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The story of the Cohen–Boyer patents

Rajendra K. Bera

In 1972, Stanley Cohen, then an associate professor of medicine at Stanford University, and Herbert Boyer, a biochemist and genetic engineer at the University of California at San Francisco, met at a conference on bacterial plasmids in Hawaii and got interested in each other's work. Boyer's team had isolated an enzyme that could cut DNA strings precisely into segments that carried the code for a predetermined protein and such segments could also be attached to other DNA strands. Cohen, on his part, had developed a method for introducing antibiotic-carrying plasmids into certain bacteria, as well as a method of isolating and cloning genes carried by the plasmids. A collaboration ensued in which Boyer's enzymes allowed Cohen to introduce specific DNA segments to plasmids, and then use the resulting plasmids as a vehicle for cloning precise, previously targeted strands of DNA. Within four months they had a breakthrough. They had succeeded in cloning predetermined patterns of DNA¹. The technique of recombinant DNA was born. Their paper (including two other co-authors) was published in the *Proceedings of the National Academy of Sciences USA*² in 1973.

Their pioneering method of cloning genetically engineered molecules in foreign cells, that is, the ability to manipulate genetic material from different organisms allowed many new medical products, such as synthetic insulin for those with diabetes, a clot-dissolving agent for heart-attack patients, and a growth hormone for underdeveloped children, to be developed subsequently. The Cohen–Boyer method of gene splicing revolutionized biological research and essentially launched the multi-billion dollar biotechnology industry. It has provided immensely valuable tools for genetic engineering. But in 1973, Cohen and Boyer had no interest in patenting the method. Academic researchers of that time preferred the seclusion of their ivory tower, devoid of taints of commercialism.

Niels Reimers, founder of Stanford University's technology commercialization programme in 1970, recalls that when he learnt of the published paper, he

immediately recognized the huge potential of the gene splicing method in industry applications. He contacted Cohen about filing a patent application; Cohen did not want to have anything to do with patents³. Well aware of the one-year grace period allowed in the US patent law between the dates of publication and filing of a patent application, Reimers persisted and eventually persuaded Cohen about the merits of seeking a patent. The patent application was filed just one week before the deadline³, on 4 November 1974, with Cohen and Boyer as inventors. Their two co-authors on the 1973 paper were not included as they did not fulfil the legal requirements for being named as inventors, that is, they were not the first to come up with any of the novel and non-obvious ideas mentioned in the patent application. (In this respect, conventions of authorship and legal requirements of inventorship are different.) If a patent was issued, it was to be assigned to Stanford University. In 1976, Boyer co-founded Genentech with Robert A. Swanson, a venture capitalist.

The patents

The original 1974 patent application had claimed both the process of making recombinant DNA and any products that resulted from using that product. The application was subsequently divided into a process patent application and two divisional product patent applications (one for recombinant DNA products produced in prokaryotic cells and the other for products produced in eukaryotic cells). The original patent application was abandoned, but the subsequent three patent applications claimed priority of invention on the basis of the original application.

Some six years after the 1974 patent application was filed, the first patent⁴ titled 'Process for producing biologically functional molecular chimeras' (US Patent No. 4,237,224) was granted on 2 December 1980; the second patent⁵ titled 'Biologically functional molecular chimeras' (US Patent No. 4,468,464) was granted on 28 August 1984, and the third patent⁶ also titled 'Biologically func-

tional molecular chimeras' (US Patent No. 4,740,470) was granted on 26 April 1988. Under the US patent laws, all three patents would expire simultaneously on 2 December 1997 because they had claimed priority of invention on the basis of their 1974 patent application. The three patents were assigned to Stanford University. In an unusual gesture of transparency, Stanford had opened the confidential patent prosecution file to the public during the prosecution stage⁷.

With the grant of the first patent, Reimers immediately set about launching a licensing programme, which became a trailblazer. Even though profit was not a primary motive, by the end of 2001, Stanford University and the University of California had made US \$255 million in licensing revenues from the patents, from licenses granted to a total of 468 companies on behalf of both universities. The licensees list not only included big names such as Amgen, Lilly, Genentech, and Merck, but also many fledgling biotech companies who used the license to establish their legitimacy^{7,8}. More importantly, a total of 2442 known products were developed from the patented technology that included drugs to mitigate the effects of heart disease, anaemia, cancer, HIV–AIDS, diabetes, etc. Commercial recombinant DNA products developed by the licensees generated over US \$35 billion in sales during the life of the patent⁷. The expiry of the patents on 2 December 1997 brought a sudden drop in the IP revenues of both Stanford University and the University of California. However, outstanding royalty payments continued to trickle in for some time after that⁹.

The confluence of actors and events

The obvious star actors in the story are Cohen and Boyer who invented the gene splicing method, but without the persuasive powers of Reimers no patent application would have been filed. He had an unusual talent for balancing academic values and industry's needs. He strived to maintain the independence and public trust of the university and its faculty

while interacting with the industry. The technology transfer programme that he launched for Stanford in 1970 put the university in an excellent position to take advantage of the Bayh–Dole Act¹⁰ of 1980, which gave US universities ownership of any patents developed using government funds. The Cohen–Boyer patent was granted ten days prior to the passing of the Bayh–Dole Act by the Congress on 12 December 1980. Reimers eventually showed the world that cutting-edge university-centred research, patents, and industry collaboration can make a formidable system that can propel a country's economic agenda, without the university sacrificing its core values. Reimers was a co-founder of the Association of University Technology Managers (AUTM).

The fact that it took six years for the first patent to be granted only shows that the patent application did not have an easy passage. At the time it was generally assumed that inventions related to the manipulation of living matter were not patentable. The 5–4 decision of the US Supreme Court in *Diamond v. Chakrabarty* on 16 June 1980 made the patenting of life-forms lawful. The Court said that 'anything under the sun that is made by man' is patentable. It further clarified that for patenting, 'the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions'¹¹. This finally cleared the way for the Cohen–Boyer patent application filed on 4 November 1974. Six months later, the patent was granted on 2 December 1980 and was assigned to Stanford University.

In the Cohen–Boyer case it was fortuitous that questions of patenting had not arisen prior to publication, hence the question of delaying publication did not arise. Just as well, since several other researchers were also zeroing in on the method and a delay could have robbed Cohen and Boyer of priority and a place in the history of science³. Fortunately, the US provides for a grace period in its patent law, not available in other countries. Thus the Cohen–Boyer technique could be patented only in the US if an application was made within the grace period. In retrospect, the loss of patent protection in other countries was perhaps a reasonable price to pay to win the race in scientific discovery, so close to a researcher's heart.

Apart from the debate whether universities should at all seek patents, there were other controversies that surrounded the recombinant DNA technology. There were concerns that innocuous microbes could be engineered into human pathogens resistant to then known antibiotics, or enable them to produce toxins, or transform them into cancer-causing agents¹². The fears turned out to be unfounded. Recombinant DNA technology now dominates research in biology.

Reimers strategy

The acquisition of a patent is usually made with some commercial intent in mind. The commercial angle that Stanford had in mind was generating revenues by licensing the patent without unduly compromising its public-service mission. They did this by providing sufficient incentives for private industry to invest the requisite additional resources to bring products to market while generating licensing fees for the university⁷ during the life of the patent (1980–97). In this Reimers eminently succeeded.

Reimers founded Stanford University's technology commercialization programme in 1970 and directed it for 22 years. During this period he also reformed and directed the technology commercialization office of MIT in 1985–86, and later, founded and directed the University of California Berkeley's technology commercialization office in 1989–90. In 1996, he founded the University of California's (San Francisco) technology commercialization office and directed it for two years³. His style provides an insight into the factors that enable successful interaction between a university and industry for public benefit.

Reimers had run a pilot programme in 1968. In one year, it produced more than ten times the amount received by Stanford in its previous 15 years of licensing through an outside corporation. He therefore conceived of Stanford University's Office of Technology Licensing (OTL) not just as a patent office, but as a marketer that would actively pursue discoveries, market them to potentially interested companies, and collect royalties on them⁸. In the process he created a licensing programme that has been hailed as coming from a genius. He conceived of a strategy that (1) was consistent with the public-service ideals of the university by

broadly licensing the technology (as opposed to high-value exclusive licensing) at affordable license fees, (2) provided incentives for private companies to commercialize derivative products, (3) contributed to the creation of an innovation system that not only benefited Silicon Valley but the entire biotech industry in America, and (4) provided income for the university's academic and R&D programmes. OTL is seen as the gold standard in the field of technology transfer from university to industry⁸. Its current IP policies have been mentioned elsewhere¹³.

Stanford faculty gradually learnt that interaction with industry often led to interesting research problems and research funding.

Stanford University

Stanford is generally credited with kick-starting the Silicon Valley high-tech industry, and subsequently spawning 'a hugely influential brood of physical- and life-science businesses across the United States and the world'⁸. Stanford's enormous influence stems from its symbiotic relationship with Silicon Valley that surrounds it and was built over a period. Its OTL has given life to many marketable technologies, but far more important is the cutting-edge doable ideas its researchers produce. Page⁸ notes that in the 1920s, Stanford's professor of electrical engineering, Fred Terman, played a key role that ultimately enabled the OTL to market technologies with phenomenal success. With the intention of creating job opportunities for his students, Terman set about attracting companies to the vicinity of the University. He attracted the core founders of Varian Associates (radar and microwave), William Shockley (co-inventor of the transistor), William Hewlett and David Packard (the duo later launched Hewlett Packard). Terman became known as the father of the Silicon Valley. When Reimers, the visionary, came to Stanford, he was at the right place at the right time for his pilot programme in 1968 to build a strong bridge between laboratory research and industry.

It is difficult to emulate Stanford's culture. There, you are almost expected to start a company before becoming a tenured professor⁸. Its strategy of protecting IP is to seed the market with as many technologies as possible, because it

is not possible to predict which of them will eventually succeed⁸. Over the years, researchers' attitudes too have changed; they are now more receptive to this strategy. Indeed many are now eager to see the potential of their technology in the marketplace. Of course, not every invention succeeds. Only about one in seven inventions from Stanford generates US \$1 million-plus a year. Generally, about 10% of the inventions have the potential to generate significant income, about 60–70% will bring in almost nothing, while the remaining will about break-even⁸.

Therefore, OTL exercises judgment in what it patents. Its licensing associates enjoy tremendous autonomy. They are well-versed in IP and contract law and draft agreement clauses without being a patent attorney³. Usually OTL will sign licenses before the patents are granted, and often negotiations begin even before patent applications are filed. Quite often, they look to the ultimate licensee to cover patent filing expenses in exchange for a six-month option on the technology⁸.

The 17 years during which the Cohen–Boyer patents were licensed, Stanford consulted widely across various stakeholders before settling on the licensing terms. Non-profit research institutions were granted research-use exemption⁷. To simplify the licensing procedure for others, it categorized the different potential recombinant DNA products into four: basic genetic products, bulk products, end products, and process improvement products. For each category, during the lifespan of the patents, it then experimented with five versions of the standard license agreements and provided three special licensing agreements that would best match the capabilities of a company with its potential for generating revenues based on the licensed technology. It kept annual fees and royalty rates reasonable⁷. In 1989, it offered especially lower licensing fees and royalty rates to 209 small, fledgling biotech firms⁷.

Stanford's licensing strategy was contrary to conventional wisdom, which was to make a killing by licensing the technology exclusively. For Stanford, the logic was that rDNA was a platform technology and it was not possible for any one company to exploit all the possible applications. Non-exclusive licensing allowed a large number of companies to push the technology forward in diverse ways, simultaneously⁷. As a matter of

precaution, Stanford set up a litigation reserve fund to enforce the patent licenses. Amazingly, it was able to settle its disputes informally without going to court⁷. An important reason was that licensing fees were affordable and licensing terms were decided upon keeping public interest in mind. That practice also made any attempt to annul the patents through formal litigation far more expensive than acquiring a license and abiding by the terms of licensing, especially when Stanford was also striving to be as transparent in its dealings as it possibly could. Trust was an important factor.

Another reason for Stanford's success appears to be the OTL's reluctance to involve lawyers even when drawing agreements because they, by nature, are risk-averse, whereas unusual success requires taking risks⁸. Reimers notes that when companies are approached by a lawyer, the chance of licensing success reduces by over 50%, because then a company's lawyer will focus on the legal strength of the patent and overlook the intrinsic value to the company that will result from the collaboration with the university and its inventors³.

Stanford's policy of sharing royalty income is straightforward. OTL receives 15%, and the remaining 85% is divided three ways between the inventor, the inventor's department, and the inventor's school/faculty^{3,8}. Sometimes inventors do not take their share (some think it is inappropriate), in which case they can ask the amount to be signed over to a research account under their control or other academic use^{3,8}.

After the Cohen–Boyer patent

When the Cohen–Boyer patent expired, Stanford's licensing revenues dipped sharply. The event stimulated several years of intense activity. The university became receptive to industry ideas and became even more user-friendly to the industry. Within six years Stanford was able to top its record royalty year⁸.

The legendary success of the Cohen–Boyer patents has greatly influenced technology transfer from university to industry. To appreciate the scale of licensing income top US universities have become capable of, consider the figures for FY 2007 (the latest year for which figures are available)^{14,15}: New York University (approx. US\$ 791.2 mil-

lion), Coloumbia University (US\$ 135.6 million). The University of California system (US\$ 97.6 million), Northwestern University (US\$ 85 million), and Wake Forest University (US\$ 71.2 million). Most US universities earn most of their IP income from biomedical discoveries, rather than from physical sciences technologies. Even in biomedical discoveries, it is often licensing income from a blockbuster patent that strikingly stands out. For example, the bulk of New York University's licensing income for 2007 came from an undisclosed portion of its worldwide royalty interest in the monoclonal antibody Remicade¹⁴ – it was US\$ 650 million! Because patents have a finite lifespan, as a blockbuster patent expires, the owning university's licensing income also takes a sharp dip till it finds another blockbuster.

Finally, what Stanford has shown is that by initiating the creation of the Silicon Valley, it not only created employment opportunities for its graduates, but was able to opportunistically use the Valley as a platform to help create a thriving biotechnology industry both in the Valley and the entire United States using the Cohen–Boyer patents as a vehicle. It did this in an exemplary manner without compromising its core academic values. It showed that by being transparent, acting in a considerate manner, and keeping public good in mind, it is possible to augment university funds without getting involved in litigation. But this high level of ethical commercialization required a genius called Niels Reimers.

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