Current Strategies in HIV-1 Vaccine Development
Using Replication-Defective Adenovirus as a Case Study

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Note: I have added some clarifying comments to the slides -- please click on “Comments” under “View” to see them.
Background

- Although antiretroviral therapy had led to a decrease in the occurrences of AIDS-related conditions and AIDS-related death, there are several complicating factors:
  - Life-long use
  - High failure rates
  - Significant toxicities
  - Adherence difficulties
  - Development of resistance

- The rapid spread of AIDS, in addition to the complicating factors and difficulties associated with the availability of antiretroviral therapy, highlights the need for a safe and effective vaccine against HIV-1 infection.
Background

- Challenges facing HIV vaccine development
  - HIV isolates include a genetically diverse population of viruses
  - Genetic diversity is continuously generated in a single infected individual
  - Vaccine needs to elicit both mucosal and systemic immunity
  - High levels of viral replication persist in face of seemingly robust anti-viral antibody and cell-mediated immune responses

Presentation Note:
While discussing genetic diversity, mention that the viruses of the HIV-1 type include various clades that are clustered epidemiologically in geographic regions. Also, mention that perhaps no vaccine-elicited immune response is fully capable of eliminating or containing HIV replication.
Presentation Note:

How would a vaccine stimulate antibodies? -- First an HIV vaccine would alert the body that the virus is present and stimulate immune cells, known as B cells, into making disease-fighting antibodies. Once the immune system detects the infection, B cells bind to the virus and digest it. Once it's digested, the B cells display pieces of the virus' protein on their surface. Stimulated by this display, helper T cells bind to the virus pieces on the B cells' surface. The helper T cells secrete a chemical that tells the B cells to multiply and form clones of the specific B cells needed to fight HIV. Some cells from the clones become memory B cells, which respond rapidly to any encounter with the same virus. Other cells from the clones mature into plasma cells and secrete antibodies to the virus. These antibodies bind to the virus and prevent it from infecting healthy cells.

How would a vaccine help kill infected cells? -- Because HIV can be transmitted as a free-floating virus or through infected cells, an HIV vaccine also would help train killer T cells to recognize immune cells infected with the virus and destroy them. Cells display markers on their surface that are unique to each individual. When a virus attaches a cell, pieces of the virus combine with the cell's marker, thus changing the marker and alerting the immune system that the cell is infected. The killer T cells bind to the new marker, and the infected cell is destroyed, thus preventing the infected cell from producing more HIV.

Background

HIV-1 Vaccine Strategies: Traditional Approaches

- **Live attenuated virus vaccines**: not feasible because live attenuated HIV-1 vaccines have pathogenic potential
- **Inactivated viruses**: not feasible because useful protective immunity is not elicited by this strategy
- **Recombinant protein vaccines**: not feasible because these vaccines cannot elicit virus-specific cytotoxic T lymphocytes, and antibodies generated are restricted in the diversity of viral isolates they can neutralize

Presentation Note:
While most viruses for which vaccines have been developed are contained mainly by neutralizing antibody, HIV is controlled by cell-mediated immunity.
Research Questions and Methods

● Research Questions
  – What strategies are currently being used?
  – Which has most promise as a potential vaccine against HIV-1 infection?

● Methods
  – Review of current medical literature
  – Input from Dr. Katzenstein
  – Review of Aventis and Merck & Co.’s current trials
Results

- Considerable effort is currently being focused on the development and assessment of two novel strategies for vaccination:
  - **Plasmid DNA immunogens**: Following inoculation of animals, plasmid DNA vaccines express encoded viral proteins and these proteins elicit both humoral and cellular immune responses.
  - **Live vector-based approaches**: Genes encoding proteins of HIV-1 can be inserted into the genomes of a variety of bacteria and viruses; and, when the resultant recombinant organisms infect a susceptible animal or human, immune responses are generated to both the parental organisms and the products of the inserted HIV-1 genes.
    - Replication-defective adenovirus
Results

- Adenovirus
  - Virus that usually infects the tissue lining of the respiratory tract, causing acute upper respiratory tract infections (colds)
  - Depending on the type of infection, it can cause other illnesses, like gastroenteritis, conjunctivitis, cystitis, and rashes

Source: http://www-micro.msb.le.ac.uk/3035/adenoviruses.html
Results

- Replication-defective adenovirus
  - Made replication-incompetent by the deletion or inactivation of certain genes
  - Used as a vector to transport a certain gene or genes into cells
  - Delivery of the HIV-1 gene stimulates body to generate a potent cellular immune response
  - Elicits high-titer antibody and high-frequency CTL responses
- Problems
  - Pre-existing antibody responses to adenovirus serotype 5 previously infected with this common pathogen dampen expression and therefore immunogenicity?
  - Localization of recombinant gene expression to the olfactory bulb of the central nervous system?
Results

● Current Trials
  - **September 17, 2003**: Aventis and Merck & Co., Inc. announce that human trials have begun to test the safety and immune responses generated by using a combination of two anti-HIV-1 vaccine candidates in a complementary way
    - Replication-defective adenovirus type 5 vector
    - Canarypox virus vector
  - **September 19, 2003**: The HIV Vaccine Trials Network (HVTN) and Merck & Co., Inc. announce that they have begun the first global clinical trial of Merck’s HIV vaccine candidate, replication-defective adenovirus type 5 vector

Presentation Note:
Trial that began on September 19 interested in whether one’s genetic background and nutritional status affect the immune response generated by the vaccine.
Conclusion

- Significant challenges face HIV vaccine development
- Traditional approaches have failed
- Current strategies include use of plasmid DNA immunogens and live, recombinant vectors
- Replication-defective adenovirus vectors represent a promising platform for the development of a vaccine against HIV-1 infection
- Effective vaccination may ultimately require two or more vaccines used in conjunction, an approach to vaccine development that differs from traditional vaccine designs
Selected Bibliography


