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Paper No. 9
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HOLOGIC, INC.,
Petitioner,

v.

BIOMÉRIEUX, INC.,
Patent Owner.

Case IPR2018-00567
Patent 9,074,262 B2

Before JAMES T. MOORE, SUSAN L. C. MITCHELL, and KRISTI L. R. SAWERT, *Administrative Patent Judges*.

SAWERT, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Hologic, Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–15 of U.S. Patent No. 9,047,262 B2 ("the '262 patent," Ex. 1002). Paper 1 ("Pet."). bioMérieux, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 7 ("Prelim. Resp.").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). We may not institute an *inter partes* review "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu,* 138 S. Ct. 1348, 1355–56 (2018). Also, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See 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).

Applying those standards, and upon consideration of the information presented in the Petition and the Preliminary Response, we determine that we should exercise our discretion under 35 U.S.C. § 325(d) and deny institution. We, therefore, deny the Petition and do not institute an *inter partes* review.

II. BACKGROUND

A. Related Matters

The parties identify *bioMérieux, S.A. v. Hologic, Inc.*, No. 1:18-cv-00021-LPS-CJB (D. Del.), as a related matter under 37 C.F.R. § 42.8(b)(2). Pet. 1; Paper 3, 2. Petitioner identifies U.S. Application Nos. 15/378,510 and 15/378,516 as related matters. Pet. 1. Petitioner states that these applications claim priority to the '262 patent and are currently pending. *Id.*

Petitioner filed a second petition for an *inter partes* review of the '262 patent, which has been designated Case IPR2018-00566. Pet. 2; Paper 3, 2. Petitioner also filed two petitions for *inter partes* review of U.S. Patent No. 8,697,352 ("the '352 patent"), which have been designated Case IPR2018-00568 and IPR2018-00569. Pet. 2; Paper 3, 2.

The '262 patent was filed as U.S. Patent Application No. 14/226,965 ("the child application"), as a divisional of U.S. Patent Application No. 11/108,233 ("the parent application"). *See* Ex. 1002, [60]. The latter application issued as the '352 patent. *Id.* Both patents were examined by the same Examiner. *See* Ex. 1001 (cover page); Ex. 1002 (cover page).

B. The '262 patent

The '262 patent, titled "Nucleic Acid Sequences That Can be Used as Primers and Probes in the Amplification and Detection of all Subtypes of HIV-1," issued on July 7, 2015. Ex. 1002, [45]. The '262 patent relates to nucleic acid sequences for diagnosing infections with Human Immunodeficiency Virus-1 ("HIV-1"), the AIDS-causing virus, via amplification and detection of HIV-1 nucleic acid. *Id.*, Abstract. According to the '262 patent, "[t]he HIV virus shows a high heterogeneity," and "[g]enetic variability has been demonstrated amongst isolates from different

continents but also between individuals and between different stages of the disease." *Id.* at 1:66–2:3. Thus, "[s]ensitive assays are . . . needed that are capable of detecting as much variants of the HIV-1 virus as possible (preferably all)." *Id.* at 2:44–46.

The nucleic acid sequences disclosed in the '262 patent are directed to the "long-terminal repeat" (LTR) portions of the HIV genome. *Id.*, Abstract. The LTRs are "the regions on the viral genome that participate in the integration of the virus with the host cell and in the regulation of transcription of the viral genes." *Id.* at 2:15–19. The '262 patent states that the disclosed nucleic acid sequences detect "all presently known subtypes of HIV-1 . . . with high accuracy and sensitivity." *Id.* at 3:19–21.

The '262 patent states that the nucleic acid sequences can be used as primers or probes in a variety of techniques for amplifying and detecting HIV-1 in a sample, including PCR (polymerase chain reaction), TAS (transcription-based amplification system), and NASBA (nucleic acid sequence-based amplification). *Id.* at 3:24–4:20. According to the '262 patent, NASBA "enables specific amplification of RNA targets even in a background of DNA." *Id.* at 4:25–26. The '262 patent discloses several primer oligonucleotide pairs "for use as a set in the amplification of a target sequence located within the LTR region of the genome of HIV-1." *Id.* at 7:19–21. The most preferred pair of oligonucleotides are "a first primer comprising the sequence of SEQ ID NO:1" (i.e., GGGCGCCACT GCTAGAGA), and "a second primer with the sequence of SEQ ID NO:5" (i.e., CTCAATAAAG CTTGCCTTGA). *Id.* at 7:27–28, 41–42, 61–64.

C. Illustrative Claim

Claim 1 is independent and illustrative of the claimed subject matter.

Claim 1 recites:

> 1. A method for amplifying HIV-1 nucleic acid in a sample, comprising:
>
> (a) contacting the sample with a pair of oligonucleotide primers that bind to a first primer binding site and a second primer binding site located within the LTR region of the HIV-1 genome; and
>
> (b) performing a nucleic acid amplification under conditions wherein said oligonucleotide primers bind only to said first and second primer binding sites, thereby amplifying HIV-1 nucleic acid in the sample;
>
> wherein said pair consisting of oligonucleotide primers consists of a first primer and a second primer,
>
> wherein said first primer consists essentially of a first oligonucleotide that is fully complementary to a sequence of the LTR region at a first primer binding site, said oligonucleotide being 15–26 nucleotides in length and comprising at least 15 sequential nucleotides of the nucleotide sequence of:
>
> SEQ ID NO: 1:
> G GGC GCC ACT GCT AGA GA;
>
> said first oligonucleotide being operably linked to a promoter; and
>
> wherein said second primer consists essentially of a second oligonucleotide that is fully complementary to a sequence which is the reverse complement of a sequence of the LTR region at a second primer binding site, said oligonucleotide being 10–26 nucleotides in length and

> comprising at least 10 sequential nucleotides of the nucleotide sequence of:
>
> SEQ ID NO: 5:
> CTC AAT AAA GCT TGC CTT GA.

Ex. 1002, 17:48–18:64.

D. The Prior Art

Petitioner advances the following references as prior art on which it relies for the asserted grounds challenging the claims of the '262 patent:

1. John W. Backus et al., U.S. Patent No. 6,001,558 (Dec. 14, 1999) ("Backus," Ex. 1006);

2. John Bell and Lee Ratner, "Specificity of Polymerase Chain Amplification Reactions for Human Immunodeficiency Virus Type 1 DNA Sequences," *in* 5(1) AIDS RESEARCH AND HUMAN RETROVIRUSES 87–95 (Dani P. Bolognesi, ed., 1989) ("Bell," Ex. 1005);

3. Roy Sooknanan et al., "Nucleic Acid Sequence-Based Amplification," *in* MOLECULAR METHODS FOR VIRUS DETECTION 261–285 (Danny L. Wiedbrauk & Daniel H. Farkus eds., 1995) ("Sooknanan," Ex. 1009); and

4. HUMAN RETROVIRUSES AND AIDS 1995 (Gerald Myers et al. eds., 1995) ("Myers," Ex. 1008).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–15 of the '262 patent on the following grounds:

Claims	Basis	References
1–15	35 U.S.C. § 103	Backus, Sooknanan, and Myers
1–15	35 U.S.C. § 103	Bell, Sooknanan, and Myers

Pet. 3. Petitioner also relies on the Declaration of Jeffrey M. Linnen, Ph.D. *Id.* at 8 n.1 (citing Ex. 1021). Patent Owner disputes that Petitioner's asserted grounds render the challenged claims unpatentable. *See generally* Prelim. Resp.

III. ANALYSIS

We explain below our decision to exercise our discretion under 35 U.S.C. § 325(d) and deny institution. First, however, we address the level of ordinary skill in the art and the parties' respective positions on claim construction. We also provide an overview of the asserted references.

A. Level of Ordinary Skill in the Art

We consider Petitioner's ground of unpatentability in view of the understanding of a person of ordinary skill in the art. Petitioner contends that a person of ordinary skill in the art as of August 8, 1997 would have: a Ph.D. in organic chemistry, biochemistry, or a related field; at least two years of experience in a chemistry or biochemistry laboratory and familiarity with designing assays involving nucleic acid amplification to detect pathogens such as viruses; and knowledge of techniques for nucleic acid amplification. Pet. 3 (citing Ex. 1021 ¶ 27). At this stage of the proceeding, Patent Owner does not dispute that Petitioner's definition is an appropriate assessment of the level of a person of ordinary skill in the art. Prelim. Resp. 3.

For this Decision, we agree with the level asserted by Petitioner. We also find, for purposes of this decision, that the prior art itself is sufficient to demonstrate the level of ordinary skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art, itself, can reflect appropriate level of ordinary skill in art). Further, based on the information presented at this stage of the proceeding, we consider Petitioner's declarant, Dr. Linnen, qualified to opine from the perspective of an ordinary artisan at the time of the invention. *See* Ex. 1021, 213–220 (resumé of Dr. Linnen).

B. Claim Construction

For an unexpired patent, the Board presently interprets claims using the "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). In this proceeding, however, the parties certified under 37 C.F.R. § 42.100(b) that the '262 patent would expire within 18 months of February 6, 2018 (i.e., the entry of the Notice of Filing Date Accorded to Petition). Paper 5, 3. Thus, the Board ordered that district court-type claim construction, rather than broadest reasonable construction, applies to this proceeding. Paper 8; *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc).

Petitioner proposes constructions for various limitations of the claims. Pet. 14–18. Patent Owner responds that "[t]hese constructions are fraught with errors and inconsistencies," but that "[t]here is no reason . . . for the Board to engage in any claim construction at this stage in the proceedings." Prelim. Resp. 3. For purposes of this Decision, we determine that no claim term requires express construction to resolve any controversy in this

proceeding. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.").

C. Asserted References

1. Backus

Backus relates to "methods and test kits for the amplification and detection of nucleic acids from" HIV-1 and HIV-2. Ex. 1006, Abstract. The methods utilize oligonucleotide primer pairs that, according to Backus, "amplify all subtypes of HIV-1, including group M[1] and group O isolates, and all subtypes of HIV-2." *Id.* Backus discloses several primers specific for the LTR region (SEQ ID NOs: 1–4) and the POL region (SEQ ID NOs: 7–8) of HIV-1. *Id.* at 3:10–24. Backus also discloses several primer pairs specific for the ENV region (SEQ ID NOs: 11–12), the LTR region (SEQ ID NOs: 14–16), and the POL region (SEQ ID NOs: 18–20) of HIV-2. *Id.* at 3:60–4:15. Backus explains that, in each reaction, a biological sample suspected of containing HIV nucleic acids is contacted with a primer set comprising at least four, and preferably more, oligonucleotides. *Id.* at 3:26–4:47. For example, Backus states that "[p]referably, the biological sample is contacted with oligonucleotides corresponding to SEQ ID NOS: 2, 3, 4, 7, 8, 11, 12, 14, and 16." *Id.* at 4:43–45. "Use of such a set of primers can amplify target nucleic acid of any known HIV-1 and/or HIV-2 subtype present in the sample." *Id.* at 4:45–47.

[1] Group M is the "major" HIV group subtype while group O "outlier" is less common. Other alphabetically designated subtypes exist. Detection of a broad range of these HIV subtype variants is an issue of concern to those of skill in the art. Ex. 1001, Abstract, 2:4–15, 41–54.

2. Bell

Bell studied the specificity of PCR using primers targeted to the LTR regions of HIV-1. Ex.1005, Abstract. Bell states that the primers "were selected based on several criteria." *Id.* at 90. "First, oligonucleotides of 17–24 nucleotides were chosen to ensure stable hybridization at 72°C . . . ." *Id.* "Second, sequences were picked that had a G[uanine] + C[ytosine] content of at least 50% to ensure stable annealing." *Id.* "Third, oligonucleotides were chosen that flanked regions of 100–300" because, according to Bell, "this is the optimal target size for amplification and detection." *Id.* "Fourth, only conserved regions of the HIV-1 genome were selected for amplification," namely, (1) sequences between the TATA box and RNA initiation site, (2) sequences between the polyadenylation signal and site, (3) the tRNA binding site, and (4) the beginning of the *gag* gene. *Id.* "Fifth," and finally, "portions of the HIV-1 genome that have potential homology to cellular sequences, such as *pol*, were avoided." *Id.*

3. Sooknanan

Sooknanan provides an overview of NASBA—an isothermal *in vitro* amplification technique. Ex. 1009, 261. Sooknanan explains that NASBA may be used for amplification of any analyte RNA or DNA sequence, but is ideally suited for RNA amplification due to the integration of the reverse transcriptase (RT) enzyme into the amplification process. *Id.* at 263, 269.

In addition to RT and analyte nucleic acid, a typical NASBA reaction mixture contains RNase H, T7 RNA polymerase, and an oligonucleotide primer pair. *Id.* at 262. Sooknanan teaches that the first primer (P1) of the primer pair should contain a 3' terminal sequence that is complementary to a sequence on the analyte nucleic acid and a 5' terminal (+) sense sequence of

a promoter that is recognized by T7 RNA polymerase. *Id.* And the second primer (P2) should contain a sequence complementary to the P1-primed DNA strand. Sooknanan states that "[t]he enzymes and primers operate in concert to amplify a specific nucleic acid sequence exponentially." *Id.*

According to Sooknanan, NASBA is particularly advantageous for detecting virus production, gene expression, or cell viability because it can directly amplify viral genomic RNA, mRNA, or rRNA. *Id.* at 270. For example, "NASBA reactions containing an HIV-1 *gag* primer set are able to detect fewer than 10 molecules of *in vitro*-generated RNA template." *Id.*

Sooknanan provides an example protocol for the detection of HIV-1 RNA in plasma or serum, consisting of three parts: (1) nucleic acid isolation, (2) NASBA, and (3) detection. *Id.* at 271–283. The primers used for the NASBA reaction Sooknanan describes amplify and detect the *gag* sequence of HIV-1. *Id.* at 273. Sooknanan states that the first two methods provide "rapid results and are convenient to perform in most laboratory settings." *Id* at 274. Detection, Sooknanan continues, may be performed using "any of the numerous detection formats using either radioactive or nonradioactive oligonucleotide probes." *Id.* at 275. Sooknanan also notes that the single-stranded RNA product produced by the NASBA technique also "provides an excellent substrate for direct sequencing." *Id.*

4. Myers

Myers presents a compendium published yearly of "all relevant molecular data concerning the human immunodeficiency viruses (HIV) and related retroviruses." Ex. 1008, iii. Myers describes the compendium as containing five parts: (1) nucleic acid alignments and sequences; (2) amino acid alignments (including consensus sequences) of all known coding

regions and open reading frames of HIV-1, HIV-2, and related viruses; (3) analysis, including summaries of viral and cellular proteins and of sequencing primers; (4) related sequences, including coding sequences for cellular proteins involved in HIV pathogenesis; and (5) database communications, such as GenBank and EMBL. *Id.* at iii–iv.

Myers teaches that HIV-1 sequences have been categorized into eight sequence subtypes (A through H) based on coding sequence. *Id.* at I-1. These sequences are collectively called group "M" sequences. *Id.* HIV-2 consists of five sequence subtypes (A through E). *Id.* at I-2. Myers provides nucleotide alignments and consensus sequences encoding HIV-1 structural proteins *gag*, *pol*, and *env*, regulatory proteins *tat* and *rev*, and auxiliary proteins *vif*, *vpr*, *vpu*, and *nef*. *See id.* at I-3. Myers also provides nucleotide alignments and consensus sequences for the HIV-1 LTR region. *See id.*; *see also id.* at I-A, 1–15 (nucleotide alignments); 16–17 (HIV-1 LTR consensus sequences).

D. Asserted Obviousness Grounds

Petitioner contends that claims 1–15 of the '262 patent are unpatentable as obvious over Backus, Sooknanan, and Myers, *see* Pet. 22–41, and over Bell, Sooknanan, and Myers, *see id.* at 41–71. In brief, Petitioner argues that Backus and Bell each disclose almost all the limitations of the challenged claims, including primers directed to the LTR region of HIV-1. *Id.* at 22–23, 41–43. Petitioner compares Backus's SEQ ID NO:4 and SEQ ID NO:2 to claim 1's first primer (SEQ ID NO:1) and second primer (SEQ ID NO:5), respectively. *Id.* at 24–26. Petitioner also compares Bell's P3 and P4 primers to claim 1's first primer (SEQ ID NO:1) and second primer (SEQ ID NO:5), respectively. *Id.* at 43–46. For each

prior-art primer, Petitioner notes that it consists essentially of an oligonucleotide that is fully complementary to a LTR-region sequence, and comprises at least 15 sequential nucleotides of SEQ ID NO:1, or 10 sequential nucleotides of SEQ ID NO:5, as recited in claim 1. *Id.* at 24–26, 43–46.

Petitioner then argues that, given that Backus's and Bell's primers meet the most sequence requirements recited in claim 1, an ordinarily skilled artisan would have been motivated to modify those prior-art primers based on Sooknanan and Myers, with a reasonable expectation of success. *Id.* at 26–34, 46–58. In particular, Petitioner asserts that the ordinarily skilled artisan would have been motivated to modify Backus's SEQ ID NO:4 primer and Bell's P3 primer by operably linking them to a promoter for use in NASBA as taught by Sooknanan. *Id.* at 26–27, 49–51, 54–56. Petitioner also asserts that the ordinarily skilled artisan would have been motivated to modify Backus's SEQ ID NO:2 primer and Bell's P4 primer as necessary to correlate to the LTR second conserved sequence disclosed by Myers. *Id.* at 27–30, 52–56. For example, Petitioner contends that an ordinarily skilled artisan would have deleted 10 nucleotides from the 5′ end of Backus's SEQ ID NO:2, "because that sequence extends beyond the LTR second conserved sequence disclosed by Myers." *Id.* at 27–30.

Patent Owner contends that the challenged claims would not have been obvious over the combination of prior art Petitioner asserts. Prelim. Resp. 14–51. But, first, Patent Owner contends that we should exercise our discretion under 35 U.S.C. § 325(d) to deny institution. *Id.* at 5–14. Patent Owner argues that we should deny institution because "the Examiner considered the same arguments the Petition advances," and Petitioner "does

not identify any new art or raise any new arguments that should lead the Board to reach a different conclusion." *Id.* at 5–6. For the reasons explained below, we agree with Patent Owner and exercise our discretion under 35 U.S.C. § 325(d) to deny institution.

1. Discretion Under 35 U.S.C. § 325(d)

Institution of *inter partes* review is discretionary. *See Harmonic Inc. v. Avid Tech, Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) ("the PTO is permitted, but never compelled, to institute an IPR proceeding"). Section 325(d) gives us express discretion to deny a petition when "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d).

In evaluating whether to exercise our discretion under Section 325(d), we weigh the following non-exclusive factors: (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, slip op. at 17–18 (Paper 8, Dec. 15, 2017) (informative).

We analyze these factors below as applied to the record in this case, and find that, on balance, the factors weigh in favor of exercising our discretion under 35 U.S.C. § 325(d).

(a) The similarities and material differences between the asserted art and the prior art involved during examination

As explained above, Petitioner relies on Backus, Bell, Sooknanan, and Myers for alleging obviousness of claims 1–15. Pet. 3. The Examiner considered both Backus and Bell during prosecution of the '262 patent, and both are listed on the cover of the patent. *See* Ex. 1002, [56]. Although the Examiner did not expressly rely on Backus to reject a claim during prosecution of the '262 patent, the Examiner used Backus to reject similar claims during prosecution of the parent application that led to the '352 patent. *See* Ex. 2001,[2] 1815–30 (Office Action of June 18, 2013); *id.* at 1852–68 (Office Action of September 16, 2013). The Examiner did not rely on Bell to reject the claims during prosecution of either patent, but the Examiner and applicants discussed Bell during interviews held during prosecution of the '352 patent. *See id.* at 1326–47 (Interview Summary dated June 26, 2009); *id.* at 1874–77 (Interview Summary dated November 21, 2013).

The Examiner considered Myers during prosecution of the '262 patent, but the yearly version of Myers published in 1996, rather than the 1995 version that Petitioner relies on here. In particular, "Scientific Report on Computer Analysis of the Alignment of the HIV LTR Sequence from the

[2] Ex. 2001 provides the complete prosecution history for the '352 patent. Ex. 2024 provides the complete prosecution history for the '262 patent. Citations to these exhibits use the pagination added by Patent Owner. *See* Prelim. Resp. 6 n.1.

Dec. 1996 Edition of the Human Retroviruses and AIDS Compendium published by the Los Alamos National Laboratory, New Mexico" and "LTR alignment from the Dec. 1996 Edition of the Human Retroviruses and AIDS Compendium published by the Los Alamos National Laboratory, New Mexico" are both listed as references cited on the cover of the '262 patent. Ex. 1002, [56]. The 1996 version of Myers is also listed in an Information Disclosure Statement initialed by the Examiner. *See* Ex. 2024, 280–81. The consensus sequences for the HIV-1 LTR region provided in Myers 1996 are identical to those provided in Myers 1995. *Compare* Ex. 1008, I-A, 16–17, *with* Ex. 2001, 583–84 (1996 LTR alignment in the prosecution history of the '352 patent). Thus, as to Myers, the Examiner considered substantively the same reference that Petitioner advances here.

The Examiner did not consider Sooknanan during prosecution of the '262 patent, and Sooknanan is not listed on the cover of the patent. *Id.*; *see also* Ex. 1002, [56].

(b) The cumulative nature of the asserted art and the prior art evaluated during examination

As explained above, the Examiner expressly considered Bell and Backus during prosecution. And, as to Myers, the Examiner considered substantively the same reference that Petitioner advances here. As further noted above, Sooknanan was not before the Examiner. Even so, we conclude that prior-art references having substantially similar teachings to Sooknanan were considered by the Examiner.

Sooknanan, as described above, provides an overview of the NASBA technique and teaches an oligonucleotide primer (P1) that contains a promoter sequence that is recognized by T7 RNA polymerase. Ex. 1009, 262. The Examiner found that the written description of the '262 patent

admits that the NASBA technique was known in the prior art and "includes the use of T7 RNA polymerase to transcribe multiple copies of RNA from a template including a T7 promoter." Ex. 2024, 267 ¶ 63. The Examiner also relied on McAllister,[3] which teaches a T7 promoter operably linked to a first oligonucleotide, and Rossi,[4] which teaches "amplification of HIV-1 nucleotide sequences wherein the primer comprise[s] the recognition sequence of T7." *Id.* at 267 ¶ 63; Ex. 3001, 4:22–35; Ex. 3002, 4:52–57. Because the Petitioner relies on Sooknanan for the same teachings that the Examiner considered admitted and well-known during prosecution (and that were further disclosed in McAllister and Rossi), we find that Sooknanan is cumulative to the prior art evaluated during examination.

(c) The extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection

None of Backus, Bell, Sooknanan, or Myers was the basis for any rejection of the claims during prosecution. Instead, the Examiner rejected the claims under 35 U.S.C. § 103 as obvious over a combination of references including, primarily, Montagnier.[5] *See* Ex. 2024, 89–97 (Office Action dated May 6, 2014); *id.* at 261–73 (Office Action dated November 17, 2014); *id.* at 325–29 (Advisory Action dated April 10, 2015). The Examiner also held several interviews with the applicants during prosecution. *See id.* at 300–03 (Interview Summary dated March 30, 2015);

[3] Diane L. McAllister and Kathleen A. Clark, U.S. Patent No. 5,622,827 (April 22, 1997) ("McAllister," Ex. 3001).

[4] John J. Rossi, U.S. Patent No. 5,622,820 (Apr. 22, 1997) ("Rossi," Ex. 3002).

[5] Luc Montagnier et al., U.S. Patent No. 5,221,610 (June 22, 1993) ("Montagnier," Ex. 2002).

id. at 333–35 (Interview Summary dated April 20, 2015); *id.* at 354–59 (Interview Summary dated April 30, 2015).

Bell was discussed during interviews held during prosecution of the parent application leading to the '352 patent. *See* Ex. 2001, 1329 (Interview Summary dated June 26, 2009); *id.* at 1877 (Interview Summary dated November 21, 2013). In the latter and final interview held between applicants, the Examiner, and a Quality Assurance Specialist (QAS), the parties discussed the rejection of the claims under 35 U.S.C. § 103(a), as well applicants' submission of a Declaration filed under 37 C.F.R. § 1.132 Declaration executed by Ali Laayoun, Ph.D., ("the Laayoun Declaration"). *Id.* at 1877. The Examiner noted that the Laayoun Declaration purported to show unexpected results "over the closely-related primer[s] disclosed in Bell and Ratner." *Id.* The Examiner further noted that, although it was not the basis for a rejection, Bell "had been cited by a foreign office." *Id.* Finally, the Examiner wrote that "Examiner Sisson and QAS Witz indicated agreement that such a showing may well be persuasive towards the withdrawal of the rejection." *Id.*

Also during prosecution of the parent application, Backus was the basis for rejection of claims similar to those Petitioner challenges here. *See* Ex. 2001, 1815–30; *id.* at 1852–68. Specifically, SEQ ID NO:1 (i.e., G GGC GCC ACT GCT AGA GA) and SEQ ID NO:5 (CTC AAT AAA GCT TGC CTT GA) are identical in both claims of the '352 and '262 patents. *See* Ex. 1001, 17:30–60; Ex. 1002, 17:48–18:64. The Examiner relied on Backus for teaching a 30-mer oligonucleotide primer (SEQ ID NO:2) that encompasses SEQ ID NO:5, which is also recited in the '262 patent's claim 1. Ex. 2001, 1863–64 ¶ 45. The Examiner also relied on Backus for

teaching a 23-mer oligonucleotide primer (SEQ ID NO:4) that "comprises the full length SEQ ID NO:1 claimed instantly." *Id.*; *see also* Ex. 1006, 3:15 (SEQ ID NO:2), 3:19 (SEQ ID NO:4). During prosecution of the '262 patent, however, the Examiner relied on applicants' admissions in the specification that SEQ ID NO:1 and SEQ ID NO:5 "are highly conserved in HIV." *See, e.g.,* Ex. 2024, 92 ¶ 36.

Petitioner relies on these same sequences for teaching the "first primer" and "second primer" limitations of the '262 patent's claim 1. Specifically, as detailed above, Petitioner argues that the ordinarily skilled artisan would have been motivated to modify Backus's SEQ ID NO:4 primer by operably linking it to a promoter sequence for use in NASBA as taught by Sooknanan. Pet. 26–27. Petitioner also argues that the ordinarily skilled artisan would have been motivated to modify Backus's SEQ ID NO:2 primer to correspond to the LTR second conserved sequence disclosed by Myers. *Id.* at 27–30.

The Examiner also relied on and discussed throughout prosecution the advanced state of the art in terms of knowledge of the HIV-1 genome, amplification techniques (including PCR and NASBA), and primer design, as well as the need for methods for detecting HIV-1 infections in humans. *See, e.g.*, Ex. 2024, 269–70, ¶¶ 68–71. For example, the Examiner emphasized that the genetic structure and nucleotide sequence of HIV-1 were known in the art at the time of filing. *Id.* at 270 ¶ 70. The Examiner also explained that, given the knowledge in the art, primer length would have been obvious because the prior art "teaches explicitly that primers can be prepared using techniques well known in the art." *Id.* at 266 ¶ 57.

Taken together, it appears to us that the Examiner made extensive fact findings about the teachings of the prior art that include much of the teachings of Backus, Bell, Sooknanan, Myers—relied upon here by Petitioner—albeit as taught in other references. We also conclude that the Examiner thoroughly considered the patentability of the '262 patent's claims.

(d) The extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art

The findings that the Examiner made during prosecution and the arguments Petitioner makes here are substantially the same. As explained above, Petitioner contends that use of the oligonucleotide primers recited in claims 1–15 in a method for amplifying HIV-1 in a sample would have been obvious because the regions of the HIV-1 genome conserved among subtypes were known, an ordinarily skilled artisan would have selected the conserved LTR regions for primers, and that artisan would have applied conventional design techniques to design oligonucleotide primer pairs suitable for amplifying HIV-1 nucleic acid in a sample. Pet. 35–36. And, as further noted above, the Examiner relied primarily on Montagnier to reject the claims for obviousness. *See, e.g.*, Ex. 2024, 91–92.

Briefly, Montagnier discloses polypeptide sequences encoded by the *nef* gene of HIV-1, and exemplifies a diagnostic method using antibody-containing sera for detecting those polypeptides in biological fluids. Ex. 2002, Abstract; *see also id.* at 7:25–8:25. Montagnier describes the need in the art for "reagents, means, and methods for the early detection of HIV infection," including "different strains of HIV and their viral components from different isolates." *Id.* at 2:54–58. Montagnier states that nucleotide

sequences can be used as probes for detecting HIV infection in tissue or body fluids, and also suggests using the nucleotide sequences for detecting current HIV infection via PCR. *Id.* at 18:12–19:13. Montagnier further states that "the PCR technique is preferably carried out with several primer pairs and probes derived from highly conserved regions of the viral genome, such as the LTR, qao [sic], and env regions of HIV-1." *Id.* at 19:67–20:2.

Based on these disclosures, the Examiner found that Montagnier expressly suggests using oligonucleotide primers and probes from the conserved LTR regions for detecting HIV infection. *See, e.g.*, Ex. 2024, 269 ¶ 65. Specifically, the Examiner stated that Montagnier teaches that PCR "is preferably carried out with several primer pairs and probes derived from the highly conserved regions of the viral genome, such as the LTR," *id.* at 271 ¶ 75, and reasoned that:

> Given such explicit guidance, the ordinary artisan would have been amply motivated to have isolated "highly conserved regions" of the LTR for primers to be used in a "PCR technique (applicant's "amplification" method) and therein arrive at the genus of primers encompassed by the current method.

Id. at 271 ¶ 76. Thus, the Examiner relied on Montagnier for essentially the same reason that Petitioner cites Myers here: namely, that Myers would have motivated a POSITA to modify the prior-art primers based on the LTR conserved sequence. *See, e.g.*, Pet. 28. We also observe that this teaching in Montagnier is as strong as (if not stronger than) that in Myers. Myers discloses conserved sequences, but—unlike Montagnier—does not expressly point to the LTR sequences for the development of primers or probes. *See* Ex. 1008 I-A, 17–18.

Montagnier does not disclose SEQ ID NO:1 or SEQ ID NO:5, as recited in the '262 patent claims. For this teaching, the Examiner wrote that the LTR regions were well known in the art at the time the application leading to the '262 patent was filed. *See, e.g.*, Ex. 2024, 266 ¶ 57. Again, Petitioner relies only on Myers to teach the conserved sequences of the LTR regions.[6]

Petitioner relies on Sooknanan, in part, for motivation to apply conventional guidelines for NASBA primer design. Pet. 31. Sooknanan teaches various guidelines for primer design. *See* Ex. 1009, 264. For example, Sooknanan states that "selection of the[] hybridizing sequences of the NASBA primers is dependent on nucleotide length, composition, and sequence." *Id.* Sooknanan also teaches that "[c]omputer programs . . . are recommended for screening primer sequences for potential interaction." *Id.* And, "[a]s in PCR, it may be necessary to select and test more than one primer pair for each target to find the one that gives the desired performance." *Id.* These guidelines for primer design, however, were well known and conventional in the art, as several references that the Examiner considered show. *See, e.g.*, Ex. 1006, 10:50–65; Ex. 2004, ¶¶ 16–20.

[6] During prosecution of the parent application, the Examiner relied on Backus for teaching a 30-mer oligonucleotide primer (SEQ ID NO:2) that encompasses the claimed SEQ ID NO:5. Ex. 2001, 1863–64 ¶ 45. The Examiner also relied on Backus for teaching a 23-mer oligonucleotide primer (SEQ ID NO:4) that "comprises the full length SEQ ID NO:1 claimed instantly." *Id.*; *see also* Ex. 1006, 3:15 (SEQ ID NO:2), 3:19 (SEQ ID NO:4). Again, Petitioner relies on both Backus and Bell for these oligonucleotide sequences.

During prosecution of the parent application leading to the '352 patent, the Examiner relied on "the well-developed state of the amplification art," and stated that "selection of the exact nucleotide sequence is deemed to be a matter of routine optimization of a finite number of possible choices." Ex. 2001, 1866–67 ¶¶ 52–53. The Examiner also recorded in an interview summary that "commercial software has been available that allows one to select primers from a given sequence, and to define such primers in terms of length, GC content, [and] secondary structure consideration(s)." *Id.* at 1329. For these reasons, we find that Petitioner's arguments about the teachings of Sooknanan add nothing material to the Examiner's discussion of what was already well known in the art.

(e) Whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art

Petitioner does not cite to, nor discuss, section 325(d) in its Petition. Petitioner makes no statements as to whether the Examiner considered the asserted prior art during prosecution. Petitioner also does not point out or make an argument as to whether the Examiner erred in evaluating the prior art that was before him during prosecution, which as explained above, is substantially similar to the prior art asserted here. *See generally* Pet.

(f) The extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments

We are of the view that the Petition does not warrant reconsideration of the prosecution history based upon the substantially similar prior art. In this regard, we observe that the Examiner allowed the claims upon submission of a Declaration under 37 C.F.R. § 1.132 executed by Ali Laayoun, Ph.D., showing unexpected results ("the Laayoun Declaration") and applicants' narrowing of the claims via amendments. *See* Ex. 2024,

125–56; *id.* at 306–11 (Amendment dated April 6, 2015); *id.* at 338–43 (Amendment dated April 28, 2015). Petitioner does not persuade us that the Examiner erred in relying on that Declaration, or that we should reconsider the contents of the Declaration.

The Laayoun Declaration provides a series of PCR and NASBA assays in which primers with SEQ ID NO:1 and SEQ ID NO:5 are compared with Bell's P3 and P4 primers. Ex. 2024, 125–26 ¶ 4. In both types of assays, the Laayoun Declaration shows that the SEQ ID NO:1 and SEQ ID NO:5 primers detected virus at lower template concentrations than the Bell primers. *See, e.g.*, *id.* at 129–35. The Laayoun Declaration states that these test results show that "the primer pairs of the claimed invention are about 1000-fold more sensitive than the LTR primer pair of Bell & Ratner" and thus "provide a clear advantage over other primer pairs derived from the LTR as exemplified by the primer pair of Bell & Ratner." *Id.* at 135 ¶ 11.

The Laayoun Declaration also provides assay results for several variants of the claimed primers with different amounts of template. *See id.* at 136–45. The Laayoun Declaration states that these test results show that the "primers of the present invention are consistently more sensitive than those of Bell & Ratner" because the claimed primers consistently detected levels of HIV-1 "as low as 10^2 IU/reaction," whereas the Bell primers were "unable to detect HIV-1 even at levels of 10^3 IU/reaction." *Id.* at 146 ¶ 14. From these results, the Laayoun Declaration states that "it is clear that the primers of the present invention provide unexpectedly better results than that provided by the primer pair of Bell & Ratner." *Id.*

Petitioner contends that the Laayoun Declaration is not persuasive evidence of non-obviousness because: (1) the Declaration does not compare

the invention to the closest prior art; and (2) the alleged unexpected results are not commensurate with the scope of the claims. Pet. 61–70. These arguments, however, do not persuade us to reconsider the Laayoun Declaration.

First, the Examiner squarely considered whether the unexpected results were commensurate with the scope of the claims, as Petitioner asserts here. Applicants initially filed the Laayoun Declaration in a Response dated August 5, 2014, following the Examiner's rejection over Montagnier. *See* Ex. 2024, 118–22. The Examiner did not find the Laayoun Declaration persuasive at that time, stating that "[t]he showing is not commensurate in scope" with the claims. *Id.* at 272 ¶ 80. In particular, the Examiner wrote that the claims encompass a large genera of primers, but that "applicant has presented no evidence that any and all primers encompassed by the claimed method . . . perform in the same manner." *Id.* at 273 ¶ 85; *see also id.* at 328 (Advisory Action).

Eventually, in response, applicants filed an Amendment and Response, amending the claims to recite that the oligonucleotide primers "bind to a first primer binding site and a second primer binding site located within the LTR region" and pointing out that the primers "are restricted in that the first and second oligonucleotides are required to be fully complementary to the LTR sequence." *Id.* at 348; *see also id.* at 338 (claim language reciting "said first primer consists essentially of a first oligonucleotide that is fully complementary to a sequence of the LTR region . . . , said oligonucleotide being 15–26 nucleotides in length" and "said second primer consists essentially of a second oligonucleotide that is fully complementary to a sequence which is the reverse complement of a

sequence of the LTR region . . . , said oligonucleotide being 10–26 nucleotides in length"). Thereafter, the Examiner issued a Notice of Allowability. *See id.* at 377. Although the Examiner did not include reasons for allowance, we infer that the claim amendments and arguments resolved the Examiner's concerns that the unexpected results were not commensurate in scope with the claims.

Second, Petitioner faults Patent Owner for "not demonstrat[ing] that Bell is the closest prior art," Pet. 62, and asserts that "Backus's primer pair is closer to the claimed primer pairs than Bell's primer pair," *id.* at 64. But it is the Petitioner that bears the burden in an *inter partes* review to prove that the issued claims are unpatentable. *In re Magnum Oil Tools Int'l*, 829 F.3d 1364, 1380–81 (Fed. Cir. 2016). Here, the Examiner accepted Bell as the closest prior art, even though the Examiner had rejected the similar claims during prosecution of the '352 patent over Backus for disclosing a 30-mer oligonucleotide primer that encompasses SEQ ID NO:5 as set forth in claim 1 of the '262 patent. *See, e.g.*, Ex. 2001, 1863–64 ¶ 45. Absent some persuasive evidence that the claimed primers would not have been unexpectedly better than Backus's primers, we decline to revisit that decision. *See* Pet. 63–64 (comparing primers of Backus to Bell's primers without presenting any evidence of how the activity of Backus' primers compares to the claimed primers).

2. Weighing the Factors

Taking into account the above factors, we find that they weigh in favor of exercising our discretion and denying institution under section 325(d). Importantly, the arguments Petitioner advances in its Petition are substantially similar to the findings the Examiner made to reject the claims,

and that the patent applicants overcame with evidence. And, in our view, Montagnier is a strong prior art reference that expressly suggests creating primers to the conserved HIV-1 LTR regions to detect the many subtypes of HIV-1 infections. Other aspects of the invention—the primer sequences, design, and amplification techniques—were undoubtedly conventional in the art. Applicants overcame the Examiner's rejections by submitting the Laayoun Declaration of experimental evidence showing 1000-times greater sensitivity than the prior-art primers. Petitioner does not persuade us that the Examiner erred in accepting that evidence as showing unexpected results. Thus, we deny institution under section 325(d).

IV. CONCLUSION

Taking account of the information presented in the Petition and the Preliminary Response, and the evidence of record, we exercise our discretion under 35 U.S.C. § 325(d) and deny institution. Accordingly, the Petition is *denied*, and no trial is instituted.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is *denied*, and no trial is instituted.

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