Golden Rice and Beyond

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EMOTIONS ARE THE PROBLEM, NOT RATIONAL DISCOURSE

The term "golden rice" was coined by a Thai businessman who is active in initiatives aimed at reducing the birth rate, a major cause of the food security problem. As it turned out, the term "golden rice" has proven to be enormously successful in piquing the interest of the public. (I gave up tallying its mention in the popular media after more than 30 television broadcasts and 300 newspaper articles, but I am still busy with requests for interviews every week.) It is difficult to estimate how much of its celebrity stems from its catchy moniker and how much is from the technological breakthrough it represents. Needless to say, we live in a society that is strongly influenced (not to say manipulated) by the media. As the popular media live by selling news, "catchy" names are especially useful in attracting the interest of media consumers. The "story," however, must also be accompanied by an important message, in this case, that the purely altruistic use of genetic engineering technology has potentially solved an urgent and previously intractable health problem for the poor of the developing world. And this is my first message and my response to Chris Somerville's (2000) contribution: I, too, believe in the power of education and rational discourse. However, after more then 10 years on the frontlines of the public debate concerning genetically modified organisms (GMOs), I have learned that even with the help of the media, rational arguments succeed in influencing only a small minority of the public-at-large. In short, rational arguments are poor ammunition against the emotional appeals of the opposition. The GMO opposition, especially in Europe, has been extraordinarily successful in channeling all negative emotions associated with the supposed dangers of all new technologies as well as economic "globalization" onto the alleged hazards presented by the release of GMOs into the food chain. This is one reason why the story of "golden rice" is so important: In the short history of GMO research, "golden rice" is unique in having been embraced by the public-at-large. The reason for this, I believe, lies in its emotional appeal: People are truly concerned about the fate of blind children, and they are willing to support a technology that offers the children at risk the opportunity to avoid blindness.

I fully agree with the opinion of Maarten Chrispeels (2000) that "food security" for developing countries is one of the major challenges for mankind. I believe that scientists, as a privileged group of citizens, have more than an academic responsibility to advance science: They must also accept a higher social responsibility and, wherever possible, use science to help solve the important problems not of industry, but of humanity. In this respect our scientific community is not in balance, and the public senses this intuitively. This, in turn, has made it easy for the GMO opposition to wage a war of propaganda against our work with arguments to the effect that we are only pretending to work for mankind, or are only satisfying our own egos, or are working merely for the profits of industry. For example, laypeople often ask if food security for developing countries is such a dire problem, and if scientists feel that GMO technology should be developed to contribute to a solution, then why are so many scientists working on Arabidopsis and so few on those plants that feed the poor? Of course, one can pontificate about the importance of basic research and how all the knowledge gained from Arabidopsis will ultimately expedite the improvement of major crops, but one realizes that the average citizen remains emotionally unswayed by such arguments. The public's skepticism is heightened by the fact that many scientists do have funds from industry and, therefore, have their sensiblities attuned to solutions of problems of interest to industry. Press releases from the agrobiotechnology industry relating to work on food security in developing countries are taken as disingenuous and serve only to foster ill will against the technology. So what can we do to improve the public sentiment about the technology? We need more examples of the "golden rice" type; namely, successful projects that were developed in public institutions using public funding that address an urgent need, are not solvable with traditional techniques, are being made available free of charge and limitations to the poor, and have no deleterious effects on the environment or human health.

GOLDEN RICE: THE SCIENTIFIC CHALLENGE

In the early 1990s, when we proposed to the Rockefeller Biotechnology Program (New York) to initiate a project to genetically engineer the provitamin-A pathway into the rice endosperm, we were fortunate that the Rockefeller Foundation had already had similar thoughts. The Foundation responded readily by

organizing a brainstorming session. The verdict of this initial session was that such a project had a low probability of success, but that it was worth trying because of its high potential benefit. That is how Peter Beyer (University of Freiburg, Germany) and I got together, and this collaboration turned out to represent an ideal combination of skills. Peter Beyer was studying the regulation of the terpenoid pathway in daffodil and was working on the isolation of those genes we would need to establish the pathway in rice endosperm, whereas I had the engineering technology and was naïve enough to believe that the project was feasible. Naïveté was an important component because all those with appropriate knowledge had cited numerous reasons for skepticism. Our research determined that the last precursor of the pathway in endosperm was geranlygeranyl-pyrrophosphate and, as a consequence, it theoretically should be possible to reach β-carotene via four enzymes: phytoene synthase, phytoene desaturase, ζ-carotene desaturase, and lycopene cyclase (Burkhardt et al., 1997). There were hundreds of scientific reasons why the introduction and coordinated function of these enzymes would not be expected to work. Those with the necessary scientific knowledge were right in not believing in the experiment. When we finally had "golden rice" I learned that even my partner, Peter Beyer, and the scientific advisory board of The Rockefeller Foundation, except for Ralph Quatrano, had not believed that it could work. This exemplifies the advantage of my ignorance and naïveté: With my simple engineering mind I was optimistic throughout and therefore carried the project through, even when Rockefeller stopped funding Peter Beyer's group. Altogether it took 8 years, but the first breakthrough came when Peter Burkhardt of my laboratory recovered phenotypically normal, fertile, phytoene synthase-transgenic rice plants, which produced good quantities of phytoene in their endosperm (Burkhardt et al., 1997). This demonstrated two important facts: It was possible to specifically divert the pathway toward β-carotene, and channeling a considerable amount of geranly geranyl-pyrrophosphate away from the other important pathways had no severe consequences on the physiology and development. Xudong Ye of my laboratory did the crucial experiment: cotransformation with two *Agrobacterium* strains containing all the necessary genes plus a selectable marker. The resulting yellow-colored endosperm contained provitamin A and other terpenoids of nutritional importance and to everybody's surprise demonstrated that it was possible to engineer the entire biochemical pathway (Ye et al., 2000). A further key figure in our research was Salim Al-Babili from Peter Beyer's group who supplied all the successful constructs. The highest provitamin-A-producing line contains enough provitamin A (1.6 $\mu g\ g^{-1}$ endosperm) to expect a positive effect in relieving vitamin-A deficiency, but of course this has to be tested with bioavailability and feeding studies. However, these cannot be performed with the few grams of rice we can produce in our containment greenhouse. This will require hundreds of kilograms, which can be produced only in the field, and field release is still a problem in Europe, as it is in developing countries. (We are faced with a strong political movement for a 10-year moratorium in Switzerland.)

GOLDEN RICE: THE CHALLENGE OF INTELLECTUAL PROPERTY RIGHTS (IPRs)

"Golden rice" was developed to prevent vitamin-A deficiency in the poor and disadvantaged of developing countries. To fulfill this goal it has to reach the subsistence farmers free of charge and restrictions. Peter Beyer had written up a patent application, and Peter and I were determined to make the technology freely available. Because only public funding was involved, this was not considered too difficult. The Rockefeller Foundation had the same concept and the Swiss Federal Institute of Technology (Zurich) supported it, but the European Commission had a clause in its financial support to Peter Beyer, stating that industrial partners of the "Carotene Plus" project, of which our rice project was a small part, would have rights to project results. (The framework [IV and V] of European Union [EU] funding forces public research into coalitions with industry and thus is responsible for two very questionable consequences: Public research is oriented toward problems of interest to industry, and public research is losing its independence.) We did not consider this to be too big a problem because the EU funding was only a small contribution at the end of the project, but we soon realized that the task of technology transfer to developing countries, the international patent application, and the numerous IPRs and technical property rigths (TPRs) we had used in our experiments were too much for two private persons to handle properly. We urgently needed a powerful partner (because of the deadline of the international patent application). In discussions with industry the definitions of "subsistence farmer" and "humanitarian use" were the most difficult problems to be solved. We wanted a definition as generous as possible, because we not only wanted the technology to be free for small-scale farmers, but we also wanted to contribute to poverty alleviation via local commercial development. It is very fortunate that the company that agreed to the most generous definition was also the company that had legal rights because of its involvement in the EU project. This facilitated the agreement, via a small licensing company (Greenovation, Freiburg, Germany), with Zeneca (Fernhurst, UK). Zeneca received an exclusive license for commercial use and in return supports the humanitarian use via the inventors for developing countries. The cutoff line between humanitarian and commercial use is $10,000 (income

from "golden rice"). This agreement also applies for all subsequent applications of this technology to other crop plants. It turned out that our agreement with Zeneca and the involvement of our partner in Zeneca, Adrian Dubock, were real assets in developing the humanitarian aspect of the project. Adrian was very helpful in reducing the frightening number of IPRs and TPRs. He also organized most of the free licenses for the relevant IPRs and TPRs such that we are now in the position of granting "freedom to operate" to those public research institutions in developing countries to proceed in introducing the trait into local varieties. Publicity sometimes can be helpful: Only a few days after the cover story about "golden rice" had appeared in *Time*, I had a phone call from Monsanto offering free licenses for the company's IPR involved.

MAKING BEST USE OF (NOT FIGHTING ABOUT) PATENTS HELPS THE POOR AND UNDERPRIVILEGED

At this point it is appropriate to add a more general comment on patents and the heavy opposition against patenting in life sciences. Because we did not know how many and which IPRs we had used in developing the "golden rice," and because further development for the humanitarian purpose required "freedom to operate" for the institutions involved, The Rockefeller Foundation commissioned an IPR audit through the International Service for the Acquisition of Agri–Biotech Applications. The outcome was shocking (International Service for the Acquisition of Agri–Biotech Applications brief nos. 20–2,000). There were 70 IPRs and TPRs belonging to 32 different companies and universities, which we had used in our experiments and for which we would need free licenses to be able to establish a "freedom to operate" situation for our partners, who were keen to begin further variety development. Because I was also blocked by an unfair use of a material transfer agreement, which had no causal relation to "golden rice" development, I was initially upset. It seemed to me unacceptable, even immoral, that an achievement based on research in a public institution and exclusively with public funding and designed for a humanitarian purpose was in the hands of those who had patented enabling technology earlier or who had sneaked in a material transfer agreement in the context of an earlier experiment. It turned out that whatever public research one was doing, it was all in the hands of industry (and some universities). At that time I was much tempted to join those who fight patenting. Upon further reflection, however, I realized that the development of "golden rice" was only possible because of the existence of patents. Much of the technology that I had been using was publicly available only because the inventors, by patenting, could protect their rights. Without patents, much of this technology would have remained secret. To take full advantage of available knowledge to benefit the poor, it does not make sense to fight against patenting. It makes far more sense to fight for a sensible use of IPRs. Thanks to public pressure there is much goodwill in the leading companies to come to an agreement on the use of IPR/TPR for humanitarian use that does not interfere with commercial interests of the companies. An interesting discussion of this issue was part of a recent satellite meeting associated with the World Food Prize Symposium 2000 in Des Moines, Iowa (for more information, contact C.S. Prakash, e-mail: prakash@acd.tusk.edu).

We are now in a situation in which we have verbal confirmation for free licenses for humanitarian use for all intellectual and technical property involved. To date, details cannot yet be disclosed because some IPR owners prefer anonymity. Thanks to the interest of the agbiotech companies to use "golden rice" for better acceptance of the GMO technology, and thanks to the pressure against GMOs built up by the opposition, the IPR situation was easier to solve than expected.

GOLDEN RICE: THE CHALLENGE OF TECHNOLOGY TRANSFER

Having overcome the scientific problems, and having achieved freedom to operate, leaves technology transfer as the next hurdle. This is a far bigger task that anyone having no personal experience should assume. "Golden rice" so far consists of a series of provitamin-A-producing laboratory lines (TP 309). The characters of these lines must be transferred to as many locally adapted varieties and ecotypes in as many rice-growing countries as quickly as possible, and this transfer has to be organized such that all rules and regulations concerning the handling and use of GMOs will be strictly followed. Although we have had requests from many institutions in many countries, we believed it would be unwise to start the technology transfer on too large a scale. To aid in this endeavor, we have established a "Golden Rice Humanitarian Board" to help make the right decisions and to provide secretarial support. Again, our decision to work with Zeneca was extremely helpful. Adrian Dubock was willing to care for the task of the secretary. We have additional invaluable help from Katharina Jenny from the Indo-Swiss Collaboration in Biotechnology (ETH Zurich), an institution jointly financed by the Indian Department of Biotechnology (DBT; New Delhi, India) and the Swiss Development Corporation (Bern, Switzerland). Golden rice will be introduced into India in the established organizational framework of the Indo-Swiss Collaboration in Biotechnology, which has 10 years of experience in technology transfer. Thanks to this situation and thanks to the strong commitment of the DBT and the Indian Council for Agricultural Research (New

Delhi, India), India will take a leading role and can serve as a model for other countries. The project will begin with a careful assessment of needs, an analysis and comparisons of the pros and cons of alternative measures, and setting a framework for the optimal and complementary use of "golden rice." Of course, there will be bioavailability, substantial equivalence, toxicology, and allergenicity assessments and we are grateful for offers from specialists to help. Careful socioeconomic and environmental impact studies will help to avoid any possible risk and make sure that the technology reaches the poor. Care will be taken that the material is given only to institutions that ensure proper handling according to rules and regulations. Traditional breeding will transfer the trait into locally best adapted lines, and again will make sure that varieties important to the poor will be used and not fashionable varieties for the urban middle class. There will be also direct de novo transformation into important varieties, and this will be done with Man selection (Lucca et al., 2000). It is fortunate that the World Bank, the Indian Council for Agricultural Research, and DBT will probably share the costs for this development in India. Agreements have been established with several institutions in Southeast Asia, China, Africa, and Latin America and as soon as the written confirmation of the "freedom to operate" is in the hands of the "Humanitarian Board," material will be transferred.

GOLDEN RICE: THE CHALLENGE OF THE GMO OPPOSITION

A scientific breakthrough promises to add an essential dietary component (provitamin A) to one of the major food staples of the poor and developing world. Against all expectations, "freedom to operate" for humanitarian use has been achieved, enabling us to provide this technology free of charge and limitations, via national and international public research institutions and local rice breeders to the subsistence farmers in developing countries. Numerous rice-growing countries have expressed great interest in embracing this novel opportunity to help reduce malnutrition, and there is the institutional organization and the technical expertise to further develop this technology within the rice-growing countries. Is there any problem left that could interfere with the exploitation of "golden rice" to the benefit of the poor and disadvantaged in developing countries? It is unfortunate that the answer is yes: Greenpeace (www.greenpeace.org) and associated GMO opponents regard "golden rice" as a "Trojan horse" that may open the route for other GMO applications. As a consequence, by their singular logic, the success of "golden rice" has to be prevented under all circumstances, irrespective of the damage to those for whose interest Greenpeace pretends to act. The strategy is simple and has proven effective in Europe: undermining the acceptance of the consumer.

"Golden rice" fulfills all the wishes the GMO opposition had earlier expressed in their criticism of the use of the technology, and it thus nullifies all the arguments against genetic engineering with plants in this specific example.

Golden rice has not been developed by or for industry.

It fulfills an urgent need by complementing traditional interventions.

It presents a sustainable, cost-free solution, not requiring other resources.

It avoids the unfortunate negative side effects of the Green Revolution.

Industry does not benefit from it.

Those who benefit are the poor and disadvantaged.

It is given free of charge and restrictions to subsistence farmers.

It does not create any new dependencies.

It will be grown without any additional inputs.

It does not create advantages for rich landowners.

It can be resown every year from the saved harvest.

It does not reduce agricultural biodiversity.

It does not affect natural biodiversity.

There is, so far, no conceptual negative effect on the environment.

There is, so far, no conceivable risk to consumer health.

It was not possible to develop the trait with traditional methods, etc.

Optimists might have expected, therefore, that the GMO opposition would have welcomed the advent of "golden rice." The GMO opposition, however, has been doing everything in its power to prevent "golden rice" from reaching subsistence farmers. This is because the GMO opposition has a hidden, political agenda. It is not so much the concern about the environment, or the health of the consumer, or the help for the poor and disadvantaged. It is a radical fight against a technology and for political success. This could be tolerated in rich countries where people have a luxurious life even without the new technology. However, it cannot be tolerated in poor countries, where the technology can make the difference between life and death or between health and severe illness.

However, because its acceptance has to be prevented under all circumstances, new arguments had to be invented. Thus, the oppposition has argued that there is no need for "golden rice" because distribution of synthetic vitamin A works perfectly, or that nobody wants it because it tastes awful, or that people who eat "golden rice" will lose their hair and sexual potential! If you are interested in further misinformation of this kind, please consult various anti-GMO Web sites on the Internet.

One is tempted to ignore these aspersions, but this would be the wrong strategy. I am afraid that Greenpeace's specious arguments against "golden rice" will lead to unwarranted opposition in some devel-

oping countries. The consequence will be millions of unnecessarily blind children and vitamin-A deficiency-related deaths. For these reasons, we have the moral obligation to enlighten the public concerning the dangerous and immoral game the GMO opposition is playing. Anti-GMO activists are using all their political power (and funds collected ostensibly to protect whales and baby seals) to prevent a humanitarian project aimed toward helping millions of people who are malnourished and in grave danger of going blind. The GMO opposition often demands that scientists be held responsible for their actions. At the same time, however, they sidestep responsibility for the harm they cause to the disadvantaged and poor with their creation of a most hostile atmosphere against GMOs in Europe and elsewhere. In my judgment, hindering a person's access to life- or sight-saving food is criminal. To do this to millions of children is so criminal that it should not be tolerated by any society. It is unfortunate that our society, especially in Europe, is unable to recognize the true face of an organization that is using the mask of a few idealists risking their lives to save a few whales. The extent to which Greenpeace can act outside the law with impunity, and how skewed the mind of a European judge can be, was recently demonstrated in a judicial court in Nottingham, UK. The vandalism by Greenpeace activists of a government-supported experimental plot examining the possible effects of transgenic maize on the environment was ruled justifiable because it had been done "in the higher interest of mankind." In my view, the Greenpeace management has but one real interest: to organize media-effective actions for fund raising. The "golden rice" case hopefully may help to unmask the true and shameful face of Greenpeace, but only if the media are willing to take them to task.

I share the optimism of Norman Borlaug (2000) concerning the potential that GMO technology has for improving the living conditions of the poor and underprivileged in developing countries. I admire his "standing up to the antiscience crowd." I wish that more internationally recognized personalities would demonstrate similar civil courage and that the scientific community (and the granting agencies) would find a bit more interest in contributing to solutions of the problems of food security. In the long run, our science has the best chance to survive if we win the support of the public. For this, it is no longer sufficient simply to do good science—we must also be activists for and popularizers of the new technology.

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