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# Lessons from Golden Rice

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Micronutrient deficiency takes a daily toll of ca. 24,000 lives (see also H.K. Biesalski, this volume). Micronutrients such as vitamins, minerals, and essential amino and fatty acids are essential for vital molecular functions of the human body and have to be taken up with the diet (see also Klaus Kraemer, this volume). For those who can afford a diversified diet this is not a problem. However, those billons of poor who survive essentially on starchy staple food crops such as rice, which are poor in micronutrients, shortage in micronutrients can be lethal. The novel concept of "biofortification" – the improvement of the micronutrient content of especially starchy staple crop plants on a genetic basis – has great potential for low cost and sustained interventions for the reduction in micro nutrient deficiencies (see also Howarth Bouis, this volume). His presentation has demonstrated that biofortification on the basis of traditional breeding techniques can indeed lead to novel varieties enriched in micro nutrients and that their consumption can improve the nutritional status of those who consume them. The data already available after less than 10 years of experimentation establish proof-of-concept for this novel concept – an impressive progress within a short time period indeed!

Micronutrient deficiency not only has dramatic negative effects on health and wellbeing for infants and pregnant women, but also severely compromises brain development, thus leading to far reaching consequences for mental, educational, and social capacity (see Martha Farah and Sebastian Lipina, this volume). Interventions via "supplementation" of diets with industrial formulations of vitamins and minerals improve the micronutrient status, but can reach only a fraction of those who need it (see Klaus Kraemer, this volume). There is no doubt that supplementation of diets with industrial formulations has an important role to play, and represents a mature technology which just requires more support for wide-scale application. Biofortification offers in comparison the comparative and complementing advantages that it does not require recurrent investment and reaches those who are out of reach for supplementation programmes. Biofortification is to be seen as complementation for the established interventions, and progress is, in view of the magnitude of the problem, urgently needed. According to the Copenhagen Consensus, investment in availability of micronutrients has, in addition, the highest economic return for investment

on interventions for development and is on top of a list of recommendations for policy makers by that renowned think tank of world-renowned economists (see also Bjørn Lomborg, this volume).

Biofortification can be approached via traditional breeding or via genetic engineering. The approach via traditional breeding is possible in cases where natural variation in the desired trait provides the necessary basis. This approach has the comparative advantage that this technology is widely accepted. "Genetic engineering" however, a technology which, in theory, represents the ideal technology for biofortification, is faced with and suffers from highly emotional opposition. The technology enables the targeted introduction of micronutrients at desired levels and specifically to those plant organs which are consumed. It further enables biofortification in all those cases, where traditional plant breeding fails because of lack of natural variation. And it allows for biofortification in those numerous cases where traditional breeding is inefficient because introgression of traits is difficult due to problems with crossbreeding. Considering those advantages the obvious question is: where are the expected examples of crops biofortified with the help of genetic engineering technology?

There is one very instructive example, which was initiated in June 1991, years before the concept of biofortification was developed, and which to date – 25 years later – and despite enormous efforts and support still did not reach the needy. This example refers to a novel variety of rice, dubbed "Golden Rice". This rice provides enough provitamin A to prevent vitamin A-deficiency from a daily serving of 40 grams, whereas normal rice does not contain any provitamin A and is one of the major causes for vitamin A deficiency. This "Golden Rice" was developed within the public domain throughout the entire progress in science, product development, and the regulatory process. It was advanced within the framework of a "humanitarian project" to be provided to subsistence farmers free of charge for the trait. This project is best suited to demonstrate the potential and the pitfalls of genetic engineering applied with the goal to contribute a public good for the reduction in micronutrient deficiency (for details please visit the homepage maintained by Humanitarian Golden Rice Board www.goldenrice.org).

Vitamin A-deficiency is one of the major public health problems of the globe. 190 million children and 19 million pregnant women are affected globally. It leads to 1-2.7 million deaths per year through immune response suppression. Ca. 500,000 children per year are blinded and ca. 600,000 pregnant women die annually at childbirth from VAD related causes. 23-34% reduction in preschool mortality can be expected from Vitamin A programs

reaching children in undernourished settings.[1] A comparison of the global mortality data sets these figures in perspective with other, well-known public health problems: Global population mortality (in million): Vitamin A-deficiency – 1.9-2.7; HIV/Aids – 1.7; Tuberculosis – 1.4; Malaria – 0.75.

Vitamin A-deficiency is widespread in poor populations depending on rice as their major staple. Rice provides up to 80% of food calories, but is poor in micronutrients and does not contain any provitamin A (which the human body converts into vitamin A). The unavoidable consequence for hundreds of millions of poor who cannot afford a diversified diet is, therefore, vitamin A-deficiency, accompanied, of course, by deficiencies in other micro nutrients. In Bangladesh e.g. children obtain from their routine diet only 30% of the recommended daily intake, woman only 40%. The US Medical Council has established that 50% RDI is sufficient to prevent clinical symptoms of VAD deficiency. According to the concept of biofortification rice should, therefore, be altered in such a way that its content in provitamin A at least fills the gap to 50%. As rice contains zero provitamin A in the endosperm, there is no natural variation traditional plant breeding could use.

What can be done to develop rice with provitamin A in the edible part of the plant – the endosperm of the seed? Rice plants contain, as all green plants, large amounts of provitamin A in all green tissues. There is, however, nothing in the endosperm. Whereas provitamin A is vital in green tissues as protectant against irradiation, it does not make any biological sense in the endosperm. Four alternative approaches were at choice: 1) find a rice plant, or a plant related to rice, with "yellow" endosperm. If this "yellow" trait turns out to be "provitamin A" this would constitute the variation rice breeders could use to "biofortify" rice with traditional plant breeding (see Howarth Bouis, this volume). This variation was not found in more than 100 000 accessions from around the world and, therefore, does not exist. 2) In such a case it is possible to provoke variation by applying mutagenesis. This has been tried extensively applying all technical possibilities. Unfortunately this did not lead to yellow endosperm either. 3) The third possibility, which was considered the most promising one when we began our project, was to try to identify the "switch" the rice plant is using to turn off provitamin A biosynthesis in the endosperm. This project has funding since 1992, but the switch has not been found up to date. It must, however, exist and may be found one day. 4) This leaves us with the last possibility, which

[1] West KP Jr, Klemm RDW, Sommer A. (2010) Vitamin A saves lives. Sound science, sound policy. *World Nutrition* 1, 5: 211-229.

was judged totally unfeasible for numerous reasons: to engineer the pathway with the help of genetic engineering. This was a gigantic task because eight genes were involved and numerous cellular prerequisites were unknown. Together with my partner Peter Beyer from the university of Freiburg/Germany, we decided to give it a serious trial.

It took eight years with continuing uncertainties and with little possible checks in between until we saw the first yellow endosperms. When we published our results[2] this totally unexpected breakthrough electrified not only academia but also the media and gained us hundreds of articles including a cover story in TIME Magazine[3] and numerous academic recognitions. Fine, there was this welcome scientific success and this would normally have been the end of the work of scientists in an academic setting. However, to prevent vitamin A malnutrition, this scientific breakthrough had to reach the needy and it was obvious that the scientific breakthrough was only a first step towards this goal. It soon became clear that if we did not take care of this problem, nobody else would do so. In cases where scientific discoveries offer the chance for an economic success, e.g. in Medicine or Pharmacy, they will be taken up by the private sector which then has all the means to develop a product. In cases where the development of a public good is at stake, which does not offer a financial return to the private sector, there is nothing in the public domain to carry this on. We realised that we had to forget about our vision, or to take care of it ourselves.

And this was the beginning of a long and cumbersome odyssey. Neither we nor anybody else in the public domain had any idea what it meant to develop a GMO product within the public domain and deliver it to the needy. We had an established collaboration with the International Rice Research Institute in the Philippines. The most successful rice breeder so far, Dr. Gurdev Khush, was assuming that Golden Rice would be available for rice farmers from 2002 onwards. And this was everybody's expectation including our own. The fact that Golden Rice was a GMO, however, had the consequence that we had to invest an additional twelve years of work and enormous financial resources. "Golden Rice" is a scientific reality since February 1999. If it hadn't been a GMO, it would have been in use since 2002 and would have saved millions of children from blindness and death. Being a GMO, it will not be available to the farmers before 2014 – with a 12-

[2] Ye, X., Al-Babili, S., Klöti, A., Zhang, J., Lucca, P., Beyer, P., Potrykus, I. (2000). Engineering provitamin A (b-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. *Science* 287, 303-305.

[3] TIME cover, July 31, 2000 www.time.com

year delay. Twelve years with all their consequences which have to be blamed on regulation and opposition. As it was impossible to achieve our goal within the public sector, we struck a deal with the private sector: transfer of the rights in our invention to the private sector for commercial development in return for support of our humanitarian project. The architect of this "public-private-partnership" was Dr. Adrian Dubock, than Syngenta, who later became our "Humanitarian Golden Rice Project Manager".[4]

The outstanding challenge for the humanitarian Golden Rice project was GMO-regulation. It delayed deployment for more than ten years! There is no scientific justification for any of those requirements! There is scientific consensus that GMO-crops are at least as safe for the environment and the consumer as the traditionally bred ones we consume without regulation and hesitation. Numerous academies have published that there is no GMO-specific risk associated with the technology, e.g. the Swiss National Science Foundation 2012, the Pontifical Academy of Sciences 2010 (6), the European Commission's Scientific Advisory Panel 2008, the International Union of Food Science and Technology 2005, the Royal Society in London, the US Natl. Acad. Sciences, the Brazilian Academy of Sciences, the Chinese Academy of Sciences, the Indian Academy of Sciences, the Mexican Academy of Sciences, the Third World Academy of Sciences 2004, the GM Science Review Panel UK, 2003, etc. Transgenic plants have been planted for more than 12 years on over 170 million hectares in 23 countries and used by more than 17 million small-scale farmers with not a single documented case of harm to the consumer or the environment. Despite this unprecedented safety track record of the technology, the Golden Rice project had to follow all the established rules and regulations set up for work with transgenic plants and had to collect all the data required for a regulatory dossier. The time required by these unjustifiable requests did not sum up to 19 years, because some tasks could be approached in parallel. Socio-economic ex ante studies have shown that e.g. in India Golden Rice could prevent death and blindness of nearly 40,000 children per year. A delay in deployment is, therefore, not just an economic loss, but responsible for dramatic social consequences!

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| Deletion of selectable marker: | 2 years |
| Screening for streamlined integration: | 2 years |
| Screening for regulatory clean events: | 2 years |
| Protection against liability problems: | 1 year |

[4] www.goldenrice.org homepage of the Humanitarian Golden Rice Project.

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|---|---|
| Trans-boundary movement of seeds: | 2 years |
| Obligatory sequence greenhouse-field: | 1 year |
| Permission for working in the field: | 2 years |
| Requirement for one-event selection: | 2 years |
| Experiments for the regulatory dossier: | 4 years |
| Deregulation procedure: | 1 year |

And it required additional financial resources, compared to the development of non-GMO varieties, of ca. USD 32 million. The regulation-caused GMO-specific costs wherewith ca. USD 32 million: so high that they are prohibitive for any comparable GMO project of the public sector.

Once authorised for deployment by national biosafety authorities, Golden Rice will be free for use according the "humanitarian" concept: agronomically optimized and locally preferred varieties are developed by public rice research institutes in countries where vitamin A-deficiency is a severe public health problem and rice is the major staple crop. Once released by national biosafety authorities, seeds will be available to farmers free of costs for the trait.[5] They are from then on the owners of the seeds, can use them in their traditional production systems, do not need any additional agrochemicals and can use part of the harvest for the next sowing. There are no new dependencies whatsoever. The entire technology is in the seed. All patents are covered by free licenses. The only conditions in this humanitarian project: local trade is permitted, export is not allowed; profit beyond USD 10,000 is not considered humanitarian. This limitation will not affect anyone from our target population – subsistence farmers and local traders. It is the consequence that in our agreement for the public-private-partnership we had to define "humanitarian" versus "commercial" and this figure was a safe borderline for our intentions.[6]

Prohibitive regulation and aggressive anti-GMO politics have a strong negative impact on numerous further projects on consumer-oriented traits from public sector scientists[7] such as

[5] www.irri.org/goldenrice Golden Rice on the homepage of the International Rice Research Institute which leads product development for the Philippines, Bangladesh, and Indonesia.

[6] I. Potrykus and K. Ammann (eds) (2010) Transgenic Plants for Food Security in the Context of Development. Proceedings of a study week of the Pontifical Academy of Sciences. *NewBiotechnology* 27 (5).

[7] Biotechnology for Enhanced Nutritional Quality in Plants. Ayse Ozgur Uncu, Sami Doganlar, and Anne Frary. *Critical Reviews in Plant Sciences*, 32:321-343, 2013.

**Protein modifications**
e.g. essential amino acids

**Antioxidant engineering**
e.g. lycopin, astaxanthin

**Carbohydrate engineering**
e.g. inulin, amylose

**Mineral content modification**
e.g. iron, zinc

**Fatty acid modification**
e.g. omega-3, polyunsaturated

**Reduction of plant allergens**
e.g. in rice, soybean, wheat

**Vitamin engineering**
e.g. vit. A, E, C, B6, B9

**Reduction of toxins**
e.g. linamarin in Cassava

Zinc biofortification for rice is possible to the required target level via traditional plant breeding approaches because natural variation is good enough for that purpose (see also Howarth Bouis, this volume). However iron biofortification, desired for nearly 3 billion needy, most probably will not reach target levels from natural variation and will, therefore rely on genetic engineering, which has already achieved proof-of-concept. Product development and deregulation will suffer from the same delay and require the same amount of financial input as just described for Golden Rice. And the same is true for most of the other traits indicated above.

Biofortification of rice is in progress on several fronts. Besides provitamin A rice which is close to deployment (see IRRI homepage), there is "high iron rice" where, thanks to genetic engineering, the target level of 14 micrograms/gram has been reached (Howarth Bouis, personal communication). For this case as for all the following more than ten years of product development and deregulation will have to follow, just as it has been the case for Golden Rice. "High zinc" rice has been reached without genetic engineering and product development, therefore can be expected to be much shorter (see Howarth Bouis, this volume). Biofortified "folate rice" was published in 2007,[8] however to the authors' knowledge, product development had problems in attracting funding. In the context of "high quality protein rice" (for provision of "essential" amino acids which our body cannot synthesise) the example of the gene from "Winged bean" (*Psophocarpus tetragonolobus*) is a perfect illustration of the irrationality against GMOs. Winged bean is a popular vegetable consumed for centuries by hundreds of millions in Southeast Asia. It contains a storage protein high

[8] S. Storozhenko *et al.* Folate fortification of rice by metabolic engineering. *Nature Biotechnology* 25, 1277-1279 (2007).

in lysine. The gene was isolated and transferred into rice where it produced the storage protein in desired quantities. Product development was blocked by regulatory authorities when Prof. Samuel Sun, Hong Kong, proposed to combine this trait with Golden Rice. The reason for refusal was a short stretch of hypothetical allergenicity. Although the protein was and is consumed at large scale from the bean without any problem, it is not acceptable as an identical protein in rice[9] (personal communication by Prof. Samuel Sun, Hong Kong). Of course, if it could be crossed in, this would be a welcome improvement! As those deficient in one micronutrient are normally deficient in several micronutrients (see also H.K. Biesalski this volume) the long-term goal of biofortification is the simultaneous improvement in several micronutrients. The combination of "provitamin A" with "high iron" and "high zinc" in rice is a realistic option for the near future, and folate could be added as well. To facilitate deregulation it is advisable to combine the traits after deregulation. The combination would be done via traditional breeding.

The "high quality protein" topic may also serve as example of the potential of genetic engineering technology. Our body requires ca. 20 amino acids for protein biosynthesis. Ten of those it can synthesise; the remaining 10 have to come from the diet. An "ideal" storage protein should contain, for that purpose, the 10 essential amino acids in the desired ratio. Such a protein does not exist in nature. But it can be approached by the construction of a "synthetic gene" coding for the 10 amino acids in the desired relative quantities. Jesse M. Jaynes, a talented protein chemist from DEMEGEN USA, constructed the gene, arranging the triplet codes for the amino acids in the desired quantitative ratio in such a way that the protein would consist of stretches of amino acids with a positively and negatively charged surface on both sides. Adding a few beta turns led to a protein with the key functions of a storage protein. My laboratory inserted this gene into rice and demonstrated that the protein was produced, though at low concentration in this first experiment. This exiting approach was no longer followed up because it was just before my retirement and such a synthetic gene and synthetic protein would have had little chance to pass regulatory requirements.

There is a host of evidence that GMO technology has the potential to contribute substantially to food/nutrition security – and that the public sector is highly motivated to explore this potential for public good. However as long as the media, politicians, churches, and our society prefer to

[9] ssun@cuhk.edu.hk email address of Prof. Samuel SM Sun.

listen to self-serving activists instead of scientists, GMO technology will not be able to substantially contribute to food- and nutrition security. Most of all, this exciting proof-of-concept work will *not* lead to products which are the prerequisite for reaching and helping the needy. Golden Rice may still represent an exception because it received, as a "pioneer" project, unusual financial support. Millions of poor are taken hostage in an ideology-driven fight for political power and campaign money – applauded by brainwashed Western societies.

The bottlenecks for public good research and development in the area of genetic engineering with plants are all related to product development and deregulation. There are no specific hurdles as far as basic research is concerned, although financial support even for basic research in the area is drying out.

## Conclusion

1. There are no public funds available for product development and deregulation.
2. The financial requirement is more than 10 times higher compared to that for proof-of-concept work.
3. There is little competence for product development and deregulation within the public sector.
4. Intellectual property rights and Material Transfer Agreements which can be ignored as long as work for basic research is progressing are becoming severe hurdles as soon as work for product development begins. Free licenses depend totally upon goodwill of the patent holder and Material Transfer Agreements may become prohibitive because of fear of putative liability problems.
5. Nothing from all the work for product development has a chance to lead to publications, because there is no chance of "scientific novelty".
6. Therefore all this work is "highly toxic" for any academic co-worker and career. With Golden Rice we were fortunate that we could use the results from the work Syngenta invested in the development towards a commercial product using input from non-academic personnel.
7. There is no "bonus for public good" to be had from regulation. Public good GMO products must follow all regulations and provide all data as required for commercial products from the private sector.
8. Compared to the private sector the public sector has no means to protect GMO work against hostility and vandalism from the anti GMO lobby.

9. The very welcome financial support from altruistic sources changes "freedom to operate" and may come with "foreign micromanagement" and even "take-over".
10. The understandable desire for absolute protection against "liability" in case of the "unintended presence" of unauthorised GMO material is the overarching problem for the private sector partner in a public-private-partnership. This is understandable because there have been extremely expensive precedents of fines of hundreds of millions of USD.
11. Public-private partnership is in theory an ideal solution which, however, suffers from this situation.
12. The root cause for all these almost prohibitive bottlenecks is GMO-specific regulation maintained in the face of worldwide scientific consensus that there is no GM technology-inherent specific risk and consequently no scientific justification for GMO specific regulation.