Ag Biotech Pipeline: What's in the Lineup?

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Throughout the nineteenth century, heredity remained a puzzle, even to scientists. How was it that after crossing two plants with different characteristics, you often got a plant with traits that were not identical to those of either parent? These questions intrigued Charles Darwin. He realized that these variations were the raw materials for natural selection. Conversely, uniformity from one generation to the next was the basis by which long-term effects were maintained. But Darwin was unable to decipher the underlying principles by which variation occurred on the one hand and uniformity was the norm on the other (Tompkins and Bird, 1973).

When Darwin published *Origin of Species* (Darwin and Appleman, 1991), Gregor Mendel was busy at work in a secluded monastery, occupied with the study of natural variation in peas. In this endeavor he was able to gain the first insights into the biological machinery behind heredity. His focus was to better understand what kept species distinct and what allowed them to be different following crosses. Studying these questions using natural variation in peas, Mendel gained an appreciation for the potential power of genetic manipulation applied to plants of agricultural importance. This work was extended by the findings of Luther Burbank (1907), a plant breeder whose prodigious production of new varieties of fruits, flowers, vegetables, grains, and grasses moved plant breeding into a more sophisticated science driven by an appreciation of genetics.

The use of genetics to modify plants and animals for agriculture moved into the current era with the identification by James Watson and Francis Crick (1953) of DNA as the element responsible for Mendel's wrinkled peas. This finding formed the platform for the development of recombinant DNA methods, first shown by California scientists Stanley Cohen and Herb Boyer who demonstrated a mechanism for moving functional DNA between unrelated organisms (Chang and Cohen, 1974), commonly referred to as biotechnology, recombinant DNA (rDNA) or genetic engineering.

Commercial Use of Genetic Engineering in Agriculture: What's Out There Now?

The first use of genetic engineering to modify plants was reported in tobacco in 1983 (Bevan *et al.*, 1983) and the first commercial genetically engineered (GE) crop, the FlavrSavr™ tomato, was developed by a California company, Calgene (http://www.accessexcellence.org/RC/AB/BA/Flavr_Savr_Arrives.html). Although the tomato was taken off the market, other GE crops were commercialized, most notably in large acreage crops like canola, corn, cotton, soy and, most recently, alfalfa. If success is measured by the increase in global acreage of these GE crops or their acceptance by farmers, certainly they have been successful. In 2005, the billionth acre was planted (James, 2005) by one of 8.5 million farmers in twenty-one countries. Most of the acreage is in the United States and almost none is in Europe. In the former, the adoption of herbicide-tolerant (HT) soybean represents 87% of total US acreage and HT cotton is at 60% (Fernandez-Cornejo and Caswell, 2006). Insect-resistant (*Bt*) cotton represents 52% and *Bt* corn 35% of total cotton and corn acreage, respectively. A few minor-acreage GE crops have met with commercial success: papaya, certain types of squash and sweet corn.

Acceptance by consumers has not come so easily. In a 2005 poll, 50% of US consumers opposed genetic modification (*i.e.*, genetic engineering) of plants and 33% strongly opposed it (http://pewagbiotech.org/resarch/2005update). Consumers were even more uncomfortable with genetic engineering of animals: 56% opposed GE animals and 66% opposed animal cloning. Despite the fact that consumers were opposed to genetic engineering of plants, 58% of US poll respondents—as recently as October 2005—weren't even aware that GE foods are being sold in grocery stores, an interesting dichotomy. Despite the majority of Americans admitting they have little knowledge of the regulatory structure governing GE food (55% in September 2004; http://pewagbiotech.org/research/2004update/2004summary.pdf), the majority of Americans (87% in July 2003; http://lists.iatp.org/listarchive/archive.cfm?id=79397) were confident that the food they eat is safe. Overall, these figures raise serious questions about the current state of consumer acceptance of foods containing GE ingredients and just exactly what is the nature of the issues they have with GE foods.

Use of Genetic Engineering in Agriculture: The Future?

Despite the large acreage, the diversity of GE crops and traits in commercially released varieties is limited. Nearly all major-acreage, commercial releases of GE crops are based on either insect protection via genes from *Bacillus thuringiensis* or herbicide tolerance, predominantly to Monsanto's Roundup® herbicide. More recently, stacked versions of these traits have been released, for example maize engineered for resistance to rootworm and European corn borer and tolerance of Roundup®. In addition, with the exception of GE papaya, which was developed by the public sector, all commercial varieties on the market in 2006 come from the private sector.

Insect-resistance and herbicide-tolerance traits are focused on improving life for the farmer. But, if used responsibly, these improved agronomic traits can also be beneficial to the environment, by increasing crop yields through the reduction of losses to insects, disease and weeds. This has been most dramatically demonstrated with decreases in insecticide applications with *Bt* cotton (Benbrook, 2004; Sankula *et al.*, 2005). Estimates of whether herbicide use has increased or decreased vary depending on the particular crop, the environment in which it was grown and the calculation method (*ibid.*). Despite the disagreement on the amount of herbicide used in GE vs. conventional crops, it is clear that there has been a shift in the herbicides used to more environmentally friendly types. It is also true that they are benefiting from the ease of application of herbicide to GE crops.

But what do end-users and consumers think about the future of this technology and where it might be most reasonably applied? In September 2004, Pew Trust poll (http://pewagbiotech.org/research/2004update/) respondents were asked about possible applications (Table 1). Clearly, some products of the technology were viewed more favorably than others. Producing more-affordable industrial compounds in plants, reducing the cost of fish such as salmon, creating fruits and vegetables that last longer and having beef with less fat were those applications that appeared least favorable. But consumers were in favor of producing more affordable pharmaceuticals using plants, although not by using animals. Also, reducing the need for pesticides, creating less-allergenic peanuts and developing vegetable oils with heart-healthy fats were viewed relatively favorably. One of the most interesting questions related to whether it is a "good or bad reason to genetically modify plants and animals" to "expand our understanding of science and nature": 46% of respondents said yes and only 10% said no.

Table 1. Are these good or bad reasons to genetically modify plants or animals?

	Very good	Very bad
	(%)	
To reduce the need to use pesticides on crops	43	12
To reduce the cost of fish like salmon	21	27
To produce more affordable pharmaceuticals using plants	54	8
To produce more affordable pharmaceuticals using animals	23	29
To produce more affordable industrial compounds using plants	2	17
To create types of grass that require less-frequent mowing	39	22
To create fruits and vegetables that last longer	27	30
To produce beef with less fat	27	32
To develop heart-healthy vegetable oils	41	18
To create hypo-allergenic peanuts	42	15
To expand understanding of science and nature	46	10

Certainly from a casual look at the scientific literature, scientists are utilizing the modern methods of genetically engineering organisms, coupled with genomic information, to gain in-depth understanding of living organisms. This information has led to a practice referred to as marker-assisted breeding. The term is used to describe the application of classical breeding methods coupled with genomics to create crops and animals with different characteristics resulting from new information gained about the location and function of genes. This information is normally determined or validated using the tools of recombinant DNA either to up- or down-regulate genes in the recipient organism. Although the technology uses information developed through the use of genetic engineering to read and manipulate the genome to determine function, the genetic information of the plants is not directly modified using recombinant DNA technology.

What's the Lineup in the Ag Biotech Pipeline?

The technologies used for marker-assisted selection can be successful for certain traits and certain crops and animals, given a long timeframe. However, when there is a desire to control precisely when and where a gene is expressed to achieve a certain outcome, manipulating these traits will not be achievable through such methods. Examples might include changes that require genes from other organisms, like insect-resistance or herbicide-tolerance genes from a bacterium, or other modifications that require genes to be linked to specific regulatory elements to control exactly when and where they are expressed, like genes mitigating allergenicity or delaying ripening that need to be altered only in the edible parts of the plant. These traits may be achieved by using antisense or gene-silencing mechanisms.

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Although commercialized GE crops are limited in traits used, proof-of-concept for many other traits has been reported. These can be divided into a number of categories: pest resistance, improved agronomic performance, tolerance to environmental stresses, increased food, feed and environmental quality, and medical and other applications.

Pest Resistance

A number of examples demonstrate the capability to improve the performance of crops through protection against pests. Starting in 1845, late blight disease attacked the potato crops that fed the densely populated island of Ireland, resulting in the infamous Irish potato famine. Now, with the globe much more crowded, potato experts report that the same disease, caused by the fungus *Phytophthora infestans*, is returning. But scientists, looking in the genome of a wild Mexican potato, discovered a gene that, when engineered into cultivated potato, allows the potato to survive exposure to the many races of *P. infestans* (Song *et al.*, 2003). Although GE potatoes show promise in resisting late blight, in May 2006 the world's largest chemical company, BASF, relinquished its plans for a GE-potato field experiment in County Meath (http://www.gmfreeireland.org/potato/), demonstrating the fear with which some European governments view GE crops, even if they address serious agricultural problems.

Another example is the identification of a native gene, *Mi*, in tomato that protects against root-knot nematodes (Milligan *et al.*, 1998). Surprisingly, at the time the gene was cloned, they discovered that the gene most similar to *Mi-1.2* is *Prf*, another tomato gene required for resistance to the bacterial pathogen *Pseudomonas syringae.* It turned out that the Prf and Mi-1.2 proteins share several structural motifs, including a nucleotide-binding site and a leucine-rich repeat region (NBS-LRR), characteristic of a family of plant proteins required for resistance to viruses, bacteria, fungi and nematodes.

Although Europe has been reluctant to embrace engineered crops, the first field trial of GE grapes took place in the northern Alsace region of France in 2005. This plant was engineered against fanleaf virus, which is transmitted by a small root-feeding nematode. Scientists inserted into rootstocks a coat-protein gene that stops replication of the virus (Bouquet *et al.*, 2003), while the scion—the portion grafted to the rootstock and which bears the fruit—is free of the foreign gene. Without a GE approach, growers must fight the fanleaf virus with a pesticide that has been banned in Germany, Switzerland and in some US states. Another viral target utilizing a GE approach was addressed with watermelon rootstocks engineered for resistance to cucumber green mottle mosaic virus (CGMMV) infection (Park *et al.*, 2005a).

Other examples outside the United States include relatively small acreage crops engineered with *Bt* genes. Indian, Canadian and French scientists collaborated to engineer cabbage with a fusion gene encoding two *Bacillus thuringiensis* crystal-endotoxin genes, which led to resistance to the diamondback moth (Anderson *et al.*, 2005). In 2000, scientists at the Centre de Coopération Internationale en Recherche Agronomique pour le Développement (CIRAD) in France planted in French Guiana GE coffee engineered with a *Bt* gene to test for protection against leaf-miner damage. In 2004 vandals removed the trial owing to fears that the engineered strains would enable richer farmers to put small farmers out of business (http://www.newscientist.com/channel/life/gm-food/). In 2005, scientists at the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) in India engineered and field-tested chickpea for resistance to legume pod-borer, *Helicoverpa armigera* (http://www.icrisat.org/gt-bt/GeneticEngineering.htm).

Improved Agronomic Performance

Such improvements are aimed primarily at the farmer, but could, given responsible usage, also have positive effects on the environment. One aspect of crop performance is yield. In 2001, transgenic rice plants expressing the maize proteins phosphoenolpyruvate carboxylase (PEPC) and pyruvate orthophosphate dikinase (PPDK) were found to exhibit higher photosynthetic capacity (up to 35%) compared to untransformed plants (Ku *et al.*, 2001). The simplicity of the change that resulted in the increased photosynthetic capacity in rice surprised many who had thought that such a dramatic increase in yield in a C3 plant relative to a C4 plant would require more complex modifications.

Another agronomic improvement involves the efficiency of utilization of nitrogen, resulting in less use of fertilizer and increased sustainability of farming practices. Japanese scientists introduced into the model organism, *Arabidopsis*, the plant-specific transcription factor, Dof1, to improve nitrogen assimilation (Yanagisawa *et al.*, 2004). Expressing

Dof1 induced up-regulation of genes encoding enzymes for carbon-skeleton production, a marked increase of amino acid content, and reduction in glucose level. Elementary analysis revealed that the nitrogen content increased by ~30%, and the engineered plants exhibited improved growth under low-nitrogen conditions.

Tolerance to Environmental Stresses

These traits aid the ability of plants to survive environmental stresses, like salinity, excessive and deficient water availability and high and low temperatures. Prior to developing a thorough molecular understanding of the regulatory mechanisms governing the plant's responses to these stresses, it appeared that strategies would have to focus independently on each individually. However, with the development of a detailed understanding of the mechanisms involved and their regulatory networks, it became possible to enable plants to deal with multiple environmental factors simultaneously with change in one gene.

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An example is the demonstration that the *CBF* genes, which are rapidly induced in response to low temperature, encode transcriptional activators that control the expression of genes containing C-repeat/dehydration-responsive regulatory elements in their promoters (Gilmour *et al.*, 2000). Constitutive expression of either *CBF1* or *CBF3* (also known as *DREB1b* and *DREB1a*, respectively) in engineered *Arabidopsis* was shown to induce the expression of target *COR* (cold-regulated) genes and to enhance freezing tolerance in nonacclimated plants.

Later, a homologue of the CBF/DREB1 proteins (CBF4) was shown to play an equivalent role during drought adaptation; CBF4 gene expression is upregulated by drought stress, but not by low temperatures (Haake *et al.*, 2002). Over-expression of CBF4 in engineered *Arabidopsis* resulted in activation of downstream genes involved in cold acclimation and drought adaptation and, as a result, engineered plants were more tolerant to freezing and drought stress. This approach was expanded to crop plants with the introduction of *DREB1A* into wheat for drought tolerance; field trials were conducted at the International Maize and Wheat Improvement Center (CIMMYT) in 2004 (http://www.cimmyt.org/english/webp/support/news/dreb.htm).

In another example, transgenic tomato plants over-expressing a vacuolar Na^+/H^+ antiport were able to grow, flower, and produce fruit in the presence of 200 m*M* sodium chloride, approximately 40% of sea-water concentration (Zhang and Blumwald, 2001). Although leaves accumulated high concentrations of sodium, the tomato fruit displayed very low sodium content. This confirmed that—contrary to prevailing thought—multiple traits do not have to be introduced by breeding to obtain salt-tolerance.

Increased Food and Feed Quality

The first demonstration of the use of GE to alter nutritional quality was the introduction of three genes into rice to create the much publicized Golden Rice, enriched in pro-vitamin A (Ye *et al.*, 2000). More recently one of the genes from daffodil, used in the original event, was replaced with a maize gene and the level of pro-vitamin A was thus increased 23-fold (Paine *et al.*, 2005) to a level likely to supply 50% of a child's recommended daily allowance in 72 g of dry rice.

Efforts have also been made to increase calcium levels three-fold in potato (Park *et al.*, 2005b). Levels of folate, an important vitamin for women of childbearing age, were increased in *Arabidopsis* to those in spinach by the introduction of a single bacterial gene (Hossain *et al.*, 2004). Indian scientists improved the nutritional quality of a staple in their diet, the potato, by introducing a nonallergenic protein from *Amaranthus*, thus increasing both total protein content and the amounts of essential amino acids (Chakraborty *et al.*, 2000). Recently, corn for animal feed was engineered for higher lysine content in order to reduce the need for lysine supplements (http://www.renessen.com/news/02.06.2006.eng.pdf).

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Plants have been engineered to produce the heart-healthy omega-3 and omega-6 oils, previously supplied mainly from fish sources (Qi *et al.*, 2004). Another area of intense interest relating to human consumption is engineering foods for decreased allergenicity, for example in rice (Nakamura and Matsuda, 1996) and wheat (Buchanan *et al.*, 1997).

Medical Applications

Many applications in this arena relate to the production of vaccines, both for animals and for humans. In one early application aimed at animal husbandry in Australia, clover was engineered to provide protection against shipping fever (Lee *et al.*, 2003). In 2006, the USDA approved a plant-based vaccine against Newcastle disease of chickens (http://www.checkbiotech.org/ blocks/dsp_document.cfm?doc_id=12154). Another approach to improved animal husbandry involved the actual engineering of a cow with higher levels of lysostaphin to lower the rate of mastitis infection by *Staphylococcus aureus* (Wall *et al.*, 2005).

Approaches utilizing GE plants to combat human disease include the development of a subunit vaccine against pneumonic and bubonic plague, which has been shown to be immunogenic in mice (Alvarez *et al.*, 2006), a potato-based vaccine for hepatitis B demonstrated to raise an immunological response in human test subjects (Thanavala *et al.*, 2005), a GE pollen vaccine that reduces allergy symptoms in sufferers (Niederberger *et al.*, 2004), and an edible rice-based vaccine targeted at allergic diseases like asthma, seasonal allergies and atopic dermatitis (Takaiwa 2006). The most successful commercial application of plant-produced protection was the synthesis in tobacco of a patient-specific vaccine for lymphoma (McCormick *et al.*, 1999); however, Large Scale Biology Inc., the commercial developer, was unable to identify investors for this approach, although proven successful in Phase-II clinical trials, and has since closed down.

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Environmental Improvement

This category of applications includes examples that extend from the Enviropig™ to engineering plants to detect landmines. Researchers in Canada have developed a new breed of Yorkshire pig—the Enviropig™—that utilizes plant phosphorus more efficiently (Golovan *et al.*, 2001). Non-engineered pigs cannot use phytate, a form of phosphorus present in cereal grains. Accordingly, producers add to the diet supplemental phosphate or an enzyme, phytase, to meet phosphorus needs for optimal growth and development. The Enviropig™ has an enzyme in its saliva that allows it to degrade phytate and absorb the phosphate, thereby negating the need for supplemental phosphate or phytase, and as a result, phosphorus content of manure is reduced by as much as 60%.

Several efforts have been made to improve the ability of plants to remove heavy metals and other pollutants from the soil. One example is the engineering of the poplar tree to remediate soils contaminated with ionic and methylmercury (Rugh *et al.*, 1998). Another improves the ability of a member of the mustard family to take up selenium from the soil and transport it to the upper portions of the plant for harvest (Banuelos *et al.*, 2005).

The utilization of plants to produce alternative sources of fuels has recently become a focus of attention given the rise in energy prices in the United States. One approach involves the engineering of green algae to produce hydrogen gas, a renewable, clean fuel source (Melis and Happe, 2001). One of the most serious environmental pollutants is paper waste, particularly newspapers that, because of compaction, can remain in landfills for decades without decomposing. Recently, bacteria were engineered to help alleviate the global wastepaper glut (Fierobe *et al.*, 2005). One extremely dangerous environmental contaminant is the presence of landmines in specific areas; the problem is how to detect their presence without having them explode. University of Alberta and Duke University scientists are trying to develop plants that will indicate the location of landmines by changing color when their roots detect explosive compounds like TNT (http://cnews.canoe.ca/CNEWS/Science/2006/05/07/1568701-cp.html).

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Other Applications

Countless amounts of energy and time are spent each year keeping the grass in home yards and on golf courses mowed. The Scotts Company has introduced a gene that slows the growth of grass, so-called Slo-Mow™, and reduces watering needs. Horticultural crops, like ornamental flowers, have also been a focus of engineering efforts. In Australia, Florigene Pty Ltd. succeeded in creating a number of new, vibrantly colored carnations, like Moonshadow™, some with delayed senescence (http://www.florigene.com.au/products/products.php?product_ name=Moonshadow). Long the "holy grail" of breeders, the blue rose was created by scientists in the Japanese company, Suntory (http://www.physorg.com/news3581.html). Breeders had attempted to make true blue roses for many years—prizes were even offered to anyone who could create them—but none were successful until they used genetic engineering technologies. First, RNAi was used to remove the gene encoding dihydroflavonol reductase (DFR) and then the delphinidin gene was introduced from pansy and the DFR gene from iris: *voilà*, a blue rose! Another aesthetic effort, this time at the pet store, was the creation of the GloFish™, accomplished by introducing a fluorescence gene into the aquarium zebra fish (http://www.glofish.com/). Under a black light, the fish appears to glow in the dark. An effort focused on eliminating the need for moths is the engineering of plants to produce silk-like proteins (Janaki Krishna, 2006).

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Closing Thoughts

A look at the lineup of future applications of genetic engineering in agriculture certainly makes it clear that, at this point, applications are not limited by the technology. Rather, progress is clouded by a number of factors that are outside the control of scientists, particularly academic scientists. Although public-sector scientists have played a role in variety development of plants and animals in the past—using classical breeding and mutational approaches—their ability to participate effectively in this arena is limited by issues like very high regulatory costs and limited access to key technologies because of intellectual-property protection. These factors, in addition to consumer-acceptance issues, will determine the future applications of genetic engineering of crops and animals. Will such approaches be used to address the specific problems of agriculture in the United States? Even if this is not the case in the near term, it is likely that these technologies will play an important role in other countries, for example China, where these issues are not likely to be key factors in their utilization.

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