

The Veggie Wars:

Edible Vaccines to Battle Diseases

By Jennifer Abelson

Chew on this: Munching on the sweet flesh of bananas may soon serve as a powerful weapon against infectious global killers, such as hepatitis B and diphtheria.

Looking to substitute fruits and vegetables for syringes, scientists at Cornell University's Boyce Thompson Institute for Plant Research are developing genetically-modified plants that produce vaccines. An inexpensive and effective way to inoculate children in developing countries, plants with built-in vaccines could eradicate widespread infectious diseases.

Despite increasing international opposition to genetically-modified foods - censured as "Frankenfood" - researchers remain cautiously optimistic about their revolutionary technology and the future of edible vaccines.

New tools for manipulating genes and proteins have spurred what some call the second "green revolution." The first one, which occurred in the eighteenth century, introduced more efficient plant breeding and farming technologies.

Nearly two centuries later, scientists - armed with gene guns and other engineering techniques - have transformed crop cultivation for both commercial and agricultural purposes. With these new technologies, scientists insert foreign genes into plants to make them resist pests, drought and other hazards, as well as to nutritionally enhance plant foods.

And now, researchers at BTI are using the same technique to shoot harmless proteins derived from live viruses or bacteria, called antigens, into plants. These antigens rally the body's defenses against the true virus or bacteria, and result in the production of specific antibodies.

With traditional inoculations, the vaccinating antigen is inserted directly into host cells without a living vector. Edible vaccines, however, both produce and deliver the antigen into the host via transgenic crops, such as potatoes.

Results from BTI's two recent human clinical trials have indicated that consumption of uncooked vaccine-containing potatoes trigger immune responses to specific diseases.

In the first two studies, more than 90 percent percent of the volunteers who ate potatoes with vaccines against bacterial and nonbacterial diarrhea produced antibodies that would provide appropriate protection against diarrhea-causing toxins, according to Dwayne Kirk, project manager for the vaccines research

program at BII. Results from a third human clinical trial, which tested the effectiveness of transgenic potato vaccines against hepatitis B, will be published next year.

Diarrheal infections, which can cause extreme dehydration, have devastating effects on individuals in developing countries with poor medical infrastructures. The World Health Organization recently reported that these gastrointestinal diseases kill more children in developing countries than any other diseases. WHO estimated that 3 to 5 million children's lives could be saved if affordable, effective vaccines are made available.

BII President Charles Arntzen has tried to answer WHO's call for alternative inoculations since 1992. A pioneer of these veggie vaccines, Arntzen is leading BII researchers toward the creation of safe, inexpensive and readily available edible vaccines for countries in urgent need for universal childhood immunization programs.

And potatoes are only a prototype for delivering plant-based vaccines. BII scientists are now working to transfer the genetic code for the hepatitis B vaccine into more palatable raw plants, such as bananas and tomatoes, grown in their greenhouse in upstate New York. Although the genetic map of bananas is less understood, Kirk said testing of transgenic bananas could begin as early as next year. If successful, these inoculations could cost as little as 10 cents per dose, whereas traditional vaccines currently cost \$50 to \$100 a dose.

Arntzen, who crafted the vaccine cuisine idea while working in developing nations such as China, India and Thailand, said, "Most of these countries can't afford to build the sophisticated factories you need to make modern vaccines. But they all grow bananas."

BII's successful human clinical trials have generated excitement about the multitude of benefits edible vaccines offer. According to Hugh S. Mason, a BII researcher, edible vaccines do not require strict sterility conditions, refrigeration or costly purification protocols - complications which usually thwart vaccination programs in developing countries.

"This is a milestone on the road to creating inexpensive vaccines that might be particularly useful in immunizing people in developing countries," said Regina Rabinovich, head of the National Institute of Allergy and Infectious Diseases' Vaccine and Treatment Evaluation Program. Following the success of BII's first human clinical trial last March, Rabinovich said, "The hope is that edible vaccines could be grown in many of the developing countries where they would actually be used."

In addition to the convenience and affordability of these transgenic plant inoculations, edible vaccines can stimulate a more robust and specific immune response to certain infections than traditional vaccines.

Mason explained that edible vaccines provoke a vigorous response in the mucousal tissues that viruses, such as influenza and E. coli, invade. Mucousal surfaces lining the gut, lungs, and genitourinary tract serve as the body's first line of defense against these infectious agents.

According to Mason, many immunologists believe that mucousal responses are more effective in combating infections at these sites than nonspecific antibodies which circulate in the blood via traditional injections. For example, although current hepatitis B vaccines effectively fight blood-borne infections, immune responses at the mucousal site might work better at preventing venereally-transmitted hepatitis B.

The implications of these edible vaccines are far reaching, as hepatitis B infects an estimated 300 million people worldwide and causes liver failure and cancer, according to WHO figures.

Despite the significant potential of these edible vaccines to combat life-threatening illnesses, researchers still confront numerous obstacles before these vaccines enter the market.

Pioneering a vaccine delivery system in the highly coveted banana is more difficult, time-consuming and labor intensive, as it requires over two years to grow, harvest and test the expression of newly introduced proteins.

In addition, BTI scientists need to stabilize the proteins so they do not breakdown when encountering the harsh digestive process. High doses of the vaccinating antigen are currently being used so that enough of the proteins can survive the digestive system and stimulate antibodies, according to Sunny Y. Wong, a Cornell senior involved in edible vaccine research at BTI.

Researchers are also working to increase the concentration of the antibody in the transgenic plants. Low amounts of the vaccine antigen typically produced by transgenic plants requires a large consumption of up to 150 grams to obtain the necessary dosage.

Furthermore, concerns about dosage mean that even if stable, concentrated transgenic banana trees were easily cultivated, their contents would have to be administered by knowledgeable health care workers.

To prevent oral tolerance - which inhibits immune responses by frequent and/or high dosages of orally delivered antigens - Mason said, "Greenhouses will likely be used to grow transgenic plants under carefully controlled conditions with trained medical experts on hand to distribute the products."

The FDA has a structured series of trials and safety milestones which need to be met before any transgenic plant product can be considered for use in human health. As the evaluation process continues, the next likely location may be in Mexico, where cheap and effective vaccines are highly sought and where there is

some health infrastructure to support such a trial.

Although visions of produce aisles lined with edible vaccines may not come to fruition, Kirk underscored the importance of developing vaccines in a form that can be easily transported to even the most remote areas.

In addition to process complications, BTI faces potential problems in galvanizing support for edible vaccines from both the pharmaceutical industry and the public sector.

According to Mason, the ability to manufacture and deliver edible vaccines for only pennies might not attract companies interested in their bottom line. "It's a potential problem because these companies are in the business to make money and they are making money with some of the present vaccines, including hepatitis B."

Mason said companies could generate positive public relations by donating vaccine material for very poor countries and developing countries. And although companies might resist losing profits in America as well, if the edible inoculations prove to be as effective as injectable vaccines, Mason predicted American parents would demand the tear-free guarantee.

Dennis Lang, an enteric disease program officer at the National Institute of Health, cited the elimination of both pain and sterilizing complications as the most attractive aspects of edible vaccines in industrialized nations.

But widespread support for genetically-modified foods seems unlikely as international public sentiment against these crops is growing. Amid protests at last week's World Trade Organization in Seattle, America stepped back from its goal of widening markets for genetically modified goods.

While supporters of genetic engineering credit it for creating foods that grow faster, last longer, provide better nutrition, taste better and are cheaper to produce, critics call it "Frankenfood," with unknown consequences that put the health of consumers and the environment at risk.

For example, protesters have charged that pollen might spread the plant virus resistance gene to regular food crops.

Although most of the opposition concerns modified food products, Mason acknowledged the need to address the critics regarding edible vaccines. Researchers fear ignorance and misinformation will handicap the progress of these revolutionary and beneficial technologies.

"We have to try to educate the public about the benefits of genetically-modified food plants used as medicines," he said. "We need to separate them from foods."

Kirk also stressed the importance of distinguishing edible vaccines from foods.

modified for taste, nutritional enhancement or pest resistance.

In a pending lawsuit against the U.S. Environmental Protection Agency, Greenpeace and other activist groups are demanding that the agency withdraw its approval of Bt crops, which are transgenic crops that produce their own pesticide.

John Sarlim, a Greenpeace spokesman, said his organization opposes all genetic modification that has unknown effects and that he has never heard of edible vaccines.

"Greenpeace really hasn't distinguished between positive and negative forms of genetic modification," Sarlim explained.

Because of this broad attack on genetically-engineered foods, Kirk expressed concerns that the increasing public discontent might affect the Food and Drug Administration's regulatory acceptance of edible vaccines.

In addition to potential FDA roadblocks, Wong said the opposition might jeopardize research funding. "If the public outcry is large enough, projects for developing transgenic vegetables might be deemed unimportant or unethical by committees that already have very limited research funds to allocate," he explained.

"We are working mainly for philanthropic and humanitarian goals. This technology is in great need around the world and edible vaccines is one application which has documented human safety monitoring as an integral part of every evaluation phase," Kirk explained.

Elena Dimuzio, a Cornell graduate student who conducts research at BTI, said increased communication between scientists and the public is imperative.

"We need to educate people about possibility and limitations of edible vaccines. It's too bad if we ignored the technology because we were afraid of it," Dimuzio said.