Novel plant products from gene technology

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Abstract

Gene technology provides substantially increased opportunities to alter the composition of grains to better match current and emerging food and industrial uses. The first such modifications to enter production and trade are likely to be major changes in the oil and protein composition of oilseeds, followed by protein and starch modifications in cereals and pulses, to better fit these products to specific end uses. Subsequently, plants with completely novel components, such as high-value pharmaceutical peptides, specialty industrial oils or biodegradable plastics, will become available. The production of diversified grain products using gene technology raises many issues in crop production and marketing systems, including proprietary ownership of new crop product technologies, increased use of contract production, and the need for identity preservation for effective supply chain management. These opportunities and issues will be discussed in detail with particular emphasis on genetically-modified (GM) oilseed products.

Introduction

Genetic engineering is one of the most powerful yet controversial technologies to impact agribusiness. Its application to develop crop plants with improved production characteristics, such as herbicide tolerance and insect resistance, and the recent introduction of these products into food markets and world trade has created considerable community debate that is shaping the way in which the technology will be further developed and its products regulated in the future. The application of gene technology to crop improvement will continue to have major ramifications throughout the agricultural supply chain. One such impact will be the ability to develop a greatly increased range of end product quality types and to protect these inventions under the patent system. This has the potential to create valuable new business opportunities and also to cause substantial changes in existing product markets.

Oilseeds have been at the forefront of application of gene technology in agriculture worldwide and provide an excellent illustration of the ability to create new and improved plant products and of the issues that surround the introduction of such products into existing agricultural production, processing and marketing systems. It is estimated that around 30 million ha of GM oilseeds (including soybean, canola and cottonseed) were grown worldwide in 1999 (mainly in USA, Canada and Argentina). This represents a 50% increase over the previous year, and accounts for almost three-quarters of all GM crop production. There have been a number of reasons for this rapid application of gene technology to oilseeds. Firstly, all oilseed species can be transformed using *Agrobacterium* techniques and regenerated from tissue culture, enabling transgenic plants to be readily produced. In this respect, oilseeds have been more amenable to gene technology than have other crops such as cereals. Secondly, developments in gene technology pioneered in the experimental plant *Arabidopsis* have been readily transferable to the closely related *Brassica* oilseed species. Thirdly, economically important oil quality characteristics are well understood biochemically and genetically, with most of the key genes involved having already been cloned.

Many of the genetic improvements in oilseeds in the foreseeable future will result from the use of molecular genetic techniques to introduce new genes, modify existing ones and to provide more efficient means to identify specific combinations of genes. Worldwide there are currently hundreds of field trials of potential new transgenic oilseed types, evaluating traits such as herbicide resistance, modified oil composition, male sterility and restoration, pharmaceutical production, stress tolerance and resistance to insects, fungi and viruses. For scientific, crop production, and grain marketing purposes, these genetic modifications have been usefully classified into two categories, “input traits” and “output traits”.

The first wave: input traits

Genetically modified crop production characteristics, such as herbicide tolerance and insect resistance, have become known as “input traits”, and constitute the first wave of GM products to reach the market. The benefits from input traits are mainly confined to crop production systems and are therefore captured principally by growers and agribusiness. However many input traits also have substantial benefits to agro-ecosystems, such as reduced chemical usage, as well as potential to reduce food costs through improvements in production efficiency. Some of the key examples of input traits that have been developed in oilseeds are outlined below.

Herbicide Tolerance

Different herbicide resistances have been incorporated into oilseeds using genes mainly isolated from microorganisms. Many of these, such as Roundup Ready®, Liberty Link®, and Bromoxynil®-tolerance, are already being used commercially in several oilseed crops, notably soybeans, canola and cotton. These resistances provide enhanced weed control by enabling highly effective broad-spectrum and low-residual herbicides to be applied to the crop, potentially leading to higher yields and better harvest quality.

Insect Resistance

The insecticidal protein (Bt) produced by the bacteria *Bacillus thuringiensis* has been used as a biological insecticide for some time. The incorporation of the bacterial gene for this protein into plants enables them to produce the Bt protein, providing an in-built insecticide that is effective when tissue is eaten by the insect. Cotton containing the Bt gene is being used commercially in Australia to provide protection against Lepidopteran pests such as native budworm. Additional genes for other Bt-type proteins with enhanced insecticidal activity are now available, and other novel proteins are also being evaluated for insecticidal properties.

Hybrid Pollination Systems

Systems for producing F1 hybrid varieties rely upon genetic mechanisms (both nuclear and cytoplasmic) that bring about male sterility in the female parental line and provide for its restoration in the hybrid. New systems are being developed that utilise novel genetic methods of preventing pollen development. The most advanced of these is the SeedLink® system developed by Plant Genetic Systems in Belgium. This involves the introduction of the *barnase* gene that encodes a ribonuclease enzyme that destroys mRNA specifically in the developing pollen to generate male-sterility in the female parent. The *barstar* gene that inhibits the action of the ribonuclease is incorporated in the male parent to restore normal fertility in the resulting hybrid plants. This system is already in commercial use by Aventis for production of hybrid canola varieties and could also be used in other crops.

Disease Resistance

Gene technology can be used to improve disease resistance in two key ways. Firstly, a series of genes that provide resistance to different races of a pathogen can be cloned and collectively inserted into the plant, thus equipping the plant with much broader resistance (e.g. multiple genes for resistance to several races of rust). Secondly, several novel genes are being evaluated for their ability to either strengthen existing resistance (e.g. blackleg resistance in canola), or to provide protection against pathogens for which the plant is otherwise completely susceptible (e.g. *Sclerotinia*).

Stacked Traits

Although most initial GM oilseed varieties carry only a single modified trait, many future GM oilseeds are likely to contain multiple transgenic traits, commonly referred to as stacked traits, or gene stacking. For example, the InVigor® canola hybrids released by Aventis contain both the Liberty Link® genetics for herbicide resistance and the Seed Link® hybridisation system, and the release of cotton varieties with both the Roundup Ready® and BT traits is imminent. Further stacking could involve the addition of genes for modified product quality. Lines with stacked traits can be developed either by multiple or sequential transformation, or by conventional crossing of single trait lines.

Because of the on-farm success of herbicide tolerance and insect resistance technologies, oilseeds incorporating these traits have been rapidly adopted by growers in countries where they have been approved for release. However, there has been notable differences in the willingness of consumers in different countries to accept GM crop products in their food supply, ranging from reluctance to purchase foods containing GM ingredients through to government moratoria on release of GM crops.

One of the criticisms frequently leveled by opponents of gene technology is that the GM products so far released have had no benefits to consumers and therefore provide little incentive for consumers to adopt them, particularly if they have concerns about potential risks of the technology. It is disappointing that many consumers are reluctant to adopt products that have been judged by regulatory authorities to be safe and which can provide substantial benefits to our agricultural ecosystems and food supply chain. Nonetheless it is probably a reality that substantially increased consumer acceptance of gene technology in the food supply will likely have to wait until products are available that provide consumers with direct benefits over the traditional products, that is, until the much-heralded "second wave" of GM products arrives.

The second wave: output traits

The modification of product quality characteristics using gene technology is built on a well-established understanding of the pathways for biosynthesis of plant products, a rapidly expanding knowledge of the genetic control of these pathways, and an increasing availability of cloned genes for key enzymatic steps.
A large inventory of genetic modifications to oilseed quality traits is being assembled as a result of transgenic research efforts worldwide (Green and Salisbury, 1998). Although modifications to the protein and minor components of oilseeds are being explored, the first genetically-modified oilseed products will almost certainly be focussed on the oil component of the seed and directed at enhancements for food use. Changes to fatty acid composition have been the major focus of work to modify seed oil quality. Gene technology can be used in oilseeds to modify the chain length and degree of unsaturation of fatty acids, to control the positional distribution of fatty acids on the triglyceride molecule, and to introduce new fatty acids. These changes are being achieved both by modifications to existing genes and by incorporation of new genes. Furthermore, the ability of gene technology to seed-specifically modify fatty acid composition has enabled more radical modifications of fatty acid composition than can be achieved by traditional plant breeding and mutational approaches. Some typical examples of the opportunities are outlined below.

Altered Proportions of Existing Fatty Acids

Major alterations in the relative proportions of existing fatty acids have recently been achieved through the use of gene silencing techniques (antisense, cosuppression, hairpin RNA) directed against fatty acid biosynthesis genes, in particular desaturase and thioesterase genes. One objective has been to develop high-stability cooking oils that can be used directly in the food service sector without the need for hydrogenation. To ensure stability during long-life cooking applications, oils must have relatively low levels of polyunsaturated fatty acids. In particular, linolenic acid must be very low as it is rapidly oxidised to give undesirable off-flavours. Currently, high-stability vegetable oils are obtained either by using imported palm oils which have naturally high stability, or by partially hydrogenating locally-produced polyunsaturated oils (cottonseed, canola, soybean) to convert polyunsaturates back to monounsaturates and saturates. Both approaches are nutritionally undesirable – palm oils because they contain high levels of cholesterol-raising saturates, and hydrogenation because it results in production of cholesterol-raising *trans* fatty acids. It would be preferable to modify the fatty acid composition of locally-grown oilseeds to have the required nutritional and functional properties. This has now been achieved by the development of high-oleic forms of all the major oilseed crops, through the inactivation of the Δ12-desaturase gene using either mutation or gene silencing techniques. Silencing of Δ12-desaturase has been used to raise oleic acid levels to 89% and 75% in canola oil from *Brassica napus* and *B. juncea* respectively (Stoutjesdijk *et al*., 2000), and to 77% in cottonseed oil (Liu *et al*., 2000). Similar approaches have been used to develop soybean oils with 88% oleic acid.

As well as being used in liquid cooking applications, vegetable oils are also hydrogenated to produce solid fats for use in margarines and shortenings. In this case, hydrogenation is used to increase the level of high melting-point saturates and *trans* fatty acids. Stearic acid (C18:0) is a high melting point saturate that is known to be neutral with respect to blood cholesterol levels, however it is only a very minor component in the main seed oils. The development of oilseeds with naturally high levels of stearic acid should provide oils having melting points high enough for their direct use in solid fat applications without the need for hydrogenation. Oils with up to 40% stearic acid have now been developed in canola (Knutzon et al., 1992) and in cottonseed (Liu *et al*., 2000) by using gene technology to silence the Δ9-desaturase gene in the seed. The use of such high-stearic oils instead of hydrogenated oils as the hardstock in margarines could have positive nutritional effects through replacement of cholesterol-raising *trans* fatty acids with neutral stearic acid.

Genetically-modified high-oleic and high-stearic oilseeds are at various stages of development and commercialisation in different countries. Their successful introduction in Australia could simultaneously provide increased local oilseed cropping opportunities, cost savings in the vegetable oil processing sector, and nutritional improvement in Australian diets.

Introduction of Nutritional Fatty Acids

Human nutritionists have demonstrated the positive nutritional effects of several fatty acids that are not naturally present in the major oilseeds. Long-chain polyunsaturated fatty acids (LC-PUFA), such as γ-linolenic acid (C18:3ω6, GLA), arachidonic acid (C20:4ω6, AA), eicosapentanoic acid (C20:5ω3, EPA) and docosahexanoic acid (C22:6ω3, DHA), have been demonstrated to have important roles in brain and retinal development, and as precursors for synthesis of various prostaglandins regulating important bodily functions, such as anti-inflammatory reactions and blood platelet aggregation. Although the human body can produce LC-PUFA by elongation and desaturation of dietary linoleic acid (C18:2) and α-linolenic acid (C18:3) it does so inefficiently. It is therefore important to have an adequate dietary intake of these fatty acids. Marine oils are a rich source of EPA and DHA and nutritionists currently recommend consumption of up to two fish meals a week to achieve desirable intake of these fatty acids. However there is concern about the ability of global fish stocks to meet this requirement in the long term, and it would therefore be desirable to develop oilseeds that naturally contain moderate to high levels of LC-PUFA. The LC-PUFA fatty acids present in fish oils are the result of accumulation of ingested fatty acids originating from microalgae. A number of research groups have now cloned elongase and desaturase genes responsible for LC-PUFA synthesis from microalgae and other organisms, and these genes are being introduced into oilseeds in order to assemble the pathway for synthesis of LC-PUFA from linoleic acid and α-linolenic acid (Parker-Barnes *et al*., 2000). Recently, the accumulation of up to 68% GLA and up to 17% stearidonic acid (C18:4ω3, SDA) has been achieved in rapeseed by the introduction of genes for Δ6-, Δ12- and Δ15-desaturases (Ursin *et al*., 2000). Furthermore nutritional studies with SDA indicate that it is efficiently converted to EPA and DHA by the human body, suggesting that it may be sufficient to produce seed oils rich in SDA rather than assembling the full EPA/DHA pathway in oilseeds. Thus it is highly likely that genetically-modified oilseeds having nutritionally effective levels of LC-PUFA will soon be a reality. Because LC-PUFAs are highly unstable, their delivery to consumers in cooking oils is not possible, but should be achievable in other food applications such as spreads, salad dressings and nutritional supplements, particularly through the use of micro-encapsulation protection technologies.

Enhanced Minor Components

Although seed oils are predominantly triglycerides, they also contain a number of nutritionally important minor constituents, such as phytosterols (e.g. brassicasterol, stigmasterol), fat-soluble vitamins and pro-vitamins (e.g. β-carotene) and antioxidants (e.g. tocopherols, tocotrienols). The biosynthetic pathways for the synthesis of these secondary metabolites are rapidly being elucidated using biochemistry, gene technology and genomics in model systems such as *Arabidopsis*. The increasing availability of key genes controlling these pathways is now enabling the content of these valuable micronutrients to be enhanced in plant foods (DellaPenna, 1999).

The nutritional value of phytosterols has recently been demonstrated by the finding that consumption of margarines containing phytosterols is able to significantly inhibit absorption of dietary and biliary cholesterol into the bloodstream. Clinical trials have shown a 10% reduction in blood LDL cholesterol levels when hypercholesterolemic individuals consumed 2g/day of phytosterol esters in margarine over a 3-week period compared with normal margarine. This reduction translates conservatively to a 20% reduction in the risk of heart disease at a whole population level, and is additive to the benefits of low saturated diet and lipid-lowering medications. Phytosterol-containing margarines have recently been introduced onto the Australian market under the Logicol® and ProActiv® brands. The phytosterols in these products are obtained either from pine extracts or from distillates produced during deodorisation of sunflower oil and are thus quite expensive. The possibility exists to use gene technology to greatly increase the naturally low levels of phytosterols in oils up to levels that have a nutritional benefit, thereby inherently improving the nutritional value of the oil in a more cost-effective way.

Seed oils also contain low levels of β-carotene, the compound which the body converts into vitamin A. One of the highest profile applications of gene technology in human nutrition has been the recent development of rice containing β-carotene, which has the potential to alleviate vitamin A deficiency in many parts of the developing world. This was achieved by the introduction of genes for the three key enzymes in the β-carotene pathway, namely phytoene synthase, carotene desaturase and lycopene β-cyclase (Ye *et al*, 2000). Similar research has shown that β-carotene levels in canola seed can be raised up to 50-fold by the introduction of just the phytoene desaturase gene targeted to the plastid (Shewmaker *et al*, 1999). As β-carotene is lipid-soluble, the majority of it will be extracted in the seed oil. Elevations in β-carotene level would be especially desirable in oils engineered to have high phytosterol levels, since it has been shown that additional dietary β-carotene can overcome the slight depression in blood carotenoid levels associated with phytosterol consumption.

The levels of antioxidants in seed oils may also be enhanced using gene technology once genes in the tocopherol and tocotrienol pathways are cloned and expressed transgenically. Already it has been shown that the relative proportions of α-tocopherol (vitamin E) and γ-tocopherol, which differ in their effectiveness as antioxidants, can be modified by gene technology (Shintani and DellaPenna, 1998). Increases in the levels of highly effective antioxidants in food oils would be a valuable addition to the human diet as well as providing enhanced stability to the oils during processing. In particular, oils that have been engineered to contain high levels of the highly unsaturated LC-PUFA referred to above would certainly benefit from concurrent elevation in antioxidant levels.

An Ideal Food Oil?

Taken together, these developments indicate that it should be possible to use gene technology to redesign the composition of plant oils to naturally match our increasing understanding of human nutritional requirements. An ideal oil would possibly consist of very low levels of saturates and moderately high levels of oleic acid to provide stability and to lower blood LDL-cholesterol levels, an appropriate nutritional balance of C18 and long-chain ω3 and ω6 PUFAs, moderately high levels of phytosterols to reduce blood cholesterol uptake, and enhanced levels of tocopherols and β-carotene to provide oxidative protection to the PUFAs, and to offset minor reduction in blood carotenoids. Such an oil could be suitable for incorporation into applications where cooking is not involved, such as in margarines, salad dressings and nutritional supplements, and would represent an example of a truly functional food. However it remains to be shown to what extent these modifications are mutually achievable in a single product, both technically and commercially.

The third wave – industrial crops

Most initial genetic modification of output traits is being directed at improved food uses. However, further into the future there is likely to be a "third wave" of GM crops where the product quality modifications will be designed for specific industrial use. Metabolic engineering research is already at an advanced stage in redirecting the biosynthetic capabilities of seeds towards the production of novel compounds that have particular non-food uses, such as industrial raw materials and pharmaceuticals. The development of GM crops having very high concentrations of industrial compounds could contribute to converting traditional agricultural crops into efficient producers of more valuable chemical commodities and thereby provide renewable plant sources of raw materials currently obtained from non-renewable petroleum. However, industrial GM crops will also provide new challenges for crop production systems and supply chain management, particularly in ensuring their safe separation from food crops and products. Some of the key areas of current interest in relation to industrial oilseeds are outlined below.

Industrial Fatty Acids

Commercially available oilseeds currently produce only a limited range of fatty acids, mainly C16 and C18 saturates and unsaturates. However, wild plants contain an enormous array of unusual fatty acids many of which have potentially valuable industrial uses, such as in the production of plastics, polymers, resins, glues, surface coatings, lubricants and other specialty chemicals. Examples include hydroxy fatty acids (e.g. ricinoleic acid from *Ricinis communis*), epoxy fatty acids (e.g. vernolic acid from *Euphorbia lagascae*, *Vernonia galamensis*, or *Crepis palaestina*), acetylenic fatty acids (e.g. crepenynic acid from *Crepis alpina*) and conjugated fatty acids (e.g. calendic acid from *Calendula officinalis*). Genes that control the synthesis of these fatty acids are being cloned from the wild plants and transformed into oilseeds with the aim of assembling the pathways for their synthesis (*Lee et al*., 1998). Results with initial transgenic plants have demonstrated that single genes for the hydroxylase, epoxygenase, acetylenase and conjugase enzymes are sufficient for providing the novel catalytic activity. However, in each case, the concentrations of the unusual fatty acids in the seeds of the transgenic plants have been relatively low. The accumulation of very high concentrations of these fatty acids in oilseeds is likely to require the introduction of genes for additional enzyme functions (Singh *et al*., 2000).

Biodegradable Plastics

Polyhydroxybutyrate (PHB) is an aliphatic polyester that is accumulated by many species of bacteria as a storage material. Both PHB and related polyhydroxyalkanoates (PHA) are potential renewable sources of biodegradable thermoplastics. One such PHA polymer, Biopol, is already produced commercially by biofermentation of the bacteria *Alcaligenes eutrophus*, however a major drawback is the high production cost. Gene technology is now making it feasible to produce such polymers in plants, particularly oilseeds, at considerably lower production cost. This has been achieved by transgenically expressing the bacterial genes that encode the three key enzymes responsible for synthesis of PHB from acetyl-CoA (3-ketothiolase, acetoacetyl-CoA reductase, and PHB synthase) in the chloroplasts of *Arabidopsis* plants (Nawrath *et al*., 1994). PHB was accumulated at up to 14% of leaf dry weight without any deleterious effects on plant performance. It is anticipated that oilseeds will prove the best vehicle for commercial production of PHB in plants, since they have naturally high movement of carbon through acetyl-CoA during oil synthesis and this should be able to be diverted to PHB synthesis. Research is now being directed at further enhancing the yield of PHB by down-regulation of competing lipid synthesis pathways; devising strategies for ensuring that seed with high germination rates can be produced for high-PHB, low-oil genotypes; exploring the possibilities of producing more desirable PHA polymers in transgenic plants; and transferring these capabilities into oilseed crops such as rapeseed and soybean (Poirier *et al*., 1995).

Pharmaceuticals Peptides and Industrial Enzymes

There is scientific and commercial interest in engineering oilseeds to produce high-value proteins, such as pharmaceutical peptides. Oilseeds are particularly useful vehicles for these products because they contain oil storage bodies that are surrounded by a mono-molecular layer of proteins called oleosins. This enables an efficient physical separation of the proteins by simple flotation of the oil bodies in an aqueous extract. Oleosin proteins have already been genetically engineered to act as carriers of pharmaceutical peptides, such as hirudin and thrombin (van Rooijen and Moloney, 1995). The peptides are expressed as fusion products, covalently linked to the oleosin protein. Following isolation of the oleosins, the peptide of interest is cleaved off by proteolysis at a pre-engineered cleavage site at the oleosin-peptide junction. Although pharmaceutical peptides are a high-value, low volume application of this technology, it could potentially also be used for the large-scale low-cost production of industrial enzymes such as cellulases, proteases and lipases.

Technology ownership and control

The application of gene technology to develop new quality types and novel products will increasingly be associated with proprietary ownership of those products, a factor which will impact strongly on crop production and marketing systems. In Australia, novel plant varieties and plant products can be the subject of two different types of intellectual property rights - patents and Plant Breeders Rights.

Patents

Patents provide the strongest form of intellectual property protection available for products of gene technology. To be eligible for a patent, an invention must satisfy the requirements of novelty, inventiveness (non-obvious) and utility. Genes and proteins are treated by the patent system in much the same way as other chemical compounds. Thus if an isolated DNA sequence satisfies the normal requirements of novelty and inventiveness it is potentially patentable. Patents may also extend to cover transgenic plants carrying the gene and to the products of those plants. Gene technology methods are also patentable. Patenting is not restricted to plants developed using gene technology - novel plants and plant products developed by conventional breeding are also patentable. For example, low-palmitic soybeans produced by mutagenesis, were able to be patented because the novelty criterion was satisfied by the fatty acid profile being outside the range that could be achieved using naturally-occurring germplasm.

Many of the enabling and trait technologies so far developed by gene technology are already covered by patents held by companies and research institutions. However, legal entitlement to particular technologies is not always clear-cut because gene technologies may have been independently developed and patented in parallel by different groups. Because patents frequently take several years to be examined and proceed to grant, multiple inventors may already have commercial products developed before it is known for certain which inventor has the earliest valid priority date and entitlement to the patent. Another major issue is uncertainty about the scope of some patents, particularly in relation to how legally valid any granted broad claims may ultimately prove to be.

Subtle differences in the technology between inventions, and the occurrence of claims which are only partially overlapping, can further complicate the situation. For these reasons there are several instances of ongoing disputes in relation to gene technology patents based on grounds such as entitlement to the inventions, breadth of coverage of patent claims, or actual validity of the patent grant.

A granted patent provides its owner with a monopoly right to commercially exploit the technology in the country of grant for the life of the patent (generally 20 years). In return, the inventor must provide a description of the invention that is sufficient to enable others to work the invention after the patent expires. A patent holder may choose to work the invention solely by themselves, or can license it to other parties on an exclusive or non-exclusive basis. The holder of the patent may take legal action against a party that makes unauthorised commercial use of the patented technology. In the case of a plant variety that is the subject of a patent or contains a patented technology, any unauthorised commercial growing of that variety or its use to develop other varieties is a potential infringement of the relevant patent.

Plant Breeders Rights

New plant varieties that are distinct from existing varieties can also be protected under the Plant Breeders Rights (PBR) legislation. The grant of a PBR makes it illegal for an unauthorised party to market planting seed (or other propagules) of the variety. This ensures that the owner of the variety is able to control the seed market for the variety either directly or through licensing this right to other parties. PBR provides legal protection for a particular genotype, but does not protect individual genes or traits that are contained in the variety. In fact, it is a deliberate feature of PBR that other parties are free to use a PBR protected variety as parental germplasm in their own variety development programs. Most eligible new varieties are now registered under PBR for two main reasons. Firstly, it is the only form of protection available if the variety is unable to be patented or does not contain a patented technology. Secondly, if the variety does contain a patented technology, PBR provides a useful back-up protection in the event that the patent does not proceed to grant or is invalidated by legal challenge at a later time. This is an important consideration regardless of whether the patent is held by the variety developer or another party.

Freedom To Operate

Development of a genetically modified plant will generally involve several component technologies (such as the plant transformation method, the gene for the trait of interest, and a suitable promoter sequence). In order to commercialise products it is necessary to have legal access to all patented technologies incorporated in the product or used during its production. This may include the rights to earlier general patents that overarch the more specific and separately patented novel technology. This ability to commercially use all component technologies is termed "freedom to operate" and can be achieved either through ownership of the patent, or by licensing from the patent owner. Licensees may have to procure patent licences from several companies if there are overlapping patents, or if it is unclear which company will ultimately have legal control of the technology. Freedom to operate is not always achievable because owners of key technologies may choose not to license their use, or may seek to charge an unacceptable price. This is a major issue for Australian plant breeding programs because many of the key gene technologies required for genetic improvement are owned by other parties, and often in foreign interests. Sometimes, access to third party technology can be gained through technology sharing under cross-licensing arrangements.

Many of the early gene technology patents are already over 10 years old and will expire during the next decade. Although improvements in many technologies are likely to be achieved and patented in their own right, the basic capability to genetically modify most crop plants will pass into the public domain within a 10 year time-frame. It can be expected that most future patenting activity will centre around novel trait technologies associated with improved crop performance and quality diversification, as companies seek to develop and protect new proprietary products that will be successful in the marketplace.

Commercialisation strategies

The commercialisation of transgenic plants incorporating patented trait technologies is entailing innovative ways of capturing the added-value associated with those traits and recouping the substantial costs associated with their development. The distinction between input traits and output traits is particularly useful in this regard.

The value of input traits accrues in the first instance to the grower by way of improved productivity. Varieties having traits such as herbicide tolerance and insect resistance potentially enable growers to produce commodity crops at lower cost, because the trait enables avoidance of some agrochemical inputs. Bt cotton, for example, can reduce the incidence of insecticide spraying by around 70%, thus avoiding a substantial agrochemical input cost. Similarly, the timely use of a broad spectrum herbicide, such as glyphosate, in a resistant crop may avoid the need for multiple applications of more selective herbicides. It may also result in better weed control than could otherwise be achieved and hence lead to higher yield. The added-value to the grower of these genetic modifications is equivalent to the increase in profit margin achieved from higher returns and lower input costs.

One way that the owner of a trait technology can capture some of its added-value is through an increased royalty on the planting seed. This approach has been adopted in some situations with herbicide tolerance genes that have been licensed non-exclusively by technology owners to multiple seed developers in order to achieve maximum penetration of the technology across the crop and hence to maximise sales of the relevant proprietary herbicide. In this situation, the commercial value of the herbicide tolerance trait is captured partially through the premium price obtained for the seed, which is usually distributed in a negotiated manner between the technology provider and the seed developer, as well as through the additional profitability associated with increased herbicide sales.

An alternative approach is for the technology provider to charge a separate technology fee related to the production of the crop. This can be done in either of two ways. One way is to require the grower to enter into a Technology Use Agreement (TUA) and to pay a licence fee based on acreage sown. This is usually done prior to or at the time of purchase of planting seed. Alternatively, an end-point royalty based on grain production can be collected at time of grain delivery. These methods effectively separate the purchase of the seed from the purchase of the patented technology, and facilitate the receipt of commercial returns in all years in which the crop is grown even if the grower is able to use farm-saved seed to establish future crops. Usually the provider of an input technology is unable to capture its full added-value because there needs to be some financial incentive for a grower to adopt the technology. The size of this incentive is related to the amount of risk associated with the effectiveness of the technology. Thus, input technologies are usually priced at somewhat less than the expected added-value that will accrue from their use. The use of a TUA can also facilitate compliance with any conditions that may have been imposed by regulatory authorities approving the release of the genetically modified plant, such as those expected to apply under approved crop management plans.

In contrast to the situation with input traits, the value of output trait technologies is realised in the post-harvest value of the grain produced. As is the case for an input trait, the owner of an output trait technology can capture its value through seed royalties, technology licence fees, or end-point royalties. These may be appropriate approaches where there is a clear price premium for the modified quality product in a high-volume open market. Thus a grower could be free to market his grain on the open market and obtain the price premium. The seed royalty or technology licence fee would be struck in relation to the likely market price premium. However, an alternative approach that is being used increasingly for specialty quality grains involves contract production of the crop. In this arrangement a grower enters into a contract which requires return of all harvested grain to the contractor. The contractor then capitalises on the added-value of the quality trait either through the use of the product in their own downstream operations or by on-sale to other parties. This production system is sometimes referred to as “closed-loop marketing”, and can be implemented whether the crop is GM or conventionally bred. However the incidence of closed-loop marketing arrangements will increase as owners of proprietary quality trait technologies developed by gene technology seek to capture the maximum added-value of the technology through marketing of the end product rather than just the planting seed.

Business implications

The licensing of trait technologies to growers under various contractual arrangements can provide integrated agrochemical and biotechnology businesses with some important commercial advantages. Firstly, it enables companies traditionally reliant on sales of chemical crop protectants such as insecticides to move their businesses to genetic “in-crop” protection, rather than suffer decline from the loss of chemical sales. This is in the first instance a business replacement strategy to capitalise through the seed for the loss of chemical sales. However, ultimately it may prove to be a more profitable strategy as the initial “once-only” cost of production of the genetic protection amortised over its product lifetime may well be considerably lower than the cost of repeated production of the insecticide. Secondly, genetic technology for resistance to proprietary herbicides could be used to support herbicide sales through integrated marketing past the patented life of the chemical. For example, a company may seek to sustain a dominant share of a herbicide market after any patent on the chemical ingredient expires, by contractually locking growers of the company’s herbicide-resistant crops into use of its own brand of the herbicide rather than that of alternative suppliers. Thirdly, ownership and commercial control of highly demanded output traits has the potential through vertical integration to create major changes in market share in both the upstream planting seed business and the downstream processing sectors in favour of the company owning the technology.

Supply chain management

Australian agriculture has traditionally been mainly commodity-based, with our principal grain products having amongst the lowest unit value of internationally-traded grains. This has been gradually improving with increased production of higher-value specialty grain products targeted to particular end-market uses (e.g. durum wheats for pasta making; culinary grain legumes). An increased array of new quality types in cereal, legumes and oilseeds in the future as a result of the application of gene technology should provide growers with further enhanced flexibility in their crop production and marketing decisions. Some new products will probably represent such a significant quality improvement that they become the new standard for the commodity itself, while others will become established only as higher-value specialty types with much smaller markets than the traditional commodity. Of course some novel products being researched may never actually be commercialised because their incremental market value may turn out to be insufficient to offset the high costs of development and regulatory approval. Capitalising on the opportunities provided by this expanded range of diversified grain quality types presents a number of significant challenges for crop production systems and for supply chain management.

Maintaining Variety Integrity

The need for variety integrity is likely to be more important with the introduction of GM crops, particularly those with new output traits, than is currently the case with traditional crop varieties. Although strict measures are already taken during planting seed production to minimise the risks of cross contamination with other varieties, the consequences of very low admixture levels are generally not significant with traditional varieties. Within quality types of a species the main consequence is the potential for dilution in the overall agronomic performance of superior varieties, which is probably insignificant with low levels of contamination. Between quality types, the consequences can be greater because of the possible failure to meet end product quality specifications if significant contamination occurs. However, with GM crops the consequences of contamination are much more serious, firstly because of the strict requirements for regulatory approval for release of transgenic plants and plant products, and secondly because of the much more significant genetic and compositional differences that GM crops will have from their traditional counterparts.

It is particularly important to ensure that a GM variety that is being grown either experimentally in pre-release field trials, or commercially for a particular market where it is approved for release, does not contaminate planting seed or commercial grain of other varieties that are destined for markets where the GM trait is not approved for release. This is an important consideration because of the significant international movement of planting seed during multiplication and because most of our grain crop production is destined for export to other regulatory jurisdictions. The extent of concern for this aspect will relate to the degree of contamination tolerance that is allowable in the market. During the current early phase of introduction of GM crops it is generally the case that regulatory approvals are not yet available in all potential markets and there is also considerable niche marketing of GM-free products. Both circumstances currently have zero tolerance for GM contamination. As an example of the possible pitfalls, some canola growers in Europe had to plough in crops of an Advanta non-GM canola variety when DNA testing revealed that it contained plants carrying the glyphosate resistance transgene that was not approved for release in Europe. The contamination was believed to have occurred during pedigree seed production of the variety in Canada, presumably either by outcrossing with nearby RoundupReady® canola varieties or by physical seed contamination during production, harvest or subsequent seed handling. This example highlights the difficulty in guaranteeing 100% purity in agricultural systems and underlines the need for introduction of practical minimal tolerance levels in order for both GM and non-GM crops to coexist.

In relation to the specific transgenic traits present in GM varieties, the initial concern with varietal integrity has mainly been about ensuring that transgenes conferring traits that may have agro-ecological consequences, such as herbicide tolerance, do not transfer to or contaminate varieties that do not contain these traits. This is important because of the desire to deploy such genes in a controlled manner both to minimise the risk of them transferring to other varieties or related weed species, as well as to avoid the possible unintended development of genotypes that carry resistances to multiple herbicides. The regulatory approval process for release of such GM varieties in Australia will require the proponent to develop approved crop management plans that, among other requirements, address the need to contain the transgenic traits within the GM variety. In the longer term this issue will also become particularly important for GM varieties that carry output traits. In some cases, such as where both the conventional and GM varieties are destined for similar food markets, the practical consequences of contamination will be similar to those that exist between conventionally bred quality variants. However, in the case of future GM varieties producing non-food products there may be serious adverse consequences associated with even low level contamination. For example, it will probably be unacceptable for edible oilseeds destined for human consumption to have even low level contamination from oilseeds that contain say a particular industrial fatty acid that may be potentially toxic to humans, or a pharmaceutical peptide that should be tightly controlled in its human applications. In these cases, its will be extremely important to maintain strict varietal integrity.

Minimising the risk of gene transfer between industrial and food crops can be achieved more easily in highly self-pollinating crops than in open-pollinated crops. It would therefore seem more advantageous to develop specialty industrial fatty acid products in oilseeds such as soybean and linseed rather than say sunflower or rapeseed. However, because this may not always be possible on technical or economic grounds, scientists are already conceiving of genetic methods by which novel varieties can be prevented from inter-crossing with other varieties. It may be possible to develop systems that ensure that varieties with particular attributes that require segregation, are reproductively isolated from all other varieties in the same way that different plant species are unable to interbreed. Such systems could be valuable ways to provide certainty that herbicide tolerance genes would not transfer to related weed species, and that industrial product quality traits do not transfer to food-grade varieties.

Identity Preservation

Even with the strictest attention to detail in maintaining the integrity of varietal planting seed, there is still potential for cross-contamination of grains during commercial crop production, storage, handling and processing. For crops that have modified output traits and that therefore need to be channeled towards particular markets or specialty uses, it will be necessary to implement strict procedures for segregation and identity preservation during production and processing in order to capture the added-value associated with the particular output trait. In some markets it may be commercially advantageous to market crop products based on their non-GM status, particularly during the early stages of introduction of GM crops. In this case, the non-GM status can be regarded as a type of output quality trait, and identity preservation may be necessary in order to be able to guarantee this status to the final customer. In contrast, in most circumstances it should not be necessary to maintain segregation and identity preservation for GM varieties that carry only input traits and produce end products that are substantially equivalent to the conventional variety.

Identity preservation is simply a system of crop supply chain management that preserves the identity of the source and nature of the product. It is not a new concept in agriculture since it is already in use for the production of a number of non-GM specialty crop types. Furthermore, the seed industry has in principle been routinely undertaking identity preservation in the production of varietal planting seed. It is a relatively straightforward process in situations of low volume specialty crops grown either in-house or under contract where the owner of the product has full control of the production process, takes delivery of all of the final grain, and usually manages its passage through the primary processing stages of the supply chain. In this situation, the implementation of audit trails and quality control monitoring is relatively easy. However, it is a much harder task for high-volume products that are widely-grown and marketed openly by growers because it may be difficult to ensure that all growers comply with all the grain production and handling procedures necessary to ensure product purity. In this situation, quality testing needs to implemented at all initial grain receival points and be completed prior to any aggregation of grain. Ensuring segregation of the grain further downstream is also more difficult where multiple processors are involved.

When the product is a grain with particular new quality attributes, there will be incentive throughout the supply chain to maintain the identity preservation in order to achieve the price premiums for the product at each stage. However, when the product does not have any different processing properties or pricing structure, such as for GM grain carrying only input traits, there is greater potential for identity preservation to fall down. Recently, U.S. processors and retailers had to withdraw a number of corn-based food products from sale when DNA testing revealed that they contained corn carrying the Aventis StarLink® insect resistance trait which had been granted approval by regulatory authorities for non-food use only. Aventis had introduced a stewardship program to ensure that StarLink® corn would only be used for industrial purposes. However, the StarLink® trait appears to have been found in other conventional corn varieties developed by StarLink®-licensed corn seed producers, thereby escaping the dedicated marketing channels. Aventis has now voluntarily withdrawn StarLink® corn from commercial sale until a full food clearance is obtained from the U.S. Environmental Protection Agency. This incident demonstrates the greater difficulty in implementing fully-effective identity preservation and supply segregation in situations where traits are licensed to multiple seed producers for crops that are to be sold on open markets, compared to that within closed-loop contract production and marketing systems.

The need for effective identity preservation, combined with proprietary ownership of many quality trait technologies, should lead to a significant increase in contract production and closed-loop marketing. This type of supply chain management has significant additional costs that will need to be recouped in premiums for the final product to be economically viable. The cost of identity preservation will vary depending on the precise circumstances of the crop and the range of products derived from it, the uses to which they are put, the tolerances and specification set, and the sophistication of the distribution system. However, initial experience indicates that the cost range is generally in the order of 5-10% of the price of the grain (Buckwell et al., 1999). Identity preservation will only be economically viable for products that have end market price premiums significantly in excess of this amount. This requirement will be a primary factor in determining the commercial success of new product quality types developed by gene technology, as well as in determining the long-term sustainability of the current niche markets for non-GM products that offer no other advantage.

It is clear that gene technology provides tremendous capability for improvement of plant performance and diversification of product quality characteristics beyond what can be achieved by conventional plant breeding. Introduced and managed correctly, GM crops should provide one of most effective means of achieving further improvements in crop productivity, of better fitting crop products to market requirements, and of reducing industrial reliance on non-renewable resources.

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