22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Symposium 3 - Inflammation and HAM/TSP

Chairs: Steve Jacobsen and Fatah Kashanchi

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Senescence-driven inflammaging in HTLV-1 Infection: a multi-omics in vivo and in vitro signature

Johan Van Weyenbergh
KU Leuven, Belgium

Thomas Jefferson University | Drexel University | Drexel Medicine

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Senescence-driven inflammaging in HTLV-1 Infection: a multi-omics *in vivo* and *in vitro* signature

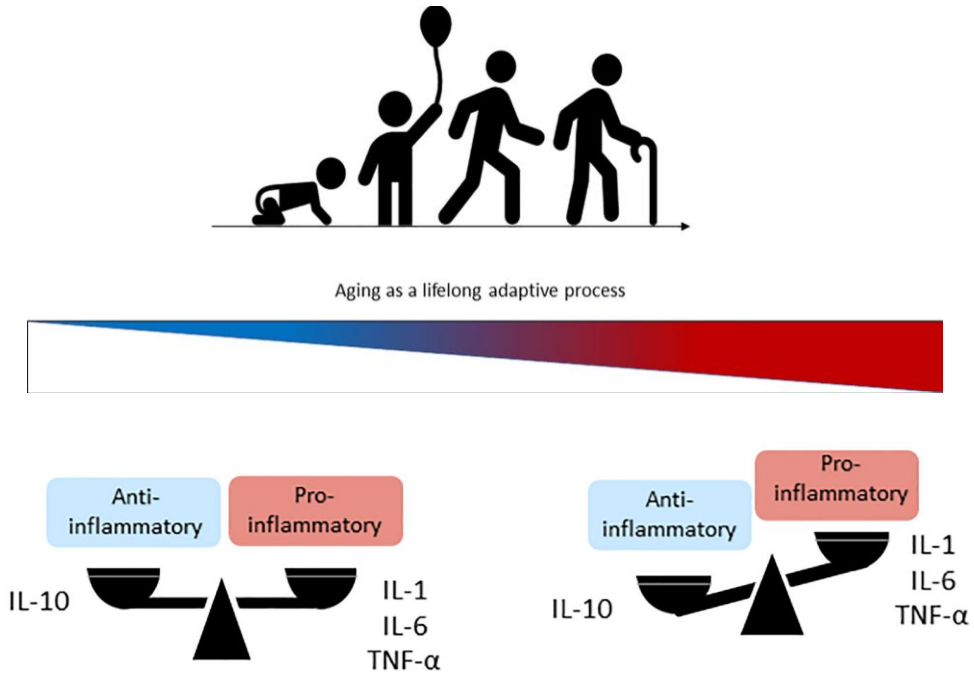
Johan Van Weyenbergh
Rega Institute for Medical Research, KU Leuven, Belgium

Conflicts of interest

I have no conflicts of interest

Background - Inflammaging

Inflammaging: a systemic, chronic, low-grade inflammation during ageing



Inflammaging

2000

Review > Ann N Y Acad Sci. 2000 Jun:908:244-54. doi: 10.1111/j.1749-6632.2000.tb06651.x.

Inflamm-aging. An evolutionary perspective on immunosenescence

C Franceschi [1], M Bonafè, S Valensin, F Olivieri, M De Luca, E Ottaviani, G De Benedictis

Affiliations + expand

PMID: 10911963 DOI: 10.1111/j.1749-6632.2000.tb06651.x

"*we argue that a global reduction in the capability to cope with a variety of stressors and a concomitant progressive increase in the proinflammatory status, which we will call "inflamm-aging".*

2023

Review > Cell. 2023 Jan 19;186(2):243-278. doi: 10.1016/j.cell.2022.11.001. Epub 2023 Jan 3.

Hallmarks of aging: An expanding universe

Carlos López-Otín [1], Maria A Blasco [2], Linda Partridge [3], Manuel Serrano [4], Guido Kroemer [5]

Affiliations + expand

PMID: 36599349 DOI: 10.1016/j.cell.2022.11.001

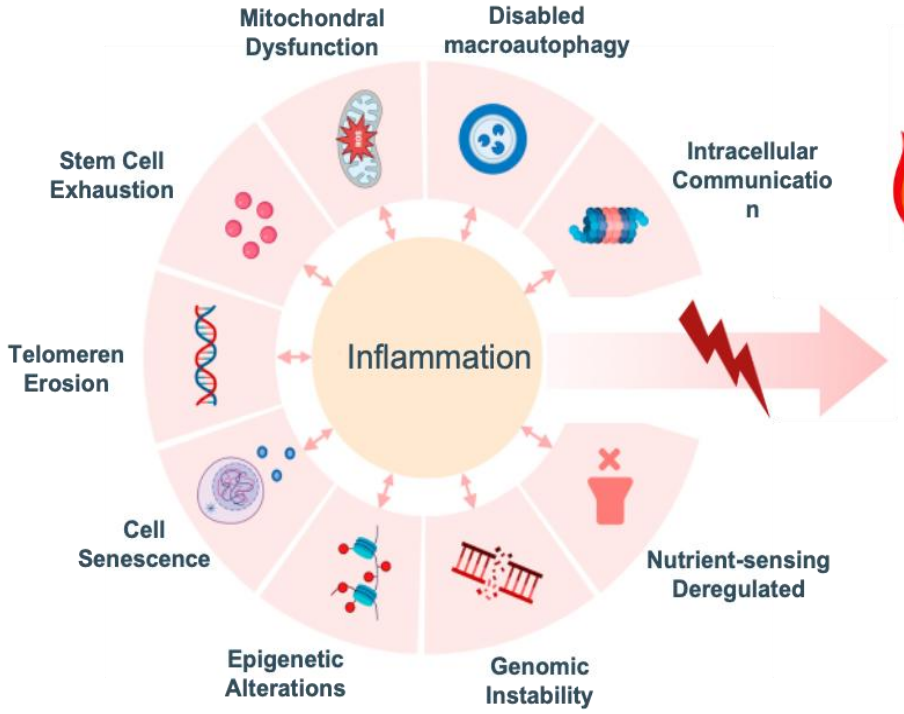
"*Inflammation increases during aging ("inflammaging") with systemic manifestations, as well as with pathological local phenotypes including arteriosclerosis, neuroinflammation, osteoarthritis, and intervertebral discal degeneration*"

Background - Inflammaging

Inflammaging arises from a complex interplay of intrinsic and extrinsic factors

Internal: Increased barrier permeability

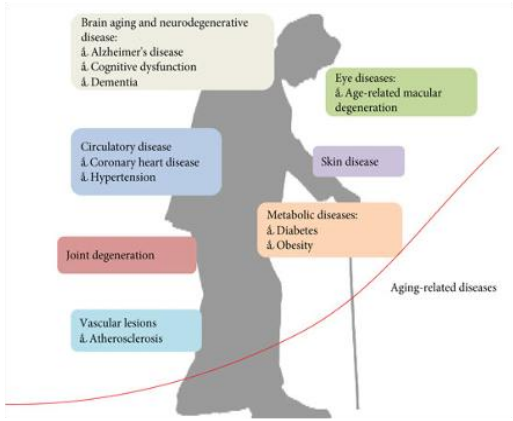
External: chonic Viral infection(HIV, CMV)



IL-1, IL-6, CRP, IFNα,IFNβ, TNF

Inflammaging

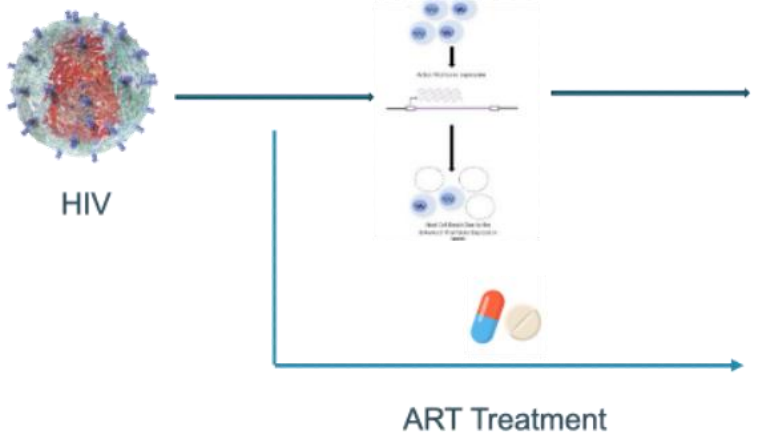
Aging

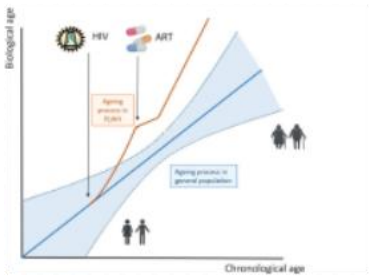


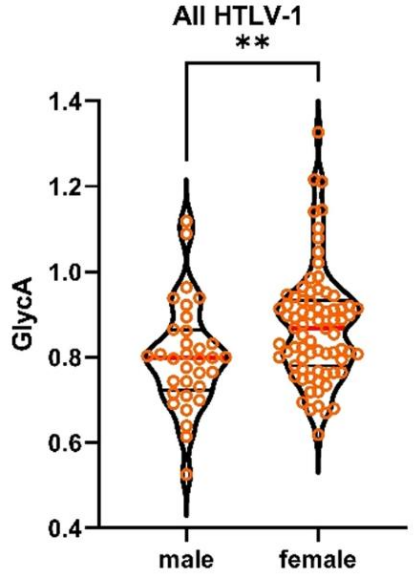
Aging-related diseases

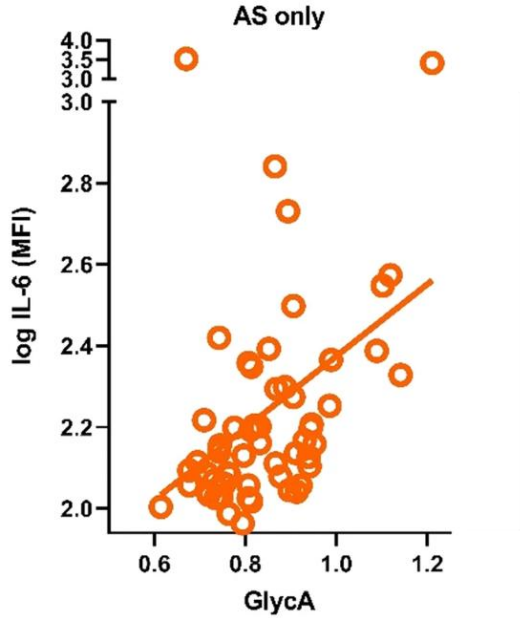
Background - HIV and HTLV-1

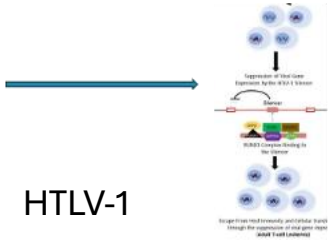
Does retroviral persistence fuel chronic inflammation and aging comorbidities?











"Asymptomatic" ?? ——95%

Adult T-cell leukemia/lymphoma (ATLL)——2-3%

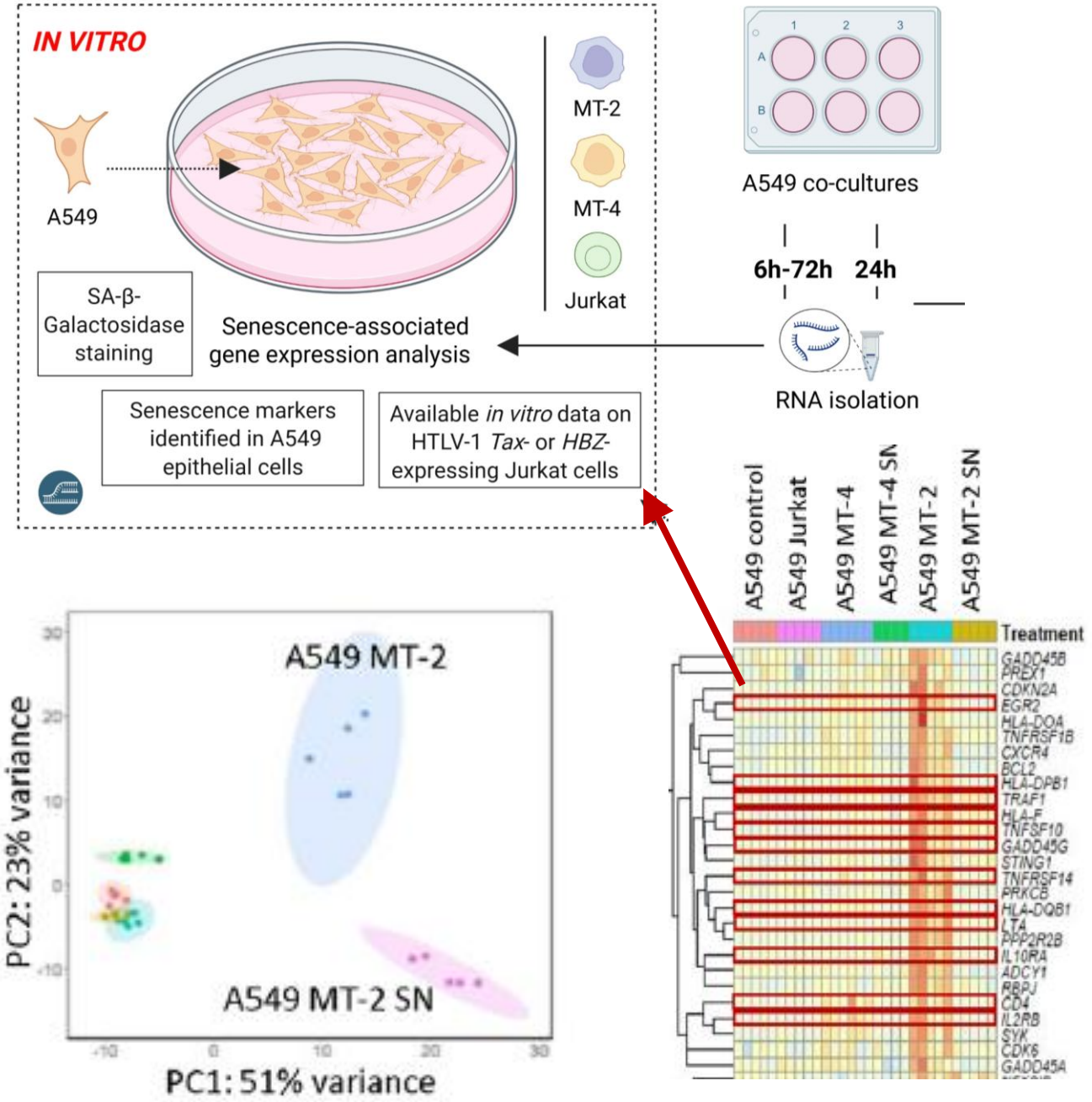
HTLV-1–Associated Myelopathy / Tropical Spastic Paraparesis——0.25–3.8%

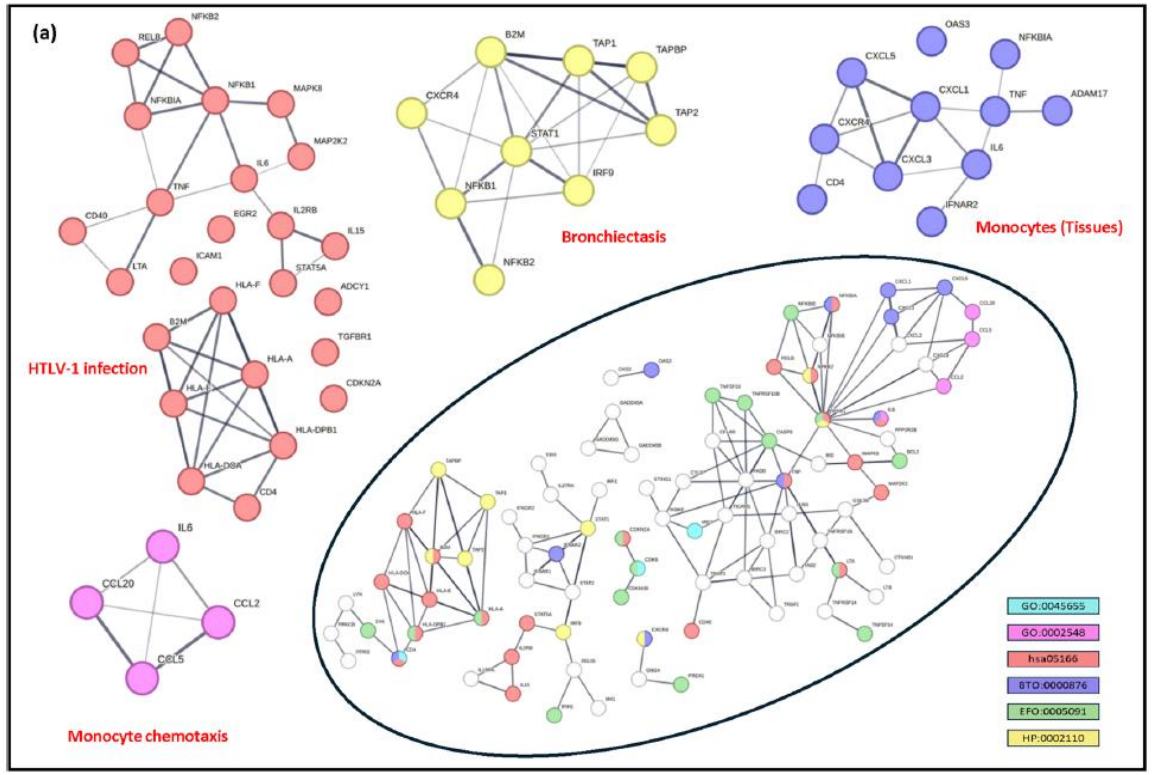
Uveitis, dermatitis, thyroiditis **pulmonary pathology** myositis, arthritis

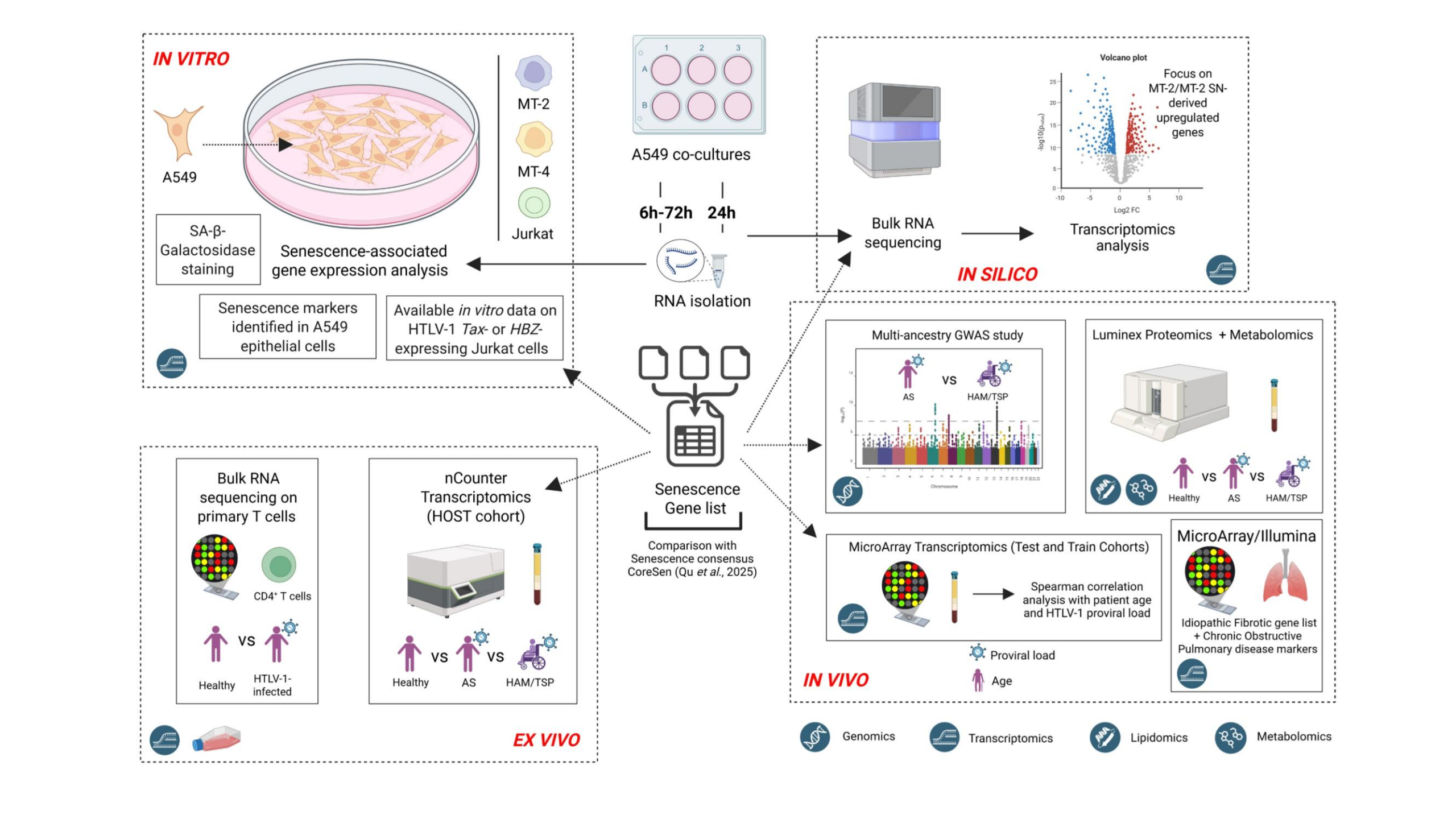
Heymann *et al. Molecular Medicine* (2026) 32:85
https://doi.org/10.1186/s10020-026-01482-9

RESEARCH Open Access

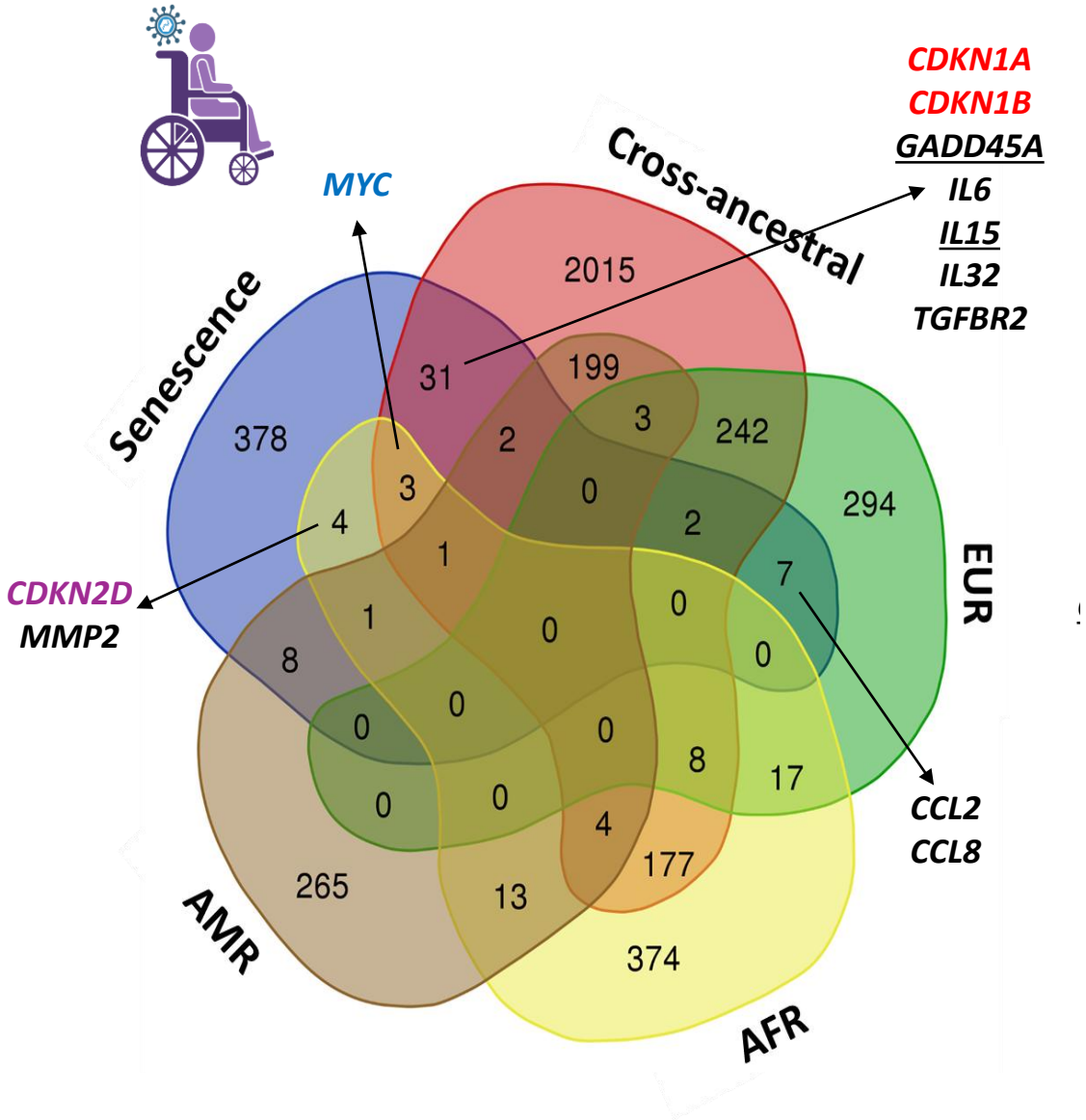
Integrated *in vitro* and multi-cohort cross-omics analysis of HTLV-1-associated lung pathology reveals a RelA-dependent mechanism for monocyte recruitment and differentiation






IN VITRO
A549
MT-2
MT-4
Jurkat
SA-β-Galactosidase staining
Senescence-associated gene expression analysis
Senescence markers identified in A549 epithelial cells
Available in vitro data on HTLV-1 Tax- or HBZ- expressing Jurkat cells
A549 co-cultures
6h-72h
24h
RNA isolation
Bulk RNA sequencing
Volcano plot
Focus on MT-2/MT-2 SN-derived upregulated genes
Log2 FC
Transcriptomics analysis
IN SILICO
Senescence Gene list
Comparison with Senescence consensus CoreSen (Qu et al., 2025)
Multi-ancestry GWAS study
AS
vs
HAM/TSP
Luminex Proteomics + Metabolomics
Healthy
AS
HAM/TSP
MicroArray Transcriptomics (Test and Train Cohorts)
Spearman correlation analysis with patient age and HTLV-1 proviral load
Proviral load
Age
MicroArray/Illumina
Idiopathic Fibrotic gene list + Chronic Obstructive Pulmonary disease markers
IN VIVO
Bulk RNA sequencing on primary T cells
CD4+ T cells
Healthy
HTLV-1-infected
nCounter Transcriptomics (HOST cohort)
EX VIVO
Genomics
Transcriptomics
Lipidomics
Metabolomics

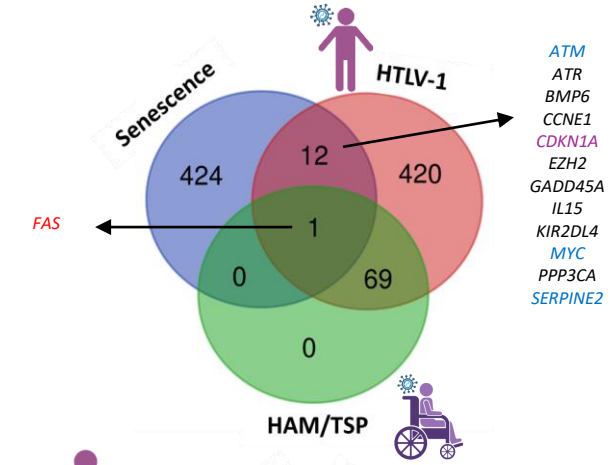
Senescence signature in GWAS for HAM and PVL (Brazil cohort)

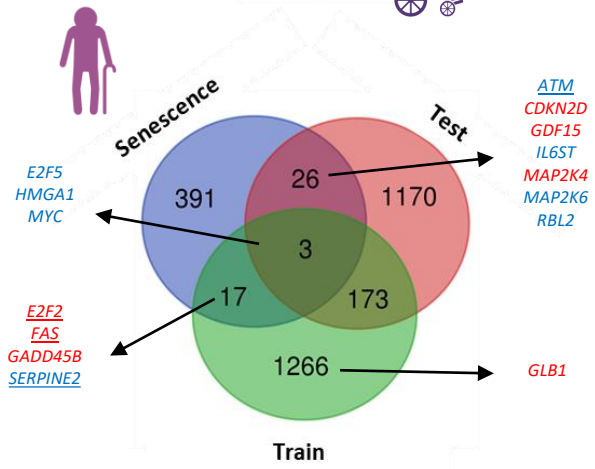


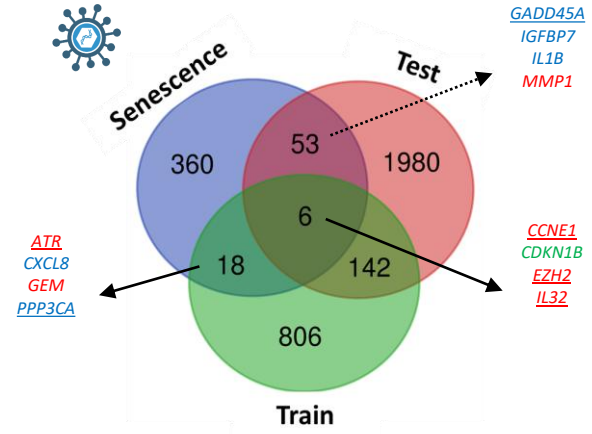
Senescence signature in whole blood transciptome

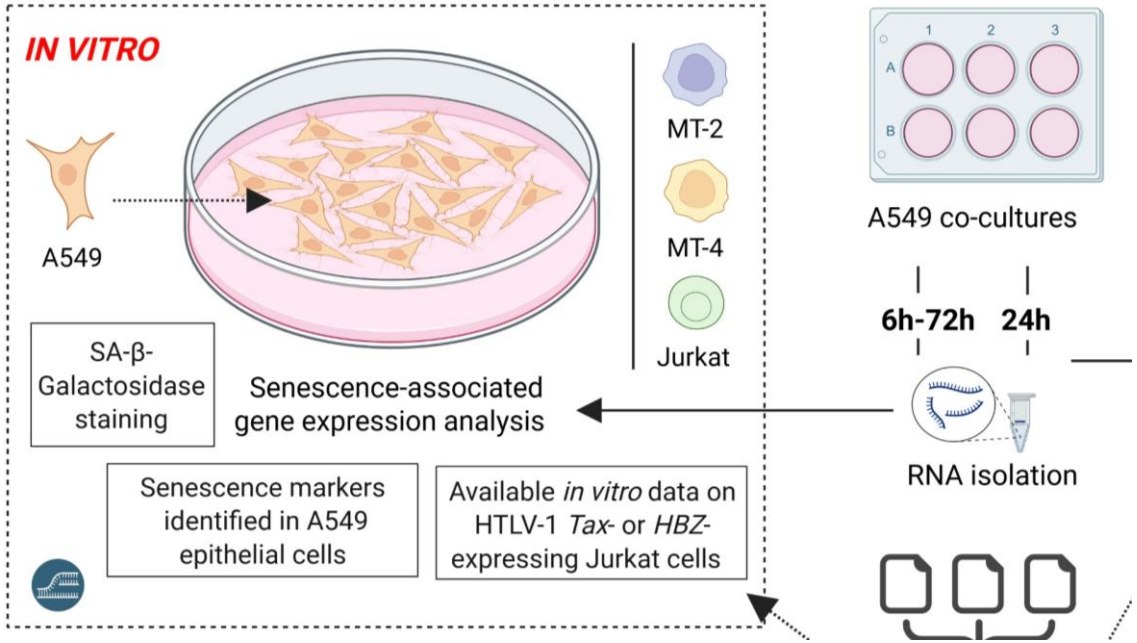
(UK, Tattermusch et al.)

1. Overlap HTLV-1 not HAM signature
2. Senescence genes correlated to age in both cohorts include *MYC*
3. Senescence genes correlated to PVL in both cohorts include *CDKN1B, EZH2, IL32*





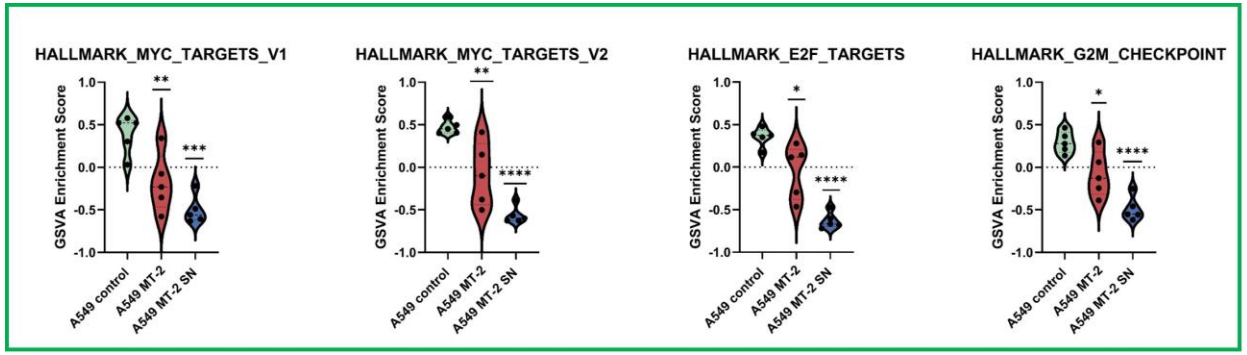


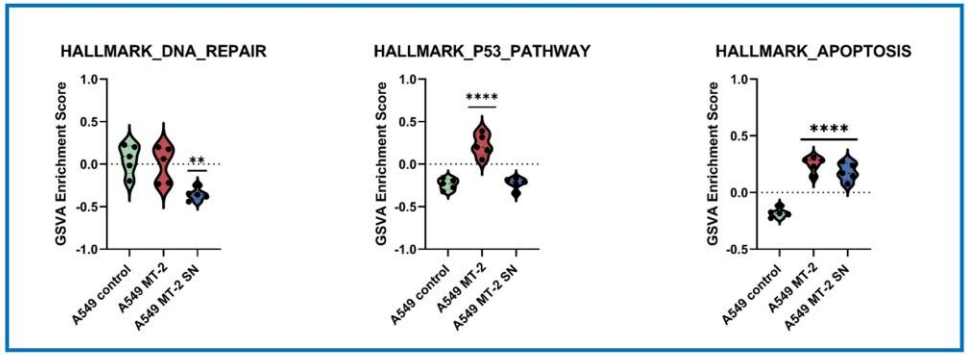


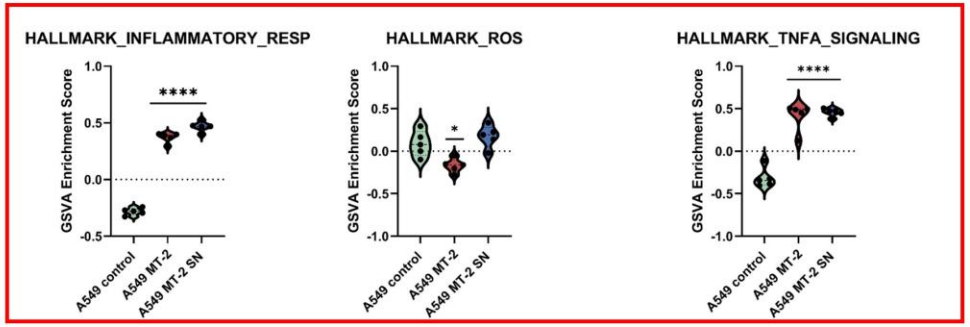
A549 co-cultures

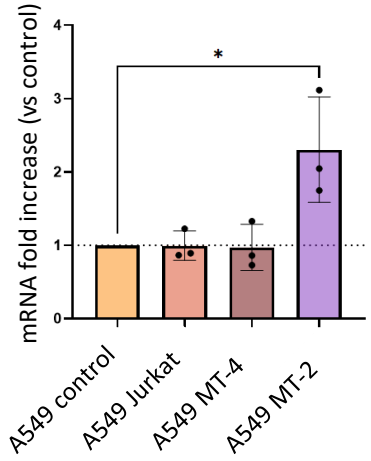
6h-72h 24h

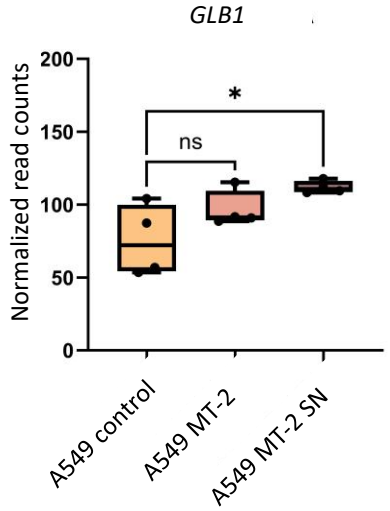
RNA isolation

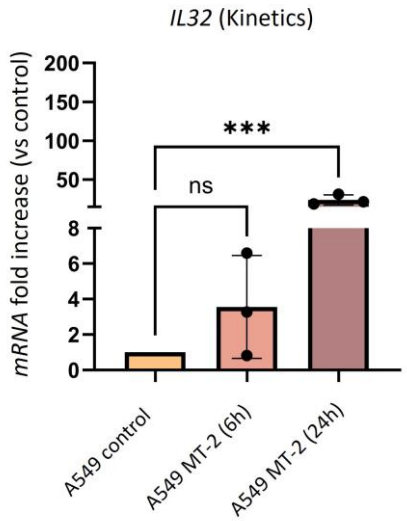


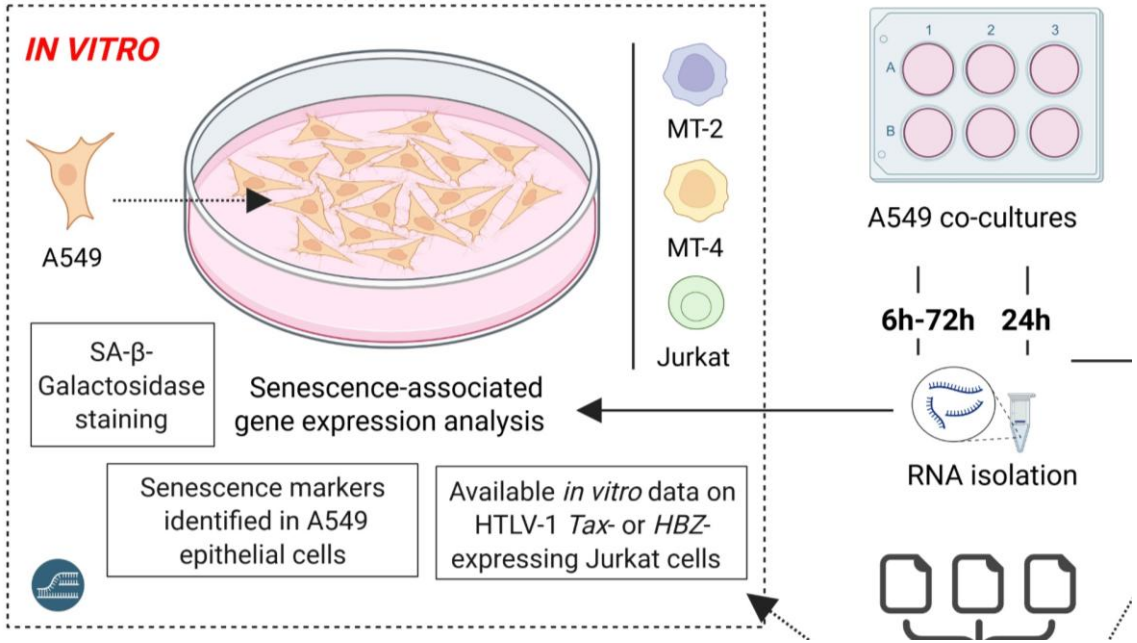








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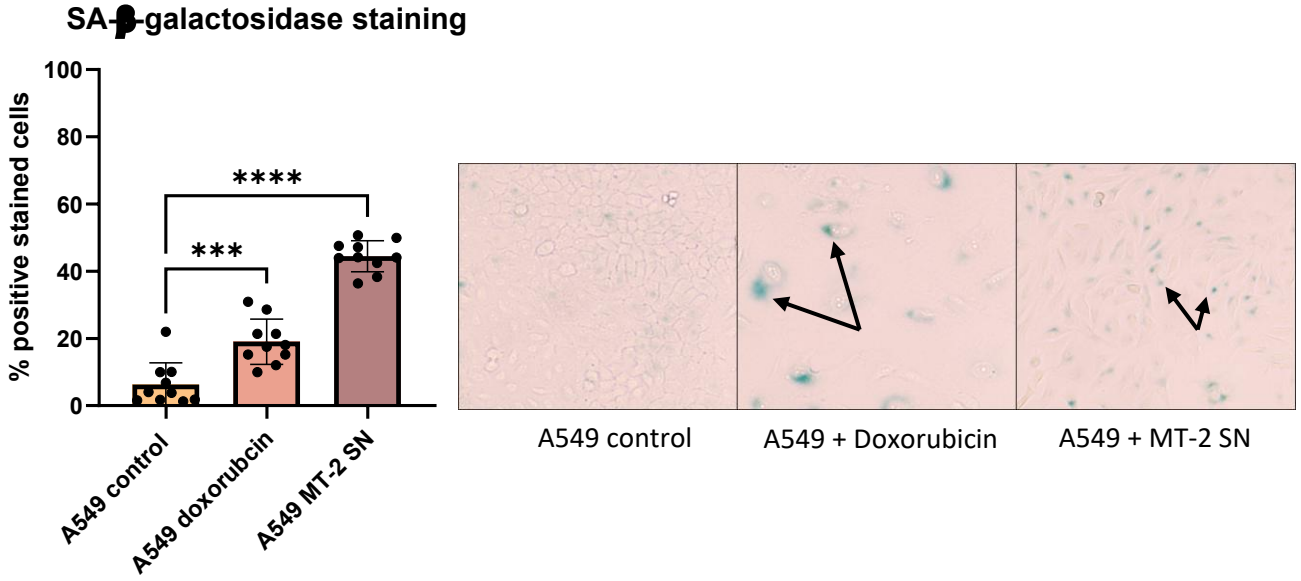
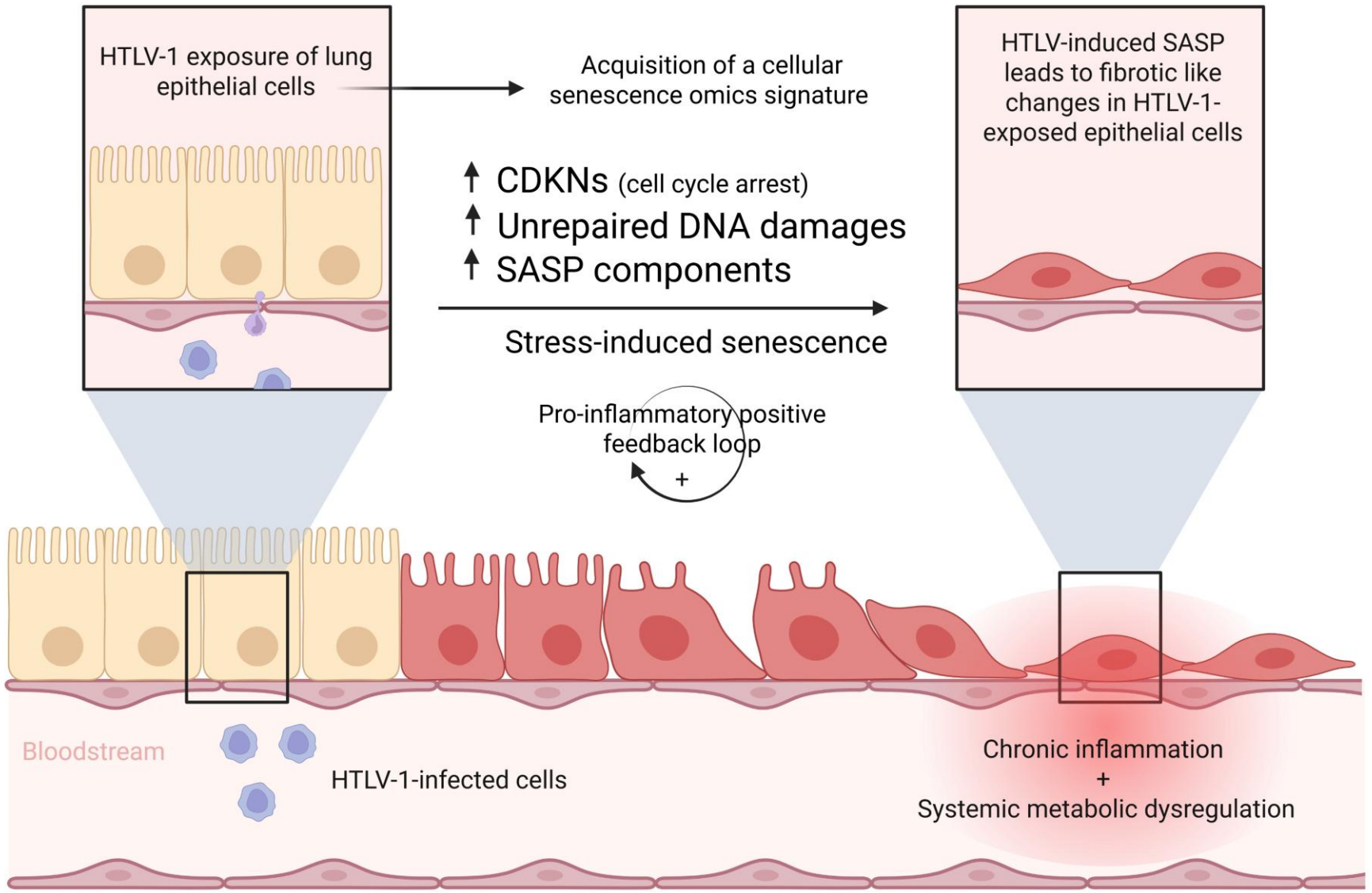
Available *in vitro* data on HTLV-1 *Tax*- or *HBZ*-expressing Jurkat cells


SA-β-galactosidase staining
% positive stained cells
100
80
60
40
20
0
****
***
A549 control
A549 doxorubcin
A549 MT-2 SN

A549 control
A549 + Doxorubicin
A549 + MT-2 SN

A549

Can in vitro model recapitulate in vivo findings in humans, macaques, baboons?



Myeloid IL8, IL6, TNF,…

Acknowledgements

Clément J. F. Heymann[1], Evelien Vanderlinden[1], Giovanni Lopez[2], Carolina Alvarez[2], Michael Talledo[2], Jean-Claude Twizere[3], Sandra Claes[1], Tatiana Assone[3], Jorge Casseb[3], Isaac Racine[4], Isabelle Cleynen[4], Edward L. Murphy[5], Roberta Bruhn[6], Eduardo Gotuzzo, Dominique Schols[1]

BRAZIL

US

PERU

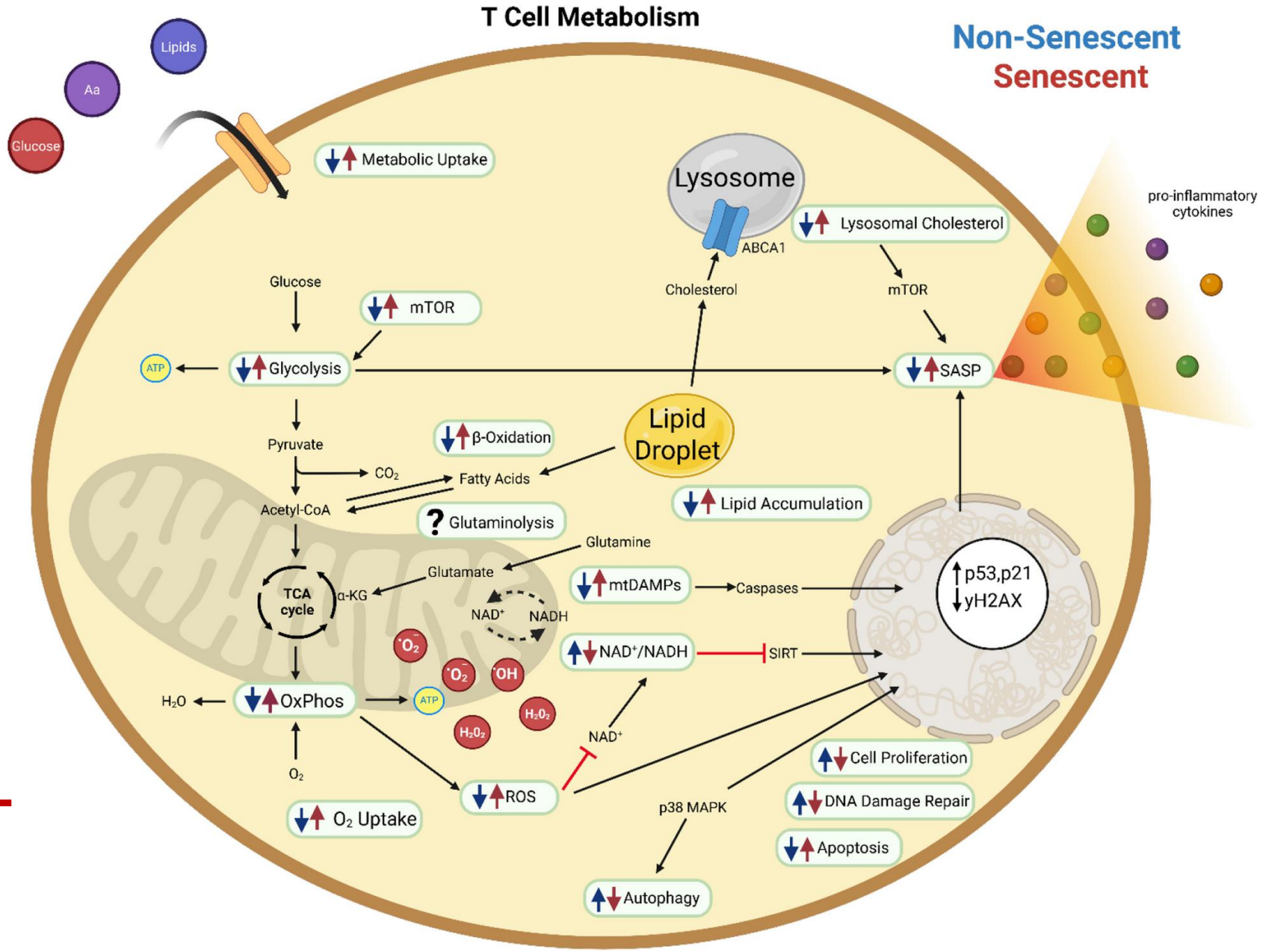
BELGIUM

Funding: FWO, KU Leuven “Vaast Leysen Leerstoel”

HTLV-1

HAM

ATL



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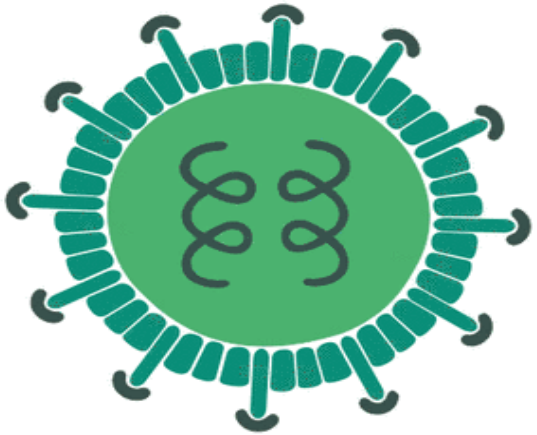
Transcriptional reprogramming in immune cells of HTLV-1 asymptomatic carriers and HAM/TSP patients following antiretroviral therapy

Sai Chaitanya Rajendra Gaekwar
Drexel Medicine, Philadelphia, USA



Transcriptional reprogramming in immune cells of HTLV-1 asymptomatic carriers and HAM/TSP patients following antiretroviral therapy

Sai Chaitanya R G, Salwa Ahmed, Felice Deminco, Carlos Brites, Alexander Lemenze, Ritesh Tandon, Prince Baffour Tonto, Reem Alatrash, Bobby Brooke Herrera, and Pooja Jain

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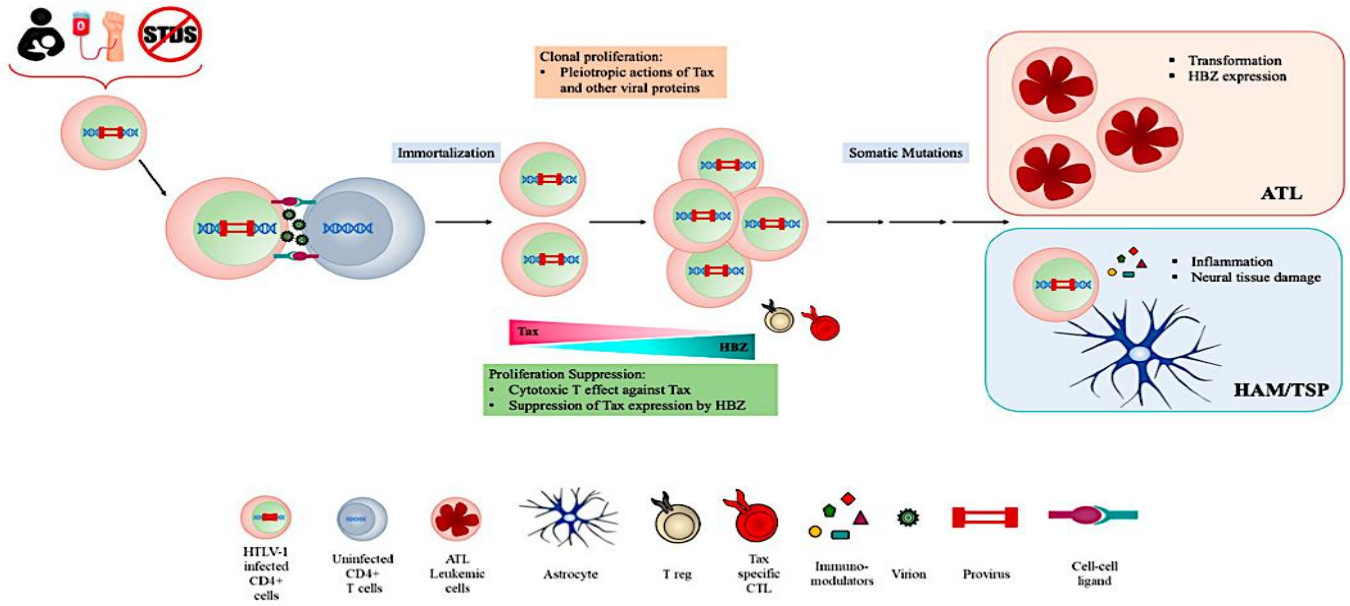
HTLV-1 pathogenesis – Infection and diseases

- **Entry & spread:** HTLV-1 binds HSPGs/NRP1/GLUT1 and spreads cell-to-cell via a virological synapse (free virions are inefficient).
- **Integration & persistence:** Viral cDNA integrates (provirus); long-term burden is driven mainly by clonal expansion of infected cells.
- **Key drivers:** Tax activates NF-κB and proliferation;
  HBZ supports persistence and immune evasion → chronic inflammation.

Distinct Disease Outcomes of HTLV-1 Infection



Forlani et al., Int. Journal of Mol. Sciences, 2021

ATLL

Driven primarily by:
- Clonal proliferation
- Transformation of infected T cells
- Oncogenic transcriptional changes

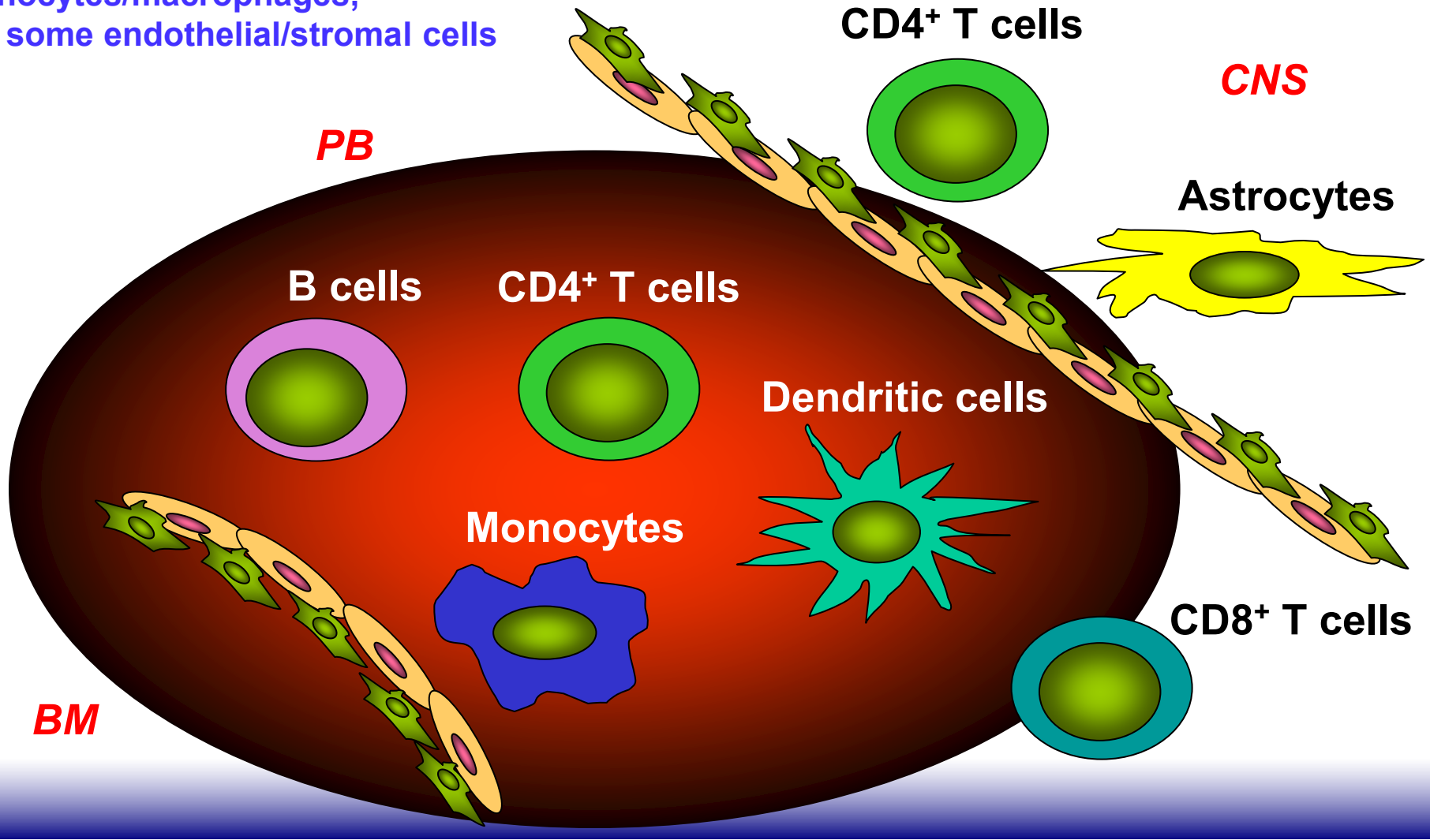
HAM/TSP

Characterized by:
- chronic neuroinflammation
- Immune-cell trafficking into CNS
- inflammatory transcriptional remodeling

Monocytes and myeloid cells contribute to:
- cytokine dysregulation
- endothelial migration
- CNS inflammation

In vivo cellular tropism of HTLV-1

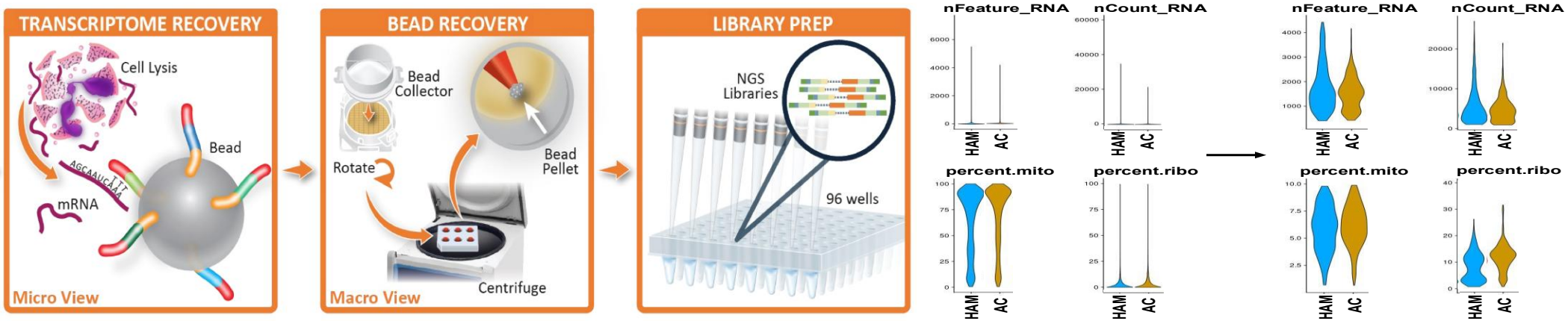
HTLV-1 Reservoir extends beyond $CD4^+$ T cells to $CD8^+$ T cells, dendritic cells, monocytes/macrophages, B cells, and some endothelial/stromal cells



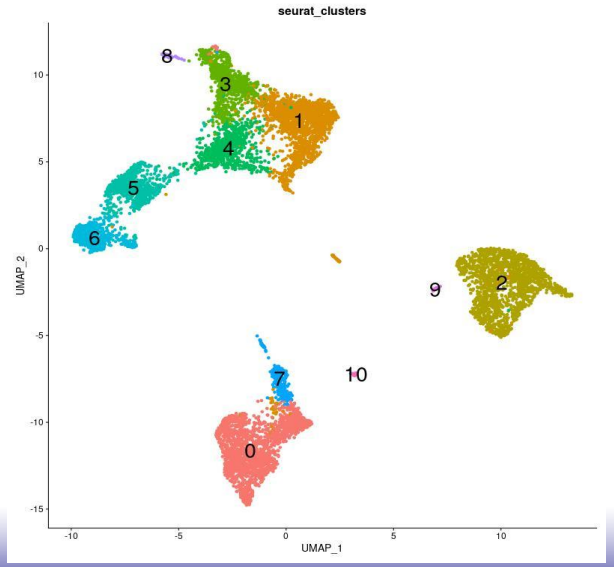
Rationale for the study

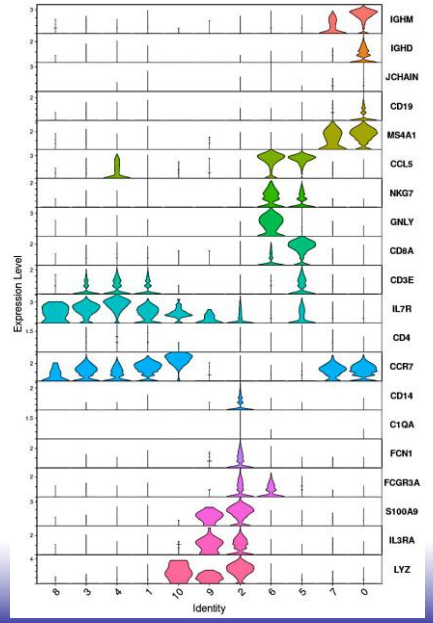
To understand the relative Importance of different cell types in asymptomatic carriers and HAM/TSP patients by utilizing innovative Honeycomb single-cell sequencing technology, and to assess how these immune signatures are modulated during dolutegravir therapy

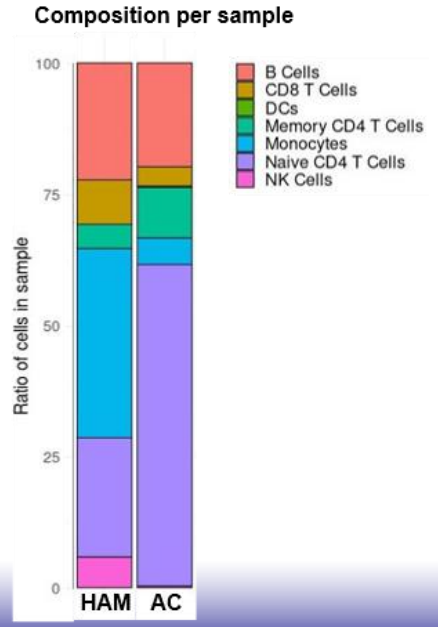
Single cell sequencing of ACs and HAM/TSP patients using an innovative Honeycomb technology



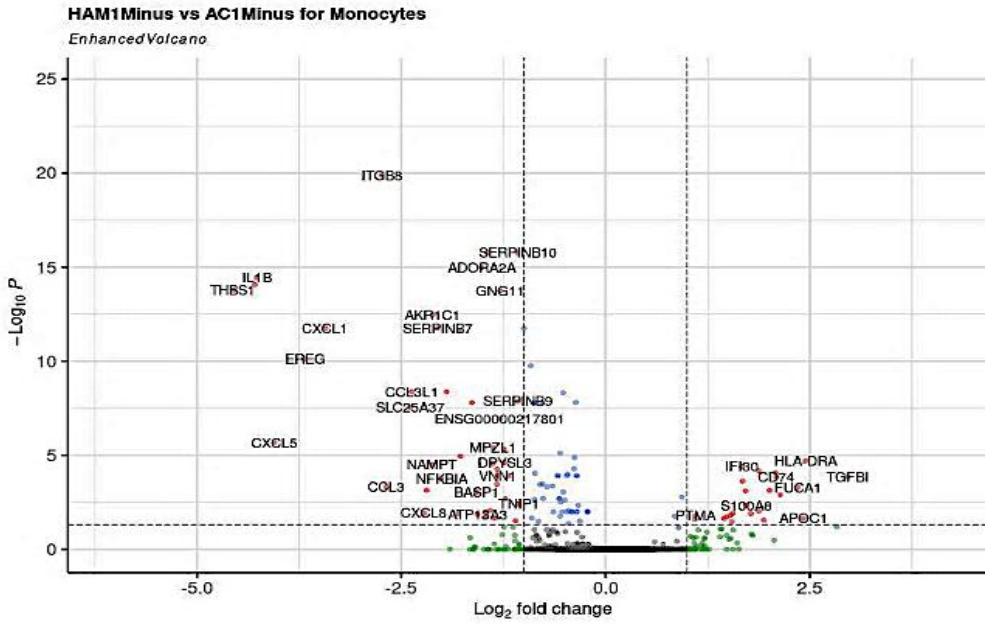
All cells had ~4500 genes (multiplets), > 100 genes (noise), <10% mitochondrial content (dead/dying cells), and <45% ribosomal or <20% hemoglobin content (noise)

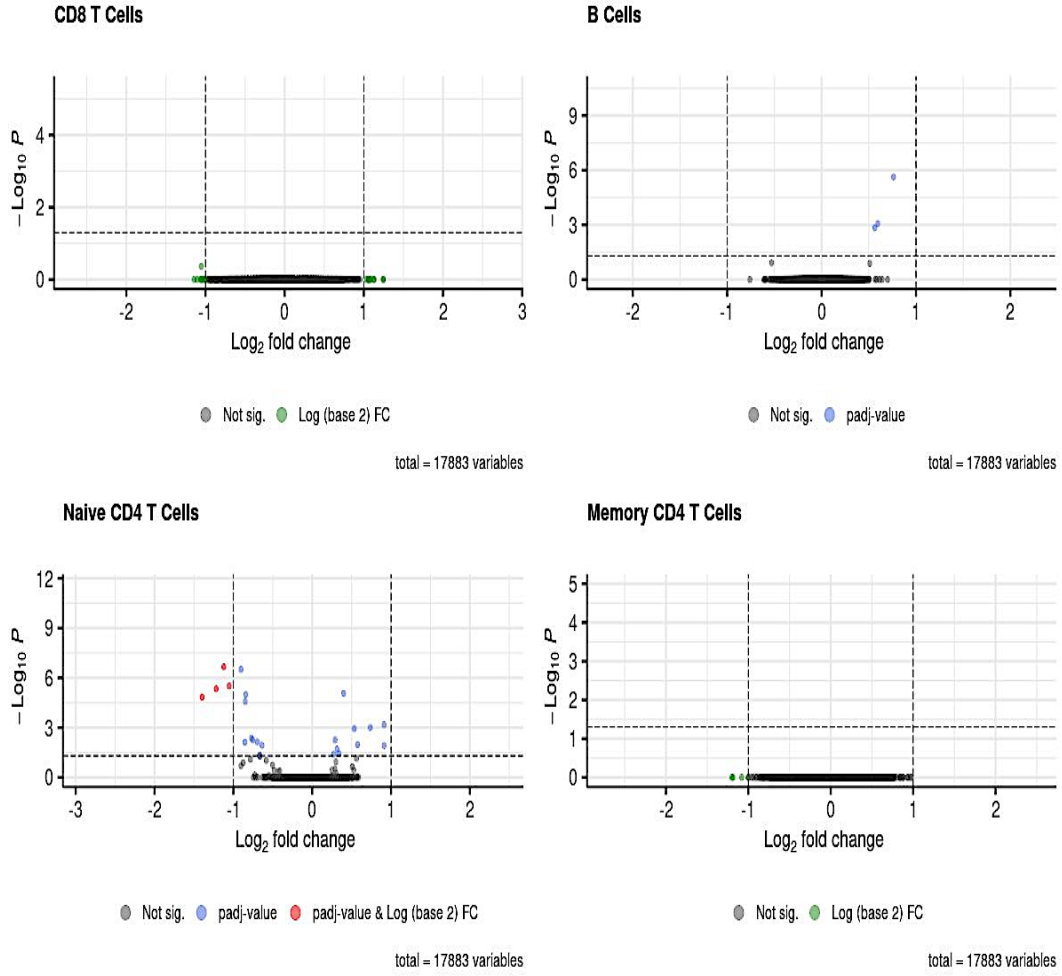






differential gene expression analysis between HAM/TSP patients and ACs

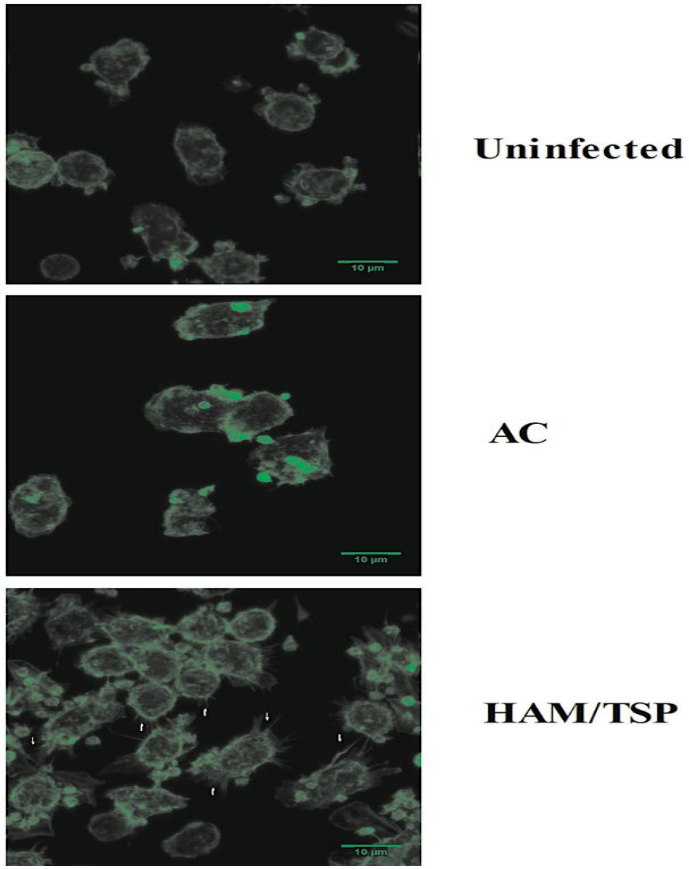




Monocytes and their role in HTLV pathogenesis

- Monocytes are innate immune cells that initiate responses to infection and differentiate into macrophages and dendritic cells.
- They are divided into three subsets based on surface markers:
  - Classical ($CD14^{+}CD16^{-}$) – circulate in blood
  - Intermediate ($CD14^{+}CD16^{+}$) – transitional, proinflammatory
  - Nonclassical ($CD14^{-}CD16^{+}$) – patrol vascular endothelium *(Amarante et al., 2016).*
- In HTLV-1 infection, intermediate monocytes are elevated and exhibit increased adhesion and transmigration across the endothelium.
- This enhanced activity may facilitate T-lymphocyte migration into the spinal cord - a key process in HAM/TSP pathogenesis *(E-Lima et al., 2018).*

Differential cytoskeleton organization in monocytes from HAM/TSP patients and uninfected donors

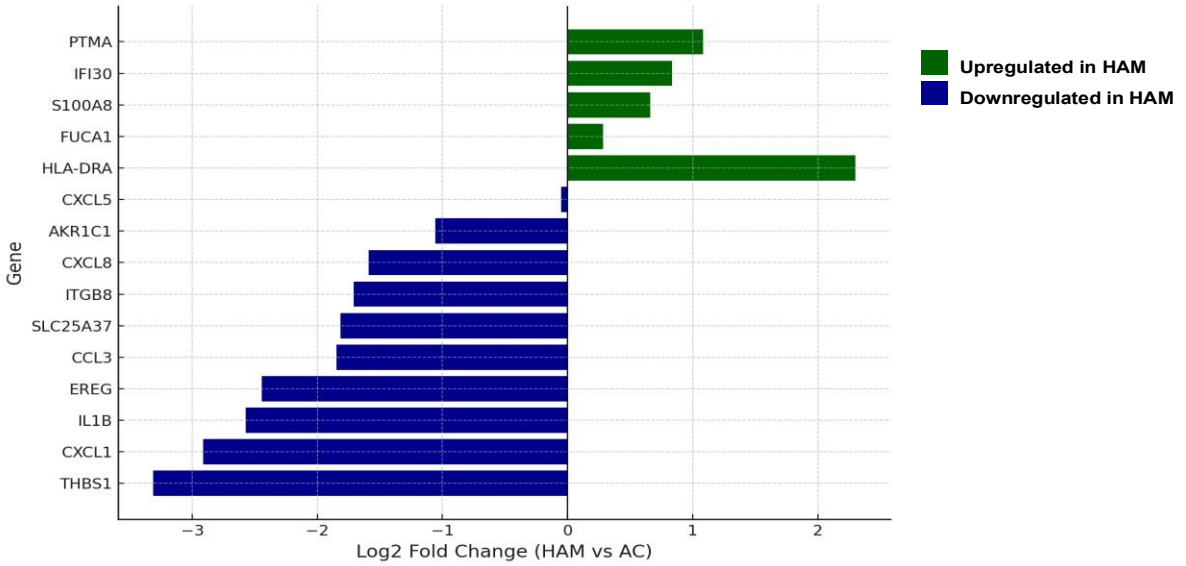


Echevarria-Lima et al, Sci. Rep., 2018

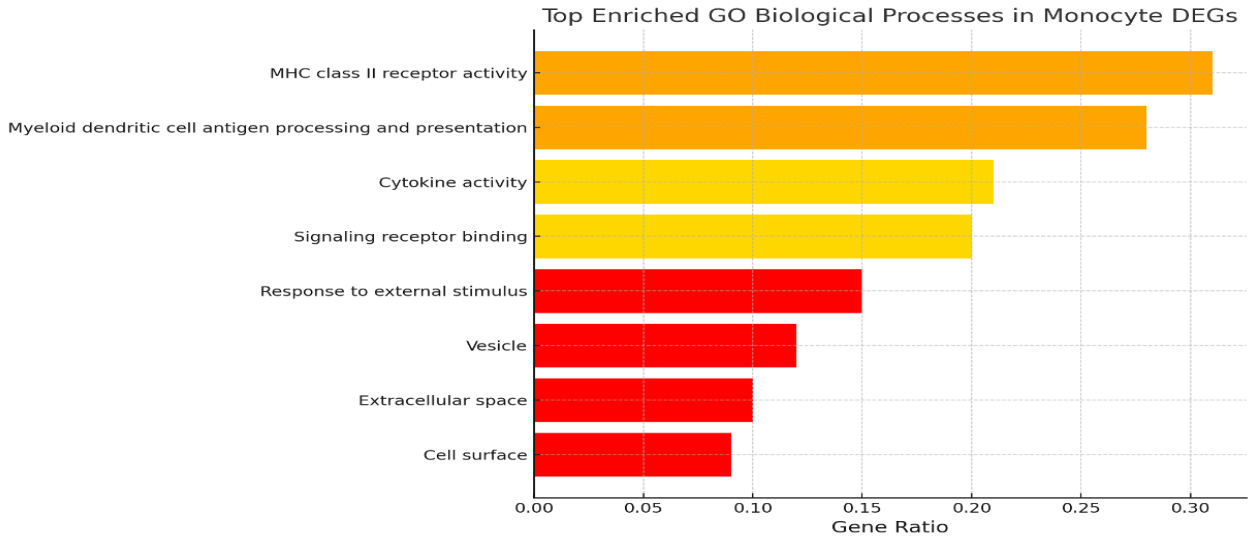
Differential Gene expression pattern in monocytes of AC vs HAM/TSP

Gene	Gene Description	Log2 FC
	Up Regulated	
TGFBI	transforming growth factor beta induced	3
CCL2	C-C motif chemokine ligand 2	2.8
HLA-DRA	major histocompatibility complex, class II, DR alpha	2.5
APOC1	apolipoprotein C1	2.4
FUCA1	alpha-L-fucosidase 1	2.4
PLXDC2	plexin domain containing 2	2.1
CD74	CD74 molecule	2.1
CYBB	cytochrome b-245 beta chain	2.1
APOE	apolipoprotein E	2.1
HLA-DRB1	major histocompatibility complex, class II, DR beta 1	2
CLEC5A	C-type lectin domain containing 5A	1.9
HLA-DPB1	major histocompatibility complex, class II, DP beta 1	1.9
S100A6	S100 calcium binding protein A6	1.9
MRC1	mannose receptor C-type 1	1.8
HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	1.8
ABHD2	ABHD2 abhydrolase domain containing 2, acylglycerol lipase	1.8
S100A8	S100 calcium binding protein A8	1.7
TMEM176B	transmembrane protein 176B	1.7
CTSD	cathepsin D	1.7
IFI30	IFI30 lysosomal thiol reductase	1.7
SPP1	secreted phosphoprotein 1	1.6
MCEMP1	mast cell expressed membrane protein 1	1.6
LYZ	lysozyme	1.6
GBP1	guanylate binding protein 1	1.6
ATP6V1G1	ATPase H+ transporting V1 subunit G1	1.6
LAP3	leucine aminopeptidase 3	1.5
FPR3	formyl peptide receptor 3	1.5
STAT1	signal transducer and activator of transcription 1	1.5
PLD3	phospholipase D family member 3	1.5
GPNMB	glycoprotein nmb	1.5
CD84	CD84 molecule	1.5
SAMHD1	SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1	1.5
HLA-DPA1	major histocompatibility complex, class II, DP alpha 1	1.4
OLR1	oxidized low density lipoprotein receptor 1	1.4
KCTD12	potassium channel tetramerization domain containing 12	1.4

Gene	Gene Description	Log2 FC
	Down Regulated	
THBS1	thrombospondin 1	-4.6
SERPINB2	serpin family B member 2	-4.3
IL1B	interleukin 1 beta	-4.3
CXCL5	C-X-C motif chemokine ligand 5	-4.1
EREG	epiregulin	-3.7
CXCL1	C-X-C motif chemokine ligand 1	-3.4
ITGB8	integrin subunit beta 8	-2.7
CCL3	C-C motif chemokine ligand 3	-2.7
SLC25A37	solute carrier family 25 member 37	-2.4
CCL3L1	C-C motif chemokine ligand 3 like 1	-2.4
CXCL8	C-X-C motif chemokine ligand 8	-2.2
CXCL2	C-X-C motif chemokine ligand 2	-2.2
NAMPT	nicotinamide phosphoribosyltransferase	-2.1



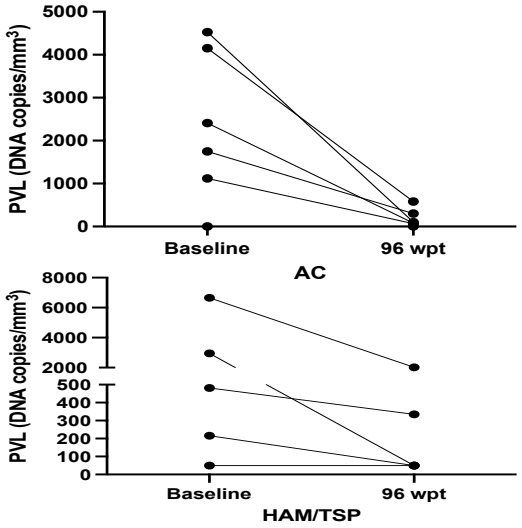
Enriched GO biological processes in monocytes DEGs

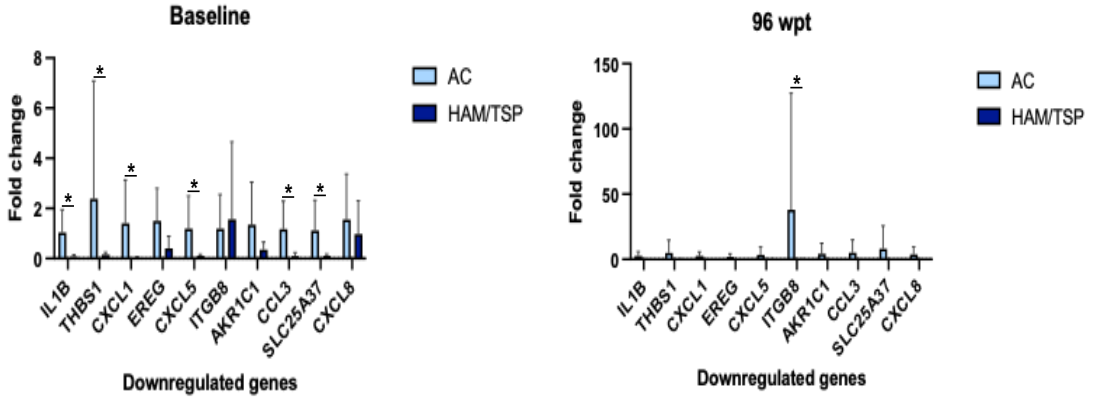


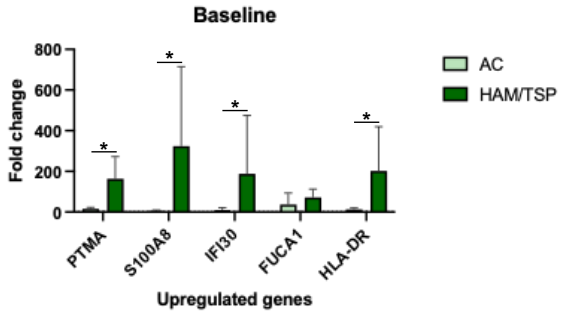
Validation of differential gene expression in monocytes from AC and HAM/TSP patients

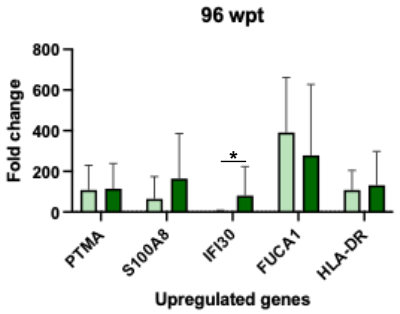
Patient ID	Infection	Group	Gender	Age
DTG-11	HTLV-1	AC	M	44
DTG-24	HTLV-1	AC	F	49
DTG-17	HTLV-1	AC	F	57
DTG-38	HTLV-1	AC	F	46
DTG-43	HTLV-1	AC	F	28
DTG-46	HTLV-1	AC	F	44
DTG-25	HTLV-1	HAM/TSP	F	47
DTG-29	HTLV-1	HAM/TSP	F	55
DTG-35	HTLV-1	HAM/TSP	F	38
DTG-58	HTLV-1	HAM/TSP	F	61
DTG-109	HTLV-1	HAM/TSP	F	59

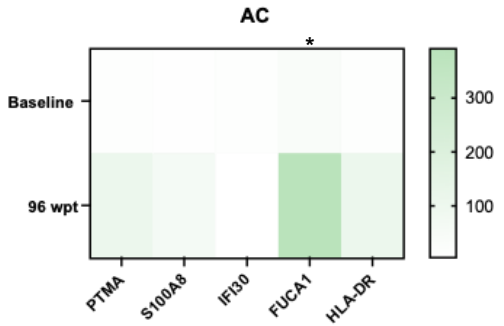
Joseph et al., Viruses, 2024

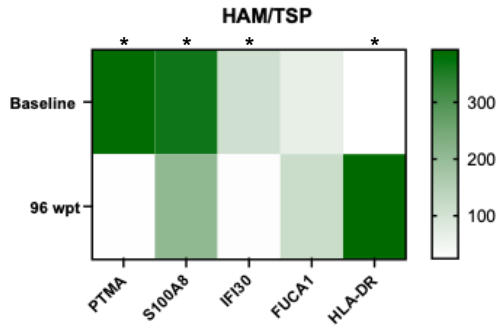


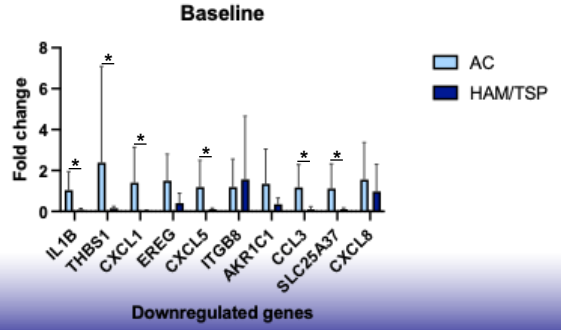


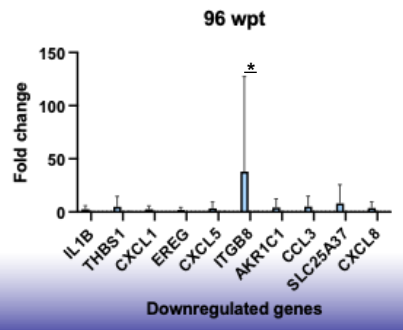


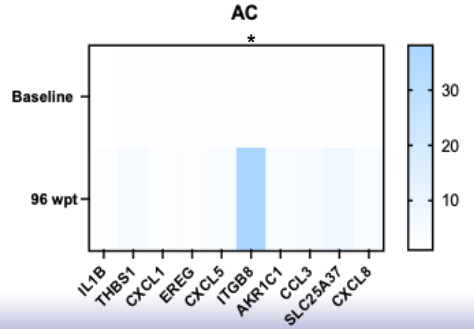


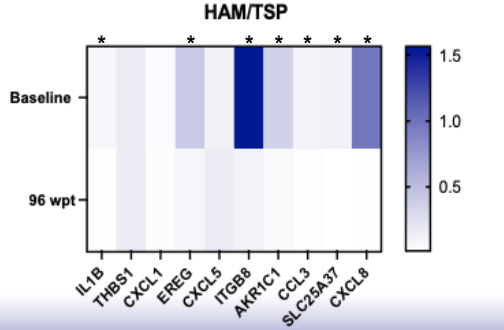




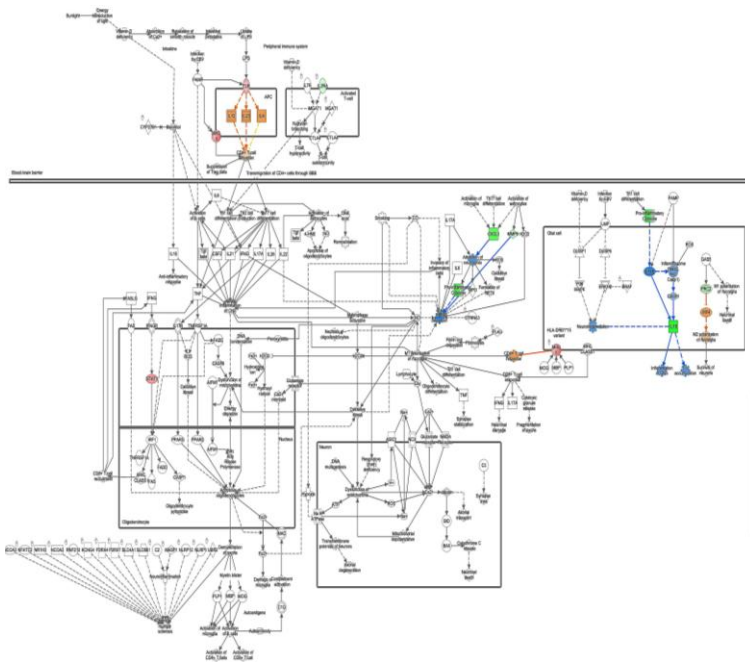




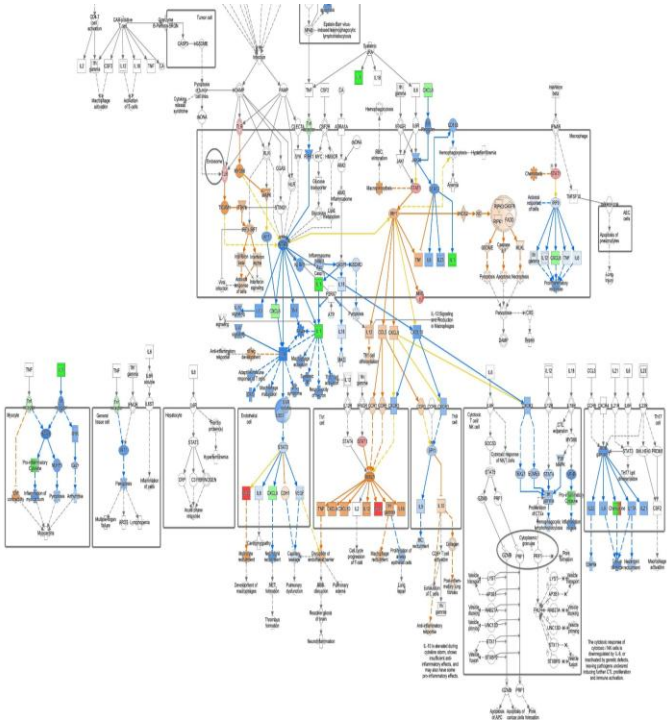




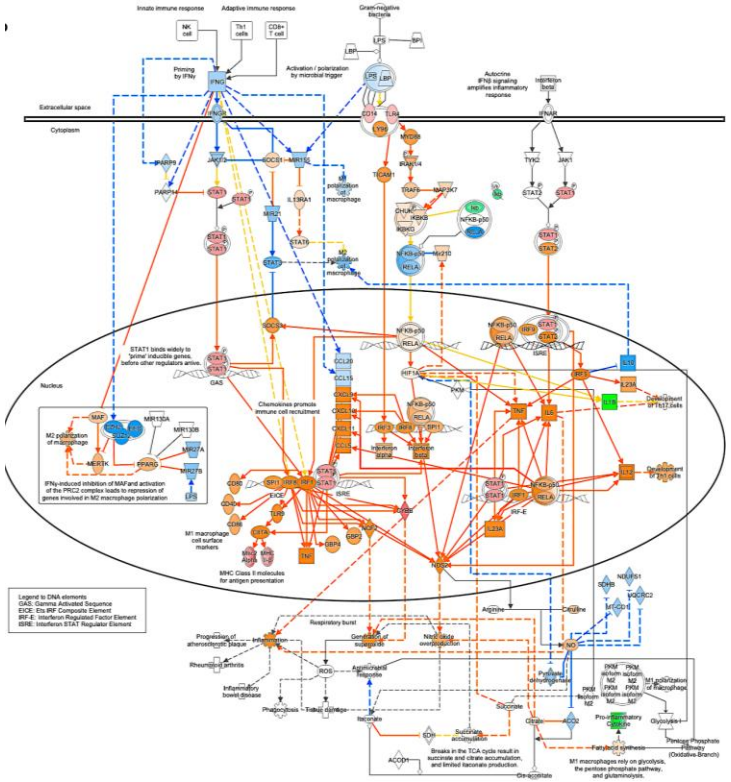
Major signaling pathways



Multiple Sclerosis Signaling Pathway



Pathogen Induced Cytokine Storm Signaling Pathway



Macrophage Classical Activation Signaling Pathway

Conclusions & Future Direction

- *Single-cell RNA-seq identified monocytes as the most transcriptionally remodeled immune compartment in HAM/TSP.*
- *Differential expression and IPA analyses support a progressive inflammatory model characterized by*
  - Macrophage classical activation
  - Cytokine amplification
  - Multiple sclerosis signaling
- *Upregulation of HLA-DRA, IFI30, PTMA, and S100A8 suggests activated APC-like inflammatory monocytes.*
- *Suppression of IL1β, CXCL1, CXCL8, and THBS1 indicates dysregulated chronic inflammatory adaptation rather than acute immune activation.*
- *Collectively, these findings support a model in which HTLV-1-driven monocyte reprogramming promotes persistent neuroinflammation and contributes to HAM/TSP pathogenesis.*
- *In the Brazil cohort, dolutegravir (DTG) is associated with PVL decline (more pronounced in AC) and attenuation of selected monocyte signature genes by ~96 weeks (qPCR).*

Road ahead……

- *Expand validation in a larger Brazil cohort with purified $CD14^+$ monocytes from AC and HAM/TSP at BL/24/48/96 weeks; retain the vitamin-C arm for contrast.*
- *Resolve monocyte subsets (classical/intermediate/nonclassical) by flow cytometry and run subset-specific qPCR panels.*
- *Track viral clonality: combine PVL with integration-site/clonal expansion analyses (e.g., ddPCR/IS-seq) to separate new infection from expansion under DTG.*

Gaekwar et al., Genes and Immunity, 2026

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22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026
June 3-6, 2026 | Philadelphia, Pennsylvania, USA

Elucidating the relationship between Neuroinflammation and Brain White Matter Lesions in HTLV-1 infection

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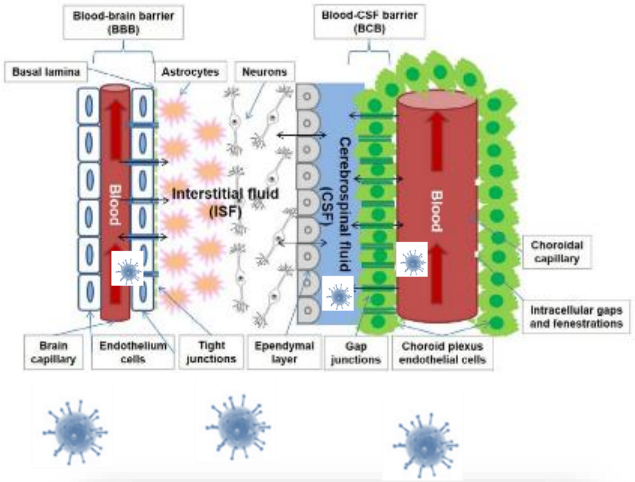
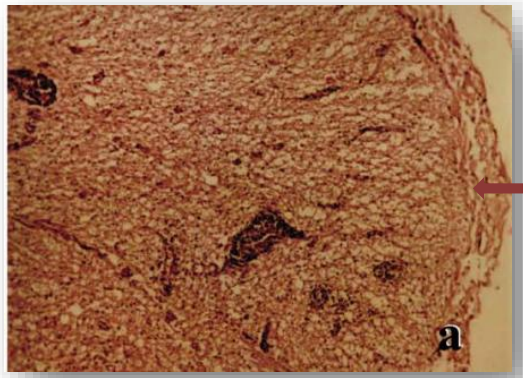
Conflicts of interest

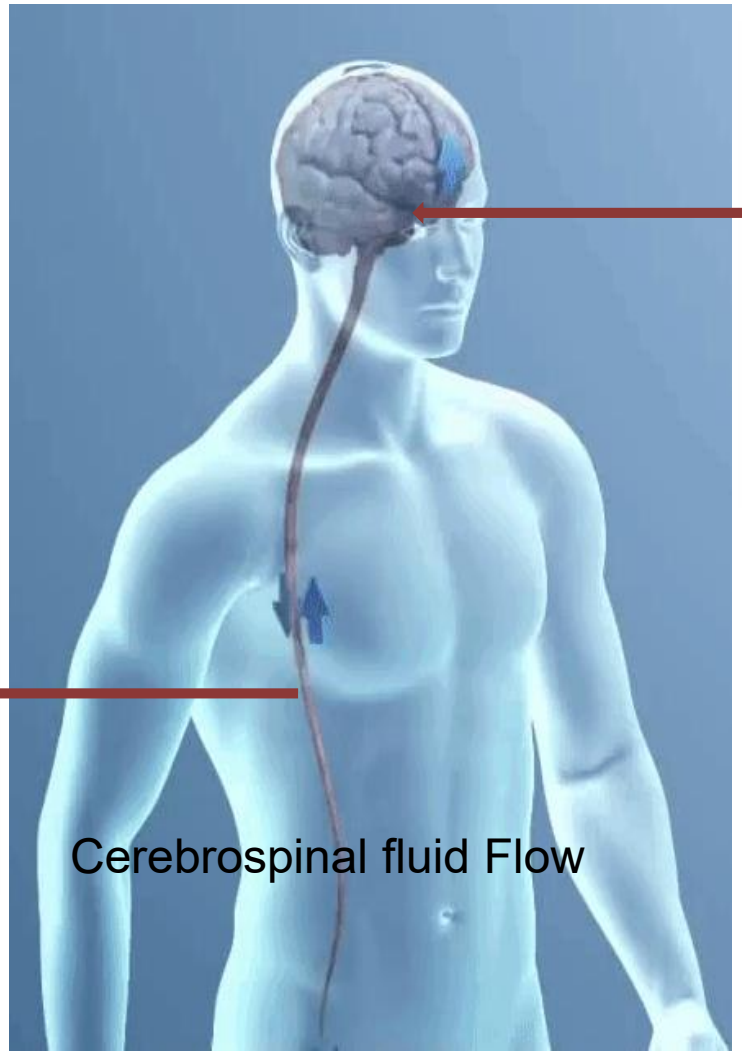
I have no conflicts of interest

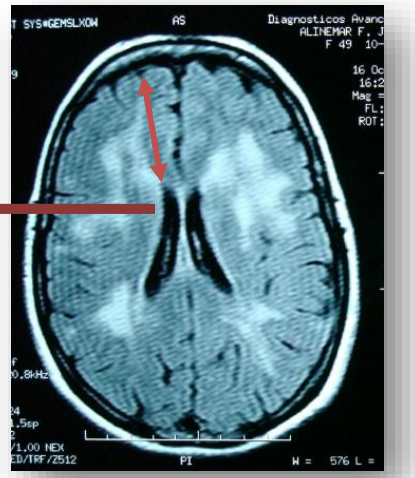
Compared to Brain, Spinal-Predominant Inflammation (HAM) in HTLV-1 Driven by CSF Dynamics and CNS Barriers





Spinal-Predominant Inflammation (HAM)





Brain MRI Lesion? T2/FLAIR hyperintensities (demyelination/ gliosis)

Felgenhauer & Beuche, 1999; Tumani et al. 2017; Puccioni-Sohler et al, 2003, 2012;

Brain Involvement in HTLV-1: From Subclinical Findings to Clinical Manifestations

Brain Damage HTLV-1

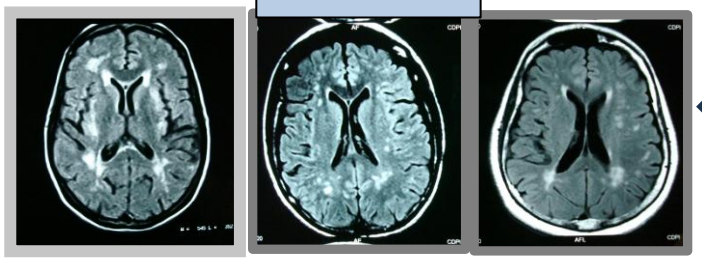
CLINICAL (rare)

- ✓ Perceived symptoms;
- ✓ Detectable on neurological examination;
- ✓ **Confirmed** by additional tests:

SUBCLINICAL

- ✓ Asymptomatic
- ✓ Detectable on neurological examination or not;
- ✓ **Detected** by additional tests:

BRAIN MRI



Puccioni-Sohler et al, 2012

- ✓ Neuropsychological tests,
- ✓ **Neuroimaging**
- ✓ Evoked potentials,
- ✓ Laboratory tests (blood, cerebrospinal fluid, etc.),
- ✓ Autopsy

DTI • "silent" axonal damage
PET*(¹¹C-PBR28)*-active microglial inflammation *(Dimber et al, 2016)*
MRI • late-stage structural lesions (demyelination/gliosis) *(Kira et al, 1988; Morgan et al 2007; Stalker et al 2024)*

Diffusion tensor image (DTI), Positron emission tomography (PET), Magnetic resonance imaging (MRI)

Elucidating the relationship between Neuroinflammation and Brain White Matter Lesions in HTLV-1 infection

Aim: To determine whether HTLV-1-associated neuroinflammation in the brain and spinal cord (HAM) shares or differs in mechanisms.

Design: Retrospective observational study, incorporating clinical, imaging, and laboratory data obtained through paired lumbar puncture and blood sample collection.

Subjects: 52 HTLV-1–infected individuals (33 HAM, 19 non-HAM) seen at University Hospital (HUGG/UNIRIO), Rio de Janeiro, Brazil.

Methods

HTLV-1 BIOMARKER PROFILE

PERIPHERAL COMPARTMENT

Systemic Viral Persistence
HTLV-1 Proviral Load in PBMC (Nagai et al, 1998);

Systemic Immune Activation (serum)
Neopterin (nmol/L)
CXCL-10 (pg/mL)

NEUROINFLAMMATION (INTRATHECAL)

Cytology and Biochemistry
Pleocytosis >4 cells/mm^3
Hyperproteinorrachia >45mg/dL
Blood-CSF Barrier (Albumin Quotient) $\geq 8x10^{-3}$

Macrophage/microglial activation
Neopterin >15 nmol/L (da Silva et al, 2025)

Intrathecal Chemotaxis
CXCL-10 >110 pg/mL(da Silva et al, 2025)
CXCL-10 CSF/serum >1

Intrathecal Antibody Synthesis
IgG Index >0.7/ IgG IF >0%
HTLV-1 Antibody index ≥ 1.5
(Reiber & Felgenhauer, 1987; Puccioni-Sohler et al, 2001)

NEUROIMAGING [redacted]

Structural Damage
Brain Magnetic Resonance Imaging - 3.0 Tesla Scanner (siemens TIM trio) - Detection of White matter Lesions (WML)

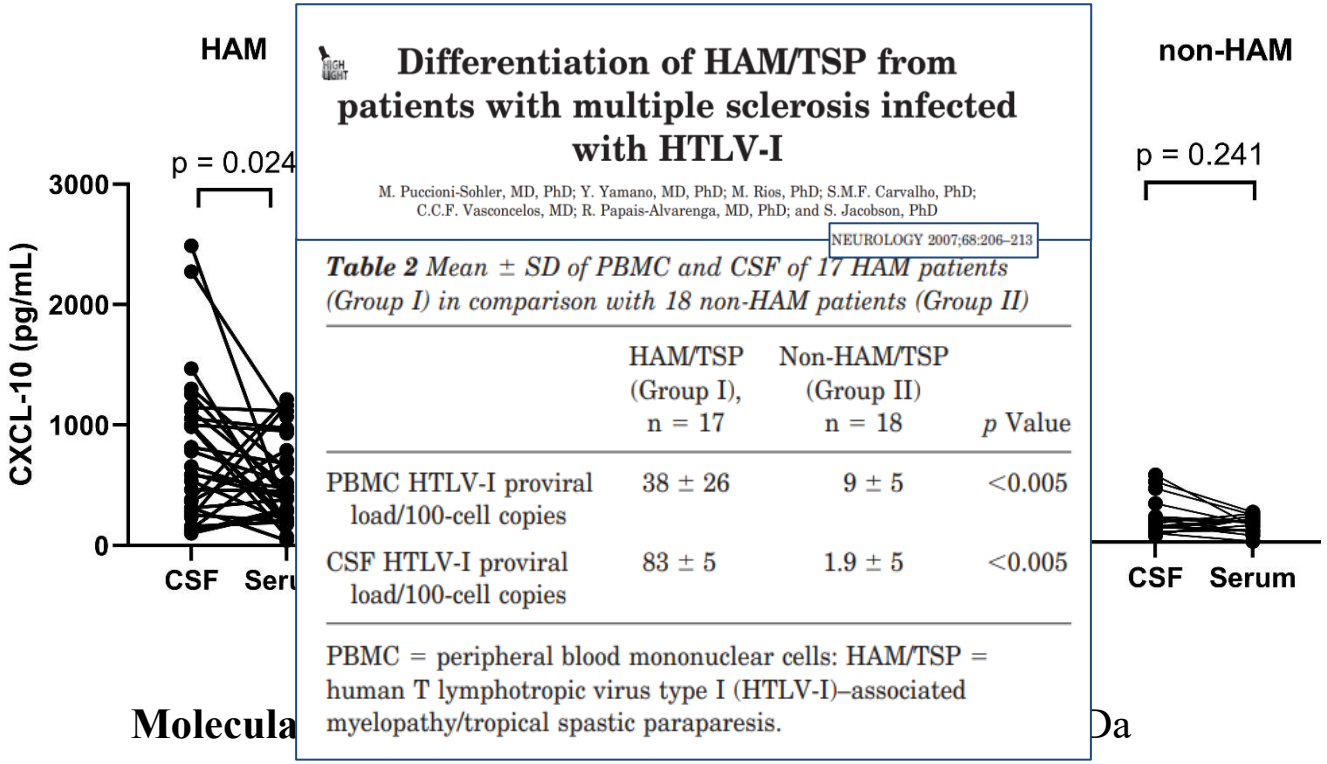
Results – Neuroinflammation in HAM vs Non-HAM

Findings	HAM (n = 33)	Non-HAM (n= 19)	p-value*
Age (yrs) mean ± SD	51.1 ± 11.4	49.9 ± 13.9	0.732
Female (%)	20/33 (60.6%)	14/20 (73.7%)	0.382
Time of Follow up	3.3 (1.7-8.6)	3.8 (2.3-6.3)	0.669
White Brain Matter Lesion in MRI (%)	19/26 (73.1%)	8/17 (47.1%)	0.084
Peripheral Blood			
HTLV-1 PVL (copies/100 PBMC)	7.6 (1.6-12.8)	0.8 (0.1-2.5)	**0.024**
Neopterin in serum (nmol/L)	9.8 (6.8-13.3)	10.6 (6.5-12.9)	0.892
CXCL-10 in serum (pg/mL)	427 (220-825)	189 (140 -345)	**0.03**
Cerebrospinal Fluid			
Cells > 4/mm^3	23/33 (69.7%)	4/19 (21.1%)	**0.001**
Protein ≥ 45mg/dL	14/33 (42.4%)	3/19 (15.8%)	0.068
Albumin quotient ≥ 8x10^{-3}	8/33 (24.2%)	2/19 (10.5%)	0.293
IgG index > 0.7	16/33 (48.5%)	4/19 (21.1%)	0.076
HTLV-1 Antibody Index ≥ 1.5	28/33 (84.8%)	10/19 (52.6%)	**0.021**
Neopterin >15 nmol/L	25/33 (75.8%)	4/19 (21.1%)	**<0.001**
CXCL-10 > 110 pg/mL	29/33 (96.7%)	14/19 (73.7%)	**0.027**

Median (75% IQR) $p < 0.05$—statistical significance

Results-Neuroinflammation in HAM vs Non-HAM - Intrathecal synthesis of neopterin and CXCL-10

Findings	HAM (n = 33)	Non-HAM (n= 19)	p-value*
Cerebrospinal Fluid/ Serum			
Neopterin Q >1	29/33 (87.9%)	13/19 (68.4%)	0.089
CXCL-10 Q >1	21/30 (70%)	10/17 (58.8%)	0.535



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

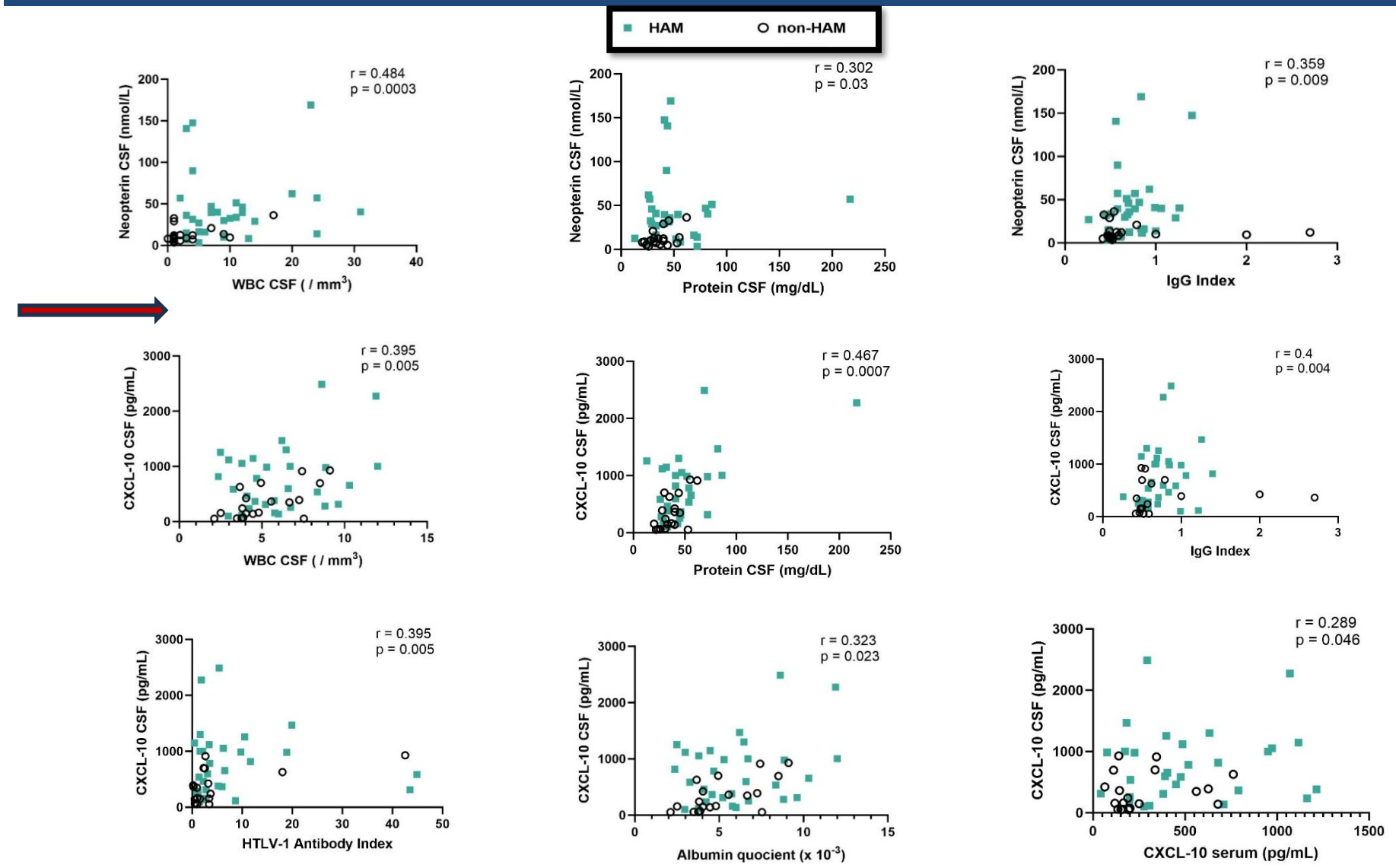
Table 2 *Mean ± SD of PBMC and CSF of 17 HAM patients (Group I) in comparison with 18 non-HAM patients (Group II)*

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

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

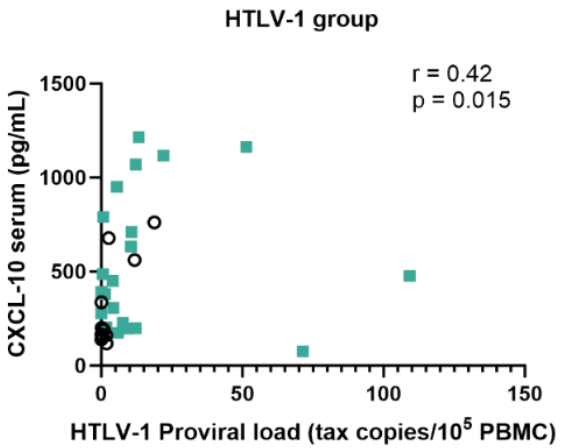
Paired comparisons were performed using the Wilcoxon signed-rank test. $p < 0.05$—statistical significance

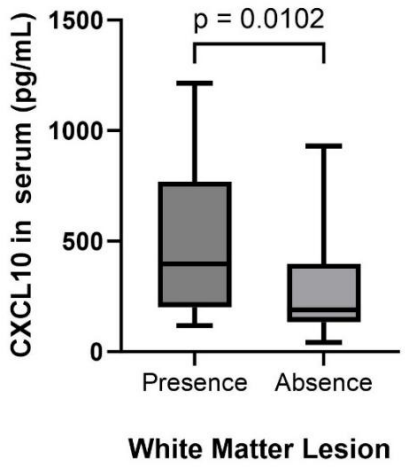
Results - Interconnected Intrathecal Inflammatory Networks in HTLV-1 Infection (n=52)

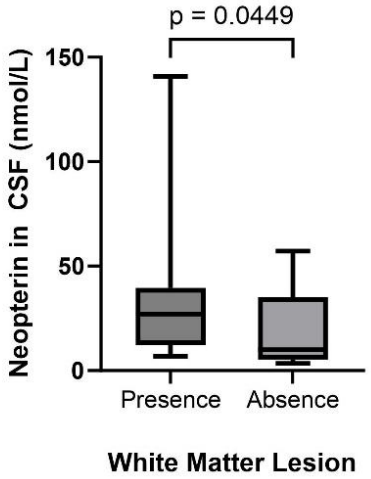


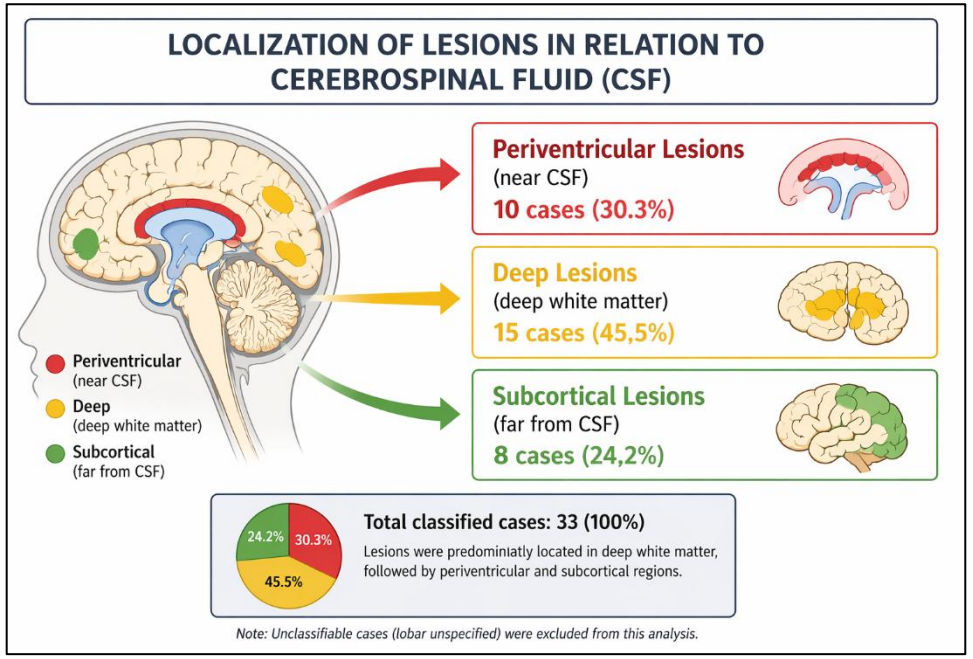
Spearman correlation test (r). P value < 0.05 for statistical significance

Results - Brain Involvement in HTLV-1: Beyond Spinal Cord Disease



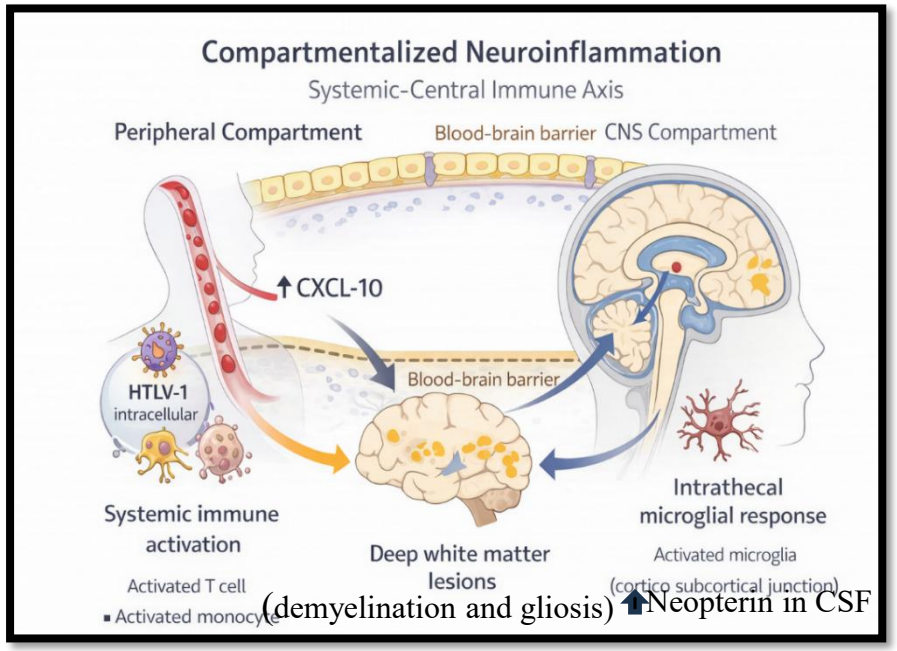






Conclusion:

- High Peripheral PVL: viral reservoir that sustains and fuels systemic and CNS immune activation;
- Peripheral high proviral load **increases** serum CXCL-10, **promoting migration** of infected T cells into the brain;
- In the brain: chronic inflammation with structural damage by macrophage/microglial activation, as measured by neopterin in the CSF ⟹ demyelination and gliosis.
- Compared with HAM, brain lesions show a more compartmentalized inflammatory profile, suggesting predominantly microglia/macrophage-driven CNS injury.



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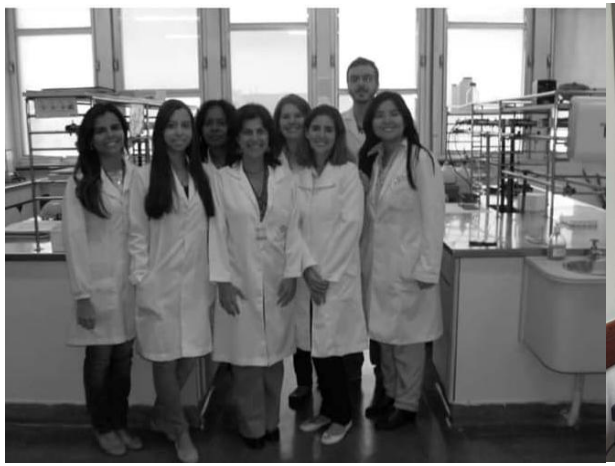

22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
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HTLV-1 associated myositis: A case series

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HTLV-1 Associated Myositis: A Case Series

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Neurological Associations With HTLV-1

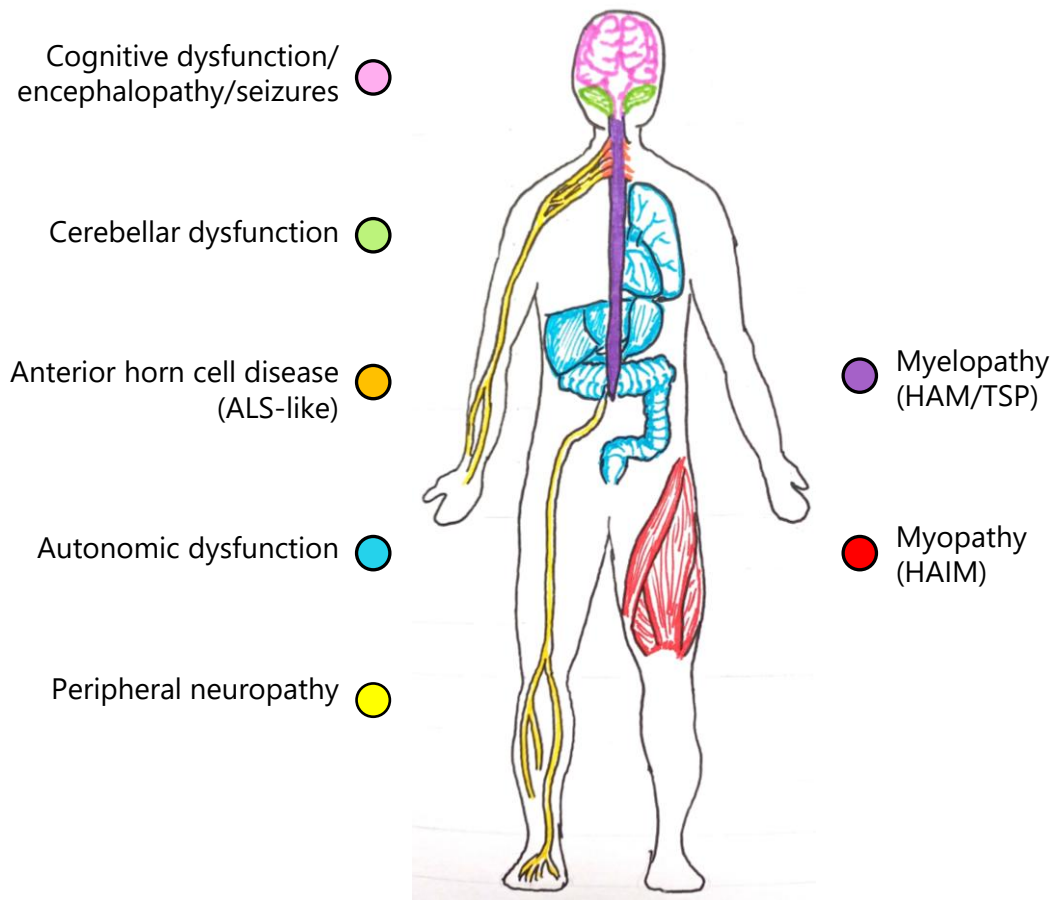
HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) affects up to 5% of HTLV-1 patients

Other neurological manifestations are reported infrequently but consistently

The concept of an **HTLV-1 neurological complex** was first proposed by Araujo and Silva in 2006 as "*a spectrum of disease beyond classical myelopathy*"

Current understanding in HTLV-1-associated myopathy (HAIM)

- 1989 – The first association between muscle inflammation and HTLV-1 is observed in Jamaica 11/13 (85%) patients with polymyositis were found to be HTLV-1 seropositive (Morgan et al,1989)
- Associated with polymyositis and inclusion body myositis phenotypes, with axial myopathies also recognised
- "Bystander damage model" - Muscle inflammation is not due to direct, persistent infection of the muscle fibre, but to a T-cell-mediated immunological process (Higuchi et al, 1995)
- Estimated HAIM prevalence of 0.6% in a 503-patient cohort in Brazil (Viriato et al, 2025)



Our Study

Aims

- Describe the **clinical phenotype** of patients with HTLV-1-associated muscle inflammation
- Investigate for **biochemical**, **radiological**, and **histopathological** commonalities
- Report **treatment choices** and **outcomes**

Methods

- Retrospective medical records review
- **8 patients** identified through unexplained myopathy or elevated creatine kinase
- From a cohort of 1,086 patients within **The National Centre for Human Retrovirology (UK)**

Patient Demographics

n= 8

Median age of symptom onset

- 59 (24 – 68)

Median age at HTLV diagnosis

- 66 (24 – 72)

Sex

- Female 6 : Male 2

Ethnicity

- Black Caribbean 6
- Mixed race (Black Caribbean/White British) 1
- Unknown 1

Region of birth

- Caribbean 6
- UK 2

Comorbidities (n)	
Malignancy (prostate, breast, oesophageal x2)	4
Hypertension	3
Thyroid disease	3
Diabetes	2
Hepatic disease	2
Respiratory disease	2
Rheumatological disease	2
Psychiatric disease	2
Cardiac disease	1
Obesity	1
Statin use	0

Concomitant HTLV-associated disease	
HAM/TSP	3
ATLL	0

History and Clinical Examination

Presenting symptoms (n=8)	At onset	At follow up
Impaired mobility (requiring walking aid)	4	5
Difficulty with stairs	4	4
Falls	2	3
Myalgia	2	3
Dysphagia	1	4
Exertional dyspnoea	2	3

Examination (n=8)	At onset	At follow up
Lower limb weakness only	4	4
Upper and lower limb weakness	4	4
Upper limb weakness only	0	0
Proximal weakness only	8	6
Proximal and distal weakness	0	2
Symmetrical weakness	3	3
Asymmetrical weakness	5	5
Facial weakness	0	1
Neck weakness	0	1

Key findings:

- Distribution of weakness was predominantly **proximal, lower limb and asymmetrical**
- We did not observe isolated upper limb weakness
- **Pain was not a predominant feature** - 25% reported myalgia at presentation

Initial Investigations

Creatine kinase

- Mean at presentation: **996 U/L** (336 - 1989)
- Mean peak: **1313 U/L** (444 - 3441)

Myositis autoantibodies*

- All negative (n=5)

ANA**

- All negative (n=7)

HMG-CoA reductase

- All negative (n=3)

EMG (n = 3)

- 1 patient had changes suggestive of a primary myopathy with:
  - Fibrillation potentials
  - Motor units showed simple waveforms of short duration and amplitude
- 2 patients had neurogenic changes in keeping with anterior horn cell loss/HAM

*Ro-52, OJ, EJ, PL-12, PL-7, SRP, Jo-1, PM-Scl75, PM Scl 100, Ku, Mi-2

** U1RNP(RNP 70, A, C) , Sm proteins, Ro60, Ro52, La, Scl-70, Jo-1, Centromere B, Fibrillarin, RNA Pol III, Rib-P, PM-Scl, PCNA, Mi-2 proteins, dsDNA

Inflammatory Phenotype

Criteria for inflammatory phenotype:

- Proviral load **>2.1%**
- β2 microglobulin **>1.7%**
- CD4+CD25+ **>35%**
- CD4+HLADR+ **>15%**
- CD8+CD25+ **>5%**
- CD8+HLADR+ **>19%**

Proviral load (n = 8)

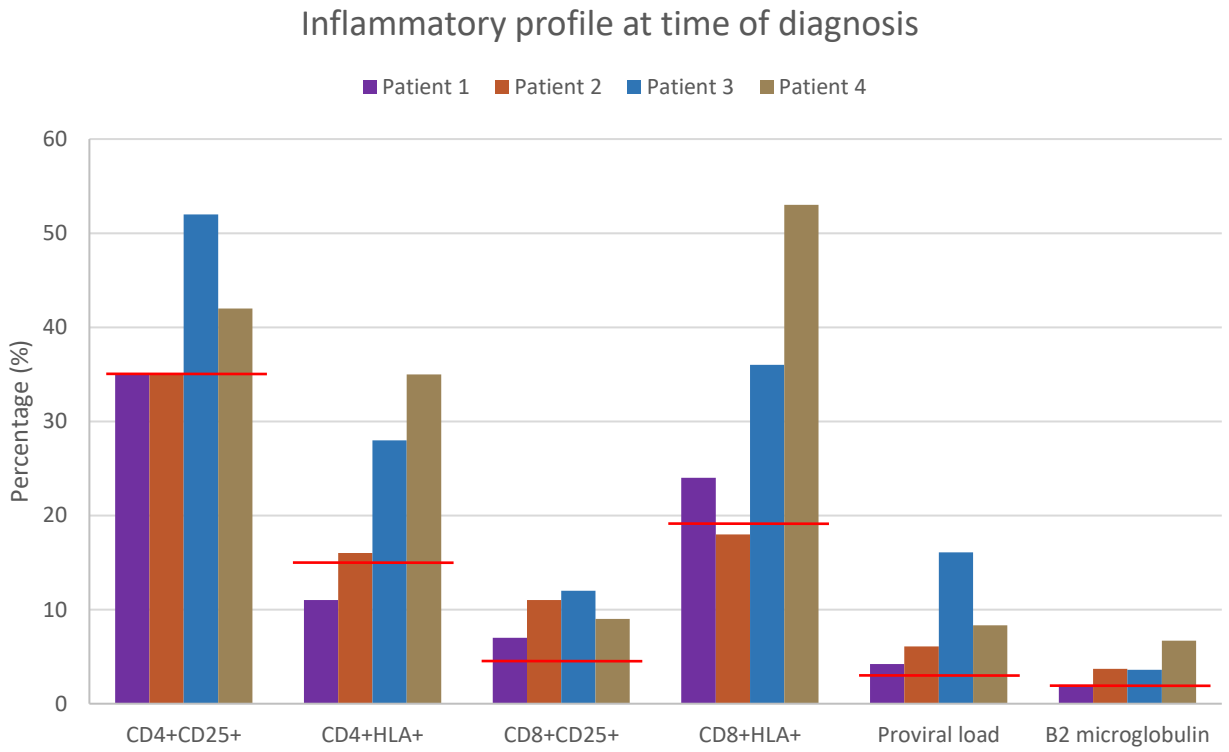
- Median at diagnosis: 6.1 copies/100 PBMCs (range 2.3 - 39.9)

β2 microglobulin (n = 6)

- Mean at diagnosis: 3.4 ml/L (range 2.0 - 6.7)

HAM inflammatory phenotype

- 4 patients had T-cell activation markers measured at presentation
- **2 of 4 (50%) met criteria for HAM inflammatory phenotype**



Specialist Investigations

MRI		
Thigh MRI (n=4)	Anterior compartment involvement	4
	Posterior compartment involvement	3
	Muscle oedema	3
Lower leg MRI (n=2)	Gastrocnemius involvement	2
Upper limb MRI (n=2)	Proximal fatty infiltration	1
	Distal involvement	0
Spinal MRI* (n=4)	Paraspinal muscle oedema	1
	Paraspinal fatty atrophy in the absence of HAM/TSP	1

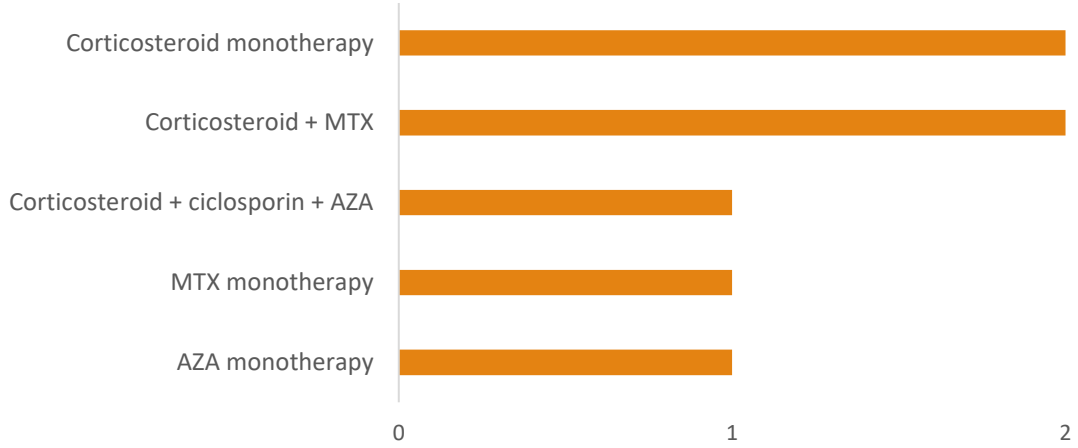
*In patients with additional muscle imaging

Muscle biopsy (n=5)	
Inflammatory features	4 (80%)
Mitochondrial dysfunction	2 (40%)
Meeting criteria for inclusion body myositis (IBM)	2 (40%)
Neurogenic features	2 (40%)

Histopathological features by patient **Patients with concomitant HAM/TSP

Patient #	Inflammatory features	Mitochondrial dysfunction	Meets criteria for IBM	Neurogenic
1	Yes	No	No	No
2**	Yes	Yes	No	Yes
3	Yes	No	Yes	No
4	Yes	No	Yes	No
5**	No	Yes	No	Yes

Treatment



Medication dosing

Corticosteroids:

- 3 patients received a single course of IV methylprednisolone
- 2 patients received high-dose oral prednisolone

Methotrexate maintenance dosing 12.5 - 17.5mg weekly (n=3)

Azathioprine maintenance dosing 75mg BD (n=2)

Ciclosporin dosing 2.5mg/kg BD (n=1)

- 7 of 8 patients received immunosuppressive treatment
- **Biochemical improvement in CK** (>30% reduction over three months) **observed in 4 patients following treatment**
- **6 patients reported early symptomatic improvement**
- **1 patient reported sustained symptomatic benefit** past 12 months*
- 3 patients reported continued functional decline despite treatment*
- No observed improvement in timed walk testing*

*excluding patients with concurrent TSP/HAM

Patient A

73M, Black Caribbean origin

Unable to run

Diagnosed with HTLV
- CK 1998 U/L
- Proviral load 6.1 copies/100 PBMCs

Prednisolone 50mg OD
- CK improved from 1989 -> 95
- Transient symptomatic improvement

Outcome
- Improved proximal weakness on examination
- Subjective improvement in mobility

Age 62

Age 68

Age 69

Age 71

Age 72

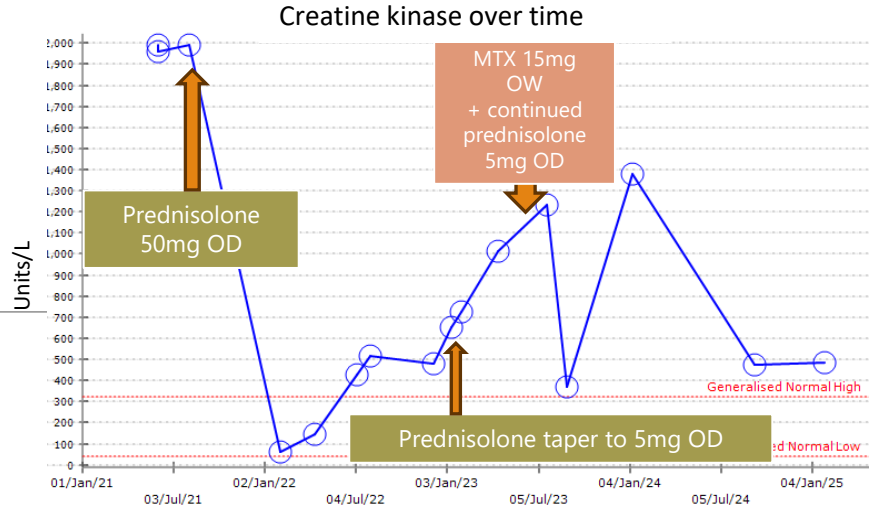
Walking with stick

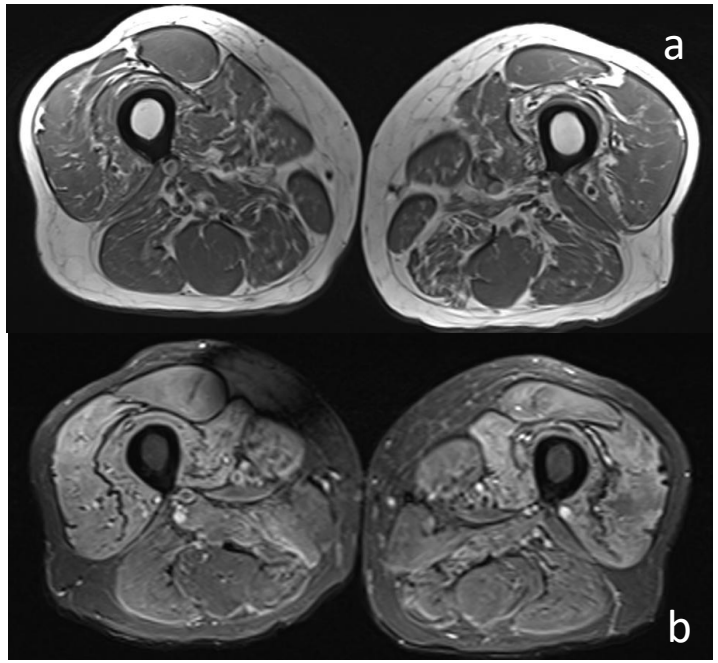
Unable to climb stairs

MRI thigh
- Anterior and posterior compartment involvement

Muscle biopsy
- IBM histotype

MTX 17.5mg once weekly
- with continuing 5mg prednisolone





(a) Axial T1 images show mild symmetrical fatty atrophy in the anterior and posterior compartments, relative sparing of semitendinosus, rectus femoris and adductors.
(b) Axial STIR images show symmetrical muscle oedema in the anterior and posterior compartments, more prominent in the anterior compartments.

Patient B

67F, Black Caribbean origin

Reduced mobility, using walking stick

Difficulty with stairs

Falls

Proximal LL myalgia

Diagnosed with HTLV-1 associated myelopathy (TSP)

Treatment

- IVMP followed by methotrexate

Age 56

Age 66

Age 67

Diagnosed with HTLV

- Peak CK 486 U/L
- Proviral load 16.1 copies/100 PBMCs

MRI thigh

- Fatty infiltration and oedema

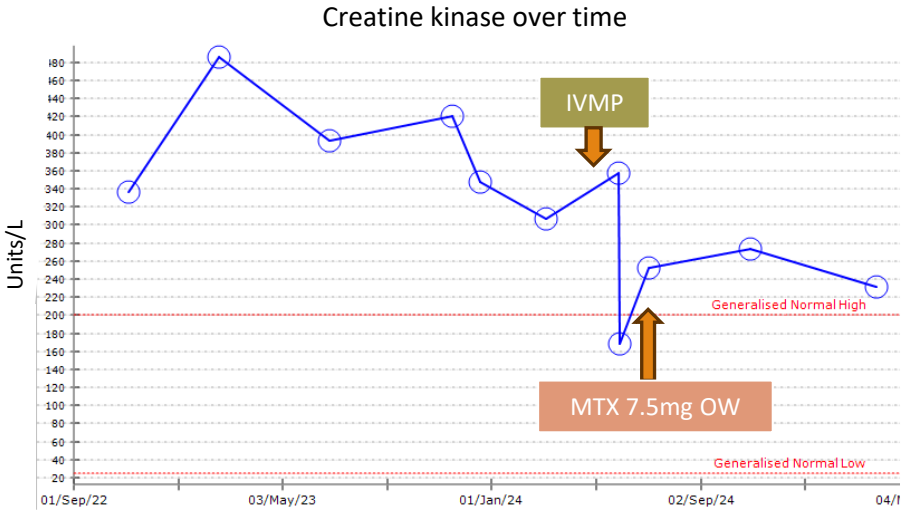
Muscle biopsy

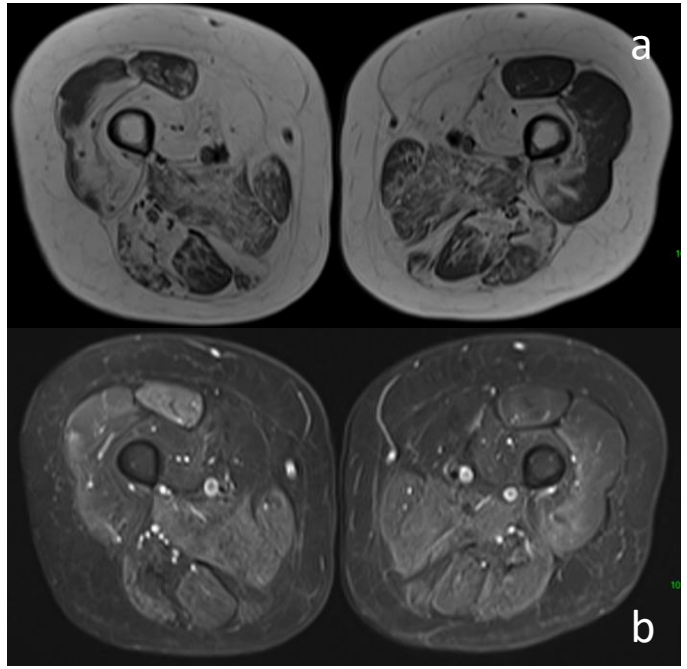
- Inflammatory features, mitochondrial dysfunction, neurogenic change

Subjective improvement in mobility

Objective improvement in sit-to-stand

CK response to treatment





(a) Axial T1 shows symmetrical and advance fatty infiltration of the quadriceps (most pronounced in the medial Vasti, with patchy changes in the adductors and hamstrings
(b) Axial STIR demonstrates minor muscle oedema in the right vastus lateralis, rectus femoris. On the left there is mild oedema in Vastus lateralis.

What Our Study Adds

1. Clinical phenotype
   - Progressive gait impairment in keeping with myopathic disease may be the presenting feature
   - Median age of symptom onset was 59 years
   - Muscle weakness is typically proximal, lower limb, and asymmetrical
   - Myalgia may be present, but is not a dominant feature
2. Biochemical investigation
   - Serum creatine kinase (CK) is likely to be high at presentation, but may be within normal range
   - T cell activation markers, β2 microglobulin, and PVL may be in keeping with inflammatory phenotypes seen in HAM/TSP
3. Radiological investigation
   - Inflammatory muscle changes (oedema, fatty infiltration) are typically seen on MRI
   - Paraspinal muscle involvement may be seen on spinal MRI
4. Biopsy
   - Histopathological phenotype may be variable, demonstrating features of inflammation, mitochondrial dysfunction or IBM
5. Management
   - Immunosuppressive treatment may lead to both symptomatic and biochemical (CK) improvement

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LONDON, UNITED KINGDOM

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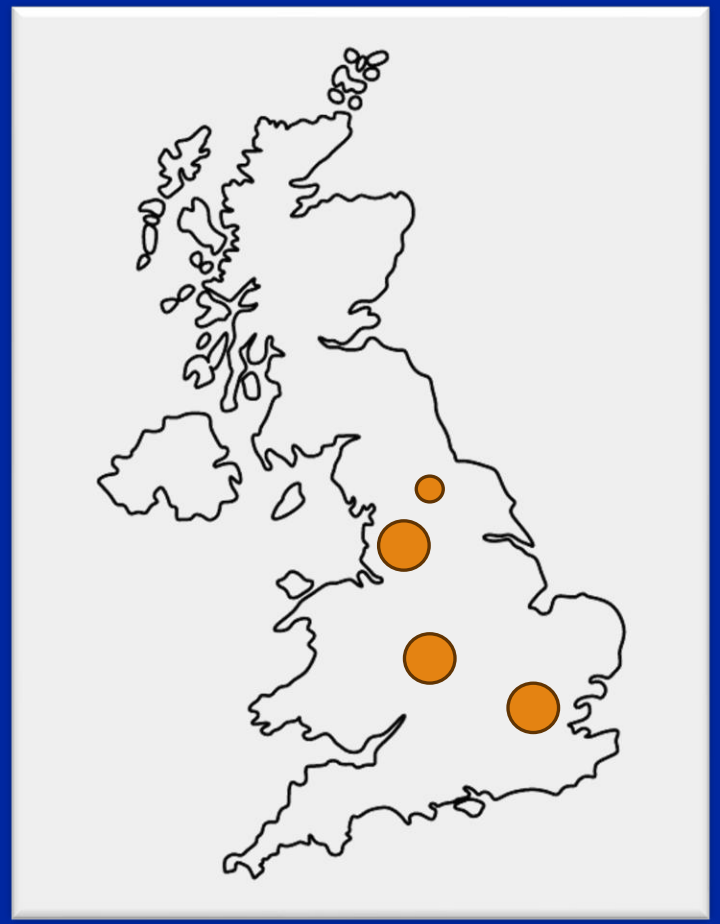
Services for HTLV-1 in England, Wales and NI are provided by three hospitals in England.

The lead service is provided at **St Mary's Hospital** (Imperial College Healthcare NHS Trust)

Satellite clinics:

- Queen Elizabeth Hospital (University Hospitals **Birmingham** NHS Foundation Trust)
- North **Manchester** General Hospital (The Pennine Acute Hospitals NHS Trust)
- **Community clinic in York** (York Teaching Hospital NHS Foundation Trust).



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22nd International Conference on Human Retrovirology:
HTLV and Related Retroviruses
HTLV2026

June 3-6, 2026 | Philadelphia, Pennsylvania, USA

HTLV-1c infection and pulmonary disease is defined by chronic T-cell activation and high expression of TIM-3

Ashley Hirons

Doherty Institute, University of Melbourne

Conflicts of interest:

I have no conflicts of interest

HTLV-1 subtype-C is commonly associated with pulmonary disease (HAPD)

Subtype-C is endemic in Central Australia

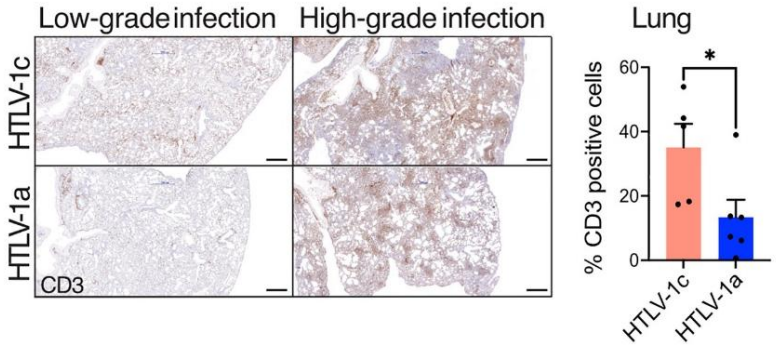
Highest adult prevalence rates worldwide

Propensity of subtype-C to mediate pulmonary disease in vivo

-human infection (Einsiedel et al.)

-macaque model (Sarkis et al.)

-humanised mouse model (Cooney et al.)



Cooney, Hirons et al., *Cell*, 2025

HAPD encompasses bronchiectasis, bronchiolitis, chronic obstructive pulmonary disease

Determine the **host immune response** to subtype-C infection and features that mediate HAPD

- Cytokine profile
- Antigen specific T-cell responses
- T-cell phenotypes
- Associated plasma biomarkers

Investigating plasma cytokine profile in HTLV-1c infection

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Investigating plasma cytokine profile in HTLV-1c infection

Subtype-A

HAM – pro-inflammatory signature

Higher TNF-α, IFN-γ, IL-4, IL-6, IL-8 in plasma

(Muniz et al. 2006, Starling et al. 2013, Hanon et al. 2001)

Higher CXCL10, CXCL9, Lower MCP-1 in CSF

(Neco et al 2017, Guerreiro at al. 2006, Sato et al 2013)

ATL – immunosuppressive signature

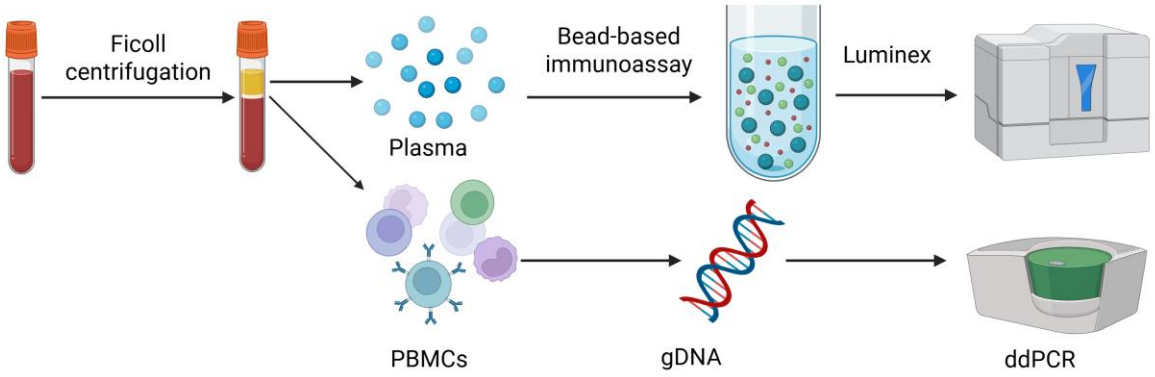
Higher IL-10, IL-6, TGF-β, Lower IFN-γ

(Mori et al. 1996, Yamamura et al. 1998, Niitsu et al. 1988, Tendler at al. 1991)

Subtype-C

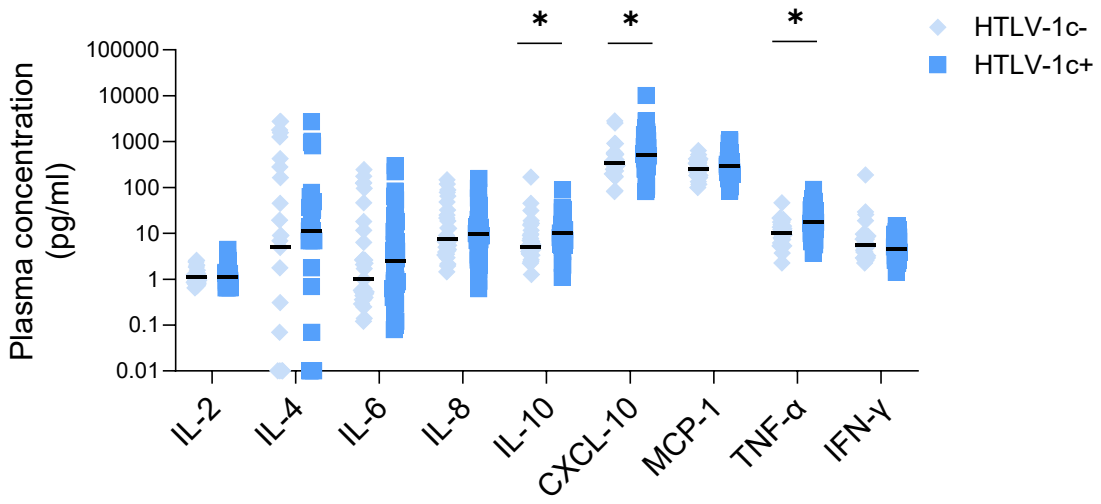
Matching plasma and PBMC
From Alice Springs Hospital in Central Australia
n=77; HTLV-1c- (33) , HTLV-1c+ (44)

Measured IL-2, IL-4, IL-6, IL-8, IL-10, CXCL-10, MCP-1, TNF-α, IFN-γ



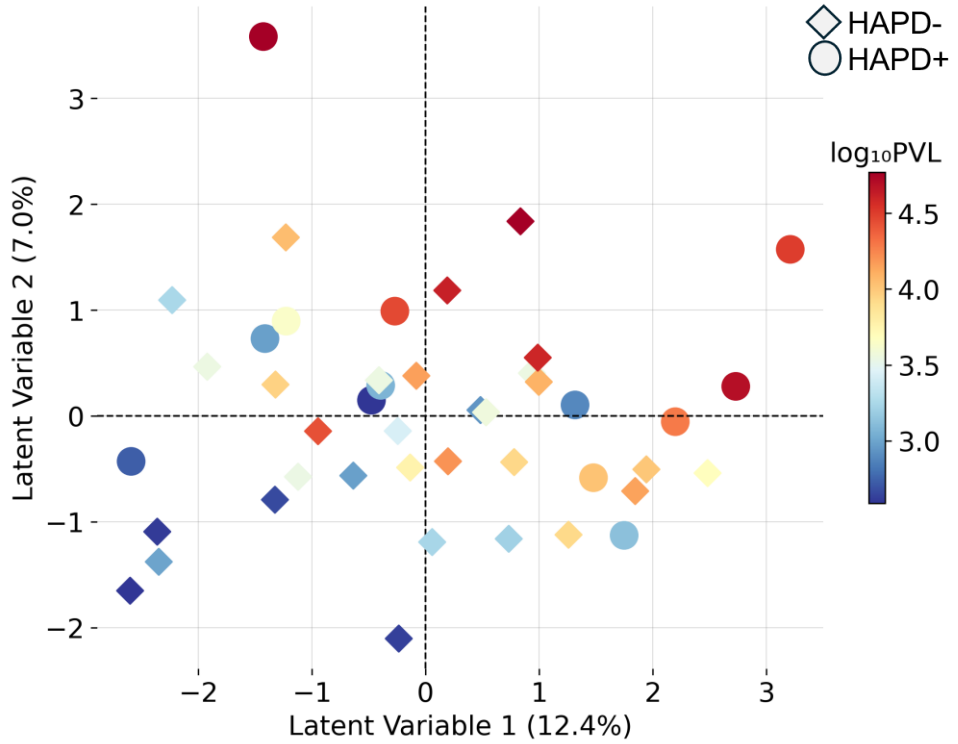
Juxtaposed inflammatory and immunomodulatory cytokine signature in subtype-C infection

Cytokine signature of HTLV-1c infection



Logistic regression Outcome = HTLV-1c infection		
Variable	*Association*	*p-value*
IL-2	Positive	**0.013**
IL-8	Negative	**0.014**
TNF-α	Positive	**0.017**
IFN-γ	Negative	**0.004**
Age	Positive	**0.036**

Multivariable analysis (PLS-DA) of HTLV-1c+ donors



No separation by HAPD status
PVL is associated with overall cytokine signature

Investigating HTLV-1c-specific T-cell responses

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Investigating HTLV-1c-specific T-cell responses

Subtype-A

CD4 T-cells show Th1 phenotype (Goon et al 2002)

- Ag-specific CD4 produce higher IFN-γ and IL-2 in HAM (Goon et al, 2004)

Immunodominant antigens

- Env CD4 (Goon et al 2002, 2004)
- Tax CD8 (Goon et al 2004, Kubota et al 2000)

Magnitude of HTLV-1-specific CD8 response correlates to PVL (Kubota et al, 2000)

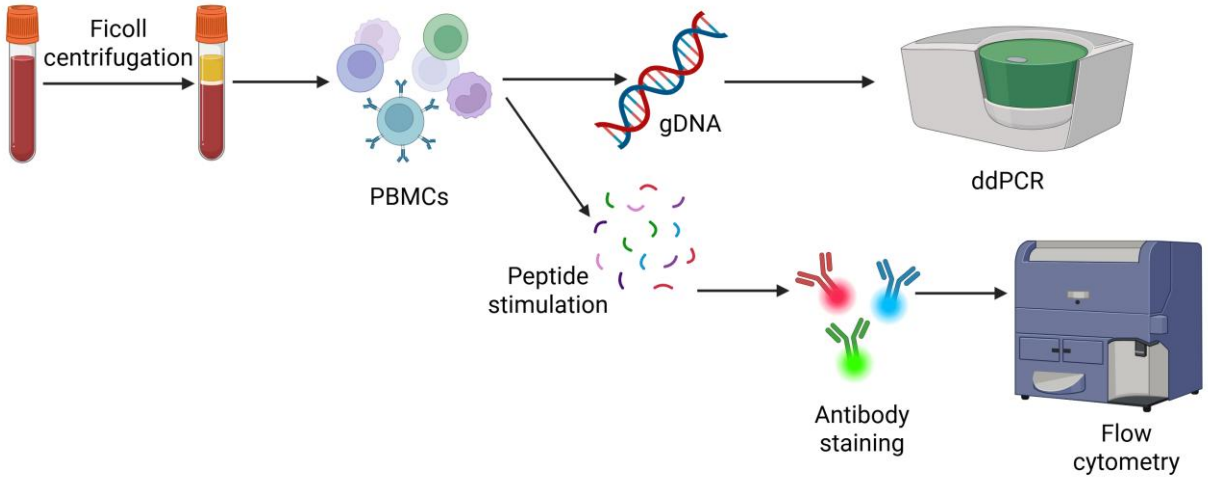
HAM and ATL: reduced CTL functionality compared to ACs (Sabouri et al 2008, Bangham 2008, Kozako et al., 2007, Takamori et al. 2011)

Subtype-C

Investigate the response to Env, Tax, HBZ

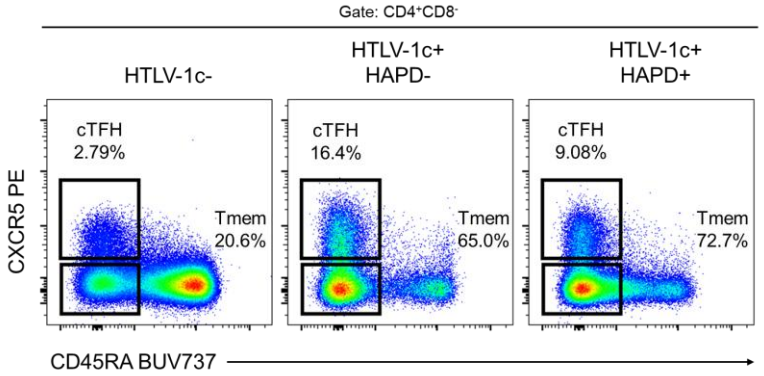
T-cell phenotypes: CD4+ cTFH, Tmem (Th1, Th2, Th17, Th1/17), CD8+

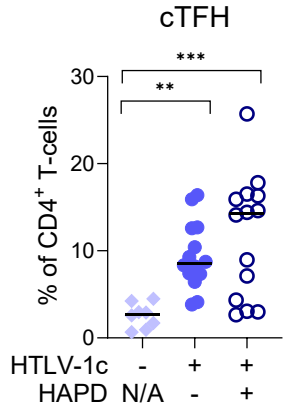
n=36, (8 HTLV-1c-, 28 HTLV-1c+) from Central Australia



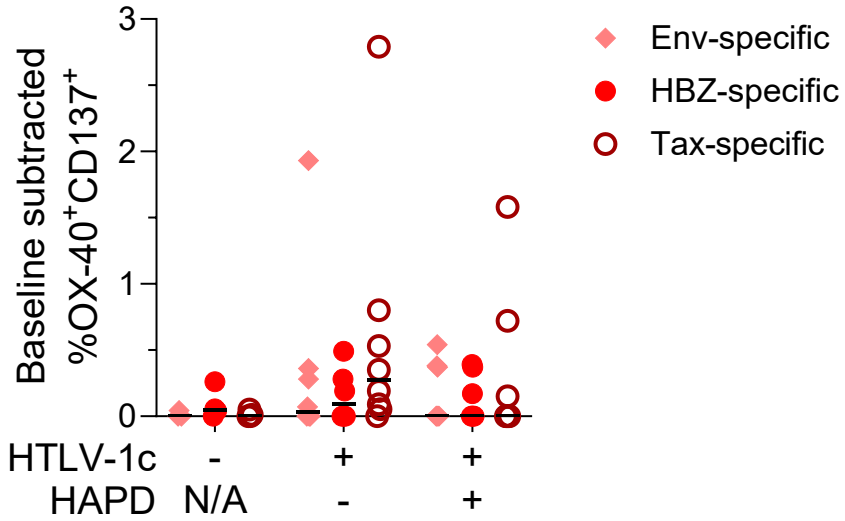
Tax-specific cTFH detected less frequently in HAPD+ donors

Expansion of cTFH cells

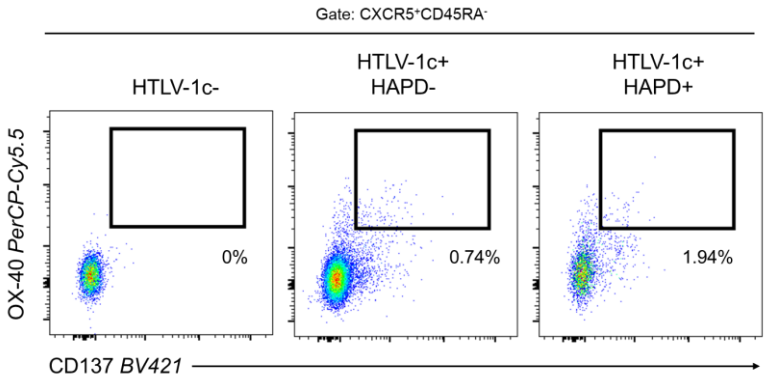


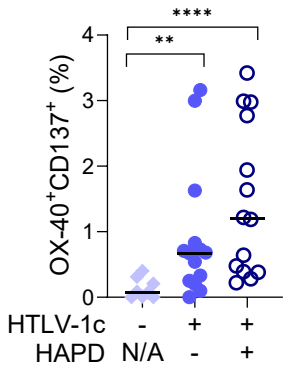


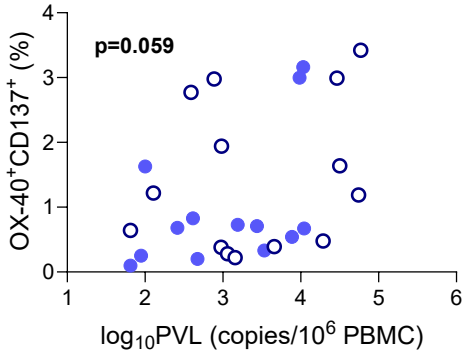
HTLV-1c-specific cTFH cells



High baseline cTFH activation



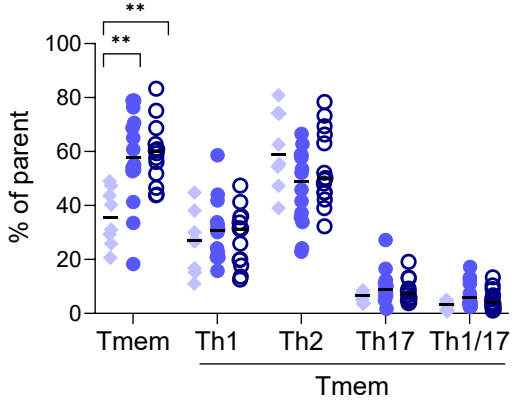


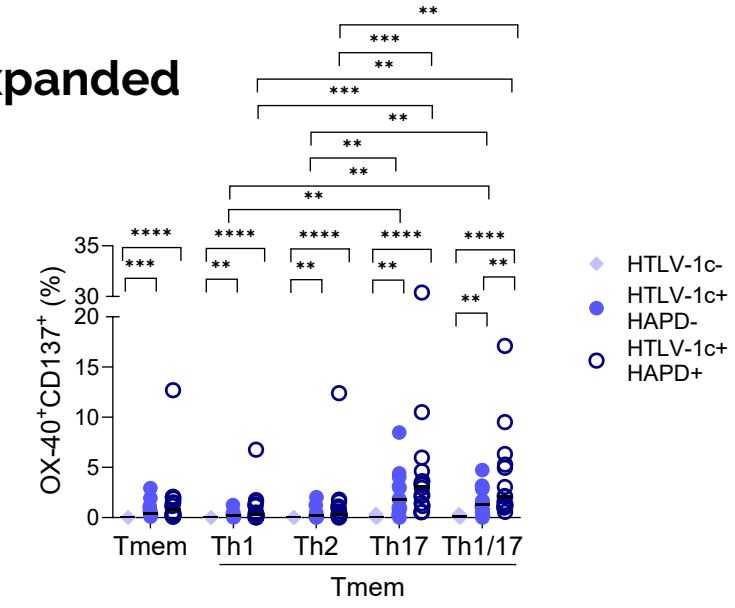


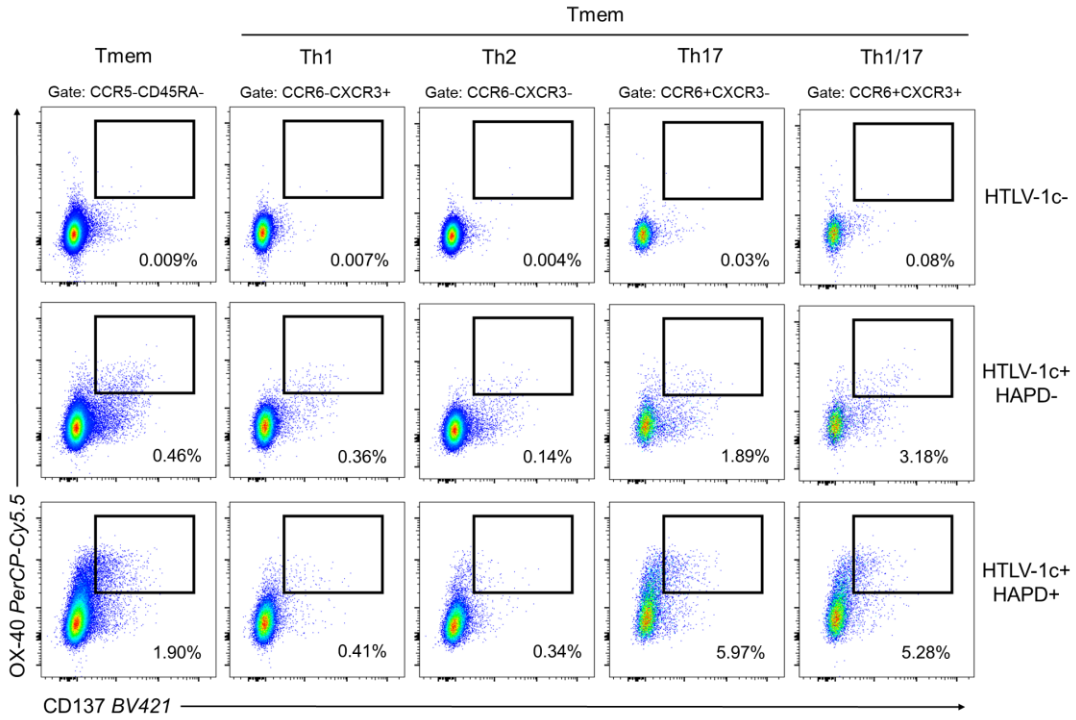
Increased Tax and HBZ cTFH responses in HAPD- donors

CD4⁺ Tmem baseline activation strongly correlates to PVL in HTLV-1c infection

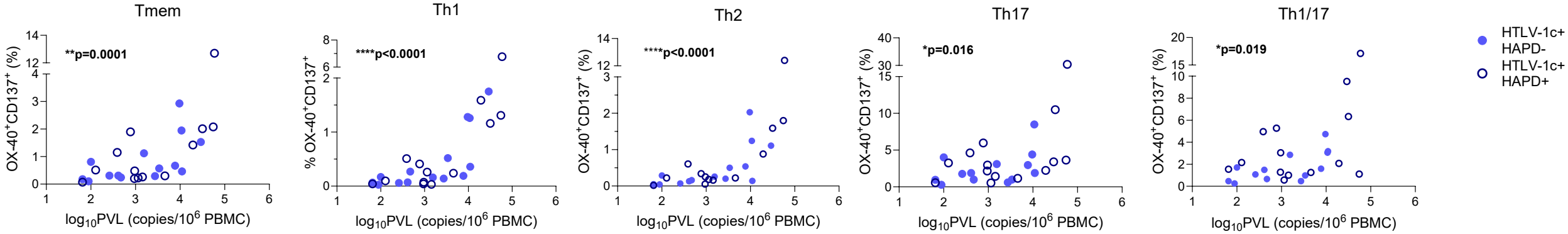
Memory T (Tmem) cells expanded and highly activated



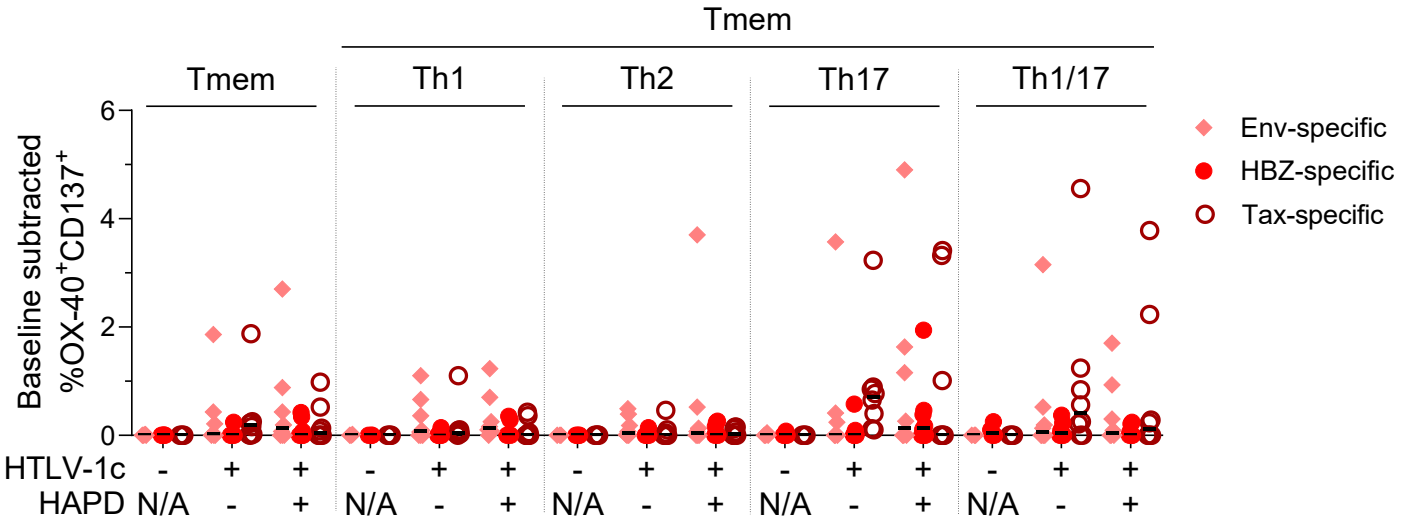




Tmem activation correlates with PVL



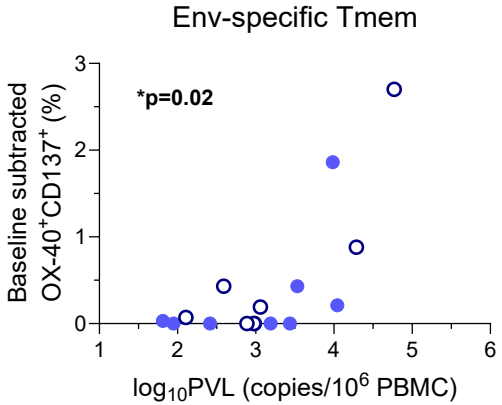
Envelope-specific CD4⁺ Th response strongly correlates to PVL in HTLV-1c infection

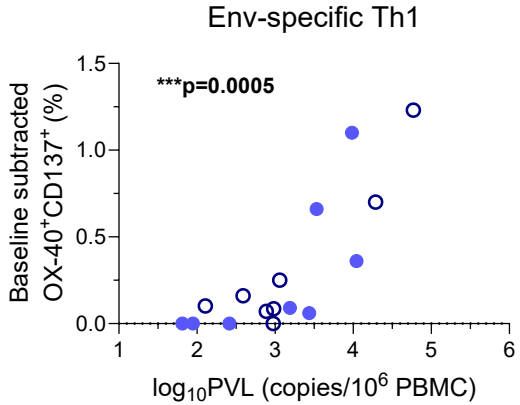


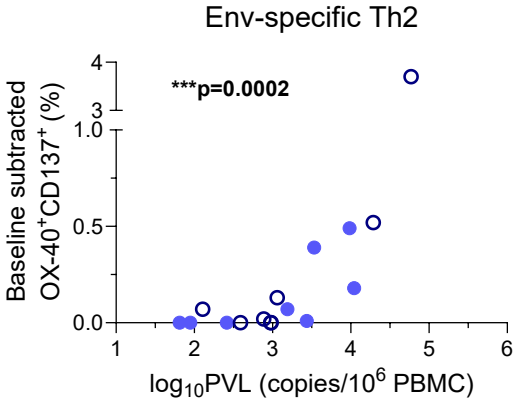
Immunodominant antigens:
Env – Th1
Tax – Th17, Th1/17

Association with pulmonary disease:
Env-response higher in HAPD+
Tax-response higher in HAPD-

Env-Th cells correlate with PVL

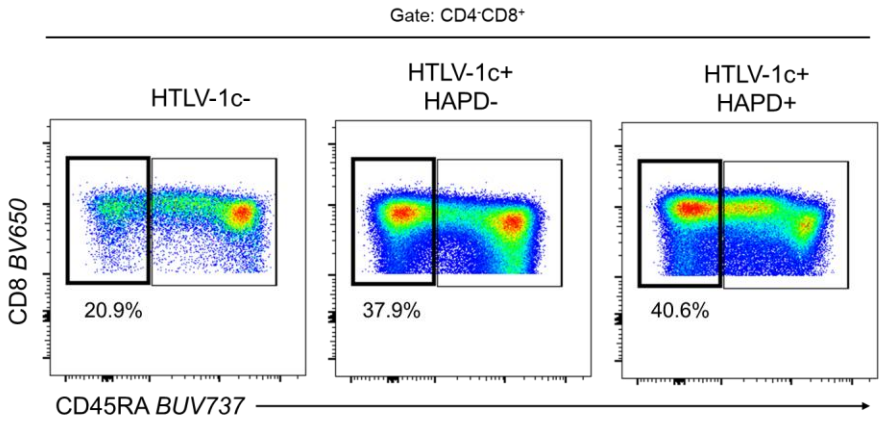


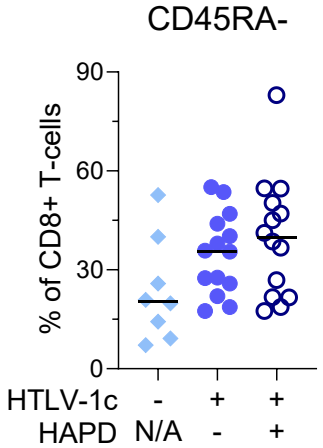




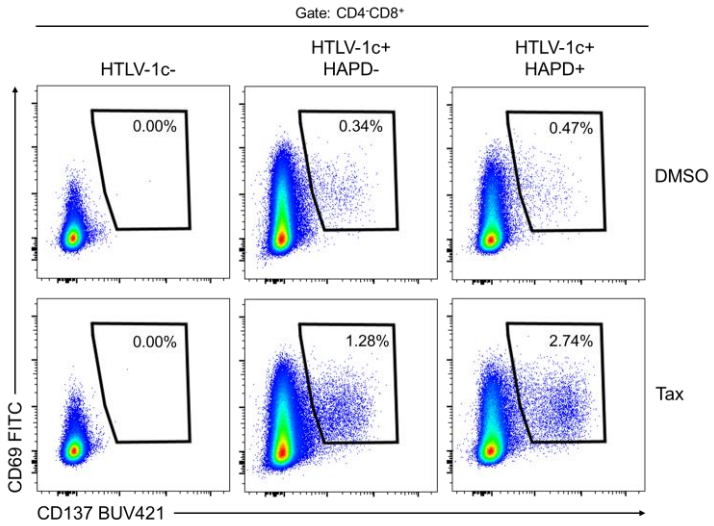
High levels of Tax-CD8⁺ T-cells are present in HTLV-1c infection

CD8+ effector/memory cells expanded

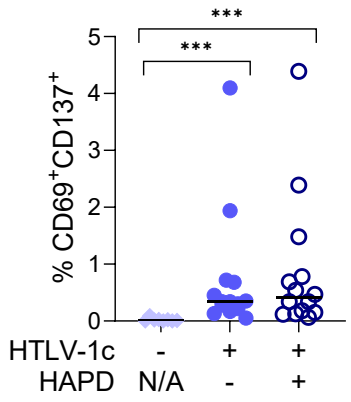


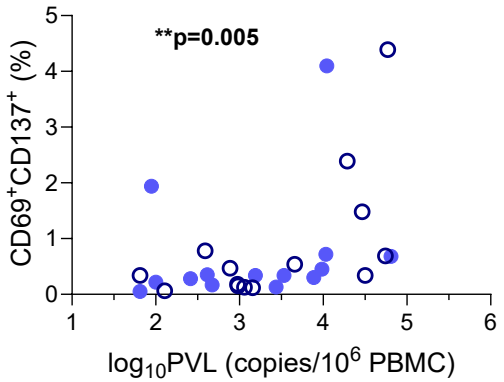


Immunodominant CD8+ antigen: Tax

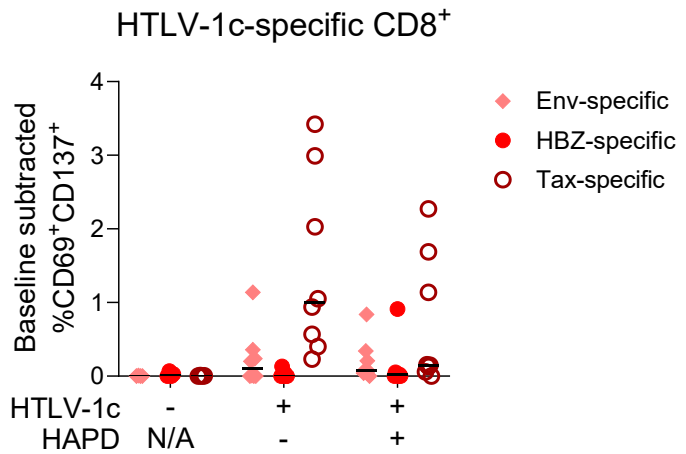


High baseline CD8+ activation correlated to PVL





HAPD- have higher Tax responses



Investigating the phenotypes of memory T-cell compartment in HTLV-1c infection

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Investigating the phenotype of memory T-cell compartment in HTLV-1c infection

Subtype-A

Expansion of CD4+ TEM and TEMRA (Saeed et al. 2020)

Activation of T-cells (Tan et al. 2021)

Upregulation of PD-1 on CD8+ in ATL, downregulation in HAM (Kozako et al. 2009, 2011)

Downregulation of TIM-3 in HAM

(Ndhlovu et al. 2011, Abdelbary et al. 2011)

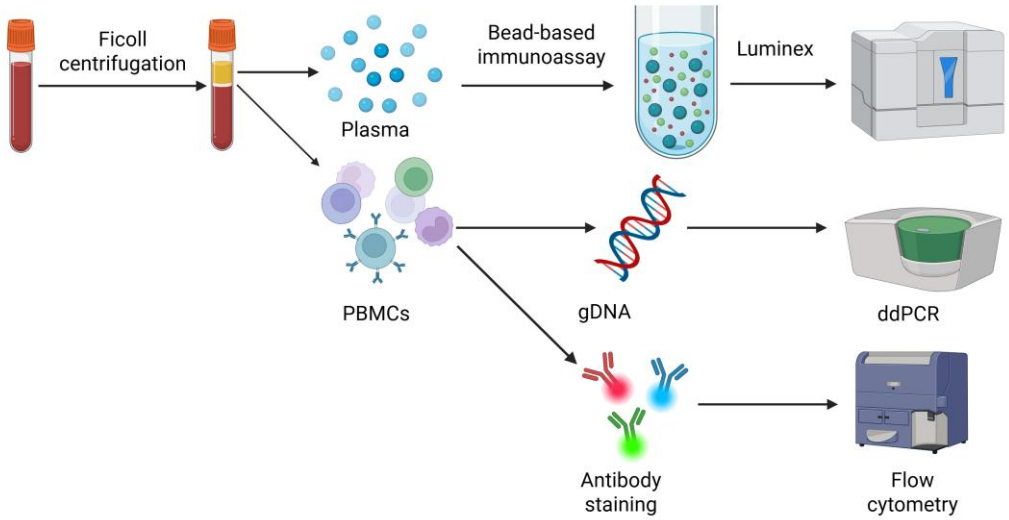
Subtype-C

CD4+ and CD8+ TEM and TEMRA subsets

Chronic activation, inhibitory surface receptors, effector molecules, terminal differentiation

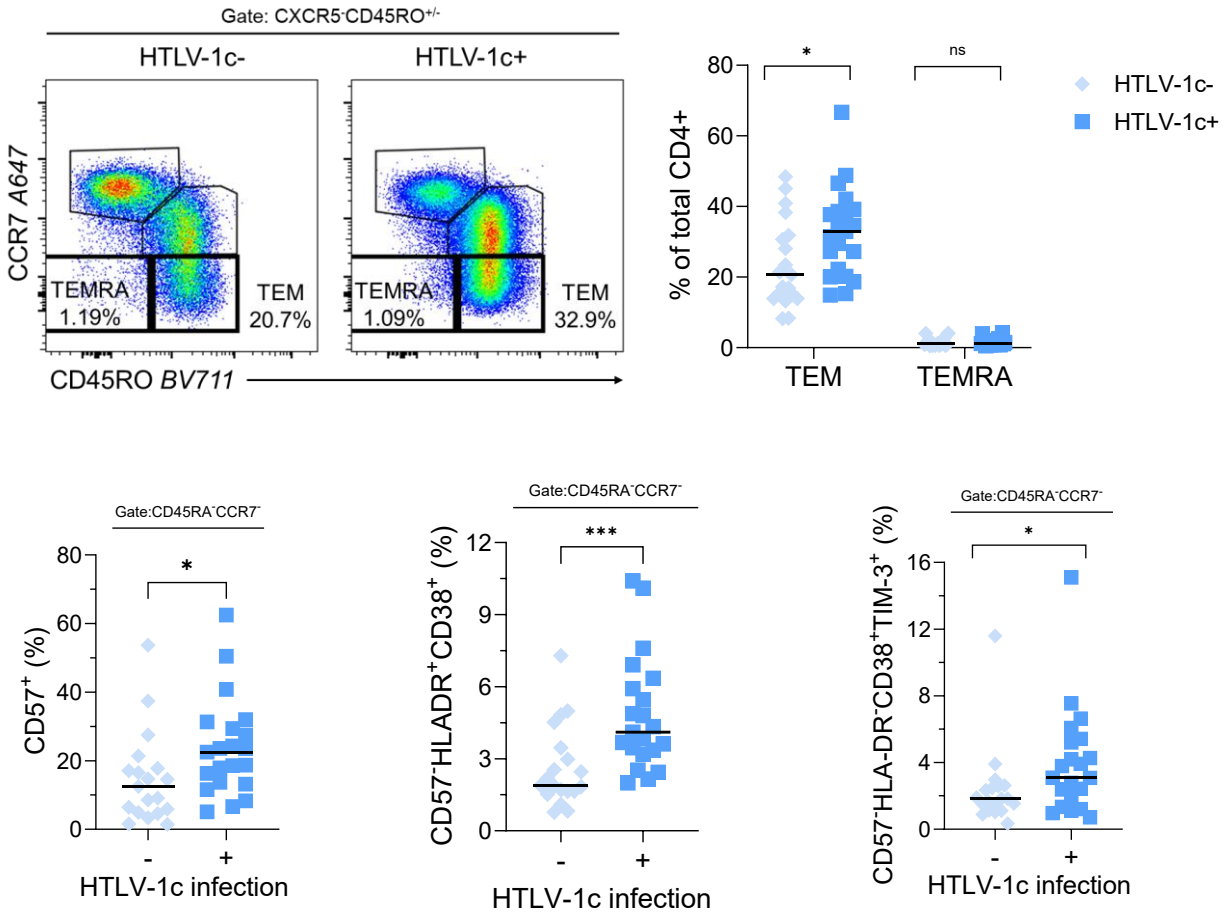
- HLA-DR, CD38, PD-1, TIGIT, TIM-3, GzmB, CD57, KLRG1

n=40 (HTLV-1c- 19, HTLV-1c+ 21)

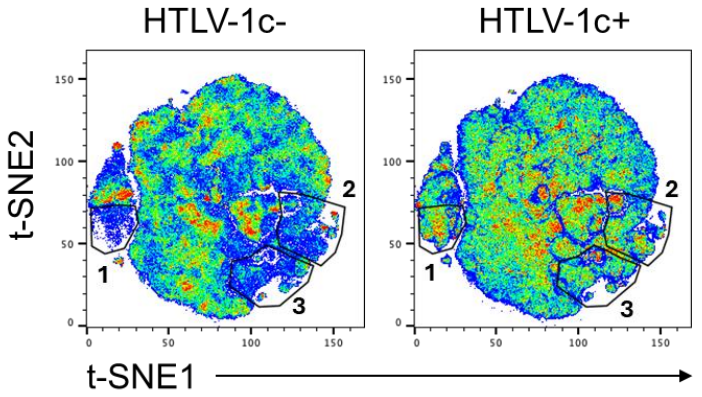


Three discrete populations of CD4+ TEM cells significantly elevated in HTLV-1c infection

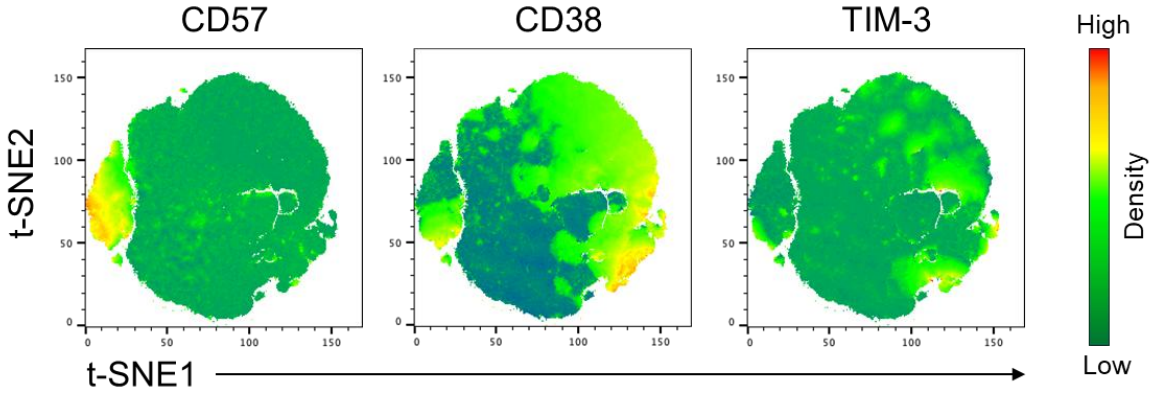
Expansion of CD4+ effector/memory (TEM) cells



Three significant populations of CD4+ TEM associated with infection

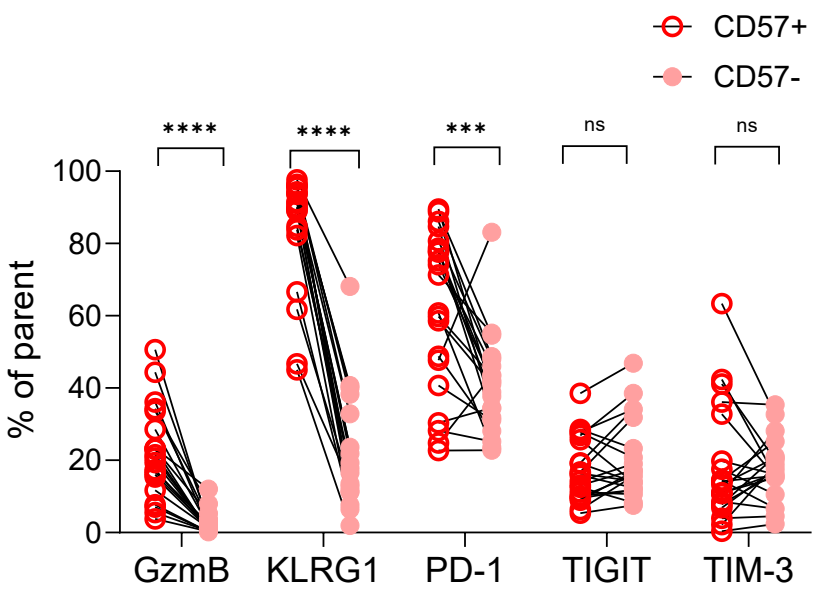


1. CD57+
2. CD57-HLA-DR+CD38+
3. CD57-HLA-DR-CD38+TIM-3+



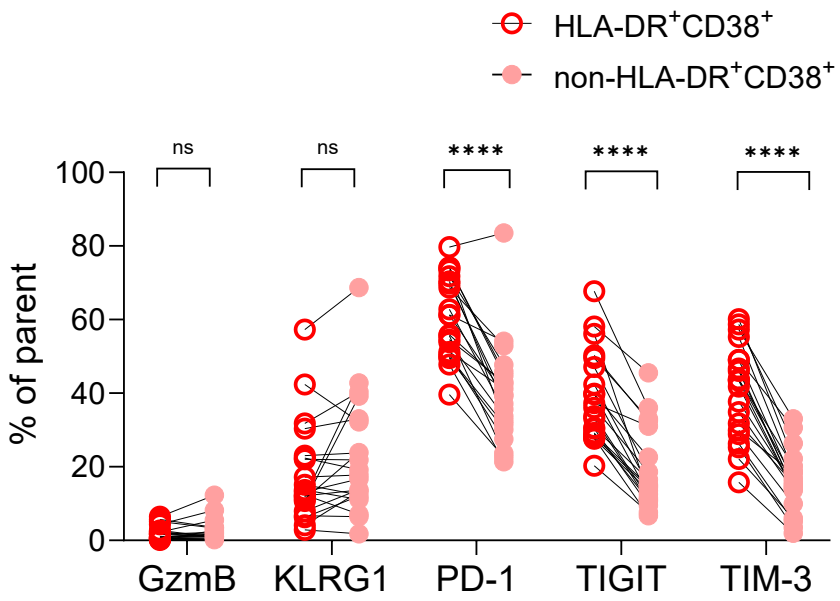
$CD4^+$ TEM populations exhibit hallmarks of exhaustion and terminal differentiation

(1) CD57+



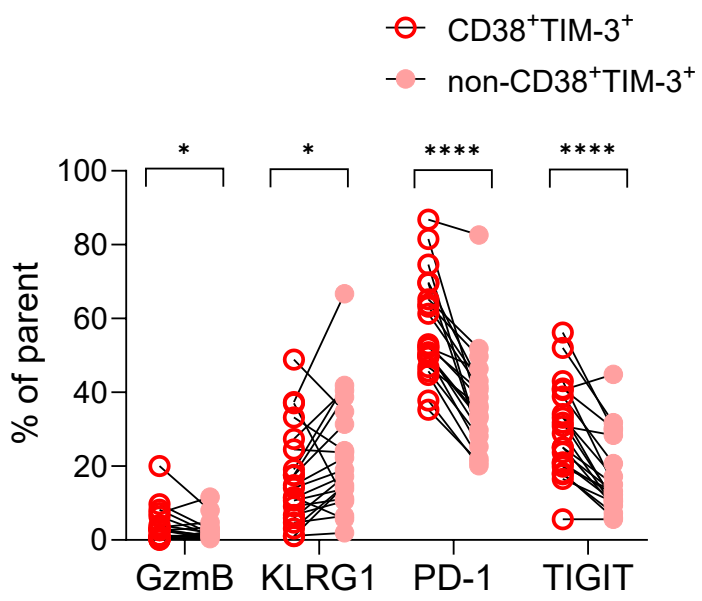
Senescent
Terminally differentiated
Cytotoxic-like

(2) $CD57^-HLA\text{-}DR^+CD38^+$



Chronically activated
Exhausted

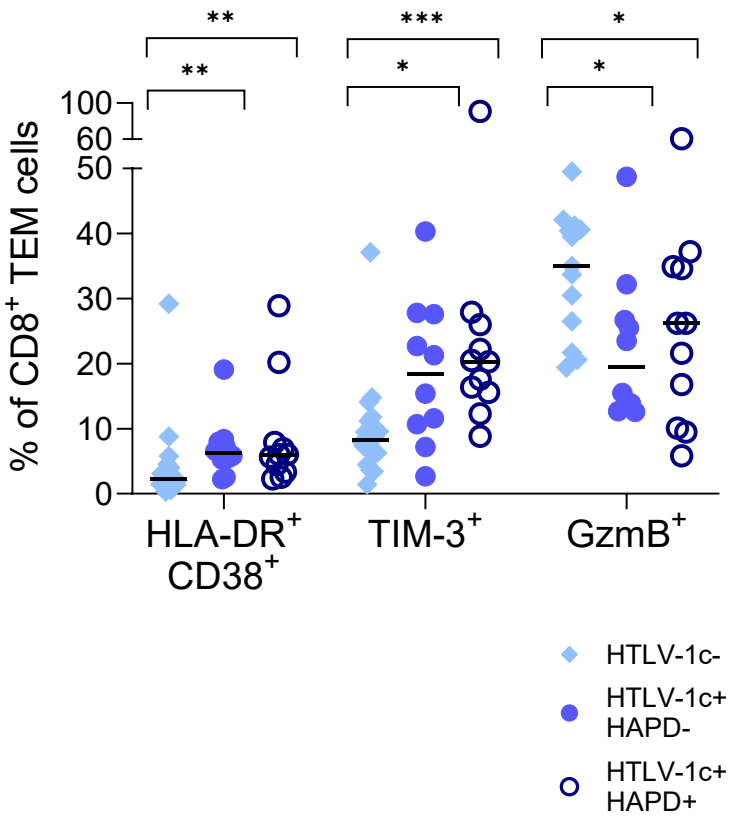
(3) $CD57^-HLA\text{-}DR^-CD38^+TIM\text{-}3^+$

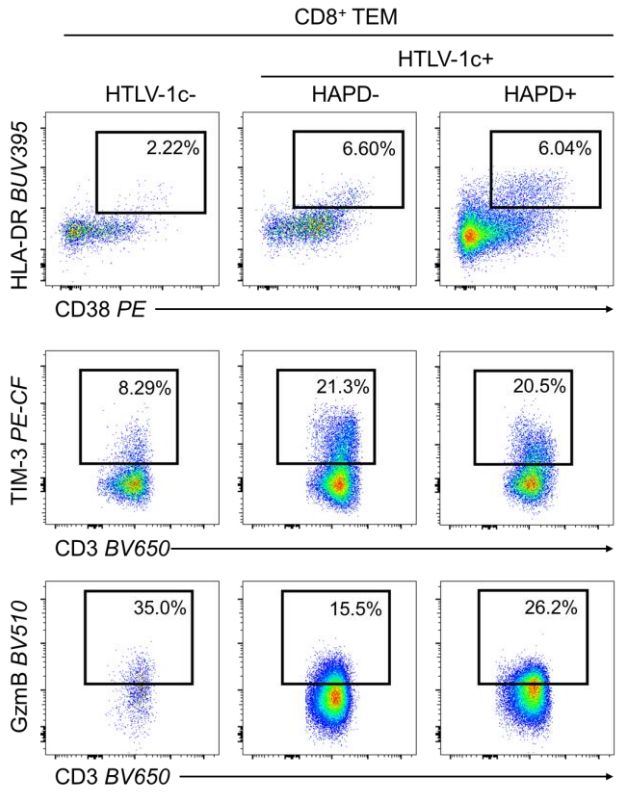


Cytotoxic-like
Exhausted
Non-terminally differentiated

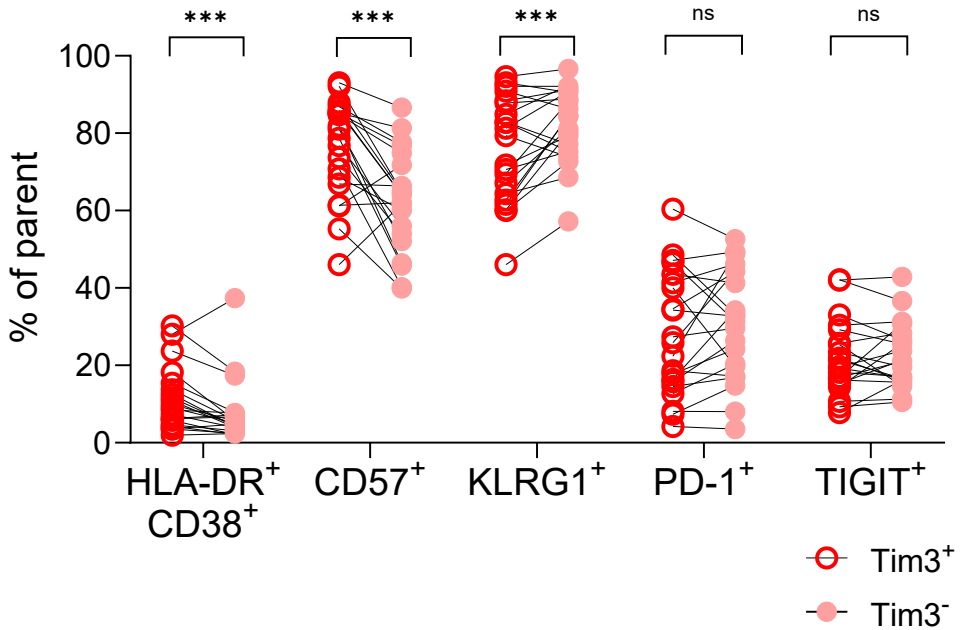
CD8⁺ TEM cells with TIM-3⁺ expression are linked to HTLV-1c infection

CD8+ TEM cells are chronically activated and exhausted





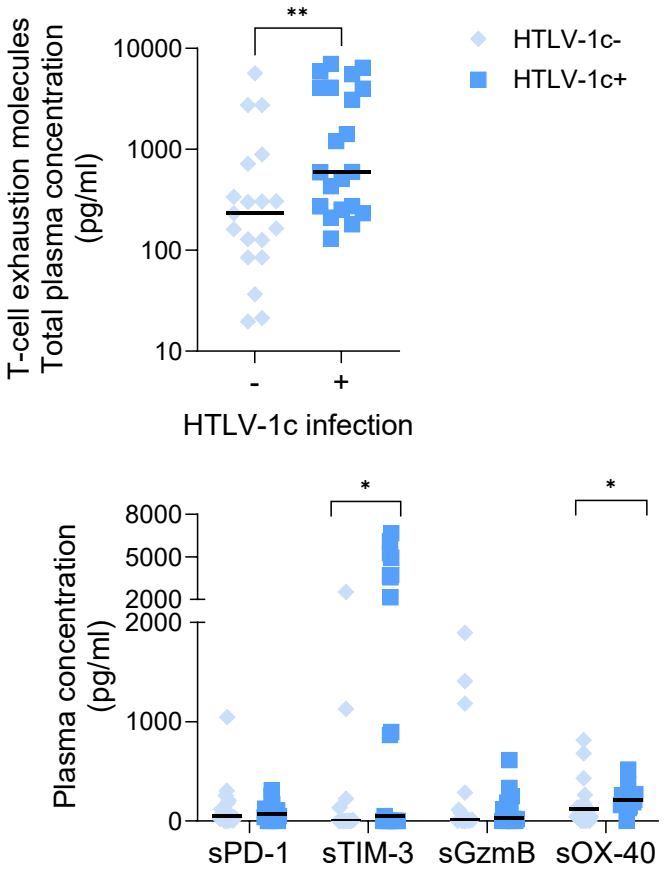
TIM-3+ CD8 TEM cells



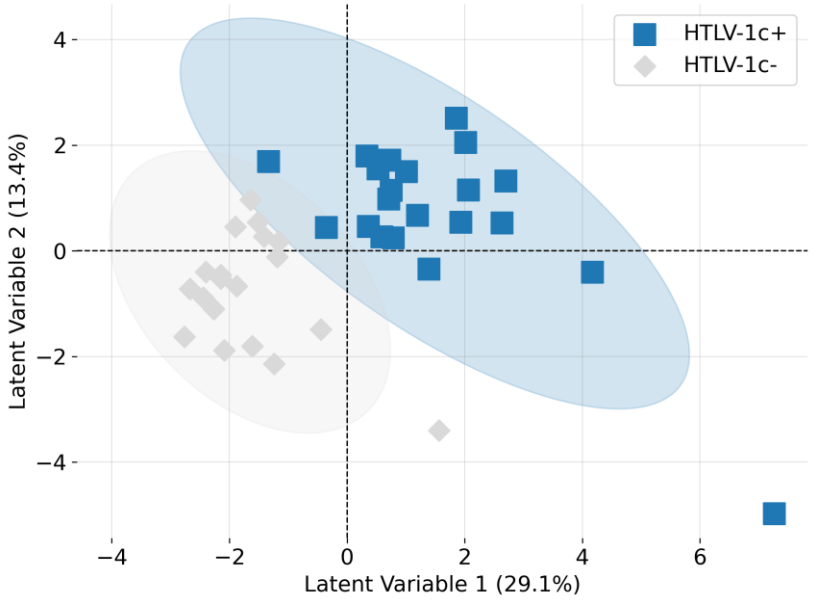
Chronically activated
Senescent

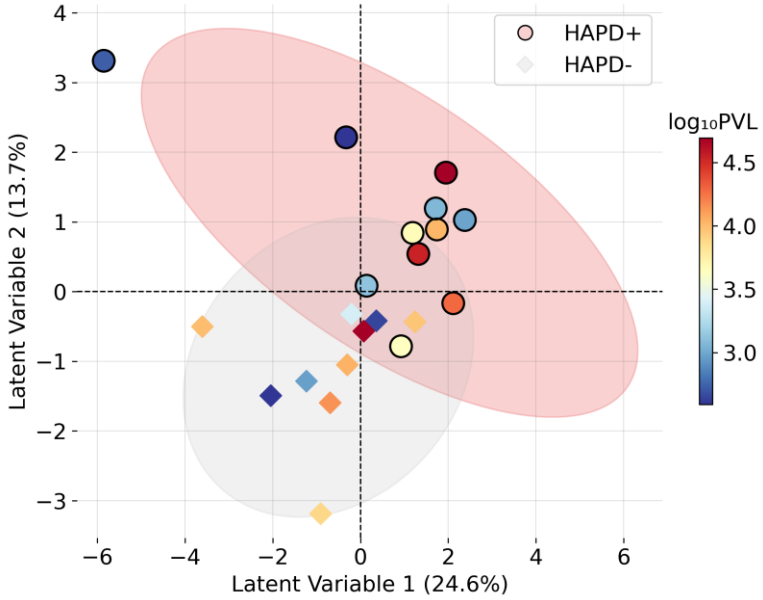
T-cell exhaustion and senescence in HTLV-1c infection and HAPD

T-cell activation and exhaustion plasma markers



Multivariable analysis (PLS-DA) of all T-cell phenotypes and plasma markers





T-cell senescence and exhaustion are defining features of HTLV-1c infection and HAPD

Summary
HTLV-1c chronic T-cell activation and exhaustion

First study examining the immunological associations of HTLV-1c infection in remote Australia and in the context of HAPD

Tax-specific cTFH and Th17 cells may be important in preventing HAPD

Extensive chronic activation of memory CD4 and CD8 T-cell phenotypes

These cells exhibit hallmarks of exhaustion and senescence

Targeting TIM-3 presents as promising subtype-C therapeutic strategy

→ Chronic T-cell activation and immune exhaustion signatures suggest that host adaptive immune dysfunction likely contributes to HAPD and overall poor health outcomes for PLW HTLV-1c in Central Australia

Acknowledgements and Contributors

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