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Correspondent Link Between a Protein and Nucleic Acid Sequence Does Not Render the Gene Obvious

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"CORRESPONDENT LINK" BETWEEN A PROTEIN AND NUCLEIC ACID SEQUENCE DOES NOT RENDER THE GENE OBVIOUS

In Re Bell, 991 F.2d 781 (Fed. Cir. 1993)

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On 20 April 1993, the United States Court of Appeals for the Federal Circuit reversed a decision by the Board of Patent Appeals & Interferences (Board), and granted a patent directed to genes which code for insulin-like human hormones to Chiron Corporation (Emeryville, CA).[1]

The decision written by Judge Lourie,[2] overturned the Examiner's final rejection of Bell's patent application Serial No. 065,673, entitled "Preproinsulin-like Growth Factors I and II," on the ground of obviousness under 35 U.S.C. § 103. The Federal Circuit ruled that the "Board erred in concluding that the claimed nucleic acid molecules would have been obvious in light of the cited prior art."[3]

BACKGROUND

The claims of the application in dispute are directed to nucleic acids (DNA and RNA)[4] which encode human insulin-like growth

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1. In re Bell, 991 F.2d 781 (Fed. Cir. 1993). The application was filed in the names of three inventors, Graeme I. Bell, Leslie B. Rall and James P. Merryweather. Hereinafter, the patent application and its components are referred to as "Bell." Chiron Corp. is the assignee.

2. The case was heard before Judges Rich, Lourie, and Schall.

3. *Bell*, 991 F.2d at 782.

4. The two major types of nucleic acid are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the "genetic blueprint" for the vast majority of organisms (including humans). DNA is a double helix, similar in shape to a spiral staircase. The four "bases"—adenine, thymine, guanine, and cytosine form the steps of the staircase; sugar and phosphate molecules comprise the handrails. RNA is similar to DNA in that it contains adenine, guanine, and cytosine. However, it contains uracil, rather than thymine. For a description of basic genetics and recombinant DNA technology, the reader is referred to such texts as BENJAMIN LEWIN, GENES (2d ed. 1985); BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL (1983); MAXINE SINGER AND PAUL BERG, GENES AND GENOMES (1991). In re O'Farrell, 853 F.2d 894, 895-899 (Fed. Cir. 1988), also contains a general discussion of the technology involved here.

factors I and II (IGF).[5] Claim 25 (conceded by the parties to be representative of the claims at issue) includes the following:

> A composition comprising nucleic acid molecules containing a human sequence encoding insulin-like growth factor (hIGF) substantially free of nucleic acid molecules not containing said (hIGF) sequence, wherein said hIGF sequence is selected from the group consisting of (a) . . . ; (b) . . . ; (c) nucleic acid sequences complementary to (a) or (b); and (d) fragments of (a), (b), or (c) that are at least 18 bases in length and which will selectively hybridize to human genomic DNA encoding hIGF.[6]

The relevant prior art consisted of two publications which disclose the amino acid sequences[7] of IGF I and II,[8] and U.S. Patent No. 4,394,443 issued to Weissman et al., entitled "Method for Cloning Genes." The Weissman patent describes a general method for the isolating genes for which at least a short amino acid sequence is known.[9] This method involves preparation of a nucleic acid probe[10] which corresponds to the known amino acid sequence and using this probe to isolate the gene of interest. Weissman teaches that it is advantageous to design and use a probe which is based on amino acids specified by unique codons.[11]

The Examiner rejected Bell's claims as obvious over the combined teachings of Rinderknecht and Weissman, after determining that it would have been obvious, "albeit tedious," to prepare probes according to Weissman, based on the Rinderknecht amino acid sequences.[12] The Examiner argued that an ordinary artisan would know how to determine the nucleic acid sequence which corresponds to a known amino acid sequence.[13] Based on this argument,

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5. These growth factors are single-chain serum proteins involved in the mediation of cell growth following the administration of growth hormones.

6. *Bell*, 991 F.2d at 782, n.3. The text omitted here discloses the nucleic acid sequences.

7. Amino acids are the "building blocks" of proteins.

8. Rinderknecht et al., *The Amino Acid Sequence of Human Insulin-Like Growth Factor I and Its Structural Homology with Proinsulin*, 253 J. BIOL. CHEM., 2769-76 (1978); and Rinderknecht et al., *Primary Structure of Human Insulin-like Growth Factor II*, 89 FEBS LETTER, 283-86 (May 1978).

9. Specifically, Weissman describes the isolation of a gene which encodes a human histocompatibility antigen, a protein unrelated to IGF.

10. A probe is a sequence of DNA or RNA which is used to identify a particular sequence of interest in DNA or RNA of unknown sequence.

11. A "codon" is a sequence of three nucleotides which codes for one of the twenty natural amino acids. Because there are twenty animo acids and sixty-four possible codons, most amino acids are coded for by more than one codon.

12. *See Bell*, 991 F.2d at 783.

13. *Id.*

the Examiner rejected the application because the claimed sequences and hosts[14] would have been readily determinable by and obvious to, those of ordinary skill in the art at the time the invention was made.[15]

The Board upheld the Examiner's rejection of Bell's claims, by holding that the Examiner had established a prima facie case of obviousness for the claimed sequences, despite the lack of conventional indicia of obviousness.[16] The Board's rationale was that although a protein and the DNA encoding it are not structurally similar, they are linked based on the DNA code. In view of Weissman, the Board determined that there was no evidence "that one skilled in the art, knowing the amino acid sequences of the desired proteins, would not have been able to predictably clone the desired DNA sequences without undue experimentation."[17]

Bell argued that the Patent and Trademark Office (PTO) failed to establish its prima facie case of obviousness, because it did not show how the prior art references, alone or in combination, taught or suggested their invention. Importantly for Bell, these arguments are in agreement with previous decisions which have held that the PTO bears the burden of establishing a prima facie case of obviousness.[18] Thus, despite the Board's support of the Examiner's rejection, the Court agreed with Bell.

DISCUSSION

The Federal Circuit reviews the Board's rejection of patent applications based on obviousness grounds *de novo*.[19] As previously stated, "[a] prima facie case of obviousness 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."[20]

The Court indicated that the Examiner's rationale that a "correspondent link" between a gene and its protein via the genetic code renders the gene obvious if the amino acid sequence is known,[21] amounts to a rejection based on the two Rinderknecht publications

14. The "hosts" are the cells used to prepare the probes.

15. *Bell*, 991 F.2d at 783.

16. *Id.* This rejection was based on structural similarity between the DNA encoding for IGF-I and the amino acid sequence of the IGF-I polypeptide.

17. *Id.*

18. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

19. In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991).

20. In re Rinehart, 531 F.2d 1048, 1151 (CCPA 1976).

21. *Bell*, 991 F.2d at 783.

alone.[22]

The Court realized that unlike chemical homologs, analogs and isomers, which may create a prima facie case of obviousness,[23] the established relationship between a gene and its correspondent protein does not make a gene prima facie obvious over its correspondent protein.[24] The Court recognized that while the knowledge of the protein structure and sequence may be used to hypothesize about the gene sequence, the degeneracy of the genetic code results in a vast number of potential nucleotide sequences which might code for a specific protein.[25]

However, the Court also stressed that when the amino acid sequence is known to be specified exclusively by unique codons, the gene may be rendered obvious.[26] In this case, Bell argued, without contradiction, that the Rinderknecht amino acids could be coded for by more than 10^{36} different nucleotide sequences, only a few of which are the human sequences claimed in the patent application.[27] The Court found that the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of these possibilities were the human sequences claimed, rendered Bell's sequences non-obvious.[28] Thus, because there was nothing in the prior art to suggest which of the 10^{36} Rinderknecht sequences correspond to the IGF gene, the Court found that the PTO did not meet its burden of establishing that the prior art would have suggested the claimed sequences.[29] The Court stressed that Bell did not claim all possible 10^{36} nucleic acids which potentially code for IGF, nor did he claim all nucleic acids coding for a protein with the biological activity of IGF.[30]

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22. *Id.*

23. *See* In re Dillon, 919 F.2d 688, 696 (Fed. Cir. 1990)(*en banc*), *cert. denied*, 111 S. Ct. 1682 (1991).

24. *Bell*, 991 F.2d at 784.

25. This degeneracy is based on the fact that there are sixty four possible codons, but only twenty natural amino acids. In addition to "degeneracy" in the genetic code, the tendency for similar amino acids to be represented by related codons is believed to minimize the effects of mutations. This helps to ensure that a single random base change has an increased probability (as compared with a completely random assignment of codons) of resulting in either no amino acid substitution or substitution by an amino acid of similar character. *Lewin, supra* note 4, at 96.

26. *Bell*, 991 F.2d at 784. In footnote 6, the Court indicated that it "express[ed] no opinion concerning the reverse proposition, that knowledge of the structure of a DNA, *e.g.*, a cDNA, might make a coded protein obvious." *Id.* Thus, the Court has left this avenue open for continuing debate.

27. *Bell*, 991 F.2d at 784.

28. *Id.*

29. *Id.*

30. *Id.*

The Court also reviewed obviousness determinations based on combinations of references. It reiterated the requirement that obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination."[31] The Court also repeated the rule that the teachings of a reference and the determination of whether it teaches toward or away from the claimed invention are questions of fact.[32]

The Weissman patent suggests that it is generally advantageous to design probes based on amino acid sequences specified by unique codons.[33] The PTO argued that this suggestion would be "easily" applied to the isolation of genes for an array of proteins, including peptide hormones. The PTO further argued that, in view of Weissman, a gene is rendered obvious once the amino acid sequence of the corresponding protein is known. However, the Court refused to view Weissman in such a broad scope. The Court indicated that Weissman teaches away from the present invention because it is directed toward situations in which unique codons are known. In contrast, the present invention involves no unique codons (or only one).[34]

While reaffirming that "a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests,"[35] the Court found that because Weissman does not suggest how to apply its teachings to amino acids sequences lacking unique codons, it could not say Weissman "fairly teaches" that its methods should be combined with the teachings of Rinderknecht.[36]

The Court also discussed the emphasis the PTO placed on the similarities in the methods used by Bell and Weissman to produce their respective isolated genes. As Bell claims compositions of matter, rather than a method, the PTO's focus was found to be misplaced. This is due to settled law that for composition of matter claims, the issue is the obviousness of claimed compositions, not the

31. ACS Hosp. Sys. v. Montefiore Hosp., 732 F.2d 1572, 1577 (Fed. Cir. 1984).

32. *See* Raytheon Co. v. Roper Corp., 724 F.2d 951, 960-1 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984).

33. *Bell*, 991 F.2d at 784.

34. In contrast to the Weissman sequences, Bell used a probe with 23 nucleotides based on a sequence of eight amino acids, none of which were unique. Rinderknecht indicates that IGF-I has only a single amino acid coded with a unique codon and IGF-II has none. Thus, Weissman is in opposition to Bell.

35. In re Burckel, 592 F.2d 1175, 1179 (CCPA 1979).

36. *Bell*, 991 F.2d at 785.

obviousness of the method by which the composition is made.[37]

CONCLUSION

The Court concluded that: (1) the Board was clearly in error in its determination that Weissman teaches toward, rather than away from Bell's claimed sequences; (2) the requisite teaching or suggestion to combine the prior art references was absent; and (3) the PTO did not establish that the claimed sequences would have been obvious over the combination of Weissman and Rinderknecht.[38] The Court's conclusion that the combination of prior art references does not render the claimed invention obvious, resulted in reversal of the Board's decision to affirm the Examiner's rejection of Bell's Claims 25-46.

The importance of *Bell* is that it is in opposition to the PTO's policy to declare as gene derived from known amino acid sequences by use of general cloning methods to be obvious.[39] This decision will require Examiners to take a closer look at this type of patent application on an individual basis in order to make a decision regarding obviousness.

The *Bell* decision is an addition to a growing body of case law dedicated to the unique concerns related to biotechnology.[40] This case law should provide encouragement for biotechnology companies desiring to protect their inventions which are the products of expensive, labor and time-intensive research. This law provides attractive incentives (i.e., patent protection) to companies who devote their resources to research. It is an indication that the current boom in biotechnology will continue long into the future.

37. In re Thorpe, 777 F.2d 695 (Fed. Cir. 1985). "Patentability of a product does not depend upon its method of production." *Id.*, at 697.

38. *Bell*, 991 F.2d at 785.

39. *See* Rex Bossert, *Ruling Hailed as Protection for the Future*, DAILY JOURNAL, April 26, 1993, at 1.

40. For example, this decision is consistent with other recent Federal Circuit cases, in which the Court granted patents for genetic materials used in treatment of anemia and multiple sclerosis.