New Vaccines for Old Diseases

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Opportunities for advances that will improve livestock productivity are greater today than ever before through the powerful new products of the biotechnological process. Each year, because of disease, the productivity of livestock and poultry in the United States is reduced by an estimated 15 to 20 percent. Investigations show that many animal diseases can be controlled by combinations of procedures, such as improved diagnosis, control of the insect carriers of disease, vaccination of susceptible animals, enhancement of the immune system, and improved therapy.

Most vaccines against pathogenic (disease-producing) organisms of viral, bacterial, fungal, or parasitic origin consist of the organism being either killed or chemically weakened or genetically modified to reduce its virulence. The animal's immune system responds to vaccines by producing antibodies that bind to antigens or surface structures of the infecting organism, labeling it for attack and destruction by the immune system. Antibodies produced in response to the modified or killed pathogen circulate throughout the animal's body and render the animal resistant to later infections by the live pathogenic organism.

Vaccinia Virus Vectors

During the last few years, several groups of U.S. scientists have designed vaccine vectors (carriers) that may someday be universally used to safely vaccinate a variety of animal species against a number of infectious agents. Vaccinia virus vaccines were used extensively worldwide during the smallpox eradication campaign 10 to 20 years ago. These same smallpox vaccines have recently been genetically engineered to express foreign proteins from different disease-causing organisms, allowing their potential use as vaccine vectors for domestic animals as well as humans. The genetically modified vaccinia virus grows in most animal species and can be engineered to express one or more foreign protein antigens, thus increasing their general utility and potential effectiveness.

The use of modified, weakened live viruses to stimulate immune responses exemplifies the exciting and powerful recent advances in applying genetic engineering and recombinant DNA technologies to the problems of control and eradication of infectious diseases in domestic animals, both in the West and Third World countries.

Vesicular Stomatitis Virus

Vesicular stomatitis virus (VSV) is a highly contageous disease of cattle, horses, and pigs, characterized by vesicular lesions on the tongue and other areas inside the mouth. The lesions are similar to those seen in animals infected with foot-and-mouth disease, another highly contageous and fatal cattle disease. Humans also are susceptible to VSV, and exhibit influenza-like symptoms. Outbreaks of VSV have been devastating to the livestock industry, as exemplified by a recent epizootic outbreak in 13 Western States.

VSV has five distinct proteins, only one of which, the G-glycoprotein, has been shown to promote protective immunity. Vaccinia virus has recently

been genetically engineered to express the VSV G-glycoprotein. Experiments recently completed with this vaccine indicated that immunity to the G protein was induced in vaccinated cattle. It effectively protected animals from a controlled infection by VSV under laboratory conditions, whereas unvaccinated animals were susceptible to mouth infection of VSV. Field trials are planned to determine this vaccine's effectiveness in a natural setting.

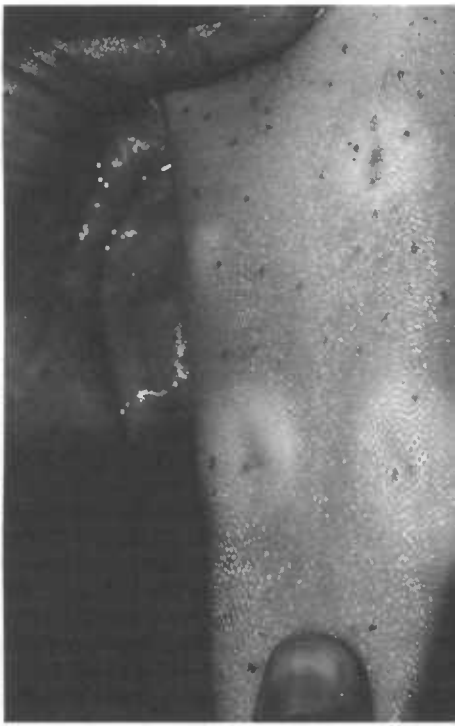
Bluetongue Virus

Bluetongue (BTV) is an arthropod-transmitted viral disease of both domestic and wild ruminants in the United States, Asia, Australia, Europe, and Africa. The virus can be transmitted between cattle and sheep by gnats.

The disease is characterized by fever, erosion, and ulceration inside the nose, lameness, weight loss, and eventual death of some infected animals. Direct losses from subclinical disease, fetal death or abortion, and the hazards of animals introducing the infection to a susceptible flock or herd are well appreciated by ranchers and veterinarians. A segment of the bluetongue virus genome (set of chromosomes with genes) has been cloned recently. Construction of a recombinant vaccinia virus expressing one of the BTV capsid structural proteins is under way. Limited experimental trials of the recombinant virus under controlled conditions are contemplated for the near future.

Anaplasmosis

Anaplasmosis is a parasitic blood disease of cattle and other ruminants caused by the micro-organism rickettsia *Anaplasma marginale*. Anaplasmosis occurs worldwide in tropical and subtropical areas, including several regions of the United States, where



Courtesy of Dr. T. Yilma, Washington State University

Lesions on a cow's tongue show the presence of vesicular stomatitis virus.

annual losses amount to 50,000 cattle deaths with an estimated value of $100 million.

The rickettsia is transmitted by ticks and biting flies to susceptible cattle where it infects the red blood cells. During the acute infection the parasite increases geometrically in number, causing extreme anemia. The next step is a marked weight loss, abortion in pregnant cows, and even death. Cattle that recover suffer persistently from low-level infection and serve as a reservoir for transmitting the organism to other susceptible cattle.

Recently, one of the major surface antigens of the anaplasma parasite was identified. Current research focuses on more fully characterizing the genetic material (DNA) coding for

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A sheep receives an injection of a killed-virus bluetongue vaccine.

this gene. It is envisioned that this gene could be genetically engineered into vaccinina virus vectors.

To be completely effective, a parasite vaccine must provide sufficient immunity to eliminate 100 percent of the infecting organisms, since at each stage of the parasite's life cycle, different surface proteins may be present. Because a vaccine against one stage may not be effective against a later stage of the same parasitic disease, it may be necessary to construct vaccines expressing surface antigens from each stage of the parasite's life cycle for complete protection.

Immunoadjuvants

The antiviral and immunoregulatory effects of bovine interferons and interleukin-2 are being assessed in cattle for their potential to increase the cattle's immune response to specific viral antigens. Interferon is one of several lymphokines (proteins) that act directly on B-cells and stimulate immunoglobulin secretion by twofold to fivefold in experimental animals. Interleukin-2 (IL-2), an immunomodulator, is released from antigen-stimulated lymphocytes and functions to switch T lymphocytes into a proliferative phase, thus allowing for clonal expansion of the stimulated population of cells.

The bovine genes for these biologically important immunomodulators will soon be inserted into vaccinia virus vectors so that their potential to enhance the immune response can be assessed in a domestic animal. If these immunomodulators can increase the immune response, the concept of vaccination may be revolutionized.

Advantages of Live Vaccines

Live vaccines, such as vaccinia virus vectors, have distinct advantages over inactivated, subunit, or synthetic vaccines because they multiply in the vaccinated host and produce more antigen, and potentially a higher level of and more durable immunity. In addition, several related or unrelated foreign protein antigens can be simultaneously expressed from a single vaccine preparation, allowing the vaccination of a herd of animals against several diseases simultaneously.

Recombinant vaccines expressing varied combinations of foreign proteins can be constructed, allowing vaccines to be targeted specifically for diseases of extreme veterinary concern in different regions of the world. The eventual exportation of these vaccines and their technologies to Third World countries is an endeavor toward which everyone associated with basic research in disease prevention is striving.