No. 2010–1406

# United States Court of Appeals for the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, M.D., ARUPA GANGULY, PH.D., WENDY CHUNG, M.D., PH.D., HARRY OSTRER, M.D., DAVID LEDBETTER, PH.D., STEPHEN WARREN, PH.D., ELLEN MATLOFF, M.S., ELSA REICH, M.S., BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, AND KATHLEEN RAKER,
*Plaintiffs-Appellees*

*v.*

UNITED STATES PATENT AND TRADEMARK OFFICE,
*Defendant,*

*and*

MYRIAD GENETICS, INC.,
*Defendant-Appellant,*

*and*

LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, AND MICHAEL K. YOUNG, in their official capacity as Directors of the University of Utah Research Foundation,
*Defendants-Appellants*

Appeal from the United States District Court for the Southern District of New York in Case No. 09 Civ. 4515, Senior Judge Robert W. Sweet

## BRIEF OF AMICI CURIAE SCHOLARS OF BIOTECHNOLOGY PATENT LAW IN SUPPORT OF PLAINTIFFS-APPELLEES, SUPPORTING AFFIRMANCE

ANDREW CHIN
University of North Carolina School of Law
160 Ridge Road, CB #3380
Chapel Hill, North Carolina 27599-3380
(919) 962-4116
*Counsel of Record for Amici Curiae Scholars of Biotechnology Patent Law*

December 7, 2010

## CERTIFICATE OF INTEREST

Counsel for Amici Curiae Scholars of Biotechnology Patent Law certifies the following:

1. The full name of every party or amicus curiae represented by me is listed in Appendix A.

2. The name of the real parties in interest (if the party named in the caption is not the real party in interest) represented by me is: None.

3. All parent corporations and any publicly held companies that own 10 percent of the stock of the party or amicus curiae represented by me are: None.

4. 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 curiae now represented by me in the trial court or are expected to appear in this court are: None.

Dated: December 7, 2010


_____

ANDREW CHIN
University of North Carolina
School of Law
160 Ridge Road
Chapel Hill, NC 27599-3380
(919) 962-4116
*Counsel of Record for Amici Curiae Scholars of Biotechnology Patent Law*

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## STATEMENT OF INTEREST OF AMICI CURIAE

*Amici curiae* submit this brief pursuant to Fed. R. App. P. 29 and Rule 29 of this court. All parties have consented to the filing of this brief.

*Amici* are professors who teach and/or write about biotechnology patent law at universities throughout the United States. A list of *amici* appears at Appendix A. No part of this brief was authored by counsel for any party, person, or organization besides *amici*. No other person has contributed money that was intended to fund preparing or submitting this brief.

*Amici* represent no institution, group, or association and have no personal interest or stake in the outcome of this case. Our sole interest in this case is furtherance of the patent system's constitutional purpose of "promot[ing] the Progress of Science and useful Arts."

This brief is filed to present to the court an argument that (1) the novelty and nonobviousness analyses of patent claims directed to DNA oligonucleotides (short DNA molecules) are uniquely susceptible to diversion into considerations unrelated to progress in the field of biotechnology; and (2) such analyses should be pre-empted by holding DNA oligonucleotides to be unpatentable under the printed matter doctrine.

## SUMMARY OF ARGUMENT

The isolated DNA oligonucleotide compositions (short DNA molecules) claimed in claims 5 and 6 of U.S. Patent No. 5,747,282 can be synthesized by general methods that have been widely known and used since at least the early 1980s. A pre-1993 publication describing these methods and listing any of the claimed oligonucleotide sequences would have anticipated and invalidated these claims under § 102(b). Yet it is trivial (and was trivial then) to computer-generate and publish a list of all oligonucleotide sequences of a given length, provided that such a list can be stored feasibly on a medium that can be made accessible to the public. Thus the novelty of DNA oligonucleotide claims hinges largely on whether structural definitions of the claimed sequences have previously been typed out as A's, C's, G's and T's in such a computer-generated list and published. Such a consideration has more to do with the norms of the scientific community regarding scholarly communication and with the availability of low-cost, high-capacity information storage media, than with the state of the art in biotechnology.

*Amici* contend that the patentability analysis of DNA oligonucleotide claims should not reach these irrelevant considerations, because DNA

oligonucleotides should be held ineligible for patenting under patent law's printed matter doctrine. The printed matter doctrine serves to pre-empt inapposite analyses of differences between the claimed invention and the prior art — e.g., analyses focused on the management of stored information rather than on the field of invention — that would otherwise be applied under the novelty doctrine of § 102 or the nonobviousness doctrine of § 103.

The printed matter doctrine is applicable to the claimed oligonucleotides because DNA oligonucleotide molecules are disposed to store nucleotide sequence information in a manner analogous in all relevant respects to other substrates that may be more intuitively recognizable as information storage media, such as laser-printed text on paper. Moreover, to the extent that a hybridization reaction involving a claimed oligonucleotide is recognized as having specific and substantial utility, it is by virtue of the semantic properties that scientists have attached to the complementary DNA sequence, not an inventive functional relationship between the sequence information and its molecular substrate. While hybridization reactions involving the claimed oligonucleotide probes may impart new and unobvious information regarding cancer, such information is useful and intelligible only to the human mind and cannot confer patentability.

## ARGUMENT

### I. The Focus of this Brief Is Limited

The focus of this brief is directed solely to the patentability of short DNA molecules, also known as oligonucleotides, such as those claimed in claims 5 and 6 of U.S. Patent No. 5,747,282.[1] *Amici* contend that both of these claims should be held invalid under the printed matter doctrine. *Amici* take no position with respect to (1) the patentability of any other claims in issue in this case or (2) the applicability of the product of nature doctrine to claims 5 and 6.

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[1] Claims 5 and 6, both dependent claims, read: "An isolated DNA having at least 15 nucleotides of the DNA of claim 1" and "An isolated DNA having at least 15 nucleotides of the DNA of claim 2," respectively. Corresponding independent claims 1 and 2 are directed to longer DNA molecules. Claim 1 reads: "An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." Claim 2 reads: "The isolated DNA of claim 1, where said DNA has the nucleotide sequence set forth in SEQ ID NO:1."

## II. The Printed Matter Doctrine Precludes the Awarding of Patents for Inventive Contributions That Subsist Merely in Stored Information

The printed matter doctrine states that "'[m]ere printed matter can not impart a patentable feature to a claim.'" *In re Gulack*, 703 F.2d 1381, 1385 (Fed. Cir. 1983) (quoting *In re Miller*, 418 F.2d 1392 (C.C.P.A.1969)). The doctrine does not apply, however, when there is a "new and unobvious functional relationship between the printed matter and the substrate." 703 F.2d at 1386.

As Judge Linn explained in *In re Nuijten*, 500 F.3d 1346 (Fed. Cir. 2007), the printed matter doctrine precludes patentability where the differences between the claimed invention and the prior art subsist merely in stored information:

> Under the "printed matter" doctrine, if the only distinction between a prior art storage medium and a claimed storage medium is the information stored thereon — rather than a different "functional relationship between the printed matter and the substrate" — then the claimed storage medium (with associated information) is unpatentably obvious over the prior art because the information lacks "patentable weight."

*Id.* at 1365 (Linn, J., concurring-in-part and dissenting-in-part).

### A. The Printed Matter Doctrine Extends to All Information Storage Media

The printed matter doctrine has survived the progression of printing technologies from typewriters and treadle presses to laser printers and nanolithography without having been limited to any particular kind of storage medium. *See id.* Instead, it extends to any physical substrate capable of holding information, subject to the "functional relationship" limitation noted above. Accordingly, courts over the years have proceeded to apply the doctrine and its accompanying limitation in cases involving a wide range of substrates. *See, e.g.*, *In re Bryan*, 323 Fed.Appx. 898 (Fed. Cir. 2009) (unpublished) (game boards); *In re Gulack*, 703 F.2d 1381 (Fed. Cir. 1983) (paper, fabric or plastic bands); *In re Miller*, 418 F.2d 1392 (C.C.P.A.1969) (measuring cups and spoons); *Ex parte Gwinn*, 112 U.S.P.Q. 439 (B.P.A.I 1955) (dice in a "parlor golf game"); *In re Kothny*, 96 F.2d 289 (C.C.P.A. 1938) (scales for measuring cylindrical records); *In re McKee,* 75 F.2d 991 (C.C.P.A. 1935) (meat products); *In re Johns,* 70 F.2d 913 (C.C.P.A. 1934) (animal carcasses); *In re Sterling*, 70 F.2d 910 (C.C.P.A. 1934) (checkbooks); *Cincinnati Traction Co. v. Pope*, 210 F. 443 (6th Cir. 1913) (trolley transfer tickets).

### B. The Printed Matter Doctrine Serves to Pre-empt Inapposite Novelty and Nonobviousness Analyses

The printed matter doctrine has traditionally been viewed as an elaboration of the § 101 patentable subject matter requirement, *see* 1 CHISUM ON PATENTS § 1.02[4], at 1-24 (2006) ("'[P]rinted matter' by itself did not constitute a 'manufacture'"); *see also* Examination Guidelines for Computer-Related Inventions, 61 Fed. Reg. 7478, 7481 (Feb. 28, 1996) (instructing examiners to reject non-functional descriptive material under § 101). The doctrine's reliance on "patentable weight" considerations, however, is more akin to a *Graham* analysis of the nonobviousness of the "differences between the prior art and the claims at issue," *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), than the "claim as a whole" approach that pervades modern patentable subject matter doctrine, *see Diamond v. Diehr*, 450 U.S. 175, 189-91 (1981). Accordingly, the printed matter doctrine has also sometimes been applied as part of a § 102 or § 103 analysis. *See, e.g.*, *In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004); *In re Gulack*, 703 F.2d 1381 (Fed. Cir. 1983); *see also In re Nuijten*, 500 F.3d 1346, 1365 (Fed. Cir. 2007) (Linn, J., concurring-in-part and dissenting-in-part)

(characterizing the doctrine as supporting a conclusion of obviousness). Despite this ambiguous statutory locus, the printed matter doctrine has survived to the present day. *See infra* section II.C.

As this court recently explained in *King Pharmaceuticals, Inc. v. Eon Labs.*, 616 F.3d 1267 (Fed. Cir. 2010), the rationale behind the printed matter cases is "preventing the indefinite patenting of known products by the simple inclusion of novel, yet functionally unrelated limitations." *Id.* at 1279. The printed matter doctrine guards against the diversion of patentability analysis into assessments of the novelty and nonobviousness of information fixed in, but not conferring new and nonobvious functionality upon, the underlying substrate.

In so doing, the printed matter doctrine serves alongside the judicially created exceptions to patentable subject matter to pre-empt inapposite analyses of differences between the claimed invention and the prior art that would otherwise be applied under the novelty doctrine of § 102 and/or the nonobviousness doctrine of § 103. *Cf.* Kevin E. Collins, *Semiotics 101: Taking the Printed Matter Doctrine Seriously,* 85 IND. L.J. 1379, 1387 (2010) (explaining that the doctrine in effect "excludes certain useful and nonobvious products of human ingenuity from the patent regime"). Courts

do not inquire into the nonobviousness of newly discovered natural principles, because "the discovery of some of the handiwork of nature . . . is not patentable . . . however ingenious the discovery of that natural principle may have been." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948). Similarly, where "the only distinction between a prior art storage medium and a claimed storage medium is the information stored thereon," *Nuijten*, 500 F.3d at 1365, a *Graham* analysis of the nonobviousness of the "differences between the prior art and the claims at issue" would entail inquiries into the nonobviousness of the stored information relative to prior art stored information and the level of ordinary skill in information recombination, regardless of the field of the underlying invention. *See Graham v. John Deere Co.*, 383 U.S. at 17-18.

Courts have consistently regarded such information-management considerations as inapposite to the assessment of inventive contributions in the relevant field of endeavor. For example, *In re Russell,* 48 F.2d 668 (C.C.P.A. 1931) dealt with a directory in which surnames were arranged phonetically. The applicant argued that his invention comprised "finished tangible subject matter bearing specifically arranged data or means, combined to produce a novel result." *Id*. at 668. The court affirmed the

Patent Office's rejection, holding: "The mere arrangement of printed matter on a sheet or sheets of paper, in book form or otherwise, does not constitute 'any new and useful art, machine, manufacture or composition of matter.'" *Id.* at 669. This expression of the printed matter doctrine served to obviate an irrelevant inquiry into the novelty and nonobviousness of the applicant's "finished tangible" directory as an information source relative to prior art directory and phonetic information sources.

Similarly, in *Guthrie v. Curlett,* 10 F.2d 725 (2d Cir. 1926), the patentee asserted a claim to a "consolidated tariff index" that compiled the shipping rates set by numerous transportation companies, using a system of symbols to facilitate a compact presentation. *Id.* at 725. The court credited the patentee with showing "how to compress into small space a lot of information about freight tariffs," but explained that the proper subject of the patentability inquiry was the "means . . . for making a consolidated index." *Id.* at 726. Finding the disclosed means to consist solely of the non-novel "employment of symbols," the court concluded that the claim was directed to unpatentable subject matter. *Id.* The court thereby refrained from an inapposite inquiry into the ability of one skilled in the art to combine and compress the information from prior art individual tariff schedules into a

single compact document.

In *In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004), the applicant invented a new procedure for normalizing and amplifying RNA using a known reagent. *Id.* at 1337. The Patent Office allowed his method claims, but rejected a claim directed to a kit combining the reagent with instructions for performing the new procedure. *Id.* at 1337-38. This court affirmed the rejection under the printed matter doctrine, finding that the claimed invention amounted to "the addition of new printed matter to a known product" with no functional relationship between the two: "Here the printed matter in no way depends on the kit, and the kit does not depend on the printed matter. All that the printed matter does is teach a new use for an existing product. . . . If we were to adopt [applicant's] position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product." *Id.* at 1338-39. The court's application of the printed matter doctrine thereby avoided a *Graham* inquiry as to whether one of ordinary skill would have been able to assemble the claimed kit from the prior art — a task that would entail producing and storing instructions for a new and nonobvious procedure. *See id.* at 1338 (noting applicant's attempt to distinguish the kit claim by "argu[ing] that . . . prior art does not

teach a limitation of 'instructions describing the method of [the method claim],' combined with an amplification kit").

Patent law's novelty and nonobviousness doctrines are particularly ill-suited to fact-specific assessments of the inventiveness embodied in stored information, because these doctrines artificially construct the knowledge of the person having ordinary skill in the art as including all publicly accessible information resources, no matter how obscure. *See, e.g.*, In re Hall, 781 F.2d 897 (Fed. Cir. 1986) (finding that "a single cataloged thesis in one university library" was sufficiently accessible to one exercising reasonable diligence to constitute a § 102(b) "printed publication"). By obviating an analysis directed to stylized facts and inapposite information-management considerations, the printed matter doctrine preserves the integrity of the novelty and nonobviousness doctrines as promoters of progress in the useful arts.

### C. The Supreme Court's Decision in *Bilski v. Kappos* Did Not Disturb the Printed Matter Doctrine

The printed matter doctrine is a long-established principle of patent law that survived the enactment of the 1952 Patent Act. *See, e.g.*, *In re Miller*,

418 F.2d 1392 (C.C.P.A. 1969); *In re Russell*, 42 F.2d 668 (C.C.P.A. 1931); *U.S. Credit System Co. v. Am. Credit Indemnity Co.*, 59 F. 139, 143 (2d Cir. 1893); *see generally* Harold C. Wegner, *The Disclosure Requirements of the 1952 Patent Act: Looking Back and a New Statute for the Next Fifty Years*, 37 AKRON L. REV. 243, 243 (2004) ("The great bulk [of the 1952 Act] was a mere codification of principles, going back in some cases to the earliest patent laws of the eighteenth century ...."). While there is some ambiguity today as to which section of the 1952 Act supplies its statutory basis, *see supra* section II.B, the doctrine has never been repudiated in over a century. *See, e.g.*, *In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004).

In particular, the Supreme Court's recent decision in *Bilski v. Kappos,* 130 S.Ct. 3218 (June 28, 2010) did not disturb the printed matter doctrine, not least because the doctrine does not arise solely in connection with claims to § 101 "process[es]." *See* CHISUM, *supra* ("'[P]rinted matter' by itself did not constitute a 'manufacture'"). Moreover, none of the Court's reasoning in *Bilski* affects the operation of the printed matter doctrine.

As discussed in Section II.B *supra*, the printed matter doctrine's functional role in preempting inapposite analyses of differences between the claimed invention and the prior art is essentially complementary to that of

the judicially created exceptions to patentable subject matter affirmed in *Bilski* and *Diehr*. Thus, even though the Supreme Court in these decisions has required an "invention as a whole" approach to § 101 patent-eligible subject matter analysis, see *Bilski*, 130 S.Ct. at 3230 (citing *Diehr*, 450 U.S. at 188), this requirement has not affected the printed matter doctrine's reliance on "patentable weight" considerations, as the post-*Diehr* decisions of this court plainly show. *See, e.g.*, *In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004). Since *Bilski*, this court has continued to treat the printed matter doctrine as operative and relevant to patentability analysis. *See King Pharmaceuticals, Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1278-79 (Fed. Cir. Aug. 2, 2010) (citing printed matter cases as persuasive authority for point-of-novelty analysis of method claim).

The *Bilski* Court clarified that the only exceptions to patentable subject matter supported by the Court's precedents are for laws of nature, physical phenomena, and abstract ideas, 130 S.Ct. at 3226, definitively retiring the idea of a categorical exclusion for business methods. *Id.* at 3228. The printed matter doctrine's precedential support, however, is in no way undermined by the Court's repudiation of the supposed "business method" exception.

It may be observed that the printed matter doctrine originated in part from cases involving printed business forms. *See, e.g.*, *Hotel Security Checking Co. v. Lorraine*, 160 F. 467 (2d Cir. 1908); *United States Credit System Co. v. American Credit Indemnity Co.*, 59 F. 139 (2d Cir. 1893). The applicability of the doctrine, however, has never been limited to business methods. *See, e.g.*, *In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004). Moreover, since the early business-form cases, the role of the printed matter doctrine has developed independently of any putative justification for excluding the category of business methods from patentability. *See, e.g.*, *In re Nuijten*, 500 F.3d 1346, 1365 (Fed. Cir. 2007) (Linn, J., concurring-in-part and dissenting-in-part) (describing the printed matter doctrine as "potentially more apposite as a consequence of the 'useful' requirement of § 101"); *Boggs v. Robertson*, 13 U.S.P.Q. 214, 214 (D.C. Sup. Ct. 1931) (applying the doctrine as an extension of the abstract ideas exception); *see also supra* Section II.B (describing the doctrine's complementary role to the exceptions for laws of nature, physical phenomena, and abstract ideas); Collins, *supra*, at 1402 (arguing that the abstract ideas exception "comes the closest to a source of support for the doctrine").

## III. The Printed Matter Doctrine Precludes the Patentability of the Claimed Oligonucleotide Compositions

### A. The Inventive Contributions of the Claimed Oligonucleotide Compositions Subsist Merely in Stored Information

As the printed matter doctrine is a generally applicable principle of patent law, *see supra* section II.A, *amici* do not consider it necessary to appeal to "the unique properties of DNA that distinguish it from all other chemicals and biological molecules found in nature" on which the district court's opinion purportedly relies. *See Association for Molecular Pathology v. U. S. Patent & Trademark Office*, 702 F. Supp. 2d 181, 228 (S.D.N.Y. 2010). Nor do *amici* appeal here to policy concerns expressed elsewhere about the impacts of oligonucleotide patenting on valuable downstream research. *See, e.g.*, Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1626 (2003); Andrew Chin, *Research in the Shadow of DNA Patents*, 87 J. PAT. & TRADEMARK OFF. SOC'Y 846, 857-58 (2005); Yvonne Cripps, *The Art and Science of Genetic Modification: Re-Engineering Patent Law and Constitutional Orthodoxies*, 11 IND. J. GLOBAL LEGAL STUD. 1, 5-7 (2004); Johanna Dennis, *Divergence in Patent Systems*, 1 INT'L J. PRIVATE L. 268, 281 (2008); Donna M. Gitter, *International Conflicts Over Patenting Human DNA Sequences in the United States and*

*the European Union*, 76 N.Y.U. L. REV. 1623, 1667-71 (2001); Jon F. Merz *et al.*, *Diagnostic Testing Fails the Test: The Pitfalls of Patents Are Illustrated By the Case of Hemochromatosis*, 415 NATURE 577 (2002); *see also* Keith Aoki, *Distributive and Syncretic Motives in Intellectual Property Law*, 40 U.C. DAVIS L. REV. 717, 797-98 (2007) (describing harms to biodiversity). Moreover, *amici* fully agree with Myriad's characterization of DNA as "a real and tangible molecule, a chemical composition made up of deoxyribonucleotides linked by a phosphodiester backbone" and offer no suggestion that "the term 'DNA' refers merely to information." 702 F. Supp. 2d at 216. What is germane to the printed matter doctrine, however, are the facts that a DNA molecule is a physical substrate capable of holding information, and that the claimed DNA oligonucleotide compositions exhibit no new and unobvious functional relationship between their sequence information and their molecular substrates. *See supra* section II.A.

The synthesis and use of isolated DNA oligonucleotides as hybridization probes has been known in the published literature since at least 1975. *See* Edwin Mellor Southern, *Detection of Specific Sequences Among DNA Fragments Separated by Gel Electrophoresis*, 98 J. MOLECULAR BIOLOGY 503 (1975). The claimed oligonucleotides differ from the

oligonucleotides used in prior art hybridization probe procedures only with respect to the nucleotide sequences carried thereon. *See, e.g.*, U.S. Patent No. 5,198,338, col. 3 (issued May 30, 1993) (describing the use of Southern hybridization with isolated DNA oligonucleotide probes "of a suitable hybridizable length (generally longer than 15 nucleotides)" for the detection of T-cell malignancy). Thus, the inventive contributions of the claimed oligonucleotide compositions subsist merely in the nucleotide sequence information stored in the claimed molecules. *See* Kevin Emerson Collins, *Semiotics 101: Taking the Printed Matter Doctrine Seriously*, INDIANA L.J. 1379, 1390 (2010) ("The difference between a newly isolated and purified strand of DNA and prior art DNA molecules resides in the content of the DNA-as-information. . .").

By structure and function, DNA oligonucleotides are disposed to store nucleotide sequence information in a manner analogous in all relevant respects to other substrates that may be more intuitively recognizable as information storage media. Structurally, characters comprising textual information are physically represented on a laser-printed page by defined patterns of toner powder fused to a paper surface. *See Laser Printer*, WIKIPEDIA <http://en.wikipedia.org/wiki/Laser_printer> (accessed Nov. 28,

2010). Similarly, nucleotide sequence information is physically represented in the DNA molecule by four defined types of submolecular units called "bases," wherein each base is bonded to a 5-carbon sugar that has a phosphate group attached to form a sequential unit called a "nucleotide." *See In re O'Farrell*, 853 F.2d 894, 896 (Fed. Cir. 1988). The resulting structure in each case physically manifests the specific information stored in the substrate, thereby enabling that information to be retrieved.

Functionally, laser printing stores textual information on a paper substrate through a computer-automated procedure that sequences and controls the process of placing and fusing the toner powder onto the page. *See Laser Printer, supra*. Analogously, automated oligonucleotide synthesis stores nucleotide sequence information in a DNA molecule through a computer-automated procedure that sequences and controls the process of placing and binding nucleotides onto the molecule, which is covalently bonded to a solid support.[2] The user of an oligonucleotide synthesizer

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[2] Oligonucleotide synthesis dates back to the early 1950s, soon after the discovery of the structure of DNA. *See* Daniel M. Brown, *A Brief History of Oligonucleotide Synthesis*, in 20 PROTOCOLS FOR OLIGONUCLEOTIDES AND ANALOGS 1, 1 (1993). Phosphotriester technology for oligonucleotide synthesis was primarily developed in the 1960s and 1970s and refined and popularized in the 1980s. *See* Brown, *supra*, at 7-9; *see also* Keiichi Itakura

merely has to type in the sequence and "press[] a few buttons." *See* Richard Pon, *Solid-Phase Supports for Oligonucleotide Synthesis*, *in* 20 PROTOCOLS FOR OLIGONUCLEOTIDES AND ANALOGS 465, 465 (1993). Nucleotide sequence information can subsequently be retrieved from a DNA oligonucleotide using modern sequencing procedures. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002) (finding that one of ordinary skill can use known sequencing techniques to obtain nucleotide sequences from deposited DNA molecules).

While the fixation of nucleotide sequence information in the DNA molecule occurs on an intramolecular level, the microscopic scale of this phenomenon does not belie the fact that DNA oligonucleotides are analogous in structure and function to other physical substrates that store and

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*et al.*, *Synthesis and Use of Synthetic Oligonucleotides*, 53 ANN. REV. BIOCHEMISTRY 323, 353 (1984) ("[T]he chemical synthesis of oligodeoxyribonucleotides has become a routine laboratory procedure."). In phosphotriester synthesis, the most widely used methodology, there are four steps in each nucleotide addition, and at each step appropriate compounds are added and washed out as the reaction proceeds. The four steps are: (1) de-blocking of the DMT group on the last nucleotide added, (2) coupling to the next nucleotide, (3) capping against any unreacted nucleotides, and (4) oxidation of the linkage to render it stable. *See Oligonucleotide Synthesis*, WIKIPEDIA <http://en.wikipedia.org/wiki/Oligonucleotide_synthesis#Synthetic_cycle> (visited Nov. 28, 2010).

manifest information as printed matter, such as laser-printed paper. Any structural differences between the claimed oligonucleotide compositions and prior art DNA oligonucleotides are simply the physical manifestation of differences in nucleotide sequence information as it is stored in the respective molecular substrates. Under the printed matter doctrine, therefore, any inventive contributions of the claimed oligonucleotide contributions should be found to subsist merely in stored information.

### B. The Novelty and Nonobviousness Analyses of the Claimed Oligonucleotide Compositions Are Contingent on Inapposite Information-Management Considerations

As explained in section II.B *supra*, the printed matter doctrine serves to pre-empt the diversion of patent law's novelty and nonobviousness analyses into information-management considerations unrelated to progress in the field of the underlying invention. The analysis of the patentability of oligonucleotide probes is uniquely susceptible to such diversion, because of two interrelated facts. First, as this court has recently explicitly recognized, general methods of making isolated DNA oligonucleotides of arbitrary sequence have long been well known. *See In re Gleave*, 560 F.3d 1331, 1336 (Fed. Cir. 2009) (finding prior art to be enabling based on applicant's

admission that "it is well within the skill of an ordinary person in the art to make any oligodeoxynucleotide sequence"); Brown, *supra* note 2. Second, large databases providing nucleotide sequence information, but not listing all oligonucleotide subsequences thereof, have been available to the public since the early 1980s. *See GenBank*, WIKIPEDIA< http://en.wikipedia.org/wiki/GenBank#History> (visited Nov. 28, 2010); David S. Roos, *Bioinformatics: Trying to Swim in a Sea of Data*, 291 SCIENCE 1260 (2001) (noting GenBank "continues to more than double in size every year").

At least until recently, this court has characterized both of these facts as largely irrelevant to the novelty and nonobviousness analyses of claims to particular isolated DNA oligonucleotides. In *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995), this court held that the availability of general methods of making isolated DNA molecules "is essentially irrelevant to the question whether the specific [claimed] molecules themselves would have been obvious" to one of ordinary skill. *Id.* at 1559; *but see In re Kubin*, 561 F.3d 1351, 1358-59 (Fed. Cir. 2009) (noting the Supreme Court's repudiation of *Deuel* to the extent that *Deuel* foreclosed arguments that a combination of elements was "obvious to try"). Databases of nucleotide sequences, without more, typically do not anticipate claims to isolated oligonucleotides

comprising specific subsequences thereof, because such databases usually do not teach all limitations of an isolated oligonucleotide claim, e.g., by listing the sequence of every such oligonucleotide. *See generally In re Gleave*, 560 F.3d at 1336-38 (discussing different treatment of lists and genera under anticipation case law).

*Gleave* implies that the patentability analysis of claimed DNA oligonucleotides would be very different if scientists were in the practice of publishing lists of oligonucleotide subsequences in addition to the full-length sequences from which they were derived. In *Gleave*, this court reviewed the Patent Office's rejection of a claim to an antisense DNA oligonucleotide substantially complementary to genes encoding two types of insulin-dependent growth factor binding protein. *Id.* The examiner imposed, and the Board approved, a § 102(b) rejection over a reference that listed each of the more than 1400 fifteen-base-long sense oligonucleotides contained in one of the genes and suggested making antisense oligonucleotides capable of interacting with the listed sense oligonucleotides. *Id.* at 1333-34. Noting that "a person of ordinary skill in the art equipped with an IGFBP sequence is admittedly capable of envisioning how to make any antisense sequence," this court found the reference to anticipate all of the listed sense

oligonucleotides and their antisense counterparts. *Id.* at 1338.

That the proliferation of nucleotide sequences in public databases has not been accompanied by equally extensive and particularized documentation of oligonucleotide sequences does not reflect limitations in the state of the art in biotechnology, but norms in scholarly communication. Given any long nucleotide sequence, it is a trivial matter to identify all of the oligonucleotides of a given length contained therein; to list all of them would contribute nothing to the advancement of science and be a frivolous waste of space. It is not surprising that the lengthy oligonucleotide listing cited as prior art in *Gleave* was from a patent application rather than a professional scientific publication.

It is an equally trivial (though scientifically uninteresting) matter to list all oligonucleotide sequences of a given length that can be made with known synthesis techniques, and thereby to generate a defensive publication that anticipates a broad class of oligonucleotide compositions. As one *amicus* has demonstrated, the potential impact of such defensive publications on the patentability of oligonucleotides is limited only by the capacity of digital storage media. *See* Andrew Chin, *Artful Prior Art and the Quality of DNA Patents*, 57 ALA. L. REV. 975, 1021-23 (2006).

In March 2002, Chin prepared a text document entitled "On the Preparation and Utilization of Isolated and Purified Oligonucleotides," containing (1) a technical explanation of how to make and use isolated and purified oligonucleotides of arbitrary sequence (derived from the presumably enabling specifications of previously issued patents), and (2) a computer-generated list of 11 million nucleotide sequences 8 to 12 bases in length that could be made and used by the disclosed methods. *See id.* at 1036-38 & n. 410. This document was recorded on CD-ROM and deposited in the University of North Carolina School of Law's library, where it was indexed, cataloged and shelved under the Library of Congress subject heading for oligonucleotides on March 14, 2002. *See id.* at 1010. This "shotgun reference" has been effective § 102(b) prior art against oligonucleotide composition claims filed on or after March 15, 2003.[3]

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[3] See 35 U.S.C. § 102(b).

As of October 15, 2010, Chin's publication has been cited in the prosecution history of 39 issued patents, including 35 whose applications originally contained oligonucleotide composition claims. *See* U.S. Patents Nos. 6946267, 6953669, 7049067, 7087733, 7090980, 7098192, 7105319, 7108973, 7132233, 7166430, 7176181, 7186537, 7198898, 7229976, 7291725, 7339041, 7342109, 7345161, 7393641, 7393950, 7407943, 7414033, 7416725, 7468431, 7495094, 7514241, 7553618, 7589190, 7618947, 7622455, 7678895, 7700574, 7709628, 7718628, 7732590, 7737264, 7759318, 7759479. In all 35 cases, the oligonucleotide

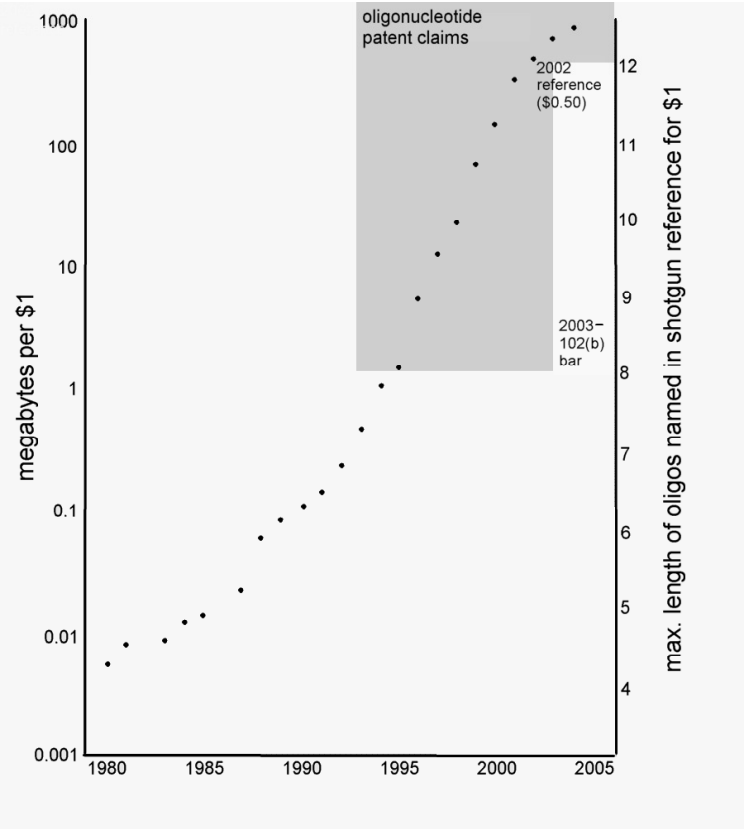


**Fig. 1. Impact of the Chin reference on patentability of oligonucleotides. Chin, *supra*, at 1022.**

Chin's reference was limited to 11 million sequences only by the capacity of a CD-ROM in 2002. As Fig. 1 illustrates, at any given time, the feasibility of producing a shotgun reference as effective prior art against

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composition claims were either canceled or narrowed by amendment to exclude sequences of 8 to 12 bases in length. In one case, the patent examiner also cited the Chin reference in a § 103 rejection of several method claims. *See* U.S. Patent No. 7090980 (final rejection of Oct. 14, 2005).

oligonucleotides of a given length is dependent on the availability of high-capacity, low-cost digital media. In Fig. 1, the impact of Chin's 2002 reference is represented by the white segment that has been carved out of the shaded rectangle; the right scale indicates that as of 2003, broad claims to oligonucleotides of 8 to 12 bases were no longer patentable. As the data points plotted against the left scale illustrate, continuing advances in information storage technology may be expected to make it feasible to generate and publish shotgun references covering oligonucleotides of ever-increasing lengths.

There is a deep incongruity in these results. Known methods of synthesizing arbitrary isolated DNA oligonucleotides represent a significant part of the state of the art in biotechnology.[4] In contrast, the existence (or nonexistence) of shotgun references listing the sequences of arbitrary isolated oligonucleotides is of no significance to the state of the art in biotechnology. The feasibility of generating and publishing a shotgun reference of a given scope is determined solely by the state of information storage technology. Yet patent doctrine holds that such a sequence listing anticipates an oligonucleotide composition claim, *see Gleave*, 560 F.3d at

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[4] *See* Brown, *supra* note 2.

1336-38, while oligonucleotide synthesizers do not even render such a claim obvious. *See Deuel*, 51 F.3d at 1559.

Chin's reference (and the patent system's response thereto) concretely demonstrates that the novelty and nonobviousness analyses of oligonucleotide composition claims are deeply and inextricably contingent on information-management considerations that are irrelevant to the state of the art in biotechnology. The printed matter doctrine can serve its functional role by obviating such analyses. *See* section II.B.

*Amici* acknowledge that the courts have not previously applied the printed matter doctrine to preclude the patenting of DNA molecules. *See* Collins, *supra*, at 1389 n. 40 (noting that "printed matter challenges have not been brought against gene patents"). *Amici* submit, however, that it has only been relatively recently that unrelated but contemporaneous developments in biotechnology and information technology have thrown the doctrinal incongruity described above into high relief. It is only a matter of time until information technology supports the publication of shotgun references that foreclose the patenting of oligonucleotides of any given length. The printed matter doctrine can declare an end to this irrelevant waiting game.

### C. The Claimed Oligonucleotide Compositions Exhibit No New and Unobvious Functional Relationship Between the Sequence Information and the Molecular Substrate

"Additional advantageous activity" may distinguish a claimed species as nonobvious over a known genus. *See In re Albrecht*, 514 F.2d 1389 (C.C.P.A. 1975). While the specific utility of the claimed oligonucleotide compositions in clinical testing for breast cancer may represent "additional advantageous activity" in which nonobviousness subsists, this utility is not the result of a "new and unobvious functional relationship between the printed matter and the substrate." *In re Gulack*, 703 F.2d at 1386. Accordingly, the printed matter doctrine should be applied to invalidate the oligonucleotide composition claims.

In *Gulack*, the claimed invention was an endless band on which had been printed the first $P-1$ significant digits in the repeating decimal expansion of $1/P$, where $P$ is a prime number. *See id.* at 1383. This number has the property that cyclic shifts of the digits produce integer multiples of the original number.[5] *See id.* The inventor claimed the band as "an educational and recreational mathematical device" that would display cyclic

[5] For example, the decimal expansion of 1/7 is .142857142857…. A cyclic shift of the number 142857 has the property that 428571=3*142857.

shifts of the original number, whose multiplicative properties might be used, *inter alia*, "to perform magic tricks or to display various aspects of number theory." *See id.* The specification and claims included such embodiments as a belt, hatband, necklace, or ring. *See id.*

The examiner rejected several claims under the printed matter doctrine, and the Board affirmed, finding "no functional relationship of the printed material to the substrate." *See id.* at 1384. This court reversed, finding that "the digits of Gulack's invention are functionally related to the band." *Id.* at 1385. The court reasoned:

> The appealed claims, on the other hand, require a particular sequence of digits to be displayed on the outside surface of a band. These digits are related to the band in two ways: (1) the band supports the digits; and (2) there is an endless sequence of digits — each digit residing in a unique position with respect to every other digit in an endless loop. Thus, the digits exploit the endless nature of the band.

Id. at 1386-87.

Crucial to the court's analysis was its finding that "there is an endless sequence of digits" that could not have been stored on anything other than a distinctive kind of substrate; i.e., one with an "endless nature." Gulack's specification, however, teaches that "the sequence of digits imprinted on the band" is the finite sequence of $P$–1 digits described above. *See id.* at 1383.

The *Gulack* court thus appears to have construed "the digits of Gulack's invention" as intrinsically incorporating a special mathematical property that could be manifested only by also including all cyclic shifts of those digits.

In contrast, the nucleotide sequences of the claimed oligonucleotide compositions do not possess any intrinsic property that necessitates a distinctive kind of substrate. An oligonucleotide synthesizer fixes the sequence information of the claimed oligonucleotides into the substructures of a DNA molecule in the same way as it processes any other sequence information. *See supra* note 2.

*Amici* acknowledge that the claimed oligonucleotides manifest higher-order structures that dispose them to hybridize specifically with the complementary DNA sequences described in the specification as associated with various human breast and ovarian cancers. From a functional standpoint, however, the causal disposition of oligonucleotides to hybridize with complementary DNA sequences — the *only* causal disposition that the oligonucleotides of each of the claimed genera have in common[6] — is

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[6] In contrast to oligonucleotides, longer DNA molecules that encode proteins with metabolic functions may have both meaning that is semantic and information content that is non-semantic, *see* Peter Godfrey-Smith, *Genes Do Not Code for Phenotypic Traits*, *in* CONTEMPORARY DEBATES IN

common to *all* oligonucleotides, and is neither new nor unobvious. *See In re Deuel*, 51 F.3d at 1554-55 (explaining that DNA probes "exploit the fact that the bases in DNA always hybridize in complementary pairs"). The sequence information of the claimed oligonucleotides possesses no intrinsic property that distinguishes the functional properties of their underlying substrates from those of other oligonucleotides.

To the extent that a hybridization reaction involving a claimed oligonucleotide is recognized as having specific utility, it is by virtue of the semantic properties that scientists have attached to the complementary DNA sequence, not a new and unobvious functional relationship between the sequence information and the molecular substrate. *See* U.S. Patent No. 5,747,282, col. 7 (describing the observation of "large extended families . . . with multiple cases of breast cancer" to support scientists' inferences regarding the locus of the BRCA1 gene); *see also* Godfrey-Smith, *supra* note 6, at 283 (arguing that apart from protein synthesis, causal claims

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PHILOSOPHY OF SCIENCE 275, 281-94 (Christopher Hitchcock ed. 2004), and therefore might not be covered by the printed matter doctrine. *Cf. In re Fisher*, 421 F.3d 1365, 1373 (Fed. Cir. 2005) (finding expressed sequence tags that were "unable to provide any information about the overall structure let alone the function of the underlying [protein-encoding] gene" to lack patentable utility as research tools).

linking genes and phenotypic traits are grounded in semantic description). While hybridization reactions involving the claimed oligonucleotide probes may impart new and unobvious information regarding cancer, such information is useful and intelligible only to the human mind and cannot confer patentability. *See In re Lowry*, 32 F.3d 1579 (Fed. Cir. 1994) (citing *In re Bernhart*, 417 F.2d 1395, 1399 (C.C.P.A. 1969)) ("The printed matter cases 'dealt with claims defining as the invention certain novel arrangements of printed lines or characters, useful and intelligible only to the human mind.'"); *see also* Collins, *supra*, at 1383 ("Standing alone, newly invented semiotic meanings are not eligible for patent protection. Similarly, attaching new semiotic meanings to old worldly things does not make the worldly things patentable.").

## CONCLUSION

For the foregoing reasons, the court should affirm the district court's judgment of invalidity of claims 5 and 6 and hold that the printed matter doctrine precludes the patenting of oligonucleotides capable of being synthesized by known general methods.

Respectfully submitted,

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ANDREW CHIN
University of North Carolina
School of Law
160 Ridge Road
Chapel Hill, NC 27599-3380
(919) 962-4116
*Counsel of Record for*
*Amici Curiae Scholars of*
*Biotechnology Patent Law*

*Research Assistants*
*to Professor Chin*
SHAHID KHAN
JOHN KIVUS

## APPENDIX A

### List of Signatories

Professor Keith Aoki
University of California at Davis School of Law

Professor Adam Candeub
Michigan State University School of Law

Professor Andrew Chin
University of North Carolina School of Law

Professor Yvonne Cripps
University of Indiana School of Law

Professor Johanna Dennis
Vermont Law School

Professor Llewellyn Joseph Gibbons
University of Toledo College of Law

Professor Donna M. Gitter
Associate Professor of Law
Zicklin School of Business
Baruch College, City University of New York

Professor Jon Merz
Senior Fellow, Center for Medical Ethics
Associate Chair for Faculty Affairs, Department of Medical Ethics
University of Pennsylvania School of Medicine

## CERTIFICATE OF FILING AND SERVICE

I hereby certify that on this 7th day of December, 2010, I caused twelve true and correct copies of the foregoing Brief for Amicus Curiae Scholars of Biotechnology Patent Law in Support of Plaintiffs-Appellees and an original Entry of Appearance of Andrew Chin to be mailed via Federal Express to the Court, and for two true and correct copies of the Brief and one true and correct copy of the Appearance to be served via first class U.S. mail, postage prepaid, upon the following counsel of record:

Christopher A. Hansen
American Civil Liberties Union
125 Broad Street, 18th Floor
New York, NY 10004
chansen@aclu.org
*Counsel for Plaintiffs-Appellees*

Gregory A. Castanias
Jones Day
51 Louisiana Avenue, N.W.
Washington, D.C. 20001
gcastanias@jonesday.com
*Counsel for Defendants-Appellants*

Mary M. Calkins
Foley and Lardner
3000 K Street, N.W., Suite 500
Washington, DC 20007
*Counsel for Amicus Alnylam Pharmaceuticals*

Barbara R. Rudolph
Finnegan, Henderson, Farabow, Garrett & Dunner
901 New York Avenue, N.W.
Suite 1100
Washington, DC 20001-4413
*Counsel for Amicus American Intellectual Property Law Association*

Seth P. Waxman
Wilmer Hale
1875 Pennsylvania Avenue, N.W.
Washington, DC 20006
*Counsel for Amici Biotech Industry +Organization et al.*

Erik P. Belt
McCarter & English
265 Franklin Street
Boston, MA 02110
*Counsel for Amicus Boston Patent Law Association*

Christopher M. Holman
5100 Rockhill Road
Kansas City, MO 64110
*Counsel for Amici Christopher Holman et al.*

Jennifer Gordon
Baker Botts
30 Rockefeller Center
New York, NY 10112
*Counsel for Amicus Croplife International*

Maxim H. Waldbaum
Schiff Hardin
900 Third Avenue, 23rd Floor
New York, NY 10022
*Counsel for Amicus Fédération Internationale des Conseils en Propriété Industrielle (FICPI)*

David S. Forman
Finnegan, Henderson, Farabow, Garrett & Dunner
901 New York Avenue, N.W.
Washington, DC 20001-4413
*Counsel for Amicus Genetic Alliance*

William G. Gaede, III
McDermott, Will & Emery
275 Middlefield Rd., Suite 100
Menlo Park, CA 94025
*Counsel for Amici Genomic Health et al.*

J. Timothy Keane
Harness, Dickey & Pierce
7700 Bonhomme Avenue, Suite 400
St. Louis, MO 63105
*Counsel for Amici Gilead Sciences et al.*

Herbert C. Wamsley
McDonnell, Boehnen, Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
*Counsel for Amicus Intellectual Property Owners Association*

Brian R. Dorn
Merchant & Gould
80 South 8th Street, Suite 3200
Minneapolis, MN 55402-2215
*Counsel for Amicus Kane Biotech*

Judy Deleon Jarecki-Black
Merial Limited
3239 Satellite Blvd.
Duluth, GA 30096
*Counsel for Amicus Merial Limited*

Kent D. McClure
Animal Health Institute
1325 G Street, NW, Suite 700
Washington, DC 20005
*Counsel for Amicus Animal Health Institute*

Aaron Stiefel
Kaye Scholer
425 Park Avenue
New York, NY 10022
*Counsel for Amicus Novartis Corp.*

Kurt G. Calia
Covington & Burling
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
*Counsel for Amicus Pharmaceutical Research and Manufacturers of America*

Jacqueline D. Wright-Bonilla
Foley and Lardner
3000 K Street, N.W., Suite 500
Washington, DC 20007
*Counsel for Amici Rosetta Genomics et al.*

Mark R. Freeman
U.S. Department of Justice
950 Pennsylvania Avenue, N.W.,
Room 7644
Washington, DC 20530-0001
*Counsel for Amicus United States*

Ann M. McCrackin
University of New Hampshire
School of Law
2 White Street
Concord, NH 03301
*Counsel for Amicus University of New Hampshire School of Law*

---

ANDREW CHIN
University of North Carolina
School of Law
160 Ridge Road
Chapel Hill, NC 27599-3380
(919) 962-4116
*Counsel of Record for Amici Curiae Scholars of Biotechnology Patent Law*

## CERTIFICATE OF COMPLIANCE

I certify that the foregoing Brief for Amicus Curiae Scholars of Biotechnology Patent Law contains 6,719 words, including footnotes, and excluding the parts of the brief exempted by FRAP 32(a)(7)(B)(iii), as measured by the word processing software used to prepare this brief.

I certify that this brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of the Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Times New Roman 14 point font.

Dated: December 7, 2010

_____

ANDREW CHIN
University of North Carolina
School of Law
160 Ridge Road
Chapel Hill, NC 27599-3380
(919) 962-4116
*Counsel of Record for Amici Curiae Scholars of Biotechnology Patent Law*