

ARTFUL PRIOR ART AND THE QUALITY OF DNA PATENTS

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ABSTRACT

In reviewing patent applications and prior art references in biotechnology, the patent system often unduly focuses on the extent to which these documents explicitly disclose structural formulae for specific nucleic acid molecules. This Article argues that this approach to patentability has caused well-known generic and methodological references to be disregarded as potentially relevant prior art, and thereby allow low-quality DNA patents to issue. To provide empirical support for this doctrinal argument, this Article also describes the creation and publication of an “artfully drafted” prior art reference that provides an enabling disclosure of more than 11 million DNA sequences on CD-ROM and has already been cited in a number of patents and patent applications. The reference is still too small to offer a complete solution to the problems caused by the patent system’s approach. Because the size of the reference is constrained only by the capacity of the CD-ROM, however, the reference provides a “proof of concept” that may be generalized and extended as more capacious storage media become available.

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I. INTRODUCTION

For its effectiveness as an instrument of innovation policy, the U.S. patent system presupposes a well-informed Patent Office able to ensure that patents are granted only to those inventions that significantly advance the

state of technology and thereby “promote the [P]rogress of . . . useful [A]rts.”¹ To inform itself regarding the state of technology as of a given date, the Patent Office consults preexisting references—other inventions, patents, patent applications, and printed publications—which are collectively known as prior art.

As long as the prior art available to the Patent Office accurately captures all material information concerning the technological background of a claimed invention, there can be a sound basis for determining whether the invention meets the required standards for issuance of a patent. When the available prior art falls short of that ideal, however, problems may arise. Significant bodies of technological knowledge have not been documented to the satisfaction of the Patent Act’s formal requirements for prior art.² If such knowledge is not available as prior art, low-quality patents may be issued on inventions that are already known or represent only an obvious advance in the field.

This Article argues that genetic research has not been well-served by the prior art requirements under U.S. patent laws. Specifically, in reviewing patent applications and prior art references, the patent system has invoked a “registry model” of DNA discovery that focuses on the extent to which these documents explicitly “register,” or disclose structural formulae for, specific nucleic acid molecules. This approach has led to an unduly narrow view of the genetic research literature, which often reports on advances that apply to general classes of nucleic acids rather than specific molecules. As a consequence, there has been a significant discrepancy between the prior art that is recognized as effective by the patent system and the scientific community’s understanding of the state of the art.

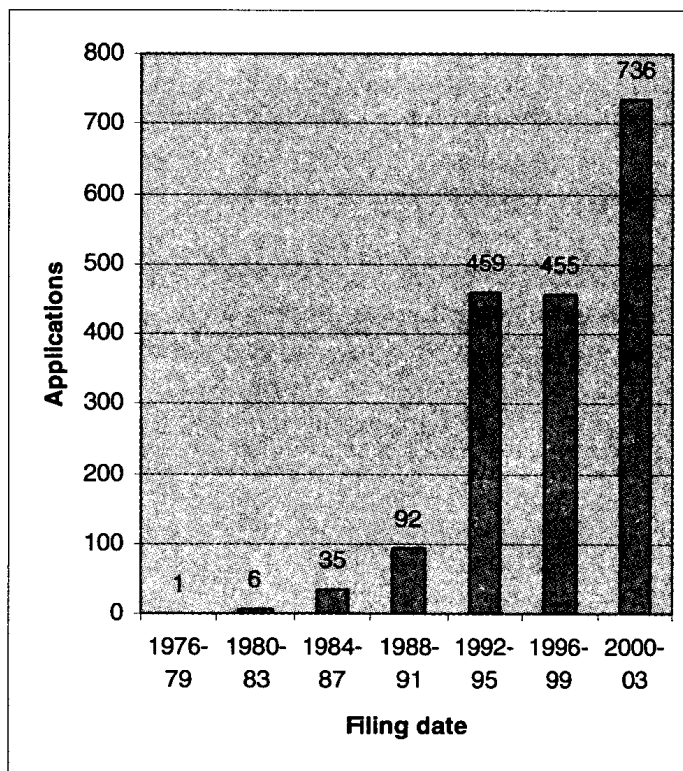
Many techniques for making and using DNA molecules have been published in the literature, but they have been ineffective as prior art against patent claims to specific molecules because they do not specifically disclose the structural formula for each such molecule. By simply appending a listing of structural formulae to these references, it may be possible to create a document that effectively “registers” each of the listed molecules and is therefore cognizable as material prior art against DNA patent claims.

1. U.S. CONST. art. I, § 8, cl. 8.

2. Though not addressed in this Article, the most commonly cited example is the traditional knowledge of indigenous populations outside the United States. See, e.g., Margo A. Bagley, *Patently Unconstitutional: The Geographical Limitation on Prior Art in a Small World*, 87 MINN. L. REV. 679, 724-27 (2003); Leanne M. Fecteau, Note, *The Ayahuasca Patent Revocation: Raising Questions About Current U.S. Patent Policy*, 21 B.C. THIRD WORLD L.J. 69, 74-75 (2001); Nancy Kremers, *Speaking with a Forked Tongue in the Global Debate on Traditional Knowledge and Genetic Resources: Are U.S. Intellectual Property Law and Policy Really Aimed at Meaningful Protection for Native American Cultures?*, 15 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 1, 28-47 (2004); Lakshmi Sarma, Note, *Biopiracy: Twentieth Century Imperialism in the Form of International Agreements*, 13 TEMP. INT’L & COMP. L.J. 107, 130 (1999); Sivashree Sundaram, Comment, *Battling Bills, Beans & Biopiracy*, 15 ALB. L.J. SCI. & TECH. 545, 554-60 (2005); Michael Woods, *Food for Thought: The Biopiracy of Jasmine and Basmati Rice*, 13 ALB. L.J. SCI. & TECH. 123 (2002).

To demonstrate this, in 2002, I authored and published a digital document that discloses the sequences of 11 million oligonucleotides (short DNA molecules) and general methods of making and using them taken from the research literature. The oligonucleotide reference might be described as an example of “artful prior art,” derived from the previous scientific literature without any further inventive skill or effort and tailored to the patent law’s formal requirements for prior art references. It represents a mere change of form in the reporting of advances in genetic research, and (not least because I have no background in genetics beyond high school biology) offers no further technical contributions. While the reference is of little interest to the scientific community, it has proven to be of significant interest to the biotechnology patent bar, having been cited in connection with at least one issued patent and 25 pending U.S. patent applications.³

That mere artful drafting should bear on the validity of so many oligonucleotide patent claims calls into question the patent system’s view of the prior art relative to these claims. Figure 1 illustrates the rapid increase in oligonucleotide-related patent applications since the early 1990s. As I will argue, the patenting of many oligonucleotides during this period appears to have depended in part on the form in which technological advances were reported in the genetic research literature during this period, rather than the substance of the advances themselves.



3. See *infra* app. E.

Figure 1. The past decade has seen a significant increase in the number of U.S. patent applications filed relating to oligonucleotides.⁴ The last complete year for which data are available is 2003.

To a working scientist, it may seem peculiar that artful prior art, which contributes nothing to scientific knowledge, should be material to the patentability of so many claimed inventions. The legal explanation for this is that the same economy of expression that is a virtue in scientific writing is regarded as a deficiency in a prior art reference. To conform methodological genetic research publications to the patent system's registry model, it is necessary in drafting prior art to diverge from the scientific community's norms with an eye to structural disclosure—i.e., to produce artful prior art. An artful prior art reference simply restates the generic teachings of previous publications so as to satisfy the Patent Act's formal requirements. It turns out that only a trivial amount of additional disclosure—the recitation of explicit structural formulae for specifically identified molecules—is required.

While the artful prior art oligonucleotide reference does not purport to anticipate a large fraction of existing or future patent claims, it provides empirical evidence of the contingent nature of DNA patenting. The industry's response since the reference's publication suggests that in the past many oligonucleotides have been patented even though generic methods of making and using those oligonucleotides were already in the possession of the public, and that only a trivial change in form would have been needed to produce an anticipating reference.

The oligonucleotide reference is intended primarily as an empirical contribution in support of a richer, positive analysis of the current state of DNA patentability doctrine. To the extent that the implications of the reference may be seen as anomalous or undesirable; however, this work may also lend support to normative critiques of DNA patenting.⁵

4. Statistics for Figure 1 were compiled by a search of Westlaw's US-PAT database for patents and patent applications with a title containing the stem "oligonucleotide" and a filing date within each of the given intervals. While this search technique yielded some patents claiming oligonucleotide-related technologies rather than oligonucleotides themselves, the statistics clearly indicate the continuing growth in patenting activity in this field.

5. For utilitarian critiques, see Utility Examination Guidelines, 66 Fed. Reg. 1092, 1094 cmt. 7 (Jan. 5, 2001) [hereinafter Utility Guidelines]; Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 699 (1998) ("[G]athering the necessary licenses [for preclinical testing of pharmaceutical products] may be difficult or impossible."); Martin Bobrow & Sandy Thomas, Commentary, *Patents in a Genetic Age*, 409 NATURE 763 (2001) ("The patenting system should help people to channel their energy towards inventions of genuine therapeutic or diagnostic value and discourage the frenetic cataloguing of DNA sequences that are a long way from being a final, useful product."); Thomas D. Kiley, *Patents on Random Complementary DNA Fragments?*, 257 SCIENCE 915, 915 (1992) ("These patents cluster around the earliest imaginable observations on the long road toward practical benefit, while seeking to control what lies at the end of it."); Bartha Maria Knoppers, *Status, Sale and Patenting of Human Genetic Material: An International Survey*, 22 NATURE GENETICS 22, 23-26 (1999); Jon F. Merz et al., *Disease Gene Patenting is a Bad Innovation*, 2 MOLECULAR DIAGNOSIS 299, 301 (1997); Jon F. Merz et al., *Diagnostic Testing Fails the Test*, 415 NATURE 577 (2002); Kate H. Murashige, *Patenting and Ownership of*

The remainder of this Article is organized as follows. Part II defines some basic genetic concepts that will be used throughout the Article. Part III reviews the prevailing legal doctrines governing the patentability of DNA molecules and argues that those doctrines are largely predicated on a "registry model" of DNA discovery in which a new and useful DNA molecule is regarded as discovered if, and only if, its structural formula has been reduced to writing. Part IV describes the oligonucleotide reference and explains its significance as prior art for anticipation. Part V discusses the oligonucleotide reference in additional contexts as an illustration of the legal distinction between novelty and nonobviousness as an example of strategic

Genes and Life Forms: U.S. Perspective, INT'L BUS. LAW., Mar. 2000, at 100, 103 ("[P]atents on materials . . . that are essentially research tools . . . for example . . . receptors needed to screen candidate drugs . . . [And] the stacking of royalties required greatly escalates research costs."); C. Thomas Caskey et al., *HUGO Statement on Patenting of DNA Sequences*, GENOME DIG., Apr. 1995, at 6; Am. Coll. of Med. Genetics, Position Statement on Gene Patents and Accessibility of Gene Testing (Aug. 2, 1999), available at <http://www.faseb.org/genetics/acmg/pol-34.htm> ("[R]estricting the availability of gene testing . . . retards the usually very rapid improvement of a test that occurs through the addition of new mutations or the use of new techniques by numerous laboratories that have accumulated samples from affected individuals over many years."); cf. Utility Guidelines, *supra*, at 1095 cmt. 13 (noting that because techniques for DNA sequencing have become so routine, all DNA molecules should be considered obvious as a matter of law).

For public health policy critiques, see Kimberly Blanton, *Corporate Takeover: Exploiting the U.S. Patent System*, BOSTON GLOBE, Feb. 24, 2002, (Magazine), at 10 (reporting patent notification letters received by Dr. Debra Leonard); Kurt Eichenwald, *Push for Royalties Threatens Use of Down Syndrome Test*, N.Y. TIMES, May 23, 1997, at A1 (reporting abandonment of prenatal testing in response to fears of patent litigation); Margaret Graham Tebo, *The Big Gene Profit Machine*, A.B.A. J., Apr. 2001, at 51 (reporting concerns by Lori Andrews and Jeremy Rifkin that DNA patents will prevent some patients from obtaining needed medical procedures).

For arguments that DNA patents violate human dignity, see Utility Guidelines, *supra*, at 1093 cmt. 4; see also Mark J. Hanson, *Biotechnology and Commodification Within Health Care*, 24 J. MED. & PHIL. 267, 277 (1999) ("If the rhetoric regarding our genes becomes increasingly commodified at a time when media reports continue to strengthen the link between genes and human traits that centrally define us both as a species and as individuals, a subtle but not insignificant offense to notions of personhood and concomitant self-perception may occur."); cf. Margaret Jane Radin, *Market-Inalienability*, 100 HARV. L. REV. 1849, 1881 (1987) ("Systematically conceiving of personal attributes as fungible objects is threatening to personhood, because it detaches from the person that which is integral to the person."). But see David B. Resnik, *DNA Patents and Human Dignity*, 29 J.L. MED. & ETHICS 152, 152 (2001) (arguing that DNA patents do not violate human dignity because they do not constitute complete commodification of human beings).

For arguments that DNA patents appropriate the common heritage of humankind, see Utility Guidelines, *supra*, at 1094 cmt. 6; Melissa L. Sturges, Comment, *Who Should Hold Property Rights to the Human Genome? An Application of the Common Heritage of Humankind*, 13 AM. U. INT'L L. REV. 219, 245-47 (1997); Ned Hettinger, *Patenting Life: Biotechnology, Intellectual Property, and Environmental Ethics*, 22 B.C. ENVTL. AFF. L. REV. 267, 286-87 (1995). Cf. Barton Beebe, Note, *Law's Empire and the Final Frontier: Legalizing the Future in the Early Corpus Juris Spatialis*, 108 YALE L.J. 1737 (1999) (predicting that the vision of the human genome as the common heritage of humankind will serve an important cultural purpose regardless of its ultimate effect on legal doctrine).

For arguments that DNA patent claims are directed to "products of nature" and therefore violate the Patent Act's § 101 limitations on patentable subject matter, see Utility Guidelines, *supra*, at 1093 cmt. 2; Hettinger, *supra*; John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents* (pt. 1), 85 J. PAT. & TRADEMARK OFF. SOC'Y 301 (2003); Linda J. Demaine & Aaron Xavier Fellmeth, *Reinventing the Double Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent*, 55 STAN. L. REV. 303, 393-400 (2002); Burton T. Ong, *Patenting the Biological Bounty: Re-Examining the Status of Organic Inventions as Patentable Subject Matter*, 8 MARQ. INTELL. PROP. L. REV. 1, 19-20 (2004); Jon F. Merz & Mildred K. Cho, *Disease Genes Are Not Patentable: A Rebuttal of McGee*, 7 CAMBRIDGE Q. HEALTHCARE ETHICS 425 (1998).

disclosure in the biotechnology industry and as an artifact of the current state of information technology. Part VI concludes.

II. THE STRUCTURE OF DNA MOLECULES

The entire collection of genetic material of a particular organism is known as its “genome.” Each cell in an organism contains a copy of the same genome in the form of a set of structures called “chromosomes,” which are made up of DNA. A DNA molecule consists of two long chains or “strands,” each made up of smaller molecules called “nucleotides.” Each nucleotide consists of a sugar (“deoxyribose”), a phosphate, and a base. There are four kinds of bases: adenine (A), thymine (T), cytosine (C) and guanine (G). Each base has a unique complement: in a DNA molecule, an A on one strand is always paired with a T on the other, and a C on one strand is always paired with a G on the other (and vice versa).⁶ The order of bases occurring along one strand of a DNA molecule is referred to as the molecule’s “structural formula,” “nucleotide sequence,” or “DNA sequence.”⁷ The last term is also sometimes used to refer to the DNA molecule itself.⁸

Numerous variations, or “polymorphisms,” exist among the genomes of different individuals of the same species. Some of these variations occur in the form of “single nucleotide polymorphisms” (SNPs)—regions in the genome where there is a difference of only one nucleotide in a longer sequence of nucleotides.⁹ As recognizable markers of individuality in the human genome, SNPs can serve as the basis for the study of statistical associations between DNA sequences and the prevalence of disease among different individuals.¹⁰

The two ends of each strand of a DNA molecule are distinguishable in that the sugar at one end (the “5’ end”) has a free fifth carbon atom and the sugar at the other end (the “3’ end”) has a free third carbon atom.¹¹ The sequence of each strand is the order of bases in the strand, reading from the 5’ end to the 3’ end. Two strands can join, or “hybridize,” to form a DNA molecule (the familiar “double helix”) if, when the 5’ end of a strand is aligned with the 3’ end of another, there is a correspondence of complementary base pairs between their two sequences. Since the sequence of each strand can be inferred from the other by reversing the sequence and replac-

6. See J.D. WATSON ET AL., *MOLECULAR BIOLOGY OF THE GENE* (1987).

7. See Oak Ridge Nat’l Lab., *Genome Glossary*, available at http://www.ornl.gov/sci/techresources/Human_Genome/glossary/glossary_d.shtml (last visited Mar. 3, 2006) (defining DNA sequence as “[t]he relative order of base pairs, whether in a DNA fragment, gene, chromosome, or an entire genome”).

8. See, e.g., U.S. Patent No. 5,935,837, claim 13 (filed July 28, 1997) (issued Aug. 10, 1999) (using the language “[a]n isolated and purified DNA sequence” to claim an isolated and purified DNA molecule).

9. See DESMOND S.T. NICHOLL, *AN INTRODUCTION TO GENETIC ENGINEERING* 175 (2d ed. 2002).

10. See *id.*

11. See JOÃO SETUBAL & JOÃO MEIDANIS, *INTRODUCTION TO COMPUTATIONAL MOLECULAR BIOLOGY* 5-6 (1997).

ing each base with its complementary base, such sequences are called “reverse complements.”

Closely related to DNA molecules are ribonucleic acid (RNA) molecules. Although RNA and DNA encode essentially the same genetic sequence information, RNA molecules differ chemically from DNA molecules in that their nucleotides use a different base, uracil (U) instead of thymine (T), as the complement of adenine (A). RNA molecules also use a different sugar, ribose instead of deoxyribose.

Genetic sequence information is inherited through processes of reproduction. Certain contiguous segments of chromosomal DNA, known as “genes,” constitute the basic units of inheritance. Typically within each gene are segments of DNA that encode protein chains (“polypeptides”) to be synthesized by the cell interspersed with non-coding segments of DNA. The coding regions of a gene are called “exons,” and the non-coding regions are called “introns.”

Genes provide the original blueprints for protein synthesis but do not participate directly in the building of polypeptides. Instead, a working copy of the DNA sequence information from each of a gene’s exons is “transcribed” from one strand (the “antisense” strand) of the gene to a complementary single-stranded messenger RNA (mRNA) molecule. Ribosomes in the cell then use the sequence information in the mRNA molecule to arrange amino acids into a polypeptide. This process may be repeated with thousands of mRNA molecules and polypeptides being derived from a single DNA molecule.¹² Genes and exons that serve in this way as the source of sequence information for protein synthesis are said to be “expressed.”

Each group of three consecutive bases in the mRNA strand (a “codon”) corresponds to a specific amino acid, according to a scheme generally known as the “genetic code.” For example, the mRNA sequence 5'-AUGCAGACA-3' corresponds to the amino acid sequence Methionine-Glutamine-Threonine. While there are sixty-four possible sequences of three bases that can be derived from the four RNA bases A, C, G, and U, only twenty kinds of amino acids are used in the building of polypeptides. Some of the sixty-four codons encode the same amino acids, while others do not encode amino acids at all, but signal the end of the polypeptide chain (“stop codons”). The resulting redundancy in the encoding scheme is known as the “degeneracy” of the genetic code. This degeneracy implies that many different DNA molecules may encode the same amino acid sequence.

In cloning and other genetic engineering procedures, it is often useful to have a DNA molecule that is reverse-complementary to a particular mRNA molecule. Such a DNA molecule may be synthesized from the mRNA molecule by using a special enzyme known as “reverse transcriptase” to create a reaction called “reverse transcription.” The resulting product is re-

12. See Elisa Izaurralde & Iain W. Mattaj, *RNA Export*, 81 *CELL* 153 (1995).

ferred to as a complementary DNA molecule, or “cDNA” for short.¹³ A cDNA molecule may be single-stranded or double-stranded.

An “oligonucleotide” is a relatively short single strand of a DNA molecule, typically two to fifty bases in length. The suffix “mer” may be used to create a shorthand term for an oligonucleotide of a given length. For example, a “10-mer” refers to an oligonucleotide ten bases in length.

Oligonucleotides bearing a particular DNA sequence can hybridize at locations on other single-stranded DNA molecules where the reverse-complementary sequence occurs. This sequence-specific hybridization property makes oligonucleotides useful for detecting DNA molecules that contain a particular subsequence and for causing chemical interactions to occur at a particular location on a DNA molecule. More detailed descriptions of the many uses for oligonucleotides are provided in the appendices.

Oligonucleotides with a given nucleotide sequence can be synthesized from scratch in the laboratory through an iterative sequence of chemical reactions whereby each DNA molecule is built up one nucleotide at a time in reverse order (from the 3' end to the 5' end).¹⁴ This process is often performed by an automated instrument, known as a “DNA synthesizer,” capable of creating trillions of oligonucleotides in a single run.¹⁵ Typically the procedure produces a mixture of both full-length oligonucleotides and shorter, incomplete molecules. A variety of methods, including gel electrophoresis and reversed-phase chromatography,¹⁶ are available to remove the shorter molecules from the mixture, thereby leaving the oligonucleotides in an isolated and purified form.

III. THE PATENTABILITY OF DNA MOLECULES

Research results on the functional characterization of genes have led many scientific organizations to seek patents claiming particular DNA molecules as having biological significance. The resulting patent applications have raised difficult questions regarding the eligibility of the claimed inventions under the relevant provisions of the Patent Act.¹⁷

The Patent Act provides that, to be eligible for a U.S. patent, a claimed invention must constitute patentable subject matter¹⁸ and meet certain standards of utility,¹⁹ novelty,²⁰ and nonobviousness.²¹ Also, the applicant must

13. NICHOLL, *supra* note 9, at 90-92.

14. JOSEPH SAMBROOK & DAVID W. RUSSELL, *MOLECULAR CLONING: A LABORATORY MANUAL* 10.42 (2001).

15. *See id.* at 10.46 (estimating the minimum amount of an oligonucleotide synthesized by an automatic machine as five to fifty nanomoles). DNA synthesizers have recently been used to replicate the entire genome of the polio virus. *See* Jeronimo Cello et al., *Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template*, 297 *SCIENCE* 1016 (2002).

16. *See* SAMBROOK & RUSSELL, *supra* note 14, at 10.48-49.

17. 35 U.S.C. §§ 1-376 (2000).

18. *See id.* § 101.

19. *See id.*

20. *See id.* § 102(a), (e)-(g).

provide an adequate disclosure of the invention²² and must file the application promptly after the commencement of certain activities deemed to place the public in possession of the invention.²³

In this Part, I will describe how the courts and the Patent Office have interpreted each of these statutory provisions in establishing the doctrines governing the patentability of DNA molecules. Much of what follows will serve as an introduction to patent law, with an emphasis on biotechnology. In the course of this exposition, however, I will also show how the patentability analysis of DNA patent claims implicitly relies on a key simplifying assumption about the nature of DNA discovery. This observation in turn will inform the drafting of the artful prior art reference for DNA oligonucleotides—the subject of the remainder of this Article.

A. *The Registry Model of DNA Discovery*

In analyzing the patentability of DNA molecules, the courts and the Patent Office have frequently appealed to what I will call a “registry model” of DNA discovery. I will use this term to refer to the assumption, in various doctrinal contexts, that the discovery of every new and useful DNA molecule is contemporaneous with the act of reducing the molecule’s name (i.e., its structural formula) to writing. Such writings may appear in patents, patent applications, and prior art references, and collectively constitute a registry of discovered DNA molecules.

The registry model of DNA discovery is problematic as a basis for patentability doctrine in at least two respects. First, the model does not accurately reflect the writings of research scientists. In describing a general methodology, scientific publications typically do not enumerate every possible way the methodology can be applied. For example, while articles describing generic methods of making and using oligonucleotides of any given sequence have existed for many years, these publications do not individually list the structural formula for each oligonucleotide that can be made and used by those methods and do not suggest the selection of any particular oligonucleotide to be made and used.²⁴ The fact that a claimed oligonucleotide is not named specifically in writing does not diminish the public’s ability to make, and interest in using, the oligonucleotide for the generic purposes disclosed in this literature; however, the patent system does not recognize this literature as relevant prior art.

Second, while the model assumes that the discoverer of a DNA molecule has reduced the molecule’s structural formula to writing at the asserted time of discovery, the patent system does not make a similar assumption about inventors in general. Instead, an inventor is entitled under the doctrine

21. See *id.* § 103.

22. See *id.* § 112.

23. See *id.* § 102(b)-(d).

24. See generally *infra* Part IV (describing preparation and utilization of arbitrary oligonucleotides).

of constructive reduction to practice to rely on a particular reduction of the invention to writing (i.e., the filing of a patent application that adequately discloses the claimed invention) for the date of invention.²⁵ The date of this writing need not be taken to be the date of invention; the inventor may prove an earlier date of invention by showing an actual reduction to practice.²⁶

Despite these problems with the registry model, it continues to enjoy great currency in patent doctrine. In the following sections, I will show how the model influences the patent system's consideration of DNA molecules, as the subjects of both patent claims and prior art references under each of the principal patentability requirements.

B. Section 101: Patentable Subject Matter

To be eligible for a patent, an invention must fit within one of the statutory categories of patentable subject matter established in § 101 of the Patent Act.²⁷ "Whoever invents or discovers any new and useful *process, machine, manufacture, or composition of matter*, or any new and useful *improvement thereof*, may obtain a patent therefore, subject to the conditions and requirements of this title."²⁸ This list of categories, which has origins in the earliest U.S. patent statutes,²⁹ has been interpreted as implementing the constitutional requirement that patent protection be limited to the useful arts—in modern terms, the "technological arts."³⁰

Courts have interpreted the patentable subject matter requirement of § 101 to exclude products of nature,³¹ discoveries in non-technological

25. See, e.g., *Hyatt v. Boone*, 146 F.3d 1348, 1352 (Fed. Cir. 1998) ("The filing of a patent application serves as conception and constructive reduction to practice of the subject matter described in the application.").

26. See *Bates v. Coe*, 98 U.S. 31, 34 (1878) ("[T]he presumption in respect to the invention described in the patent in suit, if it is accompanied by the application for the same, is that it was made at the time the application was filed; and the complainant or plaintiff may, if he can, introduce proof to show that it was made at a much earlier date.").

27. § 101.

28. *Id.* (emphasis added).

29. See Act of Apr. 10, 1790, ch. 7, 1 Stat. 109 (repealed 1793) (authorizing patents for "any useful art, manufacture, engine, machine, or device, or any improvement therein not before known or used"); Act of Feb. 21, 1793, ch. 11, 1 Stat. 318 (amended 1836) (current version at 35 U.S.C. §§ 101-112 (2000)) (amending statutory categories of patentable subject matter to "any new and useful art, machine, manufacture or composition of matter, or any new and useful improvement [thereon], not known or used before the application").

30. See *In re Bergy*, 596 F.2d 952, 959 (C.C.P.A. 1979) ("[T]he present day equivalent of the term 'useful arts' employed by the Founding Fathers is 'technological arts.'" (citing *In re Musgrave*, 431 F.2d 882, 893 (1970))), *cert. granted*, *Diamond v. Bergy*, 444 U.S. 924 (1979), *vacated in part*, *Diamond v. Chakrabarty*, 444 U.S. 1028 (1980), *aff'd sub nom.* 447 U.S. 303 (1980); *In re Toma*, 575 F.2d 872, 877 (C.C.P.A. 1978) (stating that claim must be directed to "technological arts" to be patentable subject matter); *In re Waldbaum*, 457 F.2d 997, 1003 (C.C.P.A. 1972) (same). See generally John R. Thomas, *The Patenting of the Liberal Professions*, 40 B.C. L. REV. 1139 (1999) (examining various definitions of technological arts as alternative approaches to delineating patentable subject matter).

31. See *Diamond v. Diehr*, 450 U.S. 175, 185 (1981) ("Excluded from such patent protection [under section 101] are laws of nature, natural phenomena, and abstract ideas."); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) ("He who discovers a hitherto unknown phenomenon of nature

fields (such as pure mathematics)³² and the liberal arts.³³ As the Supreme Court famously noted in *Diamond v. Chakrabarty*,³⁴ however, these categorical exclusions are strictly construed, permitting patents to issue on “anything under the sun that is made by man.”³⁵ In *Chakrabarty*, the Court interpreted the term “composition of matter” to include “all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids.”³⁶ The Court concluded that a genetically-altered bacterium did not fall within the product of nature exclusion as it was “not nature’s handiwork, but [Chakrabarty’s] own; accordingly it is patentable subject matter.”³⁷ Since *Chakrabarty*, the scope of patentable subject matter under § 101 has been extended to cover an ever-widening range of biological materials that have been genetically altered, purified, or otherwise changed through human intervention into forms not found in nature.³⁸

DNA patent claims are usually directed to DNA molecules in “purified and isolated” form.³⁹ The claim terms “isolated” and “purified” typically do not refer to an absolutely homogeneous condition but more broadly encompass mixtures in which biological substances and large molecules other than the claimed DNA molecule are substantially absent. To give a typical example, a patent issued in 1998 to Chiron Corporation⁴⁰ claims “[a] purified and isolated polynucleotide comprising a contiguous subsequence of at least fourteen nucleotides of SEQ ID NO: 2,”⁴¹ where SEQ ID NO: 2 is a nucleotide sequence listing of 1485 base pairs.⁴² The patent specification further states that a DNA molecule is “purified” if it “is present in the substantial

has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end.”); *Am. Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. (23 Wall.) 566, 593-94 (1874); *Ex parte Latimer*, 1889 Dec. Comm’r Pat. 123; *see also* Conley & Makowski, *supra* note 5, at 319-30 (describing the application of the product of nature doctrine to biological and chemical substances in the pre-biotechnology era).

32. *See, e.g.*, *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972) (holding that an invention consisting of the use of a mathematical algorithm is a mental process and therefore not patentable subject matter under § 101).

33. *See, e.g.*, *In re Toma*, 575 F.2d at 877; *In re Waldbaum*, 457 F.2d at 1003.

34. 447 U.S. 303 (1980).

35. *Id.* at 309 (quoting S. REP. NO. 82-1979, at 5 (1952); H. REP. NO. 82-1923, at 6 (1952)).

36. *Id.* at 308 (quoting *Shell Dev. Co. v. Watson*, 149 F. Supp. 279, 280 (D.D.C. 1957), *aff’d*, 252 F.2d 861 (D.C. Cir. 1958)) (ellipsis in original).

37. *Id.* at 310.

38. *See, e.g.*, *J.E.M. AG Supply Inc. v. Pioneer Hi-Bred Int’l, Inc.*, 534 U.S. 124, 145 (2001) (newly developed plant breeds); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1203-04 (Fed. Cir. 1991) (isolated and purified DNA molecules); *Ex parte Allen*, 2 U.S.P.Q.2d (BNA) 1425, 1428 (B.P.A.I. 1987), *aff’d*, 846 F.2d 77 (Fed. Cir. 1988) (genetically modified oysters); U.S. Patent No. 4,736,866 (issued Apr. 12, 1988) (genetically altered mice); U.S. Patent No. 5,817,479 (issued Oct. 6, 1998) (expressed sequence tags); *see also In re Bergy*, 596 F.2d 952, 967, 987 (C.C.P.A. 1979) (biologically pure culture of a microorganism), *cert. granted*, *Diamond v. Bergy*, 444 U.S. 924 (1979), *vacated in part*, *Diamond v. Chakrabarty*, 444 U.S. 1028 (1980), *aff’d sub nom.* 447 U.S. 303 (1980).

39. Nucleic Acids Encoding a Gap—Associated Proteins, U.S. Patent No. 5,731,427 (filed May 19, 1995) (issued Mar. 24, 1998).

40. *Id.*

41. *Id.* at col. 27, cl.1.

42. *See id.* at col. 2 (identifying figures depicting the DNA sequence of SEQ ID NO: 2).

absence of other biological macromolecul[es], e.g., polypeptides, polynucleic acids, and the like of the same type,” while a DNA molecule is “isolated” if it is “separated not only from other [DNA molecules] that are present in the natural source of the macromolecule but also from other macromolecules.”⁴³ Thus, a DNA molecule excised from a living cell and stored in a saline solution, with no other DNA present, would be “isolated” and “purified” within the meaning of the patent claim, since water and salt are considered small molecules.⁴⁴

Doctrinal support for the patentability of DNA under § 101 is grounded in the structural and functional distinctions between an isolated and purified DNA molecule⁴⁵—a chemical union constituting a “composition of matter”—and its naturally-occurring, impure (i.e., less pure) counterpart. Under the 1952 Patent Act, the courts have generally regarded the purification of natural substances as one of the many forms of human intervention that are capable of producing a “new and useful . . . composition of matter” within the meaning of § 101.⁴⁶ For isolated and purified DNA molecules, this means that the product of nature doctrine retains little independent significance in the patentability analysis, simply collapsing into the generally applicable § 102 novelty requirement⁴⁷ and a slightly stricter version of the § 101 utility requirement.⁴⁸

New and useful methods of using DNA molecules are also eligible for patenting, under the § 101 subject matter category of “new and useful process.” As the statutory language suggests, the “new and useful” requirement applies to the claimed method of using the DNA molecule (the “new use”), and not to the DNA molecule itself. Thus, a new use for a DNA molecule may be patentable even if the DNA molecule itself is already well known and therefore unpatentable.⁴⁹ Being limited in scope to the claimed use, a new use claim is much less preclusive than a composition of matter claim to the DNA molecule itself, which encompasses all uses of the claimed DNA molecule.⁵⁰

43. *Id.* at cols. 6-7.

44. *See id.* at col. 7.

45. *See supra* note 16 and accompanying text.

46. *See Merck & Co., Inc. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156, 161 (4th Cir. 1958). The court noted:

All of the tangible things . . . for which patent protection is granted are products of nature in the sense that nature provides the basic source materials. . . .

. . .

The fact . . . that a new and useful product is the result of processes of extraction, concentration and purification of natural materials does not defeat its patentability.

Id.

47. *See infra* Part III.D.

48. *See infra* Part III.C.

49. *See* 35 U.S.C. § 100(b) (2000) (“The term ‘process’ means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.”).

50. *See id.* § 154(a)(1) (stating that a patent confers, among other things, “the right to exclude others from . . . using . . . the invention throughout the United States”).

By settling the question of patentable subject matter in the case of composition of matter claims to isolated and purified DNA molecules, the patent system has held itself open to applications that disclose and claim DNA molecules in the same manner as in the Chiron example. The disclosure of the structural formula for a DNA molecule, together with a claim directed to subsequences of that structural formula, provide a chemical basis for distinguishing the claimed molecules from the other macromolecules that accompany them in nature. This chemical distinction in turn provides a legal basis for distinguishing the isolated and purified form of each of the claimed molecules from its naturally occurring counterpart. Thus, the structural disclosure of DNA molecules in a patent application comports not only with the registry model of DNA discovery, but also with the § 101 patentable subject matter requirement.

C. Section 101: Utility

Section 101 expressly requires that an invention must be “useful” to be eligible for a patent.⁵¹ This utility requirement derives from the constitutional restriction of patent protection to the “useful Arts” and, like the patentable subject matter requirement, dates from the earliest patent statutes.⁵²

Historically, courts have interpreted the utility requirement as a de minimis standard, requiring only “that the invention should not be frivolous or injurious to the well-being, good policy, or sound morals of society.”⁵³ In *Brenner v. Manson*,⁵⁴ a 1966 decision, however, the Supreme Court determined that the constitutional purpose “[t]o promote the [P]rogress of . . . useful [A]rts”⁵⁵ and the text of § 101 contemplate a “basic quid pro quo” in which the grant of a patent is exchanged for “the benefit derived by the public from an invention with substantial utility.”⁵⁶ Accordingly, the Court held that a claimed invention does not have patentable utility “[u]nless and until . . . specific benefit exists in currently available form.”⁵⁷

While the *Brenner* holding indicated the minimum degree of utility that a patent applicant must assert, it did not address the standard of proof re-

51. See *id.* § 101. In requiring the patent disclosure to enable any person skilled in the art to use the invention, the § 112 enablement requirement also implicitly imposes a utility requirement. See *id.* § 112. While the enablement of utility under § 112 necessarily implies the existence of a utility under § 101, the converse is not necessarily true. For example, if the disclosure enables one use but not a second, a claim that encompasses both utilities will meet the § 101 requirement (because the first use supports utility) but not the § 112 requirement (because the second use is not enabled). Because this distinction is not important for purposes of this Article, the discussion here is confined to the § 101 utility requirement.

52. See Act of Apr. 10, 1790, ch. 7, 1 Stat. 109 (repealed 1793) (authorizing the Secretary of State, the Secretary of War, and the Attorney General to issue patents “if they shall deem the invention or discovery sufficiently useful and important”).

53. See *Lowell v. Lewis*, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8568), *abrogation recognized by In re Fisher* 421 F.3d 1365 (Fed. Cir. 2005).

54. 383 U.S. 519 (1966), *superseded by statute*, Patent Law Amendments Act of 1984, Pub. L. 98-622, 98 Stat. 3383, *as recognized in In re Van Geuns*, 946 F.2d 845 (Fed. Cir. 1991).

55. U.S. CONST. art. I, § 8, cl. 8 (emphasis added).

56. *Brenner*, 383 U.S. at 534 (emphasis omitted).

57. *Id.* at 534-35.

quired to demonstrate the asserted utility.⁵⁸ The Federal Circuit considered this question in *In re Brana*.⁵⁹ The applicants in *Brana* claimed a group of compounds, asserting that they had antitumor activity.⁶⁰ In support of this assertion, the applicants provided declaratory evidence of in vivo activity against a mouse model tumor.⁶¹ The Patent Office rejected the claim for lack of utility, citing two studies that had suggested only a weak relationship between antitumor activity in mice and therapeutic value in humans.⁶² The Federal Circuit reversed, concluding that the Patent Office had failed to meet its “initial burden of challenging a presumptively correct assertion of utility in the disclosure.”⁶³ The court held that this initial burden required the Patent Office to show that “one of ordinary skill in the art would reasonably doubt the asserted utility”; only after this burden was met was the applicant required to “provide rebuttal evidence sufficient to convince such a person of the invention’s asserted utility.”⁶⁴ Because the asserted utility was antitumor activity in mice and not therapeutic activity in humans, the court found the Patent Office’s references insufficient to raise a reasonable doubt of utility.⁶⁵

The Patent Office’s Utility Examination Guidelines⁶⁶ represent the agency’s current approach to examining the utility of claimed DNA molecules, which is to require that the patent application disclose at least one “specific, substantial, and credible” utility for the claimed molecules.⁶⁷ The disclosure of one use for a DNA molecule can thereby support an award of the right to exclude others from all uses of that molecule.⁶⁸ Some commentators have criticized the patent grant as overbroad⁶⁹ and have argued for limiting its scope to a method of using a DNA molecule,⁷⁰ as in a “new use” patent claim.⁷¹ The Patent Office, however, regards its approach to DNA molecules as consistent with the utility requirement for other chemicals⁷²

58. See *id.* at 531 n.17 (“In light of our disposition of the case, we express no view as to the patentability of a process whose sole demonstrated utility is to yield a product shown to inhibit the growth of tumors in laboratory animals.”).

59. 51 F.3d 1560 (Fed. Cir. 1995).

60. See *id.* at 1562.

61. See *id.*

62. See *id.* at 1565-66 & n.15.

63. See *id.* at 1566.

64. See *id.* (citing *In re Bundy*, 642 F.2d 430, 433 (C.C.P.A. 1981)).

65. See *id.* In dicta, the Federal Circuit also found that the applicants’ declaratory evidence would have been sufficient rebuttal evidence in support of the asserted utility. See *id.* at 1566-67.

66. Utility Guidelines, *supra* note 5, at 1092. The 2001 Guidelines superseded guidelines published in 1995. See Utility Examination Guidelines, 60 Fed. Reg. 36,263 (July 14, 1995).

67. Utility Guidelines, *supra* note 5, at 1098. If the application does not disclose such a utility and no well-established utility is readily apparent from the application, then the examiner is to impose an initial rejection, which can then be rebutted. See Utility Examination Guidelines, *supra* note 66, at 36,263.

68. See *id.* at 1094 cmt. 5.

69. See *id.*

70. See *id.* at 1094-95 cmt. 10.

71. See *supra* text accompanying notes 49-50.

72. See Utility Guidelines, *supra* note 5, at 1094 cmt. 5 (“When patents for genes are treated the same as for other chemicals, progress is promoted . . . because a new chemical is made available as a

and compelled by the absence of any legal basis for treating DNA molecules differently.⁷³

In training materials accompanying the guidelines, the Patent Office provides further instructions to examiners on how to apply the “credible, specific, and substantial”⁷⁴ standard for utility. A utility is “specific” if it is applicable “to the subject matter claimed,” rather than “to the broad class of the invention.”⁷⁵ For example, a claim to a DNA molecule for use as a “gene probe” is considered specific only if the application discloses a specific DNA target.⁷⁶ A utility is “substantial” if it defines a “real world” context of use and is not a “throw away” utility.⁷⁷ For example, the use of a DNA molecule in assaying a material “which has a stated correlation to a predisposition to the onset of a particular disease condition” is considered substantial, while the use of a DNA molecule in assaying a material that itself has no disclosed specific and substantial utility is not.⁷⁸ Examples of throw away utilities for a particular protein molecule would be using it as an animal food supplement or a shampoo ingredient.⁷⁹ Finally, a utility is “credible” unless the logic underlying the assertion of utility would be considered seriously flawed or inconsistent with the asserted facts from the standpoint of one of ordinary skill in the art.⁸⁰ For example, it is credible that DNA molecules “could be used as probes, chromosome markers, or forensic or diagnostic markers,”⁸¹ but it is not facially credible that a disclosed chemical compound could be 100% effective in preventing HIV infection.⁸²

The Patent Office appears to invoke the registry model of DNA discovery in reconciling its approach to examining the utility of DNA molecules with the constitutional and statutory purposes of the utility requirement. In comments accompanying the guidelines,⁸³ the Patent Office concludes that an applicant’s disclosure of a DNA molecule with at least one patentable utility promotes progress because, *inter alia*, “a new chemical is made available as a basis for future research.”⁸⁴ This description of the research proc-

basis for future research.”).

73. See *id.* at 1094 cmt.7 (“As long as one specific, substantial and credible use is disclosed and the statutory requirements are met, the USPTO is not authorized to withhold the patent until another, or better, use is discovered.”); *id.* at 1095 cmt. 10 (“Patent law provides no basis for treating DNA differently from other chemical compounds that are compositions of matter.”).

74. See U.S. PATENT & TRADEMARK OFFICE, REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS 4, available at <http://www.uspto.gov/web/menu/utility.pdf> (last visited Mar. 8, 2006).

75. See *id.* at 5.

76. See *id.*

77. See *id.* at 6-7.

78. See *id.* at 6; see also *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) (“[I]n addition to providing a ‘substantial’ utility, an asserted use must also show that that claimed invention can be used to provide a well-defined and particular benefit to the public.”).

79. See U.S. PATENT & TRADEMARK OFFICE, *supra* note 74, at 7.

80. See *id.* at 5.

81. See *id.*

82. See *id.* at 39.

83. See Utility Guidelines, *supra* note 5, at 1092-97.

84. See *id.* at 1094 cmt. 5; see also *id.* at 1094 cmt. 9 (discussing the interpretation of the patent

ess closely parallels the registry model, in which the discovery of a DNA molecule for use in future research coincides with the disclosure of its structural formula.⁸⁵

D. Section 102: Novelty and Loss of Right Provisions

Under § 102, a claimed invention must be new to be eligible for a patent.⁸⁶ Section 102 also includes several loss of right provisions that deny patentability in certain situations where the applicant's conduct or other intervening events are deemed to have altered the terms of the basic quid pro quo between the patentee and the public.⁸⁷ Both the novelty requirement and loss of right provisions of § 102 call for a review of the relevant "prior art," including the teachings of printed publications.

1. The Novelty Requirement

Section 102(a) requires that the applicant have invented the claimed invention prior to its use by others in the United States and prior to its patenting or description in a printed publication anywhere in the world.⁸⁸ Section 102(f) further specifies that the applicant must have been the true first inventor and may not have derived the invention from others.⁸⁹

A patent application is treated as confidential by the Patent Office⁹⁰ and is generally not made available to the public until either it is published eighteen months after its initial filing,⁹¹ or it ripens into an issued patent.⁹² In either case, once the application has become public, it is deemed by § 102(e) to have been published as of the initial filing date.⁹³

In a priority contest between two inventors, the general rule is that the first to both conceive the invention and reduce the invention to practice (either "actually," by building a working model or "constructively," by filing a patent application) is the first true inventor.⁹⁴ Section 102(g), however, provides that the first to conceive the invention can demonstrate priority by showing reasonable diligence in reducing the invention to practice from a

bargain in the case of "the disclosure of a DNA sequence").

85. It may be possible for an applicant to disclose a DNA molecule without disclosing its structural formula. *See* Utility Guidelines, *supra* note 5, at 1095 cmt. 14 ("[D]escribing the complete chemical structure, *i.e.*, the DNA sequence, is one method of describing a DNA molecule but it is not the only method."). *But see* *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998) (adequate disclosure will "usually [be] achieved" by reciting the molecule's structural formula).

86. *See* 35 U.S.C. § 102(a), (e)-(g) (2000).

87. *See id.* § 102(b)-(d).

88. *Id.* § 102(a).

89. *Id.* § 102(f).

90. *See id.* § 122(a).

91. *See id.* § 122(b).

92. *See id.* § 102(e)(2).

93. *See id.* § 102(e).

94. *See id.* § 102(g).

time prior to conception by the other inventor.⁹⁵ In this analysis, an applicant who applies for a U.S. patent within one year after filing a foreign patent application may claim the priority of the foreign filing date.⁹⁶

In *Amgen, Inc. v. Chugai Pharmaceutical Co.*,⁹⁷ the Federal Circuit rejected an argument that one of the defendants' scientists, Edward Fritsch, had conceived the claimed DNA molecule in 1981 with reasonable diligence prior to the patentee's invention in September 1983.⁹⁸ Noting that Fritsch did not sequence the molecule until 1984, the court concluded that he had no conception until that date:

[U]ntil Fritsch had a complete mental conception of [the claimed DNA molecule] and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.⁹⁹

Consequently, under § 102(g), Fritsch could not claim a date of invention earlier than his actual reduction to practice in 1984, when "the gene ha[d] been isolated."¹⁰⁰

2. *Loss of Right Provisions*

Section 102(b) requires that the applicant file within one year after the first "sale" or "public use" of the invention in the United States or its patenting or description in a "printed publication" anywhere in the world.¹⁰¹ Each of these statutory conditions is a term of art. A "sale" can include a commercially firm offer for sale, even if the sale is not consummated.¹⁰² "Public use" can include non-secret uses of the invention by anyone¹⁰³ and secret uses of the invention by the applicant,¹⁰⁴ but does not include entirely non-commercial, experimental uses.¹⁰⁵ Finally, as discussed more fully below,¹⁰⁶

95. *Id.*

96. *See id.* § 119.

97. 927 F.2d 1200 (1991).

98. *Id.* at 1208.

99. *Id.* at 1206.

100. *Id.*

101. § 102(b).

102. *See* A.B. Chance Co. v. RTE Corp., 854 F.2d 1307, 1311-12 (Fed. Cir. 1988).

103. *See, e.g.,* Egbert v. Lippmann, 104 U.S. 333, 333, 337 (1881) (holding the private use of corset springs for eleven years to be a "public use"); Abbott Labs. v. Geneva Pharm., Inc., 182 F.3d 1315, 1315 (Fed. Cir. 1999) (holding a third party's sale of a drug containing the claimed compound sufficient to raise the "on sale" bar of § 102(b), even though the third party did not recognize that the drug contained the claimed invention).

104. *See, e.g.,* Metallizing Eng'g Co. v. Kenyon Bearing & Auto Parts Co., 153 F.2d 516, 520 (2d Cir. 1946) (L. Hand, J.) (holding the commercial use of a secret process sufficient for reconditioning machine parts to raise the "public use" bar of § 102(b)).

105. *See, e.g.,* Madey v. Duke Univ., 307 F.3d 1351, 1362 (Fed. Cir. 2002) (holding that the experimental use defense "does not immunize use that is in any way commercial in nature").

“the touchstone in determining whether a reference constitutes a ‘printed publication’” is its “public accessibility,”¹⁰⁷ not its widespread dissemination or reproduction in print.

Section § 102(c) provides that one who abandons one’s invention loses the right to a patent on the invention.¹⁰⁸ Also, under § 102(d), if more than one year has passed after an inventor has filed for a patent in a foreign country, and the foreign patent has already issued, the inventor can no longer file an application for a U.S. patent on the same invention.¹⁰⁹

3. *Prior Art; Anticipation*

Section 102 calls for, *inter alia*, an examination of evidence of a claimed invention’s public use, sale, patenting, or description in a printed publication, which is collectively referred to as “prior art.” Under §§ 102(a) and (b), such prior art may include public uses and sales occurring in the United States and patents and printed publications published worldwide, either more than a year before the filing date or prior to the date of invention.¹¹⁰ Certain other references may also be included as prior art under § 102(d), (e), (f), and (g), as discussed above.¹¹¹ A prior art reference is said to “anticipate” a claimed invention, thereby defeating the novelty requirement of § 102(a) or triggering the loss of right provisions of § 102(b), if the reference contains every element of the claim.¹¹²

Anticipation requires that “some single prior article, patent, or publication contain[s] within its four corners every element of the claim in question”; such as, claim elements may not be “distributed among several prior publications or devices.”¹¹³ Incorporation by reference allows material not explicitly contained within the four corners of a prior art document to be considered in the anticipation analysis, as such material “is effectively part of the host document as if it were explicitly contained therein.”¹¹⁴ For incorporation by reference to be effective, “the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.”¹¹⁵ The question of whether the material to be incorporated has been identified with sufficiently detailed particularity is to be determined from the perspective of one reasonably skilled in the art.¹¹⁶

106. *See infra* Part III.D.4.

107. *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986).

108. 35 U.S.C. § 102(c) (2000).

109. *See id.* § 102(d).

110. *Id.* § 102(a), (b).

111. *Id.* § 102(d)-(g).

112. *See Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988).

113. *Paeco, Inc. v. Applied Moldings, Inc.*, 562 F.2d 870, 875 (3d Cir. 1977).

114. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

115. *Id.*

116. *See id.* at 1283.

An anticipating reference must also “be enabling and describe the applicant’s claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention.”¹¹⁷ Under the prevailing Federal Circuit interpretation of the enablement requirement, a § 102 reference must disclose a method of making the claimed invention in any case where the method is not obvious to one with ordinary skill,¹¹⁸ but need not disclose a use for the claimed invention.¹¹⁹ By comparison, the § 112 enablement requirement for a patent application is more stringent: a patent application must teach anyone skilled in the art both how to make and how to use the claimed invention.¹²⁰

In the case of claims to chemical compounds, courts have generally required either that a method of making the compound be disclosed by the reference or be known or obvious to one of ordinary skill in the art.¹²¹ Because the behavior of chemical compounds is often difficult to predict, courts have also had to consider the possibility that a disclosed method for making a genus of chemical compounds may not work for every compound in the genus.¹²² Courts have not hesitated to reverse § 102 rejections where the claimed compounds “could not possibly have been made by the process taught by the reference,” or have “properties *completely* different from those attributed to them by the reference description.”¹²³ Also, in cases where attempts to prepare the claimed compounds using the disclosed generic methods have failed, courts have viewed such failures as “strong evidence that the disclosure of the publication was nonenabling.”¹²⁴ As long as the list of compounds is commensurate with the reference’s teachings, however, the reference will be found to satisfy the enablement requirement for anticipation.¹²⁵ Moreover, there is no requirement that any compounds in the ge-

117. *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994); see also *Seymour v. Osborne*, 78 U.S. (11 Wall.) 516, 555 (1870) (holding that an anticipating foreign publication must “contain and exhibit a substantial representation of the patented improvement, in such full, clear, and exact terms as to enable any person skilled in the art or science to which it appertains, to make, construct, and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent”); 1 DONALD S. CHISUM, CHISUM ON PATENTS § 3.04[1][b], at 3-91 (2005) (“[M]ost lower courts, including the Federal Circuit adopt the enablement standard of *Seymour*.”).

118. See *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) (“Such possession is effected if one of ordinary skill in the art could have combined the publication’s description of the invention with his own knowledge to make the claimed invention.”); see also *In re Payne*, 606 F.2d 303, 314 (C.C.P.A. 1979) (“An invention is not ‘possessed’ [by one of ordinary skill] absent some known or obvious way to make it.”); *In re Coker*, 463 F.2d 1344, 1348 (C.C.P.A. 1972) (“Since it has not been established that methods for making the compound named in the Tsou reference were known or were described in that reference, it cannot be said that the reference would have placed the public in possession of the invention.”).

119. See *In re Schoenwald*, 964 F.2d 1122, 1124 (Fed. Cir. 1992).

120. 35 U.S.C. § 112 (2000).

121. See *In re Payne*, 606 F.2d at 314 (“An invention is not ‘possessed’ absent some known or obvious way to make it.”); 1 CHISUM, *supra* note 117, § 3.04[1][c], at 3-106 (“A method of making the compound must either be obvious to one with ordinary skill in the art or be disclosed by the [anticipating] reference.”).

122. See 1 CHISUM, *supra* note 117, § 3.04[1].

123. *In re Wilder*, 429 F.2d 447, 451 (C.C.P.A. 1970).

124. *In re Donohue*, 766 F.2d at 533 (citing *In re Wiggins*, 488 F.2d 538 (C.C.P.A. 1973)); *In re Sheppard*, 339 F.2d 238 (C.C.P.A. 1964).

125. Indeed, such a disclosure would satisfy the more stringent section 112, paragraph 1 enablement

nus previously have been made by the disclosed method, or indeed any method.¹²⁶ the anticipating reference need only enable one of ordinary skill in the art to make at least one claimed compound.¹²⁷

As far as the Federal Circuit is concerned, there is no requirement that an anticipating reference disclose a utility for a claimed chemical compound.¹²⁸ Some lower courts, however, have held that an anticipating reference must disclose “a minimum of one significant useful property” of a claimed compound.¹²⁹ Even for these courts, there is no requirement that a § 102 reference disclose a specific utility. Under either line of caselaw, then, the disclosure of a “significant” generic utility for the listed compounds is sufficient for an anticipating reference. Thus, an anticipating reference is not held to the “specific, substantial utility” standard of § 101.¹³⁰ This apparent “double standard” is no accident; to the contrary, it is “implicitly if not explicitly, required by law.”¹³¹ It also comports with the policy behind § 102: that a patent should issue only when the disclosure by the applicant of how to practice the claimed invention will “increase ‘the store of common knowledge.’”¹³² If generic methods of making and using a particular compound have already been disclosed in a prior art reference, then a patent applicant’s disclosure of a specific and substantial utility for the same compound does not add the compound itself to the store of common knowledge, but only a new use for the compound. Accordingly, the applicant may be entitled to a patent covering the new use¹³³ but is not entitled to exclude the

requirement in the context of a patent application. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) (“[W]hat is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought.”); *In re Vaack*, 947 F.2d 488, 496 (Fed. Cir. 1991) (“It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed.”) (citation and footnote omitted).

126. See *In re Donohue*, 766 F.2d at 533 (“It is not . . . necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.”). But see *In re Wiggins*, 488 F.2d at 543 (finding that a compound listed in a reference was not “described” within the meaning of § 102(b) where the reference failed to teach “a method suitable for its preparation” and the reference provided “nothing more than speculation about [the listed compounds]’ potential or theoretical existence”).

127. See *In re Donohue*, 766 F.2d at 533 (“It is well settled that prior art under 35 U.S.C. § 102(v) must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the publication’s description of the invention with his own knowledge to make the claimed invention.”) (citations and footnote omitted).

128. *In re Schoenwald*, 964 F.2d 1122, 1124 (Fed. Cir. 1992) (describing this rule as “beyond argument”).

129. *Revlon, Inc. v. Carson Prods. Co.*, 602 F. Supp. 1071, 1083 (S.D.N.Y. 1985), *aff’d*, 803 F.2d 676 (Fed. Cir. 1986); *Warner-Jenkinson Co. v. Allied Chem. Corp.*, 477 F. Supp. 371, 383 (S.D.N.Y. 1979), *aff’d*, 633 F.2d 208 (2d Cir. 1980) (unpublished decision).

130. *In re Hafner*, 410 F.2d 1403, 1405 (C.C.P.A. 1969).

131. *Id.*

132. See 1 CHISUM, *supra* note 117, § 3.01, at 3-5 (quoting *Dewey v. Almy Chem. Co.*, 124 F.2d 986, 989 (2d Cir. 1942)).

133. Section 100(b) of the Patent Act provides that a “new use of a known . . . composition of mat-

public from making the compound for other uses, including the generic uses described in the reference.¹³⁴

4. Publication

For a printed publication to be published and therefore available as a prior art reference under § 102, it must be sufficiently disseminated such that it is accessible to the interested public.¹³⁵ Widespread dissemination, however, is unnecessary. For example, in *In re Hall*,¹³⁶ the Federal Circuit concluded that “a single cataloged thesis in one university library” could serve as the basis for a § 102 “printed publication” bar.¹³⁷

In *Hall*, the application at issue had an effective filing date of February 27, 1979.¹³⁸ The examiner rejected the claims under § 102(b) as anticipated by a dissertation that had been written by a chemistry doctoral student and deposited into the library collections at Freiburg University in Germany.¹³⁹ The examiner relied on an affidavit from the University’s library director stating that the dissertation was freely available to the public as of December 1977, more than a year before Hall’s filing date.¹⁴⁰ When the applicant appealed, the Patent Office obtained further affidavits from the director describing the library’s general procedures for indexing, cataloging, and shelving dissertations, stating that the library received the dissertation on November 4, 1977 and concluding that “the dissertation most probably was available for general use toward the beginning of the month of December, 1977.”¹⁴¹ Based on this information, the board affirmed the rejection.¹⁴²

The Federal Circuit agreed with the Patent Office’s approach.¹⁴³ The court held that to sustain a § 102 printed publication bar, a reference must be “sufficiently accessible, at least to the public interested in the art, so that such a one by examining the reference could make the claimed invention

ter” may be considered a “process” and is therefore eligible subject matter for a patent under § 101. See 35 U.S.C. §§ 100(b), 101 (2000).

134. See *In re Schoenwald*, 964 F.2d 1122, 1124 (Fed. Cir. 1992) (“The compound appellants are attempting to patent is not new—the use they discovered is, and they received a method patent for that. . . . Their contribution was finding a use for the compound, not discovering the compound itself. Therefore they are being rewarded fully for their contribution; any more would be a gratuity.”); see also *In re Bayer*, 568 F.2d 1357, 1361 (C.C.P.A. 1978) (“The publication bar of 35 U.S.C. § 102(b) . . . operates upon the theory that the invention in controversy is in the public domain, and once there, is no longer patentable by anyone.”) (emphasis omitted). But see John T. Soma & Alexander J. Neudeck, *The Internet and the Single Document Rule: Searching for the Four Corners of the Electronic Paper*, 78 J. PAT. & TRADEMARK OFF. SOC’Y 751, 778 (1996) (“Equating the enablement requirement for § 112 and § 102 furthers the purposes of the Patent Act.”).

135. See *In re Hall*, 781 F.2d 897, 898-99 (Fed. Cir. 1986).

136. *Id.*

137. *Id.* at 900.

138. *Id.* at 897.

139. *Id.* at 897-98.

140. *Id.*

141. *Id.* at 898.

142. *Id.*

143. *Id.*

without further research or experimentation.”¹⁴⁴ While noting that more precise evidence would be desirable, the court also held that “competent evidence of the general library practice may be relied upon” to support an accessibility determination.¹⁴⁵ In this case, the court inferred that the director “was relying on his library’s general practice for indexing, cataloging and shelving theses in estimating the time it would have taken to make the dissertation available to the interested public.”¹⁴⁶ The court noted that the accessibility determination “rests on the facts of each case,” but concluded that in these circumstances, the director’s affidavits established a prima facie, un rebutted case that the dissertation was accessible more than a year before Hall’s filing date.¹⁴⁷ Accordingly, the court affirmed the board’s decision.¹⁴⁸

5. Anticipation by “Shotgun” Disclosures

A “shotgun” reference that specifically names thousands or even millions of chemical compounds can anticipate every one of them, provided that the reference is also enabling. For example, in *Ex parte A*,¹⁴⁹ the Board of Patent Appeals and Interferences reviewed an examiner’s § 102(a) rejection of a claim to a compound as anticipated by a European patent specification.¹⁵⁰ The reference listed forty-six formulae, including the formula for the claimed compound, and described “synthetic procedures” suitable for the preparation of the claimed compound.¹⁵¹ The applicants objected to the reference, citing a previous Court of Customs and Patent Appeals decision, *In re Wiggins*.¹⁵² In *Wiggins*, the court reversed a § 102(b) rejection over a reference that named two claimed compounds “whose syntheses were unsuccessfully attempted,”¹⁵³ holding:

The mere naming of a compound in a reference, without more, cannot constitute a description of the compound, particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed until a date later than that of the reference.

If we were to hold otherwise, lists of thousands of theoretically possible compounds could be generated and published which, assuming it would be within the level of skill in the art to make them,

144. *Id.* at 899.

145. *Id.*

146. *Id.*

147. *Id.* at 899-900.

148. *Id.* at 900.

149. 17 U.S.P.Q.2d (BNA) 1716 (B.P.A.I. 1990).

150. *Id.* at 1718.

151. *Id.*

152. 488 F.2d 538 (C.C.P.A. 1973).

153. *Id.* at 542.

would bar a patent to the actual discoverer of a named compound no matter how beneficial to mankind it might be.¹⁵⁴

The board in *Ex parte A* distinguished *Wiggins*, noting the existence of a “known synthetic method of producing”¹⁵⁵ the compound disclosed in the European patent specification. On the basis of uncontroverted findings that the claimed compound was both named and enabled by the reference, the board concluded that the examiner’s rejection was correct.¹⁵⁶ The board went on to emphasize that an enabling reference would be found to anticipate every named compound, regardless of how many compounds were named:

Even if the number of compounds disclosed in the reference were several orders of magnitude greater, we would come to the same conclusion. The tenth edition of the *Merck Index* lists ten thousand compounds. In our view, each and every one of those compounds is “described,” as that term is used in 35 U.S.C. § 102(a), in that publication. A similar conclusion would be appropriate with respect to the approximately 1.5 million compounds disclosed in the *Beilstein Handbook* (*Handbuch der Organischen Chemie*).¹⁵⁷

The Patent Office’s Manual of Patent Examining Procedure cites *Ex parte A* for the rule that “[a] genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named.”¹⁵⁸

The Court of Customs and Patent Appeals reached a similar result in *In re Sivaramakrishnan*.¹⁵⁹ In that case, the applicant claimed, inter alia, a chemical composition combining a polycarbonate resin with cadmium laurate.¹⁶⁰ The Board of Patent Appeals and Interferences imposed a § 102 rejection for anticipation by a patent issued to Gable, which had disclosed a generic formula for polycarbonate resins combined with any of about seventy metal salts, including cadmium laurate.¹⁶¹ On appeal, the applicant argued that Gable’s listing of metal salts was not a “description” of the compounds within the meaning of § 102, citing *Wiggins* to support his

154. *Id.* at 543 (footnote omitted).

155. *Ex parte A*, 17 U.S.P.Q.2d (BNA) at 1718.

156. *Id.* at 1717-18.

157. *Id.* at 1718.

158. See U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2131.02 (8th ed. 2001) [hereinafter MPEP] (citing *Ex parte A*, 17 U.S.P.Q.2d (BNA) at 1716), available at <http://www.uspto.gov/web/offices/pac/mpep/> (scroll down screen; click on “2100 pdf”).

159. 673 F.2d 1383 (C.C.P.A. 1982).

160. *Id.*

161. *Id.* at 1383-84.

claim.¹⁶² The court distinguished *Wiggins* by noting that Gable had enabled the claimed composition: “[T]he polycarbonates of interest were well known to the art, as was cadmium laurate,” and there was nothing to suggest any difficulty in combining them.¹⁶³ The court also noted that it was irrelevant that Gable had not actually made the composition; the issue was whether the mixture was “described in a printed publication,” which it was.¹⁶⁴ Citing *Sivaramakrishnan*, Martin Adelman’s patent law treatise summarizes the court’s approach to “shotgun” disclosures: “In conclusion, the rule of law derivable from *Sivaramakrishnan* appears to be that if the material is specifically *named* in the prior art, it is described within the meaning of Section 102 even if a very large number of other materials are also named.”¹⁶⁵

In a related case, *In re Petering*,¹⁶⁶ the Court of Customs and Patent Appeals considered the anticipatory effect of prior art generic formulae that encompassed many specific chemical compounds in addition to the claimed compositions. In *Petering*, the examiner rejected claims to compounds as anticipated by a prior art generic formula, and the Board of Appeals affirmed the rejection. The court found that in addition to the generic formula, the reference disclosed a preferred class of compounds described by the formula.¹⁶⁷ Given that the class was “limited” to “only 20 compounds” and represented only a “limited number of variations” within the generic formula, the court reasoned that “one skilled in this art would, on reading the [reference], at once envisage each member of this limited class, even though this skilled person might not at once define in his mind the formal boundaries of the class as we have done here.”¹⁶⁸ Because the author of the reference had “described to those with ordinary skill in this art each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name,” the court concluded that the claimed compounds within the preferred class had been “described in a printed publication” within the meaning of § 102.¹⁶⁹

At first, it may seem incongruous that in *In re Petering* the court’s finding of anticipation rested on the “limited” number of compounds encompassed within one of the reference’s generic disclosures, whereas *Ex parte A* and *In re Sivaramakrishnan* indicate that there is no limit to the number of compounds that can be anticipated by a reference. The anticipating reference in *Petering*, however, did not disclose the claimed compounds explicitly by specific names or formulae but only implicitly, as instances of a generic chemical formula. *Petering* therefore stands for the proposition that in

162. *Id.* at 1384.

163. *Id.*

164. *Id.* at 1384-85.

165. MARTIN J. ADELMAN, 1-2 PATENT LAW PERSPECTIVES § 2.2 (2d ed. 2004).

166. 301 F.2d 676 (C.C.P.A. 1962).

167. *Id.* at 682.

168. *Id.* at 681 (emphasis omitted).

169. *Id.* at 682 (emphasis omitted).

certain limited circumstances, a generic formula may describe a claimed compound as fully as a specific name for purposes of § 102.¹⁷⁰ *A* and *Sivaramakrishnan* stand for the proposition that an unlimited number of compounds can be described within a single reference for purposes of § 102, provided that they are enabled and specifically named. Read together, these decisions focus the § 102 description inquiry on which compounds one of skill in the art would envisage in reading the reference, rather than either the number or format of the formulae describing the disclosed compounds.

It is also implicit in each of these decisions that in an enabling reference, a specific name or formula suffices as a § 102 description of a chemical compound.¹⁷¹ In enabling one of skill in the art "at once [to] envisage each member"¹⁷² of the disclosed class,¹⁷³ a "shotgun" reference that provides the specific names or formulae of numerous compounds does not raise the vagueness concerns that might attend a less particularized form of disclosure. For example, in *In re Arkley*,¹⁷⁴ the Board of Patent Appeals and Interferences had sustained a § 102(e) anticipation rejection, having found all of the elements of the claimed compound by taking them from different examples and teachings scattered throughout the prior art patent specification.¹⁷⁵ The Court of Customs and Patent Appeals reversed,¹⁷⁶ holding that an anticipating reference "must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."¹⁷⁷ Such forbidden "hindsight anticipations"¹⁷⁸ are not in issue when the prior art reference explicitly discloses the specific name or formula of the claimed compound.

170. See also *In re Schaumann*, 572 F.2d 312, 316-17 (C.C.P.A. 1978) ("When we consider also that [the reference] embraces a very limited number of compounds closely related to one another in structure, we are led inevitably to the conclusion that the reference provides a description of those compounds just as surely as if they were identified in the reference by name."). On the limited circumstances underlying the *Petering* holding, see *In re Ruschig*, 343 F.2d 965, 973 (C.C.P.A. 1965) ("Petering involved a very special situation which we do not consider comparable to the situation at bar.").

171. See *supra* text accompanying notes 158, 165, 169; see also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art." (citing *In re Petering*, 301 F.2d at 682)).

172. *In re Petering*, 301 F.2d at 681.

173. See *supra* text accompanying note 168; see also *In re Petering*, 301 F.2d at 681-82.

174. 455 F.2d 586 (C.C.P.A. 1972).

175. *Id.* at 586-87.

176. *Id.* at 590.

177. *Id.* at 587.

178. See *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965) (explaining that *Petering* does not provide "a precedent for the mechanistic dissection and recombination of the components of the specific illustrative compounds in every chemical reference containing them, to create hindsight anticipations with the guidance of an applicant's disclosures, on the theory that such reconstructed disclosures *describe* specific compounds within the meaning of section 102."); see also *Air Prods. & Chems., Inc. v. Charles S. Tanner Co.*, 219 U.S.P.Q. (BNA) 223, 231 (D.S.C. 1983) ("Furthermore, a prior art reference which contains a broad general disclosure requiring guessing, testing, speculation or 'picking and choosing' from an encyclopedic disclosure will not anticipate.").

Specific DNA molecules are usually named by structural formulae, at least in their first occurrence in the genetic research literature.¹⁷⁹ References that teach methods for making and using DNA molecules generically, however, usually do not name each specific DNA molecule that can be made and used by those methods. Nevertheless, *Petering, A.* and *Sivaramakrishnan* focus the § 102 description inquiry on the disclosure of structural formulae in accordance with the registry model of DNA discovery. Under this caselaw, a “shotgun” reference that lists the structural formulae for millions of specific DNA molecules anticipates claims to any of the molecules, but a reference that teaches only a generic formula anticipates claims to each species only in limited circumstances.

E. Section 103: Nonobviousness

A claimed invention that “is not identically disclosed or described” in a § 102 prior art reference may still be ineligible for a patent under § 103 “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.”¹⁸⁰ For purposes of the nonobviousness analysis, prior art is generally limited to references that are either “in the field of the applicant’s endeavor” or “reasonably pertinent to the particular problem with which the inventor was concerned.”¹⁸¹ Such prior art may include references that could be considered under § 102(a), (b), (e), (f), and (g), except that § 102(e), (f), and (g) references are excluded if they deal with subject matter co-owned with the claimed invention.¹⁸²

As the text of § 103 indicates, the nonobviousness requirement calls for a comparison between the prior art and the elements of the claimed invention from the perspective of one of ordinary skill in the art.¹⁸³ A claimed invention may be found obvious under § 103 if there is some combination of prior art references that together contain all elements of the invention, and if one of ordinary skill in the art, at the time the invention was made, would have found the invention as a whole to be obvious in light of these

179. Some genes and gene fragments may also be named according to functional characteristics or other conventions. Given the relative ease of DNA sequencing, *see infra* text accompanying notes 402-409, and the conventions of genetic research, however, it is very unlikely that a scientist would report an initial functional characterization of a gene or gene fragment without also identifying the gene’s sequence.

180. *See* 35 U.S.C. § 103(a) (2000).

181. *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992); *see also In re Wood*, 599 F.2d 1032, 1036 (C.C.P.A. 1979) (“[W]e attempt to more closely approximate the reality of the circumstances surrounding the making of an invention by only presuming knowledge by the inventor of prior art in the field of his endeavor and in analogous arts.”).

182. *See* § 103(c); *OddzOn Prods., Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1403 (Fed. Cir. 1997) (“[T]he language [in § 103(c)] that states that § 102(f) subject matter is not prior art under limited circumstances clearly implies that it is prior art otherwise.”).

183. *See supra* notes 168-69 and accompanying text.

references.¹⁸⁴ Such a combination of references can serve as the basis for an obviousness rejection, however, only if there is a motivation or suggestion in the prior art to combine the references.¹⁸⁵ Absent such a teaching, “[p]atentability shall not be negated by the manner in which the invention was made,”¹⁸⁶ even if the techniques used were routine in the art¹⁸⁷ or automated.¹⁸⁸

In *Graham v. John Deere Co.*,¹⁸⁹ the Supreme Court described the nonobviousness inquiry as a case-by-case analysis in which “the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.”¹⁹⁰ The Court also identified several indicia of nonobviousness—“commercial success, long felt but unsolved needs, failure of others, etc.”—that might be incorporated into the analysis as “secondary considerations.”¹⁹¹ The Federal Circuit has subsequently elevated the doctrinal importance of “secondary considerations,” declaring that:

[E]vidence rising out of the so-called “secondary considerations” must always when present be considered en route to a determination of obviousness. Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.¹⁹²

1. *Prior Art Methods of Isolating DNA Molecules*

The nonobviousness inquiry focuses on a comparison between the claimed invention and the relevant prior art. A DNA patent claim typically identifies the claimed DNA molecules by reciting their structural formulae—disclosing and referring to the specific sequences of nucleotides that make up the molecules. The recited structural formulae therefore serve as

184. *Id.*

185. *See* *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984); *see also* *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998) (describing motivation to combine as an “essential evidentiary component of an obviousness holding”).

186. § 103(a).

187. *See* Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1070 (2003) (noting that biotechnology firms have filed “tens of thousands of patent applications on DNA sequences that they have been able to generate quickly through routine, automated sequencing methods”).

188. *See* John H. Barton, *Rational Limits on Genomic Patents*, 18 NATURE BIOTECHNOLOGY 805 (2000) (noting with concern that DNA molecules identified through automated gene sequencing might be considered nonobvious).

189. 383 U.S. 1 (1966).

190. *Id.* at 17.

191. *Id.* at 17-18.

192. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983) (citations omitted).

elements of the claim which are to be compared with the prior art in applying the nonobviousness requirement.

If a claimed DNA molecule's structural formula is neither disclosed nor suggested by the prior art, the invention may be considered nonobvious even though general procedures leading to the making and use of the molecule are well-known and described in the prior art. In effect, this approach equates the disclosure of a new and nonobvious structural formula for a useful DNA molecule with the act of making "a new chemical . . . available as a basis for future research."¹⁹³

For example, in *In re Deuel*,¹⁹⁴ the Federal Circuit reviewed a § 103 rejection of claims directed to isolated and purified cDNA molecules encoding certain proteins known as heparin-binding growth factors (HBGFs).¹⁹⁵ The inventors had produced the claimed invention by first isolating bovine uterine HBGF protein and determining the first twenty-five amino acids at one end of the protein.¹⁹⁶ Next, they analyzed the amino acid sequence information to design an oligonucleotide probe, which they then used to find a complementary molecule from within a library of cDNA molecules that were known to encode bovine uterine proteins in general.¹⁹⁷ Finally, the inventors determined the nucleotide sequence of this cDNA molecule and its corresponding amino acid sequence.¹⁹⁸

In rejecting the claims, the patent examiner cited two references, Bohlen and Maniatis.¹⁹⁹ The Bohlen reference disclosed proteins known as heparin-binding brain mitogens (HBBMs) and a short portion of the amino acid sequence at one end of each protein.²⁰⁰ The Maniatis reference described a method of isolating cDNAs by screening a library of cDNAs with a gene probe.²⁰¹ The examiner found that it would be obvious to one of ordinary skill to design a gene probe based on Bohlen's amino acid sequences and to use this probe in screening a cDNA library using Maniatis's method to isolate a gene encoding an HBGF.²⁰² In upholding the rejection, the Board of Patent Appeals and Interferences further asserted that HBBMs are the same as HBGFs and that the genes encoding them were identical.²⁰³ The Board found that one of ordinary skill would be motivated to isolate a gene for HBBM using Bohlen's amino acid sequence information and Maniatis's cDNA screening method.²⁰⁴

193. See Utility Guidelines, *supra* note 5, at 1094 cmt. 5.

194. 51 F.3d 1552 (Fed. Cir. 1995).

195. *Id.* at 1555.

196. *Id.*

197. *Id.*

198. *Id.*

199. *Id.* at 1555-56.

200. *Id.* at 1556.

201. *Id.*

202. *Id.*

203. *Id.* at 1556-57.

204. *Id.* at 1557.

The Federal Circuit took a different view of the two references. Because the patent claims were directed to “new chemical entities in structural terms,” the court focused its inquiry on whether the references contained any teachings that made the structure of the claimed cDNA molecules obvious.²⁰⁵ The court found the Bohlen reference inadequate in this regard because it disclosed only amino acid sequences for proteins and not nucleotide sequences for cDNA molecules.²⁰⁶ Because of the degeneracy of the genetic code, the court concluded that one skilled in the art could not have conceived the structural formulae of the claimed cDNA molecules from the teachings in Bohlen alone.²⁰⁷ The court also found the Bohlen reference insufficient when read in conjunction with the Maniatis reference because Maniatis taught methods for potentially isolating cDNA molecules and not cDNA molecules themselves.²⁰⁸ In particular, the Maniatis reference contained no teaching regarding the precise structure of the claimed cDNA molecules.²⁰⁹ Even assuming that one of ordinary skill had the motivation and knowledge to apply Maniatis’s method to identify the cDNA molecules encoding Bohlen’s proteins, the court concluded that “a conceived method of preparing some undefined DNA does not define it with the precision necessary to render it obvious over the protein it encodes.”²¹⁰ Accordingly, the court held “that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs,”²¹¹ and reversed the Board’s rejection.

2. *Prior Art Generic Disclosures of DNA Molecules*

Unlike the prior art references at issue in *Deuel*, many other references do disclose specific DNA molecules. Given the astronomical number of possible DNA molecules, however, any particular claimed DNA molecule is more likely to be described in a prior art generic disclosure encompassing many molecules (a “genus”) than in a more specific disclosure of the claimed molecule or molecules (the claimed “species” or “subgenus”). In particular, generic methods of making²¹² and using²¹³ oligonucleotides of

205. *Id.* at 1557-58 (“In all of these cases . . . the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.”).

206. *See id.*

207. *See id.*

208. *Id.*

209. *See id.* at 1558 (“[T]he prior art does not disclose any relevant cDNA molecules Maniatis suggests an allegedly obvious process for trying to isolate cDNA molecules, but that, . . . does not fill the gap regarding the subject matter of claims 5 and 7.”).

210. *Id.* at 1560.

211. *See id.* at 1559.

212. *See, e.g.,* J. SAMBROOK ET AL., *MOLECULAR CLONING: A LABORATORY MANUAL* 10.42-46 (3d ed. 2001); K. Itakura et al., *Synthesis and Use of Synthetic Oligonucleotides*, 53 ANN. REV. BIOCHEMISTRY 323 (1984); M.D. Matteucci & M.H. Caruthers, *Synthesis of Deoxynucleotides on a*

arbitrary sequence are well known in the literature. In this “genus-species” situation, the focus of the obviousness inquiry is on “whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus.”²¹⁴

For example, in *In re Baird*,²¹⁵ the applicant claimed toner compounds comprising a bisphenol A polyester and a dicarboxylic acid selected from the group consisting of succinic acid, glutaric acid, and adipic acid.²¹⁶ The prior art reference disclosed a generic formula that encompassed more than 100 million diphenols (including bisphenol A)²¹⁷ and twenty dicarboxylic acids (including succinic acid, glutaric acid, and adipic acid).²¹⁸ The reference also identified a smaller number of preferred diphenols, none of which was bisphenol A.²¹⁹ The examiner rejected the claim as obvious, reasoning that bisphenol A “may be easily derived from the generic formula of the diphenol in [Knapp] and all the motivation the worker of ordinary skill in the art needs to arrive at the particular polyester of the instant claim[] is to follow [that formula].”²²⁰ The Board affirmed the rejection, and the applicant appealed. In reversing the Board’s rejection, the Federal Circuit found that the reference did not “teach or fairly suggest the selection of bisphenol A. A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.”²²¹

The Federal Circuit followed similar reasoning in *Deuel*. Recalling *Petering*,²²² the court acknowledged that the claimed cDNA molecules might be found obvious “if there were prior art, e.g., a protein of sufficiently small size and simplicity, so that lacking redundancy, each possible DNA would be obvious over the protein.”²²³ The proteins at issue in *Deuel*, however, were sufficiently complex that “the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein.”²²⁴ Citing *Baird*, the court concluded that “[n]o particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.”²²⁵

Polymer Support, 103 J. AM. CHEM. SOC’Y 3185 (1981); S.A. Narang, *DNA Synthesis*, 39 TETRAHEDRON 3 (1983).

213. See *infra* app. A.

214. MPEP, *supra* note 158, § 2144.08(II)(A)(4).

215. 16 F.3d 380 (Fed. Cir. 1994).

216. *Id.* at 381.

217. *Id.* at 382.

218. *Id.* at 381-82.

219. *Id.* at 382-83.

220. *Id.* at 382 (alterations in original).

221. *Id.* at 383 (citation omitted).

222. See *supra* note 162 and accompanying text.

223. *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995); see also *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

224. *In re Deuel*, 51 F.3d at 1558.

225. *Id.* at 1558-59; see also *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993) (reversing a § 103 rejection).

Summarizing *Deuel*, *Baird*, and other Federal Circuit decisions relevant to the examination of oligonucleotide claims, former Patent Office examiner Jeffery Fredman concludes that the § 103 caselaw “supports the obviousness of primers and probes where the prior art teaches the entire sequence. Where the prior art does not teach the sequence, this same set of case law support a finding of nonobviousness.”²²⁶ In other words, the Federal Circuit has adopted the registry model of DNA discovery in its consideration of oligonucleotide prior art under § 103.

Both *Deuel* and *Baird* illustrate the situation where a prior art reference did not render a claimed compound obvious even though its teaching of a generic method for making the claimed compound, as one species of a disclosed genus, would most likely have been found sufficient to satisfy the enablement requirement for anticipation.²²⁷ Such a reference, though cited in a § 103 rejection, could have been used to support a § 102 rejection but for the fact that the claimed compound was disclosed generically rather than by its specific name or formula.²²⁸

F. Section 112: Adequate Disclosure

Section 112, first paragraph, requires that a patent application’s specification “shall contain a written description of the invention, and of the manner and process of making and using it” in such terms as to enable one of ordinary skill “to make and use the same,” and must also “set forth the best mode contemplated by the inventor of carrying out his invention.”²²⁹ By its terms, this provision encompasses three substantive requirements for an adequate patent disclosure: enablement, best mode, and written description. The enablement and best mode requirements aim to ensure that patentees fulfill their part of the patent system’s “carefully crafted bargain” by teaching the public to practice their claimed and disclosed inventions.²³⁰ The written description requirement “ensures that, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims.”²³¹

tion of a claimed nucleic acid molecule where the prior art disclosed only an amino acid sequence and failed “to suggest which of [the more than 10³⁶ possible nucleotide sequences] is the human sequence”).

226. Jeffery Fredman, Comment, *Are Oligonucleotide Primers and Probes Prima Facie Obvious over Larger Prior Art Nucleic Acids?*, 19 SANTA CLARA COMPUTER & HIGH TECH. L.J. 285, 313 (2002).

227. See *supra* text accompanying notes 117-127. As Arti Rai has observed, the Federal Circuit’s “contorted logic” implies that “a DNA sequence can be nonobvious even though the information necessary for isolating the sequence is publicly available.” Arti Rai, *Addressing the Patent Gold Rush: The Role of Deference to PTO Patent Denials*, 2 WASH. U. J.L. & POL’Y 199, 205 (2000).

228. See *supra* text accompanying notes 171-173.

229. 35 U.S.C. § 112 (2000).

230. See *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 150-51 (1989) (“The federal patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years.”).

231. *Union Oil Co. v. Atl. Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000).

The written description requirement has not been read to prescribe *per se* rules regarding the suitability of any particular format for the patent specification, so long as “the invention as claimed is adequately described to one skilled in the art.”²³² In particular, the courts have long held that the written description requirement permits an invention to be claimed generically, “without describing all species that claim encompasses.”²³³ In *Regents of the University of California v. Eli Lilly & Co.*,²³⁴ however, the Federal Circuit found that a specification that provided only a general method for obtaining the claimed cDNA molecule and the amino acid sequences encoding the molecule was not an adequate description of the molecule.²³⁵ The court held that for a patent specification to satisfy the written description requirement with respect to a claimed DNA molecule, the disclosure “requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the [DNA].”²³⁶ In requiring a structural description and rejecting a methodological disclosure as proof of the molecule’s discovery as of the filing date, the Federal Circuit invoked the registry model of DNA discovery.

In an effort to reconcile the *Lilly* decision with the court’s previous holdings, the Patent Office in 2001 issued examination guidelines²³⁷ stating that “[t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by . . . disclosure of relevant, identifying characteristics . . . sufficient to show the applicant was in possession of the claimed genus”²³⁸ Under the guidelines, examiners do not require the “identifying characteristics” to take the form of a structural formula; description by one or more “functional characteristics alone or coupled with a known or disclosed correlation between structure and function” may also be acceptable.²³⁹ The Federal Circuit has subsequently adopted the guidelines’ positions on these points.²⁴⁰

232. See *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996) (stating that an applicant may overcome a written description rejection by showing by a preponderance of the evidence that “the invention as claimed is adequately described to one skilled in the art”).

233. *Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988).

234. 119 F.3d 1559 (Fed. Cir. 1997).

235. See *id.* at 1567.

236. *Id.* at 1569 (citing *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993)); cf. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1214 (Fed. Cir. 1991) (finding a lack of enablement where applicant had “claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make [the gene itself] and a very few analogs”).

237. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, “Written Description” Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001).

238. *Id.* at 1106.

239. *Id.*

240. See *In re Wallach*, 378 F.3d 1330, 1333 (Fed. Cir. 2004); *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002).

G. Summary

The registry model of DNA discovery powerfully influences the patent system's treatment of DNA molecules in patent claims and prior art references. For a DNA molecule whose discovery is claimed by a patent applicant, the reduction of the molecule's name to writing simultaneously evidences the discovery to the patent system and confers knowledge of the discovery upon the public. Insofar as the recitation of a structural formula may be necessary to distinguish a claimed DNA molecule from other materials, the Federal Circuit regards the discovery of a DNA molecule as occurring contemporaneously with the identification of its sequence.²⁴¹ As the Federal Circuit has interpreted the § 112 written description requirement, the applicant's demonstration to the patent system that a DNA molecule has been discovered is "usually achieved" by disclosure of the molecule's structural formula.²⁴² Under the § 101 utility requirement, a patent applicant who first discloses a DNA molecule's structural formula along with at least one "specific, substantial and credible" utility for the molecule is credited with the discovery of the molecule itself and with making "a new chemical . . . available as a basis for future research."²⁴³ The disclosure of a DNA molecule's structural formula also serves to distinguish the molecule from other macromolecules for purposes of defining a composition of matter claim to the isolated and purified form of the molecule that satisfies the § 101 subject matter requirement.²⁴⁴

Where methods of making and using a DNA molecule are already known, the reduction of the molecule's name to writing in an enabling reference is viewed by the patent system as the most effective way of placing the molecule into the prior art. As the Patent Office has interpreted the Court of Customs and Patent Appeals' § 102 jurisprudence, a "clearly named" compound listed in an enabling reference will anticipate a claim to that compound "no matter how many other [compounds] are additionally named" in the reference.²⁴⁵ As long as the structural formula enables one of skill in the art to "envisage" and make the specific molecule in question, the fact that the formula appears in a "shotgun" reference does not diminish the reference's teaching.²⁴⁶ In contrast, the Federal Circuit's § 103 caselaw holds that methodological and generic disclosures of DNA molecules do not render a claimed molecule obvious absent a teaching that makes the structure of the claimed molecule obvious.²⁴⁷ Similarly, disclosures of generic

241. See *supra* text accompanying notes 97-100.

242. See *supra* text accompanying note 236.

243. Utility Guidelines, 66 Fed. Reg. 1092, 1094 (Jan. 5, 2001); see *supra* text accompanying note 193.

244. See *supra* text accompanying note 45.

245. MPEP, *supra* note 158, § 2131.02; see *supra* text accompanying note 158.

246. See *supra* text accompanying notes 171-173.

247. See *supra* text accompanying notes 205-211, 226.

formulae are found to anticipate claimed compounds under § 102 only in very limited circumstances.²⁴⁸

In some respects, the registry model is simply a trope that reframes a longstanding debate. Many previous commentators have criticized the Federal Circuit's focus on structural disclosure in *Deuel* and *Lilly*.²⁴⁹ Having identified the descriptive model of DNA discovery underlying the Federal Circuit's reasoning, however, it is now possible to go beyond these criticisms to construct a response to the model in the form of artful prior art. The next part presents an example of such artful prior art: a registry of readily makeable and usable oligonucleotides that I created and published in 2002.

IV. AN ARTFUL PRIOR ART REFERENCE FOR DNA OLIGONUCLEOTIDES

A. Creation of the Reference

As I have suggested, the Federal Circuit's *Deuel* and *Baird* decisions leave open the possibility that a deficient § 103 reference may be amended to produce an effective § 102 reference by listing specific names of compounds instead of, or in addition to, disclosing them generically.²⁵⁰ In particular, it is a straightforward matter to cure the deficiencies in the scientific literature on oligonucleotides so as to satisfy the requirements for anticipation.

For example, a published article describing generic methods of making and using arbitrary oligonucleotides of twelve bases in length could be

248. See *supra* note 170 and accompanying text.

249. For criticism of *Deuel*, see A PATENT SYSTEM FOR THE 21ST CENTURY 92 (Stephen A. Merrill et al. eds., 2004); Anita Varma & David Abraham, *DNA Is Different: Legal Obviousness and the Balance Between Biotech Inventors and the Market*, 9 HARV. J.L. & TECH. 53, 78-79 (1996); Jeffrey S. Dillen, Comment, *DNA Patentability: Anything but Obvious*, 1997 WIS. L. REV. 1023, 1041-44; Philippe Ducor, *The Federal Circuit and In re Deuel: Does § 103 Apply to Naturally Occurring DNA?*, 77 J. PAT. & TRADEMARK OFF. SOC'Y 871, 889-90 (1995); Rebecca S. Eisenberg & Robert P. Merges, *Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial DNA Sequences*, 23 AIPLA Q.J. 1, 32 (1995); Rai, *supra* note 203; Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1071 (2003).

The *Lilly* requirement of structural disclosure for the written description of claimed DNA molecules, see *supra* note 236 and accompanying text, has also been widely criticized as replacing a standard based on the perspective of one of ordinary skill in the art with a per se rule. See, e.g., *Univ. of Rochester v. G.D. Searle & Co., Inc.*, 375 F.3d 1303, 1307-08 (Fed. Cir. 2004) (Rader, J., dissenting) (arguing that the *Lilly* decision's "judge-made doctrine has created enormous confusion which this court declines to resolve"); 2-3 ADELMAN, *supra* note 165, § 2.9; MERRILL, *supra*, at 94; Dan L. Burk & Mark A. Lemley, *Biotechnology's Uncertainty Principle*, 54 CASE W. RES. L. REV. 691, 695-700 (2004); Robert A. Hodges, *Black Box Biotech Inventions: When a "Mere Wish or Plan" Should Be Considered an Adequate Description of the Invention*, 17 GA. ST. U. L. REV. 831, 860-61 (2001); Arti K. Rai, *Intellectual Property Rights in Biotechnology: Addressing New Technology*, 34 WAKE FOREST L. REV. 827, 835 (1999); 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, 244 (2004); Warren D. Woessner, "Do-Over!" —The Federal Circuit Takes a Second Look at *Enzo v. Gen-Probe*, 85 J. PAT. & TRADEMARK OFF. SOC'Y 275, 285 (2003).

250. See *supra* text accompanying note 228.

amended by appending a list of all 4^{12} DNA sequences. As augmented, the article would then be a single reference containing a written description of every possible 12-mer and enabling one of ordinary skill to make and use each. Alternatively, 4^{12} versions of the same article could be produced, each describing methods of making and using a single oligonucleotide, with each document subject to review on its own merits for sufficiency as a prior art reference. Whether in a unitary document or distributed across numerous documents, the resulting registry should be found to anticipate each of the listed oligonucleotides.²⁵¹

As an empirical proof of concept, a CD-ROM entitled "On the Preparation and Utilization of Isolated and Purified Oligonucleotides," was created by the author on March 9, 2002 and deposited in the Kathrine R. Everett Law Library at the University of North Carolina School of Law on March 11, 2002. The CD-ROM was immediately shelved in the library's non-circulating reference collection, and was indexed (under the Library of Congress subject heading "Oligonucleotides," call number QP625.O47 C45 2002) and added to the University's online catalog on March 14, 2002. The document was subsequently listed with the International Online Computer Library Center (No. 49930387).

The principal file on the disk, DISCLOSE.TXT, was specifically designed to satisfy each of the § 102 anticipation requirements with respect to each of the listed oligonucleotides. Out of an abundance of caution, the list was restricted to the oligonucleotides that are least likely to form secondary structures and are therefore among the easiest to make and most versatile to use.²⁵² An excerpt from the file DISCLOSE.TXT is provided in Appendix D. More than 11 million sequences are listed in the full file. The CD-ROM also contains SHORT.TXT, an abridged version of the article that lists only 8-mers, 9-mers, and 10-mers, and README.TXT, which describes the two files and grants permission to copy the disk.

251. The single reference is sufficient to place all 4^{12} recited oligonucleotides into the prior art. See *supra* Part III.D.5.

The latter approach of generating 4^{12} individualized documents arguably yields an even stronger case for invalidating claims to the listed oligonucleotides, as each such document would also support an obviousness rejection of any claim covering the specific molecule whose structural formula was recited therein. In contrast, under current § 103 genus/species doctrine, see MPEP § 2144.08 ("Obviousness of Species When Prior Art Teaches Genus"), it is questionable whether the disclosure of 4^{12} structural formulae in a single reference would be found to render any of the listed species obvious. Compare *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993) ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences suggested by [the prior art reference] corresponds to the [claimed] gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences."), and *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) ("A disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds."), with *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962) (holding that a prior art chemical formula generically describing twenty compounds inherently anticipated a claim directed to one species because "one skilled in [the] art would . . . envisage *each member*" of the genus); see also *supra* Part III.E.2.

252. See *infra* text accompanying notes 360-363.

B. Legal Sufficiency of the Reference

Under *In re Hall*,²⁵³ each document on the CD-ROM should be regarded as a § 102 “printed publication” as of March 14, 2002. The determination that the digital document DISCLOSE.TXT is a printed publication is consistent with the Federal Circuit’s interpretation of the term, focusing on the document’s availability to the interested public in light of “ongoing advances in the technologies of data storage, retrieval, and dissemination.”²⁵⁴ Although the CD-ROM is non-circulating, it is available to the public for viewing and printing in the library. Specifically, DISCLOSE.TXT can be viewed and printed on any of the library’s personal computers via the DOS commands TYPE and PRINT, respectively. The library also fulfills interlibrary loan requests by making copies of the CD-ROM to order.

DISCLOSE.TXT readily satisfies the enablement requirement, in view of the advanced state of the art in DNA synthesis. Despite the reference’s technical language, the reference breaks no new scientific ground; it merely reports on known generic methods of making and using certain oligonucleotides.²⁵⁵ Indeed, the Federal Circuit (in a 1993 unpublished opinion) has found it “beyond dispute” that various genetic research laboratory techniques, including “oligonucleotide synthesis techniques,” already existed in the art.²⁵⁶ Also, DISCLOSE.TXT incorporates disclosures of generic methods of making and using oligonucleotides that were taken directly from the specifications of issued patents and may therefore be presumed to be enabling.²⁵⁷

As a § 102 reference with an effective date of March 14, 2002,²⁵⁸ DISCLOSE.TXT satisfies the single source, printed publication, and enablement requirements for anticipation of composition of matter claims to each of the 11 million oligonucleotides described in the sequence listing. It is therefore effective prior art against claims covering any of the listed oligonucleotides where either the claimed invention occurred on or after

253. 781 F.2d 897 (Fed. Cir. 1986).

254. *Id.* at 898; see also *In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981) (“Given the state of technology in document duplication, data storage, and data-retrieval systems, the ‘probability of dissemination’ of an item very often has little to do with whether or not it is ‘printed’ in the sense of that word when it was introduced into the patent statutes in 1836.”); *Philips Elec. & Pharm. Indus. Corp. v. Thermal & Elec. Indus., Inc.*, 450 F.2d 1164, 1170 (3d Cir. 1971) (“[T]here have been revolutionary developments in techniques for reproduction, printing and dissemination of documents and data. The traditional process of ‘printing’ is no longer the only process synonymous with ‘publication.’ The emphasis, therefore, should be public dissemination of the document, and its availability and accessibility to persons skilled in the subject matter or art.”).

255. See *supra* text accompanying note 24.

256. See *In re Sun*, No. 93-1261, 1993 WL 533128, at *3-*4 (Fed. Cir. Dec. 23, 1993) (unpublished opinion).

257. See 35 U.S.C. § 282 (2000) (“A patent shall be presumed valid.”).

258. The effective date of the reference is March 14, 2002, the date the CD-ROM was indexed, catalogued, and shelved in the Kathrine R. Everett Library. See *supra* text accompanying notes 138-141 (discussing *In re Hall*, 781 F.2d 897).

March 15, 2002²⁵⁹ or the patent application was filed on or after March 15, 2003.²⁶⁰

C. Industry Response to the Reference

While it is still too early to measure the full effect of the publication of DISCLOSE.TXT on the patenting of oligonucleotides, early industry response indicates that the reference has succeeded as a proof of concept. Many applicants for DNA patents have become aware of the reference and its possible relevance as prior art against their oligonucleotide claims.

Section 122(b) of the Patent Act provides for the publication of most U.S. patent applications eighteen months after the filing date.²⁶¹ In September 2003, when oligonucleotide-related patent applications filed on or after March 15, 2002 began appearing on the Patent Office's Web site, inventors and attorneys were notified of the oligonucleotide reference and provided with a copy of the CD-ROM.²⁶² As of August 2004, the oligonucleotide reference had been cited in the prosecution history files of at least twenty-five pending patent applications and one issued patent. Details are provided in Appendix E.

During the prosecution of these applications, if the oligonucleotide reference is found to disclose the subject matter of one or more claims, such claims should be rejected as anticipated under § 102. In particular, the oligonucleotide reference should be found to anticipate composition of matter claims directed to any of the listed molecules. Applicants who filed between March 15, 2002 and March 14, 2003 will have the opportunity to "swear behind the reference"—file a verified statement of facts establishing a date of invention before March 14, 2002.²⁶³

Applicants who cannot swear behind the reference or who filed on or after March 15, 2003 will have to amend or cancel the rejected composition of matter claims. Assuming that the application discloses a specific, substantial, and credible utility, a new use claim limited to the disclosed utility for the oligonucleotide might be allowable over the oligonucleotide refer-

259. See *supra* text accompanying note 88.

260. See *supra* text accompanying note 101.

261. See § 122(b)(1)(A).

262. The approach of contacting the applicants rather than the Patent Office had two advantages. First, I avoided paying the administrative fee for filing a third-party submission of a publication relevant to a pending published application. See 37 C.F.R. § 1.99(b)(1) (2005); *id.* § 1.17(p) (stating that the fee for such "Sec. 1.99" submission is currently \$180). Second, by leaving the applicants to decide whether or not to disclose the reference to the Patent Office, I obtained an early indication of the likelihood that the anticipatory effect of the oligonucleotide reference would eventually be addressed during the prosecution of the application. Inventors and attorneys are required to disclose to the Patent Office all information they know to be material to the patentability of any claim in a pending application. See *id.* § 1.56. While the disclosure of any such information does not constitute an admission that the information is material to patentability, see *id.* § 1.97(h), the time and expense involved might be expected to deter the disclosure at least of facially irrelevant information. See *id.* § 1.17(p) (stating that the fee for filing an information disclosure after the first office action on the application is \$180).

263. See *id.* § 1.131.

ence. Such a new use claim, however, would be much narrower in scope than the rejected composition of matter claim.²⁶⁴

V. THE OLIGONUCLEOTIDE REFERENCE IN CONTEXT

A. *The Reference as an Illustration of the Distinction Between Section 102 and Section 103 Doctrines*

In referring to the relative stringency of the single-reference requirement for anticipation, patent practitioners often say that “anticipation is the epitome of obviousness.”²⁶⁵ This aphorism has led some litigants and courts to reason that the existence of an anticipating reference is conclusive proof of obviousness.²⁶⁶ It is, however, improper to proceed from a finding that a claim is anticipated under § 102 to conclude, *a fortiori*, that the claim is also obvious under § 103. The oligonucleotide reference may be viewed as an instructive reminder that the requirements for anticipation under § 102 are separate and distinct from, and not subsumed by, the inquiries required to support a finding of obviousness under § 103.²⁶⁷

As Judge Giles Rich described in *In re Bergy*,²⁶⁸ the patentability requirements of § 101, § 102, and § 103 are analogous to “three doors” that are to be approached “in succession.”²⁶⁹ Accordingly, § 103(a) expressly states that the nonobviousness analysis presupposes that “the invention is not identically disclosed or described as set forth in section 102 of this title.”²⁷⁰ In other words, after a patent claim has been held anticipated under § 102, no factual inquiry into the obviousness of the claim should take place. As Professor Adelman’s treatise explains:

Obviousness as the basis for invalidity means that Section 103 has come into play bringing with it the full significance of the eviden-

264. See *supra* text accompanying notes 49-50.

265. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) (quoting *In re Fracalossi*, 681 F.2d 792, 794 (C.C.P.A. 1982)); see also *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983).

266. See, e.g., *In re Fracalossi*, 681 F.2d at 794 (upholding a § 103 rejection because it showed “the ultimate obviousness—lack of novelty”); *In re Avery*, 518 F.2d 1228, 1234 (C.C.P.A. 1975) (affirming a § 103 rejection because “[t]he claimed product is completely disclosed in the prior art. The complete disclosure of an invention in the prior art is the ultimate or epitome of obviousness”); *In re Pearson*, 494 F.2d 1399, 1402 (C.C.P.A. 1974) (“[T]his court has sanctioned the practice of nominally basing rejections on § 103 when, in fact, the actual ground of rejection is that the claims are anticipated by the prior art. The justification for this sanction is that a lack of novelty in the claimed subject matter, e.g., as evidenced by a complete disclosure of the invention in the prior art, is the ‘ultimate or epitome of obviousness.’”) (citation omitted).

267. See *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002) (“[T]hough anticipation is the epitome of obviousness, [they] are separate and distinct concepts.” (citing *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984))) (alteration in original).

268. 596 F.2d 952 (C.C.P.A. 1979), *aff’d in relevant part sub nom.* *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

269. *Id.* at 960.

270. 35 U.S.C. § 103(a) (2000).

tiary issues which are bedrock to a Section 103 situation. Thus, for example, if the patent is invalid because anticipated by the prior art under Section 102, evidence having to do with the level of ordinary skill in the art and the related objective criteria which the Supreme Court had so fully enunciated in [*Graham*] simply do not come into play. They need be neither introduced nor considered; they may not be used by way of arguing the validity of the patent.²⁷¹

In a 1983 decision, the Federal Circuit stated: “*Though it is never necessary to so hold*, a disclosure that anticipates under § 102 also renders the claim invalid under § 103, for ‘anticipation is the epitome of obviousness.’”²⁷² By noting that such a holding “is never necessary,” the court implicitly acknowledged that a § 102 anticipation finding forecloses the § 103 inquiry even in the face of the aphorism.²⁷³ Subsequent Federal Circuit decisions have removed this crucial proviso, however, suggesting that a finding of anticipation under § 102 can serve as the sole basis for a finding of obviousness under § 103.²⁷⁴

The problematic nature of this approach is illustrated in *In re Meyer*,²⁷⁵ a 1979 Court of Patent and Customs Appeals decision. Patent Office regulations permit an applicant to respond to a new ground of rejection by amending claims or requesting a rehearing.²⁷⁶ In *Meyer*, the Board of Appeals sustained the examiner’s § 103 rejection on the grounds that the claim was anticipated under § 102, and concluded that no new ground of objection had been made since “anticipation is the epitome of obviousness.”²⁷⁷ The court rejected this reasoning:

While it is true that prior cases from this court have used such phrases as “anticipation is the epitome of obviousness” or “anticipation is the ultimate in obviousness,” the board’s reliance on those cases to support its conclusion that it had not made a new ground of rejection is totally misplaced. The use in prior cases of the aforementioned phrases is nothing more than the recognition of the

271. ADELMAN, *supra* note 165.

272. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (emphasis added); *see also* *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

273. *Connell*, 722 F.2d at 1548.

274. *See* *MercExchange, L.L.C. v. eBay, Inc.*, 401 F.3d 1323, 1330 (Fed. Cir. 2005) (“Because ‘anticipation is the epitome of obviousness,’ the defendants’ obviousness arguments preserved their right to argue invalidity based on anticipation.” (quoting *Connell*, 722 F.2d at 1548)), *cert. granted*, 126 S. Ct. 733 (2005); *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1357 n.21 (Fed. Cir. 1998) (“We note that although the court granted a new trial on the issue of *obviousness*, it was not improper for CellPro to subsequently present an argument that the claims were *anticipated*: ‘[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for “anticipation is the epitome of obviousness.”’” (quoting *Connell*, 722 F.2d at 1548)) (alteration in original).

275. 599 F.2d 1026 (C.C.P.A. 1979).

276. *See* 37 C.F.R. 1.196(b) (1998). The regulations were changed in 2004. *See* 69 Fed. Reg. 50,000 (2004).

277. *Meyer*, 599 F.2d at 1029-30.

commonsense fact that a rejection for obviousness under § 103 can be based on a reference which happens to anticipate the claimed subject matter. Those cases do not provide a license for the board to shift the statutory basis of rejection from § 103 to § 102 while denying appellant the procedural due process provided for by [the Patent Office regulations].²⁷⁸

As Professor Adelman has pointed out, a court's failure to distinguish between the anticipation and obviousness inquiries could also result in a denial of due process if the anticipation finding turns out to be incorrect as a matter of law.²⁷⁹

By calling attention to the procedural separateness of, and the substantive distinctions between, the § 102 and § 103 patentability inquiries, the oligonucleotide reference can serve as an intuitive counterweight to an aphorism that has sometimes led courts and patent practitioners astray. For students and teachers of patent law, the oligonucleotide reference provides a useful and vivid caveat to the aphorism. If it were literally true that "anticipation is the epitome of obviousness," it would seem incongruous that a listing of structural formulae, which itself contributes nothing to the state of DNA discovery from the perspective of one skilled in the art of genetic research, should be capable of transforming a set of ineffective § 103 references²⁸⁰ into an effective § 102 reference.²⁸¹ It would be as if a scientifically trivial appendix had propelled the teachings of Sambrook and Russell from beneath the base of a figurative mountain of effective § 103 references to the summit, without needing to negotiate the complicated terrain of nonobviousness doctrine described in *Graham*.²⁸² Given the prevailing doctrines governing patentability under § 102 and § 103, however, it is easy to see why the listing of structural formulae in the oligonucleotide reference can assume such critical importance. In the registry model on which review of DNA prior art is premised, such a listing in a § 102 reference is taken to signify the state of DNA discovery.²⁸³

278. *Id.* at 1031 (footnote omitted).

279. See ADELMAN, *supra* note 165 (discussing *Hughes Tool Co. v. Ingersoll-Rand Co.*, 437 F.2d 1106 (5th Cir. 1971)).

280. Like the prior art references at issue in *Deuel* and *Baird*, see *supra* Parts III.E.1-III.E.2, the methodological teachings cited in the oligonucleotide reference do not disclose any specific DNA molecules. For example, the principal reference, Sambrook and Russell's *MOLECULAR CLONING: A LABORATORY MANUAL*, see *supra* note 14, describes procedures for synthesizing, isolating, and purifying arbitrary oligonucleotides up to twenty-five nucleotides in length and using the oligonucleotides as primers, see *supra* app. D, but does not provide the structural formulae for any oligonucleotides that can be made or used by these methods. Even viewing these references in combination, there is nothing to suggest any particular oligonucleotides that might be the subject of a patent claim. Accordingly, it is unlikely that Sambrook's manual and the other scientific publications would be found to render obvious any claim to one or more specifically identified DNA molecules under § 103. See *supra* text accompanying notes 221-226.

281. See *supra* Part III.D.5.

282. 383 U.S. 1 (1966); see *supra* text accompanying notes 189-191.

283. See *supra* text accompanying notes 245-248.

As an example of an enabling shotgun reference, the oligonucleotide reference is also especially well suited to highlighting one particular distinction between the § 102 and § 103 analyses of prior art. Under § 103, a broad generic disclosure that fails to teach toward the claimed compounds²⁸⁴ (or worse, teaches away²⁸⁵) will not render the claim obvious. An enabling shotgun reference will anticipate every one of an arbitrary number of named compounds under § 102;²⁸⁶ however, even if there is no teaching in the reference toward the selection of the claimed compounds and even if the reference teaches away from the selection of the claimed compounds. This is because the requirement of anticipation is fully satisfied by an enabling reference that discloses every element of the invention; there is no further requirement that the reference teach toward the invention.²⁸⁷

B. The Reference as a Strategic Publication

1. Related DNA Sequence Publication Projects

The oligonucleotide reference may be viewed as the latest in a series of strategic efforts to publish DNA sequence information at least in part for the express purpose of defeating the patenting of DNA molecules.²⁸⁸ In September 1994, Merck & Co., Inc. announced that it would sponsor a human cDNA sequencing project at the Washington University School of Medicine in St. Louis wherein the results would be published immediately in the "Merck Gene Index," a public domain database.²⁸⁹ Merck described its decision as motivated by the concern that other research organizations would restrict the scientific community's access to "basic biology" by "'cornering the market on the human genome.'"²⁹⁰ Merck also stood to benefit from improved public access to DNA sequence information, since it was primar-

284. See *supra* text accompanying note 225.

285. See *supra* text accompanying note 221.

286. See *supra* text accompanying notes 157-165.

287. See *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998) ("[T]he question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis."); *In re Malagari*, 499 F.2d 1297, 1302 (C.C.P.A. 1974) ("If the rejection under § 102 is proper, however, appellant cannot overcome it by showing such unexpected results or teaching away in the art, which are relevant only to an obviousness rejection."); ADELMAN, *supra*, note 165 ("Inventions which are anticipated and thus are nonnovel . . . are not subject to [the Graham] inquiry. . . . [N]o matter how long those skilled in the art searched for a solution to a problem, regardless of whether the art led to or away from the invention in question, regardless of the nature of the impact which the invention had on the art, a patent may not be granted on the invention."); see also *In re Fracalossi*, 681 F.2d 792, 796 (C.C.P.A. 1982) (Miller, J., concurring) ("[T]he so-called 'secondary considerations' relevant to a case of prima facie obviousness are not considered for purposes of determining anticipation . . .").

288. In addition, the scientific community has established numerous public databases of genomic DNA sequences for its own use without expressly invoking a patent-defeating purpose. See "Bioinformatics Resources," <http://www.genet.sickkids.on.ca> (follow "Bioinformatics Resources" hyperlink; then follow "General Nucleotide Sequence Databases" hyperlink) (last visited Feb. 21, 2006).

289. See David Dickson, *Merck to Back "Public" Sequencing*, 371 NATURE 365 (1994).

290. *Id.*

ily engaged in the business of developing drugs, not in identifying new DNA sequences.²⁹¹

In February 1996, participants in the first International Strategy Meeting on Human Genome Sequencing in Bermuda unanimously endorsed the proposition that genomic DNA sequence information should be “freely available and in the public domain to encourage research and development and to maximize the benefit to society.”²⁹² Under the resulting terms of the “Bermuda Accord,” members of the publicly funded Human Genome Project agreed to publish all of their sequence data in free, public databases such as GenBank within twenty-four hours.²⁹³ According to the National Human Genome Research Institute, such disclosures have served in part to address the public concern that “patent applications on large blocks of primary human genomic DNA sequence could have a chilling effect on the development of future inventions of useful products.”²⁹⁴

In April 1999, the Wellcome Trust and thirteen pharmaceutical and technology companies formed the SNP Consortium, a non-profit foundation sponsoring university research efforts to identify and analyze single nucleotide polymorphisms in the human genome.²⁹⁵ As of August 2004, these efforts had resulted in the discovery and characterization of nearly 1.8 million SNPs.²⁹⁶ The consortium does not immediately publish newly identified SNPs, but seeks instead to “[m]anage publication of the resulting SNP map in a manner intended to maximize the number of SNPs that enter the ‘public domain’ [as that term is understood in the patent law].”²⁹⁷ The consortium’s strategy involves the filing of Statutory Invention Registrations under § 157 of the Patent Act,²⁹⁸ which are apparently effective as prior art as of their filing dates, even though they remain unpublished pending Patent Office review.²⁹⁹ The consortium delays the public release of each identified SNP by approximately three months, thereby permitting the filing of an SIR that can effectively “prevent facilitating the patenting of the same SNP[] by third

291. See Rebecca S. Eisenberg, *Intellectual Property at the Public-Private Divide: The Case of Large-Scale cDNA Sequencing*, 3 U. CHI. L. SCH. ROUNDTABLE 557, 569-71 (1996).

292. See Human Genome Program, U.S. Dep’t of Energy, *International Large-Scale Sequencing Meeting*, HUMAN GENOME NEWS, Apr.-June 1996, at 6, available at http://www.ornl.gov/sci/techre/sources/Human_Genome/publicat/hgn/v7n6/19intern.shtml.

293. See Robin Marantz Henig, *The Rush to Claim a Little Slice of Life*, WASH. POST, Jan. 9, 2000, at B5; see also Rebecca S. Eisenberg, *The Promise and Perils of Strategic Publication to Create Prior Art: A Response to Professor Parchomovsky*, 98 MICH. L. REV. 2358, 2363-64 (2000) (referring to “Bermuda rules”); Karen Hall, *Genomic Warfare*, AM. LAW., June 2000, at 68 (referring to “Bermuda Statement”).

294. NAT’L HUMAN GENOME RES. INST., NHGRI POLICY ON AVAILABILITY AND PATENTING OF HUMAN GENOMIC DNA SEQUENCE PRODUCED BY NHGRI PILOT PROJECTS (1996), <http://www.genome.gov/10000926>.

295. See *supra* text accompanying note 9 (defining SNPs).

296. See The SNP Consortium Ltd., Single Nucleotide Polymorphisms for Biomedical Research, <http://snp.cshl.org> (last visited Mar. 9, 2006).

297. See The SNP Consortium Ltd., Full Genome Representative SNP Map Program Summary, <http://snp.cshl.org/about/program/html> (last visited Mar. 9, 2006) (alteration in original).

298. 35 U.S.C. § 157 (2000).

299. See 1 CHISUM, *supra* note 117, § 3.07[2], at 3-213 to -214 (“The legislative history [of section 157], while awkwardly phrased, seems to confirm that indeed a SIR is effective as prior art as of its filing date.”).

parties.”³⁰⁰

# of 8-mers to 12-mers claimed	% of possible claims anticipated
1	49.6
2	74.6
3	87.2
10	99.9
25	99.99999+

Table 1. Anticipation of oligonucleotide patent claims by the oligonucleotide reference.

The Merck, Human Genome, and SNP Consortium projects appear to have had only a relatively limited effect on the patenting of oligonucleotide probes for the full-length genes and other long DNA sequences that have been published in the public databases.³⁰¹ The oligonucleotide reference has been designed to accelerate the project of defeating the patenting of oligonucleotides significantly beyond these previous efforts. By publishing more than 11 million DNA sequences, the oligonucleotide reference specifically targets oligonucleotide patent claims, particularly the most preclusive claims covering multiple molecules.

As Table 1 illustrates, the oligonucleotide reference may eventually have a dramatic impact on the validity of patent claims covering multiple oligonucleotides of eight to twelve bases in length. If so, the reference will also contribute significantly to preserving the freedom of scientists to conduct several important research procedures.³⁰² Based on the quantitative evidence thus far,³⁰³ it appears that the degradation of these procedures in general can be substantially halted if the proportion of patented oligonucleotides of a given size can be kept below a critical threshold. While the scientific community will never again be able to ignore the impact of DNA patenting on its work, the oligonucleotide reference and other strategic publication efforts can play a vital role in ensuring that socially beneficial research can effectively continue.

300. See The SNP Consortium Ltd., *supra* note 297.

301. Jeffrey Fredman has argued persuasively that an oligonucleotide should be found *prima facie* obvious where “the invention is solely based upon routine selection of a small DNA piece from a larger prior art sequence of DNA.” See Fredman, *supra* note 226, at 313. Still, a patent claim to an oligonucleotide primer or probe is rarely based *solely* on such a rudimentary act. Generally, the invention of a claimed oligonucleotide primer or probe is incident to the discovery of a specific association between the underlying DNA sequence and some meaningful biological function, in which certain prerequisites for patentability (utility and nonobviousness) inhere. See Utility Guidelines, *supra* note 5, at 1097-99. Thus, applications claiming oligonucleotide probes for human genes have continued apace even after the publication of a complete human genome in February 2001. See, e.g., *infra* Table 2.

302. See *infra* app. C.

303. See Andrew Chin, *Research in the Shadow of DNA Patents*, 87 J. PAT. & TRADEMARK OFF. SOC’Y 846, 898-904 (2005).

2. *Strategic Motivations for Publication*

Public disclosures of research results typically serve to reward a firm's scientists and to attract prestige and investment capital to the firm. Other motivations, however, appear to have been responsible for at least some of the recent organized efforts to publish DNA sequence information.

Recent patent law scholarship has sought to identify and examine the strategic motivations that may influence a firm to disclose research results publicly rather than seek a patent. In general terms, the strategic significance of prior art is that it can result in the extension of a patent race and the dedication of technology to the public domain. As Gideon Parchomovsky has argued, where the extension of a patent race could give a lagging firm time to overtake more advanced researchers, the lagging firm may choose to publish prior art for the purpose of defeating or narrowing the patentability of their rivals' inventions.³⁰⁴ Douglas Lichtman, Scott Baker, Kate Kraus,³⁰⁵ and Rebecca Eisenberg,³⁰⁶ however, have noted an important limitation of the lagging-firm strategy, namely that a first inventor who applies for a patent can swear behind a prior art reference dated within one year of the application. Eisenberg allows that such a strategy might be "plausible" in the case of Merck, which trailed two other private firms in developing similar databases,³⁰⁷ but she notes that the Human Genome Project and SNP Consortium initiatives were both led not by lagging firms in the race for DNA patents, but by research organizations seeking to preserve low-cost access to DNA sequences for their future work.³⁰⁸

The extension of a patent race may also benefit leading firms, specifically by raising the costs to rivals of continuing the pursuit of a patent.³⁰⁹ For example, IBM's prior art citations to its own journal, the *IBM Technical Disclosure Bulletin*, appear to be consistent with the implementation of such a strategy.³¹⁰ Also, leading firms that control platform technologies may choose to dedicate them to the public domain in order to encourage other firms to invest in the development of complementary technologies.³¹¹ More generally, in research fields characterized by cumulative innovation, firms may dedicate technologies to the public domain as a credible commitment to the facilitation of subsequent improvements.³¹²

304. See Gideon Parchomovsky, *Publish or Perish*, 98 MICH. L. REV. 926 (2000).

305. See Douglas Lichtman et al., *Strategic Disclosure in the Patent System*, 53 VAND. L. REV. 2175, 2186-87 (2000).

306. See Eisenberg, *supra* note 291, at 2359-60.

307. *Id.* at 2365-66.

308. *Id.* at 2369.

309. See Lichtman, *supra* note 305, at 2204-15.

310. See Scott Baker & Claudio Mezzetti, *Disclosure as a Strategy in the Patent Race*, 48 J.L. & ECON. 173, 176 (2005).

311. See Douglas Lichtman, *Property Rights in Emerging Platform Technologies*, 29 J. LEGAL STUD. 615, 630 (2000).

312. See Oren Bar-Gill & Gideon Parchomovsky, *The Value of Giving Away Secrets*, 89 VA. L. REV. 1857, 1860-61 (2003).

In contrast to these strategic disclosure scenarios, artful prior art such as the oligonucleotide reference does not purport to describe any new or recent developments in genomic research, and therefore, it serves neither as an alternative to a patenting strategy (like the Merck Gene Index) nor as a time-critical public disclosure to the research community (like the Human Genome and SNP Consortium projects). Instead, it simply conforms previously reported research findings to the patent system's registry model, thereby creating effective anticipatory references under § 102(b).

As the oligonucleotide reference illustrates, the production of artful prior art documents based on previously published generic references costs almost nothing and entails no disclosure of proprietary information. Under the rational choice models that have informed the recent strategic disclosure literature, institutions seeking to prevent the patenting of DNA molecules—including for-profit firms such as Merck³¹³ and Affymetrix³¹⁴—would be expected immediately to undertake the conversion of the scientific literature into effective anticipating references. Their failure to do so in the twenty years prior to the publication of the oligonucleotide reference suggests either that patenting considerations have not dominated the strategic behavior of these institutions, or that their rationality has been limited by significant information imperfections (for example, the Patent Act's technicalities and the difficulty of locating appropriate generic disclosures in the scientific literature).

In either case, the gap between theory and practice is highly significant in the industry context, for it constitutes the period during which firms have been able to apply for patents covering DNA molecules that were previously enabled (but not specifically described) by the generic disclosures.³¹⁵ Since such firms can continue their patenting activities for a limited period of one year after publication of the artful prior art documents (provided that they can swear behind the documents), it is rational for the publishing organization to proceed “quietly,” as in *In re Hall*,³¹⁶ as the oligonucleotide

313. See *supra* notes 290-291 and accompanying text.

314. Affymetrix depends heavily on defensive licensing to secure the rights to include certain oligonucleotide probes on its microarrays. At a symposium in 2002, Affymetrix's general counsel, Barbara Caulfield, stated in response to a question from the author:

We have defensively licensed, to protect ourselves and our freedom to operate. It is costly, because . . . when you're looking generally at whole-genomic, multiprobe, multigenic, you know, setting the groundwork, people get very self-motivated about how they give you a license, and they have a right to do it, and they should do it, and the price is high. And the more you want it, the higher the price. And we are very sophisticated players in the licensing field, there's no two ways about it. We do it every day, I do it every day. We run quite remarkable economic models. But there's limited resources.

Symposium, *Commercialization of Human Genomics: Consequences for Science and Humanity*, Duke University, Sept. 27, 2002, <http://www.law.duke.edu/webcast/index.html> (providing archived Webcast of symposium). Caulfield's remarks occur at approximately one hour and forty-two minutes into Panel 2.

315. See *infra* Part V.C.

316. See Lichtman, *supra* note 305, at 2184 & n.20 (“[I]n many cases, the disclosure will not preempt the patent application, but will instead spur . . . the original inventor to file. This is not always true, however, because under modern interpretations an inventor can sometimes disclose in such a quiet way that the original inventor will not even be aware of the disclosure.”).

reference illustrates. By extending their rational choice frameworks to accommodate the production of artful prior art references as a rational strategy, strategic disclosure theorists may be better able to account for the observed behavior of research organizations.³¹⁷

C. The Reference as an Artifact of the State of Information Technology

In the not too distant past, the time and expense involved may have deterred parties affected by DNA patents from producing and publishing comprehensive DNA registries.³¹⁸ Today, however, the production of such massive prior art documents is well within the capabilities of a desktop personal computer. The oligonucleotide reference may be viewed as an artifact of the state of data storage technology as of 2002, when the CD-ROM was produced.

A list of the DNA sequences for all 4^{12} possible 12-mers, together with a relatively short technical disclosure, can be stored as a single text file of about 300 megabytes on a standard CD-ROM. Multiple versions of a scientific article would require considerably more space, but may be accommodated in a small library of high-capacity DVD-ROMs. For example, 4^{12} versions of the same article, each in the form of a text file of six kilobytes varying only in the DNA sequence described, can fit on seven 15-gigabyte DVD-18 disks. In these examples, a patent applicant could completely avoid the prior art by drafting claims directed only to oligonucleotides of at least thirteen nucleotides in length. As new and more commodious digital media formats are developed, however, it will become feasible to generate prior art libraries that enumerate all of the possible oligonucleotides of progressively greater lengths. Furthermore, even larger capacities will be possible if the libraries can be hosted on one or more dedicated servers.

Figure 2 illustrates the emergence of shotgun references as a feasible response to oligonucleotide patenting as a result of the exponentially declining cost of digital data storage. As the graph shows, the exponentially growing capacity of low-cost digital media³¹⁹ (left axis) has made it feasible to publish comprehensive shotgun references that can anticipate claims to DNA molecules of ever-increasing length³²⁰ (right axis). Thus the oligonu-

317. A similar suggestion for further research has recently been made elsewhere. Yochai Benkler has argued that economic models would more accurately capture the aggregate welfare effects of intellectual property laws if they accounted for the different strategies and motivations of information producers. See Yochai Benkler, *Intellectual Property and the Organization of Information Production*, 22 INT'L REV. L. & ECON. 81, 98 (2002).

318. Assuming that 300 sequences could be printed on a page, a listing of 4^{12} sequences would fill more than 55,000 pages. Even with the aid of computers to generate such a document, its production and publication would represent a major undertaking.

319. See *Historical Notes About the Cost of Hard Drive Storage Space*, CREATIVE COMPUTING, Dec. 1981, at 6, available at <http://www.littletechshoppe.com/ns1625/winchest.html> (providing examples of retail prices for hard drives from 1980 to 2004), cited in *United States v. Thompson*, 281 F.3d 1088, 1095 n.1 (10th Cir. 2002) (Seymour, J., dissenting). The plotted data points correspond to the lowest-cost examples cited in the reference for each calendar year.

320. The labels on the right axis assume that the oligonucleotide sequences are disclosed in an ASCII

cleotide reference, published in 2002 at a cost of fifty cents, became effective as a § 102(b) bar in 2003 to anticipate most claims to oligonucleotides eight to twelve bases in length (shaded area).³²¹

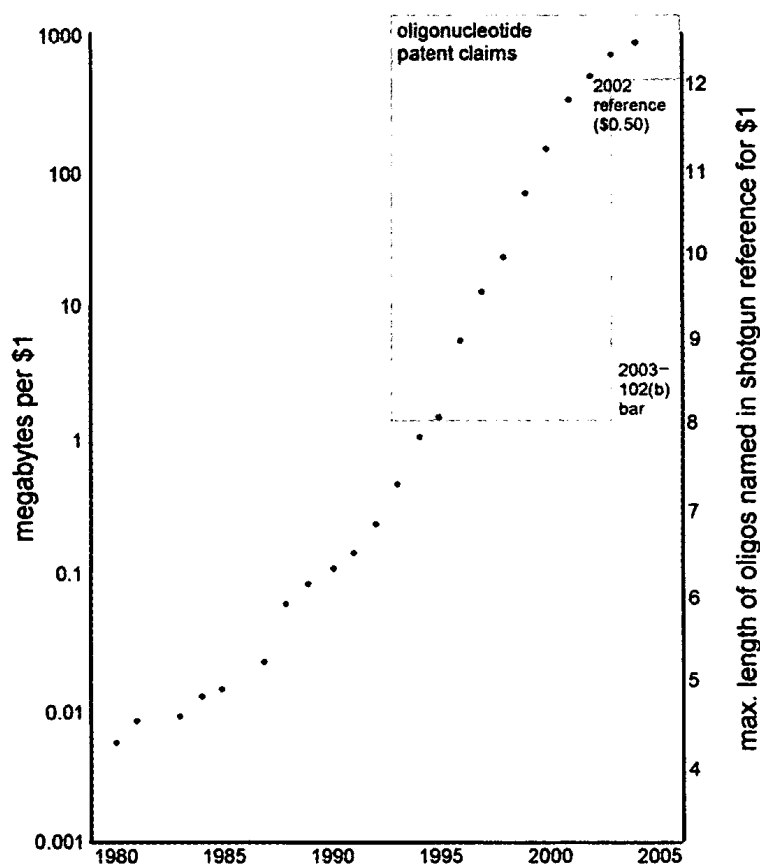


Figure 2. *The availability of high-capacity, low-cost digital media has made it increasingly feasible to produce comprehensive shotgun references for oligonucleotides.*

As Figure 2 shows, the cost of producing the oligonucleotide reference would have been much higher if the same project had been undertaken several years earlier. More generally, Figure 2 indicates that at any given time, the ability of the genetic research community to conform its findings to the

file with three bytes reserved at each end of an oligonucleotide to indicate the 5' and 3' termini and one byte reserved between consecutive oligonucleotides to accommodate a separator.

321. See *supra* Table 1. The left edge of the shaded region in Figure 2 reflects the fact that the earliest patent claiming an oligonucleotide named in the 2002 oligonucleotide reference was issued in 1993. See U.S. Patent No. 5,185,244 (filed Dec. 8, 1989) ("An oligonucleotide probe . . . consisting essentially of about ten to about forty-two consecutive nucleotides, including the nucleotide corresponding to said 11778 position, selected from the group of nucleotide sequences consisting of [four sequences, each 42 nucleotides in length, in which 'said 11778 position' occurs as the 21st nucleotide in each sequence].").

registry model of DNA discovery has depended heavily on advances in information storage technology. To the extent that prevailing patentability doctrines are predicated on this model,³²² future observers may regard the patenting of oligonucleotides at the turn of the twenty-first century³²³ as a consequence not only of rapid advances in the state of genetic research, but also of the relatively primitive state of digital information technology.

VI. CONCLUSIONS

The recognition that mere artful drafting can transform an ineffective § 103 reference into an effective § 102 reference can serve as either a normative or a positive response to the patent system's registry model of DNA discovery. As a normative response, it can serve as the dubious consequence of a *reductio ad absurdum* that calls into question the premises of the registry model, especially the Federal Circuit's focus on structural disclosure in *Deuel* and *Lilly*. As a positive response, it serves as a "proof of concept" demonstrating that the registry model can be invoked not only in support of the patentability of composition of matter claims to DNA molecules, but also in support of the effectiveness of shotgun § 102 references. Thus, even if normative critics of the prevailing patentability doctrines are unsuccessful in changing the law to preclude patenting DNA molecules as compositions of matter,³²⁴ as a positive matter it is becoming increasingly possible for artful prior art to effect significant changes in the underlying facts by conforming research findings to the registry model.

While the possibility of producing artful prior art in the field of genetics is of independent interest as a development in patent law, its larger significance lies in its impact on biotechnology. By limiting oligonucleotide-related patents to new use claims, artful prior art will help preserve public access to oligonucleotides for generic uses. As described in Appendix C, some generic uses for oligonucleotides may be involved in the future discovery of associations between DNA sequences and meaningful biological functions that form the basis for the identification of new and useful oligonucleotide probes. While the unpatentability of composition of matter claims may diminish private incentives for inventors to discover specific and substantial utilities for oligonucleotides,³²⁵ it may also have the indirect effect of stimulating and accelerating other discoveries of patentable DNA molecules.³²⁶ Ultimately, any assessment of the overall impact of artful prior art on genetic research is for the scientific community to make as it will depend on the rapidly evolving roles of various laboratory procedures that use oligonucleotides.

322. See *supra* Part III.A.

323. See *supra* Figure 1.

324. See *supra* note 249.

325. See *supra* note 134 and accompanying text.

326. In a companion article, I argue this point more fully by quantifying the preclusive effect of oligonucleotide patents on certain genetic research procedures. See Chin, *supra* note 303.

Given further advances in information storage technology, it may become possible to extend the methods of this Article to other generically known compositions of matter whose structural formulae are amenable to automated enumeration. In particular, the burgeoning field of combinatorial chemistry is increasingly automating the discovery of useful pharmaceutical compounds.³²⁷ Such developments may eventually lead the patent system to question whether machine-created inventions are patentable (and, if so, to whom).³²⁸ Until that day, patent applicants will be able to claim compounds whose structural formulae cannot be located within the patent system's registry model of chemical innovations. In the meantime, artful drafting will be necessary to ensure that the registry model accurately represents the state of the art.

APPENDICES

A. *Oligonucleotide Microarrays*

Miniaturization technologies have made it possible to fabricate small chips, known as "microarrays" (or, colloquially, as "DNA chips"), that can hold thousands of isolated, purified, single-stranded DNA molecules ("probes") in separate, identified locations. When a solution containing an unknown sample of DNA molecules is washed against a microarray under conditions favorable for hybridization, the microarray probes are able to hybridize specifically with DNA molecules in the sample that contain their reverse-complementary sequences. In this way, a single microarray can be used to test a sample for the presence of thousands of DNA sequences simultaneously.

Oligonucleotides produced by a DNA synthesizer and cDNAs produced by reverse transcription³²⁹ are both suitable for use as probes on a microarray. Some manufacturers fabricate microarrays by preparing the probes first and then depositing them into the appropriate locations on the chip. Other firms synthesize the probes directly on the chip, using technologies such as photolithography, ink jet printing, and electrochemistry to regulate the locations where chemical reactions are to occur.

One manufacturer in particular, Affymetrix, Inc., has marketed microarrays called GeneChips that can hold up to 400,000 different oligonucleotide probes.³³⁰ Affymetrix holds broad patents covering photolithography meth-

327. See COMBINATORIAL CHEMISTRY AND MOLECULAR DIVERSITY IN DRUG DISCOVERY (Eric M. Gordon & James F. Kerwin, Jr. eds., 1998).

328. See Barton, *supra* note 188; Karl F. Milde, Jr., *Can a Computer Be an "Author" or an "Inventor"?*, 51 J. PAT. OFF. SOC'Y 378 (1969); cf. William T. Ralston, *Copyright in Computer-Composed Music: HAL Meets Handel*, 52 J. COPYRIGHT SOC'Y USA 281 (2005) (discussing the eligibility of computer-created works for copyright); Tal Vigderson, Comment, *Hamlet II: The Sequel? The Rights of Authors vs. Computer-Generated "Read-Alike" Works*, 28 LOY. L.A. L. REV. 401 (1994) (same).

329. See *supra* text accompanying note 13.

330. See Randall Osborne, *Affymetrix Venture Raises \$100M to Exploit Wafers for Genomics*, BIOWORLD TODAY, Apr. 4, 2001.

ods for controlling chemical synthesis³³¹ and the fabrication of high-density microarrays that can be achieved using such methods.³³² Because of the scalability of photolithography technology, the number of oligonucleotide probes that can fit on a microarray has been increasing exponentially,³³³ creating unprecedented opportunities for genetic research.³³⁴

Noting the potential benefits from such massive parallelism in clinical experimentation, leading scientists³³⁵ and a former U.S. president³³⁶ have singled out microarrays as a technology that may eventually unlock the secrets of human genetic variation. In practical terms, this means that physicians will someday use microarrays to determine the diseases a newborn infant will be prone to later in life,³³⁷ tailor medications to patients' individual genomes,³³⁸ or, less ambitiously, to decide whether a sore throat is treatable with antibiotics.³³⁹ Although clinical medicine has yet to embrace predictive gene testing as a diagnostic approach,³⁴⁰ microarrays are already being used to test for drug-resistant mutations in the HIV virus,³⁴¹ cancer-related mutations in breast tumors,³⁴² and polymorphisms related to the abil-

331. See U.S. Patent No. 5,753,788 (filed May 19, 1995) ("Photolabile nucleoside protecting groups").

332. See U.S. Patent No. 5,744,305 claim 1 (filed June 6, 1995) ("An array of oligonucleotides, the array comprising: a planar, non-porous solid support having at least a first surface; and a plurality of different oligonucleotides attached to the first surface of the solid support at a density exceeding 400 different oligonucleotides/cm.sup.2, wherein each of the different oligonucleotides is attached to the surface of the solid support in a different predefined region, has a different determinable sequence, and is at least 4 nucleotides in length.").

333. See *Gene Expression; New Analysis Product Line Launched*, GENOMICS & GENETICS WKLY., May 12, 2000, at 23 (quoting Affymetrix's Stephen Fodor's comment that photolithographic technology has allowed for the shrinkage of "feature sizes" according to Moore's Law); Julia Boguslavsky, *Chip Market is Evolving*, R&D MAG., Mar. 1, 2001, at 20, 22 (quoting Affymetrix's Thane Kreiner's statement that GeneChip customers "are benefiting from the principles of Moore's Law"); Osborne, *supra* note 330 (reporting that an Affymetrix venture has been developing microarrays that can hold up to 60 million probes); Alexandra Stikeman, *Biochips Go Big Time*, MIT TECH. REV., Mar. 2001, at 31 ("In the last few years, the biotech industry has set out to establish its own version of Moore's Law . . .").

334. See Appendices A-C; see also Eric S. Lander, *Scientific Commentary: The Scientific Foundations and Medical and Social Prospects of the Human Genome Project*, 26 J.L. MED. & ETHICS 184, 187 (1998) (predicting future uses of microarrays to "tease apart the genetic factors contributing to heart disease, cancer risk, schizophrenia, manic depression, and attention deficit disorder"), and David Stipp, *Gene Chip Breakthrough*, FORTUNE, Mar. 31, 1997, at 56 (describing ongoing advances in genetic research attributable to microarrays). For surveys of oligonucleotide microarray applications, see MICROARRAY BIOCHIP TECHNOLOGY (Mark Schena ed., 2000).

335. See, e.g., Lander, *supra* note 334.

336. See 144 CONG. REC. S20, S24 (Jan. 27, 1998) (text of President William J. Clinton's 1998 State of the Union address) ("Within a decade, 'gene chips' will offer a roadmap for prevention of illness throughout a lifetime.").

337. Stipp, *supra* note 334; Tim Studt, *Gene Chip Technologies Transform Biological Research*, R&D MAG., Feb. 1, 1998, at 38.

338. See Robert F. Service, *Microchip Arrays Put DNA on the Spot*, 282 SCIENCE 396, 396 (1998).

339. See Stipp, *supra* note 334, at 72 ("That's 40 gazillion sore throats a year times, say, \$5 a chip—zounds, this is enough to make Andy Grove feel *déjà vu* all over again!").

340. See Michael J. Malinowski, *Separating Predictive Genetic Testing from Snake Oil: Regulation, Liabilities, and Lost Opportunities*, 41 JURIMETRICS J. 23, 33-41 (2000).

341. Tom Foremski, *Biological and Man-Made Designs Converge to Create DNA Chips*, ELECS. WKLY., Jan. 11, 1995, at 20; Jon Mainwaring, *Gene-ius*, ELECS. WKLY., May 28, 1997, at 18.

342. See Stipp, *supra* note 334.

ity to metabolize various drugs.³⁴³ The microarray market is expected to grow to \$10 billion within the next five to ten years.³⁴⁴

B. Some Utilities for Specific Oligonucleotides

1. Probes for DNA Molecules of Known Sequence

Oligonucleotide probes may be used to detect the presence or absence of particular DNA molecules that contain a reverse-complementary subsequence. For example, a researcher who knows the sequence of a gene can design and synthesize an oligonucleotide probe that hybridizes specifically to one strand of the gene.³⁴⁵ An unknown sample of DNA molecules can be broken into single strands ("denatured") and combined with the probe under conditions favorable to hybridization.³⁴⁶ Observations of hybridization products will then indicate the presence and prevalence of the targeted gene. For example, synthetic oligonucleotide probes have been designed that are specific to genes of *E. coli*³⁴⁷ and *E. coli* toxins,³⁴⁸ cholera toxins,³⁴⁹ HIV-1,³⁵⁰ hepatitis C,³⁵¹ anthrax,³⁵² listeria,³⁵³ staphylococcus,³⁵⁴ shigella,³⁵⁵ and the Lyme disease bacterium.³⁵⁶

2. PCR Primers

The polymerase chain reaction (PCR), for which Kary Mullis received the 1993 Nobel Prize in chemistry, provides a method for rapidly synthesizing numerous copies ("amplifying") of a DNA molecule.³⁵⁷ The technique exploits the ability of each strand of a DNA molecule to serve as the template for the synthesis of its reverse complement. As shown in Figure 3, the

343. See Tam Harbert, *A Chip off the Old Block?*, ELEC. BUS. TODAY, Apr. 1, 2000, at 60, 64.

344. See Stikeman, *supra* note 333.

345. See GEORGE H. KELLER & MARK M. MANAK, DNA PROBES (1993); SAMBROOK & RUSSELL, *supra* note 14, at 10.1-10.

346. See SAMBROOK & RUSSELL, *supra* note 14, at 10.2-4.

347. See U.S. Patent No. 5,041,372 (filed Nov. 2, 1988).

348. See Tatsuo Yamamoto et al., *Sequence Analysis of the Heat-Labile Enterotoxin Subunit B Gene Originating in Human Enterotoxigenic Escherichia Coli*, 152 J. BACTERIOLOGY 506 (1982).

349. See Suvath Hanchalay et al., *Non-O1 Vibrio Cholerae in Thailand: Homology with Cloned Cholera Toxin Genes*, 21 J. CLINICAL MICROBIOLOGY 288 (1985).

350. See U.S. Patent No. 5,599,662 (filed Feb. 17, 1995).

351. See U.S. Patent No. 5,527,669 (filed May 10, 1994).

352. See Oligonucleotides for Detection of Bacillus Cereus Group Bacteria Harmful to Mammals, and Method of Detection with the Oligonucleotides, U.S. Patent No. 6,087,104 (filed Mar. 24, 1998).

353. See Atim R. Datta et al., *Cloning of the Listeriolysin O Gene and Development of Specific Gene Probes for Listeria Monocytogenes*, 56 APPLIED ENVTL. MICROBIOLOGY 3874 (1990).

354. See Serve Notermans et al., *Synthetic Enterotoxin B DNA Probes for Detection of Enterotoxigenic Staphylococcus Aureus Strains*, 54 APPLIED ENVTL. MICROBIOLOGY 531 (1988).

355. See U.S. Patent No. 5,041,372 (filed Nov. 2, 1988).

356. See U.S. Patent No. 5,977,339 (filed Jan. 17, 1997).

357. See Kary Mullis et al., *Specific Enzymatic Amplification of DNA In Vitro: The Polymerase Chain Reaction*, 51 COLD SPRING HARBOR SYMPOSA ON QUANTITATIVE BIOLOGY 263 (1986). For detailed descriptions of the polymerase chain reaction, see M.J. MCPHERSON & S. G. MØLLER, PCR (2000); NICHOLL, *supra* note 9, at 115-31.

DNA to be copied (the “target” DNA) is initially denatured in a solution containing an excess of each of the four kinds of nucleotides and a special kind of enzyme known as a “polymerase.”³⁵⁸ To begin the copying, an oligonucleotide (called a “primer” in this context) must hybridize with each of the single strands of the target DNA, so that the exposed 3' end of the oligonucleotide is adjacent to an unmatched nucleotide on the target strand.³⁵⁹ Since the two strands have different nucleotide sequences, PCR uses a pair of different primers for this purpose. The polymerase then extends the 3' end of the attached primer by adding nucleotides one at a time complementary to the adjacent nucleotides on the target DNA, until a complete double-stranded DNA molecule has been assembled. The molecule can be denatured and the procedure repeated. The entire process takes place in a machine called a “thermal cycler,” which produces the temperatures necessary for the different chemical reactions to occur. Since each PCR cycle doubles the number of copies of the target DNA, the procedure is capable of rapidly producing any desired quantity.

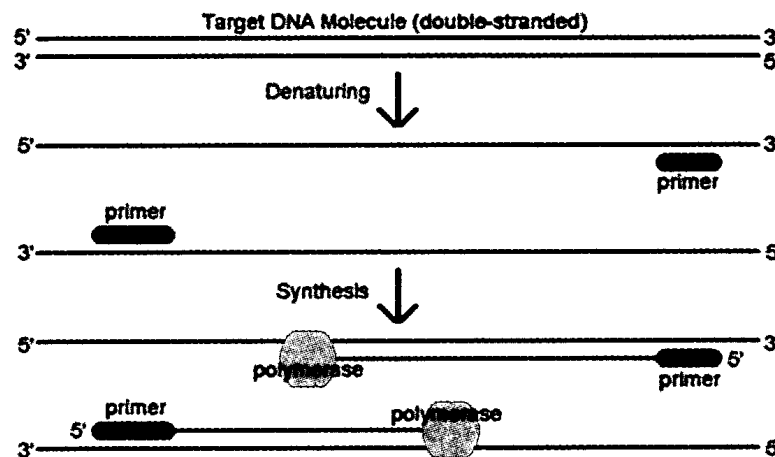


Figure 3. One cycle of the polymerase chain reaction in progress. Each strand of the target DNA molecule serves as a template for the synthesis of its reverse complement, yielding a product of two double-stranded molecules.

For an oligonucleotide to serve as an appropriate primer, it must hybridize specifically to the appropriate strand of the target DNA during each PCR cycle.³⁶⁰ Thus, in designing a pair of PCR primers, laboratories must consider not only the sequence of the target molecule, but also the primer's thermodynamic properties and the possibility of unwanted hybridization

358. Mullis, *supra* note 357, at 263.

359. *Id.* at 264.

360. See SAMBROOK & RUSSELL, *supra* note 14, at 8.13.

reactions. As Figure 4 illustrates, if a primer contains segments that are reverse complements of each other, hydrogen bonds can form between them, causing unwanted folds, loops, and other topological features known as “nonlinear secondary structures” to occur in the molecule.

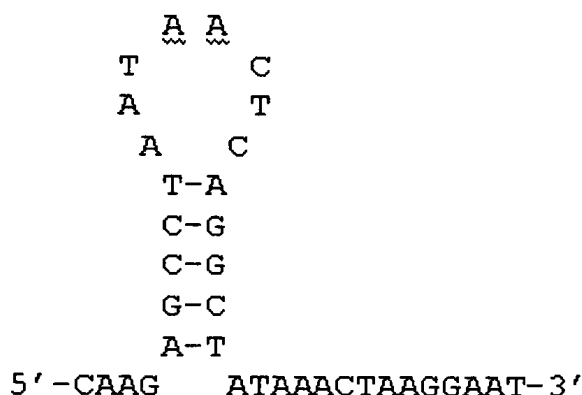


Figure 4. Formation of a hairpin loop in the oligonucleotide whose sequence is 5'-CAAGAGCCTAATAACTCAGGCTATAAACTAAGGAAT-3'. The loop results from the self-complementary regions AGCCT and AGGCT occurring at bases 5-9 and 18-22 of the sequence, respectively.

During the denaturing step, bonds between A and T nucleotides separate at a lower temperature than bonds between G and C nucleotides. As a rule of thumb, a primer may be expected to denature and hybridize correctly during PCR if it is composed of between 40-60% G and C nucleotides and it contains no self-complementary sequences of four or more nucleotides.³⁶¹ The preferred length for a PCR primer is between eighteen and twenty-five nucleotides,³⁶² although oligonucleotides as short as ten nucleotides may be appropriate in some cases.³⁶³ Many other heuristics for designing PCR primers have been developed, thereby providing a systematic procedure for the amplification of virtually any DNA molecule.³⁶⁴

As the public has been aware ever since the O.J. Simpson trial, PCR can be used to enhance the sensitivity of tests for detecting the target DNA, including oligonucleotide probes.³⁶⁵ By increasing the prevalence of the target

361. See *id.* at 8.13-.15.

362. See *id.* at 8.14.

363. See U.S. Patent No. 5,976,791 claim 1 (filed July 8, 1996) (claiming, *inter alia*, a PCR primer comprising an oligonucleotide “having at least eight consecutive nucleotides” from a group of disclosed sequences); U.S. Patent No. 6,004,754 claim 5 (filed Jan. 21, 1998) (claiming, *inter alia*, a new use for a PCR procedure using a primer “consisting of at least 10 consecutive nucleotides” of a disclosed sequence).

364. See SAMBROOK & RUSSELL, *supra* note 14, at 8.13-.15.

365. See, e.g., Gerald D. Robin, *DNA Evidence in Court: The Odds Aren't Even*, 9 CRIMINAL JUSTICE 8, 8 (1994).

DNA relative to other DNA molecules that may be in the solution, PCR can effectively “amplify” the target DNA to a detectable level.³⁶⁶ As burgeoning literature indicates, the research community is continuing to discover many other applications for PCR.³⁶⁷

Until recently, the potential usefulness of PCR to the scientific community has been constrained somewhat by the fact that it was a patented procedure. Patents covering the use of PCR to amplify, detect, and differentiate DNA molecules were issued to Mullis and his colleagues in 1987, assigned to their employer, Cetus Corporation,³⁶⁸ and were subsequently acquired by Hoffman-La Roche, Inc. (“Roche”) in 1991.³⁶⁹ In licensing and enforcing the PCR patents, Roche was often seen as responsive to public pressure and the concerns of the scientific community,³⁷⁰ although not to the satisfaction of some commentators.³⁷¹ The patents expired in July 2004.³⁷²

366. *Id.*

367. See MCPHERSON & MØLLER, *supra* note 357, at 6-8 (charting the rapid increase in the number of publications citing PCR between 1985 and 1999); 2 T.A. BROWN, *ESSENTIAL MOLECULAR BIOLOGY: A PRACTICAL APPROACH* 11 (T.A. Brown ed., 2d ed. 2001) (“New applications for PCR are being discovered virtually every month.”).

368. See U.S. Patent No. 4,683,202 claim 1 (filed Oct. 25, 1985) (claiming a process for using PCR to “amplify[] at least one specific nucleic acid sequence contained in a nucleic acid or a mixture of nucleic acids”); U.S. Patent No. 4,683,195 claim 1 (filed Feb. 7, 1986) (claiming a process for using PCR to “detect[] the presence or absence of at least one specific nucleic acid sequence in a sample containing a nucleic acid or mixture of nucleic acids, or distinguishing between two different sequences in said sample, wherein the sample is suspected of containing said sequence or sequences”).

The PCR technique was independently described more than a decade before Mullis’s work by Gobind Khorana, see K. Kleppe et al., *Studies on Polynucleotides XCVI: Repair Replication of Short Synthetic DNA’s as Catalyzed by DNA Polymerases*, 56 J. MOLECULAR BIOLOGY 341 (1971), although not in sufficient detail to invalidate any claims in the ’202 patent. See *E.I. du Pont de Nemours & Co. v. Cetus Corp.*, No. C-89-2860 MHP, 1990 WL 305551, at *1 (N.D. Cal. Dec. 3, 1990).

369. See *Chiron Cleared to Acquire Cetus Corp. in Stock Swap*, WALL ST. J., Dec. 11, 1991, at B3. Another Roche patent, claiming a particular form of polymerase that can be used in PCR, has been held unenforceable for inequitable conduct. See *Hoffman-La Roche, Inc. v. Promega Corp.*, No. C-93-1748, 1999 WL 1797330 (N.D. Cal. Dec. 7, 1999), *construed by* 323 F.3d 1354 (Fed. Cir. 2003).

370. See Janice M. Mueller, *No “Dilettante Affair”: Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 WASH. L. REV. 1, 3 (2001) (discussing Roche’s decision not to name “pure research” scientists as defendants in its PCR patent infringement suits); Ron Winslow, *Hoffman-La Roche to Ease Curb on Gene Technology*, WALL ST. J., Jan. 27, 1992, at B1 (reporting Roche’s decision to ease restrictions on licensing of PCR to academic and private diagnostic labs); NAT’L RES. COUNCIL, *PCR and Taq Polymerase: A Patented Research Tool for Which Licensing Arrangements Were Controversial*, in *INTELLECTUAL PROPERTY RIGHTS AND RESEARCH TOOLS IN MOLECULAR BIOLOGY* ch. 5 (1997) (reporting opinion of Tom Caskey, Senior Vice-President for Research at Merck Research Laboratories, that Roche “has behaved fantastically” with regard to granting access to PCR for scientific research).

371. See Mueller, *supra* note 370, at 3 (reporting Nobel laureate Arthur Kornberg’s criticism of Roche’s patent enforcement activity as “violat[ing] practices and principles basic to the advancement of knowledge for the public welfare”) (alteration in original); NAT’L RES. COUNCIL, *supra* note 370 (describing scientific community’s continuing dissatisfaction with the high cost of Taq polymerase and “dismay” as an after-effect of Cetus’s initial licensing terms, which included reach-through royalties on second-generation products derived through PCR).

372. See U.S. Patent No. 4,683,202 (filed Oct. 25, 1985); U.S. Patent No. 4,683,195 (filed Feb. 7, 1986).

3. Aptamers

Although secondary structures are generally undesirable in oligonucleotides that are to be used as primers, certain strands of DNA and RNA known as “aptamers” possess secondary structures that, because of their unique shapes, are useful for identifying and binding with specific sites on nucleic acid or protein structures (“ligands”).³⁷³ For example, given a protein that is necessary for a virus to function, it may be possible to synthesize an oligonucleotide that serves as an aptamer for binding the protein, thereby inhibiting the virus.³⁷⁴ Oligonucleotide aptamers can also be used as probes for the detection of particular ligands, although the principle of target recognition in this case is ligation rather than hybridization.³⁷⁵

Oligonucleotides that bind specifically with a particular ligand can be derived from a pool of random oligonucleotides through an iterative process, reminiscent of natural selection, known as “systematic evolution of ligands by exponential enrichment (SELEX).”³⁷⁶ Generally, oligonucleotides at least thirty to forty nucleotides in length are used in order to assure the occurrence of secondary structures that can bind tightly with the target ligand.³⁷⁷ Random oligonucleotides can be generated on a DNA synthesizer by using mixtures of nucleotides in place of individual nucleotides at appropriate stages of the synthesis process.³⁷⁸ By incorporating random nucleotides into thirty or more positions of the synthesized oligonucleotides, researchers can produce mixtures of trillions of individual species.³⁷⁹ From this diverse population of nucleic acids, those that bind with the target ligand can be selected (using a technique known as an “affinity column”) and amplified (using PCR, reverse transcription, or both). By repeating this process, researchers can eventually refine the mixture to contain only the nucleic acids that bind most strongly and specifically to the ligand.

The principal advantage of the SELEX procedure is that it requires no prior knowledge of the geometric relationship between the ligand and aptamer molecular structures.³⁸⁰ Instead of designing an aptamer around the ligand’s molecular structure, a researcher can simply generate a sufficiently large pool of candidates and let the SELEX procedure identify and synthesize those that can serve as aptamers.³⁸¹ The procedure’s inventors,

373. See Scott E. Osborne et al., *Aptamers as Therapeutic and Diagnostic Reagents: Problems and Prospects*, 1 CURRENT OPINION CHEMICAL BIOLOGY 5, 5-6 (1997).

374. *Id.* at 5.

375. See *id.* at 7-8; see also V.A. Spiridonova & A.M. Kopylov, *DNA Aptamers as Radically New Recognition Elements for Biosensors*, 67 BIOCHEMISTRY (MOSCOW) 706 (2002).

376. See Craig Tuerk & Larry Gold, *Systematic Evolution of Ligands by Exponential Enrichment: RNA Ligands to Bacteriophage T4 DNA Polymerase*, 249 SCIENCE 505, 505 (1990).

377. *Id.* at 506.

378. See, e.g., U.S. Patent No. 5,808,022 (filed June 5, 1995); U.S. Patent No. 5,639,595 (filed Dec. 2, 1993).

379. See Tuerk & Gold, *supra* note 376, at 505 & n.9.

380. *Id.* at 510 (“[W]e require no scorable phenotype other than binding to the partitioning agent . . .”).

381. *Id.* (concluding that the SELEX procedure “can be used to determine the optimal binding se-

Craig Tuerk and Larry Gold, have suggested that the method “heralds a new era in novel molecular design” and will be capable of generating “nucleic acids and proteins with any number of targeted functions.”³⁸²

4. Antisense Therapies

As described above, protein synthesis in the cell requires the transcription of the sense strand of an exon into mRNA, which is then translated by a ribosome into a protein.³⁸³ If an oligonucleotide having the same sequence as the antisense strand of the exon is introduced into the cell, it may be able to interrupt the translation process by hybridizing with the mRNA before a ribosome can act on it.³⁸⁴ In this way, oligonucleotides can inhibit the expression of particular genes. The first commercialized drug based on antisense oligonucleotides, Vitravene³⁸⁵ (fomivirsen), is a treatment for cytomegaloviral retinitis (a viral infection of the eye).³⁸⁶ Antisense therapies for HIV-AIDS, asthma, hair loss, acne, and certain forms of cancer and cardiovascular disease are currently under development.³⁸⁷

Effectiveness and safety requirements raise special considerations for the design of antisense oligonucleotides for therapeutic use. Such oligonucleotides must be short enough to maintain a high likelihood of hybridization, yet long enough to ensure that they bind only to the target mRNA—generally between twelve and twenty nucleotides.³⁸⁸ Often the oligonucleotides are modified to increase the likelihood that they will enter the target cells and hybridize with the target mRNA.³⁸⁹

5. Oligonucleotide-Directed Mutagenesis

The study of mutations, or changes in an organism’s DNA, is yielding important insights into the relationship between DNA sequences and protein

quences for any nucleic acid binding protein”).

382. *Id.*

383. *See supra* Part II.

384. *Id.*

385. Vitravene is a registered trademark of Isis Pharmaceuticals, Inc. *See* ISIS Pharmaceuticals, Vitravene, <http://www.isispharm.com/vitravene.html> (last visited Mar. 9, 2006).

386. *See* Justin Gillis, *Researchers Cheer Approval of Drug that Targets Genes*, WASH. POST, Aug. 28, 1998, at A2.

387. *See* Douglas W. Green et al., *Antisense Oligonucleotides: An Evolving Technology for the Modulation of Gene Expression in Human Disease*, 191 J. AM. C. SURGEONS 93 (2000); Janice Kane, *The Promise of Antisense Drugs*, CHEM. MKT. REP., Nov. 9, 1998, at FR11.

388. Green, *supra* note 387, at 96 (“Sequences 15 to 20 bases long, and even longer, have traditionally been used in antisense studies, in part to avoid the possibility of a similar sequence being present in an unrelated gene.”); Susanna Wu-Pong, *Oligonucleotides: Opportunities for Drug Therapy and Research*, BIOPHARM, Nov. 1994, at 20 (stating that a minimum length of twelve nucleotides is necessary to ensure acceptable specificity); Paul C. Zamecnik & Mary L. Stephenson, *Inhibition of Rous Sarcoma Virus Replication and Cell Transformation by a Specific Oligodeoxynucleotide*, 75 PROC. NAT’L ACAD. SCI. USA 280, 280 (1978) (describing an antisense therapy study involving a 13-mer).

389. *See* DMITRI KNORRE ET AL., DESIGN AND TARGETED REACTIONS OF OLIGONUCLEOTIDE DERIVATIVES 263-98 (1994); Wu-Pong, *supra* note 388.

functions. A major problem in protein engineering is determining the effect of a mutation on the physical structure of the resulting protein. Researchers have not yet developed computational models that can accurately predict such effects. For this reason, researchers find it useful to have a procedure for inducing specified mutations ("mutagenesis") in the laboratory.

An oligonucleotide carrying a particular mutation can be synthesized and incorporated into the template that is used by the polymerase in the *in vitro* synthesis of DNA. The resulting double-stranded DNA, which carries the mutation, can then be inserted into a gene to be expressed as a mutant protein.³⁹⁰ The traits of the resulting mutant organism may then provide a clue to the function of the mutated gene.³⁹¹ Oligonucleotides used in this procedure need to include a sufficient number of unchanged bases on both sides of the mutation so that they will hybridize at the appropriate location on the target molecule.³⁹² Depending on the complexity of the desired mutation, oligonucleotides of between twenty-five and eighty bases in length may be required.³⁹³

C. Some Utilities for Random and Arbitrary Oligonucleotides

1. RAPD-PCR Primers

A variation of the PCR technique known as "Random Amplified Polymorphic DNA" PCR (RAPD-PCR)³⁹⁴ or "arbitrarily primed PCR (AP-PCR)"³⁹⁵ has been developed that permits the amplification of segments of a target molecule even when its nucleotide sequence is unknown. Instead of designing pairs of primers with reference to the sequence of the target molecule, researchers use a single primer with a known, randomly generated sequence. The PCR procedure is then run under "low stringency" conditions, which allow the primer to bind to one or more locations on the target molecule even though some pairs of adjacent nucleotides may be mismatched. The locations of the priming sites determine which segments of DNA are synthesized by the polymerase and amplified.

The list of molecules that are amplified by RAPD-PCR with a given primer forms a profile, or "fingerprint," that can be used to identify and differentiate among DNA samples.³⁹⁶ For greater accuracy, a more detailed

390. See generally SAMBROOK & RUSSELL, *supra* note 14, at 13.2-.10.

391. See Thomas A. Kunkel et al., *Rapid and Efficient Site-Specific Mutagenesis Without Phenotypic Selection*, 154 METHODS ENZYMOL. 367, 367 (1987).

392. SAMBROOK & RUSSELL, *supra* note 14, at 13.82-.83.

393. *Id.* at 13.4.

394. John G.K. Williams et al., *DNA Polymorphisms Amplified by Arbitrary Primers are Useful as Genetic Markers*, 18 NUCLEIC ACIDS RES. 6531, 6531 (1990).

395. John Welsh & Michael McClelland, *Fingerprinting Genomes Using PCR with Arbitrary Primers*, 18 NUCLEIC ACIDS RES. 7213, 7213 (1990).

396. See, e.g., Ilan Levin et al., *Genetic Map of the Chicken Z Chromosome Using Random Amplified Polymorphic DNA (RAPD) Markers*, 16 GENOMICS 224 (1993); Bryan B. Wardell et al., *The Identification of Y Chromosome-Linked Markers with Random Sequence Oligonucleotide Primers*, 4 MAMMALIAN GENOME 109 (1993).

profile can be achieved by repeating the procedure with several different random primers. The Michael Smith Laboratories at the University of British Columbia markets various kits each containing one hundred randomly generated 10-mers for use as primers in RAPD-PCR profiling.³⁹⁷

2. *Random Primers for the Synthesis of Radiolabeled Probes*

In genetic research, it is often desirable to label DNA probes with radioactivity so that hybridization reactions can be readily detected. The ability of polymerases to synthesize DNA strands that are reverse-complementary to regions of a given target DNA molecule³⁹⁸ provides a convenient procedure for making radiolabeled probes.³⁹⁹ The procedure resembles one cycle of PCR, except that some of the nucleotides in the initial solution have been made radioactive, and the procedure uses a mixture of different random primers instead of a single primer pair to hybridize at numerous sites along the target molecule.⁴⁰⁰ When very short random primers (six to ten nucleotides in length) are used, the prevalence of hybridization reactions can be statistically predicted. By adjusting the concentration of primers used in the reaction, researchers can control the expected distance between primed sites on the target molecule, and thus also the expected length of the radiolabeled probes that are synthesized by the polymerase.⁴⁰¹

3. *Sequencing by Hybridization*

The sequence of nucleotides in a DNA molecule entirely determines its chemical structure and biological function.⁴⁰² In an organism for which the nucleotide sequences of the entire genome is known, the sequence of a particular molecule can serve to locate it on a chromosome within the genome, thereby enabling researchers to integrate biological data regarding the molecule into the scientific community's genome-wide knowledge base.⁴⁰³ For

397. See Michael Smith Labs., Univ. of B.C., Primer Sets, http://www.michaelsmith.ubc.ca/services/NAPS/Primer_Sets/ (last visited Apr. 10, 2007).

398. See *supra* text accompanying note 357.

399. See Michael D. Brush, *Probing Questions*, SCIENTIST, May 1, 2000, at 24; Andrew P. Feinberg & Bert Vogelstein, *A Technique for Radiolabeling DNA Restriction Endonuclease Fragments to High Specific Activity*, 132 ANALYTICAL BIOCHEMISTRY 6 (1983).

400. See SAMBROOK & RUSSELL, *supra* note 14, at 9.4-9.6; Feinberg & Vogelstein, *supra* note 399.

401. The expected number of nucleotides in a radiolabeled probe synthesized through random priming is proportional to $(\ln P_c)^{-1/2}$, where P_c is the concentration of the primer. See Clague P. Hodgson & Renee Z. Fisk, *Hybridization Probe Size Control: Optimized "Oligolabelling"*, 15 NUCLEIC ACIDS RES. 6295, 6295 (1987).

402. See *supra* Part II.

403. See, e.g., C. Lee & K. Irizarry, *The GeneMine System for Genome/Proteome Annotation and Collaborative Data Mining*, 40 IBM SYS. J. 592 (2001) (describing a computer implementation of a collaborative genome-wide knowledge base); D.D. Shoemaker et al., *Experimental Annotation of the Human Genome Using Microarray Technology*, 409 NATURE 922 (2001) (describing the use of genome-wide sequence information to identify authentic exons from among a set of DNA probes).

these reasons, procedures for “sequencing,” or determining the sequence of nucleotides in a DNA molecule, are of considerable importance in genetic research.

The most common methods for DNA sequencing utilize a technique called “gel electrophoresis,” wherein macromolecules are sorted according to length while passing through the matrix structure of an electrified gel.⁴⁰⁴ To sequence a DNA molecule, chemical or enzymatic methods are used to generate a mixture of fragmented copies of the molecule, with longer fragments containing more of the original molecule’s nucleotide sequence than shorter molecules. Next, fragments that contain the initial (5′) end of the original molecule are isolated and sorted by length through gel electrophoresis. As long as the mixture is sufficiently diverse, there will be fragments on the gel that terminate at every position in the original nucleotide sequence. Finally, the sequence is read from the nucleotides at the terminal (3′) end of each fragment in the order in which they have been sorted on the gel.

Gel electrophoresis methods are limited by the gel’s “resolution” or its ability to distinguish between DNA molecules of different lengths. For example, to sequence a 600-nucleotide molecule, the gel must be able to separate 590-nucleotide fragments from 589-nucleotide fragments and 591-nucleotide fragments. While gel resolutions of up to 1000 nucleotides have recently been achieved,⁴⁰⁵ the laws of thermodynamics are expected to limit further advances in this field.⁴⁰⁶

An alternative DNA sequencing technique, known as “sequencing by hybridization,” combines the power of microarrays with high-speed data processing to determine the sequence of an unknown DNA molecule.⁴⁰⁷ This patented procedure⁴⁰⁸ uses a microarray containing all possible oligonucleotides of a given length (all 4^k possible k -mers). The molecule will hybridize to the oligonucleotides whose reverse complements occur somewhere within the unknown sequence. Observing which hybridization reactions take place thus yields a list of all the k -base sequences that occur as subsequences in the target molecule (the “ k -spectrum” of the target molecule). Computers can efficiently reconstruct the unknown sequence from this hybridization data with high probability, provided that the length of the sequence n is not too large as a function of the oligonucleotide size k .⁴⁰⁹

404. See SAMBROOK & RUSSELL, *supra* note 14, at 5.4-5.13.

405. See Yongseong Kim & Edward S. Yeung, *Separation of DNA Sequencing up to 1000 Bases by Using Poly(ethylene oxide)-Filled Capillary Electrophoresis*, 781 J. CHROMATOGRAPHY 315 (1997).

406. See Gary W. Slater et al., *Recent Developments in DNA Electrophoretic Separations*, 19 ELECTROPHORESIS 1525, 1533 (1998).

407. See William Bains & Geoff C. Smith, *A Novel Method for Nucleic Acid Sequence Determination*, 135 J. THEOR. BIOL. 303 (1988); Radoje Drmanac et al., *Sequencing of Megabase Plus DNA by Hybridization: Theory of the Method*, 4 GENOMICS 114 (1989); Lysov et al., *DNA Sequencing by Hybridization with Oligonucleotides*, 303 DOKLADY ACAD. SCI. USSR 1508 (1988).

408. See, e.g., U.S. Patent No. 5,202,231 (filed June 18, 1991) (“Method of sequencing of genomes by hybridization of oligonucleotide Probes”).

409. See Richard Arratia et al., *Poisson Process Approximation for Sequence Repeats, and Sequenc-*

In the example shown below, $n=10$ and $k=3$. When a sample consisting of an isolated and purified DNA molecule with sequence 5'-TGCGGCACAT-3' is reacted with a microarray containing all possible 3-mers, the hybridization reactions indicated in Figure 5 will occur in the wells shaded in Figure 6. From this pattern, it may be possible to identify the original sequence computationally.

TGC GCA (probes)
 GTG CGC (probes)
3'-TACACGGCGT-5' (sample)
 ATG GCC (probes)
 TGT CCG (probes)

Figure 5. Out of the sixty-four possible 3-mers, eight will hybridize to a DNA molecule with the sequence 5'-TGCGGCACAT-3'.

AAA	ACA	AGA	ATA
AAA	ACC	AGC	ATC
AAG	ACG	AGG	ATG
AAT	ACT	AGT	ATT
CAA	CCA	CGA	CTA
CAC	CCC	CGC	CTC
CAG	CCG	CGG	CTG
CAT	CCT	CGT	CTT

ing by Hybridization, 3 J. COMPUTATIONAL BIOLOGY 425 (1996); Martin Dyer et al., *The Probability of Unique Solutions of Sequencing by Hybridization*, 1 J. COMPUTATIONAL BIOLOGY 105 (1994).

GAA	GCA	GGA	GTA
GAC	GCC	GGC	GTC
GAG	GCG	GGG	GTG
GAT	GCT	GGT	GTT
TAA	TCA	TGA	TTA
TAC	TCC	TGC	TTC
TAG	TCG	TGG	TTG
TAT	TCT	TGT	TTT

Figure 6. Example of a microarray used in a sequencing by hybridization experiment. Probes that hybridize to the DNA sample (top) are shaded (below). Using a computer algorithm, the sequence of the DNA molecule can be reconstructed from the pattern of hybridization reactions on the microarray.

D. Excerpt From the File DISCLOSE.TXT⁴¹⁰

ON THE PREPARATION AND UTILIZATION OF ISOLATED AND PURIFIED
OLIGONUCLEOTIDES

The term "isolated" as used herein refers to a nucleotide sequence that has been manually produced and is separated from its native, in vivo, cellular environment and is present in the substantial absence of other biological molecules of the same type. The term "purified" as used herein for nucleo-

410. Andrew Chin, On the Preparation and Utilization of Isolated and Purified Oligonucleotides (Mar. 9, 2002) (CD-ROM on file with The Katherine R. Everett Law Library, University of North Carolina at Chapel Hill) (Appendix D is entirely excerpted from the CD-ROM) (internal cites were modified to comport with proper citation form).

tide sequences preferably means lacking significant quantities of other biological macromolecules of the same type (but water, buffers, and other small molecules, can be present).

Preparation of Isolated and Purified Oligonucleotides

As described in U.S. Patent No. 5,808,022 (filed Sept. 15, 1998) (William D. Huse), oligonucleotide synthesis proceeds via linear coupling of individual monomers in a stepwise reaction. The reactions are generally performed on a solid phase support by first coupling the 3' end of the first monomer to the support. The second monomer is added to the 5' end of the first monomer in a condensation reaction to yield a dinucleotide coupled to the solid support. At the end of each coupling reaction, the by-products and unreacted, free monomers are washed away so that the starting material for the next round of synthesis is the pure oligonucleotide attached to the support. In this reaction scheme, the stepwise addition of individual monomers to a single, growing end of an oligonucleotide ensures accurate synthesis of the desired sequence. Moreover, unwanted side reactions are eliminated, such as the condensation of two oligonucleotides, resulting in high product yields.

Oligonucleotides are constructed by conventional procedures such as those described in J. SAMBROOK ET AL., *MOLECULAR CLONING: A LABORATORY MANUAL* 10.42-46 (3rd ed. 2001); K. Itakura et al., *Synthesis and Use of Synthetic Oligonucleotides*, 53 ANN. REV. BIOCHEMISTRY 323 (1984); M.D. Matteucci & M.H. Caruthers, *Synthesis of Deoxynucleotides on a Polymer Support*, 103 J. AM. CHEM. SOC'Y 3185 (1981); S.A. Narang, *DNA Synthesis*, 39 TETRAHEDRON 3 (1983). Oligonucleotide chains up to about 70 nucleotide residues long are preferably synthesized on automated synthesizers well known in the art (such as the Beckman Oligo 1000 or the Applied Biosystems ABI 392 DNA Synthesizer). Present-day DNA synthesizers are so efficient that oligonucleotides up to about 25 nucleotides in length generally do not contain significant quantities of truncated DNA fragments and hence do not require purification by gel electrophoresis. If necessary, however, purification of synthetic oligonucleotides can be achieved by one of several methods, as described in J. Sambrook, *supra*, at 10.48-49; including denaturing polyacrylamide gel electrophoresis, as described in J. SAMBROOK [et al.], *supra*, at 10.11-16; T. Atkinson & M. Smith, *Solid-Phase Synthesis of Oligodeoxyribonucleotides by the Phosphate-Triester Method*, in *OLIGONUCLEOTIDE SYNTHESIS: A PRACTICAL APPROACH* 35-82 (M.J. Gait ed. 1984).

Utilization of Oligonucleotides

As described in U.S. Patent No. 6,316,191 (issued Nov. 13, 2001) (Radoje T. Drmanac), hybridization depends on the pairing of complementary bases in nucleic acids and is a specific tool useful for the general recogni-

tion of informational polymers. Diverse research problems using hybridization of a synthetic oligonucleotide of known sequence include, amongst others, the different techniques of identification of specific clones from cDNA and genomic libraries, detecting single base pair polymorphisms in DNA, generation of mutations by oligonucleotide mutagenesis, and the amplification of nucleic acids in vitro from a single sperm, an extinct organism, or a single virus infecting a single cell.

Synthetic oligonucleotides of arbitrary nucleotide sequence are utilized in biological research, wherein oligonucleotides of specified length and random nucleotide sequence are synthesized using known procedures such as those described in Huse, *supra*; U.S. Patent No. 5,639,595 (issued June 17, 1997) (Christopher K. Mirabelli et al.). Arbitrary oligonucleotide primers of specified length may be used in the synthesis of cDNA probes from mRNA as described in Sambrook, *supra*, at 9.38-.40; J.G. Williams et al., *DNA Polymorphisms Amplified By Arbitrary Primers Are Useful As Genetic Markers*, 18 NUCLEIC ACIDS RESEARCH 6531 (1990), in the systematic evolution of ligands by exponential enrichment as described in U.S. Patent No. 6,331,398 (issued Dec. 18, 2001) (Larry Gold & Craig Tuerk); C. Tuerk & L. Gold, *Systematic Evolution of High-Affinity RNA Ligands of Bacteriophage T4 DNA Polymerase in Vitro*, 249 SCIENCE 505 (1990), and in sequencing by hybridization as described in Drmanac, *supra*. Preferably, oligonucleotide primers and probes are characterized by sequences of 8 to 20 nucleotides that have moderate G+C content, are free of both homopolymeric runs and directly or inversely repeated regions.

The disclosures of all publications and patents set forth hereinbefore are expressly incorporated herein by reference.

Sequence Listing

The listing of sequences set forth hereinafter consists of all sequences of 8 to 12 nucleotides that have between 40 and 60 percent G+C content and are free of homopolymeric runs of 4 or more bases and directly or inversely repeated regions of 4 or more bases. Based on the disclosures herein and the knowledge of a person of ordinary skill in the art, it will be apparent to such a person how to make and use an isolated and/or purified oligonucleotide characterized by any of the following nucleotide sequences:

5'-AAACACCC-3'
5'-AAACACCG-3'
5'-AAACACGC-3'
5'-AAACACGG-3'
5'-AAACAGCC-3'
5'-AAACAGCG-3'
5'-AAACAGGC-3'
5'-AAACAGGG-3'
5'-AAACCACC-3'

...

E. Patent Office Filings Disclosing the Oligonucleotide Reference

The oligonucleotide reference was cited in U.S. Patent No. 6,946,267, "Method for Detecting Staphylococcus Aureus," issued to Lu-Yieng Liu et al. on September 20, 2005, and U.S. Patent No. 6,953,669, "Human GAK-Related Gene Variants Associated With Lung Cancer," issued to Ken-Shwo Dai on October 11, 2005. Table 2 provides a listing of other patent applicants who are known to have cited the oligonucleotide reference in information disclosure statements filed with the Patent Office as of August 2004.

First Inven- tor	Patent Firm	Application Serial No.(s)	Application Filed	Disclosure Filed
Dai	Ladas & Parry	09/964,275	9/26/01	2/13/04
		10/102,547	3/20/02	2/9/04
		10/102,548	3/20/02	2/9/04
		10/102,553	8/2/02	2/9/04
		10/102,554	3/20/02	2/13/04
		10/102,555	3/20/02	2/9/04
		10/102,556	3/20/02	2/9/04
		10/103,334	3/21/02	2/9/04
		10/103,335	3/21/02	2/9/04
		10/103,336	3/21/02	2/9/04
		10/103,380	3/21/02	2/9/04
		10/103,957	3/22/02	2/9/04
		10/103,959	3/22/02	2/9/04
Takahashi	Oblon, Spivak	10/239,090	9/19/02	7/06/04
Barton	Fish & Richardson	10/354,437	1/28/03	3/16/04
Nishio	Fish & Richardson	10/392,536	3/20/03	7/12/04
Hirai	Morrison & Foer- ster	10/410,888	4/9/03	7/15/04
Kasid	Leydig, Voit & Mayer	10/411,931	4/10/03	5/18/04
Metz	Sheridan Ross	10/438,784	5/14/03	4/5/04
Gokhale	Leydig, Voit & Mayer	10/443,273	5/22/03	5/18/04
Parkin	Jones Day	10/612,600	7/1/03	7/14/04
Kalpana	Amster, Rothstein & Ebenstein	10/624,080	7/21/03	6/22/04
Lee	Cantor Colburn	10/663,857	9/15/03	7/21/04
Eritja	Buchanan Ingersoll	10/700,118	11/3/03	8/19/04

Table 2. Pending applicants for DNA patents who cited the oligonucleotide reference during prosecution before U.S. Patent and Trademark Office.

