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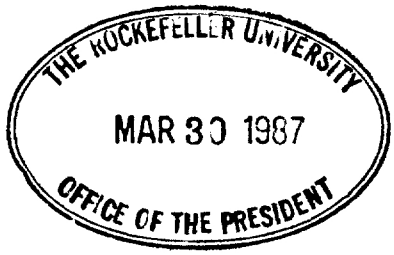

Dr. Joshua Lederberg
President
Rockefeller University
1230 York Avenue
New York, NY 10021

Dear Josh:

David Hamburg had written me relating to the husband of one of his former students (I believe he has sent you a copy of his letter to me). I thought you might be interested in the follow-up. I am also enclosing, for your interest, the articles I sent to Dr. Benedict as well as a copy of an article specifically related to therapy which is scheduled for publication in the New England Journal of Medicine next month.

I was interested in your thoughts about approaches to AIDS. There are two areas that we have been considering in relation to this disorder.

First, as you know, although originally it was thought that the CD4+ (helper/inducer) T-lymphocyte was the only target cell of the virus, it is now recognized that mononuclear phagocytes (including human alveolar macrophages) can be infected with the virus (perhaps because the alveolar macrophage also expresses the CD4 antigen). In this context, since the alveolar macrophage plays a major role in defending the lung (and one of the major problem these individuals eventually die from is lung infection, particularly with opportunistic organisms), HTLV-III infection of normal human alveolar macrophages would be an interesting model in regards the effect of integration of the virus into the alveolar macrophage genome and its effect on other macrophages genes (i.e., is the insertion random, are certain classes of genes more selectively affected, etc.).

Second, we have been interested in the concept of very restricted subsets of T-lymphocytes as being targets (as well as effectors) in disorders of the lower respiratory tract. For example, in sarcoidosis, we have evidence that there is a limited clonal population of T-lymphocytes that may be involved in the disorder (see attached paper submitted for publication). In AIDS, despite the fact that the CD4+ lymphocytes in the blood are decreased in number, there is an expansion in the numbers of lymphocytes in the lung, particularly CD8+ (suppressor/cytotoxic) T-lymphocytes. This is of interest because (although not described in the paper I have enclosed) we have some recent evidence that in sarcoidosis at least some of the "clonal" T-cells found in the lung are

CD8+, despite the fact that the disease is one in which there is an accumulation of CD4+ T-cells at the site of disease. This has let us to wonder whether or not there may be very limited subsets of CD8+ T-cells that are involved in inflammatory reactions in organs (such as the lung) generally i.e., very restricted T-cell subsets that "direct" these chronic inflammatory reactions. With our ability to recover compartmentalized populations of T-cells from the lower respiratory tract and compare those with the blood, it may be possible to clone (using single cell cloning techniques) the important representatives of these regulatory T-cells subsets. As an alternative approach, we have already made a genomic DNA library from the T-cells of the lower respiratory tract of a patient with very active sarcoidosis. This is being used to attempt to "pull-out" the rearranged genome of the T-cell antigen receptor β-chain involved in such regulatory T-cell subsets.

I am looking forward to discussing this in more detail with you when we meet again.

Sincerely yours,

Ronald G. Crystal, M.D.
Chief, Pulmonary Branch
National Heart, Lung, and Blood Institute

Enclosures (3)

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