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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.,
Petitioner,

V.

GLAXOSMITHKLINE BIOLOGICALS SA,
Patent Owner.

Case IPR2019-00241
Patent No. 9,422,345 B2

Before SHERIDAN K. SNEDDEN, JO-ANNE M. KOKOSKI, and RICHARD J. SMITH, *Administrative Patent Judges.*

SMITH, *Administrative Patent Judge*.

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

I. INTRODUCTION

Merck Sharp & Dohme Corp. ("Petitioner") filed a Petition to institute an *inter partes* review of claims 1, 2, 4–14, and 16–21 ("the challenged claims") of U.S. Patent No. 9,422,345 B2 (the "'345 patent"). Paper 1 ("Pet.").

GlaxoSmithKline Biologicals SA ("Patent Owner") filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). Patent Owner, however, did not submit a declaration with its Preliminary Response. Furthermore, other than its claim construction arguments, and the argument that the '345 patent is entitled to a filing date of October 8, 2009, Patent Owner's Preliminary Response does not substantively address any of the validity challenges asserted by Petitioner. *See generally* Prelim. Resp.

We have authority under 35 U.S.C. § 314(a) to determine whether to institute an *inter partes* review. To institute an *inter partes* review, we must determine that the information presented in the Petition shows "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). For the reasons set forth below, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims of the '345 patent. Therefore, we institute an *inter partes* review for claims 1, 2, 4–14, and 16–21 of the '345 patent.

In instituting this *inter partes* review, we address the disputed issues raised by Patent Owner in its Preliminary Response.

A. Related Proceedings

Petitioner concurrently filed a second petition for *inter partes* review of the '345 patent on other grounds (IPR2019-00230), and previously filed petitions for *inter partes* review (now instituted) of U.S. Patent

No.9,265,839 (IPR2018-01234 and IPR2018-01237), and U.S. Patent No. 8,753,645 (IPR2018-01229 and IPR2018-01236). Pet. xvi; *see* Paper 4, 1.

B. The '345 Patent (Ex. 1001)

The '345 patent "relates to the field of the expression of bacterial toxins, in particular diphtheria toxins (including mutant forms of diphtheria toxin, such as CRM197)," and states that it "provides novel polynucleotides and polypeptides which can be used or produced during the processes of the invention." Ex. 1001, 1:9–15.

The '345 patent states that "CRM197 is a non-toxic form of the diphtheria toxin but is immunologically indistinguishable from the diphtheria toxin," and that CRM197 "differs from [diphtheria toxin] by a single base change in the structural gene . . . [leading] to a glycine to glutamine change of amino acid at position 52." *Id.* at 1:39–40, 44–48. CRM197 is a component in vaccines providing immunity against *C. diphtheriae*, and has been used in vaccines as safe and effective T-cell dependent carriers for saccharides. *Id.* at 1:52–54, 59–61. SEQ ID NO:32 in the '345 patent is the amino acid sequence for mature[1] CRM197. *Id.* at Fig. 9E.

The '345 patent also states that the disclosed polynucleotides comprise a 5' signal sequence portion and a 3' toxin portion wherein "(a) the 5' signal sequence portion encodes a polypeptide having an amino acid

[1] The '345 patent indicates that a "mature" bacterial toxin is one in which the signal peptide has been removed. Ex. 1001, 2:37–38; 16:10–13; *see also* Ex. 1002, 527 ("'Mature' refers to a diphtheria toxin polypeptide lacking the signal sequence, see e.g. paragraphs 0153 and 0204 of the present specification.").

sequence capable of directing transport of a heterologous protein to the bacterial periplasm and wherein the 5' signal sequence is not derived from *C. diphtheriae;"* and "(b) the 3' toxin portion encodes a polypeptide having an amino acid sequence at least 90% identical to SEQ ID NO: 32 or fragments thereof encoding at least 15 amino acids and/or at least one B or T cell epitope." *Id.* at 2:60–3:4. The '345 patent also describes various amino acid sequences of a signal peptide encoded by the 5' signal portion. *Id.* at 3:7–19.

C. Illustrative Claims

Claims 1 and 6 are the only independent claims:

> 1. A polynucleotide comprising a 5' signal sequence portion and a 3' toxin portion wherein:
>
> (a) the 3' toxin portion encodes a mature bacterial toxin polypeptide having an amino acid sequence at least 90% identical to SEQ ID NO: 32; and
>
> (b) the 5' signal sequence portion encodes a polypeptide having an amino acid sequence capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm when expressed in a bacterial host cell, and wherein the 5' signal sequence is not derived from *C. diphtheriae*.

Ex. 1001, 49:54–64.

> 6. A polynucleotide comprising a 5' signal sequence portion and a 3' toxin portion, wherein:
>
> (i) the 3' toxin portion encodes a mature bacterial toxin polypeptide having an amino acid sequence at least 90% identical to SEQ ID NO:32; and
>
> (ii) the 5' signal sequence portion encodes a polypeptide having an acid sequence capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm when expressed in a bacterial host cell, and wherein the 5' signal sequence is not derived from *C. diphtheria*, and wherein the encoded polypeptide has an amino acid sequence selected from:
>
> (a) SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26;
>
> (b) variants of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, or 26, varying from the corresponding sequences by

> 1, 2 or 3 point mutations, amino acid insertions or amino acid deletions, which variants are capable of directing transport of said bacterial toxin polypeptide to the periplasm of said bacterial host cell; and
>
> (c) fragments of at least 10 amino acids of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, or 26, which fragments are capable of directing transport of said bacterial toxin polypeptide to the periplasm of said bacterial host cell.

Id. at 51:13–37.

Claims 2, 4, 5, and 18–21 depend directly on claim 1, and claims 7–14, 16, and 17 depend directly on claim 6. *See id.* at 49:65–52:42.

D. The Asserted Grounds of Unpatentability

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. §§ 102 and 103 based on the following grounds.[2] Pet. 5.

Reference[s]	**Basis**	**Claims challenged**
Retallack[3]	§ 102(e)	1, 2, 18, 19, and 21
Retallack and Huber[4]	§ 103	4–14, 16, 17, and 20
Retallack-719[5]	§102(e)	1, 2, 18, 19, and 21
Retallack-719	§103	1, 2, 18, 19, and 21

[2] Petitioner states that all of the statutory bases are "Pre-AIA." Pet. 5.
[3] Retallack et al., WO 2011/123139, filed Apr. 9, 2010, published Oct. 6, 2011 ("Retallack"). Ex. 1009. Retallack claims priority to US Provisional Application 61/319,152, filed Mar. 30, 2010 ("Retallack Provisional"). Ex. 1071.
[4] D. Huber et al., *Use of Thioredoxin as a Reporter To Identify a Subset of Escherichia coli Signal Sequences That Promote Signal Recognition Particle-Dependent Translocation*, J. BACTERIOLOGY 187(9) (2005) ("Huber"). Ex. 1008.
[5] Retallack et al., US Patent No. 9,580,719 B2, filed Oct. 30, 2009, issued Feb. 28, 2017 ("Retallack-719"). Ex. 1010.

Retallack-719 and Huber	§103	4–14, 16, 17, and 20

Petitioner also relies on the Declaration of Matthew P. DeLisa, Ph.D. ("DeLisa Declaration" or "Decl."). Ex. 1006.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioner asserts that a person having ordinary skill in the art ("POSA"), as of October 7, 2010, would have "(a) possessed or have been pursuing a post-undergraduate degree, *e.g.*, Ph.D., in Bioengineering, Biomedical Engineering, Biomolecular Engineering, Chemical Engineering, Biotechnology, Biochemistry, Microbiology, Molecular Biology, or a comparable discipline, and (b) had at least 2-3 years of research experience relating to recombinant protein expression in bacteria." Pet. 5 (citing Ex. 1006 ¶ 22).

Patent Owner does not respond to Petitioner's proposed level of skill in the art or set forth an alternative description. *See generally* Prelim. Resp.

For purposes of this Decision, and based on the current record, we adopt Petitioner's assessment, which is undisputed and appears to be consistent with the level of ordinary skill in the art at the time of the invention as reflected in the prior art in this proceeding. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

In this *inter partes* review, filed November 7, 2018,[6] the claims of the '345 patent, which has not expired, shall be given their broadest reasonable construction in light of the specification. 37 C.F.R. § 42.100(b) (2018); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We emphasize that the following constructions are preliminary and invite the parties to develop them further during trial.

1. "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm"

Petitioner argues that this term is not defined in the specification of the '345 patent and should be given its plain and ordinary meaning in light of the specification. Pet. 23. Petitioner further argues that the claims are not limited to "expression in a particular type of bacteria, or require any particular amount of transport to the periplasm." *Id.* at 25–26.

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[6] The claim construction standard to be employed in *inter partes* review has changed for proceedings in which the petition was filed on or after November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42).

Patent Owner argues that Petitioner parses the phrase "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm" into two components, and ignores the express definition of that term provided in the specification of the '345 patent. Prelim. Resp. 6. In particular, Patent Owner refers to the statement in the '345 patent that

> [a] signal sequence ***is capable of directing an expressed protein to the periplasm*** if, when it is attached to a polypeptide of interest, during translation of the polypeptide in a gram negative bacteria, more of said polypeptide is found in the periplasm of a gram negative bacteria than in the absence of the signal sequence.

Id. at 7 (citing Ex. 1001, 7:33–39 (emphasis added by Patent Owner)). Patent Owner refers to this statement as an "express definition" of the disputed term provided by the inventors acting as lexicographers, and argues the meaning of the claim term is supported by the specification as a whole. *Id.* at 7–11.

We are not persuaded on this record and at this stage of the proceeding that the '345 patent expressly defines the term "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm." When a patentee seeks to act as its own lexicographer, it "must clearly express that intent in the written description." *See Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1381 (Fed. Cir. 2008). We find no such clearly expressed intention regarding the term "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm."

The phrase identified by Patent Owner as an express definition appears to describe whether a signal sequence is capable of achieving a particular function (directing an expressed protein to the periplasm) in a

particular type of bacteria (gram-negative). Namely, if more of the polypeptide of interest is found in the periplasm of a gram negative bacteria when a signal sequence is attached (during translation) than when the signal sequence is not attached to the polypeptide of interest, the signal sequence is "capable of directing an expressed protein to the periplasm." *See* Ex. 1001, 7:33–39. Here, independent claims 1 and 6 recite a polynucleotide, and thus the scope of the challenged claims depends on the structure of the polynucleotide (e.g. nucleotide sequence). The disputed claim term ("capable of . . ."), however, does inform the structure of the polynucleotide.

Giving the claim term its plain and ordinary meaning, we determine that the term "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm" means that the structure of the 5' signal sequence portion of the polynucleotide encodes a polypeptide having an amino acid sequence (claim 1) or acid sequence (claim 6) that is capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm when expressed in a bacterial host cell.

2. "wherein the 5' signal sequence is not derived from C. diphtheriae"

Petitioner argues that the term "wherein the 5' signal sequence is not derived from *C. diphtheriae*" means "wherein the signal sequence of a polypeptide is different in amino acid sequence to the signal sequence of the mature bacterial toxin polypeptide found in native (not recombinant) *C. diphtheriae*." Pet. 26.

First, Petitioner contends that, although that exact claim term is not defined in the '345 patent, "a similar term 'polypeptide **not derived from** *C. diphtheriae*' is defined as 'a polypeptide **which is different in sequence** to a polypeptide **found in native (not recombinant)** *C. diphtheriae.*'" *Id.* at 26–

27 (citing Ex. 1001, 7:22–24 (emphases added by Petitioner); Ex. 1006 ¶ 103). Second, Petitioner contends that "[a]lthough [Patent Owner] argued during prosecution that 'not derived from *C. diphtheriae*' excluded '**modified** native *C. diphtheriae* signal sequence[s],' that argument is irrelevant to the clear guidance supplied by the specification." *Id.* at 27 (citing Ex. 1002, 527 (emphasis added by Petitioner)).

Patent Owner disputes Petitioner's proposed construction and argues that the specification of the '345 patent does not expressly define the term "the 5' signal sequence is not derived from *C. diphtheriae*," and that, during prosecution, "Patent Owner expressly excluded all *C. diphtheriae* signal sequences from the scope of claim 1, whether having wild-type[7] or modified amino acid sequences." Prelim. Resp. 12–16; *see id* at 15 (citing Ex. 1002, 526–27). According to Patent Owner, Petitioner erred in taking the definition of a different term and modifying it, such that the resulting construction is completely detached from the specification and contradicts the prosecution history. *Id.* at 16. Patent Owner contends that because the term is not defined in the specification, it should be given its plain and ordinary meaning, which is "5' signal sequence that is not a wild-type or modified *C. diphtheriae* signal sequence." *Id.*

We agree that the term "wherein the 5' signal sequence is not derived from *C. diphtheriae*" is not defined in the specification of the '345 patent.

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[7] Patent Owner uses the term "wild-type," which it contends "refers to a naturally-occurring sequence found within the *C. diphtheriae* organism." Prelim. Resp. 12 n.2 (citing Ex. 2002, 1282). We use the term "native" because that is the term used by the Examiner and Patent Owner during prosecution of the '345 patent. *See* Ex. 1002, 511, 526–27; *see also* Ex. 3001, 689 (definition of "wild-type" in the Oxford Dictionary of Biology, 6th ed. (2008)).

Petitioner's attempt to apply the definition of another term to the term at issue does not meet the standards of clarity, deliberateness, and precision required for the definition of a claim term. *See Paulsen*, 30 F.3d at 1480. We also agree that the prosecution history should be considered in determining the meaning of the term. *See Trivascular,* 812 F.3d at 1062–64.

During prosecution of the '345 patent, Patent Owner added the claim term "wherein the 5' signal sequence is not derived from *C. diphtheriae*" in response to an anticipation rejection based on Murphy.[8] Ex. 1002, 522, 570–71, 574. According to the Examiner, Murphy disclosed "introducing a positively charged asparagine residue in the native diphtheria toxin signal to transport the tox polypeptide into the periplasmic compartment of the recombinant E. coli host." *Id.* at 511 (citing Ex. 3002, 12). In its Remarks regarding the amendment that added the claim term, Patent Owner stated that "Murphy discloses only the use of a modified native *C. diphtheriae* signal sequence," i.e., having an extra asparagine and proline residue. *Id.* at 526–27.

Based on the foregoing, we determine that the term "wherein the 5' signal sequence is not derived from *C. diphtheriae*" means a 5' signal sequence portion of a polynucleotide that encodes a polypeptide that is not derived from or originated from a native *C. diphtheriae* signal sequence, including a signal sequence that is not a native *C. diphtheriae* signal sequence and a signal sequence that is not a modified native *C. diphtheriae* signal sequence.

[8] Murphy, WO 90/10015, published Sept. 7, 1990 ("Murphy"). Ex. 3002.

3. Other Terms

Petitioner also advances proposed constructions for the terms "encodes a mature bacterial toxin polypeptide" and "an amino acid sequence at least 90% identical to" or "at least 95% sequence identity to." Pet. 20–23. Patent Owner does not challenge those proposed constructions in its Preliminary Response. *See generally* Prelim. Resp. We determine, however, for purposes of this Decision, that we need not expressly construe any undisputed terms. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'") (*quoting Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. Priority Date of the Challenged Claims

The '345 patent issued from national stage Application No. 13/500,244, that originated from PCT/EP2010/065047, filed October 7, 2010 (Ex. 1003, "the '047 PCT"). Ex. 1001, 1. The '047 PCT claims priority to Great Britain Patent Application No. 0917647, filed October 8, 2009 (Ex. 1004, "GB-647"). *Id*. Retallack (filed April 9, 2010)[9] and Retallack-719 (filed October 30, 2009) were filed after GB-647 but before the '047 PCT (October 7, 2010).

Petitioner argues that GB-647 does not provide written description support for the claim terms "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm" and "wherein the 5' signal

[9] Petitioner also cites the Retallack Provisional throughout the Petition along with Retallack. *See, e.g.*, Pet 35 (citing both Ex. 1009 and Ex. 1071). We refer herein to Retallack rather than the Retallack Provisional.

sequence is not derived from *C. diphtheriae*," such that the effective filing date of the '345 patent is no earlier than October 7, 2010. Pet. 28–35. Patent Owner disagrees, and seeks to predate Retallack and Retallack-719 by showing that the challenged claims are entitled to a filing date of October 8, 2009, the filing date of GB-647. Prelim. Resp. 16–31. Thus, according to Patent Owner, neither Retallack nor Retallack-719 is prior art to the '345 patent. *Id.* at 31.

Legal Standard

For a claim in a later-filed application to be entitled to the filing date of an earlier application, the earlier application must provide written description support under 35 U.S.C § 112, first paragraph,[10] for the claimed subject matter. *Anascape, Ltd. v. Nintendo of Am. Inc.*, 601 F.3d 1333, 1337 (Fed. Cir. 2010). To satisfy the written description requirement, "the disclosure of the earlier application, the parent, must reasonably convey to one of skill in the art that the inventor possessed the later-claimed subject matter at the time the parent application was filed." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998); *see also Hologic, Inc. v. Smith & Nephew, Inc.*, 884 F.3d 1357, 1361 (Fed. Cir. 2018). The written description inquiry is a question of fact. *Ariad Pharms. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Accordingly, "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.*

[10] Because the application that led to the '345 patent was filed before September 16, 2012, pre-AIA § 112 applies here. *See* Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 12–29, § 4(e), 125 Stat. 284, 297 (2011).

Discussion

We address the claim limitations that Petitioner contends do not have written description support in GB-647 to determine at this stage of the proceeding whether Retallack and Retallack-719 qualify as prior art to the challenged claims.

"capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm"

Petitioner contends that because the '345 patent expanded the scope of signal sequences "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm," GB-647 does not provide written description support for the challenged claims. Pet. 33–35. In particular, Petitioner refers to Table 1 and Example 5 of GB-647, and contends that GB-647 stated that there was no expression of four particular signal sequences (OmpA, FocC, Yra1, and PhtE), whereas that language was removed from the '345 patent, and the claims of the '345 patent recite that these four signal sequences are "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm." *Id.* (citing Ex. 1004, 10 (Table 1), 29–32; Ex. 1001, 19:58–20:54, 21:50–22:46). Thus, according to Petitioner, that "change demonstrates that [Patent Owner] was not in possession of the full scope of the claimed subject matter at the filing date of GB-647." *Id.* at 33, 35.

Patent Owner contends that Petitioner's position is inconsistent with the teachings of GB-647 and the '345 patent. Prelim. Resp. 24–31. Patent Owner points to Figure 5 in GB-647 and the identical Figure 5 in the '345 patent, illustrating expression of CRM197. *Id.* at 24–25. Patent Owner also refers to Petitioner's acknowledgement that the results of Example 5 had been achieved by the filing date of GB-647. *Id.* at 25 (citing Pet. 34

("Examples 1, 4, and 5 in the '345 patent describe the same experiments as Examples 1, 4, and 5 in GB-647.")). Patent Owner asserts that "Figure 5, Example 5, and Table 1 of the GB-647 priority application all describe the same results from the same experiments disclosed in the '345 patent," and "[t]he modified description of the inventors' already achieved results in the later-filed application does not amount to adding new matter." *Id*. at 26–27. Patent Owner also points to claim 1 of GB-647 as specifically reciting signal sequences OmpA, FocC, Yra1, and PhtE, and the claim limitation of "capable of directing an expressed protein to the periplasm." *Id.* at 29 (citing Ex. 1004, 35).[11]

On this record and at this stage of the proceeding, we find that GB-647 provides written description support for the claim limitation "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm." We agree with Patent Owner that Figure 5, Example 5, and Table 1 of GB-647 show that the inventors had possession of the limitation "capable of directing transport of said bacterial toxin polypeptide to the bacterial periplasm" as of the filing date of GB-647, particularly because GB-647's claims recite the same signal sequences and a similar claim term as the '345 patent. *Compare, e.g.*, claim 1 of GB-647 *with* claim 4 of the '345 patent.

"wherein the 5' signal sequence is not derived from C. diphtheriae"

Petitioner advances several arguments in support of its contention that GB-647 does not provide written description support for the claim limitation "wherein the 5' signal sequence is not derived from *C. diphtheriae.*" Pet.

[11] Patent Owner cites to the native page numbers of GB-647 (Ex. 1004).

29–33. For example, Petitioner argues that there is no disclosure of that limitation in GB-647. *Id.* at 29. In support of that argument, Petitioner notes that Table 2 of GB-647 does not disclose the origin of the listed signal sequences, but that their origin is disclosed in the corresponding Table 2 of the '345 patent, and that Patent Owner cited only to the application issuing as the '345 patent when it amended its claims during prosecution of the '345 patent to include the limitation "wherein the 5' signal sequence is not derived from *C. diphtheriae.*" *Id.* at 30–33.

Petitioner also argues that GB-647 defines the term "heterologous peptide" as a peptide that is not native to the cell type in which it is expressed, and that GB-647 further states that the polynucleotide comprises a 5' signal portion that encodes a heterologous polypeptide. *Id.* at 30 (citing Ex. 1004, 7, 14; *see also id.* at 40 (claim 15)). Petitioner further argues that GB-647 discloses that the bacterial host cell can be *E. coli* as well as species other than *C. diphtheriae*, thereby allowing both native and mutant *C. diphtheriae* signal sequences to be used in non-*C. diphtheriae* hosts. *Id.* (citing Ex. 1004, 19).

Patent Owner argues that Petitioner's priority attack rests entirely on an improper claim construction,[12] that GB-647 and the '345 patent need not use identical words in describing the same subject matter, and that Patent Owner's citation supporting the amendment of the claims to add "wherein the 5' signal sequence is not derived from *C. diphtheriae*" used an "*e.g.*," thereby not excluding GB-647 from providing written description support for that claim amendment. Prelim. Resp. 17–19, 23.

[12] We did not adopt Petitioner's proposed claim construction of this term at this stage of the proceeding. *See* Section II.B.2 *supra*.

We are not persuaded by these arguments. Merely arguing that the respective disclosures need not use identical words in describing the same subject matter, or that Patent Owner did not exclude GB-647 from providing written description support, does not show that the written description of GB-647 supports the challenged claims. *See Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1379–80 (Fed. Cir. 2015).

Patent Owner further argues that a POSA would have understood that the disclosure of GB-647 "show[s] the inventors' possession of constructs containing 5' signal sequences not derived from *C. diphtheriae*." *Id.* at 19–22. Patent Owner points to Table 2 and Figure 9 of GB-647, describing signal sequences, to argue that a POSA would have understood that none of those sequences were derived from *C. diphtheriae*, and that a POSA would have immediately identified the genus of signal sequences conceived by the inventors as those that are not derived from *C. diphtheriae* (native or modified). *Id.* (citing Ex. 1004, Table 2, Figure 9, Examples 1–7; Ex. 1008, 2983, 2987).

Patent Owner also points to the disclosure in GB-647 that "expression of [the tox signal sequence] in *Escherichia coli* involves certain difficulties." Prelim. Resp. 22–23 (citing Ex. 1004, 2–3). Relying on that paragraph, Patent Owner contends that GB-647 "discloses the problems associated with prior bacterial toxin expression systems using the native *tox* signal sequence derived from *C. diphtheria*," and the use of "improved expression constructs containing other particular signal sequences, including those non-*C. diphtheriae* sequences disclosed in Table 2 and recited in the claims, to achieve successful diphtheriae toxin protein production in the bacterial periplasm." *Id.* at 22 (citing Ex. 1004, 2–3, 10, 25, 35, Table 2). Thus, according to Patent Owner, GB-647 demonstrates "unequivocal exclusion of

native *C. diphtheriae* signal sequences (either in wide [sic, wild] type or modified forms) from the claim scope." *Id.* (citing Ex. 1004, 3, Table 2, 10, 25, 35).

On this record and at this stage of the proceeding, we find that GB-647 does not provide written description support for the claim limitation "wherein the 5' signal sequence is not derived from *C. diphtheriae.*" Patent Owner's arguments regarding what a POSA would have understood from the disclosure of GB-647 rely primarily on unsupported attorney argument rather than evidence. For example, Patent Owner's contention that a POSA "would have immediately identified the genus of signal sequences" conceived by the inventors from "the collection of signal sequences discussed, used, and claimed" in GB-647 is unpersuasive, at least because claim 1 of the '345 patent includes all 5' signal sequences other than a 5' signal sequence that is derived from *C. diphtheriae*. *See* Ex. 1001, 49:54–64. That is, claim 1 of the '345 patent is not limited to just the disclosed "genus" of signal sequences described in GB-647, such as those listed in Table 2 of GB-647.[13] Moreover, "the collection of signal sequences . . . claimed in the GB-647 priority application" (Prelim. Resp. 20) does not exclude native or modified signal sequences derived from *C. diphtheriae.* *See* Ex. 1004, 40 (claim 14).

[13] If it is Patent Owner's position that a POSA would identify the genus as *all* signal sequences other than those derived from *C. diphtheriae*, Patent Owner does not persuasively explain why a POSA would have identified other signal sequences that are not described in GB-647 as part of that genus, and only exclude those derived from *C. diphtheriae*. *See Ariad*, 598 F.3d at 1350 (discussing requirements for sufficient description of a genus).

Patent Owner cites *Hologic*, 884 F.3d at 1362 and *Trading Technologies International, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1361 (Fed. Cir. 2010) in support of its "genus" argument. Prelim. Resp. 21. But *Hologic* held that intrinsic evidence and expert testimony from Patent Owner's experts (i.e. regarding "what the specification reasonably conveys to the skilled artisan who has knowledge of the prior art") supported the Board's finding that a POSA "would have understood that the inventor had possession of a 'permanently affixed' light guide." *Hologic*, 884 F.3d 1363–64. No such expert testimony is provided by Patent Owner at this stage of the proceeding. Similarly, the quote from *Trading Technologies* cited by Patent Owner refers to the court's consideration of "the undisputed knowledge of those skilled in the art" (i.e. the parties' experts) to find that the disclosure of a species in that case provided support for a claim directed to "a very similar and understandable genus." *Trading Technologies*, 595 F.3d at 1360–61.

Patent Owner also argues that a POSA "would have immediately understood from the sequences disclosed in Table 2 and Figure 9 of the GB-647 priority application that none of the signal sequences were derived from *C. diphtheriae*," and that GB-647 "provide[s] ample evidence that the inventors possessed an invention that utilized signal sequences not derived from *C. diphtheriae*." Prelim. Resp. 21–22 (citing Ex. 1004, Table 2, Figure 9, Examples 1–7). But the written description inquiry is not whether there is written description support for signal sequences such as those disclosed in Table 2 of GB-647, but rather whether there is written description support for "wherein the 5' signal sequence is not derived *C. diphtheriae*," as we have preliminarily construed that term. *See* Section II.B.2 *supra*; *see also Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) ("It is

not sufficient for purposes of the written description requirement of § 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose.").

Patent Owner's arguments regarding GB-647's statements related to "certain difficulties" of using native tox signal sequences are also unpersuasive on this record and at this stage of the proceeding. We acknowledge, however, that our reviewing court has held that "[n]egative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation." *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1351 (Fed. Cir. 2012) (finding that "[t]he claim limitation that the [] formulations contain no sucralfate is adequately supported by statements in the specification expressly listing the disadvantages of using sucralfate.").

In the present case, GB-647 describes "certain difficulties" in using the tox signal sequence, including "decreased viability of the host cells" and "increased proteolysis of the recombinant protein." Ex. 1004, 6–7. But whether that language supports a claim limitation "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *See Ariad*, 598 F.3d at 1351. Such an inquiry includes, for example, GB-647's disclosure that allows for native and modified *C. diphtheriae* signal sequences to be used. *See* Ex. 1004, 7, 14, 19, 40; Pet. 30.

Even if GB-647 provided written description support for a claim limitation such as "wherein the 5' signal sequence is not the *tox* signal sequence," such support would not be commensurate in scope with the claims of the '345 patent. *See Atl. Research Mktg. Sys., Inc. v. Troy*, 659

F.3d 1345, 1353–55 (Fed. Cir. 2011) ("The purpose of the written description requirement is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.") (citation omitted). Here, for example, the statement in GB-647 regarding the *tox* signal sequence does not exclude a modified native *C. diphtheriae* signal sequence. *See* Section II.B.2 *supra*.

Based on the foregoing, we find on this record that GB-647 does not provide written description support for the claim limitation "wherein the 5' signal sequence is not derived from *C. diphtheriae*," and that the earliest effective filing date of the challenged claims of the '345 patent is October 7, 2010. Petitioner has thus made a sufficient threshold showing that Retallack and Retallack-719 qualify as prior art to the challenged claims.

We emphasize that these findings are preliminary at this stage of the proceeding, particularly in view of the fact that written description is a question of fact. Such a fact-based question may best be developed during trial, and we invite the parties to do so.

D. Principles of Law

To anticipate a claim under 35 U.S.C. § 102, "a single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art," *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002), but "the reference need not satisfy an *ipsissimis verbis* test," *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009).

In an anticipation analysis, "it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). Thus, "the dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from a prior art reference that every claim element is disclosed in that reference." *Eli Lilly v. Los Angeles Biomedical Research Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017) (quoting *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (internal brackets and quotation marks omitted)).

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 that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418.

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

E. Anticipation by Retallack

Petitioner asserts that claims 1, 2, 18, 19, and 21 of the '345 patent are anticipated by Retallack under pre-AIA 35 U.S.C. § 102(e). Pet. 35–43.

1. Retallack (Ex. 1009)

Retallack discloses "a nucleotide sequence encoding a CRM197 protein fused to a secretion signal that directs transfer of the CRM197 protein to the periplasm" of a *Pseudomonas* host cell. Ex. 1009 ¶ 6. Retallack also discloses that the host cell can be an *E. coli* cell. *Id.* ¶ 47. The polynucleotides disclosed by Retallack comprise a 3' toxin portion encoding CRM197 and a 5' signal sequence encoding a secretion leader. *Id.* ¶¶ 36, 80; Ex. 1006 ¶ 118.

Retallack discloses that "Figure 1 shows the amino acid and DNA sequences of the expressed synthetic CRM197 gene," wherein the amino acid sequence is of mature CRM197, which lacks a signal sequence and is 100% identical to SEQ ID NO: 32 of the '345 patent. Ex. 1009 ¶ 79, Fig. 1; Ex. 1006 ¶¶ 120–124. Retallack also discloses that the secretion leader or signal directs transfer of the CRM197 protein to the periplasm. Ex. 1009 ¶¶ 6, 18, 80–81, claim 1; Ex. 1006 ¶ 125. Retallack discloses the use of signal sequences that are native to *P. fluorescens*, not *C. diphtheriae*. Ex. 1009 ¶ 80, Table 6; Ex. 1006 ¶¶ 128–129.

2. Analysis

Claim 1

The Petition includes a limitation-by-limitation comparison of independent claim 1 to the disclosure of Retallack, including citations to the DeLisa Declaration as support. Pet. 37–41. For example, Petitioner contends that Retallack "provides a working example that generates a number of polynucleotides each of which encodes CRM197 fused to one of

ten different *P. fluorescens* signal sequences, 'included to target the protein to the periplasm . . . for recovery in the properly folded and active form.'" *Id.* at 39 (citing Ex. 1009 ¶ 80; Ex. 1071 ¶ 78; Ex. 1006 ¶ 125). Based on our review of the arguments and evidence in this record, we determine that Petitioner has established a reasonable likelihood of prevailing on its assertion that Retallack anticipates claim 1 of the '345 patent.

Dependent Claims

The Petition includes a limitation-by-limitation comparison of dependent claims 2, 18, 19, and 21 to the disclosure of Retallack, with supporting citations to the DeLisa Declaration. Pet. 41–43. For example, claim 18 recites "[t]he polynucleotide of claim 1 wherein the 3' toxin portion encodes CRM197." Ex. 1001, 52:34–35. Petitioner cites to Retallack's disclosure of that limitation. Pet. 42. We determine that, based on the current record, Petitioner has established a reasonable likelihood of prevailing on its assertion that Retallack anticipates claims 2, 18, 19, and 21 of the '345 patent.

F. Obviousness over Retallack and Huber

Petitioner asserts that claims 4–14, 16, 17, and 20 of the '345 patent would have been obvious, under pre-AIA 35 U.S.C. § 103, over the combined teachings of Retallack and Huber, and relies on the DeLisa Declaration in support of those assertions. Pet. 43–48. The discussion of Retallack's disclosure is set forth above.

1. Huber (Ex. 1008)

Huber discloses polynucleotides that encode a polypeptide with signal sequences for export of the protein to the periplasm of a bacterium, such as *E. coli*. Ex. 1008, 2983–84. Huber discloses the use of multiple signal sequences, including FlgI. *Id.* at 2987–88, Fig. 3, Table 2. Huber further

discloses that the signal sequences were *E. coli* sequences obtained from the SwissProt databank. *Id.* at 2984.

2. Analysis

Claim 6

Petitioner refers to Retallack's disclosure regarding the limitations of claims 1, 2, 18, 19, and 21, as well as Retallack's teaching that the signal sequences useful for producing CRM197 are not limited to the exemplary *P. fluorescens* sequences disclosed therein. Pet. 44–45 (citing Ex. 1009 ¶¶ 33–34; Ex. 1006 ¶ 141). Petitioner also cites to Retallack's disclosure of a need for increasing the production yield or expression level of CRM197. *Id.* at 45 (citing Ex. 1009 ¶ 5). Petitioner argues that Retallack's disclosure that signal sequences other than its exemplary *P. fluorescens* signal sequences could be used "would have motivated POSAs to try additional signal sequences to increase yield." *Id.* Petitioner further argues that "[s]ubstitution of one signal sequence for a different one was a routine approach for optimizing protein expression and/or yield," and that "POSAs would have been motivated to use other signal sequences to optimize, and therefore increase these yields." *Id.* (citing Ex. 1025, 909, 911; Ex. 1009 ¶ 85; Ex. 1006 ¶ 142).

Petitioner also argues that "Huber discloses nine of the thirteen signal sequences recited in the '345 patent claims, including FlgI (which is present in each of claims 4–14, 16–17 and 20)," and that Huber demonstrates that these nine *E. coli* signal sequences can successfully transport the normally cytoplasmic thioredoxin reporter polypeptide to the periplasm. *Id.* at 45–46 (citing Ex. 1008, 2983–84, 2988, Fig. 3, Table 2). According to Petitioner, a POSA would have been motivated to combine Huber's teachings with Retallack's because Huber supplies additional signal sequences that can be

used for periplasmic transport, and because a POSA "would have been motivated to turn to Huber's *E. coli* signal sequences in view of Retallack's teaching that *E. coli* signal sequences can be used in its methods for periplasmic transport of CRM197." *Id.* (citing Ex. 1006 ¶ 143).

Petitioner further argues that a POSA would have expected that the same signal sequences that can transport thioredoxin to the periplasm, as taught by Huber, would also be able to transport proteins already known to be exportable to the periplasm, such as DTx mutants (including CRM197). *Id.* at 46–47 (citing Ex. 1006 ¶ 144). Thus, according to Petitioner, a POSA "would have also had a reasonable expectation that combining the teaching of Retallack and Huber would successfully produce the polynucleotides of claims 4–14, 16–17 and 20." *Id.* at 47 (citing Ex. 1006 ¶ 145).

Based on our review of the record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing that the combined teachings of Retallack and Huber would have rendered obvious claim 6 of the '345 patent.

Dependent Claims

As noted above, Petitioner's arguments are applicable to independent claim 6, as well dependent claims 4, 5, 7–14, 16, 17, and 20. *See* Pet. 43–47. Petitioner also provides additional arguments and evidence that claim 11 would have been obvious in view of the combined teachings of Retallack and Huber. *See* Pet. 47–48. On the current record, we find that Petitioner has established a reasonable likelihood that it would prevail in showing that claims 4, 5, 7–14, 16, 17, and 20 would have been obvious over the combined teachings of Retallack and Huber.

G. Conclusion: Grounds based on Retallack

For the reasons articulated by Petitioner, and in view of the record as a whole at this stage of the proceeding, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that at least one of the challenged claims is anticipated by Retallack or would have been obvious in view of the combined teachings of Retallack and Huber.

H. Other Challenges

Petitioner asserts that claims 1, 2, 18, 19, and 21 are anticipated by or obvious over Retallack-719, and provides arguments and evidence in support thereof. *See* Pet. 48–56. The disclosure of Retallack-719 relied on by Petitioner is similar to the disclosure of Retallack relied on by Petitioner. *Compare* Pet. 49–53 *with* Pet. 37–41. Petitioner also asserts that claims 4–14, 16, 17, and 20 would have been obvious over Retallack-719 and Huber. *See* Pet. 57–60. These grounds are also included in our institution decision. *See SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348 (2018).

III. CONCLUSION

Based on the record as a whole and for the foregoing reasons, we conclude that Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims of the '345 patent.

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, 2, 4–14, and 16–21 of U.S. Patent No. 9,422,345 B2 is instituted with respect to all grounds set forth in the Petition; 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 a trial commencing on the entry date of this Decision.

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