United States Court of Appeals for the Federal Circuit

PACIFIC BIOSCIENCES OF CALIFORNIA, INC.,
Plaintiff-Appellant

v.

OXFORD NANOPORE TECHNOLOGIES, INC.,
OXFORD NANOPORE TECHNOLOGIES, LTD.,
Defendants-Appellees

2020-2155, 2020-2156

Appeals from the United States District Court for the District of Delaware in Nos. 1:17-cv-00275-LPS, 1:17-cv-01353-LPS, Chief Judge Leonard P. Stark.

Decided: May 11, 2021

EDWARD R. REINES, Weil, Gotshal & Manges LLP, Redwood Shores, CA, argued for plaintiff-appellant. Also represented by ROBERT S. MAGEE, DEREK C. WALTER.

MICHAEL HAWES, Baker Botts, LLP, Houston, TX, argued for defendants-appellees. Also represented by ELIZABETH FLANNERY; STEPHEN M. HASH, Austin, TX.

Before LOURIE, TARANTO, and STOLL, *Circuit Judges*.

TARANTO, *Circuit Judge*.

Pacific Biosciences of California, Inc. (PacBio) sued Oxford Nanopore Technologies, Inc. and Oxford Nanopore Technologies, Ltd. (collectively, Oxford), accusing Oxford of infringing several of its patents, including U.S. Patent Nos. 9,546,400 and 9,772,323. A jury found all asserted claims infringed but also determined that they are invalid under 35 U.S.C. § 112 for lack of enablement. The district court denied PacBio's motion for judgment as a matter of law (and for a new trial) on enablement. The district court also denied PacBio's request that the court grant a new trial because of Oxford's improper remarks during opening, remarks that included references to the potential applications of its accused products to the then-emerging global COVID-19 crisis. PacBio argued that the remarks caused prejudice that could not be remedied by the curative instruction the district court gave at PacBio's request. We affirm.

I

PacBio owns the '400 and '323 patents, which share a specification, so we generally cite only the '400 patent's specification. The patents describe methods for sequencing a nucleic acid, such as deoxyribonucleic acid (DNA). The methods use nanopore technology, described in one form as follows: nucleic acids are drawn through nanometer-sized holes formed in a substrate, and while they transit the holes, their sequences of nucleotides are identified or characterized based on changes in electric current passing through the substrate. *See* '400 patent, col. 1, lines 25–27; *id.*, col. 8, lines 55–61. The '323 patent issued from a continuation of a continuation of the application that issued as the '400 patent; and both claim priority to a provisional application filed on April 10, 2009.

The patents, in discussing the prior art, explain that "rapid determination of the nucleotide sequence . . . is a major goal of researchers seeking to obtain the sequence

for the entire genome of an organism." *Id.*, col. 1, lines 19–22. The patents' solution includes a system with "upper and lower fluidic regions" above and below a membrane having a nanopore passage from one region to the other, with electrodes that permit application of a voltage to create a potential difference that causes molecules to "translocate" between the two regions. *Id.*, col. 8, lines 35–38, 48–61; *id.*, col. 9, lines 6–15, 47–53; *id.*, col. 10, line 64 through col. 11, line 5. The membrane in which the nanopores are formed, as described by the patents, can use lipid or solid-state materials and may include "hybrid" nanopores, formed by treating substrate material with organic molecules, such as proteins, that serve as "spacers" to narrow the nanopores so that only single strands of DNA (ssDNA) or ribonucleic acid (ssRNA) pass through, "in a sequential, single file order." *Id.*, col. 1, lines 28–31; *id.*, col. 14, lines 1–60; *id.*, col. 15, lines 3–10; *id.*, col. 17, lines 42–53; *see also id.*, Fig. 5.

The patents further describe using "processive DNA-binding enzyme[s] to enzymatically regulate the rate of ssDNA translocation through the nanopore." *Id.*, col. 25, lines 11–13; *see also id.*, col. 24, lines 53–54 ("In certain embodiments, polymerases are used to modulate the passage of a nucleic acid strand through a nanopore."). Too fast a rate may impair accuracy, and enzymes can "promote efficient sequence detection, e.g., by allowing a reaction to proceed at a rate that provides for a desirable balance between accuracy and throughput." *Id.*, col. 25, lines 3–10. The patents state that enzymes can bind to ssDNA in the fluid, then combine with the protein "spacer" in the nanopore to "act as a plug," but that "[a]pplying a strong enough [electric] potential can rip the ssDNA from the tightly bound exonuclease, advancing the ssDNA through the nanopore." *Id.*, col. 25, lines 29–34; *see also id.*, Fig. 25(A) & (B). Pulses that alternate large and small potential differences, when used in connection with the enzyme, "can pull the ssDNA through the nanopore in steps, for

example one base at a time. The rate and duty cycle of the pulses could be altered to optimize the translocation rate and measurement duration." *Id.*, col. 25, lines 34–40.

For the sequencing of ssDNA (identifying the sequence of its individual nucleotides), the patents describe use of "an array of electrical/CMOS [complementary metal-oxide-semiconductor] components (amplifiers)" that measure aspects of a current through the substrate—*e.g.*, amplitude and duration of "current blockage," and "interpulse duration"—as ssDNA moves through the nanopore. *Id.*, col. 20, lines 6–9; *id.*, col. 29, lines 43–46; *id.*, col. 41, lines 46–56. The patents note, however, that such measurements "can overlap significantly" between different nucleotides, creating "miscall errors." *Id.*, col. 29, lines 46–50; *see also id.*, col. 41, lines 60–63 ("Thus, if the probability distribution of current blockage (likely Gaussian-like) for a nucleotide is highly overlapping with that of a different nucleotide, then there may be a large probability of miscall if only this metric is used."). This problem, the patents state, prevented prior art systems from "achiev[ing] single nucleotide resolution, especially in embodiments that might be scaled to a commercially viable DNA sequencing system." *Id.*, col. 39, lines 49–51.

The patents state a reason for the resolution troubles: "[T]he amplitude of electric current passing through the nanopore (which constitutes the signal) depends on the identity of several bases that reside in the pore throughout the duration of the current measurement." *Id.*, col. 39, lines 52–55. Given that there are four different nucleotides, there are 4^N possibly different current levels if "N=the number of bases that affect the current measurement." *Id.*, col. 39, lines 55–60; *see also id.*, col. 41, lines 46–56. But, the patents note, there may not be 4^N distinct current levels for the 4^N possible N-long nucleotide sequences ("some of [the possibilities] may be degenerate"). *Id.*, col. 39, lines 59–60.

The sole independent claim of the '400 patent, claim 1, recites:

> 1. A method for sequencing a nucleic acid template comprising:
>
> a) providing a substrate comprising a nanopore in contact with a solution, the solution comprising a template nucleic acid above the nanopore;
>
> b) providing a voltage across the nanopore;
>
> c) measuring a property which has a value that varies for N monomeric units of the template nucleic acid in the pore, wherein the measuring is performed as a function of time, while the template nucleic acid is translocating through the nanopore, wherein N is three or greater; and
>
> d) determining the sequence of the template nucleic acid using the measured property from step (c) by performing a process including comparing the measured property from step (c) to calibration information produced by measuring such property for 4 to the N sequence combinations.

'400 patent, col. 47, line 37 through col. 48, line 6. Dependent claim 4 of the '400 patent includes the additional requirement that "the translocation rate through the pore is enzymatically controlled." *Id.*, col. 48, lines 11–12. The sole independent claim of the '323 patent, claim 1, is similar to claim 1 of the '400 patent, but not identical: for example, it requires a "plurality of template nucleic acids above the nanopore" and includes an "enzymatically controlled" limitation (as in dependent claim 4 of the '400 patent). *See* '323 patent, col. 47, lines 13–34. PacBio asserted claims 1, 4, and 15 of the '400 patent, and claims 1, 4, and 18 of the '323 patent. The parties agree that the patents and the asserted claims are materially similar for purposes

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.