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Just (don't) do it.

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Editorial

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In this issue (1) David Montefiori and his colleagues have demonstrated both how far we have come since Margaret Heckler's 1984 prediction of an AIDS vaccine within 24 months, and how far we have to go before this promise is realized. This work extends to human vaccine trials' earlier observations related to the cooperativity in neutralization between antibodies directed at epitopes located within the hypervariable V3 loop of the HIV-1 envelope, and a conformationally determined domain overlapping the CD4 binding region of the viral envelope. In this report, the investigators have begun to dissect the humoral immune response evoked by sequential vaccination of HIV-1 seronegative individuals with a vaccinia/HIV-1 envelope recombinant virus and baculovirus derived HIV-1 recombinant gp160. This effort has demonstrated that much of the neutralizing activity derived from this vaccination strategy is from antibodies directed at the V3 loop of the virus. Although this is not particularly surprising, in and of itself, given the conformational characteristics of the CD4 binding domain and the "nonphysiologic" secondary structure of the baculovirus derived HIV-1 recombinant gp160 vaccine (2), these investigations illustrate both the increasingly sophisticated mechanistic understanding of HIV-1 neutralization, and the ongoing maturation of the AIDS Vaccine Evaluation Group of the National Institute of Allergy and Infectious Diseases. Several previous human HIV-1 vaccine trials have provided primarily descriptive information cataloging various HIV-1 specific humoral and cellular immune responses. These trials have aided in the development of clinical trial methodology, and have provided safety data that have spurred an acceleration of clinical trials in this area. This trial, however, has gone a step further by providing a detailed dissection of the components of the immune responses generated and pointing out the absence of a potentially pivotal aspect of the immune response, namely, antibodies directed at the CD4 binding domain that might be expected to enhance greatly the potency and to broaden the specificity of the neutralizing antibody response.

In addition to the lessons about the nature of the immune response generated by this particular vaccination strategy, there are several other messages in this report. The first is that such intensive investigation of a relatively small human experiment has the potential to provide much more insight into where the AIDS vaccine development effort should be focused than might several much larger, but more superficial field trials in which prevention of infection is the goal. A large field trial launched because the problem is pressing, and because "vaccines" can be vialed and administered, will tell us very little in terms of where to invest the next several million dollars and several years if it is not supported with intensive hypothesis-driven, basic scientific investigations that include both a detailed immunologic characterization of the vaccines and a genotypic and phenotypic characterization of viral strains circulating in the area of the trial. Indeed, a great danger exists in terms of wasted resources and delayed development of an effective AIDS vaccine if we succumb too easily to the temptation to revert to a Nike approach to AIDS vaccine development and "Just Do It" by stripping out the science in the name of economy as larger trials are launched over the next several years. Secondly, although the vaccinia recombinant/gp160 boost regimen has provided among the most potent HIV-1 specific immune responses in human clinical trials to date, additional approaches are urgently needed. The good news is that many potentially powerful approaches to human vaccination have evolved over the past several years. These include new adjuvants, novel vectors such as attenuated salmonella, adenovirus, or mycobacterial recombinants, "naked" DNA (3), and even the possibility of the development of live attenuated HIV-1 (4). Strategies directed at eliciting immunity to the CD4 binding domain (5), as well as those directed at inducing effective humoral and cellular immune responses at mucosal surfaces are developing rapidly. The final message is that coordinated planning of the clinical trials effort is in the best interest of all involved. As novel vaccine approaches move into the clinic, it will be essential to continue to develop the capacity to generate comparative data about these approaches in early stages of development to sharpen our ability to discern which leads to follow, and to foster the unimpeded development of strategies that combine the best attributes of all available approaches. This will require the use of both standard assays performed in central laboratories, and the continued support of the kinds of innovation in the hands of individual investigative groups illustrated by this report. Finally, like the drug development effort, vaccine development will require the active cooperation and collaboration of investigators, industry, and constituency groups.

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