HIV VACCINES AND IMMUNITY

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Worldwide an estimated 42 million people are living with HIV/AIDS and more than 20 million people have already died of AIDS.1 More than 95% of all new HIV infections are in developing countries, making HIV/AIDS among the most serious threats not only to global health, but to global development. It is now widely accepted that an effective, protective HIV vaccine would provide the best method for controlling the catastrophic HIV/AIDS pandemic, especially in less developed countries.2,3

Clinical trials of HIV vaccines have been under way for more than 15 years but the first phase III efficacy trial was completed only recently. Vaccine development and assessment have primarily taken place in developed, Western countries and most early-phase human clinical trials have been done in the USA and Europe. Globally, there have been more than 80 phase I and II trials but only one product – a bivalent, recombinant gp120 vaccine, AIDSVAX – has reached large-scale phase III efficacy testing in North America, The Netherlands and Thailand. Despite many years of research, most of the experimental vaccines are still limited to testing in animal models and no efficacious HIV vaccine for humans has yet been identified.

A wide variety of vaccine approaches are currently being pursued. For many years the vaccine pipeline was limited to monomeric gp120 or gp160 proteins based on laboratory strains of the virus, different synthetic peptides and simple poxvirus-HIV-1 recombinant vectors. This has recently expanded to include gp120 constructs based on clinical isolates of HIV-1, conformational envelope antigens, complex canarypox vectors expressing multiple HIV-1 genes, different constructs of naked DNA vaccines, new live vectors, including the modified vaccinia Ankara (MVA), and the Venezuelan equine encephalitis virus replicon. Vaccine classes and types are summarised in Table I.4

CELLULAR IMMUNE RESPONSES

Cytotoxic T-lymphocytes (CTLs) are part of the cellular immune response and are associated with control of viral replication. CTLs are capable of directly destroying HIV-infected cells. Therefore vaccines designed to stimulate CTL responses are more likely to lead to control of viral replication, and thus viral load, as opposed to creating sterilising immunity which would prevent primary HIV infection. A subset of T-lymphocytes (CD8+ T cells) have CD8 receptors on their surfaces and are the dominant effector cells responsible for defending the host against cellular level viral infections. Other CD8+ T cells are capable of suppressing HIV replication without necessarily killing the infected cell. CD8+ T cells may be critical to resisting HIV infection. A further component of cellular immunity includes the regulatory T cells which are capable of directing anti-}

<table>
<thead>
<tr>
<th>Class</th>
<th>Product name</th>
<th>Producer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Canarypox vectors</td>
<td>ALVAC vCP 1452</td>
<td>Aventis Pasteur</td>
</tr>
<tr>
<td>2. DNA plasmids</td>
<td>TBD - Clade C Gag-Env plasmids EP HIV-1090 pGA2/JS2 DNA Gag and Env DNA/PLG microparticles VRC-HIVDNA-009 WL063</td>
<td>Chiron Epimmune Emory Chiron</td>
</tr>
<tr>
<td>3. Fowlpox vectors</td>
<td>TBC-F357; TBC-F349</td>
<td>Therion</td>
</tr>
<tr>
<td>4. Lipopeptides</td>
<td>LIPO-5</td>
<td>Aventis Pasteur/ANRS</td>
</tr>
<tr>
<td>5. Modified Vaccinia</td>
<td>MVA pGA/JS2</td>
<td>NIAID-LVD</td>
</tr>
<tr>
<td>Anchora vectors</td>
<td>TBC-M358</td>
<td>Therion</td>
</tr>
</tbody>
</table>
| 6. Non-replicating adenovirus vectors | MRKAd5 HIV-1 Gag VRC-HIVDNA-010 | Merck /
|                         |                                       | NIH VRC         |
| 7. Peptides             | Wyeth me CTL peptide vaccine          | Wyeth           |
| 8. Proteins             | AIDSVAX B/B gp120 MN TBD - Clade C Env subunit gp140 SF-162 — oligomeric V2-deleted Nef Tat + gp120W61D | VaxGen Chiron VaxGen Chiron |
|                         |                                       | GlaxoSmithKline |
| 9. VEE vectors          | AVX-101                               | AlphaVax        |
| 10. Yeast vectors       | HIVAX-GS                              | Globelimmune    |
| 11. Live attenuated vector | VSV                                   | Wyeth           |

Source: The Pipeline Project. HIV vaccines in development.4
body- and cell-mediated immune responses. The main regulatory T cell, the helper T cell or CD4+ T cell, is also HIV’s main target.

CD4+ T helper function is typically measured by measuring T-cell proliferation following incubation with viral antigens. Most HIV-infected subjects have weak or undetectable proliferative responses to HIV antigens.6 Monitoring of cellular immune response to vaccination has advanced significantly in the last few years; the more complex chromium release assay has been superseded by new assays that allow a rapid identification of T-cell responses. Specifically, the gamma-interferon enzyme linked immunospot (Elispot) assay and the intracytoplasmic cytokine (ICC) assay are now being commonly utilised worldwide to measure T-cell functional response to HIV-1.

The failure of vaccinated or infected subjects to develop virus-specific proliferative responses is common and may result from infection and subsequent death of HIV-specific CD4+ T cells when they encounter an HIV-infected antigen-presenting cell. Relatively vigorous HIV-1-specific CD4+ T helper responses have been reported in HIV-infected long-term non-progressors and patients who received potent antiretroviral therapy early in the course of primary infection.1 Induction of strong HIV-specific proliferative responses may therefore be an important goal for candidate vaccines, although there is at present no definitive evidence for this conclusion.

HUMORAL IMMUNE RESPONSES

Humoral (antibody-mediated) immunity refers to protection provided by antibodies, the secreted products of B-lymphocytes. Antibodies are important because they are the immune system’s first line of defence and are thought to be the key to preventing viruses from ever contacting the cells they infect.

Antibodies function by either binding to part of the virus which may or may not have antiviral effects (binding antibodies) or are capable of inactivating or preventing the virus from infecting cells (neutralising antibodies). Finding ways to induce the production of antibodies able to neutralise HIV has proved difficult. These difficulties have arisen because HIV has the ability to mutate at a rapid rate3 and several clades of the virus exist.9

Gp160, a protein located in the outer envelope of HIV, has been identified as important for stimulating neutralising antibodies. However, several features of the HIV-1 envelope, e.g. glycosylation and the oligomeric form, limit its ability to be neutralised by antibodies.15

A variety of different assays have been used to characterise humoral responses against HIV, including binding to viral proteins (as assessed by either ELISA or Western blot), inhibition of syncytia formation, complement fixation, ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC), ability to neutralise infectivity or cell fusion, and ability to block CD4-gp120 interactions. At present, whether any of these assays is more likely than another to measure antibody responses relevant to protective immunity is unknown.11

Current HIV candidates elicit reasonably potent cellular immune responses, but only low levels of neutralising antibodies. Such CTL-based vaccines (e.g. DNA vaccines) do not prevent infection, but can have a beneficial effect on disease course. A combination of both humoral and cell-mediated immune responses may be needed for effective protection.3

MUCOSAL IMMUNE RESPONSES

In addition to cellular and humoral immune responses, the stimulation of mucosal immunity may also be necessary to achieve protection against HIV. The majority of HIV infections occur via mucosal routes and stimulating the mucous membranes that line the rectal and genital tract to induce mucosal immunity may be an essential requirement of an effective HIV vaccine.

Induction of protective immunity against mucosal challenge with SIV or SHIV has been reported in several macaque models.12,13 Although these animal model results cannot be assumed to hold true for humans exposed to HIV, there is evidence from studies on highly exposed persistently seronegative (HEPS) individuals that mucosal immune responses are possible.14,15

THE PRIME-BOOST STRATEGY

One way to enhance immune responses to HIV, which is currently in vogue, is the combination approach called prime-boost strategy. This strategy endeavours to get the immune system to make both neutralising antibodies and to launch a strong cell-mediated response. The immune system is first primed with one vaccine, e.g. naked DNA, and then boosted with a different vaccine, e.g. live vector/protein.5

By itself, a naked DNA vaccine stimulates production of memory T cells but few antibodies. The prime-boost combination, however, can stimulate a strong cellular immune response, including persistent killer CD8+ T cells as well as antibodies that neutralise the virus. The prime-boost method has shown promise in animal models and better protection has been achieved using this method than any other HIV vaccine strategy to date. This strategy has also been tested in human clinical phase I and II trials, where it has been found to be safe and effective.

IMPLICATIONS OF THE VaxGen TRIAL RESULTS

The results of the first phase III AIDS vaccine (AIDSVAX B/B) trial were announced in February 2003. Although safe, the vaccine did not show an overall reduction of HIV infection in the vaccination arm of the entire study population.16 These results suggest that narrowly defined antibodies are not effective in providing protection against HIV infection.

Protein-based vaccines, such as AIDSVAX B/B, generally elicit only a humoral response, without significant stimulation of the cellular arm of the immune system. The reasons the vaccine was not successful may be either that the antibodies generated by the vaccine did not coincide with the antigens on the viruses which led to infection in the study population or that the antibodies on their own were not sufficient to protect against HIV infection. More phase III trials are needed to better understand this.

CONCLUSION

The HIV vaccine pipeline includes many types of candidate and specific epitope vaccines that are being developed in parallel. Despite significant advances in AIDS vaccine research, considerable challenges remain. The AIDS vaccine research field will move forward with further phase III efficacy trials. An AIDS vaccine remains an important hope for the control of HIV/AIDS, but its realisation is still several years away.

REFERENCES

4. The Pipeline Project. HIV vaccines in development. (http://chi.ucsf.edu/vaccines)

ALLSA AGM

ALLSA members please note details for the Annual General Meeting of ALLSA.

DATE: Wednesday 27th August 2003
TIME: 16h00
VENUE: International Convention Centre, Cape Town