The DNA-MVA/HIV A Vaccine: Successes and Challenges

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Kenyan Sex Workers

■ 1994-1999 Rowland-Jones studies
  - 71 highly exposed, persistently seronegative (HEPS) sex works in Nairobi

■ Cellular immunity?
  - Number of HIV-specific CTLs lower than HIV+ sex workers
  - BUT different epitope specificity

■ Conclusion: Immunity relies on CTLs targeting right epitopes
Vaccine design

- What are the “right” epitopes?
  - Number of HEPs with CTLs specific to $env$ increased with duration of uninfected exposure
  - HEPs tend to respond to $pol$ and B18 $p24$ while HIV+ workers do not

- Vaccine designed with:
  - clade A $gag$ $p24/p17$ epitopes
  - string of ~25 clade A epitopes ($gag$, $pol$, $nef$, $env$)
Vaccine design

- **Goal**: Make the body produce CTLs specific to “right” HIV epitopes

- **2 delivery methods**
  - Directly inject DNA epitopes
  - Incorporate DNA epitopes into other vector
    - Modified vaccinia ankara (MVA) virus
    - Cellular response to MVA tricks body into also recognizing and responding to HIV epitopes

- **Solution – Combine delivery methods**
  - DNA prime with MVA boost
  - 10-100 times higher T-cell counts than either alone in macaques
Vaccine Immunogenicity

- Amara, 2002 study – 24 macaques
  - 2 DNA prime with 1 MVA boost (SIV and HIV epitopes)
Vaccine Immunogenicity

- Humans – phase I and I/II trials on each vaccine alone since 2001 in Oxford and Nairobi
- Preliminary data
  - HIV vaccine - 12/18 volunteers showed responses in ELISPOT assay
  - MVA vaccine – 4/5 volunteers showed responses in ELISPOT assay
Vaccine safety

Safety – Murine studies
- DNA and MVA alone and in combination safe
- No evidence of pharmacological effects
- Genes cleared from all organs except injection sites by 5 weeks post-vaccination

Published safety data from human phase I trials not yet available
Challenge – Not true immunity

- Vaccine reduces pathogenicity (viral load)
- Doesn’t produce sterilizing immunity
- Sex workers resistant, not immune
  - 12 seronegative workers who reduced or took a break from sex work became seropositive
  - Infection associated with switch in specificity
  - Suggests that repeated exposure to epitopes maintains resistance

Implications – Regular boosting may be necessary.
  - More expensive
  - Many will miss their boosts
Barouch, 2002 – vaccine study on 8 rhesus monkeys
- 7 had successful disease reduction
- 1 had successful reduction until week 24 when viral replication breakthrough occurred, led to disease and death
- Findings – single nucleotide mutation in targeted gag epitope resulted in viral escape, vaccine failure

HIV strain diversity – Will the vaccine produce resistance to other clades?

Implications – Evolving boosts with old and new epitopes
- Ex. Flu vaccine evolves with changing virus
- Burden on research to keep up with virus
Challenge – Mucosal Immunity

- Progression of infection:
  1. Sexual contact – virus enters mucus membrane
  2. Establishes lymphatic tissue virus reservoir
  3. Systemic virus replication begins

- If response is only systemic, won’t block lymphatic reservoir (Pope and Haas, 2003)

- Mucosal response critical to protect against mucosal challenge in mice (Belyakov, 1998)

- Implication – Effective vaccine must elicit mucosal immunity to combat virus at initial contact
Conclusions

- Promising vaccine based on animal and preliminary human data
- Even if no sterilizing immunity, reduction in viral load and replication
  - Slowed disease progression
  - Reduction in transmission
- Outlook – Phase III trials scheduled for 2004
References


Heeney JL. The critical role of CD4+ T-cell help in immunity to HIV. Vaccine 2002; 20: 1961-63.


