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INTERNATIONAL TREATY ON PLANT GENETIC RESOURCES FOR FOOD AND AGRICULTURE

FIRST SESSION OF THE GOVERNING BODY

Madrid, Spain, 12-16 June 2006

PROGRESS REPORT ON WORK TOWARDS THE ASSESSMENT OF PATENT DATA RELEVANT TO AVAILABILITY AND USE OF MATERIAL FROM THE INTERNATIONAL NETWORK OF EX SITU COLLECTIONS UNDER THE AUSPICES OF FAO AND THE INTERNATIONAL TREATY ON PLANT GENETIC RESOURCES FOR FOOD AND AGRICULTURE: A DRAFT PATENT LANDSCAPE SURROUNDING GENE PROMOTERS RELEVANT TO RICE

1. International, regional and national patent systems provide extensive information about technological developments in fields of concern to agricultural policymakers, such as in the area of agricultural biotechnology and the use of plant genetic resources for food and agriculture. Patent information can therefore provide a tool for agricultural policymakers and other stakeholders. But the sheer quantity and complexity of information can make it difficult to use for those without specialist expertise and the technical capacity to conduct the necessary searches and analysis of patent information. FAO has thus identified a need for clear, accessible information products that can be used by the agricultural policy community.[1]

2. WIPO has cooperated extensively with the FAO on intellectual property (IP) and plant genetic resources for food and agriculture (PGRFA) since the early stages of negotiations on the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGR or 'the Treaty'). One increasing area of cooperation has been the development of patent searches and landscapes to inform policymakers of current IP trends and to provide a point of reference for a wide range of stakeholders engaged in consideration of issues relating to PGRFA; this has the objective of realizing the considerable potential of patent information systems to support policy dialogue.

3. Reflecting the most recent outcomes of this cooperation, the attached document is a working draft of a report on some draft patent searches and landscapes that have been undertaken

[1] See, *Report of the Commission on Genetic Resources for Food and Agriculture*, Ninth Regular Session, Rome, 14-18 October 2002 (para. 31, CGRFA-9/02/REP).

at the request of the FAO Commission on Genetic Resources for Food and Agriculture (CGRFA) at its ninth session and it illustrates some of the draft interim outcomes of the searches. As a first, interim outcome, the attached draft report is a factual description of the international patent landscape surrounding gene promoters relevant to rice.

- **Rice** was selected for the initial searches and for this interim draft landscape due to its crucial importance for food security; further searches are also being conducted for maize, potato and soybean to be added to the draft landscape at a later stage.

- The FAO selected **gene promoters** as an illustrative technology for the initial set of patent searches and analysis. Gene promoters regulate the transcription of genetic information from DNA (gene expression). They are therefore key tools in agricultural biotechnology and in the use of PGRFA in research and development. While the technology is complex, promoters can regulate whether, and where, target traits are expressed in a plant.

Some initial observations that have arisen from this first review include:

- The first review of patent landscapes provides information about trends in research and development on these key research tools, including the comparative degree of public and private sector activity, the emergence of research collaborations, and the genes and the traits they express that are of interest to the research community.

- Equally, at this stage, no conclusions can be drawn about the legal scope of the patent families identified, and their impact on the freedom of third parties to use these technologies. Records may be applications only, or if in force are likely only to have legal effect in a relatively small number of countries; the scope of the claims of any granted patent would need to be analyzed. This highlights that considerable additional analysis needs to be undertaken before making any judgement about the scope of legal availability of these technologies. However, it is likely that the technologies disclosed in these patent families would be available for open use in many developing countries. However, to give greater clarity, the scope of patent information examined needs to be extended to a far wider range of national jurisdictions, particularly developing countries.

- Finally, as pointed out in the earlier analyses in this area, the implications for the FAO International Treaty are difficult to assess. Further clarification may be helpful especially in relation to whether the forms of access to and use of PGRFA under the Treaty would involve the kind of genetic manipulation that entails the use of research tools such as gene promoters.

The draft is circulated as a work in progress to illustrate the general direction that the work is taking, and the kind of methodologies that are evolving in this work.

- Part 1 provides a brief institutional and historical background of the ongoing work.

- Part 2 provides an introduction to the role of gene promoters and the patent literature on them relevant to rice.

- Part 3 contains an analysis of the bibliographic data of the patent landscape surrounding gene promoters for rice, including sectorial analysis of assignees, research collaborations, patenting trends over time, geographical and sector-wise distribution, and location of the patents in the International Patent Classification (IPC).

- Part 4 provides an analysis of the technological and substantive data contained in the patent landscape, including the source genes and target genes of the promoters, types of promoters (constitutive, tissue-specific, etc) and monocot and dicot distribution.

It is to be emphasized that these draft interim outcomes are provisional and do not provide a legal opinion or freedom to operate analysis.

ANNEX

Draft
patent landscape
on
gene promoters in rice

CONTENTS

1. Background

2. This paper forms part of the ongoing cooperation between FAO and WIPO, which has existed since the early stages of the negotiations on the ITPGR. It has been prepared as a follow up to a Preliminary Report submitted by WIPO in 2004 to the Interim Committee of the Treaty[2] at the request of the CGRFA. While the overall work following up the request of the CGRFA and the preparation of similar landscapes for other crops are still under way, this tentative draft is made available in preliminary form to the first meeting of the Governing Body as a progress report on the cooperation between FAO and WIPO. This section provides a brief description of the background and evolution of this work.

3. At its ninth session, the CGRFA considered a 'Report on the International Network of Ex Situ Collections under the Auspices of FAO'[3] and requested WIPO to 'cooperate with FAO in preparing a study on how intellectual property rights may affect the availability and use of material from the International Network and the International Treaty.'[4]

4. Following this request by the CGRFA, WIPO conducted a few sample searches, using existing patent search algorithms, in order to test the methods and broadly illustrate the type of information that could be generated for the CGRFA. Beyond their illustrative purpose, these searches provided only a rough and generalized indication of broad patenting activity over time in relation to the general industrial and technological potential of the individual crops and forages, including many forms of industrial use of these crops and extracts of crops altogether beyond the ambit of the Commission's work.[5] One of the main outcomes of the Preliminary Report was, therefore, to illustrate the limitations of the conclusions that can be drawn from broad-brush patent searching or classification, and to underscore the need for careful analysis of the content, scope and implications of specific patents and patent families before any substantive assessments can be made.

It also clarified the distinction between using patent information as a means of tracking trends and developments in areas of technology – useful analysis that fills an important policy needs – and the resource-intensive search and analysis that is required to make a concrete assessment of the legal availability or otherwise of the specific technologies disclosed in patents, particularly if this were to cover numerous legal jurisdictions.

5. To report the searches to the CGRFA, WIPO submitted a 'Preliminary report on work towards the assessment of patent data relevant to availability and use of material from the International Network of Ex-Situ Collections under the Auspices of FAO and the International Treaty on Plant Genetic for Food and Agriculture (ITPGR)' to the Second Meeting of the

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[2] See, *Preliminary report on work towards the assessment of patent data relevant to availability and use of material from the International Network of Ex-Situ Collections under the Auspices of FAO and the International Treaty on Plant Genetic for Food and Agriculture (ITPGR)* Second meeting of the Commission on Genetic Resources for Food and Agriculture acting as Interim Committee for the International Treaty, Rome, 15 – 19 November 2004 (CGRFA/MIC-2/04/Inf.5)

[3] See, *Report on the International Network of Ex situ Collections under the Auspices of FAO* (Ninth Regular Session, Rome, 14-18 October 2002 (paras 23 to 26, CGRFA-9/02/11).

[4] See, *Report of the Commission on Genetic Resources for Food and Agriculture*, Ninth Regular Session, Rome, 14-18 October 2002 (para. 31, CGRFA-9/02/REP).

[5] The sample patent searches were conducted by the Institute for Genome Sciences and Policy at Duke University, Durham, North Carolina, USA, and this contribution is gratefully acknowledged.

CGRFA acting as the Interim Committee of the Treaty.[6] The Interim Committee "welcomed this Preliminary Report, which was of significant value to the agricultural community, and the continuing cooperation with WIPO".[7] In its Report, the Interim Committee "looked forward to receiving the report of the next stage of this work, in line with the follow-up activities identified in the preliminary report."[8]

6. The Preliminary Report concluded that, above all, this initial exercise had illustrated the need for more extensive examination of the patent landscape, and the broader legal context that surrounds particular crops and their utilization, before any practical assessment can be made about the effect on availability and use of material that may be covered by patents. It was clear that no substantive conclusions can or should be drawn from these basic data, and these data were unlikely to yield overall insights on availability or non-availability of PGRFA from the Nework and the Treaty. Given these limitations discerned by the initial searches, the Preliminary Report therefore identified possible followup activities, which included:

> "*[d]eepening the study of IP issues by focusing on specific technologies* … Such studies would provide detailed information about the patent landscape surrounding selected inventions that constitute PGRFA covered by the International Network and the International Treaty. Certain specific technology areas would need to be selected for pilot studies in this area. Such follow-up studies could focus on particular patent families and technologies"[9]

The present document provides exactly such a patent landscape surrounding selected inventions that constitute PGRFA, namely gene promoters used in rice. The next section describes how these particular technologies were selected, how the relevant patent families were identified and what the limitations of the resulting patent landscape are.

a. An illustrative draft patent landscape: gene promoters relevant to rice

7. As suggested by the Preliminary Report, one initial pathway to gaining insights on the question posed by the CGRFA is to develop an accurate assessment of patents and patent applications surrounding key technologies which make use of PGRFA. There are different forms of use of PGRFA – use for genetic modification to create genetically modified crops, such as use in conventional breeding, use in agriculture and use as food. The kinds of use in question will greatly influence the relevance and scope of patents that are searched for and analyzed. Once the scope of relevant technologies is clarified, patent landscapes or patent maps can be developed which set out the geographical and legal scope of patents on an individual technology or group of technologies. Compared to quantitative patent counting in a general field of technology, such a landscape, which incorporates a substantive analysis of the patent families concerned, may provide for a more in-depth, qualitative and accurate understanding of whether, and if so how, existing patents may have implications for the availability and use of genetic material from the Network and the Treaty. Existing studies of structure of intellectual property ownership in

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6 See, CGRFA/MIC-2/04/Inf.5

7 CGRFA/MIC-2/04/REP, paragraph 31.

8 Ibid.

9 Paragraph 56(ii), Preliminary Report (CGRFA/MIC-2/04/Inf.5).

agricultural biotechnology have found that a thorough understanding of the structure of assignment of IP rights in agricultural biotechnology is a prerequisite to provide a basis for considering broader questions of science policy in agriculture, public sector IP policies and the design of more effective IP management strategies.[10]

8. As mentioned in the Preliminary Report, the follow-up activity was to select specific technologies that constitute PGRFA covered by the International Network and the International Treaty and produce patent landscapes thereof, in order to gain a deeper understanding of the possible implications for availability and use of material in the Network and Treaty. In this case, the technology selected were gene promoters relevant to rice, maize, potato and soybean. Gene promoters were selected for a number of reasons which include:

- promoters may illustrate that for some technologies the application of a patented invention that constitutes PGRFA from one crop covered by the International Network and Treaty might cut across to application in other crops, which might be either inside or outside the Network and Treaty. When such an invention is patented, this cross-cutting factor complicates the possible implications of intellectual property rights for the availability and use of material under the Network and Treaty. To illustrate and further explore this complex question, it was decided to select gene promoters for rice, maize, potato and soybean as an example of such a technology. The selection of gene promoters allows a deeper understanding of this question, while still maintaining a focus on a specific technology and a manageable set of patent literature.
- constitutive promoters, such as the CaMV 35S promoter, represent an important class of molecular research tools for which public agricultural research has been conducted.[11] Promoters are regarded as research tools crucial for the regulation of the expression of genes of interest in PGRFA. As such, they may have an influence on follow-on research and down-stream development of PGRFA.[12] As has been observed with regard other agricultural research tools, such as transformation technologies, “the complexity of the patent landscape has created both real and perceived obstacles to the effective use of this technology for agricultural improvements by many public and private organizations worldwide.”[13] The selection of gene promoters for a sample landscape might also shed some light on these questions.
- while the present draft focuses only on rice promoters and analyzes those in depth, it was possible, in preparing the draft, to build upon high-quality past reports on the patent landscape of gene promoters and agricultural biotechnology more generally.[14] However, the present draft reflects only a patent sample that was selected for its relevance to the

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[10] See, for example, Wright, DB, 1998. Public germplasm development at a crossroads: biotechnology and intellectual property. *Californian Agric.*, **52**, 8-13; and, Graff GD, Cullen SE, Bradford KJ, Zilberman D and Bennett AB, 2003. The public-private structure of intellectual property ownership in agricultural biotechnology. *Nature Biotechnology*, **21**, 989-995.

[11] Ibid., 993.

[12] Rodriguez C R, 2003. Promoters used to regulate gene expression, Chapter 1 and 2 , Cambia Intellectual Property Resources, Australia, 2.

[13] Broothaerts W, Mitchell HJ, Weir B, Kaines S, Smith LMA, Yang W, Mayer JE, Rodrıguez C R, Jefferson RA, 2005. “Gene transfer to plants by diverse species of bacteria.” *Nature* **433**, 629.

[14] See, for examples, Graff GD, Cullen SE, Bradford KJ, Zilberman D and Bennett AB, 2003. The public-private structure of intellectual property ownership in agricultural biotechnology. *Nature Biotechnology*, **21**, 989-995, and Rodriguez C R, 2003. Promoters used to regulate gene expression, Chapter 1 and 2 , Cambia Intellectual Property Resources, Australia.

International Network, the International Treaty and the request from the CGRFA at its ninth session. It is intended as an illustrative sample to exemplify some of the policy implications, rather than to provide a full patent landscape for operational use by researchers;

- within existing assessments of the overall agricultural biotechnology patent landscape,[15] different types of gene promoters (see Section 2 below) fall on either side of the distinction between enabling technologies, which constitute the research tools required to create transgenic crops on the one hand (e.g., constitutive promoters), and trait technologies, which provide the genetic basis for new functionalities, on the other hand (e.g., tissue-specific and developmental-specific promoters). Thus the choice of gene promoters as an initial focus for the landscapes allows an exploration of possible implications of IP rights over both enabling technologies and trait technologies for availability of material in the Network and Treaty. It thus might provide an additional perspective on the question of how far downstream in the innovation chain IP rights might have implications for availability and use of material.

9. Once gene promoters were selected as the subject matter of the sample landscape, the following methodology was applied in producing the draft.

b. Methodology

10. The search methodology for obtaining patent publications relating to the area of rice promoters was mainly based on keyword searches in six international patent databases. In addition, various search strategies based on applicant, owner or assignee and country-wise coverage queries were also used. The search for relevant patents was conducted using keywords in title, abstract and claims fields of all patents from 1836 to date available in the databases.[16]

11. The search algorithms used included the following parent string:

"Rice" and ("Promoter" or "Regulatory" or "Transcription" or "control") and ("tissue" or "seed" or "root" or "pollen" or "stamen" or "anther" or "flower" or "leaf" or "callus" or "constitutive" or "inducible").

Other keywords such as parts of the parent string, assignee name, etc. were also used.

12. The databases searched included publicly available ones, for example, the PatentScope database of the PCT, USPTO, Espacenet, etc. and subscription-based databases, for example, Delphion, Derwent, PatWeb (Micropatent), etc. The data retrieved from the different sources was stored in a standard worksheet template. This consisted of about 750 patent documents, which were then assessed and filtered to ensure their relevance to this draft sample landscape.

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[15] Graff GD, Cullen SE, Bradford KJ, Zilberman D and Bennett AB, 2003. The public-private structure of intellectual property ownership in agricultural biotechnology. *Nature Biotechnology*, 21, 992

[16] For coverage limitations see important disclaimers in Section 1.c.

13. It was found that not all the patents were related to rice promoters directly. Most of the patents were in the field of genetic engineering of rice. Many of these patents employed promoters are well known in the art like, ubiquitin, actin, 35S promoter and hybrid promoters. After sorting the patents that were directly related to rice promoters, 250 patents were obtained, which were then reduced to one patent per patent family. The resulting data, containing 69 records, was subsequently organized in a final worksheet under relevant bibliographic and technical subject fields. The list of the 69 records contained in the final worksheet is given in Appendix-1.

14. The bibliographic subject fields in the final worksheet include PCT and national publication number, family members, application number, title, assignee or applicant, date of publication, priority date, IPC classes and inventor.

15. The technical subject fields in the final worksheet include objective/Derwent title, abstract, independent and dependent claims, source plant, source gene, reporter gene, target gene, assay, expression pattern or specificity, and transformed plant.

16. The data set obtained was analyzed to generate bibliographic and technical landscapes.

c. Limitations and disclaimers of the draft patent landscape

17. Based on this methodology, a draft patent landscape was established in order to broadly illustrate the type of information that could be generated. When reviewing the draft and querying what it can tell us about the degree to which patents may affect the availability of material from the International Network or the International Treaty, it is important to emphasize that, at the current stage of the work, this preliminary landscape in itself gives no substantive guidance on the availability of genetic material from the selected crop. The current draft contains merely a factual description of the patent landscape and literature and has not yet been analyzed with regard to possible impact on availability and use. In other cases, it depends critically on how patents have been licensed and on specific patent claims. The numbers of patents or patent applications counted should not be taken even as a final or static reflection of the likely number of relevant patents.

18. The main function of this preliminary draft is to illustrate the importance of looking in detail at the individual patents and patent families if one wishes to obtain a differentiated understanding of the question raised by the CGRFA. Beyond such illustrative purposes the data provide merely a general indication of overall patenting activity in relation to gene promoters in rice. This Section therefore contains a number of important disclaimers on the coverage and contents of the draft landscape described in the next chapters.

19. The following important disclaimers must therefore be recognized, before reviewing the draft patent landscape described in Sections 3 and 4:

- This is merely a factual description of the patent landscape, i.e. an analysis of the patent applications and granted patents in various jurisdictions surrounding the selected technology. It is not possible to infer any effects of the patenting activity on the availability and use of genetic material without further research, which is still under way.

Therefore, at its present stage of development, this patent landscape is merely a general description of the patent activity in relation to gene promoters for rice;

- Database coverage and geographical limitations: the patent databases used cover only certain years from certain jurisdictions. The coverage of certain jurisdictions in the search engines and data sets of existing databases do not adequately cover all data. In particular, developing country jurisdictions are not fully covered. Efforts are currently under way to obtain additional patent data from key developing country jurisdictions such as China, India and other patent-granting authorities;
- The draft described in Sections 3 and 4 does not constitute an exhaustive landscape on agrobiotechnology in general and gene promoters specifically. Rather, it is a sample that was selected for its relevance to the request from the CGRFA, focused on the ITPGR and the International Network of Ex-situ Collections. There are other, full scale patent landscapes on gene promoters, which include, but are not limited to, rice promoters and have been conducted for operational use in freedom-to-operate analyses[17] and topical reports and exchanges on recent developments in the patent situation surrounding gene promoters.[18] This sample is intended as a sample to illustrate some of the policy implications of the study, rather than provide an operational landscape for use by scientists.
- A patent landscape such as the draft contained in Sections 3 and 4 would normally need to be periodically updated. However, it is not foreseen that this draft would be periodically updated, because it is intended to serve illustrative and policy purposes, rather than as a concrete freedom to operate analysis.
- What could not be firmly validated in the initial searches was whether they missed some patents that should have been covered through the searches (i.e., confirming the full sensitivity of the searches). This will still be verified in the further development of the draft landscape;
- This draft landscape does not address the legal status and licensing status of the patents. If anyone wanted to draw freedom to operate conclusions from such a draft, it would be essential to reflect legal and licensing status of the patents. Since this is not included, it is not possible to read the draft landscape as any legal or technical advice on freedom-to-operate in the use of rice gene promoters.

d. Current status and next steps

20. The present document is merely a progress report. It does not contain the finalized and completed landscape on gene promoters. It contains a draft, which is a work in progress.[19] A peer group will review the draft landscape and provide comments, inputs and improvements to the current draft. These comments and inputs will be incorporated into a final version, which will eventually be published by FAO and WIPO.

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[17] See, Rodriguez C R, 2003. Promoters used to regulate gene expression, Chapter 1 and 2 , Cambia Intellectual Property Resources, Australia.

[18] http://www.patentlens.net/jiveforums/forum.jspa?forumID=21

[19] The initial patent searches and landscape analysis for Sections 4 and 5 below were prepared by Dr. Malathi Lakshmikumaran of Lakshmikumaran & Sridharan, New Delhi.

2. Introduction: gene promoters

21. The utilization of PGRFA for crop genetic improvement, whether by means of farmers' selection, classical plant breeding or transgenic technology, is essential in adapting to unpredictable environmental changes and future human needs, as recognized by the International Treaty.[20] Genetic engineering of PGRFA enables researchers and plant breeders to bring together useful genes from a wide range of living sources in one plant, not just from within the crop species or from closely related plants. It thus expands the possibilities for developing PGRFA beyond the limitations imposed by traditional cross-pollination and selection techniques. Many traits have already been incorporated into PGRFA covered by the Network and Treaty through transgenic technology, including herbicide resistance, drought and salt tolerance, improved colors in fiber and flower crops, resistance to water logging, nutritional benefits, and longer shelf lives.

22. The underlying reason that transgenic plants can be constructed is the universal presence of DNA (deoxyribonucleic acid) in the cells of all living organisms. Genes are discrete segments of DNA that encode the information necessary for assembly of a specific protein. The proteins then function as enzymes to catalyze biochemical reactions, or as structural or storage units of a cell, to contribute to expression of a plant trait. The general sequence of events by which the information encoded in DNA is expressed in the form of proteins via an mRNA intermediary is broadly referred to as gene expression and is shown in Figure 1. As shown below, gene promoters play a crucial role in this process.

Fig. 1

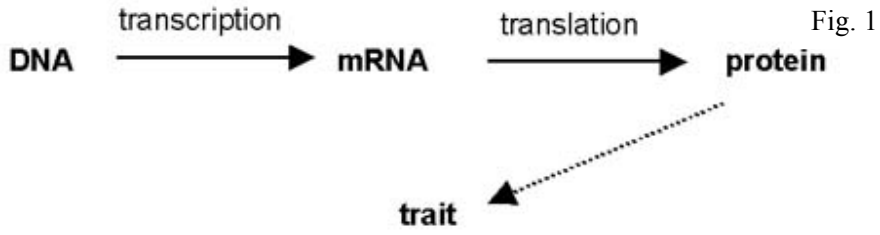

Fig. 1: Steps of Gene Expression

23. One of the earliest findings in plant transgenic research was that in order to be expressed, a transgene needed to be linked to a plant specific promoter i. e. a promoter derived either from a plant gene or a plant pathogen, which is normally expressed in plant cells. Promoters from plant sources generally direct expression in a developmental and/or tissue specific manner and this specificity of expression is generally reflected in their expression patterns in novel hosts.

24. Plant promoters have played a very critical and significant role in many successful genetic transformation experiments that have resulted in the production of crops with value-added traits. During the early phase of genetic engineering, very few promoters were available and these were used for a wide range of traits. Promoters derived from pathogens have generally been used to direct the expression of transgenes in plants because they promote high expression of the transgene.

25. The identification of the cauliflower mosaic virus promoter (Ow *et al*., 1986) was a big step in plant molecular genetics, and it became an almost universally used promoter. Another example of the promoter derived from a pathogen includes the mannopine synthase 1'2' dual

[20] See, paragraph 6, Preamble, FAO International Treaty on Plant Genetic Resources for Food and Agriculture of 2001.

promoter (Peach and Veltin, 1991) and the nopaline synthase promoter (An *et al*., 1990) both derived from the T-DNA of *agrobacterium*. However, the most generally used promoter is that of the 35S RNA of cauliflower mosaic virus.

26. The CaMV 35S RNA, a polycistronic viral replicative intermediate, accumulates to high levels during infection. Though CaMV normally infects *Brassica* plants, the 35S RNA promoter extending to – 400 bp directs high levels of transgene expression in different tissues in a wide range of plants, both monocotyledons and dicotyledons. Extensive promoter analysis of CaMV shows that it comprises differing domains, each producing expression in different tissues that in combination produce the observed constitutive mode of expression.

27. There are virtually an endless number of promoters; potentially as many as there are genes (e.g. a diploid flowering plant has an estimated 25,000 genes). As full genome sequences of different organisms are becoming available (e.g. Arabidopsis, Rice), a great number of promoters are being identified, isolated and evaluated, and many more are likely to come up in the near future (Rodriguez CR, 2003).

Structure of a Promoter

28. A promoter may be defined as a regulatory element which is located upstream to the coding sequence of a gene. The structure of a plant (eukaryotic) gene promoter can formally be divided into two parts; the 'minimum promoter' or 'core promoter', which constitutes the minimum amount of DNA which allows the gene to express, and a 'proximal promoter region' containing the regulatory elements which increase and control the expression of the minimum promoter. See figure 2.

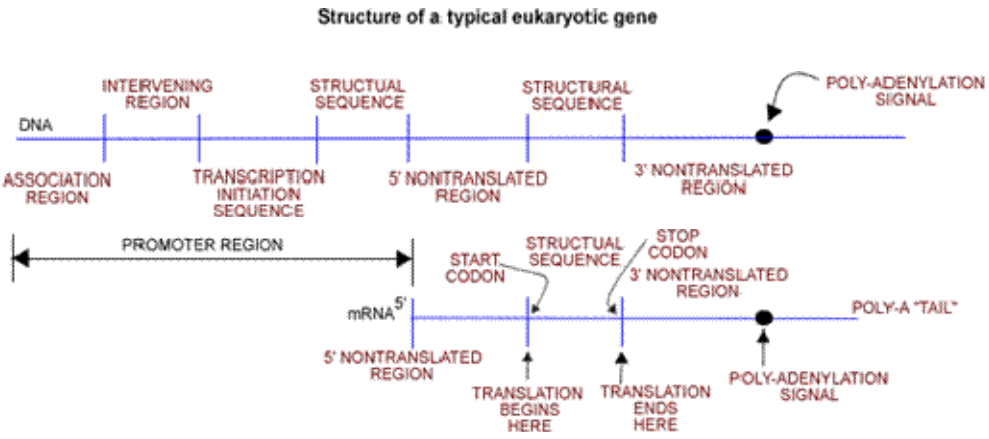

Figure 2.

* Rodriguez C R, 2003. Promoters used to regulate gene expression, Chapter 1 and 2 , Cambia Intellectual Property Resources, Australia.

29. The minimal region consists of a transcription start site (TSS) from where the actual transcription starts. The transcription start site is also called 'CAP site' or 'start site' and is designated as +1. The region where RNA polymerase II binds in the minimal promoter region is referred to as "TATA box", the most conserved region of the promoter and is located at 25 to 45 bp upstream of the TSS. The TATA box itself is not thought to play a role in the control of gene expression, although its presence is necessary for accurate initiation of transcription. For genes transcribed by RNA polymerase II, the minimum promoter consists of approximately 100 bp of DNA 5' of the transcription start (the 5' flanking sequence), including the TATA box (TATAA), and the "CAAT box" (GGCCAATCT) if present.

30. The CAAT box is a consensus sequence located at -80 bp from TSS. It plays an important role in promoter efficiency by increasing its strength, and it seems to function in either orientation. In some plant promoter sequences the CAAT box is replaced by a consensus sequence called the "AGGA box". These are the DNA sequences which are necessary for assembly of the transcription initiation complex. Many highly expressed genes contain the TATA box in the minimal promoter region but it has been reported that a large group of genes like housekeeping and photosynthetic genes lack the TATA box and such promoters are called TATA less promoters.

31. The region (–90 to –400) upstream to the minimum promoter constitutes the proximal promoter region. The proximal promoter region contains the regulatory sequences where DNA-binding proteins are specifically bound at these regulatory elements and control the expression of specific genes by interacting with components of the transcription initiation complex. Several conserved DNA sequences have been found in the upstream regions of genes encoding seed storage proteins (Casey and Domoney, 1987) including a 'vicilin box' and 'legumin box' (Fig. 3) (Gatehouse *et al*., 1986). The structure of a seed specific promoter is depicted in Figure 3.

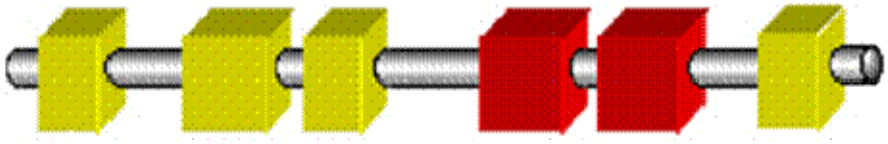

Figure 3: Structure of a seed specific promoter of a legumin gene

Types of Promoter:

32. Promoters are classified based on the expression pattern of the gene. Promoters can direct different expression patterns of a gene in a plant. The expression pattern is constitutive for some genes, i.e. it is expressed in the whole plant. Whereas, for some other genes, constitutive expression may be detrimental and expression is limited to specific organs such as the nodule, stamen, or specific tissue types, such as callus. Some genes are expressed upon certain environmental cues such as exposure to heat, light, pathogen infection, insect damage or exposure to certain chemicals. Thus, depending on the expression pattern of the gene, promoters are classified into the following categories:

(a) *Constitutive promoter:* The gene under the control of the constitutive promoter expresses throughout the plant regardless of the tissue types, developmental stage and environmental conditions. CaMV 35S is the best example of a widely used constitutive plant promoter.

(b) *Tissue-specific and developmental stage specific promoters*: The gene under the control of the tissue specific and/ or developmental stage specific promoter is expressed in specific tissue(s) or at certain stages of development. For example, some genes express only in tubers, leaf, stem, photosynthetic tissue, callus, roots, flower, petal, stamen, anther, tapetum, ovary, fruit, xylem, phloem, seeds, and other parts of the plant.

(c) *Inducible promoters*: Inducible promoters are quite popular in recent years because their performance is not conditioned to endogenous factors, but rather to external factors that ideally can be artificially controlled. Within this group, there are promoters modulated by abiotic factors such as light, oxygen level, heat, cold and wounding. Since some of these factors are difficult to control outside an experimental setting, promoters that respond to chemical compounds, which are not found naturally in the organism of interest, are of particular interest. Along those lines, promoters that respond to antibiotics, copper, alcohol, steroids, and herbicides, among other compounds, have been adapted and refined to allow the induction of gene activity at will and independently of biotic or abiotic factors.

(d) *Synthetic promoters*: Synthetic promoters are composed of different domains of the same or different promoters. Various strategies have been used to develop synthetic promoters. The problem of homology-based gene silencing can be avoided by constructing synthetic promoters which are functionally equivalent to the parent promoter with minimum sequence homology.

***Cis* and *Trans*-Acting Elements:**

The regulatory elements in the promoter sequence are termed *cis*-acting sequences (since they affect the activity of transcription units they are adjacent to), and the DNA-binding proteins are referred as trans-acting factors (since they are the products of genes removed from their site of action). The *cis*-acting sequences are required to be at a (more or less) fixed distance from the transcription initiation point, and in the correct orientation relative to it, in order for the protein-protein interaction between the transcription initiation complexes to form correctly. All genes that are examined in this patent landscape contain multiple *cis*-acting sequences, which interact with multiple *trans*-acting factors. Some of these interactions have been readily detectable, others less so, possibly corresponding to the abundance and binding strengths of the different DNA-binding proteins.

Importance of Tissue Specific Promoters

33. Promoters are regarded as molecular tools crucial for the regulation of the expression of genes of interest. As such, these have a significant influence on downstream research and development in breeding and agrobiotechnological research on PGRFA. For example, tissue- and time-specific expression of toxins in transgenic plants were proposed to limit production of toxin

to the most economically sensitive or most vulnerable part of the plant or to a specific time[21]. This strategy does not require external refuge; the plant itself acts as such.[22]

34. However, the use of a constitutive promoter has several drawbacks, one of them being that the gene of interest is expressed in almost all tissues and at times when it is not needed or even unwanted. Therefore, a second generation of promoters became available in the early 1990's which were tissue-specific, for example leaf-, tuber-, root-, or seed-specific.

35. Spatial, temporal, and inducible expression of a transgene, such as the insecticidal Bt gene, in transgenic plants is one of the features of current resistance management strategies. Continuous and constitutive expression of the Bt gene in the plant results in significant selection pressure on pest populations. Tissue-specific (i.e., leaf-, stem-, root-, boll-, pod- or seed-specific), stage-specific (vegetative or reproductive), and wound-specific promoters can be employed to rationalize Bt gene expression. Along with increased interest in certain PGRFA as model systems for developmental molecular biology, numerous genes and associated promoters have been described which exhibit a wide range of tissue and/or developmental expression patterns. However, in order to improve both agronomic and grain quality traits in transgenic crops, it will be important to precisely control gene expression in both a tissue-specific and temporal manner.

Target Genes

36. The region located downstream to the promoter region is called the coding region of the gene or 'target gene'. It contains the coded information which designates the amino acid sequence of the protein to be produced. The amino acid sequence of the protein determines its shape and thus the function of that protein. During protein production, a complimentary copy of the coding region, referred to as 'mRNA', is made, which travels from the nucleus of the cell (where the immobile DNA is located) to the cytoplasm (where the amino acids for building proteins are located).

37. Target genes include reporter genes, selectable marker genes and genes of important agronomic traits:

Agronomically Important Genes

38. This category includes genes that confer resistance to herbicides, insect pests, viruses, fungal and bacterial infection and environmental stresses such as drought, salt, heat, freezing etc. They also include genes that increase nutritional value and improve crop productivity.

Reporter Genes

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[21] See. Gould F, 1988a. Trends in Ecology and Evolution, **3**, 515-518; Gould F, 1988c. In: *Biotechnology, biological pesticides and Novel Plant-Pest resistance for Insect Pest Management*, Proceedings, pp. 146-151 (eds. D. W. Roberts and R. R Granadoes). Ithaca, New York: Boyce Thompson Institute for Plant Research; and Gould F, and Anderson A, 1991. Effects of Bacillus thuringiensis and HD-73 delta-endotoxin on growth, behavior and fitness of susceptible and toxin0-adapted strains of Heliothis virescens (Lepidoptera: Noctuidae). *Environmental Entomology*, **20**, 30-38.

[22] Gould F, 1988b. Evolutionary biology and genetically engineered crops. *BioScience,* **38**, 26-33.

39. The investigation of plant gene promoters has been greatly advanced by the use of reporter gene constructs in transgenic PGRFA. The coding sequence 'driven' by a promoter sequence under investigation can be chosen for ease of assay, to allow the activity of the promoter to be determined, i.e. in which cells, in response to which stimuli, the promoter is active. For example, the coding sequence from the E. coli bacterial β-glucuronidase (GUS) gene is the most common reporter gene used in plants. It is readily assayed qualitatively by histochemical staining using substrate 5-bromo-4-chloro-3-indolyl glucuronide (X-gluc). Various reporter genes used for the assay of the promoter activity are given in Table1.

40. Promoter-reporter gene fusions have been widely used in the analysis of gene expression in PGRFA. If an assay for the normal product of a gene is not available, or if it is desired to investigate the precise cell types where a particular gene is being expressed, the coding sequence of a gene can be replaced with that of a 'reporter' gene. Such constructs are usually referred to as promoter-reporter gene fusions.

41. Common reporter genes include the bacterial genes coding for antibiotic resistance to chloramphenicol (*chloramphenicol acetyltransferase- CAT*) and kanamycin (*neomycin phosphotransferase- nptII*). Reporter genes which allow the visualization of expression in whole tissues include *luciferase* (*Luc*), *β-glucuronidase* (*GUS*) and aqueorin and green fluorescent protein (*GFP*). The most extensively used plant reporter gene is the *E. coli* β-*glucuronidase* (*GUS*) gene.[23] Transformation vectors have been developed in which the GUS coding region has been placed downstream of a polylinker restriction enzyme sequence within a binary *agrobacterium* vector, allowing the easy insertion of any desired promoter fragment.

42. GUS is an very stable enzyme, resistant to thermal denaturation, detergents and alkali, can tolerate large N and C terminus additions without loss of activity. In the histochemical assays, the substrate X-gluc (5-bromo-4-chloro-3-indolyl glucuronide) is cleaved by β-glucuronidase to produce an indoxyl derivative that subsequently undergoes an oxidative dimerization to form an insoluble and highly coloured dye. This blue dye can be easily visualized and provide precise marker of the cell type in which the fusion gene is expressed.

Table 1: Commonly used reporter genes

Protein	**Activity & Measurement**
CAT (chloramphenicol acetyltransferase)	Transfers radioactive acetyl groups to chloramphenicol; detection by thin layer chromatography and autoradiography
GAL (β−galactosidase)	Hydrolyzes colorless galactosides to yield colored products.
GUS (β−glucuronidase)	Hydrolyzes colorless glucuronides to yield colored products.
LUC (luciferase)	Oxidizes luciferin, emitting photons.
GFP (green fluorescent protein)	Fluoresces on irradiation with UV.

[23] Jefferson RA, 1987. Assaying chimeric genes in plants: the GUS gene fusion system. *Plant Molecular Biology Reporter*, **5**, 387-405.

Selectable Marker Genes

43. Selectable marker genes are used to recover transformants after gene transfer experiments. It encodes a protein that confers on transformed cells the ability to grow on media containing a compound toxic for untransformed cells. The introduced gene encodes for the enzyme insensitive to inhibition by the selective agent.

44. The commonly used selectable marker genes are antibiotic resistant genes such as herbicide resistant genes, such as the 'pat gene' from S. *viridiochromogenes*, encoding *phosphinothricin acetyltransferase* that allows selection with the herbicide *Basta*; the 'bar gene' (*bialaphos* resistant gene) from *Streptomyces hygroscopicus* encoding *phosphinothricin* a*cetyltransferase* that is able to detoxify the herbicide *phosphinothricin*; the 'nptII gene', also known as aphA2 or aph(3)II, which encodes for neomycin *phosphotransferase* and detoxifies a number of *aminoglycoside* antibiotics including neomycin, *kanamycin* and *geneticin*; the 'hptII gene' (hph or aph (3')IV) that encodes for *hygromycin phosphotransferase* and detoxifies *hygromycin* B; and the 'spt gene' that encodes for streptomycin *phosphotransferase*.

Genetic Transformation

45. 'Transformation' is the heritable change in a cell or organism brought about by the uptake and establishment of introduced DNA. PGRFA have been transformed using vectors comprising of the promoter and the target gene (gene of interest) for expression. Transformation of the gene of interest into a plant may be done through several methods:

46. Direct gene transfer: This is a method of gene transfer by which direct uptake of naked DNA by the plant cell occurs. It does not require any biological vector system and since it is a physical process there is no problem of host range specificity. In the chemical method the recombinant DNA is transferred into plant protoplasts under the presence of calcium phosphate or polyethylene glycol (PEG). In the physical method, which is called electroporation, electrical impulses of high field strengths are used to reversibly permeabilize cell membranes to facilitate the uptake of large molecules, including foreign DNA. Thus, insertion of DNA fragments into the cells requires proper instrumentation and a high degree of dexterity.

47. Another technique that has attained major importance is the biolistic approach. In this approach, microscopic tungsten or gold particles (4mm) carrying the recombinant DNA are accelerated to 400m/s and allowed to penetrate intact cell walls of calli or protoplast. In liposome-mediated transformation DNA is loaded into phospholipid spheres (liposomes) and these liposomes are mixed with protoplasts to result in lipofection.

48. Another approach is a*grobacterium*-mediated transformation. A*grobacterium,* a gram negative plant pathogen, is a natural genetic engineer and is therefore a very effective vehicle for introducing foreign DNA into plant species. Upon infection at plant wound site, a*grobacterium* transfers its segment of oncogenic DNA into the plant genome by illegitimate recombination. The T- DNA is flanked by 26-bp direct repeats, generally referred to as border repeats, and the DNA that lies between these border repeats is transferred and integrated into the plant genome. A foreign gene inserted in the T-DNA of the bacterial plasmid (Ti or Ri) is thus integrated into the genome of the PGRFA.

49. The efficiency of T-DNA transfer via *agrobacterium* to a plant varies considerably, not only among plant species and cultivars, but also among tissues. Various protocols for *agrobacterium*–mediated transformation of PGRFA use leaves, shoot apices roots, hypocotyls, cotyledons, seeds and calli derived from various parts of a plant. In other methods, the transformed tissue is not removed from the plant but left in its natural environment, thus the transformation takes place *in planta. In planta* transformation is very successful in Arabidopsis.

RICE PROMOTERS

50. Rice is the most important food crop in the world. Almost half of the world's population depends on rice as their staple food. During the last few years, rice genetic transformation has taken rapid strides and the focus has shifted to use rice as a model monocotyledon system, similar to the use of *Arabidopsis* as a model for dicotyledons. Additionally, rice was the first crop plant that had its genome sequenced and the sequencing of a complete rice genome sequence has opened up innumerable opportunities not only for rice but also for the development of PGRFA and the agricultural research and breeding community at large.

51. Plant breeders can use the rice genome map to precisely select the best progeny from plant breeding crosses. This could accelerate the improvement of rice varieties. The map can also be used by agrobiotechnological inventions to select and transfer single genes from one rice variety to another, so that discrete improvements can be made without mixing together all of the genes from both varieties.

52. The rice genome sequence is useful as a research tool to understand how crops resist stress or how they confer health benefits to food. Because of the considerable genetic similarity between rice and other cereals, such as wheat and maize, the rice genome map has also been describeed as a virtual map of cereal species. Therefore, the rice genome sequence could accelerate the improvement of all cereal species.

53. The promoter is a significant region of a gene which regulates transcription, the first and the most important step of gene expression. Isolation and analysis of promoters from rice genes is therefore essential for understanding the mechanisms of gene expression and also for controlling foreign gene expression in transgenic rice. Rice gene promoters have been identified from a variety of rice genes, such as rice act-1 gene, ubiquitin gene, Beta.-glucanases gene, Adenylate kinase gene, Peroxidase gene, Germin protein, Catalase A gene, etc. These promoters belong to various categories of promoters' i.e. constitutive, tissue specific and inducible.

54. Rice has been engineered to withstand different abiotic stress conditions, such as drought, heat, cold, salinity, and mineral deficiency or to enhance its nutritive value. Some of these genes of important agronomic traits like *CryI* gene, 2. *β-hydroxylase* gene, *Carotene desaturase*, *Proline transporter* gene, *Cysteine proteases*, MADS-Box Genes etc, are operably linked to rice promoters.

55. Commonly rice transformation is efficiently mediated either through biolistic transformation or a*grobacterium*. *Agrobacterium*-mediated transformation has an advantage over particle bombardment, because it is relatively simple and inexpensive method of transformation.[24]

56. Numerous inventions resulting from the research on rice gene promoters have been patented. The next sections describe the state of the art in this field as can be derived from an analysis of the patents related to rice promoters.

3. Bibliographic Landscapes

A. RESEARCH COLLABORATIONS

It is noteworthy that about 20% of the patents related to rice promoters, i.e. 14 out of 69 patents, are in the name of several applicants, owners or assignees. The data suggest that the percentage of research collaborations is a significantly A key factor is that the costs involved in agri-biotech research are very high. Hence, universities, institutes and companies look for optimal utilization of expertise and resources available across the various research facilities.

The table below lists the major research collaborations on inventions related to rice promoters.

Major Research Collaborations

Assignee 1	Assignee 2	Assignee 3	No of Patents
Plant Functional Genomics Co.Ltd	Plant Genome Center Co. Ltd.	-	4
Toudai Tlo, Ltd.	National Institute of Agrobiological Sciences	Nippon Paper Industries Co., Ltd	1
Japan Tobacco Inc.	Syngenta Limited	-	1
Hokko Chem Ind Co Ltd	National Agriculture Research Center	-	1
Japan Science & Technology Agency	National Agriculture & Bio-Oriented Research Organization	National Institute Of Agrobiological Sciences	1
Mitsui Gyosai Shokubutsu Bio Kenkyusho:kk	Mitsui Petrochem Ind. Ltd.	-	1

[24] For a patent landscape on *agrobacterium*-mediated transformation see, www.cambia.org.

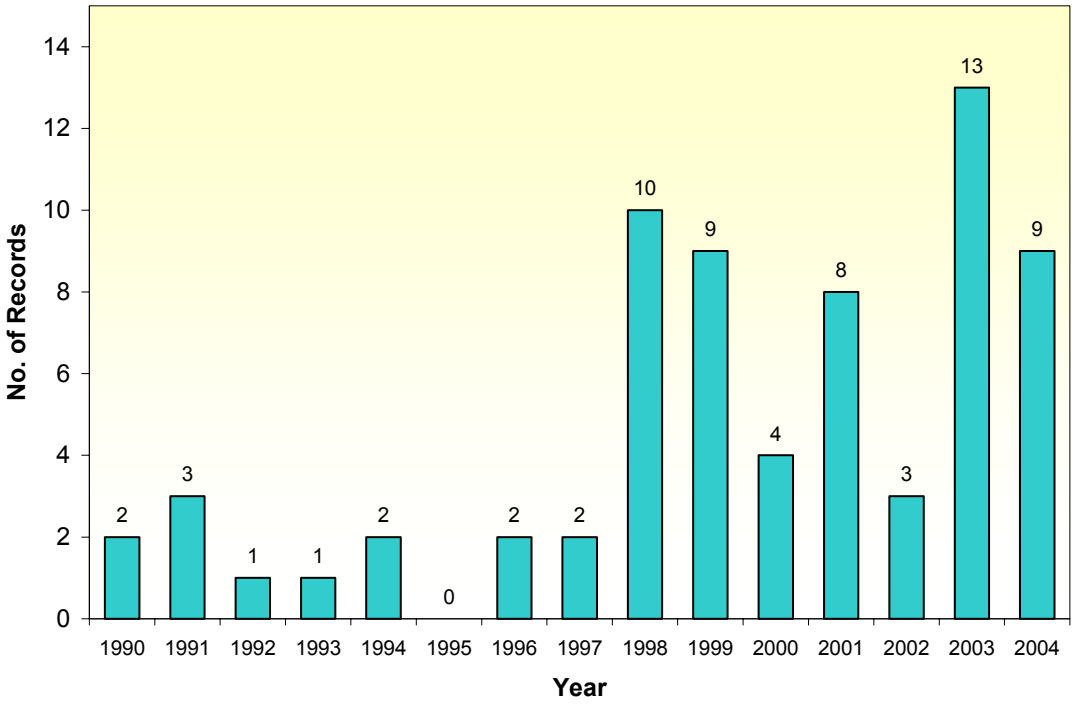
Dekalb Genetics Corp.	Cornell Research Foundation, Inc.	-	1
Japan International Research Center For Agricultural Sciences	Bio-oriented Technology Research Advancement Institution		1
Natiobal Institute of Agrobiological Sciences	Bio-Oriented Technology Research Advancement Institution		1
Mitsubishi Corp	Mitsubishi Chem Corp	-	1
Japan International Research Center for Agricultural Sciences	National Agriculture and Bio-Oriented Research Organization	-	1

B. PATENTING TRENDS OVER TIME

57. There was sporadic patenting activity in this field until 1997. The mid 1990s saw a radical advancement in the research tools and methods crucial to agro-biotech research. A number of genes of agronomic importance were identified and a need to have different types of promoters was felt in order to produce transgenic plants using these genes. Further, many groups world-wide were simultaneously involved in the sequencing of the rice genome. This led to identification and characterization of promoters in the rice genome towards the later nineties.

58. Hence, there was a sudden spurt in the number of patent applications filed and patents granted from 1998. Since then, the number of patents has been consistently higher with the exception of the years 2000 and 2002. The year 2003 saw the maximum number of patents filed in a single year.

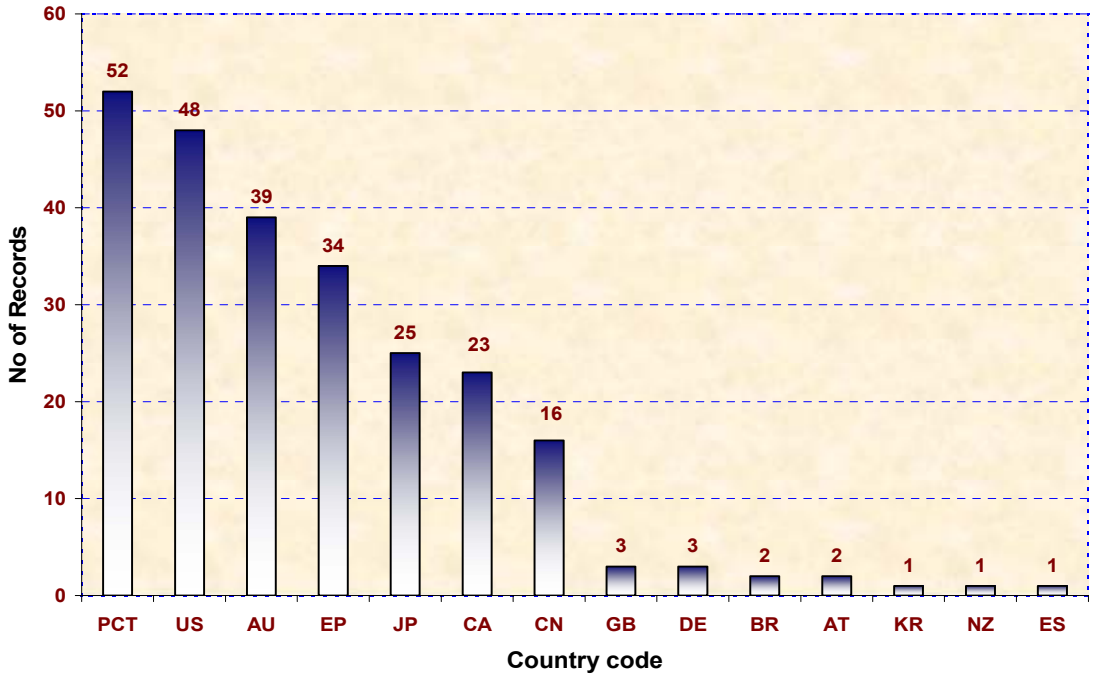
59. The patents filed over time chart shows how patenting related to rice gene promoters has evolved over the past 15 years.



C. GEOGRAPHICAL DISTRIBUTION OF PATENTS

60. The chart below shows the geographical distribution of all the 250 patents related to rice promoters i.e. the 69 identified patents and their patent family members.

Geographical distribution of patents



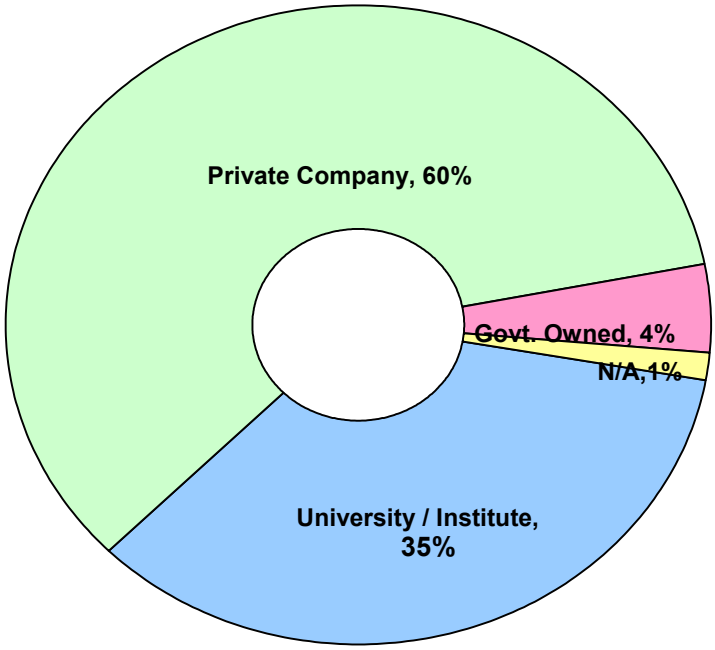
61. A noteworthy fact is the number of patents that have been filed through the PCT route (i.e. international patent applications filed under the Patent Cooperation Treaty). Of the 69 patents analyzed, 52 were filed as PCT applications. This indicates that these applications are intended to be filed in many jurisdictions and that these applicants plan to protect their inventions in multiple countries. However, the PCT filings in themselves do not give evidence of the actual scope of jurisdictions in which applicants actually seek protection. This is a key area of need for further patent searching to strengthen the value and use of the evolving patent landscape.

62. The graph identifies the United States as a clear leader in terms of the total number of patents filed in a single country. This reflects the fact that some of the main assignees are US based universities and companies. Other significant countries are Australia, Europe, Canada, Japan and China. It is important to recognize, however, that this graph combines different types of data, which must be carefully and consistently distinguished: (1) the graph labelled 'PCT' concerns international applications under the PCT, whereas the other patent graphs, refer to granted patent titles. The PCT applications may subsequently enter into the national phase, and may lead to multiple national patents being granted.

D. SECTOR-WISE DISTRIBUTION OF PATENTS

63. The patent documents have been categorized according to whether they are in the names of private sector entitities, government agencies, and University or Institutes.

Sector-wise distribution of patents

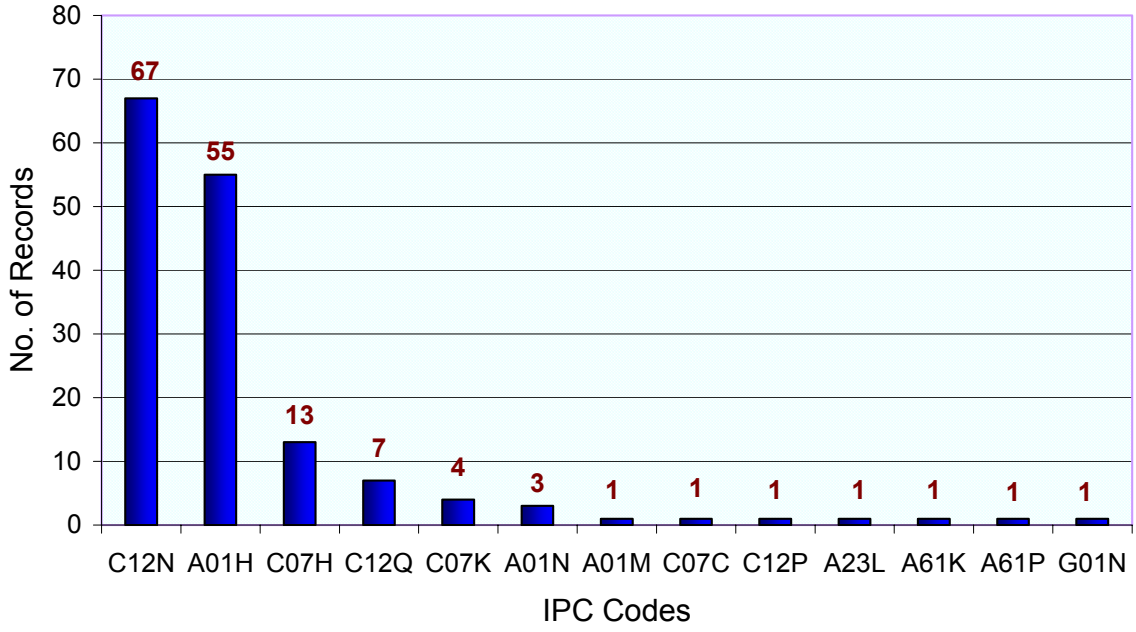


64. There has been a mounting concern for increasing the yield of plant crops and making high quality food available to an ever-increasing population. Countries are aiming to ensure food security by developing more productive, disease resistant crop varieties with high nutrient quality. This has led to a lot of research work being sponsored and conducted by academic institutions. Universities and research institutes have rights to about 35% of the patents related to rice promoters.

65. About 60% of the patents are a result of research work conducted by the private sector, while government ownership is at about 4% of the patents. It has also been observed that patents that emanate from universities and research institutes are often finally licensed to companies for commercialization since they lack the funds and resources to commercialize their invention.[25] Hence, the rights to a higher percentage of patents are ultimately worked by the private sector.

E. IPC CODE CLASSIFICATIONS

66. Distribution of patents according to the major IPC code classifications is shown below.



C12N	Micro-organisms or enzymes; Compositions thereof; propagating, preserving, or maintaining micro-organisms; mutation or genetic engineering; culture media
A01H	New plants or processes for obtaining them; plant reproduction by tissue culture techniques
C07H	Sugars; derivatives thereof; Nucleosides; Nucleotides; Nucleic Acids
C12Q	Measuring or testing processes involving enzymes or micro-organisms; compositions or test papers thereof; Processes of preparing such compositions; Conditions responsive control in microbiological or enzymological processes

[25] Graff GD, Cullen SE, Bradford KJ, Zilberman D and Bennett AB, 2003. The public-private structure of intellectual property ownership in agricultural biotechnology. *Nature Biotechnology*, **21**, 989-995.

C07K	Peptides
A01N	Preservation of bodies of humans or animals or plants parts thereof; biocides, e.g. as disinfectants, as pesticides, as herbicides; Pest repellants or attractants; Plant growth regulators
A01M	Catching, Trapping or scaring of animals; apparatus for the destruction of noxious animals or noxious plants
C07C	Acyclic or carbocyclic compounds
C12P	Fermentation or enzyme-using processes to synthesise a desired chemical compound or composition or to separate optical isomers from a racemic mixture
A23L	Foods, Foodsstuffs, or non-alcoholic beverages, not covered by subclasses A23 B to J; Their preparation or treatment, e.g. cooking, modification of nutritive qualities, physical treatment; Preservation of foods or foodstuffs
A61K	Preparation for medical, dental or toilet purposes
A61P	Therapeutic activity of chemical compounds or medicinal preparations
G01N	Investigating or analyzing materials by determining their chemical or physical properties

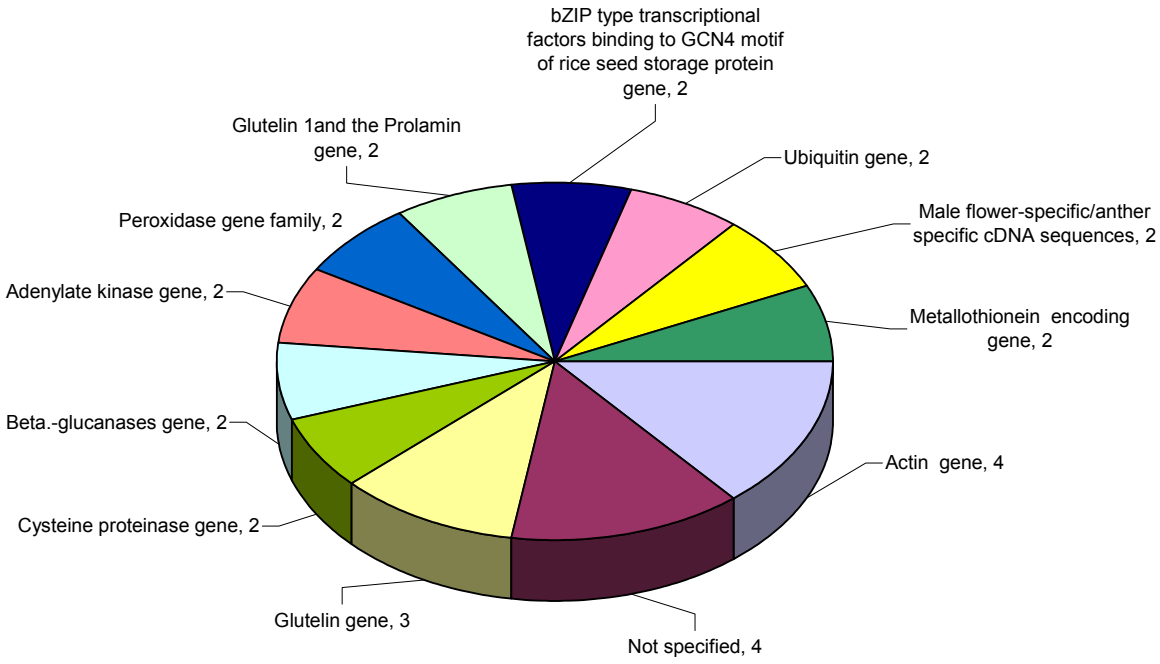
67. The IPC code classifications identify the field of the invention and the topic to which it broadly relates. As is seen in the chart and table above, most of the patents related to rice promoters can be classified as being associated to genetic engineering, new plants and plant reproduction by tissue culture techniques, micro-organisms and enzymes. A small number relate to other topics such as sugars, nucleotides, nucleic acids, peptides, plant parts, measuring and testing methods etc.

68. Promoters are commercially used in transgenic plants to drive the expression of important traits in plants such as resistance to disease, crop yield, etc. The promoter sequence *per se* does not have any commercial utility. Hence the patents seek to obtain protection for whole transgenic plant varieties and methods for their culture, rather than a nucleic acid sequence or peptide alone.

4. Technological Landscapes

A. SOURCE GENE FOR PROMOTERS

69. The chart below shows the main genes from the rice genome from which promoters were identified.



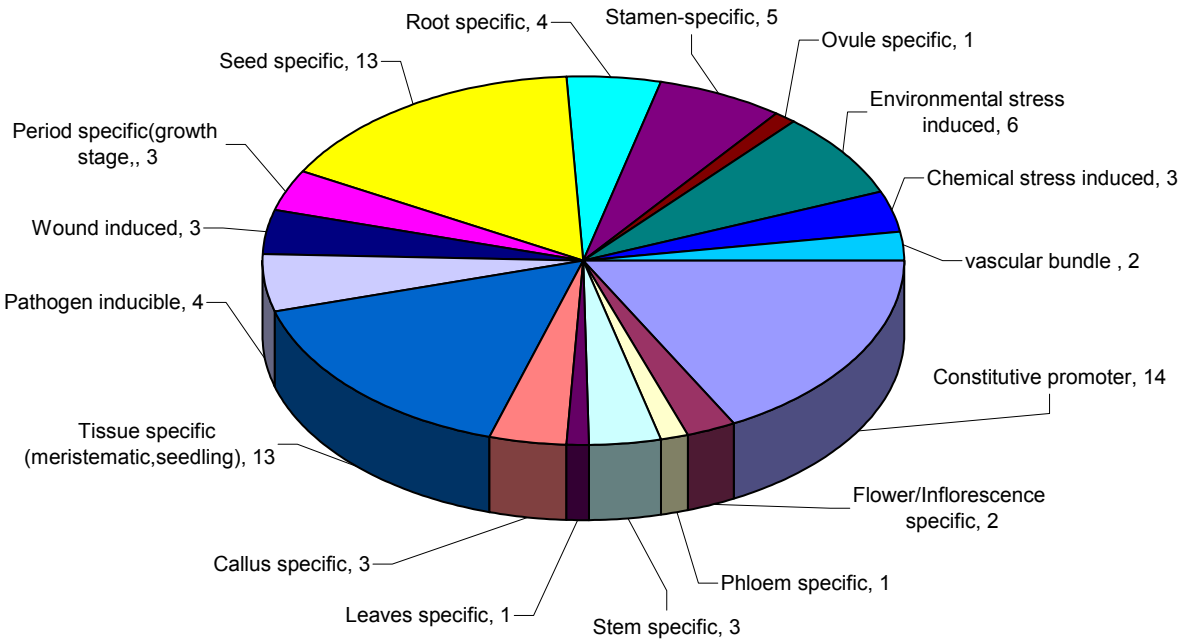
70. In order to improve the expression of foreign genes in transformed plants, promoters located upstream of a number of rice genes such as actin, glutelin, cysteine proteinase, adenylate kinase, ubiquitin, peroxidase gene family, metallothionein, etc., have been identified. The list of all source genes identified is given in Appendix-3**.**

71. The regulatory regions of the rice Act-1 gene have been most successfully used for expressing target genes of interest in transgenic plants. There are 4 patents out of 69 patent documents based on a promoter region derived from rice Act-1 gene.

72. There are also a few patents that are related to hybrid promoters such as promoters constructed of the rice act-I promoter region and the CaMV 35S (Cauliflower Mosaic Virus) promoter region. Further, it is expected that the sequencing of the rice genome would lead to the identification and characterization of many new rice promoters in the future.

B. TYPES OF PROMOTERS

73. The chart below shows distribution of patent activity based on types of rice promoters. As described earlier, promoters are of different types based on the expression pattern of the target gene operably linked to the promoter.



74. About 70% patents identified in the present mapping are tissue specific promoters, which drive the expression only in certain specific tissue of the plant such as seed, stamen, root, stem, callus, vascular bundle, flower and leaves. A number of the tissue specific promoters analyzed are seed specific in nature. This can be attributed to the fact that the seed (grain) is the most important and commercially exploited part of the rice plant.[26]

75. Constitutive promoters account for 20% of patents related to rice promoters. Such promoters induce the expression of the downstream-located coding region in virtually all tissues irrespective of environmental or developmental factors and therefore drive the expression of the gene in the whole plant.

76. Another major research topic is inducible promoters, which accounts for 23% of the patents. These relate to promoters induced by various abiotic stresses such as physical and chemical stresses, and by biotic stresses such as pathogens. This area of research looks at producing high yielding varieties of rice by reducing the yield loss caused by the various abiotic and biotic factors.

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[26] Rangnekar D, 2001. Access to Genetic Resources, gene-based inventions and agriculture. University of London.

C. TARGET GENES

77. The data shows that the most common target genes identified in rice promoter patents are those of herbicide, pathogen, stress resistant genes, male sterility genes, bar gene, genes for sucrose induction, peroxidases genes, anti-ageing or anti-senescent proteins gene, genes encoding non-plant protein (antibody or antibody fragment), etc.

78. The table below illustrates various target genes identified in all 69 rice promoter patents. As mentioned earlier, a target gene is a gene which is operably linked downstream to the promoter. Thus, it can be a reporter gene, a selectable marker gene or gene of important agronomic trait.

79. In addition, it was observed that the reporter gene commonly used to study the activity of rice promoters is *GUS,* which is β–glucuronidase. It hydrolyzes colorless glucuronides to yield colored products which are easily assayable and thus helps in selecting the transformed cells and to quantify their expression.

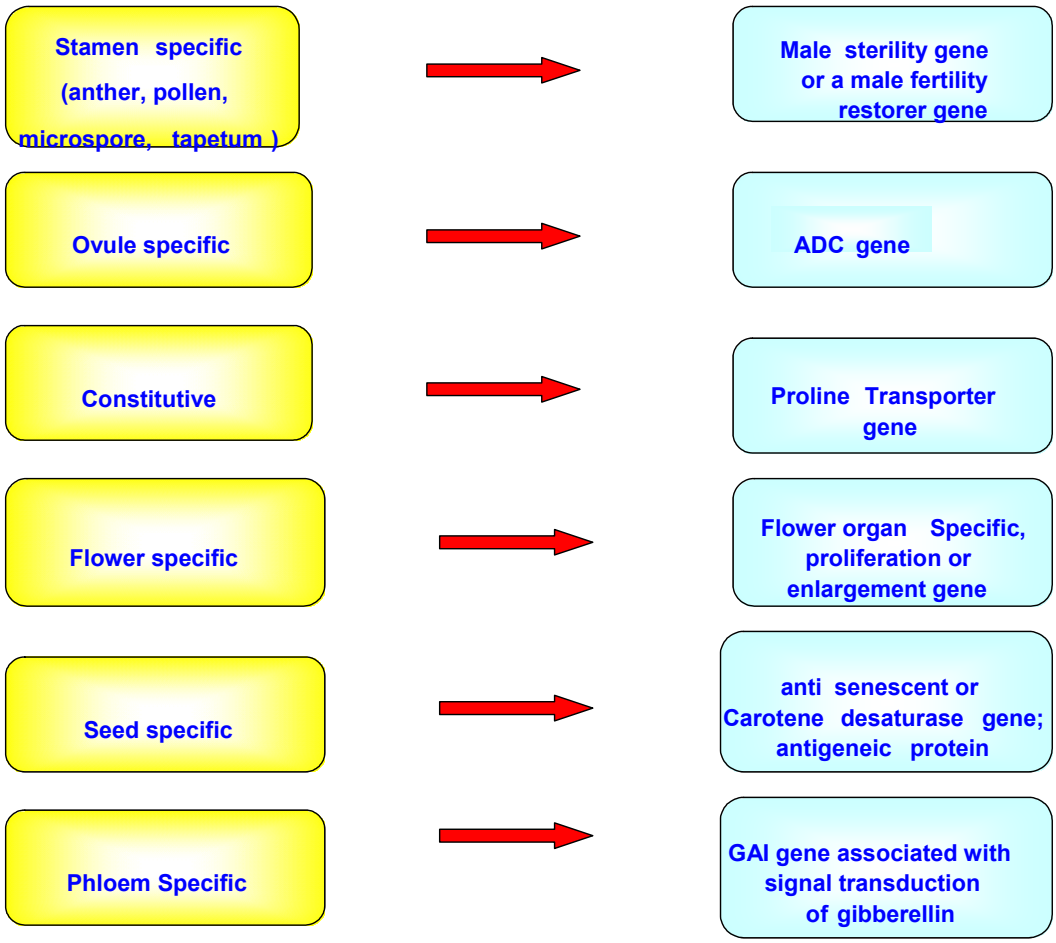
Target gene	**No of Patents**
Herbicide, Insect ,Environment or Stress Resistance genes etc.	12
Male-sterility DNA or a male fertility-restorer DNA	3
Anthers and/or pollen formation inhibiting gene like genes coding for nuclease, protease, glucanase, etc.	3
Bar gene	3
Exogenous nucleic acid which alters carbon metabolism in the plant cell.	2
Peroxidases genes	2
Anti-ageing or anti-senescent proteins gene	2
Gene for sucrose induction	2
Genes encoding non-plant protein (antibody or antibody fragment)	2
Genes encoding commercially-important proteins such as an enzyme, therapeutic or diagnostic protein, or peptide, or a heterologous Gns chimeric gene, fungal defense gene such as chitinase etc.	1
2. beta. Hydroxylase gene	1
Carotene desaturase	1
Soybean glycinin gene	1
ADC nucleic acid from rice,oat wheat and corn	1
Carotene desaturase	1
DNA encoding antigeneic protein	1
Rice MADS-Box Genes (OsMADS1)	1
Flower organ-specific proliferation or enlargement gene	1

Gene encoding hygromycin phosphotransferase	1
GAI gene associated with the signal transduction of gibberellin	1
Rice Cysteine proteases (rCysP1) gene	1
Proline Transporter gene	1
Proline synthesis (P5CS gene), the AtGolS3 gene for galactinol synthesis, the Arabidopsis thaliana-derived DREB transcription factor gene, the rice-derived OsDREB transcription factor gene, and the NCED gene which is a key enzyme for the synthesis of ABA	1
β-1,3-endoglucanase gene	1
Potato protease inhibitor II and inhibitor I genes, cowpea trypsin inhibitor (CPTi) gene, and various Bacillus thuringiensis endotoxin genes viral coat protein	1

D. SPECIFIC RICE PROMOTERS AND TARGET GENE

80. As described earlier, promoters are used to drive expression of genes. The patent analysis indicated that certain specific rice promoters were used to drive the expression of specific target genes in plants. The figure below indicates the specific promoter and the target gene operably linked to it as described in the patent documents.

Specific Rice Promoters and Target Genes



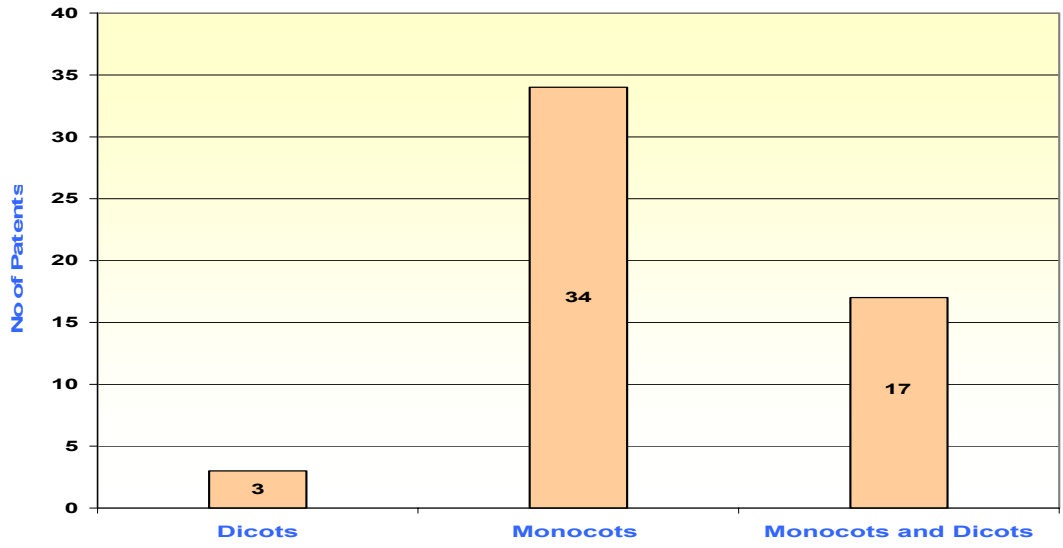
81. For example, stamen specific promoters, i.e. anther, pollen, microspore or tapetum specific promoters, are used to drive expression of male sterility or male fertility restorer genes. Similarly, a flower specific promoter is operably linked to flower organ specific proliferation or enlargement genes.

E. MONOCOT AND DICOT DISTRIBUTION

82. It may be noted that 34 of 69 rice promoter patents are exclusively for transformation of monocots. It shows that with the recognition of new regulatory DNA sequences from monocots and improvement in transformation techniques, the production of transgenic plants which was earlier restricted to dicots, has now been extended to crops-grains and grasses known as monocots.

83. The chart below displays patenting activity based on genetic transformation of Monocots and Dicots.

Distribution amongst monocot and dicot



84. In addition, the above analysis also shows that 17 of 69 rice promoter patents are for transformation of all kinds of plants (both monocots and dicots).

[Appendix follows]

I. Appendix

Appendix 1: List of the 69 patent records identified for mapping and analysis after reduction to one patent per patent family

Record No.	Patent Number/ Pub. No	Record No.	Patent Number/ Pub. No
1.	WO03027249, WO03008540 WO03000897, WO03000904 WO03000905 WO03000906 WO03007699	21.	WO0026356A1
2.	WO0070067	22.	WO0050585A1
3.	WO9859046	23.	WO0071732A2
4.	WO0142475	24.	WO0140470A1
5.	WO9213956	25.	WO0231154A1
6.	US6388067	26.	WO03020937A2
7.	US6376750	27.	WO03038102A1
8.	US20050278799	28.	WO04001040A1
9.	WO02077247	29.	WO04062365A2
10.	WO02077248	30.	WO04062366A2
11.	WO0058454	31.	WO04081213A1
12.	US6528701	32.	WO04085641A1
13.	WO9306713 WO9109948	33.	WO04085656
14.	WO9306713 WO9109948	34.	WO04092364
15.	WO9401571	35.	WO04092380
16.	WO0001830A1	36.	WO04092381
17.	WO0008161A1	37.	WO05067699
18.	WO0015811A1	38.	WO05096806
19.	WO0015812A1	39.	WO05100575A2
20.	WO0026345A1	40.	WO9307279A1

Appendix 1 contd.

Record No.	Patent Number/ Pub. No	Record No.	Patent Number/ Pub. No
41.	WO9611566A1	56.	US20050262582A1
42.	WO9810062A1	57.	WO0181606A2
43.	WO9943818A1	58.	US2005009061
44.	WO9967406A1	59	WO2005017167
45.	WO2004065596A2	60.	US20040060084
46.	WO2002055689A1	61.	JP2003259868 A
47	JP2003189877A	62.	JP11290082 A
48.	JP2000342277A	63.	JP07274752 A
49.	JP2002360253A	64.	JP10248570 A
50.	JP07184657A	65.	JP2004357517 A
51.	JP10014575A	66.	JP2005013165 A
52.	JP05168482A	67.	US2005125861
53.	US20050160498A1	68.	JP2005224118 A
54.	GB2355265A	69.	JP2005224112 A
55.	WO2004070039A2		

Appendix 2: List of all the assignees of the 69 patent records identified for mapping and analysis after reduction to one patent per patent family.

Assignee	No. of Records
National Institute Of Agrobiological Sciences	9
Academia Sinica	3
Cropdesign N.V.	2
Nissan Chemical Industries, Ltd.	3
Plant Genetic Systems Nv	3
The Texas A & M University System	2
Cornell Research Foundation, Inc.	2
Monsanto	3
Iwate Prefecture	3
Syngenta	3
Korea University	1
Applied Phytologics, Inc	1
Bayer Bioscience N.V.	1
Bio-Oriented Technology Research Advancement Institution	1
Board Of Supervisors Of Louisiana State University And Agricultural And Mechanical College)	1
Ceres, Inc.	1
Greengene Biotech Inc	1
Hitachi Limited(Jp)	1
Hokko Chem Ind Co Ltd	1
Japan Science And Technology Corporation	1
Japan Turf Glass:Kk	1

Appendix 2 contd.

Assignee	No. of Records
Kws Kleinwanzlebener Saatzucht Ag Vorm. Rabbethge Und Giesecke	1
Kws Kleinwanzlebener Saatzucht Ag Vorm. Rabbethge Und Giesecke	1
Maxplanck-Gesellschaft Zur Forderung Der Wissenschaften E.V.	1
Mitsui Toatsu Chem Inc	1
Smart Plants International, Inc.|	1
The Regents Of The University Of California	1
Ventria Bioscience	1
Washington State University Research Foundation	1
Akkadix Corporation	1
n/a	1

Appendix 3: List of all the source genes of the 69 patent records identified for mapping and analysis after reduction to one patent per patent family.

Source Gene	Source Gene
Rice actin gene	Rice albumin specific gene
Rice glutelin gene	Rice peroxidase gene family
Cysteine proteinase (rCysP1) gene	Rice cytochrome c gene
Beta.-glucanases gene	Nicotianamine synthase gene
Rice adenylate kinase gene	Glutelin 1 and the Prolamin gene
Tublin gene (gene)	Ubiquitin gene
Germin protein 4 gene	chloroplast liposome protein L11 gene
PAL Gene	Pyruvate orthophosphate dikinase (C4 photosynthesis-related) gene
Sucrose transporter gene	triosephosphate isomerase (TPI) gene
Rice 3.beta. hydroxylase 2 gene	Flower organs specific cDNA sequences
Gene expressed in glume, lemma and pale	Rice allergen gene
Alpha-subunit gene of a second isozyme of anthranilate synthase	Rice glycine-rich RNA binding protein gene
Rice catalase A gene	Rice GOS2 gene
bZIP type transcriptional factors binding to GCN4 motif of seed storage protein gene	Rice metallothionein encoding gene
RezA gene	Transcription factor binding to rice starch branching enzyme 1 (RBE1 gene)
SalT and the OsNAC6 gene	Os 39486 gene
DNA sequence from Oryza sativa	Pollen-preferential gene
Elongation factor gene	OSDIM gene
Male flower-specific/anther specific cDNA sequences	transcriptional enhancer derived from αAmy8 gene of rice

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