UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

Life Technologies Corporation et al., Plaintiff, vs. Illumina Inc. et al., Defendants.	CASE NO. 11cv00703-CAB (DHB) ORDER GRANTING MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT and DENYING OTHER PENDING MOTIONS WITHOUT PREJUDICE [Doc. Nos. 320, 323, 328, 329, 330, 333, 336, 337, 338, 339]

Before the Court is Illumina, Inc.'s and Solexa, Inc.'s (jointly, "Illumina") motion for summary judgment of non-infringement of the patents asserted by Life Technologies Corporation, Applied Biosystems, LLC, Institute for Protein Research, Alexander Chetverin, Helena Chetverina and William Hone (jointly, "Life Tech").[1] Life Tech alleges that Illumina's Genome Analyzer and Genome Analyzer II products infringe U.S. Patents Nos. 5,616,478 ("the '478 patent"), 5,958,698 ("the '698 patent") and 6,001,568 ("the '568 patent"). [Doc. No. 235.] The patents are directed at a method and product for exponential amplification and/or expression of nucleic acids in an immobilized medium to form detectable colonies of nucleic acids.

The case originated in the United States District Court for the Eastern District of Delaware. A claim construction order was entered on December 15, 2010 by Senior

[1] The briefing for this motion is found on the docket as follows: Defendants' Opening Memorandum, Doc. No. 320 (sealed version 435); Plaintiffs' Response in Opposition, Doc. No. 370 (sealed version 453); Defendants' Reply, Doc. No. 420 (sealed version 461).

District Judge Robert F. Kelly. [Doc. No. 132.] The case was transferred to the Southern District of California on April 6, 2011 [Doc. No 184] and assigned to the undersigned on March 12, 2012 [Doc No. 271]. This motion, filed November 12, 2012, was argued on January 17, 2013.

I. Legal Standard

Illumina moves for judgment as a matter of law that its accused products do not literally infringe the asserted claims of the three patents at issue.[2] To establish literal infringement, every limitation set forth in a claim must be found in the accused product or method. The analysis of literal infringement is a two step process. First the asserted claims must be interpreted by the court to determine their meaning and scope. Second, the trier of fact determines whether the construed claims read on the accused product or method. *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995) (internal citations omitted).

The parties presented their infringement arguments based on the claim constructions entered by Judge Kelly. The Court applies those constructions to the evidence presented. Summary judgment is appropriate when the record demonstrates that there is no genuine issue of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56. The evidence must be viewed in the light most favorable to the nonmoving party. *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1116 (Fed. Cir. 1985) (en banc). When no reasonable jury could find for the non-movant, the movant is entitled to judgment as a matter of law. *Karsten Mfg, Corp. v. Cleveland Golf Co.*, 242 F.3d. 1376,1379 (Fed. Cir. 2001).

II. Infringement Analysis of '478

A. The Construed Claim

The '478 patent claims a method of exponential nucleic acid amplification. [Doc. No. 1-1.] Life Tech alleges infringement of independent claim 1, and dependent

[2] Life Tech did not dispute Illumina's representation that Life Tech has not advanced a theory of infringement under the Doctrine of Equivalents [Doc. No. 320/435, n. 7]. No infringement analysis under that theory was presented to the Court in response to Defendants' motion.

claims 3, 7, 11 and 12. Claim 1 claims:

> A method of exponential nucleic acid amplification to form detectable colonies of nucleic acids compromising the steps of
>
> (a) providing an immobilized medium, said medium including
> (i) an aqueous liquid phase that includes a cell-free enzymatic, exponential nucleic acid amplification system; and
> (i) [*sic*] a solid, water-insoluble matrix having an average pore size ranging from 100 μm to 5nm, completely entrapping said liquid phase, and
>
> (b) distributing in said aqueous liquid phase nucleic acid molecules, at least one of which may comprise a template for said amplification system; and
>
> (c) incubating said immobilized medium containing said distributed molecules under conditions promoting synthesis of an exponentially amplified nucleic acid product by said amplification system from said at least one template,
>
> wherein said matrix is stable under said conditions, and wherein said step of distributing separates individual templates, resulting in nucleic acid amplification to form at least one separate, detectable colony of said nucleic acid product in said medium.

The parties disputed the meaning of the term *amplification system* although both agreed that the amplification system in the context of this patent is "a set of components that together can amplify a nucleic acid." The independent method claim is not limited to any particular system or set of components. The court found it includes any system of exponential amplification as long as "whatever exponential enzymatic nucleic acid amplification is selected for use in the applicant's method, the necessary components for that amplification system must be provided so that the templates for that system will be amplified." [Doc. No. 132 at 4-5 (citing the prosecution history of the '468 patent).] The components of an exponential

amplification system therefore are all the components necessary to achieve exponential amplification in accordance with the specific system implemented.

The parties also disputed the meaning of the term *aqueous liquid phase that includes a cell-free, enzymatic, exponential nucleic acid amplification system*. The court determined that the term should be read as "liquid water-based phase" that includes the amplification system. [Doc. No. 132 at 7.]

B. The Accused Method

Illumina exponentially amplifies DNA in a "flow cell."[3] A flow cell, about the size of microscope slide, has eight tiny tubes called channels. The channels have openings at either end for receiving and expelling fluid. Reagents flow through the channels during the amplification process.

The flow cell channel is first coated with a polyacrylamide surface, and oligonucleotide primers are covalently bonded to the surface. DNA template strands with adapters are flowed through the channel and the strand's adapters hybridize with the primers (the adapter sequence of the template strand bonds with the primers). Polymerase enzymes and nucleotides are then flowed through the channel, the polymerase incorporates the nucleotides into a new strand of DNA attached to surface-bound primer that is complementary to the template strand. A wash buffer is flowed through the channel, then the reagent formamide is flowed through the channel. The formamide denatures the new double-stranded DNA (separates it into single strands) and flushes out templates not anchored to the surface, enzymes and free nucleotides. The formamide is then pushed out of the channel. The remaining surface-bound complementary strands "bend over" to hybridize with an available primer forming a bridge. Polymerase enzymes and nucleotides are then flowed through

[3] The description of Illumina's amplification process, summarized here, is set forth in Doc. No. 435-1. It is also summarized in the August 3, 2012 Rule 26 Report prepared by plaintiff's expert Dr. Annelise Barron, who describes Illumina's amplification cycle as a formamide wash, followed by the addition of BST polymerase enzyme, buffer, and dNTPs to create copies of the immobilized template DNA. [Doc. No. 370-2, Ex. 2, ¶44.]

the channel, forming complementary strands to each bridged single strand. The bound single strand becomes a double strand bound to the surface. Formamide is again flowed into the channel, pushing out the previous reagents, and separating the double strands into two single strands each covalently bound to the surface. These strands form bridges with available primers, and the cycles are repeated, replicating the bridged strands, separating them, and replicating them again, until the primers are exhausted and clusters or colonies of nucleic acid products are formed.

Formamide, an amide derived from formic acid, is not water-based or present in a water-based liquid phase. It is flowed through the channel apart from the polymerase enzymes and nucleotides. It is the reagent that denatures (separates) the double-stranded DNA so it can be copied, and is introduced separately from the components that form the complementary DNA strands. These facts are not in dispute.

C. Discussion

An amplification system, as discussed in the court's claim construction order is a combination of components that can accomplish the necessary exponential amplification. [Doc. No.132 at 5.] Illumina contends that formamide is a component of its amplification system pursuant to the court's claim construction – it is one of "the set of components that together can amplify a nucleic acid." [Doc. No. 320/435 at 3.] Without the introduction of formamide in its process to separate the double strands, the other components cannot exponentially replicate the nucleic acid. Formamide works in combination with the other components to achieve exponential, nucleic acid amplification. It is a necessary component of Illumina's amplification system.

Life Tech argues that formamide is not a component of Illumina's exponential amplification system. Although previously acknowledging the exponential amplification process includes the denaturing wash to separate the double-strands [Doc. No. 370-2, Ex. 2, ¶44, n. 25], Life Tech contends the components of Illumina's amplification system are limited those reagents that perform the copying portion of the amplification process. *See* Decl. of Jeremy Edwards, ¶¶ 19-25 [Doc. No. 373-1.] Life

Tech compares the role of formamide in Illumina's system to the use of heat in the PCR amplification system to denature the double strands. In PCR, the reaction components are mixed, and amplification occurs using cycles of heating and cooling. *Id.*, at ¶22; '486 Patent, Col. 1:65- 2:15. Life Tech opines that heat is not considered a component of the PCR amplification system, so neither should Illumina's denaturing reagent be considered a component of its system.

Life Tech's argument that the court's construction of amplification system does not encompass the necessary denaturing component is not supported by the language of the claim construction order or the specification. The court construed the "system" as a set of components that together can amplify a nucleic acid. The court noted that whatever system is employed the necessary components for that amplification system must be provided so that the templates for that system will be exponentially amplified. [Doc. No. 132 at 4-5.] Illumina's system will not perform exponential amplification without formamide. It is a necessary component of this particular system. Life Tech opines it is not, but offers nothing more than the conclusory opinion of Dr. Edwards that formamide should be excluded as a component of Illumina's system because it is a "denaturant," despite another Life Tech expert, Dr. Barron, having earlier acknowledged that the denaturing wash is part of the amplification process. [Doc. No. 373-1, ¶22; Doc. No. 370-2, Ex. 2, ¶44, n. 25.]

Illumina's argument that the court's construction of an exponential amplification system includes all necessary components of exponential amplification is supported by the patent specification. The patent identifies an amplification process that includes as a component of its system, an enzyme that provides the denaturing function. "The method can employ any *system of exponential amplification* of nucleic acids in vitro, *such as ... 3SR reaction*." '468 Patent, Col. 4:66-5:1 (emphasis added). The patent describes 3SR (isothermal multienzyme) amplification as the "concerted action of three enzymes: a DNA-directed RNA polymerase, a reverse transcriptase, and RNase H." *Id.*, Col. 2:35-38. The RNase H is a component of the 3SR amplification system that

"destroys the RNA template involved in the RNA:DNA heteroduplex after the first-strand cDNA sysnthesis, enabling the second strand of the cDNA to be synthesized." The 3SR reaction is identified as an amplification system. *Id.*, Claim 5 at Col. 24:11-12. RNase H, the denaturing enzyme, is identified as a component of that system by the patent and plaintiff's expert Dr. Edwards. [Doc. No. 420/461 at 3; Doc. No. 418-1, Ex. 24 at 257:2-8.] The specification, therefore does not support Life Tech's opinion that denaturants are never considered to be components of an amplification system. The court's construction identified the system as the necessary components to produce exponential amplification and there is no factual dispute that formamide is a necessary component for the exponential amplification process to take place in Illumina's system.

Life Tech argued that RNase H, unlike formamide, is part of the 3SR amplification system because it is present together in the mix with the components that replicate the nucleic acids in the 3SR reaction. Life Tech advocates that "because polymerase and the other components of [Illumina's] amplification system cannot perform amplification in the presence of formamide, it is clear that the set of components that can *together* amplify a nucleic acid must exclude formamide." [Doc. No. 370/453 at 7 (emphasis in the original).] Life Tech applies "together" too narrowly. Illumina's system achieves exponential amplification using formamide to denaturize the double strands. It works in combination, i.e., together, with the other components to achieve exponential amplification. It is a component of Illumina's exponential amplification system. That formamide does not work in the same solution as the other components does not exclude it from being a component of the system. It does, however, exclude Illumina's system from being covered by the patent.

The '486 patent requires that the aqueous liquid phase, construed as a liquid water-based phase, include the exponential nucleic acid amplification system. Formamide is a component of Illumina's exponential nucleic acid amplification system and it is not included in the water-based phase. It is flushed in and out of the channel

separately from the water-based phase with the other components of the system. Consequently, the Court finds that Illumina's system does not meet this limitation of claim 1 of the '486 patent and **GRANTS** Illumina's motion for summary judgment of non-infringement of this patent.

III. Infringement Analysis of '568

A. The Construed Claim

The '568 patent claims a solid medium for amplification and expression of nucleic acids as colonies. [Doc. No. 1-3.] It is a division of the '478 patent, based on the same specification. Life Tech alleges infringement of independent claim 1 and dependent claim 2. Claim 1 claims:

> A preformed immobilized medium suitable for producing, from individual nucleic acid molecules applied thereto, separate detectable colonies by cell-free enzymatic exponential amplification process, comprising
>
> a) an aqueous liquid phase that includes a cell-free nucleic acid polymerase enzyme system capable of performing said process, and
>
> b) a thin layer, from 1 μm to 10 mm in thickness, of a solid, water-insoluble matrix having an average pore size ranging from 100 μm to 5nm, completely entrapping said liquid phase.

The court found that the "polymerase enzyme system" of claim 1 is a system that performs an exponential amplification process, and therefore also construed it as "a set of components that together can amplify a nucleic acid." [Doc. No. 132 at 4.]

B. Discussion

For the reasons set forth above, the Court finds that formamide is a component of the Illumina exponential amplification system so it will be capable of performing the exponential amplification process. Formamide is not included in the aqueous liquid phase. Consequently, the Court finds that Illumina's system does not meet this limitation of claim 1 of the '586 patent and **GRANTS** Illumina's motion for summary judgment of non-infringement of this patent.

IV. Infringement Analysis of '698

A. The Construed Claim

The '698 patent claims a method for amplification and expression of nucleic acids in solid media and its application for nucleic acid cloning and diagnostics. [Doc. No. 1-2.] Life Tech alleges infringement of independent claims 1 and 17, and dependent claims 2, 3, 6, 12, 16, 18 and 23. Claim 1 claims:

A method of detecting nucleic acid sequence in a sample that may contain said sequence comprising the steps of:

(a) providing a cell-free, enzymatic, exponential amplification system;

(b) forming a liquid mixture of the sample and said amplification system;

(c) entrapping said liquid within solid surfaces comprising a thin layer;

(d) incubating said trapped mixture under conditions promoting synthesis of an exponentially amplified nucleic acid product from said nucleic acid sequence; and

(e) screening to detect said amplified product,

wherein the average distance between the nearest solid surfaces is smaller than the distance which the synthesized nucleic acid product can migrate by diffusion during the reaction, and

wherein copies of said nucleic acid sequence, if present in said sample, are sufficiently widely distributed in said liquid mixture to produce separate, detectable colonies of synthesized nucleic acid product.

The parties asked the court for a construction of the following language from claim 1:

wherein the average distance between the nearest solid surfaces is smaller than the distance which the synthesized nucleic acid product can migrate by diffusion during the reaction.

The court responded that the purpose of the invention is the amplification and detection of nucleic acids as distinct colonies. The claimed immobilized medium prevents the progeny of the amplified nucleic acids from spreading all over the reaction volume and forms colonies by entrapping the nucleic acid products in limited zones. It achieves this by the solid surfaces of the matrix having pore sizes that are less than the distance at which the synthesized products can migrate by diffusion during exponential amplification. The court concluded that "one skilled in the art would be able to apply this term to achieve that goal and no further construction [was] necessary." [Doc. No. 132 at 18-19.]

Claim 17 claims:

A method of detecting nucleic acid sequence in a sample that may contain said sequence compromising the steps of

(a) providing an immobilized medium, said medium including

(i) an aqueous liquid phase that includes a cell-free enzymatic, exponential nucleic acid amplification system; and
(ii) a solid, water-insoluble matrix having an average pore size ranging from 100 μm to 5nm, completely entrapping said liquid phase, and

(b) distributing in said aqueous liquid phase nucleic acid molecules, at least one of which may comprise a template for said amplification system;

(c) incubating said immobilized medium containing said distributed molecules under conditions promoting synthesis of an exponentially amplified nucleic acid product by said amplification system from said at least one template; and

(d) screening said colonies,

wherein said matrix is stable under said conditions, and wherein said step of distributing separates individual templates, resulting in nucleic acid amplification to form at least one separate, detectable colony of said nucleic acid product in said medium.

B. Discussion

For the reasons set forth above, the Court finds that formamide is a component of the Illumina exponential amplification system so it will be capable of performing the exponential amplification process. Formamide is not included in the aqueous liquid phase. Consequently, the Court finds that Illumina's system does not meet this limitation of claim 17 of the '698 patent and **GRANTS** Illumina's motion for summary judgment of non-infringement of this claim.

Claim 1 of the '698 patent does not include the limitation that the exponential amplification system be included in the aqueous liquid phase so the non-infringement analysis applied to the other independent claims does not apply to this claim. The parties however dispute whether claim 1 covers Illumina's method because of the claim limitation that requires *the average distance between the nearest solid surfaces is smaller than the distance which the synthesized nucleic acid product can migrate by diffusion during the reaction*.

Illumina's method, as described above, uses a flow cell, in which the flow cell channels are coated with a polyacrylamide surface and primers are covalently bound to that surface. Life Tech's expert stated in her August 2012 report that during the steps of the exponential amplification reaction the products of the reaction, the DNA strands, are covalently bound to the polyacrylamide surface, the matrix, and therefore cannot diffuse. Barron Report, ¶¶33 & 44 [Doc. No. 370-2, Ex. 2.] In her comparison of the Illumina accused system to the claims of the '698 patent, Dr. Barron unequivocally states with regard to this limitation that "the average distance between nearest solid surfaces in Illumina's SPF matrix is approximately 15-40nm" and that "synthesized nucleic acid products cannot migrate by diffusion as they are covalently attached to the SFA hydrogel via the P7 and P5 primers." [Doc. No. 370-2, Appendix

E, at 2.][4] She offers no explanation as to how the claim limitation is therefore met.

In light of this admission by Life Tech, that in Illumina's system of exponential amplification the synthesized nucleic acid products cannot migrate by diffusion, Illumina contends that the limitation in claim 1, requiring that the solid surfaces of the matrix have pore sizes be less than the distance at which the synthesized products can migrate by diffusion during exponential amplification, would require its matrix have pore sizes less than 0nm. While the parties disagree as to the approximate pore size of the Illumina polyacrylamide surface, they both agree the size is not less than 0nm.

Consequently, the method by which Illumina immobilizes its synthesized nucleic acid products, by covalently binding them to the surface so that they cannot migrate by diffusion, does not meet the limitation of claim 1. Claim 17 does not have this limitation, so to the extent Life Tech argues that the patent discloses systems in which the synthesized nucleic acid products are covalently bound to the matrix, such systems may be covered by independent claim 17, but the requirements of claim 1 are not met by Illumina's system.

Court finds that Illumina's system does not meet this limitation of claim 1 of the '698 patent and **GRANTS** Illumina's motion for summary judgment of non-infringement of this claim.

V. Conclusion

The Court finds that in applying the construed claims of each of the asserted independent claims of the patents at issue, Life Tech cannot establish, as a matter of law, that the accused Illumina systems infringe. Illumina's Motion for Summary Judgment of Non-Infringement of the '478, 568 and 698 patents [Doc. Nos. 320/435] is **GRANTED**. In light of this finding of non-infringement, the Court declines to reach the parties' Motions for Summary Judgment of Invalidity [Doc. No. 323], on

[4] The Court declines to consider declarations filed by Life Tech in opposition to Illumina's Motion for Summary Judgment of Non-Infringement offered to recant or contradict the Rule 26 Report of Life Tech's expert on this issue. *Delaware Valley Floral Group, Inc. v. Shaw Rose Nets, LLC,* 597 F.3d 1374, 1381 (Fed. Cir. 2010).

Inequitable Conduct [Doc. No. 337]; and on Lost Profits [Doc. No. 329], as well as the motions to exclude the testimony of certain witnesses [Doc. Nos. 328, 330, 333, 336, 338 and 339.] The pending motions are **DENIED WITHOUT PREJUDICE**. Judgment **SHALL** be entered for defendants Illumina, Inc. and Solexa, Inc., on plaintiffs' First Amended Complaint for Patent Infringement. [Doc. No. 235.]

Finally, the Court **SETS** a telephonic status conference for **April 4, 2013** at **2:00 p.m.** Counsel should jointly place the call to Chambers with all parties already on the line. For purposes of the status conference, on or before **April 2, 2013**, the parties shall file a joint status report (no more than five pages in length) regarding the stayed infringement counterclaims and any other open issues that should be addressed by the Court.

DATED: March 20, 2013

CATHY ANN BENCIVENGO
United States District Judge