TOUGH LESSONS FROM GOLDEN RICE

It was supposed to prevent blindness and death from vitamin A deficiency in millions of children. But almost a decade after its invention, golden rice is still stuck in the lab.

IT'S EASY TO RECOGNIZE INGO POTRYKUS AT the train station in Basel, Switzerland. Quietly waiting while hurried travelers zip by, he is holding, as he promised, the framed and slightly yellowed cover of the 31 July 2000 issue of *Time* magazine. It features Potrykus's bearded face flanked by some bright green stalks and a bold headline: "This Rice Could Save A Million Kids A Year."

The story ran at a time when Potrykus, a German plant biotechnologist who has long lived in Switzerland, was on a roll. In 1999, just as he was about to retire, Potrykus and his colleagues had stunned plant scientists and biotechnology opponents alike by creating a rice variety that produced a group of molecules called pro-vitamin A in its seeds. The researchers thought this "golden rice"—named for the yellow hue imparted by the compounds—held a revolutionary promise to fight vitamin A deficiency, which blinds or kills thousands of children in developing countries every year.

Almost a decade later, golden rice is still just that: a promise. Well-organized opposition and a thicket of regulations on transgenic crops have prevented the plant from appearing on Asian farms within 2 to 3 years, as Potrykus and his colleagues once predicted. In fact, the first field trial of golden rice in Asia started only this month. Its potential to prevent the ravages of vitamin A deficiency has yet to be tested, and even by the most optimistic projections, no farmer will plant the rice before 2011.

The delays have made Potrykus, who lives in Magden, a small village in an idyllic valley near Basel, a frustrated man. For working on what he considers a philanthropic project, he has been ridiculed and vilified as an industry shill. Relating the golden rice saga at his dinner table while his wife serves croissants and strong coffee, he at times comes off as bitter.

There's more at stake than golden rice and personal vindication, he says. In his view, 2 decades of fear-mongering by organizations such as Greenpeace, his prime nemesis, have created a regulatory climate so burdensome that only big companies with deep pockets can afford to get any genetically modified (GM) product approved. As a result, it has become virtually impossible to use the technology in the service of the poor, Potrykus says.

Not everybody is so gloomy. Potrykus's co-inventor and main partner, plant biochemist Peter Beyer of the University of Freiburg in Germany, agrees that it's been a difficult decade. But a more cheerful character by nature, Beyer believes rules are just something to be dealt with; complaining about them does little, he says. A handful of other researchers working on GM crops to fight malnutrition also feel confident that their work will eventually pay off.

Many scientists agree with Potrykus, however, that GM technology has become so controversial that for now, there's little point in harness-

Fields of gold. The only field studies of golden rice to date took place in Louisiana in 2004 and 2005.

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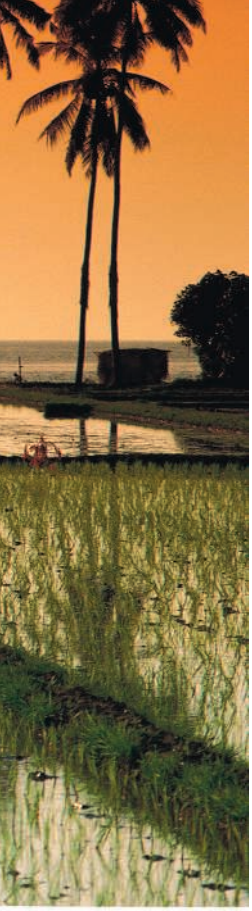
Published by AAAS



Time flies. The hope expressed in a 2000 *Time* cover story about Ingo Potrykus remains unfulfilled.

CREDIT: MARTIN ENSERINK/*SCIENCE*

ing it for the world's poorest. HarvestPlus, a vast global program at public research institutes aimed at creating more nutritious staple crops, is forgoing GM technology almost entirely and using conventional breeding instead, despite its built-in limitations. GM products just might end up on the shelf, says HarvestPlus Director Howarth Bouis.

Potrykus, now 75 years old, worries that he may not live to see his invention do any good. "It's difficult for me not to get upset about this situation," he says.

A dream takes root

The idea for golden rice was born at an international agricultural meeting in the Philippines in 1984, says Gary Toenniessen of the Rockefeller Foundation, a philanthropy in New York City. It was the early days of genetic engineering, and over beers at a guesthouse one evening, Toenniessen asked a group of plant breeders how the technology of copying and pasting genes might benefit rice. "Yellow endosperm," one of them said.

That odd answer alluded to the fact that a quarter-billion children have poor diets lacking in vitamin A. This deficiency can damage the retina and cornea and increase susceptibility to measles and other infectious diseases. The World Health Organization (WHO) estimates that between 250,000 and 500,000 children go blind every year as a result, and that half of those die within 12 months. Vegetables such as carrots and tomatoes, as well as meat, butter, and milk, can provide the vitamin or its precursors, but many families in poor countries don't have access to them. A rice variety producing precursors to vitamin A in its endosperm, the main tissue in seeds, might provide a solution—and it would have yellow kernels.

Classical breeding cannot produce such a rice, however, because although pro-vitamin A is present in the green parts of the rice plant, no known strain makes it in its seeds. The only option is to tinker with rice's DNA to produce the desired effect. Throughout the 1980s, the Rockefeller Foundation funded several exploratory studies, but the plan didn't gel until a brainstorming meeting in New York City in 1992, at which scientists discussed the bold idea of reintroducing the biochemical pathway leading to beta carotene, the most important pro-vitamin A, into rice but putting it under control of a promoter that's specific to endosperm.

Potrykus, then a pioneer in rice transgenics at the Swiss Federal Institute of Technology (ETH) in Zürich, attended, as did Beyer, who specialized in carotenoid biochemistry and molecular biology. The two met on the plane to New York and hit it off; their fields of expertise were complementary, and the fact that Zürich is less than 2 hours from Freiburg was helpful. They soon had a proposal written up.

Beyer admits he barely believed in the idea himself, and the Rockefeller's scientific advisory board was equally skeptical. Introducing an entire genetic pathway into rice seemed like a stretch. Still, the foundation rolled the dice and supported the project.

It took 7 years, but Potrykus and Beyer eventually succeeded in making golden rice by splicing two daffodil genes and a bacterial gene into the rice genome. The eureka moment arrived late one night in Freiburg, Beyer recalls. He was analyzing the molecular content of seeds produced in Potrykus's lab, as he often did, using a technique called high-performance liquid chromatography. This time, peaks showed up on the screen where they had never appeared before—the signals of carotenoids. When Beyer went back to look at the batch of seeds, he noticed something he had missed: The grains had a faint yellow hue. Golden rice had been born.

The battle begins

Potrykus says he always knew golden rice—a Thai businessman suggested the catchy name—would be controversial. As a professor in Switzerland, one of the most fiercely anti-GM countries in Europe, he had been confronted with angry students since the 1980s. To protect his plants, ETH spent several million dollars on a grenade-proof greenhouse. For Beyer, unofficial road signs declaring the Upper Rhine Valley a "GM technology-free region" are a twice-daily reminder that the climate in Germany isn't much better.

But golden rice posed a special dilemma to GM crop opponents, admits Benedikt Haerlin, who coordinated Greenpeace's European campaign at the time and now works for the Foundation on Future Farming. Unlike the existing GM crops that primarily helped farmers and pesticide companies, it was the first crop designed to help poor consumers in developing countries. It might save lives. The decision whether to oppose it weighed heavily on him, Haerlin says, which is why he consulted with WHO experts on vitamin A and why he traveled to Zürich to spend a day at Potrykus's lab to talk. Potrykus, impressed by Haerlin's intelligence, hoped to convince his fellow countryman.

He failed. Although Greenpeace pledged not to sabotage field trials, it did launch an aggressive campaign against golden rice. It argued that the crop was an industry PR ploy—seed company Syngenta was involved in the project, the group pointed out—designed to win over a skeptical public

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Seeds of discontent. Although Potrykus has retired, Peter Beyer is still working on golden rice at the University of Freiburg.

and open the door to other GM crops. Golden rice did not attack the underlying problem of poverty, Greenpeace said; besides, other, better solutions to vitamin A deficiency existed.

Perhaps Greenpeace's most effective argument, however, was that golden rice simply wouldn't work. The most successful strain created in 2000 produced 1.6 micrograms of pro-vitamin A per gram of rice. At that rate, an average 2-year-old would need to eat 3 kilos of golden rice a day to reach the recommended daily intake, Greenpeace said, and a breastfeeding mother more than 6 kilos. To drive the point home, an activist in the Philippines sat down behind a giant mound of golden rice during a press conference. "Fool's gold," Greenpeace called it.

A photo of the event, which quickly found its way around the world, still makes Haerlin chuckle—and it still makes Potrykus angry. Greenpeace assumed that children had to get *all* of their vitamin A from rice, which was unrealistic; it also ignored the fact, says Potrykus, that even half the recommended intake may prevent malnutrition. And Greenpeace assumed that the uptake of beta carotene by the human gut and its conversion into vitamin A were quite inefficient, resulting in one vitamin molecule for every 12 molecules of beta carotene. Nobody knew the true rate at the time, but a recent, soon-to-be-published study among healthy volunteers who ate cooked golden rice, led by Robert Russell of Tufts University in Boston, suggests that it's more like one for every three or four. "That's really quite good," says Russell, who supports the golden rice project. (A similar study is planned among people with marginal vitamin A deficiency in Asia.)

Haerlin says his calculations were based on the best data at the time. But even if they were correct, Potrykus says, the first golden rice was just a proof of principle. Greenpeace might as well have blamed the Wright brothers for not building a transatlantic airplane, he says.

Industry gets in

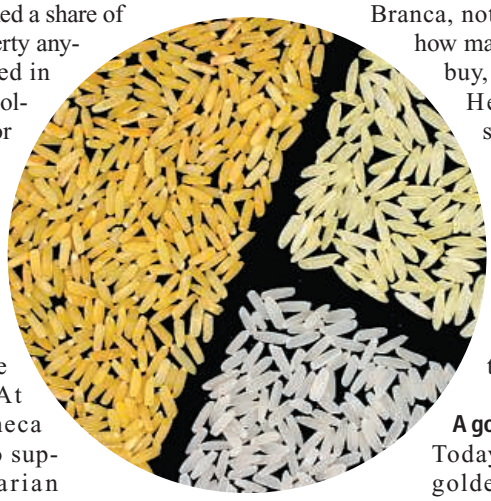
The low beta-carotene yield would eventually be tackled by Syngenta—even though Potrykus resented the way the company got involved. Between 1996 and 1999, Beyer's lab received funding through a European Commission contract that also included agrochemical giant Zeneca (called AstraZeneca after a merger in 1999). Under the program's rules, any benefits had to be shared by the signers. AstraZeneca had not worked on golden rice per se, Potrykus says, but the company claimed a share of that intellectual property anyway; it was interested in developing the technology commercially, for instance in health foods, says Potrykus, who was initially "furious" that a big corporation now had a say in his project.

David Lawrence has a different take on those events: At the time, AstraZeneca primarily wanted to support the humanitarian development of golden rice, says the current head of research at Syngenta; the company didn't have any commercial plans. (AstraZeneca's agribusiness division merged with that of Novartis to form Syngenta in 2000.) But whoever's right, the move proved a blessing in disguise, Potrykus now says. At Syngenta, he found a new partner in Adrian Dubock, a bubbly, fast-talking Brit with experience in patents, product development, regulation, and marketing—subjects Potrykus and Beyer admit they were clueless about.

Dubock helped work out a deal in which Syngenta could develop golden rice commercially, but farmers in developing countries who make less than $10,000 a year could get it for free. He also helped solve patent problems with several other companies. Dubock retired from Syngenta in 2007 but remains involved as a member of the Golden Rice Humanitarian Board, a group Potrykus chairs. "Without him, the project would have ended already," Potrykus says.

But perhaps most important, Syngenta scientists replaced a daffodil gene with a maize gene, thus creating a new version of golden rice, dubbed GR2, that produces up to 23 times more beta carotene in its seeds. Even with the one-in-12 conversion factor, that meant 72 grams of dry rice per day would suffice for a child, the company's scientists said in 2005. A 2006 paper by Alexander Stein of the University of Hohenheim in Stuttgart, Germany, estimated that the rice could have a major public health impact at a reasonable cost.

Those results didn't convince the skeptics. Real-world studies are still lacking, says WHO malnutrition expert Francesco Branca, noting that it's unclear how many people will plant, buy, and eat golden rice. He says giving out supplements, fortifying existing foods with vitamin A, and teaching people to grow carrots or certain leafy vegetables are, for now, more promising ways to fight the problem.



Gold fever. GR2 (*left*) contains more than 20 times more pro-vitamin A than GR1 (*top right*). Ordinary rice (*bottom right*) contains none.

A golden future?

Today, the debate about golden rice has quieted down, in part because its inventors are keeping a low profile. Syngenta stopped its research on golden rice and licensed the rights to GR2 to the humanitarian board on World Food Day in 2004; given consumers' distrust, there was no money in it, says Lawrence. Most golden rice work is now taking place at six labs in the Philippines, India, and Vietnam, the countries chosen as the best candidates for the crop's launch.

CREDITS (TOP TO BOTTOM): MARTIN ENSERINK/*SCIENCE*; GOLDEN RICE HUMANITARIAN BOARD

Published by AAAS

There's a long way to go. Both the original golden rice, now called GR1, and GR2 were created with *Japonica* cultivars that are scientists' favorites but fare poorly in Asian fields. Researchers are now backcrossing seven GR1 and GR2 lines with the long-grained, nonsticky *Indica* varieties popular among Asia's farmers. In early April, researchers at the International Rice Research Institute in the Philippines finally started a field trial with a GR1 backcrossed into a widely used *Indica* variety called IR64—the first field trial ever in Asia. (The only other outdoor studies were two done in Louisiana in 2004 and 2005.) The new varieties must not only produce enough beta carotene but also pass muster in terms of yield, seed quality, and appearance.

The project could have been much further along, Potrykus says, if there weren't so many rules governing GM crops that make little sense. Conventional breeders can bombard plant cells with chemicals and radiation to create useful mutants without having to check how it affects their DNA; a GM insertion must be "clean"—that is, the extra genes must sit neatly in a row without disrupting other genes—which adds months or even years to the lab work. Because field trials take long to get approved, researchers have been confined to greenhouses, in which they have trouble growing the large numbers required for breeding and feeding studies. These requirements have caused "year after year of delays," Potrykus complains.

Even if field trials are successful, there are no guarantees that golden rice will eventually be approved in the target countries. Use of other GM crops, such as Bt cotton, has exploded in Asia in recent years (see infographic, p. 466). But GM rice has languished. In India and China, regulatory agencies have shied away from approving insect-resistant GM rice despite extensive testing. "The expectation is that they will [be approved] eventually," says Toenniessen, "but it's a major decision for any Asian country." Thailand, a major rice exporter, has decided to steer clear of GM rice altogether.

Kavitha Kuruganti of the Centre for Sustainable Agriculture, an anti-GM group in Hyderabad, India, promises a major battle should golden rice head to the market in India. She thinks that the crop is unnecessary and probably unsafe to eat and that a massive switch would reduce diversity and threaten India's food security. "We will try to organize a broad public debate," she says.

Not worth funding?

Whether justified or not, the turmoil over golden rice has shaped other efforts to improve the nutritional value of crops. Take HarvestPlus. With a $14 million annual budget that targets 12 crops, it aims to boost levels of three key nutrients: vitamin A, iron, and zinc. It relies almost entirely on conventional breeding—which has Greenpeace's blessing—because it wants to have an impact fast, says Bouis, the director. What little GM technology HarvestPlus supports is a "hedge," in case the political and regulatory climates shift.

But in plants that have little or no natural ability to produce a nutrient, breeders have nothing to work with. Thus, vitamin A–enriched non-GM rice and sorghum are essentially off the table, says Bouis, as is boosting zinc and iron in sweet potatoes and cassava. Iron in rice is a question mark.

The uncertainty about the future of GM foods also tends to scare off the financial donors on which programs like HarvestPlus depend. Rockefeller, for instance, is frustrated that a GM rice whose field trials it helped pay for in China is stalled, says Toenniessen. "To avoid making the decision to approve it, the Chinese keep asking for more field trials," he says. "In the end, that becomes a foolish use of our funds."

The only charity still investing massively in GM crops with enhanced nutritional value is the Bill and Melinda Gates Foundation. Through its Grand Challenges in Global Health initiative, it is spending more than $36 million to support not only golden rice but also GM cassava, sorghum, and bananas. The foundation declined to comment for this story. But the researchers it supports say that they are optimistic that their products will make it through the pipeline.

James Dale of Queensland University of Technology in Brisbane, Australia, who heads a project to add iron, vitamin A, and vitamin E to bananas, says he has learned several lessons from golden rice, including the importance of local "ownership"—which is why he has teamed up with researchers in Kampala. "This will be a Ugandan banana made by Ugandans," he says.

Not that this mollifies opponents. Greenpeace will fight to keep GM bananas, cassava, and sorghum from poor countries' fields, just as it will keep opposing golden rice, says Janet Cotter of Greenpeace's Science Unit in London.

Battle-scarred, Potrykus says he hasn't given up hope that the regulatory system can be overhauled so that GM technology can benefit the poor. He believes a massive, multimillion-dollar information campaign might help convert the public. He has tried in vain to contact Bill Gates in hopes of tapping his wealth for such a media blitz.

He also wrote the late Pope John Paul II to ask for support for golden rice. "You know the definition of an optimist?" he jokes: "Someone who's asking the church for money." His Holiness declined, but Potrykus was invited to join the Pontifical Academy of Sciences, where he hopes to convene a meeting on golden rice next year—the 10th anniversary of his tarnished invention. **–MARTIN ENSERINK**

Eat your dinner. Greenpeace said more than 3 kilos of golden rice daily were needed to meet dietary standards for vitamin A.

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