

## Review article

# Barriers and paths to market for genetically engineered crops

Caius M. Rommens\*

J.R. Simplot Company, Plant Sciences, Boise ID 83706, USA

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\*Correspondence (fax (208) 327 3212;

e-mail crommens@simplot.com)

## Summary

Each year, billions of dollars are invested in efforts to improve crops through genetic engineering (GE). These activities have resulted in a surge of publications and patents on technologies and genes: a momentum in basic research that, unfortunately, is not sustained throughout the subsequent phases of product development. After more than two decades of intensive research, the market for transgenic crops is still dominated by applications of just a handful of methods and genes. This discrepancy between research and development reflects difficulties in understanding and overcoming seven main barriers-to-entry: (1) trait efficacy in the field, (2) critical product concepts, (3) freedom-to-operate, (4) industry support, (5) identity preservation and stewardship, (6) regulatory approval and (7) retail and consumer acceptance. In this review, I describe the various roadblocks to market for transgenic crops and also discuss methods and approaches on how to overcome these, especially in the United States.

## Introduction

Genetic engineering (GE) is often described as a technology that is critical for future food, feed and energy needs (Castle *et al.*, 2008; Eckardt *et al.*, 2009; Edgerton, 2009). However, progress has been limited to the incorporation of a few 'input' traits into a small number of crops, and the increasingly complex barriers to market for transgenic products threaten to impede new developments. The successful application of GE requires a new approach to product development that is based on an open interaction between key players: scientists in basic and applied research, patent lawyers, retailers and industry representatives, regulatory officials, and, most importantly, consumers.

## From gene function to trait efficacy

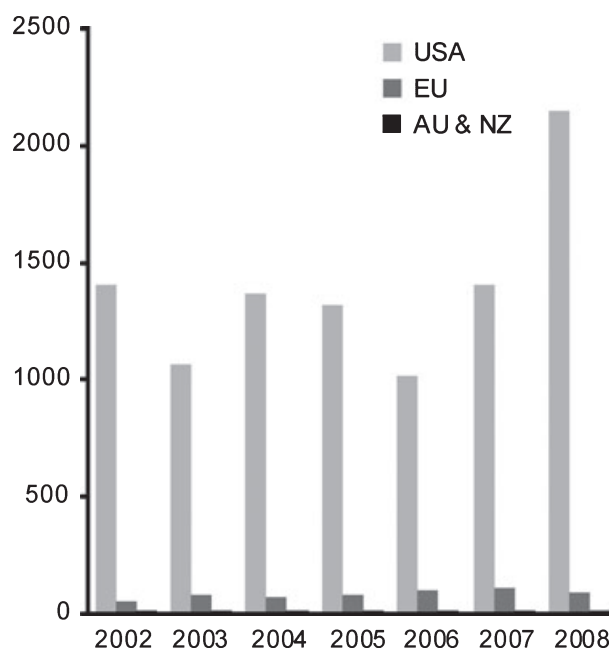
Conventional variety development programmes are often based on recurrent selection systems in the field. Agronomists score plants for important phenotypes to identify lines that display the highest levels of stress tolerance and yield across multiple sites. In contrast to this selection of plants 'by the environment', artificial and environment-

controlled laboratory assays are employed to identify genes controlling biotic and abiotic stress tolerance. The apparent success of the latter approach is exemplified by the large number of sequences, articles and patent applications that have been published by molecular biologists during the last two decennia (Vain, 2007). However, only a few of the many identified genes were tested in the field, and the results from these trials have generally been disappointing, often indicating that indoor effects are not a reliable indicator for what happens outdoors (Mittler, 2006). For example, overexpression of the Arabidopsis biotic stress tolerance gene *Npr1* triggered enhanced tolerance against a broad spectrum of viral, bacterial and fungal pathogens in the laboratory (Cao *et al.*, 1997). But subsequent field trials demonstrated that this 'systemic acquired resistance' (SAR) was already induced naturally by environmental stresses. Transgenic plants were hardly distinguishable from untransformed controls, and slightly reduced infection rates were completely off-set by greater susceptibility to insects (Felton and Korth, 2000; Rayapuram and Baldwin, 2007; Walters and Fountaine, 2009). Other once-promising genes in SAR, such as *cpr1*, *cpr5* and *cpr6*, are now also known to trigger negative pleiotropic effects in the field (Heidel *et al.*, 2004; Century

*et al.*, 2008). Similarly, plants carrying the *Rpm1* gene, which provides resistance against *Pseudomonas syringae* pv *psis*, exhibited a lower shoot biomass, fewer siliques, and an average decrease in seed production of 9% relative to control lines (Tian *et al.*, 2003). Candidate genes for tolerance against drought, salt and other abiotic stresses also often failed to display field efficacy (Yamaguchi and Blumwald, 2005; Mittler, 2006). And the difficulties in studying stress tolerance are dwarfed by attempts to assess the efficacy of candidate yield genes. Despite some promising results for modified nitrogen assimilation, to date, there are no conclusive data on enhanced yield for any transgene (Ameziane *et al.*, 2000; Jing *et al.*, 2004; Hirel *et al.*, 2007).

The small group of effective input traits developed through GE consists mainly of insecticidal protein genes from *Bacillus thuringiensis*. Discovery of these genes was facilitated by the fact that strains of this soil bacterium have been used to control insect pests since the 1920s (Lemaux, 2008). Molecular biologists have also succeeded in controlling certain RNA viruses, especially potyviruses, through targeted RNA silencing (Prins *et al.*, 2008). A more-recently developed strategy provided enhanced stress tolerance through expression of the bacterial RNA chaperone-encoding gene *cspB* (Castiglioni *et al.*, 2008). Gene efficacy was demonstrated at both the vegetative and reproductive stages of various plant species. More testing is required, however, to confirm there is no fitness cost to the incorporated stress tolerance.

The execution of field trials earlier in the development process should address some of the issues that limit trait discovery. One organization that embraces this new paradigm is Ceres, which, in collaboration with the Chinese Academy of Agricultural Sciences, evaluated the efficacy of more than 600 transgenes in the field (R. Flavell, pers. commun.). These field trials were designed to ensure uniform soil composition, irrigation and fertilization across the crop sites. Beyond these soil parameters, remaining position effects need to be minimized by growing plants of each line in multiple randomly designated blocks/trial in at least three different locations. The professional execution of field trials is critical for success because failure in doing so yields meaningless data that may be misinterpreted and lead to overestimations of yield benefits or the premature abandonment of gene technologies (see Marris, 2008). Currently, field testing is mainly carried out during the late stages of product development in the USA and China (Stone, 2008) and even such activities are hampered by tight regulations in the Europe and Oceania (Figure 1).



**Figure 1** Field trials of genetic engineering crops in the United States (light grey bars), the European Union (dark grey), and Australia and New Zealand (see, for data and links, <http://www.isb.vt.edu/>).

A second essential component for field trials is the availability of robust high-throughput assay systems, which make it possible to screen plants before, during, and after harvest. Near-infrared spectroscopy is most suitable for non-destructive determinations of abundant macromolecules including protein, water, starch and fibre (Sinclair *et al.*, 2004; Montes *et al.*, 2007), and methods such as metabolomics can be applied for parallel assessments of the levels of a broad range of metabolites (Fernie and Schauer, 2009). The resulting comprehensive data sets can be effectively managed, analysed, and interpreted by using software systems designed to predict genetic value (Antofie *et al.*, 2007).

A focus on input traits seems prudent given that the global population is predicted to grow by at least 50% to 10 billion in the next 50 years (Eckardt *et al.*, 2009). However, input traits do not speak to the imagination of consumers and may be perceived as just a new way for seed companies to increase their revenues and market share. The perceived value of GE would be improved with the delivery of traits of interest to consumers, including enhanced flavour, texture, taste, aroma and colour. Although we are still very early in this process of improving consumer-desired traits, researchers have made some progress in creating attractive deep-purple and high-antioxidant tomatoes (*Solanum lycopersicon*) and potatoes (*S. tuberosum*) (Butelli *et al.*, 2008; Rommens *et al.*,

2008), tomatoes with enriched aroma (Davidovich-Rikanati *et al.*, 2007) and potatoes with enhanced crispness (Rommens *et al.*, 2006). The prevalence of coronary heart disease has also urged scientists to develop methods that support higher dietary intake levels of long chain omega-3 polyunsaturated fatty acids. One of these methods introduces genes for  $\Delta 6$  and  $\Delta 15$  desaturases into rapeseed (*Brassica napus*) and soybean (*Glycine max*) to produce stearidonic acid that, upon intake, is converted into 20:5 *n*-3 eicosapentaenoate. Recent feeding studies in rat have shown that daily intake doses of 1.5 and 4.0 g transgenic soybean oil/kg body weight did not trigger any adverse effects (Hammond *et al.*, 2008). However, attempts to increase food quality through metabolic engineering often compromise the yield potential of the targeted crop (Tanaka and Ohmiya, 2008; Ufaz and Galili, 2008; Allen *et al.*, 2009), implying, again, the importance of careful agronomic evaluations.

### From trait to product concept

Many genetically engineered agronomic traits that are efficacious in the field may not be valuable enough to justify their commercial application. An example of such a trait is Colorado potato beetle resistance conferred to transgenic plants by the insecticidal *B. thuringiensis* protein Cry3A (Carpenter and Gianessi, 2001). Commercial production of potato plants expressing the associated synthetic gene made good business sense for companies that specialize in plant-incorporated pest resistance. However, Colorado potato beetle infestation is not a major issue for American growers, who use imidacloprid-based insecticides to effectively control various pests including the potato bug. The resulting lack of 'pull' from the industry was one reason transgenic potatoes were eventually removed from the market (Grafius and Douches, 2008). Similarly, herbicide tolerance, though highly desirable for row crops such as soybean (*Glycine max*), is not sufficiently important in the wheat (*Triticum aestivum*) and potato industries to overcome agribusinesses' hesitance to grow and process transgenic varieties (Mauro *et al.*, 2009).

In contrast to the common belief that innovation starts with basic research, is followed by applied research and development, and ends with product diffusion (Bush, 1945), most commercially successful innovations rely on multi-directional relationships to identify critical needs of end-users, which are then channelled back as 'product concepts' to those engaged in research ([http://www.econ.iastate.edu/research/webpapers/paper\\_13060\\_09007.pdf](http://www.econ.iastate.edu/research/webpapers/paper_13060_09007.pdf)).

An example of a realized concept that averted a looming disaster in horticulture is the transgenic papaya (*Carica papaya*) variety 'Rainbow'. Rainbow expresses the viral coat protein gene of papaya ringspot virus (PRSV-P) and, consequently, displays resistance against a pathogen that threatened to eliminate the Hawaiian papaya industry during the 1990s (Tripathi *et al.*, 2007). It was developed by the University of Hawaii in close collaboration with the United States Department of Agriculture (USDA) and Upjohn Company, and is currently being used extensively by growers in Hawaii. Another specialty crop that suffers from devastating pathogens is banana (*Musa acuminata*). The seedless banana variety Cavendish, which is the predominant commercial variety worldwide, is extremely sensitive to the fungal pathogens *Mycosphaerella fijiensis* and *Fusarium oxysporum*, causal agents of black shigatoka and Panama disease respectively. But virulence of the two fungi is linked to their ability to necrotize plant tissues, which suggests that transgenic anti-apoptotic strategies may limit disease progression in a manner similar to those developed in transgenic tobacco (*Nicotiana tabacum*) (Dickman *et al.*, 2001). A third important disease that causes major crop losses is potato late blight. While the late blight resistance trait has not yet tipped the balance in favour of transgenic crops in the European Union (EU), the estimated 1 billion US dollar net present value for Indian farmers has accelerated efforts to commercialize this trait in the subcontinent (Hijmans *et al.*, 2000; Ramasamy *et al.*, 2007; Pel *et al.*, 2009). Similar efforts are gaining momentum in countries such as Indonesia, which rely on relatively small-scale agricultural systems.

A very different product concept for GE relates to a quality improvement and was formulated after Swedish scientists demonstrated that starch-rich processed foods accumulated the carcinogenic Maillard reaction product acrylamide (Tareke *et al.*, 2002). The formation of this reactive compound was reduced to negligible amounts in processed potato products by inhibiting the biosynthesis of its precursor asparagine through silencing of the asparagine synthetase 1 (*Asn1*) gene (Rommens *et al.*, 2008). This new molecular approach represents a unique and possibly critical tool for companies that recently agreed, in a settlement with the state of California, to substantially decrease acrylamide levels in their food products (<http://ag.ca.gov/newsalerts/release.php?id=1595>). A second health-related product concept relates to the removal of potentially lethal allergens from food crops such as peanut and wheat (Rommens, 2007). While conventional plant breeding efforts have not been successful in addressing these genetically

complex issues, it appears possible to eliminate most or all allergens by cross-silencing families of allergen-encoding genes (Gallo and Sayre, 2009; Scheurer and Sonnewald, 2009). Replacement of conventional varieties by their transgenic allergen-free counterparts may be driven by consumer demand and strongly encouraged by the governmental agencies that are responsible for food safety.

### From academic freedom to freedom-to-operate

Academic freedom, which allows professors to exercise their professional judgment in pursuing specific research topics, has proven to be an important requisite for innovation. However, as valuable as unencumbered choice in line of research may be, pursuing marketable applications of such work often involves attending to intellectual property issues (Yancey and Stewart, 2007). To enable products to ultimately be brought to market, research efforts with commercial ambitions must create a freedom-to-operate (FTO) path by considering all relevant enabling technologies and genetic elements needed to incorporate a new trait into a crop. In most cases, an FTO path requires both commercial licenses for some patented technologies and work-around methods for others. Expert support from patent attorneys for legal assessments and opinions is often necessary to protect the developer from wilful infringement charges by patent holders.

There are thousands of issued patents that relate to transgenic plants in the United States (Koo *et al.*, 2004; Lacroix *et al.*, 2008). Some of these patents represent powerful barriers to commercialization and are held closely by companies with a strong interest in agricultural biotechnology (Dunwell, 2005). Syngenta owns patent US/6051757, which claims proprietorship of vectors that lack a functional cytokinin gene for the transformation of dicotyledonous plants. A patent application of its competitor Monsanto, which is currently in interference, makes broad claims on the use of disarmed T-DNA vectors. DuPont developed an alternative strategy, described in US/6570067, which is based on bombarding explants with DNA-coated gold particles. A second barrier to entry was created through Monsanto's US/6174724, which claims antibiotic-based selection systems for transformed cells. Monsanto also owns one of the dominant patents in gene silencing, US/5107065, which makes broad claims on antisense-based methods (Sanders and Hiatt, 2005). Intellectual property owners have generally not sued basic researchers that infringe on their issued patent claims. However, they would

be expected to do so when outcomes of academic research prove commercially viable (Yancey and Stewart, 2007).

A select group of companies secured broad licenses for Monsanto's intellectual property for the development and commercialization of transgenic specialty crops. These companies include Forage Genetics (alfalfa), Scotts Company (various turf grasses), and ArborGen (trees). The down-side of such licensee agreements is that the royalty fees are as high as the market can bear. Furthermore, the licensees have to commit to both licensor-imposed restrictions to gene stacking and specific requirements on how to deal with regulatory approval and stewardship. It may, therefore, be worthwhile to invest in developing new and unencumbered paths to market. Indeed, an increasing number of research groups are challenging the monopoly position of a few large companies in agricultural biotechnology by developing novel and non-obvious methods for transformation and crop improvement.

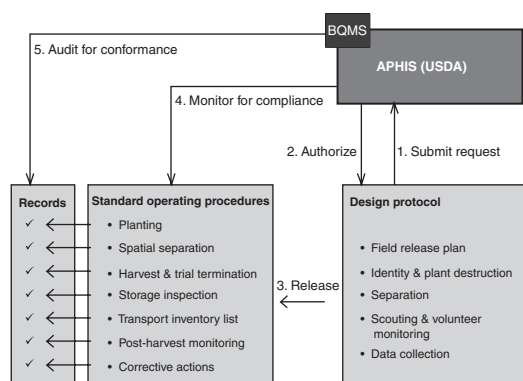
Responding to consumer concerns about the use of foreign DNA (see discussion below for more details), the Simplot Company developed marker-free and all-native DNA transformation methods (Rommens *et al.*, 2004, 2005). The genetic elements incorporated into a plant's genome are derived from either the targeted plant species or a plant that is sexually compatible with that species. The transformation vectors contain a cytokinin gene inserted in their backbone to facilitate selection against the inadvertent transfer of superfluous vector DNA. The use of these vectors makes it unnecessary to supplement tissue culture media with phytohormones and selection agents, and yields marker-free and backbone-free 'intragenic' plants at species-dependent frequencies between 1.8% and 9.9% (Richael *et al.*, 2008). Simplot also developed a highly efficient method for gene silencing that is based on the production of unprocessed and variably sized transcripts through convergent and collisional transcription (Yan *et al.*, 2006).

The Public-Sector Intellectual Property Resource for Agriculture (PIPRA) (Atkinson *et al.*, 2003) is in the process of developing a vector that contains both a transposable element carrying the gene-of-interest and the Arabidopsis selectable marker gene *Atwbc19* (Mentewab and Stewart, 2005; Rommens, 2006) inserted between T-DNA borders. Upon transformation and recovery of kanamycin-resistant plants, induction of transposition is expected to produce multiple independent integration events. PIPRA also developed a comprehensive *Handbook and Executive Guide* that provides interesting insights into new opportunities in agricultural biotechnology (<http://www.iphandbook.org/handbook/about/>).

Cambia is another non-profit research organization whose goals include the promotion of existing patents for further research and creation of new products. Cambia scientists demonstrated that several species of bacteria outside the *Agrobacterium* genus can be modified to mediate gene transfer to a number of diverse plants. These plant-associated symbiotic bacteria were made competent for gene transfer by acquisition of both a disabled Ti plasmid and a suitable binary vector (Broothaerts *et al.*, 2005). The significance of this new development was questioned by Mary-Dell Chilton, one of Syngenta's lead scientists, who stated that 'a transforming bacterium, whatever its Latin name, is but a small piece of the technology needed to produce a transgenic plant' (Chilton, 2005). Cambia's interest in creating transparency in the patent system resulted in creation of Patent Lens, an informatics resource that serves as a platform for open innovation (<http://www.patentlens.net/>). The Cambia initiatives, together with those of PIPRA, Simplot, and others, increasingly support public crop improvement programmes that are currently hampered by FTO issues. Such collaborations are expected to result in the development of practical applications for technologies developed within the public domain.

### From notebooks to identity preservation

Corporate research is carried out according to standard operating procedures, whereby data are recorded in labo-



**Figure 2** Preparation and conductance of a regulated field trial. Compliance with guidelines set by The Animal and Plant Health Inspection Service of the United States Department of Agriculture is required for authorization to release regulated plants in the field. The field trial must be carried out in accordance with the Field Release Plan, which specifies the location of the trial (GPS coordinates), labelling of all plots, sufficient separation between different lines, scouting and volunteer monitoring after harvest, and data collection. The Biotechnology Quality Management System provides additional support by auditing for conformance to Standard Operating Procedures that are linked to records for critical control points.

ratory notebooks, and entries are signed, dated, and counter-signed to secure accuracy and patent support (Taylor, 2006). Additional levels of organizational complexity need to be implemented as soon as transgenic plants leave the laboratory setting. Any transfer of transgenic plants across state lines requires USDA-authorized movement permits, and additional release permits are needed for field trials. These permits require a commitment to a system of standards, records and audits throughout the entire crop production, harvesting, handling and storage process to assure that regulated materials remain segregated and are ultimately destroyed (<http://www.aphis.usda.gov/biotechnology/permits.shtml>). Any inadvertent release of transgenic material that has not been approved for deregulation can have severe consequences for the owner of the material. For example, failure to eliminate transgenic volunteer plants that sprouted up 1 year after a regulated field trial of transgenic corn resulted in the collapse of the biotechnology company Prodigene (Ellstrand, 2003). Similarly, the inadvertent release of unapproved glufosinate tolerant rice (*Oryza sativa*) into commercial supplies in 2006 triggered substantial financial losses for the rice industry (Ledford, 2007).

Early in 2009, the Animal and Plant Health Inspection Service (APHIS) of the USDA launched a pilot development project with five volunteer participants including the Simplot Company to develop, implement, and maintain a Biotechnology Quality Management System (BQMS; Figure 2). This new programme was designed to enhance compliance with regulatory requirements for field trials and movement of regulated organisms. As part of the programme, the participants identified vulnerabilities in their processes for working with transgenic organisms, developed or revised standard operating procedures that address these vulnerabilities, properly trained personnel on the standard operating procedures, and underwent a third-party audit to determine effectiveness of their quality management system. Soon, any university, small business or large company will be able to supplement existing APHIS regulatory and inspection requirements and qualify for BQMS certification ([http://www.aphis.usda.gov/biotechnology/news\\_bqms.shtml](http://www.aphis.usda.gov/biotechnology/news_bqms.shtml)). Whereas BQMS helps to preserve the identity of a product prior to its launch, a new 'Excellence Through Stewardship' system is currently being developed by the Biotechnology Industry Organization (BIO) to ensure segregation during the full product life cycle, from production through seed marketing and distribution to product discontinuation (<http://www.excellencethroughstewardship.org/>). BIO membership is

available to organizations that promote biotechnology research and support the growth and development of the biotechnology industry (<http://www.bio.org/join/>).

### Obtaining support for a disruptive technology from a conservative industry

Development of the first transgenic soybean plant during the mid 1990s caused much commotion among the growers, processors and retailers that, together, represent the soybean industry. Widespread concerns were mainly related to the potentially devastating effects of transgenic soybean on international trade. There was concern that some countries might close their borders to all soybeans and soybean products from the United States out of fear that some lots could have been contaminated with transgenic material. History has shown that Monsanto's transgenic soybean crop penetrated the market in an unprecedented way, resulting in significant benefits for all members of the soybean industry. Similar successes were achieved for other crops destined for animal feed and food ingredients, such as maize and canola. In all cases, the final products offered to consumers were not distinguishable from conventional products when tested using methods such as polymerized chain reaction or enzyme-linked-immunosorbent serologic assay. In contrast, transgenic vegetables and fruits still contain the newly introduced genes and, in most cases, the proteins encoded by these genes. The ability to detect the transgenic nature of such foods is believed to represent one of the reasons for their relatively slow commercialization (McHughen, 2000).

Soon after the launch of NewLeaf potatoes by NatureMark in the United States in 1999, traces of this transgenic crop were detected in a potato snack in Japan, where the product had not yet been approved for commercial use. The discovery of the presence of this regulated material prompted an immediate recall and a requirement for all importers of potato products into Japan to conform to identity preservation (IP) handling regulations (Akiyama *et al.*, 2002). This obligation remained in place until the industry had removed all NewLeaf potatoes from the system through testing, field rotations and winter freezes in 2007. Reluctant to repeat the NatureMark disaster, the United States Potato Board urged developers of genetically engineered potatoes to implement strong IP systems and ensure approval of their products in the countries that play an important role in international trade. The National Association of Wheat Growers also voiced their support for biotechnology and

outlined similar conditions for commercialization (<http://www.wheatworld.org>).

Large food retailers play an important role in influencing the direction of new product development and, therefore, represent one of the main targets for non-governmental organizations (NGO) that oppose the commercial production of transgenic foods (Kalaitzandonakes and Bijman, 2003). The first product withdrawn from sales in the EU because of pressures from NGO was a purée made from transgenic tomatoes (Harvey, 1999). In the United States, supermarkets also discontinued the sale of transgenic tomatoes. However, they currently offer a diversity of products with ingredients from genetically engineered crops including maize (*Zea mays*), rapeseed, and soybean. Their support for new transgenic vegetables or fruits will depend on whether the benefits that such products bring to consumers outweigh the risk of being targeted by NGO. Thus, it will be imperative for developers of GE products to consider the incentives and strategies of key players in the food supply chain. Indeed, the importance of frequent and open discussions between representatives of all aspects of the industry cannot be underestimated. Labelling requirements are currently believed to further complicate efforts to commercialize GE foods in the EU (Gruère *et al.*, 2008). However, consumers may gradually understand that the labelling of GE foods represent a new quality control system because no other crops have been more rigorously evaluated for safety (Delaney *et al.*, 2008). Furthermore, the paradigm shift from input to output (consumer) traits may trigger a new interest and curiosity in GE labelled foods.

### Receiving regulatory approval

Existing crop varieties are generally considered to be natural and safe, even though they may contain various endogenous toxins and allergens. Consequently, governmental agencies allow the transfer of a potentially lethal allergen-encoding gene from, for instance, an existing to a new peanut (*Arachis hypogaea*) variety if conventional methods in plant breeding are used. This leniency towards new product development employing traditional breeding methods contrasts sharply with the extreme caution that is applied in the regulatory approval process of transgenic crops (Rommens, 2007). In addition to the justifiable exclusion of allergen-encoding genes, it would also be sensible for agencies such as the U.S. Food and Drug Administration to block the transfer of genes that encode 'allergen-like' proteins. Such proteins may have a sequence or secondary structure that is similar to that of a

known allergen or may share a specific physiological characteristic, such as heat stability or resistance to digestion. An example of an allergen-like protein is the antifungal protein AFP1 from alfalfa. Expression of this protein in potato provides resistance in the field against the important pathogen *Verticillium dahlia*, which causes early dying disease in potatoes (Gao *et al.*, 2000). However, the presence of eight disulphide-linked cysteines render AFP1 resistant to proteolytic digestion, suggesting that it might eventually provoke an allergic response upon intake (Delaney *et al.*, 2008). Similarly, the potato gene encoding patatin, a protein that already represents 40% of the total soluble protein of tubers, cannot be overexpressed in potato roots for control of corn root worm because patatin is an IgE-binding protein for children with a positive skin prick test response to raw potato (Seppälä *et al.*, 1999).

Although the creation of unintended effects is an oft-cited fear of plant modification (Filipecki and Malepszy, 2006), transgenic plants with modified primary carbohydrate metabolism, polyamine biosynthesis and glycoprotein processing were not biochemically different from controls in unexpected manners (Shepherd *et al.*, 2006). Broader scale metabolomics (Defernez *et al.*, 2004), and proteomic (Lehesranta *et al.*, 2005) analyses led to similar conclusions. However, GE may trigger unintended effects, especially if applied to express genes that have never before been used in agriculture (see, Chen *et al.*, 2009). Transgenic crops containing new genes are therefore carefully assessed for biosafety, nutritional equivalence and environmental impact (Rommens *et al.*, 2007). In addition to addressing these potential risks, it is important to also consider the distance between gene source and target crop as part of the regulatory process. Disclosure of the sources of the genetic material introduced may prove necessary to define further research directions, maintain product identity, and increase consumer familiarity through categorization, and thus improve the response to engineered organisms and their products (Nielsen, 2003). But a case by case approach remains the pragmatic option, even for genes that are already expressed in the edible parts of food crops. Thus, the transformation of a plant with the disease resistance (*R*-) gene of its wild relative still requires a biochemical analysis of the *R*-gene encoded protein, despite the fact that traditional plant breeders already demonstrated the beneficial effect of *R*-gene introgression.

Governmental agencies in the United States are considering a diversification of the approval process for trans-

genic crops that is based on a risk assessment of the molecular strategy applied ([http://www.aphis.usda.gov/biotechnology/340/340\\_index.shtml](http://www.aphis.usda.gov/biotechnology/340/340_index.shtml)). Such an updated system might assign a lower risk to native genes not implicated in the formation of allergens or toxins than to synthetic genes that are new to the food supply. Among GE strategies, gene silencing approaches are considered the easiest and safest. Without the need to study proteins encoded by transgenes, regulatory approval packages for crops derived from gene silencing only need to confirm that the modified plant is agronomically and nutritionally equivalent to its untransformed counterpart.

The regulatory process is more complicated in the EU, where politicians have assumed a gatekeeper role for what type of products can enter the marketplace. In addition to a rigorous safety assessment from its scientific advisory body, the European Food Safety Authority, the process requires approval from both the European Commission and the Member States. Individual countries maintain the right to domestically ban particular transgenic crops approved for cultivation by the European Commission (Meldolesi, 2009). The involvement of politicians has diminished the desire of most EU countries to develop and produce genetically engineered crops (Hodgson, 2008; Meldolesi, 2009), with the exception of Spain where *Bt* corn is currently planted on over 50 000 ha (Gómez-Barbero *et al.*, 2008). Many developing countries have recently become more skeptical about whether policies for GE that are modelled after those of the EU are in their best interest (de Greef 2004). Stakeholders in these countries hold rather pragmatic views and emphasize the need for more sustainable and economically independent agricultural systems (Gupta and Chandak 2005; Aerni and Bernauer, 2006; Marshall, 2009).

### From pushing the scientific facts to responding to public perception

The lack of public support for transgenic crops, especially in some EU countries, is often considered to be a consequence of widespread scientific illiteracy and a failure to educate consumers on the benefits of GE (Einsele, 2007; McHughen, 2007). It is also possible, however, that consumers simply find no reason to support a new technology that does not provide any benefits to them. A recent experiment in the EU demonstrated that reluctance to buy transgenic food turns into a purchasing preference when these foods are spray-free and discounted by 15%

(Knight *et al.*, 2007). Genetically engineered foods would also be more desirable if they offered added health benefits. In a series of experimental auctions with food label and information treatments, consumers indicated that they were actually willing to pay more for transgenic vegetables than for non-modified products if the transgenic options offered enhanced expression of antioxidants and vitamin C (<http://ageconsearch.umn.edu/bitstream/6407/2/469580a.pdf>). Various consumer preference studies conducted in the United States yielded similar findings (Hossain and Onyango, 2004; Onyango and Nayga, 2004).

Naturalness has long been known by the advertising industry to represent a positive factor in selling food products. Its role in public perception issues associated with transgenic foods was studied by Rozin *et al.* (2004). Their research indicated that gene modifications involving the inter-species transfer of genes resulted in the greatest drop in the perception of naturalness (Rozin, 2006). Indeed, various surveys have shown that GE is perceived as more acceptable if it does not result in the incorporation of foreign DNA into the food supply. Whereas only 17%–25% of respondents were willing to consume a food that is transformed with a bacterial gene, about 77%–81% would accept a vegetable that contains an introduced gene endogenous to another variety of that same vegetable (Lusk and Sullivan, 2002; Lusk and Rozan, 2006). An independent unpublished study performed by Scott Smith (Qualtrics, Inc., Provo, UT, USA) based on an email survey of 779 consumers confirmed these findings, with 26% of respondents supporting inter-species transgenic modifications versus 70% of respondents supporting modifications that only involved genetic material already present within the species. In an effort to bridge the gap between agricultural biotechnology companies on one side and consumers and NGO on the other side, several companies and institutes developed the 'intragenic initiative'. This new approach to GE enhances the quality of crops by transforming them with genetic elements that are derived from the target species itself or species that are sexually compatible with the target species (Rommens, 2004; Conner *et al.*, 2007; Rommens, 2007; Schouten *et al.*, 2006). The approach is also linked to efforts aimed at establishing official guidelines for the values, principles and standards associated with the commercial application of GE. Public wariness of GE may be moderated by a 'code of ethics' for molecular biologists that seeks to maintain genome integrity by limiting chromosome alterations while also considering the naturalness of an incorporated trait (Rommens, 2008). In contrast to the issues

associated with the commercialization of GE foods in Europe, this continent's animal industry has become heavily reliable on the import of GE soybean and maize. Therefore, the genetic modification of crops destined for animal feed represents the easiest route to market.

## Summary

The following guidelines may facilitate overcome barriers to market genetically engineered crops: (1) carefully assess the efficacy of genes in the field by employing the full toolbox for agronomy, (2) focus on product concepts that address critical issues and/or needs, (3) ensure FTO by licensing, and/or developing work-around methods for, all applicable methods and genetic elements, (4) implement robust IP systems that comply with governmental guidelines, (5) obtain early buy-in from growers, processors, and retailers, (6) ensure that the gene-of-interest does not code for proteins which raise concerns with regard to potential toxicity and allergenicity, and maintain frequent and forthright communication with the regulatory agencies involved, (7) obtain end-user support by addressing perception issues and providing clear consumer benefits. Given these recommendations, R&D efforts in agricultural biotechnology should rely on effective multi-disciplinary teams that interact closely, and communicate openly, with relevant governmental agencies, patent attorneys, industry representatives, and consumer groups.

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