Edible vaccines not ready for main course

Edible vaccines produced in genetically modified crops promise cheap and effective protection against infectious diseases in the developing world. But vaccine manufacturers are reluctant to take a bite out of the projects.

Since 1992, when biologist Charles Arntzen proposed genetically modifying bananas to serve as cheap vaccines against infectious diseases, research on plant-based pharmaceuticals has grown rapidly. In July, the European Union promised €12 million to European and South African scientists developing vaccines or antibodies against HIV/AIDS, rabies and tuberculosis. Work is further ahead in the US, where several acres of crops, most of them still experimental, are planted each year.

Researchers have thus far produced more than 45 different antigens in a wide range of plants. “In 10–15 years,” says Hilary Koprowski, a veteran vaccine researcher at Thomas Jefferson University, “plant-derived vaccines will be fully appreciated.”

At least in theory, plant-based vaccines would be safer than those produced in animal tissues because the chances of unknown human pathogens hitching a ride would be extremely small. Costs per dose would be low, and scaling up would just mean planting a larger crop. During transport and storage, vaccine-containing seeds or dried leaves would not need refrigeration, a significant advantage in developing countries. Oral vaccines especially, administered as juices or tablets to circumvent dose variability, would pave the way for mass vaccinations in those countries.

But even Arntzen now says his original idea of distributing vaccine-bearing fruit was naive, because regulatory agencies will not approve vaccines with variable dosing.

Many in the field say that, at least in animals, plant-based oral vaccines have been proven to be safe and effective. For instance, corn loaded with proteins from a gastroenteritis virus is effective, at least when used as a booster, in protecting pigs against the disease, says John Howard, founder of the Texas-based firm ProdiGene.

In humans, several vaccines have passed safety trials. Arntzen’s group at Arizona State University tried vaccines produced in genetically modified potatoes and corn against enterotoxic Escherichia coli and Norwalk virus. Koprowski’s group fed volunteers spinach containing a rabies booster vaccine. Both groups have tested oral hepatitis B vaccines, either as primary or booster vaccine, in lettuce, spinach and potatoes.

Although small phase 1 trials like these can’t prove protection, volunteers in the studies showed an “appropriate,” though not always strong, immune response, Arntzen says.

Arntzen is collaborating with companies in Egypt, South Africa and South Korea, but outside developing nations, where there is an urgent need for such vaccines, finding manufacturers willing to finance larger trials to demonstrate efficacy has been a formidable challenge. “I’ve talked to all of the [big companies],” says Koprowski, “and so far I regard it a waste of time.”

Vaccine manufacturers have little reason to replace existing production lines, as most vaccines are economically unattractive. The medical community is also focused on high-tech approaches, making farm-grown vaccines a tough sell, Koprowski says. But smaller companies, led by young people willing to take risks, could challenge the current thinking, he says. “Then, others will follow.”

Part of the hesitation stems from the fact that plant-based oral vaccines constitute a new technology from both a regulatory and scientific perspective, says renowned vaccinologist Stanley Plotkin, who now advises Aventis Pasteur.

Before they can be approved, Plotkin says, plant-based vaccines will have to consistently generate stronger immune responses, which would need to be studied carefully for every crop. “If vaccines are intimately presented together with food, the gut’s immune system faces a conundrum,” he notes. The gut is designed not to react to antigens in food, but must produce a useful response against the vaccine. Instead of being immunized, patients could even end up being ‘tolerized,’ meaning an immune response against future invaders would be weakened, not intensified.

Researchers say they have not yet seen signs of such tolerance, but Plotkin says experiments to convince regulators have yet to be designed. “Immunologists will have to figure out how the gut can do this, and do it right 99.9999% of the time,” he says. Producing veterinary vaccines first, followed by human booster vaccines, could be the sensible way forward, he adds.

Convincing the general public that it is safe to grow vaccines in fields poses a bigger challenge. Citing fears over supermarket shelves stocked with vaccine-contaminated foods, consumer groups have called for a ban on using food crops to produce pharmaceuticals. Some companies are avoiding the issue by developing injectable plant-based vaccines, by using nonfood crops or by not using genetically modified crops.

For instance, California-based Large Scale Biology uses genetically engineered mosaic viruses to infect tobacco plants. A few weeks later, says Larry Grill, the company’s chief scientific officer, antibodies can be purified from the harvested leaves. The company has produced patient-specific antibodies against cancer cells just months after biopsies were taken.

Once the scientific and regulatory hurdles are cleared, convincing skeptics will be easier, researchers note. “If I could save millions of lives in developing countries,” says Arntzen, “I think I’d have a pressure group that could stand up even against Greenpeace in Europe.”

Peter Vermij, Amsterdam
Researchers in Europe are benefiting from the European Patent Office’s (EPO) decision to prune several high-profile patents, a result of key differences between US and European policy. The EPO’s rulings broaden avenues of research that would otherwise be choked off by licensing fees, but some scientists and citizen groups say the decisions are still not enough.

On 6 July, the EPO restricted a patent on the OncoMouse model for cancer research from including all rodents to just mice. In May, the agency revoked one of three patents Salt Lake City–based Myriad Genetics has on the breast cancer gene BRCA1. Months earlier, the EPO had granted a patent similar to Myriad’s on another breast cancer gene, BRCA2, to Cancer Research UK. The charity announced in August that it would allow free access to academic researchers, undermining Myriad’s position.

Unlike the US, Europe forbids patents that threaten “ordre public” or morality. The EPO invoked this clause against the OncoMouse patent and, in July 2002, the Edinburgh patent on stem cells.

The agency is also less flexible in allowing corrections to patents, says Siobhan Yeats, EPO’s director of Examination and Opposition in Biotechnology. Corrections to Myriad’s initial BRCA1 patent, which was found to have gene sequencing errors, would not be allowed in Europe, says Yeats.

Those sequencing errors might be enough to overturn the other two BRCA1 patents in Myriad’s portfolio, says Gert Matthijs, a geneticist at the University of Leuven, Belgium. But scientists cannot rely on such technicalities to battle patents, he notes. “What will happen with other major patents that don’t have errors?”

Matthijs says he is worried about patents on BRCA2, against which he and others filed an opposition earlier this year, and on a gene related to the disease hemochromatosis, for which a European patent is expected next year. Those patents lack an “inventive step,” he says. Isolating and sequencing a mapped gene “is a major breakthrough but not a major invention.”

Fortunately for Matthijs, the EPO allows ‘routine’ questioning of patents, and about 80% end up being limited. One reason for this is that the cost for opposition is in the tens of thousands of dollars, compared with hundreds of thousands in the US, giving even citizen and animal rights groups the opportunity to contest patents.

Still, the road ahead for these patents is unclear. Patent opponents argue that the OncoMouse patent, which had already been restricted in 2001 from covering all mammals, should be overturned completely. “It just solves a small controversy on the broad scope of the patent,” says Marcos Malumbres, a researcher at the Spanish National Cancer Centre.

The OncoMouse patent can no longer be challenged except at the level of EPO member-states. The BRCA1 and Edinburgh decisions are awaiting appeals. In the case of BRCA2, the existence of two conflicting patents on the same gene has led to confusion among researchers—and at the EPO itself. Asked what a researcher should do in the BRCA2 case, says EPO’s Yeats, “Consult a lawyer.”

David Cyranoski, Tokyo

California dreaming about ‘ill-conceived’ stem cell plan

Come November, California might become the first state to fund stem cell research, in direct opposition to the federal government’s policy. If voted in, Proposition 71 would allow the state to issue bonds for up to $3 billion over ten years for the research. But given the state’s $10 billion deficit, some groups are questioning whether the proposal is financially sound.

Dismayed by the restrictive federal policy, researchers Irving Weissman and Lawrence Goldstein, Hollywood producer Jerry Zucker and real estate developer Robert Klein conceived the proposal in 2003. Klein and Zucker both have children with diabetes—a leading candidate for stem cell therapies.

By mid-August 2004, the campaign had garnered widespread publicity and about $5.3 million. The goal is to raise $20 million by November. The project could be just what the doctor ordered for the state’s ailing high-tech industry, says Jim Cunneen, president of the Silicon Valley Chamber of Commerce. Apart from researchers—and, presumably, patients—the initiative could indirectly benefit venture capitalists, biotechnology companies and real estate developers.

But the project’s hefty price tag has provoked some groups—such as Doctors, Patients and Taxpayers for Fiscal Responsibility—to call it “ill-conceived.” Although the proposal is structured to postpone draining tax revenue, repaying the bond is expected to cost $6 billion over 30 years.

Opponents argue that much of the money would line the pockets of California’s real estate developers. Up to 10% of the $3 billion pie would go to building new research centers. But if the federal government limits stem cell research in buildings funded with federal grants, scientists will need independent labs, says Zena Werb, a researcher at the University of California in San Francisco. “It costs over $100 million to build a single research building,” Werb says. “That’s one of the reasons that the bond calls for so much money.”

Another 3% of the funds would create the California Institute for Regenerative Medicine, which will administer independent audits, public hearings and annual reports. Funds would be monitored by a public committee and a board of directors including scientific experts, patient groups and California businesses. Evaluation of grant applications would be modeled after the NIH’s system, says Goldstein.

The bond’s size would give researchers a stable framework unaffected by politics or the economy, Goldstein says. “We can’t work in this political environment,” he says. “Scientists need to know that they can start a long-term research project without having to worry about the next election.” The stability would help encourage young investigators to enter the field, he adds. California might also benefit from royalties on research discoveries, and potential cures could cut its healthcare costs, which at $110 billion are the nation’s highest.

Asked whether the funds might not instead go to California’s struggling school system or other problems, Goldstein says, “Sure, there are lots of other things that the state could do with the money, but it’s not as though there are five other proposals put forward with credible plans … We have an actual plan.”

Kris Novak, San Francisco
‘Fast-track’ drug approvals hit speed bumps in Japan

Families of patients who died after receiving the controversial cancer drug Iressa (gefitinib) in July filed a lawsuit against manufacturer AstraZeneca and the Japanese government for ¥33 million, alleging that the drug, approved in Japan in 2002 after only five months of review, showed neither adequate safety nor efficacy in clinical trials. The case highlights increasing concern about Japan’s growing tendency to speed up drug approvals.

Iressa is known to cause interstitial lung disease (ILD) in some patients. Six months after its release, 124 Iressa-related deaths had been reported, prompting Japan’s Ministry of Health, Labor and Welfare to issue stricter prescription and informed consent parameters for the drug. But by the end of March 2004, the ministry had tallied 444 deaths and 1,151 cases of the disease.

Rokuro Hama, who heads the Japan Institute for Pharmacovigilance, has been a vocal critic of the scientific basis for Iressa’s approval in Japan. “The classification of adverse effects in both the toxicology and the clinical trials was arbitrary and poorly designed, and the post-marketing studies showed no survival advantage,” Hama says. “Iressa should never have been approved.”

In 2003, Hama filed his own suit against the Japanese government, petitioning for release of the full results of animal toxicity tests, which he says might reveal flaws or inconsistencies in preclinical studies of the drug.

AstraZeneca has denied legal responsibility for the deaths, saying it complied fully with government regulations in marketing the drug in Japan. Iressa has been approved in 20 countries without similar reports of adverse events, notes Tomoko Haruna, a spokesperson for the company. “Obviously, there can be side effects with any drug.”

Akira Inoue, who published one of the earliest case studies of Iressa-related deaths, says that given the high mortality rate among people with lung cancer, Iressa’s risk-benefit profile is acceptable. But it’s important to identify individual risk factors, such as possible genetic differences in patients who experience adverse reactions, says Inoue, a researcher at Tohoku University.

Scrutiny of the case in Japan has focused in part on the speed of Iressa’s approval, the fastest for the company. “Obviously, there can be side effects with any drug.”

The new report is “clearly the strongest statement yet of the government on the issue and leaves no doubt at all that they intend to resolve the problem,” says Mark Mattfield, executive director of the Research Defence Society, which represents scientists engaged in animal research.

UK cracks down on animal-rights activists

Animal-rights activists were dealt a dual blow in late July when the UK government and the pharmaceutical industry announced new legislation and funds to support animal research.

Activists seemed to have scored another victory when the building contractor Montpellier on 19 July withdrew from plans to build an £18 million animal research center at Oxford University, after its shareholders received threatening letters. The University of Cambridge in January dropped a plan for a new primate research center after a similar campaign (Nat. Med. 10, 215; 2004).

But on 30 July, the UK government made protesting outside an individual’s home an arrestable offense, and warned that animal-rights extremists are “organised in a quasi-terrorist cellular structure.” Under the new policy, harassment laws will be extended to cover groups of employees, and a specialist police unit and 43 specialist prosecutors will tackle violent protesters.

The new report is “clearly the strongest statement yet of the government on the issue and leaves no doubt at all that they intend to resolve the problem,” says Mark Mattfield, executive director of the Research Defence Society, which represents scientists engaged in animal research.

On the same day, drug giants GlaxoSmithKline, AstraZeneca and Pfizer also launched a four-year £4 million research fund to pay for animal experiments. The companies said they would back fellowships and pay for lab equipment to help universities continue animal testing.

Supporters of animal research welcomed the developments, but some caution that activists will not so easily be thwarted. “Identification of the seriousness of the problem is a step forward, [but] I doubt if it will inhibit the more determined political activists,” says Ian Gibson, chair of the House of Commons Science and Technology Committee.
Soaring drug prices send experts scrambling for a fix

Amid intense pressure to reduce skyrocketing drug prices, pharmaceutical and biotech companies are trying to devise models that would give poor countries access to medicine while still covering high drug development costs and maintaining incentives for investors.

Experts say differential drug pricing would transfer some of the financial burden—an estimated $800 million to bring a new drug to market—from the US to other developed nations. Proposals include pricing drugs according to countries’ gross domestic product (GDP), or a uniform pricing system in which individual countries would negotiate confidential rebates.

These options are better than price controls, which would ultimately discourage investors and stall drug development, says Judy Lewent, head of Merck’s Human Health Asia division. Lewent cites Europe’s declining pharmaceutical industry as an example of price caps’ negative impact.

Drug prices are higher in the US than in many European countries because the healthcare systems in those countries can negotiate better prices from pharmaceutical companies than can individual American insurers. Critics of differential pricing plans say that countries with effective plans for buying drugs shouldn’t be forced to pay more. But changing the way money is allocated to buy drugs could be one solution, says Mark McClellan, former head of the US Food and Drug Administration. McClellan now heads Medicaid, a medical assistance program for low-income US families.

Generic drugs are relatively inexpensive and make up the majority of prescriptions in the US—but not in Italy or France. Negotiating cheaper rates for generics in those countries would encourage competition in that market and leave more money to spend on higher-priced medicines, says McClellan. Representatives at a conference in August at the Massachusetts Institute of Technology (MIT) suggested various new pricing models. Una Ryan, chair of the Massachusetts Biotechnology Council, proposed a scheme where countries with high GDPs would pay higher prices, subsidizing costs for poorer nations. But a potential snag with this is that countries that qualify for cheap drugs could sell them elsewhere, much like the current parallel trade between the US and Canada.

Another option is to have countries pay a uniform price but negotiate confidential rebates, suggests Patricia Danzon, a health care professor at the Wharton School of Management in Pennsylvania. In this system, countries wouldn’t know how much their neighbors pay for the same drugs, thus preventing parallel trade. Some researchers doubt it would be possible to maintain confidentiality.

But Ernst Berndt, an economist with MIT’s Sloan School of Management, says the model would be widely applicable to different types of drugs, from medicines for rare orphan diseases to injectable vaccines, he says, but the real hurdle will be convincing countries they are getting a good deal.

NIH lab shutdown raises concerns about US prion research

When the US National Institutes of Health (NIH) closed a pioneering prion research lab last month, the timing seemed a bit off.

British researchers had just identified a second case of variant Creutzfeldt-Jakob disease (vCJD) transmitted through a blood transfusion. The UK Medical Research Council is set to launch a trial of potential vCJD treatments, but there are no such trials in the US. A report released last winter by the National Academy of Sciences says the US research program on prion diseases is “small, aging, and inadequately funded.”

The NIH quickly responded that the lab’s closure is meant to address those concerns, not exacerbate them. The Laboratory for Central Nervous System Studies, founded in the 1960s, was narrowly focused on the transmissibility and infectiousness of prion diseases, says Eugene Major, acting director of basic neuroscience programs at the US National Institute of Neurological Disorders and Stroke.

The agency now wants to develop a broader intramural program that includes research on prion structure and circulation, Major says.

“This is the time to look at where the field is going in order to ask the most important questions.”

Major notes that lab chief Paul Brown’s retirement is just the latest of many exits. The lab’s founder, D. Carleton Gajdusek, won a Nobel Prize in medicine for his work tracing the ‘kuru’ disease in New Guinea to the ritual consumption of human brains. Gajdusek left the NIH in 1997 after pleading guilty to charges of sexually abusing one of many boys he informally adopted during his fieldwork.

His successor, Joe Gibbs, died in 2001. Earlier this year, Brown described himself to the Wall Street Journal as “the last living relic” of that team and complained that his lab had no funding. The NIH has not yet decided how it will realign the work done in Brown’s lab, but it will probably reflect the agency’s new drive for cooperation between various institutes, Major says.

Last month, for instance, scientists began moving into the $261 million Porter Neuroscience Research Center, designed to encourage collaboration. Instead of small, isolated labs, a full third of the center’s space is devoted to a large, open lab surrounded by walls of windows. The goal is to have researchers from as many as 11 different institutes work there. NIH officials expect to announce a plan in September to promote the same kind of collaboration among extramural neuroscience researchers.

Over the years, the NIH has increasingly farmed out research on prion diseases to extramural researchers. A review of the agency’s grants database turns up 121 grants with the word ‘prion’ in the title for 2004, compared with 46 in 1994.

Still, it would be helpful to have a central government facility, says neurologist Richard Johnson, who chaired the National Academy of Sciences committee. Individual investigators cannot tackle certain high-risk projects that require infrastructure and long-term support, Johnson notes. Although he is confident that the NIH is moving in the right direction, he says, “It’s a different kind of commitment that universities can’t provide.”

Tinker Ready, Boston
**Britain issues first therapeutic cloning license**

UK researchers applauded the country’s decision to grant its first license for therapeutic cloning experiments, saying it will help develop stem cell–based therapies.

The country’s Human Fertilisation and Embryology Authority on 12 August approved Newcastle University researchers’ application to create embryonic stem cells. Although their research is still a long way from the clinic, the team aims to make insulin-producing cells that could be transplanted into diabetic patients without risk of immune rejection.

UK law prohibits reproductive cloning but allows therapeutic cloning under heavy review. The permit is a first for the UK and Europe, although the research is allowed in other European countries. In February, South Korean researchers reported that they had cloned the first human embryos.

The announcement also establishes the country’s position on cloning two months before UN member states are scheduled to meet to develop an international agreement on the issue. The UK and other countries are advocating for a decision to ban reproductive cloning but allow individual countries to define their own policies on therapeutic cloning.

**WHO pulls Indian generics off AIDS drugs list**

The World Health Organization (WHO) has removed three generic AIDS drugs made by the Indian manufacturer Ranbaxy from its list of safe medicines.

In May, the agency delisted two drugs made by another Indian company, Cipla, shortly after the European Union called for routine inspections of quality-control laboratories. In both cases, inspectors found that operations at the laboratories were substandard and the drugs could not be proven to be therapeutically identical to the patented originals.

Ranbaxy has said it is now testing the drugs at a different laboratory, and will resubmit quality data to the WHO. The company also announced on 2 August that it will seek approval from the US Food and Drug Administration (FDA) for its combination antiretrovirals by the end of the year. Ranbaxy would be the first to participate in an FDA initiative announced in May, inviting overseas generics companies to file for agency approval on a ‘fast-track’ status.

The US does not recognize the WHO’s drug assessment system and has questioned the quality of generic HIV drugs. But experts have criticized the US policy, saying it caters to pharmaceutical company interests and elevates drug prices beyond the reach of most developing countries.

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Written by Alla Katsnelson

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**Francis Crick, 88, discoverer of DNA’s secrets**

Francis Crick, who in 1953 burst into a Cambridge pub and announced that he had found the secret of life, died on 28 July of colon cancer.

The secret, of course, was the double helical structure of DNA, and its discovery earned Crick the Nobel Prize, which he shared in 1962 with James Watson and Maurice Wilkins. But the accomplishment was just the start of a brilliant and varied career. Over the next 25 years, Crick’s contributions to molecular biology, including the discovery of DNA transcription and amino acid coding, laid the foundation for understanding the genetics of inheritance.

In 1977, Crick left Cambridge for the Salk Institute for Biological Studies in San Diego, where he turned to his other intellectual passion, the study of the human brain. His work there gave credence to a then-radical theory—that consciousness is generated by the firing of neurons.

A true theoretician and visionary, Crick was heralded by colleagues for his intellectual rigor and fearlessness in the face of controversial ideas. As he once said, “a man who is right every time is not likely to do very much.”
Malik Peiris really needs a holiday. The Hong Kong–based virologist has always been busy, but since December 2002, he has grappled with crisis after crisis. First, there was severe acute respiratory syndrome (SARS), which surfaced as a mysterious pneumonia-like illness, then bird flu, then SARS again, then more bird flu … and on and on.

When reports of SARS first emerged in the Guangdong province of China, Peiris was away with his family on Christmas vacation and had to rush back—and that pattern has held ever since. “I’ve taken a few days [off] here and a few days there, but every time I go on vacation something happens,” he says.

The outbreaks brought a whirlwind of activity, recognition and the world’s attention to Peiris and the first-rate team he has assembled at Hong Kong University since his arrival there in 1995. They also presented fascinating scientific puzzles at his doorstep. But to say that he is exhausted is an understatement.

“One of Malik’s assets is his great capacity to collaborate with people and work as a team. He gets on very nicely with people,” says Sarathnanda ‘Chubby’ Arsecularatne, Peiris’ mentor and, later, his father-in-law. “That’s a very important aspect to Malik that has defined his success.”

Malik Peiris

As a non-Chinese leader of a lab in China, Peiris is sometimes in a delicate position, but Webster and others say he handles the situation with aplomb. His colleague Guan, who holds a junior position at the university, manages operations on the mainland and shares grants and responsibility for the team.

In many ways, the two researchers could not be more different. “Malik is a pretty quiet person, a good gentleman,” says Guan. “His personal style is more UK-like. I am more American style. American style is very aggressive. British working is more political, more gentle,” Guan says.

Guan likes venturing into the field, where Peiris is essentially a lab biologist, interested in unraveling infectious-disease mechanisms. Although he trained in medicine, in 1974, Peiris joined the microbiology department at the University of Peradeniya, then called the University of Ceylon.

The department lacked a virologist, so Peiris set up a virology laboratory. “Straight away, he got on to some important research,” recalls Arsecularatne, who is emeritus professor of microbiology at the university. “I pinned my hopes on him because he is one of those people who are so easy emphatic in their interest in research,” says Arsecularatne. Although research in most resource-poor third-world countries is difficult, Peiris consistently did good work, Arsecularatne says. “Malik amply justified my expectations. I’m very proud of him.”

“I would really like some peace and quiet from infectious disease for the next two to three years so we can all catch our breath a bit.”

In 1977, Peiris began working at the University of Oxford on the mechanisms of dengue hemorrhagic fever. When he returned to Sri Lanka in 1982, he set up a virology department at Peradeniya. “Except maybe for the SARS story, what I’m most proud of is what I managed to do during those six years in Sri Lanka,” Peiris says.

Peiris then went to work at the University of Newcastle upon Tyne and, in 1995, joined Hong Kong University. Still, he continues to visit Sri Lanka twice a year and in his lectures there, always emphasizes the importance of research on diseases that affect the country. Asked if he feels compelled to return to Sri Lanka, Peiris says, “I do feel an obligation, but equally there are some important things that can be done from a place like Hong Kong.”

Peiris is indeed needed in Hong Kong to keep an eye on SARS—which he says is likely to pop up unpredictably—and bird flu, which he predicts will reemerge in the winter. Of the two, influenza is a bigger threat, but a more familiar enemy, he says.

Somewhere in between, he would also like to make time for all the things he has had to brush aside in the past two years: books, music, art, travel, simple walks and—most important—his wife and two children. And he fervently hopes that SARS and bird flu are staggered enough to give him and his colleagues enough room to collect their wits.

“Either one is bad enough on its own, but if they were to emerge in the human population at the same time—I dare not think of it,” he says. “I don’t think nature would be so unkind. I hope.”

Apoorva Mandavilli, Hong Kong