

Public Health and University Priorities in the Era of Patent Failure

by

Robert W. Shafer, M.D.

Associate Professor of Medicine

Stanford University

May 3, 2009

“Based on the brief description of the patent, it would seem that research Stanford did and published 30 years ago, including MYCIN, would predate the patent. We do not give in to patent extortion; we also don't, as a general rule, seek to fix the problems of the patent office.”. In March 2008, I received this response from Stanford University President John Hennessy in response to an email that I had sent the previous day decrying an agreement that the Stanford University Office of Technology Licensing (OTL) had signed with a company named Advanced Biological Laboratories (ABL) that owned two patents purported to provide a monopoly on the use of computers to help physicians choose medical treatments. This manuscript describes the events preceding and following my email exchange with Stanford University's president. The manuscript highlights a trend in which biological knowledge and medical reasoning are increasingly considered property that can be bought and sold but not shared. I explain this trend within the context of a dysfunctional U.S. patent system and the changing priorities of academic institutions that have chosen to pursue of patent licensing revenue to the detriment of the public interest in medical progress.

In 1998, I created a free publicly available HIV Drug Resistance Database (<http://hivdb.stanford.edu>) to help clinicians interpreting HIV drug resistance tests and scientists developing new antiretroviral drugs. The database website provides users with graphical query interfaces for retrieving data and interactive programs for analyzing HIV sequences. The database relies on contributions by medical researchers and has been funded by NIH grants and unrestricted funding from multiple pharmaceutical and diagnostic companies.

Also in 1998, a company named TherapyEdge filed a patent on the using computers to help physicians make treatment decisions. In 2000, a patent examiner for the US Patent and Trademark Office (USPTO) approved the patent's claims and issued US patent 6,081,786 based solely on one feature the examiner considered novel: “The specific allowable feature, which distinguishes the present invention over the prior art is the generation of a ranked listing of available therapeutic treatment regimens for the patient.” In 2001, the USPTO issued a “continuation” of the original TherapyEdge patent, US patent

6,188,988, which that is nearly identical to the 6,081,786 patent but does not require the ranked listing of treatment regimens. In contrast to the USPTO, the European Patent Office (EPO) rejected all claims of the European counterpart to the TherapyEdge patent application, citing the absence of novelty and many previously described expert medical systems ¹.

In 2004 ABL purchased TherapyEdge and proclaimed their intention to widely license the TherapyEdge patents: "The patents broadly cover the computer analysis of multiple databases, which lead to a report meant to guide physicians towards the optimal therapy for a given patient. Historically, such reports were principally associated with the treatment of HIV, but we envision that eventually the diagnosis and treatment of most chronic diseases will fall under the claims of these patents as well. We intend to widely license the patents to diagnostic companies, diagnostic service providers and therapeutic manufacturers. ²"

In 2007, ABL sued two companies for patent infringement in the Eastern District of Texas – a court described as a haven for patent pirates ^{3, 4} – and contacted Stanford University, claiming the HIV Drug Resistance Database contained online programs that infringed their patents ⁵. In October 2007, Stanford University, concerned that it would be sued in the Eastern District of Texas, sued ABL in San Francisco stating that ABL's patents were invalid and enjoining ABL from asserting any claim of the patents against Stanford University. However, Stanford University's OTL, then rapidly negotiated an agreement with ABL, which was signed in March 2008 without my knowledge or participation.

The Stanford-ABL agreement stipulated the following: (1) ABL would not sue Stanford for patent infringement for the commercial use of the HIV Drug Resistance Database by Stanford University Hospital; (2) Stanford would not sue ABL for infringement of a set of four Stanford patents on the concept of genotypic resistance testing to help physicians choose therapy; (3) Stanford would post a statement on the HIV Drug Resistance Database to "put the HIV community on notice about ABL's patents"; and (4) ABL and Stanford would issue a press release publicizing the agreement ⁶.

When I learned of the Stanford-ABL agreement, I refused to place ABL's statement on the database website because many database users are small commercial laboratories that rely on the database

to provide physicians with information about drug-resistance mutations in viruses from patient samples. By providing commercial-use immunity only to Stanford University, the agreement gave the appearance of sanctioning future ABL lawsuits against commercial laboratories and non-Stanford affiliated physicians who rely on the database.

I hired the law firm of Day Casebeer to petition the USPTO to reexamine and invalidate the ABL patents based on the existence of prior art not considered at the time the patents were issued ^{7, 8}. Our petitions were based in part on descriptions of several expert medical decision support systems published in the 1970s, 1980s, and early 1990s. The most well known system, MYCIN, was developed at Stanford University ⁹.

In December 2008, ABL sued Stanford for breach of contract and sued me for interfering with a contract, negligent interference with business advantage, and defamation ⁶. In March 2009, after receiving a cash settlement from Stanford, ABL amended their lawsuit naming me as the sole defendant.

U.S. Patent System Dysfunction

The conversion of the USPTO in 1980 into a self-supporting institute dependent entirely on patent fees stripped the organization of any incentive to adequately assess patent applications for novelty and non-obviousness ¹⁰⁻¹³. The USPTO ignored traditional exclusions to what had previously been considered patentable and issued tens of thousands of patents on abstract concepts, software, business methods, biomedical discoveries, and methods to diagnose and treat medical illnesses ¹⁰⁻¹⁴.

In 2000, U.S. President Bill Clinton and UK Prime Minister Tony Blair issued a joint statement that “raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere ¹⁵.” This pronouncement led to the widespread but false impression that genetic information is no longer being patented. Although the USPTO eventually discontinued issuing patents on expressed sequence tags (ESTs), criteria for genomic patenting remained unapologetically lax ¹⁶. Thousands of genome-related patents have since been issued, including patents on gene sequences, cDNA sequences, haplotypes, mutations, and single nucleotide

polymorphisms. While a few of these patents describe legitimate inventions, most lay claim to a natural phenomenon that until recently would not have been considered patentable¹⁵.

The rapid accumulation of exclusive patent rights on genomic discoveries jeopardizes affordable health-care. Existing gene patents, exemplified by Myriad's patents on the familial cancer genes BRCA1 and BRCA2, have resulted in expensive diagnostic tests that face no competition and often produce erroneous results¹⁷⁻¹⁹. In the best case scenario, the dense web of overlapping patents around many medical discoveries will simply raise the costs of downstream products; in other cases the requirement for extensive licensing fees will completely thwart downstream development of useful medical products.

While the hazards of gene patents are well recognized, those posed by the increasing number of patents on methods of diagnosis and treatment ("medical process patents") are only now receiving attention. The most well-known medical process patent dispute involved a patent on the physiological relationship between homocysteine levels and vitamin B12 and folate deficiency²⁰. The commercial laboratory LabCorps was recently found liable for patent infringement simply for providing physicians reading material about this association²⁰.

Stanford University Law Professor John Barton summarized the distinction between traditional patents on medical inventions and the medical process patents currently being issued by the USPTO: "for the first time, the patent system is effectively controlling the use of natural information, and taking out of the public domain information that is there for anyone to measure. We are now issuing patents with claims analogous to claims on the use of blood pressure to evaluate health as distinguished from the more traditional claims on the use of a specific device to measure blood pressure."²¹

Shifting University Priorities

The Bayh-Dole Act was passed in 1980, to foster technology transfer from academia to industry²². The act mandated that universities patent, license, and commercialize innovations developed using federal funds. In response, universities created OTLs and required faculty to assign ownership of their work to the university. The number of patents issued annually to universities rose

from about 250 in 1980 to more than 3,600 in 2007²³. The idea that university patenting and licensing—rather than the inventions themselves—are essential for technological advances has become an article of faith among the Association of University Technology Managers (AUTM): “Licensing is the process that provides the institution the guarantee that a given technology will be used to further the public good and perhaps, generate revenue for the institution.”²³

Critics of “campus capitalism” highlight four negative consequences of aggressive university patenting, licensing, and, increasingly, patent litigation: (1) As universities restructure to optimize licensing revenue their priorities shift towards research that is considered profitable and away from research that may have greater societal benefits^{24, 25}; (2) University OTLs impede collaborations and the sharing of data and reagents between researchers at different institutions^{22, 24-26}; (3) Some university OTLs engage in patenting and litigation designed to extract money from companies that have independently developed new technologies, thus hindering, rather than facilitating, technology transfer²⁷⁻²⁹; and (4) University OTLs have increased the vulnerability of their faculty to patent infringement lawsuits and removed the last vestiges of a research exemption for using patented inventions on academic campuses³⁰.

Two prolonged expensive patent infringement lawsuits filed by Stanford University are particularly relevant to this discussion. The patents giving rise to these lawsuits assert a broad monopoly on two HIV treatment concepts. Both were asserted against companies that developed products independently rather than through technology transfer. One patent on the concept of detecting HIV drug resistance mutations to help physicians choose therapy was the basis for a two-year lawsuit against a start-up company Visible Genetics^{31, 32}. Another patent on the concept of quantifying HIV levels in a patient to determine the effectiveness of HIV therapy is the basis of an ongoing four-year lawsuit against Roche Diagnostics³³.

The Stanford patent on the concept of detecting HIV drug resistance mutations to help physicians choose therapy is a controversial royalty-earning patent. This Stanford-ABL agreement therefore strengthened the alleged non-obviousness of the ABL and Stanford patents, making it harder for future

targets of litigation to defend themselves. That the agreement attempted to restrict the use of the HIV Drug Resistance Database – a free public health resource – might be considered an acceptable sacrifice for a for-profit company but not for a university whose faculty developed this resource through NIH research grants.

The licensing fees and litigation resulting from obvious biomedical patents needlessly raise the cost of medical diagnostics and therapeutics and belie the AUTM claim that “licensing is the process that provides the institution the guarantee that a given technology will be used to further the public good”. Stanford University Law Professor Mark Lemley describes several other high profile cases in which universities obtained and asserted legal rights over inventions independently developed by others. Lemley concludes “A private university is more than just a private for-profit entity. It is a public-regarding institution that should have as its goal maximizing the social impact of technology, not merely maximizing the university’s licensing revenue”²⁹.

Conclusion

This case study is an object lesson that draws attention to the failings of the U.S. patent system and the complicity of universities that have allowed their missions to be distorted by the pursuit of licensing revenues. I wrote this commentary because I believe that recognizing, acknowledging and understanding this issue are vital first steps to solving the problem. Biomedical researchers, medical care providers, and their patients cannot afford to wait until legislative or judicial reform reverse the deterioration of the patent system. In the immediate future, publicity can have a remedial effect on patenting and licensing practices by universities, which are public institutions expected to be acting in the public interest. Publicity can also spur the collective action of biomedical researchers, medical care providers, and patients most affected by harmful patents.

References

1. European Patent Office. Decision to refuse a European Patent application. The Examining Division - at the oral proceedings dated 28.02.2006 - has decided: European Patent Publication No. 99 916 262.1 is refused. Title: Systems, methods, and computer program products for guiding the selection of therapeutic treatment regimens. <http://tiny.cc/YiH7x> (2006).
2. Advanced Biological Laboratories. Evidence Medical, LLC and Advanced Biological Laboratories SA complete licensing agreement of seminal IT related patents. www.ablsa.com/site/en/press/2004-11-22_ABL_EvidenceMedical_Final.pdf (last accessed February 2009) (2004).
3. Williams, S. A Haven for Patent Pirates: In one federal court in East Texas, plaintiffs have such an easy time winning patent-infringement lawsuits against big-tech companies that defendants often choose to settle rather than fight. Technology Review (http://www.technologyreview.com/InfoTech-Software/wtr_16280,300,p1.html) (2006).
4. Wikipedia. United States District Court for the Eastern District of Texas. http://en.wikipedia.org/wiki/United_States_District_Court_for_the_Eastern_District_of_Texas (last accessed March 16, 2009) (2009).
5. Mullin, J. The fight of his life. IP Law & Business, 44-48 (2009) Available at <http://www.law.com/jsp/iplawandbusiness/index.jsp>.
6. Advanced Biological Laboratories, S. A. Advanced Biological Laboratories, S.A. vs. The Board of Trustees of the Leland Stanford Junior University and Robert W. Shafer, M.D. (United States District Court, Northern District of California). Docket available at "https://ecf.cand.uscourts.gov/cgi-bin/DktRpt.pl?234629579328577-L_801_0-1" upon registration or at "http://harmfulpatents.org/ABLvsStanford_Shafer.pdf" (2008).
7. Shafer, R. Request for *Ex Parte* Reexamination of U.S. Patent No. 6,081,786 (10/10/08). U.S. Patent Office reexam No. 90/010,313 (available at <http://portal.uspto.gov/external/portal/pair>) (2008).

8. Shafer, R. Request for *Inter Partes* Reexamination of U.S. Patent No. 6,188,988 (10/10/08). U.S. Patent Office reexam No. 95/001,088 (available at <http://portal.uspto.gov/external/portal/pair>) (2008).
9. Buchanan, B. & Shortliffe, E. H. Rules-Based Expert Systems: The MYCIN Experiments of the Stanford Heuristic Programming Project (Addison-Wesley Publishing Company, Reading, Massachusetts, 1984).
10. Federal Trade Commission. To promote innovation: The proper balance of competition and patent law and policy. A Report by the Federal Trade Commission, October 2003, 1-315 (2003).
11. Jaffe, A. & Lerner, J. Innovation and its discontents: How our broken patent system is endangering innovation and progress, and what to do about it (Princeton University Press, Princeton, 2004).
12. National Research Council (U.S.). Committee on Intellectual Property Rights in the Knowledge-Based Economy: A patent system for the 21st century. (National Academies Press, 2004).
13. Bessen, J. & Meurer, M. Patent failure: How judges, bureaucrats, and lawyers put innovators at risk (Princeton University Press, Princeton, NJ, 2008).
14. Barton, J. H. Emerging patent issues in genomic diagnostics. *Nat Biotechnol* 24, 939-41 (2006).
15. National Research Council (U.S.). Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation: Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health. (National Academies Press (<http://www.nap.edu/catalog/11487.html>), 2006).
16. Mossinghoff, G. J. The evolution of gene patents viewed from the United States Patent Office. *Adv Genet* 50, 13-21; discussion 507-10 (2003).
17. Walsh, T. et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *Jama* 295, 1379-88 (2006).
18. Soini, S., Ayme, S. & Matthijs, G. Patenting and licensing in genetic testing: ethical, legal, and social issues. *Eur J Hum Genet* 16 Suppl 1, S10-50 (2008).

19. Ledbetter, D. H. Gene patenting and licensing: the role of academic researchers and advocacy groups. *Genet Med* 10, 314-9 (2008).
20. Klein, R. D. & Mahoney, M. J. LabCorp v. Metabolite Laboratories: The Supreme Court listens, but declines to speak. *J Law Med Ethics* 36, 141-9, 4 (2008).
21. Barton, J. H. Patents, genomics, research, and diagnostics. *Acad Med* 77, 1339-47 (2002).
22. So, A. D. et al. Is Bayh-Dole good for developing countries? Lessons from the US experience. *PLoS Biol* 6, e262 (2008).
23. Association of University Technology Managers. AUTM U.S. Licensing Activity Survey: FY2007.
http://www.autm.net/AM/Template.cfm?Section=FY_2007_Licensing_Activity_Survey (2008).
24. Heller, M. A. & Eisenberg, R. S. Can patents deter innovation? The anticommons in biomedical research. *Science* 280, 698-701 (1998).
25. Boettiger, S. & Bennett, A. B. Bayh-Dole: if we knew then what we know now. *Nat Biotechnol* 24, 320-3 (2006).
26. Greenberg, D. *Science for Sale: The Perils, Rewards, and Delusions of Campus Capitalism* (University of Chicago Press, London, 2007).
27. Litan, R., Mitchell, L. & Reedy, E. Commercializing university innovations: A better way. National Bureau of Economic Research working paper.
http://www.brookings.edu/papers/2007/05_innovations_litan.aspx?rssid=education (2007).
28. Rai, A. The role of federally-funded university research in the patent system. Hearing before the United States Senate Committee on the Judiciary, 110th Congress. Available:
<http://science.house.gov/publications/Testimony.aspx?TID=7129>. Accessed February 2009 (2007).
29. Lemley, M. Are Universities Patent Trolls? Stanford Public Law Working Paper No. 980766. Available at SSRN: <http://ssrn.com/abstract=980776> (2008).

30. Miller, J. Sealing the coffin on the experimental use exception. *Duke Law & Technology Review* <http://www.law.duke.edu/journals/dltr/articles/2003dltr0012.html> (last accessed April 09) (2003).
31. Board of Trustees of the Leland Stanford Junior University. Complaint for patent infringement; demand for jury trial against Visible Genetics, Inc. (U.S. District Court of Northern California: Case No 3:01-cv-03671-CRB). (2001).
32. Board of Trustees of the Leland Stanford Junior University v. Bayer Healthcare. U.S. District Court for the Northern District of California: Case No: 3:01-cv-03671-CRB. (2003).
33. Patel, M. The Board of Trustees of the Leland Stanford Junior University, Plaintiff v. Roche Molecular Systems, Inc., et al., Defendants (No. C 05-04158). *Biotechnology Law Report* 5, 499-520 (2008).