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HIV Vaccine Development in the Post STEP/Phambili Era

AIDS Vaccine 2008 Meeting

Cape Town, South Africa

October 14, 2008

Big Picture Issues

- Should clinical trials in humans continue?
- Should we still try to develop T cell based vaccines?
- Should we just wait for antibody based vaccines?
- Why did the MRK Ad 5 gag/pol/nef vaccine fail?
  - Was the increased acquisition in Ad 5 seropositive uncircumcised men real?
  - Was this all lack of circumcision or did Ad5 immunity have something to do with this?
  - Why did we not alter post acquisition viral load?
- If the answer to several of the prior queries is yes, then what studies do we do next?

Should Clinical Trials in Humans Continue?

- Both NIH Summit and Enterprise meetings have confirmed that studies of the immunobiology of HIV vaccines must proceed in humans.
- NHP model is useful, but to date this model neither accurately predicts immunogenicity nor efficacy in humans.
  - This does not mean work in this arena should be reduced; HVTN/CHAVI/NIAID are supporting an initiative ($9.5 Million) to better link the field for young investigators.

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Should Clinical Trials in Humans Continue?

Answer:

Definitive and of course a knowledgeably biased – Yes!

Should We Just Wait For Antibody Based Vaccines?

- It would be great to have novel immunogens that neutralize tier 2/3 viruses
  - While significant progress is being made we are not there yet.
- Should we place all our eggs in the antibody basket alone?
- Genital HSV-2 vaccines were immunogens that neutralized all clinical isolates in US and Europe at levels that equal the tier 2/3 neutralization target we have established for an HIV vaccine
  - Also elicited high levels of ADCC antibodies
  - Yet, only partial efficacy; likely because it failed to elicit the correct T cell responses;
  - While there is no predictive animal model for HSV-2 , data continue to accumulate that CD-8 T cell responses are required for effective control of reactivation.

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We Will Need Both Potent Neutralizing Immunogens and Potent T Cell Immunogens

Combination vaccines with different targets similar to combination antiretroviral therapy.

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Should We Still Try To Develop T Cell Based Vaccines?

Answer: Yes

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- Why did the MRK Ad 5 gag/pol/nef vaccine fail?

- Was the increased acquisition in Ad 5 seropositive uncircumcised men real?

- Was this all lack of circumcision or did Ad 5 immunity have something to do with this?

Post STEP Findings

- Phambili data suggest that prior wild type Ad 5 infection does play a role in the increased acquisition after the MRK Ad 5 vaccine
- Post STEP studies suggest human adenoviruses are found in GI tract more frequently than previously thought; persistence of these viruses may be a factor in reservoir of Ad specific T cells in humans
- Specific immune complexes may play a role in altering the types of immune response or altering DC function/maturation
- Post STEP studies indicate prior Ad 5 immunity alters:
  - innate signatures
  - differs in type of neutralization responses
  - may narrow the CD-8 T cell response
  - may alter the character of the T cells induced by vaccination

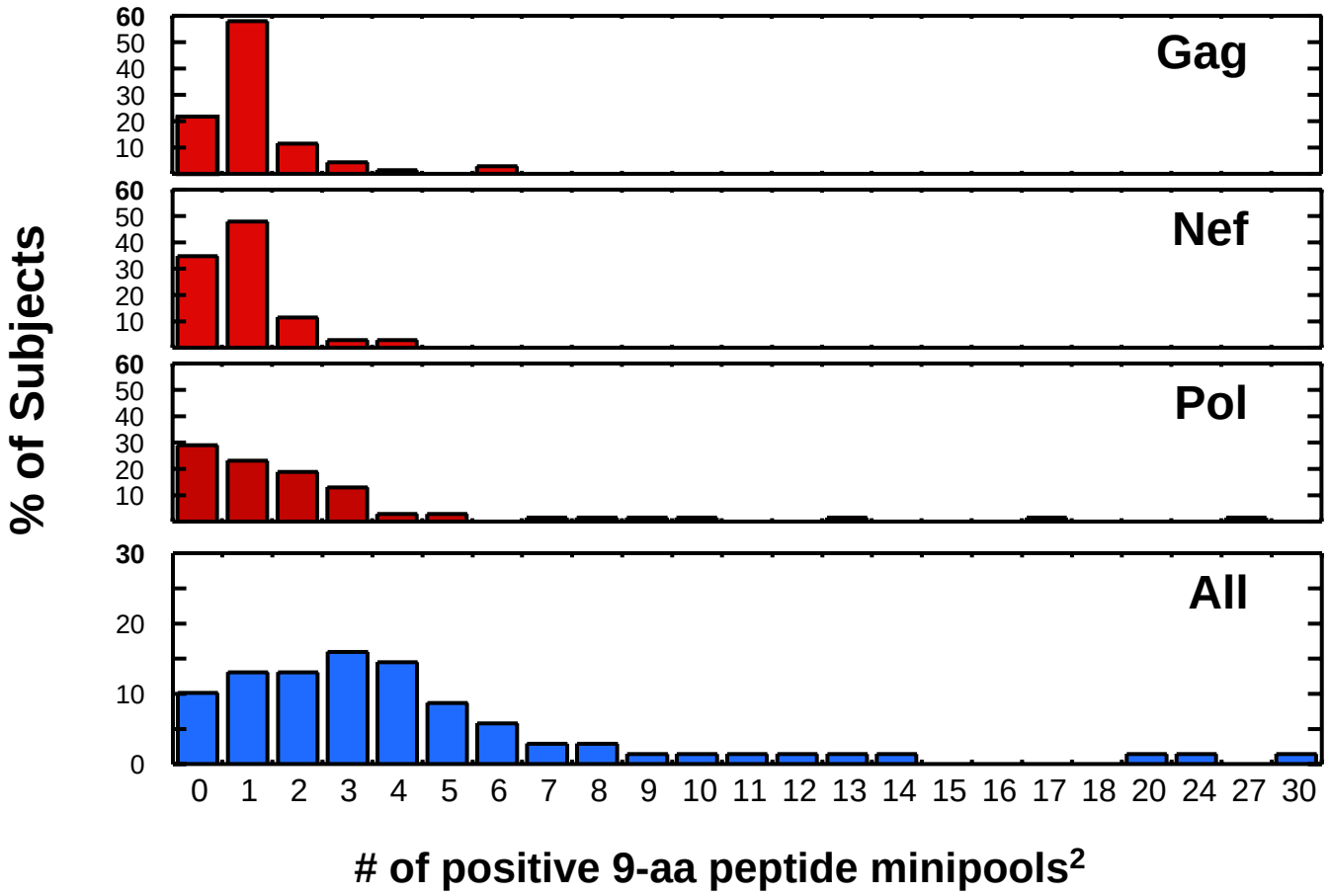
Bottom Line

- We do not yet have a mechanistic explanation for the increased acquisition among Ad 5 seropositives
- Scientific community has, however, generated several leads
  - understanding tissue based immune responses and vector related immunity is important
- Importantly, increasing amount of data also suggests that Ad 5 seronegative persons are not at increased risk of acquisition and hence, conduct of vaccine trials in this population can be safely performed

Why Did We Not Alter Post Acquisition Viral Load?

- Breadth of the CD 8 response is not enough
- We knew going in that it was 1 epitope per gene
  - We did not know that the epitopes induced were largely to the variable region
- We need to know what magnitude and character of response are needed to control viremia

Breadth of CTL responses induced by MRKAd5 Trivalent Vaccine from Phase I trial using 9-mer peptide pools[1]



	Median #
Gag	1
Nef	1
Pol	1
All	3

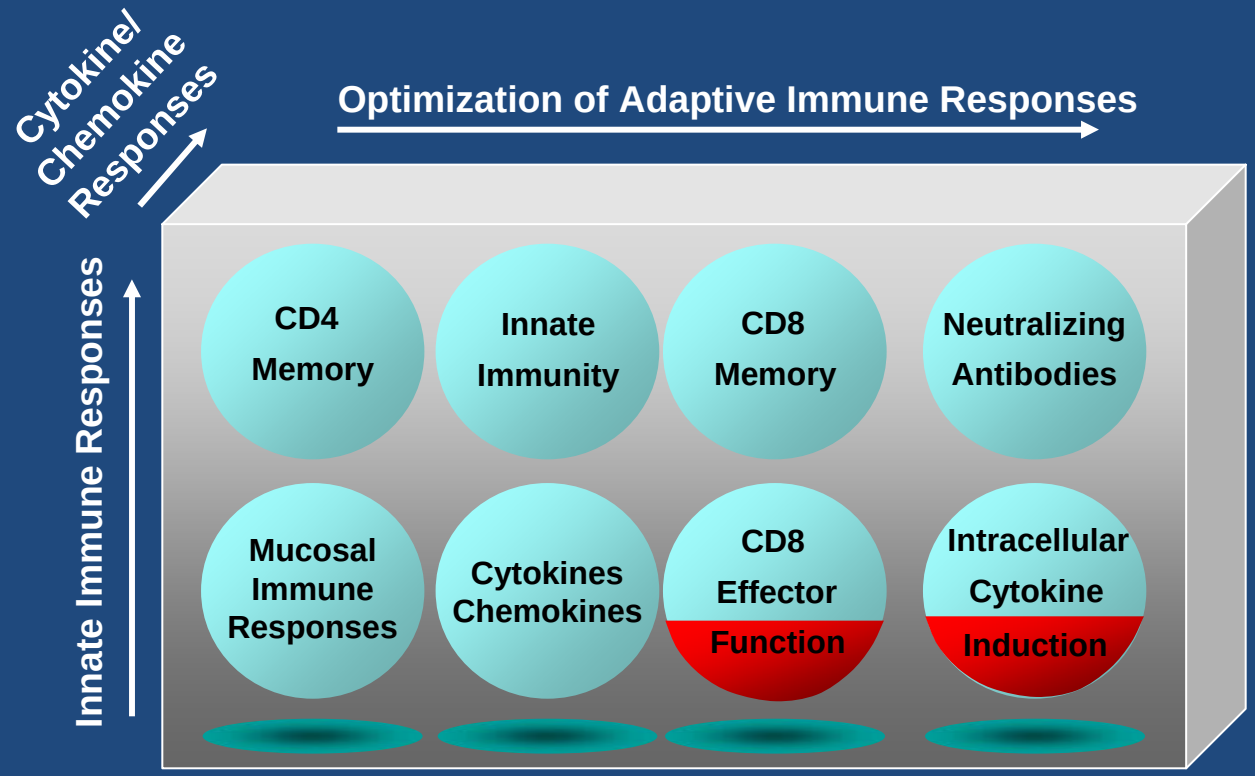
[1]Other epitopes (helper T) are likely not detected in this screen

[2]Gag: 62 peptide minipools; Pol: 105 minipools; Nef: 27 minipools; each minipool consists of eight 9-aa peptides (with 8-aa overlaps)

Summary

- Clinical trials of T cell vaccines should be directed at ways to increase breadth of T cell responses,
- While we can develop many new assays to evaluate T cell responses post vaccination, only efficacy trials will define the targetsand types of T cell responses required to be clinically useful
- Judicious balance of test of concept efficacy trials and Phase 1 trials will need to be performed

Filling in the Immunological Space



Pre-Clinical Assessment of Immune Responses

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