

Functional foods from biotech—an unappetizing prospect?

Kendall Powell

In the early 1990s, functional foods promised to solve global malnutrition and put palatable options for treating ailments on grocery shelves. Since then, a meager number of products have ripened while the rest have turned sour.

Functional foods were once touted as the next wave in the food and beverage industries. Yet as these products—defined as “any modified food or food ingredient that may provide a healthful benefit beyond that of the traditional nutrients it contains”¹—have begun to make their way to customers’ carts, they have suffered some major setbacks and disappointing flops.

Predicting which enhancements consumers are willing to pay extra for is not straightforward. GM products that seemed to be shoo-ins for solving global malnutrition or filling a niche market have been stymied by multiple problems. Other GM products, such as seed oils used for cooking and food processing, are moving forward and expected to be snapped up by food ingredient companies (Fig. 1). Learning from past product failures and reacting to consumers’ wishes should help propel the next cohort of products further (Table 1).

One thing is clear from the front-runners: demand must be high enough to pull these products through more complicated development stages and to offset the cost increases in staples, such as bread. In most cases, this means the health benefit must be clearly seen or felt by those eating the foods. As such, categories like medical foods—which have, until recently, only addressed limited populations such as diabetics—may enjoy a wider popularity.

Today, numerous barriers continue to stymie the rise of functional foods—from financial concerns in the tight margins of grocery and produce profits to trickier technologies for producing less harmful fats. And introducing



Figure 1 Field of dreams? Soybeans with altered fatty acids grow in a field in Iowa.

genetically enhanced nutrition to the world’s neediest stomachs will likely remain an uphill battle.

Remedies in the kitchen?

“There will be multiple channels into the healthy living or wellness market,” says Roger Wyse, managing director of the San Francisco venture capital firm Burrill and Company. “It could be through supplements, probiotics, functional foods or medical foods—they could all address the needs of the consumer who is trying to access products to maintain a healthier lifestyle,” he says (see Box 1 for definitions). Wyse

sees improved scientific evidence of efficacy as the key to success in any of these paths.

That philosophy is reflected in the seven companies in Burrill’s nutraceuticals portfolio—many of which are bringing new strategies to conventional functional foods. For example, CreAgri (Hayward, CA, USA) makes an olive extract with increased polyphenols that have both antioxidant and anti-inflammatory effects. Polyphenols are found in many plant foods, including berries, teas and chocolate, and they may reduce the risk of cardiovascular disease and cancer.

CreAgri’s extract is available both as a dietary supplement at health food stores and as a concentrated product sold as a food ingredient to manufacturers. Straddling two categories allows the product to be sold right away to the ‘early adopter’ crowd—typical high-end natural foods store shoppers—while the food ingredient version goes through formulation and testing in food labs.

Young companies like CreAgri would do well to learn from products already being consumed that have both stumbled and succeeded. Consumers readily recognize the heart-healthy benefits of eating a diet rich in omega-3 fatty acids, which are found in nature in certain seed oils and in cold-water fish. Martek Biosciences (Columbia, MD, USA) and Ocean Nutrition Canada (Dartmouth, Nova Scotia) produce omega-3 fatty acids as food additives, by fermenting marine algae and purifying fish oil, respectively.

There was a time when the Western diet included plenty of omega-3 fatty acids naturally, as they bioaccumulated in livestock grazing on a wide variety of plants. Modern agriculture, however, has obliterated this with the practice of fattening cattle in feedlots on primarily corn and hay. In many cases, modern

*Kendall Powell is a freelance writer based in Boulder, Colorado.
e-mail: kendall2@nasw.org*

breeding has selected for yield at the detriment of nutritional value and has created a need to add back nutrients somewhere down the line of the food's life².

Adding back purified omega-3s has its downsides, though—namely, it is incredibly expensive to ferment or purify the oils so that they do not have a 'fishy' taste. These downsides have led to limited success. Martek's product has been picked up by the manufacturers of infant formulas, and Ocean Nutrition has had success with a micro-encapsulated version of its product that can be included in baked goods and dairy products. But even though consumers are

ready to gobble up these fatty acids, they aren't necessarily willing to shell out extra dollars for them—and the food companies know it.

Adding a dollar to the cost of a loaf of bread—a rough estimate for adding omega-3 fatty acids—is a "tough sell," says Wyse. Whereas an early adopter might pay almost \$1 a day for fish oil supplements in pill form, most consumers want high-quality, low-cost food in their grocery bags. "The margins are so tight in food that it is very hard to get back the investment for adding one of these bioactives," says Wyse.

On the flip side, the Dannon Company's Activia brand of probiotic yogurt has become

a blockbuster product, surpassing \$100 million in sales in the United States in its first year. So why will consumers pay more for yogurt and not bread?

"Yogurt has permission to deliver nutrients; it's a natural carrier," says Michelle Barry, senior vice president for consumer insights and trends at the Hartman Group, a consumer market research and consulting firm in Bellevue, Washington. So do juice and wellness bars and other things that consumers view as inherently healthy. But putting fish fatty acids into bread presents an imaginary conflict in consumers' minds, Barry says. "It becomes a symbolic issue.

© 2007 Nature Publishing Group <http://www.nature.com/naturebiotechnology>



Table 1 Selected functional food products

Products	Company	Description of functionality	Status
Food ingredient			
Vistive1	Monsanto (St. Louis, MO, USA)	Oil from soybeans containing low levels of linolenic acid that produces no trans fats when used in cooking; achieved through conventional breeding	In market
Vistive3	Monsanto	Oil from soybeans containing low levels of linolenic acid, high oleic acid, and reduced saturated fat that has a heart-healthy profile and increased stability for frying; achieved through a combination of breeding and biotechnology	Mid-stage development; projected launch early next decade
Omega-3 soybean oil	Monsanto	Transgene added to soybean for production of stearidonic acid, which when consumed is converted to heart-healthy eicosapentanoic acid	Late development; projected launch early next decade
High oleic	DuPont (Wilmington, DE, USA) and Bunge (White Plains, NY, USA)	Adding transgene for high oleic acid for increased stability in frying	Late development; going through regulatory approval currently
High oleic, high stearic	DuPont and Bunge	Adding transgenes for high oleic acid and high stearic acid for wider uses in frying and baked goods	Early development?
Omega-3 soybean oil	Solae (a joint venture between DuPont and Bunge) and Monsanto	A number of approaches for producing fish-oil-like heart-healthy fatty acids	Advanced research stage
WG0401	WellGen (New Brunswick, NJ, USA)	Theaflavin extract derived from tea to be used as functional food ingredient to control inflammation	Advanced stage; launch expected in third quarter 2007
WG0301	WellGen	Polymethylated flavone-enriched extract to interfere with adipocyte development (obesity); functional food ingredient	Human clinical trial to start in third quarter 2007
Probiotics			
Activia yogurt	Groupe Danone (Paris, France)	Contains a strain of bifidobacteria that reduces intestinal transit time to improve regularity	In market
Attune wellness bars	Attune Foods (San Francisco, CA, USA)	Contains three strains of bacteria to balance digestion and support immunity	In market
Medical foods			
Efficas Care products	Efficas (Boulder, CO, USA)	Contains a proprietary ratio of γ -linolenic acid and eicosapentanoic acid, essential fatty acids for reducing inflammation associated with asthma, allergies and eczema	In market
Whole foods			
Sugar beet with fructans	Florimond Desprez (Cappelle-en-Pévèle, France)	Added onion transgene for enzyme that converts sucrose to fructan, a source of soluble fiber and low-calorie sweetener	Advanced research stage; no plans for development
High-protein cassava	BioCassava Plus International Consortium	Adding genes from other cassava varieties to produce 2–4% dry weight protein in African cassava	Early research stages
High-folic-acid tomato	University of Florida (Gainesville, FL, USA)	Adding transgenes to increase folic acid by 25 times in the ripened fruit for treating folic acid deficiency, a cause of birth defects and anemia	Early research stages
Dietary supplements			
PMI-5011	Phytomedics (Jamesburg, NJ, USA)	Antidiabetic extract from an edible plant used to treat type 2 diabetes	Phase 2 clinical trial
Oliveoil	CreAgri (Hayward, CA, USA)	Olive extract containing the polyphenol hydroxytyrosol, which has antioxidant properties	In market

‘Do I want fishy bread?’ It doesn’t line up.”

Barry also notes that yogurt falls into a broader trend in ‘live’ products—dairy, meat, fish, poultry and eggs—which consumers recognize as being under a halo of naturally occurring functionality. Consumers are more enthusiastic about eggs enhanced with the omega-3 fatty acid DHA (incorporated naturally through the chickens’ feed) than bread with DHA added artificially.

“The food culture is shifting toward real, authentic, fresh foods, and the consumer trend is toward naturally functional foods such as really high antioxidant berries and chocolates,” says Barry. Shoppers also recognize that yogurt already has live bacterial cultures in it, which minimizes objections to the new strain in Activia that is supposed to aid digestive regularity. But others note that, perhaps more importantly, the health effect can be felt in as little as two weeks.

Pointing to a pomegranate juice container among a display of functional food products at his Boulder, Colorado office, Dean Stull, chief science officer of Efficas, explains further why some functional food trends are so short-lived. Although heavily marketed as chock-full of antioxidants, pomegranate juice became a product that many consumers tried once and

Box 1 Glossary

Functional food. Any modified food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains. Conventional functional foods include foods that have benefits added back in the form of food additives, dietary supplements, probiotics or medical foods. Genetically modified functional foods include whole foods or foods processed from crops that have been genetically engineered to include health benefits.

Dietary supplement. A product that contains a vitamin, mineral, herb or other botanical, amino acid, concentrate, metabolite, constituent, extract, or combinations of these ingredients (modified from the Dietary Supplement Health and Education Act).

Probiotic. Bacterial or yeast strains that when ingested may provide health benefits through colonizing the digestive tract.

Medical food. A food consumed under the supervision of a physician that is intended for the specific dietary management of a disease or condition (modified from the Orphan Drug Act).

KP

never again. Because the antioxidant effects in it do not translate into less aging or lower cancer rates until many years later, consumers are not likely to incorporate this exotic-tasting juice into their daily routines, according to Stull.

“People want to take control through their diet and daily lives,” says Stull. “They want something they can feel, see or measure today.” His company began with that idea and a goal

to find a product that could be marketed as a medical food. A medical food is a food or ingredient that is considered generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA). In addition, the product has clinical trial data behind it, which allows its maker to place on it the highest level of health claim afforded to any products short of drugs: a “disease management” claim (Box 2).

Box 2 Give us our daily medicine

The term ‘medical food’ might sound rather unappetizing, but the space such foods occupy in US regulation is appealing to manufacturers. Only the definition of a medical food is set by law in the 1988 Orphan Drug Act Amendments; it is defined as a food that is specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by a normal diet alone.

Originally, such products addressed the special nutritional needs for people with rare metabolic disorders such as phenylketonuria, or they were used to enhance nutrition for the very old, very young, or burn patients in hospitals. Such foods do not require FDA approval for their health claims, but they must be labeled as a medical food for management of a specific disease, and the label must indicate that they are intended for use under medical supervision. Such light oversight leaves the definition of medical foods open to interpretation.

The allergy, eczema, and asthma care products manufactured by Efficas fit the definition, but they are intended to be used by a much wider patient population. The fruit-flavored gel provides a ratio of two essential fatty acids, γ -linolenic acid and eicosapentaenoic acid, that would be “nearly impossible to get through a normal diet alone,” says chief science officer Dean Stull.

Because medical foods contain ingredients that are GRAS, they fall somewhere between a conventional food and a drug. Makers of medical foods avoid the high safety requirement set for drugs, but they are allowed to make a health claim that their product can alleviate specific disease symptoms, which is much stronger language than the structure-function types of claims that

are afforded to most conventional functional foods. For example, orange juice fortified with calcium may claim that it builds stronger bones, whereas Efficas’s Asthma Care can claim to reduce the inflammation that causes allergy symptoms.

Such claims must be backed by “sound, scientifically defensible evidence,” and Efficas chooses to test its products in traditional clinical trials that are double-blind, randomized and placebo-controlled. In 1996, the FDA proposed new rule-making on the regulation of medical foods in response to the number of products being marketed as such and to a few cases in which medical foods were found to be dangerous for patients because good manufacturing practices had not been followed. These were products being used in hospital intensive care settings that were either too potent or not potent enough for their patient populations.

The FDA withdrew the proposed rule-making in 2004 as part of an effort to clean up its regulatory backlog, but those guidelines still reflect the agency’s framework for regulating medical foods (see <http://www.cfsan.fda.gov/~lrd/fr961129.html>).

Efficas’s products are being sold online and marketed to the target patient populations, but Stull ultimately sees these products being sold as an over-the-counter product alongside other allergy and asthma medicines in the drug aisle of a retail store. Analysts say that products such as this, which are low risk and have a low-risk patient group, will be the most likely to benefit from the ability to make strong health benefit claims without FDA approval. And should the FDA formalize their rules in this area, these products will be unlikely to attract negative action by the agency.

KP

Efficas's asthma, respiratory allergy and eczema care products are a proprietary ratio of two essential fatty acids delivered in a fruit-flavored gel (Fig 2). Clinical trials show that the fatty acids work to reduce the production of proinflammatory leukotrienes³. In test marketing in the fall of 2006, Efficas found that consumers needed about two weeks of taking the daily dose of gel to see benefits in their health and quality of life.

"This verification of benefit is missing" in the dietary and herbal supplement market, says Stull. "There's still controversy over the benefits of vitamin C," he notes. Also, the studies coming out of the US National Center for Complementary and Alternative Medicine have debunked the health benefits of some of the most popular herbal remedies, most notably echinacea as a cold remedy and black cohosh for hot flash relief. Conversely, a distrust of pharmaceutical companies and doubts about drug safety are driving consumers to seek out safe and effective products somewhere in between drugs and foods.

"Medical foods are unique in the market" right now, says Stull. As an investor in Efficas, Wyse agrees. "If we are going to invest in the up-front development costs, which in many cases are clinical trials, then it's very difficult to capture that value in the food dollar," he says. The Efficas gel costs about \$1.40 a day and is being marketed directly to patient groups via the internet. That cost becomes acceptable to a buyer because the gel is positioned as a healthcare treatment rather than as a snack, says Wyse. "We are going to have to position these products to capture some of the healthcare dollars."

Dysfunctional foods

The approach of focusing on proven, easily recognized health benefits also dominates the development of GM functional foods for both humanitarian efforts and commercial ventures. But when asked why Burrill had not yet invested in GM foods, Wyse's answer reveals one of the most stubborn obstacles facing these efforts: marketplace acceptance.



Figure 2 An appetizing dose? Efficas's fruit-flavored gel delivers two fatty acids that reduce the production of proinflammatory leukotrienes.

"As investors, we need to get in, create value, and get out in three to five years. Even though we are very supportive of [GM technology], the regulatory uncertainty is too high," says Wyse. That uncertainty is one of many uncertainties (about consumer acceptance, higher technical hurdles, and concerns about recovering development costs) that have stopped many projects cold.

"The industry knows how to handle additives, but the different rules and regulations for GE foods is just a different ball game."

The business model for genetically engineered (GE) functional foods is completely different than the business model for the agricultural biotechnology products already on the market, says Michael Fernandez, executive director of the Pew Initiative on Food and Biotechnology (PIFB; Washington, DC). "What benefit are you getting from the GE aspect of it?" he asks.

Altering nutrient levels in whole foods can be a much more difficult task that requires engineering in multiple genes for a biochemical pathway. In addition, if a nutrient can be

cheaply added into a processed food, then the only incentive becomes to include it in a better banana or potato. Unfortunately, the profit margins for produce are even tighter than in processed foods. But there may be hope for nutrients that cannot so easily become additives, and for products that eliminate anti-nutrients or food allergens.

The end user of these new products is no longer the farmer; it is now the consumer. That shift brings a number of adjustments with it. Companies must figure out "how to share that benefit to the consumer along the business food chain," says Fernandez. Companies will be going after the big US markets of corn and soybean first, but "will it be worth it to go for fruits and vegetables?" he asks.

So far, the answer is no. Only a handful of nutritionally enhanced whole foods have made it beyond early research phases. Even GM products that appear to address a niche that cannot be handled conventionally have faltered, their creators say. Though there has been much speculation about Monsanto's (St. Louis, MO, USA) 2005 acquisition of Seminis (Oxnard, CA, USA), a major fruit and vegetable seed company, the GM giant says it does not intend to develop functional produce through biotechnology at this time⁴. The company is pursuing research on improvements in taste, texture, shelf life and nutritional content; however, these are all based on marker-assisted breeding or genomics, says Seminis communications director Mica Veihman. The 8–10 years and \$50–100 million investment in biotech traits does not make sense at this time for the much smaller scale of vegetable crops, she says. Nor have they found any valuable consumer traits to add that cannot be accomplished through breeding.

"There is so little stomach or interest from the major and minor food companies to do [biofortification] through biotechnology" right now, says Roger Beachy, president of the Donald Danforth Plant Science Center in St. Louis. "The industry knows how to handle additives, but the different rules and regulations for GE foods is just a different ball game."

Left on the shelf

Even GM produce projects that would seem to be so valuable commercially as to be worth the extra cost and effort of regulation have stalled out. Sjeff Smeekens and his laboratory at the University of Utrecht in The Netherlands created a transgenic sugar beet that converts 70–80% of its sucrose into fructan⁵. Fructans are polymers of fructose that, depending on their length, are used as either a low-calorie natural sweetener or a fat replacement when emulsified—two of the holy grails of the food additive

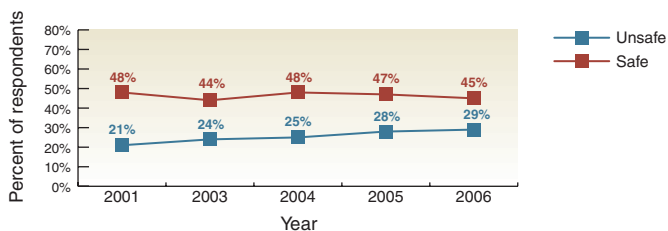


Figure 3 Public perception of food safety. Polls have shown that public perception of the safety of genetically modified foods has changed only slightly over the past six years. Source: PIFB, Washington, DC, USA

industry. To humans, fructans taste like other sugars; but, they cannot be digested.

Fructans are already commercially available and are mainly extracted from chicory roots. However, the extraction from this source is relatively inefficient, making fructan a more expensive additive. In theory, extracting fructan from the larger body of the sugar beet would be cheaper, says Smeekens. But he fears he may never know because the company that now owns the technology, Florimond Desprez (Cappelle-en-Pévèle, France), is taking a “sit and wait” approach.

“Our results are so impressive that the company does not want to kill the project, but they do not invest in it, either,” he says. Smeekens chalks this up to the strong anti-GM movement in Europe that keeps food processors opposed to adopting even cost-saving technologies.

Similarly, transgenic brewer’s yeast strains developed 15 years ago sit in the deep freeze at the VTT Technical Research Centre of Finland in Espoo. One such strain uses a bacterial gene to cut the lagering process from two weeks to two hours.

“It’s here if anyone wants to use it,” says John Londesborough, senior research scientist in the brewing and malting technologies group at VTT, a government research center that does contract work for the brewing industry. “The brewers must have funded it, but they don’t want to use it. They are frightened that word would get around that their beer has [GM yeast] in it.”

When VTT realized GM approaches would not work, they used them to find non-GM alternatives. In the lagering case, they designed a bioreactor that would do the same trick. And they have also used GM yeast strains to confirm the metabolic pathways that produce fruity or flowery flavors in beer. Once the pathway is known, researchers can then design ‘smart’ selection screens to identify natural mutants that produce the desired flavors.

“The refusal of the public to accept genetic engineering is driving people to find these other solutions,” says Londesborough. He says VTT’s clients hold a wide range of opinions about using the GM yeast strains in the future, with some wanting to be ready to capitalize on an advantage should public opinions change.

Smeekens calls the anti-GMO feelings “damaging” to European plant biotechnology research. He says the only hope for turning the tide of opinion toward accepting GM functional foods is an undeniable medical reason. “The moment there is a danger or advantage for human health,” all discussion stops, he says. He cites the example of French cheese producers switching to recombinant enzymes rather than continuing to use enzymes isolated from

calf intestine when the threat of bovine spongiform encephalopathy (BSE) emerged.

But others say that the sluggishness in realizing the potential of GM functional foods should not be attributed simply to consumer resistance to the idea. “I think it would be a mistake to attribute too much to market resistance,” says Val Giddings, a GM food expert who runs the consulting business Prometheus AB (Silver Spring, MD, USA).

Giddings admits that it is clear that a portion of the world’s consumers (ranging from 20–50% depending on the poll) has reservations about various biotech applications, including GM food. But he also says that polls are “mis-

Companies must convince not only the growers that the new variant will yield as much as a traditional crop, but also the food processors and preparation companies that the oil, grain or produce will perform and taste similar to its conventional counterpart.

erable predictors of purchasing behavior” and that the overwhelming factors that rule at the checkout counter are food quality and the price tag [see p 507]. A bigger contribution, he says, is the resistance that is coming mainly from the conservative brand managers who see losing even a few percent of their customers as too great a risk and completely avoidable.

Even in the United States, it seems that GM foods have lost ground in consumer opinion polls. The latest poll by the PIFB shows that in the last five years, the number of Americans who believe that GM food is safe has dropped slightly, and those who believe GM food is unsafe has risen slightly (Fig. 3). In 2001, after being told how many processed products contain food from GM plants, 48% of consumers thought GM foods were basically safe and 21% thought them unsafe. In 2006, when asked the same question, 45% of Americans thought GM foods basically safe and 29% thought them unsafe. In addition, consumers consistently underestimate the amount of GM food that they have most likely eaten.

Some advocates of GM food criticize the technical nature of the questions asked in the PIFB surveys as likely to overestimate consumer opposition. Nonetheless, the survey illustrates that even in GM-friendly markets, developers of these technologies need to do a

better job of getting their message out about the safety data already in hand. “In the last ten years, there have been literally billions of meals [containing GM food] consumed by humans and livestock, without a single confirmed case of a negative impact on health or the environment greater than organic or conventional crops,” says Giddings.

Those human meals Giddings mentions come in two widely consumed forms: (i) processed foods containing soybean and corn oils or meals, and (ii) restaurant or prepared foods cooked in those oils. The genetic modification of soybean and corn plants in the United States is almost exclusively from transgenes that confer pest or herbicide resistance to the crops. Currently, about 89% of US soybean crops and 61% of US corn crops are transgenic⁶, so avoiding GM foods becomes increasingly difficult around the world unless one exclusively eats foods labeled non-GMO. However, none of these GM foods being consumed offer any functional improvement in nutrition to those munching on them.

Giddings is not surprised that the functional food GM traits are taking longer to see the light of day than the “rosiest projections” of ten years ago. The more complicated traits usually involve synthesis pathways to make or increase a nutrient, and using multiple enzyme genes can also shift the makeup of a food in unintended ways. In other words, such traits may require metabolic engineering to find ways to increase a desired nutrient without a concomitant decrease in other desirables or increase of unwanted by-products. On top of that, Giddings says, the companies must convince not only the growers that the new variant will yield as much as a traditional crop, but also the food processors and preparation companies that the oil, grain or produce will perform and taste similar to its conventional counterpart. As such, dozens of ideas for enhanced fruits and vegetables have been abandoned because their returns would never justify the expense of their development to shareholders. Beachy notes that many of the Danforth Center’s projects in biofortification (such as sweet potatoes enriched with folate) are moving forward only as humanitarian efforts for the developing world (Box 3).

Making healthier fats

For commercially biofortified products, Beachy says the only ‘pull’ large enough to override GM food concerns is a government mandate to improve health. Just such a mandate kick-started the one type of GM functional food that is moving forward through development. The FDA has stated that there is no room in a healthy diet for any level of trans fat—a

Box 3 Biofortification falters

But what about humanitarian efforts, which aren't beholden to shareholders and slim profit margins? Though these efforts continue to advance the science of biofortification of foods, they have also run up against public resistance and regulatory obstacles that threaten to derail even the most advanced projects.

The leading humanitarian GM food, Golden Rice, which is designed to combat vitamin A deficiency in developing countries, overcame the last of its technical hurdles in early 1999, says co-creator Ingo Potrykus. Had it not been a GM product, it would have been handed out to farmers in Southeast Asia and India in 2003. Potrykus predicts that it will take until 2012 before Golden Rice reaches farmers, and he attributes the extra nine years solely to the almost worldwide adoption of "extreme precautionary regulation" of GM organisms.

Many developing countries that do not already have their own regulatory systems in place for GMOs have been encouraged by the United Nations, environmental organizations, and development agencies to adopt the regulations suggested by the Cartagena Protocol on Biosafety, which were designed to protect biodiversity.

"This is both totally nuts and entirely pernicious," says Giddings, because the protocol assumes that crops improved through biotech pose a threat to biodiversity and also imposes a burden to disprove those risks. "The regulators leap past the essential first step of hazard identification," he says.

Potrykus says this is why Golden Rice still has not received permission for field testing in India and the Philippines, even though "no environmental scientist can construct any hypothetical risk" from the product. And, he adds, the excessively high regulatory

safety bar creates a catch-22 by making the public more wary of GM foods.

"The entire system is not working on a logical basis, but rather on an emotional one," says Potrykus, obviously frustrated that a program that could save lives and prevent blindness has been held up not by financial or technical difficulties, but by regulatory red tape.

Others who work on humanitarian efforts point out the flawed logic in holding up conventional products as risk-free. William Folk, a biochemist at the University of Missouri-Columbia, works on improving the quality of protein in cereal plants. He notes that quality protein maize was developed in Mexico through almost 20 years of breeding selected mutants that were generated by chemical mutagenesis, which might have caused additional changes in the structure of various proteins.

"With conventional breeding using mutagenesis, you are hunting for something you don't really understand," he says. The impression that it doesn't carry risks is misguided, he says.



Figure 4 Biofortification efforts. An international team is working to improve the nutritional content of cassava, a staple to over 250 million Africans.

fat found in partially hydrogenated oils that raises bad cholesterol and lowers good cholesterol, thereby contributing to heart disease. Beginning in January 2006, the FDA required all food nutrition labels to list the amount of trans fat. And in December 2006 and February 2007, New York City and Philadelphia, respectively, banned the use of trans fat in the cities' restaurants, a step that numerous other locales are pondering as well, including Calgary, Boston and the state of California.

In response, food manufacturers such as Kellogg's (Battle Creek, MI, USA) and fast food chains such as Kentucky Fried Chicken (Louisville, KY, USA) have turned to a functional food that had been developed a decade earlier: the low-linolenic-acid soybean. Referred to as 'low-lin', the soybean oil produced from these seeds is trans-fat free, and soybean oil processors can hardly keep up with demand.

Although this first-generation soybean was produced through conventional breeding, both Monsanto and DuPont (Wilmington, DE, USA) are working on products that blend conventional breeding and genetic engineering to produce soybean oils that have even healthier fat profiles and that can be used for different applications, such as baking, frying and processing.

DuPont, for example, has a transgenic high-oleic-acid soybean making its way through regulation now. Oil from this product would have a higher stability for frying foods. And a third-generation product, a high-oleic-acid, high-steric-acid oil, could be used in baked goods—yes, even donuts.

Similarly, Monsanto's Vistive3 soybean, currently in laboratory testing, combines three traits: low-lin, high-oleic and lower saturated fats. Timothy Conner, senior director of oil seeds and food technology at Monsanto, says he expects the company to launch Vistive3 sometime early in the next decade.

Both companies are also pursuing GM soybeans that have omega-3 essential fatty acids added, recognizing that a demand already exists for an inexpensive and sustainable source of omega-3s. "The food companies tell us they would be putting [omega-3 soybean oil] in food today if it was available," says Anthony Kinney, research supervisor at DuPont Crop Genetics. The companies are also banking on both their expertise in guiding GM soybeans through regulation and consumers' recognition of the health benefits of omega-3s.

Magic formula

Healthier soybean oils have the right combination of factors that make for a successful GM functional food, proponents say. For starters, in many cases it is technically impossible to conventionally breed in the multiple traits needed to create a specific fat profile inside a seed. In other words, as you select traits that lower one type of bad fat, you might also lower another type of desired fat as you shift the balance of precursor metabolites. And making the oil inside a seed crop means cheaper oils and a guaranteed supply.

"If you are going to commit to having a product in your foods, availability is important," says Conner. "There is a 70 million acreage base in the US [for soybeans]." And soybean oil is a familiar commodity for food processors, he adds.

Because GM functional foods take a chain of groups—seed producers, growers, processors and food companies—to deliver the added value to the consumer, the traits must carry a high enough value to cover the chain's higher costs. For trans-free soybean oil, that value was built in by a government mandate. For the omega-3 oils, almost 80% of consumers recognize that omega-3 fatty acids may reduce heart disease risk (see <http://www.ifc.org>).

Smeeckens and Potrykus warn that the attitudes toward GM foods and the strict regulations are stifling academic researchers. Smeeckens abandoned his work on the sugar beet more than a year ago, citing an inability to secure funding for the work. And Potrykus estimates that taking a public project through the required regulatory burdens would cost about \$20 million.

Others say that research projects are moving forward despite the climate and that it may take creative models to overcome some hurdles. Beachy says that most of his center's biofortification projects are truly aimed at the third world. But then, he asks, "How do you fund the research to get it done?" These projects also require contemplating making discoveries freely available and working with local scientists in the countries in need to ensure adoption of new crop varieties. Ideally, Folk says, countries would set up programs similar to those used by US land-grant universities to transfer agricultural advancements to farmers. For GM technologies, this will rest on the scientific capabilities of local universities and, perhaps more importantly, whether governments have the regulatory competence to move technologies into field trials⁷.

One group is at least already structured to do this successfully. The BioCassava Plus consortium (<http://biocassavaplus.org/>), funded by the Grand Challenges in Global Health Initiative, brings together research groups from Columbia, Kenya, Nigeria, Switzerland, Tanzania, the UK and the US. The project has six goals to improve the nutrition, yield and virus resistance of cassava (also known as yucca and manioc), a staple in the diet of 250 million sub-Saharan Africans (Fig. 4).

But what does the future hold for other GM functional foods? Will they progress without this magic formula to overcome public opposition? "I think the market needs to be reanalyzed every 18 months," says Beachy. He says that a decade ago food companies were keenly interested in the technology, and those attitudes could swing back that way just as swiftly.

Or it could easily be the case that genetic technology will continue to serve as a research platform for finding conventional ways around an issue, such as happened with brewer's yeast. Conner notes that marker-assisted breeding—that is, using genetic polymorphisms to identify desired traits in germplasm—is one area in which genomic knowledge has paid off in non-GM ways. Whether conventional or GM, functional food products must have a tie-in to human health to overcome public and private

The group is relying on new biotechnology—such as gene stacking, the completed genome sequence of cassava (due in July 2008), and the biodiversity of cassava cultivars found in South America—to address a plethora of problems with the starchy tubers. Although there are species of cassava found in Columbia that have higher levels of β -carotene and protein naturally, it remains to be seen whether the genes responsible for those traits can be transferred to the African version of cassava with higher yield and virus resistance, says Claude Fauquet, director of the Danforth Center's International Laboratory for Tropical Agricultural Biotechnology.

"If you want to better nourish millions of people, you can increase the productivity of the crop to get them out of the circle of poverty or you can embed the nutrition needed at ages three to six years for building up your body for the rest of your life," says Fauquet. "The idea is that we can do both." He says the BioCassava Plus researchers now have good evidence that increasing the vitamin A content of cassava is technically possible, but the project will need another three years before researchers will know whether they can also increase protein levels.

If not, the project may turn to other options, such as convincing Africans to grow the more nutritious South American versions of cassava for their children in yard gardens, while still producing the starchier version for sale. And just like the food brand managers in the West, researchers working on humanitarian projects cannot ignore the bottom line of people's taste preferences. Referring to an African cassava dish, Fauquet says, "They will still make a choice for a good fu-fu versus a bad fu-fu. Even if you are poor, you still make some choices about taste."

KP

concerns about the risks involved in bringing these products to market.

Will the front-runner conventional products that are targeted to 'early adopters' translate into benefits seen across the population? Maybe, says the Hartman Group's Barry. "It's not a perfectly black and white situation. Consumers want to know what are the benefits, what's the carrier, and do they symbolically make sense together?" People reading labels more closely are looking more for the absence of negatives right now, rather than the presence of positives, she notes.

Will those positive traits ever trickle down into the less fancy foods bought and consumed by the masses? That seems likely in the case of soybean oils. And if they are widely adopted, will those products pave the way for humanitarian efforts to move forward—getting nutrients into the bellies of those

who need them for basic survival? Perhaps. Or maybe, as Beachy suggests, "nutrition enhancement is best given away."

1. Thomas, P.R. & Earl, R.O. *Opportunities in the Nutrition and Food Sciences* (The National Academies Press, Washington, DC, 1994).
2. Morris, C.E. & Sands, D.C. The breeder's dilemma—yield or nutrition? *Nat. Biotechnol.* **24**, 1078–1080 (2006).
3. Surette, M.E. *et al.* Inhibition of leukotriene biosynthesis by a novel dietary fatty acid formulation in patients with atopic asthma: a randomized, placebo-controlled, parallel-group, prospective trial. *Clin. Ther.* **25**, 972–979 (2003).
4. Herrera, S. Monsanto branches out into fruits and vegetables. *Nat. Biotechnol.* **23**, 403 (2005).
5. Weyens, G. *et al.* Production of tailor-made fructans in sugar beet by expression of onion fructosyltransferase genes. *Plant Biotechnol. J.* **2**, 321–327 (2004).
6. Lawrence, S. Agbiotech booms in emerging nations. *Nat. Biotechnol.* **25**, 271 (2007).
7. Cohen, J.I. Poorer nations turn to publicly developed GM crops. *Nat. Biotechnol.* **23**, 27–33 (2005).