Intellectual Property Rights on Research Tools—Incentives or Barriers to Innovation?

Case Studies of Rice Genomics and Plant Transformation Technologies

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I. 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 protection. These debates particularly focus on platform technologies, which are defined as specific technical developments that can be applied to various research areas and which could potentially give rise to multiple and 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 location and the functions of those genes. The defining attribute of platform technologies is that whereas they have generally no direct commercial value to end users, they are often a critical input to developing such 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 (2000a) and Eisenberg and Heller (2000) 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 would not only increase costs for sequential innovators, but would also increase incentives for upstream innovators diverting scarce research resources. In addition there exist a real possibility that upstream innovators might simply block the commercialization of some downstream technologies.

Compounding these issues is the legal and ethical matter of whether private agents should be permitted to patent or license innovations that build on years of research by the public sector and then withhold them from other public and private research institutes. The public sector's approach to research activities comes from a longstanding tradition of open science, which calls for free flow of new knowledge in the public realm. This spirit of sharing public knowledge will be eroded if patents on innovations that build on public knowledge are used to ultimately prevent the sharing of the knowledge.

This paper examines the role of patents in inducing and constraining biotech research by way of two in-depth case studies of platform technologies namely plant transformation techniques and the mapping of the rice genome. Both these platform technologies are important for improving the 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 is 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 is to identify some of the benefits and cost of patenting of platform technologies. The benefits include more rapid development of new platform technologies while the costs are the negative impacts on downstream research activities in both public and private sectors. Specifically, we search for evidence of hold-ups of technologies that slow the pace of downstream research and reduce efficiency. Our third objective is draw lessons from these case studies about what the public sector might do to reduce the negative consequences of patents.

The paper is organized as follows: Section 2 provides a conceptual framework for analyzing instances that lead to hold-ups and strategies that could be used to circumvent them. Section 3 contains the transformation case study. Section 4 presents the case of rice genome mapping. Section 5 attempts to draw some common lessons from both case studies and discusses ways in which we develop some quantitative analysis of these issues.

2. Conceptual Framework

Patents are a government intervention that can help provide incentives to research by "privatizing" the public goods aspect of innovations by sanctioning monopoly rights of an innovation to the inventor for a limited period of time. In exchange, the inventor is required to reveal all information related to the innovation so that other researchers can build on the disclosed knowledge. In effect, patents provide the necessary incentive to conduct research and disclose new knowledge, but at the social cost of limiting the widespread utilization of the innovation during the life of the patent.

At issue is how large the social costs are and whether effective mechanisms exist for efficient bargaining between the suppliers of inventions and its consumers. This in turn depends on the nature of the technology and the number of follow on users of the innovation. Consider, for example, the stylized view of sequential innovations as shown in figure 1. The development of a significant commercial technology (C) may require intermediate technologies (denoted B_1 to B_n), either collectively or individually. These intermediate technologies may themselves be due to a key precipitating technology (denoted A).[1] If both A and B are patented (or patentable), then of interest is the impact A will have on the development of any the B technologies. Scherer (2002) identifies two possibilities. First,

[1] Technology A itself builds on prior knowledge and technologies as indicated by the arrows left of A.

patent *A* might be so critical in the development of *B* intermediate technologies, that without patent *A*, technology *B*, and thereby any subsequent commercial possibilities, may not occur. Second, a less extreme variation of this possibility would have *A* reducing developmental cost of *B*, without necessarily preventing the development of *B*. In either case it is clear that *A* confers upon *B* (and thereby the commercial technology) some benefits that may not be realized without its absence. A correct evaluation of the value of *A* would there have to account for any direct commercial value of *A* plus the indirect benefits that result from *B* due to A. If *A* is indispensable in the creation of *B* then a relatively large share of indirect benefits will go to the owners of *A*. On the other hand if *A* simply reduces the production cost of B, then the benefits would be relatively small.

If *A* has no commercial value as a stand alone technology, but is valuable to only a small set of *B* technology owners then it is easy to see the circumstances under which holdups occur. First, in the presence of patents, the patent holder of *A* by exercising her monopoly position may extract rents from the owners of *B* and possibly *C*. Given the uncertain nature of technology development (risk, asymmetric information) efficient bargaining may not be possible. Technology owner *A* could therefore threaten to hold up the development of *B* unless it receives a large share of the benefits. If the claims of the *A* technology patent are sufficiently broad, then a greater number of downstream innovators will be affected from such hold-ups.

Second, in the absence of patents, it is unclear whether *A* would even be developed. The development of *A* might require large R&D investments that can only be recovered if profits can be appropriated through patents. Without patents or any other type of government intervention, such as R&D subsidies, *A* may never come into existence. If *A* is critical in *B*'s development then the absence of patents creates a more serious type of holdup as there is no possibility of any bargaining if *A* simply does not exist.

How might holdups due to a patent monopoly on a platform technology be circumvented? One possibility would be where the development of *B* technology depends on not just one A, but multiple *A*s as illustrated in figure 2. Here, intermediate technology holders could source any of the holders of *A* technology to develop the commercial product as the market for *A* technology would be competitive. For this to occur, one must assume that there exist several technology *A*s that are broadly substitutable. Technological limitations and small markets are just two reasons that might preclude such possibility.

Government policy towards R&D that encourages several pathways of technology development would limit holdups. These policy instruments such as R&D grants and

subsidies including support for public research would complement patent policy in providing the necessary incentive and push for technology development. Whatever policy is employed, it is clear that a balance needs to be sought that results in technology generation [i.e. the creation of *A*] while providing a sufficiently competitive environment that does not cause the monopolization of key platform technologies.

The sequential schema presented above is admittedly a very simple characterization of technology development. The more realistic case is one where new commercial technology is a consequence of the convergence of several pathways as illustrated in figure 3. Here different precursor technologies (*A* technologies) lead to the development of B technology which ultimately results in a commercial technology. A classic and contemporary example is the case of vitamin A rice which required negotiating licenses on 70 patents originally held by about 30 institutions. If all the different platform technologies represented by the *A*s are required for the development of *B*, then the hold up problem is further amplified and more severe.

We next seek to explore, by way of our case studies, whether holdups have occurred in practice and, if so, how researchers have overcome the constraint. For each case study we begin first by giving a brief historical overview of the technology to assess the role the public sector has contributed. Second, based on our preliminary interviews and available literature, we identify some of the key patents in this area. Then we assess the impact of patents and public sector research on developments of the platform technology and finally identify hold-ups due to patenting.

3. Transformation Case Study

3.1 History

Most of the 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. The main techniques of transforming plants are listed along with institution where they were developed and the current owners of the technology in Table 1. Scientists have performed controlled plant transformation with specific genes since the mid-1970s. One of the most common methods for introduction of 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 coated particles are 'fired' into plant cells and the DNA of interest is often incorporated at random 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 was first achieved in the early 1980s by four groups working independently at Washington University in St. Louis, Missouri, the Rijksuniversiteit in Ghent, Belgium, the Monsanto Company in St. Louis, Missouri, and and the University of 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. Most initial successful transformations were limited to tobacco, although a Wisconsin group had successfully inserted a bean gene into sunflower. During the 1980s the plants that could be transformed using the *Agrobacterium* method was increased to include most dicots such as cotton in 1987 and soybeans in 1988.

The second major category of transformation techniques uses some type of particle gun. The problem was that agrobacterium did not work will in corn and soybeans and so another transformation method was needed. The use of a particle gun for plant transformation was also developed in the early 1980s. The projectile gun, called the Helium Biorad particle gun, was developed at Cornell University by John Sanford funded by the Cornell Biotechnology Institute in the 1980s. The first published report of using microprojectiles to transform living cells was in 1987. The first transgenic plants produced using this method was tobacco in 1988 followed by corn in 1990 (Goldberg 1995). The electric discharge particle gun was developed in the late 1980s by Dennis McCabe, Paul Christou, and colleagues at Agracetus. Agracetus published an article describing the transformation of soybeans in 1988.

Agrobacterium was not successfully used on monocots until the 1990s. As such, initial successful transformations of grain crops used the polyethylene glycol (PEG) induced DNA uptake, the electroporation and the microprojectile bombardment-mediated (biolistic) gene transfer method. The majority of the successful transformation of grain crops that have been reported have been due to the biolistic method. Transformation methods based on the use of *Agrobacterium* are preferred in many instances because of the following properties: (i) they are easy to handle, (ii) they have a higher efficiency, and (iii) there is a more predictable pattern of foreign DNA integration (Ignacmuthu et al., 2000). The U. of Washington, Seattle was the first to show transformation of rice cells with *Agrobacterium* in a callus but they did

not produce a transformed rice plant. A Japanese scientist who worked in the U. of Washington lab took a job at Japan Tobacco Industries and developed the technique improving the efficiency of transformation and producing transformed rice plants.

3. 2 Patenting of Transformation Technologies

One can think of three types of patents that are important for plant transformation. The first, most obvious type is a patent on the transformation system itself e.g. the agrobacterium mediated system or the biolistic gun. The second type of patent is on the all of the components of the system that make the transformation possible – anti-biotic resistance genes for selecting transformed e coli, promoter genes that make the added gene work effectively in the plant, etc. Third, there are patents on the use of these transformation systems or on novel in specific crops or classes of crops.

The public and private groups working on agrobacterium transformation that were mentioned above all applied for and received patents on their methods. Patents on one *Agrobacterium* transformation method was applied for by the Max Planck Institute in 1983 and by Monsanto in the same year. In the U.S. these patent applications are still in interference proceedings almost twenty years later. The Washington University group applied for a patent on the transformation of dicots with an *Agrobacterium* vector (US 6,051,757) in 1983, but was issued to Washington University in 2000, almost 17 years after it was applied for. It is not clear whether this was by accident or design, but it is clearly more valuable now that it would have been in 1983. Japan Tobacco holds the patent on using *Agrobacterium* to transform monocots (US5591616), 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 provides a detailed inventory of all patents issued and related to the agrobacterium-mediated transformation of plants. This shows some of the patents on the complementary inputs that are needed to produced transformed plants. Since 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 alternatives are the kanamycin marker gene (the alternatives

are not easily available), and the patents on agrobacterium transformation of dicots by Washington U. 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 multitudes of 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 (for example a Bt gene or a herbicide tolerant gene). Compounding this further is the fact that a novel plant variety may also be patent protected. One well publicized example of such a "patent thicket" is in the research on beta-carotene enhanced rice ("golden rice"). Kryder, Kowalski and Krattiger (2000) report that the golden rice innovation involves using as many as 70 pieces of intellectual property and 15 pieces of technical property spread over 31 institution.

While the public sector is credited for developing some of the key transformation techniques, almost two-thirds of the gene transformation patents are held by private entities. Figure 1, shows patents issued in the class that predominantly cover transformation methods by application date[2]. The first patent to be classified under this class was in 1978, but not until 1983 did sustained patenting begin to occur.

3.3. Impact of Patents on Progress in Transformation Technology

The impact of awarding patents on transformation technologies will be different for private and public researchers. From the perspective of a profit maximizing private researcher, the incentive to patent plant transformation technologies will be due to the appropriability that the patents provide and by the disclosure made by other patents. Not only will the owner of a patent make money on licensing, but she may also be able to keep others from working on products that will compete with her products. American Cyanamid could not get access to the biolistic gun from Cornell gun which was licensed to DuPont because DuPont and Cyanamid both wanted to use it to create competing transgenic crops. Competitors who fear being left out or cannot gain access to a technology will attempt to invent alternative techniques. The information in the patents and the cost of licensing these technologies may stimulate competitors to try to develop new methods of transformation or to increase the efficiency of older methods. Private research firms would still have an incentive to do research on transformation even if they could not patent the transformation process.

[2] In the U.S. patent system, most transformation technologies fall under the class and subclasses of 935/052: "Methods of introducting a gene into a host cell"

The impact on public research will be somewhat different. The incentive affect of expected profits is less than for private firms because public institutions have other goals in addition to generating licensing revenues. Moreover, the incentives for inventing around the inventions were less because universities can usually get access to the technologies for research purposes without too much difficulty. Now that universities are finding that they do not have freedom to commercialize genetically modified varieties that were produced using patented processes, they once again have a strong incentive to develop new methods of transformation.

The major problem for universities in most cases is not for obtaining access to a transformation technique for research use, but it is freedom to commercialize. If companies do not have this freedom, then they may avoid a commodity or an area of research (in one interview we were told that DuPont avoids tomatoes because of Calgene/Monsanto patents).

The result of these different policies and motivations has been continuous progress in transformation technology, which has dramatically increased the efficiency and reduced the cost of transforming plants. 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.

Since 1990 the most important increases in efficiency have been from the first two methods – increasing the efficiency of techniques and moving them to new crops or classes of plants. In the mid 1990s the biolistic gun was the only transformation process that could be used for transforming grains. It was very inefficient process. The last column of Table 1 shows the differences in efficiency at present. It indicates that Japan Tobacco's achievement at transforming grain 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 the machinery, the gun; second, you do not have to shoot and reload the gun while with agrobacterium you can do hundreds of transformations simultaneously, making it more effective for high through put screening; third, the probability of transformation is greatly increased and fourth, there is a 'cleaner' pattern of DNA integration with agrobacterium which reduces the cost of biosafety regulation.

3.4. Impact of Patents on Biotechnology Research Investments and Productivity

Private research investments in transformation research appears to be negatively related to the cost of doing downstream research. Patented technology such as agrobacterium

has substantially increased the investments needed to develop new varieties of plant but it has probably increased productivity of research even more. Presumably this is why so many companies invested in using these techniques, although it is possible that they greatly overestimated the increase in research productivity that they have gotten so far from these technologies. These patents may also reduce the cost of doing research for the patent holder since he gets money from other firms for the use of the patented technology (but not if he is spending a lot on legal fees to defend the patent).

Cyanamid was slowed in their attempt to make herbicide tolerant maize and rice by Cornell's exclusive licensing of the gun to DuPont. They were not able to negotiate a deal with DuPont to use the biolistic gun which was their main rival in one type of herbicide production. Thus, it took them several more years to produce herbicide tolerant crops than it would have.

Our interviews suggest that a problem for companies using some transformation technologies is that nobody knows who owns them in the U.S. It could be one of their main competitors and that competitor could then block the use of varieties developed using that method unless large royalties were paid. For example, there is an interference proceeding in the U.S. that has been going on for 18 years with at least 4 parties that claim agrobacterium methods – the Max Planck Group, the Mogen/Zeneca group, the Washington U. group, and Monsanto. For this reason Dow does not use agrobacterium in its transformation work. Dow chose to use the whisker technique which is a less efficient method because of the mess with establishing priority on agrobacterium transformation methods.

Patents on transformation technologies and fact that Japanese companies did not start doing biotech research until 1983 were the two major reasons that Japanese companies got out of biotech (Shimamoto 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 seemed like a reasonable deal – they felt that no matter how much the offered, Monsanto and other companies would have refused.

The other major hold up that we have identified so far was Liberty Link (Basta herbicide resistant) corn and maybe soybeans. Agrevo (now Bayer) bought PGS which was doing research on corn that was resistance to Agrevo's herbicide, Basta, and understood that the Basta resistance gene was public. Agrevo did 3 or 4 years of research to develop Basta (the commercial name is Liberty) resistant corn. They knew that DeKalb had applied for a patent, but thought it was on basta resistant corn using projectile transformation technique. So they used another transformation technique (protoplast fusion). They worked with Holden's

to develop good Basta resistant corn parental lines and hybrids. Holden's had geared up to produce enough foundation seed to produce up to a million acres of Liberty Link

However, DeKalb had applied for a patent on all Basta resistant corn. DeKalb's patent on BAR corn was approved for any type of transformation process. DeKalb hired a firm to go around to all of Holden's customers. They said pay $12/bag or see us in court. Holden's could have fought it, but they told the seed companies that they would have to get licenses from DeKalb and from Agrevo. This was impossible because Agrevo had decided to fight DeKalb over this patent. This effectively killed Liberty link maize. Agrevo is continuing to fight in court and may win. DeKalb's patent may not meet the non-obviousness requirement. But Agrevo will have lost the war to RR corn.

Another major cost of the patenting system is in law suits. One such suit was just filed on July 25, 2002 in Delaware. Syngenta claims that Monsanto and Delta and Pine Land infringed on their patents on Agrobacterium to transform dicots such as cotton and soybeans. The believe that Monsanto should start paying them royalties on their Bollguard and Yieldgard, and Roundup Ready crops or stop selling them (Syngenta 2002). This is likely to be major, long battle. Which will be great for lawyers but expensive for both companies.

4. Rice Genome Research

The determination of the genome sequences of many organisms from bacteria to fruit flies, crops, and humans is a watershed event in biology. Since the first completed sequencing of an autonomous living organism in 1995, there have been nearly 221 more organisms that been sequenced and the results published, with another 961 projects that are ongoing (GOLD, 2004). Perhaps the most important and widely publicized was the sequencing of the human genome in 2000, a project that took nearly ten years to complete and cost $3 billion dollars (Collins et al, 2003). In agriculture, rice was the first commercially important crop to have its genome sequenced in 2001. Sequencing the genome, although an important step, may however be the easy part in the ultimate goal of understanding gene function and turning that information into economic and social gains.

The issue of claiming property rights over certain genetic sequences has been contentious, if not the most publicized, aspects of genomics research. Controversy in intellectual property protection results in uncertainty, which in turn creates distorted incentives, higher transaction costs and a sub-optimal level of investment in R&D (Long, 1999). This has been particularly true for the case of expressed sequence tags (ESTs) which are short DNA sequences but whose biological function may be undetermined at the time of the discovery. Proponents of

patenting gene sequences have argued that even if the biological function of a sequence is unknown, a patent should be granted as at some later time the discovery of the function may become known. Since patent law prevents the patenting of innovations that are in the public domain for more than a year, by not granting patents on such sequences private firms may be less willing to undertake further research (Long, 1999). On the other hand, those opposed to patenting of sequences have argued that it would result in wasteful research as firms rush to patent ESTs of dubious significance. Interestingly, opponents of patenting gene sequence also suggest that firm's will have a disincentive to undertake further research if they have already obtained a patent on the actual gene. Needless to say, the uncertainty created during much of the 90's regarding ESTs may have held up new research which prompts Long (1999) to suggest that "at some point an imperfect solution, expeditiously reached, becomes preferable to a perfect solution that takes a long time to reach."

There are a number of reasons why the study of rice genomics as a case study for IP issues is relevant. 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 have arose during the course of the sequencing effort. Second, due to its close genetic relatedness to other complex, but more commercially lucrative, crops there was considerable research that was conducted by private sector firms. The behavior of the private sector and how it uses intellectual property not only to protect its discoveries, but in the research process as well, will be instructive. In this regard we are also interested in exploring the role public sector technology has had on the sequencing efforts of the private sector and vice versa. By cataloging the key IP related developments of genomics research we pose some counterfactuals and ask whether the technological development would have occurred at the same pace as the one observed.

The balance of this section is organized as follows. In the next (sub)section we seek to trace the development of research in sequencing the rice genome in an effort to understand the role played by different public and private researchers. Specifically we ask whether, and to what extent, the proprietary technology used in DNA sequencing, was a source of hold-up for firms either through unreasonable licensing terms (high fees, reach-through provisions, etc) or simply withholding of sequencing of technology from potential users. Next we explore the reasons for the rapid increase in sequencing that has taken place between 1999 onwards and whether the incentive mechanism of patents was a reason. The motivation behind Monsanto's and Syngenta's to effectively donate their sequence database is also examined.

4.2 History

Sequencing of the rice genome began in earnest in the late 1990's, but much of the ground work was laid in the two decades preceding it, when a series of methods used in determining the sequence of base pairs ultimately led to effort behind the different genome projects. As was the case with the human genome project, the rice genome project got its start within the public and nonprofit sector. In the late 80's the USDA funded the Plant Genome Project to develop genetic maps for more than 50 crops (McCouch, 1998). Maps were used to localize genes and quantitative trait loci (QTLs) and used in plant breeding activities. Starting in the late 80's Rockefeller funded rice mapping research at institutes in developed and developing countries and 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 mapping was considered commodity specific (McCouch, 1998). This thinking changed as molecular linkage data suggested an entire plant family could be studied as a single genetic system and the most extensive accumulation of data supporting this concept has been for the grass family[3]. It was observed that the 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 speicies (Phillips and Freeling, 1998). For the case the grass family, rice had the smallest genome and later would become a natural candidate to have its genome extensively studied and sequenced.[4] .

In the late 90's there was a further realization by the public sector researchers that many of the molecular genetic and bioinformatics tools developed as part of the Human, Arabidopsis, and Drosophila Genome Projects, could be directly be adopted or provide guidance to meet plant specific needs. As with these other genome projects, the expectation was that sequencing of a plant genome would allow one to identify all useful gene that in turn would be invaluable to plant breeders interested in introducing novel genes and traits via biotechnology.

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[3] The grass family consists of five principal subfamilies and about 10,000 diverse species, including important food crops such as rice, wheat, and maize.

[4] 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.

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 which consisted of research institutes spanning 10 countries in Asia, Europe and the Americas. These groups divided up the genome of a *japonica* rice variety name Nipponbarre and aimed to have 40 percent of the genome sequence by 2003 and the whole genome sequenced by 2008 (Saegusa, 1999).. Budgets were increases 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. Rice sequencing research obtained $12.5 million from the U.S. 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 completely map the rice genome for $30 million, but no one took them up on the offer. Monsanto had its map constructed by the U. of Washington, Seattle in the laboratory of Dr. Leroy Hood under contract for Monsanto. They used the same basic approach (mapping the genome piece by piece from identified locations on a physical or genetic map) and 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 BACs available to the MAFF Rice Genome Project. On January 26, 2001 Syngenta and its partner Myriad Genetics announced that they had completed the sequencing of the rice genome. In April 2002 Syngenta and the Beijing Genetics Institute both published drafts of rice genomes in Science. The cost of the Syngenta project was $30 to 50 million (Shantaram personal communication 2002). They used Myriad's proprietary DNA sequencing technology. Syngenta says that it will make most of the information that they have discovered available to legitimate scientists working on the problems of the poor, but that they 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 an *Indica* hybrid rice cultivar in 2001 (China Daily 2001). In January 2002 the group announced that it was making all of the information publicly available. They used the whole-genome shotgun approach and covered at least 95% of the genome. The public international rice genome project which used the slower but more complete piece by piece sequencing method completed its sequencing effort in December

2002. It makes all of its findings available on the web through GenBank as they are discovered.

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 the Japanese government which substantially boosted their investment in rice sequencing in 1998. 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 their BAC library and map to the IRSGP increased the productivity of the public research program (Normile in Science 2002). Monsanto disclosure of their data and then word that the BGI was about to publish their draft of the *indica* genome appears to 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 have stimulated IRGSP to announce that they will publish their draft sequence which is more complete that any of the others by December 2002.

4.3 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, in any way, may have hindered the sequencing effort. It is interesting to note that 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 Sanger or Maxam or 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 used extensively in mapping such as RFLPs were also developed in the public sector but also never patented.

Although many of the fundamental technologies used in genomics research are not patented, patents do exists 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 instrument and its reagents covering patent fees. The issue, of course, is not so much whether a technology is simply patented but they way it is disseminated so that other researchers could put it to more productive use. The contrasting cases of the PCR patent and the Cohen-Boyer patent is instructive. The patent on polymerase chain reaction, discovered by Cetus in 1983, was controlled through a complex arrangement of high-fee

licenses for various applications and reagents (Cook Deegan, 1994). On the other hand one of the most important techniques in molecular biology, the Cohen-Boyer process for recombinant DNA, was also patented but licensed at relatively low fees. These different ways of handling the dissemination of research tools obviously affected who could use them, and perhaps the pace of innovation.

Private investments induced in part by patents have, however, made an enormous contribution to the research process. Sequencing equipment and the microchip arrays were based on ideas developed at Universities and are now advancing rapidly in the private sector which is driven by patents and pulled by the demand from the human genome project and medical research.

Did patents hinder the sequencing effort? Perhaps the strongest evidence against hold-ups at the level of DNA sequencing is the extremely competitive nature of sequencing race that occurred. This competition not only speeded up the sequencing effort of the rice genome—moving the completion date of the public sector project nearly six years early—but spread the technology so much that it is now almost routine as evidenced by the fact that nearly 1000 genome projects are underway. Over the course of a decade the productivity of the sequencing technology has improved exponentially. Figure 4 (from Carlson, 2003), estimates the potential daily productivity of DNA sequencing based on three commercially available machines as of 2002, namely those manufactured by Applied Biosytems (subsidiary of Applera Corporation), Egea Biosciences (acquired by Johnson and Johnson) and Pyrosequencing AB (now Biotage). The productivity of the most widely used synthesizer—the ABI Synthesizer—has increased from $8x10^5$ bases sequenced per person per day in 1994 to $3x10^7$ in 2002. These estimates include the time required for pre-processing and sample handling on each instrument but does not include the time required for sequence analysis.

The cost of sequencing has also decreased substantially (figure 5). For the period covered by figure 2, the cost of sequencing (expendables such as reagents) have fallen exponentially. Lander et al (2001) estimate that the cost of sequencing had fallen by a factor of 100 in ten years by 2000 and that costs have been falling by a factor of 2 every eighteen months. Shifts to new technologies and increased capability at lower cost will ensure that these trends will likely 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 done by a technician. The pace at which productivity increased is why companies like Celera were able to claim that they could sequence the rice genome in 18 months for $30 million. Leaders of

the Japanese rice genome project report that the new sequencing machinery that they bought from Applied Biosystems in 2000 increased the speed of their sequencing process by 5 times over machinery that they had bought 5 years earlier (Personal communication - Higo November 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 (IRGSP, 2002). When Monsanto produced its draft sequence of the rice independent of the IRGSP effort, it made its BAC clones available to the public sector effort. By combining the Monsanto BAC clone data with the data that was being generated, the IRGSP was able to generate a high quality sequence data which also helped accelerate its sequencing effort. Syngenta's decision to provide its draft sequence to IRGSP in 2002 also was useful as it extended the PAC/BAC contigs and thereby extending the gaps in the physical map (IRGSP, 2002).

One, however, should be mindful that initial release of the Monsanto and Syngenta data were greeted by many with skepticism and even controversy. When Syngenta published its results of the rice genome in the journal *Science* in 2001, it did not release the data to GenBank which was the norm. Rather, the data was put up on Syngenta's website and access was restricted to academic researchers, who supposedly ceded any commercial applications of their research to Syngenta (Butler, 2002). Monsanto's data too when first released in 2000 was accessible only when researchers agreed to certain conditions. Many researchers were weary of signing up to these databases as they felt that the withholding of such information is contrary to the conduct of scientific inquiry. Moreover the demand for access for such data was low, considering the Beijing Genomic Sciences had released its data to GenBank and that IRGSP would have make available its data once sequenced. It has been reported that after the initial announcement by BGI and Syngenta, 350 researchers accessed the BCI data on GenBank and only 65 used the Syngenta data (BGI, 2001). Clearly the low demand for their proprietary contributed to Syngenta's decision to donate the rice data to IRGSP. It is, of course, unclear whether any data has been held back.

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 intial techniques involved in sequencing were developed by the public sector, and later perfected and commercialized the by private both public and private 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 1) the cost of sequencing has been rapidly decreasing, making sequencing technology accessible and widespread and 2) there was sharing of sequence data that helped the public sector meet its goal quickly

IPRs Post-Sequencing Stage

The issue of IPRs however is likely to be controversial in the "post sequencing" stage, especially in the matter of finding genes of interest and structural genomics. It is estimated that rice has 60,000 genes, but for only half of these has some gene function been assigned, but not definatively (Cyranoski, 2003). It is for only 100 rice genes has an accurate, demonstrated function been determined. Researchers reported that the availability of gene maps of the rice genome will lead to an enormous increase in the efficiency of research that is developing improved rice varieties and improved varieties of other grains (Ronald and Leung 2002). Research that used to take years to do can now be done in minutes – for example finding out whether a gene that has been identified in corn also exists in rice

In many ways a second stage race to identify the function of thousands of genes has begun, having much greater economic and agronomic significance. In contrast to the race to sequence the rice genome, which was largely done collaboratively with the sharing of data, the functional genomics research is likely going to be less collaborative as researchers would want to lay proprietary claim to 1) any tools used in gene identification, 2) actual genes coding for specific protein, or 3) protein structures that are discovered and developed. We discuss, in turn, the nature of these three "research tools" and the IPR issues surrounding them.

There are several approaches in identifying gene function. First, large libraries of mutant plants can be created that have within their genome randomly inserted bits of tagged DNA that disrupt or promote nearby gene. By observing which traits are expressed relative to normal non-mutant plants, gene function can be assigned. Researchers in Japan and South Korea have creater mutant libraries that are as large as 100,000 mutants (Cyranoski, 2003). A second approach is to knock out genes specific genes and thereby disrupting the function of particular gene. A tool developed by Shiger Iida uses the knock out approach and exploits the occasional tendency of DNA to insert itself into at points where the sequence matches its own—known as homologous recombination (Cyranoski, 2003). Lastly, DNA microarrays have also been employed in identifying gene function. Microarracys--which consist of thousand of known genes--allow for rapid screening of a plant's genetic make-up or gene function. Microarrays are useful in that they reveal a network of genes, which are difficult to

understand using the knock-out or mutant approach. For example a microarray chip developed by Syngenta has been used to identify the 269 genes that expressed in the development of a rice grain (Cyranoski, 2003).

However access to the tools used in gene identification are restricted, and therein lies the danger of holdups. Most microarrays, such as that of Syngenta are proepriatary. The knock-out technology of Iida is patented. And then there is the example of Japan which is restricting the use of such tools to its researchers (Cyranoski, 2003). This has resulted in China developing its own functional genomic resources, and will likely prompt other countries to follow suit if they don't want to be shut out completely.

Although there were some patents granted early on for sequences of the genes, now sequences can not be patented unless there is strong evidence of the utility of the gene or genes that have been sequenced. Thus, the raw output of the sequencing process can not be patented and the entire sequence or map of an entire genome of a plant also does not seem to be patentable in the U.S. However, the computer programs to identify genes and their functions can be patented or copyrighted. Some of the specialty companies that do contract functional genomics rely on patented software or software protected by trade secrets. 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.

Some reach through requirements have been reported between the providers of inputs into the sequencing process and the sequencers. In order to get access to the latest computer chip technology, the Japanese government had the choice of paying large lump sum payments to a private U.S. firm or paying much less but giving the firm some control over the rice technology that was developed. However, reach throughs from platform technology to downstream research do not seem to be common. Table 3 indicates that in most of the genomics deals for which information is available the research is being done by the owners of technology on a contract basis which included up front payments and benchmark payments by the major chemical or seed companies rather than royalties on the sale of products. Only Myriad had a deal for a share of the sales of the technology and Millenium formed a joint venture with Monsanto called Cereon, which will share the profits of products sales.

There are no reach through requirements between the private providers of the rice genomics information, Monsanto and Syngenta, and the public sector. The information is not available to other private firms until it s modified and becomes public through through the Rice Genome Project.

At the next step down the research ladder companies that provide specific patented genes to seed companies for the development of transgenic varieties provide these genes in contracts that provide not only royalties but considerable control over how and when the technology is used.

The absence or presence of these reach through or royalty agreements is partially due to the relative power and circumstances of the companies who are selling and buying the technologies. The sellers of the platform technologies were either medium to large sized firms that primarily supply technology to the human health or smaller start ups that concentrate more in agriculture. The buyers are much larger chemical and seed companies who have fairly steady revenues while the small start-ups are just trying to survive and the more successful medical start ups are not interested in a long term involvement in agriculture. Sellers of genes have so far been large companies like Monsanto and Dow[5] usually selling to smaller seed companies.

So far these genome projects have not had many obvious impacts at the farmer level. The Rice Genome Project in Japan is probably typical. It is generating an immense amount of knowledge, but so far no useful technology. Leaders of that project recently reported that 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 MAS which used markers 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 to 16 genes have been identified using this technique (Higo personal communication Nov. 2001).

5. Conclusions

This paper indicates that these two platform technologies – plant transformation techniques and structural genomics - required major inputs by the public sector to initiate their development and to continue to ensure that they made progress. They also indicate that private firms played a major role in the development of these tools, although less so in the gene sequencing case.

Would the private sector have made the investment that they made in the absence of IPRs to protect the tools or IPRs to protect plant genes? Our reading of the evidence is that it is very unlikely that they would have and that this would have considerably slowed the

[5] The genes were often from small start-ups that spun off from university research like Mycogen, Calgene. and Agrigenetics.

development and application of these techniques. These are powerful techniques. Transformation technology has already had a major impact on world agriculture through insect resistant cotton and corn and herbicide resistant cotton. Structural genomics has so far had little measurable impact on farmers, but its potential impact through crop improvement that uses marker aided selection and through genetic engineering is immense.

The price we pay for these contributions are the hold-ups and increased cost of research that are described in the paper. So far these costs do not appear to have not been as important as the contribution of the private technologies, but we have not done an empirical investigation of this yet.

In addition there is the feeling that the private sector should not be profiting extensively from research financed by the public sector. This is particularly frustrating to the public sector when private firms or university patent offices make it difficult to get access to a platform technology which was originally finance and developed by the public sector . However, as in the medical field, if major investments are required to make the university technology work, patents or exclusive licenses may be necessary for the public good.

The fact that our initial reading of the anecdotal evidence suggests that so far biotech patents have induced a response from the public sector that outweighs their costs does not mean that the situation could not be improved. Patents on plant transformation technology have probably increased the production of more efficient transformation technology by private firms. However, it is creating some hold ups which as yet we have not been able to evaluate in economic terms. It has also helped increase the market power of a few firms – namely Monsanto and Syngenta – which control key patents on transformation and also the marker genes which have few alternatives.

The major problem for universities and corporations in most cases is not obtaining access to a transformation technique for research use, but it is freedom to commercialize. If companies do not have this freedom, then they may avoid a commodity or an area of research (in one interview we were told that DuPont avoids tomatoes because of Calgene/Monsanto patents) strengthening the power of the first firms in the market.

It appears that universities could help avoid some of these problems in several ways. First, by providing better information about public sector alternatives to expensive private technology. This is one of the aims of the IP clearinghouse that has just been established by the Rockefeller and McKnight Foundations. Second, by charging flat fees for the use of their patented technology and not having contracts that require permission or royalties for commercialization on platform technologies, they would be available to more companies and

they would push the price of using the techniques down. If a few major technologies in each category of platform technologies are reasonably inexpensive to obtain, then monopoly power would be considerably reduced. Third, new research is needed in some areas to overcome existing monopolies. For example, public alternatives to Monsanto's antibiotic marker gene would be very useful. One of the goals of future work in this research project is to evaluate the costs and benefits of some of these Universities activities.

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Figure 1:

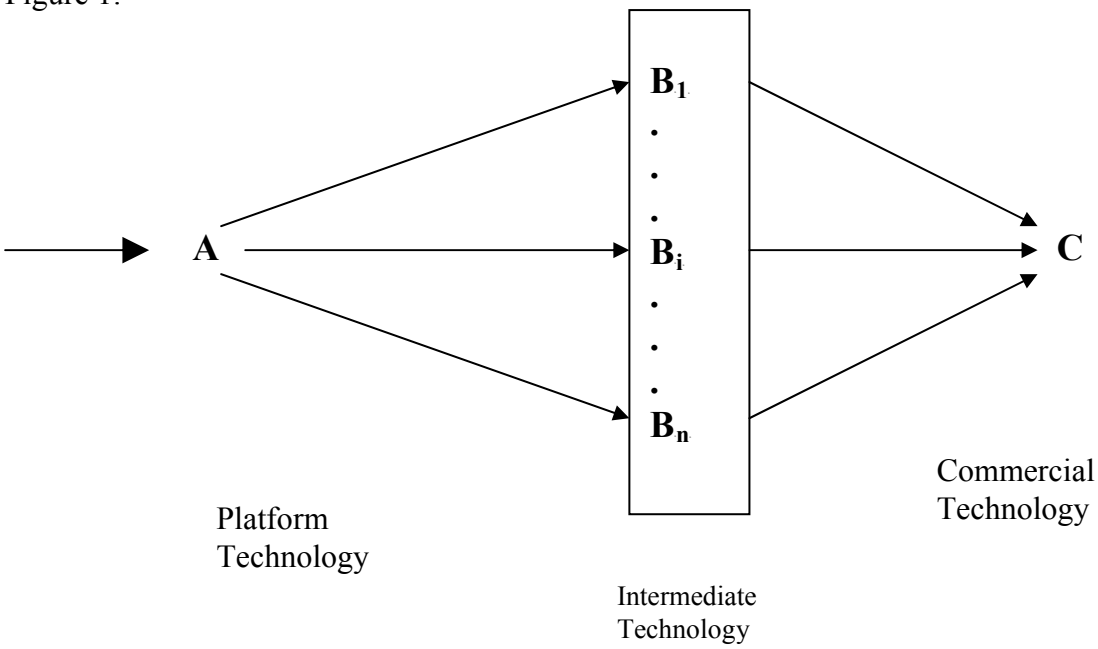


Figure 2: More competition and substitutability of A technology lowers holdups

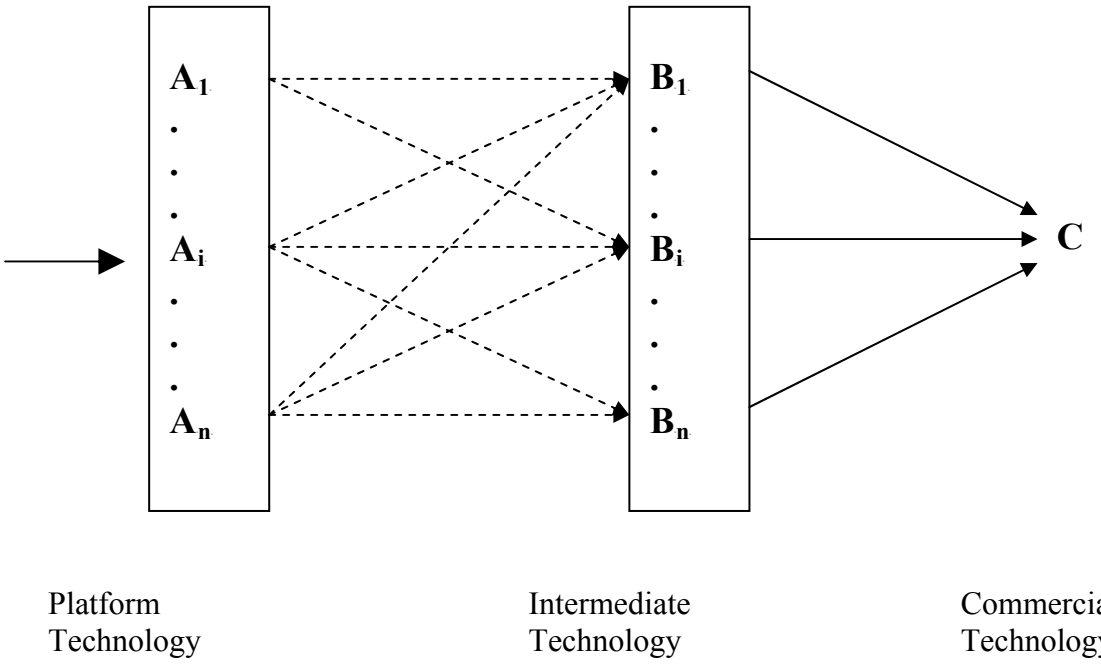


Figure 3: Multiple holders of A can also lead to holdups

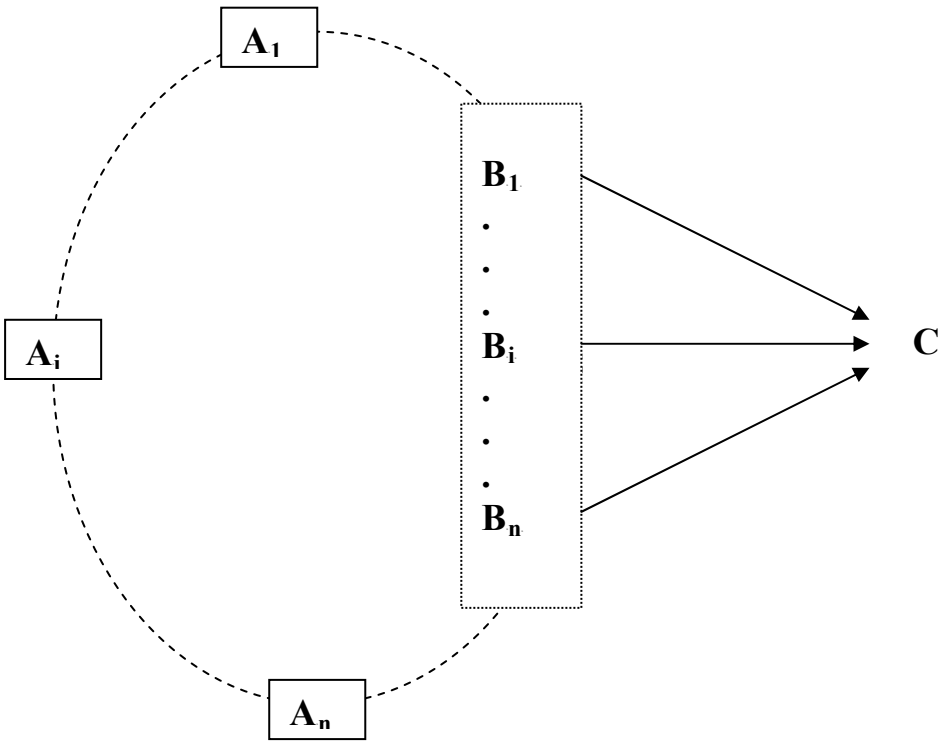
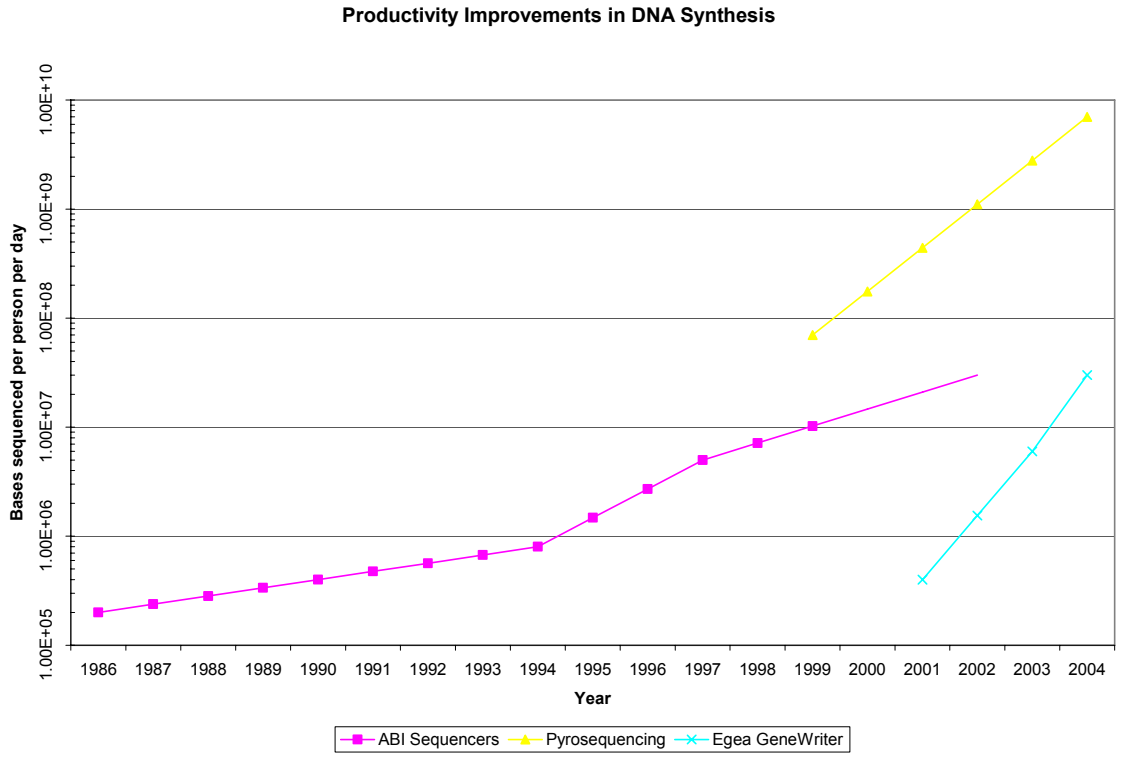
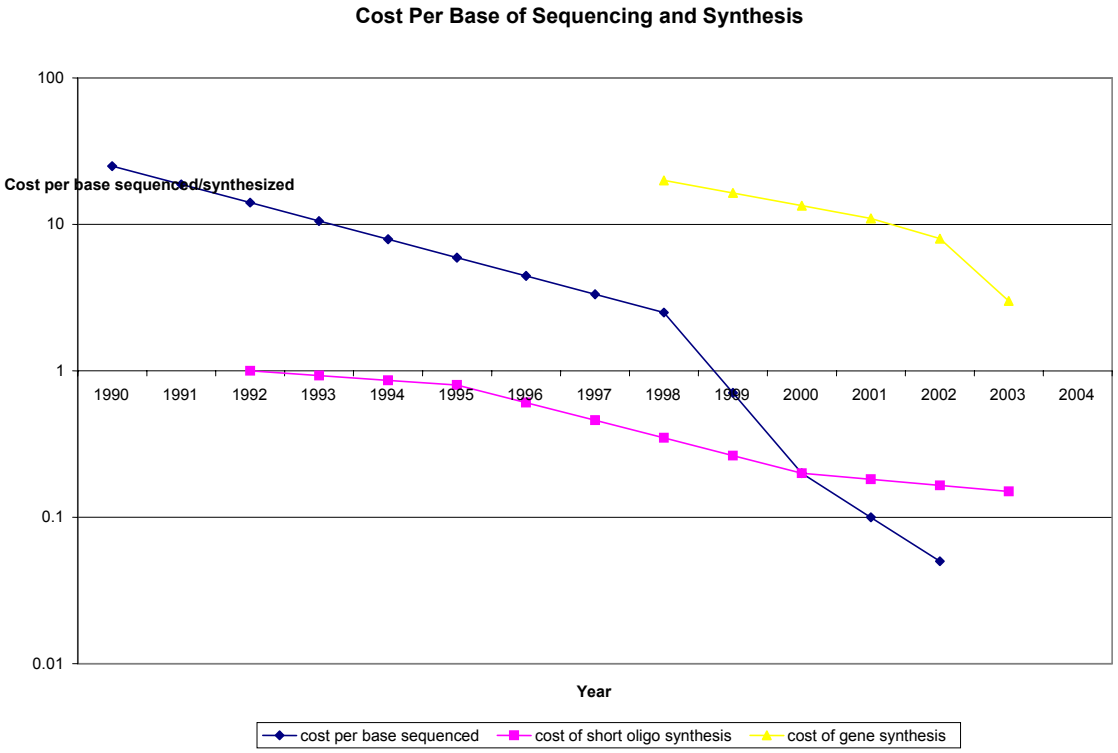


Figure 4: Productivity Improvement in DNA synthesis



Source: Carlson (2003)

Figure 5:



Look at the CAMBIA – new info on agrobacterium

Table 1. Main Transformation Techniques

Technique	Research Conducted at:	U.S. Patent Holder /Licensee	Remarks
Agrobacterium - Binary vector method	U.of Leiden Netherlands	US 4,940,838 Mogen (Netherlands) now owned by Syngenta	30% trans-formation in corn. Most commonly used trans-formation method
Agrobacterium Co-transformation method	Max Plank Institute & Monsanto	Max Plant & Monsanto U.S. applications in interference proceedings.	Not extensively used
Turn off Agrobacterium	Washington U.	US 6,051,757 and 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	U.S. 5,015,580 Agracetus - Monsanto now owns Agracetus	7-10 % transformation
Silicon carbide fiber (or"whisker")	Zeneca	US 5,302,523 Zeneca	Inefficient (<1% transformation)

Table 2—Jurisdictional extent of IP for agrobacterium-mediated transformation of plants

Technology	Property rights holder	Jurisdictions	Selected patents
Co-integrated and binary vectors for Agrobacterium-mediated transformation			
Assembling and using co-integrated vectors	Monsanto Max Planck Institute	United States (in interference), Europe,	EP 131620 B1 EP 131624 B1 AU 559562 B2 SU 1582990 A3
Binary vectors and transformation of dicots with binary vectors	AstraZeneca /Mogen (Syngenta)	United States, Europe, and Japan (pending)	US 4 940 838 US 5 464 763 EP 120516 B1
Transformation of dicots and monocots			
Transformation of dicots with an *Agrobacterium* vector	Washington University	United States (Additional US application in interference)	US 6 051 757
Transformation of monocots with *Agrobacterium*	Japan Tobacco	United States, Europe, Australia, Japan, and Canada (pending)	US 5 591 616 EP 604662 B1 EP 672752 B1
Widely used markers in transformation			
Herbicide resistance			
Phosphinothricin, (*bar* gene)	Hoechst/AgrEvo (Aventis)	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			
Antibiotic resistance gene under control of plant promoter	Monsanto	United States	US 6 174 724 B1
Kanamycin resistance gene under control of CaMV 35S or 19S promoter	Monsanto	United States and Europe	US 5 034 322 EP 131 623 B2
Hygromycin resistance	Novartis (Syngenta)	Europe, United States,	EP 68740 B1,EP 135291 B1 EP 186425 B1 US 4 727 028, US 4 960 704 US 5 668 298
Widely used reporter gene in transformation			
gus gene (β-glucuronidase)	CAMBIA	United States and Great Britain	US 5 268 463US 5 432 081 US 5 599 670, GB 2197653
Widely used promoter			
CaMV 35S promoter	Monsanto	United States, Europe, and Japan	US patents 5 352 605, 5 530 196, and 5 858 742; EP 131 623 B2 (currently being opposed) JP 2645217 B2
	Rockefeller University	United States	US 5 110 732 US 5 097 025

Source: Pardey et al. (2001). (Background paper of UNDP Human Development Report)

Notes: 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.

Table 3. Companies doing plant genomics research

U.S. Companies	Who is financing?	Size of Contract	Year	Crops
Affymetrix	Pioneer		1997	Corn
ArQule	Monsanto	$12 mil_royalties	1997	
Biosource technologies	Dow Agrosciences	?	1998	
Celera AgGen	Aventis	?	1999	Corn
Curagen	Pioneer	$20 million	1998	Corn
Diversa	Novartis	$12.5 mil	1999	
Genetrace	Monsanto	$17.2 mil	1998	
Global Agro(Salk Inst.)	Agrobiotech	Equity stake	1998	Forages
Human Genome Sciences	Pioneer	$16 million	1996	Corn
IBM	Monsanto		1997	
Incyte Pharmaceuticals	Monsanto	Royalties on Monsanto's products	1996	
Institute of Genomic Research (TIGR)	National Corn Initiative - USDA		1998	Corn
Maxygen	Pioneer	$35-85 million	1999	Corn
Mendal Biotechnology	Monsanto/Savia	$30 mil	1997	Fruits, veg. Corn
Millenium Pharmaceuticals	Monsanto	$218 mil	1997	
Myriad Genetics	Novartis	$33.50	1999	Cereals
Paradigm Genetics	Monsanto	$55 mil	2000	

Source. GRAIN Genomics: Whole Genome, Total Control Seedling March 2000. http://www.grain.org/publications/mar00/mar003.htm

Companies doing plant genomics research