

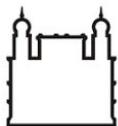
Webinário

Vírus linfotrópico de células T humanas (HTLV): a ameaça silenciosa e suas manifestações neurológicas

30 Nov, 2023, 13:00 GMT/10:00 BR/AR

Registre-se

Tradução simultânea
PT-ESP-ING



Ministério da Saúde

FIOCRUZ
Fundação Oswaldo Cruz



Panel

Chair: Augusto César Penalva de Oliveira - Supervising Physician, Neurology Medical Team, Emílio Ribas Infectious Diseases Institute, Brazil

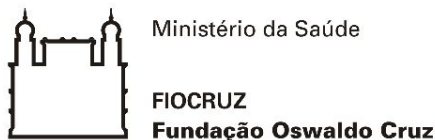
Steven Jacobson - Senior Investigator, Viral Immunology Section, Neuroimmunology and Neurovirology Division (NND), National Institutes of Health (NIH), USA

Lucia Brito - Neurophysiologist, Reference Center for the Care of Patients with Demyelinating Diseases, Restauração Hospital, Ministry of Health, Brazil

Carlos Pardo - Director, Johns Hopkins Myelitis & Myelopathy Center, Baltimore, Maryland, USA

Clarice Neuenschwander - Senior Researcher at the Laboratory of Virology and Experimental Therapy, Fiocruz Pernambuco, Fiocruz, Brazil.

Cristiane Campello Bresani – Senior Researcher at the Laboratory of Virology and Experimental Therapy, Fiocruz Pernambuco, Fiocruz, Brazil.



Resources

- <https://portal.fiocruz.br/en>
- <https://fiocruz.tghn.org/>
- <https://lac.tghn.org/>
- <https://www.instagram.com/HTLVBrasil/>
- <https://www.gov.br/aids/pt-br/assuntos/ist/htlv>
- <https://fiocruz.tghn.org/health-topics/neuroinfeccoes/grupo-neuroinfeccoes/>



HTLV and the human host: a long-standing interaction



Dr Steven Jacobson, PhD

**Viral Immunology Section, Neuroimmunology and Neurovirology
Division, National Institutes of Health, USA**



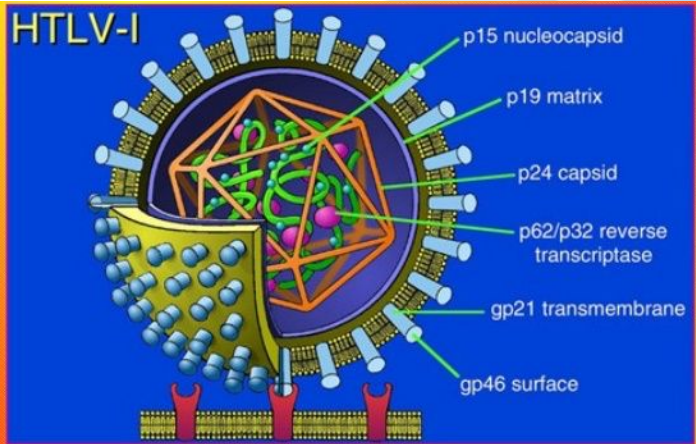
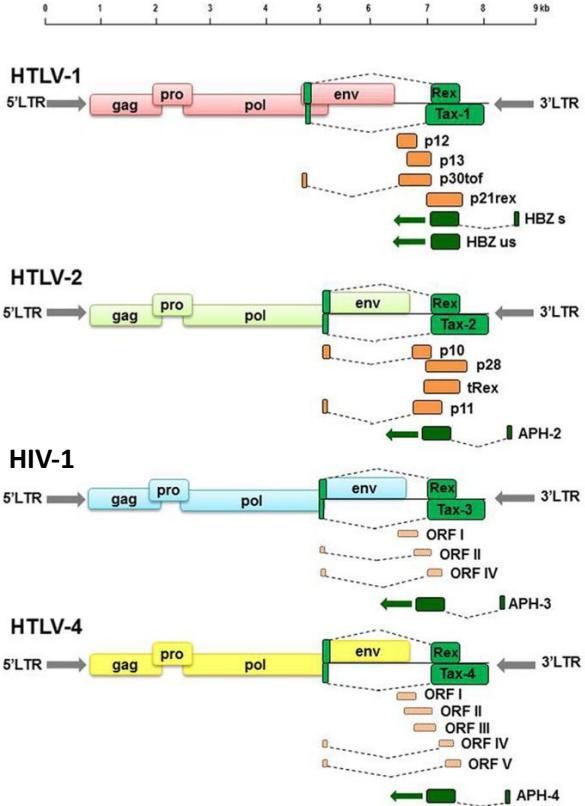
National Institutes
of Health



Immunopathogenesis of HTLV-I Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP)



Human T-cell lymphotropic virus type 1 (HTLV-1)



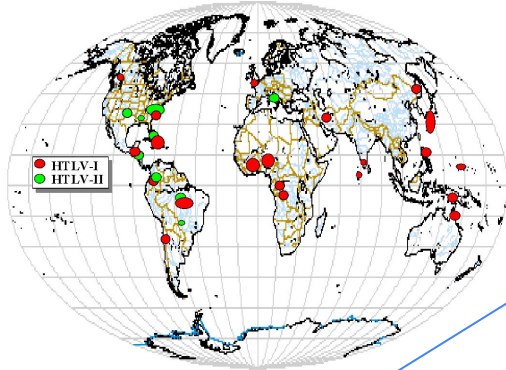
Research of rare diseases can inform understanding of common neurological disorders



HTLV-I Associated Myelopathy/Tropical Spastic Paraparesis: Similarities and Differences with Multiple Sclerosis

	HAM/TSP	MS
Clinical	Chronic progressive myelopathy	Resembles primary progressive "spinal" form of MS.
Oligoclonal Bands	Yes To HTLV-I antigens.	Yes To unknown antigens.
MRI	Atrophy of spinal cord. Mimics CNS demyelination in brain similar to MS.	Demyelinating lesions of CNS white matter.
Disease for life	Yes	Yes
Etiologic Agent	HTLV-I	Unknown: Viruses considered.
Demyelination	Yes Predominantly of corticospinal tracts, mild in posterior columns.	Yes Diffuse involvement of spinal cord white matter; Corticospinal and posterior columns severely affected
Inflammation	Yes Present at all levels of CNS; Predominates in spinal cord at levels of severe demyelination.	Yes Moderate in CNS lesions.
Lymphocytes In lesions	Yes CD4 and CD8 early in disease; CD8 persist in late disease.	Yes Combination of CD4 and CD8.
Immune Response	Yes Spontaneous lymphoproliferation; High HTLV-I specific antibody and CTL.	Yes Activated T cells in CSF and blood.
HLA association	Yes Japanese associated alleles	Yes HLA DRB1*1501

Sceroprevalence of HTLV-I/II

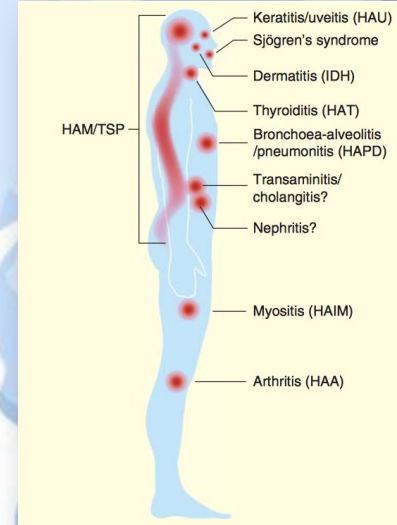
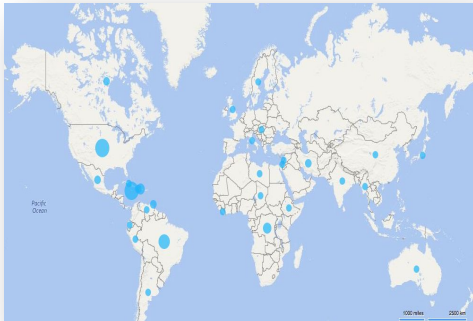


Outcomes of HTLV-1 infection

HTLV-1
10-20 million people
infected

- Asymptomatic carrier (90-95%)
- Adult T cell leukemia/lymphoma (2-5%)
- HTLV-1 associated myelopathy/tropical spastic paraparesis (0.25-3.8%)
- Other inflammatory manifestations:
Arthropathy, uveitis, dermatitis,
polymyositis pneumonitis, other (?)

Viral Immunology Section- HTLV-I/II Clinic Protocol Participants: Country of Origin



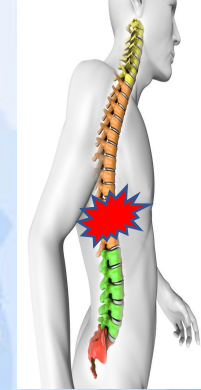
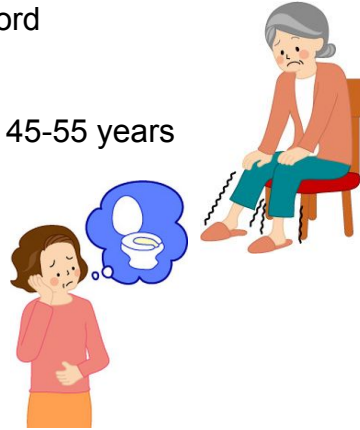
Martin, Taylor, Jacobson, Exp Rev Clin Immunol; 2014

HTLV1 Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP)

- Myelopathy – disease related to the spinal cord
- Demographics: females > males, median age 45-55 years

- Symptoms:

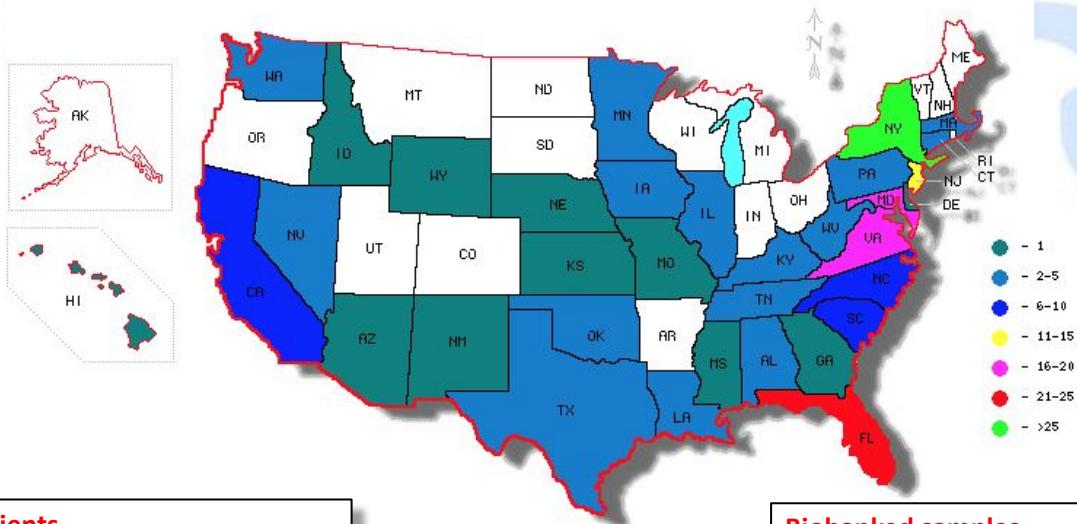
- Back pain
- Lower extremity weakness, falls
- Stiffness
- Urinary incontinence
- Bowel incontinence or constipation
- Sexual dysfunction
- Sensory disturbances



Clinically suggests disease process is in thoracic cord

VIS –Clinical Cohort (US)

Immuno-Virological Evaluation of HAM/TSP (protocol # 98N-0047)



425 patients

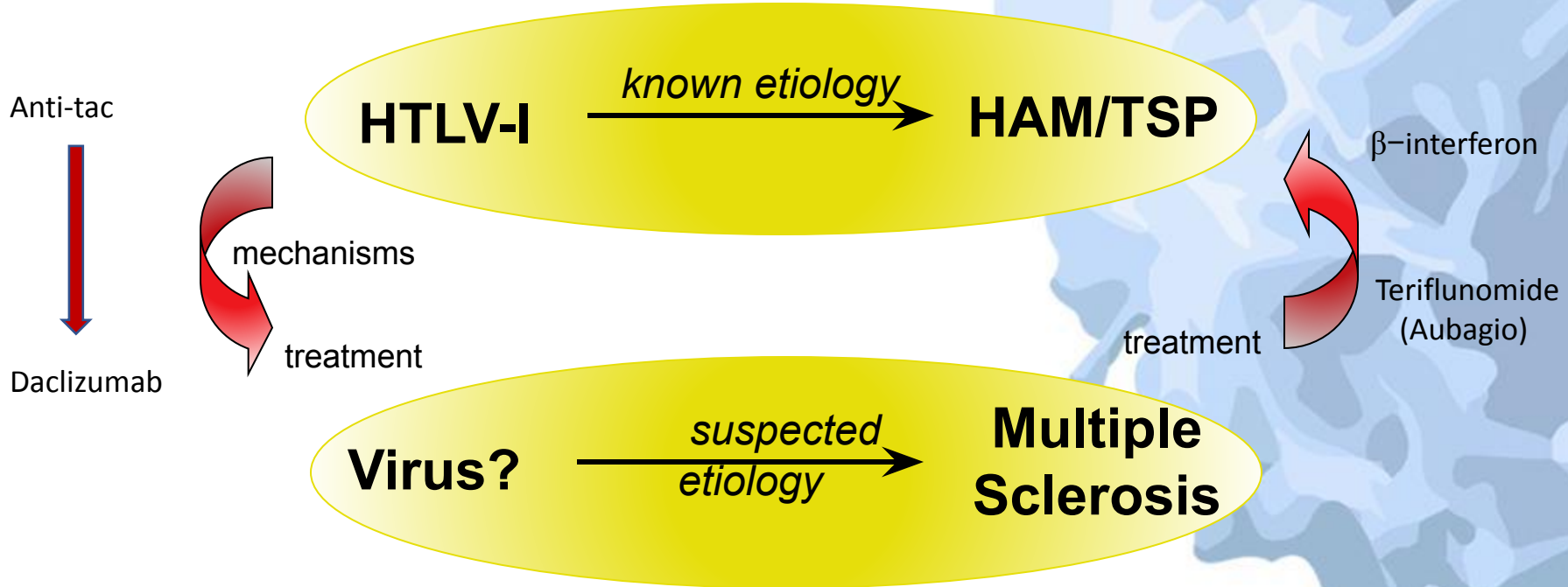
(HAM/TSP, Asymptomatic carriers (AC), HTLV-2 patients, HTLV-I/II seroindeterminates, family members)

Biobanked samples

31710 PBMCs
5585 serum
922 CSF
102 saliva
250 plasma

Association of Viruses and Chronic Progressive Neurologic Disease

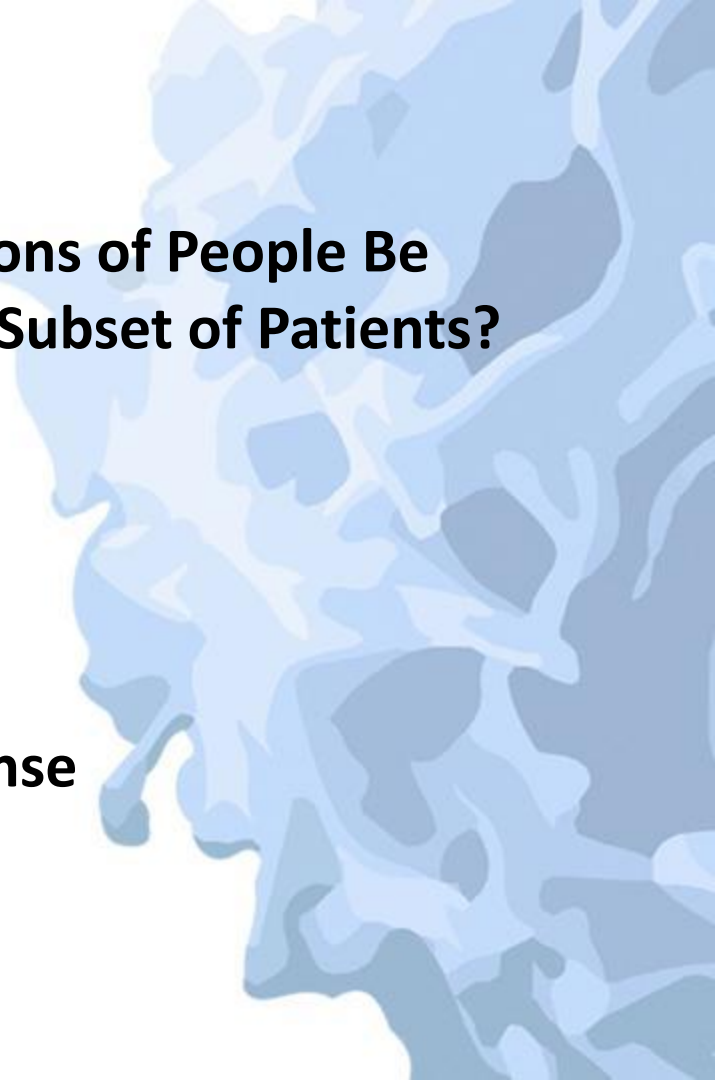
Translational Studies



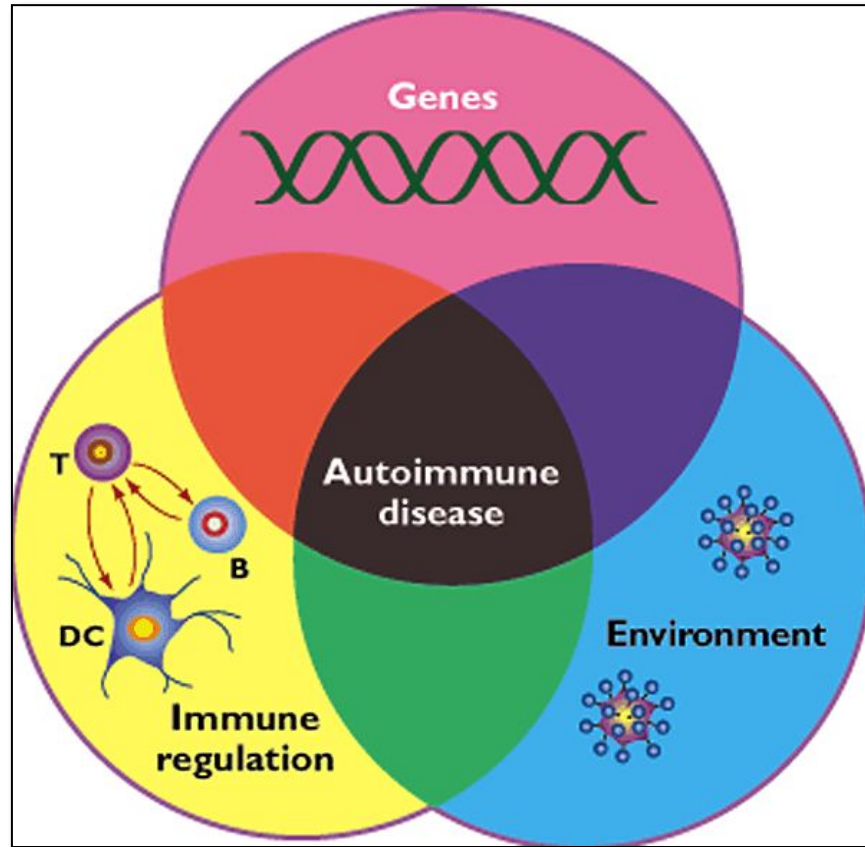
HTLV-I

How Can Virus That Affects Millions of People Be Associated With Disease in a Small Subset of Patients?

- **Virus**
- **Genetics**
- **Host Immune Response**

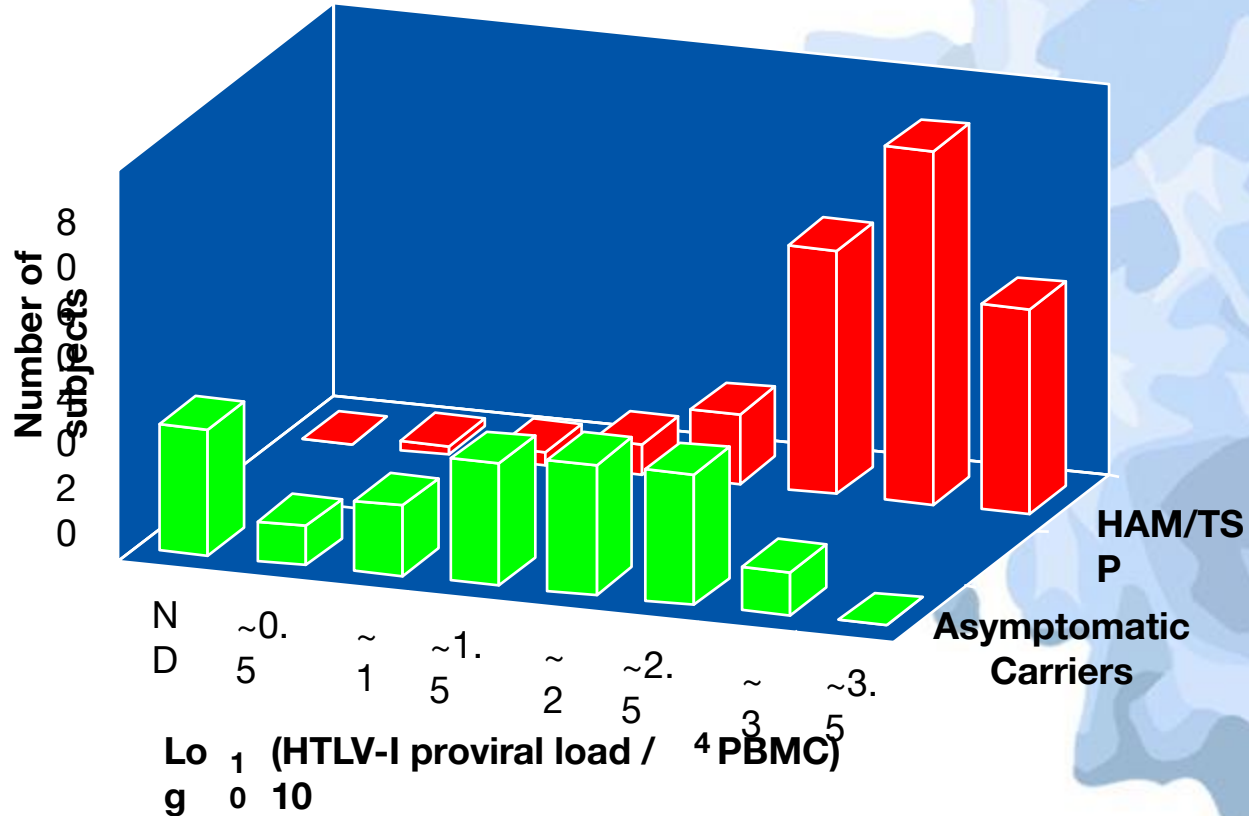


Etiology of Multiple Sclerosis

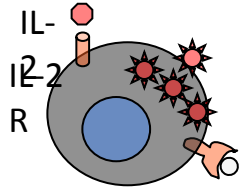


● Relationship to EAE

Distribution pattern of HTLV-I Proviral Load in PBMC of HAM/TSP Patients and Carriers

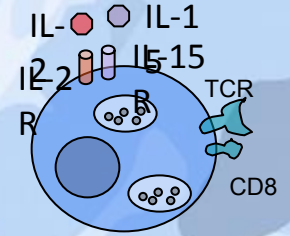
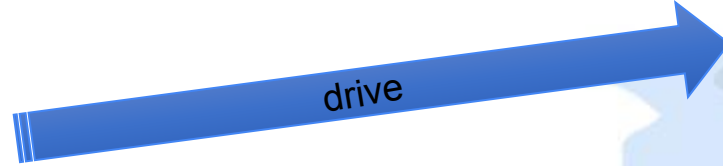


HAM/TSP is Characterized by an Activated Immune Response



HTLV-I infected cells

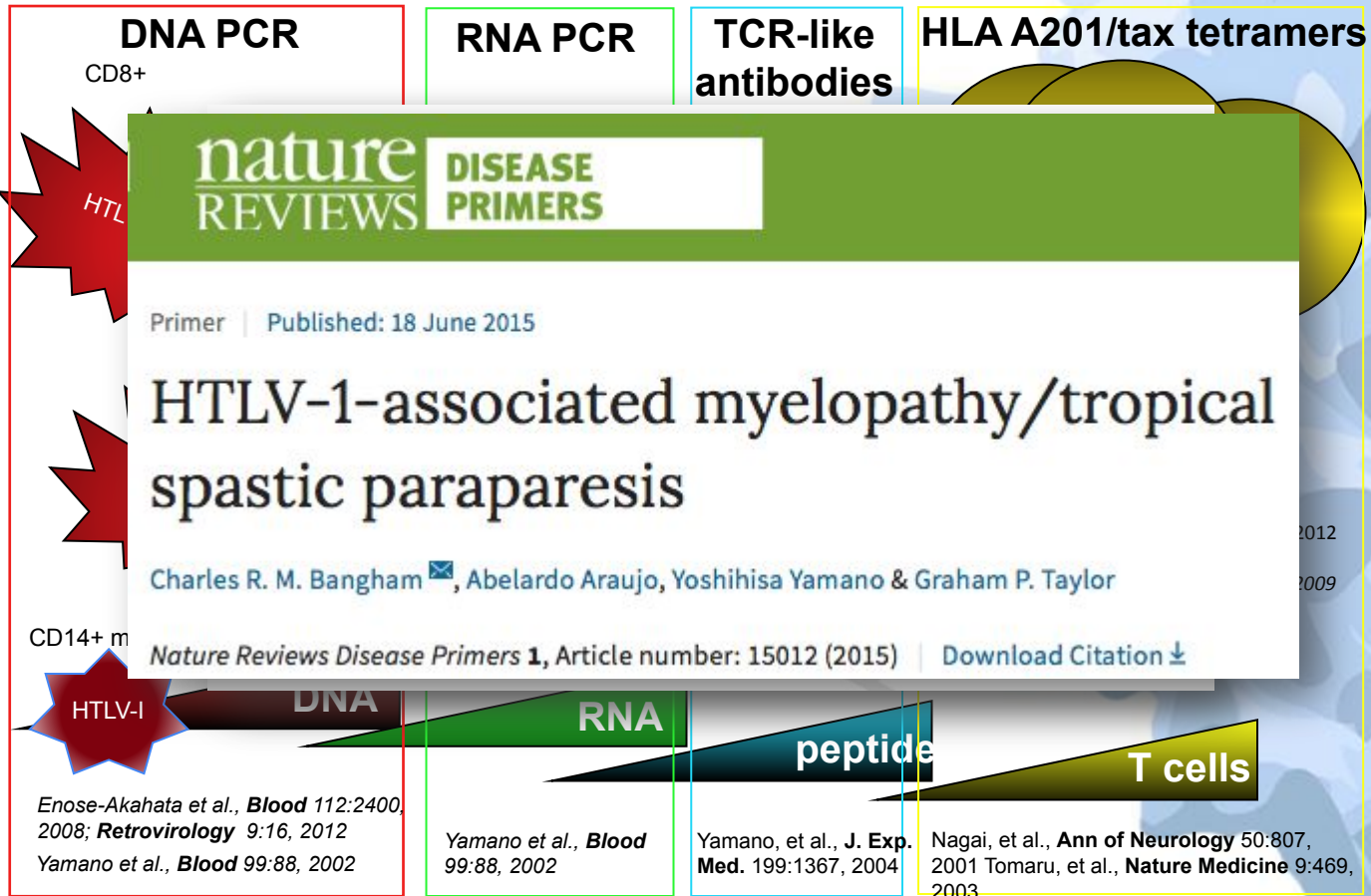
- HTLV infection
- Viral mRNA and protein expression
- Inflammatory cytokine expression



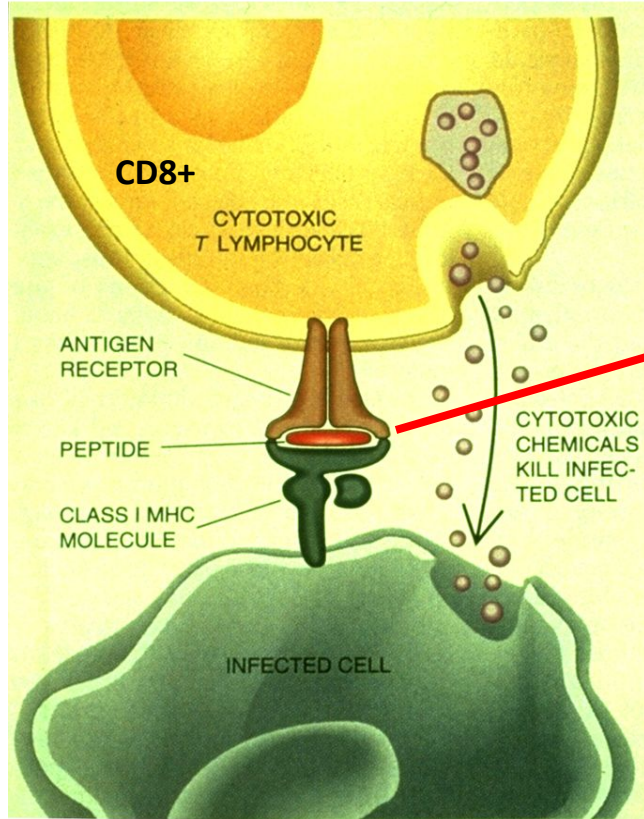
CD8⁺ T cells

Biomarkers	Asymptomatic carriers	HAM/TS
Proviral DNA load	Lo w	Hig h
Viral mRNA load	Lo w	Hig h
Virus-specific CD8 ⁺ T cell	Lo w	Hig h
Spontaneous proliferation	Lo w	Hig h
Inflammatory cytokine production (IFN- γ , TNF- α)	Lo w	Hig h

Induction of HTLV-I specific T cell Responses



T cell Recognition of MHC/peptide Complexes



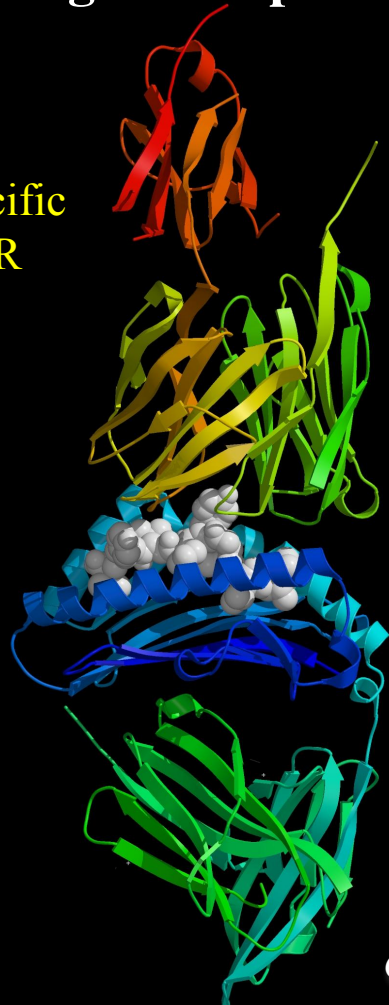
**HLA A201/tax
tetramers**

Research of rare diseases can inform understanding of basic immunology



T cell antigen-receptor complex

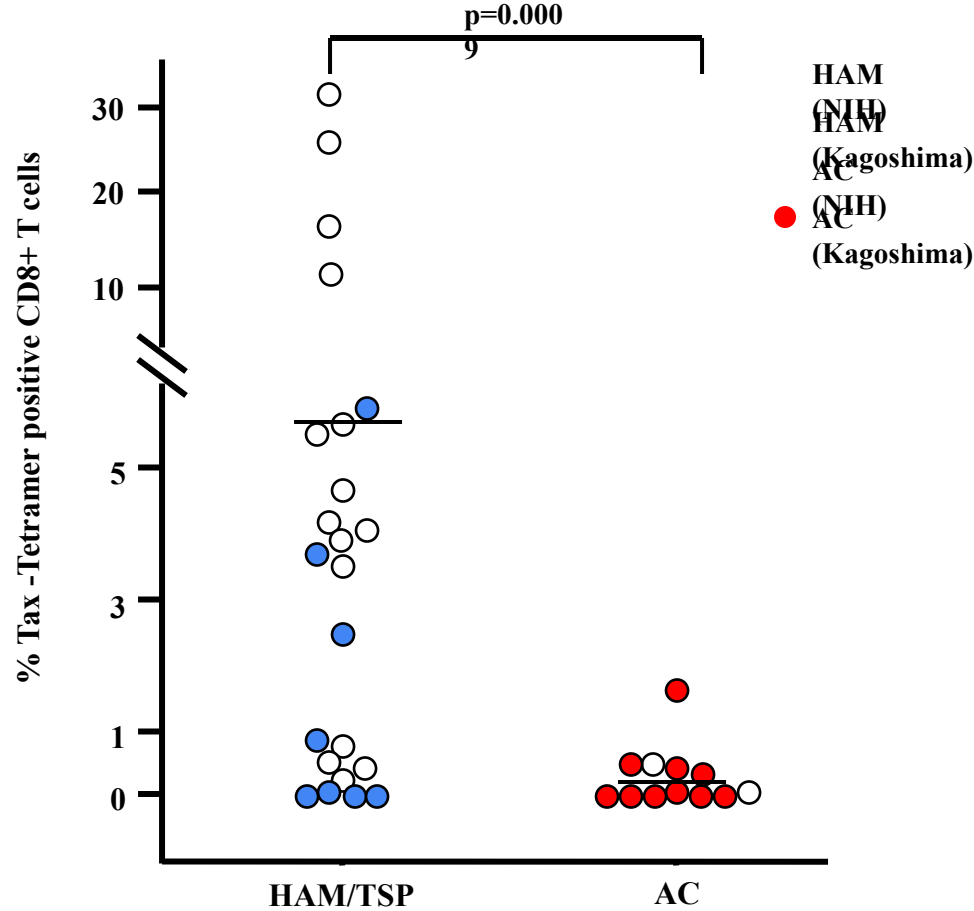
HTLV-I-specific
CD8+ TCR



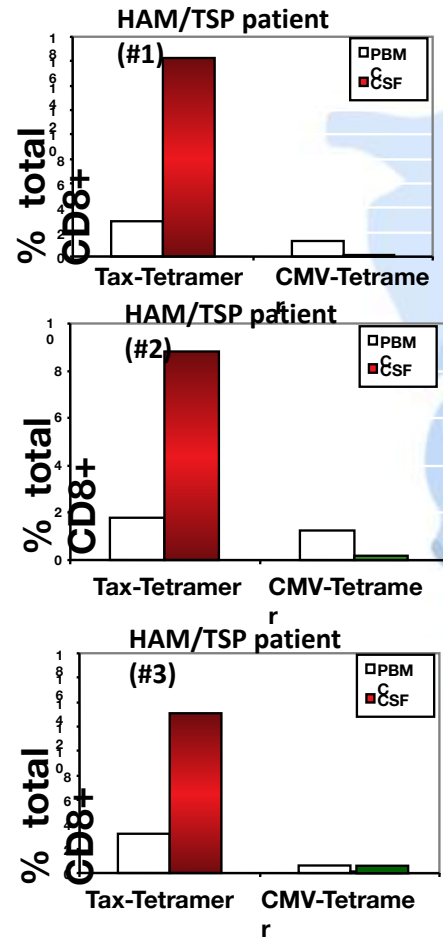
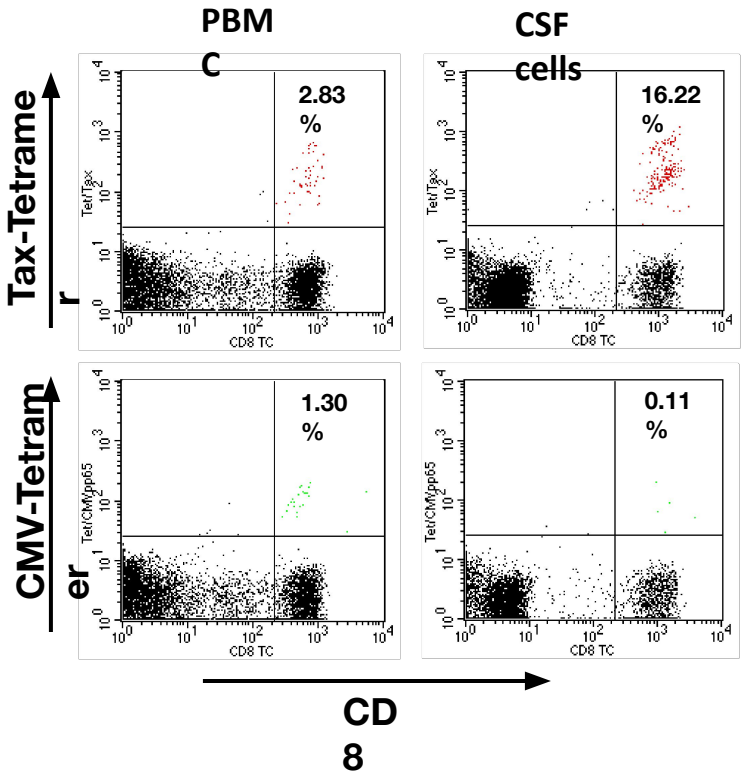
HTLV-I Tax peptide:
L L F G Y P V Y V

Class I MHC (HLA-A2)

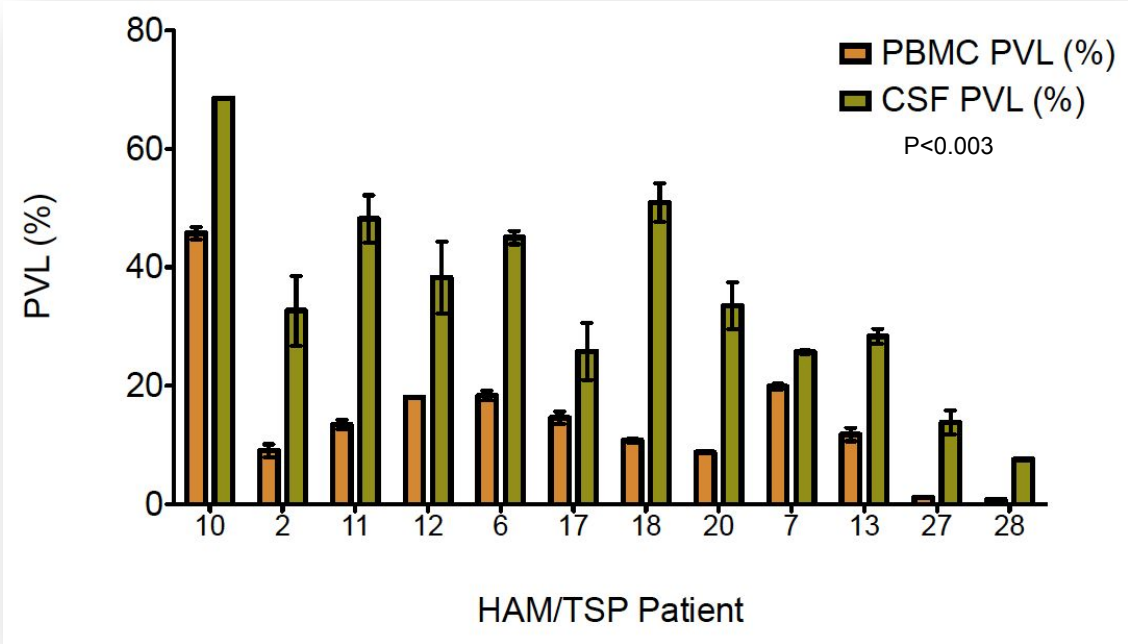
HTLV-I Tax-specific CD8+ T cells increased in HLA A201 PBMC from HAM/TSP patients (NIH and Japan)



Expansion of HTLV-I tax11-19 Tetramer Reactive CD8+ Cells in the CSF of HAM/TSP Patients



HTLV-I proviral load is increased in CSF of HAM/TSP patients digital droplet PCR (ddPCR)





Differentiation of HAM/TSP from patients with multiple sclerosis infected with HTLV-I

M. Puccioni-Sohler, MD, PhD; Y. Yamano, MD, PhD; M. Rios, PhD; S.M.F. Carvalho, PhD; C.C.F. Vasconcelos, MD; R. Papais-Alvarenga, MD, PhD; and S. Jacobson, PhD

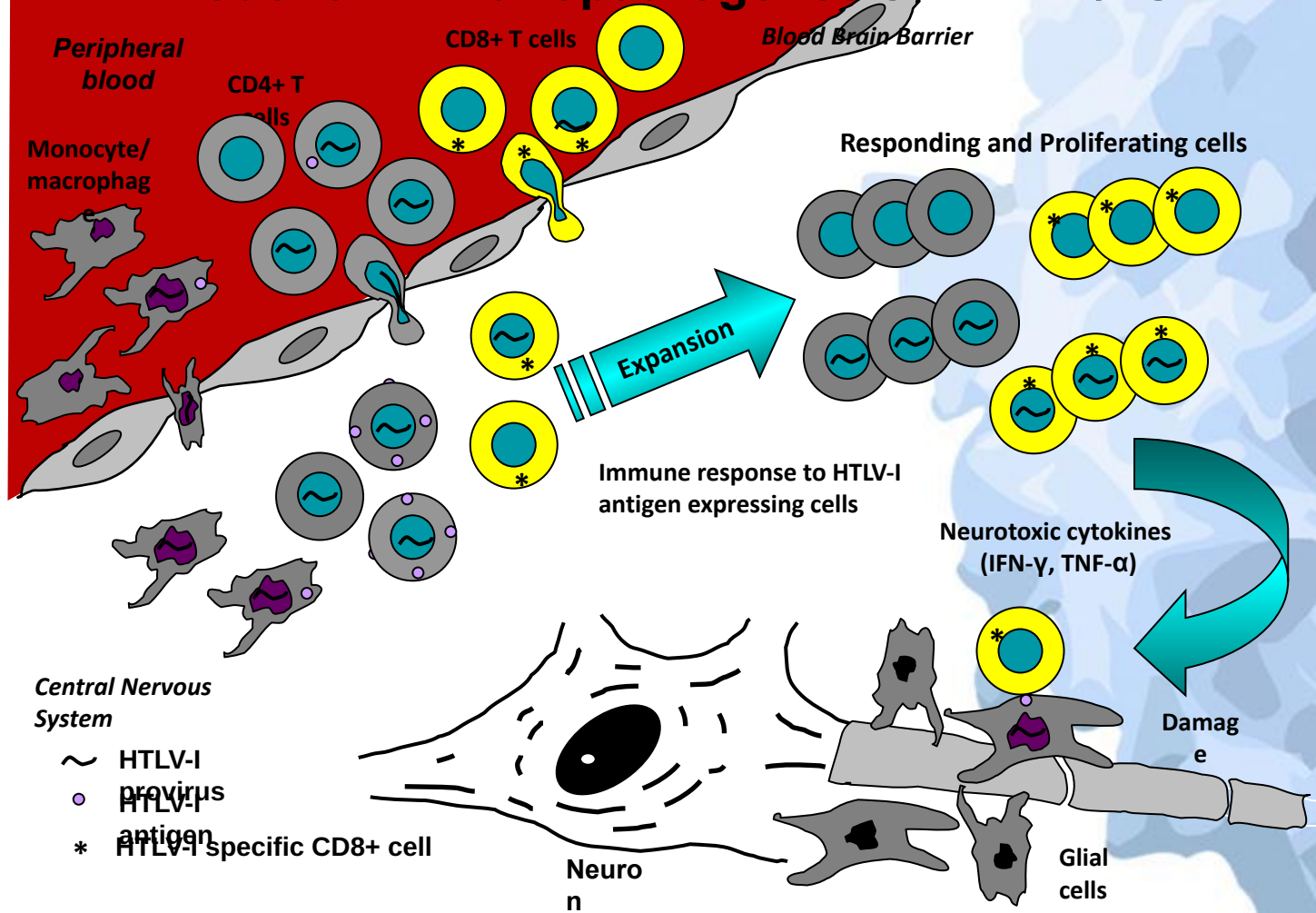
NEUROLOGY 2007;68:206–213

Table 2 Mean \pm SD of PBMC and CSF of 17 HAM patients (Group I) in comparison with 18 non-HAM patients (Group II)

	HAM/TSP (Group I), n = 17	Non-HAM/TSP (Group II) n = 18	<i>p</i> Value
PBMC HTLV-I proviral load/100-cell copies	38 \pm 26	9 \pm 5	<0.005
CSF HTLV-I proviral load/100-cell copies	83 \pm 5	1.9 \pm 5	<0.005

PBMC = peripheral blood mononuclear cells; HAM/TSP = human T lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis.

Model of Immunopathogenesis in HAM/TSP



Can HTLV-I Specific CD8+ T cells be detected in The CNS of HAM/TSP Patients?



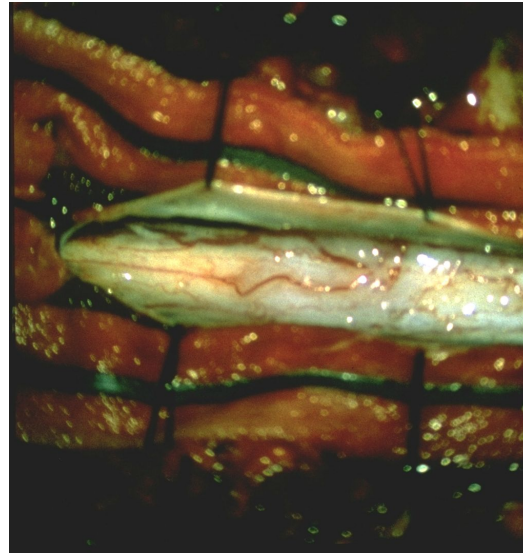
The NEW ENGLAND
JOURNAL of MEDICINE

IMMUNOLOGIC ANALYSIS OF A SPINAL CORD-BIOPSY SPECIMEN FROM A PATIENT WITH HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE I-ASSOCIATED NEUROLOGIC DISEASE

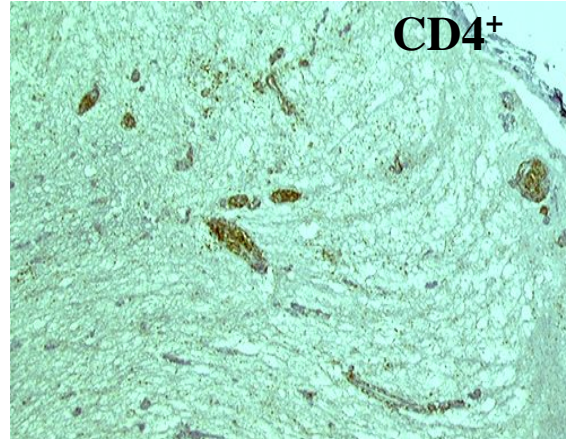
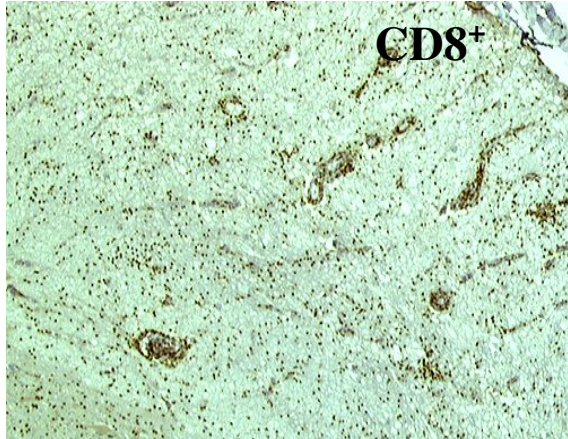
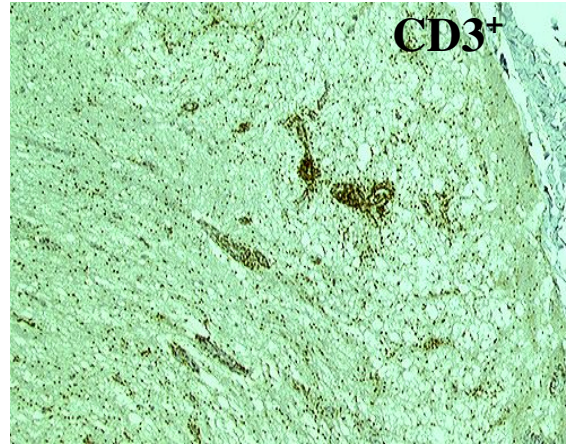
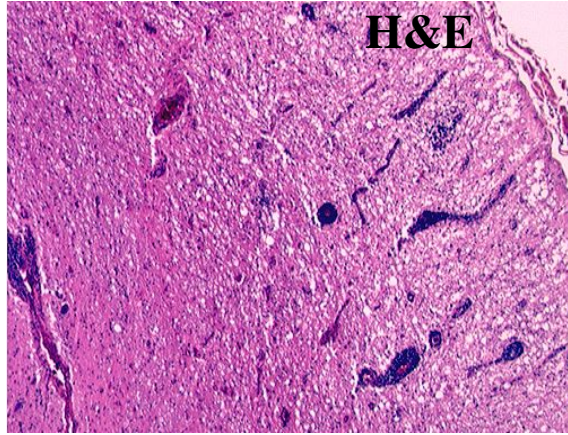
MICHAEL C. LEVIN, M.D., TANYA J. LEHKY, M.D.,
ALFRED N. FLERLAGE, B.S., DAVID KATZ, M.D.,
DOUGLAS W. KINGMA, M.D., ELAINE S. JAFFE, M.D.,
JOHN D. HEISS, M.D., NICHOLAS PATRONAS, M.D.,
HENRY F. MCFARLAND, M.D.,
AND STEVEN JACOBSON, PH.D.

Volume 336 Number 12 March 20, 1997

Spinal Cord Biopsy of HAM/TSP Patient

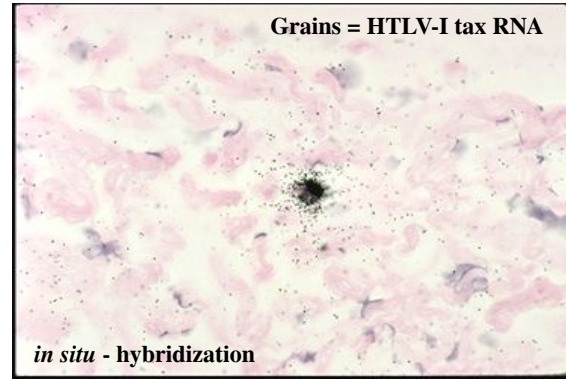
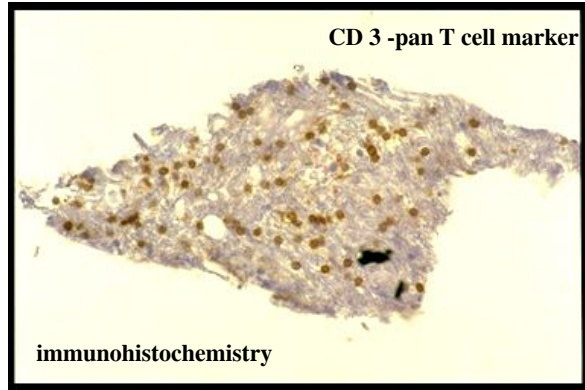


Inflammatory CD8+ Cells in HAM/TSP Spinal Cord



Detection of HTLV-I in GFAP+ cells in HAM/TSP CNS Samples

HAM/TSP - biopsy

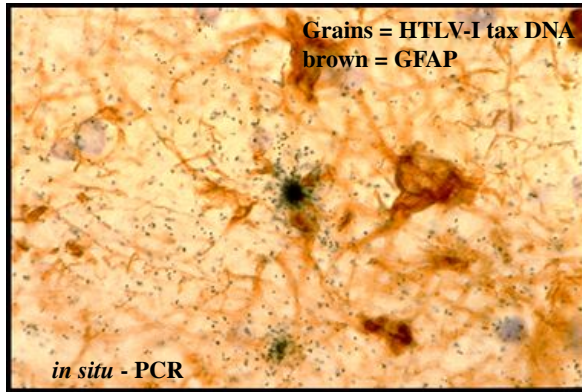


HAM/TSP - autopsy

case 1

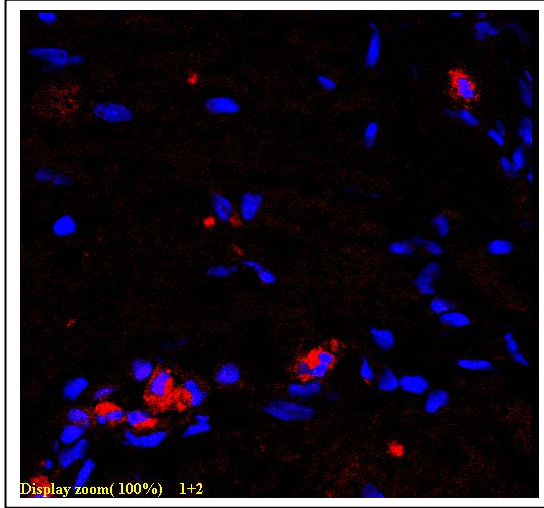


case 2

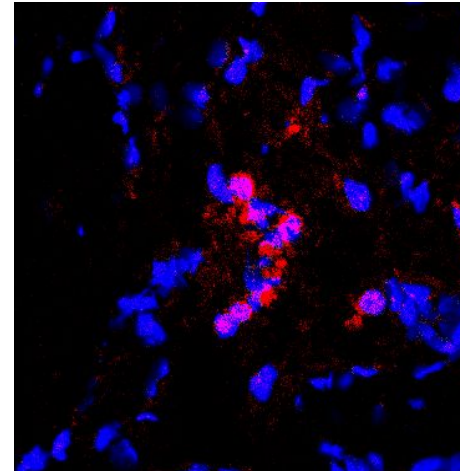
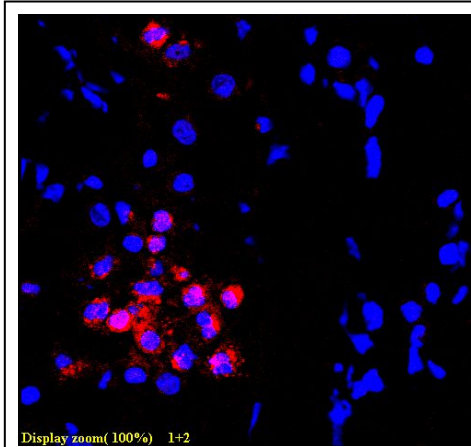


HTLV-I specific CTL in HAM/TSP Spinal cord autopsy:

HAM/TSP spinal cord parenchyma



HAM/TSP spinal cord meninges



**HTLV-I
Tax11-19
tetramer (red)**

Spinal Cord Atrophy in HAM/TSP and Correlation with CSF Immunophenotyping

Research Article | Full Access

In vivo imaging of spinal cord atrophy in neuroinflammatory diseases

Winston Liu, Govind Nair PhD, Luisa Vuolo MD, Anshika Bakshi BS, Raya Massoud MD, Daniel S. Reich PhD, Steven Jacobson PhD

First published: 04 July 2014 | <https://doi.org/10.1002/ana.24213>



NeuroImage: Clinical 30 (2021) 102680

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Cervical and thoracic cord atrophy in multiple sclerosis phenotypes: Quantification and correlation with clinical disability

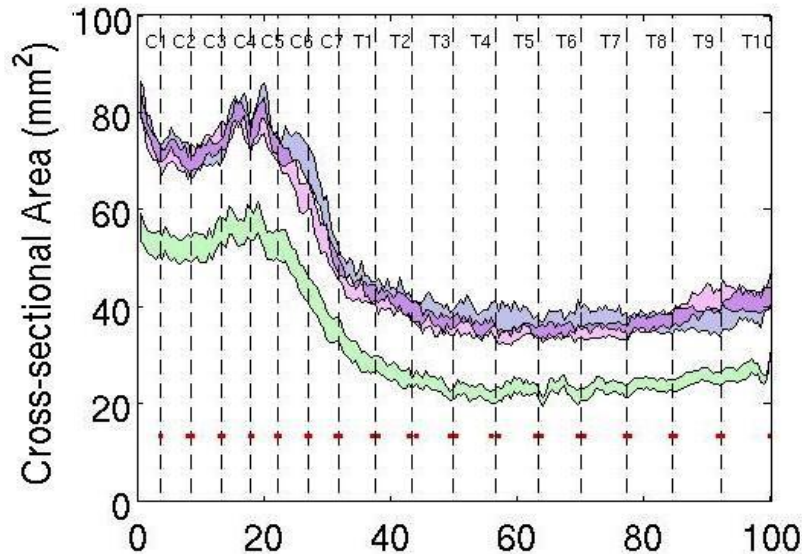
Yair Mina^{a,b,1}, Shila Azodi^{a,c,1}, Tsemacha Dubuche^a, Frances Andrada^c, Ikesinachi Osuorah^c, Joan Ohayon^c, Irene Cortese^e, Tianxia Wu^d, Kory R. Johnson^e, Daniel S. Reich^f, Govind Nair^{g,h}, Steven Jacobson^{h,i}

Research Article | Full Access

Imaging spinal cord atrophy in progressive myelopathies: HTLV-I-associated neurological disease (HAM/TSP) and multiple sclerosis (MS)

Shila Azodi MD, Govind Nair PhD, Yoshimi Enose-Akahata PhD, Emily Charlip, Ashley Vellucci BS, Irene Cortese MD, Jenifer Dwyer BS, B. Jeanne Billioux MD, Chevaz Thomas BS, Joan Ohayon MSN, Daniel S. Reich MD, PhD, Steven Jacobson PhD ... See fewer authors

First published: 10 October 2017 | <https://doi.org/10.1002/ana.25072>



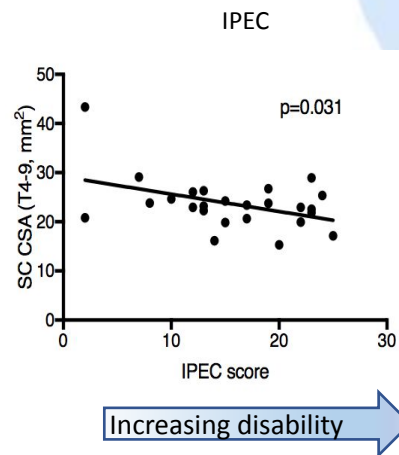
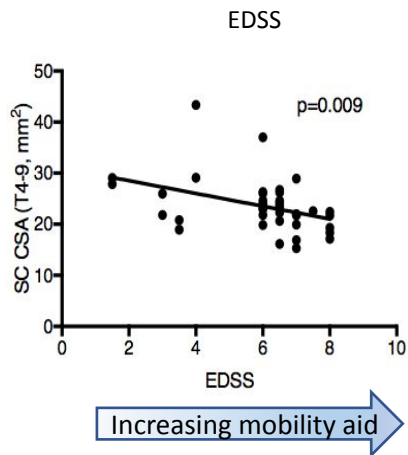
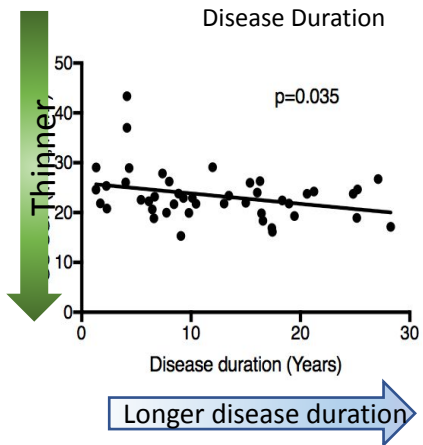
Asymptomatic Carrier n = 17

Healthy Volunteer n = 24

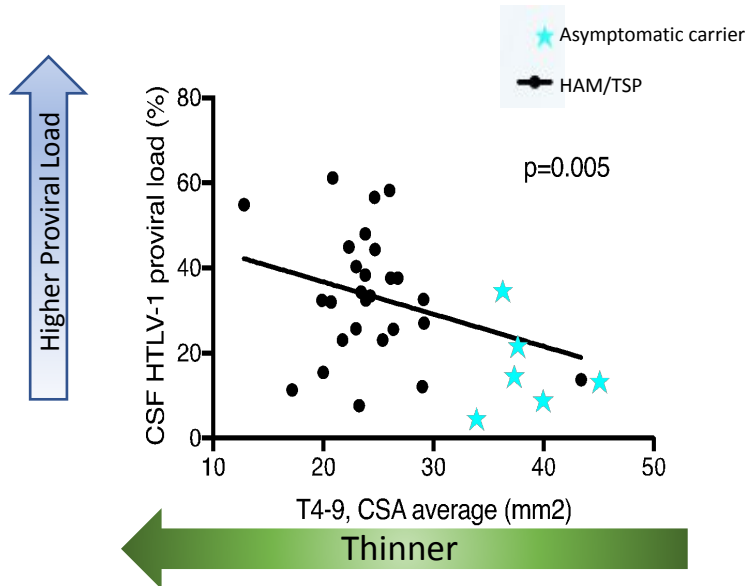
HAM/TSP n = 45

Increased disease duration, EDSS, and IPEC are associated with decrease in thoracic spinal cord cross sectional area

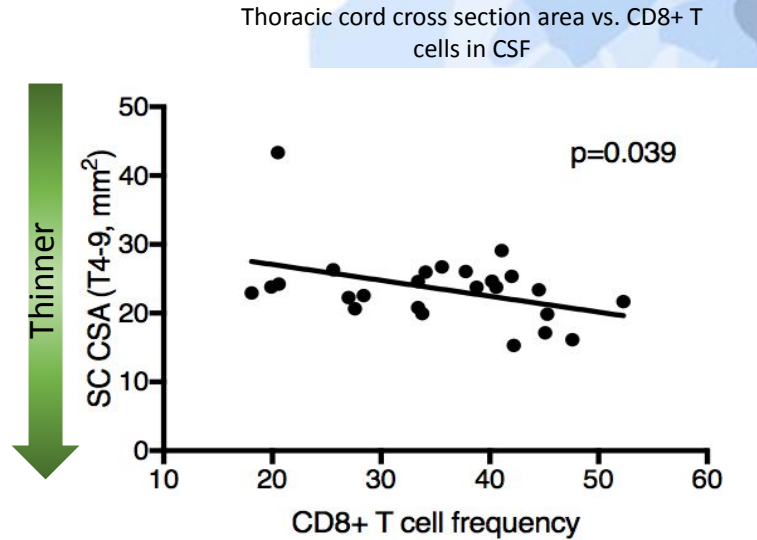
Functional disability scales



Higher HTLV-1 Proviral load correlates with thinner spinal cord in HTLV-1 infection

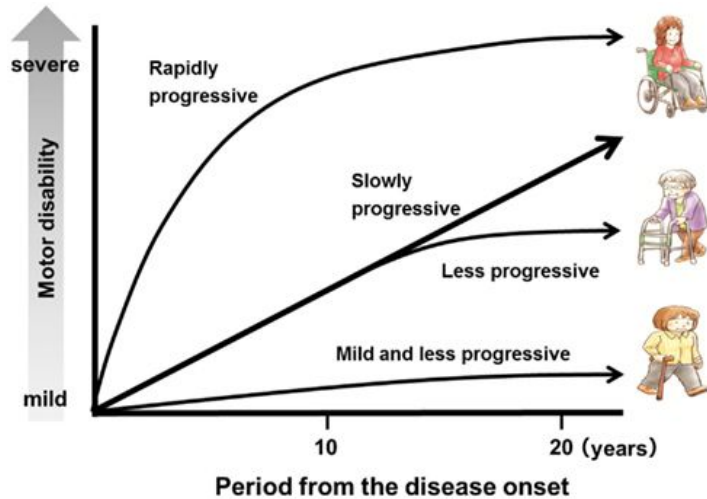


Decrease in spinal cord cross sectional area associated with increased CD8+ T cells in the CSF

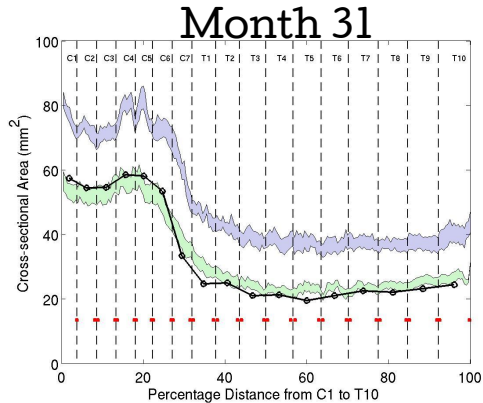
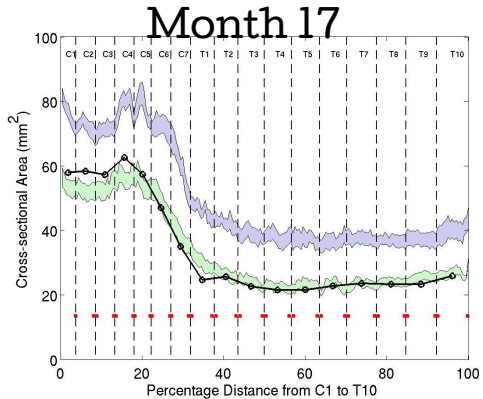
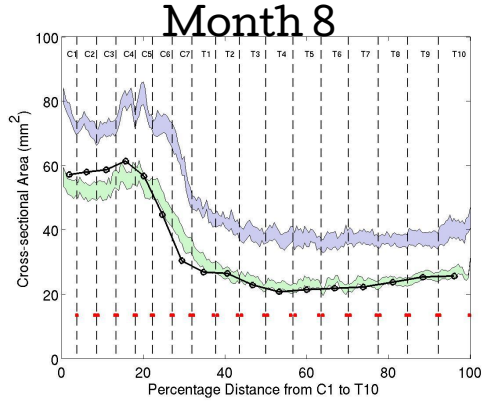
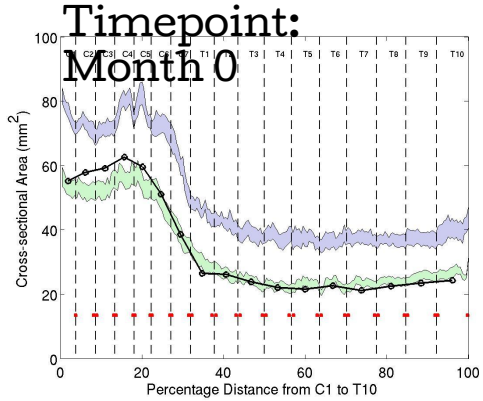


Disease progression in HAM/TSP

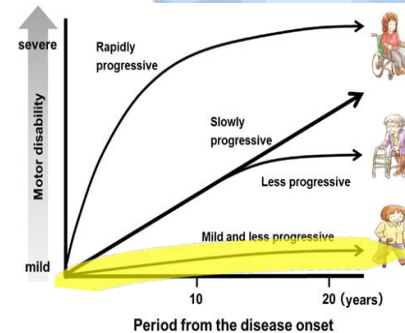
- First signs of disease can occur months to years after infection
- Progression of disease can occur slowly or rapidly



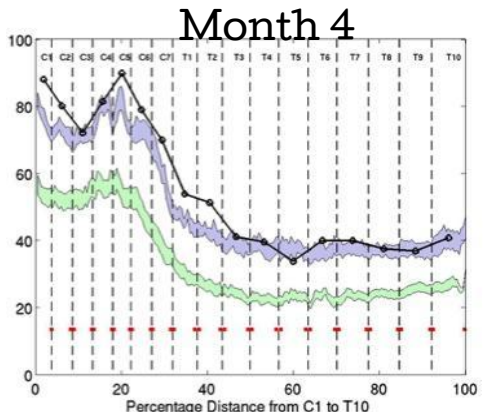
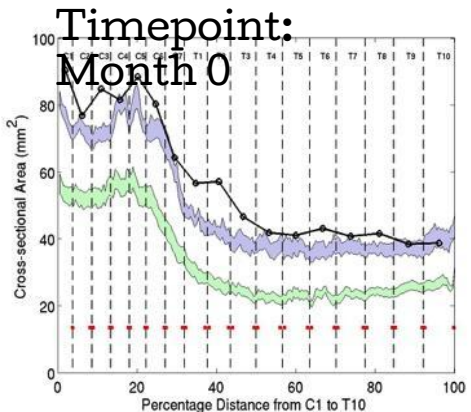
Longitudinal Studies – Subject H1



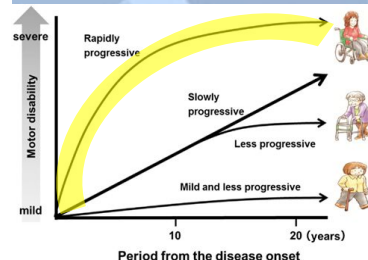
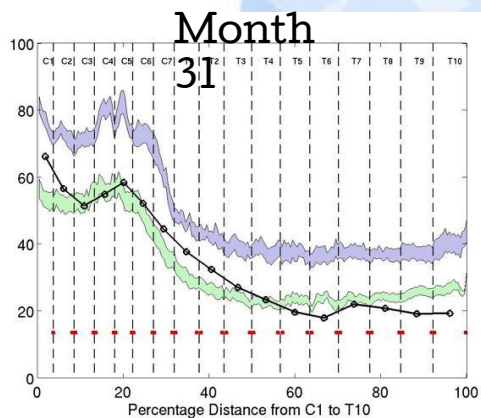
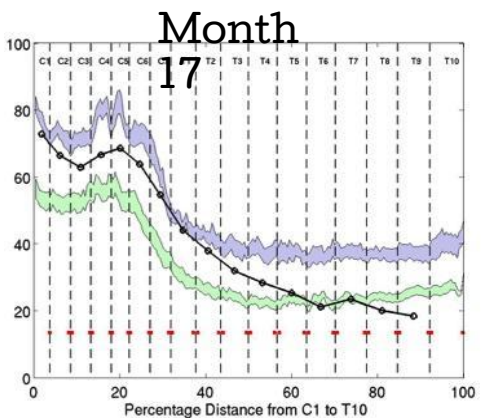
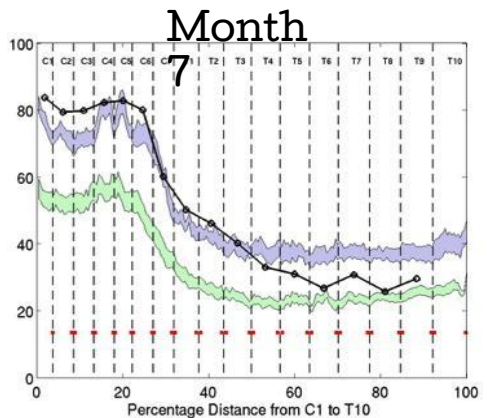
HAM/TSP – presented to NIH with an 8 year history of weakness in left leg, then dragging both feet. Repeated falls prompted medical evaluation and use of cane 2 years before the first scan at “Month 0”. Little or **no clinical progression** since then.



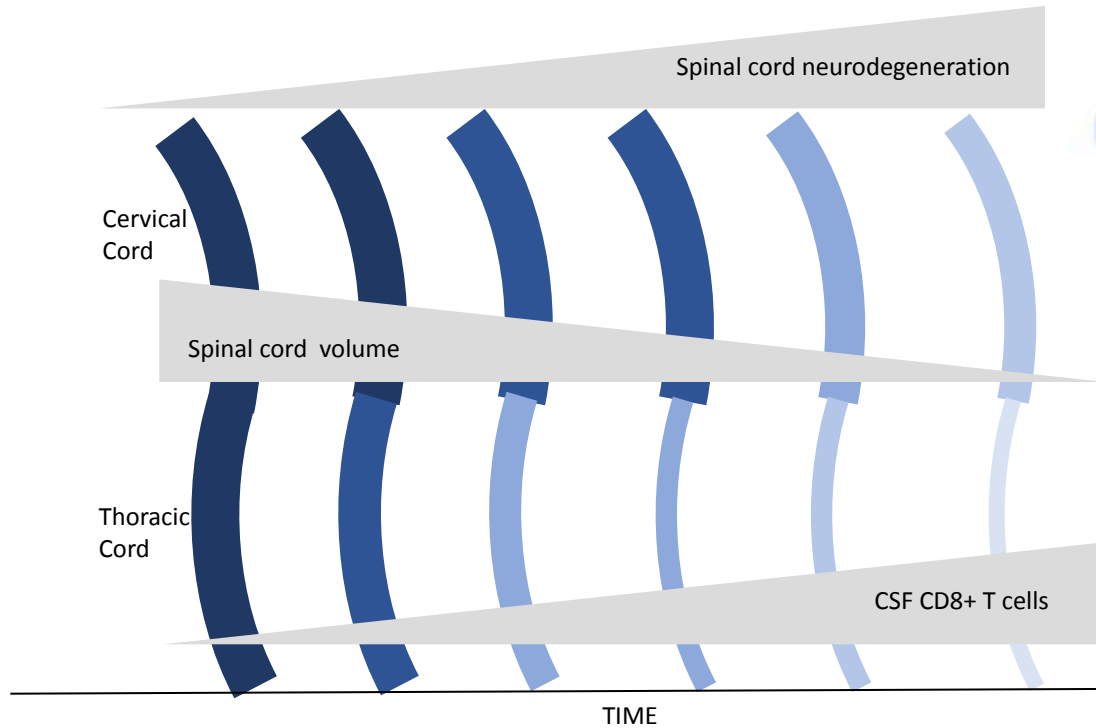
Longitudinal Studies – Subject H3



HAM/TSP – Patient noticed weakness in his legs as he worked on construction sites 7 months before “Month 0” scan. Between month 0 and month 7 patient progressed from using cane to being dependent on a wheelchair for all mobility. **Rapid clinical progression** seen.



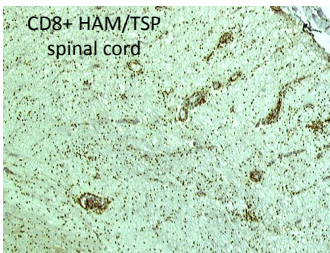
Model of Spinal Cord Atrophy in HAM/TSP



Hypothesis: The neuroinflammatory process in the thoracic cord causes thoracic degeneration and retrograde axon degeneration (explaining no upper body involvement in HAM/TSP)

Summary

(Neuroimmunology of HAM/TSP)



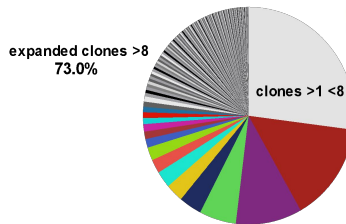
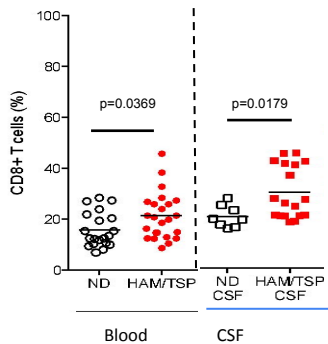
Pathology:

Increased CD8+ T cells in lesions

Immunology:

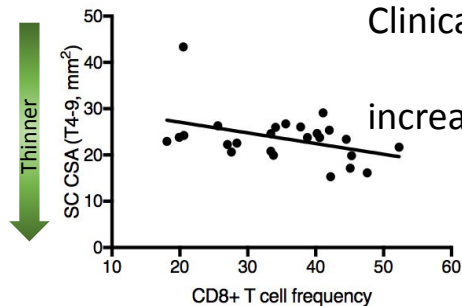
Increased CD8+ T cells in periphery and CSF

Expanded CD8+ TCRB



Clinical:

Spinal cord atrophy associated with increase in CD8+ T cells



Research of rare diseases (HTLV-I – HAM/TSP)

(20 million people worldwide infected: how can a virus cause disease in only a subset of infected individuals?)

can inform understanding of common
neurological disorders
(EBV- Multiple Sclerosis)

(95% of all people infected with EBV: how can a virus cause disease in only a subset of infected individuals?)



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