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Paper No. 51
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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*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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

I. INTRODUCTION

A. Statement of the Case

In this Final Written Decision, we address the patentability of three claims, i.e., claims 10, 17, and 18, in U.S. Patent No. 8,673,550 B2 (Ex. 1001, "the '550 patent").

As background, Oxford Nanopore Technologies Ltd. ("Petitioner") filed a first Petition (Paper 1, "Pet.") requesting *inter partes* review of claims 1, 5, 6, 10–13, 16, 17, 18, 19, 23, 24, 25, 29–31 and 34–41 of the '550 patent. The University of Washington and UAB Research Foundation (collectively, "Patent Owner") filed a Preliminary Response. Paper 10 ("Prelim. Resp.").

Upon review of those papers and cited information, we instituted trial as to two anticipation grounds presented by Petitioner in relation to claims 1, 5, 6, 10–12, 16–19, 23, 25, 29, 30, 34, 37, and 41 of the '550 patent. Paper 12, 29 ("Decision to Institute," or "Dec.").

After we instituted trial, Petitioner filed a second Petition for *inter partes* review of the same claims subject to review in the first case. IPR2015-00057, Paper 1 ("Supplemental Petition" or "Supp. Pet.").[2] Petitioner also timely filed a motion seeking joinder of IPR2015-00057 with the instant proceeding. IPR2015-00057, Paper 3. In the second case, we instituted trial as to one obviousness ground presented by Petitioner in relation to claim 10 only, and joined IPR2015-00057 with the instant proceeding. Paper 28, 28.

[2] Petitioner entered the Supplemental Petition into the proceeding as Exhibit 1059.

Thereafter, Patent Owner filed a Response (Paper 16; "PO Resp."), and Petitioner filed a Reply (Paper 26, "Reply") in relation to instituted grounds in the first proceeding. In addition to its Response, Patent Owner filed a non-contingent Motion to Amend the '550 patent, cancelling all challenged claims except for claims 10, 17, and 18. Paper 17, 1–3.

In addition, after IPR2015-00057 was joined to the instant proceeding, Patent Owner filed a Supplemental Response (Paper 32, "Supp. Resp."), and Petitioner filed a Supplemental Reply (Paper 35, "Supp. Reply") in relation to the instituted obviousness ground.

Patent Owner subsequently filed a Motion to Exclude Evidence (Paper 39, "Mot. to Exclude"), Petitioner filed an Opposition to that Motion (Paper 44, "Opp."), and Patent Owner filed a Reply to that Motion (Paper 47, "Reply Opp.).

Patent Owner also filed a Motion for Observations on Cross Examination (Paper 40, "Mot. Obs."), and Petitioner filed an Opposition to that Motion (Paper 46, "Opp. Mot. Obs.").

Oral Hearing was held on December 3, 2015, in relation to the joined proceedings and the Hearing Transcript has been entered in the record. Paper 49 ("Tr.").

In light of Patent Owner's Motion to Amend, the joinder of IPR2015-00057 to the instant proceeding, and the record developed during trial, the following asserted grounds of unpatentability are before us for review:

(1) Claim 10, under 35 U.S.C. § 102(b),[3] for anticipation by Butler;[4]

(2) Claims 17 and 18, under 35 U.S.C. § 102(b), for anticipation by the Wong Poster;[5]

(3) Claims 17 and 18, under 35 U.S.C. § 102(b), for anticipation by the Wong Abstract;[6] and

(4) Claim 10, under 35 U.S.C. § 103(a), for obviousness over the '782 patent[7] and Butler.

We have jurisdiction under 35 U.S.C. § 6(c). This Final Written Decision is entered pursuant to 35 U.S.C. § 318(a). "In an inter partes review instituted under this chapter, the petitioner shall have the burden of

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[3] The application which issued as the '550 patent was filed on March 22, 2011. Ex. 1001, cover page. Accordingly, the versions of §§ 102 and 103 in effect before the Leahy-Smith America Invents Act ("AIA") apply to the claims of the '550 patent. *See* AIA, Public Law 112–29 § 3, 125 Stat. 288.

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

[5] 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).

[6] Although Petitioner presented the Wong Poster and the Wong Abstract in a single Exhibit (Ex. 1008), which is designated collectively as "Wong" in our first Institution Decision (Paper 12, 3), Patent Owner contends that the Poster and Abstract "are in fact separate and distinct from each other." PO Resp. 10 (citing Ex. 2004 ¶ 6 (Declaration of Jennifer Harris; Declaration executed Dec. 8, 2014) ("Harris Declaration" or "Harris Decl.")). Petitioner does not dispute Patent Owner's contention. *See* Reply 7–15. We, therefore, evaluate the Wong Poster and Wong Abstract separately.

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

proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e).

We conclude that Petitioner has not proved by a preponderance of the evidence that claim 10 of the '550 patent is anticipated by Butler under 35 U.S.C. § 102(b).

We conclude that Petitioner has not proved by a preponderance of the evidence that claims 17 and 18 are anticipated by the Wong Poster under 35 U.S.C. § 102(b).

We conclude that Petitioner has not proved by a preponderance of the evidence that claims 17 and 18 are anticipated by the Wong Abstract under 35 U.S.C. § 102(b).

We conclude that Petitioner has proved by a preponderance of the evidence that claim 10 is unpatentable for obviousness over the '782 patent and Butler under 35 U.S.C. § 103(a).

Patent Owner's Motion to Amend is *granted*.

Patent Owner's Motion to Exclude Evidence is *denied*.

B. Related Proceedings

Concurrently with the first Petition filed in the instant proceeding, Petitioner filed another Petition advancing additional challenges to the claims of the '550 patent. Pet. 1; IPR2014-00512. No trial was instituted in IPR2014-00512. IPR2014-00512, Paper 12.

C. The '550 patent

The '550 patent discloses using a "*Mycobacterium smegmatis* porin (Msp)" to detect analytes in liquid media. Ex. 1001, 7:54–8:55. The '550 patent explains that a porin is a tunnel-forming protein through which nutrients pass in living mycobacteria. *Id.* at 7:53–55, 18:32–58. Wild-type

M. smegmatis porins include "MspA," "MspB," "MspC", and "MspD." *Id.* at 18:59–61. The '550 patent discloses that the tunnel of an Msp porin has a "goblet" shape, which includes two sections, a cone-shaped "vestibule," and a narrower "constriction zone." *Id.* at 27:9–16; Fig. 1.

As to its analytical methods, the '550 patent explains that, when an Msp porin is placed in a lipid bilayer that separates first and second conductive liquid media, application of an electrical field can cause an analyte to be driven into, and/or through, the porin. *Id.* at 7:53–8:16. The '550 patent explains:

> The electric field moves an analyte such that it interacts with the tunnel. By "interacts," it is meant that the analyte moves into and, optionally, through the tunnel, where "through the Msp tunnel" (or "translocates") means to enter one side of the tunnel and move to and out of the other side of the tunnel.

Id. at 28:1–6.

The analyte may be detected by "measuring an ion current as the analyte interacts with an Msp porin tunnel to provide a current pattern, wherein the appearance of a blockade in the current pattern indicates the presence of the analyte." *Id.* at 8:13–16. A "'blockade' is evidenced by a change in ion current that is clearly distinguishable from noise fluctuations and is usually associated with the presence of an analyte molecule at the pore's central opening." *Id.* at 33:38–41. "More particularly, a 'blockade' refers to an interval where the ionic current drops below a threshold of about 5–100% of the unblocked current level, remains there for at least 1.0 μs, and returns spontaneously to the unblocked level." *Id.* at 33:43–46.

The '550 patent discloses that "an analyte may be a nucleotide, a nucleic acid, an amino acid, a peptide, a protein, a polymer, a drug, an ion, a

pollutant, a nanoscopic object, or a biological warfare agent. Optionally, an analyte is a polymer, such as a protein, a peptide, or a nucleic acid." *Id.* at 8:45–49.

The '550 patent discloses that the negatively charged amino acids in the tunnel of the wild-type MspA were thought to inhibit the entry of negatively charged DNA into the porin. *Id.* at 42:15–19. Thus, the '550 patent describes embodiments of mutant porins in which negative amino acids in the constriction zone, vestibule, and around the entrance of wild-type MspA, are replaced with positively charged residues, so as to allow more optimal translocation of single-stranded DNA through the mutated porin. *Id.* at 42:19–22, 45:45–46:13.

Claims 1, 10, 17, and 18, recite the subject matter under consideration herein, and read as follows:

> 1. A method for detecting the presence of an analyte, comprising:
>
> applying an electric field sufficient to translocate an analyte from a first conductive liquid medium to a second conductive liquid medium in liquid communication through a *Mycobacterium smegmatis* porin (Msp) having a vestibule and a constriction zone that define a tunnel; and
>
> measuring an ion current, wherein a 5% or more reduction in the ion current for at least 1.0 µs compared to an ion current level for the Msp without an analyte present indicates the presence of the analyte in the first medium.

> 10. The method of claim 1, wherein at least one of the first or second conductive liquid media comprises a plurality of different analytes.
>
> 17. A system comprising a *Mycobacterium smegmatis* porin (Msp) having a vestibule and a constriction zone that define a tunnel,
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> wherein the tunnel is positioned between a first conductive liquid medium and a second conductive liquid medium allowing liquid communication between the first and second conductive liquid media,
>
> wherein at least one conductive liquid medium comprises an analyte, and
>
> wherein the system is operative to detect the analyte when the system is subjected to an electric field sufficient to translocate the analyte from one conductive liquid medium to the other.
>
> 18. The system of claim 17, wherein the Msp is a mutant comprising at least a first mutant MspA monomer.

II. ANALYSIS

A. Claim Construction

The Board interprets claims in an unexpired patent using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Tech., LLC*, 793 F. 3d 1268, 1275 (Fed. Cir. 2015), *cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee*, 84 U.S.L.W. 3218 (U.S. January 15, 2015) (No. 15-

446). Under that standard, the Board applies to claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech. Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

1. "electric field sufficient to translocate an analyte"

Challenged claim 10 of the '550 patent depends from now-canceled claim 1, which requires "applying an electric field sufficient to translocate an analyte from a first conductive liquid medium to a second conductive liquid medium in liquid communication through a *Mycobacterium smegmatis* porin (Msp) having a vestibule and a constriction zone that define a tunnel." Ex. 1001, 104:40, 103:35–39. Claim 17 includes similar language. *Id.* at 105:22–23.

Petitioner contends that this language does not require the analyte to be actually translocated from the first medium to the second medium. Pet. 17–19.

As we note in our Decision to Institute (Dec. 8–9), however, the express language in claims 1 and 17 requires applying an electric field sufficient to translocate an analyte from a first medium to a second medium, and the Specification of the '550 patent explains that translocate means to move into and out of the other side of the tunnel. Ex. 1001, 28:4–6. Accordingly, we construe claims 1 and 17 as requiring that an analyte, if present, must translocate, that is, move, from the first medium through the Msp porin to the second medium, when the electric field is applied.

2. "analytes"

Claim 10 recites that "at least one of the first or second conductive liquid media comprises a plurality of different analytes." Ex. 1001, 104:39–

41. In our Decision to Institute, we concluded that, when giving claim 10 its broadest reasonable construction consistent with the Specification of the '550 patent, the term "analyte" or "analytes" encompasses any compound detectable by the methods recited in the claims. Dec. 8–9.

Patent Owner contends that, viewing the plain language of claim 10 and its antecedent claim 1 in light of the Specification of the '550 patent, the term "analyte" does not reasonably encompass the ions that form the ion current measured in the claimed analyte detection process, because those ions are not detectable by the claimed methods. PO Resp. 2–7.

Petitioner contends that, because the Specification states that detectable analytes can be ions, the term "analytes" in claim 10 encompasses any ions present in either the first or second conductive media, including the ions forming the measured ion current. Pet. 17; Reply 1–4. Petitioner contends further that Patent Owner's proffered construction improperly limits the scope of claim 10 by importing limitations into the claim from the Specification. Reply 2 (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc)).

We agree with Patent Owner. In particular, we conclude that the term "analytes" in claim 10 encompasses only those substances detectable by measuring a reduction in ion current of 5% or more for at least 1.0 microsecond (as recited in independent claim 1), as compared to an ion current level for the Msp without an analyte present. That is, the term "analytes" does not encompass the ions forming the ion current that is measured in the claimed analyte detection process.

We acknowledge, as noted above, the '550 patent Specification's broad disclosure that detected analytes may include any of a variety of

substances, including ions. Ex. 1001, 8:45–49. Nonetheless, to detect an analyte, claim 1, from which claim 10 depends, requires its practitioner to compare (1) a first measured ion current obtained from the first liquid medium suspected of containing the analyte, with (2) a second measured ion current, obtained "without an analyte present," that is, a known control containing no analyte. *Id.* at 103:42. As claim 1 states, the presence of the analyte is indicated by a reduction in the first measured ion current of 5% or more for at least 1.0 microsecond, as compared to the second measured ion current level without an analyte present. *Id.* at 103:40–44.

Thus, as Patent Owner contends (PO Resp. 3–4), if the ions forming the first and second measured ion currents were considered "analytes," the comparison required by claim 1, and its dependent claim 10, could not be performed, because removing the current-forming ions to prepare a sample "without an analyte present" (as recited in claim 1) would make it impossible to measure the ion current necessary to perform the required comparison. This conclusion is consistent with Examples 2, 3, and 6 of the '550 patent, each of which is described as comparing ion current blockades "with and without [a]nalyte" (Ex. 1001, 41:55, 42:27, 45:49), yet each of which uses an ion-containing buffer including potassium and chloride ions to generate the measured current (*id.* at 41:15–16 (describing all ion conductance experiments as being performed in 1M KCl, 10 mM Hepes/KOH buffered at pH 8)).

Accordingly, we conclude that, consistent with the Specification of the '550 patent, the broadest reasonable interpretation of the term "analytes" in claim 10 encompasses only those substances detectable by measuring a reduction in ion current of 5% or more for at least 1.0 microsecond, as

compared to an ion current level for the Msp without an analyte present, and does not encompass the ions forming the measured ion current, or other buffer components present in the liquid media used in the analyte detection process.

Because the ions forming the measured ion currents are necessary to the comparison required by claim 10, and because the current-forming ions and other buffer components are described in Examples 2, 3, and 6 as being present in samples lacking analyte, we are not persuaded that our claim construction improperly reads limitations into the claims, as Petitioner argues. *See* Reply 2. Rather, by evaluating the functions of the various claimed components in light of the examples in the Specification, our claim construction ensures that the term "analytes" is interpreted in a manner consistent with the '550 patent's disclosure of how the claimed process actually works.

B. Anticipation of Claim 10 by Butler (Ex. 1003)

1. Overview of Butler

Butler discloses experiments that tested the capacity of a mutant Msp porin ("SSN-MspA") to detect DNA, using an apparatus that contained a lipid bilayer that separated two pools of electrically-conductive liquid media containing potassium chloride as a buffer, the porin being placed in the lipid bilayer. Ex. 1003, 33 (Fig. 3.1), 95 (explaining that the system shown in Figure 3.1 was used in the Msp porin experiments), 102 (disclosing mutations in SSN-MspA).[8] Butler discloses that when voltages of 160 mV, 180 mV, and 200 mV were applied to the apparatus, and the resulting

[8] In citing to Butler, we cite to the page numbers inserted by Petitioner at the bottom of each page.

current was measured, single stranded DNA molecules ("ssDNA") 50 nucleotides in length ("dA_{50}"), caused "blockades," that is, reductions in current of 50 percent or more, lasting from 10 to 100 microseconds, as compared to a control containing no ssDNA. *Id.* at 108, 109 (Fig. 6.8).

2. Analysis

Petitioner contends that Butler's process has all of the steps and features of claim 1, from which claim 10 depends. Pet. 22–23. As to claim 10, Petitioner contends that, "[b]ecause an ion qualifies as an analyte and because potassium ions were present in the experiments Butler performed to detect DNA, another analyte, the limitation of 'a plurality of different analytes' is met by Butler." *Id.* at 29.

Patent Owner contends that, because the potassium ions in Butler's experiments were used to generate the measured ion current indicative of the presence of DNA in the same manner as Examples 2, 3, and 6 of the '550 patent, the potassium ions are not "analytes" encompassed by claim 10 of the '550 patent. PO Resp. 7–9 (citing Ex. 2003 ¶¶ 14–18 (Benner Decl.)).[9] Thus, according to Patent Owner, the liquid media used in Butler contained only a single analyte, the DNA molecules Butler tested. *Id.* Accordingly, Patent Owner contends, Butler fails to meet claim 10's requirement that at least the first or second liquid medium contains a plurality of different analytes. *Id.* at 9.

As discussed above, we agree with Patent Owner that the term "analytes" in claim 10 does not encompass the ions that produce the ion current that is measured in the claimed process. Petitioner does not dispute

[9] Declaration of Steven A. Benner, Ph.D. (Declaration executed Dec. 5, 2014) (Ex. 2003; "Benner Declaration" or "Benner Decl.").

Patent Owner's contention that the potassium ions in Butler's experiments form the ion current that Butler measured. *See* Reply 1–6. Moreover, we discern no error in Patent Owner's assertion, and supporting testimony of its witness, Dr. Benner, that Butler's system is essentially identical to the system described in Examples 2, 3, and 6 of the '550 patent, all of which use the potassium ions to generate the measured ion current.

Accordingly, we agree with Patent Owner that the term "analytes" in claim 10 does not encompass the potassium ions in Butler's experiments. Because Petitioner relies on the potassium ions in Butler's experiments, along with the DNA in those experiments, as corresponding to the plurality of different analytes required by claim 10 (*see* Pet. 29), we agree with Patent Owner that Petitioner has not shown that Butler describes a process which includes all of the features of claim 10. We conclude, therefore, that Petitioner has not shown by a preponderance of the evidence that Butler anticipates claim 10 of the '550 patent.

Petitioner's arguments do not persuade us to the contrary. Petitioner contends that the potassium and chloride ions used in Butler's experiments could be detected in a system using sodium and bromide ions as the current-forming ions. Reply 4, n.2. That a system using liquid media different than the media used by Butler might be able to detect potassium and chloride does not persuade us that the system actually described in Butler, which uses potassium to form an ion current, can detect potassium ions based on a 5% or more reduction in ion current for at least one microsecond, as claim 10 requires. Again, moreover, if Butler's potassium ions were considered analytes, their removal to perform the claim-required comparison "without

an analyte" would render the system incapable generating the ion current necessary to that comparison.

In its Reply, Petitioner also advances a theory of unpatentability distinct from that presented in its Petition. Specifically, Petitioner contends that, in addition to the potassium ions used to generate the current measured in Butler, the liquid media used in Butler's experiments inherently included contaminants which would generate a reduction in ion current of 5% or more for at least 1 microsecond. Reply 4–6. Accordingly, Petitioner contends, beyond the potassium ions discussed above, Butler's liquid media included, in addition to the DNA Butler tested, substances encompassed by the term "analytes," thereby meeting claim 10's requirement for a plurality of different analytes. *Id.*

As provided in 37 C.F.R. § 42.23(b), a "reply may only respond to arguments raised in the corresponding opposition or patent owner response." Thus, "a reply that raises a new issue or belatedly presents evidence will not be considered and may be returned." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012). One indication that a new issue has been raised in a reply is where a petitioner submits "new evidence necessary to make out a *prima facie* case" of unpatentability of an original claim. *Id.* In contrast, where evidence submitted in support of a reply responded only to contentions presented in a Patent Owner response, and was not relied upon or necessary to the prima facie case of unpatentability, our reviewing court found no abuse of discretion by the Board in admitting the reply evidence. *Belden Inc. v Berk-Tek LLC*, 805 F.3d 1064, 1077–79 (Fed. Cir. 2015).

Here, Petitioner contends that, in advancing its new contentions, its Reply merely responds to Patent Owner's argument that the only substance in Butler's liquid media that would be considered an analyte is the single stranded DNA tested by Butler. Reply 5, n.3; *see also id.* at 4 (citing Ex. 2003 ¶ 17 (Benner Decl.)).

It might be true that Patent Owner's Response argued that the DNA tested by Butler was the only analyte encompassed by claim 10. The basis for that argument, however, was Patent Owner's response to contentions and evidence raised by Petitioner in its Petition. Specifically, Patent Owner responded that the potassium ions identified in the Petition as the second analyte were not reasonably considered "analytes" under the broadest reasonable construction of claim 10 consistent with the Specification. *See* PO Resp. 2–9. In its Reply, Petitioner now raises an entirely novel theory of unpatentability, a theory Patent Owner would not have addressed in its Response, as it was not raised in the Petition. We are not persuaded that presenting this novel theory of unpatentability, distinct from that originally presented in its Petition, truly responds to Patent Owner's arguments about the reasonableness of considering potassium ions "analytes" as that term is used in claim 10. Rather, because the Reply presents new evidence in an effort to raise a new theory of anticipation, we conclude that the Reply exceeds its proper scope. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012).

Nonetheless, even if we were to overlook the procedural infirmities in Petitioner's Reply arguments, which we do not, we would not find the arguments persuasive.

To show that Butler anticipates claim 10, Petitioner must show that Butler discloses "every limitation of the claimed invention, either explicitly or inherently." *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997).

Petitioner contends that, in addition to the $d\text{A}_{50}$ molecules Butler tested, Butler also discloses two types of contaminants in its experiments that would be considered "analytes": (1) divalent and trivalent ions, and (2) less than full-length oligonucleotides. Reply 5. Petitioner has not shown sufficiently that Butler explicitly or inherently discloses that those substances were present in the DNA experiments cited by Petitioner.

As to the alleged divalent and trivalent ion impurities, Butler states only that "*[i]f* these *hypothetical* contaminant molecules are present in the $d\text{A}_{50}$ aliquots that we add to the cis compartment, then we would observe the correlation between increased blockade rate and the presence of $d\text{A}_{50}$." Ex. 1003, 107 (emphasis added). Butler's hypothetical guess at potential causes of ion current blockades does not equate to an explicit disclosure of the presence of those contaminants in its experiments. Moreover, because Butler's disclosure, at best, suggests that such contaminants might possibly have been present, Butler does not inherently disclose the presence of those contaminants. *See Agilent Techs., Inc. v. Affymetrix, Inc.*, 567 F.3d 1366, 1383 (Fed. Cir. 2009) ("The very essence of inherency is that one of ordinary skill in the art would recognize that a reference *unavoidably* teaches the property in question.") (emphasis added); *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.").

As to the alleged less than full length oligonucleotide contaminants, we acknowledge Butler's disclosure that oligonucleotide impurities were present in the RNA samples used to test the capacity of a different pore protein, α-hemolysin, to detect nucleic acids. *See* Ex. 1003, 69, 72. Petitioner does not show sufficiently, however, that Butler's disclosure of RNA impurities in a different sample, used in experiments different from the Msp porin experiments relied upon to show anticipation, equates to either an explicit or inherent disclosure that the DNA used in Butler's Msp porin experiments contained the same impurities.

As to Butler's Msp porin experiments, Butler discloses that the "homogeneous" dA_{50} molecules it used "were synthesized by Integrated DNA Technologies" (IDT). Ex. 1003, 38. As to those molecules, Butler states that "[a]ll samples were PAGE purified by the suppliers," thereby indicating that the tested samples were pure, i.e., did not contain contaminants. *Id.* Accordingly, we find that Butler does not explicitly disclose that the DNA used in its Msp porin experiments contained oligonucleotide contaminants that, along with the dA_{50} molecules, would be considered "analytes," as required by claim 10.

Petitioner contends, nonetheless, that literature from IDT, Butler's DNA supplier, establishes that less than full length oligonucleotide contaminants were inherently present in the DNA samples Butler used in the allegedly anticipating experiments. *See* Reply 6 (citing Exs. 1043,

1051).[10, 11] Thus, Petitioner contends, even if IDT were able to attain a sample purity of 99%, the 1% of the sample representing incompletely synthesized oligonucleotides, "in the context of the system described in Butler would result in more than a trillion contaminating nucleic acid molecules − in a system designed to detect single molecules." *Id.* (citing Ex. 1004 ¶ 31).[12]

Petitioner does not explain with specificity which disclosures in Exhibit 1051 it relies upon to show that IDT's PAGE-purified products necessarily contain impurities. Nonetheless, we acknowledge the disclosure that, as to unmodified oligonucleotides, "purity of >90% is routinely achieved" using PAGE purification. Ex. 1051, 1. We acknowledge also the disclosure in Exhibit 1043 that, "[f]or the most demanding applications, IDT offers Dual HPLC Purification and Dual PAGE and HPLC Purification. These methods result in oligos of the highest possible purity." Ex. 1043, 2.

Although these disclosures might show a degree of probability that the IDT PAGE-purified products used in Butler contained less than full length oligonucleotide contaminants, as noted above, a showing of inherency may not be based on probability or possibility, but instead requires establishing that the reference unavoidably teaches the limitation at issue. *In re Oelrich*, 666 F.2d at 581; *Agilent*, 567 F.3d at 1383.

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[10] IDT Webpage - IDT DNA PAGE and HPLC Purification (http://www.idtdna.com/pages/products/dna-rna/hplc-page) (accessed Feb. 9, 2015) (Ex. 1043).

[11] IDT Webpage - Purification of Oligonucleotides Quick Look (2009) (Ex. 1051).

[12] Declaration of Daniel Branton, Ph.D. (Declaration executed Mar. 11, 2015) (Ex. 1044; "Branton Reply Declaration" or "Branton Reply Decl.").

To that end, we note that IDT's disclosure of routinely achieving greater than 90% purity encompasses the possibility of products having 100% purity. Indeed, Dr. Benner testified in his deposition that he had tested IDT products of the type used by Butler, and found no detectable contaminants:

> We typically analyze all IDT-generated nucleotides. I have not, of course, to my recollection, ever, I don't believe I have ever ordered a 50 specifically. We actually order things, we run gels on them, we do mass specs on them. *We are not able to detect impurities in PAGE-purified oligos*, and, therefore, I would probably refer to the webpage, first sentence, which is that "PAGE obtains extremely high purity," where I would refer to the greater than 90 percent as something that their legal counsel introduced in to give the lowest possible level of -- that is, the highest possible level of impurity that they could conceivably have.
>
> We have never seen an IDT oligo that has been PAGE-purified delivered to us with less than 99-point-something, *that is, we've never been able to detect other things in that oligo as it's delivered.*

Ex. 1042, 61:20–62:14 (Benner Deposition) (emphasis added); *see also id.* at 57:13–16 ("[W]hat we get from IDT -- and we pay them for it -- is molecules for which there is no detectable impurity by any of a number of standards that are common in the art to detect them.").

Thus, given Dr. Benner's testimony that the IDT-provided, PAGE-purified oligonucleotides he has tested did not contain detectable impurities, contrasted with the mere probabilistic implication from the IDT webpages (Exs. 1043 and 1051) that IDT's products might contain impurities, Petitioner has not shown by a preponderance of the evidence that the IDT-supplied dA_{50} molecules used in Butler's experiments inherently

contained contaminants detectable as "analytes," as required by claim 10 of the '550 patent. Accordingly, in the contentions of unpatentability advanced in its Reply, Petitioner has not shown by a preponderance of the evidence that Butler, explicitly or inherently, describes a process that includes a plurality of different analytes, as required by claim 10.

In sum, for the reasons discussed, Petitioner has not shown by a preponderance of the evidence that Butler anticipates claim 10 of the '550 patent.

C. Anticipation of Claims 17 and 18 by the Wong Poster (Ex. 1008, 2)

1. Overview of the Wong Poster

The Wong Poster and the Wong Abstract, which Petitioner filed as separate pages in Exhibit 1008, were cited as a single item in an Information Disclosure Statement submitted during prosecution of the '550 patent. Pet. 12; PO Resp. 10. The Wong Poster was presented by an undergraduate student, Risa Wong, at a poster session conducted at the University of Washington on August 16, 2007. Pet. 12; PO Resp. 10.

Page 3 of Exhibit 1008 is a title page reading "UW Summer Research Poster Session." Ex. 1008, 3. The date, time, and location of the poster session are indicated as August 16, 2007, 9:00 AM to noon, and Mary Gates Hall Commons. *Id.*

Page 4 of Exhibit 1008 includes the following welcoming statement:

> This poster session is a collaboration among several summer programs hosting UW and non-UW undergraduates from around the country, including the Amgen Scholars Program, Biostatistics Summer REU, Clinical Research Experience for Engineers, Genetically Engineered Materials Science & Engineering Center, Hooked on Photonics STC-MDITR, Intel Summer Research Experience, National

> Nanotechnology Infrastructure Network, and University of Washington Engineered Biomaterials.

Id. at 4. As to authorship, the Wong Poster indicates "Risa Wong, Junior, UW Amgen Scholars Program." *Id.* at 2, center column.

As to its substantive disclosure, the Wong Poster describes an apparatus in which an MspA mutant porin is placed in a lipid bilayer between two containers ("wells"), each of which contains an electrically conductive liquid medium, with liquid communication occurring between the two wells through the porin. Ex. 1008, 2 (center column). Wong describes one of the wells as containing single stranded DNA. *Id.* Wong discloses that application of voltages of 140 mV and 180 mV allows detection of the DNA because the ion current blockades occurring during voltage application are consistent with DNA translocation through the porin. *Id.* (right column); *see also* Ex. 1008, 2 (left column) (voltage potential moves the DNA through the MspA mutant porin temporarily reducing ion current).

2. The Parties' Contentions

Petitioner contends that the poster session at which Ms. Wong displayed the Wong Poster was "open to the public." Pet. 12. Petitioner contends also that the date of the poster session was more than one year before the effective filing date of the '550 patent. *Id.* Accordingly, Petitioner contends, the Wong Poster qualifies as a "printed publication" under 35 U.S.C. § 102(b). *Id.* (citing *In re Klopfenstein*, 380 F.3d 1345, 1348 (Fed. Cir. 2004)). Petitioner contends that the Wong Poster describes a system having all of the features recited in claims 17 and 18. Pet. 41–43.

Patent Owner does not dispute that the date of the poster session was more than one year before the effective filing date of claimed subject matter at issue. *See* PO Resp. 10–18, 20–21. Nor does Patent Owner dispute that the Wong Poster describes a system having all of the features recited in claims 17 and 18. *Id*. Rather, Patent Owner contends that, given the circumstances of its display at the poster session, the Wong Poster is not a printed publication under § 102(b). *Id.* Patent Owner relies primarily on the testimony of Dr. Jennifer Harris, an employee of the University of Washington, to explain the circumstances of the poster session. *Id.* at 10, 14–18 (citing Ex. 2004 (Harris Decl.)).[13]

Petitioner replies that the circumstances of the Wong Poster's display at the poster session support a conclusion that it qualifies as prior art under § 102(b). Reply 7–12. Petitioner also relies on testimony by Dr. Harris. *Id.* at 8–12 (citing Ex. 1045 (Harris Deposition)).

3. Principles of Law

"The determination of whether a reference is a 'printed publication' under 35 U.S.C. § 102(b) involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *In re Klopfenstein*, 380 F.3d at 1350. "The 'printed publication'

[13] Dr. Jennifer Harris was the Associate Director of the University of Washington's Undergraduate Research Program from September 2005 through March 2014. Ex. 2004 ¶ 1. Dr. Harris has been Director of the Program since April 2014. *Id.*

Dr. Harris's duties as both Director and Associate Director "include developing and managing programs designed to educate undergraduate students and prepare them for careers in research in all fields, including science, technology, engineering and mathematics ('STEM'), by giving them the opportunity to conduct research under the supervision of faculty members." *Id.*

bar is grounded on the principle that once an invention is in the public domain, it is no longer patentable by anyone." *Id.* at 1349 (quoting *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986)) (internal brackets removed).

Thus, "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d at 899. "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)). In other words, "[a]ccessibility goes to the issue of whether interested members of the relevant public could obtain the information if they wanted to." *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569 (Fed. Cir. 1988).

As to disclosures at communal events, in *In re Klopfenstein* the Federal Circuit set out a list of "factors [to] aid in resolving whether or not a temporarily displayed reference that was neither distributed nor indexed was nonetheless made sufficiently publicly accessible to count as a 'printed publication' under § 102(b)." *In re Klopfenstein*, 380 F.3d at 1350. The court listed those factors as follows: "[1] the length of time the display was exhibited, [2] the expertise of the target audience, [3] the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and [4] the simplicity or ease with which the material displayed could have been copied." *Id.*

Applying those factors, the court held that a fourteen-slide presentation, printed and pasted onto poster boards and presented at two professional conferences for a total of nearly three days, was a printed publication, despite the fact that no copies of the presentation were disseminated at either meeting, and the presentation was never catalogued or indexed in any library or database. *Id.* at 1347–51. As to the target audience, the court noted that the intended viewers at the first conference were persons of ordinary skill in the pertinent art, and the intended viewers at the second conference "most likely also possessed ordinary skill in the art." *Id.* at 1351.

The Federal Circuit's holding in *Massachusetts Institute of Technology v. AB Fortia*, 774 F.2d 1104 (Fed. Cir. 1985), underscores the importance of the target audience at such communal events. There, the court held that an oral presentation of a paper describing optimization of a component used in cell culture media, made at a conference attended by 50 to 500 cell culturists having ordinary skill in the art, with copies of the paper being distributed without restriction to the conference leader and at least six persons of ordinary skill, was a printed publication under § 102(b). *Id.* at 1108–1109.

Addressing the issue in a summary judgment appeal, the Federal Circuit similarly highlighted the importance of the target audience, noting that, if proven, distribution of the document at issue at a "trade show . . . would constitute a publication under 35 U.S.C. § 102(b)." *TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1157–58 (Fed. Cir. 2004).

In contrast, in vacating a summary judgment of anticipation, the Federal Circuit in the *SRI* case, on that record, analogized the disclosure of the document at issue to "placing posters at an unpublicized conference with no attendees," despite evidence that individuals with sufficient knowledge and know-how regarding the document's non-confidential posting on an open server might have been able to access the document. *SRI Int'l*, 511 F.3d at 1197. Indeed, the *SRI* panel expressly contrasted the circumstances of dissemination of the document at issue there from the events at which the *Klopfenstein* poster was displayed. *Id.* at 1196 ("In *Klopfenstein*, two professional conferences displayed posters. These posters were printed publications because their entire purpose was public communication of the relevant information.") (citing *Klopfenstein*, 380 F.3d at 1347–50).

4. Discussion

Patent Owner persuades us that Petitioner has not shown by a preponderance of the evidence that persons interested and ordinarily skilled in the art pertinent to claims 17 and 18 of the '550 patent, exercising reasonable diligence, would have been able to locate the Wong Poster.

As Patent Owner contends, Dr. Harris testified that the poster session at which Risa Wong displayed the Wong Poster was an event at which approximately 80 undergraduate students presented posters and discussed their summer research projects at the University of Washington's 2007 Undergraduate Research Program. Ex. 2004 ¶¶ 2–4 (Harris Decl.); PO Resp. 14–15. Dr. Harris testified that, in accordance with the Undergraduate Research Program's mission, "the purpose of the abstract and the poster session was to educate the students by giving them presentation experience

that would prepare them for graduate school and careers in science." Ex. 2004 ¶ 4.

As Patent Owner contends, in the complete event program (Ex. 2002), the full list of abstracts for which the students presented posters shows a variety of technical subjects, including mutated enzymes, robots, coronary artery disease, magnetic levitation, and power conversion in titanium oxide-containing bilayer devices. PO Resp. 16 (citing Ex. 2002, 6, 7, 9, 11, 51).

As to the target audience, Dr. Harris testified that, before the poster session, "the Undergraduate Research Program sent e-mail invitations to the students and their mentors, faculty members, program staff, and campus administrators, and encouraged the students to invite family and friends," and also "posted a brief announcement on the Undergraduate Research Program's home page shortly before the event listing the time, date, and place of the poster session. Neither the invitations nor the announcement specified the scientific subject matter of the student presentations." Ex. 2004 ¶ 5.

Dr. Harris testified that she attended the poster session, and recalled that the attendees "predominantly were connected to the individual student presenters (e.g., mentors, friends, family members, and members of the laboratories where the students worked over the summer) or to undergraduate education at the University of Washington," which is "consistent with the fact that the primary purpose of the poster session was to give the students presentation experience." *Id.* ¶ 8. Dr. Harris testified that, "[a]t the conclusion of the three-hour event, we immediately removed the posters, including Risa Wong's poster, from the room. After the posters

were removed, neither I nor the Undergraduate Research Program took steps to catalogue or index the posters." *Id.* ¶ 9.

Thus, the poster session at issue plainly was not an unpublicized conference with no attendees. Nonetheless, because invitation to the session was based primarily on affiliation with a particular student, as opposed to interest or skill in any particular technical subject matter, we agree with Patent Owner that the poster session's intended viewers were not comparable to the technology-specific or industry-specific audiences targeted in the professional conferences and trade show discussed in the *Klopfenstein*, *MIT*, and *TypeRight* cases.

Petitioner's rebuttal contentions do not persuade us that, despite the poster session's limited target audience, interested and ordinarily skilled artisans exercising reasonable diligence would have been able to locate the Wong Poster if they wished. To that end, Petitioner directs us to Dr. Harris's deposition testimony, which is asserted to "reveal[] that more than 50 Ph.D. level mentors and lab group members, all of whom were interested in the field of molecular analysis, were either directly invited by administrators or were expected to be invited to the event by students. (Ex.1045 at 117-54 [Harris Deposition]; Ex. 2002)." Reply 8; *see also id.* at 11 (citing Ex 1045, 95:18–96:16). Petitioner also quotes a statement in an email from Dr. Harris, apparently to participants in the Amgen Scholars program, that "[t]he event is open to the public. Please INVITE YOUR LAB GROUP, FRIENDS, FAMILY, ETC. The more the merrier." *Id.* (citing Ex. 1046, 2).

Petitioner does not explain specifically why the cited portions of Dr. Harris's deposition demonstrate that more than 50 of the invited attendees

were interested or actively engaged in molecular analysis. *See* Reply 8. We acknowledge, nonetheless, that Dr. Harris testified that the Undergraduate Research Program would have invited all University of Washington faculty members that were mentoring poster-presenting students in the Amgen Scholars Program, and that those faculty mentors included practitioners in biochemistry, chemistry, chemical engineering, immunology, electrical engineering, genome sciences, neuropathology, medicinal chemistry, bioengineering, and biology. Ex. 1045, 150–153.

Petitioner does not explain specifically, however, why the invited faculty members would have been interested persons of ordinary skill in the relevant art. Petitioner advances the following testimony of Dr. Branton regarding the level of ordinary skill in the relevant art:

> In my opinion, the level of ordinary skill in the art as of the priority date of the '550 patent was high, at the Ph.D. level or at least the masters level with several years of experience with molecular analysis. The person of ordinary skill in this art area, a cross-disciplinary field spanning biophysics and molecular biology, would have training in both the physical and biological sciences or training in one of those disciplines with access to those with training in the other. The person of ordinary skill in the art might have academic degrees in e.g., physics, biophysics, molecular biology, biochemistry or various bioengineering disciplines, but, *more importantly, would have knowledge or comprehension of the biological and physical phenomena relevant to using nanopores to make highly precise measurements at the molecular level.*

Ex. 1012 ¶ 34 (emphasis added).[14]

[14] Declaration of Daniel Branton, Ph.D. (Declaration executed Mar. 18, 2014) (Ex. 1012; "Branton Declaration" or "Branton Decl.").

As to the requirement of a Ph.D. or master's degree, we note that the full event program to which Petitioner directs us (Reply 8 (citing Ex. 2002)), does not indicate the degrees of the faculty mentors. *See* Ex. 2002, 6–54. A number of the cited pages of Dr. Harris' deposition, nonetheless, expressly suggest that five of the discussed mentors had doctorates. Ex. 1045, 118 ("Dr. Klevit" (biochemistry)), 130 ("Professor Zhang" (material science and engineering)), 131 ("Dr. Pun" (bioengineering)), 133 ("Professor Yager" (bioengineering)), 143 ("Dr. Swanson" (genome sciences)).

Even assuming, however, that it is self-evident that those individuals, or other faculty members in the subjects presented at the poster session, had relevant doctoral degrees, as noted above, "more important[]" than the practitioner's degree or academic discipline, Petitioner's definition of an ordinarily skilled artisan requires "knowledge or comprehension of the biological and physical phenomena relevant to using nanopores to make highly precise measurements at the molecular level." Ex. 1012 ¶ 34. Petitioner does not direct us to clear or specific evidence showing that the invited faculty mentors in the disciplines represented at the poster session, or other invitees, would have had knowledge or comprehension relevant to using nanopores to make highly precise measurements at the molecular level, nor does Petitioner otherwise explain why that is the case. Nor does Petitioner direct us to evidence showing that any of the invitees were members of the public interested in the subject matter of the '550 patent.

Petitioner does not, therefore, show sufficiently that the intended audience of the poster session necessarily included interested persons of ordinary skill in the art pertinent to claims 17 and 18 of the '550 patent. Indeed, the broad range of subjects included in the full event program to

which Petitioner directs us (Ex. 2002) bolsters rather than undermines Patent Owner's assertion that the poster session's intended audience was based on affiliation with the presenting students, rather than being focused on a particular technical discipline.

Petitioner also directs us to evidence that, before the poster session, the Undergraduate Research Program's publicly-available website included information about Jens Gundlach and the nanopore-based work a student in his laboratory would perform in connection with the Amgen Scholar's Program, as well as a biography of Ms. Wong describing the type of work she was performing in Dr. Gundlach's laboratory. Reply 9 (citing (Ex. 1045, 46:15–51:12, 54:16–56:10 (Harris Deposition)). Petitioner further notes that the invitations (Ex. 1047) to the poster session included a link to the Undergraduate Research Program website and the Program's telephone number. Reply 9. Accordingly, Petitioner contends, "given the content and breadth of the invitations, including the website link, relevant persons exercising reasonable diligence would have known about, and could easily have accessed, the Wong Poster – and this alone qualifies the Poster as a 'printed publication.'" *Id.* at 9–10.

As discussed above, however, Petitioner has not shown sufficiently that the intended audience of the poster session, the invitees, included interested persons of ordinary skill in the relevant art. Thus, that the poster session's invitees may have been able to access information about the subject of Dr. Gundlach's and Ms. Wong's research through the Undergraduate Research Program's website does not persuade us that the poster session itself was accessible to interested and ordinarily skilled artisans exercising reasonable diligence. Nor has Petitioner explained

convincingly why, aside from the invitations, the public accessibility of the Undergraduate Research Program's website, by itself, would have adequately publicized the poster session at issue to the set of individuals required to render the poster a printed publication under § 102(b).

We acknowledge that the Wong Poster is a single static poster that was presented for three hours, as Petitioner contends. Reply 9. We acknowledge, as Petitioner contends also, that Dr. Harris testified that Ms. Wong was trained to convey the Wong Poster's subject matter concisely, and stood in front of the poster and interacted with people walking past the poster during the three-hour session. *Id.* at 10 (citing Ex. 1045, 171:12–19, 193:10–194:6 (Harris Deposition)). We acknowledge, as Petitioner further contends, that Dr. Harris testified that audience members were not restricted from photographing the poster. *Id.* at 11–12 (citing Ex. 1045, 109:10–14).

As discussed above, nonetheless, although the poster session at issue was open to the public, Petitioner has not shown sufficiently that the group of people to whom the session was actually announced, the invitees, included interested persons of ordinary skill in the relevant art. To the contrary, the circumstances of the Wong Poster's display—a three-hour event whose target audience was based on affiliation with a group of undergraduate students presenting posters of widely varying technical subject matter, rather than focusing on a particular art or discipline—differ significantly from a trade show or the multi-day, widely attended professional conferences discussed in the *Klopfenstein* and *MIT* cases. Thus, although the physical act of copying the Wong Poster might have been a simple matter of taking a photograph, given the totality of the circumstances of the poster's display, the absence of restrictions or ease of copying does

not persuade us that the Wong Poster would have been located by interested and ordinarily skilled artisans exercising reasonable diligence.

In sum, for the reasons discussed, Petitioner has not shown, by a preponderance of the evidence, that the facts and circumstances of the display of the Wong Poster were such that the Wong Poster would have been accessible to interested and ordinarily skilled artisans exercising reasonable diligence. Because Petitioner has not shown that the Wong Poster is a printed publication under 35 U.S.C. § 102(b), Petitioner has not shown by a preponderance of the evidence that the Wong Poster anticipates claims 17 and 18 of the '550 patent, under that statutory provision.

D. Anticipation of Claims 17 and 18 by the Wong Abstract (Ex. 1008, 1)

1. Overview of the Wong Abstract

The Wong Abstract appears in the printed program of the 2007 poster session, discussed above, at which the Wong Poster was presented. Ex. 1008, 1; Ex. 2002, 52. As to its substantive disclosure, the Wong Abstract outlines the technical concepts underlying the use of Msp porins in detecting and analyzing DNA, and discloses that experiments were performed in which certain mutant porins demonstrated current blockages in the presence of single-stranded DNA. Ex. 1008, 1; Ex. 2002, 52.

2. Analysis

Petitioner contends that, because the Wong Abstract was presented in the event program of the poster session at which the Wong Poster was displayed, the Wong Abstract, like the Wong Poster, constitutes prior art under § 102(b). Pet. 12.

Patent Owner concedes that the Wong Abstract "was included in the event program (Ex. 2002) that was posted to the University of Washington

Undergraduate Research Program's website." PO Resp. 19. Patent Owner contends, nonetheless, that Petitioner has not advanced evidence showing either that the abstract was posted on the website prior to the critical date for claims 17 and 18, or that the posted document was accessible to the relevant audience. *Id.* at 19–20. Patent Owner contends, moreover, that Petitioner has not advanced evidence that either the event program or Wong Abstract was meaningfully indexed or catalogued such that interested and ordinarily skilled artisans would have been able to locate them. *Id.* at 20.

Petitioner replies that, because physical copies of the event program were distributed "during and after" the 2007 poster session, the Wong Abstract was accessible without restriction to ordinarily skilled artisans exercising reasonable diligence. Reply 13.

Patent Owner persuades us that Petitioner has not shown that the Wong Abstract is a printed publication under § 102(b).

We acknowledge Dr. Harris's testimony that copies of the event program, which included the Wong Abstract, were available at the entrance to the room at which the poster session was held. Ex. 2004 ¶ 6 (Harris Decl.); Ex. 1045, 61–62. We acknowledge also the following statements in an email by Dr. Harris to "Summer REU Program Staff," to which Petitioner directs us (Reply 13): "I also want to let you know that we have plenty of programs left over and I can send each of you a stack so that you can have them for your use. Please let me know how many you would like." Ex. 1049, 1.

As discussed above, however, we are not persuaded that Petitioner has shown that the intended audience of the poster session, the invitees, included interested persons of ordinary skill in the relevant art. Nor are we persuaded

that Petitioner has explained convincingly why, other than invitation, interested and ordinarily skilled artisans would have known about the session. Accordingly, that copies of the Wong Abstract were available to the target audience at the entrance to the poster session does not persuade us that the Wong Abstract was accessible to interested persons of ordinary skill in the relevant art. In addition, notwithstanding Dr. Harris' email discussed above, insufficient evidence exists to show that event programs were distributed to anyone outside of the poster session. Petitioner, moreover, does not direct us to clear or specific evidence explaining how distribution of copies of the Wong Abstract to members of the Undergraduate Research Program staff, even if done without restriction, would have made the abstract accessible to interested and ordinarily skilled artisans exercising due diligence. For example, the evidence presented by Petitioner does not establish that the Wong Abstract was ever catalogued or indexed in any library or database such that an interested and ordinarily artisan exercising due diligence could have located the document.

Accordingly, Petitioner has not shown by a preponderance of the evidence that the facts and circumstances of the distribution of the Wong Abstract were such that the Wong Abstract would have been accessible to interested and ordinarily skilled artisans exercising reasonable diligence. Because Petitioner, therefore, has not shown that the Wong Abstract is a printed publication under 35 U.S.C. § 102(b), we are not persuaded that Petitioner has shown by a preponderance of the evidence that the Wong Abstract anticipates claims 17 and 18 of the '550 patent, under that statutory provision.

E. Obviousness of Claim 10 over the '782 patent (Ex. 1024) and Butler (Ex. 1003)

1. Prior Art Evidence of Obviousness

We instituted trial based on Petitioner's challenge to claim 10 of the '550 patent for obviousness under 35 U.S.C. § 103(a) over the '782 patent and Butler. Paper 28, 28.

As the Supreme Court has stated, when evaluating claims for obviousness, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)). Secondary considerations, if present, also must be considered. *Id.*

As to the level of ordinary skill, as discussed above, Petitioner contends that the level in this art is high, at the Ph.D. level or at least master's level with several years of experience in molecular analysis, with training in both the physical and biological sciences, or training in one of those disciplines with access to those with training in the other, and with "knowledge or comprehension of the biological and physical phenomena relevant to using nanopores to make highly precise measurements at the

molecular level." Ex. 1056 ¶ 28 (Second Branton Decl.);[15] Ex. 1057 ¶ 19 (Second Benz Decl.).[16]

Patent Owner does not assert error in the opinion of Petitioner's experts on this issue. *See* Supp. Resp., generally. Accordingly, we adopt Petitioner's definition for our obviousness analysis.

As to the scope of the prior art, and its differences from the challenged claim, Petitioner contends that the '782 patent describes a process having all of the steps and features of claim 10, except that the '782 patent does not describe using an Msp porin as its tunnel-containing protein through which its preferred analytes, nucleic acid molecules, are translocated. *See* Supp. Pet. 24, 38–39 (Ex. 1059). Petitioner contends that an ordinary artisan would have been motivated to modify the '782 patent's process and use Butler's mutant MspA porin as the tunnel-containing protein, given the references' expressed common goals of using a nanopore to effect rapid nucleic acid analysis. *Id.* at 24–25. In particular, Petitioner contends that an ordinary artisan would have considered the use of Butler's MspA mutant porin in the methods of the '782 patent to be "nothing more than the predictable use of a prior art element according to its established function." *Id.* at 29, 31.

Patent Owner does not assert error in Petitioner's contention that the '782 patent's process differs from claim 10's process only in that the '782 patent's process does not use the Msp porin required by claim 10. Rather,

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[15] Declaration of Daniel Branton, Ph.D. (Declaration executed Oct. 11, 2014) (Ex. 1056; "Second Branton Declaration" or "Second Branton Decl.").

[16] Declaration of Roland Benz, Prof., Dr., Dr. h.c. (Declaration executed Oct. 13, 2014) (Ex. 1057; "Second Benz Declaration" or "Second Benz Decl.").

Patent Owner contends that an ordinary artisan would not have considered it obvious to use Butler's Msp porin in the '782 patent's process because of the poor understanding of the interactions between nucleic acids and tunnel-forming proteins, and because an ordinary artisan, for a number of reasons, would not have had a reasonable expectation that Butler's Msp porin would be able to translocate nucleic acids. Supp. Resp. 12–39. Patent Owner contends also that an ordinary artisan would not have had a reasonable expectation that Butler's Msp porin would be able to characterize a heterogeneous mixture as taught in the '782 patent. *Id.* at 39–42.

Having reviewed Petitioner's analysis and supporting evidence in light of Patent Owner's arguments and evidence, we find that a preponderance of the evidence supports Petitioner's position that an ordinary artisan would have been prompted to use Butler's MspA mutant porin in the '782 patent's process of analyzing a heterogeneous mixture containing a plurality of different DNA molecules, thereby performing a process having all of the steps and features required by claim 10 of the '550 patent.

The '782 patent, like the '550 patent, discloses processes for evaluating polymeric molecules, such as DNA or RNA, in which two separate pools of electrically conductive media are separated by an ion permeable passage, and an electrical potential between the two pools is created, such that ionic current can flow through the ion permeable passage. Ex. 1024, 2:35–42. The '782 patent explains that "[w]hen 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. Thus, as to DNA or RNA, the method of the '782 patent involves

> measurements of ionic current modulation as the monomers (e.g., nucleotides) of a linear polymer (e.g., nucleic acid molecule) pass through or across a channel in an artificial membrane. During polymer passage through or across the channel, ionic currents are reduced in a manner that reflects the properties of the polymer (length, concentration of polymers in solution, etc.) and the identities of the monomers.

Id. at 6:52–59.

The '782 patent explains further that "[s]everal 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." *Id.* at 1:51–54; *see also id.* at 4:51–56 ("The mixture of polymers used in the invention does not need to be homogenous. Even when the mixture is heterogenous [sic], only one molecule interacts with a passage at a time, yielding a size distribution of molecules in the mixture, and/or sequence data for multiple polymer molecules in the mixture.").

Example 6 of the '782 patent discloses measurement of current blockades of shorter and longer RNA molecules of known length, thereby showing the "[r]elationship between polymer length and channel blockade duration," and "lending credibility to the accuracy of the methods of the invention for measuring polymer length by measuring signal duration." *Id.* at 20:11–46.

As to ion permeable passages, rather than the Msp porin required by claim 10, the '782 patent discloses that "[p]referred channels for use in the invention include the α-hemolysin toxin from *S. aureus* and maltoporin

channels." *Id.* at 4:65–67. As Petitioner discusses (Supp. Pet. 26), however, the '782 patent discloses that "[a]ny channel protein which has the characteristics useful in the invention (e.g., minimum pore size around 2 Å, maximum around 9 nm; conducts current) may be employed." Ex. 1024, 10:13–15.

As Petitioner discusses (Supp. Pet. 26–27), Butler discloses that, in general, the MspA porin "has many advantageous characteristics for nucleic acid analysis including a short, narrow inner constriction, remarkable robustness, ease of use, and the retention of pore-forming activity despite the introduction of multiple amino-acid substitutions." *Id.* Ex. 1003, 88.

As Petitioner further discusses (Supp. Pet. 29), Butler discloses that an MspA mutant porin with excess negatively charged amino acids removed, "SSN-MspA," exhibited properties consistent with the translocation of single stranded DNA through the protein's pore, using essentially the same system as that described in the '782 patent. Ex. 1003, 107 ("The data in Fig. 6.8 are consistent with the scenario where dA_{50} molecules are electrophoretically driven into the SSN-MspA pore and cause transient blockades of the ionic current. Perhaps . . . the increase in the rate of Short Deep events represents translocation of dA_{50} through SSN-MspA."); *see also id* at 88 ("We are presently working to verify the exciting possibility that these blockades are a result of interaction between ssDNA and the MspA mutant.").

Given Butler's disclosure that its SSN-MspA mutant porin exhibited properties consistent with the DNA translocation required in the methods of the '782 patent, and given also the advantageous properties of the MspA porins disclosed by Butler for use in nucleic acid analysis, the same pursuit

as the ’782 patent, Petitioner persuades us that an ordinary artisan would have been prompted to use Butler’s SSN-MspA mutant porin in the ’782 patent’s nanopore-based nucleic acid analysis processes. In addition, given the reference’s teachings, an ordinary artisan would have had a reasonable expectation that Butler’s porin would work in the ’782 patent’s processes.

Patent Owner’s arguments do not persuade us to the contrary. Patent Owner contends that, despite the assertion that any channel protein with suitable properties might be employed in analyzing nucleic acids, the ’782 patent discloses limited experiments with only its two preferred proteins, α-hemolysin and maltoporin, and of the two, only α-hemolysin was able to demonstrate a relationship between current blockade duration and nucleic acid length. Supp. Resp. 15–16. Patent Owner contends that, because α-hemolysin was the only pore-forming protein that had been used effectively in prior art nucleic acid analyses, and because its mechanism of action was not well understood, the state of the art was not such that an ordinary artisan would have viewed substituting other pore-forming proteins for the ’782 patent’s α-hemolysin a matter of simple substitution with a reasonable expectation of success. *Id.* at 16–19.

We are not persuaded. We acknowledge the testimony of Drs. Benner and Branton that, as of 2007, only α-hemolysin had been used in nucleic acid analyses in published papers. Ex. 2018 ¶ 15 (Second Benner Decl.);[17] Ex. 2036, 36:19–21 (Branton Deposition) (“But published papers, I have not seen using other protein pores that have been identified.”). As discussed above, however, the Butler reference, a 2007 doctoral thesis that neither

[17] Declaration of Steven A. Benner, Ph.D. (Declaration executed June 26, 2015) (Ex. 2018; “Second Benner Declaration” or “Second Benner Decl.”).

party disputes is prior art, describes the use of the SSN-MspA mutant in experiments with results consistent with DNA translocation through the pore protein. Ex. 1003, 107. Butler, moreover, presents a side-by-side comparison of the structures of MspA and α-hemolysin, illustrating the similar sizes of the pores, including their constriction zones, *see id.* at 94 (Fig. 6.2), leading Butler to state that "MspA structure is promising for nanopore analysis." *Id.* at 91 (italics removed). Thus, while prior art other than the Butler reference might not have provided a reasonable expectation of using porins other than α-hemolysin in nucleic acid analyses, that fact does not explain why an ordinary artisan, presented with the teachings in Butler about the similarities between SSN-MspA and α-hemolysin, lacked a reasonable expectation that, like α-hemolysin, Butler's SSN-MspA would be useful in the nucleic acid analyses of the '782 patent.

To that end, Patent Owner contends that the properties of the current blockade events, which Butler characterized as potentially showing translocation of DNA through the SSN-MspA porin, would not have led an ordinary artisan to conclude that DNA actually had translocated through the porin, in a manner that would have provided an ordinary artisan with a reasonable expectation that the SSN-MspA could be successfully substituted for the α-hemolysin taught in the '782 patent. Supp. Resp. 19–21. Moreover, Patent Owner contends, although Butler was hopeful that the results obtained demonstrated translocation, Butler nonetheless recognized that phenomena other than translocation may have been responsible for the observed data. *Id.* at 22–23. Further, Patent Owner contends, the disclosures in Butler, upon which Petitioner relies to show translocation, at best show that DNA was driven into, rather than through, Butler's SSN-

MspA porin, as evidenced by Petitioner's own witness, Dr. Branton. *Id.* at 23–27.

We acknowledge Patent Owner's evidence that, when observing current blockades in α-hemolysin, long and deep current blockades were generally considered indicative of translocation of DNA through the protein, whereas shorter duration blockades were not. *See* Supp. Resp. 19–21, 27 (citing Ex. 1003 (Butler), Ex. 2018 (Second Benner Decl.), Ex. 1022 (Kasianowicz),[18] Ex. 2015 (Nakane),[19] Ex. 1024 (the '782 patent)),[20] Ex. 2036 (Branton Deposition)).

As Petitioner notes (Reply 14), however, when evaluating the data obtained using α-hemolysin, Butler states that it is "clear from the dC$_{50}$ panel that *many translocation-associated states were shorter than our 30 μs cutoff time.* Events demonstrating these short translocation signals were classified as 'Other', and we hypothesize that fast translocation accounts for a significant fraction of dC$_{50}$ 'Other' type events listed in Table 4.1." Ex. 1003, 44 (emphasis added). Accordingly, Butler does not teach that short duration current blockades cannot be indicative of translocation.

As Patent Owner itself notes, moreover (Supp. Resp. 21), when testing SSN-MspA, Butler observed that long and deep current blockades occurred independently of whether single stranded DNA (dA$_{50}$) was added

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[18] John J. Kasianowicz et al., *Characterization of individual polynucleotide molecules using a membrane channel*, 93 PNAS 13770-13773 (1996) (Ex. 1022). In citing to Kasianowicz, Patent Owner uses an incorrect exhibit number. *See* Supp. Resp. (citing Ex. 1011).

[19] Jonathan J Nakane et al., *Nanopore sensors for nucleic acid analysis*, 15 J. PHYS.: CONDENS. MATTER R1365–R1393 (2003) (Ex. 2015).

[20] In citing to the '782 patent, Patent Owner uses an incorrect exhibit number. *See* Supp. Resp. 21, 27 (citing Ex. 2006).

to the liquid media. Ex. 1003, 107 ("The rates of Short Mid, Short Deep and Long Mid events always increase by at least a factor of 10 in the presence of $d\text{A}_{50}$, while the rate of Long Deep events seems independent of the presence of $d\text{A}_{50}$."). Given the apparent differences between α-hemolysin and SSN-MspA as to the measured characteristics of their current blockades in the presence of DNA, we are not persuaded that Patent Owner has explained convincingly why an ordinary artisan necessarily would have considered results obtained using α-hemolysin predictive of whether SSN-MspA translocated DNA.

Moreover, rather than suggesting only that DNA entered the SSN-MspA molecule, but did not translocate through, Butler states expressly that, "[p]erhaps . . . the increase in the rate of Short Deep events represents translocation of $d\text{A}_{50}$ through SSN-MspA." Ex. 1003, 107; *see also id.* at 110 ("It will be necessary to obtain direct proof of translocation by directly detecting single-stranded DNA molecules on the *trans* side of the bilayer after an experiment.") (citations omitted); *id.* at 111 ("The first critical milestone for this project will be verification of ssDNA translocation through a mutant MspA pore."). Thus, while an ordinary artisan viewing Butler's statements regarding interaction of SSN-MspA with DNA might not have understood translocation necessarily to have been proved, Patent Owner does not persuade us that, reading the reference as a whole, a preponderance of the evidence fails to support Petitioner's contention that there was a reasonable expectation that Butler's protein would be suitable in the methods of the '782 patent.

We acknowledge the speculative nature of Butler's disclosures regarding translocation. It is well-settled, however, that "[o]bviousness does

not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)) (emphasis removed).

In the instant case, as discussed above, Butler presents a side-by-side comparison of the structures of α-hemolysin, used in the methods of the '782 patent, and the MspA porin, illustrating the similar sizes of the pores, including their constriction zones. Ex. 1003, 94 (Fig. 6.2). Summarizing its structural attributes, Butler states that "MspA structure is promising for nanopore analysis." *Id.* at 91 (italics removed). Butler also explains that the MspA porin "has many advantageous characteristics for nucleic acid analysis including a short, narrow inner constriction, remarkable robustness, ease of use, and the retention of pore-forming activity despite the introduction of multiple amino-acid substitutions." *Id.* at 88. Butler then describes a single specific mutant version of that protein, SSN-MspA, which exhibited properties causing Butler to opine that it was capable of translocating DNA, though that property had not yet been verified. *Id.* at 107, 111.

Thus, rather than requiring the ordinary artisan to vary numerous parameters, select from numerous choices, or apply a promising but unguided general approach (*In re O'Farrell*, 853 F.2d at 903), Butler provided a single specific protein, and identified a number of properties explaining why that protein reasonably would have been expected to be equivalently useful to α-hemolysin in methods of nucleic acid analysis. An ordinary artisan, therefore, need only have substituted Butler's SSN-MspA

porin for the α-hemolysin in the ’782 patent’s nucleic acid analysis methods to verify the usefulness of the SSN-MspA in those methods.

Indeed, the facts in the instant case are similar to those in *In re O’Farrell*, where the court found that a reasonable expectation of success had been established. In *O’Farrell*, the claims were directed to expressing a hybrid protein in bacteria. 853 F.2d at 895. As here, the cited prior art reference did not conclusively establish that those proteins would be produced using the methods the reference described. *Id.* at 900. Instead, as here, the cited reference only speculated at success, and explained how success might be verified. *Id.* at 901 (“*It would be interesting to examine* the expression of a normally translated eukaryotic sequence in pBGP120. *If* an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript *might* allow for extensive translation of a functional eukaryotic polypeptide.”) (quoting cited reference; emphases added).

In summarizing its conclusion in *O’Farrell*, the court pointed to facts similar to those presented in the instant case, stating that “the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.” *Id.* Thus, given the overall teachings in Butler, discussed above, the speculative nature of Butler’s disclosure regarding translocation does not persuade us that an ordinary artisan lacked a reasonable expectation that Butler’s SSN-MspA protein, like α-hemolysin, would be capable of translocating nucleic acids, and, therefore, would be useful the ’782 patent’s nucleic acid analysis methods.

Patent Owner seeks to discredit Dr. Branton's obviousness testimony by pointing out that, when reviewing a draft paper that included the experimental results reported in the Butler thesis, as well as additional results, Dr. Branton questioned whether translocation had occurred. Supp. Resp. 27–29. Patent Owner directs us to evidence purporting to show that, before recommending the paper for publication, the group reviewing the draft, which included Dr. Branton, required the authors to perform additional experiments to conclusively prove that nucleic acid had been translocated through the MspA porins. *Id.* at 30–34. Patent Owner contends that the instant facts are, therefore, consistent with those in *In re Carroll*, 601 F.2d 1184, 1186–87 (CCPA 1979), in which an ordinarily skilled reviewer's negative assessment of a master's thesis, made prior to filing the application at issue, was held to demonstrate that the thesis did not establish the obviousness of the subject matter disclosed therein. Supp. Resp. 34–35.

We do not find these arguments persuasive. As to the alleged inconsistencies in Dr. Branton's testimony, as discussed above, we find that the teachings in the references themselves support finding that an ordinary artisan would have been motivated to substitute Butler's SSN-MspA for the '782 patent's α-hemolysin, and would have had a reasonable expectation that Butler's protein would work in the '782 patent's nucleic acid analysis methods. As to the proposition that ordinary artisans would not have viewed Butler's data as conclusively proving that DNA had translocated through the porin, as discussed above, *O'Farrell* makes it clear that conclusive proof is not required to show a reasonable expectation of success. Thus, even assuming evidence indicates that a group reviewing a relevant scientific manuscript for publication requested additional experiments to "prove"

translocation of nucleic acid, such evidence does not dictate that we find no reasonable expectation of success here.

Patent Owner also contends that the testimony of Petitioner's expert witnesses, submitted with the first Petition in this proceeding to show that the '550 patent's claims are not entitled to priority to the earlier filed provisional application (Ex. 1016), demonstrates the absence of a reasonable expectation of translocation, because the relevant disclosures in Butler and the provisional application are similar. Supp. Resp. 36–39. We are not persuaded.

We first note that the standards for obviousness and written description support differ. As noted above, absolute certainty is not required to show a reasonable expectation of success in obviousness determinations. *O'Farrell*, 853 F.2d at 903–04. In contrast, when evaluating disclosures for descriptive support, "[o]ne shows that one is 'in possession' of *the invention* by describing *the invention*, with all its claimed limitations, not that which makes it obvious." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

We are not persuaded, moreover, that the current blockade events described in the provisional application are similar to those described in Butler. Specifically, the provisional application describes the events as "too brief to . . . estimate the depth of the blockade." Ex. 1016, 14. In contrast, Butler was able to ascertain the depths of the blockades posited as representing translocation, with accuracy sufficient to allow their presentation in a graph. Ex. 1003, 109 (Fig. 6.8). Butler also expressly characterized the events posited as representing translation as "Short Deep events." *Id.* at 107. Accordingly, the testimony of Petitioner's expert

witnesses regarding the disclosure in the provisional application does not undermine Butler's suggestion of a reasonable expectation of success.

Patent Owner contends that analysis of multiple analytes, as taught in the '782 patent, requires discriminating between different polymers based on their constituent monomers, a capacity that an ordinary artisan would not have reasonably expected Butler's SSN-MspA to have. Supp. Resp. 39–42 (citing Ex. 2015 (Nakane), Ex. 1026 (Deamer), Ex. 2018 (Second Benner Decl.)). We are not persuaded, however, that the '782 patent's disclosure of characterizing heterogeneous mixtures is limited to monomer-dependent analysis.

As noted above, and as Patent Owner recognizes (Supp. Resp. 16), Example 6 of the '782 patent uses α-hemolysin to establish that there is a "[r]elationship between polymer length and channel blockade duration." Ex. 1024, 20:11–12. Because of this relationship between polymer length and channel blockade duration, the '782 patent explains that a heterogeneous sample containing a plurality of analytes (as required by claim 10) can be analyzed, "yielding a size distribution of molecules in the mixture." *Id.* at 4:54–55.

As discussed above, Butler's SSN-MspA and the '782 patent's α-hemolysin are closely similar as to pore size and structure. Ex. 1003, 94 (Fig. 6.2). Accordingly, even assuming that an ordinary artisan did not reasonably expect Butler's SSN-MspA to be able to distinguish between different polymers in a mixed sample based on the polymers' constituent monomers, that fact does not persuade us that an ordinary artisan lacked a reasonable expectation that SSN-MspA would have been able to provide a size distribution in a mixed sample containing a plurality of different

analytes, as taught in the ’782 patent, in a fashion similar to α-hemolysin. To the contrary, given the structural and size similarities between Butler’s SSN-MspA and the ’782 patent’s α-hemolysin, an ordinary artisan would have reasonably expected SSN-MspA to be useful in the ’782 patent’s processes of providing a size distribution in a mixed sample containing a plurality of different analytes, encompassed by claim 10.

In sum, for the reasons discussed, having considered the prior art advanced by Petitioner in light of Patent Owner’s arguments and evidence regarding the cited references’ teachings, we find, based on the teachings in those references, that an ordinary artisan would have been prompted to substitute Butler’s SSN-MspA for the α-hemolysin used in the processes of analyzing nucleic acid taught in the ’782 patent, and would have had a reasonable expectation that the SSN-MspA would work in those processes. Accordingly, an ordinary artisan would have had reason to perform, and would have had a reasonable expectation of successfully performing, a process having all of the steps and features required by claim 10 of the ’550 patent.

2. Secondary Considerations/Objective Indicia

When assessing obviousness, in addition to the teachings in the prior art, the objective indicia of nonobviousness must be considered “as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.” *Eurand, Inc. v. Mylan Pharm. Inc. (In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.)*, 676 F.3d 1063, 1076–77 (Fed. Cir. 2012) (citation omitted).

Although Petitioner bears the ultimate burden of persuasion under 35 U.S.C. § 316(e), as Petitioner contends (Supp. Reply 22), Patent Owner

must establish a nexus between the objective evidence of nonobviousness and the claimed subject matter. *See In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.").

In particular, the objective indicia "must be tied to the novel elements of the claim at issue" and must "'be reasonably commensurate with the scope of the claims.'" *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) (quoting *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013)).

Patent Owner contends that objective evidence of nonobviousness shows that that "(1) the claimed method performed unexpectedly better than the methods using α-HL (the nanopore of choice prior to the inventors' discovery); (2) Illumina, the world leader in DNA sequencing, licensed the '550 patent; and (3) the claimed method garnered industry-wide praise, including from Petitioner itself." Supp. Resp. 43.

We agree with Petitioner that Patent Owner's objective evidence of nonobviousness is not sufficiently commensurate in scope with the subject matter encompassed by claim 10. *See* Supp. Reply 23–24.

Claim 1, from which claim 10 depends, recites a process of using an Msp porin to detect an "analyte" in a first liquid medium. Ex. 1001, 103:33–43. Claim 10 requires either the first liquid medium, or a second liquid medium, to contain a plurality of different analytes. *Id.* at 104:39–41. As noted above, the '550 patent states that the term "analyte" encompasses a wide variety of different substances, having widely varying properties, including "a nucleotide, a nucleic acid, an amino acid, a peptide, a protein, a

polymer, a drug, an ion, a pollutant, a nanoscopic object, or a biological warfare agent." *Id.* at 8:45–48.

In contrast, the evidence to which Patent Owner directs us to show that Msp porins function unexpectedly better than α-hemolysin only relates to DNA. *See* Ex. 2014, 16060 ("Passing DNA with a series of double-stranded sections through MspA provides proof of principle of a simple DNA sequencing method using a nanopore.");[21] Ex. 2031, 56 ("We have combined Phi29 DNA polymerase (DNAP) as a molecular motor with a mutant MspA nanopore to allow controlled movement of a DNA strand through the pore.");[22] *id.* at 61, 62 ("using [a] Phi29 DNA polymerase to control the movement of intact DNA strands through a nanopore"); Ex. 2023, 1 ("DNA passed through the protein nanopore");[23] Ex. 2037, 1 (sequencing bacteriophage genome).[24] Patent Owner does not direct us to any clear or specific evidence suggesting that the alleged superiority of the claimed Msp porin over α-hemolysin as to DNA analysis would extend to any other analytes encompassed by claim 10. Accordingly, we agree with

[21] Ian M. Derrington et al., *Nanopore DNA sequencing with MspA*, 107 PNAS 16060-16065 (2010) (Ex. 2014).

[22] James Clarke et al., WO 2012/107778 A2 (published Aug. 16, 2012) (Ex. 2031).

[23] Monica Heger, *Proof-of-Principle Study Shows MspA Is Superior to Alpha-Hemolysin for Protein Nanopore Sequencing*, http://www.genomeweb.com/print/948013 (2010) (Ex. 2023).

[24] Monica Heger, *Pre-print Study Demonstrates Nanopore Sequencing of Bacteriophage Genome with MspA Pore*, http://www.genomeweb.com/print/1407801?utm_source=SilverpopMailing&utm_medium=email&utm_campaign=In%20Sequence%3A%20MspA%20Nanopore%… (2014) (Ex. 2037).

Petitioner that the evidence advanced by Patent Owner to show unexpectedness is not reasonably commensurate in scope with the subject matter recited in claim 10.

Similarly, the evidence Patent Owner advances regarding the company Illumina licensing the claimed technology all relates to DNA sequencing. *See* Supp. Resp. 47–48; Ex. 1014 ("Illumina Inc. has licensed the rights to a DNA sequencing technology . . . ");[25] Ex. 2026, 2 ("nanopore DNA sequencing").[26] The evidence of industry praise all relates to DNA sequencing also. *See* Supp. Resp. 48–50 (citing Exs. 2013, 2030, 2026, 2021, 2027–2029, 2031, 2038–42).

As with the evidence of unexpected results, Patent Owner does not direct us to clear or specific evidence suggesting that the asserted licensing activity or industry praise extends to the detection of any of the many and varied analytes, other than DNA, encompassed by claim 10. Accordingly, we agree with Petitioner that the evidence advanced by Patent Owner to show licensing activity and industry praise is not reasonably commensurate in scope with the subject matter recited in claim 10.

3. Ultimate Conclusion of Obviousness

As discussed above, having considered the prior art advanced by Petitioner in light of Patent Owner's arguments and evidence regarding the cited references' teachings, we find, based on the teachings in the '782 patent and Butler, that an ordinary artisan would have had reason to perform,

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[25] UAB News, *Licensing deal marks coming of age for UAB-UW nanopore sequencing technology*, http://www.uab.edu/news/innovation/item/3847-licensing-deal-marks-coming-of-age-for-u... (accessed 2014) (Ex. 1014).

[26] Hagan Bayley, Nanopore sequencing: from imagination to reality, *Clin. Chem*. Author manuscript; available in PMC 2015 April 21 (Ex. 2026).

and would have had a reasonable expectation of successfully performing, a process having all of the steps and features required by claim 10 of the '550 patent. As also discussed above, having considered Patent Owner's evidence and arguments regarding objective indicia of nonobviousness, we find that Patent Owner's evidence is not sufficiently commensurate in scope with the subject matter recited in claim 10. Considering the record before us, Patent Owner's evidence and argument do not outweight Petitioner's showing of obviousness here.

Accordingly, under these circumstances, taking into consideration the record as a whole, we conclude that Petitioner has shown by a preponderance of the evidence that an ordinary artisan would have considered the process of claim 10 obvious in view of the '782 patent and Butler.

F. Patent Owner's Motion to Exclude Evidence

Patent Owner moves to exclude lines 21–25 of page 136 of Dr. Benner's Deposition (Ex. 1058), cited on page 15 of Petitioner's Reply, and lines 15–19 of page 153 of Dr. Benner's Deposition, cited on pages 3 and 10 of Petitioner's Reply. Mot. to Exclude 1.

We deny Patent Owner's motion to exclude the disputed testimony.

Patent Owner contends that Petitioner uses the testimony on page 136 of Dr. Benner's deposition in a misleading fashion, and that Petitioner cites it out of context, and, therefore, the testimony should be excluded under Federal Rule of Evidence ("FRE") 403. Mot. to Exclude 2–6. For essentially the same reasons, Patent Owner contends that the disputed testimony on page 153 of Dr. Benner's Deposition also should be excluded under Rule 403. *Id.* at 6–7.

The Board "may exclude relevant evidence if its probative value is substantially outweighed by a danger of one or more of the following: unfair prejudice, confusing the issues, misleading the jury, undue delay, wasting time, or needlessly presenting cumulative evidence." FRE 403. That Petitioner may have cited the disputed testimony out of context, or used it to support positions contrary to positions taken elsewhere in the proceeding, does not persuade us that the disputed testimony itself should be excluded under FRE 403. The Board, unlike a lay jury, has significant experience in evaluating expert testimony. Accordingly, the danger of prejudice in this proceeding is considerably lower than in a conventional district court trial. We are not persuaded, moreover, that the issue of whether a party's argument cites testimony in proper context relates to the admissibility of that testimony. The Board is capable of determining for itself whether a party's argument cites testimony in its proper context.

As to relevance, Patent Owner does not contend that the disputed testimony on page 136 of Dr. Benner's Deposition fails to meet any of the broad criteria expressly set out in FRE 401. *See* Mot. to Exclude 2–4. Rather, Patent Owner contends that the disputed testimony is irrelevant because it is improper hindsight evidence, and is evidence of the inventor's viewpoint, rather than that of an ordinary artisan. *Id.*

We are not persuaded. The issue of whether Dr. Benner's disputed testimony should be viewed as improper hindsight goes to its weight, rather than its admissibility. Similarly, the issue of whether Dr. Benner testified as to the perspective of an inventor, rather than an ordinary artisan, also goes to the testimony's weight, rather than its admissibility. Indeed, none of the cases Patent Owner cites stands for the proposition that, in an obviousness

determination, testimony or other evidence is inadmissible under FRE 402 because it relates to improper hindsight, or the perspective of an inventor rather than an ordinary artisan. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364–65 (Fed. Cir. 2008); *Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00453, 2015 WL 4467403, at *8 (PTAB July 13, 2015)); *Amgen, Inc. v. F. Hoffmann- La Roche, Ltd.*, 580 F.3d 1340, 1363 (Fed. Cir. 2009).

In sum, for the reasons discussed, we deny Patent Owner's motion to exclude lines 21–25 of page 136 of Dr. Benner's Deposition (Ex. 1058), and lines 15–19 of page 153 of Dr. Benner's Deposition.

III. CONCLUSION

For the foregoing reasons, Petitioner has not proved by a preponderance of the evidence that claim 10 of the '550 patent is anticipated by Butler under 35 U.S.C. § 102(b).

For the foregoing reasons, Petitioner has not proved by a preponderance of the evidence that claims 17 and 18 are anticipated by the Wong Poster under 35 U.S.C. § 102(b).

For the foregoing reasons, Petitioner has not proved by a preponderance of the evidence that claims 17 and 18 are anticipated by the Wong Abstract under 35 U.S.C. § 102(b).

For the foregoing reasons, Petitioner has proved by a preponderance of the evidence that claim 10 is unpatentable for obviousness over the '782 patent and Butler under 35 U.S.C. § 103(a).

IV. ORDER

It is ORDERED that claim 10 of the '550 patent has been shown by a preponderance of the evidence to be unpatentable;

FURTHER ORDERED that Patent Owner's Motion to Amend is granted;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied; and

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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