SUPPORTING INNOVATION IN TARGETED TREATMENTS: LICENSES OF RIGHT TO NIH-FUNDED RESEARCH TOOLS

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Support for new drug development has taken some interesting turns in current patent law jurisprudence. Beginning with the severe curtailment of scope of the common law experimental use doctrine in *Madey v. Duke University*,[1] and culminating with the recent Supreme Court decision in *Merck KGaA v. Integra Lifesciences I, Ltd.*,[2] broadening the scope of the statutory research exemption, the freedom to conduct experimental

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1. *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2002).

2. Merck KGaA v. Integra Lifesciences I, Ltd., 125 S. Ct. 2372, 545 U.S.____ (2005)(No. 03-1237)(June 13, 2005).

research using another's patented inventions becomes dependent in part on the purpose of the research. That the patent at issue in *Merck* was characterized by the Federal Circuit as being directed to a research tool raised the question of the extent of protection that should be afforded to such inventions. In other words, as new drug development necessarily involves some degree of exploratory research, research tools are often employed to facilitate the search for new drugs. Consequently, patents on such inventions provide an interesting anomaly to the innovation incentive argument for patent rights. The question of whether patents on research tools retard rather than enhance innovation have been discussed at length without any clear conclusion.[3] Interestingly, the patent code, which in its present form was promulgated in large part through heavy lobbying by the pharmaceutical companies, now serves as a sword of Damocles hanging over these companies' research activities using patented research tools.[4]

The environment for drug development by large pharmaceutical companies is changing. Previously chemistry dictated new development by defining new structures or active isomers of chemical compounds. The focus has now shifted to biology as targeted treatments are taking the forefront in drug development.[5] The shift can be credited in large part to the success of the Human Genome project, which served to redefine medical research by fusing biological systems with advances in information technology. Pharmacogenomics, as it is termed, describes the science behind targeted pharmaceuticals, which serves as a novel business model for the pharmaceutical industry.

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3. *See* John P. Walsh, Ashish Arora and Wesley M. Cohen, *Effects of Research Tool Patents and Licensing and Biomedical Innovation*, *in* PATENTS IN THE KNOWLEDGE-BASED ECONOMY 285 (Wesley M. Cohen and Stephen A. Merrill, eds. 2003); *see also*, Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017 (1989); *see also* Iain M. Cockburn, *The Changing Structure of the Pharmaceutical Industry*, 23 HEALTH AFFAIRS 10 (2004).

4. Defining research tools has proven tricky, but at its most general, research tools include the full range of resources that scientists use in a laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools, methods, laboratory equipment and machines, databases and computer software. *See* REPORT OF THE NATIONAL INSTITUTES OF HEALTH (NIH) WORKING GROUP ON RESEARCH TOOLS June 4, 1998, available at http://www.nih.gov/news/researchtools/.

5. *See* The Economist, Economist Intelligence Unit, White Paper, *Targeted Treatments and the Prospects for Pharmaceuticals*, 2005, *available at* http://www.agilent.com/about/newsroom/tools/whitepaper_pharma.pdf. A targeted treatment is a treatment that is directed towards an identified "target." For example, in cancer research, where targeted treatments originated, such a treatment would attack the abnormal cell while preserving the normal cells in the surrounding area. An example of a commercially available targeted treatment is Genetech's breast cancer drug, Herceptin, a monoclonal antibody aimed at the population who over-express the HER-2 receptor.

These advances in science come at a critical time for the pharmaceutical industry. Between 2002 and 2007, 35 drugs with sales totaling more than $73 billion (US) will lose patent protection. Moreover, while previously it would take more than a year for a drug to lose 70% of its market share following patent expiration, now a drug can lose 80–90% of its market share within weeks after expiration of the patent, in large part due to the availability of generics immediately after expiration of the patent. A survey conducted by the Economist Intelligence Unit ranked patent expiration after research and development (R&D) as the most significant factor affecting business development in the next three years.[6]

Targeted treatments could be the next generation of "blockbuster pharmaceuticals" the industry has been waiting for, in that it will shift the focus from traditional blockbuster one-for-all medications to more selective products. However, much of the success of these drugs depends on the discovery and validation of new targets using existing and developing research tools. One noteworthy example of the importance of research tools in developing targeted treatments is the discovery of gene slicing by RNA interference (RNAi), which offers a promising possibility for treating AIDS and other diseases. The FDA also jumped on the bandwagon criticizing the disparity between advances in the understanding of diseases and the dearth of new pharmaceutical products. As a result, the clinical diagnostics business will play an important role in developing targeted treatments.

Moreover, legislation facilitating overt and explicit contact between scientific discovery and product development has created changes that has led many commentators, both critics and advocates, to agree that there is something significant occurring.[7] The scientific lab is now directly linked with commercial outlets through a systematic infrastructure of the venture capital market, the insurgence of biotechnology start up companies, and the convergence of university and industry.[8] Due to the complexity of pharmacogenomics, access to many proprietary research tools is necessary to conduct research in this field.

Thus the significance of the availability of research tools becomes apparent. However, broad patents on upstream products arguably

6. *Id.* Specifically, 63% of the respondents listed R&D as the most significant factor in a company's business performance while 51% listed patent expiration.

7. *See* PRIVATE SCIENCE: BIOTECHNOLOGY AND THE RISE OF THE MOLECULAR SCIENCE (Arnold Thackray ed. 1998)

8. *See* MARTIN KENNEY, BIOTECHNOLOGY: THE UNIVERSITY-INDUSTRIAL COMPLEX (1986); *see also*, Walter W. Powell & Jason Owen-Smith, *Universities and the Market for Intellectual Property in the Life Sciences*, 17 J. POLICY ANALYSIS MANAGEMENT 253 (1998). For a more detailed discussion on the changes in the biotechnology environment, see Peter Shorett, Paul Rabinow & Paul R. Billings, *The Changing Norms of the Life Sciences*, 21 NAT. BIOTECH. Feb. 2003 at 123.

adversely affect innovation in this area. This article will address the limitations on the use of research tools and propose a means to ensure its continued accessibility to promote innovation in pharmacogenomics.[9] Part I will address the development of biotechnology in the United States and the legislation that has helped spur innovation in the field. Part II will discuss the arguments put forth in support of open science and the legal issues surrounding access to patented tools for research purposes. Part III will discuss the current literature on research tools, including the economics and legal policies relating to patents on research tools and alternatives to patenting. Finally, Part IV will propose a policy incorporating licenses of right to ensure continued accessibility of patented research tools developed using NIH funding.

I. PHARMACOGENOMICS

Pharmacogenomics is a fusion between chemistry, biology and information technology. Specifically, it is the study of how an individual's genetic inheritance affects the body's response to drugs. The term comes from the words pharmacology and genomics and is thus the intersection of pharmaceuticals and genetics. Pharmacogenomics was made possible through the completion of the human genome sequence as well as the development of processes for the collection and analysis of biomedical data. Essentially, pharmacogenomics allows for the identification of genes and genomes responsible for modifying an organism's response to drugs and also includes the use of genomics in the search for new therapeutic treatments.[10] Through this research, pharmaceutical companies

9. Cumulative innovation in pharmacogenomics refers to innovation occurring prior to commercialization, rather than innovation on the end-product. Competition with the end-product is usually achieved through design-arounds or generic products. For further discussion on cumulative innovation, see Arti. K. Rai, *Fostering Cumulative Innovation in the Biopharmaceutical Industries: The Role of Patents and Antitrust*, 16 BERK. TECH. L. J. 813 (2001).

10. *See* L.T. Vazar, G.D. Rosen, T.A. Raffin, *Pharmacogenomics and the Challenge to Privacy*, 2 PHARMACOGENOMIC J. 144 (2002); Norbert W. Paul and Allen D. Roses, *Pharmacogenetics and pharmacogenomics: recent developments, their clinical relevance and some ethical, social and legal implications*, 81 J. MOL. MED. 135 (2003);135–140; U.A. Meyer, *Introduction to Pharmacogenomics: Promises, Opportunities, and Limitations*, in PHARMACOGENOMICS—THE SEARCH FOR INDIVIDUALIZED THERAPIES 1 (J. Licinio and M.L. Wong, eds., 2002). The FDA defines pharmacogenomics as involving:

> [A]n assay intended to study interindividual variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expressions or inactivation that may be correlated with pharmacological function and therapeutic response.

Food and Drug Administration, *Guidance for Industry: Pharmacogenomic Data Submissions at* http:// www.fda.gov/cder/guidance/5900dft.pdf.

will be, in theory, able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases.

Current use of pharmacogenomics is limited. One example is the cytochrome P450 (CYP) family of liver enzymes that is responsible for breaking down more than 30 different classes of drugs. The ability of the enzyme to break down the drugs is dependent on the DNA in the genes coding for these enzymes; hence, variations in the DNA can make the CYP enzyme less effective, which can allow for a drug overdose in the patient. Consequently, variations of the enzyme are being studied and many pharmaceutical companies screen their compounds to determine how well they are broken down by variant forms of the CYP enzymes. As pharmacogenomics requires the use of molecular biological research tools, for example in the screening of the compounds broken down by enzyme variations, access to the tools is critical for supporting such research. This article will focus on research tools in the pharmacogenomics industry, and more broadly in the biopharmaceutical industry.

A. *Biotechnology Industry in the U.S.*

To many, biotechnology evidences the last of America's technical superiority. As the foundation of biotechnology rests in basic research in molecular biology, furthering this research is tantamount to maintaining a stronghold in the face of increasing foreign competition. The biotechnology industry in the U.S. was spurred in large part due to the U.S. Supreme Court decision in *Diamond v. Chakrabarty*.[11] While it is generally accepted that laws and products of nature are not patentable and that there has to be some element of human devising, in *Chakrabarty*, the Supreme Court was faced with the patenting of "life."[12] Specifically, the Court was called upon to determine the patentability of a microorganism that was genetically engineered to biologically decompose and control oil spills.[13] The claims were initially rejected as being drawn to a living organism and, in the alternative, drawn to a product of nature.[14] The Supreme Court found that the products at issue

11. 447 U.S. 303 (1980).

12. *See id.*

13. *See id.*

14. In *Chakrabarty*, the examiner initially rejected the claims as unpatentable for being a living organism or alternatively, a product of nature. On appeal, the Board of Patent Appeals only upheld the rejection that the invention was drawn to a living organism but reversed on the latter issue. The Court of Customs and Patent Appeals reversed the ruling of the Board,

were not "products of nature" and thus, patentable. The Court held that the statutory language of "manufacture" and "composition of matter" encompassed living organisms altered by genetic engineering. The broad Court mandate that "anything under the sun made by man" is patentable led to an insurgence of early biotechnological inventions. The passage of the Bayh-Dole Act that same year only increased the incentives to conduct biotechnology research.

B. *Bayh-Dole Act*

The National Institutes of Health (NIH) provides a significant source of funding for basic research.[15] Research funded by the NIH is subject to the requirements of the Government Patent Policy Act of 1980, more commonly known as the Bayh-Dole Act,[16] which mandates that the public use of research findings be maximized by transferring them to industry for development. The Act was promulgated in response to concerns regarding access to government-funded patented inventions. Previously, patents on government-funded inventions belonged to the federal government, wherein the majority was not commercialized.[17] Indeed, one of the identified needs for the legislation was the decline in expenditures for research and development and the failure of American industry to keep pace with the increased productivity of foreign competitors.[18] The goal of the legislation was to increase public access to

holding that claims are not to be considered unpatentable simply because they are alive. *In re Chakrabarty*, 596 F.2d 952, 977 (C.C.P.A. 1979).

15. For example, in 2003, the NIH awarded $18,461,462,170 in noncompeting and competing research grants. *See* NIH Competing and Noncompeting Research Grants, Fiscal Years 1993–2003, *available at* http://grants1.nih.gov/grants/award/research/rgmechtype9303.htm.

16. Act of Dec. 12, 1980, Pub. L. No. 96-517, § 6(a), 94 Stat. 3015, 3019–28 (1980) (codified as amended at 35 U.S.C. §§ 200 et. seq. (2000)). The Stevenson-Wydler Act also played a role in promoting a nexus between universities and private industry. *See* Stevenson-Wydler Technology Innovation Act of 1980, Pub. L. No. 96-480, § 2, 94 Stat. 2311–2320 (1980)(codified as amended at 15 U.S.C. §§ 3701–3714 (2000)).

17. For example, in 1979, the year prior to the passage of the Bayh-Dole Act, less than five percent of the 28,000 government-owned patents had been commercialized. *See* 126 CONG. REC. S1, 994–99 (Feb. 6, 1980) (statement of Sen. Stevenson).

18. Specifically, the legislative history of the Act notes that "according to the Committee for Economic Development, 'the slowing of productivity improvement during the past few years parallels the discouraging decline in the rate of investment in plant and equipment.' " *Id.* (quoting *Stimulating Technological Progress*, A STATEMENT BY THE RESEARCH AND POLICY COMMITTEE FOR ECONOMIC DEVELOPMENT, Jan. 1980, pp. 2–7). Moreover, the House highlighted the discrepancy in the rate of investment between foreign nations and the U.S.: "The rate of investment as a proportion of GNP has averaged about one half the rate for France and Germany and about one third the rate for Japan. Further, the situation does not appear to be improving. There has been a significant decline in total U.S. expenditures for research and development, as measured in constant dollars since 1970." *Id.* (citing SCIENCE INDICATORS, NATIONAL SCIENCE BOARD, 1976, pp. 108–115).

inventions.[19] The sponsors of the legislation believed that the ability to convey exclusive licenses to private industry would motivate the private sector to commercialize the patented inventions, something with the government was failing to do.

Essentially, the recipient of government funding, typically universities for NIH funding,[20] has the right to determine whether to pursue patent protection on a particular invention. Should the university decide not to pursue patent protection, the funding agency, *e.g.*, the NIH, has the right to pursue the patent and in turn, claim ownership on the patent.[21] By extending the right to patent to all parties involved in the research, the fears that led to the passage of the Bayh-Dole Act were appeased.

Nevertheless, the rights granted to the patentee are not absolute. The government retained the right to "march-in" and grant a license to applicants in one or more fields of use under certain circumstances:

> (a) [A]ction is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the [government-funded] invention in such field of use;
>
> (b) [A]ction is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees;
>
> (c) [A]ction is necessary to meet the requirements for public use specified by federal regulations . . .; or

19. Specifically, the state policy and objective of the Bayh-Dole Act is:

> to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise; to promote the commercialization and public availability of inventions made in the United States by United States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area.

Government Patent Policy Act of 1990, 35 U.S.C. §§ 200 et. seq. (2005).

20. The original title of the act was the "University and Small Business Patent Procedures Act." Hence, the Bayh-Dole Act also gives small businesses the right to seek patents on their federally funded research. Large businesses were extended the same rights under the *Trademark Clarification Act of 1984*, 15 U.S.C. § 1501 (2000); 35 U.S.C. § 210(c) (2000).

21. *See* 35 U.S.C. § 202(c)(2) (2000).

> (d) [A]ction is necessary because the [agreement requiring substantial manufacture in the United States] has not been obtained . . .;[22]

Hence, it was understood that the possibility that the patentee could use his patent in an anti-competitive manner, for example, by refusing to license the invention without taking steps to commercialize it himself, was very real. Nevertheless, the availability of these provisions to increase access to patented inventions in biotechnology is uncertain. The problem is that at the time of the passage of the Bayh-Dole Act, there was still a relatively clear demarcation between the biotechnology and pharmaceutical industries so, at least in theory, it would not be difficult to ascertain whether the patentee was acting within the stated goals of the Act. Moreover, it would be unwise to rely on this provision to open up access to patented inventions, as the recent actions that have been decided under this section requesting the government to march in and grant licenses were not successful. For example, in 1997, CellPro, Inc., petitioned the Government to exercise its march-in rights under the Bayh-Dole Act with regard to certain patents owned by Johns Hopkins University and licensed to Baxter Healthcare Corporation ("Baxter").[23] CellPro was found to have infringed the patents and was enjoined from further sale. CellPro asserted that the action was necessary under section (b), i.e., to alleviate health or safety needs. Specifically, CellPro maintained that Hopkins and Baxter had failed to take reasonable steps to commercialize the invention. It is important to note that at the time of the petition, CellPro was the only company that had an FDA-approved device that was commercially available.[24] The NIH concluded that march-in was not warranted because 1) Hopkins and Baxter had taken steps to achieve practical application;[25] and 2) there was not enough evidence to support assertions that patient health was at risk. Importantly, the NIH focused on Hopkins' and Baxter's restraint in enforcing their patent rights to their full extent, thereby allowing CellPro to continue to manu-

22. 35 U.S.C. § 203(1) (2000).

23. *See* Cell-Pro, Inc., March-In Petition (Mar. 3, 1997), *available at* http://www.nih.gov/icd/od/foia/cellpro/.

24. *See id.*

25. The NIH found that practical application was demonstrated by the licenses granted by Hopkins, Baxter's manufacture, practice and operation of their device and the device's availability to and use by the public to the extent permitted under law, including clinical research use in the United States and foreign sales. *See Determination in the Case of Petition of CellPro, Inc.* (Aug. 1, 1997) *available at* http://www.nih.gov/icd/od/foia/cellpro/.

facture and sell its device within the U.S. until their alternative was approved by the FDA.[26]

In its reasoning, the NIH discussed its reluctance to influence the market forces for fear that it would adversely affect future willingness by companies and other investors to invest in federally funded medical technologies. Underlying this reasoning was the assumption that the patent system ensures development and dissemination of new medical technologies and that it proves an effective means for the development of health care technologies. It is this assumption whose validity is questioned when dealing with upstream research, or research about particular genes or gene fragments, particularly as the legislation does not differentiate between research having a clear product development phase and that which is useful for furthering research. Indeed, it is plausible that march-in cannot be warranted because, in accordance with the reasoning in CellPro, the actual medical benefits of upstream research are speculative.

More recently, however, the NIH received requests that the Government exercise its march-in rights in connection with patents owned by Abbott Laboratories due to concerns of the pricing of the drug ritonavir.[27] As this drug was partly developed through the use of Federal funds, it was subject to the provisions of the Bayh-Dole Act. It was argued that Abbott Laboratories did not achieve "practical application" of its invention, thereby allowing for an exercise of march-in rights, or alternatively, that march-in was necessary to alleviate health or safety needs.[28]

In its analysis, the NIH referred to its decision in Cell-Pro to support its finding that Abbott Laboratories achieved "practical application" of the invention by its "manufacture, practice, and operation of ritonavir and the drug's availability and use by the public."[29] Further, the NIH maintained that there was no evidence in support of the argument that march-in was necessary to alleviate health or safety needs; instead, the argument set forth was that the drug should be available at a lower cost.[30] Not surprisingly, the NIH concluded that march-in was an "extraordinary remedy" and should not be used as a means to control prices.[31]

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26. For a more detailed discussion of the CellPro case, see Amy R. Schofield, *The Demise of Bayh-Dole Protections Against the Pharmaceutical Industry's Abuses of Government-Funded Inventions*, 32 J.L. MED. ETHICS 777 (2004).

27. Ritonavir is manufactured under the tradename Norvir®. *See* NIH Office of the Director, In the Case of Norvir ® Manufactured by Abbott Laboratories, Inc. July 2, 2004, *available at* http://ott.od.nih.gov/Reports/March-In-Norvir.pdf.

28. *See id.*

29. *See id.*

30. *See id.*

31. *See id.*

II. "ACADEMIC FREEDOM": OPEN SCIENCE

University research has changed significantly, fueled in large part by the passage of the Bayh-Dole Act. The changes appear for the most part in a shift from pure research to more commercially focused and high-risk research.[32] Industry supports this shift in research goals as it allows it to focus instead on near-term returns and allow universities to indulge in pioneering research.[33] Indeed, corporate sponsored university research increased from $236 million in 1980 to $1.3 billion in 1992.[34] Currently, more than 200 universities are licensing technology to industry, an 800% increase from 1980.[35] Indeed, with the passage of Bayh-Dole, the number of patents issued to universities every year has increased from less than 250 to more than 1600.[36] According to Dr. Mary L. Good, past President of the American Association for the Advancement of Science and former Under Secretary of Commerce for Technology, "Intellectual property rights allow universities to work with industry in a way they would not be able to without them. They give universities something to bargain with."[37]

The exclusive right that a patent grants, i.e. the right to exclude others from making, selling or using the patented invention,[38] gives patents the status as being the strongest of intellectual property rights. It is generally accepted, though not without question, that the exclusive right serves to

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32. For example, much of university research is marketed through incubation programs, spin-off companies, technology transfer efforts and sponsored research.

33. According to the University of Wisconsin (UW):

> [I]ndustry can and does provide universities with important intellectual stimulation, as well as interpretations and reinterpretations of academic research results from a different and valuable perspective. In fact, one of the primary assets of the UW is its interactive relationship with industry, which keeps it informed of industrial needs and interests, and provides important feedback on the results of our research.

University of Wisconsin-Madison Graduate School, *Policies Concerning Research Sponsored by Industry*, at 1 *available at* http://www.rsp.wisc.edu/indres_sra.pdf.

34. *See* U.S. Department of Commerce, Report, *The Advanced Technology Program: Reform with a Purpose*, Feb. 2002 at 6 *available at* http://www.atp.nist.gov/atp/secy_rept/report.pdf.

35. *See id.*

36. *See id*. at 11.

37. *See id*. at 12 (based on a telephone interview on January 10, 2002).

38. *See* 35 U.S.C. § 154(1) (2000) which states, in part, that:

> Every patent shall contain a short title of the invention and a grant to the patentee, his heirs or assigns, of the right to exclude others form making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States, and, if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States, or importing into the United States, products made by that process, referring to the specification for the particulars thereof.

provide an incentive to innovate. Specifically, the basis of the argument is that the patentee is given an exclusive right in return for bringing the invention to the public. This exclusive right theoretically allows for the patentee to recoup the cost of his research and development, which, in turn, spurs innovation. That patents place a limitation on free competition is inherent in the grant. The exclusivity a patent grants defines an area where market forces are not free to determine price and availability. The courts have been hesitant to limit the exclusivity of the grant, for example, through the use of the experimental use doctrine.[39] Indeed, the NIH based much of its decision in CellPro on the beneficial role patents play in the marketplace.

Commentators have argued that patents on research tools hinder access to the tools needed for upstream research by charging premium prices or simply refusing to license.[40] Litigation or re-examination attempting to invalidate such patents can also be quite expensive. Moreover, it is arguable that the reasoning that patents create an incentive for innovation and without them, there would be no motivation to incur the expenses associated with research and development, is more applicable to inventions where the product or process has a direct commercial application and thus is of interest to private investment rather than governmental funds.

The underlying assumption in these arguments is that basic or upstream research, i.e., research that has at most speculative commercial value, should be research that is accessible to everyone. The public access aspect of the Bayh-Dole Act simply adds greater weight to the argument for research conducted using government funds. Some have argued that free and open exchange is necessary for scientific advancement.[41] Indeed, this dialogue is often conducted in academic settings, such as universities and research institutions and it is believed that research conducted in such settings inherently should be open and accessible. Skeptics may argue that the passage of the Bayh-Dole Act evidences the lack of utilization of such open science and therefore the public does not, in fact, benefit, when research is not privatized, as then there is no incentive for commercial exploitation. However, again, the Bayh-Dole Act was passed at a time not only when commercial and non-commercial research was more clearly demarcated, but also when, with respect to pharmaceuticals, chemistry dictated the commercial product. In other words, upstream genetic research did not play a significant role in product development and commercialization.

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39. See *infra* notes 45–55 and accompanying text for a discussion on the experimental use doctrine.

40. *See, e.g.*, Arti K. Rai and Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 LAW & CONTEMP. PROBS. 289 (Winter/Spring 2003).

41. *See, e.g.*, R.K. Merton, *Science and Technology in a Democratic Order,* reprinted as *The Normative Structure of Science*, *in* THE SOCIOLOGY OF SCIENCE, (R.K. Merton 1973).

The difficulty in identifying to what extent open science should apply to research tools is further highlighted by the consideration that one entity's tool can be another company's product. The term "research tool" takes on a less ambiguous meaning when using it in the context of upstream research or discoveries. Nevertheless, it is still possible for upstream discoveries to be a commercially viable end product for research institutions or companies. For example, a gene can be a product for companies specializing in gene therapy or a research target for a company seeking a small-molecule drug. Further, it is understandable that a company that spent years identifying and developing the gene would be unwilling to distribute it freely.

On the other hand, many pharmaceutical companies recognize the merit in allowing academic institutions to conduct research and some representatives have noted that it is not good form to sue researchers in academic institutions as it stifles their progress.[42] Hence, while much patent litigation has been held at bay, whether this "rational forbearance,"[43] will continue is questionable. For example, Ariad Pharmaceuticals, the exclusive licensee on a patented covering messenger protein and all disease treatment methods that affect the proteins pathway, required licenses for any corporate-sponsored academic research projects on the pathway.[44] This fear is underscored in light of recent case law curtailing the scope of the research exemption.

A. *Experimental Use*

The common law experimental use doctrine was first invoked in the case of *Whittemore v. Cutter*,[45] where Justice Story identified the need to balance the rights of exclusivity enjoyed by the patent owner with the rights of others to construct a patented invention "merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine

42. *See, e.g.*, *Perspective of Leon Rosenberg of Bristol-Myers Squibb* in INTELLECTUAL PROPERTY RIGHTS AND THE DISSEMINATION OF RESEARCH IN MOLECULAR BIOLOGY, Chapter 6, *Perspectives from Different Sectors*, *available at* http://books.nap.edu/html/property/.

43. *See id.*

44. *See* Agres, Ted. *The Cost of Commercializing Academic Research, Does University Licensing Impede Life Science Research and Development?* 17 THE SCIENTIST 58, 59 (August 25, 2003). The patent in the case related to the NF-KB cell-signaling pathway, an important biological trigger. The patent was issued to Massachusetts Institute of Technology, Whitehead Institute of Biomedical Research, and Harvard University. As it was based on federally funded research, it was subject to the provisions of the Bayh-Dole Act. The technology was subsequently licensed exclusively to Ariad Pharmaceuticals. Subsequent to the issuance of the patent, Ariad filed suit against Eli Lilly and Co., asserting that two of Lilly's drugs infringed the patent. *See id*. Nevertheless, Ariad limited its "rational forbearance" to academic and not for profit institutions conducting noncommercial research.

45. 29 F. Cas. 1120 (D. Mass. 1813) (No. 17600).

to produce its desired effects."[46] Later cases established the need to show an injury for a finding of infringement, in that though damages can be presumed to arise from a violation of some incorporeal right, such as a patent right, when no profit ensues from such violation, there was thought to be no injury.[47]

Subsequent courts created a "business purpose" test that attempted to demarcate between commercial benefit and pure research.[48] Typically, as non-commercial research was unlikely to provoke a lawsuit, the defense was invoked in cases between commercial competitors. Academic research, which historically would have little impact on the profitability of a patent, becomes less likely to have a strictly philosophical purpose with the passage of the Bayh-Dole Act. In this environment, the Federal Circuit decided *Madey v. Duke University*.[49] The infringing act was Duke University's use of equipment in the physics lab of a former faculty member, John Madey. The Federal Circuit held that the University's use was not protected under the experimental use exemption because it was in "keeping with the alleged infringer's legitimate business," reasoning that though the University often conducts research with no commercial application, it is nevertheless in furtherance of the institution's legitimate business objectives, including "educating and enlightening students and faculty participating in these projects."[50] The Supreme Court denied review of the case.[51]

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46. *Id.* at 1121. Specifically, Story noted that "it could never have been the intention of the legislature to punish a man who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects." *Id.*

47. *See, e.g.*, Ruth v. Stearns-Roger Mfg. Co., 13 F.Supp. 697 (D.Colo. 1935) (holding that the making and using of patented machines in a school laboratory for experimental purposes without any intent to derive profits of practical advantage was not an infringement); Sawin v. Guild, 21 F.Cas. 554 (D. Mass. 1813) (No. 12391) (holding that the making of a patented machine must be with an intent to infringe and deprive the patent owner of the lawful rewards of his discovery).

48. *See*, *e.g.*, Spray Refrigeration Co. v. Sea Spray Fishing, Inc., 322 F.2d 34 (9th Cir. 1963) (holding that the use of a patented invention for freezing fish on board a vessel at see was a commercial, not experimental, use).

49. 307 F.3d 1351 (Fed. Cir. 2002).

50. *Id.* at 1362. In addition, the court found that such research also benefits Duke's reputation which, in turn, attracts more research grants, students and faculty. Interestingly, in *Embrex, Inc. v. Service Enginnering Corp.*, 216 F.3d 1343 (Fed. Cir. 2000), the Federal Circuit just two years before their decision in *Madey*, discussed the experimental use defense and *de minimus* infringement and reasoned that the defendant's use of the patented method was not immunized by the defense because of the commercial character of the tests:

> While SEC tries to cloak these tests in the guise of scientific inquiry, that alone cannot immunize its acts. The district court determined on the record before it that SEC performed the tests expressly for commercial purposes. SEC's chief commercial purpose was to demonstrate to its potential customers the usefulness of the methods performed by its *in ovo* injection machines.

Id. at 1349.

51. *See* Duke University v. Madey, 539 U.S. 958 (Mem.) (2003). The case was remanded to the Middle District of North Carolina, where the court, not surprisingly, found that Duke was not

It is not difficult to understand why the court did not want to extend the research exemption to the University's activities. The experimentation in this case was not trying to understand or experimenting on the equipment; rather, the experimentation was the economic purpose of the equipment. Extending the research exemption to such use would effectively immunize all academic institutions from infringing any patents on laboratory equipment. Consequently, exempting use of inventions with significant markets among researchers, such as patented laboratory equipment, would deprive patent owners of the profits they may have otherwise expected to earn. Unfortunately, the court's holding was made much broader by its failure to differentiate between experimenting on patented technology and experimenting with patented technology.[52] By doing so, the availability of the exemption is now uncertain for research tools, where the product at issue may be experimented with, experimentation on, or is a final commercial product.

The Supreme Court finally decided to step into the research exemption arena when it granted certiorari in *Integra Lifesciences, Ltd. v. Merck KGaA*,[53] a case decided by the Federal Circuit soon after its decision in *Madey*.[54] However, *Integra* involved the statutory research exemption, not the common law exemption, and specifically, Section 271(e) of the patent laws. Moreover, while *Madey* was concerned with laboratory equipment, the Federal Circuit characterized the invention in *Integra* as being a research tool.[55]

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entitled to summary judgment on the experimental use defense. Indeed, Duke had previously conceded that its activity was "in furtherance of the school's educational purpose." *See Madey v. Duke University*, 336 F.Supp.2d 583, 592 (M.D.N.C. 2004)(quoting Def.'s Mem. Supp. Pat. Mot. at 9).

52. For a detailed discussion on "experimenting on" vs. "experimenting with," see Katherine Strandberg, *What Does the Public Get? Experimental Use and the Patent Bargain*, 2004 WIS. L. REV. 81.

53. 331 F.3d 860 (Fed. Cir. 2003)

54. *See* Merck KGaA v. Integra Lifesciences I, Ltd., 331 F.3d 860 (Fed. Cir. 2003), *cert. granted*, 125 S. Ct. 823, 160 L.Ed.2d 609, 72 USLW 3568, 73 USLW 3059, 73 USLW 3386, 73 USLW 3396, 05 Cal. Daily Op. Serv. 210 (U.S. Jan 07, 2005) (NO. 03-1237). The Supreme Court declined certiorari in *Madey v. Duke University*, likely following the recommendation of the Solicitor General of the United States. *See* Brief for the United States as Amicus Curiae, at 5, *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2002)(No. 02-1007).

55. Whether the invention at issue in *Integra* is a research tool per se, is disputed. For example, Judge Newman argues that:

> My colleagues on this panel appear to view the Integra patents as for a "research tool." That is a misdefinition. The RGD-containing peptides of the Integra patents are not a "tool" used in research, but simply new compositions having certain biological properties. The Scripps/Merck syntheses and evaluations of new RGD peptides were not use of the Integra products as a research tool.

See Integra Lifesciences I, Ltd. v. Merck KGaA, 331 F.3d at 878 (dissenting opinion of Judge Newman).

B. Integra Lifesciences I, Ltd. v. Merck KGaA

In *Integra*, the court was faced with the issue of whether pre-clinical trials were exempt under Section 271(e)(1).[56] The scope of § 271(e) has been subject to some analysis by the courts, particularly with respect to whether testing is "solely for uses reasonably related to the development and submission of information under a Federal law." Prior to *Integra*, the courts applied this language quite broadly. For example, in *Intermedics, Inc. v. Ventritex, Inc.*,[57] the court found that the test under § 271(e) was whether the defendant could reasonably believe that there was a "decent prospect" that the activity would generate information relevant to the FDA approval process.[58] More recently, in *Nexell Therapeutics, Inc. v. Amcell Corp.*,[59] the District Court for the District of Delaware stated "activities should only be found to exceed the scope of the § 271(e) exemption when they have no objectively reasonable application towards obtaining FDA approval."[60]

The court in *Integra*, however, shifted direction and limited the scope of the exemption. In *Integra*, the experiments at issue used a patented sequence owned by Integra to determine the best drug candidate for inhibiting angiogenesis for clinical development and clinical trials were expected to commence within three years.[61] Viewing the legislative history of the Hatch-Waxman Act, specifically that it was "designed to benefit the makers of generic drugs, research-based pharmaceutical

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56. *See Integra*, 331 F.3d at 865. 35 U.S.C. § 271(e) (2000) provides, in relevant part, that:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

57. 775 F.Supp. 1269 (N.D. Cal. 1991).

58. *See id.* at 1280. In *Intermedics*, the defendant used clinical trial data to solicit capital funding for additional trials and to prepare for production upon the expiration of the patent. Ventritrex also used the data to obtain patent rights and import approval in foreign countries. In deciding whether the activities fell under the statutory exemption, the court ruled in favor of the defendant. *See id.* at 1277–27, 1281. The Federal Circuit affirmed the district court's decision without substantial analysis. *See Intermedics v. Ventritex, Inc.*, 991 F.2d 808 (Fed. Cir. 1993)(unpublished disposition).

59. 199 F. Supp. 2d 197 (D.Del. 2002)

60. *Id.* at 204–05.

61. 331 F.3d at 863. In *Integra*, Dr. David Cheresh at The Scripps Research Institute ("Scripps") discovered that by blocking the αvβ3 receptors, angiogenesis (i.e. the process of generating new blood vessels) was inhibited, thereby potentially providing a means to eliminate tumor growth and treat several other diseases. Merck and Scripps entered into an agreement wherein Scripps would fund the "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials. *Id.*

companies, and not incidentally the public," the Federal Circuit emphasized that the otherwise infringing act must "reasonably relate" to the development and submission of information for the FDA regulatory approval process in order to avail itself of the exemption.[62] Noting that the FDA "has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval,"[63] the court held that the research was not "solely for uses reasonably related" to clinical testing for the FDA.[64]

The Supreme Court granted certiorari in this case, possibly because the decision by the Federal Circuit seemingly limits the availability of the 271(e)(1) exemption to research conducted for bioequivalency purposes, for example in the form of clinical trials, but does not extend to pre-clinical trial research.[65] This limitation arguably conflicts with the Supreme Court's decision in *Eli Lilly & Co. v. Medtronic, Inc.*,[66] which held that the statutory exemption is not limited to generic drugs but also covers medical devices.

Several briefs and amicus curiae briefs were filed in support of both parties. Initially, the briefs submitted by the petitioner, Merck KGaA, focused on the adverse impact the Federal Circuit decision would have on new drug development. In its Petition for Certiorari, Merck maintained that the Federal Circuit devised an unprecedented reading of the statutory exemption that allows the patent holder to enjoin researchers from conducting clinical trials even if there is no commercial use for the compound and that any such commercialization would not occur until after patent expiration.[67] It emphasized that the Federal Circuit's decision jeopardizes innovation in the pharmaceutical industry in the United States[68] and that the previous understanding of the breadth of the 271(e) exemption induces foreign companies to partner with U.S. firms to con-

62. *See id.* at 866.

63. *Id.*

64. *See id.*

65. In an Errata opinion issued on December 3, 2003, the Federal Circuit clarified that the scope of the exemption is not limited to generic drug approval: "While the scope of the safe harbor is not limited to generic drug approval*, Eli Lilly & Co. v. Medtronics Co.*, 496 U.S. 661 (1990), the history of the 1984 Act informs the breadth of the statutory test." *Id.*

66. 496 U.S. 661 (1990).

67. It is important to note that the facts of the case supported Merck's assertion of patent expiration. In other words, Integra patents were due to expire between 2003–2006. Though supportive of its position in the proceedings, it is not vital to the resolution of the legal issue.

68. See Petition for Writ of Certiorari, *Merck KGaA v. Integra Lifesciences I, Ltd.* No. 03-1237, Mar. 2, 2004, 2004 WL 406591. The Petition cited an Industry Profile of the Pharmaceutical Research and Manufacturers of America noting that the United States is host to 80% ($26.3 billion out of $32 billion) of the worldwide research on new drugs. *Id.* citing Industry Profile at 10, *available at* http://www.phrma.org/publications/publications/profile02/indez.cfm.

duct research. Merck expounded on this point in its Reply Brief, where it emphasized that "[i]t cannot be assumed, as the Federal Circuit did, that licenses for research will be available from patent owners. As a consequence, the development of some new pioneer drugs will be foreclosed or delayed."[69]

Interestingly, the Amicus Curiae Brief submitted by Wyeth argued that the lack of any meaningful common law exemption for research makes the safe harbor in Section 271(e) vital as there is no other means to research and develop new drugs without fear of patent infringement.[70] Wyeth also noted that curtailing the scope of the safe harbor would reduce new drug research and development in the United States.[71]

Whether this assumption is correct is questionable. In an interview with Dr. Arno Hartmann, Head of Patents-Pharmaceuticals at Merck KGaA, Dr. Hartmann noted that should the Court decide in favor of *Integra*, there would not be a substantial change in research and development in the U.S. This is in large part due to the fact that for FDA approval, it is theoretically better to have the experimentation conducted in the U.S. rather than abroad. In other words, it would be very difficult to market a product where all of the research and development was conducted outside of the U.S. In addition, other factors that favor U.S. research and development are that permission is easier to obtain for some types of research and there is a long-standing tradition of conducting research in the U.S.[72] Moreover, from a pragmatic viewpoint, companies prefer to conduct research and development in the U.S. as it allows them to monitor more easily their competitors' activities. Nevertheless, it was noted that as the obstacles to conducting research and development grow, if a company such as Merck KGaA, for example, cannot clarify the licensing situation, they consider moving the research back to Germany or another country with a more patented research-friendly environment.[73]

Accordingly, it was promising that the Court, in light of the denial of certiorari in *Madey v. Duke University*, (which some see as effectively sanctioning an elimination of the common law experimental use exemption), decided to visit the issue regarding the scope of the statutory research exemption. In its decision, the Supreme Court held that "the use of patented compounds in preclinical studies is protected under

69. Reply Brief, Merck KGaA, Petitioner v. Integra Lifesciences, Inc., Aug. 10, 2004, No. 03-1237, 2004 WL 1799833

70. *See* Brief of Amicus Curiae in Support of Petitioner, *Merck KGaA v. Integra Lifesciences I, Ltd.*, No. 03-1237, Apr. 2, 2004, 2004 WL 741062.

71. *See id.*

72. Interview with Dr. Arno Hartmann of Merck KGaA.

73. *Id.*

§ 271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce 'the types of information that are relevant to an IND or NDA.' "[74] While the holding is quite broad, its applicability to research tools is questionable: in its reasoning, the Court noted that the invention at issue in *Merck* was not being used as a research tool and declined to comment on the availability of the exemption to patents on research tools.[75]

Nevertheless, though supporting pre-clinical research through some form of exemption from patent infringement has its merits, it should be questioned whether broadening the statutory exemption while at the same time leaving the common law experimental use exemption in its limited form suggests that only in the drug development industry is research more important than patent rights on other technologies, including, possibly even research tools. Commentators have shown that in fact, the application of the patent laws is industry-dependent. For example, in a study by Burk and Lemley, it was shown that in the field of biotechnology, courts have imposed strict enablement and written description requirements, in large part because of the uncertainty of the technology itself.[76] However, it is one thing to apply the law as industry-dependent as it relates to validity of a patent. Indeed, as pointed out by Burk and Lemley, the degree of variance was in large part due to a determination of what constitutes the "ordinary skill in the art"[77] for determining not only obviousness and enablement but also when construing claim scope. Yet, it is quite another concern to make the exclusive rights a patent bestows on the patent owner industry-dependent. This is not a question of uncertainty in language or scope of protection, which is inherently dependent on uncertainty in the field of science. On the contrary, applying different legal norms to different in-

74. Merck KGaA v. Integra Lifesciences I, Ltd., 125 S. Ct. 2372, 545 U.S._____(2005) (No. 03-1237) (June 13, 2005).

75. *See id.* ("We therefore need not—and do not—express a view about whether, or to what extent, § 271(e)(1) exempts from infringement the use of "research tools" in the development of information for the regulatory process").

76. Dan L. Burk and Mark A. Lemley, *Biotechnology's Uncertainty Principle*, The Law, Technology & the Arts Symposium: The Past, Present and Future of the Federal Circuit, 54 CASE W. RES. L. REV. 691 (2004).

77. In order for a patent to be granted on an invention, the invention must be new, useful, not obvious and meet strict written description and enablement standards. *See* 35 U.S.C. §§ 101–103, 112 (2000). When determining nonobviousness and enablement, courts use a standard of whether one of ordinary skill in the art would find the invention obvious in view of prior art and whether the written description enables one of ordinary skill in the art to make and use the claimed invention. *See*, *e.g.*, In re Moore, 439 F.2d 1232, 1235 (C.C.P.A. 1971); *but see* University of Rochester v. G.D. Searle & Co, Inc. et. al., 69 USPQ 2d. 1886 (Fed. Cir. 2004) (" . . . the statute applies to all types of inventions. We see no reason for the rule to be any different when non-genetic materials are at issue . . .")

dustries to satisfy current economic demands reduces economic certainty and in turn, undermines the strength of the patent system. Moreover, with respect to technology subject to the Bayh-Dole Act, there is no basis for a less stringent application of the patent laws.[78]

Further, while the decision in *Bayer AG v. Housey Pharmaceuticals, Inc.*, illustrates that it is possible to circumvent the limitation on experimentation with patented research tools in the U.S. simply by moving the experimentation offshore,[79] this is a viable option only for large pharmaceutical companies who can afford to have research and development sites in other countries where the technology is either not patented or where the experimental use doctrine is more leniently applied.[80] Moreover, as discussed above, by moving research and development offshore, the social economic benefits associated with research and development are also moved offshore, a concept that runs afoul of the economic underpinnings of a strong patent system. On the other hand, however, by broadening the statutory exemption to encompass all pre-clinical trial research effectively reduces the incentive prong for research and development by a potential patentee. In other words, without some reward for innovation, innovation in research tools will, in theory, be stifled. So while the fear that innovation in drug development may be adversely affected if the exemption is not available because, as noted by Merck KGaA, the patent holder may refuse to license the technology, there is an opposing fear that innovation will be adversely affected if the exclusivity grant of the patent is severely curtailed.

78. *See* University of Rochester v. G.D. Searle & Co, Inc. et. al., 69 USPQ 2d. 1886, 1896 (Fed. Cir. 2004) (" . . . none of the eight policy objectives of the Bayh-Dole Act encourages or condones less stringent application of the patent laws to universities than to other entities.").

79. 340 F.3d 1367 (Fed. Cir. 2003). In *Bayer*, the use of a patented method for screening compounds for the purpose of finding new chemical compounds was held not to infringe the patent when only the information characterizing or identifying the compound, which was acquired via the patented method, was imported into the United States. The court found that 35 U.S.C. § 271(g), the provision which prohibits the importation of products made by the patented process, did not apply. Specifically, the Federal Circuit held that "product" is limited to physical goods and does not include information generated by a patented process. In doing so, the court disregarded the fact that the purpose of the patented method was to generate such information. *See id.* The net result is that under *Bayer*, basic research can be undertaken using research tools outside the country, and the information derived using such tools can be imported into the U.S. without fear of an infringement suit.

80. *See* Tanuja V. Garde, *The Effect of Disparate Treatment of the Experimental Use Exemption on the Balancing Act of 35 U.S.C. § 104*, 35 IIC 241–264 (2004).

III. PATENTS ON UPSTREAM RESEARCH TOOLS

The assumption made in the arguments presented to the Supreme Court is that patents on upstream research tools do interfere with innovation. Whether that is in fact true is questionable. Indeed, there has been much debate over whether patents on upstream research impede scientific progress. For example, it has been noted there is informal price differentiation between licenses to academic institutions and commercial entities; hence, access is not hindered. Nevertheless, the fear of patents on research tools has led to Heller and Eisenberg terming the patenting of upstream technology as a tragedy of the anticommons.[81] Specifically, Heller and Eisenberg noted that in biomedical research, an "anticommons" exist where too many patents block each other causing an underuse of resources.[82] To explain further, the authors noted that:

> The tragedy of the anticommons refers to the more complex obstacles that arise when a user needs access to multiple patented inputs to create a single useful product. Each upstream patent allows its owner to set up another tollbooth on the road to product development, adding to the cost and slowing the pace of downstream biomedical innovation.[83]

In theory, the anticommons problem arises when several companies hold parallel rights into the finished product.[84] With respect to research tools, the anticommons arises because upstream research serves as inputs into a final product of downstream innovation.[85] On the flip side, Kieff suggests that treatment of patent rights as property provides incentives for investment.[86] In response to the anticommons problem, Kieff argues that neither multiple inputs nor overlapping patent rights are enough to

81. Michael A. Heller and Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, SCIENCE, 1 May 1998, at 698.

82. *Id.*

83. *Id.* at 699.

84. A commonly cited example to illustrate the problem of an anticommons with property rights is that of toll stations operated by two different parties on a river. With increased tolling, the traffic on the river is reduced, thereby decreasing the revenue to the toll operators, which in turn reduces the social welfare of the travelers. *See*, *e.g.*, James Buchanan & Yong J. Yoon, *Symmetric Tragedies: Commons and Anticommons*, 43 J.L. & ECON. 1 (2000).

85. Many scholars have assumed that the proper policy for addressing an anticommons problem is to limit, or at the extreme, eliminate, property rights in upstream research tools, including, e.g., DNA sequences. *See*, *e.g.*, Rai, *Fostering Cumulative Innovation*, *supra* note 9.

86. Kieff argues that clear and enforceable boundaries in property rights provide incentives for investment at the same time as giving the public notice of what is not infringing. *See* F. Scott Kieff, *Facilitating Scientific Research: Intellectual Property Rights and the Norms of Science—A Response to Rai and Eisenberg*, 95 NW. U. L. REV. 691 (2001) Kieff maintains that Rai's argument is based on a mischaracterization of the pre-1980 basic biological research community. *See id.*

prevent an industry, in this case the biotech industry, from operating successfully.[87] In addition, Kieff asserts that the problem raised by Heller and Eisenberg are not applicable to current issues, namely that "there is little risk a patent on a small gene fragment would support a judgment of infringement against a larger DNA sequence, such as a substantial portion of an entire gene."[88]

Unfortunately, the issues surrounding the use of research tools is more complex than a case of asserting that a genus infringes a species, particularly when considering the lack of clarity in the scope of protection afforded to biotechnology patents.[89] The mere existence of a patent on a research tool, or multiple patents in the case for an anticommons, implies that the bargaining position for the non-authorized researcher is subordinate to the patentee.[90] Whether the patentee is aggressive in maintaining its position is a separate issue. In a study by Walsh, Arora and Cohen, empirical evidence suggested that while patenting of upstream research has increased, thereby potentially limiting access, none of the respondents to the study claimed that significant projects were stopped because of denied access. Instead, the report stated that the industry adopted so called "working solutions", namely licensing, designing around patents, going offshore, using public databases, challenging the patents in court, or simply infringing the patent.[91] Importantly, though, each of these solutions increases the cost of the end product, *e.g.* the targeted treatment or other biopharmaceutical. In addition, these solutions do not shift or otherwise alleviate the bargaining position of the patent holder; instead, the licensee or other researcher depends upon the patent owner's goodwill in not taking an aggressive position when wielding its patent rights.

However, none of these working solutions are truly within the interests of the ultimate target, i.e. the consumer, as they either transfer the

87. *See* F. Scott Kieff, *Property Rights and Property Rules for Commercializing Inventions*, 85 MINN. L. REV. 697, 721 (2001).

88. *Id.* Kieff suggests that the correct argument is that the larger segment of DNA does not infringe gene fragments in the biotechnology industry. This is based on the requirements for novelty and adequacy of disclosure, namely that an attempt to delineate the scope of a claim to cover a larger fragment of DNA would raise issues of prior art and enablement. *See id.* at 722. Under a literal infringement analysis, Kieff's argument has merit; however, with the uncertainty surrounding scope of protection of biotechnology patent claims, it is too simplistic of an analysis in any situation where the doctrine of equivalents plays a role.

89. *See* Burk and Lemley, *supra* note 76 and accompanying text.

90. A premise to the argument is that fundamental research is such that it cannot be designed around. Hence, public access becomes a central inquiry. It is also worth nothing that many research tools are in fact products valued for the information they give (e.g., genetic sequences) rather than what they do.

91. John P. Walsh, Ashish Arora, and Wesley M. Cohen, *Working Through the Patent Problem*, SCIENCE, 14 Feb. 2003, at 1021.

social benefits of research and development offshore[92] or transfer the social costs of drug development, including higher licensing fees and attorneys' fees in the case of infringement, to the cost of the treatment. Interestingly, the authors noted the severe limitation on the availability of the experimental use doctrine in *Madey v. Duke University*,[93] but the study did not seem to account for the limitation when it identified that at least a third of the industrial respondents, and all nine of the university and governmental labs, justified infringing patented technology under the research exemption.[94]

Whether the curtailment of the research exemption will have any effect on the infringing use of patented technology, specifically research tools, is unclear. It stands to reason that fear of a large infringement action will deter unauthorized use. Indeed, as Walsh, et. al. suggest, the decision in *Madey* may undermine the informal use of the exemption and therefore an exemption for research intended for the public domain should be constructed. As stated above, the difficulty lies in crafting an exemption that balances the interests of the patentee with the interests of the public. It has been suggested that the U.S. should follow the approach taken by some European countries, *e.g.,* Germany, which provides that the experimental use defense apples to all experimental acts that relate to the subject matter of the invention, regardless of whether the tests produce purely scientific or predominantly industrially exploitable results.[95] Others have argued that courts should differentiate between "experimenting on" versus "experimenting with" when deciding on the availability and scope of the exemption.[96] Dreyfuss suggests that the exemption should be crafted such that anyone can invoke the research exemption but that they then cannot claim any proprietary rights in the results of that research.[97] In this case, though, and as Rai pointed

92. *See* Garde, *supra* note 80 at 241–64.

93. 307 F.3d 1351 (Fed. Cir. 2002).

94. *See* Walsh, et. al., *supra* note 91; *See also*, John P. Walsh, *Ashish Arora, and Wesley M. Cohen*, Research Tool Patenting and Licensing and Biomedical Innovation*, (forthcoming in W.M. Cohen and S. Merrill, eds. Patents in the Knowledge Based Economy. Wash. D.C.: National Academies Press (February 21, 2003)).*

95. *See* Klinische Versuche II (Erythropoetin), [1998] R.P.C. 423 (German Federal Supreme Court); *see also*, Joseph Straus, *On the Admissibility of "Biological Equivalence Tests" During the Patent Term for Obtaining Regulatory Approval for Patented Drugs by Third Parties: A Study in German Comparative Law*, 23 A.I.P.P.I. JOURNAL 211 (1998); for a discussion on the merits of applying the German standard of experimental use in the U.S., see Garde, *supra* note 80 at 254.

96. *See, e.g.*, Katherine J. Strandburg, *What does the Public Get?: Experimental Use and the Patent Bargain*, 2004 WIS. L. REV. 81 (2004). However, as Strandburg notes, distinguishing between "experimenting on" and "experimenting with" is tricky because of the difficulty in separating the use of the invention with the use of the inventive idea. *See id.*

97. Specifically, Dreyfuss suggests that a university or nonprofit research institute that chooses to use the patented technology and cannot obtain a license on reasonable terms from

out, commercialization may be an issue if there is no exclusivity incentive. Rai suggested a royalty free license to noncommercial use but recognized its inherent limitations, namely how to define the boundary between noncommercial and commercial research in today's environment of the commercial value of basic research.[98] Further, Rai and Eisenberg suggest that the NIH be given greater latitude in dedicating research results to the public domain.[99]

The problem in the approaches discussed above is that none of them provides a useful means to balance the rights of the patent holder with the rights of the public. In each case, either the bargaining position rests with the patentee, thereby potentially hindering access through cost-prohibitive licenses or merely refusals to license, or alternatively the incentive to innovate is reduced by severely curtailing or eliminating the patentee's or more commonly, the licensee's right to profit from commercialization of the invention, whether in the form of further research or product development.[100] There is a considerably body of literature that discusses the role intellectual property protection plays in innovation, much of it focusing on knowledge as a public good and the trade-offs when intellectual property protection is weak.[101] This article does not purport to discuss the merits of the intellectual property system as a means for driving innovation, but rather takes it as given that the pharmaceutical and biotechnology industries are heavily dependent on patent rights.[102]

In any event, access to research tools, whether in the form of a gene, a screening assay, etc., is questioned when there is a patent thicket

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the patentee can still use the technology without authorization if it is willing to sign a waiver. The waiver would require the institution to publish the results of the work conducted using the technology and is precluded from patenting discoveries made in the course of that work. *See* Rochelle Dreyfuss, *Protecting the Public Domain of Science: Has the Time for an Experimental Use Defense Arrived?*, 46 ARIZ. L. REV. 457 (2004). Dreyfuss' approach explicitly favors university research over corporate research and in some ways, attempts to redirect university research away from commercial applications or revenue-generating potential.

98. *See* Arti K. Rai, *Complexities of Designing a Research Exemption*, presentation to the American Association for the Advancement of Science, *available at* http://sippi.aaas.org.

99. *See* Rai and Eisenberg, *supra* note 40. In their article, Rai and Eisenberg propose to eliminate the "exceptional circumstances" language such that the authority for the NIH to eliminate the right to retain title in the contractor would be subject to a discretionary standard for promoting the policies and objectives of the Act. *See id.* at 311. They also suggest that the requirement that one seeking the government to assert its march-in rights must wait until all court appeals by the government contractor have been exhausted must be changed. *See id.* at 312.

100. Intrinsic to the anticommons theory is the risk of a breakdown in the bargaining due to the increased leverage enjoyed by a patent owner of multiple inputs.

101. *See, e.g.*, Robert P. Merges and Richard R. Nelson, *On the Complexities of Patent Scope*, 90 COLUMBIA L. REV. 839 (1990).

102. *See, e.g.*, Edwin Mansfield, *Patents and Innovation*, 32 MGMT SCI. 173 (1986).

covering the tool. In theory, such a patent thicket may slow the pace of research and development in the field. On the other hand, severely limiting the patentee's exclusive right by shifting all research results to the public domain, whether for research or otherwise, may have adverse long-term effects on technological innovation. Accordingly, it is herein proposed that a balance between the two objectives can be found by subjecting patents on research tools funded by the NIH to a license of right.

IV. LICENSE OF RIGHT

Initially, in order to make any policy proposal on access to research tools, it is important to clearly delineate what does and does not constitute a research tool. Some scholars have limited the term to include only those tools used in the development of novel biotechnological and pharmaceutical products that "do not themselves physically incorporate the tool" and where access to the tools is problematic.[103] Because the suggestions in this paper are linked to inventions stemming from NIH funded research, the analysis will use the NIH definition of research tools. As will be clarified below, attempting to demarcate between those tools that are use only vs. those that can constitute "end products" as well fails to distinguish between those tools that serve both purposes.

The NIH Working Group on Research Tools (NIH Working Group) presented a Report in June 1998[104] to address the difficulties and delays many scientists and institutions were having when negotiating access to research tools. In defining 'research tools,' the NIH Working Group defined the term "research tool" to include "the full range of resources that scientists use in the laboratory," encompassing those resources that can also be used as "end products," including cell lines, monoclonal antibodies, etc.[105] The Report noted the increased use of license agreements and

103. *See* Janice J. Mueller, *No "Dilettante Affair:" Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 WASH. L. REV. 1 (2001). Mueller proposes a "liability rule" that would allow a "non-consensual 'development use' of patented research tools that are not readily available for licensing or purchase, while providing an ex post royalty payment" to the right holder of the patented research tool. *Id.* at 54.0

104. *See* Report of the National Institutes of Health (NIH) Working Group on Research Tools, June 4, 1998, *available at* http://www.nih.gov/news/researchtools/ (last accessed on May 17, 2005). The recommendations included the "free dissemination of research tools without legal agreements wherever possible, especially when the prospect of commercial gain is remote." *Id.*

105. The report noted that the term includes "cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software."

material transfer agreements (MTAs)[106] that stipulated the conditions for the use of research tools.[107]

A. *Case Studies Illustrating Technology Transfer of Research Tools*

Popular examples of proprietary research tools in molecular biology include the Cohen-Boyer technology for recombinant DNA, polymerase chain reaction technology, DNA sequencing instruments, and expressed sequence tags (ESTs). To illustrate the bargaining positions of the proprietors, a brief discussion of the history of each of these technologies is provided.

1. Recombinant DNA

The Cohen-Boyer technology for recombinant DNA was a combination of three patents, one directed to making the molecular chimeras and two product patents.[108] The technology was co-owned by Stanford, UCSF, and the two inventors, Stanley Cohen and Herbert Boyer. The licenses issued were non-exclusive and generated over $100m in revenues. Seen as a paragon of technology transfer by supporters of the Bayh-Dole Act, its success was primarily due to the fact that the license was inexpensive, it was a pioneer patent (in that there were no other alternatives at that time) and it became a necessary tool for research in molecular biology. Indeed, it is deemed the founding technology of the biotechnology industry.[109]

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106. The NIH defines MTAs as:

> An MTA generally is utilized when any proprietary material and/or information is exchanged, when the receiving party intends to use it for his/her own research purposes, and when no research collaboration between scientists is planned. Neither rights in intellectual property nor rights for commercial purposes may be granted under this type of agreement.

http://ott.od.nih.gov/MTA_over.html.

107. In 1999, in response to the recommendations provided by the Working Group on Research Tools, the National Institutes of Health published for public comment a proposed policy entitled *Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts*. *See* 64 FR 28205 (May 25, 1999). Pursuant to the comments received, a Notice was issued presenting the final principles and Guidelines in conjunction with the NIH's response to the public comments. *See* 64 FR 72090 (Dec. 23, 1999). The NIH policy makes clear that reach-through royalty terms as a condition for the use of a research tool is inconsistent with the policy. Further, the policy emphasizes that royalties on the sale of a final product that does not embody the tool is not appropriate. *See id.*

108. The two product patents included one for proteins produced using recombinant prokaryote DNA and the other for proteins formed by using recombinant eukaryote DNA.

109. Tim Beardsley, *Big Time Biology,* SCI. AMER. Nov. 1994, at 90.

2. Polymerase Chain Reaction

Polymerase Chain Reaction, or PCR, allows for the amplification of DNA or RNA sequences. *Taq* polymerase is the enzyme used in the amplification. The technology created a means to conduct research more efficiently and to analyze genes in biological samples. It became an essential tool in molecular biology research, and as Tom Caskey, senior vice-president for research at Merck Research Laboratories and past-president of the Human Genome Organization noted: "The fact is that, if we did not have free access to PCR as a research tool, the genome project really would be undoable . . ."[110] The PCR technology, however, was licensed in a different manner from the Cohen-Boyer patents. Specifically, Hoffman-LaRoche bought the patents from the original owners, Cetus Corporation, and because of its nature as a business rather than a university, it set licensing terms linking the use of the technology with the purchase of its products. It did differentiate between the users of the technology, e.g. the Human Genome Project, studies of gene expressions, diagnostic applications, etc., when setting its licensing terms. Its licensing practice was met with far more criticism than the Cohen-Boyer technology, even though it was understood that both Cetus and Hoffman-LaRoche were in the business of selling products and thus had to recoup on their investment in developing or purchasing the PCR technology, respectively. For example, Bernard Poiesz, a professor of medicine at the State University of New York in Syracuse noted that while the company did support research in its licensing practices, he opined that some of the licenses are "of the highest royalty rates I have personally experienced,"[111] citing the example of the high royalty rates charged for diagnostic tests of HIV RNA. In a workshop held by the National Academy of Sciences in 1996, several participants stated that the high cost of *Taq* polymerase made some research unfeasible.[112] It was further noted that the high cost of the PCR technology is cost-prohibitive for many small biotech entrant companies and consequently, inhibits the development of PCR-related research tools.[113]

110. *Intellectual Property Rights and Research Tools in Molecular Biology*, Summary of Workshop Held at the National Academy of Sciences, Feb. 15–16, 1996, Ch. 5, CASE STUDIES, *available at* http://books.nap.edu/html/property.

111. *Id.*

112. *Id.*

113. *Id.* In March 2003, the Court of Appeals for the Federal Circuit sustained some findings of the district court that the patent on Taq polymerase was obtained by inequitable conduct and remanded the case to the district court to determine if, in view of all circumstances, the sustained incidents of inequitable conduct are such as to justify rendering the patent unenforceable. *See* Hoffmann-La Roche, Inc. v. Promega Corp., Fed. Cir. 2003 (No. 00-1372). On remand, the District Court for the Northern District of California found that the

3. DNA Sequencing

DNA sequencing instruments allowed for more efficient DNA sequencing, a tool useful for determining gene function. The technology was developed by scientists at the California Institute of Technology and because of the speculative nature of the research, the university had difficulty in finding licensees to invest in the research. One company, Advanced Biosystems, agreed to license the technology on the condition that the license be exclusive. Through further negotiation, an exclusive license was granted with the condition that the company must issue sublicense under "reasonable terms." Not surprisingly, many companies argued that the terms offered by ABI were far from reasonable.

4. Expressed Sequence Tags (ESTs)

ESTs are short strands of DNA that are part of a cDNA molecule[114] and can act as identifier of a gene. ESTs are used in locating and mapping genes. They are derived from short DNA sequences whose location and base sequences are known. Problems with patenting ESTs from a legal perspective stem in large part from the question of their utility.[115] The entities involved in developing ESTs all took a different approach with respect to public access, some placing the information in the public domain, and others offering exclusive and nonexclusive licenses. Though the actual use of the EST is questionable with respect to granting patent protection, discoveries of gene function that have greater biological utility may be derived from research on ESTs.[116]

5. Stem Cell Research

Recently, the Wisconsin Alumni Research Foundation (WARF) was granted a patent on pluripotent embryonic stem cells and the method for isolating such cells. There is no doubt that human embryonic stem cells are very important research tools. The patent is exclusively licensed to Geron Corporation. To alleviate concerns that access would be limited by academic researchers, WARF signed a Memorandum of Understanding

patent on the Taq polymerase was unenforceable due to inequitable conduct. *See* Hoffmann-La Roche, Inc. v. Promega Corp., 319 F. Supp. 2d 1011 (N.D. Cal. 2004).

114. cDNA, or complementary DNA, is DNA that is synthesized in the laboratory from a messenger RNA template. For more information on cDNA, see Human Genome Project Information, *available at* http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml.

115. Utility is one of the requirements for patent protection under Title 35 of the U.S. Code. Specifically, Section 101 states that: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title." 35 U.S.C. § 101 (2000).

116. *See Intellectual Property Rights*, *supra* note 110. The Workshop highlighted fear of infringement by researchers using patented ESTs on future discoveries.

with the NIH allowing researchers at the NIH and other not for profit institutions with NIH grants to be able to access the cell lines for a nominal cost.[117]

Each of the cases highlights that access to research tools plays a critical role in the research of molecular biology and consequently, the future development of targeted treatments. Due to the leverage enjoyed by a patent holder, case studies on access necessarily focus on the intent of the patent holder to license the technology and in some cases, the reality that even when the intent was for public access, the terms of licensing were arguably cost-prohibitive. Public access is an important goal of the NIH when granting funding; indeed, and as noted above, this was a driving factor behind the passage of the Bayh-Dole Act. Unfortunately, by shifting the leverage from a nonprofit university or other research institution to a for-profit organization, theoretical access is achieved for commercialization but not for purposes of further research due to the potentially high costs involved in obtaining access to the technology. This was a situation highlighted in the DuPont Cre-lox case, which was only resolved after a collective refusal by several prominent institutions, including the NIH, to license the technology on DuPont's terms.[118]

With march-in rights having limited scope and questionable applicability to research tools, the focus of the inquiry should not be on discretion as suggested by Rai and Eisenberg but rather guaranteed public access to research tools developed with NIH funding. Not only does such a guarantee fall into the scope and purpose of the Bayh-Dole Act but is also gives a degree of certainty to the availability of the tool. Rai has suggested a royalty free license but correctly noted that it may be contrary to the purposes of the Bayh-Dole Act.[119] Moreover, compulsory royalty free licenses countermand the foundation of the patent system, a concern that the NIH expressed when issuing its decision on march-in rights in CellPro.[120]

The problem with previous proposals for ensuring access was that they did not account for the source of the investment at the time of the invention. In other words, with Bayh-Dole, the focus was always on the

117. The cost covers the handling fees. *See* OECD Report, *Genetic Inventions, Intellectual Property Rights and Licensing Practices*, 2002, *available at* www.oecd.org.

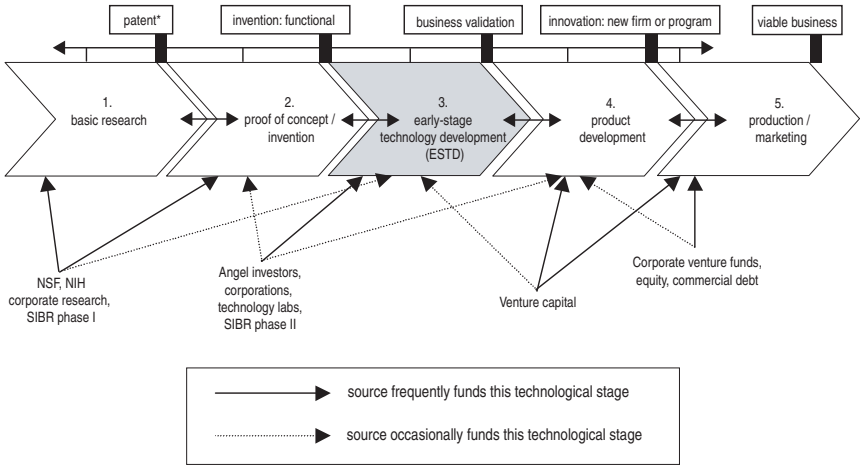
118. *See id*. at 14. The technology at issue was for a gene-splicing tool patented by Harvard University and exclusively licensed to DuPont Pharmaceutical Co. It allowed researchers to make what are called "knock out mice" by deleting a single gene from specific cells. This tool was very useful for identifying gene function.

119. *See* Art. K. Rai, *Complexities of Designing a Research Exemption*, Presented to the Research Exemption Working Group of the Science and Intellectual Property in the Public Interest (April 18–19, 2004) *available at* http://sippi.aaas.org/rschexemption.shtml.

120. *See Determination in the Case of Petition of CellPro, Inc.* (Aug. 1, 1997) *available at* http://www.nih.gov/icd/od/foia/cellpro/.

later commercialization and hence the invention was purported as being supported by commercial funding. On the contrary, however, much of the invention in basic sciences is occurring with NIH or other government funding, not with private investment. Innovation in universities on the other hand, which is the basis for a strong patent system, typically occurs later, thanks to Bayh-Dole, with private investment. A survey of 62 U.S. universities suggests that much of university research is no more than a "proof of concept" while a minority is "ready for practical use" at the time of the license.[121] Branscomb and Auerswald have studied the different stages of technology development.[122] Figure 1 illustrates the development stages for invention to innovation:[123]

FIGURE 1



121. *See* Jerry G. Thursby and Marie C. Thursby, *Enhanced: University Licensing and the Bayh-Dole Act*, SCIENCE, Aug. 22, 2003, at 1052, *available at* http://www.sciencemag.org/cgi/content/full/301/5636/1052. Specifically, 45% of the inventions are nothing more than a "proof of concept" while only 12% of the inventions are "ready for practical use." Moreover, the failure rate for these inventions is also quite high, namely 46% for all inventions and 72% for those that are only a proof of concept.

122. Lewis M. Branscomb & Philip Auerswald, *Between Invention and Innovation, An Analysis of Funding for Early Stage Technology Development*, NIST 2002. *See* NIST GCR 02-841 *Between Invention and Innovation, An Analysis of Funding for Early-Stage Technology Development* Economic Assessment Office, *available at* http://www.atp.nist.gov/eao/gcr02-841.

123. Lewis M. Branscomb & Philip Auerswald, *Early Stage Technology Development: the Transition from Invention to Innovation in the US Economy*, Presentation to the *Science and Technology Advisory Group, Taipei, Taiwan*, July 22, 2002. For a more detailed discussion on the stages of technology development, see LEWIS M. BRANSCOMB AND PHILIP AUERSWALD, TAKING TECHNICAL RISKS, HOW INNOVATORS, MANAGERS, AND INVESTORS MANAGE RISK IN HIGH-TECH INNOVATIONS (2001).

As shown in Figure 1, basic research is supported by NIH funding. Patent applications follow and then licenses to further innovation occur. The problem rests in translating basic research into a commercially viable innovation, a process that is becoming more and more difficult.[124] Innovation has been defined as "the successful implementation (in commerce or management) of a technical idea new to the institution creating it."[125] In other words, an innovation is the consequent application of technical, market or business-model creativity to produce a new or improved product, process or service that can be entered into the market.[126] On the other hand, an invention can be characterized as a manifestation of pure knowledge, i.e. information vs. product. Thus, incentives to invent should be differentiated from incentives to innovate, the space between having earned the term "the Valley of Death" or the "Darwinian Sea."[127]

It is understandable how the distinction is blurred as technological innovation is seen as critical to long-term economic growth. The ability to turn science-based inventions into commercially viable innovations is necessary to achieve sustained growth.[128] Government funding for science-based inventions is vital, as efficient markets do not exist for allocating risk capital to early-stage inventions. When the distinction between invention and innovation is blurred, the focus of the patent bargain shifts to the bargaining position of the actors during technological innovation rather than their positions at the time of the invention. Instead, however, at the time of invention, the funding source, i.e. the federal government, is in the dominant position in the bargain with the future patentee, i.e. the university or academic researcher, holding the subordinate position. Thus, when constructing a model or proposal for encouraging public access to research tools, this demarcation must be understood as any model needs only balance the incentive to invent (rather than only the incentive to innovate) with public access to NIH funded research tools.

Accordingly, it is herein proposed that guaranteed access should take the form of a license of right for all NIH funded research tools. Since the government is in a stronger bargaining position at the time of the grant of funding, requiring a license of right clause in the offer of grant would

124. *See*, *e.g.*, U.S. Department of Commerce, February 2002, *available at* http://www.atp.nist.gov/atp/secy_rept/report.pdf.

125. Lewis M. Branscomb, *Technological Innovation*, *in* INTERNATIONAL ENCYCLOPEDIA OF SOCIAL AND BEHAVIORAL SCIENCES 15498 (Neil J. and Paul B. Baltes, eds., 2001).

126. *See* JOHN A. ALIC ET AL., BEYOND SPINOFF: MILITARY AND COMMERCIAL TECHNOLOGIES IN A CHANGING WORLD (1992).

127. *See* Branscomb & Auerswald, *Between Invention and Innovation*, *supra* note 122; *see also* INVESTING IN INNOVATION: CREATING A RESEARCH AND INNOVATION POLICY THAT WORKS (Lewis M. Branscomb and James Keller, eds., 1998).

128. *See* NIST GCR 02-841 *supra* note 122.

not be detrimental to the negotiation. Essentially, a license of right provides that a license to the technology is available as of right.[129] Licenses of right are not unheard of in other jurisdictions. It is, for example, a form of license recognized in the United Kingdom. In the United Kingdom, the incentive for the proprietor to make an entry into the register that licenses are available as of right is that renewal fees are reduced by half. Once such an entry is made to the satisfaction of the comptroller,[130] any person is entitled to a license under the patent. The terms of the license are negotiated between the patentee and the potential licensee but, importantly, if no agreement can be reached as to the terms, the comptroller decides the terms.[131] Moreover, unless otherwise agreed between the parties, a licensee under a license of right has the standing to institute infringement proceedings against an unauthorized user.[132]

The license of right was introduced into the domestic law of the UK by the Patents and Designs Act 1919. Interestingly, under that Act, not only could the proprietor register the patent as being available as of right, but also any interested party could request the comptroller issue a license of right on the ground that there had been an abuse of monopoly rights under the patent. The consequences, i.e. a license could not be refused to any applicant, were the same regardless of whether the entry was made voluntarily or compulsorily.[133] Due to the United Kingdom's accession to GATT, compulsory licensing provisions in accordance with GATT-TRIPS are included in separate sections of the 1977 Patents Act, which provide a basis for the Comptroller to make an entry in the Register for a license of right.[134] It is also important to note that attempts

129. UK Patents Act 1977 Section 46.

130. *See* Section 46(2):

> when a patent owner makes an application for a license of right to be entered under the patent, the comptroller must give notice to any person registered as having a right under the patent and an entry will be made only after it has been determined that the applicant is not precluded from granting licenses to make such entry.

131. *See* UK Patents Act 1977 Section 46(3).

132. *See* UK Patents Act 1977 Section 46(4):

> The licensee under a licence of right may (unless, in the case of a licence the terms of which are settled by agreement, the licence otherwise expressly provides) request the proprietor of the patent to take proceedings to prevent any infringement of the patent; and if the proprietor refuses or neglects to do so within two months after being so requested, the licensee may institute proceedings for the infringement in his own name as if he were a proprietor, making the proprietor a defendant or defender.

133. *See* Allen & Hanbury's Ltd. V. Generics (UK) Ltd and Gist-Brocades NV and others and the Comptroller-General of Patents [1986] ROC 203, HL, Lord Diplock. [Hereinafter "Gist-Brocades"]

134. *See* UK Patents Act Sections 48, 48A and 48B.

to reach an agreement on a license are not a precondition for an application for a license of right.[135]

Settlement of terms follows typically what is seen as a reasonable royalty. In *Gist-Brocades*, the royalty was settled so as to ensure that "the inventor or other person beneficially entitled to the patent shall receive a reasonable remuneration having regard to the nature of the invention."[136] Essentially, a reasonable royalty is that which would have been agreed upon between a willing licensee and willing licensor for the terms granted.[137]

Licenses of right are also provided for under the German patent laws. Such a license is called a *Lizenzbereitschaft*.[138] The provisions and incentives for applying for a *Lizenzbereitschaft* are very similar to those provided for under the UK law. Moreover, Article 43 of the draft Community Patent Convention also provides for a means to obtain a license of right using similar language as that found in the UK and German patent laws.[139]

Skeptics may claim that a license of right for research tools funded by the NIH is nothing more than a compulsory license. In a way, it is correct to suggest that a license of right is related to compulsory licensing; indeed the UK courts look to case law deciding issues arising under the compulsory licensing provisions as persuasive for cases decided un-

135. *See Roussel-Uclaf (Clemence & le Martret's) Patent*, [1987] R.P.C. 109.

136. *See* Allen & Hanbury's Ltd. V. Generics (UK) Ltd and Gist-Brocades NV and others and the Comptroller-General of Patents [1986] ROC 203, HL, Lord Diplock.

137. *See*, *e.g.*, American Cyanamid Co.'s (Fenbufen) Patent, [1991] RPC 409 (Court of Appeal).

138. German Patent Law, Section 23.

139. *See* Community Patent Convention Art. 43, which states in part:

> Licences of right
>
> 1. Where the proprietor of a Community patent files a written statement with the European Patent Office that he is prepared to allow any person to use the invention as a licensee in return for appropriate compensation, the renewal fees for the Community patent which fall due after receipt of the statement shall be reduced; the amount of the reduction shall be fixed in the rules relating to fees. Where there is a complete change of proprietorship of the patent as a result of legal proceedings under Article 23, the statement shall be deemed withdrawn upon the entry of the name of the person entitled to the patent in the Register of Community Patents.
>
> . . .
>
> 4. On the basis of the statement, any person shall be entitled to use the invention as a licensee under the conditions laid down in the Implementing Regulations. A licence so obtained shall, for the purposes of this Convention, be treated as a contractual licence.

der Section 46, licenses of right.[140] As stated above, royalty free compulsory licensing has been suggested, though it raises the question of whether such licenses would promote the goals of Bayh-Dole.[141] In contrast, a license of right allows the patent proprietor to maintain the position of dictating terms. The threat that a court or other governmental entity will dictate the terms in case of an impasse can only serve as an incentive for the patentee to be reasonable in negotiation. Moreover, this proposal is limited to those research tools inventions that are developed using government funding. Hence, there is no need to show abuse of patent rights, as is required under compulsory licensing provisions; instead, the license of right is a precondition to the grant of funds.

Furthermore, licenses of right to research tools reduce economic waste. When viewing the dominant economic theories explaining the costs and benefits of a patent system,[142] many commentators have cited to Kitch's "Prospect Development Theory"[143] when arguing open access to research tools. Kitch proposed that the utility of a patent occurs subsequent to the initial invention.[144] The idea is that when there is an abundance of appropriable inventions after the initial invention, many

140. *See*, *e.g.*, Allen & Hanbury's Ltd. V. Generics (UK) Ltd and Gist-Brocades NV and others and the Comptroller-General of Patents [1986] ROC 203, HL, Lord Diplock

141. *See, e.g.*, Eisenberg, Patents and the Progress of Science, *supra* note 3 at 1076–77. John Barton has also suggested a form of compulsory licensing, which he termed "dependency licensing." In theory, these licenses would be available only to improvers that make significant contributions and would only pay a reasonable royalty. See John H. Barton, Patents and Antitrust: A Rethinking in Light of Patent Breadth and Sequential Innovation, 65 ANTITRUST L.J. 449 (1997). Rai is somewhat critical of compulsory licensing in the biopharmaceutical industry because of its heavy dependence on patent law. See Rai, Fostering Cumulative Innovation, *supra* note 9.

142. Generally, there are four broad economic theories explaining the principle purposes of patents: 1) invention-inducement theory which provides that the expectation of receiving a patent provides motivation for useful invention, *see, e.g.*, Kenneth J. Arrow, Economic Welfare and the Allocation of Resources for Invention, in THE RATE AND DIRECTION OF INVENTIVE ACTIVITY: ECONOMIC AND SOCIAL FACTORS 609 (Richard R. Nelson ed., 1962); 2) disclosure theory which states that patents provide an incentive for inventors to disclose inventions they would otherwise keep secret; *see, e.g.*, Richard C. Levin et. al., Appropriating the Returns from Industrial Research and Development, 3 BROOKINGS PAPER ON ECONOMIC ACTIVITY 783 (1987); 3) development and commercialization theory, stating that patents induce investment needed to develop and commercialize inventions, *see, e.g.* Willard F. Mueller, The Origins of the Basic Inventions Underlying DuPont's Major Product and Process Innovations, in THE RATE AND DIRECTION OF INVENTIVE ACTIVITY: ECONOMIC AND SOCIAL FACTORS 323 (Richard R. Nelson ed., 1962); and 4) the prospect development theory, providing that patents enable a systematic exploration of broad prospects for derivative inventions, *see, e.g.* Edmund W. Kitch, The Nature and Function of the Patent System, 20 J.L. & ECON. 265 (1977).

143. *See, e.g.* Rai, *supra* note 98. Interestingly, though, the Bayh-Dole Act was passed based largely on the assumptions underlying the "Development and Commercialization Theory."

144. *See* Kitch, *supra* note 142.

inventors rush to "mine the prospect."[145] Consequently, it has been argued that a broad initial patent would allow for a less-wasteful and less-duplicative mining.[146] These arguments become secondary when the patents are subject to a license of right, as a broad patent would not be necessary to avoid economic waste.

In addition, as stated above, the grantee of NIH funding is interested in inventing, not innovating. Hence, basic research subject to this license of right is not inherently limiting as such research may not necessarily result in a commercially viable innovation. Again, the researcher is in a weak bargaining position at the time of the NIH funding decisions; thus such a provision is unlikely to deter applications for funding. Moreover, and as stated above, agreeing to grant a license of right to any patents that may be granted on research tools invented under the application would simply be a consideration for the grant of the funds. With respect to the innovation arm, the patent owner is guaranteed reasonable remuneration for the innovation. However, this proposal for a license of right provision is not intended to be as broad as the UK or German laws or the approach by the CPC, but rather limits the license to the use of the invention. Accordingly, a license granted under this proposal does not guarantee public access to the products developed under the license, for example, targeted treatments. In other words, the licenses would not include so called "reach through" clauses that would allow the licensor to receive royalties on the products developed using the research tools.[147] This limitation would provide the incentive for potential licensees to be "willing parties" in the negotiations and in turn, allow for the licensor to recoup reasonable remuneration from multiple parties, similar to the manner in which the Cohen-Bayer technology was licensed. In addition, a patent subject to a license of right under this proposal does not significantly diminish its assignability value, as other proposals suggesting royalty free licenses would do. More importantly, potential licensees, including other universities, would not be dependent on the rational forbearance of a patent owner.

It is plausible, and indeed theoretically likely that requiring a license of right may adversely affect the degree of investment by private entities in research tool innovation. Some critics of a guaranteed right of access to research tools may extrapolate from this point and argue that the long term effects of a license of right would reduce the incentive for biotechnology companies to invest in the innovation of new research tools.

145. *See id.*

146. *See id.*

147. This limitation is in accordance with the NIH proposed policy entitled "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts." *See supra* note 107 and accompanying text.

However, it can also be argued that the exclusivity appeal of a patent to investors lies in the economic value of the exclusive right rather any intrinsic value. In other words, by being granted an exclusive right, the right to dictate the price rests in the patent holder or exclusive licensee and is only subject to market forces to the extent that the price demanded is not cost-prohibitive to the consumer.[148] A refusal to deal is simply a loss of opportunity, a consequence that encourages various forms of cooperation.[149] To exemplify, Dr. Hartmann pointed out that in the company Merck KGaA, approximately 15% of significant research projects are stopped because of blocking patents where obtaining a license was cost-prohibitive.[150] What is proposed herein does not reduce the economic incentive. Rather by requiring reasonable remuneration or royalty terms determined by "willing parties", the economic benefit to the right-holder remains constant. Though there may be an initial decrease in investment in the innovation arm due to the novelty of a guaranteed non-exclusive right, where the cost for conducting private research is significantly higher than investing in research conducted using NIH funding, this lack of exclusivity becomes the norm. Indeed, although Bayh-Dole permits exclusive licenses, it does not require it and surveys have shown that many licenses are in fact nonexclusive.[151] The proposed

148. In a hearing before the Federal Trade Commission on the issue of access to research tool patents, the following was noted:

> One panelist observed: 'licensors tend to be 'fairly sensitive' to the implications of royalty-stacking for product commercialization. If the licensor . . . is about to propose a royalty that's going to kill the product, [the licensor] is not going to make any money. And most of the players in this field are sophisticated enough to understand that.

FTC Report, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy*,` Oct. 2003, *available at* http://www.ftc.gov/os/2003/10/innovationrpt.pdf. Nevertheless, the FTC still conjectured that "biotechnology patents might harm follow-on innovation through the creation of an anticommons and by restricting access to inventions."

149. In economic terms, patents have been described as wasting assets as they are not only limited in duration but also subject to improvements which can chip away at the patent's dominance in the marketplace. *See, e.g.* Richard A. Epstein and Bruce N. Kuhlik, *Navigating the Anticommons for Pharmaceutical Patents: Steady the Course on Hatch-Waxman*, John M. Olin Law and Economics Working Paper No. 209, 2004.

150. Much research in drug development occurs using a pipeline process, where the research groups attempts to find inhibitors, e.g., to compounds. Concurrently, a study of existing patents is undertaken. Due to the competition, research is usually continued and when the research is encouraging, the legal situation is clarified and licenses are obtained as necessary. About 15% of the higher priority projects were stopped because obtaining a license proved impossible, either through unavailability or it was cost-prohibitive. This is in contrast to the report by Walsh, et al. who noted that the participants stated that no significant research was stopped.

151. A survey conducted by the Association of University Technology Managers show that half of the licenses are nonexclusive. *See* Association of University Technology

policy achieves a balance between the financial reward to the right holder with guaranteed public access to the research tool, thereby fulfilling not only the goals of the patent system but also those of the Bayh-Dole Act.

CONCLUSION

The debate over access to research tools has taken a forefront in the drug development arena. Proposals regarding broadening the common law experimental use doctrine, the statutory research exemption under Hatch-Waxman, and even suggesting royalty free licenses have been put forth to address the problem of access to research tools. While the economic analysis suggests that access is not a deterrent to continued research, the underlying assumption in the analysis is that the patentee is exhibiting a sort of rational forbearance. With drug development moving towards a more genomic approach, e.g. targeted treatments, basic research using molecular biological research tools takes on greater importance. Limiting access through patenting of such tools has the potential of stifling innovation. On the other hand, weakening the patent rights in the tools under general economic theory will also adversely affect the rate of innovation.

With research tools, though, it is important to define where the invention in basic research is occurring and identifying the bargaining position of the actors at that point. In basic molecular biological research, invention is occurring primarily at the university level using NIH-funding. Such funding is thus not linked to innovation but rather invention. The NIH holds the stronger bargaining position in this situation and can require a license of right provision in the grant of funding without adversely affecting the rate of invention.

By doing so, licenses of right would allow for greater access to any resultant patents on such tools, which would necessarily result in rational forbearance on behalf of the patent owner. Licensees would be granted access while licensors would be guaranteed a reasonable remuneration under the patent. Increasing access would allow for more players in the drug development arena and in theory, advance the rate of innovation, a goal shared not only by advocates of open science but also by supporters of a strong patent system.

Managers, *AUTM Licensing Survey* (FY 1991 and FY 2001). It is not known how often research tools are exclusively licensed.