Licensing DNA Cloning Technology

A first-hand report on Stanford University's licensing of recombinant DNA invention

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Universities in general have three major purposes: education, expansion of knowledge through research, and dissemination of information. Because university research furthers knowledge rather than manufactured products, the only ownable properties of significant value stemming from research are usually intangible or tangible properties which are licensable. "Licenses" and their resulting transfer of technology then are really one form of a university's product. Stanford University in Palo Alto, California is no exception.

Stanford's most well-known licensed "product" is the Cohen/Boyer DNA Cloning invention. This invention has lauched much more than a *product* in the marketplace; it has, in fact, launched an industry and is transforming many existing industries planning to use this technology.

Recombinant DNA technology is the most revolutionary development in biology in recent years. It will have its most immediate and profound effects in medicine and in the prevention of disease. One observer has said, "If we live another 30 years, biotechnology will enable us to live another 100!" In the long term, the agricultural, veterinary, foods, chemical, oil and mining industries will all be affected.

BACKGROUND OF THE TECHNOLOGY

The ABCs of gene-splicing start with DNA. The form and function of every living plant and animal are determined by molecules of deoxyribonucleic acid, commonly known as DNA.

Whenever cells divide, the DNA duplicates itself, passing on its genetic inheritance to the next generation of cells. DNA also guides the cell in the manufacture of proteins essential for life, including hormones like insulin, antibodies to fight disease, hemoglobin to carry oxygen, and enzymes that carry out chemical reactions.

DNA molecules are formed into the famous double helix elucidated by Watson and Crick in 1953. DNA resembles a spiral ladder. The sides are formed of sugars and phosphates. The rungs are formed of pairs of four chemical bases—adenine (A), guanine (G), cytosine (C) and thymine (T). To form a rung, A always joins with T and C with G. The sequence of bases running along a strand of DNA forms a four-letter code (analogous to our alphabet or the "1's" and "O's" of the computer language) that tells the cell what protein to make.

In DNA cloning, also commonly known as recombinant DNA or gene-splicing, DNA from one type of cell is spliced *in the laboratory* to the DNA of another type of cell (hence gene-splicing). (It is important to note that recombination of genes occurs naturally and is a part of the evolutionary process. The invention involves recombination in the laboratory of genes which do not naturally recombine.)

Researchers take bacteria, viruses, animal cells or plant cells, break them apart and extract the DNA. They use enzymes (called restriction enzymes) to chemically cut the DNA at specific points along its length (like scissors). They can then isolate a particular DNA fragment of interest.

E. coli is a bacterium that normally flourishes harmlessly in the intestinal tract. E. coli contains chromosomes and rings of DNA called plasmids.

In the process of DNA cloning, the researchers remove a plasmid, open the ring with a restriction enzyme and insert the fragment of DNA isolated from another cell. They close the ring (i.e. "recombined") and put the plasmid back into a bacterium, called "the host." The new bacteria are called transformants or "DNA Chimeras" after the mythological three-headed beast that combined the head of a lion, the body of a goat and the tail of a serpent. Each time the bacterial cell divides, it will pass the new gene along to the next generation. In a matter of hours, the researchers have thousands of bacteria containing the hybrid DNA. The new colony, called a genetic clone (hence DNA cloning), can produce the specific protein determined by the inserted gene.

The historical perspective of some of the events which surrounded the development of the invention sets the stage for understanding the marketing of the invention.

The beginning of the recombinant DNA (r-DNA) story really starts in the 1950s with the research of Watson & Crick when the structure of DNA was deduced. Many scientists contributed to the early chapters of the story. For purposes of this discussion, however, we begin with Professors Cohen and Boyer.

After attending a U.S.-Japan joint meeting on bacterial plasmids held in November 1972, Herbert Boyer of the University of California and StanleyCohen of Stanford discussed their research at a delicatessen in Waikiki, Hawaii. Boyer had been doing research in the area of restriction enzymes and Cohen had been working with plasmids. Together they con-

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ceived of the DNA cloning technique.

By March of 1973, Cohen and Boyer had shown the basic feasibility of DNA cloning, thus, reducing the invention to practice. They presented their results at a scientific conference (called the Gordon conference) in June 1973 and described it in a publication which appeared in November.

In May 1974 the work of Cohen/Boyer came to the attention of a science writer at the *New York Times* who wrote an article describing this recombinant DNA research. The article included quotes from a number of scientists describing the practical applicability of DNA cloning. Stanford News Director, Bob Byers called the article to the attention of Niels Reimers, Stanford's Director of Technology Licensing. Reimers contacted Cohen and proposed that the university apply for a patent on the DNA cloning procedures. After much discussion because of Cohen's initial reluctance, Cohen finally agreed to cooperate in seeking patent protection.

Stanford approached Boyer, who was willing to cooperate, and University of California officials, who were also willing to cooperate. Stanford eventually was able to obtain approval from the three research sponsors (American Cancer Society, National Science Foundation (NSF) and National Institutes of Health (NIH) to administer the invention under Stanford's Institutional Patent Agreement with NIH just in time to file a patent application on November 4, 1974, one *week* before the one-year U.S. publication bar was to occur. The two universities agreed that Stanford would manage the licensing, that 15% of any gross income would be deducted by Stanford for administrative costs, and that after out-of-pocket patent and licensing expenses were deducted by Stanford, the remaining net revenues would be split 50/50.

Events on a national level affected the patent situation and licensing plans.

As mentioned, in June 1973, a Gordon Conference was held at which the advent of recombinant DNA was discussed: this was Pandora's box to some people. One month later, two renowned scientists (Singer & Soll) wrote a letter to the National Academy of Sciences which triggered the debate over the safety of r-DNA research. By the next year the National Academy of Sciences had called on scientists to postpone or abandon their r-DNA research because of "potential hazards."

At about the same time, Nobel Laureate Paul Berg of Stanford and 10 other scientists (including Cohen and Boyer) wrote a letter to *Science,* calling for NIH to establish safety guidelines for r-DNA research and asking scientists to observe a moritorium on such DNA research pending those guidelines.

In December 1974, scientists were invited to an international conference to be held the next February (1975), sponsored by the National Academy of Sciences with funding provided by NIH and NSF. The purpose of the meeting, held at the Asilomar conference centers on California's Monterey Peninsula, was to review the progress, opportunities, potential dangers and possible remedies associated with the construction and introduction of engineered recombinant DNA molecules into living cells. After the meeting, r-DNA research was resumed but under strict, self-imposed laboratory safety guidelines.

In May 1976, a meeting was arranged with Stanford scientists and administrators to discuss the policy and practice of patenting biotechnology discoveries, particularly the r-DNA patent. There were concerns that patens would interfere with scientific communication, and that there might be a perception that Stanford would have a conflict of interest with respect to r-DNA safety if it were to hold a proprietary interest in r-DNA work. It was decided that Stanford would discuss the issues at a high, public policy level in Washington, and with those at NIH and NSF, specifically.

Robert Rosenzweig, Stanford Vice-President of Public Affairs, wrote NIH Director Dr. Donald Fredrickson, soliciting NIH's and NSF's views on the appropriateness of Stanford patenting and licensing the invention. Rosenzweig aptly summarized: ". . . the issues we are dealing with are complex, interesting and important, and the way they are resolved is likely to have a lasting effect on science and education."

Congress eventually got involved and there were public hearings throughout the Summer and Fall of 1976, including Senate hearings conducted by Senator Edward Kennedy on the r-DNA issue.

Ultimately, two years after Rosenzweig's letter, NIH reaffirmed its approval that, "yes," universities in general, should patent and license r-DNA inventions provided that industry licensees comply with standards set forth in the NIH Guidelines on Research involving r-DNA Molecules.

Overlaying all this national and Stanford activity was the now famous GE patent application claiming microorganisms *per se.*

In 1972, Ananda Chakrabarty, a microbiologist working for the General Electric Company, made a bacterium capable of breaking down multiple components of crude oil. Chakrabarty's organisms were not a result of gene-splicing and cloning but conventional genetic manipulations wherein a genetic mutation is "forced." Because of the oil eating property, possessed by no naturally occuring bacteria, Chakrabarty believed his invention to have significant value for the treatment of oil spills.

GE filed a patent application with claims of three types: first, the method of producing the bacteria; second, the bacteria combined with a carrier material; and third, the bacteria themselves. The patent examiner allowed the process and combination claims but he rejected claims for the bacteria *per se,* saying that the microorganisms are "products of nature," and that as living things, they are not patentable subject matter. GE appealed and kept appealing all the way to the Supreme Court. After eight years, on June 16, 1980, the Supreme Court held 5-4 that a living, human-made microorganism is patentable subject matter.

The Supreme Court based its decision on the fact that Congress used expansive terms in writing the patent laws and therefore they should be given wide scope. The court cited the evidence that Congress intended statutory subject matter to "include anything under the sun that is made by man."

Supreme Court Chief Justice Burger, writing for the majority, stated that "the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having potential for

significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under section 101."

The Cohen/Boyer patent application originally filed November 4, 1974, covered both the process of making, and composition for, biologically functional chimeras. During the course of prosecution, the examiner indicated that he was willing to allow process claims which described the basic method for producing transformants, but that he was not willing to allow claims on the biological material *per se*, i.e "products." It was decided that the original patent application would be divided in two. The "process" patent issued December 2, 1980; the "product" application, which had been held up awaiting the Supreme Court decision, is still pending in the Patent Office.

Niels Reimers, Director of Stanford's Office of Technology Licensing, (longtime LES member and past-president of LES U.S.A./Canada), is really the person behind the marketing of the invention, the connective tissue who ties it all together. In a memo dated July 11, 1976, Reimers wrote:

"At the onset, we must acknowledge that we are going to have to act on imperfect information. Ten months or 10 years from now we'll know what we should have done."

Stanford was trying to license an invention for which products had never been sold, and which would apply to many diverse, established industries, in addition to the then newly emerging biotechnology industry.

Objective/Philosophy Behind Market Strategy

Stanford and the University of California wanted the terms of the license agreement: (a) to be consistent with the public service ideals of the universities; (b) to provide the appropriate incentives to industry to bring genetic engineering technology forward to public use and benefit, in an adequate and timely manner; (c) to minimize the potential for biohazardous development; and (d) to provide income for educational and research purposes.

No genetic engineering research, academic or industrial, was to be inhibited by Stanford's licensing program. It was recognized, however, that commercial organizations might not conduct research in the area unless there was some assurance that they could receive a license to market if a successful product were developed.

Although exclusive licenses in limited fields of use were initially considered, it was decided early on that nonexclusive licensing of this broad, far-reaching invention would best serve the public and the universities' interests.

As noted, the license needed to be suitable for many industries, including the new companies specializing in biotechnology, and existing companies in the chemical, agricultural, pharmaceutical, mining and oil industries. It was necessary to make the terms of the license reasonable for companies big and small, rich and not-so-rich.

It is important to understand the extent of the "property" that Stanford had to license. U.S. patent applications had been filed on the methods and products of Boyer and Cohen. Because of prior publication, only U.S. patent rights were available; therefore, the policing of sales in the U.S. of unpatented products made in a foreign country using the Cohen/Boyer method could be difficult.

It was recognized that if the patent(s) was important, which it was expected to be, Stanford would have to accept and anticipate the likelihood that the validity of the patent(s) would be "challenged" particularly if it became more economic for companies to litigate rather than pay royalties.

In addition, since a patent grant is limited to 17 years, and development, testing and regulatory approvals could take up to 10 years or more, there was also the possibility that the patent could expire before useful, royalty-bearing products would reach the marketplace.

Strategy

Beginning from the first public notice that a patent application for gene-splicing had been filed, Stanford presented the discovery as "underlying the entire field of genetic engineering." Stanford consistently stated that the patents, if granted, would be licensed broadly, nonexclusively, and at modest royalties. As mentioned before, the market targeted was and is very large, therefore, the fundamental strategy was directed to encouraging companies to take nonexclusive licenses early on.

Credits—The biggest incentive for encouraging companies to take a license early on was to offer companies who signed up by December 15, 1981, a five times credit on the $10,000 minimum annual advance royalties, i.e. for each $10,000 payment, the licensee received a $50,000 credit against future earned royalties. This credit was accruable for five years or until the first calendar year in which one million dollars of end product was sold.

It was believed that the offer of five times credit for a limited time would encourage companies to take a license sooner rather than later (which could be *much* later) when products were finally on the market.

Certainty—The availability of the license was announced in early August 1981. Companies were advised that the terms of the license were only guaranteed for companies taking the license by December 15. Any possible future changes were not divulged so that, if a company wanted certainty, the company should sign up. The license was printed in order to emphasize to potential licensees that the terms were standard.

Opened Patent Prosecution—Given Stanford's intent to license as broadly as possible, challenge to the patent(s) in the courts seemed certain. As a strategic move to enhance the validity of the patent(s) and tomake the patent process open to the public.

Anyone who was aware of factors which would affect the patent's validity was asked to make them known to the Patent Office. Any company seeking to challenge the validity of the patent after its issue would then have the burden of justifying why they had not raised those issues with the Patent Office before the patent issued.

International Trade Commission—Since Stanford only had a U.S. process patent, a company could make a product overseas and sell that produce in the U.S.

without infringing the U.S. process patent.

Stanford looked to the International Trade Commission (ITC) as a means of addressing this potential problem. Section 337 of the Tariff Act of 1930 prevents certain methods of competition and unfair acts in the importation of articles into the United States.

In particular, the act was intended to cover the situation where a U.S. manufacturer licensed under a process patent is subject to unlicensed competition which practices the patented method abroad and sells the non-infringing products in the U.S. The ITC may issue remedies including exclusion orders or cease and desist orders directed to preventing the importation of the goods involved in an unfair method of competition or unfair act.

Visits to firms in Europe and Japan were made so that foreign companies would understand Stanford's intent to employ the ITC. As Tom Kiley of Genentech reported: Stanford's message to the Japanese was interpreted as "Take a license or get your socks sued off."

Personal Contacts/Media Blitz—In the period from the August announcement of the license until the December 15 closing, companies throughout the U.S., Europe and Japan were visited to explain the license.

It was decided that a short "sale" time (six months) would be optimum to develop interest and keep momentum going. Beginning August 1, 1981, Stanford advertised extensively. Stanford publicized the early signing up of companies, which also served to notify stockholders and the public of a company's entrance into the field of genetic engineering.

Royalties—It was decided that earned royalties should be modest so as to encourage companies to take a license rather than contest the patent(s). It was also decided that a stepdown earned royalty schedule would reward those companies whose sales were high without unduly penalizing the smaller company for smaller sales volumes.

Discussions with several companies of differing sizes and markets were held while license terms, particularly earned royalty terms, were being formulated. By doing this, the license was "presold" and unrealistic license terms were avoided.

Royalty-bearing sales have been divided into four categories: Basic Genetic Products, Bulk Products, End Products and Process Improvement Products. A very brief and general description is given below; the details are described in the license.

Basic Genetic Products include DNA chimeras (transformants) or chimera plasmids. For example, the "bug" (transformant) which makes insulin is a basic genetic product with a royalty of 10%. Since these products are "closest" along the chain of manufacture to the claims of the patent, they have the highest royalty.

Bulk products are products which will be processed further by a manufacturer and not used by the end user. An example of a bulk product is the disaccharide sweetener which will be used in soft drinks, diet foods, etc. The royalty ranges from 3% to 1%.

End product is a product for use by the *ultimate end* user, e.g. insulin, vaccines, antibodies. The royalty ranges from 1 to 1/2%.

Process improvement product is a material developed for or by a manufacturer to improve an existing process. An example is an enzyme which catalyzes a reaction. If the enzyme is genetically engineered and improves an existing process, the royalty would be 10% of the cost savings and economic benefit.

A logical question would be: did the strategy work? We feel that it did. Seventy-three licensees (including many foreign companies) signed up by December 15, 1981—and each received $100,000 credits as of January 1, 1983.

The DNA story is still unfolding. In general, the license was, and is, designed to be as fair and reasonable as possible, to be accomodating when there is a gray issue, to give companies the advantage when possible. For instance, companies which are working together can decide between themselves which will pay the royalty. Only one royalty payment is required along the chain of manufacture for each infringing act, i.e. a "terminal royalty concept" and licensees can decide where along the chain the royalty will be paid. Licensees can estimate quarterly royalties, with a final accurate accounting at the end of the calendar year.

Post-December 15, 1981, licenses are available; the terms do not include the five times credit on the $10,000 minimum annual royalty. Companies are expected to sign up as products begin to move into the marketplace.

Stanford is determined to monitor the license thoroughly. At present, there is a full-time market research person and a full-time licensing person basically dedicated to the case. If other staff are needed, they will be added.

Stanford recently closed the pending patent application file because of concerns about the media treatment of the prosecution of the "product" application. It was felt that the media was giving the public a misconception about what occurs in a typical patent prosecution. Stanford will, however, keep licensees generally informed of new developments.

A royalty calculation form has been developed for the licensees. For convenience, estimated quarterly payments and final accounting at the end of the year is acceptable.

Stanford is developing extensive company portfolios and building "product" files. We are following journal articles to stay abreast of new technologies, and watching newly issued patents to find out what companies are doing. By keeping licensees informed of new developments in Stanford technology, we plan to foster good relationships with our licensees. We are going to actively recruit new licensees as well as vigorously enforce the patent.

The first r-DNA product, insulin, has been introduced by Eli Lilly under the trade name of Humulin. On the near term horizon, interferon, animal and human growth hormones, and animal vaccines will be coming forward to the marketplace. Just like the phonograph, radio, television, calculators, and computers, pencillin, vitamins . . . biotechnology is going to make a difference in our lives.