

HTLV-I (long latency; virus is not
expressed in tumors)

Lee Ratner MD PhD

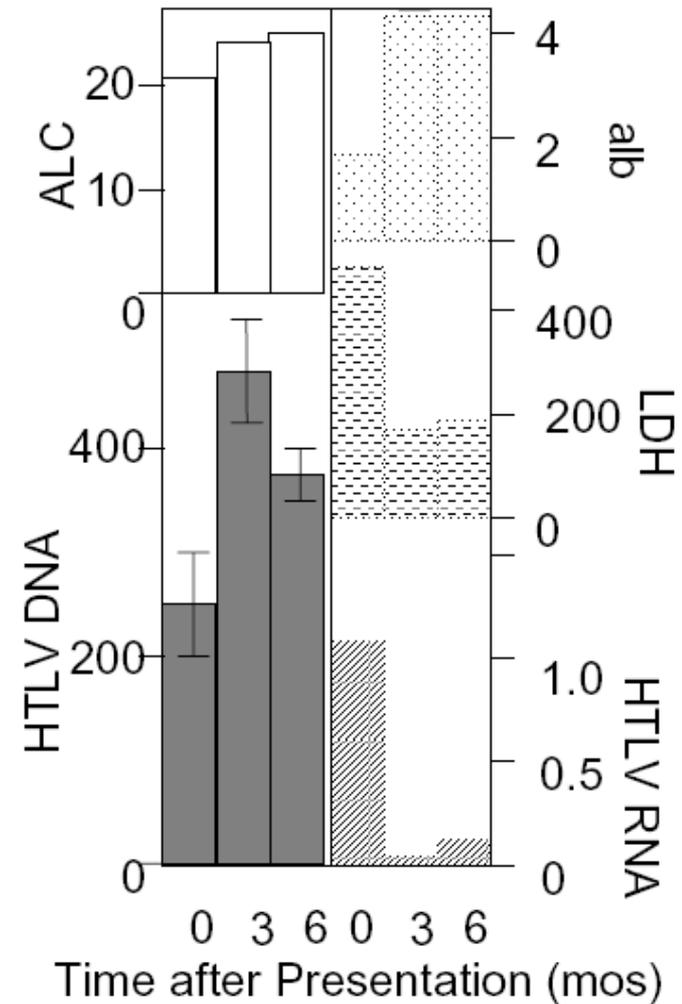
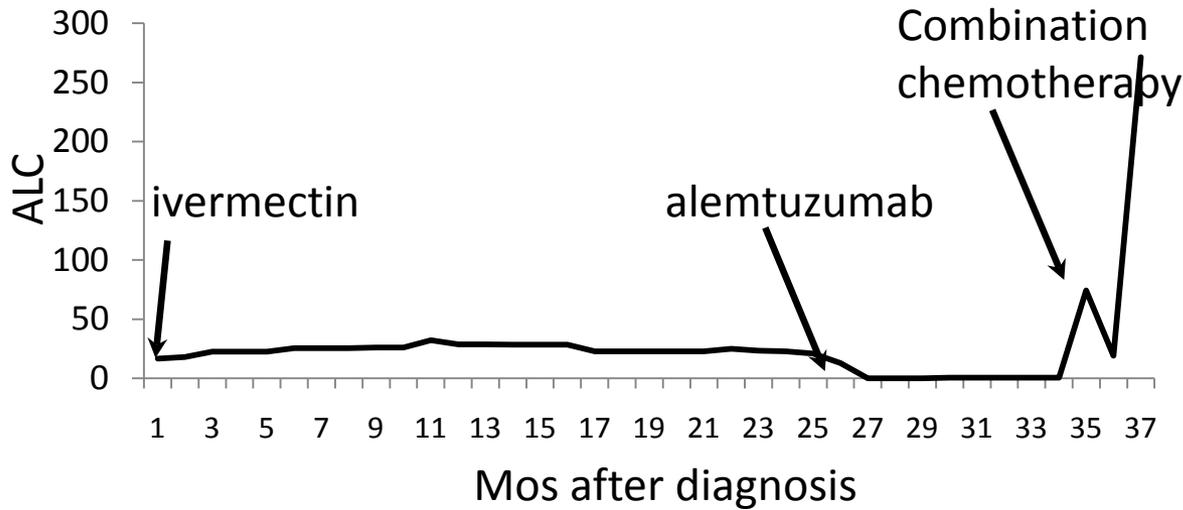
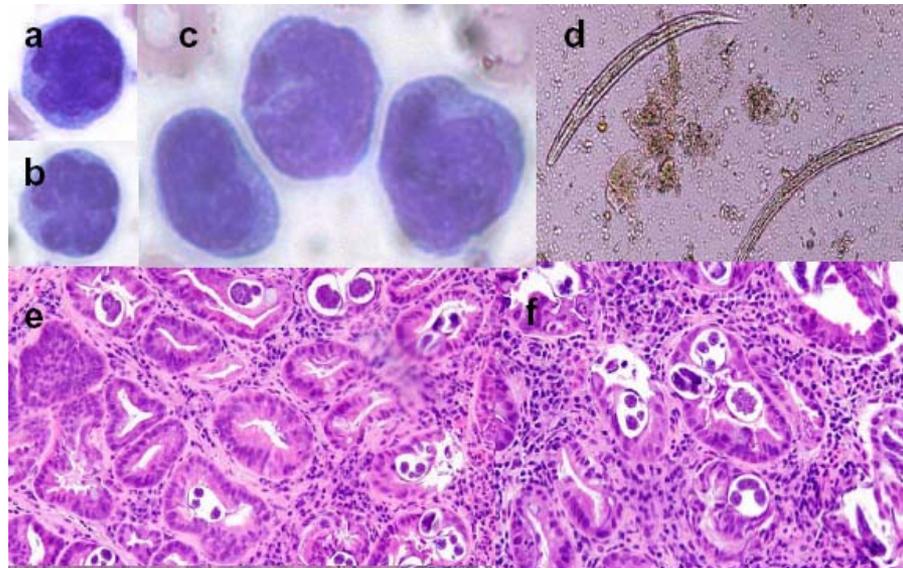
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Case (Ratner et al Am J Hematol, 2009)

72 yo Okinawan, emigrated to US in 1960s

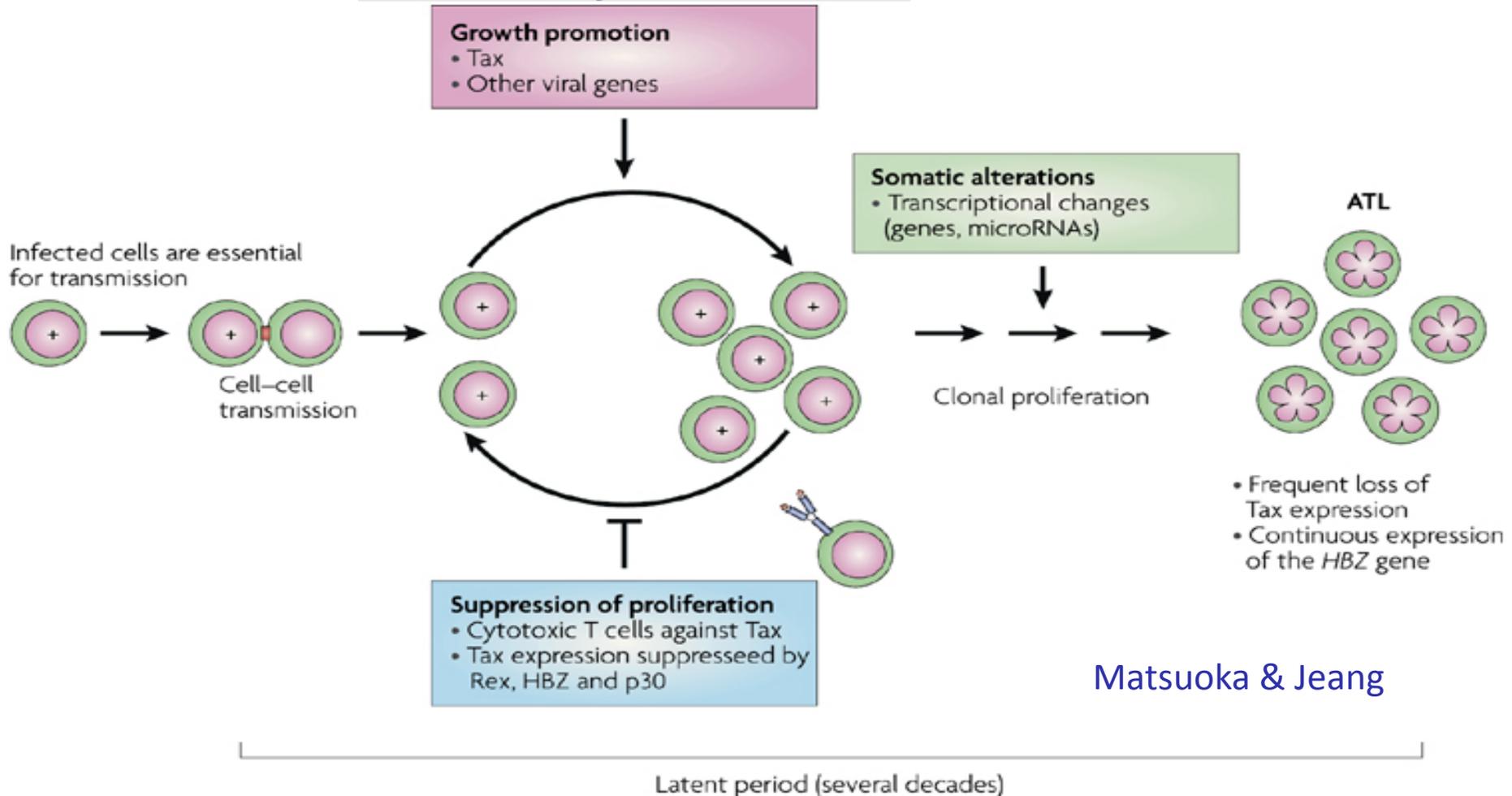
3/06: SBO, anasarca, alb 1.8, wbc 48, 75%L



Role of HTLV-1 in Tumorigenesis

- Viral replication
- Abnormal pRB and p53 function
- Activation of survival factors & Cdk4
- Centrosome duplication errors
- Aneuploidy, SAC loss
- Telomerase dysfunction

- Tax expression no longer needed
- Functional loss of pRB and p53
- Committed centrosome abnormalities
- Committed aneuploidy
- Structural genetic changes
- Mutator phenotype



HTLV-1 vs HTLV-2

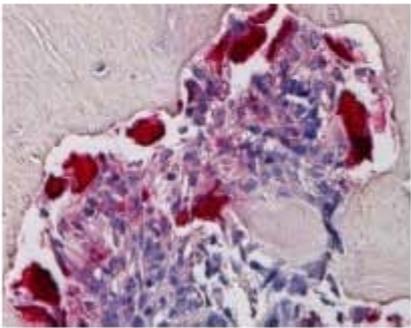
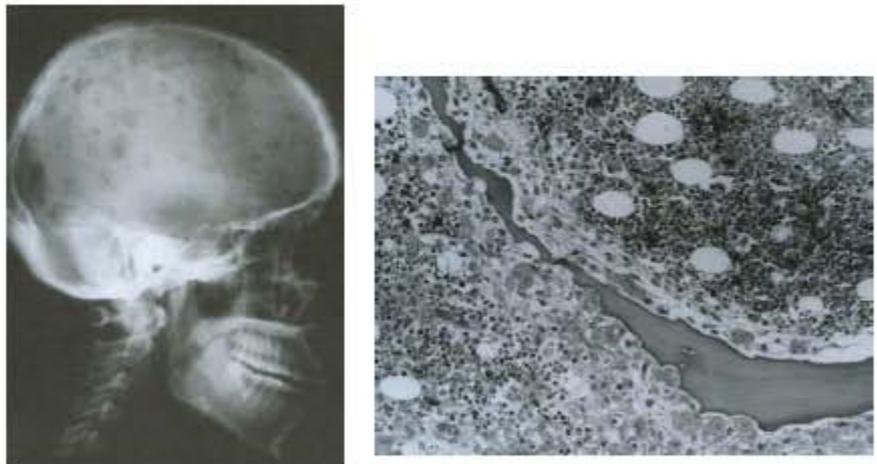
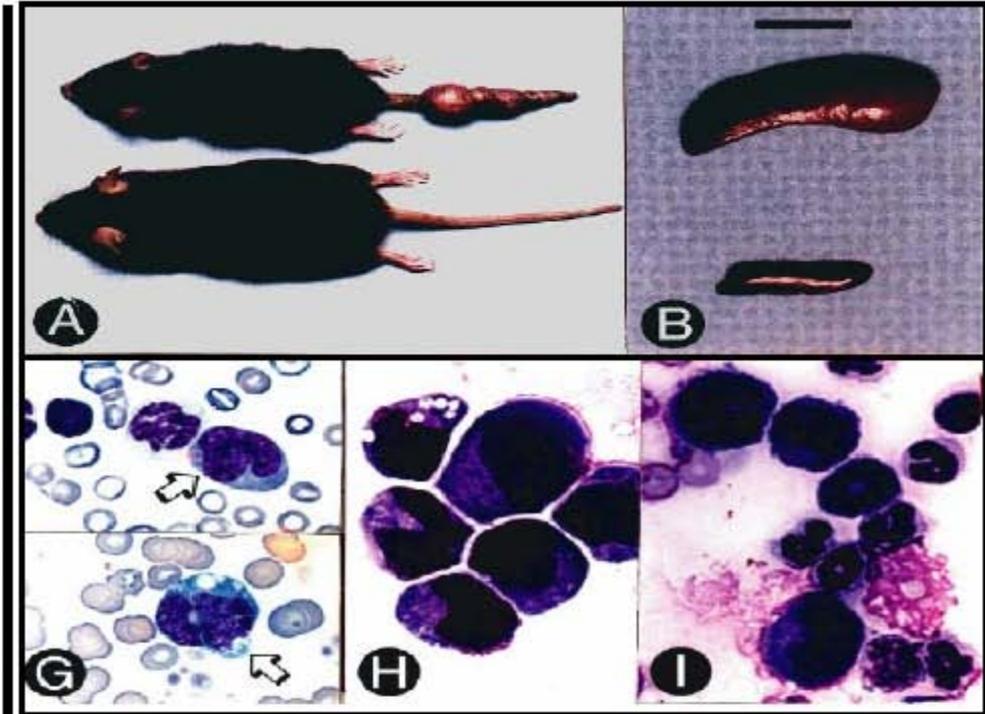
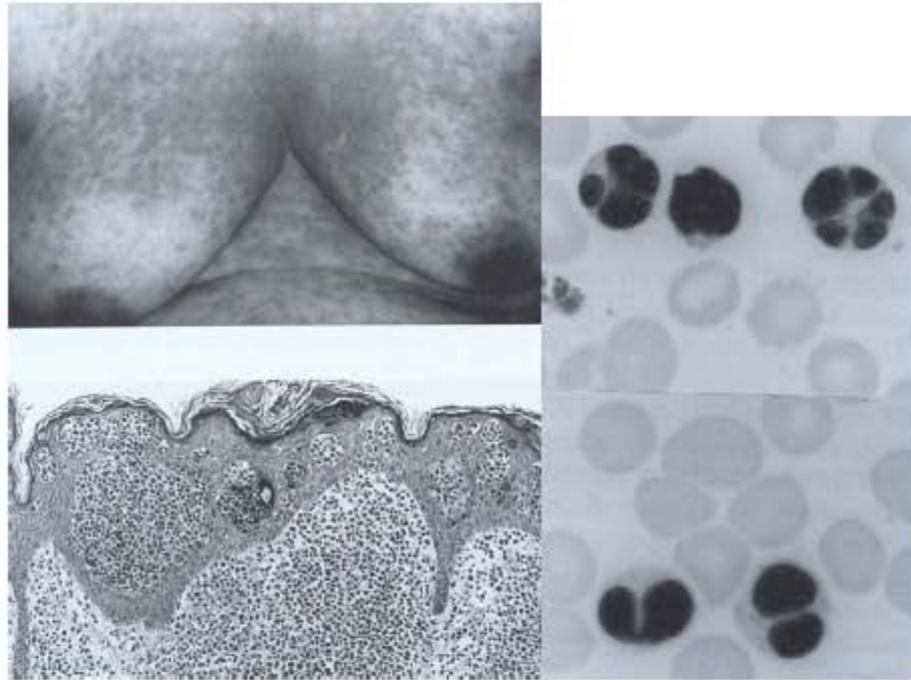
	HTLV-1	HTLV-2
Endemic	Caribbean, S Japan	Amerindians, IV drug abusers
Pathogenesis	Myelopathy, Adult T-Cell Leukemia/Lymphoma	? Neurological Disease ? Skin Disorder
Tropism	CD4	CD8
Activity in culture	Transforming	Transforming
Differentiated by immunoblot or PCR		

Oncogenic Activities of Tax

Activated by Tax	Consequences
Cell-cycle phase activators (CDK2 and CDK4; cyclin D2; cyclin D3; WAF1; E2F1)	Accelerated G1–S progression and DNA hyper-replication
Growth receptors and proliferative factors (IL2 and IL15; IL2R α and IL15R α ; telomerase; PCNA)	Increased cellular proliferation and decreased NER DNA repair
Transcription factors (CREB; AP1; SRF)	Increased cellular proliferation
Survival factors (Akt; NF κ B)	Suppression of apoptosis and/or senescence; aneuploidy
Centrosome amplification (RANBP1; TAX1BP2)	Aneuploidy
Inactivated by Tax	
Cell-cycle phase inhibitors (p15, p16 and p18; RB; DLG1)	Increased cell-cycle phase transition
DNA repair factors (DNA polymerase β ; MMR)	Increased ambient DNA breaks and microsatellite instability
DNA damage response (p53; CHK1; CHK2; telomerase; KU80)	Suppression of apoptosis and/or senescence; abrogation of tumorigenesis barrier
Chromosome instability checkpoint (MAD1; CHK1)	Aneuploidy

AP1, activator protein 1; CDK, cyclin-dependent kinase; CHK1, checkpoint kinase 1; CHK2, checkpoint kinase 2; CREB, cyclic AMP responsive element binding protein; DLG1, discs large homologue 1; IL, interleukin; IL15R α , interleukin 15 receptor α ; IL2R α , interleukin 2 receptor α ; MAD1, mitotic arrest deficiency protein 1; MMR, mismatch repair; NER, nuclear excision repair; NF κ B, nuclear factor κ B; PCNA, proliferating cell nuclear antigen; RANBP1, Ran-binding protein 1; RB, retinoblastoma; SRF, serum response factor (also known as MCM1); TAX1BP2, Tax-binding protein 2.

Comparison of ATLL with Tax Transgenic Mice



Background - ATLL

Subtype of ATLL	% of Cases	Median Survival
Smoldering	5%	5 yr
Chronic	15%	2 yr
Acute – Leukemic	60%	0.5-2 yr
Acute – Lymphomatous	20%	0.5-2 yr

REAL classification – peripheral T cell neoplasm

Opportunistic infection common

See JCO 2009

Copies of pX/HGPRT (x 10,000)

Initial Viral RNAs

- 0
- 0
- 0
- 0
- 0
- 0
- 1.6
- 1.6
- 1.8
- 2.3
- 4
- 16
- 24
- 180
- 14,000
- 283,000

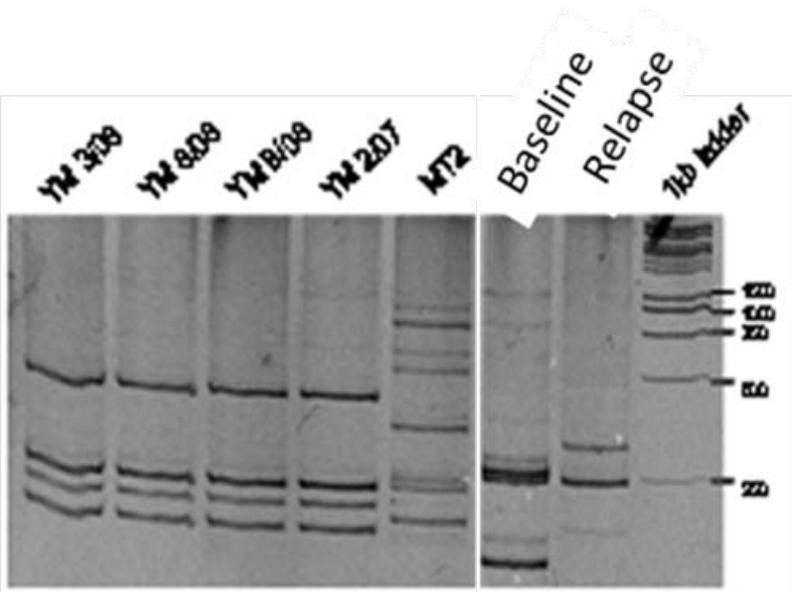
6 patients with undetectable viral RNA

7 patients with 1.6-24 copies viral RNA

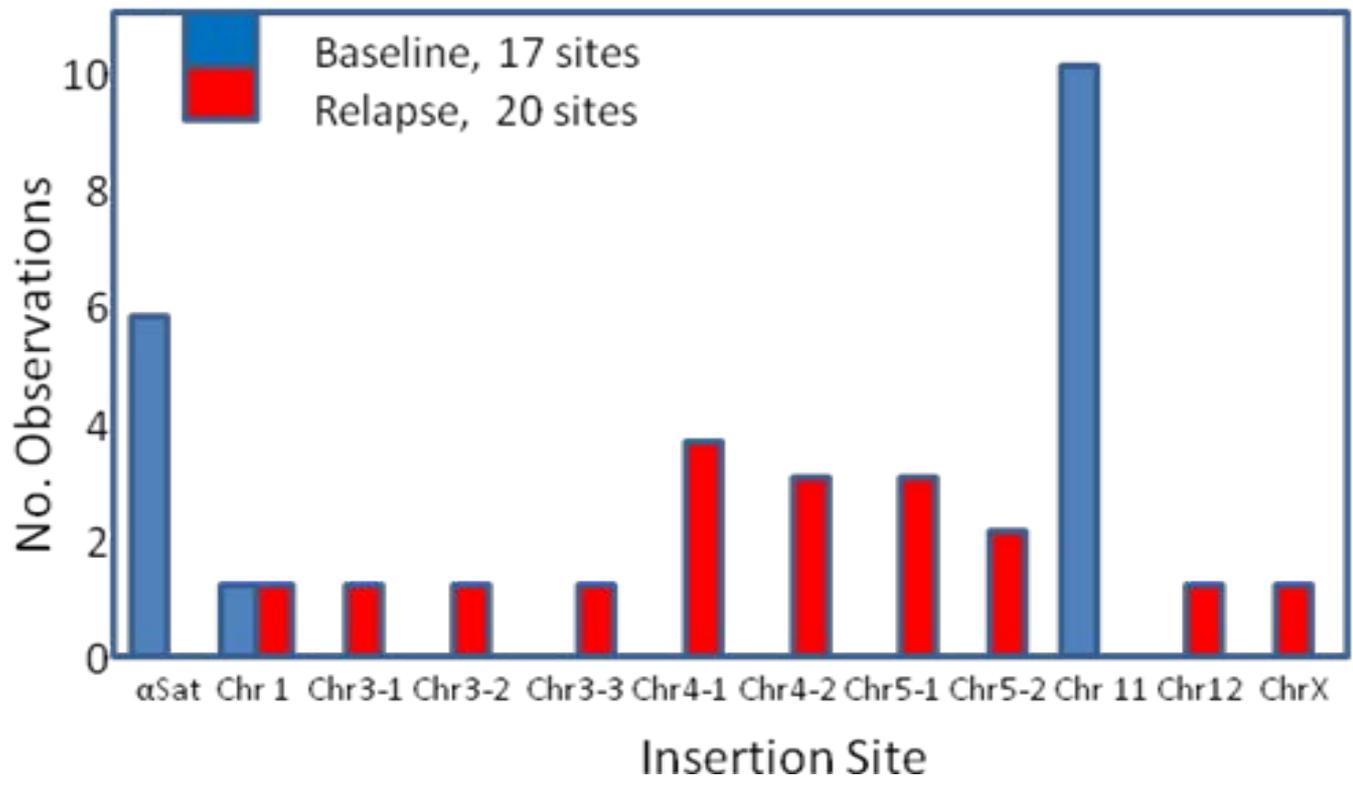
3 patients with 180-283,000 copies viral RNA

Viral RNA and Pol Sequence Changes during Treatment

	Patient	Initial RNA Values (copies tax/HGPRT x 10 ⁴)	Subsequent RNA Values	Changes in Pol aa	Best Clinical Response
No changes in viral RNA	5	0	0	2	CR
	8	0	0	0	NE
	14	0	0	0	PR
Variable viral RNA	10	1.6	0.6, 55, 1.8	0	CR
	16	14000	2250,5660	nd	PD
Increasing viral RNA	11	4	47	0	PR
	19	8.7	186	2	PR
	3	0	0, 0, 0, 240	4	PR
	14	24	3340	1	PR
	2	7	4900, 44100	0	PR
	7	0	10000, 48900	2	PR
Decreasing viral RNA	18	4200	1.4	1	PR

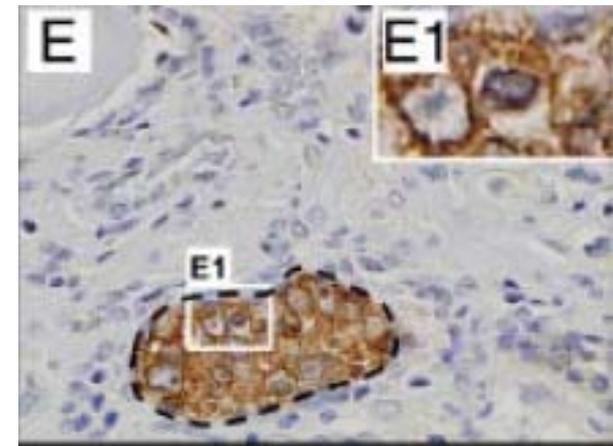
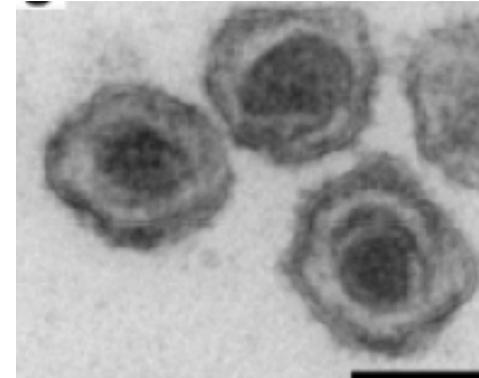


Changes in Integration Site with Disease Progression



Xenotropic Murine Leukemia Related Virus (XMRV)

- RNaseL (interferon-response pathway) is hereditary prostate cancer susceptibility gene
- XMRV discovered on “virus chip”
- Identified by PCR, RT-PCR, ISH, direct sequence analysis
- 2-25% of prostate cancers, 0-4% of BPH
- ? Association with chronic fatigue syndrome
- 7% different from MLV
- Androgen-response element
- ? Association with RNaseL polymorphism
- ? Found in stromal or epithelial cells
- Transgenic mouse models with the virus and receptor



Conclusions

- New genomics technologies for identification of etiological agents
- Retroviruses and other micro-organisms cause cancer through multiple different mechanisms
- Studies in culture, animals, and patients can provide molecular details of oncogenic pathways
- Identification of an etiological agent can provide information for prognosis, treatment, and prevention