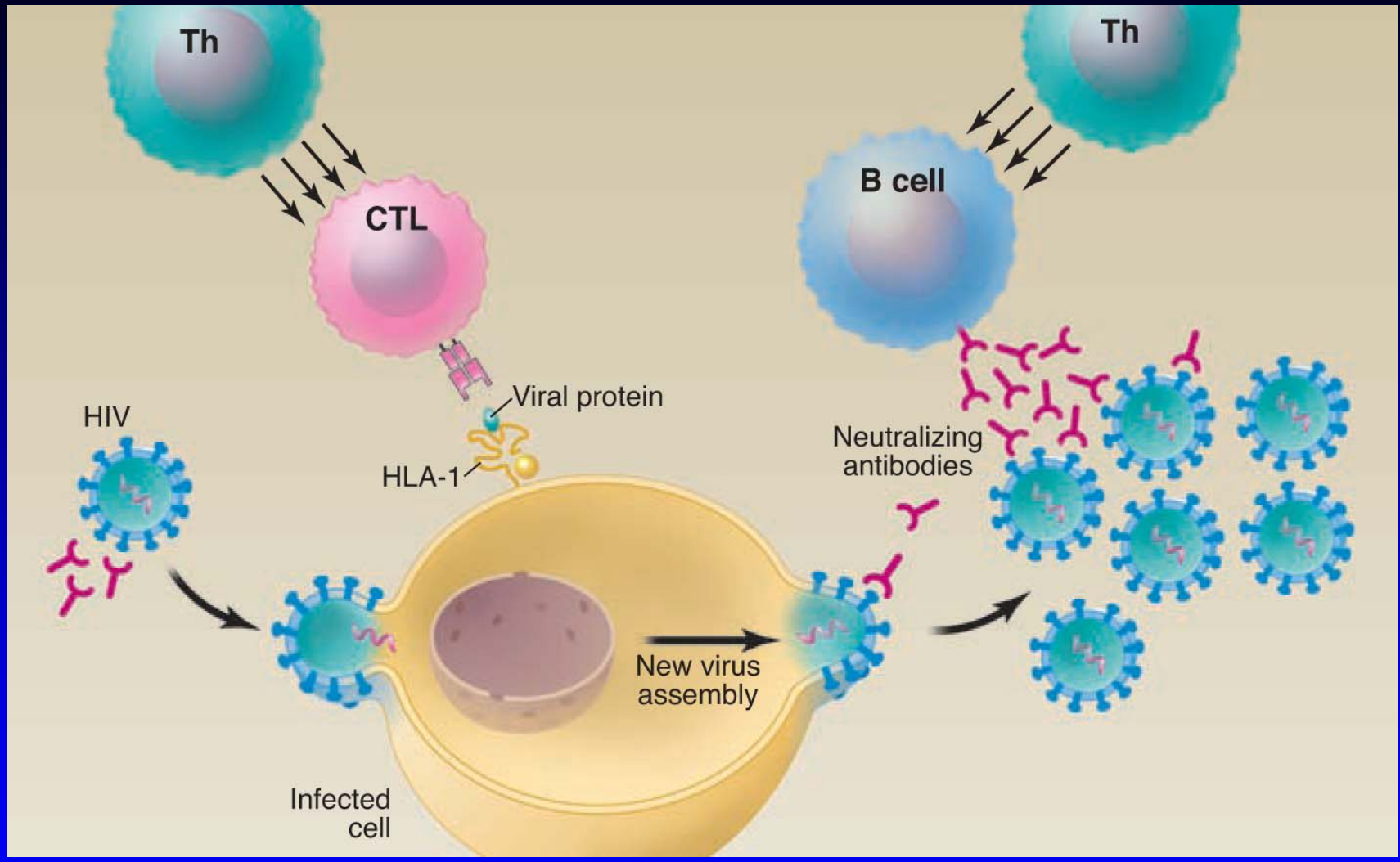
Antibodies and T cells: horses for courses

Dennis Burton
The Scripps Research Institute

Cape Town, October 15th 2008



Walker and Burton (2008) Science 320, 760.

Should there be Further Large Scale Efficacy Testing of T-Cell Based Vaccines that do not Induce Broadly Neutralizing Antibodies?

No, not large-scale, because there are too many uncertainties at this point in time.

But a STOC trial of a T cell only vaccine, particularly one showing promise in robust macaque models, is appropriate.

Possible scenarios for an HIV vaccine

1. Sterilizing immunity (no virus integration):

-highly effective NAb response

-NAb response + “enough and soon enough” (Haase) of a T cell response

2. Infection (integration) but reduced gut damage in primary infection and lowered sustained set point

-T cell response +/- NAb response

Are we likely to achieve sterilizing immunity by inducing neutralizing antibodies alone?

Neutralizing antibodies (NAbs) are often quoted as critical to vaccine protection against viral diseases because:

- **Correlation of serum NAbs with vaccine protection in humans**
- **Passive transfer of NAbs provides protection in animal models**

Vaccine correlates of protection

- **“Neutralizing antibodies are the best, if not the only, correlate of protection for all successfully working vaccines known to date”.**
  Miedema (2008) AIDS 22, 1699.

- **“Even today, with our advances in cutting-edge immunological techniques, the Jennerian vesicle remains the only universally accepted correlate of successful vaccination” (for smallpox).**
  Amanna et al (2008) Human Vaccine 4, 316.

Correlation of NAbs with protection

Smallpox

- Neut titer < 1:32 (vaccinia), 3/15 disease
- Neut titer >1:32, 0/127

- Neut titer <1:20, 6/43
- Neut titer >1:20, 0/13

- Longevity of protection (>20 years) “implies that CD8+ T cell memory is not absolutely required for protection and that CD4+ T cell memory or NAb responses (or both) may constitute the main components of long-term immunity against smallpox after CD8+ T cell memory has faded.”

Hammarlund et al (2003) Nat Med 9, 1131.

Correlation of NAbs with protection

Measles

- Neut titer < 1:120, 8/9 got clinical measles
- Neut titer >220, 0/71 got clinical measles

- Neut titer 216-874, 64% get subclinical measles infection
-
- Neut titer >1052, no indication of subclinical infection

Amanna et al (2008) Human Vaccines 4, 316.

Correlation of NAbs with protection

Chickenpox

- **Risk for breakthrough varicella in vaccinated individuals is inversely related to ELISA Ab titers at 6 weeks (titer of >5 gives 96% protection first year).**
- **But, risk of infection increases greatly while ELISA Ab titer is maintained (titer >5 for 9 years as infection risk increases by 30-fold)**
- **"This may require….. a better understanding of the combined roles of humoral and cellular immune responses in vaccine-induced protection against VZV".**

Amanna et al (2008) Human Vaccines 4, 316.

Neutralizing antibodies (NAbs) are often quoted as critical to vaccine protection against viral diseases because:

- **Correlation of serum NAbs with vaccine protection in humans**
- **Passive transfer of NAbs provides protection in animal models**

Passive transfer studies in macaques generally suggest relatively high neut titers of antibodies required for protection

- and it may be particularly hard to achieve these titers against multiple isolates
- on the other hand, lower titers needed for some specificities (2G12) and in low dose challenge

Possible scenarios for an HIV vaccine

1. Sterilizing immunity (no virus integration):

-highly effective NAb response

-NAb response + “enough and soon enough” (Haase) of a T cell response

2. Infection (integration) but reduced gut damage in primary infection and lowered sustained set point

-T cell response +/- NAb response

Vaccine protection mechanism in humans may depend on:

- Virus
- Challenge route
- Challenge dose
- Genetics of vaccinee
- Immune status of vaccinee