The Pathophysiology of JC Virus infection leading to progressive multifocal leukoencephalopathy
NINDS LMMN and CLIA Laboratory

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FDA/NIH PML Workshop
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E.O. Major, Ph.D. Disclosures

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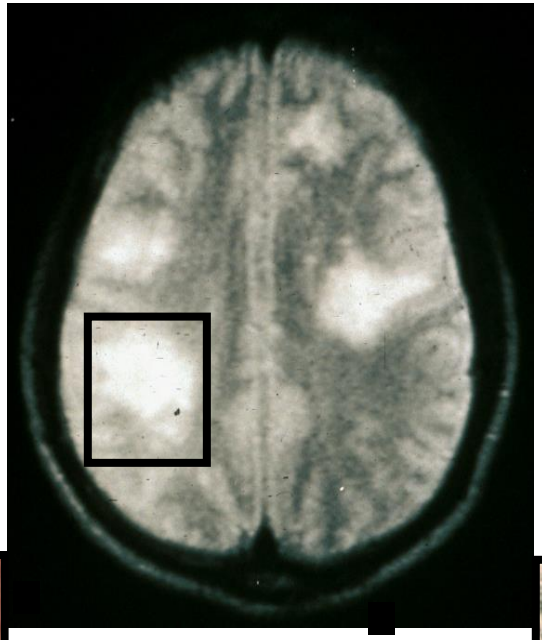

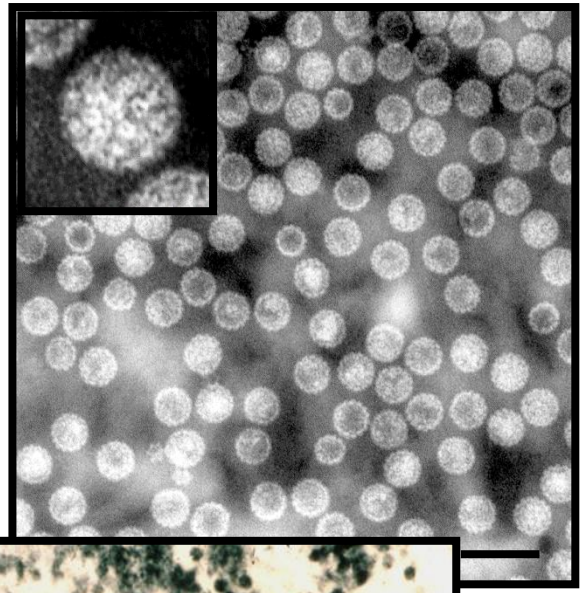

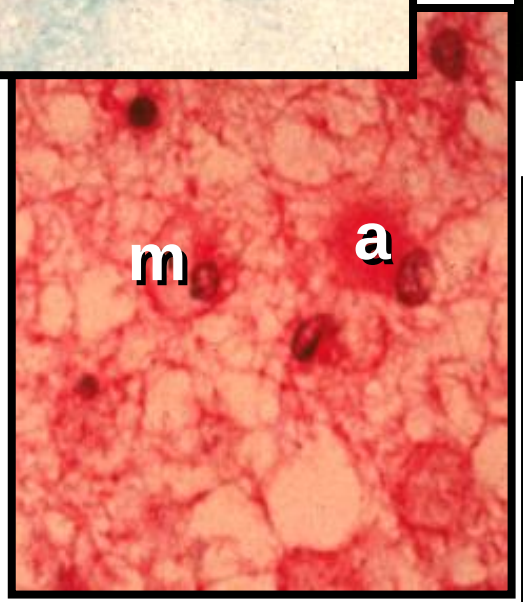
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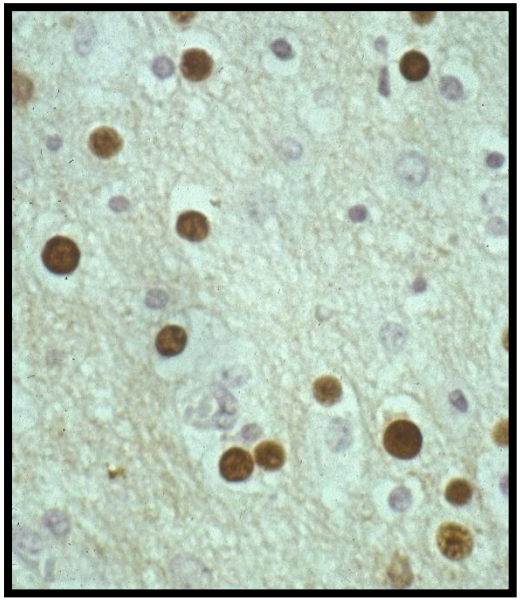
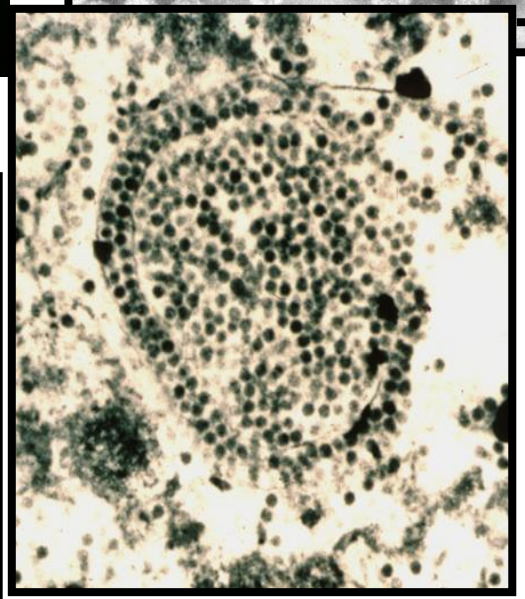
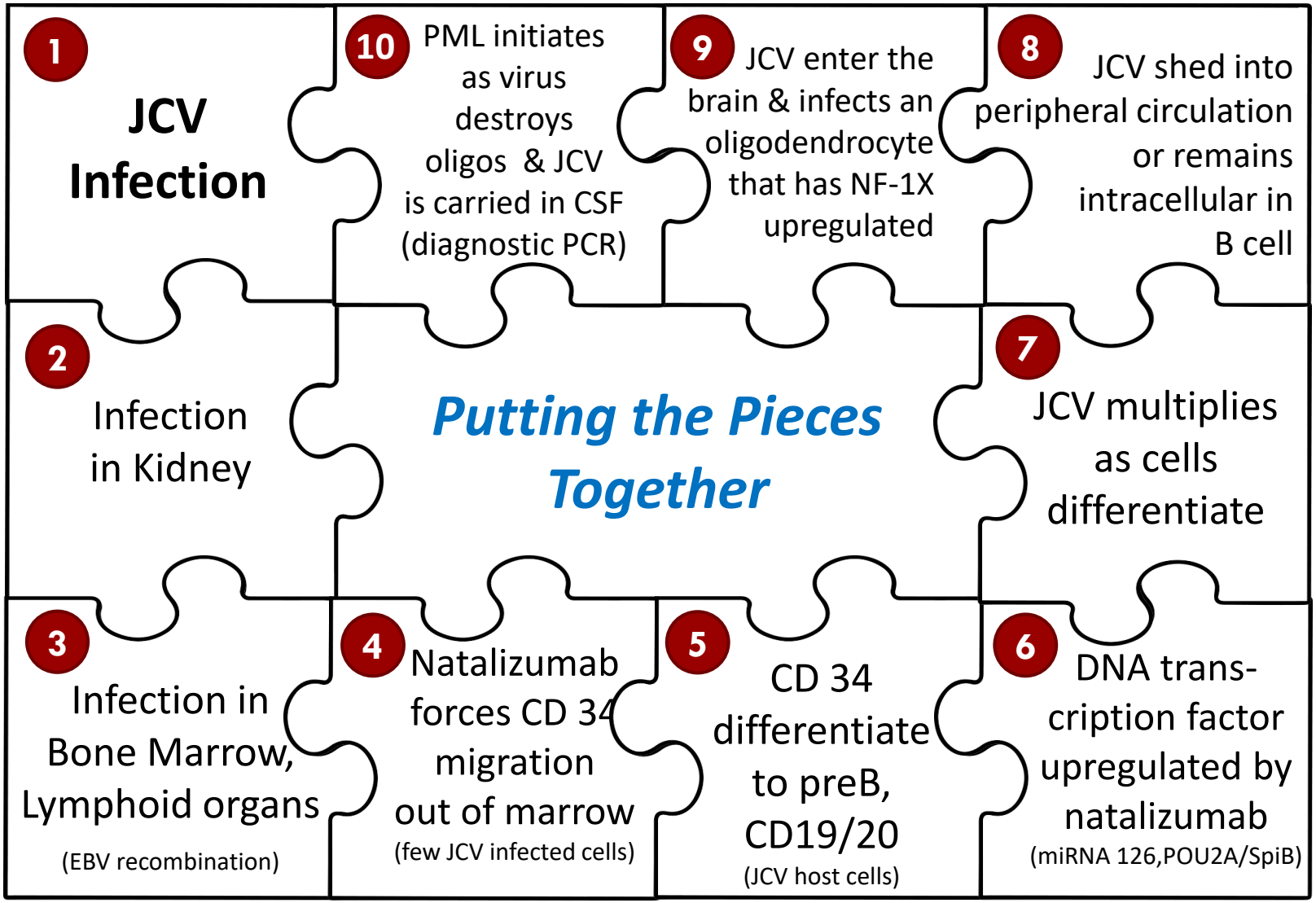


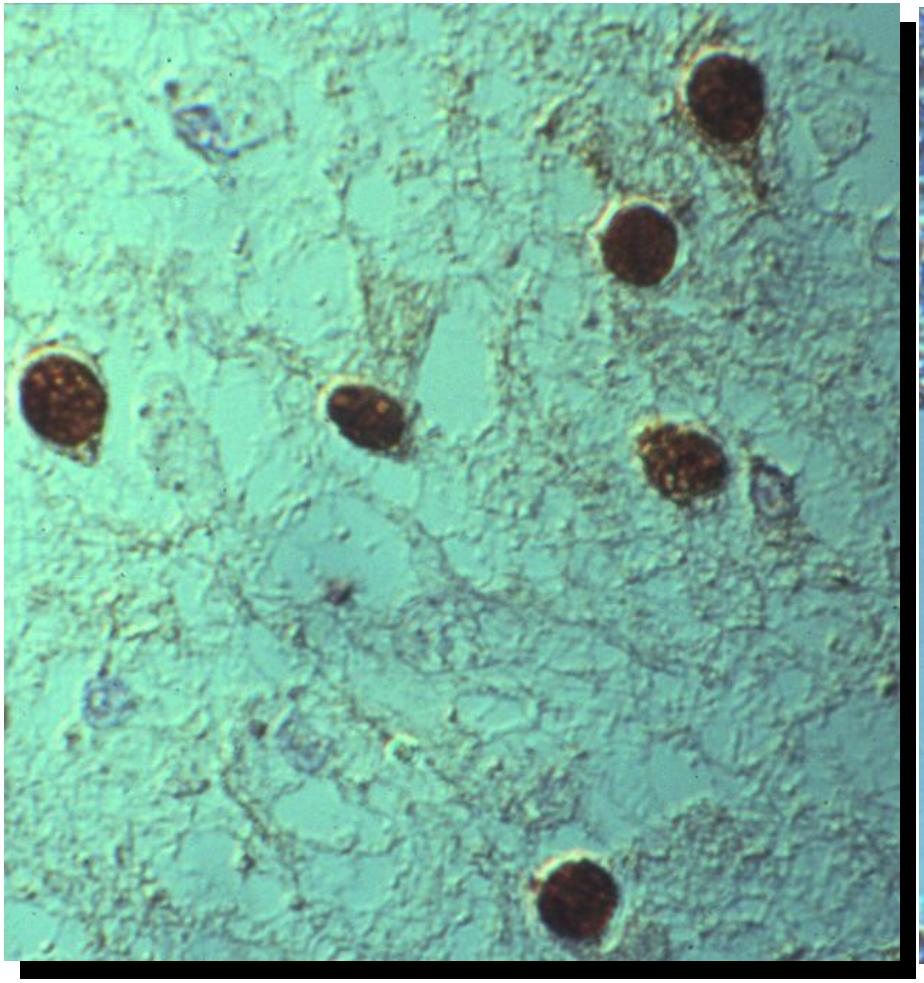


JCV Pathogenesis of PML:

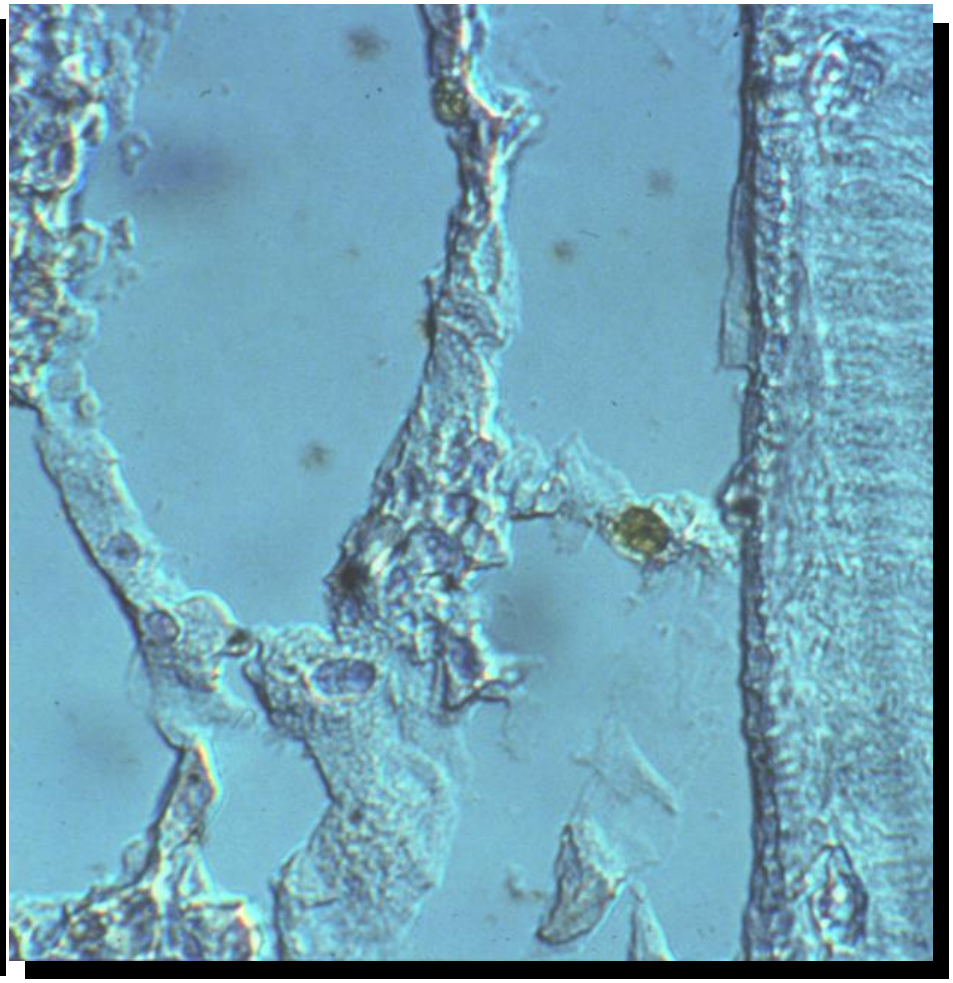


In Situ Hybridization of Biopsy Tissue with Genomic JCV DNA Probe

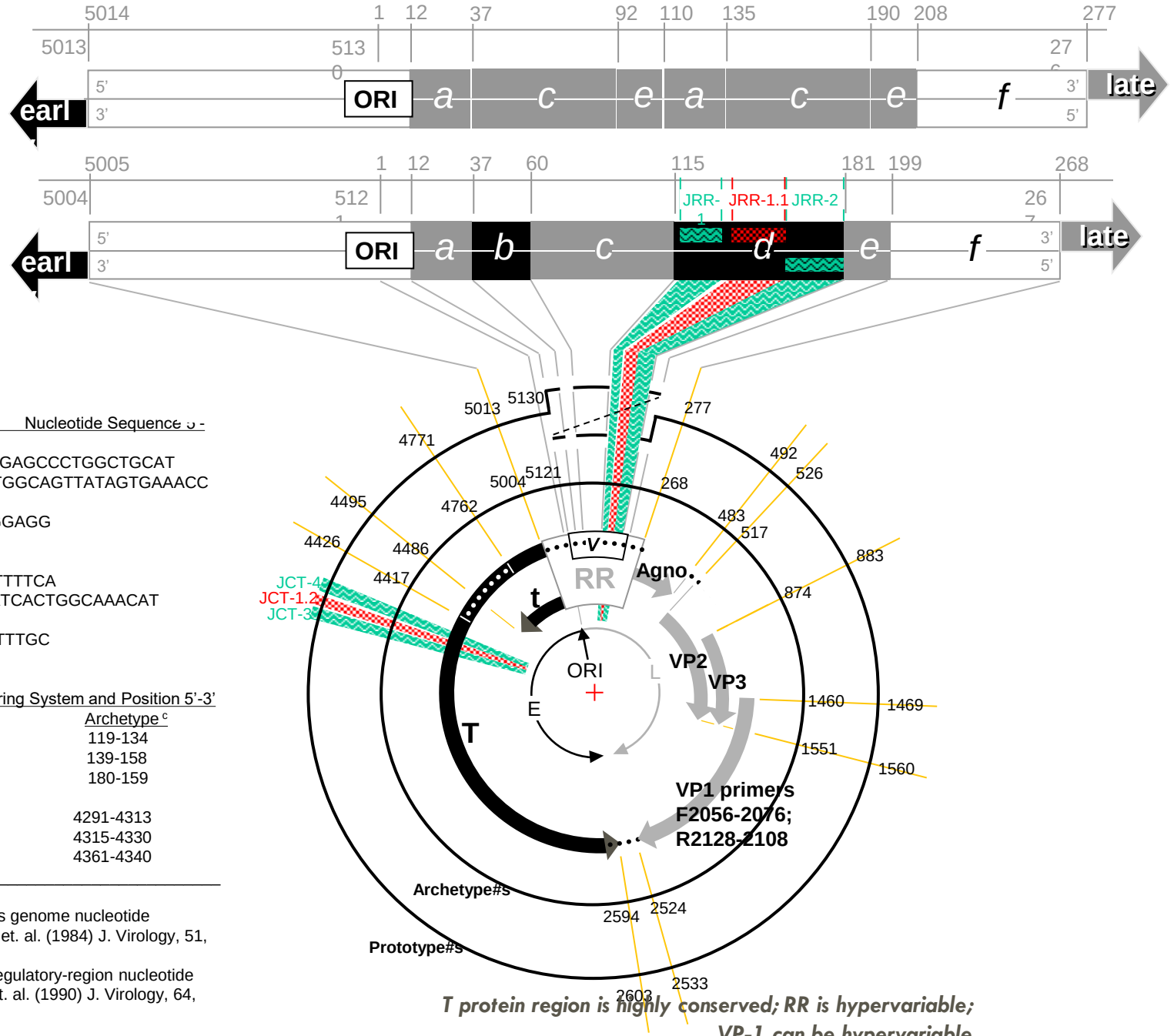
BRAIN



BONE MARROW



JCV genome map: Tri-Plex qPCR assay targets T, NCCR, and VP-1 genome regions and defines variants



T protein region is highly conserved; RR is hypervariable; VP-1 can be hypervariable

Primers and Probes

ID [a]	Label	Nucleotide Sequence 5'-3'
JRR-1	na	GGAGCCCTGGCTGCAT
JRR-1.1	VIC	CTGGCAGTTATAGTGAAACC
JRR-2	na	TGTGATTAAGGACTATGGGAGG
JCT-3	na	AGTGTTGGGATCCTGTGTTTTCA
JCT-1.2	FAM	CATCACTGGCAAACAT
JCT-4	na	GTGGGATGAAGACCTGTTTTGC

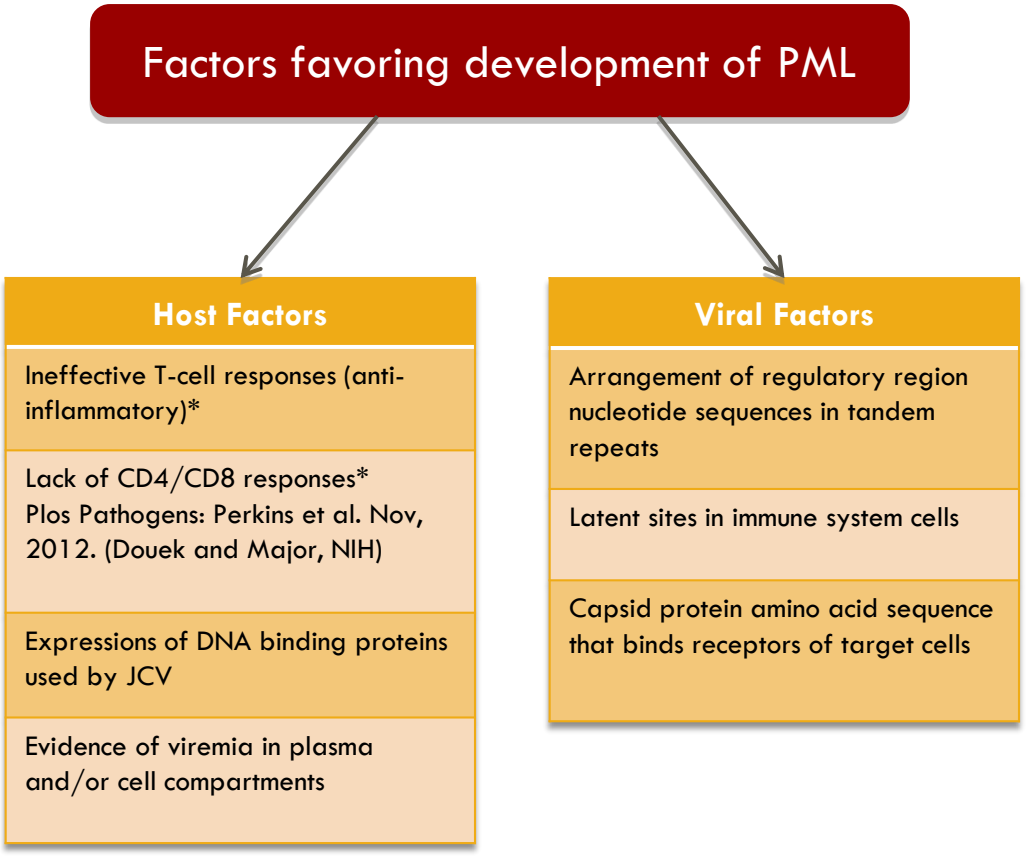
	Nucleotide Numbering System and Position 5'-3'	
	Prototype [b]	Archetype [c]
JRR-1	na	119-134
JRR-1.1	na	139-158
JRR-2	na	180-159
JCT-3	4300-4322	4291-4313
JCT-1.2	4324-4339	4315-4330
JCT-4	4370-4349	4361-4340

[b] Prototype (Mad-1) JC Virus genome nucleotide numbering-system; Frisque,et. al. (1984) J. Virology, 51, 458-469. for T and VP-1

[c] Archetype (CY) JC Virus regulatory-region nucleotide numbering-system; Yogo, et. al. (1990) J. Virology, 64, 3139-3143.

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.



Summary for JCV/PML

1. Antibody levels can rise during active infection but no evidence for protection. *Issue: Routine/Reliable assay; standards are needed*
2. T cell responses directed to structural and non structural proteins; controls infection. *Issue: CD 4 and CD 8 responses to viral antigens*
3. JCV latency is associated with cells of the immune system; reactivation can follow alteration of normal immune cell function and traffic virus to brain *Issue: sites of viral latency; outside/inside the brain*

Risk 'assessment' markers for PML that can be measured in blood:

1. ***Rising antibody titers 2. Any evidence of viremia with pathogenic genotype 3. Ineffective T cell responses 4. Molecular host factors that support JCV infection***

Major E.O. et al. Annals of Neurology 69: 430-431, 2011.