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THE NONOBVIOUSNESS REQUIREMENT FOR
BIOTECHNOLOGICAL INVENTIONS—
RESOLVING UNCERTAINTY IN FAVOR
OF INNOVATION

Song Huang†

I. INTRODUCTION

The biotechnology industry is primarily concerned with the commercial development of therapeutic, biochemical, and pharmaceutical products and processes, many of which are derived from manipulation of DNA molecules and their encoded proteins. Over the last thirty years, patents have emerged as an important, and sometimes controversial, tool for protecting these biotechnological products and processes. However, with the rapid scientific advances in this field, a degree of uncertainty regarding the nonobviousness requirement involving certain biotechnological inventions has been encountered.¹ Accordingly, there is a need to clarify the legal standards for determining the nonobviousness requirement—also referred to as the ultimate condition of patentability. While this determination is ultimately a question of public policy, based on underlying factual inquiries,² the U.S. Court of Appeals for the Federal Circuit (“Federal Circuit”) has attempted to articulate legal standards of nonobviousness applied specifically in certain biotechnological inventions. Through the analysis of five major cases

† Song Huang is a partner with the law firm of Haiwen & Partners in Shanghai. He received his LL.B degree from the China University of Political Science and Law (Beijing, China) in 1989, his LL.M degree from the University of Pennsylvania Law School in 1995 and his LL.M degree in Intellectual Property Law from Santa Clara University in 2004. He is licensed to practice law in the State of New York, Washington D.C. as well as the People’s Republic of China. The author wishes to thank Kui Zhang (B.S., Capital University of Medical Sciences, Beijing, 1990 and M.S., Santa Clara University, Santa Clara, 2003) for her assistance in verifying the accuracy of the descriptions of the biotechnological inventions discussed in this paper.


2. See JANICE M. MUELLER, AN INTRODUCTION TO PATENT LAW 131 (Aspen Publishers 2003).
decided by the Federal Circuit dealing with biotechnological inventions from 1988 to 1995,3 this paper will explore the legal standard for obviousness in this field and the related public policy considerations.

Generally, there exist two major themes surrounding the nonobviousness standard: (1) in the three decisions before the decision in In re Bell4 in 1993, the Court of Appeals for the Federal Circuit focused its analysis on the scientific methods involved in the invention and primarily gave weight to two factors: (i) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (ii) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success;5 and (2) through the Bell decision in 1993 and the decision in In re Deuel6 in 1995, an emphasis on the analytical framework has been shifted from the scientific methods to the obviousness of the claimed composition (e.g., a particular purified, isolated and sequenced DNA or cDNA molecule encoding a protein).7 The reasoning underlying the two themes might seem to be related to the fact that the claimed inventions in the earliest three decisions were essentially directed to a method or process while the subject matters sought to be patented in the most recent two cases involved a product or composition.

Despite the particular facts that may largely dictate the particular analytical framework in each of the five cases to be discussed, this paper will also argue that the Federal Circuit should be conscientious about a general responsibility to make an ultimate judgment as to which inventions should be patented and which should not, by taking into account the broad public policy implications and ramifications in order to realize the goal of promoting the progress of "useful arts" mandated by the United States Constitution.8 One example regarding the practical effects of the two decisions in Bell and Deuel was that companies specializing in genomic research have filed many DNA sequence applications. This new trend of patent filings within the

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3. See In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995); In re Bell, 991 F.2d 781 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharm. Co. 927 F.2d 1200 (Fed. Cir. 1991); In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991); In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988).
4. In re Bell, 991 F.2d 781 (Fed. Cir. 1993).
5. See infra Part II.D.
7. See infra Parts II.D, II.E.
biotechnology field is problematic because genomic research companies are stockpiling DNA sequence patents directed merely to partial DNA sequences that have no known function. An apparent public policy implication of this trend is that innovation in the biotechnology field may be impeded, rather than promoted, if scientists will have to negotiate and obtain a license from, and pay a royalty to, the multiple patent holders for making or using patented DNA sequences in their scientific research.

Part II of this paper will analyze the five cases decided by the Federal Circuit dealing with biotechnological inventions (including processes and products). The aim of the analyses is to expose a uniform standard of nonobviousness as applicable to gene-related inventions. Another position of this paper is that the Federal Circuit should give greater deference in its review of the decisions of the United States Patent and Trademark Office ("PTO") because the PTO appears to be the appropriate institution to make factual findings in respect of biotechnology inventions. In Part III, this paper will identify three specific proposals regarding how to apply the nonobviousness standard under 35 U.S.C. §103(a) with respect to gene-related inventions for the purpose of creating more certainty in courts’ decisions.

II. CASE STUDIES

Before embarking upon the case studies, some background information regarding the basic principles of the nonobviousness standard is useful.

In general, under the 1952 Patent Act, the nonobviousness requirement states that "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," the invention is not patentable.

In the 1966 decision of Graham v. John Deere Co., the Supreme Court presented an exposition of how the above nonobviousness requirement embodied in §103 of the Patent Act should be applied. The Court held that nonobviousness is ultimately a question of law with underlying factual inquiries under 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.\textsuperscript{12} In addition, secondary considerations (also known as objective evidence of nonobviousness) such as "commercial success, long felt but unresolved needs, failure of others, etc." that "may have relevancy" can also be considered as "indicia of obviousness or nonobviousness."\textsuperscript{13} The foregoing factors are frequently referred to as the "Graham factors" or "Graham test" for making nonobviousness analyses.

The Federal Circuit has suggested various refinements of the Graham test. For example, an invention can be deemed obvious if an inventor merely pieced together parts of different prior art references; there must be a reason, suggestion or motivation in the prior art to combine the prior art elements in the way in which they are combined in the patentee's invention.\textsuperscript{14} The rationale underlying this requirement is that hindsight should not be used in such a way that the inventor's specification is used as a blueprint in deciding nonobviousness.\textsuperscript{15} Further, an invention will not be obvious if practicing the invention was merely "obvious to try."\textsuperscript{16} Thus, the standard for nonobviousness should involve a reasonable expectation of success by a person having ordinary skill in the art. In other words, if the prior art provided only general guidance or general direction as to the possibility that the claimed invention can be attempted or experimented (thereby arguably making it "obvious to try"), and those skilled in the art would not believe that the general guidance provided or general direction pointed to by the prior art would have a reasonable expectation of success to practice the claimed invention, the invention that may be obvious to try is nevertheless nonobvious.

I will now turn to the discussions of five cases decided by the Federal Circuit to demonstrate how the foregoing principles of nonobviousness have been applied to patents or patent applications directed to biotechnological inventions.

\textsuperscript{12} See id. at 17.
\textsuperscript{13} Id. at 17–18.
\textsuperscript{15} See Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138 (Fed. Cir. 1985).
\textsuperscript{16} See, e.g., Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 807 (Fed. Cir. 1989); In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1988).
A. In re O'Farrell (1988)\textsuperscript{17}

The Patent and Trademark Office Board of Patent Appeals and Interferences ("Board") rejected O'Farrell's patent application on grounds of obviousness.\textsuperscript{18} The patent applicants appealed to the Federal Circuit for judicial review of the decision by the Board.\textsuperscript{19} The Federal Circuit found that the prior art contained an explicit suggestion to modify the prior art for practicing the claimed invention and certain predictable methods to carry out the suggestion are available.\textsuperscript{20} The court further held that for obviousness under 35 U.S.C. §103, all that is required is a "reasonable expectation of success."\textsuperscript{21}

I. Claimed invention

The claimed invention involved manipulating a bacterium to produce a protein from a completely different species. Specifically, the patent application concerned a method for producing a foreign, fused protein in a transformed species of bacteria.\textsuperscript{22} The process involved isolating the stretch of DNA (i.e., the gene coding for that foreign protein), incorporating the gene into a cloning vector (called plasmid\textsuperscript{23}), and inserting the cloning vector into the bacterium.\textsuperscript{24}

All organisms, whether man, mouse or lowly bacterium, use the same molecular rules (i.e., three nucleotides code for an amino acid) to make proteins under the control of genes, and the biochemical machinery that replicates and translates DNA is the same among all organisms.\textsuperscript{25} As such, genes from one species can be inserted into the genome of another; a gene for a human protein can be expressed in a bacterium.\textsuperscript{26} These genes from a foreign source are said to be heterologous genes.\textsuperscript{27} Bacteria that contain foreign genes are said to

\begin{itemize}
\item \textsuperscript{17} In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988).
\item \textsuperscript{18} Id. at 901.
\item \textsuperscript{19} Id. at 895
\item \textsuperscript{20} Id. at 902–03.
\item \textsuperscript{21} Id. at 904.
\item \textsuperscript{22} Id. at 895.
\item \textsuperscript{23} Bacteria are single-celled organisms whose DNA exists in a simpler form than that of multi-cellular organisms such as humans. A bacterial genome includes small, circular loops of DNA called plasmids. These plasmids allow manipulation of bacterial DNA. Plasmids can be isolated, manipulated, and reintroduced to the bacterial species.
\item \textsuperscript{24} In re O'Farrell, 853 F.2d at 895.
\item \textsuperscript{25} Id. at 898.
\item \textsuperscript{26} Id.
\item \textsuperscript{27} Id.
\end{itemize}
be transformed.\textsuperscript{28}

The claimed invention in O'Farrell was a method to produce a predetermined foreign protein in a transformed host species of bacteria.\textsuperscript{29} This was accomplished by creating a plasmid (a cloning vector) that includes a portion of a gene indigenous to the bacteria.\textsuperscript{30} Linked to this gene is the DNA coding for the desired foreign protein (\textit{i.e.}, the heterologous gene).\textsuperscript{31} Upon successful insertion of the plasmid into the bacteria, the biochemical machinery of the bacteria will recognize the indigenous gene and begin to express it (the process whereby the information in the gene is used to synthesize the new protein).\textsuperscript{32} Since the desired foreign protein gene is physically linked to the indigenous gene of the host bacteria, the bacteria will continue reading along the DNA ("read-through" occurs from the indigenous gene portion into the heterologous gene in the same reading frame) and produce a "fused" protein consisting of the indigenous and foreign protein.\textsuperscript{33}

2. Analysis

The Federal Circuit followed the analytical framework by making factual inquiries relating to the four Graham factors: "(1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of non-obviousness, if any."\textsuperscript{34}

The court evaluated prior art and found an explicit suggestion for the claimed invention.\textsuperscript{35} The prior art in this case primarily consisted of (i) a scientific paper published by the co-inventors that described a method for making a cloning vector with indigenous genes; and (ii) a scientific paper published by another group of scientists that taught the method to insure the inserted foreign gene has the same reading frame as the rest of the plasmid.\textsuperscript{36} The court found that the main difference between the prior art and the claimed invention was the

\begin{itemize}
\item \textsuperscript{28} \textit{Id.}
\item \textsuperscript{29} \textit{Id. at} 895
\item \textsuperscript{30} \textit{In re O'Farrell,} 853 F.2d at 895.
\item \textsuperscript{31} \textit{Id.}
\item \textsuperscript{32} \textit{Id. at} 895–902.
\item \textsuperscript{33} \textit{Id.}
\item \textsuperscript{34} \textit{Id. at} 902.
\item \textsuperscript{35} \textit{Id. at} 903.
\item \textsuperscript{36} \textit{In re O'Farrell,} 853 F.2d at 899–902.
\end{itemize}
nature of the heterologous (or foreign) gene used. The paper by the other group of scientists discussed using a foreign gene from a frog that coded for a ribosomal RNA as their test gene. The frog gene was chosen as a test gene for reasons of convenience and availability, although a ribosomal RNA is not normally translated into protein. In contrast, the claimed invention substitutes a gene for a known, predetermined protein. The paper further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, "a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Thus, the prior art explicitly suggested that the substitution is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins. The court concluded that the prior art provided detailed methods and techniques that supplied "a reasonable expectation of success," thereby making the claimed invention obvious at the time the invention was made.

The court found that the prior art "explicitly suggested the substitution" of a known protein for the ribosomal RNA gene. However, it is generally understood that a mere suggestion is not enough for a finding of obviousness. Accordingly, the appellants in this case argued that the suggestions were merely invitations to attempt the experiment and rejection of the claimed invention would constitute "the application of a standard of 'obvious to try' to the field of molecular biology." The Federal Circuit acknowledged that it had previously rejected the "obvious to try" as the standard under §103. The court admitted

37. Id. at 901–02.
38. Id. at 900.
39. Id. at 899–902.
40. Id.
41. Id. at 901. Man, other animals, plants, protozoa, algae, and yeast are eukaryotic organisms: their DNA is packaged in chromosomes in a special compartment of the cell, the nucleus. Proteins are large polymeric molecules consisting of chains of smaller building blocks, called amino acids, that are linked together covalently. The chemical bonds linking amino acids together are called peptide bonds, so proteins are also called polypeptides.
42. In re O'Farrell, 853 F.2d at 901–04.
43. Id.
44. Id. at 901.
45. Id. at 902.
46. See, e.g., In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 688 (Fed. Cir. 1987).
that every obvious invention is also, in a sense, obvious to try. This seems to say that the contrary is not always true. In other words, an invitation to attempt an experiment (which is obvious to try) may or may not make that experiment obvious. The question then posed by the court is: "[W]hen is an invention that was obvious to try nevertheless nonobvious?" The answer lies in whether or not "a reasonable expectation of success" is also provided by the prior art.

The court supplied the following two situations in which the given suggestion would only point in the general direction of the invention but is short of supplying the requisite detail in order to form "a reasonable expectation of success" to practice the claimed invention:

The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful . . . . In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

The scenarios described by the court characterize the nature of scientific techniques made available by the prior art. The court concluded that neither of the two situations applied to the O'Farrell invention. The court considered that the suggestion disclosed or described in the prior art had provided an explicit and detailed methodology to make a fused protein in transformed bacteria. In other words, the types of techniques and information described or disclosed in the prior art are not merely "parameters," "numerous possible choices," or "general guidance," but "detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." In view of this, the court finally concluded that an invention would be deemed obvious when

47. In re O'Farrell, 853 F.2d at 903.
48. Id.
49. Id. (citations omitted).
50. Id.
51. Id. at 902-03.
the prior art contained an explicit suggestion to modify the prior art and also supplied detailed methods to realize the suggestion with "a reasonable expectation of success."\textsuperscript{52} In this connection, the court made the following holding:

Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious . . . . For obviousness under §103, all that is required is a reasonable expectation of success.\textsuperscript{53}

What the court was citing here was a rule that a prima facie case of obviousness can be rebutted by evidence of a possibility of unexpected results.\textsuperscript{54} In other words, an invention would be nonobvious if the patentee or patent applicant could come up with evidence that there is a possibility of unexpected results. Although the court did not elucidate further, it seems that the appellants in this case failed to show evidence proving the possibility of unexpected results. In response to the appellants’ argument that successful synthesis of protein was still uncertain after the publication of the scientific paper prepared by two of the co-inventors, the court observed in the prior art that expression of the transcribed RNA produced indigenous gene has "predictive value."\textsuperscript{55} Further, the study in the scientific paper "directly proved" that a readthrough transcript messenger RNA had been produced.\textsuperscript{56} The preliminary observation showed that this messenger RNA was read and used for successful translation.\textsuperscript{57}

The court further stated that it was

well known in the art that ribosomal RNA was made of the same nucleotides as messenger RNA, that any sequence of nucleotides could be read in groups of three as codons, and that reading these codons should specify a polypeptide chain that would elongate until a stop codon was encountered.\textsuperscript{58}

\begin{thebibliography}{8}
\bibitem{52} See id. at 903–04.
\bibitem{53} \textit{In re O'Farrell}, 853 F.2d at 903–04 (emphasis added).
\bibitem{54} \textit{In re Davies}, 475 F.2d 667, 670 (CCPA 1973).
\bibitem{55} \textit{In re O'Farrell}, 853 F.2d at 902.
\bibitem{56} \textit{Id.} at 903.
\bibitem{57} \textit{Id.}
\bibitem{58} \textit{Id.}
\end{thebibliography}
The preliminary observations thus showed that codons beyond the end of the indigenous gene were being translated into peptide chains. This would "reasonably suggest to one skilled in the art" that if the codons were inserted beyond the end of the indigenous gene coded for a predetermined protein, that protein would be produced. The court concluded, "it would have been obvious and reasonable to conclude from the observation reported in Polisky [Note: the scientific paper cited against the appellants as the prior art] that since nonsense RNA produced nonsense polypeptides, if meaningful RNA was inserted instead of ribosomal RNA, useful protein would be the result."  

The O'Farrell invention concerned a method for producing a fused protein in transformed bacteria. The court's analysis focused on the availability of scientific techniques and the reasonable predictability of the result as disclosed in the prior art to find obviousness. This pattern of analysis is consistent with the nature of biotechnology invention in this case: the inventive step involved in this research is the techniques necessary for the discovery of a DNA sequence rather than patenting the discovery of the DNA sequence itself.


The case decided by the Federal Circuit again focused on the availability of scientific methods. The contested patent in this case concerned the discovery of the DNA sequences encoding the human protein erythropoietin ("EPO"). Amgen, the patent owner, sued Genetics Institute, Inc. and Chugai for infringement by producing EPO using recombinant DNA technology. Chugai challenged the validity of Amgen's patent for the DNA sequences. The invention was found by the Federal Circuit to be nonobvious over the prior art because of the availability of the unique screening and probing methods for identifying and isolating DNA sequences. In this case, the court extended its analytical framework for nonobviousness of methods and techniques in the field of biotechnology to inventions.

59. Id.
60. Id.
62. Id. at 1203–04.
63. Id. at 1204.
64. Id.
65. Id. at 1209.
incorporating DNA sequences.

1. The Invention

EPO is a protein that stimulates the production of red blood cells.\(^6\) It is a useful therapeutic agent in the treatment of patients suffering from anemia or other disorders characterized by red blood cell deficiency.\(^67\) Amgen's patent claims cover isolated and purified DNA sequences that code for EPO and host cells transformed or transferred with a DNA sequence.\(^68\)

The court described, in part, the techniques for isolating a gene coding for a specific protein in a footnote contained in its opinion.

In order to prepare a protein using recombinant DNA technology, the gene for the protein must first be isolated from a cell's total DNA by screening a library of that cell's DNA. The DNA library is screened by use of a probe, a synthetic radiolabelled nucleic acid sequence which can be used to detect and isolate complementary base sequences by hybridization. To design a probe when the gene has not yet been isolated, a scientist must know the amino acid sequence, or a portion thereof, of the protein of interest. Because some amino acids have several possible codons and the researcher cannot know which of the possible codons will actually code for an amino acid, he or she may decide to design a set of probes that covers all possible codons for each amino acid comprising the protein, known as a 'fully-degenerate' set of probes. A library to be screened can be a genomic library (gDNA), which contains a set of all the DNA sequences found in an organism's cells or a complementary DNA (cDNA) library, which is much smaller and less complex than a gDNA library, and is used frequently when the tissue source for a given gene is known.\(^69\)

In biology, the above process of screening and selecting a particular DNA can be described as "cloning."\(^70\)

Cloning a gene sometimes can refer to success in identifying a gene associated with some phenotype. For example, when biologists say that the gene for disease X has been cloned, they mean that the gene's location and DNA sequence has been identified, although the ability to specifically copy the physical

\(^6\) \textit{Id.} at 1203.
\(^67\) \textit{Amgen, Inc.}, 927 F.2d at 1203.
\(^68\) \textit{Id.} at 1203–04.
\(^69\) See \textit{Id.} at 1208 n.4.
\(^70\) See CHISUM, supra note 1, TECHNOLOGY PRIMERS (Supp. 2004).
DNA is a side-effect of its identification.\textsuperscript{71} Cloning involves first discerning the amino acid sequence of the desired protein. An approximate DNA sequence can then be deduced and generated. This DNA sequence, or "probe," can be used to find the exact chromosomal location of the gene that can then be isolated and purified. The difficulty in cloning the DNA sequences of EPO (or EPO gene) was that the amino acid sequence of the EPO protein was uncertain.\textsuperscript{72}

2. Analysis

The district court judge found that the claimed subject matter met the nonobviousness requirement.\textsuperscript{73} The district court determined that the disputed patent claims covering the DNA sequences were not invalid under §103, concluding that the unique probing and screening method employed by the inventor in isolating and purifying the EPO gene and the extensive effort required to employ that method made the invention nonobvious over the prior art.\textsuperscript{74} The judge stated that one must inquire whether the prior art would have suggested to one of ordinary skill in the art that the inventor's probing and screening method should be carried out and would have a reasonable expectation of success, viewed in light of the prior art.\textsuperscript{75} The court cited a rule established by a case decided by the Federal Circuit that "[b]oth the suggestion and the [reasonable] expectation of success must be founded in the prior art, not in the applicant's disclosure."\textsuperscript{76} The district court found that in September or October of 1983, the inventor succeeded in cloning the EPO gene using a "unique" technique, two sets of fully-degenerate probes to screen a genomic library.\textsuperscript{77} The district court specifically found that, as of 1983, none of the prior art references this unique technique and that no one had


\textsuperscript{72} See Amgen, Inc., 927 F.2d at 1207.

As expert testimony from both sides indicated, success in cloning the EPO gene was not assured until the gene was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until reduction to practice had been achieved; Lin was first to accomplish that goal.

\textsuperscript{73} Id. at 1207–08.

\textsuperscript{74} Id. at 1207.

\textsuperscript{75} Id.

\textsuperscript{76} Id. (quoting In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988)).

\textsuperscript{77} Id. at 1207.
successfully screened a genomic library using fully-degenerate probes of such high redundancy as the probes used by the inventor.\textsuperscript{78} While it found that defendants had shown that these procedures were "obvious to try" (which is not the proper standard of obviousness under §103), the references did not show that there was a reasonable expectation of success in cloning the EPO gene based on this probing strategy.\textsuperscript{79}

The Federal Circuit affirmed and reasoned that there was not a reasonable expectation of success in cloning the EPO gene using either the inventor's unique gene probing strategy (screening a human genomic library with two fully-degenerate sets of probes), or the infringer's alternative suggested strategy (screening a library with the already known monkey EPO gene as a probe).\textsuperscript{80} Trial testimony supported the district court's conclusion. The Federal Court stated in relevant part, that:

> While this testimony indicates that it might have been feasible, perhaps obvious to try, to successfully probe a human gDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success. Neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with the monkey EPO gene was known at the time... While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious. There were many pitfalls. Hindsight is not a justifiable basis on which to find that ultimate achievement of a long sought and difficult scientific goal was obvious.\textsuperscript{81}

The Federal Circuit briefly recognized the methodological focus of obviousness analysis. In a footnote, the court noted the following:

> [B]oth the district court and the parties have focused on the obviousness of a process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider independently whether the products would have been obvious aside from the alleged obviousness of a method of making them.\textsuperscript{82}

\textsuperscript{78.} Amgen, Inc., 927 F.2d at 1207–08.  
\textsuperscript{79.} Id.  
\textsuperscript{80.} Id. at 1209.  
\textsuperscript{81.} Id. at 1208–09.  
\textsuperscript{82.} Id. at 1207 n.3.
It seems that the Federal Court intended to consider the nonobviousness of the products in the context of whether or not the processes for isolating the DNA sequences are obvious. However, the court's subsequent analysis and the holding rely entirely on the scientific methods and techniques (i.e., the processes of making the products) available for identifying and isolating the EPO gene. Thus, the nonobviousness in these experiments is not the DNA sequence itself, but the actual scientific methods/techniques needed to identify and isolate the gene.

The court's conclusion that the invention was not obvious is based on the analysis focusing on the nonobviousness of the scientific techniques over the prior art. The DNA sequence for the EPO gene was not readily ascertainable through standard techniques disclosed in the prior art. In other words, the methods of discovery supplied by the prior art would not stand a reasonable likelihood of success. One commentator remarked that this approach to obviousness discards the conventional focus on the invention itself. In another case, the Board of Patent Appeals and Interferences speculated that the reasoning underlying this approach might be related to the nature of the gene. The proper query is whether this approach contradicts the Federal Circuit precedent that "[t]he patentability of a product does not depend on its method of production." In other words, if the preceding rule is true, one may be precluded from arguing that a composition will not be obvious simply because the method of its discovery or production is not obvious. This issue will be re-visited in two other cases involving the patentability of nucleic acids molecules to be discussed in Parts II.D.2 and II.E.2 infra, in which the Federal Circuit appears to have shifted from the analysis focusing on the nonobviousness of the scientific techniques in the prior art to the analysis of the claimed compositions.

83. Id. at 1209.
84. See Brian C. Cannon, Toward a Clear Standard of Obviousness for Biotechnology Patents, 79 CORNELL L. REV. 735 (1994). The author stated that the approach recognizes that the inventive step in biotechnology is not the end product of research, but the research itself.
85. See Ex parte Deuel, 33 U.S.P.Q.2d (BNA) 1445, 1447 (Bd. of Patent App. and Interference 1993). The Board surmised that the reasoning behind this approach was related to the fact that the gene in question had been placed into the public domain when the sequence of the protein encoded by the gene had also been placed into the public domain. But I think this speculation is not well reasoned because the fact that the protein may be known does not necessarily render the gene a public knowledge. In fact, it is the following two factors that are determinative: (i) the Federal Circuit found that the EPO gene was not unknown at the time of the invention; and (ii) the method for isolating the gene was not obvious.
86. See In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985).


C. In re Vaeck (1991)87

The Board affirmed a rejection made by the examiner of the PTO in respect of a patent claim on grounds of obviousness.88 The Federal Circuit reversed the findings of the PTO examiner and the Board, and held that the invention was not obvious because no explicit or implicit suggestion was disclosed from the prior art and no "reasonable expectation of success" for the experiment could be made.89 The analysis of the Federal Circuit on nonobviousness in this case closely followed the reasoning adopted in O'Farrell, although the conclusion reached is opposite to that reached in O'Farrell because both an explicit suggestion and a "reasonable expectation of success" were present in O'Farrell.

1. The Invention

The claimed invention was directed to the use of genetic engineering techniques for producing proteins that are toxic to insects such as larvae of mosquitoes and black flies.90 The Bacillus bacteria produced proteins that were toxic to insects and therefore useful for clearing insects from swamps.91 Prior art methods of combating the insects involved spreading or spraying crystalline spores of the Bacillus proteins over swamps.92 The spores were environmentally unstable, however, and would often sink to the bottom of a swamp before larvae were ever exposed to it, thus rendering this method prohibitively expensive.93 Therefore, there was a need for a lower-cost method of producing the Bacillus proteins in high volume with application in a more stable vehicle.94 The claimed invention met this need by providing for the production of the Bacillus proteins within host cyanobacteria (which in the past had been referred to as "blue-green algae"),95 a much less studied species of bacteria that grows on the swamp surface where they can be consumed by insects.96 The inventors took an isolated Bacillus gene and combined it with a DNA

88. Id. at 489.
89. Id. at 493–95.
90. Id. at 489–90.
91. Id.
92. Id. at 489.
93. In re Vaeck, 947 F.2d at 489.
94. Id.
95. Cyanobacteria are unique among procaryotes in being capable of oxygenic photosynthesis.
96. In re Vaeck, 947 F.2d at 489.
fragment from cyanobacteria to create a hybrid gene. The DNA fragment in the hybrid gene allowed expression of the foreign *Bacillus* protein in cyanobacteria, which was transformed by a plasmid containing the hybrid gene.

The Federal Circuit gave much weight to the difficulties with the experiments involved in the invention, *i.e.*, the difference between cyanobacteria and *Bacillus* and the lack of prior knowledge about the cyanobacteria genus, and found the invention not obvious.

2. Analysis

During the prosecution of the claimed invention, the PTO examiner combined two sets of scientific work to find obviousness in the claimed invention: (a) an article describing the successful expression of a hybrid gene, which comprised an antibiotic marker gene and a chloroplast promoter sequence, in cyanobacteria; and (b) three articles that described expression of *Bacillus* proteins in other bacterial hosts. The PTO reasoned that it would have been obvious to one of ordinary skill in the art to substitute the three described *Bacillus* genes for the marker gene in a hybrid gene disclosed in the first article. This would result in expression of *Bacillus* proteins in transformed cyanobacteria.

The Federal Circuit began its majority opinion by setting out the analytical standards, *i.e.*, where the claimed invention has been rejected as obvious by combining prior art references, a proper analysis under §103 requires, among other things, consideration of two factors:

(1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

By focusing on the methods revealed by the prior art, the court found neither the suggestion (whether explicit or implicit) nor the expectation of success and concluded that the claimed invention was

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97. *Id.* at 489–90.
98. *Id.*
99. *Id.* at 494.
100. *Id.* at 490–91.
101. *Id.* at 492.
102. *In re Vaeck*, 947 F.2d at 493.
The court distinguished O'Farrell by noting that the invention at issue in that case involved an explicit suggestion and detailed enabling methodology, thus making the invention obvious. In contrast, the court stated, "the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art." Likewise, the court did not find any explicit suggestion that a hybrid gene containing Bacillus gene can be expressed in cyanobacteria. The court reasoned that "[t]he expression [of a marker gene] in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes." This was because "it is only in recent years that the biology of cyanobacteria has been clarified." Furthermore, the court did not find any implicit suggestion for the invention either. The court acknowledged that the scientific methods for transforming cyanobacteria were unpredictable; if methods for transforming cyanobacteria were interchangeable with those for other bacteria, the substitution of cyanobacteria for other bacteria to express the hybrid gene would have been implicitly obvious. By the same token, no "reasonable expectation of success" could be found by the court because of the unpredictability of the same methods for transforming cyanobacteria.

A related aspect of this case surrounds the review standard for obviousness determinations by the Board, i.e., whether the Federal Circuit can replace its own fact-finding with that made by the Board. The dissenting opinion in this case indicated that:

The mere denomination of obviousness as a question of law does not give the court license to decide the factual matters afresh and ignore the requirement that they be respected unless clearly erroneous . . . . There may be more than one way to look at the prior art, but on this record we are bound by the PTO's interpretation of the evidence because it is not clearly erroneous

103. Id.
104. Id. at 494–95.
105. See id. at 495.
106. Id. at 493.
107. Id. at 494.
108. See In re Vaeck, 947 F.2d at 494.
109. See id. at 495.
110. See DONALD S. CHISUM, CHISUM ON PATENTS § 5.04 (Matthew Bender & Company, Inc. 1997) (explaining that the majority's detailed discussion of the technology is not dissimilar to a typical exercise in fact finding).
and its conclusion is unassailable.\textsuperscript{111}

Although ultimately a question of law, the nonobviousness determination of §103 must be based on underlying findings of fact.\textsuperscript{112} The concern expressed by the dissenting view here is that the Federal Circuit should not attempt to retry the entire case in the absence of a "definite and firm conviction that a mistake was committed."\textsuperscript{113} In short, the dissenting opinion seems to suggest that as long as the analytical approach adopted by the PTO and the Board (by making factual inquiries regarding, among other things, two factors: the suggestion to make the invention and a "reasonable expectation of success" in making or carrying out what has been suggested) was not incorrect, the way in which the prior art was looked at by the PTO and the Board should be given deference.

This case also reveals the tension between the PTO (and the Board) and the Federal Circuit as to which institution is competent in making the final judgment on factual findings. In this connection, the dissenting opinion took the position that the Federal Circuit should not attempt to replace its own interpretation of factual issues with the factual findings made by the PTO (and the Board) that are not clearly erroneous.

\textbf{D. In re Bell (1993)\textsuperscript{114}}

This case was appealed to the Federal Circuit from the rejection decision made by the Board affirming the examiner's rejection of a patent application for an invention involving nucleic acid (DNA and RNA) molecules containing human sequences coding for proteins on the ground of obviousness.\textsuperscript{115} The Federal Circuit reversed the Board's decision.\textsuperscript{116} The Federal Circuit in this case shifted from its analysis focusing on obviousness in known scientific methods for isolating a gene to the availability of the sequence of the gene coding for the proteins in question (as disclosed or described in the prior art). This analytical framework appears to be significantly different from the previous line of cases from the Federal Circuit dealing with inventions involving recombinant DNA technology (\textit{e.g.}, \textit{O'Farrell}, \textit{Amgen}, and \textit{Vaeck}).

\begin{itemize}
\item \textsuperscript{111} \textit{In re Vaeck}, 947 F.2d at 497.
\item \textsuperscript{112} \textit{See Mueller, supra} note 2, at 152.
\item \textsuperscript{113} \textit{Ruiz v. A.B. Chance Co.}, 234 F.3d 654, 663 (Fed. Cir. 2000) (citations omitted).
\item \textsuperscript{114} \textit{In re Bell}, 991 F.2d 781 (Fed. Cir. 1993).
\item \textsuperscript{115} \textit{Id.} at 782.
\item \textsuperscript{116} \textit{Id.}
\end{itemize}
1. Invention

The claimed invention was directed to a DNA sequence encoding for human insulin-like growth factors I and II (IGF-I and IGF-II), which are proteins.\textsuperscript{117} These proteins play a role in the mediation of somatic cell growth following the administration of growth hormones.\textsuperscript{118}

The relevant prior art consists of (a) two publications that disclosed the putative amino acid sequences for IGF-I and IGF-II; and (b) a prior patent that described a general method for isolating a gene, specifically describing gene isolation for a protein unrelated to IGF.\textsuperscript{119} The patent suggested that the disclosed method "can 'easily' be applied to isolate genes for an array of proteins including peptide hormones," and taught that "it is advantageous to design a probe based on amino acids specified by unique codons."\textsuperscript{120}

In particular, the two publications show that IGF-I has only a single amino acid with a unique codon and IGF-II has none.\textsuperscript{121} The prior patent describes a general method for isolating a gene for which at least a short amino acid sequence of the encoded protein is known.\textsuperscript{122} The method involves preparing a nucleotide probe corresponding to the known amino acid sequence and using that probe to isolate the gene of interest.\textsuperscript{123} "It teaches that it is advantageous to design a probe based on amino acids specified by unique codons."\textsuperscript{124} The prior patent specifically described the isolation of a gene that codes for human protein unrelated to IGF.\textsuperscript{125} It described the design of the probe employed, stating that it was based on amino acids specified by unique codons.\textsuperscript{126}

2. Analysis

The PTO rejected the claims as obvious in view of the two prior art sources.\textsuperscript{127} The PTO reasoned that the applicants' claimed DNA

\textsuperscript{117} Id.
\textsuperscript{118} Id.
\textsuperscript{119} Id. at 783.
\textsuperscript{120} \textit{In re Bell}, 991 F.2d at 783, 785 (explaining that the term "unique" refers to an amino acid coded for by a single codon).
\textsuperscript{121} Id. at 784.
\textsuperscript{122} Id. at 783.
\textsuperscript{123} Id.
\textsuperscript{124} Id.
\textsuperscript{125} Id.
\textsuperscript{126} \textit{In re Bell}, 991 F.2d at 783.
\textsuperscript{127} Id.
sequences were *prima facie* obvious "despite the lack of conventional indicia of obviousness, e.g., structural similarity between the DNA which codes for IGF-I and the amino acid sequence of the polypeptide" because "although a protein and its DNA are not structurally similar, they are correspondently linked via the genetic code." The Board affirmed the PTO's rejection.

The Federal Circuit phrased the issue before it as whether "the Board correctly determined that the amino acid sequence of a protein in conjunction with a reference indicating a general method of cloning renders the gene *prima facie* obvious."

Treating the PTO's correspondent link theory as amounting to a rejection based on the two prior publications alone, the court reversed.

It may be true that, knowing the structure of the protein, one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene. However, because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein. In the case of IGF, Bell has argued without contradiction that the \[relevant\] amino acid sequences could be coded for by more than \(10^{36}\) different nucleotide sequences, only a few of which are the human sequences that Bell now claims. Therefore, given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the claimed sequences would not have been obvious.

The court further reasoned "[a]bsent anything in the cited prior art suggesting which of the \(10^{36}\) possible sequences . . . corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences." The court went on to explain:

This is not to say that a gene is never rendered obvious when the amino acid sequence of its coded protein is known. Bell concedes that in a case in which a known amino acid sequence is specified exclusively by unique codons, the gene might have been obvious.

128. *Id.* (citations omitted).
129. *Id.*
130. *Id.*
131. *Id.* at 785
132. *In re Bell*, 991 F.2d at 784.
133. *Id.*
Such a case is not before us. Here, where [the prior art] suggests a vast number of possible nucleic acid sequences, we conclude that the claimed human sequences would not have been obvious.\footnote{Id.}

The Federal Court rejected the PTO's argument that knowing a general method for identifying genes through the use of nucleotide probes, as well as the complete or partial amino acid sequence of a protein, establishes a \textit{prima facie} case for the obviousness of the DNA sequence encoding for the protein.\footnote{Id. at 784–85.} The Federal Circuit finally held that, with respect to patent claims to DNA sequences, the nonobviousness determination should focus on the DNA molecules as compositions (or chemical compounds) rather than on the method for isolating DNA sequences.\footnote{Id. at 785.} This approach appears to be consistent with the precedent set by the Federal Circuit (discussed in Part II.B.2, \textit{supra}) stating that "the patentability of a product does not depend on its method of production," which the \textit{Amgen} court failed to follow.\footnote{In re Thorpe, 777 F.2d 695, 697 (Fed. Cir. 1985).} The Federal Circuit reasoned, "[t]he PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made."\footnote{In re Bell, 991 F.2d at 785.} In other words, any given DNA sequence (whether a full DNA sequence that encodes a protein or a mere sequence fragment) is obvious \textit{only if} the prior art actually recites a similar or identical sequence and not simply a method for isolating the sequence.

One of the scholars observed that

Under this logic, DNA sequences can be nonobvious no matter how easy or routine it is to isolate the sequences. This significant lowering of the patentability bar has resulted in a situation where many biotechnology companies are seeking patents on hundreds of thousands of DNA sequence fragments that they have been able to isolate quickly through routine, automated methods.\footnote{See also In re Thorpe, 777 F.2d at 697 ("[T]he patentability of a product does not depend on its method of production.").}
I would posit that a more serious concern over the ruling of this case is that the lower bar for patentability with respect to the nonobviousness requirement will ultimately impede the progress of "useful arts" because the patent owners of hundreds of thousands of DNA sequence fragments can potentially exclude other scientists from making or using the patented DNA sequences. The ramification of the decision in this case may have the effect of tilting the balance of interests between those of the public and those of the inventors, favoring the inventors, and thereby frustrating the constitutional goal of "promoting the Progress of . . . useful Arts."\textsuperscript{140}

This case might have been decided differently if the Federal Court had recognized the PTO's argument that the established relationship via the genetic code between a nucleic acid and the protein it encodes makes a gene \textit{prima facie} obvious over its correspondent protein.\textsuperscript{141} It appears that this argument is an extension of the conventional indicia of obviousness in the field of biotechnology, \textit{e.g.}, structural similarity in the field of chemistry can find its equivalent in the genetic code relationship between codons (\textit{i.e.}, the DNA sequence that codes for amino acids) and the amino acid sequence of the polypeptide that constitutes the protein.

Alternatively, the court would arrive at a different result if the analytical framework established by the prior cases (\textit{e.g.}, \textit{O'Farrell}, \textit{Amgen}, and \textit{Vaeck}) were followed. In these cases, the analytical framework is (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. As urged by the PTO, the prior patent made an explicit suggestion that the disclosed method can "easily" be applied to isolate genes for an array of proteins including peptide hormones.\textsuperscript{142} An argument made by the PTO was that "in view of [the prior art], a gene is rendered obvious once the amino acid sequence of its translated protein is known."\textsuperscript{143}

My view is that the prior art would have suggested to those skilled in the art to practice the invention with a reasonable

\textsuperscript{140} U.S. CONST., art. I, § 8, cl. 8.

\textsuperscript{141} See In re Bell, 991 F.2d at 783–84.

\textsuperscript{142} Id. at 785.

\textsuperscript{143} Id.
expectation of success. For instance, the inventive steps can be illustrated as following: (1) the complete amino acid sequences as disclosed by the two publications would have motivated a person of ordinary skill in the art to clone a gene; (2) the explicit suggestion disclosed in the prior patent would have taught a technique or method to design and synthesize probes, which correspond to all possible codon combinations based on the amino acid sequences; and (3) the probes can then be used to hybridize with and isolate the DNA sequences (from an appropriate gDNA and/or cDNA library) that encode the amino acids described in the two publications.

Nonetheless, there are at least two potential counter-arguments to my proposition above which the Federal Circuit has touched upon in its opinion—(i) the prior patent taught away from the claimed invention by emphasizing the importance of unique codons for the amino acids; and (ii) the prior patent did not "fairly suggest" how to apply its teachings to amino acid sequences without unique codons. This is because the degeneracy of the genetic code will be the single reason why the amino acid sequence without unique codons may not render the correspondent DNA sequence sought to be patented obvious.

That said, I think the key test is whether those skilled in the art could practice the invention with a reasonable expectation of success using the suggestion and method taught by the prior art. In this context, the observation of the PTO on the level of ordinary skill in the pertinent art at the time the invention was made should be given more deference because the PTO may be more competent to address this issue.

E. In re Deuel (1995)

Similar to the situation in In re Bell, this case reached the Federal Circuit from an appeal of an affirmation by the Board of a rejection made by the PTO examiner of a patent application involving an invention concerning cDNA molecules encoding proteins that stimulate mitogenic activity (cell division) as well as the isolated and purified proteins on the ground of obviousness. The Federal

144. Id.
145. See JAMES D. WATSON, MOLECULAR BIOLOGY OF THE GENE 611 (Benjamin Cummings Publishing Co. 1987) (explaining that because all amino acids but one are specified by more than one codon, it is not possible to go from an amino acid sequence to a DNA sequence unambiguously).
146. In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995).
147. Id. at 1553–54.
Circuit reversed the Board's decision. The issue and the analysis of this case are quite similar to those presented in *Bell*. In addition to reaffirming the principle in *Bell* that focus must be on the obviousness of the claimed compositions if the subject matter sought to be patented is directed to the product (gene) rather than the method of making it, the Federal Circuit further clarified the role to be played by the method for making the claimed compound in the context of a patentability determination.

1. Invention

The subject matter of the application pertains to heparin-binding growth factors ("HBGFs"), which "are proteins that stimulate mitogenic activity (cell division) and thus facilitate the repair or replacement of damaged or diseased tissue." It is useful to summarize what the applicants discovered or performed in terms of the inventive steps:

1. Applicants "isolated and purified HBGF from bovine uterine tissue, found that it exhibited mitogenic activity, and determined the first 25 amino acids of the protein's N-terminal sequence";

2. Applicants "isolated a cDNA molecule encoding bovine uterine HBGF by screening a bovine uterine cDNA library with an oligonucleotide probe designed using the experimentally determined N-terminal sequence of the HBGF";

3. Applicants "purified and sequenced the cDNA molecule, which was found to consist of a sequence of 1196 nucleotide base pairs";

4. Applicants, "from the cDNA's nucleotide sequence, ... predicted the complete amino acid sequence of bovine uterine HBGF";

5. Applicants "isolated a cDNA molecule encoding human placental HBGF by screening a human placental cDNA library using the isolated bovine uterine cDNA clone as a probe";

6. Applicants "purified and sequenced the human placental cDNA clone, which was found to consist of a sequence of 961 nucleotide base pairs"; and

7. Applicants, "from the nucleotide sequence of the cDNA

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148. *Id.* at 1560.
149. *Id.* at 1559.
150. *Id.* at 1554.
molecule encoding human placental HBGF . . . predicted the complete amino acid sequence of human placental HBGF . . . . The predicted human placental and bovine uterine HBGFs each have 168 amino acids and calculated molecular weights of 18.9 kD. Of the 168 amino acids present in the two HBGFs discovered by [Applicants], 163 are identical.\(^{151}\)

At issue were four claims directed to purified and isolated DNA and cDNA sequences. Two claims (5 and 7) were directed to the specifically disclosed cDNA molecules encoding human and bovine HBGFs, respectively, while the remaining two claims generically encompassed all isolated and purified DNA sequences (natural and synthetic) encoding human and bovine HBGFs.\(^{152}\)

2. Analysis

The examiner rejected all the claims as obvious in light of two prior art references.\(^{153}\) The first reference described "a general technique for cloning a gene."\(^{154}\) The second reference disclosed heparin-binding brain mitogens (HBBMs) isolated from human and bovine brain tissue.\(^{155}\) The second reference (1) determined the HBBMs' first 19 amino acids (N-terminal sequence), which were identical for the human and bovine versions (and the same as the N-terminal sequence the applicant disclosed for its HBGFs), (2) taught that HBBMs are brain-specific, and (3) suggested that the proteins may be homologous between species.\(^{156}\) It disclosed no DNA or cDNA sequences for the HBBMs.\(^{157}\) The examiner reasoned that (1) "[The second reference's] published N-terminal sequence would have motivated a person of ordinary skill in the art to clone [the] gene because cloning the gene would allow recombinant production of HBGF, a useful protein," and (2) "a person of ordinary skill in the art could have designed a gene probe based on [the second reference's] disclosed N-terminal sequence, then screened a DNA library in accordance with [the first reference's] gene cloning method to isolate a gene encoding an HBGF."\(^{158}\)

The applicant argued that the second reference taught away from

\(^{151}\) Id. at 1555.
\(^{152}\) In re Deuel, 51 F.3d at 1555.
\(^{153}\) Id. at 1555–56.
\(^{154}\) Id. at 1556.
\(^{155}\) Id.
\(^{156}\) Id.
\(^{157}\) Id. at 1556.
\(^{158}\) In re Deuel, 51 F.3d at 1556.
the claimed cDNA molecules because it suggested that HBBMs were brain-specific, discouraging one from trying to isolate cDNA clones from human placental and bovine uterine cDNA libraries. The examiner made the rejection final, commenting that

it was well known in the art at the time the invention was made that proteins, especially the general class of heparin binding proteins, are highly homologous between species and tissue type. It would have been entirely obvious to attempt to isolate a known protein from different tissue types and even different species.

The Board affirmed. Similar to the issue presented in Bell, the issue was "whether or not knowledge of the partial amino acid sequence of a protein, in conjunction with a reference indicating a general method of cloning, renders the invention as a whole, i.e., the [sequences of] gene[s], prima facie obvious." The Board indicated that

[W]e are constantly advised by the patent examiners, who are highly skilled in this art, "that cloning procedures are routine in the art." . . . One of ordinary skill in this art, advised of the existence and isolation of a functional protein, is also necessarily advised of the existence of a gene which codes for the protein, but does not know the gene's structure. There is incentive or motivation to isolate (clone) the gene for any functional and useful protein because it would then enable production of large amounts of the protein for further study and commercial use. We do not subscribe to appellants' proposition that the failure of the references to teach the structure of the claimed DNA precludes the teachings thereof from serving as evidence to establish a prima facie case of obviousness. The argument is contrary to a body of law which holds that a product may be described by the process of making it . . . . Though those skilled in the art may be unaware of the exact chemical structure of a gene they are aware that it is composed of an unknown but established, relatively unchanging array of nucleotides which code for the particular protein. Importantly, they are also aware that the gene will hybridize with another DNA having the same assemblage of adjacent nucleotides for at least a portion of the gene. Those skilled in the art are also aware of established procedures for isolating the gene using the

159. Id. at 1557-58.
160. Id. at 1556.
161. Id.
hybridization phenomenon.\textsuperscript{163}

The Board went on to distinguish \textit{Bell}:

Although the Court described the issue using broad language, it did not render a broad decision. Rather, the Court limited its decision to the facts of the case. First, the \textit{Bell} Court decided that the reference which provided the amino acid sequence of the protein did not, by itself, make obvious the specifically claimed \ldots correspondent gene because of the degeneracy of the genetic code. The Court then looked to the secondary reference to determine whether the cloning technique taught therein pointed the way to the gene. The Court reviewed the secondary reference and determined that it taught away from a viable process which could be used for cloning the particular gene set forth in the \textit{Bell} application.\textsuperscript{164}

The Board was not persuaded by applicants' argument that its DNA was isolated from bovine uterus and human placenta tissue whereas the prior art used brain tissue and taught that the protein was tissue specific.\textsuperscript{165} In other words, the Board affirmed the PTO's finding that it was obvious to one skilled in the art at the time the invention was made that a known protein could be isolated from different tissue types and from different species.

Like in the case of \textit{Bell}, the Federal Circuit reversed the Board's decision and holding that rejection of the claims to specific cDNA sequences (claims 5 and 7) was improper because nothing in the prior art suggested the claimed structures.\textsuperscript{166} Case law on \textit{prima facie} obviousness of chemical compounds did not apply.\textsuperscript{167}

Again, the court did not accept the position that given the established genetic code relationship between nucleic acids and the correspondent amino acids and the routine method of gene cloning, a partial amino acid sequence disclosed in a prior art reference may render the DNA and cDNA molecules encoding the protein \textit{prima facie} obvious. The court reasoned,

one could not have conceived the subject matter of claims 5 and 7 based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would

\textsuperscript{163} \textit{Id.} at 1447–49 (citations omitted).
\textsuperscript{164} \textit{Id.} at 1449.
\textsuperscript{165} \textit{Id.} at 1450.
\textsuperscript{166} \textit{In re} Deuel, 51 F.3d 1552, 1560 (Fed. Cir. 1995).
\textsuperscript{167} \textit{Id.} at 1558–59.
have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.\textsuperscript{168}

The court stressed that "[a] general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search,"\textsuperscript{169} and that "[t]he genetic code relationship between proteins and nucleic acids does not overcome the deficiencies of the cited references."\textsuperscript{170}

A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein. No 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. We recently held in \textit{In re Baird}... that a broad genus does not necessarily render obvious each compound within its scope. Similarly, knowledge of a protein does not give one a conception of a particular DNA encoding it. Thus, \textit{a fortiori}, [the second prior art reference's] disclosure of the N-terminal portion of a protein, which the PTO urges is the same as HBGF, would not have suggested the particular cDNA molecules defined by claims 5 and 7. This is so even though one skilled in the art knew that some DNA, albeit not in purified and isolated form, did exist. The compounds of claims 5 and 7 are specific compounds not suggested by the prior art.\textsuperscript{171}

It conceded that "[a] different result might pertain... if there were prior art, \textit{e.g.}, a protein of sufficiently small size and simplicity, so that lacking redundancy, each possible DNA would be obvious over the protein."\textsuperscript{172}

As in \textit{Bell}, the court held that the PTO erred in focusing on isolation \textit{methods} when the claims defined compounds.

We today reaffirm the principle, stated in \textit{Bell}, 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

\textsuperscript{168} \textit{See id. at 58.}
\textsuperscript{169} \textit{Id.}
\textsuperscript{170} \textit{Id.}
\textsuperscript{171} \textit{Id.} at 1558–59.
\textsuperscript{172} \textit{In re Deuel}, 51 F.3d at 1559.
other prior art that suggests the claimed DNAs. A prior art disclosure of a process *reciting a particular compound* or obvious variant thereof as a product of the process is, of course, another matter, raising issues of anticipation under 35 U.S.C. § 102 as well as obviousness under § 103. Moreover, where there is prior art that suggests a claimed compound, the existence, or lack thereof, of an enabling process for making that compound is surely a factor in any patentability determination . . . . There must, however, still be prior art that suggests the claimed compound in order for a *prima facie* case of obviousness to be made out . . . .

In this context, the court seemed to clarify that the existence of a general method of isolating cDNA or DNA molecules is "essentially irrelevant" to the question of nonobviousness if the claimed invention directs to a compound rather than a method of making it. 174 This ruling appears to be directly inconsistent with the position in Amgen that the nonobviousness of an invention should be based on the analysis focusing on the nonobviousness of the scientific techniques for making the invention. The focus on the nonobviousness of the product (*i.e.*, the DNA molecules) rather than the method to derive the product represents a rejection of the Amgen analysis while the prior holding of the Federal Circuit (discussed in Part II.B.2, supra) is now back in favor.

The court finally reversed the rejections because the PTO did not articulate any separate reasons for holding these claims unpatentable. 175 The second reference did not fully anticipate these generic claims, but the court appears to have hinted that the specification might not provide adequate enabling support due to the lack of enabling process for making the claimed compound. 176

In sum, the Federal Circuit's focus on the obviousness of the claimed invention (*i.e.*, DNA sequences or molecules) may be correct if the invention claims the composition rather than the method to produce the composition. However, from a technological standpoint, it may not be accurate to say that a DNA composition is not obvious if the prior art reference does not recite a similar or identical DNA sequence because, as the PTO observed, the corresponding link (in the form of a genetic code) between a DNA sequence and its encoded protein must be considered.

173. *Id.*
174. *Id.*
175. *Id.* at 1560.
176. *Id.*
III. SPECIFIC PROPOSALS

To ensure that more certainty will result from the Federal Court's decisions relating to the nonobviousness standards, I would like to identify below three specific proposals regarding the nonobviousness standard under §103 of the Patent Act as applied to gene-related inventions:

(1) By adapting to the latest advances in the research strategies in the genetic engineering field, the Federal Circuit should accept the position that the corresponding link between a gene and its encoded protein via a genetic code renders the gene obvious when the complete or partial amino acid sequence is known and the implicit position that this relationship raises a *prima facie* case of structural obviousness similar to the relationship between closely related homologues, analogs, and isomers in chemistry. This proposed approach would cure the defective analysis made by the Federal Circuit in *Bell* and *Deuel* that a similar or identical DNA sequence be referenced in the prior art before obviousness can be found.

(2) Another proposal put forward by some commentators is for a heightened nonobviousness standard under which the patent applicant must sequence a complete gene, or at least enough of a gene necessary to determine its function and preliminary diagnostic applications. Some public policy purposes behind this proposal include (1) maintaining uniformity with other biotechnological requirements of the patent statute; (2) reducing irresponsible gene patenting behavior in the industry; and (3) regaining the public's bargaining power in granting gene-related patents. Furthermore, this heightened standard would promote the progress of "useful Arts" as intended by the United States Constitution. This proposal should tend to counter-balance the shift of focus (in *Bell* and *Deuel*) from the nonobviousness of methods or techniques to

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177. See CHISUM, supra note 1 at 682. Biological investigators have devised certain experimental strategies to facilitate the isolation of the desired gene once the amino acid sequence is known. See also Dastgheib-Vinarov, supra note 9. This article summarizes a number of new research strategies designed to reduce or eliminate the guesswork in synthesizing the best oligonucleotide probes for obtaining full-length cDNAs and genes, such as computer programs, algorithms, DNA and protein databases, etc.

178. See Dastgheib-Vinarov, supra note 9.
the nonobviousness of products (i.e., DNA sequences) by emphasizing the usefulness or the "utility" standard of the claimed DNA sequences.

(3) Given the PTO's comparative institutional advantage, the Federal Circuit should show greater deference to the factual findings of the PTO. Attention should be directed to which institution (i.e., the PTO or the Federal Circuit) has the resources to investigate and understand an expanding amount of complex, constantly changing information. A comparative analysis of the available institutions suggests that the PTO may be the institution best situated to address technological change in biotechnology. This proposal would alleviate the existing tension between the PTO and the Federal Circuit in making factual findings (as discussed in relation to Vaeck) and in determining the level of ordinary skill in the biotechnology field (as discussed in relation to Bell and Deuel).

IV. CONCLUSION

From the review of the above five cases in which the nonobviousness issue relating to gene-related inventions has been thoroughly discussed by the Federal Circuit, a two-step standard can be identified: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The PTO has strictly followed the above standard in making their factual inquiries and evaluation surrounding the nonobviousness issue (e.g., as in Bell and Deuel). One of the differences between the approach of the PTO and that of the Federal Circuit appears to be that the PTO showed familiarity with the developments in the biotechnology industry at the time the invention was made, and therefore was more stringent (as compared with the position of the Federal Circuit) in deciding the nonobviousness issue. After all, the use of the PTO's approach is more likely to ensure that the nonobviousness requirement be met only 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 nonobvious at the time
the invention was made to a person having ordinary skill in the art. In this context, then, the Federal Circuit should give greater deference to the PTO as far as the factual findings and specific knowledge of the technological changes in biotechnology field are concerned.