

Intellectual Property Rights on Research Tools: Incentives or Barriers to Innovation? Case Studies of Rice Genomics and Plant Transformation Technologies

Carl E. Pray

*Department of Food, Agriculture, and Resource Economics,
Rutgers University*

Anwar Naseem

*International Food Policy Research Institute, Addis Ababa,
Ethiopia*

This paper examines the role of patents in the development and use of two platform technologies for plant biotechnology—plant transformation techniques and structural genomics. We find that patents were important in inducing private firms to develop these platform technologies. Their development led to the commercialization of more genetically modified (GM) varieties more rapidly than would have been the case otherwise. We identified some examples of research and GM variety marketing that were slowed down by the patents on tools. However, our preliminary assessment of the evidence suggests that the benefits from patents on tools outweigh the costs.

Key words: genomics, holdup, intellectual property rights, patents, platform technology.

Introduction

Patenting of innovations from several types of biotechnology research has led to much debate among scientists and policy makers on the appropriate role of such intellectual property (IP) protection. These debates particularly focus on *platform technologies*, which are defined as specific technologies that can be applied to various research areas and that lead to a diverse set of innovations. Platform technologies include transformation methods to introduce foreign gene constructs into unrelated organisms and the sequencing and mapping of genomes that will help researchers identify the locations and functions of genes. The defining attribute of platform technologies is that whereas they generally have no direct commercial value to end users, they are a critical input to developing commercial products.

Considerable concern has been expressed by biotech scientists, legal scholars, and academics that the patenting of platform technologies and research tools may encumber downstream research. Eisenberg (2000) and Heller and Eisenberg (1998) fear that excessive patenting upstream would result in increased transaction costs for downstream innovators, stifling efficient research activities. In particular, there is great unease about “reach-through” provisions, which give patent holders of platform technologies the ability to extract rents from downstream innovators. Reach-through provisions not only increase costs for downstream innovators but also increase incentives for innovators to divert scarce research resources from product development to “reinventing the wheel” in order to go around existing roadblocks. In addition, there exists a real possibility that

upstream innovators might simply block or “hold up” the commercialization of some downstream technologies.

This paper examines the role of patents in inducing and constraining biotech research by way of two in-depth case studies of platform technologies: plant transformation techniques and the mapping of the rice genome. Each of these platform technologies are important for improving major field crops and are at the center of the debates about the role of patenting in biotechnology. Our first objective in conducting these two case studies was to understand the role of patents and the public sector in the development of these technologies. This objective is realized by an analysis of patenting by public and private sectors, a historical analysis to examine how research has evolved in these areas, and key interviews with researchers active in the field. Our second objective was to identify some of the benefits and cost of patenting of platform technologies. The benefits include more rapid development of new platform technologies, which can make downstream research more efficient; the costs are the increased expense of downstream research activities in both public and private sectors and less innovation. On the cost side, we looked specifically at examples of where research and/or innovation was stopped or slowed due to patents on platform technology. Our third objective was to draw lessons from these case studies about what the public sector might do to reduce the negative consequences of patents.

Table 1. Main transformation techniques.

Technique	Research conducted at	US patent holder/licensee	Remarks
Agrobacterium binary vector method	University of Leiden	US 4,940,838 Mogen (Netherlands); now owned by Syngenta.	30+% transformation in corn. Most commonly used transformation method.
Agrobacterium co-transformation method	Max Planck Inst. & Monsanto	Max Planck and Monsanto. US applications in interference proceedings until October 2004, when Monsanto was awarded patent in United States (Max Planck won in Europe).	Not extensively used.
Turn off agrobacterium virus	Washington University	US 6,051,757; US 6,051,409.	
Particle gun Helium Biorad	Cornell	US 4,945,050. Cornell owns patent; DuPont has license.	7–10% transformation.
Particle gun electric discharge	Agracetus	US 5,015,580 Agracetus. Monsanto now owns Agracetus.	7–10% transformation.
Silicon carbide fiber (“whisker”)	Zeneca	US 5,302,523 Zeneca.	<1% transformation.

Transformation Case Study

History

Most plant transformation technology came out of research conducted at public-sector labs. The major private biotech firms also contributed to the development of these techniques and now own (or have exclusive licenses to) all of the major technologies. Table 1 lists the main techniques of transforming plants along with the institutions where they were developed and the current owners of the technology. Scientists have performed controlled plant transformation with specific genes since the mid-1970s. The most common methods for the introduction of foreign DNA into plant cells uses latent *Agrobacterium tumefaciens*—bacteria in which the DNA of interest has replaced the disease genes. Another transformation method, known as *particle bombardment* or *biolistics*, uses rapidly propelled tungsten microprojectiles that have been coated with DNA. These DNA-coated particles are fired into plant cells, and the DNA of interest is often incorporated into the plant DNA.

The research to produce the first transformed plant (and particularly the first transformed plants of important commercial crops) had all the aspects of a classic research race. The genetic transformation of plants using *Agrobacterium* was first achieved in the early 1980s by four groups working at Washington University in St. Louis, Missouri; the Rijksuniversiteit in Ghent, Belgium; the Monsanto Company in St. Louis, Missouri; and the University of Wisconsin in Madison, Wisconsin. The university-based groups were primarily funded by public sources, although the researchers at

Washington University and the Rijksuniversiteit also worked as consultants for Monsanto. Taylor and Fauquet (2002) suggested that transformation methods based on the use of *Agrobacterium* are preferred by many scientists who find them easier to handle, less expensive to use, more efficient, and having a more predictable pattern of foreign DNA integration. However, they also noted that some of these advantages may not be as great as previously thought.

Agrobacterium was not successfully used on monocots until the 1990s, when the University of Washington, Seattle was the first to show transformation of a monocot cells, namely rice cells. However, they were unsuccessful in their attempts to produce a transformed rice plant. A Japanese scientist who worked in the Washington lab took a job at Japan Tobacco Industries and developed the technique of producing transformed rice plants.

The use of a particle gun for plant transformation was also developed in the early 1980s. The projectile gun was first developed in the 1980s at Cornell University by John Sanford, funded by the Cornell Biotechnology Institute. The first published report of using microprojectiles to transform living cells was in 1987. The first transgenic plants produced using this method were tobacco in 1988 followed by corn in 1990 (Taylor & Fauquet, 2002). The electric discharge particle gun was developed in the late 1980s by Dennis McCabe, Paul Christou, and colleagues at Agracetus.

Patenting of Transformation Technologies

The public and private groups working on *Agrobacterium* transformation mentioned above all applied for

Table 2. Patents on techniques used with *Agrobacterium*-mediated transformation of plants.

Technology	Property rights holder	Jurisdictions	Selected patents
Widely used markers in transformation			
Phosphinothricin (<i>bar</i> gene; herbicide resistance)	Hoechst/AgrEvo (now Bayer)	United States, Europe	US 5,767,371, 5,767,370, 5,668,297, 5,650,310, 5,637,489, 5,077,399, 5,276,268, 5,273,894
Antibiotic resistance gene under control of plant promoter	Monsanto	United States	US 6,174,724 B1
Kanamycin (antibiotic) resistance gene under control of CaMV 35S or 19S promoter	Monsanto	United States, Europe	US 5,034,322; EP 131,623 B2
Hygromycin resistance	Novartis (now Syngenta)	Europe, United States	EP 68,740 B1, 135,291 B1, 186,425 B1; US 4,727,028, 4,960,704, 5,668,298
Widely used reporter gene in transformation			
<i>gus</i> gene (β-glucuronidase)	CAMBIA	United States, Great Britain	US 5,268,463, 5,432,081, 5,599,670; GB 2,197,653
Widely used promoter			
CaMV 35S promoter	Monsanto	United States, Europe, Japan	US 5,352,605, 5,530,196, 5,858,742; EP 131,623 B2 (currently being opposed); JP 2,645,217 B2
	Rockefeller University	United States	US 5,110,732, 5,097,025

Note. Data from Pardey and Beintema (2001). The information provided above is fairly detailed but not exhaustive. The listed patents and applications are considered to be key documents, and some of them contain fairly broad claims. Note that other patents and applications not listed here are also relevant to the different elements forming part of the *Agrobacterium* transformation technology, marker, and reporter genes.

patents on their methods. Patents on one *Agrobacterium* transformation method were applied for by the Max Planck Institute in 1983 and by Monsanto in the same year. In the United States, these patent applications were in interference proceedings at the US patent office for almost twenty years. The Washington University group applied for a patent on the transformation of dicots with an *Agrobacterium* vector (US 6,051,757) in 1983, but it was not issued until 2000, almost 17 years after the application. Japan Tobacco holds the patent on using *Agrobacterium* to transform monocots (US 5,591,616), Cornell holds the patent on the Helium Biorad particle (US 4,945,050), and the patent for the electric discharge particle gun is held by Agracetus.

Table 2 shows some of the patents on the complementary inputs that are needed to produce transformed plants. Because the success of plant transformation depends very much on promoter sequences, a large number of promoters have been used in transformation. The promoter CaMV 35S and its derivatives have been used extensively. Like the different transformation techniques, the gene expression efficiency of a promoter varies for different plants and different parts of the plant. Two of the patents for which there seem to be few alter-

natives are the kanamycin marker gene (the alternatives are not easily available), and the patents on *Agrobacterium* transformation of dicots by Washington University and monocots by Japan Tobacco.

Researchers wishing to transform plants not only have to seek permission from the owner of the patents on the transformation methods but also have to contend with the patents on the promoter and marker genes as well as patents on the actual gene of interest that is being introduced in to the plant (e.g., a Bt gene or a herbicide tolerance gene). Compounding this further is the fact that a novel plant variety may also be patent protected.

Impact of Patents on Progress in Transformation Technology

The result of patenting and the incentives that have been created has been continuous progress in transformation technology. The patent holders and their collaborators have increased the efficiency of each technique, they have extended the most efficient techniques to new plants, and they have developed some new techniques, all of which have acted to reduce the cost of genetically transforming plants.

Since 1990, some of the most important increases in efficiency have been from improvements in existing transformation techniques and moving these techniques to new crops or classes of plants. The last column of Table 1 shows the differences in efficiency of the different transformation techniques as estimated by public and private sector scientists in 2001. Japan Tobacco's achievement of transforming monocots with *Agrobacterium* greatly increases the grain transformation efficiency. This method of using *Agrobacterium* to transform monocots led to a drop in the cost of transforming grain crops for several reasons: First, there is no need for expensive machinery, such as the particle gun; second, because one does not have to shoot and reload the gun, with *Agrobacterium* it is possible to do hundreds of transformations simultaneously, making it more effective for high-throughput screening; third, the probability of transformation is increased; and fourth, some scientists argue that *Agrobacterium* produces a "cleaner" pattern of DNA integration, which reduces the cost of biosafety regulation.

Impact of Patents on Research Investments and Innovation

Did patents on transformation techniques slow down the development of new genetically modified crops? Officials from American Cyanamid claimed that they were delayed in their attempt to make herbicide-tolerant maize and rice by Cornell's exclusive licensing of the particle gun to DuPont. Negotiations between DuPont and Cyanamid were protracted because the two were competitors in one of the herbicide markets. The companies were never able to come to a deal that they both felt was acceptable, and Cyanamid had to spend several more years in research before it could produce herbicide-tolerant crops.

Other interviews suggested that a problem for companies using some transformation technologies is that the ultimate ownership of the many patents remains largely unknown. The owner of certain patents and technology could be a competitor; that competitor could then block the use of varieties developed using that method unless large royalties were paid. For example, there were patent interference proceedings in the United States that went on for 20 years between at least four parties that claimed *Agrobacterium* methods—the Max Planck Group, the Mogen/Zeneca group, the Washington University group (who licensed it to Syngenta), and Monsanto. Given the difficulty with establishing who owns *Agrobacterium* transformation methods, Dow

chose not to use it in its transformation work and instead uses the less efficient whisker technique.

Patents on transformation technologies were one of the reasons that Japanese companies got out of biotech (K. Shimamoto, personal communication, November 21, 2001). They had their own transformation techniques (PEG mediated), but they needed the promoters and the marker genes. They negotiated with Monsanto and others but could not reach anything that they felt was a reasonable deal—they felt that no matter how much they offered, Monsanto and other companies would have refused.

Another example of a holdup was described by former seed industry employees (who wished to remain anonymous in 2002) and concerned Liberty Link (Basta herbicide resistant) corn. AgrEvo bought Plant Genome Systems in 1995, which at the time was doing research on Basta-resistant corn.¹ AgrEvo did several years of research to develop Basta-resistant corn, in the belief that the Basta resistance gene was not patented. To avoid patent conflicts, AgrEvo used a nonproprietary transformation technique (protoplast fusion). AgrEvo partnered with Holdens Foundation Seed Company to develop Basta-resistant corn parental lines and hybrids. Holdens had prepared enough foundation seed to produce up to a million acres of Basta-resistant corn, which would be produced and distributed to the seed companies that were their customers.

However, the DeKalb's patent claimed Basta-resistant corn made with any transformation processes. DeKalb asked Holden's customers for a technology fee of \$12 per bag of seed or face the prospect of being sued. Holdens told its customers that they would have to get licenses from both DeKalb and AgrEvo to be sure that they did not violate any patents, even though AgrEvo challenged the validity of the DeKalb patent. This slowed the commercialization of herbicide-resistant corn for at least a year or two until DeKalb could increase its production of LibertyLink and eventually Roundup Ready corn.

Another major cost of the patenting system is the cost of lawsuits, which can easily cost millions of dollars to litigate. One example of such a suit was filed on July 25, 2002, in Delaware. Syngenta claimed that Monsanto and Delta and Pineland infringed their patents on *Agrobacterium* to transform dicots such as cotton and soybeans. Syngenta believed that Monsanto should

1. *Basta is the commercial name of LibertyLink herbicide outside the United States.*

either start paying royalties on their Bollgard, Yieldgard, and Roundup Ready crops, or stop selling them (Syngenta, 2002). Monsanto launched countersuits; this became a long, expensive battle that was not settled for several years.

Rice Genome Case Study

There are a number of reasons why the study of rice genomics as a case study for IP issues is useful. First, rice was one of the first commercially important crops that had its genome sequenced. As such, any IP issues that were specific to genomics research would therefore become known in the course of the sequencing effort of the rice genome. Second, due to its close genetic relationship to other complex but commercially lucrative crops such as corn, private-sector firms have made significant investments towards sequencing the rice genome. The behavior of the private sector and how it uses intellectual property not only to protect its discoveries but also in the research process is instructive. We also explore the role that public-sector technology had on the sequencing efforts and their relationship to the private sector.

History

Sequencing of the rice genome began in earnest in the late 1990s, but much of the groundwork was laid in the two preceding decades, when a series of methods used in determining the sequence of base pairs of DNA ultimately led to investments in the different genome projects. In the late 1980s, the United States Department of Agriculture funded the Plant Genome Project to develop genetic maps for more than 50 crops (McCouch, 2001), which were used in plant breeding activities. Starting in the late 1980s, the Rockefeller Foundation funded rice mapping research at institutes in developed and developing countries; Cornell University served as headquarters of the gene mapping project. In 1991 the Japanese government started a large project (> \$5 million per year) to map the rice genome.

It was initially assumed that a map had to be developed for each crop, as the mapping was considered commodity specific (McCouch, 2001). This thinking changed as molecular linkage data suggested an entire plant family could be studied as a single genetic system. The most extensive accumulation of data supporting this concept has been for the grass family.² It was observed that one could arrange the chromosome of various species in concentric circles such that a radial line from the central species with the smallest genome would pass

through regions of similar genetic content of other species (Phillips & Freeling, 1998). For the case the grass family, rice had the smallest genome and became the natural candidate to have its genome extensively studied and sequenced.³

To take advantage of the advances in sequencing technology and to coordinate the sequencing of rice, the International Rice Genome Sequencing Project (IRGSP), led by Japanese government researchers, was launched. Initially IRGSP was a 10-year, \$200 million project consisting of research institutes in 10 countries in Asia, Europe, and the Americas. These groups divided up the genome of a *japonica* rice ('Nippon-barre' variety) and aimed to have 40% of the genome sequenced by 2003 and the whole genome sequenced by 2008 (Higo, personal communication, November 19, 2001). Budgets were increased in 1998, with the Japanese government committing \$20 million a year for sequencing and another \$28 million a year for functional genomics, building a cDNA library, and DNA marker research. The rice sequencing research effort obtained \$12.5 million from the US government starting in 1999.

At the same time, parallel efforts were going on in the private sector. Monsanto, Syngenta, and others were funding their own proprietary rice maps. Celera offered to map completely the rice genome for \$30 million, but no one took them up on the offer. Monsanto had its map constructed by the University of Washington, Seattle in the laboratory of Dr. Leroy Hood. Both Monsanto and Syngenta mapped the same genome as the public-sector project. Syngenta worked with Myriad Genetics and the Clemson University Genomics Institute (Syngenta, 2001).

On April 5, 2000, Monsanto announced that it had produced a map of the rice genome that was nearly complete and was making its map and its collection of genes and information available to the Japanese Rice Genome Project (Monsanto, 2000). On January 26, 2001, Syngenta and its partner Myriad Genetics announced that they had completed the sequencing of the rice genome, using Myriad's proprietary DNA sequencing technology. In April 2002 Syngenta and the Beijing Genetics

-
2. *The grass family consists of five principal subfamilies and about 10,000 diverse species, including important food crops such as rice, wheat, and maize.*
 3. *McCouch (1998) reports that initially the USDA sponsored Plant Genome Initiative were focused on applying genomic research to the study of maize due to its commercial importance.*

Institute both published nearly complete drafts of rice genomes in *Science*. The cost of the Syngenta project was \$30–50 million (S. Shantaram, personal communication, October 28, 2002). Syngenta said that it hoped to make most of the information they discovered available to legitimate scientists working on the problems of the poor. Originally they had hoped to make money from this project by selling information from their database to other biotech and seed firms.

The Beijing Genomics Institute, a Chinese public research group, announced completion of the sequencing of the genome of the first *Indica* hybrid rice cultivar in 2001, using the whole-genome shotgun approach that covered at least 95% of the genome (“Scientists draw map,” 2001). In January 2002 the group announced that it was making all of the information publicly available. The IRGSP (which used the slower but more complete piece-by-piece sequencing method) produced a nearly complete genome map in December 2002 and published the completed rice genome in August 2005 three years ahead of schedule (Normile, 2005). It makes all of its findings available on the web through GenBank as the discoveries are made.

Competition between the public sector and the private sector clearly accelerated the research and disclosure of the components of the rice genome. Celera’s 1999 offer to sequence the entire rice genome was a wake-up call to the Japanese government, which substantially boosted its investment in rice sequencing. The announcements by Monsanto in 2000 and Syngenta in 2001 that they had draft maps of the rice genome were a further stimulus to Japanese government spending. Monsanto’s provision of their BAC library and map to the IRGSP increased the productivity of the public research program (Normile, 2002). Monsanto’s disclosure of their data and then news that the BGI was about to publish their draft of the *Indica* genome may have induced Syngenta to publish their findings in *Science* and make their genomes available to the IRGSP in the spring of 2002. These developments in turn stimulated IRGSP, which published the complete rice genome sequence in August 2005.

The Public and the Private in Genome Sequencing and Role of IPRs

The historical overview of the race to sequence the rice genome provides us a basis to discuss the incentives behind the sequencing efforts of the private and public sectors. In particular, we ask to what extent patents spurred innovative behavior and whether they may have

hindered the sequencing effort in any way. It is interesting to note that in the long list of citations to the technical antecedents of the genome project, some tools have been patented whereas others have not. Consider the sequencing techniques that were developed by Nobel laureates Fredrick Sanger or Walter Gilbert, which were never patented but, as suggested by Cook-Deegan (1994), were surely patentable. These sequencing techniques are central to today’s automated genomic research. Some of the earliest molecular markers that were used extensively in mapping (such as RFLPs) were also developed in the public sector but also never patented.

Although there were some patents granted early on for simply base pair sequences of the genes, such sequences can no longer be patented unless there is strong evidence of the utility of the gene that has been sequenced. Thus, the raw output of the sequencing process cannot be patented, and the entire sequence or map of an entire genome of a plant also does not seem to be patentable in the United States.

Patents do exist on enzymes, sequencing machinery (computers, biochips, robots, etc.), and software. Lab instruments such as DNA sequencers and DNA synthesizers are sold with the price of the instruments, the required reagents, and the royalties on the patents all bundled together. The issue, of course, is not so much whether a technology is simply patented but the way it is disseminated so that other researchers can put it to productive use. Some of the specialty companies that do contract functional genomics rely on patented software. Further downstream, genes that can be shown to have a useful purpose can be patented if they also meet the novelty and nonobviousness requirements of the patent law. Methods for finding and identifying these genes can also be patented.

Private investments induced in part by patents on research tools have made an enormous contribution to the research process. Sequencing equipment and the microchip arrays were based on ideas developed at universities. These ideas and technologies were patented and then licensed to private startup companies such as Affymetrics and Applied Biosystems that were able to attract venture capital and greatly improve the efficiency of these techniques. Sales of these technologies increased rapidly in the private sector, pulled by the demand from the human genome project and medical research.

Did patents hinder the rice sequencing effort? It seems clear that patents did drive up the cost of equipment above what it would have been in the absence of

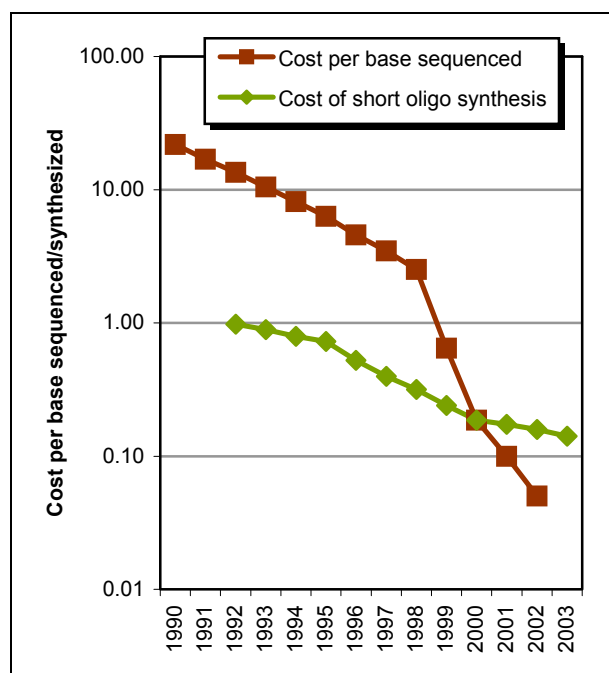


Figure 1. Cost per base of sequencing and synthesis.

Note. Data from Carlson (2003).

the patents. On the other hand, patents led to an immense increase in the efficiency of sequencing, as shown in Figures 1 and 2. Over the course of a decade, the productivity of the sequencing technology has improved exponentially. Figure 1 estimates the potential daily productivity of DNA sequencing based on three commercially available machines as of 2002—those manufactured by Applied Biosystems, Egea Biosciences, and Pyrosequencing AB. The productivity of the most widely used synthesizer—the ABI Synthesizer—has increased from 80,000 bases sequenced per person per day in 1994 to 30 million in 2002.⁴

This increase in productivity has been much greater than the increase in the cost of machinery and chemicals, and as a result the cost of sequencing has decreased dramatically (Figure 2). It was estimated in 2000 that the cost of sequencing fell by a factor of 100 in 10 years to between \$.10 and \$.20 per base and was still falling (Casey & Stodlolsky, 2000). Shifts to new technologies and increased capability at lower cost will ensure that these trends continue. A major cost saving is due to automation, which means that labor is only required to load the samples on the machines, a task that could be

4. These estimates include the time required for preprocessing and sample handling on each instrument but do not include the time required for sequence analysis.

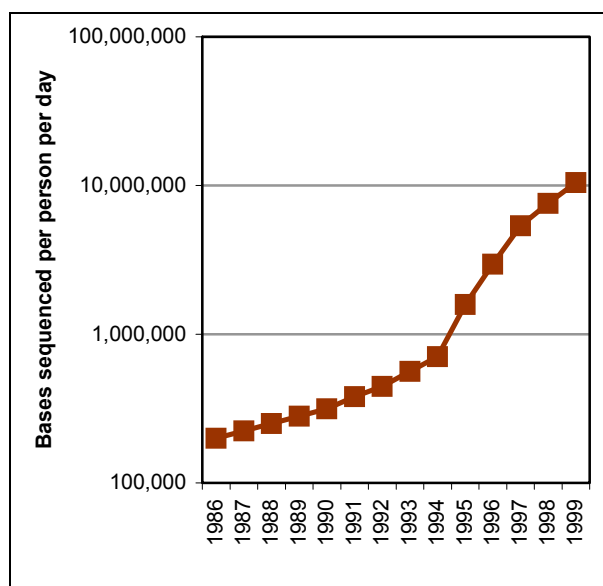


Figure 2. Productivity improvements in DNA synthesis (ABI sequencers).

Note. Data from Carlson (2003).

done by a technician. Leaders of the Japanese rice genome project reported that the new sequencing machinery that they bought from Applied Biosystems in 2000 increased the speed of their sequencing process by five times over machinery that they had bought five years earlier (Higo, personal communication, November 19, 2001).

It is also noteworthy that the public-sector sequencing effort of the rice genomes has greatly benefited from the draft sequences produced by Monsanto and Syngenta (Sasaki & Burr, 2002). By combining the Monsanto sequence data with the data that it was generating, the IRGSP was able to generate high-quality sequence data which helped accelerate its sequencing effort. Syngenta's decision to provide its draft sequence to IRGSP in 2002 also was useful, as it helped reduce the gaps in the physical map (Sasaki & Burr, 2002).

However, one should be mindful that initial release of the Monsanto and Syngenta data was not completely unrestricted. When Syngenta published its results of the rice genome in the journal *Science* in 2002, it did not release the data to GenBank, which was the norm for articles published in *Science*. Rather, the data was put up on Syngenta's website and access was restricted to academic researchers, who ceded any commercial applications of their research to Syngenta (Butler, 2002). When Monsanto's data was first released in 2000, it also was accessible only when researchers agreed to certain conditions. Many researchers were wary of signing up for

these databases, as they felt that the withholding of such information is contrary to the appropriate conduct of scientific inquiry (Butler, 2002). Moreover, the demand for access to such data was low, perhaps because the Beijing Genomic Sciences had released its data to GenBank and IRGSP was making its data available once it was sequenced. It has been reported that after the initial announcement by BGI and Syngenta, 350 researchers accessed the BGI data on GenBank and only 65 used the Syngenta data (Ho, n.d.). The low demand for their proprietary information may have contributed to Syngenta's decision to donate the rice data to IRGSP.

The rice genome sequencing effort was therefore a rather unique research process where the roles of the public and private sectors clearly departed from the traditional linear research paradigm of basic-applied-developmental research. Although many of the initial techniques involved in sequencing were developed by the public sector and later perfected and commercialized by the private sector, both public and private sectors actively engaged in competitive behavior followed by collaborative effort. There is little evidence to suggest that there were any hold-ups in the actual sequencing phase. This is because (a) the cost of sequencing has been rapidly decreasing, making sequencing technology more accessible and widespread, and (b) there was sharing of sequence data that helped the public sector meet its goal quickly.

Perhaps the main negative impact of the patenting of research tools for rice genomics in its initial phases was to drive up the initial capital cost required to enter the sequencing business. This meant that large government organizations (such as the Japanese government) or large corporations (like Monsanto and Syngenta) were the only entities who could realistically get into this game. The knowledge gained by the two large corporations may have given them a substantial advantage in the race to identify and patent useful genes.

So far these genome projects have not had many obvious impacts at the farmer level. The Rice Genome Project (RGP) in Japan is probably typical. It is generating an immense amount of knowledge but no useful technology so far. There are no transgenic rice varieties planted commercially in Japan or anywhere else in the world. It is unlikely that there are any rice varieties in which marker-aided selection based on the RGP played a big role. Finally, although the identification of genes is accelerating due to the use of map based cloning, only 15–16 genes had been identified using this technique by the end of 2001 (Higo, personal communication, November 19, 2001).

Conclusions

This paper indicates that these two platform technologies—plant transformation techniques and structural genomics—required major investments in research by the public sector to initiate their development and to continue to ensure that they made progress. The paper also indicates that private firms played a major role in the development of these tools.

Would the private sector have made the investments they made if they had no patents or exclusive licenses on these research tools but could protect the biotechnology products that they sell to farmers and consumers? This scenario would have been possible, because many of the key technologies (or close substitutes) were developed by or at least conceptualized by public-sector scientists, and the public sector could have patented them and then licensed them free of charge or at a nominal fee. Our reading of the evidence is that it is very unlikely that there would have been as much investment in the improvement of these technologies—particularly in the case of tools for genomics. The lower levels of investment probably would have slowed the improvement and reduced the development of downstream technology. The patents on the plant transformation techniques and the sequencing equipment, chemicals, and software allowed the university or government scientists who developed these techniques to interest venture capital or large firms in financing startup companies and research to improve these techniques. Venture capital supported the firms that developed the techniques that could be used both in human and plant genomics, such as biochips (Affymetrics) and automation of sequencing (Applied Biosystems). Large companies, such as DuPont and Japan Tobacco, financed the improvement of the biolistic system and the application of *Agrobacterium* to monocots.

Monsanto and Syngenta did not need patents on DNA sequences, the rice maps, or the rice genome to invest in the sequencing process. They wanted the information from sequencing the rice genome to help them find genes of rice, corn, and other grain crops, which they could identify the function of and then patent. The sequencing information could also be useful in marker-aided selection of conventional varieties.

The role of the public-sector research and research funding was also essential for the rapid development of these technologies. Government-funded research at universities and public research institutes produced most of the key concepts or actual platform technologies. Much of the improvement of the plant transformation technol-

ogies then took place in the private sector motivated primarily by the companies' need for efficient methods to produce transgenic varieties for commercialization. In the gene sequencing case, much of the efficiency improvement of sequencing was generated by private-sector firms, but the enormous investments by governments and foundations in the human genome project ensured them a market for improvements in sequencing techniques. These same techniques were then available for use by rice genome sequencers who were funded by the Rockefeller Foundation, the Japanese government, and other governments, as well as the private sector.

However, it does seem clear to us that government-funded research on plant transformation technologies or genomics without patents on research tools would not have been enough to develop the research tools that are available today. The competition for scientific recognition and prestige, along with government funding of research, was a motivating factor for public scientists to develop technology. This would have kept improvements in basic technology going, but less quickly because the venture capital, corporate money, and business incentives would not have been there.

The patents on plant transformation technology did produce some identifiable holdups, which slowed the commercialization of some herbicide-tolerant plant varieties by a few years. A more important impact was perhaps their impact on industry structure. The difficulty of getting access to the whole package of plant transformation technology appears to have kept some firms from entering the plant genetic engineering business. Likewise, the large upfront investment needed to get into gene sequencing has limited this technology to major companies and large consortia of publicly funded research institutes. This limited access gives the major companies an advantage in seeking and patenting important genes for commercial use. Both the major companies' control of transformation technologies and their information advantage work together to strengthen the leadership position of Monsanto and Syngenta in the plant biotechnology industry and make it more difficult for new firms to enter the industry.

The net impact of patents on research tools at this time seems to have been positive. They have stimulated research on these tools that have led to major increases in their technical efficiency. These increases in efficiency have dramatically reduced the cost of sequencing despite the high price tag on the equipment. The cost of plant transformation has also dropped dramatically—although possibly much more for the patent holders than the licensees. Our impression is that the benefits in

terms of improved technology to farmers have outweighed the few examples of holdups that we were able to find. However, we were not able to get any numbers to quantify either the benefits or costs, so no firm conclusion is possible at present.

References

- Butler, D. (2002). Geneticists get steamed up over public access to rice genome. *Nature*, 416(6877), 111-112.
- Casey, D., & Stodolsky, M. (2000). On the shoulders of giants: Private sector leverages HGP successes. *Human Genome News*, 11(1&2).
- Carlson, R. (2003). The pace and proliferation of biological technologies. *Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science*, 1(3), 203-214. Available on the World Wide Web: http://www.molsci.org/~rcarlson/Carlson_Pace_and_Prolif.pdf.
- Cook-Deegan, R.M. (1994). Origins of the human genome project. *RISK: Health, Safety & Environment*, 5, 97-119.
- Eisenberg, R. (2000). Genomics in the public domain: Strategy and policy. *Nature Reviews Genetics*, 1(1), 70-74.
- Heller, M.A., & Eisenberg, R.S. (1998). Can patents deter innovation? The anticommons in biomedical research. *Science*, 280, 698-701.
- Ho, Mae-Wan (n.d.) *Public/private partnerships: Too close for comfort?* London: The Institute of Science in Society. Available on the World Wide Web: <http://www.i-sis.org.uk/RiceIsLife1.php>.
- McCouch, S.R. (2001). Genomics and synteny. *Plant Physiology*, 125(1), 152-155.
- Monsanto. (2000, April 4). *Scientists achieve major breakthrough in rice; data to be shared with worldwide research community* [news release]. St. Louis, MO: Monsanto Company. Available on the World Wide Web: <http://www.monsanto.com/monsanto/layout/media/00/04-04-00.asp>.
- Normile, D. (2002). From standing start to sequencing superpower. *Science*, 296, 36-39.
- Normile, D. (2005). Genomics: Painstaking approach pays off for rice sequencing project. *Science*, 309, 997.
- Pardey, P., & Beintema, N. (2001). Losing ground? What's happened with agricultural research in less developing countries (background paper). *UNDP Human Development Report 2001*. United Nations Development Programme.
- Phillips, R.L., & Freeling, M. (1998). Plant genomics and our food supply. *Proceedings of the National Academy of Sciences*, 95, 1969-70.
- Sasaki, T., & Burr, B. (2002). *IRGSP response to publication of draft sequences of the rice genome*. Available on the World Wide Web: <http://demeter.bio.bnl.gov/March28.html>.
- Scientists draw map of rice genome. (2001, October 13). *China Daily*.

Syngenta. (2001, January 26). *Researchers complete rice genome map* [news release]. Basel: Syngenta. Available on the World Wide Web: <http://www.syngenta.com/en/media/article.aspx?pr=010126&Lang=en>.

Syngenta. (2002, July 26). *Syngenta files suit to enforce biotechnology patents* [news release]. Basel: Syngenta. Available on

the World Wide Web: <http://www.syngenta.com/en/media/article.aspx?pr=072602&Lang=en>.

Taylor, N.J., & Fauquet, C.M. (2002). Microparticle bombardment as a tool in plant science and agricultural biotechnology. *DNA and Cell Biology*, 21(12), 963–977.