

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SPECTRUM SOLUTIONS LLC
Petitioner,

v.

LONGHORN VACCINES & DIAGNOSTICS, LLC
Patent Owner.

IPR2021-00860
Patent 9,683,256 B2

Before ZHENYU YANG, WESLEY B. DERRICK, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

A. Background

Spectrum Solutions LLC (“Petitioner” or “Spectrum”) filed a Petition for an *inter partes* review of claims 1–20 of U.S. Patent No. 9,683,256 B2 (“the ’256 patent,” Ex. 1001). Paper 1 (“Pet.”). Longhorn Vaccines & Diagnostics, LLC (“Patent Owner” or “Longhorn”) timely filed a Preliminary Response. Paper 6 (“Prelim. Resp.”). With our authorization (*see* Paper 3001), Petitioner filed a Reply to the Preliminary Response (Paper 7, “Reply”); Patent Owner filed a corresponding Sur-reply (Paper 10, “Sur-reply”).¹

B. Summary of the Institution Decision

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has demonstrated a reasonable likelihood that at least one claim of the ’256 patent is unpatentable, we institute an *inter partes* review of all challenged claims on each of the grounds raised in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018); *see also* Guidance on the Impact of *SAS* on AIA Trial Proceedings (April 26, 2018) (available at <https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial>) (“Guidance”).

¹ Patent Owner filed duplicative copies of its Sur-reply as Papers 9 and 10, which, absent a word-for-word comparison, appear identical but for minor differences in formatting. In an abundance of caution, we expunged Paper 9 in favor of the second-filed copy. Patent Owner subsequently indicated that the expunged version contained a formatting error. Ex. 3003.

C. Real Parties-in-Interest

Petitioner identifies itself, Spectrum Solutions LLC as a real party-in-interest. Pet. 1. Petitioner further identifies two companies having a financial interest in, or potentially substantially affected by the outcome of, this proceeding: its parent company, Spectrum Holdco LLC, and Spectrum Intermediate LLC. *Id.* Petitioner does not expressly identify those companies as real parties-in-interest.

Patent Owner identifies only itself, Longhorn Vaccines & Diagnostics, LLC, as the real party-in-interest in this proceeding. Paper 3, 1.

D. Related Matters

Petitioner concurrently challenges claims of related U.S. Patents Nos. 8,084,443 (“the ’443 patent”); 8,293,467; 8,415,330; 8,669,240; and 9,212,399, in IPR2021-00847, -00850, -00851, -00854, and 00857, respectively. According to the parties, the same patents are at issue in *Longhorn Vaccines & Diagnostics, LLC v. Spectrum Solutions LLC*, C.A. No. 2:20-cv-00827 (D. Utah). Pet. 1; Paper 3, 1; Ex. 1007 ¶¶ 9–15.

E. Asserted Challenges to Patentability

Petitioner challenges the patentability of claims 1–20 on the following basis: (Pet. 11):

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–10, 13, 15–19	§ 103(a)	Birnboim, ² Mori, ³ Farrell ⁴

² Birnboim, US 2004/0038269 A1, published Feb. 26, 2004. Ex. 1003.

³ Mori, WO 2005/111210 A1, published Nov. 24, 2005. Ex. 1011.

⁴ Robert E. Farrell, Jr., Ph.D., “RNA Methodologies: A Laboratory Guide for Isolation and Characterization,” (3rd Ed., 2005). Ex. 1026.

Ground	Claims Challenged	35 U.S.C. §	Reference(s)/Basis
2	11	§ 103(a)	Birnboim, Mori, Farrell, Das ⁵
3	12, 20	§ 103(a)	Birnboim, Mori, Farrell, Helftenbein ⁶
4	14	§ 103(a)	Birnboim, Mori, Farrell, Heineman ⁷

In support of its patentability challenge, Petitioner relies on, *inter alia*, the Declaration of Richard F. Taylor, Ph.D. Ex. 1002. Based on the preliminary record before us, we determine that Dr. Taylor is qualified to offer testimony on the knowledge of one of ordinary skill in the art as of any of the asserted priority dates of the '256 patent. *See, e.g., id.* ¶¶ 2–23, 51–65 (Dr. Taylor's statements as to his background and qualifications, and background on the relevant technology), ¶¶ 34–35 (Dr. Taylor's opinion regarding the definition of one of ordinary skill in the art); Ex. 1040 (Dr. Taylor's curriculum vitae)

Patent Owner relies on, *inter alia*, the Declaration of Louis DeFilippi Ph.D. *See* Ex. 2001. Based on the preliminary record before us, we determine that Dr. DeFilippi is qualified to offer testimony on the knowledge of one of ordinary skill in the art as of any of the asserted priority dates of the '256 patent. *See, e.g., id.* ¶¶ 1–4 (Dr. DeFilippi's statements as to his background and qualifications, and background on the relevant technology); *id.* at pages 31–43 (Dr. DeFilippi's curriculum vitae).

⁵ Das et al., US 2005/0123928 A1, published June 9, 2005. Ex. 1008.

⁶ Helftenbein, US 6,776,959 B1, Aug. 17, 2004. Ex. 1019.

⁷ Heineman et al., US 2005/0079484 A1. April 14, 2005. Ex. 1033.

F. The '256 Patent and Related Background

The '256 patent, titled Biological Specimen Collection and Transport System, issued to Fischer et al., from U.S. Application 14/969,339, filed April 10, 2019, via a series of continuation and continuation-in-part applications first filed on October 1, 2008, and further claims benefit of priority to US provisional Application No. 60/976,728, filed on October 1, 2007. Ex. 1001, code (21), (22), (54), (60), and (63). In addressing the art of record, Petitioner presumes the earliest possible priority date (October 1, 2007). *See, e.g.*, Pet. 4; Ex. 1002 ¶ 1. Patent Owner presently does not dispute the prior art status of the asserted references. Prelim. Resp. 6.

1) Background and Specification

The '256 patent relates to “aqueous compositions for collection, transport, and storage of a biological specimen containing a population of nucleic acids in a single reaction vessel, which can then be purified and/or analyzed using conventional molecular biology methods.” Ex. 1001, 1:21–25. Petitioner and its declarant, Dr. Taylor, note that, as of the earliest possible priority date of the '256 patent, aqueous reagents for extracting, “stabilizing, and preserving nucleic acids were wide-spread and well-known in the prior art.” *See, generally*, Pet. 4–7; Ex. 1002 ¶¶ 51–65 (citations omitted). Petitioner and its declarant point to, for example, the 1982 Maniatis Laboratory Manual as disclosing the isolation of RNA using a buffered, nuclease-free, aqueous solution of guanidinium isothiocyanate (a potent chaotropic agent), sodium lauryl sarkosinate (a detergent), β -mercaptoethanol (a reducing agent), and EDTA (a chelator). Pet. 4–5; Ex. 1002 ¶¶ 51–53; Ex. 1004, 189–190.

The Specification, however, asserts that prior art methods could result in the degradation of nucleic acids, even when stored under freezing temperatures, and had the potential for exposure to infectious agents during collection, transfer, and testing. Ex. 1001, 1:42–2:22. Moreover, the Specification asserts, “clinical laboratory methods for pathogen detection were labor-intensive, expensive processes that required highly knowledgeable and expert scientists with specific experience.” *Id.* at 2:23–26.

Against this background, the ’256 patent, purports to disclose “new and useful compositions . . . that may advantageously improve conventional collection, lysis, transport and storage methods for the preparation of nucleic acids from one or more biological sources.” *Id.* at 3:9–13. In particular, the ’256 patent discloses a one-step, aqueous stock solution that:

- a) inactivates viruses or microbes in the sample, b) lyses the biological cells or tissues to free the nucleic acids from cellular debris and extraneous biomolecules, c) protects the nucleic acids from degradation by endonuclease activity, and
- d) preserves the nucleic acids for subsequent isolation, detection, amplification, and/or molecular analysis.

Id. at 1:20–39; *see id.* at 6:32–40. The Specification further discloses exemplary stock solutions comprising a buffered solution of nuclease-free water containing:

- a chaotrope, e.g., guanidine thiocyanate, guanidine hydrochloride, or guanidine isocyanate;
- a detergent, e.g., sodium dodecyl sulfate (SDS), lithium dodecyl sulfate (LDS), sodium taurodeoxycholate (NaTDC), sodium taurocholate (NaTC), sodium glycocholate (NaGC), sodium deoxycholate (NaDC), sodium cholate, sodium alkybenzene sulfonate (NaABS), or N-lauroyl sarcosine (NLS);

- a reducing agent, e.g., β -mercaptoethanol (β -ME), dithiothreitol (DTT), dimethylsulfoxide (DMSO), formamide, or phosphine (TCEP);
- a chelator, e.g., EGTA, HEDTA, DTPA, NTA, EDTA, citrate anhydrous, sodium citrate, calcium citrate, ammonium citrate, ammonium bicitrate, citric acid, diammonium citrate, ferric ammonium citrate, or lithium citrate);
- a surfactant/defoaming agent, e.g., a silicone polymer such as Antifoam A®, or a polysorbate such as Tween®; and
- a short chain alkanol, e.g., methanol, ethanol, propanol, butanol, pentanol, hexanol.

Id. at 4:19–7:36, 7:49–67; *see also* Ex. 2001 ¶ 2 (“The disclosure of the ’256 Patent provides multiple examples including of a PrimeStore™ solution that improves significantly on the collection and transport systems disclosed in the references of record and asserted in the Petition.”).

According to the Specification:

In certain embodiments, the composition containing the sample suspected of containing nucleic acids will stabilize the nucleic acids to the extent that they either remain at least substantially non-degraded (i.e., at least substantially stable) even upon prolonged storage of the composition at ambient, refrigerator, or sub-zero temperatures. It will be desirable that this stability provides that at least about 70%, at least about 85%, more preferably at least about 90%, more preferably at least about 95%, or even more preferably, at least about 98% of the polynucleotides contained within the stored sample will not be degraded upon prolonged storage of the sample. In certain embodiments, substantially all of the polynucleotides contained within the sample will be stabilized such that the original integrity of the polynucleotides is preserved during the collection, lysis, storage, and transport of the processed sample.

Ex. 1001, 9:57–10:5; *see also id.* at 10:34–50 (asserting that “no more than about 1 or 2% of the sample will be degraded even when the composition is

stored at a temperature from 0° C. to about 40° C. for periods of several days to several weeks”).

2) Challenged Claims

Petitioner challenges claims 1–20 of the ’256 patent. Of these, claims 1, and 15 are independent. Claim 1 is representative of the challenged claims and reproduced below.

1. A stock solution comprising components with concentrations as follows:

- [a] a chaotrope present in an amount from 0.5 M to 6M;
- [b] a detergent present in an amount from 0.1% to 1% (wt./vol.);
- [c] a reducing agent in an amount from 0.5 mM to 0.3 M;
- [d] a chelator present in an amount from 0.01 mM to 50 mM;
- [e] a surfactant present in an amount from 0.0001% to 0.3% (wt./vol.);
- [f] a short-chain alkanol present in an amount from 1 to 25% (vol./vol.);
- [g] a buffer present in an amount from 1 mM to 1 M;
- [h] an acid or base present in an amount that provides a pH from 5 to 7 to the stock solution; and
- [i] nuclease-free water,
- [j] wherein the stock solution, when combined with a biological sample suspected of containing a pathogen, denatures proteins, inactivates nucleases, and kills pathogens all without degrading nucleic acids of the sample.

Ex. 1001, 31:57–32:46 (bracketing added as per pages 16–17 of the Petition). Independent claims 15 and 17, respectively, recite a method for

detecting a nucleic acid and a diagnostic kit, each of which recite the stock solution of claim 1. *Id.* at 34:9–18, 23–24.

II. ANALYSIS

A. Legal Standards

“In an IPR, the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

Petitioner contends that each claim of the ’256 patent is invalid as obvious under § 103(a). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is unpatentable as obvious under 35 U.S.C. § 103 as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and (4) considering objective evidence indicating obviousness or non-obviousness, if present.⁸ *KSR*, 550 U.S. at 406.

⁸ At this stage of the proceeding, there is no evidence pertaining to objective indicia of non-obviousness. *See* Prelim. Resp.

“[W]hen a patent ‘simply arranges old elements with each performing the same function it had been known to perform’ and yields no more than one would expect from such an arrangement, the combination is obvious.” *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). But in analyzing the obviousness of a combination of prior art elements, it can also be important to identify a reason that would have prompted one of skill in the art “to combine . . . known elements in the fashion claimed by the patent at issue.” *Id.* at 418.

“[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.” *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). Moreover, a precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *KSR*, 550 U.S. at 418. Rather, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *In re Magnum Oil Tools International, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (quotations and citations omitted).

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the

rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *See Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *see also Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Relying on the testimony of Dr. Taylor, Petitioner asserts that

A person of ordinary skill in the art (“POSA”) would have had (1) a Ph.D. in microbiology, molecular biology, biochemistry, or related discipline; (2) at least two years of post-graduate experience in the area of nucleic acid extraction and analysis; and (3) experience with the development or use of nucleic acid extraction formulations, and the literature concerning nucleic acid extraction and analysis.

Pet. 10 citing Ex. 1002, ¶¶34–35. Patent Owner presently does not dispute Petitioner’s proposed definition. Prelim. Resp. 6.

For purposes of this Decision, at this stage of the proceeding, we accept Petitioner’s proposed definition of the person of ordinary skill in the art, which is not substantively opposed by Patent Owner and appears to be consistent with the level of skill in the art reflected in the prior art of record and the disclosure of the ’256 patent. *Cf. Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (“the prior art itself [may] reflect[] an appropriate level” as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b) (2020). Under this standard, we construe the

claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

According to Petitioner, we should apply the plain and ordinary meaning of “stock solution” as meaning “a formulated supply of solution for future use,” which, in the context of the instant claims, refers to “the aqueous composition before it is mixed with a sample.” Pet. 8 (citing Ex. 1029; Ex. 1002 ¶ 38). Patent Owner neither contests Petitioner’s definition of “stock solution” nor requests that we construe any other claim term, but reserves its right to do so. Prelim. Resp. 7.

At this stage of the proceeding, we apply the plain and ordinary meaning of “stock” solution as Petitioner proposes. In section II.D.4, below, we note that Patent Owner implicitly relies on narrow constructions of “kills pathogens” and “without degrading nucleic acids.” As these terms may be critical to our final determination but have not been briefed by either party, we provisionally apply their plain and ordinary meaning.

D. Ground 1: Obviousness in View of Birnboim, Mori, and Farrell

As to Ground 1, Petitioner challenges claims 1–10, 13, and 15–19 as unpatentable for obviousness in view of Birnboim, Mori, and Farrell. Pet. 11, 16–55. Patent Owner opposes. Prelim. Resp. 9–34. We begin with an overview of the asserted references.

1) Overview of Birnboim (Exhibit 1003)

Birnboim discloses “compositions and methods for preserving nucleic acids at room temperature for extended periods of time and for simplifying the isolation of nucleic acids,” most particularly, DNA or RNA from sputum or saliva. Ex. 1003 ¶¶ 2, 27. According to Birnboim, nucleic acid isolated

can be that of the sputum or saliva donor or “from a bacterium or a virus that is residing in the buccal, nasal, or respiratory passages of the subject.” *Id.*

¶ 27; *see id.* ¶ 43 (defining “nucleic acid” as meaning “a chain of the nucleotides, including deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), typically found in chromosomes, mitochondria, ribosomes, bacteria, or viruses”); ¶ 18 (“The nucleic acid to be preserved can be . . . viral RNA.”); ¶ 27 (“If the nucleic acid is RNA, desirably it is mRNA or viral RNA.”) ¶ 45 (discussing quantitation of “high molecular weight nucleic acid (DNA, RNA, mRNA, or viral RNA)”); claims 7, 16.

Birnboim discloses stock solutions (“nucleic acid preserving compositions”) for use in a one-step method to lyse nucleic acid-containing cells or viruses, release the nucleic acids into the composition, inactivate nucleases in the sample, and stabilize the extracted nucleic acid for future analysis. *See generally, id.* ¶¶ 11, 22, 27, 64, 114–122. Birnboim further teaches “inclusion of an inhibitor of ribonuclease in the composition of the invention . . . when the nucleic acid to be preserved is RNA, desirably mRNA, or when the nucleic acid to be preserved is from a virus or a bacterium.” *Id.* ¶ 22; *see also id.* ¶ 68 (stating that in addition to the use of various denaturing agents, “reagents such as heparin, heparian sulfate, or oligo(vinyl)sulfonic acid) . . . are known to inhibit the action of deoxynucleases and /or ribonucleases”).

Birnboim explains:

When sputum is mixed with a composition of the present invention, cells are disrupted, nucleic acids are liberated from the cells, membranous material is solubilized, proteins are stripped from the nucleic acids, and protein digestion begins If transferred to a laboratory soon after collection, incubation at 55° C. for 4 to 16 hours is sufficient to allow the

activated protease to digest the majority of protein to small peptides or amino acids. Under such conditions, nucleic acids and polysaccharides remain relatively intact.

Once digestion is complete, nucleic acid isolation can be performed using any technique known in the art.

Id. ¶¶ 84–85.

Example 1 discloses an embodiment wherein a subject spits saliva into a collection tube which is mixed with an equal volume of stock solution.

Id. ¶¶ 107–109. Once the container is capped and the contents shaken, the nucleic acid is “in an intermediate preserved state” and “can be maintained in a frozen state or at any temperature up to about 60° C.” *Id.* ¶ 110.

Alternatively, “[t]he container can be mailed back to the testing lab at room temperature.” *Id.* ¶ 111.

Example 3 discloses the collection and extraction of DNA using a stock solution comprising “33 mM TRIS-HCl, 0.67 M urea, 0.67 M LiCl, 0.6% sodium dodecyl sulfate, 3.3 mM CDTA, 30% ethanol, and 0.25 M sodium ascorbate, all adjusted to a final pH of 8.0.” *Id.* ¶¶ 114–122.

In Example 4, Birnboim subjects the DNA to agarose gel electrophoresis and ethidium bromide staining, noting “the characteristic band of chromosomal DNA present in all samples.” *Id.* ¶ 117, Fig. 1; *see also id.* ¶ 13 (disclosing preferred reducing agents erythiorbate, N-acetylcysteine, dithiothreitol, 2-mercaptoethanol and, “most desirably. . . ascorbic acid”), ¶ 25 (disclosing that isolated DNA is preferably stable for “more than 60 days” and “when . . . the composition does not contain ascorbic acid, the DNA is stable for more than 60 days, and desirably more than 360 days”).

In Examples 5 and 6, Birnboim prepares “[m]inimally purified DNA” from samples prepared using the nucleic acid-preserving solution by

centrifuging the samples to remove insoluble material and precipitating the DNA with ethanol prior to using polymerase chain reactions to detect the DNA. *Id.* ¶¶ 118–121.

2) Overview of Mori (Exhibit 1011)

Mori discloses the isolation of nucleic acids from a test sample (e.g., bodily fluids, plants, animals, bacteria, viruses, and cultured cells) by treating the sample with a “nucleic acid-solubilizing reagent,” which “dissolves cell membranes and nuclear membrane, and solubilizes nucleic acid.” Ex. 1011, 57.⁹ Exemplary nucleic acid-solubilizing reagents may include “a chaotropic salt, a surfactant, a defoaming agent, a protease and a nucleic acid stabilizing agent.” *Id.* at 58; *see also id.* at 63 (indicating that the nucleic acid stabilizing agent assists in inactivating nuclease activity).

According to Mori, preferred chaotropic salts are guanidine hydrochloride, guanidine isothiocyanate and guanidine thiocyanate (*id.* at 61); the nucleic acid stabilizing agent is a reducing agent, and preferably a mercapto compound (*id.* at 63); and the defoaming agent may be any number of silicon-, alcohol-, ether-, fatty oil-, fatty acid-phosphate ester-, amine-, or amide-based compounds, “preferably in a range of 0.1 to 10% by weight” (*id.* at 64).

With respect to the surfactant, Mori teaches the use of a wide variety of compounds including an anionic surfactant, an amphoteric surfactant and, preferably, either a nonionic or cationic surfactant. *Id.* at 61.

Nonionic surfactants include a polyoxyethylene alkyl phenyl ether-based surfactant, a polyoxyethylene alkyl ether-based surfactant, and fatty acid alkanolamide, and the preferable one is a polyoxyethylene alkyl ether-based surfactant. Among the

⁹ Where possible, we refer to native pagination.

polyoxyethylene (POE) alkyl ether surfactant, POE decylether, POE lauryl ether, POE tridecyl ether, POE alkylendecyl ether, POE sorbitan monolaurate, POE sorbitan monooleate, POE sorbitan monostearate, tetraoleic polyoxyethylene sorbit, POE alkyl amine, and POE acetylene glycol are more preferred.

Cationic surfactants include cetyl trimethyl ammonium bromide, dodecyl trimethyl ammonium chloride, tetradecyl trimethyl ammonium chloride, cetyl pyridinium chloride.

Id. at 61–62. With respect to surfactant concentration, Mori states: “The concentration of the surfactant in the nucleic acid-solubilizing reagent is preferably from 0.1 to 20% by weight.” *Id.* at 62.

3) Overview of Farrell (Exhibit 1026)

Farrell is a laboratory guide describing the isolation and characterization of ribonucleic acids. Ex. 1026, Title. Farrell discloses that it was widely known that nucleases, which are enzymes that degrade nucleic acids, should be purged from solutions when trying to isolate RNA. *Id.* at 48–49. Farrell discloses that numerous compounds have been used to inhibit RNase activity including, vanadyl ribonucleoside complexes, RNasin, heparin, iodoacetate, polyvinyl (dextran) sulfate, cationic surfactant, macaloid and bentonite clays, and hydrogen peroxide.

Farrell further states that “stock solutions and buffers prepared in the laboratory can be treated, directly or indirectly, with the potent chemical RNase inhibitor DEPC” or diethylpyrocarbonate. *Id.* at 55. Farrell notes that “DEPC is an efficient, nonspecific inhibitor of RNase,” but “must be destroyed completely” since “[e]ven trace amounts of residual DEPC will result in chemical modification of the base adenine” and, thus, should not be added directly to cell suspensions or lysates containing RNAs to be purified. *Id.* at 55. Farrell discloses that there are additional “legitimate reasons” not

to use DEPC in the laboratory and that making solutions with nuclease-free water is a more desirable alternative for solutions that isolate nucleic acids.

Id. at 57. In this respect, Farrell states:

A suitable alternative to DEPC treatment of water to render it nuclease-free is to simply buy nuclease-free water from one's favorite vendor. For those laboratories affiliated with hospitals, it is interesting to note that water labeled "sterile water for irrigation," is free of contaminants and is good for RNA work. Purified RNA may be rehydrated in this water and stored at -80°C . This water is also excellent for making dilutions of nuclease-free stock solutions.

Id.

4) Analysis

In asserting that claims 1–10, 13, and 15–19 are obvious in view of Birnboim, Mori, and Farrell, Petitioner provides a detailed analysis of where each claim element is found in the cited references and discusses why one of ordinary skill in the art would have been motivated to combine those elements with a reasonable expectation of success. *See e.g.*, Pet. 34–42 (discussing motivation to combine and reasonable expectation of success with respect to claim 1). For the purpose of institution, we focus on independent claim 1.

In short, Petitioner argues that Birnboim discloses stock solutions comprising the chaotrope, detergent, reducing agent, chelator, short-chain alkanol, buffer, and acid or base, recited in limitations 1[a]–[d] and [f]–[h] of claim 1. *Id.* at 16–23, 25, 29. Petitioner argues that one of ordinary skill in the art would have been motivated to further include a surfactant (element 1[e]) and nuclease free water (element 1[i]) as taught by Mori and Farrell, respectively. *Id.* at 23–25, 29, 34–39. According to Petitioner, one of ordinary skill in the art would have had a reasonable expectation of success

that this combination would “denature[] proteins, inactivate[] nucleases, and kill[] pathogens all without degrading nucleic acids of the sample,” as required by element 1[j]. *Id.* at 30-34, 39–42.

With respect to Birnboim, Petitioner’s reference to the stock solution of Example 3 is instructive. *See* Pet. 31–32; Ex. 1002 ¶ 130. The disclosed stock solution comprises:

- 0.67 M urea (a chaotrope in the range of element 1[a]);
- 0.6% wt./vol. sodium dodecyl sulfate (a detergent in range of element 1[b]);
- 0.25 M sodium ascorbate (a reducing agent in the range of element 1[c]);
- 3.3 mM CDTA (a chelator in the range of element 1[d]);
- and
- 33 mM TRIS-HCl (a buffer in the range of element 1[d]).

Ex. 1003 ¶ 115; Ex. 1002 ¶ 130. The stock solution further contains 30% ethanol, which is higher than the range of 1 to 25% of short-chain alkanol recited in element 1[f]. *See* Ex. 1003 ¶ 115. As Petitioner notes, however, Birnboim more generally discloses that, “the alcohol is 10%-60% of the total composition volume,” which overlaps with the claimed 1–25% range. *See* Pet. 32–33 (citing Ex. 1003 ¶ 20; Ex. 1002 ¶ 132). And though at pH 8.0, the solution in Birnboim’s Example 3 is more alkaline than the pH 5–7 range of element 1[h], the broader disclosure of Birnboim teaches “a pH from about 5.0 to about 7.0, desirably from about 6.5 to about 6.8.” Ex. 1003 ¶ 19; *see* Pet. 31 (citing Ex. 1002 ¶ 133).

With respect to element 1[e], a “surfactant present in an amount from 0.0001% to 0.3% (wt./vol.),” Petitioner argues that “[t]he ’256 patent treats surfactants and defoaming agents as synonymous reagents in the claimed solution.” Pet. 23–24 (citing Ex. 1001, 5:5–16, 6:61–64, 7:26–27,

claim 6; Ex. 1003 ¶ 107). Accordingly, Petitioner argues, Mori’s recitation of either surfactants (e.g., polysorbate surfactants) or defoaming agents (e.g., silicone polymers) reads on the surfactant of element 1[e]. *Id.* Pointing to Mori’s use of surfactants in an amount of “from 0.1 to 20% by weight” and a defoaming agent in amount of “0.1 to 10% by weight,” Petitioner further argues that both of these concentration ranges overlap the claimed surfactant concentration range of “from 0.0001% to 0.3% (wt./vol.),” and thus satisfy the limitations of element 1[e]. *Id.* at 25 (citing Ex. 1011, 62, 64; *E.I. DuPont DeNemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018)).

Petitioner provides reasoned bases for why one of ordinary skill in the art would have combined the cited references to arrive at the claimed invention. *See* Pet. 34–42 (citations omitted). Summarizing its arguments, Petitioner concludes that one of ordinary skill in the art

would have been motivated to prepare solutions comprising a chaotrope, a detergent, a reducing agent, a chelator, a shortchain alkanol, and a buffer (with the associated acid and base) at a pH of 5–7 with a reasonable expectation that, when combined with a biological sample, the solution would denature proteins, inactivate nucleases, and kill pathogens, all without degrading nucleic acids of the sample. Ex. 1002, ¶151. The POSA would have been motivated to use Mori’s surfactants or defoaming agents along with Farrell’s nuclease-free water in Birnboim’s stock solution and would have had a reasonable expectation of success in doing so. Ex. 1002, ¶¶137–152.

Pet. 41–42.

In response, Patent Owner contends that Ground 1 fails because Birnboim does not expressly distinguish between “chaotropes and detergents as individual and separate components” and, accordingly, fails to “teach[] the need to select a detergent in combination with a chaotrope, or . . . what

concentrations are suitable.” Prelim. Resp. 9–11 (citations omitted). Patent Owner appears to base its argument on Birnboim’s broad use of the term “denaturing agent” as encompassing a wide range of compounds including (1) chaotropes such as urea and guanidinium compounds, (2) detergents such as dodecyl sulfate salts, and (3) alcohols, such as “ethanol above 10%.” *Id.* at 9–10 (citing Ex. 1003 ¶¶ 41, 68).

With respect to Birnboim’s Example 3, in particular, Patent Owner argues that the disclosed stock solution “happens to include a denaturing agent that works as a chaotrope (urea) and a second denaturing agent that works as a detergent (SDS), as well as a third denaturing agent, ethanol in an amount greater than 10%.” Prelim. Resp. 11. But, Patent Owner argues, nothing in Birnboim explains why these particular agents were selected, or “how to determine appropriate proportions or concentrations of different denaturing components in Example 3.” *Id.* (citing Ex. 2001 ¶ 17; Ex. 1003 ¶ 115). As articulated by its expert, Patent Owner further argues that “Birnboim’s Example 3 compositions include additional components – LiCl or NaOAc – whose roles are not otherwise discussed in Birnboim. Removal of either component in Example 3 could require a compensating adjustment in the proportion or relative concentration of one or more the denaturing agents of Example 3,” yet Birnboim fails to explain whether stocks solutions excluding LiCl or NaOAc (or including other compounds disclosed in Birnboim) would perform the functions of claim element 1[j]. Ex. 2001 ¶ 17; Prelim. Resp. 11 (citing Ex. 2001 ¶¶ 16–17).

On the present record, we do not find Patent Owner’s argument persuasive. Birnboim discloses compositions and methods for isolating and preserving nucleic acids including nucleic acid from bacteria or viruses. *See,*

e.g., Ex. 1003 ¶¶ 22, 27, 44. The exemplary composition of Example 3, contains a chaotrope (urea) and a “strong detergent” (SDS) in amounts within the ranges set forth in claim 1. *See* Ex. 1003 ¶ 68. The record as a whole indicates that one of ordinary skill in the art understood that the use and identity of chaotropes and detergents for the purification of nucleic acids. *See e.g.*, Ex. 1002 ¶¶ 14, 16, 17, 51–65. We are not persuaded that Birnboim’s general reference to various classes of such compounds as “denaturing agents” obviates the understanding of the ordinarily skilled artisan as to their individual properties and uses.

As indicated by paragraphs 14 and 51–65 of Dr. Taylor’s declaration, those of ordinary skill in the art at the time of the invention were well versed in methods and reagents that could be used in isolating nucleic acids. *See also, e.g.*, Ex. 1004, 192, 192 (use of NaOAc to wash/precipitate nucleic acids); Ex. 1009, 1:66–68 (same); Ex. 1013, 4.3.1, 4.5.2 (use of LiCl for selective precipitation of RNA and as buffer component); 1018, 15:55–67 (commercial RNA extraction kits comprising LiCl in combination with chaotrope); Ex. 1016, 8:26–9:2 (“Typically, the nucleic acid releasing composition will further include salt . . . The type of salt included in the nucleic acid releasing composition is not critical . . . however, optimum results are obtained with . . . [NaOAc].”).

Given the extensive background knowledge of one of ordinary skill in the art, we are unpersuaded by Patent Owner’s implication that one of ordinary skill in the art would not have understood the role of LiCl or NaOAc in Birnboim’s Example 3 or, according to Patent Owner’s hypothetical example, lacked the knowledge to modify a composition that excluded one or both of these compounds. In this respect, we note that

Birnboim's Example 3 discloses a second embodiment that "stabilizes DNA for longer periods of time." Ex. 1003 ¶ 115. Insofar as this embodiment has more NaOAc but entirely omits LiCl, we infer (1) that LiCl is not an essential ingredient in the first embodiment and (2) that the ordinarily skilled artisan knew how to vary the concentrations of stock solution components such as NaOAc and LiCl to obtain desired results. *See id.* Finally, we note that claim 1 is drafted in "comprising" format, and, thus, does not exclude the compounds in addition to those expressly recited.

Despite our present reservations as to the strength of Patent Owner's arguments, this initial determination is subject to facts and arguments adduced at trial. Accordingly, the parties are encouraged to further address the understanding of one of ordinary skill in the art with respect to the above issues.

Patent Owner next argues that Ground 1 fails because "Birnboim does not expressly disclose killing pathogens with its composition," nor has Petitioner shown the teachings of the combined references would inherently kill pathogens." Prelim. Resp. 11–20 (emphasis removed). Patent Owner appears to argue that Birnboim is "focused on collection and preservation of nucleic acids from native human cells" in a saliva sample and teaches merely *inhibiting* pathogens, rather than lysing, or otherwise killing them. *Id.* at 13–14.¹⁰

In support, Patent Owner argues that Birnboim's express teachings to isolate nucleic acid "from a bacterium or a virus that is residing in the

¹⁰ In this context, we understand Patent Owner's reference to "nucleases" "human nuclease material" and "human cell nucleases" as indicating "nucleuses" or, more commonly, "nuclei," as opposed to enzymes capable of cleaving the phosphodiester bonds between nucleotides of nucleic acids.

buccal, nasal, or respiratory passages of the subject,” and to include a ribonuclease inhibitor “when the nucleic acid to be preserved is from a virus or bacterium, are merely “off-hand” or “prophetic” references that “fail[] to expressly teach killing pathogens because extracting the small amount of DNA necessary for testing does not ‘kill pathogens’ in the meaning of the ’256 Patent.” Ex. 1003 ¶¶ 22, 27.¹¹ Patent Owner’s arguments are unavailing.

As an initial matter, “a reference . . . is prior art for all that it teaches,” and we decline to dismiss the express teachings of Birnboim because they are not the main focus of its disclosure. *See Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) (citation omitted). Moreover, in addressing obviousness, we consider “what the combined teachings of the references would have suggested to those of ordinary skill in the art.” *In re Keller*, 642 F.2d 413, 425 (CCPA 1981) (citations omitted).

On page 16 of the Preliminary Response, Patent Owner appears to equate the claim language, “kill[ing] pathogens,” with complete sterilization of a sample “to prevent ‘dissemination of live infections pathogens.” Prelim. Resp. 16 (citing Ex. 1001, 2:9–10, 6:35–37; Ex. 2001 ¶ 7); *see also id.* at 12

¹¹ In arguing that Birnboim teaches neither “killing pathogens” nor preventing nucleic acid degradation, Patent Owner characterizes Birnboim as directed to extracting a “small amount” of nucleic acid. *See* Prelim. Resp. 16, 28; *see* Sur-reply 1–2 (arguing that “Birnboim does something very different from the ’256 Patent and thus does not teach the same functional limitations, such as killing pathogens, claimed in the ’256 Patent). On the present record we are not persuaded that amount of nucleic acid extracted has any bearing on limitations of element 1[j]. *See e.g.*, Reply 1–3 (citations omitted). To the extent it wishes to pursue this argument at trial, Patent Owner should clarify what constitutes a “small amount,” particularly in light of Birnboim’s extraction of sufficient DNA to visualize on an ethidium bromide stained agarose gel. *See* Ex. 1003 ¶ 117, Fig. 1.

(asserting the Birnboim “does not require lysing all or even most of the cells in a sample”). On their face, however, the claims do not require killing every potential pathogen in a sample. *See In re Self*, 671 F.2d 1344, 1348 (CCPA 1982) (holding that such “arguments fail from the outset because . . . they are not based on limitations appearing in the claims”); *see also* Ex. 1001, 26:59–29:30 (the ’256 patent itself disclosing killing bacteria only in Example 8). Birnboim expressly teaches the isolation of nucleic acids from bacteria and viruses. *See* Ex. 1003 ¶¶ 18, 22, 27. The reference does not appear to suggest that such isolation is non-destructive, we presume that at least some of these potential pathogens are “killed” in the extraction process according to the ordinary meaning of the term.

Considering the present record as whole, Petitioner persuades us that compositions taught or suggested in Birnboim kill at least *some* bacteria and/or viruses. To be clear, we do not read the challenged claims as suggesting that *every* pathogenic agent including, for example, prions and bacterial spores, must be so susceptible, nor that the addition of stock solution should clear an entire sample of all such agents. *See e.g.*, Ex. 2003 (CDC Guidance), 9–10, 34, 102 (discussing difficulty of eliminating bacterial spores and prions as opposed to, for example, lipid encapsulated viruses and vegetative bacteria); Sur-reply 3 (Patent Owner noting that some strains of gram negative bacteria “were not sensitive to 0.05% SDS *relative to control bacteria*” (citing Ex. 1044) (emphasis added); *see also* Ex. 2001 ¶ 22 (Dr. DeFilippi testifying that “Birnboim fails to kill pathogens” because it

only references “bacteriostatic” and “bactericidal” components and does not teach killing “any pathogen including fungi, spores, or viruses”).¹²

To the extent Patent Owner implies that we should assign some special meaning to the “kills pathogens” requirement of claim element 1[j], Patent Owner neither raises this issue in the claim construction portion of its brief, nor anywhere proposes a specific construction of the term. *See* Prelim. Resp. 7 (“Claim Construction”), 16–18. And although Patent Owner points to the purported “purpose and value” of stock solutions disclosed in the ’256 Patent as killing pathogens “to facilitate safe handling” of biological samples, and evidence that a commercial embodiment showed “effectiveness . . . in killing methicillin-resistant *Staphylococcus aureus*,” Patent Owner provides insufficient reasoned argument why we should import such limitations into the challenged claims. Prelim. Resp. 16–18 (citing e.g., Ex. 1001, 2:9–10, 2:13–14, 3:2–3, 6:35–37, 9:25–35, 14:61–64, 25:66–26:4, 27:63–28:35). Accordingly, we decline to do so on the instant record. *See SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004). (“Though understanding the claim language may be aided by the explanations contained in the written description, it is important not to import into a claim limitations that are not a part of the claim.”).

¹² On page 1 of its Reply, Petitioner contends Dr. DeFilippi admitted that “[Birnbom] does not teach killing of anything but bacteria”) (citing Ex. 2001 ¶ 22). Although Patent Owner reasonably argues that we should read this portion of Dr. DeFillippi’s report indicating that “that the word ‘bactericidal’ itself . . . ‘does not teach the killing of anything but bacteria,’” Birnbom, nevertheless, expressly teaches compositions comprising antimicrobial agents, that “can be bacteriostatic, bactericidal or both.” Sur-reply 1; Ex. 1042 ¶ 21.

Patent Owner similarly contends that Ground 1 fails because “Birnboim does not disclose a solution with the claimed reagents that perform the functional limitations of claim 1.” Prelim. Resp. 20 (heading capitalization normalized); Sur-reply 20 (same), *id.* at 20–21 (“nothing in Birnboim teaches using the solution recited in Claim 1, as opposed to utilizing additional unclaimed substances, to kill pathogens”).

Patent Owner argues, for example, that although Birnboim teaches the use of antimicrobial agents, and preferably ethanol, the stock solution of Example 3 contains only 30% ethanol which, Patent Owner asserts, “is not sufficient to have a bactericidal effect, much less kill viruses or vegetative bacteria.” Prelim. Resp. 14 (citing Ex. 1003 ¶¶ 20, 21, 41, 64, 73; Ex. 2001 ¶¶ 21, 25–26; Ex. 2003). In this respect, Patent Owner states that Birnboim teaches the use of such agents “in a way that is merely “bacteriostatic,” and that “an antimicrobial agent is bacteriostatic if it inhibits cell division *without affecting the viability of the inhibited cell*,” i.e. without killing the cell. *Id.* at 14 (citing Ex. 1003 ¶ 21).

Patent Owner also argues that the lithium chloride and NaOAc in the stock solution of Example 3, are not recited in challenged claim 1, suggesting that these unclaimed reagents “were important for one or more of the functions of denaturing proteins, inactivating nucleases, and preventing degradation of nucleic acids,” as required by claim element 1[j]. *Id.* at 23–24 (citing Ex. 2001 ¶ 19). Patent Owner further argues that Birnboim relies on proteases to digest proteins, and “states in Example 4 that the enzyme proteinase K is added to the solution of Example 3 to prepare the solution for precipitating DNA.” *Id.* at 22–23 (citing Ex. 1003 ¶¶ 26, 83, 84, 117; Ex. 2001 ¶¶ 41, 44, 45, 47). Thus, Patent Owner argues, addition of

proteinase K to digest proteins as a subsequent step in Example 4 demonstrates that the composition of Example 3 does not “denature proteins” because, if it did, the composition of Example 3 would have denatured the proteinase K added in Example 4, rendering it inoperable.” *Id.* at 23 (citing Ex. 2001 ¶¶ 45, 47).

As an initial matter, Patent Owner’s reference to bacteriostatic antimicrobial agents in paragraph 21 of Birnboim omits much from that passage. In particular, Birnboim states that

An antimicrobial agent can be bacteriostatic, bactericidal or both. . . . An antimicrobial agent is bactericidal if it causes cell death. Cell death is commonly detected by the absence of cell growth in liquid growth medium (e.g., absence of turbidity) or on a Solid Surface (e.g., absence of colony formation on agar). Those of skill in the art know that a substance or group of substances which is bacteriostatic at a given concentration may be bactericidal at a higher concentration.

Ex. 1003 ¶ 21. Accordingly, Birnboim not only teaches the use of bactericidal agents, but indicates that their efficacy can be tested using the same type of assays employed in the ’256 patent. *See* Prelim. Resp. 27 (referencing Ex. 1001, 26:59–29:30) (colony forming assay testing bactericidal effect on *Staphylococcus aureus* strain ATCC33592).

Further, and as discussed at the beginning of this section, Petitioner’s arguments with respect to Birnboim are not limited to the exemplary composition of Example 3. *See, e.g.*, Ex. 1003 ¶ 21 (“most desirably the composition includes ethanol”) ¶ 20 (“the alcohol is 10%-60% of the total composition volume”). Nor, with respect to the stock solution of Example 3, does the preliminary record make clear that the 30% ethanol component alone, is responsible (or even necessary) for killing viruses or bacteria, or that one of ordinary skill in the art reading Birnboim would understand that

protease, lithium chloride, and NaOAc are required to perform the functions of claim element 1[j].

Finally, with respect to Patent Owner's assertion that adding proteinase K to the solution of Example 3 "would have denatured the proteinase K added in Example 4, rendering it inoperable," we note that this step involved diluting the stock solution of Example 3 with "an equal volume of saliva," and then treating a 0.25 mL portion of that sample with proteinase K. Prelim. Resp. 23; Ex. 1003 ¶ 117. In asserting that the proteinase K would have been rendered inoperable, Patent Owner fails to account for factors such as the amount and effect of dilution on stability of the proteinase K, the time course of any inactivation, or the rate and extent of proteolysis expected prior to any such inactivation. *See e.g.*, Ex. 1003 ¶ 69 (Birnboim's teaching that "a balance must be struck between the concentration of denaturing agents that will, on the one hand, inhibit deoxyribonucleases or ribonucleases and denature other proteins in saliva and, on the other hand, not significantly inhibit the proteolytic enzymes"). Accordingly, it is of little moment whether denaturants in the stock solution might *eventually* render the proteinase K component of Example 4 inoperable. And though Patent Owner cites paragraphs 45 and 47 of Dr. DeFillippi's testimony in support of its position, those passages do not even reference proteases, let alone the understanding of one of ordinary skill in the art with respect to the addition of proteinase K in Example 4. *See* Prelim. Resp. 23 (citing Ex. 2001 ¶¶ 45, 47). As such, Patent Owner's arguments are both unsupported and unpersuasive on this preliminary record.

Patent Owner's arguments with respect to element 1[j] are also undercut by its assertion before the district court that, in the context of the '256 patent:

It is common knowledge to one skilled in the art that an aqueous composition that comprises a) one or more chaotropes; b) one or more detergents and/or surfactants; c) one or more reducing agents; d) one or more chelators; and e) one or more buffers [all components of the stock solution in Birnboim's Example 3] serves the purpose of denaturing proteins, inactivating nucleases, killing pathogens, and not degrading nucleic acid of a sample suspected of containing pathogens when the sample is contacted with the composition.

Ex. 1007 ¶ 17. Petitioner argues that this statement constitutes a prior admission that the reagents in Birnboim's stock solutions "perform the functions recited in claim 1 of the '256 patent." Pet. 34, fn.4; *see* Ex. 1002 ¶¶ 51–65. Patent Owner responds that it "does not admit anything regarding what was known in the art at the time of the invention" but refers to "what is known in the art *as a result* of Patent Owner's disclosures." Prelim. Resp. 33, fn.5; Sur-reply 3–4.

Considering the arguments and evidence presently before us, we find Petitioner's reading more plausible, particularly in light of Birnboim's disclosure of compositions comprising all the named ingredients and the general skill in the art regarding methods and reagents for isolating nucleic acids. Accordingly, we infer that the above reference to the "common knowledge [of] one skilled in the art" encompasses the knowledge of one of ordinary skill in the art as of the filing date of the '256 patent. *See* Ex. 1007 ¶¶ 14, 266. As such, we are hard pressed to credit Patent Owner's arguments that Birnboim alone, or in combination with other asserted references, fails to teach or suggest a "stock solution, [that] when combined with a biological

sample suspected of containing a pathogen, denatures proteins, inactivates nucleases, and kills pathogens all without degrading nucleic acids of the sample,” as set forth in element 1[j].

We invite the parties to explore these issues at trial.

As Patent Owner points out, Petitioner does not expressly invoke inherency to establish that the stock solutions taught or suggested by the prior art kill pathogens. Prelim. Resp. 14, fn.3, 19. Addressing inherency, nevertheless, Patent Owner states that it has presented evidence that the SDS and CDTA of Example 3 “would not *necessarily* be expected to be bactericidal.” Prelim. Resp. 24–26. Patent Owner also argues that “[t]he ’256 patent aims to denature proteins broadly,” whereas “Birnboim selectively degrades nucleases” and thus, performs a function “very differently, and in a way that omits one or more of the required limitations in claim 1.” Prelim. Resp. 31–32 (citing Ex. 1001, 9:57–10:5, 10:34–50, Ex. 1003 ¶¶ 7, 45, 116–122; Ex. 2001 ¶ 42 (quoting Ex. 1003 ¶ 69)).

As indicated above, rather than the selective degradation of nucleases, we understand Birnboim to employ sequential reaction conditions for generally denaturing proteins followed by proteinase K digestion—an understanding the parties are welcome to explore at trial. Moreover, with respect to the function of denaturing proteins in general, the prior art recognized that “[u]rea is a protein denaturant.” Ex. 1034; *see also* Ex. 1003 ¶ 20 (“Desirably, the denaturing agent is urea, dodecyl sulfate, or an alcohol, wherein the alcohol is 10%-60% of the total composition volume.”). Similarly, with respect to deactivating nucleases, Dr. DeFillippi testifies that “Birnboim specifically addresses the use of denaturing agents to

destroy the “complex structures” of deoxyribonucleases and ribonucleases.” Ex. 2001 ¶ 28 (citing Ex. 1003 ¶ 68).

Relying on the testimony of Dr. DeFilippi, Patent Owner points to “submitted evidence” that the SDS in Birnboim’s “Example 3 would not necessarily be expected to be bactericidal.” Prelim. Resp. 25–26 (citing Ex. 2001; ¶¶ 29, 31, 33–35; see Reply 3–4. Dr. DeFilippi asserts, for example that “[b]acteria are known to degrade SDS.” Ex. 2001 ¶ 29 (citing Ex. 2006 “Shahbazi”).¹³ Shahbazi, however, is a bioremediation study showing that bacteria isolated from car wash waste water could degrade low concentrations of SDS. Ex. 2006, Abstract, 154 (screening media comprising 1.5 mM SDS), 156–157 (reporting degradation of 7 mM SDS by “a consortium *Acinetobacter calcoaceticus* and *Pantoea agglomerans*”).

Dr. DeFilippi also points to Woldringh¹⁴ as evidence that SDS “is quite poor as a lysis agent,” insofar as it reports that “[d]uring prolonged SDS interaction” only “25% of the ribonucleic acid and 40% of the deoxyribonucleic acid were released from [bacterial] cells.” Ex. 2001 ¶¶ 29–30 (quoting Ex. 2007, Abstract). Woldringh, however, was studying the controlled dissolution of the *E.coli* plasma membrane using 0.05% SDS, a “comparatively low concentration of detergent” and substantially lower than the 0.60% SDS used in Birnboim’s Example 3. Ex. 2007, 801; Ex. 1003 ¶ 115. Nevertheless, as Petitioner points out, even at this low concentration

¹³ Shahbazi, et al. “Screening of SDS-degrading bacteria from car wash wastewater and study of the alkylsulfatase enzyme activity,” 5(2) Iranian journal of microbiology 153–158 (2013).

¹⁴ Woldringh et al., (1972). “Effects of treatment with sodium dodecyl sulfate on the ultrastructure of *Escherichia coli*,” 111(3) J. Bacteriol, 801–813 (1972). (Ex. 2007). Exhibit 2007 includes a series of thumbnails followed by the complete, full-size article. We cite to the native pagination of the latter.

of SDS, Woldringh reported dissolution of bacterial plasma membranes and the release of nucleic acids indicating that, “the cells are, of course, dead.” Reply 3 (citing Ex. 2007, 801 (Abstract), 807, 809, Figs. 2, 12); *see also id.* at 4 (quoting Ex. 1044 (McDaniel))¹⁵ (citing Woldringh for the proposition that “SDS has been shown more than 40 years ago to cause *significant bacterial membrane damage* with subsequent *release of DNA, RNA and protein*”).¹⁶ Thus, irrespective of whether Patent Owner’s above-quoted statement before the district court refers to the state of the art before or after the filing date of the ’256 patent, it would appear at odds with Patent Owner’s position that Birnboim’s stock solution lacks any of the functionality recited in claim element 1[j]. Nevertheless, as above, we invite the parties to further explore the inherency and obviousness arguments and their factual underpinnings at trial.

Patent Owner further argues that even if Birnboim’s “Example 3 composition may have liberated nucleic acids from native human cells [this] does not establish that the same composition would necessarily have been

¹⁵ McDaniel, et al., “A Putative ABC Transporter Permease is Necessary for Resistance to Acidified Nitrite and EDTA in *Pseudomonas aeruginosa* under Aerobic and Anaerobic Planktonic and Biofilm Conditions,” 7(291) Frontiers in Microbiol. 1–14 (April 2016). (Ex. 1044).

¹⁶ Patent Owner appears to assert that McDaniel’s determination that some strains of *Pseudomonas aeruginosa* “were not sensitive to 0.05% SDS relative to control bacteria,” contradicts Petitioner’s contention that 0.05% SDS kills *e. coli* as shown by Woldringh. Sur-reply 3 (citing Ex. 1044). This argument is unavailing insofar as Patent Owner does not explain how one of ordinary skill in the art would understand McDaniel’s statement that the *P. aeruginosa* strains were “not sensitive . . . relative to control bacteria.” More to the point, we do not read the claims to require complete sterilization of a sample, nor efficacy against every potential species of pathogen, as discussed more fully above.

effective either to extract nucleic acids from pathogens or to kill pathogens and render a sample safe for transportation and evaluation.” Prelim. Resp. 26; *see also id.* at 28–30 (similarly arguing that Mori and Farrell do not fill this gap); Sur-reply 1–2. Moreover, Patent Owner argues, “even if it were able to extract DNA from a single “bacterium or virus,” it fails to teach or disclose a solution as claimed that kills pathogens, for example to facilitate safe handling and transport of the collected specimen,” or “necessarily prevent[s] degradation of nucleic acids.” Prelim. Resp. 26–28 (citations omitted).

Throughout these arguments, Patent Owner implicitly relies on narrow constructions of “kills pathogens” and “without degrading nucleic acids” that have not been briefed or argued by either party. For the purpose of institution, however, we apply the plain and ordinary meaning. As such, Birnboim’s instruction to isolate nucleic acid “from a bacterium or a virus that is residing in the buccal, nasal, or respiratory passages of the subject,” necessarily “kills pathogens.” *See* Ex. 1003 ¶ 27.

In this respect, we also consider the asserted reference Das, and Dr. Taylor’s presently uncontested testimony thereon, in the context of Ground 2. Ex. 1008; Ex. 1002 ¶¶ 202–209. As Dr. Taylor explains:

Das is directed to techniques for detecting the mycobacteria that cause tuberculosis. Ex. 1008, ¶[0037]. Das specifically discloses “methods of nucleic acid extraction and mix of reagents to lyse mycobacteria and purify nucleic acid from a clinical specimen.” *Id.*, ¶[0038]. Das discloses a lysis buffer to lyse the mycobacteria cells in a specimen sample and extract the nucleic acid, where the lysis buffer contains a chaotrope (guanidinium isothiocyanate), detergent (N lauryl Sarcosyl), reducing agent (2-mercaptoethanol), chelator (EDTA), and buffer (Tris). *Id.*, ¶¶[0063]–[0064], [0089]. Das discloses obtaining saliva samples from tuberculosis patients and using

the lysis buffer to lyse the mycobacteria cells in the samples and extract the bacteria nucleic acid. *Id.*, ¶¶[0083]–[0085], [0089].

Ex. 1008 ¶ 203. Dr. Taylor reasonably testifies that Das discloses specific ranges and amounts of the above ingredients falling within the scope of those recited in claim 1 including 0.5–9 molar guanidinium isothiocyanate (exemplified at 4 M), and 0.5–2% N lauryl Sarcosyl (exemplified at 1%).

Ex. 1002 ¶¶ 206–207 (citing Ex. 1008 ¶¶ 63, 64, 89).

Das explains that prior methods “often fail to kill all mycobacteria present in a clinical specimen and thus could be hazardous for the user.”

Ex. 1008 ¶ 38. In contrast, Das asserts, the disclosed use of a strong chaotrope such as guanidinium isothiocyanate “helps to inactivate all mycobacteria present in a clinical specimen, lyse tough mycobacterial cell and denature and remove proteins thus results into cleaner preparation of DNA (Table 3) and also ensure safety for the operator.” *Id.* Das further states that a detergent in the formulation “helps in solubilization of cell wall lipid and of protein and thus result in complete lysis of the mycobacterial cell wall.” *Id.* ¶ 39.

In view of the above, we accept, for purposes of institution, Dr. Taylor’s assessment that one of ordinary skill in the art at the time of the invention would understand that Das’ composition kills pathogens, specifically, mycobacteria. *See* Ex. 1002 ¶ 207. Because Birnboim also discloses the use of a chaotrope and a detergent within the range taught by Das, the present record suggests that Birnboim’s stock solutions would likewise kill bacteria, i.e., pathogens, as required by claim element 1[j]. *See e.g.*, Ex. 1003 ¶ 114 (stock solutions comprising 0.67 M urea and 0.6% sodium dodecyl sulfate).

Further with respect to Patent Owner’s argument that Birnboim’s stock solution does not necessarily prevent degradation of nucleic acids, we note the reference’s definition of stability as requiring retention of “at least about 50% of the initial amount of” nucleic acid in a sample after an unspecified period of storage and demonstrating “the characteristic band of chromosomal DNA” following agarose gel electrophoresis.¹⁷ See, Ex. 1001 ¶¶ 45, 117, Fig. 1. We also note that Patent Owner nowhere proposes a construction of “without degrading nucleic acids of the sample,” as recited in independent claim 1. At best, Patent Owner’s expert, Dr. DeFilippi, contrasts Birnboim’s disclosure with preferred embodiments of the ’256 patent as having, *e.g.*, “at least about 70%” to “at least about 98% of the polynucleotides contained within the stored sample . . . not be[ing] degraded upon prolonged storage.” See Ex. 2001 ¶¶ 10–11 (quoting Ex. 1001, 9:57–10:5). See also Reply 4–5 (arguing that Applicant, during examination of the related ’443 patent, amended claims in response to Examiner’s statement that “preventing ‘total polynucleotide degradation . . . from happening does not appear to be the tenor of the present specification, and nowhere in the present specification is it shown that polynucleotide degradation may totally

¹⁷ On pages 4 and 5 of its Sur-reply, Patent Owner points to a non-party assertion “that the Birnboim I Family does not enable, teach, or suggest RNA preservation.” Even if this statement were true with respect to Exhibit 1003, its import is unclear insofar as there is no suggestion on this record that Birnboim does not enable the preservation of another nucleic acid within the scope of the challenged claims, specifically, DNA. With our authorization (see Paper 3002), Patent Owner further submitted Petitioner’s Answer in *DNA Genotek v. Spectrum Solutions*, Case 3:21-cv-00516-DMA-LL (S.D. Cal., Aug. 18, 2021), wherein Petitioner details the non-party assertions regarding non-enablement in its inequitable conduct defense. Ex. 2013, 9–26. But again, the challenged claims do not specify that the preserved nucleic acid is RNA.

be kept from ever occurring” (citing Ex. 1045, 4)); *see* Sur-reply 4 (addressing prosecution history of the ’433). Contrary to our reading of Dr. Fillippi’s argument, however, no such limitations appear in the challenged claims.

Considering the above, and for the purpose of institution, we read Birnboim’s disclosure as satisfying the “without degrading nucleic acids of the sample” portion of element 1[j] under the plain and ordinary meaning. The parties are, nevertheless, invited to explore these issues at trial.

Patent Owner also appears to argue that one of ordinary skill in the art would not have been motivated to add a surfactant/defoaming agent as taught by Mori to the compositions taught by Birnboim because (1) “the compositions of Mori differ in one or more respects from the compositions of Birnboim;” (2) Mori teaches homogenization by ultrasound or high-speed stirring, whereas Birnboim teaches “vigorously shaking of the container; and (3) there would have been “unknown interaction of the defoaming agents with various components in the Birnboim composition and thus unknown effects.” Prelim. Resp. 30–33 (citations omitted).

Although Petitioner has set forth a reasoned basis why one of ordinary skill in the art would have been motivated to combine Birnboim, Mori, and Farrell with a reasonable expectation of success, it has not had the opportunity to address Patent Owner’s contentions. *See* Pet. 34–42. These and other factual issues raised in the Preliminary Response are better addressed on the fuller record adduced at trial.

At this stage of the proceeding, Petitioner has addressed sufficiently how Birnboim, Mori, and Farrell would have rendered obvious dependent claim 1 to show a reasonable likelihood of prevailing on its obviousness

challenge under Ground 1. Patent Owner provides no additional argument with respect to claims 9, 10, 13, or 15–19 also challenged under Ground 1. Prelim. Resp. 33. Grounds 2–4 are directed to certain dependent claims. Pet. 11. Patent Owner does not further address Grounds 2–4 on the merits. Prelim. Resp. 34–35.

III. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one challenged claim of the '256 patent is unpatentable. We therefore institute trial on all challenged claims under the grounds raised in the Petition. *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review “require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition.”); Guidance at 2–3. At this stage of the proceeding, we have not made a final determination with respect to the patentability of any of the challenged claims.

Any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. In addition, nothing in this Decision authorizes Petitioner to supplement information advanced in the Petition in a manner not permitted by the Board’s Rules.

IV. ORDER

ORDERED, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–20 of the '256 Patent is instituted with respect to the grounds set forth in the Petition; and

FURTHER ORDERED, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), that the *inter partes* review of the '256 Patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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