



Microarray technology – an intellectual property retrospective

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The recent sequencing of the human genome is a critical milestone that has provided a framework for the identification of thousands of novel potential drug targets and the common genetic factors that affect drug metabolism and toxicity. Microarrays represent a novel genetic platform which is being widely exploited to bridge the gap between gene sequence and function. Microarray technology has found broad use in the areas of disease diagnosis, pharmacogenomics and toxicogenomics, and many opportunities continue to be created in the marketplace. As the field matures and enters the clinical arena, we will witness further innovation in both the public and private sectors, which ultimately will improve the technology. However, the exercise of intellectual property rights in this area has shadowed the evolution of this technology. This report provides a retrospective review of microarrays, highlighting the key patents and litigation that have shaped the industry.

Introduction

The drug discovery process seeks to develop a biological or chemical entity that, when administered to a patient, will improve disease symptomatology or actually treat the underlying pathophysiological basis of a particular disease state [1]. A target is defined as the biological entity, usually a gene, mRNA or protein, with which a pharmaceutical interacts. The cost of developing therapeutics has increased considerably in recent decades. US-based companies are likely to spend over US\$60 billion by 2005, and a minimum of 25% of all pharmaceutical sales revenue will be invested in research and development. Currently, the average cost of bringing a new drug to market is US\$750 million and this involves 10–12 years of arduous development and clinical trials. The success of a pharmaceutical company is therefore dependent on the overall efficiency of this process and an accelerated development time. Bioinformatics and microarray technologies are an integral component of this process. In 2000, the global bioinformatics market was ~ US\$350 million, and by 2005 it is projected to be US\$1045 million. Bioinformatic approaches coupled with DNA microarray data are uncovering novel biological mechanisms and predicting the effects of drug treatments [2–4]. They are a necessary prelude to the expensive and time-consuming preclinical and clinical tests. After genome sequencing, data derived from DNA microarray approaches has become the source of genomic information most widely used by the pharmaceutical industry. Conse-

quently, the market for DNA microarrays is expected to increase at a rate of 33% a year.

The increasing use and acceptance of microarrays and GeneChip™ technology to study genetic and cellular processes is clearly demonstrated by the increasing number of citations yearly in the published literature. Microarray technology makes it possible to evaluate in parallel the expression of thousands of genes. The microarray is comprised of a library of genes, represented by corresponding nucleotide sequences that are immobilized in a grid on a solid surface. Two dominant methodologies have evolved for array fabrication. Affymetrix (Santa Clara, CA, USA), Oxford Gene Technologies (Oxford, UK) and Agilent (Palo Alto, CA, USA) employ *in situ* synthetic approaches where oligonucleotides are built base by base on the chip. The alternative is 'spotted microarrays', where the probe DNA consists of polymerase chain reaction (PCR) amplicons or oligonucleotides that are deposited on the arrays using contact or non-contact printing methods [5–8]. The Affymetrix GeneChip is widely used in many research applications and is manufactured with rigorous quality control standards, a necessity for accurate and sensitive genetic measurements. Rival commercial oligonucleotide chip formats with similar genetic content have emerged from Amersham Biosciences, (Piscataway, NJ, USA) the CodeLink™ platform and Agilent [7–9].

The DNA microarray market is expected to double in the next 5 years. This expansion will encompass the areas of robotics, slide and attach-

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ment chemistries, labeling and detection strategies, and informatics and data management systems. This growth is not surprising given the powerful nature of this technology and its application to understanding the genomic basis of disease.

This article surveys the brief history of the microarray field, from the perspective of intellectual property (IP) defense and litigation that have shaped the field today. We identify and discuss the major microarray related patents that have been issued.

Patentable subject matter

Technological developments can be protected either in the form of a trade secret indefinitely by refraining to disclose the details of the invention, or in the form of a patent where in exchange for exclusively utilizing the invention for a defined period of time (20 years) details of the technology are comprehensively described to the public. In order to be awarded a patent, the invention must have utility and be sufficiently novel so that it is not an obvious variation on something that has already been created. The US has a history of patent law dating back to 1790, with the first patent laws enacted shortly after the Constitution was drafted. In Europe, France was the first nation to adopt patent laws that were established in 1791. Currently, in the US, patent applications are reviewed at the United States Patent & Trademark Office (USPTO) in Arlington, Virginia. In Europe, the European Patent Convention was signed in 1973 in order to harmonize patent laws amongst the various member states, and subsequently the European Patent Office (EPO) was established with its primary location in Munich, Germany. Generally, both US and European patent laws are complementary, with the exception of obtaining priority rights. In the US, the inventor claims priority on the date of conceiving the invention whereas in Europe the priority date is the date of filing the patent application.

Drug discovery research is in many ways a unique field in that in the course of daily experimentation, scientists typically perform processes using technology or reagents that are protected by patents. Many biological patents have been issued to protect these processes, the most controversial in recent times being PCR [10]. License, royalties and patent fees are paid to companies and universities, which help to recoup the costs incurred in the development of the particular technology. This maintains an active research

and development stream, ensuring the viability of technology innovation. Patenting of inventions in proteomic and genomic fields has been prolific in the last few years. Warburg *et al.* recently reviewed the legal principles governing patentability and the infringement of biotechnology patents [11].

Requirements for patentability

In order for an invention to be patented it must be novel and useful (a concept known as utility) and must not have been obvious 'to one of ordinary skill in the art'. Furthermore a patent application must comply with a series of standard requirements, namely a written description, enablement and best mode. The invention must be new, believable and possess real world use. Although a product or process may be novel, the invention may not obtain patent protection if the differences between the invention and the prior art are such that the invention as a whole would have been obvious at the time the invention was made. A patent application must contain a written description of the particular invention sufficient to enable any person skilled in the art to which it pertains to make and use the invention. The specification must disclose the best way the inventor knows of making the invention and using it at the time the application was filed. The test for satisfying the best mode requirement is subjective, as it depends entirely on what was in the inventor's mind at the time of filing the application, regardless of the knowledge or skill level [11].

The early development of microarray technology led the leaders in the market to compete amongst themselves in establishing their respective IP space. In order to understand to what extent these companies' patent portfolios cover, one needs to look at the legal requirements for obtaining a patent. Generally in order for an invention to be considered patentable in the US, it must meet the requirements of 35 United States Code (USC) Sections 101, 102 and 103. In Europe, the requirements stated in European Patent Convention (EPC) Articles 52, 54 and 56. 35 USC Section 101 and EPC Article 52 require that an invention be new and useful. Section 102 and Article 54 require that it must be novel. Section 103 and Article 56 refer to the requirement that an invention must be non-obvious, which means that differences between the subject matter sought to be patented and prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art. Further, in order for an issued patent to be valid, the inventor must describe the invention so that a person of ordinary skill in the art can make or use it as required by 35 USC. Section 112, paragraph 1. The invention must also be described in certain and definite terms under Article 35 USC Section 112, paragraph 2. Under EPC Article 83, a patent application must disclose the invention in a sufficiently clear manner, allowing it to be reproduced by a person skilled in the art.

Microarray patents issued and their enforcement

DNA analysis methods are inherently ligand assays that rely on the binding of target molecules to a specific recognition reagent. DNA analysis techniques thus frequently employ approaches historically exploited in an immunoassay context [12]. Two approaches employed in immunoassays are competitive (reagent limited) and immunometric (reagent excess). The basic principle of a competitive immunoassay is that a constant amount of labeled antigen competes with the unlabeled antigen in a specimen (serum, plasma or cell lysate) for a limited number of antibody binding sites. The amount of labeled antigen bound to the antibody is thus inversely proportional to the amount of unlabeled antigen in the specimen. The immunometric assay such as a 'two-site' sandwich assay is based on the formation of a sandwich complex between the capture antibody, the antigen and the labeled antibody. The capture antibody and the labeled antibody bind two distinct epitopes on the antigen. The amount of labeled antibody bound to the antigen is thus directly proportional to the concentration of the antigen in the specimen. The 'ambient analyte immunoassay' pioneered by Ekins and colleagues, has been utilized in the development of multi-analyte immunoassays, enabling the multiplexing of hundreds of analytes from a single specimen [13]. In 1989, Ekins described a ratiometric immunoassay utilizing antibodies conjugated to two separate fluorescent dyes. Immunoassays have relied on antibodies attached to solid supports, an analogous approach being later applied to DNA measurement. Microarrays were initially developed for immunodiagnostic purposes because immunoassay constituted a methodology of unique biomedical importance in the 1980s.

In this same year that Ekins published his seminal paper, Abbott Laboratories was issued a

patent describing a system that precisely microdispenses chemical reagents in defined regions for the purposes of developing chemical diagnostic assays [101]. However, it was not until the early 1990s that the first patents covering DNA microarrays were issued. Hyseq (Sunnyvale, CA, USA), Affymetrix (Affymax) (Santa Clara, CA, USA), Oxford Gene Technologies (Oxford, UK) and Stanford University (CA, USA) received patents that covered microarray manufacturing, experimental processing and genomic profiling. Difficulties in understanding the extent of these various patents led to a series of infringement lawsuits, as these parties sought to define their IP space.

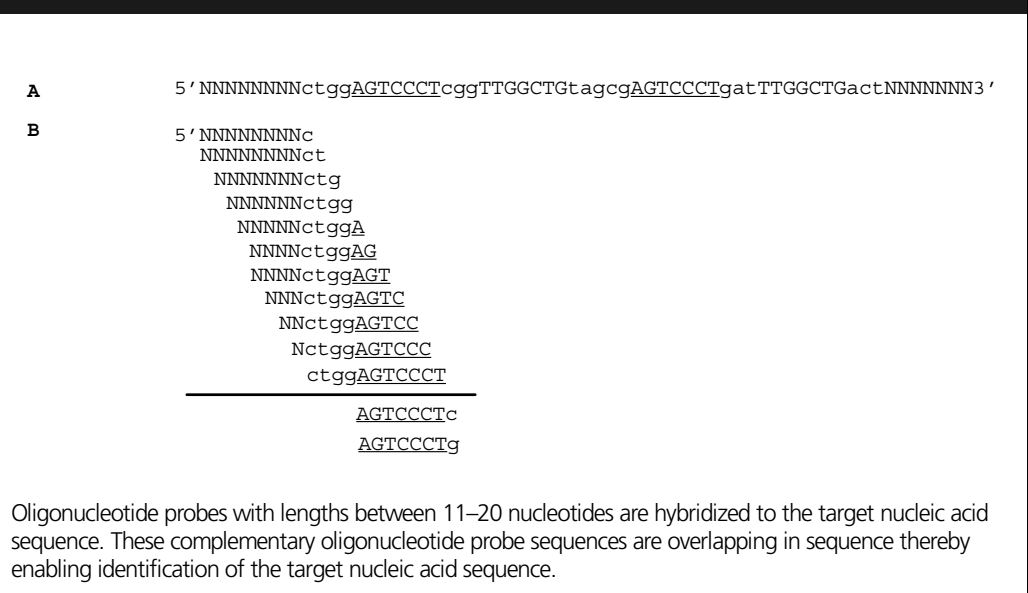
Hyseq and Affymetrix

Hyseq issued patents US5202231, US5695940 and US5525464; these patents issued over a 4-year period cover a method of sequencing DNA by hybridization on an array [102-104]. This method involves using oligonucleotide probes with lengths between 11–20 nucleotides that are hybridized to the target nucleic acid sequence. These complementary oligonucleotide probe sequences are overlapping in sequence thereby enabling identification of the target nucleic acid sequence. A graphical schematic of this process is illustrated in Figure 1. This method can discriminate perfect hybrids from hybrids containing a single nucleotide mismatch thereby enabling accurate DNA sequencing in a high-throughput array format [14,105,106].

Affymetrix issued many early patents regarding the microarray manufacturing process. Patents US5445934, US5744305 and US5677195 claim methods of manufacturing polymers on solid supports using light-directed spatially parallel chemical synthesis [107,108]. These manufacturing techniques utilize Very Large Scale Immobilized Polymer Synthesis (VLSIPS™) substrate technologies that can be applied for the synthesis of peptides and oligonucleotides on solid supports. The manufacturing process utilizes photoremoveable groups attached to solid supports. Upon exposure to light, selected areas become activated and permissible to attachment to monomers such as nucleotides and amino acids. A generalized illustration of the process is described in Figure 2. Patent US5744305 relates to arrays of polynucleotides at densities > 400 polynucleotides/cm².

Affymetrix also issued patents regarding the array experimental applications and analysis [107-112]. US5800992 and US5871928 claim differ-

Figure 1. Method of sequencing DNA by hybridization on an array.



ent applications for which arrays are used. These applications include DNA sequencing, DNA fingerprinting, chromosomal mapping and specific interaction screening. The US5800992 patent claims analyzing two different samples simultaneously using different fluorescent colors. US5795716 claims a computer system that identifies unknown sequences by analyzing the fluorescent intensities of hybridized nucleic acid probes. It also claims using a set of match and mismatch oligonucleotide probes to determine the identification of a given sequence. In addition, this patent describes a means of analyzing the image of the hybridized chip to identify sample sequences [110].

In March 1997, Hyseq filed a lawsuit against Affymetrix for infringement of Hyseq's US5202231 and US5525464 patents, and in December 1997, Hyseq filed another lawsuit for infringement of US5695940. Affymetrix responded to these claims, stating that the US5795716 patent represented a novel technique because it employed a set of matched and mismatched oligonucleotide probes to identify DNA sequences whereas the Hyseq technology utilizes overlapping perfectly matched probes. Additionally, Affymetrix alleged that Hyseq infringed on the US5744305 patent regarding array densities greater than 400 polynucleotides/cm².

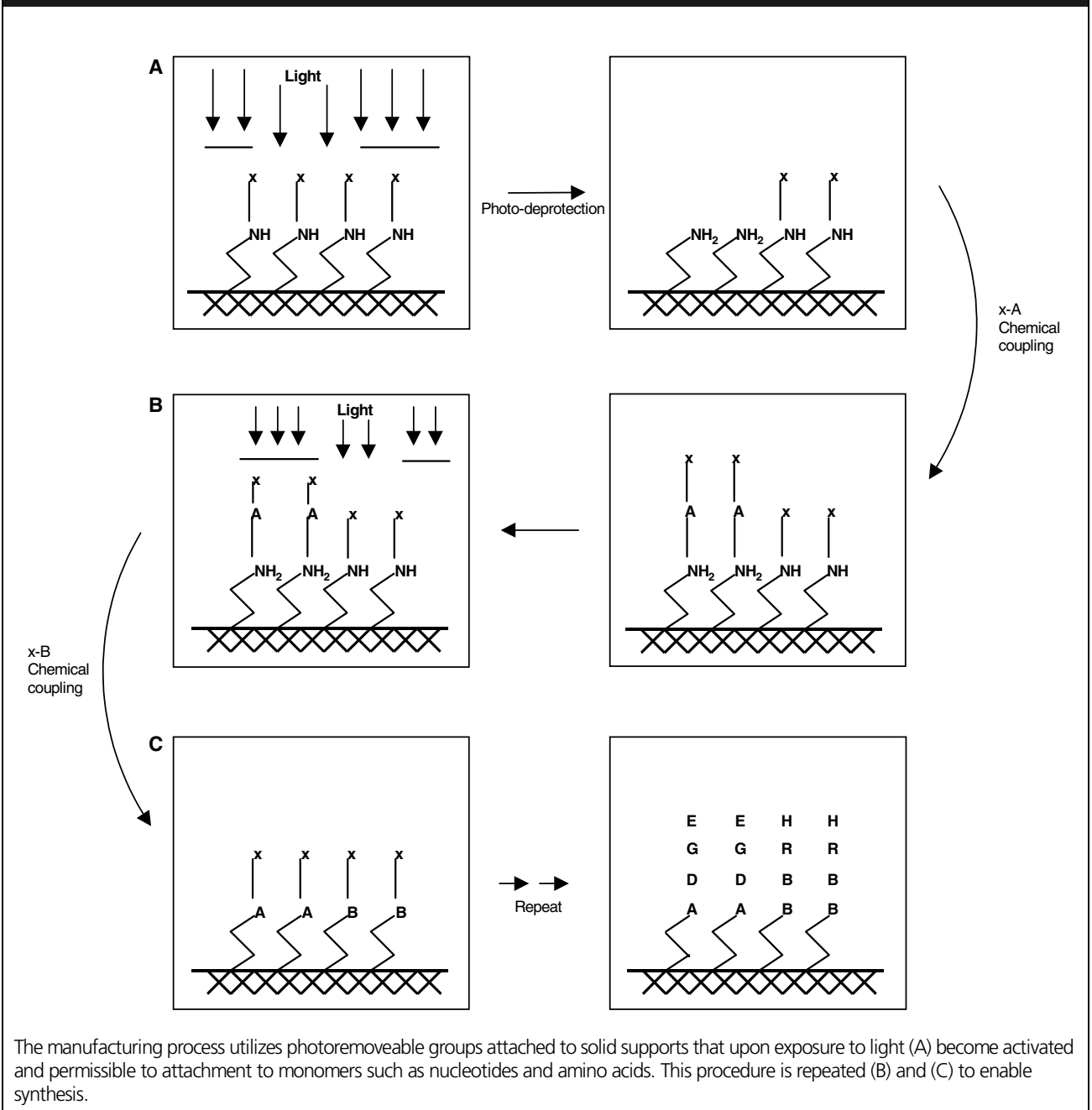
In January 2001, the US District Court of the Northern District of California issued a Markman ruling, which is used to provide clarity to disputed patent claims. This ruling established

that Affymetrix patents US5795716 and US5744305 were valid and rejected all of Hyseq's arguments regarding infringement by Affymetrix. Affymetrix and Hyseq arranged a settlement in October 2001 that dismissed all pending lawsuits and established universal acknowledgment of the validity of both companies' patents. As a result, Affymetrix gained access to a commercial license of Hyseq's array related technologies, and Hyseq gained access to an internal use license of Affymetrix technology for its pharmaceutical business. Both companies also formed a collaborative venture known as Nmer, Inc. to develop the sequencing by hybridization applications using both Hyseq's and Affymetrix's technologies.

Oxford Gene Technologies and Affymetrix

Oxford Gene Technologies (OGT) (Oxford, UK), a company established by Edwin Southern, issued two fundamental patents regarding the manufacture and use of DNA microarrays, US5700637 and US6054270 [113,114]. Southern is globally recognized for his key insight over 25 years ago that labeled nucleic acid molecules can be used to interrogate genetic material, to determine DNA sequences. Both the US5700637 and US6054270 patents claim using a solid support, such as a glass plate or film, containing an array of oligonucleotides to identify DNA sequences, under hybridization conditions where discriminations can be made between matched and mismatched oligonucleotide probes. The US5700637 patent claims the

Figure 2. Light-directed spatially parallel chemical synthesis for the synthesis of peptides and oligonucleotides on solid supports.



The manufacturing process utilizes photoremoveable groups attached to solid supports that upon exposure to light (A) become activated and permissible to attachment to monomers such as nucleotides and amino acids. This procedure is repeated (B) and (C) to enable synthesis.

synthesis of oligonucleotide arrays *in situ* whereas the US6054270 patent covers attaching synthesized oligonucleotides to solid supports.

Litigation proceedings between OGT and Affymetrix began on June 4, 1999, when OGT filed against Affymetrix for infringement of the US5700637 patent. At issue was whether Affymetrix secured a valid license to use the patent. In 1991, OGT (then Isis Innovations) issued an exclusive license to Beckman Coulter

to commercialize Southern's technology [15]. The provisions of this agreement included that the license could be shared if Beckman Coulter entered a consortium with a collaborator. Alternatively the license could be transferred if Beckman Coulter sold the part of the company that was developing this technology. In May 1998, Affymetrix attempted to acquire Southern's license by entering into a consortium with Beckman Coulter to commercialize the technology,

and in July 1999 they entered into an agreement with Beckman Coulter to purchase the patent license. The Court of Appeals in the UK ruled in November 2000 that Affymetrix possessed a valid license to the OGT microarray technology when it purchased Beckman Coulter's microarray business. A separate OGT lawsuit at the High Court in the UK for revocation of Affymetrix EP 619,321 patent, which also included density claims, was settled in March 2001 and Affymetrix agreed to license OGT's technology.

In December 2002, OGT initiated litigation proceedings against several companies, including Nanogen (San Diego, CA, USA), BD Biosciences Clontech (Palo Alto, CA, USA), Genomic Solutions (Ann Arbor, MI, USA), Perkin Elmer (Boston, MA, USA), Axon Instruments, Inc. (Union City, CA, USA) and Biodiscovery (Marina Del Rey, CA, USA) for infringement of the US6054270 patent. Currently, several parties are challenging the validity of the US5700637 patent at the EPO. Thus, the lawsuits for the most basic filings are not settled completely.

Incyte versus Affymetrix

Spotted microarrays represent an important format of this technology. This system was developed by Patrick Brown and colleagues at Stanford University, CA, USA and is claimed in the US5807522 and US6110426 patents [115,116]. This method involves dispensing a known volume at each selected array position by tapping a capillary dispenser on a support in order to deposit a defined volume of liquid. An illustration of the process is depicted in Figure 3. This patent also claims an automated apparatus for forming a microarray. The US5807522 patent demonstrates the manufacture of arrays consisting of genomic DNA fragments and cDNAs in addition to multiplexed colorimetric hybridizations. Synteni, founded in 1994, initially commercialized this technology until it became the microarray division of Incyte when it was acquired in 1997. Incyte acquired from Stanford University the patents that cover basic methodologies of preparing samples for hybridization experiments. Patents US5716785 and US5891636 claim methods of amplifying RNA from cDNA where cDNA synthesis is primed with a promoter sequence that initiates transcription fused with an oligo dT sequence [117,118]. This technique has greatly improved the sensitivity of microarray experimentation, allowing expression profiling with very small amounts

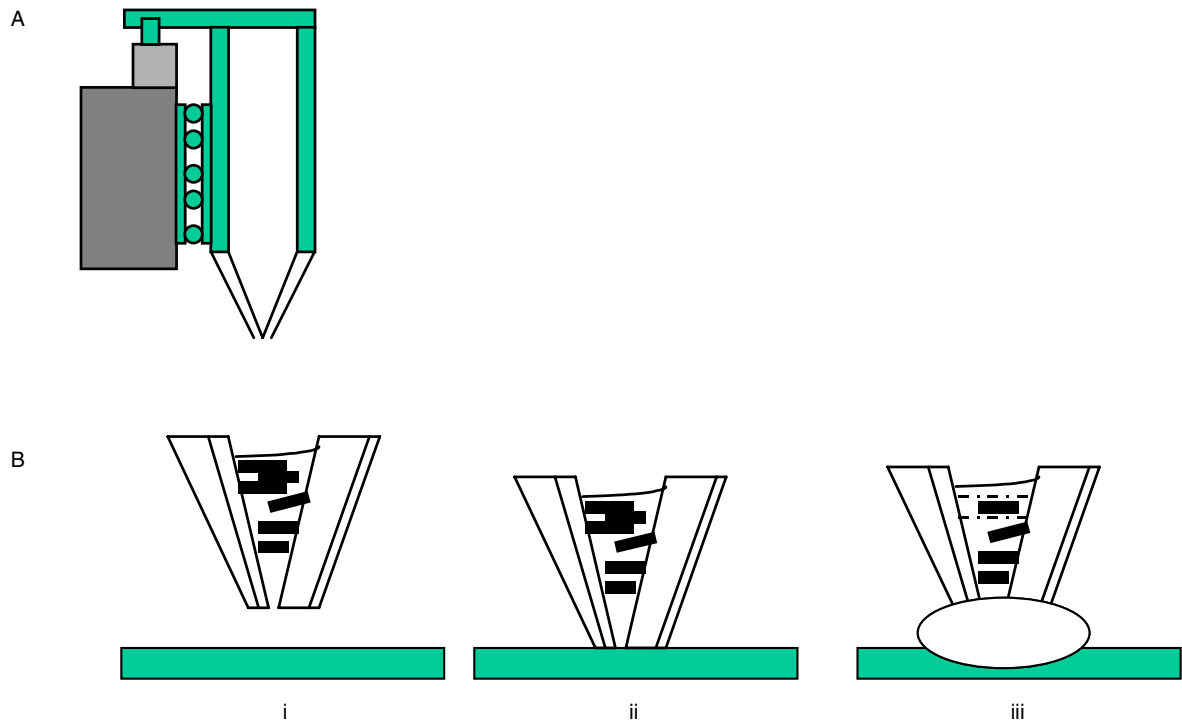
of RNA, such as that typically available from tissue biopsy and laser-capture material.

Affymetrix filed a lawsuit on January 6 1998 against Incyte for infringement of the US5445934 patent, on the basis that this patent covers arrays of 1000 or more oligonucleotides in a square centimeter. Regarding this patent, Incyte argued that the patent described the word 'oligonucleotides' to mean single-stranded polymers synthesized monomer by monomer [16]. Affymetrix contended that oligonucleotides mean small polymeric stretches of nucleotides ranging from 2 to ~100 nucleotides. The 9th Circuit District Court eventually rejected Incyte's argument by looking at the plain definition of oligonucleotides, which is small polymers of nucleotides. The court held that Incyte's interpretation of the word oligonucleotide is unconventional and that Incyte failed to support any portion of the specification or prosecution as evidence to show that the patentee intended the word oligonucleotide to have this unconventional meaning.

The issue regarding the interpretation of the phrase 'discrete known regions' was also a topic in this litigation. Incyte argued that this meant a localized area on a surface intended to be activated for synthesis of a polymer. Affymetrix articulated this to mean a localized area intended to be 'activated for formation of a polymer'. The patentee went further to state that formation encompasses both synthesis on a surface and immobilization of pre-existing polymers on the surface. Affymetrix's definition was problematic because in the patent there was no explicit definition for the term, 'activated'. The court used the patent's specification to determine that this word means an energy source adapted to cause a chemical group active for polymer formation. Further, the court also found that 'formation' means immobilization of polymers and therefore rejected Incyte's contention that 'discrete known regions' should be limited to what was described in the patentee's specification.

At the time of the initiation of this lawsuit, Incyte/Synteni were engaged in an interference proceeding to invalidate the US5744305 and US5800992 patents. In the US5744305 patent, Affymetrix in one of its claims replaced the word 'oligonucleotides' with the word 'polynucleotides' which was intended to mean a polymer of nucleotides of length two or more. Incyte argued that 'polynucleotides' means a strand of DNA that is generally naturally-occurring and longer than an oligonucleotide. The court rejected

Figure 3. Microarray printing.



Microarray printing involves dispensing a known volume at each selected array position by tapping a capillary dispenser (A) on a support to deposit a defined volume of liquid. (B) depicts the process of (i) pre contact, (ii) contact with the solid support and (iii) spot formation.

Incyte's assertion by using the plain meaning of the word polynucleotide that encompasses short oligonucleotides as well as longer stretches of DNA.

The US5800992 patent concerns the usage of adding mixtures of nucleic acids derived from two different cell types with different labels into an array in order to measure differential gene expression. In September 1998, Affymetrix sued Incyte for infringement of this patent. Incyte argued that this patent did not cover using cDNA as a means to measure differential expression since cDNA is made outside the cell, and the patent is limited to using nucleic acids from the cell. The court agreed with this argument. This was an important ruling since nucleic acids are generally converted into cDNA before microarray processing. In August 2000, Incyte sued Affymetrix for infringement of the US5716785 and US5891636 patents regarding the Eberwine sample preparation technique for microarrays that use the cDNA synthesis technique.

In December 2001, the companies settled all pending litigation and each agreed to certain

non-exclusive, royalty-bearing licenses and internal use licenses under their respective IP portfolios. Affymetrix paid Incyte US\$4.5 million for use of the RNA amplification technology covered by the US5716785 and US5891636 patents. This settlement does not include Incyte's appeal to the Board of Patent Appeals and Interferences regarding the interferences with Affymetrix's US5744305 and US5800992 patents which are still pending.

Incyte used the enabling requirement under Section 112 to argue that no infringement had occurred of the US5445934, US5744305 and US5800992 patents because these patents failed to demonstrate methods for manufacturing cDNA arrays. This is possibly why Affymetrix was unable to establish that Incyte was liable for infringement, although this issue was not actually decided in a courtroom as the parties opted to settle their litigation. Incyte has continued to enforce the US5807522 patent for methods of manufacturing cDNA arrays, and in November 2001, the company filed a lawsuit against Invitrogen (Carlsbad, CA, USA) for infringement of

this patent as well as the US5716785 and US5891636 sample preparation patents. In 2002, Incyte terminated their microarray business, selling all of their microarray technology assets to Quark Biotech (Cleveland, OH, USA). However, Affymetrix is recognized as the patent holder for microarrays printed at various densities. Affymetrix has reported in its press releases that NEN Life Science Products, MWG-Biotech AG and Genomic Solutions are three of 25 companies that have obtained a license to make and use spotted microarrays.

In the case of Genomic Solutions, securing a license from Affymetrix to manufacture spotted microarrays did not protect the company from potential liability. OGT sued the company for infringement of the US6054270 patent for spotting synthesized oligonucleotides on arrays. Thus, in order to understand which companies to secure licenses from, it is very important to examine the patents granted and ensure that the specifications include all of the methods covering the type of technology that will be utilized.

Outlook – microarrays and the future

The boundaries of IP space will be continually challenged as this technology progresses. Many different approaches to manufacturing and processing samples using microarrays are being developed. Standard phosphoramidite DNA oligonucleotide synthesis has been performed *in situ* using an inkjet printing method [8]. Combimatrix (Mukilteo, WA, USA) have established a solid-phase oligonucleotide synthesis system using a method that electrochemically places monomers at specific locations on substrates [119]. Alternatives to conventional photolithography with chromium masks are evolving [17]. One alternative to photolithographic masks for *in situ* oligonucleotide synthesis is the use of a digital micromirror device (DMD or DLP) which is employed within the technologies of Nimblegen (Madison, WI, USA), Febit (Mannheim, Germany) and Xeotron (Houston, TX, USA). Nimblegen have described a technology for a centralized production facility that can synthesize microarrays containing 195,000 features using a digital light processor that creates digital masks to synthesize specific polymers [17]. Whereas Nimblegen and Xeotron have used a conventional microscope slide as the reaction carrier, Febit has introduced an integrated benchtop instrument that generates microarrays within 3-dimensional microstructures (microchannels). Xeotron have recently switched from microscope slides to microstructures. Microarray apparatuses containing microfluidic structures are also being developed. Microfluidic-based systems have been established that detect hybridization events using electrochemical methods such as voltammetry, amperometry and conductivity, that will alleviate the need for target sample labeling [120]. Metragenix (Gaithersburg, MD, USA) have developed a Flow-Thru Chip™ four-dimensional microarray for high-throughput assays. Unlike conventional arrays the molecular interactions occur within the three-dimensional volumes of ordered microchannels rather than on two-dimensional flat surfaces. A fourth dimension is created by microchannels, which connect the upper and lower faces of the chip, allowing fluid to flow through the chip [18].

In addition to the evolving technical approaches of DNA microarray systems, new

Highlights

- Technological developments can be protected either in the form of a trade secret indefinitely or in the form of a patent where in exchange for exclusively utilizing the invention for 20 years details of the technology are comprehensively described to the public.
- In order to patent an invention it must be novel and useful and must not have been obvious 'to one of ordinary skill in the art'.
- DNA analysis methods are ligand assays that rely on the binding of target molecules to a specific recognition reagent.
- Difficulties in understanding the extent of various microarray patents led to a series of infringement lawsuits. The lawsuits for the most basic filings are not settled completely.
- Hyseq issued patents covering a method of sequencing DNA by hybridization on an array. This method involves using oligonucleotide probes with lengths between 11 and 20 nucleotides that are hybridized to the target nucleic acid sequence.
- Affymetrix issued many early patents regarding methods of manufacturing polymers on solid supports using light-directed spatially parallel chemical synthesis. These manufacturing techniques utilize Very Large Scale Immobilized Polymer Synthesis (VLSIPSTM) substrate technologies. Affymetrix also issued patents regarding DNA sequencing, DNA fingerprinting, chromosomal mapping and specific interaction screening.
- Oxford Gene Technologies issued two fundamental patents regarding the manufacture and use of DNA microarrays. They claim using a solid support such as a glass plate or film, containing an array of oligonucleotides to identify DNA sequences, under hybridization conditions where discriminations can be made between matched and mismatched oligonucleotide probes.

applications for microarrays are being developed. Microarrays are being employed as gene delivery vectors that transfect cell monolayers grown on the array surface [19]. Furthermore, tissue microarrays are enabling researchers to perform tissue analysis in a high-throughput, parallel manner [20]. Microarrays are currently poised to enter the clinical arena. Automated chip platforms permitting multiplexed assays such as the INFINITI™ System from Autogenomics (Carlsbad, CA, USA) will facilitate improved genetic testing [21]. Their emergence and success in the clinical laboratory will be

dependent on their ability to adapt to the rigorous environment of routine usage [3].

Expert opinion

The challenge for technology platform companies is to effectively establish and communicate the degree of their respective exclusivities in order to remain competitive in this continually developing market place. Close attention to detail regarding this IP space is very important in this highly competitive field. Utilizing professional consultation and resources is highly recommended when developing or working with this type of technology.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Weiner DM: Microarray technologies in target validation and drug discovery. In: *Microarray Methods and Applications – Nuts and Bolts*. DNA Press, Eagleville, PA, USA 131-140 (2003).
- **Review of the complexity of the drug discovery process and the role microarray technologies are playing.**
2. Chin KV, Kong AN: Application of DNA microarrays in pharmacogenomics and toxicogenomics. *Pharm. Res.* 12, 1773-1778 (2002).
- **This review discusses the molecular analysis of pharmaco- or toxicogenomic gene expression profiles following exposure to cancer chemotherapeutic and chemopreventive agents.**
3. Petricoin EF 3rd, Hackett JL, Lesko LJ *et al.*: Medical applications of microarray technologies: a regulatory science perspective. *Nat. Genet.* 32(Suppl.), 474-479 (2002).
4. Gerhold DL, Jensen RV, Gullans SR: Better therapeutics through microarrays. *Nat Genet.* 32(Suppl.), 547-551 (2002).
- **Realizing the potential of microarrays in the clinic is a challenge, as breakthroughs that show great promise at the bench often fail to meet the requirements of clinicians and regulatory scientists. This review explores the potential that microarrays hold for drug development, regulatory science, medical practice and public health.**
5. Chee M, Yang R, Hubbell E, Berno A *et al.*: Accessing genetic information with high-density DNA arrays. *Science* 274, 610-614 (1996).
6. Brown PO, Botstein D: Exploring the new world of the genome with DNA microarrays. *Nat. Genet.* 21(Suppl. 1) 33-37 (1999).
7. Ramakrishnan R, Dorris D, Lublinsky A *et al.*: An assessment of Motorola CodeLink™ microarray performance for gene expression profiling applications. *Nucleic Acids Res.* 30, E30-0 (2002).
8. Hughes TR, Mao M, Jones AR *et al.*: Expression profiling using microarrays fabricated by an ink-jet oligonucleotide synthesizer. *Nat. Biotech.* 4, 342-347 (2001).
9. Hardiman G: Microarray technologies 2003 – an overview. *Pharmacogenomics* 4, 251-256 (2003).
10. Beck S: Do you have a license? Products licensed for PCR in research applications. *Scientist* 12, 21 (1998).
11. Warburg RJ, Wellman A, Buck TB, Ligler Schoenhard A: Patentability and maximum protection of intellectual property in proteomics and genomics. *Pharmacogenomics* 4(1), 81-90 (2003).
- **Increasing numbers of patents are invalidated, and there is a rise in the number of exceptions to patent infringement. This is whittling away the value of new biotechnology patents. This review explores patent issues in the proteomics and genomics arena.**
12. Ekins R, Chu FW: Microarrays: their origins and applications. *Trends Biotech.* 17, 217-218 (1999).
13. Ekins RP: Multi-analyte immunoassay. *J. Pharm. Biomed. Anal.* 7, 155-168 (1989).
- **The concept of ‘multi-analyte’ immunoassay systems, enabling the simultaneous measurement of tens or even hundreds of substances simultaneously in the same small sample is explored in detail.**
14. Wallace RB, Shaffer J, Murphy RF, Bonner J, Hirose T, Itakura K: Hybridization of synthetic oligodeoxyribonucleotides to phi chi 174 DNA: the effect of single base pair mismatch. *Nucleic Acids Res.* 6, 3543-3557 (1979).
- **This paper explores the decrease in thermal stability which results from a single base mismatch. It is therefore possible to eliminate the formation of mismatched duplexes by choosing an appropriate hybridization temperature. These results are discussed with respect to the use of oligonucleotides as probes for the isolation of specific cloned DNA sequences.**
15. Robertson D: Affymetrix license valid, rules court. *Nat. Biotech.* 19, 13-14 (2001).
16. Hong C: The Microarray Battle. *Germeshausen Center Newsletter* 5-6 (2001).
17. Nuwaysir EF, Huang W, Albert TJ *et al.*: Gene expression analysis using oligonucleotide arrays produced by maskless photolithography. *Genome Res.* 12, 1749-1755 (2002).
- **Microarrays containing 195,000 *in situ* synthesized oligonucleotide features have been created using a benchtop, maskless photolithographic instrument by NimbleGen Systems. This instrument, the Maskless Array Synthesizer (MAS), uses a digital light processor (DLP) to create the patterns of UV light used in the light-directed synthesis of oligonucleotides.**
18. Cheek BJ, Steel AB, Torres MP, Yu YY, Yang H: Chemiluminescence detection for hybridization assays on the flow-thru chip, a three-dimensional microchannel biochip. *Anal. Chem.* 1573, 5777-5783 (2001).
19. Ziauddin J, Sabatini DM: Microarrays of cells expressing defined cDNAs. *Nature* 3(411), 107-110 (2001).

- **By printing sets of complementary DNAs cloned in expression vectors, the authors created microarrays whose features are clusters of live cells that express a defined cDNA at each location.**
20. Kononen J, Bubendorf L, Kallioniemi A *et al.*: Tissue microarrays for high-throughput molecular profiling of tumor specimens. *Nat. Med.* 4(7), 844-847 (1998).
- **As many as 1000 cylindrical tissue biopsies from individual tumors can be distributed in a single tumor tissue microarray. Sections of the microarray provide targets for parallel *in situ* detection of DNA, RNA and protein targets in each specimen on the array.**
21. Mahant V, Kureshy F, Vairavan R, Hardiman G: The INFINITI™ system – an automated multiplexing microarray platform for clinical laboratories. *Microarray Methods and Applications – Nuts and Bolts*. DNA Press, Eagleville, PA, USA 325-338 (2003).
- **Description of a fully automated protein microarray platform facilitating the parallel analysis of a multitude of proteins with high specificity, sensitivity, reproducibility and sample-throughput.**
- ### Patents
101. Abbott Laboratories: US4877745 (1989).
102. Drmanac RT, Crkvenjakov RB: US5202231 (1993).
103. Hyseq, Inc.: US5695940 (1997).
104. Hyseq, Inc.: US5525464 (1996).
105. Hyseq, Inc.: US6018041 (2000).
106. Hyseq, Inc.: US5972619 (1999).
107. Affymax Technologies NV: US5445934 (1995).
108. Affymetrix, Inc.: US5744305 (1998).
109. Fodor SPA, Solas DW, Dower WJ: US5800992 (1998).
110. Chee MS: US5795716 (1998).
111. Affymetrix, Inc.: US6040193 (2000).
112. Fodor SPA, Solas DW, Dower WJ: US5871928 (1999).
113. Isis Innovation Ltd: US5700637 (1997).
114. Oxford Gene Technology Ltd: US605270 (2000).
115. The Board of Trustees of the Leland Stanford Junior University: US5807522 (1998).
116. The Board of Trustees of the Leland Stanford Junior University: US6110426 (2000).
117. The Board of Trustees of the Leland Stanford Junior University: US5716785 (1998).
118. The Board of Trustees of the Leland Stanford Junior University: US5891636 (1999).
119. Combimatrix Corp.: US6093302 (2000).
120. Beier M, Stahler CF: Methods and apparatuses for electronic determination of analytes. US0160427 (2002).