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Popular Article

Immunology of Edible Vaccines and its Veterinary Importance

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The greatest numbers of immune cells are associated with the gastrointestinal tract. At least 80% of all plasma cells are found in the intestinal lamina propria, and together they produce more IgA than all other immunoglobulin isotypes combined. IgA is found in enormous amounts in saliva, intestinal fluid, nasal, and tracheal secretions, tears, milk, colostrum, urine, and the secretions of the urogenital tract. When animals are vaccinated against organisms that invade the intestinal or respiratory tracts, it makes sense to stimulate a mucosal IgA response.

To trigger an IgA response, the vaccine antigen can simply be ingested or inhaled. Unfortunately, such vaccines are not always effective. Inactivated antigens administered orally fail to trigger an IgA response because they are immediately washed off or simply digested when applied to mucous membranes. The only way a significant IgA response can be triggered is to use live vaccines, in which the vaccine organism can invade mucous membranes. The vaccine must persist for a sufficient time to trigger an immune response yet not cause significant damage.

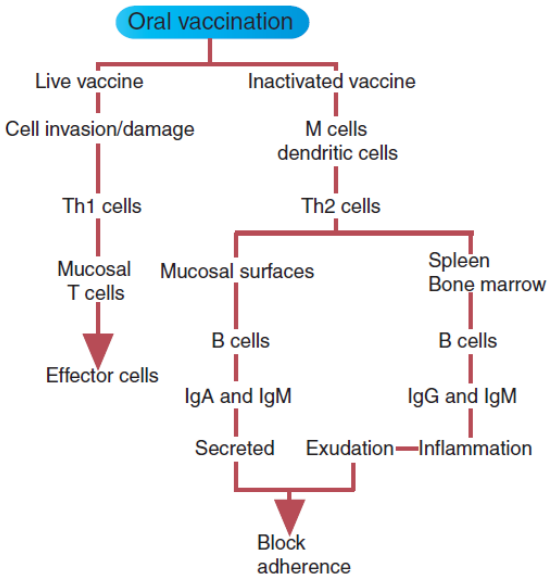

Figure 01 – The mechanism of action of oral

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Ruminants present specific problems when considering oral vaccination. The presence and large capacity of the rumen mean that ruminal microorganisms may destroy antigens before they reach the intestine or be simply highly diluted. On the other hand, if antigen can be expressed in a fibrous plant such as alfalfa, then it will be carried to the oral cavity during rumination and thus presented to the nasopharyngeal mucosa. For example, cattle fed recombinant alfalfa hay engineered to express the leukotoxin of *Mannheimia haemolytica* increased their production of antileukotoxin IgA. Orally delivered poxviruses, as used when vaccinating wild animals against rabies, are effectively targeted to the mouth rather than lower down the intestinal tract. The poxviruses presumably exploit small cuts and abrasions to establish lesions. Excipients that can prolong the time in the oral cavity or abrade the oral mucosa may help this process. Generally, these oral vaccines stimulate a strong humoral response. Despite the obvious desirability of using mucosal vaccines, few effective ones have been developed.

Oral vaccines for animals may be administered in the feed or drinking water, as is done with *Lawsonia intracellularis* and *Erysipelothrix rhusiopathiae* vaccines in pigs and against Newcastle disease, Infectious Laryngotracheitis, and avian encephalomyelitis in poultry. Plague vaccine coated candy has been fed to prairie dogs in the western United States and effectively prevents this disease.

Edible vaccines are created by introducing selected desired genes into plants and inducing these genetically modified plants to manufacture the encoded proteins. This process is known as "transformation," and the altered plants are called "transgenic plants." When an antigen of a pathogen can produce an immunogenic response when delivered orally, it is considered as a likely candidate for an edible vaccine. The gene encoding the orally active antigenic protein is isolated from the pathogen, and a suitable vehicle for constitutive or tissue-specific expression of the gene is prepared.

This gene vehicle is then introduced and stably integrated into the genome of selected plant species, and is then allowed to express to produce the antigen. The appropriate plant parts containing the antigen are then fed raw to animals or humans to bring about immunization. This is obviously more humane, and more economical, than the traditional “injection” method generally followed. Animals may sometime develop a tolerance to the components of their routine food, so that these become non-immunogenic in them. Therefore, edible vaccines cannot be used as a regular component of animal/human food. Several genes encoding antigenic proteins have been expressed in plants where they are produced in their native immunogenic forms. Various plant tissues are fed to animals, other plants such as alfalfa, maize and wheat could be valuable vehicles to deliver vaccines (and perhaps other pharmaceuticals) for the betterment of animal health.

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Table 1- **Antigens produced in transgenic plants**

S.No.	Protein	Plant
1	Hepatitis B surface antigen	Tobacco
2	Rabies virus glycoprotein	Tomato
3	Norwalk virus capsid protein	Tobacco
4	*E.coli* heat-labile enterotoxin B subunit	Potato
5	Cholera toxin B subunit	Potato
6	Mouse glutamate decarboxylase	Tobacco
7	VP1 protein of foot and mouth disease virus	Potato
8	Insulin	Arabidopsis
9	Glycoprotein	Potato
10	Swine-transmissible gastroenteritis	Arabidopsis
11	Influenza antigen	Tobacco
12	Rabies antigen	Spinach
13	HIV-1 antigen	Tobacco
14	Mink enteritis virus antigen	Black eye bean
15	Colon cancer antigen	Tobacco

Table 2- Antibodies and antibody fragments produced in transgenic plants

S. No.	Antibody	Antigen	Plant
1	IgG (k)	Transition stage analog	Tobacco
2	IgM (λ)	NP(4-hydroxy-3-nitrophenyl) acetyl hapten	Tobacco
3	Single domain (dAb)	Substance P	Tobacco
4	Single chain Fv	Phytochrome	Tobacco
5	Single chain Fv coat protein	Artichoke mottled virus	Tobacco
6	Fab; IgG (k)	Human creatin kinase	Arabidopsis
7	IgG (k)	Fungal cutinase	Tobacco
8	IgG (k) and SIgG/A hybrid	S. mutagens adhesin	Tobacco
9	Single chain Fv	Abscisic acid	Tobacco
10	Single chain Fv	Nematode antigen	Tobacco
11	Single chain Fv β-1,4 endoglucanase	β-glucuronidase	Tobacco
12	Single chain antibody fragment	Atrazin, Paraquat	Tobacco
13	IgG	Glycoprotein B of Herpes simplex virus	Soybean

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Plant-based vaccines represent the way of the future primarily because of two considerations - cost and safety. “When fully developed, plant-based vaccines will be much less expensive than current vaccines. In the future, thanks to plant-based vaccines, the same immunization will cost a fraction of that and, therefore, be available to more people.

Plants are also the safest vaccine delivery vehicle imaginable. When produced in animal tissue culture and in human cells, each vaccine lot requires extensive testing for safety reasons. One concern is contamination by unknown pathogens. "These necessary safety measures add to the cost of our current vaccines.

Plant derived veterinary vaccines

1. Swine transmissible gastroenteritis

One of the most promising studies showing protection with a mucosally delivered plant-based vaccine involved the swine transmissible gastroenteritis virus (TGEV) S protein expressed in corn. Ten-day-old, specific pathogen-free, TGEV-seronegative piglets were fed daily with non-transgenic corn, mixed with 50 g of transgenic corn, containing 2 mg of the S protein, in a medicated milk replacer over a 10-day period, and control groups were orally immunized with either a commercial modified live vaccine or non-transgenic corn. All piglets were then orally challenged with a virulent form of the virus, and clinical symptoms were evaluated. While 50 % of the pigs vaccinated with transgenic corn developed diarrhea, 78 % in the group immunized by the commercially available vaccine and 100 % of those that were fed with non-transgenic corn became ill. These observations suggest that the corn-derived S protein generated an immune response adequate to confer partial protection from the virus.

2. Foot-and-mouth-disease

Recently Yang and colleagues reported the induction of protecting immunity against foot and-mouth disease virus (FMDV) in swine using a plant chimeric virus particles (CVPs) approach **(Yang *et al.*, 2007).** Several groups of two month old specific pathogen free swine were immunized with different doses of CVPs by intramuscular injection and, six weeks later, boosted by the same route with the same amount. Four weeks after the boost all swine were challenged with the FMDV and monitored for symptoms. All of the negative control group animals showed serious symptoms of FMD, while all swine immunized with the CVPs showed no symptoms after challenge.

3. Infectious bursal disease

Protection studies on chickens have been conducted for the infectious bursal disease (IBD) using leaf extracts of transgenic Arabidopsis thaliana stably expressing the major host protective immunogen VP2 protein of the IBD virus. Vaccine efficacy orally administered by gavage was

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evaluated and compared to a commercial live attenuated vaccine. Upon challenge infection chickens orally immunized with the plant extract showed 80 % protection while chickens primed with the commercial vaccine followed by an oral boost of plant expressed VP2 proved 90% protection, the commercial vaccine showed 78 % of survival and all the control immunized animals died from the exposure. Recently, another group used the same VP2 antigen but this time stably transformed and specifically expressed in rice seeds. Specific pathogen-free chickens, orally vaccinated with transgenic seeds, produced neutralizing antibodies against IBDV and had a protection rate of more than 80 % when challenged with a highly virulent IBDV strain. All together these data demonstrate that IBD can be efficiently controlled using a plant derived vaccine strategy.

Vaccine production includes multiple technological steps for production, concentration, purification, packing, and delivery of the vaccines. Moreover, implementation of vaccination requires significant organizational and financial resources, such as capacity for storage (cold chain), transport, and trained human resources for performing the vaccination campaigns. Additionally, in most cases, vaccination requires direct contact with and manipulation of individual animals.

Recombinant technologies have enabled the expression of subunit antigens on vector carriers, thus offering a wide range of vaccine production possibilities. The use of plants as vaccine production and delivery systems has attracted much scientific attention, as they offer possibilities for antigen expression on different parts of the plant (root, seed, grain, fruit/vegetable, or leaf), and they allow for simplified and large-scale production, thus decreasing the price per unit produced. Additionally, the thermo-stability of the antigens (especially in grains) gives rise to significantly extended shelf-life, the oral application enables a better stimulation of mucosal immunity, specifically important in ruminants, and safety concerns are minimized, as there is no manipulation with highly contagious animal pathogens.

As plants must be genetically modified to produce these immunogens, planting these will need close supervision to avoid spillover into the natural vegetation. An alternative to overcome this limitation is the use of transfected chloroplasts which do not transfer the altered genes to next generations via pollination. An additional limitation of plant-derived vaccines is the low level of antigen expression, which should be improved by chloroplast transformation, plant breeding, or food processing technology.

Since the first report of successful immunization using plant-derived antigens (*Streptococcus mutans* surface protein A on tobacco leaf) in the early 1990s, there have been many reports on the adaptation and improvement of the system to other animal and human diseases, such

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as avian influenza, peste des petits ruminants (PPR), transmissible gastroenteritis virus **(Lamphear *et al.*, 2004),** bovine pasteurellosis, *Fasciola hepatica*, and many others. Moreover, during 2006, the first vaccine expressed on a plant cell culture was approved for commercial use in the USA by the USDA. It is a vaccine against Newcastle disease in poultry.

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