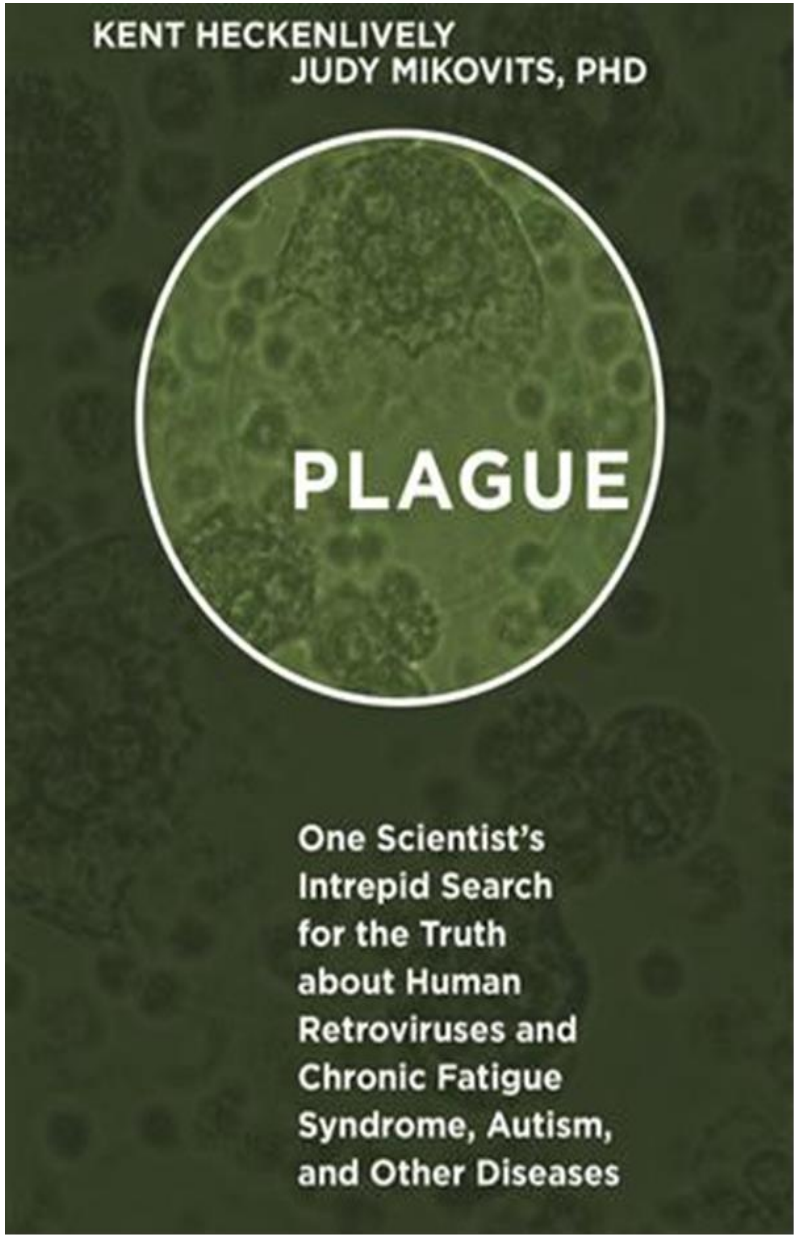
Healing After Plague: Lessons Applied



Emerging Concepts

- Recombination events in animal and human cells can generate families of infectious related gamma retroviruses
- Greatest concern is that they have acquired the ability to infect humans as our data shows consistently 6% in control populations
- Are XMRV-like sequences and proteins important in human disease pathogenesis?

Clinical features of patients infected with human retroviruses:

- Reduced Natural Killer (NK) cell numbers and NK cell cytotoxicity
- Abnormal $CD4^+$ and $CD8^+$ T cell numbers and ratio
- Reduced T cell response to antigens
- Presence of auto antibodies
- Alteration in cytokine profile
- Hyperactivation of T cells
- Decreased Antibody dependent cellular cytotoxicity (ADCC)

In: Chronic Fatigue Syndrome
Editors: Connor Hudson

ISBN: 978-1-63321-961-8

Chapter VI

Innate Immune Changes in the Peripheral Blood of Chronic Fatigue Syndrome Patients: Risk Factors for Disease Progression and Management

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[3]Private CFS Practice, Arizona, US

Experimental Design

- Investigate the nature of the immune cells in peripheral blood patients with Neuroimmune Disease
  - Phenotypic analysis using Multi-parameter Flow Cytometry.
  - Mutliplex proteomic analysis on the Luminex platform

GOAL

- Determine phenotypic and cytokine signatures that could be used as biomarkers of infection and disease subgroups.

Summary of Phenotypic Results

	ME/CFS, CLD vs. healthy
Total Cellularity	No Difference
CD45+ Leukocytes	No Difference
CD45+ Lymphocytes	Reduced in ME/CFS
CD45+ CD3- Lymphocytes	Reduced in ME/CFS
CD3+ CD56+ NKT cells	Increased in ME/CFS, CLD
CD3- CD56+ NK cells	Reduced in ME/CFS, CLD
$CD56^{DIM}$ NK subpopulation	Reduced in ME/CFS
$CD56^{DIM}$ CD16+ NK subpopulation	Reduced in ME/CFS
CD19+ B cells	Reduced in ME/CFS
CD19+ CD20+ CD23+ B subpopulation	Increased in ME/CFS
CD33+ CD14+ CD123- myeloid Population	Reduced in ME/CFS
Activated APCs	Increased in ME/CFS, CLD

Chronic innate immune activation leads to chronic immunosuppression

- 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 HIV.
- 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.

Conclusion

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

Chronic Diseases Potentially Associated with Human Retroviral Infection

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

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

Detection of serum reverse transcriptase activity in patients with ALS and unaffected blood relatives

A.J. Steele, PhD; A. Al-Chalabi, PhD, FRCP; K. Ferrante, BA; M.E. Cudkowicz, MD, MSc; R.H. Brown, Jr., MD, DPhil; and J.A. Garson, MD, PhD

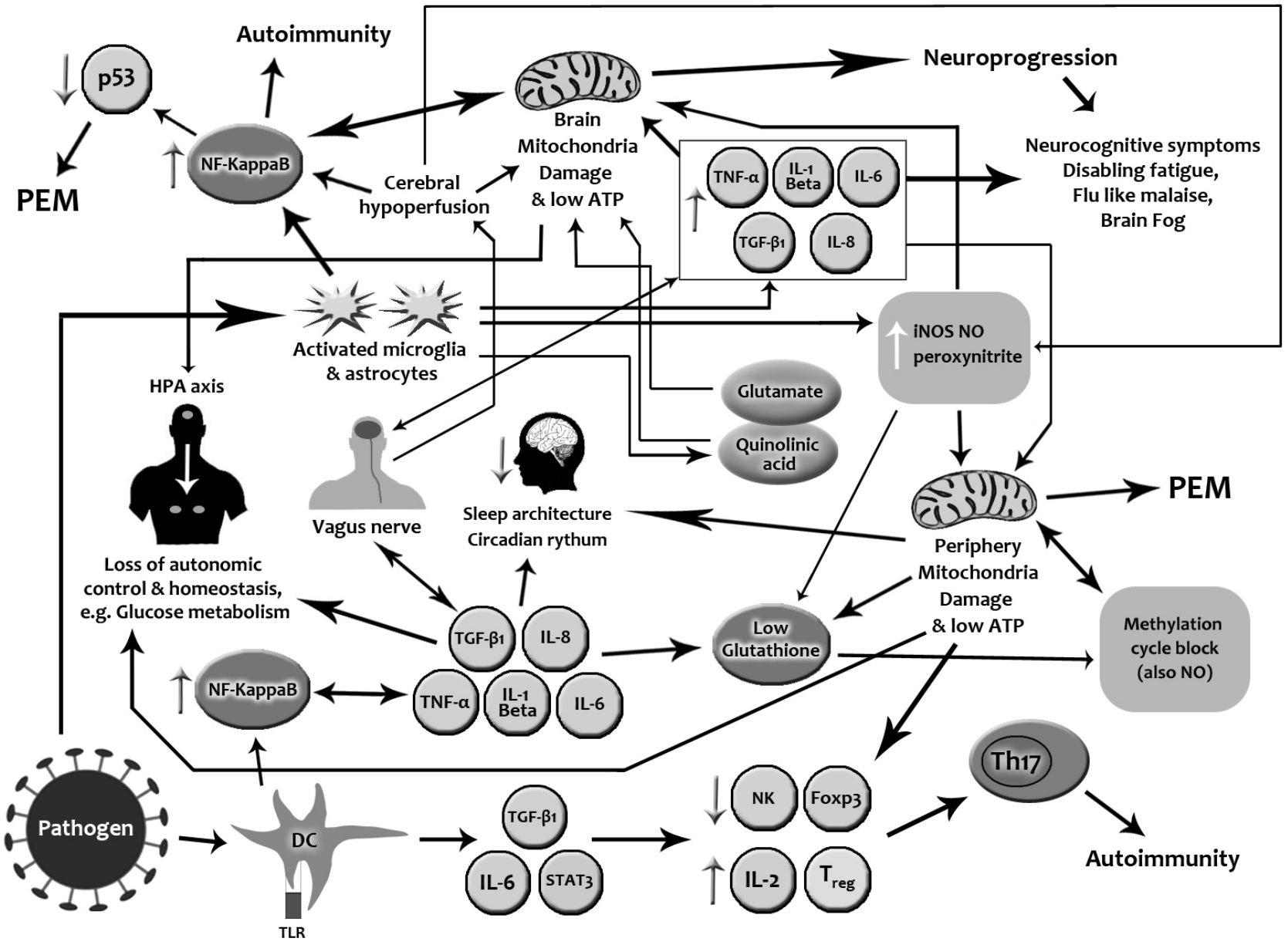
NEUROLOGY 2005;64:454–458

Quantification of reverse transcriptase in ALS and elimination of a novel retroviral candidate

Neurology® 2008;70:278–283

That Novel Candidate was XMRV

Pathways shared in Autoimmune and Neuroimmune Disease



Autoimmunity Reviews 11 (2011) 88–97

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Autoimmunity Reviews

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

Review

Autoimmune disease: A role for new anti-viral therapies?

David H. Dreyfus *

Pediatrics, Yale SOM, United States

ARVs provide therapeutic benefit in some patients with autoimmune, Neuroimmune Disease and Cancer

Beneficial Effects could be against:

- An exogenous Replication Competent Retrovirus
- An expressed endogenous virus in an immune compromised individual
- A defective virus expressing only viral proteins
- Aberrantly expressed cellular RNA including microRNA (regulatory)

miR-155 a new target in ME/CFS?

- miR-155 has distinct expression profiles
- Plays crucial role in various physiological and pathological processes such as hematopoietic lineage differentiation, immunity, inflammation, cancer, and cardiovascular diseases; miR-155 has been implicated in chronic DNA viral infections
- Been implicated in viral infections, particularly in those caused by DNA viruses.

ORIGINAL ARTICLE

Annals of Neurology 2013

miR-155 as a Multiple Sclerosis–Relevant Regulator of Myeloid Cell Polarization

Craig S. Moore, PhD,[1] Vijayaraghava T.S. Rao, PhD,[1] Bryce A. Durafourt, MSc,[1] Barry J. Bedell, PhD, MD,[2] Samuel K. Ludwin, MD,[3] Amit Bar-Or, MD,[1] and Jack P. Antel, MD[1]

- Endogenous retroviruses (sleeping giants) are reactivated in immune deficient individuals (ME/CFS, CLD, CLL, ASD, HIVAIDS), likely because of dysregulated DNA methylation

- Co-infections, reactivated viruses, GMOs, genetic susceptibilities can create perfect storm of aberrant methylation immune activation (including microglia and inflammation seen in ASD, ME/CFS, other neuroimmune disease and cancer

Hypothesis

Aberrant evolution of the human genome by:

- Increased zoonosis of novel retroviruses in human and animal populations

Handbook of Clinical Neurology, Vol. 123 (3rd series)
Neurovirology
A.C. Tselis and J. Booss, Editors

Chapter 22

Human endogenous retroviruses and the nervous system

RENÉE N. DOUVILLE[1] AND AVINDRA NATH[2]*
[1]*Department of Microbiology, University of Winnipeg, Winnipeg, Manitoba, Canada*
[2]*Section of Infections of the Nervous System, National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, MD, USA*

Human endogenous retrovirus (HERV) families associated with neurologic disease

HERV	Family	Neurologic diseases	Known triggers	Pathogenic contribution
HERV-W	Gammaretrovirus	Multiple sclerosis Schizophrenia	Herpesviruses *Toxoplasma* Proinflammatory cytokines	MSRV virions Env superantigen Env alters glial function
HERV-H/F	Gammaretrovirus	Multiple sclerosis	Unknown	Virions Env superantigen
HERV-K	Betaretrovirus	Schizophrenia ALS HIV infection	Herpesviruses HIV HTLV-1 Toxoplasma	Env superantigen Neoepitopes for CTLs

The replicative activity of human endogenous retrovirus K102 (HERV-K102) with HIV viremia

Marian P. Laderoute[a,b], Antonio Giulivi[a,b], Louise Larocque[a], Deana Bellfoy[a], Yangxun Hou[a], Hong-Xing Wu[a], Keith Fowke[c], Jun Wu[a] and Francisco Diaz-Mitoma[d]

Results: Both the peptide serology and ddCt qPCR excess ratio methods suggested the activation of HERV-K102 in about 70–80% of HIV viremic cases whereas only 2–3% of normal healthy adults had marginally activated HERV-K102 ($P < 0.0001$). Moreover, by

Conclusions: Our work uniquely suggests the common activation of HERV-K102 with HIV viremia and may be first to directly demonstrate HERV-K102 cDNA production *in vivo*. The potential implications of the induction of HERV-K102 activation and replication for the prevention and control of HIV are discussed.

AIDS 2007, **21**:2417–2424

Review

CellPress

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

Trends in Parasitology, April 2014, Vol. 30, No. 4 205

Agustín Estrada-Peña[1], Richard S. Ostfeld[2], A. Townsend Peterson[3], Robert Poulin[4], and José de la Fuente[5,6]

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Entropy **2013**, *15*, 4748-4781; doi:10.3390/e15114748

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Review

The New Genetics and Natural *versus* Artificial Genetic Modification

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Received: 2 August 2013; in revised form: 9 October 2013 / Accepted: 10 October 2013 / Published: 4 November 2013

Hazards of GMOs

1. Uncontrollable, unpredictable impacts on safety due to the genetic modification process *
   - 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 *
2. Toxicity of transgene protein(s) introduced (intentionally or otherwise)
   - Transgene protein toxic *
   - Transgene protein allergenic or immunogenic *
   - Trangenic protein becoming allergenic or immunogenic due to processing *
   - Unintended protein created by sequence inserted may be toxic or immunogenic
3. Effects due to the GM insert and its instability *
   - 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 *
4. Toxicity of herbicides used with herbicide tolerant GM crops *

NYAS 29 March 2011

What are the detection rates in 1000 blood donors using these serological assays?

Analyzed to CA, TM and SU

SU is the most reactive antigen (subjects vs donors)

- 4% reactive
- 13% 'indeterminate'
  - Values above cut-off, but also reactive to neg ctrl antigen

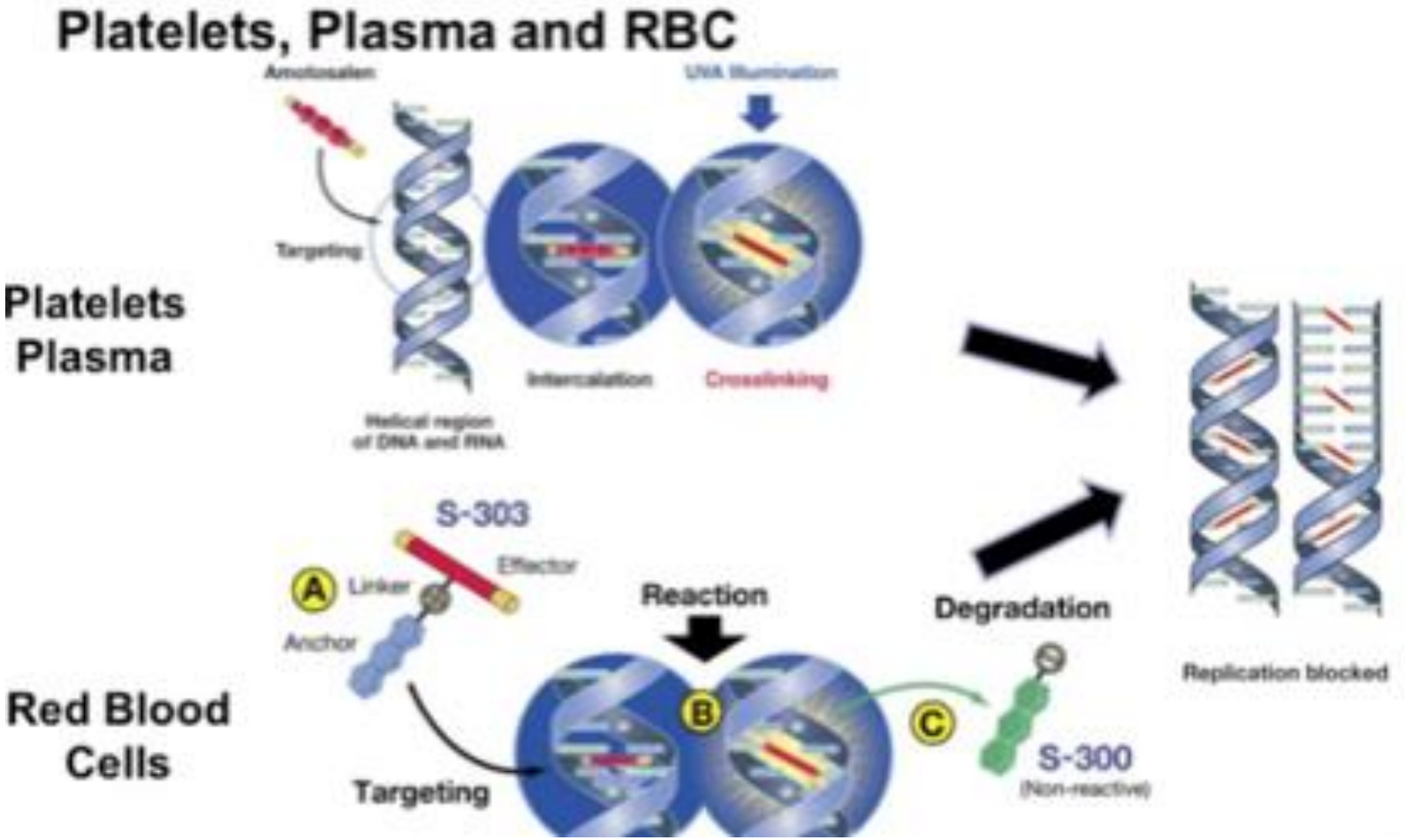
Test reactives and indeterminates by Western Blot: Found SU most unstable protein

NYAS March 29 2011

by Intercept Blood System is consistent with results for other human Retroviruses

Organisms	Extent of Inactivation (log_{10} reduction)		
	Platelets[a]	Plasma[b]	RBC[c]
HIV-1 (cell associated)	>6.1	>6.1	>5.9[d]
HIV-1 (cell free)	>6.2	>6.8	NA
HTLV-I	4.7	≥4.5	>4.2[d]
HTLV-II	5.1	>5.7	> 5.1[d]
XMRV & MLV-Related virus	**>4.0[e]**	**NA**	**>4.0[e]**

2014 December 1 FDA Approval



NYAS March 29 2011

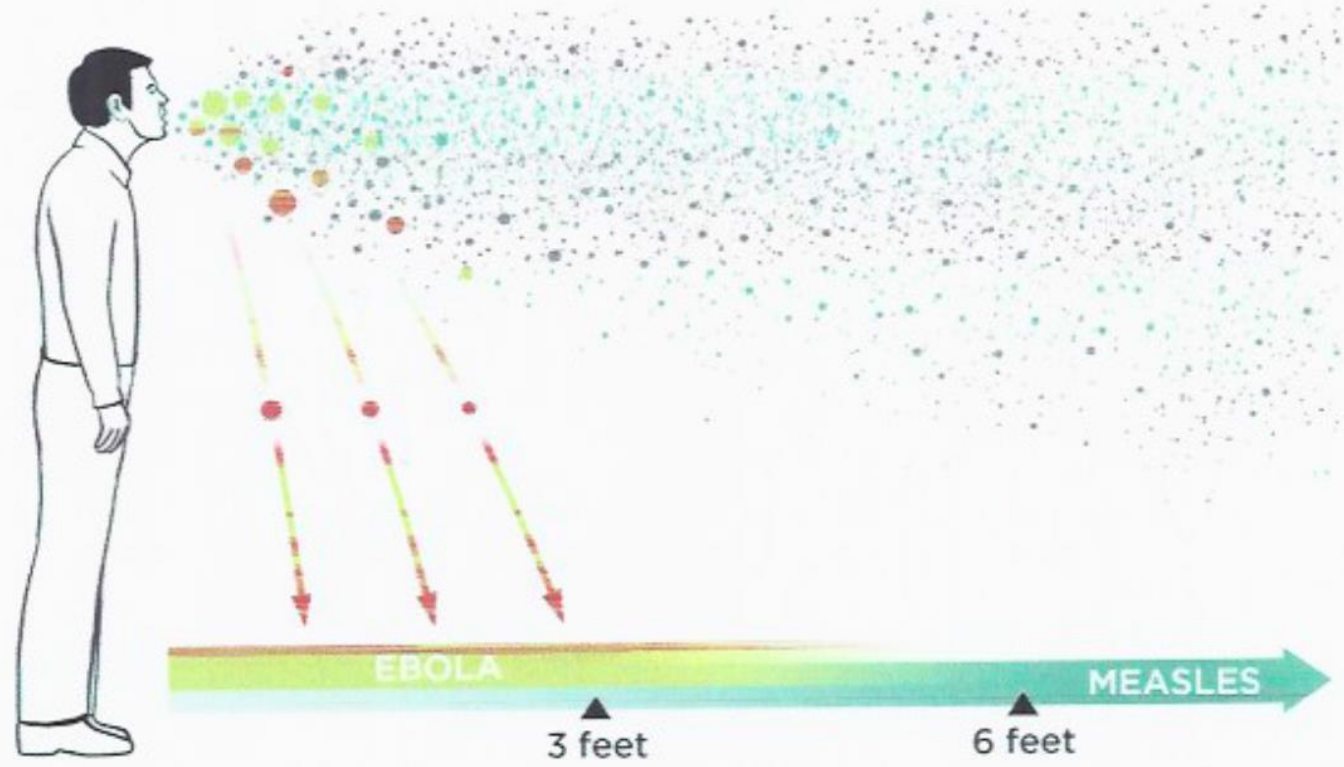
Summary/Conclusions

- Data suggest there are different strains of Gamma Retroviruses that can infect humans
- Assays that capture the variation of these viruses in the blood supply are the best i.e. Serology and transmission
- Technologies can inactivate infectious strains of XMRV in Blood Components
- New Disease associations include leukemia, lymphoma and the platelet disorder, ITP

Ebola In The Air: What Science Says About How The Virus Spreads

DECEMBER 01, 2014 12:29 PM ET

MICHAELEEN DOUCLEFF



Viruses can spread through the air in two ways: inside large droplets that fall quickly to the ground (red), or inside tiny droplets that float in the air (gray). In the first route, called droplet transmission, the virus can spread only about 3 to 6 feet from an infected person. In the second route, called airborne transmission, the virus can travel 30 feet or more.

Adam Cole/NPR

Here's an Ebola puzzle for you: If the virus isn't airborne, why do doctors and nurses need to wear full protective suits, with face masks, while treating patients?

BIOMARKERS

Distinct plasma immune signatures in ME/CFS are present early in the course of illness

Mady Hornig,[1,2]* José G. Montoya,[3] Nancy G. Klimas,[4] Susan Levine,[5] Donna Felsenstein,[6] Lucinda Bateman,[7] Daniel L. Peterson,[8] C. Gunnar Gottschalk,[8] Andrew F. Schultz,[1] Xiaoyu Che,[1] Meredith L. Eddy,[1] Anthony L. Komaroff,[9] W. Ian Lipkin[1,2,10]

10.1126/sciadv.1400121

Thank You

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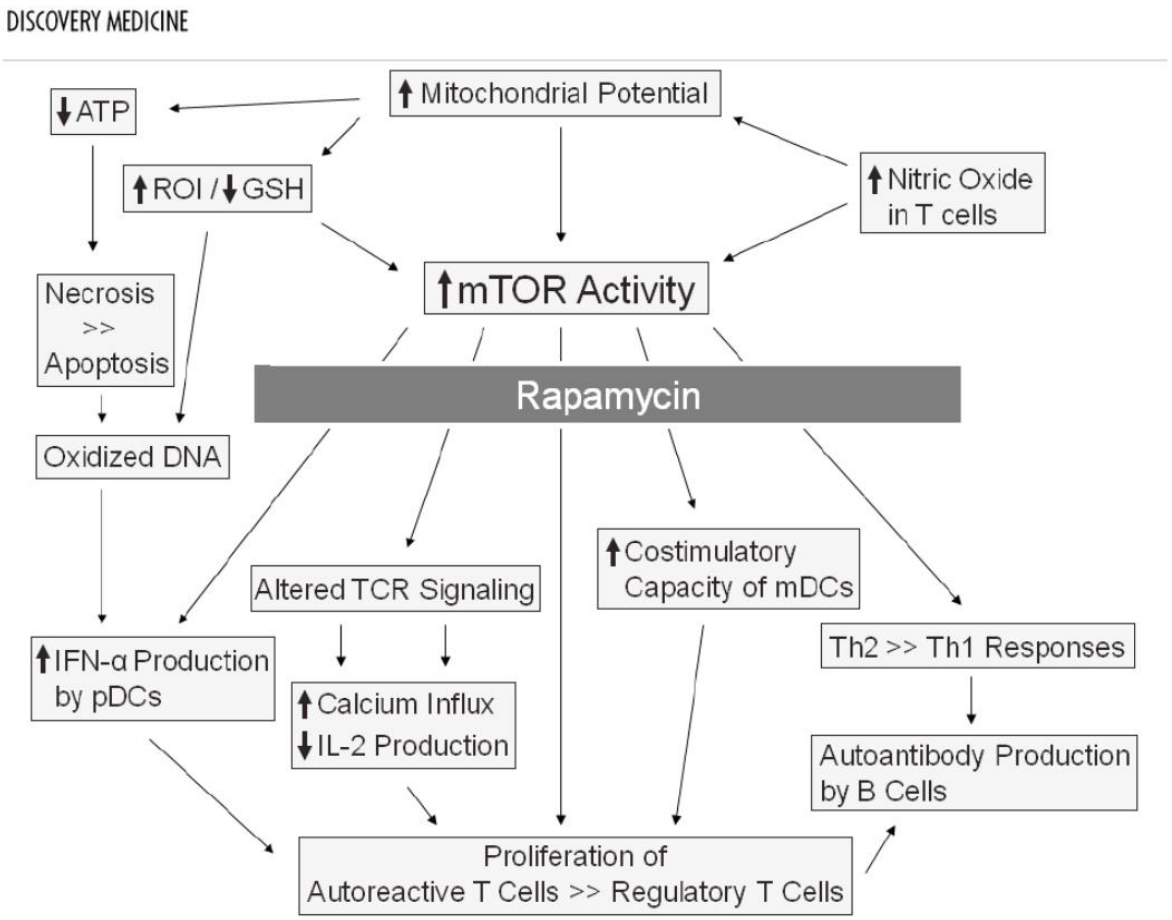
Here we are not afraid to follow the truth wherever it may lead,
Nor tolerate error so long as freedom is left to combat it
Thomas Jefferson

mTOR a master regulator of Neuroimmune Disease?

http://www.discoverymedicine.com/David-Fernandez/files/2010...



Ramesh et al

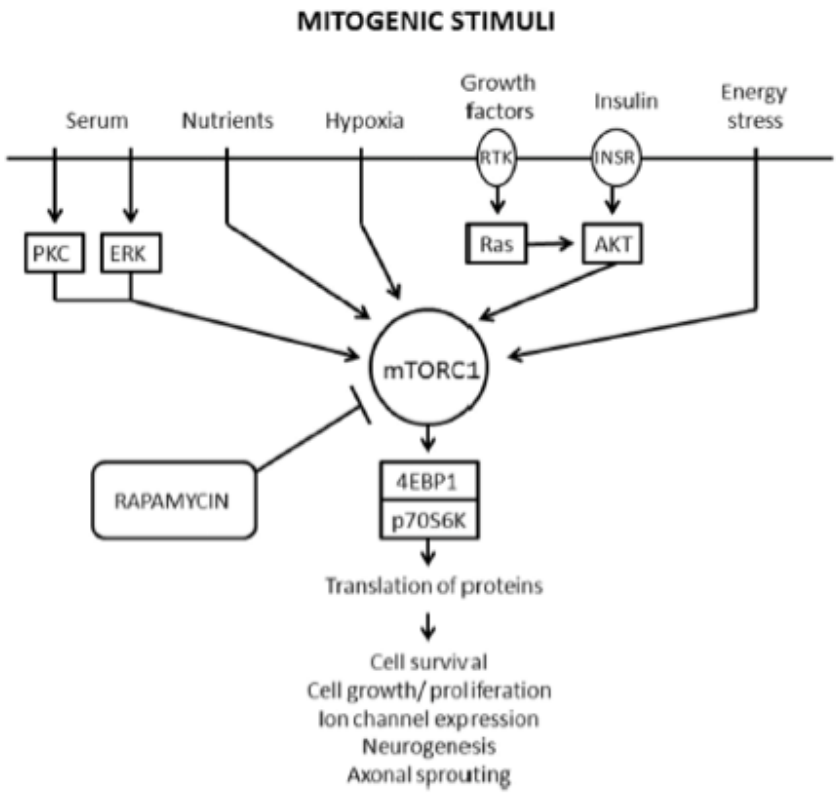
Yates et al. Acta Neuropathologica Communications 2013, 1:3
http://www.actaneurocomms.org/1/1/3

ACTA NEUROPATHOLOGICA COMMUNICATIONS

RESEARCH Open Access

Dysfunction of the mTOR pathway is a risk factor for Alzheimer's disease

Sharon C Yates[1], Amen Zafar[1], Paul Hubbard[1], Sheila Nagy[1], Sarah Durant[2], Roy Bicknell[2], Gordon Wilcock[3], Sharon Christie[3], Margaret M Esiri[4], A David Smith[5] and Zsuzsanna Nagy[1*]



Immune Reconstitution Inflammatory Syndrome

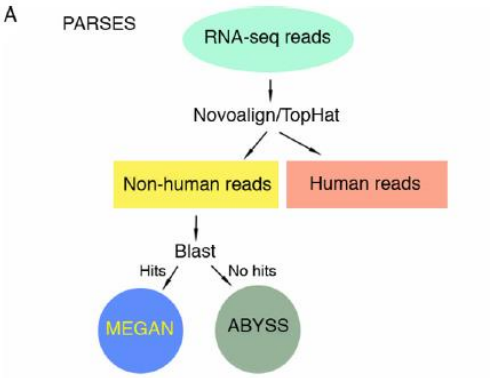
Form of IRIS	Progression of events leading to IRIS					
	Infection or iatrogenic immunosuppression	Immune defect	High microbial load without normal inflammation	Clinical intervention	Full inflammation restored	Pathology
HIV-associated	HIV	↓ $CD4^+$ T cells	Many, including mycobacteria and cryptococci	ART	↑ $CD4^+$ T cells	Many manifestations
Exacerbation of TB after withdrawal of TNF blockade	TNF blockade	↓ TNF	*M. tuberculosis*	Stop TNF blockade	↑ TNF	Lung pathology, lymphadenitis
PML-associated	α4 integrin blockade	↓ Immune cell migration into CNS	JC polyoma virus	Stop α4 integrin blockade	↑ Immune cell migration into CNS	Leukoencephalopathy
Organ transplant-associated	Anti-graft rejection treatment	Broad immunosuppression	*C. neoformans*	Decrease immunosuppressive treatment	Many factors?	Meningitis
Mouse model	TCRαKO or *scid* mice	T cell deficiency	*M. avium* or *P. carinii*	Inject $CD4^+$ T cells	↑ $CD4^+$ T cells	Wasting, lung pathology

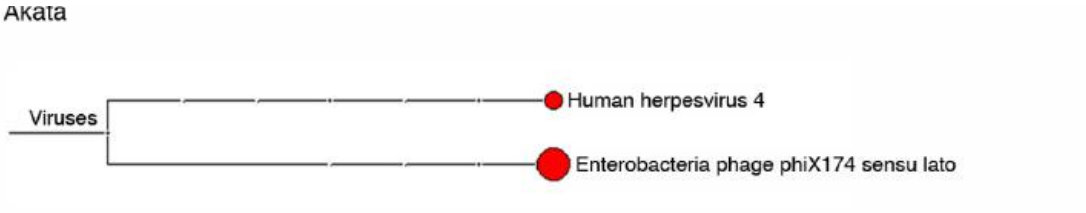
JVI
Journals.ASM.org

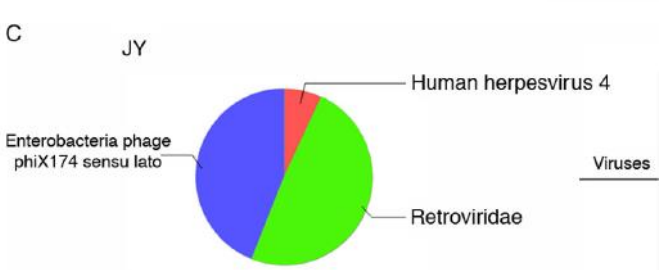
Detection of Murine Leukemia Virus in the Epstein-Barr Virus-Positive Human B-Cell Line JY, Using a Computational RNA-Seq-Based Exogenous Agent Detection Pipeline, PARSES

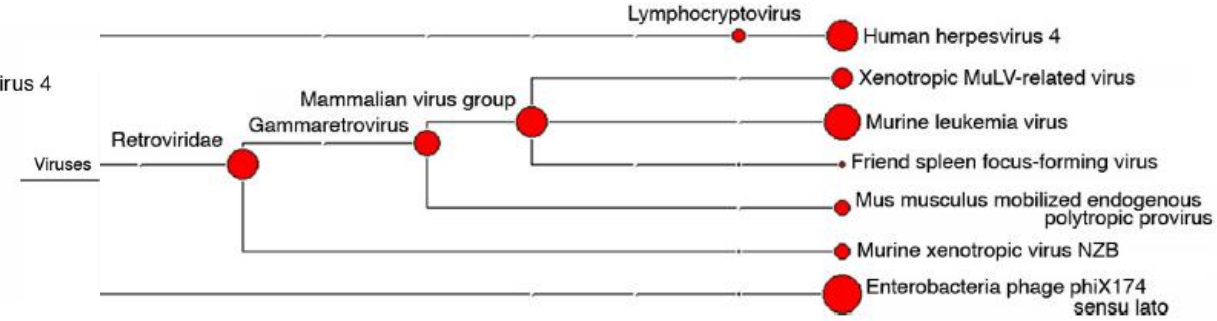
Zhen Lin,[a] Adriane Puetter,[a] Joseph Coco,[b] Guorong Xu,[b] Michael J. Strong,[a] Xia Wang,[a] Claire Fewell,[a] Melody Baddoo,[a] Christopher Taylor,[b] and Erik K. Flemington[a]

Tulane University Health Sciences Center and Tulane Cancer Center, New Orleans, Louisiana, USA,[a] and University of New Orleans, New Orleans, Louisiana, USA[b]









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Adoptive T cell Transfer for Cancer Immunotherapy in the Era of Synthetic Biology

Michael Kalos and **Carl H. June**
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