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Review: intellectual property aspects of plant transformation

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Summary

One of the recurring themes of the debates concerning the application of genetic transformation technology has been the role of Intellectual Property Rights (IPR). This term covers both the content of patents and the confidential expertise usually related to methodology and referred to as 'Trade Secrets'. This review explains the concepts behind patent protection, and discusses the wide-ranging scope of existing patents that cover all aspects of transgenic technology, from selectable markers and novel promoters to methods of gene introduction. Although few of the patents in this area have any real commercial value, there are a small number of key patents that restrict the 'freedom to operate' of new companies seeking to exploit the methods. Over the last 20 years, these restrictions have forced extensive cross-licensing between ag-biotech companies and have been one of the driving forces behind the consolidation of these companies. Although such issues are often considered of little interest to the academic scientist working in the public sector, they are of great importance in any discussion of the role of 'public-good breeding' and of the relationship between the public and private sectors.

Keywords: crop, genetic modification, patent, promoter, selectable marker, transgenic.

Introduction

The present and future status of genetically modified (GM) (transgenic) crops has been the subject of several recent reviews (Dunwell, 2000, 2002, 2004). Although these reviews have included some information extracted from patent databases, this analysis has been necessarily limited in scope. The present review expands on the information published previously (Sechley and Schroeder, 2002) and extends to a discussion of intellectual property from the perspective of the research scientist (Shear and Kelley, 2003) and of those interested in international developments (Blakeney, 2000; Binenbaum *et al*., 2003), globalization (DaSilva, 1998; Parayil, 2003) and the more general ethical aspects of the public- and private-sector relationships (Korn and Heinig, 2003; Hails, 2004).

What are patents?

Discussions concerning the merits, or otherwise, of patenting plants are not a recent occurrence. For example, during the Third International Conference on Genetics, organized by the Royal Horticultural Society, held in London in 1906, and most famous for the coining of the term 'genetics' by William Bateson, there was a session entitled: ' "Copyright" for Raisers of Novelties' (Anonymous, 1907). It is reported that Mr George Paul, whilst remarking on the absence of several well-known plant breeders, stated: 'The fact is, these gentlemen do not like to tell us, or to show, what they have done in their experiments, because once their knowledge becomes public, they have not the slightest chance of receiving any pecuniary reward for their labours. If they were properly protected from being deprived of the due reward of their labours, they would no doubt be much more willing to come forward and help us and place their experience at our disposal'. During discussion, Professor Hansen responded: 'I believe, in law, a seedling is regarded as the gift of God, and it would be hard to patent that; but could we not hope to have some law fashioned that would give a bonus to the man who does such skilled and valuable work as that which has come before us over and over again during the sessions of this conference'.

The chairman of the session, whilst sympathizing with Mr Paul, concluded that it would be unwise to pass a resolution

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on the subject as the discussions had demonstrated: 'What very great difficulty there would be in enforcing such a law, because we have gentlemen from all parts of the world maintaining that a thing is new, and others, equally capable, maintaining that it is old'. Much of the debate today, almost 100 years later, follows the same themes.

The history of patent law dates back several centuries but, in summary: 'A patent gives an inventor a period of exclusive exploitation (up to 20 years in the UK) in return for a disclosure of the invention' (Huskisson, 1996). Central to the patent system are the criteria that have to be met for the granting of a patent. These criteria are for the invention to be novel, non-obvious, industrially applicable and not in several excluded categories. Considering these requirements in more detail:

1 novel: 'new' means more than 'state of the art', i.e. everything made available to the public prior to the 'priority date' of the patent;

2 non-obvious: an inventive step, not obvious to the 'skilled man' (who knows everything and has no imagination, may be a team);

3 industrially applicable: something which can be made or used in any kind of industry, including agriculture;

4 exclusions: (i) anything immoral; (ii) plant and animal varieties *per se* (except in USA); (iii) essentially biological processes for the production of plants and animals; (iv) ideas, theories, computer programs, etc.

One of the most important features of this process is the need for any invention to be kept confidential and not to be disclosed prior to the filing date of the patent application. In European patent law, an invention counts as published if it forms 'part of the state of the art', with the 'state of the art' being defined as: 'everything made available to [even one member of] the public [anywhere in the world] by means of a written or oral description, by use, or in any other way'. Examples of publication include: learned papers, journals and magazines; abstracts; theses; the Internet; poster displays; exhibitions and open days; oral and casual disclosure; and confidential disclosure to many people (http://www.btgplc.com/info/links_lit.php).

More generally, the role of the patent system is to encourage industry and innovation by rewarding invention and protecting investment in product development. The concept behind most patent legislation is that disclosure and publication allow others to test the invention and attempt improvements, whilst expressly not allowing the routine use of a patented process or processes. This disclosure takes the form of a publication from the relevant patent office. In the case of most authorities, the patent procedure involves submission (filing) of a preliminary patent application followed, after 12 months, by a final application, which is published 6 months later and is then available for inspection. Exceptionally, until 15th March 2001, the USA maintained secrecy until the time the patent was granted, a period that can range from an average of 2–3 years upwards to more than 20 years. As an example of the lengths of time sometimes required for the resolution of complicated cases, the main US case, which covered elements of *Agrobacterium*-based transformation of dicotyledonous crops, was only finally resolved in October 2004, some 20 years after the date of filing. It was reported subsequently (February 2005) (http://www.bayercropscience.com/bayer/cropscience/cscms.nsf/id/Patent_dispute_resolved) that, under a related agreement, Max Planck Society, Bayer CropScience, Garching Innovation and Monsanto will cross-license their respective *Agrobacterium*-mediated transformation technologies worldwide. Bayer CropScience, Max Planck's exclusive licensee, and Monsanto will provide each other, in selected areas of the world, non-exclusive licences related to the development, use and sale of transgenic crops. Monsanto will also provide Max Planck Society with a licence in the USA for research purposes. In a similarly delayed resolution, the US patent claiming the direct transformation of *Brassica* protoplasts with a plasmid was granted in the USA (6 603 065) on 5th August 2003, some 18 years after the first application on this subject filed on 3rd May 1985.

Another important difference between the US and other systems is that the 17 years' duration of a US patent filed prior to 2001 only starts from the time at which it was granted, whereas, in Europe (and now in the USA), the 20-year period of exclusivity starts from the time of filing the application. Some of the consequences of this change are discussed in more detail below.

At a practical economic level, the submission costs of patent applications are small (> £100) initially, but may rise rapidly if professional agents are employed, if the patent coverage is geographically extensive and if the granted patent is maintained over several years. Individual patent offices should be consulted for precise costings.

Sources of patent information

During the preparation of this review, extensive use has been made of the freely available patent databases in the USA (http://www.uspto.gov/patft/index.html), Europe (http://ep.espacenet.com/), World International Patent Organization (http://pctgazette.wipo.int/) and other international sites (e.g. http://www.surfip.gov.sg/sip/site/sip_home.htm; http://www.cambiaip.org/cgi-bin/cipr/TT3/simple.cgi). A very useful site with a summary of granted US ag-biotech patents from 1976 to 2000 is provided by the Economic Research Service (ERS) of the US Department of Agriculture (USDA) (http://www.ers.usda.gov/Data/AgBiotechIP/). Some sites are dedicated to specific species. For example, details of *Arabidopsis* patents are available from Lehle Seeds (http://www.arabidopsis.com/home_RR03.html), and information about trees can also be obtained (Sedjo, 2004). It should be noted that the most detailed forms of patent analysis require commercial subscription from companies such as Derwent (http://www.derwent.com), MicroPatent (http://www.micropat.com) or patentmaps.com. The last two companies have advanced graphical methods of displaying the relationships between patents within given sectors of technology.

In addition, this review includes data from various sites providing information on the field tests of GM crops in the USA (http://www.nbiap.vt.edu/cfdocs/fieldtests1.cfm) and elsewhere (http://www.nbiap.vt.edu/cfdocs/globalfieldtests.cfm) (http://gmoinfo.jrc.it), as these often provide useful perspectives into future commercial products and international trends. Another source of data on the release of GM crops is available at http://www.agbios.com/dbase.php.

Patents and agricultural biotechnology

There are a range of methods that can be used to protect novel types of plants produced by one company from being exploited by commercial competitors, with these methods varying from one country to another (Bennett, 1994; Erbisch and Velazquez, 1998; Blakeney *et al*., 1999; Cahoon, 2000). An introduction to the various approaches, namely plant breeders rights and patents (known collectively as Intellectual Property Rights – IPR), is available from several authors (Scalize and Nugent, 1995; Mauria, 2000; Henson-Apollonio, 2002; Brown, 2003; Fagerlin, 2003), and from the Intellectual Property Division of CAMBIA (Center for the Application of Molecular Biology to International Agriculture) based in Australia (http://www.cambiaip.org/Tutorials/Plant_Protection/plant_protection.htm). Specific information relating to individual countries is available at the respective patent offices. For example, the latest note on patenting of plants in the UK, '*Examination Guidelines for Patent Applications Relating to Biotechnological Inventions in the UK*', was published by the Patent Office in November 2003 (http://www.patent.gov.uk/patent/reference/biotechguide/plant.htm). The relevant paragraphs of this document are as follows:

Par. 65 As confirmed by the EC Directive plant and animal varieties are not patentable. Plant varieties are currently protected under the Plant Varieties Act 1997. Both the 1997 Act and a separate European Community regime (Council Regulation (EC) No. 2100/94) are based on the 1991 UPOV Convention (http://www.upov.int/en/about/upov_system.htm). In the UK the system for granting plant variety rights is administered by the Plant Variety Rights Office (PVRO) at Cambridge. This system differs substantially from the patent system and to gain protection a variety must be tested for distinctness from other varieties, uniformity and stability.

Par. 66 Plant variety rights are confined to individual varieties. Patents may claim plant genera or species but they cannot claim individual varieties.

Par. 67 In the early days of granting plant patents neither the EPO nor the UK Patent Office had a problem with granting claims to plants in general even though it could be argued that such claims could be regarded as covering, in reality, a number of plant varieties. The EPO's Enlarged Board of Appeal was eventually called on to consider this issue. The Enlarged Board found:

A claim wherein specific plant varieties are not individually claimed is not excluded from patentability under Article 53(b) EPC even though it may embrace plant varieties;

When a claim to a process for the production of a plant variety is examined, Article 64(2) EPC is not to be taken into consideration;

The exception to patentability applies to plant varieties irrespective of the way in which they were produced. Therefore, plant varieties containing genes introduced into an ancestral plant by recombinant gene technology are excluded from patentability.

Thus, claims to transgenic plants are perfectly acceptable, unless expressed in plant variety terms or the invention is confined to modifying a particular plant variety. It may be therefore that if all the examples in an application are directed towards modifying a single variety, there could be a presumption that the invention is specifically for a plant variety.

Similar information is available concerning the patentability of plants in the USA (Merrill *et al*., 2004), Europe (Perdue, 1999; Fleck and Baldock, 2003), New Zealand (Ministry of Economic Development, 2002) and China (http://www.cnpvp.net/old-www/rules_and_regulations.htm#REGULATONS%20OF%20THE%20PEOPLE'%20S%20REPUBLIC%20OF%20CHINA%20ON%20THE%20PROTECTION%20OF%20%20NEW%20VARIETIES%20OF%20PLANTS). In addition, the results of a detailed survey of actual practice of patent examiners in the three key patent offices, USA, Europe and Japan, has been published recently (Howlett and Christie, 2003). As opposed to the speculation that is widespread in this area, this survey gives information about what is actually happening in relation to gene patenting and, it is suggested, therefore, that it provides a basis for informed decisions and policy development.

In a complementary study restricted to the present and future position in the USA (Merrill *et al*., 2004), the authors conclude that the continuing high rates of innovation suggest that the patent system there is working well and does not require fundamental changes, although they note that both economic and legal changes are putting new strains on the system. Specifically, patents are being more actively sought and vigorously enforced. The consequence of this activity is that the sheer volume of applications to the US Patent and Trademark Office (USPTO) – more than 300 000 a year – threatens to overwhelm the examination staff by reducing the quality of their work and creating a huge backlog of pending technology; cases of defending against patent infringement violations in court are also rising rapidly. This report also states that, in some cases, patenting appears to have departed from its traditional role, as firms build large portfolios to gain access to others' technologies and reduce their vulnerability to litigation (Evenson, 2000). This issue and the effect on company interaction are considered below.

There have been several extensive reviews of the consequences and implications of applying patent (and other IPR) protection to plants (Plant Intellectual Property, 2001; Farnley *et al*., 2004), and the reader is referred to these publications, most of which are freely available on the Web. In one of the most comprehensive of these reviews (Binenbaum *et al*., 2003), the important conclusion is reached that, as patenting becomes even more prevalent in biotechnology, the diversity of innovations utilized in developing modern cultivars will mean that the number of separate rights needed to produce a new innovation will proliferate. Where ownership of relevant rights is sufficiently diffuse, the multilateral bargaining problem can become very difficult, although not impossible (see section on 'Golden rice' below), to resolve. This problem is further compounded by uncertainty. For example, those who develop new technology by building on existing technologies often know neither the extent to which the latter has been claimed as Intellectual Property nor the strength of any claims. Both the conduct of research and development and subsequent commercialization therefore entail navigating through a potential minefield of patent applications that have been filed but remain invisible pending publication by the patent office. For example, public breeders in the USA received an unwelcome surprise when a patent issued to Monsanto for the cauliflower mosaic virus (CaMV) 35S promoter (see below) surfaced after they had used it in the breeding of crop cultivars on the brink of commercialization. Fortunately, the uncertainty arising from such 'submarine' patents is becoming less important as the USA has harmonized with the rest of the world, first by awarding a patent term of 20 years from the date of filing (previously 17 years from the date the patent was awarded), and secondly by publishing (from November 2000) patent applications within 18 months of filing. In addition, the existence of 'submarine patents' can sometimes be inferred from the publication of foreign filings (e.g. EU/World Intellectual Property Organization), although detailed claims and coverage may differ.

Despite the complexity of biotechnological IPR, it should be pointed out that similar problems exist in the electronics industry where products are assembled from numerous internationally sourced components covered by a multiplicity of patents.

Patents and plant transformation

During the period since the production of the first transgenic plants, a wide diversity of patents have been sought on all aspects of the process, ranging from the underlying tissue culture methods through to the means of introducing the heterologous DNA, and to the composition of the DNA construct so introduced (Kesan, 2000). It would be impossible to summarize all this information in the space available here; the amount of patent information available in the area of plant transformation (Tables 1 and 2) can be judged by the fact that a search of the US application database for 'transgenic plant' and 'method' returned 2160 records on 26th August 2004, with at least six relevant patent applications being submitted on the single day in question.

For a detailed analysis of several of the key areas under discussion, the reader is referred to the extensive summaries published elsewhere, for example in the series of comprehensive CAMBIA White Papers (Roa-Rodrigues, 2003; Roa-Rodrigues and Nottenburg, 2003a, b; Mayer *et al*., 2004), aspects of which are considered below.

The first point to be emphasized is that patents only operate in the countries in which they are granted, subject to the caveat that products exported to countries in which the

Table 1 Summary of granted US utility patents (1979–2000) in the category 'genetic transformation' (adapted from http://www.ers.usda.gov/AgBiotechIP/)

Subcategory	Patents (no.)
Transformation platforms	928
Mutagenesis	153
Genetic markers	624
Selectable marker techniques	486
Culture growth, cell differentiation, etc.	1632
Transformation stability/heritability	33
Diagnostic techniques	1399
Total	4129

Note: Some patients are included in more than one subcategory.

Table 2 Selection of recent US patent applications

Method	Company/institution	Patent number
February to August 2004		
Use of auxin precursor (Matsunaga *et al*.)	Nippon Paper	20040163143
Whisker-mediated method (Petolino *et al*.)	Dow Agrosciences	20040128715
Monocot transformation (Elliot *et al*.)	CSIRO	20040123342
Transformation of *Brassica* (Chen *et al*.)	Cargill	20040045056
Micro-vibration and ovary injection (Liou)	Unknown	20040045048
Electrical shock and ovary injection (Liou)	Unknown	20040045047
Transformation of soybean (Khan)	Syngenta	20040034889
Transformation of *Camelina sativa*	Unknown	20040031076
26th August 2004		
Enhanced tissue culture response (Lowe *et al*.)	Pioneer	20040168217
Seed targeting (Jiang and Sun)	Unknown	20040168215
Phloem promoter (Kwart *et al*.)	Max Planck	20040168214
Nematode resistance (Verbsky *et al*.)	Monsanto	20040168213
Antifungal enzyme (Duvick *et al*.)	Pioneer	20040168212
Altered nicotine levels (Conkling *et al*.)	Unknown	20040168211

patent operates may also infringe. Frequently, however, the main point of interest has been the coverage of the patent(s) in question. There are some well-known examples of patents with very broad coverage and this is often a topic of debate and the cause of concerted opposition. For example, European Patent 301749, granted to Agracetus (then a subsidiary of WR Grace & Co.) on 2nd March 1994, is an exceptionally broad 'species patent' which grants this company rights to all forms of transgenic soybean varieties and seeds – irrespective of the genes used or the transformation technique employed. Agracetus was purchased by Monsanto in April 1996, after which it withdrew its previous opposition to this patent. However, opposition continued from other companies and organizations and a hearing was finally agreed by the European Patent Office (EPO) in May 2003, at which the patent was upheld, with the exception of Claim 25 covering plants other than soybean (http://www.european-patent-office.org/news/pressrel/2003-05-06_e.htm; http://www.european-patent-office.org/news/pressrel/pdf/bginfo_soya_e.pdf). The patent is due to expire in July 2008.

Transformation methods

There are several techniques for the introduction of recombinant vectors containing heterologous genes of interest into plant cells, and the subsequent regeneration of plants from such cells. The two main methods are the use of *Agrobacterium* or the direct introduction of DNA on microparticles of metal, a technique known as biolistics. Some of the patents covering these methods are summarized in Table 3, which also includes details of other, related patents on techniques such as direct uptake into protoplasts, electroporation or vortexing with needle-shaped crystals (whiskers) of silicon carbide (Dunwell, 1999). Most of these methods involve a tissue culture step (Hall *et al*., 1996), and many of these enabling protocols are also the subject of patent claims. Recent related applications in this area are given in Table 4.

The most extensive publication in this area is the 360-page CAMBIA White Paper (Roa-Rodrigues and Nottenburg, 2003a) on *Agrobacterium*-mediated transformation. This document focuses on the patents directed to the methods and materials used for transformation, mainly of plants, but also of other organisms such as fungi. It should be stressed that, although much of the early development of this technique was performed in universities, most of the patents are consolidated in the hands of a few companies. In the case of one of the most important of the US applications, that covering *Agrobacterium*-mediated transformation of dicot plants, there was a 12-year dispute between applicants before the case was decided in favour of Monsanto in late 2004.

One recent advance that might circumvent the IPR limitations to *Agrobacterium* technology is the development of gene transfer techniques using other bacteria, such as *Sinorhizobium* (Broothaerts *et al*., 2005). It is claimed that these methods may offer an 'open source' alternative to the established transformation technologies.

Patents and DNA sequences

Almost all the significant components of the constructs used in plant transformation have been the subject of patent coverage. These include the 'effect gene' as well as its

Table 3 Selection of patents/applications covering plant transformation methods

Method	Company/institution	Patent number
Particle bombardment	Cornell	US 4945050
	DowElanco	US 5141131
	Dekalb	US 5538877, 5538880
	Agracetus	US 5015580, 5120657
Agrobacterium	University Toledo	US 5177010, WO 02/102979
	Texas A & M University	US 5104310, WO 03/048369
	Leiden University	EP 120516, 159418, 176112
		US 5149645, 5469976, 6464763
		US 4940838, 4693976
	Max Planck	EP 116718, 290799, 320500
	Japan Tobacco	US 5591616
		EP 604662, 627752
	Ciba-Geigy	EP 267159, 292435
	Washington University	US 6051757
	Calgene	US 5463174, 4762785
	Agracetus	US 5004863, 5159135
	Monsanto	WO 03/007698
	BASF	WO 03/017752
	Purdue	WO 01/020012
Protoplasts	Ciba-Geigy	US 5231019
Whiskers	Zeneca	US 5302523, 5464765
Electroporation	Boyce-Thompson Instit.	WO 87/06614
	Dekalb	US 5472869, 5384253
	PGS	US 5679558, 5641664
		WO 92/09696, 93/21335

associated regulatory sequences (Kay *et al*., 1987), the selectable or screenable marker and additional sequences that might be required for the subsequent excision of the transgene. This review does not cover details of the gene of interest (Martin, 1998) and the reader is referred to other recent reviews that include summaries of the range of present and future transgenic crops (Dunwell, 2002, 2004).

Much of the debate in this area concerns the ability to apply for patents on DNA sequences of unproven function. There have been several attempts to do so, and the decisions on such applications have not been finalized. However, the fact remains that there is much useful sequence information available in patent databases and much of it is ignored by academic research scientists. Specifically, it is estimated that some 30–40% of all DNA sequences are only available in patent databases, as there is of course no obligation for commercial (or other) applicants to submit their sequences to public databases. Possibly, the best way to access this information is via the GENESEQ system, a commercial (Derwent) service.

Selection and identification of transformants

The production of transgenic organisms, including plants, involves the delivery of a gene of interest and the use of a selectable marker that enables the selection and recovery of transformed cells. This is necessary because only a minor fraction of the treated cells become transgenic, while the majority remain untransformed. It has been estimated recently (Miki and McHugh, 2004) that approximately 50 marker genes used for transgenic and transplastomic plant research or crop

Table 4 Selection of patents covering selectable marker genes (adapted from Pardey *et al*., 2003)

Selectable marker	Company/institution	Patent number
Phosphinothricin, Basta	Aventis/AgrEvo	EP 531716 *et al*.
		US 5767371 *et al*.
Kanamycin	Monsanto	EP 131623
		US 6174724 *et al*.
Hygromycin	Novartis	EP 186425 *et al*.
		US 5668298 *et al*.
Sulphonamide	Rhône-Poulenc	US 5714096
Cyanamide	Syngenta/Mogen	EP 97201140
		US 6660910
Aldehyde	Calgene	EP 0800583
		US 5633153
Mannose/xylose	Novartis	US 5767378 *et al*.
Glucosamine	Danisco	US 6444878
2,4-Dichlorophenoxyacetic acid	Unknown	EP 0738326
		US 5608147

development have been assessed for efficiency, biosafety, scientific applications and commercialization.

Selectable marker genes (see Table 4 for selected patents) can be divided into several categories depending on whether they confer positive or negative selection and whether selection is conditional or non-conditional on the presence of external substrates.

The most common strategy currently used for selection is negative selection, the elimination of non-transformed cells in conditions in which the transformed cells are allowed to thrive. Elimination is often effected by treatment of cells with chemicals (e.g. antibiotics or herbicides) in conjunction with a transgene that confers resistance or tolerance to the chemical through detoxification or modification of the chemical. Much of the original work was conducted using antibiotic resistance marker (ARMs) genes, which confer resistance to antibiotics such as neomycin, kanamycin and hygromycin. A summary of the most important scientific aspects of such resistance genes has been published recently, together with an analysis of selected patents that relate to the most widely used ARMs (Roa-Rodrigues and Nottenburg, 2003b). Positive selectable marker genes are defined as those, such as phosphomannose isomerase, that promote the growth of transformed tissue. Many of these marker genes are covered by patents or patent applications (Table 4), with the most thorough Intellectual Property analysis available probably being that published on antibiotic markers and Basta resistance by CAMBIA (Mayer *et al*., 2004). A notable example of patent coverage is that of Monsanto which holds patent rights on the use of any antibiotic resistance gene as a selectable marker for plant transformation. Importantly, these proprietary rights apply only in the USA and are covered by three granted patents (US 5034322, US 6174724 and US 6255560).

As an alternative, or addition, to the use of selectable markers, transformants are often identified through the use of reporter or visualization molecules. The term 'reporter' relates to genes and their products used to identify transformed cells. In agricultural biotechnology, the most common reporters are β-glucuronidase (GUS) and green fluorescent protein (GFP).

Promoters and other regulatory elements

Regulatory elements are crucial to gene expression in all organisms. The patent landscape of transcriptional regulators that are constitutively active, spatially active (e.g. tissue-specific) and temporally active (e.g. induced or active in response to a certain chemical or physical stimulus) has been well summarized recently (Roa-Rodrigues, 2003). In this review, an assessment is presented of the possibilities for and limitations on further development of regulation of gene expression. The analyses include general patent information, such as patent numbers, total number of patents on a particular promoter, applicant names, dates of filing and grant. In addition, the analysis includes claims of relevant patents, including aspects of the prosecution history of the patents where appropriate.

Although the inventions protected by individual patents cannot be exactly the same, in certain cases there are patents that, due to the breadth of their scope, may encompass other protected inventions, or there may be patents that share common features. Where this is the case, this review points out the juxtaposition of the different inventions and the possible room left to manoeuvre around the different entities in the field. It also needs to be taken into account that there are patents that, although not totally directed to promoters, may have an effect on gene expression control. This is the case for the restrictive reproductive technologies, for example those termed 'terminator technologies', which may have a great impact on the use and development of methods to regulate the expression of genes related to plant reproduction and seed generation.

Although many people regard promoters as being confined to the research community, media press releases and information provided by ag-biotech companies illustrate how patent rights are often used as commercial assets in this industry. Patents on plant regulatory regions play a role in the subsequent development and innovation in promoters and in areas that rely heavily on mechanisms for controlling gene expression, such as chemically switchable systems (Sweetman *et al*., 2002).

Novel products and the freedom to operate

One of the issues of overriding importance to all companies is whether or not they are free to commercialize any particular product (Shear, 1999; Lence *et al*., 2002). Such 'freedom to operate' is determined by the status of any IPR that might cover the product in question, and the analysis of such IPR requires continuous (and therefore expensive) surveillance (Rausser and Small, 1996).

A well-known example that can be used to demonstrate the complexity of this issue is 'golden rice', a transgenic line that is enhanced for β-carotene (provitamin A) (Ye *et al*., 2000). It provides hope for alleviating the severe vitamin A deficiency that causes blindness in half a million children every year (Brooks and Barfoot, 2003). It has been suggested that extensive patenting has hampered the delivery of this

Table 5 Simplified list of patents covering the pBIN19hpc plasmid used in the production of vitamin A rice (adapted from Kowalski *et al*., 2002)

Component	Reference	Patents (no.)*
Phytoene desaturase *crt*	Fraser *et al*. (1992)	1 US
	Misawa *et al*. (1993)	2 PCT
Phytoene desaturase *psy*	Schledz *et al*. (1996)	3 US, 1 EP
	Burkhardt *et al*. (1997)	1 JP, 3 PCT
HPT aphIV	Waldron *et al*. (1985)	1 US
	Wünn *et al*. (1996)	
CaMV 35S promoter		3 US, 1 PCT
CaMV 35S terminator	None found	None found
Nopaline synthase termin.	None found	None found
Rice glutelin promoter	Okita *et al*. (1989)	1 JP, 1 PCT
Pea rubisco transit peptide	Schreier *et al*. (1985)	3 US

*EP, European Patent; JP, Japan; PCT, Patent Convention Treaty; US, USA.

rice to those in need as some 40 organizations hold 72 patents on the technology underlying its production (Kryder *et al*., 2000). The range of patents covering various components of the pBIN19hpc plasmid, used in the production of this rice, are shown in Table 5. These include patents on the phytoene trait genes (Fraser *et al*., 1992; Misawa *et al*., 1993; Burkhardt *et al*., 1997; Schledz *et al*., 1996), the promoter sequences (Okita *et al*., 1989), the selectable marker (Waldron *et al*., 1985; Wünn *et al*., 1996) and the transit peptide (Schreier *et al*., 1985). Such perceived problems with access to golden rice and essential medicines have stimulated debate within the USA on the obligations of American universities to facilitate the provision of goods for the public benefit (Kowalski and Kryder, 2002), an issue also considered below in the section on 'Public- and private-sector issues'. A recent symposium (www.lifesci.consortium.umn.edu/conferences/ip.php) at the University of Minnesota addressed this specific question (Phillips *et al*., 2004).

Patents and commercial consolidation

One classic example of the effect of patent coverage and the difficulty of acquiring freedom to operate (see above) concerns the history of the *bar* gene that is used both as a selectable marker and as a gene providing resistance to the herbicide Basta (Botterman and Leemans, 1989). An excellent summary of this case has been published by CAMBIA (Mayer *et al*., 2004).

The acquisition in 1996 of the Belgian company Plant Genetic Systems (PGS) by AgrEvo (part of the German chemical company Hoechst) was an important strategic move to gain access to a broad portfolio of traits and enabling technologies required to participate in the highly competitive market of transgenic crops. At the time, AgrEvo had fallen behind Monsanto and the ag-biotech section of Novartis (now Syngenta) in securing a competitive market position in the area of GM insect- and herbicide-resistant crops. With the acquisition of PGS, AgrEvo made a major effort to enter the US and the Canadian markets, two of the largest markets in the world. By this acquisition, AgrEvo also gained access to the PGS Intellectual Property portfolio that included such areas as gene promoters, marker genes, techniques to insert specific genes into plant cells and gene expression technology to optimize the efficacy of expression of foreign genes in plants. In addition, PGS had engaged in research and development of novel technologies, particularly in the area of functional genomics, but also in engineering disease-tolerant plants and modifying certain quality traits. PGS's products included corn, oilseed rape (canola) and selected vegetables engineered for insect protection (based on the expression of *Bacillus thuringiensis* toxin), herbicide tolerance and pollination control.

PGS's herbicide tolerance technology was developed in collaboration with AgrEvo, based on tolerance to AgrEvo's herbicide Liberty™ (glufosinate) by virtue of the *bar* gene. PGS's SeedLink™ pollination control technology is also based on tolerance to Liberty™. After the subsequent merger of AgrEvo and Rhône-Poulenc, which gave rise to Aventis, the agricultural section of this merger was called Aventis Crop Science. The Hoechst conglomerate, holder of Aventis and other companies, finally decided to shed its agrichemicals section by selling to Bayer AG, which recently gave rise to Bayer Crop Science, explaining thereby the migration and inheritance of the *bar* gene portfolio over time.

Similar analyses could be conducted on the other remaining large companies, namely Syngenta, Monsanto and DuPont, and their respective Intellectual Property portfolios.

Public- and private-sector issues

The most detailed review of this aspect of ag-biotech patents is probably that conducted by Graff *et al*. (2003), who have summarized the ownership of critical patents and compared the relative significance of the private and public sectors in each area of research relevant to the commercialization of transgenic plants. The main findings of this review, and others (Huete-Perez, 2003), are given below.

Six companies hold 75% of all agricultural patents and it has been suggested that such concentration exacerbates the challenge of delivering agricultural inventions to the most needy segments of the world's population (Solleiro, 1995). One solution could be the compulsory licensing of patented

Table 6 Numbers of Intellectual Property documents assigned to the public and private sectors, according to the introduced trait (adapted from Graff *et al*., 2003)

Technology	Private (%)	Public (%)
Plant enzymes	291 (92)	25 (8)
Bacillus thuringiensis toxin	497 (90)	57 (10)
Industrial enzymes	229 (89)	29 (11)
Metabolic pathways	198 (86)	32 (14)
Rice disease resistance	206 (77)	61 (23)
Male sterility systems	133 (75)	44 (25)
Viral proteins	378 (71)	153 (29)
Herbicide resistance	194 (69)	88 (31)
Product quality	291 (65)	157 (35)
Flowering control	48 (58)	35 (42)
Pathogen resistance	53 (44)	67 (56)

inventions that have failed to reach the most needy markets (see below for further details). An alternative would be based on the fact that, while the public sector holds less than 3% of all patents, it does have 24% of agricultural biotechnology patents, many covering genes of great potential interest (Table 6). By exploiting these resources, universities and other public organizations therefore have opportunities to deliver affordable biotechnological innovations.

Concern has also been expressed about the potential dangers (financial or otherwise) associated with the use of patented technologies by academic establishments. This is a complicated issue involving 'experimental use exception' (Janis, 2003; Hoffman, 2004), the concept that allows others to examine and test the patented discovery, but not to put it to routine use. In the past, industry brought few lawsuits against research universities, but the implications can be significant. One of the most notable is the 11-year battle over the widely used DNA-replicating enzyme, *Thermus aquaticus* DNA polymerase, known as *Taq*. Swiss drug giant, Roche, argued that 200 scientists who had published research using *Taq* obtained from Promega (Madison, WI, USA) were patent infringers. The outcome of the case is likely to determine whether researchers have to pay more or less for *Taq* polymerase chain-reaction products (Agres, 2004).

Patents, ethics and international development

Some people consider that the commercialization of biotechnology, especially research and development, by transnational pharmaceutical and ag-biotech companies is already excessive and is increasingly dangerous to distributive justice, human rights and access of marginal populations to basic human goods (Cahill, 2001). Focusing on gene patenting in particular, this author argues that such patenting ought to be more highly regulated, that this regulation should be conducted with international participation and that account should be taken of solidarity and the common good.

The various trends associated with the socio-economic aspects of ag-biotech development have also been reviewed recently (Parayil, 2003). In the words of this author: 'The dynamics of technology development along the technological trajectories of the Green Revolution and the Gene Revolution could be explicated by the social morphologies of modernization and globalization. The Green Revolution was shaped by the exigencies of modernization, while the Gene Revolution is being shaped by the imperatives of neo-liberal economic globalization'. In other words, the processes of innovation, development and diffusion of technologies followed different paths during these two periods because of the different innovation systems. The success of the Green Revolution was based on international collaboration that included the free exchange of genetic diversity and information. Most of the 'added value' present in modern crops has been accumulated over the centuries by farmers themselves as they selected their best plants as the source of seed for the next planting. These 'land races' have traditionally been provided free of charge by developing countries to the world community. Amongst the agencies involved, the various Consultative Group on International Agricultural Research (CGIAR) centres add value through selective breeding, and the superior varieties they generate are widely distributed without charge, thereby benefiting both developing and developed countries (Bragdon, 2000; Anon, 2001).

During the Gene Revolution, the situation changed, and much has been written over the last few years on the potentially deleterious effects of plant IPR on the freedom and commercial opportunities of farmers in developing countries (DaSilva, 1998; Conway and Toenniessen, 1999; Lesser *et al*., 1999; Blakeney, 2000; Wright, 2000; Nuffield Council on Bioethics, 2003; Toenniessen *et al*., 2003). One of the major reasons that IPR have become an important factor in plant breeding is through the greater use of utility patents (Summers, 2003). Such patents have stimulated greater investment in crop improvement research in industrialized countries, but they are also creating major problems and potentially significant additional expense for the already financially constrained public-sector breeding programmes that produce seeds for poor farmers. For example, it has been calculated (Phillips *et al*., 2004) that developed countries spend about $5 in research and development for every $100 in agricultural output, whereas developing countries spend only 66 cents.

Table 7 Vitamin A rice patents in rice-producing and rice-importing countries (adapted from Kryder *et al*., 2000)

Producers	Patents (no.)	Importers	Patents (no.)
China	11	Iran	0
India	5	Brazil	10
Indonesia	6	Nigeria	0
Bangladesh	0	Philippines	1
Vietnam	9	Iraq	0
Thailand	0	Saudi Arabia	0
Myanmar	0	Malaysia	0
Japan	21	South Africa	5
Philippines	1	Japan	21
Brazil	10	Ivory Coast	10
USA	44	Senegal	10
South Korea	10	UK	35
Pakistan	0	France	37
Egypt	0	Indonesia	6
Nepal	0	USA	44

Patents on biotechnology methods and materials, and even on plant varieties, are thus complicating and undermining the collaborative relationships between international institutions. Public-sector research institutions in industrialized countries no longer fully share new information and technology. Rather, they are inclined to patent and license (Erbisch and Fischer, 1998), and have special offices charged with maximizing their financial return from licensing (Brazell, 2000). Commercial production of any GM crop variety requires dozens of patents and licences (see above, Table 5). It is only the big companies that can afford to put together the IPR portfolios necessary to give them the freedom to operate (Barton, 1997). In addition, now, under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement of the World Trade Organization, most developing countries are required to put in place their own IPR systems, including IPR for plants (Giannakas, 2001). Furthermore, all of this 'ownership' of plant genetic resources is causing developing countries to rethink their policies concerning access to the national biodiversity they control (Lesser, 2000), and new restrictions are likely. The trade-related aspects of patents covering the specific example of vitamin A rice (see above) are summarized in Table 7, which shows the number of relevant patents in each of the major rice-producing and rice-importing countries. The complexity of trade between any two countries increases with the sum of the patents in the countries involved.

Several proposals have been made on how the international community should deal with these present IPR realities affecting agriculture (Conway and Toenniessen, 1999; Delmer *et al*., 2003; Toenniessen *et al*., 2003). With little competitive loss, seed companies could agree to use the Plant Variety Protection (PVP) system (including provisions allowing seed saving and sharing by farmers) in developing countries in cooperation with public plant-breeding agencies (Atkinson *et al*., 2003; Wang and Liu, 2003). In this context, it is noteworthy that most multinationals have given a specific undertaking not to use 'terminator technologies' to protect their varieties. To speed the development of biotechnology capacity in developing countries, companies that have IPR claims over certain key techniques or materials might agree to license these for use in developing countries at no cost (Nottenburg *et al*., 2002). These authors also propose an agreement to share the financial rewards from IPR claims on crop varieties or crop traits of distinct national origin, such as South Asian Basmati rice or Thailand's Jasmine rice. The granting of free licences to use such materials in breeding programmes in the country of origin of the trait might gain the appreciation of developing country researchers and governments.

For all the reasons discussed above, new organizations, such as Public Intellectual Property Resource for Agriculture (http://www.pipra.org/) and the African Agricultural Technology Foundation (http://www.aftechfound.org/), have been established as a means of rationalizing the huge proliferation of patents, especially in plant biotechnology. It is the intention of these organizations to develop a freedom-to-operate information database, to help public-sector agricultural research institutions achieve their public missions (Cantley, 2004) by ensuring access to intellectual property required to develop and distribute improved staple crops and speciality crops, and to facilitate the delivery of patented technologies to poor farmers whilst limiting patent holders' liability.

Present status of GM crops

The application of biotechnology to crops, a process founded on the exploitation of IPR, has rapidly transformed the agricultural economy of the USA for the commodity crops, soybeans, corn, cotton and canola, by providing genetic resistance to herbicides and insects. The rapid uptake of these novel products by the agricultural industry is demonstrated by the fact that, since the first large-scale introduction in 1996, the global area planted to such transgenic crops has grown to 200 million acres in 2004, of which 118 million acres (59%) were in the USA (http://www.isaaa.org/). In that year, GM varieties providing herbicide or insect resistance represented 56% of soybeans, 26% of cotton, 19% of oilseed rape and 14% of corn grown on a global basis. However, biotechnology has had limited commercial success to date in horticultural crops, including fruits, vegetables, flowers and landscape plants (Bradford *et al*., 2004; Cook, 2004), partly because of IPR constraints (Graff *et al*., 2004). Even though the first transgenic crop to reach the market was the Flavr Savr tomato, and sweetcorn, potato, squash and papaya varieties engineered to resist insects and viruses have been approved for commercial use and marketed, papaya is the only horticultural crop for which transgenic varieties (SunUp and Rainbow) have achieved a significant market share (about 70% of the Hawaiian crop shipped to the continental USA is transgenic) (Fermin *et al*., 2004; Gonsalves, 2004).

Conclusion

Although this review has summarized a range of information related to IPR and transgenic plants, it should not be considered as a definitive guide to IPR in any specific area. Although most research workers in the academic sector will probably be unaffected by any of the issues raised (Kimpel, 1999; Agres, 2003, 2004; Korn and Heinig, 2003), at least with respect to their day-to-day work (Brickley, 2003), anyone with commercial ambitions, or working in the commercial sector, needs to be well briefed in this complex subject (Kowalski *et al*., 2002; Lopez, 2004) and should seek local specialized advice. In addition, anyone interested in seeking patent protection should be aware of the absolute need to keep detailed and unambiguous records (Shear and Kelley, 2003). Excellent advice on this subject can be obtained in two publications, '*Keeping a Laboratory Notebook*' and '*Publish and be Damned – How to Avoid Inadvertent Publication of your Invention*', both available from the British Technology Group (BTG) (http://www.btgplc.com/info/links_lit.php).

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