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Transgenic crops, biotechnology and ownership rights: what scientists need to know

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Summary

Ownership of intellectual and tangible property (IP/TP) rights in agricultural biotechnology (ag-biotech) and transgenic plants has become critically important. For scientists in all institutions, whether industrialized or developing country, public or private sector, an understanding of IP/TP rights is fundamental in both research and development. Transgenic plants and ag-biotech products embody numerous components and processes, each of which may have IP/TP rights attached. To identify these rights, a transgenic plant or ag-biotech product must be dissected into its essential components and processes, with each 'piece' analysed under the IP/TP 'microscope'. This product deconstruction is an integral step in product clearance (PC) analysis leading to freedom to operate (FTO). To facilitate a PC analysis, the following points are important: (1) knowing what one has and where it's from, (2) organizing material transfer agreements and licences, (3) researching scientific and patent databases and relevant literature, (4) instituting a laboratory notebook policy, (5) keeping track of ownership of germplasm and plant genetic resources, and (6) promoting ongoing IP/TP management, awareness and training. However, a FTO opinion does not solve the IP/TP issues of releasing a transgenic plant or ag-biotech product; rather, it is a management tool for assessing the risks of litigation. When transferring transgenic plants or ag-biotech to developing nations, scientists from industrialized countries have the heightened responsibility of verifying that IP/TP issues are fully addressed and documented. Successful technology transfer goes beyond research, development and licensing; it is an holistic package leading to long-term partnerships in international development. Managing IP/TP requires capacity-building in scientists and technology transfer offices, in both industrialized and developing countries.

Keywords: agricultural biotechnology, transgenic crops, technology transfer, intellectual property, freedom to operate, germplasm

Introduction

The increasing private sector involvement in agricultural research has required that intellectual and tangible property (IP/TP) rights protection (Table 1) be sought for the products of this research. Since the early 1990s, most industrialized country research organizations have restricted the free movement of IP/TP associated with agricultural biotechnology (ag-biotech) and transgenic

crops. In addition to private sector corporations, public sector universities, government research institutes and international research centres (i.e. the CGIAR system, Table 1) have implemented IP/TP policies. As this continues, scientists will need to appreciate what this entails (Wright, 2000). Indeed, everyone involved needs to understand that IP/TP rights protection of potentially

Table 1. Definitions of commonly used terms

Terminology	Definition	Reference
Capacity building	A phrase frequently used in international development literature. Broadly meaning 'the strengthening and/or development of human resources and their institutional support structures.'	Maredia and Erbisch (1998)
CGIAR	The Consultative Group on International Agricultural Research, established in 1971, is an informal association of 52 public and private sector members that supports a network of 16 international agricultural research centres (e.g. IRRI, CIP, CIMMYT). The World Bank, FAO, UNDP and UNEP are co-sponsors of the CGIAR. The mission of the CGIAR is to contribute, through its research, to the promotion of sustainable agriculture for food security in developing countries.	http://www.cgiar.org/
Designated germplasm	Germplasm held 'in trust' for the benefit of the international community by the CGIAR centres under an agreement with the FAO. The agreement further stipulates that the centres shall not claim legal ownership nor seek IP rights over the material and that dissemination of the material should be under the same terms.	Bragdon (2000)
Discovery	'Compulsory disclosure, at a party's request, of information that relates to the litigation. The primary discovery devices are interrogatories, depositions, requests for admission and requests for production.'	Black's Law Dictionary (Garner, 2001)
Freedom to operate (FTO)	'Freedom-to-operate (FTO) means the ability to undertake research projects and/or commercial development and sales activities involving a particular technology or product with a minimal risk of infringing the unlicensed patent or tangible property ownership rights of another party.'	Duesing (1997)
Intellectual property (IP)	IP is taken to mean, without limitation, intellectual property rights, including patent rights, plant variety protection certificates, unpublished patent applications, and any inventions, improvements, and/or discoveries that may or may not be legally protectable, including know-how, trade secrets, research plans and priorities, research results and related reports, statistical models and computer programs and related reports, and market interests and product ideas.	Kryder <i>et al.</i> (2000)
Licence	A binding, revocable privilege to transfer IP rights in exchange for royalties or other consideration. Licences are contractual agreements, and should, among other things, specify term, territory, and whether rights granted are exclusive or non-exclusive.	Erbisch and Fischer (1998); Tang and Williamson (1996)
Material transfer agreements (MTAs)	A type of contractual agreement that offers a variety of proprietary protection, frequently for materials (e.g. TP) not covered by patents. In agricultural research, MTAs are used in the transfer of plant genetic resources, plasmid constructs, transformation vectors, etc.	Blakeney <i>et al.</i> (1999); Pistorius (1995); Soong (1999)
National Agricultural Research System (NARS)	'The research system comprised of all entities responsible for organizing, coordinating, or executing agricultural research within a country to contribute to the development of agriculture and maintenance of natural resources'.	Cohen (1999)
Patent(s)	'An exclusive right given to an inventor to exclude all others from making, using and/or selling the invention. The right the inventor has depends on which country issued the patent.'	Erbisch and Velazquez (1998); Scalise and Nugent (1995)
Plant variety protection (PVP)	A form of protection for plant varieties similar to a patent, but with some significant exemptions. Also known as 'plant breeders rights'; an international convention (UPOV) sets minimum standards. The US Plant Variety Protection Act of 1970 (amended in 1994) provides plant variety protection certificates for crops that reproduce sexually and clonally (i.e. tuber-bearing crops). Among other requirements, varieties must be distinct, uniform and stable.	Goss (1996); Kimpel (1999); Scalise and Nugent (1995); http://www.ams.usda.gov/science/pvp/htm
Plant patents	Expansion of the US patent law of 1930, which provided provisions for the patenting of asexually propagated plants (excluding uncultivated and tuber-propagated species).	Goss (1996); Kimpel (1999); Scalise and Nugent (1995)

Table 1 (continued)

Terminology	Definition	Reference
Product clearance (PC)	The process that tracks FTO for a product under development. Information pertaining to the product (technical, patent, licence) is assembled and documented. The initial step is to define the technical content of the product, i.e. all of the ingredients, processes and combinations thereof used to achieve the product. In an agricultural biotechnology product, these might include genes, gene promoters, selectable markers, transformation methodology, etc.	Duesing (1997)
<i>Sui generis</i> system	Latin phrase meaning 'of its own kind of class.' This is the system for WTO member states that do not allow patents on plants/plant varieties, to provide an effective alternative means for protection. Although not specifically defined in the TRIPs agreement, minimum requirements are indicated.	Blakeney (2000); Blakeney <i>et al.</i> (1999)
Tangible property (TP)	TP is taken to mean, without limitation, tangible property such as computer software, germplasm and the biological materials and derivatives thereof, and related materials.	Kryder <i>et al.</i> (2000)
Transgenic crops, 1st generation	Transgenic crops with agronomic traits intended as production-side, cost-reducing innovation(s), e.g. herbicide and insect resistance, Bt maize or Roundup Ready™ soybeans	Dunwell (1999); Rausser and Small (1996)
Transgenic crops, 2nd generation	Transgenic crops with product quality and/or value-added innovation(s), directed towards markets and consumers, e.g. delayed ripening and enhanced nutritional characteristics (β -carotene rice).	Dunwell (1999); Rausser and Small (1996)
UPOV	International Convention for the Protection of New Varieties of Plants. Stipulates minimum requirements for national plant-breeders rights. The most recent act, 1991, is the only one open to new members and most developing nations are utilizing this to comply with the requirement for IP rights under WTO/TRIPs.	Mauria (2000); http://www.upov.org
Valuation	Evaluation of technologies in order to assess their value, as well as the value of related patents and portfolios. One common objective in valuation is determining potential royalty rates coupled with licensing of technology.	Bramson (1999); Degnan (1998)

valuable ag-biotech encourages investment, fosters research and generates commercial products with significant consumer utility.

The public sector knows that IP/TP rights management will facilitate the development of ag-biotech to further its altruistic mission, but it is, at the same time, unable to develop advanced ag-biotech alone. The private sector, with its substantial investment in product development, is not inclined to distribute its ag-biotech without a clear proprietary advantage. Therefore, if the public sector clearly demonstrates that it has operable IP/TP rights management, agreements and licences (Table 1) can be negotiated and public/private sector partnerships can proceed. In this manner, international research centres can also acquire technologies that might otherwise be unavailable, and ag-biotech can thus serve humanitarian purposes in developing countries where it is sorely needed, e.g. Golden Rice as a pro-vitamin A source for malnourished young children in developing countries (Potrykus, 2001).

Ag-biotech from industrialized countries is increasingly important to developing countries for food security and economic development (Briggs, 1998; Purnell, 1995; Serageldin, 1999; Toenniessen, 1995). However, many

developing countries lack the requisite capacity and resources to conduct IP/TP management that would enable legitimate access to this ag-biotech. Therefore, as with movement of ag-biotech from the private to public sectors, IP/TP management capacity-building (Table 1) is of vital importance for transferring ag-biotech from industrialized to developing countries.

This paper describes the issues involved in IP/TP rights management of ag-biotech and transgenic crops, both for the benefit of plant scientists and their institutions and also within the context of the transfer of ag-biotech from industrialized to developing countries. Because there are a number of specialized terms used, Table 1 lists definitions and references. It should be stressed that nothing in this paper constitutes a legal opinion and the authors recommend that legal advice be obtained to ensure appropriate counsel in completing a freedom to operate review (FTO, Table 1).

The complexity of transgenic plants: Golden Rice

From an IP/TP rights perspective, ag-biotech and transgenic crops contain multiple layers of complexity. There is the product itself, with the processes and components

used in its development; one must determine who owns or controls these, how were they obtained, whether there are material transfer agreements (MTAs, Table 1) attached, whether they were purchased or if their origin is simply unknown. The IP/TP rights landscape must also be evaluated; where the product will be produced, marketed, used/consumed, e.g. domestic consumption or export. It must be determined what laws, country-by-country, govern patents, trademarks, plant variety protection (PVP) regimens, copyrights and/or contracts (Table 1). Licences may be required to move the product either to market or for purposes of international development. Each of these layers involves challenges, risks and rewards, and requires a sophisticated set of IP/TP management skills. Foreknowledge of the IP/TP landscape will facilitate a transgenic crop's development, distribution and utilization.

The product clearance (PC, Table 1) analysis of transgenic β -carotene-enhanced Golden Rice (Ye *et al.*, 2000) exemplifies the challenge that scientists and their organizations face as they develop, commercialize and distribute ag-biotech and transgenic crops. Whereas first-generation transgenic crops (Table 1) primarily involved single-gene expression systems, Golden Rice, as a second-generation crop containing multiple transgenes (Table 1), typifies the complexity involved in engineering metabolic pathways in plants (ap Rees, 1995; Martin, 1998). The corollary of this is the increasing complexity in IP/TP rights (Cahoon, 2000); that is, as the genes, proteins and methodologies, accumulate, so do the issues surrounding the product's patents, MTAs and licences. For example, the transformation construct pBin19hpc, one of those used to produce Golden Rice, includes numerous components; a summary IP/TP clearance table lists potentially applicable patents and patent applications (Figure 1). Furthermore, this is just one of three constructs used in the engineering of the initial transgenic plant, all of which need to be considered along with the transformation protocol and the germplasm in which Golden Rice is eventually released (Kryder *et al.*, 2000).

Unravelling the complexity: deconstruction and product clearance

The example of Golden Rice is a general and practical introduction to PC leading to FTO (Duesing, 1997). PC involves analysis of a product's IP/TP ownership issues to identify the components to be licensed and the sources of such licences, and one way of considering this process is included in Figure 2. The steps involve deconstructing the product – identifying and collecting information about each component and method, followed by identifying all of the potential patents and licences relating to each of these and thereby generating a PC spreadsheet listing all IP/TP. This information is collected via discussions with

scientists and by researching patent and scientific literature. Then a PC profile is extracted from the PC spreadsheet, containing all of the issues that require attention, and is used to determine the actions and strategies needed to obtain FTO. Developing these documents is rarely linear, rather a reiterative cycle of discovery, analysis and summary. Whereas an FTO opinion does not solve the IP and TP issues of releasing a new product, it does provide information concerning the risks of litigation that are involved in using the various components to produce an ag-biotech product or transgenic plant (Kowalski and Kryder, 2002). Hence, as a risk management tool, it is extremely useful – establishing clear-cut ownership of the IP and TP of a new product is an issue that all researchers and research institutions need to consider carefully.

A word of caution should be given to organizations as they initiate FTO reviews. When such work is conducted under the guidance and supervision of an attorney, in many jurisdictions it is protected from 'discovery' (Table 1) under provisions of 'attorney–client privilege'. However, if conducted outside such a protected relationship, the resulting documents may be subject to discovery during litigation. Each research institution needs to weigh up the risks that this involves.

A critical part of the PC analysis is access to all of the information – usually involving open and frequent discussion with scientists involved. Scientists might see this as an interruption of their work, failing to see the PC analysis as relevant to their research or important to their institution, and thus unwittingly omit important information. Tact and goodwill on the part of the reviewer can help to minimize such problems. A PC analysis may also identify other management issues that have been overlooked in the drive for data and results, such as proper cataloguing and storage of clones or the information surrounding their construction. It may even identify significant new IP developed in the project, but overlooked by the scientists. This can help to cast the PC analysis as a management process producing positive and useful results.

Finding all of the salient information can be difficult. One reason is the mobility of researchers in this age of short-term research contracts. Another may be that the new product is being developed from work that was begun many years (and researchers) ago. Finding and following a product's paper trail to fully understand what techniques and components were used can be arduous and maddening. This underscores the importance of good laboratory notebooks and record-keeping.

For the scientist and others conducting a PC analysis, it is important to understand and connect to both scientific and patent literature. Whereas these sources of information are distinct, each having its own specialized purposes, for a PC analysis they are complementary. Scientists might regard patent literature as opaque, finding it difficult to

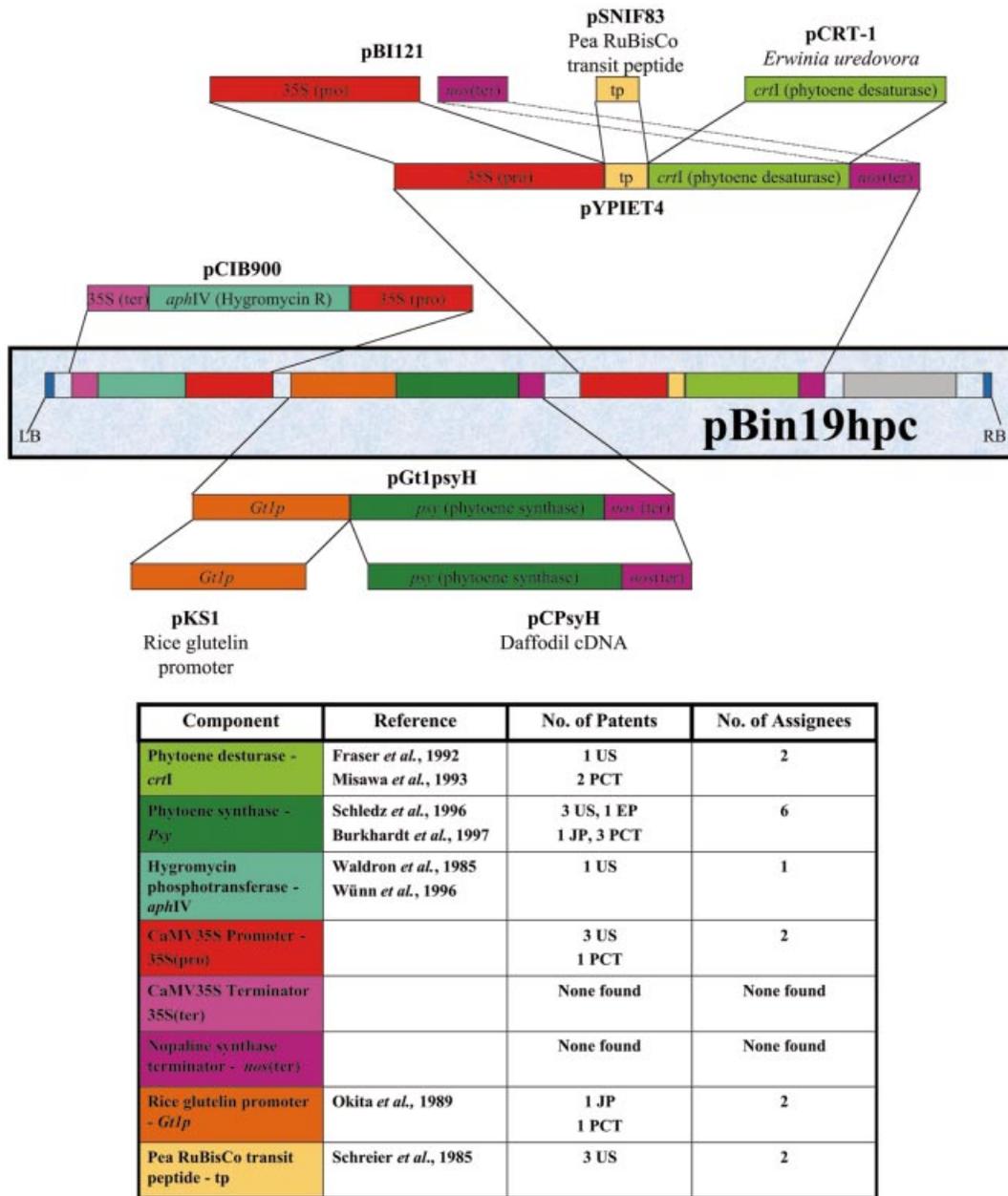


Figure 1. Diagrammatic representation of the cloning steps involved in the construction of pBin19hpc (Ye *et al.*, 2000) and a simplified listing of the IP embedded in the final plasmid (Kryder *et al.*, 2000). US, granted United States patents; EP, granted patents and applications made under the European Patent Convention; JP, Japanese granted patents and applications; PCT, international patent applications made under the Patent Cooperation Treaty (Kesan, 2000)

identify relevant patents, yet such documents often have a far greater amount of experimental information than a research publication. At the same time, the scientific literature will provide useful terms for searching patent databases, although designations for genes, proteins and regulatory regions used in patent applications sometimes change by the time the papers are published. One way to

overcome this and find relevant patents is to search using the authors of scientific papers as inventor's names. It must always be remembered that, similar to the time lag in publishing journal articles, there is also typically a time lag (18 months or more) between filing and publication of patent applications, and it may take several years before a patent is finally granted for a particular invention.

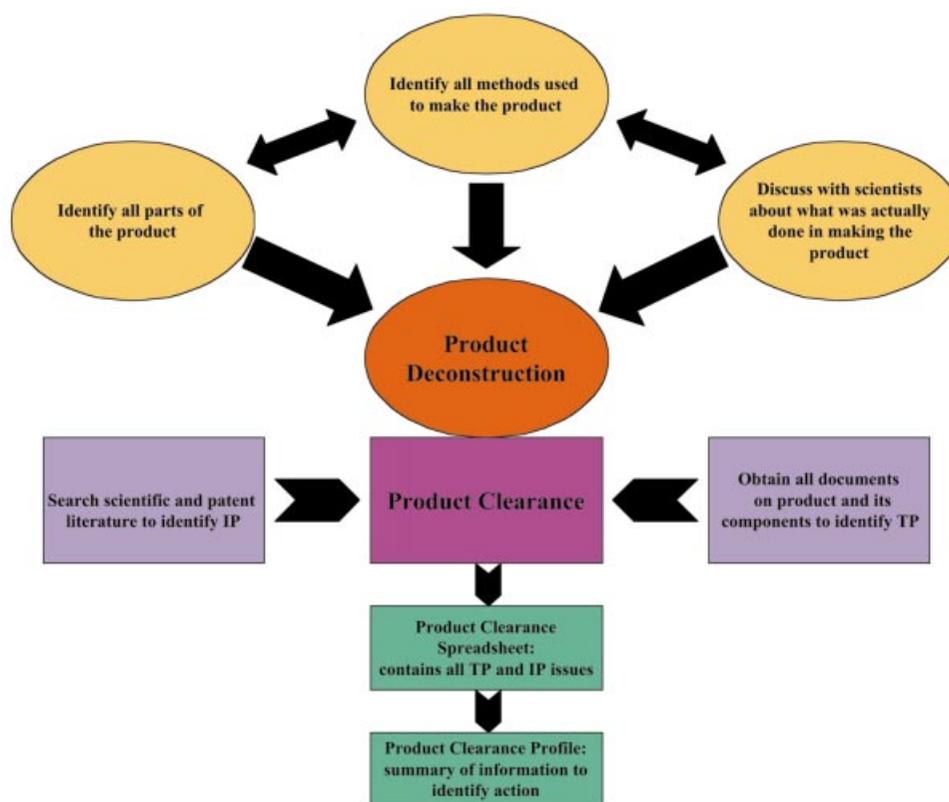


Figure 2. The general areas and organization of a product deconstruction and a product clearance review

Nonetheless, a coordinated search of both the patent and scientific literature (databases) is a key part of a PC analysis, and, as a bonus, sometimes reveals additional, potentially relevant, scientific information.

A fictional example of a product deconstruction: Murphy's plasmid

A hypothetical plasmid illustrates the methods, and problems, in a product deconstruction. Although some well-known plasmids and components have been included to illustrate real-life problems, this is a fictional construct, with neither intended nor implied connection to real researchers.

Freda Murphy built a construct which produces enzyme XYZ in leaves (Figure 3). She obtained the cDNA from plasmid pXYZc, isolated from a λ -based cDNA library made by Dr Sarek of the University of Vulcan. Sarek initially created the library using a commercial cDNA cloning kit. Murphy subcloned the cDNA, replacing a marker gene in a plant expression plasmid (obtained from the laboratory next door) to provide promoter and terminator fragments, and then subcloned this into a binary

vector for plant transformation (supplied to Murphy's institute by Dr M. Bevan in 1987).

Thus, the deconstruction begins by looking at three major components:

- 1 the cDNA clone (pXYZc, from Sarek),
- 2 the plant expression vector (pBI121, from the laboratory next door), and
- 3 the binary transformation vector (pBin19, from Bevan).

Each of these may have TP rights attached, and some of the subcomponents, e.g. promoters, terminators and resistance genes, may also have IP rights attached (Table 2).

The cDNA for XYZ appears to have both TP and IP rights attached. As TP of the University of Vulcan, it is unclear whether Dr Sarek was authorized to sign on behalf of his university, but he nevertheless signed the MTA transferring plasmid pXYZc to Murphy. Murphy's supervisor co-signed the MTA on behalf of Murphy's institute. The MTA gives Murphy the right to use the TP of the plasmid for research only; however, it does not provide any rights to the IP embedded in the plasmid. IP rights to the cDNA for XYZ are held by Plant Gene Patents Inc. as a patent application on the enzyme (Patent Cooperation Treaty

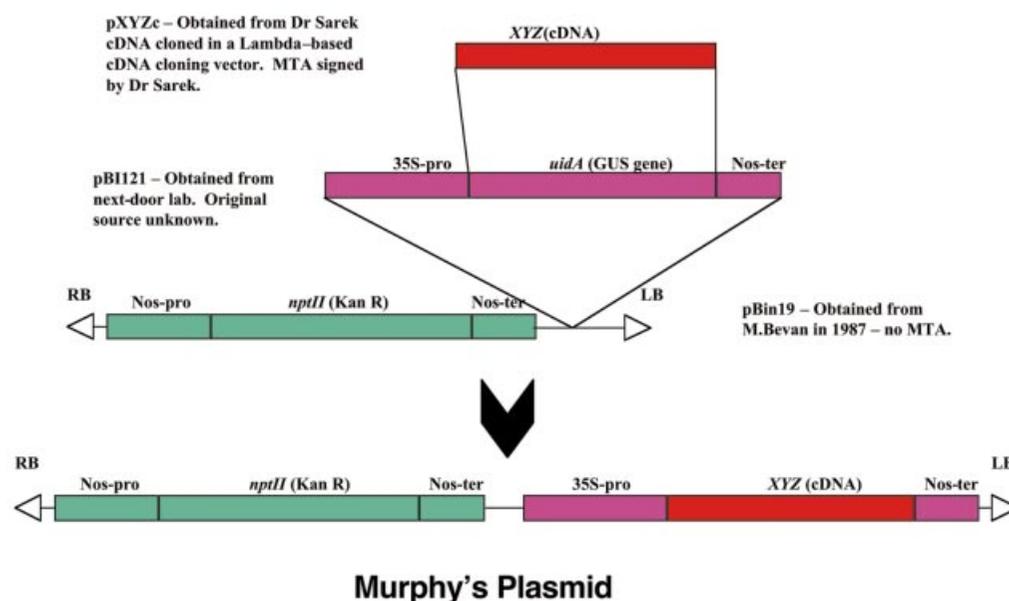


Figure 3. Outline of cloning procedure for the fictional Murphy's plasmid

Table 2. Summary of the TP and IP in Murphy's plasmid

Component	Source	Owner	Patent number or licence	TP or IP
1 pXYZc	Dr Sarek, University of Vulcan	University of Vulcan	MTA – Research only	TP
1.1 cDNA cloning kit	Stratagene	Stratagene	US5128256 US5286636 EP0286200	IP
1.2 XYZ cDNA	Dr Sarek, University of Vulcan	Plant Gene Patents Inc.	WO9999999	IP
2 pBI121	?	?	?	TP
2.1 35S-pro	?	Monsanto	US5352605 US5530196 US5855742	IP
2.2 Nos-ter	?	Monsanto	US5352605	IP
3 pBin19	Dr M. Bevan	Plant Breeding Institute, Cambridge	None signed	TP
3.1 Nos-pro	Dr M Bevan	Monsanto	US5034322	IP
3.2 <i>nptII</i>	Dr M Bevan	Monsanto	US5034322	IP
3.3 Nos-ter	Dr M Bevan	See above	See above	IP

(PCT) application number WO9999999) which has been published, but (as yet) no patent has been issued. Dr Sarek cloned the cDNA using a proprietary cloning kit purchased from Stratagene, which is covered by two issued US patents and one issued European patent. Although purchase of the Stratagene kit carries an explicit right to use the kit for cloning, expression and characterization of genes (contained in the documentation accompanying the kit), further rights to use the cloned products are unclear.

Plasmid pBI121, having resided in Murphy's neighbour's freezer for an indeterminate period, had no records regarding its source, and so the TP situation is uncertain. Embedded IP consists of the 35S promoter and the Nos

terminator, both covered under US (and other) patents held by Monsanto. Note that the GUS gene is not present in the final product, nor was it used to produce it, and is therefore not considered.

The binary vector pBin19, when obtained by Murphy's institute, had no accompanying MTA. Therefore, from the TP standpoint, Murphy's rights to use this plasmid remain ambiguous. However, as with pBI121, there appears to be IP embedded in the plasmid, i.e. the Nos promoter, kanamycin resistance gene and Nos terminator. These three appear to be covered by patents issued to Monsanto.

The story of Murphy's plasmid illustrates the distinction between IP and TP rights (Table 1). Ownership of the IP for

the various genes/components is unaffected by TP ownership of the three constructs and any available MTAs. But note, even if Murphy went to the trouble of chemically re-synthesizing the genes/components in the plasmid, although the TP rights of the original suppliers would be extinguished, the IP rights situation would remain unchanged. Another question that arises is how far TP rights can reach. That is, how far forward can the claims of ownership of a piece of DNA go when it has been moved from one plasmid to another and then transformed into a plant? Unfortunately, there are no clear rules to give an answer, but this example illustrates how important it is to identify the original sources of as many components as possible so that informed decisions can be made.

Practical considerations and useful examples

Although the PC analysis may look complex and daunting, good planning, thoughtful organization and assiduous record-keeping will make it a lot more straightforward. Here we offer five practical recommendations to assist scientists in preparing for or participating in a PC analysis. It is neither exhaustive nor are the points particularly difficult or clever, rather just basic common sense.

Start early

Second-generation transgenic plants (Table 1) have numerous components. Keeping them all properly recorded, while not difficult, may seem tedious, time-consuming and not much like research at the time, but by the end of a long development process it is a great deal more complicated to go back and try to work out what was done where, when and by whom. Additionally, when a commercial product is being contemplated, it is a good idea to obtain commercial use licences as the product is being developed, well before it is ready for release. This ensures a stronger bargaining position; the negotiation position is weaker if significant resources have already been invested. Furthermore, once others recognize that an ag-biotech product or transgenic plant has significant commercial potential, it will be considerably more expensive to negotiate a licence; negotiations become quite complex when there is \$1 000 000 on the table (H. Walter Haeussler, personal communication). Scientists therefore need to carefully consider the scientific utility of a component along with the potential IP/TP complexity attached, complexity that could have an impact on downstream commercial development and/or other deployment.

A transgenic plant with clear humanitarian value, such as Golden Rice, might induce some owners of IP and TP to donate or waive their rights (for example see <http://www.cbsnews.com/stories/2000/08/04/world/main221973>.

[shtml St Louis, August 4, 2000](http://www.cbsnews.com/stories/2000/08/04/world/main221973) (CBS) 'Monsanto announced it will give away free licences to use its patented technology for so-called "golden rice" and other genetically engineered rice varieties that advocates say could save millions of Third World children'). However, in a global business environment driven by competition, investment and profit, assessing the IP landscape based on such expectations of humanitarian leveraging of IP/TP rights may represent an impracticable approach to IP/TP management. Therefore, whereas relying on external pressures to compel IP owners to grant licences is an option, it is inherently risky and should be done only with some fore-knowledge of which licences will be required and from whom. Even if a decision is made to not negotiate a commercial licence before the product is ready for release, such a decision should only be made from a fully-informed perspective. Table 3 presents options for the timing of a PC analysis, with the pros and cons of each.

Update regularly

IP rights are time-sensitive; new patents are issued and others expire. The patent laws of most countries provide for a patent term of 20 years from the date of filing. Therefore, many of the early ag-biotech patents that were filed before the mid-1980s are now close to expiry. Over the next few years, their expiry may make the IP landscape simpler to traverse. However, be aware that, under certain circumstances, there may be extensions to patent terms. Furthermore, the time for patent applications to be granted is indeterminate, and even the applications may not be published for up to two years after filing. Thus there is a time lag between what can be identified through the various patent databases and what may actually be protected. This may have serious implications and indicates that a PC analysis will be valid only for a relatively short period of time and should therefore be reviewed at least annually to ensure that newly issued patents are considered.

Keep track of MTAs

MTAs (Table 1) are a special class of contract, typically granting the recipient a 'research-only licence' for the material transferred and often containing other grants and prohibitions. It is important to use the transferred materials within the scope of authorization as delineated in the MTA. Often there is a prohibition against the recipient seeking statutory protection on the research results and the transfer of the material to third parties. There may be other clauses that limit the research to a specified target crop, for a limited time, or that define the basis for future commercial licence negotiations. The MTA might specify

Table 3. Options for timing a PC analysis of an ag-biotech product or transgenic plant

Timing of PC analysis	Strategy	Pros	Cons
1. Before research work is started	A search of the relevant patent and scientific literature is often sufficient (early prophylactic strategy).	Can plan development and make decisions on how to proceed with FTO in mind. Little investment at this stage so loss is minimized.	May interfere with scientists, hold back promising lines of research, and may be seen as waste of time before there is any proof that product is even possible.
2. After proof of concept, before product development, research phase	Need to consider materials and methods used as well as products and processes (late prophylactic strategy).	Know that product is possible, but if there are IP/TP rights constraints, still have time to redesign product, rather than negotiate.	Product under development, possibly containing third-party IP/TP. At this stage, significant resources may already be invested, making changes difficult and expensive.
3. After product has been developed, pre-marketing	Must consider aspects of large-scale production as well as marketing/licensing opportunities (negotiation strategy).	Know that product has commercial potential, and have data on how to estimate potential value (i.e. at this stage, valuation is possible, Table 1).	Have invested significant resources, therefore risk large loss if product does not get FTO. Potential for owners of third-party IP/TP to delay marketing via protracted licence negotiations.
4. Product ready to ship	Need to work through who owns what, and what options might be available for accessing IP rights (damage control strategy).	Few, in any; you have run out of time.	Every technology owner with a piece of your product may have an advantage and be in a superior position to dictate the terms of licences.

certain 'reach-through' rights for the provider, e.g. rights or an option to obtain rights in research conducted using the transferred materials. When faced with an option of whether to obtain materials from either corporate or academic sources, it is wise to carefully consider the relative level of restrictions written into the MTAs.

Proper management of MTAs is extremely important. Only an officer of the research organization who has been granted binding signatory authority should sign an MTA. Each research organization should establish a protocol ensuring that an officer reviews all MTAs. Researchers, when approached directly for transgenic plants or other ag-biotech components, should know where to forward such requests. And, importantly, copies of MTAs and other licences should be stored in a central file, not 'stuck' in a laboratory notebook or 'filed' in a laboratory drawer. These documents are contracts, requiring careful study to determine what limitations are placed on the use of the transferred material.

Know what you have

To assess the IP landscape of a new ag-biotech product or transgenic plant, it is important to know what components and process were used throughout research and development. This entails detailed knowledge of the science, accurately kept records and appreciation for scientific terminology. Only when scientists clearly recount and

communicate this information can a PC analysis progress and/or preparations be made if litigation is threatened.

Sometimes the map or other written description that accompanies an MTA may have inaccuracies. For example, when the T-DNA region of pBin19, used in the construction of Golden Rice, was re-sequenced, it was found to contain components that were not on the maps routinely distributed with the plasmid (Genbank accession number U12540). Although unintentional, such inaccuracies could nonetheless have a serious impact on the downstream development of a transgenic plant, both from the scientific and FTO perspectives.

A PC analysis can only be conducted when the various components and processes used have been sorted out and details are clear. Terminology can be complex; ag-biotech components and processes may have multiple designations, which can be confusing and must be resolved before the PC analysis can proceed smoothly. In general, it is helpful to use standard scientific terminology. A few examples illustrate how the complexity of terminology can affect a PC analysis.

Bt. A complex and sometimes bewildering nomenclature categorizes the genes, and their insecticidal crystal proteins, derived from *Bacillus thuringiensis* (Bt) (Crickmore *et al.*, 1998; Höfte and Whiteley, 1989). To evaluate the IP associated with a Bt gene, a thorough knowledge is critical: molecular mass, gene designations, sequence information and target insect are all important.

As patent abstracts and claims relating to Bt genes are frequently inconclusive and opaque, a more comprehensive study of the entire patent, particularly its claims, is often required.

PCR. If one searches the patent databases with the term 'PCR', few hits occur. To execute a successful search on this technology, other search terms, such as 'polymerase chain reaction', 'DNA amplification', '*Thermus aquaticus*' or 'DNA polymerase' are more useful.

35S. Scientists use the 35S gene promoter from cauliflower mosaic virus in several forms (Kay *et al.*, 1987): single CaMV35S, double CaMV35S, single CaMV35S with tandem enhancer region, and often as a minimal CaMV35S promoter fragment linked to regulatory sequences from other sources. Depending on which version of the 35S promoter is used, different IP/TP rights and issues might apply. However, if it is unclear which 35S promoter is in a gene construct, it is then nearly impossible to clarify the IP situation.

Bar. The *bar* gene (Botterman and Leemans, 1989), found in the bacteria *Streptomyces hygroscopicus* and *Streptomyces viridochromogenes*, imparts resistance to the herbicides phosphinothricin (PPT; glufosinate; methyl [homooalanin-4-yl] phosphinic acid) and bialaphos (L-alanaphos; L-phosphinothricinyl-L-alanyl-L-alanine). The mode of action of these herbicides (antibiotics) is the inhibition of plant glutamine synthetase, with a subsequent rapid accumulation of toxic levels of ammonia. The *bar* gene product, phosphinothricin acetyl transferase (PAT), detoxifies phosphinothricin, as its name suggests, by acetylation. Glufosinate/phosphinothricin is chemically synthesized, whereas bialaphos is produced by fermentation of *S. hygroscopicus*. In addition, the class of phosphinothricin herbicides have numerous trade names (Basta[®], Rely[®], Liberty[®], Finale[®]), which sometimes appear in the literature. The number of potential identifiers used in this paragraph underscores the terminological complexity of this product and the possible search terms that may need to be considered when undertaking a PC analysis.

Keep good laboratory notebooks

Keeping accurate and up-to-date laboratory notebooks is essential for many reasons, not just related to PC analysis. This is particularly important in the USA, where patents are granted on a first-to-invent basis; but accurate record-keeping also has implications outside the US because, although patents are issued on a country-by-country basis, prior-art is global and clear notebook entries may become

a significant factor in determining the novelty of a non-US patent application.

Most research organizations now have laboratory notebook policies requiring timely and accurate signing, dating and witnessing of each scientist's laboratory notebook. However, some scientists may view such policies as annoying, tedious, a waste of time and an additional (and unwelcome) imposition by administrators. One way of making a laboratory notebook policy less onerous is by stressing how proper notes can help future scientists build on previous research. Notebooks provide institutional memory long after a researcher has left the project, the institution or the profession. Of course, a PC analysis, which always involves questions that could be easily answered by referring to organized notebooks, is a germane example of their practical importance.

Germplasm

From a IP/TP perspective, transgenic plants are both the germplasm (cultivar, variety, etc.) and the transformed gene(s). Therefore, germplasm must be considered in a PC analysis of a transgenic plant. Often the initial transgenic plants are not suitable as a new variety, e.g. the first Golden Rice transgenics were produced in a japonica cultivar – Taipei 309 (Ye *et al.*, 2000). When this occurs, the transgenes have to be introgressed into more suitable germplasm. Consequently, in a PC analysis, plant breeders must carefully clarify the IP rights in the germplasm used to produce these final lines, so that they can be appropriately distributed and used. The gene–germplasm relationship is complex, with at least several possible scenarios; for example, a gene isolated from a developing country's germplasm is transformed (in an industrialized country) into an advanced breeding line, e.g. an advanced commercial (proprietary) elite maize inbred line (Solleiro, 1995), or a patented gene (owned by an industrialized country corporation) is transformed into a crop (cultivar/variety) grown in the developing world (Shear, 1999).

IP for plants can be obtained in a variety of ways, varying from country to country. For countries that have acceded to the conventions of the International Union for the Protection of New Varieties of Plants (UPOV, Table 1), plant variety protection (PVP, Table 1) may offer IP protection for new plant varieties, yet provides little protection for transgenes or the biotechnology required for transformation. In addition to PVP protection regimes, some countries have laws permitting the patenting of plants. In the US, for example, plants can gain IP protection not only with PVP, but also under either utility patents (sexually propagated plants) or plant patents (asexually propagated plants) (Tables 1 and 4). Patents are increasingly viewed as more suitable than PVP for protecting transgenic plants and their products, as there is a specific

Table 4. Comparison of IP rights protection regimens available for plants in the USA

	Plant Patent Act	Plant Variety Protection Act	Utility patents
Protects	Asexually reproduced plants, including cultivated sports, mutants, and hybrids	Sexually reproduced plants	Plant genotypes not found in nature
Excludes	Uncultivated or tuber-propagated plants	Bacteria and fungi, first-generation hybrids, uncultivated plants	Nothing – anything invented by man can be patented in the USA
Requires	Novelty, distinctness, stability	Distinctness, uniformity, stability	Novelty, utility, non-obviousness, enablement
Disclosure	As complete as reasonably possible Photographs or drawings required No deposit of material required	Description of novel characteristics and genealogy Seed deposit required	Enabling disclosure required Best mode disclosure required Deposit of novel material required
Claims	Single varietal claim	Single varietal claim	Varietal claim, generic claims Claims to plant genes, gene transfer vectors, processes for producing plants, and so on
Rights	Prevent others from asexually reproducing, selling, or using claimed plant Does not protect sexual reproduction of claimed plant Does not protect plant products	Prevents others from importing or selling, sexually or asexually reproducing, distributing without proper notice Prevents others from producing a hybrid or new variety using the claimed plant Exemptions for developing a new hybrid or variety and for farmers' saving and sale of seed, compulsory licence provision	Prevents others from making, using, selling claimed invention Prevents others from selling a component of the claimed invention
Duration of protection	20 years from effective filing date for applications filed on or after 8 June 1995; 17 years from issue date for applications filed prior to 8 June 1995	Protected while application is pending, plus 20 years from issue date (25 years for vines and trees)	20 years from effective filing date for applications filed on or after 8 June 1995; 17 years from issue date for applications filed prior to 8 June 1995.
Priority	First to invent in USA	First to file in USA or another UPOV member country	First to invent in USA

Modified from Bennett (1994). Refer to Table 1 for basic definitions and additional references.

exemption in PVP legislation permitting the use of a protected variety for further breeding (Blakeney, 2000).

Two international conventions govern international access to and exchange of germplasm: the Convention on Biological Diversity (CBD) and the Trade-Related Aspects of Intellectual Property Rights (TRIPS) under the World Trade Organization (WTO) (Lesser *et al.*, 1999; Lesser, 2000). In 1993, the CBD came into force and recognizes the sovereign rights of acceding nations over their genetic resources, and addresses access to and benefit sharing of germplasm. TRIPS is designed to harmonize IP protection among its members, and accordingly requires WTO members to offer IP protection for plant varieties. Such IP protection for plants can be either by patents, PVP, or a *sui generis* system (Mauria, 2000). Although the CBD contains provisions that many countries do not wish to accept and thus has not been universally accepted, most of the developed world has adopted the

TRIPS requirements and many developing nations are actively developing legislation to adopt this as a requirement for joining the WTO.

In November 2001, the International Treaty on Plant Genetic Resources for Food and Agriculture was approved by a conference of the Food and Agriculture Organization (FAO) and is intended to formalize the previous International Undertaking on Plant Genetic Resources (IU), signed in 1994 by the CGIAR centres and the FAO. Part of the original undertaking was the recognition that genetic resources are the heritage of mankind and that property rights could not be sought over the genetic resources collected, a perspective clearly in conflict with the CBD (Bragdon, 2000). However, this treaty still leaves some significant areas of contention in the area of how property rights can be sought over genetic resources, as well as the mechanism by which countries can be recompensed for the use of their 'property'.

International movement of ag-biotech and transgenic plants

For effective movement of ag-biotech from industrialized to developing countries, it is crucial for both the donor and recipient to be aware of the IP/TP management issues involved; for all parties, capacity-building (Table 1) is an ongoing priority. Ag-biotech transfer to a developing country is more involved than simply drafting and executing a licence. A total package of technology, knowledge and business/legal acumen often needs to be transferred, and, ideally, a sustainable relationship is built. Greater contact, both before and after the technology transfer, is required, and a partnership is needed in which all parties can feel involved and there is mutual trust between them. As many countries are still developing capacity in IP/TP management, donating industrialized-country institutions need to conscientiously supply IP/TP-clean products.

IP rights are based on national rather than international law. Even in those cases where regional groupings of countries (e.g. Europe or East Africa) have a common application and examination system, patents are still national rights (Barton, 1997). Although global harmonization of IP rights is continuing (Brazell, 2000; DaSilva, 1998; Evenson, 2000; Ravishankar and Archak, 2000), there is still no 'international' patent system.

A Patent Cooperation Treaty (PCT) filing, sometimes erroneously called a 'world patent', actually only stakes a claim, defining a priority date for a patent application. With the exception of the US, which defines patent priority on the first-to-invent basis, other countries establish priority by the patent application filing date. The PCT system allows an inventor to establish a priority filing date with a single application, by designating any (or all) of the 116 signatory countries (see <http://www.uspto.gov/web/offices/pac/dapp/pctstate.html>). The PCT filing also initiates a novelty search and offers an option for an examination before the PCT applicant has to decide to file in individual countries. Thus, an applicant can stake a claim and obtain a reading on validity before committing to the much greater expense of full national filings, with up to 30 months after the initial application to decide where or whether to file in national systems (Kesan, 2000).

In contrast with the (currently) minimal IP constraints on the transfer of ag-biotech to developing countries, TP rights present a more immediate challenge. Many TPs are exchanged under MTAs placing restrictions on their use and further transfer. In addition, some products from commercial sources have accompanying licences specifying their use and the distribution of associated downstream results. Some research institutions may poorly understand and manage MTAs and licences, which, as contracts, are subject to national contract law often in a jurisdiction defined in the contract. Therefore, when ag-

biotech and/or transgenic plants are transferred internationally under MTAs or licences, the terms of the agreement and the laws of the respective countries, i.e. industrialized transferor and developing transferee, are important to understand and observe.

As most patents for ag-biotech of potential use to developing countries are valid only in industrialized countries, there might appear to be few IP constraints to technology transfer. However, developing countries without adequate IP rights protection and/or enforcement may encounter problems if transgenic crops (or products thereof in which the patented ag-biotech is embedded) are subsequently exported to countries where IP rights prevail. Nations generally regard it as infringement to import a product that is protected by a patent or one that is made by a process that would infringe a patent. The exact scope of this process-oriented protection varies from nation to nation, but usually it is the direct product of a patented process that cannot be imported (Barton, 1997).

Developing countries lacking reliable IP legal systems and/or enforcement might access and utilize ag-biotech, owned by industrialized country sources, without concern for potential repercussion, i.e. 'pirating'. However, such a short-term strategy of unauthorized use has a longer-term price tag. Misappropriation of ag-biotech indicates that IP/TP protection systems are not in place, and, over the longer-term, owners of ag-biotech will have little incentive to invest in or do business with these countries as it would be difficult (or impossible) to protect their property and/or recoup their investments. Therefore, developing countries need IP/TP management capacity in order to build sustainable relationships with owners of ag-biotech, relationships that can significantly benefit international development by moving such technology to where it is needed most (Kowalski and Kryder, 2002).

There are several criteria for success in ag-biotech product development, beyond simply making a product that meets the needs of one specific user (e.g. farmers in the industrialized north). Of course, when a product performs as expected this is a scientific success, with licensing of the technology as one objective. However, in a global setting, success is determined by the ag-biotech product's acceptance in the world marketplace and adoption by developing country farmers. This extended definition of success suggests that industrialized country scientists will need to continue their involvement long after the actual international transfer of the technology, building long-term partnerships based on mutual respect, understanding and trust, with their counterparts in developing countries.

Summary and conclusions

Effective management of IP/TP connected to transgenic plants and/or ag-biotech products facilitates their eventual

commercialization and distribution. This is additionally important if the goal is transfer to the developing world, where expertise in IP/TP management may be lacking. A PC analysis (leading to FTO) does not solve the IP/TP rights issues of releasing a new product. In fact, such issues are never actually solved; more precisely, risks are managed. An indispensable part of this is IP/TP management capacity-building for all involved, whether developing or industrialized countries, public or private sectors. From a practical standpoint, to implement this, scientists and their organizations should:

- 1 educate staff on the basic principles of IP/TP management and maintenance,
- 2 bookmark patent and scientific databases on web browsers,
- 3 remain aware of the complexity of germplasm issues,
- 4 stress the importance of good laboratory records and institute a notebook policy,
- 5 document what comes into and goes out of the laboratory,
- 6 establish clear lines of responsibility for signing MTAs and licences (both incoming and outgoing), and ensure researchers know who has to sign,
- 7 manage and organize licences and MTAs and the various documents and correspondence associated with them; an electronic database as a contract management tool is an example of how this information can be both secured and made available at the same time,
- 8 personally and institutionally seek opportunities to gain IP/TP management skills, and
- 9 identify and learn to work with a competent patent attorney.

When working alone or in collaboration, nationally or internationally, everyone must know how IP/TP rights affect development, commercialization and successful transfer of ag-biotech products and/or transgenic plants. It is no longer sufficient to simply produce ag-biotech; pro-active, pre-emptive IP/TP analysis and management must also be pursued throughout research and development.

However, having said all this, don't let IP/TP issues give you sleepless nights. Remember that, as with purchasing laboratory supplies, inventory of isotopes, radiation and chemical safety, IP/TP management is just another aspect of doing business in the modern ag-biotech research laboratory, and this will continue, in all ag-biotech research and development institutions, whether in industrialized or developing countries.

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