IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

LADATECH, LLC,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 09-627-SLR
	)	
ILLUMINA, INC. and SOLEXA, INC.,	)	
	)	
Defendants.	)	

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MEMORANDUM OPINION

Dated: January 24, 2012
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

Plaintiff LadaTech, LLC ("plaintiff or "LadaTech") brought this action on August 21, 2009 alleging direct and indirect infringement of U.S. Patent No. 6,107,023 ("the '023 patent") by defendant Illumina, Inc. ("Illumina"). (D.I. 1) Plaintiff filed an amended complaint on February 2, 2010 adding allegations of infringement of the '023 patent against defendant Solexa, Inc. ("Solexa"). (D.I. 7) Illumina and Solexa (collectively, "defendants") answered on February 19, 2010, asserting defenses of noninfringement, invalidity, and unenforceability, and related counterclaims. (D.I. 9) Discovery is now complete and the parties have briefed several claim construction issues. Currently pending are defendants' motions for summary judgment of noninfringement (D.I. 126) and invalidity and patent expiration (D.I. 119) and plaintiff's motion for summary judgment of no anticipation by certain references (D.I. 124). The court held a hearing on these issues November 4, 2011 and a jury trial is scheduled to commence on February 21, 2012. The court has jurisdiction over these matters pursuant to 28 U.S.C. § 1338.

II. BACKGROUND

A. The Parties

LadaTech is a Delaware limited liability company with its principal place of business in Larchmont, New York. (D.I. 7 at ¶ 1) When it was formed, LadaTech was jointly owned by Genelabs Technologies ("Genelabs"), which has since been acquired by GlaxoSmithKline Plc, and IP-Finance Holdings, LLC. (D.I. 9 at 9-10, ¶ 3; D.I. 14 at ¶ 3) LadaTech owns the '023 patent, but has not commercialized the technology

described therein. (D.I. 120 at 2)

Illumina is a Delaware corporation with its principal place of business in San Diego, California. (D.I. 9 at ¶ 2) Solexa, a wholly owned subsidiary, was a Delaware corporation with its principal place of business in Hayward, California as of the date of the first amended complaint, but has since merged into Illumina (as of February 8, 2010). (*Id.* at ¶ 3) Illumina has developed and markets an array of DNA sequencing products used by academic, government, pharmaceutical, biotechnology and other institutions globally.[1] While Illumnia also sells DNA sequencing instruments, the present litigation concerns Illumina's sample preparation kits and cluster generation instruments, discussed *infra*.

B. Technology Overview[2]

This litigation involves DNA sequencing technology. DNA, or deoxyribonucleic acid, is a hereditary material that contains the genetic instructions used in the development and functioning of living cells. DNA is made of nucleotides, or chemical building blocks, made of three parts: a phosphate group, a 2'-deoxyribose sugar and

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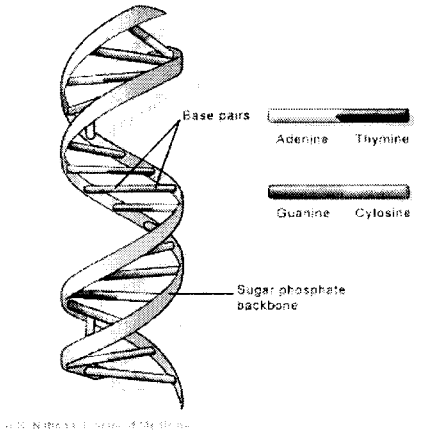
[1]*See www.illumina.com/company/about_us.ilmn* (last accessed December 28, 2011).

[2]Where uncited, the court has compiled the background from defendant's expert's report (D.I. 120, ex. C at ¶¶ 17-23), plaintiff's expert's report (D.I. 125, ex. A at ¶¶ 17-48), and has included general reference from the U.S. National Library of Medicine's publication "Genetics Home Reference, Your Guide to Understanding Genetic Conditions," available at *http://ghr.nlm.nih.gov/handbook* (published Dec. 27, 2011), "Deoxyribonucleic Acid (DNA)," published by the National Human Genome Research Institute, available at *http://www.genome.gov/25520880#al-1* (published March 23, 2011), and the National Human Genome Research Institute's "Talking Glossary of Genetic Terms;" available at *http://www.genome.gov/glossary* (last accessed January 3, 2012). The parties' disputes on summary judgment supercede the background of this complex technology.

four nitrogen bases (deoxyadenosine monophosphate, or adenine ("A"), deoxyguanosine monophosphate, or guanine ("G"), deoxycytosine monophosphate, or cytosine ("C") and thymidine monophosphate, or thymine ("T")). DNA is a linear molecule analogous to a chain, and nucleotides are akin to "links" in this chain. Nucleotides are arranged in two long strands that are anti-parallel (that is, they are oriented in opposite directions to each other) and form a spiral called a double helix.

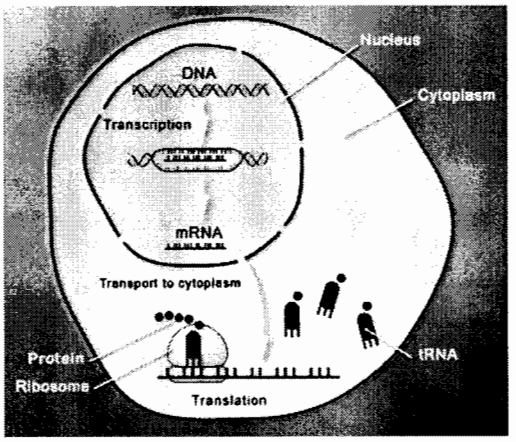


Each single DNA strand is a polymer of nucleotides joined by covalent (phosphodiester) bonds between the phosphate group at the "5'-end" position of the deoxyribose sugar of one nucleotide and a hydroxyl (–OH) group at the "3'-end" position of the deoxyribose sugar of the next nucleotide. This configuration allows for the two strands to be held together by hydrogen bonds formed by base pairing A with T and C with G nucleotides. Two single strands of DNA that come together by way of hydrogen bonding between stretches of complementary (or substantially complementary) bases are said to be "hybridized" or "annealed" to one another.

Genes contain information needed to make proteins, which play many critical

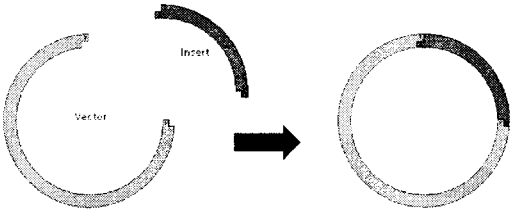
roles in the body. The process whereby proteins are made is complex, but may be summarized as consisting of two major steps: transcription and translation (which, together, are known as gene expression). During transcription, information stored in a gene's DNA is transferred to a ribonucleic acid (or RNA) molecule in a cell's nucleus. RNA is similar to DNA insofar as both are nucleic acids, but RNA is a shorter and (typically) single-stranded nucleotide chain. RNA also differs by its sugar (ribose, rather than DNA's 2'-deoxyribose) and base pairs (RNA utilizes uracil ("U") rather than the thymine (T) of DNA).

The type of RNA that contains protein-making information is called messenger RNA (or mRNA). mRNA leaves the cell's nucleus and enters the cytoplasm, where translation occurs. The mRNA's sequence of bases is "read" by a complex called a ribosome. Each sequence of three base pairs is called a codon, and usually codes for one particular amino acid, the building blocks of proteins. Protein is assembled by transfer RNA (or tRNA) one amino acid at a time, until the ribosome encounters a "stop" codon, or a codon that does not code for an amino acid.



As explained in the '023 patent, the ability to identify and isolate unique nucleic acid sequences has become an important facet of medicinal research. The presence or absence of a particular mRNA is indicative of disease. For example, an absent or altered mRNA coding for a specific protein in a specific cell type may cause a hereditary disease, while the presence of an added mRNA (such as a virus-specific mRNA) may be indicative of the beginning of a malignant transformation or the latent presence of an otherwise undetectable infectious agent. ('023 patent, col. 1:41-col. 2:2)

"Cloning" is a process used to produce identical copies of a desired DNA sequence. A common method of cloning involves inserting a DNA fragment[3] into a "vector," or a nucleic acid sequence that can be replicated in a host organism such as the bacteria E. coli. There are several types of vectors. A plasmid is a small, circular DNA molecule found in bacteria and other cells. A desired DNA fragment may be inserted to create a plasmid vector, as generally depicted below.



Once introduced into a suitable host cell (most commonly, Escherichia coli (or "E. coli"), the foreign DNA (of the plasmid vector) is replicated along with the host's DNA each time the cell divides. By contrast, another type of vector, called a bacteriophage (or a "phage" for short), is a type of virus that infects E. coli. Bacteriophages use the infected

[3]Fragmentation may occur by various means, for example, cleavage with restriction endonucleases or shearing.

cell's enzymes to replicate their genomes and package the DNA into new viral particles.

The polymerase chain reaction (or "PCR") is a technique for amplification of DNA across several orders of magnitude.[4] In PCR, the complementary strands of the double-helix are denatured, or separated, by heating. Two pieces of synthetic DNA, or "primers," each complement a specific sequence of DNA. The primers are each hybridized to the 3' end of the sequence of interest within the single-stranded DNA. Following primer hybridization, polymerase (enzyme) replicates the template strand from the primer in a 5' to 3' direction, synthesizing a complement strand to the template strand. In subsequent cycles, double-stranded molecules of both the original DNA and the copies are separated; primers again bind to the complementary sequences; and the polymerase replicates them. At the end of many cycles, exponential replication has been achieved (in theory, 2^n, where n = the number of cycles) and this amplified genetic information is available for further analysis, such as for cloning.

C. The '023 Patent

The '023 patent was filed as U.S. Patent Application No. 07/208,512 on June 17, 1988 and issued on August 22, 2000. The '023 patent names as inventors Greg Reyes and Jungsuh Kim; Genelabs (plaintiff's predecessor) is the named assignee. A request for *ex parte* reexamination of the '023 patent was filed by Illumina on January 18, 2008. The United States Patent and Trademark Office ("PTO") issued an *ex parte* reexamination certificate on November 17, 2009, confirming the patentability of the reexamined original claims (nos. 12-14), as well as one newly added claim (no. 15).

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[4]The parties agree that PCR was developed and first described in the mid-1980s. (D.I. 120, ex. C at ¶ 23; D.I. 125, ex. A at ¶ 42)

Plaintiff asserts infringement of these four claims in the present litigation.

By way of background, the '023 patent explains that many hereditary diseases[5] are likely to be caused by the absence or alterations of low-abundance mRNAs. A major problem in detecting and isolating such mRNAs (among 10,000 to 30,000 types of distinct mRNA species that may be present in a given cell type) is interference from other, higher-abundance species in the source material. ('023 patent, col. 2:9-18) High background levels require high sensitivity, which is not achieved by the number of nucleic acid hybridization techniques in the art, for example, cDNA probing,[6] filter hybridization to a conventional cDNA library, and nucleic acid subtraction techniques. (*Id.*, col. 2:19-56)

The specification and claims of the '023 patents are directed to two distinct (but related) inventions: a method of amplifying a mixture of different sequence duplex DNA fragments; and a method of isolating complex DNA fragments. The inventors provide a method "for isolating RNA or genomic sequences which are unique to one or two mixtures," more specifically, "allowing for identification of unique species which are present at low concentration and/or low molar ratio in a mixture of genomic or RNA-

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[5]For example, Lesch-Nyhan Syndrome, Hunter's Syndrome, Tay-Sachs Disease and adenosine deaminase deficiency. ('023 patent, col. 1:55-58)

[6]Complementary DNA (or "cDNA") is made by converting purified mRNA into single-stranded DNA (using the enzyme reverse transcriptase) and then making that strand a double-stranded DNA (using the enzyme DNA polymerase). cDNA is more stable than mRNA and does not contain the non-coding regions of the mRNA, only an expressed DNA sequence. A cDNA library is a large collection of such fragments. *See gen.* National Center for Biotechnology Information, "Molecular Genetics: Piercing it Together," available at *http://www.ncbi.nlm.nih.gov/About/primer/genetics_molecular.html* (last accessed January 11, 2012).

deprived duplex DNA fragments." (*Id.*, col. 2:59-67) In practicing the isolation method,

> double-strand linkers are attached to each of the fragment mixtures, and the number of fragments in each mixture is amplified by successively repeating the steps of (i) denaturing the fragments to produce single fragment strands, (ii) hybridizing the single strands with a primer whose sequence is complementary to the linker region at one end of each strand, to form strand/primer complexes and (iii) converting the strand/primer complexes to double-strand fragments in the presence of polymerase and deoxynucleotides. After the desired fragment amplification is achieved, the two fragment mixtures are denatured, then hybridized under conditions in which the linker regions associated with the two mixtures do not hybridize. DNA species which are unique to the positive-source mixture, i.e., which are not hybridized with DNA fragment strands from the negative-source mixture, are then selectively isolated.

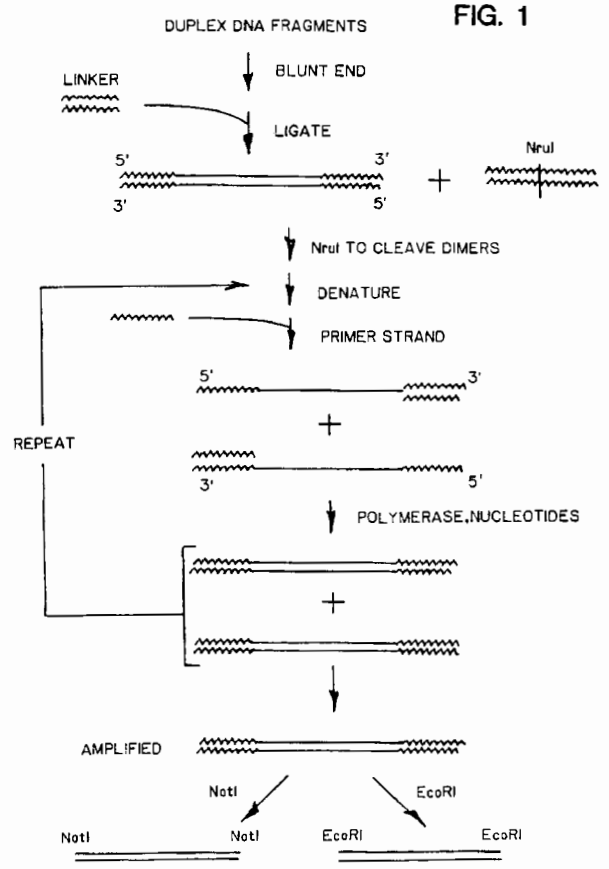
(*Id.*, col. 3:13-28) The method for amplifying duplex DNA fragments includes

> attaching a double-strand linker to the fragments, and replicating the two strands in each fragment by denaturing the fragments to produce single fragment strands with linker-strand ends, hybridizing the single strands with a primer whose sequence is complementary to a linker-strand end on each fragment strand, to form strand/primer complexes, and converting the strand/primer complexes to double-strand fragments in the presence of polymerase and deoxynucleotides. The fragment-replication steps are repeated until a desired degree of amplification is achieved.

(*Id.*, col. 3:49-59)

As the claims at issue in this litigation (claim 12 and dependent claims) concern the linker/primer duplex amplification method of the invention, the court hereinafter focuses on this aspect of the disclosure. This amplification method is exemplified by figure 1 of the '023 patent, reproduced below.

FIG. 1



(*Id.* fig. 1; col. 3:66-67) "According to an important feature of the invention, the duplex DNA fragments to be amplified are ligated at their opposite end to a linker, to provide a priming sequence for strand duplication." (*Id.*, col. 5:41-55) While the "linkers" will be discussed in more detail *infra*, the linker-carrying fragments produced in this step are then treated with an endonuclease to cut linker multimers[7] at their blunt-end junctions. (*Id.*, col. 5:57-67; col. 6:45-46)

The linker-fragments are then amplified by repeated fragment duplication

[7]Generally, a protein consisting of multiple monomers (small molecules).

according to the following steps. First, fragments are mixed with a large molar excess of single-stranded oligonucleotide primer. The primer has a sequence that is "homologous to the fragment end linker" and must be "capable of priming polymerase-catalyzed strand replication." (*Id.*, col. 6:49-59) The denatured fragments and primer are cooled "to allow primer hybridization with the fragment linker ends." (*Id.*, col. 7:1-3)

The "primer-addition" stage follows, whereby "the four deoxynucleotides and, optionally a DNA polymerase capable of catalyzing second-strand, primed replication are added, and the reaction mixture is brought to a temperature suitable for enzymatic strand replication." (*Id.*, col. 7:6-11) The single-stranded primer hybridizes with the 3'-end linker region in each DNA strand, doubling the fragment number. "The above replication procedure, which involves fragment denaturation by heating, cooling to form a fragment strand-primer complex, and second strand replication of the complex in the presence of DNA polymerase, is repeated until a desired concentration of fragments is achieved." (*Id.* at col. 7:23-28)

Reexamined claims 12-14 and newly-issued claim 15 are directed to the amplification method of the invention. Independent claim 12 reads as follows.

> 12. A method of amplifying a mixture of different sequence duplex DNA fragments, comprising
>
> attaching a double-strand linker to the fragments, by ligating the linkers to both strands of the fragments, at both fragment ends,
>
> denaturing the fragments to produce single fragment strands with linker regions at both strand ends,
>
> hybridizing the single strands with a primer whose sequence is complementary to a linker region on each fragment strand, to form strand/primer complexes,
>
> converting the strand/primer complexes to double-strand fragments in the

presence of polymerase and deoxynucleotides, and

repeating said denaturing, hybridizing, and converting steps until a desired degree of amplification is achieved.

Dependent claims 13-14 add the requirements that the fragments of claim 12 are genomic fragments (claim 13) or that they are produced by converting messenger RNA species to double-strand cDNA fragments (claim 14). Dependent claim 15 recites "[t]he method of claim 12 wherein the linkers ligated to the ends of the fragments are the same."

III. STANDARD OF REVIEW

A court shall grant summary judgment only if "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). The moving party bears the burden of proving that no genuine issue of material fact exists. *See Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 n.10 (1986). "Facts that could alter the outcome are 'material,' and disputes are 'genuine' if evidence exists from which a rational person could conclude that the position of the person with the burden of proof on the disputed issue is correct." *Horowitz v. Fed. Kemper Life Assurance Co.*, 57 F.3d 300, 302 n.1 (3d Cir. 1995) (internal citations omitted). If the moving party has demonstrated an absence of material fact, the nonmoving party then "must come forward with 'specific facts showing that there is a genuine issue for trial.'" *Matsushita*, 475 U.S. at 587 (quoting Fed. R. Civ. P. 56(e)). The court will "view the underlying facts and all reasonable inferences therefrom in the light most favorable to the party

opposing the motion." *Pa. Coal Ass'n v. Babbitt*, 63 F.3d 231, 236 (3d Cir. 1995). The mere existence of some evidence in support of the nonmoving party, however, will not be sufficient for denial of a motion for summary judgment; there must be enough evidence to enable a jury reasonably to find for the nonmoving party on that issue. *See Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 249 (1986). If the nonmoving party fails to make a sufficient showing on an essential element of its case with respect to which it has the burden of proof, the moving party is entitled to judgment as a matter of law. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986).

IV. DISCUSSION

A. Infringement

1. Standards

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* Construction of the claims is a question of law subject to de novo review. *See Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Direct infringement requires a party to perform each and every step or element

of a claimed method or product." *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). A product that does not literally infringe a patent claim may still infringe under the doctrine of equivalents if the differences between an individual limitation of the claimed invention and an element of the accused product are insubstantial. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 24, 117 S. Ct. 1040, 137 L. Ed. 2d 146 (1997). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

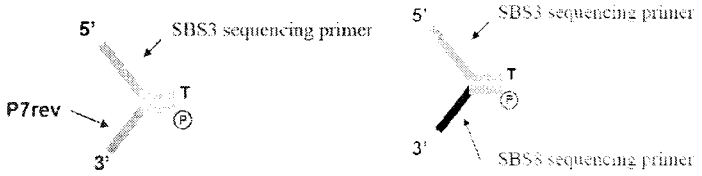
2. Accused technology

Defendants move for summary judgment that Illumina's "pre-TruSeq"[8] and Tru-Seq forked adapters and "Nextera" products, used alone or with Illumina's "cluster generation" products, cannot infringe the asserted claims of the '023 patent.

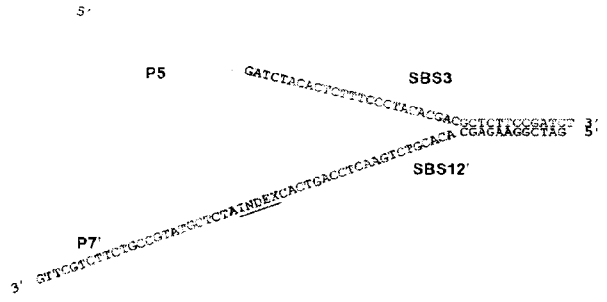
[8]The parties refer to Illumina's "pre-TruSeq" sample preparation technology to distinguish from the "TruSeq" process introduced by Illumina in 2010. (D.I. 134 at 5, n.3) As defendants do not often distinguish between the two in their papers, the court addresses defendants' arguments made under each product combination in turn.

a. Sample preparation kits

Illumina sells sample preparation "kits" that can be used to prepare libraries of samples suitable for cluster generation (and, ultimately, sequencing), a process which will be explained *infra*. (D.I. 127, ex. C at ¶ 39)[9] Illumina sample preparation protocols involve the ligation of double-stranded, "forked" adapters to the 3' and 5' ends of DNA fragments, and subsequent amplification using primers complementary to the sequences introduced via the adapters. (*Id.*, ex. C at ¶ 38) Below are depictions of Illumina's forked adapters.



Single Read Adapter Paired End Adapter



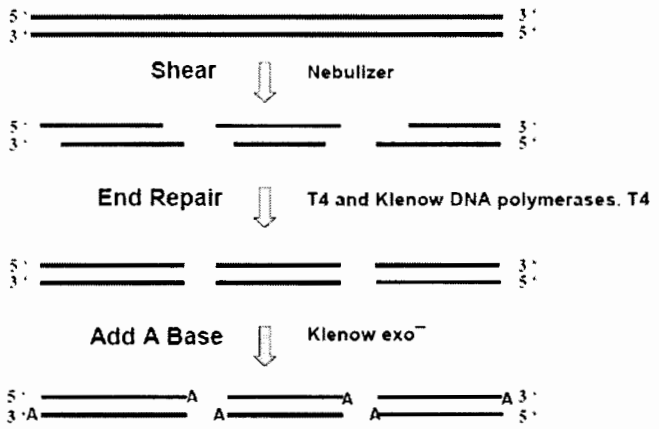
TruSeq Adapter

(D.I. 127, ex. B at ¶¶ 16, 53, 59)

The first step of Illumina's sample generation process is the generation of DNA fragments of roughly 100-500 base pairs (by various known methods), to which the

[9]Where defendants cite to plaintiff's expert's report for the relevant description of Illumina's process, the court does the same.

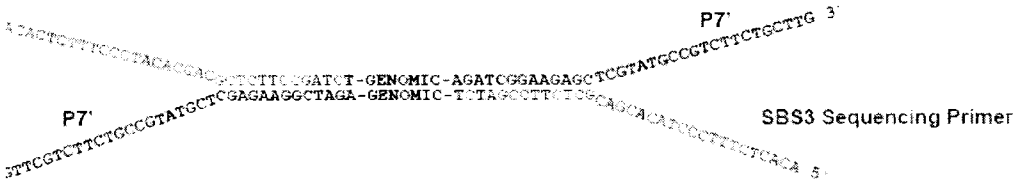
adapters will be attached. (D.I. 127, ex. C at ¶ 40) Once these double-stranded DNA fragments have been generated, they are "repaired" by a DNA polymerase, resulting in double-stranded fragments that are "blunt ended" (fully hydrogen-bonded at each terminus). (*Id.* at ¶ 41) This occurs due to the incorporation of nucleotides where single strands occur at 5' overhangs, and by removing 3' overhangs. (*Id.*) Next, a single adenosine (A) nucleotide is added to the 3'-ends of both blunt-ended strands using a "Klenow polymerase;" the fragments are now said to be "adenylated." (*Id.*) The following is a schematic of these fragmenting ("shearing"), end repair, and adenylation ("add A base") steps prepared by defendants' expert.



(D.I. 127, ex. B at ¶ 15)

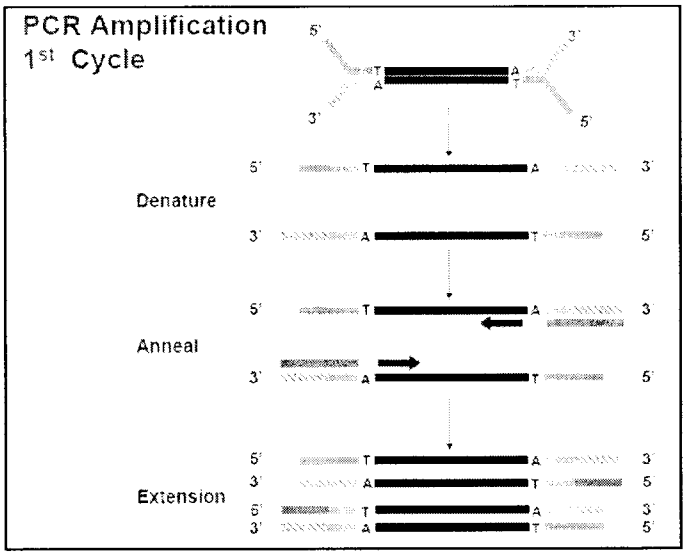
After these preparatory steps, the forked adapters depicted above are added to each DNA fragment at each end. As depicted *supra*, Illumina's forked adapters have a 12 or 13 pair duplex portion and two non-complementary "forked" regions. (*Id.* at ¶¶ 17, 54) The T overhang (at the 3' end of one of the strands of the duplex region) ensures that the forked adapters are correctly oriented when they are ligated to the fragments,

as shown below.



(*Id.* at ¶ 18)

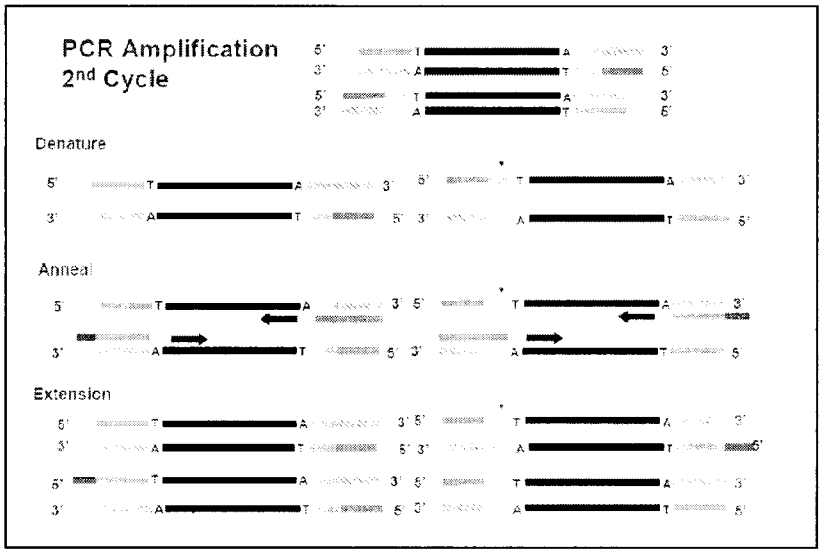
After addition of the forked adapters, the molecules are put through several cycles of PCR. The diagram below illustrates the first amplification cycle for fragments containing forked adapters with the SBS3 sequence (in orange) and the complement of the P7 primer (in green, labeled "P7rev"). SBS3' and P7' sequences are shown with orange and green hash marks. Primers P7 and P5 are added with the appropriate buffers in this cycle.



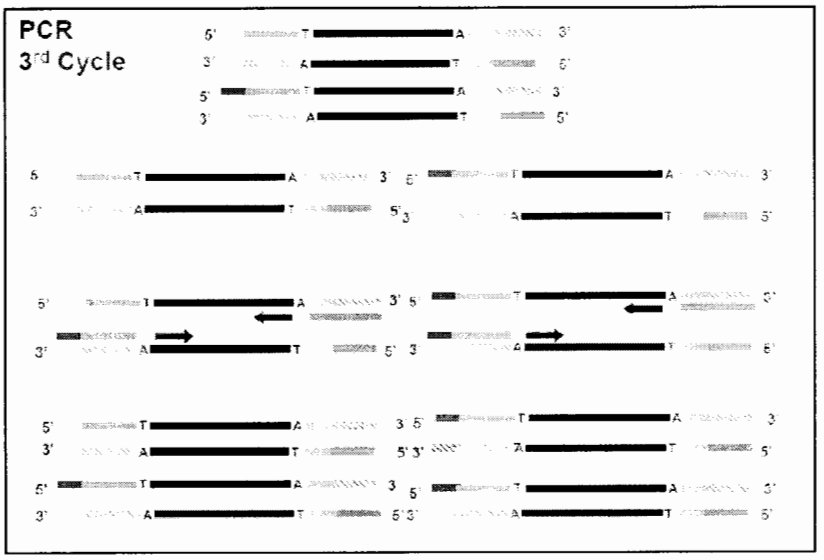
(*Id.* at ¶¶ 19, 20) After the first round, there are four strands, as follows: (1)

SBS3–fragment–P7'; (2) SBS3'–fragment–P7; (3) P7–fragment–SBS3'; and P7'–fragment–SBS3. (*Id.* at ¶ 20)

After these strands are again denatured, in a second round of PCR, the P7 primers again hybridize to the P7' regions of two of the four strands, while the other strands are hybridized by a P5 primer (as shown below, in pink) and a sequence complementary to the SBS3' portion of the strand (in orange).



(*Id.* at ¶¶ 21-22) The end result after extension is eight strands: four strands of P7–fragment–SB3; two strands of SBS–fragment–P7'; and two strands of P5–SBS–fragment–P7'. (*Id.* at ¶ 22) One half of the third round of PCR is identical in result to the second round. The other half of the third round of PCR is depicted below. The net result of this round is 16 strands, 5 of which have P5 on one end and P7' at the other end.



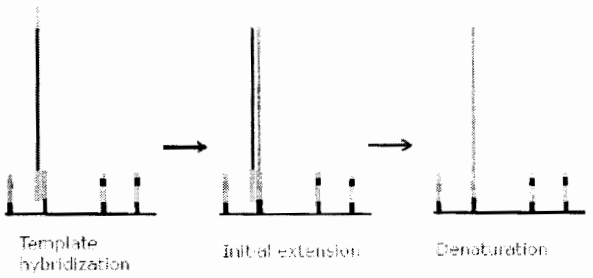
(*Id.* at ¶ 23)

b. Cluster generation

After sample preparation, further amplification occurs on the surface of a flow cell, or a flat slide that will eventually be loaded into the sequencer. (*Id.*, ex. C at ¶ 57) This stage is called "cluster generation," and refers to the synthesis of "clusters" of DNA on the flow cell sufficient to undergo sequencing reactions. (*Id.* at ¶ 55) Illumina's cluster generation process is automated and has been performed by its "Cluster Station" and "cBot Cluster Generation System" (or "cBot") devices. (*Id.* at ¶ 56)

On the surface of each of eight lanes in a particular flow cell is a "lawn" of P5 and P7 primers that are bound at one end to the flow cell. (*Id.* at ¶ 58) The P5 and P7 primers are the same sequences attached (along with their complementary sequences) to opposite ends of each of the fully-double stranded fragments built in the library

during sample preparation. (*Id.*) To form clusters, the fragments are denatured to yield single-fragment strands. (*Id.* at ¶ 59) The single strands then anneal or hybridize to surface-bound primers.[10] (*Id.*) After annealing, a polymerase builds a strand off of the surface-bound primer that is complementary to the library strand. In the next denaturation step, the untethered template strands are washed away, leaving surface-bound single strands having (at their 3' ends) sequences complementary to surface-bound primers, as depicted below.



(*Id.* at ¶ 60)

Due to the length of the strands, they are able to anneal to surface-bound primers, forming an inverted "'U'-shaped bridge" with a different surface-bound primer. During the next (and subsequent) primer extension, a surface-bound strand is used as a template. Subsequent denaturation yields two single strands tethered at their 5' ends.

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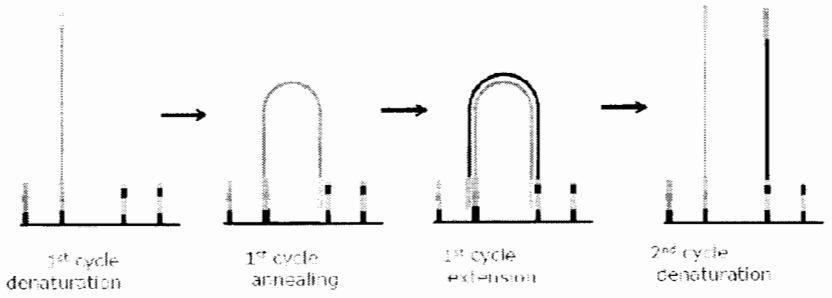
[10]The primers greatly outnumber the library sequences that are applied to the flow cell, ensuring that the individual molecules to be amplified are substantially spacially isolated from each other. (D.I. 127, ex. C at ¶ 59)



(*Id.*) The new strands are bound at their 5'-ends and can then anneal to different primers. (*Id.* at ¶ 61) The cycles are repeated to form dense clusters. (*Id.*)

3. Illumina sample prep kits

a. "Double strand linker"

Defendants' first argument for noninfringement of the '023 patent is that the Illumina sample prep products do not have a "double-stranded linker" as required by the claims. Their argument in this regard is that the limitation requires that the two strands of the linker are "complementary and hybridized to each other along substantially their entire lengths." (D.I. 127 at 16; D.I. 97 at 3) Each of Illumina's forked adapters have 12 or 13 bases that are "paired" and longer, single-stranded arms. The quantity of paired bases in Illumina's forked adapters vis a vis the single-stranded portions is summarized below for ease of reference.

	Single read adapter (1)	Single read adapter (2)	Paired end adapter	TruSeq adapter (1)	TruSeq adapter (2)
single strands	20	21	19	45	51
base pairs	12	12	13	12	12
percentage of paired bases in total[11]	(12/32) 38%	(12/33) 35%	(13/31) 42%	(12/57) 21%	(12/63) 19%

(D.I. 127 at 17; *id.*, ex. B at ¶¶ 35, 54, 62)

Defendants also point to the following testimony by plaintiff's expert, Dr. Kevin Struhl, Ph.D. ("Struhl"), regarding the perception of forked adapters in 1988.

> It's a molecule that has a double-stranded portion, and two single-stranded tails. And people wouldn't say it's double stranded or single stranded because it's clearly not fully double stranded or fully single stranded. They see what it is. They might like the term formed adapter. . . Doesn't really matter. It's – to sit there and force it into one or the other is scientifically meaningless. . . . It's got a double stranded region and a single stranded region. It does not have a uniform characteristic over its entire length[.]

(D.I. 127 at 18; *id.*, ex. F at 130:22-131:21[12]) Finally, defendants argue that expanding "double strand" to cover structures that are not "substantially" double stranded would completely vitiate that claim limitation and, therefore, the doctrine of equivalents should not be available. (*Id.* at 18-19)

The infringement dispute is, essentially, one of claim construction. By its memorandum order of the same date, the court has declined to adopt defendants'

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[11]Rounded to the nearest whole percentage.

[12]The court exceeds the portion of the transcript cited by defendants for completeness.

claim construction of "double strand linker" as it disagrees that the intrinsic record supports narrowing this limitation to require complete hybridization between the two strands "along substantially their entire lengths." As there is no dispute that Illumina's forked adapters are at least partially double stranded, in this regard, "sufficiently hybridized to maintain the linker's double-stranded nature" (as the court has construed the term), defendants' motion for summary judgment of noninfringement is denied on this ground.[13]

b. "Complementary to a linker region"

Defendants next argue that Illumina's products do not have "a primer whose sequence is complementary to a linker region on each fragment strand" as that phrase should be construed, or that "the entire sequence of the primer used is complementary to a linker region on every fragment strand in the mixture." (D.I. 127 at 21-22) Defendants emphasize that Illumina's P5 and P7 primers are each complementary to roughly half of the fragment strands. (*Id.*) (citations omitted) Similar to the above, in construing this limitation, the court does not require the primer to be completely complementary. Rather, per the court's construction, the primer need only be sufficiently complementary to a linker region to allow for copying of DNA. Accordingly, defendants' motion is denied on this ground.

4. Pre-TruSeq products: "linker region"

Defendants argue that the pre-TruSeq products lack a "linker region" at each end

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[13]Insofar as the court adopts plaintiff's claim construction (with minor modification), the court need not address defendants' arguments that the doctrine of equivalents is not available, or that Struhl's doctrine of equivalents analysis in his expert report is insufficient. (D.I. 127 at 20-21)

strand. The dispute again presents itself as an issue of claim construction. Defendants define "linker region" as "a region found on the linker itself," while plaintiff construes "linker region" as "part of the linker sequence." (D.I. 97) In the context of their noninfringement motion, however, defendants argue that the "linker region" must stay at the "strand ends" throughout the claimed process. (D.I. 127 at 23-25) That is, assuming the claims cover the ligation of forked adapters to the DNA fragments, the "linker regions" (SBS3 sequence at one end and P7' sequence at the other) are present at both fragment ends only after the first round of amplification. (*Id.*) In subsequent rounds of amplification, a P5 sequence is added to one end of the molecule (at the strand end) and, therefore, the "linker region" of the first round (SBS3 sequence) is no longer at the strand terminus. (*Id.*) Defendants make a similar argument with respect to the paired end forked adapters: the SBS8 and SBS3 sequences do not stay at the "strand ends," rather, P7 and P5 sequences (or their complements) are added to the ends during subsequent rounds of PCR. (*Id.* at 24-25) Plaintiff does not dispute these basic facts.

In its memorandum order of the same date, consistent with its understanding that double-stranded linkers can have noncomplementary ends (or "tails"), the court has declined to limit "linker region" to linker sequences at the extreme termini of the strands. Because the court declines to add the requirement that the "original" linker sequence remains at the terminus of the strand during all reaction steps, defendants' motion is denied on this ground.

5. Nextera kit

Defendants seek summary judgment that the Nextera sample prep kit does not infringe. According to defendants, "[p]roving that the Nextera sample prep kit include[s] an infringing 'attaching' step is a necessary element of the proof required from LadaTech to establish that the accused cluster generation kits infringe when used with Nextera sample prep kits." (D.I. 127 at 28)

As an initial matter, plaintiff argues that the Nextera products "are not in the case and are irrelevant before the damages period" because: (1) Illumina only purchased the company that developed and marketed the Nextera kits (Epicentre) this year, after the close of document production; (2) defendants did not produce all of the Nextera documents in this case, only selected examples; and (3) no individuals involved with Nextera were identified by defendants in their discovery responses as witnesses having material information. (D.I. 134 at 30) Defendants do not argue that the Nextera products should be excluded based on this procedural posture. Rather, defendants seek summary judgment that the process performed by the Nextera products, when used with Illumina's cluster generation products, omit the step of "attaching a double-strand linker to the fragments by ligating the linkers to both strands of the fragments at both fragment ends." (D.I. 127 at 27-32; *id.*, ex. B at ¶ 76)

While plaintiff does not proffer specific rebuttal evidence in response, the court takes plaintiff at its word that the Nextera products are not part of this case and, therefore, an analysis on the merits (on what plaintiff asserts is an incomplete record) is not warranted at this juncture. (D.I. 134 at 30-31) Commensurately, however, plaintiff may only recover damages based on products (and product combinations) found to be infringing.

6. Cluster generation products

The parties do not appear to dispute that Illumina's cluster generation products cannot infringe alone, because these products perform PCR (amplification), and do not attach double-stranded linkers. That is, the "attaching" step of claim 12 (in full, "attaching a double-strand linker to the fragments, by ligating the linkers to both strands of the fragments, at both fragment ends") must be performed by a sample prep kit.[14] In this regard, defendants rehash their argument that the Illumina sample prep kits, used with Illumina cluster generation products, do not infringe because they lack a "double-stranded linker." (D.I. 127 at 30; *id.*, ex. B at ¶ 76) Because the court rejected defendants' claim construction in this regard, and defendant does not offer an alternative rationale in support of noninfringement, plaintiff is not precluded from arguing that Illumina's sample prep kits used in combination with its cluster generation products results in infringement of the '023 patent.

The court next turns to defendant's argument that Illumina's cluster generation products do not infringe when used in combination with third-party sample prep kits. (*Id.* at 30-31) According to defendants, plaintiff has "made absolutely no attempt" to show that third-party sample prep kits (for example, kits sold by "Aligent, Beckman Coulter, Bio Scientific, New England BioLans and Epicentre") used with Ilumina's

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[14]Plaintiff's expert testified that the cluster station simply performs PCR, and does not involve ligation – the "attaching" step of claim 12. (D.I. 127, ex. F at 256:10-257:24) Plaintiff states in its answering papers that "[t]he amplification performed with Illumina sample preparation methods continues during cluster generation," and does not state that ligation occurs in the cluster amplification process. (D.I. 134 at 27) Insofar as plaintiff does not argue that the cluster generation products infringe, the court grants defendants' motion for partial summary judgment of noninfringement with respect to these products (used alone).

cluster generation products infringe, for example, through testimony by plaintiff's infringement expert (Stuhl).[15] (*Id.* at 31)

In response, plaintiff does not point to specific instances of customers' use of particular kits with Illumina's cluster generation products, but generally argues that there is no question that customers use Illumina's method for sample preparation regardless of the source of the reagents they purchase. (D.I. 134 at 28) Specifically, plaintiff points to an exhibit containing several published, scientific papers (listed on Illumina's website) describing work done by Illumina customers and indicating that Illumina's protocol for sample preparation was used. (*Id.* (citing *id.*, ex. 14)) Insofar as no particular pages or excerpts of any of these articles were called out, however, the court cannot ascertain the veracity of that characterization.

Plaintiff also states that Illumina sells products to various "core" facilities (at universities and other institutions, including certain "certified" service providers) that advertise services utilizing Illumina methods. (*Id.* at 28) The deposition testimony cited indicates that customers use Illumina equipment and reagents, but is not specific to methods performed. (*Id.*, ex. 2 at 71:24-72:25, 259:4-11[16])

Plaintiff also argues that Illumina "publishes its sample preparation method and

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[15]According to defendants, these third-party combinations make for 90-95% of marketplace combinations; Illumina's own sample prep kits are only used with Illumina's cluster generation products 5-10% of the time. (D.I. 127 at 31 (citing *id.*, ex. D at 171:18-172:22)) The court agrees with plaintiff that the number of customers using particular prep kits is a damages issue, not an infringement issue. (D.I. 134 at 29-30)

[16]With respect to exhibit 2, while it is clear that the deponent, Suresh Pisharody, is an Illumina employee, it is not clear from the very few deposition pages attached what title or role he holds at Illumina.

provides sequence information so that its customers may synthesize the oligonucleotides that make up Illumina's forked adapters used in sample preparation, even if the customers do not purchase sample prep kits from Illumina." (*Id.*) In support, plaintiff provides an Illumina customer letter providing "particular oligonucleotide sequences"[17] (for adapters, PCR primers, and "Genomic DNA Sequencing Primer") for use with Illumina's sequencer. (*Id.*, ex. 15) Additionally, Struhl testified that his lab purchases reagents from third-party vendors, and that he "can't imagine that people preparing samples for Illumina sequencing are using a different protocol." (*Id.*, ex. 6 at 78:18-79:15, 99:13-16) New England Biolabs ("NEB"), a third party, instructs on its website that its reagents are compatible with protocols "such as Illumina's Genomic DNA Sample Prep protocol for the Genome Analyzer."[18] (*Id.*, ex. 16) Finally, plaintiff points to an Illumina PowerPoint slide stating, with respect to Nextera technology, that "adapters are ligated on the ends." (*Id.*, ex. 17) As explained above, however, Nextera is not at issue.

What is absent from the foregoing is evidence that any customer actually performed the method of the '023 patent using a third-party sample prep kit (or equivalent reagents) with Illumina's cluster generation products. Plaintiff offers no expert testimony on the subject. There is no testimony by defendants' employees or actual customers that may demonstrate direct infringement. The remaining question is,

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[17]Illumina states that the sequences are protected by copyright.

[18]Defendants argue that this website printout was not produced in discovery and is inadmissible. (D.I. 139 at 17-18) The court need not decide the issue in view of its holding.

therefore, to what extent may plaintiff attempt to utilize the foregoing evidence to establish an inference that infringement necessarily occurred.[19]

The Federal Circuit has instructed that summary judgment should not be granted based on lack of direct infringement evidence if the record reflects that a defendant encouraged customers to use an accused product in an infringing manner and, importantly, customers can only use defendant's supplied products in an infringing manner. *See Symantec Corp. v. Computer Assocs. Int'l, Inc.*, 522 F.3d 1279, 1293 (Fed. Cir. 2008); *compare Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003) ("[W]here a product has substantial non-infringing uses, intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent."). Within its limited opposition, plaintiff does not argue that there are no noninfringing uses for third-party sample prep kits. There is no basis in the record to deny defendants' motion for summary judgment of noninfringement, and the court shall enter judgment accordingly.

B. Validity

Defendants move for summary judgment of invalidity of the asserted claims of the '023 patents on three grounds: anticipation by an article written by Saiki et al. ("Saiki") if defendants' claim construction of "linker" and the effect of the preamble are adopted; inadequate written description if plaintiff's claim construction of "a primer whose sequence is complementary to a linker region on each fragment strand" is

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[19]The court notes at this juncture that plaintiff does not frame its argument in opposition to defendants' motion in terms of inducement of infringement, therefore, there is no discussion of Illumina's specific intent to encourage another's infringement.

adopted; and expiration for payment of an incorrect maintenance fee. Plaintiff cross-moves for summary judgment of no anticipation by Saiki or a related reference by Liang et al. ("Liang").

1. Expiration

The court first addresses defendants' argument that the '023 patent expired in 2004 because Genelabs failed to timely pay the applicable maintenance fee pursuant to 35 U.S.C. § 41, providing that,

> [u]nless payment of the applicable maintenance fee under paragraph (1) is received in the Office on or before the date the fee is due or within a grace period of 6 months thereafter, the patent shall expire as of the end of such grace period. The Director may require the payment of a surcharge as a condition of accepting within such 6-month grace period the payment of an applicable maintenance fee.

There is no dispute between the parties concerning the relevant facts. On April 25, 2011, plaintiff filed a "Notification of Loss of Entitlement to Small Entity Status and Payment of Maintenance Fee Deficiency" with the PTO. (D.I. 120, ex. P) Therein, plaintiff stated that, while it paid the eighth-year fee under the correct schedule, it discovered that it inadvertently paid the fourth-year maintenance fee as a small entity, and enclosed the deficiency (of $525). (*Id.*) Defendants argue that Genentech lost its ability to claim small entity status in 2002 when it licensed the '023 patent to a large entity (Affymetrix), *see* 13 C.F.R. § 121.802, and the 2004 payment was erroneous. (D.I. 120 at 32)

As defendants acknowledge, the Federal Circuit has considered the issue and held that a district court has no obligation or authority to analyze whether a patent has expired where the submission of a deficiency fee payment is accepted by the PTO

pursuant to 37 C.F.R. § 1.28(c).[20] *Ulead Systems, Inc. v. Lex Computer & Management Corp.*, 351 F.3d 1139, 1149-50 (Fed. Cir. 2003). The court declines to accept defendants' invitation to find that the Federal Circuit would have held differently had a more thorough review of 35 U.S.C. § 41 been undertaken by the panel. (D.I. 133 at 25-27) Their motion is denied on this ground.

2. Written description

a. Standards

The statutory basis for the enablement and written description requirements, § 112 ¶1, provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

The written description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (citation and quotations omitted). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of

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[20] If status as a small entity is established in good faith, and fees as a small entity are paid in good faith, in any application or patent, and it is later discovered that such status as a small entity was established in error, or that through error the Office was not notified of a loss of entitlement to small entity status as required by 1.27(g)(2), the error will be excused upon: compliance with the separate submission and itemization requirements of paragraphs (c)(1) and (c)(2) of this section, and the deficiency payment requirement of paragraph (c)(2) of this section.

37 C.F.R. § 1.28(c) (2001) (emphases added).

the claimed subject matter as of the filing date." *Id.* (citations omitted). "The level of detail required to satisfy the written description requirement depends, in large part, on the nature of the claims and the complexity of the technology." *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, — F.3d —, 2012 WL 45398 at *12 (Fed. Cir. Jan. 10, 2012) (citing *Ariad*, 598 F.3d at 1351). Neither examples nor actual reduction to practice is required; "a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Id.* (citing *Ariad*, 598 F.3d at 1352).

Defendants must ultimately prove that the written description fails these standards by clear and convincing evidence. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1307 (Fed. Cir. 2008) (citing *Invitrogen Corp.*, 429 F.3d at 1072-73 (Fed. Cir. 2005)). While compliance with the written description requirement is a question of fact, it is amenable to summary judgment in cases where no reasonable fact finder could return a verdict for the nonmoving party. *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, — F.3d —, 2012 WL 45398 at *12 (Fed. Cir. Jan. 10, 2012) (quoting *PowerOasis, Inc.*, 522 F.3d at 1307).

b. Discussion

In its claim construction order of this same date, the court has construed the limitation "a primer" (as used in "a primer whose sequence is complementary to a linker region on each fragment strand") as one or more primers. Defendants argue that, under this construction, the '023 patent is invalid for failure to suggest how to implement the invention using multiple primers. In support, defendants substantially reiterate their

claim construction arguments. For example, in figure 1, a single, double-stranded linker is added to the fragments, and figure 1 is described as a flow diagram of the method of "the invention." ('023 patent, col. 3:66-67) (*see also*, *id.* at col. 7:20-23 ("It will be appreciated from the above, and from fig. 1, that the single added primer hybridizes with the 3'-end linker region in each DNA strand, and thus a doubling of fragment number occurs.")) As an additional example, figure 2A of the patent depicts double-stranded linkers containing one primer sequence (GGAATTCGCGGCCGCTCG) on each strand (at the 5' end).[21] Defendants assert, without citation to expert testimony, that "[u]nder the circumstances, one of ordinary skill in the art would not recognize that the inventors possessed an invention with multiple primers or multiple primers with identical linkers." (D.I. 120 at 31)

In response, plaintiff cites the opinion of its validity expert, Dr. Michael L. Metzker, Ph.D. ("Metzker"), that an ordinary artisan[22] "would have understood that multiple primers could have been used, and that multiple primers could have been used with a linker with one or more priming sites." (D.I. 125, ex. 6A at ¶ 157) More

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[21]Defendants do cite the deposition testimony of inventor Reyes, stating that figure 2 "is a key difference in terms of utilizing a single primer of defined sequence rather than two different primers in the standard PCR procedure." (D.I. 120 at 30 (citing *id.*, ex. G at 175:16-176:5)) If anything, this citation supports plaintiff's argument that persons of ordinary skill in the art would recognize that multiple primers are used in standard PCR.

[22]Metzker defines a person of ordinary skill in the art as someone with a Ph.D or its equivalent with "sufficient direct ('hands-on') experience with cDNA library construction, molecular cloning, PCR and DNA sequencing to be familiar with the techniques." (D.I. 125, ex. 6A at ¶ 68) Defendants' expert, Dr. Saul J. Silverstein, Ph.D. ("Silverstein"), also states that a person of ordinary skill in the art "would have had several years of laboratory experience and would have had experience with cloning technology and PCR amplification." (D.I. 120, ex. C at ¶ 15)

specifically, it is Metzker's opinion that

> one of skill in the art, informed by the '023 patent of the use of linkers as binding sites for PCR primers, would understand that the inventors were in possession of such stranded variations as the use of different primers for forward and reverse amplification, or primers with unhybridized portions. Standard PCR typically will involve different forward and reverse primers, and once informed of the use of a single linker, one of skill in the art would understand that this aspect of the invention extends to multiple primers (i.e., different forward and reverse primers in a given reaction) and the use of two different linkers. For example, the '023 patent cites Maniatis, which states on page 219 "[i]n the original description of this method (Kurtz and Nicodemus 1981), two different linkers were simultaneously ligated to cDNA. During this process, it would be expected that 50% of the cDNA molecules would receive the same linker at each end; such molecules could not be inserted into the plasmid DNA by directional cloning." . . . The implication here is that the other 50% of cDNA molecules would have two different linkers at each end.

(*Id.* at ¶ 158) (internal citation omitted) During his deposition, defendants' expert, John P. Johnson, M.D. ("Johnson"), testified as follows:

> Q. So back in the late 1980 time period when using PCR was it generally understood that you could use two primers?
> A. I think almost everybody thought, yea, we need to be using two primers.
> Q. And you said that you could use one but that was for rare instances; is that right?
> [Objection to form.]
> A. If you created, if you had a plasmid of some kind with the same primer sequence on each end you could have used one primer. We were actually looking at a piece of DNA that was a mirror image, so the primer on one end on one strand would actually be the same as the primer on the other end of the strand and we actually did an experiment to try to get that to work. We thought it worked, we reported it out at a couple of meetings but when we sequenced it it wasn't quite what we wanted.
> But, yes, most people were using two primers because the sequences they were investigating had differences on each end and weren't mirror images or something like that.

(D.I. 125, ex. 7 at 34:4-25) Further, Johnson agreed that the use of a single primer versus a double primer was a design choice in the experiment, as "you could only use a single primer when you knew you had some sort of inverted sequence, so at some point

the sequences were complementary at the ends of what you were interested to [sic], so you could use the same primer on each end." (*Id.* at 83:9-84:4) Defendants' other expert, Silverstein, generally agreed that a double-stranded structure does not require the use of a single primer. (*Id.*, ex. 5 at 156:4-21) Finally, plaintiff argues that dependent claim 15, reciting the method of claim 12 wherein the linkers ligated to the ends of the fragments are the same, supports the use of multiple primers in the invention of claim 12. (D.I. 125 at 26)

In response, defendants emphasize that plaintiff does not rely on the specification as supporting disclosure for the use of multiple primers, only claim 15, which was added during reexamination. (D.I. 133 at 21-22) The court disagrees that plaintiff improperly expanded the scope of the '023 patent on reexamination by adding claim 15 to broaden claim 12, as defendants suggest, insofar as claim 12 was not limited to single primers in the first instance.

While defendants are correct that plaintiff could not rely on expert testimony, in and of itself, to satisfy the written description requirement, this misconstrues plaintiff's argument. It is, at times, appropriate to rely on information that is "well known in the art" to satisfy written description, insofar as the four corners of the specification must be viewed from the perspective of one of ordinary skill in the art. *Streck,* 2012 WL 45398 at *12 (citing *Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011)).

The court is careful not to place the burden of proof on plaintiff to demonstrate the validity of the '023 patent; the inquiry must focus on whether defendants have adduced clear and convincing evidence of invalidity or, alternatively, whether questions

of fact preclude such a determination at this juncture. Defendants do not contradict plaintiff's assertions that the use of multiple primers was well known in the art as of the filing date. (D.I. 133 at 18-25) There appears to be no dispute, therefore, that under the court's construction adopted today, the "a primer" limitation is supported by knowledge well-known in the art.

The court pauses to note defendants' emphasis on an article published by the inventors after filing the application for the '023 patent (entitled "Sequence-Independent, Single-Primer Amplification (SISPA) of Complex DNA Populations" (the "SISPA article"), which inventor Reyes acknowledged was a "description of the linker/primer **methodology**" described in the patent. (D.I. 120, ex. J; ex. G at 173:14-18 (emphasis added)) Defendants call out the following excerpts from the SISPA article:

> Sequence-independent, single-primer amplification (SISPA) differs significantly from the original PCR methodology in that non-selective nucleic acid amplification is achieved through the use of a single primer.

(D.I. 120, ex. J at 474, col. 2)

> The SISPA procedure differs from standard PCR in several ways. The technique requires (1) modification of target sequences in order to (2) utilize a single primer of defined sequence that will result in (3) the simultaneous amplification of DNA fragments of both heterogeneous size and sequence.

(*Id.* at 478) Reyes testified that, with respect to the foregoing, (2) above "is a key difference in terms of utilizing a single primer of defined sequence rather than two different primers in the standard PCR procedure." (*Id.*, ex. G at 175:24-176:5)

As an initial matter, defendants' own reliance on extrinsic evidence runs afoul of its position that plaintiff fails to cite disclosure within the four corners of the

specification. Notwithstanding, the crux of defendants' argument is that the inventor's subjective view of the invention is narrower than the scope of the claims as construed by the court. The subjective/objective nature of the written description requirement has been recognized as difficult to apply in this regard. *See Ariad*, 598 F.3d at 1366 (Rader, J., dissenting-in-part and concurring-in-part) ("This Court still asks the fact finder to imagine what a person of skill in the art would have understood the inventor to have subjectively possessed based on the description in the specification (which of course by definition describes the exact same invention according to this Court's claim construction rules)."). In the case at bar, however, defendants have adduced no evidence that the specification of the '023 patent does not convey to a person of ordinary skill in the art that the inventors had possession of the use of one or more primers in the claimed method. Defendants' motion for summary judgment of invalidity is denied on this record.

3. Anticipation

As noted above, defendants move for summary judgment of anticipation by Saiki, and plaintiff cross-moves for summary judgment of no anticipation by Saiki or Liang. These references will be discussed in detail following a resuscitation of the relevant legal standards.

1. Standards

An anticipation inquiry involves two steps. The first step requires construing the claims (a matter of law), and the second step requires that the finder of fact compare the construed claims to the prior art. *See Enzo Biochem, Inc. v. Applera Corp.*, 599

F.3d 1325, 1332 (Fed. Cir. 2010) (citing *Power Mofset Techs., LLC v. Siemens AG*, 378 F.3d 1396, 1406 (Fed. Cir. 2004)). A patent claim is invalid due to anticipation if, "within the four corners of a single, prior art document . . . every element of the claimed invention [is described], either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009) (quoting *Advanced Display Sys. Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)). "[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102."[23] *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (citing *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008)).

While the elements of the prior art must be arranged or combined in the same manner as in the claim at issue, the reference need not satisfy an *ipsissimis verbis* test. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (citations omitted). "[T]he dispositive question regarding anticipation [is] whether one skilled in the art would reasonably understand or infer from a [prior art reference]" that every claim element is disclosed in that reference. *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (citing *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991)).

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[23]The prosecution history and the prior art may be consulted "[i]f needed to impart clarity or avoid ambiguity" in ascertaining whether the invention is novel or was previously known in the art. *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). (internal citations omitted).

"While anticipation is a question of fact, it may be decided on summary judgment if the record reveals no genuine dispute of material fact." *Encyclopaedia Britannica, Inc. v. Alpine Electronics of America, Inc.*, 609 F.3d 1345, 1349 (Fed. Cir. 2010) (citing *Leggett & Platt, Inc. v. VUTEk, Inc.*, 537 F.3d 1349, 1352 (Fed. Cir. 2008)).

b. Saiki

(1) Disclosure

Saiki is an article entitled "Primer-Directed Enzymatic Amplification of DNA with a Thermostable DNA Polymerase," published in volume 239 of Science in January 1988.[24] (D.I. 120, ex. B) The parties agree that Saiki is prior art against the '023 patent under 35 U.S.C. § 102(b).

For purposes of background, the Saiki abstract reads as follows:

> A thermostable DNA polymerase was used in an in vitro DNA amplification procedure, the polymerase chain reaction. The enzyme, isolated from *Thermus aquaticus*, greatly simplifies the procedure and, by enabling the amplification reaction to be performed at higher temperatures, significantly improves the specificity, yield, sensitivity, and length of products that can be amplified. Single-copy genomic sequences were amplified by a factor of more than 10 million with very high specificity, and DNA segments up to 2000 base pairs were readily amplified. In addition, the method was used to amplify and detect a target DNA molecule present only once in a sample of 10^5 cells.

(*Id.* at 487) The parties agree that Saiki was a groundbreaking reference. "*Taq* polymerase" enzyme, an enzyme that does not denature during the heating cycles in the PCR reaction, greatly increased the usefulness of the PCR method by eliminating

[24]Saiki is dated October 9, 1987 and lists the acceptance date for publication as December 17, 1987. (D.I. 120, ex. B at 491)

the need for adding new polymerase with every cycle.[25] (*Id.*, ex. F at 72:21-74:19; ex. G at 180:25-181:4)

Saiki disclosed that, "[i]n an application exploiting this capability of *Taq* polymerase, complementary DNA (cDNA) inserts in the phage λgt11 cloning vector were amplified from crude phage suspensions with primers that flank the Eco RI insertion site of the vector."[26] (*Id.*, ex. C at 489, col. 3) The parties do not dispute the nature of the experiments performed by Saiki et al. according to this disclosure. Saiki used a cDNA library that it purchased commercially from another company, Clontech. (*Id.* at 490, fig. 5) Saiki does not describe how the cDNA library was generated by Clontech. (D.I. 125, ex. 5 at 194:5-8; ex. 8 at 181:7-17; D.I. 120, ex. B at fig. 5) Figure 5 of Saiki depicts the amplification of inserts in a phage λ cDNA library, and states as follows:

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[25]As stated in Saiki itself: "Since this heat-resistant [*Taq*] polymerase is relatively unaffected by the denaturation step, it does not need to be replenished at each cycle. This modification not only simplifies the procedure, making it amenable to automation, it also substantially improves the overall performance of the reaction by increasing the specificity, yield, sensitivity, and length of targets that can be amplified." (D.I. 120, ex. B at 487, col. 2)

[26]"Eco RI" is a restriction endonuclease (enzyme) that cleaves DNA at a specific sequence:

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      ↓
5'–G–A–A–T–T–C–3'
3'–C–T–T–A–A–G–5'
          ↑
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See, gen., Halford et al., *The EcoRI restriction endonuclease with bacteriophage λ DNA*, 191 BIOCHEM. J. 581-92 (1980). As the arrows above indicate, EcoR1 digestion produces "sticky" (or non-blunt) ends. The "Eco RI" restriction site is the location on the λgt11 vector recognized by this restriction enzyme. Johnson included a map of the λgt11 vector in his report, highlighting the location of the Eco RI restriction site (generally, near the center of the vector). (*See* D.I. 120, ex. S at ¶ 19)

> A λgt11 human fibroblast cDNA library (Clontech) was plated on X-gel plates at high dilution by standard techniques (*20*). Well-isolated plaques[27] were selected at random, 15 clear (with insert) and 1 blue (without insert), and excised with the top of a Pasteur pipette. The agarose plugs were eluted in 0.2 mL of deionized water for 30 minutes, and 50 µl of the eluates was subjected to 25 cycles of amplification as described (Fig. 1). The primers used were two 24-base sequencing primers, 1218 and 1222 (New England Biolabs) that flank the Eco RI insertion site of the vector. Each of the amplified samples (10 µl) was resolved on a 1.4% SeaKem agarose gel.

(D.I. 120, ex. C at fig. 5)

Silverstein, defendants' expert, explained that "plating" the cDNA library as recited in the first sentence above means that the phage is mixed with an appropriate host, in this case, E. coli, the E. coli becomes infected, and the cells are placed in a tube with agarose. The mixture is then put on an arga plate, and the infected bacteria allow for propagation of the virus, infecting adjacent, uninfected cells. What results is "a clear plaque which represents a single phage particle or the progeny of the single phage particle." (D.I. 125, ex. C at 54:18-55:12) Sixteen "well-isolated" plaques were sampled according to Saiki; this means that the number of phages placed in the mixture before plating was sufficiently low so that individual plaques could be seen after growth, without overlap. (*Id.* at 58:5-59:2) After 16 samples were collected, they were each, separately subjected to PCR amplification. (*Id.* at 61:17-62:5)[28] Metzker, plaintiff's expert, explains that the "amplification" discussed in figure 5 is not "amplification" of the cDNA library itself, but "amplification in separate reactions of randomly picked single λ

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[27]Generally, a plaque is a clear zone formed in a lawn of cells formed due to cell lysis (destruction) by phage.

[28]Plaintiff does not contest Silverman's cited testimony, rather, it relies on it in support of its cross-motion. (D.I. 125 at 6)

clones, themselves isolated from a library. In other words, the starting material for each of the 16 separate PCR amplifications, the results of which are shown in figure 5, is a single cloned sequence – a bacteriophage λ vector with a single cloned DNA sequence." (D.I. 125, ex. 6A at ¶ 76) In sum, Saiki figure 5 discloses the steps of planting, lawn growth, plaque picking and DNA extraction prior to PCR amplification of each of 16 distinct sequences.

(2) Amplifying a mixture

The first dispute between the parties is whether Saiki discloses "[a] method of amplifying a mixture of different sequence duplex DNA fragments," as recited in the preamble of claim 12. Defendants' argument that Saiki anticipates is that only the first step of claim 12 (the "attaching" step) needs to act on a "mixture" and, accordingly, Saiki started with such a mixture – the cDNA library. (D.I. 133 at 6-8) By its memorandum order of the same date, the court has rejected defendants' claim construction argument and held that the "preamble is limiting, in that **each of** the steps of the method claim must be performed on fragments in a mixture." Defendants do not argue that Saiki amplified a mixture of DNA fragments,[29] necessitating the denial of its invalidity motion. (*Id.*)

(3) Linkers

While the foregoing, alone, justifies granting plaintiff's motion for summary

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[29]Silverstein agreed that Saiki, which selected 16 plaques and did not pool them back together, does not literally encompass the claim. (D.I. 125, ex. 5 at 76:23-77:11) Defendants' other expert, Johnson, testified that Saiki does not teach amplification of a mixture of different sequence fragments. (*Id.*, ex. 7 at 50:24-51:21 (Saiki "amplified in the sense of a mixture 15 different pieces of DNA but did them separately"))

judgment of no anticipation based on Saiki, the court addresses at this juncture an alternative underpinning for this holding. The parties dispute whether Saiki discloses claim 12's step of "attaching a double-strand linker to the fragments, by ligating the linkers to both strands of the fragments, at both fragment ends."

There are two facets to the inquiry: (1) whether Saiki teaches "linkers" under the parties' constructions in the first instance;[30] and (2) whether Saiki discloses "ligating the linkers" to the fragments. The court need not resolve the first issue as, even assuming (as defendants argue) that the arms of the λgt11 vector that flank the inserted sequence serve as the claimed "linkers," there is no dispute of record that Saiki does not disclose the ligating step. Defendants admit that "the process [of making a cDNA library] is not described in the Saiki article," but argues that "commercial cDNA libraries of this sort were commonly used" and made by a known process. (D.I. 120 at 20) Per defendants,

> [i]n these libraries, many different cDNA fragments or "inserts" are placed in a mixture in a test tube. Ligase and the vector (in this case λgt11), along with other chemicals necessary to make the reaction work are added to the test tube.

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[30]Defendants argue that the "linkers" in Saiki are the λgt11 phage arms that are attached to DNA fragments by ligation. (D.I. 133 at 10) As noted previously, bacterioplages use the infected cell's enzymes to replicate their genomes and package the DNA into new viral particles. The λgt11 cloning vector is cleaved (at the Eco RI restriction site) resulting in λ vector "arms" on either side of the Eco RI site. The two separated fragments (halves) of the λgt11 phage are ligated to both ends of the cDNA fragment to be amplified, "flanking" the cDNA. The recombinant DNA is then packaged into a bacteriophage (a virus), which may then be used to infect bacterial cells in culture. (D.I. 120 at 20-21, *id.*, ex. S at ¶ 19)

Plaintiff disagrees that the λgt11 phage vector, a linear molecule roughly 42,000 base pairs in length (and representing the entire genome of a bacteriophage virus), could be considered a "linker" per its construction, which has been adopted by the court ("[a] relatively small piece of DNA having a known sequence and of sufficient length to bind at least one primer"). (D.I. 125 at 13)

> This causes the "arms" of the vector on either side of the Eco RI site to ligate to the various fragments. At this point, there would still be a mixture of cDNA fragments that have each been ligated at both ends to the phage vector. The result is that known DNA fragments (the two halves of the λgt11 phage) are ligated to both ends of the cDNA fragment to be amplified. These two DNA fragments qualify as linkers under Illumina's definition of the term.

(D.I. 120 at 20-21) (citing *id.*, ex. G at 194:22-24, 195:20-23 and *id.*, ex. E at 88:24-92:3[31])

Put most simply, defendants argue that "Clontech necessarily attached linkers (the λgt11phage arms) to the DNA fragments in the library using ligation" and points out the plaintiff does not offer another alternative for how Clontech could have made the library but for ligation. (D.I. 133 at 10-11 (citing D.I. 120, ex. C at ¶¶ 39-41)) This argument misses the mark, as it is ultimately defendants' burden to demonstrate that Saiki discloses each of the limitations of claim 12 of the '023 patent (arranged as in the claim). There is no evidence at bar that Saiki discloses how the cDNA library was generated, and defendants do not argue that the step is "inherently" disclosed by Saiki. Defendants' arguments relating to how cDNA libraries could have been made at the time of the invention, rather than how the actual library purchased and used by Saiki was made, are relevant to an obviousness analysis, not anticipation. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576-77 (Fed. Cir. 1991) ("If it is necessary to reach beyond the boundaries of a single reference to provide

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[31]Metzker testified that "[t]here was no information in the paper of how the cDNA library was constructed," and then explained a method by which he constructed a cDNA library. (D.I. 120, ex. E at 88:5-92:5) Metzker stated that cDNA libraries were constructed during the relevant time period in two ways, and differentiated between cDNA ligated onto a vector (a circular plasmid) and cDNA ligated onto a phage (a linear molecule). (*Id.*)

missing disclosure of the claimed invention, the proper ground is not § 102 anticipation, but § 103 obviousness.").

Insofar as defendants contend that the "ligation" step was accomplished during the preparation of the commercial cDNA library that Saiki purchased, and there is no dispute that Saiki does not describe how the cDNA library was generated by Clontech, Saiki cannot anticipate. (D.I. 125, ex. 5 at 194:5-8; D.I. 120 at 20 (conceding that "the process is not described in the Saiki article")) Defendants' motion for summary judgment of invalidity is denied on this alternative ground. Accordingly, the court also grants plaintiff's motion for summary judgment of no anticipation with respect to Saiki.

c. Liang

Plaintiff also seeks summary judgment of no anticipation by Liang, a one-page article published in the journal Nucleic Acids Research entitled "Rapid plasmid insert amplification with polymerase chain reaction."[32] The entire text of Liang (exclusive of figure and references) is reproduced below.

> A DNA probe used for prenatal diagnosis of cystic fibrosis, 5'met (1), cloned in vector pUC19, has been amplified with M13 sequencing primers by the polymerase chain reaction technique, PCR (2). The amplification provides high yield, pure probe which gives a signal with low background. The procedure is much quicker and easier than conventional plasmid preparation, digestion and insert fragment isolation.
>
> We isolated plasmid DNA by alkaline extraction and PEG precipitation. Five ng of this DNA was subjected to PCR for 30 cycles in a total volume of 100 µl, with 3 units of Taq DNA polymerase (Cetus), 1 X Taq PCR buffer, 100 picomoles of each of the two primers (New England Biolabs sequencing primer #

[32]While plaintiff provided the citation to Liang (as published at page 3579 of volume 16, number 8 of Nucleic Acids Research in 1988) and a copy of the reference through its hyperlinked iBrief, it does not appear that Liang has been docketed. (D.I. 125 at 3, n.1)

1211 and reverse sequencing primer #1201), and 80 nanomoles of dNTP (dATP + dCTP + cGTP + dTTP, Boehringer Mannheim). The 100 µl mixture was covered by 30 µl of light mineral oil (Sigma). Plasmid DNA was denatured by heating to 95°C for 2 minutes followed by a 2 minute annealing of primers and plasmid at 50°C, and then incubation at 72°C for 2 minutes to extend synthesis of the insert.

The inserted copy was amplified by a factor of about 103 to 104 (1 ng to µg quantities). This is less than genomic copy amplification due to limitation of the yield by primer and dNTP concentrations and by enzyme activity. The insert DNA was isolated by spermine precipitation and resuspended inTE^{-4}. One fourth of this was labeled by the random primer technique with 32p- dCTP and used as a probe.

This procedure can be applied to any insert cloned in a vector with available flanking sequencing primers. The only limitation is the length of insert, but recent reports indicate success with up to 2kb.

Plaintiff argues that summary judgment is appropriate because only one sequence was used in Liang and, as with Saiki, the reference does not teach amplifying a mixture of different sequence DNA fragments. (D.I. 125 at 10-11) Plaintiff also asserts that Liang does not disclose a "linker," because the pUC19 plasmid of Liang is approximately 2,700 base pairs long. (*Id.* at 13)

Defendants admit that the specific example in Liang was limited to amplification on an individual isolate of phage growths, but argue that the reference contains a broader teaching. (D.I. 133 at 14) For support, defendants cite to only one paragraph of Johnson's report, stating that Liang's disclosure of amplification of "any insert cloned in a vector" renders the amplification of different probes simultaneously (using the same method) obvious. (*Id.* at 18 (citing D.I. 120, ex. S at ¶ 35)) On this record, the court grants plaintiff's motion for summary judgment of no anticipation by Liang. Insofar as there is no evidence that Liang disclosed amplifying a mixture of different sequence DNA fragments, the court need not decide whether an issue of fact exists with respect

to Liang's disclosure of a "linker."

V. CONCLUSION

For the aforementioned reasons, the court grants defendants' motion for summary judgment of noninfringement with respect to Illumina's cluster generation products (alone) and the use of third-party prep kits with Illumina's cluster generation products, and denies the motion in all other respects (D.I. 126); denies defendants' motion for summary judgment of invalidity and expiration (D.I. 119); and grants plaintiff's motion for summary judgment of no anticipation by Saiki or Liang (D.I. 124). An appropriate order shall issue.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

LADATECH, LLC,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 09-627-SLR
	)	
ILLUMINA, INC. and SOLEXA, INC.,	)	
	)	
Defendants.	)	

ORDER

At Wilmington this 24th day of January, 2012, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that:

1. Defendants' motion for summary judgment of invalidity and expiration (D.I. 119) is denied.

2. Plaintiff's motion for summary judgment of no anticipation by certain references (D.I. 124) is granted.

3. Defendants' motion for summary judgment of noninfringement (D.I. 126) is granted in part and denied in part.

United States District Judge