United States District Court,
N.D. California.

EXONHIT THERAPEUTICS S.A., a French societe anonyme, and Exonhit Therapeutics, Inc., a Delaware corporation,
Plaintiff.
v.
JIVAN BIOLOGICS, INC., a Delaware corporation,
Defendant.

No. C 07-01427 WHA

March 7, 2008.

William E. Thomson, Clive Miles McClintock, Wei-Ning Yang, Hogan & Hartson L.L.P., Los Angeles, CA, for Plaintiff.

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CLAIM CONSTRUCTION ORDER

WILLIAM ALSUP**, District Judge.**

INTRODUCTION

This is a claim construction order for United States Patent No. 6,881,571. This order addresses one phrase selected for construction by the parties. A technology tutorial, as well as a full round of briefing preceded this order.

STATEMENT

This claim construction order comes after a convoluted and prolonged claim construction briefing. Plaintiff Exonhit Therapeutics, Inc., is the assignee of the '571 patent. In their joint claim construction and prehearing statement, the parties identified four terms that required construction. Defendant Jivan Biologics, Inc., then withdrew its proposed constructions for all four claims and agreed to all constructions provided by plaintiffs. At this time, defense counsel also indicated that its client was short on funds and no longer able to afford a protracted litigation. Defendant then admitted that under the claim constructions agreed to that some of its products infringed the '571 patent. At this point, it seemed as though the only remaining loose end was to calculate a proper level of damages. With this in mind, defendant was ordered to produce all documents necessary to calculate damages and to stipulate to infringement. After the further discovery, however, the parties realized that there was still a dispute over the scope of infringement due to a disagreement over the meaning of one of the terms originally acquiesced to by defendant. Defendant was then allowed to withdraw its stipulation to construction and challenge any term whose meaning remained in dispute. This claim

construction order ensued.

The patent itself is directed to a method for identifying and screening differences in gene expression that are associated with physiological conditions. DNA consists of a long polymer of simple units called nucleotides. Each nucleotide in human DNA has one of four characteristic chemical structures, or bases: adenine, cystosine, guanine, or thymine. It is the sequence of these bases that encodes information about the functioning of living organisms. The bases interact with one another to create a structure known as a double helix consiting of two intertwined strands of DNA. These two strands are perfectly complementary to one another, such that adenine bonds with thymine and cytosine bonds with guanine.

Genes are specific regions in an organism's DNA that contain the instructions necessary to make proteins in a body. The first step in making a protein is copying the gene from DNA to RNA, or ribonucleic acid, through a process called "transcription." The initial RNA transcript is known as pre-mRNA. While RNA is similar to DNA, its characteristic chemical structure differs slightly in that the base thymine of DNA is replced by uracil in RNA. Although RNA is capable of binding to DNA to form a double helix, it usually exists in a single strand. The second step in making protein is physically cutting out portions of the pre-mRNA that are unnecessary for the protein synthesis. This process known as "splicing" results in a shortened RNA molecule, mRNA, which specifies the required structure to code the protein. The third and final step in making protein is actually using the spliced RNA molecule to create the protein in a process called "translation."

The invention of the '571 patent concerns the second step for making the protein, or "splicing." When the pre-mRNA is spliced certain portions of the sequence are cut out. The term "intron" refers to those regions of the pre-MRNA that are spliced out of the transcription process during the formation of the final mRNA molecule and ultimately not translated into a protein. The term "exon" refers to those regions of the pre-mRNA that are transcribed during the formation of the final mRNA molecule and ultimately used in the creation of the protein. The decision of which portions of the pre-mRNA to cut out and which to retain, however, may vary. RNA can be spliced differently in different tissues or under different physiological conditions (*e.g.,* toxicity) to code for a variety of different proteins. This process is known as "alternative splicing."

Spliced RNA can be used as a template to create matching DNA through a process called "reverse transcription." When a spliced mRNA molecule is reverse transcribed to create a DNA sequence, the resulting DNA molecule is named "complementary DNA" or "cDNA." cDNA is useful for scientists because it contains the same sequence as the spliced mRNA, but with the properties of a DNA molecule. The mRNA can bind, or "hybridize," with the cDNA to form different chemical structures. The '571 patent explains a method for identifying regions of genetic code that may be spliced differently under varying physiological conditions. Alternative splicing events may be identified by analyzing the differences between hybridized RNA or cDNA molecules obtained from various splicing events occurring under different physiological conditions (col.9:38-41).

When two samples of RNA or cDNA result from a differential splice they typically have a majority of sequences in common, but because at least one of the samples has been spliced differently than the other, the samples are not fully complementary. When such samples hybridize with one another, the result is a partially hybridized fragment consisting of portions of the sequence that have hybridized and portions for which have been retained in one strand and spliced out in the other (Fig.6A). The portions of the strand that have not hybridized, or "loops," may be identified and cloned (col.12:28-30).

Cloning these loops creates structures that are complementary to alternative exons and introns of the two samples used in the hybridization. These structures allow the junction sequences formed by the deletion of an exon or intron at the splice site of the RNA or cDNA missing the sequence to be identified (col.8:57-62). Using this method for identifying alternative splicing events allows the user to create a set of two types of probes, one to query exons or introns and one that is specific to the junction (*i.e.,* where the splicing event occurs) formed by the spliced sequences. These probes allow the user to specify future alternative splicing events by comparing the probes to the splicing events (col.12:45-61).

Different probes may then be collected to form large libraries of sequences of nucleic acids that represent qualitative differences occurring between two conditions created by varying physiological conditions. The '571 patent teaches the use of a probe (containing the library of sequences) attached to a solid support, such as a membrane or chip, that can detect for any given splicing event occurring in both the reference unspliced form of mRNA (*i.e.,* the loop portion) and the junction region between the two domains separated by the spliced form of the mRNA (col.16:10-18). When the probe is exposed to a sample containing an unknown gene sequence, only those sequences that are complementary to the sequences of the probe will hybridize. Those sequences that hybridize may then be tracked using known labeling techniques in the prior art (col.17:55-64). By identifying those sequences in the probe that hybridize, the identity of the unknown gene sequence can be determined and the gene sequence can be screened for the physiological condition (*e.g.,* toxicity) that was used to develop the probe library.

This action was filed on March 12, 2007, alleging that defendant infringed each of the claims in the '566 patent. A technology tutorial was held on January 9, 2008, but no claim construction hearing was held. Trial is set for June 23, 2008.

ANALYSIS

1. LEGAL STANDARD.

Claim construction is a matter of law to be decided by a judge, not a jury. Markman v. Westview Instruments, Inc., 517 U.S. 370, 388, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Courts must give words in the claims their ordinary and customary meaning, which "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." Phillips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed.Cir.2005) (en banc).

Where this ordinary and customary meaning is not immediately clear, courts must primarily look to intrinsic evidence (*i.e.,* the claims, the specification, and the prosecution history) to determine the meaning. Id. at 1314. With respect to the specification, although a difficult task, a court must distinguish "between using the specification to interpret the meaning of a claim and importing limitations from the specification into the claim." Id. at 1323. The latter is not permissible.

Although courts have the discretion to consider extrinsic evidence, including expert and inventor testimony, dictionaries and scientific treatises, such evidence is "less significant than the intrinsic record in determining the legally operative meaning of claim language." Id. at 1317 (citation omitted). "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." Id. at 1315. "Nonetheless, any articulated definition of a claim term ultimately must relate to the infringement questions it was intended to answer." E-Pass Tech., Inc. v. 3Com Corp., 473 F.3d 1213, 1219 (Fed.Cir.2007) (citing Wilson Sporting Goods Co. v. Hillerich & Bradsby Co.,

442 F.3d 1322, 1326 (Fed.Cir.2006)).

2. DISPUTED CLAIM TERM.

Plaintiffs and defendant have stipulated to all but one phrase: "region of variability." The other terms whose meaning have been stipulated to have not been vetted by the Court and should not be considered authoritative for any future litigation involving the patent. Claim 1 is representative of the entirety of claims asserted. It recites (col.49:40-63):

A device for identifying at least one differentially spliced gene product,

wherein said device comprises a solid support material and single-stranded oligonucleotide of between 5 and 100 nucleotides in length attached to said support material,

wherein said oligonucleotides comprise at least a first and a second oligonucleotide molecule arranged serially on the support material,

wherein said first oligonucleotide molecule comprises a first sequence that is complementary to and specific for an exon or an intron of a first gene, and wherein said first sequence corresponds to a *region of variability* in at least one product of said first gene due to differential splicing,

and wherein said second oligonucleotide molecule comprises a second sequence that is complementary to and specific for an exon-exon or exon-intron junction region of said first gene,

and wherein said second sequence corresponds to a *region of variability* in at least one product of said first gene due to differential splicing, said device allowing, when contacted with a sample containing at least said device allowing, when contacted with a sample containing at least one nucleic acid molecule under conditions allowing hybridization to occur, the determination of the presence or absence of said differentially spliced gene product.

A. "Region of Variability."

Plaintiffs propose that "region of variability" should mean "a segment of DNA within a gene or gene product that serves one role (exon, intron, exon-intron junction or exon-exon junction) with respect to one isoform of the gene product and a different role with respect to another isoform of the gene product." Defendant objects to the inclusion of "exon-intron junction or exon-exon injunction" in the definition of the types of roles that the segment used on the probe may take on.

The term "region of variability" is meant to convey that a given segment of a gene may serve different roles depending on how that gene is spliced in the resulting isoform of the gene product. Segments of DNA are retained in some gene product isoforms and spliced out of others. Some isoforms of the gene may include the sequence (*e.g.,* exon), while other isoforms of the gene may have cut the sequence out (*e.g.,* intron). Accordingly, the role of the given segment varies with respect to the differing isoforms of the gene product, giving rise to a region of variability.

The only question is whether this region of variability includes exon-intron junctions or exon-exon junctions as argued by plaintiffs. This order finds that it does. The specification explains, "[t]his variant is advantageous in that it reveals not only alternative introns and exons but also, and within a same nucleic

acid library, specific junctions formed by deletion of and exon or an intron" (col.8:61-63). The specification further teaches (col.12:50-55):

Cloning these fragments generates an alternative splicing library in which, for each splicing event, positive and negative fingerprints are present. This library therefore gives access not only to alternative exons and introns but also to the specific junctions formed by the excision of these spliced sequences.

In this respect, the specification specifically recognizes that the libraries created to screen for specific physiological conditions include the specific sequences associated with specific junctions created by the splicing event. The specific sequences screened for may be an intron in one isoform of a gene or an extron in another isoform of a gene depending on the splicing event. These same sequences may also be junctions in yet another isoform of the same gene. It is these variations that give rise to a "region of variability." Defendant points to no language from the claims, specification, or any expert testimony that suggests that the region of variability should be limited to only introns and exons.

Accordingly, this order finds that "region of variability" means "a segment of DNA within a gene or gene product that serves one role (exon, intron, exon-intron junction or exonexon junction) with respect to one isoform of the gene product and a different role with respect to another isoform of the gene product."

CONCLUSION

This claim construction order will govern for the remainder of this action.

IT IS SO ORDERED.

N.D.Cal.,2008.
Exonhit Therapeutics S.A. v. Jivan Biologics, Inc.