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Paper 8
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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 IPR2019-00230
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 (IPR2019-00241), 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. xv; *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 sequence capable of directing transport of a heterologous protein to the

[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.").

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 pre-AIA grounds. Pet. 5.

Reference[s]	**Basis**	**Claims challenged**
Collier[2]	§ 102(b)	1 and 19
Neville[3]	§ 102(b)	1, 2, 18, 19, and 21
Collier and Giannini[4]	§103	2 and 18
Collier and Huber[5]	§103	4–14, 16, 17, and 20
Collier and state of the art, as exemplified by	§103	21

[2] Collier, US 6,455,673 B1, issued Sept. 24, 2002 ("Collier"). Ex. 1005.

[3] Neville, Jr. et al., US 2003/0157093 A1, published Aug. 21, 2003 ("Neville"). Ex. 1007.

[4] G. Giannini et al., *The Amino-Acid Sequence of Two Non-Toxic Mutants of Diphtheria Toxin: CRM45 and CRM197*, NUCLEIC ACIDS RESEARCH 12 (10) (1984) ("Giannini"). Ex. 1011. Petitioner refers to Giannini as Giannini-1.

[5] 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.

Sambrook,[6] Horton,[7] and Heckman[8]		
Neville 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 either October 8, 2009, or 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. 5–6 (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

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[6] J. Sambrook et al., *Enzymes Used in Molecular Cloning*, Ch. 5, 5.1–5.95, *Site-directed Mutagenesis of Cloned DNA*, Ch. 15, 15.1–15.113, and *Expression of Cloned Genes in Escherichia Coli*, Ch. 17, 17.1–17.44, MOLECULAR CLONING, 2ed. (1989). Ex.1029.

[7] R.M. Horton et al., *Gene Splicing by Overlap Extension*, METHODS IN ENZYMOLOGY 217, 270–79 (1993) ("Horton"). Ex. 1069.

[8] K.L. Heckman et al., *Gene Splicing and Mutagenesis by PCR-driven Overlap Extension*, NATURE PROTOCOLS 2(4), 924–32 (2007) ("Heckman"). Ex. 1070.

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,[9] 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).

[9] 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).

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. 28. 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 30–31.

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 in the specification of the '345 patent 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. 31.

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 31–32 (citing Ex. 1001, 7:22–24 (emphases added by Petitioner); Ex. 1006 ¶ 106). 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 32 (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[10] or

[10] 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.

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 15–16. 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.* at 16.

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. 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.[11] 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

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3001, 689 (definition of "wild-type" in the Oxford Dictionary of Biology, 6th ed. (2008)).

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

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.

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. 24–28. 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

Patent Owner argues that the '345 patent is entitled to the priority filing date of Great Britain Patent Application No. 0917647 filed October 8, 2009 (Ex. 1004, "GB-647"). Prelim. Resp. 16–31; Ex. 1001, 1. Patent Owner advanced that argument in *Merck Sharp & Dohme Corp. v.*

GlaxoSmithKline Biologicals SA, Case IPR2019–00241 (Paper 6, 16–31) (PTAB Feb. 14, 2019). In that co-pending case (IPR2019-00241), Patent Owner argued that Petitioner could not prevail because two of the three prior art references were dated after the October 8, 2009, priority date. In the present case, all of the cited references predate the asserted priority date of October 8, 2009, by at least two years. We thus understand Patent Owner's priority date argument in this case to reassert the argument set forth in its Preliminary Response in IPR2019-00241. We addressed that argument, reasserted in the Preliminary Response in this case, in our institution decision in IPR2019-00241.

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 Neville

Petitioner asserts that claims 1, 2, 18, 19, and 21 of the '345 patent are anticipated by Neville under pre-AIA 35 U.S.C. § 102(b). Pet. 43–49.

1. Neville (Ex. 1007)

Neville discloses methods of treatment that can include administration of a non-toxic DT mutant, such as DTM2 or CRM197, followed by administration of an immunotoxin. Ex. 1007 ¶¶ 47, 51. Neville discloses constructs that encode a mutant of CRM197 with at least 99% identity to CRM197, and that all of its constructs "can be expressed in *E. coli* using

pelB signal sequences or other appropriate signal sequences." *Id.* at ¶¶ 178–179, 184–185.

Neville discloses an Example 11 that describes a polynucleotide construct having a 5' signal sequence portion and a 3' toxin portion. *Id.* at ¶¶ 177–178; Ex. 1006 ¶ 126. Example 11 describes production of a polynucleotide having a 3' portion that encodes the DTM2 DTx mutant polypeptide, such that the 3' portion encodes a mature bacterial toxin polypeptide (DTM2) that lacks a signal sequence. Ex. 1007 ¶¶ 177–179; Ex. 1006 ¶ 128. The amino acid sequence of DTM2 is 99.6% identical to SEQ ID NO: 32 in the '345 patent. Ex. 1007 ¶¶ 47, 50, 176–180, 184; Ex. 1006 ¶¶ 130–131.

Example 11 of Neville also discloses a polynucleotide sequence having a 5' portion that encodes the PelB leader (signal) sequence, wherein that signal sequence directs transport of the protein (e.g. DTM2) to the periplasm for high level production in *E. coli*. Ex. 1007 ¶¶ 178, 184–185; Ex. 1006 ¶ 49. The PelB signal sequence is native to *E. carotovora*, not *C. diphtheriae*, and is not derived from *C. diphtheriae*. Ex. 1006 ¶ 136.

2. Analysis

Claim 1

The Petition includes a limitation-by-limitation comparison of independent claim 1 to the disclosure of Neville, with supporting citations to the DeLisa Declaration. Pet. 43–47. For example, Petitioner refers to Example 11 of Neville as disclosing a polynucleotide construct comprising a 5' signal sequence portion and a 3' toxin portion. *Id.* at 43–44 (citing Ex. 1007 ¶178; Ex. 1006 ¶ 126). Petitioner also explains, with reference to the DeLisa Declaration testimony, that Neville discloses an amino acid sequence (DMT) that is 99.6% identical to SEQ ID NO: 32. *Id.* at 45 (citing Ex. 1007

¶ 184; Ex. 1006 ¶ 131. Petitioner also explains that the PelB signal sequence "was a well-known signal sequence, routinely used prior to the earliest filing date of the '345 patent, and known to direct transport of polypeptides, including DTx mutant polypeptides, to the bacterial periplasm." *Id.* at 46 (citing Ex. 1021, 38; Ex. 1005, 4:64–6:3; Ex. 1013, 8467; Ex. 1030, 6:15–7:22).

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 Neville 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 Neville, with supporting citations to the DeLisa Declaration. Pet. 47–49. For example, claim 19 recites "[t]he polynucleotide of claim 1 wherein the 3' toxin portion encodes a polypeptide having at least 95% sequence identity to SEQ ID NO: 32." Ex. 1001, 52:36–38. In arguing that claim 19 is anticipated, Petitioner refers to its discussion of Example 11 of Neville disclosing a 3' toxin that encodes a mature bacterial toxin polypeptide having an amino acid sequence (DTM2) that is 99.6% identical to the '345 patent SEQ ID NO: 32. Pet. 48.

We determine that, based on the current record, Petitioner has established a reasonable likelihood of prevailing on its assertion that Neville anticipates claims 2, 18, 19, and 21 of the '345 patent.

F. Obviousness over Neville in view of Huber

Petitioner asserts that claims 4–14, 16, 17, and 20 of the '345 patent are unpatentable as obvious, under pre-AIA 35 U.S.C. § 103, over Neville in view of Huber, and relies on the DeLisa Declaration in support of those assertions. Pet. 45–55. Neville's disclosure is discussed 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 Neville's disclosure regarding the limitations of claims 1, 2, 18, 19, and 21, as well as Neville's teaching that "[a]ll of the constructs reported here can be expressed in *E. coli* using pelB signal sequences or other appropriate signal sequences." Pet. 59 (citing Ex. 1007 ¶ 185). According to Petitioner, that teaching "would have motivated POSAs to try signal sequences in addition to PelB," and that "[s]ubstitution of one signal sequence for a different one was a routine approach for optimizing protein expression and/or yield." *Id.* (citing Ex. 1025, 911, 909; Ex. 1006 ¶ 178).

Petitioner also argues that "Huber demonstrated that 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), are capable of directing transport of a normally cytoplasmic polypeptide (thioredoxin) to the *E. coli* periplasm." *Id.* at 60 (citing Ex. 1008, 2984; Ex. 1006 ¶ 179).

Petitioner argues further that the knowledge that DTx mutants, including CRM197, were exportable to the bacterial periplasm, along with Huber's positive results that were obtained with a protein (thioredoxin) that is normally cytoplasmic, but is capable of being exported when modified at

the N-terminus with a signal sequence, "would have provided POSAs with a reasonable expectation that combining the teaching of Neville and Huber would successfully produce the polynucleotides of claims 4-14, 16-17 and 20." *Id.* (citing Ex. 1006 ¶ 180).

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 Neville 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. Petitioner also provides additional arguments and evidence that claim 11 would have been obvious in view of the combined teachings of Neville and Huber. *See* Pet. 60–61.

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 Neville or would have been obvious in view of the combined teachings of Neville and Huber.

G. Other Challenges

Petitioner asserts that claims 1 and 19 are anticipated by Collier,[12] that claims 2 and 18 would have been obvious over Giannini in view of Collier

[12] Petitioner refers to Collier as Collier-1. Pet. 2.

and the state of the art, that claims 4–14, 16, 17, and 20 would have been obvious over Collier in view of Huber, and that claim 21 would have been obvious over Collier in view of the state of the art as exemplified by Sambrook, Horton, and Heckman. *See* Pet. 33–42, 49–59. 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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