Trials@uspto.gov
571-272-7822

Paper 8
Date: April 24, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BLUEBIRD BIO, INC.,
Petitioner,

v.

SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH,
Patent Owner.

IPR2023-00070
Patent 7,541,179 B2

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JAMES A. WORTH, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

Bluebird bio, Inc. ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 10, 19, and 22 of U.S. Patent No. 7,541,179 B2 (Ex. 1001, "the '179 patent"). Paper 1 ("Petition" or "Pet."). Sloan Kettering Institute for Cancer Research ("Patent Owner") filed a Preliminary Response to the Petition. Paper 5 ("Prelim. Resp."). With our authorization, Petitioner filed a Reply (Paper 6, "Reply") and Patent Owner filed a Sur-Reply (Paper 7, "Sur-reply").

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314 (2018). Upon considering the parties' arguments and evidence, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of all claims and all grounds asserted in the Petition.

A. Real Parties in Interest

Petitioner identifies itself and Third Rock Ventures, LLC as the real parties-in-interest. Pet. 2.

Patent Owner identifies itself, San Rocco Therapeutics, LLC, formerly known as Errant Gene Therapeutics, LLC, and Memorial Sloan-Kettering Cancer Center as the real parties-in-interest. Paper 4, 1.

B. Related Matters

Petitioner and Patent Owner identify *San Rocco Therapeutics, LLC v. bluebird bio, Inc., et al.*, No. 1-21-cv-01478 (D. Del.)[1] as a related district court litigation. Pet. 2–3; Paper 4, 2–3. Patent Owner also identifies *Errant*

[1] Patent Owner captions this case "*Errant Gene Therapeutics, LLC v. Bluebird Bio, Inc*., 1-21-cv-01478, (D. Del. October 21, 2021)." Paper 4, 2.

Gene Therapeutics, LLC v. Memorial Sloan-Kettering Cancer Center and Sloan Kettering Institute of Cancer Research, 1-21-cv-08206 (S.D.N.Y.) as a related litigation involving the '179 patent. Paper 4, 3.

The parties further identify IPR2023-00074, challenging certain claims of U.S. Patent No. 8,058,061 B2 ("the '061 patent"), as a related matter. Pet. 2–3; Paper 4, 2–3. The '061 patent issued from a divisional application of U.S. application number 10/188,221 ("the '221 application"), which issued as the '179 patent. Ex. 1001, code (21).

C. The '179 Patent

The '179 patent is directed to a recombinant vector, e.g., a lentiviral vector, incorporating a functional globin gene and large portions of the β-globin locus control region ("LCR"). Ex. 1001, 1:47–51. The Specification defines a "recombinant lentiviral vector" as "an artificially created polynucleotide vector assembled from a lentiviral-vector and a plurality of additional segments as a result of human intervention and manipulation." *Id.* at 2:36–40. The Specification defines "functional globin gene" as "a nucleotide sequence the expression of which leads to a globin that does not produce a hemoglobinopathy phenotype, and which is effective to provide therapeutic benefits to an individual with a defective globin gene." *Id.* at 2:41–45. "The functional globin gene may encode a wild-type globin," "a mutant form of globin," "α-globin, β-globin, or γ-globin." *Id.* at 2:45–53. The recombinant lentiviral vector is used as a gene therapy vector to provide "therapeutically meaningful levels of human globin for sustained periods of time." *Id.* at 1:36–44.

The Specification describes the recombinant vector as including "large portions of the locus control region (LCR) which include DNase I hypersensitive sites HS2, HS3 and HS4." *Id.* at 2:54–56. The Specification

defines "large portions" as "portions of the locus control region which encompass larger portions of the hypersensitive sites as opposed to previously tested fragments including only the core elements." *Id.* at 2:60–64. In a specific vector, designated TNS9, the LCR is 3.2 kilobases ("kb") in size and "consists of an 840 [base pair ('bp')] HS2 fragment (SnaBI-BstXI), a 1308 bp HS3 fragment (HindIII-BamHI) and a 1069 bp HS4 fragment (BamHI-BanII)." *Id.* at 3:24–26. Figure 1, reproduced below, illustrates the TNS9 vector.

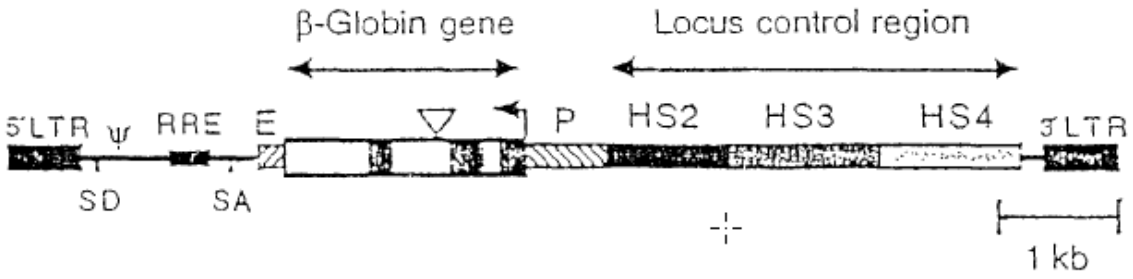

Fig. 1

Figure 1 illustrates the TNS9 vector with exons represented by filled boxes and introns represented by open boxes. *Id.* at 3:14–16. The TNS9 vector includes, from the 5′ end to the 3′ end, a splice donor (SD), packaging region (Ψ), rev-response element (RRE), splice acceptor (SA), 3'-β-globin enhancer (E), β-globin gene, human β-globin promoter (P), and LCR (including HS2, HS3, and HS4). *Id.* at 3:16–19. The 5′ and 3′ ends include long terminal repeat (LTR) sequences. *See* Fig. 1.

D. Illustrative Claim

Petitioner challenges claims 1, 10, 19, and 22 of the '179 patent. Claim 1, set forth below, is the only independent claim and is illustrative of the claimed subject matter.

> 1. A recombinant vector comprising a nucleic acid encoding a functional globin operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR), the three fragments being a BstXI and SnaBI HS2-spanning nucleotide fragment of said LCR, a BamHI and HindIII HS3-spanning nucleotide fragment of said LCR and a BamHI and BanII HS4-spanning nucleotide fragment of said LCR, said vector providing expression of the globin in a mammal in vivo.

Ex. 1001, 11:55–65. Dependent claim 19 recites that the functional globin is β-globin, and dependent claim 10 recites that the functional globin is human β-globin. *Id.* at 13:4–5, 14:6–7. Dependent claim 22 recites that the vector is a lentiviral vector. *Id.* at 14:12–13.

E. Asserted Grounds of Unpatentability

Petitioner asserts that claims 1, 10, 19 and 22 would have been unpatentable on the following four grounds:

Claims Challenged	35 U.S.C. §[2]	Reference/Basis
1, 19, 22	102	May Thesis[3]

[2] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the application from which the '179 patent issued has an effective filing date before that date, the pre-AIA version of §§ 102 and 103 apply.

[3] May, *Therapeutic Hemoglobin Synthesis in Beta-Thalassemic Mice Expressing Lentivirus-Encoded Human Beta-Globin*, Cornell University (2001) (Ex. 1004, "May Thesis").

Claims Challenged	35 U.S.C. §[2]	Reference/Basis
1, 19, 22	102	May Article[4,5]
1, 19, 22	103	May Article
1, 10, 19, 22	103	May Abstract[6]

Petitioner also relies upon the Declarations of Jörg Bungert, Ph.D. (Ex. 1002) and Ingrid Hsieh-Yee, Ph.D.[7] (Ex. 1036). Patent Owner relies upon the Declarations of James Riley, Ph.D. (Ex. 2002); Michel Sadelain, M.D., Ph.D. (Ex. 2006); Chad May, Ph.D. (Ex. 2007); Stefano Rivella, Ph.D. (Ex. 2008); Lucio Luzzatto, M.D., Ph.D. (Ex. 2009).[8]

II. ANALYSIS

A. Discretionary Denial under 35 U.S.C. § 325(d)

Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d). Prelim. Resp. 38–44. We have discretion to deny review when "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). In that respect, § 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the

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[4] May, et al., *Therapeutic Haemoglobin Synthesis in β-Thalassaemic Mice Expressing Lentivirus-Encoded Human β-globin*, 406 NATURE 82–86 (2000) (Ex. 1005, "May Article").

[5] In the Preliminary Response, Patent Owner refers to Exhibit 1005 as the "Nature Article." *See* Prelim. Resp. 1.

[6] May, et al., *Lentiviral-Mediated Transfer of the Human β-Globin Gene and Large Locus Control Region Elements Permit Sustained Production of Therapeutic Levels of β-Globin in Long-Term Bone Marrow Chimeras*, 1(5) MOL. THERAPY S248–49 (2000) (Ex. 1006, "May Abstract").

[7] Petitioner relies on the declaration of Dr. Hsiey-Yee, a librarian, to address authenticity and public availability of the cited references. Ex. 1036 ¶ 16.

[8] Patent Owner relies on the declarations of Drs. Sadelain, May, Rivella, and Luzzatto to address inventorship and, in some instances, conception and reduction to practice allegations.

Office.[9] *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH,* IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

In evaluating matters under § 325(d), the Board uses the following two-part framework: (1) determining whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, Paper 6 at 8.

In applying the two-part framework, we consider several nonexclusive factors, including:

(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

[9] "The Board institutes trial on behalf of the Director." 37 C.F.R. § 42.4(a); *Advanced Bionics*, Paper 6 at 7 n.7.

(f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) ("*Becton, Dickinson*") (footnote omitted).

Factors (a), (b), and (d) of the *Becton, Dickinson* factors relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics* at 10. Factors (c), (e), and (f) "relate to whether the petitioner has demonstrated a material error by the Office" in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.* "[T]his framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown." *Id.* at 9.

1. Part One of the § 325(d) Analysis

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8.

Petitioner contends that "neither the *May Thesis* nor the *May Abstract* were considered during the prosecution of the '179 patent or any related patent." Pet. 45 (citing Ex. 1001, code (56)). Although Petitioner acknowledges that the Examiner considered the May Article, Petitioner argues that the May Article was applied against the original claims of the application, and not the allowed claims reciting the specific LCR fragment. *Id.* at 45–46 (citing Ex. 1032, 19–24, 61–66). Petitioner further argues that

"the Applicants overcame the rejection not on substance, but by the filing of conclusory *Katz* declarations arguing that the *May Article* 'reflects the work of the inventors of this application.'" *Id.* at 46 (citing Ex. 1032, 106, 109–116).

Patent Owner argues that the "Examiner expressly considered the [May] Article during prosecution." Prelim. Resp. 42. Patent Owner further argues that the May Abstract and the May Thesis "describe the *same work* by the *same inventors* to develop the vector claimed in the '179 Patent." *Id.* (citing Exs. 1004–1006). Accordingly, Patent Owner argues that the May Abstract and May Thesis do not qualify as prior art, and that "the Examiner has already considered the written description requirements related to the 'functional globin' limitation," which forms the basis of Petitioner's argument for lack of priority to the provisional applications.[10] *Id.* at 42–43; *see also* 29–38.

Petitioner replies that Patent Owner "does not point to any analysis of the priority date issue by the Examiner." Reply 1. Instead, Petitioner argues that "even if the Examiner silently considered the priority issue, there is no analysis upon which the Board may discern whether the Examiner conducted a proper analysis." *Id.* at 1–2 (citing *Smith & Nephew, Inc. v. Arthrex, Inc.*, IPR2016-00487, Paper 8, 19 (PTAB July 27, 2016).

Based on our review of the record, we find that Petitioner has not shown persuasively that the Examiner did not consider the same or

[10] The '221 application claims priority to provisional application no. 60/301,861 (Ex. 1034) ("the '861 provisional application"), filed June 29, 2001, and provisional application no. 60/302,852 (Ex. 1035) ("the '852 provisional application"), filed on July 2, 2001, referred to, collectively, as "the provisional applications," "the provisionals" and "the Provisionals."

substantially the same art that Petitioner relies upon for its obviousness challenges. Petitioner's grounds rely on three different "May" references, only one of which the Examiner considered during prosecution, i.e., the May Article. The additional references relied upon by Petitioner are the May Thesis, which provides a more detailed disclosure than the May Article, and the May Abstract, which provides less detail than the May Article, in terms of the HS2, HS3, and HS4 fragments used to generate the disclosed TNS9 vector. Those differences are only material with respect to whether each reference discloses the fragments as recited in independent claim 1, or renders those fragments obvious. However, as discussed in Section II.D.2., we determine that the May Thesis is not prior art.

Because the May Abstract shares a similar disclosure as the May Article, but in less detail, the May Abstract may be considered cumulative to the May Article. Because the May Thesis provides more explicit details regarding the fragments disclosed in the May Article, it may not be considered to be cumulative to the May Article. However, as discussed in Section II.D.2., we determine that the May Thesis is not prior art.

When considering the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the May Article or Patent Owner distinguishes the May Article, we note that Patent Owner alleged during prosecution and here that the May Article is not prior art for a number of reasons, including that it is the work of the inventors and that it was published one year or less before the priority date asserted by Patent Owner for the challenged claims. We note also that Petitioner contends that the challenged claims are not entitled to the priority date asserted by Patent Owner, and recognized by the Examiner.

Based on the foregoing, we conclude that substantially the same prior art that Petitioner relies upon was previously presented to the Examiner during prosecution. The first part of the § 325(d) framework is, therefore, met. Accordingly, we turn to the second part of the § 325(d) and determine whether error by the Office has been shown. *See Advanced Bionics* at 8.

2. Part Two of the § 325 Analysis

We next consider whether Petitioner has demonstrated a material error by the Office. Material error may be demonstrated by showing that an examiner "misapprehend[ed] or overlook[ed] specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Advanced Bionics* at 8 n.9.

Petitioner asserts that "during the prosecution of the '221 application, the Examiner did not consider the appropriate priority date, nor did they consider the inventors' own prior art regarding the TNS9 vector disclosed and claimed in the '179 patent published more than one year prior to the earliest possible priority date." Pet. 46–47 (citing Ex. 1032). Petitioner further asserts that "[t]he Office plainly erred by not considering prior art up to the appropriate priority date and, therefore, not substantively engaging with the *May Article* and failing to consider the *May Thesis* or the *May Abstract* at all." *Id.* at 47.

Patent Owner argues that "Petitioner fails to identify any additional disclosures or art overlooked, or any material error made, by the Examiner that would negate or call into question the Examiner's findings." Prelim. Resp. 43. Patent Owner argues that "everything suggests the Examiner fully evaluated art and arguments and reconsideration is not warranted." *Id.* at 43–44.

Petitioner replies that the Examiner's silence on priority "suggests only that the Examiner erred by failing to consider the priority date issue." Reply 1. Petitioner further argues that the Examiner "missed key issues," particularly where Applicants cited to the passages for written description support that were not present in the provisional applications. *Id.* at 2 (citing Pet. 16–17).

In response to Petitioner's argument about Examiner error, Patent Owner argues that "the Office necessarily determined priority when distinguishing between §§ 102(a) and 102(b) art." Sur-reply 2. Patent Owner argues that the Office determined that the claims were entitled to the provisional filing date because Appellant was able to traverse the May article as § 102(a) art with *Katz* declarations from the inventors. *Id.* Otherwise, the Office would have treated the May Article as § 102(b) art and applied a statutory bar. *See id.*

Patent Owner further argues that Petitioner raises new argument in the Reply that could have been presented in the Petition, namely that "the 'Examiner missed' that the cited support for an amendment was not present in the Provisionals." Sur-reply 3.[11] Instead, Patent Owner argues that "the Provisionals explain that 'large fragments' [i.e., nucleotide sequences] of the globin gene along with the LCR fragments allow for the 'treatment [i.e., therapeutic benefits] of severe haemoglobinopathies.'" *Id.* at 3, citing (Ex. 1032, 4).

[11] We need not reach Patent Owner's allegation that Petitioner's Reply exceeds the scope authorized, as our determination regarding likely Examiner error is based upon our consideration of Petitioner's arguments presented in the Petition, as opposed to what was presented in the Reply.

As set forth below in Section II. D.1., we determine, at this stage in the proceeding that Petitioner has shown persuasively that claims 1, 19, and 22 of the '179 patent are not entitled to receive benefit of the filing date for either provisional application relied upon by Patent Owner. In particular, we find persuasive Petitioner's arguments that the provisional applications do not satisfy the written description requirements of 35 U.S.C. § 112 for those claims. Thus, we explain that for purposes of this Decision, claims 1, 19, and 22 have a priority date of July 1, 2002, the filing date of the '221 application. The Examiner did not provide an analysis of the priority date for the challenged claims. Thus, we are unable to analyze the Examiner's position regarding that issue. Based on the current record, we are constrained to consider that the Examiner likely misapprehended or overlooked the relevant facts regarding the proper priority date for the challenged claims.

Similarly, as set forth in Section II.D.2., we determine at this stage in the proceeding that the May Article is eligible as prior art under Section 102(b). As we explain, based upon the undisputed July 6, 2000 public availability date, although the May Article is the work of the inventor, it represents a disclosure made more than one year before the effective filing date, i.e., July 1, 2002, for claims 1, 19, and 22 challenged with this reference.

Finally, as set forth in Section II.G.2, we determine, based on the current record, that Petitioner has shown a reasonable likelihood of establishing that the challenged claims are rendered obvious by the May Article.

Thus, based on the current record, we determine that the Examiner likely erred in failing to consider the May Article as prior art. This apparent error, along with the testimony of Petitioner's expert, Dr. Bungert regarding the teachings and suggestions provided by the May Article to a person of

skill in the art at the time of the invention, which was not before the Examiner, persuades us that the Office's reconsideration of the prior art is justified.

3. Conclusion on § 325

Based on the foregoing analysis, we determine that the Petition does not implicate § 325(d) in a manner sufficient to warrant discretionary denial. Accordingly, we decline to exercise our discretion to deny the Petition under § 325(d).

B. Person of Ordinary Skill in the Art

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art ("POSA") "at the time of the alleged invention would have had: (1) at least an advanced degree (*e.g.*, a Master's or Ph.D.) in biochemistry, biotechnology, protein chemistry, genetics, molecular and structural biology, bioengineering, or similar disciplines." Pet. 17 (citing Ex. 1002 ¶¶ 14–15). Petitioner further asserts that a POSA would have had "(2) several years of post-graduate training or related experience in one or more of these areas" and "(3) an understanding of vector design and the effect of LCR fragments on gene expression, including experience with how the LCR regulates gene expression." *Id.*

At this stage in the proceeding, Patent Owner does not dispute Petitioner's description of the level of ordinary skill in the art. *See* Prelim. Resp. Because Petitioner's uncontested definition of one of ordinary skill in

the art is reasonable and consistent with the '179 patent and the prior art of record, we adopt Petitioner's definition for purposes of this Decision.

C. Claim Construction

The Board applies 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. § 100(b) (2019). Under that standard, claim terms "are generally given their ordinary and customary meaning" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). "In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17).

Petitioner states that "no term of the '179 patent requires construction to resolve the challenges in this Petition." Pet. 22 (citing Ex. 1002 ¶¶ 49–50) (footnote omitted). Patent Owner does not argue for any express claim constructions. *See* Prelim. Resp.

Based upon our review of the current record, we determine that no claim terms require express construction for purposes of deciding whether to institute an *inter partes* review of the challenged claims. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (Only those terms that are in controversy need be construed, "and only to the extent necessary to resolve the controversy.").

D. Priority and Prior Art Status

1. The '179 Patent Priority Date

As noted above, the '179 patent issued from the '221 application filed on July 1, 2002. Ex. 1001, code (22). The '221 application claims priority to the '861 provisional application, filed June 29, 2001, and the '852 provisional application, filed on July 2, 2001. *Id.* code (60).

Petitioner asserts that "at least claims 1, 19, and 22 of the '179 patent cannot claim priority to either provisional because [the provisional applications] do not satisfy at least the written description requirements of 35 U.S.C. § 112 for these claims." Pet. 13; *see* Reply 4. As a result, Petitioner asserts that that "the earliest date to which these claims of the '179 patent may claim priority is July 1, 2002, the filing date of the ['221] application." *Id.*

Petitioner asserts particularly that the provisional applications do not provide written description support for "a nucleic acid encoding a functional globin," recited by independent claim 1 of '179 patent. *Id.* at 14 (citing Ex. 1002 ¶¶ 51–59). Petitioner asserts that the provisional applications disclose only wild-type human β-globin. *Id.* (citing Ex. 1034, 1; Ex. 1035, 1; Ex. 1002 ¶ 54). Petitioner contrasts that disclosure with the '179 patent, which Petitioner asserts describes a "'functional globin' genus [including] 'mutant forms of globin' as well as multiple different globin types (*i.e.*, α, β, or γ-globin)." *Id.* (citing Ex. 1001, 2:41–53; Ex. 1002 ¶ 53). Petitioner contends that human β-globin species is "merely a 'corner' of the vast 'functional globin' genus" and "is not representative of the other types of globin *(i.e.*, α and γ) or of mutants." *Id.* at 16 (quoting *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299–1300 (Fed. Cir. 2014)); Ex. 1002 ¶¶ 56–58. According to Petitioner, the provisional

applications, therefore, "would not inform a [POSA] that the named inventors possessed all recombinant vectors that can express a 'functional globin' from the claimed 3.2-kb LCR in a mammal *in vivo*." *Id.* at 16 (citing Ex. 1024, 107, 109; Ex. 1025, 305; Ex. 1002 ¶¶ 56–58); *see* Reply 3.

Patent Owner argues that the provisional applications "disclose 'functional' globin genes." Prelim. Resp. 23 (citing Ex. 2002 ¶¶ 60–68). Specifically, Patent Owner points to the disclosure in the provisional applications that "the vector of the invention is used in therapy for treatment of individuals suffering from hemoglobinopathies [disorders resulted from mutations in globin (alpha, beta, or gamma) genes]." *Id.* (quoting Ex. 1034, 3; Ex. 1035, 4) (bracketed portion added by Patent Owner). Additionally, Patent Owner notes that, for one embodiment, the provisionals state that "[t]he stable introduction of a functional β-globin gene in haematopoietic stem cells could be a powerful approach to treat β-thalassemia and sickle-cell disease," and exemplifies a "recombinant lentivirus [that] enables efficient transfer and faithful integration of the human β-globin gene together with large segments of its locus control region." *Id.* (citing Ex. 1034, 4; Ex. 1035, 5). Patent Owner argues that a POSA "would understand this to disclose an approach that could be used with different functional globin (*e.g.*, epsilon, gamma, or other beta) genes as well as one specific example with regard to a successfully tested vector, *i.e.*, the TNS9 vector, using a human β-globin gene." *Id.* at 23–24 (citing Ex. 2002 ¶¶ 61–68; Ex. 2009 ¶¶ 14–15; Ex. 1036, 115–116).

Moreover, Patent Owner argues that "it was understood in the 1990s that 'the human beta-globin locus control region (LCR) is essential for high-level expression of human epsilon-, gamma-, and beta-globin genes.'" *Id.* at 24 (quoting Ex. 2011, 1). Based on that knowledge, Patent Owner asserts

that "a POSITA would understand that the human β-globin LCR region described in the Provisionals could be used with an epsilon-, gamma-, or other beta-globin gene — which had little variation in their common structure and characteristics — to similar effect." *Id.* (citing Ex. 2002 ¶ 63; Ex. 2009 ¶¶ 14–15).

Petitioner replies that Patent Owner appears to incorrectly apply an obviousness standard to show possession by asserting that a POSA would understand that the provisional applications disclose "an approach that *could be* used with different functional globin . . . to similar effect," and that "by substituting the nucleotide sequence of said globin gene(s) during the construction of the vector(s), different globin genes *would be* expressed," and "*would result* in increased expression of said genes." Reply 4 (quoting Prelim. Resp. 23–24). Petitioner asserts that Patent Owner's argument "recognizes that changes would need to be made to the vector for the possibility to allow for expression of other globin," and those changes are "not described in the provisional applications." *Id.* at 5 (citing Prelim. Resp. 24).

Patent Owner distinguishes the '179 patent claims from those in *Abbvie*, in which "the challenged claims were directed to a genus of *new* anti-human IL-12 antibodies," defined only by their functions. Prelim. Resp. 26 (citing *AbbVie*, 759 F.3d at 1292). Patent Owner contends that "[u]nlike *Abbvie*, the claims here are not directed to a new 'functional globin' but rather to a vector containing nucleotide fragments from a known LCR that served to regulate the expression of known functional globins." *Id.* (citing Ex. 1001, 11:54–14:28; Ex. 2002 ¶¶ 60–68).

Petitioner replies that Patent Owner does not distinguish *Abbvie*. Reply 5. Rather, Petitioner argues that the claims do not merely recite a

globin, but a vector that encodes a functional globin expressed in mammals *in vivo*. *Id.* In other words, Petitioner argues that, "like in *Abbvie*, the claims here *do* require a functional result." *Id.* (citing Pet. 16). Petitioner assert that also similar to *Abbvie*, "the provisional applications fail to establish a reasonable structure-function relationship between the claimed vector and all possible functional globins." *Id.* (citing *Abbvie*, 749 F.3d at 1301).

Patent Owner responds that "the invention is directed to a vector having novel LCR fragments that results in expression of known globin genes." Sur-reply 5 (citing Prelim. Resp. 9, 13). According to Patent Owner, [t]he Provisionals, which reproduce the *Nature* Article in full, make clear that the disclosed principles could be extended to express other globin genes, (Ex. 1005 at 6; Exs. 1034–35), which was well understood by POSITAs." *Id.*

In addition to the disclosures of the '179 patent and the provisional applications, both parties address the Examiner's treatment of priority during prosecution of the '179 patent. Petitioner asserts that the Examiner repeatedly rejected claims to a recombinant vector "comprising a region encoding a functional β-globin gene" on written description grounds. Pet. 16 (citing Ex. 1032, 169–170, 225–229). Petitioner asserts that, in amending the claims to overcome the written description rejection, the Patent Owner cited a disclosure in "the '221 application describing a 'functional globin,' which ***has no counterpart*** in the [provisional applications]." *Id.* at 16–17 (citing Ex. 1032, 236, 245); *see* Ex. 1032, 3:24–26 ('221 Application describing the term "functional globin gene").

Patent Owner argues that the Examiner apparently applied the provisional filing dates because the Examiner's rejection of the claims as

anticipated by the May Article was under 35 U.S.C. § 102(a), not § 102(b). Prelim. Resp. 21 (citing Ex. 1032, 19, 63). Patent Owner further argues that the Examiner acknowledged that the pending claims were entitled to the provisional applications' filing dates by accepting *Katz* declarations to obviate the May Article as a prior art reference. *Id.* (citing Ex. 1032, 83–90, 104).

"Patent claims are awarded priority on a claim-by-claim basis based on the disclosure in the priority applications." *Lucent Technologies, Inc. v. Gateway, Inc.*, 543 F.3d 710, 718 (Fed. Cir. 2008). To receive the benefit of a previous application, *every feature* recited in a particular claim at issue must be described in the prior application. *See In re Van Langenhoven*, 458 F.2d 132, 137 (CCPA 1972) ("[T]he fact that *some* of the elements of the breech claims have the support of the parent and foreign applications does not change the result. *As to given claimed subject matter, only one effective date is applicable.*" (emphases added)); *accord In re Chu*, 66 F.3d 292, 297 (Fed. Cir. 1995).

As the Federal Circuit has noted, however, "[i]n order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Rather, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

Based on our consideration of the arguments and evidence presented at this stage of the proceeding, we determine, for purposes of this Decision, that claims 1, 19, and 22 of the '179 patent are not entitled to receive benefit

of the filing date for either the '861 provisional application or the '852 provisional application. In particular, we find persuasive Petitioner's arguments that the provisional applications do not satisfy the written description requirements of 35 U.S.C. § 112 for those claims. Independent claim 1 recites, in part, "[a] recombinant vector comprising a nucleic acid encoding a functional globin operably linked to a 3.2-kb nucleotide fragment . . . said vector providing expression of the globin in a mammal in vivo." Ex. 1001, 11:55–64. Based upon our review, we agree with Petitioner that this limitation is not adequately described in the provisional applications. The '179 patent Specification (and the '221 Application) describe the term "functional globin gene" as:

> [A] nucleotide sequence the expression of which leads to a globin that does not produce a hemoglobinopathy phenotype, and which is effective to provide therapeutic benefits to an individual with a defective globin gene. The functional globin gene may encode a *wild-type globin* appropriate for a mammalian individual to be treated, or it may be a *mutant form of globin*, preferably one which provides for superior properties, for example superior oxygen transport properties. . . . Suitably, *the globin may encode α-globin, β-globin, or γ-globin*.

Ex. 1001, 2:41–52 (emphasis added); *see also* Ex. 1032, 3:24–4:3 (same). Based on this description, we agree with Petitioner that the '179 patent claims cover a recombinant vector comprising a nucleic acid encoding a "functional globin" genus that includes wild-type globin and mutant forms of globin, wherein the globin may encode different globin types, i.e., *α*-, *β*-, *or γ*-globin.

Patent Owner does not identify, nor do we see, any portion of the provisional applications describing the genus of functional globin. Rather, as Petitioner demonstrates, the provisional applications describe one species

of that genus, i.e., the wild-type human β-globin. Pet. 14–17. The provisionals do not describe the "functional globin" genus. Indeed, as Petitioner correctly asserts, during the '179 patent prosecution, Applicants/Patent Owner, relied on a description of "functional globin," quoted above, that does not appear and has not counterpart in the provisional applications. *Compare* Ex. 1001, 2:42–52 *and* Ex. 1032, 3:24–4:3 *with* Ex. 1034 *and* Ex. 1035.

Patent Owner urges us to find written description support for the genus of functional globin genes from the disclosure in the provisional applications that "the vector of the invention is used in therapy for treatment of individuals suffering from hemoglobinopathies [disorders resulted from mutations in globin (alpha, beta, or gamma) genes]." Prelim. Resp. 23 (quoting Ex. 1034, 3; Ex. 1035, 4). However, as Petitioner notes, the bracketed portion in Patent Owner's quote referring to "mutations in globin (alpha, beta, or gamma) genes" is not described in the provisional applications. Rather, that description was added by Patent Owner when quoting the provisionals in the Preliminary Response. Patent Owner asserts that missing description of "mutations in globin (alpha, beta, or gamma) genes" does not add to the provisional applications, but instead "provide[s] an uncontested understanding of hemoglobinopathies, i.e., disorders resulting from mutations in (alpha, beta, or gamma) genes fully supported by the known scientific literature." Sur-reply 3. However, Patent Owner has not shown that the provisional applications describe treating every type of hemoglobinopathies. Rather, as Petitioner notes, the provisionals mention only two disorders, each of which result from mutations in human β-globin, i.e., β-thalassemia and sickle-cell disease. Ex.1034, 2; Ex. 1035, 2;

Ex. 1002 ¶¶ 21, 23. The description of those diseases is consistent with the remainder of the provisional applications' disclosure, which is limited to vectors "capable of providing therapeutically meaningful levels of human β-globin." Ex. 1034, 2; Ex. 1035, 2.

Although "it is unnecessary to spell out every detail of the invention in the specification," satisfying the written description requirement still demands that enough detail "must be included to convince a person of skill in the art that the inventor possessed the invention." *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (citation omitted). Here, we do not find sufficient evidence demonstrating that the claimed recombinant vector comprising a nucleic acid encoding any functional globin was in the possession of the inventors.

Patent Owner's assertions that a POSA would understand the provisional applications to "disclose an approach that could be used with different functional globin (*e.g.*, epsilon, gamma, or other beta) genes," Prelim. Resp. 23–24, and that "a POSITA would understand that the human β-globin LCR region described in the Provisionals could be used with an epsilon-, gamma-, or other beta-globin gene," *id.*, are insufficient to demonstrate written description as they rely on what may have been obvious for a POSA to try rather than what is actually described in the provisionals. *See Lockwood v. American Airlines*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991)) ("One shows that one is 'in possession' of *the invention* by describing *the invention*, with all its claimed limitations, not that which makes it obvious.").

Based on the foregoing, we agree with Petitioner that neither the '861 provisional application nor the '852 provisional application provide written

description support for independent claim 1 of the '179 patent. The same is true for dependent claim 22. Claim 22 recites that the vector is a lentiviral vector. Claim 22 is directed to the same "functional globin" genus recited in claim 1, which is inadequately described in the provisionals. Similarly, the provisionals lack written description support for dependent claim 19. Claim 19 recites that "the functional globin is a β-globin," which includes the human β-globin described in the provisionals, but also includes other β-globin, e.g., mutant β-globin. For the same reasons discussed regarding claim 1, we do not find that the provisionals adequately describe the scope of β-globins in a manner that would inform a POSA that the inventors possessed all recombinant vectors that can express a functional globin that is a β-globin from the claimed LCR in a mammal *in vivo*.

Accordingly, for purposes of institution, we are persuaded that claims 1, 19, and 22 of the '179 patent are not entitled to receive benefit of the filing date for the '861 provisional application or the '852 provisional application. Thus, for purposes of this Decision, claims 1, 19, and 22 have a priority date of July 1, 2002, the filing date of the '221 application.

It remains undisputed at this stage of the proceeding that claim 10, limited to recombinant vectors "wherein the functional globin is human β-globin," is entitled to receive benefit of the '861 provisional application filing date, i.e., June 29, 2001. *See* Pet. 13–17 (challenging priority date for claims 1, 19, and 22 only). Claim 10 is not included in the grounds that rely on the May Thesis or the May Article. *See* Pet. 4–5.

In the following discussion we address the prior art status of the cited references, in view of our preliminary determination regarding the priority dates for the challenged claims.

2. Prior Art Status of Petitioner's Cited References

a) May Thesis and May Article

Petitioner asserts that the May Thesis, dated May 2001, was "publicly available on ProQuest by at least November 26, 2001." Pet. 17 (citing Ex. 1004, cover; Ex. 1036 ¶¶ 1–26). Petitioner asserts that "[t]he *May Thesis* is prior art to the '179 patent under 35 U.S.C. §§ 102(a) and (b) based on the July 1, 2002 priority date" and "because it has a different inventive entity than the '179 patent." *Id.* at 17–18 n.7.

Petitioner asserts that the May Article was published as of July 6, 2000 and has a different inventive entity than the '179 patent. *Id.* at 18–19 n.8. Petitioner contends that "[t]he *May Article* is prior art to the '179 patent under 35 U.S.C. §§ 102(a) and (b) based on the July 1, 2002 priority date, and prior art to the '179 patent under at least 35 U.S.C. § 102(a) based on the earliest possible priority date listed on the face of the '179 patent, June 29, 2001." *Id.* at 19 (footnote omitted).

Patent Owner argues that the May Thesis and May Article do not qualify as prior art under 35 U.S.C. § 102(b), assuming the '179 patent properly claims the benefit of priority to an earliest filing date of June 29, 2001. Prelim. Resp. 27–29. Both references have an earliest publication date that is less than one year before June 29, 2001, as the May Article was published July 6, 2000 and the May Thesis lists an earliest date of May 2001.[12] *Id.*

Patent Owner argues that the references do not qualify as prior art under 35 U.S.C. § 102(a) because they constitute the inventors' own work.

[12] Patent Owner argues that "the May Thesis became publicly available on November 26, 2001." Prelim. Resp. 28.

Id. at 29–31. Patent Owner argues that during the prosecution of the '221 application, every "inventor submitted a declaration attesting to the fact that they are the inventors of the subject matter disclosed in the [May] Article and that other listed authors are not inventors." *Id.* at 30 (citing Ex. 1032, 63, 80–90, 120). Patent Owner submits new declarations from the inventors explaining "that the additional co-authors of the [May] Article made non-inventive contributions to the testing of the TNS9 vector." *Id.* at 30–31 (citing Ex. 2006 ¶¶ 35–40; Ex. 2007 ¶¶ 19–20; Ex. 2008 ¶¶ 20–24). Patent Owner similarly argues that the "May Thesis is authored solely by May, a '179 Patent inventor." *Id.* at 31 (citing Ex. 1001, code (75); Ex. 1004; Ex. 2007 ¶ 23).

Additionally, Patent Owner argues that the May Thesis and May Article cannot serve as invalidating art under Section 102(a) because the inventors of the '179 patent conceived of and reduced the invention to practice before the May Article or May Thesis were published. *See id.* at 32–34. Specifically, Patent Owner argues that the inventors reduced the invention to practice in the form of the TNS9 vector, which was the subject matter of the May Article and May Thesis. *See id.* at 34 (citing Ex. 1004, 73–104; Ex. 1005, 3–6; Ex. 2002 ¶¶ 80, 87–88, 95–96).[13]

[13] We have additionally considered Patent Owner's argument that the May Article cannot serve as invalidating art based on an alleged prior conception and diligence. However, we find that showing deficient on the current record, for a number of reasons, including insufficient evidence demonstrating that an embodiment meeting all limitations of the challenged claims was reduced to practice prior to the effective date of the May Article, or that the invention was conceived prior to the effective date of that reference and coupled with due diligence in reducing it to practice. *See Apator Miitors ApS v. Kamstrup A/S*, 887 F.3d 1293 (Fed. Cir. 2018). In any event, we do not further address this alternative argument as we

As discussed above in Section II.D.1., we have determined, based on the current record, that claims 1, 19, and 22 are not entitled to receive benefit of the provisional applications' filing date. As we explained, for purposes of this Decision, we recognize a priority date of July 1, 2002, the filing date of the '221 application, for those claims.

Next, we consider whether Petitioner has established that the May Thesis and the May Article are prior art to those claims under 35 U.S.C. § 102(a) or § 102(b). We begin with a determination that Patent Owner has shown persuasively, at this stage in the proceeding, that the May Thesis and the May Article represent the inventors' own work.

The May Thesis is authored by only Chad May, who is a listed inventor of the '179 patent. Ex. 1004, 3: Ex. 1001 (75).

The May Article is authored by Chad May, along with six other individuals, Stefano Rivella, John Callegari, Glenn Heller, Karen Gaensler, Lucio Luzzatto, and Michel Sadelain. Ex. 1005, 3. May, along with Rivella and Sadelain are listed inventors for the '179 patent. Ex. 1001 (75). Patent Owner has submitted declarations from May, Rivella, and Sadelain attesting to the fact that they are the inventors of the subject matter disclosed in the May Article and that the additional co-authors of the article made only non-inventive contributions to the testing of the TNS9 vector. *See* Prelim. Resp. 30–31 (citing Ex. 2006 ¶¶ 35–40; Ex. 2007 ¶¶ 19–20; Ex. 2008 ¶¶ 20–24). Patent Owner has also submitted the declaration of Lucio Luzzatto who declares that he is listed as an author on the May Article but did not contribute to the new vector design. Ex. 2009 ¶¶ 16–17. Petitioner

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determine for a separate reason that the May Article does not qualify as 102(a) prior art.

identifies no reason for us to question the veracity or sufficiency of those declarations at this stage in the proceeding.

Accordingly, based on the current record, because Patent Owner has shown persuasively that the May Thesis and the May Article represent the work of the '179 inventors, those references are ineligible as prior art under 35 U.S.C. § 102(a) for challenged claims 1, 19, and 22. *See In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982).

With respect to 35 U.S.C. § 102(b), we find that the May Thesis remains ineligible as prior art. Petitioner provides evidence that the May Thesis was publicly available as of November 26, 2001. Pet. 17 (citing Ex. 1036 ¶¶ 1–26; Ex. 1002 ¶ 60). Patent Owner does not dispute that evidence. Based on the undisputed November 26, 2001 public availability date, the May Thesis represents a disclosure less than one year before the effective filing date, i.e., the July 1, 2002, for claims 1, 19, and 22 challenged with this reference. Based on that timing and because the disclosure was made by the inventor, the May Thesis is not available as prior art to challenged claims 1, 19, and 22 under 35 U.S.C. §102(b).

The May Article, on the other hand, is eligible as prior art under Section 102(b). Petitioner provides evidence that the May Article was publicly available as of July 6, 2000. Pet 19 (citing Ex. 1036 ¶¶ 27–45; Ex. 1002 ¶ 63). Patent Owner acknowledges that publication date also. Prelim. Resp. 33. Based on the undisputed July 6, 2000 public availability date, the May Article represents a disclosure made more than one year before the effective filing date, i.e., July 1, 2002, for claims 1, 19, and 22 challenged with this reference. Therefore, the May Article may be applied as prior art to challenged claims 1, 19, and 22 under Section 102(b).

b) May Abstract

Petitioner asserts that the May Abstract "was presented at the Third Annual Meeting of the American Society of Gene Therapy ("ASGT") held from May 31-June 4, 2000, in Denver, Colorado" and "published in print in the May 2000 edition of *Molecular Therapy*—ASGT's flagship journal." Pet. 20–21 (citing Ex. 1040, S1; Ex. 1041, 96; Ex. 1042; Ex. 1002 ¶ 69; Ex. 1038, 2; Ex. 1042; Ex. 1006). Based upon those publications, Petitioner contends that "[t]he *May Abstract* is prior art to the '179 patent under 35 U.S.C. §§ 102(a) and (b) based on the earliest possible priority date listed on the face of the '179 patent, June 29, 2001." *Id.* at 21.

Patent Owner argues that Petitioner fails to "prove the May Abstract is a 'printed publication' as of May 1, 2000." Prelim. Resp. 37. Patent Owner argues that Dr. Yee's reliance on the "date on the face of the document to prove public availability *constitutes inadmissible hearsay*, which justifies denying the Petition." *Id.* at 38 (citing *ServiceNow, Inc. v. Hewlett-Packard Co.,* IPR2015-00716, Paper 13, 16 (PTAB Aug. 26, 2015); *Apple, Inc. v. DSS Tech. Mgmt., Inc.*, IPR2015-00369, Paper 14, 6 (PTAB Aug. 12, 2015)). Patent Owner further argues that "[n]either of the two URLs relied upon by Dr. Yee have any record of being available in or around 2000." *Id.* (citing Ex. 2002 ¶¶ 82–83).

Petitioner has the burden to prove that the May Abstract qualifies as prior art. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1376 (Fed. Cir. 2016). "[A]t the institution stage, the petition must identify, with particularity, evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent and therefore that there is a reasonable likelihood that it qualifies as a printed publication." *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-

01039, Paper 29 ("*Hulu*") at 13 (PTAB Dec. 20, 2019) (precedential).

"Public accessibility" is considered to be "the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. §102(b)." *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)).

A determination whether a particular reference qualifies as a printed publication "is a legal determination based on underlying fact issues, and therefore must be approached on a case-by-case basis." *Hall*, 781 F.2d at 899. In a proceeding before the Board, there is no presumption in favor of finding that a reference is a printed publication. *Hulu*, Paper 29 at 16.

Having considered the arguments and the evidence, we determine that, for purposes of institution, and based on the totality of the evidence currently in the record, Petitioner has established a reasonable likelihood that the May Abstract is a printed publication that was publicly accessible before the critical date of the challenged patent, and therefore, qualifies as prior art. As discussed in *Hulu*, "the indicia on the face of a reference, such as printed dates and stamps, are considered as part of the totality of the evidence." *Hulu* 17–18. Here, the May Abstract includes indicia that the abstract was published in May 2000 in the Molecular Therapy, a journal of The American Society of Gene Therapy. Ex. 1006, 3. Thus, we consider that indicia, along with Petitioner's additional evidence of public accessibility.

Petitioner's declarant, Dr. Yee, provides a description of the Molecular Therapy journal as "the leading journal for research in the areas of gene transfer, vector development and design, stem cell manipulation," and explains that the journal is available in print and electronically. Ex. 1036 ¶ 51. Dr. Lee declares that "[a] common publishing practice of electronic journals is to mark the date of document availability clearly on the document webpage to inform the public of the public availability date of a document." *Id.* Mr. Lee then demonstrates that the webpage containing the May Abstract shows a publication date for the reference is "May 01, 2000." *Id.* Based on that information, Dr. Lee explains that his opinion is that the May Abstract was first publicly available on May 1, 2000, and "[a]s of that date, interested users would have been able to discover this webpage on the Internet to use the Web version of this work and the *May Abstract*." *Id.*

Based on the current record, we find that Dr. Lee's testimony, taken together with the indicia on the May Abstract itself, credibly supports Petitioner's contention that the May Abstract was made available in a manner that allowed persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence to locate it as of May 1, 2000.

Accordingly, we determine on the current record that Petitioner has adequately shown for institution that the May Abstract was publicly accessible before the critical date.

To the extent that Patent Owner asserts that the May Abstract is the work of the inventors of the '179 patent, *see* Prelim. Resp. 34 n.5, the reference is still available as Section 102(b) prior art with respect to claims 1, 19, and 22, based on the May 1, 2000 public availability date of the May Abstract, because it was disclosed more than one year before the effective filing date, i.e., July 1, 2002, for claims 1, 19, and 22 challenged with this

reference. *See* 35 U.S.C. § 102(b). Similarly, the May Abstract is available as Section 102(b) prior art with respect to claim 10, which is entitled to a priority date of June 29, 2001, because the May Abstract was disclosed more than one year before that date, as well. Therefore, the May Abstract may be applied as Section 102(b) prior art for challenged claims 1, 10, 19, and 22.

E. Principles of Law for Anticipation and Obviousness

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Schering Corp. v. Geneva Pharms*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). "An obviousness determination requires finding both '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.'" *CRFD Research, Inc. v. Matal*, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)).

Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the patent's invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the challenged

claims would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984); *see also Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Leapfrog Enters., Inc. v. Fisher–Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).[14]

F. Anticipation Based on the May Thesis

Petitioner asserts that the May Thesis anticipates claims 1, 19, and 22. Pet. 23–26. Patent Owner disagrees. Prelim. Resp. 27–37.

1. May Thesis

May Thesis describe s therapeutic haemoglobin synthesis in β-thalassemic mice expressing lentivirus-encoded human beta-globin. Ex. 1004, 3. May Thesis discloses recombinant lentivirus vector TNS9. *Id.* at 74. The TNS9 vector is illustrated in Figure 4.01(b), reproduced below:

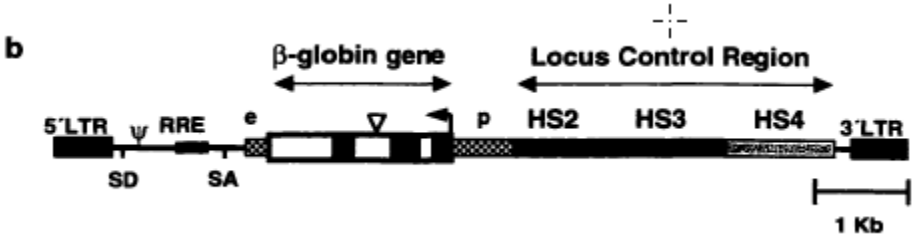

Figure 4.01(b) illustrates the TNS9 vector with exons represented by filled boxes and introns represented by open boxes. *Id.* The TNS9 vector includes, from the 5′ end to the 3′ end, a splice donor (SD), packaging region (Ψ), rev-response element (RRE), splice acceptor (SA), 3'-β-globin enhancer (E), β-globin gene, human β-globin promoter (P), and LCR (including HS2, HS3, and HS4). *Id.* The 5′ and 3′ ends include long terminal repeat (LTR) sequences. *See id.*, Fig. 4.01(b). May Thesis discloses that the TNS9 LCR element (Fig. 4.01b) includes an 840 bp HS2 fragment *(SnaBl-BstXI)*, a

[14] At this stage of the proceeding, Patent Owner does not assert evidence of objective indicia supporting nonobviousness of the challenged claim.

1308 bp HS3 fragment *(HindUI-BamHI Banll*), and a 1069 bp HS4 fragment (*BamHI-Banll)* to generate a 3.2 kb LCR element. *Id.* at 75.

2. Discussion

As discussed above in sections II.D.2.a., Petitioner has not established that the May Thesis is prior art to claims 1, 19, and 22. Consequently, Petitioner has not shown a reasonable likelihood of prevailing in its challenge of these claims based upon the May Thesis.

G. Anticipation Based on the May Article

Petitioner asserts that claims 1, 19, and 22 are anticipated by the May Article. Pet. 26–33. Patent Owner disagrees. Prelim. Resp. 44–48.

1. May Article

The May Article describes therapeutic hemoglobin synthesis in β-thalassemic mice expressing lentivirus-encoded human β-globin. Ex. 1005, 82. The May Article describes constructing two recombinant lentiviruses carrying β-globin transcription units. *Id.* The lentiviruses including RNS1 containing "a minimal LCR comprising previously tested core elements of HS2, HS3 and HS4," and TNS9 containing "large fragments encompassing HS2, HS3 and HS4 were introduced instead of the corresponding core elements." *Id.* The TNS9 vector is shown in Figure 1b, reproduced below:

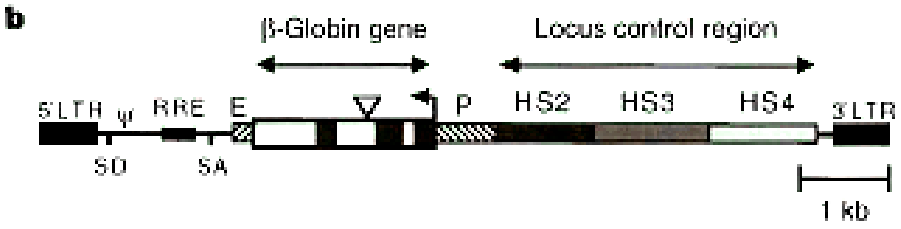

Figure 1b illustrates the TNS9 vector with the exons represented by filled boxes and the introns represented by open boxes. *Id.* The TNS9 vector includes, from the 5′ end to the 3′ end, a splice donor (SD), packaging

region (Ψ), rev-response element (RRE), splice acceptor (SA), 3'-β-globin enhancer (E), β-globin gene, human β-globin promoter (P), and LCR (including HS2, HS3, and HS4). *Id.* The 5′ and 3′ ends include long terminal repeat (LTR) sequences. *See id.*, Fig. 4.01(b). The May Article discloses that "TNS9 was generated by replacing the core HS2 element of RNS1 with an 840-bp HS2 fragment, the core HS3 element with a 1,308-bp HS3 fragment, and the core HS4 element with a 1,069-bp HS4 fragment." *Id.*

2. Discussion

Petitioner identifies the disclosures in the May Article that Petitioner asserts disclose each element of claims 1, 19, and 22. *See* Pet. 26–36. Specifically, Petitioner asserts that May Article discloses a recombinant vector, TNS9, including a nucleic acid encoding a β-globin gene, e.g., a human β-globin gene, operably linked to an LCR consisting of large segments, which are composed of three fragments (HS2, HS3, and HS4) that are adjacent, i.e., contiguous to each other. *Id.* at 26–27, 32 (citing Ex. 1005, 82–84). Petitioner asserts further that the May Article explains that the three fragments were "generated by replacing the core HS2 element . . . with an 840-bp HS2 fragment, the core HS3 element . . . with a 1,308-bp HS3 fragment, and the core HS4 element . . . with a 1,069-bp HS4 fragment." *Id.* at 27–28 (citing Ex. 1005, 82) (emphasis omitted). Additionally, Petitioner asserts that the May Article discloses that the HS2, HS3, and HS4 fragments "sum up to 3217 bp, or roughly 3.2 kb." *Id.* at 28 (citing Ex. 1002 ¶ 101). Petitioner also asserts that May Article discloses that the vector "*increased globin expression in vivo*." *Id.* at 32.

Petitioner contends that the May Article "teaches the restriction sites bounding the HS2, HS3, and HS4 fragments as recited in claim 1" by: (a)

disclosing the lengths of those fragments in the TNS9 vector as 840 bp, 1308 bp, and 1069 bp; and (b) depicting the fragments on a "drawn to scale" map of the LCR with a comparison, in size and placement, to previously published fragments for the core elements of HS2, HS3, and HS4 in a RNS1 vector. *Id.* at 28 (citing Ex. 1005, 82, Fig. 1(a); Ex. 1002 ¶¶ 103–118). Petitioner asserts that "[b]y July 1, 2002, the entire map of the LCR region was available to a POSA in the GenBank database under accession numbers 'HUMHBB,' 'U01317,' and 'NG_000007.1.'" *Id.* at 28–29 (citing Ex. 1016, 14903-05, Fig. 2; Ex. 1002 ¶¶ 104–105). Petitioner notes that Patent Owner recognized the knowledge in the art at the time of the invention during prosecution. *Id.* at 29 (citing Ex. 1032, 301) (explaining that the sequences provided by the GenBank Accession numbers "are the reference sequences for the human β-globin region and are well known to those of skill in the art").

Additionally, Petitioner asserts that "by July 1, 2002, a finite number of restriction enzymes, including *BstXI*, *SnaBl*, *BamHI*, *BamHIII*, and *Banll*, were available for sale through commercial sources." *Id.* at 30 (citing Ex. 1002 ¶ 106). Petitioner asserts that the specific sequences that these restriction enzymes recognized were also known at the time of the invention. *Id.* According to Petitioner, a skilled artisan would "have been able to map all of the possible restriction sites in the regions flanking the cores of HS2, HS3, and HS4." *Id.* (citing Ex. 1002 ¶¶ 107–110). Petitioner contends that, based on the disclosures in the May Article regarding the size and location of the TNS9's HS2, HS3, and HS4 fragments, "a POSA would have placed these fragments onto the restriction-site map of the LCR they would have had available at the time." *Id.* at 30–31 (Ex. 1002 ¶¶ 110–112). Petitioner asserts that "[i]n doing so, a POSA would have identified only six possible

combinations of restriction enzyme fragments, one of which is recited in claim 1." *Id.* at 31 (citing Ex. 1002 ¶¶ 112–117). Thus, Petitioner contends that, based on the May Article disclosures, a POSA would have "'at once envisage[d]' a limited class of restriction fragments." *Id.* (citing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381–83 (Fed. Cir. 2015) ("Thus, substantial evidence supports the Board's conclusion that [the prior-art reference] effectively teaches 15 combinations, of which one anticipates pending claim 1.")).

Patent Owner contends that Petitioner has not met its burden to show that claims 1, 19, and 22 are anticipated by the May Article. Prelim. Resp. 44–55. Patent Owner asserts that the May Article does not expressly or inherently disclose all of the claimed elements of the challenged claims. *Id.* at 44. In particular, Patent Owner asserts that nothing in the May Article discloses that the "BstXI and SnaBI HS2-," "BamHI and HindIII HS3-," or "BamHI and BanII HS4-" spanning nucleotide fragments were constructed by cutting them directly from a genomic DNA using restriction enzymes. *Id.* at 45 (citing Ex. 2002 ¶¶ 89, 104–115).

Patent Owner asserts that the reference instead discloses that the HS2, HS3, and HS4 fragments span 840-bp, 1308 bp, and 1069 bp, respectively. *Id.* According to Patent Owner, and its declarant, Dr. Riley, "[a] POSITA at the time would understand such fragments could be made in multiple different ways, including through amplification by polymerase chain reactions ('PCRs'), cutting from genomic DNAs using restriction enzymes, or otherwise." *Id.* (citing Ex. 2002 ¶¶ 89, 106–115). Patent Owner contends that "using PCR, a POSITA would understand that a fragment of a specific size could be amplified from any position along its corresponding full-length fragment in the LCR and would not be limited to known restriction sites."

Id. at 45–46 (citing Ex. 2002 ¶¶ 106–107). Patent Owner contends also that the POSITA could "obtain a fragment with any desired restriction site pair by using custom designed 5' and 3' primers." *Id.* at 46 (citing Ex. 2002 ¶ 107). Therefore, according to Patent Owner, the possible fragments spanning 840-bp, 1308 bp, and 1069 bp that could be created to encompass the HS core elements using PCR would be "astronomical." *Id.* at 45.

Patent Owner asserts further that, even if a POSITA considered generating fragments of specific size by directly cutting genomic DNA with restriction enzymes, they would be dissuaded from doing so because "there were no flanking restriction site pairs available, using the commercially available restriction enzymes identified by Petitioner's expert, to provide fragment sizes of exactly 840 bp, 1308 bp, and 1069 bp, respectively for the HS2, HS3, and HS4 fragments." *Id.* at 46 (citing Ex. 2002 ¶¶ 108–116) (emphasis omitted).

Based on our consideration of the current record, we do not find that Petitioner has shown a reasonable likelihood of establishing that the challenged claims are anticipated by the May Article. Petitioner has not shown that the May Article expressly discloses the restriction sites surrounding the hyper-specific sites, as required by the challenged claims. According to Petitioner, that limitation is inherently disclosed by the May Article's description of the lengths of the HS2, HS3, and HS4 fragments in the TNS9 vector and its depiction of those fragments on a map of the LCR. Pet. 28.

To further support its inherency argument, Petitioner additionally relies on knowledge in the art, i.e., the availability of the entire map of the LCR region, and the availability of restriction enzymes, including *BstXI*, *SnaBl*, *BamHI*, *BamHIII*, and *Banll*. *Id.* at 30. Based on that combined

information, Petitioner contends that a POSA would "have been able to map all of the possible restriction sites in the regions flanking the cores of HS2, HS3, and HS4." *Id.* Petitioner asserts further that "[g]iven the *May Article's* disclosure regarding the size and location of [TNS9's] HS2, HS3, and HS4 fragments, a POSA would have placed these fragments onto the restriction-site map of the LCR" that was available at the time, and would have identified only six possible combinations of restriction enzyme fragments, including the one recited in claim 1. *Id.* at 30–31.

Upon closer inspection, however, we appreciate from the testimony of Petitioner's declarant, Dr. Bungert, that the process involved in arriving at those six possible combinations requires a number of steps. *See* Ex. 1002 ¶¶ 112–117 (explaining that a skilled artisan would have performed steps including: (a) placing fragments that are the disclosed size of the HS2, HS3, and HS4 fragments from the TNS9 vector in the May Article onto the known restriction-site map of the LCR; (b) comparing those fragments to the "drawn to scale" map in the May Article; and then (c) identifying various fragments and determining which ones are consistent with the May Article's description and match up with the fragments on the May Article's drawn to scale map). In view of the steps required to get from what is disclosed in the May Article to arrive at the alleged "six possible LCRs (*i.e.*, combination of HS2, HS3, and HS4 fragments based on the TNS9 LCR disclosed in the *May Article*)—including the LCR recited in claim 1," Ex. 1002 ¶ 117, we do not find that Petitioner has demonstrated that fragments having the restriction sites recited in claim 1 would have been "immediately envisaged" by a skilled artisan. Indeed, we note that Dr. Bungert testifies only that the skilled artisan "would have envisaged" a limited number of possible restriction sites that could be used to generate these fragments, without

confirming that one would have done so "immediately" based upon the disclosure in the May Article. *See* Ex. 1002 ¶¶ 111, 116, 117.

Moreover, we find some merit in Patent Owner's argument that "[a] POSITA at the time would understand such fragments could be made in multiple different ways, including through amplification by polymerase chain reactions ('PCRs'), cutting from genomic DNAs using restriction enzymes, or otherwise." Prelim. Resp. 45 (citing Ex. 2002 ¶¶ 89, 106–115). Thus, Petitioner's assertion that a skilled artisan would have immediately envisaged fragments having the restriction sites in claim 1 is further undermined because there would have been more than one method of making the fragments disclosed in the May Article, one of which did not involve using restriction enzymes.

Accordingly, for at least the foregoing reasons, we find that Petitioner has not shown a reasonable likelihood of prevailing on its assertion that independent claim 1, or dependent claims 19 and 22 are anticipated by the May Article.

H. Obviousness Based on the May Article

Petitioner asserts that claims 1, 19, and 22 are anticipated and rendered obvious by the May Article. Pet. 33–36. Patent Owner disagrees. Prelim. Resp. 48–55.

1. Discussion

Petitioner asserts that, to the extent that the May Article is not considered to disclose "the three fragments being a BstXI and SnaBI HS2-spanning nucleotide fragment of said LCR, a BamHI and HindIII HS3-spanning nucleotide fragment of said LCR and a BamHI and BanII HS4-spanning nucleotide fragment of said LCR," as recited by claim 1, "that limitation nonetheless would have been obvious in view of the teachings of

the *May Article* and the knowledge of a POSA at the time of the alleged invention." Pet. 33. Petitioner relies on the same disclosures discussed for the anticipation challenge and asserts that, a POSA would have similarly "used the disclosures in the May Article regarding TNS9's LCR, especially given the general knowledge of the map of the LCR to identify the claimed restriction sites, and narrowed the options to a finite list of possibilities for HS2, HS3, and HS4." *Id.* at 34 (footnote omitted).

Petitioner asserts that a skilled artisan would have had a good reason to make the TNS9 vector disclosed in the May Article based on the findings therein that "the larger LCR fragments . . . increased globin expression *in vivo* and, furthermore, suggested that TNS9 is more resistant to transcriptional silencing." *Id.* at 35 (quoting Ex. 1005, 84; citing Ex. 1002 ¶ 132). Petitioner contends that a POSA would have reasonably expected that combining the teachings of the May Article with known elements in the field would have achieved the claimed HS2, HS3, and HS4 fragments "given the accessibility of the LCR map and the known commercially available restriction enzymes." *Id.* at 36 (citing Ex. 1002 ¶ 134). Moreover, Petitioner asserts that a POSA would have reasonably expected to succeed in making a recombinant vector with the claimed fragments as the method for doing so was well-known. *Id.* (citing Ex. 1018, 6; Ex. 1002 ¶ 134).

Patent Owner contends that Petitioner's assertion that a skilled artisan having reviewed the May Article "would have used a genomic map of the LCR region in combination with certain available restriction enzymes to map all of the possible restriction sites in the regions flanking the cores of the HS2, HS3, and HS4" is based on hindsight. Prelim. Resp. 51. Additionally, Patent Owner asserts that a skilled artisan would have been led away from using restriction enzymes to construct the fragments in the May

Article. *Id.* at 51–52. According to Patent Owner, "[h]ad a POSITA mapped all the possible restriction sites as Petitioner's expert did, they would have appreciated that no fragment, constructed using restriction enzymes, was exactly 840 bp, 1,308 bp, or 1,069 bp in length." *Id.* at 52 (citing Ex. 2002 ¶¶ 108–116; Ex. 1002, App'x A–C). Based on those results, Patent Owner asserts that "[a] POSITA would have been aware that the fragments could be constructed using PCR" and would have been "led to believe that PCR was likely used to create the restriction sites." *Id.* (citing Ex. 2002 ¶ 115).

Patent Owner argues further that, when using restriction enzymes, "Petitioner fails to look at 'all of the possible restriction site[]' options flanking the cores or to explain why certain options were excluded." *Id.* (citing Pet. 30). Patent Owner also alleges that Petitioner "fails to appreciate the significant experimentation it would take to arrive at just one of the possible combinations, using those available from both restriction enzymes, PCR, and/or another method." *Id.* at 54. Additionally, Patent Owner asserts that there would have been no "reasonable expectation of success in view of failures by others in generating a vector capable of providing high-level, stable expression of globin." *Id.* at 55.

Based on our consideration of the current record, we determine that Petitioner has shown a reasonable likelihood of establishing that the challenged claims are rendered obvious by the May Article. The dispute between the parties centers on whether Petitioner has shown that the May Article teaches or suggests the restriction sites surrounding the hyper-specific sites, recited by independent claim 1. At this stage in the proceeding, there is no dispute that the May Article discloses the remaining claim elements for each of the challenged claims, i.e., a recombinant

lentiviral vector comprising a nucleic acid encoding a functional β-globin operably linked to a 3.2-kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR), wherein said vector provides expression of the globin in a mammal in vivo. *See* Ex. 1001, claims 1, 19, 22. Thus, we focus the remainder of our discussion on the one element of the claims challenged by Patent Owner, i.e., the limitation reciting "the three fragments being a BstXI and SnaBI HS2-spanning nucleotide fragment of said LCR, a BamHI and HindIII HS3-spanning nucleotide fragment of said LCR." Ex. 1001, claim 1.

In addition to the foregoing undisputed disclosures in the May Article, Petitioner demonstrates persuasively that a skilled artisan would have known that the entire map of the LCR region was available at the time of the invention. Pet. 30, 33. Petitioner also provides persuasive evidence the skilled artisan would have known that certain restriction enzymes, including *BstXI*, *SnaBl*, *BamHI*, *BamHIII*, and *Banll*, were commercially available. *Id.* at 30, 33. Indeed, Patent Owner does not dispute those assertions. Based on that combined information, Petitioner contends, as discussed for the anticipation ground, that "a POSA would have identified only six possible combinations of restriction enzyme fragments, one of which is recited in claim 1." *Id.* at 34. Although we have determined, at this stage in the proceeding, that a skilled artisan would not have immediately envisaged those six possible combinations, as discussed for the anticipation ground, we find that the current record supports, sufficient for institution, that a skilled artisan would have been motivated to combine the teachings of the prior art references with the knowledge in the art to arrive at the claimed invention, with a reasonable expectation of success.

In particular, Petitioner explains persuasively that a "a POSA would have had a good reason to make the TNS9 vector identified in the *May Article* given the authors' disclosures that '[t]hese findings established that the larger LCR fragments . . . increased globin expression *in vivo* and, furthermore, suggested that TNS9 is more resistant to transcriptional silencing . . . than [the core elements].'" Pet. 35. Additionally, Petitioner has shown persuasively that a skilled artisan would have understood how to create the vector described in the May Article with the recited HS2, HS3, and HS4 fragments, with a reasonable expectation of success, as it "involved merely combining known elements in the field, (*i.e.*, the disclosed TNS9 vector fragments, as in the *May Article*, and a POSA's knowledge of the restriction-site map of the LCR) to yield a predictable result (*i.e.*, the claimed HS2, HS3, and HS4 fragments)." *Id.* at 35–36 (citing Ex. 1002 ¶ 133). Indeed, as outlined in our earlier discussion in Section II.G.2., Dr. Bungert testifies how a skilled artisan would have used the known restriction-site LCR map as a tool for engineering the vector disclosed by the May Article. Ex. 1002 ¶¶ 107–117. At this stage in the proceeding, and based upon the current record, we find Dr. Bungert's testimony credible and supported by the undisputed disclosures in May Article and the undisputed knowledge and skill in the art.

In reaching these determinations, we have considered Patent Owner's arguments. However, we do not find those arguments sufficiently supported at this stage in the proceeding to deny the Petition. Beyond the prior art status challenge of the May Article, addressed above in Section II.D.2.a., Patent Owner criticizes Petitioner's assertion that a skilled artisan would have used a genomic map of the LCR in combination with restriction enzyme to map the possible restriction sites for HS2, HS3, and HS4 by

arguing that it: (1) is based on hindsight; (2) would not have been a preferred method over using PCR to create restriction sites; (3) would have required significant experimentation without a reasonable expectation of success. Prelim. Resp. 51–54.

Patent Owner's hindsight argument lacks merit. According to Patent Owner, "Petitioner and its expert are using the claims, which disclose the use of restriction enzymes to construct the nucleotide fragments, as a hindsight guide to a POSITA, which is clearly prohibited." *Id.* at 51. Petitioner and Dr. Bungert, however, have explained persuasively how a skilled artisan may rely on the disclosures of the May Article and knowledge in the art to arrive at the claimed invention. Indeed, Patent Owner has acknowledged that a skilled artisan would have known that the fragments disclosed in the May Article could be made in different ways, including cutting from genomic DNAs using restriction enzymes. *See* Prelim. Resp. 45 (citing Ex. 2002 ¶¶ 89, 106–115).

To the extent that Patent Owner urges that a skilled artisan would have preferred using PCR over the method proposed by Petitioner for making the May Article fragments, we are unmoved. Patent Owner has not shown, nor do we see, any teaching or suggestion in the May Article, or based on knowledge or skill in the art, that would have excluded the use of restriction enzymes to make the May Article fragments. Nor do we find that the record supports Patent Owner's assertion that such use would have required significant experimentation without a reasonable expectation of success, as the restriction enzymes employed were commercially available, the sequences that the restriction enzymes recognized were known, and it was within the skill in the art to map all of the possible restriction sites in the regions flanking the cores of HS2, HS3, and HS4 at the time of the

invention. *See* Pet. 30 (citing Ex. 1002 ¶ 106). As Petitioner notes, Patent Owner/Applicant appears to have made statements during the prosecution of the '179 patent that acknowledge

> with respect to finding the sequences and ascertaining the claimed LCR, for all practical purposes at the time of the invention (and now), the skilled artisan would have immediately turned to the Genbank database to obtain the desired sequence, using a simple key word search without any need to know the accession numbers. Mapping the restriction sites would be done with any of a myriad of available software for analyzing sequence data.

Id. at 31 n.11 (quoting Ex. 1032, 302; citing Ex. 1002 ¶ 109).

Accordingly, for at least the foregoing reasons, we find that Petitioner has shown a reasonable likelihood of prevailing on its assertion that independent claim 1, and dependent claims 19 and 22 are rendered obvious by the May Article.

I. Obviousness Based on the May Abstract

Petitioner asserts that claims 1, 10, 19, and 22 are rendered obvious by the May Abstract. Pet. 36–42. Patent Owner disagrees. Prelim Resp. 55–61.

1. May Abstract

The May Abstract describes producing therapeutic levels of β-globin by lentiviral-mediated transfer of the human β-globin gene and large locus control region elements in long-term bone marrow chimeras. Ex. 1006, S248. May Abstract describes using recombinant lentiviruses to efficiently transfer and faithfully integrate "the human ß-globin gene together with large segments (3.2 kb) of its locus control region (LCR)." *Id.* May Abstract discloses the TNS9 vector that includes large LCR segments encompassed by hypersensitive sites 2, 3, and 4. *Id.* The "large LCR

fragments incorporated into the TNS9 lentiviral vector increased the probability and level of globin expression *in vitro* and *in vivo*." *Id.* at S249.

2. Discussion

Petitioner asserts that May Abstract discloses a recombinant vector TNS9, including a nucleic acid encoding human β-globin operably linked to a 3.2 kb nucleotide fragment which consists essentially of three contiguous nucleotide fragments obtainable from a human β-globin locus control region (LCR). Pet. 36–38. Petitioner also asserts that May Abstract discloses that the vector provides expression of the globin in a mammal *in vivo*, as required by the challenged claims. *Id.* at 41.

Petitioner asserts that the May Abstract "teaches or suggests the restriction sites bounding the HS2, HS3, and HS4 fragments as recited in claim 1, especially in light of what a POSA would have known at the time of the alleged invention." *Id.* at 38 (citing Ex. 1002 ¶¶ 145–165). Specifically, Petitioner asserts that "a POSA would have made use of the well-known LCR map and then-commercially available restriction enzymes to identify HS2, HS3, and HS4 fragments that fit a 3.2 kb LCR." *Id.* at 38 (citing Ex. 1002 ¶¶ 150-159, Appendices A–D).

Petitioner asserts here again that the entire map of the LCR was available as early as 1985 in the Genbank database. Pet. 28–29, 38 (citing Ex. 1016, 14903–05, Fig. 2; Ex. 1002 ¶¶ 104–105, 146–149). Petitioner further asserts that "by July 1, 2002, a finite number of restriction enzymes, including *BstX1*, *SnaBI*, *BamHI*, *HindIII*, and *BanII*, were available for sale through commercial sources such as New England Biolabs." *Id.* at 30, 38 (citing Ex. 1019, r192–93, r198–99, r207; Ex. 1002 ¶¶ 106, 146–149).

According to Petitioner, by applying conventional techniques, "a POSA would have grouped fragments having substantially similar flanking

sequences into 'clusters' of fragments expected to lead to comparable levels of globin expression." *Id.* at 38–39 (citing Ex. 1002 ¶¶ 150–159). As a result, Petitioner asserts that "a POSA would have identified 135 possible combinations of HS2, HS3, and HS4 fragment clusters—one of which includes the fragments recited in claim 1, and all of which would have been reasonably expected to provide globin expression in a mammal *in vivo*." *Id.* at 39 (citing Ex. 1002 ¶ 159).

Patent Owner argues that the May Abstract does not teach or suggest "the three fragments being a BstXI and SnaBI HS2-spanning nucleotide fragment of said LCR, a BamHI and HindIII HS3-spanning nucleotide fragment of said LCR and a BamHI and BanII HS4-spanning nucleotide fragment of said LCR," as recited in claim 1. Prelim. Resp. 55–56 (citing Ex. 2002 ¶¶ 130–154). Instead, Patent Owner argues that "Petitioner . . . uses hindsight reasoning and conjecture to argue that it would have been obvious to make three different nucleotide fragments having the exact same excision [sites] as claimed based only on the disclosure that the entire LCR region is 3.2 kb in length." *Id.* at 56 (citing Pet. 36–41). According to Patent Owner, Petitioner and its expert fail to adequately support their method of limiting the May Abstract potential restriction sites to 135 possibilities. *See id.* at 56–61.

Based on our consideration of the current record, we agree with Patent Owner that Petitioner has not shown sufficiently for institution that a skilled artisan would have been motivated with a reasonable expectation of success in arriving at the claimed invention based on the teachings and suggestions of the May Abstract. As acknowledged by Petitioner, the May Abstract does not disclose claim element the restriction sites bounding the HS2, HS3, and HS4 fragments as recited in claim 1. Pet. 38. Unlike in the May Article, the

May Abstract also does not disclose the length for the HS2, HS3, and HS4 fragments. As a result, Petitioner argues here that "a POSA would have made use of the well-known LCR map and then-commercially available restriction enzymes to identify HS2, HS3, and HS4 fragments that fit a 3.2 kb LCR." *Id.* (citing Ex. 1002 ¶¶ 150–59, Appendices A–D). To narrow those results, Petitioner asserts that "a POSA would have grouped fragments having substantially similar flanking sequences into 'clusters' of fragments expected to lead to comparable levels of globin expression." *Id.* at 38–39 (citing Ex. 1002 ¶¶ 150–159). Without providing much more detail, Petitioner concludes that "a POSA would have identified 135 possible combinations of HS2, HS3, and HS4 fragment clusters—one of which includes the fragments recited in claim 1, and all of which would have been reasonably expected to provide globin expression in a mammal *in vivo*." *Id.* at 39 (citing Ex. 1002 ¶ 159).

In view of the limited disclosures in the May Abstract, we agree with Patent Owner, *see* Prelim. Resp. 56, that Petitioner's rationale that it would have been obvious to make three different nucleotide fragments having the exact same excision cites as recited in claim 1 based on the May Abstract disclosure that the entire LCR region is 3.2 kb in length appears to be based on impermissible hindsight. Further, as Patent Owner asserts, Petitioner and Dr. Bungert fail to adequately explain and support their methodology for arriving at their identified 135 possible combinations of HS2, HS3, and HS4 fragment clusters, which include the fragments recited in claim 1. *See id.* at 57–59.

Accordingly, for at least the foregoing reasons, we find that Petitioner has not shown a reasonable likelihood of prevailing on its assertion that independent claim 1, or dependent claims 10, 19 and 22 are rendered obvious by the May Abstract.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood of prevailing in its assertion that at least one challenged claim of the '179 patent is unpatentable. Accordingly, in light of *SAS Institute Inc. v. Iancu*, 138 S. Ct. 1348, 1354 (2018), and the Patent Trial and Appeal Board Consolidated Trial Practice Guide 64 (Nov. 2019), *available at* https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf, we institute an *inter partes* review of the challenged claims on all asserted grounds.

Our determination in this Decision is not a final determination on either the patentability of any challenged claims or the construction of any claim term.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1, 10, 19, and 22 of the '179 patent on all grounds set forth in the Petition is instituted, commencing on the entry date of this decision; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of review.

FOR PETITIONER:

Naveen Modi
Eric Dittmann
Daniel Zeilberger
PAUL HASTINGS LLP
naveenmodi@paulhastings.com
ericdittmann@paulhastings.com
danielzeilberger@paulhastings.com

FOR PATENT OWNER:

Luke Toft
Joe Chen
FOX ROTHSCHILD LLP
ltoft@foxrothschild.com
joechen@foxrothschild.com