Comment 61 MJ Research, Incorporated / Michael Finney

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Subject: RE: Written comments on proposed guidelines

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SUBMISSION TO UNITED STATES PATENT AND TRADEMARK OFFICE
MARCH 22, 2000

SUBMISSION IN RESPONSE TO REVISED INTERIM GUIDELINES
FOR EXAMINATION OF PATENT APPLICATIONS UNDER THE 35 U.S.C. Sec, 112
ISSUED IN THE FEDERAL REGISTER 64 FR 71,427 ON DECEMBER 2l, l999

SUBMITTING PARTIES: This submission is made by and on behalf of MJ Research, Incorporated, Waltham MA 02451. Contact Michael Finney, Ph.D. mikef@mjr.com.

We respectfully submit that the United States Patent and Trademark Office (the "PTO") has erroneously interpreted the principles of the US Patent Laws by issuing (or by issuing the Revised Interim Guidelines that evidence an intention to issue) composition of matter patents on naturally-occurring nucleotide sequences or on cDNA or expressed sequence tag ("EST") derivatives of such sequences. We believe the proper interpretation and application of the Patent Laws should cause the PTO to issue only process or method patents on discoveries related to the use of DNA and/or genes, and then only where such discoveries identify clearly and fully a novel use. On the other hand, we believe that composition of matter patents should not be issued for any DNA, particularly human DNA, nor for any related cDNA, EST or other nucleotide sequences, because such compounds exist in nature, have been identified and placed in the public domain for over 15 years, or otherwise are obvious to derive in light of the current technology.

By issuing broad composition of matter patents with respect to a particular nucleotide sequence, without limiting the scope of such patent based on a strong and conclusive description of an important use or method, the PTO is likely to inflict a huge and irreparable harm on scientific research in the genomics field and to subvert the policies and purposes underlying the Patent Laws.

I. Composition of matter claims for human DNA, human genes or related cDNA should not be allowed because such compounds have been isolated and purified and have been in the public domain for over 1 year.

Human DNA, human genes, and derivative compositions based on these genes, whether cDNA, ESTs or other nucleotide sequences have been known to scientists skilled in the art of molecular biology for at least l5 years. Recently, high speed sequencing has become feasible

through technological advances, and therefore compounds that have long been isolated and purified by scientific researchers in the molecular biology field are now able to be identified and described by their specific nucleotide sequence. However, the mere fact that a long-existing and long-recognized compound can now be described based on its nucleotide sequence does not create a patentable invention.

To use a simple analogy, the compound called "water" has been known to humans since the beginning of time, but it was only in 1811 that Amedeo Avogadro first determined that water can be described and expressed by the chemical formula H_20. Identifying that water is comprised of two hydrogen atoms and one oxygen atom was a great advancement in scientific knowledge; it would be absurd, however, to take the position that Avogadro, upon making this discovery, was thereupon entitled to a patent on water. This is, however, what the PTO appears to be allowing when it purports to grant a patent on a known compound merely because that compound has now been analyzed and its nucleotide sequence identified.

The issue at stake is the absence of invention and novelty in the sequencing of a known compound. The US Supreme Court, in the landmark case of Diamond v. Chakrabarty 447 US 303, 308, (1980), drew a sharp distinction between a scientific discovery -- however ingenious or valuable it may be -- and an invention eligible for patent protection. In that case, the U.S. Supreme Court described Einstein's discovery of the Theory of Relativity and Sir Isaac Newton's discovery of the Law of Gravity as "manifestations of nature, free to all men and reserved exclusively to none." 447 US @309 (quoting Funk Brothers, 333 US @130). By contrast, looking at the facts before it in Chakrabarty, the Supreme Court held that a genetically altered living organism is patentable subject matter because it is "not a hitherto unknown natural phenomenon, but a non-naturally occurring manufacture or composition of matter ñ a product of human ingenuity 'having a distinctive name, character [and] use.'." -- 447 US @309, citing Hartranft v. Wiegmann, 121 U.S. 609 (1887). In Chakrabarty, the inventor introduced naturally occurring bacterial DNA into a living micro-organism, which in turn allowed that organism to break down crude oil. The U.S. Supreme Court held that the invention was "not nature's handiwork, but his own; accordingly it is patentable subject matter."

Sequencing of an existing human gene is no more of an invention that Avogadro's discovery of the chemical formula for water. We will demonstrate below that virtually every cDNA or genomic DNA compound that can be derived from humans is not novel because it has existed as an isolated and purified compound. The same argument can be made for various other scientifically and economically important species, but we will concentrate on human cDNA sequences for illustrative purposes.

By approximately 1985, long before the era of high-throughput sequencing, virtually all, if not all possible human cDNAs had been synthesized, isolated, and purified in the course of construction and screening of clone libraries. cDNA libraries are constructed by reverse transcription of mRNAs and ligation into a cloning vector. In a typical procedure such as was commonly performed in the 1970s and 1980s, DNA hybridization is used to select a few cDNA clones for analysis, from a library containing hundreds of thousands to tens of millions of independent clones. Construction of cDNA libraries dates to the 1970s; a procedure still in common use is that of Gubler and Hoffman (U. Gubler and B.J. Hoffman, Gene 25:263-269,

1983). Before any clones can be selected by hybridization, all clones in the library must be isolated and purified. Clones are typically isolated by transformation into bacteria (for clones using plasmid vectors) or infection of bacteria (for clones using phage vectors). These procedures typically generate multiple petri dishes containing large numbers (approximately 10^4) of isolated, independent colonies or plaques per 10 cm dish. Each of these colonies or plaques contains a single isolated, independent cDNA clone.

In order to select a single colony or plaque by hybridization, DNA must be purified from each isolated colony or plaque without mixing them together. DNA purification has long been performed by the methods of Grunstein (M. Grunstein and D. Hogness, PNAS 72:3961, 1975) for colonies, or Benton (W.D. Benton and R.W. Davis, Science 196:180, 1977) for plaques, and variations thereof. Both of these procedures result in isolated and purified DNA, containing each of the cDNA clones from the library, arrayed as isolated patches on a solid support such as nitrocellulose or nylon filter membranes.

These isolated and purified cDNA compounds have long been used in commerce. In a typical procedure, arrays of purified cDNA clones are allowed to hybridize to a radioactive probe corresponding to a sequence of interest. Purified cDNAs that hybridize to the probe are used as a guide to select a subset of clones for further analysis. However, it must be emphasized that the further analysis, such as DNA sequencing, does not create a new composition of matter; all cDNAs in the library exist as isolated, purified compounds before any clone is selected.

An extremely large number of cDNA libraries have been constructed over time, from diverse tissues, human and otherwise. cDNA libraries have been offered for sale by companies such as Clontech (Palo Alto CA; www.clontech.com) since the 1980s. For instance, the 1996/1997 Clontech catalog offers for sale cDNA libraries from the following human tissues: fetal adrenal gland, aorta, bone marrow, brain, amygdala, caudate nucleus, cerebellum, cerebral cortex, fetal brain, hippocampus, hypothalamus, substantia nigra, subthalamic nucleus, thalamus, breast adenocarcinoma, breast carcinoma, colon, colorectal adenocarcinoma, duodenum, endothelial cell, epidermis, erythrolukemia, fat cell, fibroblast, fibrosarcoma, heart, fetal heart, HeLa, hepatoma, keratinocyte, kidney, fetal kidney, leukemia, leukocyte, liver, fetal liver, lung, fetal lung, lymph node, lymphoma, mammary gland, monocyte, osteosarcoma, ovary, pancreas, pituitary, placenta, prostate, retina, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thymus, and uterus. It is a virtual certainty that a cDNA clone representing every human gene had been represented as a single colony or plaque at some time or other by approximately 1985 to 1990. Use of a variety of cloning vectors, including plasmid, phage, and eucaryotic cells, increases the likelihood that all possible clones have been represented. As a matter of course, isolated, purified DNA was prepared from all of the isolated colonies by the Grunstein, Benton, or similar procedures.

It might be argued that any particular cDNA might have escaped representation in these libraries by statistical fluke. However, it is now possible to examine preserved copies of prior art libraries quickly and easily by the polymerase chain reaction (PCR) for the presence of any particular sequence. Thus it is safe to presume that any given sequence was indeed represented unless the applicant has demonstrated that the sequence was not represented in even the most complete libraries of the prior art.

Biochemical manipulations to produce cDNA, as described above, might arguably have permitted patenting of genes when such manipulations first occurred in the 1970s and 1980s, but the claiming of patents cannot now be permitted since (i) such human gene constructs have been in the public domain since at least 1985, in the form of cloned cDNA libraries and (ii) such cDNA compounds have been for sale for longer than the 1 year time period, and therefore are no longer eligible for patent protection.

II. Sequencing of DNA, cDNA and ESTs Has Been Scientifically Obvious Since the Early to Mid 1980s.

Above we have demonstrated that certain classes of DNA sequences were in the public domain by approximately 1985. But even for those sequences that were not explicitly isolated and purified in the prior art, their isolation and purification was obvious to anyone skilled in the art of the new science of genomics.

The typical molecular biology scientific approach, described above, led to the selection of clones for analysis based on criteria such as hybridization to a probe sequence that was known or could be synthesized. By contrast, a new approach, now termed "Genomics," was published in 1983 (S.D. Putney, W.C. Herlihy, and P. Schimmel, Nature 302:718-21, 1983). Advent of rapid DNA sequencing techniques allowed isolated clones to be chosen randomly and analyzed by DNA sequencing. This method has become the dominant way of choosing genes for analysis; in fact nearly all applications under consideration for patents on genes as compositions of matter rely on DNA sequences obtained in this way.

Sequencing of genes, while is useful from a scientific and research standpoint, does not create anything new. Indeed, once the sequencing process became highly automated, identifying the sequence of any gene, cDNA, purified DNA, EST or other DNA-derived sequence became extremely obvious to the point of banality. As Dr. James Watson, aptly commented, sequencing has become so highly automated and so standardized in its procedures that it can now be done "by monkeys." Everyone knows and understands that, with the easy availability of sequencing technologies, it makes sense to sequence any and every important DNA occurring in nature, starting with the human genome, but also embracing any and every reasonably valuable DNA including zebrafish, mouse, rice, corn, and almost any and every other DNA. Indeed, at this time in the history of genomics research, being the first to sequence any particular fragment of DNA is merely matter of being the first to do the obvious: being the first to reach a summit does not mean that you are have "invented" the mountain. Human genes exist in nature, and identifying the nucleotide sequence is an act of discovery and not of invention.

Our understanding is that, with respect to cDNA compounds, the PTO apparently views these compounds as "man made" compounds that do not exist in nature, and thus are eligible for the patent protection under the principles of Chakrabarty. However, we strongly disagree with this apparent position, because these cDNA compounds are and have been obvious to anyone skilled in the art of genomics for a long time.

III. DNA, Genes, cDNA and Similar Nucleotide Sequences Should Not Be Viewed As Patentable Subject Matter

Even under the Chakrabarty standards that permit patents on living organisms that are "made by man," it was not clear why genes, cDNA sequences or ESTs should be patentable subject matter.

The rationale for distinguishing cDNA and "purified" forms of DNA from "products of nature," and thus allowing patent claims, was first put forth, also most as an aforethought, in Amgen Inc. v Chugai Pharmaceutical Company, 927 F.2d 1200 (Federal Circuit 1991), where the U.S. Court of Appeals for the Federal Circuit (the "CAFC") ostensibly held that "purified and isolated" DNA sequences constituted patentable subject matter. In that case, Amgen sued claiming patent infringement of its patent on the DNA sequence encoding human erythropoeitin ("EPO") which is a protein that stimulates the production of red blood cells. Prior to Amgen's cloning of the EPO gene, the co-defendant Genetics Institute ("GI"), had isolated and purified EPO and had disclosed a method of purifying and isolating the EPO DNA sequence. The USPTO issued a patent to GI in 1987 claiming the EPO protein. GI did not clone the EPO cDNA until August 1984 and began making recombinant EPO shortly thereafter. Amgen, by contrast, had isolated its EPO clones in 1983, and claimed priority of invention. The CAFC held that, even though GI had made an earlier disclosure in time of a probing strategy to screen a DNA library, the Amgen patent was valid, even though the GI screening strategy eventually resulted in the actual cloning of the gene by GI. In particular, the court found that GI's disclosure did not provide a sufficient written description to identify the DNA encoding EPO.

The subtle yet crucial aspect of the Amgen decision, however, was the concept that, in identifying the cDNA needed to produce EPO, there had been something created by man, namely the cDNA. The CAFC stated, almost in passing: "The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO" 927 F.2d 1206 (italics in original). We respectfully submit that this characterization of cDNA is incorrect, since in fact its structure is fixed and determined by mRNA, not by man. In general, it appears that the PTO (and for that matter the courts) have confused or improperly applied to genomics various principles that have historically been applied to chemical compounds or discoveries of drugs. In fact, each cDNA is not a wholly new and "invented" compound, but rather the product of an obvious and predictable natural process. The cDNA is basically the standard and predictable product of reverse transcription of mRNA, and all cDNA is derived from and through standard laboratory procedures. The result is a compound that may not exist in nature, but which is nonetheless an exact and predictable outcome of a standard laboratory procedure applied to compounds that do exist in nature. Indeed, human cDNA is of scientific importance and interest precisely because it is reverse transcribed from mRNA, and lacks the introns of the genomic copy of a human gene. Again, the sequence and function of the exons is determined by nature; the process of isolating cDNA and purifying DNA is simply an obvious application of the techniques of genomics, and not the same as "inventing" the underlying gene. Furthermore, cDNAs encode the same protein as the native gene; therefore, any claims protecting a translated product of a cDNA are clearly claiming an obvious product of a naturally-occurring gene.