DEVELOPING VIRAL VACCINES

APPROACHES TO IMMUNIZATION

ACTIVE IMMUNIZATION

Goal: To stimulate an individual to develop an immunologic defense in advance of a challenge. This may be accomplished by using live-attenuated virus, killed virus or a subunit vaccine.

PASSIVE IMMUNIZATION

Goal: To supply preformed human or animal antibody to provide temporary treatment or protection to individuals already exposed or about to be exposed to an infectious agent.

Examples: VZIg (VZV), Palivizumab (RSV) RIg (rabies), gammaglobulin (HAV)

VACCINES

- Live, attenuated virus - generally considered the "best" vaccines because they replicate in humans and elicit the "appropriate" immune response. However, reversion to virulence is possible.

- Killed virus - good for generating a serum antibody response, but sometimes do not provide life-long immunity.

FACTORS INFLUENCING VACCINATION STRATEGY

- Type of immune response - mucosal, serum IgG or cellular.

- Age of immunization - when is appropriate immune response possible? (Example: measles).

- Duration of immunity - will boosters be required?

- Selection of antigens - whole virus vs. subunit vaccines.

VACCINE SUCCESS STORY: ERADICATION OF SMALLPOX

- History of Smallpox - one of the reasons smallpox is virulent is because it produces proteins which block activation of the immune system.

- Development of vaccination- Jenner, 1796.

- Factors involved in eradication (1980) - see Table 1.
Table 1. Factors Involved in the Eradication of Smallpox

1. The disease is severe and clearly worthy of eradication.

2. Smallpox is strictly a human disease with no known animal or inanimate reservoirs. The outcome for an infected individual was either death or permanent recovery. Subclinical or persistent infections were virtually unknown. Individuals who recover are permanently immune.

3. Accurate diagnosis is relatively easy even by partially trained personnel; clinical features were distinctive and easy to recognize. The scarring of infected individuals leaves a record of the disease.

4. The disease spreads rather slowly. Generally it takes 2-3 weeks between generations of cases.

5. All strains of variola virus are indistinguishable antigenically. There was only one worldwide serotype.

6. The virus is relatively resistant to inactivation by physical and chemical agents. This facilitated the development of freeze-dried vaccine, essential for use in hot, rural, undeveloped countries with unreliable refrigeration facilities. Inexpensive vaccination can be carried out by unskilled medical personnel.

7. The worldwide unification of people of various political persuasions was focused toward the common goal.

Complications associated with smallpox vaccination

Vaccinia virus is not a perfect vaccine. It is a live virus vaccine, and there are substantial risks associated with the use of any live virus vaccine, especially vaccinia. From our previous experience with vaccinia, we know that deaths from complications occurred at a rate of 1 to 2 per million primary vaccines. In addition, pregnant women, persons with eczematous conditions, immunosuppressed individuals with AIDS or those undergoing chemotherapy have a higher risk of complications, and should avoid vaccination or contact with a primary vaccinee.

New vaccines, based on fowl pox virus and a more attenuated strain of vaccinia, called modified vaccinia Ankara (MVA), are under development.
Replication takes place entirely in the cytoplasm of infected cells. This virus encodes many enzymes, including DNA polymerase and viral proteins that block activation of the immune system (so called virokines and viroceptors).

**TAKE HOME MESSAGE OF POXVIRUS REPLICATION:**

1. Poxvirus replicates in the cytoplasm.
2. Poxvirus encodes its own DNA-dependent DNA polymerase and DNA-dependent RNA polymerase.
3. Poxvirus encodes proteins that are synthesized and released during viral infection which block interleukins and thereby inhibit the immune response from efficiently clearing viral infection.
POXVIRUSES AS A VACCINE VECTOR

The success of vaccinia as a live virus vaccine together with powerful recombinant DNA technology enables us to develop multivalent, economical vaccines. The "new generation" of vaccines takes advantage of the large DNA genome of vaccinia and the knowledge we have already gained from Vaccination Studies. Foreign genes are inserted into vaccinia via recombination (see Figure 2). The foreign genes are expressed when the virus replicates in the vaccinated individual. An immune response is generally made against the foreign protein.

I will show slides about the use of vaccinia expressing rabies glycoprotein as a method to vaccinate raccoons against rabies virus and reduce the incidence of disease transmission to humans. You can check out this program at:

STUDY QUESTIONS

1. Human populations are no longer immunized against smallpox. What risks do you think this may involve?

2. Assuming that the appropriate vaccinia-based recombinant poxvirus vaccines are available; would you suggest that AIDS sufferers be vaccinated against opportunistic infections using recombinant live poxvirus-based vaccines?

3. What are the reasons that poxvirus-based recombinant vaccines are particularly attractive for use in developing countries?

4. Based on the lessons of the smallpox eradication program, what other diseases, based on biological considerations, and might be plausibly targeted for worldwide eradication?

EXAMPLE OF TEST QUESTION

Small pox was eradicated in the 1970's by identifying cases and immunizing all potential contacts. This strategy won't work for poliovirus eradication because:

A. People are more mobile today.
B. Some people can shed poliovirus for life.
C. Rodents can act as a reservoir for poliovirus.
D. Most poliovirus infections are inapparent.
E. Re-assortment can generate "new polioviruses".

CORRECT ANSWER TO ABOVE QUESTION: D