IN THE UNITED STATES DISTRICT COURT

FOR THE WESTERN DISTRICT OF WISCONSIN

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DIGENE CORPORATION,

OPINION AND ORDER

Plaintiff,

07-C-0022-C

v.

THIRD WAVE TECHNOLOGIES, INC.,

Defendant.

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In this civil case for patent infringement, plaintiff Digene Corporation is alleging infringement by defendant Third Wave Technologies, Inc. of plaintiff's U.S. Patent No. 5,643,715, directed to nucleic acid hybridization probes for human papillomavirus types, particularly human papillomavirus type 52, and methods for employing such probes. The case is before the court on plaintiff's motion for reconsideration of four claim terms that were among the eleven I construed in an order entered on July 23, 2007. Order, dkt. #54. The four terms whose constructions plaintiff challenges are (1) "HPV 52 DNA labeled with a detectable label"; (2) "HPV 52 DNA consists of all or a fragment of an HPV DNA"; (3) "HPV 52 hybridization probe"; and (4) "HPV DNA hybridization probe." (Plaintiff treats the latter two terms as involving the same questions and I will do the same.)

Defendant objects to the court's hearing what it characterizes as an untimely motion for reconsideration filed by plaintiff, particularly one unaccompanied by any evidence that could not have been discovered before the claims construction hearing. I would agree with defendant and deny reconsideration of the constructions if plaintiff's only purpose were to reargue the constructions, but the truth is that plaintiff has a legitimate objection to the first construction. In deciding on a construction for this term, I relied on a misunderstanding of plaintiff's position. I understood plaintiff to be in agreement with the construction I adopted, which is "HPV 52 DNA labeled with a detectable label that is not DNA." The transcript shows that plaintiff never agreed to such a construction. In light of that mistake, I have taken a new look at the term in light of the parties' expanded briefing. Having done so, I continue to believe that the construction is valid, despite plaintiff's disagreement with it. It is not necessary to to amend the constructions given the other three claims that are the subject of plaintiff's motion because plaintiff has not shown that they are erroneous.

A. "HPV 52 DNA labelled with a detectable label"

The dispute between the parties turns on the nature of the detectable label on a hybridization probe. (The point of a hybridization probe is to detect the presence of a particular molecule and bind to it; because the binding itself cannot be seen, a label is used

to signal to the researcher that the binding has occurred and the molecule detected.). Plaintiff contends that a detectable label could be DNA and not necessarily HPV 52 DNA; defendant disagrees that it could be either. In support of its contention, plaintiff asserts that nothing in the patent or prosecution history says that the label cannot be DNA; the specification makes it implicit that DNA can be a detectable label because the specification refers to ligands, a term that encompasses DNA and any other molecule or atom that binds to something else; in addition, the patent explains that a probe may be labeled using radionucleotides, which are simply pieces of radioactive DNA; and persons of ordinary skill in the art would have known from articles published in 1988 or earlier that DNA could be used as a detectable label.

Defendant denies that the specification implies the use of DNA for a label; to the contrary, the specification's list of possible labels includes only those things that add a new detectable property to the DNA probe, which eliminates DNA as a candidate. It argues that construing the term to include DNA would be erroneous for a number of reasons, if only because it would read out of the claim the term "labeled," which has a meaning separate from "detectable label." Defendant takes issue with plaintiff's characterization of the pre-application articles, asserting that no person of ordinary skill in the art would have known from these articles that DNA could be used as a label for an HPV 52 DNA. Moreover, even if such persons would have understood as a general proposition that DNA could be used for

this purpose in some circumstances, they would not have read the term detectable label in the '715 patent as referring to DNA.

The claim term, "HPV 52 DNA labeled with a detectable label" is used in independent claims 18, 21, 24 and 26. (Claim 18 is directed to a hybridization probe; claim 21 is directed to a hybridization probe composition and claims 24 and 26 are method claims.). Claim 18 is representative of the four claims. It reads as follows:

> An HPV 52 hybridization probe comprising a member selected from the group consisting of
> (i) HPV 52 DNA labelled with a detectable label, and
> (ii) HPV 52 RNA labelled with a detectable label,
> wherein the length of the HPV 52 DNA or HPV 52 RNA is between approximately 15 and 8000 necleotide bases,
> wherein the HPV 52 DNA or HPV 52 RNA consists of all or a fragment of an HPV DNA, wherein the HPV DNA cross-hybridizes to the HPV portion of clone pCD15 to greater than 50% under moderately stringent conditions,
> wherein the HPV 52 RNA consists of all or a fragment of an HPV RNA, wherein the HPV RNA cross-hybridizes to the HPV portion of clone pCD15 to greater than 50% under moderately stringent conditions,
> wherein the HPV 52 DNA and HPV 52 RNA do not hybridize to DNA from HPV types 1 through 51 under stringent conditions.

Claim 18 says nothing about the form the "detectable label" may take. However, the patent specification includes the following information:

> The polynucleotide or oligonucleotide probe may be labeled with an atom or inorganic radical, most commonly using radionucleotides, but also perhaps heavy metals. In some situations, it may also be possible to employ an antibody which will bind specifically to the probe hybridized to the single-stranded DNA. Oligonucleotide probe technology is disclosed by Szostak, J.W., et al., *Meth. Enzymol.* 68:419-428 (1979), incorporated by reference herein.

> More commonly, a radioactive label is employed, suitable radioactive labels including ^{32}P, ^{3}H, ^{14}C, ^{35}S, ^{125}I, or the like. Any radioactive label may be employed which provides for an adequate signal and has sufficient half-life. Other labels include ligands, fluorescers, chemiluminescers, enzymes, antibodies, and the like.

'715 pat., col. 10, lns. 35-48.

It is unnecessary to spend any time on plaintiff's first argument, that nothing in the patent specifications says that the detectable label could not be DNA, because it is irrelevant unless plaintiff can demonstrate that persons of ordinary skill in the art would have known that DNA *could* be a detectable label. I suspect that plaintiff makes this argument as part of its theory that even if the use of DNA as a label was not known at the time of the filing of the application, the patent specifications are open-ended enough to encompass the use of later-discovered materials for labeling. For reasons set out hereafter, I am not persuaded that DNA could ever be a label in the context of the '715 patent.

I turn then to plaintiff's second argument, which is that persons of ordinary skill would have understood in 1988 that because the specification refers to ligands and ligand is a term that encompasses DNA and any other molecule or atom that binds to something else, a detectable label could consist of DNA. This argument rests on the flawed syllogism that a ligand is a molecule; DNA is a molecule; DNA can be a ligand; the '715 patent says that a ligand can serve as a label; therefore, the patent anticipates that DNA can serve as a ligand. It is not necessary to decide whether DNA can ever be a label; I will assume that

there are circumstances in which such a use is not only possible but helpful to the researcher. It does not follow, however, that the '715 patent can be read to cover DNA as a label.

If all that is required for a "label" is a single-stranded DNA binding to another strand of DNA, then, according to the terms of the patent, the claimed DNA would always be "labeled" because HPV 52 DNA is made up of at least 15 nucleotides bound to each other. Such a reading would eliminate any independent meaning for the "labeled with a detectable label" language in the relevant patent claims. Or, to take another example of incoherence, a sequence that is not HPV 52 DNA could include a portion homologous to HPV 52 DNA. Could the non-homologous portion be characterized as the label and if so, would it come within the claim terms? And finally, if plaintiff is asserting that the patent claim could be read as suggesting the use of HPV 52 DNA as a "detectable label," how would plaintiff avoid the risk that the claim will be unpatentable because it would cover the wild form of HPV 52 DNA? (The full length of the genome could fall within the claim if "label" is construed to include DNA and part of the viral genome is called the label.). Would this make claim 18 fail because it can be read as extending to a naturally occurring organism which is inherently unpatentable?

The natural reading of the list of possible labels in the specification is that each adds a new detectable property to the DNA probe that would help probe users know when they

had detected HPV 52 DNA and not another form of DNA. This conclusion derives from the nature of the materials listed in the specification, all of which add a new property to the HPV 52 DNA that assists detection. For example, fluorescers emit light; heavy metals produce a change in electron density; radioactive labels give off radioactive signals; biotins, antibodies and ligands bind specifically to other molecules; and enzymes produce catalyzing reactions. By contrast, DNA does not add a new property to the HPV 52 DNA.

Plaintiff does not accept the proposition that the potential labels listed in the specification call for adding on a new property. It maintains. for example, that radioactive labels are not "added on," but are an integral part of the DNA bases within the oligonucleotides. It is true that once the nucleotides are made radioactive and reinserted into the DNA bases they form an integral part of those bases, but it does not follow that nothing has been added to them. After all, they do not start out as radioactive. They become so after a radioactive isotope such as ^{32}P is attached to them. In the same way, an antibody is "added" by attachment to a probe hybridized to single-stranded DNA and heavy metals and fluorescers are "added" to the probe. None of these is part of the original probe.

It is noteworthy that in denying that the HPV 52 DNA hybridization probe could include naturally occurring HPV 52 DNA, plaintiff points out that such "HPV 52 is not 'labeled' in any way—*nothing has been done to it to make it distinct from other, unlabeled naturally occurring HPV 52 in the sample."* Plt.'s Resp. Br., dkt. #65, at 14. (Emphasis added.) In

other words, plaintiff acknowledges that labeling consists of adding a distinctive new property to existing DNA.

Plaintiff argues that the court "should bear in mind that the DNA that can be part of a detectable label may or may not be HPV 52 DNA. *Only* the DNA considered part of the HPV 52 DNA needs 'to consist[] of all or a fragment of an HPV 52 DNA,' while the DNA that forms a detectable label can be any DNA." Plt.'s Br. in Supp. of M. for Recons., dkt. #57, at 7. Plaintiff adds that the detectable label is not constrained in the same way as HPV 52 DNA. Id. This is argument in the form of *ipse dixit.* Plaintiff does not refer to anything in the patent or prosecution history that supports such a reading of the patent; it does not explain why a person of ordinary skill would contemplate using DNA as a label for a detection probe designed to distinguish particular DNA types accurately; and it does not address the apparent conflict between the use of DNA for this purpose and the emphasis in the prosecution history on eliminating DNA fragments that could interfere with the detection process. E.g., FH 0202-03. Moreover, plaintiff leaves unexplained how an HPV 52 DNA probe would be "*labeled* with a detection label" if the label were DNA, that is, what would have been done to the probe to make it distinct from an unlabeled probe. If plaintiff believes that some portion of the HPV 52 DNA or of another form of DNA can act as the label, it must explain how the probe itself is labeled. It cannot read the word "labeled" out of the claim term without violating the rules of claim construction. Merck & Co. v. Teva

Pharma, USA, Inc., 395 F.3d 1396, 1410 (Fed. Cir. 2004) (claim construction should not render claim terms superfluous).

With the exception of claim 1 and dependent claims 2-7, which claim a recombinant DNA of HPV 52 comprising a cloning vector and HPV 52 DNA, all of the '715 patent claims are limited to HPV 52 DNA. I conclude that reading the claims as including a different form of DNA, even as a label, would be reading in something the inventor did not intend and the patent office did not authorize.

Plaintiff turns next to extrinsic evidence offered by an expert witness to the effect that persons of ordinary skill in the art would have read the patent as covering labels consisting of DNA. Such extrinsic evidence is not a starting point for claim construction, but becomes relevant only when intrinsic sources of evidence are inadequate. Phillips v. AWH Corp., 415 F.3d 1303, 1317-18 (Fed. Cir. 2005) (en banc) (in general extrinsic evidence is less reliable than patent and prosecution history). Although plaintiff has not shown that the intrinsic evidence is inadequate, I will consider whether the extrinsic evidence would change my view of the proper construction of the disputed term.

In fact, the evidence in question is of little help. The expert does not explain what he considers the necessary level of ordinary skill in the art or what the person of ordinary skill would have known in 1988. (Plaintiff suggests that the operative time is 1997, when the patent issued, but the law does not support the suggestion. Id. at 1312-13 ("We have

made clear, moreover, that the ordinary and customary meaning 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, i.e., as of the effective filing date of the patent application.").) The expert does not address the essential point, which is not whether DNA can ever be a detectable label, as a general proposition, but whether a person of ordinary skill in the art would understand from reading the '715 patent that it is claiming the use of DNA as a detectable label.

In addition to its expert's opinion, plaintiff has cited two publications that it contends described the use of DNA as a label in a probe before 1988, one of which is an article by J.E. Arrand, "Preparation of Nucleic Acid Probes," Chapter 2 of Nucleic Acid Hybridization, B.D. James and S.J. Higgins, Eds., IRL Press, Washington, D.C. 1985. The patent applicant cited the reference for its explanation of choosing a piece of DNA for use as a probe and its protocol for eliminating fragments that may cross-hybridize non-specifically with the DNA or RNA being probed, FH 0203; he did not cite it for its explanation of the use of DNA as a label. Id. The article's author describes adding DNA onto the 3' ends of DNA fragments and does not suggest that the addition of DNA to probe sequences is undesirable in and of itself. Instead, the author says that the content of the DNA sequences must be considered carefully. FH 216. Given the article's focus on radioactive labeling methods, FH 0219, it falls short of showing that persons of ordinary skill would have known that DNA could be used as a label for an HPV 52 DNA

hybridization probe. To take an example, plaintiff does not explain how adding DNA to the 3' ends of DNA fragments proves that the author was describing the use of DNA as a label or was even aware of such a use. Instead, it appears that the end labeling was to be done with radioactive phosphorous isotope ^{32}P. FH 0222.

Plaintiff cites another article, this one by C. Vinson, et al, "In Situ Detection of Sequence-Specific DNA Binding Activity Specified by a Recombinant Bacteriophage," Gene & Bacteriology Development 2:801-06 (1988), which refers to using a specific DNA sequence as a ligand. Id. at 801. Although this article was published before the application for the '715 patent was filed, nothing in it suggests using DNA as a ligand for labeling purposes.

I conclude that plaintiff has failed to show that the construction I adopted for the claim term "HPV 52 DNA labeled with a detectable label" is erroneous. Therefore, its motion for reconsideration will be denied.

B. "HPV 52 DNA consists of all or a fragment of an HPV DNA"

Objecting to the construction of this term as meaning that "the HPV 52 DNA consists of all or a fragment of one HPV DNA and does not contain any other DNA," plaintiff seeks reconsideration out of concern that the jury will be confused if the construction does not acknowledge the inevitable mutations and variability that are present

in any DNA sequence. Plaintiff fears that in the absence of such acknowledgment, the jury may focus on the exactness of the match between the HPV DNA nucleotide base sequence and a known sequence of HPV DNA, rather than on whether cross-hybridization occurs under moderately stringent conditions.

Plaintiff's fears are unfounded. Nothing in the court's construction suggests or requires exclusion of mutations or subtypes. If the HPV genome from which the HPV 52 DNA must come contains mutations, those mutations will be found in the HPV 52 DNA and will be covered by the claim.

Plaintiff challenges the construction on another ground, arguing that it might suggest to the jury that the HPV 52 DNA of the claims cannot be linked to any other DNA. This, it maintains, runs counter to claims 1-7, in which the patent makes it clear that HPV 52 DNA can be connected to other DNA as part of recombinant DNA of HPV 52 comprising a cloning vector and HPV 52 DNA. This challenge is a chimera. The construction does not apply to the cloning vector in claims 1-7 of the patent. The cloning vector is listed explicitly as a claim limitation and is not modified by the term "consists of all or a fragment of an HPV DNA."

Finally, plaintiff contends that the construction may lead the jury to think that the HPV 52 DNA cannot be connected to or include even a single oligonucleotide other than a known sequence of HPV 52 DNA. This, it says, would be a mistake in light of claims 18

and 21, which are directed to HPV 52 hybridization probes *comprising* a member selected from the group consisting of either HPV 52 DNA or HPV 52 RNA, labeled with a detectable label. Plaintiff seizes on the word comprising to assert that the elements specified in the claim do not limit the probe itself, which must comprise HPV 52 DNA labeled with a detectable label but can also include other DNA sequences not meeting any of the limitations of HPV 52 DNA.

Ordinarily, the word comprising is "understood to signify that the claims do not exclude the presence in the accused apparatus or method of factors in addition to those explicitly recited." Vivid Technologies, Inc. v. American Science and Engineering, Inc., 200 F.3d 795, 811 (Fed. Cir. 1999). However, the word does not affect the scope of the structure recited within the steps, Merculon v. CBS, Inc., 773 F.2d 1261, 1271 (Fed. Cir. 1986), or allow the patentee to ignore explicit limitations that follow the word. If, as plaintiff would have it, other DNA sequences were to be "comprised" by claim 18, they could change the nature of the elements that must be present to meet the claim terms by extending the length of the probes beyond 8000 bases or by affecting the hybridization ability of the probe. In this instance, therefore, it would not be logical or consistent with principles of claim construction to read the term comprising as permitting other DNA sequences within the claim.

Plaintiff challenges this conclusion as conflicting with this court's decision in

Promega v. Applera Corp., 2002 WL 32359938 (W.D. Wis. July 7, 2002) (Promega II), granting the plaintiff's motion for reconsideration of the interpretation given to term in a patent claim. Beyond the fact that both cases involve motions for reconsideration and a patent claim including the word comprising, the cases have no apparent similarities. In Promega II, I concluded that it was error to read a claim to require that the selections in a "set" for amplification could not include other "loci." This conclusion rested on the prosecution history, the wording of the claim term "wherein the at least four loci in the set" and the rule that a product cannot infringe a dependent claim without infringing the independent claim from which the claim depends. Promega II offers no assistance in construing the disputed terms in claims 18 and 21 of the '715 patent.

C. "HPV 52 hybridization probe" and "HPV hybridization probe"

Plaintiff objects to the constructions given these two separate terms in the July 23 order. (The first term was construed as "a nucleic acid molecule that is specific for HPV 52 DNA and differentiates HPV 52 DNA from the DNA of all other HPV types"; the second was construed as "nucleic acid molecule that is specific for the DNA of any one type of HPV and differentiates the DNA of that type from DNA of all other HPV types."). Plaintiff takes issue with the specificity and differentiation requirements the constructions impose upon the probes. However, nothing in its arguments for reconsideration convinces

me that the construction was incorrect.

Plaintiff makes much of the fact that specificity for HPV 52 DNA is not necessary when a probe is used in a sample that might not reasonably be expected to include HPV 52 DNA. Apparently, in that situation, a probe that is non-specific for HPV 52 DNA would serve the purpose of determining whether any HPV is present. Such a probe, however, would not be the one claimed in claim 18; that one must be specific for HPV 52 DNA, for all the reasons set out in the July 23 order.

ORDER

IT IS ORDERED that plaintiff's motion for reconsideration incorporating its request for amendments of the claims construction set out in the court's July 23, 2007 opinion and order is DENIED.

Entered this 26th day of September, 2007.

BY THE COURT:
/s/
BARBARA B. CRABB
District Judge