



Programming of neural cells by (endo)cannabinoids: from physiological rules to emerging therapies

Nature Reviews Neuroscience **15**, 786–801 (2014)