Recombinant DNA to Make Animal Vaccines

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It has been less than 200 years since Edward Jenner, the famed English physician, discovered and then applied the concept of immunization in his work with smallpox. Jenner's work led quickly to the science of molecular biology and genetics, and to the use of altered forms of organisms to fight disease in both humans and animals. Vaccines, using altered forms of the original virus or bacterium, have since been used to prevent polio, canine distemper, brucellosis, infectious bovine rhinotracheitis, parvo, hog cholera, and many others.

Yet, as good as many of the vaccines for those diseases are, they have their limitations. For exactly that reason, the biologic industry is looking beyond conventional technology to develop something better to produce vaccines. One of the most promising new areas is that of recombinant DNA technology.

There are really three types of vaccines, the modified live vaccines, the killed or inactivated vaccines, and the subunit vaccines. The most common and generally the most effective vaccines have been those made with modified live viruses. Inside the host, they behave like the natural infection, multiplying and inducing a longer lasting immunity. But, these conventionally modified live virus vaccines also may have disadvantages. The organisms of the vaccines have been modified or hybridized in nature or by deliberate passage in an unnatural host such as an animal or cell culture. This modification has altered the ability of the organism to cause disease, but its nucleic acids are active so they can replicate and trigger an immune response. The trouble with this procedure is that, because of its trial and error nature, the genetic basis for the reduced virulence of the organisms is seldom known. There is a risk of causing disease in a weakened host or a reverse mutation back to the virulent form, advancing the disease instead of limiting it.

Killed virus vaccines are manufactured from the dead virus or parts of it. Generally speaking, they work to stimulate circulating antibodies against the viral coat proteins. The resistance they provide is limited, but for some diseases they are the only kind of vaccine available. Inactive or killed organisms generally are safer because since they are dead they cannot replicate nor revert to the original virulent strain. However, extreme care must be taken to ensure that no live virulent virus remains within the vaccine. They may be safer, but they usually do not produce as durable an immunity as the modified live virus vaccines.

The use of recombinant DNA technology to manufacture animal vaccines is a fairly recent development. However, several vaccines produced by this new technology now have been licensed by the USDA. These are mainly vaccines to prevent pseudorabies in swine but many others are in various stages of development. Veterinary practitioners need to understand the technology so that they can converse with clients about it. As more rDNA vaccine comes onto the market, clients may have questions regarding the safety and efficacy of these vaccines. It will become even more important to be knowledgeable about these products.

To understand this new technology, we must understand DNA. It is a unique molecule that carries the genetic material of all living species—plants, animals, and microorganisms, its structure is simple, yet its arrangement of components within that structure is so versatile that it can carry the genetic data for such a complex organism as the human as well as for simple microorganisms. The only exceptions to this statement is where RNA carries the genetic data. Some viruses have RNA as their genetic backbone.

The technique of gene-splicing or recombinant DNA can be visualized by thinking of DNA as two strands of twisted paper. With knowledge gathered in recent years, genetic engineers can cut out a section of one DNA paper strand and attach it to the DNA strand of another organism. Or, they can replace it with another snippet of paper from yet a third organism. Through this process, undesirable characteristics such as the virulence of a particular virus can be removed, while desirable genes that carry such desirable messages as immunity are kept or added to the virus. This cutting genes out and splicing genes in, all of this recombining of the elements of DNA, gives this new technology its name: "recombinant DNA."

Scientists actually do the cutting of the DNA molecule by using special enzymes that are isolated from organisms. Called restriction enzymes, each is specific to a particular nucleotide sequence in the DNA molecule. Their discovery was one of the most important factors in the advancement of the gene splicing technique. Now, literally hundreds of restriction enzymes are available, and by using them individually and in combination, scientists can segment precisely DNA molecules at desired locations.

Another critical element in the recombinant DNA technique is a special kind of bacterial DNA called a plasmid. These plasmids exist in certain bacteria and the

bacteria can live without them. They replicate independently within the bacteria and their structure enables them to be removed easily from it. Their availability and their "luxury" gene properties give scientists a convenient tool for recombining the DNA molecules of cells including viruses and bacteria. The plasmid molecules are "opened up" with a restriction enzyme and is then ready to be mixed with the DNA or an organism that also has been cut open, generally using the same restriction enzyme.

Re-connecting the segmented DNA is accomplished with another class of enzyme, called DNA ligase. Using these enzymes, scientists can rejoin the DNA segments not in their original form, but in new combinations! For example, fragments of DNA from one organism can be linked to fragments of the DNA of another organism. The combinations are many and their number is growing. The recombined DNA, the recombinant DNA, is then inserted into a virus cell in a procedure called transformation. Once inside that virus cell, the independently-reproducing property of the plasmid takes over, quickly yielding immense numbers and exacting duplicates of the recombinant DNA.

The end result of this new advanced technology promises to be many new vaccines produced by a logical and systematical approach to deleting undesirable characteristics and amplifying and substituting desired characteristics.

The new technology is even expected to produce live modified viruses containing the genetic materials of multiple viruses. Thus, the production of antibody against several viruses can be stimulated in an animal by inoculating the one modified virus carrier.

The question is often asked as to whether or not genetic engineering is new. The answer to that is both "yes" and "no."

"No," because scientists have been discovering genetically altered viruses for years, ever since Edward Jenner. To combat distemper, for example, a virus is placed in a foreign host, where—after many passages a naturally occurring mutation takes place. An altered virus is then selected, one that can provide immunity to distemper, without causing disease in normal healthy animals.

"Yes," the technology is new because scientists trigger the modification instead of nature, it is planned and systematic and it takes much less time, usually only weeks.

The new technology will do much to take the guesswork and chance out of the biologic production of vaccines and replace it with design and certainty. As the technology progresses, we will have in our hands new and better biologics to eliminate disease and illness. Veterinary medicine will be an even more exciting profession than it is today—for today we are on the threshold of a new generation of vaccines to prevent diseases in animals.

A major outbreak of botulism in cattle being fed ensiled poultry litter

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Eighty of a group of 150 housed beef cattle showed classical signs of botulism after eating a batch of ensiled poultry litter. Sixty-eight of the animals died and *Clostridium botulinum* type C toxin was detected in 18 of 22 sera examined. *C botulinum* organisms were isolated from the ensiled litter and type C toxin was demonstrated in samples of decomposed poultry carcases present in the litter. This outbreak of bovine botulism was the most serious to have been recorded in Europe and was the first associated with feeding ensiled poultry litter.

Conjunctivitis, red nose and skin hypersensitivity as signs of food allergy in veal calves

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The severity of diarrhoea and the degree of hyperaemia of the conjunctiva and nose were recorded in veal calves being fattened on either cows milk or milk-replacer. A skin-prick test using the milk-replacer as antigen was also performed. Control calves received only their mother's milk. Among these control calves there were no abnormalities, and in the calves fed other cows milk only slight abnormalities were seen. In contrast, in the calves fattened on milk-replacer, and especially in the calves showing the 'cachexia' syndrome, there were moderate to severe abnormalities and clear correlations were found between the severity of the diarrhoea and the hyperaemia of the conjunctiva and nose, and the scores recorded in the skin-prick test.