expression of immunoregulatory molecules on their surfaces. The *FOXP3* gene has been identified as a master gene that controls gene expressions specific to regulatory T-cells. *FOXP3* gene transcription can be detected in some ATL cases (10/17; 59%) [104]. Such ATL cells are thought to suppress the immune response via expression of immunoregulatory molecules on their surfaces, and production of immunosuppressive cytokines.

6. Pathogenesis of HTLV-I infection

ATL cells are derived from activated helper T-lymphocytes, which play central roles in the immune system by elaborating cytokines and expressing immunoregulatory molecules. ATL cells are known to retain such features, and this cytokine production or surface molecule expression may modify the pathogenesis.

ATL is well known to infiltrate various organs and tissues, such as the skin, lungs, liver, gastrointestinal tract, central nervous system and bone [95]. This infiltrative tendency of leukemic cells is possibly attributable to the expressions of various surface molecules, such as chemokine receptors and adhesion molecules. Skin-homing memory T-cells uniformly express CCR4, and its ligands are thymus and activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC). CCR4 is expressed on most ATL cells. In addition, TARC and MDC are expressed in skin lesions in ATL patients. Thus, CCR4 expression should be implicated in the skin infiltration [105]. On the other hand, CCR7 expression is associated with lymph node involvement [106]. OX40 is a member of the tumor necrosis factor family, and was reported to be expressed on ATL cells [107]. It was also identified as a gene associated with the adhesion of ATL cells to endothelial cells by a functional cloning system using a monoclonal antibody that inhibited the attachment of ATL cells [108]. Thus, OX40 is also implicated in the cell adhesion and infiltration of ATL cells.

Hypercalcemia is frequently complicated in patients with acute ATL (more than 70% during the whole clinical course) [109]. In hypercalcemic patients, the number of osteoclasts increases in the bone (Figure 3). RANK ligand, which is expressed on osteoblasts, and M-CSF act synergistically on hematopoietic precursor cells, and induce the differentiation into osteoclasts [110]. ATL cells from hypercalcemic ATL patients express RANK ligand, and induced the differentiation of hematopoietic stem cells into osteoclasts when ATL cells were co-cultured with hematopoietic stem cells [111]. In addition, the serum level of parathyroid hormone-related peptide (PTH-rP) is also elevated in most of hypercalcemic ATL patients. PTH-rP indirectly increases the number of osteoclasts, as well as activating them [112,113], which is also implicated in mechanisms of hypercalcemia.

7. Treatment of ATL – the remaining mission and challenges

Regardless of intensive chemotherapies, the prognosis of ATL patients has not so improved. The median survival time of acute or lymphoma-type ATL was reported to be 13 months with the most intensive chemotherapy [114]. Such a poor prognosis might be due to: 1) the resistance of ATL cells to anti-cancer drugs; and 2) the immunodeficient state and complicated opportunistic infections as described above. Regarding the resistance to anti-cancer drugs, one mechanism is the activated NF-κB pathway in ATL cells [115], which increases the transcription of anti-apoptotic genes such as *bcl-xL* and *survivin*. A proteasome inhibitor, bortezomib, is currently used for the treatment of multiple myeloma. One of its mechanisms is suppression of the NF-κB pathway by inhibiting the proteasomal degradation of IκB protein. Several groups have shown that bortezomib is effective against ATL cells both *in vitro* and *in vivo* [116-119]. Since the sensitivity to bortezomib is well correlated with the extent of NF-κB activation, the major mechanism of the anti-ATL effect is speculated to be inhibition of NF-κB. In addition, an NF-κB inhibitor has also been demonstrated to be effective against ATL cells [120].

During chemotherapy for ATL, chemotherapeutic agents worsen the immunodeficient state of ATL patients. In this regard, antibody therapy against ATL cells has advantages due to its decreased adverse effects. A humanized monoclonal antibody to CD25 has been clinically administered to patients with ATL [121,122]. In addition, a monoclonal antibody to CD2 is at the preclinical stage [123]. As described above, most ATL cells express CCR4 antigen on their surfaces, and a humanized antibody against CCR4 is being developed as an anti-ATL agent [124].

Advances in the treatment of ATL were brought about by allogeneic bone marrow or stem cell transplantation [125,126]. Absence of graft-versus-host disease (GVHD) was linked with relapse of ATL, suggesting that GVHD or graft-versus-ATL may be implicated in the clinical effects of allogeneic stem cell transplantation [125]. Furthermore, 16 patients with ATL, who were over 50 years of age, were treated with allogeneic stem cell transplantation with reduced conditioning intensity (RIST) from HLA-matched sibling donors [127]. Among 9 patients in whom ATL relapsed after transplantation, 3 achieved a second complete remission after rapid discontinuation of cyclosporine A. This finding strongly suggests the presence of a graft-versus-ATL effect in these patients. In addition, Tax peptide-recognizing cells were detected by a tetramer assay (HLA-A2/Tax 11–19 or HLA-A24/Tax 301–309) in patients after allogeneic stem cell transplantation [128]. In 8 patients, the provirus became undetectable by real-time PCR. Among these, 2 patients who received grafts

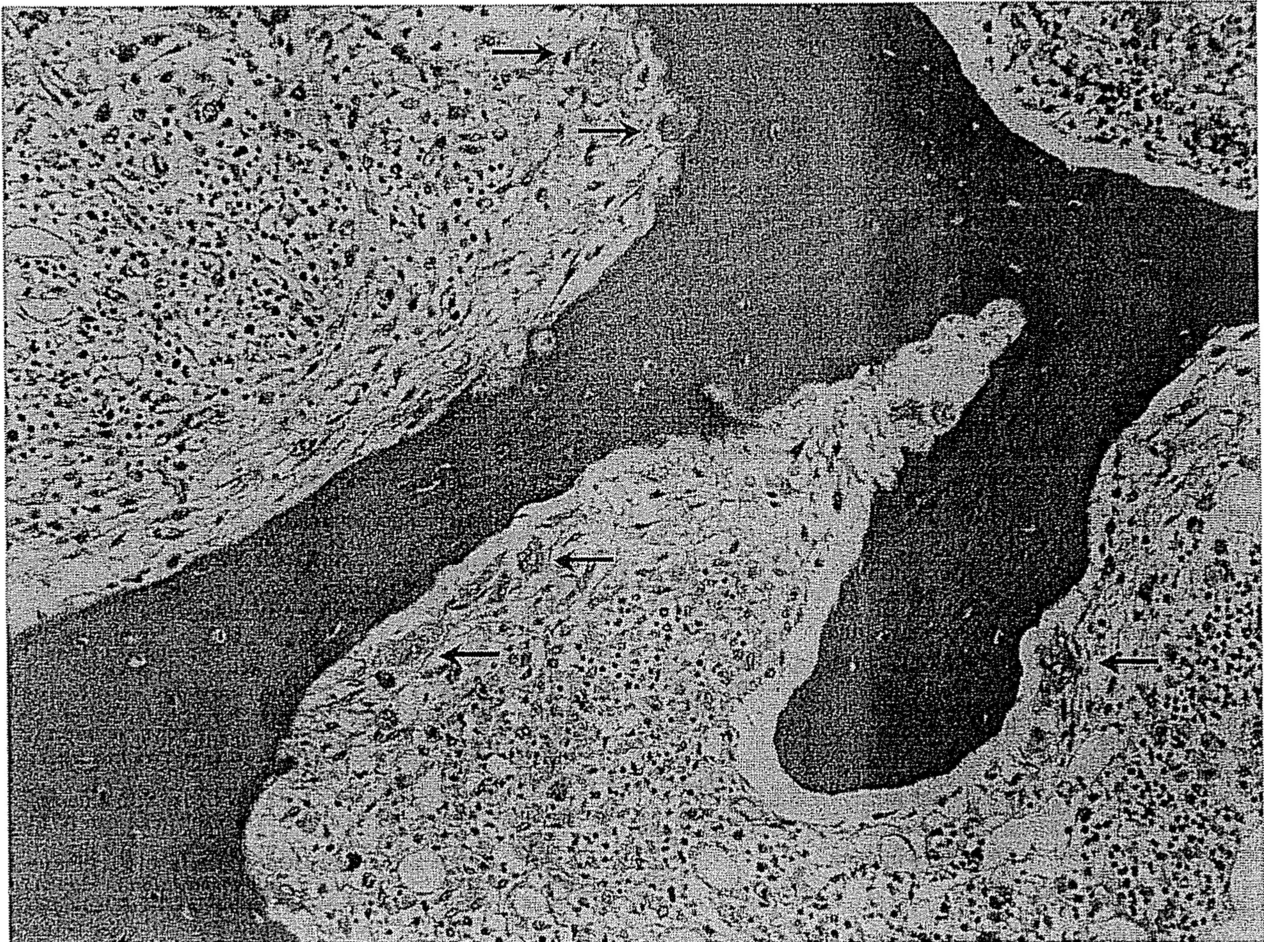

Figure 3
Increased number of osteoclasts in the bone of a hypercalcemic ATL patient. In a hypercalcemic patient, the number of osteoclast (arrows) increased in the bone, which accelerated bone resorption.

from HTLV-I-positive donors also became provirus-negative by real-time PCR after RIST. Since the provirus load is relatively constant in HTLV-I-infected individuals [53], this finding indicates an enhanced immune response against HTLV-I after RIST, which suppresses the provirus load. This may account for the effectiveness of allogeneic stem cell transplantation to ATL. However, Tax expression is frequently lost in ATL cells as described above. Many questions arise, such as whether the *tax* gene status is correlated with the effect of allogeneic stem cell transplantation, and whether the effectiveness of the anti-HTLV-I immune response is against leukemic cells or non-leukemic HTLV-I-infected cells. Nevertheless, these data suggest that potentiation of the immune response against viral proteins such as Tax may be an attractive way to treat ATL patients [94]. Such strategies may enable preventive treatment of high-risk HTLV-I carriers, such as those with familial ATL history, predisposing genetic factors to ATL, a higher provirus load, etc.

8. Two human retroviruses – HTLV-I and HIV-1

As described in the first section, HTLV-I has resided in humans for a long time. On the other hand, HIV-1 has only been recently transmitted to humans, probably from chimpanzees. Due to the comparatively small genomic differences between humans and chimpanzees, this virus can quickly adapt to human cells. These two human retroviruses are opposite in many aspects. HIV-1 vigorously replicates *in vivo*, and the maximum production of HIV-1 virions in the body can reach 10^{10} per day. Since reverse

transcriptase is an error-prone enzyme due to its lack of proof-reading activity, it produces about one mistake per replication, resulting in tremendous errors in the proviral sequence during replication. Although most of these variations ruin the virus replication due to nonsense mutations or impairment of viral gene functions, some become capable of replicating under different circumstances such as the presence of anti-HIV drugs and activation of the host immune system. This can account for why HIV-1 acquires resistance against anti-HIV drugs, and escape from CTLs. On the other hand, HTLV-I increases its copy number in two ways, namely replication of HTLV-I itself and the proliferation of HTLV-I-infected cells *in vivo*. Although immune responses (antibodies, CTLs) against viral proteins suggest the presence of active viral replication *in vivo*, most of increased HTLV-I provirus load (the number of infected cells) is considered to be due to proliferation of infected cells since CTLs efficiently eliminate virus-expressing cells. Therefore, there is much less variation in the HTLV-I provirus sequence compared with HIV-1 [129]. However, this strategy by which HTLV-I increases the number of infected cells due to clonal expansion generates unfortunate side effects for both the host and the virus, namely oncogenesis of CD4-positive T-lymphocytes and the development of ATL.

Acknowledgements

I would like to thank my colleagues Jun-ichirou Yasunaga, Kisato Nosaka, Mika Yoshida, Yorifumi Satou, Yuko Taniguchi, Satoshi Takeda, Ken-ichirou Etoh and Sadahiro Tamiya for their excellent studies.

References

1. Takatsuki K, Uchiyama T, Sagawa K, Yodoi J: **Adult T cell leukemia in Japan.** In *Topic in Hematology, the 16th International congress of Hematology* Edited by: Seno S, Takaku F and Irino S. Amsterdam, ; 1977:73-77.
2. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H: **Adult T-cell leukemia: clinical and hematologic features of 16 cases.** *Blood* 1977, **50**:481-492.
3. Takatsuki K: **Discovery of adult T-cell leukemia.** *Retrovirology* 2005, **2**:16.
4. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC: **Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma.** *Proc Natl Acad Sci U S A* 1980, **77**:7415-7419.
5. Gallo RC: **The discovery of the first human retrovirus: HTLV-1 and HTLV-2.** *Retrovirology* 2005, **2**:17.
6. Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, Kinoshita KI, Shirakawa S, Miyoshi I: **Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera.** *Proc Natl Acad Sci U S A* 1981, **78**:6476-6480.
7. Seiki M, Hattori S, Hirayama Y, Yoshida M: **Human adult T-cell leukemia virus: complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA.** *Proc Natl Acad Sci U S A* 1983, **80**:3618-3622.
8. Yoshida M: **Multiple viral strategies of htlv-1 for dysregulation of cell growth control.** *Annu Rev Immunol* 2001, **19**:475-496.
9. Van Dooren S, Salemi M, Vandamme AM: **Dating the origin of the African human T-cell lymphotropic virus type-i (HTLV-I) subtypes.** *Mol Biol Evol* 2001, **18**:661-671.
10. Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn BH: **Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes.** *Nature* 1999, **397**:436-441.
11. Edlich RF, Arnette JA, Williams FM: **Global epidemic of human T-cell lymphotropic virus type-I (HTLV-I).** *J Emerg Med* 2000, **18**:109-119.
12. Blattner WA, Gallo RC: **Epidemiology of HTLV-I and HTLV-II infection.** In *Adult T-cell leukemia* Edited by: Takahashi K. New York, Oxford University Press; 1994:p.45-90.
13. Tajima K, Inoue M, Takezaki T, Ito M, Ito SI: **Ethnoepidemiology of ATL in Japan with special reference to the Mongoloid dispersal.** In *Adult T-cell leukemia* Edited by: Takatsuki K. New York, Oxford University Press; 1994:p.91-112.
14. Gessain A, Jouannelle A, Escarmant P, Calender A, Schaffar-Deshayes L, de-The G: **HTLV antibodies in patients with non-Hodgkin lymphomas in Martinique.** *Lancet* 1984, **1**:1183-1184.
15. Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A, Matsumoto M, Tara M: **HTLV-I associated myelopathy, a new clinical entity.** *Lancet* 1986, **1**:1031-1032.
16. Arisawa K, Soda M, Endo S, Kurokawa K, Katamine S, Shimokawa I, Koba T, Takahashi T, Saito H, Doi H, Shirahama S: **Evaluation of adult T-cell leukemia/lymphoma incidence and its impact on non-Hodgkin lymphoma incidence in southwestern Japan.** *Int J Cancer* 2000, **85**:319-324.
17. Franchini G, Fukumoto R, Fullen JR: **T-cell control by human T-cell leukemia/lymphoma virus type 1.** *Int J Hematol* 2003, **78**:280-296.
18. Jeang KT, Giam CZ, Majone F, Aboud M: **Life, death, and tax: role of HTLV-I oncoprotein in genetic instability and cellular transformation.** *J Biol Chem* 2004, **279**:31991-31994.
19. Azran I, Schavinsky-Khrapunsky Y, Aboud M: **Role of Tax protein in human T-cell leukemia virus type-I leukemogenicity.** *Retrovirology* 2004, **1**:20.
20. Matsuoka M, Jeang KT: **Human T-cell leukemia virus type I (HTLV-I): a progress report.** *Cancer Research* in press.
21. Tsukahara T, Kannagi M, Ohashi T, Kato H, Arai M, Nunez G, Iwanaga Y, Yamamoto N, Ohtani K, Nakamura M, Fujii M: **Induction of Bcl-x(L) expression by human T-cell leukemia virus type I Tax through NF-kappaB in apoptosis-resistant T-cell transfectants with Tax.** *J Virol* 1999, **73**:7981-7987.
22. Nicot C, Mahieux R, Takemoto S, Franchini G: **Bcl-X(L) is up-regulated by HTLV-I and HTLV-II in vitro and in ex vivo ATLL samples.** *Blood* 2000, **96**:275-281.
23. Kawakami H, Tomita M, Matsuda T, Ohta T, Tanaka Y, Fujii M, Hatano M, Tokuhisa T, Mori N: **Transcriptional activation of survivin through the NF-kappaB pathway by human T-cell leukemia virus type I tax.** *Int J Cancer* 2005.
24. Yamaoka S, Inoue H, Sakurai M, Sugiyama T, Hazama M, Yamada T, Hatanaka M: **Constitutive activation of NF-kappa B is essential for transformation of rat fibroblasts by the human T-cell leukemia virus type I Tax protein.** *Embo J* 1996, **15**:873-887.
25. Portis T, Harding JC, Ratner L: **The contribution of NF-kappa B activity to spontaneous proliferation and resistance to apoptosis in human T-cell leukemia virus type I Tax-induced tumors.** *Blood* 2001, **98**:1200-1208.
26. Rosin O, Koch C, Schmitt I, Semmes OJ, Jeang KT, Grassmann R: **A human T-cell leukemia virus Tax variant incapable of activating NF-kappaB retains its immortalizing potential for primary T-lymphocytes.** *J Biol Chem* 1998, **273**:6698-6703.
27. Suzuki T, Uchida-Toita M, Yoshida M: **Tax protein of HTLV-I inhibits CBP/p300-mediated transcription by interfering with recruitment of CBP/p300 onto DNA element of E-box or p53 binding site.** *Oncogene* 1999, **18**:4137-4143.
28. Ariumi Y, Kaida A, Lin JY, Hirota M, Masui O, Yamaoka S, Taya Y, Shimotohno K: **HTLV-1 tax oncoprotein represses the p53-mediated trans-activation function through coactivator CBP sequestration.** *Oncogene* 2000, **19**:1491-1499.
29. Suzuki T, Kitao S, Matsushime H, Yoshida M: **HTLV-1 Tax protein interacts with cyclin-dependent kinase inhibitor p16INK4A and counteracts its inhibitory activity towards CDK4.** *Embo J* 1996, **15**:1607-1614.
30. Jin DY, Spencer F, Jeang KT: **Human T cell leukemia virus type 1 oncoprotein Tax targets the human mitotic checkpoint protein MAD1.** *Cell* 1998, **93**:81-91.
31. Van Orden K, Yan JP, Ulloa A, Nyborg JK: **Binding of the human T-cell leukemia virus Tax protein to the coactivator CBP interferes with CBP-mediated transcriptional control.** *Oncogene* 1999, **18**:3766-3772.

32. Pise-Masison CA, Mahieux R, Jiang H, Ashcroft M, Radonovich M, Duvall J, Guillerm C, Brady JN: **Inactivation of p53 by human T-cell lymphotropic virus type 1 Tax requires activation of the NF-kappaB pathway and is dependent on p53 phosphorylation.** *Mol Cell Biol* 2000, **20**:3377-3386.
33. Miyazato A, Sheleg S, Iha H, Li Y, Jeang KT: **Evidence for NF-kB- and CBP-independent repression of p53's transcriptional activity by humna T-cell leukemia virus type 1 Tax in mouse embryo and primary humna fibroblasts.** *Journal of Virology* in press.
34. Inoue J, Yoshida M, Seiki M: **Transcriptional (p40x) and post-transcriptional (p27x-III) regulators are required for the expression and replication of human T-cell leukemia virus type 1 genes.** *Proc Natl Acad Sci U S A* 1987, **84**:3653-3657.
35. Nicot C, Dundr M, Johnson JM, Fullen JR, Alonzo N, Fukumoto R, Princler GL, Derse D, Misteli T, Franchini G: **HTLV-1-encoded p30(II) is a post-transcriptional negative regulator of viral replication.** *Nat Med* 2004, **10**:197-201.
36. Basbous J, Arpin C, Gaudray G, Piechaczyk M, Devaux C, Mesnard JM: **The HBZ factor of human T-cell leukemia virus type I dimerizes with transcription factors JunB and c-Jun and modulates their transcriptional activity.** *J Biol Chem* 2003, **278**:43620-43627.
37. Matsumoto J, Ohshima T, Isono O, Shimotohno K: **HTLV-1 HBZ suppresses AP-1 activity by impairing both the DNA-binding ability and the stability of c-Jun protein.** *Oncogene* 2005, **24**:1001-1010.
38. Mori N, Morishita M, Tsukazaki T, Giam CZ, Kumatori A, Tanaka Y, Yamamoto N: **Human T-cell leukemia virus type I oncoprotein Tax represses Smad-dependent transforming growth factor beta signaling through interaction with CREB-binding protein/p300.** *Blood* 2001, **97**:2137-2144.
39. Lee DK, Kim BC, Brady JN, Jeang KT, Kim SJ: **Human T-cell Lymphotropic Virus Type 1 Tax Inhibits Transforming Growth Factor-beta Signaling by Blocking the Association of Smad Proteins with Smad-binding Element.** *J Biol Chem* 2002, **277**:33766-33775.
40. Kamada N, Sakurai M, Miyamoto K, Sanada I, Sadamori N, Fukuhara S, Abe S, Shiraishi Y, Abe T, Kaneko Y, *et al.*: **Chromosome abnormalities in adult T-cell leukemia/lymphoma: a karyotype review committee report.** *Cancer Res* 1992, **52**:1481-1493.
41. Liu B, Hong S, Tang Z, Yu H, Giam CZ: **HTLV-I Tax directly binds the Cdc20-associated anaphase-promoting complex and activates it ahead of schedule.** *Proc Natl Acad Sci U S A* 2005, **102**:63-68.
42. Endo K, Hirata A, Iwai K, Sakurai M, Fukushi M, Oie M, Higuchi M, Hall WW, Gejyo F, Fujii M: **Human T-cell leukemia virus type 2 (HTLV-2) Tax protein transforms a rat fibroblast cell line but less efficiently than HTLV-1 Tax.** *J Virol* 2002, **76**:2648-2653.
43. Hirata A, Higuchi M, Niinuma A, Ohashi M, Fukushi M, Oie M, Akiyama T, Tanaka Y, Gejyo F, Fujii M: **PDZ domain-binding motif of human T-cell leukemia virus type 1 Tax oncoprotein augments the transforming activity in a rat fibroblast cell line.** *Virology* 2004, **318**:327-336.
44. Ng PW, Iha H, Iwanaga Y, Bittner M, Chen Y, Jiang Y, Gooden G, Trent JM, Meltzer P, Jeang KT, Zeichner SL: **Genome-wide expression changes induced by HTLV-1 Tax: evidence for MLK-3 mixed lineage kinase involvement in Tax-mediated NF-kappaB activation.** *Oncogene* 2001, **20**:4484-4496.
45. Wu K, Bottazzi ME, de la Fuente C, Deng L, Gitlin SD, Maddukuri A, Dadgar S, Li H, Vertes A, Pumfery A, Kashanchi F: **Protein profile of tax-associated complexes.** *J Biol Chem* 2004, **279**:495-508.
46. Koyanagi Y, Itoyama Y, Nakamura N, Takamatsu K, Kira J, Iwamasa T, Goto I, Yamamoto N: **In vivo infection of human T-cell leukemia virus type I in non-T cells.** *Virology* 1993, **196**:25-33.
47. Manel N, Kim FJ, Kinet S, Taylor N, Sitbon M, Battini JL: **The ubiquitous glucose transporter GLUT-1 is a receptor for HTLV.** *Cell* 2003, **115**:449-459.
48. Yasunaga J, Sakai T, Nosaka K, Etoh K, Tamiya S, Koga S, Mita S, Uchino M, Mitsuya H, Matsuoka M: **Impaired production of naive T lymphocytes in human T-cell leukemia virus type I-infected individuals: its implications in the immunodeficient state.** *Blood* 2001, **97**:3177-3183.
49. Igakura T, Stinchcombe JC, Goon PK, Taylor GP, Weber JN, Griffiths GM, Tanaka Y, Osame M, Bangham CR: **Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton.** *Science* 2003, **299**:1713-1716.
50. Hino S: **Primary prevention of ATL.** In *Two decades of adult T-cell leukemia and HTLV-I research* Edited by: Sugamura K, Uchiyama T, Matsuoka M and Kannagi M. Tokyo, Japan Sicentific Societies Press; 2003:241-251.
51. Okochi K, Sato H, Hinuma Y: **A retrospective study on transmission of adult T cell leukemia virus by blood transfusion: seroconversion in recipients.** *Vox Sang* 1984, **46**:245-253.
52. Ando Y, Ekuni Y, Matsumoto Y, Nakano S, Saito K, Kakimoto K, Tanigawa T, Kawa M, Toyama T: **Long-term serological outcome of infants who received frozen-thawed milk from human T-lymphotropic virus type-I positive mothers.** *J Obstet Gynaecol Res* 2004, **30**:436-438.
53. Etoh K, Yamaguchi K, Tokudome S, Watanabe T, Okayama A, Stuver S, Mueller N, Takatsuki K, Matsuoka M: **Rapid quantification of HTLV-I provirus load: detection of monoclonal proliferation of HTLV-I-infected cells among blood donors.** *Int J Cancer* 1999, **81**:859-864.
54. Iga M, Okayama A, Stuver S, Matsuoka M, Mueller N, Aoki M, Mitsuya H, Tachibana N, Tsubouchi H: **Genetic evidence of transmission of human T cell lymphotropic virus type 1 between spouses.** *J Infect Dis* 2002, **185**:691-695.
55. Li HC, Biggar RJ, Miley WJ, Maloney EM, Cranston B, Hanchard B, Hisada M: **Provirus load in breast milk and risk of mother-to-child transmission of human T lymphotropic virus type I.** *J Infect Dis* 2004, **190**:1275-1278.
56. Hisada M, Maloney EM, Sawada T, Miley WJ, Palmer P, Hanchard B, Goedert JJ, Manns A: **Virus markers associated with vertical transmission of human T lymphotropic virus type 1 in Jamaica.** *Clin Infect Dis* 2002, **34**:1551-1557.
57. Etoh K, Tamiya S, Yamaguchi K, Okayama A, Tsubouchi H, Ideta T, Mueller N, Takatsuki K, Matsuoka M: **Persistent clonal proliferation of human T-lymphotropic virus type I-infected cells in vivo.** *Cancer Res* 1997, **57**:4862-4867.
58. Cavrois M, Leclercq I, Gout O, Gessain A, Wain-Hobson S, Wattel E: **Persistent oligoclonal expansion of human T-cell leukemia virus type 1-infected circulating cells in patients with Tropical spastic paraparesis/HTLV-1 associated myelopathy.** *Oncogene* 1998, **17**:77-82.
59. Matsuoka M: **Human T-cell leukemia virus type I and adult T-cell leukemia.** *Oncogene* 2003, **22**:5131-5140.
60. Okayama A, Stuver S, Matsuoka M, Ishizaki J, Tanaka G, Kubuki Y, Mueller N, Hsieh CC, Tachibana N, Tsubouchi H: **Role of HTLV-1 proviral DNA load and clonality in the development of adult T-cell leukemia/lymphoma in asymptomatic carriers.** *Int J Cancer* 2004, **110**:621-625.
61. LaGrenade L, Hanchard B, Fletcher V, Cranston B, Blattner W: **Infective dermatitis of Jamaican children: a marker for HTLV-I infection.** *Lancet* 1990, **336**:1345-1347.
62. Nakao K, Ohba N, Matsumoto M: **Noninfectious anterior uveitis in patients infected with human T-lymphotropic virus type I.** *Jpn J Ophthalmol* 1989, **33**:472-481.
63. Kannagi M, Harada S, Maruyama I, Inoko H, Igarashi H, Kuwashima G, Sato S, Morita M, Kidokoro M, Sugimoto M, *et al.*: **Predominant recognition of human T cell leukemia virus type I (HTLV-I) pX gene products by human CD8+ cytotoxic T cells directed against HTLV-I-infected cells.** *Int Immunol* 1991, **3**:761-767.
64. Furukawa Y, Kubota R, Tara M, Izumo S, Osame M: **Existence of escape mutant in HTLV-I tax during the development of adult T-cell leukemia.** *Blood* 2001, **97**:987-993.
65. Takeda S, Maeda M, Morikawa S, Taniguchi Y, Yasunaga J, Nosaka K, Tanaka Y, Matsuoka M: **Genetic and epigenetic inactivation of tax gene in adult T-cell leukemia cells.** *Int J Cancer* 2004, **109**:559-567.
66. Koiwa T, Hamano-Usami A, Ishida T, Okayama A, Yamaguchi K, Kamihira S, Watanabe T: **5'-long terminal repeat-selective CpG methylation of latent human T-cell leukemia virus type 1 provirus in vitro and in vivo.** *J Virol* 2002, **76**:9389-9397.
67. Tamiya S, Matsuoka M, Etoh K, Watanabe T, Kamihira S, Yamaguchi K, Takatsuki K: **Two types of defective human T-lymphotropic virus type I provirus in adult T-cell leukemia.** *Blood* 1996, **88**:3065-3073.
68. Tomlinson I, Bodmer W: **Selection, the mutation rate and cancer: ensuring that the tail does not wag the dog.** *Nat Med* 1999, **5**:11-12.

69. Sakashita A, Hattori T, Miller CW, Suzushima H, Asou N, Takatsuki K, Koeffler HP: **Mutations of the p53 gene in adult T-cell leukemia.** *Blood* 1992, **79**:477-480.
70. Cesarman E, Chadburn A, Inghirami G, Gaidano G, Knowles DM: **Structural and functional analysis of oncogenes and tumor suppressor genes in adult T-cell leukemia/lymphoma shows frequent p53 mutations.** *Blood* 1992, **80**:3205-3216.
71. Nishimura S, Asou N, Suzushima H, Okubo T, Fujimoto T, Osato M, Yamasaki H, Lisha L, Takatsuki K: **p53 gene mutation and loss of heterozygosity are associated with increased risk of disease progression in adult T cell leukemia.** *Leukemia* 1995, **9**:598-604.
72. Hatta Y, Hirama T, Miller CW, Yamada Y, Tomonaga M, Koeffler HP: **Homozygous deletions of the p15 (MTS2) and p16 (CDKN2/MTS1) genes in adult T-cell leukemia.** *Blood* 1995, **85**:2699-2704.
73. Nosaka K, Maeda M, Tamiya S, Sakai T, Mitsuya H, Matsuoka M: **Increasing methylation of the CDKN2A gene is associated with the progression of adult T-cell leukemia.** *Cancer Res* 2000, **60**:1043-1048.
74. Morosetti R, Kawamata N, Gombart AF, Miller CW, Hatta Y, Hirama T, Said JW, Tomonaga M, Koeffler HP: **Alterations of the p27KIP1 gene in non-Hodgkin's lymphomas and adult T-cell leukemia/lymphoma.** *Blood* 1995, **86**:1924-1930.
75. Nagata S: **Fas ligand-induced apoptosis.** *Annu Rev Genet* 1999, **33**:29-55.
76. Tamiya S, Etoh K, Suzushima H, Takatsuki K, Matsuoka M: **Mutation of CD95 (Fas/Apo-1) gene in adult T-cell leukemia cells.** *Blood* 1998, **91**:3935-3942.
77. Maeda T, Yamada Y, Moriuchi R, Sugahara K, Tsuruda K, Joh T, Atogami S, Tsukasaki K, Tomonaga M, Kamihira S: **Fas gene mutation in the progression of adult T cell leukemia.** *J Exp Med* 1999, **189**:1063-1071.
78. Krueger A, Fas SC, Baumann S, Krammer PH: **The role of CD95 in the regulation of peripheral T-cell apoptosis.** *Immunol Rev* 2003, **193**:58-69.
79. Yasunaga J, Taniguchi Y, Nosaka K, Yoshida M, Satou Y, Sakai T, Mitsuya H, Matsuoka M: **Identification of aberrantly methylated genes in association with adult T-cell leukemia.** *Cancer Res* 2004, **64**:6002-6009.
80. Mittelstadt PR, Ashwell JD: **Cyclosporin A-sensitive transcription factor Egr-3 regulates Fas ligand expression.** *Mol Cell Biol* 1998, **18**:3744-3751.
81. Yoshida M, Nosaka K, Yasunaga J, Nishikata I, Morishita K, Matsuoka M: **Aberrant expression of the MEL1S gene identified in association with hypomethylation in adult T-cell leukemia cells.** *Blood* 2004, **103**:2753-2760.
82. Sasaki H, Nishikata I, Shiraga T, Akamatsu E, Fukami T, Hidaka T, Kubuki Y, Okayama A, Hamada K, Okabe H, Murakami Y, Tsubouchi H, Morishita K: **Overexpression of a cell adhesion molecule, TSLC1, as a possible molecular marker for acute-type adult T-cell leukemia.** *Blood* 2005, **105**:1204-1213.
83. Yoshizuka N, Moriuchi R, Mori T, Yamada K, Hasegawa S, Maeda T, Shimada T, Yamada Y, Kamihira S, Tomonaga M, Katamine S: **An alternative transcript derived from the trio locus encodes a guanosine nucleotide exchange factor with mouse cell-transforming potential.** *J Biol Chem* 2004, **279**:43998-44004.
84. Bangham CR: **Human T-lymphotropic virus type 1 (HTLV-1): persistence and immune control.** *Int J Hematol* 2003, **78**:297-303.
85. Wodarz D, Hall SE, Usuku K, Osame M, Ogg GS, McMichael AJ, Nowak MA, Bangham CR: **Cytotoxic T-cell abundance and virus load in human immunodeficiency virus type 1 and human T-cell leukaemia virus type 1.** *Proc R Soc Lond B Biol Sci* 2001, **268**:1215-1221.
86. Vine AM, Heaps AG, Kaftantzi L, Mosley A, Asquith B, Witkover A, Thompson G, Saito M, Goon PK, Carr L, Martinez-Murillo F, Taylor GP, Bangham CR: **The role of CTLs in persistent viral infection: cytolytic gene expression in CD8+ lymphocytes distinguishes between individuals with a high or low proviral load of human T cell lymphotropic virus type 1.** *J Immunol* 2004, **173**:5121-5129.
87. Jeffery KJ, Usuku K, Hall SE, Matsumoto W, Taylor GP, Procter J, Bunce M, Ogg GS, Welsh KI, Weber JN, Lloyd AL, Nowak MA, Nagai M, Kodama D, Izumo S, Osame M, Bangham CR: **HLA alleles determine human T-lymphotropic virus-I (HTLV-I) proviral load and the risk of HTLV-I-associated myelopathy.** *Proc Natl Acad Sci U S A* 1999, **96**:3848-3853.
88. Vine AM, Witkover AD, Lloyd AL, Jeffery KJ, Siddiqui A, Marshall SE, Bunce M, Eiraku N, Izumo S, Usuku K, Osame M, Bangham CR: **Polygenic control of human T lymphotropic virus type I (HTLV-I) provirus load and the risk of HTLV-I-associated myelopathy/tropical spastic paraparesis.** *J Infect Dis* 2002, **186**:932-939.
89. Tsukasaki K, Miller CW, Kubota T, Takeuchi S, Fujimoto T, Ikeda S, Tomonaga M, Koeffler HP: **Tumor necrosis factor alpha polymorphism associated with increased susceptibility to development of adult T-cell leukemia/lymphoma in human T-lymphotropic virus type 1 carriers.** *Cancer Res* 2001, **61**:3770-3774.
90. Kawano F, Tsuda H, Yamaguchi K, Nishimura H, Sanada I, Matsuzaki H, Ishii M, Takatsuki K: **Unusual clinical courses of adult T-cell leukemia in siblings.** *Cancer* 1984, **54**:131-134.
91. Miyamoto Y, Yamaguchi K, Nishimura H, Takatsuki K, Motoori T, Morimatsu M, Yasaka T, Ohya I, Koga T: **Familial adult T-cell leukemia.** *Cancer* 1985, **55**:181-185.
92. Yamaguchi K, Yul LS, Shimizu T, Nozawa F, Takeya M, Takahashi K, Takatsuki K: **Concurrence of lymphoma type adult T-cell leukemia in three sisters.** *Cancer* 1985, **56**:1688-1690.
93. Shimamoto Y, Kikuchi M, Funai N, Suga K, Matsuzaki M, Yamaguchi M: **Spontaneous regression in adult T-cell leukemia/lymphoma.** *Cancer* 1993, **72**:735-740.
94. Kannagi M, Ohashi T, Harashima N, Hanabuchi S, Hasegawa A: **Immunological risks of adult T-cell leukemia at primary HTLV-I infection.** *Trends Microbiol* 2004, **12**:346-352.
95. Matsuoka M, Takatsuki K: **Adult T-cell leukemia.** In *Leukemia* 7th edition edition. Edited by: Henderson ES, Lister TA and Greaves MF. Philadelphia, Saunders; 2002:705-712.
96. Welles SL, Tachibana N, Okayama A, Shioiri S, Ishihara S, Murai K, Mueller NE: **Decreased reactivity to PPD among HTLV-I carriers in relation to virus and hematologic status.** *Int J Cancer* 1994, **56**:337-340.
97. Hisada M, Okayama A, Shioiri S, Spiegelman DL, Stuver SO, Mueller NE: **Risk factors for adult T-cell leukemia among carriers of human T-lymphotropic virus type I.** *Blood* 1998, **92**:3557-3561.
98. Arisawa K, Katamine S, Kamihira S, Kurokawa K, Sawada T, Soda M, Doi H, Saito H, Shirahama S: **A nested case-control study of risk factors for adult T-cell leukemia/lymphoma among human T-cell lymphotropic virus type-I carriers in Japan.** *Cancer Causes Control* 2002, **13**:657-663.
99. Hanabuchi S, Ohashi T, Koya Y, Kato H, Hasegawa A, Takemura F, Masuda T, Kannagi M: **Regression of human T-cell leukemia virus type I (HTLV-I)-associated lymphomas in a rat model: peptide-induced T-cell immunity.** *J Natl Cancer Inst* 2001, **93**:1775-1783.
100. Tobinai K, Ohtsu T, Hayashi M, Kinoshita T, Matsuno Y, Mukai K, Shimoyama M: **Epstein-Barr virus (EBV) genome carrying monoclonal B-cell lymphoma in a patient with adult T-cell leukemia-lymphoma.** *Leuk Res* 1991, **15**:837-846.
101. Hoshida Y, Li T, Dong Z, Tomita Y, Yamauchi A, Hanai J, Aozasa K: **Lymphoproliferative disorders in renal transplant patients in Japan.** *Int J Cancer* 2001, **91**:869-875.
102. Stevens HP, Holterman L, Haaksma AG, Jonker M, Heeney JL: **Lymphoproliferative disorders developing after transplantation and their relation to simian T-cell leukemia virus infection.** *Transpl Int* 1992, **5 Suppl 1**:S450-3.
103. Hanon E, Stinchcombe JC, Saito M, Asquith BE, Taylor GP, Tanaka Y, Weber JN, Griffiths GM, Bangham CR: **Fratricide among CD8(+) T lymphocytes naturally infected with human T cell lymphotropic virus type I.** *Immunity* 2000, **13**:657-664.
104. Karube K, Ohshima K, Tsuchiya T, Yamaguchi T, Kawano R, Suzumiya J, Utsunomiya A, Harada M, Kikuchi M: **Expression of FoxP3, a key molecule in CD4CD25 regulatory T cells, in adult T-cell leukaemia/lymphoma cells.** *Br J Haematol* 2004, **126**:81-84.
105. Yoshie O, Fujisawa R, Nakayama T, Harasawa H, Tago H, Izawa D, Hieshima K, Tatsumi Y, Matsushima K, Hasegawa H, Kanamaru A, Kamihira S, Yamada Y: **Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells.** *Blood* 2002, **99**:1505-1511.
106. Hasegawa H, Nomura T, Kohno M, Tateishi N, Suzuki Y, Maeda N, Fujisawa R, Yoshie O, Fujita S: **Increased chemokine receptor CCR7/EBI1 expression enhances the infiltration of lymphoid organs by adult T-cell leukemia cells.** *Blood* 2000, **95**:30-38.
107. Higashimura N, Takasawa N, Tanaka Y, Nakamura M, Sugamura K: **Induction of OX40, a receptor of gp34, on T cells by trans-

acting transcriptional activator, Tax, of human T-cell leukemia virus type I. Jpn J Cancer Res 1996, 87:227-231.
108. Imura A, Hori T, Imada K, Ishikawa T, Tanaka Y, Maeda M, Imamura S, Uchiyama T: **The human OX40/gp34 system directly mediates adhesion of activated T cells to vascular endothelial cells.** J Exp Med 1996, 183:2185-2195.
109. Kiyokawa T, Yamaguchi K, Takeya M, Takahashi K, Watanabe T, Matsumoto T, Lee SY, Takatsuki K: **Hypercalcemia and osteoclast proliferation in adult T-cell leukemia.** Cancer 1987, 59:1187-1191.
110. Arai F, Miyamoto T, Ohneda O, Inada T, Sudo T, Brasel K, Miyata T, Anderson DM, Suda T: **Commitment and differentiation of osteoclast precursor cells by the sequential expression of c-Fms and receptor activator of nuclear factor kappaB (RANK) receptors.** J Exp Med 1999, 190:1741-1754.
111. Nosaka K, Miyamoto T, Sakai T, Mitsuya H, Suda T, Matsuoka M: **Mechanism of hypercalcemia in adult T-cell leukemia: overexpression of receptor activator of nuclear factor kappaB ligand on adult T-cell leukemia cells.** Blood 2002, 99:634-640.
112. Fukumoto S, Matsumoto T, Watanabe T, Takahashi H, Miyoshi I, Ogata E: **Secretion of parathyroid hormone-like activity from human T-cell lymphotropic virus type I-infected lymphocytes.** Cancer Res 1989, 49:3849-3852.
113. Watanabe T, Yamaguchi K, Takatsuki K, Osame M, Yoshida M: **Constitutive expression of parathyroid hormone-related protein gene in human T cell leukemia virus type I (HTLV-I) carriers and adult T cell leukemia patients that can be trans-activated by HTLV-I tax gene.** J Exp Med 1990, 172:759-765.
114. Yamada Y, Tomonaga M, Fukuda H, Hanada S, Utsunomiya A, Tara M, Sano M, Ikeda S, Takatsuki K, Kozuru M, Araki K, Kawano F, Niimi M, Tobinai K, Hotta T, Shimoyama M: **A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukaemia-lymphoma: Japan Clinical Oncology Group Study 9303.** Br J Haematol 2001, 113:375-382.
115. Mori N, Fujii M, Ikeda S, Yamada Y, Tomonaga M, Ballard DW, Yamamoto N: **Constitutive activation of NF-kappaB in primary adult T-cell leukemia cells.** Blood 1999, 93:2360-2368.
116. Tan C, Waldmann TA: **Proteasome inhibitor PS-341, a potential therapeutic agent for adult T-cell leukemia.** Cancer Res 2002, 62:1083-1086.
117. Satou Y, Nosaka K, Koya Y, Yasunaga JI, Toyokuni S, Matsuoka M: **Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both in vivo and in vitro.** Leukemia 2004, 18:1357-1363.
118. Mitra-Kaushik S, Harding JC, Hess J, Ratner L: **Effects of the Proteasome Inhibitor PS-341 on Tumor Growth in HTLV-I Tax Transgenic Mice and Tax Tumor Transplants.** Blood 2004.
119. Nasr R, El-Sabban ME, Karam JA, Dbaibo G, Kfoury Y, Arnulf B, Lepelletier Y, Bex F, de The H, Hermine O, Bazarbachi A: **Efficacy and mechanism of action of the proteasome inhibitor PS-341 in T-cell lymphomas and HTLV-I associated adult T-cell leukemia/lymphoma.** Oncogene 2005, 24:419-430.
120. Mori N, Yamada Y, Ikeda S, Yamasaki Y, Tsukasaki K, Tanaka Y, Tomonaga M, Yamamoto N, Fujii M: **Bay 11-7082 inhibits transcription factor NF-kappaB and induces apoptosis of HTLV-I-infected T-cell lines and primary adult T-cell leukemia cells.** Blood 2002, 100:1828-1834.
121. Waldmann TA, White JD, Goldman CK, Top L, Grant A, Bamford R, Roessler E, Horak ID, Zaknoen S, Kasten-Sportes C, et al.: **The interleukin-2 receptor: a target for monoclonal antibody treatment of human T-cell lymphotrophic virus I-induced adult T-cell leukemia.** Blood 1993, 82:1701-1712.
122. Waldmann TA, White JD, Carrasquillo JA, Reynolds JC, Paik CH, Gansow OA, Brechbiel MW, Jaffe ES, Fleisher TA, Goldman CK, et al.: **Radioimmunotherapy of interleukin-2R alpha-expressing adult T-cell leukemia with Yttrium-90-labeled anti-Tac.** Blood 1995, 86:4063-4075.
123. Zhang Z, Zhang M, Ravetch JV, Goldman C, Waldmann TA: **Effective therapy for a murine model of adult T-cell leukemia with the humanized anti-CD2 monoclonal antibody, MEDI-507.** Blood 2003, 102:284-288.
124. Ishida T, Iida S, Akatsuka Y, Ishii T, Miyazaki M, Komatsu H, Inagaki H, Okada N, Fujita T, Shitara K, Akinaga S, Takahashi T, Utsunomiya A, Ueda R: **The CC chemokine receptor 4 as a novel specific molecular target for immunotherapy in adult T-Cell leukemia/lymphoma.** Clin Cancer Res 2004, 10:7529-7539.
125. Borg A, Yin JA, Johnson PR, Tosswill J, Saunders M, Morris D: **Successful treatment of HTLV-1-associated acute adult T-cell leukaemia lymphoma by allogeneic bone marrow transplantation.** Br J Haematol 1996, 94:713-715.
126. Utsunomiya A, Miyazaki Y, Takatsuka Y, Hanada S, Uozumi K, Yashiki S, Tara M, Kawano F, Saburi Y, Kikuchi H, Hara M, Sao H, Morishima Y, Kodera Y, Sonoda S, Tomonaga M: **Improved outcome of adult T cell leukemia/lymphoma with allogeneic hematopoietic stem cell transplantation.** Bone Marrow Transplant 2001, 27:15-20.
127. Okamura J, Utsunomiya A, Tanosaki R, Uike N, Sonoda S, Kannagi M, Tomonaga M, Harada M, Kimura N, Masuda M, Kawano F, Yufu Y, Hattori H, Kikuchi H, Saburi Y: **Allogeneic stem cell transplantation with reduced conditioning intensity as a novel immunotherapy and antiviral therapy for adult T-cell leukemia/lymphoma.** Blood 2005, in press:.
128. Harashima N, Kurihara K, Utsunomiya A, Tanosaki R, Hanabuchi S, Masuda M, Ohashi T, Fukui F, Hasegawa A, Masuda T, Takaue Y, Okamura J, Kannagi M: **Graft-versus-Tax response in adult T-cell leukemia patients after hematopoietic stem cell transplantation.** Cancer Res 2004, 64:391-399.
129. Van Dooren S, Pybus OG, Salemi M, Liu HF, Goubau P, Remondegui C, Talarmin A, Gotuzzo E, Alcantara LC, Galvao-Castro B, Vandamme AM: **The low evolutionary rate of human T-cell lymphotropic virus type-1 confirmed by analysis of vertical transmission chains.** Mol Biol Evol 2004, 21:603-611.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."
Sir Paul Nurse, Cancer Research UK

Your research papers will be:
- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

Human T-Cell Leukemia Virus Type I at Age 25: A Progress Report

Masao Matsuoka[1] and Kuan-Teh Jeang[2]

[1]Laboratory of Virus Immunology, Institute for Virus Research, Kyoto University, Kyoto, Japan and [2]Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland

Abstract

It has been 25 years since the discovery of human T-cell leukemia virus type I (HTLV-I) and its role in adult T-cell leukemia. Here, in brief, we review the current state of our understanding of HTLV-I epidemiology, viral biology, pathogenesis, and treatment. We discuss how HTLV-I may transform cells through destabilization of cellular genomic integrity and induction of cellular tolerance for chromosomal errors. (Cancer Res 2005; 65(11): 4467-70)

In 1980, Poiesz et al. (1) published a seminal article establishing for the first time a link between a retrovirus and a human cancer in a patient with cutaneous T-cell lymphoma. Several years earlier, a clinical entity called adult T-cell leukemia was described in Japan by Uchiyama et al. (2). Contemporaneous research on adult T-cell leukemia also led to the isolation of a retrovirus named adult T-cell leukemia virus by Hinuma et al. (3) and Yoshida et al. (4). Because adult T-cell leukemia virus and the virus isolated by Poiesz et al. were later shown to be identical, a single name, human T-cell leukemia virus type I (HTLV-I), was adopted. Twenty-five years after the discovery of HTLV-I, we briefly review current progress in our understanding of this transforming virus.

Epidemiology

Approximately 10 to 20 million individuals are estimated to be infected with HTLV-I worldwide. The virus is endemic in southwest Japan, the Caribbean islands, countries surrounding the Caribbean basin, parts of Central Africa, and South America. In addition, epidemiologic studies of HTLV-I have revealed high seroprevalence rates in Melanesia, Papua New Guinea, the Solomon Islands, and among Australian aborigines. In Japan, ~1.2 million individuals are estimated to be infected by HTLV-I, and more than 800 cases of adult T-cell leukemia are diagnosed each year. The cumulative risk of adult T-cell leukemia among HTLV-I carriers in Japan is estimated to be about 6.6% for men and 2.1% for women, indicating that most of HTLV-I carriers are asymptomatic throughout their life (5). Analysis of naive individuals who seroconvert after marrying an HTLV-I seropositive spouse showed that the proviral gp46 sequences are identical among married couples. This finding verified that HTLV-I is transmitted from a seropositive individual to the uninfected spouse. Interestingly, proviral loads between couples are frequently different despite infection by the same HTLV-I virus, suggesting a significant contributory role of host factors to viral replication (6).

Requests for reprints: Kuan-Teh Jeang, Building 4, Room 306, 9000 Rockville Pike, Bethesda, MD 20892-0460. Phone: 301-496-6680; Fax: 301-480-3686; E-mail: kj7e@nih.gov.

©2005 American Association for Cancer Research.

The Biology of Human T-Cell Leukemia Virus Type I

HTLV-I is a *Deltaretrovirus* of 9 kb in size with a unique transmission strategy. *In vivo* cell-free virions are not detected in the sera of HTLV-I–infected individuals. *In vitro* infectivity by virions in tissue culture is much lower than that achieved by cell-to-cell transmission. These findings suggest that optimal HTLV-I spread is cell to cell. Accordingly, when infected cells contact uninfected counterparts, "virological synapses" are formed and Gag-viral genomic RNA complexes are transferred from the infected into the uninfected cells (Fig. 1*A*; ref. 7). Moreover, because the virus can infect many types of cells (e.g., B-lymphocytes, monocytes, and fibroblasts), expression of the HTLV-I receptor is predicted to be ubiquitous. Indeed, Manel et al. (8) and Kim et al. (9) recently identified the commonly expressed glucose transporter 1 as the HTLV-I receptor, thereby explaining how the virus can infect a myriad of different cell types.

The mode of transmission of HTLV-I suggests that the virus benefits from a net increase in the reproductive rate of infected cells (Fig. 1*A*). Like other retroviruses, HTLV-I integrates as a provirus into the cellular chromosome. After integration, viral transcription proceeds in two ways. Basal transcription is first dictated by the amount of cellular cyclic-AMP responsive [e.g., cyclic AMP-responsive element binding protein (CREB), CREB-binding protein, p300, and p300/CREB-binding protein–associated factor] factors (10–12). After synthesis of viral proteins, activated transcription is then guided by the HTLV-I Tax protein (13–15). Tax activates not only the viral long terminal repeat (LTR) but also a large array of cellular genes (16, 17) via four cellular signal transduction pathways [i.e., CREB/activating transcription factor, nuclear factor-κB (NF-κB), activator protein, and serum response factor; refs. 18, 19]. Tax is also the HTLV-I–encoded cell transforming protein which serves to increase proliferation and clonal expansion of virus-infected cells (13, 20–22). In addition to Tax, the viral Rex protein (23), and other viral accessory proteins (24) also contribute to HTLV-I replication.

Progress has been made in our understanding as to how HTLV-I increases net proliferation of infected cells. A current model for cellular transformation (Fig. 1*B*), which does not exclude others, is that two types of events mediated by Tax occur after HTLV-I infects cells. First, because cancer is fundamentally a disease of genetic mistakes (25), the virus must confer to the infected normal cell a tolerance for chromosomal changes/damages. In HTLV-I cells, this occurs through the abrogation by Tax of several cellular checks (26–28), which normally sense or repair DNA mistakes and reject the propagation of uncorrected genetic errors by sending cells to apoptosis. Nevertheless, tolerance for genetic instability through checkpoint inactivation in itself neither creates DNA damage nor transforms cells. Hence, a second event, Tax interaction with cyclins, cyclin-dependent kinases (cdk), and cdk inhibitors (10), enhances genetic errors via unchecked acceleration

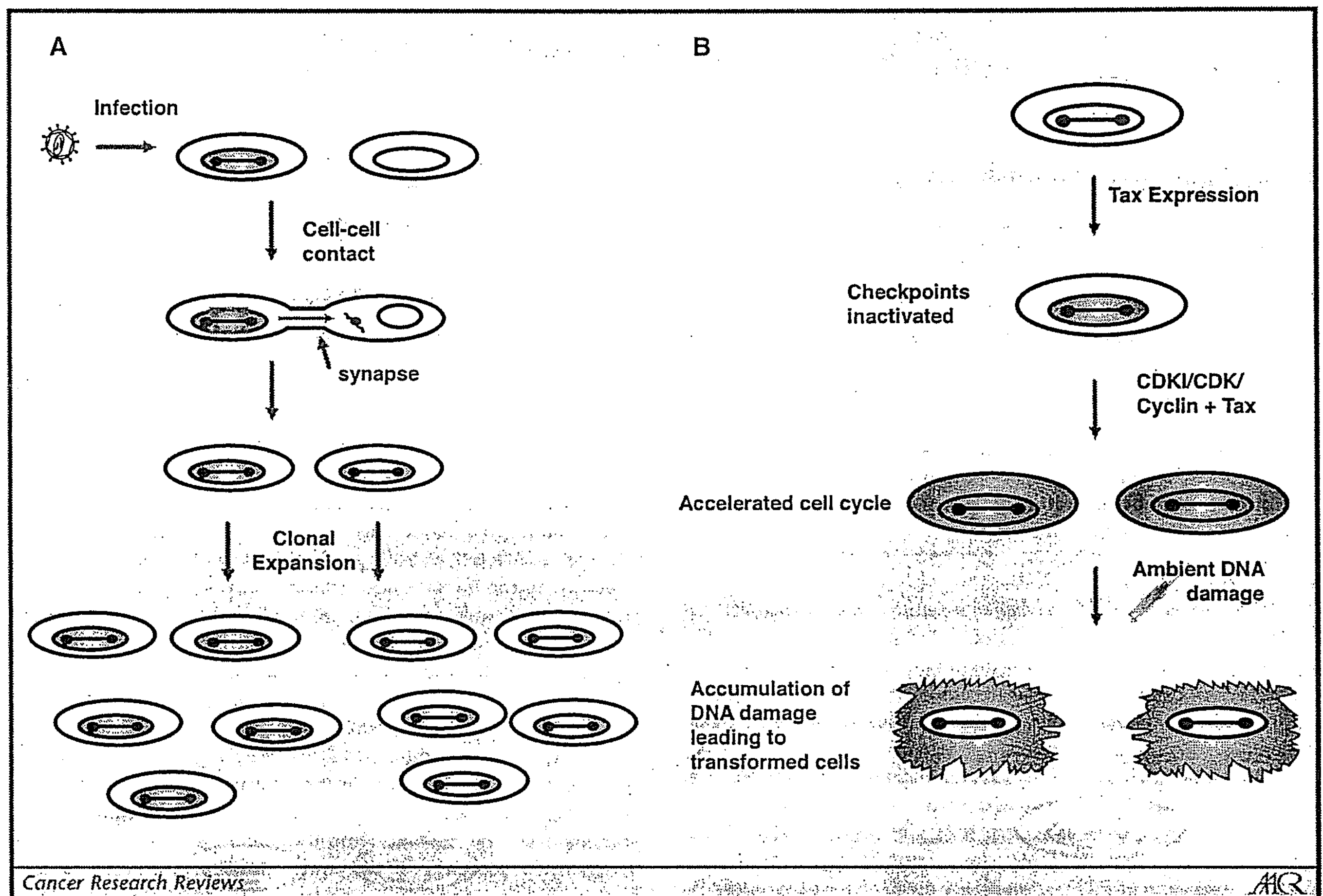

Figure 1. Cell-to-cell spread by HTLV-I and cellular transformation by Tax. *A*, HTLV-I virus infects the cell and establishes a provirus. The most efficient route of HTLV-I spread is then via cell-to-cell contact through a synapse. Once spread of infection is established, clonal expansion of infected cells facilitates future cell-to-cell spread. *B*, a model for stepwise transformation of cells by Tax. Initially, Tax (*blue*) induces tolerance by the cell of aneuploidogenic and clastogenic DNA damage through inactivation of several cellular checkpoints such as p53/retinoblastoma, spindle assembly checkpoint, and G_2-M checkpoint. Then, via interactions with cyclins, cdk, and cdk inhibitors, Tax accelerates cell cycle progression (*green*) so that cells are deprived of sufficient time to adequately correct ambient DNA damage, and genetic lesions become fixed. Accumulation of damaged DNA ultimately converts the cell to a transformed phenotype (*ruffled cells*). Once transformation is achieved, Tax is no longer required (*clear nuclei*), and its expression may be shut off through either genetic or epigenetic means (see text).

through all phases of the cell cycle (29–31). In settings whereby the actions of checkpoints are inactivated, hastening cell cycle progression increases the ambient amount of cellular genetic mistakes (10, 32).

Tax expression is frequently impaired in adult T-cell leukemia cells through genetic and epigenetic mechanisms (33) such as through mutation, insertions, and deletion of *tax* gene (34); deletion of 5′-LTR (35); or DNA methylation of 5′-LTR (36). *Tax* gene transcription was undetectable in about two thirds of adult T-cell leukemia cases by reverse transcription-PCR. These findings indicate that whereas Tax may be needed to initiate transformation, it is not always required for the maintenance of a leukemic state. Hence, whereas Tax promotes the proliferation of infected cells and inhibits their apoptosis in an early phase of transformation, once a leukemic state is achieved cells acquire the ability to proliferate without Tax expression. Loss of Tax expression seen in some adult T-cell leukemia cells suggests that genetic and epigenetic alterations are implicated when adult T-cell leukemia cells transit to a Tax-independent phase of growth. Analyses of cellular DNA changes have revealed hyper- and hypomethylated genes in adult T-cell leukemia cells (37, 38). For example, early growth response 3 (*EGR3*) gene, which is a critical transcriptional factor for induction of Fas ligand, is hypermethylated in adult T-cell leukemia cells. Accordingly, although adult T-cell leukemia cells highly express Fas antigen on their surfaces, they do not produce Fas ligand. Thus, through suppression of *EGR3*, adult T-cell leukemia cells escape Fas ligand activation–induced cell death. These findings suggest that HTLV-I–infected cells can use both genetic and epigenetic means to acquire malignant phenotypes during their long latency periods.

Pathogenesis of Human T-Cell Leukemia Virus Type I

Because adult T-cell leukemia cells are derived from activated helper T-lymphocytes, which play a central role in the immune system, their phenotype of cytokine production can influence the diverse symptoms and complications observed in patients. Approximately 70% of the time, hypercalcemia complicates adult T-cell leukemia. In adult T-cell leukemia, parathyroid hormone–related peptide has reportedly been implicated in hypercalcemia; however, the level of parathyroid hormone–related peptide does not always strictly correlate with the extent of hypercalcemia. On

the other hand, adult T-cell leukemia patients often express receptor activator of NF-κB ligand, which cooperates with macrophage colony-stimulating factor to induce the differentiation of hematopoietic precursors into osteoclasts (39); and this may account for the observed hypercalcemia. Adult T-cell leukemia patients also frequently have opportunistic fungal, protozoal, and/or other viral infections; and these concurrent pathogens may influence disease outcome. Inevitably, some impairment in T-cell function and immunodeficiency occur in adult T-cell leukemia. One contribution to this impairment may be due to decreased numbers of naive T-lymphocytes in HTLV-I–infected individuals (40). Previously, the *FOXP3* gene was identified as a master gene that controls the phenotype of immunoregulatory T-cells. *FOXP3* induces the expression of immunoregulatory surface molecules, which suppress the proliferation of T-lymphocytes. Intriguingly, *FOXP3* gene transcription is reportedly up-regulated in some adult T-cell leukemia cases [10 of 17 (59%); ref. 41], which might mechanistically explain the occurrence of immunodeficiencies.

A very small proportion of HTLV-I–infected individuals (0.1-2%) develop a separate clinically distinct neurologic disease known as HTLV-I–associated myelopathy (HAM) or tropical spastic paraparesis (TSP; refs. 42, 43). HAM/TSP is a progressive myelopathy with weakness and spasticity of the extremeties, urinary and bowel incontinence, and loss of peripheral nerve function. Patients with HAM/TSP, unlike those with adult T-cell leukemia, have high anti–HTLV-I CTL responses (44). Moreover, unlike in adult T-cell leukemia, the proliferation of HTLV-I–infected cells is polyclonal in HAM/TSP patients; this finding is consistent with a disease that does not develop from monoclonal expansion of malignant cell(s). The pathologic raison d'etre for HAM/TSP seems not to be a direct effect of the virus as much as an indirect consequence of an overly vibrant immune response by the host to the virus (43).

Treatment

Current chemotherapeutic regimens, regardless of treatment intensity, fail to improve the survival of adult T-cell leukemia patients (45). By contrast, remarkable progress in adult T-cell leukemia treatment has been observed using allogeneic hematopoietic stem cell transplantation (46). In one study, 10 patients with adult T-cell leukemia were treated with allogeneic hematopoietic stem cell transplantation, and median leukemia-free survival after allogeneic hematopoietic stem cell transplantation was 17.5 months. In a second study, 16 patients with adult T-cell leukemia were treated with reduced conditioning intensity allogeneic stem cell transplantation from human leukocyte antigen–matched sibling donors. Provirus load became undetectable in eight patients (47). Anti-Tax CTL, as measured by the tetramer assay, was markedly increased after stem cell transplantation, indicating that enhanced CTL function can effectively combat HTLV-I–infected cells. As a further measure of efficacy, Tax-specific CTLs were induced only in patients who maintained remission from disease (48).

On the horizon, new applications against adult T-cell leukemia are being investigated. Proteasome inhibitors can suppress NF-κB activity, which plays a central role in adult T-cell leukemia. Bortezomib (a proteasome inhibitor formerly known as PS-341) has been shown to exhibit anti-adult T-cell leukemia effect *in vitro* and *in vivo* (49–51). In addition, monoclonal antibodies against adult T-cell leukemia cells, such as anti-CD25 (52), anti-CD52, anti-CD2, and anti-CCR4 (53), are being developed to treat adult T-cell leukemia.

Acknowledgments

Received 2/17/2005; revised 4/15/2005; accepted 4/19/2005.

We thank all colleagues and collaborators who have provided us with advice and reagents in our HTLV-I research programs. Due to space and format constraints, we apologize for the inability to cite all the important published studies on HTLV-I. We thank Anthony Elmo and Ayako Yoshioka for assistance in the preparation of manuscript.

References

1. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci U S A 1980;77:7415–9.
2. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 1977;50:481–92.
3. Hinuma Y, Nagata K, Hanaoka M, et al. Adult T-cell leukemia: antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci U S A 1981;78:6476–80.
4. Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A 1982;79:2031–5.
5. Arisawa K, Soda M, Endo S, et al. Evaluation of adult T-cell leukemia/lymphoma incidence and its impact on non-Hodgkin lymphoma incidence in southwestern Japan. Int J Cancer 2000;85:319–24.
6. Iga M, Okayama A, Stuver S, et al. Genetic evidence of transmission of human T cell lymphotropic virus type 1 between spouses. J Infect Dis 2002;185:691–5.
7. Igakura T, Stinchcombe JC, Goon PK, Taylor GP, Weber JN, Griffiths GM, et al. Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. Science 2003;299:1713–6.
8. Manel N, Kim FJ, Kinet S, Taylor N, Sitbon M, Battini JL. The ubiquitous glucose transporter GLUT-1 is a receptor for HTLV. Cell 2003;115:449–59.
9. Kim FJ, Manel N, Garrido EN, Valle C, Sitbon M, Battini JL. HTLV-1 and -2 envelope SU subdomains and critical determinants in receptor binding. Retrovirology 2004; 1:41.
10. Jeang KT, Giam CZ, Majone F, Aboud M. Life, death, and tax: role of HTLV-I oncoprotein in genetic instability and cellular transformation. J Biol Chem 2004;279: 31991–4.
11. Okada M, Jeang KT. Differential requirements for activation of integrated and transiently transfected human T-cell leukemia virus type 1 long terminal repeat. J Virol 2002;76:12564–73.
12. Scoggin KE, Ulloa A, Nyborg JK. The oncoprotein Tax binds the SRC-1-interacting domain of CBP/p300 to mediate transcriptional activation. Mol Cell Biol 2001; 21:5520–30.
13. Yoshida M. Multiple viral strategies of HTLV-1 for dysregulation of cell growth control. Annu Rev Immunol 2001;19:475–96.
14. Azran I, Schavinsky-Khrapunsky Y, Aboud M. Role of Tax protein in human T-cell leukemia virus type-I leukemogenicity. Retrovirology 2004;1:20.
15. Ching YP, Chun AC, Chin KT, Zhang ZQ, Jeang KT, Jin DY. Specific TATAA and bZIP requirements suggest that HTLV-I Tax has transcriptional activity subsequent to the assembly of an initiation complex. Retrovirology 2004;1:18.
16. Ng PW, Iha H, Iwanaga Y, et al. Genome-wide expression changes induced by HTLV-1 Tax: evidence for MLK-3 mixed lineage kinase involvement in Tax-mediated NF-κB activation. Oncogene 2001; 20:4484–96.
17. Pise-Masison CA, Radonovich M, Mahieux R, et al. Transcription profile of cells infected with human T-cell leukemia virus type I compared with activated lymphocytes. Cancer Res 2002;62:3562–71.
18. Jeang KT. Functional activities of the human T-cell leukemia virus type I Tax oncoprotein: cellular signaling through NF-κB. Cytokine Growth Factor Rev 2001;12: 207–17.
19. Matsuoka M. Human T-cell leukemia virus type I and adult T-cell leukemia. Oncogene 2003;22:5131–40.
20. Grassmann R, Berchtold S, Radant I, Alt M, Fleckenstein B, Sodroski JG, et al. Role of human T-cell leukemia virus type 1 X region proteins in immortalization of primary human lymphocytes in culture. J Virol 1992;66:4570–5.
21. Mortreux F, Gabet AS, Wattel E. Molecular and cellular aspects of HTLV-1 associated leukemogenesis *in vivo*. Leukemia 2003;17:26–38.
22. Ross TM, Narayan M, Fang ZY, Minella AC, Green PL. Human T-cell leukemia virus type 2 tax mutants that selectively abrogate NFκB or CREB/ATF activation fail to transform primary human T cells. J Virol 2000;74: 2655–62.
23. Younis I, Khair L, Dundr M, Lairmore MD, Franchini G, Green PL. Repression of human T-cell leukemia virus type 1 and type 2 replication by a viral mRNA-encoded posttranscriptional regulator. J Virol 2004;78:11077–83.
24. Michael B, Nair AM, Hiraragi H, et al. Human T lymphotropic virus type-1 p30II alters cellular gene expression to selectively enhance signaling pathways that activate T lymphocytes. Retrovirology 2004;1:39.

25. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med 2004;10:789–99.
26. Mulloy JC, Kislyakova T, Cereseto A, et al. Human T-cell lymphotropic/leukemia virus type 1 Tax abrogates p53-induced cell cycle arrest and apoptosis through its CREB/ATF functional domain. J Virol 1998; 72:8852–60.
27. Haoudi A, Daniels RC, Wong E, Kupfer G, Semmes OJ. Human T-cell leukemia virus-I tax oncoprotein functionally targets a subnuclear complex involved in cellular DNA damage-response. J Biol Chem 2003;278:37736–44.
28. Kasai T, Iwanaga Y, Iha H, Jeang KT. Prevalent loss of mitotic spindle checkpoint in adult T-cell leukemia confers resistance to microtubule inhibitors. J Biol Chem 2002;277:5187–93.
29. Kehn K, Deng L, de La FC, et al. The role of cyclin D2 and p21/waf1 in human T-cell leukemia virus type 1 infected cells. Retrovirology 2004;1:6.
30. Neuveut C, Low KG, Maldarelli F, et al. Human T-cell leukemia virus type 1 Tax and cell cycle progression: role of cyclin D-cdk and p110Rb. Mol Cell Biol 1998;18:3620–32.
31. Liu B, Liang MH, Kuo YL, et al. Human T-lymphotropic virus type 1 oncoprotein tax promotes unscheduled degradation of Pds1p/securin and Clb2p/cyclin B1 and causes chromosomal instability. Mol Cell Biol 2003;23:5269–81.
32. Marriott SJ, Lemoine FJ, Jeang KT. Damaged DNA and miscounted chromosomes: human T cell leukemia virus type I tax oncoprotein and genetic lesions in transformed cells. J Biomed Sci 2002;9:292–8.
33. Tanaka A, Takahashi C, Yamaoka S, Nosaka T, Maki M, Hatanaka M. Oncogenic transformation by the tax gene of human T-cell leukemia virus type I *in vitro*. Proc Natl Acad Sci U S A 1990;87:1071–5.
34. Furukawa Y, Kubota R, Tara M, Izumo S, Osame M. Existence of escape mutant in HTLV-I tax during the development of adult T-cell leukemia. Blood 2001;97: 987–93.
35. Tamiya S, Matsuoka M, Etoh K, et al. Two types of defective human T-lymphotropic virus type I provirus in adult T-cell leukemia. Blood 1996;88:3065–73.
36. Koiwa T, Hamano-Usami A, Ishida T, et al. 5′-long terminal repeat-selective CpG methylation of latent human T-cell leukemia virus type 1 provirus *in vitro* and *in vivo*. J Virol 2002;76:9389–97.
37. Yasunaga J, Taniguchi Y, Nosaka K, et al. Identification of aberrantly methylated genes in association with adult T-cell leukemia. Cancer Res 2004; 64:6002–9.
38. Yoshida M, Nosaka K, Yasunaga J, Nishikata I, Morishita K, Matsuoka M. Aberrant expression of the MEL1S gene identified in association with hypomethylation in adult T-cell leukemia cells. Blood 2004; 103:2753–60.
39. Nosaka K, Miyamoto T, Sakai T, Mitsuya H, Suda T, Matsuoka M. Mechanism of hypercalcemia in adult T-cell leukemia: overexpression of receptor activator of nuclear factor κB ligand on adult T-cell leukemia cells. Blood 2002;99:634–40.
40. Yasunaga J, Sakai T, Nosaka K, et al. Impaired production of naive T lymphocytes in human T-cell leukemia virus type I-infected individuals: its implications in the immunodeficient state. Blood 2001;97: 3177–83.
41. Karube K, Ohshima K, Tsuchiya T, et al. Expression of FoxP3, a key molecule in CD4CD25 regulatory T cells, in adult T-cell leukaemia/lymphoma cells. Br J Haematol 2004;126:81–4.
42. Gessain A, Barin F, Vernant JC, et al. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet 1985;2:407–10.
43. Nagai M, Osame M. Human T-cell lymphotropic virus type I and neurological diseases. J Neurovirol 2003;9: 228–35.
44. Kannagi M, Ohashi T, Harashima N, Hanabuchi S, Hasegawa A. Immunological risks of adult T-cell leukemia at primary HTLV-I infection. Trends Microbiol 2004;12:346–52.
45. Yamada Y, Tomonaga M, Fukuda H, et al. A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukaemia-lymphoma: Japan Clinical Oncology Group Study 9303. Br J Haematol 2001;113: 375–82.
46. Utsunomiya A, Miyazaki Y, Takatsuka Y, et al. Improved outcome of adult T cell leukemia/lymphoma with allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2001;27:15–20.
47. Okamura J, Utsunomiya A, Tanosaki R, et al. Allogeneic stem cell transplantation with reduced conditioning intensity as a novel immunotherapy and antiviral therapy for adult T-cell leukemia/lymphoma. Blood 2005;105:4143–5.
48. Harashima N, Kurihara K, Utsunomiya A, et al. Graft-versus-Tax response in adult T-cell leukemia patients after hematopoietic stem cell transplantation. Cancer Res 2004;64:391–9.
49. Mitra-Kaushik S, Harding JC, Hess JL, Ratner L. Effects of the proteasome inhibitor PS-341 on tumor growth in HTLV-1 Tax transgenic mice and Tax tumor transplants. Blood 2004;104:802–9.
50. Satou Y, Nosaka K, Koya Y, Yasunaga JI, Toyokuni S, Matsuoka M. Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both *in vivo* and *in vitro*. Leukemia 2004;18:1357–63.
51. Tan C, Waldmann TA. Proteasome inhibitor PS-341, a potential therapeutic agent for adult T-cell leukemia. Cancer Res 2002;62:1083–6.
52. Zhang M, Zhang Z, Garmestani K, et al. Activating Fc receptors are required for antitumor efficacy of the antibodies directed toward CD25 in a murine model of adult T-cell leukemia. Cancer Res 2004;64:5825–9.
53. Ishida T, Iida S, Akatsuka Y, et al. The CC chemokine receptor 4 as a novel specific molecular target for immunotherapy in adult T-cell leukemia/lymphoma. Clin Cancer Res 2004;10:7529–39.

Oncogene (2005) 24, 6047–6057
© 2005 Nature Publishing Group All rights reserved 0950-9232/05 $30.00
www.nature.com/onc

Natural history of adult T-cell leukemia/lymphoma and approaches to therapy

Graham P Taylor[1] and Masao Matsuoka*,[2]

[1]Department of GU Medicine & Communicable Diseases, Faculty of Medicine, Imperial College, Norfolk Place, London W2 1PG, UK; [2]Laboratory of Virus Immunology, Center for AIDS Research, Institute for Virus Research, Kyoto University, 53 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

After cell-to-cell transmission, HTLV-I increases its viral genome by *de novo* infection and proliferation of infected cells. Proliferation of infected cells is clonal and persistent *in vivo*. During the carrier state, infected cells are selected *in vivo* by the host's immune system, the genetic and epigenetic environment of proviral integration sites, and other factors. In leukemic cells, *tax* gene expression is frequently impaired by genetic and epigenetic mechanisms. Such loss of Tax expression enables ATL cells to escape the host immune system. On the other hand, ATL cells acquire the ability to proliferate without Tax by intracellular genetic and epigenetic changes. Despite advances in support and the development of novel treatment agents, the prognosis for ATLL remains poor. A number of therapies, however, do appear to improve prognosis compared to CHOP (VEPA). These include interferon-α plus zidovudine (probably after 1–2 cycles of CHOP), intensive chemotherapy as in LSG-15 with G-CSF support and Allo-SCT (which includes the potential for cure). Emerging novel approaches include HDAC inhibitors, monoclonal antibodies, and proteasome inhibitors. Comparison between different therapeutic approaches is complicated by the range of natural history of ATLL, different recruitments of naïve-to-therapy, refractory or relapsed patients, and variations in the reporting of outcome that frequently excludes difficult-to-evaluate patients. Moreover, results from relatively small proof-of-principle studies have not been extended with randomized, controlled trials. As a result, currently, there is no clear evidence to support the value of any particular treatment approach over others. To avoid further unnecessary patient suffering and to identify optimal therapy as rapidly as possible, large randomized, controlled trials encompassing multicenter, international collaborations will be necessary.
Oncogene (2005) **24,** 6047–6057. doi:10.1038/sj.onc.1208979

Keywords: ATLL; HTLV-I; Tax; chemotherapy; transplantation; prevention

*Correspondence: M Matsuoka;
E-mail: mmatsuok@virus.kyoto-u.ac.jp

Disease course from HTLV-I infection to onset of ATL

After infection by HTLV-I, a subpopulation of carriers (6% male and 2% female subjects) develops ATL after a long latent period. Although genetic, environmental, and viral factors in addition to the host immune response should be implicated in leukemogenesis, the exact mechanism remains to be elucidated. Below, we highlight first the current understanding of the disease course leading to the onset of ATL.

Transmission of HTLV-I

HTLV-I can infect various cell types, including T cells, B cells, and synovial cells, suggesting that its receptor is ubiquitously expressed. The receptor for HTLV-I has been identified as glucose transporter type 1 (GLUT1) (Manel *et al.*, 2003). Its expression on T lymphocytes is enhanced by mitogen or TGF-β (Jones *et al.*, 2005), which has been shown to increase the infectivity of HTLV-I. *In vitro* experiment shows that transmission by free virion is very inefficient, whereas transmission by infected cells is much more efficient. This is because HTLV-I transmits naturally in a cell-to-cell fashion. When an HTLV-I-infected cell attaches to uninfected cells, the HTLV-I-infected cells form 'virological synapses' with uninfected cells. Contact between an infected cell and a target cell polarizes the microbutule-organizing center (MTOC) at the cell–cell junction, and then viral proteins, such as Gag and viral genome RNA, accumulate at this junction and the viral complex subsequently transfers into the target cell (Igakura *et al.*, 2003). In HTLV-I-infected cells, expression of ICAM-1 is upregulated, and antibody to ICAM-1 induces MTOC polarization in HTLV-I-infected cells, suggesting that increased expression of ICAM-1 facilitates cell-to-cell transmission of HTLV-I (Barnard *et al.*, 2005). Thus, transmission of HTLV-I needs living infected cells.

HTLV-I-infected cells enter into the human body via three major routes: (1) mother-to-infant transmission (mainly through breast-feeding), (2) sexual transmission, and (3) parenteral transmission. Of note, fresh frozen plasma from seropositive donors did not transmit HTLV-I (Okochi *et al.*, 1984). Hence, if living cells can be eliminated by freeze and thawing, then feeding

the mother's breast milk to infants will not increase viral transmission (Ando *et al.*, 2004). These findings clearly show that physiological transmission requires live HTLV-I-infected cells. To facilitate its transmission, HTLV-I increases clonally the population of infected cells by the pleiotropic actions of viral proteins, especially Tax (Yoshida, 2001; Gatza *et al.*, 2003; Jeang *et al.*, 2004; Matsuoka and Jeang, 2005).

HTLV-I-infected cells in vivo

In HTLV-I carriers and ATL patients, no free virion has been demonstrated *in vivo*. The presence of antibody and provirus are evidence for HTLV-I infection. After transmission of HTLV-I, reverse transcriptase generates proviral DNA from the genomic viral RNA, and the provirus is integrated into the host genome by viral integrase. Since most ATL cells contain one copy of HTLV-I provirus, and ATL cells are derived from HTLV-I-infected cells, it is reasonable to consider that most of the HTLV-I-infected cells have one copy of the provirus. Therefore, quantification of provirus is thought to reflect the number of HTLV-I-infected cells *in vivo*. Quantification of HTLV-I provirus among infected individuals demonstrates that provirus load differs more than 1000-fold among asymptomatic carriers (Etoh *et al.*, 1999). Since living HTLV-I-infected cells are essential for transmission as mentioned above, an increased number of HTLV-I-infected cells is thought to facilitate transmission. Indeed, higher provirus load in the breast milk is correlated with an increased risk of vertical transmission from seropositive mothers (Li *et al.*, 2004). In this regard, the mechanism to increase HTLV-I-infected cells by actions of accessory genes, especially *tax*, provides the rationale for enhancing infectivity.

Clonal proliferation of HTLV-I-infected cells

After transmission, HTLV-I increases viral copy number both by *de novo* infection and clonal proliferation of infected cells. In this strategy, Tax plays a central role in increasing the number of HTLV-I-infected cells by promoting proliferation and inhibiting apoptosis. Since the integration sites of HTLV-I provirus are random, the demonstration of discrete integration sites can be employed to identify individual HTLV-I-infected clones. Inverse PCR or linker-mediated PCR was utilized to characterize integration sites, and revealed that proliferation of HTLV-I-infected cells was oligoclonal (Figure 1) (Etoh *et al.*, 1997). Importantly, these clonal proliferations of HTLV-I-infected cells are persistent since the same clones can be detected at the different time points (Etoh *et al.*, 1997; Cavrois *et al.*, 1998). As an example, a HAM/TSP patient developed lymphoma-type ATL. The ATL clone was identified in a blood sample obtained before the onset of ATL, which showed that the same clone was already present during HAM/TSP (Tamiya *et al.*, 1995). In addition, the prospective study of the Miyazaki cohort identified carriers who developed ATL during follow-up. The presence of

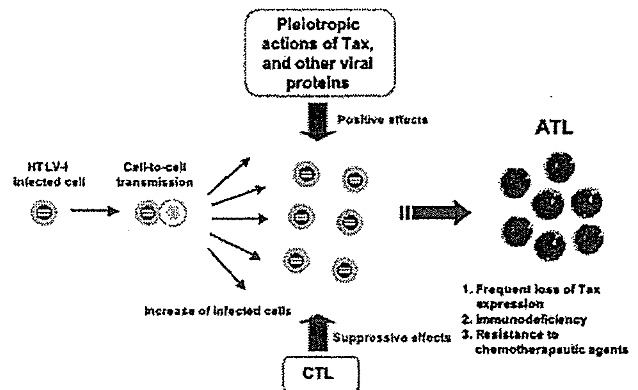

Figure 1 Natural course from HTLV-I infection to onset of ATL. HTLV-I is transmitted in a cell-to-cell fashion. After infection, HTLV-I promotes clonal proliferation of infected cells by pleiotropic actions of Tax and other viral proteins. Proliferation of HTLV-I-infected cells is controlled by cytotoxic T cells *in vivo*. After a long latent period, ATL develops in about 5% of asymptomatic carriers. The expression of Tax is inactivated by several mechanisms, suggesting that Tax is not necessary in this stage. Alternatively, alterations and errors in the host genome accumulate progressively during the latent period, finally leading to onset of ATL

leukemic clones was detected during the carrier state by inverse PCR method. Such clonal proliferation is directly associated with the onset of ATL (Okayama *et al.*, 2004), and these studies clearly illustrate that HTLV-I-infected clones can transform to malignancy during the carrier state.

HTLV-I clonal cells are more heterogeneous and less stable during seroconversion than in long-term carriers (Tanaka *et al.*, 2005). This finding suggests that during seroconversion, HTLV-I-infected cells are actively selected *in vivo*, and thereafter, selected clones predominate in long-term carriers. Such selection may be due to several factors, including the immune pressure exerted by cell-mediated immunity (Bangham, 2003), the productivity of viral proteins, and the characteristics of the integration sites which influence viral transcription.

Integration sites of HTLV-I provirus

To clarify the significance of integrated genome positions, integration sites of HTLV-I provirus are determined by inverse PCR in carrier states and ATL. The frequencies of HTLV-I provirus integration into transcription units (from the first exon to the last exon) are 26.8% (15/56) in carriers and 33.9% (20/59) in ATL. These are equivalent to the frequency calculated based on random integration (33.2%) (Doi *et al.*, 2005). By contrast, HIV-1, another human retrovirus, integrates predominantly (91%) into actively transcribed genes of T lymphocytes (Han *et al.*, 2004), and integration sites are evenly distributed within the transcription units. Additionally, the frequency of integration into transcription units is 34.2% for murine leukemia virus (MLV), and these sites are clustered near the transcriptional

start sites (Wu *et al.*, 2003). Similarly, HTLV-I provirus is prone to integration near the transcriptional start sites in leukemic cells ($P = 0.006$). Thus, integration pattern of HTLV-I is similar to MLV rather than HIV-1. HIV-1 can infect nondividing cells by passing through the nuclear pore, whereas MLV can infect only dividing cells. These data suggest that HTLV-I may infect only dividing cells.

In addition, HTLV-I integration sites in the carriers favor the alphoid repetitive sequences (11/56: 20%) whereas in leukemic cells they disfavored these sequences (2/59: 3.4%). Alphoid repeats are a component of centromeric heterochromatin and consist of monomeric 171 bp repeats. When HIV-1 is integrated into alphoid repetitive sequences, it adopts a latent state due to the influence of the surrounding heterochromatin (Jordan *et al.*, 2003). Thus, genome surrounding integration sites influences the transcription of viral genes. HTLV-I-infected cells in which the provirus is integrated into alphoid repetitive sequence are considered to be in the latent state. Such infected cells are enriched in carrier state, indicating that infected cells with less viral gene expression are favored since such cells can escape from the host's cytotoxic T lymphocytes (Bangham, 2003). However, integration into alphoid sequences is infrequent in leukemic cells, indicating that among surviving HTLV-I-infected cells those with higher production of viral proteins are more likely to transform into malignant cells.

HTLV-I provirus in ATL cells

The *tax* gene plays a central role by its pleiotropic actions in the proliferation and leukemogenesis of HTLV-I-infected cells *in vivo* (Franchini *et al.*, 2003). However, its transcription is detected in only 34% of ATL cases by RT–PCR (Takeda *et al.*, 2004). Tax production is impaired by several mechanisms: (1) genetic changes (nonsense mutation, insertion, and deletion) of *tax* gene, (2) deletion of 5′-long terminal repeat (LTR), and (3) DNA methylation of 5′-LTR. Genetic changes of *tax* gene were observed in five of 47 cases (11%) (Furukawa *et al.*, 2001; Takeda *et al.*, 2004). Deletion of 5′-LTR, which is the promoter/enhancer for viral gene transcription, was observed in 14 of 47 cases (30%). This type of defective provirus designated type 2 defective provirus (Tamiya *et al.*, 1996) lacks 5′-LTR and internal sequences, such as *gag*, *pol*, and *env* genes. The frequency of type 2 defective provirus was much higher in acute and lymphoma-type ATL than in chronic type ATL, suggesting a close association with disease progression. Heavy methylation of the 5′-LTR region was also associated with silencing of viral gene transcription (Koiwa *et al.*, 2002; Takeda *et al.*, 2004). Tax expression is absent or severely impaired in ATL cells with heavily methylated 5′-LTR. Such changes are predominantly observed in aggressive subtypes of ATL, which suggests that at this stage, ATL cells acquire the ability to proliferate without Tax expression. In turn, such changes enable ATL cells to escape from the host immune system by loss of Tax expression (Figure 1). This finding reveals a duality in the Tax protein: its expression induces proliferation and inhibits apoptosis of HTLV-I-infected cells, and also evokes the host's immune response including cytotoxic T cells to kill virus-infected cells.

Somatic changes in ATL cells

As described above, ATL cells do not always need Tax expression in the later stage of leukemogenesis. Genetic and epigenetic changes imprinted into the genome should be implicated in such multistep leukemogenesis. Regarding genetic changes, mutation of p53, and deletion of p16 have been reported in ATL. Usually, ATL cases with genetic changes in p53 and p16 have a poor prognosis (Yamada *et al.*, 1997). Therefore, these genetic changes are thought to be associated with disease progression. A transcriptional profile of ATL cells by DNA chip analysis identified aberrantly transcribed genes (Sasaki *et al.*, 2005). Among them, the expression of *tumor suppressor in lung cancer 1* (*TSLC1*) gene is upregulated in ATL cells. *TSLC1* gene was identified as a tumor suppressor gene in lung cancer cells. Since this molecule is associated with cell adhesion, loss of its expression is associated with the invasive phenotype of lung cancer cells (Kuramochi *et al.*, 2001). However, its ectopic expression is associated with leukemogenesis possibly due to the conferring of an adhesive phenotype to ATL cells.

Epigenetic changes are recognized as mechanisms implicated in oncogenesis as well as genetic changes. Since genetic changes in specific genes in ATL cells have not been identified except for p53 and p16, and there is no consistent chromosomal change, it is possible that epigenetic changes such as DNA methylation play an important role in leukemogenesis by inhibiting the transcription of tumor suppressor genes or inducing aberrant expression of oncogenes. Aberrantly methylated DNA regions were identified by a methylated CpG-island amplification/representational difference analysis method (Toyota *et al.*, 1999). *MEL1S* gene was hypomethylated and aberrantly expressed in ATL cells (Yoshida *et al.*, 2004). Since such expression conferred the resistance against TGF-β, the *MEL1S* gene expression is implicated in resistance of ATL cells to TGF-β. On the other hand, *EGR3* gene has been demonstrated to be hypermethylated in ATL cells (Yasunaga *et al.*, 2004). EGR3 is a transcriptional factor, which is essential for transcription of the *FasL* gene (Mittelstadt and Ashwell, 1998). Normal activated T lymphocytes express FasL as well as Fas antigen. Apoptosis induced by autocrine mechanisms is designated activation-induced cell death (AICD) and this controls the immune response (Krueger *et al.*, 2003). Although ATL cells express Fas antigen, they do not produce FasL, thereby enabling ATL cells to escape from AICD. Suppressed transcription of *EGR3* gene might be the mechanism allowing ATL cells to escape from AICD. Thus, epigenetic changes of the genome play an important role in oncogenesis of ATL.

Pathogenesis

Hypercalcemia

Hypercalcemia complicates more than 70% of ATL cases during the entire clinical course (Kiyokawa *et al.*, 1987), and the extent of hypercalcemia is frequently severe. In the bone of hypercalcemic patients, the number of activated osteoclasts increases, which accelerates bone resorption. In the differentiation of osteoclast from the hematopoietic precursor cells, RANK ligand, which is expressed on the osteoblasts, and M-CSF cooperatively induce the differentiation of osteoclasts (Arai *et al.*, 1999). In hypercalcemic ATL patients, ATL cells have been shown to express RANK ligand (Nosaka *et al.*, 2002), and the serum level of M-CSF is elevated in most ATL patients. ATL cells from hypercalcemic patients have been demonstrated to induce the differentiation of hematopoietic precursor cells into osteoclasts *in vitro*. These data indicate that ATL cells expressing RANK ligand induce the differentiation to osteoclast, and such increased osteoclasts accelerate bone resorption, resulting in hypercalcemia. In ATL patients, parathyroid hormone-related peptide (PTH-rP) is frequently increased (Watanabe *et al.*, 1990), which induces the RANK ligand expression on osteoblasts. Increased PTH-rP is also implicated in ATL-associated hypercalcemia.

Immunodeficiency

Opportunistic infections are frequent complications in ATL patients, and impaired cell-mediated immunity has been identified as a causative basis of immunodeficiency. Pathogens of opportunistic infections include *Pneumocystis jiroveci*, cytomegalovirus, *Strongyloides stercoralis*, and a variety of fungi. Such infections are one reason for the poor prognosis, despite treatment, of ATL patients. Mild immunodeficiency is also seen in asymptomatic carriers (Katsuki *et al.*, 1987; Welles *et al.*, 1994). Here, a decreased number of naïve T-lymphocytes is proposed as a cause of immunodeficiency (Yasunaga *et al.*, 2001). CD4+, CD25+ T cells are reported to have immunoregulatory functions, and are called as regulatory T cells (Treg). Tregs have suppressive immune functions. Tregs express *forkhead box P3* (*FOXP3*) gene, which is a master gene of immunoregulatory functions (Fontenot and Rudensky, 2005). ATL cells show the phenotype of activated helper T cell (CD4+ and CD25+), suggesting that they are derived from a Treg cell. *FOXP3* gene transcription was detected in eight of 17 ATL cases (47%) (Karube *et al.*, 2004). Such Treg phenotype of ATL cells is considered to suppress the immune response, and may be implicated in the immunodeficiency. In addition to the FOXP3+ Tregs, antigen-induced IL-10 secreting Tr1 has been identified as another subset of Treg (Thompson and Powrie, 2004), which is FOXP3 negative. Although FOXP3 expression was not detected in about half of ATL cases, ATL cells were reported to produce IL-10 suggesting that FOXP3-negative ATL cells also have regulatory contribution.

Treatment of ATLL

After 28 years of the initial description of ATLL as a discrete clinical entity, this condition continues to carry a very poor prognosis. Recent reviews cite median survivals of less than 1 year despite advances in both chemotherapy and supportive care (Siegel *et al.*, 2001). The 6 months median survival of Japanese patients with ATLL reported in Shimoyama's (1992) overview does not significantly differ from experience in Europe a decade later (Taylor *et al.*, 2001). It is therefore hard to disagree with Yamada and Tomonaga's conclusion that the vast accumulation of knowledge in the molecular biology and oncogenesis of ATLL has yet to be translated into an improved prognosis (Yamada and Tomonaga, 2003). Yet, the array of therapeutic approaches tested over the past two decades is impressive. In this section, we review extant data and attempt to determine why so many therapies, initially reported optimistically, have not been further developed. We look to how prognosis might be improved in the future.

Chemotherapy

Cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) has been, and probably remains, the standard first-line therapy for ATLL and many patients do exhibit either partial (PR) or complete remission (CR). Yet a literature search will reveal only limited data on the efficacy of this approach. Tsukasaki *et al.* reviewed the outcome of their cohort of 114 patients presenting with acute or lymphomatous ATLL between 1975 and 1989. These patients were treated with combination chemotherapy with only 17.5% achieving CR, but a further 46.5% had a partial response (Tsukasaki *et al.*, 1993). These data accord with the results of the Lymphoma Study Group in which CR was obtained in 17–18% of patients treated with CHOP (LSG-1) (Lymphoma Study Group, 1982; Shimoyama *et al.*, 1988); in 37% of patients treated with CHOP plus methotrexate (Shimoyama *et al.*, 1988). A similar response (63% CR+PR) was found in 21 patients treated with combination chemotherapy in London, UK over a 15-year period (1981–1995), but the median survival was only 5.5 months (Pawson *et al.*, 1998). Intensification of CHOP with etoposide, vindesine, ranimustine, and mitoxantrone resulted in CR in 35.8% of the 83 patients (Taguchi *et al.*, 1996) and in 43% when part of a nine-agent cycle (LSG-4) (Tobinai *et al.*, 1994). However, the median survival was only 8–8.5 months in these studies with predicted survivals of 13.5% after 3 years and 12% after 4 years, respectively. Matsushita *et al.* reported their experience of substituting etoposide for adriamycin in a weekly long-term maintenance chemotherapy. The median survival in their 79 patients with acute, lymphoma, and progressive

chronic ATLL following this regimen was 7.5 months, but the therapy was reported to be well tolerated (Matsushita *et al.*, 1999). Better survival, 18 months, was observed among a further eight patients treated with daily etoposide plus prednisolone, but this may have been due to selection bias. The best outcome with chemotherapy reported to date has been with an aggressive multidrug approach supported by G-CSF. While this regimen of seven cycles of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECP (vindesine, etoposide, carboplatin, and prednisone) was, as anticipated, highly marrow toxic with grade 4 haematological toxicity in the majority of patients, the median survival of 13 months among 96 treatment naïve patients with acute, lymphoma and progressive chronic ATLL does represent an improvement (Yamada *et al.*, 2001). The relative insensitivity of ATLL to chemotherapy may be related, at least in part, to upregulation of MDR gene (Kuwazuru *et al.*, 1990). In the Yamada study, ranimustine and carboplatin were included in the regimen because they are not affected by P-glycoprotein expression.

Part of the problem lies in the variable natural history of ATLL, and therefore the balance of disease types in the cohort may affect the outcome. For this reason, case reports are almost uninterpretable. In Uozumi's study, the median survival of 43 patients with acute and lymphoma ATLL treated with a response-orientated cyclic multidrug protocol was only 6 months, but many patients had poor prognostic factors (Uozumi *et al.*, 1995). While in Matsushita's cohort of maintenance therapy, the survival of patients with acute leukemia was 6.7 months, lymphoma 9.6, and progressive chronic leukemia 12.4 months (Matsushita *et al.*, 1999). It is difficult to judge whether this approach represents an advance in therapy as suggested by the authors although this remains a possibility. The best response rates are with the LSG-15 regime on which patients with acute ATLL survived 10.9 months and patients presenting with lymphoma 19.8 months (Yamada *et al.*, 2001). However, because renal dysfunction was an exclusion criterion, no patients with severe hypercalcemia were included in the study. This may have contributed to the superior results seen with this protocol. Overall, ATLL survival with various chemotherapy regimens is poor, with survival in several cohorts of patients presenting predominantly with acute leukemia or lymphoma ranging between 5.5 and 13 months. This approach does not offer the prospect of cure (Table 1).

Nucleoside analogues

A number of studies have addressed the role of nucleoside analogues in the management of ATLL. The purine analog 2′ deoxycoformycin (DCF) that inhibits adenosine deaminase has been investigated as an alternative approach. In a phase I dose finding safety study, 3/18 patients with ATLL had a PR with 3 days intravenous (i.v.) therapy. The suggested dose for phase II trials was 5 mg/m^2 i.v. for 3 days (Tobinai *et al.*, 1992).

In another study using DCF 4 mg/m^2/week for 4 weeks followed by fortnightly therapy, two CR and one PR were reported among 25 patients with ATLL (Mercieca *et al.*, 1994). While reported with a degree of optimism, these response rates are clearly lower than with CHOP-based chemotherapy. Using DCF in conjunction with chemotherapy, 52% of 60 patients achieved CR, but the median survival of all patients was only 7.4 months (Tsukasaki *et al.*, 2003).

Although one patient with treatment resistant acute ATLL had a prolonged partial response to another adenosine analog 2′ chlorodeoxyadenosine (cladribine) (Uike *et al.*, 1998), the follow-up phase II study showed very limited benefit in 15 patients, with only the one, presumably same, response reported. However, all patients had been treated with other agents prior to entering this study and therefore represent a poor prognosis group (Tobinai *et al.*, 2003). Another purine (adenosine) derivative has been studied in phase I. Dose-limiting marrow toxicity was observed with fludarabine phosphate (Arima *et al.*, 1999).

A parallel approach, using L-alanosine, an inhibitor of adenosine monophosphate synthesis, has been suggested based on the observation of increased sensitivity of ATLL cells to L-alanosine *in vitro*. A proportion of ATLL primary cells are deficient in methylthioadenosine phosphorylase (MTAP) which should make then more sensitive to purine synthesis inhibitors. Nonleukaemic cells can, *in vitro*, be protected from this effect by simultaneous treatment with 5′-deoxyadenosine (Harasawa *et al.*, 2002). No *in vivo* data have been published to date and the therapy would need to be selectively used in MTAP-deficient ATLL only.

Topoisomerase inhibitors

Complete remission lasting 5 months after treatment with CPT-11, irinotecan hydrochloride, an inhibitor of topoisomerase I was reported in a patient with ATLL lymphoma unresponsive to intensified chemotherapy (Makino *et al.*, 1994). However in a study of 13 patients, all pretreated and failing chemotherapy, only one patient had a CR (Tsuda *et al.*, 1994). Although PR was seen in a further four patients, this agent has not been further studied in this group, in therapy naïve, nor in combination with other agents.

MST-16, a bis(2,6-dioxopiperazine) analog and inhibitor of topoisomerase II has been studied in a phase I–II trial (Ohno *et al.*, 1993). A total of 24 patients received 1200–2800 mg/day oral MST-16 for 7 days every 2–3 weeks. Remission occurred in both patients with chronic ATLL, 46% of patients with acute ATLL, but in only 25% of patients with lymphoma, and the two CR and eight PR lasted just over 2 months. These results do not represent an improvement over conventional chemotherapy and further studies with MST-16 have not been published.

Menogaril 100 mg daily 7 consecutive days every 3–4 weeks induced CR in 2/15 patients and PR in four (Taguchi *et al.*, 1997).

Table 1 Therapy studies inclusive of acute, lymphoma, and progressing or poor prognosis chronic ATLL

First author	*Year*	*Therapy*	*Support*	*N*	*CR (%)*	*PR (%)*	*ALL (%)*	*Median survival (months)*	*Survival rate*
Lymphoma Study Group	1982	CHOP (VEPA) aka LSG-1			18			6.0	
Shimoyama, M	1988	VEPA v		54	17			6.0	4 years 8%
		VEPA-M (aka LSG-2)			37				
Tobinai	1994	VEPA-B/M-FEPA/VEPP-B (aka LSG-4)			43			8.0	4 years 12%
Tsukasaki, K	1993	Combination chemotherapy (single institution cohort)		114	17.5	46.5	64		
Uozumi, K	1995	Response-orientated chemotherapy ?All treatment naïve		43	20.9	65.1	86	6.0	
Taguchi, H	1996	CHOP + etoposide, vindesine, ranimustine and mitoxantrone	G-CSF	83	35.5	38.3	74.1	8.5	3 years 13.5%
Pawson, R	1998	Combination chemotherapy		21			63	5.5	
Matsushita, K	1999	OPEC/MPEC or etoposide/Pred (maintenance)		79	31	58.6	89.6	7.5	
Yamada, Y	2001	VCAP/AMP/VECP (JCOG9309/ LSG-15) all treatment naïve	G-CSF	96	35.5	45.2	81	13.0	2 years 31%
Tsuda, H	1994	CPT-II, topoisomerase-I inhibitor (refractory disease)		13	7.7	30.1	38.8		
Ohno, R	1993	MST-16, topoisomerase-II inhibitor		24	8.33	25.0	33.3		
Tsukasaki, K	2003	VPA/etoposide + deoxycoformycin aka LSG-11/JCOG9109		60	28	24	52	7.4	2 years 17%
Gill, P	1995	Interferon-α + zidovudine (half had refractory/relapsed disease)		19	26.3	31.5	57.8	3.0	
Hermine, O	1995	Interferon-α + zidovudine		18			66	10.0	
Matutes, E	2001	CHOP, interferon-α + zidovudine		15			67	18.0	
Hermine, O	2002	+/−CHOP, interferon-α + zidovudine		19	47	21	68	11.0	
Besson, C	2002	CHOP, interferon-α + zidovudine, etoposide		7				17.0	
Waldmann, T	1988	Anti-Tac antibody		19	11	21	33		
Waldmann, T	1995	90Y-labelled anti-Tac antibody		18	11	39	50		
Fukushima, T	2005	Allo-SCT		40	100			9.6	3 years 45.3%
Acute ATLL only									
Ohno, R	1993	MST-16, topoisomerase-II inhibitor		13	6.23	38.4	46.1		
Matsushita, K	1999	OPEC/MPEC or etoposide/Pred (maintenance)		51				6.7	
Yamada, Y	2001	VCAP/AMP/VECP	G-CSF	56	19.6	53.6	73.2	10.9	
Hermine, O	2002	+/−CHOP, interferon-α + zidovudine		15					
Lymphoma only									
Ohno, R	1993	MST-16, topoisomerase-II inhibitor		8	0	25.0	25.0		
Matsushita, K	1999	OPEC/MPEC or etoposide/Pred (maintenance)		22				9.6	
Yamada, Y	2001	VCAP/AMP/VECP	G-CSF	27	66.7	29.6	96.3	19.7	

Definitions of disease response (Yamada *et al.*, 2001): Complete remission – disappearance of all clinical and radiological evidence of disease and normalization of LDH for at least 4 weeks. Partial remission – greater than 50% reduction in disease for more than 4 weeks, and >75% reduction in absolute abnormal lymphocyte counts, and LDH <1.5 × normal upper limit

All-*trans*-retinoic acid (ATRA), an analog of vitamin A induces G1 cell-cycle arrest and induction of apoptosis in *ex vivo* ATLL cells. Exposure of cell lines derived from ATLL patient PBLs to ATRA results in increased cyclin D1 protein and an increase in complex formation with cyclin-dependent kinases 4 and 6 (cdk4/cdk6) and with proliferating cell nuclear antigen (PCNA). The effects of ATRA on these cell lines are complicated with evidence of an initial increase in cdk2 activity followed by depression of activity. Thus following ATRA, these cells were initially stimulated and then arrested in G1 (Dierov *et al.*, 1999).

Interferon

Although ineffective alone, interferon-α does have a role in the management of ATLL especially in combination with zidovudine. The first report of potential benefit was the study by Ezaki *et al.* (1991) in which 9/12 patients, some pretreated with chemotherapy, had a PR with

human lymphoblastoid interferon in combination with bestrabucil (a combination of chlorambucil with β-estradiol). However, the treatment of all patients with lymphoma or hypercalcemia with prednisolone makes this result more difficult to evaluate.

Zidovudine and Interferon plus zidovudine

The observation of clinical improvement in ATLL in a patient undergoing treatment for HIV-1 infection with zidovudine plus interferon-α led to the further investigation of this combination. In the USA, Gill *et al.* treated 19 patients, seven relapsing after chemotherapy, with zidovudine 200 mg × 5/day plus interferon-α 5–10 MU s.c. daily, effecting CR in five and PR in six. Although four patients survived beyond 1 year, the median survival of only 3 months was indicative of the advanced disease in this cohort (Gill *et al.*, 1995). In France, Hermine *et al.* (1995) treated 18 patients with ZDV/IFN and achieved a 58% CR/PR response rate and a median survival of 10 months. In the UK, a debulking approach with 1–2 cycles of CHOP followed by a switch to lower doses of interferon-α (3–5 MU) plus zidovudine 500 mg bd was preferred. In total, 15 predominantly naïve, patients were treated in an open study, 67% achieving remission (CR + PR) with a median survival of 18 months (Matutes *et al.*, 2001). In a further phase II study from France of 12 treatment naïve patients with acute and lymphoma ATLL, the 92% response rate (seven CR and four PR) with zidovudine plus interferon-α represents a significant improvement over conventional and other chemotherapies (Hermine *et al.*, 2002). If all 19 patients, including the seven who did not receive ZDV/IFN first line, are included, the overall median survival remains a disappointing 11 months but 15/19 presented with the most aggressive, acute form of ATLL. Response and survival in patients who were treated with ZDV/IFN after initial chemotherapy was less impressive than those treated with ZDV/IFN as first-line therapy, but survival from initial presentation should also be considered. The Martinique experience, which is more similar to that of the UK, is to give two cycles of CHOP followed by ZDV/IFN (or sometimes the cytosine analog ddC instead of the thymidine analog ZDV) plus etoposide. The 17-month survival with this approach was significantly better than the historical survival of 3 months (Besson *et al.*, 2002).

Interferon-α and arsenic trioxide (As_2O_3)

In vitro studies have shown a synergistic effect of IFN-α and arsenic to induce apoptosis in ATLL cells. This combination was therefore offered to seven patients with refractory/relapsing ATLL in a pilot study. Although CR was seen in one patient persisting for a minimum of 56 months and PR in three patients, all patients had discontinued therapy after a median of 22 days due to toxicity or progression, and the six PR or unresponsive patients had died within a median of 1.5 months (Hermine *et al.*, 2004; Mahieux and Hermine, 2005). The median survival of these patients from first presentation (6 months prior to As_2O_3) was, therefore, 7.5 months. Arsenic alone has been shown to block transcription of NF-κB-dependent genes in HTLV-I-infected cells and in combination with IFN-α inhibits Tax-induced NF-κB activation (Nasr *et al.*, 2003).

NF-κB blockade

A number of apparently differing approaches point to the potential importance of NF-κB activity in ATLL and the therapeutic potential of NF-κB inhibition.

In vitro Bay 11-7082 inhibits NF-κB, reduces DNA binding to NF-κB, and downregulates transcription of Bcl-x_L. Preferential apoptosis of HTLV-I-infected cell lines and primary ATLL cells was observed. Unlike the histone deacetylation inhibitor, HFR901228, described below, Bay 11-7082 did not affect AP-1 (Mori *et al.*, 2002).

Inhibition of the proteasome by PS-341, bortezomib, blocking the degradation of IκBα and thereby inhibiting NF-κB has been shown to induce programmed death of ATLL cells *in vitro* (Tan and Waldmann, 2002; Satou *et al.*, 2004). Suppression of tumour growth was also documented in a SCID mouse ATLL model (Satou *et al.*, 2004). On the other hand, Tan and Waldmann (2002) reported no benefit in their mouse model of ATLL with PS-341 alone, but CR in some animals when combined with anti-Tac antibody.

The use of histone deacetylation inhibitors (HDIs) has recently attracted attention. One such compound, HFR901228, depsipeptide, has been shown to induce apoptosis in Tax-expressing and in Tax nonexpressing HTLV-I-infected cell lines and in primary cells for patients with acute ATLL. Its effect was through a reduction of DNA binding of NF-κB and AP-1, and downregulation of Bcl-x_L and cyclin D2 expression. Partial inhibition of the growth of tumors, which result from the transplant of HTLV-I-infected cells, was seen in a SCID mouse model (Mori *et al.*, 2004). Sodium valproate, widely prescribed for the treatment of epilepsy, bipolar mood disorders, and migraine, has, among several potential antitumour properties, HDI activity (Blaheta and Cinatl, 2002). Sodium valproate is being studied as a maintenance therapy after chemotherapy for malignant glioma at a dose of 10–100 mg/kg/day. More importantly, dramatic clearance of both lymphoma and leukemia has been demonstrated in BLV-induced B-cell malignancy in sheep (Amine Achachi, Arnaud Florins, Nicolas Gillet, Christophe Debacq, Patrice Urbain, Germain Manfouo Foutsop, Fabian Vandermeers, Agnieszka Jasik, Michal Reicher, Pierre Kerkhofs, Laurence Lagneaux, Arsene Burny, Richard Kettmann, and Luc Willems: submitted for publication). While a trial of this therapy as part of the management of patients with acute and lymphoma ATLL should be considered further, possibilities include prevention of progression of chronic and smouldering ATLL. Should a protective effect be shown, the long-standing safety profile of this compound would justify a study to prevent ATLL in patients at higher risk of disease. The profile of such patients, high anti-HTLV-I

antibody titer and high soluble IL-2 receptor levels, has been described (Arisawa *et al.*, 2002).

Monoclonal antibodies

An alternative approach to the therapy of ATLL is to target cell differentiation markers on the malignant cells with monoclonal antibodies. The high expression of the IL-2α receptor, CD25, on ATLL cells has made this an attractive target. Waldmann first treated nine patients with ATLL with an anti-CD25 (anti-Tac) monoclonal antibody in the late 1980s. Responses lasting up to 8 months, including one CR, was seen in three patients (Waldmann *et al.*, 1988). Further evaluation of this agent in 19 patients revealed two CR and four PR (Waldmann *et al.*, 1993). Yttrium[90] labelling of the anti-Tac resulted in a small improvement in response with two CR and seven PR in 18 patients thus treated (Waldmann *et al.*, 1995). Eight patients were treatment naïve prior to the study and five had chronic ATLL. A humanized version of anti-CD25 was used in the next study with PR in 3/11 patients (Morris *et al.*, 2001). A study of humanized anti-CD25 antibody therapy supplementing standard CHOP chemotherapy is currently recruiting patients in the UK.

Another target is CD52. A humanized monoclonal anti-CD52 antibody, Campath-1H, effectively treated SCID mice infected with a tumor-causing HTLV-I-infected cell line. Treated mice surviving as long as HTLV-I unexposed mice (Zhang *et al.*, 2003). A National Institutes of Health (USA) sponsored phase II study of the safety and efficacy of Campath-1H in humans with ATLL (Protocol 03-C-0194) is recruiting (accessed 04/04/2005) http://clinicalstudies.info.nih.gov/detail/A_2003-C-0194.html. Unpublished data from five patients with relapsing ATLL treated at Kumamoto University Hospital indicate that while Campath-1H decreases ATL cells in the peripheral blood, it was not effective against lymphoma. The phenomenon of tumor enlargement during therapy with Campath-1H, previously observed in patients with NHL was also seen (Masao Matsuoka, unpublished).

Transplantation

The first published 'cure' of ATLL following bone marrow transplantation was in 1996. Following a 4-day infusion of cyclophosphomide, etoposide, and doxorubicin, the patient was grafted with cells donated from an HTLV-I-uninfected sister. After 2 years, HTLV-I could not be detected in peripheral blood by nested DNA PCR (Borg *et al.*, 1996) and the patient remains alive, disease free in 2005 (E Tholouli and J Yin, personal communication). Other case reports of allogeneic bone marrow transplantation with CR lasting at least 2 years with or without detectable HTLV-I genome followed (Tajima *et al.*, 2000; Ogata *et al.*, 2002). Molecular remission following autologous stem cell transplantation was reported, but the patient died of an opportunistic infection after 4 months (Nakane *et al.*, 1999). In a case series of 10 patients transplanted with allogeneic hematopoietic stem cells (Allo-SCT) (9/10 from HLA-identical siblings) after receiving total body irradiation and other conditioning agents, the median leukemia-free survival was >17.5 months but four patients died and in two ATLL relapsed (Utsunomiya *et al.*, 2001). In another series of Allo-SCT, one patient died within 30 days of transplantation but CR was seen in the remaining 10. However, six died of transplantation complications and the overall 1 year survival was only 53% (Kami *et al.*, 2003). The overall median survival from first presentation was >17.3 months and from Allo-SCT >12 months with four patients alive at the time of data census. A recent review of the outcome of 40 patients with acute or lymphoma ATLL, at seven centers in Japan, reported CR in all evaluable cases after Allo-SCT but a median survival time for all patients of only 9.6 months. The estimated 3-year overall survival of 45.3% compares favorably with historical data on chemotherapy. However, comparison across studies is always dangerous given the differences in support over time and potential selection bias (Fukushima *et al.*, 2005). The observation that some ATLL relapses could be successfully managed with a reduction in immune suppression supports the role of the graft versus leukemia effect (Harashima *et al.*, 2004; Okamura *et al.*, 2005).

PUVA can be useful for the management of cutaneous ATLL avoiding the toxicity of chemotherapy and other treatment modalities.

Prevention of ATLL

The routes of transmission of HTLV-I are well documented. ATLL seems to be associated with transmission in early life. Possible factors for this association are the prolonged incubation period between infection and disease and primary infection before maturation of the immune system. Avoidance of breast-feeding by mothers known to carry HTLV-I reduces transmission by 80%. Whether limited breast-feeding for up to 3 months should be allowed, as some data suggest, is a difficult judgment but likely to be influenced by social and cultural factors. Prevention of mother-to-child transmission through breast-feeding should reduce the incidence of ATLL, although this will not be seen for many decades. Whether, HTLV-I infection acquired *in utero* or during delivery carries the same risk of ATLL (as breast milk associated transmission) is unknown. There have been no studies of either antiretroviral therapy or mode of delivery to address the potential for further reducing mother-to-child transmission. Screening for HTLV-I in pregnancy has been introduced in some endemic areas, including Japan and Martinique, but is much less widespread than screening of blood donors. The development of ATLL following blood transfusion acquisition of HTLV-I has rarely been reported.

Alternative approaches to the prevention of ATLL might include reducing HTLV-I proviral load by

antiretroviral therapy, targeted chemotherapy or immunotherapy, whether passive (monoclonal antibodies) or active. One suggestion has been the vaccination of HTLV-I carriers with high proviral load and low HTLV-specific T-cell responses with a HTLV-I Tax-targeted vaccine (Kannagi *et al.*, 2004). ATLL-like lymphoproliferative disease in rats has been prevented by adoptive transfer of T cells immunized with HTLV-I Tax DNA (Ohashi *et al.*, 2000). This is analogous to the control of post-transplantation EBV-associated lymphoproliferation by reducing immune suppression or by infusion of EBV-specific CTL. However, the association between immune suppression and ATLL is complex. A strong and persistent response to HTLV-I infection is found in patients with inflammatory disease and asymptomatic carriers and to date no association between a lack of response and subsequent development of ATLL has been shown. The proliferation of the malignant cell, diluting, or replacing circulating virus-specific T cells may contribute to any apparent lack of cellular response to HTLV in patients with ATLL. HTLV-I-specific responses can be found in PBL from patients with ATLL (Arnulf *et al.*, 2004).

References

Ando Y, Ekuni Y, Matsumoto Y, Nakano S, Saito K, Kakimoto K, Tanigawa T, Kawa M and Toyama T. (2004). *J. Obstet. Gynaecol. Res.*, **30**, 436–438.

Arai F, Miyamoto T, Ohneda O, Inada T, Sudo T, Brasel K, Miyata T, Anderson DM and Suda T. (1999). *J. Exp. Med.*, **190**, 1741–1754.

Arima N, Mizoguchi H, Shirakawa S, Tomonaga M, Takatsuki K and Ohno R. (1999). *Gan To Kagaku Ryoho*, **26**, 619–629.

Arisawa K, Katamine S, Kamihira S, Kurokawa K, Sawada T, Soda M, Doi H, Saito H and Shirahama S. (2002). *Cancer Causes Control*, **13**, 657–663.

Arnulf B, Thorel M, Poirot Y, Tamouza R, Boulanger E, Jaccard A, Oksenhendler E, Hermine O and Pique C. (2004). *Leukemia*, **18**, 126–132.

Bangham CR. (2003). *Int. J. Hematol.*, **78**, 297–303.

Barnard AL, Igakura T, Tanaka Y, Taylor GP and Bangham CR. (2005). *Blood*, 14 April, [E-pub ahead of print].

Besson C, Panelatti G, Delaunay C, Gonin C, Brebion A, Hermine O and Plumelle Y. (2002). *Leuk. Lymphoma*, **43**, 2275–2279.

Blaheta RA and Cinatl Jr J. (2002). *Med. Res. Rev.*, **22**, 492–511.

Borg A, Yin JA, Johnson PR, Tosswill J, Saunders M and Morris D. (1996). *Br. J. Haematol.*, **94**, 713–715.

Cavrois M, Leclercq I, Gout O, Gessain A, Wain-Hobson S and Wattel E. (1998). *Oncogene*, **17**, 77–82.

Dierov J, Sawaya BE, Prosniak M and Gartenhaus RB. (1999). *Clin. Cancer Res.*, **5**, 2540–2547.

Doi K, Wu X, Taniguchi Y, Yasunaga JI, Satou Y, Okayama A, Nosaka K and Matsuoka M. (2005). *Blood*, 19 April, [E-pub ahead of print].

Etoh K, Tamiya S, Yamaguchi K, Okayama A, Tsubouchi H, Ideta T, Mueller N, Takatsuki K and Matsuoka M. (1997). *Cancer Res.*, **57**, 4862–4867.

Etoh K, Yamaguchi K, Tokudome S, Watanabe T, Okayama A, Stuver S, Mueller N, Takatsuki K and Matsuoka M. (1999). *Int. J. Cancer*, **81**, 859–864.

Ezaki K, Hirano M, Ohno R, Yamada K, Naito K, Hirota Y, Shirakawa S and Kimura K. (1991). *Cancer*, **68**, 695–698.

Fontenot JD and Rudensky AY. (2005). *Nat. Immunol.*, **6**, 331–337.

Franchini G, Fukumoto R and Fullen JR. (2003). *Int. J. Hematol.*, **78**, 280–296.

Fukushima T, Miyazaki Y, Honda S, Kawano F, Moriuchi Y, Masuda M, Tanosaki R, Utsunomiya A, Uike N, Yoshida S, Okamura J and Tomonaga M. (2005). *Leukemia*, **19**, 829–834.

Furukawa Y, Kubota R, Tara M, Izumo S and Osame M. (2001). *Blood*, **97**, 987–993.

Gatza ML, Watt JC and Marriott SJ. (2003). *Oncogene*, **22**, 5141–5149.

Gill PS, Harrington Jr W, Kaplan MH, Ribeiro RC, Bennett JM, Liebman HA, Bernstein-Singer M, Espina BM, Cabral L, Allen S, Kornblau S, Pike MC and Levine AM. (1995). *N. Engl. J. Med.*, **332**, 1744–1748.

Han Y, Lassen K, Monie D, Sedaghat AR, Shimoji S, Liu X, Pierson TC, Margolick JB, Siliciano RF and Siliciano JD. (2004). *J. Virol.*, **78**, 6122–6133.

Harasawa H, Yamada Y, Kudoh M, Sugahara K, Soda H, Hirakata Y, Sasaki H, Ikeda S, Matsuo T, Tomonaga M, Nobori T and Kamihira S. (2002). *Leukemia*, **16**, 1799–1807.

Harashima N, Kurihara K, Utsunomiya A, Tanosaki R, Hanabuchi S, Masuda M, Ohashi T, Fukui F, Hasegawa A, Masuda T, Takaue Y, Okamura J and Kannagi M. (2004). *Cancer Res.*, **64**, 391–399.

Hermine O, Allard I, Levy V, Arnulf B, Gessain A and Bazarbachi A. (2002). *Hematol. J.*, **3**, 276–282.

Hermine O, Bouscary D, Gessain A, Turlure P, Leblond V, Franck N, Buzyn-Veil A, Rio B, Macintyre E, Dreyfus F and Bazarbachi A. (1995). *N. Engl. J. Med.*, **332**, 1749–1751.

Hermine O, Dombret H, Poupon J, Arnulf B, Lefrere F, Rousselot P, Damaj G, Delarue R, Fermand JP, Brouet JC, Degos L, Varet B, de The H and Bazarbachi A. (2004). *Hematol. J.*, **5**, 130–134.

Igakura T, Stinchcombe JC, Goon PK, Taylor GP, Weber JN, Griffiths GM, Tanaka Y, Osame M and Bangham CR. (2003). *Science*, **299**, 1713–1716.

Jeang KT, Giam CZ, Majone F and Aboud M. (2004). *J. Biol. Chem.*, **279**, 31991–31994.

Jones KS, Akel S, Petrow-Sadowski C, Huang Y, Bertolette DC and Ruscetti FW. (2005). *J. Immunol.*, **174**, 4262–4270.

Jordan A, Bisgrove D and Verdin E. (2003). *EMBO J.*, **22**, 1868–1877.

Kami M, Hamaki T, Miyakoshi S, Murashige N, Kanda Y, Tanosaki R, Takaue Y, Taniguchi S, Hirai H, Ozawa K and Kasai M. (2003). *Br. J. Haematol.*, **120**, 304–309.

Kannagi M, Harashima N, Kurihara K, Utsunomiya A, Tanosaki R and Masuda M. (2004). *Expert Rev. Anticancer Ther.*, **4**, 369–376.

Karube K, Ohshima K, Tsuchiya T, Yamaguchi T, Kawano R, Suzumiya J, Utsunomiya A, Harada M and Kikuchi M. (2004). *Br. J. Haematol.*, **126**, 81–84.

Katsuki T, Katsuki K, Imai J and Hinuma Y. (1987). *Jpn. J. Cancer Res.*, **78**, 639–642.

Kiyokawa T, Yamaguchi K, Takeya M, Takahashi K, Watanabe T, Matsumoto T, Lee SY and Takatsuki K. (1987). *Cancer*, **59**, 1187–1191.

Koiwa T, Hamano-Usami A, Ishida T, Okayama A, Yamaguchi K, Kamihira S and Watanabe T. (2002). *J. Virol.*, **76**, 9389–9397.

Krueger A, Fas SC, Baumann S and Krammer PH. (2003). *Immunol. Rev.*, **193**, 58–69.

Kuramochi M, Fukuhara H, Nobukuni T, Kanbe T, Maruyama T, Ghosh HP, Pletcher M, Isomura M, Onizuka M, Kitamura T, Sekiya T, Reeves RH and Murakami Y. (2001). *Nat. Genet.*, **27**, 427–430.

Kuwazuru Y, Hanada S, Furukawa T, Yoshimura A, Sumizawa T, Utsunomiya A, Ishibashi K, Saito T, Uozumi K, Maruyama M, Ishizawa M, Arima T and Akiyama S-I. (1990). *Blood*, **76**, 2065–2071.

Li HC, Biggar RJ, Miley WJ, Maloney EM, Cranston B, Hanchard B and Hisada M. (2004). *J. Infect. Dis.*, **190**, 1275–1278.

Lymphoma Study GroupShimoyama MOta KKikuchi MTominaga S and Yunoki K. (1982). *Jpn J Clin Oncol*, **12**, 227–238.

Mahieux R and Hermine O. (2005). *Leuk Lymphoma*, **46**, 347–355.

Makino T, Nakahara K, Takatsuka Y, Shimotakahara S, Utsunomiya A, Hanada S, Tokunaga M and Arima T. (1994). *Rinsho Ketsueki*, **35**, 42–48.

Manel N, Kim FJ, Kinet S, Taylor N, Sitbon M and Battini JL. (2003). *Cell*, **115**, 449–459.

Matsuoka M and Jeang KT. (2005). *Cancer Res.*, **65**, 4467–4470.

Matsushita K, Matsumoto T, Ohtsubo H, Fujiwara H, Imamura N, Hidaka S, Kukita T, Tei C, Matsumoto M and Arima N. (1999). *Leuk. Lymphoma*, **36**, 67–75.

Matutes E, Taylor GP, Cavenagh J, Pagliuca A, Bareford D, Domingo A, Hamblin M, Kelsey S, Mir N and Reilly JT. (2001). *Br. J. Haematol.*, **113**, 779–784.

Mercieca J, Matutes E, Dearden C, MacLennan K and Catovsky D. (1994). *J. Clin. Oncol.*, **12**, 2588–2593.

Mittelstadt PR and Ashwell JD. (1998). *Mol. Cell. Biol.*, **18**, 3744–3751.

Mori N, Matsuda T, Tadano M, Kinjo T, Yamada Y, Tsukasaki K, Ikeda S, Yamasaki Y, Tanaka Y, Ohta T, Iwamasa T, Tomonaga M and Yamamoto N. (2004). *J. Virol.*, **78**, 4582–4590.

Mori N, Yamada Y, Ikeda S, Yamasaki Y, Tsukasaki K, Tanaka Y, Tomonaga M, Yamamoto N and Fujii M. (2002). *Blood*, **100**, 1828–1834.

Morris JC, Janik JE, Turner M, Lee C, Top L, Jaffe ES, Stetler-Stevenson M, Blessing JJ, Fleisher TA and Waldmann T. (2001). *10th International Conference on Human Retrovirology: HTLV and Related Viruses, Vol, 17 Suppl.* AIDS Res Hum Retroviruses: Dublin, pp. S29.

Nakane M, Ohashi K, Sato Y, Moriya A, Inoue T, Mori S, Tanikawa S, Akiyama H, Maeda Y, Sasaki T, Karasawa K, Okuyama Y, Hiruma K and Sakamaki H. (1999). *Bone Marrow Transplant*, **24**, 219–221.

Nasr R, Rosenwald A, El-Sabban ME, Arnulf B, Zalloua P, Lepelletier Y, Bex F, Hermine O, Staudt L, de The H and Bazarbachi A. (2003). *Blood*, **101**, 4576–4582.

Nosaka K, Miyamoto T, Sakai T, Mitsuya H, Suda T and Matsuoka M. (2002). *Blood*, **99**, 634–640.

Ogata M, Ogata Y, Imamura T, Ohtsuka E, Kikuchi H, Utsunomiya A, Yashiki S, Sonoda S and Nasu M. (2002). *Bone Marrow Transplant*, **30**, 699–701.

Ohashi T, Hanabuchi S, Kato H, Tateno H, Takemura F, Tsukahara T, Koya Y, Hasegawa A, Masuda T and Kannagi M. (2000). *J. Virol.*, **74**, 9610–9616.

Ohno R, Masaoka T, Shirakawa S, Sakamoto S, Hirano M, Hanada S, Yasunaga K, Yokomaku S, Mitomo Y, Nagai K, Yamada K and Furue H. (1993). *Cancer*, **71**, 2217–2221.

Okamura J, Utsunomiya A, Tanosaki R, Uike N, Sonoda S, Kannagi M, Tomonaga M, Harada M, Kimura N, Masuda M, Kawano F, Yufu Y, Hattori H, Kikuchi H and Saburi Y. (2005). *Blood*, **105**, 4143–4145.

Okayama A, Stuver S, Matsuoka M, Ishizaki J, Tanaka G, Kubuki Y, Mueller N, Hsieh CC, Tachibana N and Tsubouchi H. (2004). *Int. J. Cancer*, **110**, 621–625.

Okochi K, Sato H and Hinuma Y. (1984). *Vox. Sang*, **46**, 245–253.

Pawson R, Richardson DS, Pagliuca A, Kelsey SM, Hoque S, Breuer J, Newland AC and Mufti GJ. (1998). *Leuk. Lymphoma*, **31**, 177–185.

Sasaki H, Nishikata I, Shiraga T, Akamatsu E, Fukami T, Hidaka T, Kubuki Y, Okayama A, Hamada K, Okabe H, Murakami Y, Tsubouchi H and Morishita K. (2005). *Blood*, **105**, 1204–1213.

Satou Y, Nosaka K, Koya Y, Yasunaga JI, Toyokuni S and Matsuoka M. (2004). *Leukemia*, **18**, 1357–1363.

Shimoyama M. (1992). *Advances in Adult T-cell Leukaemia and HTLV-I Research.* Takatsuki K, Hinuma Y, Yoshida M (eds). Japanese Scientific Societies Press: Tokyo, pp. 43–56.

Shimoyama M, Ota K, Kikuchi M, Yunoki K, Konda S, Takatsuki K, Ichimaru M, Tominaga S, Tsugane S and Minato K. (1988). *J. Clin. Oncol.*, **6**, 1088–1097.

Siegel RS, Gartenhaus RB and Kuzel TM. (2001). *Curr. Treat. Options Oncol.*, **2**, 291–300.

Taguchi H, Kinoshita KI, Takatsuki K, Tomonaga M, Araki K, Arima N, Ikeda S, Uozumi K, Kohno H, Kawano F, Kikuchi H, Takahashi H, Tamura K, Chiyoda S, Tsuda H, Nishimura H, Hosokawa T, Matsuzaki H, Momita S, Yamada O and Miyoshi I. (1996). *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.*, **12**, 182–186.

Taguchi T, Ohta K, Hotta T, Shirakawa S, Masaoka T and Kimura I. (1997). *Gan To Kagaku Ryoho*, **24**, 1263–1271.

Tajima K, Amakawa R, Uehira K, Matsumoto N, Shimizu T, Miyazaki Y, Fujimoto M, Kishimoto Y and Fukuhara S. (2000). *Int. J. Hematol.*, **71**, 290–293.

Takeda S, Maeda M, Morikawa S, Taniguchi Y, Yasunaga J, Nosaka K, Tanaka Y and Matsuoka M. (2004). *Int. J. Cancer*, **109**, 559–567.

Tamiya S, Matsuoka M, Etoh K, Watanabe T, Kamihira S, Yamaguchi K and Takatsuki K. (1996). *Blood*, **88**, 3065–3073.

Tamiya S, Matsuoka M, Takemoto S, Shimizu K, Yamaguchi K, Mita S, Uchino M, Ando M, Miyaguni T, Kuniyoshi K and Takatsuki K. (1995). *Leukemia*, **9**, 1768–1770.

Tan C and Waldmann TA. (2002). *Cancer Res.*, **62**, 1083–1086.

Tanaka G, Okayama A, Watanabe T, Aizawa S, Stuver S, Mueller N, Hsieh CC and Tsubouchi H. (2005). *J. Infect. Dis.*, **191**, 1140–1147.

Taylor GP, Gessain A, Popescu DM, Zehender G, Padua E, Soriano V, Anderson S, Tosswill JHC and Weber JN. (2001). *AIDS Res. Hum. Retroviruses*, **17** (Suppl 1), S-69.

Thompson C and Powrie F. (2004). *Curr. Opin. Pharmacol.*, **4**, 408–414.

Tobinai K, Shimoyama M, Inoue S, Takayasu S, Mikuni C, Kozuru M, Oda S and Nakajima H. (1992). *Jpn. J. Clin. Oncol.*, **22**, 164–171.

Tobinai K, Shimoyama M, Takatsuki K, Tomonaga M, Araki K and Arima N. (1994). *Proc. Am. Soc. Oncol.*, **13**, 378.

Tobinai K, Uike N, Saburi Y, Chou T, Etoh T, Masuda M, Kawano F, Matsuoka M, Taguchi H, Makino T, Asano Y,