New Technologies in Veterinary Vaccine Development

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Presented at European Veterinary Vaccinology Workshop, Ghent. 9-10 May 2016.

Veterinary science has made a significant contribution to the field of vaccine research and development. Indeed many of the new vaccine technologies available today found their first commercial application within veterinary medicine. The ideal vaccine should be easy to administer, require only a single dose, produce a rapid onset and long duration of immunity, be stable on storage, stimulate the desired broadly protective immune response, and be cost effective. The majority of vaccines available today rely either on attenuation (weakening) techniques or are inactivated (killed) forms of the infectious agent. However, both approaches have their limitations and potential associated problems such as safety, stability, efficacy and economy of manufacture. Due to this and the need to tackle emerging diseases, scientists have increasingly turned their attention towards the development of new technology vaccines.

These novel vaccines can also be broadly separated into live and non-live approaches. Having identified antigens as potential non-live vaccine candidates they must then be delivered to the target animals in order to elicit the desired protective immune response. The simplest and most basic form of subunit vaccine is one in which the infectious agent has simply been solubilised or broken up into its component parts. Unfortunately, such split-product vaccines tend to display reduced immunogenicity when compared to whole pathogen products. A development which provides both polymeric presentation plus a built-in adjuvant activity for further enhancement of immunogenicity is the Immuno-Stimulating Complex (ISCOM). These offer the possibility of killed vaccine safety, combined with infection like immunity. In addition, many current bacterial vaccines are based on toxin or pilus subunits. While anti-toxin antibodies will neutralize the harmful effects of the bacterial infection, anti-pilus antibodies will block colonisation by preventing attachment. Due to problems in obtaining sufficient quantities of natural subunit proteins, it became the goal of many researchers to produce large quantities of those proteins in a sufficiently pure form to generate safe and effective vaccines using recombinant DNA technology. This meant that meant that foreign genes could be inserted into expression vectors and then introduced into cells which acted as "production factories" for the foreign proteins encoded for by those genes. In many cases the technology has provided a relatively inexhaustible and cheap source of protein for vaccination studies. Recombinant subunit vaccines have now been produced in bacterial cells, yeast, insect cells, mammalian cells, plant cells and microalgae. Some highly immunogenic methods for the polymeric presentation of these proteins are in the form of micelles, virosomes, liposomes, nanoparticles or virus like particles (VLPs).

Having identified and sequenced important immunogenic sites on infectious agents these can in many cases be mimicked using short chains of amino acid (peptides). Such peptides

can be produced synthetically or through recombinant expression. They can be manipulated to improve immunity by adding B and T-cell epitopes or presenting them in a polymeric structure. A further theoretical approach known as an anti-idiotype vaccine is based on the concept of mimicking an antigenic epitope using an anti-antibody. Thus by immunising animals with an antibody against the antigen binding site it is possible to mount an antibody response against the original pathogen. Selection of antigens for incorporation into subunit vaccines can be achieved in many ways, from predictive algorithms and antibody screening to "pepscan" and 3-D model analysis. A recent promising approach has been Reverse Vaccinology in which the whole genome is sequenced and all possible open reading frames are expressed, before purification and inoculation into animal models for the selection of those displaying activity against the infectious agent.

Certain infectious agents have polysaccharide outer surfaces and antigens that tend to be poorly immunogenic, and act in a T-independent manner. However, by linking these sugar molecules to highly immunogenic proteins such as bacterial toxoids the immune system will respond to them in a T-dependent manner. These vaccines are known as Conjugate Vaccines and they have an important role to play particularly against bacterial and parasitic infections.

Modified live vaccines offer a number of distinct advantages over conventional inactivated and subunit vaccines. By replicating in the host they more accurately mimic natural infection, they are often easy to administer, they provide long-lived immunity, and stimulate a more comprehensive immune response including humoral antibodies, secretory antibodies and cytotoxic T-cells. For these reasons scientists have looked at ways of delivering sub-unit or peptide vaccines using live recombinant vectors. The majority of virus vector studies have concentrated on relatively large DNA viruses in particular poxviruses, herpesviruses and adenoviruses. Studies on the rational attenuation of bacteria in order to produce suitable oral vaccines have also introduced the possibility of using the bacterial strains as vectors for foreign proteins. Initial studies looked at generating auxotrophic mutants by removing or modifying important genes. The majority of the work in this area has concentrated on producing invasive strains of bacteria that are sufficiently attenuated so as not to cause any pathogenic disease symptoms when delivered orally or parenterally to the host.

A relatively new vaccine technology that falls between live and killed approaches are Nucleic Acid Vaccines. These are based on DNA cloned into a delivery plasmid or the direct injection of messenger RNA. They can be produced cost effectively and the endogenous protein synthesis mimics a natural infection. Thus the antigens are presented in their native form and will elicit both MHC Class 1 and Class 11 responses. In addition there is no risk of infection and these vaccines can be used to bypass passive immunity.

New technology vaccines can also be used as a valuable tool in disease control and eradication programmes by enabling the user to differentiate infected from vaccinated animals. These Marker or DIVA Vaccines can be deletion mutants of wild-type pathogens or subunit vaccines. They will require an accompanying diagnostic test for screening and they can make it possible for vaccines to be used more readily in non-endemic situations.

Thus veterinary science has made and continues to make major contributions to the introduction of new vaccine technologies. Just a few of these commercial firsts include a vaccine produced from a genetically modified microorganism for E. coli, a subunit vaccine for a FeLV retroviral infection, a DIVA vaccines for control of Aujeszky's disease, a viral vectored vaccine for rabies, a chimeric vaccine for duel protection against both Marek's Disease and IBD, a live bacterial GMO for Strep equi, a DNA vaccine for IHN in salmon and a plant cell derived vaccine for NDV. The application of new technologies is likely to be a growing trend within future veterinary vaccines, including biotechnology, novel delivery and formulations. These will be directed against existing and new emerging disease targets. It is also probable that there will be increased regulatory standards, which in turn are likely to increase the development costs and time to market. A major focus will be customer convenience, resulting in vaccines that provide added value and improved stability. Finally there is likely to be a move away from the use of chemicals and antibiotics towards biological solutions involving vaccines.