The Center For HIV/AIDS Vaccine Immunology: An International Virtual Consortium

Barton Haynes
CHAVI Director
CHAVI: Introduction and Rationale

CHAVI is:

- The NIH component of the Global HIV Vaccine Enterprise.

- To perform basic science to break impasses in HIV vaccine development research.

- To find the enabling technology for CHAVI or others to develop a practical, safe and effective preventive vaccine.
CHAVI: Introduction and Rationale

CHAVI is:

• To perform large, adequately powered studies.

• To perform work that cannot be performed with R01 grants.

• To make data and reagents rapidly available to the field.
Original Aims and Milestones

Overall CHAVI Goals
1. To elucidate early viral and immunological events and host genetic factors associated with HIV-1 transmission, establishment of productive infection, and (partial) containment of virus replication.

2. To determine correlates of SIV immune protection in primates.

3. To design, develop, and test novel immunogens and adjuvants that elicit persistent mucosal and/or systemic immune responses in humans and primates.

4. To evaluate HIV-1 vaccine candidates in early phase clinical trials.
CHAVI Study Populations

To study the correlates of protective immunity in:

• Acutely HIV Infected Patients (All prior to seroconversion) followed over 2 years-CHAVI 001, 012

• Exposed and Uninfected Subjects-CHAVI 002, 003, CHAVI 004, 007

• Chronically Infected Subjects-CHAVI 004, 008, 006

• Autoimmune disease patients-CHAVI 005

Led by Mike Cohen with support from Family Health International
Major Concepts To Be Addressed By CHAVI-Host Response To HIV

- Role of innate immune responses in protection from mucosal transmission of HIV - Seph Borrow, Nina Bhardwaj, Marco Colonna and Team

- Correlates of immunity in NHP - Norm Letvin, Louis Picker, Julie McElrath

- Structure of native trimers - Joe Sodroski, Stephen Harrison

- Ability of vaccines to accelerate innate and adaptive immune responses to HIV: T, B, Innate and Mucosal Teams

Constantly relating the findings to vaccine design.
Studies in Acute HIV-1 Infection Patients

- CHAVI 001- NC, Durban, Aurem Health, Univ. Witswatersand, Lilongwi, Blantyre
  enrollment begun in NC, Witswatersand, Durban, Lilongwi
- CAPRISA cohort
- Trinidad cohort
- NC cohort
- US Blood Bank Industry AHI patients- 160 patients
Epitope Specific and Other Env Assays For Analysis of HIV-1 Antibody Responses

**Competitive Inhibition Assays:** 2F5, 2G12, 13H11, sCD4, 1b12

**Direct binding ELISAs:** V3 of group M and clade B and C consensus; 4E10 MPER

**Neutralization:** CD4i, 2F5, 4E10, other MPER, autologous

**Luminex:** HIV-1 gp160, 120, p65, p55, gp41, p31, p24, p17

**Isotype Assays:** IgG1, IgG2, IgG3, IgG4, IgM, IgA
Key Questions to Address:

Binding Antibodies and HIV: Antibody Type and Antigen Specificity

- What are the specificities and types of antibodies elicited during acute infection? What are the kinetics of these different responses?

- Do HIV-specific IgA and IgM appear during acute infection? Can sensitive and reproducible assays be developed for this measurement?

- What are the functional abilities of the different binding antibodies?

- What concentrations and types of antibodies are present at mucosal sites (vaginal, seminal, saliva) compared to serum/plasma?
Summary Of Antibody Responses Immediately Following Acute HIV-1 Infection

Days Of Observation

Viral Load Or Antibody Responses

0 10 20 30 40 50 60 70 80

-20 -10 0 10 20 30 40 50 60 70 80

Viral Load

Transmission

Autologous NAb

CHAVI
Summary of IgG Antibody Responses Immediately Following Acute HIV-1 Infection

Viral Load Or Antibody Responses

Days Of Observation
Timing To Peak Anti-HIV-1 Env Antibody Responses in Humans

Gp41: 42 days

V3: 52 days

CD4 Binding Site: 65 days

Autologous Neutralization: 20 wk to >1 yr
• Utilization of consensus based envelope antigens may be a key factor in the detection of this early IgA response.

• The timing of analysis during acute viremia may be a key factor since IgA decline is observed within a 10 day period. Samples are depleted of IgG to enhance detection of responses.

• The pattern of the rise in the HIV specific IgA response shown here is representative the 13/13 patients studied to date.

(To be presented at the HIV Keystone Symposium, Yates et al. 2007)
Plans for Genetically Engineered TZM-bl Cells for Measurements of FcR-ADE of HIV-1 Infection

And major polymorphisms
Collaborators: The Team

• The CHAVI Scientific Leadership Group
  Myron Cohen
  Norm Letvin
  Andrew McMichael
  George Shaw
  Joe Sodroski

• NIH Program Staff- Stuart Shapiro, Peggy Johnston, Ed Tramont, Carl Diffenbach, Jim Bradac, and Team

• CHAVI Scientific Advisory Board- Peter Doherty, Chair

• The entire CHAVI Team- Core and Discovery Team Leaders, Collaborators, Research and Administrative Staff (~400)
  Kelly Soderberg, Ralph McCaughan, Jackie Quay

• All Members of the Global HIV Vaccine Enterprise

• Patients in CHAVI Protocols
Collaborators on the B Cell Discovery Team

**Duke**
Barton Haynes
David Montefiori
Georgia Tomaras
Tony Moody
Nancy Gasper-Smith
Thomas Kepler
Garnett Kelsoe
Mattia Bonsignori
Kent Weinhold
Charles Hicks

**UNC**
Mike Cohen
Joe Eron

**SCHARP**
Craig Magaret
Doug Glover
Steve Self and Team

**National Center for Inf. Diseases, Johannesburg, SA**
Lynn Morris and Team

**Univ. of Kwazulu-Natal**
Salim Karim and CAPRISA Team

**Tulane**
James Robinson and Team

**Harvard**
Joe Sodroski and Team
Steve Harrison and Team
Norm Letvin
Joern Schmitz

**UAB**
George Shaw and Team
Beatrice Hahn and Team

**Los Alamos National Laboratory**
Bette Korber and Team
Alan Perelson
This CHAVI web site is http://www.chavi.org