Plant-Based Oral Vaccines: Results of Human Trials

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Abstract Vaccines consisting of transgenic plant-derived antigens offer a new strategy for development of safe, inexpensive vaccines. The vaccine antigens can be eaten with the edible part of the plant or purified from plant material. In phase 1 clinical studies of prototype potato- and corn-based vaccines, these vaccines have been safe and immunogenic without the need for a buffer or vehicle other than the plant cell. Transgenic plant technology is attractive for vaccine development because these vaccines are needle-less, stable, and easy to administer. This chapter examines some early human studies of oral transgenic plant-derived vaccines against enterotoxigenic *Escherichia coli* infection, norovirus, and hepatitis B.

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Introduction

As new threats to public health emerge, the demand for effective, inexpensive, easy-to-administer, and most important, safe, vaccines will increase. In recent years, these new threats have included the agents of bioterror as well as new pathogens, such as SARS and H5N1 influenza.

The gastrointestinal mucosa is the largest site for induction of immune responses and use of this site to elicit protective immunity by oral immunization began with the oral polio vaccine in the 1960s. It makes sense to immunize the mucosa against pathogens that initiate their pathogenic processes at the mucosal surface. Some mucosally active vaccines have become successful public health tools, including oral polio vaccine, Ty21a oral typhoid vaccine (Vivotif), killed whole-cell/B subunit cholera vaccine (Dukoral), live attenuated cholera vaccine CVD 103-HgR (Orochol), and, most recently, intranasal cold-adapted influenza vaccine (FluMist).

Each of the successful mucosal vaccines, except the killed cholera vaccine, is a live attenuated version of the pathogen of interest. To construct the vaccine, defined and undefined virulence factors were purposely removed from the living pathogen. The complementary strategy is to identify one or a small number of antigens (subunits) of the pathogen that by themselves stimulate protective immune responses. This strategy has been hampered by the difficulty in identifying such protective antigens; however, the hepatitis B vaccine, consisting of hepatitis B surface antigen, is an excellent example of a highly successful parenteral subunit vaccine. The development of orally administered subunit vaccines has been hindered by the harsh environment of the human stomach and intestine. Several methods of protecting oral antigens have been developed and some tested in humans. These include encapsulation in microspheres, liposomes, ISCOMS, proteosomes, cochleates, and virosomes (Edelman 1997) or expression of the gene for the protective antigen in a commensal organism or an attenuated enteric pathogen (Grangette et al. 2002; Scheppler et al. 2002; Zegers et al. 1999; Pouwels et al. 1996; Devico et al. 2002; Orr et al. 1999; DiPetrillo et al. 1999; Tacket et al. 1997, 2000a; Nardelli-Haefliger et al. 1996).

One of the most promising novel techniques for production and oral delivery of subunit vaccines is by use of transgenic plants. Genes encoding antigens of interest from viral, bacterial, and parasitic pathogens can be expressed in the plant tissues, including the edible parts. Table 1 lists many of the vaccine antigens relevant to human disease that have been expressed in transgenic plants. The edible part of the transgenic plant can be ingested or the transgenic plant can be used as a bioreactor for large-scale, high-yield production of purified protein for oral or parenteral use (Giddings 2001; Giddings et al. 2000; Larrick and Thomas 2001). Examples of this application include production of monoclonal antibodies to provide passive immunotherapy (Ma et al. 1995, 1998; Chargelegue et al. 2000; Fischer et al. 2000; Zeitlin et al. 1998); an immunocontraceptive epitope (Walmsley et al. 2003; Smith et al. 1997), drugs (Giddings et al. 2000; Hood et al. 1997, 1999; Kusnadi et al. 1998a, 1998b; Daniell et al. 2001b), and autoantigens to induce oral tolerance in autoimmune disease (e.g., multiple sclerosis and type I diabetes) (Ma et al. 1997).

Table 1 Examples of vaccine antigens from human pathogens expressed in transgenic plants. Asterisk indicates phase 1 study has been done

Antigen	Plant	Reference
*Hepatitis B surface and core antigens	Tobacco; potato; cherry tomatillo; soybean; lettuce	Mason et al. 1992; Thanavala et al. 1995; Richter et al. 2000; Kapusta et al. 1999, 2001; Gao et al. 2003; Smith et al. 2002
Hepatitis E virus ORF2	Tomato	Ma et al. 2003
*Norwalk virus capsid protein	Potato	Mason et al. 1996; Tacket et al. 2000b
Rabies virus glycoprotein	Tomatoes; spinach	McGarvey et al. 1995; Modelska et al. 1998; Yusibov et al. 2002
Cytomegalovirus glycoprotein B	Tobacco	Tackaberry et al. 1999, 2003
HIV p24	Tobacco	Zhang et al. 2002
Measles virus hemagglutinin	Carrot; tobacco	Marquet-Blouin et al. 2003; Webster et al. 2002a, b
Human papillomavirus type 16 major capsid protein	Potato; tobacco	Biemelt et al. 2003; Warzecha et al. 2003
VP6 protein of rotavirus	Potato	Matsumura et al. 2002
Respiratory syncytial virus F and G-protein	Tobacco; tomato; apple	Belanger et al. 2000; Sandhu et al. 2000
*Enterotoxigenic *E. coli*	Potato; corn	Chikwamba et al. 2002; Mason et al. 1998; Tacket et al. 1998; Lauterslager et al. 2001
Enteropathogenic *E. coli*	Tobacco	Vieira da Silva et al. 2002
Vibrio cholerae toxin	Tobacco; tomato; potato	Daniell et al. 2001a; Jani et al. 2002; Arakawa et al. 1997, 1998, 1999
Tuberculosis ESAT–6 antigen	*Arabidopsis thaliana*	Rigano et al. 2003
Anthrax protective antigen	Tobacco	Azhar et al. 2002
Taenia solium cysticercosis peptides	Carrots, papaya	Sciutto et al. 2002

From vaccine production to administration, transgenic plant-derived vaccines offer significant advantages over other vaccine development strategies. These include advantages in manufacturing, packaging, storage, transportation, and most important, advantages in the ease of administration and safety for the recipient. Plant-based vaccines would eliminate the concern about transmission of human pathogens, remove the need for needles and syringes, and reduce the need for trained medical personnel to administer the vaccine. The plant cell wall would potentially protect the antigen in the stomach and intestine. Depending on the formulation of the plant-derived vaccine, there may be reduced or no requirement for refrigerated storage. In the developing world, transgenic plant vaccines may also be produced locally near the population to be vaccinated, even if some low-technology processing of the plant is required, e.g., corn germ meal (Streatfield et al. 2003; Chikwamba et al. 2002) or dehydrated tomato powder (Walmsley et al. 2003; Sala et al. 2003). These savings in vaccine-related production, supplies, and labor reduce the cost of each dose of vaccine.

This chapter describes recent phase 1 studies of oral transgenic plant-derived active vaccines in humans. To date, human studies have involved transgenic plant-derived vaccines consisting of plant organs (leaves or fruit) or crude extracts (dry powder), formulations made by low-cost food processing technology. Reports of human studies of plant-derived monoclonal antibodies (plantibodies) for passive immunization are expected soon.

How Transgenic Plant Vaccines are Made

The first prototype plant-derived vaccines were constructed in tobacco plants because of the ease of transformation and regeneration of this plant. Edible plants, such as potato, tomato, lettuce, carrots, and corn, have joined tobacco as hosts for foreign genes. The foreign DNA can be transiently introduced by infection of susceptible plants with the recombinant virus encoding foreign DNA (Mason and Arntzen 1997) or stably expressed by integrating the foreign DNA into the plant nuclear genome or into the circular chloroplast genome (Sala et al. 2003).

Most oral, plant-derived vaccine candidates have used stably transformed plants most commonly achieved using the bacterium *Agrobacterium tumefaciens*. Within this soil organism resides a tumor-inducing (Ti) plasmid containing transfer DNA or T-DNA. The Ti plasmid encodes factors that move a portion of the T-DNA into a plant cell and integrate it stably into the plant nuclear genome (Zambryski 1988). Foreign genes can be introduced into the T-DNA and transferred to the plant nucleus and randomly inserted into the chromosomal DNA at one or more sites. The promoter for the gene of interest can be either constitutive or tissue-specific, which affects the timing or the location of expression within the plant. The codon usage of the foreign gene of interest can be optimized for plant expression.

To transform plants using *A. tumefaciens*, cut surfaces of plant tissues are inoculated with bacteria containing the foreign gene in the Ti plasmid. The bacteria attach to plant cells at the wound site. The resulting leaf pieces are cultured on nutrient agar medium along with an antibiotic to kill the *A. tumefaciens*. A single transformed plant cell can produce a shoot that can be transplanted to soil and grown in a greenhouse or growth chamber. Because insertion of T-DNA may inhibit growth, many transgenic lines are screened to identify a transformant that expresses the foreign gene at high levels and does not adversely affect the plant.

Processed preparations derived from transgenic plants offer significant advantages over the whole fruit or vegetable. The processing must involve low heat and pressure so as not to denature the antigen (Streatfield et al. 2002). Examples include corn germ meal, corn flakes, dehydrated tomato powder, and banana flakes. These formulations are suitable for oral delivery and a large amount of antigen can be contained in a small volume of material and be easily ingested.

Human Studies: Transgenic Plant-Derived Vaccines

A large number of genes from human pathogens have been expressed in plants (Table 1). A few prototypical vaccines for human pathogens have been developed and tested in humans, including vaccines against enterotoxigenic *Escherichia coli*, norovirus, and hepatitis B.

Enterotoxigenic E. coli

Enterotoxigenic *E. coli* (ETEC) is responsible for diarrhea with dehydration and death in young children in the developing world and is one of the most common causes of traveler's diarrhea. ETEC includes a family of *E. coli* organisms that differ by O:H serogroup, fimbrial colonization factor antigens, and toxin type (heat labile toxin, or LT, and heat-stable toxin). A number of experimental vaccines against ETEC have been devised and some have undergone testing in humans with some success (Savarino et al. 2002). A vaccine must include a broad spectrum of antigens to be effective against diverse ETEC strains. Plant-derived antigens, inexpensive and possibly produced locally, could provide an efficient source of the multiple components for the ETEC vaccine of the future.

The initial focus in plant-derived ETEC vaccine development has been on the highly immunogenic LT of *E. coli*. This toxin consists of an enzymatically active A subunit with ADP ribosyl transferase activity associated with five immunogenic binding, or B, subunits, designated LT-B, which bind to the GM1 ganglioside present on epithelial cells. Antibody to LT-B could prevent binding of the toxin to the epithelial, thereby protecting against diarrhea. Immune responses to LT-B may offer short-term protection against infection with LT-producing *E. coli* (Clemens et al. 1988).

Transgenic Potatoes Expressing LT-B

Haq et al. transferred the gene encoding LT-B into tobacco and potato plants via *A. fumefaciens* and fed these tobacco leaves and potatoes to mice (Haq et al. 1995). The plant-derived LT-B assembled into pentameric structures and bound to ganglioside, like bacteria-derived LT-B. Each 5-g dose of transgenic potato tuber delivered 15–20 μg of rLT-B. Mice that consumed these potatoes developed serum IgG and mucosal IgA anti-LT-B, and some responses were similar to those of animals immunized with 20-μg doses of purified LT-B expressed in bacteria and given by oral gavage (Haq et al. 1995). In a subsequent study, mice fed three weekly doses of 5 g of tuber tissue containing either 20 or 50 μg of LT-B had higher levels of serum and mucosal anti-LT-B than those gavaged with 5 μg of bacterial LT-B (Mason et al. 1998). To prove that antibodies stimulated by

the plant-derived vaccine were protective, vaccinated mice were challenged with 25 μg of LT. Although none of the vaccinated mice was completely protected, the potato vaccine provided a significant reduction in fluid accumulation in the patent mouse assay. Control mice fed nontransformed potatoes developed no antibodies and no reduction in secretion in the patent mouse assay (Mason et al. 1998).

These encouraging animal studies led to a phase 1 human study of the potato-derived vaccine (Tacket et al. 1998). Raw transgenic potatoes and control wild-type potatoes were peeled immediately before ingestion to remove the skin containing solanine, an alkaloid present in all raw potatoes, which can cause gastrointestinal upset. Potatoes were cut into small pieces and each dose weighed. Fourteen healthy adult volunteers ingested three oral doses of either 100 g of transgenic potato expressing LT-B ($n=6$), 50 g of transgenic potato ($n=5$), or 50 g of wild-type potato ($n=3$). Each dose of potato contained approximately 0.4–1.1 mg LT-B. The raw potatoes were generally well tolerated.

All volunteers who ingested transgenic potatoes developed circulating antibody secreting cells (ASCs) specific for LT after immunization (Tacket et al. 1998). These cells, detected in the peripheral blood approximately 7–10 days after immunization, reflect priming of the intestinal mucosal immune system. Similarly, ten (91%) of 11 volunteers who ingested transgenic potatoes developed at least fourfold rises in serum IgG anti-LT after immunization, and eight (73%) of 11 volunteers developed LT neutralizing antibody, indicating that the antibodies elicited by the potato vaccine were fully functional. Half the volunteers who ingested transgenic potatoes developed at least fourfold rises in sIgA in their stools.

In these studies, an oral transgenic potato-derived vaccine was successfully immunogenic even without co-administration of buffer or encapsulation to protect the antigen. This represented the first proof of the principle that transgenic plant vaccines formulated as whole vegetable could be immunogenic in humans. The door was opened for further refinement and development of other vaccines containing a cloned protective antigen.

Transgenic Corn Expressing LT-B

Vaccine antigens have also been successfully expressed in transgenic corn (Chikwamba et al. 2002; Streatfield et al. 2001). Corn-derived antigen is inexpensive to produce and can be scaled up rapidly, with corn generation time of 3–4 months. Corn-derived proteins can be expressed and concentrated at high levels of up to 10 mg/g in the corn germ, and the expressed protein is very similar to native protein (Hood et al. 1997; Woodard et al. 2003). Antigens expressed in transgenic corn are stable (Streatfield et al. 2002; Lamphear et al. 2002), and the product of the cloned gene is highly concentrated and homogeneous in corn germ (Streatfield et al. 2003; Lamphear et al. 2002).

Streatfield et al. developed a prototype transgenic corn containing the gene encoding LT-B (Streatfield et al. 2002). The transgenic corn vaccine was formulated

as defatted corn germ meal, prepared by standard commercial processing techniques. Removal of fat concentrated the LT-B in the germ and also decreased the risk of the corn material becoming rancid with storage. The grinding of the defatted germ produced uniform particle size and a homogeneous distribution of LT-B.

In preclinical studies in mice, the transgenic corn germ meal was well tolerated and stimulated serum IgG responses and fecal IgA responses (Lamphear et al. 2002). Mice fed LT-B corn, but not control corn, were protected from intestinal secretion in the patent mouse assay (Streatfield et al. 2001). The degree of protection elicited by the LT-B corn was similar to that elicited by an equivalent amount of purified bacterial LT-B.

A clinical study of the safety and immunogenicity of the transgenic corn germ meal was conducted in which transgenic corn expressing 1 mg of LT-B of *E. coli* without buffer was fed to adult volunteers in three doses, each consisting of 2.1 g of plant material (Tacket et al. 2004). Seven (78%) of nine vaccinees developed at least fourfold rises in serum IgG anti-LT after vaccination, usually after the second or third dose of transgenic corn germ meal vaccine. The IgG titer peaked at day 56. Four (44%) of nine developed fourfold rises in serum IgA anti-LT; the IgA titer peaked at day 14. Seven (78%) of nine vaccinees developed specific IgA ASC. Four (44%) of nine vaccinees developed at least fourfold rises in stool sIgA anti-LT concentrations after vaccination (mean peak fold rise of 7.6 among responders).

Norovirus

Noroviruses are members of the *Caliciviridae* family which are the major cause of epidemic gastroenteritis in the United States (Glass et al. 2000). Included in this group is Norwalk virus (NV), which is of particular epidemiologic significance (Green et al. 1993; Deneen et al. 2000).

The major capsid protein of NV, cloned and expressed in insect cells, folds spontaneously into virus-like particles (VLPs) that lack nucleic acid (Xi et al. 1990). Norwalk VLPs administered with buffer are immunogenic when given orally to volunteers and are a potential vaccine candidate (Ball et al. 1999; Tacket et al. 2003).

When expressed in tobacco and potatoes, and the plant-derived recombinant NV particles are identical to those derived from insect cell culture. When transgenic potatoes were fed to mice, the plant-derived VLP stimulated serum and fecal antibody responses (Mason et al. 1996). A human study was conducted in which 24 healthy adult volunteers were randomized in a double-blind manner to receive one of three different regimens: (a) three doses of transgenic potato on days 0, 7, and 21 (*n*=10); (b) two doses of transgenic potato on days 0 and 21 and a dose of wild-type potato on day 7 (*n*=10); or (c) three doses of wild-type potato on days 0, 7, and 21 (*n*=4) (Tacket et al. 2000b). On the morning of dosing, transgenic and wild-type potatoes were peeled and cut into uniform 1-cm square cubes. Doses of 150 g of

raw potato cubes were weighed on a scale and immediately ingested. Each dose contained approximately 500 μg of Norwalk virus capsid protein, half of which was assembled into virus-like particles.

Nineteen (95%) of 20 volunteers who ingested two or three doses of transgenic potatoes, and none who ingested wild-type potatoes, developed significant rises in the numbers of IgA ASC (range 6–280/10^6 peripheral blood mononuclear cells, PBMC). Thirteen of the 19 IgA ASC responses occurred after the first dose of transgenic potato. Four (20%) of 20 volunteers developed serum IgG anti-NVCP (mean 12-fold rise), and four (20%) of 20 volunteers (three of whom did not develop IgG responses) developed serum IgM anti-NVCP (mean sevenfold rise) after ingesting transgenic potatoes. Stool IgA anti-NVCP was detected in six (30%) volunteers who ingested transgenic potatoes (mean fold rise in titer of 17 among responders).

Hepatitis B Virus

Hepatitis B virus is prevalent worldwide and causes chronic hepatitis, cirrhosis, and hepatocellular carcinoma after parenteral or sexual transmission. The hepatitis B surface antigen (HBsAg) elicits protective immunity after intramuscular injection of three doses. An estimated 2 billion people are infected with hepatitis B virus, infections that could be prevented by vaccination. The parenteral vaccine is available and is widely used in the developed world, and the Global Advisory Group of the Expanded Program on Immunization and World Health Assembly have recommended that countries with higher than a 2% prevalence of HBV carriers add hepatitis B vaccine to their routine infant immunization schedules. However, the high price of parenteral vaccine has prevented the recommended vaccinations in some countries (Beutels 1998). An inexpensive, needle-less, plant-derived hepatitis B vaccine would therefore be a desirable public health tool for the control of hepatitis B.

Mason et al. first transformed tobacco plants with the gene encoding hepatitis B surface antigen (Mason et al. 1992). The recombinant plant-derived antigen formed spherical 22-nm particles identical to human serum-derived HBsAg. Subsequently, mice were immunized with the tobacco-derived HBsAg (Thanavala et al. 1995). The serum antibody and T cell immune responses in mice fed transgenic tobacco leaves were similar to those in mice immunized with commercial hepatitis B vaccine derived from yeast. This group then developed a transgenic potato line PAT-HB-7 expressing 1.1 μg of HBsAg per g of potato (Richter et al. 2000). When given to mice in three weekly doses of 5.5 μg HBsAg per dose along with 10 μg of cholera toxin (CT), a known mucosal adjuvant, this vaccine elicited a primary immune response measured by increases in specific serum antibody to a peak of 73 mIU/ml (Richter et al. 2000). These responses were boosted to a level of 1,679 mIU/ml by a single small dose of 0.5 μg of commercial hepatitis B vaccine delivered intraperitoneally. The plant-derived vaccine, delivering a small dose of antigen, had primed the animal for the unusually robust booster response to the intraperitoneal vaccine.

In subsequent studies, these investigators compared the immunogenicity of oral yeast-derived HBsAg and oral potato-derived HBsAg in mice (Kong et al. 2001). Yeast-derived HBsAg given as two doses of 150 μg each with bicarbonate buffer plus 10 μg of CT adjuvant did not stimulate serum antibody in mice. HBsAg given as three doses of 142 μg/dose delivered in 5 g of potatoes along with 10 μg of CT resulted in a peak of 103 mIU/ml of serum antibody after the third dose. (The protective level of serum antibody is 10 mIU/ml.) On electron microscopy, the plant-derived HBsAg had accumulated intracellularly, suggesting that a natural bioencapsulation of the antigen might protect it from degradation in the intestinal tract, while purified yeast-derived HBsg is not protected. A human study of this vaccine is not yet published.

Another group led by Kapusta introduced the HBsAg gene into lupin and lettuce plants (Kapusta et al. 1999). Mice fed transgenic lupin callus developed hepatitis B-specific antibodies. Three humans were fed two doses of transgenic lettuce containing 200 g and 150 g of lettuce leaves within 2 months (Kapusta et al. 1999). The amount of HBsAg in the lettuce varied from 0.1 to 0.5 μg/100 g, so the volunteers received approximately 0.2–1 μg of antibody in the 200-g dose. (For comparison, the licensed injectable hepatitis B vaccine contains 10 μg of HBsAg per adult dose.) After the second dose, all three volunteers developed anti-HBsAg antibody; two of the three had titers greater than 10 mIU/l, the minimum protective level of antibody against hepatitis B virus.

In a subsequent study, seven seronegative volunteers were immunized three times with fresh transgenic lettuce leaves on a 0–1-5-week schedule (Kapusta et al. 2001). The amount of HBsAg ranged from 0.51 to 0.94 μg per dose. Three weeks after the second immunization, antibody was detected in all seven volunteers, but not in control volunteers who received untransformed lettuce. The antibody responses were short-lived, but the third dose restimulated a rise in specific antibodies. Two weeks after the third dose, all volunteers had an increased level of specific antibody between 2 and 6.3 mIU/l, less than the protective level of 10 mIU/l, but still a significant rise from baseline.

Multivalent Transgenic Plant-Derived Diarrheal Disease Vaccine

Combination vaccines have been developed so that children can receive multiple vaccinations with a single injection and single encounter with a health care provider (Lagos et al. 1998). One of the advantages of plant-based vaccines is that plants that produce two or more antigens from different pathogens can be constructed. A prototype multicomponent vaccine was constructed in which cholera toxin B and A2 genes were fused to rotavirus enterotoxin and ETEC fimbrial genes and expressed in potato (Yu and Langridge 2001). When this vaccine was given to mice, serum and intestinal antibodies were detected. Such a multivalent vaccine might also include a transgenic plant-produced nontoxic derivative of LT that is a potent mucosal adjuvant when co-administered with another antigen (Douce et al. 1999).

Oral Tolerance

It is remarkable that the plant-derived vaccine protein is recognized within the context of the food delivery system, is processed as an antigen, and elicits an immune response. Immune tolerance is the usual result when the mucosal immune system encounters antigen (Strober et al. 1998). One potential safety concern about presentation of vaccine antigens in the context of food is that oral tolerance could be stimulated against the antigen. Theoretically, this could result in a suboptimal immune response if the individual were confronted with that antigen in the future during natural infection. Preliminary data in humans suggest that oral ingestion of multiple doses of KLH antigen actually primes serum and mucosal antibody responses to subsequent parenteral immunization with KLH, although T cell responses were inhibited (Husby et al. 1994). The safety and efficacy of the currently licensed oral vaccines offer reassurance that antigens can be delivered orally without induction of tolerance.

Regulatory Issues

Plant-derived vaccines should be produced, processed, and regulated as pharmaceutical biologic products (Stein and Webber 2001). The consistency and potency of the dose must be demonstrated; this may best be achieved by formulating the transgenic plant vaccine as a dehydrated powder or juice homogenate. Environmental concerns about mixing genetically modified pollen with other crops or weeds have been raised (Stokstad and Vogel 2003). This objection may be partially addressed by engineering the foreign gene into the chloroplast DNA (Ruf et al. 2001). Growing pharmaceutical crops in greenhouses or on small parcels of land will also prevent spread of genetically modified pollen. As higher levels of genetic expression are achieved through technical advances, land requirements for plant-derived vaccine production will decrease.

In the United States, the Animal and Plant Health Inspection Service (APHIS) of the USDA oversees the movement of plants between states and their release into the environment. A permit from APHIS is required to grow engineered plants that express a biologic drug in the field. Plants grown in an enclosed building such as a greenhouse or laboratory are considered contained if there are measures in place to prevent spread of pollen or seeds outside the facility. Transgenic plants must also be contained during transport. Transgenic food plants must not enter the human food supply, and the transgenic plant material must be strictly separated and clearly labeled.

Conclusion

Use of plants with medicinal properties is the traditional foundation of pharmaceutical medicine. Molecular genetic techniques allow the specific manipulation of ordinary food plants to produce drugs and biologics. In early phase 1 studies, prototype transgenic

plant vaccines have been well tolerated and immunogenic. New formulations of these vaccines, such as corn germ meal and dehydrated tomato powder, are being developed and the regulatory framework for evaluating these biological products is adapting to the issues peculiar to this technology. The important developments in the future will be improving the immunogenicity of transgenic plant vaccines by delivery of higher amounts of antigen by improved expression or concentration of antigen; the co-administration of antigen with a mucosal adjuvant; and introduction of transgenic plants expressing multiple protective antigens of different pathogens. Transgenic plant technology may be a significant step toward the goal of developing less expensive childhood vaccines as well as inexpensive vaccines against emerging diseases.

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