The present status of Golden Rice

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Abstract The development of Golden Rice to date has taken longer than anticipated. It has been proven to have the potential to assist in the alleviation of an important public health problem, vitamin A deficiency, affecting millions. Complying with the highly precautionary, and now proven unnecessary, UN Cartagena Protocol for Biosafety has impeded scientific progress and scientific collaboration, particularly by delaying the selection of phenotypes grown in the open field. So far therefore, Golden Rice has not been able to assist in combatting vitamin A deficiency, identified by the UN as an important public health target for 25 years, and which continues to cause preventable deaths and blindness. However, the inventor's original vision of the donation of the technology to assist the resource poor who want to benefit from it remains firm and achievable, subject to continuing philanthropic and public sector funding.

Keywords Golden Rice; vitamin A deficiency; Syngenta; IRRI; Cartagena Protocol for Biosafety; nutrition; public health; rice; UNICEF; UN; WHO

1 Vitamin A deficiency

Vitamin A deficiency (VAD) affects about 19 million pregnant women and 190 million preschool-age children, mostly from Africa and South-East Asia[1]. The deficiency is the leading cause of childhood blindness[2], with about 500 000 cases annually. When untreated about half of these children die. VAD has also become recognised—only recently—as a nutritionally acquired immune deficiency syndrome[3] resulting annually in the death of one to two million, mostly young children and some mothers. Most of those affected by VAD, do not become blind before dying from diseases which are survivable with a functional immune system (R Russell, *pers comm*.). This severe mortality in 2010[4] globally exceeded mortality caused by HIV/AIDS or tuberculosis or malaria[5].

High under-five mortality, and deep poverty are closely correlated with vitamin A deficiency. Under five years mortality in India is, at more than two million annually, worse than in any other country, probably due to restricted dietary variety together with poor population coverage with vitamin A supplements, and little progress has been made since the 1980's in reducing it[3].

Vitamin A deficiency is also a common nutritional problem in China among the urban and rural populations. In 2004, the prevalence of vitamin deficiency among children of 3 to 12 years old was 9.3%: in the urban areas 3.0% and in rural areas 11.2%. The prevalence of marginal vitamin A deficiency was 45% of the whole population:with 29% in urban and 50% in rural areas[6]. A 2006 survey found VAD affecting 12.2% of Chinese children 0-6 years, and severe VAD afflicting 0.5% of the same age group. Chinese children living in the poor western area having a mother with either poor education or of minority ethnicity have a high risk of VAD[7]. Reviewing a decade's data up to 2005, the World Health Organisation in 2009 reported for China little evidence of night-blindness (an early clinical sign of vitamin A deficiency) in pre-school children or mothers and a mild incidence of VAD in pre-school children. Conversely VAD was reported as a severe public health problem for pregnant women in China[8].

Fig. 1 This Indian young woman, blind in her left eye, is nevertheless lucky, most vitamin A deficiency sufferers die as young children

"Although increasing the consumption of vitamin

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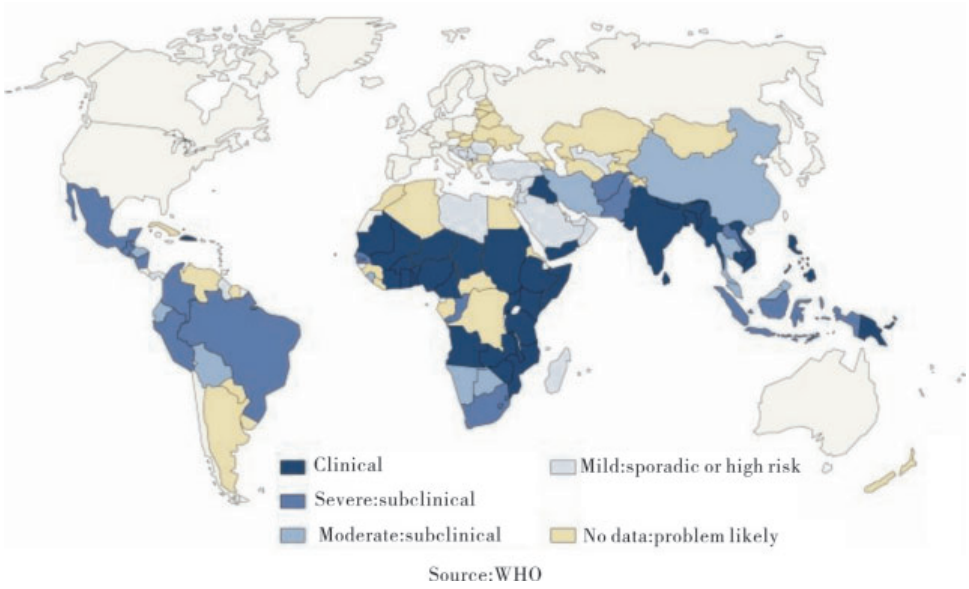

Fig.2 Public health importance of vitamin A deficiency, by country

A-rich foods may seem to be a reasonable solution, in reality, it is much more difficult for pre-school children in poor families to meet the requirements for vitamin A through diet alone. Animal products that are rich in vitamin A, such as liver, eggs, cheese, and butter, are often beyond the reach of poor families. Another critical factor that makes it difficult for pre-school children to meet their dietary requirements for vitamin A through fruit and vegetables alone is that the bioavailability of vitamin A from fruit and vegetables is not high. A young child between ages one year and three would need to eat eight servings of dark green leafy vegetables per day in order to meet the Recommended Dietary Allowance for vitamin A. The problem of the low bioavailability of vitamin A in plant foods has brought the sobering reality of 'the virtual impossibility for most poor, young children to meet their vitamin A requirements through vegetable and fruit intake alone'. The low bioavailability of vitamin A from plant foods explains, in part, the presence of vitamin A deficiency among children living amid ample supplies of dark green leafy vegetables and other plant sources of vitamin A" [3].

White rice, polished so that it can be stored without becoming rancid, contains essentially only carbohydrate, an energy source but not a source of life-essential minerals and vitamins. Vitamin A deficiency is therefore a widespread problem, especially in those large areas of the world where rice is the staple food, and for poor people in these countries 80% or more of their calories may come from rice (H Bouis, *pers comm.*).

2 VAD alleviation-possible, and affordable, but intractable

At the 1990 UN World Summit for Children more than 150 heads of government and senior government officials committed their governments to the virtual elimination of vitamin A deficiency and its consequences by the year 2000[9].

The commitment was strengthened by the 1992 UN International Conference on Nutrition which recognised that the control of vitamin A deficiency is one of the most cost-effective child health and child survival strategies governments can pursue. The conference concluded that all sectors of society should support a combination of strategies to achieve the virtual elimination of vitamin A deficiency. The strategies should include breast-feeding promotion, dietary diversification, vitamin A supplementation, and food fortification[10].

In 2003 UNICEF and the Micronutrient Initiative issued a global progress report "Vitamin and Mineral Deficiency" with the headline 'controlling vitamin and mineral deficiency is an affordable opportunity to improve the lives of two billion people and strengthen the pulse of economic development'. "Probably no other technology available today offers as large an opportunity to improve lives and accelerate development at such low cost" [11].

3 Golden Rice

The term bio-fortification had not been coined at the

time of the UN meetings above. However the research, initiated also in the early 1990s which led to the creation in 1999 of what came to be known as Golden Rice[12], was initiated by the teams of Ingo Potrykus and Peter Beyer in recognition of the same need. Golden Rice is the first purposefully created biofortified crop, designed specifically as an additional intervention for vitamin A deficiency.

Fig.3 The prototype "Golden Rice", described by Ye et al, 2000

Biofortified staple crops, that is crops bred by any method including genetic engineering when necessary, to include enhanced micronutrient—vitamin and or mineral -content or bioavailability are expected to be significantly cheaper, and more sustainable and cost effective in reaching populations than supplementation ('vitamin pills') or fortification (minerals or vitamins added to processed food) to address micronutrient deficiencies[5].

Golden Rice was first widely publicized in 2000 on the front cover of the American (illustrated) and Asian editions of Time magazine.

What progress has been made since, and what is the current status of the project?

Fig.4 Time magazine, September 2000

4 The vision for the Golden Rice project

The vision for the global humanitarian Golden Rice project remains as it was when the creators of Golden Rice started their research: to make available to those resource poor rice consumers in developing countries who wanted it and could benefit from it, a costless source of vitamin A in their staple food rice.

On 5th March 1999, the inventors filed a patent application for the nutritional technology they had invented. Following their ground breaking bio-fortification proof-of-concept success[12], the International Rice Research Institute, in the Philippines (showing an early appreciation of the potential) asked the Rockefeller Foundation to undertake an intellectual property (IP) audit of the technology. The Rockefeller Foundation contracted this task to the International Service for the Acquisition of Agri-biotech Applications (ISAAA), who in turn subcontracted it to a unit at Cornell University run by the Executive Secretary of ISAAA.

The inventors were unimpressed with the attitude of a company individual who contacted them having read about their invention. Contrary to the inventors publicly stated plans to give the technology away free to those that needed it, the manager insisted, that—due to an unrelated previous Material Transfer Agreement which also included one of the technologies used in the Golden Rice research—the nutritional technology was his companies to manage, not the inventors. In their frustration at the manager's intransigence in discussion, the inventors assigned on 20th February 2000 the relevant patents and all their rights to Greenovation, a spinoff biotech company of the University of Freiburg.

At almost the same time Zeneca Agrochemicals (soon to become Syngenta by merger with Novartis) approached the inventors for rights to the technology and were referred to Greenovation. On request, Greenovation promptly granted, on 14th April 2000, exclusive rights to Zeneca, free of charge for humanitarian applications, but royalty bearing for commercial applications.

Zeneca then, on the same day 14th April 2000, granted licenses back to the inventors in order that they could fulfil their commitments to make the technology available, free of charge, to resource poor farmers in developing countries. Through the creation of this public private partnership, the inventors traded commercial rights in the technology to Zeneca, in return for the companies support for the inventor's humanitarian vision. At the time Dr Beyer commented:"Zeneca is the only company worldwide with a long-standing reputation in investigating molecularly carotenoid biosynthesis in plants, therefore Zeneca is our natural partner". Zeneca explained in a press release that "the technology, or transformed rice

seed, will be provided to international and national research organisations, upon request, in developing countries under carefully controlled conditions, who will be assisted in its application to locally available and adapted rice varieties for biosafety and other assessments". When approved by the appropriate national authorities, who will assess safety to man and the environment, the Golden Rice seed can then be multiplied by conventional seed multiplication processes and distributed to resource poor farmers for planting, harvesting, small scale commercial activity (neighbours and local markets) and consumption.

This collaboration will provide Golden Rice and or the relevant technology free of charge to international and national research organisations, who will be licensed to make available rice seed containing the trait to resource poor farmers. Even if rice seed is sold on commercial terms locally, the trait will have to be provided free of charge. Zeneca further stated that "We can also support the necessary biosafety and risk assessment work, transform common public varieties (eg IR64) through Orynova, our Japanese rice affiliate company, with whom we have recently initiated discussions".

When published, the Cornell University IP analysis[13] was unhelpful. On 31th May 2000 Prof Potrykus e-mailed the first author:"Your analysis has led to a frightening picture of the future: how should one be able to achieve freedom to operate for the golden rice if 32 patent holders have to be asked to release their patent rights for the humanitarian project for 78 rice-growing countries". The first part of the Zeneca support to the inventors was to complete a rational IP audit, and determine that actually only a handful of patents may have been infringed by the inventors research, and to agree with the holders of that IP that it would be made available free of charge for the well-defined humanitarian purpose[14-15].

The Zeneca agreement with the inventors mandated that all improvements to the technology, from either party, would be cross licensed. (A few years later Greenovation, trying to raise capital from venture capitalists ('VC') to fund their pharmaceutical biotechnology strategy, were obligated by the VC firm, because of the contentious nature of agricultural biotechnology in Europe, to divest their commercial interests in the pro-vitamin A technology before the VC would advance any capital. Greenovation approached Syngenta for assistance who bought back the rest of the rights from them.)

Through these mechanisms the inventors donated their invention to the resource poor of the world so as to make the nutritional technology available free of charge in public sector rice varieties to those populations which could benefit from it. It is important to emphasise that no one involved with the development of Golden Rice will benefit financially from its adoption[5].

4.1 2000-2005

Following the initial agreements between the inventors and Zeneca, very quickly (and of course coincidentally) followed the merger between Zeneca a UK based agribusiness company and the agribusiness part of Novartis a Swiss based one to form Syngenta, also Swiss based.

The merger was announced to Zeneca staff on 2nd December 1999. In January 2000 Science published the breakthrough of producing beta carotene in otherwise white rice endosperm by the teams of Potrykus and Beyer[12]. The stock market listing of the new company Syngenta in New York, London and Zurich occurred on 13th November 2000, and on 20th January 2001 the Potrykus and Beyer agreement with Zeneca was novated to Syngenta. By April 2001 I had a work permit and was working with Syngenta as Global Head of Mergers & Acquisitions, Ventures and IP Licencing, and was living in Switzerland, fortuitously convenient for contact with Potrykus and Beyer who both lived and worked close by.

The levels of beta-carotene in the inventors proof-of-concept biofortified rice were criticised by Greenpeace as being insignificant for alleviation of vitamin A deficiency in a 2001 press release. Greenpeace, already opposed for 5 years to all genetically modified crops, said in a press release that a breast feeding woman would have to eat 18 kilograms of cooked Golden Rice daily to obtain any benefit. Without knowledge of the bioavailability of the carotenoids in Golden Rice, which was not known at the time, no-one was in a position to make that judgement (which has subsequently been disproved). In February 2001 Charlie Kronick of Greenpeace was reported in the Guardian Newspaper (UK) "Our view is that the billions of pounds that has been spent developing this rice is diverting resources from more sensible ways of tackling VAD"[16]. These were the first of many exaggerations by opponents. In the same Guardian Newspaper report Gordon Conway President of the Rockefeller Foundation joined anti-GMO activist Vandana Shiva in agreeing that "the public relations uses of golden rice have gone too far" [16]. It transpired that US television was showing

advertising images paid for by the US biotech industry implying fields of golden rice were growing in US fields—an embarrassing surprise to those involved in these very early stages of the project in Europe (and of course also misleading).

In any event Syngenta, now keen to optimise the technology for commercial exploitation in 'functional foods' in North America and Europe initiated its research, including a collaborative project between Syngenta's research scientists at Jealott's Hill International Research Station, Bracknell, to the west of London, and Dr Peter Beyer's lab at the University of Freiburg, investigating options for improving on the prototype.

A volunteer Golden Rice Humanitarian Board was also created by invitation to advise the inventors and guide the expected ethical challenges which may arise with the first Board meeting occurring at Zeneca, Fernhurst, UK on 18th August 2000 where a mission statement was agreed. In part it stated:"The Humanitarian Board believes that GoldenRice™ has the potential to be a valuable tool in alleviating vitamin A deficiency in malnourished populations in the developing countries. The Humanitarian Board also believes that GoldenRice™ warrants careful but urgent local work to test it for environmental effects, human safety and benefit. "

One of the first agenda items was to hear the advice of a Zeneca biotechnology regulatory specialist about the molecular characteristics required of a genetically transformed GMO-crop to ensure that it would be able to be registered for use under the regulations to be derived from the very recently (2000) published, but not yet in force (2003) Cartagena Protocol on Biosafety[17]. It was also advised, again with respect to the ramifications of the Cartagena Protocol, and agreed at that first meeting that it would be ideal for only one transformation event of Golden Rice to be developed everywhere, independent of the rice variety into which it was introduced by conventional rice breeding.

At the same time as formation of the Golden Rice Humanitarian Board, and following the agreement between Syngenta and the inventors[5], a network of public sector rice research institutions was formed to start the process required to fulfil the inventors vision. The first was the International Rice Research Institute in the Philippines where its then director Dr Ron Cantrell signed the licence agreement with Professor Potrykus with an effective date the same as that between Potrykus and Syngenta: 20th January 2001. By 22th January 2001 samples of Golden Rice had been delivered by the inventors and I, to IRRI. The Golden Rice seed was hand carried to IRRI by the inventors: the Cartagena Protocol had not yet come into force. Dr Cantrell said in a press release of IRRI, the Rockefeller Foundation and Syngenta:"The arrival of these initial samples at IRRI is a very significant step and allows us to finally start on the required testing processes using local rice varieties. IRRI expects to play a major role in the ongoing "Golden Rice" research effort and its eventual introduction to the world's millions of rice farmers and consumers. Others followed including the Philippine Rice Research Institute and similar institutions in Bangladesh, China, India, Indonesia, South Africa and Vietnam".

Following the 5th Humanitarian Board meeting in Beijing on 21th September 2002, the Board asked the licensee network to create 1 000 plus transformation events, based on the proof of concept constructs successfully created by Prof Beyer's team, from which it was hoped an improved transformation event could be selected collaboratively, to be taken forward as the one lead event by all Golden Rice licensees.

In an e-mail dated 24th March 2003, Dr Gurdev Khush, Humanitarian Board member, former rice breeder at IRRI and World Food Prize Laureate, advised "the Humanitarian Board that "regulatory clean" IR64 with only one copy of vitamin A genes does not need further breeding work. It is just like any other variety. However, during field test its yield potential and alteration in any morphological traits should be evaluated".

By the 6th Board meeting in Zurich in April 2003 no new transformation events had been created by the public sector research institution network. Excitement was created however by the announcement at the same Zurich meeting, of progress having been made by Orynova, a joint venture company between a Syngenta subsidiary company, Mogen BV of the Netherlands, and Japan Tobacco in Japan the latter of whom had novel technology for removing the selectable marker which had been used. About 800 SGR1 transformation events had been created in Japan. Ten transformation events with a single locus, good colour and no marker gene had been selected and T2 plants were growing in UK. The best of the events were expressing 13 μg/g total carotenoids, compared with 1.6 μg/g in the proof of concept Golden Rice. EU regulators had already expressed interest, and there was discussion of plans for EU and US field trials in 2004 with a T4. Additionally, about 200 transformation events had been generated in Peter Beyer's lab. Of these in total about

1 000 transformation events, 4 from Syngenta and 2 from Freiburg/ETH/Cu Long Delta Rice Research Institute, Vietnam (by Dr Hoa, in Beyer's Freiburg lab) were selected for field trialling.

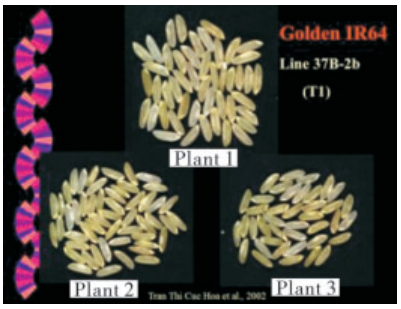

Fig. 5 Golden Rice IR64 transformed by Dr Hoa of Cu Long Rice Research Institute, Vietnam, in Prof Beyer's Lab in Freiburg, Germany

In an October 8th 2003 e-mail to the Golden Rice Network, Prof Potrykus wrote: Golden Rice field trials are "at an advanced planning stage …in Spain and USA and we would also like to involve also Bangladesh, India, the Philippines and Vietnam…these trials can generate data on agronomic performance and trait stability, and generate seed increases to be harvested during 2004, the UN Year of Rice announced by [UN Secretary General] Kofi Annan earlier this year… This is a tremendous challenge and needs to involve those members of the network who have the necessary expertise… We will also benefit from your interaction with the local regulatory authorities to assist the process as fast as possible within guidelines… Golden Rice IR64 seeds are already in Vietnam and India. Before the January [planning] meeting we will also endeavour to arrange transfer of the seed incorporating the new Syngenta events with higher level of expression for inclusion in the same trials programme, and the Rice IR64 to Bangladesh and the Philippines… Planning and funding for the human feeding trial has been achieved in the US by…Humanitarian Board member Dr Robert Russell and his collaborators. Permission, including ethical clearance, is currently being progressed for the trial to be conducted in China, planned to commence also in 2004. "

The e-mail also announced "encouraging developments in the basic science, which may eventually result in an improved "Golden Rice 2" containing further increased β-carotene levels. "

By 3rd November 2003, following this author's proposal of the need from Syngenta, IRRI had recruited a Golden Rice network coordinator, Dr Gerard Barry, funded by USAID and agreement was also in place to recruit a University of Freiburg Project Manager, to assist the Board, with Syngenta Foundation funding, expected to be in place by early 2004. (Dr Jorge Mayer filled this latter post 2004-2008, when he returned to Australia for family reasons, and then this author 2008-2010, following retirement from Syngenta).

A large planning meeting for field testing initiated by Prof Potrykus and Dr Swaminathan, with Golden Rice network participants took place in Delhi on 15th December 2003. Dr Barry took excellent minutes.

Within Syngenta, biotechnology management in 2003 and 2004 was facing tough choices. Following the creation of Syngenta, the portfolio of both legacy companies' biotechnology projects was too large for all to be properly funded. More progress could be made on those with more significant commercial prospects if more resources could be deployed, and to release those resources some of the least valuable projects needed to be dropped.

Benedikt Haerlin Greenpeace's European anti-GMO campaign director had stated in early 2001 that Golden Rice posed a moral challenge to Greenpeace which would therefore not attack field trials of Golden Rice in the Philippines. Nevertheless "The debate on the virtues and perils of biotechnology in the production of transgenic crops …has become quite contentious. . . in recent years… to the extent that it is now delaying and/or preventing the adoption of this important technology in addressing critical and urgent problems of food security and the environment"[18]. This was especially so in most of Europe. Syngenta decided, without at this stage any public announcement, to cease its commercial interest in the development of Golden Rice. It still had its legally binding contractual obligations to support the inventor's humanitarian project, which was also widely popular with Syngenta staff, including a positive role in motivating new recruits to seek to join the company.

The attitude to GMO-crops in other parts of the world was more relaxed. Following the 'approval for cultivation of three Bt-cotton hybrids last year' [Indian] Agriculture Minister Rajnath Singh announced on 18th December 2003 that "A network of projects on transgenics, covering 12 crops is on the anvil. ""The proposed Indian Council of Agricultural Research (ICAR) will cover maize, pigeonpea, chickpea, soybean, cotton, brassica, tomato, Brinjal, banana, papaya, potato and cassava" and focus on a variety of traits. Even in UK on 11th February 2004 " it was agreed between senior cabinet ministers including the foreign secretary, Jack Straw, and the environment secretary, Margaret Beckett that the government would give the green light to the first crop of GM maize in Britain…. The public is unlikely to be receptive. ""Mrs

Beckett said there was no scientific case for an outright ban on the cultivation of GM crops"[19].

In January 2004 Dr Rachel Drake, project leader for Syngenta at Jealott's Hill reported internally within Syngenta variation in carotenoid content between samples of the same SGR1 events analysed at different intervals after harvest, as well as the expected gradual drop in carotenoid content in storage. "The new data underlines the importance of the multi-location field trials in assessing the performance of the trait". By 13th February 2004 she was seeking approval from me to proceed with the internal processes necessary to donate, and archive SGR1 and move on to SGR2. The key meeting of this process occurred at Jealott's Hill on March 31th and 1st April 2004.

By March 2004, 30 high beta-carotene expressing transformation events of the new constructs anticipated in Prof Potrykus' October 8 2003 e-mail had been created by Dr Drake's team. These were already known

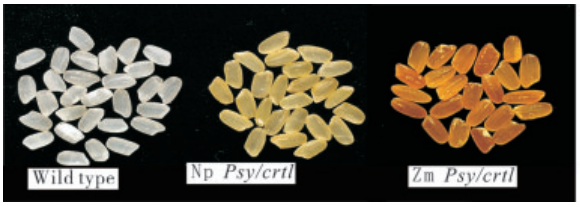

Fig.6 Wild type and transgenic rice grains containing T-DNA from daffodil psy (Np) (as in the proof of concept Golden Rice, Ye et al, 2000) or maize psy (Zm) showing altered colour due to carotenoid accumulation (From Paine et al 2005)

as SGR2 events.

The 8th Golden Rice Humanitarian Board meeting occurred in Louisiana, USA in mid-September 2004, and there was great and continuing excitement to arrive to witness for the first time open field grown and harvested Golden Rice SGR1. The colour, an indication of carotenoid content, was immensely encouraging. Many photographs were taken. Despite Syngenta having decided to cease its commercial interest in Golden Rice, the field trial was paid for by Syngenta to

Fig.7 US field grown Golden Rice SGR1, 2004

support the humanitarian project of the inventors.

On 23th June 2004 an announcement was made in Syngenta:"In Plant Science we are concentrating research and development activities at SBI [Syngenta Biotechnology Inc.] in North Carolina, bringing together the skills required for success in a more flexible organisation…. At Jealott's Hill around 130 positions will be lost. At SBI around 45 research positions will be lost, but these will be offset by planned increases in Plant Science development. "

On 14th October 2004, to mark World Food Day on October 16th, Syngenta announced to the US Securities and Exchange Commission[20] that it was donating "the new Golden Rice seeds and lines"[eg SGR1], including "new lines containing significantly higher levels of beta-carotene as well as the related technology, rights and research" [eg SGR2] "to the Golden Rice Humanitarian Board". In the same announcement Syngenta stated "The company has no commercial interest in the Golden Rice project".

The highly precautionary Cartagena Protocol on Biosafety had come into effect in 2003. In 2005 Syngenta was involved in an international regulatory issue as a result of two different transformation events of Bt-maize Bt-10 (unregistered) and Bt-11 (registered) being mixed in the research chain. Both events were found to be in commercial supplies of maize being shipped internationally. Anti-GMO organisations found this to be good political capital, and the error cost Syngenta financially and reputationally.

The SGR2 Golden Rice transformation events were described in detail in Nature Biotechnology in 2005[21], which also made clear Syngenta's support (legally obligated under its licence agreements with the inventors) for the inventor's humanitarian project:"Consistent with Syngenta's support of the Humanitarian Project for Golden Rice, Golden Rice 2 transgenic events will be donated for further research and development through license under certain conditions. Such conditions including being governed by the strategic direction of the Golden Rice Humanitarian Board and full regulatory compliance. Please direct requests to Adrian Dubock [with Syngenta e-mail address] in the first instance….". One of the SGR2 events was field trialled again in Louisiana in 2005, this time paid for by Dr Beyer's research budget.

Pre the Bt-10 scandal, Syngenta had allowed the physical materials of several SGR1 transformation events to be sent to a number of different Golden Rice network collaborating institutions in several countries using a simple 2004 Material Transfer Agreement making it clear that the materials were under the strategic management of the Humanitarian Board and

subject to the Golden Rice Humanitarian Licenses terms. However, post the Bt-10/Bt-11 embarrassment, when it came to SGR2 Syngenta product stewardship managers were concerned to more carefully manage potential 'adventitious presence' of unregistered Golden Rice transformation events.

The Golden Rice research had transferred to Syngenta Biotechnology Inc. (SBI) at Research Triangle Park, North Carolina, USA and the Jealott's Hill Syngenta team which had made the SGR2 breakthroughs had lost their jobs. At SBI the trait had been incorporated into *javanica* rice varieties, as these are the varieties commonly commercialised in USA, before cessation of Syngenta's commercial interest in the project.

Thirteen SGR2 transformation events had been identified all of which were considered by SBI scientists and regulatory specialists to be ready for and capable of complying with regulatory studies and standards. It was suggested, because of the adventitious presence concern, that one event would be selected by SBI and provided to the humanitarian project. The Humanitarian Board however suggested that it was necessary to select events in Asian germplasm and in Asian conditions, as this was where vitamin A deficiency was principally the problem. Through discussion it was agreed that 6 transformation events of the 13 would be supplied to only two Asian rice research institutions. IRRI and the Indian Agricultural Research Institute, both succumbed to and passed a physical audit by Syngenta of their capability to effectively manage programmes involving GMO-crop materials, which neither had significant previous exposure to. The SGR2 materials were then supplied to IRRI and IARI under Material Transfer Agreements with the same terms as for SGR1.

4.2 2006-2014

The plan in both India and the Philippines for SGR2, as well as other countries for SGR1, was to introgress the Golden Rice nutritional trait into locally important mega-rice varieties of *indica*, to create a breeding parent rice line containing the nutritional trait with which locally adapted and preferred rices could be crossed in each country. From the data accumulated as a result of the research programme the Humanitarian Board intended, as soon as possible, to select one lead transformation event to introgress into all varieties everywhere the trait was required, and to be registered in those territories also. Again this was to fulfil the demands of the Cartagena Protocol on Biosafety, to share the costs of developing the regulatory data package, and to reduce the possibilities of adventitious presence as had been the Humanitarian Boards strategy since the first Board meeting in August 20th. No genetic modification was necessary for Golden Rice in Asia, only conventional breeding.

In India the local regulations in place as a result of the Cartagena Protocol resulted in a very expensive construction known as 'the Phytotron' for GMO-crop research. Entry for authorised personnel was through an air lock. All plant growth in the Phytotron was in artificial environments. Regretfully this affected the plants phenotype, so that only genetic markers could be used to track trait introgression, and the normal seed breeders skills of observation and selection for phenotype could not be employed.

In the Philippines, the regulations (also based on the provisions of the Cartagena Protocol) allowed the use of screen-houses, (later adopted also in India) which allowed better use of seed breeder's skills of phenotyping.

Such breeding necessarily is slow:each backcrossing taking a growing cycle applicable to the variety and the location. The aim was to get to homozygous populations for the trait, where the only difference from the background rice variety was the introduced nutritional trait.

To assist the breeding work, IRRI requested molecular data concerning the transformation events from Syngenta. This was provided in 2006 by SBI solely to IRRI. Syngenta did not provide it, even to Dr Beyer, nor to any other institution.

Before the Humanitarian Board could select the lead event, data concerning the agronomic performance of the different transformation events, in four different rice germplasm backgrounds was generated, and also data about beta-carotene accumulation in stored polished Golden Rice. To calculate how much beta-carotene was needed in the Golden Rice as one of the criteria for event selection, it was necessary to know with what efficiency the beta-carotene in Golden Rice is converted to circulating vitamin A in the human body.

For a variety of reasons nutritionists advised that animal models were not a useful paradigm for such important human estimations. As the principal target for the potentially powerful new intervention for vitamin A deficiency was children, and children in industrialised countries do not suffer from vitamin A deficiency, as previously mentioned work was planned involving children in China and clinical researchers based in China and USA. The same methodology was to be used with the children research, as previously with

adults in USA, but given smaller blood volumes there were problems producing enough deuterium labelled beta carotene Golden Rice. The levels of expression in SGR1 proved insufficient for the quantities of Golden Rice expected to be consumed in a single small meal by a child. SGR2 levels of total carotenoids, and the higher proportion (up to 95%) of beta-carotene (the most important for benefiting changes in circulating vitamin A in the blood) both augured well for eventual success. However, due to the high (US $1.0 million) cost of the deuterium (heavy water) to be used, only a small hydroponic growth chamber could be used in Baylor college of Medicine where labelled SGR2 was produced by Dr Mike Grusak and his team, with condensate being recycled. The team had little experience of growing rice hydroponically. Two crop cycles of this expensive rice were consumed by fungus and then by mites, before sufficient Golden Rice could be produced. This delayed the field phase of the Chinese children research until 2008.

After the 10th Humanitarian Board meeting at IRRI, the new Director General, Dr Robert Zeigler, said that he wanted to join the Board replacing Drs Ren Wang and Willy Padolina, both deputy Director Generals (for research and partnerships respectively). This was immediately accepted within a few minutes of the suggestion. (The IRRI project manager and Golden Rice Network Coordinator, Dr Gerard Barry, who joined IRRI on taking up his position in early November 2003, remained an *ex officio* member of the Board until he left IRRI in December 2013, as did the Freiburg based Project manager Dr Jorge Mayer until he left Freiburg for family reasons in 2008. Dr Meyer still manages the www.goldenrice.org web site from Australia as a volunteer and very good friend of Golden Rice.)

At the 12th Humanitarian Board meeting in Delhi on 16-18 November 2006, it was suggested that for the humanitarian project it would be more acceptable to

Fig.8 Note the physical distance of the (inner area) Golden Rice from other rice, the maize pollen trap and the metal fence, all required by Cartagena Protocol derived national GMO-crop regulations

the public sector partners for the "S" (signifying the Syngenta source of the transformation events) to be dropped from SGR1 and SGR2. This was agreed and henceforth only GR1 and GR2 were used.

In 2008 IRRI planted the first confined field trial of Golden Rice at their location Los Baños, Philippines. The planting conditions included physical isolation from other rice crops, a surrounding belt of maize plants as a pollen trap, and surrounding that a high wire fence these conditions being mandated by the local regulations for GMO-crops developed to comply with the Cartagena Protocol on Biosafety. The field in the Philippines was harvested just in time before a powerful cyclone would have destroyed it a day later.

By contrast, in the 2004 and 2005 Golden Rice field trials in the USA—which is not a Cartagena Protocol signatory—only a surrounding few rows of non-GMO-rice were used as a pollen trap-with no fencing of any kind.

Fig.9 Conversely, in USA field trials of Golden Rice in 2004 (illustrated) and 2005, no extreme and expensive measures were required. USA is not a signatory to the Cartagena Protocol, and rice exhibits its true phenotype only when grown in open field conditions, as here

On 18th and 19th March 2009 the Golden Rice Humanitarian Board assembled for its 14th "watershed" meeting to select the lead event and share the plans with a licensee meeting immediately following.

The day before the meeting started Dr Guangwen Tang provided the manuscript, accepted for publication in the American Journal of Clinical Nutrition, describing the research undertaken with human adults in USA to to determine the vitamin A value of intrinsically labeled dietary Golden Rice in humans. The conversion factor of Golden Rice β-carotene to retinol was demonstrated to be 3.8 to 1 and the paper concluded that the β-carotene derived from Golden Rice is effectively converted to vitamin A in humans. The paper was published later in 2009[22].

Indian Golden Rice data was only available from the phytotron, due to the regulations governing GMO-

crops, and the phenotypes were so adversely affected by the artificial environment that useful data could not be generated.

So at the March Board meeting it was only possible to consider the agronomic data from IRRI in the Philippines. Data from 3 GR1 transformation events (146 309 and 652) and 6 GR2 transformation events(W, G, R, E, L & T) each in 4 target indica rice varieties (IR64, IR36, BR29 and Rc 82) were considered. Dr Parminder Virk, IRRI rice breeder in charge of the programme, presented comprehensive data generated covering ten agronomic measurements used by rice breeders as well as carotenoid content and degradation over time. All data was derived from rice grown in screen houses:open field growth was not permitted under the regulations in place for GMO-crops. The skilled and committed work of Bangladeshi rice breeder Alamgir Hossain and PhD Scholar Partha Biswas, then working at IRRI, were particularly acknowledged, but the team also involved, apart from Dr Virk, 12 other IRRI staff.

This was a very large, complex and expensive research programme. During the research novel systems for selecting transformed seeds without affecting germination had been developed, and it was noted that molecular markers alone were insufficient for nutritional trait selection. Carotenoid content degrades rapidly after harvest (as is common in all crops) but in rice the rate of decrease after 2 months was demonstrated to be minimal.

The Humanitarian Board's nutritionist Dr Rob Russell could not be present at the Board meeting and Professor Beyer who had briefed himself thoroughly with Dr Russell beforehand took the Board through the calculations of how much carotenoid was needed to improve retinol status of individuals. Recommended daily allowances for vitamin A include sufficient to maintain 3 months liver store in healthy individuals. The liver stores are not however necessary to combat vitamin A deficiency. All calculations(and subsequent breeding decisions) used only the retained β-carotene content after 2 months of storage. Calculations also assumed 20% losses of carotenoid through cooking, although only 6% losses had been noted by Dr Tang who sent the data on the Sunday before the meeting. This conservatism was considered sensible as there are many different systems of cooking rice: in some all water is absorbed for instance, and in some excess water is used and discarded. The advice of Dr Russell was that children, and particularly marginally or more severe vitamin A deficient individuals would be expected to demonstrate even more efficient bioconversion than adults of the β-carotene in Golden Rice to retinol the most important form of circulation vitamin A.

During the discussion Board member Dr S R Rao from the Department of Biotechnology, Government of India was initially not fully supportive of taking the lead transformation event decision without considering similar data from the Indian research. He also asked if there was any molecular data available to support the decision making. No such data was forthcoming (although IRRI had received it in 2006, it appeared to have been forgotten).

In the absence of detailed molecular data and Indian agronomic data the Board nevertheless after careful consideration and discussion accepted the IRRI recommendation for a lead Golden Rice transformation event. The recommendation was based on integration of the IRRI data and the bioconversion ratio of the β-carotene, as well as considerations of dietary intake of rice and levels of β-carotene expected after Golden Rice stored for at least two months had been cooked. The analysis demonstrated that none of the GR1 events could provide the required amount of β-carotene in a sufficiently small ingestion of Golden Rice, and that all the GR2 events could. It was agreed, based on the data, that event GR2G would be the Lead Transformation Event, with event GR2R as a back-up event if needed.

The plan was that the Lead Event would be distributed to all Golden Rice licensees for further introgression into locally adapted varieties of rice, and that the back-up event would be retained by IRRI only and progressed in backcrossing stages in parallel with the R event. Cost and resource considerations, as well as concerns to minimise potential adventitious presence problems, due to the Cartagena Protocol's influence prevented more ambitious breeding programmes including more events in more countries.

Only an hour after reaching this decision the Golden Rice Network Meeting was scheduled to start. Such close temporal alignment was always necessary in our Golden Rice Humanitarian Board meetings as the Board has never had any funding, and so time and airfare management had to be very efficient. The network meeting was excellently organised by IRRI's Golden Rice Network coordinator, Dr Barry. Representation from the network came from Bangladesh, India, Indonesia, Philippines and Vietnam with representation from each public sector rice research institution including both the involved scientists as well as the senior administrative function

responsible in the country.

Professor Potrykus, the Chairman of the Board (and the licensee of the Golden Rice technology) presented the decision of the Board that the lead event was GR2R and the reasoning in brief. Plans for destruction of previous transformation events, a sensitive issue for any researchers especially when public money has been used, but necessary for (Cartagena Protocol inspired) product stewardship reasons were discussed, and the countries (knowing in advance that there would be a selected lead event) presented their breeding plans. The meetings closed.

On 1st December 2009 I circulated the following e-mail to the Humanitarian Board, as urgent decisions were required and no physical Board meeting was planned.

"Dear Colleagues,

The following message has been approved by our Chairman, Ingo Potrykus.

I attach part of the Draft Minutes of the Humanitarian Board meeting held at IRRI in March this year. These minutes refer to that part of the meeting which decided on the lead GR event to take forward. You may remember that it was GR2G.

What follows immediately below is an excerpt from a [*Bill & Melinda Gates Grand Challenges in Global Health*] meeting in Arusha recently attended by Peter Beyer; Gerard Barry and myself together with Mike Grusak (one of the co-authors on the GR human studies papers, and part of the PVMRC project) and Hector Quemada (of the Danforth Centre who is a regulatory specialist supporting GR and funded by the Gates Foundation).

"1. There was discussion of the problems encountered with GR2G, the lead event selected at the HumBo in March 2009, relating to the sequencing of the insert, which was found by IRRI, post March 2009, to be incomplete. This may affect the tissue specificity of expression of the promoter, (being investigated by PB, and subsequent to September found not to be the case) but even if this is not the case having deletions will cause regulatory questions which will delay the submissions review.

Mike Grusak confirmed that there was no reason to expect any difference in bioconversion of β-carotene to retinol due to different transformation events being the source of the β-carotene.

It was recalled that at the Humanitarian Board the reserve event GR2R performed better agronomically and from a β-carotene accumulation perspective than the event GR2G selected as the lead. The reason, in these circumstances that GR2G was selected was because it has been used in the human bioconversion trials.

It was unanimously agreed by those present that IRRI's informal recommendation to the Golden Rice Humanitarian Board to change the lead event to GR2R and bring forward GR2E as reserve, and to drop GR2G was full supported.

ACD confirmed that for legal compliance—opposite Syngenta—this decision needs to be a Minuted Decision of the Humanitarian Board, and ACD would arrange this with I Potrykus and the Humanitarian Board.

a)Action: GB to provide ACD a summary of the evidence involved. (Done)

b)Action: ACD to arrange for the Humanitarian Board to endorse the change in lead event to GR2R in a form which satisfies the requirement for a Minuted Decision. "

The data presented by Dr Barry were that:

- ►GR2 events G, R and E sequenced entirely (in the original Kaybonnet)
  —Inserted sequences are identical to those in the original transformation vector (pSYN12124)—no mutations
  —Except, the G event has a ~400 bp deletion in the promoter for crtl
- ►This deletion will require additional explanation and studies to characterize this unexpected occurrence
- ►1 000+ bp has been sequenced on each side of the inserts
  —G is located in an exon, R is in an intron and E is in an intergenic space
- ►All sequence/data reviewed by Humanitarian Board, Biosafety Resource Network, and Food Allergy Research & Resource Program(no issues other than those identified above)

(It will be clear that much of the decision making was again driven by the regulatory system, developed by signatories to the Cartagena Protocol. Despite the summary slide provided by IRRI, The Board had not reviewed, nor did most have the training, to 'review all sequence data' in any meaningful way, and it is unclear which other individuals had or the level of scrutiny afforded to it). The Board unanimously accepted the recommendation to change the lead event to GR2R.

In July 2010 a meeting involving the Director General of IRRI, and IRRI's Network Coordinator and Syngenta occurred at the companies head office in Basel to which neither the inventors nor the author

were invited (despite all three living very close by).

Just before the 15th Humanitarian Board meeting in Singapore on 26th and 27th of August 2010, IRRI's DG and the Golden Rice Network Coordinator of IRRI met with the inventors and the author and explained the contents of some late draft agreements resulting from the July 2010 meeting. One of the documents was a more complex form of Material Transfer Agreement than had been agreed in March 2009, for use in connection with the distribution of the GR2 lead transformation event to Golden Rice licensees.

It is unclear what thinking or which organisation prompted the July 2010 meeting in Switzerland. Later in 2010 Prof Beyer was informed by the Bill and Melinda Gates Foundation that the competitive grant he had been awarded by the Health Department of the Foundation in 2005 for line extension (eg improved second generation Golden Rice products) of Golden Rice would not be renewed at its termination in 2010. Instead the Foundation intended to award a grant for development of Golden Rice itself to IRRI, for management of Golden Rice out of IRRI.

The 16th Golden Rice Humanitarian Board meeting on 13th November 2011, was followed a day later by a Golden Rice Seminar at the CGIAR institute also in Washington DC the International Food Policy Research Institute (IFPRI), where IRRI announced the upcoming Gates Grant in support of Golden Rice, which of course was very welcome.

On 3rd October 2011 I gave an interview at the 10th Anniversary Meeting of the Conselho de Informacies Sobre Biotechnolgiain Sao Paolo Brazil. Amongst a lot of other commentary in a long interview I commented:"As of today, October, 2011, more than two and a half years on [from the March 2009 Lead Event decision], the selected Golden Rice seed has been supplied to research institutes in only two countries:India and Philippines. The inventors and the public sector Golden Rice licensees in other countries are very frustrated by this slow progress, at a time when multiple rice breeding programmes could be underway in multiple countries. All licensees already have the legal ownership of the Golden Rice trait. They need the physical materials. And use of the same physical materials—the same transformation event even in different varieties of rice—is effectively mandated by the regulatory environment. "

When finally published in August 2012[4], Dr Tang's research with Chinese children, initially spoken of in 2003/2004 showed that "The β-carotene in GR [Golden Rice] is as effective as pure β-carotene in oil and better than that in spinach at providing vitamin A to children. A bowl of ~100 to 150 g cooked GR [Golden Rice] (50 g dry weight) can provide ~60% of the Chinese Recommended Nutrient Intake of vitamin A for 6-8-y-old children. ""In summary, the high bioconversion efficiency of GR β-carotene to vitamin A shows that this rice can be used as a source of vitamin A. GR [Golden Rice] may be as useful as a source of preformed vitamin A from vitamin A capsules, eggs, or milk to overcome VAD in rice-consuming populations. Awareness of the vitamin A equivalence of plant foods provides a scientific basis for designing food-based nutritional programs to improve vitamin A status in many regions of the world where VAD is still common."

Twenty two days later, on 30th August 2012 Greenpeace issued a press release condemning use of a GMO-crop, Golden Rice, with Chinese children as 'guinea pigs of American researchers'. Actually, Dr Tang, and several of the other clinicians involved in the research were born and or are resident in China. Dr Tang, with 25 years' experience of similar research, and co-workers had previously conducted similar research with Golden Rice in USA with adults[22] and with children in China with other, non GMO-crop sources of beta-carotene[23]. Only Tang's 2012 research with gmo Golden Rice was criticised by Greenpeace.

As has been mentioned, more than a decade earlier in 2001, Greenpeace had also issued a Press Release in which it was claimed that Golden Rice could not be effective as an intervention against vitamin deficiency as an adult would have to eat at least twelve times the normal intake of 300 grams (eg 3.6 kilograms) of uncooked rice to obtain the daily recommended amount of pro-vitamin A. Clearly in 2012, in the light of Dr Tang results, Greenpeace were highly motivated to discredit her published results, but were unable to substantiate their 2012 allegations.

In 2012 and 2013 IRRI and the Philippines Rice Research Institute ('Phil Rice') planned and set out 5 multi-location field trials as part of the regulatory process for the Golden Rice containing transformation event GR2R. The approximate location of the trials was published on-line, in line with regulations, and also to comply with regulations for GMO-crop trials each location was surrounded by a high fence and patrolled by security guards day and night. On 8th August 2013 one of the (very easy to find) locations was vandalized by anti-GMO demonstrators.

The local authorities recognized that the demonstrators were not farmers, as was claimed and identified leading agitators from known organizations. The Philippine agricultural authorities undertook to track down and prosecute the individuals involved[24]. The destruction of the field trial was soundly condemned by the scientific community[25].

Despite the destruction of the one field trial, sufficient data was collected from the others to suggest that there was a yield drag compared to expected yield of the wild type rice variety. For any trait, especially a consumer trait such as nutritional enhancement, commercial growers expect excellent agronomy. (Government programmes, growing a crop to supply free to the nutritionally disadvantaged may chose different criteria). Normally commercial growers adopt new crop varieties and traits only because of increased profitability, and or ease of cultivation or processing both of which have economic benefits.

In a December 2013 meeting, the IRRI Network Coordinator appeared to recall the issue summarized in his December 2009 slide:"R is in an intron". Further investigation then suggested that the molecular data provided solely to IRRI in 2006, included information concerning both the intron insertion site, and (with only four computer mouse clicks by someone knowledgeable in the field) that the intron involved was Aux1, known since 1999 to be associated with root development (P Beyer, *pers comm*.).

On 15th May 2014 IRRI posted the following information concerning their Golden Rice research on their website: "The first round of MLTs (Multi Location Trials) was conducted using one of the most advanced versions of Golden Rice: GR2 event "R" (GR2-R). This first round took place in 2012-2013 to assess how well this version of Golden Rice would perform in different locations in the Philippines. Preliminary results were mixed. While the target level of beta-carotenein the grain was attained, average yield was unfortunately lower than that from comparable local varieties already preferred by farmers. An important goal of the trials was to test whether the agronomic performance of the new rice variety would be acceptable to farmers. The initial results indicate that more research is needed, with greater focus on increasing yield. Based on these results, a decision has been reached to move forward from work solely focused on GR2-R to also include other versions of Golden Rice, such as GR2-E and others. "…"IRRI and its many research partners remain committed to developing a high-performing Golden Rice variety that benefits farmers and consumers. The important mission of the Golden Rice project, i. e. , to contribute to improving the health of millions of people suffering from micronutrient deficiency, demands that every step and aspect of the scientific study of Golden Rice produces good results. IRRI and all participating organizations will continue to rigorously follow all biosafety and other regulatory protocols in continuing the research to develop and disseminate Golden Rice"[26].

5 What can Golden Rice's development history and trajectory teach us?

Progress from scientific vision, through research to proof of concept, through optimisation of technology, into seed breeding for a staple crop was always going to be challenging. Requiring new biosynthetic pathway engineering, new transformation capability and protocols for Asian rice varieties; for a new field:biofortified crops for micronutrient food security-especially so. And for such an economically, politically and religiously important crop as rice; and with a necessarily international programme across time zones and cultures; and across the normally distinct fields of agriculture and nutrition and sociology, particularly so.

Following the initial research success of the teams of Potrykus and Beyer, an innovative public private partnership amalgamated mutual efforts for differently defined objectives:public—not-for-profit humanitarian applications in developing countries and private—commercial exploitation as 'functional foods' in Europe and North America.

International cooperation was established with very high motivation and excellent communication from all people involved. Velocity was impressive as private sector crop scientists from Japan, Netherlands and UK and then the USA improved the potential for Golden Rice. Nutritional and clinical scientists from the US and China saw the possibilities and wanted to understand the potential. Funding came from the private and the public sector, governments and philanthropy. National, and the international, rice research institutes became involved in the project with enthusiasm to share skills and resources to develop Golden Rice in important locally adapted and preferred rice varieties. All involved understood the importance of achieving the objective of reducing unnecessary human misery for the hundreds of millions suffering from poor diet lacking sufficient source of vitamin A. All involved understood that poverty was the problem, that Golden

Rice couldn't cure poverty, yet could probably assist people to survive it and make better use of their opportunities while poverty itself was addressed by other means.

Right from the first Golden Rice Humanitarian Board meeting in August 2000, and at every subsequent step, scientific progress of research has been shaped and impeded by the regulatory requirements for GMO-crops. Gradually the restraining hand of these regulations developed by country signatories to comply with the hugely overcautious Cartagena Protocol[17], reduced the commercial attractiveness of the project for industrialised countries. Syngenta renounced commercial interest in 2004[20]. The ability of the international co-operators to share Golden Rice seed and pool their seed breeding resources, initially in 2001 accomplished almost as easily for Golden Rice to IRRI as for wheat seed varieties by Normal Borlaugh in the 1960's, was increasingly restricted as the malevolence of the Cartagena Protocol took root in increasingly bureaucratic obligations.

Political activism in the guise of health and environmental concerns took advantage of the suspicion of GMO-crop technology as a proxy for much of the activists discontent with globalisation. The pure vision of the Golden Rice Humanitarian Project became a 'must win' battle for the activists, for their ideology to prevail[5]. As the debate became more intense, some institutional participants became frightened of 'potential liability issues', further eroding willingness to share research materials and further impeding collaborative research and increasingly communication. Most international organisations quietly avoided any funding or association with 'GMO-crops' even those which had clearly huge potential for good, such as Golden Rice.

This impact of the Cartagena Protocol, and it's adoption as the basis of regulation by its many country signatories, is unfortunate:"The [precautionary] principle has long been a major impediment to good sense in public policy. It is either so obvious as to be otiose ("if there is cause for concern, be careful"), or so vague as to be meaningless. But in its most common application—"where an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically"—it has been an invaluable tool for those who want to stop any new scientific development that they dislike"[27].

One of the most insidious anti-scientific impacts of the Cartagena Protocol derived regulations for GMO-crop research is preventing the skills of the plant breeder being able to select useful phenotypes of GMO-crop plants from early in the plant breeding process. This one restriction, unnecessary from any environment or human risk management perspective, delays the delivery of perfect crop varieties incorporating the trait of interest by many years, and increases the cost and complexity of the crops varieties development very significantly.

For all crop breeding, including GMO-crops, development has to involve the traditional skills of crop breeders and selection of plant phenotypes grown in the open field. Only growth of crops in the field, with all the biotic and abiotic stresses involved, allows the breeders to select useful plants, and discard the rest.

6 Conclusion

In 2004 UNICEF and the Micronutrient Initiative published a report at the World Economic Forum in Davos, Switzerland: Vitamin and Mineral Deficiency[28]. It acknowledged that "we are dealing with a global problem of enormous importance that is as yet little recognised". And that vitamin and mineral deficiencies 'debilitates the energies, intellects and economic prospects of 2 billion people and nations'. The report notes that in May 2002 the General Assembly of the UN called for the elimination of vitamin A deficiency by 2010. Vitamin A supplementation is not recommended for children younger than 6 months[1], and very young children do not consume solid food. Yet these children are the most vulnerable to vitamin A deficiency: neonate deaths in 2011 accounted for 43 percent (increased from 36 percent in 1990) of all deaths among under five-year-olds[29]. For breast milk to assist in the alleviation of vitamin A deficiency the mother must not herself be suffering from vitamin A deficiency:she must have adequate body stores of vitamin A. The beta-carotene in Golden Rice has been proven to have excellent bioavailability[4, 22] and "may

Fig.10 Golden Rice plants in the background, and around 100 g of polished Golden Rice grains in the Petri dish (The data suggests that about 40 grams of Golden Rice cooked and consumed daily will safely prevent blindness or death from vitamin A deficiency)

be as useful as a source of preformed vitamin A from vitamin A capsules, eggs, or milk to overcome VAD"[4].

For that half of the world's population where rice is the staple Golden Rice may have an important role in achieving the UN objectives laid out in the early 1990's and still not achieved 25 years later.

It is sad that current global society has to incur the human misery of blindness and death due to delays to advancement of Golden Rice caused by the regulations developed by national governments which are signatories to the UN's Convention on Biodiversity and its Cartagena Protocol, and human and institutional reactions to them. The ideas and concerns upon which the Cartagena Protocol is based were initially debated 50 years ago, and by now have been proved to have no merit. There is no risk from GMO-crops any greater than from crops bred using other technologies. Nevertheless, apart from the direct costs, the regulations feed suspicion of a useful and benign crop breeding development. It is for all these reasons that the Cartagena Protocol for Biosafety is inappropriate for GMO-crops and its effects should be nullified one way or another[17].

With respect to Golden Rice the costs of opposition to GMO-crops in India alone have been calculated at $200 million per year for the past decade[30]. Globally in 2010 vitamin A deficiency killed more children than either HIV/Aids, or TB or malaria[5]—somewhere around 2 million preventable deaths in that one year alone. That is 6 000 preventable deaths, mostly of young children, every single day. The 2004 UNICEF and Micronutrient Initiative report also says:"We have to leave behind old thinking and act in the light of new knowledge". In Golden Rice we have a simple and sustainable additional intervention for vitamin A deficiency with proven potential. The original vision is untrammelled. The "old thinking" we most have to leave behind is the UN's own Cartagena Protocol which is, without benefit, delaying its development.

With continuing patience, and subject to donors not giving up the funding and encouragement of institutional cooperation despite the political barriers erected to prevent it, the inventor's vision will be realised: sometime.

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