How Intellectual Property and Plant Breeding Come Together: Corn as a Case Study for Breeders and Research Managers

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ABSTRACT

Plant breeders and research managers need to understand how intellectual property (IP) restrictions on germplasm and traits affect freedom to operate for a breeding program. Access to patented germplasm and traits is restricted and can only be used under some form of material transfer agreement or similar contract. Patented materials have to be maintained under strict provisions of the contract. This adds to the cost of breeding, parent seed, and production programs. Moreover, maintaining separate versions and precise records of patented materials increases the number of seed lots that a program must maintain. For example, different versions of inbred lines of maize must be maintained for each patented trait. Otherwise, stacking two or more traits produces lines with each trait and also lines with every combination of those traits.

1. INTRODUCTION

As the manager of research and development at a major seed company for several years during the 1980s and 1990s, I saw firsthand how proprietary biotechnology transformed our business. Drawing on my experience, this chapter describes:

- the complexities of managing proprietary transgenic inbred lines, hybrids, and genes through the breeding, testing, parent seed, and hybrid production processes
- licensing and contracts relevant to the use of proprietary biotechnology in breeding programs
- tips to enable you to avoid costly errors in managing licensed biotechnology applications

Initially, you may wonder why it is essential that breeders and research managers learn how to manage proprietary biotechnology efficiently in any breeding program. The reasons are actually quite simple.

For breeders, a working understanding of the extra workload, costs, constraints, and potential benefits of using proprietary biotechnology is necessary to establish priorities for developing transgenic inbreds and hybrids. A breeder's lack of basic information about the licensing of proprietary biotechnology could be a costly waste of time, opportunity, and money. Ignoring issues associated with managing proprietary biotechnology will not make them go away. Indeed, the failure to make informed decisions about what traits to adopt and how to handle them will result in de facto decisions that may be neither desirable nor reversible.

For research managers, a working understanding of intellectual property (IP) in biotechnology is necessary to obtain freedom-to-operate (FTO) and to commercialize traits. Managers must understand the real costs of obtaining, backcrossing, increasing, and testing multiple biotech traits in order to properly allocate resources to breeding,

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parent seed, and production programs. Finally, to make decisions about product development and release, managers must understand contractual obligations related to product quality and efficacy.

While I use corn as the example throughout this chapter, most of the principles discussed here are equally applicable to the breeding of almost any crop. So, as you read through this module, think how the experiences I share apply to your specific job.

2. OVERVIEW OF CORN BREEDING PROGRAMS

Traditional corn breeding programs in the developed world breed hybrid varieties for farmers' use. Hybrids in the United States today are mostly crosses between two inbred lines. New inbred lines are developed by selfing plants from a source population. Source populations could include open pollinated varieties, synthetics, or crosses between two or more inbred lines.

Successful commercial corn breeding programs today often start with source populations created by crossing two relatively elite inbred lines that both combine well with another line (tester) to produce hybrids exhibiting high levels of heterosis. The source population is then self-pollinated for seven to eight generations, with several hundred selfed families being selected and advanced during each selfed generation. After one to three selfed generations, the selfed families are crossed onto an inbred of a complementary heterotic group (tester) and the hybrid progeny are evaluated in replicated trials for yield and desirable agronomic traits. Lines from the selfed families that produce the best tester hybrids are advanced to further selfing generations and recrossed onto additional testers to produce new hybrids to evaluate. As the families are selfed, each generation becomes more and more homozygous, or inbred, eventually giving rise to new inbred lines. New inbred lines that produce new hybrids 5%–10% better than the best current hybrids are advanced. New hybrids are evaluated over several hundred locations over two to three years before a selected few are released as new commercial hybrids.

The above process requires eight to ten generations of selfing and three to five concurrently run years of hybrid testing. Each year of testing is called a stage, so that hybrids advance from stage one to stage five of testing. Each successive stage is marked by fewer hybrids grown at more locations. The first three stages typically are composed of two replicated plots of each hybrid, approximately 1/1000th acre in size, grown at ten to 100 locations. The last two stages are usually produced on strips of ten to 20 rows of each hybrid, planted under farm conditions. Historically, the development of new inbred lines has taken eight to ten years. Advances in data collection and analysis technology, and the use of off-season nurseries to grow additional generations per year, can cut the development time for new inbred lines to five or six years. With concurrent testing of new hybrids, the entire process can be shortened to six or eight years.

The development of transgenic corn containing proprietary insect resistant (Bt genes) and herbicide tolerant (Roundup Ready® and LibertyLink®) genes creates additional expense and workload for corn breeding programs. Each new gene or combination of genes must be incorporated into existing and newly developed elite inbred lines, requiring multiple generations of backcrossing. In addition, new versions of hybrids carrying each proprietary gene need to be generated and tested in replicated trials over many locations for several years. Since the proprietary genes are legally protected, usually by utility patents, corn breeders must obtain FTO for use of the new genes. This requires licenses and contracts that are sometimes quite complex.

3. MODIFICATIONS TO CONVENTIONAL CORN BREEDING PROGRAMS

3.1 *Conventional breeding programs*

Commercial corn breeding programs are fast paced and very competitive. Competitive breeding programs rapidly adopt new information technologies and biotechnologies. Developing new corn inbred parents and competitive new hybrids historically took ten years or longer. The

basic process can require eight to ten generations to obtain new homozygous inbred lines to use as parents, and four to five years of testing combinations to select new hybrids for commercial release. If done in sequence, this would require 12 to 15 years to develop a new hybrid. If breeders initiate hybrid trials during the years when new inbred lines are being self-pollinated, they can effectively cut the time required to ten years or less. A fast-track breeding protocol using off-season breeding nurseries (to provide two, and sometimes three, generations of self-pollinating lines per year) can decrease the time required to develop new homozygous inbred lines and hybrids to seven or eight years (Figure 1). To produce an additional one or two generations per year, it is essential that breeding programs utilize new technologies to harvest trials of experimental hybrids and to select lines to advance in off-season nurseries.

3.2 *Super-fast-track conversion programs*

Starting in the 1990s, breeders developed, through plant transformation, corn lines into which proprietary genes from organisms un-

Figure 1: Fast-Track Inbred Development and Hybrid Testing Protocol for Corn

Year 1		
Winter-1		Cross inbred 1 and inbred 2
Winter-2	F_1	Self
Summer	S_1	Self and cross onto tester
Year 2		
Winter 1	S_2	Self
Summer	S_3	Self and evaluate early generation tests
Year 3		
Winter 1	S_4	Self and cross onto more testers
Summer	S_5	Self, evaluate stage 1 hybrids, cross new lines onto (such as cytoplasmic male sterility [cms], insect resistance [Bt], or Roundup Ready® [rr])
Year 4		
Winter	S_6	Self
Summer	S_7	Self and evaluate stage 2 hybrids
Year 5		
Summer		Evaluate stage 3 hybrids
Year 6		
Summer		Evaluate stage four hybrids "on farm"
Year 7		
Summer		Evaluate stage five hybrids "on farm," make hybrid release decisions

related to corn were inserted into the corn genome. Important traits, such as insect resistance (Bt) and tolerance to herbicides (Roundup Ready® and LibertyLink®), were developed and made available to the seed corn industry. These traits were rapidly accepted by the industry worldwide, dramatically changing traditional corn breeding.

The genes for insect resistance and tolerance to herbicides provided traits that were advantageous for corn farmers; however, the first sources of these genes were in corn lines that were not very competitive. In order to be commercially useful, the genes had to be incorporated into elite inbred lines that produced competitive hybrids. The process of incorporating a new gene into a corn inbred line usually requires between seven and eight backcross generations, during which a source of the new gene is crossed to an elite inbred line. After this, selected progeny are back crossed onto the elite inbred line for seven or eight generations (Figure 2). Even if you used two or three backcross generations per year by employing off-season nurseries, you would still need three years to recover a version of an elite line that was essentially identical to the original inbred line but also expressed the new gene. Unfortunately, because every year new hybrids are developed that out-perform older hybrids by 5%–10%, the half-life of many corn hybrids today is three to five years. This means that by the time you could convert the parents of a commercial hybrid to a new gene through traditional backcross procedures, the sales of the hybrid would likely be in decline.

Figure 2: Backcross Breeding Protocol

Year 1			
Winter	Cross elite inbred	Source of a new gene	F_1
Summer	Elite inbred	F_1	BC1
Year 2			
Winter	Elite inbred	BC1	BC2
Summer	Elite inbred	BC2	BC3
Year 3			
Winter	Elite inbred	BC3	BC4
Summer	Elite inbred	BC4	BC5
Year 4			
Winter	Elite inbred	BC5	BC6
Summer	Elite inbred	BC6	BC7
Year 5			
Winter	Elite inbred	BC7	BC8
Summer	BC8 Selfed as new version of elite inbred		

Thanks to new technologies involving molecular markers, however, it is possible to backcross a new gene into an elite inbred in three to four total generations, rather than seven to eight.[1] This means that a breeding company can utilize a super-fast-track conversion program to backcross proprietary genes into elite inbred parents before the hybrids produced become obsolete (Figure 3). Seed companies are therefore able to acquire new genes and transfer them very rapidly into elite inbred lines. Of course, super-fast-track conversion programs are not cheap. The use of off-season nurseries and molecular markers to obtain the rapid conversions adds considerable labor and expense to the process of commercial corn breeding. Also, breeding companies must obtain regulatory approval for the gene construct being converted. Obtaining regulatory approval in countries normally used for off-season nurseries, such as Mexico, Chile, and Argentina, is difficult and time consuming. This means that off-season nursery conversion must be done on U.S. soil, basically in Hawaii, Florida, and Puerto Rico, creating additional expense.

4. CRITICAL BREEDING DECISIONS

4.1 *Which lines and how many to convert?*

A typical corn-breeding company sells a number of specific hybrids of different maturities and geographical adaptation. The major seed corn companies usually have ten to 20 elite inbred lines in commercial use, plus several hundred new lines nearing inbred status in the developmental pipeline. The decision about which, and how many, inbreds to enter into a fast-track conversion program requires a lot of thought and often some bold decisions. Since financial resources dedicated to research and development are limited, directing funds to fast-track conversion often requires redirecting resources away from use in conventional breeding. Critical decisions about how much fast-track conversion you can afford are often difficult to make.

4.2 *Which genes and how many to convert?*

A number of transgenes that are available from biotech companies have been inserted into corn. Each of these genes has different uses in different genetic backgrounds. The usefulness

Figure 3: Super Fast-Track Conversion Protocol

Year 1				
Winter	Elite inbred	Source of a new gene	F_1	
Summer	Elite inbred	F_1	BC1	BC1 progeny selected with PCR markers
Year 2				
Winter	Elite inbred	Selected Progeny at @ BC4 generation	BC5	BC5 progeny selected with PCR markers
Summer	Elite inbred	Selected progeny at @ BC8 generation	BC9	BC2
Year 3				
Winter	BC9 Selfed as new version of elite inbred			

of each gene must be monitored during the conversion process, since each gene may offer a trait desired by at least one segment of the population of farmers a seed company serves. Additionally, contractual restrictions often determine how and where genes can be deployed. Breeders must test lines undergoing conversion to measure the level of gene expression and to demonstrate that all plants undergoing conversion carry the gene in an active form. It is expensive to incorporate each gene into elite and newly developing inbred lines. It is even more expensive to do all the testing required by licensing agreements. In addition, each converted line must be tested in hybrid combinations that contain each gene, as compared to the same hybrids without the genes, to demonstrate that genetically modified, or GM, hybrids perform as well as non-GM counterparts. Of course, if different genes provide traits that are desirable individually, then the combination of two or more genes in the same hybrid offers an even more desirable product. Unfortunately, each gene needs to be transferred individually (Figure 3), exponentially increasing the costs of converting each line.

5. PROPRIETARY BIOTECHNOLOGY AND HYBRID DEVELOPMENT AND TESTING

5.1 *Conventional hybrid release process*

As new lines reach the second or third selfed generation, they are crossed onto one or several tester lines to generate hundreds of hybrids for evaluation. In stage one of hybrid testing, hybrids are evaluated at three to four locations in replicated, paired row plots (Figure 4). In stage two of testing, the best 10% of these hybrids are remade and tested in paired-row plots at ten to 20 locations. Subsequently, in stage three, the best 10% of stage two hybrids are advanced to paired-row plots at 50 to 100+ locations. The best of these, presuming that they have significant performance advantage over currently grown hybrids, are produced in quantities to allow testing at 100 to several hundred locations. For a period of two years, the hybrids are planted in paired-row plots and in strip plots (roughly one-tenth of an acre) and harvested using current farming practices; this comprises stages four and five of testing. After five years of small-plot and strip-plot testing at several hundred locations per year, the best-performing hybrids are approved for sale.

Figure 4: Stages of Hybrid Testing

STAGE 1	Hundreds of new hybrids, tested in paired-row plots, 1/1000th of an acre each in replicated trials, at three to five locations
STAGE 2	The best at 10% of stage one hybrids, tested in paired-row plots in replicated trials, at ten to 50 locations
STAGE 3	The best at 10% of stage two hybrids, tested in paired-row plots in replicated trials, at 30 to 100 locations
STAGE 4	The best ten to 15 hybrids from stage three, tested again in paired-row plots, replicated at 30 to 100 locations, and also tested in one-tenth-acre strip plots on farms at 100 to 200 locations
STAGE 5	The best five to ten hybrids from stage four, tested again in paired-row plots and in strip plots

5.2 *GM hybrid test process*

GM hybrids are hybrids that contain proprietary biotech traits introduced into corn from other species through plant transformation. These GM hybrids present several challenges to the hybrid release process. First, with new gene constructs, hybrid evaluation trials must be done under an experimental use permit. This imposes restrictions on the number of hybrids and testing locations, which means that fewer hybrids can be evaluated and more years are needed to obtain data sufficient to justify commercial release.

Second, licensing agreements often impose, for each hybrid, stringent requirements for degree of expression of proprietary genes. This requires expensive, time-consuming tests to be run on all hybrids being evaluated.

Finally, the number of hybrids that must be tested increases with every new proprietary gene or combination of genes used. Even if only three new genes are used, the number of hybrids to be tested in early generations goes from several hundred to nearly one thousand. If combinations of each of the three genes are developed, you can approach two thousand hybrids to test in early generations. Even at the later stages of testing, strip tests at several hundred locations per year can increase from eight to ten new hybrids, in conventional programs, to 40 to 50, if three genes with some two-way combinations are tested. Consequently, the number of genes and hybrids must be carefully selected or the costs and logistics become prohibitive.

Fortunately, breeders can use a fast-track hybrid release process to speed the release of new GM hybrids. If there are no detrimental effects from the proprietary genes being incorporated, and the backcross conversion process is carefully monitored to get converted lines that differ from the elite line by only one to a few genes, then performance of hybrids involving the converted lines will be very similar to the performance of hybrids involving the elite, nonconverted lines. Therefore, it is possible to decrease the five-stage, five-year testing process to three years. Usually, the converted versions of hybrids are tested only at stages three, four, and five. This means that once elite inbreds are fully converted to a proprietary gene, hybrids carrying that gene could be released within three years.

6. PARENT SEED AND HYBRID PRODUCTION

6.1 *Conventional process*

Traditionally, new inbreds are advanced from research programs to parent seed programs when the inbred performs successfully in one or more hybrid combinations in stage three of research testing, usually the third year of multilocation testing across a wide geographic area. Once advanced, the parent seed department starts increasing seed of the new inbreds and producing seed of the new hybrid combinations to build up quantities needed for commercial release. Often, three generations of seed increase are needed to produce enough inbred seed of a new female parent to allow for seed sufficient for commercial release.

Normally, only one of three or four new inbreds that make it to stage three of testing actually makes it to commercial release. During testing stages four and five (strip tests on farms at many locations for two or more years), many hybrids containing new inbreds are dropped. The seed of these inbreds and new hybrids is subsequently discarded.

6.2 *GM parent seed and hybrid production process*

Each biotech trait added to an inbred produces another version of the inbred that must be increased prior to potential commercial release. So, rather than increasing one version of a new inbred, you have to increase two, three, or even more versions, many of which are never sold in any hybrids. This greatly increases the costs associated with producing hybrid and inbred seed.

7. LICENSING AND CONTRACTUAL ISSUES WITH GM TRAITS

Proprietary GM traits and converted varieties are usually protected by some form of intellectual

property (IP) protection, which defines ownership of the traits, plants, or technologies. This protection may be in the form of utility patents, plant variety protection certificates, or trade secrets. Most transgenic plants embody numerous components and processes, each of which may have IP protection. You must make sure that anyone that supplies you with proprietary traits has legal access to all proprietary components and processes used in developing the genetically modified, or GM, traits. Suppliers of proprietary traits should be willing to include appropriate warranty clauses into any agreement you execute that protects you from any IP protection infringement that may arise from commercializing the traits.[2]

Several types of legal agreements are available for gaining access to proprietary traits and technologies. These may be as simple as material transfer agreements (MTAs), or as complex as commercial licensing agreements. Often, you can gain early access to proprietary genes and technology under research agreements. These allow you to obtain and incorporate proprietary genes into your germplasm, evaluate performance, and then choose only those genes that meet your commercial objectives before having to negotiate terms of commercialization. Proprietary genes and technology that you choose not to commercialize must be returned and plants containing those genes destroyed. This allows you to test a wide range of genes/technologies without having to pay royalties or fees. However, you should ensure that such research agreements contain a mechanism that allows you to commercialize those genes/technologies that you do select. Often, commercial agreements require an up-front payment to access the genes, and afterwards royalty payments based on volume and the price of products sold containing the proprietary genes. If you do not reach an agreement with the gene supplier regarding terms of commercialization before starting your research, you ought to at least agree that you will be offered terms comparable to the seed industry standard.

The contracts or licenses required to get access to proprietary genes often contain strict limitations on what you can and cannot do with the genes. It is important that all personnel who have access to the proprietary genes understand these requirements. Also, these contracts often contain specific tests or measurements that you must conduct to verify the purity and efficacy of the genes after you have crossed them into your germplasm. These tests take time and money to perform and sometimes require breeders to learn new skills.

Newly developed proprietary traits also must be approved by governmental regulatory agencies. Until approval is obtained, the traits must be grown under experimental use permits. These restrict the size and number of test plots that you can plant and require a lot of supervision and documentation. Experimental use permits also restrict your use of off-season nurseries. You cannot grow a GM trait in any country that has not approved the trait. This prevents the use of Mexico, Chile, or Argentina for off-season nurseries, which forces you to use Hawaii, Florida, or Puerto Rico. This raises costs and limits the flexible use of off-season nurseries.

8. CONCLUSION

Since this chapter was originally written, several proprietary biotech traits have been commercialized on large acreages throughout the world. As traits like the Bt gene have become commonplace in breeding programs, new source populations have been established in which both parents contain the Bt gene. This eliminates the need for fast-track or super-fast-track conversions and reduces the complexity of producing hybrids with that trait. However, as Bt and Roundup Ready® became commonplace, new transgenic traits have appeared. Thus, as companies reduce the workload and expense associated with the first generation of transgenic traits, new traits are increasing the complexity again. Also, transgenic traits for such crops as soybeans, cotton, and canola have been developed, extending the complexity to other crop breeding programs. This cycle of managing trait complexity will continue until the traits are no longer competitive, or until the patents expire. Many of the patents on first generation traits, and on the first patented inbred lines and hybrids, were issued in the last half of the 1980s, which means that both the traits and

patented inbreds became public property starting in 2006. This could have a large and positive impact on plant breeding programs, since programs will be able to access and utilize these off patent materials without restrictions. Several inbreds from Pioneer Hi-Bred International Inc. (now a DuPont Company) and DeKalb Genetics (now owned by Monsanto) were applied for in 1986 and subsequent years. The patents are valid for 20 years after the application date. That means that the first inbreds patented came off patent in 2006. Each year additional inbreds will come off patent. Even though 20 years old, some of these inbreds represent significant sources of elite gene combinations representing some unique heterotic groups that could upgrade public plant breeding germplasm in the temperate world. As I understand it, seed of the patented inbreds is supposed to be maintained by the American Type Culture Collection and made available upon request from the U.S. Patent Office for the purpose of demonstrating the validity of the material patented. Presumably, seed will not be maintained after the patents expire. ■

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1 See the section Plant Breeding 2 in citnews.unl.edu/hscroptechnology/lessonFrames.html for a review of marker assisted back crossing.

2 Kowalski SP, RV Ebora, RD Kryder and RH Potter. 2002. Transgenic crops, biotechnology and ownership rights: what scientists need to know. *The Plant Journal*. 31 (4): 407–21)