United States District Court,
D. Massachusetts.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY and,
v.
SYSTEMS, INC.

Civil Action No. 04-10884-RGS

Aug. 7, 2007.

Background: Patent owner and its licensee brought action alleging that competitor's cancer treatment drug violated patent asserting ownership of antibody. Court set forth to construe contested claims.

Holdings: The District Court, Stearns, J., held that:
(1) phrase, "tissue specific mammalian cellular enhancer," meant DNA sequence in mammalian cell that functioned to greatly increase transcription in specific tissue-type or cell-type, but which barely worked in other tissue or cell-types, or did not work at all;
(2) phrase, "enhancer element at a site within an active region of said vector sufficiently close to said transcription unit to enhance production of mRNA independent of its orientation and position within said active region," meant enhancer element that was inserted into active region of vector at site close enough to transcription unit to enhance production of mRNA, and was operative in either position, upstream or downstream, and in either orientation with respect to the transcription unit; and
(3) phrase, "at least a portion of," meant at least part of.

Ordered accordingly.

4,663,281. Construed.

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MEMORANDUM AND ORDER ON CLAIM CONSTRUCTION

STEARNS**, District Judge.**

On May 4, 2004, the Massachusetts Institute of Technology (MIT) and its licensee, Repligen Corp. (Repligen), filed suit against ImClone Systems, Inc. (ImClone), alleging that ImClone's manufacture of the cancer-fighting drug Erbitux violates U.S. Patent No. 4,663,281, "Enhanced Production of Proteinaceous Materials in Eucaryotic Cells" (the '281 patent). Before the court are the parties' briefs on claim construction. On July 26, 2007, the court heard oral argument in a special sitting at the Springfield,

Massachusetts Federal Courthouse.

BACKGROUND

The '281 patent teaches a method of using recombinant DNA technology to produce copious amounts of protein antibodies. In the early 1980's, MIT Professors Dr. Stephen Gillies and Dr. Susumu Tonegawa (a Nobel Laureate) discovered that certain animal cells are prolific protein producers because they contain "enhancer elements" in their natural genome. Enhancer elements are DNA sequences that increase transcription. FN1

FN1. Transcription is the process by which DNA sequences are converted into messenger ribonucleic acid (mRNA), which contains the "blueprint" for producing proteins.

During their investigation, Dr. Gillies and Dr. Tonegawa identified the enhancer element responsible for the production of immunoglobulin heavy chains. They also recognized that cellular enhancers differed from previously identified viral enhancers in being "cell-specific." Unlike viral enhancers, which stimulate transcription in all cells, cellular enhancers do so only in certain cells and tissues.

Dr. Gillies and Dr. Tonegawa developed a new method for generating large quantities of proteins in mammalian cells by isolating cellular enhancers and joining, or "ligating" them, with transcriptive DNA. The "recombinant" DNA is incorporated into a vector, such as a plasmid, and "transfected" into a mammalian cell line derived from the same tissue type as the enhancer's host cell. The resulting "cell transformant" is then used to culture the cell line that generates the desired protein.

The invention had a revolutionary impact on the pharmaceutical industry because of its ability to express protein antibodies in commercial quantities. FN2 Among the invention's progeny is Erbitux, the drug manufactured by ImClone that is at the heart of this litigation. Erbitux is used to treat patients with metastatic colorectal cancer. The majority of colorectal cancer patients have tumors that express EGFR, the human epidermal growth factor receptor. Figure 10 of the ' 281 patent is an illustration of the nucleotide sequences of DNA that comprise the enhancer element for the pertinent immunoglobulin heavy chain. The DNA sequence that underlies Erbitux is a subpart of the larger sequence disclosed in Figure 10.

FN2. This is not meant to understate the contribution made by Dr. Gillies and Dr. Tonegawa to the advancement of science. According to plaintiffs' counsel at oral argument, the article they published in *Cell* magazine describing the invention is one of the most frequently cited publications in the field of biological science.

In 1989, Dr. Gillies used the invention disclosed in the '281 patent to develop a chimeric antibody FN3 known as "C225," together with a cell line for producing C225 in large quantities. The "Gillies Cell Line" binds to the extracellular domain of EGFR. According to the Complaint, ImClone infringes the ' 281 patent by using the Gillies Cell Line to make Erbitux.

FN3. A chimeric antibody is one that combines genes from different animal species.

Claim Construction

[1] [2] [3] "It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed.Cir.2005) (internal quotation marks and citation omitted). Accordingly, any infringement analysis necessarily begins

with the construction of the claims in the patent that are alleged to have been infringed. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1454 (Fed.Cir.1998) (en banc). Claim construction is a question of law for the court's determination. Markman v. Westview Instruments, Inc., 52 F.3d 967, 970-971 (Fed.Cir.1995) (en banc), aff'd, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). The court will construe only those terms "that are in controversy, and only to the extent necessary to resolve the controversy." Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed.Cir.1999).

[4] [5] [6] The court is to give the words of a claim the "meaning that the term[s] would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." Phillips, 415 F.3d at 1312, citing Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1116 (Fed.Cir.2004). The court will look first to a patent's specification when construing a claim. Because the purpose of the specification is to teach one skilled in the art to replicate the invention, the specification will be in most cases " 'dispositive; it is the single best guide to the meaning of a disputed term.' " Phillips, 415 F.3d at 1315, quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). A court may also seek guidance from the patent's prosecution history. *See* Phillips, 415 F.3d at 1317, quoting Markman, 52 F.3d at 980. While it may not be as reliable as the specification, the prosecution history "can often inform the meaning of the claim languageby demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." Phillips, 415 F.3d at 1317.

Disputed Terms

A. Tissue Specific FN4

FN4. ImClone identifies the term "tissue specific" for purposes of claim construction. Plaintiffs correctly argue that the term to be construed is "tissue specific mammalian cellular enhancement."

[7] The specification teaches that
[t]he enhancer sequences function to greatly increase transcription, but only in a specific tissue-type or cell-type; the enhancer function of the sequences is greatly diminished or totally absent in other types of cells.

'281 patent, Col. 5, ll. 63-67. The specification further provides that
[s]ince each of the cell enhancers useful in the invention are tissue-type or cell-type specific, they typically do not function, or function only at very low or undetectable levels when transfected into cell lines derived from tissues different from the tissue in which they are normally active. In some cases, the enhancers are cell-type specific and will not function if placed in a different cell-type, even one derived from the same tissue type.

Id., Col. 6, ll. 23-31. In Example III-which bears the subheading "Cellular Enhancer Genes are Tissue Specific"-the inventors concluded that the enhancer element of the immunoglobulin heavy chain gene is functional only in lymphoid cells, and not in L cells, which are non-lymphoid in nature. *See* id., Col. 11, ll. 50-56.
Plaintiffs essentially track the language of the specification in their proffered construction,FN5 while ImClone argues that the court should strike the term "cell-type" from the claim and add language to specify that transcription is greatly increased only in a "specific tissue type in which transcription is normally active." FN6

FN5. Plaintiffs contend that the phrase "tissue specific mammalian cellular enhancer" should be construed as specifying
DNA sequences in a mammalian cell that function to greatly increase transcription, but only in a specific tissue-type or cell-type; the enhancer function of the sequences is greatly diminished or totally absent in

other tissue or cell types.

They additionally state that though repetitive, the following sentence could be added to the construction. Such DNA sequences typically do not function, or function only at very low or undetectable levels when transfected into cell lines derived from tissues different from the tissue in which they are normally active.

FN6. Defendants contend that the term should be construed as
[t]he enhancer sequences function to greatly increase transcription, but only in a specific tissue-type in which transcription is normally active; the enhancer function of the sequences is greatly diminished or totally absent in other types of cells in which transcription is not normally active.

The crux of ImClone's argument is that plaintiffs' proposed construction renders the claim indefinite and poses an impossible burden for a defendant attempting to establish non-infringement. According to ImClone, plaintiffs' failure to identify "the tissue" to which an enhancer must be "specific" enables plaintiffs to manipulate the testing of a drug like Erbitux for litigation purposes. Because plaintiffs define "tissue specific" to mean only that the cellular enhancer greatly increases transcription in some tissues and cell-types and not others, ImClone argues that to make a case of infringement, plaintiffs need simply to find one cell (out of an infinite number of cells) in which the enhancer does not work (including cells that are dead).FN7

FN7. According to ImClone, the term "tissue specific" means that the enhancer must function only in "a" specific tissue-type or cell-type, that is, the biological host in which the enhanced protein is normally expressed. It argues that under plaintiffs' theory, testing could be performed with a virtually infinite number of tissue or cell-types without any final determination of whether a particular enhancer was or was not "specific," and therefore protected by the '281 patent.

ImClone additionally accuses plaintiffs of improperly "cherry-picking" the infringement test. Rather than using the same types of tissues for comparison as were disclosed in the '281 patent (lymphoids and fibroblasts), plaintiffs' litigation test is based on a type of cell known as the "293 cell," which, according to ImClone, is not mentioned in the '281 patent or in any of the contemporaneous peer-reviewed literature. Moreover, 293 cells purportedly contain foreign viral DNA that unpredictably affects the transcription rate of transfected genes. ImClone argues that plaintiffs should not be permitted to rely on a test specifically devised to bolster their infringement case, when the test disclosed in the '281 patent would result in the opposite showing. According to ImClone, the substitution of tests contradicts the teaching of Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332 (Fed.Cir.2003). The Federal Circuit in Honeywell considered a patent dispute related to a polyester based yarn that is converted into cord that is used to reinforce automobile tires. The yarn specimen could be produced in four possible ways, known as "sample preparation methods." The parties argued over whether the claims required a particular sample preparation method when determining the meaning of the claim term: "melting point elevation" (MPE). *See* id. at 1339. Depending upon which sample preparation was used, the MPE for a given sample could vary greatly. Id. at 1336. The Federal Circuit held that the claims were "insolubly ambiguous, and hence indefinite." Id. at 1340.

Because the sample preparation method is critical in determining MPE, processes utilizing different sample preparation methods will produce different yarns. Without knowing which sample preparation method to use, one cannot discern whether a yarn was produced using the claimed process. Under the "any one

method" construction, the testing results will necessarily fall within or outside the claim scope depending on the sample preparation method chosen. Competitors trying to practice the invention or to design around it would be unable to discern the bounds of the invention.

Id. at 1341.FN8

FN8. It should be noted that in Honeywell, the dispute involved issues of patent validity and not claim construction.

Finally, ImClone argues that while the "Larger Segment" of the nucleotide sequence shown in Fig. 10 of the '281 patent may be tissue specific, the "Erbitux Segment" is not. According to ImClone, the Larger Segment's tissue specificity results from tissue specific repressive elements that are not incorporated in the Erbitux Segment.

At bottom, whatever their weight, ImClone's arguments go to the issues of patent validity and infringement, and have no real bearing on claim construction. They are, in other words, arguments to be made to the jury and not to the court. Plaintiffs' proposed construction tracks the language of the specification, and is not outside the bounds of the claim itself. *See* Honeywell, 341 F.3d at 1341. Moreover, there is nothingin the ' 281 patent to justify ImClone's proposed importation of the limitation-"in which transcription is [or is not] normally active"-into the claim, or to warrant the deletion of the words "celltype." FN9 Therefore, the court will construe the term "tissue specific mammalian cellular enhancer" to mean "a DNA sequence in a mammalian cell that functions to greatly increase transcription in a specific tissue-type or cell-type, but which barely works in other tissue or cell-types, or does not work at all."

FN9. While the court has located no case specifically on point, the idea of deleting a substantive term from a claim seems counterintuitive. The court's task under Markman is to construe "the words of the claims themselves," Innova, 381 F.3d at 1116, not to ignore them.

B. "Enhancer element at a site within an active region of said vector sufficiently close to said transcription unit to enhance production of mRNA independent of its orientation and position within said active region."

[8] Plaintiffs propose that this term be construed according to its plain meaning as "an enhancer element that is inserted into an active region of the vector at a site close enough to the transcription unit to enhance production of mRNA, and is operative in either position (upstream or downstream) and in either orientation with respect to the transcription unit." ImClone argues that the characteristics of orientation independence and proximity to the transcription unit were well known in the prior art. That may be true, but prior art is not at issue for present purposes. Accordingly, the claim will be construed in terms consistent with those proffered by plaintiffs.

C. "Vector"

There is no real dispute about the interpretation of this term, whose meaning has been long established in the lexicon of molecular biologists. Consequently, the court sees no need to elaborate.

D. "At least a portion of"

[9] Claim 17 reads: "The vector of claim 10 wherein said enhancer element comprises at least a portion of the nucleotide sequences set forth in FIG. 10." Claim 22 reads: "The transformant of claim 20 wherein said enhancer element comprises at least a portion of the nucleotide sequences set forth in FIG. 10." There is no indication in the patent that this phrase was meant to have anything other than its normal meaning of "at

least a part of."

E. "Recombined therewith"

This term appears in claims 10 and 18, both of which require that the tissue specific mammalian cellular enhancer be "recombined" with the DNA containing the transcription unit for the protein of interest. According to plaintiffs, the term means the melding of two separate pieces of DNA sequences into one through an enzymatic reaction known to molecular biologists as "ligation." Plaintiffs maintain that the words "ligation" and "recombined" are used interchangeably throughout the specification. ImClone, on the other hand, argues that it does not matter whether the transcription unit and enhancer were separately excised, ligated together, and then recombined into the vector, or whether they were excised together from a single transcription unit. This "dispute" is not relevant for purposes of claim construction (or any other purpose the court can discern), as it does not affect the plain meaning of the term "recombined therewith."

CONCLUSION

The claim terms at issue will be construed for the jury and for any other purpose in this litigation in a manner consistent with the above rulings of the court.

SO ORDERED.

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