GENENTECH, INC. V. CHIRON CORP.

By Rahul Pathak

A claim to a DNA molecule is construed as a claim to a DNA molecule, not as a claim to its expressed protein. So held Judge Rich of the Federal Circuit in *Genentech, Inc. v. Chiron Corp.*[1] reversing the district court.[2] When the district court construed an interference count to a DNA molecule at issue in both cases, it based its definition of the scope of the count on the protein expressed by the DNA molecule.[3] Judge Rich disagreed stating that "[a]lthough a close relationship exists between a DNA construct and the protein it encodes, the two are not equal."[4]

This claim construction case originated as a patent interference between Genentech and Chiron over claims to DNA constructs encoding modified forms of human insulin-like growth factor-I (IGF-I).[5] The sole count of the interference was claim 22 of the Chiron application:

> A DNA construct comprising a sequence coding for human insulin-like growth factor-I joined in proper reading frame with *Saccharomyces* alpha-factor secretory leader and processing signal sequence.[6]

Ideally, *Saccharomyces* cells expressing this construct secrete some form of human IGF-I.[7] The Genentech application included a DNA construct coding for *Saccharomyces* alpha-factor secretory leader and processing sequences, human IGF-I, and, additionally, twenty-seven nucleotide bases

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1. 112 F.3d 495, 42 U.S.P.Q.2d (BNA) 1608 (Fed. Cir. 1997) [hereinafter *Genentech II*].

2. Genentech, Inc. v. Chiron Corp., No. C-94-3334, 1995 WL 450846, *1 (N.D. Cal. July 19, 1995), *rev'd,* 112 F.3d 495, 42 U.S.P.Q.2d (BNA) 1608 (Fed. Cir. 1997) [hereinafter *Genentech I*].

3. *See Genentech II,* 112 F.3d at 500, 42 U.S.P.Q.2d at 1612-13.

4. *See id.* at 501, 42 U.S.P.Q.2d at 1613.

5. *See Genentech II,* 112 F.3d at 497, 42 U.S.P.Q.2d at 1609-10. The protein insulin-like growth factor-I acts on many tissues and organs. It has been used to treat many human diseases including growth deficiency, osteoporosis, catabolic disorders, and diabetes. It might also be useful for the treatment of brain trauma and certain neurodegenerative diseases including amyotrophic lateral-sclerosis and Alzheimer's disease. *See* Sylvain Dore et al., *Rediscovering an Old Friend, IGF-I: Potential Use in the Treatment of Neurodegenerative Diseases,* 20 TRENDS IN NEUROSCIENCES 326, 326 (1997).

6. *Genentech II,* 112 F.3d at 498, 42 U.S.P.Q.2d at 1610 (italics supplied).

7. *See id.* at 498, 42 U.S.P.Q.2d at 1610.

encoding a collagenase cleavage site.[8] The addition of the sequence encoding the collagenase cleavage site results in the production of a "modified IGF-I" or a "fusion protein" rather than native human IGF-I.[9] The pivotal issue of the opinion was the proper construction of the interference count—whether the Genentech construct was within the scope of the count after the addition of the twenty-seven nucleotides encoding the collagenase site.[10] Judge Rich emphasized the distinction between the examination of a DNA construct and the examination of its expressed protein in holding that the Genentech construct is within the scope of the count.[11]

In this case, the Federal Circuit developed standards for the construction of interference counts involving DNA inventions. Rather than follow the strict structural requirements that are applied to the conception and written description of DNA molecules, the court tailored a new standard to the unique characteristics of DNA inventions.

I. BACKGROUND OF THE INVENTIONS

DNA molecules are the stable molecular sources of information in biological organisms.[12] The information encoded in the nucleotides of the DNA sequence direct, among other processes, the production of protein molecules. DNA is first transcribed into messenger RNA, another information-carrying nucleic acid molecule. Messenger RNA molecules are then translated into a protein chain. Proteins are polymers consisting of amino acid monomers. Each amino acid monomer is one of twenty amino acids found in nature. At each position in the protein chain, the identity of the amino acid is encoded by one codon, or group of three nucleotides, in the messenger RNA chain. By varying the sequence of nucleotides in the DNA chain, one varies the nucleotides in the RNA chain and the amino acids in the final protein.

Recombinant DNA technology exploits the genetic machinery of living organisms to produce novel biomolecules. One can increase the amount of a particular protein in a cell or express a protein from one organism in a foreign organism. The techniques of genetic engineering enable the manipulation of DNA molecules. Pieces of DNA from one

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8. *See id.*
9. *See id.*
10. *See id.* at 500, 42 U.S.P.Q.2d at 1612.
11. *See id.* at 501-02, 42 U.S.P.Q.2d at 1613-14.
12. For the Federal Circuit's background discussion of recombinant DNA technology, see generally *In re O'Farrell*, 853 F.2d 894, 895-99, 7 U.S.P.Q.2d (BNA) 1673, 1674-77 (Fed. Cir. 1988).

source can be joined, or ligated, to a DNA molecule from another source. For instance, DNA encoding a human protein can be ligated to sequences controlling the expression and processing of proteins in yeast. Proper expression of such a construct in yeast cells could result in the production of the human protein in yeast cells.

Human IGF-I is a protein that regulates the effects of human growth hormone.[13] The seventy amino acid sequence of human IGF-I was published in 1978.[14] The aim of both the Chiron invention and the Genentech invention is the production of some form of human IGF-I in transformed yeast cells.[15]

The yeast *Saccharomyces* naturally secretes a thirteen amino acid alpha-factor peptide.[16] Alpha-factor is initially expressed as a polypeptide consisting of a secretory leader sequence followed by four copies of the alpha-factor peptide.[17] The alpha-factor peptides are preceded by processing sequences of six or eight amino acids.[18] These four processing sequences are recognized by enzymes that cleave the polypeptide to release four copies of mature alpha-factor peptide.[19]

Chiron's DNA construct replaces the yeast DNA encoding the four alpha-factor sequences and the three intervening processing sequences with DNA encoding one human IGF-I molecule.[20] The resulting construct encodes one polypeptide including the alpha-factor secretory leader sequence, one copy of the alpha-factor processing sequence, and human IGF-I.[21] *Saccharomyces* cells transformed with a plasmid expressing this construct secrete human IGF-I.[22] In contrast, Genentech's construct encodes the alpha-factor processing sequence, a collagenase cleavage site, and human IGF-I.[23] The additional collagenase cleavage site codes for a nine amino acid sequence cleaved by the enzyme collagenase.[24] *Saccharomyces* cells transformed with a plasmid expressing Genentech's con-

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13. *See Genentech II*, 112 F.3d at 497-8, 42 U.S.P.Q.2d at 1610.
14. *See* Ernst Rinderknecht & Rene Humbel, *The Amino Acid Sequence of Human Insulin-like Growth Factor I and Its Structural Homology with Proinsulin*, 253 JOURNAL OF BIOLOGICAL CHEMISTRY 2769, 2771 (1978).
15. *See Genentech II*, 112 F.3d at 498, 42 U.S.P.Q.2d at 1610.
16. *See Genentech I, 1995* WL 450846, at *1.
17. *See id.*
18. *See id.*
19. *See id.*
20. *See id.*
21. *See id.*
22. *See id.*
23. *See Genentech II*, 112 F.3d at 498, 42 U.S.P.Q.2d at 1610.
24. *See id.*

struct secrete a fusion protein version of human IGF-I including the nine amino acid collagenase cleavage site.[25]

II. PROCEDURAL HISTORY—BOARD OF PATENT APPEALS AND INTERFERENCES

The purpose of an interference proceeding is to settle the issue of priority of invention when more than one person seeks a patent on substantially the same invention.[26] Application No. 06/922,199 was filed on October 23, 1986, with the benefit of Application No. 06/487,950 filed on April 25, 1983; this application was assigned to Chiron by inventors Philip J. Barr, James P. Merryweather, Guy Mullenbach, and Mickey S. Urdea (Barr).[27] Application No. 06/506,078 was filed on June 20, 1983, and assigned to Genentech by inventors James M. Lee, Axel Ullrich, and Arjun Singh (Lee).[28] Chiron was the senior party, and Genentech was the junior party.[29]

Before the Board of Patent Appeals and Interferences (Board), Genentech as junior party filed evidence supporting its claim of priority.[30] Their evidence showed the invention of the Lee construct and the production of the modified IGF-I fusion protein prior to the effective filing date of the Chiron invention.[31] However, they had not converted the IGF-I fusion protein to mature human IGF-I.[32] Chiron in turn presented evidence of prior invention and attempted to substitute a newly named inventor to their claim.[33] Chiron also argued that Genentech's construct was outside the scope of the interference count because it encoded a fusion protein rather than the native protein when inserted into a plasmid and transformed into a yeast cell.[34] If Genentech's construct was outside the scope of the count, Chiron would prevail in the interference.[35]

The Board held that the subject matter of the claim was comprised of two components: the DNA sequence coding for human IGF-I and the

25. *See id.*
26. *See Genentech I*, 1995 WL 450846, at *1.
27. *See Genentech II*, 112 F.3d at 497, 42 U.S.P.Q.2d at 1609-10.
28. *See id.*
29. *See id.* at 497, 42 U.S.P.Q.2d at 1610.
30. *See Genentech I*, 1995 WL 450846, at *2.
31. *See id.*
32. *See id.*
33. *See id.* at *3.
34. *See Genentech II*, 112 F.3d at 498, 42 U.S.P.Q.2d at 1611.
35. *See Genentech I*, 1995 WL 450846, at *4.

DNA sequence coding for the *Saccharomyces* processing sequences.[36] The Board also held that the term "comprising" permits the inclusion of other elements within the count.[37] Therefore, the interference count could be directed toward either the mature human protein or a fusion protein including the human sequence.[38] According to the Board, the Genentech construct fell within the scope of the count since it encoded human IGF-I as a fusion protein.[39] However, the Board rejected Genentech's priority claim because they failed to show utility for the fusion protein.[40] The Board also restricted Chiron to its effective filing date as a sanction for failing to identify the inventor in its preliminary statement.[41] As a result, the Board held that the subject matter of the count was invented by Chiron as senior party prior to invention by Genentech.[42]

III. PROCEDURAL HISTORY - DISTRICT COURT

On appeal to the District Court for the Northern District of California, Genentech moved for summary judgment restricting Chiron to its effective filing date for failure to identify the inventor of the count according to Patent and Trademark Office procedures.[43] Chiron moved for summary judgment because Genentech's invention was not within the scope of the interference count.[44] Again, "if Genentech's DNA construct [was] not within the scope of the interference count, ... Genentech [could not] prevail in the interference."[45]

The district court granted Chiron's motion for summary judgment.[46] The court held that Genentech's construct was outside the plain meaning of the language of the count.[47] The district court found that the claimed construct must "code for" human IGF-I.[48] Since the Genentech construct coded for human IGF-I plus nine additional amino acids, the construct did not code for human IGF-I.[49] In addition, the court held that the term

36. *See id.* at *2.
37. *See id.*
38. *See id.*
39. *See id.*
40. *See id.* at *3.
41. *See id.* at *7.
42. *See id.* at *1.
43. *See id.*
44. *See id.*
45. *Genentech I*, 1995 WL 450846, at *4.
46. *See id.* at *6.
47. *See id.* at *4.
48. *See id.*
49. *See id.*

"joined" in a claim requires that two elements be directly connected.[50] Genentech's construct had nucleotides between the alpha-factor sequences and the IGF-I sequence and was thus also outside the count for failing to join the two elements.[51] Genentech's arguments for broad construction of the claim terms "comprising" and "joined in proper reading frame" were dismissed by the court.[52]

IV. OPINION

Judge Rich of the Federal Circuit reversed the district court and held that the Genentech construct is indeed within the scope of the interference count.[53] The case was remanded for further adjudication on other issues.[54]

Genentech claimed that the district court's interpretation of the interference count was improperly narrow.[55] They also claimed that Chiron did not enable under section 112 of the Patent Act, first paragraph, the invention of the count as defined by the district court.[56] The Federal Circuit disposed of the second claim by holding in favor of Genentech on the first claim.[57]

As the court explained, in construing an interference count, one must look to the "language as a whole and consider grammatical structure and syntax."[58] "In the absence of ambiguity, ... the language of the count should be given the broadest reasonable interpretation it will support," and the court must "apply the language of the count in its most obvious sense."[59] Only when the claim is ambiguous will the court resort to the application to construe the count.[60] The court did not even look to the specification to determine whether there was an ambiguity in the count.[61] Both parties and the court agreed that no ambiguity existed in the interfer-

50. *See id.* at *5.
51. *See id.* at *5-6.
52. *See id.*
53. *See Genentech II*, 112 F.3d at 502, 42 U.S.P.Q.2d at 1614.
54. *See id.*
55. *See id.* at 499, 42 U.S.P.Q.2d at 1611.
56. *See id.*
57. *See id.*
58. *Id.* at 500, 42 U.S.P.Q.2d at 1612 (citing Credle v. Bond, 25 F.3d 1566, 1571, 30 U.S.P.Q.2d (BNA) 1911, 1915 (Fed. Cir. 1994)).
59. *Id.* at 500, 42 U.S.P.Q.2d at 1612 (citing *In re* Baxter, 656 F.2d 679, 686, 210 U.S.P.Q. (BNA) 795, 802 (C.C.P.A. 1981)).
60. *See Genentech II*, 112 F.3d at 500, 42 U.S.P.Q.2d at 1162.
61. *See id.*

ence count, and the court therefore construed the count according to the broadest reasonable interpretation that its language would support.[62]

The court held that the district court's interpretation of the claim erroneously equated the DNA construct and the protein that it encoded.[63] While the district court had found that a DNA construct and the protein it produces are "inextricably intertwined since the DNA construct codes for and is defined by the protein it produces,"[64] the Federal Circuit stated that a DNA construct and the protein that it encodes are not equal.[65] The plain language of the count defined a DNA construct—not a protein.[66]

The court held that, if all the DNA elements of the count are within a DNA construct, then that construct is within the scope of the count.[67] Genentech's construct included all of the DNA elements of the count.[68] Thus, it included both the sequence encoding human IGF-I and the sequence encoding the *Saccharomyces* alpha-factor secretory leader and processing sequence.[69] According to the court, the twenty-seven additional nucleotides encoding the collagenase cleavage in the Genentech construct did not remove the construct from the scope of the count.[70] The term "comprising" not only required the presence of all named elements in the count, but it also allowed the addition of other elements such as additional nucleotides.[71] Furthermore, the court held that the phrase "joined in proper reading frame" meant simply that the nucleotides are read so that "the seventy amino acids of human IGF-I are incorporated in the proper sequence in the expressed protein."[72] Thus, additional nucleotides coding for additional amino acids were not excluded from the scope of the count.[73] The court also held that the district court's construction of "joined" was "directly connected" is too narrow.[74] Instead, it held that the constructs within the count could have intervening nucleotide sequences

62. *See id.* at 500, 42 U.S.P.Q.2d at 1612.
63. *See id.* at 500-01, 42 U.S.P.Q.2d at 1612-13.
64. *Genentech I*, 1995 WL 450846, at *5.
65. *See Genentech II*, 112 F.3d at 501, 42 U.S.P.Q.2d at 1613.
66. *See id.*
67. *See id.*
68. *See id.*
69. *See id.*
70. *See id.*
71. *See id.*
72. *Id.*
73. *See id.*
74. *See id.*

between the elements as long as the proper reading frame was maintained between the two sequences.[75]

The court distinguished the holding of *Genentech, Inc. v. Wellcome Foundation Ltd.*[76] which also dealt with the construction of a claim to a biotechnological invention.[77] Since the *Wellcome* court found one of the terms of the claim to be ambiguous, that court looked to the specification for guidance in the construction of the term.[78] In *Genentech II*, the court found no ambiguity in the claim terms and needed only to look to the plain meaning of the language of the count.[79] The court also found the definition of protein in the *Wellcome* case to be consistent with definition of the construct in this case.[80] In *Wellcome*, the phrase "human tissue plasminogen activator" (t-PA) was defined to be recombinant t-PA with the same structure as natural t-PA.[81] The Genentech IGF-I construct similarly contained all of the codons for mature human IGF-I and thus the structure of natural IGF-I.[82]

In sum, the court reversed the district court and held that the fusion protein was within the interference count.[83] The case was remanded for consideration of further issues such as the utility of the invention in Genentech's priority claim and Chiron's enablement of the count.[84]

V. DISCUSSION

The case law surrounding the patentability of recombinant DNA molecules reflects the tension between the scientific understanding of the DNA molecule and the standards applied to DNA under the patent law regime. Current patent doctrine evaluates recombinant DNA inventions under the structural standards applied to chemical compounds,[85] while many molecular biologists might have only secondary interest in the chemical structure of their target genes.[86]

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75. *See id.*
76. 29 F.3d 1555, 31 U.S.P.Q.2d (BNA) 1161 (Fed. Cir. 1994).
77. *See Genentech II*, 112 F.3d at 501, 42 U.S.P.Q.2d at 1613.
78. *See id.*
79. *See id.*
80. *See id.* at 502, 42 U.S.P.Q.2d at 1613.
81. *See Wellcome*, 29 F.3d at 1563-64, 31 U.S.P.Q.2d at 1167-68.
82. *See Genentech II*, 112 F.3d at 502, 42 U.S.P.Q.2d at 1613.
83. *See id.* at 502, 42 U.S.P.Q.2d at 1614.
84. *See id.*
85. *See* Peter F. Corless, *Recombinant DNA Inventions After Fiers*, 16 HOUS. J. INT'L L. 509, 530 (1994).
86. *See id.* at 515.

In *Amgen, Inc. v. Chugai Pharmaceutical Co.*,[87] the Federal Circuit defined the standards necessary to show conception of a genetic invention.[88] The court characterized a gene as a chemical compound and applied standards from cases involving chemical inventions.[89] When the method of making a chemical compound involves conventional techniques routine to one skilled in the art of the invention, then the compound is conceived when its structure is described.[90] However, a molecular biologist cannot know the structure of a DNA molecule until the molecule is actually obtained and sequenced; hence conception of a gene usually requires actual reduction to practice.[91] In *Amgen*, Amgen's evidence supporting its priority claim was found insufficient because it failed to show that Amgen had obtained the structure of the claimed gene.[92]

In *Fiers v. Revel v. Sugano*, [93] the Federal Circuit also considered the conception of a DNA molecule. Fiers claimed a DNA sequence encoding a human protein.[94] The court did not allow Fiers to claim his date of conception because he did not disclose the actual nucleotide sequence of the DNA encoding that protein.[95] The court emphasized the chemical requirements for the disclosure of a DNA molecule stating that "conception of a DNA molecule, like conception of any chemical substance, requires a definition of that substance other than by its functional utility."[96] The court ignored the minimal interest a molecular biologist might have in the structure of a desired DNA sequence relative to interest in the expression of the encoded protein.[97] The court indicated that it might allow a product-by-process claim for a DNA molecule without disclosure of the structure of the DNA molecule itself.[98] In *Regents of the University of California v. Eli Lilly & Co.*,[99] the Federal Circuit further grounded the concep-

87. 927 F.2d 1200, 18 U.S.P.Q.2d (BNA) 1016 (Fed. Cir. 1991).

88. *See id.* at 1205-07, 18 U.S.P.Q.2d at 1020-22

89. *See id.* at 1206, 18 U.S.P.Q.2d at 1021.

90. *See* Oka v. Youssefyeh, 849 F.2d 581, 582, 7 U.S.P.Q.2d (BNA) 1169, 1171 (Fed. Cir. 1988).

91. *See Amgen*, 927 F.2d at 1206-07, 18 U.S.P.Q.2d at 1021-22.

92. *See id.* at 1207, 18 U.S.P.Q.2d at 1021.

93. 984 F.2d 1164, 25 U.S.P.Q.2d (BNA) 1601 (Fed. Cir. 1993).

94. *See id.* at 1168-69, 25 U.S.P.Q.2d at 1604-05

95. *See id.* at 1169, 25 U.S.P.Q.2d at 1604-05.

96. *See id.*, 25 U.S.P.Q.2d at 1604.

97. *See* Corless, *supra* note 85, at 522.

98. *See Fiers*, 984 F.2d at 1169, 25 U.S.P.Q.2d at 1604-05.

99. 119 F.3d 1559, 43 U.S.P.Q.2d (BNA) 1398 (Fed. Cir. 1997). *See* Michael Delmas Plimier, *Genentech, Inc. v. Novo Nordisk & University of California v. Eli Lilly and Co.*, 13 BERKELEY TECH. L.J. 149 (1998).

tion and written description requirements for recombinant DNA inventions in structural terms.

In interpreting the scope of the interference count in *Genentech, Inc. v. Chiron Corp.*, the Federal Circuit did not follow the strict structural requirements applied to the conception and written description of inventions involving DNA molecules. A structural interpretation of the interference count might narrow the scope of the count to an actual molecule disclosed in the claim. Any structural variation on this molecule, such as the addition of twenty-seven nucleotides encoding a protease cleavage site, would create a molecule outside the scope of the interference claim.

Instead, the Federal Circuit developed a standard appropriate for DNA molecules. The court first avoided the awkward standard applied by the district court of equating a DNA construct with its encoded protein. The court found new standards that reflect an understanding of DNA as a molecule with properties unlike those of conventional chemical compounds. The court loosened the strict disclosure requirements from *Amgen* and *Fiers* with a broad interpretation of the claim language in the interference count. Chiron was not required to disclose all possible variants of their DNA construct to have them included within the scope of the claim. Rather, the claim term "comprising" was read broadly but within reason to include DNA elements beyond those actually disclosed. The restrictions supplied by the phrase "joined in proper reading frame" sufficiently limit the scope of the claim. The recognition of the techniques applied to DNA in the art and the meaning of phrases like "joined in proper reading frame" might allow the court to elaborate appropriate standards of patent law for recombinant DNA inventions.

However, the holding of this case is limited. According to the legal standards for the construction of an interference count, the court's interpretation followed the broadest reasonable interpretation that the language of the count would support.[100] The court could not look to the written description of the invention or the breadth of the enablement of the invention in either application. The issues of Chiron's written description and enablement of the broadly interpreted interference count were not reached by the Federal Circuit in this case and might be considered on remand. Although the structural requirements applied to DNA inventions might be relaxed as the field of recombinant DNA advances,[101] it is likely that the

100. *See Genentech II*, 112 F.3d at 500, 42 U.S.P.Q.2d at 1612 (citing *In re* Baxter, 656 F.2d 679, 686, 210 U.S.P.Q. (BNA) 795, 802 (C.C.P.A. 1981)).

101. *See* Corless, *supra* note 85, at 531. The *Amgen* and *Fiers* decisions dealt with recombinant DNA technology of 1982. *See id.* at 524. The relevant patent application in the *Lilly* decision was filed in 1977. *See Lilly*, 119 F.3d at 1562, 43 U.S.P.Q.2d at 1401.

count will be evaluated under the standards elaborated in *Amgen*, *Fiers*, and *Lilly*. Under those structural standards, the broadly construed count would not be adequately described or enabled beyond the disclosed DNA construct. As such, the broad construction of the count, although it comports with the plain meaning of the language of the count, has little meaning for the final determination of its scope. A molecular biologist might find some comfort in the results of the interpretation of the interference count in this case, but the narrow legal context of the holding gives little indication about change in the standards applied to the breadth of claims for recombinant DNA inventions.

The Chiron application had an effective filing date of 1983, and the Genentech application was filed in 1983. *See Genentech II*, 112 F.3d at 497, 42 U.S.P.Q.2d at 1609-10.