An Analysis of the Supramolecular NanoStamping Technology for its Market Potential Based Upon a Review of DNA Microarray Intellectual Property

by

Kathy H. Li

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Submitted to the Department of Materials Science and Engineering in partial fulfillment of the requirements for the degree of

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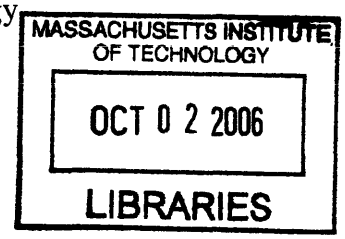

Signature of Author: .....
Department of Materials Science and Engineering
June 29, 2006

Certified by: .....
Francesco Stellacci
Finmeccanica Assistant Professor of Material Science and Engineering
Thesis Supervisor

Accepted by: .....
Samuel M. Allen
POSCO Professor of Physical Metallurgy
Chair, Departmental Committee on Graduate Students

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ABSTRACT

Supramolecular NanoStamping is a novel printing method for exploiting the supramolecular interactions between organic and biological molecules. This technology is advantageous because of the ability to transfer a massive amount of chemical and spatial information, its high resolution, the growth of masters used multiple times and the versatility of initial master fabrication. The technology may be used to make DNA microarrays which are an essential tool to genomic research assisting in gene expression and genotyping.

This paper explores the potential of bring Supramolecular NanoStamping technology to the microarray market. An in depth analysis of the current patent landscape of DNA microarrays is conducted to recognize the various competitors and the coverage of their patents. In addition, a better understanding of the landscape was achieved by assessing the major litigation that has occurred in the field. By engaging in a thorough intellectual property analysis, the commercialization potential of Supramolecular NanoStamping technology was realized through a licensing model.

Thesis Supervisor: Francesco Stellacci

Title: Finmeccanica Assistant Professor of Material Science and Engineering

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INTRODUCTION

In today's scientific world of biology, there is an overwhelming amount of genetic information that is being gathered as the human genome is sequenced. As important as it is to collect all of this knowledge, the staggering amount of data is not useful in making important discoveries unless it can be carefully deciphered into meaningful data that may be interpreted. Therefore, in this is technological age, DNA microarrays are indispensable tools for sorting through all the information to make an impact on practical applications.

DNA microarrays are able to conduct testing for experiments such as gene expression and genotyping. By determining gene expression, the DNA sequences, a gene's coded information, are transformed into the parallel structures and functions of a cell that they dictate. Treatments for and the developmental stages of diseases can then be studied from this information. DNA microarrays can also be used for genotyping which studies an individual's genotype, their genetic constitution, to determine if there are any dangerous genetic mutations that may cause disease.

As revolutionary as DNA microarrays could make the field of genetics and biology, the technology is still extremely expensive and not widely available for use in industries outside of pure research like healthcare. If the tools could be manufactured at a fraction of the current cost, then a variety of applications could utilize the technology to combat diseases from many different angles. Patients could conduct in-home diagnostics by determining the exact strain of cold or flu that they have to match it with the exact

medicine to combat it. Researchers could study single-nucleotide polymorphisms (SNPs), variations of a single nucleotide base in the DNA sequence, that occur every couple hundred bases to determine their effects. DNA microarray technology has the potential to revolutionize the scientific community, but new technological advancements will need to be made in order to make the technology a commercial success.

TECHNOLOGY

Goals

The major goal of Supramolecular NanoStamping is to achieve nano-scale resolution contact printing of bio-chemically complex patterns. In order to achieve that goal, the process must be carefully crafted to avoid mechanical forces, high temperatures and etching chemicals which would damage the organic molecules. Nature has created the perfect solution through DNA/RNA information transfer. This printing method has many key capabilities that make it the best. It is able to be carried out at room temperature and in a liquid environment as it occurs in the body. In addition, an enormous amount of information is transferred with nanometer scale resolution through the process. Supramolecular NanoStamping utilizes self-assembly and reversible van der Waals bonds to replicate this complex process.

Methodology

The novel printing method is used for printing organic bio-molecules using the supramolecular interactions that are present between molecules. To begin with, the first initial master slide must be fabricated. This slide may be fabricated using one of any of the currently available techniques, such as photolithography, electron beam (E-beam) lithography or spotting. In spotting, a machines spotter specifically made for making microarrays is used to create the master. Textured substrates are soaked in a single-stranded DNA solution to create a monolayer over the surface and then carefully printed so that only the raised parts make contact in E-beam lithography. On the other hand,

the photolithography process uses ultraviolet light shined onto a microarray with a mask so that the unprotected sections activities linker molecules to couple with DNA. Therefore, in theory, any microarray can be used as a master since the Supramolecular NanoStamping principle does not rely on the DNA binding to the substrate but rather with its complement. Although any one of these tradition methods may be used, the process works best when the initial master is packed in such a way that it is sufficiently dense and resembles a self-assembled monolayer where the DNA is standing as close to upright as possible.

After the initial master slide is produced, the substrate should be immersed in a solution containing the DNA complements of the single-stranded DNA (ssDNA) on the master. Like the DNA on the substrate, the complementary DNA (cDNA) is composed of a DNA backbone connected to a flexible linker with an attachment group on the end used to bind to a substrate. Schematics of the single-stranded DNA on the substrate and its complements can be seen in **Figures 1A and 1B**, respectively. In the solution, the complementary pairs will hybridize with the corresponding molecules on the master.

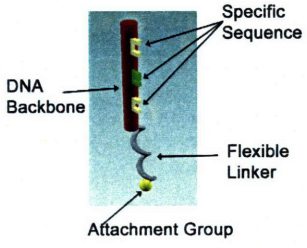

Figure 1A: Schematic of the single-stranded DNA for substrate attachment.

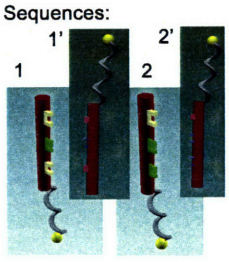

Figure 1B: Schematic of the single-stranded DNA complements for hybridization where 1 and 2 represent different sequences.

After removing the substrate from the solution, its DNA is in the double helix form with two single strands hybridized together and attachment groups on each end. A secondary substrate is gently brought into contact with the master substrate so that the free attachment group can adhere to the new substrate. After the surface approach is complete, the entire system is heated in order to de-hybridize the DNA so that the two substrates may be separated (Yu, 2005). A schematic of the entire process can be seen is **Figure 2** below.

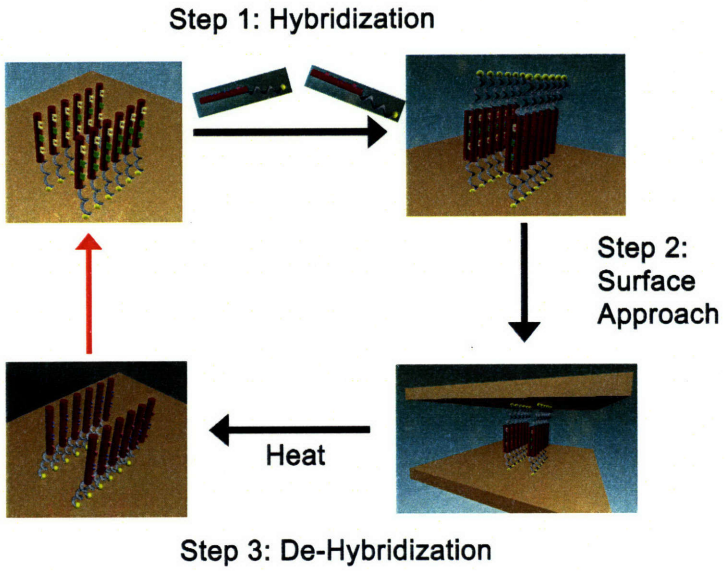

Figure 2: Schematics of the Supramolecular NanoStamping process: 1) Hybridization of DNA complements in solution, 2) Surface approach of secondary substrate with master and 3) De-hybridization of DNA by heating to separate substrates. Following the red arrow, the process may be repeated again.

From the Supramolecular NanoStamping process, a secondary substrate (a daughter master) is created from the initial master. The daughter represents a replica of the master with the exception that the DNA is the complementary strand to the master. In terms of spatial and chemical information, everything is preserved on the daughter master. If the process was carried out again, on the daughter master rather than the

initial master, then the grand-daughter master created would be an exact replica of the initial master. After only two iterations of Supramolecular NanoStamping, an exact copy of the first master can be fabricated.

Substrates

The Supramolecular NanoStamping process was first shown to work on a gold (Au) substrate. For this substrate, thiols (-SH groups) were attached to the ends of the DNA backbone for their strong adherence to gold. Although gold material provides a substrate for high resolution, it is problematic for several reasons including its poor mechanical properties and high costs. Therefore, once the concept was proven to work, a new substrate was sought to alleviate these issues (Yu, 2005).

In addition to gold, the method has also been shown to work on poly (methyl methacrylate) (PMMA) substrates. PMMA material provides several advantages that gold does not. To begin with, the cost of PMMA is only a small fraction of the cost of gold of mica. Furthermore, PMMA has several intrinsic properties that make it a good candidate for bio-array systems. The material is optically transparent, electrically insulting and flexible and mechanically robust at room temperature. In addition, it is also relatively stable and can be washed in water without deteriorating. Supramolecular NanoStamping with PMMA substrates has been able to retain the same level of resolution and coverage as with gold substrates (Yu, 2005). Although performing the process on PMMA substrates represents an important advancement in developing the binding chemistry between the DNA and new substrates, other materials are still being

investigated. Currently, research is being conducted into using polydimethylsiloxane (PDMS) substrates. By achieving adherence with this surface chemistry, an important step will be taken since silicon substrates are often used for DNA microarrays.

Advantages

Supramolecular NanoStamping holds many advantages over other DNA microarray fabrication methods such as spotting or photolithography. First, the growth and multiplication of masters is enabled as they can be used and over again to create new masters. Current research establishes that the masters may be used up to seven to eight times without losing a significant amount of resolution or coverage. Second, the extreme versatility of the initial master fabrication is crucial as it allows this process to be used with virtually any microarray or master. Third, a high resolution of less than forty nanometers can be achieved for high clarity and precision. Finally, the process provides the potential for the transfer of a massive amount of both spatial information about the DNA pattern and chemical information about the DNA sequence (Yu, 2005). Supramolecular NanoStamping technology holds much promise for future biological applications.

APPLICATIONS

Potential

Several applications utilizing the diversity of possible attachment groups can be derived from this technology. The DNA on the substrate can be modified with both organic and inorganic materials by assembling along the printed pattern of strands. This modification can be made is two ways. In one method, the negative charge of the DNA backbone can be employed, especially in the case of assembling metals. If a master substrate with a DNA pattern printed onto it is immersed in a solution of metallic nanoparticles, the nanoparticles will automatically assemble onto the DNA pattern because metal is usually positively charged in an aqueous environment. The downside to this assembly process though is that it is not sequence specific.

In another method, the sequence specific binding is exploited. The target material, whether organic or inorganic, can be attached to the DNA complements of the single-stranded DNA on the substrate pattern. Then, the material can then be easily attached to the substrate when the DNA complements hybridize together. A key advantage to this process is that many different materials can be attached onto the substrate at the same time to fabricate complex devices. Since it is dependent on the specific binding and hybridization between a pair of single-stranded DNA strands, a solution with different sequence strands (each connected to a unique attachment group) can be used to match a DNA pattern composed of the different sequence complementary strands. Currently, some complex nano-devices are manufactured in a slow manner and at high

costs. However, with this new process, nano-devices like optical biosensors, single-electron transistors, metallic wires and micro- and nano-fluidics channels can be produced efficiently and economically.

Target

Despite the potential to revolutionize the production of several different nano-devices, the target application for Supramolecular NanoStamping technology is as a new synthesis method for DNA microarrays, also known as gene chips or DNA chips. A variety of fabrication methods are currently available to make DNA microarrays (see picture in **Figure 3**) including spotting and photolithography. However, each of these methods has its disadvantages that Supramolecular NanoStamping can overcome such as being able to print DNA strands of various lengths, short or long on a relative scale.

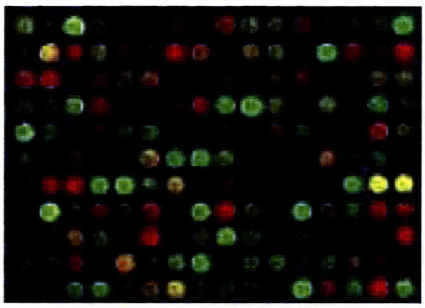

Figure 3: Photograph of a fluorescently tagged DNA microarray.

Image courtesy of: http://www2.niaid.nih.gov/newsroom/focuson/tb02/microarrays.htm

DNA microarrays are composed of tens of thousands of unique, microscopic DNA spots attached to a substrate forming an ordered array. The spots are DNA segments or probes of different sequences and are attached to substrates like glass or silicon chips. Fluorescently tagged biological samples are run over a microarray to see where the sample attaches to the substrate. Information about the sample can be obtained and the

expression levels for many genes may be evaluated simultaneously. DNA microarrays can provide knowledge that leads to finding polymorphisms for drug discovery (measuring the effect of a specific drug on a particular set of genes) and pharmacogenomics or monitoring gene expression for identifying genetic diseases (Liebeschuetz, 2003).

INTELLECTUAL PROPERTY

Competing Technologies and Patents

AFFYMETRIX

The industry's past and current leading company is Affymetrix of Santa Clara, California since their inception in 1991 (Bouchie, 2002). They were the first to commercialize their technology and push significant volume out to customers due to the high production rate of their Genechip® (as seen in **Figures 4A and 4B**) that they were able to achieve, up to 10,000 chips a month initially. A significant advantage to Affymetrix's DNA microarray is their ability to make a high density array, higher than any other commercial technology. The Genechip® is covered by patent number US 5,445,934 *Array of oligonucleotides on a solid substrate* issued in 1995. The first independent claim of this patent recites "A substrate with a surface comprising 10^3 or more groups of oligonucleotides with different, known sequences covalently attached to the surface in discrete known regions, said 10^3 or more groups of oligonucleotides occupying a total area of less than 1 cm^2 on said substrate, said groups of oligonucleotides having different nucleotide sequences."

This patent crucial to Affymetrix's portfolio was filed in 1989 and the first of a genre of patents on the microarray that would soon follow. By being the leader of the pack, Affymetrix had the advantage of setting the precedent for the field but the difficulty of presenting a new and unfamiliar type of invention to the United Patent and Trademark

Office requiring a long dialogue of communication for clarification before it would be allowed (Liebeschuetz, 2003).

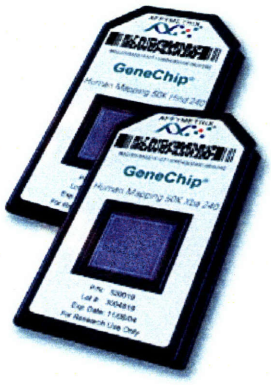

Figure 4A: Close up photograph of Affymetrix's Genechip®

Image courtesy of:
http://www.genpromag.com/ShowPR~PUB CODE~018~ACCT~1800000100~ISSUE~ 0509~RELTYPE~PR~ORIGRELTYPE~GPF ~PRODCODE~00000000~PRODLETT~B.html

Figure 4B: Photograph demonstrating the size of Affymetrix's Genechip®

Image courtesy of:
http://privatewww.essex.ac.uk/~harry/ beams/funcgenomics/

The company now holds nearly 300 patents with a continuous flow of pending patent applications. It has not been an easy road for the company though as they incurred significant initial losses of nearly $67 million until they were able to reverse their fortune in 1997. More recently though, Affymetrix has been profitable after a positive earning of $10 million that year (including $15 million in government research grants and contracts).

Due to its prominent position in the market, Affymetrix receives a great amount of attention and scrutiny—and it's not always postitive. Their executives believe that this

market is just like any business and the company has the right and responsibility to its investors to profit from its proprietary technology. From this mentality, many in the industry consider the company to be a bully trying to scare off others from trying to get into the market. The dislike towards them is magnified by the perception that their corporate philosophy is to aggressively defend their technology and monopolize the field by demanding high licensing fees for competitors to enter the market. In addition to filing patents on all technologies related to their Genechip®, they have also asserted those patents and threatened litigation. The extremely sensitive nature of the research radically touches a nerve in the scientific community. It's not just about a company dominating the electronics industry to build the fastest computer, but about a company owning the DNA microarray industry which may be the key tools for curing diseases and understanding the biological world (Alexander, 2000). The way this market shapes may determine how scientists even conduct their research which means that Affymetrix's actions have far reaching implications.

The proprietary technology that Affymetrix has patented is on its photolithography technique of producing DNA microarrays. This method combines photolithographic practices developed for the semiconductor industry with combinatorial chemistry. To begin with, a mask over the substrate, typically a silicon wafer or glass, is used to create a specific pattern for the microarray. Then, an ultraviolet light is shined on the substrate so that the linker molecules in the open regions of the mask are unprotected so that they can be coupled with DNA strands while the closed regions remain protected. Next, the surface is flushed with a DNA solution of a specific base (adenine (A), thymine (T),

guanine (G) or cytosine (C)) that will attaches to molecules on the substrate. The process is then repeated three more times, once for each base, until the entire surface is covered. After the first layer of mers is laid down, the process is continually done until a DNA strand of 25 mers is built. With four bases for each of the 25 layers, this process takes 100 steps to complete and the final product with more than 400,000 probes is schematically shown in **Figure 5** below (which also includes a drawing of the actual chip size, 1.28cm by 1.28 cm).

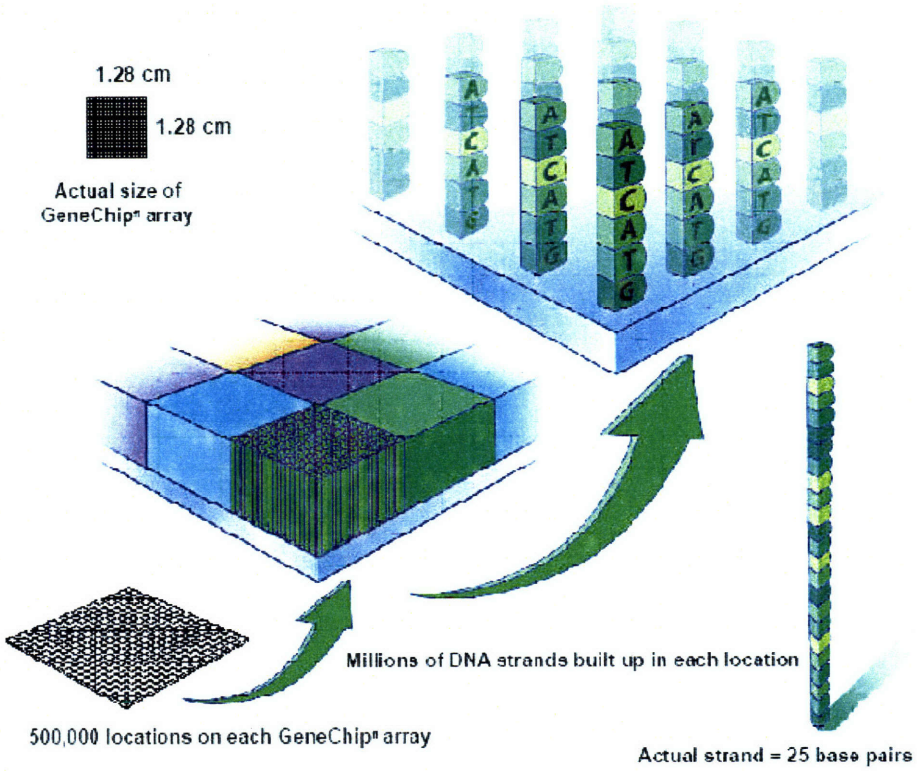

Figure 5: Schematic of the photolithography technique used by Affymetrix to create its GeneChip®

Image courtesy of: http://keck.med.yale.edu/affymetrix/technology.htm

This technology is protected by Affymetrix's pioneer patent, US 5,445,934, which describes the photolithography method of making DNA microarrays and the apparatus required for production. In addition, US 6,040,193 *Combinatorial strategies for polymer synthesis* issued in 2000 (a continuation of US 5,677,195 issued in 1997)

and US 5,744,305 *Arrays of materials attached to a substrate* issued in 1998 also cover their chemical synthesis method for manufacturing DNA microarrays. US 6,040,193 focus on the methodology while US 5,744,305 is a device patent. The first independent claim of the latter recites "An array of oligonucleotides, the array comprising: a planar, non-porous solid support having at least a first surface; and a plurality of different oligonucleotides attached to the first surface of the solid support at a density exceeding 400 different oligonucleotides/cm^2, wherein each of the different oligonucleotides is attached to the surface of the solid support in a different predefined region, has a different determinable sequences, and is at least 4 nucleotides in length." Analyzing the language of the claim is imperative to understanding the scope that the patent covers. In this particular case, competitors have been able to circumvent the patent by developing arrays made of porous substrates instead of non-porous ones. For a device to infringement a patent, every element of the device claimed in the patent must be present therefore porous substrates are valid.

A disadvantage of Affymetrix's method is that a tradeoff between efficiency and quality must be made, the more efficiently the process is completed, the poorer the quality of the resulting microarray. However, this photolithography technique is more efficient than the base-by-base technique of in situ oligonucleotide synthesis used by its competitors. Despite the limiting of its technology, Affymetrix was still the first company to get their product out to the market. Therefore, they can maintain a hold on their dominant position because of a large patent portfolio and customer loyalty resulting from reluctance to change suppliers.

AGILENT TECHNOLOGIES

Agilent Technologies is another company that synthesizes DNA microarrays (seen below in **Figure 6**) with significant market share. Their technology for fabrication is completely different and mimics ink-jet printing. This method, called in situ oligonucleotide synthesis, is made under the name of SurePrint® and combines printer technology with standard phosphoamidite chemistry. Instead of using red-blue-green sequences in this ink-jet-like printing method, different "dot" chemistries are used as the possibilities to choose from. Each dot is a different sequence of single-stranded DNA to be attached to the substrate. In this method, 60-mer DNA strands are printed onto a glass slide base by base. Since the oligonucleotide probes are synthesized directly on the array one base at a time, there is a high level of precision exhibited by this technique.

Figure 6: Photograph of DNA microarrays manufactured by Agilent Technologies

Image courtesy of:
http://www.usc.edu/schools/medicine/research/institutes/igm/content/microarray/instruments.htm

A drawback to this method though is that it is limited by the volume of liquid that must be deposited to transfer the probes onto the slide. This means that SurePrint® can only

be used to fabricate low density arrays. In addition, a slow production time results in inefficiency and high costs. However, in situ oligonucleotide synthesis results in a high quality array that provides a great amount of information with very few defects.

HYSEQ

Sequencing DNA by hybridization ("SBH") is the key technology that makes Hyseq of Sunnyvale, California another important player in the DNA microarray market. This technique uses DNA microarrays in combination with separate oligonucleotide probes, between 11-20 nucleotides in length, whose sequence is known either to identify or completely sequence genes of interest. In this method, the oligonucleotide probes are hybridized onto the target nucleic acid sequence where the complementary probe sequences are overlapping in sequences. This enables the identification of the target nucleic acid and accurate DNA sequencing due to the ability to discriminate perfect sequence hybrids from hybrids with a single nucleotide mismatch (Rouse, 2003). Hyseq has three crucial patents in its portfolio that protect its core technology and method: US 5,202,231 *Method of sequencing of genomes by hybridization of oligonucleotide probes* in 1993 and US 5,525,464 *Method of sequencing by hybridization of oligonucleotide probes* and its continuation US 5,695,940 in 1996 and 1997, respectively.

OXFORD GENE TECHNOLOGY

Another company that should also be mentioned is Oxford Gene Technology of Oxford, United Kingdom. This company was founded by Edwin Southern, inventor of the

Southern Blot which is used in molecular biology to transfer DNA molecules onto in an agarose gel electrophoresis for the purpose of detecting specific DNA sequence fragments. Oxford Gene Technology maintains several patents on methods for analyzing and making DNA microarrays including US 5,700,637 *Apparatus and method for analyzing polynucleotide sequences and method of generating oligonucleotide arrays* and US 6,054,270 *Analyzing polynucleotide sequences.*

OTHER COMPANIES

In addition, there are also several other companies who have played a crucial role in shaping the DNA microarray market. Incyte Pharmaceuticals and Applied Biosystems have also developed and manufactured chips as seen in **Figures 7A and 7B**, respectively.

Figure 7A: Incyte's DNA microarray

Image courtesy of:
http://www.devicelink.com/ivdt/archive/99/01/008.html

Figure 7B: Applied Biosystems's DNA microarray

Image courtesy of:
http://www.imgm.de/whole_genome_microarrays.php

It's not just specialized biotech companies in the DNA microarray array market though. Major companies, such as 3M, Motorola, Corning and Hitachi, are also developing their

own systems. The companies can play up their size and partner with smaller startups, like Rosetta Inpharmatics, Hyseq, Nanogen and Caliper Technologies, to help commercialize their technologies. In general, there is a lot of potential in the entire market for companies to partner together and cooperate to develop new technology.

However, due to the competitive nature of the developing microarray industry, some companies have begun to stray away from the market and apply their technologies to other areas. For example, in May of 2002, Nanogen refocused its corporate strategy and began applying its microfluidics technology to the development of diagnostics rather than for making devices for gene expression profiling (Bouchie, 2002). Corning, who entered the game later than the others, has also decided to halt its efforts in the field citing unfavorable market conditions. The companies named above are only some of the many companies that are attempting to commercialize the synthesis of DNA microarrays. There still remains a lot of competition in the industry from these other companies and none can yet be discounted for being the next major player.

Litigation

AFFYMETRIX AND HYSEQ

In order to fully understand the intellectual property patent landscape of DNA microarray technology, it is imperative to not only study the competing technologies and various patents covering those technologies but also the litigation that has occurred over the lifetime of the market. By carefully scrutinizing the patents that have been

litigated in the field, a better knowledge of the important issues that play a pivotal role in a company's proprietary technology can be obtained. Furthermore, this step is even more crucial for DNA microarray synthesis processes because of the strong reliance on patents for company survival in the industry. All of the technology is closely tied to each other causing companies to continually step on each other's patents. As a result, companies must result to asserting their patents over each other to remain dominant or settle for engaging in cross licensing agreements.

It is no surprise that in all of the major cases litigated over the synthesis of DNA microarray technology, Affymetrix has been involved as one of the parties. The two major suits that began the slew of litigation in the synthesis of DNA microarrays were between Affymetrix and Hyseq and Affymetrix and Incyte. In March 1997, Hyseq sued Affymetrix in the Northern District Court of California alleging that the company infringed its sequencing DNA by hybridization ("SBH") patents, US 5,202,231 and US 5,525,464 (Sharrott, 2006). A series of four parallel lawsuits between the companies followed starting with Affymetrix's countersuit against Hyseq in September of 1998 where they asserted US 5,445,934 and claimed Hyseq infringed by developing microarrays with densities greater than 400 polynucleotides per square centimeter. For four years, litigation continued until January 2001 when the Court issued a Markman ruling, which defines the disputed patent claim terminology, in favor of Affymetrix who asserted a position of non-infringement (Rouse, 2003).

The pending litigation was finally settled in October of that year when both companies were able to acknowledge that all the patents in dispute were valid. The settlement set up a cross-licensing agreement between the parties where Affymetrix granted Hyseq an assortment of licenses to its pertinent microarray technology while Hyseq granted Affymetrix a 10% ownership of Callida Genomics, a new subsidiary of the company established as the assignee of all Hyseq's sequencing DNA by hybridization patents. In addition to the cross licensing, the two companies also started a partnership to synthesize DNA microarrays by using both Affymetrix's GenChip® and Hyseq's sequencing DNA by hybridization technologies. The research is conducted by a new subsidiary of Hyseq's Callida Genomics, N-Mer, which Affymetrix may have majority interest in if they wish to in the future (Sharrott, 2006).

Taking a retrospective look back on the two company's patents involved in the litigation, it is possible to study how the litigation could have been prevented. Affymetrix's GeneChip® technology patents focus on a method of how to manufacture and make microarrays, while Hyseq's sequencing DNA by hybridization technology patents focuses on the application and use of microarrays. Therefore, if the two companies had strategized to play on the strengths of their respective technologies, they may have been able to work together to develop a collaboration and cross-licensing agreement without having to spend the large amount of money on litigation that they did. By anticipating the litigation before it happened and realizing the potential that a collaboration between the two may have, the companies could have spent the money

and time it had to put into the cost of the suits into developing its respective technologies instead (Sharrott, 2006).

AFFYMETRIX AND INCYTE

In addition to Affymetrix's litigation with Hyseq, the company also instigated a suit against Synteni Inc., a company acquired by Incyte. Affymetrix alleged that Incyte infringed on US 5,445,934, the same patent they asserted against Hyseq. The portion of the patent that Affymetrix claimed was infringed was for making dense arrays, arrays containing more than a thousand gene fragments per square centimeter (Service, 1998). However, Incyte claims that they do not infringe so the suit is unjustified. The company asserts that since they are using much longer gene fragments than the short fragments that Affymetrix uses, there is no case for infringement. Furthermore, by using their own proprietary technology to synthesize the microarrays rather than the photolithography technique of Affymetrix, it reaffirms that the case has no merit. In addition, like the case against Hyseq, the litigation with Incyte also continued through a series of several concurrent lawsuits filed between the two companies over several years. The Affymetrix versus Incyte litigation represents the intensity and difficulty of being a major player in the DNA microarray market. After the settlement agreed to by the two parties, Incyte Genomics decided to refocus its entire corporate strategy and sell off its microarray division in 2002 to become Incyte Corporation. The company changed its focus from the synthesis of DNA microarrays to the tools and databases needed to analyze DNA microarrays. After establishing a business model focus on bioinformatics, Incyte now uses its technology to help with testing in the pharmaceutical industry. The

knowledge can be used for the development of drugs and conducting test trials of their efficacy.

From Affymetrix's two major cases with Hyseq and Incyte, it is apparent that that their patents are strong and allow them to remain dominant in the industry. In its case against Hyseq, Affymetrix asserted its patents on the GeneChip® and DNA microarray density, US 5,445,934 and was able to agree upon a settlement. The company continued to sue with the same patent against Incyte which suggests that they were amenable towards the settlement terms they got with Hyseq and were willing to continue asserting it. On the other hand, Hyseq has not asserted its patents against other companies showing that they did not get the exact settlement terms they were interested in the settlement. Since Affymetrix is continually asserting its patents against others and settling, it means that although their patents do not have the power to stop other companies but it does have the ability to gain cross-licensing agreements.

AFFYMETRIX AND OXFORD GENE TECHNOLOGY

Affymetrix has also engaged in litigation with Oxford Gene Technology in the United Kingdom, but it this time the focus of the suit was on the more on the business rather than the technology. The technology in issue during this case was Oxford Gene Technology's method for rapidly analyzing genes by analyzing polynucleotide sequences and an apparatus for synthesizing microarrays. Affymetrix realized the importance of the patents and entered discussions on licensing the technology from Oxford Gene Technology. In June 1998, an agreement of $20 million for licensing fess

was agreed upon but right before it was finalized, Affymetrix backed out of the deal. Instead, to get a license for the technology, Affymetrix bought the company Beckman Coulter Inc. (a manufacturer of drug delivery systems) which already had a license for the technology obtained in 1991 (Rouse, 2003). The company was able to make the purchase for only $10.9 million dollars which in essence allowed them to license the technology for half the price.

Due to the method that they obtained the license from Oxford Gene Technology, Oxford Gene Technology filed suit against Affymetrix in 1999. Initially in April 2000, a trail court ruled that Affymetrix's license to Oxford Gene Technology's patents were invalid which greatly jeopardized the company's future. Oxford Gene Technology now had the power to put Affymetrix out of business by refusing a license. However, Affymetrix appealed the decision and the higher court ruled in favor of Affymetrix. They determined that there was no wrongdoing on their part in obtaining a legal license to use the technology for analyzing genes quickly. This case exemplifies the lengths at which Affymetrix, and in general companies in the industry, will go to survive in the market. Furthermore, the importance of being able to utilize all the possible technology out there to be able to develop even more new breakthroughs can be seen.

These three cases represent only a small fraction of the suits that have been filed between DNA microarray manufacturers. They represent the difficulty of carving out a substantial share of the DNA microarray market. From past litigation, lessons can be learned to circumvent potential future litigation. In addition, despite the large amounts

of time and money it takes, companies are still vying for a place in the industry due to the potential for growth.

BUSINESS STRATEGY

Market

Due to the versatility of DNA microarrays and their potential of unlocking the mysteries of disease, there is an extremely high demand for the product in the market. However, there is a significant range in the predictions for their future growth. Some analysts believe that the entire market of chips and analysis software will experience more than 30% growth per year reach up to $3.6 to $4.5 billion by next year (Bouchie, 2002). In 2004, DNA microarrays were a $700 million market with other analysts projecting a $200 million a year increase to $1.4 billion in 2010. Despite the promising market, the current hefty price tag of $500 - $2000 per array limits access of the tool primarily to research laboratories and universities. In order for the healthcare industry to be able to use DNA microarrays to diagnose diseases, the price needs to be brought down to $50-$100 per array. If this price point could be achieved, it is possible that the market could see an exponential increase in demand.

Although Affymetrix is currently dominant with 80% of the market share due to its high density DNA microarrays, the future direction of the market could make it difficult for the company to hold their position. Currently, 75% of the research conducted with DNA microarrays involved the use of high density arrays, which Affymetrix specializes in, in order to test a sample across as many polynucleotide probes as possible (Bouchie, 2002). However, once a relatively small number of genes have been associated with a certain disease, low density arrays can be used to screen those small number of genes

across many patients. Therefore, the demand is currently for high density arrays as researchers are trying to make connections between genes and diseases first. Once the associations are made though, the majority of the demand may shift to low density arrays in a few years (Bouchie, 2002). Although Affymetrix may always dominate the high density array market, the shift will give companies other than Affymetrix to capture significant microarray market share in the form of low density arrays.

Not only is the chip side, also known as the "hardware," of the market highly competitive and tangled in patents, but the "software" side of the actual genes and their functions is also not without complications since they can also be patented. Then, when a microarray manufacturer wants to use that sequences for their chip, they must obtain a license to use that sequence. The problem comes in when the scale and magnitude of how much information a chip contains is considered. In a single chip, there may be more than 40,000 different sequences and if each one of those sequences involves a patented gene, then chip prices will skyrocket and leave manufacturers with little profit. A problem that could play a larger role in creating a real obstacle to chip development is if the assignees of the gene patents are unwillingness to license their sequences. For example, they may only license the sequences to one company exclusively and prevent competitors from using it or they may not license it at all and attempt to profit from their innovation themselves. Despite these difficulties those, companies are not deterred since a lot of competition still remains so that they is not one major leader dominating the market. In addition, many gene sequences are also in the public domain

and free to any company to use so that they do not have to rely on proprietary ones (Service, 1998).

Licensing

Due to the intensely dense field of patents in the DNA microarray industry, a business model focused on protecting the intellectual property of Supramolecular NanoStamping is a necessity for survival of the technology. Currently, there are two pending patent applications on the technology that cover the concept of stamping via self-assembly to gain protection for the technology. To strengthen the impact of the patents, they encompass the potential for using various initial master types, a variety of substrate materials and applying the concept to various types of microarrays beyond DNA. Developing a strong intellectual property portfolio for the technology not only includes getting patent protection but also includes conducting extensive prior art searching and patent landscaping to determine the technology space and where it may overlap. By having a deep and thorough understanding of where Supramolecular NanoStamping fits into the DNA microarray market, it is possible to anticipate and hopefully avoid any potential litigation that may occur in the future.

Once patent protection can secured for the technology, it may be implemented into the market through a licensing strategy. The key point to Supramolecular NanoStamping technology is its ability to reliably, efficiently and economically reproduce chips from a master one. Therefore, the technology is crucial for bringing down the cost when making multiple copies of the same chip, regardless of how the initial chip is made.

This means that any company can apply the method to its own chips since Supramolecular NanoStamping's underlying concept works independent of the company's manufacturing process.

To begin with, the first companies that should be targeted for licensing are the major ones with significant market share, besides Affymetrix. The reason that Affymetrix would not want to initially be approached is because they currently enjoy the dominant position in the market and would tend not to want to jeopardize that position by implementing new technology that hadn't been commercially tested yet. By bringing the technology to market with say Affymetrix's main competitors, they have the motivation to take a chance on a technology that would increase their market share and allow them the possible opportunity to take over Affymetrix's lead. The competitors would have the opportunity to bring down the cost of their products to a fraction of what they were before so that demand for their chips would increase because of the low price. Once the technology can be established and shown to work with one or a few reputable companies, then the method of driving down costs will want to be implemented by all companies to remain competitive.

Implementing a licensing strategy rather than a start up strategy will also save on the cost of developing a start up to commercialized the process. These financial burdens would be placed on the companies willing to take a chance on the technology. With the potential to significantly bring down the price on a microarray and proof of concept showing that it works, it is anticipated that finding a competitive company to invest in

the technology is reasonable and viable. Since the process would require special machinery in clean-room like conditions, the companies would most likely already have much of the equipment and means to carry out the process without having to incur the significant initial costs that a start up would be faced with.

CONCLUSION

DNA microarrays are important tools for sorting through the enormous amount of information about the human genome. By determining gene expression and conducting genotyping efficiently, they hold promise for revolutionizing the treatments of diseases and developments of medicines. Supramolecular NanoStamping is a novel method for fabricating DNA microarrays to conduct this biological and genetic research. The process utilizes directed self-assembly to build these devices in an economical method. It is the first bio-molecule friendly printing technique with high spatial and chemical information content. Several technical advantages are available by using this method such as ease of master multiplication, high resolution printing and massive information transfer. In addition to its technical benefits, Supramolecular NanoStamping also possesses economic advantages such as fast production times and low costs. Bring this technology to market will not be without struggle though. Patents will need to be issued by the United States Patent and Trademark Office and DNA microarray technology will need to be thoroughly landscaped and search to avoid potential litigation. Supramolecular NanoStamping is an emerging technology that holds much promise for changing the DNA microarray industry.

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