Herpes Simplex Vaccines

Maurice R. Hilleman
Division of Virus and Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486

Summary

Prospects for the development of vaccines against herpes simplex virus types 1 and 2 and other herpesvirus group vaccines are discussed from the scientific, medical, and economic standpoints. Probably, the most practical development will be glycoprotein subunit vaccines, prepared from herpes simplex virus types 1 and 2, that will be tested for prophylaxis and therapy of acute viral disease and for cancer that may be caused by these agents.

Infection with particular viruses of the herpesvirus family presents 3 possible outcomes: lytic infection with resulting acute illness, latency with no evident illness, or neoplastic transformation with cancer. Herpesvirus hominis viruses may express as lytic infection or as latency. Their role as cancer-producing agents in man can be regarded at present only as likely but unproved.

H. hominis is transmitted horizontally and hence is subject to immunological intervention, specifically by vaccines that stimulate immunity and prevent or limit proliferation of the naturally acquired virus on subsequent infection.

If one could choose a candidate herpes cancer virus of man for vaccine research, one would surely select the Epstein-Barr virus that is so firmly implicated in Burkitt lymphoma and in nasopharyngeal carcinoma. For the present, such an approach is impractical because of the very limited replication of this agent in vitro. This leaves H. hominis types 1 and 2 as the most likely practical candidates and, with them, the option for killed or live virus vaccine.

Given a choice, one would prefer live virus vaccine because live virus vaccines in general afford higher level and longer lasting immunity than do killed vaccines, and only a small dose of virus is needed for immunization. There is the further background of proved success in animal herpesvirus vaccines against swine pseudorabies, infectious bovine rhinotracheitis, equine rhinopneumonitis, and avian laryngotraechitis that protect against acute illness and there is also the highly effective turkey herpesvirus vaccine against Marek’s disease, a neoplastic disease of chickens. Although live viruses offer obvious advantages, H. hominis viruses have no reliable markers for oncogenicity that might apply to man. The available information on herpesvirus cancer indicates that this is a disease of limitation of viral gene expression in which the infection is not productive of infectious virus but instead provides the opportunity for neoplastic transformation. Even killed whole virus vaccine raises doubts as to safety on the basis of data that show neoplastic transformation in vitro by virus inactivated by UV or by photodynamic effect, on the basis of other data that show induction of lymphoma in owl monkeys by heat-inactivated Herpesvirus saimiri virus. There is current preference, therefore, for subunit vaccines that contain the immunological determinants of the herpesviruses but that are free of all viral nucleic acid. All evidence for the contemporary period points to the chemical class called glycoproteins as the predominant determinants for immunity against viruses, bacteria, and cancer cells, and this is certainly true for the herpesviruses. H. hominis strains appear to produce sufficient amounts of glycoproteins in cultures of cells of embryos of chicks, derived from special leukemia-free flocks, to be economically practical for vaccines. Furthermore, their immunogenicity can likely be enhanced by coupling with larger molecules, such as polypeptides, or by formulation in Adjuvant 65. In dealing with immunological determinants in cancer, cognizance need be taken that immunological responses can sometimes enhance as well as prevent or suppress tumor. Hence, the purposeful separation of glycoproteins that are determinants for virion-neutralizing antibody from those that may be inserted into tumor cell membranes may be extremely important.

Killed whole herpes simplex virus types 1 and 2 vaccines prepared for preventing or treating primary or recurrent acute episodes of herpesvirus infection in humans have not been highly encouraging in terms of effectiveness. Although eliciting neutralizing antibody and protection against challenge infection in experimental animals, they have not given good immune responses in inexperienced human subjects and have given, at best, only mildly encouraging results for treating recurrent herpes. Neutralizing antibody is always abundant in herpesvirus carriers, and it probably has little to do with the clinical outcome in cases of recurrent disease. Vaccines aimed at preventing or limiting primary virus infections must be adequately protein, and the protective efficacy of vaccines can be measured in terms of cancer prevention. Good insight into likely efficacy might be achievable in the shorter term, however, based on tests in man to prevent the acute lytic forms of the disease, namely, herpes labialis and herpes genitalis. In this instance, limitation of viral events might be expected also to indicate limitation of the probability for the occurrence of neoplasia. It is fortunate, in the family of herpesviruses, that...
marmosets and other primates readily develop lymphomas and leukemia after inoculation with *H. saimiri* virus derived from squirrel monkeys or with *Herpesvirus ateles* from black spider monkeys. For example, *H. saimiri* vaccines, prepared by the same procedure as *H. hominis* vaccine and tested in the marmoset system, might be expected to yield a great amount of data on safety, efficacy, and regimen that can be extrapolated to the human vaccine and provide important guidelines for its use.

Important probes toward the objective of making vaccines against carcinogenic herpesviruses are in progress. Most recently, Laufs and Steinke (2) showed protection of cottontop marmosets against lymphoma induced by *H. saimiri*, using *H. saimiri* vaccine prepared by treating the whole virus with heat and formaldehyde. While live Marek’s virus vaccine is obviously the method of choice in preventing the disease in chickens, it is important to note that subunit vaccines may also be effective and may point the way to use of such vaccines in man. Kaaden and Dietzschold (1) have reported prophylactic efficacy of vaccine prepared from plasma membranes of virus-infected cells, and Lesnick and Ross (3) are stated to have achieved success using, as vaccine, soluble viral antigens from Marek’s virus-infected cells in culture. All of these data provide a basis for expectation of success in this general area of herpesvirus control in humans.

References

Herpes Simplex Vaccines

Maurice R. Hilleman


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/36/2_Part_2/857

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.