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Dear Bob,

While time is passing, it is clear that our planned joint paper on proteins is as obsolete as the other one. Thanks to sequence data, the scientific community knows that LAV and HTLV-III are remarkably similar. Flossie should not have been surprised by my letter, since at the NCI meeting of December 6, I told her that we might not co-sign her paper. Wasting time on both sides should have been avoided from the beginning, if in one of your Science papers of May 1984, you had published the comparison with the LAV1 sample you had received from us six months earlier. I am not interested in pursuing an endless polemic with you, but I wish to re-establish the scientific truth, even though this implies the demonstration that you were or you are wrong. After all, your laboratory, not mine, has spent a lot of energy, time and money to show homology with HTLV1 and 2.

You and Robin Weiss make a big fuss about two sentences we wrote on the possible homology with HTLV1 and 2. We always had an open mind on this, without "a priori" conception. The difference between you and us is that we have corrected these statements (which were not the main subject of the papers) in further papers, when we faced facts which did not support our earlier interpretation.

1/ In the Science paper of May 1983 - Immunofluorescence reactivity of the patient's serum with your HTLV-I transformed cell lines : this fluorescence disappeared after further passage of the cells, and we explain it in detail in our paper of Ann. of Virol., March 1984 (enclosed reprint).

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(Homo)

2/ The homology with HTLV2 DNA (Science 225, 301-323, 1984) : In our paper on the cloning (Nature 312, 757-760, 1984), we say that it must have been an artefact as a co-cultivation. I am still waiting for a public explanation by you of the following disputed results :

a) Homology of HTLV3 c-DNA with the PX region of HTLV-I (Arya et al., Science 225, 927,1984).

b) Antigenic cross-reactivity between the major core proteins of HTLV-II on the one hand and that of HTLV-III on the other hand : not confirmed by sequence data.

c) HTLV-III has no p19 (Science, May 1984) : we had already published that LAV had p18 (Ann. of Virol., March 1984). Now, you admit that p24/25 "has immediate juxtaposition to the aminoterminal protein" (p17, p18 ?). Your earlier statement has never been corrected.

If you believe in sequence data, why don't you leave off your previous dream and admit that the AIDS virus is not an HTLV strain ? Let me quote you : "our provisional nomenclature refers to each strain of HTLV in the order of establishment as a separate strain by roman numeral, followed with letters for the patient or cell line" (Jal. N.C.I. 69, 1211, 1982).

Here is the long (although not exhaustive) list of differences between Lymphadenopathy/AIDS virus and the HTLVs :

* No significant sequence homology that is unique to HTLV-I.

* Two extra genes (orfs), one of which is half-encoded by the LTR. I note that no open reading frame is found within U3 from Starcich et al. (Science 227, 538, 1985).

* Pol and env do not overlap, they are interrupted by orfQ and an intergenic region, a unique situation for the time being. Even in a drosophilia copia-like element orf.2 (pol-like) and orf.3 (env.like) overlap !

* The protease domain is part of pol, unlike HTLV-I, BLV and of course RSV.

* Evolutionarily the endonuclease domain of pol is most distantly related to all the other retroviruses. HTLV/BLV find themselves more closely related to SMRV, MMTV and RSV !

* Most importantly, the different LTR structure :

  a - U3, R and U5 are different in size. Despite ideas of ancestral viruses, U5 would still be only 40% that of HTLV-I, -II and BLV. Caution, U3 would be much shorter.

  b - There is an AATAAA sequence at the end of R.

  c - No long direct repeat sequences.

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d - tRNA lysine as (-) strand primer.

e - different IRs.

f - the AIDS virus causes a fine bp duplication upon integration, HTLV-I six.

g - a very different PU tract which is also found at the end of pol, suggesting discontinuous (+) strand synthesis.

The similarities you are mentioning are superficial or not specific of human retroviruses :

- Mg^{++} requirement of reverse transcriptase (what about RSV, MMTV, Visna and SMRV ?)

- Trans-acting elements : also present in Lentiviruses and perhaps others

- T lymphotropism : many animal oncoviruses are lymphotropic. In T lymphotropic retroviruses, it would not be surprising to find homology in the LTR with enhancer sequences of genes expressed in T cells. But there is another molecular basis for the T4 tropism of LAV/HTLV3, which is not shared by HTLV1 and 2, the binding to T4 molecule. The T4 tropism of HTLV1 and 2 have never been directly demonstrated. The final phenotype of the HTLV transformed cell lines is T4, but nobody has shown what was the phenotype of the initial target cells.

From your last paper in Science, it seems that you accept now to place HTLV-III in the Lentiviruses subfamily of retroviruses, as we suggested earlier on the basis of similar morphology and cross-reactivity with EIAV. But such a classification is antinomic with that of the HTLV "family". HTLV are oncoviruses, with C-type morphology.

Now, I wish to respond to a manoeuvre of you and Robin : "We are the first to call this virus Human Lymphotropic retrovirus and therefore HTLV". When we had no proven evidence that the virus was the causative agent of AIDS, we defined it by its main property known then, T lymphotropism. We never used the initials of HTLV. The initials of HTLV have been coined by you for Human T-cell Leukemia Virus and accepted by an international group, including Japanese workers (Science 222, 1178, 1983). No mention in this published letter of the way of naming future viruses ! LAV and IDAV were terms defining the association with diseases. We proposed this name at Cold Spring Harbor in September 15. 1983, and used them in our further publications (Ann. of Virol., March 1984 ; Lancet i, 753, 1984) before your own publications on HTLV-III.

Since LAV has more widely been used in literature than IDAV, we have kept LAV for all AIDS and LAS viruses. We have now definite evidence that such viruses cause more frequently LAS (or ARC) which are most often benign diseases, than AIDS.

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Therefore, I am proposing now to keep the initials LAV, standing for Lymphadenopathy/AIDS virus. This is an accurate definition of the virus by its main pathogenicity (as for most retroviruses) and which will not frighten infected people, since the more frequent pathogenicity is benign. In renaming this virus HTLV, you have induced a lot confusion amongst unaware people. It will help them and not diminish your prestige if you state clearly that your earlier interpretation has to be corrected.

Sincerely yours,

Luc

L. Montagnier, M.D.