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Paper No. 56
Date Entered: May 20, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

OXFORD NANOPORE TECHNOLOGIES LTD.,
Petitioner,

v.

UNIVERSITY OF WASHINGTON and
UAB RESEARCH FOUNDATION,
Patent Owners.

Case IPR2014-00513[1]
Patent 8,673,550 B2

Before FRANCISCO C. PRATS, JACQUELINE WRIGHT BONILLA, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

PRATS, *Administrative Patent Judge*.

DECISION
Denying Patent Owner's Request for Rehearing
37 C.F.R. § 42.71

[1] Case IPR2015-00057 has been joined with this proceeding.

I. INTRODUCTION

In the Final Written Decision in this proceeding (Paper 51; "Final Decision" or "Final Dec."), we addressed the patentability of claims 10, 17, and 18 of U.S. Patent No. 8,673,550 B2 (Ex. 1001, "the '550 patent"). In the Final Decision, we concluded that Oxford Nanopore Technologies Ltd. ("Petitioner") had not proved by a preponderance of the evidence that claim 10 of the '550 patent was anticipated under 35 U.S.C. § 102(b) by Butler,[2] nor had Petitioner shown that claims 17 and 18 of the '550 patent were anticipated under § 102(b) by either the Wong Abstract [3] or the Wong Poster.[4] Final Dec. 56.

We concluded, however, that Petitioner had proved by a preponderance of the evidence that claim 10 is unpatentable for obviousness over the '782 patent[5] and Butler under 35 U.S.C. § 103(a). *Id.*

The University of Washington and UAB Research Foundation (collectively, "Patent Owner") request rehearing of our decision that claim 10 is unpatentable for obviousness over the '782 patent and Butler. Req.

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[2] Thomas Butler, Nanopore Analysis of Nucleic Acids (2007) (Ph.D. dissertation, University of Washington, Seattle, Washington) (Ex. 1003) ("Butler").

[3] Risa Wong, *Engineering Mycobacterium smegmatis Porin A (MspA) for DNA Analysis*, University of Washington Summer Research Poster Session, pamphlet cover, program description, schedule of events, poster, and abstract (August 16, 2007) (Ex.1008, 1).

[4] Petitioner presented the Wong Abstract and the Wong Poster as separate pages in Exhibit 1008. The Wong Poster appears at page 2 of Exhibit 1008.

[5] George Church et al., U.S. Patent No. 5,795,782 (issued Aug. 18, 1998) (Ex. 1024) (" the '782 patent").

Reh'g 1. We have reconsidered our Final Decision in light of Patent Owner's points, but decline to modify that decision.

II. STANDARD OF REVIEW

A party requesting rehearing has the burden of showing that the decision should be modified, and "[t]he request must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply." 37 C.F.R. § 42.71(d).

III. ANALYSIS

Patent Owner contends that, in evaluating its arguments that an ordinary artisan lacked a reasonable expectation that Butler's SSN-MspA would be able to distinguish between different polymers, our Final Decision misapprended the meaning of "monomer-dependent analysis." Req. Reh'g 2–3. In particular, Patent Owner contends that our Final Decision "mistakenly concluded that Patent Owners' arguments were limited to distinguishing different polymers based on their constituent monomers, and did not include distinguishing different polymers based on their size, as described in the '782 patent." *Id.*

Patent Owner contends, moreover, that it advanced unrebutted evidence, in the form of the Second Benner Declaration (Ex. 2018, "Second Benner Decl."), Nakane,[6] and Deamer,[7] to support its argument that an ordinary artisan "would not reasonably have expected that analysis of heterogeneous polymer mixtures, as described in the '782 patent, could be

[6] Jonathan J. Nakane et al., *Nanopore sensors for nucleic acid analysis*, 15 J. Phys.: Condens. Matter R1365–R1393 (2003).

[7] David W. Deamer, *Nanopores and nucleic acids: prospects for ultrarapid sequencing*, 18 TIBTECH 147–151 (2000).

successfully performed using Butler's SSN-MspA." Req. Reh'g 7–8. Accordingly, Patent Owner contends, "[b]ecause the Board misapprehended the meaning of 'monomer-dependent analysis,' and mistakenly concluded that Patent Owners' arguments were focused solely on constituent monomer-based analysis, the Board failed to give proper weight to Patent Owners' unrebutted evidence." *Id.* at 8.

Patent Owner does not persuade us that we misapprehended or overlooked any arguments it made on this issue. We note initially that Patent Owner's evidence on this issue might be considered unrebutted only in the sense that Petitioner may not have advanced rebuttal evidence when traversing Patent Owner's contentions. That fact does not, however, relieve us of our responsibility of evaluating the persuasiveness of the evidence Patent Owner advanced on this issue, in light of the record as a whole.

Moreover, Patent Owner does not present arguments in its Request for Rehearing in the same fashion as those presented in the Supplemental Response (Paper 32, "Supp. Resp."). Specifically, in contrast to its emphasis on determining polymer size when citing to the '782 patent in its arguments on rehearing (*see* Req. Reh'g 4), Patent Owner's Supplemental Response arguments included no such emphasis when citing to the '782 patent, but instead, referred only to the capacity to determine a "monomer-dependent characteristic." Supp. Resp. 39 (citing Ex. 1024, 1:47–54, 2:42–47 (the '782 patent)).[8]

[8] The Supplemental Response cites to the '782 patent as Exhibit 1006. Supp. Resp. 39. That exhibit number was used for the '782 patent in IPR2015-00057. As noted above, however, IPR2015-00057 has been joined with this proceeding. In this proceeding, the '782 patent is Exhibit 1024.

Only one of the two passages of the ’782 patent cited in Patent Owner’s Supplemental Response refers to determining a “monomer-dependent characteristic,” but that passage mentions nothing specific about determining polymer size:

> Interface-dependent measurements are continued over time, as individual monomer residues of a single polymer interact sequentially with the interface, *yielding data suitable to infer a monomer-dependent characteristic of the polymer*. Several individual polymers. e.g., in a heterogenous [sic] mixture can be characterized or evaluated in rapid succession, one polymer at a time, leading to characterization of the polymers in the mixture.

Ex. 1024, 47–54 (emphasis added).

The other passage of the ’782 patent cited in Patent Owner’s Supplemental Response discloses that overall size of the polymer can be assessed by the disclosed methods, but that passage does not refer to polymer size as being a monomer-dependent characteristic:

> When the polymer interacts sequentially with the interface at the ion permeable passage, the ionic conductance of the passage will change (e.g., decrease or increase) as each monomer interacts, thus indicating characteristics of the monomers (e.g., size, identity) *and/or the polymer as a whole (e.g. size)*.

Id. at 2:42–47 (emphasis added).

The passage in the ’782 patent newly cited in Patent Owner’s Request for Rehearing states:

> The measurements may reflect the sequential interaction of the monomers with the interface, so as to permit evaluation of *monomer-dependent characteristics of the polymer molecule (e.g., size or mass of individual monomers or of the entire polymer*, or the sequence or identity of individual monomers which make up the polymer).

Ex. 1024, 2:27–34.

Although this passage may suggest that the '782 patent considers polymer size to be a monomer-dependent characteristic, Patent Owner does not direct us to where it cited that portion of the '782 patent in its Supplemental Response when advancing this argument, nor does Patent Owner explain where it argued the current emphasis on polymer size in the Supplemental Response.

Moreover, neither the Deamer nor the Nakane reference cited by Patent Owner in its arguments on this issue mention anything about determining polymer size. Rather, Deamer, although showing the capacity to distinguish between the nucleic acid homopolymers polyA and polyC, used polymers that "differ only in that one has a purine base and the other has a pyrimidine base." Ex. 1026, 3. Thus, the nucleic acids analyzed in Deamer differed only as to their constituent monomers, and did not differ as to their size. Patent Owner, therefore, does not persuade us that Deamer demonstrates that an ordinary artisan lacked a reasonable expectation that Butler's SSN-MspA pore protein could be successfully substituted for the α-hemolysin pore protein used in the methods of determining polymer size described in the '782 patent, even when Patent Owner's contentions are viewed in light of the supporting testimony in Dr. Benner's Second Declaration. *See* Ex. 2018 ¶¶ 41–45 ("Second Benner Decl."). Indeed, Patent Owner directs us to no teachings in Deamer about *M. smegmatis* pores in general, much less Butler's specific SSN-MspA pore.

Nakane discusses the fact that two pore proteins, neither of which is the '782 patent's α-hemolysin or Butler's SSN-MspA pore protein, were incapable of detecting or counting nucleic acid molecules, despite being capable of translocating nucleic acid. Ex. 2015, 18. Patent Owner fails to

direct us to any clear or specific explanation as to why the properties of protein pores, neither of which is α-hemolysin, or an *M. smegmatis* pore like Butler's SSN-MspA pore, would have been viewed as predictive of the properties of Butler's pore.

As to Patent Owner's assertion that the pattern of translocation events exhibited by Butler's SSN-MspA pore was too disperse to be able to differentiate between different polymers (Req. Reh'g 6 (citing Ex. 2018 ¶¶ 46–47)), Dr. Benner concedes that Butler's SSN-MspA pore was evaluated only as to a single nucleic acid polymer (Ex. 2018 ¶ 45). Patent Owner does not persuade us that it adequately explained why Butler's evaluation of a single polymer would have been viewed as predictive of whether the SSN-MspA would be useful in the '782 patent's methods of distinguishing between multiple polymers of different sizes. Although, as discussed above, Patent Owner and Dr. Benner contrast the allegedly disperse pattern of translocation events of Butler with the more closely patterned events shown in Deamer, Deamer evaluated polymers that differed only as to constituent monomers. As discussed above, Patent Owner has not explained adequately why that analysis disclosed in Deamer would have been considered predictive of whether Butler's SSN-MspA would be useful in the '782 patent's methods of distinguishing between multiple polymers of different sizes.

In sum, for the reasons discussed, Patent Owner does not persuade us that we misapprehended or overlooked any arguments or evidence presented on the issue of whether an ordinary artisan would have had a reasonable expectation that Butler's SSN-MspA pore protein could be successfully used

in the '782 patent's methods of analyzing heterogeneous mixtures of different polymers.

Patent Owner also does not persuade us that we misapprehended or overlooked any evidence or arguments it presented regarding the structure of α-hemolysin. Specifically, Patent Owner contends that our Final Decision "relied upon alleged structural similarities between α-hemolysin and Butler's SSN-MspA in concluding that a person of ordinary skill reasonably would have expected Butler's SSN-MspA to provide a size distribution in a mixed sample containing a plurality of different polymers." Req. Reh'g 8. Patent Owner contends that "Petitioner never raised this argument in its briefing. In fact, Petitioner emphasized the structural differences between α-hemolysin and MspA in its briefing." *Id.* (citing Supp. Reply 15 (Paper 35)).

We are not persuaded. We acknowledge Petitioner's assertion that differences in translocation behavior between α-hemolysin and Butler's SSN-MspA might have been caused by differences in the width of the channel regions flanking the constrictions, or the absence of charged residues in the constriction the SSN-MspA. Supp. Reply 15. That Petitioner acknowledged these differences between α-hemolysin and SSN-MspA in the context of the translocation behavior does not persuade us that Petitioner "emphasized" the structural differences between the two pore proteins, as Patent Owner asserts. Req. Reh'g 8.

To the contrary, as Patent Owner recognizes (Req. Reh'g 9), Petitioner emphasized the "'advantageous'" structural attributes of the SSN-MspA taught in Butler, including the "'short, narrow inner constriction,'" to show that Butler would have suggested using the SSN-MspA in the '782

patent's analytical methods. Supp. Pet. 27 (Ex. 1059) (quoting Ex. 1003, 88 (Butler)). Indeed, in determining that Petitioner had established a reasonable expectation that Butler's SSN-MspA would be useful in the analytical methods of the '728 patent, our Final Decision relied on those teachings in Butler, as well as Butler's teaching that SSN-MspA exhibited properties consistent with the DNA translocation required in the methods of the '782 patent. *See* Final Decision 40–41.

Patent Owner contends that our Final Decision overlooked "undisputed evidence that before the filing date of the '550 patent, it was not known which structural features of α-hemolysin were important for its nucleic acid analysis capability." Req. Reh'g 8–9 (citing Supp. Resp. 17–19, 31–32. We are not persuaded.

In addressing these contentions in our Final Decision (Final Dec. 41–42), we explained that, despite Butler's alleged teaching that α-hemolysin's mechanism of action was not well understood, Butler nonetheless presented a side-by-side comparison of the structures of MspA and α-hemolysin (Ex. 1003, 94 (Fig. 6.2)), which led Butler to state that the "MspA structure is promising for nanopore analysis" (*id.* at 91 (italics removed)). Patent Owner does not persuade us that, in evaluating the portions of Butler it cited to support its assertions, our Final Decision misapprehended or overlooked Patent Owner's argument by looking to Butler's teachings as a whole, including those regarding the structural similarities between α-hemolysin and SSN-MspA. That Patent Owner disagrees with our assessment of its argument and evidence does not persuade us that we misapprehended or overlooked Patent Owner's points.

Patent Owner contends that, in its Supplemental Response, it directed us to a statement by a reviewer of Dr. Butler's manuscript, in which the reviewer allegedly noted that uncertainties existed as to the relationship between the structures of α-hemolysin and SSN-MspA and their interactions with nucleic acids. Req. Reh'g 8–9 (citing Ex. 2012, 5; Supp. Resp. 30–32).

Patent Owner does not persuade us that we misapprehended or overlooked this evidence or argument. Specifically, Patent Owner advanced this evidence to show that a manuscript version of the Butler reference (a doctoral thesis) had been denied publication in a scholarly journal because Butler had not conclusively proved that translocation through the SSN-MspA pore had occurred. *See* Supp. Resp. 30–32. In addressing this argument in our Final Decision, we noted that, under *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988), conclusive proof is not required to show a reasonable expectation of success. Final Dec. 47–48. Patent Owner, therefore, does not persuade us that we misapprehended or overlooked its argument and evidence on this point.

IV. CONCLUSION

Having considered Patent Owner's Request for Rehearing, we are not persuaded, for the reasons discussed, that Patent Owner has shown that our Final Decision misapprehended or overlooked any point of law or fact.

V. ORDER

For the reasons given, it is hereby ORDERED that Patent Owner's Request for Rehearing is *denied*.

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