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Invited speaker presentation

Toward an HIV preventive vaccine: problems and prospects

Robert C Gallo

Address: Institute of Human Virology of the University of Maryland School of Medicine, MD, USA

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The special challenge for a successful HIV vaccine is due to HIV DNA integration, HIV variation, and its early harm to the immune system. Though easy to describe, the challenge is uniquely difficult compared to past successful vaccines. However, most if not all current and past vaccine candidates have not taken these features of HIV into account. What is needed and has been needed for over two decades are: (1) far more availability of primates and to a broader number of scientists; (2) an immune response which is sustained; (3) an immune response which is broad and results in sterilizing immunity or close to sterilizing immunity. The key, of course, is finding the right immunogen.

At IHV we (with G. Lewis, A. DeVico) and our collaborator at Profectus BioSciences, Inc. (T. Fouts and J. Eldridge) and at Advanced BioScience Laboratories (R. Pal) have focused our attention on a complex of gp120 and the region of CD4 (DID2) binding to gp120. Chiefly, this has been by expression of a full length single chain (FLSC) of gp120 (Bal) and human or rhesus DID2 separated by a run of sequences encoding 20 neutral amino acids. The goal was to make a fixed transitional state form of gp120 which exposes surface portions that interact with CCR5. These CCR5 binding regions are originally hidden both by their interior location in gp120 and by carbohydrate. These regions are conserved and functionally required for CCR5 binding. Consequently, the hypothesis is that epitopes derived from this region, referred to as CD4 induced epitopes (CD4i) may stimulate broad neutralizing antibodies.

In vitro studies of antibodies induced in uninfected small animals supported this concept. This was followed by three challenge studies in rhesus macaques using a SHIV162p3 challenge and vaccinating with protein derived from FLSC expressed in 293 human cells and with rhesus CD4 sequences. The results showed no sterilizing immunity but ultimate protection against this heterologous challenge. Protection correlated with CD4i antibodies but not with antibodies to gp120 (alone), soluble CD4, or conventional neutralizing antibody activity. We propose that these antibodies may have acted by ADCC activity rather than by interfering with HIV cell entry. Other studies showed that protein derived from FLSC expressed in CHO cells did not provide protection suggesting that different glycosylation forms of gp120 may yield gp120/CD4 complexes with different forms.

Further studies are in progress to verify ADCC activity, to increase the titer and sustainability of these CD4i antibodies and to verify their role in this candidate vaccine by using monoclonal CD4i antibodies in passive immunization.