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**Global HIV Vaccine
Enterprise**

EMERGING ISSUES IN THE HUMORAL IMMUNE RESPONSE TO HIV

**(Summary of the recommendations from an
Enterprise Working Group)**

Promoting innovation and collaboration
to speed the search for an HIV vaccine

The Working Group

- ❖ Reston, Virginia, May 2007
- ❖ Organized by David Montefiori (chair), Quentin Sattentau, John Mascola, Jorge Flores and Jose Esparza with the participation of 20 additional scientists.
- ❖ Major goal of the workshop was to identify key scientific gaps and potential opportunities that have emerged since the Enterprise Scientific Strategic Plan was published in February 2005.

Statement of the problem

- ❖ HIV Env is extraordinarily cunning at evading neutralizing antibodies; however, the immune evasion strategies have vulnerabilities as imposed by fitness constraints.
- ❖ Current vaccine immunogens generate antibodies that neutralize only a minority of circulating isolates (key epitopes are either poorly antigenic or poorly immunogenic).
- ❖ Magnitude and breadth of *in vitro* neutralization that will predict protection in people is not known.
- ❖ Neutralizing antibodies might not be the only benchmark for predicting success with antibody-based HIV vaccines; i.e., other antibodies that we know little about could be protective.

- ❖ Epitope-assisted immunogen design
- ❖ Structure-assisted immunogen design
- ❖ Role of Fc receptors and complement
- ❖ Assay standardization and validation
- ❖ Immunoregulation

Epitope-assisted immunogen design:

Novel approaches have been developed that allow more precise mapping of the polyclonal antibody response in serum from infected individuals (e.g.- Desrosiers, Shaw, Mascola, Binley).

Recommendations:

- ❖ Identify and characterize these epitopes for possible inclusion as monovalent and polyvalent vaccine immunogens.
 - ✓ Targets of the autologous Nab response are highly vulnerable to antibody attack on primary isolates (i.e, they are suitably immunogenic and antigenic). Variability might be limited by fitness constraints (Deeks, Draenert).
 - ✓ The Nab response broadens over time in a subset of infected individuals to target a wide spectrum of viral variants. Is this:
 - a polyclonal response to multiple epitopes?
 - an evolving response against a single variable epitope?
 - a slow response against one or more conserved epitopes?

Structure-assisted immunogen design:

X-ray crystal structures have been determined for a few gp120 molecules and these studies have revealed important antigenic features.

Recommendations:

- ❖ Efforts are needed to obtain crystal structures of non-clade B envelope glycoproteins in their unliganded state.
- ❖ Additional efforts are needed to bridge the gap between partial crystal structures and complete topology by using electron tomography for studies of envelope glycoprotein trimers.
 - ✓ Non-clade B viruses dominate the epidemic.
 - ✓ Unliganded Env trimer spikes are the relevant targets for neutralizing Abs.
 - ✓ Transmitted variants might possess unique Env features.
 - ✓ Ultimately, the design of new immunogens with stabilizing mutations in gp120 or that comprise scaffolds of conserved neutralization epitopes on other proteins may lead to more promising antibody responses.

Role of Fc receptors and complement:

Recent findings have generated renewed interest in so-called 'non-neutralizing' antibodies that are unable to block virus entry but nonetheless exhibit antiviral activity through antibody effector mechanisms involving either Fc receptors or complement (Moog, Forthal, Trkola, Huber).

Recommendations:

- ❖ In vitro assays for these antibodies need to be standardized and validated.
- ❖ Quantitative passive transfer experiments in nonhuman primates with antibodies that exhibit different functions should be used to address the biologic relevance of these assays (e.g., Burton).
 - ✓ Epitopes for non-neutralizing antibodies are present on defective Env spikes.
 - ✓ Macrophage and dendritic cells are major portals of entry during sexual HIV transmission.

Assay standardization and validation:

New assay technologies are now widely used that are responsible for an explosion of new data that was not possible before; however, recent studies have shown that some antibodies that neutralize in the PBMC assay are not detected in assays that utilize Env-pseudotyped viruses in genetically engineered cell lines (Alving, Dimitrov, Haynes).

Recommendations:

- ❖ Efforts are needed to delineate this phenomenon, to strengthen the standardization of the PBMC assay, and to explore additional assays (e.g., cell-cell transmission).
- ❖ Quantitative passive transfer experiments in nonhuman primates are needed to address the biologic relevance of different assays.
 - ✓ It may be necessary to use more than one assay to assure that all neutralizing antibodies are detected.
 - ✓ The PBMC assay is the only assay that has been partially validated in passive antibody experiments in animal models.

Immunoregulation:

Critical gaps exist in our knowledge of B cell antigen recognition and regulatory pathways that impede a more rational development of an antibody-based vaccine. For example, broadly neutralizing antibodies in patient serum bind epitopes that are present on monomeric gp120, yet this is a poor immunogen for neutralizing antibody induction in vaccine recipients.

Recommendations:

- ❖ Studies are needed to address B-cell receptor-ligand interactions and intracellular signaling pathways that govern the production of antibody-producing plasma cells, the persistence of plasma and memory B cell, the mechanism of action of adjuvants, and host genetic associations with immune responses.
- ❖ Apply high density chip arrays to study single nucleotide polymorphisms (SNPs) and to identify genes that are associated with the wide variation in neutralizing antibody responses in HIV-1-infected individuals and in vaccine recipients.

❖ Other recommendations:

- ✓ Identify and characterize new MAbs, with special attention to MAbs from non-clade B infected individuals.
- ✓ Screen various combinations of neutralizing and non-neutralizing antibodies for possible synergism. An example is seen in how sCD4 binding rearranges the structure of gp120 to expose the highly conserved coreceptor binding domain for antibody binding and virus neutralization to occur.
- ✓ New and better SHIVs are needed that contain non-clade B envelope glycoproteins and that more closely approximate the neutralization phenotype, cellular tropism and pathology of HIV-1. These SHIVs are needed for studies of the biologic relevance of *in vitro* assays and to decide which antibodies and assays are most relevant for HIV-1 vaccine design and testing.



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