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Introduction — Technology Transfer at NIH

In adopting a technology transfer policy largely dictated by the Federal Technology Transfer Act of 1986 (FTTA),[1] the National Institutes of Health (NIH) has increasingly encouraged collaborations between its researchers and private industry. Indeed, under the FTTA, technology transfer is regarded as an essential part of a researcher's job description, and promotion and positive job performance evaluation are contingent upon successful technology transfer efforts.[2] The FTTA also provides financial incentives for government scientists to transfer technology to the private sector.[3]

By implementing the FTTA, the Reagan Administration sought to increase the return on the nation's research and development (R&D) investment by generating new products and processes and by enhancing international competitiveness.[4] Furthermore, that administration predicted that the FTTA would be viewed in retrospect as "one of the seminal developments in the history of federal efforts to put technology

* The views expressed in this article are those of the author and do not reflect or suggest the views of Fish & Neave or any of its clients.

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1 The Federal Technology Transfer Act of 1986, Pub.L. No. 99-502, 100 Stat. 1785 (codified at 15 U.S.C. § 3710 (1986)).

2 15 U.S.C. § 3710(a).

3 NIH/ADAMHA/CDC/FDA Office of Technology Transfer, 1992 PHS Technology Transfer Directory.

4 Robert Mosbocher, The Federal Technology Transfer Act 1986: The First Three Years, Report to the President and the Congress from the Secretary of Commerce, (1989.

to work for the taxpayers who paid for it" even though the Act challenged "long held views on the proper role of Federal laboratories and scientists."[5]

Since the implementation of the FTTA, NIH/industry collaborations have flourished. The NIH reports that, by the end of fiscal year 1993, its researchers were actively involved in 103 separate Cooperative Research and Development Agreements (CRADAs) with collaborating companies. According to NIH, CRADAs are instrumental in achieving the FTTA's objective of assisting "universities and the private sector in broadening our national technological base by moving new knowledge from the research laboratory into the development of new products and processes."[6]

While promoting introduction of new products and enhancing American competitiveness through commercialization of federally-funded biomedical research are legitimate public policy goals, commentators have noted that there is a distinct downside to the technology transfer policies embodied by the FTTA. For example, as implemented by NIH, the provisions of the FTTA inappropriately influence the direction of biomedical research. By placing an inordinate premium on research with immediately apparent commercial rewards, the FTTA policies tend to skew the direction of research decidedly away from basic scientific investigation. Thus, over the long run, the FTTA policies threaten to adversely affect the continued vitality of the federal biomedical research establishment.[7] Furthermore, mandatory collaboration between federal researchers and private industry may have a corrupting effect on NIH research by magnifying the potential for conflicts of interest and restricted dissemination of information among scientists.[8]

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5 *Id.*, at 2.

6 NIH Office of Technology Transfer, NIH/ADAMHA/CDC Policy Statement on Cooperative Research and Development Agreements and Intellectual Property Licensing (1992).

7 *See,* Christopher J. Harnett, *Federal Technology Transfer: Should We Build Subarus in Bethesda?* 1 Risk 313 (1990).

8 *See, e.g.,* Janet Bass, *Privately University Funded Research May Breed*

The foregoing problems associated with the FTTA's policies are evident in current NIH research initiatives, including the Human Genome Project. Indeed, the recent controversial NIH decision to file applications seeking patent protection for more than 2,700 partial complementary DNA (cDNA) fragments has been met with warnings that pursuing such patents will have a negative impact on the international cooperation and open communication between genome scientists necessary for the prompt and successful completion of the Human Genome Project.[9] Critics also note the potential for conflicts of interest[10] and distortions in the conduct of basic biomedical research[11] as a result of the NIH patenting decision.

Analysis of the NIH cDNA patenting decision reveals yet another problem: the existence of patent rights to the partial cDNA fragments, and any attempts by NIH to license those rights, may significantly impede development of related products. This potential impediment to product development will be discussed in detail below.

Using the NIH decision to pursue the cDNA patents as a case study, this article will argue that the NIH decision reflects an inappropriate merger of NIH interests with the interests of the private biotechnology industry. Because the FTTA mandates collaborations between federal scientists and private industry, it is inevitable that NIH will confuse its proper technology transfer goals with the commercialization interests of private sector collaborators. NIH justifies its controversial patenting decision as an attempt to provide an incentive for private industry to commercially develop products related to the partial cDNA fragments. That decision may, therefore, be viewed as a natural and predictable outgrowth of federal technology transfer

Conflicts, United Press Intn'l, June 13, 1989; William Booth, *NIH Scientists Agonize Over Technology Transfer,* 243 Science 20, 21 (1989); Barbara Culliton, *NIH, Inc.: The CRADA Boom,* 245 Science 1036 (1989).

9 *See, e.g.,* Leslie Roberts, *Genome Patent Fight Erupts,* 254 Science 184 (1991).

10 *See, e.g.,* Christopher Anderson, *Genome Project Goes Commercial,* 259 Science 300 (1993).

11 *See,* Statement of the National Institutes of Health–Department of Energy Subcommittee for Interagency Coordination of Human Genome Research, Jan. 3, 1992.

policies. However, implementation of such policies may actually impede development of related products, thereby subverting one of the primary objectives of the FTTA. In light of this potentially paradoxical result, NIH should reexamine its implementation of FTTA policies.

NIH's cDNA Patent Applications

As noted above, NIH has been widely criticized for filing applications in June 1991 and February 1992 seeking patent protection for partial cDNA sequences identified by Dr. Craig Venter, then a genome project researcher working at the National Institute of Neurological Disorders and Stroke. Those applications were directed to, inter alia, approximately 2,700 expressed sequence tags (ESTs) that were isolated from commercially available and custom-made cDNA libraries. ESTs are short cDNA sequences, about 150-400 base pairs in length that correspond to the coding sequence of an expressed gene.[12] The ESTs described in the Venter applications correspond to individual genes expressed in the human brain.

Using conventional techniques, ESTs can serve as a starting point to fully sequence corresponding expressed genes. While ESTs indicate that a gene exists and is expressed, they do not shed light on the biological activity or function of that gene.

Both Venter patent applications claim the 2,700 expressed sequence tags, the full length genes corresponding to the ESTs, and miscellaneous antisense oligonucleotides and triple helix probes. The June 1991 application also claims proteins coded by the genes.

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12 By way of simplified relevant background, individual genes comprise: regulatory regions including a promoter that directs expression of the gene; a coding region that codes for a polypeptide; and a termination signal. Gene expression proceeds from DNA to messenger RNA (mRNA) to a polypeptide. In a two step process, mRNA can be converted to double stranded cDNA by reverse transcriptase and a DNA polymerase.

The coding regions of genes may be discontinuous: coding sequences known as exons may alternate with non-coding regions known as introns. The mRNA includes exons but does not include introns. A full length cDNA, therefore, is a double stranded DNA copy of a mRNA that contains all of the exons of a gene. ESTs, such as those described in the Venter applications, are partial cDNA sequences that can be used to identify the full-length cDNA "clone" of an expressed gene.

Critics of the NIH patent decision argue that, because Venter's ESTs do not teach the biological activity of the gene, attempts to obtain broad patent protection based on those ESTs are premature and inappropriate. For example, Nobel laureate Paul Berg commented that "patenting bits and pieces of sequence that are meaningless functionally... makes a mockery of what most people feel is the right way to do the Genome Project."[13]

NIH, however, justified its decision to file patent applications as an effort to promote the public good and to fulfill NIH's statutory technology transfer obligations and objectives.[14] Reid G. Adler, Director of the NIH Office of Technology Transfer, reported that the decision was motivated by a desire to protect Venter's invention "early enough to give meaningful patent protection to companies that might seek a license from NIH."[15] Indeed, NIH's efforts to license the Venter invention commenced within months of filing the first application.[16]

Moreover, NIH was concerned that publishing Venter's discoveries and data without first filing patent applications might render obvious and unpatentable future discoveries such as the elucidation of whole genes corresponding to Venter's ESTs.[17] NIH feared that the

13 Leslie Roberts, *NIH Gene Patents, Round Two,* 255 Science 912 (1992).

Even more strident were the comments of another Nobel laureate, James Watson, who expressed horror over NIH's attempt to obtain patent protection for Venter's ESTs because, in Watson's view, using commonly available automated sequencing machines "virtually any monkey" could identify ESTs. See, *supra* note 9.

14 Remarks of Dr. Bernadine Healy at the Fourth Annual PHS Technology Transfer Forum, November 14, 1991. Dr. Healy commented that:

> NIH has a record of utilizing the patent system in a socially responsible way. When NIH does move into the patent arena it is with the public good as a driving force and not because scientists want to get rich.

Dr. Healy also noted that "the real concern" would be if a big pharmaceutical company got all of the gene patents. Developments since November 1991, demonstrate that the NIH decision to pursue partial cDNA sequence patent did not preclude private concerns from following suit. For example, Incyte Pharmaceuticals Inc., of Palo Alto, California is reportedly planning to file patent applications for as many as 100,000 cDNA sequences a year; *see, e.g.,* Anderson, *supra* note 10.

15 *Supra* note 9, at 185.

16 *Id.*

potential loss of patentability for future discoveries would create a disincentive for companies to perform the subsequent research necessary to bring valuable products to market.[18]

The NIH justification for filing the Venter patent applications is troublesome because it suggests that NIH actions were driven by the commercial concerns of its private sector collaborators. As a public institution with its primary mission "to conduct biomedical ... research that will lead to the better health of the American people,"[19] it seems inappropriate for NIH to predicate major policy decisions on the desire to insure the existence of meaningful licenses for its private sector collaborators, and to preserve the existence of future exclusive rights for those collaborators.[20] The troublesome nature of the NIH cDNA patent decision extends beyond philosophical concerns about the proper role of the NIH vis a vis private industry — there are practical implications as well. Because of the undeveloped nature of the Venter technology, there is little likelihood that NIH patenting and subsequent licencing efforts would have effectively advanced the commercial development of related products. In fact, as will be discussed below, the existence of any patent or licensing rights would be likely to impede commercial development of clinically useful products and processes related to Venter's discoveries.

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17 A thorough discussion of the merits of this concern is beyond the scope of this article. For further discussion, *see, e.g.,* Reid G. Adler, *Genome Research: Fulfilling The Public's Expectations For Knowledge And Commercialization,* 257 Science 908 (August 14, 1992); Rebecca S. Eisenberg, *Genes, Patents, And Product Development,* 257 Science 903 (August 14, 1992).

18 *See, supra* note 9. *See also,* testimony of Dr. J. Craig Venter before the Senate Judiciary Subcommittee on Patents, Copyrights and Trademarks, Sept. 22, 1992.

19 *Supra* note 3.

20 *See,* Association of Biotechnology Companies, Statement on NIH Patent Filing for the Human Genome Project (May 1992): "Whether future patent claims are obtainable... is not the concern of the NIH, which should not become engaged in schemes designed to ensure future exclusivity."

Possible Scope of Patent Protection

NIH's ability to license its technology depended, in large measure, on the scope of the claims, if any, that would have eventually been allowed by the Patent and Trademark Office (PTO). In its initial response to the Venter applications, the PTO rejected the NIH claims because they did not satisfy the three fundamental requirements for patentability — utility, novelty and non-obviousness.[21] The NIH was expected to file a response to the initial PTO rejection by February 1993, and a final decision of the PTO was expected in early 1994. However, after NIH learned that the PTO planned to reject its claims, it abandoned the application in early February 1994.[22]

Because Venter's partial cDNA sequences do nothing to elucidate the biological activity of the genes, the issue of patentable utility with respect to the Venter disclosure has drawn considerable attention from commentators.[23] NIH argued that the Venter invention has patentable utility because the disclosed partial cDNA sequences can be used: 1) as polymerase chain reaction (PCR) primers; 2) to isolate the coding sequence of cDNAs; 3) to isolate complete genes; 4) to determine the position of genes on the human chromosome; 5) to produce antisense oligonucleotides and triple helix probes; and 6) in forensic applications.[24]

While the utility requirement is typically considered a low hurdle to patentability,[25] the U.S. Supreme Court has held that the utility requirement is not satisfied if an invention is useful only in research.[26] Because, as the PTO suggested, Venter's sequences were useful merely

21 Governed by 35 U.S.C. §§ 101, 102 and 103, respectively.

22 Christopher Anderson, *NIH Drops Bid for Gene Patents,* 263 Science 909 (1994).

23 *See, e.g.,* Thomas D. Kiley, *Patents on Random Complementary DNA Fragments?* 257 Science 915 (1992).

24 Patent application of Craig Venter: Sequences Characteristic of Human Gene Transcription Product. A partially redacted version of this application is available through the NIH Office of Technology Transfer.

25 *See, e.g.,* Stiftung v. Renishaw PLC, 945 F.2d 1173 (Fed. Cir. 1991); Envirotech Corp. v. Al George, Inc., 730 F.2d 753 (Fed. Cir. 1984).

26 Brenner v. Manson, 383 U.S. 519 (1966).

as a means for making discoveries, the claims were rejected for lack of utility.[27] Furthermore, considering the high-profile and controversial nature of the present case, the PTO may have been inclined to apply the utility standard very stringently.[28]

As noted above, the claims of both Venter patent applications encompassed much more than the disclosed ESTs. The specifications of those applications describe, in detail, procedures for identifying and sequencing the ESTs, procedures for identifying the sequence of a gene using an EST as a starting point, and procedures for accomplishing gene expression. The Venter disclosure, however, does not identify the full length sequence of previously unknown genes, identify the polypeptides coded by those genes, or teach the biological activity of those genes or polypeptides. As such, had NIH decided to appeal, there is considerable doubt that Venter would have been entitled to claims directed to full length genes or polypeptides coded by those genes.[29] Indeed, recent case law suggests that, even assuming the utility, novelty and nonobviousness standards are satisfied, Venter would not be entitled to claims that extend much beyond the specifically disclosed EST sequences.[30] Thus, it appears that even if NIH could have prevailed on the issue of utility, the scope of claims that might have been allowed is likely to have been substantially narrower than the claims filed in the applications.

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27 *Manson,* 383 U.S., at 536, "But a patent is not a hunting license. It is not a reward for the search, but a compensation for its successful conclusion."

28 The PTO occasionally applies unusually stringent utility standards to promote what it considers to be public policy objectives. For example, the PTO has recently shown reluctance to allow claims directed to treatment of HIV infection where the claimed effectiveness is supported only by *in vitro* data; *see, e.g.,* In re Balzarini, 21 U.S.P.Q.2d 1892 (B.P.A.I. 1991). In the past, claims directed to treatment of human cancers were also rejected on the basis of "incredible" utility; *see, e.g.,* Application of Citron, 325 F.2d 248 (C.C.P.A. 1963).

29 *See, e.g.,* Rebecca S. Eisenberg, *Genes, Patents, and Product Development,* 257 Science 903 (August 14, 1992).

30 *See, e.g.,* Fiers v. Revel, 984 F.2d 1164 (Fed.Cir. 1993); *see also* Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (Fed.Cir. 1991).

Possible Licensing Consequences

Federal patent laws in effect since 1980 have permitted and encouraged licensing of government owned patent rights.[31] Under the FTTA, federal laboratories can agree to grant intellectual property rights in advance to collaborators who are party to a CRADA.[32] The NIH technology transfer policy relies heavily on the patent system, and in its general licensing policy, NIH states that, "Congress and the President have chosen to utilize the patent system as the primary mechanism for transferring Government inventions to the private sector."[33] Indeed, NIH officials have suggested that patent protection for the cDNA sequences is necessary to induce potential licensees to commit the time and financial resources to develop commercially viable products derived from the NIH's cDNA discoveries.[34]

Federal statutes directed to technology licensing balance the need for exclusivity to induce commercial development against the possible adverse consequences of an unnecessary monopoly. Consequently, NIH licensing policies, in most circumstances, favor non-exclusive licenses over exclusive licenses.[35] However, consistent with a fundamental principle of the patent system,[36] NIH is willing to "grant exclusive commercialization licenses under their patent or other intellectual property rights in cases where substantial additional risks, time and costs must be undertaken by a licensee prior to commercialization."[37]

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31 *See,* Government Patent Policy Act of 1980, P.L. 96-517, 94 Stat. 3015 (codified at 35 U.S.C. § 200-212 (1990)).

32 *Supra* note 3, at 307, 309.

33 *Supra* note 3, at 309.

34 Testimony of Dr. Bernadine Healy before the Subcomm on Patents, Trademarks and Copyrights of the Senate Judiciary Comm., Sept. 22, 1992.

35 *Supra* note 3, at 310.

36 *See* Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861 (Fed. Cir. 1985), "The patent system, which is rooted in the United States Constitution serves a very positive function in our system of competition, i.e., 'the encouragement of investment based risk.'" (citations omitted).

See also, U.S. Const., Art 1. §. 8, cl. 8: "The Congress shall have power... to promote the progress of science and useful arts, by securing for limited times to authors and inventors exclusive right to their respective writings and discoveries."

37 *Supra* note 3.

Federal law, however, permits a federal agency to license its inventions on an exclusive basis only if it is determined that: 1) the public interest is served by the exclusive license in light of the prospective licensee's plans and ability to promote the public's utilization of the invention; 2) the practical development of the invention has not or is not likely to be expeditiously achieved under a non-exclusive license; 3) the exclusive license is required to attract capital and stimulate interest needed to develop the invention; and 4) the proposed scope of the exclusive license is not broader than is necessary to accomplish development of the invention.[38] Moreover, NIH reserves the right to revoke an exclusive license if the licensee fails to make reasonable progress in developing the invention or if the licensee cannot satisfy unmet public health needs.[39]

Attempts by NIH to license any patent that might have issued from its applications would be problematic. As discussed above, the claims of such a patent would likely be narrow. One commentator has suggested that claims limited to the specifically disclosed ESTs and their equivalents would not be "broad enough to offer effective protection to firms seeking to bring related products to market...."[40] The private sector, therefore, might not be interested in licensing them, either exclusively or non-exclusively. As such, the NIH patent would do nothing to advance the development of commercial products or processes and might indeed have hindered such developments by contributing to the "thicket of patent rights that firms must negotiate their way past before they can get products on the market."[41]

On the other hand, if NIH had been somehow entitled to broader patent coverage (or if private sector participants had been nonetheless interested in licensing a narrow patent), then NIH would have had to

38 35 U.S.C. § 209(c)(1); *see also* 37 C.F.R. § 404.7.

39 *Supra* note 3, at 311.

40 *Supra* note 29.

41 *Id.*, at 904. *See also,* Leslie Roberts, *Scientists Voice Their Opposition,* 256 Science 1273 (1992). Michael Roth, a patent attorney at Pioneer Hybrid comments that the NIH patent approach "does not build a road to further advances, it just builds a toll booth along the way."

determine whether an exclusive or non-exclusive license was appropriate. Because the vast majority of the 2,700 genes corresponding to Venter's ESTs were not likely to be immediately significant for clinical applications, the Venter patent applications clearly presented a situation where substantial (and risky) expenditures of time and money would be necessary before any commercially viable product could have been marketed. Thus, potential licensees are unlikely to have been interested without an exclusive license.

As discussed above, the technology claimed in the NIH applications was not well developed and encompassed vast subject matter — Venter's claims may theoretically "read on" approximately 5% of all expressed human genes. Exclusive use of those ESTs would, thus have provided an extreme disincentive for non-licensees to investigate the biological significance of the 2,700 expressed genes and polypeptides corresponding to Venter's partial cDNA sequences. Such a disincentive could have resulted in a "meta-monopoly" whereby a single entity would acquire de facto dominion over the eventual identification of 2,700 genes, their gene products and methods of exploiting their biological activity. Such a meta-monopoly may run afoul of patent licensing laws[42] and would do nothing to aid development of useful products.[43] Exclusivity over Venter's discoveries could have caused a result decried by the Supreme Court:[44]

> Such a patent may confer power to block off whole areas of scientific development, without compensating development to the public. The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is developed to this point — where specific benefit exists in currently available form — there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

42 35 U.S.C. § 209.

43 Craig Venter himself states that "The patent system wasn't designed to give me and a small group of people ownership of half the genome." *Supra* note 41.

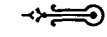
44 Brenner v. Manson, 383 U.S., at 534-535.

Thus, either exclusive or non-exclusive licenses for any patents that might have issued from the NIH applications could have stood in the way of ultimately developing clinically useful products related to Venter's ESTs. With NIH having abandoned its applications, a greater degree of access to that technology has been realized.

Conclusion

The NIH decision to seek patent protection for Dr. Venter's substantially undeveloped discoveries demonstrated that NIH's technology transfer activities were driven by the commercial objectives of its private sector collaborators, and its decision to abandon them may have been similarly motivated.[45] Merger of NIH and private sector objectives is an inevitable consequence of the NIH's implementation of the FTTA. Such a merger threatens to shift the focus of NIH research, compromise the objectivity of that research and, in certain circumstances, impede the ultimate introduction of products ultimately developed from NIH research. Thus, NIH policies that overzealously promote private commercial interests should be reconsidered.

This author believes that the progress of science and the interests of the public are best served by maintaining NIH as an objective research institution rather than a vehicle for advancing the commercial interests of private biomedical research concerns. The biotechnology industry does *not* need NIH to protect its commercial interests — those interests are adequately protected by numerous individual private companies and by their lobbying groups. The public, however, *does* need NIH to continue to perform high-level objective research in order to preserve the status of the U.S. as the world leader in biomedical sciences.



45 *Supra* note 22, at 910.