

Intellectual Property Developments in Biochip Nanotechnology

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ABSTRACT

Microfluidics is the science of devices and processes dealing with fluid volumes on the nanoliter or picoliter scale. The most popular and commercially visible applications of this technology consist of DNA microarrays, or “biochips.” DNA microarrays are most useful for their fast, efficient processing of multiple DNA sequences of genes. In this article, Douglas Sharrott and Hassen Sayeed explain the various intellectual property (“IP”) issues relating to DNA microarrays and microfluidics applications. They also examine alternative methods of protecting valuable IP, such as trade secret and “mask work” protection under the copyright laws. Finally, Sharrott and Sayeed discuss a representative case that teaches valuable lessons to those in the microfluidics industry to help guide IP strategies.

I. INTRODUCTION

Microfluidics is the science of devices and processes dealing with fluid volumes on the nanoliter or picoliter scale.¹ The most popular and commercially visible applications of this technology—DNA microarrays—have been recognized by the federal government as facilitating “an important and necessary first step in our understanding and cataloging of the human genome.”² The chief utility of DNA microarrays (often called “biochips”) comes from their fast, efficient processing of multiple DNA sequences or genes. The information product of such processing can be used by researchers to analyze relative genetic expression, genomic gains and losses, and DNA sequence polymorphisms.³

Borrowing well-known techniques from the semiconductor industry, the microarray fabrication process involves etching a layout of reservoirs on a flat support wafer (often plastic or glass) through which fluid movement is controlled.⁴ Precise flow-direction is achieved through passive or active pressure differentials, or electronic signals (“electrokinetics”). On the support wafer, genetic sequences are built and anchored to the reservoirs as experimental probes.⁵ When biological fluids are passed over

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¹ Microfluidic devices themselves have dimensions on the millimeter or micrometer scale.

² National Center for Biotechnology Information, *Microarrays: Chipping Away at The Mysteries of Medicine* (Mar. 30, 2004), <http://www.ncbi.nlm.nih.gov/About/primer/microarrays.html> (last visited Jan. 26, 2006).

³ *See id.*

⁴ *See* Juji Harimoto & Roberto Lee, Jr., *Microfluidics Technology*, in ANTHOLOGY OF HIGH TECHNOLOGY IN SOUTHERN CALIFORNIA 47-48 (2003).

⁵ *See id.*

them, the probes bind to complementary DNA targets, giving researchers a powerful tool to examine genetic sequencing and gene expression. In recent years, biochip manufacturers have explored alternative fabrication techniques, such as “spotting” DNA probes onto support wafers or synthesizing the probes directly into the support wafer itself.⁶

Not surprisingly, the pharmaceutical and medical industries have shown keen interest in DNA microarrays. One recent study projects that the total biochip market will exceed \$5 billion by 2009.⁷ Notwithstanding this commercial success, microarrays remain a somewhat novel technology from both legal and regulatory perspectives. They also raise significant intellectual property (“IP”) issues at the intersection of bioinformatics and genomics.

II. PATENT THICKETS: RECENT ANSWERS FOR DNA MICROARRAYS

Genes are patentable. The “gold rush” to claim genes was previously limited by research techniques, but the ubiquity of microfluidics in biomedical research has greatly expanded the number of potential claims to the human genome.

Until recently, the most significant IP concern about biochips involved the patentability of expressed sequence tags (“ESTs”)—gene fragments for which no known functional utility exists. When the National Institutes of Health applied for the first EST patents in 1991, the possibility arose that such patents could overlap with and possibly invalidate later patents directed toward fully-sequenced, expressed genes.⁸ Commentators describe this proliferation of overlapping patents as a potential “patent thicket”—a tangle of intellectual property rights through which companies must cut to bring new technologies to market.⁹ In the thicket, scientists and corporations might be forced to renegotiate constantly for the right to exercise any individual gene patent, or to use commercial products obtained from that gene.

In January 2001, partly as a response to questions about the patentability of ESTs, the United States Patent and Trademark Office (“PTO”) issued revised utility guidelines that were ultimately incorporated into the Manual of Patent Examining Procedure.¹⁰ These guidelines required inventions to demonstrate a “specific, substantial, and credible” utility.¹¹ While the PTO cautioned against patenting “inventions whose asserted utility requires further research to identify or reasonably confirm a ‘real world’ context,” it was unclear whether the new guidelines would guide judicial interpretations of the patent statute.¹²

On September 7, 2005, the Federal Circuit signaled its agreement with the PTO guidelines by holding that ESTs are unpatentable because of a lack of specific and substantial utility.¹³ *In re Fisher* involved an appeal from the Board of Patent Appeals and Interferences for an invention relating to ESTs

⁶ See National Center for Biotechnology Information, *Microarrays: Chipping Away at The Mysteries of Medicine* (Mar. 30, 2004), <http://www.ncbi.nlm.nih.gov/About/primer/microarrays.html> (last visited Jan. 26, 2006).

⁷ RESEARCH AND MARKETS, INC., 2005 WORLDWIDE BIOCHIPS & EQUIPMENTS MARKET REPORT (2005), available (for purchase) at <http://www.researchandmarkets.com/reports/c21981> (last visited Jan. 26, 2006).

⁸ See Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698, 699 (1998). Although the National Institutes of Health ultimately abandoned these patent applications, it solicited academic reviews as to the patentability of ESTs. See, e.g., Rebecca S. Eisenberg & Robert P. Merges, *Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial cDNA Sequences*, 23 AM. INTELL. PROP. L. ASS’N Q.J. 1 (1995).

⁹ See generally Carl Shapiro, *Navigating the Patent Thicket: Cross License, Patent Pools, and Standard-Setting* (University of California, Berkeley, Competition Policy Center, Working Paper No. CPC00-11, 2000).

¹⁰ Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

¹¹ *Id.*

¹² MANUAL OF PATENT EXAMINING PROCEDURE § 2107.01 (8th ed. 2001, rev. May 2004).

¹³ *In re Dane K. Fisher & Raghunath v. Lalgudi*, No. 04-1465, Slip. Op. at 11 (Fed. Cir. Sept. 7, 2005) (hereinafter “*In re Fisher*”).

purified from maize plants. The Federal Circuit held that, absent clear identification of the related maize plant genes, the claimed ESTs were not “researched and understood to the point of providing an immediate, well-defined, real world benefit to the public meriting the grant of a patent.”¹⁴ The Court majority was unmoved by the argument that ESTs could offer substantial utility as laboratory research tools.¹⁵

In re Fisher marks a paradigm shift in biotechnology innovation. The Federal Circuit appears intent on preventing patent thickets from taking root in genetic applications. How *In re Fisher* will affect business growth and research and development in the microfluidics industry will be of intense interest to investors in the coming months and years.

III. ALTERNATIVE SOURCES OF IP PROTECTION: TRADE SECRETS AND MASK WORK

In an effort to avoid the evolving issue of gene patents, microfluidics researchers may elect to protect their technology under trade secret law. Such protection may be cheaper and can last indefinitely, but it generates increased surveillance costs. Employee mobility between the private sector and academia creates difficulties in monitoring the competition.¹⁶ Depending on the time-to-market and ease of obtaining and reverse engineering a microfluidic product, IP attorneys might consider whether trade secret or patent law provides the best protection for their clients.¹⁷

Additionally, under U.S. copyright law, the layout of semiconductor chips is protected as an intellectual property right. Layouts must be registered with the Copyright Office, which then confers upon the owner so-called “mask work protection” (named after the lithographic photomasks from which integrated circuits are usually created).¹⁸ Some commentators have theorized that DNA microarrays might be good candidates for such protection.¹⁹ Researchers and corporations may wish to consider the value of mask work registration as an alternative or supplemental tool for defending an IP portfolio.

IV. LESSONS FOR THE INDUSTRY: A REPRESENTATIVE CASE

The importance of structured licensing agreements is particularly important after *In re Fisher*. Without EST patent portfolios to act as shields against competitors, biochip companies are well-advised to review their licensing arrangements. One prominent patent infringement case demonstrates how *ex ante* licensing strategies may resolve disputes more efficiently than traditional litigation.

In March 1997, Hyseq sued Affymetrix in the Northern District of California.²⁰ Hyseq alleged that Affymetrix infringed Hyseq’s patents for sequencing DNA by hybridization (“SBH”) on microarrays.²¹ In a series of four parallel lawsuits filed in the Northern District of California and Delaware, Affymetrix and Hyseq proceeded to litigate existing and newly issued microarray patents for the next four years.²² In

¹⁴ *Id.* at 19.

¹⁵ *Id.* at 1.

¹⁶ Terry K. Tullis, Note, *Current Intellectual Property Issues in Nanotechnology*, 2004 UCLA J.L. & TECH. 12, available at http://www.lawtechjournal.com/notes/2004/12_040809_tullis.php (last visited Jan. 26, 2006).

¹⁷ *See id.*

¹⁸ *See* 17 U.S.C. §§ 901–914 (2005).

¹⁹ Dennis Fernandez & Mary Chow, *Intellectual Property Strategy in Bioinformatics and Biochips*, LARTA VOX (Jan. 21-27, 2003), http://www.larta.org/LAVox/ArticleLinks/2003/030121_ip.asp (last visited Jan. 26, 2006).

²⁰ *Hyseq v. Affymetrix*, No. 97-20188 (N.D. Cal. Mar. 3, 1997); *see* Richard Rouse & Gary Hardiman, *Microarray Technology—An Intellectual Property Perspective*, 4 PHARMACOGENOMICS 1, 4 (2003).

²¹ *See* Rouse & Hardiman, *supra* note 20, at 3-4.

²² *See id.*; *see also* SEC Form 10-Q filing for Affymetrix, Inc. at 19-20 (June 30, 2001), available at <http://www.secinfo.com/dRqWm.4G3Pa.htm> (last visited Jan. 26, 2006).

January 2001, a court issued a *Markman* claim construction (a legal ruling that defines disputed patent claim terminology) that supported Affymetrix's position of non-infringement.²³ In October 2001, the parties agreed to a settlement that acknowledged the validity of all the patents at issue between them.²⁴

As a result of the settlement, Affymetrix obtained a 10% ownership of Callida Genomics, a new Hyseq subsidiary to which Hyseq assigned all of its SBH patents.²⁵ Affymetrix and Hyseq also entered into a corporate collaboration to develop DNA sequencing microarrays through Callida's wholly-owned subsidiary N-Mer. Affymetrix became the exclusive supplier to (and sales agent for) N-Mer's microarrays, and retained an option to purchase a majority stake in the company. In return for access to Hyseq's array-related technologies, Affymetrix granted Hyseq and Callida a variety of exclusive and non-exclusive internal licenses to its own array technology.²⁶

Ironically, Hyseq's early patents covered SBH techniques, while in contrast, many of Affymetrix's early patents covered microarray manufacturing processes.²⁷ While Affymetrix did patent some experimental applications of microarrays (e.g., screening methods, so-called "DNA fingerprinting"),²⁸ its settlement agreement with Hyseq suggests the value of analyzing respective R&D strengths in anticipation of litigation. Had Hyseq and Affymetrix focused simply on sequencing and manufacturing strengths respectively, the companies might have come to an adequate cross-licensing scheme without incurring expensive litigation.

Given the high start-up cost of developing microfluidics technology, strategic IP planning may be vital for corporate survival. For example, a re-focusing strategy helped Incyte Genomics, which sold off its microarray division in 2002 after a series of infringement lawsuits with Affymetrix.²⁹ The newly streamlined company focused its business model on bioinformatics, licensing tools, and databases developed through analyses on microarrays licensed from other parties.³⁰ By 2004, Incyte Genomics (now "Incyte Corporation") was using its technology to assist the pharmaceutical industry with pre-clinical drug development and *in vivo* trials.³¹

V. CONCLUSIONS: POLICY CHALLENGES

As microfluidics technology develops, DNA microarrays and associated health-related technologies will likely be amongst the most prominent applications. But these technologies implicate not only questions of IP, but also health care law and medical and legal ethics. Government policy intervention may be necessary to balance the competing private and public interests in microarray invention, fabrication, and utility. A policy analog would be the Hatch-Waxman Act and its balanced regulation of pharmaceutical drug innovation and competition.

²³ See Rouse & Hardiman, *supra* note 20, at 4.

²⁴ Press Release, Affymetrix, Inc., Affymetrix and Hyseq Settle All Patent Litigation (Oct. 25, 2001), available at http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=AFFX&script=412&layout=-6&item_id=220294 (last visited Jan. 26, 2006).

²⁵ See SEC Form 10-Q filing for Affymetrix, Inc., *supra* note 22.

²⁶ See *id.*

²⁷ See Rouse & Hardiman, *supra* note 20, at 3.

²⁸ See *id.*

²⁹ See *id.* at 6-8.

³⁰ Press Release, Incyte Genomics, Inc., Incyte Genomics to Become Incyte Corporation (Dec. 16, 2002), available at http://www.incyte.com/about_press_releases_20021216.html (last visited Jan. 26, 2006).

³¹ Letter from Paul A. Friedman, M.D., President & Chief Executive Officer, Incyte, Inc., to Shareholders (Apr. 2005), available at http://www.incyte.com/letter_to_shareholders.html (last visited Jan. 26, 2006).

More complex pricing regulation may also be required between competing academic institutions and private industry. Commercial exploitation of the human genome risks generating excessive rents on basic and applied research.³² Given the paucity of federal research grants, and the tenuous finances threatening many microfluidics start-up companies, an unregulated biochip market may ultimately restrain scientific innovation and circumvent patent law's goal of promoting scientific progress.

³² See Bryon V. Olsen, *The Biotechnology Balancing Act: Patents for Gene Fragments, and Licensing the "Useful Arts"*, 7 ALB. L.J. SCI. & TECH. 295, 323-324 (1997).