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Paper No. 12
Entered: December 18, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER INC.,
Petitioner,

v.

HOFFMAN-LA ROCHE INC.,
Patent Owner.

IPR2018-01219
Patent 8,314,225 B2

Before SUSAN L. C. MITCHELL, TINA E. HULSE, and WESLEY B. DERRICK, *Administrative Patent Judges*.

DERRICK, *Administrative Patent Judge*.

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

I. INTRODUCTION

Pfizer Inc. ("Petitioner") requests an *inter partes* review of claims 1–5, 10–12, and 20 of U.S. Patent No. 8,314,225 B2 ("the '225 patent," Ex. 1001). Paper 1 ("Pet."). Petitioner contends the challenged claims are anticipated and/or rendered obvious by each of the three references relied on in the Petition. *Id.* at 1. Patent Owner, Hoffman-La Roche Inc., filed a Preliminary Response. Paper 9 ("Prelim. Resp."). Patent Owner does not address the merits of Petitioner's challenge, but contends that the Petition should be denied under 35 U.S.C. § 325(d). *Id.* Patent Owner has also disclaimed all challenged claims except claim 20. *Id.* at 2–3. Under 35 U.S.C. § 314, an *inter partes* review may not be instituted "unless . . . the information in the petition . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Under 35 U.S.C. § 325(d), a petition for an *inter partes* review may be rejected if "the same or substantially the same prior art or arguments previously were presented to the Office." For the reasons set forth below, we institute an *inter partes* review on all grounds challenging claim 20.

II. BACKGROUND

A. Related Proceedings

The parties indicate that the '225 patent has been asserted in the following proceedings: *Genentech, Inc. v. Pfizer, Inc.*, Civ. Act. 1-17-cv-01672 (D. Del) (November 17, 2017); *Genentech, Inc. v. Sandoz, Inc.*, Civ. Act. 1-17-cv-13507 (D.N.J.) (December 21, 2017); and *Genentech, Inc. v. Amgen Inc.*, Civ. Act. 1-18-cv-00924 (D. Del.) (June 21, 2018). Pet. 3;

Paper 6, 1. The '225 patent is also subject to pending Reexamination No. 90/014,063 ("the '063 Reexam") at the Patent and Trademark Office. Pet. 3; Paper 6, 1.

B. The '225 Patent (Ex. 1001)

The '225 patent is titled "Heavy Chain Mutant Leading to Improved Immunoglobulin Production," and is directed to nucleic acids encoding mutant immunoglobulins, transfected mammalian cells, and methods for expressing the encoded immunoglobulin heavy chain in transfected mammalian cells to obtain immunoglobulins. Ex. 1001, 2:8–63.

C. Statutory Disclaimer of Claims 1–5 and 10–12

Patent Owner has disclaimed all claims challenged in the Petition except claim 20. Prelim. Resp. 2–3; Ex. 2001 (DISCLAIMER IN PATENT UNDER 35 C.F.R. 1.321(a), disclaiming claims 1–7, 9–13, and 15–18). Thus, no *inter partes* review will be instituted based on challenges to claims 1–5 and 10–12. *See* 37 C.F.R. § 42.107(e) ("The patent owner may file a statutory disclaimer under 35 U.S.C. § 253(a) in compliance with § 1.321(a) of this chapter disclaiming one or more claims in the patent. No *inter partes* review will be instituted based on disclaimed claims.").

D. Challenged Claim 20

Claim 20, the sole challenged claim that has not been disclaimed, is reproduced below.

> 20. A method for improving the expression of an immunoglobulin in a mammalian cell, comprising the following steps:
>
> a) transfecting a mammalian cell with a nucleic acid encoding an immunoglobulin heavy chain, wherein the nucleic acid encoding the immunoglobulin heavy chain comprises the nucleic acid ggaaaa, or the nucleic acid

ggcaaa, or the nucleic acid gggaaa, or the nucleic acid ggaaag, or the nucleic acid ggcaag, or the nucleic acid gggaag encoding the glycine-lysine-dipeptide contained in the C_H3- or C_H4-domain of the immunoglobulin heavy chain,

b) cultivating the transfected mammalian cell under conditions suitable for the expression of the immunoglobulin,

c) recovering the immunoglobulin from the culture or the cell.

Ex. 1001, 42:9–25.

E. The Asserted Grounds of Unpatentability

Petitioner asserts that the challenged claims are unpatentable under both § 102(b) and § 103[1] over the identified prior art as follows:

Prior Art	Claims
Denney[2]	1–3, 5, 10–12, 20
Loetscher[3]	1–5, 10–12, 20
Rosenthal[4]	1–3, 5, 10–12, 20

[1] The relevant sections of the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284 (September 16, 2011), took effect on March 16, 2013. Because the application from which the '225 Patent issued was filed before that date, our citations to Title 35 are to its pre-AIA version.
[2] Denney, US 2002/0160006 A1, published October 31, 2002 (Ex. 1003).
[3] Loetscher et al., WO 2007/068429 A1, published June 21, 2007 (Ex. 1003). Although contended to be § 102(b) art, Loetscher was published on June 21, 2007, less than one year prior to EP 07012774, filed June 29, 2007, to which the '225 patent claims priority. Ex. 1001, [30]; Ex. 1004, [43]. Patent Owner does not contest the prior art status of Loetscher. *See generally* Prelim. Resp.
[4] Rosenthal et al., US 2006/0292152 A1, published December 28, 2006 (Ex. 1005).

Petitioner supports the Petition with the testimony of Dr. Geoffrey Hale, Ph.D. (Ex. 1034).

III. ANALYSIS

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

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

Patent Owner contends that we should exercise our discretion and deny institution "because: *(a)* all but one challenged claim has been disclaimed; *(b)* a reexamination of the patent commenced nearly one year ahead of the Petition is addressing new claims presented by amendment; and *(c)* the Petition duplicates issues currently engaged in the reexamination." Prelim. Resp. 1.

The '063 Reexam arose out of a third-party request for *ex parte* reexamination of the '225 patent filed on January 10, 2018. Ex. 2005, 252–341. An order granting the request issued March 7, 2018. *Id.* at 93–110. The order identified substantial new questions of patentability over a number of references (*id.* at 97–107), including Loetscher (*id.* at 98–99). The first action on the merits issued June 29, 2018. Ex. 2002; Ex. 2005, 73–92. Patent Owner filed a response to the first action on September 20, 2018. Ex. 2003; Ex. 2005, 14–33. Patent Owner disclaimed claims 1–7, 9–13, and 15–

18 (Ex. 2003, 1; Ex. 2001) and added new claims 21–32, depending from claim 20 (Ex. 2003, 2–3; Ex. 2005, 15–16).

Patent Owner contends that "[n]o benefit is gained from having . . . [the Board] institute a second layer of proceedings nearly one year out of sync, especially because the issues raised in the Petition are already being addressed in the reexamination." Prelim Resp. 2. Patent Owner further contends that because "Patent Owner has not introduced new testimonial evidence in the reexamination . . . [t]he reexamination . . . is being conducted on substantially the same record as that presented in the Petition" and that "the same substantive issues raised in the Petition are being addressed." *Id.* at 3. Patent Owner highlights that Loetscher is cited in a reexamination anticipation rejection of claim 20, particularly for its SEQ ID NO:23. *Id.* (citing Ex. 2002, 4–5; Ex. 1004, 10–12). Patent Owner further contends that although Denney and Rosenthal are not cited in the reexamination rejections, "they represent issues redundant to those raised by Loetscher and the other reexamination references" as each of the rejections cites "heavy chain sequences recited in claim 20." *Id.* at 4 (citing Ex. 2002, 4–11). Patent Owner also contends that "[t]he general issue before the Office—whether the prior art discloses the claimed method involving a nucleic acid encoding an immunoglobulin with a particular sequence—is identical among the nine rejections playing out in the reexamination and the three challenges here." *Id.* at 5.

We disagree with Patent Owner as to the lack of benefit of instituting *inter partes* review. The pending reexamination rejections of claim 20 are limited to anticipation over the various references. Ex. 2002, 4–13. As such, the grounds differ, including as to the application of Loetscher to claim

20, as an obviousness challenge over that reference is raised here. Further, contrary to Patent Owner's contention, the record is significantly different between the two proceedings. While Patent Owner has not introduced new testimonial evidence in the '063 Reexam, the Petition was filed with both documentary and declaration evidence as to what Denney, Loetscher, and Rosenthal disclose, teach, or suggest to one of ordinary skill in the art, as well as to the level of ordinary skill in the art as to optimizing expression. As set forth below in our discussion of each ground, this further evidence is significant and highly relevant to whether Denney, Loetscher, and Rosenthal anticipate and/or render obvious claim 20.

Patent Owner relies on an informative decision of the Board—*Fox Factory, Inc. v. SRAM, LLC*, IPR2017-01439, slip op. at 8 (PTAB July 27, 2017) (Paper 7) (informative), 2017 WL 6271290—as supporting denial under 35 U.S.C. § 325(d). Prelim. Resp. 2, 5–6. Patent Owner contends that the circumstances in this case are "nearly identical" to those in *Fox Factory* and that we should, accordingly, also deny institution. *Id.* at 2; *see also id.* at 6. In particular, Patent Owner relies on the Board's decision to not institute a proceeding because "[a] co-pending *ex parte* reexamination had earlier presented the Office with a 'nearly identical ground' to that presented in a petition nearly one year later." *Id.* at 6. Patent Owner maintains that in *Fox Factory*

> The Board noted that the reexamination was "not yet complete" and that reconsidering "essentially the same ground" as that presented in reexamination "would be an inefficient use of the Office's resources," and . . . concluded "the interests of conservation of resources and finality to weigh strongly in favor of exercising [their] discretion of not instituting . . . ."

Id. (citing *Fox Factory*, 2017 WL 6271290, at *3).

We disagree that the circumstances are as similar as Patent Owner contends. In *Fox Factory*, the co-pending reexamination—the '831 Reexam—was preceded by a completed reexamination—the '744 Reexam. *Fox Factory*, 2017 WL 6271290, at *3. The '744 Reexam had considered prior art JP-Shimano. *Id.* The '831 Reexam was considering JP-Shimano in view of JIS. *Id.* The sole ground set forth in the petition was Thompson in view of JP-Shimano and JIS. *Id.* n.2. Thompson, however, was relied on for "the conventional elements of [the claimed subject matter]" and the Board found it did not meaningfully alter the substance of the ground of unpatentability. *Id.* at *3 n.2, *4. Taking these facts into account, the Board determined that "[t]he similarity of the grounds in [*Fox Factory*] and the '831 Reexamination, *coupled with the fact that JP-Shimano has already been considered in the '744 Reexamination,* indicates that it would be an inefficient use [of] the Office's resources to consider *essentially the same ground again*." *Id.* at *3 (emphasis added). Here, in contrast to *Fox Factory*, there is no *completed* proceeding addressing substantially similar grounds and the Petition is not limited to the grounds being addressed in the co-pending '063 Reexam.

Patent Owner's reliance on *Baker Hughes Oilfield Operations, Inc. v. Smith International, Inc.*, IPR2016-01450, slip op. at 7–11 (PTAB Dec. 22, 2016) (Paper 10), 2016 WL 8115502, is also unavailing. Prelim. Resp. 6. In *Baker Hughes*, during the pendency of an appeal to the Federal Circuit of an amended, reexamination claim, a petitioner challenged the unamended claim. *Baker Hughes*, 2016 WL 8115502, at *3. The Board recognized that whether or not Patent Owner's appeal to the Federal Circuit was successful, review of the challenged, unamended claim would be for naught because, if

successful, the claim would be replaced by the amended claim and, if unsuccessful, the claim would be declared unpatentable. *Id.* No such dilemma exists here, particularly in the absence of amendment to claim 20 in the '063 Reexam, or of any reexamination decision on appeal. Pet. 3; Ex. 2003, 2.

Patent Owner also relies on *Unified Patents Inc. v. John L. Berman*, IPR2016-01571 (PTAB Dec. 14, 2016) (Paper 10) (informative), 2016 WL 10033540, as support for denying institution on the contended basis that newly cited references are merely "evidence of the same old facts already presented to the Office." Prelim. Resp. 6–7. In *Unified Patents*, the Board denied a petition under § 325(d) that presented art that was substantially the same prior art that had been presented previously to the Office and *overcome* during prosecution. *Unified Patents*, 2016 WL 10033540, at *5. Further, the petition relied on the prior art "in substantially the same manner as the Examiner [had] used [the earlier prior art]." *Id.* As set forth above, however, none of the prior art relied on in the Petition has been considered and overcome, and we disagree that Petitioner adds nothing new over the '063 Reexam proceeding.

Patent Owner further contends that "[i]nstitution of review at this time will bring no clarity to the patentability of claim 20 for the benefit of the reexamination and cannot resolve the patentability of the new claims now pending in the reexamination." Prelim. Resp. 8.

While *inter partes* review itself may not resolve the patentability of the new reexamination claims, it can both bring clarity to the patentability of claim 20 and benefit reexamination of the new claims if we stay the '063 Reexam during review. We have discretion to stay a reexamination

involving a patent challenged in an *inter partes* review under 37 C.F.R. § 42.122(a); *see also* 35 U.S.C. § 315(d). Staying the '063 Reexam will also obviate any additional, ongoing burden on Patent Owner and the Office over that of the *inter partes* review alone.

Considering all these circumstances, and the discretionary nature of § 325(d), we decline to deny the Petition on that basis.

B. Level of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art "of the '225 Patent as of the priority date would have held a Ph.D. or equivalent (i.e., 4 or 5 years of work experience) in biochemistry, molecular biology, immunology, or a closely related field" and highlights, in particular, experience in "antibody domain and sequence manipulation and swapping, CDR grafting and sequence manipulation and swapping, CDR grafting and framework substitution in humanizing antibodies, construction, expression and purification of recombinant antibodies, assays for antibody expression levels and activity and the like." Pet. 5–6 (citing Ex. 1034 ¶ 25).

Patent Owner does not address the level of ordinary skill in the art. *See generally* Prelim. Resp.

On this record, we adopt Petitioner's definition of the level of ordinary skill. We further note that the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that "specific findings on the level of skill in the art . . . [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))).

C. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b) (2016).[5] Under that standard, we interpret claim terms using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Only those terms that are in controversy need to be construed and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017); *see also U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997) (holding claim construction is not necessary when it is not "directed to, or has been shown reasonably to affect, the determination of obviousness").

Petitioner expressly "does not request construction of any claim, but addresses the preamble of Claim 20 to the extent that Patent Owner seeks such a construction." Pet. 18. The preamble recites "[a] method for improving the expression of an immunoglobulin in a mammalian cell,

[5] The broadest reasonable construction standard applies to *inter partes* reviews with petitions filed before November 13, 2018. 77 Fed. Reg. 48,727 (Aug. 14, 2012) (codified at 37 C.F.R. § 42.100(b)), as amended at 81 Fed. Reg. 18,766 (Apr. 1, 2016); *see also* 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42) (changing the standard for interpreting claims in *inter partes* reviews filed on or after November 13, 2018).

comprising the following steps." *Id.*; Ex. 1001, 42:9–11. Petitioner contends that the preamble is not a claim limitation (Pet. 18–19), but also contends that, if it is determined to be a limitation, it would encompass codon modification (*id.* at 19–20).

As to the preamble not being a claim limitation, Petitioner relies on "the rest of the claim describ[ing] a structurally complete invention and [that] the preamble only states a purpose or intended use for the invention." *Id.* at 18–19 (citing *Catalina Mktg. Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808–809 (Fed. Cir. 2002); *STX, LLC v. Brine, Inc.*, 211 F.3d 588, 591 (Fed. Cir. 2000)). Petitioner contends that "'improving' immunoglobulin merely states the desired effect of the claimed method and not the invention itself" and that "[n]othing in the Patent or the prosecution history shows 'clear reliance' on the preamble as a patentably significant aspect of the claims." *Id.* at 19 (citing Ex. 1034 ¶ 74).

If the preamble were to be deemed a claim limitation, Petitioner contends that "the claimed 'method['] . . . would, at minimum, include codon modification . . . [because] *[c]odon modification is the only method described* in the '225 Patent to 'improv[e] the expression of an immunoglobulin in a mammalian cell'" (emphasis added). *Id.* at 20 (citing Ex. 1034 ¶ 75). Petitioner cites the '225 patent for its disclosure, as well as its citation to references, relating to modifying codons to reduce protein by-products and enhance protein expression. *Id.* (citing Ex. 1001, 1:63–2:2, 13:37–45, 22:26–29). Petitioner further relies on the Hale declaration as evidence that "a [person of ordinary skill in the art] would understand the broadest reasonable interpretation (or the plain and ordinary meaning) of

Claim 20's preamble to include codon modification." *Id.* (citing Ex. 1034 ¶ 76).

Petitioner's position that the preamble is not a claim limitation has merit, as does its fall-back position that, if it is, improved expression due to codon modification would meet the limitation. Although it is determinative for some grounds, as discussed below, we do not need to determine whether the preamble is limiting in order to reach our decision to institute *inter partes* review.[6]

D. Overview of Prior Art

1. Denney (Ex. 1003)

Denney is titled "Methods of Treating Lymphoma and Leukemia" and discloses preparing plasmids encoding recombinant immunoglobulins (Ex. 1003 ¶¶ 329–331), transfecting mammalian cells with the plasmids (*id.* ¶ 358), using the transfected cells to express the encoded immunoglobulins (*id.* ¶ 360), and purifying the expressed immunoglobulins (*id.*). Denney discloses that "the variable regions corresponding to the patient's Ig (V_H and V_L) are molecularly cloned and joined to an appropriate constant region gene contained within an expression vector." *Id.* ¶ 323. Disclosed expression plasmids include those containing "V_H region(s) joined to either a Cγ3 or Cγ4 sequence and . . . [those] containing . . . V_L region(s) joined to either a

[6] On April 24, 2018, the Supreme Court held that a decision to institute under 35 U.S.C. § 314(b) may not institute review on less than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). Also, in accordance with USPTO Guidance, "if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition." *See Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial).

Cκ or Cλ2 sequence." *Id.* ¶¶ 323, 329. Particular expression plasmids encoding recombinant heavy chains include pSRαSD9CG3C, which includes SEQ ID NO:44 encoding the Cγ3 region, and pSRαSD9CL2C, which includes SEQ ID NO:46 encoding the Cγ4 region. *Id.* ¶ 329. The amino acid sequences encoded by SEQ ID NO:44 and SEQ ID NO:46 are SEQ ID NO:45 and SEQ ID NO:47, respectively. *Id.* Both amino acid sequences, SEQ ID NO:45 and SEQ ID NO:47, terminate in a glycine-lysine dipeptide.

2. Loetscher (Ex. 1004)

Loetscher is titled "Antibodies Against Amyloid Beta 4 with Glycosylat[ion] in the Variable Region" and discloses how to prepare a purified antibody (Ex. 1004, Abstract) that includes heavy chain sequence encoded by nucleic acid sequences (*id.* at 7–12), recombinant expression systems including transfection of mammalian cells with the desired antibody genes (*id.* at 34–35), and methods for expressing and purifying the recombinantly expressed antibody molecules (*id.* at 35–37). Three nucleic acid sequences encoding heavy chain sequence are disclosed (SEQ ID NOs:5, 23, and 25), including a sequence optimized for expression (SEQ ID NO:23). *Id.* at 8–12. The first nucleic acid sequence (SEQ ID NO:5) encodes the same amino acid sequence as SEQ ID NO:23 and the third (SEQ ID NO:25) encodes the same, but with a signal peptide, i.e., an additional amino acid sequence that is proteolytically cleaved off during cellular processing. *Id.* at 8–10, 12. In particular, Loetscher discloses that "SEQ ID NO: 23 comprises the same coding sequence as the first alternative, however in a slightly different genomic organization." *Id.* at 12. SEQ ID NO:5 (and SEQ ID NO:23) encodes amino acid sequence SEQ ID NO:6. *Id.* at 7–10.

The third nucleic acid sequence, SEQ ID NO:25, encodes the amino acid sequence SEQ ID NO:26. *Id.* at 9–10. Both amino acid sequence SEQ ID NO:6 and SEQ ID NO:26 terminate in a glycine-lysine dipeptide. *Id.* at 8, 10.

3. Rosenthal (Ex. 1005)

Rosenthal is titled "Antibodies Directed Against Amyloid-Beta Peptide and Methods Using Same" and discloses a method of generating an antibody 6G, which has the heavy chain amino acid sequence SEQ ID NO:11 and the light chain amino acid sequence SEQ ID NO:12. Ex. 1005 ¶¶ 26, 53, 250. The disclosed nucleic acid SEQ ID NO:13 encodes the heavy chain sequence. *Id.* ¶¶ 53, 253. Rosenthal discloses using expression vectors containing the polynucleotides of interest, i.e., encoding the amino acid sequence of antibody 6G, (*id.* ¶¶ 170–171, 215), using suitable host cells for overexpressing the encoded antibody, including mammalian cells (*id.* ¶ 172), transfecting suitable mammalian cells with mammalian expression vectors (*id.* ¶ 215), providing for expression of antibody 6G by culturing transfected cells, or their progeny, under conditions allowing antibody 6G production (*id.* ¶¶ 26–27, 212, 214), and purifying antibody 6G (*id.* ¶¶26–27, 215–216). The heavy chain amino acid sequence SEQ ID NO:11 terminates in a glycine-lysine dipeptide. *Id.* ¶ 253.

E. Unpatentability of Claim 20 over Denney

1. Anticipation

Petitioner relies on Denney's disclosure relating to expression of immunoglobulins with nucleic acid and amino acid sequences derived from B-cell lymphoma cells. Pet. 27 (citing Ex. 1003, Abstract, ¶¶ 329, 355–360; Ex. 1034 ¶ 81). Petitioner contends that "Denney expressly discloses every

requirement of Claim 20 and therefore anticipates it." *Id.* at 36 (citing Ex. 1034 ¶ 123).

Petitioner contends both that the "preamble merely sets out the purpose of the alleged invention and is not a claim limitation" (*id.* at 37 (citing Ex. 1034 ¶ 124)) and that "[i]f the preamble is . . . a claim limitation, Denney discloses it" (*id.* (citing Ex. 1034 ¶ 125)). Petitioner contends that "Denney used codon optimization to obtain high levels of immunoglobulin expression, modifying the constant regions to use codons found most frequently in highly expressed mammalian proteins." *Id.* at 27 (citing Ex. 1003 ¶ 329; Ex. 1034 ¶ 83); *see also id.* at 37 (citing Ex. 1003 ¶¶ 2, 17, 370) (contending that "Denney discloses modifying codons to prepare vectors that contain codon optimized DNA sequences," as "Denney states that it provides 'improved methods for the amplification and expression of recombinant genes in cells'"). Petitioner also contends that "Denney explains that this improved expression is achieved through modifying (optimizing) codons," citing Haas (Ex. 1032) and Zolotukhin (Ex. 1033). *Id.* (citing Ex. 1003 ¶ 329). Petitioner cites to Haas' disclosure, with added emphasis, that "codon optimization may prove to be a **fruitful strategy for improving the expression in mammalian cells** of genes that show limited translational efficacy in their native form" (*id.* at 38 (citing Ex. 1032, 322)) and to Zolotukhin's disclosure, with added emphasis and bracketed text, "that 'the system described here [i.e., codon optimization] could be used for **efficient transduction and expression of genes into cells of mammalian origin**'" (*id.* (citing Ex. 1033, 4654)).

Petitioner contends that Denney's method also meets each recited step of claim 20. *Id.* at 38 (citing Ex. 1034 ¶ 127).

As to step (a), Petitioner relies on Denney as "disclos[ing] that '[p]lasmids encoding the chimeric heavy and light chains derived from the patient's Ig are electroporated . . . into BW5147.G.1.4 cells . . . .'" *Id.* (citing Ex. 1003 ¶ 358).

Petitioner maintains that "[e]lectroporation is a standard method for **transfecting cells** and BW5147.g.1.4 cells are **mammalian**." *Id.* at 38–39 (citing Ex. 1003 ¶ 159; Ex. 1034 ¶ 129).

Petitioner maintains that "the **plasmid pSRαSD9cG3C** contains SEQ ID NO:44 and the plasmid **pSRαSD9CG4C** contains nucleic acid SEQ ID NO:46." *Id.* at 35 (citing Ex. 1003 ¶ 329; Ex. 1034 ¶¶ 114–115). Petitioner contends "SEQ ID NO:44 . . . encod[es] an IgG3's Cγ3 region," that is, "the entire constant region (the C_H1-domain, hinge, C_H2-domain and C_H3-domain) of the IgG3, including the C-terminal part of the C_H3-domain." *Id.* at 28 (citing Ex. 1003 ¶¶ 322–329; Ex. 1034 ¶ 95). Petitioner also contends that "SEQ ID NO:46 . . . encod[es] an IgG4's Cγ4 region . . . [which] is the entire constant region of the IgG4, including the C-terminal part of the C_H3-domain." *Id.* at 29 (citing Ex. 1003 ¶¶ 322–329; Ex. 1034 ¶ 95). Petitioner contends that both of the "plasmids comprise the nucleic acid '**ggcaag**' encoding the glycine-lysine dipeptide in the heavy chain C_H3-domain." *Id.* at 39 (citing Ex. 1003 ¶ 329, SEQ ID NOs:44 & 46; Ex. 1034 ¶ 129); *see also id.* at 29–31. As set forth by Petitioner, the C-terminal glycine-lysine dipeptide comprised in Denney's amino acid SEQ ID NOs:45 and 47 is encoded by the ggcaag nucleotide sequence in SEQ ID NOs:44 and 46, respectively. *Id.* at 28–31.

As to step (b), Petitioner relies on Denney as "disclos[ing] that the transfected mammalian cells 'are then grown in selective medium followed

by growth in medium containing MTX as described in Examples 7 and 8' . . . [such that] [u]ltimately, '[t]he tumor-specific Ig [was] **expressed** by the amplified cell lines . . . .'" *Id.* at 39 (citing Ex. 1003 ¶¶ 276–305, 358, 360; Ex. 1034 ¶¶ 130–131) (emphasis added).

As to step (c), Petitioner relies on Denney as disclosing "that '[t]he tumor-specific Ig expressed by the amplified cell lines . . . is purified by chromatography of culture supernatants on Protein G Sepharose.'" *Id.* at 39 (citing Ex. 1003 ¶ 360). Petitioner further contends that this method of purification is a standard method for recovering an immunoglobulin from a cell culture. *Id.* at 39–40 (citing Ex. 1034 ¶ 133).

Petitioner contends that Denney, accordingly, anticipates claim 20. *Id.* at 40 (citing Ex. 1034 ¶¶ 134–135).

On this record, we find there is a reasonable likelihood that Petitioner will be able to establish that Denney discloses each of the recited steps of claim 20 arranged as in the claim, particularly in its use of pSRαSD9cG3C and/or pSRαSD9CG4C as the expression vector(s) for the immunoglobulin heavy chains used to transfect mammalian cells, the growth of the transfected cells for expression of the encoded immunoglobulin, and the purification of the immunoglobulin from cell culture. As to "improving the expression of an immunoglobulin in a mammalian cell," as recited in the preamble, on this record, it has not been established that the codon optimization used in the pSRαSD9cG3C and/or pSRαSD9CG4C expression vectors actually resulted in greater expression than had the codons not been optimized. Thus, despite the teaching in Denney to undertake such codon optimization, and other efforts, to optimize expression, on this record, it has

not been established that Denney achieved improved expression in a mammalian cell by use of the disclosed techniques.

Because we find below that Petitioner has established a reasonable likelihood of prevailing in showing that claim 20 is obvious over Denney, and over Loetscher, and thus institute on all grounds raised in the Petition under our *SAS* guidance,[7] we need not decide at this stage whether the preamble is limiting.

2. Obviousness

Petitioner further contends that if Denney does not anticipate claim 20, the claim is unpatentable under § 103(a) as obvious on the basis that its "anticipatory disclosures would provide a [person of ordinary skill in the art] ample motivation and a reasonable expectation of success to . . . [perform] the method of claim 20." Pet. 40.

Petitioner relies on Denney "disclos[ing] the nucleic acid 'ggcaag' encoding the glycine-lysine dipeptide in the C_H3-domain of the Ig heavy chain" (*id.* (citing Ex. 1034 ¶ 136)), as well as "each of the steps of Claim 20: (a) transfecting a mammalian cell with the nucleic acid 'ggcaag', (b) cultivating the transfected mammalian cell, and (c) recovering the immunoglobulin" (*id.* at 41 (citing *id.* at 36–40; Ex. 1003 ¶¶ 276–305, 323, 355–360; Ex. 1034 ¶ 137)).

As to the preamble, Petitioner again relies on Denney as "teach[ing] modifying the codons of the native heavy chain sequence to improve immunoglobulin expression and then expressing it in mammalian cells in the

[7] *Guidance on the Impact of SAS on AIA Trial Proceedings* (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial).

claimed manner." *Id.* (citing Ex. 1034 ¶ 138). Citing the testimony of its declarant, Dr. Hale, Petitioner further contends that "skilled antibody engineers as of June 2008 were focused on optimizing expression systems to improve recombinant protein yields and would have reasonably expected [that] Denney's method . . . would achieve this desired result." *Id.* (citing Ex. 1034 ¶¶ 125–126, 136–138); *see also id.* at 41–42 (citing Ex. 1003 ¶¶ 2, 15–17, 329; Ex. 1015; Ex. 1034 ¶¶ 125–126, 136–138).

Petitioner contends that Denney, accordingly, renders claim 20 obvious. *Id.* at 42 (citing Ex. 1034 ¶ 138).

On this record, we find Petitioner's unrebutted contentions as to the obviousness of claim 20 over Denney reasonably supported, including that one of ordinary skill in the art would have been led to modify the codons of the native heavy chain sequence, arriving at a sequence according to the claim, and to optimize expression systems to improve expression in a mammalian expression system with a reasonable expectation of success. Thus, even if the preamble is a limitation requiring improved expression in mammalian cells, on this record, we find that there is a reasonable likelihood that Petitioner will be able to establish that claim 20 is unpatentable under 35 U.S.C. § 103(a) over Denney.

F. Unpatentability of Claim 20 over Loetscher

1. Anticipation

Petitioner relies on Loetscher's disclosure relating to expression of antibodies against amyloid beta 4, including "nucleic acid and amino acid sequences for a specific human IgG1 antibody called 'Antibody A.'" Pet. 42 (citing Ex. 1004, 10, 64–72; Ex. 1034 ¶ 85). Petitioner contends that

"Loetscher expressly discloses every requirement of Claim 20 and therefore anticipates it." *Id.* at 49 (citing Ex. 1034 ¶ 168).

Petitioner again contends that the "preamble merely sets out the purpose of the alleged invention" (*id.* at 50 (citing Ex. 1034 ¶ 169)), but "[i]f the preamble is construed to be a claim limitation, Loetscher discloses it" (*id.* (citing Ex. 1034 ¶ 170)). Petitioner relies on Loetscher "stat[ing] that the 'heavy chain may be encoded by a nucleic acid that is **optimized for recombinant production** as exemplified by [SEQ ID NO:23]." *Id.* (citing Ex. 1004, 10; Ex. 1034 ¶ 170). Petitioner contends "SEQ ID NO:23 was optimized to improve the expression of Loetscher's recombinant proteins by modifying codons away from the wild-type sequence of Loetscher's SEQ ID NO:25." *Id.* (citing Ex. 1003, 10, 12; Ex. 1034 ¶ 170).

Petitioner contends that Loetscher's method also meets each recited step of claim 20. *Id.* (citing Ex. 1004, 35, 64–72 (Examples 1–3); Ex. 1034 ¶ 171); *see also* Ex. 1034 ¶¶ 172, 174, 176.

As to step (a), Petitioner relies on "Loetscher's Example 1.2 describ[ing] how '**[mammalian] CHO K1 cells** . . . were **transfected** with the vector pEE14.4Mab31 containing both heavy and light chain genes by liposomal transfection . . . .'" *Id.* at 51 (citing Ex. 1004, 64–65; Ex. 1034 ¶ 173).

Petitioner maintains that "pEE14.4Mab31 may comprise the nucleic acid '**ggcaaa**' encoding the glycine-lysine dipeptide in the heavy chain C_H3-domain." *Id.* (citing Ex. 1004, 10; Ex. 1034 ¶ 173). Petitioner relies on its contentions as to claims 1 and 10. *Id.* In those, Petitioner relies on SEQ ID NO:23 as "disclos[ing] a nucleic acid encoding the heavy chain of an IgG1 called Antibody A, including the C-terminal part of the C_H3-domain," where

the corresponding amino acid SEQ ID NO:6 terminates with a glycine-lysine dipeptide, encoded by the nucleic acid sequence ggcaaa, i.e., nucleotides 3976 to 3981 in SEQ ID NO:23. *Id.* at 43–44 (citing Ex. 1004, 7, 10–12, 58, 61–62; Ex. 1034 ¶¶ 141–144). In its contentions as to claim 10, Petitioner relies on Figure 1 as disclosing that pEE14.4Mab31 includes sequence encoding Antibody A heavy chain (*id.* at 47 (citing Ex. 1004, 64, Figs. 1A, 1C; Ex. 1034 ¶ 158)) and that an alternative sequence for encoding the heavy chain is SEQ ID NO:23, a nucleic acid sequence that is optimized for recombinant production (*id.* at 47–48 (Ex. 1004, 10; Ex. 1034 ¶ 159)). Petitioner also relies on Loetscher's claim 7 as reciting an "antibody molecule . . . [having] a heavy chain polypeptide encoded by a nucleic acid molecule as shown in **SEQ ID NO**S:5, **23**, or 25.'" *Id.* at 48 (citing Ex. 1004, 98; Ex. 1034 ¶ 159).

As to step (b), Petitioner relies on Loetscher's "Example 2 . . . detail[ing] the **cultivation of the transfected mammalian CHO cells**" and contends that "[t]he conditions described are suitable for immunoglobulin expression, as evidenced by the fact that immunoglobulin could be recovered." *Id.* at 51–52 (citing Ex. 1004, 66; Ex. 1034 ¶ 175).

As to step (c), Petitioner relies on Loetscher's "Example 3 . . . describ[ing] the **recovery** of Antibody A by purification" using a process "'based on three chromatographic steps and a diafiltration step,' all of which were standard methods for recovering immunoglobulin from a cell culture." *Id.* at 52 (citing Ex. 1004, 66–72; Ex. 1034 ¶ 177).

On this record, Petitioner has not established a sound basis for the assertion that Loetscher actually discloses the use of an expression vector including the alternative nucleotide SEQ ID NO:23 in a mammalian cell

with the result of improved expression. Although SEQ ID NO:23 is identified as an exemplary, alternative sequence "optimized for recombinant production" (Ex. 1004, 10), Loetscher discloses non-mammalian cell systems in addition to mammalian cell systems (Ex. 1004, 34; *see also* Ex. 1034 ¶¶ 159, 163–164). Despite this, Petitioner provides no explanation why SEQ ID NO:23 would be understood to be a sequence used for mammalian cell expression, rather than for expression in one or more of the contemplated non-mammalian cells. *See generally* Pet. Petitioner's further reliance on both Figure 1 and claim 7 similarly falls short because neither disclose including the alternative SEQ ID NO:23 in a mammalian expression vector, or including the alternative SEQ ID NO:23 in any kind of a vector in a mammalian cell. *See Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001) (stating that, to establish anticipation, "all of the elements and limitations of the claim must be shown in a single prior art reference, arranged as in the claim").

2. Obviousness

Petitioner further contends that if Loetscher does not anticipate claim 20, the claim is unpatentable under § 103(a) as obvious on the basis that its "anticipatory disclosures . . . would provide a [person of ordinary skill in the art] ample motivation and a reasonable expectation of success to . . . [perform] the method of claim 20." Pet. 52.

Petitioner relies on Loetscher "disclos[ing] the nucleic acid 'ggcaaa' encoding the glycine-lysine dipeptide in the C_H3-domain of an immunoglobulin heavy chain," including "in a plasmid and in isolated CHO or HEK cells" (*id.* at 53 (citing Ex. 1034 ¶ 180)), as well as "each of the steps of Claim 20: (a) transfecting a mammalian cell with the nucleic acid

'ggcaaa', (b) cultivating the transfected mammalian cell, and (c) recovering the immunoglobulin" (*id.* (citing *id.* at 49–52; Ex. 1004, 64–72; Ex. 1034 ¶ 181)).

As to the preamble, Petitioner again relies on Loetscher as "teach[ing] modifying the native heavy chain sequence to improve immunoglobulin expression and then expressing it in mammalian cells in the claimed manner." *Id.* (citing Ex. 1034 ¶ 182). Petitioner further contends that a person of ordinary skill in the art "engineering therapeutic antibodies in June 2008 would have been motivated to employ Loetscher's method to improve protein expression (i.e., to ensure economy of manufacture and relative ease of purification) and would reasonably expect it to be successful" and that this "expectation of success would be particularly reasonable in view of Loetscher's explicit teaching that SEQ ID NO:23 was 'optimized for recombinant production.'" *Id.* (citing Ex. 1004, 10; Ex. 1034 ¶ 182). Petitioner further contends that the person of ordinary skill in the art would have recognized "the use of mammalian cells . . . as a powerful technique to improve immunoglobulin expression over other expression systems." *Id.* at 53–54 (citing *id.* at 8–10; Ex. 1004, 64–65; Ex. 1034 ¶ 182).

Petitioner contends that Loetscher, accordingly, renders claim 20 obvious. *Id.* at 54 (citing Ex. 1034 ¶ 183).

On this record, we find Petitioner's unrebutted contentions relating to each of the recited steps of claim 20 reasonably supported, including as to using the alternative sequence—SEQ ID NO:23—in a mammalian expression vector and to using mammalian cells for improving protein expression. Despite the failure to identify SEQ ID NO:23 as a sequence specifically optimized for mammalian cell expression, it is still identified as

an alternative sequence "optimized for recombinant production," reasonably suggesting the use of the sequence generally in a recombinant expression system. Further, both mammalian expression vectors and mammalian host cells are reasonably identified as preferred over other expression systems, reasonably leading one of ordinary skill to use of SEQ ID NO:23 in a mammalian expression system, with a reasonable expectation of success. Thus, even if the preamble is a limitation requiring improved expression in mammalian cells, on this record, we find that there is a reasonable likelihood that Petitioner will be able to establish that claim 20 is unpatentable under 35 U.S.C. § 103(a) over Loetscher.

G. Unpatentability of Claim 20 over Rosenthal

1. Anticipation

Petitioner relies on Rosenthal's disclosure relating to monoclonal antibodies against amyloid beta, including "nucleic acid and amino acid sequences for a specific human IgG2 antibody called '6G.'" Pet. 54 (citing Ex. 1034 ¶¶ 184–185). Petitioner contends that "Rosenthal expressly discloses every requirement of Claim 20 and therefore anticipates it." *Id.* at 60 (citing Ex. 1034 ¶ 207).

Petitioner again contends that the "preamble merely sets out the purpose of the alleged invention" (*id.* at 61 (citing Ex. 1034 ¶ 208)), but "[i]f the preamble is construed to be a claim limitation, Rosenthal discloses it" (*id.* (citing Ex. 1034 ¶ 209)). Petitioner relies on "Rosenthal instruct[ing] the [person of ordinary skill in the art] to use host cells '**capable of over-expressing**' the protein of interest, such as mammalian cells." *Id.* (citing Ex. 1005 ¶ 172; Ex. 1034 ¶ 209). Petitioner contends that "Rosenthal's method also used [the well-known technique of] codon optimization, . . . to

develop the portion of Rosenthal's SEQ ID NO:13 that encodes the 6G heavy chain constant region." *Id.* (citing *id.* at 8–10; Ex. 1034 ¶ 209, Ex. C). Petitioner relies on "the distribution of codons in Rosenthal's SEQ ID NO:13 [being] strongly biased towards those which are most commonly found in humans" compared "to the nucleotide sequence of a wild-type human IgG2 heavy chain constant region." *Id.* (citing Ex. 1034 ¶¶ 91, 209, Ex. C). Petitioner also relies on Rosenthal as "explain[ing] that multiple codons can encode the same amino acid and that 'polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention,'" and further contends that "Rosenthal's method is intended to improve protein expression." *Id.* (citing Ex. 1005 ¶ 164; Ex. 1034 ¶ 209).

Petitioner contends that Rosenthal's method also meets each recited step of claim 20. *Id.* at 62 (citing Ex. 1005 ¶¶ 26–27, 207–225 (Example 1); Ex. 1034 ¶ 210).

As to step (a), Petitioner relies on Rosenthal's Example 1 disclosing "that '[f]or expression of full antibodies, heavy and light chain variable regions were cloned in mammalian expression vectors and **transfected** using lipofectamine into HEK 293 cells . . .'" (*id.* (citing Ex. 1005 ¶ 215; Ex. 1034 ¶ 212), where "the vectors comprise the nucleic acid '**ggaag**' encoding the glycine-lysine dipeptide in the heavy chain CH3-domain" (*id.* (citing Ex. 1005 ¶¶ 215–216, 253; Ex. 1034 ¶ 212) and "HEK 293 cells are **mammalian**" (*id.* (citing Ex. 1034 ¶ 212)).

Petitioner relies on Rosenthal as disclosing plasmids comprising nucleic acid SEQ ID NO:13 (*id.* at 58 (citing Ex. 1034 ¶ 200)), including "a plasmid called pDb.6G.hFc2a, '[which] is [a mammalian] expression vector

comprising the heavy chain of the 6G antibody [SEQ ID NO:13], and which is suitable for transient or stable expression of the heavy chain" (*id.* at 58–59 (citing Ex. 1005 ¶¶ 215–216; Ex. 1034 ¶ 201); *see also* Ex. 1034 ¶ 250). Petitioner contends that "nucleic acid SEQ ID NO:13 corresponds to amino acid SEQ ID NO:11," which includes the C-terminal part of the C_H3-domain, and sets forth that the glycine-lysine dipeptide at the C-terminus of SEQ ID NO:11 is encoded by the nucleotide sequence ggaaag, i.e., nucleotides 1336 to 1341 in SEQ ID NO:13. Pet. 54–55 (citing Ex. 1005 ¶¶ 53, 250, 253; Ex. 1034 ¶¶ 186–189).

As to step (b), Petitioner relies on "Rosenthal describ[ing] expression of antibody 6G" and the reasoning that this "necessarily involves cultivating the transfected cells" (*id.* at 63 (citing Ex. 1034 ¶ 214)) and that "[t]he conditions described [in Rosenthal's Example 1] are [necessarily] suitable for the expression of immunoglobulin, . . . [because] immunoglobulin was recovered" (*id.* (citing Ex. 1005 ¶ 215; Ex. 1034 ¶ 214)). Petitioner also relies on additional disclosure from The Summary of the Invention as disclosing, more generally, culturing of host cells that allow production of antibody 6G and expressing polynucleotide(s) encoding the antibody in a suitable cell to generate antibody, and on claim 40. *Id.* (citing Ex. 1005 ¶¶ 26–27, claim 40; Ex. 1034 ¶ 214).

As to step (c), Petitioner relies on Rosenthal's "Example 1 stat[ing] that '[a]ntibodies were purified using Protein A using standard methods." *Id.* (citing Ex. 1005 ¶ 215; Ex. 1034 ¶ 216). Petitioner contends that "[p]urification using protein A is a standard method of **recovering** immunoglobulin from a cell culture." *Id.* (citing Ex. 1034 ¶ 216). Petitioner also relies on additional disclosure from The Summary of the Invention as

disclosing more generally "a method of generating antibody 6G comprising . . . purifying the antibody 6G' and 'methods of generating any of the antibodies . . . by expressing . . . polynucleotides encoding the antibody . . . in a suitable cell, generally followed by recovering and/or isolating the antibody." *Id.* at 64 (citing Ex. 1005 ¶¶ 26–27, claim 40; Ex. 1034 ¶ 216).

On this record, Petitioner has shown that the recited steps (a)–(c) of claim 20 are reasonably met by Rosenthal's Example 1 as set forth by Petitioner. Nonetheless, assuming that it is established that the preamble reciting "improving the expression of an immunoglobulin in a mammalian cell" requires more than simply allowing expression, Petitioner's showing here appears to fall short. In particular, while Petitioner proffers evidence of codon bias (Ex. 1034 ¶¶ 91, 207, Ex. C), and that Rosenthal contemplates differences in codon usage (Ex. 1005 ¶ 164; Ex. 1034 ¶ 209), Rosenthal's codon usage for some encoded amino acids varies from the bias in the human database and/or in human Cγ2 (see Ex. 1034, Ex. C). Given Rosenthal's bias toward different codons for arginine, cysteine, glycine, proline, serine, and tyrosine (Ex. 1034, Ex. C), and the lack of any explanation as to the relative effects of codon bias for the different amino acids (*see generally* Pet.; Ex. 1034), Petitioner fails to provide a sound basis for why Rosenthal's codon usage as a whole would reasonably be expected to improve expression.

2. Obviousness

Petitioner further contends that if Rosenthal does not anticipate claim 20, the claim is unpatentable under § 103(a) as obvious on the basis that its "anticipatory disclosures . . . would provide a [person of ordinary skill in the

art] with ample motivation and a reasonable expectation of success to . . . [perform] the method of Claim 20." Pet. 64.

Petitioner relies on Rosenthal "disclos[ing] the nucleic acid 'ggcaag' encoding the glycine-lysine dipeptide in the C_H3-domain of the immunoglobulin heavy chain," including "in a plasmid and in isolated CHO or HEK cells" (*id.* at 64–65 (citing Ex. 1034 ¶¶ 219–220)), as well as "each of the steps of Claim 20: (a) transfecting a mammalian cell with the nucleic acid 'ggcaag', (b) cultivating the transfected mammalian cell, and (c) recovering the immunoglobulin" (*id.* at 65 (citing *id.* at 60–64; Ex. 1005 ¶¶ 215–216, 253; Ex. 1034 ¶ 220)).

As to the preamble, Petitioner contends that "Rosenthal teaches modifying the native heavy chain sequence to improve immunoglobulin expression and then expressing it in mammalian cells" and that "a [person of ordinary skill in the art] would seek to maximize protein expression . . . and would know that Rosenthal's method involving mammalian cells and codon optimization would likely achieve this desired result." *Id.* at 65 (citing Ex. 1034 ¶ 221; Ex. 1005 ¶ 172).

As with the contended anticipation by Rosenthal, Petitioner's asserted ground falls short if the preamble requires more than simply allowing expression. While Petitioner cites to § VI.B of the Petition as evidence that a person of ordinary skill in the art would have sought to maximize protein expression, Petitioner relies on Rosenthal's method as providing this result. *Id.* As discussed above, however, Petitioner fails to sufficiently address why Rosenthal's codon usage would reasonably be expected to improve expression. Petitioner's further citation to Rosenthal as "stat[ing] that the mammalian cells . . . should be capable of overexpressing the nucleic acid"

does not remedy this deficiency (*id.* (citing Ex. 1005 ¶ 172)), because there is no sufficient explanation how this supports Rosenthal's codon usage improving expression in a mammalian cell (*see generally id.*).

IV. CONCLUSION

For the foregoing reasons, we are persuaded that the Petition establishes a reasonable likelihood that Petitioner would prevail on its challenge as to claim 20. We, therefore, institute an *inter partes* review of claim 20 on all asserted grounds.

V. ORDER

For the reasons given, it is:

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted as to claim 20 of the '225 patent with respect to the 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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