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The Origin and Evolution of Human T-Cell Lymphotropic Virus Types I and II

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Abstract. Studies on human T-cell lymphotropic virus types I (HTLV-I) and II (HTLV-II) are briefly reviewed from the viewpoint of molecular evolution, with special reference to the evolutionary rate and evolutionary relationships among these viruses. In particular, it appears that, in contrast to the low level of variability of HTLV-I among different isolates, individual isolates form quasispecies structures. Elucidating the mechanisms connecting these two phenomena will be one of the future problems in the study of the molecular evolution of HTLV-I and HTLV-II.

Key words: human T-cell lymphotropic virus, molecular evolution, evolutionary rate, phylogenetic tree, genetic variation, geographical distribution

Introduction

Human T-cell lymphotropic virus type I (HTLV-I) was first identified in T-cell lymphoblastoid cell lines and fresh peripheral blood lymphocytes obtained from a patient with cutaneous T-cell lymphoma (mycosis fungoides) (1,3). This virus was associated with adult T-cell leukemia (ATL) (2) because it was observed that the cell line established from peripheral blood lymphocytes of a patient with ATL, produced antigens that reacted against sera from ATL patients (3). It was also associated with tropical spastic paraparesis/ HTLV-I-associated myelopathy (TSP/HAM) due to the prevalence of the antibody against this virus in the serum from TSP patients (4) and in the serum and cerebrospinal fluid from HAM patients (5). Neoplasmic complications of HTLV-I infection develop only after many decades of infection, whereas TSP/HAM may occur after a few years or even a few months of infection (6,7). In addition, only a small proportion of HTLV-I-infected patients develop either of the clinical disorders. The remaining majority stay asymptomatic in their entire lives (8–11).

On the other hand, human T-cell lymphotropic virus type II (HTLV-II) was first identified in a cell line established from the spleen of a patient with hairy-cell leukemia (12,13). This virus has not yet been associated with any specific disease, although some HTLV-II-infected patients have been reported to be affected by atypical T-cell hairy-cell leukemia or large granular lymphocyte leukemia (12,14–17), and tropical ataxic neuropathy (18).

It is known that HTLV-I and HTLV-II belong to the family *Retroviridae* (19). It follows that these viruses replicate through reverse transcription, and embedding their own genomes into human chromosomal DNA. In general, retroviruses show a rate of nucleotide substitutions, a million times higher than that of humans (265). However, the rates for HTLV-I and HTLV-II have not yet been estimated accurately, and are speculated to be much slower than that of other retroviruses. This is because the nucleotide diversity of HTLV-I and HTLV-II clones isolated so far, has been estimated to be somewhat lower than that of other RNA viruses (20).

The evolutionary origin of HTLV-I and HTLV-II has been a source of controversy. Although simian T-cell lymphotropic virus types I and II (STLV-I and STLV-II), which are counterparts of HTLV-I and HTLV-II in simians, have been reported to exist in various monkeys (21–47) including chimpanzees, gorillas, grivet monkeys, baboons, cynomolgus macaques, crab-eating macaques, pig-tailed maca-

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ques, stump tailed macaques, rhesus macaques, bonnet macaques, lion-tailed macaques, toque monkeys, Celebes macaques, and spider monkeys, HTLV-I was originally found in limited geographical areas of the world such as the southwestern part of Japan (48), the Caribbean basin (49), Central and South America (50), and Africa (22,51). Thus, it was maintained by some researchers, that HTLV-I and HTLV-II emerged from a common ancestor of humans and monkeys during the millions of years of primate evolution (29). Others, on the other hand, contended that HTLV-I and HTLV-II were recently brought into human populations through recurrent events of interspecies transmissions (20).

The geographical survey of HTLV-I and HTLV-II carriers in the world has led to the idea that these viruses can be good markers for tracing the history of human migration during the diversification process of various ethnic groups. This is because these viruses exhibit vertical transmission, mainly through breast milk from mothers to their children, and these viruses are found in limited geographical areas of the world.

With the aim of summarizing the general aspects of the evolutionary features of HTLV-I and HTLV-II, we have made an attempt to conduct a brief review from the viewpoint of molecular evolution, with special reference to the evolutionary rate and evolutionary relationships among theses viruses.

Transmission of HTLV-I and HTLV-II

There are four modes of transmission reported for HTLV-I. First, mothers infected with HTLV-I can transmit the virus to their babies or fetuses (52) either through lymphocytes in their breast milk (53–58) or lymphocytes in the uterus or vagina (59,60). Second, infected cells in semen can transmit the virus from male to female during sexual intercourse (52,54). It is interesting to note that the risk of sexual transmission appears to be 60.8% for male-to-female, whereas it is 0.4% for female-to-male transmission (61). Third, blood products containing infected cells can transmit HTLV-I through blood transfusions (62–65). This mode of transmission is the most efficient, with a seroconversion rate of 35–60% (66). Finally, the virus can be transmitted among intravenous drug users (IDUs), possibly through the passage of infected lymphocytes in shared needles. Cell-free HTLV-I is also infectious but much less so than cell-associated HTLV-I (67–69). HTLV-II can also be transmitted in similar ways (70,71). While HTLV is found in $CD4^+$ lymphocytes of infected individuals (72), $CD8^+$ cells represent the predominant target of HTLV-II (73).

Molecular Biology of HTLV-I and HTLV-II

The genomes of HTLV-I (74–78) and HTLV-II (79–82) are composed of single stranded, plus sense RNA with about 9000 nucleotide. Both genomes can be divided into five regions; 5′-*LTR*, *gag*, *pol*, *env*, *pX*, and 3′-*LTR* (Fig. 1) (83,84). The proteins produced are Gag, Pro, Pol, Env, and others (85) from the five open reading frames in the *pX* region, including Tax and Rex (74,79).

LTR includes the *cis*-acting sequences of Tax (86–92) and Rex response elements (93–97), which are important in the regulation of viral gene expression. Gag produces the virion core proteins which form the matrix, capsid, and nucleocapsid (98,99). Pro is a viral protease that cleaves the Gag precursor to generate the mature viral core proteins (100). Pol exhibits the enzymatic activities of reverse transcriptase, integrase, and RNase H. Env produces a surface glycoprotein and a transmembrane protein. Tax is a nuclear protein (101–105), which trans-activates transcription initiation from the promoter in 5′-*LTR* (102,104,106–111). Rex acts at the posttranscriptional level by selectively augmenting the cytoplasmic expression of both genome-length mRNA and singly spliced *env* mRNA (93–96,112–116).

Evolutionary Origin of HTLV-I and HTLV-II

HTLV-I and HTLV-II are members of the genus *HTLV-BLV* in the family *Retroviridae* (Table 1) (19). Although some recombination events were inferred,

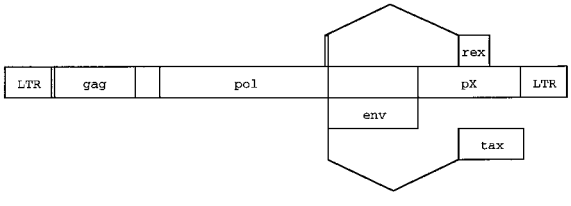

Fig. 1. A schematic diagram for the genomic structure of HTLV-I and HTLV-II. The genome can be divided into five regions, 5′-*LTR*, *gag*, *pol*, *env*, and 3′-*LTR*.

phylogenetic trees were successfully reconstructed for the viruses belonging to the family *Retroviridae* (117–128). The phylogenetic tree reconstructed by Gojobori et al. (126) is shown in Fig. 2, with some modifications. The tree shows that there are three major clusters. HTLV-I and HTLV-II conform a distinct cluster with bovine leukemia virus (BLV). The other two clusters are a cluster of human spuma retrovirus (HSRV) and mouse mammary tumor virus (MMTV), and a cluster of primate lentiviruses, including human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV). Although the phylogenetic tree in Fig. 2 does not contain STLVs, the studies of evolutionary relationships between HTLV and STLV suggest that HTLV may have come from animal viruses through interspecies transmissions between simians and humans, as will be discussed in the following section.

Interspecies Transmission

As a result of restriction mapping, it was previously believed that interspecies transmission of HTLV-I/STLV-I between humans and non-human primates was unlikely, and that they had evolved in concert with the host species (29). However, recent phylogenetic analyses of the evolutionary relationships between HTLV-I and STLV-I and among different STLV-Is demonstrated that the evolutionary history of HTLV-I and STLV-I did not follow that of their host species (Fig. 3) (20,47,129–135). This observation suggested that interspecies transmissions of HTLV-I and STLV-I had occurred between humans and non-human primates and among different non-human primates. In particular, the Melanesian, Zairian, and Cosmopolitan of HTLV-I appeared to have experienced at least one independent human-simian interspecies transmission during evolution (132). It was also indicated that more frequent, perhaps free, exchanges of viruses have occurred between simian species below the genus level. (132).

Evolutionary Rates of HTLV-I and HTLV-II

RNA viruses, generally, evolve at the rate of 10^{-3} to 10^{-5} per nucleotide site per year (Table 2) (136,137). However, genetic diversity was somewhat lower for HTLV-I and HTLV-II, compared with that of other RNA viruses (138,139). In particular, it seems that HTLV-I and HTLV-II can be embedded in the human genome for a long time before manifesting an active phase. Thus, it has been difficult to estimate the rate of nucleotide substitutions for these viruses by the conventional method using the phylogenetic tree; that is, by dividing the differences in branch lengths from different viral strains to their common ancestor, by the differences in their isolation times (140). This is because the differences in isolation times examined

Table 1. The taxonomy of retroviruses.

Family	Genus	Subgenus	Examples of Species (Abbreviations)
Retroviridae	MLV-related viruses	Mammalian type C viruses	Murine leukemia virus (MLV)
		Reptilian type C viruses	Corn snake retrovirus (CSRV)
		Reticuloendotheliosis viruses	Spleen necrosis virus (SNV)
	Mammalian type B viruses		Mouse mammary tumor virus (MMTV)
	Type D viruses		Squirrel monkey retrovirus (SMRV)
	ALV-related		Rous sarcoma virus (RSV)
	HTLV-BLV		Human T-cell lymphotropic virus type I (HTLV-I)
			Human T-cell lymphotropic virus type II (HTLV-II)
			Bovine leukemia virus (BLV)
	Lentivirus	Ovine/caprine lentiviruses	Visna virus (VISNA)
		Equine lentiviruses	Equine infectious anemia virus (EIAV)
		Primate lentiviruses	Human immunodeficiency virus (HIV)
			Simian immunodeficiency virus (SIV)
		Feline lentiviruses	Feline immunodeficiency virus (FIV)
		Bovine lentiviruses	Bovine immunodeficiency virus (BIV)
	Spumavirus		Human spuma retrovirus (HSRV)

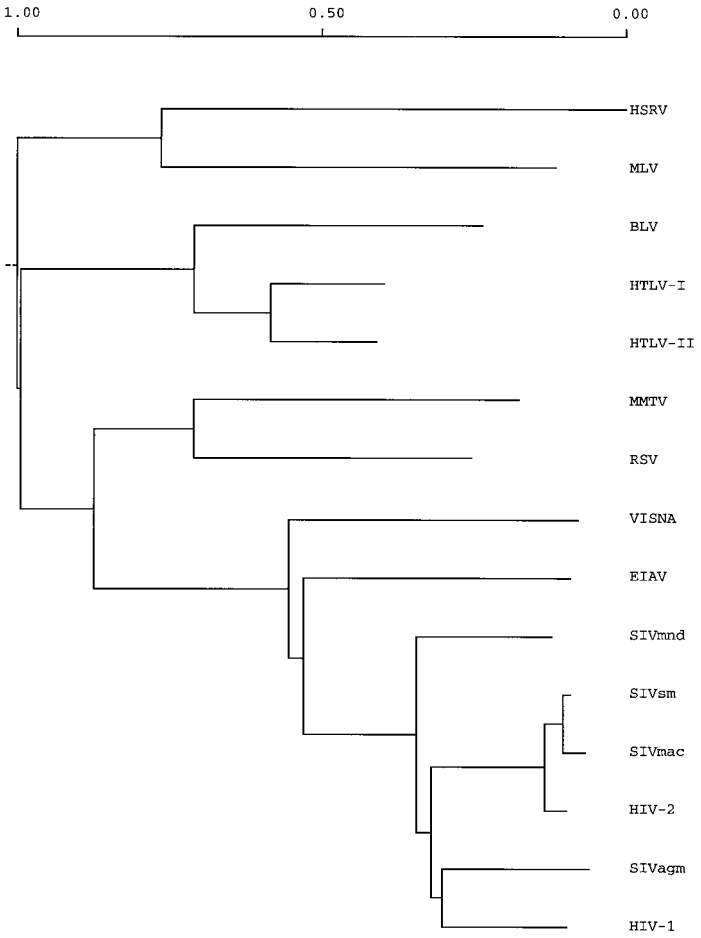

Fig. 2. A phylogenetic tree for viruses belonging to the family *Retroviridae*. Modified from Fig. 2 in Ref. 126. Abbreviations are as described in Table 1.

so far were too short to obtain an accurate estimate of the evolutionary rate.

The first attempt to obtain a rough idea of the evolutionary rate for these viruses was made by investigating the nucleotide diversity for viral isolates of HTLV-I. The diversity for the *tax* gene of HTLV-I was estimated to be about 10 times higher than that for the host genome, which may be attributed to the high mutation rate of reverse transcriptase (141–144), but it was about 20 times lower than that for influenza A virus (145), which may reflect the relatively low replication frequency of the HTLV-I genome compared with that of influenza A virus. This may be mainly because HTLV-I can be embedded in the host genome as a provirus for a long time, as mentioned before (20). A direct attempt to estimate the rate using the *gag*, *pol*, *env*, and *pX* gene regions suggested that the rate for HTLV-I is on the order of 10^{-7} per site per year, under the assumption that Japanese and rhesus macaques diverged 0.3 to 1.8 million years ago and that human occupation of Australia and Melanesia occurred 50,000 years ago (Table 2) (134,135).

As for the pattern of nucleotide substitutions for HTLV-I, it has been shown that guanine (G) to adenine (A) or A to G and cytosine (C) to thymine (T) or T to C substitutions occur at similar frequencies (146). In this study, however, only the numbers of particular nucleotide differences were counted between different isolates. Thus, the direction and frequency of nucleotide substitutions (147) have not been estimated.

It should be noted that the genomes of HTLV-I and HTLV-II are particularly rich in C and poor in A and G (148–150). This bias might have been attained

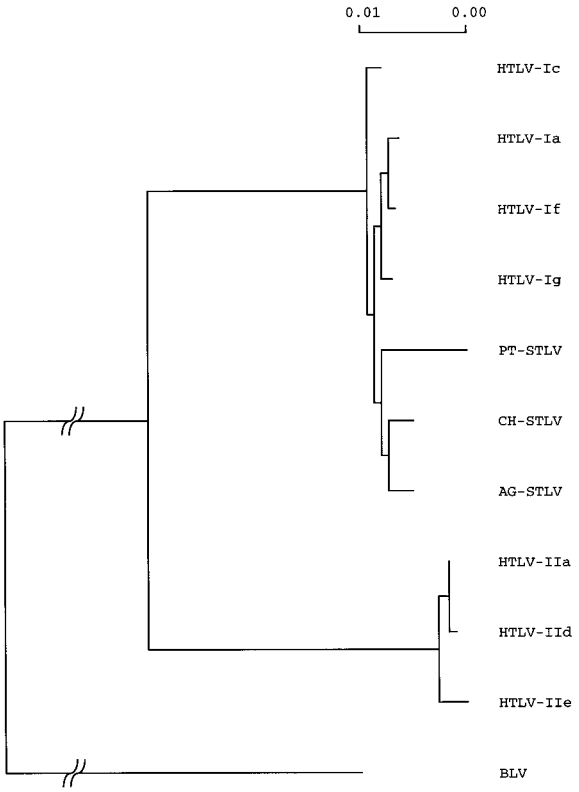

Fig. 3. A phylogenetic tree for viruses belonging to the genus *BLV-HTLV* in the family *Retroviridae*. Modified from Fig. 3 in Ref. 20. Abbreviations are as described in Table 1.

through the selective force to direct integration of the viral genome into specific segments of human chromosomes (148), or through directional mutations introduced by reverse transcriptase (150). This biased pattern of nucleotide substitutions has also been correlated with the pattern of codon usage and of amino acid compositions and substitutions for proteins encoded by these viruses (150).

Geographical Distributions of HTLV-I

HTLV-I has been identified in restricted areas of some geographical regions in the world; those are, Japan (48,151,152), the Caribbean basin (49,153), southeastern United States (154), Central America, South America (50,153,155,156), Central Africa (51), West Africa (51,157,158), South Africa (51), North Africa (159), the Seychelles Islands (160), Reunion Island (161,162), the Middle East (163,164), India (165–169), and Australo–Melanesia (170–177).

When the nucleotide sequences of an HTLV-I strain obtained over a five-year period were compared, no changes were observed (138). In addition, the mode of transmission of HTLV-I has been thought to be mainly cell-associated (67–69). These observations suggested that the investigation of viral sequences in selected populations would be useful in anthropological studies, especially in studies on past patterns of migrations of some human populations (138).

Phylogenetic analysis based on the *LTR* region has indicated that HTLV-I isolates can be classified into five clusters; the Melanesian type, Zairian type, and subtypes A, B, and C (Fig. 4) (133). Subtypes A, B, and C were previously classified as the Cosmopolitan type (76,129,130,138,146). The Melanesian type includes isolates from Papua New Guinea and the Solomon Islands. The Zairian subtype includes isolates from Gabon and Zaire. Subtype A consists of Indian, Caribbean, native South American (Colombian and Chilean), and some Japanese isolates. Subtype B consists of other Japanese isolates and the other Indian isolate. Subtype C consists of isolates from the Ivory Coast, Ghana, and the Caribbean basin. Another research group also divided HTLV-I isolates into five subtypes, Cosmopolitan, West African, Central African, Japanese, and Melanesian subtypes, using sequence alignments and phylogenetic trees (162). The Cosmopolitan, Japanese, West African, and Central African subtypes seem to correspond to subtypes A, B, and C, and the Zairian subtype, respectively. Recently, the existence of North African subgroup was indicated to be included in the Cosmopolitan type (159).

It has been hypothesized that HTLV-I originated in Africa, because of the high prevalence and high genetic diversity of this virus in Africa. Phylogenetic trees for HTLV-I isolates also supported the hypothesis (37,40,178–180). After the discovery of the Australo–Melanesian strains of HTLV-I (174,177,181), however, sequence analyses pointed out the possibility that HTLV-I originated in the Indo-Malay region rather than in Africa (129,130). In this hypothesis, dissemination from the Indo-Malay region to the African continent was thought to take place through migrations in the Indian Ocean area, via ancient Asian–African contacts in Madagascar (129). However, the observation that the strain from the

Table 2. Comparisons of the rates of nucleotide substitutions for HTLV-I with those for various viruses and cellular genes.

Organisms	Gene	Rate (/site/year)	References
HTLV-I	*gag, pol, env,* and *pX*	$(0.4–6.8) \times 10^{-7}$	134,135
HIV[a]	*gag*	$(0.2–26.0) \times 10^{-3}$	136,137,262,263
	pol	$(0.3–1.1) \times 10^{-3}$	263
	env	$(0.8–35.5) \times 10^{-3}$	137,262,263
SIV[b]	*gp*120	8.5×10^{-3}	264
MLV[c]	*gag*	0.6×10^{-3}	265
	v-*abl*	0.4×10^{-3}	266
MSV[d]	v-*fos*	$(0.7–1.1) \times 10^{-3}$	266
	v-*mos*	$(0.8–2.8) \times 10^{-3}$	136,265,266
MAV[e]	v-*myb*	$(0.1–0.3) \times 10^{-3}$	266
LLV[f]	v-*myc*	0.3×10^{-3}	266
REV[g]	v-*rel*	0.9×10^{-3}	266
RSV[h]	v-*src*	0.6×10^{-3}	266
EIAV[i]	*env*	$(0.1–1.0) \times 10^{-1}$	267
Influenza A virus	PB1	0.9×10^{-3}	268
	PB2	1.8×10^{-3}	269
	PA	1.3×10^{-3}	270
	HA (H1)	$(0.4–17.0) \times 10^{-3}$	271–273
	HA (H3)	$(2.8–13.1) \times 10^{-3}$	136,274–276
	HA (H1, H2, and H11)	2.5×10^{-3}	277
	NP	$(0.8–24.0) \times 10^{-3}$	272,278–280
	NA (N2)	$(2.7–9.7) \times 10^{-3}$	281,282
	M1	$(0.8–1.4) \times 10^{-3}$	283
	M2	$(0.9–1.4) \times 10^{-3}$	283
	NS	$(1.9–3.4) \times 10^{-3}$	284,285
Influenza C virus	HE	0.5×10^{-3}	286
FMDV[j]	VP1	$(1.4–74.0) \times 10^{-3}$	287–289
EEEV[k]	26S structural gene	0.1×10^{-3}	290
HBV[l]	P	$(1.5–4.6) \times 10^{-5}$	291
	pre-S	$(2.6–7.6) \times 10^{-5}$	291
	S	5.8×10^{-5}	291
	C	$(1.8–5.5) \times 10^{-5}$	291
	X	$(5.5–7.9) \times 10^{-5}$	291
HCV[m]	Genome	1.4×10^{-3}	292
	5′noncoding, C, E1, NS1, NS2, NS3, and NS5	1.9×10^{-3}	293
	C	$(0.6–1.4) \times 10^{-3}$	294
	E	$(0.3–6.3) \times 10^{-3}$	294
	NS1	$(0.8–3.3) \times 10^{-3}$	294
	NS3	$(0.3–4.8) \times 10^{-3}$	294
	NS5	$(0.2–7.5) \times 10^{-3}$	294
HDV[n]	Noncoding region	1.6×10^{-3}	295
GBV-C/HGV[o]	NS	$(0.8–1.9) \times 10^{-3}$	296
Cellular genes	c-*abl*	0.5×10^{-9}	266
	c-*fos*	0.8×10^{-9}	266
	c-*mos*	1.7×10^{-9}	265,266
	c-*myb*	0.6×10^{-9}	266
	c-*myc*	0.8×10^{-9}	266
	c-*src*	0.6×10^{-9}	266
	Globin	$(2.3–5.0) \times 10^{-9}$	297
	Pseudogenes	4.6×10^{-9}	298

[a]Human immunodeficiency virus; [b]Simian immunodeficiency virus; [c]Murine leukemia virus; [d]Murine sarcoma virus; [e]Myeloblastosis-associated virus; [f]Nondefective lymphoid leukemia virus; [g]Reticuloendotheliosis virus; [h]Rous sarcoma virus; [i]Equine infectious anemia virus; [j]Foot-and-mouth disease virus; [k]Eastern equine encephalomyelitis virus; [l]Hepatitis B virus; [m]Hepatitis C virus; [n]Hepatitis D virus; [o]GB virus C/Hepatitis G virus.

Reunion Island was the Cosmopolitan subtype may not be consistent with this hypothesis (162). It has, on the other hand, been indicated that the Melanesian lineage was brought to the Indo–Malay region a very long time ago, perhaps in the period of *Homo erectus* (hundreds of thousands of years before), from Africa, which is considered to be the birthplace of humans (133). Another research group suggested that HTLV-I evolved independently in the Southeast Asia landmass of Sunda and in Africa (135). At any rate, it is important to estimate the evolutionary rate and divergence time among HTLV-I isolates to solve this controversy.

The existence of two subtypes, A and C, was reported among isolates from the Caribbean basin. It was thought that subtype C had originated from West Africa probably during the slave trade era (135,138,162,182,183), and the other subtype may have migrated into the American continent via Beringia in the Paleolithic era (133). Another research group (135) indicated that the sequence similarity between HTLV-I strains from the Middle East, India, and the Caribbean islands (184) may be attributed to the early migrations of human populations from the Middle East to India more than 50,000 years ago (185), recent migrations approximately 1000 to 1300 years ago (186,187), and the migration of more than 500,000 Indians to the Caribbean basin between 1838 to 1917 to toil as indentured laborers (135,184,188).

At first, HTLV-I in Japan was hypothesized to have been imported from Portuguese adventurers and seamen in the sixteenth century (178,189). However, other researchers argued against this hypothesis because highly prevalent serum antibodies against HTLV-I were detected in two Japanese ethnic groups, the Ainu and Ryukyuans, both of which are considered to be descendants of the Old Mongoloid populations (152). Later, the presence of two subtypes of HTLV-I were reported in Japan (133,162,190–192). They were the Cosmopolitan and Japanese subtypes, of which the Japanese subtype was nearly exclusively restricted to Japan, and represented a major subtype (162). This observation was consistent with the idea that introduction of HTLV-I into Japan occurred during two or more periods in the past, and it was proposed that at least two Paleo-Mongoloid HTLV-I lineages moved to Japan in the Paleolithic period (133). Another research group suggested that visits from India to southwestern Japan, occurring during the sixteenth century (193), may account for the introduction of the Cosmopolitan subtype (184). In this context, it is noteworthy that the presence of two subtypes (Cosmopolitan and Japanese subtypes) have also been reported in India (133,184).

Since there are no nonhuman primates in Melanesia and Australia, the HTLV-I in these regions is considered to have been brought there. Thus, it has been proposed that HTLV-I existed among the Australoid people who first settled the then single continent of Australia and New Guinea (Sahul) more than 30,000 years ago and among the later Austronesian migrants who colonized the islands in Melanesia approximately 5000 years ago (76,135,162,181).

Geographical Distribution of HTLV-II

HTLV-II has also been identified in Central Africa (139,194–197), West Africa (195,198,199), and among intravenous drug users in the United States (70,200–202) and in Europe (203–210). This virus was also discovered among native Amerindians (211–222).

Restriction endonuclease mapping and nucleotide sequence analysis for the *env* region of HTLV-II indicated that there are two subtypes in HTLV-II, HTLV-IIa and HTLV-IIb, among IDUs in New York (223). Moreover, HTLV-II was further classified using the *LTR* region, which is the most divergent in the genome (79–82,224–226), into three phylogroups for HTLV-IIa and four for HTLV-IIb, by using restriction fragment length polymorphism and phylogenetic analysis (227,228). Another method of classification for HTLV-II was proposed, in which HTLV-IIa was divided into four groups and HTLV-IIb into six (229).

At first, the HTLV-II isolates from native Amerindians were found to be subtype IIb, while the isolates from North American IDUs belonged to subtypes IIa and IIb (224). Subsequent studies have demonstrated the coexistence of both subtypes in both populations (216,224,228,230–232). Taking into account the endemicity of HTLV-II among native Amerindians, the isolation of STLV-II from Central American spider monkeys (46), and the lack of evidence for STLV-II infection in Old World monkeys (233), we feel that the following hypothesis is reasonable. HTLV-II among IDUs originated from native Amerindians. The New World virus was considered to be originally brought from Asia into

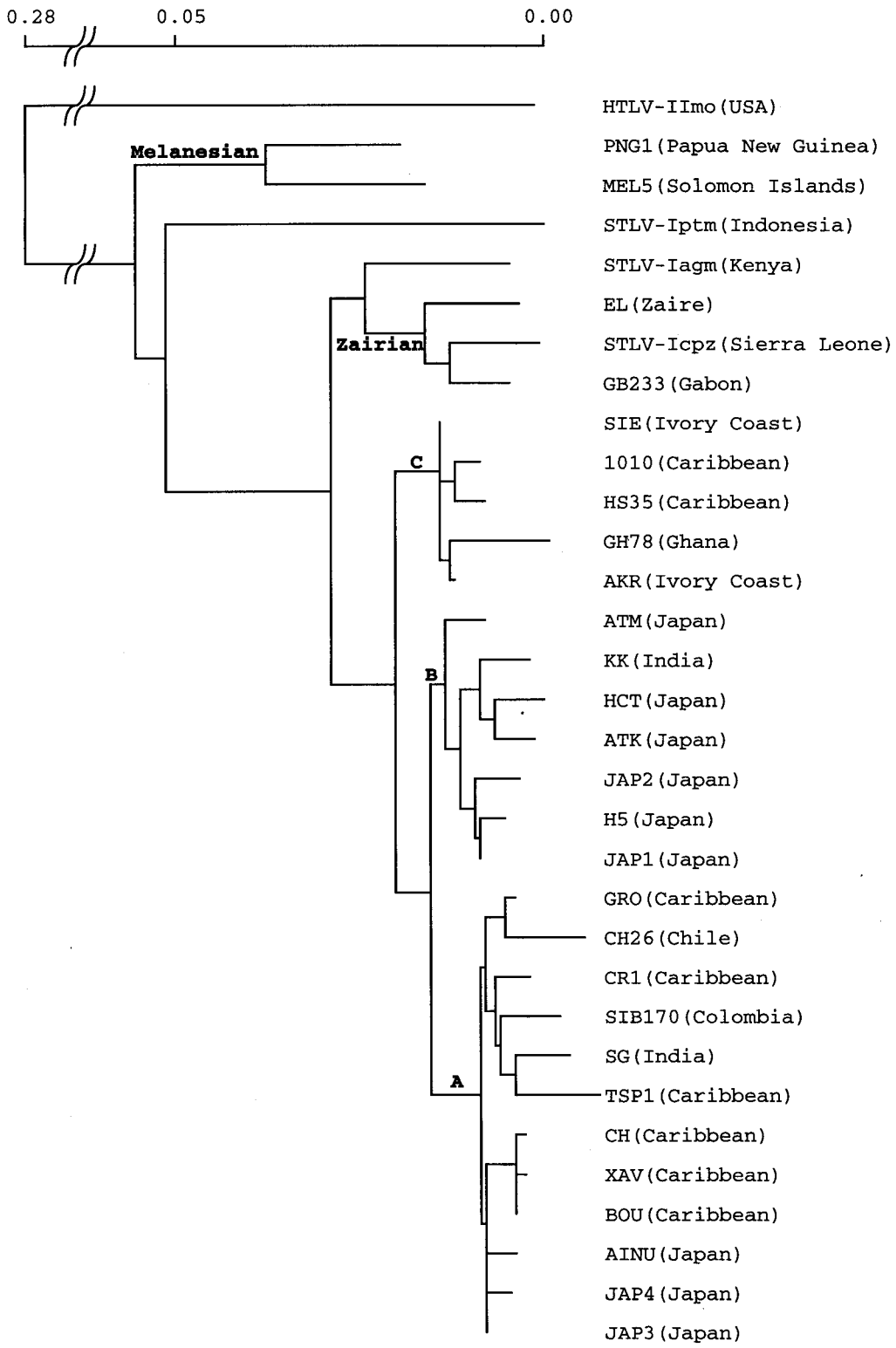

Fig. 4. A phylogenetic tree for HTLV-I and STLV-I. Modified from Fig. 1 in Ref. 133.

the Americas some 10,000–40,000 years ago during the migration of HTLV-II infected Asian populations over the Bering land bridge (81,212,215–222,224,234). However, the discovery of HTLV-II in Central and West Africa has cast doubts on a New World origin for HTLV-II (139,195,196,198,235).

The phylogenetic relationship between the two subtypes of HTLV-II, investigated at the *pol* region with the maximum parsimony (MP) method (236) and at the *env*, *pol* and *pX* regions with the MP neighbor-joining (NJ) (237), and maximum likelihood (ML) methods (238), indicated that both groups have evolved simultaneously (82,224). On the other hand, the analysis for the *LTR* region with the ML method indicated that HTLV-IIa had evolved from HTLV-IIb, although the conclusion was the same as that of the former analyses when the MP method was adopted for the same data (228). The difference in results may indicate that one of these ideas may be incorrect, or if not, that genomic recombination has occurred in the evolution of HTLV-II. At any rate, it is noteworthy that creating the alignment unambiguously for the *LTR* regions of HTLV-I and HTLV-II has been shown to be difficult (82,239).

The existence of both subtypes, HTLV-IIa and HTLV-IIb, has been reported for isolates from South European IDUs (207,225,226,240). In phylogenetic analyses, HTLV-IIa and HTLV-IIb isolates from South Europe were found to be closely related to isolates from New York (82,226). Thus, it was speculated that a limited number of infections from South European–United States IDU connections may be responsible for the HTLV-II epidemic in South Europe (82).

Pathogenicity

HTLV-I can manifest at least three forms of clinical appearances; those are, asymptomatic carrier, ATL, and TSP/HAM. Thus, it is important to investigate whether some changes in the viral genome are responsible for the clinical outcome of the host. So far, attempts have been made to detect such genomic changes by comparing the nucleotide and amino acid sequences from patients with different symptoms. In the phylogenetic analysis, however, no apparent associations have been observed between the clinical symptoms and the pattern of phylogenetic clusterings (133,162). Attempts to detect any sequence variations specific to disease outcome have also failed (138,146,191,241–243). At one time, a mutation in the nucleotide sequence of the *tax* gene (7959 T) was suggested as being associated with TSP/HAM (244). However, it seems that the mutation was associated only with the Cosmopolitan subtype of HTLV-I but not with TSP/HAM (245). The pattern of phylogenetic clusterings and specific variations in genomic sequences seems to imply the geographical origins of HTLV-I isolates (129,133,146,162,180,191,242). In addition, an attempt to find specific variations between viral samples taken from different organs in a single host has also failed (243). These results are consistent with the hypothesis that subsequent disease status may be determined by host's immunological or genetic determinants, or by environmental infectious or noninfectious factors rather than virologic factors (246–252). One of these hypotheses, for example, indicated that an extremely high frequency of precursor cytotoxic T lymphocytes against HTLV-I *tax*-encoded peptides was related to the pathogenesis of TSP/HAM, in which two epitopes 11-19 and 90-55 were restricted by HLA-A2 and HLA-B14, respectively (251,252). Another research group suggested the existence of HAM and ATL-associated haplotypes, which were also related to the high and low immune responses to HTLV-I (250).

Recently, another approach indicated that the ratio of numbers of nonsynonymous to synonymous substitutions for the proviral *tax* gene seemed greater among healthy seropositives than among TSP patients, and also greater among TSP patients than among ATL patients (253,254). This was attributed to a balancing selection operating on the Tax protein rather than the random genetic drift in healthy seropositives (254). In this regard, it is important to test the difference in numbers of synonymous and nonsynonymous substitutions statistically, to clarify the selective force operating on the Tax protein.

B-cell epitopes identified in Gag, Pol, and Env, and T-cell epitopes described in Env and Tax (255–257) were well conserved among different HTLV-I strains. This suggests that it should be possible to develop vaccines which elicit humoral and cell mediated immune responses with little type-specific variation in responses (146).

Problems to be Solved

In contrast to the low level of variability of HTLV-I among different isolates (138), a quasispecies structure for HTLV-I has been suggested because of the high variability of HTLV-I sequences within a single viral strain (130,138,241,253,254,258,259). This implies that HTLV-I is in the condition referred to as population equilibrium (260,261), or that only viruses with specific genomic sequences can be transmitted among humans. For further understanding of the molecular evolution and pathogenicity of HTLV-I and HTLV-II, it is important to investigate this seemingly inconsistent phenomenon in future.

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References

1. Poiesz B.J., Ruscetti F.W., Gazdar A.F., Bunn P.A., Minna J.D., and Gallo R.C., Proc Natl Acad Sci USA *77*, 7415–7419, 1980.
2. Uchiyama T., Yodoi J., Sagawa K., Takatsuki K., and Uchino H., Blood *50*, 481–492, 1977.
3. Hinuma Y., Nagata K., Hanaoka M., Nakai M., Matsumoto T., Kinoshita K.I., Shirakawa S., and Miyoshi I., Proc Natl Acad Sci USA *78*, 6476–6480, 1981.
4. Gessain A., Barin F., Vernant J., Gout O., Maurs L., Calender A., and de The G., Lancet *ii*, 407–409, 1985.
5. Osame M., Usuku K., Izumo S., Ijichi N., Amitani H., and Igata A., Lancet *i*, 1031–1032, 1986.
6. Kawano F., Yamaguchi K., Nishimura H., Tsuda H., and Takatsuki K., Cancer *55*, 851–856, 1985.
7. Gout O., Baulac M., Gessain A., Semah F., Saal F., Peries J., Cabrol C., Foucault-Fretz C., Laplane D., Sigaux F., and de The G., N Engl J Med *322*, 383–387, 1990.
8. Kondo T., Kono H., Nonaka N., Miyamoto N., Yoshida R., Bando F., Inouye H., Miyoshi I., Hinuma Y., and Hanaoka M., Lancet *ii*, 159, 1987.
9. Murphy E.L., Hanchard B., Figueroa J.P., Gibbs W.N., Loftrs W.S., Campbell M., Goedert J.J., and Blattner W.A., Int J Cancer *43*, 250–253, 1989.
10. Tokudome S., Tokunaga O., Shimamoto Y., Miyamoto Y., Sumidy I., Kikuchi M., Takeshita M., Ikeda T., Fujiwara K., Yoshihara M., Yanagawa T., and Nishizumi M., Japan Cancer Res *49*, 226–228, 1989.
11. Kaplan J.E., Osame M., and Kubota H., J Acquir Immune Defic Syndr *3*, 1096–1101, 1990.
12. Kalyanaraman V.S., Sarngadharan M.G., Robert-Guroff M., Miyoshi I., Golde D., and Gallo R.C., Science *218*, 571–573, 1982.
13. Rosenblatt J.D., Gasson J.C., Glaspy J., Bhuta S., Aboud M., Chen I.S., and Golde D.W., Leukemia *1*, 397–410, 1987.
14. Rosenblatt J.D., Golde D.W., Wachsman W., Giorgi J.V., Jacobs A., Schmidt G.M., Quan S., Gasson J.C., and Chen I.S.Y., N Engl J Med *315*, 372–377, 1986.
15. Loughran Jr. T.P., Colye T., Sherman M.P., Starkebaum G., Ehrlich G.D., Ruscetti F.W., and Poiesz B.J., Blood *80*, 1116–1119, 1992.
16. Martin M.P., Biggar R.J., Hamlin-Green G., Staal S., and Mann D., AIDS Res Hum Retroviruses *9*, 715–719, 1993.
17. Heneine W., Chan W.C., Lust J.A., Sinha S.D., Zaki S.R., Khabbaz R.F., and Kaplan J.E., J Acquir Immune Defic Syndr *7*, 736–737, 1994.
18. Sheremata W.A., Harrington Jr.W.J., Bradshaw P.A., Foung S.K.H., Raffanti S.P., Berger J.R., Snodgrass S., Resnick L., and Poiesz B.J., Virus Res *29*, 71–77, 1993.
19. Coffin J.M. in Levy J.A. (ed.) *The Retroviridae*, Vol. 1. Plenum Press, New York, 1992, pp. 19–49.
20. Ina Y. and Gojobori T., J Mol Evol *31*, 493–499, 1990.
21. Miyoshi I., Yoshimoto S., Fujishita M., Taguchi H., Kubonishi I., Niiya K., and Minezawa M., Lancet *ii*, 658, 1982.
22. Hunsmann G., Schneider J., Schmitt J., and Yamamoto N., Int J Cancer *32*, 329–332, 1983.
23. Ishida T., Yamamoto K., Kaneko R., Tokita R., and Hinuma Y., Microbiol Immunol *27*, 297–301, 1983.
24. Miyoshi I., Fujishita M., Taguchi H., Matsubayashi K., Miwa N., and Tanioka Y., Int J Cancer *33*, 333–336, 1983.
25. Miyoshi I., Fujishita M., Taguchi, Niiya K., Kobayashi M., Matsubayashi K., and Miwa N., Lancet *i*, 241, 1983.
26. Yamamoto No., Hinuma Y., zur Hausen H., Schneider J., and Hunsmann G., Lancet *i*, 240–241, 1983.
27. Guo H.G., Wong-Staal F., and Gallo R.C., Science *223*, 1195–1197, 1984.
28. Hayami M., Komuro A., Nozawa K., Shotake T., Ishikawa K., Yamamoto K., Ishida T., Honjo S., and Hinuma Y., Int J Cancer *33*, 179–183, 1984.
29. Komuro A., Watanabe T., Miyoshi I., Hayami M., Tsujimoto H., Seiki M., and Yoshida M., Virology *138*, 373–378, 1984.
30. Yamamoto N., Kobayashi N., Takeuchi K., Koyanagi Y., Hatanaka M., Hinuma Y., Chosa T., Schneider J., and Hunsmann G., Int J Cancer *34*, 77–82, 1984.
31. Yamamoto N., Okada M., Hinuma Y., Hirsch F.W., Chosa T., Schneider J., and Hunsmann G., J Gen Virol *65*, 2259–2264, 1984.
32. Becker W.B., Becker M.L.B., Homma T., Brede H.D., and Kurth R., S Afr Med J *67*, 445–449, 1985.
33. Botha M.C., Jones M., De Klerk W.A., and Yamamoto N., S Afr Med J *67*, 665–668, 1985.
34. Coursaget P., Barres J.L., Yvonnet B., Chiron J.P., Cornet M., Ferrara L., and Eyraud M., Biomed Pharmacother *39*, 198–199, 1985.
35. Lee R.V., Prowten A.W., Satchidanand S.K., and Srivastava B.I.S., N Engl J Med *312*, 118–119, 1985.

36. Voevodin A.F., Lapin B.A., Yakovleva L.A., Ponomaryeva T.I., Oganyan T.E., and Razmadze E.N., Int J Cancer *36*, 579–584, 1985.
37. Watanabe T., Seiki M., Tsujimoto H., Miyoshi I., Hayami M., and Yoshida M., Virology *144*, 59–65, 1985.
38. Dracopoli N.C., Turner T.R., Else J.G., Jolly C.J., Anthony R., Gallo R.C., and Saxinger W.C., Int J Cancer *38*, 523–529, 1986.
39. Lowenstine L., Pedersen N.C., Higgins J., Pallis K.C., Uyeda A., Marx P., Lerche N.W., Munn R.J., and Gardner M.B., Int J Cancer *38*, 563–574, 1986.
40. Watanabe T., Seiki M., Hirayama Y., and Yoshida M., Virology *148*, 385–388, 1986.
41. Ishikawa K., Fukasawa M., Tsujimoto H., Else J.G., Isahakia M., Ubhi N.K., Ishida T., Takenaka O., Kawamoto Y., Shotake T., Ohsawa H., Ivanoff B., Cooper R.W., Frost E., Grant F.C., Spriatna Y., Sutarman Y., Abe K., Yamamoto K., and Hayami M., Int J Cancer *40*, 233–239, 1987.
42. Daniel M.D., Letvin N.L., Sehgal P.K., Schmidt D.K., Silva D.P., Solomon K.R., Hodi Jr. F.S., Ringler D.J., Hunt R.D., King N.W., and Desrosiers R.C., Int J Cancer *41*, 601–608, 1988.
43. Fultz P.N., Gordon T.P., Anderson D.C., and McClure H.M., AIDS *4*, 619–625, 1990.
44. Estaquier J., Peeters M., Bedjabaga L., Honore C., Bussi P., Dixson A., and Delaporte E., AIDS *5*, 1385–1398, 1991.
45. Mone J., Whitehead E., Lelend M., Hubbard G., and Allan J.S., AIDS Res Hum Retroviruses *8*, 1653–1661, 1992.
46. Chen Y.-M.A., Jang Y.-J., Kanki P.J., Yu Q.-C., Wang J.-J., Montali R.J., Samuel K.P., and Papas T.S., J Virol *68*, 1149–1157, 1994.
47. Saksena N.K., Herve V., Durand J.P., LeGuenno B., Diop O.M., Digoutte J.P., Mathiot C., Muller M.C., Love J.L., Dube S., Sherman M.P., Benz P.M., Erensoy S., Galat-Luong A., Galat G., Paul B., Dube D.K., Barre-Sinoussi F., and Poiesz B.J., Virology *198*, 297–310, 1994.
48. Hinuma Y., Komoda H., Chosa T., Kondo T., Kohakura M., Takenaka T., Kikuchi M., Ichimaru M., Yunoki K., Sato I., Matsuo R., Takiuchi Y., Uchino H., and Hanaoka M., Int J Cancer *29*, 631–635, 1982.
49. Blattner W.A., Kalyanaraman V.S., Robert-Guroff M., Lister T.A., Galton D.A.G., Sarin P.S., Crawford M.H., Catovsky D., Greaves M., and Gallo R.C., Int J Cancer *30*, 257–264, 1982.
50. Merino F., Robert-Guroff M., Clark J., Biondo-Bracho M., Blattner W.A., and Gallo R.C., Int J Cancer *34*, 501–506, 1984.
51. Saxinger W., Blattner W.A., Levine P.H., Clark J., Biggar R., Hoh M., Moghissi J., Jacobs P., Wilson L., Jacobson R., Crookes R., Strong M., Ansari A.A., Dean A.G., Nkrumah F.K., Mourali N., and Gallo R.C., Science *225*, 1473–1476, 1984.
52. Tajima K., Tominaga S., Suchi T., Kawagoe T., Komada H., Hinuma Y., Oda T., and Fujita K., Jpn J Cancer Res *73*, 893–901, 1982.
53. Kinoshita K., Hino S., and Amagasaki T., Jpn J Cancer Res *75*, 103–105, 1984.
54. Nakano S., Ando Y., Ichijo M., Moriyama I., Saito S., Sugamura K., and Hinuma Y., Jpn J Cancer Res *75*, 1044–1045, 1984.
55. Hino S., Yamaguchi K., Katamine S., Sugiyama H., Amagasaki T., Kinoshita K., Yoshida Y., Doi H., Tsuji Y., and Miyamoto T., Jpn J Cancer Res *76*, 474–480, 1985.
56. Yamanouchi K., Kinoshita K., Moriuchi R., Katamine S., Amagasaki T., Ikeda S., Ichimaru M., Miyamoto T., and Hino S., Jpn J Cancer Res *76*, 481–487, 1985.
57. Ando Y., Nakano S., Saito K., Shimamoto I., Ichijo M., Toyama T., and Hinuma Y., Jpn J Cancer Res *78*, 322–324, 1987.
58. Hino S., Sugiyama H., Doi H., Ishimaru T., Yamabe T., Tsuji Y., and Miyamoto T., Lancet *ii*, 158–159, 1987.
59. Komuro A., Hayami M., Fujii H., Miyahara S., and Hirayama M., Lancet *i*, 240, 1983.
60. Saito S., Furuki K., Ando Y., Tanigawa T., Kakimoto K., Moriyama I., and Ichijo M., Jpn J Cancer Res *81*, 890–895, 1990.
61. Murphy E.L., Figueroa J.P., Gibbs W.N., Brathwaite A., Holding-Cobham M., Waters D., Cranston B., Hanchard B., and Blattner W.A., Ann Intern Med *111*, 555–560, 1989.
62. Miyamoto K., Tomita N., Ishii A. Nishizaki T., Kitajima K., Tanaka T., Nakamura T., Watanabe S., and Oda T., Int J Cancer *33*, 721–725, 1984.
63. Okochi K., Sato H., and Hinuma Y., Vox Sang *46*, 245–253, 1984.
64. Jason J.M., McDougal J.S., Cabradilla C., Kalyanaraman V.S., and Evatt B.L., Am J Hematol *20*, 129–137, 1985.
65. Minamoto G.Y., Gold J.W.M., Scheinberg D.A., Hardy W.D., Chein N., Zuckerman E., Reich L., Dietz K., Gee T., Hoffer J., Mayer K., Gabrilove J., Clarkson B., and Armstrong D., N Engl J Med *318*, 219–222, 1988.
66. Manns A., and Blattner W.A., Transfusion *31*, 67–75, 1991.
67. Chosa T., Yamamoto N., Tanaka Y., Koyanagi Y., and Hinuma Y., Gann *73*, 844–847, 1982.
68. Ruscetti F.W., Robert-Guroff M., Ceccherini-Nelli L., Minowada J., Popovic M., and Gallo R.C., Int J Cancer *31*, 171–180, 1983.
69. de Rossi A., Aldovini A., Franchini G., Mann D., Gallo R.C., and Wong-Staal F., Virology *143*, 640–645, 1985.
70. Kaplan J.E. and Khabbaz R.F., Rev Med Virol *3*, 137–148, 1993.
71. Lal R.B., Gongora-Biachi R.A., Pardi D., Switzer W.M., Goldsmith C., Goldman I., and Lal A.A., J Infect Dis *168*, 586–591, 1993.
72. Richardson J.H., Edwards A.J., Cruickshank J.K., Rudge P., and Dalgleish A.G., J Virol *64*, 5682–5687, 1990.
73. Ijichi S., Ramundo M., Takahashi H., and Hall W., J Exp Med *176*, 293–296, 1992.
74. Seiki M., Hattori S., Hirayama Y., and Yoshida M., Proc Natl Acad Sci USA *80*, 3618–3622, 1983.
75. Malik K.T.A., Eveir J., and Karpas A., J Gen Virol *69*, 1695–1710, 1988.
76. Gessain A., Boeri E., Yanagihara R., Gallo R.C., and Franchini G., J Virol *67*, 1015–1023, 1993.
77. Bazarbachi A., Huang M., Gessain A., Saal F., Saib A., Peries J., de The H., and Galibert F., Int J Cancer *63*, 494–499, 1995.
78. Chou K.S., Okayama A., Tachibana N., Lee T.-H., and Essex M., Int J Cancer *60*, 701–706, 1995.
79. Shimotohno K., Takahashi Y., Shimizu N., Gojobori T., Golde

D.W., Chen I.S.Y., Miwa M., and Sugimura T., Proc Natl Acad Sci USA *82*, 3101–3105, 1985.
80. Lee H., Idler K.B., Swanson P., Aparicio J.J., Chin K.K., Lax J.P., Nguyen M., Mann T., Leckie G., Zanetti A., Marinucci G., Chen I.S.Y., and Rosenblatt J.D., Virology *196*, 57–69, 1993.
81. Pardi D., Switzer W.M., Hadlock K.G., Kaplan J.E., Lal R.B., and Folks T.M., J Virol *67*, 4659–4664, 1993.
82. Salemi M., Vandamme A.-M., Guano F., Gradozzi C., Cattaneo E., Casoki C., and Bertazzoni U., J Gen Virol *77*, 1193–1201, 1996.
83. Haseltine W.A., Sodroski J., Patarca R., Briggs D., Perkins D., and Wong-Staal F., Science *225*, 419–421, 1984.
84. Shimotohno K., Wachsman W., Takahashi Y., Golde D.W., Miwa M., Sugimura T., and Chen I.S., Proc Natl Acad Sci *81*, 6657–6661, 1984.
85. Ciminale V., D'Agostino D.M., Zotti L., Franchini G., Felber B.K., and Chieco-Bianchi L. Virology *209*, 445–456, 1995.
86. Fujisawa J., Seiki M., Sata M., and Yoshida M., EMBO J *5*, 713–718, 1986.
87. Paskalis H., Felber B.K., and Pavlakis G.N., Proc Natl Acad Sci USA *83*, 6558–6562, 1986.
88. Shimotohno K., Takano M., Terunchi T., and Miwa M., Proc Natl Acad Sci USA *83*, 8112–8116, 1986.
89. Brady J., Jeang K.T., Durall J., and Khoury G. J Virol *61*, 2175–2181, 1987.
90. Kitado H., Chen I.S.Y., Shah N.P., Cann A.J., Shimotohno K., and Fan H., Science *235*, 901–904, 1987.
91. Ohtani K., Nakamura M., Saito S., Noda T., Ito Y., Sugamura K., and Hinuma Y., EMBO J *6*, 389–395, 1987.
92. Rosen C.A., Park R., Sodroski J.G., and Haseltine W.A., Proc Natl Acad Sci USA *84*, 4919–4923, 1987.
93. Rosenblatt J.D., Cann A.J., Slamon D.J., Smalberg I.S., Shah N.P., Fujii J., Wachsman W., and Chen I.S.Y., Science *240*, 916–919, 1988.
94. Seiki M., Inoue J.-I., Hikada M., and Yoshida M., Proc Natl Acad Sci USA *85*, 7124–7128, 1988.
95. Hanly S.M., Rimsky L.T., Malim M.H., Kim J.H., Hauber J., Duc Dodon M., De S.-Y., Maizel J.V., Cullen B.R., and Greene W.C., Genes Dev *3*, 1534–1544, 1989.
96. Ahmed Y.F., Hanly S.M., Malim M.H., Cullen B.R., and Greene W.C., Genes Dev *4*, 1014–1022, 1990.
97. Black A.C., Chen I.S.Y., Arringo S.J., Ruland C.T., Chin E., Allogiamento T., and Rosenblatt J.D., Virology *191*, 433–444, 1991.
98. Copeland T.D., Oroszlan S., Kalyanaraman V.S., Sarngadharan M.G., and Gallo R.C., FEBS Lett *162*, 390–395, 1983.
99. Hattori S., Kiyokawa T., Imagawa K., Shimizu F., Hashimura E., Seiki M., and Yoshida M., Virology *136*, 338–347, 1984.
100. Nam S.H., Kidokoro M., Shida H., and Hatanaka M., J Virol *62*, 3718–3728, 1988.
101. Miwa M., Shiomotohno K., Hoshino H., Fujino M., and Sugimura T., Gann *75*, 752–755, 1984.
102. Slamon D.J., Shimotohno K., Cline M.J., Golde D.W., and Chen I.S.Y., Science *226*, 61–65, 1984.
103. Goh W.C., Sodroski J., Rosen C., Essex M., and Haseltine W.A., Science *227*, 1227–1228, 1985.
104. Slamon D.J., Press M.F., Souza L.M., Murdock D.C., Cline M.J., Golde D.W., Gasson J.C., and Chen I.S., Science *228*, 1427–1430, 1985.
105. Slamon D.J., Boyle W.F., Keith D.E., Press M.F., Golde D.W., and Souza L.M., J Virol *62*, 680–686, 1988.
106. Lee T.H., Coligan J.E., Sodroski J.G., Haseltine W.A., Salahuddin S.Z., Wong-Staal F., Gall R.C., and Essex M., Science *226*, 57–61, 1984.
107. Cann A.J., Rosenblatt J.D., Wachsman W., Shah N.P., and Chen I.S.Y., Nature *318*, 571–574, 1985.
108. Felber B.K., Paskalis H., Keinman-Ewing C., Wong-Staal F., and Pavlakis G.N., Science *229*, 675–679, 1985.
109. Fujisawa J., Seiki M., Kiyokawa T., and Yoshida M., Proc Natl Acad Sci USA *82*, 2277–2281, 1985.
110. Sodroski J., Rosen C., Goh W.C., and Haseltine W., Science *228*, 1430–1434, 1985.
111. Shah N.P., Wachsman W., Souza L., Cann A.J., Slamon D.J., and Chen I.S.Y., Mol Cell Biol *6*, 3626–3631, 1986.
112. Inoue I., Seiki M., and Yoshida M., FEBS Lett *209*, 187–190, 1986.
113. Inoue J., Yoshida M., and Seiki M., Proc Natl Acad Sci USA *84*, 3653–3657, 1987.
114. Hidaka M., Inoue J., Yoshida M., and Seiki M., EMBO J *7*, 519–523, 1988.
115. Ohta M., Nyunoya H., Tanaka H., Okamoto T., Akagi T., and Shimotohno K., J Virol *62*, 4445–4449, 1988.
116. Kim J.H., Kaufman P.A., Hanly S.M., Rimsky L.T., and Greene W.C., J Virol *65*, 405–414, 1991.
117. Clark S.P. and Mak T.W., J Virol *50*, 759–765, 1984.
118. Chiu I.-M., Callahan R., Tronick S.R., Schlom J., and Aaronson S.A., Science *223*, 364–370, 1984.
119. Toh H. and Miyata T., Nature *316*, 21–22, 1985.
120. Sonigo P., Barker C., Hunter E., and Wain-Hobson S., Cell *45*, 375–385, 1986.
121. Thayer R.M., Power M.D., Bryant M.L., Gardner M.B., Barr P.J., and Luciw P.A., Virology *157*, 317–329, 1987.
122. Yokoyama S., Moriyama E.N., and Gojobori T., Proc Jpn Acad *63*, 147–150, 1987.
123. McClure M.A., Johnson M.S., Feng D.-F., and Doolittle R.F., Proc Natl Acad Sci USA *85*, 2469–2473, 1988.
124. Yokoyama S., Chung L., and Gojobori T., Mol Biol Evol *5*, 237–251, 1988.
125. Doolittle R.F., Feng D.F., Johnson M.S., and McClure M.A., Q Rev Biol *64*, 1–30, 1989.
126. Gojobori T., Moriyama E.N., Ina Y., Ikeo K., Miura T., Tsujimoto H., Hayami M., and Yokoyama S., Proc Natl Acad Sci USA *87*, 4108–4111, 1990.
127. Lewe G. and Flugel R.M., Virus Genes *3*, 195–204, 1990.
128. Doolittle R.F., and Feng D.F., Curr Top Microbiol Immunol *176*, 195–211, 1992.
129. Saksena N.K., Sherman M.P., Yanagihara R., Dube D.K., and Poiesz B., Virology *189*, 1–9, 1992.
130. Sherman M.P., Saksena N.K., Dube D.K., Yanagihara R., and Poiesz B.J., J Virol *66*, 2556–2563, 1992.
131. Saksena N.K., Herve V., Sherman M.P., Durand J.P., Mathiot C., Muller M., Love J.L., DeGuenno B., Barre-Sinoussi F., Dube D.K., and Poiesz B.J., Virology *192*, 312–320, 1993.
132. Koralnik I.J., Boeri E., Saxinger W.C., Monico A.L., Fullen J., Gessain A., Guo H.-G., Gallo R.C., Markham P.,

Kalyanaraman V., Hirsch V., Allan J., Murthy K., Alford P., Slattery J.P., O'Brien S.J., and Franchini G., J Virol *68*, 2693–2707, 1994.
133. Miura T., Fukunaga T., Igarashi T., Yamashita M., Ido E., Funahashi S., Ishida T., Washio K., Ueda S., Hashimoto K., Yoshida M., Osame M., Singhal B.S., Zaninovic V., Cartier L., Sonoda S., Tajima K., Ina Y., Gojobori T., and Hayami M., Proc Natl Acad Sci USA *91*, 1124–1127, 1994.
134. Song K.-J., Nerurkar V.R., Saitou N., Lazo A., Blakeslee J.R., Miyoshi I., and Yanagihara R., Virology *199*, 56–66, 1994.
135. Yanagihara R., Saitou N., Nerurkar V.R., Song K.-J., Bastian I., Franchini G., and Gajdusek D.C., Cell Mol Biol *41*, 5145–5161, 1995.
136. Gojobori T., Moriyama E.N., and Kimura M., Proc Natl Acad Sci USA *87*, 10015–10018, 1990.
137. Gojobori T., Yamaguchi Y., Ikeo K., and Mizokami M., Jpn J Genet *69*, 481–488, 1994.
138. Gessain A., Gallo R.C., and Franchini G., J Virol *66*, 2288–2295, 1992.
139. Gessain A., Mauclere P., Froment A., Biglione M., Hesran J.Y.L., Tekaia F., Millan J., and de The G., Proc Natl Acad Sci USA *92*, 4041–4045, 1995.
140. Li, W.-H., Tanimura M., and P. M. Sharp P.M., Mol Biol Evol *5*, 313–330, 1988.
141. Preston B.D., Poiesz B.J., and Loeb L.A., Science *242*, 1168–1171, 1988.
142. Roberts J.D., Bebenek K., and Kunkel T.A., Science *242*, 1171–1173, 1988.
143. Lazcano A., Valverde V., Hernandez G., Gariglio P., Fox G.E., and Oro J., J Mol Evol *35*, 524–536, 1992.
144. Williams K.J. and Loeb L.A., Curr Top Microbiol Immunol *176*, 165–181, 1992.
145. Nei M., Molecular Evolutionary Genetics. Columbia University Press, New York, 1987.
146. Ratner L., Philpott T., and Trowbridge D.B., AIDS Res Hum Retroviruses *7*, 923–941, 1991.
147. Gojobori T., Li W.-H., and Graur D., J Mol Evol *18*, 360–369, 1982.
148. Kypr J., Mrazek J., and Reich J., Bioch Biophy Acta *1009*, 280–282, 1989.
149. Berkhout B. and van Hemert F.J., Nucleic Acids Res *22*, 1705–1711, 1994.
150. Bronson E.C. and Anderson J.N., J Mol Evol *38*, 506–532, 1994.
151. Yoshida M., Miyoshi I., and Hinuma Y., Proc Natl Acad Sci USA *79*, 2031–2035, 1982.
152. Ishida T., Yamamoto K., Omoto K., Iwanaga M., Osato T., and Hinuma Y., J Infect *11*, 153–157, 1985.
153. Catovsky D., Rose M., Goolden A.W.G., White J.M., Bourikas G., Brownell A.I., Blattner W.A., Greaves M.F., Galton D.A.G., McDluskey D.R., Lampert I., Ireland R., Bridges J.M., and Gallo R.C., Lancet *i*, 639–643, 1982.
154. Blayney D.W., Blattner W.A., Robert-Guroff M., Jaffe E.S., Fisher R.I., Bunn P.A., Patton M.G., Rarick H.R., and Gallo R.C., J Amer Med Ass *250*, 1048–1052, 1983.
155. Zamora T., Zaninovic V., Kajiwara M., Komoda H., Hayami M., and Tajima K., Jpn J Cancer Res *81*, 715–719, 1990.
156. Zaninovic V., Sanzon F., Lopez F., Velandia G., Blank A., Blank M., Fujiyama C., Yashiki S., Matsumoto D., Katahira Y., Miyashita H., Fujiyoshi T., Chan L., Sawada T., Miura T., Hayami M., Tajima K., and Sonoda S., AIDS Res Hum Retroviruses *10:* 97–101, 1994.
157. Biggar R.J., Saxinger C., Gardiner C., Collins W.E., Levine P.H., Clark J.W., Nkrumah F.K., and Blattner W.A., Int J Cancer *34*, 215–219, 1984.
158. Delaporte E., Dupont A., Peeters M., Josse R., Merlin M., Schrijvers D., Hamono B., Bedjabaga L., Cheringou H., and Boyer F., Int J Cancer *42*, 687–689, 1988.
159. Gasmi M., Farouqi B., d'Incan M., and Desgranges C., AIDS Res Hum Retroviruses *10*, 1313–1315, 1994.
160. Roman G.C., Schoenberg B.S., Madden D.L., Sever J.L., Hugon J., Ludolph A., and Spencer P.S., Arch Neurol *44*, 605–607, 1987.
161. Mahieux R., Gessain A., Truffert A., Vitrac D., Hubert A., Dandelot J., Montchamp-Moreau C., Cnudde F., Tekaia F., Musenger C., and de The G., AIDS Res Hum Retroviruses *10*, 745–752, 1994.
162. Ureta Vidal A., Gessain A., Yoshida M., Tekaia F., Garin B., Guillemain B., Schulz T., Farid R., and De The G., J Gen Virol *75*, 3655–3666, 1994.
163. Gurtsevitch V., Senjuta N., Pavlish O., Shih J., Stepina V., Syrtsev A., Potekhin O., and Lenoir G.M., Int J Cancer *51*, 835–836, 1992.
164. Gabarre J., Gessain A., Raphael M., Merle-Beral H., Dubourg O., Fourcade C., Gandjbakhch I., Jault F., Delcourt A., and Binet J.L., Leukemia *7*, 1904–1909, 1993.
165. Advani S.H., Fujishita M., Kitagawa T., Taguchi H., and Miyoshi T., Indian J Med Res *86*, 218–220, 1987.
166. Kelkar R., Ishida T., Bharucha Z., Advani S.H., and Hayami M., Indian J Haematol *8*, 11–14, 1990.
167. Chandy M., Babu P.G., Saraswathi N.K., Ishida T., and John T.J., Lancet *338*, 3810–3811, 1991.
168. Babu P.G., Gnanamuthu C., Saraswathi N.K., Nerurkar V.R., Yanagihara R., and John T.J., AIDS Res Hum Retroviruses *9*, 499–500, 1993.
169. Singhal B., Lalkaka J.A., Sonoda S., Hashimoto K., Nomoto M., Kubota R., and Osame M., AIDS *7*, 138–139, 1993.
170. Goudsmit J., Asher D.M., Garruto R.M., Mora C., Yanagihara R., Jenkins C., pomeroy K.L., Askins H., and Gajdusek D.C., in Abstracts of the XVI Pacific Science Congress. 1987, Seoul, Korea, p. 73.
171. Kazura J.W., Saxinger W.C., Wenger J., Forsyth K., Lederman M.M., Gillespie J.A., Carpenter C.C.J., and Alpers M.A., J Infect Dis *155*, 1100–1107, 1987.
172. Brindle R.J., Eglin R.P., Parsons A.J., Hill A.V.S., and Selkon J.B., Epidemiol Infect *100*, 153–156, 1988.
173. Garruto R.M., Slover M., Yanagihara R., Mora C.A., Alexander S.S., Asher D.M., Rodgers-Johnson P., and Gajdusek D.C., Am J Hum Biol *2*, 439–447, 1990.
174. Yanagihara R., Garruto R.M., Miller M.A., Leon-Monzon M., Liberski P.P., Gajdusek D.C., Jenkins C.L., Sanders R.C., and Alpers M.P., N Engl J Med *323*, 993–994, 1990.
175. Gessain A., Yanagihara R., Franchini G., Garruto R.M., Jenkins C.L., Ajdukiewicz A.B., Gallo R.C., and Gajdusek D.C., Proc Natl Acad Sci USA *88*, 7694–7698, 1991.
176. Yanagihara R., Ajdukiewicx A.B., Nerurkar V.R., Garruto R.M., and Gajdusek D.C., Jpn J Cancer Res *82*, 240–244, 1991.

177. Bastian I., Gardner J., Webb D., and Gardner I., J Virol *67*, 843–851, 1993.
178. Gallo R.C., Sliski A., and Wong-Staal F., Lancet *ii*, 962–963, 1983.
179. Wong-Staal F. and Gallo R.C., Nature *317*, 395–403, 1985.
180. De B.K., Lairmore M.D., Griffis K., Williams L., Villinger F., Quinn T.C., Brown C., Sugimoto M., Araki S., and Folks T.M., Virology *182*, 413–419, 1991.
181. Yanagihara R., Nerurkar V.R., Garruto R.M., Miller M.A., Leon-Monzon M.E., Jenkins C.L., Sanders R.C., Liberski P.P., Alpers M.P., and Gajdusek D.C., Proc Natl Acad Sci USA *88*, 1446–1450, 1991.
182. Gessain A., Koralnik I.J., Fullen J., Boeri E., Mora C., Blank A., Salazar-Gruesco E.F., Kaplan J., Saxinger W.C., Davidson M., Lairmore M.D., Levine P., and Franchini G., AIDS Res Hum Retroviruses *10*, 103–106, 1994.
183. Song K.-J., Nerurkar V.R., Pereira-Cortez A.J., Yamamoto M., Taguchi H., Miyoshi I., and Yanagihara R., Am J Trop Med Hyg *52*, 101–108, 1995.
184. Nerurkar V.R., Babu P.G., Song K.-J., Melland R.R., Gnanamuthu C., Saraswathi N.K., Chandy M., Godec M.S., John T.J., and Yanagihara R., J Gen Virol *74*, 2799–2805, 1993.
185. Nei M. and Roychoudhury A.K., Mol Biol Evol *10*, 927–943, 1993.
186. Undevia J.V., Blake N.M., Kirk R.L., and McDermid E.M., Hum Heredity *22*, 274–282, 1972.
187. Balkrishanan V., J Hum Evol *7*, 67–75, 1978.
188. Dutt E., India Abroad *23*, 18–23, 1993.
189. Gallo R.C., Sliski A.H., de Noronha C.M., and de Noronha F., Nature *320*, 219, 1986.
190. Siomi H., Nasaka T., Saida T., Miwa H., Hinuma Y., Shirakawa S., Miyamoto N., Kondo T., Araki K., Ichimaru M., Miura A.B., and Hatanaka M., Virus Genes *1*, 377–383, 1988.
191. Komurian F., Pelloquin F., and de The G., J Virol *65*, 3770–3778, 1991.
192. Komurian-Pradel F., Pelloquin F., Sonoda S., and de The G., AIDS Res Hum Retroviruses *8*, 429–434, 1992.
193. Kantha S.S., Nature *321*, 733, 1986.
194. Delaporte E., Louwagie J., Peeters M., Monplasir N., D'auriol L., Ville Y., Bedjabaga L., Larouze B., Vander Grown G., and Piot P., AIDS *5*, 771–772, 1991.
195. Goubau P., Liu H.F., de Lange G.G., Vandamme A.M., and Desmyter J., AIDS Res Hum Retroviruses *9*, 709–713, 1993.
196. Gessain A., Tuppin P., Kazanji M., Cosnefroy J.Y., George-Courbot M.C., Georges A.J., and de The G., AIDS Res Hum Retroviruses *10*, 753–754, 1994.
197. Tuppin P., Gessain A., Kazanji M., Mahieux R., Cosnefroy J.Y., Tekaia F., Georges-Courbot M.C., Georges A., and de The G., J Med Virol *48*, 2–32, 1996.
198. Froment A., Delaporte E., Dazza M.C., and Larouze B., AIDS Res Hum Retroviruses *9*, 707–708, 1993.
199. Igarashi T., Yamashita M., Miura T., Osei K.M., Aysi N.K., Shiraki H., Kurimura T., and Hayami M., AIDS Res Hum Retroviruses *9*, 1039–1042, 1993.
200. Robert-Guroff M., Weiss S.H., Giron J.A., Jennings A.M., Ginzburg H.M., Margolis B., Blattner W.A., and Gallo R.C., J Amer Med Ass *255*, 3133–3137, 1986.
201. Lee H., Swanson P., Shorty V.S., Zack J.A., Rosenblatt J.D., and Chen I.S.Y., Science *244*, 471–475, 1989.
202. Khabbaz R.F., Hartel D., Lairmore M., Horsburgh C.R., Schoenbaum E.E., Roberts B., Hosein B., and Kaplan J.E., J Infect Dis *163*, 252–256, 1991.
203. Tedder R., Shanson D., Jeffries R., Cheingsong-Popov R., Clapham P., Dalgleish A., Nagy K., and Weiss R.A., Lancet *ii*, 125–128, 1984.
204. Zella D., Mori L., Sala M., Ferrante P., Casoli C., Magnani G., Achilli G., Cattaneo E., Lori F., and Bertazzoni U., Lancet *335*, 575–576, 1990.
205. de Rossi A., Mammano F., de Mistro A., and Chieco-Bianchi L, Eur J Cancer *27*, 835–838, 1991.
206. Tosswill J.H.C., Parry J.V., and Weber J.N., J Med Virol *36*, 167–171, 1992.
207. Calabro' M.L., Luparello M., Grottola A., Del Mistro A., Fiore J.R., Angarano G., and Chieco-Bianchi L., J Infect Dis *168*, 1273–1277, 1993.
208. Flo R.W., Samdal H.H., Kalland K.-H., The Oslo HIV Cohort Study Group, Nilsen A., and Haukenes G., Clin Diagn Virol *1*, 143–152, 1993.
209. Soriano V., Calderon E., Esparza B., Cilla G., Aguilera A., Gutierrez M., Tor J., Pujol E., Merino F., Perez-Trallero E., Leal M., and Gonzalez-Lahoz J., Int J Epidemiol *22*, 716–719, 1993.
210. Vignoli C., Zandotti C., de Lamballerie X., Tamalet C., Gastaut J.A., and de Micco P., Eur J Epidemiol *9*, 351–352, 1993.
211. Hjelle B., Scalf R., and Swenson S., Blood *76*, 450–454, 1990.
212. Lairmore M.D., Jacobson S., Gracia F., De B.K., Castillo L., Larreategui M., Roberts B.D., Levine P.H., Blattner W.A., and Kaplan J.E., Proc Natl Acad Sci USA *87*, 8840–8844, 1990.
213. Reeves W.C., Levine P., Cuevas P., Quiroz M., Maloney E., and Saxinger C., Am J Trop Med Hyg *42*, 374–379, 1990.
214. Hjelle B., Mills R., Swenson S., Merts G., Key C., and Allen S., J Infect Dis *163*, 435–440, 1991.
215. Duenas-Barajas E., Bernal J.E., Vaught D.R., Briceno I., Duran C., Yanagihara R., and Gajdusek D.C., AIDS Res Hum Retroviruses *8*, 1851–1855, 1992.
216. Hjelle B., Zhu S.W., Takahashi H., Ijichi S., and Hall W.W., J Infect Dis *168*, 737–740, 1993.
217. Maloney E.M., Biggar R.J., Neel J.V., Taylor M.E., Hahn B.H., Shaw G.M., and Blattner W.A., J Infect Dis *166*, 100–107, 1992.
218. Biglione M., Gessain A., Quiruelas M., Fay O., Taborda M.A., Fernandez E., Lupo S., Panzita A., and de The G., J Acquired Immune Defic Syndr *6*, 631–633, 1993.
219. Ferrer J.F., Del Pino N., Esteban E., Sherman M.P., Dube S., Dube D.K., Basombrio M.A., Pimentel E., Segovia A., Quirulas S., and Poiesz B.J., Virology *197*, 576–584, 1993.
220. Fujiyama C., Fujiyoshi T., Miura T., Yashiki S., Matsumoto D., Zaninovic V., Blanco O., Harrington Jr.W., Byrnes J.J., Hayami M., Tajima K., and Sonoda S., J Infect Dis *168*, 1075–1077, 1993.
221. Ijichi S., Zaninovic V., Leon F.E., Katahira Y., Sonoda S., Miura T., Hayami M., and Hall W.W., Jpn J Cancer Res *84*, 1215–1218, 1993.
222. Levine P.H., Jacobson S., Eliot R., Cavallero A., Colclough G.,

Stephenson C., Knigge R.M., Drummond J., Ishimura M., Taylor M.E., Wiktor S.Z., and Shaw G., AIDS Res Hum Retroviruses *9*, 123–127, 1993.
223. Hall W.W., Takahashi H., Liu C., Kaplan M.H., Scheewind O., Ijichi S., Nagashima K., and Gallo R.C., J Virol *66*, 2456–2463, 1992.
224. Dube D.K., Sherman M.P., Saksena N.K., Bryz-Gornia V., Mendelson J., Love J., Arnold C.B., Spicer T., Dube S., Glaser J.B., Williams A.E., Nishimura M., Jacobsen S., Ferrer J.F., Del Pino N., Quiruelas S., and Poiesz B.J., J Virol *67*, 1175–1184, 1993.
225. Zella D., Cavicchini A., Salemi M., Casoli C., Lori F., Achilli G., Cattaneo E., Landini V., and Bertazzoni U., J Gen Virol *74*, 437–444, 1993.
226. Salemi M., Cattaneo E., Casoli C., and Bertazzoni U., J Acquired Immune Defic Syndr *8*, 516–520, 1995.
227. Switzer W.M., Owen S.M., Pieniazek D., Nerurkar V., Duenas-Barajas E., Heneine W., and Lal R.B., Virus Genes *10*, 153–162, 1995.
228. Switzer W.M., Pieniazek D., Swanson P., Samdal H.H., Soriano V., Khabbaz R.F., Kaplan J.E., Lal R.B., and Heneine W., J Virol *69*, 621–632, 1995.
229. Eiraku N., Monken C., Kubo T., Wei Zhu S., Rios M., Bianco C., Hjelle B., Nagashima K., and Hall W.W., AIDS Res Hum Retroviruses *11*, 625–636, 1995.
230. Takahashi H., Zhu S.H., Ijichi S., Vahlne A., Suzuki H., and Hall W.W., AIDS Res Hum Retroviruses *9*, 721–732, 1993.
231. Biggar R.J., Taylor M.E., Neel J.V., Hjelle B., Levine P.H., Black F.L., Shaw G.M., Sharp P.M., and Hahn B.H., Virology *216*, 165–173, 1996.
232. Eiraku N., Novoa P., da Costa Ferreira M., Monken C., Ishak R., da Costa Ferreira O., Zhu S.W., Lorenco R., Ishak M., Azvedo V., Guerreiro J., de Oliveira M.P., Loureiro P., Hammerschlak N., Ijichi S., and Hall W.W., J Virol *70*, 1481–1492, 1996.
233. Rudolph D.L., Keesling S.S., Lerche N., Yee J.A., and Lal R.B., AIDS Res Hum Retroviruses *9*, 721–722, 1991.
234. Essex M., N Engl J Med *330*, 209–210, 1994.
235. Goubau P., Desmyter J., Ghesquiere J., and Kasereka B., Nature *359*, 201, 1992.
236. Eck R.V. and Dayhoff M.O., Atlas of Protein Sequence and Structure. 1978, Natl Biomed Res Found, Silver Spring, Maryland.
237. Saitou N. and Nei M., Mol Biol Evol *4*, 406–425, 1987.
238. Felsenstein J., J Mol Evol *17*, 368–376, 1981.
239. Vandamme A.-M., Liu H.-F., Goubau P., and Desmyter J., Virology *202*, 212–223, 1994.
240. Vallejo H. and Garcia-Saiz A., J Aquired Immune Defic Syndr 7, 57–5119, 1994.
241. Daenke S., Nightingale S., Cruickshank J.K., and Bangham C.R.M., J Virol *64*, 1278–1282, 1990.
242. Paine E., Garcia J., Philpott T.C., Show G., and Ratner L., Virology *182*, 111–123, 1991.
243. Yamashita M., Achiron A., Miura T., Takehisa J., Ido E., Igarashi T., Ibuki K., Osame M., Sonoda S., Melamed E., Hayami M., and Shohat B., Virus Genes *10*, 85–90, 1995.
244. Renjifo B., Borrero I., and Essex M., J Virol *69*, 2611–2616, 1995.
245. Mahieux R., de The G., and Gessain A., J Virol *69*, 5925–5927, 1995.
246. Clapham P., Nagy K., and Weiss R.A., Proc Natl Acad Sci USA *81*, 886–2889, 1984.
247. Kannagi M., Sugamura K., Kinoshita K., Uchino H., and Hinuma Y., J Immunol *133*, 1037–1041, 1984.
248. Mitsuya H., Matis L.A., Megson M., Cohen O.J., Mann D.L., Gallo R.C., and Broder S., Lancet *i*, 649–653, 1984.
249. Yamaguchi K., Matutes E., Catovsky D., Galton D.A.G., Nakada K., and Takatsuki K., Lancet *ii*, 94–95, 1987.
250. Usuku K., Sonoda S., Osame M., Yashiki S., Takahashi K., Matsumono M., Sawada T., Tsuji K., Tara M., and Igata A., Ann Neurol *23*, S143–S150, 1988.
251. Elovaara I., Koenig S., Brewah Y., Woods R.M., Lehky T., and Jacobson S., J Exp Med *177*, 1567–1573, 1993.
252. Koenig S., Woods R.M., Brewah Y.A., Newell A.J., Jones G.M., Boone E., Adelsberger J.W., Baseler M.W., Robinson S.M., and Jocobson S., J Immunol *151*, 3874–3883, 1993.
253. Niewiesk S., Daenke S., Parker C.E., Taylor G., Weber J., Nightingale S., and Bangham C.R., J Virol *68*, 6778–6781, 1994.
254. Niewiesk S. and Bangham C.R.M., J Mol Evol *42*, 452–458, 1996.
255. Kurata A., Palker T.J., Streilein R.D., Scearce R.M., Haynes B.F., and Berzofsky J.A., J Immunol *143*, 2024–2030, 1989.
256. Ralston S., Hoeprich P., and Akita R., J Biol Chem *164*, 16343–16346, 1989.
257. Lal R.B., Rudolph D.L., Griffis K.P., Kitamura K., Honda M., Coligan J.E., and Golks T.M., J Virol *65*, 1870–1876, 1991.
258. Berneman Z.N., Gartenhaus R.B., Reitz M.S., Klotman M.E., and Gallo R.C., Leukemia *6*, 67S–71S, 1992.
259. Ehrlich G.D., Andrews J., Sherman M.P., Greenberg S.J., and Poiesz B.J., Virology *186*, 619–627, 1992.
260. Domingo E., Sabo D.L., Taniguchi T., and Weissmann C., Cell *13*, 735–744, 1978.
261. Steinhauer D.A., de la Torre J.C., Meier E., and Holland J.J., J Virol *63*, 2072–2080.
262. Hahn B.H., Shaw G.M., Taylor M.E., Redfield R.R., Markham P.D., Salahuddin S.Z., Wong-Staal F., Gallo R.C., Parks E.S., and Parks W.P., Science *232*, 1548–1553, 1986.
263. Yokoyama S. and Gojobori T., J Mol Evol *24*, 330–336, 1987.
264. Burns D.P.W. and Desrosiers R.C., J Virol *65*, 1843–1854, 1991.
265. Gojobori T. and Yokoyama S., Proc Natl Acad Sci USA *82*, 4198–4201, 1985.
266. Gojobori T. and Yokoyama S., J Mol Evol *26*, 148–156, 1987.
267. Clements J.E., Gdovin S.L., Montelaro R.C., and Narayan O., Annu Rev Immunol *6*, 139–159, 1988.
268. Kawaoka Y., Krauss S., and Webster R.G., J Virol *63*, 4603–4608, 1989.
269. Gorman O.T., Donis R.O., Kawaoka Y., and Webster R.G., J Virol *64*, 4893–4902, 1990.
270. Okazaki K., Kawaoka Y., and Webster R.G., Virology *172*, 601–608, 1989.
271. Raymond F.L., Caton A.J., Cox N.J., Kendal A.P., and Brownlee G.G., Virology *148*, 275–287, 1986.
272. Rocha E., Cox N.J., Black R.A., Harmon M.W., Harrison C.J., and Kendal A.P., J Virol *65*, 2340–2350, 1991.
273. Sugita S., Yoshioka Y., Itamura S., Kanegae Y., Oguchi K.,

Gojobori T., Nerome K., and Oya A., J Mol Evol *32*, 16–23, 1991.
274. Both G.W., Sleigh M.J., Cox N., and Kendal A.P., J Virol *48*, 52–60, 1983.
275. Daniel R.S., Skehel J.J., and Wiley D.C., J Gen Virol *66*, 457–464, 1985.
276. Bean W., Schell M., Katz J., Kawaoka Y., Naeve C., Gorman O., and Webster R., J Virol *66*, 1129–1138, 1992.
277. Air G.M., Proc Natl Acad Sci USA *78*, 7634–7643.
278. Altmuller A., Fitch W.M., and Scholtissek C., J Gen Virol *70*, 2111–2119, 1989.
279. Gorman O.T., Bean W.J., Kawaoka Y., and Webster R.G., J Virol *64*, 1487–1497, 1990.
280. Gorman O.T., Bean W.J., Kawaoka Y., Donatelli I., Guo Y., and Webster R.G., J Virol *65*, 3704–3714, 1991.
281. Martinez C., del Rio L., Portela A., Domingo E., and Ortin J., Virology *130*, 539–545, 1983.
282. Nerome K., Kanegae Y., Yoshioka Y., Itamura S., Ishida M., Gojobori T., and Oya A., J Gen Virol *72*, 693–698, 1991.
283. Ito T., Gorman O.T., Kawaoka Y., Bean W.J., and Webster R.G., J Virol *65*, 5491–5498, 1991.
284. Buonagurio D.A., Nakada S., Parvin J.D., Krystal M., Palese P., and Fitch W.M., Science *232*, 980–982, 1986.
285. Krystal M., Buonagurio J.F., Young J.F., and Palese P., J Virol *45*, 547–554, 1983.
286. Muraki Y., Hongo S., Sugawara K., Kitame F., and Nakamura K., J Gen Virol *77*, 673–679, 1996.
287. Gebauer F., de la Torre J.C., Gomes I., Mateu M.G., Barahona H., Tiraboschi B., Bergmann I., Auge de Mello P., and Domingo E., J Virol *62*, 2041–2049, 1988.
288. Villaverde A., Martinez M.A., Sobrino F., Dopazo J., Moya A., and Domingo E., Gene *103*, 147–153, 1991.
289. Martinez M.A., Dopazo J., Hernandez J., Mateu M.G., Sobrino F., Domingo E., and Knowles N.J., J Virol *66*, 3557–3565, 1992.
290. Weaver S., Scot T.W., and Rico-Hesse R., Virology *182*, 774–784, 1991.
291. Orito E., Mizokami M., Ina Y., Moriyama E.N., Kameshima N., Yamamoto M., and Gojobori T., Proc Natl Acad Sci USA *86*, 7059–7062, 1989.
292. Okamoto H., Kojima M., Okada S.-I., Yoshizawa H., Iizuka H., Tanaka T., Muchmore E.E., Peterson D.A., Ito Y., and Mishiro S., Virology *190*, 894–899, 1992.
293. Ogata N., Alter H.J., Miller R.H., and Purcell R.H., Proc Natl Acad Sci USA *88*, 3392–3396, 1991.
294. Ina Y., Mizokami M., Ohba K., and Gojobori T., J Mol Evol *38*, 50–56, 1994.
295. Krushkal J. and Li W.-H., J Mol Evol *41*, 721–726, 1995.
296. Masuko K., Mitsui T., Iwano K., Yamazaki C., Okuda K., Meguro T., Murayama N., Inoue T., Tsuda F., Okamoto H., Miyakawa Y., and Mayumi M., N Engl J Med *334*, 1485–1490, 1996.
297. Li W.-H. and Gojobori T., Mol Biol Evol *1*, 94–108, 1983.
298. Li W.-H., Gojobori T., and Nei M., Nature *292*, 237–239, 1981.