BRIEF FOR AMICUS CURIAE AFFYMETRIX, INC. IN SUPPORT OF APPELLEE

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

04-1465

IN RE DANE K. FISHER AND RAGHUNATH V. LALGUDI

Appeals from the United States Patent & Trademark Office, Board of Patent Appeals and Interferences, Application No. 09/619,643

Of Counsel:
John M. Conley
University of North Carolina School of Law
Van Hecke-Wettach Hall
100 Ridge Road, CB #3380
Chapel Hill, NC 27599-3380
Telephone: (919) 962-8502

George C. Yu (Counsel of Record)
Michael J. Malecek
Daniel R. Reed
Andrea Gross
Affymetrix, Inc.
6550 Vallejo Street, Suite 100
Emeryville, California 94608
Telephone: (510) 428-8500

Attorneys for *Amicus Curiae* Affymetrix, Inc.

December 14, 2004

BRIEF FOR AMICUS CURIAE AFFYMETRIX, INC. IN SUPPORT OF APPELLEE

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

04-1465

IN RE DANE K. FISHER AND RAGHUNATH V. LALGUDI

Appeals from the United States Patent & Trademark Office, Board of Patent Appeals and Interferences, Application No. 09/619,643

Of Counsel:
John M. Conley
University of North Carolina School of Law
Van Hecke-Wettach Hall
100 Ridge Road, CB #3380
Chapel Hill, NC 27599-3380
Telephone: (919) 962-8502

George C. Yu (Counsel of Record)
Michael J. Malecek
Daniel R. Reed
Andrea Gross
Affymetrix, Inc.
6550 Vallejo Street, Suite 100
Emeryville, California 94608
Telephone: (510) 428-8500

Attorneys for *Amicus Curiae* Affymetrix, Inc.

December 14, 2004

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

Cases

Other

INTEREST OF AMICUS CURIAE

Founded in 1993, Affymetrix is the worldwide leader in providing commercial DNA microarrays to the scientific research community. Customers use Affymetrix's GeneChip® technologies for two central applications: gene expression monitoring and DNA variation detection. Affymetrix and its customers and collaborators develop clinical applications of GeneChip technologies for diagnosing and treating disease. Because of the ability the GeneChip technology provides for studying complex biological systems, over 1,000 peer-reviewed publications in 2003 alone cited GeneChip technology. Thus, Affymetrix is in a unique position to address Appellants' arguments relating to the utility of the claimed expressed sequence tags in a microarray.[1]

SUMMARY OF ARGUMENT

The claimed expressed sequence tags (ESTs) lack the specific and substantial utility required by controlling precedent to be patentable. Appellants do not describe a function for the claimed ESTs. Rather, they only indicate some ways the ESTs could be *used* without demonstrating their *usefulness*. The claimed ESTs are analogous to a chemical intermediate of a final product with no known function—a composition of matter that does not have patentable utility under the controlling precedent. Any nucleic acid sequence that does not have a known function, whether it is an EST or full-

[1] Affymetrix has obtained consent from the parties to file this brief of *amicus curiae*. Counsel for a party did not author this brief in whole or in part. No person or entity other than the *amicus curiae*, its employees, or its counsel made a monetary contribution to the preparation and submission of this brief.

length RNA molecule, does not have patentable utility. To allow patenting of ESTs will only inhibit further research into the function, if any, of the ESTs.

In addition, as products of nature, the claimed ESTs are not patentable subject matter. The claimed nucleic acid sequences have not been subject to sufficient human action to acquire "markedly different characteristics" from their naturally-occurring counterparts. The only difference is that the claimed EST is removed from its natural environment. That trivial difference is insufficient to render the claimed ESTs patentable subject matter.

ARGUMENT

I. INTRODUCTION

Appellants in the application at issue describe no function, nor any *specific* use, for the claimed nucleic acid sequences. The claimed nucleic acid sequences having no known function (hereinafter, "ESTs") are only fragments—usually 150 to 450 bases in length according to Appellants—from longer RNA sequences. These ESTs may not even be fragments of full-length RNAs that encode proteins or have known functions. Rather, the claimed nucleic acid sequences serve only as objects of further research. A nucleic acid sequence that lacks a known function, whether it is a full-length molecule or an EST, fails the requirement that an invention have a specific and substantial utility and therefore is not patentable.

Amicus curiae, Affymetrix, Inc., disagrees with Appellants' assertion that an EST must be "a fragment of the protein-coding portion of an expressed gene." (App. Corrected Open. Br. at 8.) The scientific literature

indicates that many DNA sequences that are transcribed into RNA do not encode a protein at all. Thus, Appellants cannot even claim correlation between the expression levels of the claimed ESTs with the expression of a protein. The claimed ESTs are essentially an intermediate for a full-length nucleic acid sequence of unknown function and, under the controlling case law, lack patentable utility.

Affymetrix also addresses one of the arguments raised by Appellants: whether using an EST as a probe in a microarray represents a specific utility. Affymetrix will show, with reference to recent peer-reviewed research articles, that use of ESTs that do not have a known function in a nucleic acid microarray does not satisfy the standard for utility. An EST used as a probe in a microarray allows a researcher to begin to explore the function of that EST. Such an EST may contribute to a genetic profile for a given disease condition, or it may have nothing whatsoever to do with the condition of interest to the researcher. This situation contrasts with the use of well-characterized genes, where the expression level of the gene may be associated with a particular condition based on prior research.

Affymetrix also believes that the claim on appeal may be rejected as not directed to patentable subject matter under Section 101. The claimed ESTs are a product of nature. These nucleic acids do not have "markedly different characteristics from any found in nature" as required by the Supreme Court in *Chakrabarty*. *Diamond v. Chakrabarty,* 447 U.S. 303, 310 (1980). To grant Appellants the right to exclude others from using the claimed ESTs when they have not provided the public with a useful disclosure or changed a product of nature would only inhibit further

research. Affymetrix, therefore, respectfully urges affirmation of the decision below to reject Appellants' claim.

II. LEGAL REQUIREMENTS FOR UTILITY

A. A CHEMICAL WITHOUT A KNOWN FUNCTION DOES NOT SATISFY THE UTILITY REQUIREMENT

In *Brenner v. Manson*, 383 U.S. 519, 534-35 (1966), the Supreme Court held that a claimed chemical composition must have a "specific utility." *See also* Manual of Patent Examining Proc. ("MPEP") § 2107.1. The inventor claimed a process for producing a steroid (an organic chemical compound), but did not disclose a function for the steroid. The *Brenner* Court held that a chemical composition that was "useful only in the sense that it may be an object of scientific research" did not meet the specific utility requirement of Section 101. *Brenner*, 383 U.S. at 534. Addressing the claims at issue, the Court reasoned that "[s]uch a patent may confer power to block off whole areas of scientific development, without compensating benefit to the public." *Id.* (footnote omitted). Put another way, a patent "is not a reward for the search, but compensation for its successful conclusion." *Id.* at 536.

In 2001, the United States Patent and Trademark Office ("PTO") propagated a set of utility examination guidelines that require an invention have both a "specific utility" and a "substantial utility." *See* MPEP § 2107.01. To satisfy the specific utility requirement, a patent application must describe a use specific to the claimed subject matter as opposed to a use that would be applicable to the broad class of the invention. *Id.* To satisfy the substantial utility requirement, applicants must describe a "real

world" use without requiring further experimentation. *Id.* Appellants' claimed ESTs fail to satisfy either of these requirements.

B. A CHEMICAL INTERMEDIATE FOR A COMPOUND WITHOUT A KNOWN USE LACKS PATENTABLE UTILITY

Shortly after *Brenner*, the Court of Customs and Patent Appeals considered whether a novel chemical intermediate—a chemical composition used to make another chemical of unknown utility—was useful. *See Application of Joly*, 376 F.2d 906, 908 (C.C.P.A. 1967); *Application of Kirk*, 376 F.2d 936, 945 (C.C.P.A. 1967). As in *Brenner*, the appellants in these cases did not disclose a specific utility for each of the claimed chemical intermediates other than to make the final steroid product, which did not have a known use. *Joly*, 376 F.2d at 908; *Kirk*, 376 F.2d at 942. The *Kirk* appellants filed an affidavit from a Dr. Petrow stating that "one skilled in the art would be able to determine biological uses of the claimed compounds by routine tests." *Kirk*, 376 F.2d at 939. The CCPA disagreed, finding these assertions of utility too nebulous under the standard announced by *Brenner*:

> We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.

Kirk, 376 F.2d at 942. Thus, because the applicants in *Joly* and *Kirk* had failed to show a specific utility for their chemical intermediates, their claims were rejected as lacking utility.

C. THE ASSERTED USES FOR THE CLAIMED ESTs ARE NOT SUBSTANTIAL OR SPECIFIC

The application at issue does not provide a single *substantial* use for the claimed ESTs that is also *specific* to the claimed ESTs. In *Kirk,* the CCPA rejected the applicant's general assertions that the claimed chemical intermediate was "useful in research" as insufficient to warrant a finding of patentable utility. *Kirk,* 376 F.2d at 945. Similarly, the specification here describes expressing the claimed EST, for example, "in a sufficient amount and/or fashion to produce a desirable agronomic effect." (JA0037.) The application does not describe how much of the EST to use, how to use it, or even if there is a desirable agronomic effect associated with the EST. This description only invites others to perform research with the claimed EST. Such a speculative use fails to satisfy the requirement of a "substantial utility." *See Kirk*, 376 F.2d at 944-45; *see also* MPEP § 2107.01 (directing that, *e.g.*, "[a] method of treating an *unspecified* disease or condition" does not define a substantial utility) (emphasis added).

The general suggestions of potential uses of the claimed ESTs also fail to satisfy the specific utility requirement. *See Kirk*, 376 F.2d at 1124 (finding "nebulous expressions" of potential uses insufficient); *Brenner*, 383 U.S. at 535 (noting that use as "an object of scientific research" is insufficient). As discussed in the MPEP:

> A "specific utility" is *specific* to the subject matter claimed. This contrasts with a *general* utility that would

> be applicable to the broad class of the invention. . . . For example, indicating that a compound may be useful in treating unspecified disorders, or that a compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Similarly, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered *specific* in the absence of a specific DNA target.

MPEP § 2107.1 (emphasis in original). Appellants list a number of other possible "uses" for the claimed EST in the specification, such as determining the expression level of an mRNA or providing a source of primers. (App. Corrected Open. Br. at 12-21, 37-38.) Each of the potential uses apply just as well with any other cDNA isolated from maize, not just the claimed ESTs. One could just as easily use nucleic acids with other sequences from maize to determine the mRNA expression level of that nucleic acid or as a source of primers. The uses suggested by Appellants are too general to satisfy the specific utility requirement.

D. THE CLAIMED ESTs ARE FRAGMENTS OF FULL-LENGTH NUCLEIC ACIDS OF UNKNOWN FUNCTION

Like the chemical intermediates in *Joly* and *Kirk*, an EST is an intermediate on the path to a final product of an unknown function. An EST is by definition a fragment of a longer RNA sequence. The application describes "a method for obtaining full length genes using maize ESTs or complements thereof or fragments of either." (JA0041.) Appellants argue that an EST represents a "fragment of a [full-length] cDNA clone, and thus the protein-coding portion of an expressed gene." (App. Corrected Open. Br. at 8.) However, the scientific literature indicates that this assumption is

simply wrong and cannot provide a basis for finding the claimed ESTs patentably useful.

Prior to Appellants' filing of the application at issue, scientists found that many genes produce RNAs that do not code for proteins and have unknown functions. A 1999 article described a number of other noncoding RNAs, some having unknown functions. Sean R. Eddy, *Noncoding RNA Genes*, 9 CURRENT OPINION IN GENETICS & DEVELOPMENT 695, 695-696 (1999). According to the author, scientists often missed noncoding RNAs "because only protein-coding genes are expected." *Id.* at 696.

In another study with Arabidopsis (a plant commonly used for genetic research), scientists found that several ESTs corresponded to previously known noncoding RNAs of unknown function. Gustavo C. MacIntosh *et al.*, *Identification and Analysis of Arabidopsis Expressed Sequence Tags Characteristic of Non-Coding RNAs*, 127 PLANT PHYSIOLOGY 765, 768 (2001). Thus, just because the claimed ESTs were isolated from a cDNA library made from maize RNA, it does not follow that the ESTs are fragments of an mRNA encoding a protein. In other words, the EST may be a noncoding RNA of unknown function. The specification does not provide enough information to tell whether the Appellants derived the claimed ESTs from coding or noncoding RNAs.

If an EST is thought of as an intermediate to a full-length RNA, one cannot assume that the function of the full-length RNA is to encode a protein. As discussed in the scientific articles described above, the function of noncoding RNAs is not well understood and is the focus of significant research. Like the claimed chemical intermediates in *Joly* and *Kirk*, the

claimed EST is an intermediate to an RNA of unknown function, and thus does not possess patentable utility.

III. BY ITSELF, USE OF ESTs WITHOUT A KNOWN FUNCTION IN MICROARRAYS DOES NOT PROVIDE A PATENTABLE UTILITY

Using the claimed ESTs as probes on a DNA microarray does not represent a specific utility because any nucleic acid sequence could be used as a probe. Appellants argue that the claimed ESTs would be "useful to measure the level of mRNA in a sample through use of microarray technology. . . ." (JA0020-21; *see also* App. Corrected Open. Br. at 42.) To address this argument, Affymetrix will present some background on microarray technology and then discuss how Affymetrix's customers actually use Affymetrix microarrays to develop a genetic profile for a given phenotype, such as cancer. But the phenotype of interest may have nothing to do with the expression of the claimed ESTs—*i.e.*, the expression levels of the ESTs do not change significantly in the different states tested. Thus, the determining the relative expression level of the claimed ESTs is not a specific utility. The use of ESTs in a microarray is at best a general utility of any nucleic acid sequence and not specific to the claimed sequences.

A. AFFYMETRIX'S MICROARRAY TECHNOLOGY

The National Institute of Health defines a microarray as

> [a] tool used to sift through and analyze the information contained within a genome. A microarray consists of different nucleic acid probes that are chemically attached to a substrate, which can be a microchip, a glass slide or a microsphere-sized bead.

http://www.niehs.nih.gov/nct/glossary.htm. Prior to the commercialization of microarrays, it was difficult for a scientist to monitor the expression level of more than a few genes at once. Affymetrix's commercial microarrays currently can interrogate up to 54,000 different genetic sequences from an organism using 1.2 million different single-stranded nucleic acid sequences as probes, each probe being 25 bases in length.

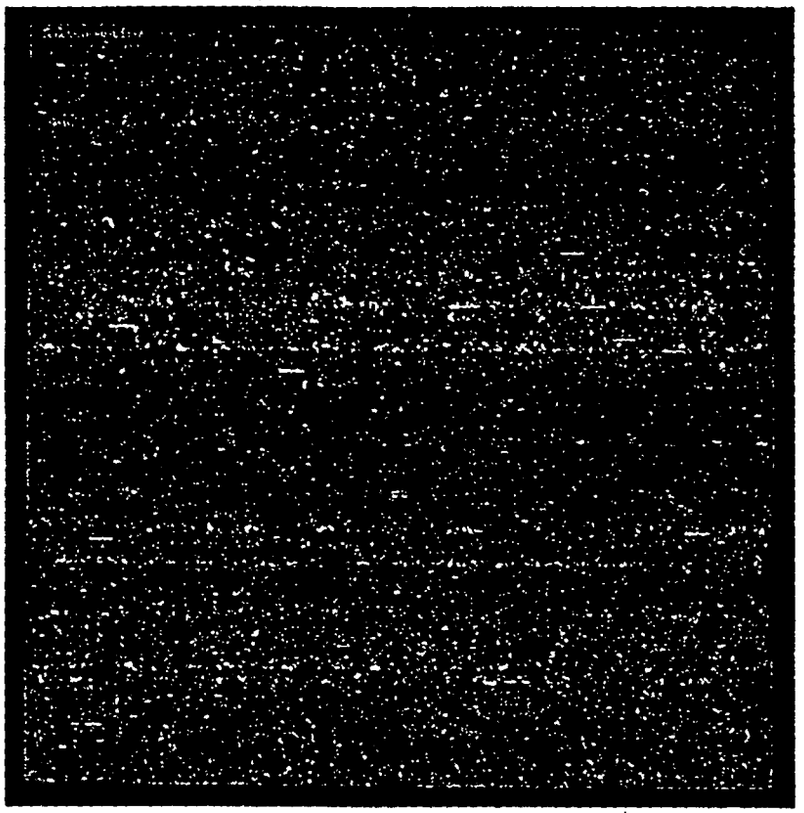
Affymetrix derives most of the probes on its catalog microarrays from the sequences of well-characterized genes, while other probes use the sequences of ESTs. Affymetrix obtains this sequence information from public sources, including "dbEST," the National Center for Biotechnology Information's EST database. *See* Technical Note: Design and Performance of the GeneChip Human Genome U133 Plus 2.0 and Human Genome U133A 2.0 Arrays at 2 (available at http://www.affymetrix.com/support/technical/technotes/hgu133_p2_technote.pdf); *see also* http://www.ncbi.nlm.nih.gov/dbEST/. Affymetrix seeks to provide the most comprehensive coverage of genetic sequences from a genome to satisfy its customers' various research interests.

For each genetic sequence represented on its microarrays, Affymetrix uses a set of 25-base probes distributed over the genetic sequence of interest. Each 25-base probe is chosen to be uniquely representative of a gene sequence. The use of different 25-base sequences from a well-characterized gene or EST provides multiple independent measurements of the expression of that gene or EST. By considering all the probes from a probe set together, the Affymetrix system provides a more statistically relevant analysis.

Sometimes, a research community studying a particular organism will work together with Affymetrix to design a microarray. The barley research

community met beginning in 1998 to design a microarray using sequences from databases containing 350,000 barley ESTs, as well as 1,145 well-characterized barley gene sequences. *See* Timothy J. Close *et al.*, *A New Resource for Cereal Genomics: 22K Barley GeneChip Comes of Age*, 134 PLANT PHYSIOLOGY 960-68 (2004). Ultimately, the Affymetrix barley microarray contained 22,792 probe sets and was released for public distribution in June 2003. The barley microarray will enable "functional analyses of complex pathways and gene families to be performed quickly with a high degree of precision." *Id.* at 966.

A user of an Affymetrix expression microarray typically prepares a test sample from cells or tissues by isolating the mRNA (the poly(A^+) RNA) and enzymatically converting it to cDNA. The cDNA is then amplified into RNA molecules ("cRNA") that are labeled with a tag to allow subsequent detection. The user then applies the cRNA to the microarray and allows it to hybridize to the probes on the array by base-pairing: A to T and C to G to form duplex molecules where the sequences are complementary. The duplexes are then labeled with a fluorescent marker, and the relative amount of hybridization is determined with a laser scanner. This is a scanned image from a human expression microarray (HG U133A) with the fluorescence intensity represented by pseudo-color:



Affymetrix software then analyzes the fluorescence signal from each probe of a probe set that relates to a particular genetic sequence, either a well-characterized gene or an EST, to provide a measure of the relative level of expression of that genetic sequence. Thus, in a single experiment using Affymetrix microarrays, a scientist can ascertain the relative expression level of thousands of well-characterized genes and ESTs at the same time.

However, without knowing the function of an EST, a scientist could only use the microarray to begin to explore the function of the EST. For example, elevated expression of an EST may be correlated to a particular cancer, but it is not diagnostic of the cancer because the elevated level of the EST could also be correlated with a number of other conditions, such as an autoimmune condition. Knowing the relative amount of that EST that a cell expresses is meaningless without some idea of the function of the gene from

which the EST is derived and how that function correlates with the phenotype of the cell. Thus, the use of an EST without a known function does not provide a specific utility under *Brenner*.

B. HOW SCIENTISTS USE AFFYMETRIX'S MICROARRAYS

Scientists have used Affymetrix microarrays to study the genetic basis for a number of diseases and other conditions. Typically, researchers compile a genetic profile or signature for a given condition based on a statistically significant set of microarray experiments. In other words, the experiments do not determine whether an increase or decrease in a particular well-characterized gene or EST is associated with a disease. But, instead, a pattern of thousands of genes and ESTs across the entire genome, expressed at different levels, correlates with a disease. Affymetrix reviews a few recent studies below.

1. Gene Expression Studies of Various Cancers

Researchers have used Affymetrix microarrays to develop genetic profiles relating to various cancers. Because cancers are often associated with changes in the expression level of many genes, Affymetrix microarrays offer scientists a valuable tool to study the expression of genes on a genome scale as opposed to a few genes at a time. The types of profiles researchers develop may compare gene expression in normal versus cancerous cells, in different types of cancers from the same type of tissue, or in treated versus untreated cancer cells. In the future, these genetic profiles may lead to improved diagnostics or treatments for the cancers.

In January 2004, a team from the University of Minnesota Medical School published their correlation of gene expression profiles with prognosis in head and neck cancer patients. *See, generally*, Matthew A. Ginos *et al.*, *Identification of a Gene Expression Signature Associated with Recurrent Disease in Squamous Cell Carcinoma of the Head and Neck*, 64 CANCER RESEARCH 55-63 (2004). The research team sought to determine whether they could develop genetic profiles for recurrent versus non-recurrent head and neck cancer so that patients with one type of cancer could receive the appropriate treatment. Using Affymetrix human genome microarrays, the authors identified a set of 80 genetic sequences that statistically correlated either with non-recurrent or recurrent head and neck cancers. *See id.* at 59 (Fig. 2). Of the 80 correlated genetic sequences, 78 sequences were from well-characterized genes, while two were from ESTs. *Id.* The scientists thus found two ESTs to be part of the genetic signature of a type of cancer, but did not have enough information to conclude that the expression level of the ESTs by ithemselves could be correlated to a type of cancer. Other ESTs on the Affymetrix microarray apparently had no association with head and neck cancer.

In another study, researcher investigating renal cancer asked whether the gene expression profile of certain white blood cells from cancer patients could be distinguished from those of normal volunteers. Natalie C. Twine *et al.*, *Disease-Associated Expression Profiles in Peripheral Blood Mononuclear Cells from Patients with Advanced Renal Cell Carcinoma*, 63 CANCER RESEARCH 6069-6075 (2003). The use of more accessible blood cells as a surrogate to diagnose a solid tumor would greatly increase the ability of clinicians to monitor the course of a cancer and responsiveness to

drug treatment. *See id.* at 6073 (right column). The authors found 132 sequences—including four ESTs—that had a significant increase in expression in the white blood cells from cancer patients compared to those from the normal volunteers. *Id.* at 6071-72 (Table 1). Other ESTs on the microarray apparently did not correlate with renal cancer. As with the head and neck cancer study, the authors did not have enough information from the ESTs alone on the Affymetrix array to determine a correlation with renal cancer.

2. Studies Relating to Caloric Restriction

"Caloric restriction," which means the consumption of fewer calories while avoiding malnutrition, has been found to slow the aging process and the development of age-related diseases. *See* Joseph M. Dhahbi *et al.*, *Temporal Linkage between the Phenotypic and Genomic Responses to Caloric Restriction*, 101 PROCEEDING OF THE NATIONAL ACADEMY OF SCIENCES (USA) 5524-29 (2004). The authors, using Affymetrix mouse genome microarrays, found that there was a correlation between changes in the expression pattern of certain nucleotide sequences, including several ESTs, and an extended lifespan in the caloric-restricted animals. *See id.* at 5526-28 (Tables 1-3). The expression of some of the ESTs increased in response to caloric restriction, while others decreased. *See id.* Other ESTs apparently had no correlation with caloric restriction.

These peer-reviewed articles show that scientists use microarrays to develop a genetic profile of a particular condition that includes the expression levels of well-characterized genes as well as of ESTs. The genetic profile, however, does not indicate what role or function the ESTs

have in the condition. Moreover, other ESTs on the microarray apparently had no connection with the condition of interest.

The expression level of the claimed ESTs may correlate with, for example, the plant's reaction to drought, or it may have nothing to do with that condition at all. The specification simply does not describe how the claimed ESTs may be specifically used. *See Kirk*, 376 F.2d at 941-42 (finding an *ex post facto* declaration as to a potential use irrelevant to the determination of whether the specification as filed disclosed a patentable utility). Merely stating that a nucleotide sequence could be used as a probe in a microarray is a general utility that does not distinguish that particular sequence from *any other sequence*. Using a nucleic acid sequence of unknown function as a probe on a microarray does not provide a specific utility for that sequence.

IV. THE CLAIMED ESTs SHOULD NOT BE PATENTABLE BECAUSE THEY ARE A "PRODUCT OF NATURE"

Alternatively, this Court may affirm the Board's rejection on Section 101 subject matter grounds. The Court may consider this issue even though it was not relied upon in the PTO. As Judge Gajarsa of this Court noted in a recent concurrence, "[t]he centrality of patentable subject matter to the entire scope of the patent law suggests that there are times when [*sua sponte*] inquiries are critical." *SmithKline Beecham Corp. v. Apotex Corp.*, 365 F. 3d 1306, 1321 (Fed. Cir. 2004) (Gajarsa, J., concurring). In that case, Judge Gajarsa concluded that the claim at issue was "invalid because it is broad enough to claim subject matter that is unpatentable under Section 101." *Id.* at 1325. So is the claim here, and for the same reason that

troubled Judge Gajarsa: violating the longstanding prohibition against patenting "products and processes of nature." *Id.* at 1330.

This prohibition has an ancient lineage, dating back at least to *Ex parte Latimer*, 1889 Comm'r Dec. 123 (1889), where the Commissioner of Patents rejected a claim on "a new article of manufacture . . . consisting of the cellular tissues of the Pinus australis [southern pine] eliminated in full lengths from the silicious, resinous, and pulpy parts of the pine needles and subdivided into long, pliant filaments adapted to be spun and woven." *Id.* In the initial rejection of the claim, the examiner emphasized the identity of the claimed substance and its natural counterpart: "The claim and description do not set forth any physical characteristics by which the fiber can be distinguished from other vegetable fibers. . . . Hence, since the fiber claimed is not, and cannot be, distinguished from other fibers by any physical characteristic, the claim therefor must be refused." *Id.* at 124. In affirming the rejection, the Commissioner wrote that the allowance of such a patent would make it "possible for an element or principle to be secured by patent," with the ultimate consequence that, "successively, patents might be obtained upon the trees of the forest and the plants of the earth." *Id.* at 125.

Early post-*Latimer* cases emphasized that a statutory invention must be clearly distinguishable from a naturally occurring precursor or counterpart. A striking example is the Third Circuit's 1928 decision in *General Electric Co. v. De Forest Radio Co.*, 28 F.2d 641 (3d Cir. 1928), a case that involved the development of tungsten wire, a major advance in the history of the electric light bulb. The patent in suit claimed "[s]ubstantially pure tungsten having ductility and high tensile strength." *Id.* at 642. The court of appeals stated the critical question pertaining to "the subject matter

of the patent" as follows: "Whether the tungsten of which the patent speaks is the tungsten of nature with its inherent quality of ductility or is a new metal produced by Coolidge [the inventor] which is wholly different from anything that nature provides." *Id.* The court relegated the claimed invention to the former, nonstatutory category because, even though Coolidge was the first to purify tungsten, and even though the pure version was not known to occur in nature,[2] the properties of the purified version did not differ materially from those of the natural precursor. *Id.* at 642-43. *See also In re Marden,* 47 F. 2d 957 (C.C.P.A. 1931) (rejecting on product of nature grounds claims drawn to ductile uranium and purified vanadium).[3]

The Supreme Court took up the product of nature doctrine twice during the twentieth century, in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), and *Diamond v. Chakrabarty,* 447 U.S. 303 (1980). *Funk,* which rejected a claim to a mixture of nitrogen-fixing root-nodule bacteria, stated the doctrine as follows: "[M]anifestations of laws of nature [are] free to all men and reserved exclusively to none. He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes." 333 U.S. at 130. The Court repeated this language in *Chakrabarty,* and characterized "laws of nature, physical phenomena, and abstract ideas" as being beyond the realm of

---

[2] This point was made in the district court opinion. *General Electric Co. v. De Forest Radio Co.*, 17 F.2d 90, 92 (D. Del. 1927).

[3] *Compare Merck & Co. v. Olin Mathieson Chemical Corp.*, 253 F.2d 156, 162, 116 U.S.P.Q. 484, 489 (4th Cir. 1958), in which the court allowed a patent on fermentation-derived B-12 compound because previously "there were no such B-12 active compositions," but noted that "the purification of a product is not a patentable advance, except, perhaps, as to the process, if the new product differs from the old 'merely in degree and not in kind.'"

section 101. 447 U.S. at 309. Chakrabarty's claim was deemed statutory because he had, through genetic engineering, "produced a new bacterium with markedly different characteristics from any found in nature." *Id.* at 310.

The subject matter question facing this Court is thus whether the claimed nucleic acid sequences have been subjected to sufficient human intervention to acquire "markedly different characteristics" from their naturally occurring counterparts. On the contrary, the interest in these sequences depends on their being functionally indistinguishable from their natural precursors. As the Deputy Director of the World Intellectual Property Organization has recently written, under *Chakrabarty,* "isolated, purified and synthesized human genes are not statutory patentable subject matter because, when isolated from the human body, they maintain identical or very similar characteristics to those found in nature . . . [and] because they realize exactly the same function that genes inserted in their natural environment perform." Nuno Pires de Carvalho, *The Problem of Gene Patents,* 3 WASH. U. GLOBAL STUD. L. REV. 701, 723 (2004) (footnotes omitted).

The rationale for this conclusion is that, even when claimed—unlike here—in "isolated, purified and synthesized form," a cDNA molecule differs from its natural counterpart only in trivial and functionally irrelevant ways. The only differences are that the DNA has been removed from its natural environment and that its noncoding regions have been excised. Consequently, despite nominal chemical distinctiveness, what is claimed is functionally indistinguishable from natural DNA and RNA. It contains exactly the same genetic information as its natural counterpart. It can do

precisely the same work as a naturally occurring gene—protein synthesis or perhaps some other function—and it employs precisely the same processes to do it, whether in the body or in the laboratory. Critically, these informational and functional properties are the whole reason for seeking DNA patents. In *Chakrabarty's* terms, such a gene does not have "markedly different characteristics from any found in nature." 447 U.S. at 310.

This conclusion applies *a fortiori* to the nucleic acid fragments at issue in this case. Appellants' claim is breathtakingly broad: "a substantially purified nucleic acid molecule that encodes a maize protein or fragment thereof comprising [one of five specified sequences]." "Substantially purified" requires only that the molecule be "separated from substantially all other molecules normally associated with it in its native state." (App. Corrected Open. Br. at 12 n. 11.) This is a minimal limitation at best, falling well short of the "isolated, purified, and synthesized" language that is typical of DNA claims. *See* John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents,* 85 J. PAT. & TRADEM. OFF. SOC'Y 301, 314-316 (2003) (Part I). Moreover, the term "nucleic acid" can encompass both DNA and RNA.[4] Finally, as the Board held, the claim encompasses not only the five specified sequences, but any others that can be formed by adding to them "preceding or trailing nucleotides, or other molecules." (JA0005.) Accordingly, allowing the claim could result in the

[4] The sequences referenced in the claim appear to be DNA rather than RNA, and the written description makes reference to cDNA. However, the claim language "nucleic acid" is not explicitly so limited anywhere in appellants' application.

monopolization of an unknowable number of nucleotide sequences whose function and distinctiveness from their natural counterparts are impossible even to predict.

For the foregoing reasons, Affymetrix urges this Court to affirm the Board's rejection on the additional Section 101 ground that the claimed molecules lack the "markedly different characteristics from any found in nature" that *Chakrabarty* and the predecessor cases require.

V. CONCLUSION

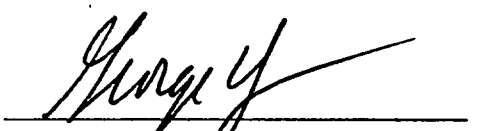
A microarray is a useful device that allows the simultaneous monitoring of thousands of genetic sequences, including well-characterized genes as well as ESTs of unknown function. However, associating the claimed EST with a useful device does not confer utility on the EST. To allow patenting of the claimed ESTs may inhibit further research that would lead to the determination of the function of the ESTs.

Moreover, the Court should find that the claimed ESTs are an unpatentable product of nature. The claimed EST has at best minor differences from the naturally occurring nucleic acid. The very reasons why the claimed ESTs might be useful at all depends on how the EST functions in the maize plant. Appellants have not subjected the claimed EST to sufficient human intervention to warrant a patent. For the foregoing reasons, Affymetrix requests that the Court affirm the Board's decision rejecting Appellants' claim for lack of utility under Section 101 and lack of

enablement under Section 112, first paragraph, or for not being patentable subject matter under Section 101.[5]

December 14, 2004

Respectfully Submitted,



George C. Yu
Attorney for *Amicus Curiae*
Affymetrix, Inc.

[5] If the Court requests, Affymetrix would be willing to participate in oral argument in this case.

FORM 9. Certificate of Interest

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

In re Dane K. Fisher and Raghunath V. Lalgudi

No. 04-1465

CERTIFICATE OF INTEREST

Counsel for the (petitioner) (appellant) (respondent) (appellee) (amicus) (name of party) amicus, Affymetrix, Inc., certifies the following (use "None" if applicable; use extra sheets if necessary):

1. The full name of every party or amicus represented by me is:

Affymetrix, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

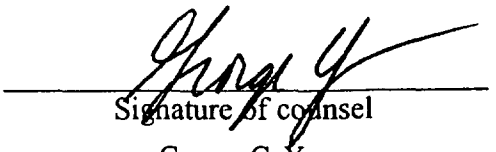
None

4. X There is no such corporation as listed in paragraph 3.

5. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

None

12/14/2004
Date


Signature of counsel

George C. Yu
Printed name of counsel

FORM 19. Certificate of Compliance With Rule 32(a)

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B).

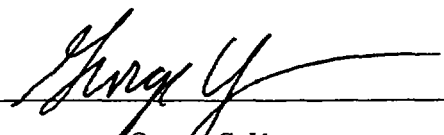
x The brief contains 5559 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii), or

☐ The brief uses a monospaced typeface and contains [*state the number of*] lines of text, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6).

x The brief has been prepared in a proportionally spaced typeface using Microsoft Word 2002 (10.2627.2625) in Times New Roman, 14 pt. font.

☐ The brief has been prepared in a monospaced typeface using [*state name and version of word processing program*] with [*state number of characters per inch and name of type style*].

(s) 

George C. Yu
(Name of Attorney)

Amicus Curiae, Affymetrix, Inc.
(State whether representing appellant, appellee, etc.)

12/14/2004
(Date)

IN THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

04-1465

IN RE DANE K. FISHER AND RAGHUNATH V. LALGUDI

Appeals from the United States Patent & Trademark Office, Board of Patent Appeals and Interferences, Application No. 09/619,643

CERTIFICATE OF SERVICE

I hereby certify that on this 14th day of December 2004, I served the foregoing BRIEF FOR AMICUS CURIAE AFFYMETRIX, INC. IN SUPPORT OF APPELLEE upon counsel by causing two copies to be delivered by Federal Express overnight courier to:

John M. Whelan
Solicitor
United State Patent and Trademark Office
Office of the Solicitor
Madison West, 08C43
600 Dulany Street
Alexandria, VA 22314
Telephone: (571) 272-9035
Counsel for Appellee

Seth P. Waxman
Wilmer Cutler Pickering
Hale & Dorr LLP
2445 M. Street, NW
Washington, DC 20037-1420
Telephone: (202) 663-6800
Counsel for Appellant

Alison Solari

Alison K. Solari
Litigation Paralegal
Affymetrix, Inc.