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LILLE, LE 10/5/91

ROCKEFELLER UNIVERSITY
1991

Dr. Joshua Lederberg

Dear Dr Lederberg,

Thank you for your Fax from May 9. I did not want to influence you in any way by mentioning that this paper had been successively submitted to - and rejected by - Nature (submitted November 27, 1990; resubmitted February 5, 91; rejected February 8) and Science (submitted February 28; rejected April 10). I hope you will excuse me if you consider this to have been inappropriate. I was puzzled by the very different reasons for rejection by Nature and by Science, and felt I should let you proceed with review from your own perspective.

I am enclosing the editor and reviewer comments from Nature and from Science, and give you a brief chronological account.

I submitted the first version of my hypothesis in May 90 to Immunology Today's Editor, who commissionned it, depending on reviewer approval, for publication in the April 91 issue.

In November 90, we submitted the experimental work performed on the basis of this hypothesis to Nature. One reviewer was supportive and recommended publication, the second was very critical. On January 18, 91, the editors proposed that we submit a revised version. After resubmission, the paper was rejected without reconsultation of referees. Since the editor's letter (enclosed) was obscure I called, and was told that, since T cells from HIV-infected individuals did not behave exactly as normal immature thymocytes, the editorial board felt that our paper was not of sufficient general interest for Nature's readership.

We then submitted our paper to Science, with additional data that had not been asked for by Nature, including results on purified CD4+ T cells, and antigen-mediated deletion of T cells. The reviewers did not make any criticism similar to that of Nature's editors, but asked for clarifications and for a lot of additional data, including investigation of patients with other diseases, and testing of potential causal mechanisms that may lead to the priming of T cells for activation-induced death.

The paper was rejected on April 10 by the editor on grounds of insufficient enthusiasm of the referees, the letter precluding resubmission.

The modifications we have included in the paper that I submitted to you for PNAS are: 1) statistical significance in T cell proliferation (fig 1 and 5) and death (fig 2) assays; 2) anti-CD28 mab control, and two additional HIV-infected individuals in Table 1; 3) Comparative percentage of dead cells in total PBMC, versus CD8 or CD4 T cell depleted PBMC, and purified CD4 or CD8 T cells (fig 3 a. and b.); 4) mention, in the discussion, of our preliminary results showing that pretreatment of normal CD4 T cells with anti-CD4 antibody or gp120 does not result in their priming for activation-induced death, and that anti-interferon γ antibody do not prevent activation-induced death of T cells from HIV-infected individuals.

The two Science ~~reviewers~~ reviewers also asked for investigation of activation-induced death in T cells from patients with other infections or inflammatory diseases. Although this obviously is an important question, that we are investigating, it represents an entire research field in itself, and I feel it hard to consider it just as additional data to be included in this paper. This is also true for the identification of the mechanism that is involved in vivo in HIV-infected individuals in the priming of CD4+ T cells for apoptosis. We are working on both questions, as well as on the additional possibility that activation-induced T cell death might account in normal mature T cells for regulatory mechanisms

that have been previously described as suppression and anergy.

I thank you again for your kindness and help, and hope that you will forgive me for having thought appropriate not to tell you from the beginning the whole story of this work.

Sincerely Yours

[signature]

PS Thank you for the reference on ATP-induced apoptosis, and for the reprint of your work.