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# Gene activation therapy: from the BLV model to HAM/TSP patients

**Agnes Lezin[1], Stephane Olindo[1], Gildas Belrose[1], Aissatou Signate[1], Raymond Cesaire[1], Didier Smadja[1], Derek Macallan[2], Becca Asquith[3], Charles Bangham[3], Amel Bouzar[4], Nicolas Gillet[3], Julien Defoiche[4], Arnaud Florins[4], Olivier Verlaeten[4], Arsene Burny[4], Luc Willems[4]**

*[1]Laboratory of Virology-Immunology, Neurology and JE 2503, University Hospital of Fort-de-France, 97200 Fort-de-France, Martinique, France, [2]Center for infection, St George's, University of London, London, UK, [3]Department of Immunology, Wright-Fleming Institute, Imperial College London, St Mary's campus, London, UK, [4]Molecular and Cellular Biology, University Academia Wallonie Europe, Gembloux, Belgium*

## TABLE OF CONTENTS



## 1. ABSTRACT

HTLV-1 (human T-lymphotropic virus type 1) and BLV (bovine leukemia virus) are two related retroviruses infecting CD4+ and B lymphocytes in humans and ruminants, respectively. During infection, the host-pathogen interplay is characterized by very dynamic kinetics resulting in equilibrium between the virus, which attempts to proliferate, and the immune response, which seeks to exert tight control of the virus. A major determinant of disease induction by both viruses is the accumulation of provirus in peripheral blood. In the absence of viral proteins, virus infected cells escape recognition and destruction by the host immune response. We propose a novel therapeutic strategy based on transient activation of viral expression using epigenetic modulators; this exposes infected cells to the immune response and results in significant reductions in proviral loads. In the absence of satisfactory therapies, this viral gene-activation strategy might delay progression, or even be curative, for HTLV-1 induced myelopathy / tropical spastic paraparesis (HAM/TSP).

## 2. INTRODUCTION

The deltaretrovirus genus comprises a series of related viruses infecting lymphocytes of human, primates and ruminants (1). The prototypes of this genus are HTLV-1 (human T-lymphotropic virus type 1) and BLV (bovine leukemia virus). These two viruses share a series of structural and functional properties but also harbor unique characteristics (Table 1).

The host range of both viruses is quite distinct: HTLV-1 infects human and primates whereas BLV naturally persists in cattle and water buffalo. There is currently no evidence for infection of human with BLV, even in countries with high prevalence or in regions where consumption of raw milk and meat from infected cows is a habit. Although species tropism may not be completely exclusive in cultures in vitro, the cell types infected in vivo by HTLV-1 and BLV are different, CD4+ or CD8+ T cells and B lymphocytes, respectively. In contrast, phylogenetic comparison of a series of viral isolates, using the *pol* gene as a reference, indicates that HTLV-1 and BLV sequences

**Table 1.** Prevalence, distribution, pathologies and cell type specificities of HTLV-1 and BLV

| | HTLV-1 | BLV |
|---|---|---|
| Prevalence and distribution | 20 million people infected worldwide, mostly in endemic regions in Japan, Caribbean, South America and Africa | - Naturally infects cattle and water buffalo - Worldwide distribution but eradicated from Europe |
| Viral persistence | Asymptomatic in 95 % of infected subjects | Mostly asymptomatic but one third of infected cows develop a benign persistent lymphocytosis |
| Pathologies | 4 % of Adult T-cell leukemia (ATL) or HTLV-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) after 20-70 years of clinical latency | 3-5 % of leukemia or lymphoma after 4-10 years latency period |
| Cell type specificity | CD4 + CD45RO + (memory) T cell and CD8 + T cell | CD5+ CD11+ B lymphocytes |

**Table 2.** Key features of HTLV-1 and BLV pathogeneses

| **Transmission** | **is strictly horizontal. Although pseudo-vertical might occur via transplacental routes, germ lines are devoid of proviruses (6, 7)** |
|---|---|
| Infection | is cell-associated, free virions being very unstable (8-10) |
| Integration | occurs randomly in the cellular genome, although A/T sequences and transcription initiation sites might be preferred. There is no evidence for activation in cis of cellular oncogenes or integration into actively transcribed regions (7, 11-13) |
| Replication | occurs via cell-to-cell transmission early after infection and through clonal expansion by cell mitosis thereafter (14, 15) |
| Expression in vivo | lack of detectable expression in most infected cells in vivo (16, 17) |
| Expression *ex vivo* | viral expression is induced upon short term culture (18, 19) |
| Persistence | the majority of detectable infected cells harbor a silent provirus (12, 19, 20) |
| Immune response | active humoral and cytotoxic immune responses against viral antigens (21-23) |
| Cell dynamics | Infected cell turnover is accelerated (24, 25) |
| Virus genomic deletions | dead-end replication-defective viruses harboring provirus internal or 5' end deletions are frequent in leukemic cells (12, 26, 27) |

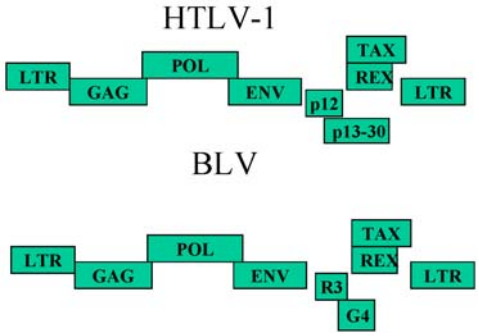


**Figure 1.** Genomic structure of BLV and HTLV-1. LTR are long terminal repeats. GAG (group specific antigen), POL (RNA-dependent DNA polymerase, RNAse H and integrase), ENV (envelope) are structural/enzymatic genes. TAX (transcriptional activator), REX (post-transcriptional regulator), R3/p12, G4/p13/p30 are accessory/regulatory genes.

differ by 42 % (2). Both viruses share common epitopes in the *gag*-encoded capsid antigens (CA) further supporting a close evolutionary relationship between the two viruses (3). Genomic organization and gene functions are also remarkably similar: in addition to the structural *gag*, *pol* and *env* genes required for the synthesis of the viral particle, both viral genomes contain a particular region pertaining to the deltaretrovirus genus (Figure 1). Located between the envelope gene and the 3' long terminal repeat, these sequences encode at least 4 regulatory genes: Tax-1 / Tax-BLV, Rex-1 / Rex-BLV, $p12^{I}$ / R3 and $p13^{II}$ + $p30^{II}$ / G4 in HTLV-1 / BLV, respectively. Tax and Rex are transcriptional and post-transcriptional activators of viral expression. Whereas Tax-1 and Tax-BLV only activate transcription of HTLV-1 or BLV, respectively, Rex-1 and Rex-BLV proteins are interchangeable (4). Similarly, $p13^{II}$ and G4 accessory proteins share their interaction with farnesyl pyrophosphate synthetase, an enzyme involved in the mevalonate/squalene pathway and in synthesis of FPP, a substrate required for prenylation of Ras (5).

The mechanisms of viral pathogenesis induced by HTLV-1 and BLV are also similar in many aspects (Table 2). In view of the similarities between the two viruses in terms of pathogenic mechanisms, it is likely that improved understanding in one viral system may be informative for the other. For example, furthering our understanding of the involvement of viral genetic determinants in infection, persistence and pathogenesis has been pioneered in the field of BLV (recently reviewed in reference (1)). In contrast, the fundamental mechanisms of viral expression (e.g. Tax transactivation and transformation), metabolic pathways (e.g. NFκB regulation) or immune response regulation (e.g. cytotoxic T cells) have been far better characterized in the HTLV-1 system. Here, we develop a hypothesis that originated from an apparently fortuitous observation in the BLV model which may ultimately lead to a novel therapeutic approach for HAM/TSP.

## 3. HYPOTHETICAL MODELS OF VIRUS PERSISTENCE

When peripheral blood lymphocytes are isolated from BLV-infected animals and directly analyzed by flow cytometry, viral protein expression cannot be detected but short term culture reveals progressively increasing levels of staining for the viral CA protein (Figure 2A). Despite numerous and ancient reports (17, 28-33), a frequently ignored observation in HTLV-1 infection is that this is also true for PBLs from infected subjects at all stages of infection i.e. asymptomatic carriers, TSP and even in ATL (Figure 2B). Originally, this process was interpreted as "reactivation of expression by a silent virus" (34, 35) consistent with a simplistic model (#1 on Figure 3). This model has two major caveats: (i) if the virus is silent, what would be the driving force allowing infected cells to persist or accumulate preferentially? and (ii) in the absence of viral proteins, why would the anti-viral immune response be so

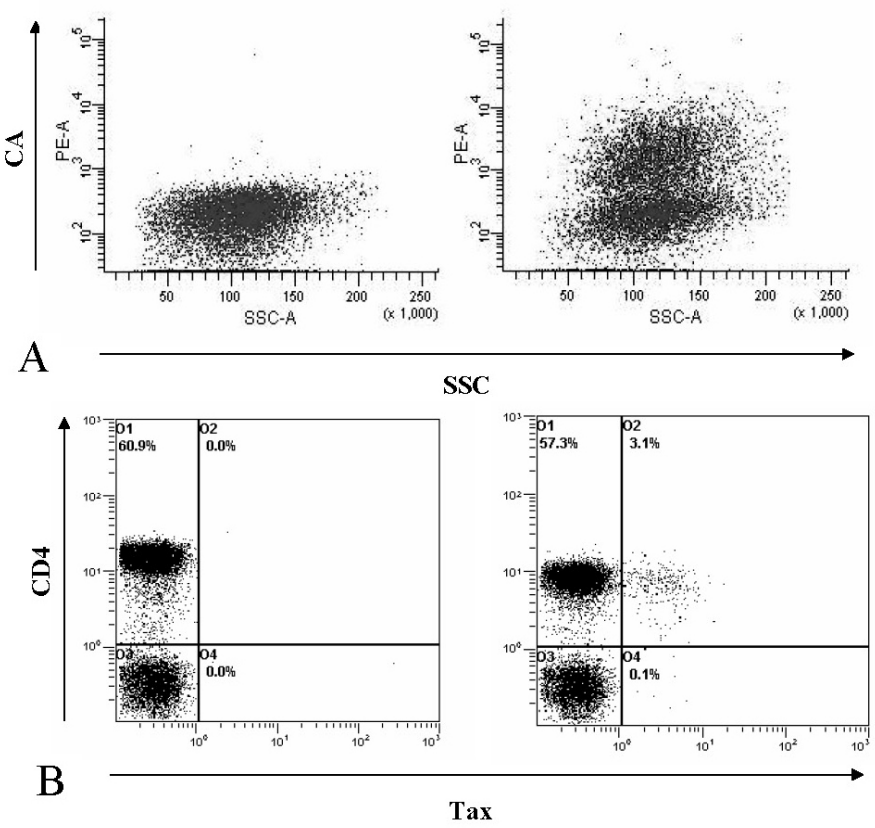


**Figure 2.** Viral expression upon ex vivo cell culture. A. Peripheral blood mononuclear cells (PBMCs) from BLV-infected sheep were cultivated for 1 hour (left plot) of 24 hours (right panel), labeled with anti-p24 capsid antigen and analyzed by flow cytometry (FACS dot plot X axis = side scatter; Y axis = p24). B. PBMCs from a HTLV-1 infected individual were depleted from CD8+ cells and analyzed by FACS (X axis = Tax-1 , Y axis = CD4+ cells) before (left panel) or after 12 hours of culture (right panel) using a Tax-specific antibody.

vigorous for a chronic infection, being characterized by high titers of cytolytic antibodies and activated cytotoxic T cells? In view of these caveats, an alternative model has been proposed, postulating that viral Tax oncoprotein promotes preferential proliferation of infected cells (#2, Figure 3). This hypothetical mechanism is still the widely-accepted model but it does not address two key issues: (i) if Tax is expressed in all infected cells, they would be expected to be destroyed by the host immune response (e.g. the CTL response to peptide 11-19 is very efficient (36-38)) and (ii) Tax-positive cells cannot be detected in vivo (e.g. only very few cells are positive by single cell RT-PCR or in situ immunochemistry (17, 28-30)). Importantly, very low level of viral expression in each infected cell has not been detected in the absence of culture by any sensitive technique such as single cell or in situ RT-PCR. It thus appears that RT-PCR positivity in fresh cells results from very high expression in a few rare cells rather than from very low expression in all infected cells. Therefore, we recently proposed a third conceptual model (#3, Figure 3), which best reconciles all available experimental evidence (39). In this model, the virus plays an active role by continuously expressing a viral oncogenic factor such as Tax, BLV G4 or HTLV Hbz RNA (40-43) which is able to promote cell proliferation and transformation. Tax expression could be permanent, provided that cells escape from immune response (which is a rare event), or could be initiated indirectly via cellular activation or immune stimulation. Concomitantly, Tax expression would also trigger the host's anti-viral immune response, which in turn would clear the infected cells. Escape from the immune response would require shut off of viral expression through a still imperfectly characterized process which could be (i) uneven distribution of viral proteins between the daughter cells (44), (ii) epigenetic regulation (e.g. histone acetylation, histone methylation or DNA methylation) (45-47), (iii) inhibition by a viral accessory factor (such as $p30^{II}$, Rex or Hbz) (48, 49) or MHC-I downregulation (50). In this model, Tax or Hbz would be the driving force providing a selective advantage and leading to clonal expansion of infected cells. Ultimately, abnormal accumulation of infected cells could favor onset of virus-independent events leading to rapid propagation and escape from immune defense system.

Our hypothetical model #3 reconciles the following experimental findings which include (i) the oncogenic potential of Tax, (ii) continuous stimulation of the immune system, (iii) low levels of detectable cells expressing viral proteins in vivo, (iv) apparent stability of

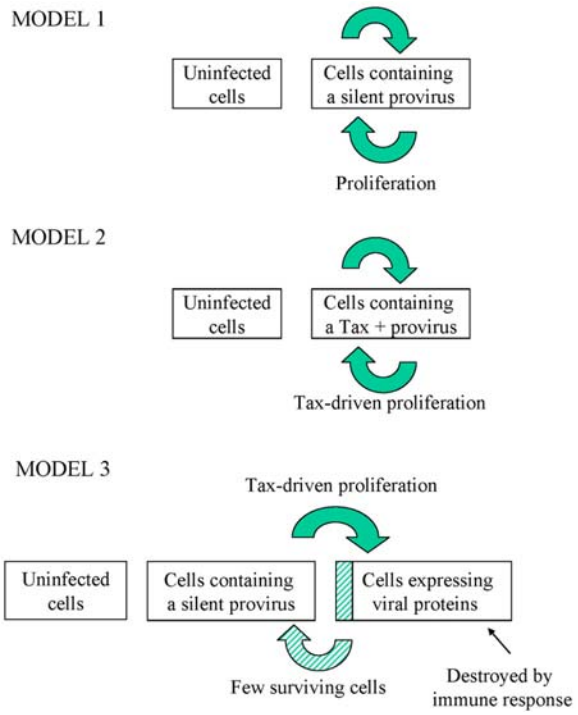


**Figure 3.** Hypothetical models of viral persistence in infected cells. Model #1 considers that infected cells proliferate in absence of any viral gene expression. In model #2, all infected cells express an oncogenic factor such as Tax that promotes their preferential proliferation. Model #3 incorporates all available experimental evidence including (i) the oncogenic potential of Tax, (ii) continuous stimulation of the immune system, (iii) low levels of detectable cells expressing viral proteins in vivo, (iv) apparent stability of individual proviral clones and (v) increased turnover in infected cells.

individual proviral clones (20), and (v) increased turnover in infected cells (24, 25). During chronic infection, the host-pathogen interplay is thus characterized by very dynamic kinetics generating equilibrium between viral proliferation and an active immune response. In this model, the virus persistently transits between latent and transcriptionally active phases resulting in progressive accumulation of viable infected cells. We hypothesize that activation of viral expression creates an imbalance in this dynamic equilibrium. However, the net outcome of this type of treatment on infected cell numbers is difficult to predict since induction of Tax expression promotes cell proliferation but also allows destruction of the silent pool by the host immune response. Therefore, the validity of this concept was first tested in the BLV model.

## 4. GENE ACTIVATION THERAPY OF BLV-INDUCED LEUKEMIA IN SHEEP: A PROOF OF CONCEPT

Many therapies fail not because they are inefficient but simply because the compounds used are insufficiently tolerated. We have previously tested a series of molecules such as phorbol esters (PMA); they very efficiently induce viral expression in vitro (34), but are extremely toxic in BLV-infected sheep (unpublished observations). To test the principle of a gene activation therapy in vivo, we therefore selected valproate (VPA), a compound that, although not the best agent for inducing viral expression, has far better tolerability. Indeed, this short-chain fatty acid exhibits very low toxicity in adults and has been used for several decades for long-term treatment of epilepsy. With a bioavailability of 90 %, VPA can be given orally and, with a half life of 16–17 hours, has adequate pharmacokinetic properties in vivo (51). Considering that the major point to address is the efficiency / toxicity ratio, VPA provides an optimal tool to evaluate the effectiveness of a gene activation chemotherapy in an animal model.

VPA has pleiotropic effects in cells including inhibition of lysine deacetylation (52). More importantly, interference with the level of histone acetylation modulates chromatin condensation, which is an essential component of the gene expression pattern. In fact, this process results from an intrinsic balance between the activity of two families of antagonistic enzymes, histone deacetylases (HDAC) and histone acetyltransferases, respectively removing or incorporating acetyl groups into core histones. Although this model is probably oversimplified, acetyl removal by HDACs restores a positive charge to the lysine residues in the histone N-terminal tails and is thought to increase the affinity of histones for DNA, leading to transcriptional repression. Conversely, impairment of HDAC function with specific inhibitors activates both cellular and viral gene transcription.

VPA promotes BLV LTR-directed transcription in luciferase reporter assays and CA expression in *ex vivo* primary cell cultures (45). Concomitantly, VPA is also pro-apoptotic for most cells in vitro, thereby sometimes interfering with efficient induction of viral expression. However, when normalized to the percentages of live cells, VPA definitely favors viral expression. VPA treatment of BLV-infected leukemic sheep results in a progressive reduction in the number of neoplastic B lymphocytes (45). Importantly, the numbers of CD4+, CD8+ and γ/δ T cells remain surprisingly constant in VPA-treated animals, contrasting with the toxicity of classical chemotherapy. This observation is consistent with our hypothetical model which predicts that specific activation of viral expression, rather than VPA toxicity, creates an imbalance in the dynamics of infected cell turnover. According to this model, it also appears that the potential advantage conferred by increased Tax expression is overcome by destruction of infected cells by the host immune response. Whatever the mechanism, the net outcome of VPA treatment is a reduction in leukemic cell counts.

Since sheep represent an experimental model for BLV in cattle, several issues remain to be addressed mainly: (i) can VPA reduce the number of infected cells in cows? (ii) is treatment well tolerated? (iii) is VPA curative for persistent lymphocytosis and / or lymphoma and (iv) can VPA impede viral transmission in herds ? These

important points should be considered to reduce prevalence in regions where BLV is widespread such as for example US, Japan or Argentina.

## 5. GENE ACTIVATION THERAPY OF HAM/TSP IN HTLV-1 INFECTION

Even more important is the potential use of VPA as a treatment for HTLV-1 induced diseases. Of the approximately 10 to 20 million HTLV-1 infected people worldwide, a significant fraction (about 2-3 %) will develop Adult T cell leukemia (ATL) while a similar proportion will develop HAM/TSP (HTLV-Associated Myelopathy/Tropical Spastic Paraparesis), a neuroinflammatory disease of the central nervous system (CNS). ATL has a very poor prognosis due to its intrinsic resistance to classical chemotherapy such as CHOP. A regimen of azido-thymidine (AZT) and alpha-interferon (IFN-$\alpha$) induces a proportion of complete remission and lengthens survival (53). Treatment of relapsed/refractory ATL with arsenic trioxide combined with IFN-$\alpha$ is usually very limited by toxicity or immunosuppression (54). Finally, allogenic bone-marrow transplantation, when feasible, can prevent relapse but is associated with significant risks (55). HAM/TSP is still an incurable disease evolving from diagnosis (expanded disability status scale DSS stage 1) to permanent wheelchair-confinement (DSS score 8) within a median time of 14 years (56). Palliative treatments for HAM/TSP include steroids to decrease inflammation (45, 57-59). Attempts to treat HAM/TSP by interfering with cell invasion into the CNS using inhibitors of matrix metalloproteinases (60) have been unsuccessful. Similarly, other strategies aimed at inhibiting cell activation and/or viral replication with cytokines (IFN-$\alpha$ or -$\beta$) (59) or anti-viral compounds (61-63) have not shown appreciable efficacy and have not been well tolerated in the long term. For both HTLV-1 induced diseases, the discovery of efficient yet non-toxic therapies is thus mandatory.

Based on the relationship between BLV and HTLV and spurred by the successful treatment of leukemic sheep, we investigated the possibility that HAM/TSP patients might be treated with VPA. In vitro, the parallelism between the two viral systems is indeed obvious. First, VPA stimulates HTLV LTR directed transcription in luciferase reporter assays performed with transfected T-lymphocytes (64). In short term cultures of peripheral blood mononuclear cells isolated from HAM/TSP subjects, VPA hyperacetylates histone H3 as expected for an HDAC inhibitor, increases expression of the viral core protein p19 in the supernatant and induces apoptosis of CD4+ and CD8+ T-lymphocytes. As observed for BLV, the pro-apoptotic effect of VPA is not specific for HTLV-infected cells cultivated *ex vivo*.

The dilemma was next to decide whether HAM/TSP patients should be treated, since there is a risk that VPA could worsen the disease by favoring viral spread. However, in a 14 year follow-up study of 123 patients, a high proportion (86.4%) died as a direct result of HAM/TSP complications. The mean age at death from HAM/TSP was about 15 years younger than the life expectancy in Martinique (56). Therefore, an exploratory trial was initiated with 4 HAM/TSP volunteers with high disability scores (DSS 5-7). VPA was provided orally at doses routinely used for long term treatment of epilepsy (20 mg/kg/day). Contrasting with the relative stability of the proviral loads (PVL), VPA treatment had a significant effect on the number of viral DNA copies detected in the peripheral blood. Indeed, a transient increase in the PVL was observed after 2 weeks followed by a rapid drop around day 45. The reduction in PVL after 2 months was significantly greater than normal fluctuations seen in 36 untreated HTLV-1 infected subjects from the Martinique cohort. To further broaden this pilot study, a series of 16 HAM/TSP subjects were enrolled in a larger clinical trial aimed at evaluating the therapeutic benefit of VPA (64).

Although there is no absolute link between PVL and development of HAM/TSP, the mean PVL is significantly higher in HAM/TSP patients than in asymptomatic carriers (AC) (56, 65-67). In addition, HLA haplotypes associated with a low PVL correlate with a reduction of evolving risk from AC to HAM/TSP (68, 69). For these reasons, we think that reduction of PVL by VPA might limit disease progression in HAM/TSP patients.

## 6. HOW DO MODELS OF VIRUS PERSISTENCE FIT WITH THE OBSERVED PROVIRAL LOAD KINETICS ?

Considerable controversy persists regarding the dynamics of HTLV-1 persistence and spread: experiments on integration sites suggest that the virus is latent (14, 15) and apparently conflict with observations on infected cell kinetics and the immune response (24, 25, 70). Modulation of the PVL by VPA offers a unique opportunity to evaluate the different hypothetical models of viral persistence presented in # 3.

In principle, variations in proviral loads can occur by several mechanisms including reduced apoptosis, increased proliferation, and mobilization of cells in the peripheral blood from lymphoid organs. Model 1 postulates that a cell containing a silent provirus proliferates in the absence of expressed viral RNA or proteins. It is hard to believe that VPA could have a specific effect on an infected cell that only differs from its normal counterpart by the presence of 9 Kb of proviral DNA. Model 2 incorporates the oncogenic potential of the virus that expresses a factor (the Tax oncoprotein and/or the Hbz RNA or protein) favoring its selective advantage on persistence and spread. It is conceivable that VPA could increase the proviral loads by stimulating expression of these oncogenic factors but it is harder to understand the subsequent PVL drop. Furthermore, we did not detect significant viral protein expression in freshly isolated uncultured cells by any technique (ELISA, FACS, western blot) and only trace levels of RNA by RT-PCR ((64) and ongoing experiments). Presently, we cannot formally exclude that the virus is expressed at very low levels in all infected cells since we did not yet perform single cell RT-PCR and in situ immunochemistry experiments in VPA treated patients.

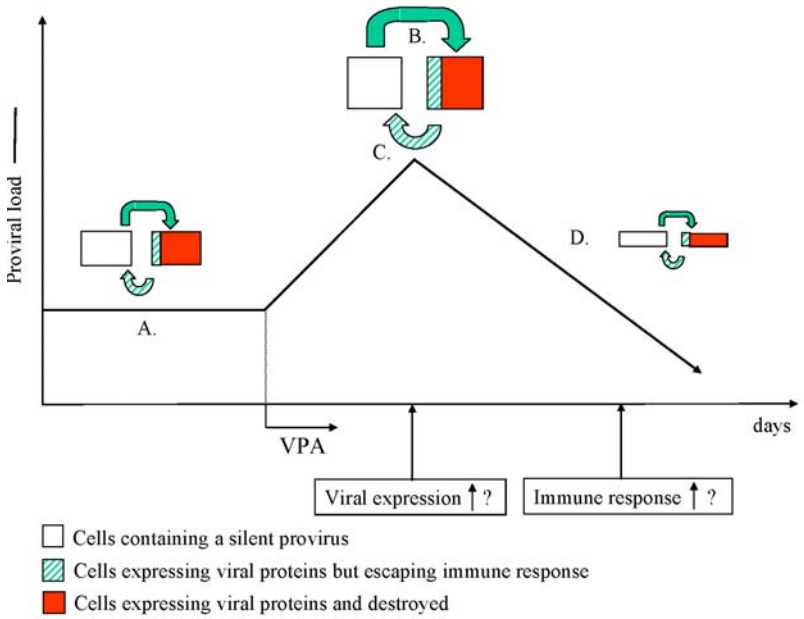


**Figure 4.** Concordance of model #3 with PVL kinetics in HAM/TSP patients treated with VPA. A. In absence of VPA, the PVL equilibrate at a level defined by the capacity of infected cells to proliferate under the control of the host immune response. B. Upon VPA treatment, the PVL increases in HAM/TSP patients consistent with enhanced expression of an oncogenic factor favoring preferential expansion of infected cells. C. If viral silencing occurs, infected cells having underwent proliferation could escape destruction by the host immune response. D. The PVL then decreases because additional cells express viral proteins and are destroyed by the host immune response. Two major predictions derive from this model: (i) viral expression should increase upon VPA treatment and (ii) the immune response should be transiently overtaken allowing a transient increase in the PVL but would thereafter clear cells expressing viral proteins.

However, model #2 does provide a clear rationale for the biphasic pattern of PVL kinetics and therefore, we favor the concept of model #3.

In the absence of VPA, PVL equilibrates at a level defined by the capacity of infected cells to proliferate under the control of the host immune response (A. on Figure 4). Upon VPA treatment, PVL have been shown to increase in several HAM/TSP patients (64), consistent with enhanced expression of an oncogenic factor favoring preferential expansion of infected cells (see green arrow B on Figure 4). Although such a rise in PVL might result from increased proliferation, decreased apoptosis or cell mobilization from lymphoid organs, we think that the former mechanism is involved based on preliminary kinetic data based on deuterated glucose incorporation assays (Defoiche et al, ongoing experiments). Conceptually, if the cell population expressing viral proteins expands, additional cells could also escape immune response, depending on its efficacy to destroy the infected pool. If viral silencing adequately occurs in these cells, the PVL would be expected to increase, as indeed observed in VPA treated patients (C on Figure 4). The immune response would get the upper hand after 2 weeks, thereby decreasing the number of cells undergoing transcriptional silencing of viral expression (D on Figure 4).

According to this model, the mode of action of VPA would be to activate viral expression, thereby exposing infected cells to immune response clearance and resulting in a PVL reduction. This mechanism would have two major predictions: (i) that VPA induces viral expression, which occurs in vitro (64) but remains to be directly demonstrated in vivo and (ii) that the immune response is temporarily overtaken, allowing a transient increase in the PVL.

## 7. PROSPECTS AND CONCLUSION

In the absence of any other successful therapy, VPA remains a very promising option for mitigating disease severity in HAM/TSP and perhaps for treatment. However, several restrictions may potentially limit the efficacy of this type of approach.

Firstly, in terms of anti-HTLV immune response, there is a theoretical hazard that using VPA might reduce the cytotoxic T-cell (CTL) efficiency (71), possibly leading to immunosuppression and secondary infections. Since the CTL response is believed to be an important factor in the immune control of HTLV-1 infection (70, 72, 73), we recently addressed this question directly and showed that the capacity of CTL cells to kill HTLV-1 infected targets was not affected by VPA treatment (Gillet et al, ongoing experiments). Safety of the host immune response is further supported by several lines of evidences among which the most convincing is lack of any identifiable defect in the patients' immune response upon long term administration

of VPA. These conclusions are further corroborated by larger epidemiological surveys with epileptic patients treated with VPA for decades (74, 75).

Despite reassuring evidences about safety and efficiency, a theoretical disadvantage of VPA treatment is that the transient PVL peak associated with increased viral expression might favor CNS invasion and thus worsen inflammation. Although no increase of disability score was clearly identified in patients (64), this specific issue will be addressed in a future phase II trial by titrating proviral loads and intrathecal anti-HTLV antibodies in cerebrospinal fluid (CSF) before and after VPA administration. If CNS invasion by HTLV infected lymphocytes is promoted during the initial PVL increase, it might be possible to combine VPA treatment with humanized neutralizing antibodies specific for $\alpha_4$ integrin (natalizumab from Biogen), used for treatment of multiple sclerosis (MS) (76). Natalizumab blocks interaction between $\alpha_4$ integrins on the surface of lymphocytes with vascular-cell adhesion molecule 1 (VCAM-1) of endothelial cells in brain and spinal cord blood vessels, thereby abrogating cell migration to the CNS (77). This strategy might also apply for HTLV-infected cells, known to overexpress $\alpha$4 integrin (78).

Since Natalizumab must be provided intravenously and is not completely devoid of risks (several cases of encephalitis were responsible for its temporary withdrawal by the U.S. Food and Drug Administration), we believe that significant and permanent PVL restriction with VPA remains the best strategy for HAM/TSP patients, in order to reduce the risk of CNS invasion by infected cells. Since VPA is also not completely devoid of minor side effects (weight gain, loss of spasticity, minor alopecia, drowsiness,...), improved tolerability might be achieved by dose reduction, provided that similar effects on PVL are observed. Alternatively, treatment could be titrated against PVL absolute loads or fluctuations indicating disease severity. Our data show that splitting therapy in consecutive VPA pulses would be possible since PVL increases only very slowly upon interruption of treatment (64).

HAM/TSP is a complex disease involving both immune and neurological components, resulting in inflammation, demyelination and necrotic lesions in the spinal cord. Collateral damage in the CNS is thought to result from release of proinflammatory, neurotoxic cytokines such as IFN-$\gamma$ and TNF-$\alpha$ by invading CD4+ and CD8+ infected and HTLV-1-specific T cells. The anti-viral immune response controlling viral infection may therefore also become detrimental and ultimately participate in mediating HAM/TSP progression. The idea behind VPA treatment is to decrease the number of provirus carrying cells, hoping that subsequent CNS invasion and damage would also be attenuated. In absence of efficient treatment for HAM/TSP, VPA is probably the only currently available option that may indirectly restrict collateral damage in the CNS and thus also limit disease progression. This prediction is supported by experimental evidence demonstrating therapeutic potential of HDAC inhibitors in models of autoimmune encephalomyelitis (EAE) (79). In particular, VPA therapy could be beneficial to early stage HAM/TSP patients harboring high proviral loads, known to progress from DSS 1 to 8 with a median time of 14 years (56). In this case, early clinical intervention would thus be required to avoid demyelination and subsequent axonal damage.

Until very recently, irreversibility of collateral damage in the CNS has been accepted as an immutable dogma. This firm conviction has however been challenged by experimental evidence of reversible neurodegeneration induced by HDAC inhibitors (80). Even more exciting is the discovery of an antagonist of LINGO-1 (Nogo receptor-interacting protein) that promotes spinal cord remyelination and axonal integrity in EAE models (81). Hope thus also remains, even for highly disabled HAM/TSP patients.

## 7. ACKNOWLEDGEMENTS

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**Send correspondence to:** Luc Willems, National Fund for Scientific Research, University Academia Wallonie Europe, Molecular and Cellular Biology laboratory, 13 avenue Marechal Juin, 5030 Gembloux, Belgium, Tel: 32-81-622157, Fax: 32-81-613888, E-mail: willems.l@fsagx.ac.be

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