TOWARDS AN HIV VACCINE
why is it so hard to make an HIV vaccine and where are we now?

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Estimated number of persons living with HIV/AIDS, December, 2004

Global total: 39.4 million

- 26.8 million
- 8 million
- 1 million
- 360,000
- 220,000
- 520,000
- 360,000
- 920,000
- 1.3 Million
- 12,000

Source: UNAIDS
TOWARDS AN HIV VACCINE

- Why is it so hard to make an AIDS vaccine?
- ‘Sterilizing’ or ‘partial’ immunity?
- Immune correlate of protection?
- Cellular immunity: provides protection?
- Neutralizing antibody: a daunting challenge
- Cross-clade immunity?
- Current status of AIDS vaccines?
TOWARDS AN HIV VACCINE

WHY IS IT SO HARD TO MAKE AN AIDS VACCINE?
TOWARDS AN HIV VACCINE

RESEARCH EXPERIENCE
• HIV env protein fails to induce neutralizing Ab
• Live attenuated SIVs protect but cause AIDS

BIOLOGICAL ISSUES
• First HIV infection may not attenuate a second HIV infection?
• Persistence of HIV and progression to AIDS

IMPLICATION
• Immunobiological questions must be addressed
• Mechanisms of vaccine protection?
TOWARDS AN HIV VACCINE

VAXGEN TRIAL OF rgp120
multiple immunizations, 3 year cumulative infection percentage
Science 2003, 299: 1290

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TREATMENT</th>
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<th>INFECTIONS</th>
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TOWARDS AN HIV VACCINE
FIRST HIV INFECTION MAY NOT PROTECT AGAINST SECOND INFECTION?

HIV INFECTION IN SEX WORKERS, NAIROBI, KENYA
CASE # 3
OVERBAUGH ET AL, 2005, UNPUBLISHED

HIV-1 viral RNA levels
log10 copies/ml

Estimated days since infection

D
A

101 485 1262
TOWARDS AN HIV VACCINE

THE DAUNTING TRIAD: FAILURE TO PREVENT INFECTION; PERSISTENCE; LOSS OF CD4 T CELLS

DYNAMICS OF HIV INFECTION ILLUSTRATING PROBLEMS IN PRE-EXPOSURE IMMUNIZATION
TOWARDS AN HIV VACCINE

“STERILIZING” OR “PARTIAL” IMMUNITY?
“STERILIZING” OR “PARTIAL” IMMUNITY?

For viruses causing acute infections, subjects who have been adequately immunized usually undergo an abortive infection when exposed to a potentially virulent wildtype virus.

- Will such ‘partial’ protection confer adequate resistance to an HIV challenge or is ‘absolute’ protection (‘sterilizing’ immunity) needed?

- Do studies of immunized monkeys challenged with SIV provide a useful reference?

- Do studies of viral set points and survival curves in HIV-infected humans provide a useful predictor?
TOWARDS AN HIV VACCINE

PROTECTION OF Rhesus Macaques AGAINST SIV SM E660 IV CHALLENGE BY RECOMBINANT VACCINIA (MVA) IMMUNIZATION
Ourmanov, J Virology, 2000, 74: 2740

WEEKS AFTER CHALLENGE

0 4 8 12 16

RNA COPIES PER ML PLASMA GEOMETRIC MEAN

CONTROL
RAPID PROGRESSORS 2
PROGRESSORS 3

MVA gag-pol-env
PROGRESSORS 1
NONPROGRESSORS 5
VIRUS SETPOINT DETERMINES THE COURSE OF THE INFECTION

TOWARDS AN HIV VACCINE

IMMUNE CORRELATES OF PROTECTION?
TOWARDS AN HIV VACCINE

CORRELATE HYPOTHESIS?
- Does protection correlate with a specific immune response parameter, such as antibody, CTL killing, or CD4+ proliferation?

BARRIER HYPOTHESIS?
- Might a combination of antibody plus CTLs plus associated cytokine responses act in concert to constitute a sufficient barrier?
- Could different immunizing protocols protect by a different mix of immune defenses?
TOWARDS AN HIV VACCINE

CELLULAR IMMUNITY PROVIDES PARTIAL PROTECTION
CD8 CELLULAR IMMUNE RESPONSE GOVERNS VIRUS SETPOINT
TOWARDS AN HIV VACCINE

VACCINE FAILURE DUE TO ESCAPE FROM A SINGLE CD8 EPITOPE
recombinant env-gag DNA/IL-2 vaccine; SHIV challenge

\[
\begin{align*}
\text{WEEKS AFTER INFECTION} & \quad 0 \quad 10 \quad 20 \quad 30 \quad 40 \quad 50 \\
\log_{10} \text{mRNA PER ML PLASMA} & \quad 6 \quad 5 \quad 4 \quad 3 \quad 2 \\
\text{CD4 PER } \mu\text{L} & \quad 1200 \quad 800 \quad 400
\end{align*}
\]
TOWARDS AN HIV VACCINE

NEUTRALIZING ANTIBODY: A DAUNTING CHALLENGE
NEUTRALIZING ANTIBODY INFLUENCES VIRUS SETPOINT
chimp anti-HIV passive antibody; challenge: iv virulent SHIV (matched gp120)

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TOWARDS AN HIV VACCINE

PASSIVE ANTIBODY PROTECTS MONKEYS AGAINST SUBSEQUENT CHALLENGE WITH VIRULENT SHIV
Nishimura, 2002
THE NEUTRALIZING ANTIBODY ENIGMA

- Using gp120, it is difficult to raise neutralizing antibody
- Using MHC Class II, anti-SIV neutralizing antibody can be readily induced

Inference?

- The problem lies with gp120 and not in any intrinsic ability of SIV to resist neutralization
- Query: is SIV gp120 a poor target for neutralization? Do gp120 neutralization escape mutants play a role?
HIV INFECTION INDUCES AUTOLOGOUS NEUTRALIZING ANTIBODY THAT SELECTS FOR ESCAPE VARIANTS
Richman et al, PNAS 2003, 100: 4144

plasma neutralizing titer
months after infection

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TOWARDS AN HIV VACCINE

THE NEUTRALIZING ANTIBODY ENIGMA

if CD4 can dock why can’t IgG block attachment?
Influenza virus has a receptor site on each trimer head and can be neutralized by antibodies that bind to any of four different sites that are near the receptor binding site. Viral escape mutants can be selected for each of these neutralizing antibody sites.
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CROSS CLADE IMMUNITY?
TOWARDS AN HIV VACCINE

THERE ARE ABOUT 10 DISTINCT CLADES (GENOTYPES) OF HIV-1

GLOBAL DISTRIBUTION OF HIV-1 SUBTYPES AND RECOMBINANTS

Source: Florence E. McCaughan, Henry M. Jackson Foundation Rockville, Maryland. McCaughan and colleagues are indebted to the many international collaborators who helped develop the data used to generate this map.
ARE THE ~10 CLADES DISTINCT IMMUNOTYPES?

• Will neutralizing antibody cross clades?
• Will cellular immunity cross clades?
• Relevance of conserved vs variable epitopes?
• Are multivalent HIV-1 vaccines needed?
**TOWARDS AN HIV VACCINE**

**MULTICLADE VACCINE IS EQUAL TO MONOCLADE VACCINE**
Rhesus monkeys immunized with env DNA @ 0, 4, 8 wks; rAdV env DNA @ 26 wks
Tested 1 week post vaccine
Letvin et al, 2003

<table>
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<th>env IMMUNOGEN BY CLADE mg DNA</th>
<th>env RESPONSES BY CLADE IFN ELISPOT/10⁶ PBL</th>
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<td>A  B  C</td>
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TOWARDS AN HIV VACCINE

CURRENT STATUS OF AIDS VACCINES
TOWARDS AN HIV VACCINE

vaccine provides partial protection in SIV model

rDNA plus rAdv (SIV239 gag, pol, env) immunization

iv SIV 251 (heterologous) challenge

Letvin et al, unpublished, 2005

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**Graph:**

- **Y-axis:** % Survival
- **X-axis:** Days Post-SIVmac251 Challenge
- **Legend:**
  - Vaccinated (n = 24)
  - Control (n = 6)

**Statistical Notation:**

- \( p = 0.007 \) (Vaccinated vs. Control)
- \( P = 0.007 \) (Overall comparison)
“In 1945, Professor Burnet of Melbourne wrote ‘While I was in America recently I had good opportunity to meet with most of the men actively engaged on research in poliomyelitis...The part played by acquired immunity to poliomyelitis is still completely uncertain, and the practical problem of preventing infantile paralysis has not been solved. It is even doubtful whether it ever will be solved.’

...most of us doing research on poliomyelitis in 1945 were mainly motivated by curiosity, rather than by the hope of a practical solution in our lifetime.”

David Bodian, 1976