

**DNA IS DIFFERENT:
LEGAL OBVIOUSNESS AND THE BALANCE BETWEEN
BIOTECH INVENTORS AND THE MARKET**

Anita Varma and David Abraham***

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* J.D., Georgetown University Law Center, Class of 1996. Ms. Varma is a former Patent Examiner (Group 1800) and is currently a student associate at Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

** J.D., George Washington University Law School, The National Law Center, Class of 1997. Mr. Abraham is a former Patent Examiner (Group 1500) and is currently a student associate (patent agent) at Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

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I. INTRODUCTION

Advanced biotechnology holds the staggering promise to change fundamentally the way life is viewed and handled by mankind. Genetic material, particularly deoxyribonucleic acid ("DNA"), is central to this promise as it is involved in the propagation of nearly all significant life forms on this planet. Understanding DNA's role in cellular processes is not just an academic exercise, however. Using modern genetic engineering techniques to manipulate DNA, biotechnologists are able to influence the development and metabolism of a wide range of living things, from plants to animals to human beings. This capability has spawned, and will continue to spawn, entire industries.¹

Intellectual property law, particularly patent law, plays a key role in the creation of wealth through the application of advanced biotechnology techniques. For example, the grant of a U.S. patent, with its right to exclude others from practicing the invention for a period of twenty years from the date of filing,² provides intellectual "capital" to inventive biotechnologists for creation of a business. Of course, these inventive biotechnologists would prefer their patents to have as sweeping a scope as possible. A "sweeping" patent reads on a wide variety of possible embodiments of the invention, and enhances the inventor's bargaining position with respect to potential licensees. There is a penalty to be paid

1. For example, sales of non-food products from genetically transformed plants are predicted to grow from about \$15 million per year today to \$320 million by 2005. Anne Simon Moffat, *Plants as Chemical Factories*, 268 *Sci.* 659, 659 (1995). Treatment of people with DNA-based gene therapy has even more market potential: tests to detect DNA defects of such diseases as cystic fibrosis or colon cancer are predicted to become a multi-billion dollar industry by early next century. John Carey, *The Gene Kings*, *BUS. WK.*, May 8, 1995, at 72.

2. Uruguay Round of Multilateral Trade Negotiations of 1994, Pub. L. No. 103-465, 108 Stat. 4809.

for such patents, however, especially in a rapidly growing field, such as DNA-based biotechnology. The monopoly granted by sweeping patents can foreclose entire portions of developing technologies in exchange for either insufficient or already available information.³ When the information contained in a patent is already available to the market, the patent system accomplishes an inefficient transfer of wealth: the patentee has not added to the total store of public knowledge in return for his right to exclude others from making or using his invention.

Patent law employs a concept termed "obviousness" to minimize such inefficient transfers. Obviousness, in patent law, is judged by what an ordinary practitioner in the inventor's field would be expected to know already.⁴ If an invention is within the grasp of that ordinary practitioner, then the invention is obvious, as a matter of law.⁵

This article concerns the question of obviousness in the context of patent prosecution. If the definition of obviousness is too lax, a patent claiming obvious subject matter may be allowed, thus permitting the patent owner to exclude previously accessible knowledge from the market. If the definition of obviousness is too stringent, then many biotechnologists may be unable to obtain the intellectual capital needed to start their businesses. Therefore, it is incumbent upon the Court of Appeals for the Federal Circuit and the Patent and Trademark Office ("PTO"), the institutions primarily charged with granting and construing DNA-based patents, to balance the needs of individual biotech patent applicants with the needs of the market. When this balancing act goes awry, industry and consumers suffer the stultification of technological growth.

In one particular area, that of the obviousness of the relationship between DNA and proteins, the Federal Circuit's guidance has upset the

3. See Andy Coghlan, *Sweeping Patent Shocks Gene Therapists*, NEW SCIENTIST, April 1, 1995, at 4 (commenting that sweeping patents on gene therapy could hold back medical advances); Richard Stone, *Sweeping Patents Put Biotech Companies on the Warpath*, 268 SCI. 656, 656 (1995) (discussing the negative reaction of the biotech community to several "overly broad" patents for various plants).

Insufficient disclosure of information in patents, as compared to disclosure of already available information, is generally controlled through the application of 35 U.S.C. § 112 ¶ 1 (1988) in the course of prosecution, in what is known as a "scope of claims" rejection.

4. Obviousness is a relative determination. The standard of comparison is one of "ordinary skill in the pertinent art." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The level of ordinary or average skill in the art varies from art to art. The obviousness inquiry requires the fact finder to make a finding as to the level of ordinary skill in the art at issue. *Id.*; see also *infra* note 63 and accompanying text.

5. It should be noted that the word "invention" is used as a term of art, referring to an "innovation." *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983). It is distinguished from a "patentable invention," i.e., one that satisfies the criteria of the patent laws. *In re Allen*, 343 F.2d 482, 487 (C.C.P.A. 1965) (Almond, J., dissenting).

delicate balance between patentees and the market, and threatens the development of DNA-based technology.

In a series of recent decisions,⁶ the Federal Circuit has effectively tilted the balance far in favor of biotech patent applicants through its definition of the legal test of what constitutes a proper *prima facie* case of legal obviousness. Specifically, this occurs in cases where the applicants are attempting to patent a DNA sequence for which the protein it codes is partially or fully known in the art.

This Article provides:

- (1) a general overview of the technology involved in DNA cases;
- (2) a more detailed discussion of the technology, including specific prior art references;
- (3) a discussion of the doctrine of legal obviousness, in the context of patent prosecution, particularly DNA cases;
- (4) an analysis of the Federal Circuit cases, *In re Bell* and *In re Deuel*, which have attempted to balance the legal issues;
- (5) a proposal for a new legal test to restore the balance; and
- (6) application of the new test to fact patterns.

II. A GENERAL OVERVIEW OF THE TECHNOLOGY

Patent law, as distinct from other types of law, is fundamentally technology-driven. New advances in various "useful Arts"⁷ force the creation and adaptation of existing patent case law. Therefore, to achieve a grasp of patent case law, a reasonable understanding of the underlying technology is essential.

Two key materials in cellular biochemistry are DNA⁸ and proteins.⁹ If DNA is the genetic "blueprint" of an organism, then proteins are, in large part, the cellular "machines" built according to that blueprint.

6. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995), *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993).

7. U.S. CONST. art. I, § 8, cl. 8.

8. DNA, a "nucleic" acid, is the genetic unit of a cell. It is made up of strands of repeating units called nucleotides. Each nucleotide consists of a five-carbon sugar, a base which may be adenine ("A"), guanine ("G"), thymine ("T"), or cytosine ("C"), and a phosphate. The complementary strands of DNA are oriented such that the bases from one strand weakly bond to the bases of the opposite strand. A bonds with T, and G with C, to form complementary base pairs. A strand of nucleotides is often referred to as an oligonucleotide. Background information presented in this article may be found in such standard biochemistry or molecular biology texts as BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* 95-100 (2d ed. 1989); ROGER L.P. ADAMS ET AL., *THE BIOCHEMISTRY OF THE NUCLEIC ACIDS* 5-13 (10th ed. 1986).

9. Proteins are large polymers of linearly linked amino acids bound together by peptide bonds. ALBERT L. LEHNINGER, *PRINCIPLES OF BIOCHEMISTRY* 95-104 (1982).

Proteins *directly* influence cellular biochemistry, as exemplified by the catalytic activity of enzymes and the immunological role of antibodies. Therefore, the value of DNA lies in its ability, when manipulated, to induce a cell's existing mechanisms to produce a desired protein in large quantities.

A gene is a region of DNA on a chromosome¹⁰ whose sequence encodes a specific protein.¹¹ A triplet of nucleic acids in the gene sequence, called a "codon," specifies individual amino acids. The order of this series of codons determines the amino acid sequence of the protein.

Given the triplet nature of the codon and the four possible nucleic acid bases,¹² the resulting genetic "code"¹³ generates sixty-four possible permutations, sixty-one of which code for amino acids.¹⁴ There are twenty different amino acids found in human proteins. Having sixty-one codons coding for only twenty amino acids results in "degeneracy," meaning that an amino acid may be coded for by more than one codon.¹⁵ For example, the amino acid leucine can be coded for by six separate codons. This degeneracy of the genetic code presents a challenge to a biotechnologist attempting to determine the DNA sequence from the amino acid sequence that it codes for: which of the various possible codons actually codes for the amino acid present in the sequence?

In cells, protein synthesis is accomplished in two stages: transcription and translation. During transcription, chromosomal DNA functions as a template for ribonucleic acid ("RNA")¹⁶ molecules which are transcribed from the DNA template. The RNA so transcribed is called messenger RNA ("mRNA") and is complementary to (i.e., matches) the

10. Chromosomes are single, large, genetically-specific DNA molecules, condensed into compact structures by attachment to a large number of proteins that maintain chromosome structure and regulate gene expression. JAMES D. WATSON ET AL., *RECOMBINANT DNA* 25 (2d ed. 1992).

11. Proteins are composed of chains of amino acids, as are polypeptides. Generally, the term polypeptide refers to the chain, whereas the term protein implies a three-dimensional structure and biological functionality, as well as the sequence of amino acids. LEHNINGER, *supra* note 9, at 95-115.

12. ALBERTS ET AL., *supra* note 8.

13. This code is widely available in standard textbooks in the art. See, e.g., *id.* at 102-03.

14. The remaining three codons are called "stop codons" because they do not code for any amino acid, and thus tell the cell to cease manufacturing the polypeptide. *Id.* at 209.

15. Only methionine and tryptophan are coded for by a single codon. *Id.*

16. RNA consists of repeating nucleotide units of adenine ("A"), guanine ("G"), cytosine ("C"), and uracil ("U"), a ribose sugar, and a phosphate. Like DNA, RNA is a nucleic acid. ADAMS ET AL., *supra* note 8.

corresponding DNA template. The mRNA initially consists of both coding sequences (exons)¹⁷ and non-coding sequences (introns).¹⁸

Transcribed mRNA¹⁹ moves from the nucleus to the cytoplasm, or "body," of the cell, where the proteins are produced from these mRNA templates. The nucleotide sequences in the mRNA are translated to give the corresponding amino acid sequence of the protein. This translation process is dependent upon the use of "adaptor molecules"²⁰ which recognize both the mRNA codon and an amino acid. This process further requires a ribosome²¹ which moves along the mRNA molecule and translates nucleotide sequences into amino acid sequences, one codon at a time. The polypeptide chain being synthesized is released from the ribosome when one of the three stop codons is reached.

This knowledge, together with the availability of restriction enzymes,²² has given the biotechnologist the tools needed to "recombine" DNA and arrive at a desired sequence. Recombinant DNA work usually starts with the making of genomic libraries²³ or complementary DNA

17. Coding sequences are called exons, because the processed mRNAs without the introns "exit" the nucleus to the cytoplasm. *Id.* at 289.

18. The regions of the chromosomal DNA not present in the mature mRNA are called introns. *Id.*

19. This mRNA undergoes certain post-transcriptional changes before it moves to the cytoplasm. It results in mRNA which possesses only the coding sequences and a poly-adenylic tail at the 3'-end. This unique feature is utilized in affinity chromatography to isolate or separate out mRNA, by using oligo(dT) which binds to the poly(A) tail of the mRNA. WATSON ET AL., RECOMBINANT DNA, *supra* note 10, at 102-04.

20. These are transfer RNAs ("tRNAs") which are usually about 80 nucleotides in length and have a folded three-dimensional L-shaped conformation. One end forms the "anticodon" that base-pairs to a complementary codon in the mRNA molecule, while the other end is attached covalently to the amino acid specified by that codon. ALBERTS ET AL., *supra* note 8, at 205-13.

21. Ribosomes catalyze protein synthesis and are large complexes of RNA and protein molecules. Each ribosome is made up of one large and one small subunit. The ribosome contains three binding sites for the RNA: two for tRNA and one for mRNA. The smaller subunits bind the mRNA and the tRNA, while the larger subunit catalyzes the peptide bond formation. The growing polypeptide chain must be kept in register with the mRNA molecule to ensure that each successive codon in the mRNA engages precisely with the anticodon of a tRNA molecule and does not slip by one nucleotide, as this would change the reading frame. *Id.* at 210.

22. These are enzymes that recognize and cut very specific nucleotide sequences of DNA. *Id.* at 258.

23. Such a library contains all the DNA in a given organism inserted as discrete fragments into plasmid, lambda, or cosmid vectors. The size of an organism's complete genomic library correlates with its genetic complexity. A lambda library requires 250,000 particles to contain a complete copy of the human genome. Constructing such a library even of this size is now a trivial problem. JAMES D. WATSON ET AL., MOLECULAR BIOLOGY OF THE GENE 596 (4th ed. 1987).

("cDNA")²⁴ libraries. These libraries are then "screened" for the desired sequence using a DNA probe.²⁵ The ease with which these procedures are practiced and the level of skill they require are important issues in both *Bell* and *Deuel*.

Biotechnologists can use recombinant techniques to produce human proteins in bacteria. The process involves taking a portion of DNA that codes for a desired protein, such as human insulin or human growth hormone, and inserting that portion into a bacterial plasmid vector.²⁶ In a successful recombination, the bacteria will "express," or produce, the desired protein in large quantities, and will reproduce, thus ensuring a continuing supply of the protein.

III. THE TECHNOLOGY IN DETAIL

A. *The DNA Technology Available at the Time of Bell and Deuel*

After reviewing the background information needed to understand the inventions of *Bell* and *Deuel*, it is useful to consider what constituted valid prior art as of the constructive date of the inventions.²⁷ This requires both a more detailed investigation of the technology, and a determination of the date it was known.

One of ordinary skill in the art can obtain a DNA sequence, once the protein coded for by that DNA is known, by (1) constructing a cDNA library, (2) designing an oligonucleotide probe, and (3) using the probe to screen the library.²⁸

24. Complementary DNA contains all the information present in the mRNA. Using reverse transcriptase, the information present in mRNA is copied into cDNA. This is advantageous because the processed mRNA contains only the coding information found in exons. *Id.* at 609-11.

25. A DNA probe is a single-stranded DNA fragment that is complementary to the target DNA sequence. ALBERTS ET AL., *supra* note 8, at 188-89.

26. Plasmid vectors are small circular molecules of double-stranded DNA capable of self-replication within a bacterial host. *Id.* at 259.

27. Prior art is information in the public domain available as of the date of the invention. Valid prior art is that prior art which conforms to the definition in 35 U.S.C. § 102 (1988). Only valid prior art can be used by a patent examiner to deny a patent to an invention. The constructive date of invention is the filing date of the patent.

28. See WATSON ET AL., RECOMBINANT DNA, *supra* note 10, at 100-11.

B. Constructing cDNA Libraries

By the early 1980s the advantages of constructing cDNA libraries were well known in the art.²⁹ Practitioners took advantage of the fact that mRNA represents a contiguous protein-coding functional domain of a gene. The cDNA library represents the mRNA population of an appropriate tissue or cell type, and thus represents only those genes which are expressed in a particular cell. Such libraries are prepared by purifying cellular mRNA using oligo(dT) affinity chromatography,³⁰ and synthesizing cDNA copies using reverse transcriptase.³¹ The cDNA produced in this manner has its 3'-end folded to form a "hairpin loop." This short sequence of double-stranded cDNA ("dscDNA") serves as a primer for the synthesis of a DNA strand which is complementary to the cDNA strand. The dscDNA, after certain modifications, is ready for insertion into a vector. Such cDNA constructions (clones) were available by the mid-1970s.³²

The above process has been refined and simplified by targeting and using sources rich in mRNA, which increases the concentration of the desired mRNA.³³ Processes such as immunoprecipitation,³⁴ use of drugs to overexpress particular proteins,³⁵ and protein synthesis inhibition that results in extended transcription³⁶ have been used by the skilled artisan to increase concentrations of the mRNA of interest. Increasing the concentration of the mRNA helps control the size of the cDNA libraries

29. J.G. Williams, *The Preparation and Screening of a DNA Clone Bank*, in 1 GENETIC ENGINEERING 1-59 (Williamson R. ed., 1981). Construction of both cDNA and genomic libraries are well documented in the art. This article concentrates on the use of cDNA libraries because these were used by the inventors in both *Bell* and *Deuel*. The inventors in *Bell* used cDNA libraries developed by Woods. See Brief for Appellee at 2, *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (No. 92-1375) (citing Derek E. Woods et al., *Isolation of cDNA Clones for the Human Complement Protein Factor B, a Class III Major Histone Compatibility Complex Gene Product*, 79 PROC. NAT'L. ACAD. SCI. 5661-65j (1982)). The inventors in *Deuel* also used cDNA libraries. See Brief for Appellant at 6, *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995) (No. 94-1202).

30. WATSON ET AL., RECOMBINANT DNA, *supra* note 10, at 102.

31. *Id.*

32. See JOSEPH SAMBROOK, EDWARD F. FRITSCH & THOMAS MANIATIS, MOLECULAR CLONING: A LABORATORY MANUAL, 8.2 (2d ed., 1989) [hereinafter MANIATIS].

33. R.K. Craig & L. Hall, *Recombinant DNA Technology: Application to the Characterisation and Expression of Polypeptide Hormones*, in 4 GENETIC ENGINEERING 57-125, 64 (Williamson R. ed., 1983).

34. See MANIATIS, *supra* note 32, at 8.3.

35. See, e.g., Kenneth L. Luskey et al., *Amplification of the Gene for 3-hydroxy-3-methylglutaryl Coenzyme A Reductase, But Not for the 53-kDa Protein, in UT-1 Cells*, 258 J. BIOLOGICAL CHEMISTRY 8462, 8462-69 (1983).

36. See, e.g., Håkan Persson et al., *Adenovirus Early Gene Products May Control Viral mRNA Accumulation and Translation In Vivo*, 23 CELL 485, 485-96 (1981).

which have to be screened. Size of cDNA libraries becomes an important factor when the desired mRNA is a rare or low-abundance message.³⁷ Thus, preparing cDNA libraries, even for rare messages, was well within the purview of the skilled artisan by 1980.

C. Designing the Probe

The next element in the process is designing the appropriate oligonucleotide probe to screen the libraries. The probes bind or "hybridize" to complementary strands of cDNA in the libraries. The theoretical basis of hybridization has been elucidated³⁸ and probes of varying lengths and specificities can be easily prepared. Two approaches that have been used in the past are: mixed degenerate pools of short oligonucleotides used under stringent conditions,³⁹ and longer single oligonucleotides used under less stringent conditions.⁴⁰ Stringency is a measure of how much "slop" or mismatching is tolerated during hybridization. The design of such probes is based mainly on two considerations: reduction in the number of false positive results using uniqueness of the target sequence, and reduction of degeneracy problems through codon selection.

A simple calculation illustrates how long a DNA sequence must be to make it "unique" in the human genome. The DNA sequence must have a probability of occurrence of less than once in three billion

37. See, e.g., John J. Toole et al., *Molecular Cloning of a cDNA Encoding Human Antihemophilic Factor*, 312 NATURE 342, 342-48 (1984); William I. Wood et al., *Expression of Active Human Factor VIII from Recombinant DNA Clones*, 312 NATURE 330, 330-35 (1984). These references disclose cloning cDNA when the mRNA was at levels of one molecule/cell.

38. See Michael Grunstein et al., *Colony Hybridization: A Method for the Isolation of Cloned DNAs That Contain a Specific Gene*, 72 PROC. NAT'L. ACAD. SCI. 3961, 3961-65 (1975); Michael Grunstein et al., *Colony Hybridization*, 68 METHODS IN ENZYMOLOGY 379, 379-89 (1979).

39. See Sidney V. Suggs et al., *Use of Synthetic Oligonucleotides as Hybridization Probes: Isolation of Cloned cDNA Sequences for Human β_2 -Microglobulin*, 78 PROC. NAT'L. ACAD. SCI. 6613, 6613-17 (1981); Ashwani K. Sood et al., *Isolation and Partial Nucleotide Sequence of a cDNA Clone for Human Histocompatibility Antigen HLA-B by Use of an Oligodeoxynucleotide Primer*, 78 PROC. NAT'L. ACAD. SCI. 616, 616-20 (1981); David V. Goeddel et al., *Human Leukocyte Interferon Produced by E. Coli Is Biologically Active*, 287 NATURE 411, 411-16 (1980); R. Bruce Wallace et al., *The Use of Synthetic Oligonucleotides as Hybridization Probes. II. Hybridization of Oligonucleotides of Mixed Sequence to Rabbit β -Globin DNA*, 9 NUCLEIC ACIDS RES. 879, 879-94 (1981).

40. See Michael Jaye et al., *Isolation of Human Anti-Haemophilic Factor IX cDNA Clone Using a Unique 52-Base Synthetic Oligonucleotide Probe Deduced from the Amino Acid Sequence of the Bovine Factor IX*, 11 NUCLEIC ACIDS RES. 2325, 2325-35 (1983); Stephen Anderson & I. Barry Kingston, *Isolation of a Genomic Clone for Bovine Pancreatic Trypsin Inhibitor by Using a Unique-Sequence Synthetic DNA Probe*, 80 PROC. NAT'L. ACAD. SCI. 6838, 6838-42 (1983).

nucleotides.⁴¹ If it is assumed that the bases are randomly distributed, the occurrence probability of any DNA sequence can be calculated by taking 4^n , where n equals the total number of nucleotides in the sequence of interest.⁴² The table on the following page sets forth the occurrence probabilities of DNA sequences.

This calculation shows that a sixteen(-mer) nucleotide sequence would occur only once in 4,294,967,296, which suggests that any sequence of sixteen nucleotides or longer is likely to be unique in the human genome,⁴³ and would consequently increase the probability of success in screening for a desired clone.

Next is the choice of the specific codons used in constructing this oligonucleotide probe. Once the amino acid sequence is known, the selection of the probe is based upon the genetic code.⁴⁴ One of ordinary skill would minimize the deleterious effects of degeneracy by selecting regions which have amino acids coded for by only one or two possible codons, and avoiding those that are rich in amino acids coded for by five to six possible codons. This selection process is further simplified through the use of "codon catalogs," which list the preferences various species have shown in codon selections.⁴⁵ Degeneracy problems often can be resolved by taking advantage of these recorded preferences to arrive at the expressing cDNA sequence.

41. The twenty-three human chromosomes have a total genetic size of 3,300 centimorgans (centimorgans are units of recombination; two genes are one centimorgan apart if they recombine in meiotic cell division every 100 opportunities that they have to do so) and the total number of base pairs is about three billion. WATSON ET AL., RECOMBINANT DNA, *supra* note 10, at 604.

42. The number four in the expression 4^n comes from the total number of base choices found in human DNA. ALBERTS ET AL., *supra* note 8, at 97.

43. DAVID A. MICKLOS ET AL., DNA SCIENCE: A FIRST COURSE IN RECOMBINANT DNA TECHNOLOGY 67 (1990).

44. WATSON ET AL., RECOMBINANT DNA, *supra* note 10, at 104.

45. R. Grantham et al., *Codon Catalog Usage and the Genome Hypothesis*, 8 NUCLEIC ACIDS RES. r49, r49-r62 (1980) [hereinafter Grantham I]; R. Grantham et al., *Codon Catalog Usage Is a Genome Strategy Modulated for Gene Expressivity*, 9 NUCLEIC ACIDS RES. r43, r43-r72 (1981) [hereinafter Grantham II].

For example, Taniguchi et al. analyzed the coding region of the human fibroblast interferon mRNA and concluded that codons were utilized in a non-random manner—the use of *CUG* and *CUC* for leucine and *AAG* for lysine were the preferred choices in eukaryotic mRNAs. T. Taniguchi et al., *The Nucleotide Sequence of Human Fibroblast Interferon cDNA*, 10 GENE 11, 11-15 (1980).

Table: Occurrence Probabilities of DNA Sequences of Increasing Number of Nucleotides

Nucleotides	Occurrence Probability ($1/x$)
1	4
2	16
3	64
4	256
5	1,024
6	4,096
7	16,384
8	65,536
9	262,144
10	1,048,576
11	4,194,304
12	16,777,216
13	67,108,864
14	268,435,456
15	1,073,741,824
16	4,294,967,296

Thus most, if not all, problems caused by degeneracy may be easily solved by proper selection and design of probes. When the specific cDNA sequence is completely unknown, one can use degenerate pools of short oligonucleotides containing all sequences that could possibly code for a given sequence of amino acids.⁴⁶ On the other hand, when portions of the cDNA sequence are known, single oligonucleotide probes that are longer in length may be used under less stringent hybridization conditions.⁴⁷

D. Screening the Library

In 1981, Suggs designed two sets of mixed oligonucleotide probes and successfully used them to isolate the cloned cDNA for the human β_2 -microglobulin.⁴⁸ The fifteen-mer oligonucleotide probes they designed were based on the known amino acid sequence of the protein and accounted for the degeneracy of the code. A total of 535 clones were screened to detect the desired clone.⁴⁹ Similar methods were also used for the isolation of rabbit β -globin⁵⁰ and bovine trypsin inhibitor.⁵¹ These references illustrate that using probes to locate specific gene sequences in clone libraries of specific to moderate complexities was well within the purview of the skilled artisan. Degenerate pools of short oligonucleotide probes can be used to isolate the cDNA for *any* protein with a known amino acid sequence.⁵²

A method using a single oligonucleotide probe has been disclosed by Jaye.⁵³ Jaye established that the synthetic DNA probes disclosed therein are capable of isolating cDNA probes of extremely low-abundance mRNAs from any cDNA library. The probe in this case was a fifty-two-mer and was designed using the known amino acid sequence for bovine factor IX.⁵⁴ Anderson and Kingston taught the isolation of a genomic clone using unique sequence synthetic probes. The probe was designed using the known amino acid sequence for bovine pancreatic trypsin inhibitor and the consensus codon usage data compiled from the sequences of twenty-six mammalian genes.⁵⁵ The probe sequence was

46. See Suggs et al., *supra* note 39, at 6615-16.

47. See Jaye et al., *supra* note 40, at 2325-26.

48. Suggs et al., *supra* note 39, at 6613.

49. *Id.*

50. See Wallace et al., *supra* note 39.

51. See Anderson & Kingston, *supra* note 40.

52. See Suggs et al., *supra* note 39.

53. Jaye et al., *supra* note 40.

54. *Id.* at 2325.

55. Anderson & Kingston, *supra* note 40, at 6838-39.

compared using a computer program called DIAGON⁵⁶ to detect self-complementary regions that might interfere with the construction of the probe.

E. The Current State of Technology

DNA-related biotechnology has progressed significantly since the time of the inventions in *Bell* and *Deuel*. There are cDNA libraries now commercially available from most chemical companies that can be custom-made to suit the inventor's needs. Use of the polymerase chain reaction allows one of ordinary skill in the art to circumvent the problem of choosing the appropriate probe.⁵⁷ Automatic DNA sequencers now perform gel electrophoresis and determine the DNA sequence using a laser detection system.⁵⁸ Finally, commercial gene sequencing firms have been storing genomic sequences for a variety of organisms, including humans, in supercomputers for computerized matching of protein sequences. This avoids the need for any exploratory laboratory "wet matching." This technique allows the current biotechnologist to isolate a protein of interest, partially sequence it, log on to a computer data bank in order to predict the protein's entire sequence, and obtain the probable cDNA sequence and location(s) of the cDNA sequence in the human (or other) genome.

IV. THE LEGAL DOCTRINE OF OBVIOUSNESS

A. Obviousness Generally

As noted above, the balance of intellectual property rights between biotechnology patent applicants and the market is set, at least partially, through the instrument of obviousness. According to the patent statute, an inventor cannot receive a patent for an invention:

[I]f 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.⁵⁹

56. See Rodger Staden, *An Interactive Graphics Program for Comparing and Aligning Nucleic Acid and Amino Acid Sequences*, 10 NUCLEIC ACIDS RES. 2951, 2951-61 (1982).

57. See, e.g., Cheng Chi Lee et al., *Generation of cDNA Probes Directed by Amino Acid Sequence: Cloning of Urate Oxidase*, 239 SCI. 1288, 1288-91 (1988).

58. See WATSON ET AL., RECOMBINANT DNA, *supra* note 10, at 99-119.

59. 35 U.S.C. § 103 (1988 & Supp. V 1993) (emphasis added).

The statute was underscored by the defining Supreme Court case, *Graham v. John Deere Co.*⁶⁰ In *Graham*, the Court laid out a four part obviousness inquiry:⁶¹

- (1) determine the scope and content of the prior art;
- (2) ascertain the differences between the claimed invention and the prior art;
- (3) resolve the level of ordinary skill in the pertinent art;
- (4) consider secondary indicia of non-obviousness, such as commercial success, and long-felt need in the art.⁶²

In the context of prosecution, or the business of actually obtaining a patent from the U.S. Patent and Trademark Office, there is a further procedural wrinkle to obviousness: the prima facie case of obviousness. This is a procedural tool that facilitates burden-shifting during prosecution. A patent application properly filed with the Patent Office is presumed patentable; thus the burden falls upon the Patent Office, in the person of the patent examiner, to show otherwise.⁶³ Failure to carry this burden must result in a patent grant.⁶⁴

If a valid prima facie case of obviousness is made, the burden then shifts to the applicants to produce objective evidence of non-obviousness. Once such evidence is produced, the prima facie presumption

60. 383 U.S. 1 (1966).

61. *Id.* at 17.

62. Since *Graham*, the "secondary indicia of non-obviousness" have become known as "objective evidence of non-obviousness," and are always considered if they are present:

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 the light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.

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

63. See *In re Warner*, 379 F.2d 1011, 1016 (C.C.P.A. 1967) (stating that the precise language of 35 U.S.C. § 102 concerning novelty and unobviousness places the burden on the Patent Office to produce the factual basis for its rejection of an application), *cert. denied*, 389 U.S. 1057 (1968).

64. *Cf. In re Jones*, 958 F.2d 347, 351 (Fed. Cir. 1992) (holding that because the Patent Office did not establish a prima facie case of obviousness, the burden did not shift to the applicant to come forward with objective evidence of non-obviousness).

drops from the case, and the examiner must review all of the evidence anew to determine the obviousness of the invention.⁶⁵

The question quite naturally arises: what creates a prima facie case of obviousness? The answer to this is far from clear. The general statement, known as the "suggestion test," is that a prima facie case "is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art."⁶⁶ Coupled with this is the requirement that the prior art must provide one of ordinary skill in the art a reasonable chance of success.⁶⁷ Absent a reasonable chance of success, an assertion that it would have been prima facie obvious to try to make the applicant's invention, in light of the prior art teachings, would be improper.⁶⁸

An alternative to the suggestion test is the doctrine of structural similarity that is used for chemical inventions. This doctrine existed prior to the 1952 Patent Act, and the Federal Circuit in *In re Dillon* definitively restated that:

[I]n reconsidering this case *in banc*, [this court] reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness, and that the burden (and opportunity) then falls on an applicant to rebut that prima facie case.⁶⁹

65. See *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984), where the court noted:

After a prima facie case of obviousness has been established, the burden of going forward shifts to the applicant. Rebuttal is merely "a showing of facts supporting the opposite conclusion," . . . and may relate to any of the *Graham* factors including the so-called secondary considerations. . . . If rebuttal evidence of adequate weight is produced, the holding of prima facie obviousness, being but a legal inference from previously uncontradicted evidence, is dissipated. Regardless of whether the prima facie case could have been characterized as strong or weak, the examiner must consider all of the evidence anew.

66. *In re Rinehart*, 531 F.2d 1048, 1051 (C.C.P.A. 1976).

67. See *In re Clinton*, 527 F.2d 1226, 1228 (C.C.P.A. 1976) ("Obviousness does not require absolute predictability, but a reasonable expectation of success is necessary.")

68. See *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (reporting that "obvious to try" is not the doctrine under 35 U.S.C. § 103 (1988)); *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (holding that a prima facie case of obviousness is valid when references suggested the applicant's invention to one of ordinary skill, and restating that "obvious to try" is not the standard under § 103).

69. *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991). But see *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963) (holding that structural similarity, without evidence, does not give rise to prima facie obviousness: "[f]rom the standpoint of patent law, a compound [']s structure] and all of its properties are inseparable").

Structural similarity is a vague concept. But roughly speaking, it means that if the structure of a prior art compound or the key elements of a prior art composition are found to have closely analogous functional groups and/or structural formulae to the invention of the applicant, then, as a matter of law the compounds are structurally similar.⁷⁰

B. Structural Similarity Does Not Work for the DNA/Protein Relationship

Biotechnology case law typically evolves from similar chemical case law. Therefore, it was natural for the doctrine of *prima facie* obviousness based on structural similarity to be applied to the patentability of DNA. The Federal Circuit views DNA as "a chemical compound, albeit a complex one."⁷¹ This is arguably correct, as DNA is simply a polymer of nucleic acids. However, DNA differs from traditional polymers in a number of important ways.

Traditionally, polymers have found their use as physical components of tangible items. Therefore, it is the polymer and its "inseparable properties"⁷² that are valuable. A similarity in the structural representation of two polymers would lead one of ordinary skill to believe that the polymers would behave similarly, if put to similar use. Thus, if a patent applicant makes a relatively minor change to a prior art compound, this minor change is deemed, as a matter of law, to be unworthy of a patent grant, because it does not fundamentally add anything to the store of public knowledge.⁷³

Minor changes in the DNA sequence, however, may produce major changes in the function of DNA. Unlike the majority of chemical compounds around which the "structural similarity" doctrine emerged, the main technological significance of DNA is wrapped up in its central role in mediating cell physiology. As discussed in detail above, it is the mediation of cell physiology, through directed expression of proteins, which is currently the most commercially important function of DNA. A minor change in the DNA's chemical structure (e.g. a pinpoint mutation) may completely eliminate the DNA's ability to direct

70. For further discussion on structural similarity up to the *Dillon* decision, see Helmuth A. Wegner, *Prima Facie Obviousness of Chemical Compounds*, 6 AM. PAT. L. ASS'N Q.J. 271 (1978). For discussions of the en banc *Dillon* decision, see Cary W. Brooks, Comment, *In re Dillon* en banc, 32 IDEA: J.L. & TECH. 299 (1992); Chris P. Konkol, *The "Problem Solved" in In re Wright and In re Dillon*, 31 IDEA: J.L. & TECH. 131 (1990).

71. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991), cert. denied, 502 U.S. 856 (1991).

72. *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963).

73. See *Patlex Corp. v. Mossinghoff*, 758 F.2d 594, 599 (Fed. Cir. 1985).

expression of a desired protein. The DNA sequence alone is thus subjectively useless.

Therefore, the relationship between the DNA and the protein(s) it codes for, rather than the actual DNA sequence, creates value. The biotechnologist patent applicant is usually *not* interested in the DNA as a product in its own right, as was the case in traditional chemistry and chemical patent law. Rather, the biotechnologist is interested in the DNA as an apparatus or tool to obtain the desired product: the coded for protein.

Whereas there is a relationship between DNA and its protein — they are related through the biochemistry of translation — this relationship is not *structural*, per se. Proteins are made of amino acids. DNA, as well as RNA, are made up of nucleic acids. Structurally, DNA and proteins are quite unrelated.

Based on this dissimilarity, biotechnologists have persuasively argued that application of the “structural similarity” doctrine to the DNA-protein relationship is inappropriate. The Federal Circuit has agreed with this reasoning.⁷⁴ This makes it difficult for the government to deny a DNA patent, because most chemical compound cases of prima facie obviousness are made using the doctrine of structural similarity.⁷⁵ This occurs not because the DNA is particularly non-obvious, but rather because there is no well defined test to replace structural similarity as a test for prima facie obviousness.⁷⁶

C. Choosing One Out of Many — The Doctrine of Selection Inventions

As noted above, the degeneracy of the genetic code makes it difficult to predict the exact DNA sequence based solely on the protein sequence.⁷⁷ Furthermore, only portions of the “natural” DNA sequence

74. See *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993).

75. See Charles Craig, *Appeals Court Ruling May Make Patenting Genes Easier*, *BIO WORLD TODAY*, Mar. 30, 1995, at 5 (stating the general perception that the decision in *Deuel* strengthens the ruling in *Bell*, and makes it easier to get a patent on DNA when the protein it codes for is known).

76. The Federal Circuit’s reasoning leaves open the possibility of arguing the obviousness of DNA sequences homologous between species. For example, in *Ex parte Movva*, 31 U.S.P.Q.2d (BNA) 1027 (Bd. Pat. App. & Interferences 1993), the applicant claimed DNA encoding mature swine growth hormone. The prior art in this case disclosed genes encoding bovine, rat, and human growth hormones, and disclosed that these sequences from different species displayed great sequence identity. The Board of Patent Appeals and Interferences was convinced by the Examiner’s reasoning that such amino acid sequence information could be used to isolate the desired sequence using pools of short degenerate synthetic oligonucleotides.

77. See *supra* note 15 and accompanying text.

actually are involved in coding for the protein of interest.⁷⁸ This is of significance when attempting to perform the second step of the *Graham* analysis — comparing the prior art with the invention. If a protein sequence is disclosed in the prior art, either completely or partially, is all of the natural DNA that codes for it *prima facie* obvious? What of the reverse: if a DNA sequence is taught in the prior art, does that render the protein it codes for *prima facie* obvious?⁷⁹

The Federal Circuit's analysis involves consideration of the doctrine of "selection inventions." Selection inventions claim a narrow range within a broad range disclosed by the prior art.⁸⁰ For example, a prior art disclosure for a method of taffy pulling might teach that the taffy can be heated to a temperature of anywhere from 25°C to 250°C, when pulling it. The applicant might discover that a narrow range, say from 70°C to 110°C, is far superior to any other point of the range for taffy pulling, noting that at temperatures below that range, the taffy becomes solid and unpullable, and that above that range the taffy turns into a liquid and eventually chars. The question is whether the prior art broad temperature disclosure would have provided one of ordinary skill in the art with enough information to give rise to a case of *prima facie* obviousness, which the applicant would then have the opportunity to rebut.

The answer involves the yin and yang of "reasonable chance of success" and "obvious to try": Would one of ordinary skill, if handed the prior art disclosure, have a reasonable expectation of successfully arriving at the patent applicant's invention, or would it merely be obvious to try to arrive at the patent applicant's invention? If there were a reasonable expectation of success, based on the prior art, then the applicant's invention might very well be *prima facie* obvious.

Unfortunately, the chemical case law is split on this issue. A first line of cases is based upon *In re Susi*.⁸¹ In *Susi*, the court held a chemical invention to be *prima facie* obvious where the broad prior art disclosure included at least some of the compounds claimed by the applicant, and the prior art chemicals were of a class to be used for the same purpose as the compounds of the applicant.⁸² This could be taken to mean that any disclosure which includes the chemical materials claimed by the applicant would render the claimed materials obvious, requiring the applicants to rebut the *prima facie* case with objective

78. See *supra* notes 17-18 and accompanying text.

79. The Federal Circuit suggests, in dicta, that protein sequences may be predicted if the DNA sequences coding for them is known. *In re Deuel*, 51 F.3d 1552, 1554 (Fed. Cir. 1995).

80. See David J. Abraham, *Shinpo-Sei: Japanese Inventive Step Meets U.S. Non-Obviousness*, 77 J. PAT. & TRADEMARK OFF. SOC'Y 528, 538 n.16 (1995).

81. 440 F.2d 442 (C.C.P.A. 1971).

82. *Id.* at 446.

evidence of non-obviousness. Note that this reasoning can be considered to evolve from the structural similarity arguments, since it is the inclusion of the claimed chemical *structure* within the class of prior art *structures* that gives rise to a case of prima facie obviousness.

Susi was followed by several cases along similar lines, such as *In re Corkill*,⁸³ and *Merck & Co. v. Biocraft Laboratories Inc.*⁸⁴ In *Merck*, the applicant claimed only one out of 1200 embodiments disclosed by the prior art. The *Merck* court held, however, that when the prior art instructs the artisan that any of the 1200 embodiments would work, this gives rise to a case of prima facie obviousness. This was especially true, according to the court, because the claimed composition was used for the same purpose taught by the prior art.⁸⁵

The case law began to split, however, with the Federal Circuit's decision in *In re Jones*.⁸⁶ In *Jones*, the court decided that a prima facie case of obviousness based on structural similarity was not made where the claimed chemical species was one of a broad genus, holding that "[w]e decline to extract from *Merck* the rule that . . . regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."⁸⁷ The court distinguished *Merck* by stating that, unlike *Merck*, the claimed species was not specifically disclosed, but merely was encompassed by the broad and general prior art teaching.⁸⁸

This was followed by *In re Baird*,⁸⁹ which was decided after *Bell*, but further elucidated the Federal Circuit's thinking on selection inventions. In *Baird*, the applicant's claim to bisphenol A was rejected as being prima facie obvious over prior art disclosure of a broad genus of diphenols. The court rejected this argument stating that there was nothing in the prior art suggesting that one of ordinary skill should select bisphenol A from among the more than 100 million diphenols contained in the broad genus taught by the prior art.⁹⁰ The court went on to say that "[a] disclosure of millions of compounds does not render obvious a

83. 771 F.2d 1496, 1500 (Fed. Cir. 1985) (affirming examiner's rejection based on argument where prior art taught that a class of chemicals would be functional, thus the applicant's selection of a single member of that class would have been prima facie obvious).

84. 874 F.2d 804 (Fed. Cir. 1989), cert. denied, 493 U.S. 975 (1989).

85. *Id.* at 807.

86. 958 F.2d 347 (Fed. Cir. 1992).

87. *Id.* at 1943.

88. *Id.*

89. 16 F.3d 380 (Fed. Cir. 1994).

90. *Id.* at 382.

claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.⁹¹

The Federal Circuit's selection invention analysis in *Bell*, discussed further below, focused on what it considered to be an inordinately large number of possibilities⁹² that faced one of ordinary skill in the art trying to arrive at the claimed DNA sequence. The Federal Circuit cleaved to the *Jones* analysis, and away from the *Susil/Corkill/Merck* analysis, to reason that a prima facie case of obviousness that required one of ordinary skill to make too many choices was not a properly made case.⁹³

D. Review of *In re Bell* and *In re Deuel*

1. *In re Bell*

The stage is now set for an understanding of the Federal Circuit's approach in *In re Bell*,⁹⁴ an appeal from the PTO's Board of Patent Appeals and Interferences. In *Bell*, the applicant claimed a DNA sequence which coded for the human insulin-like growth factors I and II ("IGF-I" and "IGF-II"). These proteins' sequences are each seventy amino acids long, but were already disclosed by the prior art.⁹⁵ From the genetic code, it is apparent that 10^{36} possible DNA sequences may encode either protein.⁹⁶ The primary issue in *Bell* was whether one of ordinary skill in the art would be able to determine the DNA sequence that coded for IGF-I and IGF-II using the recombinant techniques known at the time, given that the entire amino acid sequence was known.

91. *Id.* at 383. This position was so controversial at the Patent Office that the Commissioner of Patents, Bruce Lehman, specifically instructed the Patent Examining Corps to disregard *Baird* when making obviousness rejections, 1174 OFFICIAL GAZETTE 314 (1994), although this position was later revised, 1174 OFFICIAL GAZETTE 68 (1995).

92. The court stated the chances as being 1 in 10^{36} . *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993).

93. *See id.* at 784.

94. For a good discussion of key Federal Circuit cases dealing with the patentability of genetic material generally, see John Storella, Amgen, Fiers, and Bell: *The Federal Circuit Court and the Patentability of Genes*, 13 BIOTECH. L. REP. 459 (1994). For an alternative look at *Bell*, see Stephen B. Maebius, *Patenting DNA Claims After In re Bell: How Much Better Off Are We?*, 76 J. PAT. & TRADEMARK OFF. SOC'Y 508 (1994).

95. Ernst Rinderknecht & René E. Hummel, *The Amino Acid Sequence of Human Insulin-Like Growth Factor I and Its Structural Homology with Proinsulin*, 253 J. BIOLOGICAL CHEMISTRY 2769, 2769-76 (1978) [hereinafter Rinderknecht I]; Ernst Rinderknecht et al., *Primary Structure of Human Insulin-Like Growth Factor II*, 89 FEBS LETTERS 283, 283-86 (1978) [hereinafter Rinderknecht II].

96. The initial sequence listing is as follows: *gly-pro-glu-thr-leu*—. *See* Rinderknecht I, *supra* note 95; Rinderknecht II, *supra* note 95. These amino acids may be coded for by four, four, two, four, and six codons respectively. The number of possible sequences which can code for the protein will be the factorial: $4 \times 4 \times 2 \times 4 \times 6$ —.

Basing its opinion upon the references cited by the examiner, Rinderknecht⁹⁷ and Weissman,⁹⁸ the court was convinced that the cited prior art failed to render the claimed DNA sequence obvious for several reasons.

First, the court opined that the established relationship in the genetic code between a nucleic acid and the protein it encoded did not make the gene prima facie obvious over the protein for which it coded. Without explicitly citing *Jones*, the court employed the same version of the selection invention doctrine to reason that, because 10^{36} possible sequences could code for the protein, the particular sequence claimed by the inventors in *Bell* would not be obvious over all of the 10^{36} or "nearly infinite number of possibilities."⁹⁹

Unfortunately, 10^{36} was probably *not* the correct number. This is because the prior art suggests that, although the theoretical number of possibilities appears to be mind-boggling, the state of cloning procedures at the time of the invention in *Bell* allowed routine handling of such large numbers of possible sequences. For example, a simple calculation based upon the amino acid sequence disclosed shows that the protein in *Suggs* can be coded for by 10^{46} possible sequences.¹⁰⁰ Similarly, the protein disclosed by *Anderson and Kingston* can be coded for by 10^{43} possible sequences.¹⁰¹ Thus, the "nearly infinite" (or 1 in 10^{36}) argument was merely an artifact of a clever strategy by the attorney in *Bell*,¹⁰² rather than an insurmountable barrier for one of ordinary skill.¹⁰³

Second, the court in *Bell* explicitly rejected the proposition that the structural obviousness doctrine was applicable to the facts of *Bell*.¹⁰⁴ Given the broad language used by the court in this rejection, it is difficult to imagine anyone using the structural obviousness doctrine to successfully argue prima facie obviousness under facts similar to those of *Bell*. As noted earlier, this unequivocal rejection upsets the balance between

97. Rinderknecht I, *supra* note 95; Rinderknecht II, *supra* note 95.

98. Sherman M. Weissman et al., U.S. Patent No. 4,394,443 (issue date: July 19, 1983).

99. *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993).

100. The reference discloses the one sequence obtained by the cloning procedure; this sequence would have been seen as representative of the other equivalent sequences. *Suggs et al.*, *supra* note 39, at 6616.

101. *Anderson & Kingston*, *supra* note 40, at 6841. It should be noted that both *Suggs* and *Anderson & Kingston* would represent valid prior art as to the invention in *Bell*, which was afforded a constructive date of invention (i.e., the filing date) of July 13, 1984.

102. Brief for Appellant at 19, *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (No. 92-1375).

103. Although, to be fair to the court, the Solicitor for the Patent and Trademark Office never pointed out the fallacies behind the "1 in 10^{36} " argument, leaving the court with the impression that this was an accurate representation of the difficulties faced by the inventors in *Bell*. 991 F.2d at 784.

104. *Id.*

biotechnologist patent applicants and the rest of the market, and fails to propose a counter-balancing analysis.

Third, the court stated that Weissman taught away from the methodology used by the inventors in *Bell*.¹⁰⁵ The court reasoned that Weissman emphasized the importance of using amino acid segments coded for by "unique codons,"¹⁰⁶ and that using probes greater than thirteen to fourteen nucleotides in length was impractical due to greater possibilities of mismatches. The inventors in *Bell* had used a twenty-three-mer oligonucleotide probe, none of which were coded for by unique codons.¹⁰⁷ In view of this teaching away from the invention, the court concluded there was no suggestion in the prior art that rendered the claims in *Bell* *prima facie* obvious.

The use of unique codons, i.e., only methionine and tryptophan, is most desirable because it affords the least possible degeneracy. From a practical standpoint, however, finding a contiguous sequence made up of only methionine and tryptophan would be extremely unusual. In fact, IGF-I has only one unique codon which codes for methionine, and IGF-II has no unique codons — as one of ordinary skill could have observed from the Rinderknecht references.¹⁰⁸

Although Weissman emphasized the use of unique codons, the primer used by Weissman corresponds to the tetra-peptide sequence *met-trp-arg-arg*.¹⁰⁹ Both *met* and *trp* are coded for by unique codons, but *arg* is coded for by six possible codons. Thus, the primer of Weissman cannot be considered unique. Further, the short tetra-peptide in Weissman was used as a primer to synthesize a longer oligonucleotide probe; when the length of the probe is smaller, more stringent hybridization conditions are used, requiring fewer degenerate sequences.¹¹⁰ When longer probes are used, there is greater flexibility with regard to the degeneracy of the probe because hybridization is conducted under conditions of lower stringency.¹¹¹ It logically follows from this teaching that when one designs a tetrameric probe, one would use the region of the protein with the least possible degeneracy — preferably the region with the maximum number of unique codons — as Weissman did. It is clear then that dependence upon the absolute presence of unique codons is not only impractical, but impossible in most instances. An interpretation that the primer construction teachings of Weissman were only

105. *Id.*

106. See *supra* note 15 and accompanying text.

107. 991 F.2d at 784.

108. See Rinderknecht I, *supra* note 95; Rinderknecht II, *supra* note 95.

109. See Weissman et al., *supra* note 98, col. 8, ll. 23-36.

110. This was the process used by Suggs et al., *supra* note 39, at 6615-16.

111. See Jaye et al., *supra* note 40, at 2329-31.

applicable to a protein containing *met* or *trp* would not have occurred to one of ordinary skill. Instead, the Weissman reference clearly would have suggested that minimized degeneracy was preferred but not required.¹¹²

Finally, the court noted, "the issue is the obviousness of the claimed compositions, not of the method by which they are made."¹¹³ This method/product distinction is taken up in more detail in the court's opinion in *Deuel*, and discussed further below. One point to note: the court's argument, at least in *Bell*, is based ultimately on the logic of two earlier cases, *In re Thorpe*,¹¹⁴ and *In re Pilkington*,¹¹⁵ which dealt with product-by-process claims. Product-by-process claims, however, are of an entirely different nature than questions of whether prior art methods can be used to hold product claims obvious. Their use in this instance is at least marginally suspect.

2. *In re Deuel*

The facts in *In re Deuel* are similar to those of *Bell*, with an important exception.¹¹⁶ The claimed invention was drawn to a DNA sequence that encoded for a growth factor protein, called a "heparin-binding growth factor." The difference in this case was that the prior art Bohlen patent disclosed only the nineteen amino acid N-terminal sequence of the protein, not the complete 168 amino acid sequence.¹¹⁷ The teachings of Bohlen were combined with cloning techniques disclosed by Maniatis¹¹⁸ to find the claimed DNA sequence obvious in view of the combined prior art teachings.

112. It is ironic that the court finds convincing the fact that Weissman's methodology would not reasonably suggest or provide the claimed nucleic acid sequences, but goes on to argue that methodology is not of consequence when the claimed subject matter is drawn to compositions. *In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993).

113. *Id.*

114. 777 F.2d 695, 697 (Fed. Cir. 1985).

115. 411 F.2d 1345, 1348 (C.C.P.A. 1969).

116. For an additional comparison of *Bell* and *Deuel*, along with a perspective on the impact of these cases, see Steven L. Highlander, *Patent Law Meets Science and Fails: The In re Bell Fiasco*, 13 BIOTECH. L. REP. 469 (1994). A further significant issue not stressed by the parties or the court was that the prior art only disclosed *brain* mitogens. The protein isolated in *Deuel* was from uteral or placental tissue. It is now known that the prior art brain mitogens are similar to the placental and uteral growth factors, but this homology was not known at the time of the invention. This fact is significant because one of ordinary skill wanting to construct a cDNA library may have been motivated to use brain rather than uteral or placental tissue for mRNA.

117. P. Bohlen et al., European Patent No. 326,075 (publication date: Aug. 2, 1989).

118. See Maniatis, *supra* note 32.

The court in *Deuel* did not focus as much on the selection invention doctrine problems that troubled it in *Bell*.¹¹⁹ Rather, the issues in *Deuel* are reducible to two questions of sufficient information. First, is knowledge of only the nineteen amino acid N-terminal sequence of a 168 amino acid sequence protein sufficient to recover the entire protein? Second, is knowledge of a protein sufficient to provide one of ordinary skill with the cDNA sequence that codes for it?

E. "General Processes"

The answer to these questions depends upon how the prior art method information is viewed. The court in *Deuel* stated that the prior art neither taught nor mentioned the specific claimed compound, but rather taught only a general method of isolating cDNA molecules.¹²⁰ From this the court went on to reason: "[t]he fact that one can conceive a general process in advance for preparing an *undefined* compound does not mean that a claimed *specific* compound was precisely envisioned, and therefore obvious."¹²¹ The term "general process" seems to refer to prior art methods that teach some, but not all, of the steps needed to arrive at the claimed invention. Clearly, the court did not see so-called general processes as being helpful to one of ordinary skill in the art to arrive at the particular claimed compound.

However, this position is not entirely satisfactory. It is well established that the entire prior art must be taken into consideration when determining patentability,¹²² and thus prior art general processes must also be considered for what they teach. Furthermore, the court should have considered not only the specific teachings of the prior art, "but also the inferences which one skilled in the art would draw therefrom."¹²³

One is thus left with the question: Why can prior art general processes not be used in obviousness determinations? There is no compelling reason why these processes cannot or ought not be used. In fact, there is important and time-proven precedent for the use of prior art

119. One reason might be that the Böhlen reference would have provided a bonanza to one of ordinary skill in the art: the 19-mer sequence in this case was extremely rich in uncommon amino acids like lysine — seven of the first 12 amino acids were lysine residues. The problems posed by the degeneracy of the code are not as imposing because of this unique make-up of the N-terminal sequence. See Böhlen, *supra* note 116.

120. See *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995). The court suggests, however, that if the prior art had taught or mentioned the specific compound, questions of anticipation or obviousness would be raised. See *id.*

121. *Id.*

122. See, e.g., *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, 48 (1923).

123. *Parker v. Motorola*, 524 F.2d 518, 532 (5th Cir. 1975), *cert. denied*, 425 U.S. 975 (1976).

general processes in holding a product claim to be obvious over the prior art. In *DeForest Radio Co. v. General Electric*,¹²⁴ the Supreme Court considered a patent to a cutting-edge technology of that day — the vacuum tube. The vacuum tube amplifier formed the basis of electronic technology in 1930, and ownership of that technology was of great commercial importance. The patent at issue was U.S. Patent 1,558,436 to Langmuir, owned by General Electric (“GE”), and covered a vacuum tube with “high” vacuum.¹²⁵ GE sued DeForest for infringement of the Langmuir patent, whereupon DeForest defended by asserting invalidity for “want of invention,” i.e., obviousness.¹²⁶ All parties agreed that the Langmuir high-vacuum tube was the same as the prior art DeForest low-vacuum tube, but with a greater vacuum, i.e., a lower pressure.¹²⁷ But, was the high-vacuum element of the tube disclosed by the prior art, thus rendering the Langmuir patent invalid for obviousness? The Supreme Court looked to several prior art publications that suggested increasing the vacuum in an electrical discharge device would improve the effectiveness of that device.¹²⁸ The Court then specifically rejected the argument that the prior art publications had to teach the making of the high-vacuum tube itself.¹²⁹ Rather, all that was required was a disclosure of the general relationship between increased vacuum and improved performance, and the general process to achieve that increased vacuum.¹³⁰ Hence, the Court found Langmuir’s innovation legally obvious and invalidated GE’s patent.¹³¹

F. How Much Protein Is Enough?

Returning to the *Deuel* facts, the Maniatis reference is analogous to the prior art publications of *DeForest*. In both cases, the prior art references generally taught one of ordinary skill how to arrive at the missing elements in the claimed product. The Supreme Court, in *DeForest*, rejected the need to find an application of that prior art method to the product as claimed. It is difficult to see how the Federal Circuit can hold otherwise without overruling *DeForest* and its progeny.

From this viewpoint, it is possible to reanalyze the first question raised: Was enough of the amino acid sequence disclosed to arrive at the entire protein? In 1983, Weissman disclosed a generally applicable

124. 283 U.S. 664 (1930).

125. *Id.* at 669-70.

126. *Id.* at 669.

127. *Id.* at 677.

128. *Id.* at 679-81.

129. *Id.* at 682.

130. *Id.*

131. *Id.* at 685.

method for cloning genes for polypeptides where the amino acid, the DNA, or the mRNA sequences are not completely known.¹³² The reference states that the sole requirement is the knowledge of a short (e.g., five to twenty-five, preferably at least fifteen) amino acid sequence in the peptide of interest.¹³³ This teaching supports the Examiner's conclusion that knowledge of the nineteen-mer sequence of the protein enables one of ordinary skill in the art to obtain the entire 168 amino acid protein with confidence, absent a rebuttal showing of objective evidence of non-obviousness.

G. *Bell Revisited*

This leaves the *Bell* question of whether a prior art protein plus a cloning method render a cDNA claim obvious. As noted in the *Bell* discussion, the application of the selection invention doctrine is unsatisfactory because the art routinely handled the range of choices faced by the inventors in *Bell* and *Deuel*.¹³⁴ All that remains is the question of whether a general process can be used to conclude that the claimed compound is obvious. *DeForest* shows that general processes can be used to conclude that specific products are obvious; therefore, the court's argument is not entirely persuasive.

H. *The Legacy of Deuel*

Unfortunately, the reasoning in *Deuel* leaves a biotechnologist of ordinary skill in the art in an awkward position. On the one hand, based on prior art knowledge, the biotechnologist knows that sequencing around twenty amino acids is sufficient to obtain the cDNA sequence that codes for a particular protein, absent unforeseen difficulties. On the other hand, under current law, the expected product of this scientifically obvious manipulation is legally unobvious and thus patentable. Such a convoluted result is unsettling.

V. PATENTING DNA BEYOND STRUCTURAL OBVIOUSNESS

After *Bell* and *Deuel*, the protection balance has tilted too heavily against the first inventor to file a patent application, and also too far away from the market that has already had access to the publicly available information. The imbalance is due to the failure of the case law to properly address the unique nature of the DNA-protein relation-

132. See Weissman et al., *supra* note 98, col. 3, ll. 29-43.

133. See *id.*

134. See *supra* notes 100-01 and accompanying text.

ship. The structural similarity doctrine formulated to handle traditional chemical patent relationships is not suited to biotechnology patent law. Biotechnology has advanced to the point where a revision of the elements of the prima facie case of obviousness, as applied to DNA over a prior art protein, is necessary.

The "suggestion test" provides an answer. If the prior art teachings suggest the claimed subject matter to a person of ordinary skill in the art, and a reasonable expectation of success, then the claimed subject matter is prima facie obvious.¹³⁵ Such a test is more amenable than the structural obviousness doctrine to treating biotechnology inventions.¹³⁶

The suggestion test would address the underlying concern that the Federal Circuit seems to have expressed in the *Jones/Bell/Baird* selection invention cases. Recall that the court rejected the notion that picking one out of a potentially infinite number of possibilities is prima facie obvious.¹³⁷ Unfortunately, the court in the *Jones/Bell/Baird* line of cases did not address the fact that the breadth of the choices is relative, not absolute. All of the prior art comparisons are made relative to one of ordinary skill in the art, as required by the statute and by *Graham*. Simply calculating the total number of possibilities is an absolute measure of the task. The enormity of the task on a relative scale was routine at the time the invention in *Bell* was made, even though the magnitude sounds astounding on an absolute scale.¹³⁸ The impact of this knowledge on the obviousness of the invention cannot be ignored.

The suggestion test takes all of this into account by requiring that the prior art suggest the claimed invention without specifying the required precision of the suggestion, per the *Susi/Corkill/Merck* line of cases. The relative comparison is made by the additional requirement that the prior art have provided a reasonable expectation of success for one of ordinary skill. Thus, this two-part test represents a compromise which addresses concerns from both sides of the selection invention question.

135. See *supra* notes 66-68 and accompanying text.

136. Such a test can be applied beyond the cDNA-protein and the natural DNA-cDNA relationship. For example, the suggestion test might be applied to situations where DNA sequences are homologous between organisms, if the doctrine of structural similarity is found to be unsuitable. See *supra* note 76.

As another alternative to structural obviousness, one commentator has proposed a test based upon the chemical case law concerning purification of natural products. See Highlander, *supra* note 116, at 477. Another approach attempts a "harmonization" between chemical and biotechnology patent law based on motivation and set size. Todd R. Miles, *Motivation and Set-Size: In re Bell Provides a Link Between Chemical and Biochemical Patent Claims*, 2 U. BALT. INTELL. PROP. L.J. 89 (1993).

137. See *supra* notes 99-103 and accompanying text.

138. See *id.*

The forerunner of such a test has already been applied by the Board of Patent Appeals and Interferences. In *Ex Parte Hudson*,¹³⁹ the claims were drawn to porcine preprorelaxin, a hormone produced during pregnancy. The prior art disclosed the amino acid sequence of porcine relaxin¹⁴⁰ and rat preprorelaxin.¹⁴¹ The Board affirmed the Examiner's rejection by stating that once the amino acid sequence is known, one of ordinary skill in the art would be motivated to construct the synthetic gene for biosynthesis of that protein.¹⁴² According to the Board, the critical inquiry in such cases is whether there would have been a reasonable expectation of success applying knowledge evinced by the prior art.¹⁴³ The Board took the position that total synthesis of the DNA sequence was possible by one of ordinary skill because both the amino acid sequence was known and total synthetic procedures were disclosed by the prior art.¹⁴⁴

A. Statement of the Suggestion Test

What factors are to be considered in determining a "reasonable expectation of success"? A succinct statement of these factors are found in the three situations listed in the case of *In re O'Farrell*.¹⁴⁵ In *O'Farrell*, the first two situations were examples of "obvious to try," and the third situation represented a "reasonable expectation of success":¹⁴⁶

"Obvious to Try"

- (1) Varying all parameters or trying each of numerous possible choices until one possibly arrives at a successful result, where the prior art gives either no indication of which parameters are critical, or no direction as to which of many possibilities are likely to be successful.¹⁴⁷

139. 18 U.S.P.Q.2d (BNA) 1322 (Bd. Pat. App. & Interferences 1990).

140. Robert James et al., *Primary Structure of Porcine Relaxin: Homology with Insulin and Related Growth Factors*, 267 NATURE 544, 544-46 (1977).

141. P. Hudson et al., *Molecular Cloning and Characterization of cDNA Sequences Coding for Rat Relaxin*, 291 NATURE 127, 127-31 (1981).

142. *Ex Parte Hudson*, 18 U.S.P.Q.2d (BNA) at 1324.

143. *Id.*

144. *Id. But cf. Fiddles v. Baird*, 30 U.S.P.Q.2d (BNA) 1481, 1485 (Bd. Pat. App. & Interferences 1993) (distinguishing from *Hudson* on the grounds that because prior art did not reveal homology between a native gene encoding bovine FGF and a native gene encoding human FGF, the inventor's discovery was non-obvious and hence did not interfere with the existing patent).

145. 853 F.2d 894, 903 (Fed. Cir. 1988).

146. *Id.* at 903-04. These situations as listed are direct paraphrases from the *O'Farrell* court's opinion.

147. *Id.* at 903.

- (2) Exploring a new technology or general approach that seems to be a promising field of experimentation, where the prior art gives only general guidance as to the particular form of the claimed invention or way to achieve it.¹⁴⁸

"Reasonable Expectation of Success"

- (3) Where the prior art provided specific guidance as to how to modify the teachings of the prior art to arrive at the claimed invention, and provided evidence that the suggested modification would be successful.¹⁴⁹

Thus, the suggestion test can be simply stated as requiring the prior art to:

- (1) suggest the claimed subject matter to a person of ordinary skill in the art; and to
- (2) demonstrate a reasonable expectation of success by:
 - (a) providing specific guidance as to how to modify the teachings of the prior art to arrive at the claimed invention; and
 - (b) providing evidence that the suggested modification would be successful.

This test might be controversial to the biotechnology industry patent bar. For example, the appellant in *Bell* referred to this sort of approach as an "obviousness 'per se' standard."¹⁵⁰ The suggestion test in no way represents a per se standard of obviousness, because it can only establish a prima facie case of obviousness, not obviousness itself. It is procedurally incorrect to equate proof of the prima facie case with proof of the underlying substantive issue.¹⁵¹ A prima facie case of obviousness, established by the suggestion test or any other test, can be overcome by a successful showing of objective evidence of non-obviousness.¹⁵² There is considerable reluctance, however, in the biotechnology industry patent community to accept that DNA may be obvious in view of a prior art protein because of the perception that it is extremely difficult to

148. *Id.*

149. *Id.* at 903-04.

150. Brief for Appellant at 33, *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (No. 92-1375).

151. For a discussion of the difference, see *supra* notes 63-65 and accompanying text.

152. See *supra* note 65 and accompanying text.

overcome an examiner's prima facie case of obviousness once established.¹⁵³

B. Application of the Suggestion Test to Fact Patterns

What would be the result of applying the suggestion test to the facts in *Bell*? The first step is to consider whether there was a suggestion of the claimed subject matter in the prior art. The cited references disclosed the complete amino acid sequence of the two polypeptides: IGF-I and IGF-II.¹⁵⁴ It seems reasonable to conclude that the presence of a functional protein would have suggested to one of ordinary skill that there was a DNA sequence that coded for the protein. The first element of the suggestion test is thus satisfied.

The next step would be to demonstrate a reasonable expectation of success by: (1) showing that the prior art provided specific guidance as to how to modify the teachings of the prior art to arrive at the claimed invention; and (2) showing that the prior art provided evidence that the suggested modification would be successful.

The inventors in *Bell*, who were provided with the entire sequence of the IGF proteins,¹⁵⁵ would have known that any probe which is sixteen nucleotides or longer in length would be unique.¹⁵⁶ The inventors in *Bell* used a twenty-three-mer probe predicted from an eight amino acid sequence known to be present in both IGF-I and IGF-II.¹⁵⁷ By way of comparison, Suggs used two sets of fifteen-mer sequences¹⁵⁸ and Jaye used a fifty-two-mer probe in length.¹⁵⁹ These references used diverse lengths and also manipulated the hybridization process used. Given the varied use of probe lengths, the specific guidance concerning probe length, and the adjustment of hybridization conditions, the choice of such a twenty-three-mer probe would have been reasonably suggested by the prior art.

153. "This position puts a significant burden on prospective patentees, which in many cases will not be carried, implying a chilling effect on basic research." Highlander, *supra* note 116, at 476 n.109. Similar comments are also found in appellant's brief stating that the PTO policy of requiring a showing of "special ingenuity" is improper. Brief for Appellant at 11, *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995) (No. 94-1202).

154. See Rinderknecht I, *supra* note 95; Rinderknecht II, *supra* note 95.

155. See *id.*

156. As discussed *supra* notes 41-47 and accompanying text.

157. See Brief for Appellee at 2, *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) (No. 92-1375).

158. See Suggs et al., *supra* note 39, at 6613.

159. See Jaye et al., *supra* note 40, at 2325.

Similar procedures were used by Jansen to isolate IGF-I clones.¹⁶⁰ The reference states that five putative clones were isolated by screening approximately 60,000 clones of an adult human liver cDNA library with a fourteen-mer oligonucleotide probe.¹⁶¹

Because the Rinderknecht references disclosed the entire sequences of the proteins,¹⁶² selection of the codon constituents for the DNA sequence of the probe was considerably simplified. Certain specific guidance suggested by the prior art included: the use of segments of the amino acid sequence with the least number of possible codon choices; codon usage based on already sequenced, related proteins; the relative stability of *G:T* versus *G:A* mismatches while screening the cDNA; and the sequence of the probe permitting minimum predictable secondary structure in the oligonucleotide.¹⁶³ This task was further facilitated by the use of computers. As early as 1980, Queen and Korn¹⁶⁴ had flexible computer programs which performed count and search functions; examined sequences for repeated, palindromic or self-complementary regions; compared two or more sequences for common features; and translated the genetic code.¹⁶⁵ In addition, the codon catalogs disclosed by Grantham¹⁶⁶ provide specific guidance with respect to the preferred codon usage of various species. Armed with this library of information, it is clear that the prior art provided specific guidance to one of ordinary skill in the art as to probe design. The use of such procedures by

160. See Jansen et al., Conference Abstract, *Nucleotide Sequence of a cDNA Clone Encoding Human IGF-I — Insulin Like Growth Factor DNA Sequence*, DBA No. 84-01078 (Dept. of Pediatrics, State Univ. of Utrecht, The Netherlands 1983).

161. See *id.* Given the subject matter and the date of publication of the reference, it is quite possible that this reference might have anticipated the claims in *Bell*. See *id.* However, because a full length English translation was unavailable, the authors could not make a definite conclusion as to proper anticipation. Of course, these comments are those of the authors alone, and should *under no circumstances* be attributed in any way to be the official view of the PTO.

162. The complete amino acid sequence of IGF-I has been disclosed in Rinderknecht I, *supra* note 95, at 2771, and the complete amino acid sequence of IGF-II has been disclosed in Rinderknecht II, *supra* note 95, at 283-84.

163. These suggestions were present in the Jaye reference. See Jaye et al., *supra* note 40, at 2325.

164. See Cary L. Queen & Laurence J. Korn, *Computer Analysis of Nucleic Acids and Proteins*, 65 *METHODS IN ENZYMOLOGY* 595, 595-609 (1980).

165. A quick survey shows that by the early 1980s numerous computer programs were available to one of ordinary skill in the art, which would help in the choosing of an appropriate design for a probe. These references include Laurence J. Korn et al., *Computer Analysis of Nucleic Acid Regulatory Sequences*, 74 *PROC. NAT'L ACAD. SCI.* 4401, 4401-05 (1977); W. Sege et al., *A Conversational System for the Computer Analysis of Nucleic Acid Sequences*, 9 *NUCLEIC ACIDS RES.* 437, 437-44 (1981).

166. See Grantham I, *supra* note 45, at r49.

Suggs,¹⁶⁷ Anderson and Kingston,¹⁶⁸ Sood,¹⁶⁹ and Weissman¹⁷⁰ all provide concrete evidence that these procedures had been used routinely by the practitioner and could be expected to be successful. Therefore, it follows forthrightly that one of ordinary skill would have had a reasonable expectation of success because the prior art provided specific guidance as to how to modify the teachings of the Rinderknecht I reference to arrive at the claimed invention. In addition, the prior art, taken *in toto*, provided evidence that the suggested modification would be successful.

Another foreseeable fact pattern might involve the rejection of a five amino acid sequence from a protein isolated from a pancreatic cDNA library over a cDNA sequence arrived at from a protein isolated from brain tissue. Imagine further that the actual codons found to express the desired protein are generally non-preferred in the host organism, according to the codon catalogs¹⁷¹ — representing an extreme version of the *Deuel* facts. While the prior art might suggest the existence of a cDNA sequence that coded for the pancreatic protein, the fact that: (1) only five amino acids were disclosed (on the low edge of acceptability for isolating the cDNA, as taught by the prior art); and (2) the prior art protein was found in the pancreas (and thus might have a very different overall structure than a brain protein) would *not* have provided a reasonable expectation of success of arriving at the claimed cDNA molecule. Furthermore, the fact that the expressing cDNA was found to utilize codons listed as non-preferred in the codon catalogs for that host fails the reasonable expectation of success prong of the test. This failure is due to the prior art specifically providing evidence that the suggested modification would be unsuccessful and thus discouraging this line of experimentation.¹⁷²

VI. CONCLUSION

The decision to deny a patent for obviousness over the prior art involves a balancing of public and private interests. Erring one way or the other can have undesirable consequences for the biotechnology industry, as well as to the public, by providing either too great or too

167. See Suggs et al., *supra* note 39, at 6613-17.

168. See Anderson & Kingston, *supra* note 40, at 6838-42.

169. See Sood, *supra* note 39, at 616-20.

170. See Weissman et al., *supra* note 98.

171. For general discussion of codon catalogs, see *supra* note 45 and accompanying text.

172. Finally, it should again be noted that even if the suggestion test resulted in a conclusion of *prima facie* obviousness, the applicant could submit objective evidence of non-obviousness to overcome this showing. For example, such showings could be of unexpected difficulty in cloning the gene or of unexpected difficulty in probe design.

little of an incentive to obtain patents. The current state of biotechnology DNA patent case law has shifted the balance undesirably in favor of the patent applicant by applying ill-fitting and inapplicable traditional chemical patent law doctrines. The PTO thus cannot utilize the most appropriate prior art to reject an application or claim. The proposed suggestion test would rectify this situation by providing a test fair to both the biotechnology industry and the public, thus restoring needed balance to the law.

