Project Title: Revolutionizing Insect Control: *Bt* technology
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Short description of most recent milestone and date:
On June 22, 2010, U.S. patent number 7,741,118 B1 was issued to Monsanto for the genetically based technology used to modify structural gene sequences to enhance the expression of *Bacillus thuringiensis* (*Bt*) insecticidal proteins in plants. This is the fundamental technology underlying *all* biotechnology-derived insect-resistance traits commercialized by Monsanto or any other seed company, including competitors of Monsanto, in corn and cotton, which in 2010 represented 65 percent of all corn grown in the United States and 75 percent of all cotton grown in the United States. (*Adoption of Genetically Engineered Crops in the U.S.*, United States Department of Agriculture, Economic Research Service, 2011).

Eligibility for small business or academic award: No

Nomination Category:
An industry sponsor for a technology that includes the design of greener chemicals

Focus area(s):
The design of greener chemicals

Statement of the activities that took place within the U.S.:
Monsanto Company's research, development, testing and marketing related to the invention, development and commercialization of *Bt* technology used to produce insect-resistant crops, was and continues to be largely based at Monsanto's headquarters in St. Louis, Missouri. Extensive testing and pre-market stewardship was conducted in major markets within the United States.

Abstract:
Crop insect pests have limited food production for centuries. Until the 1990s, chemical insecticides were the most advanced tools for insect control; however, they created significant challenges, including undesirable environmental effects, toxic effects against non-target organisms and the need for repeated applications, increasing farmers' costs and efforts. Soon, a new scientific vision became a reality – biotechnology.

The application of biotechnology means pesticide manufacturing and chemical pesticide applications are less necessary. This innovative technology provides an escape from manufacturing and synthesizing chemical pesticides in large sophisticated labs by creating natural chemicals through soft manufacturing mechanisms.

Unlike traditional pesticide manufacturing, this recently patented technology utilizes insect control present in nature. *Bacillus thuringiensis* (*Bt* - a ubiquitous soil microbe) produces insecticidal toxins. Using biotechnology, Monsanto has taken advantage of the characteristics of these toxins – Cry (crystal) proteins – combining this knowledge with plant molecular genetics to create plants that express specific toxins to control pests by producing a chemical through biological mechanisms in the plants themselves. In addition to reducing the use of pesticides, the specificity of Cry proteins ensures only target organisms are affected – not humans, animals or non-target beneficial insects

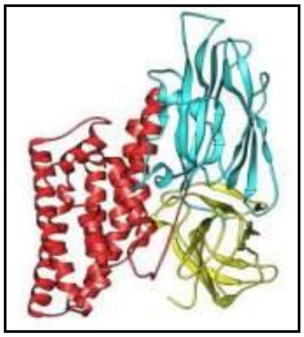
Bt technology has been and continues to be applied across many plant varieties, increasing yields and reducing the need for chemical pesticides. All *Bt* traits in commercial use have been created through the use of Monsanto's patented synthetic *Bt* gene technology, and Monsanto's developed traits have been licensed to and sold by numerous seed companies, as well as by Monsanto itself. In addition, some companies have developed their own insect resistance traits, but all of these traits have utilized Monsanto's synthetic gene technology covered by the recently issued '118 patent. In 2010, 65 percent of all corn grown in the United States and 75 percent of all cotton grown in the United States included one or more *Bt* traits.

Farmers planting insect-resistant crops experience improved safety and health because of reduced handling and use of pesticides. They spend less time applying insecticides, and reduced applications mean fewer containers and less fuel and aerial spraying, all factors that benefit the environment while also increasing yields and enhancing farmers' lives.

Scope of the Program

This document will briefly describe the development of a revolutionary technology that has changed the way farmers around the world control insect pests, therefore reducing the impact of harsh chemical pesticides – the discovery of synthetic gene technology to effectively express *Bt* proteins in plants and create important new insect control products with significant environmental benefits. This Monsanto invention resulted from a convergence of biochemistry, insect pathology, microbiology, plant and bacterial molecular biology, agronomy, entomology and physiology. Since its conception and commercialization, this technology has enabled farmers across many crops to spend less time, money and energy on insecticide application and more time focusing on producing higher yields while very significantly reducing the use of chemical insecticides.

<u>Science innovation:</u> In the past, the application of chemical insecticides was a common method of combating insect pests, but their control was often far from complete because timing was a challenge. In addition, the chemicals themselves were costly and presented a variety of environmental and health risks. Because of these challenges, a small team of scientists at Monsanto began working on a genetic answer to insect control, concentrating on isolating the genes from *Bacillus thuringiensis* (*Bt*), a naturally occurring bacterium that produces Cry (crystal) proteins toxic to certain types of insects. During growth, many strains of *Bt* produce inclusion bodies, which contain, in crystalline form, Cry proteins – highly selective and specific insecticidal proteins. When the *Bt* Cry proteins are ingested by a susceptible insect, the Cry proteins solubilize in the insect's gut and bind to specific receptors on the brush border membrane epithelium lining the gut and insert themselves into that membrane, creating pores that compromise the integrity of the midgut lining. Gut paralysis and cessation of feeding occur rapidly, leading to the death of the susceptible insect shortly thereafter (*Insecticidal Crystal Proteins of Bacilllus thuringiensis,* Hofte & Whiteley, 1989). These *Bt* proteins are highly selective, so only the pest insects feeding on the plant are killed, with no effect on other beneficial insects or animals. The thinking was if the *Bt* gene could be inserted directly into plants, crops would produce their own "pesticide," which would be much more selective for pest insects than the chemical insecticides generally used, and would greatly reduce or even eliminate the need for chemical insecticides in some crops.



The image above is a model of the key protein Cry1Ab, which is derived from the bacterium *Bacillus thuringiensis*, or *Bt*. Some of the first ever genes to be inserted into plants were derived from *Bt*. Once inside the plant, the *Bt* genes created the protein shown above. When an insect bites into the actual plant, this protein binds to the insect's gut, killing the insect.

The process began by isolating the gene for one of the *Bt* Cry proteins and determining the best way to insert it into plants. The initial results were disappointing. Although the *Bt* gene could be inserted into the plants, no *Bt* protein could be detected, and there was no effect on insects.

This problem resulted in a major scientific breakthrough. The team of scientists at Monsanto discovered that, for the particular *Bt* gene they had isolated (called *Cry1Ab)*, only the first half of the *Bt* gene was needed to produce a protein toxic to insects. Taking advantage of this, the team used only the half-gene for the plant experiments. When this truncated gene was put into tomato plants, the plants successfully killed the predatory insects. At this point, the team revealed for the first time that *Bt* genes could work to produce insect-resistant plants. Although these results were exciting, it was also clear that while the needed *Bt* protein was being manufactured in the plants, it was produced at very low levels and not nearly enough to produce the consistent dramatic results needed for commercial viability and to replace chemical insecticides.

Within months, the team began working on a radical solution – development of a synthetic *Bt* gene. This was a complete departure from traditional scientific thinking, and many within the industry were skeptical. Monsanto's team of scientists believed that because the large *Bt* gene was so different from plant genes, the insertion of naturally occurring *Bt* genes could never produce as much protein as was needed. Their idea was to synthetically re-create the *Bt* gene to look more like a plant gene, by identifying and then reducing or eliminating DNA sequences within the *Bt* gene that the Monsanto scientists had predicted were deleterious for expression of the gene in plants. In essence, the Monsanto scientists made a *Bt* gene that was simple for plants to "read" and understand the "message."

This idea was an unqualified success. The initial plants with the synthetic *Bt* gene made a thousand times more *Bt* protein than plants with the native gene. This level of increase in gene expression was unprecedented in any area of biotechnology. Plants with the synthetic *Bt* gene offered complete control of insect larvae that was even more effective than chemical pesticides, while leaving helpful insects and the plants themselves unharmed. This breakthrough enabled Monsanto to develop successful commercial products, and the full patent for this innovative technology was granted in June 2010.

The Monsanto scientists showed that the synthetic gene approach worked for numerous *Bt* genes in many plant species, including major plants such as corn, cotton and potato. As science has progressed since their earliest work, Monsanto scientists and scientists around the world have continued to discover new *Bt* genes that produce new Cry proteins with insecticidal activity against different insects species, increased potency against insects, and novel “modes of action” in the insect gut; in addition, Monsanto scientists and others developed novel variants of Cry proteins by combining portions of existing Cry proteins or using protein engineering techniques. Importantly, the synthetic *Bt* gene technology developed by Monsanto scientists and described by the ‘118 patent covers all of these new *Bt* genes to dramatically increase their expression in plants. The synthetic gene technology has seen its greatest commercial application so far in corn and cotton, but it has been used successfully in many other plant species including tomato, tobacco, potato, rice, soybean, broccoli, eggplant, cowpea, sugarcane and others. Thus, the approach described in the recently issued ‘118 patent has been proven to be a solution to the problem of increasing expression of *Bt* genes in plants to produce insect resistant plants. This solution has been commercially developed by Monsanto for products sold by Monsanto’s seed companies, or licensed to other seed companies for sale within their own seed brands. In addition, some seed companies have developed their own insect resistance traits, but all have used Monsanto’s synthetic gene technology.

Human health and environmental benefits: *Bt* technology, currently commercially available in two major row crops in the United States, cotton and corn (and which was also commercialized for a period of time in potatoes), is not only safe for the environment, it also helps reduce chemical pesticide applications.

Bt products provide significant environmental and human health benefits resulting in advantages for growers globally, including a reduction of pesticide active ingredient (ai) application by 21.8 percent for insect-resistant cotton and a reduction of pesticide ai application by 40.6 percent for corn from 1996 to 2009 (PG Economics, *Focus on Yields – Biotech crops: evidence of global outcomes and impacts 1996-2009*, June 2011).

Reduction in insecticide use means a reduction in the need for multiple chemical applications, which means less environmental exposure and impact. Farmers are less exposed to toxic pesticides, and consumers benefit from reduced risk of harmful pesticides being present in foods they purchase. Additionally, it enables farmers to spend less time and money on insecticide applications.

From 1996 to 2009, active ingredient pesticides used on *Bt* corn and cotton decreased by 416.9 million pounds. In addition, the commercialization of *Bt* technology has contributed to an increase of global farm incomes by $64.7 billion between 1996 and 2009 (PG Economics, *Focus on Yields – Biotech crops: evidence of global outcomes and impacts 1996-2009*, June 2011).

In addition to direct reduction of environmental pesticide release, Brookes & Barfoot (2011) suggest that in 2009, 3 billion pounds of carbon dioxide savings resulted from reduced fuel use for pesticide application for insect-resistant cotton. Additional environmental benefits include saving on all materials needed to manufacture, transport and apply insecticides, as well as eliminating the need to use and dispose of insecticide containers (PG Economics, *Focus on Yields – Biotech crops: evidence of global outcomes and impacts 1996-2009*, June 2011).

The discovery of the synthetic gene technology, which allowed the effective commercial use of *Bt* in plants has also led to “stacking” or combining this technology with herbicide-tolerance traits. The stacked trait combinations of *Bt* genes plus herbicide tolerance are very attractive product offerings in both corn and cotton. The availability of “stacked” products has enabled farmers, their families and farming communities in general to significantly reduce their exposure to chemical pesticides, making farming safer.

Additionally, farmers have reported that biotech products have allowed them to have more time with their families and dramatically improved their quality of life. Rather than the almost continuous chemical pesticide application needed pre-biotech, farmers now spend less time working in their fields, spend less money on pesticides, fuel and labor costs, and enjoy better yields and increased profit.

When *Bt* genes are inserted into the genome of crop plants, whether single genes or in stacked combinations, those inserted genes are as stable as any other gene in the genome. The genes are not lost, nor is their expression changed, even after many, many generations. This demonstrates that the *Bt* gene is as stable as any other gene in the plant genome. This stability is true of all *Bt* biotech traits, whether alone or in stacks.

Applicability and impact: The advantages of *Bt* technology are vast, and it’s clear that the development of this technology has forever changed the agricultural landscape. The implementation of *Bt* technology in crops has enabled growers to lower input costs because the need to apply numerous pesticides has greatly decreased. *Bt* crops provide growers with an efficient, easy-to-implement pest management option because insect control is built into the seeds they plant. This translates into fewer pesticide purchases and a higher yield, which means farmers experience increased profits.

Since crops with *Bt* technology need to be sprayed less, the environment benefits, too. Insect-resistant crops reduce the need for multiple chemical applications. And, because spraying, by air or by tractor, is less necessary, energy is saved. Fuel for crop-spraying aircraft and farm machinery is also reduced (*GM Crops: Global Socio-Economic and Environmental Impacts 1996-2009* Brookes & Barfoot, 2010).

One of the greatest advantages to *Bt* technology is its broad applicability across virtually any crop. *Bt* technology was first implemented in cotton, but it has since extended to include corn and was also commercialized for a period of time in potatoes, with many other *Bt* crops in development. All of the instances of *Bt* genes in plants that have been commercialized, or that are in development, utilize the Monsanto-invented synthetic gene technology that is the subject of the recently issued patent. This includes *Bt* traits in cotton and corn that have been developed and commercialized by other major agriculture and seed companies, including DuPont, Syngenta, Dow Agrosciences and others.

As new *Bt* genes producing Cry proteins with specificity against different insects have been discovered, the breadth of insect resistance traits has expanded. For example, for many years, there were no known Cry proteins active against corn rootworm, a major pest of corn. As Monsanto scientists discovered and developed rootworm-active *Bt* genes, they were able to quickly apply synthetic gene technology to produce rootworm-resistant corn plants. More recently, Monsanto scientists developed *Bt* genes active against Lygus bugs, a major pest of cotton. Historically, no Cry proteins with the ability to eliminate Lygus bugs or other “piercing and sucking” insects were known. With the development of Lygus-active Cry proteins, Monsanto now has an active program to develop Lygus-resistant cotton, based on synthetic gene technology.

Among the *Bt* crop products in advanced development are soybeans in Brazil, rice in China and eggplant in India. Many other crops have been engineered with *Bt* genes using synthetic gene technology including cowpea, broccoli, sweet corn, sugarcane and tomato. Significant enhancements to *B*t technology have been made since the first products were introduced, all of which depend on the synthetic gene technology developed by Monsanto. Additional *Bt* genes that are effective against insects have been and continue to be identified. In some cases, second *Bt* genes effective against pests targeted by the original *Bt* gene have been added. Rather than producing a single insect-control protein, additional proteins specific to devastating pests can be identified and produced, which increases durability against the potential development of insect resistance compared with a single-protein product.

In other cases, *Bt* genes active against different insects have been “stacked,” which increases the overall effectiveness of the plant products. For example, in corn, the original *Bt* plants had a gene active against above-ground pests such as European corn borer. In subsequent years, *Bt* genes active against below-ground corn rootworm were discovered. Now, products with both types of *Bt* genes in a single corn plant are available to farmers.

Monsanto’s team invented the synthetic gene technology used to modify structural gene sequences to enhance the expression of the naturally occurring *Bt* protein in plants and has partnered with other companies to provide enhanced products to growers around the globe. Additionally, scientists at competing companies and in academic and public laboratories around the world have used Monsanto’s patented technology and approach to develop *Bt* products. Monsanto and Dow AgroSciences have collaborated utilizing *Bt* technology to create SmartStax®, a corn product with six *Bt* genes that provides above- and below-ground insect protection against a broad spectrum of insects including corn rootworm, corn earworm, European corn borer, southwestern corn borer, sugarcane borer, fall army worm, western bean cutworm and black cutworm.

Products incorporating *Bt* insect resistance by Monsanto, their partners and competitors, have been commercialized since 1996 and continue to expand. The table on page 8 includes a historical list of *Bt* insect-resistant products from Monsanto and others, as well as the crops that benefit from utilizing them.

Approval Year	*Bt* Product Name	Protected Crops
1996	Monsanto – Bollgard	Cotton
1996	Sandoz/Northrup King (now Syngenta) – YieldGard	Corn
1997	Monsanto – Bollgard II	Cotton – adds second mode of action
1997	Monsanto – YieldGard Corn Borer	Corn – provides above-ground insect protection
2001	Mycogen (Dow Agro) and Pioneer (DuPont) – Herculex I	Corn – provides above- ground insect protection, provides new mode of action
2003	Monsanto – YieldGard Rootworm	Corn – targets rootworm
2004	Monsanto – YieldGard Plus	Corn – provides above-ground insect protection and targets rootworm
2004	Dow Agrosciences – Widestrike Cotton	Cotton
2004	Dow Agrosciences – Herculex RW Insect Protection	Corn – targets rootworm, provides new mode of action
2005	Syngenta – VipCot Cotton	Cotton
2007	Monsanto – YieldGard VT Rootworm/Roundup Ready 2	Corn – targets rootworm
2007	Syngenta – Agrisure RW	Corn – targets rootworm
2008	Syngenta – Agrisure Viptera	Corn – provides new mode of action
2009	Monsanto – YieldGard VT Triple Pro	Corn – provides above-ground insect protection and targets rootworm
2009	Monsanto – Genuity SmartStax Corn	Corn – combines above- and below-ground insect protection and combines multiple modes of action for above-ground insects and rootworm
2009	Monsanto – YieldGard VT Pro	Corn – provides above-ground insect protection and adds second mode of action
2011 (Brazil)	Bayer – TwinLink	Cotton

The versatility of *Bt* technology means its impact will continue by extending to include a diverse range of crops grown around the world. International scientists are already identifying ways to incorporate Monsanto's patented *Bt* technology into a variety of crops, and companies are collaborating to provide growers with enhanced *Bt* products that decrease dependency on insecticides, which reduces negative environmental impacts and protects farmers' health. Monsanto's invention of *Bt* technology makes traditional pesticide manufacturing less necessary because natural chemicals can be created through soft manufacturing mechanisms instead of in large chemical manufacturing facilities. *Bt* technology has single-handedly reshaped the way pests are controlled and will continue to reduce future pesticide dependency.