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An Introduction to the Current State of HIV Vaccine Research

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Since 1987, more than 30 candidate HIV-1 vaccines have advanced to human clinical trials, of which some were large-scale phase IIb and III trials [1-3]. Of all these trials, only the Thai Phase III RV144 trial, based on a recombinant canarypox-HIV vector prime and recombinant HIV-1 envelope gp120 subunit protein, showed modest protection against HIV-1 infection [4]. This result came as a surprise because the RV144 trial, which had initially been fiercely condemned as ill-conceived and unjustified [5-7], instilled a new feeling of optimism into the field, because it suggested that developing a preventive HIV-1 vaccine may after all be feasible. Three years later, it seems appropriate to devote a special issue of the Journal of AIDS and Clinical Research to review what progress has been made in the search for a preventive HIV-1 vaccine.

The first contribution by Leopold Kong and Quentin Sattentau, entitled "Antigenicity and immunogenicity in HIV-1 antibody-based vaccine design", reviews in considerable detail the many studies aimed at developing an HIV-1 preventive vaccine by rational, structure-based design. This strategy, also known as reverse vaccinology [8,9], attempts to generate a vaccine from the crystallographic structure of broadly neutralizing monoclonal antibodies (bnMabs) bound to epitopes of the HIV-1 envelope (Env) glycoprotein.

These studies were initiated because of the availability of a small number of Mabs that recognize five different antigenic sites of the Env protein, i.e. the conserved CD4-binding site [10], the CD4-induced antigenic site that becomes accessible after Env interacts with the CD4 receptor [11], the semi-conserved V3 loop [12], the membrane-proximal external region of the gp41 protein [13] and the glycan antigenic site [14]. In subsequent years, many additional bnMabs directed to Env epitopes were isolated from HIV-1 infected persons [15-17] and had their structures elucidated by X-ray crystallography [18-22]. These bnMabs were then used as templates to reconstruct one of the epitopes that such Mabs are able to recognize using structure-based design technology. It was assumed that such reconstructed epitopes designed to fit bnMabs outside of the context of the Env antigen would possess the immunogenic capacity of inducing a neutralizing polyclonal antibody response in immunized hosts. When this was found not to be the case, attempts were made to improve the antigenic reactivity of the epitopes recognized by bnMabs using various strategies, such as adding flanking residues to the epitopes, constraining them in various conformations [23] and grafting them into various protein scaffolds [24-26].

Although some of these approaches increased the ability of the engineered epitopes to bind the bnMabs, none of these epitopes were found to be effective immunogens able to induce bnAbs [27-29].

In their discussion of these results, Kong and Sattentau suggest that the failure of the engineered epitope mimics to elicit broadly neutralizing antibodies could be due to their insufficient immunodominance, to an inadequate mimicry of the tertiary and quaternary structure present in native Env or because the epitopes possessed a low affinity for the germline B cell receptors (BCRs) present in the immunized hosts. They also stressed the basic quantitative/qualitative divide that separates the chemical description of an antigen and its biological effect on immunity. Although antigenicity can be reduced to the chemical level of an interaction between an epitope and a paratope, such a reduction is not feasible for immunogenicity which is a biological property determined mainly by the context of the host being immunized, namely its Ig gene repertoire and numerous cellular and regulatory mechanisms extrinsic to the immunizing epitope [30]. These host factors cannot be controlled when one uses as immunogen, an HIV-1 epitope designed to fit a particular bnMab since antigenic reactivity is not necessarily accompanied by the immunogenic capacity to elicit the same type of neutralizing antibodies.

The second contribution by Jason Okulicz is entitled "Elite controllers and long-term nonprogressors: models in HIV vaccine development". It reviews the characteristics of these two groups of HIV-infected individuals and discusses the issues related to their potential use as models for HIV vaccine design. Elite controllers are a very small subset of HIV-infected persons who control plasma viral load in the absence of antiretroviral therapy (ART). Long-term nonprogressors (LTNP) are somewhat more common and showed a prolonged elevation in CD4+ cell counts in the absence of ART [31]. Both elite controllers and LTNPs exhibit a high degree of heterogeneity with respect to host genetics, immunologic characteristics, rates of HIV disease progression and clinical outcomes. Although each of these two phenotypes present characteristics which one would like a vaccine to induce, i.e. virologic suppression and elevated CD4+ cell counts for prolonged periods, we unfortunately do not know how to elicit such responses by vaccination [32].

The third contribution by Hioe et al. and her coworkers from the New-York Langone Medical Center is entitled: "Targeting a neutralizing epitope of HIV envelope gp120 by immune complex vaccine". It has been known for many years that immunization with antigen-antibody complexes, instead of with antigen alone, can either up or down regulate the antibody response, although the precise mechanisms of these effects are poorly understood. Suppression of antibody responses may occur through the masking of epitopes or through the elimination of immune complexes by receptor-mediated phagocytosis. Enhancement on the other hand could result from specific Fc receptor targeting or from antibody-induced conformational changes in the antigen that exposes previously hidden epitopes [33]. Vaccines based on immune complexes have been found for instance to enhance the immune response to hepatitis B antigens in humans [34] as well as to various viral infections in animals [35]. The Hioe group immunized mice wih immune complexes of HIV Env bound to human Mabs directed to the CD4-

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binding site and observed enhanced neutralization Ab titers to Env and to the V3 loop compared to titers obtained by immunization with Env alone [36-38]. However, the mice did not produce Abs to the CD4bs because that site was blocked by the Mabs used to form the complexes. Since human IgG1 Mabs were used to form the complexes whereas the immunization experiments were done in mice, it will be important to confirm these results by small scale phase I trials in humans for human IgG1 Fc does not have the same affinity for murine and for human Fc receptors. It was also found that immune complexes, formed when an Env mutant lacking a glycan at position 448 in the C4 region was bound to an anti-CD4bs Mab, were able to elicit higher levels of neutralizing anti-V3 Abs than immunization with wild type Env complexes.

In their review the authors suggest that several mechanisms could be responsible for the enhanced immunogenicity of the immune complexes involving CD4bs Mabs, for instance an increased accessibility of the V3 epitopes, an increased resistance of gp120 against degradation by proteases or a modulation of CD4+ T cell responses to various Env epitopes. Experiments are currently in progress to determine whether a regimen consisting of DNA priming/protein boost with immune complexes could further improve the immunogenicity of HIV neutralization epitopes.

The fourth contribution by Ray Greek entitled: "Animal models and the development of an HIV vaccine" discusses the experimental evidence that animal models used for studying HIV vaccine responses are not suitable for predicting what the response will be in humans. This is a controversial issue because policy makers and funding bodies continue to demand that nonhuman primate (NHP) models should be used in HIV vaccine research as predictors of human responses in spite of the fact that there is now good evidence that these models have no predictive value [39-42]. Showing protection in NHPs is no longer accepted as a gatekeeper for advancing a vaccine product into human efficacy trials since a product that works in macaques may not work in humans while a product that shows no efficacy in NHPs could nevertheless work in humans. Unfortunately, strategies that do not work in NHPs are not tested in humans with the result that potentially efficacious vaccines may have been lost.

If NHPs are not predictive, results with less closely related species such as mice and rabbits are of course even less likely to predict human responses. The review provides an exhaustive list of 224 references to back its numerous claims. It is well-known, for instance, that chimpanzees do not develop AIDS when infected with HIV-1 and that the pathology and immune responses observed in monkeys infected with simian immunodeficiency virus (SIV) and simian-HIV virus (SHIV) differ from what is observed with HIV infection. Statistical procedures used to calculate the positive predictive value of a vaccine intervention are described and the values that are obtained clearly demonstrate that NHP models are not a predictive modality. The last section of the review analyzes the complexity of biological systems and organisms that share a fairly recent common ancestor (such as monkeys and humans) and explains why small differences in gene interactions and regulatory networks can result in vastly different outcomes to the same immune system perturbation. The take home message is that: "When it comes to testing HIV vaccines, only humans will do" [43] which implies that currently used inter-species extrapolations should be abandoned and replaced by small scale human trials to test the safety and efficacy of candidate vaccine immunogens.

The fifth contribution from Stefano Butto and his group at the Institute of Health in Rome is entitled: "Characterization of variable regions of the gp120 protein from HIV-1 subtype C virus variants obtained from individuals at different disease stages in Sub-Saharan Africa". In this study, the authors tested the hypothesis that the selection of virus variants during the course of disease is caused by changes in the sequence characteristics of variable regions of the HIV Env protein. They examined HIV-1 clade C-infected individuals, naïve for antiretroviral therapy, at different disease stages, in order to characterize the V1 to V5 variable regions with respect to sequence length, glycosylation pattern and net electric charge. In the chronic stage of the disease, they observed in the V1, V2 and V4 loops, an increase in sequence length, amino acid variability and putative N-glycosylation sites but very little change in the V3 loop as reported previously for clade C [44]. These data suggest that the V1 and V4 loops are likely to be the main drivers of clade C HIV-1 virus evolution which agrees with the finding that the V4 loop is a major target of neutralization activity in clade C infections [45].

The last contribution by Rachel Lai and Jonathan Heeney, entitled: "Perspectives in HIV vaccine development: what we have learned and how we proceed forward" reviews the advances made in HIV vaccine development in the context of the overall failure so far to develop a protective vaccine. Both T cell-based and antibody-based vaccine strategies are discussed and the limitations of reverse vaccinology are underlined. It is indeed often overlooked that all anti-HIV-1 bnMabs are polyspecific and harbor numerous binding sites capable of binding viral epitopes different from the one identified when the structure of bnMab-HIV-1 complex was solved [29]. There is therefore no reason why the HIV-1 epitope identified by crystallography should be the one that triggered the immune response that gave rise to the bnMab. Furthermore, the antigenic capacity of an epitope to bind to an Ab does not necessarily entail that the epitope also possesses the immunogenic capacity to induce that Ab in an immunized host [29]. In addition, since somatic hypermutation of germline BCRs leading to antibody affinity maturation is required to obtain bnAbs [46,47], it seems unlikely that epitopes selected because they fit hypermutated bnMabs will be successful vaccine immunogens since the corresponding affinity-matured BCRs are not present in naïve, vaccinated individuals.

Calls for a greater focus on basic and preclinical research in immunology are often made because of the belief that this will provide the knowledge needed to guide the design of an effective HIV-1 vaccine [3,48]. Basic research may indeed give us an understanding of how an immune response sometimes arises in certain HIV-1 infected persons but whether this knowledge will bring us closer to the applied research goal of developing an effective vaccine remains an open question. It may therefore be wise to continue with exploratory early phase human trials testing a variety of immunization strategies [40] rather than waiting until we more fully understand all the intricacies of various types of immune responses to HIV-1 infection.

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