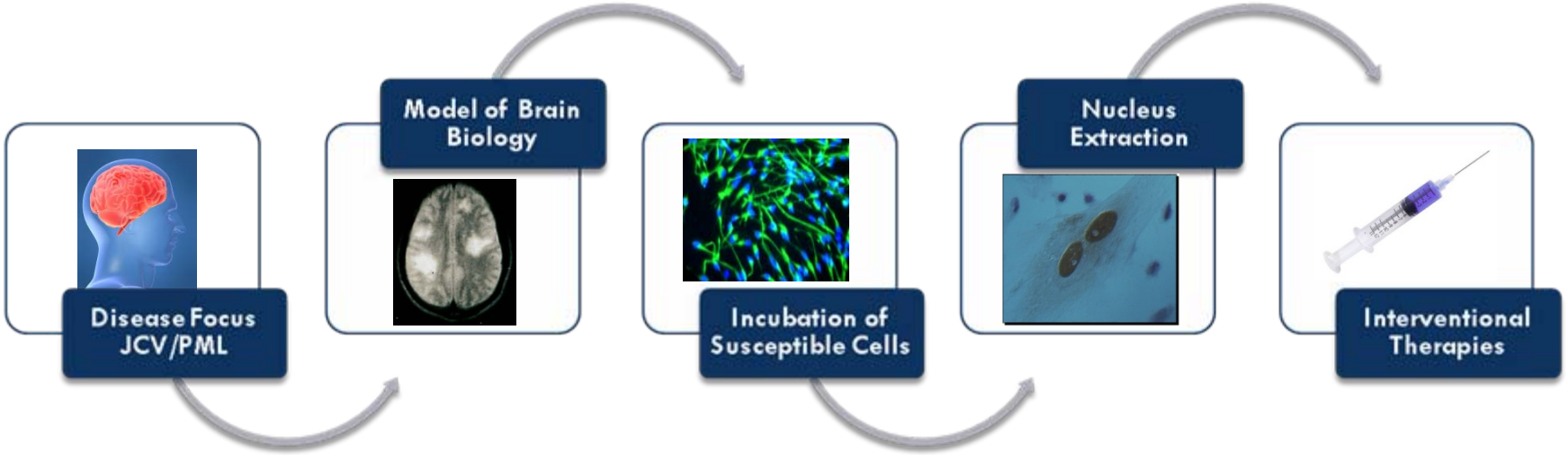
THE POSSIBLE MECHANISMS OF THE DISEASE

Eugene O. Major, Ph.D.
NIH/NINDS Laboratory of Molecular Medicine & Neuroscience

Laboratory of Molecular Medicine and Neuroscience
Division of Intramural Research, NINDS



LMMN Members

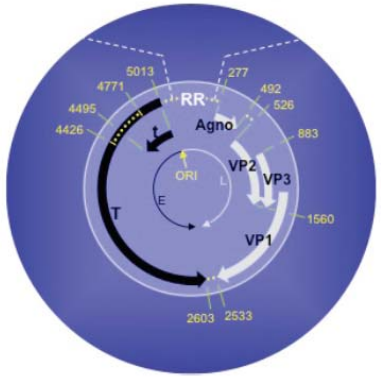
Karen Augustine Maria Barhams, M.H.S.A.
Paul Howell Carol Ibe, M.S.
Eugene O. Major, Ph.D.
Maria Chiara Monaco-Kushner, Ph.D.
Beth Daley Linda Durham, M.S. Mike Ferenczy, Ph.D.
Peter Jensen Zhi-Gang Jiang, M.D., Ph.D.
Leslie Marshall, Ph.D Matt Mirsky
Caroline Ryschkewitsch, M.T.

PML is a viral-induced demyelinating disease

- Prevalence classifies PML as rare disease (fewer than 200,000 cases in the US*); no known animal viral reservoir
- Lytic infection of oligodendrocytes (necrotic; lytic cell death; progressive, slow release of virus intercellular- no burst of virus)
- Cerebral hemispheres and cerebellum with no evidence for spinal cord involvement or optic nerve
  - Multifocal, acute and persistent
  - Latent in several tissue compartments (ie. kidney and immune system)
- Immune system dysfunction (suppression/modulation)
- No effective therapies other than 'intact' immune clearance

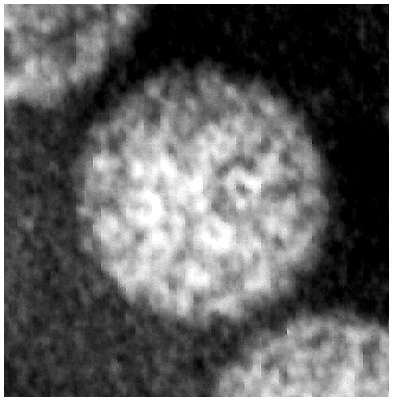
* NIH Office of Rare Disease Research

JC Virus Characteristics

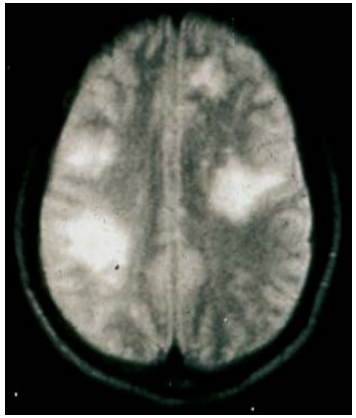


JC viral genome:

*Early (T-protein)
*Regulatory Region (non-coding promoter enhancer)
*Late VP1,2,3(capsid proteins)



Virion particle

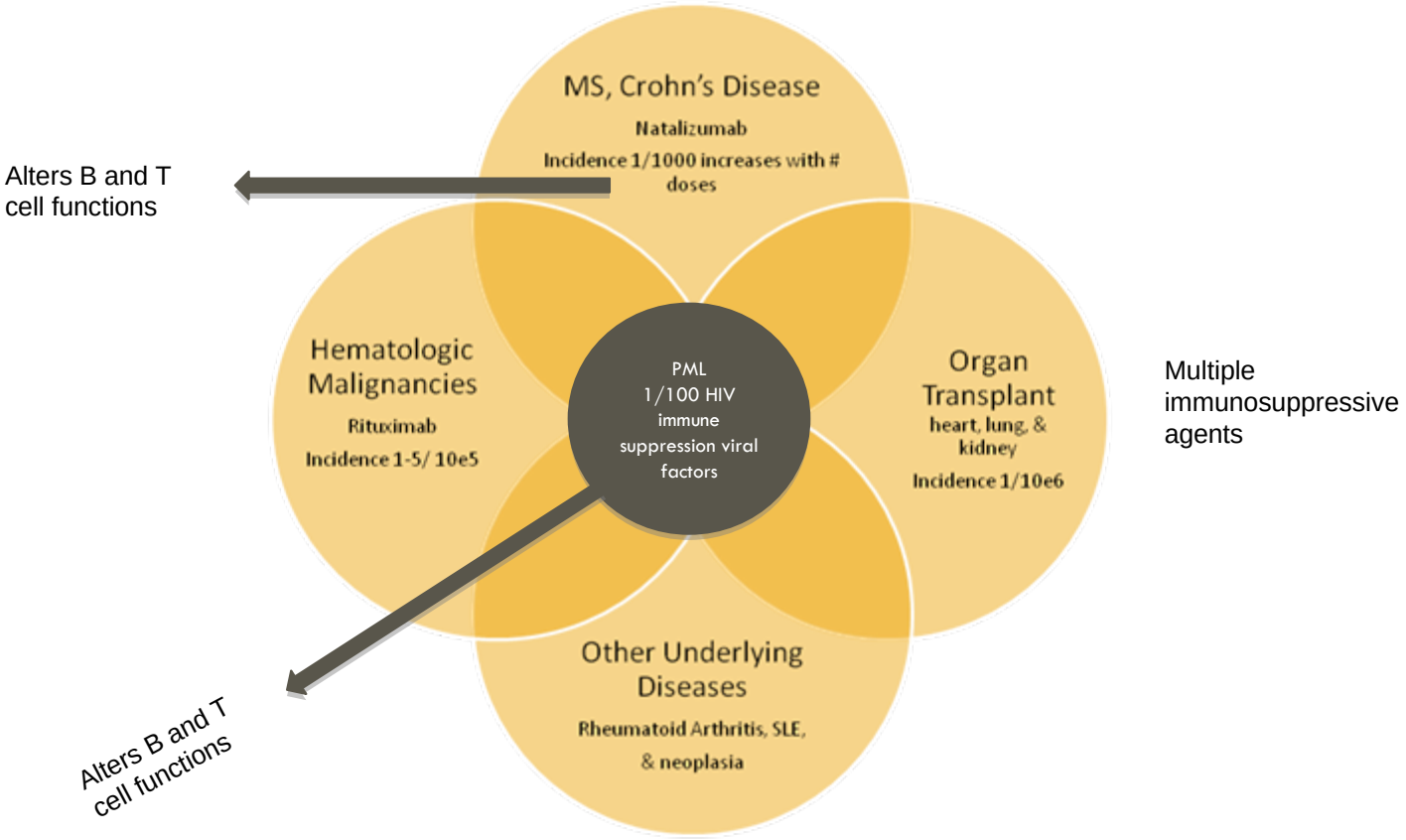


Virions in PML lesions

Progressive Multifocal Leukoencephalopathy in Patient Populations

- HIV/AIDS
- Autoimmune Diseases
  - Multiple Sclerosis
  - Crohn's Disease
  - Rheumatoid Arthritis
  - Systemic Lupus Erythematosus
- Neoplastic Diseases
- Organ Transplant Patients

Progressive Multifocal Leukoencephalopathy Incidence

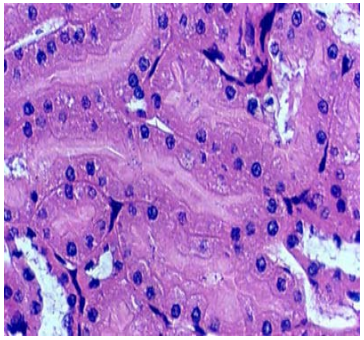


Research Question: What is the link between immune-suppressive agents or monoclonal antibody therapies that results in development of PML? Are there different mechanisms for pathogenesis? Is PML the same disease regardless of underlying disease?

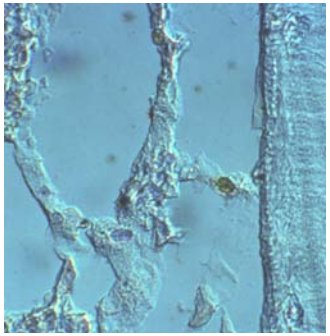
Tissues Correlating with JC Virus Presence in Brain

Possible Pathway

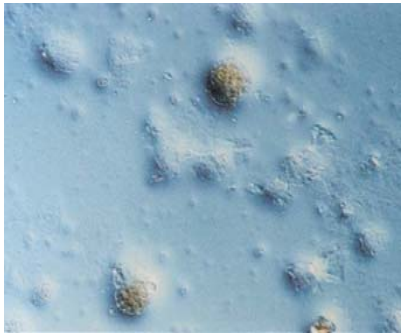
Kidney*



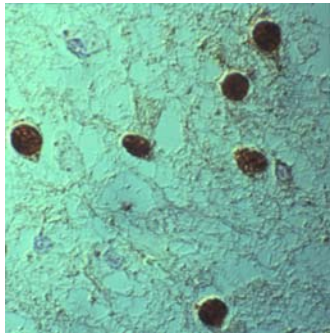
Bone Marrow (pre B cell?)



Peripheral Blood (B cells)



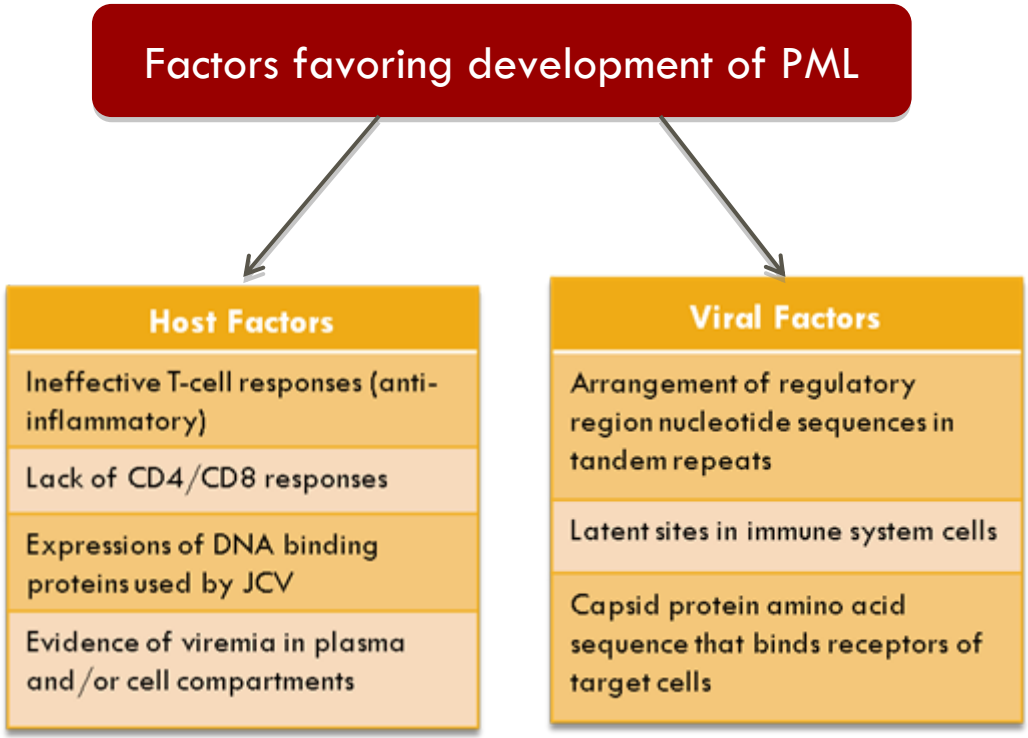
Brain (Oligodendrocytes)



Reference: Brew, et al. (2010) Progressive Multifocal Leukoencephalopathy and other JC virus diseases. Nat Rev Neur 6, 667-679.

Pathogenic Mechanisms in Patient Populations

- Lack of immune surveillance (T cell)
  - Cellular immune response against the virus (functional/ineffective)
  - Humoral immune response (unknown role of antibody)
- Virus reactivated from latency in peripheral compartments that are affected by alterations of immune function i.e. natalizumab, rituximab, efalizumab; 'stochastic event' but linked with mechanism of immune modulation/suppression (*no data suggest that therapies assist in establishment of viral latency*)
- Different mechanisms for viral reactivation depending upon patient history and treatment for underlying disease; HIV infection differs from Mab treatments differs from small molecule drugs like mycophenylate.



Traffic of Virus to Brain

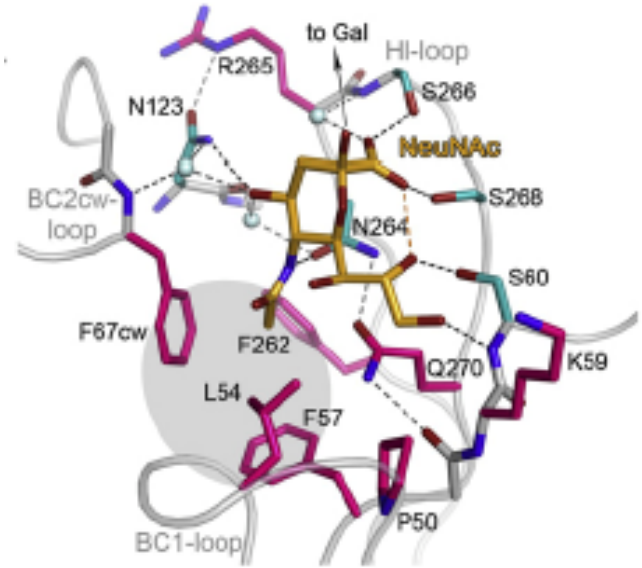
Traffic of virus to the brain following release of virus from sites of latency (initial infection also possible but rare; initial site of infection is unknown but thought to be common site following respiratory inhalation or ingestion.

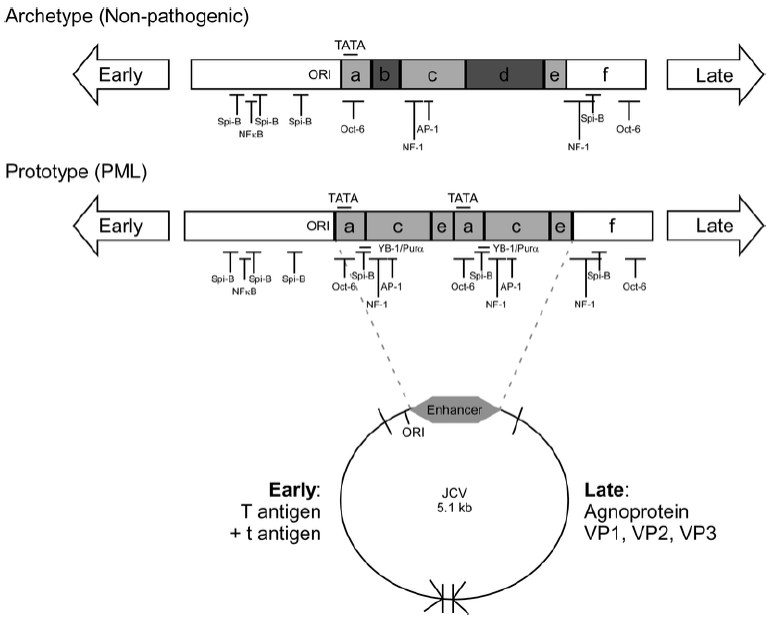
Potential Methods:

- Immune system cells (CD34+,CD10, CD19/20)
- Free Virus
- Kidney (release virus into peripheral circulation)
- Latency in the brain (under investigation)

Hypothesis

- Coding sequences for viral capsid protein VP1 can be altered following latency
- Non-coding regulatory sequences show direct tandem repeat structures in pathologic tissues compared with kidney (no repeats)





In Summary…

Therapies for underlying disease

Occurrence of Progressive Multifocal Leukoencephalopathy

There is a '*direct link*' between immune modulatory agents and PML

HIV-1/AIDS > Integrin inhibitors Natalizumab (Efalizumab) > Rituximab > Small molecules