The challenge of an HIV vaccine from the antibody perspective

Dennis Burton
The Scripps Research Institute
AIDS Pandemic Nov 2005

North America
1.2 million
[650 000 – 1.8 million]

Caribbean
300 000
[200 000 – 510 000]

Latin America
1.8 million
[1.4 – 2.4 million]

Western & Central Europe
720 000
[570 000 – 890 000]

North Africa & Middle East
510 000
[230 000 – 1.4 million]

Sub-Saharan Africa
25.8 million
[23.8 – 28.9 million]

Eastern Europe & Central Asia
1.6 million
[990 000 – 2.3 million]

East Asia
870 000
[440 000 – 1.4 million]

South & South-East Asia
7.4 million
[4.5 – 11.0 million]

Oceania
74 000
[45 000 – 120 000]
HIV binding via cell surface receptors

- p24
- Reverse transcriptase
- RNA
- protease
- gp120
- CD4 receptors
- Chemokine receptor
- CD4 lymphocyte
HIV ready to make contact with a target cell
Antibody sterically interferes with viral attachment and/or fusion

For a vaccine, want to induce antibodies that recognize virus spikes (neutralising antibodies).

How?

Generally, where natural infection with a virus gives good neutralising antibody responses the favoured strategy has been *mimicry of infection*. 
Live attenuated vaccines

e.g. Sabin (oral) polio, MMR, smallpox (vaccinia), VZV, Yellow fever

Killed vaccines

e.g. Salk polio, hepA, rabies, influenza

Subunit vaccines

e.g. hepB, influenza
“….but what renders the Cow Pox so extremely singular is that the person who has been thus affected is for ever after secure from the infection of the Small Pox…”

Edward Jenner, 1798.
If natural infection does not give good neutralising antibody responses then *simple mimicry may not be the best way to a vaccine.*

HIV infection does *not* give good neutralising antibody responses of the type that are required in a vaccine i.e. *broadly neutralising* antibody responses.

HIV is a *highly variable virus.*
HIV variability - the 800 lb gorilla sitting on our shoulders
Variation in influenza virus and HIV-1

Influenza

Outbreak in Canada 1997-98

Global outbreak 1996

HIV

Single individual 6 years post infection

Amsterdam 1990-1991

Congo, 1997
A successful vaccine should induce antibodies against (most of) the global HIVs i.e. should induce *broadly neutralising antibodies*. By definition, these are antibodies to the *conserved* parts of the HIV spike.
The HIV-1 Spike:
thrust out the variable parts; hide the conserved parts; sugar coating
But can antibodies be made to conserved parts of the HIV spike—are there any chinks in the armour?

Yes—although very rare, broadly neutralising monoclonal antibodies to HIV have been isolated.
The HIV-1 Broadly Neutralising Antibodies

Broadly neutralising Abs; do they work?

**In vitro:**

b12: 45/90 viruses neutralised

4E10: 90/90

**In vivo:**

b12 and 2G12 shown to protect against vaginal challenge in monkey models
Can we design vaccines that induce broadly neutralising antibodies?
Retrovaccinology

phage display,
EBV transformation
or human hybridomas

human neutralizing mAbs

molecular characterization
of Ab-pathogen Ag interaction

immunogen design
and testing

combination of several immunogens
= vaccine

Can we engineer gp120 so it induces b12-like antibodies?

Structure of antibody 2G12 bound to sugar $\text{Man}_9\text{GlcNAc}_2$

Model of mAb 2G12 antibody bound to HIV spike

Calarese et al. (2003)
Science 300, 2065-2071.
Qβ - Man₉ as an immunogen to mimic the sugar shield of HIV

Rena Astronomo, M.G. Finn, Chi-Huey Wong
Model of antibodies bound close to the HIV membrane

(Burton et al (2005) PNAS 102, 14943-8)
Structural data has given us promising vaccine leads

Protein design

Sugar design

Peptide design
Conclusions

Simple mimicry of natural infection may not be the best way to an HIV vaccine (or to vaccines for other “difficult” pathogens such as malaria and hepatitis C).


Need to dissect antibody responses, find the protective responses (“chinks in the armour”) and learn how to induce these responses by vaccination.
Ian Wilson, Scripps
Raymond Dwek, Oxford
Chi-Huey Wong, Scripps
Phil Dawson, Scripps

The Neutralizing Antibody Consortium of the International AIDS Vaccine Initiative (IAVI)

NIAID, IAVI, Pendleton Trust