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Prospects for an AIDS vaccine

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Several lines of evidence indicate that development of an effective vaccine for HIV-1 is going to be, at best, extremely difficult. The inability to solve fundamental scientific questions is the root cause for why a successful vaccine is not currently within our grasp. A renewed, organized, focused effort is needed to overcome these scientific obstacles.

"Who are only undefeated because we have gone on trying."
—T.S. Eliot
The Dry Salvages

Twenty years have elapsed since the discovery of HIV and its association with AIDS. Despite much hope and promise, there is no vaccine to protect vulnerable populations around the globe. This brief commentary attempts to give a realistic assessment of where efforts stand to develop an effective vaccine against HIV-1 for worldwide use.

There is ample evidence to indicate that development of an effective vaccine for HIV-1 is going to be, at best, extremely difficult. The most promising vaccine approaches currently being forwarded in the clinic stand little chance of being effective. I present five lines of evidence to support these contentions.

Natural immune response is not effective

The natural immune response to HIV-1 is almost never effective. Individuals infected with HIV-1 mount apparently strong antibody responses and viral-specific $CD8^+$ cellular responses. Yet, HIV-1 continues to replicate week after week, month after month, eventually killing the host. It is now clear that HIV has evolved a number of specific immune evasion strategies to allow continuous viral replication (reviewed in refs. 1,2). Immune evasion strategies used by the virus include: selection for genetic variants that are antigenic escape variants; inherent resistance to antibody-mediated neutralization; downregulation of major histocompatibility class I molecules from the surface of infected cells by a viral gene product (Nef); and destruction of viral-specific $CD4^+$ T helper cells. For a vaccine to be effective, it will need to generate immune responses that are superior to the natural immune responses to wild-type HIV-1 infection. "Superior" does not necessarily mean greater in magnitude, but different in the sense that it is protective in a way that the natural immune response is not.

Failure to protect monkeys

Promising vaccine strategies making their way through human clinical trials include recombinant adenovirus and prime-and-boost protocols that use initial priming with a plasmid DNA vector encoding HIV-1 antigen(s), followed by boosting with a recombinant poxvirus or adenovirus encoding the same antigen(s). These vaccines express the viral gag protein or gag plus additional viral antigens. Although these vaccine approaches have protected against SHIV89.6P challenge in monkeys[3–5], they have failed to protect against SIV239 challenge[6]. The explanation for the very different outcomes using SHIV89.6P challenge is not entirely clear. It should be noted, however, that the pathogenesis of SHIV89.6P is not the same as that of lentiviruses, and that virtually every vaccine approach that has been tried—even immunization with peptides[7,8]—protects against SHIV89.6P. In contrast to SHIV89.6P, key biological properties of SIV239 in rhesus monkeys parallel those of HIV-1 in humans: SIV239 uses CCR5 as a coreceptor for entry into cells, is difficult to neutralize, and induces progressive declines in CD4 counts and a progressive disease course in rhesus monkeys. What is most disappointing about the failure to protect against SIV239 is that the challenge strain was matched exactly in sequence to that of the vaccine strain, and challenge occurred at or near the peak of vaccine-induced immune responses. If we cannot protect against cloned, homogeneous SIV239 by vaccines exactly matched in sequence under ideal conditions, there is little reason for optimism.

Superinfection

The failure of controlled HIV-1 infection to protect against pathogenic superinfection is illustrated by a case study published recently by Altfeld *et al.*[9] A man who was seen in the clinic shortly after exposure to HIV-1 was placed on antiretroviral therapy during primary infection. After several rounds of strategic therapeutic interruption, the man had low viral loads and quite good immunologic control of HIV-1 in the absence of continued antiretroviral therapy. Nonetheless, after a high-risk activity, the individual became superinfected with a different strain of the same clade (B) and developed persistent moderate to high viral loads. Thus, immunologic control of the first strain did not protect against superinfection and high viral load upon subsequent exposure to a different strain of HIV-1. This startling inability of a controlled HIV-1 infection to protect against superinfection by a naturally occurring HIV-1 field strain is, of course, only a single example, and it is not known how protective (or nonprotective) controlled HIV-1 infections may be in general. However, the situation described by Altfeld *et al.* is actually not very different from what

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has been observed with live attenuated, *nef*-deleted SIV. Although live attenuated, *nef*-deleted SIV has provided very good protection against homologous challenge[10,11], live attenuated, *nef*-deleted SIV239 has not provided strong protection against heterologous challenge with the SIV strain E660 (ref. 12). The degree of sequence variation between SIV239 and SIVE660 is representative of the level of sequence variation among field isolates of HIV-1.

Sequence variability

There is enormous sequence heterogeneity among individual isolates of HIV-1. The HIV Sequence Compendium, a large database of HIV-1 sequences, reveals that they can be ordered into nine discrete major phylogenetic groupings, or clades[13]. There is no evidence to suggest that individual clades represent neutralization serotypes. The vaccines in clinical trials incorporate only one, or in a few cases two, HIV-1 gene sequences. The nature of the sequences that should be included in HIV-1 vaccines—a regional consensus sequence, sequences from a representative local isolate or reconstructed 'ancestral state' sequences—has been discussed in publications and at strategic planning sessions[14,15]. The goal of these deliberations is to reduce the average sequence distance between vaccine antigen and circulating HIV-1 proteins. However, it has been suggested that HIV-1 sequences circulating in a population may largely represent cytotoxic T-lymphocyte escape variants for human leukocyte antigen types that predominate in that population[16]. This would not bode well for the ability of cytotoxic T lymphocyte–based vaccines to provide protection. In any event, we do not yet know how to construct vaccines in a way that can deal with the enormous sequence heterogeneity of HIV-1.

Failure of VaxGen trial

The results of the first phase 3 HIV-1 vaccine trials—the VaxGen gp120 trials—were released in 2003. In these trials, volunteers were immunized with a recombinant HIV-1 gp120 protein (one of the subunits of the virus envelope) in an attempt to generate virus-neutralizing antibodies that would protect against subsequent exposure to HIV-1. Vaccine and placebo recipients were followed for 30 months. The vaccine did not provide any protection against infection and did not lower viral loads. Given what we now know regarding the resistance of HIV-1 to antibody neutralization, it is no surprise that the VaxGen gp120 vaccine failed.

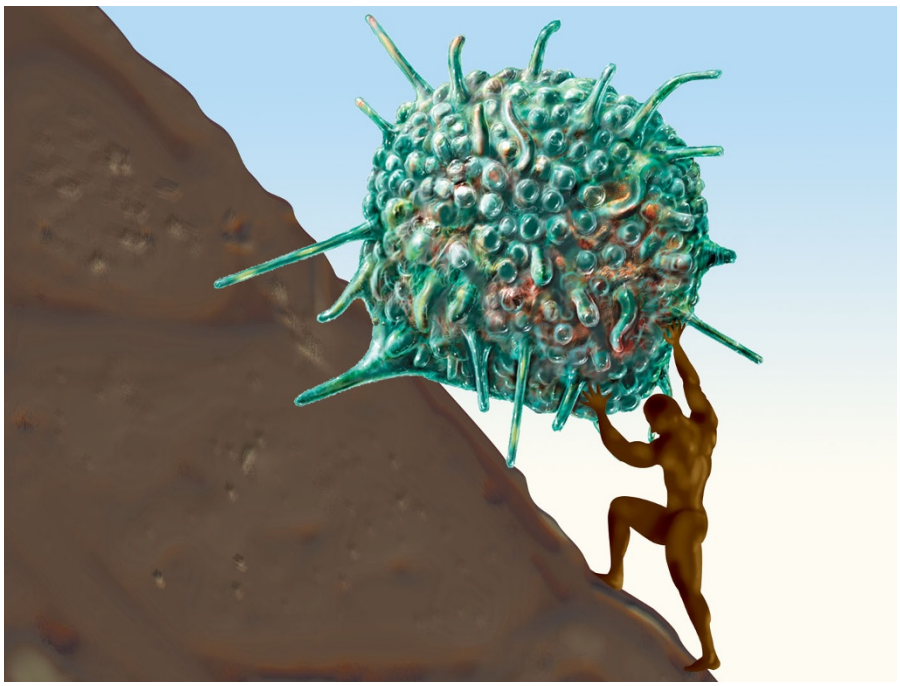

Figure 1 Modern-day Sisyphus? An uphill struggle for HIV vaccines (image suggestion: Jeff Lifson. HIV cell: Science Photo Library).

Where do we go from here?

The HIV vaccine development effort has been laregly driven by the philosophy of more products in the pipeline and more clinical testing. At present, at least 13 different products are at varying stages of clinical testing in more than 20 individual human trials. A bold proposal has been presented for a massive investment in a global enterprise to hasten the development of an AIDS vaccine[17]. The philosophy of the proposed enterprise, driven by a perceived problem with translation into clinical application, seems to embody prevailing attitudes toward what is needed: more products in the pipeline and more clinical testing. The vision of this philosophy calls for expansion of the capacity to conduct clinical trials, assurance of manufacturing capacity and harmonization of regulatory approaches. If we can get more products into clinical testing, so the thinking goes, we will eventually find our way to success. While it is true that empirical trial-and-error approaches have been sufficient for the development of other successful vaccines, it is highly unlikely, based on what we know today, that this is going to be enough to make an effective vaccine against HIV-1. The major difficulties blocking development of an effective vaccine against HIV-1 are fundamental scientific questions, not issues of manufacturing, numbers of trial sites, international site preparation or validated testing procedures.

What are the principal scientific obstacles to development of an effective vaccine against HIV-1? First, we do not know how to elicit antibodies with potent neutralizing activity. Second, we do not know how to deal with the enormous sequence variability of the virus. This sequence variability is a serious impediment to the effectiveness of both neutralizing antibody responses and viral-specific $CD8^+$ cellular responses elicited by any vaccine. Third, although live attenuated SIV has provided spectacular protection against homologous challenge by SIV239 and other such strains[10–12], we do not understand the crucial components of the protective immune response. The experiments of Lifson *et al.*[18] and recent results from my own laboratory indicate that high levels of antiviral immune responses measured in the peripheral blood by standard assays are not necessary to achieve strong vaccine protection against homologous challenge, even against strains such as SIV239. What is responsible for this remarkable protection and by what other methods can we induce this type of immunity? Finally, we do not know whether immunologic memory will ever be sufficient to protect against HIV-1. If it will not be sufficient, we need to learn how to elicit protective immune responses in a way that will persist.

If what I believe is true—that major discoveries are needed to make a vaccine feasible—then the scientific obstacles need to become the major targets of our intermediate goals. I believe that a renewed, organized and focused effort is required to deal with these funda-

mental scientific obstacles. These problems are not likely to be overcome by repeated clinical testing of weak products that stand little chance of being effective. While continued testing of feeble long-shots in the clinic is inevitable (and even useful), we need to do a much better job of bringing promising products to the clinic. Much has been made of the concept that the clinical testing process needs to be iterative. In the absence of answers to the major scientific questions, the iterative process will necessarily continue to rely on blind guesses. Although it is true that correlative analyses from human vaccine trials may help answer some of the fundamental questions, the major fundamental discoveries—if indeed they ever occur—are much more likely to come from the laboratory bench, from mice and from monkeys. The huge cost of these human trials must be weighed against their likelihood for failure and what is likely to be learned from them.

Where do we go from here? The concept of dedicated AIDS vaccine research centers roughly outlined in the proposal of Klausner *et al.*[17] would be an efficient means of achieving targeted goals. But the principal focus of such research centers should be solving the fundamental scientific obstacles. Let there be no mistake: a successful course will require enormous will, dedication in the face of doubt, lots of money, scientific leadership and a structure that will allow concerted, organized, systematic, creative solutions to the scientific problems. And even then there are no guarantees of a successful outcome. Given this pessimistic outlook (**Fig. 1**), every opportunity should be taken to think laterally. For example, prophylactic use of antiviral therapies, which has been a very successful approach in monkey trials[19], needs to be aggressively pursued in high-risk humans. Prophylactic use of antivirals has a certain feasibility that is lacking in attempts to elicit adaptive immune responses that will be protective against HIV-1.

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