Dear colleagues,

regretfully, I was unable to present my lecture on the development of the Golden Rice at the meeting of the Emeritenstamm on February 27, due to my poor physical condition. As you nevertheless may be interested in hearing the story, I am offering a short version of my lecture below.

To set the perspective, let me start with the global annual rates of mortality due to a number of diseases threatening public health:

Global mortality (millions)	2010[a]	2014[a]	2016/2017
Vitamin A deficiency	1.9–2.8	1.4–2.1	1.3–1.9 (2016)[b]
HIV/AIDS	1.8	1.2	0.94 (2017)[c]
Tuberculosis (TB)	1.4	1.1	1.6 (2017)[d]
Malaria	0.7	0.6	0.45 (2016)[e]

Table 1.
Annual mortality from different public health diseases (VAD deaths exclude significant maternal mortality).

[a] Source: [6]
[b] Source: 23–34%—see text—of 5.6 months <5 years children in 2016 [37]
[c] Source: http://www.unaids.org/en/resources/fact-sheet [Accessed: January 10, 2019]
[d] Source: https://www.who.int/news-room/fact-sheets/detail/tuberculosis [Accessed: January 10, 2019]
[e] Source: https://reliefweb.int/report/world/world-malaria-report-2017 [Accessed: January 10, 2019]

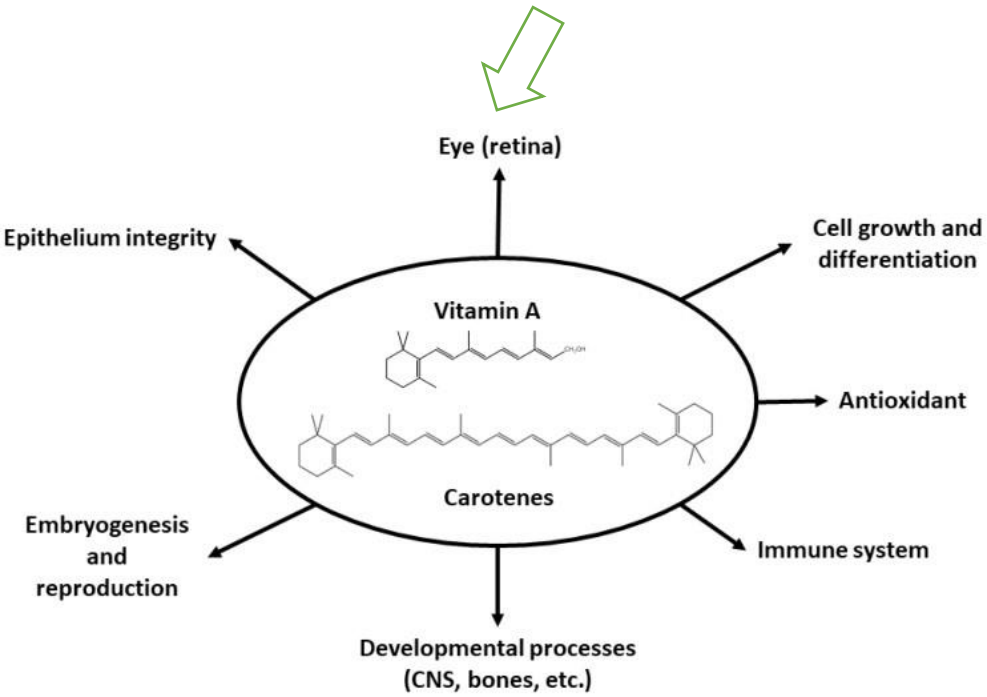
Vitamin A deficiency (VAD)

Obviously, VAD is of major concern worldwide, but it goes largely unnoticed in our part of the world, because it occurs only under certain conditions of malnutrition in developing countries.

Vitamin A (retinol) has many functions in humans and animals, the best known being that in vision, as its oxidation product, retinal, is a constituent of rhodopsin in the retina. As it is also involved in developmental processes and in the immune system, children and pregnant and lactating mothers are particularly sensitive to vitamin A deficiency. “An estimated 2.8 million preschool-age children are at risk of blindness from VAD, and the health and survival of 251 million others are seriously compromised” (WHO 1995; https://www.who.int/publications/i/item/WHO-NUT-95.3).

Vitamin A as such occurs only in animals, mainly in the liver, with particularly high concentrations in the liver of certain fish (hence cod liver oil as a source of the vitamin). Plants contain β-carotene and a few other carotenoids, which humans and most animals can cleave to produce vitamin A. β-Carotene is therefore provitamin A. It has an orange colour, as in carrots and oranges, but is also present in all green tissues, where it functions in photosynthesis.

Polished rice grains, which essentially are the storage tissue (endosperm) of the seed, do not contain any β-carotene. Thus, in areas where rice is the exclusive or predominant staple food, VAD is common. Consumption of unpolished rice is not a solution, because it contains fats in the hulls which easily turn rancid under hot and humid storage conditions. The advice to eat fruits and vegetables is well-meant but hardly realizable. The WHO provides vitamin A supplements (capsules) to schoolchildren in these areas, but VAD is nevertheless an unresolved serious problem.

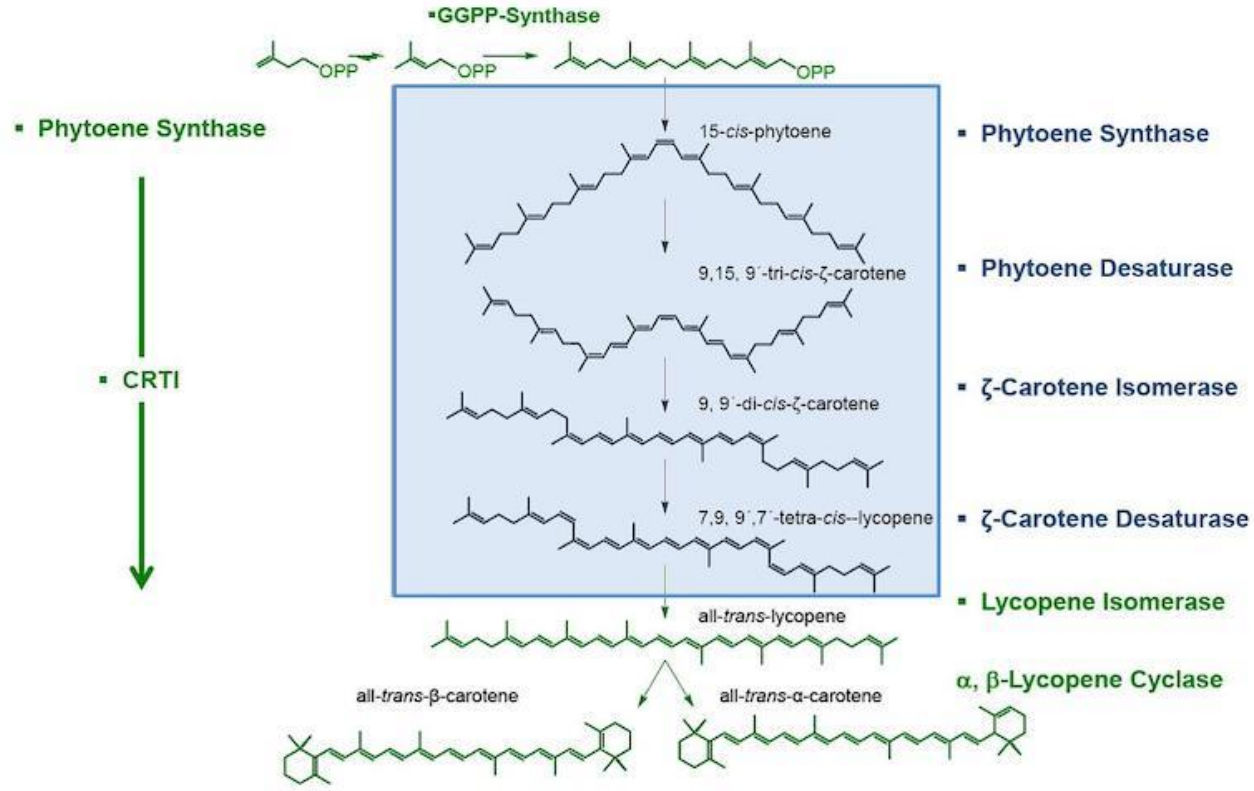


Functions of vitamin A

(Pro)Vitamin A Biosynthesis

Even though the rice genome contains the genes required for β-carotene synthesis, they are not functional in the endosperm. As among the thousands of known rice varieties none have ever been found which synthesize β-carotene in the endosperm, it is not possible to breed rice with such properties by conventional means. Therefore, in the early 1990-ies, we decided to introduce the pathway into rice endosperm by way of genetic engineering. I will not go into the technical details. The Herculean task of introducing eight genes required to produce β-carotene took almost

10 years to succeed, and in 2000 my group, together with that of Peter Beyer in Freiburg (Germany), published this breakthrough. (Ye et al., Science **287**, 303-305 [2000]).



Pathway of β-Carotene Biosynthesis

GR1

In the picture above, kernels of the first self-pollinated transgenic population are shown. In the yellow kernels the pathway is active. This was the “first generation” Golden Rice (GR1), the prototype. In the picture below, you can see a variety of Golden Rice with a modified set of genes (“second generation”, GR2, obtained in 2005) after five backcrosses. *Golden Rice is the first purposefully created biofortified food*.

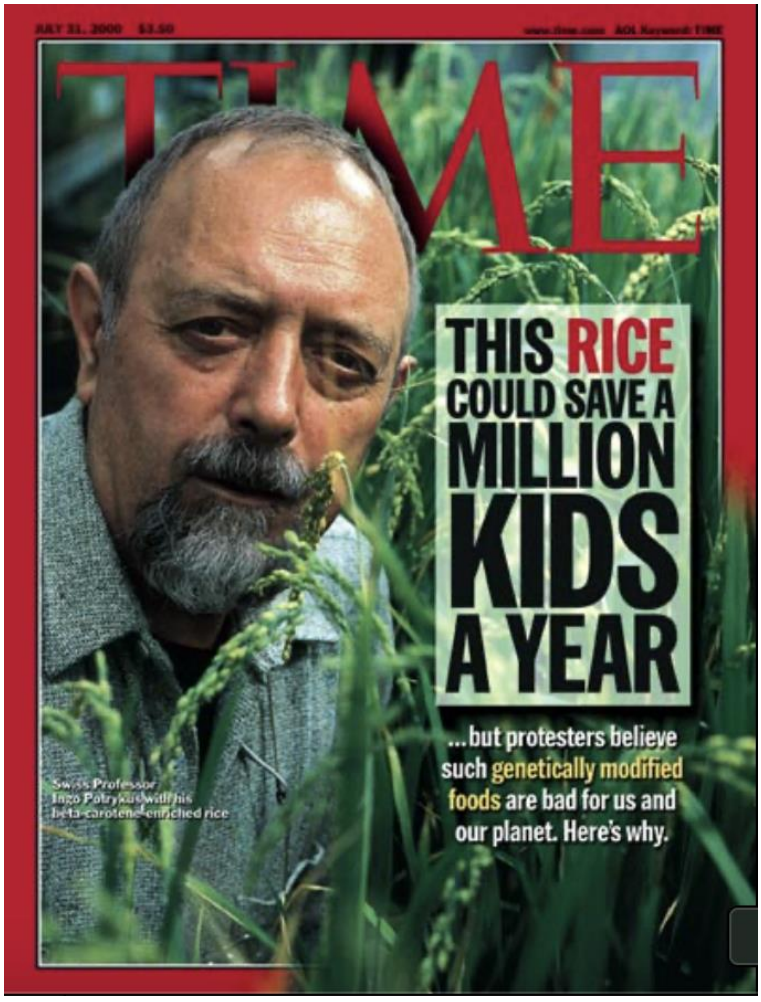
The scientific community and the public were excited, and there were numerous reports in the scientific literature and in the public media such as the TIME Magazine.

The widespread attention to the Golden Rice ceased around 2005.

Now, all of a sudden in 2022, there again appeared reports on the Golden Rice, and again prominently in TIME Magazine.

WHAT HAD HAPPENED WITH GOLDEN RICE IN THE COURSE OF THESE MORE THAN 20 YEARS?

Normal Rice and GR2



2000

This cover was accompanied by a commentary and a lead article.

10 Ways the World Got Better In 2022

Harvesting Golden rice from am IRRI field trial in 2010. Twelve years later, the genetically modified rice is finally being grown at scale. Courtesy of the International Rice Research Institute (IRRI).

BY TONY MORLEY

DECEMBER 28, 2022 10:24 AM EST

Over the past year, the headlines have been dominated by alarming events: the Russian invasion of Ukraine, high inflation, supply chain shortages, and the threat of food insecurity for many nations. But 2022 was also a year of milestones toward a better future, scientific breakthroughs, and

2022

TIME 17/01/2023

From Vaccines to Golden Rice:
10 Ways the World Got Better In 2022

1. **We found out that civilization reached peak agricultural land**
2. **We deployed a malaria vaccine for the first time**
3. **The James Webb telescope brought the universe into focus**
4. **Wild mammals rebounded in Europe**
5. **Farmers in the Philippines harvested the first large-scale genetically engineered "golden" rice crop**

One of the best stories of progress this year unfolded quietly in 17 rice fields in the Philippines this October. For the first time in world history, farmers in the Philippines harvested golden rice on a large scale—some 74 tons that had been cultivated over the previous year. Golden rice is a powerful tool in the fight against vitamin A deficiency, a condition that claims the eyesight and lives of hundreds of thousands of children annually. In 2009 the WHO estimated that "250,000–500,000 children who are vitamin A-deficient become blind every year, and half of them die within 12 months of losing their sight."

6. **Guinea worm disease reached near-eradication levels.**
7. **India developed its first cervical cancer vaccine**

9. **The SARS-Cov-2 vaccine saved millions of lives.**
10. **CRISPR for cancer had a major breakthrough.**

Golden Rice history
milestones from scientific breakthrough 1999 to deployment of the final product 2022.

00) Provitamin pathway engineering in rice endosperm 1991-1999.
Prototype completed Ingo Potykus and Peter Beyer
01) Decision for a ‚Humanitarian' Project - 2000.

Work for deployment:

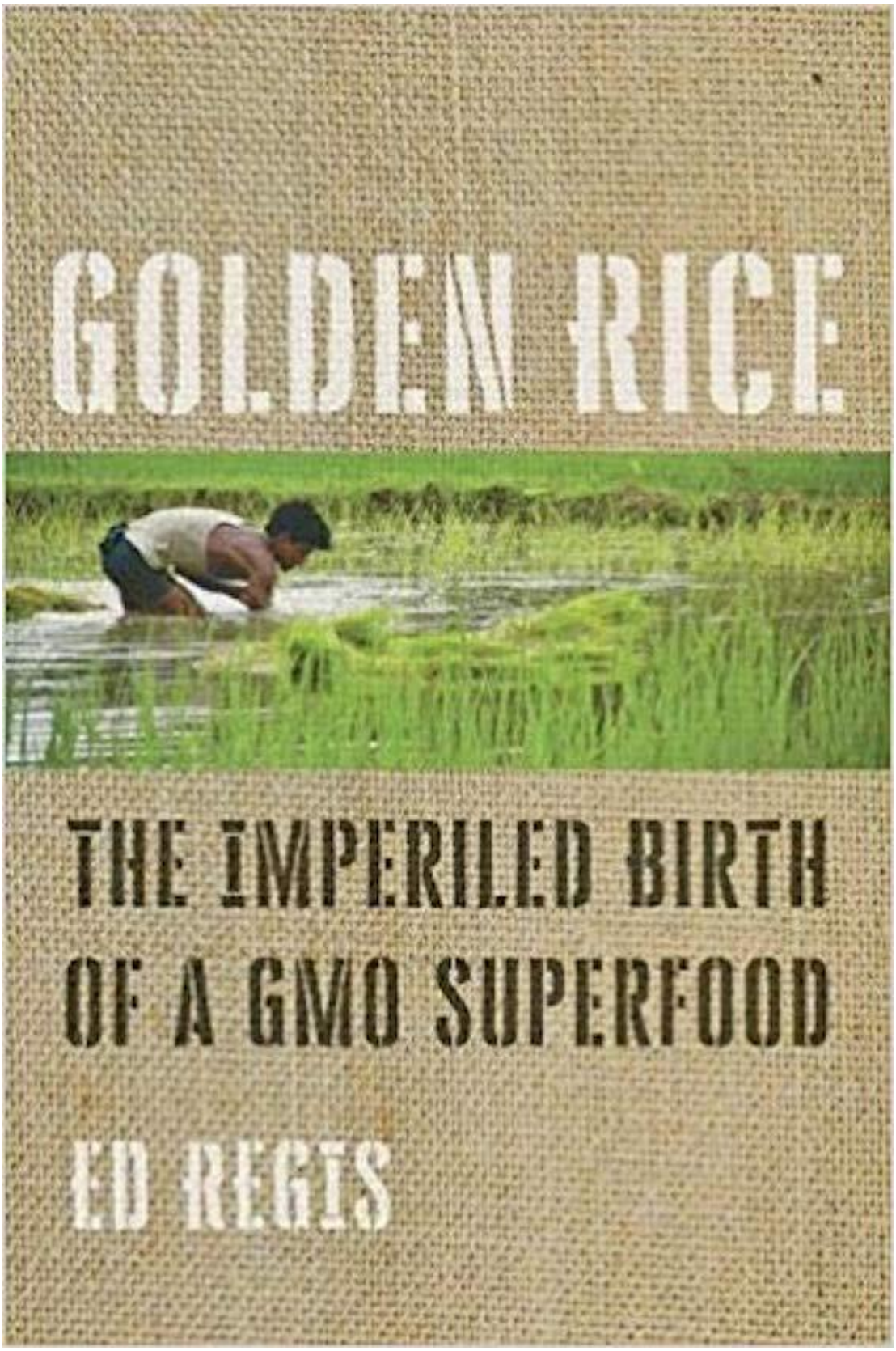
The Humanitarian Golden Rice Board

01) The mission
02) Foundation of a „Humanitarian Golden Rice Board"
02) Release from patent restrictions 2000.
03) Search for an GMO-experienced partner 2000.
04) Sub-sub-licence agreement and strategic responsibilities.
05) Network of SouthEast Asian public rice research institutes.
06) Increase of provitamin level 2005.
07) ‚Regulatory' clean transgenic events 2006.
07) Decision for ‚one event only' and the network results
07) The Chinese children experiment and Greenpeace
08) Recruitment of financial support from altruistic organisations 2000-2022 - up to a total of ca. $ 70 million.
08) Data collection for the regulatory dossier 2006-2016
09) Lead variety selected without agronomic data - 2016.

International and National Rice Research Institutes IRRI and PhilRice

10) Breeding without permission for field testing 2012 - 2018.
11) Variety development and multiple site testing 2016-2021.
12) Submission of the regulatory dossier (Don McKenzie).
14) Permission for consumption 2017 - 2022.
15) Permission for growth 2021 - 2022.
16) Variety registration 2022.
17) Large-scale seed production (PhilRice) 2022
18) The Bangladesh Rice Research Institute

To learn about the events in detail up to 2019, I recommend reading the book on Golden Rice by science writer Ed Regis (see below)



Johns Hopkins University Press (2019)

In short:

A **Product** had to be developed.

More importantly, a **GMO-Product.**
(GMO = Genetically Modified Organism)

And even more importantly, a **Public-Good GMO-Product.**

This sequence of the increasing complexity of the **Product**, i.e. Golden Rice produced by farmers in the fields, hardly mirrors the increasing number and the severity of obstacles we encountered on this way.

It was our vision to make the Golden Rice freely available to the poor needing it most. What started in good faith and rather naively, soon turned out to be a heavy fight for the inventors, i.e. Peter Beyer and myself, and our teams and supporters. This fight against fierce GMO opposition, in particular Greenpeace, and public opinion lasted more than 20 years.

As scientists, we had not been trained for such an endeavor. It soon became obvious that the Public Sector was neither prepared, nor willing, nor capable, nor even interested, to meet that challenge. The best example: The WHO (World Health Organization) has the UN-mandate, and the financial resources, to fight VAD. They spend hundreds of millions of US dollars on the distribution of vitamin A-capsules, yet have refused persistently to support the development of Golden Rice. If we would not have met the challenge ourselves, blindness and death from VAD would continue forever. But we needed support from a professional product manager and from experienced industry. We found both in Dr. Adrian Dubock of Syngenta. With his help we organized the Humanitarian Golden Rice Board (www.goldenrice.org). Adrian was also instrumental in arranging a collaboration with Syngenta on the basis of mutual and complementary interest.

The **Humanitarian Golden Rice Board** provides expertise and strategic guidance in bringing the Golden Rice to the field. The Board is an honorary body that benefits from the expertise of international authorities, including:

Prof. **Ingo Potrykus** (co-inventor of Golden Rice), emeritus professor, ETH Zurich, Chairman of the Humanitarian Board (public relations and information)

Prof. **Peter Beyer** (co-inventor), Univ of Freiburg, Germany (the science of biofortification)

Dr. **Gurdev Khush**, retired rice breeder from IRRI (bred some of the most successful rice varieties for Asia)

Dr. **Gary Toenniessen**, The Rockefeller Foundation (food security in developing countries)

Dr. **Adrian Dubock**, Golden Rice Project Manager, Agricultural Consultancy for Development GmbH, Switzerland (private sector approaches to project management)

Dr. **Howarth Bouis**, Director of HarvestPlus, International Center for Tropical Agriculture (CIAT), Cali-Colombia, and International Food Policy Research Institute (IFPRI) Washington DC (biofortification)

Dr. **Robert Bertram**, USAID Washington DC (development in Third World agriculture)

Prof. **Matin Qaim**, Center for Development Research at the University of Bonn, Germany (socioeconomic aspects)

Prof. **Robert Russell**, Former Director and Senior Scientist, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University Boston (vitamin A malnutrition)

Dr. **Sunkeswari R. Rao** Dept of Biotechnology, India (national cooperation in rice research)

Prof **Jean Pierre Jeannet**, Babson College, Massachussets (global marketing)

Our Vision

To create a public-good source of vitamin A, free of charge for the added trait (of provitamin A content) and freely available to those who want to grow, propagate and consume it, as an additional intervention in the combat against vitamin A deficiency.

Critical Steps

Sub-licence Agreement with Syngenta and the Golden Rice Patent

Syngenta had an interest in the development of a *commercial* provitamin A-producing rice. We had an interest in the development of a *humanitarian*, freely available, Golden Rice. We reached an agreement under the following terms:

The two parties collaborate and results from each side are available to the respective other side. The strategic guidance of the *humanitarian* aspect is provided by the Humanitarian Board. *Humanitarian* is defined through the farmer's income: All farmers with a total income of less than 10,000 US dollars per year are exempt from royalties for our patent as well as for the additional critical 12 patents which restrict the technology used in the production of Golden Rice and belong to a number of companies.

Release from patent restrictions

Basic science is free to use patented knowledge in scientific non-commercial work. In our development of Golden Rice, we had made free use of **72** patents belonging to more than **30** companies. When product development started, the situation changed dramatically. Each patent must be honoured. With the help of Syngenta lawyers, the number of patents involved was reduced to the essential **12** mentioned above, and free licenses were granted for humanitarian use by all partners involved.

"Tough Lessons"

We had naively thought that solving the restrictions imposed by patent laws would be the major task and the solution of this problem would then swiftly pave the way towards approval of Golden Rice for cultivation in the field, but we had not anticipated the well organized and fierce opposition to GMO and the thicket of regulations on transgenic crop plants, the latter becoming increasingly obstructive as they tried to meet the concerns of the opposition. Thus, in 2008, a

comment in *Science* concluded: “Golden Rice is still a promise” (Science **320**, 468-471 [2008]: Tough Lessons from Golden Rice).

The “Chinese Children Scandal”

The negative image of Golden Rice was again in the press in 2015. To prove the efficient bioconversion of β-carotene of Golden Rice to vitamin A in children, nutrition tests must be conducted with this target group. Such a study was undertaken in China in 2008 under the lead of scientists from Tufts University (Boston), and the promising results were published in 2012 under the title “β-Carotene in Golden Rice is as good as β-carotene in oil at providing vitamin A to children” (Tang et al., Am. J. Clin. Nutr. (2012) **96**: 658-664). Greenpeace claimed that ethical standards of experiments with humans had been violated, and the paper was retracted by the publisher in 2015. It is still being debated whether this decision was justified

Finances

While Greenpeace had claimed that the humanitarian Golden Rice project was just a Trojan Horse used by industry to pave the way for the acceptance of commercially profitable transgenic crops, the withdrawal of Syngenta from the project, and the scare and unwillingness of the Public Sector to support Golden Rice development, meant that we had to attract funding from charitable foundations. The largest donors were the Rockefeller Foundation and the Bill and Melinda Gates Foundation, and a total of ca. 70 million US dollars has been recruited to date.

Quiet Progress at IRRI and PhilRice

Within the network of Southeast Asian public rice research institutions work on Golden Rice progressed without much public interference. In the Philippines, these were the International Rice Research Institute (IRRI) and the Phlippine Rice Research Institute (PhilRice). Greenhouse and field tests were conducted at multiple sites, the provitamin A trait crossed into local varieties, regulatory dossiers established and submitted.

The first large-scale Golden Rice crop

In 2021, the government of the Philippines gave the green light to the large-scale production of a local variety of Golden Rice (Malusog Rice) in the field. In 2022, a total of 100 tons was harvested in 17 fields and is now available for sowing and further tests this year. Local farmers are reported to be satisfied with both yield and quality. Eating the first Golden Rice meal was a festive occasion, and Philippine newspapers reported extensively on this event.

It is now in the Philippines farmers’ own hands to fight VAD! Malusog Rice is now expected to be commercially available in 2024.

Bangladesh is likely to follow soon.

The harvest of Malusog rice in different fields in the Philippines in 2022. (PhilRice)

First Malusog Rice Harvest served during NBW

The Philippine Star, January 2023. NBW= National Biotechnology Week.

My entire life as emeritus has been devoted to achieving this goal!

Don’t hesitate to contact me for more information under: ingo@potrykus.ch

With best wishes,

Ingo Potrykus