Technology Transfer: A Review for Biomedical Researchers

Robert Kneller
Department of Intellectual Property, Research Center for Advanced Science and Technology, University of Tokyo, Tokyo 153-8904, Japan

Abstract

Why is technology transfer important for cancer and other biomedical research? What do biomedical researchers need to know about technology transfer? This report will address these questions in the context of the United States technology transfer system, which is now ~20 years old. To accomplish this goal, this report first summarizes the importance of technology transfer and the role of intellectual property rights. Then it describes the sequential steps in technology transfer from universities to industry. Next, it describes technology transfer from the NIH intramural laboratories and other federal laboratories to industry. Finally, it describes unique aspects of technology transfer involving clinical trials. URL citations to the latest federal guidelines and regulations governing technology transfer are provided. Where appropriate, comparisons will be made with technology transfer systems in other countries. I hope that this step-by-step description of the technology transfer process will enable cancer researchers to play a more proactive role in this process and thus increase the likelihood that their discoveries will be successfully commercialized. I also hope that this report will assist such researchers to understand the policy and institutional considerations that underlie current debates concerning technology transfer.

Introduction

Technology transfer is the mechanism by which societies try to ensure that publicly funded research discoveries are transferred to companies so that they can be developed and commercialized as products that benefit the public. Approximately one-third of all R&D and one-third of all biomedical R&D in the United States and most Western European countries is funded by government (1–3). In the case of medical research in United States academic institutions, ~60% is funded by government (1). Thus society, academic institutions, and publicly supported biomedical researchers all ought to have an interest in the effective development of publicly supported discoveries. However, most governments that support scientific research cannot commercialize research discoveries. The private sector can. But there must be an effective system to transfer information to industry, and there must be incentives for industry to develop and commercialize discoveries originating in academic laboratories.

For most pharmaceutical and many diagnostic-related academic discoveries, patent protection is essential to encourage their development by companies. From discovery to marketability, much costly development work is needed. Only 1 in every 250 drugs that enter preclinical testing is approved by the FDA, and the cost of developing each new drug is $350-$500 million after factoring in the cost of failures (2). However, once marketing approval is obtained, it is often easy to copy and manufacture the chemical entity at the core of most pharmaceutical and many diagnostic inventions. IP rights, primarily patents, confer the legal right to prevent or stop such copying or to require fair compensation. This right is crucial to most academic-based bioventure companies. Most such companies have no sales income. The only resources they have to attract development funding are their researchers and IP. Without strong IP protection, most bioventures could not obtain funding. Therefore, one of the main focuses of this report will be the role of IP rights in technology transfer.

Of course, technology transfer can occur by publication of information, transfers of personnel, and other avenues. However, technology transfer of biomedical technologies to companies with the expectation that the recipients will actively exploit or develop the technology and share benefits with the academic inventors usually occurs under one of the following three types of arrangements: (a) licenses or assignments of preexisting technologies; (b) collaborative or sponsored research agreements to develop new information or technologies; and (c) formation of start-up companies, usually financed largely by private venture capital. Taken together, these methods constitute the technology transfer “system” between publicly supported research institutions and industry.

Technology transfer under any of these three types of arrangements usually involves the transfer of IP rights, although sometimes corporate sponsors of research ask only for information. Transfers of IP rights involve either licenses or assignment (i.e., complete sale or transfer) of IP rights. Therefore understanding how IP rights are acquired and transferred is key to understanding any technology transfer system.

Received 8/8/00; revised 11/20/00; accepted 11/30/00.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 To whom requests for reprints should be addressed, at Department of Intellectual Property, Research Center for Advanced Science and Technology, University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8904, Japan. E-mail: kneller@ip.rcast.u-tokyo.ac.jp.

2 The abbreviations used are: R&D, research and development; FDA, Food and Drug Administration; IP, intellectual property; DHEW, Department of Health, Education, and Welfare; USC, United States Code; CFR, Code of Federal Regulations; TLO, technology licensing office; MTA, Materials Transfer Agreement; USPTO, United States Patent and Trademark Office; PCT, Patent Cooperation Treaty; FTFA, Federal Technology Transfer Act; CRADA, Cooperative Research and Development Agreement; NCI, National Cancer Institute.

3 Available at: http://www.phrma.org/publications.
The United States Technology Transfer System: Part 1. Universities

Scope of Technology Transfer Past and Present. In the United States prior to 1980, there was no uniform policy regarding IP rights to university discoveries made with United States Government support. Procedures differed according to the laws or policies of each funding agency. In general, IP rights to such discoveries vested in the United States Government, unless the funding agency waived its rights (4). Agencies tended to license discoveries on a nonexclusive basis. In 1980, fewer than 250 patents were issued to universities per year (5), only a fraction of which were for inventions made with Government support.

However, between 1969 and 1974, universities did manage to hold or obtain title to 329 inventions generated under research support from the DHEW. During this period, the universities negotiated 78 exclusive licenses and 44 nonexclusive licenses for these inventions. The patent counsel for DHEW noted that there was increasing pressure from the pharmaceutical industry to license university inventions made with DHEW support, and several United States universities were working out Institutional Patent Agreements with the DHEW under which the DHEW would more or less automatically grant the universities ownership of the inventions so that they could be licensed to private companies (4, 6).

Today, the situation is dramatically different. In 1998, the 158 United States universities, research institutes, and research hospitals responding to the annual survey of the Association of University Technology Managers received 10,520 invention disclosures, filed 4,596 new United States patent applications, received 3,088 United States patents, issued 3,394 licenses or license options for a total of 6,834 income earning licenses, received $726 million in license income, received over $2.18 billion from industry for sponsored research and formed 305 start-up companies for a total of 2,400 start-ups formed since 1980, 75% of which remain operational (7). Probably the majority of this activity is biomedical related.4

The respondents to the Association of University Technology Managers survey identified 385 products based on their inventions that were first made commercially available in 1998. Just a few examples of such products commercialized in previous years include hepatitis B vaccine and a method of using yeast to produce IFN from the University of Washington, phy- cobiliproteins developed at Stanford to detect tumors, cisplatin developed at Michigan State University, a nicotine patch developed at UCLA, a method developed by a Florida State chemist to synthesize paclitaxel and thus conserve Pacific Yew trees, and Panretin from the Salk Institute to treat Kaposi’s sarcoma and Targetrti to treat lymphoma (7, 10).

This tremendous growth in technology transfer activities by United States universities and academic medical centers has been attributed to two factors: (a) the growth of new biomedical technologies, which increased incentives for companies to cooperate with universities where the new fundamental discoveries were being made, and thereby impelled universities to work out mechanisms to ensure development of these discoveries; and (b) reforms of United States technology transfer laws that reduced administrative barriers and increased incentives for universities to take an active role to manage their technologies and ensure their effective commercialization (9).

Legal Basis of the Present System. The legal basis of university-industry technology transfer is set forth in 1980 amendments to United States Patent Law (Public Law 96-517 codified as 35 USC sections 200–212) and regulations issued in 1987 implementing these amendments (37 CFR section 401). The Patent Law amendments are known as the “Bayh-Dole Act” after the sponsors of the Senate bill, and the regulations are known as the Bayh-Dole Regulations. The Bayh-Dole Act and Regulations allow universities to claim worldwide patent rights on inventions made under United States Government grants and contracts. The Regulations also require universities to establish procedures to ensure that university employees inform their universities of such inventions soon after they are made and of any public disclosures or sales of such inventions. Furthermore, they require universities to report such information to the Government funding agencies and to inform the agencies whether the universities will elect title to such inventions (i.e., apply for United States and foreign patents in a timely manner). If a university chooses not to file for patents, it must so inform the funding agency, which then has 60 days to request in writing that the university transfer title to the funding agency.

In 1995, NIH introduced a confidential electronic reporting system for inventions made with NIH funding. Grantees are encouraged to use the system, named “Edison,” and >120 institutions are authorized users. Approximately 3–4% of NIH grants result in invention reports, and >75 new inventions are reported to the system per week. As of December 1997, the institutions with the highest number of invention reports using Edison were Scripps Research Institute (n = 1221), University of California (n = 635), University of Wisconsin Madison (n = 433), Stanford (n = 409), and Harvard (n = 365) (communication from the NIH Office of Extramural Research).5

The Bayh-Dole Act and Regulations do not require inventors to assign their inventions to their universities. However, beginning in the 1930s and following the example of Massachusetts Institute of Technology and private industry, many

---

4 In 1996, ~86% of licensing revenue was for life science inventions (8). An analysis of technology transfer activity at Stanford and Columbia Universities and the University of California showed that biomedical inventions accounted for the majority of invention reports at the latter two universities throughout the 1980s, and that the majority of licensing revenue in all three of these universities was from biomedical discoveries (9). The overwhelming importance of biomedical discoveries was confirmed in a study of technology transfer activities in 10 major United States universities after passage of the Bayh-Dole Act (10). In 1994, life science companies supported over $1.5 billion of research in United States academic institutions, ~12% of all R&D funding in United States academic institutions (11). Equivalent NIH support was $6.2 billion (1). United States university faculty participated in founding 24 Fortune 500 companies and over 600 smaller life science companies (12). By the mid-1990s, over a thousand small businesses were developing life science technologies (11).

5 Detailed information on Edison is available at http://era.info.nih.gov/Edison.
universities began to require such assignment (13). By the year 2000, the incentives that the Bayh-Dole laws gave universities to manage their inventions and the strict Bayh-Dole reporting requirements had lead almost all major United States universities to require assignment of employee inventions, at least when the inventions arise in part under Government funding. (The University of Wisconsin requires assignment only of inventions made with Government funds. Case Western does not require assignment from graduate students who are not federally supported.)

Some universities require employees and graduate students to assign to the university prospectively and in writing any inventions related to their university work. Others (for example, Texas A&M) simply state that faculty must report all inventions to the university and, upon request, execute a formal assignment document.

The Bayh-Dole Act permits funding agencies to grant inventors’ requests to retain title, provided the universities have waived election of title. However, if universities believe an invention is valuable, they will usually elect title, apply for patents, and then license rights exclusively back to the inventors. This is the procedure usually followed in the case of inventors who obtain venture capital to form venture companies to develop their discoveries. However, a number of universities, among them Stanford and the University of California, have been supportive of employees who wish to retain title to their inventions, provided they have realistic plans to ensure development.

Most universities also assert ownership over nonpatentable materials created by their employees and recorded information generated by their employees. Whether universities can assert ownership over copyrightable works (particularly software) or tacit knowledge are issues of current debate but beyond the scope of this report (14).

Although the Bayh-Dole Act applies only to inventions made with United States Government funding, such inventions account for a significant proportion of all university inventions. Therefore, the procedures set forth in the Bayh-Dole Regulations have influenced the way universities manage technology, regardless of the source of funding. The Regulations have become the “operating manual” for technology transfer officials in United States universities. They have encouraged universities to assert control over all their technologies and to ensure that discoveries are transferred to companies that will effectively develop and commercialize them. They have prompted the creation of technology development offices or TLOs, which have become the focal point of university technology transfer activities.

Deciding Whether and How to Commercialize. Technology transfer begins with individual researchers, with their discoveries and their reporting of such discoveries to their universities’ TLOs. Universities typically require the reporting of any discoveries that researchers think might be patentable or might have commercial applications. Once TLOs receive invention reports, they must determine whether a discovery has commercial potential and, if so, how to best to ensure its development. This usually requires consideration of the following factors:

(a) What are the likely uses of the discovery? Does it have commercial potential, or is it useful primarily in noncommercial research or as an observation that should simply be published? Discoveries that have only noncommercial research use are usually transferred using MTAs.

(b) If a discovery has commercial potential, is significant additional investment (research, development, obtaining regulatory approval, marketing, and other considerations) needed to commercialize it? If so, patent protection and an exclusive license of these patent rights are likely necessary to attract such investment, at least in the case of most pharmaceutical and many medical diagnostic discoveries.

6 Thirty-five leading universities reported that in 1989 and 1990, they received 4380 invention disclosures from employees, of which they attributed 1072 to NIH or National Science Foundation funding. During the same period, licensing revenues reported by these universities amounted to $113 million, of which $82 million was attributable to inventions supported by NIH or the National Science Foundation (15).
However, TLOs may patent inventions that do not need significant additional investment and then license such inventions nonexclusively to (i) provide a royalty stream to the university; (ii) ensure recognition of the university’s contribution; (iii) monitor use of the invention; and (iv) try to ensure that the university shares in rights to derivative inventions or at least is kept appraised of improvements made to the original invention.

(c) What is the anticipated commercial value of the discovery? Stanford’s Office of Technology Licensing generally will not patent or license inventions that will not be able to generate at least $100,000 per year in royalties at some point.8

(d) Is there a company that is already interested in the invention and capable of developing it? Advice from the inventors can be very helpful in this regard. In the case of inventions arising under sponsored research agreements, the sponsoring company will usually become the licensee if the invention has commercial value.

(e) Are patent rights obtainable? The basic requirements for obtaining a patent under most national patent systems are that the invention be novel, useful (or have “industrial utility”), and non-obvious (or “embodie an inventive step”). In addition, United States patent law requires that the description of the invention in the patent application be sufficient to “enable any person skilled in the art to duplicate the invention” (35 USC 101–103, 112). A detailed analysis of these requirements is beyond the scope of this article. However, several points are germane to academic biomedical inventors.

First, publication of research results prior to filing a patent application, whether by presentation at a conference open to the public or outside persons, publication in a journal, posting on the internet, and so forth, destroys the novelty requirement for an invention based upon the disclosed information. Even submission in a grant application of information that allows a person skilled in the art to duplicate the invention can constitute publication, if the grant application is obtainable under the Freedom of Information Act (16). The United States has a 12-month grace period within which inventors can file for patent protection, the inventor makes the choice (5).

Third, there is considerable debate in the United States concerning what constitutes sufficient “utility” and “enablement,” particularly in the context of partial genetic sequences that are submitted to support a patent claim to the corresponding complete genes or to proteins coded for by the genes, or when the function of a gene can only be inferred from similarity with other genes (sometimes from nonhuman organisms), the functions of which are known. In December 1999, the USPTO issued guidelines imposing stricter standards to meet the utility and enablement requirements, but uncertainty remains concerning patentability in the above contexts (see Federal Register: 21 Dec. 1999).9

(f) How long will it take to obtain patent protection? Currently, United States patents issue 2–3 years after filing, on average. In cases where technology is changing rapidly and there is immediate demand for new discoveries, for example software or biological probes and reagents (often classified as “research tools”), it may be better from a scientific and financial perspective simply to license such inventions without applying for patent protection. Even without patent protection, such research tools often are valuable, because they save other laboratories the time and expense of making them themselves. NIH has developed streamlined procedures to allow TLOs to license nonpatented inventions made with NIH funds.10 NIH’s policy behind these procedures is to ensure that the nonprofit research community will have access to such tools. Thus, NIH usually requires that TLOs agree either to license nonpatented research tools nonexclusively or to license them exclusively to a company that will then undertake to make them widely available at reasonable cost.

(g) How much time does a TLO have before it must make a patenting decision? Usually this depends upon when disclosures will occur that might jeopardize patentability. If disclosures are not imminent, patenting may be deferred until the technology can be developed more or a prospective licensee can be found. As a general principle, freedom to publish is paramount, and if a choice must be made between publication and securing patent protection, the inventor makes the choice (5).

(h) How much will patent protection cost and what are the TLO’s resources? A United States TLO spends on average $10,000 to obtain a United States patent. Approximately 90% of this cost is attorneys’ fees. Costs in Japan and Europe for domestic inventors are similar. Unless the invention arose under a sponsored research agreement or a licensee is waiting in the wings, TLOs with lower revenues must often make patenting decisions based upon uncertain estimates of future commercial value. Relatively few universities have TLOs whose license

8 Internet address: http://www.stanford.edu/group/OTL.
income substantially exceeds expenditures (17). Many universities, e.g., Case Western, Texas A&M, and the University of Maryland, defray some of the patenting or personnel expenses of their TLOs. Some of these have become profitable after 5 or 10 years of operation, suggesting that strategic long-term investments in patent protection and marketing can pay off. Conversations with representatives of several TLOs suggest that if 25–50% of inventions for which patents are applied ultimately are licensed, this is consistent with an appropriate level of patenting of invention disclosures.

A “provisional” application can be filed simply by submitting to the USPTO the names of the invention and the inventors, the $75 provisional application fee for not-for-profit institutions, and the manuscript or other document on which the invention is based. No claims are necessary (37 CFR 1.51). (A normal patent application consists principally of the “specifications,” which describe the invention, and one or more claims that state concisely and precisely the type and scope of the patent protection that is sought.) Unless a provisional application is converted into a normal United States or PCT application within 1 year, it is considered abandoned. A provisional application is not examined. Its purpose is to provide an inexpensive, simple, fast way of establishing a filing priority date. In other words, if the inventor or another researcher publishes in print or at a conference the findings that are described in the provisional application, the inventor can still go on to make a full application for non-United States as well as United States patents. Also, if a competitor makes a similar invention after the filing date of the provisional application, the inventor will have priority to discoveries revealed in the provisional application, even if the competitor files a complete application before the inventor does. Thus, provisional applications are useful for universities with meager patenting budgets as a way of buying time to further develop an invention and to find a licensee. However, the value of a patent depends greatly upon the breadth and clarity of its claims and the extent to which the body of the patent (i.e., the specifications) supports such claims. Otherwise, the scope of patent protection may be unclear or narrow, allowing competitors to design around the patent. Therefore, simply submitting a manuscript with no claims or hastily drafted claims as a provisional application leaves open the door for competitors to submit well-drafted complete applications that claim many of the potential commercial uses that the provisional application did not clearly spell out. This is particularly likely if the first inventor discloses his discoveries soon after filing the provisional, so that rivals have an opportunity to submit well-drafted applications that design around the disclosed information or that claim inventions that the first inventor could have anticipated but did not claim in the provisional application.

Obtaining foreign patent protection increases costs substantially. Fortunately, the decision of whether to obtain foreign patent protection can be made in stages. The first stage in obtaining such protection is the filing of a PCT application in one of three designated “receiving offices,” the USPTO, the European Patent Office, or the Japanese Patent Office. This must occur within 1 year of the initial patent application. Eighteen months after the initial patent application, the PCT receiving office publishes the PCT application. (Note that if a United States patent applicant has no intention to file a foreign patent application, the United States patent application is not published until the United States patent is issued, thus keeping a veil of secrecy over the invention that is unique in the world.) Approximately 28 months after the initial application, the PCT receiving office issues a nonbinding opinion on the patentability of the invention. However, the real value of the PCT process is that it delays until 30 months after the initial application the time at which applications must be made in the individual patent offices of foreign countries. This final “national stage” is expensive because of translation costs, foreign patent attorneys’ fees, and the application fees of individual patent offices. A United States applicant needs about $50,000 to obtain a Japanese patent and a similar amount to obtain patents in the major European countries. Japanese and European applicants face similarly high costs to obtain foreign patent protection. Even Stanford’s TLO, which has one of the highest revenues of any TLO, seldom seeks foreign patent protection.

Thus, decisions on whether and how to develop inventions submitted to TLOs often involve complex considerations. TLOs must assess the technical merits of an invention and whether it is patentable, and they must try to find a licensee. Close communication with the inventors is vital to success. The staff of a TLO in a major research university typically has expertise in marketing, licensing, and various areas of science and engineering. In the case of a decision to apply for a patent, the patent prosecution work is usually contracted to private patent law firms. The Stanford TLO has no attorneys on its entire staff of 27 persons, whereas Massachusetts Institute of Technology has only 1 among its entire staff of 28.11

The experiences of technology transfer organizations that are remote from inventors, such as Research Corporation Technologies, BTG (formerly British Technology Group), the technology transfer office for the various Max Planck institutes, and the Japan Science and Technology Corporation (JST) suggest that TLOs that are based in individual universities are better able to work with inventors to find ways to develop high risk but nevertheless promising technologies. However, an in-depth analysis of these experiences is beyond the scope of this report.

Marketing and Licensing. Although TLOs often list available technologies on the internet and mail information about new technologies to possibly interested companies, one study suggests that targeting a few potential licensees and building upon long-standing personal contacts are the most effective ways to interest companies in university technologies. Examples of successful marketing methods include face-to-face or telephone conversations to discuss new technologies, visits to university laboratories by company officials, or visits to company laboratories by university scientists (18). Often the inventors themselves are the best source of information about potential licensees.

TLOs almost always license, rather than assign, their rights in inventions. Under the Bayh-Dole Regulations, universities must obtain permission from the funding agency before they assign any invention made under United States Government

funding. In addition, sometimes the best way to develop an invention is to license separate fields of use to different companies. For example, in the case of a method to detect precancerous lesions by distinctive mRNA or protein markers, one company may be best suited to develop the discovery for lung cancer, whereas another company might be best suited to develop the technology for bladder or colon cancer. Finally, universities often want to retain some control over their discoveries to ensure their development. For example, even under an exclusive license for the lifetime of a patent, a university usually exercises its residual ownership rights through “due diligence” or “benchmark” clauses in the license. Such clauses enable the TLO to revoke the license if the licensee does not develop the invention. In the case of biomedical technologies, such clauses often involve both annual (often graduated) license renewal fees and development milestones.

Examples of such milestone clauses are: “licensee must develop two water soluble analogues within one year of executing the license agreement”; “licensee must complete initial preclinical pharmacology and toxicology studies within two years of executing the license”; and “licensee must obtain FDA approval to begin human clinical trials within three years of executing the license.” Such benchmark commitments are best derived from business plans that all applicants for exclusive licenses should be required to submit during the license negotiation process. In other words, the benchmark clauses merely reflect what the licensee’s own business plan says the licensee will do and the revenues it expects to earn. Most TLOs will renegotiate benchmark clauses in the event the licensee is making a good faith attempt to develop an invention but unforeseen circumstances have prevented it from meeting the benchmarks. However, such clauses are an important means to pull an invention back from a licensee that has lost interest in developing the invention.12

The provisions discussed above are incompatible with assignment agreements but are easily accomplished using licenses. Therefore, license agreements have become the common means of technology transfer in the United States. As a general principle, nonexclusive licenses are preferred because this allows university discoveries to be widely used and avoids one company obtaining control over an important new discovery (17). However, as noted in (b) above, exclusive licenses are often necessary to provide incentives for companies to develop biomedical inventions. Rationales for nonexclusive licensing, rather than simply open publication or distribution, were discussed in (b) and (f) above.

Even if an invention has commercial value and could be licensed exclusively, if its main value is as a “research tool,” TLOs should try to ensure that researchers in other non-profit laboratories can easily use it.7 NIH is particularly concerned about the following three scenarios: (a) in the case of a research tool developed by a university researcher with NIH funds, the university’s TLO grants an exclusive license to the research tool. Subsequently, the TLO’s licensee restricts access to the tool by researchers in other universities, either by charging high prices or by requiring that other universities agree to transfer to the licensee any discoveries their researchers make using the tool or a portion of any royalties the university earns from commercializing such discoveries. (These requirements are known as “reach through” provisions.); (b) the same scenario as (a), except that the licensee is a company that co-funded the development of the research tool along with the NIH; and (c) in the case of an NIH-supported scientist who needs a proprietary research tool from another organization, the provider requires the TLO to agree to “reach through” provisions, giving the provider the right to commercialize any inventions made using the tool or to share in any royalties from such commercialization.

In December 1999, the NIH issued “Principles and Guidelines on Obtaining and Disseminating Biomedical Research Resources” to address these situations.13

To avoid scenario (a), the Guidelines state that exclusive licenses for research tools that require no further development should generally be avoided, except in cases where the licensee undertakes to make the tool widely available through unrestricted sale, or the TLO retains rights to make the tool widely available. When an exclusive license is necessary to promote development of the tool, the TLO should ordinarily limit the license to the commercial field of use, while retaining for itself the right to use the discovery and distribute it to not-for-profit institutions.

To avoid scenario (b), the Guidelines recommend that universities include in sponsored research agreements terms that either (i) allow the university to distribute research tools freely to not-for-profit organizations or (ii) that obligate the sponsoring company to make the research tools available to the academic research community on reasonable terms. The underlying rationale for this recommendation, as well as that related to scenario (a), is that universities’ Bayh Dole rights to patent and license NIH-sponsored inventions are accompanied by corresponding obligations to promote the utilization, commercialization, and public availability of these inventions. The statement of principles preceding the Guidelines states, “Restrictive licensing of such an invention, such as to a for-profit sponsor for exclusive internal use, is antithetical to the goals of the Bayh Dole Act.” To avoid scenario (c) when obtaining research tools from a not-for-profit institution, the Guidelines state “It is expected that agreements to acquire NIH-funded materials . . . for use in NIH-funded research will not include commercialization option rights [e.g., exclusive license options], royalty reach-through, or product reach-through rights back to the provider.” To mitigate scenario (c) when negotiating for research tools from a for-profit entity, the Guidelines state, “Agreements to acquire materials . . . for use in NIH-funded research may . . . provide an option for an exclusive . . . commercialization license to new inventions arising directly from the use of the

---

12 Benchmark clauses are less important in licenses to venture companies, partly because the development path for such technologies is less certain but also because the private capital investors and the managers whom they appoint can usually be relied upon to push forward the development of the technology.

material. [Such agreements] should be limited to circumstances where the material sought . . . is unique . . . and not reasonably available from any other source . . . . In determining the scope of the license or option rights . . . . Recipient should balance the relative value of the provider’s contribution against the value of the rights granted, cost of the research and importance of the research results . . . . Recipients should reserve the right to negotiate license terms that will ensure: (1) continuing availability to the research community if the invention is a unique research resource; (2) that the provider has the technical and financial capability and commitment to bring all potential applications to the marketplace in a timely manner; and (3) that if an exclusive license is granted, the provider will provide a commercial development plan and agree to benchmarks and milestones for any fields of use granted.” In other words, universities should try to assure that other academic researchers will have access to any inventions they make with research tools obtained from private companies, and that the companies that provide such tools will have exclusive rights to commercialize these inventions only to the extent that they remain able and committed to such commercialization.

Successful implementation of these guidelines will depend upon researchers, TLOs, and companies developing consensus concerning what constitutes “research tools,”7 and on appropriate limits to companies demanding exclusive rights to university inventions and on the universities’ freedom to license their inventions exclusively.

The licensing of diagnostic inventions raises similar concerns. Athena Diagnostics obtained exclusive licenses from Baylor for genetics tests for Charcot-Marie-Tooth disease type 1A, from Duke for use of the apolipoprotein E gene to detect predisposition to Alzheimer’s disease, and from the University of Minnesota for genetic diagnosis of spinocerebellar ataxia type 1 (19). It remains to be seen whether companies such as Athena Diagnostics will permit clinical laboratories to perform these tests under reasonable sublicense terms.

Many TLOs may favor exclusive licenses of research tools and diagnostic technologies, because they find it burdensome to negotiate, collect, and audit a large number of nonexclusive licenses. However, Stanford and the University of California licensed the patent rights to the Cohen and Boyer’s recombinant DNA (gene splicing process) technology nonexclusively, and this invention has generated more license revenue ($250 million from 1981 to 1997) than any other university invention. Also, Columbia University’s single most profitable invention has been the Axel patents for a new process to insert genes into mammalian cells to make proteins (9). These examples suggest that nonexclusive licensing of research tools and diagnostics can generate great financial returns to TLOs and university inventors.

Important factors in most royalty negotiations are the type of technology, the perceived risk associated with the technology, its stage of development, the projected cost of bringing a product to market, the size of the potential market, the anticipated profit margin, the strength of the patent claims, whether patents have actually issued, the prospects for pending patent applications, the estimated cost of the research that lead to the invention, the scope of the license (exclusive or nonexclusive, field of use, geographic scope, among others), and royalty rates for comparable inventions. Initial fees for exclusive licenses often are under $100,000, because technologies usually are in early stages, have uncertain commercial potential, and require considerable investment to be developed into marketable products. The majority of running royalty rates based on net sales are probably in the range of 1–8% (5, 1997 personal communication from the NIH Office of Technology Transfer, in 1997). However, royalties can also be very high. In 1995, Amgen paid Rockefeller University $20 million in up-front royalties for exclusive rights to the mouse leptin obesity gene and pledged to pay considerably more if it chose to continue the license (4).

The Bayh-Dole Regulations impose specific obligations on licenses of inventions made with Government support:

(a) University inventors must receive a share of royalty income with the remainder to be used for research, education, and expenses associated with technology management. Usually, TLOs will use initial royalty income to pay inventors a minimum level of royalties and to cover TLO operations and patent expenses. Then they will divide any remaining income between the inventors, their departments, and the university as a whole, according to formulas that vary from university to university.

(b) Universities must make efforts that are “reasonable under the circumstances” to attract small business licensees and give licensing preference to a small business if the TLO determines that the small business is equally as likely as a large company to “bring the invention to practical application.”

The decision of whether to give such a preference in any particular case is at the discretion of the university, although the Department of Commerce has authority to review the licensing programs of individual universities to determine whether they need to implement this provision more effectively. I know of no cases of such a review. The GAO report on university administration of the Bayh-Dole Act (10) found that major research universities license the majority of their inventions to small businesses, despite the absence of specific university policies to implement this provision of the Bayh-Dole Act and despite NIH and other government funding agencies not collecting data to monitor compliance with this provision. In other words, TLOs appear to be complying with the small business licensing preference largely on their own accord. Therefore, they will probably continue to preserve their discretion on how to implement this provision.

(c) If a university grants an exclusive license to use or sell in the United States an invention made with Government funds, the licensee must agree to manufacture substantially in the United States products made using the invention. This requirement does not apply to licenses that do not cover the United States market. The funding agency may waive this requirement if the university shows it has made reasonable but unsuccessful efforts to find a company that would manufacture in the United States.

7The following are criteria to qualify for “small business” status: independent ownership and operation (i.e., not affiliated with a larger organization); total employees (including those of any affiliates) do not exceed 500; not dominant in its field of operation; principal place of business located in the United States; at least 51% owned (or in the case of a company whose stocks are publicly traded, at least 51% of its voting stock is owned) by United States citizens or permanent resident aliens (13 CFR 121.4).
According to NIH guidelines for handling requests for waivers of this requirement, NIH may take into account benefits other than domestic manufacturing such as: (i) the rapid availability of a product that will benefit public health; (ii) investment by the potential licensee in United States facilities, equipment, or research; (iii) the creation of new or higher quality United States jobs; and (iv) the enhancement of job skills among United States workers.

(d) Universities must report annually to funding agencies on the utilization of inventions, including development status, date of first sale, and royalties received. The agencies must keep this information confidential. NIH encourages TLOs to use the Edison electronic reporting system for such reports.

(e) The Government must receive a nonexclusive, nontransferable, irrevocable royalty-free license to practice the invention throughout the world or to have the invention practiced on its behalf. This ensures that the Government can continue to use for its purposes the inventions it has funded. It functions primarily as a research use license for the Government. Commercialization of inventions or assisting competitors of licensees to commercialize inventions is not regarded as a legitimate government purpose. I know of no examples where companies have disputed the Government’s use of this license.

(f) The Government can require third-party licensing if the university or its licensee is not taking effective steps to develop the invention or such action is necessary to meet health or safety needs. The Government has never fully exercised these “march-in rights.” To do so would be difficult and would require many procedural steps designed to protect the interests of universities and their licensees.

(g) In United States patent applications, universities must acknowledge Government support that lead to the invention and the Government’s residual rights mentioned in (e) and (f) above. They must also inform licensees of these rights and the other requirements set forth in (a)–(f) above.

**Sponsored Research Agreements and Academic Biotechs.** Although licensing is at the heart of technology transfer, technology transfer involves more than licensing. As noted above, income from sponsored research agreements with industry is three times greater than license income. Often a simple license agreement or MTA leads to a sponsored research agreement offering long-term benefits in the form of interesting and practical research opportunities for faculty and students, employment opportunities, interchanges with industry scientists, development of university discoveries, as well as increased research funding (17). In 1998, the leading academic users of industry-sponsored research funds were the University of California ($162 million), Massachusetts Institute of Technology ($74 million), Penn State ($66 million), Duke ($65 million), and Georgia Tech ($57 million). For comparison, the leading 1998 recipients of adjusted gross license income were University of California ($73 million), Columbia ($62 million), Stanford ($43 million), Florida State ($47 million), and Sloan Kettering ($38 million; Ref. 7).

However, increased collaboration with industry raises concerns related to academic freedom, inappropriate shift in research emphasis away from fundamental research, conflict of interest, and misappropriation of publicly funded research. Discussion of these issues is beyond the scope of this report, except to note the following:

(a) About 20% of academic life scientists responding to a survey said that companies had delayed publication of their research results by >6 months, and 9% reported refusing to share research results with academic colleagues on at least one occasion. Refusal to share research results was more common among researchers collaborating with industry, genome researchers, and more productive faculty members (20–22).

(b) A time series analysis of patenting and licensing at the University of California and Columbia and Stanford detected little evidence that the Bayh-Dole reforms were associated with a shift toward applied research topics (9). Analysis of publication data also does not indicate that increasing cooperation with industry is skewing university research toward more applied topics or lower quality research. In fact, scientific papers that are co-authored by university and industry researchers are somewhat more likely to be highly cited papers than those written by university researchers alone (23).

(c) Conflict of interest policies (regarding whether faculty may have a financial interest or management position in a company that might be affected by their research, what extent of disclosure is required, and so forth) vary between universities (24) (see also 42 CFR 50.603–605). In 1998, the FDA issued regulations requiring companies submitting drug approval applications to the FDA to disclose compensation to investigators or any financial interests the investigators may have had in the outcome of their research (21 CFR 54).

(d) The grant of future exclusive license options to corporate research sponsors should be specific to the scope of the sponsored research, and TLOs should not grant to corporate research sponsors rights to all Government-supported inventions from major units of the university, such as departments, centers, and laboratories (5). NIH guidelines state that in considering whether universities should grant sponsors the right to license future NIH-supported inventions, universities should: (a) take into consideration if the sponsor has the capability and commitment to develop the inventions; and (b) require development commitments before a sponsor can exclusively license a particular technology. Also, sponsors should have only 6 months to exercise their option to license inventions. These guidelines were developed in the wake of criticisms that a 10-year $300 million sponsored research agreement between Sandoz and the Scripps Research Institute (which received $123 million in NIH support in 199917) could restrict academic freedom and could give Sandoz too much control over Scripps’s research projects and results (25). NIH concluded this agreement was unique among sponsored research agreements, and Scripps and Sandoz subsequently modified the agreement (26). The fact that NIH continues to support the vast majority of university biomedical research.

---


16 Internet address: http://era.info.nih.gov/Edison/sponsored.html.

17 Internet address: http://grants.nih.gov/grants/award/award.htm.
R&D should ensure that the NIH guidelines carry considerable influence.

One aspect of government- and corporate-sponsored research funding that is not common in Europe or Asia is that United States faculty, not tenured researchers, and technicians often depend on such "soft money" for a significant proportion of their salaries. The percentage of salaries that are guaranteed for tenured faculty varies between universities, but most researchers know their economic as well as professional survival depends on being able to receive government and industry grants. Such soft money supports a much larger manpower pool in universities than would be possible if salaries were guaranteed. This large soft money-based manpower pool, coupled with levels of government support for biomedical research unparalleled and the competitive peer-review mechanism to allocate such support, has made United States academic institutions important generators of new biomedical technologies, whereas European and Japanese academic institutions have lagged in this regard (1, 27–29).

Another unique feature of technology transfer in the United States is the important roll start-up or bioventure companies play in developing university discoveries to the point where larger companies become interested in commercializing them. The only European country where bioventures have played an important role in the technology development process is the United Kingdom (27). Recently, the number of bioventures has increased in Germany, but German companies face significant labor mobility constraints not faced by United States companies and tend to focus on niche areas of process technologies rather than on pharmaceutical and diagnostic development (30). In Japan, the current number of independent bioventures is probably <50, and those based upon university technologies or that have significant links with university researchers are even fewer in number.

Formation of a bioventure can be an effective means to mobilize committed researchers, private capital, and management expertise to push forward the development of promising biomedical discoveries that are not immediately attractive to large companies or that do not fit within the competencies of established companies (27, 31). In effect, venture companies can take over from TLOs the task of championing promising university technologies and shepherding them through the intermediate development process between university research and end-stage commercialization. In 1998, the universities that spun off the most new companies were Massachusetts Institute of Technology (19), University of California (19), Cal Tech (11), Georgia Tech (9), and Stanford [(9) (Ref. 7)]. Some universities, such as Massachusetts Institute of Technology, play an active role in the formation of their start-up companies (raising capital, recruiting management, developing a business plan, and other activities). Others, such as Stanford, expect entrepreneurial faculty to rely on their own or locally available resources.

Many universities are willing to support venture start-ups by their faculty by exclusively licensing to them key inventions (often the faculty members’ own inventions) in return for equity in the new companies rather than cash royalties. In 1998, the universities executing the largest number of licenses with equity were Johns Hopkins (19), University of North Carolina Chapel Hill (16), University of Tennessee Research Corp. (12), Cal Tech (10), and Massachusetts Institute of Technology [(10) (Ref. 7)]. Only recently has Stanford begun to take equity from its start-ups in lieu of up-front royalties. Some universities have created their own venture funds to support their start-up companies. Atkinson provides a history of the early experience of the funds established by Harvard, Johns Hopkins, and University of Texas Southwestern to develop biomedical discoveries (32). Lerner (33) examined the experience of ARCH Venture Partners (Argonne National Laboratory/University of Chicago) and the management challenges faced by university venture funds.

The conflict of interest issues discussed above are especially pertinent in the case of faculty who also have a financial, management, or scientific interest in venture companies. Researchers who are contemplating forming a company, especially those who are considering assuming a management position or having their graduate students work in the new company, should consult with their universities’ administrators and review their universities’ policies on these issues.

The United States Technology Transfer System: Part 2. NIH and Other Government Laboratories

In 1993, federal government laboratories performed ~10% of all health R&D in the United States, compared with 43% by industry. Of the federal laboratory share, 60% was performed in the intramural laboratories of the NIH (3).

Prior to 1980, the DHEW owned work-related inventions made by NIH intramural scientists. In 1976, the IP portfolio of DHEW consisted of ~400 patents and patent applications, most for inventions made by employees of DHEW laboratories, particularly the NIH. A small proportion of these patents were licensed. Between 1969 and 1976, the DHEW had issued 19 exclusive licenses and 90 nonexclusive licenses (6).

The authority of the DHEW to issue such licenses had not been clarified in laws or regulations. This clarification came under section 207 of the Bayh-Dole Act, which specifically granted the Department of Health and Human Services and other federal agencies authority to patent and license inventions arising within their respective laboratories. Section 209 of the Bayh-Dole Act imposed many of the same conditions that it imposed on licenses from universities: specifically, the United States manufacturing preference, march-in rights, and submission of a development and commercialization plan (conditions imposed on all licenses), as well as the small business preference in the case of exclusive licenses. In addition, it stipulated that exclusive licenses be granted only after public notice and comment—a condition not imposed on university licenses.

However, the Bayh-Dole Act did not give individual laboratories, such as the NIH, IP ownership or management rights. The first step in this direction came the same year under the Stevenson-Wydler Technology Innovation Act of 1980 (Public Law 96-480) authorizing individual federal laboratories to...

---

18 Available at: http://www.nber.org/papers/w6846.
establish “Research and Technology Applications Offices” to promote technology transfer to industry and local governments.

However, the key legislation authorizing federal laboratories to manage their own discoveries was the FTTA of 1986 (Public Law 99-502). The FTTA explicitly gave individual laboratories authority to patent and license inventions by their employees. It also specified that the inventors should receive at least 15% of annual royalty payments and that the laboratory should receive at least half of the remaining royalties. (Agencies have the option to distribute the remaining royalties among their other laboratories, but it appears that most agencies let the inventing laboratory manage 100% of royalties.) Under separate legislation, the Government must obtain rights to all work-related inventions by its employees (37 CFR 501 and 45 CFR 7). Thus, the FTTA gave individual federal laboratories incentives to manage their employees’ inventions that are similar to those that the Bayh-Dole Act gave to universities.

In terms of number of licenses and royalties, the NIH is far ahead of any other federal laboratory. In fiscal year 1999, NIH employees made 294 invention disclosures, and the NIH filed 169 patent applications, received 163 patents, executed 204 licenses, and received $45 million in license royalties, which would rank the NIH in first to fourth place in comparison with United States universities (7). From fiscal years 1996–1998, the NIH granted 87 exclusive licenses and 514 nonexclusive licenses and received $102 million in license royalties (95% of total royalties received by the NIH, Department of Energy, National Aeronautics and Space Administration, Army, Navy, and Air Force combined). Fifty-seven % of the NIH’s licenses were to small businesses, and 86% to domestic entities (34).19 It should be noted that the NIH’s largest source of royalties, the HIV/AIDS diagnostic kit co-invented with French researchers at the Institut Pasteur, has been licensed nonexclusively, again showing that nonexclusive licensing can result in wide, reasonably priced access and high royalty income.

The FTTA also authorized federal laboratories to enter into CRADAs, the federal laboratory equivalent of sponsored research agreements. CRADAs are the only mechanism under which a company or other non-government organization can support research in federal laboratories and, in exchange for research support, receive the right to license resulting inventions or other rights to future inventions.

The basic exchange that occurs under CRADAs is: (a) research support (personnel, equipment, laboratory space, know-how, and/or money) contributed by the CRADA partner in return for (b) (i) research support (personnel, equipment, laboratory space, and/or know-how, but not money) contributed by the Government laboratory and (ii) IP rights to inventions that may arise under the CRADA research. The NIH grants CRADA partners “an exclusive option to elect an exclusive or nonexclusive commercialization license” to any inventions by Government employees made under the scope of the CRADA research plan. However, the CRADA partner must still negotiate fair licensing terms with the NIH, including due diligence clauses.

Certain restrictions apply to CRADAs that do not apply to university-industry sponsored research agreements. The NIH is reluctant to use CRADA funds to pay part of the salaries of permanent professionals, although CRADA funds are often used to hire postdoctoral-level researchers and technicians. CRADA opportunities must be advertised in the Federal Register prior to execution, unless the laboratory can demonstrate that only one company could be a suitable CRADA partner. Also, the FTTA requires that the Government retain a nonexclusive, irrevocable, paid-up license to any CRADA inventions, including those made solely by employees of the CRADA partner. The CRADA partner has only 30 days (plus an additional 30 days upon written request) to review proposed publications of CRADA data to prepare patent applications or to make sure that confidential information is not being divulged. However, CRADA partners have the exclusive right to use CRADA data for drug approval applications to the FDA or for other regulatory applications.20

A special short form “Materials Transfer” CRADA has been in use since 1997 to enable NIH researchers to obtain research materials from companies that would not release the materials absent an option to license inventions made using the materials. In effect, this Materials Transfer CRADA represents a pragmatic response to the same situation described as “scenario c” in “Marketing and Licensing” above; to obtain proprietary research materials, scientists and their institutions sometimes have no choice but to promise the providers rights to inventions made using these materials. The issue for negotiation becomes the nature and breadth of such rights.

In fiscal year 1999, the NIH executed 48 standard CRADAs and 78 Material Transfer CRADAs. Under a CRADA signed in the mid-1990s, Bristol-Myers Squibb and the National Cancer Institute collaborated on clinical trials to develop paclitaxel (Taxol) as a first-line treatment for breast and ovarian cancer. Paclitaxel is one of the most important cancer drugs introduced in the past 15 years. A unique feature of the paclitaxel CRADA was that Bristol-Myers did not receive license rights to the basic compound, because the compound was not patentable, its structure having been published many years previously. However, it did receive exclusive access to clinical data from NIH-supported researchers, which it needed to obtain regulatory approval from the FDA.

Some Government-owned contractor-operated laboratories, for example Los Alamos, Lawrence Livermore, and most of the Department of Energy’s other university-operated laboratories, have agreements with Department of Energy that collaborative research with companies will be conducted under CRADAs. In such cases, the Government-owned contract-operated laboratory functions almost as if it were a Government-owned laboratory, and the only way a collaborating company can obtain future IP rights to discoveries made in the laboratory is through a CRADA.

19 Available at: http://www.nih.gov/od/ott/.

20 See the NIH model CRADA at http://www.nih.gov/od/ott.
Clinical Trials and Regulatory Approval in the United States

Background. Clinical trials involve the testing of new drugs, diagnostics, and medical devices in humans to demonstrate safety and efficacy and to determine suitable doses. The goal of most clinical trials is to obtain regulatory approval for marketing. Marketing in the United States requires approval from the FDA. Approval requires three trial phases. Phase I determines safe doses and pharmacology with an eye to therapeutic effects. Usually 15–80 patients are involved. In the case of oncology drugs, these are patients who have already failed conventional therapy. In the case of noncancer drugs, healthy volunteers are sometimes used. Phase II estimates the response rate and also identifies risks of side effects in a defined patient population, usually consisting of 30–300 subjects. Phase III involves hundreds to thousands of patients to determine whether the new drug offers significant advantages over standard therapies and to monitor adverse reactions. In almost all Phase III trials, matched or randomized controls are required (2, 35). In the case of new cancer drugs, the number of patients in each phase is usually in the lower ranges cited above.

The approval process for oncology drugs is expensive but less so than for most other new prescription drugs. The NCI of the NIH spends on average $2500 to $3000 per patient enrolled in NCI-sponsored clinical trials just to cover study management, data collection, and data monitoring costs. Costs of the drug, physicians’ and nurses’ time, additional tests, other hospital charges, and data analysis are all additional. My review of all new oncology drugs approved by the FDA from 1990 through 1999 indicates that over half the new drugs received initial approval without Phase III trials. Often approval was granted on the basis of results from 2 to 5 Phase II trials that were preceded by less than 10 Phase I trials. For a new oncology drug, typically 100–500 trial participants are needed for approval. The average approval time for an initial indication for a new oncology drug is usually 2–3 years. Approval criteria and data collection procedures (satisfying good clinical practice guidelines) so that if one regulatory authority approves a drug, the other authorities will also approve, requiring at most one or two relatively small “bridging” trials. More information on harmonization is available at http://www.fda.gov/cder/guidance/index.htm.

NIH-supported Clinical Trials. Unlike other governments, the United States Government provides substantial financial as well as scientific support for such trials. Most of this support is from the NIH, which spent $1.2 billion to support clinical trials in 1995, ~13% of its R&D budget (36). The NIH justifies its support for clinical trials on the basis that such support is necessary (a) to bring drugs for some rare diseases closer to commercialization; and (b) to test existing drugs or combinations of drugs for diseases or populations that otherwise would not be the subject of clinical trials. In addition, the NIH has active drug discovery and preclinical development programs, and often it is willing to support clinical trials to accelerate the commercialization of drugs emerging from these programs.

Although the NIH has its own 250-bed hospital, most NIH-supported clinical trials are conducted in extramural academic medical centers. NIH awards grants to individual researchers who submit well-qualified clinical trial proposals. It also supports clinical trial centers or units in a number of teaching hospitals. For example, the NCI funds about 17 centers for Phase I trials and an equal number for Phase II trials. The NCI pays the costs of study management, data collection, and data analysis plus overhead. However, non-experimental costs must be covered by the patients’ normal health insurance, the providing hospital, or some other source.

Often NIH-supported clinical trials involve collaboration with industry, particularly the company that owns the investigational drug. Such cooperation usually occurs under either a Clinical Trial Agreement or a CRADA between the company and the NIH. In either case, NIH scientists, the university principal investigators, and the company jointly develop the protocol.

Under a typical NIH Clinical Trial Agreement, the company will supply the NIH-supported university researcher with enough of its drug to complete the trial. In return, the company will receive the trial data that it needs to obtain FDA approval. Under a typical clinical trial CRADA, an NIH-sponsored university researcher will receive sufficient drug from the company. The NIH will receive some money to offset its costs. The company will receive (a) exclusive access to the data it needs to obtain FDA approval and (b) the right to obtain an exclusive license to inventions that arise under the CRADA research, including inventions consisting of methods of medical treatment.

Industry Support for Clinical Trials. As noted above, ~80% of support for United States clinical trials comes from industry. Companies contract either directly with medical centers or with Contract Research Organizations that will manage the trials for the companies. In general, corporate funds can be used to pay salaries of physicians, nurses, and other personnel. Some physicians and nurses working in clinical research units of major university hospitals rely on soft money from corporate contracts, or grants from the NIH or other non-profit outside institutions, for well over half their salaries.

There is concern that corporate support may influence researchers’ conduct of trials or their interpretation of trial data. Conflict of interest concerns also arise when investigators are shareholders or managers in companies formed to commercialize their discoveries. Since 1998, companies submitting drug

21 Although marketing in other countries requires approval of respective national regulatory agencies, substantial progress has been made to harmonize regulatory approval procedures in the United States, Japan, and the European Union. The goal of this effort is to have similar approval criteria and data collection procedures (satisfying good clinical practice guidelines) so that if one regulatory authority approves a drug, the other authorities will also approve, requiring at most one or two relatively small “bridging” trials. More information on harmonization is available at http://www.fda.gov/cder/guidance/index.htm.

22 Available at: http://www.fda.gov/cder/.
approval applications to the FDA must disclose compensation to investigators and any financial interests investigators may have in the outcome of the research (21 CFR Part 54). However, when investigators themselves discuss or publish their findings, their understanding varies concerning when and to what extent they should disclose financial interests in the outcome of their research (37).

**IP Rights and Regulatory Exclusivity.** Rights to inventions arising in the course of clinical trials are determined in the same way as other inventions; extramural institutions receiving NIH funds can patent and license such inventions, NIH can patent and license intramural NIH inventions, and medical centers and industry can decide among themselves how to patent and license inventions arising under industry-funded trials. Inventions arising under clinical trials are usually method-of-use inventions, e.g., a new combination of drugs, a new route of administration, or a new duration of administration. Although not as valuable as inventions claiming a new chemical compound, such inventions may be valuable to companies, particularly if it is not possible to obtain a patent on the basic chemical compound, as in the case of paclitaxel. Therefore, corporate sponsors of clinical trials sometimes will bargain hard to ensure they have the right to patent or exclusively license such inventions.

If a new drug is either a new chemical entity or an orphan drug, a company seeking FDA approval also receives a period of regulatory exclusivity, regardless of whether it obtains patent protection. Under the 1984 Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act, Public Law 98-417), once the FDA approves a drug that does not contain a previously approved active moiety, no other person may submit an application for a drug based upon the same (or substantially the same) active moiety for 5 years (21 USC 355). Under the Orphan Drug Act (Public Law 97-414), the FDA may designate as “orphan drugs” drugs for diseases affecting <200,000 persons in the United States per year. If the FDA approves an orphan drug, it will not replace the same drug submitted by another company for the same indication for a period of 7 years (21 CFR 316).

In the case of paclitaxel, Bristol-Myers Squibb used data from NCI-sponsored clinical trials to obtain FDA marketing approval as a new chemical entity, which it subsequently marketed as Taxol. Because patent protection on paclitaxel was not obtainable, Bristol-Myers had only the 5 years of regulatory exclusivity to market Taxol before generic manufacturers of paclitaxel began marketing competing versions of the same drug.

**Concluding Observations from an International Perspective**

I hope this report has given biomedical scientists an understanding of the United States technology transfer system that enables them to deal effectively with TLO officials and industry representatives to increase the chance that their discoveries will be developed into commercially successful or widely used products. I also hope it helps scientists understand current trends and policy concerns regarding technology transfer, and that it helps persons outside the United States to understand better a system that is being imitated in Europe, Canada, China, and other countries.

The system described above, characterized by ownership and management of IP by the research institutions, is not the only model of technology transfer. Alternative models include: (a) leaving ownership and management of publicly financed discoveries in the hands of the inventors; (b) ownership and management by central government agencies; (c) emphasis on putting publicly financed discoveries in the public domain with decreased emphasis on patenting and, in particular, exclusive licensing; and (d) voluntary assignment of ownership rights to for-profit corporations that will assume responsibility for technology management.

A systematic comparative analysis of these models is the subject of future reports. Suffice to note that Japanese, German, and Scandinavian universities have followed system (a). However, Denmark has recently switched to university ownership and management of IP, and Germany is seriously considering the same change, leaving Japan as the only major industrialized country that for the foreseeable future will leave ownership and management of most university inventions in the hands of faculty-inventors. Also, it should be noted that a combination of (b) and (c) characterized the pre-Bayh-Dole United States system and the United Kingdom system when the British Technology Group (BTG) was still a public corporation responsible for managing university technologies. It still characterizes a small percentage of inventions made in Japanese universities (so-called “national inventions”), as well as the majority of inventions made in Japanese government research institutions (28, 38, 39). Examples of (d) include today’s privatized BTG; traditional United States technology management corporations (e.g., Research Corporation Technologies), the numbers of which have dwindled in recent years; and a host of relatively small, new technology brokers.

Criticism of the United States system, with its emphasis on financial rewards to motivate individual research institutions to perform effective technology transfer, often centers around perceived tendencies for these institutions to charge high royalties and unnecessarily grant exclusive licenses (see the discussions of research tools and diagnostics in “Marketing and Licensing”), thereby imposing multiple “rents” or “highway tolls” on the technology transfer process (4, 9, 19, 40). These criticisms emphasize the benefits of (c) and advocate the issuing of exclusive licenses only when necessary to mobilize private sector investment in technologies that need further development. An analysis of these criticisms is beyond the scope of this report. However, it seems likely that the following factors have driven the development of the United States system and accounted for many of its indices of “success” (e.g., increases in licenses and royalties, increases in sponsored research, and imitation in other countries):

(a) Strong IP protection is often essential to encourage development of early-stage biomedical discoveries, particularly those that may be the basis for future drugs. Therefore, the demand for exclusive licenses in this field will remain high.

(b) Most university inventions are early-stage technologies, the ultimate feasibility and marketability of which is uncertain, although this is often not the case for clinical research inventions. Most early-stage inventions need a champion (more
likely, a series of champions) if they are to have a chance for successful development. Such champions or innovation agents need to push forward the development of their discoveries from both scientific and business perspectives. They must recruit and motivate researchers, acquire capital, develop business plans, seek development partners, and obtain customers. An important part of this championship process involves TLOs making far-sighted, sometimes risky patenting decisions, selecting committed licensees, and negotiating license terms that require development commitments from the licensees. However, much more is needed. Scientists must believe that they stand a reasonable chance of reaping significant rewards (not only monetary) if they invest energy and time to develop promising but risky discoveries. The same is true for companies that provide venture capital, pharmaceutical and biotechnology companies that invest in such discoveries, and administrators who attempt to build successful technology-business incubator facilities.

Financial incentives are necessary to motivate the many actors involved in this complex process. Whether the present incentives are necessary for the system to work or whether they encourage excessive patenting, exclusive licensing, and royalty collection by publicly supported institutions is at the heart of the present debate.

My 3 years in Japan studying university-industry cooperation suggests that one of the fundamental flaws of the Japanese technology transfer system is that neither inventors, university officials, nor companies have significant incentives to develop inventions made in university or government research institutes. Public sector inventors, if they bother at all with technology transfer, usually pass inventions informally to companies with whom they have long-standing relationships. The terms of transfer impose few if any obligations on companies to develop the inventions or to pay royalties. Because these companies receive publicly financed discoveries essentially for free, they lack incentives to invest in development, except in the case of clearly spectacular inventions. Japanese TLOs manage only inventions that inventors voluntarily pass to them, and thus universities are still largely left out of the technology transfer process. Available evidence suggests that they vast majority of university discoveries are undeveloped, and this may have profound negative implications for several high technology Japanese industries, including biomedicine and software (28, 38, 39). Although this observation does not validate aggressive patenting and licensing by United States universities and government laboratories, it reinforces the importance of IP rights in creating financial incentives for public research institutions and the private sector to champion risky, early-stage discoveries.

However, scientists, universities and other public research institutions should keep in mind that the essential purpose of technology transfer from not-for-profit institutions is the development of publicly financed discoveries for the public good. Generating money for inventors, universities, and private investors is not the goal. However, it is an important incentive to make the system work.

Fortunately, the present United States system of technology transfer and the model outlined in (c) above are not necessarily incompatible. For example, a policy of issuing exclusive licenses only when necessary to provide incentives to commercialize university inventions may result in an attractive revenue stream for many TLOs while minimizing situations where exclusive licenses can impede other researchers and companies from carrying forward further development.

REFERENCES


Technology Transfer: A Review for Biomedical Researchers

Robert Kneller

Clin Cancer Res 2001;7:761-774.

Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/7/4/761

Cited articles
This article cites 11 articles, 4 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/7/4/761.full.html#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/7/4/761.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.