

**Conference Highlights of the 15th International Conference on Human Retrovirology:
HTLV and Related Retroviruses, 4-8 June 2011, Leuven, Gembloux, Belgium**

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Abstract

The June 2011 15th International Conference on Human Retrovirology: HTLV and Related Viruses marks approximately 30 years since the discovery of HTLV-1. As anticipated a large number of abstracts were submitted and presented by scientists new and old to the field of retrovirology from all five continents. The oral presentations and discussions as well as all abstracts can be revisited online: <http://htlv.net> and <http://www.retrovirology.com/supplements>. The aim of this review is to distribute the scientific highlights of the presentations as analysed and represented by experts in specific fields of epidemiology, clinical research, immunology, animal models, molecular & cellular biology and virology.

Introduction:

The biannual Conference on Human Retrovirology: HTLV and Related Viruses, where 325 delegates from 17 countries gathered, was held in Leuven, Belgium in June 2011. Two hundred and sixty one abstracts were submitted and those accepted divided into 77 oral and 184 poster presentations. Experts in seven fields of retrovirology were asked to summarise and comment on the most intriguing novel data and share their views on future research directions.

EPIDEMIOLOGY

Epidemiology of HTLV: Two studies used the blood bank setting to measure HTLV prevalence on a large scale. A study from United States ¹ included all first-time blood donors at a large blood bank network over a ten-year period from 2000 through 2009. Among a total of 1,904,155 first-time blood donors, confirmed HTLV-1 and -2 prevalence was 1.43 per 10⁴ (95% CI 1.19-1.72), including HTLV-1 0.40 per 10⁴; HTLV-2 0.87 per 10⁴; and HTLV untypable 0.25 per 10⁴. HTLV-1/2 prevalence decreased from 2000 to 2009 (p trend <0.0001), consistent with a birth cohort effect for HTLV infection in the United States as also described in Japan. *Proietti AB, et al.* performed a similar analysis in Brazil for 2007-2009 among 281,760 first-time blood donors ². Overall HTLV-1 prevalence was 12.9 per 10⁴ (95% CI 11.6-14.2), with regional variation but little change over the three years of the study. The same study calculated the HTLV-1 incidence among blood donors in Brazil at 3.6 per 10⁵ person-years, leading to an estimated residual transfusion risk after current blood bank testing of 5.0 per 10⁶ blood units transfused, about 10 times higher than in the United States ³. HTLV prevalence data from Africa are rare, but *Caterino-de-Araujo A, et al.*, studied several

hundred patients attending public health clinics in northern, central and southern Mozambique, respectively ⁴. An overall HTLV-1/2 prevalence of 2.3% was observed, with regional variation; one HTLV-1 isolate was sequenced as the Cosmopolitan subtype.

Molecular epidemiology of HTLV: In the STLV section, below Dr. Switzer has covered some interesting new findings on HTLV-2 molecular epidemiology in the Cameroonian rainforest, confirming the close sequence homologous between HTLV-2 in Bakola pygmies with that found in South American Indians, consistent with ancient human migrations. Changing continents, *Desrames A, et al.* analyzed LTR sequences from 55 HTLV-1 carriers from the Caribbean and Africa and found that all of the West Indian strains except one belong to the Cosmopolitan subtype, and only the Noir Marron ethnic group from French Guiana was infected by the West African strain ⁵. *Magri M, et al.* analyzed samples from Brazil and found concordance with HTLV-1 isolates from Angola and Mozambique. These data suggest that HTLV molecular studies may shed new light on historical information regarding slavery-related human transport and the transmission of HTLV-1 from Africa to the New World.

Disease associations and pathogenesis: A multicenter collaborative investigation of biomarkers which might predict ATL was reported by *Birmann B, et al.*⁶. A total of 53 incident ATL cases and 150 carefully matched asymptomatic HTLV-1 carriers were obtained from population-based studies in Japan, Jamaica the United States and Brazil, and multiple biomarkers were measured on PBMC's and serum. Elevated levels of soluble interleukin-2 receptor alpha (sIL2R α) and anti-Tax antibody were both significantly associated with ATL. Elevated levels of total immunoglobulin E (IgE) predicted a lower risk of ATL. The authors suggest that a biomarker pattern predictive of heightened T-cell activation and HTLV-1 replication as well as diminished type II immunity may be associated with ATL.

Izumo S, et al. reported on a large national survey of HAM/TSP across 829 neurology clinics in Japan during 2007 and 2008 ⁷. Response rate was 33.5% and 790 cases of HAM/TSP were reported, leading to a national estimate of 3600 HAM/TSP cases; half of the patients lived in Kyushu and 15% each lived in the Tokyo and Osaka metropolitan areas. *Costa D, et al.* reported on the neurological manifestations of 102 HTLV-1 patients without HAM/TSP ⁸. The prevalence of neurologic symptoms as well as arm and leg weakness on examination was significantly associated with overactive bladder after adjusting for age and sex. Two studies examined neuropsychiatric outcomes of HTLV infection. *Guiltinan A, et al.* found no association between HTLV-1 or HTLV-2 and depression or generalized anxiety in a prospective cohort study of former blood donors, after adjusting for education, alcohol intake and self-reported health status ⁹. Poor health status early in the study, as measured by the

general well-being scale, predicted depression and anxiety about 15 years later. In an uncontrolled study, *Galvao-Phileto AV, et al.* found a 35% prevalence of depression among persons living with HTLV-1 infection in Salvador de Bahia, Brazil. Depression was associated with poor reported quality of life ¹⁰ Taken together, these studies suggest that HTLV related health problems and social environment, rather than viral infection alone, lead to psychiatric symptoms.

Arruda S, et al. performed a meta-analysis of the association between HTLV infection and active tuberculosis and yielded an estimated relative risk of 3.25 for the association between HTLV infection and active tuberculosis ¹¹. The author suggests that tuberculosis chemoprophylaxis might be considered in HTLV-1 carriers living in tuberculosis endemic areas. *Einsiedel L, et al.* reported an association between HTLV-I infection and bronchiectasis and pulmonary mortality among Australian aborigines ¹².

Future directions: Ongoing, large-scale surveillance of HTLV prevalence is needed in endemic countries, and blood donor data provides an inexpensive and largely comparable way of doing this across countries. Molecular epidemiologic studies may be increasingly useful in identifying fine scale patterns of HTLV dissemination, but would be even more useful if they incorporated parallel data on human genetics to complement viral sequence data. Especially in endemic countries, prospective cohort studies are needed to better define prognostic markers for HTLV diseases.

CLINICAL RESEARCH

Clinical Presentations: For the last 30 years clinicians and scientists have been searching for a disease dependent diagnostic, disease progression predictive and therapy responsive biomarker in HTLV-1 infection, similar to HIV-1serum RNA and CD4⁺ T cell count. So far we know that high HTLV-1 proviral load/100 PBMCs ($\geq 10\%$), high CD4⁺/CD25⁺ T cell lymphocyte count and oligoclonal expansion is associated with HTLV-1 associated disease, such as HTLV-1 associated myelopathy and ATL.

Similarly *Demontis et al.*, reported that 15% of their asymptomatic carriers (AC) had a proviral load (pVL) $> 10\%$ PBMCs and 3% even had a pVL $> 20\%$ PBMCs ¹³. These carriers might need long term, close surveillance. She also reported a high mean intra-patient variability of pVL, not only in AC (65%, SD 21) but also in patients with HAM/TSP (51%, SD 23). If reproduced this should be taken into consideration for a HTLV- 1 clinical trial sample size calculation.

The association between HTLV-1 pVL and HAM/TSP was confirmed by *Grassi et al.* but it did not differentiate between the three Belem diagnostic criteria of HAM/TSP (possible, probable and definite)¹⁴. *Yamano et al.* reported high levels of CXCL10 (Interferon γ -induced protein) in cerebrospinal fluid (CSF) and serum, neopterin in CSF and soluble IL-2 receptor in serum to correlate with severity of HAM/TSP disease (n=30). He also classified patients into different stage of disease HAM/TSP¹⁵. This would allow the recruitment of patients with similar disease severity into clinical trials.

Treatments for HAM/TSP: *Gotuzzo et al.* observed that routine treatment of patients with rapidly progressive HAM/TSP (<2 years onset) with oral prednisolone together with lamivudine +/- zidovudine for 12 months led to a significant decrease in HTLV-1 pVL in 7/11 patients (p= 0.01) and an insignificant increase in 4/11 patients (p=0.06) at 7 months follow up¹⁶. An early but only transient clinical improvement was observed (personal communication). Only a randomised control trial will be able to control for the natural fluctuation of pVL within patients and show true treatment effect. Raltegravir, an integrase inhibitor, is a licensed antiviral drug against HIV and also inhibits cell free and cell associated transmission of HTLV-1 as well as the immortalisation of HTLV-1 positive PBMCs ex vivo¹⁷. Contrary to previous reports *Fox et al.* detected 1 and 2 episomal long terminal repeat (LTR) HTLV-1 DNA circles in freshly and chronically HTLV-1 infected cell lines and patient PBMCs (n= 16). These were readily detected in patients with HAM/TSP and ATL but not in AC. A significant rise in 2LTR DNA circles was observed in freshly infected and raltegravir treated CEM cell lines, especially within the first three days of infection¹⁸. In vivo however, *Trevino et al.* observed only a transient decrease of HTLV-1 pVL in two HAM/TSP out of five HTLV-1 positive patients and no clinical improvement, when treated for 12 months with raltegravir mono-therapy¹⁹.

Treatments for ATLL: HSCT remains so far the only curative intervention for ATL albeit with high myeloablation associated mortality. *Uike et al.* reported the long term survival of 9/10 patients with ATL treated in the NST-1/NST-2 clinical trial (HSCT + reduced intensity conditioning) regime²⁰ at a median 115 months follow up. All patients showed complete donor chimera and 3/10 patients had undetectable HTLV-1 pVL at last follow up²¹. Relapse of ATL is frequent and difficult to treat, despite the modernisation of first line chemotherapy with additional azidothymidine (AZT) and interferon (IFN). *Suarez et al.* treated patient with ATL with arsenic trioxide + IFN α combination as maintenance therapy following induction chemotherapy +/- AZT and IFN α . Five/11 patients (4 CR, 1 PR) were alive at follow up (9 to 46 months) of whom 3/5 patients had lymphomatous ATL. However 6/11 patients who were

progressing at the time of maintenance therapy did not respond and died ²². Larger randomised controlled phase III trials are needed to reduce this selection bias.

Following a phase I trial ²³, *Utsunomiya et al.* treated 13 patients with CCR4+ relapsed ATL with anti-CCR4 antibody (KW-0761, i.v.1 mg once weekly for 8 weeks) in multicentre phase II trial. The overall response in 26/28 patients was 50% (8 CR, 5PR). Notably there was a marked difference between median overall and progression free survival (13.7 vs 5.2 months) ²⁴.

HTLV-1 persists by driving clonal proliferation of infected T lymphocytes ²⁵, and several studies tested the reinstatement of polyclonal versus oligoclonal T lymphocytes as a marker of treatment response. *Ramos et al.* presented preliminary clinical trial data of adding histone deacetylase (HDAC) inhibitor valproic acid to maintenance therapy AZT+INF- α in 13 patients with acute ATL, and observed a serial decrease in clonal ATL disease followed by molecular clearance in one patient. In vitro testing of newer, more potent HDAC inhibitors are planned ²⁶. *Hodson et al.* observed a 33% response rate in acute ATL (n=3, median OS: 3 months, 1CR) and 100% in chronic ATL (n=5, median OS: 20 months) to AZT+ INF- α as first line therapy alone ²⁷. Again not only a reduction in pVL but also the re-emergence of polyclonal integration patterns were associated with disease remission.

Future directions: In summary randomised controlled trials remain urgently needed to determine reliable biomarkers of HTLV-1 disease and of treatment response as well as to establish a treatment strategy especially for lymphomatous ATL, relapsed ATL and any stage of HAM/TSP.

ANIMAL MODELS

Presentations during the Animal Models section illustrate ongoing efforts to understand the pathogenesis of HTLV-1-associated diseases using a variety of model systems. The development of accurate and reproducible animal models is critical to the understanding of the pathogenesis of HTLV-1-associated diseases. No perfect model exists that recapitulates all aspects of HTLV-1 diseases syndromes. Transmission and viral spread of HTLV-1 has been studied in rabbits and non-human primates, but lesion development and reagents are limited in these species. As reflected in the meeting abstracts, the mouse provides a cost effective and highly reproducible model in which to study factors related to lymphoma development and the preclinical efficacy of potential therapies against adult T-cell lymphoma and leukemia (ATL). These include important transgenic mouse models that have been utilized to study viral determinants of lymphocyte transformation in vivo.

Immunodeficient mice: The six presentations chosen for platform presentations covered a variety of relevant topics. Xenografts of adult T-cell leukemia/lymphoma (ATL) cells or cell lines into immunodeficient mice replicate features of ATL and allow systems to test therapies against the neoplastic disease ²⁸. *Tezuka K et al.* reported their development of ATL-like disease in humanized mice (huNOG) by the intra-bone marrow transplantation of NOG-SCID mouse with CD133⁺ hematopoietic stem cells purified from human cord blood infected with HTLV-1 ²⁹. Inverse PCR analysis of provirus integration sites revealed oligoclonal expansion of infected T cells in CD4⁺/CD25⁺ T-cells similar to HTLV-1-infected humans. *Villaudy J et al.* reported that HTLV-1 induce alterations of the thymus of Rag2/IL-2R γ ^c mice leading to expanded populations of mature CD4⁺/CD25⁺ T cells and other pathological features such as splenomegaly and lymphomas compared with mock-infected mice ³⁰. This unique model system was then used to test anti-cancer drugs in a related abstract further illustrating the usefulness of the model. *Van den Broeke et al.* ³¹ utilized NOD-Scid- γ immunodeficient mice to test in vivo kinome profiles from BLV-induced leukemic sheep.

Transgenic mice: transgenic mouse models continue to provide new insights into the molecular mechanisms of HTLV-1 Tax. *Swaims A et al.* reported on the role HTLV-1 expression in chronically-infected CD4⁺ T cells using LTR-Tax transgenic mice ³². In this system, immune activated Tax CD4⁺ T cells express characteristics of several different CD4⁺ T cell subtypes, suggesting that HTLV-1 Tax induces changes in the normal pattern of CD4⁺ subtype specification. In an interesting study using a bioinformatics approach, *Suzuki T et al.* ³³ identified proteins differentially expressed in a model of Tax-induced lymphoma ³⁴. Among the more than 700 proteins detected, levels of 53 proteins were increased in stem cells, including one membrane protein, which might potentially serve as a new target of antibody-based therapy.

Shinagawa M et al. ³⁵ constructed a transgenic (Tg) rat expressing human CRM1 (hCRM1), a cellular cofactor of Rex, and provided data that T cells derived from Tg rats allowed production of HTLV-1 as efficiently as human T cells ³⁶. Their results suggest the presence of inhibitor(s) during the entry process in rat dendritic cells. *Rosewick N et al.* ³⁷ reported ongoing studies in the bovine leukemia virus (BLV) model using high-throughput sequencing to reveal down-regulation of viral mRNAs that might contribute to tumor-associated virus silencing and play a role in immune escape mechanisms ³⁸. *Ohsugi & Kumasaka* reported their findings of a transgenic mouse model of arthropathy expressing Tax in mature thymocytes and peripheral T lymphocytes ^{39,40}. *Rauch et al.* reported that Tax expression in IL-15 knockout mice ^{41,42} develop larger and more aggressive tumors suggesting caution

against IL-15 blockade as an ATLL therapy [8]. *Taguchi N et al.*⁴³ investigated the production of cytokines in HBZ transgenic (HBZ-Tg) mice and provided data to support the concept that altered Foxp3 expression in iTreg cells may result in systemic inflammation⁴⁴.

Non human primates: *Moura et al.* provided promising data for new targeted therapy against ATL in a monkey model⁴⁵. They demonstrated that HTLV-1-infected cells constitutively express high levels of surface transferrin receptor (TfR) in acute forms of ATL and tested a monoclonal antibody (mAb A24) on ATL cells ex vivo. Importantly, in squirrel monkeys (*Simia Sciureus*) administration of single and repeated doses of A24 did not induce significant toxicity yet increased of transferrin and elicited apoptosis in lymph node samples in areas of high lymphocyte proliferation (germinal centres). This new agent (A24) is a potential new treatment of acute forms of ATL.

Rabbits: *Haines et al.* provided data on the development of an oral model of HTLV-1 transmission in rabbits to allow testing of the mucosal microenvironment during the early stages of orally-acquired HTLV-1⁴⁶.

BLV studies: several investigators provided data on host and viral determinants of BLV infection. *Gutiérrez et al.*⁴⁷ provided intriguing data on the efficacy of a life-attenuated BLV vaccine to prevent viral transmission in cattle⁴⁸. *Aida et al.* in a highly collaborative project identified genetic markers of BLV induced disease⁴⁹.

Future directions: There exist great needs to continue to develop models that reflect all stages of the infection and the full range of disease syndromes in humans infected with HTLV-1. Important gaps exist in the knowledge of early mucosal transmission and cell-to-cell transmission, such as early target cells and the tissue environmental influences that allow the virus to spread following oral and sexual routes of transmission. In addition, few animal models accurately mimic the neurologic disorders associated with HTLV-1 infection. Finally, models to reproduce the influence of co-infections with HTLV-1 and how these agents exacerbate the spectrum of HTLV-1 disease are needed to fully understand the pathogenesis of HTLV-1 in humans and to assist in the development of new therapeutic agents to ablate these devastating diseases.

MOLECULAR AND CELLULAR BIOLOGY

Regulation of HTLV-1 5'LTR: The primary activity of Tax is to modulate viral expression through the CREB/ATF pathway. Using HTLV-1 integrated chromatin templates, *Easley et al.* showed that an active viral promoter uses the chromatin remodeling complex PBAF⁵⁰. *McCabe et al.* suggested that the cellular FHL3 protein is involved in Tax-mediated

transactivation. On the other hand⁵¹, *Robette et al.* described that, in latently infected cells but not in cells that actively produce HTLV-1 virions, the CTIP2 complex (which contains histone deacetylases and a methyltransferase) is recruited onto the 5'LTR and inhibits Tax-mediated transcription, similar to what was described for HIV-1⁵².

Tax post-translational modifications and NF- κ B activation: Tax is also involved in cell transformation, notably through the constitutive activation of the NF- κ B pathway that can be divided into cytoplasmic and nuclear events. Ubiquitinated Tax is mostly found in the cytoplasm, while SUMOylated Tax is located in the nucleus. However, how Tax precisely shuttles between the cytoplasm and the nucleus, and which fractions play a role in the NF- κ B pathway is still a matter of debate. *Kfoury et al.* demonstrated that the same Tax molecule shuttles between the cytoplasm and the nucleus^{53,54}. Ubiquitination targets Tax to nuclear bodies, but interestingly both ubiquitination and SUMOylation control IKK γ targeting to the centrosome where NF- κ B activation begins. *Bex et al.* demonstrated that Tax co-localizes with TAB2- and IKK γ -positive structures in the cytoplasm, suggesting that they represent an important domain in the NF- κ B activation process⁵⁵. Whether the Tax species that are present there are ubiquitinated or not was not determined. *Yasunaga et al.* showed that the ubiquitinated fraction of Tax is a substrate of USP20, an ubiquitin specific peptidase, leading to Tax deubiquitination and to the suppression of NF- κ B activation^{56,57}. Interestingly, USP20 levels are low in HTLV-1-infected cells, where NF- κ B is usually elevated. It would now be of interest to determine whether this protein promotes the accumulation of SUMOylated Tax. By contrast, *Lavorgna et al.* described that STAMBPL1, another deubiquitinating (DUB) enzyme, is necessary for Tax activity⁵⁸. Importantly, STAMBPL1 does not induce Tax deubiquitination but protects Tax from degradation. The target of STAMBPL1 now remains to be identified. *Fryrear et al.* showed that the SUMOylated nuclear fraction of Tax might be the target of RNF4, a SUMO-targeted ubiquitin ligase⁵⁹. This promotes Tax translocation from nucleus to cytoplasm, its ubiquitination and allows an increase of NF- κ B activity. In contrast, using T lymphocytes, *Bonnet et al.* showed that a Tax mutant that is ubiquitinated but not SUMOylated can reach the nucleus, but is severely impaired for NF- κ B activation⁶⁰. Adding to the complexity, *Journo et al.* demonstrated that the HTLV-2 Tax protein is barely ubiquitinated⁶¹. Nevertheless, it efficiently recruits IKK γ , promotes RelA nuclear translocation and leads to NF- κ B activation. *Turci et al.* showed partially conflicting results by suggesting that Tax2 is ubiquitinated and SUMOylated when ubiquitin or SUMO is overexpressed⁶². *Shembade et al.* demonstrated that Tax prevents TAX1BP1 phosphorylation and therefore allows a constitutive NF- κ B activation⁶³. *Fu et al.* also showed that both the

canonical and the non-canonical NF- κ B pathways play a role during Tax-mediated tumorigenesis *in vivo* ⁶⁴. Even if NF- κ B is activated, Tax expression is usually low in leukemic cells. *Yamagishi et al.* showed that mir-31 is down regulated in these cells. Interestingly, a target of mir-31 is NIK, a kinase that is involved in NF- κ B activation ⁶⁵. Altogether, these results suggest that (i) both HTLV-1 Tax ubiquitination and SUMOylation are important for the activation of the NF- κ B pathway, (ii) several DUBs are directly or indirectly involved in the regulation of this process, (iii) HTLV-2 Tax does not function as its HTLV-1 counterpart, (iv) in ATL cells, the NF- κ B pathway is possibly activated through the down-regulation of cellular miRNAs.

HBZ and cellular transformation: Expression of Tax is rarely detected in ATL cells, thus favoring a model in which Tax is necessary for the induction, but not the maintenance, of the transformed phenotype. The HBZ viral protein might play a major role at this stage by preventing transcription from the 5'LTR. *Wright et al.* showed that, in addition to its physical interaction with CBP/p300 proteins, HBZ inhibits their Histone Acetyl Transferase (HAT) activity and consequently represses 5'LTR transcription. Inhibition of CBP/p300 HAT function also leads to a decreased activity of other cellular transcription factors such as p53 or p65/RelA ⁶⁶. It would now be important to determine the fate of these cells, where CBP/p300 functions are impaired. *Peloponese et al.* determined how the HBZ promoter is regulated and suggested that, in addition to Tax, HBZ itself regulates its own promoter through its interaction with JunD and its action on the Sp1 binding sites ⁶⁷. Working on viral latency and viral expression, *Choudhary et al.* demonstrated that HBZ expression results in a lower p30 mRNA expression ^{68,69}. Given the fact that p30 is a negative regulator of Tax, these results would suggest that HBZ indirectly favors Tax expression. Consistent with previous reports demonstrating that HBZ promotes cell proliferation, *Mukai & Ohshima* suggested that HBZ activates the mTOR signalling which plays a role in cell proliferation ⁷⁰, while *Zhi et al.* reported that HBZ down-regulates NF- κ B and prevents Tax-mediated senescence, therefore allowing the infected cells to divide ^{71,72}. Given that ATL cells display a constitutively active NF- κ B pathway, these results suggest that the negative effect of HBZ on the NF- κ B pathway is counteracted, possibly through mir-31 down-regulation.

Marban et al. demonstrated that APH-2 (the HTLV-2 counterpart of HBZ) binds c-Jun, but contrary to HBZ enhances its ability to activate AP-1 ⁷³. Interestingly, *Larocque et al.* showed that the APH-3 and APH-4 proteins (encoded respectively by HTLV-3 and HTLV-4) also activate JunB, c-Jun and JunD-mediated transcription ⁷⁴. Altogether, these results suggest

that, apart from HBZ, and despite having very divergent amino-acid sequences, all APH proteins activate AP-1 factors. Whether this plays a role *in vivo* remains to be determined.

Alteration of cell transcription/post-transcription regulatory mechanisms: Using T cell clones derived from HTLV-1 infected individuals, *Thenoz et al.* demonstrated that HTLV-1 infection promotes a deregulation of alternative splicing⁷⁵. Interestingly, and consistent with those results, *Mocquet et al.* demonstrated that Tax alters the Nonsense Mediated mRNA decay pathway⁷⁶, while Nakano et al.⁷⁷ suggested that this alteration was due to Rex. *Van Duyne et al.* further reported that Tax co-localizes with Drosha, an important actor of the RNAi pathway⁷⁸. In addition, Drosha levels were lower in HTLV-1 infected cells. Altogether, these results suggest that HTLV-1 proteins interfere with post-transcriptional regulatory mechanisms.

HTLV auxiliary proteins: The p12, p13, p30 proteins play an important role in the HTLV-1 viral cycle and in viral persistence *in vivo*. *Edwards et al.* showed that following palmitoylation and localization to membrane lipid rafts, both p12 and its cleavage product p8 can form homo- and hetero-dimers⁷⁹. Interestingly, some HTLV-1 infected individuals carry a virus encoding a mutated, dimerisation-impaired p8 protein. Because p8 is involved in viral transmission, this could suggest that some patients are better transmitters than others. *Silic-Benussi et al.* demonstrated that p13 increased mitochondrial ROS production resulting in activation of primary T-cells and sensitization to death of tumour T- cells^{80,81}. *Andresen et al.* suggested that, in the presence of Tax, p13 partially co-localizes with Tax in nuclear speckles and alters Tax function^{82,83}. This suggests that p13 also negatively regulates the viral expression and therefore favours latency. Finally, *Turpin et al.* demonstrated the existence of two spliced mRNAs encoded by STLV-3 pX ORFs. One of these mRNA encodes a protein (tentatively named p8) which function seems similar to that of the HTLV-1 p30 or HTLV-2 p28, although its precise mechanism of action remains unknown⁸⁴.

Future directions: despite a number of recent findings a number of questions subsist: i) how exactly does Tax activate the NF-kB and especially what is the exact role of Tax post-translational modifications in this event? ii) At least 3 HTLV-1 proteins repress Tax expression: how is the HTLV-1 cycle exactly regulated *in vivo*? On a global point of view, the intimate interplay between Tax and HBZ and their consequence on cell cycle, NF-kB and HTLV-1 pathogenesis also needs more work.

VIROLOGY

Viral transmission: HTLV-1 propagation and persistence in vivo depends on both de novo entry into host cells ("infectious transmission") and "mitotic transmission" of the integrated viral genome to daughter cells. Studies on HTLV-1 entry focused on the importance of dendritic cells (*Jones KS et al.*⁸⁵; *Manuel SL et al.*⁸⁶) and on the HTLV-1 binding and entry into cells, which involves the hierarchical interaction of viral envelope glycoproteins with three molecules on the surface of target cells: heparan sulfate proteoglycans, Neuropilin 1 and the glucose transporter GLUT1 (*Pique C et al.*⁸⁷). *Jensen SMR et al.* also showed evidence for a role in HTLV-1 entry of Xylosyltransferase 2, an enzyme encoded on chromosome 17q⁸⁸. Efficient cell-to-cell spread of HTLV-1 occurs via a highly organized cell-cell contact known as the virological synapse (VS). *Nejmeddine M et al.* showed exclusion of actin microfilaments in the VS in infected T-cells, a change that may cell facilitate viral transmission⁸⁹. Mother-to-child transmission through breastfeeding is a major mode of HTLV-1 transmission. *Martin-Latil St al.* developed an in vitro model to study passage of HTLV-1 through an epithelial barrier. Results showed that, although enterocytes were not susceptible to infection, HTLV-1 virions were detected in the basal compartment, suggesting a transcytotic mechanism of passage⁹⁰.

Dynamics of HTLV-1 propagation/expression in vivo: *Bangham CRM et al.* investigated the selection forces that determine the size of HTLV-1-infected clones in vivo. Results indicated that: (i) the CTL response to HBZ is a major determinant of proviral load and inflammatory diseases; (ii) anti-Tax CTL response is immunodominant but does not protect against HAM/TSP; (iii) HLA Class I and KIR genotypes determine CTL efficiency; (iv) the site and orientation of HTLV-1 provirus integration determine the size of each clone in the host⁹¹. *Gillet NA et al.* demonstrated that negative selection (possibly exerted by CTLs) dominates during chronic infection, favouring proviruses integrated in transcriptionally silenced DNA⁹².

Using splice site-specific qRT-PCR, *Rende F et al.* demonstrated a two-phase kinetics of HTLV-1 gene expression in PBMCs from infected patients, with the expression of Tax/Rex mRNA preceding that of other viral transcripts; the authors also demonstrated the Rex-dependency of this kinetics and showed that over 90% of the HBZ mRNAs were localized in the nucleus⁹³. *Bender C et al.* showed that HTLV-2 exhibits similar a 2-phase kinetics. However, a distinguishing characteristic of HTLV-2 was its higher expression of

mRNAs encoding potential inhibitors of Tax and Rex, i.e. p28 and truncated isoforms of Rex⁹⁴. Future studies should be aimed at testing whether HTLV-2 exhibits a more latent pattern of expression compared to HTLV-1. *Belrose G et al.* also analyzed HTLV-1 expression in PBMC from infected patients and showed that the HDAC inhibitor Valproate enhanced Tax while it blocked HBZ expression, suggesting that the balance between Tax and HBZ may determine the outcome of VPA treatment⁹⁵. *Oka T et al.* reported that the number of genes with methylated CpG islands increased with ATLL progression, especially in ATLL lymphomas. The high number of methylated genes correlated with a shorter patient survival⁹⁶. HTLV-1 and HTLV-2 tropism and spread were also studied by *Kannian P et al.* in a rabbit animal model. Results showed that HTLV-2 proviral loads were lower than HTLV-1 and infection was prevalent in CD8+ cells⁹⁷.

Effects of HTLV-1 proteins on the DNA damage response: *Boxus M et al.* showed that Tax associates with the minichromosome maintenance MCM2-7 helicase complex and localizes to origins of replication. Through this interaction, Tax fires supplementary origins at the onset of S phase, thus accelerating S phase progression, but also generating replicative stress and activation of the DNA damage response⁹⁸; this pathway is also engaged by HTLV-1 p30 through its ability to bind ATM and REG γ (*Anupam R et al.*⁹⁹) and by HBZ, which increases the sensitivity of Jurkat cells to cell death induced by DNA damaging drugs (*Wurm T et al.*¹⁰⁰).

Post-transcriptional effects of Tax: Effects of Tax at the post-transcriptional level are also emerging: *Mocquet V et al.* demonstrated that Tax interacts with INT6, sequestering it from the Nonsense Mediated mRNA Decay (NMD) factors UPF1/2. Tax also increases the size and number of P bodies, the site of UPF1 accumulation with mRNAs targeted by NMD. These data suggest that Tax regulates mRNA degradation through NMD⁷⁶. *Van Duyne R et al.* reported a down regulation of the RNAi component Drosha in HTLV-1 infected cells; the colocalisation of Tax with Drosha in nuclear speckles suggests functional interactions of Tax with the RNAi machinery⁷⁸.

Minus-strand genes of HTLV-1 and HTLV-2: *Borowiak M et al.* showed that primary leukemic cells isolated from ATLL patients express high amounts of hTERT, the catalytic subunit of the telomerase complex, and exhibit elevated expression of HBZ and Menin, an inhibitor of hTERT expression¹⁰¹. *Douceron E et al.* observed that expression of HTLV-2 APH-2 and Tax are correlated with HTLV-2 proviral load but not with lymphocytosis; consistent with this, APH2 (contrary to HBZ of HTLV-1) did not promote cell proliferation in vitro¹⁰². The nuclear localization of minus strand transcripts of both HTLV-1 and HTLV-2⁹⁴

might favour viral persistence by reducing translation and exposure of the infected cell to the CTL response while allowing function as a non-coding transcripts.

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It is now accepted that an efficient CD8⁺ cytotoxic T cell (CTL) response to HTLV-1 reduces the proviral load and the risk of inflammatory diseases such as HAM/TSP. But it remains possible that CD8⁺ T cells also contribute to the tissue damage that leads to neurological symptoms. It is also unknown, although it seems highly probable, whether an efficient anti-HTLV-1 CTL response also protects against ATLL.

CTL response: The Tax protein of HTLV-1 remains a focus of much work on the CTL response, because the frequency of Tax-specific CTLs is higher than that of CTLs specific to any HTLV-1 antigen: that is, the Tax protein is immunodominant in the CTL response. *Kubota et al.*¹⁰³ found that HLA-A24-restricted CTLs can recognize low concentrations of Tax, and they suggest that such cells might contribute to the pathogenesis of HAM/TSP. The expression of surface molecules associated with T cell exhaustion (PD-1; Tim-3) is low on HTLV-1-specific CTLs which may help to preserve a functional antiviral response^{104,105}. However, it is now apparent that the protective CTL response to HTLV-1 may not in fact be directed against Tax, but against other HTLV-1 proteins. Although the Tax protein is immunodominant, and HLA-A2 is protective in HTLV-1 infection in southern Japan, and Tax peptides can bind strongly to HLA-A2, there is no direct evidence that the strong anti-Tax CTL response itself is protective. Indeed, recent evidence shows that it is efficient CTL recognition of the HBZ protein, not Tax, that confers protection in HTLV-1 infection⁹¹.

Interferon, interleukins and chemokines: *Kannagi et al.*¹⁰⁶ reported the potentially important finding that type 1 interferon (IFN) can reduce HTLV-1 Gag protein expression in vitro. If this is true in vivo, it provides an attractive explanation for the puzzling observation that HTLV-1 proviral expression spontaneously and dramatically rises in freshly isolated PBMCs. Proviral transcription may be suppressed in vivo by type 1 IFN produced by, for example lymphatic endothelium; this repression would then be released when the cells are incubated ex vivo, away from the endothelium. Type 1 IFN has been tried as a treatment for HAM/TSP, albeit with limited success. *Moens et al.*¹⁰⁷ reported that ascorbic acid has more powerful anti-viral and anti-proliferative effects than IFN- α on freshly isolated PBMCs from HTLV-1-infected people. Just as the CTL response might exert detrimental effects as well as the observed protective effects in HTLV-1 infection, so IFNs may exert mixed effects. *Tattermusch et al.*¹⁰⁸ used gene expression microarray analysis and discovered an IFN

signature in HTLV-1 infection: high level expression of IFN-stimulated genes was associated with the presence of HAM/TSP, independently of the proviral load. Perhaps a local excess of both IFNs and CTL activity in the CNS is detrimental, although each is beneficial in the host as a whole. The role of chemokines and cytokines other than IFNs deserves more attention in HTLV-1 infection. IL-15, which promotes replication and survival of NK cells and CD8⁺ T cells (CTLs), is upregulated in HTLV-1 infection. *Rauch et al.*⁴¹ provided a warning, however, that IL-15 can also promote tumour growth in Tax-transgenic mice. IL-18 is a cytokine that stimulates the production of the potentially inflammatory IFN- γ by NK cells and T cells. *Wagatsuma et al.*¹⁰⁹ reported that certain polymorphisms in the IL-18 gene promoter were more frequent in patients with HTLV-1 infection than uninfected controls in Brazil. However, there was no significant difference in allele frequency between asymptomatic HTLV-1 carriers and patients with HAM/TSP, and it remains in question whether IL-18 plays a role in the pathogenesis of HAM/TSP. HTLV-1 Tax protein has previously been shown to cause infected T cells to secrete the chemokine CCL22, which maintains the high frequency of CD4⁺ FoxP3⁺ cells observed in HTLV-1 infection. *Barrios et al.*¹¹⁰ provided evidence that recombinant Tax from HTLV-1 (Tax-1) and HTLV-2 (Tax-2) can stimulate production of 3 CC chemokines by PBMCs in vitro. Further work is needed to assess the possible significance of this observation in vivo.

HBZ: It is now realized that the HBZ gene, encoded on the negative strand of the HTLV-1 provirus, plays a critical role in several aspects of HTLV-1 biology. Its importance as the antigen recognized by the protective class 1 HLA-associated immune response was mentioned above. HBZ itself may also counter the immune response: *Douville et al.*¹¹¹ found that HBZ may inhibit IFN type 1 responses when transfected into human PBMCs and astrocytes, by down regulating IRF3-dependent signalling. *Miyazato et al.*¹¹² reported that HBZ both upregulated expression of the transcription factor FoxP3, which is characteristic of regulatory T cells (T_{regs}), and simultaneously diminished the suppressive (regulatory) functions of the FoxP3⁺ cells. Intriguingly, both of these effects have also been reported to be exerted by Tax. *Sugata et al.*¹¹³ observed that HBZ can also repress transcription from the IFN gamma promoter, and the authors suggested that this repression might contribute to the severe immunosuppression characteristic of adult T cell leukaemia/lymphoma.

Antibody response: The antibody response to HTLV-1 has been much less studied than the T cell response. It has long been known that anti-HTLV-antibody can reach very high titres, especially in patients with HAM/TSP. *Akahata et al.*¹¹⁴ have devised a luciferase immune-precipitation system to quantify anti-HTLV-1 antibodies, and suggest that the assay may be

useful as a prognostic or diagnostic test. *Kuo et al.*¹¹⁵ used recombinant Env proteins to generate potentially antiviral monoclonal antibodies in mice. This system may prove useful to identify potentially protective antibody epitopes in Env protein, which varies little in sequence compared with the Env protein of HIV-1.

Future directions: The findings summarized above raise many important questions that deserve more attention in future research. Among these questions, we identify four of particular interest: i) Since HTLV-1 with the same sequence causes the full range of malignant and inflammatory diseases, the outcome of infection must be determined by variation among hosts. The class 1-restricted CTL response accounts for about 50% of the observed risk of HAM/TSP: what accounts for the remaining 50%? And does HLA class 1 genotype also determine the risk of ATLL? ii) How does KIR genotype determine the efficiency of HLA class 1-mediated protection? iii) What is the balance of beneficial and harmful effects of interferons in HTLV-1 infection? What are the causes and consequences of the observed reduction in the number and activity of NK cells in HTLV-1 infection?

ENDOGENOUS RETROVIRUSES, FOAMY VIRUSES AND XMRV

The growing importance of non-HTLV human retroviruses was highlighted by the Scientific Committee organizing two sessions entitled “Endogenous retrovirus, foamy viruses and XMRV”. Debate and discussion of whether xenotropic murine leukemia virus (MLV) related viruses (XMRV) represent genuine human viruses or laboratory artifact continued during these two sessions.

XMRV: Two presentations did not find XMRV or related viruses in persons with chronic fatigue syndrome (CFS) or multiple sclerosis (MS) while a third reported finding only polytropic MLV in both CFS patients and healthy controls¹¹⁶⁻¹¹⁹. However, two articles published in *Science*, the week of the conference, helped elucidate the origin and significance of XMRV. *Propotka et al.* provided strong evidence, that XMRV was not present in the human prostate cancer cell line 22Rv1 but rather is a novel mouse gammaretrovirus, generated via recombination during the passage of human prostate tissue xenografts in nude mice, containing near perfect chimeras, the 5' and 3' halves of the consensus XMRV genome¹²⁰. *Knox et al.* using serology, culture, and PCR methods, failed to confirm XMRV infection in persons with chronic fatigue syndrome (CFS)¹²¹, including those found positive in the original study by *Lombardi et al.*¹²². *Knox et al.* showed that sera containing complement from CFS patients and matched controls both inactivated XMRV and MLV *in vitro*, restricting infection of human cells with these viruses, suggesting that sustained infection in

humans is highly unlikely¹²¹. They reported evidence of contamination of mouse monoclonal antibodies used in hot start PCR enzymes and cell sorting/staining. Contamination and non-specific serologic reactivity, as sources of false positive results in XMRV studies, were further emphasized in presentations by *Erlwein et al.*¹²³ and *Qiu et al.*¹²⁴. Qiagen columns used for DNA extraction from paraffin-embedded tissues contained both MLV and XMRV *gag* sequences, adding to the plethora of reagents, such as PCR enzymes, monoclonal antibodies and cell lines, were found to be contaminated with these viruses and sequences. *Qiu et al.* presented data showing cross-reactivity of sera from HTLV-1-infected persons with a conserved peptide region in the XMRV p15E envelope surface protein. They also reported an absence of reactivity in a large number of US blood donors and HIV-1-infected Africans using well-validated assays, suggesting that previous sero-reactive results obtained by others may be due to cross-reactivity or non-specific binding using incompletely validated tests¹²⁴. Combined with the majority of the negative reports, these findings have led laboratories previously reporting positive results questioning their original results and attempting to replicate those data, while now having to exclude possible sources of contamination. Such was the case in the presentation by *Hanson et. al* who described the extensive testing done and still to be performed to rule out false positive MLV results in the persons with CFS and healthy controls in their study¹¹⁶. Although the field is now heavily favouring the end of investigations of XMRV and MLV as human viruses, two ongoing studies at multiple institutions, one led by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH as presented by Graham Simmons¹²⁵ and one led by Ian Lipkin at Columbia University, should finally clarify whether XMRV and MLV are present in blood donors and persons with CFS, respectively.

Simian foamy viruses: While the end is seemingly near for XMRV, much more research is needed to better understand the public health importance of human infection with other retroviruses, including simian foamy virus (SFV), a common infection in nonhuman primates (NHPs)¹²⁶. From the meeting, it is clear that SFV is widely distributed across central Africa (Cameroon, Democratic Republic of Congo, Gabon), mostly in persons with exposure to NHPs, but also in persons without reported NHP exposure^{119,127,128}. For example, one wife of an SFV-infected hunter in Cameroon was reported to be seropositive, suggestive of person-to-person transmission¹²⁷. However, additional work is needed to determine, if SFV is transmitted secondarily and if so, at what frequency.

STLVs: In addition to SFV, other simian retroviruses are known to cross species and infect humans¹²⁹. For example, *Calvignac-Spencer et al.* provided evidence for zoonotic

transmission of simian T-lymphotropic virus type 1 (STLV-1) from colobus monkeys and chimpanzees in Côte d'Ivoire¹³⁰. In contrast, the lack of a closely related STLV has been an enigma for understanding the evolutionary history and origin of HTLV-2. STLV-2 in captive and wild bonobos is genetically similar but very distinct from HTLV-2¹³¹. The finding of only HTLV-2 subtype b strains in Baka pygmies, some of the oldest inhabitants of Cameroon, phylogenetically related to HTLV-2b in Amerindians suggests an African origin for both STLV-2 and HTLV-2. HTLV-2b may have co-migrated with the ancient movement of Africans through Asia, across the Bering Strait, and into the Americas¹³². Alternatively, HTLV-2b in the Baka may be due to a more recent introduction into Africa. An expanded search for STLV-2-like viruses in NHPs and testing of other ancient African and Asian populations will help clarify these possibilities.

Endogenous retroviruses: ERVs integrated into the human genome million of years ago and have been associated with a variety of illnesses, including cancer and multiple sclerosis (MS), though these associations remain controversial¹³³. At the conference, several presentations¹³⁴⁻¹³⁷ addressed the role of ERVs in MS and various cancers. However, case-control studies and animal model studies using infectious molecular clones are required to fully understand what role, if any, ERVs may play in human disease.

Future directions: Screening people for retroviruses in conjunction with other blood borne and sexually transmitted infections in endemic areas would help to determine, if these viruses are entering the general population, and if co-infections facilitate this transmission.

Longitudinal, long-term follow-up studies will determine the pathogenicity of these viruses in humans. Establishing the prevalence of so called "harmless" retroviruses, such as SFV, in specific patient cohorts with common chronic conditions, malignant and inflammatory, in endemic regions, would add to our understanding of how these viruses might be contributing to human disease. Genetic characterization of complete genomes and studying the intra-host and inter-host evolution of these viruses, coupled with animal model studies, will help understand the possible pathogenicity of these novel human viruses. Together, population-based and expanded molecular epidemiologic studies will determine how widespread these viruses are and determine their natural history in their primate hosts and humans.

Conclusions

As anticipated the 15th HTLV Conference on Human Retrovirology, HTLV and Related Viruses led to the early distribution of exciting new data, especially in the field of molecular

and animal model science. Although little progress had been made specifically in the development of treatment for lymphomatous ATL and HAM/TSP since the 14th Conference in Bahia, Brazil, this conference supported the formation of two clinical trial groups: HAM/TSP and ATL Clinical Trial Subgroup. The aim of these groups are three fold: i) to inform members of relevant published clinical data; ii) to introduce working groups planning future clinical trials and iii) to inform members of ongoing clinical trials and expand recruitment. The HAM/TSP CTSG is currently developing a multicentre, international phase III clinical trial in patients with active HAM/TSP, with principle investigators from Brazil, Japan, Peru, USA and UK. These groups and much more are accessible through the HTLV association website (<http://htlv.net>). The HTLV 16th conference will be held in Montreal, Canada in June 2013.

Authors' contributions

FM, CRMB, VC, MDL, ELM, WMS, RM wrote the manuscript. FM and RM edited the manuscript.

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Conflict of Interests:

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References

- 1 Kaidarova, Z. & Murphy, E. HTLV-I and -II seroprevalence among United States blood donors, 2000-2009 (Abstract). *Retrovirology* **8**, A74 (2011).
- 2 Carneiro-Proietti, A. *et al.* HTLV-1/2 prevalence in Brazilian blood donors: regional and demographic variation (Abstract). *Retrovirology* **8**, A83 (2011).
- 3 Carneiro-Proietti, A. *et al.* HTLV-1 and -2 seroprevalence, incidence and residual transfusion risk among blood donors in Brazil during 2007-2009. *AIDS Res Hum Retroviruses* **in press** (2011).
- 4 Caterino-de-Araujo, A., Magri, M., Costa, E. & Manuel, R. Prevalence of HTLV-1/2 and HIV-1/2 in individuals attending Public Health Center in Mozambique. One HTLV-1 symptomatic case report (Abstract). *Retrovirology* **8**, A69 (2011).
- 5 Desrames, A. *et al.* Molecular epidemiology of HTLV-1 infection in the caribbean area as compared to West Africa : relationship with the slave trade (Abstract). *Retrovirology* **8**, A90 (2011).
- 6 Birman, B. *et al.* Altered host immunity, human T lymphotropic virus type I replication, and risk of adult T-cell leukemia/lymphoma: a prospective analysis from the ATL Cohort Consortium (Abstract). *Retrovirology* **8**, A81 (2011).
- 7 Matsuzaki, T., Kodama, T., Kubota, R. & Izumo, S. Recent epidemiologic trends of HAM/TSP in Japan (Abstract). *Retrovirology* **8**, A77 (2011).
- 8 Costa, D. *et al.* Neurological manifestations in HTLV-1 patients with overactive bladder syndrome. A precursor of HAM/TSP? (Abstract). *Retrovirology* **8**, A78 (2011).
- 9 Guiltinan, A. *et al.* Major depression and generalized anxiety disorder among HTLV-I/II infected former blood donors (Abstract). *Retrovirology* **8**, A70 (2011).
- 10 Galvao-Phileto, A., Boa-Sorte, N., Kruschewsky, R. & Galvao-Castro, B. Quality of life (QOL) and depression in HTLV-1 carriers (Abstract). *Retrovirology* **8**, A65 (2011).
- 11 Arruda, S. *et al.* Association between Human T-Cell Lymphotropic Virus Type 1 and 2 (HTLV 1/2) infection and tuberculosis: systematic review and meta-analysis (Abstract). *Retrovirology* **8**, A80 (2011).
- 12 Einsiedel, L., Fernandes, L., Spelman, T. & Gotuzzo, E. Infection with Human T Lymphotropic Virus 1 is associated with bronchiectasis among Indigenous Australians (Abstract). *Retrovirology* **8**, A38 (2011).
- 13 Demontis, M., Hilburn, S. & Taylor, G. The clinical utility of HTLV-1 viral load measurement. *Retrovirology* **8**, A46 (2011).
- 14 Grassi, M. *et al.* HTLV-1 proviral load of HAM/TSP patients according to new diagnostic criteria of HAM/TSP. *Retrovirology* **8**, A248 (2011).
- 15 Yamano, Y. *et al.* Clinical subtype of HAM/TSP based on clinical course and laboratory findings. *Retrovirology* **8**, A42 (2011).
- 16 Gotuzzo, E. *et al.* Changes in proviral load (PVL) among patients with rapidly progressive HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) receiving empirical therapy. *Retrovirology* **8**, A58 (2011).
- 17 Seegulam, M. E. & Ratner, L. Integrase inhibitors effective against human T-cell leukemia virus type 1. *Antimicrob Agents Chemother* **55**, 2011-2017, doi:AAC.01413-10 [pii] . 10.1128/AAC.01413-10 (2011).
- 18 Fox, J. *et al.* Circularised 1 and 2 LTR DNA circles are present in freshly- and chronically-infected cell lines and patient PBMCs, indicating ongoing reverse transcriptase usage. *Retrovirology* **8**, A51 (2011).

- 19 Trevino, A. *et al.* Treatment with Raltegravir, a retroviral integrase inhibitor, in patients infected with HTLV-1. *Retrovirology* **8**, A55 (2011).
- 20 Uike, N., Tanosaki, R., Utsunomiya, A., Choi, I. & Okamura, J. Can allo-SCT with RIC cure ATLL? Long-term survivors with excellent PS and with heterogenous HTLV-1 proviral load level. *Retrovirology* **8**, A33 (2011).
- 21 Choi, I. *et al.* Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials. *Bone Marrow Transplant* **46**, 116-118, doi:bmt201092 [pii]
10.1038/bmt.2010.92 (2011).
- 22 Suarez, F. *et al.* Arsenic trioxide in the treatment of HTLV1 associated ATLL. *Retrovirology* **8**, A59 (2011).
- 23 Yamamoto, K. *et al.* Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. *J Clin Oncol* **28**, 1591-1598, doi:JCO.2009.25.3575 [pii]
10.1200/JCO.2009.25.3575 (2010).
- 24 Utsunomiya, A. *et al.* Promising results of an anti-CCR4 antibody, KW-0761, for relapsed Adult T-Cell Leukemia-Lymphoma (ATL). *Retrovirology* **8**, A40 (2011).
- 25 Gillet, N. *et al.* HTLV-1 clonality during chronic infection and BLV clonality during primary infection. *Retrovirology* **8**, A185 (2011).
- 26 Ramos, J. *et al.* Targeting HTLV-I latency in Adult T-cell Leukemia/Lymphoma. *Retrovirology* **8**, A48 (2011).
- 27 Hodson, A. *et al.* First line treatment of acute and chronic ATLL with zidovudine (AZT) and interferon alpha (IFN-alpha): haematological and molecular responses. *Retrovirology* **8**, A53 (2011).
- 28 Zimmerman, B., Niewiesk, S. & Lairmore, M. D. Mouse models of human T lymphotropic virus type-1-associated adult T-cell leukemia/lymphoma. *Vet Pathol* **47**, 677-689, doi:0300985810370009 [pii]
10.1177/0300985810370009 (2010).
- 29 Tezuka, K. *et al.* Inverse correlation between Tax and CD25 expressions in HTLV-1 infected CD4 T-cells in vivo. *Retrovirology* **8**, A14 (2011).
- 30 Villaudy, J. *et al.* HTLV-1 propels thymic human T cell development in "human immune system" Rag2^{-/-} IL-2R^{gamma}^{-/-} Mice. *Retrovirology* **8**, A10 (2011).
- 31 Van den Broeke, A. *et al.* Kinome profiling of BLV-induced ovine leukemia: an approach for identifying altered signaling pathways associated with oncogenesis. *Retrovirology* **8**, A16 (2011).
- 32 Swaims, A. Y. *et al.* Immune activation induces immortalization of HTLV-1 LTR-Tax transgenic CD4⁺ T cells. *Blood* **116**, 2994-3003, doi:blood-2009-07-231050 [pii]
10.1182/blood-2009-07-231050 (2010).
- 33 Suzuki, T. *et al.* Comparative proteomic analysis of cancer stem cells in a Tax-transgenic (Tax-Tg) mouse model of adult T-cell leukemia/lymphoma. *Retrovirology* **8**, A9 (2011).
- 34 Hasegawa, H. *et al.* Thymus-derived leukemia-lymphoma in mice transgenic for the Tax gene of human T-lymphotropic virus type I. *Nat Med* **12**, 466-472, doi:nm1389 [pii]
10.1038/nm1389 (2006).
- 35 Shinagawa, M. *et al.* Entry inhibition of human retroviruses in rat cells. *Retrovirology* **8**, A20 (2011).
- 36 Hakata, Y., Yamada, M. & Shida, H. Rat CRM1 is responsible for the poor activity of human T-cell leukemia virus type 1 Rex protein in rat cells. *J Virol* **75**, 11515-11525, doi:10.1128/JVI.75.23.11515-11525.2001 (2001).

- 37 Rosewick, N. *et al.* High-throughput sequencing reveals novel microRNAs in the Bovine Leukemia Virus (BLV)-induced ovine model of leukemia. *Retrovirology* **8**, A15 (2011).
- 38 Merimi, M. *et al.* Epigenetics and leukemia: unraveling oncogenic processes in the BLV ovine model. *Front Biosci (Schol Ed)* **1**, 154-163, doi:15 [pii] (2009).
- 39 Ohsugi, T. & Kumasaka, T. Low CD4/CD8 T-cell ratio associated with inflammatory arthropathy in human T-cell leukemia virus type I Tax transgenic mice. *PLoS One* **6**, e18518, doi:10.1371/journal.pone.0018518 (2011).
- 40 Ohsugi, T. & Kumasaka, T. Altered CD4+/CD8+ T-cell ratio in splenocytes of human T-cell leukemia virus type I Tax transgenic mice with inflammatory arthropathy. *Retrovirology* **8**, A2 (2011).
- 41 Rauch, D., Bokhari, S., Harding, J. & Ratner, L. IL-15 deficiency promotes tumor growth in tax transgenic mice. *Retrovirology* **8**, A24 (2011).
- 42 Rauch, D. *et al.* T-cell activation promotes tumorigenesis in inflammation-associated cancer. *Retrovirology* **6**, 116, doi:1742-4690-6-116 [pii] 10.1186/1742-4690-6-116 (2009).
- 43 Taguchi, N., Satou, Y., Ohshima, K. & Matsuoka, M. HTLV-1 bZIP factor induces systemic inflammations in vivo. *Retrovirology* **8**, A8 (2011).
- 44 Matsuoka, M. & Green, P. L. The HBZ gene, a key player in HTLV-1 pathogenesis. *Retrovirology* **6**, 71, doi:1742-4690-6-71 [pii] 10.1186/1742-4690-6-71 (2009).
- 45 Moura, I. *et al.* A neutralizing monoclonal antibody (mAb A24) directed against the transferrin receptor induces apoptosis of tumor T lymphocytes from ATL patients. *Retrovirology* **8**, A60 (2011).
- 46 Haines, R., Urbiztondo, R., Haynes, R., Niewiesk, S. & Lairmore, M. Development of a model of HTLV-1 oral transmission in the rabbit. *Retrovirology* **8**, A19 (2011).
- 47 Gutierrez, G. *et al.* A life-attenuated BLV deletant as a candidate vaccine to inhibit viral transmission in bovine herds. *Retrovirology* **8**, A12 (2011).
- 48 Florins, A. *et al.* Cell dynamics and immune response to BLV infection: a unifying model. *Front Biosci* **12**, 1520-1531, doi:2165 [pii] (2007).
- 49 Aida, Y. *et al.* Bovine MHC class II DR molecule plays a key role in bovine leukemia virus (BLV)-induced lymphoma. *Retrovirology* **8**, A7 (2011).
- 50 Easley, R. *et al.* Human T-Lymphotropic Virus Type 1 transcription and chromatin-remodeling complexes. *Retrovirology* **8**, A178 (2011).
- 51 McCabe, A., Hall, W. & Sheehy, N. Physical and functional interaction between the HTLV-1 Tax oncoprotein and the cellular LIM domain protein FHL3. *Retrovirology* **8**, A160 (2011).
- 52 Robette, G. *et al.* Role of the cofactor CTIP2 (COUP-TF Interacting Protein 2) in the transcriptional repression of HTLV-1 (Human T-lymphotropic Virus 1). *Retrovirology* **8**, A130 (2011).
- 53 Kfoury, Y. *et al.* Tax ubiquitylation and SUMOylation control the dynamic shuttling of Tax and NEMO between Ubc9 nuclear bodies and the centrosome. *Retrovirology* **8**, A146 (2011).
- 54 Kfoury, Y. *et al.* Tax ubiquitylation and SUMOylation control the dynamic shuttling of Tax and NEMO between Ubc9 nuclear bodies and the centrosome. *Blood* **117**, 190-199, doi:10.1182/blood-2010-05-285742 [pii] 10.1182/blood-2010-05-285742 (2011).
- 55 Bex, F. *et al.* Cytoplasmic and nuclear events controlling Tax-mediated activation of the NF-kappaB pathway: involvement of TAB2, IKKgamma/NEMO and calreticulin. *Retrovirology* **8**, A138 (2011).

- 56 Yasunaga, J., Lin, F., Lu, X. & Jeang, K.-T. HTLV-1 Tax-induced NF-kappaB activation is negatively regulated by Ubiquitin-specific peptidase 20 (USP20). *Retrovirology* **8**, A129 (2011).
- 57 Yasunaga, J., Lin, F. C., Lu, X. & Jeang, K. T. Ubiquitin-Specific Peptidase 20 Targets TRAF6 and Human T Cell Leukemia Virus Type 1 Tax To Negatively Regulate NF- κ B Signaling. *J Virol* **85**, 6212-6219, doi:[10.1128/JVI.00079-11](https://doi.org/10.1128/JVI.00079-11) [pii]
- [10.1128/JVI.00079-11](https://doi.org/10.1128/JVI.00079-11) (2011).
- 58 Lavorgna, A. & Harhaj, E. STAMBPL1 is a deubiquitinating enzyme that regulates HTLV-I Tax subcellular localization and NF-kB activation. *Retrovirology* **8**, A190 (2011).
- 59 Fryrear, K., Kerscher, O. & Semmes, O. The SUMO-targeted ubiquitin ligase RNF4 regulates localization and function of the HTLV-1 oncoprotein Tax. *Retrovirology* **8**, A126 (2011).
- 60 Bonnet, A. *et al.* Predominant role of Tax sumoylation in Tax-induced NF-kB activation in T cells. *Retrovirology* **8**, A132 (2011).
- 61 Journo, C. *et al.* Exclusion from the Golgi and very low levels of HTLV-2 Tax ubiquitination do not prevent IKK-gamma/NEMO relocalization and NF-kappaB activation. *Retrovirology* **8**, A134 (2011).
- 62 Turci, M. *et al.* Comparison of Tax-1 and Tax-2B post-translational modifications using specific lysine mutants in relation to activation of NF-kappaB and intracellular localization. *Retrovirology* **8**, A143 (2011).
- 63 Shembade, N. & Harhaj, E. The human T-cell leukemia virus type I (HTLV-I) oncoprotein Tax promotes persistent NF-kappaB activation by blocking the phosphorylation of the adaptor molecule TAX1BP. *Retrovirology* **8**, A158 (2011).
- 64 Fu, J. *et al.* Coordination of the canonical and noncanonical IKK/NF-kappaB signaling pathways in HTLV-I Tax-mediated tumorigenesis. *Retrovirology* **8**, A157 (2011).
- 65 Yamagishi, M. *et al.* Genetic and epigenetic loss of miR-31 activates NIK-dependent NF-kappaB pathway in Adult T-cell Leukemia. *Retrovirology* **8**, A128 (2011).
- 66 Wright, D., Wurm, T., Polakowski, N., Mesnard, J.-M. & Lemasson, I. HBZ inhibits the HAT activity of the cellular coactivators p300 and CBP. *Retrovirology* **8**, A150 (2011).
- 67 Peloponese, J.-M., Lemasson, I., Barbeau, B. & Mesnard, J.-M. JunD/HBZ enhances HBZ enhances HTLV-1 antisense transcription. *Retrovirology* **8**, A135 (2011).
- 68 Choudhary, G. & Ratner, L. The HTLV-1 hbz antisense gene indirectly promotes tax expression via down-regulation of p30(II) mRNA. *Virology* **410**, 307-315, doi:S0042-6822(10)00737-3 [pii]
- [10.1016/j.virol.2010.11.019](https://doi.org/10.1016/j.virol.2010.11.019) (2011).
- 69 Choudhary, G., Rauch, D. & Ratner, L. The HTLV-1 hbz antisense gene indirectly promotes tax expression via down-regulation of p30-II mRNA. *Retrovirology* **8**, A136 (2011).
- 70 Mukai, R. & Ohshima, T. HTLV-1 HBZ activates mTOR signaling pathway via inhibition of GADD34. *Retrovirology* **8**, A155 (2011).
- 71 Zhi, H. *et al.* NF-kappaB hyper-activation by HTLV-1 Tax induces cellular senescence, but can be alleviated by the viral anti-sense protein HBZ. *Retrovirology* **8**, A200 (2011).
- 72 Zhi, H. *et al.* NF-kappaB hyper-activation by HTLV-1 tax induces cellular senescence, but can be alleviated by the viral anti-sense protein HBZ. *PLoS Pathog* **7**, e1002025, doi:[10.1371/journal.ppat.1002025](https://doi.org/10.1371/journal.ppat.1002025) (2011).
- 73 Marban, C., Hall, W. & Sheehy, N. Regulation of AP-1 activity by the HTLV-2 APH-2 protein. *Retrovirology* **8**, A161 (2011).
- 74 Larocque, E., Lemay, G., Mesnard, J.-M., Switzer, W. & Barbeau, B. HTLV-3 and HTLV-4 antisense proteins activate JunB-, c-Jun- and JunD-dependent transcription. *Retrovirology* **8**, A141 (2011).
- 75 Thenoz, M. *et al.* HTLV-1 modulates alternative splicing in CD4+ T cells in vivo. *Retrovirology* **8**, A168 (2011).

- 76 Mocquet, V. *et al.* The HTLV-1 Tax protein inhibits nonsense-mediated mRNA decay by interacting with INT6/EIF3E and UPF1. *Retrovirology* **8**, A139 (2011).
- 77 Nakano, K. *et al.* A novel function of HTLV-1 Rex in inhibition of the host mRNA surveillance mechanism (NMD) for protection of the viral genomic mRNA. *Retrovirology* **8** (2011).
- 78 Van Duyne, R. *et al.* Localization and sub-cellular shuttling of HTLV-1 Tax with the RNAi machinery component Drosha. *Retrovirology* **8**, A159 (2011).
- 79 Edwards, D. *et al.* Role of dimerization and palmitoylation on the function of HTLV-1 p12 and p8. *Retrovirology* **8**, A124 (2011).
- 80 Silic-Benussi, M. *et al.* Control of ROS production and T-cell turnover by HTLV-p13. *Retrovirology* **8**, A154 (2011).
- 81 Silic-Benussi, M. *et al.* Redox regulation of T-cell turnover by the p13 protein of human T-cell leukemia virus type 1: distinct effects in primary versus transformed cells. *Blood* **116**, 54-62, doi:[blood-2009-07-235861 \[pii\].10.1182/blood-2009-07-235861](https://doi.org/10.1182/blood-2009-07-235861) (2010).
- 82 Andresen, V. *et al.* Tax-mediated re-routing of the HTLV-1 p13 protein to nuclear speckles. *Retrovirology* **8**, A125 (2011).
- 83 Andresen, V. *et al.* Suppression of HTLV-1 replication by Tax-mediated re-routing of the p13 viral protein to nuclear speckles. *Blood*, doi:[blood-2010-06-293340 \[pii\].10.1182/blood-2010-06-293340](https://doi.org/10.1182/blood-2010-06-293340) (2011).
- 84 Turpin, J. *et al.* Identification and characterization of auxiliary proteins encoded by the STLV-3 retrovirus pX region. *Retrovirology* **8**, A133 (2011).
- 85 Jones, K. *et al.* Continuous long-term growth of plasmacytoid dendritic cells following in vitro infection with HTLV-1. *Retrovirology* **8**, A174 (2011).
- 86 Manuel, S. *et al.* Dynamics of dendritic cells and T cells in HTLV-1-associated neuroinflammatory disease: implications in immunomodulatory therapies and diagnostic tools. *Retrovirology* **8**, A187 (2011).
- 87 Pique, C., Hermine, O., Ruscetti, F. & Jones, K. New insights into HTLV entry. *Retrovirology* **8**, A183 (2011).
- 88 Jensen, S. *et al.* Xylosyltransferase 2, a protein encoded on chromosome 17q, is involved in HTLV entry. *Retrovirology* **8**, A201 (2011).
- 89 Nejmeddine, M., Clerc, I., Taylor, G. & Bangham, C. Exclusion of actin microfilaments from the cell-cell contact zone in HTLV-1 infected T-lymphocyte during the establishment of a functional virological synapse. *Retrovirology* **8**, A199 (2011).
- 90 Martin-Latil, S. *et al.* Mother-to-child transmission of HTLV-1: in vitro study of HTLV-1 passage across a tight human epithelial barrier. *Retrovirology* **8**, A194 (2011).
- 91 Bangham, C. R. M. *et al.* HTLV-1 persistence in vivo: clonality, dynamics and immune response. *Retrovirology* **8**, A97 (2011).
- 92 Gillet, N. A. *et al.* The host genomic environment of the provirus determines the abundance of HTLV-1-infected T-cell clones. *Blood* **117**, 3113-3122, doi:[blood-2010-10-312926 \[pii\].10.1182/blood-2010-10-312926](https://doi.org/10.1182/blood-2010-10-312926) (2011).
- 93 Rende, F. *et al.* Kinetics and intracellular compartmentalization of HTLV-1 gene expression. *Retrovirology* **8**, A204 (2011).
- 94 Bender, C. *et al.* Analysis of temporal expression of HTLV-2 reveals similarities and functional differences from HTLV-1. *Retrovirology* **8**, A192 (2011).
- 95 Belrose, G. *et al.* Opposite effect of Valproate on Tax and HBZ expression in T-lymphocytes from HTLV-1 asymptomatic carriers and HAM/TSP patients. *Retrovirology* **8**, A198 (2011).
- 96 Oka, T. *et al.* Cumulative kinetics of epigenetic abnormalities during initiation and progression of Adult T-cell Leukemia/Lymphoma (ATLL). *Retrovirology* **8**, A195 (2011).
- 97 Kannian, P., Yin, H., Doueiri, R. & Green, P. Cellular tropism exhibited by human T lymphotropic virus type 1 (HTLV-1) and type 2 (HTLV-2). *Retrovirology* **8**, A176 (2011).

- 98 Boxus, M., Twizere, J.-C., Legros, S., Kettmann, R. & Willems, L. Interaction of HTLV-1 Tax with minichromosome maintenance proteins accelerates the replication timing program. *Retrovirology* **8**, A140 (2011).
- 99 Anupam, R. *et al.* Human T-lymphotropic virus type 1 p30 interacts with REGgamma and ATM (Ataxia Telangiectasia Mutated) to promote cell survival. *Retrovirology* **8**, A202 (2011).
- 100 Wurm, T. & Lemasson, I. Potential interference of HTLV-1 HBZ protein with the DNA damage response pathway. *Retrovirology* **8**, A203 (2011).
- 101 Borowiak, M., Kuhlmann, A.-S., Girard, S., Gazzolo, L. & Dodon, M. HBZ impedes the Menin function and up-regulates the transcription of the hTERT gene in leukemic cells. *Retrovirology* **8**, A182 (2011).
- 102 Douceron, E. *et al.* APH-2 and Tax expression are correlated with a HTLV-2 proviral load but not with lymphocytosis. *Retrovirology* **8**, A184 (2011).
- 103 Kubota, R., Takenouchi, N., Matsuzaki, T., Takashima, H. & Izumo, S. HLA-A24-restricted HTLV-I-specific CTL response reduces the HTLV-I proviral load but the HLA increases the risk of HAM/TSP. *Retrovirology* **8**, A113 (2011).
- 104 Abdelbary, N. *et al.* Reduced Tim-3 expression on HTLV-I Tax-specific cytotoxic T lymphocytes in HTLV-I infection. *Retrovirology* **8**, A112 (2011).
- 105 Leal, F. *et al.* HTLV-1 Tax Specific CD8+ T cells express low levels of Tim-3 in HTLV-1 infection: implications for progression to neurological complications. *Retrovirology* **8**, A94 (2011).
- 106 Kannagi, M. *et al.* The roles of innate and acquired immune responses on HTLV-I infection. *Retrovirology* **8**, A100 (2011).
- 107 Moens, B. *et al.* Ascorbic acid has superior antiviral and antiproliferative effects over IFN-alpha in HAM/TSP PBMC ex vivo. *Retrovirology* **8**, A61 (2011).
- 108 Tattermusch, S. *et al.* An interferon signature is associated with HAM/TSP but not viral containment in HTLV-1 infection. *Retrovirology* **8**, A108 (2011).
- 109 Wagatsuma, V. *et al.* Association of interleukin - 18 gene polymorphism with susceptibility or protective effect to HTLV-1 infection. *Retrovirology* **8**, A118 (2011).
- 110 Barrios, C. *et al.* Recombinant human T-cell leukemia virus types 1 and 2 Tax proteins induce high levels of CC-chemokines and downregulate CCR5 in human peripheral blood mononuclear cells. *Retrovirology* **8**, A98 (2011).
- 111 Douville, R., Olier, S., Green, P., Lin, R. & Hiscott, J. HTLV-1 HBZ protein inhibits IRF3-mediated innate immune responses. *Retrovirology* **8**, A99 (2011).
- 112 Miyazato, P. *et al.* HTLV-1 bZIP factor-mediated dysfunction of regulatory T cells in vivo. *Retrovirology* **8**, A111 (2011).
- 113 Sugata, K., Satou, Y., Yasunaga, J.-i., Nosaka, K. & Matsuoka, M. HTLV-1 bZIP factor perturbs immune response to the pathogens in vivo by inhibiting IFN-gamma production. *Retrovirology* **8**, A102 (2011).
- 114 Akahata, Y., Abrams, A., Goedert, J., Maloney, E. & Jacobson, S. Quantitative differences in antibody responses between normal donors HAM/TSP patients, asymptomatic carriers, and ATL patients from Jamaica: can they be used to estimate risk of disease? *Retrovirology* **8**, A110 (2011).
- 115 Kuo, C.-W., Tulloch, L. & Brighty, D. Robust neutralising activity and activation of neutrophil cytotoxic responses mediated by antibodies targeting the HTLV-1 envelope glycoprotein. *Retrovirology* **8**, A170 (2011).
- 116 Hanson, M., Lee, L., Lin, L., Bell, D. & Ruppert, D. Detection of MLV-like gag sequences in blood samples from a New York state CFS cohort. *Retrovirology* **8**, A234 (2011).
- 117 Maric, R. *et al.* Absence of xenotropic murine leukaemia virus-related virus in Danish patients with multiple sclerosis. *Retrovirology* **8**, A213 (2011).
- 118 Satterfield, B. C. *et al.* Serologic and PCR testing of persons with chronic fatigue syndrome in the United States shows no association with xenotropic or polytropic murine leukemia virus-related viruses. *Retrovirology* **8**, 12, doi:1742-4690-8-12 [pii].10.1186/1742-4690-8-12 (2011).

- 119 Switzer, W. *et al.* Serologic and PCR testing of persons with chronic fatigue syndrome in the United States shows no association with xenotropic or polytropic murine leukemia virus-related virus. *Retrovirology* **8**, A232 (2011).
- 120 Paprotka, T. *et al.* Recombinant Origin of the Retrovirus XMRV. *Science*, doi:science.1205292 [pii].10.1126/science.1205292 (2011).
- 121 Knox, K. *et al.* No Evidence of Murine-Like Gammaretroviruses in CFS Patients Previously Identified as XMRV-Infected. *Science*, doi:science.1204963 [pii].10.1126/science.1204963 (2011).
- 122 Lombardi, V. C. *et al.* Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science* **326**, 585-589, doi:DOI 10.1126/science.1179052 (2009).
- 123 Erlwein, O. *et al.* XMRV infection in human diseases. *Retrovirology* **8**, A238 (2011).
- 124 Qiu, X. *et al.* Prevalence of XMRV in blood donors, HTLV and HIV cohorts. *Retrovirology* **8**, A222 (2011).
- 125 Simmons, G. *et al.* The Blood Xenotropic Murine Leukemia Virus-Related Virus Scientific Research Working Group: mission, progress, and plans. *Transfusion* **51**, 643-653, doi:10.1111/j.1537-2995.2011.03063.x (2011).
- 126 Switzer, W. *et al.* Simian Foamy Virus (SFV) infection from multiple monkey species in women from the Democratic Republic of Congo. *Retrovirology* **8**, A233 (2011).
- 127 Betsem, E., Patricia, T., Alain, F. & Gessain, A. Frequent acquisition of simian foamy viruses from gorillas, chimpanzees and monkeys through severe bites in central African hunters with no evidence for intra-familial dissemination. *Retrovirology* **8**, A237 (2011).
- 128 Mouinga-Ondeme, A., Caron, M., Gessain, A. & Kazanji, M. High level of inter-species transmission of simian foamy virus from non-human primates to humans in Gabon, central Africa. *Retrovirology* **8**, A229 (2011).
- 129 Wolfe, N. & Switzer, W. in *Primate Parasite Ecology* 353-370 (Cambridge University Press, 2009).
- 130 Calvignac-Spencer, S., Adjogoua, E., Hedemann, C., Akoua-Koffi, C. & Leendertz, F. PTLV-1 transmission from preys to hunters in Cote d'Ivoire. *Retrovirology* **8**, A89 (2011).
- 131 Ahuka-Mundeke, S. *et al.* Evidence of STLV-2 and STLV-3 infections in wild-living bonobos (*P. paniscus*) from the Democratic Republic of Congo. *Retrovirology* **8**, A92 (2011).
- 132 Mauclere, P. *et al.* HTLV-2 in Central Africa: HTLV-2 subtype B strains similar to those found in Amerindian tribes are endemic in Bakola Pygmies from south Cameroon but not in surrounding Bantus and Baka Pygmies. *Retrovirology* **8**, A82 (2011).
- 133 Kurth, R. & Bannert, N. Beneficial and detrimental effects of human endogenous retroviruses. *International Journal of Cancer* **126**, 306-314, doi:10.1002/ijc.24902 (2010).
- 134 Brudek, T., Christensen, T., Petersen, T. & Moller-Larsen, A. Expression of HERV-H/W env epitopes on PBMCs from MS patients with active disease. *Retrovirology* **8**, A210 (2011).
- 135 Petersen, T. *et al.* Innate and adaptive anti-viral immune responses in MS patients treated with interferon-beta. *Retrovirology* **8**, A214 (2011).
- 136 Romano, C., de Melo, F. & de A Zanotto, P. Preferential expression of human endogenous retrovirus K (HERV-K/HML-2) type 1 in tumor cells. *Retrovirology* **8**, A216 (2011).
- 137 Romano, C. *et al.* Lack of evidence of ERVWE1/Xq22.3 involvement in MRSV transcripts detected in Multiple Sclerosis patients. *Retrovirology* **8**, A217 (2011).