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Vaccine Research Center

National Institute of Allergy and Infectious Diseases
National Institutes of Health

Development of Vaccine Research Center HIV Candidate Vaccines for the Developing World

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Meeting Summary

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INTRODUCTION AND SUMMARY

Dr. Gary Nabel, Director of the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), welcomed the international and domestic participants of this meeting and made note of the extensive scientific and regulatory expertise, talent, and perspective present at the meeting. Dr. Nabel expressed his hope for a successful consensus regarding which vaccine candidates should move forward for the developing world. An additional goal of this meeting was to obtain information about existing and proposed infrastructure available to support vaccine development and clinical trials in developing countries. The VRC now has a series of prototype vaccine candidates designed to enhance the breadth and potency of the CTL response, and to elicit neutralizing antibody responses. The VRC has also made identical versions of these constructs for various genetic subtypes (clades), including versions for clades B, C, A, and E (recombinant virus). Dr. Nabel indicated that the ultimate goal of the meeting was to help the VRC choose which of its candidate vaccines would be of most interest to developing countries.

Information was presented regarding ongoing and potential programs, trials and products by Drs. Gary Nabel, Director of the VRC; Ed Tramont, Director, DAIDS; Peggy Johnston, Assistant Director AIDS Vaccines; and Lawrence Corey, HIV Vaccine Trials Network (HVTN). These presentations indicated that the NIAID and HVTN are increasing their domestic and international programs and budgets to address the problem of AIDS, particularly prevention via vaccines. Dr. Nabel also informed participants of the VRC efforts and expertise in immunity and clinical analysis that can be shared with and transported to developing countries. Participants were encouraged to speak with Dr. Richard Koup (Chief, VRC Immunology Laboratory) and Dr. Barney Graham (Chief, VRC Clinical Trials Core) about these issues.

INTERNATIONAL PRESENTATIONS

The international presentations noted that approximately 95% of the new HIV infections are occurring in developing countries and that a vaccine is the most effective way to control the epidemic. Thus, a continued dialogue between those institutions with the expertise to develop vaccines and those countries in which testing is needed is critical to the process of development of an effective vaccine. Many questions need to be answered, such as what type of vaccine strategy will be effective, what level of efficacy can be attained, what level of efficacy will be needed, and whether viral genotype or route of transmission affect efficacy.

In order to address these questions, multiple parallel trials in different populations, as well as close and continuous international coordination and cooperation, are needed. Current trials were summarized; however, it was acknowledged that better coordination of future phase I, II, and III trials are needed to optimize the information obtained.

To provide context for the discussion, Dr. Jose Esparza (WHO/UNAIDS) and the other international participants, including Dr. William Makgoba (SA), Dr. Timothy Tucker (SA), Dr. John Nkengason (Cote d'Ivoire), Dr. Rosemary Musonda (Zambia), Dr. Cissy Mutuluuza (Uganda), Dr. Simon Agwale (Nigeria), Dr. Nirman Ganguly (India), Dr. Yiming Shao (PRC), and Dr. Luis Fernando Macedo de Brigido (Brazil), presented information regarding the status of the epidemic and clade distribution in developing countries (Table 1). It is important to note that the geographic distribution of genetic subtypes is continually changing and current data offer incomplete estimates. It is also worth noting that subtype C causes >50% of the infections throughout the world, and it is the most widely distributed genetic subtype. Also, there are numerous recombinant viruses that are not yet classified as distinct subtypes.

Table 1. Overview of Current Clade Distribution in Developing Countries

Country/Region	Clade(s)
AMERICAS	
Caribbean and most of Latin America	B
Brazil Southern Brazil	B Variants (GWGR) B and C
Southern South America (Argentina, Uruguay)	B and BF recombinants (CRF12); B is predominantly compartmentalized to gay men; BF predominantly compartmentalized to Intravenous Drug Users (IVD) and heterosexuals
ASIA	
Thailand and neighboring countries	B among IVD and CRF01 (AE) - largely in heterosexuals
India	Mostly C (variants); B increasing; all subtypes present
China	B, C, E, and BC recombinants
Japan, Australia, New Zealand	B
AFRICA	
Southern Africa (South Africa, Swaziland, Zambia, Botswana), Ethiopia	C
Eastern Africa has many recombinants Kenya Tanzania Uganda (Rakai cohort)	 70% A plus recombinants AD,AC,AG, CD 50% C; 10 % A, plus recombinants A, D Mostly A and D plus recombinants AD 70% D, 10% A, plus recombinants AD

West Africa	Mostly AG recombinants (CRF02)
Cote d'Ivoire	Mostly AG recombinants
Cameroon	Multiple subtypes and recombinants

Many countries have organizations designated to address the epidemic, and have developed the infrastructure, ongoing international collaborations, research network, and cohort populations to support clinical trials. Also, many countries have participated in other clinical trials, and some have produced other types of vaccines.

DISCUSSION OF VACCINE STRATEGIES

Dr. Nabel noted that the VRC has made several clade B constructs and comparable constructs from other clades. Discussants agreed that these constructs looked promising because of the immune responses they elicited in preclinical experiments. In addition, there was enthusiasm about the availability of constructs from various clades. Regarding the issue of geographic dispersal of genetic subtypes, presenters from each country emphasized that surveillance data show that subtypes are quickly evolving into recombinant forms and new subtypes are arising in each country. Given the dynamic changes among the viruses and the fact that it takes approximately 10-12 years to design and implement a vaccine, presenters discussed whether it is useful or feasible to develop vaccines based on each subtype.

There is a scientific need to understand the difference between clades. At the same time, there is an urgent need to develop a vaccine that can protect against a wide variety of genetically diverse viruses. It is important to note that some regions of the HIV-1 genome are highly conserved among the clades. Dr. Nabel presented information showing that while some regions of the genome are conserved, each gene product has differing degrees of sequence conservation. An understanding of this diversity is important for vaccine design. For example, when considering the genes for Pol, Gag, Nef, and Env: Pol genes from different clades are ~ 90% identical (at the amino acid level). Thus, the VRC used the same pol gene in constructs for different clades. Gag is 85-90% identical across all clades, but Nef is only 75-85% conserved, and Env is very diverse, being only 70-85% conserved. For these latter proteins, the diversity within a clade was no less than between clades.

Given the above discussion, and the fact that there is a practical limit to the number of different parallel vaccines that can be made, the majority of the participants agreed that it was not necessary to construct and evaluate vaccine candidates based on strains from each individual country. The group agreed, for example, that an African clade C could be evaluated in India, where clade C also predominates. It was noted that safety is of paramount importance. Discussion of multivalent vaccines centered on two issues: 1) will multivalent vaccines be necessary to elicit broadly effective immune responses, and 2) could there be inhibition of individual components in multivalent vaccines. Participants agreed that preclinical animal experiments, as well as phase I trials, should be performed to address these key issues.

Dr. Nabel expressed his gratitude for the informative and productive discussion and noted that a plasmid DNA vaccine candidate based on two clades (e.g. clade B and C) could be ready for Phase I testing in about one year. The participants expressed their belief that this meeting was an important first step towards international collaboration and a good chance for full discussion of the issues. The international participants also expressed their appreciation for all the NIH staff that have worked very hard on behalf of these issues.

RECOMMENDATIONS

Recommendation 1: There was consensus that testing of multivalent vaccines should proceed and that, due to practical limitations, the clades selected should be representative rather than country specific. The VRC will make production and phase I testing of a clade B/C vaccine candidate the highest priority. In addition, the VRC will initiate parallel animal studies to evaluate the immunogenicity of B/C and A/B/C combination vaccines. Clade A vaccine products will also be constructed and considered for testing as they become available. The multivalent vaccine products will be evaluated in phase I trials with the goal of advancement into Phase II and Phase III trials, if the results are promising.

Rationale: The clade C component of a vaccine candidate will be particularly useful since clade C viruses are now responsible for over 50% of the world's HIV infections and are spreading to additional countries and expanding in relative prevalence. The combination of B+C genes in a vaccine may enhance the breadth of the immune response and should be acceptable to most regions of the world. Clade A vaccine products are also under development and could be added to a multivalent vaccine product since this subtype is second most prevalent after C.

Recommendation 2: Time is of the essence. Thus, safe multi-valent vaccine candidates that elicit consistent measurable immune responses should advance as quickly as possible.

Rationale: It takes about 3 years for a country to prepare to conduct a phase I clinical trial. Thus, preparation needs to begin now for evaluation of existing vaccine candidates.

Recommendation 3: There should be comparisons of different constructs and subtype combinations in parallel trials in different geographic regions.

Rationale: Since information about the immunogenicity of any candidate vaccines (VRC's plus others) is very limited, all combinations of platforms, adjuvants, and constructs should be tested, particularly in Phase I/II trials. Parallel experiments provide the most rigorous data.

Recommendation 4: There should be international and interagency coordination of the Phase III trials.

Rationale: If possible, efficacy trials should try to maximize information by evaluating vaccine efficacy against different genetic subtypes and routes of transmission. This is a global pandemic that will require collaboration between groups with diverse resources and skills. Resources will need to be combined to address these complex studies in the most time efficient manner.

Recommendation 5: The public and leaders of countries/organizations should be informed of ongoing and planned vaccine studies and on information arising from ongoing HIV research. The relative importance of clade diversity for vaccine efficacy is unknown and requires further study.

Rationale: We do not currently know what breadth and potency of immune responses will be required to protect against diverse strains of HIV-1. Likewise, it is not clear if a broadly effective vaccine will require components from multiple clades. It may be possible for vaccines to take advantage of the conserved regions among the HIV-1 subtypes. Given the tremendous genetic diversity of HIV-1, it is not feasible to develop independent vaccines based on strains from all countries; however, there is sufficient capacity and scientific rationale to develop a multi-clade vaccine for human trials.

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