IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PACIFIC BIOSCIENCES OF CALIFORNIA, INC. *Plaintiff,* vs. OXFORD NANOPORE TECHNOLOGIES, INC. *Defendant.*	Civil Action No. _____ JURY TRIAL DEMANDED

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Pacific Biosciences of California, Inc. ("Plaintiff" or "PacBio") for its complaint against Defendant Oxford Nanopore Technologies, Inc. ("Oxford") alleges and states the following:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the United States Patent Act, 35 U.S.C. §§1, *et seq*., including 35 U.S.C. § 271.

2. PacBio brings this action to halt Oxford's infringement of PacBio's rights under the Patent Laws of the United States 35 U.S.C. § 1, *et seq.*, which arise under U.S. Patent Nos. 9,678,056 (the "'056 patent," attached as Exhibit 1) and 9,738,929 (the "'929 patent," attached as Exhibit 2).

THE PARTIES

3. PacBio is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1305 O'Brien Drive, Menlo Park, California 94025.

4. PacBio was founded in the year 2000. PacBio develops, manufactures, and sells a novel DNA sequencing platform that helps researchers resolve genetically complex problems. PacBio's DNA sequencing technology is based on real-time detection of the incorporation of nucleotides into a single strand of DNA. That technology goes by the name "SMRT®" sequencing, which is short for "Single Molecule, Real-Time" sequencing. PacBio's SMRT® sequencing platform encompasses not just DNA sequencing instruments but also novel sequencing chips and chemical reagents for use with PacBio's DNA sequencing instrument and sophisticated software for analyzing the data that emerges from PacBio's sequencing instruments.

5. PacBio's SMRT® Sequencing Platform and technology allows researchers to carry out numerous applications, including at least: (1) de novo genome assembly to finish genomes in order to more fully identify, annotate, and decipher genomic structures; (2) targeted sequencing to more comprehensively characterize genetic variations; and (3) identification of DNA base modifications to help characterize epigenetic regulation and DNA damage. PacBio's SMRT® Sequencing Platform and technology provides high-accuracy, ultra-long reads and uniform coverage, and is believed to be the only DNA sequencing technology that provides the ability to simultaneously detect epigenetic changes.

6. In addition to the commercialization of its flagship SMRT® sequencing platform, PacBio has broad expertise in single-molecule sequencing and is engaged in exploratory work related to single-molecule sequencing, including techniques related to single-molecule sequencing based on detection platforms such as nanopores. Collectively, PacBio's research and development efforts have resulted in a patent portfolio that includes over 330 issued U.S. patents and pending applications related to single-molecule sequencing techniques.

7. Defendant Oxford is a corporation organized under the laws of Delaware with its principal place of business at 1 Kendall Square, Bldg. 200, Cambridge, Massachusetts 02139. On information and belief, Oxford is engaged in the commercialization throughout the United States of nanopore-based single-molecule sequencing products, including at least the MinION, GridION X5, PromethION, and SmidgION sequencing instruments, reagents and kits for use with these instruments, and the 2D and 1D Squared products.

JURISDICTION AND VENUE

8. This action arises under the Patent Laws of the United States, Title 35, United States Code, §§ 1 *et seq.*, including 35 U.S.C. §§ 271 and 281.

9. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

10. This Court has personal jurisdiction over defendant Oxford. Oxford has substantial contacts with the forum as a consequence of conducting business in Delaware, and has purposefully availed itself of the benefits and protections of Delaware state law by incorporating under Delaware law.

11. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and (c), and 1400(b) because Oxford is a Delaware corporation and Delaware is a convenient forum for resolution of the parties' disputes set forth herein.

BACKGROUND

12. On information and belief, in the 2015 timeframe, Oxford began commercializing single-molecule sequencing products based on the use of protein nanopores. Oxford purports to offer a single-molecule sequencing product that, like PacBio's products, is capable of determining the sequence of long stretches of DNA in a single pass. The ability to generate such

"long reads" is an area where PacBio has and continues to be widely recognized as the technical and commercial leader. PacBio and Oxford compete in the single-molecule sequencing market.

13. Oxford's single-molecule sequencing products include at least the MinION, GridION X5, PromethION, and SmidgION sequencing instruments and reagents, consumables, and software for use with same, including without limitation reagents and kits used to generate "2D reads" and "1D squared reads" using Oxford's sequencing instruments (collectively, the "Accused Products"). For example, two views of a representative MinION device are shown below:



Figure 4. (A) MinION MkI (B) flow cell (C) nanopore array (Individual nanopore cells reproduced, modified, with permission from Oxford Nanopore).

Exhibit 5; Exhibit 6 at 292. The top image shows a working MinION device, and the bottom view shows the interior of the device. The portion labeled "C" in the above photograph depicts a flow cell with an array of individual nanopores. Nanopores are tiny holes embedded into a membrane and are formed by inserting proteins that have a hollow tube through their center into a polymer membrane, as shown in the image below:

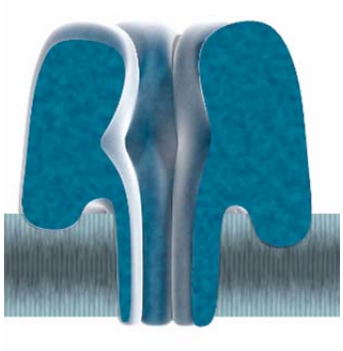


Exhibit 7. The Accused Products each include one or more flow cells that include a "nanopore array."

14. While the MinION instrument includes a single flow cell, the PromethION instrument includes 48 flow cells and has been described as a "whole box of MinION sequencers." Exhibit 8. A representative PromethION instrument with its 48 flow cells is shown below:



Id.

15. Similarly, the GridION X5 is an instrument that is described by Oxford as containing "up to five MinION Flow Cells." Exhibit 15. A representative GridION X5 instrument with its 5 flow cells is shown below:



Id.

16. The SmidgION is an instrument that contains a single flow cell. Oxford describes the SmidgION as "us[ing] the same core nanopore sensing technology as MinION" in a "smaller device" "for use with smartphones or other mobile, low power devices." Exhibit 14. A representative image of the SmidgION instrument is shown below:



Id.

17. To sequence DNA using any one of the Accused Products, one first applies a voltage across the membrane such that an electrical current flows through the hole. A strand of DNA is then drawn through the hole:



Exhibit 9. As the DNA passes through the hole, it disrupts the electrical current that is passing through the hole, thus producing a signal. To evaluate the sequence, one can attempt to correlate this signal with the DNA bases that are passing through the hole.

18. More particularly, in nanopore-based DNA sequencing systems, such as the Accused Products sold by Oxford, the signal that results from passage of the DNA through the nanopore arises not just from a single DNA base, but from a contiguous group of DNA bases that interacts with the nanopore at a given time. Therefore, to determine the DNA sequence, the software made available by Oxford for use with the Accused Products uses calibration information produced by measuring the signals from the different combinations of bases that may interact with the nanopore at a given time.

19. To increase accuracy, Oxford's products utilize at least two additional features. First, Oxford utilizes a motor protein consisting of modified enzyme that modulates the rate of

translocation, allowing one to better capture the signals that arise from the nanopore. Second, Oxford uses techniques based on redundant sequencing in which one sequences complementary strands of DNA to generate a consensus sequence.

COUNT I

(Infringement of U.S. Patent No. 9,678,056)

20. Plaintiff repeats and re-alleges each and every allegation contained in the preceding paragraphs of this Complaint as if stated in their entirety herein, and incorporates them herein by reference.

21. The ’056 patent, entitled “Control of Enzyme Translocation in Nanopore Sequencing,” issued on June 13, 2017, to inventors Steven Turner and Benjamin Flusberg. The ’056 patent is assigned on its face to Plaintiff PacBio. PacBio is the owner of all rights, title to and interest in the ’056 patent.

22. Oxford infringes, literally or under the doctrine of equivalents, both directly and indirectly (by inducement and by contribution), PacBio’s ’056 patent through its activities connected to at least the Accused Products.

23. On information and belief, Oxford has directly infringed and continues to directly infringe at least claim 1 of the ’056 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by using within the United States without authority the Accused Products. As an example, attached as Exhibit 3 is a preliminary and exemplary claim chart detailing Oxford’s infringement of this claim of the ’056 patent. This chart is not intended to limit PacBio’s right to modify the chart or allege that other products and/or activities of Oxford infringe the identified claim or any other claims of the ’056 patent or any other patents. Exhibit 3 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 3 that is

mapped to Oxford's Accused Products shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

24. For instance, claim 1 of the '056 patent is listed below:

> A method for sequencing a nucleic acid template comprising:
>
> [a] providing a substrate having an upper solution above the substrate, a lower solution below the substrate, the substrate comprising a nanopore connecting the upper solution and lower solution, the nanopore sized to pass a single strand of nucleic acid;
>
> [b] providing a voltage across the nanopore to produce a measurable current flow through the nanopore;
>
> [c] controlling the rate of translocation of a single stranded portion of the nucleic acid template through the nanopore with a translocating enzyme that is associated with the nucleic acid template under reaction conditions whereby the translocating enzyme and the reaction conditions are selected such that the translocating enzyme exhibits two kinetic steps wherein each of the kinetic steps has a rate constant, and the ratio of the rate constants of the kinetic steps is from 10:1 to 1:10;
>
> [d] measuring the current through the nanopore over time as the nucleic acid template is translated through the nanopore; and
>
> [e] determining the sequence of a portion of the nucleic acid template as it translates through the nanopore using the measured current over time.

25. Use of Oxford's products leads to direct infringement of this claim in at least the following way: Oxford's products include a nucleic acid sequencing instrument having a substrate, which is a nanopore in a membrane, and an upper solution above the membrane and a lower solution below the membrane (step a). Nucleic acid molecules are sequenced by passing a nucleic acid molecule strand through the nanopore, which connects the upper and lower solutions and is sized to pass a single strand of nucleic acid through. A voltage is then applied across the membrane to drive a current across the membrane (step b). The rate of translocation of a single

stranded portion of the nucleic acid template through the nanopore is controlled via a translocating enzyme that is associated with the nucleic acid template under reaction conditions. The translocating enzyme exhibits two steps where the rate constant for portions of the template molecule translocation would fall within the claimed range of 10:1 to 1:10 (step c). The current through the nanopore is measured over time as the nucleic acid template is translated through the nanopore (step d). As a nucleic acid molecule to be sequenced is drawn through the nanopore, the current is disrupted and measured using an ASIC chip which is part of the sequencing instrument. The sequence of the nucleic acid template is then determined using Oxford's basecalling software, based on the current measurements as the nucleic acid template is translated through the nanopore (step d).

26. On information and belief, Oxford has monitored PacBio's patent filings and has been aware of the '056 patent since its issuance on June 13, 2017. At a minimum, Oxford has had knowledge of and notice of the '056 patent and its infringement since at least, and through, the filing and service of PacBio's complaint in this action and despite this knowledge continues to commit the aforementioned infringing acts.

27. Oxford actively, knowingly, and intentionally has induced, or has threatened to induce, infringement of at least claim 1 of the '056 patent through a range of activities. First, on information and belief, Oxford has induced infringement by controlling the design and manufacture of, offering for sale, and selling the Accused Products with the knowledge and specific intent that its customers will use the Accused Products to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Oxford has admitted in an ongoing International Trade Commission

investigation that it imports, sold for importation, and or/sells its MinION product and PromethION product within the United States. *See* Exhibit 10 ¶ 53.

28. Second, on information and belief, Oxford has induced infringement by its customers through the dissemination of promotional and marketing materials relating to the Accused Products with the knowledge and specific intent that its customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Oxford promotes the Accused Products on its website, stating that its products offer numerous benefits such as real-time DNA/RNA sequencing, no capital cost, long reads, scalability, high-fidelity, and rapid library preparation time. *See* Exhibit 11.

29. Third, on information and belief, Oxford has induced infringement by its customers through the creation of distribution channels for the MinION and/or PromethION instruments in the United States with the knowledge and specific intent that its customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Oxford's website allows customers in the United States to purchase starter packs of Oxford's MinION and GridION X5 instruments that, when used, will lead to infringement of the '056 patent. As Oxford's website states, "[b]uy a Starter Pack to join the growing numbers in the Nanopore Community." *See* Exhibit 12. As another example, Oxford has created an early access program for its PromethION instrument that provides access to a PromethION device, site installation support, flow cells and reagents, and further information and support. *See* Exhibit 13. As another example, Oxford's website allows potential customers in the United States to register their interest in Oxford's

SmidgION instrument, so that they can "be one of the first to start using SmidgION." Exhibit 14.

30. Fourth, on information and belief, Oxford has induced infringement through the distribution of other instructional materials, product manuals, and technical materials with the knowledge and the specific intent to encourage and facilitate its customer's infringing (either literally or under the doctrine of equivalents) use of the Accused Products. Oxford is liable for its induced infringement of the '056 patent pursuant to 35 U.S.C. § 271 (b).

31. Oxford has contributed to, or has threatened to contribute to, the infringement by its customers of the '056 patent by, without authority, selling and offering to sell within the United States materials and apparatuses for practicing the claimed invention of the '056 patent, including, at least, the Accused Products. When, for example, any of the Accused Products is used by Oxford's customers for nucleic acid sequencing, the claimed method of the '056 patent for sequencing a nucleic acid template is performed, thereby infringing, literally or under the doctrine of equivalents, at least claim 1 of the '056 patent.

32. On information and belief, Oxford knows that the Accused Products each constitute a material part of the inventions of the '056 patent and that they are not a staple article or commodity of commerce suitable for substantial noninfringing use. As documented above, the Accused Products consist of specialized substrates containing protein nanopores that are used in conjunction with specialized reagents for the purpose of sequencing nucleic acid templates. *See supra* ¶¶ 12–19, 22-25. As such, none of the Accused Products nor any of the reagent kits for use with the Accused Products is a staple article of commerce suitable for substantial non-infringing use. Oxford knows that the Accused Products are not staple articles or commodities of commerce suitable for substantial non-infringing use because the Accused Products have no

use apart from infringing the ’056 patent. Oxford is liable for its contributory infringement of the ’056 patent pursuant to 35 U.S.C. § 271(c).

33. Oxford’s infringement of the ’056 patent has injured PacBio in its business and property rights. PacBio is entitled to recover monetary damages for such injuries pursuant to 35 U.S.C. § 284 in an amount to be determined at trial. Oxford’s infringement of the ’056 patent has caused irreparable harm to PacBio and will continue to cause such harm unless and until Oxford’s infringing activities are enjoined by this Court.

COUNT II

(Infringement of U.S. Patent No. 9,738,929)

34. Plaintiff repeats and re-alleges each and every allegation contained in the preceding paragraphs of this Complaint as if stated in their entirety herein, and incorporates them herein by reference.

35. The ’929 patent, entitled “Nucleic Acid Sequence Analysis,” issued on August 22, 2017, to inventors Stephen Turner, Jon Sorenson, Kenneth Mark Maxham John Eid, Cheryl Heiner, and Kevin Travers. The ’929 patent is assigned on its face to Plaintiff PacBio. PacBio is the owner of all rights, title to and interest in the ’929 patent.

36. Oxford infringes, literally or under the doctrine of equivalents, both directly and indirectly (by inducement and by contribution), PacBio’s ’929 patent through its activities connected to at least the Accused Products when used with at least Oxford’s kits and reagents for generating “2D reads” and “1D squared reads.”

37. On information and belief, Oxford has directly infringed and continues to directly infringe at least claim 1 of the ’929 patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by using within the United States without authority the Accused Products when used with at least Oxford’s kits and reagents for generating “2D reads” and “1D

squared reads." As an example, attached as Exhibit 4 is a preliminary and exemplary claim chart detailing Oxford's infringement of this claim of the '929 patent. This chart is not intended to limit PacBio's right to modify the chart or allege that other products and/or activities of Oxford infringe the identified claim or any other claims of the '929 patent or any other patents. Exhibit 4 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 4 that is mapped to Oxford's Accused Products shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each allegation is required.

38. For instance, claim 1 of the '929 patent is listed below:

> A method of determining a nucleotide sequence of a region of interest in a polynucleotide, the method comprising:
>
> [a] introducing a polynucleotide comprising a region of interest to a sequence analysis system comprising a nanopore in a membrane, wherein the polynucleotide comprises a double-stranded portion comprising complementary strands of the region of interest;
>
> [b] applying a voltage across the membrane;
>
> [c] monitoring variations in ionic current through the nanopore of the sequence analysis system during enzyme chaperone-regulated passage of the polynucleotide through the nanopore;
>
> [d] analyzing the monitored variations in ionic current to obtain nucleotide sequence information for the polynucleotide, wherein the nucleotide sequence information comprises redundant sequence information for the region of interest, wherein the redundant sequence information comprises the nucleotide sequence of the complementary strands; and
>
> [e] determining a consensus sequence for the region of interest based on the redundant sequence information.

39. Use of Oxford's products leads to direct infringement of this claim in at least the following way: Oxford's products include a sequence analysis system having a nanopore in a membrane (step a). A double-stranded polynucleotide is sequenced by unzipping the double

strand to form a long single strand which is fed through the nanopore. A voltage is then applied across the membrane to drive a current across the membrane (step b). An enzyme regulates the passage of the polynucleotide through the nanopore, and variations in the ionic current through the nanopore of the sequence analysis system is measured and monitored (step c). The sequence of the polynucleotide is then determined using Oxford's basecalling software, based on the variations in the monitored ionic current as the polynucleotide is passed through the nanopore When Oxford's sequencing instruments are used with Oxford's kits and reagents for generating either "2D reads" or "1D squared reads," redundant sequence information is generated and the analysis uses redundant sequence information including the sequence information from the sense and antisense strands of DNA. (step d). Based on the analysis of redundant sequence information, a consensus sequence is determined (step e).

40. On information and belief, Oxford has monitored PacBio's patent filings and has been aware of the '929 patent since its issuance on August 22, 2017. At a minimum, Oxford has had knowledge of and notice of the '929 patent and its infringement since at least, and through, the filing and service of PacBio's complaint in this action and despite this knowledge continues to commit the aforementioned infringing acts.

41. Oxford actively, knowingly, and intentionally has induced, or has threatened to induce, infringement of at least claim 1 of the '929 patent through a range of activities. First, on information and belief, Oxford has induced infringement by controlling the design and manufacture of, offering for sale, and selling the Accused Products with the knowledge and specific intent that its customers will use the Accused Products to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Oxford has admitted in an ongoing International Trade Commission

investigation that it imports, sold for importation, and or/sells its MinION product and PromethION product within the United States. *See* Exhibit 10 ¶ 53.

42. Second, on information and belief, Oxford has induced infringement by its customers through the dissemination of promotional and marketing materials relating to the Accused Products with the knowledge and specific intent that its customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for sequencing a nucleic acid template. For instance, Oxford promotes the Accused Products on its website, stating that its products offer numerous benefits such as real-time DNA/RNA sequencing, no capital cost, long reads, scalability, high-fidelity, and rapid library preparation time. *See* Exhibit 11.

43. Third, on information and belief, Oxford has induced infringement by its customers through the creation of distribution channels for the MinION and/or PromethION instruments in the United States with the knowledge and specific intent that its customers will use these instruments to infringe, literally or under the doctrine of equivalents, by performing the claimed method for determining a nucleotide sequence of a region of interest in a polynucleotide. For instance, Oxford's website allows customers in the United States to purchase starter packs of Oxford's MinION and GridION X5 instruments that, when used, will lead to infringement of the '929 patent. As Oxford's website states, "[b]uy a Starter Pack to join the growing numbers in the Nanopore Community." *See* Exhibit 12. As another example, Oxford has created an early access program for its PromethION instrument that provides access to a PromethION device, site installation support, flow cells and reagents, and further information and support. *See* Exhibit 13. As another example, Oxford's website allows potential customers in the United States to

register their interest in Oxford's SmidgION instrument, so that they can "be one of the first to start using SmidgION." Exhibit 14.

44. Fourth, on information and belief, Oxford has induced infringement through the distribution of other instructional materials, product manuals, and technical materials with the knowledge and the specific intent to encourage and facilitate its customer's infringing (either literally or under the doctrine of equivalents) use of the Accused Products. Oxford is liable for its induced infringement of the '929 patent pursuant to 35 U.S.C. § 271 (b).

45. Oxford has contributed to, or has threatened to contribute to, the infringement by its customers of the '929 patent by, without authority, selling and offering to sell within the United States materials and apparatuses for practicing the claimed invention of the '929 patent, including at least Accused Products. When, for example, any of the Accused Products is used by Oxford's customers for sequencing a polynucleotide, the claimed method of the '929 patent for determining a nucleotide sequence of a region of interest in a polynucleotide is performed, thereby infringing, literally or under the doctrine of equivalents, at least claim 1 of the '929 patent.

46. On information and belief, Oxford knows that the Accused Products each constitute a material part of the inventions of the '929 patent and that they are not a staple article or commodity of commerce suitable for substantial noninfringing use. As documented above, the Accused Products consist of specialized substrates containing protein nanopores that are used in conjunction with specialized reagents for the purpose of determining a nucleotide sequence of a region of interest in a polynucleotide. *See supra* ¶¶ 12–19, 35-39. As such, none of the Accused Products nor any of the reagent kits for use with the Accused Products is a staple article of commerce suitable for substantial non-infringing use. Oxford knows that the Accused

Products are not staple articles or commodities of commerce suitable for substantial non-infringing use because the Accused Products have no use apart from infringing the ’929 patent. Oxford is liable for its contributory infringement of the ’929 patent pursuant to 35 U.S.C. § 271(c).

47. Oxford’s infringement of the ’929 patent has injured PacBio in its business and property rights. PacBio is entitled to recover monetary damages for such injuries pursuant to 35 U.S.C. § 284 in an amount to be determined at trial. Oxford’s infringement of the ’929 patent has caused irreparable harm to PacBio and will continue to cause such harm unless and until Oxford’s infringing activities are enjoined by this Court.

PRAYER FOR RELIEF

WHEREFORE, prays for relief as follows:

A. Judgment that Oxford has infringed the ’056 and/or the ’929 patent;

B. An order permanently enjoining Oxford from further infringement of the ’056 and/or the ’929 patent;

C. An award of damages pursuant to 35 U.S.C. § 284 plus pre-judgment and post-judgment interest;

D. An award to PacBio of its costs and reasonable expenses to the fullest extent permitted by law;

E. A declaration that this case is exceptional pursuant to 35 U.S.C. § 285, and an award of attorneys’ fees and costs; and

F. An award of such other and further relief as the Court may deem just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Federal Rule of Civil Procedure 38(b), PacBio hereby demands a trial by jury on all issues so triable.

Dated: September 25, 2017

Respectfully submitted,

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