United States District Court,
D. Massachusetts.

BIOGEN, INC,
v.
AMGEN INC.

Civil Action No. 95-10496-RGS

Aug. 6, 1998.

Patentee brought action alleging infringement of its patent involving a recombinant deoxyribonucleic acid (DNA) technique. Following *Markman* hearing, the District Court, Stearns, J., held that patent claim required plasmid vector to contain the entire cellular transcription agent extracted from virus and at least one endonuclease recognition site located at one known site, or downstream of that site within 300 base pairs of another known site.

Ordered accordingly.

Patent claim seeking to describe a plasmid vector created by the manipulation of deoxyribonucleic acid (DNA) using recombinant DNA technique required plasmid vector to contain the entire cellular transcription agent extracted from virus and at least one endonuclease recognition site located at one known site, or downstream of that site within 300 base pairs of another known site.

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MEMORANDUM AND ORDER ON THE CONSTRUCTION OF CLAIMS 1 AND 9 OF THE '702 PATENT

STEARNS**, District Judge.**

This decision results from a hearing held under the auspices of Markman v. Westview Instruments, Inc., 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). *Markman* requires a trial judge in a patent case to construe and define the contested claims of a patent. The task committed to the judge is to explain what the protected invention is, and sometimes what it is not, ideally in language that will be accessible to a lay jury.

While several claims of several related Biogen patents are at issue, the parties recognize that the construction of claim 1 of the '702 patent is at the crux of the dispute. Claim 1 reads as follows.

A plasmid vector comprising at least one DNA sequence comprising the leftward promoter and operator derived from bacteriophage (lambda), P_LO_L, said DNA sequence further comprising at least one endonuclease recognition site located less than 300 base pairs downstream from P_LO_L and located between P_LO_L and any sequences of (lambda) DNA downstream of the *Hae* III site at 73.1% of bacteriophage (lambda) in said DNA sequence.

Stated simply, claim 1 seeks to describe a plasmid vector created by the manipulation of deoxyribonucleic acid (DNA) using recombinant DNA technique, a process by which a selected segment of a DNA molecule is inserted into and combined with all or part of another DNA molecule. The vector described in claim 1 contains P_LO_L, a promoter (cellular transcription agent) extracted from the virus bacteriophage lambda, or "phage (lambda)," and an endonuclease recognition site, a DNA sequence that is recognized by a restriction endonuclease (a cutting enzyme that isolates a specific sequence of DNA). FN1

FN1. The DNA segment is attached by DNA ligases at compatible cut sites in the host molecule. The technique, called "ligation," can be envisioned as a "cut-and-paste" process.

At this point, it may be useful to simply lay out the competing constructions of claim 1, beginning with the patent holder, Biogen.FN2

FN2. The emboldened phrases are those elements of claim 1 that Biogen and Amgen believe are important to a resolution of the dispute.

Biogen's Construction

A plasmid vector means a molecule which includes the DNA sequences that enable it to reproduce in a host cell, as well as a marker gene(s) used to identify host cells which have been successfully transformed by that vector. Often the marker gene(s) provides resistance to an antibiotic such as tetracycline or ampicillin.

The leftward promoter and operator derived from bacteriophage (lambda), P_L O_L, means that the DNA sequence has both structural and functional limitations. Structurally, this element is the DNA sequence from nucleotide positions -69 through -1 as shown in Figure 6 of the '702 patent. Functionally, this element has three properties: (1) a promoter capable of initiating transcription; (2) initiation of transcription of mRNA at a characteristic distance downstream from the "Pribnow" box located at around nucleotide position -10 relative to the start site of transcription; and (3) negative regulation by the cl repressor of bacteriophage (lambda).

At least one endonuclease recognition site located less than 300 base pairs downstream from P_LO_L means that the DNA sequence further has an endonuclease recognition site which (1) is suitable for placement of a DNA sequence coding for a desired polypeptide in the vector, and (2) which is located less than 300 base pairs downstream from the *Hinc* II site at nucleotide position -33 in the P_LO_L region. An endonuclease recognition site is a sequence of nucleotides which is recognized by an endonuclease restriction enzyme.

Which site is located **between P_LO_L and any sequences of (lambda)>>DNA downstream of the *Hae* III site at 73.1% of bacteriophage (lambda)>> in said DNA sequence** means that there cannot be (lambda) DNA sequences, normally found downstream of the *Hae* III site at 73.1% of bacteriophage (lambda), between P_LO_L and the endonuclease recognition site. The term "sequences of (lambda) DNA" refers to a

sequence of nucleotides having sufficient identify to a sequence normally present in the (lambda) genome that it would be statistically unlikely that such identity occurred by chance.

Amgen's Construction

A plasmid vector comprising at least one DNA sequence **containing the (lambda)>>>>>>>> DNA of Figure 6 comprising** the leftward promoter and operator derived from bacteriophage (lambda), P_LO_L, said DNA sequence further comprising at least one endonuclease recognition site located less than 300 base pairs downstream from P_LO_L and located between P_LO_L and any sequences of (lambda) DNA downstream of the *Hae* III site at 73.1% of bacteriophage (lambda) in said DNA sequence.FN3

FN3. Figure 6 of the '702 patent, which is at the core of the parties' dispute over the construction of claim 1, is attached to this opinion as Exhibit 1.

The Legal Framework

"[C]onstruction of a patent claim is a matter of law exclusively for the court." Markman v. Westview Instruments, Inc., 52 F.3d 967, 977 (Fed.Cir.1995) (citations omitted). A court should first "look to the words of the claims themselves, both asserted and nonasserted, to define the scope of the patented invention." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996), *citing* Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 620 (Fed.Cir.1995). In construing claims, the court must adopt the perspective of one skilled in the art as of the date of the application for the patent. Wiener v. NEC Electronics, Inc., 102 F.3d 534, 539 (Fed.Cir.1996).FN4 The court should also look to the patent specification. "The specification contains a written description of the invention which must be clear and complete enough to enable those of ordinary skill in the art to make it and use it. Thus, the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." Vitronics, 90 F.3d at 1582. Finally, the prosecution history of the patent may be consulted. "[T]he record before the Patent and Trademark Office is often of critical significance in determining the meaning of the claims." Vitronics, 90 F.3d at 1582.

FN4. The application for the '702 patent was submitted to the Patent and Trademark Office on April 3, 1981. The patent claims its earliest priority from an application filed in Britain on September 8, 1980.

The claims, specifications and file history constitute the patent's "public record ... on which the public is entitled to rely." Vitronics, 90 F.3d at 1583. Thus, it is inappropriate for a court to consider extrinsic evidence, such as expert testimony, unless the testimony is necessary to understand the meaning or scope of a technical term in the claims. Id., *citing* Pall Corp. v. Micron Separations, Inc., 66 F.3d 1211, 1216 (Fed.Cir.1995); Markman, 52 F.3d at 980-981 (same). "[W]here the public record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper." Vitronics, 90 F.3d at 1583.

DISCUSSION

Although much is disputed, the limitation in claim 1 of the '702 patent "located between P_LO_L and any sequences of (lambda) DNA downstream of the *Hae* III site at 73.1% of bacteriophage (lambda) in said DNA sequence," is critical for *Markman* purposes.FN5 It is this limitation that ultimately persuaded the Patent and Trademark Office (PTO) to issue the '702 patent.

FN5. Claim 9 of the '702 patent incorporates claim 1 (which is technically not in suit).

According to Biogen, the words "downstream from the *Hae* III site" FN6 modify the preceding phrase, "any sequences of (tau)(upsilon) DNA," rather than serving to further define any limitation on the location of the required endonuclease recognition site. In other words, the limitation excludes only those potential sites within 300 base pairs of P_LO_L that follow a (lambda)>>>>>>>>> DNA sequence "identical to the sequences of wild-type (lambda)> DNA downstream of *the Hae* III site at 73.1%." FN7 Biogen Reply Brief, at 11.FN8 Biogen's gloss on the disputed phrase is most clearly expressed in its Reply Brief: "Biogen always considered its invention to be the placement of the desired DNA sequence anywhere within 300 base pairs downstream from P_LO_L so long as there were no downstream (lambda)> sequences between P_LO_L and that site." Endnote, at 3.

FN6. "Downstream" simply refers to the direction in which the sequence of the base components of the nucleotides is read, left to right being "downstream," right to left being "upstream."

FN7. Similarly, the concluding phrase "in said DNA sequence," according to Biogen, refers to the downstream (tau)(upsilon) DNA rather than the entire plasmid vector.

FN8. Each party filed opening briefs which are designated in this opinion as "Amgen's Brief" and "Biogen's Brief." Biogen then filed a "Reply Brief" and Amgen a "Surreply Brief."

There are several problems with Biogen's reading of the limitation. First, if this is what Fiers and Remaut meant, it is difficult to understand why the patent application did not simply say so in plain English (as Biogen in its Reply Brief proves is possible). The answer can be found by looking to what was actually known about phage (lambda) in 1980, when Fiers and Remaut were preparing to make their submission to the PTO. It is clear that at the time, Fiers and Remaut did not know the precise location of P_LO_L in phage (lambda)>>>>>>>>>, only the approximate contours.FN9 This is demonstrated by Figure 6 of the patent, which does not identify the 5' site of P_L. FN10 (The *Hinc* II site which is at nucleotides -36 to -31 on Figure 6 was represented by Biogen to the PTO as the 3' site of P_L. See October 2, 1987 Amendment, at 13*). While Biogen states that Figure 6 was drawn to conform to prior art, and not because the inventors did not know the exact location of P_LO_L, there is nothing in either the patent or the prosecution history (or for that matter in the testimony of Fiers and Remaut) that supports Biogen in this regard.FN11

FN9. Fiers and Remaut were not alone. The precise boundaries of P_L O_L were still a matter of investigation for those practicing the art in 1980. Indeed, Dr. Panayotatos, Biogen's expert, could not identify the 5' or the 3' ends of P_L in his deposition in 1996. Amgen Surreply Brief, at 20. From where in the patent or the prosecution history Biogen derives the assertion that P_LO_L has its 3' end at nucleotide -1, I cannot determine. Nor do any of the references cited in the patent specifications define nucleotide -1 as the 3' end of P_LO_L. See Amgen Surreply Brief, at 25-27. It is equally unclear from where Biogen gleans the information that nucleotide -69 is the 5' end of P_LO_L . As late as 1994, Biogen told the European Patent Office that P_L O_L "spanned" nucleotides -85 to +5. Id. at 24.

FN10. 5' and 3' are the terms used to describe respectively the left and right ends of a nucleic acid molecule reading in the "sense" direction.

FN11. This is a matter of some importance as the claim language specifies a "DNA sequence comprising the

leftward promoter and operator derived from bacteriophage (lambda), P_LO_L." Thus, the claimed invention requires the presence of the complete P_LO_L sequence. As Amgen points out, a person skilled in the art in 1980 "would not have known which sequences of Figure 6 could be changed or eliminated without affecting the structure [function] of P_LO_L." Amgen Brief, at 18. As Amgen demonstrates, a careful student of the references cited in the patent would have likely concluded that P_LO_L spanned at least nucleotides -69 to +20 as shown on Figure 6. Id. at 18-19. Dr. Fiers, as late as his first deposition in 1997, was unable to say with any certainty where P_L O_L "starts or ends." Amgen Brief, at 17.

The fact that Fiers and Remaut were unaware of the exact parameters of P_L O_L at the time of the patent application underscores a fact that is devastating to Biogen's proposed claim construction. As of May of 1981, most of the (lambda) DNA downstream of *Hae* III had not been sequenced. See Daniels & Blattner, "Nucleotide Sequence of the Q Gene and the Q to S Intergenic Region of Bacteriophage Lambda," *Virology,* Vol. 177, pp. 81-92 (1982). As Amgen notes, "[u]nder Biogen's construction, to determine the scope of the claims, a person of ordinary skill in the art in 1980 would have had to compare certain sequences of a plasmid vector with an enormous stretch of (lambda)> DNA sequence (greater than 35,000 base pairs) to ensure that the plasmid vector did not contain any of this 'downstream' (lambda) DNA sequence between P_LO_L and the endonuclease recognition site.... Worse, even if it were proper to resort to the prior art, clairvoyance would have been required to recognize and exclude the 'downstream' (lambda) DNA." Amgen Surreply Brief, at 4, 5. Biogen's response, that "[i]t was well within the skill of the art in 1980 to compare a particular DNA sequence to the sequence of wild-type (lambda) from downstream of the *Hae* III site (73.1%) to determine whether any sequence identity was present only by chance or was present because the particular DNA sequence was derived from bacteriophage (lambda)>>," FN12 to the extent that it is intelligible, is no response at all. Without sequencing, no amount of statistical manipulation could establish such an "identity" (a concept which is given no definite meaning in the patent). The patent, in other words, fails to identify any of the downstream (lambda) DNA sequences that Biogen now contends it meant to exclude.FN13

FN12. Biogen Reply Brief, at 11.

FN13. As Amgen points out, Biogen'spresent position that the (lambda)bda>> > > > > > > DNA to be excluded runs from the identified *Hae* III site to the end of the genome conflicts with Dr. Fiers' deposition testimony that the (lambda) DNA to be excluded runs down to "around 38 percent." Amgen Surreply Brief, at 6. Biogen's further late-blooming suggestion, that the essence of the Fiers and Remaut invention was the elimination of coding for the N gene from the vector was, as Amgen points out, rejected three times by the PTO. Id. at 3. It is therefore foreclosed as a matter of law. See Modine Manufacturing Co. v. United States Int'l Trade Comm'n, 75 F.3d 1545, 1551 (Fed.Cir.1996).

[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Biogen, Inc. v. Amgen Inc., 973 F.Supp. 39, 45 (D.Mass.1997), quoting Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed.Cir.1997).

While I am persuaded that Fiers and Remaut did not know the precise parameters of P_LO_L, it is clear that

they did know that P_LO_L encompassed the *Hinc* II site at -36 to -31, and designated (if not very clearly) the *Hinc* II site as the landmark for counting purposes. This is demonstrated by the reference in the patent specifications to the *Hae* III- *Eco* RI converted site as being "about 150 nucleotides downstream from P_L." '702 patent, col. 10, line 11. FN14 (It is in fact 149 base pairs downstream, close enough to be "about"). Because the *Hinc* II cut site is between nucleotides -34 and -33, a person skilled in the art would have recognized that Fiers and Remaut intended nucleotide -33 to be the starting point for counting.

FN14. In a 1987 Amendment, Biogen stated that the *Hinc* II site served to "define" the P_L promoter, although it mistakenly described the converted *Eco* RI site as being approximately 140 base pairs downstream from *Hinc* II. Despite the discrepancy, I agree with Biogen that one skilled in the art would have understood that the *Hinc* II site was being used as a landmark to demarcate P_LO_L. Biogen Brief, at 25-26.

From a 1980 perspective, the most plausible reading of the disputed claim language describes a plasmid vector consistent with Figure 6, containing P_L O_L and an endonuclease recognition site located at or downstream from the *Hae* III site at 73.1% of phage (lambda), within 300 base pairs of the *Hinc* II site (counting from base pair -33), and prior to any sequences of (lambda) DNA found downstream of *Hae* III. The *Hae* III site, in other words, "defines the downstream end of the contiguous (lambda) DNA of Figure 6." Amgen Surreply Brief, at 7. This reading is grammatical. It gives the word "downstream" its natural meaning as a modifier of the term "sequences of (lambda)>>>>>>>>> DNA," while recognizing the dangling modifier "in said DNA sequence" as a reference to "plasmid vector," the subject of the sentence. FN15 It also comports with the prosecution history of the '702 patent. Biogen's original patent application was rejected several times by the PTO because of its descriptive inadequacy. On June 27, 1988, Biogen offered a "compromise" amendment that purported to "recite the specific structure of the plasmid vectors of the application," FN16 by adding the contested language "located between P_LO_L and any sequences of (lambda) DNA downstream of the *Hae* III site at 73.1% of bacteriophage (lambda) in said DNA sequence" as a limitation to claim 1.

FN15. The identical phrase, "said DNA sequence," is used earlier in the sentence to refer to "plasmid vector."

FN16. June 27, 1988 Amendment, at 6.

According to what Biogen told the PTO, the new limitation meant that "each plasmid of the application contains the P_LO_L- *Eco* RI modified (lambda)>>region of the pPLa23, as depicted in Figure 6." June 27, 1988 Amendment, at 8.FN17 In Figure 6, the (lambda) region is shown as spanning the sequence of nucleotides running from the *Bg* III site to the *Hae* III site (-133 to +129).FN18 As Biogen explained to the PTO,

FN17. Biogen went on to tell the PTO that "the substitute claims identify a structural characteristic of the plasmids of the invention." Id. at 9.

FN18. When the plasmid vector is constructed, the *Hae* III site is converted to an *Eco* RI site, and the *Bg* III site is converted to a *Sau* 3A site.

[a] person of skill in the art, employing the methods disclosed in the specification as filed, would not place a

recognition site at any location other than in the region identified more precisely by the substitute claims. The application does not refer to any site in the natural (lambda) sequence "a short distance downstream from P_L" other than the *Hae* III site.

June 27, 1988 Amendment, at 8-9.

Seen in the context of the prior art, Fiers' and Remaut's invention constituted a progression and improvement on the work that their predecessors had done using the P_LO_L sequence of (lambda) DNA. Fiers and Remaut had constructed what at the time was the shortest (and therefore most efficient) sequence of its type.FN19 That this is what Fiers and Remaut thought was the essence of their invention is confirmed by the fact that every one of the plasmid vectors described in the claims specifications contains the entire, intact (lambda) DNA sequence shown in Figure 6. Amgen Brief, at 8. FN20 Cf. Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1480 (Fed.Cir.1998) (a limited disclosure may serve to narrow the permissible breadth of a patent's claims).FN21

FN19. With the exception of Horn and Wells, Fiers and Remaut were the first to use the *Hae* III site as a potential end site for the P_LO_L vector. All earlier sequences using P_LO_L had placed the endonuclease recognition site further downstream. For a discussion of the Horn and Wells plasmid vector pRW601, see Biogen, Inc. v. Amgen Inc., 973 F.Supp. 39 (D.Mass.1997).

FN20. As Biogen, at page 9 of the June 27, 1988 Amendment, stated: "[e]ach of the plasmid constructions of this application utilizes the same regions of phage (lambda) and the same operative site, *Hae* III (reconstructed to *Eco* RI)." Biogen's complaint that Amgen reads its patent as covering only endonuclease recognition sites inserted at *Hae* III does not fairly characterize Amgen's position. As Amgen makes clear, the *Hae* III site is merely the most upstream location claimed for the location of an endonuclease recognition site. As written, "the claims allow the insertion of a variety of endonuclease recognition sites to be located downstream of the P_LO_L- *Eco* RI modified (lambda) DNA region of Figure 6.... The only limitation is that to fall within the claims the endonuclease recognition site must be downstream of the Figure 6 (lambda) DNA and not extend further than 300 base pairs downstream of P_LO_L ." Amgen Surreply Brief, at 10.

FN21. I agree with Amgen that there is nothing in the patent specifications that teaches "trimming" of the desired (lambda) DNA sequence to less than the entire (lambda) DNA segment depicted in Figure 6. See Amgen Surreply Brief, at 12-15.

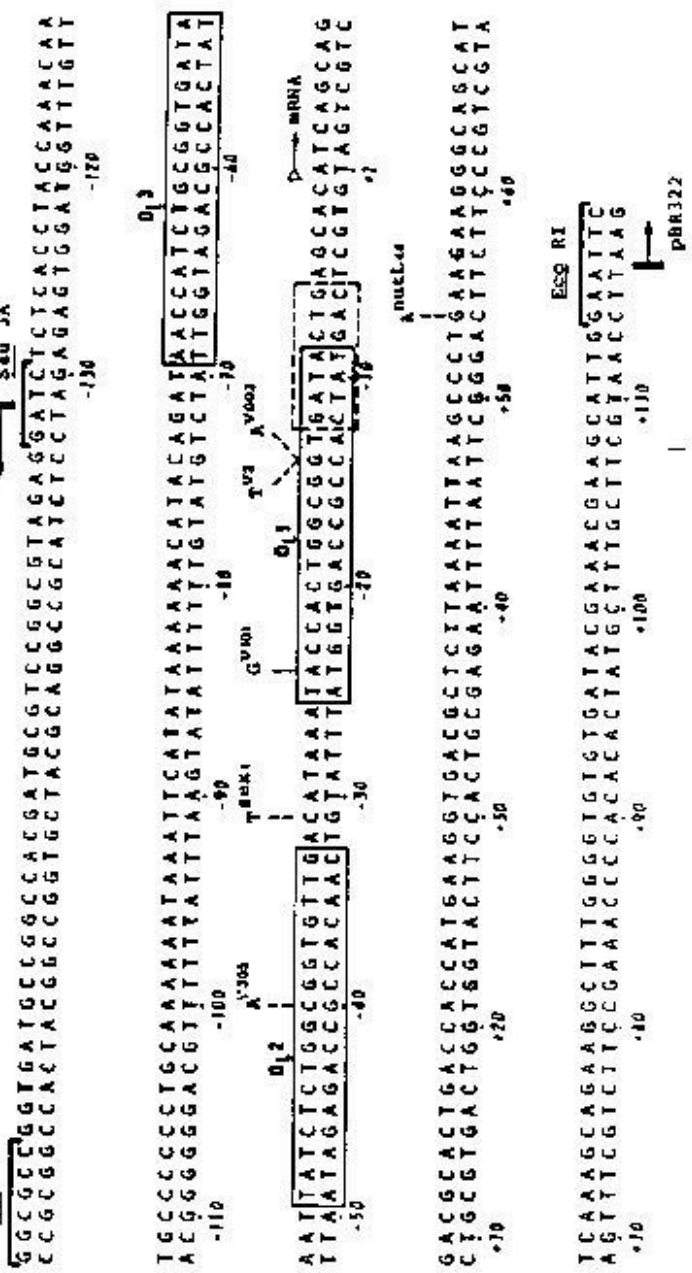
CONSTRUCTION

For the foregoing reasons, I construe claim 1 of the '702 patent as follows. To be covered by the patent, a plasmid vector must contain the entire P_LO_L of bacteriophage (lambda) as represented in Figure 6 of the patent and at least one endonuclease recognition site inserted at the converted *Hae* III site at 73.1% of bacteriophage (lambda) or at another site downstream of *Hae* III, said endonuclease recognition site being within 300 base pairs of the *Hinc* II site at -33, and prior to any sequences of (lambda) DNA downstream of the *Hae* III site.

SO ORDERED.

EXHIBIT 1

FIG.6



D.Mass.,1998.
Biogen, Inc. v. Amgen, Inc.

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