VACCINES

ANTI-IDIOTYPIC ANTIBODIES: A SAFER WAY TO IMMUNIZE AGAINST AIDS?

BOSTON—Vaccination without direct exposure to any viral nucleic acid, protein, or peptide could become possible using anti-idiotypic antibodies.

Researchers here are developing these substances as immunizing agents for two classes of human T-cell leukemia viruses (HTLV): HTLV-I, which causes adult T-cell leukemia, and HTLV-III, the virus believed to cause acquired immunodeficiency syndrome (AIDS). Other investigators are using the same strategy to develop vaccines against a variety of pathogens, including hepatitis, rabies, influenza, trypanosomes, and *Escherichia coli*, as well as for cancer therapy.

An anti-idiotypic antibody is a third-generation image of an immunogen. If an antigen is a key, then the antigen-combining site on the antibody is a soft wax mold made from the key. This impression is the idiotype of the original key. The anti-idiotype is a second key made from the wax mold of the first. This new key may have a different overall shape, but the part that fits the lock will be exactly congruent to that on the first key. So a second wax mold, made from the second key, should also fit the teeth of the first key.

Perhaps the most successful anti-idiotypic antibody vaccine yet produced is for reovirus. A group lead by Mark I. Greene of Harvard and Tufts Medical Schools here developed the vaccines as part of a model system. Greene is applying this strategy to production of HTLV vaccines.

Greene's method resembles strategies used by other laboratories, but it focuses on careful screening and purification of antibodies. Ultimately, their two-tier selection system isolates antibody molecules that mimic a single immunogenic determinant present in the virus.

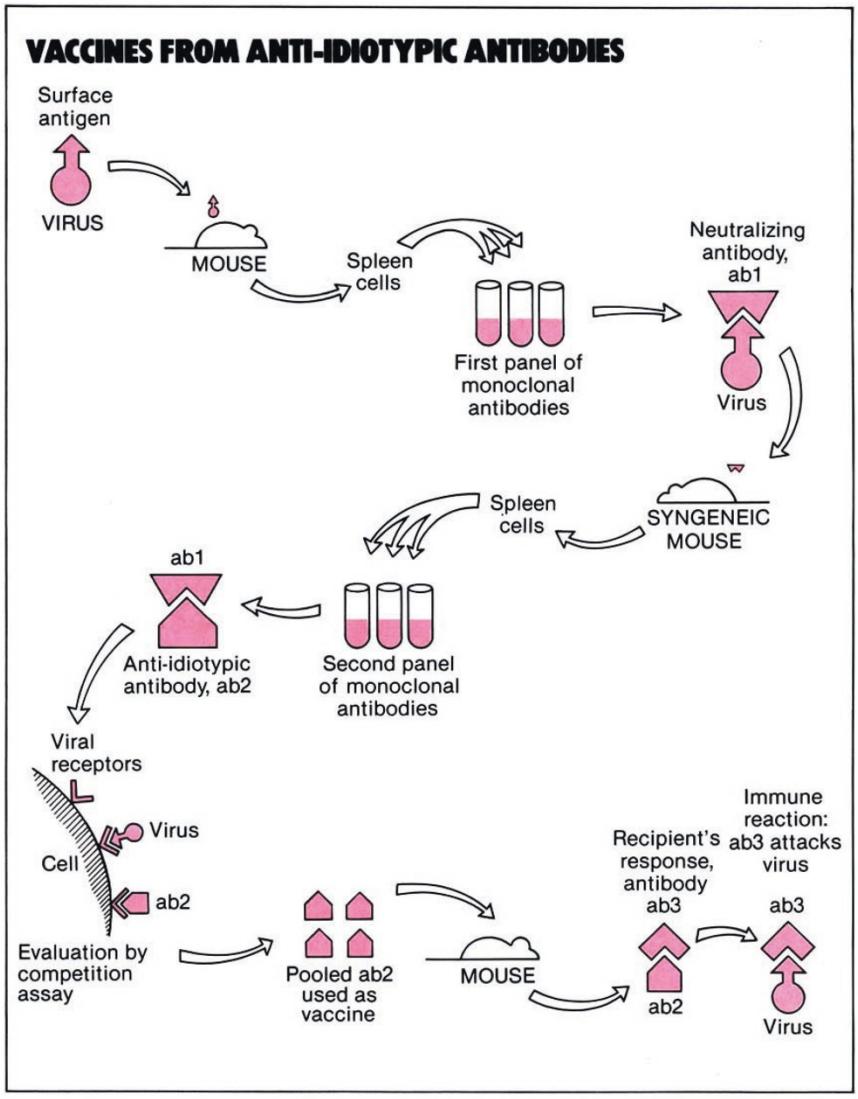
To make such an anti-idiotype to reovirus, for example, researchers first expose a mouse to reoviral immunogens. They then generate a panel of monoclonal antibodies for those immunogens and select the antibody that interferes most with reoviral infectivity *in vitro*.

This antibody is injected into a syngeneic mouse—a mouse genetically identical to the first, so that its immune system accepts normal proteins and nucleic acids from the first mouse. The recipient mouse's system reacts only to the antibody's antigen-recognition determinant, its idiotype. The second mouse obligingly produces a second panel of antibodies that recognize and bind to the idiotype of the first antibody.

Some of these second-round, anti-idiotypic antibodies contain exact images of part of the original viral immunogen. This "internal image" makes the antibody useful as a viral vaccine, while the rest of the antibody molecule supplies additional immunogenic stimuli that enhance immune responses to the vaccine.

Competition assays demonstrated the structural identity of the reovirus and one of its anti-idiotypic antibodies: the "internal-image" antibody competed effectively with virus for binding to cellular receptors.

Vaccination provided the ultimate proof of the anti-idiotypic antibody's mimicry. In mice, the antibody vaccine for reovirus actually induced immunity at least as efficiently as the



virus itself. "108 antibody molecules immunized to the same extent as 109 replicating viruses," says Greene.

"I anticipate that anti-idiotypic antibodies might work better than more conventional vaccines for HTLV due to the breadth of the immune response they induce and the small amount of viral antigen required to develop them," said Dani Bolognesi, deputy director of the Duke University Cancer Center and chair of a National Cancer Institute (NCI) subcommittee on AIDS.

"In the past, vaccines made from anti-idiotypic antibodies were primarily of interest as tools of basic research," noted Bolognesi. "Their importance is now enhanced since they can be brought to bear on a national health problem."

Anti-idiotypic antibodies are considered much safer than inactivated or attenuated viruses, particularly for vaccinating against tumor viruses such as HTLV.

Vaccines have been made of immunogenic viral proteins, either purified from the virion or produced by recombinant DNA methods using an isolated viral gene. Both these methods require purification schemes that are often more difficult than antibody purifications. Proteins made by cloned genes may also require post-translational modifications to make them useful antigens.

Synthetic peptides that mimic critical immunogenic sites are being developed for vaccines, but in some cases it can be difficult to make these peptides assume a proper immunogenic conformation. This problem has, for example, stymied efforts to develop a rabies peptide vaccine, noted Kevin Reagan of the Wistar Institute (Philadelphia), who is developing an anti-idiotypic antibody vaccine for rabies.

Reagan emphasized, however, that the anti-idiotypic approach is not without its own shortcomings. "Production of the antibody can be tricky since it is largely a black box method." He cited investigations in which anti-idiotypic antibodies for herpes virus were injected into mice. Instead of stimulating an anti-herpes response, this treatment suppressed immunity. Careful selection of the antibody, using methods like those devised by Greene, may eliminate some of this uncertainty, he said.

Another question regarding the potential efficacy of any vaccine for HTLV is whether the presence of circulating antibody will attenuate viral infectivity. "Almost everyone with AIDS and lymphadenopathy who carries HTLV-III also has antibody directed against the virus," noted Jerome Groopman of New England Deaconess Hospital (Boston). "The question remains whether immunity to HTLV-III is mediated by an antibody or by cellular immunity."

It took the Harvard group about five years to perfect its now-patented method for producing an anti-idiotypic antibody vaccine for reovirus. Now that the technique is established, Greene predicted that it may only take a few months to develop vaccines for HTLVs or other viruses.

Greene's laboratory has already begun to produce monoclonal antibodies directed against an important immunogen of HTLV-I. They are attempting to use these antibodies to prepare anti-idiotypic reagents. For HTLV-III, the first-stage antibodies are being isolated.

Greene sits on the scientific advisory board of Cambridge BioScience Corporation (Hopkinton, MA). He is not receiving any financial support from the company to develop HTLV vaccines, but he expects that the company will be interested in producing and testing the vaccine once a prototype has been made.

Gerald Buck, president of Cambridge BioScience, confirmed his company's interest in the HTLV vaccines being developed by Greene. Cambridge BioScience is trying to find corporations willing to support large-scale development and testing. One possibility is an NCI vaccine-development contract.

Cambridge BioScience has a particular interest in vaccines and diagnostic reagents for retroviruses. It already produces these products for feline leukemia virus, a cat retrovirus considered a model for HTLV. The company is also interested in production of more conventional vaccines for HTLV, as well as reagents for diagnosis of HTLV infections.

The market for HTLV vaccines is estimated to be very large. Potential recipients of a HTLV-III vaccine include groups with a high incidence of AIDS, such as homosexuals, intravenous drug users, and hemophiliacs, explains Groopman. Additional likely recipients are residents of regions where the virus seems endemic, such as Haiti and central Africa. A vaccine for HTLV-I would also have its greatest impact in areas where the infection is endemic—southwestern Japan, the Caribbean basin, and the southeastern United States, particularly among blacks. **—Mitchel L. Zoler**