

AIDS Vaccine 07, Seattle, August 20-23, 2007



**Global HIV Vaccine
Enterprise**

**EMERGING ISSUES in
mucosal and innate immunity to HIV
(Summary of the recommendations from an Enterprise
Working Group)
Thursday 13.30 Grand Ballroom**

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

The Working Group

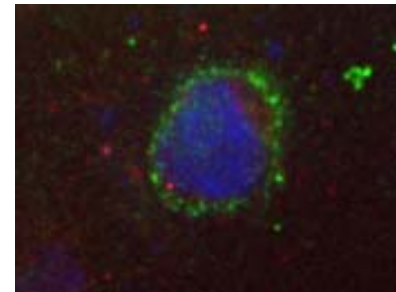
- Durham NC, June 2007.
- Organized by Barton Haynes, Robin Shattock, Bali Pulendran, Jorge Flores and Jose Esparza.
- With the participation of 27 scientists from the USA, Europe, Canada, South Africa and Asia.
- Major goal of the workshop was “*Improving Defences at the Portal of Entry*” with specific emphasis on “*Mucosal*” (section I) and “*Innate Immunity*” (section II).

Section 1.

1. The mechanisms of HIV infection across mucosal surfaces and the ability of immune responses to modulate these events.

A number of critical questions remain unanswered

- The relative role of cell free vs. infected cells in mucosal transmission,
- The potential mechanism of viral transport across mucosal surfaces,
- The identity, frequency, location and role of the primary targets,
- The relative importance of these by mucosal route,
- The relative impact of mucosal responses on these different pathways.



- *Develop tools for tracking the earliest events in HIV transmission and dissemination.*
- *Cross reference and standardize cellular, tissue and non-human primate models of mucosal transmission*
- *Develop better and more relevant panels of HIV and SHIVs from transmitted sequences for human cellular, tissue and NHP studies*
- *Evaluate the impact of vaccines on initial events and determine the point at which infection can be aborted.*

2. Elucidation of acute mucosal events that need to be prevented or subverted by HIV vaccines

- Acute infection leads to rapid depletion of CD4 T cells within the GALT
- is this paralleled at other mucosal sites?
- The underlying mechanisms are not fully understood.
- Little is known about the impact of immune response (innate and adaptive) in their modulation
- or whether infection can be prevented or aborted
after their initiation

- *Define why HIV fails to induce robust HIV-specific mucosal IgA and IgG responses in acute HIV/SIV infection*
- *Monitor mucosal immune responses, T-cell depletion and gut permeability in naïve NHP*
- *Determine the mechanistic features that render the GI tract permeable to bacterial products*
- *Define key differences following vaccination*



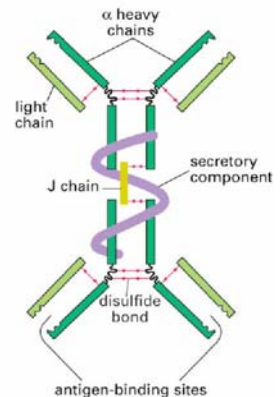
3. Defining the role of the common mucosal system in protection

- Is the central dogma that protection is best primed by mucosal vaccination valid?
- Can systemic immunization induce protection at mucosal surfaces?
- Is this better achieved with mucosal priming and/or boosting?
- Is it possible to determine the point of protection in vaccinated animals?
- Cross comparison between NHP and human trials (and the tools to facilitate this) is seen as vital.

- *Establish a broad paradigm of the commonalities of the mucosal immune system*
- *Determine the role of mucosal immunity in protection afforded by parenteral vaccines*
- *Define the potential of mucosal immunization in different prime-boost strategies*
- *Establish the role of mucosal antibodies in prevention of mucosal transmission*

4. Characterization of protective mucosal antibody responses

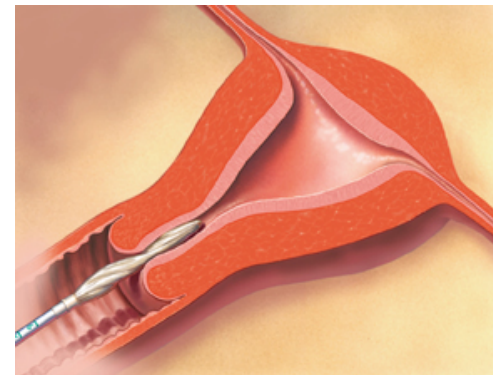
- Are neutralizing antibodies the only responses contributing to robust protection?
- Do other functional characteristics have equal or additional importance at mucosal surfaces?
- How is this modulated by antibody isotype?
- What is the role of locally produced antibodies?
- How much spill over of systemic antibodies is there into mucosal compartments?
- Are luminal antibodies important?



- *Optimise tools for detecting mucosal humoral responses*
- *Determine the role of local versus systemic antibodies in mucosal protection*
- *Define the role of antibody isotype in these events*
- *Characterise their efficacy against cell free virus and infected cells*
- *Determine the impact of immune complexes on transmission and vaccine induced responses*
- *Define the kinetics of protective antibodies- induction, duration*
- *Determine the concentrations needed for an effective response.*

5. Definition of the role of T-cell responses in eliciting mucosal protection

- Can we improve the tools for measuring T cell responses?
- Is there any compartmentalization of T cell responses that would require differences in prime/boosting by vaccines?
- What are the relative contributions of specific mucosal memory vs. effector cell numbers to the robustness and duration of protection.
- What are the correlates of protection and/or non-progression in elite controllers (systemic/mucosal)?



- *Establish optimized technology for evaluation of mucosal T cell responses*
- *Perform in depth comparison of mucosal and systemic responses following acute infection and vaccination*
- *Define any correlation with protection/viral control*
- *Characterize the role of durable low-level infection (vectors, attenuated virus) in inducing mucosal T cell responses*
- *Define the correlates of non-progression in elite controllers*

Section 2

Roadblocks to inducing protective innate immunity to HIV-1

- Innate immune responses occur within minutes or hours of pathogen entry
- Innate antiviral factors (intracellular and secreted) modulate viral replication
- Their role in modulating transmission/susceptibility is not fully understood
- Most vaccines activate specific innate immune receptors.
- TLRs and non-TLR pattern recognition receptors play critical roles in modulating the strength, quality and persistence of adaptive immune responses.
- Their role in inducing protective systemic and/or mucosal responses has not be fully realized

1. Harnessing TLRs and non-TLRs in HIV vaccine development

- *Elucidate how innate immune activation controls the quality of adaptive immune responses.*
- *Determine how to use TLRs, non-TLRs to induce protective immune responses, systemically and at mucosal surfaces.*
- *Learn how to exploit such knowledge in the generation of new vaccines against HIV.*
- *Use systems biological approaches to identify signatures of early innate immune activation that can predict the immunogenicity of vaccines.*

2. The role of innate cells in mediating the interface between innate and adaptive immunity in HIV.

- *Characterize the role of innate antiviral cytokines in modulating adaptive immune responses to HIV*
- *Determine if NK, NK-T, gamma/delta T cells have biologically relevant roles in control of HIV-1 during the transmission event.*
- *Determine if innate B cells (B-1) can be induced to rapidly produce protective antibodies in response to AHI by previous vaccination.*

3. Understanding the role of innate immunity in early HIV infection

- *Role of innate antiviral cytokines in curtailing early HIV infection*
- *Role of innate intracellular antiviral factors in controlling early replication*
- *Role of other innate immune cells – NK, macrophages, marginal zone, B-1 B cells in mediating innate and adaptive immunity to HIV in early infection*
- *The ability of these responses to halt or abort infection*



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