HIV Research and nef Alleles

R. C. Desrosiers and E. Hunter (Letters, 31 May, p. 1231) suggest that laboratory scientists should work with strains of human immunodeficiency virus 1 (HIV-1) that contain nef deletions. They argue, on the basis of the recent finding by Desrosiers and his colleagues (1), that strains of simian immunodeficiency virus (SIV) with nef deleted have decreased virulence and that using strains of HIV-1 with nef deleted will reduce the risk of disease after laboratory exposure and infections.

I disagree with this suggestion. Our current understanding of nef does not permit the conclusion that strains of HIV-1 with nef deleted are nonpathogenic or even less pathogenic in humans. The use of such strains for the purpose of increased safety may foster a false sense of security among those who work with the virus and encourage them to relax their vigilance. The consequence to laboratory workers of working with HIV-1 with nef deleted may be to increase rather than to decrease the actual risk of working with the virus.

It is not yet certain that the SIV with nef deleted described by Desrosiers and his coworkers (1) is nonpathogenic; the mutant virus may be only reduced in its pathogenic effects. The small number of monkeys used in the study and the limited amount of time they were observed make it difficult to extrapolate the effect of SIV in monkeys to that of HIV-1 in humans, particularly when safety practices are at issue.

Variation of the effect of different nef alleles in HIV-1 replication has been shown (2). Some nef alleles speed viral replication in cell cultures, whereas others retard replication. Regions of the HIV-1 genome outside of nef modulates nef effects on viral replication.

The use of laboratory-derived strains of HIV with nef deleted for drug screening tests is also undesirable. Laboratory strains of HIV-1 were used as a basis for the introduction of soluble CD4 as a therapeutic modality. We now know that the sensitivity to soluble CD4 of those strains does not correspond to the sensitivity of primary isolates (3). It is clear from this experience that it is important to use primary virus isolates and primary cells for antiviral drug screening. Indeed, if nef is important for pathogenesis, an important class of anti-nef drug would be missed in a screening based on a virus with nef deleted.

The greatest quantity of HIV-1 virus grown is for use in diagnostic testing and in vaccine trials. Viral antigens can be produced relatively safely by using recombinant DNA techniques. Rather than using virus with nef deleted, researchers should substitute, whenever possible, antigens produced by recombinant DNA technology for antigens prepared from the virus itself.

It is critical that those seeking to develop antiviral drugs and those hoping to gain insight into HIV-1 replication and pathogenesis remain fully conscious of the risk they take in working with this deadly pathogen.

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The recent letter by Desrosiers and Hunter was disturbing in its advocacy of the use of HIV mutants with nef deleted in laboratory procedures. The authors state that in the simian system, this type of manipulated viral strain is not associated with the development of disease (1). Thus, they conclude that the strain with nef deleted is attenuated. They disregard two important issues: (i) the function of the nef gene may not be similar in SIV and in HIV, and (ii) in their study, the SIV strains with nef deleted regained their nef gene expression, but changes in other gene products (that may be more important in pathogenesis) were not monitored. Our data with nef mutants of HIV, for example, suggest quite different conclusions (2). HIV- 1_{SF2} with a deletion in the nef gene replicates to much higher levels and is more cytopathic in culture than is the wild-type nef-containing virus. Moreover, we have determined that, when nef is expressed in T cells, HIV replication can be markedly suppressed, most likely at the transcription level (3). Thus, at least with some HIV strains, nef may help "silence" the virus and its pathogenesis. Data on HIV and SIV from other laboratories (4) also argue against the use of nef-mutant viruses as potentially more attenuated or less pathogenic strains. In these cases as well, the nef gene appears to inhibit virus expression.

Obviously, more work in this area needs to be conducted before there can be a recommendation that a particular HIV strain should be used in the laboratory for safety reasons. In principle, an attenuated strain for use in commercial endeavors or for killed vaccines (if appropriate) would offer an obvious advantage. We have described an HIV-2 strain that does not kill lymphocytes, does not down-modulate CD4, and is not cytopathic in culture (5). Future studies of this virus in primate species may determine its potential lack of pathogenicity in a host and its potential value as an attenuated strain. In the meantime, caution should be used concerning the recommended use of HIV strains on the basis of limited observations in primates or tissue culture studies.

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LBL Helmsman

I am writing to correct the erroneous impression given by the caption "Jumping ship . . . " under my picture in the 14 June News & Comment article "Bell Labs: Shakeout follows breakup" (p. 1482). When I left Bell Labs in September 1989, it was to accept an exciting research management opportunity as director of the Lawrence Berkeley Laboratory.

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Erratum: In figure 4A (p. 1024) of the report "Alteration of α l Na⁺, K⁺-ATPase ⁸⁶Rb⁺ influx by a single amino acid substitution" by Victoria L. M. Herrera and Nelson Ruiz-Opazo (31 Aug. 1990, p. 1023), the 5' and 3' end labels were inadvertently interchanged.

Erratum: In the heading of the review of Ingrao and Israel's The Invisible Hand (21 June, p. 1727), Ingrao's first name was misspelled; the correct name is Bruna.