An AIDS vaccine: Why is it so difficult?

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Chairman of the Board CPCD
CSO, Crucell Holland BV
An AIDS vaccine: Why is it so difficult?

• How is HIV & AIDS transmitted?

• Is a vaccine ultimately the only way out?

• What about antibodies and T cells?

• Correlate of protection is key to success.

• Do T cell vaccines have a chance?
HIV & AIDS transmission

- Spread of AIDS is dependent on the spread of HIV

- Spread of a virus can be blocked by stopping the transmission of the virus

- Stopping the transmission of a virus depends on transmission routes:

**Indirect transmission routes:**
Virus needs port of entry

- Unprotected sex with an infected partner
- Transmission from infected mother to fetus

**Direct transmission routes:**
Virus has direct access to a susceptible cell

- Infection from blood products
- Sharing needles with infected person
Efficacy of transmission & transmission risks

Blood transmission: direct
- Safety blood
- reducing intravenous drug use

Sexual transmission: genital tract
- Everybody has sex
- intervention before a certain age

Mother to child: oral
- Prophylactic antiviral drugs
- Cesarian section
- Breast milk replacement
Where to place the block to stop HIV transmission?

- Awareness, counseling, education: **2 way block**
- Harm reduction programs for drug users: **1 way block**
- Condom social marketing: **2 way block**
- Microbicides: **1 way block**
- Circumcision: **1 way block**
- Antiretroviral therapy: **1 way block**
  - Highly active antiretroviral therapy (HAART)
- Vaccine: **2 way block**

1 way block: blocking infection
2 way block: blocking infection and spread

www.immunisation.nhs.uk/About_Immunisation
Awareness, Counseling, Education: 2 way block

Education on HIV in schools

- Primary curriculum
- Secondary curriculum
- Teacher training

After appearing to stabilize in the early 2000s, Mozambique’s epidemic has again grown, with HIV prevalence rising in all parts of the country. [UNAIDS report]

The HIV epidemics continue to disproportionately affect African Americans in the United States and Aboriginal persons in Canada. [UNAIDS report]

GGD Amsterdam luidt noodklok over toename soa’s

Uitgegeven: 3 april 2009 07:16
Laatst gewijzigd: 3 april 2009 22:34

AMSTERDAM - Het aantal mensen in Amsterdam dat geïnfecteerd is met seksueel overdraagbare aandoeningen (soa’s) als hiv, chlamydia, syfilis en hepatitis C is in het afgelopen jaar sterk toegenomen.

Dat blijkt uit vrijdag gepubliceerde cijfers van de GGD Amsterdam. De gezondheidsdienst maakt zich zorgen over de voortdurende stijging en is bang voor een piek vergelijkbaar met die van midden jaren tachtig.

De hoofdstedelijke GGD registreerde in 2008 het grootste aantal nieuwe hiv-diagnosen ooit: 178. Dat is bijna de helft van alle hiv-infecties die bij de acht soa-poll’s worden gevonden.

Behaviour change in Kenya seems to be associated with a recent decline in HIV prevalence. [UNAIDS report]
Circumcision: 1 way block

Circumcision — A Surgical Strategy for HIV Prevention in Africa
Ingrid T. Katz, M.D., M.H.S., and Alexi A. Wright, M.D.

In a radical departure from earlier strategies, public health officials are now arguing that circumcision of men should be a key weapon in the fight against infection with the human immunodeficiency virus (HIV) in Africa. Recent studies have shown that circumcision reduces infection rates by 50 to 60% among heterosexual African men. Experts estimate that more than 3 million lives could be saved in sub-Saharan Africa alone if the

Male Circumcision for the Prevention of HSV-2 and HPV Infections and Syphilis


CONCLUSIONS
In addition to decreasing the incidence of HIV infection, male circumcision significantly reduced the incidence of HSV-2 infection and the prevalence of HPV infection, findings that underscore the potential public health benefits of the procedure.

MALE CIRCUMCISION AND HIV PREVENTION

Male circumcision—a surgical procedure carried out on young men and infant boys in many parts of the world—reduces the risk of heterosexual HIV transmission in men. Numerous observational studies over the past 20 years have suggested that the geographical correlation between low HIV prevalence and high levels of male circumcision in countries in Africa and elsewhere was, at least in part, a causal association. Now, compelling evidence from three randomized controlled trials

UNAIDS report
Drugs versus vaccine for prevention
only blocking infection does not work

Drugs
1 way block

- Extended lifetime treatment
- Drug-resistance
- Spreading continues
- Possible re-occurrence
- Long-term effect
  - Heart disease
  - Diabetes
  - Liver disease
  - cancer
- Expensive

Vaccines
2 way block

- Short treatment
  - 1 to 3 shots
- Long time immunity
- Limit or stop spreading
- Prevent re-occurrence
- Cheap
An AIDS vaccine: Why is it so difficult?

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- Is a vaccine ultimately the only way out?
- What about antibodies and T cells?
- Correlate of protection is key to success.
- Do T cell vaccines have a chance?
Vaccine against viruses

- Definition:
  - A vaccine is a life attenuated virus or killed wild type virus that prevents viral disease in the exposed and prevents the population to be exposed by ‘teaching’ the body how to defend itself against a virus.

Remarkable that immune cells in the body have memory for years
Vaccine

Protects an individual at risk against development of a disease

Protects the population against spread of the virus

www.immunisation.nhs.uk/About_Immunisation
Vaccine

- The vaccine ‘teaches’ the body how to defend itself against a virus by creating an immune response.
  - The immune response may consist of:
    - B cells: respond to a virus by producing neutralizing antibodies (NAb).
    - CD8⁺ T cells: have the ability to kill infected cells
    - CD4⁺ T cells: help B cells and CD8⁺ T cells to respond

Of all immune cell types memory cells are generated
The benefit of vaccination

Vaccines in particular, ...... are an inexpensive and extremely effective means of improving health and overall welfare. Their impacts, moreover, are much greater than previously thought.

The Value of Vaccination

WORLD ECONOMICS • Vol. 6 • No. 3 • July–September 2005

David E. Bloom, David Canning & Mark Weston

Vaccines are prerequisite for successful development
Vaccines WORK!

- Launched Nov 1979

Tetanus

Diphteria

Pertussis

Source: Pan American Health Organization, Family and Community Health Area, Immunization Unit
Proven long-term efficacy of vaccination

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percent Decrease in Morbidity &amp; Mortality by Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>100</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>99.99</td>
</tr>
<tr>
<td>Measles</td>
<td>99.99</td>
</tr>
<tr>
<td>Mumps</td>
<td>99.85*</td>
</tr>
<tr>
<td>Pertussis</td>
<td>92.09</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>100*</td>
</tr>
<tr>
<td>Rubella</td>
<td>99.99*</td>
</tr>
<tr>
<td>Congenital Rubella Syndrome</td>
<td>99.88</td>
</tr>
<tr>
<td>Tetanus</td>
<td>98.47*</td>
</tr>
<tr>
<td><em>Record lows</em></td>
<td></td>
</tr>
</tbody>
</table>

*Record lows

*H. influenzae, type b and unknown (<5 yrs)*
Herd protection provided by vaccines

Matlab, Bangladesh cholera vaccine trial

<table>
<thead>
<tr>
<th>Level of vaccine coverage %</th>
<th>Target population</th>
<th>Risk per 1000 population</th>
<th>Protective efficacy (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>24954</td>
<td>2.66</td>
<td>7.10</td>
</tr>
<tr>
<td>28-35</td>
<td>25059</td>
<td>2.47</td>
<td>5.87</td>
</tr>
<tr>
<td>36-40</td>
<td>24583</td>
<td>1.57</td>
<td>4.72</td>
</tr>
<tr>
<td>41-50</td>
<td>24159</td>
<td>2.25</td>
<td>4.65</td>
</tr>
<tr>
<td>&gt;51</td>
<td>22394</td>
<td>1.27</td>
<td>1.47</td>
</tr>
</tbody>
</table>

*Vaccine protective efficacy for those residing in baris with the cited level of vaccine coverage

Risk of cholera and protective efficacy of killed cholera vaccine, by level of cholera coverage of the bari during the first year of follow up

Level of coverage required to control endemic cholera in remains unknown
An AIDS vaccine: Why is it so difficult?

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HIV vaccine

An ideal vaccine against HIV would protect against infection and provide sterilizing immunity.

An suboptimal vaccine against HIV would result in decreased peak and setpoint viral loads after infection.

The goals for an AIDS vaccine

Prevent the establishment of persistent HIV infection:
- **Induction of neutralizing antibodies**
- Induction of immunity at mucosal site

Reduce viral load and slow progression to AIDS:
- **Induction of HIV-specific T cells**
Vaccine Principles (1)

- All vaccines that are used today are licensed on the basis of an assay measuring protective antibodies as correlate of protection.

**Protective immunity is about survival within an evolutionary context. It is particularly important early in life, because the immune system is immature at birth. Successful vaccines induce optimal levels of neutralizing antibodies against acutely cytopathic agents. In contrast, long-lasting cell-mediated immunity is much more difficult to induce through vaccination.**

*Maternal Antibodies, Childhood Infections, and Autoimmune Diseases*

ROLF M. ZINKERNAGEL, M.D.

Vaccine Principles (2)

- Not a single vaccine to date has reached the market that is licensed on the basis of an assay measuring protective T-cell responses as correlate of protection

Hit and run viruses evade immune destruction by infecting new hosts and rarely persist. Hit and stay viruses evade immune control by sequestration, blockade of antigen presentation, cytokine escape, evasion of natural killer cell activities, escape from apoptosis, and antigenic change. Twelve prophylactic vaccines against hit and run agents exist, and there are only three vaccines against hit and stay viruses, all of which are of DNA composition. Several new vaccines against hit and stay viruses are feasible, but protective vaccines against RNA HIV and hepatitis C agents are highly unlikely, short of a major breakthrough.
Vaccines against AIDS

• Approaches to induce neutralizing antibodies prove ineffective to date.

• Approaches to induce potent T cell responses are now investigated:
  - Result in reduction viral load
  - Lower viral load = less HIV transmission & less disease
The unprecedented concept of a vaccine that induces exclusively T-cell responses but no virus neutralizing antibodies
Scientific challenges in the development of an AIDS vaccine

• Which HIV antigens are required for protection?

• Limitation in the animal models for HIV/AIDS

• Correlates of protective immunity remain undefined
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- How is HIV & AIDS transmitted?
- Is a vaccine ultimately the only way out?
- What about antibodies and T cells?
- Correlate of protection is key to success.
- Do T cell vaccines have a chance?
Licensure of vaccines

Licensure of vaccines requires demonstrated evidence of:

- Safety
- Efficacy
  - Correlates of Protection (CoP) demonstrate vaccine efficacy
Correlate of Protection definition

- Definition
  - A specific Immune response to a vaccine that is closely related to protection against infection, disease, or other defined end point
Correlates of Protection enable swift development of vaccines

- Correlates of Protection identify which type of immune response must be induced (antibodies and/or T cells)
- Correlates of Protection enable evaluation of vaccine efficacy without the need for challenging
- Correlates of Protection allow comparison of vaccine efficacy with other vaccine candidates
Correlates of protection support licensure of vaccines

• Proven Correlates of Protection support vaccine licensure by providing a scientific mechanism of protection, and justification of the read out assays

• Correlates of Protection are a surrogate end point for efficacy end point in field trials
  – Reduced nr of subjects
  – Reduced duration of trials
Investigation of Correlates of Protection

Correlates of Protection should be defined early in research / development:

• To develop the right assays measuring the Correlates of Protection

• To select the best vaccine format

• To facilitate bridging of animal models to clinical trials
Investigation of Correlates of Protection

• Current practices for defining which parameters are Correlates of Protection
  – Observation of a cut point (protective threshold)
  – Linear regressions

• Possible improvements:
  – Scientific approach for finding the cut point
  – Combine different parameters
  – Statistical rigor
Investigation of Correlates of Protection

Alternative method:

- Receiver Operating Characteristic (ROC) curve
  - Originally used for analysis of diagnostic assay sensitivity and specificity

- Hypothesis:
  - ROC is suited for analysing extensive datasets to determine the correlates of protection
  - ROC can combine multiple parameters
ROC Analysis:
Historical Development (1)

Derived from early radar in WW2 Battle of Britain to address:

Accurately identifying the signals on the radar scan to predict the outcome of interest – Enemy planes – when there were many extraneous signals (e.g. Geese)?
ROC Analysis: Historical Development (2)

- True Positives = Radar Operator interpreted signal as Enemy Planes and there were Enemy planes (Good Result: No wasted Resources)

- True Negatives = Radar Operator said no planes and there were none (Good Result: No wasted resources)

- False Positives = Radar Operator said planes, but there were none (Geese: wasted resources)

- False Negatives = Radar Operator said no plane, but there were planes (Bombs dropped: very bad outcome)
ROC Analysis: Historical Development

- **Sensitivity** = Probability of correctly interpreting the radar signal as Enemy planes among those times when Enemy planes were actually coming
  - \( SE = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}} \)

- **Specificity** = Probability of correctly interpreting the radar signal as no Enemy planes among those times when no Enemy planes were actually coming
  - \( SP = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}} \)
Receiver operating characteristic curve

- A method for accurately predicting the outcome of interest given a test result.

- For each test result, the sensitivity and specificity is calculated.

- The ROC curve is a plot of sensitivity versus 1-specificity of all test results.

- The area under the curve indicates the probability that the predictor is a correlate of protection.
WNV - Proof of concept Receiver operating characteristic curve

- Experimental setup
  - Mice were vaccinated with inactivated WNV vaccine using a dose escalation from 1 to 1000 EU per mouse, adjuvated with AlOH₃

- Dataset
  - WNV neutralizing titers (VNA) were determined at time of challenge
  - Primary outcome: Prevention of WNV disease

- Is the neutralizing titer a correlate of protection?
  - Perform a ROC curve analysis
WNV - Experimental design

- Vaccination dose range
  1 EU – 1000 EU/injection/mouse
- Challenge
  100*MID50 / mouse

IM injections  0 weeks  3  6  9

VNA titer  symptoms

BALB/c mice
Female
N=5 / group
9 dose groups
Creating a ROC curve – I
WNV neutralizing titers at time of challenge
Receiver operating characteristic curve: A closer look

- For each titer level (cut-off value) a two-by-two table is made

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th>No Disease</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of mice above</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>No. of mice below</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

- Sensitivity = The proportion of mice with no disease and with a titer above the cut-off value = $a/(a+c)$.

- Specificity = The proportion of mice with disease and with a titer below the cut-off value = $b/(b+d)$.
Receiver operating characteristic curve: example

- Example 1
  - Non predictive
  - Sensitivity = 1-Specificity
  - Area under the curve is 0.5

- Example 2
  - Predictive
  - Area under the curve is > 0.5
  - Statistics to test the difference from 0.5 (non-informative)
Creating a ROC curve - II

Clinical Outcome
Disease No disease

VNA titer
2 3 4 5

Receiver Operating Characteristic
Protection against Disease

0.00 0.25 0.50 0.75 1.00
0.00 0.25 0.50 0.75 1.00

Sensitivity

45 25 20 Total Sensitivity = 18/20 = 0.9
1- Specificity = 1-(22/25) = 0.12

Disease
24 22 2 No. of mice below
21
Total
18
No. of mice above
No Cut-off = 2.40

45 25 20 Total Sensitivity = 17/20 = 0.85
1- Specificity = 1-(23/25) = 0.08

Disease
26 23 3 No. of mice below
19
Total
17
No. of mice above
No Cut-off = 2.50

45 25 20 Total Sensitivity = 16/20 = 0.80
1- Specificity = 1-(24/25) = 0.04

Disease
28 24 4 No. of mice below
17
Total
16
No. of mice above
No Cut-off = 2.70

45 25 20 Total Sensitivity = 15/20 = 0.75
1- Specificity = 1-(24/25) = 0.04

Disease
29 24 5 No. of mice below
16
Total
15
No. of mice above
No Cut-off = 2.80

45 25 20 Total Sensitivity = 16/20 = 0.80
1- Specificity = 1-(23/25) = 0.08

Disease
27 23 4 No. of mice below
18
Total
16
No. of mice above
No Cut-off = 2.60

45 25 20 Total Sensitivity = 14/20 = 0.70
1- Specificity = 1-(25/25) = 0

Disease
31 25 6 No. of mice below
14
Total
14
No. of mice above
No Cut-off = 2.90

45 25 20 Total Sensitivity = 18/20 = 0.9
1- Specificity = 1-(19/25) = 0.24

Disease
21 19 2 No. of mice below
24
Total
18
No. of mice above
No Cut-off = 2.25

45 25 20 Total Sensitivity = 20/20 = 1
1- Specificity = 1-(0/25) = 1

Disease
0 0 25
Yes
45
Total
20
No. of mice above

Sensitivity = 10/20 = 0.90
1- Specificity = 1-(15/25) = 0.08
Is there a minimum level of neutralization which protects against WNV disease?

- Higher neutralizing titers are correlated with absence of WNV disease
- Can the lowest titer with optimal protection be identified?
**Receiver operating characteristic curve: A closer look**

- For each titer (cut-off value) a two-by-two table is made:

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th>No Disease</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of mice above</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>No. of mice below</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

- Sensitivity = The proportion of mice with no disease and with a titer above the cut-off value = \( \frac{a}{a+c} \).

- Specificity = The proportion of mice with disease and with a titer below the cut-off value = \( \frac{b}{b+d} \).

The optimal cut-off value is **the** titer with the highest sensitivity and specificity. An objective approach is by using Youden’s index:
- Youden (\( J \)) = sensitivity + specificity – 1.
- When the cut-off value is optimal, Youden’s index is close to 1.
### Receiver operating characteristic
A closer look at the WNV data

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>No</th>
<th>Yes</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden’s Index (J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.25</td>
<td>18</td>
<td>6</td>
<td>0.90</td>
<td>0.76</td>
<td>0.66</td>
</tr>
<tr>
<td>≥2.40</td>
<td>18</td>
<td>3</td>
<td>0.90</td>
<td>0.88</td>
<td>0.78</td>
</tr>
<tr>
<td>≥2.50</td>
<td>17</td>
<td>2</td>
<td>0.85</td>
<td>0.92</td>
<td>0.77</td>
</tr>
<tr>
<td>≥2.60</td>
<td>16</td>
<td>2</td>
<td>0.80</td>
<td>0.92</td>
<td>0.72</td>
</tr>
<tr>
<td>≥2.70</td>
<td>16</td>
<td>1</td>
<td>0.80</td>
<td>0.96</td>
<td>0.76</td>
</tr>
<tr>
<td>≥2.80</td>
<td>15</td>
<td>1</td>
<td>0.75</td>
<td>0.96</td>
<td>0.71</td>
</tr>
<tr>
<td>≥2.90</td>
<td>14</td>
<td>0</td>
<td>0.70</td>
<td>1.00</td>
<td>0.70</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- A Youden’s index of 0.78 corresponds to a cut-off value of $\geq 2.40$
- With this cut-off value
  - 90% (= sensitivity) of the mice with no disease are correctly identified
  - 88% (= specificity) of the mice with disease are correctly identified

- What is the probability that a titer of $\geq 2.40$ is protective?
For each titer (cut-off value) a two-by-two table is made

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th>No disease</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of mice above</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>No. of mice below</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

• Positive predictive value (PPV)
  - The probability that a mouse with a titer above the cut-off value will remain healthy = \( a/(a+b) \).

• Negative predictive value (NPV)
  - The probability that a mouse with a titer below the cut-off value will develop disease = \( d/(c+d) \).

• Incidence equals to \( (b+d) / (a+b+c+d) \).
Receiver operating characteristic curve: A 2\textsuperscript{nd} closer look

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Clinical symptoms</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden’s Index (J)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.25</td>
<td>No</td>
<td>90</td>
<td>76</td>
<td>0.66</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>≥2.40</td>
<td>Yes</td>
<td>90</td>
<td>88</td>
<td>0.78</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>≥2.50</td>
<td>No</td>
<td>85</td>
<td>92</td>
<td>0.77</td>
<td>89</td>
<td>88</td>
</tr>
<tr>
<td>≥2.60</td>
<td>Yes</td>
<td>80</td>
<td>92</td>
<td>0.72</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>≥2.70</td>
<td>No</td>
<td>80</td>
<td>96</td>
<td>0.76</td>
<td>94</td>
<td>86</td>
</tr>
<tr>
<td>≥2.80</td>
<td>Yes</td>
<td>75</td>
<td>96</td>
<td>0.71</td>
<td>94</td>
<td>83</td>
</tr>
<tr>
<td>≥2.90</td>
<td>No</td>
<td>70</td>
<td>100</td>
<td>0.70</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>20</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- With a cut-off value of 2.40
  - there is a 86\% (PPV) probability that a mouse with a titer ≥ 2.40, will be protected against disease
  - there is a 92\% (NPV) probability that a mouse with a titer < 2.40, will develop disease

*PPV and NPV depending on the incidence observed within the study*
Receiver operating characteristic curve: WNV - Proof of concept - conclusion

- WNV neutralizing titers are a correlate of protection.

- A cut-off value of 2.40 results in the optimal sensitivity and specificity

- A neutralizing titer of ≥ 2.40 provides a 86% probability that the mouse will be protected against disease.

ROC analysis is a valuable tool for determining correlate and level of protection
An AIDS vaccine: Why is it so difficult?

- How is HIV & AIDS transmitted?
- Is a vaccine ultimately the only way out?
- What about antibodies and T cells?
- Correlate of protection is key to success.
- Do T cell vaccines have a chance?
Possible strategies to develop an AIDS vaccine
Live attenuated measles vectors

WT Measles virus → Measles vaccine → Measles vector

+ TG rescue → HIV

Live attenuated measles vector = Vaccine

Vaccinate

New vector and transgene protein

Limited replication/transgene expression in cells
Antigen presentation
Immune response
Live replication-deficient adenovectors

- Wt Adenovirus
- E1
- Adenovector
- TG
- + strong promotor
- HIV

Replication-deficient Adenovector = Vaccine

- Vaccinate
- Transgene protein
- Transgene expression in cells
- Antigen presentation
- Immune response
Immunogenicity of live attenuated versus replication deficient vector expressing SIVgag

Measles vector

Adenovector

C57BL/6 mice (CD46TG or WT)

Human dose measles vaccine = 5x10^4 pfu

Estimated max human dose adenovector vaccine = 10^{11} vp
Human data in agreement with preclinical studies with Ad5 in SIV challenge model

Mamu-A*01-Positive Rhesus Monkeys

Merck vaccine did not reduce viral load upon the SIV challenge
Improving the antigens in the vaccine: Evidence for HIV env as an important antigen

Single dose vaccination in a stringent SIV model

Mamu-A*01-Negative Rhesus Monkeys

rAd5HVR48 gag/pol/nef/env
rAd5HVR48 gag/pol/nef
Sham

* two-tailed Wilcoxon rank-sum test

Addition of env to gag/pol/nef significantly decreased the viral load after the challenge
Improving the antigens in the vaccine: Mosaic antigens

HIV-1 can be divided into different clades and recombinants between clades based on genetic differences.

The breadth and potency of a vaccine may be increased if it induces cross-clade immunity.

**Mosaic antigen:**

assembled antigen that contains of one particular viral protein the immunological epitopes derived from different HIV-1 clades
Immunogenicity of HIV-1 mosaic antigens in rhesus monkeys

The mosaic vaccine yielded many more Gag, Pol, and Env epitope-specific T lymphocyte responses to PTE peptides than did a single M group consensus vaccine or an optimal natural C clade vaccine.

Broader vaccine coverage is indeed better

(Data D. Barouch/ B. Korber)
Evidence for the importance of CD4+ central memory T cells

CD4+ central memory T cells may predict efficacy of a vaccine

Preserved CD4+ Central Memory T Cells and Survival in Vaccinated SIV-Challenged Monkeys

Norman L. Letvin,1,2,5 John R. Mascola,3 Yue Sun,5 Darci A. Gorgone,5 Adam P. Buzby,5 Ling Xu,1 Zhi-yong Yang,1 Bimal Chakrabarti,1 Srinivas S. Rao,2 Jörn E. Schmitz,2 David C. Montefiori,3 Brianne R. Barker,2 Fred L. Bookstein,4,5 Gary J. Nabel1

Science. 312:1530 (2006)
Multiple component vaccine strategy

Mamu-A*01-Negative Rhesus Monkeys

Confirmed and published in Nature 2008

Immune control of an SIV challenge by a T-cell-based vaccine in rhesus monkeys
Jinyan Liu¹, Kara L. O'Brien¹, Diana M. Lynch¹, Nathaniel L. Simmons¹, Annalena La Porte¹, Ambryce M. Riggs¹, Peter Abbink², Rory T. Coffey¹, Lauren E. Grandpre¹, Michael S. Seaman³, Gary Landucci¹, Donald N. Forthal², David C. Montefiori², Angela Carville¹, Keith G. Mansfield⁴, Menzo J. Havenga⁵, Maria G. Pau⁶, Jaap Goudsmit⁶ & Dan H. Barouch²

Ad26/Ad5 combination induced high number of T cells and reduced the viral load.

T cell vaccines are still alive

- Induction of T cells does result in reduction of viral load if:
  - A multiple component vaccine, such as a heterologous prime/boost (that is, immunization with at least two different vaccines expressing the same antigen) is used.
  - Correct antigens are incorporated
Acknowledgement

Dan Barouch

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