

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

THE TRUSTEES OF COLUMBIA)	
UNIVERSITY IN THE CITY OF NEW)	
YORK and QIAGEN WALTHAM, INC.,)	
)	
Plaintiffs,)	
)	
v.)	C.A. No. _____
)	
ILLUMINA, INC.,)	JURY TRIAL DEMANDED
)	
Defendant.)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs The Trustees of Columbia University in the City of New York (“Columbia University”) and QIAGEN Waltham, Inc. (“QIAGEN”) (collectively “Plaintiffs”), by and through their undersigned counsel, for their Complaint against Defendant Illumina, Inc. (“Illumina”), allege as follows:

THE PARTIES

1. Plaintiff Columbia University is one of the world’s leading institutions of higher education, located at 535 West 116th Street, New York, New York 10027. It is a non-profit educational corporation formed by special act of the Legislature of the State of New York.

2. Plaintiff QIAGEN Waltham, Inc. is a Delaware corporation having its principal place of business at 35 Gatehouse Drive, Waltham, Massachusetts 02451.

3. Upon information and belief, Defendant Illumina, Inc. is a Delaware corporation having its principal place of business at 5200 Illumina Way, San Diego, California 92122.

JURISDICTION AND VENUE

4. This action arises under the Patent Laws of the United States of America, 35

U.S.C. § 1 *et seq.*

5. This Court has federal question subject matter jurisdiction over this action under 28 U.S.C. § 1331 and 28 U.S.C. § 1338(a) because this is a civil action arising under the Patent Act.

6. This Court has personal jurisdiction over Illumina because Illumina is incorporated in the State of Delaware.

7. Venue is proper in this District under 28 U.S.C. § 1400(b) because Illumina is incorporated in the State of Delaware and thus resides in this District.

BACKGROUND

The '358 Patent

8. On July 18, 2017, the United States Patent and Trademark Office (“USPTO”) duly issued United States Patent No. 9,708,358 (“the ’358 Patent”), entitled “Massive Parallel Method for Decoding DNA and RNA,” in the name of inventors Jingyue Ju, Zengmin Li, John Robert Edwards, and Yasuhiro Itagaki.

9. Columbia University owns by assignment all right, title and interest in and to the ’358 Patent.

10. QIAGEN is the exclusive licensee of the ’358 Patent.

11. On March 30, 2017, the application that issued as the ’358 Patent published as US2017/0088574 (“the Published Application”). A true and correct copy of the Published Application is attached hereto as Exhibit 1.

12. The invention as claimed in the ’358 Patent is identical to the invention as claimed in the Published Application.

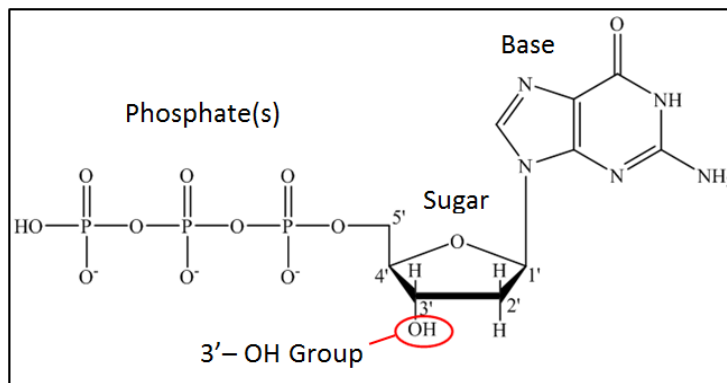
13. Illumina is a large and sophisticated company that has had patent litigation in

Delaware with Columbia and QIAGEN, and thus, on information and belief, Illumina monitors patent applications involving DNA sequencing technology and was aware of the content of claim 1 of the '358 Patent on or after it was published on March 30, 2017.

Nucleotides and DNA Sequencing

14. The '358 Patent relates to modified versions of nucleotides (known as “nucleotide analogues”) for use in methods of sequencing DNA (deoxyribonucleic acid). DNA encodes the genetic information of living organisms. DNA consists of smaller building blocks called nucleotides; the sequence of the nucleotides determines hereditary traits in living organisms. DNA sequencing—i.e., determining the order of the nucleotides in a DNA strand—is of enormous importance for a wide variety of applications in medicine, biotechnology, and other fields. For example, by sequencing the DNA of individuals with a particular disease or the DNA in tumor cells, medical researchers and physicians may learn the genetic basis for the disease or tumor and may design or provide therapies specifically targeted to it.

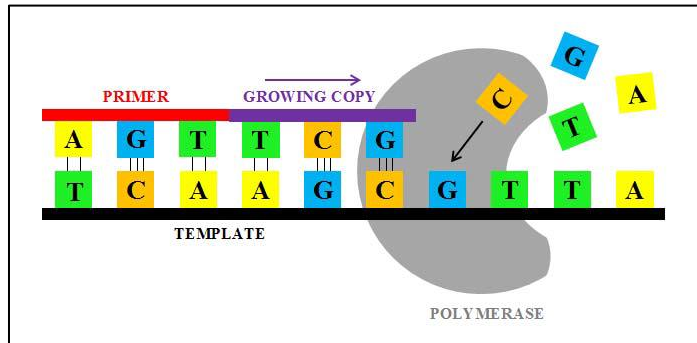
15. A nucleotide consists of a sugar, a base, and one or more phosphate groups, as shown below. Nucleotides are determined by their base, which is where the genetic code of DNA resides. There are four different nucleotide bases—an adenine (“A”), a guanine (“G”), a cytosine (“C”), and a thymine (“T”). A and G are known as “purine” bases, while C and T are “pyrimidine” bases. The sugar in the nucleotide contains five carbon atoms, conventionally numbered 1' through 5'. When the nucleotide is found in isolation, a hydroxyl group (OH) is attached at the 3' position and is referred to as the 3'-OH group (circled below). The nucleotide depicted below is called a deoxyribonucleotide triphosphate.



16. DNA consists of a chain of nucleotides, held together by bonds between a phosphate group of one nucleotide and a 3'-OH group of another nucleotide. In nature, two such chains of nucleotides form a double helix structure (forming a DNA double helix). Bonds between complementary base pairs hold the chains together, and base pairs always bond in the same way: A always pairs with T; C always pairs with G. These bonds between complementary base pairs form the “cross-bars” in the DNA double helix while the bonds between the phosphate group of one nucleotide and the 3'-OH group of the adjacent nucleotide forms the “backbone” of the DNA double helix.

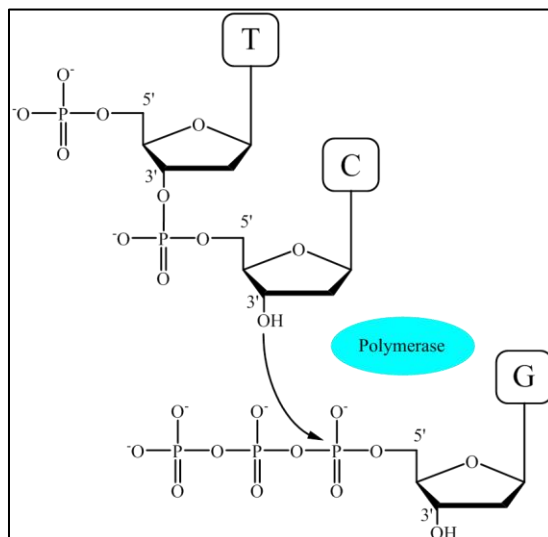
17. To duplicate, or “synthesize,” DNA, the two strands of the DNA double helix are first unwound and separated. Each strand of nucleotides can then serve as the *template* for the production (or *copying*) of a complementary strand. Synthesis of DNA typically begins with the use of a short strand of nucleotides, called a *primer*, which is designed to match, and therefore bind to, the corresponding nucleotides at the beginning of the *template* strand to be copied, as shown below. An enzyme called a *polymerase* extends the primer along the template by adding nucleotides with bases that are complementary to the nucleotides of the template being copied via the base-pairing rules: A-T and C-G. For example, if the next nucleotide in the template to be copied has a G base, the polymerase would incorporate into the growing primer chain a

nucleotide with a complementary C base.



18. As shown above, each letter in a square is a nucleotide. The polymerase also facilitates the formation of a bond between a phosphate group at the 5'-position of a free nucleotide and the 3'-OH group of the last nucleotide incorporated into the growing copy, thus adding the next nucleotide to the growing strand.

19. This reaction can only occur when the last nucleotide in the growing strand has a 3'-OH group available for linking to a phosphate group of an incoming nucleotide, as shown below.



Columbia's '358 Patent

20. The '358 Patent discloses and claims nucleotide analogues for use in a type of

“next generation sequencing” (or “NGS”) technology called “sequencing by synthesis” (“SBS”). NGS technologies are used in a variety of medical and research applications, including identifying genes and polymorphisms associated with disease and with individual variability in drug response, and are important to genomics research and discovery, particularly in the emerging field of personalized precision medicine, which seeks to use a patient's own genomic DNA sequence information as the basis for individualized healthcare.

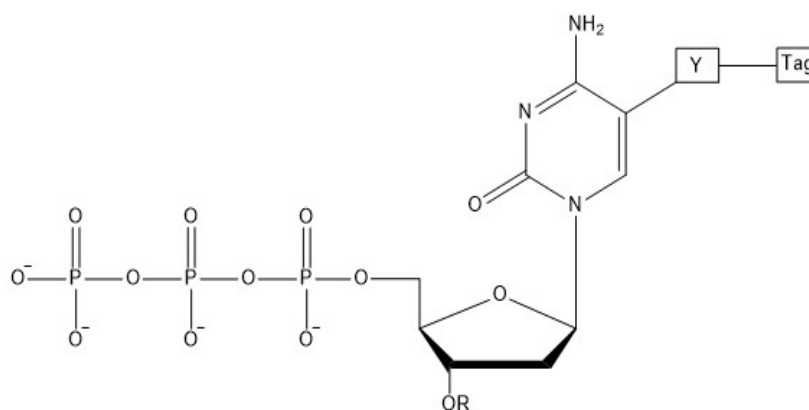
21. Generally speaking, SBS involves the use of modified nucleotides that take advantage of the foregoing reaction used to grow a DNA strand. The method uses modified nucleotides with removable, “caps” (also called “protecting groups,” or “blocking groups”) attached to the 3'-OH group on the sugar portion of the nucleotide. The modified nucleotides also have detectable labels attached to them, to signal whether the nucleotides are an A, C, T, or G. When a polymerase incorporates such a nucleotide into a growing chain, the synthesis stops because the 3'-OH group—where the polymerase would otherwise join the phosphate group of the next nucleotide—is blocked by the cap. Once the process is stopped, the label on the nucleotide is detected to identify which base was incorporated. After the label is detected, the label and the cap are removed (or “cleaved”), allowing the polymerase to add another labeled nucleotide to the chain for continuous DNA sequencing.

22. The '358 Patent teaches a nucleotide analogue that uses a small cleavable chemical moiety to cap the 3'-OH group of the deoxyribose, along with cleavable labels attached to the base of each nucleotide. The '358 Patent further teaches that the cleavable chemical cap “is stable during the polymerase reaction,” and “does not interfere with the recognition of the nucleotide analogue by polymerase as a substrate,” and that “the growing strand of DNA should survive the . . . cleavage process [].”

23. In addition to teaching the use of small chemically cleavable capping groups, the '358 patent also *excludes* certain chemical groups for use as caps in this SBS method. For example, the '358 patent claims that the "OR" of the nucleotide shall not be either a methoxy or an ester group. Similarly, the '358 patent claims that the cleavable chemical group used as a cap in the SBS method should not include a ketone group.

24. Claim 1 of the '358 Patent recites:

1. A cytosine deoxyribonucleotide analogue having the structure:



wherein R (a) represents a small, chemically cleavable, chemical group capping the oxygen at the 3' position of the deoxyribose of the deoxyribonucleotide analogue, (b) does not interfere with recognition of the analogue as a substrate by a DNA polymerase, (c) is stable during a DNA polymerase reaction, and (d) does not contain a ketone group;

wherein OR is not a methoxy group or an ester group;

wherein the covalent bond between the 3'-oxygen and R is stable during a DNA polymerase reaction;

wherein tag represents a detectable fluorescent moiety;

wherein Y represents a chemically cleavable, chemical linker which (a) does not interfere with recognition of the analogue as a substrate by a DNA polymerase and (b) is stable during a DNA polymerase reaction; and

wherein the cytosine deoxyribonucleotide analogue:

- i) is recognized as a substrate by a DNA polymerase,
- ii) is incorporated at the end of a growing strand of DNA during a DNA polymerase reaction,
- iii) produces a 3'-OH group on the deoxyribose upon cleavage of R,
- iv) no longer includes a tag on the base upon cleavage of Y, and
- v) is capable of forming hydrogen bonds with guanine or a guanine nucleotide analogue.

Illumina Makes, Uses, and Sells Nucleotide Analogues that Infringe the '358 Patent

25. Illumina manufactures, uses, imports and/or sells DNA sequencing instruments in the United States. These DNA sequencing instruments include at least the following: HiSeq X Ten system, HiSeq X Five system, HiSeq 2500 system, HiSeq 3000 system, HiSeq 4000 system, MiSeq system, MiSeqDx system, MiniSeq system, NextSeq 500 and 550 systems, NovaSeq 5000 system, and NovaSeq 6000 system (collectively "Accused Instruments").

26. Illumina manufactures, uses, imports, and/or sells a number of reagent kits for use with the Accused Instruments that contain nucleotide analogues that infringe claim 1 of the '358 Patent. These include, but are not limited to, at least the following: HiSeq 3000/4000 SBS Kit, HiSeq Rapid SBS Kit v2, HiSeq SBS Kit v4, MiSeq FGx Reagent Kit, MiSeq Reagent Kit v3, MiSeq Reagent Kit v2, MiniSeq Reagent Kit, NextSeq 500/550 v2 Kits, NovaSeq Reagent Kits, TruSeq Rapid SBS Kits (200 Cycle and 50 Cycle) – HS, TruSeq SBS Kit v3-HS, and TruSeq SBS Kit v5-GA (collectively "Accused Kits").

27. Illumina also offers a DNA lab service, in which it tests samples for a fee, on information and belief using the Accused Kits and Accused Instruments to do so. As Illumina states on its web site, "Illumina FastTrack Sequencing Services has been providing whole-

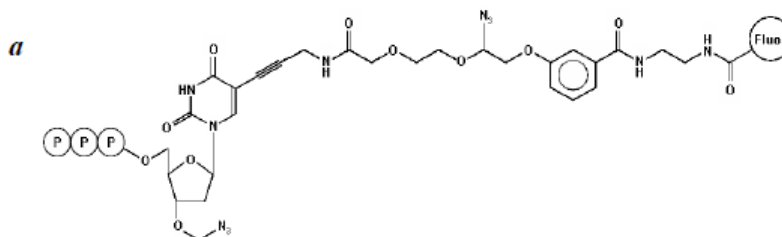
genome sequencing services for years. . . . The lab offers years of experience with proven Illumina sequencing technology, and production continues to grow year over year.” (See <https://www.illumina.com/services/sequencing-services.html> (emphasis added) (attached as Exhibit 5).)

28. On November 6, 2008, authors from Illumina and others published an article in *Nature* titled “Accurate Whole Human Genome Sequencing using Reversible Terminator Chemistry” (“Bentley article”). A true and correct copy of the Bentley article is attached hereto as Exhibit 2. Along with the Bentley article, *Nature* also published “Supplementary Information” that provides more detail regarding Illumina’s sequencing methods that Illumina published in the Bentley article. A true and correct copy of the Supplementary Information is attached hereto as Exhibit 3.

29. Illumina states in the Bentley article that the sequencing methods shown in the article are “the basis for the standard protocols now available from Illumina, Inc.” Ex. 2 at 58. Accordingly, on information and belief, the nucleotide analogues described in the Bentley article and Supplementary Information are the same as (or substantially the same as) the nucleotide analogues contained in the Accused Kits.

30. Illumina disclosures in the Bentley article and its Supplementary Information confirm that Illumina uses the claimed deoxyribonucleotide analogue in Illumina’s sequencing technology. For example, the Bentley article provides that “[t]o ensure base-by-base nucleotide incorporation in a stepwise manner, [Illumina uses] a set of four reversible terminators, 3’-O-azidomethyl 2’-deoxynucleoside triphosphates (A, C, G and T) each labelled with a different removable fluorophore (Supplementary Fig. 1a).” Ex. 2 at 53. Fig. 1a from the Supplementary Information provides the “[s]tructure of the reversible terminator 3’-O-azidomethyl 2’-

deoxythymine triphosphate (T) labeled with a removable fluorophore.” Ex. 3 at 14, Fig. S1.a.



Although only the structure for the thymine (T) nucleotide is provided, the Bentley article indicates that the A, C, and G nucleotides each have the same protecting group. Ex. 2 at 53.

31. To demonstrate how Illumina’s nucleotide analogues infringe claim 1 of the ’358 Patent , attached as Exhibit 4 is a preliminary and exemplary claim chart. This chart is illustrative only and not intended to limit Plaintiffs’ right to modify this chart or provide any other claim chart or allege that other Illumina nucleotide analogues infringe claim 1 of the ’358 Patent. Exhibit 4 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 4 that is mapped to Illumina’s nucleotide analogues shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

32. On information and belief, Illumina directly infringes claim 1 of the ’358 Patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by making, using, offering for sale, selling, and/or importing into the United States the Accused Kits. Illumina also actively induces infringement of the ’358 Patent pursuant to 35 U.S.C. § 271(b).

CLAIM FOR RELIEF

Infringement of U.S. Patent No. 9,708,358

33. Plaintiffs re-allege and incorporate by reference the allegations contained in paragraphs 1-32 above.

34. Illumina directly infringes claim 1 of the '358 Patent, literally or under the doctrine of equivalents, by making, using, offering for sale, selling and/or importing into the United States the Accused Kits. Attached as Exhibit 4 is a claim chart showing specifically element-by-element how Illumina's Accused Kits infringe claim 1 of the '358 Patent.

35. At least as of the service of this Complaint, Illumina also is actively inducing infringement of claim 1 of the '358 Patent in violation of 35 U.S.C. § 271(b). Users of the Accused Kits, including Illumina's customers, directly infringe claim 1 of the '358 Patent when they use the Accused Kits with the Accused Instruments. Illumina knowingly induces the users of the Accused Kits by selling such users the Accused Instruments with instructions (attached hereto as Exhibit 6) that the Accused Instruments can only be used with the Accused Kits. *See, e.g.,* Ex. 6 at 14 ("To perform a [sequencing] run on the MiSeq, you need a single-use MiSeq Reagent Kit, which is available in different types and sizes. Each type of MiSeq Reagent Kit includes a kit-specific flow cell type and all reagents required for performing a [sequencing] run."). Based on the allegations in this Complaint and the attached claim chart, Illumina has knowledge that use of the Accused Kits by its customers infringes claim 1 of the '358 Patent.

36. Illumina's infringement of the '358 Patent is damaging and will continue to damage Plaintiffs.

37. Illumina's continuing infringement of the '358 Patent will irreparably harm Plaintiffs, and Illumina's infringement will continue unless enjoined by this Court pursuant to 35 U.S.C. § 283.

38. Illumina is a large and sophisticated company that has had patent litigation in Delaware with Columbia and QIAGEN, and thus, on information and belief, Illumina monitors patent applications involving DNA sequencing technology and was aware of the content of claim

1 of the '358 Patent on or after it was published on March 30, 2017.

39. This is an exceptional case entitling Plaintiffs to reasonable attorneys' fees pursuant to 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully requests that this Court enter judgment against Illumina, granting Plaintiffs the following relief:

A. A judgment holding Illumina liable for direct and indirect infringement of the '358 Patent and for violating Plaintiffs' provisional rights in the '358 Patent;

B. Damages resulting from Illumina's infringement of the '358 Patent in an amount to be proven at trial, but no less than a reasonable royalty, together with pre-judgment and post-judgment interest;

C. A reasonable royalty resulting from Illumina's violation of Plaintiffs' provisional rights under 35 U.S.C. § 154(d), together with pre-judgment and post-judgment interest;

D. An injunction permanently enjoining Illumina under 35 U.S.C. § 283 from infringing the '358 Patent, including by specifically prohibiting Illumina from making, using, offering for sale, selling and/or importing into the United States any product which falls within the scope of the '358 Patent;

E. A judgment holding this to be an exceptional case, and an award to Plaintiffs of their attorneys' fees and costs pursuant to 35 U.S.C. § 285; and

F. Such other and further relief as the Court deems just and equitable.

DEMAND FOR JURY TRIAL

Pursuant to Federal Rule of Civil Procedure 38(b) and D. Del. LR 38.1, Plaintiffs hereby demand a trial by jury on all issues so triable.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

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