AgBioForum, 10(3): 154-160. ©2007 AgBioForum.

Crop Case Study: GMO Golden Rice in Asia with Enhanced Vitamin A Benefits for Consumers

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Golden Rice is genetically modified to provide beta-carotene in the rice grain and it could potentially address widespread Vitamin A deficiency in poor countries where rice is a staple. Political opponents have viewed Golden Rice as representing the interests of multi-nationals and as inherently unsafe for consumption. Progress has been made towards adapting this crop to tropical-rice growing environments, but it has not yet been introduced into farmer's fields. Efficacy and safety have not yet been fully tested. Substantial work remains to target and deliver this intervention to Vitamin A-deficient populations, and to overcome remaining resistance to this technology. The political response to the on-going development of Golden Rice is reviewed to draw lessons for biofortification efforts that employ modern biotechnology. Within Asian countries, successful development and delivery will require policy dialogue among agriculturalists, health specialists, and advocates for the poor.

Key words: rice, biotechnology, Vitamin A deficiency.

Introduction

Genetically modified rice that contains beta-carotene, widely known as Golden Rice (GR), has not yet been introduced in any country. It was developed to address Vitamin A deficiency (VAD) in low-income rice consumers, but currently needs much more development and testing before it can be introduced into farmers' fields. GR is the most famous biofortification effort undertaken with modern biotechnology, due to the initial publicity (e.g., the cover of Time magazine on July 31, 2000). As such, it has been a lightening rod for the debate about the use of GMOs in meeting nutritional needs. Thus, for this special issue on GM foods and biofortification, a review of the lessons learned from the GR case is crucial to understanding the political landscape for other biofortification efforts. GR shows both the dramatic nutritional benefits that can be achieved with use of modern biotechnology and the considerable hurdles to eventual adoption and impact.

Below, this article presents the story of GR, including a review of the controversies regarding its development and the literature estimating ex-ante benefits, risks, and costs. The article closes with an assessment of the current prospects for GR and lessons for other biofortification efforts.

Impetus, Development, and Initial Reactions

The polished rice grain does not contain beta-carotene, a Vitamin A precursor that the body converts into Vitamin A. In low-income populations where rice is the primary staple, several micronutrient deficiencies are chronic problems, including lack of Vitamin A. Such deficiencies are particularly pronounced in small children, who need greater nutrient density in food to meet their higher nutrient needs. While the link between VAD and blindness captures public attention, VAD also lowers immune response and increases the death rate from common childhood diseases in developing countries, and as such VAD is often considered primarily in terms of childhood-mortality effects.

VAD is widely recognized as a globally significant problem. The United Nations Children's Fund (UNICEF) (2004, p. 4) estimates that "Vitamin A deficiency is compromising the immune systems of approximately 40% of the developing world's under-fives and leading to the early deaths of an estimated one million young children each year." VAD is often a problem where rice gruel is used as a weaning food. It is most important in the poorest nations of the world, including most of South and Southeast Asia where rice is the main staple, and that situation has not changed during the past decade.

The idea of using rice as a vehicle to address micronutrient deficiencies dates at least to the early 1980s. This idea emerged within the Consultative Group on International Agricultural Research (CGIAR) system and led to conventional breeding efforts to increase iron and zinc in rice in the 1990s. Creating rice with beta-carotene content was not possible until the advent of modern biotechnology techniques. The Rockefeller Foundation (RF) funded the initial GR research through its Rice Biotechnology Network, which was specifically established to address the need for basic biotechnology research on this important food crop that was likely to be ignored by the private sector in industrialized countries. With support from the RF in the 1990s, Ingko Potrykus at the Swiss Federal Institute of Technology and Peter Beyer at the University of Freiburg, Germany, collaborated to introduce daffodil genes into rice. The science was complex and cutting edge at that time, as it was an early example of the use of pathway engineering. Their success was hailed as a significant breakthrough in the application of modern biotechnology, and the work appeared in *Science* (Ye et al., 2000).

In conjunction with scientific publication, Potrykus appeared on the cover of Time (July 31, 2000). Interestingly, the cover itself posed the debate that has dogged this idea from the beginning: “This rice could save a million kids a year, but protesters believe such genetically modified foods are bad for us and our planet.” The article appeared at the height of the relatively new debate about the acceptance of GM foods, largely triggered by trade conflicts between exporting countries that had adopted the technology (the United States, Canada, and Argentina) and the importing countries (largely the European Union [EU] and other European nations).

Part of the publicity focused on the donation of intellectual property (IP) rights for the GR technology so that it could be further developed and adapted for introduction in the developing world. Apart from the patent held by Potrykus, several enabling technologies were also needed for further development. Potrykus formed a partnership with Zeneca (which later became Syngenta Seeds AS after its merger with Novartis), due to their history of work in carotenoids. Syngenta negotiated to put together a package of rights to be donated for humanitarian use, including patents held by Bayer AG, Monsanto Co., Orynova BV, and Zeneca Mogen BV. The condition for use of these patents include a) that seeds are developed for distribution to farmers in developing countries earning less than $10,000 per year from farming and 2) that release only takes place in countries with adequate biosafety regulations. The donation of this package of IP rights for humanitarian purposes was advertised as a model for the future transfer of this technology to developing countries.

Negative reactions to GR were immediate and in many cases quite emotional. The groups reacting included environmental advocacy groups already engaged in arguing against GM crops in general, as well as non-governmental organizations (NGOs) engaged in nutrition and food-security issues in developing countries. In Southeast Asia, such groups included Biodiversity and Community Rights Action (BIOTHAI) in Thailand, the Cambodian Center for Study and Development in Agriculture (CEDAC), the Development Research Communication and Services Centre (DRCSC) in India, GRAIN-MASIPAG (Farmer-Scientist Partnership for Development, Inc.) in the Philippines, and PAN-Indonesia and Policy Research for Development Alternatives (UBINIG) in Bangladesh (BIOTHAI et al., 2001). First-world opposition includes organizations opposed to GM technology, such as Greenpeace, Friends of the Earth, and Food First, as well as various groups in Europe (e.g., Institute for Science in Society in the United Kingdom). Nutrition intervention groups do not seem to have been as vocal in the debate.

Many of these reactions reworked long-standing concerns about Green Revolution technologies and the commercialization of smallholder agriculture and thus were not specific to GR. All of the opposing groups agree that VAD is an important problem but objected to GR either as an *inappropriate* or an *ineffective* solution. To summarize, the negative reactions were based on these points:

1. Malnutrition is a result of poverty and interventions already exist to address micronutrient deficiencies. Instead of developing GR, resources should be focused on poverty alleviation, sustainable farming, and proven strategies for nutrition intervention, such as supplementation and diet diversification through backyard or community gardens.
2. GM foods are inherently unsafe to human health and the environment. GR poses risks of these kinds and thus will not achieve its humanitarian goals.
3. Rice is directly consumed by the poor, and thus the poor would be “guinea pigs” for any human health impacts. Either GR will not provide enough Vitamin A to do any good or will provide too much, resulting in Vitamin A toxicity.
4. The IP arrangements are so convoluted that they do not preclude commercial abuse and do not represent a useful replicable model. The idea of “donation” is an anathema to those who object to commercial control of any agricultural IP.
5. GR is part of the continued use of “Green Revolution” technologies that are unsustainable and harmful to the poor.

It is not this case study's purpose to debate these points but rather to delineate issues that are under debate.

The virulence of the debate is surprising to someone who is agnostic on the subject. On the one hand, scientists, multi-national seed companies, and the CGIAR felt that they deserved credit for addressing a humanitarian issue head-on and for donating technology for beneficial use. Admittedly, multi-nationals were in need of positive publicity following the negative reactions to first-generation GM crops in Europe, and this was a strong motivation for their action on IP issues. But it does seem that scientists involved were surprised to have their motives questioned, as they genuinely believed in the positive humanitarian potential of this technology. On the other hand, those opposed to GM technology for ethical, environmental, or health concerns seem to have felt that this represented a commercial conspiracy to win over the public. They wanted to debunk this technology because it diverts attention from potential *negative* impacts to potential *positive* ones, thus changing the terms of the debate. They labeled it a "Trojan horse" for other biotechnology products in less-developed countries. For the NGOs involved in poverty alleviation, it represents competition for resources and influence. Thus, the debate has been quite hostile in that each side accuses the other of acting in bad faith.

Subsequent Evolution and Current Status

The public attention to this potential new technology reinforced for its advocates the need to address several issues in its development. It is perhaps unfortunate that the first scientific breakthrough generated so much attention when it remained fairly far removed from implementation. The initial strains of GR utilizing daffodil genes did not contain very much beta-carotene and might have had little impact on VAD in most Asian diets. This point was noted almost immediately by astute advocates for the opposition (e.g., Shiva, 2000). Later GR1 lines contain as much as 5 times more beta-carotene, although Dawe, Robertson, and Unnevehr (2002) found that even this level may not have much impact in some populations that are severely affected by VAD and for whom rice is not the only staple.

Subsequent research has utilized cereal genes rather than daffodil genes to generate much higher levels of beta-carotene in so-called GR2 lines (Paine et al., 2005). In these lines, the enzymatic activity in the PSY genes found within maize or rice is utilized to produce much higher levels of beta-carotene in the rice grain. The new levels of beta-carotene in GR2 lines are 20 times higher than the original line, and these materials could provide all of the Vitamin A requirements for children eating rice-based diets (Stein, Sachdev, & Qaim, 2006). This improvement in beta-carotene content brought forth a few restatements of the same general objections from those originally opposed to the technology (e.g., see Greenpeace, 2005).

The initial framework to donate GR technology for humanitarian purposes remains under the control of Potrykus and Beyer, who are advised by a Golden Rice Humanitarian Board (Golden Rice Humanitarian Project website). This Board does not make funding decisions. Much of the current funding for development comes from USAID grants to the International Rice Research Institute (IRRI), as well as country-mission grants to National Agricultural Research Systems (NARS). Other funding sources include the Bill & Melinda Gates Foundation, the Swiss Development and Collaboration Agency, the Syngenta Foundation, and the Rockefeller Foundation.[1] Research collaborators include IRRI, as well as NARS institutions in Bangladesh, Vietnam, the Philippines, India, China, and Indonesia.

Field trials of the GR1 lines were conducted for the first time in 2004 at Louisiana State University (as US regulations allowed this step to move forward more quickly than in any Asian country). The first trials demonstrate that the crop is agronomically sound and may have higher beta-carotene when grown under field conditions. Limited field trials for the GR2 lines have also been carried out, but these GR1 and GR2 lines need to be crossed into appropriate indica varieties for use in Asia.

In Asia, research samples of the initial GR arrived at IRRI in 2001. Attempts were made to create new transgenic variants of IR64, BR29, and other widely grown varieties in Asia with high levels of beta-carotene, using the same genes for beta-carotene synthesis. Breeding work (back-crossing) into leading Asian varieties was also undertaken with the initial GR lines. With the availability of the new GR1 and GR2 lines with higher beta-carotene content, the activities with the initial lines were ended in 2003, and back-crossing work with the new lines began in 2004. As of yet, no field trials have been conducted in Asia, although such trials of backcrossed GR1 and GR2 lines may be conducted in the Philippines

1. *Rockefeller has shifted almost all of its agricultural development funding to Africa and currently has only some funding that is partly for GR in Vietnam, the Philippines, and China. These are legacy grants from earlier investments in the Rice Biotechnology Network.*

in 2007 and are possible in India in 2008 (G. Barry, personal communication, June 20, 2007). These countries have relatively well established biosafety guidelines, and have already approved other GM crops for commercial purposes.

Beyond issues of agronomic viability, there are other development efforts required to address issues of acceptance, safety, and impact. Some taste tests have been carried out (Dubock, 2005), although not yet in Asia. Bioavailability testing is currently ongoing at Tufts University, using GR2 lines (Stein, Sachdev, & Qaim, 2007), and the next phase will be a study in Asia (G. Toenniessen, personal communication, August 1, 2006). Detailed work for biosafety risk assessment will continue as the crop-development work advances. This risk assessment work will be mostly carried out in Asia by NARS and will take several years to complete.

Preliminary stability and retention studies are also underway in Germany, the United States, and the Philippines in order to take account of varying storage and cooking conditions in different socioeconomic and cultural settings. For example, exposure to air, light, and moisture during storage will vary across locations. As another example, rice is parboiled in Bangladesh before eating. Conditions and food preparation processes such as these could have large effects on the quantity of beta-carotene in the cooked grain, so the results of these studies will be critical for making a better assessment of the potential contribution of GR to alleviating VAD. More work of this kind will need to be done as more material adapted to local conditions is developed.

An Ex-Ante Analysis of Benefits, Costs, and Risks

As discussed above, the importance of VAD is widely recognized. Its persistence is testimony to the limitations of current interventions (discussed more fully in other papers in this special issue). GR has the potential to reach important subpopulations that have not been targeted by current interventions, most notably small children in parts of rural Asia where rice is the predominant staple and weaning food. Several different studies have now tried to assess the potential benefits of GR using different economic methods and building their analyses on some strong assumptions about nutritional benefits. Because GR is still so far from actual production and consumption, little is known about bioavailability, losses in storage or cooking, or many other factors that would influence the actual delivery of Vitamin A. These studies are beginning and will help define the deployment options for the product.

Costs of development will include basic research, adaptation to local conditions, biosafety testing, and costs of consumer and producer education, as well as any specific marketing regulations and future maintenance breeding. In 2002, Dawe et al. made very crude estimates of GR costs for Asia, which now appear to have underestimated the costs of development and promotion. Stein's (2006) estimates of the costs for bringing GR to market in India are $21-28 million total for the next 30 years (discounted to the present), or $0.7-0.9 million annually. This includes costs of development within India of $4.1-8.7 million, $2.2-2.5 million for regulatory review, and $15.6-30.7 million for promotion and marketing. These estimates show that significant investments must still be made to bring GR to farmers' fields in Asia, above and beyond international research and development (R&D) to support understanding of bioavailability and biosafety.

Every ex-ante study has shown benefits from GR, and these are usually substantial and cost-effective. Dawe et al. (2002) found that the initial GR strain would deliver very modest amounts of Vitamin A in the diets of VAD children in one area of the Philippines. They also estimated that the initial GR was very cost-effective compared with other interventions, such as wheat fortification or supplementation. Zimmermann and Qaim (2004) estimated the benefits in terms of saved disability-adjusted life years (DALYs), and found potential reductions in annual health-related costs of $16-88 million in the Philippines. Anderson, Jackson, and Nielsen (2004) used their results to estimate benefits of better health for unskilled workers in a general equilibrium framework and found that health benefits potentially dwarf any agricultural productivity benefits from GM rice, maize, and oilseed crops in Asia.

The most recent study is by Stein (2006) for India, and it finds that the newer GR would reduce the burden of VAD in India by 5-54%, depending upon assumptions about adoption and who consumes it. The cost-per-DALY-saved would be $3.40-35.47 for GR, which compares favorably with alternative interventions. However, these costs-per-DALY-saved for GR are significantly higher than equivalent costs for biofortification of rice or wheat with either iron or zinc. The latter biofortifications are easier to achieve and to promote, as they involve less complex breeding applications and fewer consumer-acceptance issues. The Stein (2006) study confirms that major benefits are possible from GR, but also that it may be a more challenging biofortification application than other potential biofortification interventions.

What are the risks for supporters of GR? One risk that seems minimal at this stage is that NGOs will be able to derail field testing on a large scale. Several countries in Asia (including the Philippines and India) have already approved GM crops for commercial purposes, and there are procedures for such approval in many countries. If the data support the effectiveness and safety of the new crops, it seems politically likely that field testing will proceed. However, exporting countries like Thailand and Vietnam are cautious about GM content that might reduce export prospects. GR at least provides a visible marker (golden color) that would facilitate market segmentation.

However, NGOs may have more influence on adoption by farmers and consumers than on field testing. Many large NGOs are likely to support GR if it is safe and effective, e.g., the influential NGOs in Bangladesh such as Grameen, Bangladesh Rural Advancement Committee (BRAC), and Proshika. These NGOs are unlikely to take a major lead in promoting GR, but they will probably not oppose it and may lend some support to its dissemination if there is strong evidence it will help the poor. But many other NGOs advocate organic farming, and it seems unlikely that any amount of evidence will convince them to support GR: their objections are due to ethical or ideological considerations, not scientific skepticism. Their influence is not to be ignored, and if GR is to be adopted, educational campaigns targeted to farmers and the general public will be of crucial importance.

There are several other risks that could be important. First, after substantial investment, GR may not be widely adopted and will have little semblance of the impact envisioned. Farmers who wish to sell it in markets (most rice in Asia is traded in markets, not consumed at home) may not want to take the risks of adopting a new variety (e.g., lower yield, susceptibility to pests and diseases) unless they are compensated with higher prices or yields. However, such higher prices would work against its incorporation into the diets of the poor, possibly causing it to wind up as a niche product for rich consumers. One possibility to counter these incentives would be to bundle the increased beta-carotene content with other new desirable traits that farmers find helpful. Alternatively, GR could be grown by poor farmers for their own consumption, although again they may be discouraged by the risks noted above. Furthermore, this strategy would limit the potential impact of GR because the poorest of the poor typically buy much of their rice on markets. Yet another possibility would be for governments to subsidize the production and/or consumption of GR through public distribution systems to encourage adoption by farmers and consumption by poor consumers. However, it should be noted that targeted government subsidies in agriculture and food are difficult to deliver without substantial leakage of financial resources.

Second, GR may cause unforeseen health risks, particularly if it is the first GMO to be widely consumed by children. This speaks to the importance of extensive testing to ensure that GR has limited side effects and, after storage and cooking, has enough bioavailable beta-carotene to substantially reduce VAD. The lengthy approval process still underway for commercialization of Bt rice in China shows the concerns that governments have over GM food crops (as opposed to Bt maize intended for animal feed or Bt cotton). These issues are discussed more fully in the China and Philippines case studies elsewhere in this special issue. If Bt rice is approved in China, this will most likely smooth the path for approval of GR—certainly in China and possibly in other countries as well.

Third, GR may be adopted and have a positive impact, but one that is difficult to perceive or measure, so that little "credit" is given to the innovation. To remedy this situation, it will be important to undertake education campaigns to inform any skeptical farmers, consumers, or NGOs about the nutritional benefits of GR (assuming a successful variety is developed) and its benefits for farmers. Such campaigns will be important for ensuring widespread adoption as well as giving due credit once it is adopted.

Many members of the educated general public in Asia are convinced that most new technologies hurt farmers, especially if the corporate sector is involved in the technology. To some extent, this is a legacy of the Green Revolution, which is still viewed with skepticism by many even though it increased productivity, has been adopted widely by farmers, and was a major force in averting the widespread famines forecast by many observers. As a specific example, many people assume that because of the corporate sector's involvement in the origins of GR, farmers will need to purchase this seed every year. While this is true for many crops in developed economies, no company at present has plans to commercialize GR in developing countries. In addition, the technology to create GR was donated by its inventors and private companies holding intellectual property licenses so that any organization or farmer can freely distribute or replant seed. Thus, farmers will be under no compulsion to buy new seeds every year, but this fact will need to be clearly and creatively communicated to the public. The public may also need to be convinced that a reasonable share of benefits from adoption of GR goes to farmers. Economists typically assume that adoption by farmers is *prima facie* evidence that it provides them benefits, but this line of reasoning is not necessarily convincing to others.

Future Potential and Lessons for Other Biofortification Efforts

GR technology still needs considerable research investment to be viable in farmers' fields and to meet a rigorous standard for consumer safety. Moving past regulatory hurdles will not be easy, and thus, this crop is unlikely to play a role in meeting micronutrient needs before the next decade.

From the political standpoint, there are still no advocates for this technology within Asian countries. Ministries of Agriculture and NARS are production-oriented by training and mandate; thus, they have little interest in a project that diverts attention from production goals and requires innovative cooperation with nutritional science. The IP arrangements have not given participating NARS a sense of ownership or control of this technology. Ministries of Health may find that biofortification poses a threat to their traditional programs, although it can potentially save lives and government expenditures in the long run. NGOs have yet to embrace this technology.

To move forward, it seems clear that GR must be agronomically viable at a minimum. To be acceptable to consumers and accomplish its nutritional goals will require that countries make some strategic decisions about implementation, adoption, and promotion. Such decisions include desirable beta-carotene levels, target populations, desirable agronomic characteristics, and methods for distribution and promotion. These choices would be best informed if the health and agricultural policy-makers can agree on the need for and potential benefits from this technology and if NGOs who work with the poor embrace it. As this approach to biofortification is relatively challenging, future investments in research need to increasingly be driven by policy dialogue.

The GR story provides guidance for other biofortification efforts. First, any biofortification of a staple crop using GM technology will likely encounter greater political resistance, as well as more challenges in safety assessments and delivery, than non-GM approaches. Second, any biofortification effort will need support and guidance from NARS and NGOs within countries with nutritionally deficient populations in order to be designed and targeted appropriately. These lessons for future strategy are explored further in the final article in this special issue.

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