CHAPTER 20

The impacts of intellectual property rights on MAS research and application for agriculture in developing countries

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SUMMARY

Although the impact of marker-assisted selection (MAS) in commercial and public sector breeding programmes in developing countries is to date limited to a few crops and traits, the potential benefits of using markers linked to genes of interest in breeding programmes for improving the productivity of crops, livestock, forest trees and farmed fish is substantial. While more recent methods associated with the use of MAS are technically demanding and often expensive, most applications of basic MAS were initially described in the literature, and thus will likely have very few intellectual property (IP) restrictions associated with their use irrespective of the agricultural sector involved. For example, isolating DNA, amplifying specific gene sequences from that DNA (with most available primers), separating fragments using gel/polyacrylamide electrophoresis and imaging of fragments with standard techniques are likely to be available without restriction to scientists and breeders in the developing world, even as part of a commercial service. Problems arise when there is a need to use or develop high throughput modes, which require more sophisticated technologies. For high throughput use, a breeder will want to use the most efficient techniques that are currently available. This means that the more advanced processes/methods, reagents, software applications/simulations and equipment that provide the most effective means to fully exploit MAS, are most likely covered by intellectual property rights (IPRs) such as patent rights, confidential information (trade secrets) and copyrights, both in industrialized countries and also in many developing countries such as Brazil, China and India. In situations where breeders wish to use cutting edge technologies and the most efficient markers, care must be taken to avoid activities that may infringe IPRs when using MAS methodologies.

INTRODUCTION

Other chapters in this book describe the usefulness and applicability of MAS for developing germplasm with superior qualities, in a timely manner. Markers have been developed and used by plant and animal breeders (Dekkers, 2004), for fish and shellfish (Consuegra and Johnston, 2006), and for forest trees (Kellison, McCord and Gartland, 2004; Lee, A'Hara and Cottrell, 2005). Introduction of MAS to developing country scientists has been taken up by a variety of projects such as the Generation Challenge Program (cgiar.org/exco/exco8/exco8_generation_report), supported by the Consultative Group on International Agricultural Research (CGIAR) and MAS jamborees sponsored by the Syngenta Foundation for Sustainable Development (syngentafoundation.org/pdf/Report%20Nairobi%20meeting%20.pdf and Terese St. Peter, personal communication). MAS is also being used by many of the centres belonging to the CGIAR, notable examples being the International Center for Tropical Agriculture (CIAT), the International Potato Centre (CIP), the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) and the International Institute for Tropical Agriculture (IITA), as well as the International Maize and Wheat Improvement Centre (CIMMYT), in programmes such as the Asian Maize Biotechnology Network (AMBIONET), and the International Livestock Research Institute (ILRI) in the areas of livestock production and health through the Biosciences Facility for east and central Africa (BecA).

In this chapter, a brief review of general intellectual property law is used to introduce a variety of aspects regarding intellectual property potentially associated with the use of the techniques, reagents and equipment that are necessary for implementing MAS. This intellectual property "primer" is followed by a description of specific cases and some recommendations regarding steps that should be taken by scientists and breeders in developing countries who are contemplating using MAS in breeding programmes to avoid restrictions or incurring risks of infringing the IPRs of others.

INTELLECTUAL PROPERTY RIGHTS AND PUBLIC ACCESS TO INNOVATION

Intellectual property rights (IPRs) are awarded on the basis of national laws. There are, however, a few examples of regional cooperation institutions granting IPRs on a regional basis, such as the African Regional Intellectual Property Organization (ARIPO), the Gulf Cooperation Council (GCC) and the European Patent Office. In addition, under the Patent Cooperation Treaty (PCT), an international agreement administered by the World Intellectual Property Organization (WIPO) that facilitates patent filing, a single international application can be filed in a national PCT-receiving office, which can then subsequently be submitted to all PCT member national patent offices[1]. In addition, an example situation is given in Box 1 that illustrates the, perhaps unexpected, "far" reach of national patent law.

IPRs comprise original and novel assets that involve the use of human intellect. The awarding of such rights is intended to balance the needs of society to access and use the products of human ingenuity, with rewards for the endeavours going to the individuals from whom these intellectual assets originated. Obviously, there is a certain amount of tension in this balance

[1] See www.wipo.int/pct/en/texts/pdf/pct_paris_wto.pdf, for a list of countries that are members of important IP international treaties, including the PCT.

between private rights and the needs of society (Murchie *et al*., 2006). Society is presumed to benefit from public disclosure in the form of patent disclosure requirements and copyrights which are awarded to creative works that have been fixed (made tangible)[2]. In addition, through the combination of the requirement of full disclosure in the written description (manifested in a patent application), combined with the time limitation over patents rights, inventions are put into the public domain when the rights expire. The pharmaceutical industry's experience with the success of "generics" is a testament to the value of "expired" inventions (CBO, 1998). In some specific cases however, such as patents on certain drugs, rights may be extended for a certain period of time upon request to compensate for long delays in obtaining authorization for drug commercialization, e.g. the "Hatch-Waxman" act in the United States. The filing, prosecuting and maintenance of patents are business decisions that are put into place as a part of the strategy for bringing products to the consumer. An additional part of such a strategy can also include a plan for maintaining profitability when patent rights expire (Smyth, 2006). For example, depending upon the creativity of inventors, it may be that improvements allow for the filing of additional patents to cover these improvements, thus having the effect of extending patent rights for additional terms. This is a fact-based process, in that the improvement must meet the requirements of invention[3].

[2] Not that efficient and sincere disclosure is not without problems - see Fromer (2007).

[3] Note that concerns regarding the abuse of the patenting of incremental changes versus incremental improvements are often raised by a practice of patent time extension called "evergreening". For further discussion of evergreening from the view of generic pharmaceutical manufacturers, see Hore (2004)..

The balance between public and private rights is considered by some to be tilted in favour of private rights, leaving elements of some societies wondering if IPR systems work at all except to protect the monopolies that they award (Epp, 2004). A number of civil society organizations are monitoring the potential effect of changing India's patent law to include patents over pharmaceutical products and agricultural chemicals (Sreedharan, 2007).

INTELLECTUAL PROPERTY LAW AS IT RELATES TO MAS

The standard steps employed in MAS generally include: selecting individuals to be tested; harvesting material; extraction of DNA from the material; polymerase chain reaction (PCR) amplification of the DNA to enrich for gene sequences/ fragments associated with a particular trait or phenotype; separation of these fragments; visualization/identification of DNA fragments; and interpretation and utilization of the information. Each of these stages involves certain methods and the use of particular reagents and/or equipment associated with the particular methodological steps. For the purposes of this chapter, a series of tables (numbers 1-3) has been prepared to exemplify the types of intellectual property and associated IPR that exist for materials and/or processes within each of these seven steps.

There is a general set of categories of IPRs that are awarded in most countries/ jurisdictions. These include industrial or utility patent rights, plant variety protection/ plant breeders' rights, copyrights, rights of appellation/geographic indications, trademarks, and secrecy rights, (trade secrets) associated with undisclosed or confidential information. Other types of patent rights can be awarded in many jurisdictions. For

example, in addition to utility patents, two others types of categories of patents are available to inventors in the Unites States: a design patent for a new original or ornamental design for an article of manufacture, granted to protect the external appearance rather then the function of a product, and plant patents, awarded for the invention or discovery of a cultivated plant variety that can be asexually reproduced, (except via tubers, but including grafts and spores). Other countries have additional categories regarding subject matter (e.g. designs, plants) and also with respect to examination rigour and length of the patent rights grant (e.g. "short-term" patents in Belgium and the Netherlands, (see e.g. http://www.ipr-helpdesk.org/docs/docs.EN/invencionesTecnicasBP.pdf), and innovation patents in Australia (http://www.ipaustralia.gov.au/patents/what_innovation.shtml).

Patent rights are awarded to inventions on the basis of criteria associated with usefulness (industrial applicability), originality (newness or novelty), and an "inventive step" (non-obviousness to persons with technical skills in the particular field where the invention is applicable). There are also rules governing the subject matter of the invention for utility patent rights to be awarded. For example, all countries' patent rights prohibit the awarding of patent rights for elucidating the "laws of nature". Thus, the fact that scientists have described laws of chemistry and physics, natural selection, or other such natural laws, does not render them as products of a person's intellect in intellectual property law. However, an innovation that applies one of these laws may well qualify for protection. Similarly, in many countries a new plant variety, a variety, type or breed of livestock used for food production, or computer software cannot be the subject of patent rights. Japan and the United States are notable exceptions in this regard. While the European Union (EU) (Directive 98/44/EC of the European Parliament and of the Council, 1998 on the legal protection of biotechnological inventions) does not permit the patenting of plant and animal varieties, it does allow patents for inventions concerning animals or plants the feasibility of which is "not confined to a particular plant or animal variety". The fact that the term "variety" is not well defined in the context of animal breeding means that the scope of this exemption is far from clear.

Irrespective of whether one is dealing with patent rights, plant breeders' rights (PBRs), copyrights, trademarks, trade secret, etc. the type of IPR sought or awarded varies with the type of intellectual asset over which protection is being sought. It is also possible for one asset to be protected by several types of rights, depending upon the law in the applicable territory. For example, it is not unusual to have "double protection" i.e. for an invention to be patented and the product resulting from that invention to be trademarked. The trademark for Aspirin® for the formerly patent-protected acetylsalicylic acid is such a case in many parts of the world. It is not uncommon for a process or a piece of machinery to be treated in a similar fashion. This situation pertains to IPRs associated with MAS, two notable examples being "Selective restriction fragment amplification: a general method for DNA fingerprinting", a patented process paired with rights associated with the AFLP® trademark or the "Methods for genotyping by hybridization analysis" patent and the associated DArT™ trademark.

PATENTS

Patent rights are awarded on the basis of claims based on the inventor's description

to explain the new, non-obvious patentable subject matter in a way that clearly distinguishes its novel characteristics from all other available solutions. This explanation is called a patent "claim", and using the words of the patent drafter a claim will describe the "metes and bounds" (Gallagher, 2002) of the invention. Patent drafters are usually licensed patent agents, patent attorneys, scientists working for legal firms in this capacity or rarely, the inventors themselves. Drafting patent claims is an arcane art that requires detailed knowledge of the scientific and technical basis of the invention as well as a current understanding of the state-of-the-art, regarding the judicial interpretation of claims, in the context of national patent law.

One patent can have many claims. In fact, patent law requires that every patent must contain at least one claim. Each claim is "directed to" an invention, ranging from its broad use, to the most narrow use for which an inventor may wish to seek rights. For example, a broad claim could be for the use of an enzyme class to perform a type of function (where this combination is not found in nature). A narrow claim could then specify the particular enzyme, the quantity of enzyme and/or the specific function. A distinction should be made between a patent application (often numbered in a different style such as the "WO" designation for PCT-filed patent applications), and an issued patent (generally numbered with a country prefix, e.g. CA 2172863, a patent issued by the Canadian Patent Office) to avoid confusion.

Patent applications contain claims that are untested and unexamined and these claims are therefore often very broad. During the patent prosecution process, the patent examiner seeks to limit claims to the new invention held by the applicant at the time the patent was filed. The claims are accompanied by written descriptions that would allow someone else familiar with technology in the same general area ("Person having ordinary skill in-the-art" or "PHOSITA"), to understand how to make and carry out or "work" the claimed innovation. This useful written description accompanying claims is directed by law to provide "enablement", and is a required part of a patent disclosure, in order to make the invention "available to the public". (This is part of the social contract to balance private rights and public good). The written descriptions can also be important for interpreting the exact limits of patent claims. Patent rights are given to inventions that cover the reduction of ideas and concepts to practical use, and these rights may also extend to other treatments/variations that are of a nature sufficiently similar to be equivalent to the patented innovation. Such a "doctrine of equivalents", as it is called in patent lingo, means that ideas/concepts that are the basis of the useful innovation are a part of the patent claim coverage. Therefore, it is often stated that patents cover conceptual ideas as well as the practical application of the idea (see http://www.dwalkerlaw.com/patent.asp). This means that it is often difficult to discern whether a party is committing infringement, without the interpretation of a court. Literal infringement, whereby the invention is practised exactly as it is described in a claim can usually be identified without a problem. Equivalent infringement is often used as a strategic business tool by either the patent rights holder and/or the infringer. This confusion over the exact limits of patent claims can often lead to company mergers or buy-outs, just to minimize the risk associated with the IPRs! (Fulton and Giannakas, 2001; Kattan, 2002).

BOX 1

BOX title needed

Developing country scientists and breeders should be aware that patent rights are only enforceable within the jurisdiction of the country or countries where the patent rights have been awarded. The caveat to this is that patent laws in most countries cover material that is imported into a country when patent rights exist on that material in the country where the importation would take place. The language that is included in such patent laws contains the terms: "making", "selling" or "using" within a country's boundaries. For example, if patent rights over the formula for a particular herbicide had been awarded in Country AA, but no patent rights over this same herbicide composition had been awarded in Country BB, then the herbicide could be made in Country AA only with the permission of the patent rights holder. However, the herbicide could be made in Country BB without permission of the rights holder in Country AA; no infringement would be possible in Country BB. If someone wanted to import the herbicide that was made in Country BB into Country AA, then the importer in Country AA would need to obtain permission (a license) from the rights holder in Country AA.

The situation for Argentinian soybean containing a transgene covered by patent rights issued to Monsanto in Europe is a good illustration of the territoriality of patent rights. Monsanto holds plant breeders' rights over the variety, but does not have patent protection for the gene in Argentina. Many farmers in Argentina are growing herbicide resistant soybeans developed by Monsanto, (often using seed multiplied by companies that do not have a license from Monsanto). The company has taken the strategy of preventing the importation of Argentinian-grown soybeans or *products* made from Argentinean-grown soybean into any country where Monsanto has patent rights by informing potential buyers of Argentinean-grown soybeans that they will be infringing Monsanto's patent rights if they bring such material into a country such as the United States or a EU country, where Monsanto has patent rights over the technology embedded in the seed or over the seed itself (Balch, 2006), and therefore also present in the soyabean imported grain. Monsanto's patent covers the final product, that is the gene, and extends its protection to the seed and the grain containing the gene sequence. The European Commission (EC), in fact, recognizes the right of Monsanto to prevent import of the soyabean grain, but not the soyabean flour, where the gene sequence can no longer be expressed.

What, however, is the relevance of such action to MAS, where there is no technology embedded in the seed, remaining in the seed itself? Patent law is usually interpreted to cover any material where a patented technology was used to produce a product, even though such a product does not literally contain the technology. This means that in most situations, if patent-protected techniques, methods, processes, or products are used in a MAS scheme, the resulting products are covered by these patent rights. Of course, this type of infringement can be very difficult to prove and therefore is rarely the subject of a legal suit, but the risk is present and occasionally is enforced (AsiaLaw, 2004). However, for developing country farmers who are not going to be exporting a product to an industrialized country, in actuality, the risk of an infringement is minimal (Binnebaum *et al.,* 2003). Nevertheless, the situation of using a patented invention without permission of the patent rights holder is not straightforward, and if such a course involves public resources, it should only be embarked upon on the advice of an IP counsel or an IP lawyer.

TABLE 1
Examples of patents relevant to MAS

Technique		Selected patent examples[1]	Public domain equivalent	Status of selected patent example	Implications
Harvesting DNA	Use of Silica particles	US 5 234 809	Many, e.g. Doyle and Doyle, 1987 and Saghai-Maroof *et al.* 1984	In effect in the US; related patents in effect in: Austria, Australia, Canada, Denmark, Germany, the EU, Greece, Japan, Korea, the Netherlands, South Africa and Spain	License needed; often supplied with reagents, kits, and/or equipment such as thermal cyclers
	Equipment "Matrix Mill"	US 6 063 616	Many e.g. Edwards, Johnstone and Thompson, 1991. combination with centrifuge tube	In effect in the US	If specialized equipment is used, license may be needed. Likelihood that coverage would extend to developing country areas
Amplification of specific DNA seqs	Reagents	US 4 683195	None	Expired in all countries (therefore in public domain)	Advance or improvement likely will require licensing, many even in developing countries
	Primers/genes	Primers for identifying "Soybean Sudden Death Resistance: US 6,300,541	Many e.g., Röder *et al.*, 1998. *gwm493* in wheat	In effect in the US	Sequence(s) to be used should be checked by a patent searcher such as Gene-IT.com if breeding product is valuable and would be grown for export
	Equipment	Applied Biosystems Thermal Cycler; US 5 656 493	Other equipment is available; Contentious legal issues associated with many	In effect is the United States and most other developed countries, and a few developing countries including Brazil, China, Korea, South Africa	
Identification of marker genes	Reagents	Agarose, no applicable patents found	Polyacrylamide	No patent rights on traditional gel/ acrylamide media	
	Equipment	Charge-coupled device imaging apparatus US 5 672 881	Cameras	Many systems that are no longer under rights protection	
MAS methods, in general	Methods and compositions	Use of selective DNA fragment amplification products for hybridization-based genetic fingerprinting, MAS, and high-throughput screening. US 6 100 030 QTL mapping in plant breeding populations. US 6 399 855	Numerous	In effect in the United States	Likely defensive patents. Could be problematic with imports to the United States

[1] There will inevitably be innovative improvements or technological advancement associated with each these methods and materials, many of which will have been awarded IPRs to the inventor and/or the inventor's company.

Examples of published patents where rights have been awarded in the area of MAS include the basic PCR amplification process patents in the United States, US Patent nos. 4 683 195, 4 683 202 and 4 965 188, originally issued to the Cetus Company and then assigned to Hoffman-Roche in 1992, on the use of DNA polymerase based on the Taq polymerase enzyme isolated from the organism *Thermus aquaticus.* As these amplification patents expired worldwide in March 2006, when only the basic techniques and reagents covered by these patents are used, one does not now have to be concerned with infringement of these patents anywhere. However, the equipment used to control the reaction conditions may also carry IPRs on their own and most PCR techniques currently used are patented as improvements to the basic technology. For example, Applied Biosystems' PCR and real-time instrument patents and other PCR-related patents such as US Patent no. 5 656 493, are still in effect. A license to these instruments and other patents may be needed in the United States in order to use their thermal cyclers to carry out PCR, although this is normally granted as part of the purchase price of the equipment and reagent kits. Table 1 contains additional examples of selected patents that are associated with MAS.

Another strategy that should be pointed out is the concept of "defensive" patents. Patent rights may be awarded in most jurisdictions over processes (actions/processes), and machines, manufactures and compositions of matter (things). Enforcement of patent rights e.g. bringing a lawsuit against a person or forcing a licensing situation when they are practising your invention (infringing your rights) without permission is less equivocal when the infringement involves making, using, possessing, or selling an object or composition. However, the detection of infringement of methods claims is often much less straightforward. A patent owner would need to have insight into or gain access to how something was made or formed by the other party (potential infringer), in order to know whether his/her patented process or method was being used. This means that it can be even more costly and time-consuming to pursue potential infringers of methods claims, than lawsuits involving infringement of making, buying or selling a patent-protected material or composition. Thus, sometimes a company or institution will decide to file a patent application, seeking rights over a method where such a filing will simply represent an attempt to preclude a competitor from preventing the company from carrying out a method, without concerns of infringement. Such a method or process patent, would likely never be enforced except in blatant infringement and is only sought to provide insurance for the filing organization to lower the risk that the organization will be sued by someone else. The distinction between a patent that is filed defensively and one that is filed to prevent someone from practising the claimed invention can be very subtle. A discussion of patenting strategies including defensive patents can be found at http://271patent.blogspot.com/2006/09/valuing-patents-and-patent-paradox-why.html. This is an area of patent law that is always in flux and enforcement can be very complicated and expensive.

COPYRIGHTS

These rights are awarded for creative innovations that are "fixed" in a printed, video, audiotape or other recorded form. Copyrights only cover the form of the fixation, and not the ideas or concepts

TABLE 2
Examples of copyrighted software, relevant to MAS

Technique	Use	Selected Software examples	Licensing conditions	Comments
Analysis of QTLs	For use primarily in analysing animal pedigree associations	Loki http://www.stat.washington.edu/thompson/Genepi/Loki.shtml	Very liberal, freeware-type of license http://www.stat.washington.edu/thompson/Genepi/license.shtml	To be downloaded only if License is accepted by user
	List of open source or freeware	http://www.stat.wisc.edu/~yandell/qtl/software/	Open source or as freeware	Source code provided.
Analysis of fragment patterns	For use with ABI electrophoresis equipment	Genotyper□	Usually licensed with ABI equipment purchase. (Applera Corporation). Additional individual personal copies cost ~ US$1 500. Stand-alone copy costs ~ US$5 000. Software manual is also licensed with software	Source code is not provided; explicit prohibition in license
Creation of binary table of fragment patterns	For use with Genotyper□	PeakMatcher http://crop.scijournals.org/cgi/content/full/42/4/1361	Licensed under GNU-GPL v 2	Source code is provided.
Analysis of fragment patterns	For use with electrophoresis with fluorescently labeled markers	Genographer http://hordeum.msu.montana.edu/genographer/	Licensed under GNU-GPL v 2	Source code is provided.
Genotyping Software for Linkage Mapping Applications	For use with ABI electrophoresis equipment	GeneMapper□	Licensed by ABI (Applera corp.) with equipment. Manual is licensed with software. Manual has own independent copyright	Source code is not provided; explicit prohibition in license
Simulation of biophysical processes in farming systems	Predictive software	ApSim	See, http://www.apsru.gov.au/apsru/Products/APSIM/ Access%20and%20Pricing%20Policy.pdf Also an annual license fee	Reduced licensing fee (On a case-by-case basis for NARs.)
Simulation platform for quantitative analysis of genetic models	Predictive software	QuGene Original Reference:http://bioinformatics.oxfordjournals.org/cgi/reprint/14/7/632.pdf	Now only available under license from University of Queensland/CSIRO	Reduced licensing fee (On a case-by-case basis for NARs.)???

associated with the innovation (as is the case with patents). Although, articles written about MAS, drawings of breeding schemes and the like would be products for which copyrights are awarded, it would be quite rare for someone to be concerned about infringing copyright in carrying out MAS. However, most MAS as currently practised, especially at high throughput levels, involves the use of computer software to analyse the often complex data that result from marker detection. While software applications can be patented in a few countries, most jurisdictions only allow software to be covered by copyrights. (In many jurisdictions, there is ongoing discussion regarding whether software code is an appropriate matter to be covered by copyrights. While in Europe, the EC Directive on the Protection of Computer Programs (91/250EEC), has clearly established that in the EU, computer programs are protected on the same basis as literary works, other countries have a more checkered history (Starkoff, 2001). Such copyrights are used as the basis for "Open Source" licensing of software. Most software used in conjunction with MAS must be licensed before it can be utilized in MAS breeding schemes or analysis.

The ethical aspects of copyright should also be understood. For example, breeders need to be respectful and careful when giving talks or other presentations to ensure that the material they use is original, or that the owner of the copyright has given permission for its use. Just because there is no "©" sign on an article, drawing, slide, picture, etc. does not mean that the material has not been copyrighted. Copyright is attached to almost any fixation with immediate effect. There is no need for an author or creator (or employer of the creator), to apply for copyright in most countries because of the conditions set forward in the Berne Convention for the Protection of Literary and Artistic Works (1886) which requires its signatories to protect the copyright on works of authors from other signatory countries in the same way it protects the copyright of its own nationals. A main principle of the Berne Convention, and incorporated into the WTO's Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPs), is the general principle of national treatment, "which requires each member state to accord to nationals of other member states the same level of copyright protection provided to its own citizens." (www.wipo.int/treaties/en/ip/berne/summary_berne.html). There are exceptions, e.g. publications that originate from the United States Federal Government cannot be covered by copyright, although sometimes copyright owners will register a copyrighted article with the government to take advantage of governmental assistance in infringement cases. Table 2 provides some examples of copyrighted materials that have relevance to the practise of MAS.

TRADEMARKS

These are registered marks given to an applicant as a result of a trademark application being made with a fee payment, and such an application withstanding a search by a trademark examiner for similar marks and use of marks (along with an opportunity for opposition to the awarding of the exclusive use by anyone in the public, based on use of the mark by someone else prior to the application to the trademark office). Trademark rights are different from patents, plant variety rights, and copyrights, in that they are renewable, and thus, if national procedural rules are followed correctly, can likely last

TABLE 3
Examples of trademarks relevant to MAS

Mark	Holder	Product	Use	Comments
AFLP®	KeyGene	Associated with the AFLP process/method and reagents	Creation of Polymorphic markers based on difference in DNA sequence	Widely used system; Developing country institutions often negotiate a low/no cost-license on a case-by-case basis
DArT®	CAMBIA	Diversity array technology	Selection of markers based on variation from reference panels	Proprietary technology, often licensed under a BiOS license
ABI®	Applera Corp.	Instruments such as capillary electrophoresis	Various electrophoresis equipment, sequencers, etc.	Widely used, associated with many patented technologies
Sybr®	Invitrogen	Fluorescent dyes	Visualization of DNA fragments	Widely used, patent on original dye in this series has expired in many jurisdictions
GeneChip®	Affymetrix	Microarray on glass substrate	Microarrays can be used for detection of nucleic acid sequences –DNA or RNA	Widely used methodology. Affymetrix one of the leaders in this field

indefinitely. As mentioned earlier, "AFLP" is one example of a trademark. This means that in practice when this method is referred to, the "®" symbol should accompany the term, i.e. the correct use of the term would be AFLP®. Another relevant example would be the Certified Angus Beef ® protected by federal trademark law in the United States. In addition, the names of new markers, new varieties or types of crops, livestock, etc. would need to be checked by a professional trademark searcher if a breeder wished to be sure that no trademark infringement might occur by such naming. This is not precluding the fact that PBRs legislation requires the breeder to give its candidate variety a denomination that cannot be registered as a trademark, as it remains the generic denomination of the variety. Table 3 contains examples of trademarks that are often used as "brand" names, associated with products/processes used in MAS technologies. Commercial MAS practitioners need to be aware that use of a trademarked name in conjunction with a product requires the permission of the trademark holder.

TRADE SECRETS AND CONFIDENTIAL INFORMATION

These are not registered, and although considered to be non-statutory IP rights, they are protected by trade secret law in most countries. Crop breeders have used this approach for many years to protect the parent lines and information used to produce hybrid seeds for sale, and similar approaches are adopted in the poultry and pig industries. This type of intellectual property is defined as commercially useful information that can be said to have the qualities of being any method, technique, process, formula, programme, design, or other information that may be used in the course of production, sales, or operations. It must also meet requirements such as not being known to persons generally involved in information of this type; having an actual or potential economic value due to its secretive and useful nature; and the owner has taken reasonable measures to maintain its secrecy. Infringement or non-authorized disclosure/use or misappropriation of a trade secret can result in criminal penalties. These rights

might be of concern to scientists and breeders who are working under conditions that require the use of confidentiality agreements or non-disclosure agreements (NDAs). Examples include MAS work being carried out by an employee of a company that requires employees to sign confidentiality agreements, or MAS carried out as part of joint work where breeders have been required to sign confidentiality agreements.

This is a very common type of protection used by commercial breeding companies involved in the development and use of markers and software in all sectors of agriculture. If a company becomes concerned that a trade secret risks being exposed, it may file a defensive patent application to ensure that a competitor will not obtain rights that would preclude use of its own trade secret. Obviously, when a patent application is filed on an invention that includes confidential information, the information will no longer be a trade secret. The applicant presumably would only resort to such a move, if the possibility of "independent invention" were high, and thus the risk of disclosure in a patent application balances the risk of having the competition "know" of your trade secret. This will happen because of the way in which patent examiners normally decide if an invention is "new". Often such decisions are based upon the national IP law's definition of "new", as in the United States where there is a grace period of one year to file a patent application after an invention is made public and also where only use within the United States is considered to render an invention "not" new. A patent examiner cannot know that an invention has been used or described prior to the filing of a patent application if the invention is kept as confidential information. Therefore patent rights could be awarded to someone who actually copies a trade secret and companies must then consider filing for a patent or run the risk that a secret will be the subject of a competitor's patent.

Why would a company not simply file a patent application for each marker that it identifies? There are several strategic reasons. It is expensive to file for patent protection and also, the applicant must disclose the invention and all of the specifics of the invention to satisfy the written description requirement of enablement. For a marker, this means that the applicant would need to disclose its nucleic acid sequence if it is known, and by wanting the rights over the use of the marker in MAS, also the trait(s) that is(are) associated with the presence (or absence) of detection of the marker, etc.

Obviously, it is impossible to list specific trade secrets that exist in MAS technology, although one indication of the existence of these can be a reference to a "personal communication" as, for example, in the case of the "15PICmarq" marker listed in Table 1 of the paper by Dekkers (2004). However, there are examples of information that is of the opposite nature, i.e. information that is publicly available and that can be used without permission because it is in the public domain such as information published by the United States Federal Government, or because no attempts are made to enforce rights. The company www.resgen.com, for example, sells kits comprising simple sequence repeat (SSR) primers mainly for use as MAS markers for many different species and based on sequences that have been published. These may therefore be covered by copyright, but these rights are not enforced.

CONTRACTUAL ARRANGEMENTS

An additional, "non-statutory" system of rights (Ricketson, 1984 as referenced in Drahos, 2005), such as rights/requirements covered by conditions associated with a contract are often described as an IPR, although technically these types of rights or conditions are not the subject of IP law in most countries, but rather are a part of legal codes that deal with private rights. These requirements might be of concern to breeders working under conditions that require the use of contracts such as material transfer agreements (MTAs). Conditions that result from entering into agreements or contracts could carry a minimum level of awareness of the duties or responsibilities incurred by one agreeing to the terms. Other "non-statutory" rights could include contractual/legal terms, such as those included in a license or a "Technology Use Agreement" (TUA). Enforcement and practice associated with contract law vary in all jurisdictions and can even vary at the local level. O'Conner (2006), has recently pointed out the degree to which MTAs are used to confer a license to both patent rights and biological materials themselves. He refers to this arrangement as a "lease-license" model wherein the IPRs and the physical property rights are "woven" together. Again, if the documents are read carefully, these conditions will not take anyone by surprise, in that they are a part of a contract or license or other permission granted by an owner or provider of material. However, sometimes this permission may be agreed to in a manner that does not make a strong impression on a recipient. For example, the so-called "shrink-wrap" license that accompanies software, or the "click-wrap" license that covers software or other material downloaded from the Internet, may be too subtle for most people to be really aware that they have agreed to a license. In agriculture, "bag-tag" or "seed wrap" licenses exist, that have the same sort of connotation (Kershen, 2004). Many courts have looked at the enforcement of these licensing/contract issues, with slightly varying results. The web site www.lex2k.org/shrinkwrap/shrinkwraprev.html describes individual cases and discusses these cases with regard to enforceability of "shrink-wrap" contracts in different jurisdictions and conditions.

EXAMPLES OF IPR PRACTICES ASSOCIATED WITH THE USE OF MAS AND RECOMMENDATIONS FOR SCIENTISTS AND BREEDERS

The type of formal IPRs most likely to cause a problem with the utilization of MAS are patent rights. Some examples of patents in this area are given in Table 1. Patents/patent applications are also listed in the paper by Concibido, Diers and Arelli (2004). Also, as mentioned in the preceding section, contractual arrangements/obligations may interfere with unfettered use of products and processes associated with MAS.

Patent rights have been awarded for most of the materials and methods that are involved in practising MAS within all fields of agricultural production. A careful researcher will choose methods and marker sequences that have been published and then carry out at least a cursory search of patent databases such as the European Patent Database (http://ep.espacenet.com) to make a first pass for determining the likelihood that the method and/or sequence(s) of choice are not covered by patent rights in the jurisdiction where they work. Depending upon the level of risk that one is willing to assume, for work that could result in a commercial product more investigation is likely needed and

perhaps the services of a patent information specialist (see www.piug.org/) or an IP lawyer will be required.

Most patents will be of concern primarily to those in developed countries, particularly the United States where many private companies have their base. For example, taking the company Pioneer, 209 US patents assigned to Pioneer are identified when the US Patent Database is searched for the terms "breeding" in the patent and "marker" in the claims. This is reduced to eight when the additional term "assisted" is searched in the claims of these 209. At the time of writing, Pioneer had 46 published US patent applications covering the "breeding"+"marker" category; reduced to one with the addition of "assisted". Monsanto, Bayer and Syngenta, have utilized MAS practices for a number of years and accumulated patent portfolios and very likely many trade secrets in perfecting MAS techniques for their particular uses (Cahill and Schmidt, 2004). Monsanto announced in February 2007 that it would begin sharing its markers for soybean cyst nematode (SCN) resistance with academic and public institution researchers, worldwide. (See www.prnewswire.com/cgi-bin/stories.pl?ACCT=109&STORY=/www/story/02-20-2007/0004531135&EDATE). According to the announcement, "Academic researchers and public institutions who request access will be given a royalty-free license for using the rhg1 marker under a patent that was granted to Monsanto in December 2006 (US Patent no. 7 154 021)". It is of interest to note that the company, Genome and Agricultural Biotechnology, LLC., with five issued US patents and five US patent applications covering SCN inventions, has been sued for patent infringement in the use of SCN markers in conjunction with MAS (Genome and Agricultural Biotechnology had sought patent protection in order to establish "freedom-to-operate" testing services for material supplied by breeders who lack the facilities to perform MAS techniques for assessing the presence of particular disease-resistance alleles [www.siuc.edu/~psas/faculty/pubs/lightfoot_achv.htm and www.gaabdal.com/SoybeanMAS.htm]). As this situation indicates, persons wishing to establish their rights to use markers, by filing patent applications and even obtaining patent rights, need to understand that one cannot presume that an issued patent means that one then can practice the inventions, described in the claims, without concern that one may also be engaging in infringement of another patent or set of claims that have been allowed in other patents.

As of February 2007, a cursory search of the US Patent Database as an indicator of overall patenting activity related to MAS and plants revealed 372 issued patents and 112 published US patent applications. Of these 112 US patent applications, 79 were associated with plant breeding and 33 with animal MAS.

These numbers do not include most of the patents covering equipment, PCR and PCR-related technologies like AFLP®, such as US Patent no. 6 045994 that may be especially useful for generating markers. Also, analysis of the data indicates an increase in the number of applications submitted over the four years up to 2005, but most of these applications (58 percent) are for IPRs over specific plant varieties and sets of markers that allow identification of the germplasm variety. In recent years many patents have been granted that cover genes and markers associated with economically important traits in livestock species (Rothschild, Kim and Anderson, 2006; Barendse and Reverter-Gomez,

BOX 2

Representative claims that illustrate the breadth of patent claims over sequence information

US 6 235 972 , "Maize Rad23 genes and uses thereof" issued 22 May 2001

What is claimed is:

1. An isolated RAD23 polynucleotide comprising a member selected from the group consisting of:
   (a) a polynucleotide having at least 85 percent sequence identity to the polynucleotide of SEQ ID NO: 1; wherein the percent sequence identity is based on the entire region coding for SEQ ID NO: 2 and is calculated by the GAP algorithm under default parameters;
   (b) a polynucleotide encoding the polypeptide of SEQ ID NO: 2;
   (c) a polynucleotide encoding the polypeptide of SEO ID NO: 4;
   (d) a polynucleotide amplified from a Zea mays nucleic acid library using primers which selectively hybridize, under stringent hybridization conditions, to loci within the polynucleotide of SEQ ID NO: 1;
   (e) a polynucleotide which selectively hybridizes, under stringent hybridization conditions and a wash in 0.1.times.SSC at 60 degree C., to the polynucleotide of SEQ ID NO: 1;
   (f) the polynucleotide of SEQ ID NO: 1;
   (g) the polynucleotide of SEO ID NO: 3;
   (h) a polynucleotide which is complementary to a polynucleotide of (a), (b), (d), (e), or (f);
   (i) a polynucleotide which is complementary to a polynucleotide of (c) or (g); and
   (j) a polynucleotide comprising at least 75 contiguous nucleotides from a polynucleotide of (a), (b), (d), (e), (f), or (h); wherein the polynucleotides of parts (a), (d)-(e), (h)-(j) each encode monocot Rad23 polypeptides.

US 6 815 578 "Polynucleotide encoding MRE11 binding polypeptide and uses thereof" issued 9 November 2004

Claim 9. An isolated polynucleotide comprising of polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding a polypeptide having at least 95 percent sequence identity over its entire length to SEQ ID NO: 2; as determined by the GAP program under default parameters, wherein the encoded polypeptide binds to a MRE11 polypeptide; and

(b) a polynucleotide which is fully complementary to the polynucleotide of (a).

2007). Potential commercialization of such inventions was predicted by Rothschild, Plastow and Newman (2004), as well as the associated development of inventions for methods covering breeding management and breeding–related computer applications (Schaeffer, 2002).

Previous search of patent literature

As mentioned earlier, and irrespective of the agricultural sector in which they are operating, breeders and scientists should adopt a habit of checking on-line patent databases such as the database of the European Patent Office and the US Patent

Database (www.uspto.gov) for patents and patent applications that may cover information and/or innovations relevant to their area of breeding and research.

It can be quite difficult to search for sequences and combinations of SSRs that might be covered in patents and patent applications. It is beyond the scope of the non-professional patent searcher to definitively state whether or not a particular sequence is covered by patent rights. Searching patents for specific DNA sequence coverage is not quite as easy as it may seem because of the peculiarity of the language used in drafting patent claims. A few example claims taken from two US Patents, numbers 6 235 972 and 6 815 578 are reproduced in Box 2 to illustrate the complexity of this type of claim language. However, there are companies, such as Gene-IT, that have developed software to search for all possible matches that might occur in any patent (available in electronic form), and where unlicensed use would be considered an infringement. A good patent drafter will attempt to cover as much ground as possible when writing a patent claim as the broader the claim, the larger its technical spread over the landscape of that particular area of science/technology. This results in claims to a sequence and its uses being written so that the inventor claims the sequence and any sequences that are closely similar. Just how broadly a claim is written is a matter of how much the patent drafter/prosecutor can get a patent examiner to accept. Without the assistance of sophisticated computer software, it can be difficult to determine whether the use of a particular genetic sequence would infringe existing patents. Fortunately, however, biotechnology patents are now examined by biologists and molecular geneticists, instead of, as in the "early days", by chemists.

Copyright aspects

Others have thought that copyrights would be of little concern to the breeder or scientist interested in using MAS, in that copyright infringement might only occur if a material such as text, a design, photograph, or video was copied and re-used without permission, such as in a publication or video that was to be distributed widely or sold. However, most results of marker testing need to be analysed by a computer program for the breeder to obtain maximum value from such testing. Most software is covered by (at least) copyrights and therefore must be licensed from the rights holder. Even software that is distributed under an "Open Source" type of license is indeed licensed, and the conditions of the license must be adhered to when the product is used and/or improved.

In addition, care should be taken by persons creating training materials that will be distributed widely or sold as a part of a workshop, to either refrain from using materials written and created by others or to obtain permission before use, especially if such use might be part of a course where participants pay for instruction or must buy the training materials, or where materials might be distributed in an electronic format.

Trademarks aspects

In general, the same is true for_trademarks as for copyright. A minor point would be to remind authors that terms such as AFLP® and "Breeding by Design ™", both trademarks of Keygene, Inc. should carry the "®" or "™" designation. In this regard, breeders would be primarily concerned with the correct use of their own trademarks, both by themselves and others. When naming varieties etc., care should be taken to ensure that the trademark

of another entity is not being infringed. Those responsible for creating names should therefore check public trademark databases such as the UK Trademarks database (www.patent.gov.uk/tm/dbase/), and the services of a professional trademark searcher or attorney should be sought before proceeding with the registration of a "new" trademark.

Plant breeders' rights aspects

Breeders using basic MAS protocols with non-proprietary breeding materials (e.g. germplasm that does not qualify as an "Essentially Derived Variety" (Wendt and Izquierdo, 2001) generally do not need to be concerned with using materials covered by PBRs, for breeding purposes.

Contractual aspects

It is very important that licenses, contracts and agreements are monitored for restrictions as these often contain provisions dealing with IPRs that last until a contract expires or is renegotiated. Permission to use equipment and associated reagents is normally granted as a license granted as a part of the purchase price. However, this type of license may often contain limitations on the use of equipment, reagents, and kits for non-research applications. As an example, and as stated in its legal information web page, Applied Biosystems has an exclusive license with Roche/Hoffman-La Roche for their PCR patents: "Applied Biosystems is the exclusive licensee of Roche Molecular Systems, Inc. and F. Hoffmann-La Roche, owner of the basic PCR process and reagent patents, for the field of research and development, and for applied fields such as quality assurance and control, environmental testing, food testing, agricultural testing (including plant disease diagnostics), forensics and identity testing in humans (other than parentage testing), and animal identity and breeding applications." This means that when a researcher buys (or has legal access to) and uses an Applied Biosystems machine, the rights to use this machine for certain specified purposes (rarely commercial), is included in the purchase agreement. Note, however, that the use of kits or other products of Applied Biosystems that involve any processes or reagents licensed from Roche/Hoffman-La Roche to carry out MAS is not specifically mentioned as a "field of use" in the terms of this license. While it could be assumed that use for MAS is possible under the Applied Biosystems license, if it was considered necessary to have the lowest probable level of risk associated with the use of equipment/reagents for MAS, then legal advice in the jurisdiction of the user should be sought.

An equipment or reagent license could also contain provisions for what are called "reach-through" rights. These arise when improvements are made to an existing technology. When such innovations come about through use of the existing technology the rights to them may have to go back to the owner of the original existing technology. Such a transfer of sharing of the rights is called "reach-through rights". Some argue, for example, that the requirement in some Open-Source licenses for improvements going back to the original creator of the software for distribution are a form of "reach-through".

Agreements to purchase and "package insert" licenses should therefore be routinely checked to ensure that these sorts of license are avoided.

MTAs can also cause problems, depending upon the conditions that are set down in such agreements. Laboratory personnel need to make sure that MTAs are only signed by persons authorized to

do so and that efforts are made to check MTA language for provisions that restrict or interfere with the intended use of the germplasm that is produced using MTA-associated materials. A practical explanation of MTAs is available in COGR (2003).

Breeders and scientists need to keep a file and/or database of all licenses, package inserts, purchase agreements, and MTAs as part of their routine record keeping. They also need to learn to reject documents that contain provisions which indicate an assertion of rights or include a restriction; to negotiate for terms that they require; or source replacement brands/materials. Contracts can be enforced long after patent rights expire.

Of all the types of IPRs/proprietary restrictions that could affect scientists and breeders in developing countries, licenses and agreements have the most potential to impede the use of MAS technologies, unless a sophisticated, high-throughput laboratory is sought. MAS has considerable potential and relevance to developing country breeding systems for capturing desirable characteristics from widely disparate germplasm. IPRs should not hold this back.

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