The Intellectual and Technical Property Components of pro-Vitamin A Rice (*Golden*Rice™):

A Preliminary Freedom-To-Operate Review

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Introduction

Rice is a staple food for millions of people, predominantly in Asia, but lacks essential nutritional components such as Vitamin A. This is very important for over 180 million children and women of child bearing age who suffer from Vitamin A deficiency in Asia alone. For this reason, an improvement was made under an effort led by Profs. Ingo Potrykus and Peter Beyer by inserting several genes into rice to produce an improved product called "*Golden*Rice™" (on the trademark, see *Note on Trademark and Domain Names* below). Because *Golden*Rice™ has the potential to be easily integrated into the farming systems of the world's poorer regions, the advent of *Golden*Rice™ promises to go a long way towards solving Asia's Vitamin A deficiency problem in an effective, inexpensive, and sustainable way.

Objectives, Limitations and Definitions

As a result of the increasing complexity of the intellectual property (IP) framework under which the international agricultural development community operates, the Rockefeller Foundation funded an ISAAA project to conduct a selective Freedom-To-Operate (FTO) analysis of *Golden*Rice™ with the objectives of:

a. reviewing the IP and Technical Property (TP; or tangible property) components associated with *Golden*Rice™;
b. providing institutions interested in distributing *Golden*Rice™ with the information needed to develop strategic options for handling the proprietary science embedded in the product; and
c. developing possible alternative strategies on how the IP/TP constraints could be managed effectively.

Any FTO opinion is a risk management opinion and its results vary on a country-by-country basis. It is a dynamic opinion; never a definitive answer. Hence the present document serves as an analytical framework that can serve as the basis of a legal FTO review. While it contains information on ownership and statutory protection issues, it is not intended to be a final legal opinion.

In addition, this report is not aimed at commenting on any institution's current IP/TP strategy, but on providing relevant information to make sound policy and strategy decisions. Neither is this study intended to promulgate any particular approach about how to overcome the IP and TP challenges while dealing with the proprietary science of agriculture and plant breeding.

Proprietary Property, or proprietary science, as used throughout this document, is comprised of:

- IP or Intellectual Property, which has been taken to mean, without limitation, intellectual property rights, including patent rights, plant variety protection certificates, unpublished patent applications, and any inventions, improvements, and/or discoveries that may or may not be legally protectable, including all know-how, trade secrets, research plans and priorities, research results and related reports, statistical models and computer programs and related reports, and market interests and product ideas; and
- TP or Technical Property, which has been taken to mean, without limitation, tangible property such as computer software, germplasm and the biological materials and derivatives thereof, and related information.

Results of the Deconstruction of *Golden*Rice™

Under the product deconstruction process of *Golden*Rice™, we reviewed plant/seed source; gene constructs (TP and IP) of cloning vectors pBin19hpc, pZPsC and pZLcyH; transformation, plant regeneration, and other techniques; and DNA amplification technologies.

Technical Property

At least fifteen TP components went into the three different genetic constructs; many of which were acquired by ETH-Zürich under Material Transfer Agreements or by use licenses. Some of this complexity stems from the product being a multi-transformant, in which three genes/enzymes (phytoene synthase, phytoene desaturase, and lycopene cyclase) were introduced in the carotenoid biosynthetic pathway (Figure 1 shows the flow chart of the elements that went into one of the three constructs or plasmids). This required three transformation vectors and the application and use of many other processes and components. For reasons related to the confidentiality embedded in these agreements, we are not providing details of these agreements nor our interpretation of them in this published version of the FTO.

Determining what entity has the right to grant licenses or sub-licenses is a relatively tedious process, one which continually evolves as companies re-structure, sell or assign patents, or grant licenses with or without the right to sub-license. Hence at this stage we only identified the patents according to the original assignee and have not determined which entity would have to be approached for licensing the various components.

Intellectual Property

Depending on the country where the current form of *Golden*Rice™ would be used we identified between zero and 44 patents which applied to the product. In the USA and most countries of the European Union, around 40 patents apply. In the 10 top rice producing countries, many fewer patents apply, namely: China (11), India (5), Indonesia (6), Bangladesh (0), Vietnam (9), Thailand (0), Myanmar (0), Japan (21), the Philippines (1) and Brazil (10). Similarly, in the top ten rice

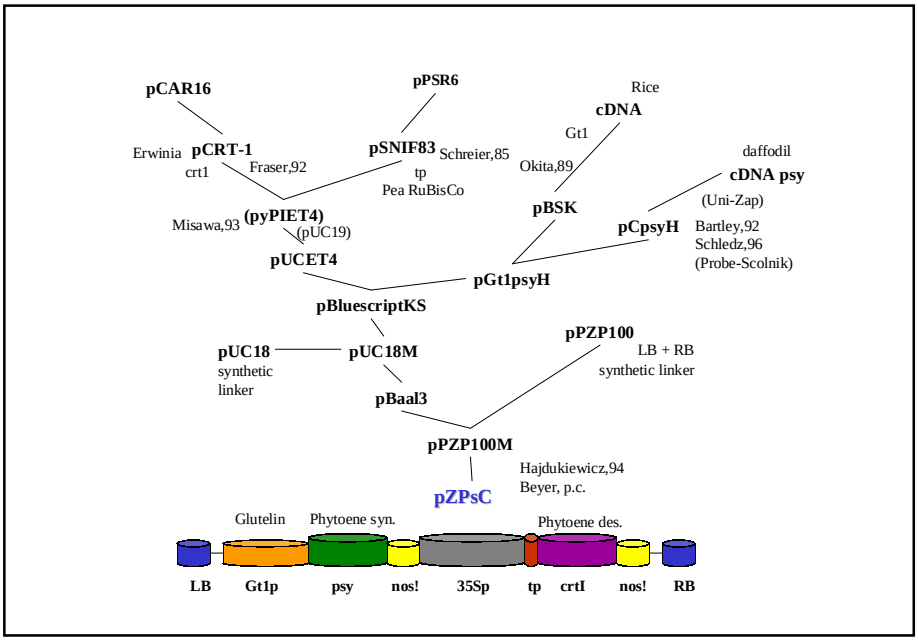

Figure 1. Flow chart of Tangible Property Transfers for pZPsC

importing countries, relatively few patents apply: Iran (0), Brazil (10), Nigeria (0), the Philippines (1), Iraq (0), Saudi Arabia (0), Malaysia (0), South Africa (5), Japan (21) and Côte d'Ivoire (10).

Recognizing that patent claims may be granted for different kinds of inventions, claims may be worded to cover products *per se,* products-by- process, uses, or processes. Whereas the first three types of claims generally extend to the products that embed the new discoveries, "process" claims or claims for the claimed technical procedures do not extend to the products that are produced by the claimed processes. What is of great importance for "process" claims is the country in which the process is applied. If the product is made in a country where those "process" claims have not been issued, then a license for such claimed processes are not required.

A total of 26 of the approximately 70 patents identified in this study contain primarily process claims thus reducing somewhat the number of applicable patents which could inhibit FTO in a given country. A detailed analysis on a country-by-country basis may reduce the complexity of the IP landscape.

Discussion on Alternative IP/TP Management Strategies

Transfer and use of *Golden*Rice™, depending on the country in which it is to be deployed, would, at a minimum, require agreements from a dozen or so entities (public and private) for the TP transfer and use. In addition, again depending on the country of use, between zero and 40 licenses for IP rights would be required, from a dozen or so entities. In total, negotiations with 12 to 20 entities might be required, again depending on the country of release. Noteworthy is that if a regional or international organization, such as the International Rice Research Institute (IRRI), wishes to obtain FTO, say for national use in all developing countries in Asia, licenses for around 30-40 patents would need to be obtained (in addition to the resolution of TP).

All in all, the widespread release of the current version of *Golden*Rice™ will require significant licensing activity if it is to legitimately become available to the world, either commercially or for humanitarian purposes.

We identify and discuss the advantages and disadvantages of six alternative strategies on how to gain FTO for *Golden*Rice™, namely:

1. **Invent around current patents:**
   Research alternative ways to develop pro-Vitamin A rice, generating new inventions.

   This option, which is a science and research based approach, leads to less reliance on other institution's patents but is likely to be very costly and time consuming (if at all feasible). It would arguably not constitute a wise use of development funds.

2. **Re-design constructs**:
   Re-design each construct to reduce number of applicable patents, whenever possible synthesize own genes to reduce reliance on TP of others.

   This strategy, which is a product development based approach, is a likely one as it may be necessary for scientific reasons to re-design the product. It is an effective way to reduce other institution's IP and particularly efficient if an FTO analysis is done prior to initiation of the research. This approach would almost certainly be the approach favored by any company as the TP issues are potentially the most difficult ones to resolve.

3. **IP/TP owners to relinquish claims**:
*All FTO issues for all Golden*Rice™ *related activities, commercial or otherwise, are eliminated through public (or private) statements and related activities by the certified owners/assignees of each set of IP/TP rights for making, having made, using, having used, importing, exporting, selling, and having sold all Golden*Rice™ *plants, plant parts, and all related products and processes. This humanitarian strategy focuses on public perception.*

Some companies (e.g. Zeneca and Monsanto) already publicly declared that they will make their technologies available for *Golden*Rice™. This will greatly simplify licensing negotiations although a royalty-free license may still need to be negotiated, at least for liability/indemnity reasons.

4. **Ignore all IP and TP**:
*All FTO issues for all Golden*Rice™ *related activities, commercial or otherwise, are ignored, and research and product development as well as plans for general distribution proceed.*

This approach is a strategy that certainly has the lowest near-term costs but may lead to long terms costs, especially if a lawsuit ensues, and may lead to the longest delay in product dissemination.

5. **Seek Licenses for all IP and TP:**
*All FTO issues are resolved by the process of any party (individually or through consortia) acquiring an appropriate (commercial or other) license from the certified owners/assignees for each set of IP/TP rights for the Golden*Rice™ *related activities that are of interest to the licensee. This license may be commercial in nature (a grant to make, have made, use, have used, import, export, sell, or have sold all Golden*Rice™ *plants and plant parts and all related products and processes) or a more restrictive one as the licensee and licensor mutually determine to be required.*

This licensing approach is complex and costly, but may lead to stronger public-private relationships whereby corporations are also willing to transfer know-how and future biotechnology inventions. It is also the safest route and ensures good relations with IP owners (be they from the public or private sectors).

6. **Mix of all Options (1 to 5):**
While research and development plans are made to optimize the product, re-design of constructs and acquisition on TP is planned to minimize IP and TP conflicts (OPTION 2); selected FTO issues are removed through public (or private) rescinding of rights by selected holders of certain IP/TP rights (OPTION 3); this "moral high ground" is used to leverage additional rights holders to either rescind their claims (OPTION 3) or to reduce their demands within the context of license negotiations (OPTION 5). In the end all remaining unrescinded IP/TP rights can be either licensed (OPTION 5) or ignored (OPTION 4).

This strategy is again complex from the perspective of IP/TP management but seems to be the most pragmatic and realistic. It capitalizes on the upsides of most of the other options while reducing the risks of future complications.

Discussion on Risk Management Strategies

Developing a sound IP management strategy is, in many ways, primarily a matter of risk management. No one ever definitively knows who has rights to do what with all IP, because new patents are continually being issued, older patents expire and patent-related court settlements take place around the world. All that any organization can do is try to comply with the FTO opinions that they commission, establish protocols to defend (or proactively fight) themselves, and seek whatever licenses they believe that they need to reach their goals.

For international institutions, licensing issues are further clouded because their donors and clients are from many different nations. Thereby the statutory protection laws required for full FTO are as varied as their client list. This leaves such institutions, particularly the centers of the Consultative Group on International Agricultural Research (CGIAR) with the challenge as to whether or not to distribute improved germplasm with full FTO or to pass this responsibility for obtaining FTO along with their improved germplasm, on to the client nation with a caveat regarding these matters.

For the present FTO, we also had to make strategic decisions on how wide a net to cast in terms of listing certain patents where it is not entirely clear whether or not they apply to *Golden*Rice™, and whether or not to include patent applications or only issued patents. We opted to cast a wide net so as to provide those institutions who wish to further develop and distribute *Golden*Rice™ with a broad base of information to make sound risk management decisions. ISAAA, through the Global IP/TT Initiative, can be assisting institutions in developing appropriate and pragmatic IP management options or strategies.

Conclusions

Regardless of which option discussed above or which scenario is chosen, there are a series of tasks that should be completed in order to adequately manage the IP/TP. These are:

1. Complete and regularly update the present FTO analysis, preferably on a country-by-country basis.
2. Develop a scientific strategic plan (who manages, what is to be done, which biotech and germplasm components are to be used, where is the research to be done, who is to do the research, what are the timelines for completion) for finalizing the current scientific initiative.
3. Draft and negotiate a strategic plan for distribution (who manages, what must be licensed, list of licensors/licensees, acceptable terms, timelines) of the finished product(s).
4. Complete a cost/benefit analysis for the preferred options.

It will be for the developing countries, which wish to benefit from *Golden*Rice™ and for the organizations whose mandate is to assist these countries to make choices on the best options to follow. The dominating consideration must be the impact of *Golden*Rice™ on the health and well being of rice producing and consuming populations. These and related factors will condition the speed and configuration of the eventual broad release of *Golden*Rice™.

National Agricultural Research Services, once they obtain access to *Golden*Rice™, may still wish to conduct their own FTO review in order to confirm which IP issues and TP issues are covered in their country. This is particularly true if the recipient country foresees an export market for its *Golden*Rice™. Additionally, any country to which they export their *Golden*Rice™ will likely present a different IP/TP landscape.

Because a preliminary FTO analysis such as this one and a related version done by a patent attorney is dynamic, it is essential that a strategic plan be developed by any entity wishing to develop and disseminate the product in light of an extensive cost/benefit analysis and list of alternative strategies. Resolving the IP and TP issues still provides a formidable challenge to the ultimate release of *Golden*Rice™. We hope that the systematic review, presentation and discussion of the IP and TP situation will lead to sound planning and eventual resolution of the issues. In this way, *Golden*Rice™ will deliver its benefits to both resource-poor farmers and consumers in developing countries and to commercial farmers and related entities. It can become a clear example of how the benefits of genetically modified products can be extended to both developing and developed countries. Sound planning and resolution of the IP/TT issues will contribute to a timely release of this and future essential products for the benefit of all people.

Note on Trademark and Domain Names

ISAAA has filed for a United States Trademark for the words "*Golden*Rice" and "Golden Rice", and for the logo as provided on the cover of this report, and registered the domain names "www.Golden-Rice.com" and "www.GoldenRice.org".

These protections have been sought to ensure that the name *Golden*Rice™ remains in the public domain for the benefit of resource-poor farmers. ISAAA will be pleased to transfer the trademark rights and domain names, at no cost, to a philanthropic, academic, or international development organization who shares a similar mandate in assisting resource poor farmers.

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1.1 Rice Consumption and Vitamin A Deficiency in Asia

Rice is one of the world's oldest cereal crop, and together with wheat and corn, it is one of the core staple cereals worldwide today. Nearly 94% of all the world's rice is grown and consumed on the Asian continent, where it is by far the most important food crop.

While rice is a good source of calories, it lacks essential nutritional components. In particular, rice contains neither Vitamin A nor beta-carotene, which humans can convert into Vitamin A.

Note that the rice endosperm, however, does contain a beta-carotene precursor compound but that the plant is unable to convert the precursor into beta-carotene itself. As a consequence, it is theoretically possible that some landraces of rice may contain beta-carotene.

For children and women of child bearing age, Vitamin A is absolutely essential. Worldwide, nearly 134 million children are at risk for diseases related to Vitamin A deficiency. Some 3.1 million preschool age children suffer from eye damage, and nearly 2 million children under 5 years of age die each year from diseases linked to persistent Vitamin A deficiency. In Southeast Asia alone, 5 million children become at least partially blind every year. In the past, attempts to solve this problem by fortifying rice with Vitamin A have been stymied because of the costs involved and a general lack of infrastructure for efficient distribution in many developing countries. But thanks to the recent efforts of scientists working on this problem, Vitamin A producing beta-carotene can now be genetically added to rice. This invention has the potential to alleviate the suffering of many millions of people, especially those who are too poor to diversify their diets with green vegetables.

The improved product is called "*Golden*Rice™" because of the slightly yellow endosperm resulting from the added beta-carotene. In its current formulation, *Golden*Rice™ could supply more than 10% of an adult's daily Vitamin A requirement. As the technology is further developed and enhanced, *Golden*Rice™ will be able to provide 100% of the daily Vitamin A requirements for adults living in poor regions with high per capita rice intake (110-180 kg per year). Because *Golden*Rice™ can easily be integrated into the farming systems of the poor in these regions, this new variety has the potential to make the greatest impact where it is most needed. The advent of *Golden*Rice™ promises to solve Asia's vitamin A deficiency problem in an effective, inexpensive, and sustainable way.

1.2 Biotechnology Research and the Development of "pro-Vitamin A Rice" (*Golden*Rice™)

Focusing their research and development efforts either on model plants, such as tobacco or *Arabidopsis*, or on commercially important crops such as maize, soybeans, and cotton, biotechnology companies at first had no commercial interest in rice. Instead, rice research was pursued by the public sector. A major international rice biotechnology effort in the early 1980's was initially funded by the Rockefeller Foundation, which has since invested well over US $110 million in rice biotechnology research and capacity building. This has been a most successful scientific investment that trained a large number of scientists from developing countries and led to enabling the transformation of rice.

One of these projects, led by Professor Ingo Potrykus, undertook to determine whether beta-carotene could be added to rice through transformation. A collaborative effort between

the Swiss Federal Institute of Technology (ETH-Zurich) and the University of Freiburg, Germany, allowed scientists to begin their work in the early 1990's. The project received funding from ETH-Zurich itself, the no longer existing European Community Biotechnology Program, and the Rockefeller Foundation.

The research team engineered a *japonica* variety of rice with the three genes (*psy, crt1*, and *lyC*) necessary for the rice grain to produce and store beta-carotene. Two simultaneous transformations were necessary, and this inevitably led to complex plasmid constructs. In fact, the Vitamin A package included two genes from daffodil and a third from a bacterium in order to complete the beta-carotene pathway in rice.

The research group worked with *japonica* rice, which is mainly grown in the temperate zones of East Asia, because the transformation systems for it were well established at the time the original work was done. In the future, the successful transformation events in *japonica* rice may be crossed into *indica* rice either by IRRI or by NARS directly. IRRI is also planning to introduce the genes for beta-carotene synthesis into elite tropical *indica* rice by transformation and evaluation before release to NARS. *Indica* is prevalent in the less favorable ecosystems where many of Asia's poorest people reside.

1.3 The Institutional Context of *Golden*Rice™

Since its inception exactly 40 years ago, the International Rice Research Institute (IRRI) has made incredible strides in meeting the food needs of poor people in developing countries, particularly in Asia. Its main strength has been its ability to freely receive and distribute improved rice germplasm and related information. In fact, this free flow of material and related information has been used by many of IRRI's funding sources to measure performance. Given this success, IRRI management and scientists understandably place a high value on the free exchange of information and material.

By 1990, IRRI launched its own biotechnology unit (although it had practiced tissue culture, isozyme screening, anther culture, and embryo rescue for quite some time). From its inception, IRRI biotechnology researchers sought assistance in the form of materials and related information from outside sources. Nearly all of this assistance included proprietary material comprising Intellectual Property (IP) and Technical Property (TP) rights. When such proprietary material was transferred to IRRI, it was often under restrictive conditions such as material transfer agreements and other sorts of licensing arrangements. Receipt of such protected materials and related information induced IRRI to institute certain restrictions on confidentiality, review its publication procedures, modify its processes for the release of IRRI-held germplasm, and seek a clearer path forward regarding IRRI's use of the progeny of transferred materials and related information for later release to its clients.

With the rapid expansion of plant biotechnology, particularly since the early-1990s, it has become apparent that IRRI's open approach is unlikely to be sustained. For IRRI to ensure that its clients will continue to have access to the best available germplasm, some form of intellectual property protection system may have to be implemented. Accordingly, its historically open and free system of germplasm and information exchange might have to be modified over time, particularly for certain projects and for certain genetic materials produced under those projects. This is partly because the private sector's large R&D investments led to many patents in plant biotechnology—including rice—that are no longer freely available to the international development community. In addition, many public

universities and research institutes are, by necessity, becoming more and more secretive about their research projects and are increasingly seeking intellectual property protection for their own discoveries.

In the mid-1990s, the Consultative Group on International Agricultural Research (CGIAR) also began to study the effect of biotechnology on its plant operations. It set-up two panels. The first focused on how the Centers of the CGIAR could fulfill their international mandate from the scientific and technical perspective. The second focused on the implications of the increasingly proprietary nature of biotechnology. As a result of these deliberations, most of the CGIAR Centers commissioned an IP audit from 1999-early 2000. These audits generally reported on the overall handling of IP by the Centers. To chart a path forward, the Rockefeller Foundation commissioned ISAAA to conduct a preliminary FTO review of the *Golden*Rice™ project for IRRI.

2. Objectives, Limitations and Methodology of the Freedom-to- Operate Review

2.1 Objectives and Purpose

As a result of the increasing complexity of the IP framework under which IRRI, the research collaborators, and the NARS operate, the Rockefeller Foundation commissioned ISAAA for IRRI, to conduct a selective FTO analysis of the transgenic product containing beta-carotene produced by ETH-Zurich. The impetus for the FTO analysis also stems from significant changes in the statutory protection environment in the last decade, particularly in regards to the World Trade Organization's Trade Related Intellectual Property agreement (WTO/TRIPs). IRRI is now seeking to ensure open access to the services and improved products that emanate from its research programs and those of its collaborators.

The objective of the Freedom-To-Operate (FTO) review is to provide IRRI with the information it needs to develop strategic options for handling the proprietary science embedded in the Vitamin-A rice (*Golden*Rice™). This also includes information to enable IRRI the development of strategic options on how best to release such improved products.

IRRI's efforts to reach its goal will be most effective if they are based on all the information available about the ownership of the proprietary and intellectual property that IRRI uses in each step of the development process (see Section 3.1 below). The primary purpose of an FTO review is to identify the owners of such property. Accordingly, this review provides IRRI and the Rockefeller Foundation with a worldwide inventory of patents that apply to specific products and processes that were used in the production of *Golden*Rice™. It also discusses the possible significance of these findings in regards to the proprietary technologies that have been used. In preparing this review, ISAAA has consulted with a retained Attorney specializing in these matters.

The present preliminary FTO is aimed at providing IRRI and any other organization interested in *Golden*Rice™ with a picture of the current situation in terms of ownership issues around the particular rice product. This will allow any organization to decide, based on rational information, what strategy to follow. Thus the report is not aimed at commenting on IRRI's current strategy, nor on recommending a particular strategy, but on providing relevant information to make sound policy and strategy decisions.

2.2 Limitations

Given the ever-changing biotechnology and IP environment in which every plant breeding and biotechnology institution operates today, virtually no transfer of germplasm or research is without some degree of risk. As transgenic strategies begin to dominate crop improvement practices, both the risks and rewards of transferring and releasing products by national programs can be expected to rise.

An FTO opinion is a risk management opinion. It is a document written by an attorney (or for a preliminary FTO, written by paralegal staff and reviewed by an attorney) and is prepared for the purpose of guiding an organization through or around perceived risk (see Section 3 for further details on FTO reviews/opinions). These include aspects related to technical property (such as constructs, plasmids, vectors) and intellectual property (patents on products and processes) that may influence an organization's freedom to enter into the product development phase, or distribute and use the materials derived therefrom. When an FTO is broadened to cover biosafety and other regulatory aspects and obligations, it becomes a Product Clearance (PC) profile.

It should be noted that the FTO opinion, including the information presented in this report:

- varies on a country-by-country basis because most statutory protection is founded in national law, and patents are issued by national governments;
- is dynamic because patent status is dynamic (new patents are issued or expire daily, sold or licensed, disputed or rendered invalid by courts—therefore ownership changes, and the impact of specific claims are constantly changing); and
- is <u>always an opinion</u> and <u>never a definitive answer.</u>

As a consequence, the present paper—as indeed any review of FTO—must be regularly reviewed, updated, and specifically adapted to the country that will receive the material. Similarly, the opinions presented herein are for the sole purpose of assisting any organization that wishes to develop and distribute *Golden*Rice™ in determining its strategy for in-licensing, out-licensing, and material transfer, so that the organization's behavior can be justified should a dispute arise.

2.3 Methodology

Conducting this IP/TP Audit of *Golden*Rice™ required a methodical series of steps. The deconstruction of this product was systematic, utilizing any and all information that could shed light on the product's components and assembly. In sum, these were:

- Scrutiny of the original review article on *Golden*Rice™ (Ye et al. 2000) and several others.
- Discovery of all related and relevant references by searching scientific databases (CAB, BIOSIS, AGRICOLA).
- Careful examination of all related information, including, where available but not limited to, additional articles, project proposals and grant funding agreements.
- Review of employment agreements.
- Examination and construction of the origin and movement of technical property (construction of flow-diagrams of plasmids).
- Patent searches on ISAAA's proprietary patent database and others, such as Micropatent, USPTO, and IBM.
- Patent examination, particularly in regards to claims.
- Construction of an IP/TP spreadsheet.

- Simultaneous examination of all components (i.e., IP/TP scientific commodity), in order to assess the IP/TP landscape.
- Report preparation, including discussion on implications and possible options.

3. Biotechnology Product Management: The Role of Freedom-to-Operate Reviews

3.1 Why Biotechnology Product Management is Important

Reduced to its simplest form, in regards to germplasm development there are only three goal-directed steps by any plant breeding organization, be it a NARS or a center of the CGIAR, or a private company. Beginning with the goal—or the end product—and moving backward, these steps are:

- **Final Step**: Enable the release of improved germplasm and related information (either directly or through third parties);
- **Middle Step**: Develop and produce improved germplasm (intermediary or finished) and related information through scientific and technical "value added" research, processes, and discoveries; and
- **Initial Step**: Conserve, use, and distribute germplasm and information, and obtain information and/or germplasm, and obtain or generate and develop the biotechnology tools and components needed to produce improved (including transgenic) varieties.

More specifically for the Centers of the CGIAR, to reach their goal, the center's strategy has long been to work through various partnerships to include a wider range of collaborators and expertise. One set of collaborators is "downstream" to ensure the delivery of the Center's improved germplasm to farmers through national programs. The other set of "upstream" collaborators strengthens the CGIAR Centers' access to new technologies, particularly biotechnology, through various types of collaborative projects. With time, these may increasingly include the private sector.

There are several reasons to form various types of partnerships with the private sector. Principal among them is that the private sector owns the majority of the pieces required for any of the biotechnological applications that hold so much promise for farmers, particularly in the poorer areas of the developing world. This is irrespective of Monsanto's announcement on April 3, 2000 that it will make its rice genomics information freely available to scientists. Relationships, however, are built on legal arrangements founded on mutual trust, and are nurtured and sustained by the ability of each partner to understand and supply the needs of the other partner. Through the vehicle of agreements, organizations define how they will interact, and all such legal arrangements should be unambiguous to avoid creating confusion and ill will. Furthermore, for any organization to be able to collaborate effectively with private sector organizations, a good understanding of the other side's *needs* and *wants* are important. Only then can costs (monetary or non-monetary) be estimated realistically and the relative value of different alliances compared. Thus, proprietary science rights management issues are both about legal documents and about building, strengthening, and maintaining relationships. In sum, mutual trust and understanding is needed to establish sound legal arrangements, and legal arrangements are needed to maintain trust.

3.2 What is a Freedom-to-Operate Review and How is it Done ?

Much of the material in this section is drawn from ISAAA's Intellectual Property *Virtua*Workshop™ Module,[1] a web-based training course with interactive evaluation and laboratory exercises, glossaries, and template agreements prepared by Dr. Stanley Kowalski of ISAAA.

An FTO opinion refers to the legal opinion regarding IP and TP. It should be conducted as early as possible, even during the conceptualization of a research project. This approach makes it possible to decide in advance which components, technologies, and processes are best incorporated into the product under development and thereby how to reduce or avoid certain IP and TP issues.

To reach FTO opinion, the first step is to create a Product Clearance (PC) profile. The PC process systematically dissects both the product's scientific (acquisition of materials, agreements, and laboratory techniques) and business aspects (biosafety, varietal registration, and distribution status). This "dissection" is referred to as the deconstruction of the product.

Deconstruction can take place when the product is in the planning stage, when development is underway, or when the product is ready for distribution. But it is in any organization's strategic best interest to conduct a deconstruction at the earliest possible phase in product development.

To conduct a deconstruction four key questions have to be asked:

- What are the methods and procedures that went into product development?
- What are the components of the product?
- What are the ingredients that constitute each component?
- What are the IP and TP rights that may be attached to these components and their ingredients?

As new patents are issued or old ones expire, as companies merge, and as public and private sector organizations alike license or assign certain rights to patents, the IP landscape for any product evolves and changes. Hence FTOs and PCs are developed in a fluid, dynamic environment. The timely initial PC determination and development of FTO opinions are only steps in an ongoing process that must be regularly updated. With 50-100 new plant biotechnology patents and applications issued each month, as well as numerous patents expiring, regular monitoring and updating of PC files is essential.

The preparation and content of a product profile can be easily illustrated using a loaf of bread as an example: "We can list the generic ingredients used to make the bread (flour, liquid, yeast, salt, and shortening) and the generic technologies (sifting, mixing, kneading, baking, slicing, and packaging) used to assemble the ingredients and to manufacture the bread. Each ingredient in the profile can be specified more precisely. We can indicate whether the flour is soy, corn, or wheat, whether a wheat flour is whole wheat, or enriched, bleached, and whether the liquid is water, milk, or beer. Similarly, the technologies can be defined in greater detail. The completed product profile then represents the entirety of the bread's construction" (Duesing, 1997).

[1] The entire Intellectual Property VirtualWorkshop™ , prepared by a number of experts from around the world, is accessible upon subscription. One module, entitled "How to draft a Confidentiality Agreement?" can be viewed by visiting www.isaaa.org/ip.html.

Of course, the biotechnological products will be considerably more complex than a loaf of bread, and will require a much more sophisticated repertoire of knowledge, skills, and resources. Above all, however, clear, organized records detailing all of the procedures, components, material transfers, and agreements that went into the product undergoing deconstruction must be in place. In this context, a laboratory notebook is a critical management tool for later reference during the FTO process.

In addition to uncovering useful scientific terminology (see also Section 3.2.3 below), a search of the scientific databases will also yield publication dates, authors, and affiliated institutions pertaining to key scientific papers. All of these can also be utilized in a patent search. Useful scientific databases for searching agricultural biotechnology and related topics are:

- BIOSIS - http://www.biosis.org/
- CAB International - http://www.cabi.org/
- AGRICOLA - http://www.nalusda.gov/ag98/
- Current Contents Connect© - http://www.isinet.com/

In order to determine relevant patents associated with the product under deconstruction, the next step is to search the patent databases. These databases could include, among others:

- IBM Intellectual Property Network - http://www.patents.ibm.com/ibm.html
- MicroPatent© - http://www.micropat.com/
- European Patent Office - http://ep.espacenet.com/
- US Patent and Trademark Office - http://www.uspto.gov/patft/index.html

Most major companies have their own attorneys, and scientists review each and every biotech patent issued and annotate them in their own proprietary databases[2]. Since each database has distinctive, salient features, it is a good strategy to combine and integrate different databases in a comprehensive search, since this combination will produce a broad and thorough result. It also serves to cast the widest net possible for identifying all possible relevant patents.

Searching out TP involves a different strategy. To discover who obtained what from where, when, and how is the heart of the TP search. Obviously, databases are not available for this. Extensive networking is the way to proceed with all scientists who worked on the product. The objective is to discover, uncover, and obtain copies of any and all material transfer, licensing or "notice to purchaser" agreements, as well as grant proposals, funding agreements, employment agreements, and confidentiality agreements.

4. Deconstruction of the *Golden*Rice™ Product

4.1 Overview

The product deconstruction of *Golden*Rice™ was complex. It yielded over fifteen tangible property components and approximately seventy patents and related IP that seem to have been integral to the product's development. Some of this complexity stems from the product being a multi-transformant, in which three genes/enzymes (phytoene synthase, phytoene desaturase, and lycopene cyclase) were introduced in the carotenoid biosynthetic pathway. This required three transformation vectors (pBin19hpc, pZPsc and pZLcyH) along with the application and

[2] ISAAA has obtained such a truncated database from a donor for ISAAA use. That database was used for this present FTO, among others.

use of many other processes and components (e.g., *Agrobacterium*-mediated co-transformation).

Table 1 (Product Clearance Profile) presents a summary of the relevant patents that were identified and that are potentially applicable to the *Golden*Rice™ product. It lists these patents according to the original assignee. Note that although a company may have acquired another company by purchase or some other manner (e.g., DuPont's purchase of Pioneer Hi-Bred International Inc. in 1999), the ownership of certain IP and TP may be retained by the acquired company. In this case, from an FTO point of view, licenses may have to be obtained from Pioneer rather than DuPont. Determining what entity has the right to grant licenses is a relatively tedious process, one which continually evolves as companies re-structure, sell or assign patents, or grant licenses with or without the right to sub-license. The present study did not determine which entity would have to be approached for licensing certain components.

Table 1: Product Clearance Profile: Possible Required Licenses and/or Agreements for Golden*Rice*™

Name of Institution	Possible Applicable Patents
1. AMOCO	US5545816, EP0471056, US5530189, WO9113078, US5530188, US5656472
2. Bio-Rad Inc.	US5186800
3. Biotechnica	WO8603516
4. Calgene	WO9907867, WO9806862
5. Centra National de la R.S.K.	WO9636717
6. Cetus	WO8504899, US4965188, EP0258017
7. Columbia Univ. of New York	US4399216, US4634665, WO8303259
8. DuPont	WO9955889, WO995588, WO9955887
9. Eli Lilly	US5668298
10. Hoffman-La-Roche	US4683202, EP0509612, EP0502588, US4889818
11. ICI, Ltd.	WO9109128,
12. Japan Tobacco	EP0927765, US5591616, EP0604662, EP0672752, US5731179, EP0687730, WO9516031
13. Kirin Brewery	JP3058786, US5429939, US5589581, EP0393690, US5350688
14. Life Technologies	
15. Max Planck Gesell.	EP0265556, EP0270822, EP0257472
16. Monsanto	US5352605, US5858742, WO8402913
17. National Foods RI	JP63091085
18. N.R.C. Canada	WO9419930
19. Novartis AG	
20. Nederlandse O.V.T.	EP0765397, WO9535389
21. Phytogen	US4536475
22. Plant Genetic Systems	US5717084, US5778925, WO8603776, WO9209696
23. Promega	US4766072
23. Rhone-Poulenc Agro	USRE36449, WO9967357
24. Rutgers University	
25. Stanford University	US4237224
26. Stratagene	US5128256, US5188957, US5286636, EP0286200, WO880508
27. University of Maryland	WO9963055
28. University of California	US4407956, WO9916890
29. Washington State University	
30. Yissum R.D.C.	US5792903, EP0820221, WO9628014
31. Zeneca Corp.	US5750865, EP0699765A1

Note that these are the names of the owners or assignees of the rights under the relevant patents. Because of possible subsequent licensing or assignment, these are not necessarily the current entities to approach for licenses.

Table 2 lists the tangible property received by ETH-Zurich, including the apparatuses used in the transformation. Some components were obtained under research-only licenses or research only material transfer agreements (MTA), whereas others included use licenses. For reasons related to maintaining a certain level of confidentiality embedded in these agreements, we are not providing details of these agreements nor our interpretation of them in this published version of the FTO.

It should be noted that the absence of an MTA does not necessarily mean that no restrictions apply to the further use or transfer of a particular piece of tangible property. In fact, the absence of an MTA or license may signal the need for greater caution when proceeding with the release of *Golden*Rice™.

4.2 Movement of Tangible Property

The development of the product also led to a number of material transfers. Figures 1, 2, and 3 present the flow of material for each plasmid that went into *Golden*Rice™.

As with most transformated plant products, a number of events were produced with each of different constructs (see Table 1, 2 and 3). This present analysis is based on ISAAA's review of published research papers and various interviews.

4.3 Intellectual Property Analysis: Deconstruction of the Components

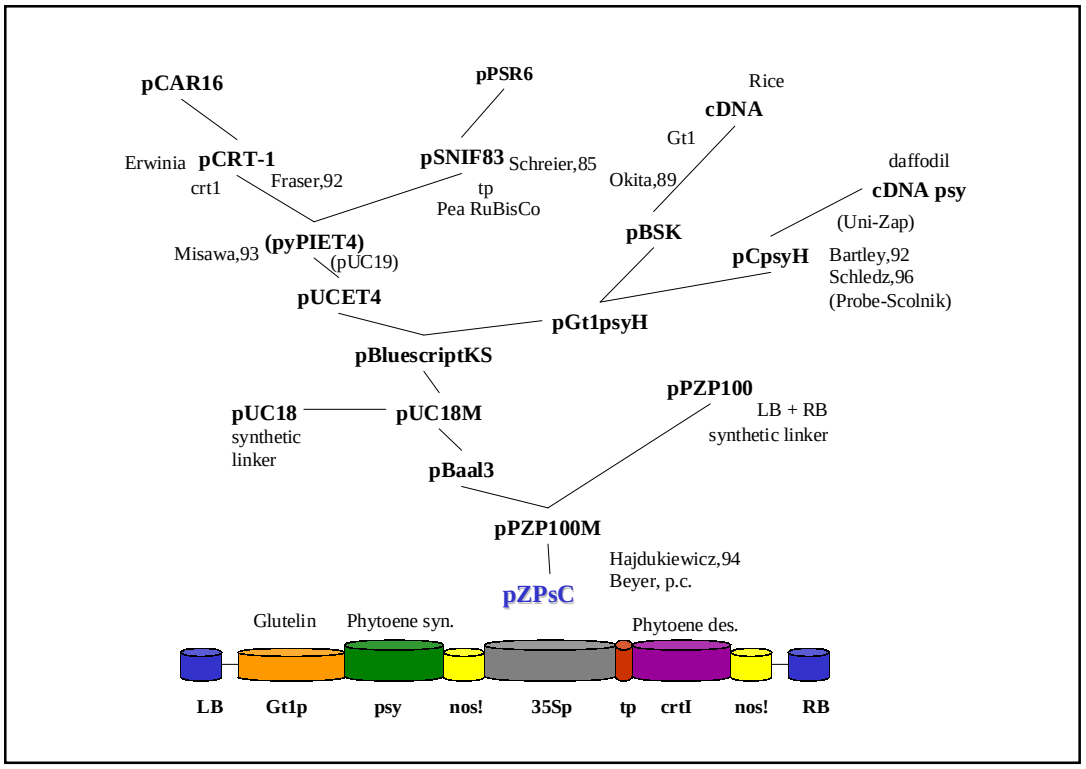
The detailed analysis of the intellectual and tangible property of each component used to produce *Golden*Rice™ led to the Product Clearance Spreadsheet (Table 3); the summary of which had been given as the PC profile (see Table 1). The comprehensive analysis of the deconstruction process is presented under four major categories:

1. Plant/seed source
2. Gene constructs (cloning vectors):
   - The plant transformation vector, pBin19hpc
   - The plant transformation vector, pZPsc
   - The plant transformation vector, pZLcyH
3. Transformation, plant regeneration, and other techniques
4. DNA amplification.

Table 2: MTAs, Licenses, Documents and Agreements Relevant to Golden*Rice™*

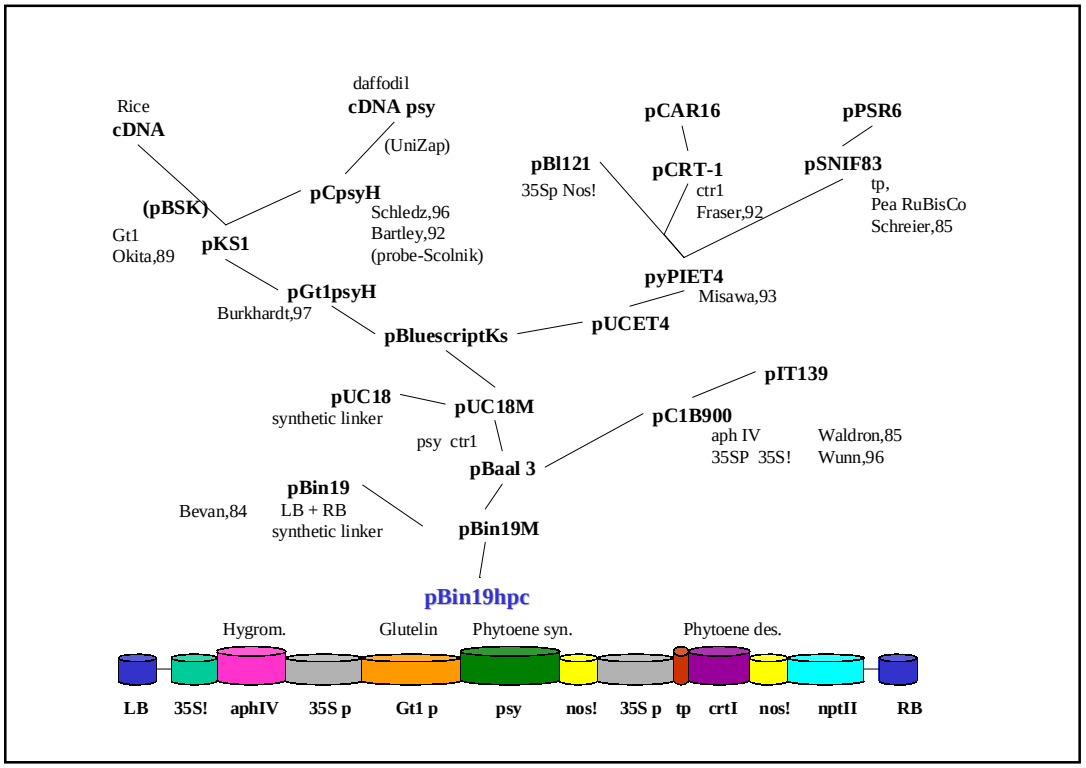
Product Component	Source of component
1. Rice germplasm transformed with gene construct(s)	Taipei 309, obtained from IRRI
2. PGEM4	Promega
3. PbluescriptKS	Stratagene
4. PCIB900	Ciba-Geigy Limited (now Novartis Seeds AG)
5. Camv35S Promoter (component of pCIB900)	Monsanto
6. Camv35S Terminator (component of pCIB900)	Monsanto
7. AphIV gene: hygromycin Phosphotransferase (component of pCIB900)	Ciba-Geigy Limited (now Novartis Seeds AG)
8. PKSP-1	Thomas Okita, Washington State University
9. GT1 Promoter: glutelin storage protein (component of pKSP-1)	Thomas Okita, Washington State University
10. PUCET4	N. Misawa, Kirin Brewery Co., Ltd.
11. Pea Rubisco transit peptide (component of pUCET4)	N. Misawa, Kirin Brewery Co., Ltd
12. CrtI gene: phytoene desaturase (component of pUCET4)	N. Misawa, Kirin Brewery Co., Ltd
13. PPZP100	Pal Maliga, Rutgers University
14. pYPIET4	Clontech, but now marketed by Life Technologies
15. Electroporation Apparatus	Bio-Rad Corp., Gene Pulser II System
16. Miroprojectile Bombardment Apparatus	Bio-Rad Corp.

Figure 1. Flow chart of Tangible Property Transfers for pZPsC



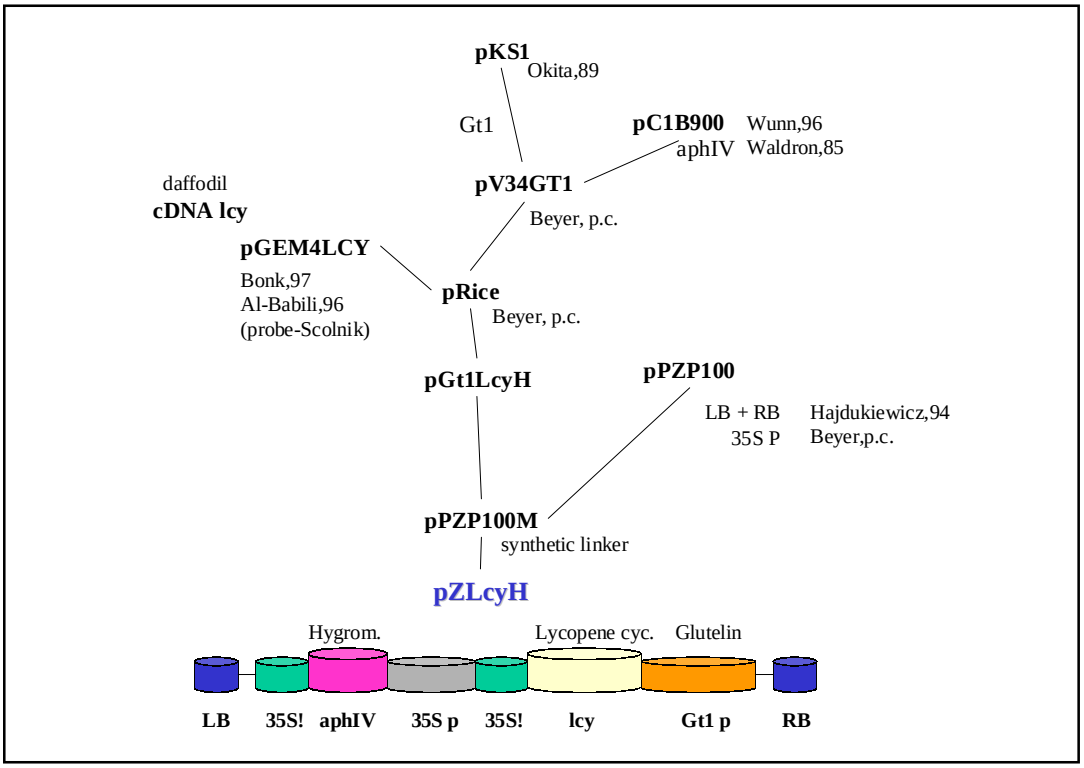
Source: Compiled by Maria Jose Amstalden Sampaio while on an IP Management training internship with ISAAA. For references quoted, see list of references at the end of this document.

Figure 2. Flow chart of Tangible Property Transfers for pBin19hpc



Source: Compiled by Maria Jose Amstalden Sampaio while on an IP Management training internship with ISAAA. For references quoted, see list of references at the end of this document

Figure 3. Flow chart of Tangible Property Transfers for pZLcyH



Source: Compiled by Maria Jose Amstalden Sampaio while on an IP Management training internship with ISAAA. For references quoted, see list of references at the end of this document

These four categories are further expanded into 43 sub-categories yielding over 70 US and ex-US patents that appear to comprise the intellectual property rights of this version of *Golden*Rice™. Fifteen instances of tangible property rights connected to the development of the product were also identified, (See Section 4.2 above), and those rights are summarized and included in Table 1.

Please refer to Table 3 at the end of this Section for the entire Product Clearance Spreadsheet.

4.3.1 Plant/Seed Source

The transformed rice line, TP 309 (Taipei 309), a japonica rice, was obtained by ETH-Zurich from IRRI in the mid-1980s without any known information or conditions that IRRI may have attached at that time.

4.3.2 Gene Constructs (cloning vectors)

Both pGEM4 (Promega) and pBluescriptKS (Staratagene) were used in the production of *Golden*Rice™. The vector pGEM4 was critical to the generation of pZLcyH and the vector pBluescriptKS was critical to the generation of pBin19Hpc.

4.3.2.1 The plant transformation vector, pBin19Hpc

pBin19Hpc is a highly complex construct, with a wide range of components that are potentially covered by numerous patents and MTAs:

- Plant gene promoters identified as Camv35S as used in this construct is covered by patents held by Monsanto Company in the US and certain other countries.

- The Gt1 promoter may be covered by patents held by The University of California and the National Foods Research Institute (Japan).
- The *nptII* (kanamycin resistance) marker may be covered under a patent held by Japan Tobacco.
- The pea Rubisco Small subunit transit peptide may be covered by patents held by Plant Genetic Systems and Rhone-Poulenc Agro.
- The *aphIV* marker (hygromycin resistance) may be covered by patents held by Eli Lilly.
- The *psy* (phytoene synthase) gene may be covered by patents held by Amoco, DuPont, Zeneca, Kirin Brewery, and ICI.
- The *crtI* (phytoene desaturase) gene may be covered by patents held by Amoco Corp. and DuPont Corp.

4.3.2.2 The plant transformation vector, pZPsc

pZPsc is another highly complex construct, with a wide range of components that are potentially covered by numerous patents and MTAs:

- Plant gene promoters identified as Camv35S as used in this construct is covered by patents held by Monsanto Company in the US and other countries.
- The Gt1 promoter may be covered by patents held by The University of California and the National Foods Research Institute (Japan).
- The pea Rubisco Small subunit transit peptide may be covered by patents held by Plant Genetic Systems and Rhone-Poulenc Agro.
- The *psy* (phytoene synthase) gene may be covered by patents held by Amoco, DuPont, Zeneca, Kirin Brewery, and ICI.
- The *crtI* (phytoene desaturase) gene may be covered by patents held by Amoco and DuPont.

4.3.2.3 The plant transformation vector, pZLcyH

pZLcyH is a highly complex construct, with a wide range of components that are potentially covered by numerous patents and MTAs:

- Plant gene promoters identified as Camv35S as used in this construct is covered by patents held by Monsanto Company in the US and other countries.
- The Gt1 promoter may be covered by patents held by The University of California and the National Foods Research Institute (Japan).
- The pea Rubisco Small subunit transit peptide, may be covered by patents held by Plant Genetic Systems and Rhone-Poulenc Agro. It was provided by Kirin Brewery Co., Ltd.
- The *aphIV* marker (hygromycin resistance), may be covered by patents held by Eli Lilly.
- The *lcy* (lycopene cyclase) gene, may be covered by patents held by Kirin Brewery, Amoco Corp., Yissum RDC, University of Maryland, Centra National de al Recherche Scientifique, and DuPont Corp.

4.3.3 Transformation vectors, techniques, and plant regeneration

The intellectual property landscape in transformation vectors, techniques, and regeneration is also quite complex, with numerous patents having potentially overlapping claims.

- *Agrobacterium* transformation (general) is connected to a considerable array of potentially applicable patents, with assignees such as Max Planck Gesellschaft, Cetus Corp., Biotechnica Int., Inc., among others.[3]

[3] Note that here is a four-way patent litigation involving the *Agrobacterium* transformation system and precise ownership cannot be established at this stage.

- *Agrobacterium* transformation (monocots) is likely to be connected to a series of patents, with assignees such as Max Planck Gesellschaft, Japan Tobacco Inc., and the NRC of Canada.
- Co-transformation technique may be covered by several patents, both in general terms, with the patent assignee being Columbia University, and in more specific terms (i.e, as in co-transformation of monocots), with the patent assignee being Japan Tobacco, Inc.
- Rice regeneration technology is patented, with the NRC of Canada and Kirin Beer Corp. of Japan as assignees. These patents may apply to the *Golden*Rice™ product.

4.3.4 DNA amplification

PCR was not used in the construction of the expression cassettes at ETH-Zurich but the possibility that PCR was used in the construction of one of the components and/or other up-stream vectors remains a possibility. We did not investigate this further. We decided, however, at least for informational purposes, to include in the list the fundamental PCR and Taq polymerase patents, whose original assignees are Cetus Corp. and Hoffman-La Roche. Note that recent court determinations may change the enforcement of these patents in certain areas and may involve Promega Corp. in the final decisions.

Table 3. Product Clearance Spreadsheet for *Golden*Rice™

1. Plant source		Primary Patent Details						
		Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
Common name	rice							
Scientific name	*Oryza sativa*							
Variety	TP 309 (Taipei 309) *japonica*	IRRI						
Pedigree	IRGC Acc. # 42576							

Note that in the USA, the term of a utility patent depends on when the patent application was filed. If the patent issued from an application filed prior to June 8, 1995, the term is the later of (1) 17 years from the date if issuance of the patent, or (2) 20 years from the first U.S. filing date for the patent. If the patent issued from an application filed on or after June 8, 1995, then the term is 20 years from the first U.S. filing date for the patent. For further information, see http://www.patents.com/patents.

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

2. Gene construct (cloning vectors)	Primary Patent Details						
	Source	**Patent no.**	**Title**	**Inventor(s)**	**Assignee**	**Filing date**	**Issue date**
Promega Corp.: pGEM4 was used in the construction of pGt1lcyH (below)		US4766072	Vectors for in vitro production of RNA copies of either strand of a cloned DNA sequence.	Jendrisak et al.	Promega Corp.	17-Jul-85	23-Aug-88
Stratagene Corp.: pBluescriptKS was used in the construction of pBaal3 (below), and also for the construction of the cDNA library rot the isolation of *psy* and *lcy* (below).		US5128256	DNA cloning vectors with in vivo excisable plasmids.	Huse et al.	Stratagene	20-Apr-89	7-Jul-92
		US5188957	Lambda packaging extract lacking beta-galactosidase activity	Short and Kretz	Stratagene	26-Feb-91	23-Feb-93
		US5286636	DNA cloning vectors with in vivo excisable plasmids.	Huse et al.	Stratagene	21-May-92	15-Feb-94
		EP0286200	DNA cloning vectors with in vivo excisable plasmids.	Sorge et al.	Stratagene	12-Jan-88	12-Oct-88
		WO8805085	DNA cloning vectors with in vivo excisable plasmids.	Huse et al.	Stratagene	12-Jan-88	14-Jul-88

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

3. pBin19hpc		Primary Patent Details					
	Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
	CAMV 35S Promotor	US4407956	Cloned cauliflower mosaic virus DNA as a plant vehicle	Howell	The Regents of the University of California	13-Mar-81	4-Oct-83
		US5352605	Chimeric genes for transforming plant cells using viral promoters	Fraley et al.	Monsanto Co.	28-Oct-93	4-Oct-94
		US5858742	Chimeric genes for transforming plant cells using viral promoters	Fraley et al.	Monsanto Co.	24-Jun-96	12-Jun-99
		WO8402913	Chimeric genes suitable for expression in plant cells	Fraley and Rogers	Monsanto Co.	16-Jan-84	2-Aug-84
	35S Terminator	None found					
	Gt1 Promotor	JP63091085	Rice glutelin gene and preparation thereof	Fukazawa Res Inst	Natl Food	6-Oct-86	21-Apr-88
		WO9916890	Production of proteins in plant seeds	Lemaux et al.	Univ. of CA	30-Sep-98	8-Apr-99
	nos terminator	None found					
	transit peptide	US5717084	Chimaeric gene coding for a transit peptide and a heterologous peptide	Herrera-Estrella et al.	Plant Genetic Systems N.V., Bayer A.G.	6-Jun-95	10-Feb-98
		US5728925	Chimaeric gene coding for a transit peptide and a heterologous polypeptide	Herrera-Estrella et al.	Plant Genetic Systems N.V., Bayer A.G.	28-Apr-95	17-Mar-98
		USRE36449	Chimaeric gene for the transformation of plants	Lebrun et al.	Rhone-Poulenc Agro	17-Feb-98	14-Dec-99

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

		Primary Patent Details						
3. pBin19hpc		**Source**	**Patent no.**	**Title**	**Inventor(s)**	**Assignee**	**Filing date**	**Issue date**
		npt II	EP0927765	Method for selecting transformed cells	Komari	Japan Tobacco Inc.	23-Jul-98	7-Jul-99
		aph IV	US5668298	Selectable marker for development of vectors and transformation systems in plants	Waldron	Eli Lilly and Co.	7-Jun-95	16-Sep-97
	psy (phytoene synthase)	The heterologous probe tomato *psy1* was provided by Pablo Scolnik, DuPont Corp., with no MTA. P.Beyer, p.c.	US5545816	Phytoene biosynthesis in genetically engineered hosts	Ausich et al.	Amoco Corp.	19-Jul 93	13-Aug 96
			US5705624	DNA sequences encoding enzymes useful in phytoene biosynthesis	Fitzmaurice et al.	N/A	27 Dec 95	6 Jan98
			US5750865	Process for modifying the production of carotenoids in plants, and DNA, constructs and cells therefor	Bird et al.	Zeneca Ltd.	2 Sep 94	12 May98
			EP0471056	Biosynthesis of carotenoids in genetically engineered hosts	Ausich et al.	Amoco Corp.	4 Mar 91	19 Feb 92

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

3. pBin19hpc		Primary Patent Details						
		Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
			JP3058786	DNA strand useful for synthesis of carotinoid	Misawa et al.	Kirin Brewery Co. Ltd.	5 Mar 90	13 Mar 91
			WO9109128	DNA, constructs, cells and plants derived therefrom	Bird et al.	Imperial Chemical Industries PLC	10 Dec 90	27 Jun 91
			WO9806862	Methods for producing carotenoid compounds and speciality oils in plant seeds	Shewmaker	Calgene LLC	8-Aug-97	19-Feb-98
			WO9955889	Carotenoid bio-synthesis enzymes	Cahoon et al.	E. I. Du Pont Nemours and Co.	22 Apr 99	4 Nov 99
	crtI (phytoene desaturase)	Misawa/ Kirin Brewery	US5530189	Lycopene biosynthesis in genetically engineered hosts	Ausich et al.	Amoco Corp.	22 Jul 93	25 Jun 96
			WO9113078	Biosynthesis of carotenoids in genetically engineered hosts	Ausich et al.	Amoco Corp.	4 Mar 91	5 Sep 91
			WO9955888	Carotenoid bio-synthesis enzymes	Cahoon et al.	E. I. Du Pont Nemours and Co.	21 Apr 99	4 Nov 99

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

3. pBin19hpc		Primary Patent Details						
		Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
plasmid sources:								
pBin19, pBin 19m	pUC derivative plasmid: public domain?	Mike Bevan						
pBaal3	pUC derivative plasmid: public domain?							
pCIB900		Plasmid pCIB900: source of the hygromycin phosphotransferase marker (*aph* IV). Obtained from M. Koziel and N. Carozzi, Ciba-Geigy, R.T.P., NC, USA.						
pUC18, pUC18m	pUC derivative plasmid: public domain?							
pBluescriptKS	US, World and EU patentsmay be applicable, please see above.	Stratagene (see above for relevant IP and TP connections)						

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

3. pBin19hpc		Primary Patent Details						
		Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
Pgt1PsyH	Pgt1PsyH was derived from the plasmid pKS1 (T. Okita). pKS1 is a derivative of Stratagene's Bluescript plasmid (above).	The rice glutelin 1 promoter (Gt1) was obtained from T. W. Okita, Washington State University.						
pUCET4	pUC derivative plasmid: public domain?							
pYPIET4	pYPIET4 (N. Misawa) was derived from the binary plant expression vector pBI121,purchased from Clontech Laboratories, now marketed by Life Technologies.	Plasmid pYPIET4: source of *crtI* linked to the transit peptide sequence of the pea Rubisco small subunit (*tp*). Obtained from N. Misawa of the Kirin Brewery Co., Ltd., Yokohama , Japan. Misawa obtained *tp* from J. Schell, Max-Planck-Institut.						

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

4. pZPsc		Primary Patent Details						
		Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
components:								
	35S Promotor			See above				
	35S Terminator			See above				
	Gt1 Promotor			See above				
	nos terminator			See above				
	transit peptide			See above				
	psy (phytoene synthase)			See above				
	crtI (phytoene desaturase)			See above				
plasmid sources:								
pPZP100, pPZP100m	Agrobacterium binary vector, contains chloramphenicol resistance gene (*cmr*).	Paul Maliga laboratory						
pBaal3	pBaal3 is derived from: pYPIET4, pUCET4, Pgt1PsyH, pBluescriptKS, pUC18, pUC18m, pCIB900. Refer to pBin19hpc (above) for relevant details attached.							

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

5. pZLcyH		Primary Patent Details						
		Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
components:								
	35S Promotor			See above				
	35S Terminator			See above				
	Gt1 Promotor			See above				
	aph IV			See above				
	lcy (lycopene cyclase)	A hetero-logous probe from *Arabidopsis thaliana* was provided by Pablo Scolnik, DuPont, with no MTA. P.Beyer, p.c.	US5429939	DNA sequences useful for the synthesis of carotenoids	Misawa et al.	Kirin Beer Kabushiki Kaisha	23 Oct 91	4 Jul 95
			US5530188	Beta-carotene biosynthesis in genetically engineered hosts	Ausich et al.	Amoco Corp.	21 Jul 93	25 Jun 96
			US5589581	DNA sequences useful for the synthesis of carotenoids	Misawa et al.	Kirin Beer Kabushiki Kaisha	10 Mar 94	31 Dec 96
			US5656472	Beta-carotene biosynthesis in genetically engineered hosts	Ausich et al.	Amoco Corp.	7 Jun 95	12 Aug 97
			US5792903	Lycopene cyclase gene	Hirschberg et al.	Yissum RDC Jerusalem, Univ. of MD	7 Mar 95	11 Aug 98
			EP0393690	DNA sequences useful for the synthesis of carotenoids	Misawa et al.	Kirin Beer Kabushiki Kaisha	20 Apr 90	24 Oct 90

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

5. pZLcyH

Source	Primary Patent Details					
	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
	EP0699765	DNA, constructs, cells and plants derived therefrom	Bird et al.	Zeneca Ltd.	10 Dec 90	6 Mar 96
	EP0820221	Lycopene cyclase gene	Hirschberg et al.	Yissum RDC Jerusalem	5 Mar 96	28 Jan 98
	WO9628014	Lycopene cyclase gene	Hirschberg et al.	Yissum RDC Jerusalem	5 Mar 96	19 Sep 96
	WO9636717	DNA sequences encoding a lycopene cyclase, antisense sequences derived therefrom and their use for the modification of carotenoids levels in plants	Kuntz	Centre National de la Recherche Scientifique Kuntz	17 May 96	21 Nov 96
	WO9907867	Methods for producing carotenoid compounds and speciality oils in plant seeds	Shewmaker	Calgene LLC	6 Aug 98	18 Feb 99
	WO9955887	Carotenoid biosynthesis enzymes	Cahoon et al.	E. I. Du Pont Nemours and Co.	16 Apr 99	4 Nov 99
	WO9963055	Genes of carotenoid biosynthesis and metabolism and methods of use thereof	Cunning-ham and Sun	Univ. of MD	2 Jun 99	9 Dec 99

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

5. pZLcyH		Primary Patent Details					
		Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
plasmid sources:								
pPZP100, pPZP100m	Agrobacterium binary vector, contains chloramphenicol resistance gene (*cmr*).	Paul Maliga laboratory						
pGT1LcyH	Consturct contains: *lcy*, *aphIV* expression cassettes.	Original source of components in pGT1LcyH still need to be determined. The lcy gene is likely from Beyer.						
pKS1	see under Pgt1PsyH above	See Stratagene above						
pCIB900	see above							
pGEM4LCY		See Promega above						

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

6. Transformation vectors, techniques, plant regeneration	Primary Patent Details						
	Source	**Patent no.**	**Title**	**Inventor(s)**	**Assignee**	**Filing date**	**Issue date**
Agrobacterium tumefaciens LBA4404	Obtained from Barbara Hohn's labroatory, originally from Hookaas' laboratory (Netherlands)						
Agrobacterium mediated transformation/ vectors (general)		US4536475 EP0265556	Plant Vector Stable binary agrobacterium vectors and their use	Anderson Leemans et al.	Phytogen Max Planck Gesellschaft (DE)	5 Oct 82 31 Oct 86	20 Aug 85 4 May 88
		EP0270822	Stable binary agrobacterium vectors and their use	Leemans and Deblaere	Max Planck Gesellschaft (DE)	30 Oct 87	15 Jun 88
		WO8504899	Methods and vectors for transformation of plant cells	Gelfand and Barton	Cetus Corp.	16 Apr 85	7 Nov 85
		WO8603516	Plant transformation vector	Buchanan and Cannon	Biotechnica Int. Inc.	13 Dec 85	19 Jun 86

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

6. Transformation vectors, techniques, plant regeneration	Primary Patent Details						
	Source	**Patent no.**	**Title**	**Inventor(s)**	**Assignee**	**Filing date**	**Issue date**
Agrobacterium mediated transformation/ vectors (monocotyledons)		US5591616	Method for transforming monocotyledons	Hiei and Komari	Japan Tobacco Inc.	3 May 94	7 Jan 97
		EP0257472	Transgenic monocotyledonous plants, seeds, therof and process for the preparation of the plants	De La Pena et al.	Max Planck Gesellschaft (DE)	13 Aug 87	2 Mar 88
		EP0604662	Method for transforming monocotyledon	Hiei and Komari	Japan Tobacco Inc.	6 Jul 93	6 Jul 94
		EP0672752	Method of transforming monocotyledon by using scutellum of immature embryo	Saito et al.	Japan Tobacco Inc.	1 Sep 94	20 Sep 95
		WO8603776	Process for preparing genetically stably transformed monocotyledonous plant cells	Hernalsteens et al.	Plant Genetic Systems N.V.	20 Dec 85	3 Jul 86
		WO9209696	Process for transforming monocotyledonous plants	D'Halluin and Gobel	Plant Genetic Systems N.V.	21 Nov 91	11 Jun 92
		WO9419930	Enhanced regeneration system for cereals	Nehra et al.	NRC of Canada	10 Mar 94	15 Sep 94
		WO9967357	Agrobacterium-mediated transformation of monocots	Dong et al.	Rhone-Poulenc Agro	22 Jun 99	29 Dec 99

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Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

6. Transformation vectors, techniques, plant regeneration	Primary Patent Details						
	Source	**Patent no.**	**Title**	**Inventor(s)**	**Assignee**	**Filing date**	**Issue date**
Co-transformation technique: Two non-linked plasmids transformed simultaneously.		US4399216	Process for inserting DNA into eucaryotic cells and for producing proteinaceous materials.	Axel et al.	The Trustees of Columbia Univ. in the City of New York	25 Feb 80	16 Aug 83
		US4634665	Process for inserting DNA into eucaryotic cells and for producing proteinaceous materials.	Axel et al.	The Trustees of Columbia Univ. in the City of New York	11 Aug 83	6 Jan 87
		WO8303259	Method for introducing cloned, amplifiable genes into eucaryotic cells and for producing proteinaceous products	Axel et al.	The Trustees of Columbia Univ. in the City of New York	8 Mar 83	29 Sep 83
		US5731179	Method for introducing two T-DNAs into plants and vectors therefor	Komari et al.	Japan Tobacco Inc.	8 Aug 95	24 Mar 98
		EP0687730	Method of transforming plant and vector therefor	Komari et al.	Japan Tobacco Inc.	12 Jun 94	20 Dec 95
		WO9516031	Method of transforming plant and vector therefor	Komari et al.	Japan Tobacco Inc.	6 Dec 94	15 Jun 95
Agrobacterium electroporation		US5186800	Electroporation of prokaryotic cells	Dower	Bio-Rad . Laboratories, Inc	14 Mar 90	16 Feb 93
		EP0765397	Method for introduction of genetic material into microorganisms and transformants obtained therewith	Leer et al.	Nederlandse Organisatie Voor Toegepast	16 Jun 95	2 Apr 97

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

6. Transformation vectors, techniques, plant regeneration	Primary Patent Details						
	Source	**Patent no.**	**Title**	**Inventor(s)**	**Assignee**	**Filing date**	**Issue date**
Agrobacterium electroporation		WO9535389	Method for introduction of genetic material into microorganisms and transformants obtained therewith	Leer et al.	Nederlandse Organisatie Voor Toegepast	16 Jun 95	28 Dec 95
Transformation (general)		US4237224	Process for producing biologically functional molecular chimeras	Cohen and Boyer	Stanford University	4 Jan 79	2 Dec 80
Regeneration of rice		US5350688	Method for regeneration of rice plants	Matsuno and Ishizaki	Kirin Beer Kaburshiki Kaisha	16 Jun 92	27 Sep 94
		WO9419930	Enhanced regeneration system for cereals	Nehra et al.	NRC Canada	10-Mar-94	15-Sep-94

continued...

Table 3 continued. Product Clearance Spreadsheet for *Golden*Rice™

7. DNA Amplification techniques, plant regeneration	Primary Patent Details						
	Source	Patent no.	Title	Inventor(s)	Assignee	Filing date	Issue date
PCR Technique		US4683202	Process for amplifying nucleic acid sequences	Mullis	Cetus thereafter to Hoffman-La Roche	25 Oct 85	28 Jul 87
		US4683195	Process for amplifying, detecting, and /or-cloning nucleic acid sequences	Mullis et al.	Cetus	7 Feb 86	28 Jul 87
		US4965188	Process for amplifying, detecting,and/or cloning acid sequences using a thermostable enzyme	Mullis et al.	Cetus	17 Jun 87	23 Oct 90
		EP0509612	Process for amplifying and detecting nucleic acid sequences	Mullis et al.	Hoffman-La Roche	27 Mar 86	21 Oct 92
		EP0502588	Process for amplifying nucleic acid sequences	Mullis	Hoffman-La Roche	27-Mar-86	9-Sep-92
		EP0502589	Kit for use in amplifying and detecting nucleic acid sequences	Mullis et al.	Hoffman-La Roche	27-Mar-86	9-Sep-92
Taq polymerase		US4889818	Purified thermostable enzyme	Gelfand et al.	Cetus thereafter to Hoffman-La Roche	17 Jun 87	26 Dec 89
		EP0258017	Purified thermostable enzyme and process for amplifying detecting, and/or cloning nucleic acid sequences using said enzyme	Erlich et al.	Cetus	21 Aug 87	2 Mar 88

4.4 Discussion of Special Cases

Throughout the course of the *Golden*Rice™ product deconstruction, questions arose that sometimes could not be readily answered. We discuss these and address their implications in the sub-sections below.

4.4.1 The *nptII* gene

An examination of the pBin19Hpc expression cassette reveals that the selectable marker *nptII* lies between the LB and RB (left and right border regions) of the binary vector. However, during the course of the deconstruction, we could not rationalize this orientation. The source of *nptII* is pBin19 (see Bevan, 1984), and in this construct it is clearly outside of the LB-RB region. Through communication with Peter Beyer, we ascertained that *nptII* had likely moved to this new location.

Although intriguing as a scientific question, for our purposes its real importance was within the context of the IP that might be associated with *nptII*, contingent on its specific location in the transformation vector. Whereas the *nptII* gene should fall outside of the T-DNA region, on the distal side of the plasmid, in pBin19Hpc it is within the T-DNA region. Patent EP0927765, entitled "Method for Selecting Transformed Cells," states in Claims #8&9 that "A method for producing a rice transformant by a desired gene comprising: a) providing a strain belonging to the genus *Agrobacterium* which has a plasmid containing a paromomycin (*nptII*) resistance gene and a desired gene, in the T-DNA region in said plasmid, in such a way as to allow expression of each of said genes." It appears that the location of *nptII* will have significant impact on the likelihood of the product being covered under this patent's claims. Indeed, what first appears as an anomaly or scientific curiosity can (very rapidly) complicate the IP landscape of the product.

4.4.2 Method of Plant Transformation

The method by which the precultured, immature rice embryos were transformed using *Agrobacterium* is first referenced in Uze et al., 1997. The Uze reference lists two techniques of transformation: with a wounding pretreatment (biolistic bombardment) or without, followed by immersion in *Agrobacterium*. If the wounding pretreatment had been used, patent WO9209696 may apply, since in the claims it describes "A method of transforming, with a DNA, a genome, particularly the nuclear genome of a monocotyledonous plant.....comprising the steps of, wounding and/or degrading either an intact tissue of said plant that is capable of forming compact embryogenic sector thereof, obtained from said intact tissue of said plant, so as to render a cell of said intact tissue of callus competent with respect to uptake of said DNA, integrative transformation of said DNA in said plant genome and regeneration." Additionally, if the biolistic pretreatment had been used, then the array of patents associated with microprojectile bombardment of plants and/or plant tissues would have required careful scrutiny, along with all potentially applicable licenses. However, Professor Potrykus informed us that the procedure used was osmoticum treatment of 7-10 day old calli (without bombardment).

4.4.3 Overlapping Patent Claims in Carotenoid Biosynthetic Option Genes

The interpretation of claims in patents dealing with the genes and enzymes in the carotenoid biosynthetic option(s) can be extraordinarily complex, with certain patents having claims that appear to cover multiple enzymes/genes in the option. The homologous carotenoid biosynthesis gene clusters found in *Erwinia uredovora* (Kirin) and *Erwinia herbicola* (Amoco) are examples. There appear to be

overlapping patent claims with several of the patents we have listed in Table 1. For example,

- US5589581 has claims apparently covering the genes encoding zeaxanthin glycosylase, lycopene cyclase, phytoene dehydrogenase, and phytoene synthase.
- WO9113078 has claims apparently covering genes encoding geranylgeranyl pyrophosphate synthase, phytoene synthase, lycopene cyclase, and others.
- US5429939 has claims apparently covering genes encoding enzymes for phytoene synthase, phytoene dehydrogenase, lycopene cyclase, and others.

From a practical standpoint, the patents listed on Table 1 dealing with the three carotenoid biosynthetic genes in *Golden*Rice™ should not necessarily be considered as mutually exclusive in terms of their claims. The possibility of substantial overlap is quite likely.

4.4.4 Interpreting Patent Claims: From Greater to Lesser Uncertainty

Reviewing potentially applicable patents, and determining whether their claims might apply to the *Golden*Rice™ product is not a simple "yes or no" situation. Rather, it is a process of decreasing levels of uncertainty, and appropriate judgment is necessary. As an example, we can consider four patents dealing with genes in the carotenoid biosynthetic option.

- US5744341(not listed in Table 1) is highly unlikely to be attached to the *Golden*Rice™ product. Its claims specifically relate to genes for the enzymes epsilon cyclase, isopentenyl pyrophosphate isomerase, and beta-carotene hydroxylase; these genes have not been used in the production of *Golden*Rice™.
- US5656472 is somewhat likely to be attached to the *Golden*Rice™ product and requires more careful evaluation. This patent describes a gene for lycopene cyclase, which is associated with *Golden*Rice™. The claims call for 80% identity with said gene, as well as hybridization under high stringency conditions (Southern blot). To determine what the relationship is between the gene in question and the patent claim would involve some laboratory experiments.
- WO9955888 is more likely to be attached to the *Golden*Rice™ product. This patent deals with a carotene desaturase. The claims are broadly written, (e.g., claim #2, "an isolated nucleic acid fragment that is substantially similar to an isolated nucleic acid fragment encoding all or a substantial portion of (a zeta carotene desaturase)."
- WO9907867 is highly likely to be connected to the *Golden*Rice™ product and deserves special attention. The claims are broadly and skillfully written, such that any transformation process of a plant seed with a gene from the carotenoid biosynthetic option leading to an alteration of xanthophyll levels is likely to be covered. In the case of *Golden*Rice™, accumulation of zeaxanthin (a xanthophyll) was detected in the pBin19hpc transformants.

4.4.5 Pea Rubisco Small Subunit Transit Peptide

The transit peptide was obtained from a company, with a letter specifying restrictions on use attached. However, this situation is further complicated, since that company had originally obtained the transit peptide from Jeff Schell, who is a co-inventor on the patents US5717084 and US5728925; the assignee is Plant Genetic Systems N.V. These patents appear to substantially cover the use of the transit peptide. The question that needs to be sorted out, particularly in terms of tangible property under what conditions that company acquired the gene from Plant Genetic Systems (now AVENTIS).

5.1 Introduction

The development of *Golden*Rice™, a transgenic *japonica* rice with elevated levels of pro-Vitamin A producing beta carotene, has gained a great deal of worldwide media attention. It has been proposed as a way to reduce blindness and its related suffering which results from Vitamin A deficiency. Further, as a transgenic food, *Golden*Rice™ is seen as the agri-biotech industry's "poster child" and—by donating the IP and TP components—a tangible way for the industry to show their concern for humankind. Wide availability of *Golden*Rice™ would, it is argued, focus attention on the societal good of plant biotechnology. It is a tangible example of the benefits which biotechnology has already brought to humanity through the pharmaceutical industry in which virtually all new drug releases are produced using essentially the same kinds of biotech processes and components that were used to produce *Golden*Rice™. Biotech food has been plagued by detractors, particularly in Europe, whose scientifically unsound arguments belie a hidden agenda that is more anti-corporate than pro-environment, as is so loudly proclaimed.

In spite of these distractions from Europe and elsewhere, there is broad agreement among the leadership of most developing and transitional countries, that appropriate IP rights protection is necessary to entice investment in their economy, provide additional employment for their citizens, and produce hard currency through the export of high tech products. These leaders recognize that the enforcement of IP related laws protect not only the innovations and discoveries of foreign investors, but also protect the increasingly occurring discoveries of their own scientists, engineers, and entrepreneurs. In this way the countries get closer towards obtaining the food security and technological standard of living that is common in the industrialized world. Although skeptics reject such development efforts as being "neo-colonial", few will deny that food biotechnology products have a tremendous potential to decrease hunger and suffering, increase food security, and reduce many of the negative environmental impacts of modern agricultural practices.

Given all of these benefits that *Golden*Rice™ can potentially produce, questioning the legitimacy of the IP and TP rights issues related to its discovery and dissemination may be considered a questionable activity. Yet such questions must be asked. The questions behind this study involve what IP and TP rights limitations, if any, stand in the way of the broad distribution of *Golden*Rice™ to the world's resource-poor who can benefit most. Further, once such questions are identified, articulated, and catalogued it must be asked how such obstacles can be overcome.

5.2 Potentially Applicable Patents (or IP) to the Current Form of *Golden*Rice™

Patents grant only "negative" rights. That is, a patent holder can prevent others, for a specified period of time (typically 12 – 20 years, depending upon a country's patent laws), from making, using, exporting or selling items infringing the issued claims of his/her patent. Of course the patent holder, through license or assignment, can grant permission to others to function under their issued patent claims.

TP rights are established under a country's laws governing personal property and contracts. These rights too, are enforced on a country-by-country basis. However, unlike IP rights, personal property (and most aspects of contract law) rights are much more uniformly acknowledged and enforced around the

world, even in countries which do not have enforceable IP laws. Further, such rights seldom have a time limitations on their enjoyment or enforcement.

Trademarks are claimed on a country-by-country basis. Like other personal property rights trademarks seldom have a time limitation on their enforcement.

Domain names, a new sort of right that has developed with the advent of the World Wide Web ("WWW"), require re-registration from time-to-time. Such re-registration, with a minor fee, maintains worldwide exclusivity of a particular domain name. Adjudication of alleged domain name violations are similar to that of other personal property rights.

The present study identified between zero and 40 plus patents applying to the product depending on the country where the current form of *Golden*Rice™ would be used (for a total of approx. 70 patents applying across different countries). **It must be clearly stated that, because patents are country specific, not all 70 patents apply to all of the major rice producing, exporting, importing and consuming countries. Further, many of the developing and transitional countries for which *Golden*Rice™ will have the greatest positive impact, have the fewest patents.**

Widespread distribution of the product would require licenses from zero to a dozen or so entities for the IP components, plus agreements from another dozen entities for the TP transfer and use. In addition to the patented materials, processes, and reagents that the inventors used, certain trademark related issues may need to be addressed as *Golden*Rice™ is widely distributed. All in all, the widespread release of the current version of *Golden*Rice™ would require significant licensing activity if it is to legitimately become available to the world, either commercially or for humanitarian purposes.

Until recently, individuals and firms from the industrialized world typically withheld patenting in developing countries. The developing countries thereby were denied access to the latest technological advancements, except in some cases as markets for such new products. In more recent years however, to induce the introduction of technologically advanced manufacturing into developing countries with their abundant supply of qualified yet inexpensive labor, many developing countries have signed the WTO/TRIPS agreements. These international agreements require the signatories to establish and maintain a prescribed level of IP rights protection. Thus, with the rise of a more global economy, technologically advanced products such as *Golden*Rice™ may be produced, distributed and consumed on a worldwide basis. Therefore, the effects of IP and TP rights matters must be considered on a more global scale than was previously necessary.

Table 4 lists the number of patents that might be applying on a country per country basis for the 15 top rice producing, exporting and importing countries. For example in China, the world's leading rice producer, there are only 11 patents that apply to the current form of *Golden*Rice™ analyzed in this report. In Thailand and in Iran, the world's leading rice exporter and rice importer, respectively, no patents have been identified as currently impinging upon *Golden*Rice™. India, second in world rice production, has 5 patents covering the studied versions of *Golden*Rice™ while rice producers in Vietnam, the world's second biggest exporter of rice, would require licenses to nine patents in order to obtain freedom-to-operate. Grain importers to Brazil, the world's second biggest importer of rice, would require licenses to 10 patents in order to obtain full freedom under known IP rights to import *Golden*Rice™ into this South American country.

Table 4: Major Rice Producing, Exporting and Importing Countries (FAO 1997) and the Number of Applicable Patents to Golden*Rice*™ *in its Current Form*

	Production		
Country	Million MT	% of World	No. of Patents
China	198.47	34.6	11
India	123.01	21.5	5
Indonesia	50.63	8.8	6
Bangladesh	28.18	4.9	0
Vietnam	26.40	4.6	9
Thailand	21.28	3.7	0
Myanmar	18.90	3.3	0
Japan	12.53	2.2	21
Philippines	11.27	2.0	1
Brazil	9.33	1.6	10
USA	8.12	1.4	44
South Korea	7.10	1.2	10
Pakistan	6.55	1.1	0
Egypt	5.59	1.0	0
Nepal	3.71	0.6	0
Total World	**573.30**	**100.0**	
		Export	
Thailand	3.24	17.9	0
Vietnam	3.00	16.6	9
USA	2.30	12.7	44
India	2.13	11.8	5
Pakistan	1.77	9.8	0
China	1.01	5.6	11
Uruguay	0.65	3.6	0
Australia	0.65	3.6	15
Italy	0.63	3.5	29
Argentina	0.54	3.0	0
Guyana	0.29	1.6	0
Spain	0.27	1.5	27
Egypt	0.20	1.1	0
UAE	0.18	1.0	4
Benelux	0.14	0.8	34
Total World	**18.10**	**100.0**	
		Import	
Iran	0.97	5.2	0
Brazil	0.82	4.4	10
Nigeria	0.73	3.9	0
Philippines	0.72	3.9	1
Iraq	0.68	3.7	0
Saudi Arabia	0.67	3.6	0
Malaysia	0.64	3.4	0
South Africa	0.59	3.2	5
Japan	0.57	3.1	21
Cote D'Ivoire	0.47	2.5	10
Senegal	0.40	2.2	10
UK	0.39	2.1	35
France	0.37	2.0	37
Indonesia	0.35	1.9	6
United States	0.36	1.9	44
Total World	**18.60**	**100.0**	

Note: Appendix A provides a list of the designated patent numbers that may apply in each of the countries listed in this table.

The above always supposes that the TP issues have been resolved with the Table 4 only addressing IP rights, which can vary widely from country to country. TP rights that are related to this version of *Golden*Rice™ may be more uniformly applied across all countries, whether the country is considered to be developing, transitional or industrialized.

5.3 Product *vs.* Process *vs.* Use Claims[4]

Depending on the country in which one files, patent claims may be granted for different kinds and levels of inventions. The categories of granted claims most applicable to this study are:

- Products *per se* (covering any yet-to-be determined use of an invention and product)
- Product-by-process
- Uses
- Processes

These categories of claims are not specifically identified as such, only a thorough reading will indicate the distinctions between them.

Claims may be worded to cover product *per se,* products-by- process or uses. However, the fourth category of claims listed above is of particular importance here because whereas "product *per* se", "product-by-process" and "use" claims generally extend to the products that embed the new discoveries, "process" claims or claims for the claimed technical procedures do not extend to the products that are produced by the claimed processes. What is of great important for "process" claims is the location where (i.e. in which country) the process is applied.

For clarity, the three examples below illustrate claims on Product, Process, and Product/ Process patents, in terms of their claim structures:

- **Product:** US5589581, "DNA sequences useful for the synthesis of carotenoids", claims stipulate isolated and purified DNAs which encode enzymes involved in the biosynthesis of several carotenoids.
- **Process:** EP0604662, "Method of transforming monocotyledon", claims stipulate methods, and details thereof, for *agrobacterium*-mediated transformation of monocotyledons (including rice).
- **Product/Process:** WO9419930, "Enhanced regeneration system", claims stipulate both the methods for the regeneration of cereal plants, as well as the transgenic cereal plants (including rice) produced in the process.

In the case of *Golden*Rice™, much of the work was done in Switzerland. As a consequence, for any "process" claims a license for such claimed processes is required if the claims to the processes are issued in Switzerland.

However, if the product had been made in a country where those "process" claims have not issued, then a license for such claimed processes would not be required. This is the crux of this matter. If a product is produced in a country using process X and process X is not patented in that country, then the export of the product so produced using process X to another country where process X is patented does not require a license for process X. The reason is that the product was produced in a country where process X was not patented and because process patents do not extend to the products that are produced by the process. The country where the process is applied is the determining factor.

In contrast, "product *per se*" claims extend to any form of the claimed product. A scenario that illustrates this would be this.

Suppose that a researcher in country M transforms a plant with gene G, in a country

[4] See also Lesser (1991) for an concise discussion on issues and approaches on patent protection in the developing world.

where the gene G is not patented. Once the transformed product is exported to another country, say country N, where a patent claiming gene G has issued, a license for the transformed plant and any product using or containing the transformed plant that contains gene G in country N would likely be required, irrespective of where the transformation work had been done.

Some of the patent claims applicable to *Golden*Rice™ cover processes. The primary ones are listed in Table 5. Of the total patents identified, 26 seem to contain process claims. Other of the patents (not listed in Table 5) has claim structures which are a mix of process claims and product *per se* claims. In Switzerland, where much of the original *Golden*Rice™ research was done, only the first 12 patents listed in Table 5 have issued. As a consequence, someone developing a *Golden*Rice™ product in Switzerland would require licenses under these 12 patents but not under the remainder of the patents listed in Table 5.

Similarly, a researcher who obtained *Golden*Rice™ that had been transformed in Switzerland for use in a country where none of the process claims of the 12 patents were issued would not require a license under any of the 12 patents.

Whereas sorting out the types of patents and types of licenses that may be required appears a complex task, "process" patents at least simplify the IP landscape in many situations and countries.[5]

Table 5. Patents containing essentially Process Claims

EP0258017	US4683195
EP0286200	US4683202
EP0502588	US4766072
EP0502589	US4889818
EP0509612	US4965188
EP0604662	US5128256
EP0672752	US5186800
EP0687730	US5188957
EP0765397	US5286636
WO9209696	US5350688
WO9516031	US5591616
WO9535389	US5731179
US4237224	WO8805085

5.4 The Important Distinction between IP and TP

Although we have discussed at several locations in this document the distinction between IP and TP rights, it is worth reviewing briefly the practical implications. Scientists have traditionally exchanged materials among themselves for research purposes and this system has served the scientific community very well. Such exchanges are often formalized through material transfer agreements (MTA) that stipulate the conditions by which materials are provided to a third party (including matters on confidentiality, under what conditions, if any, the material may be transferred to another party, what happens if an invention takes place based on work with the material, etc.). What is often ignored is that such transferred material (which is the subject of Technical Property or TP) may contain intellectual property (IP) of others and that MTAs typically do not provide the recipient with rights to use such IP. Similarly, even if the right for using IP

[5] It should be noted, however, that a bill which has been in the US Senate for several years calls for a change in this system. Should the bill pass, any product imported into the USA and produced abroad by a process patent granted in the USA would require a license.

embedded in the transferred material has been granted through licenses, such licenses do not *a priori* provide authorization to use the material (or TP) which was originally transferred.

Suppose researcher X constructs a vector with the following components:

a. a synthetic gene constructed in his/her laboratory (and files a patent application)
b. the 35S promoter (owned by Monsanto and obtained through an MTA from Monsanto for research purposes only)
c. a plasmid which is in the public domain.

Researcher X now transfers that construct to another researcher, Y, with an MTA for research purposes only. If researcher Y then wishes to use a product containing the construct, the following agreements may be necessary:

- A license from researcher X for use of the synthetic gene (TP) and any related patents that may have been granted (IP) as specified in "a" above.
- A license from Monsanto for use of the 35S promoter
- A license from researcher X for use of the plasmid (TP). Note that despite the fact that the plasmid is in the public domain, researcher Y obtained it under an MTA and therefore requires a license to use that TP.

As a consequence, resolving the IP and TP issues becomes often much more complex than originally envisaged, particularly if MTAs are involved. These MTAs are often prepared without consideration for what happens when research leads to a developed product. MTAs are straightforward and provide an easy way to access TP and advance research. Yet that easy route often complicates life further down the road. It should not be concluded that MTAs are therefore to be avoided, quite on the contrary, but the practical implications of MTAs are often misunderstood.

5.5 IP Management Options or Strategies

Many, perhaps most, people agree with the humanitarian objective of making *Golden*Rice™ available to resource-poor farmers and rice consumers within developing countries. The present preliminary FTO analysis was conducted to better understand the current situation so that options and alternative future strategies might be discussed and developed. Yet the alternative options may be obscured by the desire to achieve the valued end. This end is always very straight forward, whether it is a private entity or a public/non-profit entity that pursues it, namely providing farmers with a superior product. The typical difference between a public and a private entity is that the private entity needs to share in the benefits, but both must provide superior products in order to survive. Evidently, the way products are disseminated by the two entities will vary also. Hence the IP management options and strategies of most private entities will be different to those of public entities.

Table 6 lists the broad ranges of strategic options that are available to any type of entity, public or private. The options tackle the FTO issue from different perspectives and are discussed in the sub-sections below. Note that our discussion of possible alternative strategies will not address all the issues that may arise from the commercialization of *Golden*Rice™; we are focusing our discussion specifically to options on how to possibly overcome obstacles related to making *Golden*Rice™ available to resource-poor farmers.

Table 6. Alternative and/or Complementary IP/TP Management Options to Obtaining Freedom-to-Operate for *Golden*Rice™

Title	Emphasis	Description	Pros	Cons
1. Invent around current patents	Science and research based approach	Research alternative ways to develop pro-Vitamin A rice, generating new inventions	•Less reliance on patents owned by others	•Time consuming •Costly research •May not be feasible
2. Re-design constructs	Product development based approach	Re-design each construct to reduce number of applicable patents, whenever possible synthesize own genes to reduce reliance on TP of others	•Normally re-design is necessary after successful research demonstration •Effective way to reduce IP issues	•May require a few additional years for product to be developed (which in any case may be unavoidable from a scientific point of view)
3. IP/TP Owners to Relinquish Claims	Humanitarian approach focused on public perception	All FTO issues for all *Golden*Rice™ related activities, commercial or otherwise, are eliminated through public (or private) statements and related activities by the certified owners/assignees of each set of IP/TP rights for making, having made, using, having used, importing, exporting, selling, and having sold all *Golden*Rice™ plants, plant parts, and all related products and processes.	•Some companies (e.g. Zeneca and Monsanto) already publicly declared that they will make their technologies available for *Golden*Rice™ •Greatly simplifies licensing negotiations	A royalty-free license may still need to be negotiated, not least for liability/indemnity reasons
4. Ignore all IP and TP	Short term perspective	All FTO issues for all *Golden*Rice™ related activities, commercial or otherwise, are ignored, and research and product development as well as plans for general distribution proceed.	•Lowest cost in the short term	•Once product deployed lawsuits may ensue •Potential future delay of product distribution •Difficult relations with IP owners

continued...

Table 6 continued. **Alternative and/or Complementary IP/TP Management Options to Obtaining Freedom-to-Operate for *Golden*Rice™**

Title	Emphasis	Description	Pros	Cons
5. Seek Licenses for all IP and TP	Licensing approach	All FTO issues are resolved by the process of any party (individually or through consortia) acquiring an appropriate (commercial or other) license from the certified owners/ assignees for each set of IP/TP rights for the *Golden*Rice™ related activities that are of interest to the licensee. This license may be commercial in nature (a grant to make, have made, use, have used, import, export, sell, or have sold all *Golden*Rice™ plants and plant parts and all related products and processes) or a more restrictive one as the licensee and licensor mutually determine to be required.	• Safest route leading to the distribution of *Golden*Rice™ • Ensures good relations with IP holders for future development of products	• Complex • Time consuming
6. Mix of all Options (1 to 5)	Pragmatic, realistic	While research and development plans are made to optimize the product, re-design of constructs and acquisition on TP is planned to minimize IP and TP conflicts (OPTION 2); selected FTO issues are removed through public (or private) rescinding of rights by selected holders of certain IP/TP rights (OPTION 3); this "moral high ground" is used to leverage additional rights holders to either rescind their claims (OPTION 3) or to reduce their demands within the context of license negotiations (OPTION 5). In the end all remaining unrescinded IP/TP rights can be either licensed (OPTION 5) or ignored (OPTION 4).	• Effective route leading to the distribution of *Golden*Rice™ • Taking advantage of all available options • Ensures good relations with IP holders for future development of products	• Relatively complex • Relatively time consuming

5.5.1 OPTION 1: Invent Around Current Patents

Research on alternative ways to develop pro-Vitamin A rice, generating new inventions.

In certain cases it is possible to invent around existing patents or inventions. Companies, for example, will typically evaluate at the outset whether it is advantageous to invest in research to circumvent other corporations' patents or to license technologies from such competitors.

In the case of public entities, the equation of the benefits and risks is very different. Quite often, they do not have the same critical mass in research nor do they necessarily have the freedom to allocate resources to invent around existing claims. In addition, in the case of *Golden*Rice™, it would significantly delay the benefits to poor farmers even if inventing around were possible. Hence this is not a realistic option in this case for public entities and NARS.

5.5.2 OPTION 2: Re-design Constructs

Re-design each construct to reduce number of applicable patents, whenever possible synthesize own genes to reduce reliance on TP of others

The *Golden*Rice™ as announced by Potrykus/ Beyer in recent months is primarily the product of basic research. Quite naturally, such research products are rarely ready for commercialization or widespread distribution although the proof of concept has been demonstrated in a few selected plants. In practical terms, genes may have to be optimized or new constructs made with different promoters or selectable markers. It can reasonably be expected that the same would be true for the current version of *Golden*Rice™. As a consequence, this study should provide the scientists and research managers with some of the information needed to design the constructs in such a way as to reduce the number of applicable patents (or IP).

Re-design of constructs would also go a long way towards reducing or even eliminating the TP complexities since many genes can be synthesized commercially at low costs and public plasmids can be used without major contractual limitations.

Re-designing the production of *Golden*Rice™ for scientific reasons may be the most feasible option available to deliver a high quality product to resource poor farmers. Further, it may also be the best complementary option to reduce the IP and particularly the TP complexity (see also Section 6.1.2 below for further discussion) of such a re-designed product.

5.5.3 OPTION 3: IP/TP Owners to Relinquish Claims

*All FTO issues for all Golden*Rice™ *related activities, commercial or otherwise, are eliminated through public (or private) statements and related activities by the certified owners/assignees of each set of IP/TP rights for making, having made, using, having used, importing, exporting, selling, and having sold all Golden*Rice™ *plants, plant parts, and all related products and processes.*

With this option, the IP/TP rights holders rescind all of their rights for all components of *Golden*Rice™. Then any entity involved with *Golden*Rice™ would essentially be freed from all IP and TP related obligations. It may not necessarily mean that entities wishing to distribute and use *Golden*Rice™ would not have to enter into a royalty-free licensing agreement with the owners of IP and TP since such owners typically would want to ensure that they do not bear any liabilities with a product developed by third parties and for which they, the technology donor, do not receive any royalties.

This matter is dealt with through indemnity clauses by which the recipient agrees to hold the donor harmless of any liabilities that might flow from making, using or selling the products developed by the recipient. Commercial licenses, whether royalty-free or not, generally include indemnity clauses. No entity knowingly wishes to allow another entity to develop a product and then be held liable for the product for which the entity had no control over. This is especially true in cases where a technology is given free of charge.

There may, however, be a significant time and resource expenditure required to determine which IP and TP rights are to be rescinded, to authoritatively determine who the IP/TP rights owners/assignees are, under what conditions, if any, the IP/TP rights owners/assignees will rescind their respective rights, and to conduct the negotiations that may be necessary for all rescission to take place. Moreover, there would be a need to compile and manage information relating to obtaining FTO in this manner. Because IP/TP rights are accrued on a country-by-country basis, such information management is no small matter and would have to be addressed on an on-going basis.

This option is appealing, but entities still face the challenge of significant FTO management requirements and solving liability/indemnity issues.

5.5.4 OPTION 4: Ignore all IP and TP

*All FTO issues for all Golden*Rice™ *related activities, commercial or otherwise, are ignored, and research and product development as well as plans for general distribution proceed.*

On this option, the entities involved in the development and distribution of *Golden*Rice™ would ignore the claims of all owners/assignees of each set of IP/TP rights for all *Golden*Rice™ related activities.

This option may accrue risks from both patent-related (IP) and private property-rights (TP) owners/assignees who would feel slighted. Such risks may vary widely according to the degree of enforcement that the IP/TP rights owners/assignees find within each country where they claim IP/TP rights and to the willingness of such owner/assignees to invoke action against potential infringers.

This option has a significant appeal to a number of entities, not least because of its perceived ability to partially equalize the resources and power differences between the developing and industrialized portions of the world. However, this option is likely to create a negative attitude among the holders of various IP/TP rights when advocates for the resource-poor seek to obtain additional biotechnology components in the future.

This option eliminates all need to ascertain who are the IP/TP rights owners/assignees but it flies in the face of current international treaties signed by the majority of developing countries and widely accepted national laws in virtually every country of the world.

Another potentially more significant downside with this approach is its potential impact on future negotiations with those ignored IP/TP rights owners/assignees. Future collaboration and donations would most likely become impossible under such a climate. It should be noted here that in addition to obtaining freedom to use a certain technology owned by the entity owing a patent, licensing agreements generally also allow for the transfer of know-how and trade secrets which may be very valuable in order to ensure high quality products and faster or more efficient and less costly product development.

5.5.5 OPTION 5: Seek Licenses for all IP and TP

*All FTO issues are resolved by the process of some party (individually or through consortia) acquiring an appropriate (commercial or other) license from the certified owners/ assignees for each set of IP/TP rights for the Golden*Rice™ *related activities that are of interest to the licensee. This license may be commercial in nature (a grant to make, have made, use, have used, import, export, sell, or have sold all Golden*Rice™ *plants and plant parts and all related products and processes) or a more restrictive one as the licensee and licensor mutually determine to be required.*

This option appears at first glance to be a little desired option. Indeed, in the short term it may be so. It requires an overall IP/TP rights management strategy that parallels the scientific research and product development effort for *Golden*Rice™. It requires that some entity definitively determine all IP/TP rights owners/assignees, draft and negotiate appropriate license agreements, report and track the appropriate changes in the IP/TP rights landscape over time, and confirm to the various licensees all of these variables.

As a practical matter of license negotiation, adopting this strategy may segment the various licensees into different categories. Such segmentation would likely be according to the level of the licensee's needs, with more generous license terms being offered to the poorest. Such segmentation might also result from the licensors' business plans, the licensee's level of capacity in IP/TP management, issues of domestic production/ consumption *vs.* desire to export, regulatory issues of biosafety/food safety, bans on the transfer of certain technologies from one country to another (ex. Pre-1996 US ban on exporting technologies to Vietnam), and general IP/TP management capacity and resources.

License segmentation raises other questions about equity, compliance and enforcement, cultural and historical values, germplasm origin, and product development resource investment, to name only a few. Furthermore, questions about the rights and values to be exchanged between licensor and licensee are profound and far-reaching. There is no clear template readily available.

As mentioned above, this option may appear the least appealing, at least in the short term, because of the resources required to answer all the questions and manage the issues of IP/ TP FTO. However, it has the appeal of being the most effective in terms of a model for capacity building among the licensees, a set of skills that such licensees will undoubtedly need in future negotiations, particularly if they wish to export higher value food biotechnology products.

Finally, this option is appealing in that instead of creating a negative attitude, it builds bonds of trust between the licensors and the licensees. This is an important issue since it also allows the transfer of know-how related to certain IP, including trade secrets, which could be instrumental in the efficient development of products for resource-poor farmers. In implementing this strategy, the same bonds of trust will hold licensor and licensee together during future aspects of the development of *Golden*Rice™, which will empower future negotiations between the parties and may extend to other technologies.

5.5.6 OPTION 6: Mix of all Options (1 to 5)

While research and development plans are made to optimize the product, re-design of constructs and acquisition on TP is planned to minimize IP and TP conflicts (OPTION 2); selected FTO issues are removed through public (or private) rescinding of rights by selected holders of certain IP/TP rights

(OPTION 3); this "moral high ground" is used to leverage additional rights holders to either rescind their claims (OPTION 3) or to reduce their demands within the context of license negotiations (OPTION 5). In the end all remaining unrescinded IP/TP rights can be either licensed (OPTION 5) or ignored (OPTION 4).

This option contains components of each of the above (except the first Option [inventing around inventions]). It still requires significant resource expenditures to document and manage each IP/TP component. Furthermore, many questions arise similar to those indicated in Option 5.

As noted above, separating commercially licensed activities from other activities involving *Golden*Rice™ may establish additional variants on each of these four options. However, this document is directed primarily toward obtaining access to *Golden*Rice™ for resource-poor farmers/ consumers, not toward commercial licensing.

Considering each of these options, a strong argument can be made to manage FTO in a manner similar to the management of the technological research and product development that is making *Golden*Rice™ a reality.

5.6 Practical Considerations on Where the Final Product is Developed

Sections 5.3 and 5.4 discussed the *product* and *process* patents and the distinction between *IP* and *TP*. This section will discuss the practical implications of these differences based on a hypothetical example.

Suppose an entity in Vietnam wishes to develop *Golden*Rice™ for farmers in Vietnam with further transfer to Pakistan. Vietnamese and Pakistani farmers would be growing the GoldenRice™. Vietnam would also export the *Golden*Rice™ to the Philippines. A rice researcher in Vietnam, therefore, has essentially three options for managing the IP of *Golden*Rice™, namely:

***Option A: Re-making of Golden*Rice™ in Vietnam by producing entirely new constructs**

A rice researcher in Vietnam isolates the same key carotenoid biosynthetic genes as used by Potrykus and Beyer, remakes all of the gene constructs and components of *Golden*Rice™, reassembles the same transformation vectors and systems, and essentially produce her/his own version of *Golden*Rice™ that is identical to the Potrykus–Beyer version.

- Currently, such a product would have 9 patents (or IP) impinging upon it in Vietnam.
- The distribution of such re-made *Golden*Rice™ to Pakistan would not pose a problem since no patents on such a product are issued in Pakistan.
- Export of the product to the Philippines might require the license under 1 patent[6].
- If no TP from other sources is used then the researcher would not have to seek licensing agreements for TP rights.

***Option B: Re-making of Golden*Rice™ in Vietnam by extracting the relevant genes from the Potrykus—Beyer *Golden*Rice™**

A rice researcher in Vietnam removes the key carotenoid biosynthetic genes from the Potrykus–Beyer *Golden*Rice™ constructs and re-clones these for the purpose of re-making his/her own version of *Golden*Rice™.

[6] The patent issued in the Philippines does, technically speaking, not extend to the Potrykus/Beyer product because strictly speaking it covers only a protoplast-based method of rice transformation.

- Currently, such a re-made product would have 9 patents (or IP) rights attached to it in Vietnam.
- The distribution of such a re-made *Golden*Rice™ to Pakistan would not pose a problem since no applicable patents are issued in Pakistan.
- Export of the product to the Philippines might require the license for 1 patent.
- The most important obstacle, however, would be the TP rights associated with the Potrykus—Beyer *Golden*Rice™ which would still require an agreement from the TP rights owners.
- In the future event that the Potrykus-Beyer *Golden*Rice™ patents issue in Vietnam, Pakistan, or in the Philippines, depending on the specific issued claims, licenses under that patent may also be required.

***Option C: Acquire the Potrykus/Beyer Golden*Rice™**

A rice researcher in Vietnam, using traditional breeding methods, crosses the Potrykus–Beyer transformed *japonica Golden*Rice™ with selected *indica* rice varieties in order to transfer the beta-carotene trait into more desirable cultivars.

- The transfer of *Golden*Rice™ from ETH Zurich to the entity in Vietnam would likely be done under a MTA for the TP embedded in the transferred material. Such a MTA would dictate any limitations on the TP which ETH Zurich would wish to impose on the Vietnamese entity.
- Currently, that re-made product would have 9 patents (or IP) rights impinging upon it in Vietnam.
- The distribution of such re-made *Golden*Rice™ to Pakistan would likely not pose a problem since no patents on the current Potrykus-Beyer version of *Golden*Rice™ have issued in Pakistan.
- Export of the product to the Philippines might require the license for 1 patent. The Philippine entity, depending on the terms of the MTA, may also be required to negotiate a license with the TP owners.

If, under any of the three situations described above, either the Potrykus–Beyer *Golden*Rice™ patent or other patents that are applicable to *Golden*Rice™ and/or its components or embodiments, are filed and issued in Vietnam, the Philippines or Pakistan, then the IP landscape significantly changes. Monitoring of the IP landscape and newly issued patents would be done by regular FTO updates by the IP/TP manager.

6. Conclusions: Implementing IP/TP Management Systems

There are many challenges regarding FTO for *Golden*Rice™ at both the country and international levels because:

1. The technology is quite complex, comprising of many sophisticated components and processes.
2. There are many potential IP/TP owners/ assignees.
3. The range of potential producers/ consumers of *Golden*Rice™ is widely varied.
4. There exists a rapidly evolving global IP landscape.
5. TP rights in plant biotechnology, while not as widely understood as IP rights, are very broadly accepted and generally enforced on a worldwide basis.
6. *Golden*Rice™ may have significant value in the world commodity market.

The FTO issues for commercial activities and for humanitarian activities are nearly identical, although the solutions may vary.

6.1 Major Options on the Management of IP associated with *Golden*Rice™

These FTO challenges can be understood by reviewing some background information and by studying several alternative options forward. One immediate issue, for example, concerns the appropriate type of license that should be sought for resource-poor farmers/ consumers. This example also allows the examination of some of the alternatives that are available to those entities that wish to see *Golden*Rice™ broadly distributed.

Note that no clear, legal, internationally accepted definition of the term "non-commercial license" exists. That term has crept into discussions regarding *Golden*Rice™ but it is not universally defined. On the other hand, a "commercial license" for IP rights is broadly accepted to mean a grant of rights under the objects, designs, or technologies claimed in the issued patent that is being licensed. Such commercial licenses often use the language of patent law, as promulgated in many countries, by granting a right "…to make, use, import, or sell…." all claimed products or processes. Increasingly, the granting language in many commercial biotech seed and/or plant licenses has been expanded beyond mere patent law language to include a broader grant under both the IP and TP rights. This expanded language for such licenses grants the licensee rights "…to make, have made, use, have used, import, export, sell or have sold all plants, plant parts and all related products and processes...." under the defined technology. A *Golden*Rice™ commercial license would likely contain such expansive language. Any other sort of license might or might not contain such language.

The question then arises, "Is a commercial license the most appropriate way to deliver *Golden*Rice™ to resource-poor farmers/ consumers in developing countries?", even if granted royalty-free (which would be equivalent to a donation free-of-charge). It is not the purpose of this study to answer questions regarding the particular licensing language that the parties may prefer. However, it is important to raise these questions so that licensee and licensor can properly discuss such issues.

Regardless of which option discussed above or which scenario is chosen, there are a series of tasks that should be completed in order to adequately manage the IP/TP rights on any *Golden*Rice™ product:

1. Complete and regularly update the present FTO analysis.
2. Develop a scientific strategic plan (who manages, what is to be done, which biotech and germplasm components are to be used, where is the research is to be done, who is to do the research, what are the timelines for completion) for finalizing the current scientific initiative.
3. Draft and negotiate a strategic plan for distribution (who manages, what must be licensed, list of licensors/licensees, acceptable terms, timelines) of the finished product(s).
4. Complete a cost/benefit analysis for the preferred options.

6.1.1 Complete and Regular Updates to the FTO

This preliminary FTO analysis is based on a thorough study of the scientific research (as was documented to ISAAA) that has been completed to date. However, because the research and product development regarding *Golden*Rice™ is continuing, and the IP landscape is dynamic, an annual (at least) update to the present FTO analysis may be necessary.

6.1.2 Strategic Science Plan

The development of a scientific strategic plan (who manages, what is to be done, which biotech and germplasm components are to be used, where is the research to be done, who is to do the research, what are the timelines for completion) for finalizing the current scientific initiative may be under way. Such a plan would include an analysis of the technological and IP/TT barriers that could limit the successful scientific introduction of a final product, either within developing countries for the benefit of resource-poor farmers/consumers or for commercial purposes in any part of the world. Also, if and when new biotech constructs and/or transformation events are produced, such a plan would allow the scientists, with a keen eye toward the reduction of FTO barriers as well as for the normal scientific purposes of elegance and/or convenience, to re-design components of *Golden*Rice™.

The elimination of FTO barriers noted here might include:

- Establishing authentic title to all component parts and using those components that are more freely available,
- Assuring that signatories to all germane agreements (material transfer agreements, licenses, sub-licenses, etc.) are empowered to sign such documents,
- Documenting full compliance with all germane agreements,
- Determining and documenting that all inventors' employment obligations *vis-à-vis* all inventions are fulfilled,
- Establishing and maintaining an adequate paper trail on all aspects of related transactions, and
- Identifying and complying with requirements that financial donors may have imposed when research funding was obtained.

6.1.3 Strategic Distribution Plan

The development of a strategic plan for distribution (who manages, what must be licensed, list of licensors/licensees, acceptable terms, timelines) of the finished product(s) may, likewise, be firmly underway. Determining whether one or several entities should manage the distribution process may be desirable to achieve economies of scale and efficiencies of operation.

Several alternatives for distribution could be:

- Release *Golden*Rice™ on a country-by-country basis with each recipient country obtaining all of the licenses that it will need to benefit its rice growers, processors, exporters/importers, and consumers. This approach could be facilitated through a consortium of research/development institutions (such as those of the CGIAR).
- Distribute *Golden*Rice™ through a consortium of regional countries.
- Identify and license a single country per region and grant that country the right to sub-license its *Golden*Rice™.

Each of these approaches has merits and some demerits. A distribution plan will help determine which approach will have the greatest impact and the highest cost/benefit ratio. In any case, whatever licensing strategy is pursued, practical issues regarding license negotiations need to be reviewed and answered:

- Which party within a country has both the authority and the capacity to negotiate with the licensors? Should there be only a single licensee within each country? Within each region? Why?
- Should licenses be sought on a country-by-country basis, a regional basis, or in some other manner?
- What is the correct value for a license? How is such value determined? By whom?

- Should any entity be denied a license? Under what conditions? For how long?
- Should licenses be solely for domestic production and consumption?
- Should export, if permitted at all, be allowed only from one developing country to other developing country? Should exports to a developed country be licensed in the same way that exports to a developed country are treated?
- Should all licenses be commercial with merely the terms varied? If so, varied according to what criterion?
- Should all licensors treat every licensee the same? Why? Why not?
- What are the alternatives to commercial licenses?
- What defines a "developing country" as compared to a "developed country"? Who determines the distinction? Is such a distinction permanent?

Raising these questions, of course, does not resolve them. And even answering these questions does not provide an exhaustive list of answers to all the potential questions that might arise if this option is followed.

This list of questions, however, can serve as a checklist for various entities as they complete the pragmatic working out of licensing *Golden*Rice™. For example, even though there is likely to be more than one source of *Golden*Rice™ licenses, all of the same questions impinge upon the licensing decisions. Likewise, even though *Golden*Rice™ may be transferred under a MTA to a developing country, the issues embedded in the list above must be addressed.

Finally, whether the licensing of *Golden*Rice™ is done one country (or entity) at a time when each rice research/producing/consuming country or organization is capable or is licensed to a broker who in turn makes additional sub-licenses to the appropriate entities, the same concerns must be addressed. The only significant difference may be one of efficiencies and economies of scale. However, these and related questions will have to be approached and answered for any option followed.

6.1.4 Cost/Benefit Analysis

Consideration of aspects of the distribution plan ought to be coupled with a cost/benefit analysis. Such an analysis considers what constitutes appropriate license terms, sufficient regulatory apparatus, and a predictable IP/TP management framework. Which countries have such institutions in place and what are the costs of putting them in place are also appropriate questions to ask.

Part of such an analysis would consider not only the costs, but also the costs *to whom*. It should also analyze the current relationship that *Golden*Rice™ recipients have with technological components and financial donors as well as the potential relationships created by distributing *Golden*Rice™.

6.2 Outlook

It should be noted that the present study was not intended to promulgate any particular approach on how to overcome the IP and TP challenges that impinge upon *Golden*Rice™ nor to advocate a certain approach to IP management. The objectives were two-fold:

a. review the IP and TP components associated with *Golden*Rice™ as developed by Potrykus-Beyer (with significant funding from the Rockefeller Foundation)
b. develop and discuss possible alternative strategies on how to overcome the IP and TP constraints.

It will be for the developing countries which wish to benefit from *Golden*Rice™ and for the organizations whose mandate is to assist these countries to make choices on the best options to follow. The dominating consideration must

be the impact of *Golden*Rice™ on the health and well being of rice producing and consuming populations. These and related factors will condition the speed and configuration of the eventual broad release of *Golden*Rice™.

Because a preliminary FTO analysis such as this one and a related version done by a patent attorney is dynamic, it is essential that all strategic plans be developed in the light of an extensive cost/benefit analysis and an extensive list of likely options. In this way, *Golden*Rice™ will deliver its benefits to both resource-poor farmers and consumers in developing countries and to commercial farmers and related entities. It can become a clear example of how the benefits of genetically modified products can be extended to both developing and developed countries. Sound planning and resolution of the IP/TT issues will contribute to a timely release of this and future essential products for the benefit of all people.

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Appendix A. List of Major Producing/Importing/Exporting Countries and Designated Patents Potentially Applicable in these Countries to *Golden*Rice™

Country	Designated Patent	Country	Designated Patent
Australia	WO8303259	Benelux	EP0257472
	WO8603776		WO9955889
	WO9109128		WO9963055
	WO9209696		WO9967357
	WO9419930	Brazil	WO9109128
	WO9516031		WO9419930
	WO9535389		WO9806862
	WO9628014		WO9955887
	WO9636717		WO9955888
	WO9806862		WO9955889
	WO9907867		WO9636717
	WO9916890		WO9916890
	WO9955888		WO9963055
	WO9963055		WO9967357
	WO9967357	China	WO8603776
Benelux	EP0257472		WO9907867
	EP0258017		WO9916890
	EP0265556		WO9419930
	EP0270822		WO9636717
	EPO286200		WO9806862
	EP0471056		WO9955887
	EP0604662		WO9955888
	EP0672752		WO9955889
	EP0687730A1		WO9963055
	EP0699765A1		WO9967357
	EP0927765	Cote D'Ivoire	WO9209696
	EP502588A2		WO9916890
	EP509612A2		WO9419930
	WO8303259		WO9806862
	WO8402913		WO9955887
	WO8504889A1		WO9955888
	WO8603516		WO9955889
	WO8603776		WO9963055
	WO9109128		WO9636717
	W09209696		WO9967357
	WO9419930	France	EP0257472
	WO9516031		EP0258017
	WO9535389		EP0265556
	WO9907867		EP0270822
	WO9113078		EP0286200
	WO9628014		EP0393690
	WO9636717		EP0471056
	WO9806862		EP0604662
	WO9916890		EP0672752
	WO9955887		EP0687730A1
	WO9955888		EP0699765A1
			EP0765397

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Appendix A continued. **List of Major Producing/Importing/Exporting Countries and Designated Patents Potentially Applicable in these Countries to *Golden*Rice™**

Country	Designated Patent	Country	Designated Patent
France	EP0927765	**Italy**	EP509612A2
	EP502588A2		WO8504889A1
	EP502589A2		WO8603516
	EP509612A2		WO8603776
	WO8303259		WO9113078
	WO8402913		WO9516031
	WO8504889A1		WO9535389
	WO8603516		WO9628014
	WO8603776		WO9636717
	WO9109128		WO9806862
	WO9113078		WO9907867
	W09209696		WO9916890
	WO9419930		WO9955887
	WO9516031		WO9955888
	WO9535389		WO9955889
	WO9628014		WO9963055
	WO9636717		WO9967357
	WO9806862	**Japan**	JP3058786A
	WO9907867		JP3091085
	WO9916890		WO8303259
	WO9955887		WO8402913
	WO9955888		WO8504889A1
	WO9955889		WO8603516
	WO9963055		WO8603776
	WO9967357		WO8805085
India	WO9955887		WO9113078
	WO9955888		WO9209696
	WO9955889		WO9419930
	WO9963055		WO9516031
	WO9967357		WO9628014
Indonesia	WO9916890		WO9636717
	WO9955887		WO9806862
	WO9955888		WO9916890
	WO9955889		WO9955887
	WO9963055		WO9955888
	WO9967357		WO9955889
Italy	EP0257472		WO9963055
	EP0258017		WO9967357
	EP0265556	**Senegal**	WO9109128
	EP0270822		W09209696
	EP0286200		WO9916890
	EP0393690		WO9419930
	EP0471056		WO9806862
	EP0604662		WO9955887
	EP0687730A1		WO9955888
	EP0699765A1		WO9955889
	EP0927765		WO9967357
	EP502588A2		WO9963055

continued...

Appendix A continued. **List of Major Producing/Importing/Exporting Countries and Designated Patents Potentially Applicable in these Countries to *Golden*Rice™**

Country	Designated Patent	Country	Designated Patent
South Africa	WO9955887	UK	EP0286200
	WO9955888		EP0471056
	WO9955889		EP0604662
	WO9963055		EP0672752
	WO9967357		EP0687730A1
South Korea	WO9109128		EP0699765A1
	WO9209696		EP0927765
	WO9419930		EP502588A2
	WO9806862		EP502589A2
	WO9955887		EP509612A2
	WO9955888		WO8303259
	WO9955889		WO8402913
	WO9963055		WO8504889A1
	WO9636717		WO8603516
	WO9967357		WO8603776
Spain	EP0257472		WO9109128
	EP0258017		WO9113078
	EP0265556		WO9209696
	EP0270822		WO9419930
	EP0286200		WO9516031
	EP0393690		WO9535389
	EP0604662		WO9628014
	EP0672752		WO9636717
	EP0687730A1		WO9806862
	EP0699765A1		WO9907867
	EP0927765		WO9916890
	WO9109128		WO9955887
	WO9113078		WO9955888
	W09209696		WO9955889
	WO9419930		WO9963055
	WO9516031		WO9967357
	WO9535389	USA	USRE36449
	WO9907867		US350688
	WO9916890		US4237224
	WO9955887		US4399216
	WO9955888		US4407956
	WO9955889		US4536475
	WO9628014		US4634665
	WO9636717		US4683195
	WO9806862		US4683202
	WO9963055		US4776072
	WO9967357		US4889818
UAE	WO9955887		US4965188
	WO9955888		US5128256
	WO9955889		US5186800
	WO9963055		US5188957
UK	EP0257472		US52886636
	EP0258017		US5352605
	EP0265556		US5429939
	EP0270822		US5530188

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Appendix A continued. **List of Major Producing/Importing/Exporting Countries and Designated Patents Potentially Applicable in these Countries to *Golden*Rice™**

Country	Designated Patent	Country	Designated Patent
USA	US5530189	**USA**	WO9535389
	US5545816		WO9628014
	US5591616		WO9806862
	US5668298		WO9955887
	US5702903		WO9955888
	US5705624		WO9955889
	US5717084		WO9963055
	US5728925		WO9636717
	US5731179	**Vietnam**	WO9419930
	US5750865		WO9806862
	US5858742		WO9916890
	WO8303259		WO9955887
	WO8603776		WO9955888
	WO9109128		WO9955889
	WO9209696		WO9636717
	WO9419930		WO9963055
	WO9516031		WO9967357

Appendix B. List of Abbreviations and Acronyms

aphIV	hygromycin phosophotransferase (gene)
BoT	Board of Trustees
CaMV	Cauliflower mosaic virus
CGIAR	Consultative Group on International Agricultural Research
crtI	phytoene synthase (gene)
ETH	Eidgenossische Technische Hochschule
FAO	Food and Agriculture Organization
FTO	Freedom-to-Operate
GATT	General Agreement on Tariffs and Trade
Gt1	(rice) Endosperm-specific glutelin (gene)
HPLC	High-performance liquid chromatography
IARC	International Agricultural Research Center
IFPRI	International Food Policy Research Institute
IIML	Integrated Information Management Laboratory
IP	Intellectual Property
IRRI	International Rice Research Institute
ISAAA	International Service for the Acquisition of Agri-biotech Applications
LB-RB	Left-right border region (of *Agrobacterium* Ti plasmid)
lcy	Lycopene cyclase (gene)
mpi	Mannose phosphoisomerase
MTA	Material Transfer Agreement
NARS	National Agricultural Research Systems
NGO	Non-Governmental Organization
nptII	Neomycin phosphotransferase (gene)
NRC	National Research Council (Canada)
PC	Product Clearance
PCR	Polymerase chain reaction
PCT	Patent Cooperation Treaty (System)
pds	Phytoene desaturase
PP	Proprietary Property (comprising IP and TP)
psy	Phytoene synthase (gene)
TP	Technical Property
tp	Transit peptide
TRIPs	Trade-Related Intellectual Property
UPOV	International Convention for the Protection of New Varieties of Plants
USAID	United States Agency for International Development
USPTO	United States Patent and Trademark Office
WTO	World Trade Organization
zds	(zeta)-carotene desaturase

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