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Patenting and Licensing of University-Based Genetic Inventions – A View from Experience at Stanford University's Office of Technology Licensing

Kirsten Leute

Office of Technology Licensing, Stanford University, Palo Alto, Calif., USA

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University technology transfer · Gene licensing · Patent application

Abstract
University technology transfer offices license inventions created at universities to companies looking for tools, additions to their product pipelines, improvements or start-up opportunities. This paper will cover the motivations for conducting university technology transfer, an overview of Stanford's Office of Technology Licensing and its patenting and licensing practices, models of royalty sharing at university technology transfer offices, and patenting and licensing genetic information inventions at Stanford University. The terms 'invention' and 'technology' are used interchangeably throughout the paper.

Motivations behind University Technology Transfer

Protection and transfer of intellectual property created at universities to industry began in the early to the middle of the twentieth century, in part due to a report written by Bush [1], but did not flourish until the passage of the Patent and Trademarks Amendment Act in 1980, also known as the Bayh-Dole Act (Public Law 96–517).

Before 1980, the government owned most inventions created under federal sponsorship. Universities could only own the technologies created at universities under federal funding if universities petitioned and were granted ownership by the federal government. This was the case with the Cohen-Boyer Recombinant DNA Cloning patent, which will be briefly discussed later. However, the government granted few licenses to companies for the inventions. In the early 1980s, the government was also searching for ways to stimulate the economy.

The Bayh-Dole Act facilitated the ability of universities to take title to inventions created at the universities under federal sponsorship. In return, universities must comply with certain provisions of the Act, including:

- granting the government a non-exclusive, royalty-free license for the technology and 'march-in rights', under which the government may grant further licenses for the technology if the licensee (the company that licensed the technology) is not effectively developing the technology, as defined under US Code Title 35, § 203
- requiring substantial manufacture of any product created from the technology to occur in the United States
- sharing the royalties generated from a license with the inventors whose discovery had been publicly funded
- showing a preference to small businesses when licensing
- supporting further research with the income derived from licensing.

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Kirsten Leute
Office of Technology Licensing, Stanford University
1705 El Camino Real
Palo Alto, CA 94306-1106 (USA)
Tel. +1 650 723 4374, Fax +1 650 725 7295, E-Mail kirsten.leute@stanford.edu

How has the Bayh-Dole Act performed? According to the annual surveys of the Association of University Technology Managers (AUTM), academic technology transfer supports tens of billions of dollars in economic activity and over 200,000 jobs [2]. In a letter recently written to the Washington Post by former Senators Birch Bayh and Robert Dole, the co-authors of the Act reaffirmed their belief in the Act and its results. As they note, the law was passed to encourage 'a partnership that spurs advances to help America' [3]. Other countries are looking at or are implementing similar policies and practices.

Stanford's Office of Technology Licensing

The mission of Stanford's Office of Technology Licensing (OTL) is to promote the transfer of Stanford technology for the use and benefit of society while generating unrestricted income to support research and education. Technology transfer is viewed as a cycle: technology is created at a university through a variety of types of funding, transferred to industry, and products are created using the technology (licensed products). The university derives revenue through the license fees received from the technology, including upfront payments (payments made upon signing the license), milestone payments (payments made when the company achieves certain product development events) and earned royalties from the sales of licensed products, which are often a percentage of the net sales of the licensed products. These revenues received by universities are used in large part to support further research in the areas that originally generated the technology.

At Stanford's OTL, the goal is not to find the company that will pay the most money for a license, but to find the best 'home' for the technology, where it will be developed into a product that will benefit people, whether it be a vaccine for chickenpox or a microchip for faster computers. If the company is truly the best match for the technology, this company may well generate the most revenue in the long run, but this is not the basis of the original decision of OTL.

The revenues brought in through university technology licensing do not approach the amount universities receive from sponsored research, let alone the overall budgets at universities. At Stanford, which arguably has one of the most successful technology transfer programs, OTL brought in USD 49.5 million in revenues in the fiscal year 2003–2004. Compare this with the sponsored research support of USD 923 million in the same fiscal year for Stanford and the overall budget of over USD 2.3 billion for the university [4].

Deciding whether or Not to Pursue Patent Rights

Not all inventions at universities are patented or even make it through the patenting process. Stanford currently files at least preliminary patent applications (provisional or original) on about 50% of incoming invention disclosures, but the university does not follow through to an issued patent with all of these inventions. Whether Stanford proceeds with a patent application on an invention depends on the following questions.

Can Stanford License the Technology as Material without Having to Patent It?

Often a company will choose to take a license for the material of the university because it would take more time and effort for the company to recreate the material than to simply take a license. In such cases, a university may choose not to patent the material because (1) a patent is not needed in order to convey the property of the university, in this case, the material, and (2) patenting can be expensive and the licenses from the material may not generate as much money as a patent would cost. For Stanford, a typical US patent application costs between USD 20,000 and 25,000 to issue. As an example, Stanford currently licenses many antibodies to companies; however, these materials are not patented. Many of these antibodies have low licensing fees (partly because they are not patented) but Stanford may receive larger amounts if the licensees make products from them. Choosing not to patent the product removes the risk of not bringing in as much revenue, if any, as patenting costs are high.

If the Invention Is Software, Would a Copyright Suffice?

Copyright, although sometimes more difficult to enforce than patents, has a longer term (70–120 years). Copyright is also automatic and therefore does not cost a university anything to procure. Stanford has numerous bioinformatics software programs that it licenses out under copyright to both end-user companies as well as software developers.

Is the Invention Patentable?

Under US patent law, an invention must be novel, useful and not obvious in order to receive a patent on the invention. Additionally, if the invention was published more than 1 year before a patent application is filed, patenting is no longer possible. If the invention fails any of these tests, Stanford, like other organizations, does not pursue patent rights.

If Stanford Pursues a Patent, Would It Be Enforceable?

In other words, would the university be able to tell whether a company was using the technology or not? If Stanford would not be able to determine this or if it would be very expensive to determine, Stanford may not try to obtain patent protection on the invention.

Should the Invention Simply Be in the Public Domain?

There may be a variety of reasons why the inventors or the university believe the invention should be open to the public at the present time, and then patent rights are not pursued.

Primer on Patent Rights

Even if an organization does seek patent rights, the US patent system is set up for the sharing of information. Since March 2001, the US Patent and Trademark Office publishes US patent applications 18 months after they are filed, except under certain circumstances. When a patent is granted, it is also published, and anyone can review not only the published patent but all of the prosecution that led to the issuance of the patent.

A patent provides the owner with a negative right, i.e. the owner has the right to exclude others from practicing the patent. The owner can choose to exercise this right or not and has only a limited time to do so. Currently, patent life is 20 years from the date of filing a non-provisional patent application. A patent owner may not assert any rights previous to patent issuance. Since the university finds most of its patents take 3–5 years to issue, if not longer, it has the right to exclude others from practicing the invention for 15–17 years. Considering the still long development cycle and large amounts of money required to support the development of therapeutic products (including those created from genetic information), this period could be considered relatively short.

Licensing: Exclusive and Non-Exclusive

Stanford would like to grant non-exclusive licenses in order that more companies may have access to discoveries, such as potential target genes, from which products can be developed for people's benefit. However, if, after marketing the gene extensively, there is only one company interested in taking a license and the company will only take an exclusive or field exclusive license, OTL must carefully consider whether to grant such an exclusive license, abandon the patent application or risk further patenting costs on the technology without a licensee in place to reimburse such costs. If Stanford cannot license a technology non-exclusively, it will often go forward with exclusive licenses.

In Stanford's experience, small businesses are more likely to request exclusive licenses than non-exclusive licenses. As they are often searching for further capital and partnerships, they find exclusive licenses more attractive to investors and collaborators because they give the company a competitive proprietary edge. Exclusive licenses also provide companies incentive to invest in the development of products made from the technology.

When granting an exclusive license, each technology manager at Stanford considers how the company will use the technology. In order to prevent the technology sitting on the shelf, each license contains a defined field of use. For genetic inventions, simple distinctions of fields may be therapeutic and diagnostic. The therapeutic field could be subdivided further into disease types or mode of delivery.

Nearly all licenses contain diligence provisions, including non-exclusive licenses. If a non-exclusive licensee is not developing a technology, its license blocks the university from granting exclusive or field exclusive licenses to a company that is more willing to develop the technology and needs exclusivity in order to conduct this development, perhaps because of funding issues. Exclusive licenses contain more stringent diligence provisions, including product developmental milestones, which a company must meet in order to retain its license for the technology. Stanford's OTL creates these milestones to coincide with the business plan of the company, but also recognizing that certain events may change the timing of the plan or the path of the company.

An important element in all of Stanford's exclusive or field exclusive licenses is the right of the university to use and publish its technologies. Stanford's clause reads as follows:

'Stanford retains the right, on behalf of itself and all other non-profit academic research institutions, to prac-

Table 1. Stanford University royalty sharing chart (in %)

	Inventor/ creator	Inventor's department	Inventor's school
Net cash royalty income	33	33	33

Table 2. Indiana University revenue sharing chart (in %)

	Inventor/ creator	Campus(es) at which invention was created	University
Of the first USD 100,000	50	25	25
Of the next USD 300,000	40	25	35
Of the next USD 600,000	30	25	45
Net revenue in excess of USD 1,000,000	25	25	50

The net revenue is divided after deducting all direct expenses necessary for obtaining protection, and licensing for applicable intellectual property.

Table 3. Pennsylvania State University sharing chart (in %)

	Inventor/ creator(s)	Administrative unit	Penn State research foundation
Net royalties and fees	40	20	40

The net royalties and fees are distributed after recovery of any direct patent or copyright prosecution, maintenance or infringement litigation costs incurred by the university.

tice the Licensed Patent and use Technology for any purpose, including sponsored research and collaborations. Licensee agrees that, notwithstanding any other provision of this Agreement, it has no right to enforce the Licensed Patent against any such institution. Stanford and any such other institution has the right to publish any information included in the Technology or a Licensed Patent.'

Stanford's main goal as an academic institution is to teach and conduct research. The university does not want technology licensing to limit education and research. Therefore, universities should preserve the right to use the technology in any manner. Likewise, the university must maintain its researchers' ability to publish at all times. Dissemination of the information is key to many faculty jobs, as well as allowing researchers to collaborate and make further discoveries based on each others' works.

Models of Royalty Sharing

If a company licenses a patent or other property from a university, the company will make certain payments to the university in consideration of the license. In this paper, the term 'royalties' is defined as all cash payments a university receives for the grant of a license. The sharing of the royalties differs from university to university. For each invention on which Stanford receives income, the royalty sharing policy of Stanford OTL stipulates that OTL receives 15% off the top of gross revenues received per year. OTL pays its budget of USD 2.5–3 million per year through the 15%, and any surplus is given to the Dean of Research. Following the 15% administrative fee, any out-of-pocket expenses still remaining on the particular licensed technology are then deducted. The remaining net amount for the technology (85% if there are no expenses to reimburse) is divided into three parts – one third goes to the inventors, one third to the inventors' departments (e.g., Genetics or Chemistry) and one third to the inventors' schools (e.g., the School of Medicine or the School of Engineering). The net royalty income sharing at Stanford is shown in table 1.

Examples of royalty sharing policies at the Advanced Research and Technology Institute of Indiana University [5], at Pennsylvania State University [6] and at Vanderbilt University [7] are given in tables 2–4 to exemplify the variety between universities. As is shown, sharing of royalties can vary between universities, as well as within a university, depending on where in the university the technology was created and how much is received in royalty payments. Many universities also receive equity as part of their licensing agreements, and the equity is often handled under separate sharing policies.

University Technology Transfer 'Success'

The vast majority of US universities do not bring in enough royalties to cover their office expenses. In Stanford's experience, it took over 10 years to break even for 1 year, then an additional 5 years to be completely out of the red, excluding patent expenses. Patent expenses at Stanford currently cost between USD 5 and 6

Table 4. Vanderbilt University royalty sharing chart (in %)

	Inventor/creator	Inventor's laboratory	Inventor's department	Inventor's school	Technology promotion	Technology research fund
Non-medical: first USD 100,000 per year	50	10[a]	0	30	10	0
Non-medical: above USD 100,000 per year	40	10	10	25	5	10
Medical center: first USD 100,000 per year	50	0	20	20	10	0
Medical center: above USD 100,000 per year	40	0	25	20	5	10

[a] For as long as the inventor remains at Vanderbilt. If the inventor leaves Vanderbilt, the inventor's school share is increased by 10%.

million each year. Reimbursement from licensees normally accounts for about one third of patent expenses at Stanford. If a technology is never licensed, OTL writes these expenses off as a loss. In 2004, Stanford's OTL wrote off over USD 700,000 in unreimbursed patent expenses.

When the licensing manager at OTL first meets with the inventors at Stanford, one of the facts she always mentions is the low likelihood of the invention being a major financial success. Our office dubbed this the 'sobering statistics' talk. Although Stanford is viewed as being one of the more successful technology transfer offices, which includes over 5,000 invention disclosures since its inception in 1969, it has had only two very successful inventions in terms of number of successful products created and income produced (over USD 50 million in cumulative income) – the most famous example being the Cohen-Boyer recombinant DNA cloning technology, which was filed before the Bayh-Dole legislation was enacted. Over the patent life of this technology, OTL brought in USD 255 million. So far, no other technology has approached these numbers. In addition, as noted earlier, Stanford's OTL brought in USD 49.5 million in the fiscal year 2003–2004. Only six inventions generated over USD 1 million in 1 year.

In the Licensing Survey of AUTM for the fiscal year 2000, AUTM reports that 0.6% of licenses granted by academic institutions generated more than USD 1 million. By informing inventors and other constituents of these numbers, Stanford's OTL hopes to provide an awareness of how incredibly rare very successful inventions are. At the same time, many of Stanford's technologies do make it into products that benefit people, which is the main goal of Stanford's OTL.

Types of Genetic Information Patents at Stanford

James Severson, President of the Cornell Research Foundation, reflected the beliefs and processes of universities on patenting genetic information in his remarks before a congressional hearing on July 13, 2000. He said: 'Most universities are not engaged in gene sequencing to the same extent as companies, and universities have not engaged in the broad-scale patenting of genetic information. For the most part, ... gene sequences are considered for patenting on a case-by-case basis and in the context of the requirements of Bayh-Dole' [8]. Universities could chose not to patent many types of genetic information, but a company is less likely to develop a product unless there is no intellectual property protection.

Stanford only patents certain types of genetic information. As with most universities, Stanford does not pursue patents on expressed sequence tags or genes with little known functionality or phenotype. It may pursue patents on single nucleotide polymorphisms (SNPs) with a known indication. For example, it is currently pursuing a patent on certain Y chromosome SNPs with discovered correlations to certain ethnicities. These SNPs may enable high-quality forensic tools. If a gene sequence has a known or highly likely function, Stanford's OTL may pursue patenting. Large pharmaceutical companies are interested in learning whether altering the function of a gene (targeting the gene) has pharmacological potential. They often want non-exclusive licenses toward that end. However, pharmaceutical companies have expressed less interest in exclusive licenses for gene targets because the chance of success may not justify the cost and they do not consider exclusive licenses necessary for their purposes. They license potential target genes less often from OTL than start-up or small businesses, which are generally inter-

ested in exclusive or field exclusive licenses. As noted earlier, this is due in part to the interest of investors and companies in only investing in technologies in which they will have a competitive advantage.

Licensing Genetic Inventions

An example of a genetic invention that Stanford patented is Dr. Mark Krasnow's and Dr. Nir Hacohen's findings of a new class of sprouty proteins. The sprouty protein plays a role in the growth and development of new capillaries. Control of this growth could treat numerous diseases, including cancer and rheumatoid arthritis [9]. Numerous companies were interested in a license for the sprouty protein technology, but all of the companies only wanted exclusive licenses. After an extensive period examining all of the companies and their licensing proposals, Stanford exclusively licensed the technology to one company. After a few years, the company terminated their license and Stanford is once again seeking a company that would like to move this project forward.

In order to examine the licensing potential of some of Stanford's genetic inventions, OTL analyzed its gene target technologies in 2001. The university had 16 gene targets available at the time. In order to address the interest of large pharmaceutical companies in non-exclusive licenses for targets, OTL drafted a program under which large pharmaceutical companies could obtain the first right to a non-exclusive license for one or more of these technologies for set licensing fees. It was an attempt to set up programs similar to the Pfizer Drug Pfinder [10] and Bayer Baytarget programs (now defunct), but in reverse; the companies would sign up for Stanford's target program instead of Stanford submitting each of its targets to their programs. The Stanford OTL target program would include a yearly fee, which would be evenly divided among the target technologies and would offset some of our patenting costs on these technologies.

After establishing guidelines on how the program might work, OTL spoke with ten large pharmaceutical companies. The main issue for the companies was that Stanford did not have enough new targets each year to entice them to pay a yearly fee to be a part of the program. OTL considered joining with some other universities in such a program to increase the pool of the available targets, but did not pursue this further due to the difficulties of working with a number of universities at once and the dilution of the annual fees across the additional technologies.

Conclusion

Stanford's OTL continues to patent and license certain types of genetic inventions. As mentioned in the paper, many companies will not develop a technology into a product without some sort of intellectual property protection on the invention. Patents have a limited term that can provide companies an incentive to produce a product that may benefit people. Patents also guarantee that the general public will learn about the invention since patents require that the substance of the invention be published.

As noted, the main mission of OTL is to promote the transfer of Stanford technology for the use and benefit of society. Its object is not to receive the highest potential amount of revenue, but instead, to have as many quality technologies researched, developed and productized as possible. It is the hope of OTL that it provides a service that helps better every person's life.

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