Research Tool Case Study

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Sangamo and Zinc Finger Nuclease Technology[1]

Sangamo Biosciences, Inc. performs research, development and commercialization of engineered Zinc Finger DNA-Binding Proteins (ZFPs) for targeted regulation of gene expression and for targeted modification of genes. The technology is applied in human therapeutics and in the enhanced production of biopharmaceuticals. In essence the technology allows for the direct regulation or modification of disease related genes, which includes: 1) activating the expression of a therapeutically important gene, yielding all of the natural forms of the protein and, as a consequence, all of the relevant biology; 2) specifically repressing the expression of a disease-related gene – a potentially improved approach for therapeutically important targets for which small molecule drugs or antibodies cannot now be generated (a growing list of so-called "non-druggable" targets); and 3) physically modifying a DNA sequence within cells permitting the correction of a gene that causes a "monogenic disease" or disrupting the expression of a gene that previously permitted a disease or infection to occur.

In particular, the company is developing a class of compounds known as Zinc Finger Nucleotides (ZFNs), which allow for so-called "Genome Editing." Using this technology scientists can specifically and efficiently edit to correct genes that cause disease. The ZFN is engineered to introduce a double-stranded break at a specific single chromosomal locus and induce homology-directed repair with an exogenously added DNA sequence. This represents an entirely new means of gene replacement in cells and whole organisms, which, unlike traditional therapies, may avoid problems of insertional

[1] Sangamo Biosciences, Inc., *2004 Annual Report & Form 10-K* (available at http://library.corporate-ir.net/library/12/120/120938/items/152881/AR_2004.pdf).

mutagenesis, eliminate the need for large exogenous donor DNA sequences and not suffer from inappropriate tissue specificity, timing and level and duration of expression.

Current applications of the technology include: correcting the gene encoding human interluken 2 receptor-γ, which underlies X-linked SCID, conferring long-term resistance to HIV by disabling the gene for CC-chemokine receptor 5, correcting the β-globin mutation in stem cells from patients with sickle cell anemia, correcting of the X-linked genetic mutation in the Wiskott-Aldrich Syndrome gene, and correcting the genetic mutation in the β-globin gene in stem cells from patients with β-Thalassermia.

Consequently, researchers want access to the technology to optimize and refine the ZFN platform for applications in gene therapy, gene regulation and gene replacement.[2] However, Sangamo maintains that it must control the Intellectual Property (IP) to maintain value and ensure its survival; making the IP freely available to academic laboratories relinquishes that control. It is exactly this tension between industry and academia that has fueled the emerging research tool debate.

What is a Research Tool?

NIH defines research tools broadly considering whether: (1) the primary usefulness of the resource is as a tool for discovery rather than an FDA-approved product or integral component of such a product; (2) the resource is a broad, enabling invention that will be useful to many scientists (or multiple companies in developing multiple products), rather than a project or product-specific resource; and (3) the resource is readily useable or distributable as a tool rather than the situation where private sector involvement is necessary or the most expedient means for developing or distributing the

resource.[3] However, as NIH notes, what constitutes a research tool may be a matter of perspective[4] - what one sees as a research tool, others see as a product.

In the not too distant past, non-profit research institutions published virtually all research results and rarely patented.[5] Consequently, investigators had relatively unfettered access to fundamental knowledge developed by prior researchers. However, this changed with the passage of the Bayh-Dole Act,[6] which granted non-profit research institutions the right to own patents covering government-funded inventions. The purpose of this legislation was to promote widespread utilization of federally sponsored inventions.[7] Although the effect of the Bayh-Dole Act on technological advancement is debatable, university patenting has accelerated significantly since its passage in 1980.[8]

Biomedical discoveries account for a major share of these patents, particularly in terms of licensing revenues, and despite the increasing involvement of industry, the majority of this research is publicly funded.[9] In the United States, 71.6% of citations to papers in biotechnology patents are to government-funded research; a compelling

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[2] Christopher Thomas Scott, *The Zinc Finger Nuclease Monopoly*, 23 Nat. Biotechnolo. 915-918 (2005).
[3] 64 Fed. Reg. 72090, 72094 (Dec. 1999)
[4] *Id*.
[5] Joshua A. Newberg & Richard L. Dunn, *Keeping Secrets in the Campus Lab: Law, Values and Rules of Engagement for Industry-University R&D Partnerships*, 39 Am. Bus. L.J. 187, 196 (2002) (Only about 250 patents a year were issued to US universities in the 1970s).
[6] 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. §§ 200-212 (1994)).
[7] *Id*.
[8] D.C. Mowery & A.A. Ziedonis, *Academic Patent Quality and Quantity Before and After the Bayh-Dole Act in the United States*, 31 RESEARCH POLICY 399, 414-15 (2002)
[9] *Id*.

demonstration of the practical value of government research to the private sector.[10] Many of these patents do not cover commercial end products, but rather fundamental research discoveries and research tools.[11] In fact, a recent study of Columbia University's patent portfolio indicates that more than 50% of its licensed patents represent research tools.[12]

However, inappropriate licensing of research tools may thwart rather than promote utilization, commercialization and public availability.[13] Therefore, the question that arises is whether Bayh-Dole, through its promotion of patent protection and commercial development, has inhibited research and scientific advancement for the public good. In other words, is Bayh-Dole unintentionally promoting early-stage patenting of research tools better left in the public domain? The answer to this question is at the heart of the research tool debate. Indeed, there are those who argue Bayh-Dole has and will continue to inhibit research while others content that Bayh-Dole is performing exactly as intended.

Unintended Consequences?

As the conceptual gap between fundamental research and commercial application narrows, the once serendipitous art of drug discovery, has become critically dependent on basic knowledge of genes, proteins, and associated biochemical pathways. Thus, the foreseeable practical payoffs of this fundamental research make it easier to obtain patents for discoveries that, previously, would have seemed too far removed from useful

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[10] John M. Golden, *Biotechnology, Technology Policy and Patentability: Natural Products and Invention in the American System*, 50 Emory L.J. 101, 117 (2001).
[11] Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 Law and Contemporary Problems 289 (Winter/Spring 2003).
[12] Annetine C. Geljins & Samuel O. Thier, *Medical Innovation and Institutional Interdependence: Rethinking University-Industry Connections*, 287 JAMA 72, 75 (2002)

applications for patent protection.[14] Because Bayh-Dole draws no distinction between inventions that lead directly to commercial products and those that provide fundamental advances enabling further scientific studies, some institutions have patented research tools in order to preserve the possibility of future profits. Consequently, Bayh-Dole may hinder rather than accelerate biomedical research."[15]

Paul Berg, Nobel Prize-winning biochemist and director emeritus of the Beckman Center for Molecular and Genetic Medicine at Stanford University, puts it more bluntly; Bayh-Dole "is likely to damage the health of the scientific enterprise in the long term, notwithstanding the financial benefits in the short term."[16] Furthermore, commercial firms that once viewed academic researchers as benign benefactors of pre-market science have today come to view them instead as potential commercial rivals.[17] Adding fuel to the fire is the way universities hold up technology transfer offices as an academic equivalent to collegiate football teams, bringing recognition, prestige, and sometimes even profits to their home school.[18] And with university-licensing income in topping $1.3 billion in 2003, the technology transfer system has become increasingly focused on deriving revenue from IP rather than widespread dissemination of technology.[19]

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[13] *Id*.
[14] Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 Law and Contemporary Problems 289 (Winter/Spring 2003).
[15] *Id*.
[16] Ted Agres, *The cost of Commercializing Academic Research: Does university licensing impede life science research and development*? 17 The Scientist 58-59 (2003)
[17] *Id*.
[18] Rochelle Dreyfus, *Biotechnology Patents Get Special Treatment: Protecting the Public Domain of Science: Has the Time for an Experimental Use Defense Arrived*?, 46 Ariz. L. Rev. 457, 463-464 (2004).
[19] AUTM Licensing Survey, *FY 2003 Survey Summary*, editors Ashley J. Stevens and Frances Toneguzzo.

Another of Bayh-Dole's "unintended effects" is to restrict dissemination of faculty research. For example, Mildred K. Cho, co-director of Stanford University's Center for Biomedical Ethics, and colleagues surveyed 121 US laboratories involved in developing or performing clinical genetic tests. More than half of the labs (54%) had decided not to develop or perform one or more tests because of concerns over patent infringement.[20] Cho further asserted, "Information sharing and the ability to do research... has been negatively impacted by patenting."[21] The decision not to perform research may also be due to the costs of subsequent experimentation, first because all researchers wishing to use patented research tools must first obtain a license, and second, because patent licensing agreements frequently contain provisions restricting permissible uses of the proprietary technology.[22] The higher transaction costs may in turn prevent researchers from making new discoveries or commercializing new technologies.[23]

Business as Usual?

Companies, however, require exclusive licenses to compensate for the risks and expenses in commercializing discoveries, especially those emerging from early-stage research.[24] Indeed, it is widely believed that patents on "upstream" discoveries – such as genes and useful chemical molecules – and the corresponding potential for exclusive licenses, are essential to induce private investment in developing applications for the

[20] M.K. Cho, etal, *Effects of gene patents and licenses on the provision of clinical genetic testing services*, 5 J. of Mol. Diagn. 3 (2003).
[21] *Id*.
[22] David C. Hoffman, *A Modest Proposal: Toward Improved Access to Biotechnology Research Tools by Implementing a Broad Experimental Use Exception*, 89 Cornell L. Rev. 993 (2004).
[23] *Id*.

fruits of "basic" government science. This need is especially strong in the case of biotechnology and pharmaceuticals because patent law facilitates innovation not so much by "spurring" invention as by "enabling" it, by providing small biotechnology firms, which are the heart of the American biotechnology industry, with an immediate product – patents – that they can use to attract investment.[25] Exclusive licenses give the licensee legal benefits not otherwise available. As one prominent attorney noted, "Anybody who is bemoaning the impact of Bayh-Dole on the free flow of information among research scientists is not a research scientist. Scientists prefer to keep their discoveries to themselves as a matter of human nature. You keep that stuff close to your chest because you don't want to get scooped."[26]

Furthermore, one cannot assume that withholding patent protection from research tools will improve their availability. Indeed, in the absence of patent protection, firms may be more likely to resort to trade secrecy than to dedicate their research tools to the public domain, which could aggravate the problem rather than resolve it.[27]

The conclusion that patents on upstream research tools interfere with innovation is based an assumption whose factual basis is questionable. Indeed, there has been much debate over whether patents on upstream research impede scientific progress. For

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[24] National Research Counsel, *Intellectual Property Rights and Research Tools in Molecular Biology: Summary of a Workshop Held at the National Academy of Sciences*, ch. 2 (1996)
[25] John M. Golden, *Biotechnology, Technology Policy and Patentability: Natural Products and Invention in the American System*, 50 Emory L.J. 101, 117 (2001).
[26] Ted Agres, *The cost of Commercializing Academic Research: Does university licensing impede life science research and development*? 17 The Scientist 58-59 (2003)
[27] National Research Counsel, *Intellectual Property Rights and Research Tools in Molecular Biology: Summary of a Workshop Held at the National Academy of Sciences*, ch. 2 (1996)

example, it has been noted there is informal price differentiation between licenses to academic institutions and commercial entities; hence, access is not hindered.[28]

Regardless of who is right or wrong, the arguments illustrate the competing interests that must be balanced when licensing research tools. To better understand the research tool landscape and the factors that technology transfer professional should consider the National Institute of Health (NIH) presented the following case studies.

Research Tool Case Studies[29]

Recombinant DNA - patented research tool nonexclusively licensed with low fees

The Cohen-Boyer recombinant DNA technology is based on three patents, which were jointly awarded to Stanford and UCSF and shared with the inventors Herbert Boyer and Stanley Cohen, and constitute the foundation of the biotechnology industry. As of February 13, 1995, the licensing agreements had generated $139 million in royalties, which have shown an exponential increase in value since their beginning. It is important to note, however, that not all inventions are as universally critical.

The technology was developed in universities through publicly funded research. Furthermore, licenses were inexpensive and attached minimal riders. Nevertheless, the sheer volume of licenses made the patent very lucrative. Paradoxically, the Cohen-Boyer patent is antithetical to the classic model of technology transfer. Indeed, the Bayh-Dole Act is premised on university protection of intellectual property and exclusivity inducing

[28] Tanuja V. Garde, *Supporting Innovation in Targeted Treatments: Licenses of Right to NIH-Funded Research Tools,* 11 MICH. TELECOMM. TECH. L. REV. 249 (2005)
[29] National Research Counsel, *Intellectual Property Rights and Research Tools in Molecular Biology: Summary of a Workshop Held at the National Academy of Sciences*, ch. 5 (1996)

development. Instead, the Cohen-Boyer model offers non-exclusive licenses, no incentives, and small royalties.

The NIH Working Group concluded that the decision to negotiate non-exclusive licenses was critical to the industry. If the technology had been licensed exclusively to one company, allowing one company to control the technology, the industry might never have developed. Furthermore, exclusivity may have motivated major pharmaceutical firms to challenge the validity of the patent. Based on their analysis, the NIH working group identified three key elements present in this case:

- First, the technology was inexpensive and easy to use; from a purely technical standpoint, there were only minimal impediments to widespread dissemination.
- Second, there were no alternative technologies.
- Third, the technology was critical and of broad importance to research in molecular biology.

<u>PCR - patented research tool for which licensing arrangements were controversial</u>

Like the Cohen-Boyer Recombinant DNA patents, polymerase chain reaction (PCR) technology is widely used and critical for molecular biology research. In less than a decade, PCR has become a standard technique in almost every molecular biology lab, and its versatility as a research tool continues to expand.

Unlike the Recombinant DNA patents, which resulted from inter-university collaboration, PCR was invented in a corporate environment and its widespread applicability as a research tool was unanticipated. As a company owned technology, the rights to use the technology could be provided with the purchase of the product, rather

than under direct license agreements. Controversy, however, developed concerning the amount of royalty fees.

Different categories of licenses were developed depending on the application and the users. They included: research applications, diagnostic applications, production of large quantities of DNA, and human diagnostic testing services. Many university researchers and small biotechnology companies could not afford to conduct PCR experiments. The effect was delayed development of PCR-related research tools and consequent reductions or delays in the total royalty stream.

The technology is problematic because it is both a commercial product and a discovery tool. Consequently, it is unclear whether the technology would have been widely disseminated in the absence of patent rights or whether they have been more fully developed because of the existence of patent rights. Whatever the answer, NIH noted that patent rights added considerable value to the technology.

Protein and DNA Sequencing - research tools to which strong patent protection promoted broad access

The ability to synthesize and sequence proteins and DNA revolutionized molecular biology. The technology was developed in the California Institute of Technology's (Cal Tech) research laboratories between 1970 and 1986. However, both the government and industry were reluctant to invest in developing the sequencing instrumentation. Eventually funding was obtained from Applied Biosystems (ABI) who demanded an exclusive license. Cal Tech agreed but under the stipulation that ABI would sublicense it under what Cal Tech considered reasonable terms.

This case study provides a clear example of how patent protection promoted the development and dissemination of a research tool. Through the help of substantial private investment these research tools were widely disseminated, and both the public and private sector seemed to gain equally.

In sum, NIH concluded that problems associated with licensing research tools are difficult and defy simple solutions. NIH found that intellectual property restrictions could stifle the broad dissemination of new discoveries and limit future avenues of research and product development. At the same time, reasonable restrictions on the dissemination of research tools are sometimes necessary to protect legitimate proprietary interests and to preserve incentives for commercial development.

NIH Research Tools Guidelines[30]

Based on these findings, NIH developed the following principles to set forth the fundamental concepts and assist recipients of NIH funding in determining reasonable terms and conditions for disseminating research tools:

- Ensure academic freedom and publication
- Ensure appropriate implementation of the Bayh-Dole Act
- Minimize administrative impediments to academic research
- Ensure dissemination of research resources developed with NIH funds

These policies were given teeth in 1999 when they became conditions that must be followed to qualify for NIH grants and contracts.[31] Still, much depends on whether the holders of exclusive rights can figure out how to disseminate research tools broadly without undermining their value as intellectual property. Because useful applications of

[30] 64 Fed. Reg. 72090, 72094 (Dec. 1999)

advances in molecular biology are so closely tied to basic research, it is particularly important to strike the right balance between the twin goals of fostering the growth of scientific knowledge and promoting private investment in the development of applications for new technology.

Where does Sangamo fit?

The development of Sangamo's strong IP position in the field of ZFN's begins with the work of Srinivasan Chandasegaran (Chandra) at Johns Hopkins. Sangamo secured an exclusive license to Dr. Chandra's hybrid restriction enzyme, which embodies the fusion of a DNA binding domain of three zinc fingers to a cleavage domain of bacterial restriction enzyme and allow site-specific binding of DNA. Subsequently, Sangamo secured exclusive licenses to technology directed to the design, selection, and use of ZFNs for gene regulation and modification from the following institutions:[32]

- Massachusetts Institute of Technology (MIT)
    - Worldwide exclusive license to technology and patents relating to the design, selection and use of ZFPs for all fields of use, including the right to sublicense. This agreement will terminate on May 16, 2021.
- The Johns Hopkins University
    - Worldwide exclusive license to technology and patents relating to gene targeting technology for all fields of use, including the right to sublicense. This agreement will terminate on January 30, 2013.

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[31] *Id*.
[32] Sangamo Biosciences, Inc., *2004 Annual Report & Form 10-K* (available at http://library.corporate-ir.net/library/12/120/120938/items/152881/AR_2004.pdf).

- The Scripps Research Institute
    - Worldwide exclusive license to technology and patents for the research, development and commercialization of products and services using engineered ZFPs, excluding the use of engineered ZFPs in plant agriculture, therapeutics and diagnostics. This agreement will terminate on June 5, 2018.
- The California Institute of Technology
    - Worldwide exclusive license to intellectual property covering the use of chimeric nucleases to stimulate gene targeting, in all fields except research tools and diagnostics. Products and services developed under this agreement relate to the use of ZFNs for therapeutic gene correction in human healthcare and gene targeting in plant agriculture. This agreement will terminate on September 5, 2023.
- The University of Utah
    - Worldwide exclusive license to technology and patents for the use of zinc finger nucleases for targeted genomic cleavage, mutagenesis and gene targeting in all fields of use except plants. This agreement will terminate on January 21, 2023.

As of February 1, 2005, these licenses included the following patents:[33]

Patent Owner	Source of Funding	Patent Numbers	Patent Title
Johns Hopkins	NIH – GM 42140 NSF – MCB 9415861	5,436,150	Functional domains in Flavobacterium okeanokoites (FokI) restriction endonuclease
		5,487,994	Insertion and deletion mutants of FokI restriction endonuclease
		5,792,640	General method to clone hybrid restriction endonucleases using lig gene
		6,265,196	Methods for inactivating target DNA and for detecting conformational change in a nucleic acid
	N/A	5,356,802	Functional domains in Flavobacterium okeanokoites (FokI) restriction endonuclease
		5,916,794	Methods for inactivating target DNA and for detecting conformational change in a nucleic acid
MIT	NIH – P01 CA42063 NSF – CDR-8803014 NCI – P30 CA14051	6,479,626	Poly-zinc Finger proteins with improved linkers
	N/A	5,789,538	Zinc Finger proteins with high affinity new DNA binding specificities
		6,410,248	General Strategy for selecting high-affinity Zinc Finger proteins for diverse DNA target sites
Harvard	NIH – GM 44025 NSF – DMB 9157255	5,925,523	Interaction trap assay, reagents and uses thereof
		6,200,759	Interaction trap assay, reagents and uses thereof
The Scripps Research Institute	NIH – GM 36643 NIH – GM 47530 NIH – GM 53910	6,790,941	Zinc Finger protein derivatives and methods therefore
	N/A	6,140,466; 6,242,568	Zinc Finger protein derivatives and methods therefore
Mathew Porteus; David Baltimore	NIH – R01 GM39458	20050026157	Use of chimeric nucleases to stimulate gene targeting
Dana Carroll	NIH – R01 GM58504	20050208489	Targeted chromosomal mutagenesis using Zinc Finger Nucleases

[33] *Id*.

Currently, Sangamo is the owner of 55 patent family filings, including 18 issued U.S. patents, 19 granted foreign patents, 69 pending U.S. patent applications and 78 pending foreign patent applications.[34] These patent filings are directed to improvements in the design, composition, and use of ZFPs and ZFNs.[35] In the aggregate, the company believes that its licensed patents and patent applications, as well as the issued patents and pending patent applications, will provide a substantial proprietary position in the commercial development of ZFP technology.[36]

Interestingly, 10 of the 16 licensed patents that represent the company's foundational technology were developed with NIH funds at non-profit research institutions. Furthermore, ZFN technology seems to straddle the research tool line. The ZFN hybrid restriction enzyme invented by Chandra, is, itself, both a commercially viable product and a powerful research tool used in targeted modification of cells, plants and animals. The technology demonstrated its potential as a commercial product when a pair of high specificity four-finger ZFNs were used to correct the X-linked SCID gene reported in the April issue of *Nature*.[37] However, as Chandra notes, even if ZFNs never reach the therapeutics stage, they will still remain powerful research tools for targeted modification cells, plants and animals. Additionally, the 'rule set' (bioinformatics used to select and assemble ZFNs for specific applications) is also a research tool. Although this

[34] *Id*.
[35] *Id*.
[36] *Id*.
[37] Christopher Thomas Scott, *The Zinc Finger Nuclease Monopoly*, 23 Nat. Biotechnolo. 915-918 (2005).

enabling technology is not incorporated into the ZFN end product, it is the primary source of the technology's value.[38]

Considered in light of the case studies discussed earlier, ZFN and PCR technology have the most in common. Unlike recombinant DNA technology, which was inexpensive, easy to use and presented minimal impediments to widespread dissemination, constructing a properly functioning ZFN is extremely difficult.[39] Furthermore, recombinant DNA had no alternative technologies, whereas ZFN is an alternative to traditional gene therapy techniques. Unlike gene and protein sequencing technology, ZFNs do not lack government and industrial interest. Instead, like PCR, ZFN technology is both a commercial product and a discovery tool. It is important to note, however, that PCR was developed privately while ZFN was developed primary with government funds, which favors those who argue that the technology should be available to university researchers.

In light of Sangamo's strong proprietary position, the question that arises is whether the collective decisions of technology transfer offices to exclusively license the technology has slowed innovation, or whether they have done their job, in that commercialization of the technology required private investment under an exclusive license. In Sangamo's case, the answer appears to lie somewhere in-between. In fact, even the scientists whose inventions the company is founded on lie on opposite sides. In Chandra's opinion, "the collective decision of Universities to exclusively license their technology to Sangamo has slowed innovation in this field." While the University of

[38] *Id*.

Utah's Dr. Dana Carroll, who reduced ZFNs to practice and licensed his technology to Sangamo, believes that, in the private sector, Sangamo has extended the technology in a number of ways, certainly faster than would have occurred without their investment in their own work. Despite these differing opinions, the NIH principles discussed earlier provide a helpful roadmap for evaluating the dissemination of this technology.

Ensure Academic Freedom and Publication

Under this principle, institutions that receive NIH research funding have an obligation to preserve research freedom and ensure timely disclosure of their scientist's findings.[40] In this case, each university that licensed ZFN technology to Sangamo retained rights to use their patented inventions; thereby preserving their own research freedom. However, because the licenses were exclusive, all other users of the patented inventions, including other universities, are infringers.[41] Although, technically, this places a large restriction on academic freedom and publication, university researchers continue to practice the inventions without fear of a potential patent infringement lawsuit. In fact, Dr. Carroll and Dr. Matthew Porteus, both of whom continue to research using ZFN technology that infringes Sangamo's patent rights, noted that they are not dissuaded from using the technology in an academic environment.

To the their credit, each of the universities that licensed technology to Sangamo after the NIH guidelines issued restricted the field of use; thereby freeing up alternative

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[39] Id.; National Research Counsel, *Intellectual Property Rights and Research Tools in Molecular Biology: Summary of a Workshop Held at the National Academy of Sciences*, ch. 5 (1996).
[40] 64 Fed. Reg. 72090, 72094 (Dec. 1999)
[41] *See Madey v. Duke University,* 307 F.3d 1351 (Fed. Cir. 2002) (holding that universities may not assert experimental use as a defense to patent infringement).

avenues of research. And, by filing patents on the technology, universities, though restricting access, have ensured timely disclosure.

Ensure Appropriate Implementation of the Bayh-Dole Act

In general, this principle requires recipients of NIH funding to maximize the use of their research findings by making them available to the research community and the public, and through their timely transfer to industry.[42] It is important to note that the right to retain title to inventions made with NIH funds comes with an obligation to promote utilization, commercialization, and public availability.[43] Patenting and licensing research tools is one, but not the only, way of implementing the Act.[44] NIH notes that utilization, commercialization and public availability of technologies that are useful primarily as research tools rarely requires patent protection, and suggests non-patent publication, deposit in an appropriate databank or repository, or widespread non-exclusive licensing for nominal or cost recovery fees.[45]

This principle, however, is not helpful when analyzing the dissemination of ZFN technology. The difficulty arises, in part, because the first ZFN patents had characteristics of both a product and a research tool. Furthermore, much of the initial IP for the 'rule set' was not U.S. government funded, and instead came from the London-based company Gendaq, which Sangamo acquired. Consequently, the arguments for public availability of the 'rule set' are diminished. Finally, the initial patents on the actual ZFN molecule were filed and licensed prior to the issuance of the NIH guidelines.

[42] 64 Fed. Reg. 72090, 72094 (Dec. 1999)
[43] *Id*.
[44] *Id*.
[45] *Id*.

The NIH notes that patenting and exclusively licensing a research tool is likely to thwart rather than promote utilization, commercialization and public availability.[46] However, the opposite is true in this case. Indeed, the ZFN 'rule set' could not be legally used by anyone not also having rights in the ZFN molecule. Consequently, widespread dissemination would have added nothing to the availability of technology.

Minimize Administrative Impediments to Academic Research

Although this principle only applies to recipients of NIH funding, NIH hopes that for-profit organizations will minimize the encumbrances they seek to impose upon non-profit organizations for the academic use of their tools.[47] In this regard, Sangamo has put dozens of material transfer agreements in place. However, the 'rule set' remains protected and unavailable for academic research. Investigators who want ZFNs send the specifications to the company who, in turn, builds the ZFNs and sends them back. Furthermore, all of the researchers with whom I spoke noted that they make their own ZFNs and Sangamo has threatened them in no way. Consequently, while administrative impediments to academic research may not be minimized, practically, there seems to be few, if any, obstacles to academic research.

Ensure Dissemination of Research Resources Developed with NIH Funds

The principle simply requires widespread distribution of research tools in order to advance science.[48] However, as noted earlier, distribution of the 'rule set' to anyone other than the owner of the rights to use ZFNs would have added no value to the technology. Indeed, in light of the fact that the ZFN molecule was exclusively licensed prior to the

[46] *Id*.
[47] *Id*.
[48] *Id*.

development of the research tools, the only way to ensure advancement of the subsequent technology was to grant rights to the owner of the underlying technology, in this case, Sangamo.

Summary

Access to research tools is a prerequisite to continuing scientific advancement.[49] In this case, the exclusive license of the ZFN molecule prior to issuance of the NIH guidelines, rather than the collective decisions of universities to exclusively license subsequent research tool technology, is the likely cause of restricted access to the technology. Despite the anomalous character of this case, it still highlights some lingering questions regarding Bayh-Dole and non-profit licensing practices. What will be done with non-profit researchers' continued practicing of patents exclusively licensed to Sangamo. Under current law, their activity constitutes patent infringement.[50] However, change is in the air. More specifically, Congress is considering amendment of the patent laws to include a more inclusive research exemption,[51] and the courts may validate the government license defense articulated in *Madey v. Duke*.[52]

Lingering Questions…

Research Exemption

The federal research exemption is found at 35 USC § 271(e)(1) – defining a safe harbor against infringement for use of patented inventions for purposes of complying with FDA regulations. However, this exemption is very limited and only allows

[49] *Id*.
[50] *Madey v. Duke University,* 307 F.3d 1351 (Fed. Cir. 2002).
[51] See Patent Reform Legislation (HR2795)
[52] *Madey v. Duke University,* 307 F.3d 1351 (Fed. Cir. 2002).

companies to use patents without threat of infringement so long as use is limited to getting drugs through the FDA.

The common law experimental use defense was first articulated by Justice Story who, in dicta, argued that the legislature could not have intended to punish a man who built "a [patented] machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects."[53] Justice Story later distinguished infringing uses, "making with an intent to use for profit," and non-infringing uses, "for the mere purpose of experiment, or to ascertain the verity and exactness of the specification."[54] Thus, under his view, to avoid infringement charges "the making must be with an intent to infringe the patent-right, and deprive the owner of the lawful rewards of his discovery."[55]

Subsequent cases strictly construed the defense, limiting it to experiments conducted "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry."[56] Currently, the experimental use exception is characterized as "truly narrow."[57] In the court's view, "arguments that the experimental use rule deserved a broad

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[53] *Whittemore v. Cutter*, 29 F.Cas. 1120 (C.C.D. Mass. 1813)
[54] Sawin v. Guild, 21 F. Cas 554, 555 (C.C.D. Mass. 1813).
[55] *Id*.
[56] *Roche Prods., Inc. v. Bolar Pharm. Co*., 733 F.2d 858, 863 (Fed. Cir. 1984); *See Dugan v. Lear Avia, Inc*., 55 F. Supp. 223, 229 (S.D.N.Y. 1944) ("[The allegedly infringing device] can be eliminated from consideration [under the experimental use exception] for it affirmatively appeared, without contradiction by plaintiff, that defendant built that device only experimentally and that it has neither manufactured it for sale nor sold any."); *Ruth v. Stearns-Roger Mfg. Co*., 13 F. Supp. 697, 713 (D. Colo. 1935) ("The making or using of a patented invention merely for experimental purposes, without any intent to derive profits or practical advantage therefrom, is not infringe-ment." (citation omitted)); *Bonsack Mach. Co. v. Underwood*, 73 F. 206, 211 (C.C. E.D.N.C. 1896) ("It is true that ... [a] machine ... made or used [only] as an experiment ... does not ... constitute an infringement.").
[57] *Roche Prods., Inc. v. Bolar Pharm. Co*., 733 F.2d 858, 863 (Fed. Cir. 1984).

construction [are] not justified."[58] Indeed, any infringing activity with "definite, cognizable, and… substantial commercial purposes" cannot use the defense.[59] When applying this test, the experimental use exception applies if "the accused devices are used for amusement, to satisfy idle curiosity, or for philosophical inquiry"[60] but not if a use is "in keeping with the legitimate business of the using agency" or "has a definite, cognizable, and not insubstantial commercial purpose."[61]

Following these decisions, the court, in *Madey v. Duke University*, stated, "regardless of whether a particular institution or entity is engaged in an endeavor for commercial gain, so long as the act is in furtherance of the alleged infringer's legitimate business… the act does not qualify for the very narrow and strictly limited experimental use defense. [Moreover]… the profit or non-profit status of the user is not determinative."[62] Therefore, research conducted by non-profit institutions is not exempt from liability for patent infringement on the basis of "experimental use."

Nevertheless, academic institutions continue to practice patented inventions by without a license. However, government and industry appear to have acquiesced. In fact, in 2003 the Government Accounting Office, although recognizing the incompatibility with the *Madey v. Duke*, reported the "generally accepted practice" by both federal agencies and nonprofit organizations to use patented technologies for research without obtaining a license, a so-called general research exception."[63]

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[58] *Id*.
[59] *Id*.
[60] *Douglas v. United States*, 181 U.S.P.Q. (BNA) 170, 177 (Ct. Cl. 1974),
[61] *Roche Prods., Inc. v. Bolar Pharm. Co*., 733 F.2d 858, 863 (Fed. Cir. 1984).
[62] *Madey v. Duke University,* 307 F.3d 1351 (Fed. Cir. 2002).
[63] *Technology Transfer: Agencies' Rights to Federally Sponsored Biomedical Inventions*, GAO-03-536 (July 7, 2003).

At best, the future of the experimental use defense is uncertain. On the one hand, Judge Rader of the CAFC would eliminate the exception because "the Patent Act leaves no room for any de minimis or experimental use excuses for infringement."[64] Indeed, continued recognition of the experimental use defense may effectively destroy the value of research tool patents.[65] With unlimited experimental rights, universities could use – and profit from – everybody else's patents, and not be obligated to share their own patents freely in return.[66]

Conversely, AIPLA has included an expanded research exemption in the current Patent Reform Legislation.[67] However, according to Robert Hardy, Director of Contracts and IP Management at the Counsel of Governmental Relations in Washington DC, the current agenda in Congress is to strip down the pending legislation so there is very little chance that a research exemption will be included. Nevertheless, Mr. Hardy notes that in the second round of patent reform this should be a major issue. The difficulty, of course, is crafting a workable exemption that does not threaten too many interests.

If the research exemption is expanded by Congress to include non-profit research institutions, the concerns regarding infringement by academic investigators will be quelled. However, if the current research exemption remains intact, or Judge Rader

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[64] *Embrex, Inc. v. Serv. Eng'g Corp*., 216 F.3d 1343, 1352 (Fed. Cir. 2000) (Rader, J., concurring).

[65] *Integra Lifescis. I, Ltd. v. Merck KGaA,* 331 F.3d 860, 867 (Fed. Cir. 2003) (Rader, J.) (in trying to solve the problem of access to proprietary research tools, academic researchers and the biotechnology industry have often caused the precise problems that Judge Rader anticipated from *35 U.S.C. 271*(e)(1) (2000) and a broad experimental use exception.)

[66] Aaron Miller, *Repairing the Bayh-Dole Act: A Proposal for Restoring Non-Profit Access to University Science*, 2005 B.C. Intell. Prop. & Tech. F. 093001 (2005).

[67] H.R. 2795, 109th Cong. (June 8, 2005)

succeeds in removing the research exemption altogether, the need to develop the government license defense, expressed in *Madey v. Duke*,[68] may become more pressing.

Government License Defense

The government license defense may allow currently infringing non-profit research institutions to assert third-party beneficiary rights to practice patents developed with government funds, on the government's behalf, because of the government's rights in the patents and the use of the technology in the performance of government sponsored research. In *Madey v. Duke*, the university, in addition to its reliance on the experimental use defense, claimed it had "a license to practice the patents for government research purposes pursuant to the Bayh-Dole Act," the so-called government license defense.[69] The Bayh-Dole Act states in pertinent part as follows:

> (c) Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following:
>
> ....
>
> > (4) With respect to any invention in which the contractor elects rights, the Federal agency shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world…[70]

[68] *Madey v. Duke University,* 307 F.3d 1351 (Fed. Cir. 2002).
[69] *Id*.
[70] 35 U.S.C. § 202(4).

Before the Federal Circuit, Duke argued that the government had a confirmatory license to have the patents at issue practiced on its behalf. However, the court was concerned that the short notations on the patents, expressly providing that the government has rights to the patents, were insufficient to define the scope of the government's rights.[71] Although Duke argued that Bayh-Dole provides the scope of the rights granted to the government, the court concluded that the government license issue needed further development before the district court could provide the defense.[72]

Now on remand, the district court has allowed the parties to submit additional dispositive motions and briefs, including evidence and arguments as appropriate, on the viability of Duke's government license defense.[73] Specifically, the court required clarification of the following issues:[74]

- The scope of the government's rights in the patents based upon an awarded contract or grant;
- Whether the government has rights in the patents under the Bayh-Dole Act, or whether the relevant provisions of the Bayh-Dole Act are inapplicable;
- Whether use of the patents is on behalf of the government or whether they are used for other means; and
- Arguments or evidence relevant to determining the viability and scope of the government license defense.

With regard to the first issue, the scope of the government's rights, the Government Accounting Office has stated, "the government license right extends both to

[71] *Madey v. Duke University,* 307 F.3d 1351 (Fed. Cir. 2002).
[72] *Id*.
[73] *Madey v. Duke University*, 336 F.Supp.2d 583 (M.D.N.C. 2004).

federal agencies and to their funding recipients, including grantees, when specifically authorized to use the invention.[75] Furthermore, the language "for…the United States" in the Bayh-Dole Act should encompass, at the least, all uses that would be considered under 28 U.S.C. § 1498, since the language is identical.[76] Due to the nature of the government's rights under Bayh-Dole, the scope of the government's license should be construed broadly.[77] The government paid for and encouraged the development of the funded research. Consequently, it should reap the benefits of its contractors' labor. Furthermore, "Inventions made under a government contract are the product of expenditures from the public treasury in the course of a governmental function; the public having in a sense ordered and paid for the invention through its representatives, should not again be taxed for its use, nor excluded from its use, nor permitted to use it upon restrictive conditions."[78]

Similarly, the plain language of the Bayh-Dole statute resolves the second issue, whether the government has rights, by explicitly granting the government a nonexclusive, nontransferable, irrevocable, paid-up license to any invention in which the contractor

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[74] *Id*.
[75] *Technology Transfer: Agencies' Rights to Federally Sponsored Biomedical Inventions*, GAO-03-536 (July 7, 2003).
[76] *Madey v. Duke University*, 336 F.Supp.2d 583 (M.D.N.C. 2004) (Defendant Duke University's Supplemental Memorandum of Law in Support of its Motion for Summary Judgment on the Patent Infringement Claims p. 17 (Nov. 19, 2004)).
[77] *Id*.
[78] *Mine Safety Appliances Co. v. United States*, 364 F.2d 385, 392 (Ct. Cl. 1966); *see also Technitrol, Inc. v. United States*, 440 F.2d 1362, 1373 (Ct. Cl. 1971) ("What *Mine Safety* teaches is that the issue of license vel non should be approached liberally asking what the United States (acting for its taxpayers) can fairly be said to have purchased through its sponsorship of the contract project. The Federal Government has the right to use, royalty free, those ideas, improvements, discoveries and inventions – crystallized during performance of the federal contract – which have a close and umbilical relationship to the

elects rights.[79] In fact, one of the stated goals of the Bayh-Dole Act is "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 invention."[80]

As a funding recipient, universities are acting as a government contractor, which partially addresses the third issue, whether use of the patent is on behalf of the government. Note that contractor is defined as any person, small business firm or non-profit, which is party to a funding agreement.[81] Thus, the statutory language is clear on its face; the government may have a third party contractor practice the patent for the government, or on behalf of the government. Consequently, government funding agencies can specifically authorize funding recipients to use patents developed with government funds, thereby ensuring the use is on behalf of the government and within the scope of the government's rights. Finally, arguments regarding the viability and scope of the government license defense include:

- Validating the government license defense does not require amendment of the Bayh-Dole statute and only requires funding agencies to specifically authorize recipient use of patents developed with government funds.
- Validating the government license defense removes the need to amend the patent statute to include broader research exemption.

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work and research funded by the United States. Having borne the expense of that effort, the public is entitled to enjoy the fruits without further charge.)

[79] 35 U.S.C. § 202(4)

[80] 35 U.S.C. § 200

[81] 37 C.F.R. § 301.2 (2005)

- Validating the government license defense ensures government control over patents developed with government funding to ensure widespread dissemination of research tools, in accordance with the purpose of the Bayh-Dole Act.
- It is antithetical to the purpose of the government's retained rights to restrict the government's ability to ensure utilization, commercialization and public availability of an invention for which it (and the taxpayers) have already paid.
- The government license defense is double-edged -- any intellectual property rights secured under government sponsorship would be subject to the same "government license" defense to infringement by others.[82]

Unfortunately, however, the situation in *Madey v. Duke* is not ideal. Duke is a private institution that practiced patents assigned by Stanford to Madey, a private party.[83] In other words, the case involves a private institution asserting the government license defense to patent rights that are owned by a private party. As a private institution, Duke is less likely to be considered a government contractor capable of asserting the government license defense. Furthermore, Stanford may have assigned the government's patent rights to Madey. Therefore, even if Duke is considered a government contractor for purposes of the government license defense, the government may have no rights left to assert.

Nevertheless, it seems likely that the court will validate the government license defense in some form or another. Whether or not its scope will encompass university research use of government sponsored patents remains to be seen.

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[82] Barry Newberger, *Intellectual Property and Nanotechnology*, 11 Tex. Intell. Prop. L.J. 649 (2003).
[83] *Madey v. Duke University,* 307 F.3d 1351 (Fed. Cir. 2002).