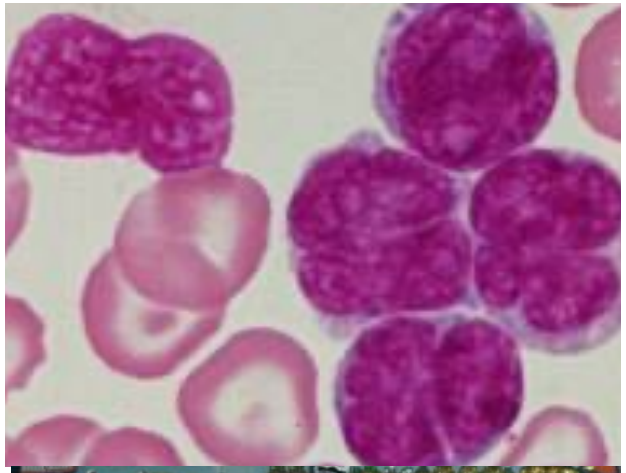
Human Retroviruses, Innate immunity and the Development of immunotherapy

Judy A. Mikovits, PhD

April 1, 2017

Four decades of Immune Therapy: Lessons learned?

1980 Discovery of HTLV-I



Pathogenesis:

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

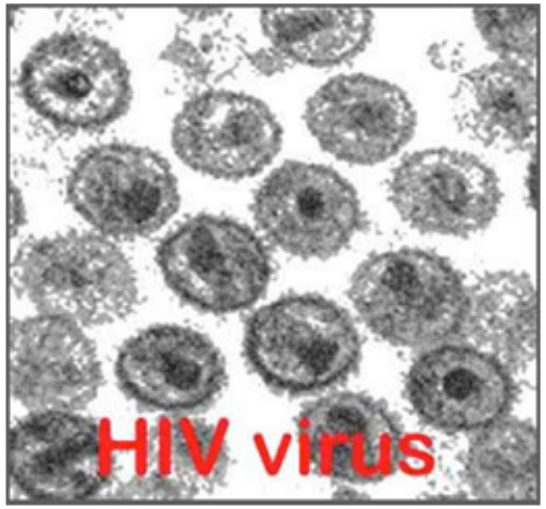
- **Adult T cell leukemia**
  - Clonal malignancy of $CD4^+$ T cells.
  - Long latency; Immune deficiency

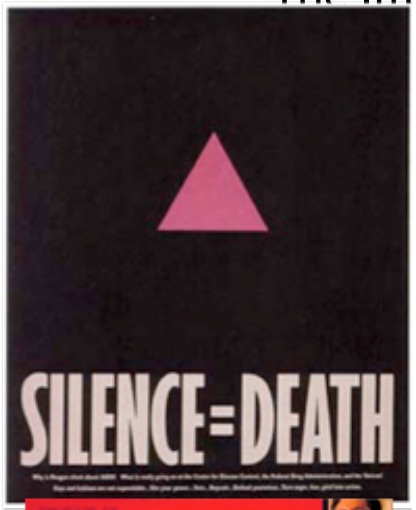
- **Inflammatory syndromes not realized until decade later**

HTLV-I associated myelopathy/Tropical spastic paraparesis
- Uveitis
- Arthropathy
- Sjogren's Syndrome

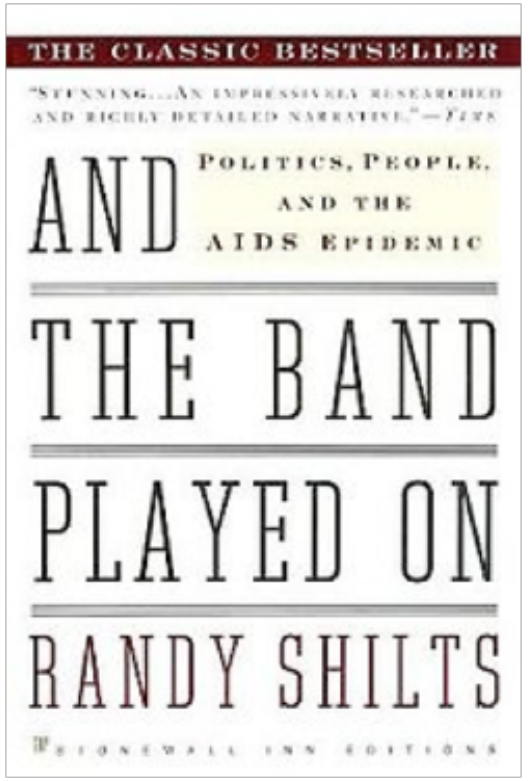
Political Influence on Scientific Research
The Impact it has on us ALL

HIV -1 Isolation- 1982





November 7,1991



MANY DEATHS BEFORE ESTABLISHMENT BELIEVED IN RETROVIRAL CAUSE

Chronic Diseases :IT ALL ABOUT THE FAMILY
NOT AT ALL HIDDEN

Cancer	Auto-Immune Diseases	CNS
Prostate*	Lupus	ME/CFS*
Breast*	Crohn's*	Gulf War Syndrome*
Multiple Myeloma*	Hashimoto'sThyroiditis*	Autism/ASD*
Non Hodgkin's Lymphoma*	Polymyositis	MS*
Chronic Lymphocytic Leukemia*	Sjogren's syndrome	Parkinson's*
Mantle Cell Lymphoma*	Bechet's Disease*	ALS*
Hairy Cell Leukemia	Primary Billary Cirrhosis*	Fibromylagia
Bladder*	IBD*	Chronic Lyme Disease*
Colorectal	Psoriasis, dermatitis	OCD
Kidney*		ADHD
Ovarian*		

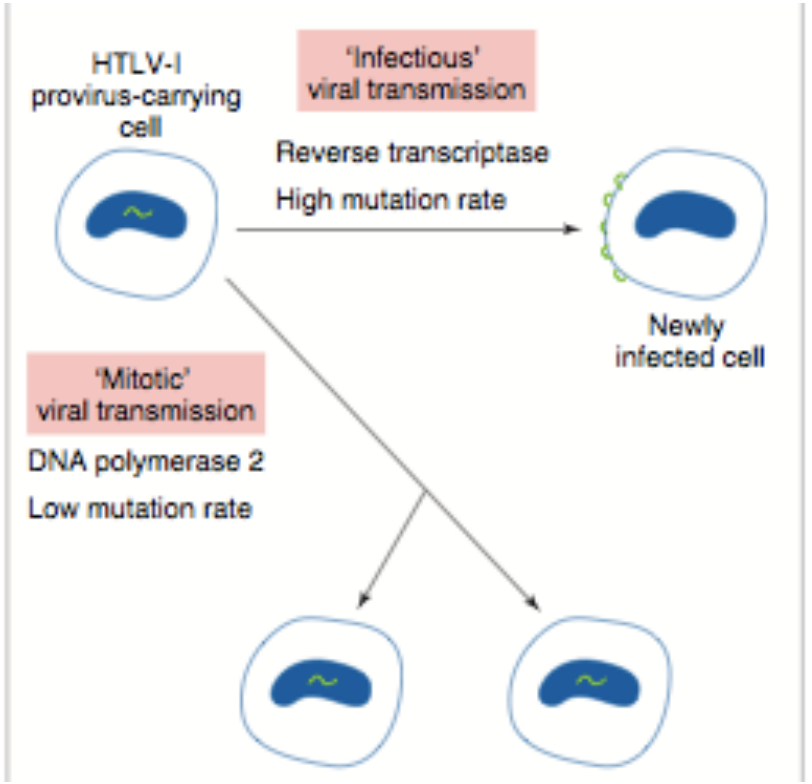
* RT Activity, RV sequences or proteins, antibodies to RV proteins

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

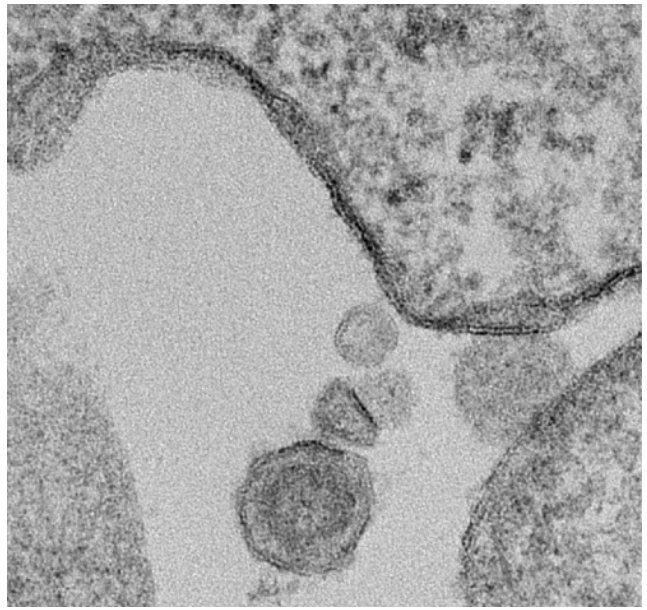


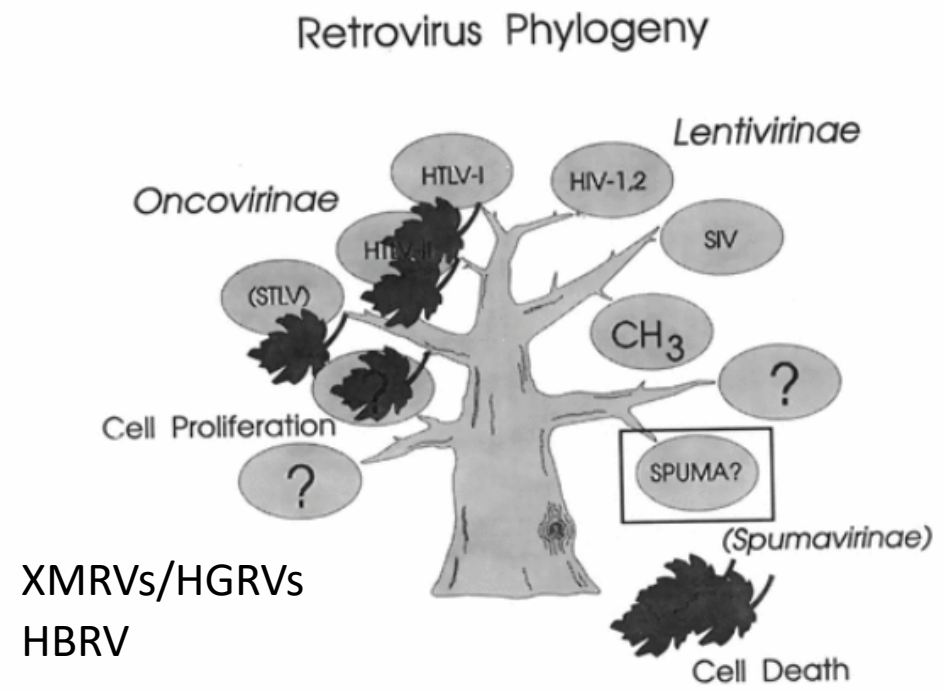
HAM/TSP Usually Chronic Slowly progressing

- 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

A Primer: the role human retroviruses in Chronic Disease

Lessons learned from 36 years of Human retrovirus study





XMRVs/HGRVs
HBRV

Retroviruses have RNA genomes which must first be reverse transcribed then Integrate into the genome.. forever part of DNA of host.

As much as 15% of human genome is made up of Endogenous Retroviruses that have been crippled by the immune system. That is they cannot produce ***infectious particles*** which can be transmitted to others. ***OR CAN THEY?***

Pathways of Retrovirus Elicited Pathogenesis

- Inflammation / hormone regulation
- Highly elevated ROS / RNS
- Immune deficiency
- Epigenetics — change in gene expression without a DNA change
- Insertional mutagenesis
- RVs can be vertically transmitted
- RVs can recombine with aberrantly expressed endogenous RVs creating RCRs

Two important lessons learned from studying MuLVs

- **While insertional mutagenesis by MuLVs can result in transformation of cells and the development of leukemias and lymphomas, the envelope proteins encoded by these viruses can also have profound biological effects.**
  So it's important to study the biological effects of the XMRV envelope protein.

- **MuLVs can be expressed in the CNS, triggering an inflammatory response that can cause severe neurological damage. Since similar inflammatory responses are associated with ME/CFS, XMRV could be playing a role.**

ENV proteins from MLV related retroviruses impact tumor pathogenesis (change microvasculature)

Murgai *et al. Retrovirology* 2013, **10**:34
http://www.retrovirology.com/content/10/1/34

RETROVIROLOGY

RESEARCH Open Access

Xenotropic MLV envelope proteins induce tumor cells to secrete factors that promote the formation of immature blood vessels

Meera Murgai[1], James Thomas[2], Olga Cherepanova[1], Krista Delviks-Frankenberry[4], Paul Deeble[3], Vinay K Pathak[4], David Rekosh[5] and Gary Owens[1*]

Similarities to Vascular Pathologies seen in ME/CFS

These Microvasculature aberrations caused solely by XMRV ENV protein

Xenograft approaches commonly used in these studies of human cancer promote the evolution of novel retroviruses with pathogenic properties. Similar retroviruses may have evolved to infect humans!”

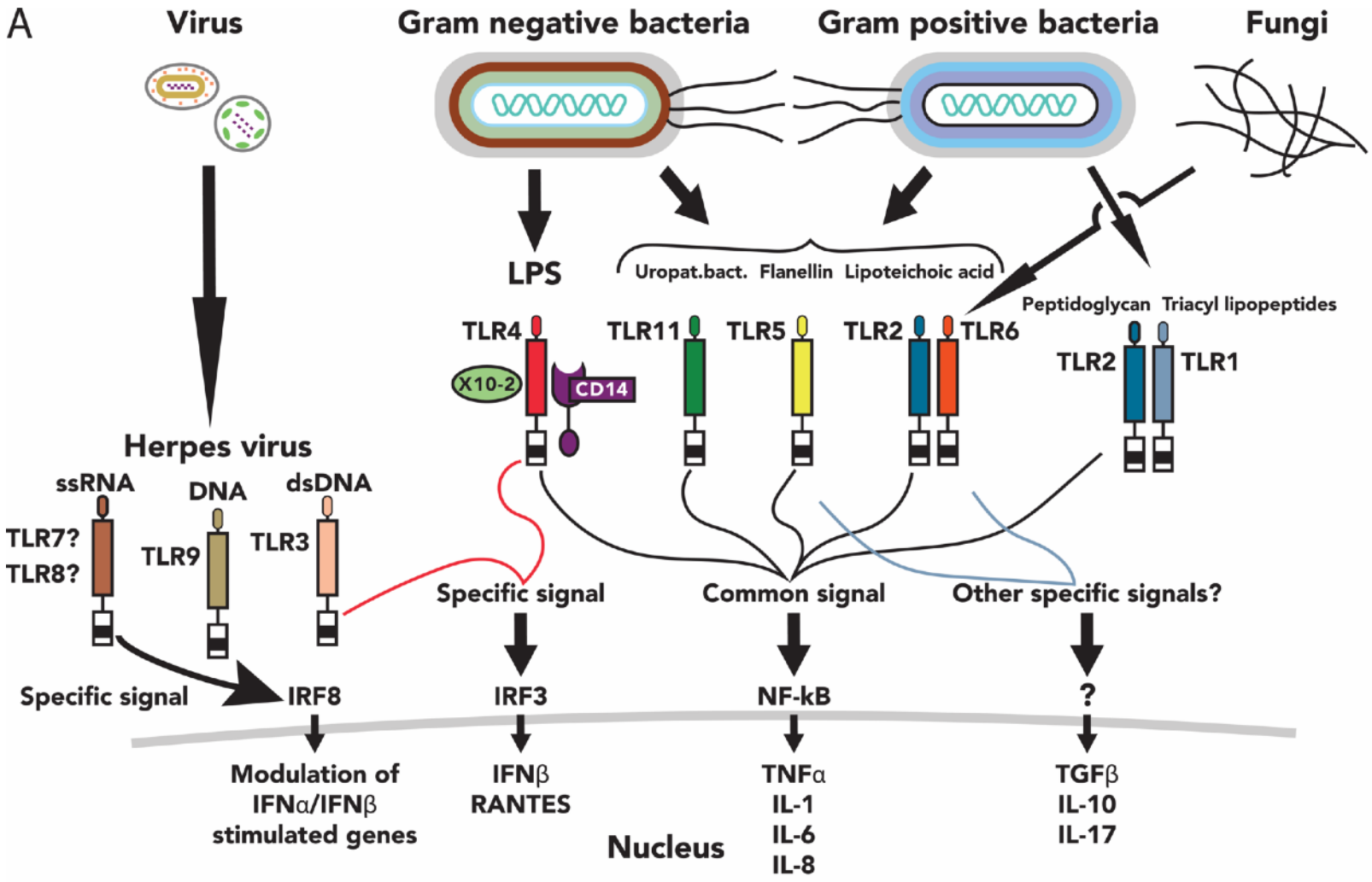
In Chronic Diseases Viruses Seldom Come Alone

Table 1. Mechanisms of Interactions between HIV-1 and Coinfecting Viruses

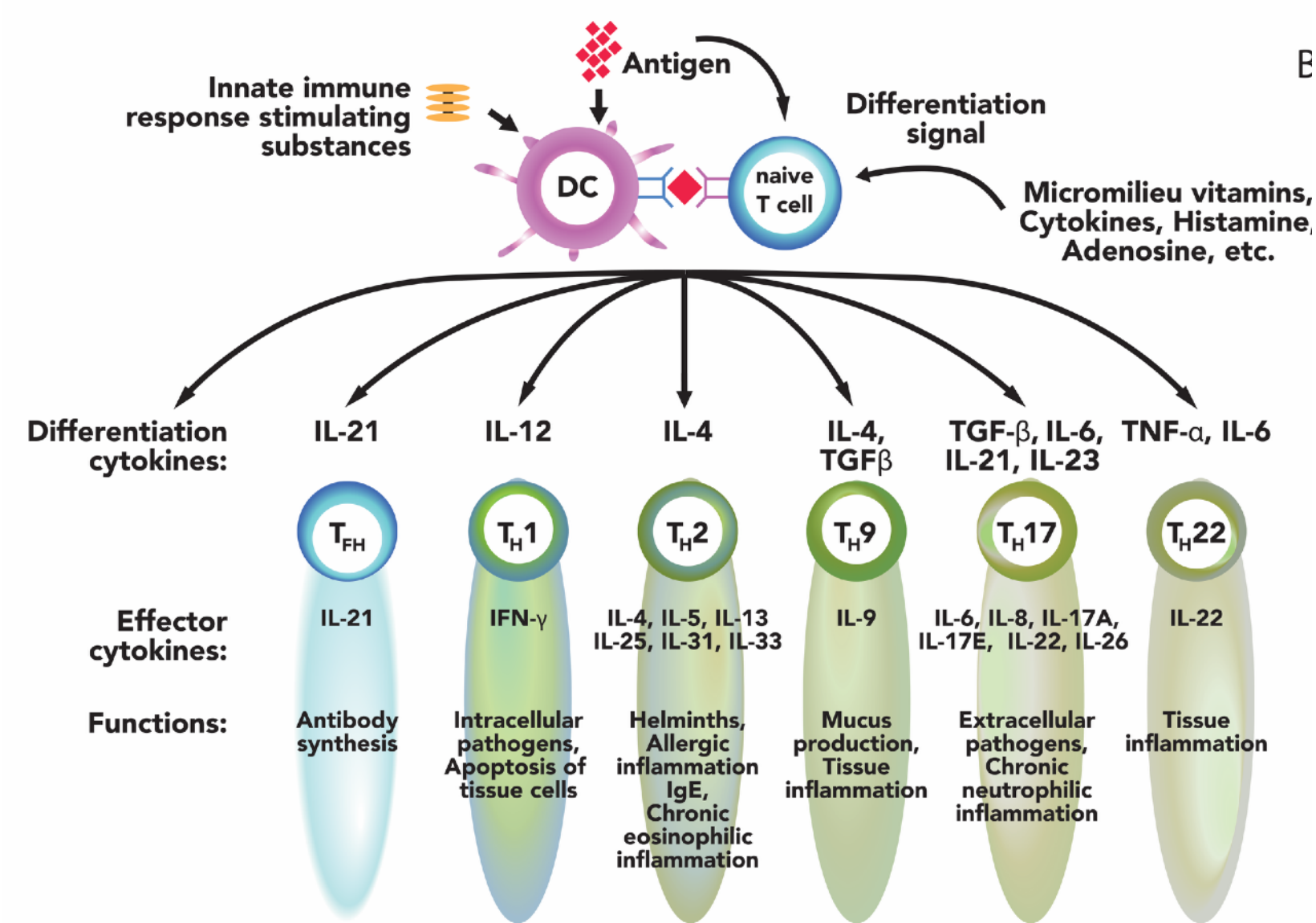
Mechanisms	Viruses
Immunoactivation	HCV, HSV-2, CMV, EBV, HTLV-2[a]
HIV-1 *trans*-activation	HSV-2, HTLV-1, JCV[a]
Abnormal production of chemokines	HTLV-1, HHV-6, HTLV-2, MV, GBV-C
CD4, CCR5, or CXCR4 downregulation	HHV-7, GBV-C
Expression of virokines and viroceptors	CMV, HHV-6, HHV-7
Blockage of CD4 T cell cycle	MV
Modulation of cytokine signaling	EBV, adenovirus
Inhibition of apoptosis	CMV, EBV
Aberrant activation of autologous complement	HHV-6, HHV-7
MHC downregulation	CMV, HHV-6, HHV-7

War and Peace between Microbes: HIV-1 Interactions with Coinfecting Viruses:
Cell Host & Microbe 6, November 19, 2009 A. Lisco, C Vanpouille, & L Margolis

Chronic Immune activation by coinfections and Environmental toxins drives aberrant immune responses



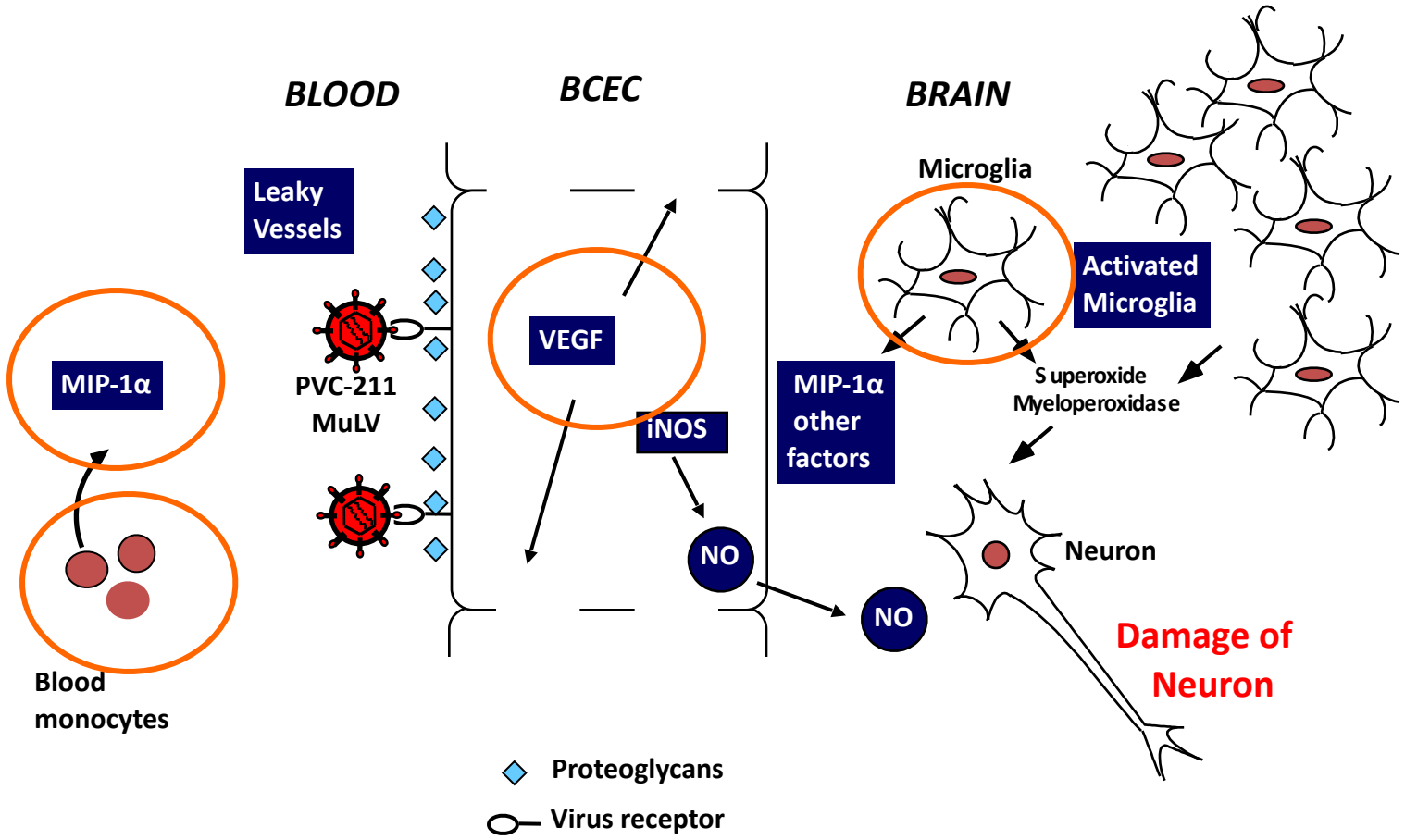
Activation of the cellular Immune system is important in the pathogenesis of human Retrovirus Associated Disease



Dysregulated Cytokine/Chemokine Production Detected in Plasma from ME/CFS patients: Inflammatory Signature of XMRV/HGRV infection

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

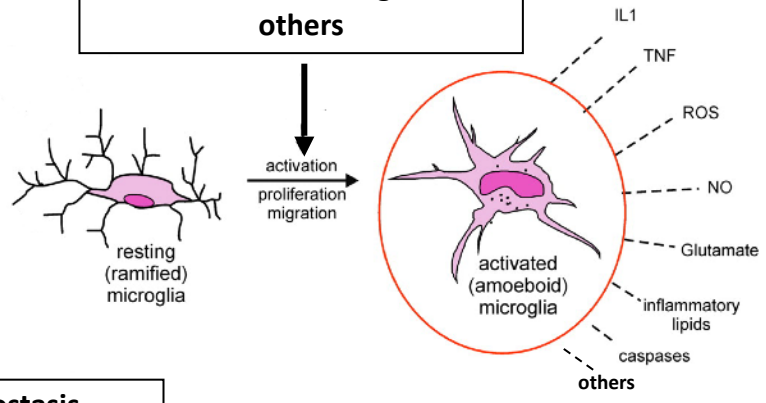
Model for the Induction of Neurodegeneration by one strain of MLV in an animal model



Are these immune pathways see in other neurological diseases?

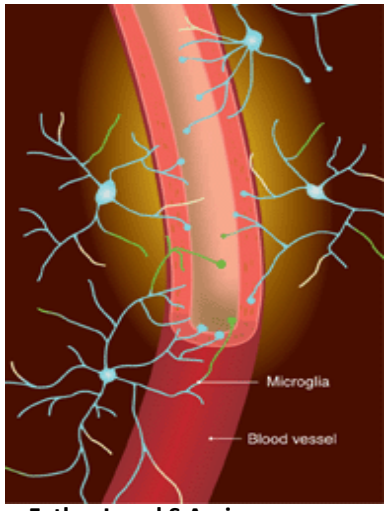
Microglia Activation in Neurodegeneration

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



Homeostasis
Phagocytosis of debris, neurotrophins

Damage
Neurotoxins, phagocytosis of normal neurons, apoptosis



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

Neurodegenerative disorders

- **Parkinson's disease**
- **Alzheimer's disease**
- **Multiple sclerosis**

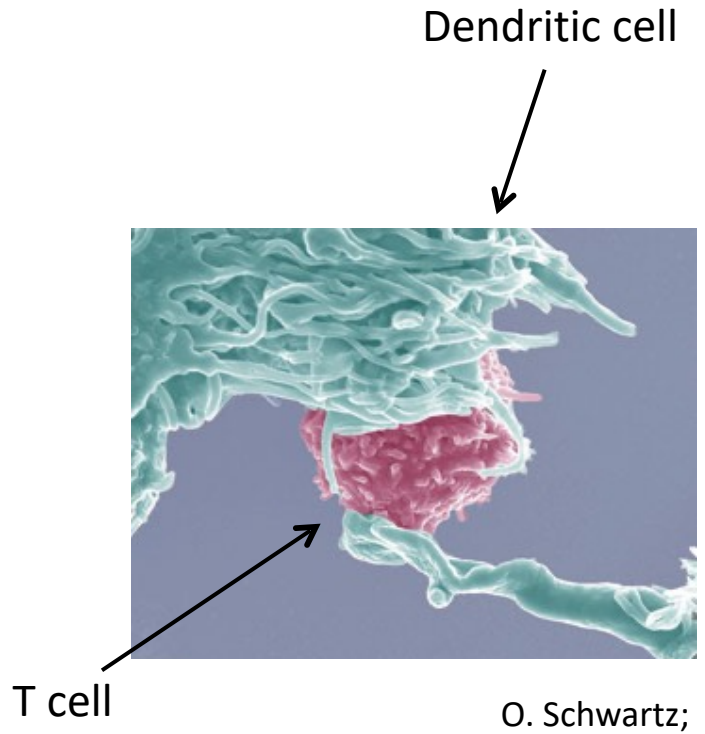
Dendritic Cells vs. Viruses

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

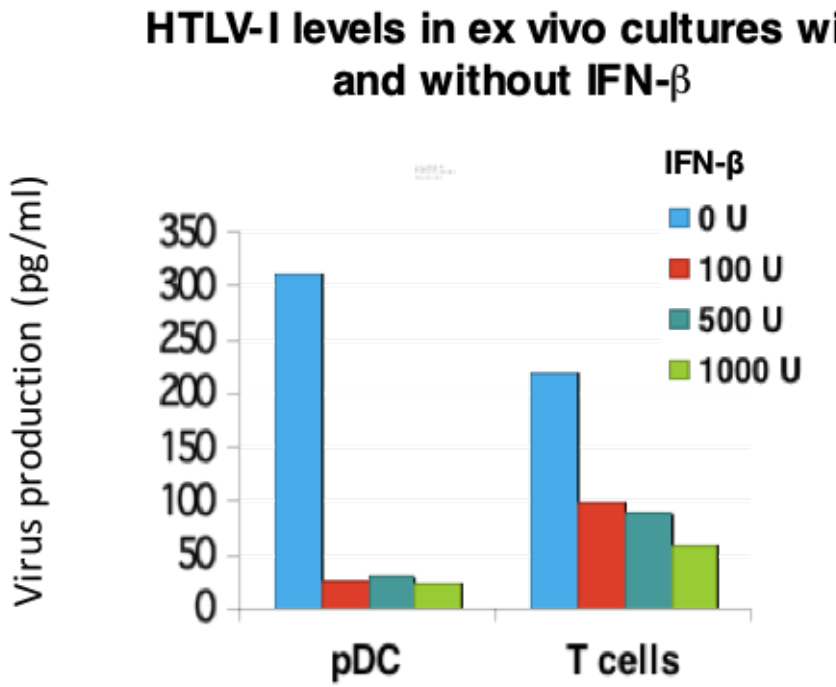
Viruses can interfere with immune responses:

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



O. Schwartz;
Nat Cell Bio

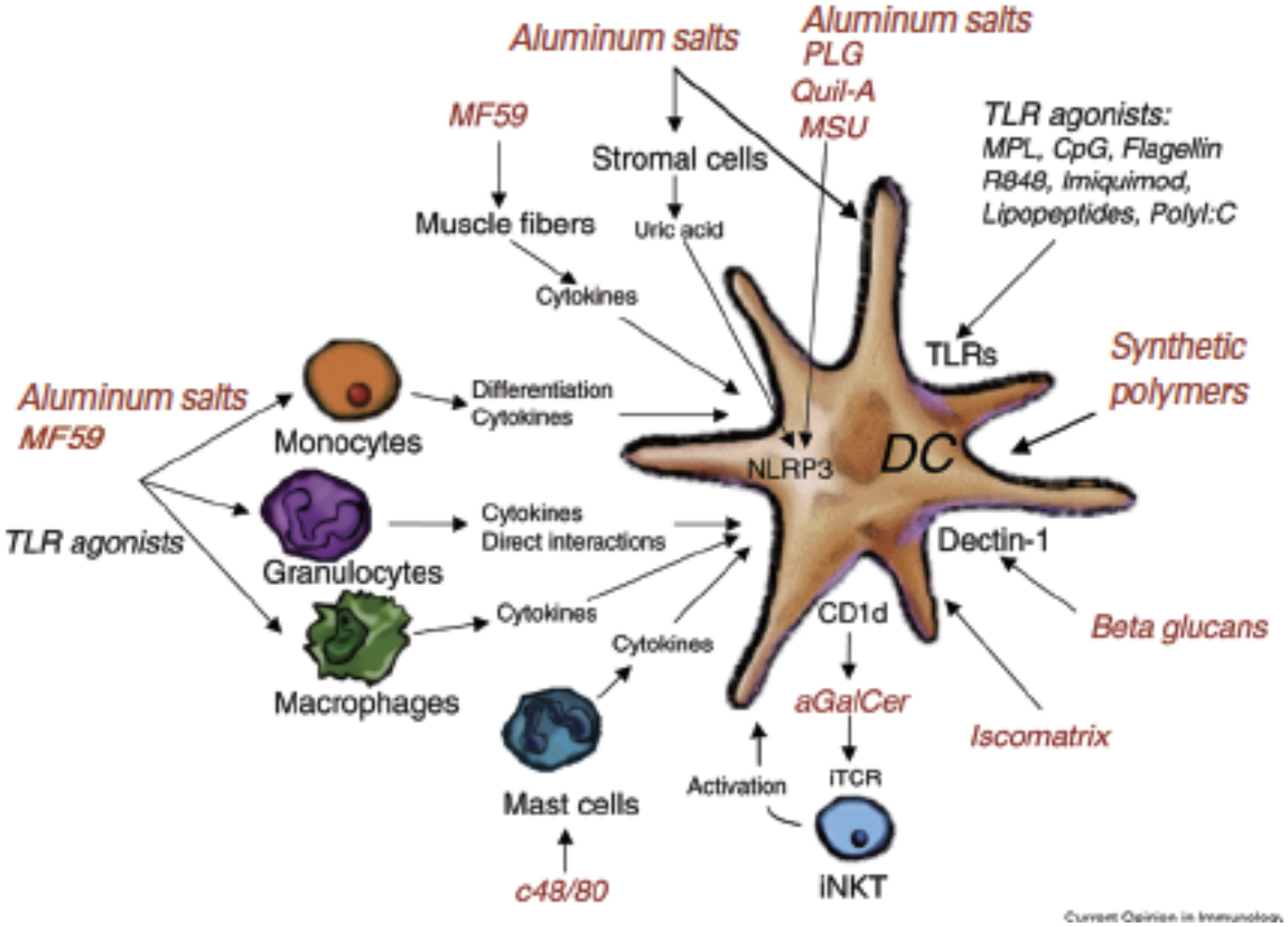
Expression of HTLV-I Is Controlled by Type I IFNs



Like malignant ATL cells, pDCs from individuals with ATL:

- express low or undetectable levels of HTLV-I proteins *in vivo*
- rapidly express virus following culture
- pDCs remains sensitive to inhibition by type I IFN
  - previously shown for T cells (Kinpara, 2009)

Unintended Consequences of Inappropriate Immune Activation



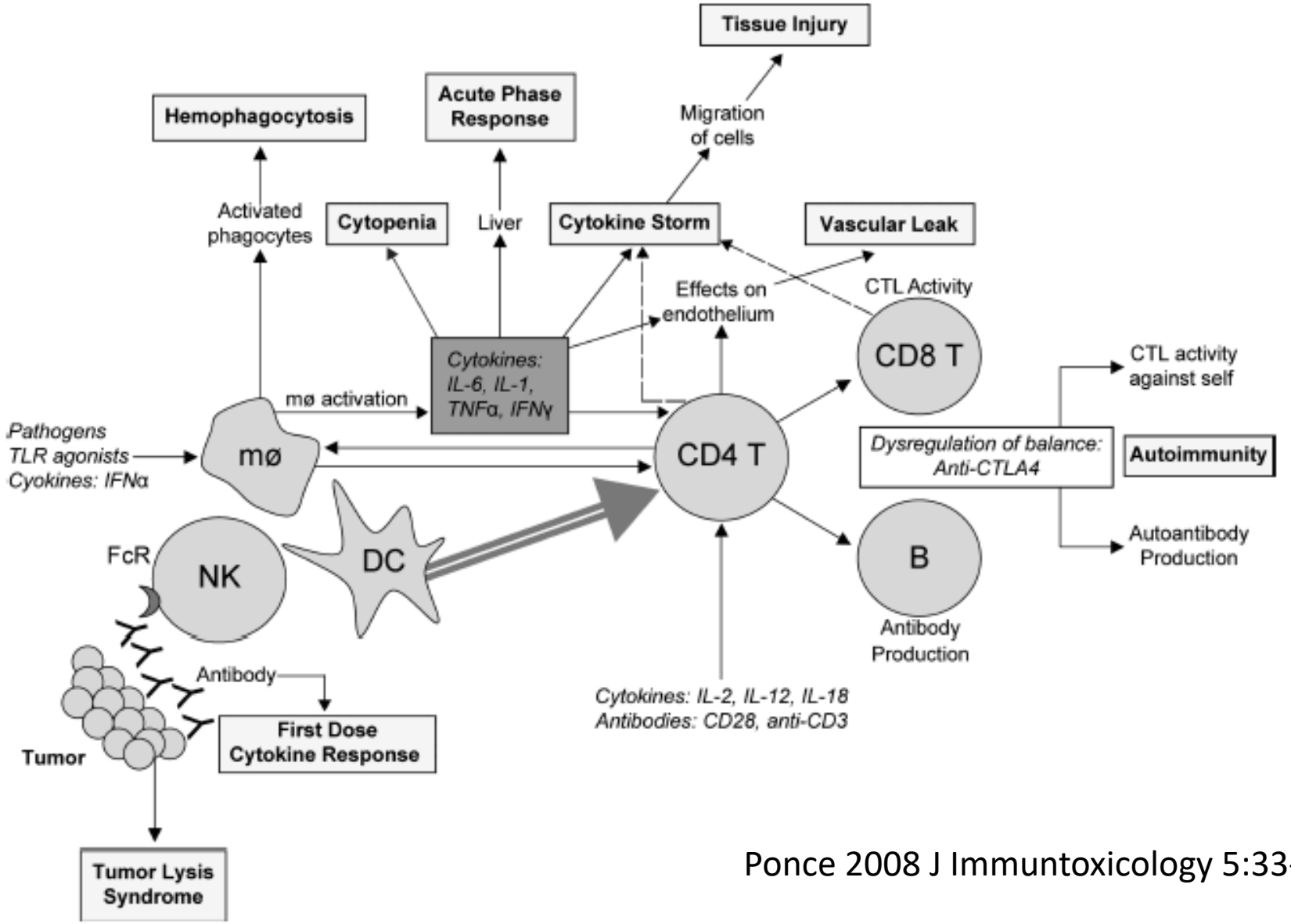
Chronic innate immune activation leads to inflammation and immune dysregulation

- Presence of CD20+ CD23+ B cells, not normally seen in healthy subjects, and activated APCs in some ME/CFS, CLD patients are similar to the myeloid and B cell defects described in other retroviral associated Diseases.
- The significant changes in the myeloid compartment including phenotypes are suggestive of activation of Antigen Presenting Cells (APCs) .
- Increased , γδT Cells clonality in ME/CFS, CLD, CLL, MCL
- Increased NKT compartment together with increased NKT to NK ratio.
- Major changes in inflammasome

Conclusion

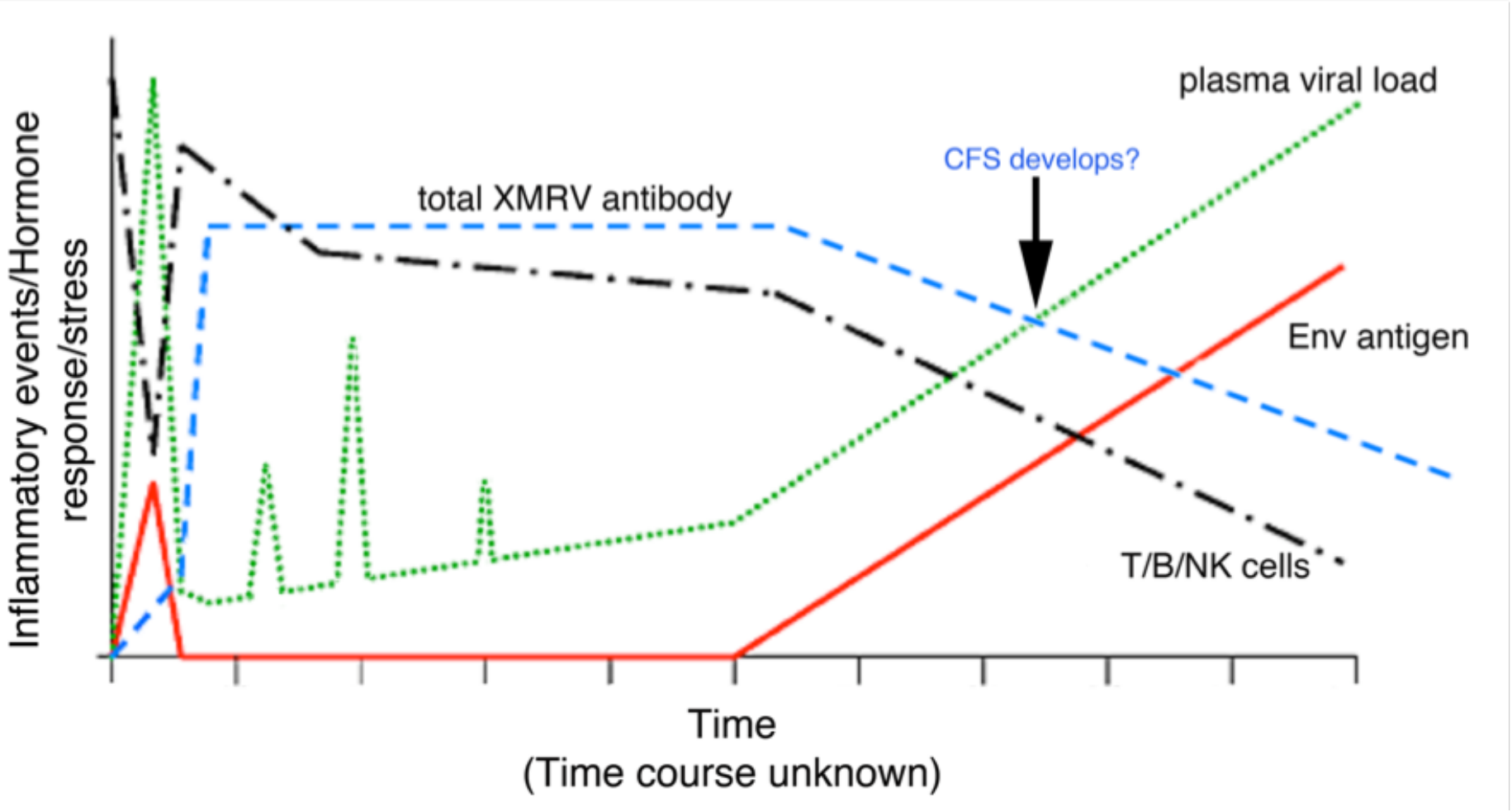
Results suggests a similar Disease cycle of chronic innate immune activation leading to an immune dysregulation and chronic immunosuppression and may guide future research towards the development of biomarkers and treatment targets

Toxicity from Chronic Immuno-stimulation



Ponce 2008 J Immuntoxicology 5:33-41

HYPOTHESIS of XMRV INDUCED PATHOGENESIS:
Chronic infection with XMRV may lead to an Immune Deficiency



Xenotropic Murine Leukemia Virus Related Virus (XMRV): Current Research, Disease Associations, Therapeutic Opportunities (Future Medicine, Therapy, Sept 2010)

Conclusion:

New technologies and increased understanding of mechanisms of the pathophysiology human retrovirus associated diseases offer tremendous opportunity for treatment strategies for neuroimmune Disease and Cancer

Cell Host & Microbe
Short Article

Gut Dysbiosis Promotes M2 Macrophage Polarization and Allergic Airway Inflammation via Fungi-Induced PGE_2

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,*]
[1]Department of Immunology, Faculty of Medicine
[2]Japan Science and Technology Agency, Core Research for Evolutional Science and Technology (CREST)
[3]Life Science Center of Tsukuba Advanced Research Alliance (TARA)
University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan
[4]Department of Pediatrics and Communicable Diseases, Microbiology, and Immunology
[5]Pathology and Comprehensive Cancer Center
University of Michigan Medical School, Ann Arbor, MI 48109, USA
*Correspondence: ashibuya@md.tsukuba.ac.jp
http://dx.doi.org/10.1016/j.chom.2013.12.010

Celebrex-originally identified to block PGE2 induced inflammation

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

New Technologies provide new opportunities for drug repurposing:
Comprehensive Sequence Analysis of Nuclear mitochondrial genes

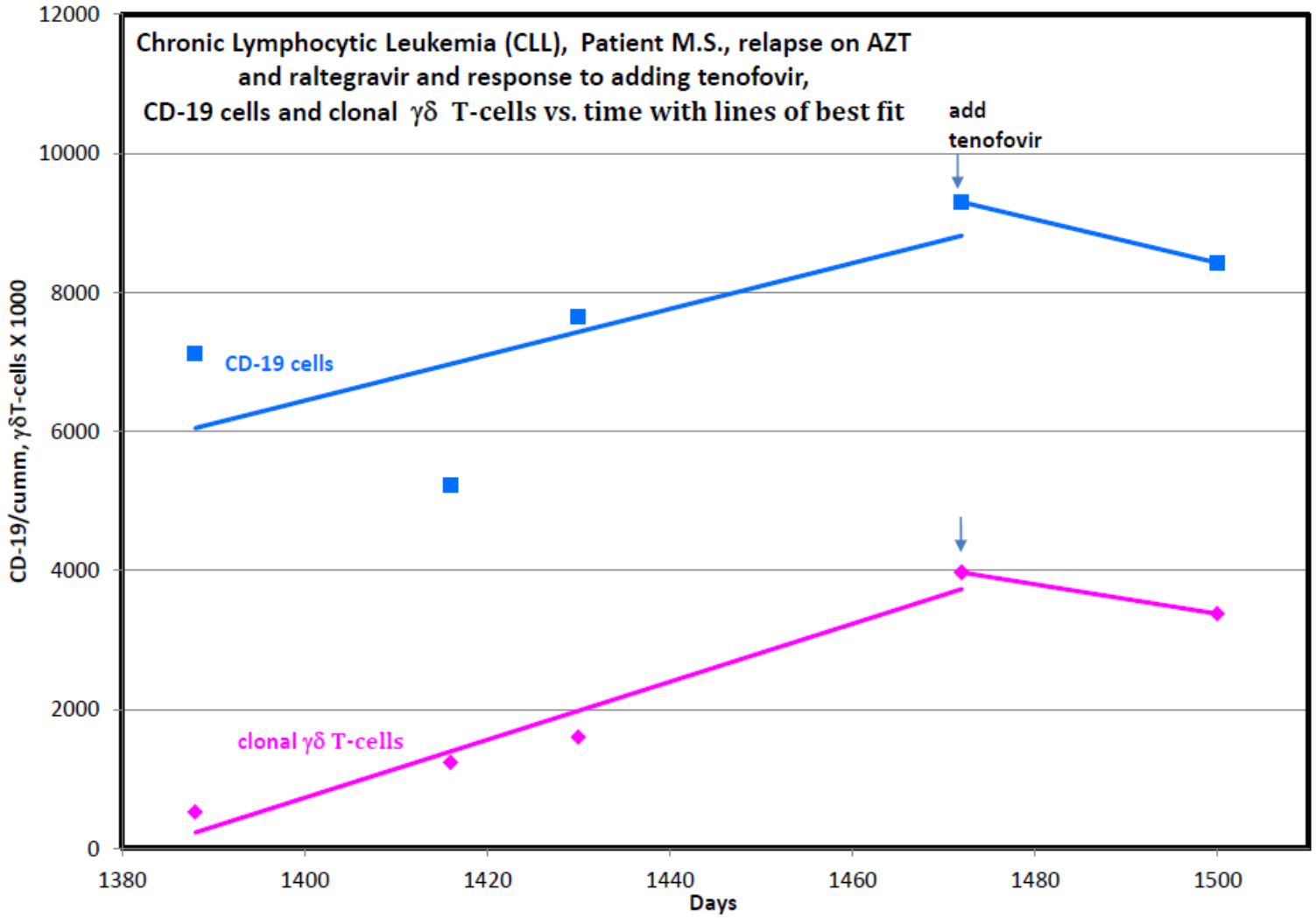
- NGS for variants in the nuclear mitochondrial exome that contribute to neurological disorders whose symptoms resemble mitochondrial disease.

Case Reports In CFS patients Results:

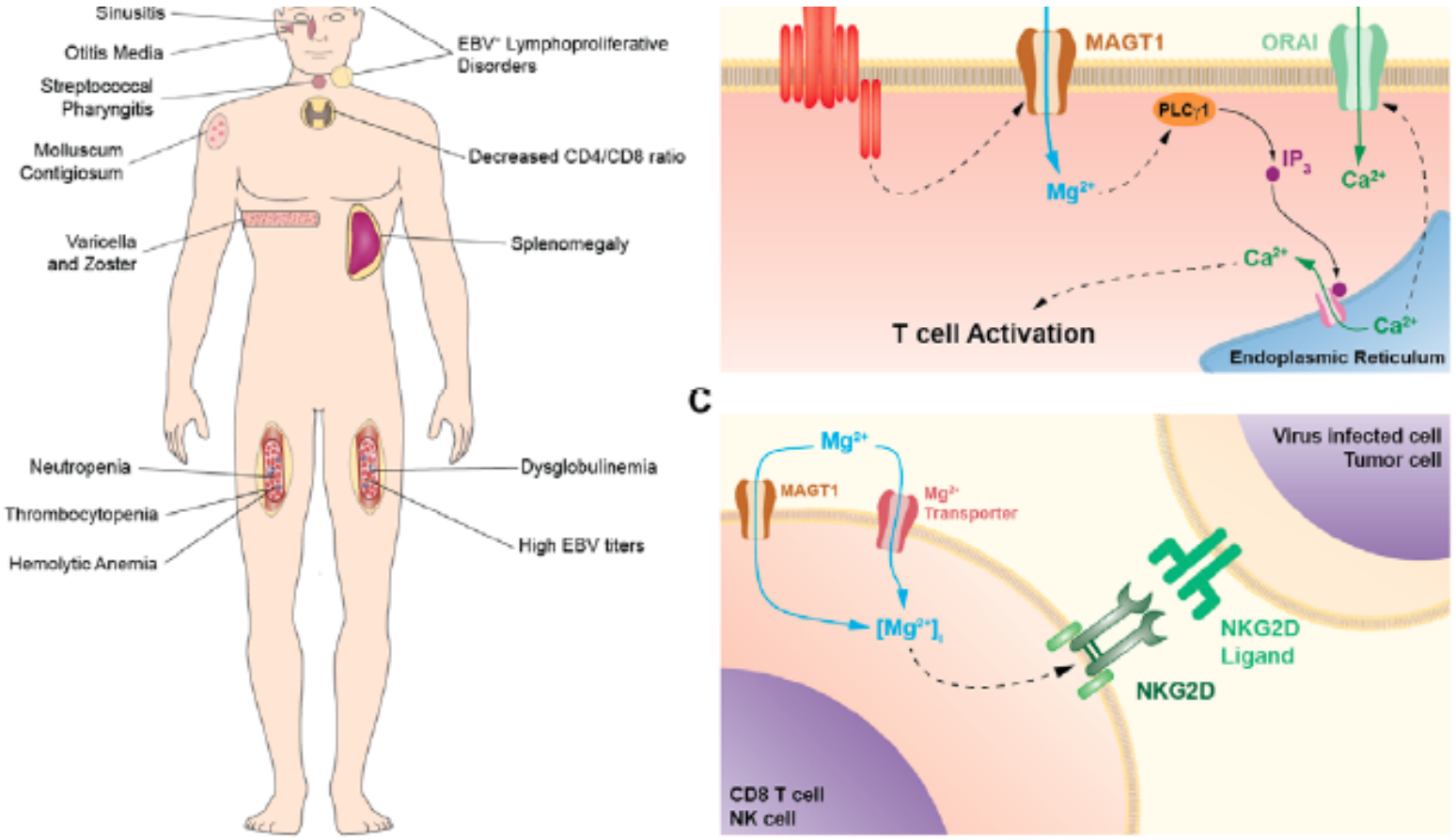
- Abnormal autosomal dominant Variant was found in SCN4A gene that is likely a pathological mutation
- Pathological mutations found in two other patients also with multiple functional conditions (ME/CFS)

- Drugs targeting channelopathies (Diamox)
- mitochondrial targets mTOR (Rapamycin)
- apoptosis

Antiretroviral Therapy of CLL and CFS



XMEN- New Primary Immune Deficiency



First PID associated with specific loss of NKG2D expression

Rituximab

Magnesium threonate supplementation

The Latest “ome” : Metabolome studies reveal new uses for old drugs

OPEN ACCESS Freely available online

PLOS | ONE

Antipurinergic Therapy Corrects the Autism-Like Features in the Poly(IC) Mouse Model

Robert K. Naviaux[1,2,3,4*], Zarazuela Zolkipli[1,5], Lin Wang[1,2], Tomohiro Nakayama[1,5], Jane C. Naviaux[1,6], Thuy P. Le[1,3], Michael A. Schuchbauer[6], Mihael Rogac[1,2¤], Qingbo Tang[2], Laura L. Dugan[2], Susan B. Powell[6]

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Suramin