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Paper No. 12
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC. and
SAMSUNG BIOEPIS CO., LTD.,
Petitioners,
v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01488
Patent 6,407,213 B1[1]

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

POLLOCK, *Administrative Patent Judge*.

FINAL WRITTEN DECISION

Claims 1, 2, 4, 25, 29, 30, 31, 33, 62–64, 66, 67, 69, 72, 78, 80, and 81 Shown to Be Unpatentable

35 U.S.C. § 318(a); 37 C.F.R. § 42.73

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[1] IPR2017-02139 has been joined to this case.

ORDERS

Denying Patent Owner's Motion to Exclude (Paper 63)

37 C.F.R. § 42.64(c)

Denying Petitioner's Motion to Exclude (Paper 67)

37 C.F.R. § 42.64(c)

Denying Patent Owner's Motion to Strike (Paper 61)

37 C.F.R. § 42.5

Denying Patent Owner's Motion to Seal (Paper 43) without Prejudice

37 C.F.R. § 42.55

Denying Petitioner's Motions to Seal (Papers 54 and 66) without Prejudice to Patent Owner

37 C.F.R. § 42.55

Modifying Previous Order Granting Patent Owner's Motion to Seal

37 C.F.R. § 42.55

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–67, 69, and 71–81 of U.S. Patent No. 6,407,213 B1 ("the '213 patent," Ex. 1001). We have jurisdiction under 35 U.S.C. § 6.

Having reviewed the arguments of the parties and the supporting evidence, we find that Petitioners have demonstrated by a preponderance of the evidence that claims 1, 2, 4, 25, 29, 30, 31, 33, 62–64, 66, 67, 69, 72, 76, 78, 80, and 81 of the '213 patent are unpatentable. Petitioners have not made that showing with respect to claims 12, 42, 60, 65, 71, 73–75, 77, and 79.

A. Procedural History

Petitioner Pfizer, Inc. filed a Petition for an *inter partes* review of claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–67, 69, and 71–81 the '213 patent. Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 6 ("Prelim. Resp."). Based on the record before us at the time, we instituted trial with respect to all challenged claims. Paper 34, 34–35 ("Dec."); Paper 35 (Erratum).

Petitioner Samsung Bioepis Co., Ltd. ("Bioepis") timely submitted a Petition presenting substantially the same challenges as set forth in Pfizer's Petition along with a request for joinder to IPR2017-01488. IPR2017-02139. Paper 1. We granted Bioepis's Petition and associated request for joinder to this case. IPR2017-02139, Paper 11, 6–7.

After institution of trial and our grant of joinder, Patent Owner filed its Patent Owner Response (Paper 44, "PO Resp.") and Petitioners filed a Reply to the Patent Owner Response (Paper 56, "Pet. Reply"). Patent Owner filed a motion to strike evidence and argument presented in Petitioners' Reply. Paper 61. Petitioners opposed. Paper 73.

With respect to technical experts, Petitioners rely on the declarations of Jefferson Foote, Ph.D. (Exs. 1003, 1202) and Timothy Buss (Ex. 1004); Patent Owner relies on the declarations of Dr. Leonard G. Presta (Ex. 2016), Dr. Paul J. Carter (Ex. 2017), and Dr. Ian A. Wilson (Ex. 2041). Patent Owner further relies on the testimony of research technician, Mr. John Ridgway Brady (Ex. 2018), as well as on the testimony of Dr. Edward Ball, M.D., from IPR2016-01694 (Ex. 2018). With respect to records management and authentication, Petitioners rely on the testimony of Mr. Benjamin Lasky (Ex. 1204) and Mr. Christopher Lowden (Ex. 1203);

Patent Owner similarly relies on the testimony of Ms. Irene Loeffler (Ex. 2019).

Patent Owner filed a motion for observations on the deposition of Dr. Foote (Paper 64), to which Petitioners provide a response (Paper 71).

Patent Owner submitted one motion to exclude evidence. Paper 63. Petitioners opposed (Paper 70), and Patent Owner submitted a reply in support of its motion (Paper 74). Petitioners also submitted one motion to exclude evidence. Paper 67. Patent Owner opposed (Paper 72), and Petitioners submitted a reply in support of its motion (Paper 73).

Patent Owner submitted a first, unopposed motion to seal (Paper 8), which we granted (Paper 25), concurrent with entry of the Modified Default Standing Protective Order governing this case (Ex. 2030). The parties have since submitted additional, unopposed motions to seal. *See* Paper 43 (by Patent Owner); Papers 54 and 66 (by Petitioners).

We heard oral argument on July 16, 2018, in a joint proceeding involving this case and IPR2017-01489 (joined with IPR2017-01240). A transcript of that proceeding is entered as Paper 84 ("Tr.").

B. Related Proceedings

According to the parties, the '213 patent is at issue in *Amgen Inc. v. Genentech, Inc.*, No. 2-17-cv-07349 (C.D. Cal.); *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01407 (D. Del.); *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01471 (D. Del.); *Genentech, Inc.. v. Pfizer, Inc.* (D. Del.) 1:17-cv-01672 (D. Del); *Celltrion, Inc. v. Genentech, Inc.*, No. 3-18-cv-00274 (N.D. Cal.); *Genentech, Inc. v. Celltrion, Inc.*, No. 1-18-cv-00095 (D. Del.); *Genentech, Inc. v. Amgen, Inc.*, No. 1-18-cv-00924 (D. Del.); and *Genentech Inc. v.*

Celltrion, Inc., No. 1-18-cv-01025 (D. Del.). Paper 16, 1; Paper 29, 1; Paper 40, 1; Paper 41, 1; Paper 78, 1–2.

The '213 patent was the subject of two earlier IPR proceedings filed by Mylan Pharmaceuticals Inc., IPR2016–01693 and IPR2016–01694, which we terminated on March 10, 2017, in response to the parties' Joint Motion to Terminate. *See* IPR2016–01693, Paper 24; IPR2016–01694, Paper 23.

In addition to the present case, the '213 patent is the subject of the following pending matters: IPR2017-01489, brought by Pfizer, Inc.; IPR2017-01373 and IPR2017-01374, brought by Celltrion, Inc.; and IPR2017-02139 and IPR2017-02140, brought by Samsung Bioepis Co., Ltd.

The '213 patent was also the subject of IPR2017-02031 and IPR2017-02032 brought by Boehringer Ingelheim Pharmaceuticals, Inc. but these cases have been terminated in light of the Petitioners' unopposed motions for adverse judgement. IPR2017-02031, Paper 32; IPR2017-02032, Paper 30.

C. The '213 Patent and Relevant Background

The '213 patent issued to Drs. Leonard G. Presta and Paul J. Carter on June 18, 2002, bearing the title "Method for Making Humanized Antibodies." Ex. 1001, (54), (75). According to the Specification, the patent relates to "methods for the preparation and use of variant antibodies and finds application particularly in the fields of immunology and cancer diagnosis and therapy." *Id.* at 1:12–14.

A naturally occurring antibody (immunoglobulin) comprises two heavy chains and two light chains. *Id.* at 1:18–20. Each heavy chain has a

variable domain (V_H) and a number of constant domains. *Id.* at 1:21–23. Each light chain has a variable domain (V_L) and a constant domain. *Id.* at 1:23–24.

The variable domains are involved directly in binding the antibody to the antigen. *Id.* at 1:36–38. Each variable domain "comprises four framework (FR) regions, whose sequences are somewhat conserved, connected by three hyper-variable or complementarity determining regions (CDRs)." *Id.* at 1:40–43. The constant domains are not involved directly in binding the antibody to an antigen, but contribute to various effector functions. *Id.* at 1:33–34.

Monoclonal antibodies are generally derived from animals, frequently mice, and target a specific antigen. *See id.* at 1:51–53. Prior to the filing of the '213 patent, it was recognized that these antibodies were frequently antigenic in human clinical use, resulting in, for example, undesirable anti-globulin responses during therapy. *Id.* at 1:54–56. Researchers attempted to address this problem by constructing chimeric and humanized antibodies comprising mixtures of rodent and human protein sequences. The '213 patent defines chimeric antibodies as those "in which an animal antigen-binding variable domain is coupled to a human constant domain" (*id.* at 1:60–62), whereas "humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies" (*id.* at 2:32–35).

The '213 patent also acknowledges the following as known in the prior art: The function of an antibody is dependent on its three-dimensional structure, and amino acid substitutions can change the three-dimensional structure of an antibody. *Id.* at 3:40–43. Although substituting the CDRs of

a human antibody with CDRs from a rodent antibody may be sufficient to transfer high antigen binding affinity from the rodent antibody, it is sometimes necessary to further replace one or more of the human framework residues with a non-human residue. *Id.* at 2:53–61. Thus, "[f]or a given antibody[,] a small number of FR residues are anticipated to be important for antigen binding" because they either directly contact an antigen or "critically affect[] the conformation of particular CDRs and thus their contribution to antigen binding." *Id.* at 2:62–3:8. In addition, an antibody variable domain "may contain glycosylation sites, and that this glycosylation may improve or abolish antigen binding." *Id.* at 3:9–12. Further, the antigen binding affinity of a humanized antibody can be increased by mutagenesis based upon molecular modelling. *Id.* at 3:44–46.[2]

Despite such knowledge in the field, according to the '213 patent, at the time of its invention, humanizing an antibody with retention of high affinity for antigen and other desired biological activities was difficult to achieve using then-available procedures. *Id.* at 3:50–52. The '213 patent purportedly provides methods for rationalizing the selection of sites for substitution in preparing humanized antibodies and thereby increasing the efficiency of antibody humanization. *Id.* at 3:53–55.

[2] Although undisputed that humanization tends to reduce immunogenicity as compared to the non-human parent antibody, Patent Owner points out that framework substitutions tend to "increase the potential for immunogenicity by introducing non-human residues into the humanized sequence," and "[t]he purpose of framework substitutions is to improve binding affinity, which must be balanced against the increased risk of immunogenicity." PO Resp. 61 n.12 (citing Ex. 2041 ¶¶ 83, 223; Ex. 2039 55:5–9).

D. Challenged Claims and Reviewed Ground of Unpatentability

We instituted trial on claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–67, 69, and 71–81 under the following Grounds:

Ground	Claim(s)	Basis	Reference(s)
1	1, 2, 25, 29, 63, 66, 67, 71, 72, 75, 76, 80, and 81	§ 102	Kurrle[3]
2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990[4]
3	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81	§ 103	Kurrle and Queen 1990
4	12	§ 103	Kurrle, Queen 1990, and Furey [5]
5	73 and 77	§ 103	Kurrle, Queen 1990, and Chothia & Lesk[6]
6	74	§ 103	Kurrle, Queen 1990, and Chothia 1985[7]
7	65 and 79	§ 103	Kurrle, Queen 1990, Chothia & Lesk, and Chothia 1985
8	30, 31, 33, and 42	§ 103	Queen 1990 and Hudziak[8]
9	42	§ 103	Queen 1990, Hudziak and Furey

[3] Kurrle, et al., European Patent Application Publication No. 0403156 A1, published December 19, 1990. Ex. 1071.
[4] Queen, et al., International Publication No. WO 1990/07861, published July 26, 1990. Ex. 1050.
[5] Furey et al., *Structure of a Novel Bence-Jones Protein (Rhe) Fragment at 1.6 Å Resolution*, 167 J. MOL. BIOL. 661–92 (1983). Ex. 1125.
[6] Chothia and Lesk, *Canonical Structures for the Hypervariable Regions of Immunoglobulins*, 196 J. MOL. BIOL. 901–17 (1987). Ex. 1062.
[7] Chothia et al., *Domain Association in Immunoglobulin Molecules: The Packing of Variable Domains*, 186 J. MOL. BIOL. 651–63 (1985). Ex. 1063.
[8] Hudziak et al., *p185^{HER2} Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor*, 9 MOL. CELL BIOL. 1165–72 (1989). Ex. 1021.

Ground	Claim(s)	Basis	Reference(s)
10	60	§ 103	Queen 1990, Hudziak, and Chothia & Lesk

Claims 1, 30, 62–64, 66, 79, and 80 are independent. Claim 1 is illustrative:

> 1. A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, utilizing the numbering system set forth in Kabat.[9]

II. ANALYSIS

A. Legal Standards

To anticipate a claim under 35 U.S.C. § 102, "a single prior art reference must expressly or inherently disclose each claim limitation."[10] *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.

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[9] *See* Ex. 1001, 10:45–56 (indicating that the Kabat numbering scheme for antibodies "assign[s] a residue number to each amino acid in a listed sequence").

[10] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '213 patent have an effective filing date before the effective date of the applicable AIA amendments, throughout this Final Written Decision we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

2002). While the elements must be arranged in the same way as is recited in the claim, "the reference need not satisfy an *ipsissimis verbis* test." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). Moreover, "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).

In order to support an anticipation rejection, a prior art "reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972)(emphasis omitted). Moreover, when a

> prior art reference merely discloses a genus and the claim at issue recites a species of that genus . . . the issue of anticipation turns on whether the genus was of such a defined and limited class that one of ordinary skill in the art could "at once envisage" each member of the genus.

Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356, 1361 (Fed. Cir. 2012) (citing *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006)).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented 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 based on 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, if present. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[T]he [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. Moreover, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (citations omitted).

We analyze the instituted grounds of unpatentability in accordance with these principles.

B. Person of Ordinary Skill in the Art

The parties propose similar definitions of a person of ordinary skill for the '213 patent. *See* Pet. 15–16; Prelim. Resp. 18; PO Resp. 18. In our institution decision, we adopted Patent Owner's proposal that "[a] person of ordinary skill for the '213 patent would have had a Ph.D. or equivalent in chemistry, biochemistry, structural biology, or a closely related field, and experience with antibody structural characterization, engineering, and/or biological testing, or an M.D. with practical academic or industrial experience in antibody development." Dec. 8. Petitioners do not contest

this definition in its Reply and we find no reason to revise our earlier determination.

We further note that the prior art itself demonstrates this 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 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))).

C. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted 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) (2018); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016) (upholding the use of the broadest reasonable interpretation standard). Under that standard, we presume that a claim term carries its "ordinary and customary meaning," which "is the meaning that the term would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *see also Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016) ("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."). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Limitations, however, may not be read from the specification into the claims (*In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993)), nor may the Board "construe

claims during [an *inter partes* review] so broadly that its constructions are unreasonable under general claim construction principles" (*Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015), *overruled on other grounds by Aqua Products, Inc. v. Matal*, 872 F.3d 1290 (Fed. Cir. 2017)).

1. "Consensus human variable domain"

Patent Owner proposes that we construe the term "consensus human variable domain," which appears in claims 4, 33, 62, and 69, to mean "a human variable domain which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." Prelim. Resp. 18–19; PO Resp. 19. Patent Owner correctly points out that this "construction comes directly from the definition provided in the '213 patent." Prelim. Resp. 19 (citing Ex. 1001, 11:32–38). Petitioners expressly adopt this construction in their Reply. Pet. Reply 5–6. We do not agree, however, that the claims demand a consensus of "all" human immunoglobulins in the literal sense. Indeed, Petitioners point out that "the 'consensus' sequence used for the patent variants was generated using the most common residue at each position identified in [Kabat 1987[11]]." Pet. Reply 15 (citations omitted). And though Patent Owner attempts to distinguish Queen 1990 as describing "a consensus framework from ***many*** human antibodies,' not ***all*** as in the '213 patent,'" it presents no argument as to why we should interpret the claim in this manner.

[11] Kabat et al., *Sequences of Proteins of Immunological Interest: Tabulation and Analysis of Amino Acid and Nucleic Acid Sequences of Precursors, V-Regions, C-Regions, J-Chain, T-Cell Receptor for Antigen, T-Cell Surface Antigens β_2-Microglobulin, Major Histocompatibility Antigens, Thy-1 Complement, C-Reactive Protein, Thymopoietin, Post-Gamma Globulin, and α_2-Macroblobulin*, 41–175 (4th Ed. 1987). Ex. 1052.

See PO Resp. 47. Moreover, in a parallel proceeding involving the same patent, Patent Owner did not dispute that the reference to "all sequences" in the patent, "refer[s] to all known sequences and there's no dispute . . . that was really synonymous with Kabat 1987." *See* IPR2017-01374 Paper 82, Tr. 15:4–16:4; *see* Ex. 1202 ¶ 157; Ex. 2105 ¶¶ 24–25; Ex. 2107 ¶¶ 18–19; Ex. 1198, 56:20–61:24; Ex. 1199, 27:14–28:13, 29:25–36:2, 57:1–58:6, 115:7–17, 165:17–169:9. Indeed, in a similar parallel proceeding, counsel for Patent Owner acknowledged that the term "all human immunoglobulins" refers to "all reasonably available[,] all known at the time of the invention." IPR2017-01373, Paper 83, 47:21–48:5. Accordingly, we adopt the parties' proposed construction, with a clarifying modification, specifically, "a human variable domain which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure, as set forth in Kabat 1987."

2. "lacks immunogenicity compared to a non-human parent antibody"

Independent claim 63 is directed to "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient." In our institution decision, we determined that this claim language "refer[s] to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody." Dec. 10–12. Neither party disputes this interpretation. *See* PO Resp. 19; Pet. Reply 5–6.

Consistent with claim 63's express comparison between the immunogenicity of the claimed humanized antibody and that of its non-human parent, the Specification states that one object of the invention is to

"to provide methods for the preparation of antibodies which are less antigenic in humans than non-human antibodies but have desired antigen binding and other characteristics and activities." Ex. 1001, 4:24–28. The Specification similarly states that embodiments within the scope of the claims have "low immunogenicity," or are designed to "minimize the potential immunogenicity of the resulting humanized antibody in the clinic." *Id.* at 52:54–58, 61:56–61. Moreover, with reference to claim 63 in particular, Patent Owner points to the '272 application as "explain[ing] that the purpose of humanizing antibodies using its consensus sequence approach is to reduce immunogenicity versus the non-human parent antibody. (*Id.*, 6:24–30, 84:24–30.)." Prelim. Resp. 42 (citing Ex. 2032 (File History for U.S. Patent Application No. 07/715,272 ("the '272 application")); *see also id.* at 38 (indicating that the limitation is satisfied where "[o]nly 1 out of 885 patients experienced an immunogenic response . . . which was a substantial improvement over the murine 4D5 antibody").

In light of the above, we do not alter our prior determination that "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient," refers to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody.

3. Other Limitations

On pages 16–18 of its Petition, Petitioners propose constructions for "humanized" (claims 1, 30, 62–64, 66, 79, 80); "and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of" (claims 1, 30, 62, 63, 66, 79, and 80); "numbering system set forth in Kabat" (claims 1, 30, 62, 63, 66, 79, and 80); and "up to

3-fold more" (claim 65). Patent Owner does not dispute Petitioners' proposed constructions, but asserts that "[n]o construction of those terms is necessary." Prelim. Resp. 19; PO Resp. 19. On the present record, we agree with Patent Owner that the terms identified by Petitioners need not be construed to resolve the issues presently before us. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (instructing that claim terms need only be construed to the extent necessary to resolve the controversy).

D. Prior-Art Status of Kurrle and Queen 1990

Petitioners assert that Kurrle and Queen 1990 are prior art for all challenged claims. Pet. 1–2 & n.3, 13, 19–23, 27. Patent Owner disagrees, at least with respect to claims 12, 42, 60, 65, 71, 73–74, and 79.[12] PO Resp. 23–44. In particular, Patent Owner contends that each element of those claims was reduced to practice prior to the publication of Kurrle and Queen 1990, i.e., before July 26, 1990. *Id.*

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never

[12] Patent Owner initially attempted to disqualify Kurrle and Queen 1990 as prior art with respect to all challenged claims, arguing that each claim was actually reduced to practice before either Kurrle or Queen 1990 was published (Prelim. Resp. 20–43), but now limits it antedation contentions to claims 12, 42, 60, 65, 71, 73–74, and 79 (*see* PO Resp. 24).

shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). The petitioner also has the initial burden of production to show that an asserted reference qualifies as prior art under 35 U.S.C. § 102. *Id.* at 1379; *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) (holding that the challenger "bore the burden of persuasion . . . on all issues relating to the status of [the asserted reference] as prior art"). Should Petitioners meet that initial burden, the burden of production shifts to the patent owner to argue or produce evidence that either the asserted reference does not render the challenged claims unpatentable, or the reference is not prior art. *Dynamic Drinkware*, 800 F.3d at 1378 (citing *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008)). Patent Owner may, therefore, antedate Kurrle and Queen 1990 by establishing reduction to practice prior to the earliest priority date of the '213 patent. *See Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1365 (Fed. Cir. 2001) ("To antedate . . . an invention, a party must show either an earlier reduction to practice, or an earlier conception followed by a diligent reduction to practice.") (citation omitted).

The '213 patent issued from application number 08/146,206 ("the '206 application"), which is an application that entered the national stage on November 17, 1993, from a PCT application filed on June 15, 1992. Ex. 1001, (21), (22), (86). The '206 application is also a continuation-in-part of the '272 application, filed on June 14, 1991. *Id.* at (63). Kurrle was published on December 19, 1990 (Ex. 1071, (43)), and Queen 1990 was published on July 26, 1990 (Ex. 1050, (43)), both of which predate the earliest possible priority date, June 14, 1991, shown on the face of the '213 patent. Accordingly, Petitioners have satisfied their initial burden of

showing that Kurrle and Queen 1990, on their face, qualify as prior art to the challenged claims. We next consider whether Patent Owner has antedated these references.

1. Whether Kurrle and Queen 1990 are prior art under § 102(b)

As a preliminary matter, antedating a reference is unavailable if the reference qualifies as prior art under 35 U.S.C. § 102(b). *See* 37 C.F.R. § 1.131(a)(2). Accordingly, we need not address Patent Owner's antedation evidence unless the challenged claims are entitled to benefit of priority no more than one year from the publication date of Kurrle and Queen 1990. *See id.* To make that assessment we first consider the priority date entitlement of claims 12, 42, 60, 65, 71, 73–74, and 79.

As noted by Petitioners, "the '272 application identifies . . . eight humanized antibody variants made by the inventors—huMAb4D5-1 through 8." Pet. Reply 7 (citing Ex. 2032, 93). Relying on the characterization of those variants in the '272 application, and the detailed testimony of Dr. Wilson (Ex. 2041 ¶¶ 88–95), Patent Owner argues that claims 12, 42, 60, 65, 71, 73–74, and 79 are entitled to a priority date of June 14, 1991, because each element of those claims finds written description and enablement support in the '272 application. PO Resp. 42–44. Accordingly, Patent Owner argues, Kurrle and Queen 1990 do not qualify as prior art under § 102(b) because they were published within one year of the critical date (December 19, 1990 and July 26, 1990, respectively). *Id.*

In opposing Patent Owner's position, Petitioners broadly contend that the '272 application fails to support the full scope of the claims because "[e]ven if one or more variants was within the claims, the claims also encompass countless other variants with any combination of recited

substitutions, most being unrepresented in any '272 embodiment." Pet. Reply 8. We do not find Petitioners' argument persuasive in light of Patent Owner's evidence showing that the '272 application discloses, *inter alia*, each of the framework substitutions recited in claims 12, 42, 60, 65, 71, 73–74, and 79 (collectively, 66L, 71H, 73H, 78H, 93H), along with "a generalized scheme for humanizing any non-human antibody." *See* PO Resp. 43–44 (citing Ex. 2032, 87–90, 93; Ex. 2041 ¶¶ 91–95).

Petitioners further reference the language of claims 1 and 30 (from which claims 12, 42, 60, 65, 71, and 73–74 depend), requiring a "non-human Complementarity Determining Region (CDR)," and corresponding language in claim 79 ("Complementarity Determining Region (CDR) amino acid residues of the non-human parent antibody"). *See* Pet. Reply 7. According to Petitioners, this claim language requires "the ***entire*** CDRs to be from mouse," whereas the eight exemplified humanized antibody variants in the '272 application incorporate CDRs having both human and mouse residues. *Id.* We do not find Petitioners' argument persuasive.

As an initial matter, we are not convinced that the plain language of claims 1 and 79 requires the absence of any human residues in the CDR regions. Because human sequences, by definition, do not encompass mouse-specific sequences, the "non-human Complementarity Determining Region" of claim 1 encompasses CDRs with a mixture of mouse and human residues. In other words, the language "comprising non-human Complementarity Region (CDR) amino acid residues" means that the sequence must contain non-human amino acid residues but does not exclude other residues absent express language to the contrary. Similarly, with respect to claim 79, the "Complementarity Determining Region (CDR) amino acid residues of the

non-human parent antibody" is, on its face, broad enough to encompass a non-human parent antibody having a CDR that includes some human residues.

Petitioners point to nothing in the Specification or prosecution history to support their position, but base this interpretation on a brief passage from Dr. Presta's deposition. *Id.*; Ex. 1202 ¶¶ 85–86. As we read the relevant passage, however, the questioning is focused on "how many CDR residues, which bind an antigen, must be brought over into the humanized antibody," to which Dr. Presta, eventually answered: "[T]he first step [was] bringing over [all] the CDRs." *See* Ex. 1199, 23 (85:10–87:7).

Taken in context, Dr. Presta does not, as Petitioners urge, admit that the CDRs of the claimed humanized antibody comprise solely mouse (or other non-human) sequence, only that "the first step" in constructing an antibody within the scope of claim 1 may involve the transfer of CDRs from a non-human source. Nor does Dr. Presta suggest that the non-human CDRs must consist solely of non-human residues—either during the "first step" or the subsequent construction of the humanized antibody.

Petitioners further contend that Applicants did not have possession of the claimed sequences because each of the exemplified humanized antibodies had at least one framework substitution "***outside*** the recited Markush groups. . . . . [and] PO has not rebutted the presumption the Markush groups are closed." Pet. Reply 7–8. We do not find Petitioners' argument persuasive. Claim 1 recites "a humanized antibody variable domain . . . further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of : . . ." Although the plain language of claim 1 requires at least one framework substitution set

forth in the Markush group, the "comprising" language of the claim does not prohibit additional framework substitutions. *See* PO Resp. 53 (stating that the claims "do not exclude substitutions in addition to those specifically recited"). Had Applicants so intended, they would have drafted the claim to make that clear. Absent such language, we interpret claim 1 as permissive of additional framework region substitutions.

In view of the above, we agree with Patent Owner that claims 12, 42, 60, 65, 71, 73–74, and 79 are entitled to a priority date of June 14, 1991, which is less than one year before the publication dates of Kurrle and Queen 1990. Accordingly, Kurrle and Queen 1990 are not prior art under § 102(b).

2. Patent Owner's Evidence of Prior Invention

Reduction to practice is a question of law predicated on subsidiary factual findings. *Brown v. Barbacid*, 276 F.3d 1327, 1332 (Fed. Cir. 2002). To establish an actual reduction to practice, the inventor must prove that: (1) an embodiment of the invention was constructed that meets all the limitations of the claim at issue; and (2) the inventor appreciated that the invention would work for its intended purpose. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998).

Relying largely on the declaration testimony of Drs. Presta and Carter (Exs. 2016 and 2017, respectively) and their contemporaneous notebooks (Exs. 2001–2004), Patent Owner presents a detailed account of the construction and testing of humanized antibody variants with CDR residues from the mouse 4D5 antibody, which binds to $p185^{HER}$. *See* PO Resp. 23–44. Among these variants, Patent Owner focuses on the development of humanized antibodies HuMAb4D5-5 and HuMAb4D5-8 prior to the publication date of Kurrle and Queen 1990. *See id.*

Petitioners respond that Patent Owner's evidence is insufficient to antedate Kurrle and Queen 1990 because a) HuMAb4D5-5 and HuMAb4D5-8 do not meet all limitations of claims 12, 42, 60, 65, 71, 73–74, and 79; b) the inventors did not establish that HuMAb4D5-5 and HuMAb4D5-8 would work for their intended purpose; and c) the inventor's testimony is not properly corroborated. Pet. Reply 8–12, Paper 67. We address Petitioners' arguments in turn.[13]

a) Whether HuMAb4D5-5 and HuMAb4D5-8 Meet All Limitations of the Claims

According to Petitioners, "none of the variants made by the inventors is an 'embodiment' that meets 'all the limitations.'" Pet. Reply 11. As we understand the argument, Petitioners again contend that the claims require "the ***entire*** CDRs to be from mouse," whereas HuMAb4D5-5 and HuMAb4D5-8 incorporate CDRs having both human and mouse residues. *See* Pet. Reply 7. For the reasons discussed in section II(C)(1), above, with respect to the '272 application, we do not find this argument persuasive.

We also do not find persuasive Petitioners' argument that Patent Owner "provides no expert testimony comparing the inventors' work to the claims, nor did the inventors perform such analysis." Pet. Reply 11. Petitioners point to no legal authority requiring an expert or inventor to conduct this analysis. Considering Patent Owner's detailed references to the proffered evidence, we are persuaded that that HuMAb4D5-5 and

[13] As Patent Owner points out, during the prosecution leading to issuance of the '231 patent, applicants successfully antedated another reference with evidence of prior invention of HuMAb4D5-5. *See* PO Resp. 11; Ex. 1002-9, 4432–37, 4443.

HuMAb4D5-8 embody claims 12, 42, 60, 65, 71, 73–74, and 79. *See, e.g.*, PO Resp. 36–39 (claim chart and other comparisons between claim elements and record evidence).

b) Whether HuMAb4D5-5 and HuMAb4D5-8 would Work for Their Intended Purpose

Petitioners further argue that Patent Owner's antedation evidence fails to establish that HuMAb4D5-5 and HuMAb4D5-8 would work for their intended purpose. Pet. Reply 11. In particular, Petitioners assert that the intended purpose of the invention is to treat humans, which Petitioners contend requires both sufficient binding and "reduced immunogenicity." *Id.* Although Patent Owner sufficiently documents the binding properties of HuMAb4D5-5 and HuMAb4D5-8 (*see* PO Resp. 39–40), Petitioners argue that Patent Owner fails to provide any evidence of immunogenicity testing. Pet. Reply 11–12.

We do not find Petitioners' arguments persuasive. First, notwithstanding the testimony of Drs. Carter, Presta, and Wilson, indicating that a goal of the project was to develop an antibody that was less immunogenic than its non-human parent, none of claims 12, 42, 60, 65, 71, 73–74, and 79 require "reduced immunogenicity." *See* Pet. Reply 11 (citing Ex. 1198, 29:17–32:15; Ex. 1199, 110:21–111:22; Ex. 1197, 101:19–103:5. In contrast, claim 63 of the '213 patent is expressly directed to a humanized antibody that "lacks immunogenicity compared to a non-human parent antibody." Claim differentiation would thus suggest that "reduced antigenicity" is not an element of claims 12, 42, 60, 65, 71, 73–74, and 79. *See* Section II(C)(2), above (equating "lacks immunogenicity" with "reduced immunogenicity").

Petitioners' argument is also undercut by their assertion that "immunogenicity compared to a non-human parent [is] an inherent aspect of the claimed humanized antibodies." Pet. 31. In light of Petitioners' admission, HuMAb4D5-5 and HuMAb4D5-8 would necessarily have such "reduced immunogenicity." Alternatively, to the extent Petitioners are incorrect about the inherency of reduced immunogenicity, neither Kurrle nor Queen 1990 provides evidence of immunogenicity testing, and Patent Owner has antedated as much of the claimed invention as shown in those references. *See In re Stempel*, 241 F.2d 755, 759 (1957) ("all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference"); *In re Stryker*, 435 F.2d 1340, 1341 (1971). In either case, Petitioners do not persuade us that Patent Owner's antedation proofs are insufficient for failing to establish that HuMAb4D5-5 and HuMAb4D5-8 would not work for their intended purpose.

c) Whether the Inventor's Testimony Is Credible and Sufficiently Corroborated

Petitioners argue that we should reject Patent Owner's antedation evidence for lack of sufficient corroboration. In particular, Petitioners attack 1) the credibility of the inventor's testimony; 2) Patent Owner's evidence of corroboration; and 3) the authenticity of documents Patent Owner relies on for corroboration. Although we do not find any of Petitioners' arguments persuasive, we address only the first two of these arguments here, whereas Petitioners' authenticity contentions are addressed in the context of their motion to exclude evidence. *See* section III(A)(1), below.

Petitioners first argue that the inventors' testimony lacks credibility because during their respective depositions, each inventor took credit for first suggesting the "consensus" approach. Pet. Reply 9 (citing Ex. 1199, 26:7:27–13 (Dr. Presta testifying that he shared his idea of a consensus sequence with Dr. Carter "soon after we started the project"; Ex. 1198, 50:17–51:11 (Dr. Carter testifying that: "To the best of my recollection, more than 30 years later, it was my idea. Clearly, it requires expertise from Dr. Presta to really reduce to practice.")). Given the passage of time—and the lack of any suggestion that some third party conceived of an underlying basis for the invention—we find it irrelevant that there is some uncertainty about which of the two named inventors first suggested the "consensus" approach. We find far more pertinent the evidence of Patent Owner's internal documents showing that Drs. Presta and Carter worked together–with the assistance of Genentech technical staff–to reduce the invention of claims 12, 42, 60, 65, 71, 73–74, and 79 to practice. *See* generally, PO Resp. 23–42.

With respect to those documents, Petitioners note that the inventors' notebooks are "***unwitnessed*** and, on some pages, ***unsigned***," and, thus, "[s]uch undated, unwitnessed notebooks ***cannot*** corroborate [the] invention." Pet. Reply 9–10.[14] In support, Petitioners cite *Medichem S.A. v.*

[14] Although Petitioners correctly note that the inventor's notebooks are unwitnessed, we disagree with Petitioner's suggestion that they are substantially unsigned and undated. The four inventor notebooks in evidence are clear, well organized, and each set of experiments bears the inventor's dated signature. *See* Ex. 2001, 13–14, 16–19, 20, 23, 24, 27–41, 43–63, 65, 68–71, 73, 74, 77–84, 90; Ex. 2002, 25, 29, 31–43, 46, 51, 59–61, 64–68; Ex. 2003, 13–110; Ex. 2004, 13–36, 38–102, 104–109.

Rolabo, S.L., 437 F.3d 1157, 1170 (Fed. Cir. 2006) and *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 998-99 (Fed. Cir. 2009) for the proposition that an "unwitnessed notebook alone [is] insufficient to support reduction to practice." Pet. Reply 10.

We agree with Petitioners that Patent Owner's evidence of prior invention cannot "depend solely on statements or writings by the inventor himself." *Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998). But Patent Owner's evidence is not limited to the inventors' notebooks and testimony. *See Medichem* 437 F.3d at 1171 ("Independent corroboration may consist of testimony of a witness, other than the inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor.") (citation omitted). Moreover, "[s]ufficiency of corroboration is determined using a 'rule of reason' analysis, under which *all* pertinent evidence is examined when determining the credibility of an inventor's testimony." *Medichem* 437 F.3d at 1170 (emphasis added). As the Federal Circuit recently explained, the rule of reason demands requires consideration of this evidence

> as a whole, not individually. Thus, an inventor's conception can be corroborated even though no one piece of evidence in and of itself establishes that fact, and even through circumstantial evidence. At bottom, the goal of the analysis is to determine whether the inventor's story is credible.

NFC Tech., LLC v. Matal, 871 F.3d 1367, 1372 (Fed. Cir. 2017) (internal citations and quotes omitted).

In the present case, Patent Owner's corroboration evidence includes, but is not limited to, Dr. Carter's Synthetic DNA Request for oligonucleotides matching those recited in his notebooks, which were

authorized, approved, and attested to by at least four non-inventors (Ex. 2012; Ex. 2013; *see* Ex. 2017 ¶¶ 40–44, 72–74); the declaration, notebooks, and deposition testimony of John Ridgeway Brady attesting to his work for Dr. Carter expressing and purifying six humanized antibody variants including HuMAb4D5-5 and HuMAb4D5-8[15] (Ex. 2018; Ex. 2005; Ex. 2006; Ex. 1201); and the laboratory notebooks of Ms. Ann Roland (Ex. 2007), Tim Hotaling (Ex. 2008), and Monique Carver (Ex. 2009), documenting binding assays on the variant Fabs and full-length antibody variants (*see* Ex. 2017 ¶¶ 14, 53, 55). We also take note of a Genentech Interoffice Memorandum reporting the minutes of an August 8, 1990, meeting (i.e., well before the December 19, 1990, publication date of Kurrle and within a few weeks of the July 26, 1990, publication date of Queen 1990), congratulating Drs. Carter and Presta for "human[izing] the anti-HER2 Mab 4D5 with impressive speed." Ex. 2015, 1.

We are unpersuaded by Petitioners' argument that Mr. Ridgeway Brady's testimony fails to corroborate the design of the tested antibodies because he did not know what he was testing. *See* Pet. Reply 10; Tr. 55:18–56:4. Not only do these tests correlate with entries in Dr. Carter's notebooks (as do those of at least Ms. Roland and Mr. Hotaling (*see* Ex. 2017 ¶¶ 54, 55), but they eventually resulted in a publication on which Mr. Ridgeway Brady is listed as coauthor. *See* Ex. 2017 ¶¶ 75–76; Ex. 2081 ¶ 5, Ex. 2016

[15] HuMAb4D5-5 and HuMAb4D5-8 are also represented as "variant 1" and "variant 6," respectively, in Patent Owner's antedation proofs. *See e.g.*, Ex. 2017 ¶¶ 31, 76, 77

¶ 5; Ex. 2020). Accordingly, we do not find credible Petitioners' implication that Genentech's technicians were testing something unrelated to HuMAb4D5-5, HuMAb4D5-8, and related variants of the invention.

We are also unpersuaded by Petitioners' suggestion that we disregard Dr. Presta's notebook evidence and testimony because Dr. Presta "admitted he changed dates [in his notebook] without following PO's procedures." Pet. Reply 9 (emphasis omitted). Having considered Dr. Presta's testimony that he changed a date from 1988 to 1989 where the surrounding dates indicated that it was January 1989 and he "was a year behind," gives us little reason to doubt authenticity of that document, and, under the circumstances, speaks to a desire for accuracy. *See* Ex. 1199, 178:24–180:15. In similar regard, we also take into account the testimony of Petitioners' expert, Dr. Foote, who knew Dr. Presta's coinventor, Dr. Carter, by reputation and from their time together in Dr. Gregory Winter's laboratory. *See* Ex. 2039, 153:9–24. Dr. Foote testified the he "considered him a good scientist" and has "no reason to think of Paul Carter as being sloppy or dishonest." *Id.*. at 159:12–16.

3. Kurrle and Queen 1990 are Not Prior Art with Respect to Claims 12, 42, 60, 65, 71, 73–74, and 79

In sum, Patent Owner's evidence of prior invention leaves us with the strong impression that the inventors' story is credible. We find that Patent Owner has sufficiently demonstrated reduction to practice of HuMAb4D5-5 and HuMAb4D5-8 prior to the publication of Kurrle and Queen 1990 such that these references are not prior art with respect to claims 12, 42, 60, 65, 71, 73, 74, and 79. Because each of Petitioners' grounds depends on Kurrle

and/or Queen 1990, Petitioners have not established that any of claims 12, 42, 60, 65, 71, 73, 74, and 79 are unpatentable.

E. Unpatentability of Claims 1, 2, 25, 29, 80, and 81

Petitioners challenge each of claims 1, 2, 25, 29, 80, and 81 as anticipated and obvious over Kurrle and/or Queen 1990. Pet. 28–44; Pet. Reply 6. Patent Owner expressly waives it defenses with respect to these claims, repeatedly stating it "does not defend the patentability of claims 1, 2, 25, 29, 80, and 81." PO Resp. 20–21. A party may request judgment against itself at any time during a proceeding. 37 C.F.R. § 42.73(b). Pursuant to 37 C.F.R. § 42.73(b)(4), "[a]bandonment of the contest" is construed as a request for adverse judgment. On this record, we interpret Patent Owner's express decision not to defend the patentability of a subset of the challenged claims as a request for adverse judgment as to those claims. Under these circumstances, the entry of judgment adverse to the Patent Owner and cancellation of the claims is appropriate. *See Dish Network L.L.C. v. TQ Beta, LLC*, IPR2015-01791, Paper 30 at 5–6 (PTAB 3/16/2017). In the alternative, considering the totality of the evidence and Petitioners' arguments, we find claims 1, 2, 25, 29, 80, and 81 unpatentable as anticipated and obvious in view of Kurrle and/or Queen 1990.

Having determined that Petitioners ***have not*** established by a preponderance of the evidence that any of claims 12, 42, 60, 65, 71, 73, 74, and 79 are unpatentable because neither Kurrle or Queen 1990 is prior art, and, conversely, ***have*** shown by a preponderance of the evidence that claims 1, 2, 25, 29, 80, and 81 are unpatentable as anticipated and obvious in view of Kurrle and/or Queen 1990, we address below the remaining claims—claims 30, 31, 33, 62–64, 66, 67, 69, 72, 75, 76, and 78.

F. Anticipation by Kurrle (Ground 1) and Queen 1990 (Ground 2)

Of the remaining claims at issue, Petitioners challenge claims 63, 66, 67, 72, 75, and 76 as anticipated by Kurrle (*see* Pet. 28–34) and claims 4 and 62–64 as anticipated by Queen. *See* Pet 28–40.

1. Overview of Kurrle (Ex. 1071)

Kurrle discloses "humanised and civilised versions" of monoclonal antibodies against the human alpha/beta T-cell receptor.[16] Ex. 1071, Abstract; *see* Ex. 1003 ¶ 122. In particular, Kurrle discloses the production of chimeric antibodies, i.e., those "having mixed murine and human characteristics in order to improve their effectiveness and/or lower their immunogenicity in patients." Ex. 1071, 3:3–5. In one embodiment, "[o]nly the complementarity deter[min]ing regions and selected framework amino acids necessary for antigen binding are maintained murine. The remaining framework regions are converted to human sequences." *Id.* at 3:9–11. Such alterations to the framework regions "can advantageously be made in the sequence immediately before and after the CDRs." *Id.* at 8:25–26. In particular, Kurrle discloses:

> Molecular models of antibodies have shown that the actual CDR loops can contain amino acids up to 4 amino acids away from the "Kabat" CDRs. Therefore, maintaining at least the major amino acid differences (in size or charge) within 4 amino acids of the CDRs as murine may be beneficial.

Id. at 8:27–29.

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[16] According to Kurrle, "'humanization' has been associated with chimeric constructions in which murine V regions are expressed with human C regions. To avoid confusion, the term 'civilized' is used herein for constructions of 'humanized' V regions expressed with human C regions." Ex. 1071, 8:13–15.

Kurrle also discloses using "a simplified computer model . . . based on sequence homology to other antibodies with solved structures" to "judge proximity of framework amino acids to the CDRs." *Id.* at 8:33–35. Kurrle further discloses changing existing framework residues in accord with the consensus sequences for particular human antibody subgroups. *Id.* at 8:36–47.

Applying these principles, Kurrle discloses four humanized antibodies encompassing mouse-for-human substitutions, including framework region substitutions at positions 1L, 3L, 4L, 42L, 46L, 47L, 48L, 63L, 70L, 71L, 81L, 100L, 106L, 27H, 28H, 30H, 38H, 40H, 48H, 66H, 67H, 69H, 71H, 73H, 76H, 83H, 89H, 90H, 91H, 94H, 105H and 107H. Ex. 1071, Tables 6A, 6B. Ex. 2029, 295:14–21, 297:14–19; Ex. 2041 ¶¶ 130–131; Ex. 1003 ¶¶ 124 & n.12, 158, Exhibit D.

Kurrle further exemplifies the construction of "civilized" antibodies having CDRs of mouse antibody BMA 031 incorporated into the light and heavy changes of human antibody EU, which was selected for its homology to the mouse antibody. Ex. 1071, 8:8–29:40. Kurrle then made further substitutions of residues "in the sequence immediately before and after the CDRs" and "up to 4 amino acids away." *Id.* at 8:25–29. The resulting antibodies were designated BMA 031-EUCIV1 through BMA 031-EUCIV4. *See* id. at 8:40–43, Tables 6A–B. According to Patent Owner's expert, Dr. Wilson, these antibodies had 6, 13, 23, and 34 substitutions, respectively. Ex. 2041 ¶¶ 130–134. Petitioners' expert, Dr. Foote, similarly states that "Kurrle made a total of 13 framework substitutions in the light chain[,] . . . 20 framework substitutions in the heavy chain," and inserted two amino acid residues in the human Eu framework heavy chain to fill the

gap between the mouse and human sequences at positions 103H and 104H. Ex. 1003 ¶ 124 & n.11. Of Kurrles' four constructs, BMA 031-EUCIV4 includes framework region substitutions at positions 4L, 69H, 71H, 73H, and 76H. Ex. 1071 Tables 6A, 6D; Ex. 2041 ¶ 134; Ex. 1003 ¶¶ 111, 123–124, 158, Exhibit D.

2. Analysis of Ground 1

a) Non-human CDRs which Bind Antigen

Petitioners challenge claims 63, 66, 67, 72, 75, and 76 as anticipated by Kurrle. Pet. 28–34. Patent Owner contends that this challenge fails "because Petitioners have not shown that the prior art taught a humanized antibody heavy chain variable domain with the recited substitutions that incorporates non-human CDRs 'which bind antigen,'" as required by independent claims 63 and 66. *See* PO Resp. 45. In particular, Patent Owner contends that although Kurrle discloses an antibody, designated EUCIV-4, having the recited amino acid substitutions, it does not establish that the antibody can bind antigen. *Id.* at 2–3, 45–47. Patent Owner further points out that although Kurrle teaches the need for "[e]xtreme caution . . . . to limit the number of changes," EUCIV-4 contains 34 substitutions. *Id.* at 46 (citing Ex. 1071, 8:42–43; Ex. 2041 ¶¶ 130–34; Ex. 2039, 310:2–10). According to Patent Owner, "Kurle states that other humanized antibodies incorporating the same CDRs [but fewer framework substitutions] were unable to bind antigen." *Id.* at 46 (citing Ex. 1071, 9:17) (emphasis omitted) ("The BMA-EUCIV1 and BMA-EUCIV2 antibodies were unable to bind T cells."). Patent Owner further argues that a scientific publication elaborating on some of the work disclosed in Kurrle fails to mention EUCIV4, "further suggesting that the CDRs incorporated into that antibody sequence were

unable to bind antigen." *Id.* at 46 (citing Ex. 2033, 4366; [17] Ex. 2041 ¶¶ 136, 166).

Relying on the testimony of Dr. Foote, Petitioners respond that it is irrelevant that Kurrle presents no binding data for EUCIV4 because its anticipation argument depends on following Kurrle's criteria for identifying framework region substitutions and testing them one at a time, then in combination, where the resulting humanized antibodies necessarily will include the claimed substitutions. Pet. Reply 13–14. According to Dr. Foote:

> a skilled artisan faced with a set of candidates for substitution would first look to see which were for positions where mouse and human frameworks differed, and then would try the candidates individually and then in combination, consistent with Kurrle's warning to exercise "caution" to limit the numbers of substitutions. (Ex. 1199 (Presta Tr.) at 98:25-99:20, 100:11-102:19; Ex. 1071 (Kurrle) at 8:40-43.) In this way, Kurrle teaches a set of humanized antibodies comprising one or more of the candidate substitutions, depending on the antibody being humanized and the sequence chosen for the framework, which necessarily includes antibodies that include one or more of ***4L***, ***69H***, ***71H***, ***73H*** and ***76H***, and therefore fall within the challenged claims.

Ex. 1202 ¶ 126.

We find Petitioners' inherency argument persuasive with respect to claims 63, 66, 67, 72, and 75, which require single substitutions at position 4L, 69H, 71H, 73H or 76H. We note that Kurrle discloses as many as 48 potential substitutions (Ex. 2029, 295:14–21, 297:14–19; Ex. 2041 ¶¶ 64,

[17] Shearman, et al. *Construction, expression and characterization of humanized antibodies directed against the human a/b T cell receptor*, J. Immunol. 147(12):4366–73, (1991).

131) whereas, in practice, the number of substitutable positions for any particular antibody may be fewer than 48 because the mouse and human sequences of particular amino acids of the framework region may initially be the same. *See* Pet. Reply 3–5; Ex. 1199, 93:19–99:20 (Dr. Presta testifying that "you normally in a humanization end up with ten or less possible sequences, and you make ten, and you test them experimentally, binding being the first step."). As Dr. Foote points out, the '231 patent discloses that "although 'it is not entirely possible to predict in advance what the exact impact of a given substitution will be,' identifying antibodies with the 'desired characteristic' (*i.e.*, binding antigen), is 'per se routine and well within the ordinary skill of the art.'" Ex. 1202 ¶ 133 (citing Ex. 1001, 10:28–34).

On balance, we agree with Petitioners that one of ordinary skill in the art applying Kurrle would necessarily identify substitutions of claims 63, 66, 67, and 72 as binding antigen.[18] Although it may be difficult to predict in advance which of Kurrle's substitutions preserve binding affinity, binding is an inherent property of the antibody itself, and which would become evident upon routine testing.

We do not, however, find Petitioners' argument persuasive with respect to claims 75 and 76, which require substitutions at position 71H and

[18] We further note that twenty-four of the amino acid residues recited in the Markush group of claim 63 are also recited in the Markush group of claim 1. Because Patent Owner has sought adverse judgment against itself as to claim 1 (and Petitioner has shown the unpatentability of claim 1 by a preponderance of the evidence), the selection of amino acid residues alone cannot sustain the patentability of at least claim 63.

at least one other position (selected from the Markush group in claim 75, or specifically 73H in claim 76). The 48 potential single substitutions disclosed in Kurrle provide a large number of potential two-way combinations.[19] Despite Dr. Foote's testimony that one of ordinary skill "faced with a set of candidates for substitution . . . . would try the candidates individually and then in combination" (Ex. 1202 ¶ 126), Petitioners do not persuade us that, faced with need to create and test this many variants, one of ordinary skill in the art would "at once envisage" this particular combination as having enhanced antibody binding ability. *See Wm. Wrigley Jr. Co.*, 683 F.3d at 1361. Moreover, under the present circumstances, where Kurrle provides little guidance as to which substitutions to use and, for example, fails to disclose any antibody binding data for the sole embodiment having substitutions at 71H and 73H, the selection of both of these residues amounts to improper "picking and choosing." *See Arkley*, 455 F.2d at 587.

[19] Merely by way of comparison, the number of unique combinations of n items in groups of size (k) where order is not important can be calculated using the formula n!/k!(n-k)!—which can be simplified for even number groups of paired items as n(n-1)/2. Accordingly, 48 single substitutions can be divided into 1128 unique pairs. Similarly, and pertinent to claims 77 and 79, which require more two substitutions, applying n!/k!(n-k!), 48 items divided into groups of 3 provides 17,296 unordered sets. *See e.g.*, https://www.hackmath.net/en/calculator/combinations-and-permutations?n=48&k=2&order=0&repeat=0. This does not, of course, account for individual cases in which certain framework region amino acids will likely be the same in both the mouse and human sequence. *See* Pet. Reply 3–5; Ex. 1199, 93:19–99:20.

b) Claim 63

Claim 63 recites "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient," which refers to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody. *See* section II(C)(2), above. Petitioners contend that "lacking immunogenicity compared to a non-human parent [antibody is] an inherent aspect of the claimed humanized antibodies." Pet. 31; *see* Ex. 1003 ¶¶ 162–164. According to Petitioners, "because the structural components are the same, the same function (*i.e.*, 'which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient') is also present." Pet. 30–31. Petitioners also refer to Kurrle for stating that after humanization of the variable regions, the resulting chimeric antibody is "essentially a human antibody with a much lower immunogenicity in patients." *Id.* (quoting Ex. 1071, 3:8–12).

Patent Owner responds that "Kurrle contains no data indicating that any of its disclosed antibody sequences are any less immunogenic than the parent non-human antibody," and its "statement that '[t]he resulting mAB of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients' . . . is simply a statement of intended result." PO Resp. 59 (citations omitted). Patent Owner further points to Dr. Foote's admission that, absent testing, "you can't tell" whether a given patient will have an immune response to a particularly humanized antibody. *Id.* (citing Ex. 2013 181:16–23).

Because, as discussed above, one of ordinary skill in the art applying the method of Kurrle would necessarily have identified a substitution within the Markush group of claim 63, we agree with Petitioners that the property of reduced immunogenicity would also be present. Pet. 30–31. Even if, as Patent Owner argues, the statement in Kurrle is merely aspirational, "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Accordingly, and in view of the record as a whole, we conclude that Petitioners have shown by a preponderance of the evidence that claims 63, 66, 67, and 72 are anticipated by Kurrle. Petitioners have not made that showing with respect to claims 75 and 76.

3. Overview of Queen 1990

Queen 1990 notes that humanization of framework amino acids frequently reduces the binding affinity of non-human (e.g., mouse) antibodies. Ex. 1050, 11:27–12:8.[20] To account for this observation, Queen 1990 suggests that human amino acids in the framework region close to the mouse CDRs may result in (1) distortions in the CDRs and (2) the loss of amino acids in framework regions that made contact with the antigen in the original mouse antibody. *Id.* Accordingly, Queen 1990 discloses methods for designing humanized immunoglobulins "hav[ing] a very strong affinity for a desired antigen," by comparing amino acid sequences of a non-human

[20] Unless otherwise noted, we refer to a reference's native page numbers rather than those applied by the parties.

"donor immunoglobulin to corresponding sequences in a collection of human immunoglobulin chains, and selecting as the human immunoglobulin one of the more homologous sequences from the collection." *Id.* Abstract, 12:9–15. Queen's methods apply the following four criteria:

> Criterion I: As acceptor, use a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized, or use a consensus framework from many human antibodies . . . .
>
> . . . .
>
> Criterion II: If an amino acid in the framework of the human acceptor immunoglobulin is unusual (i.e., "rare", which as used herein indicates an amino acid occurring at that position in no more than about 10% of human heavy (respectively light) chain V region sequences in a representative data bank), and if the donor amino acid at that position is typical for human sequences (i.e., "common", which as used herein indicates an amino acid occurring in at least about 25% of sequences in a representative data bank), then the donor amino acid rather than the acceptor may be selected . . . .
>
> Criterion III: In the positions immediately adjacent to the 3 CDR[]s in the humanized immunoglobulin chain, the donor amino acid rather than acceptor amino acid may be selected. These amino acids are particularly likely to interact with the amino acids in the CDR[]s and, if chosen from the acceptor, distort the donor CDR[]s and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen . . . and selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.
>
> Criterion IV: A 3-dimensional model, typically of the original donor antibody, shows that certain amino acids outside of the CDR[]s are close to the CDR[]s and have a good probability of interacting with amino acids in the CDR[]s by hydrogen bonding, Van der Waals forces, hydrophobic interactions, etc. At those amino acid positions, the donor amino

> acid rather than the acceptor immunoglobulin amino acid may be selected. Amino acids according to this criterion will generally have a side chain atom within about 3 angstrom units of some site in the CDR[]s and must contain atoms that could interact with the CDR atoms according to established chemical forces, such as those listed above.

Id. at 12:8–14:25 (internal citations omitted)(some formatting added). According to Queen 1990, "[w]hen combined into an intact antibody, the humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen." *Id.* at 6:21–25.

4. Analysis of Ground 2

Petitioners challenge claims 4 and 62–64 as anticipated by Queen 1990. Pet. 28–34.

a) Framework Region Substitutions That Bind Antigen

As with respect to anticipation by Kurrle, Patent Owner contends that the Ground 2 challenge fails because Queen 1990 does not expressly or inherently disclose "an antibody with the claimed framework substitutions with non-human CDRs that 'bind an antigen.'" PO Resp. 49–50.[21] We do not find Patent Owner's arguments persuasive.

As an initial matter, we credit Petitioners' argument that Queen 1990 Criterion III "inevitably require[s] substitution" of residues 98L and 36H, both of which are expressly recited in the Markush groups of claim 1 (from which claim 4 depends), claim 62, and claim 63, because these residues are

[21] Patent Owner's argument does not expressly include claim 63, which includes the "bind an antigen" limitation. To the extent this is an oversight, we include it here.

"immediately adjacent" to the CDRs. *See* Pet. 35–37. Further, each of claims 4 and 62–64 requires, *inter alia*, at least one framework region substitution. With respect to the number of single-site substitutions taught by Queen 1990, Patent Owner references 23 in connection with Criterion III and 19 associated with Criterion IV. PO Resp. 51 (citing Ex. 1003 ¶ 268; Ex. 2041 ¶ 231), which could account for up to 42 potential single-site substitutions. In parallel with their similar argument as to Ground 1, Petitioners argue that it is irrelevant that Queen 1990 fails to provide binding data as it provides criteria for identifying framework region substitutions, which one of ordinary skill in the art would test one at a time, and where the resulting humanized antibodies necessarily will include the claimed substitutions. Pet. Reply 12–13; *see also* Ex. 1050, 9:3–7 (disclosing "human-like immunoglobulins . . . which have binding affinities of at least about 10^8 M^{-1}, and preferably 10^9 M^{-1} to 10^{10} M^{-1} or stronger"). Considering the evidence presented, we find Petitioners' arguments persuasive for essentially the same reasons discussed in section II(F)(2), above.

b) Claim 63

Also in parallel with its arguments as to Ground 1, Patent Owner argues that Queen 1990 fails to "disclose[] an actual antibody with less immunogenicity than the non-human parent or make it obvious how to achieve that result." PO Resp. 59. For essentially the same reasons as set forth in section II(F)(2), above, we agree with Petitioners that one of ordinary skill in the art applying the method of Queen 1990 would necessarily identify a framework region substitution within the Markush

group of claim 63 (e.g., 98L or 36H), and that variant would inherently have reduced immunogenicity. *See* Pet. 30–31.

c) Consensus Sequence Limitations of Claims 4, 62, and 64

Claims 4 and 62 recite a "consensus human variable domain," which we define as "a human variable domain which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." *See* section II(C)(1), above. Claim 64 similarly recites a "a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup." Patent Owner contends that Petitioners have failed to establish that Queen 1990 teaches the use of a "consensus human variable domain," because rather than deriving a consensus sequence from **all** known antibody sequences of a particular subclass or antibody structure, Queen 1990 describes "a consensus framework from ***many*** human antibodies," for example, "[a] representative collection" of at least 10 to 20 distinct human heavy or light chains. PO Resp. 48–49 (citing Ex. 1050, 12:19–20, 13:3–11; Ex. 2041 ¶¶ 210–211).[22] Patent Owner further argues that Criterion II of Queen 1990 is inapplicable to a consensus sequence generated from all known antibody sequences as it pertains to rare or unusual amino acids residues and in applying that criterion to a subset of all sequences could result in a consensus sequence different from one generated

[22] Although page 47 of the Patent Owner Response refers to a plurality of asserted references, its arguments appear limited to Queen 1990.

using all sequences. *Id.* at 49 (citing Ex. 1050, 13:22–33; Ex. 2041 ¶¶ 208–214; Ex. 2039, 222:12–17).

Defending its position, Petitioners argue that Queen 1990 distinguishes between a best fit/homologous sequence approach and a consensus approach. Pet. 36; Pet. Reply. 15–16. In particular, Petitioners note that Criterion I of Queen 1990 teaches one of skill in the art to use, as the acceptor, "a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized, ***or*** use *a consensus framework from many human antibodies*." Pet. 36; Pet. Reply. 15; Ex. 1050 12:17–20 (emphasis added). Petitioners reasonably argue that Queen 1990's discussion of both "a representative collection of at least about 10 to 20 distinct human heavy chains" and the discussion of rare or unusual amino acids in Criterion II is in reference to the best fit/homologous sequence approach. *See* Pet. Reply 16. With respect to the alternative consensus framework approach, Petitioners presents credible evidence that one of ordinary skill in the art at the time of the invention seeking to employ the consensus approach would rely on or recreate the data of Kabat 1987, and thus derive a consensus framework from many human antibodies as recited in Queen 1990. *See id.* at 15–16 (citations omitted). We further note Petitioners' evidence that, with respect to the end product, there is no meaningful difference between antibodies generated using the "'consensus' approach" as compared to the "best fit" approach. *See id.* at 16.

Accordingly, and in light of our construction of "a consensus human variable domain" as meaning "a human variable domain which comprises the most frequently occurring amino acid residues at each location in all

human immunoglobulins of any particular subclass or subunit structure, as set forth in Kabat 1987," we agree with Petitioners that Queen 1990 teaches the "consensus human variable domain," limitation of claims 4 and 62, and the similar limitation of claim 64.

Accordingly, and in view of the record as a whole, we conclude Petitioners have shown by a preponderance of the evidence that claims 4 and 62–64 are anticipated by Queen 1990.

G. Obviousness (Grounds 3, 5, and 8)

Of the remaining claims at issue, Petitioners challenge claims 4, 62–64, 66, 67, 69, 72, 75, 76, and 78 as obvious in view of Kurrle and Queen 1990 (Ground 3); claim 77 as obvious in view of Kurrle, Queen 1990, and Chothia & Lesk (Ground 5); and claims 30, 31, and 33 as obvious in view of Queen 1990 and Hudziak (Ground 8). *See generally*, Pet. 41–68. We need not specifically address Grounds 4, 6, 7, 9, and 10 for the reasons set forth in sections II(D) and II(E), above.

1. Kurrle and Queen 1990

With respect to Ground 3, Petitioners challenge claims 4, 62–64, 66, 67, 69, 72, 75, 76, and 78 as obvious in view of Kurrle and Queen 1990. Pet. 38–47. Petitioners assert that Queen 1990 "disclosed a detailed pathway for humanizing non-human monoclonal antibodies, with the expectation that the resulting humanized antibodies 'will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin,'" thereby providing "motivation to humanize monoclonal antibodies along with a detailed roadmap for production of humanized monoclonal antibodies" that can be used in human therapeutics. *Id.* at 41–42 (citing Ex. 1050, 6:21–26; Ex. 1003 ¶¶ 203–204).

As Patent Owner points out, Queen 1990 does not expressly disclose any antibody sequence that contains the claimed framework substitutions. Prelim. Resp. 49–51; PO Resp. 15. Petitioner, instead, relies on Queen 1990 for teaching substitution of framework residues "immediately adjacent" to the CDRs as taught in Queen 1990's Criterion III. Pet. 35–36 (citing Ex. 1050, 14:1–12; Ex. 1003 ¶¶ 173–183, Exhibit E). According to Petitioners' expert, even taking into account the slightly different CDR boundaries assigned by Kabat as compared to Chothia and Lesk, only 12 framework residues of the light chain and 12 residues of the heavy chain are immediately adjacent to CDR regions, including the 98L and 36H positions recited in claim 1. Ex. 1003 ¶ 179.[23]

Petitioners contend that Kurrle likewise provides motivation and "a similar roadmap" to obtain a humanized antibody. *Id.* at 43 (citing Ex. 1071, 8:16–40). According to Petitioner, "[u]sing these guidelines, Kurrle made a total of 13 substitutions in the light chain framework region and 18 substitutions in the heavy chain framework region,"[24] including substitutions at positions 4L, 69H, 71H, 73H, and 76H recited in the challenged claims. *Id.* (citing Ex. 1003 ¶¶ 155–158, 206); *see id.* at 20.

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[23] With respect to Ground 5, Petitioner further relies on Chothia & Lesk, and Chothia 1985 for suggesting the importance of substitutions at positions 4L, 62L, 73L, 4H, 36H, 69H, 78H, 92H, and 93H. *See* Pet. 24–25, 52–54.

[24] Patent Owner interprets Kurrle as exemplifying 34 substitutions, whereas Petitioner's expert identifies 32, comprising 13 human to mouse substitutions in the light chain framework region and 19 in the heavy chain framework region, plus a two amino acid insertion between Kabat positions 103 and 104 of the heavy chain. *See* Ex. 2041 ¶¶ 130–134; Ex. 1003 ¶ 124 & n.11. This difference in nomenclature does not affect our analysis.

Noting that the two references were published fewer than six months apart and contain interrelated teachings, Petitioners further argue that one of ordinary skill in the art would have looked to Queen 1990 and Kurrle "to gather as much information as they could to guide their selection of specific residues for substitution in order to maintain the affinity and strength of a particular non-human antibody." *Id.* at 43–44. According to Petitioners, "[t]he combination of Queen 1990 and Kurrle thus provided ample motivation and a reasonable expectation of success that a humanized monoclonal antibody could be obtained with 'a much lower immunogenicity in patients' . . . while maintaining the binding affinity and specificity of the donor monoclonal antibody" by targeting the very species residues satisfying the challenged claims. *Id.* at 44 (quoting Ex. 1071, 3:11–12).

Petitioners note that, before the '213 patent, "[t]he field recognized that earlier efforts (*e.g.*, chimeric antibodies, CDR grafting) often resulted in non-or poor binding, with immunogenicity remaining a concern." Pet. 27 (citing Ex. 1050, 3:30–33; Ex. 1073, 9:12–19; Ex. 1003 ¶¶ 252–253; Ex. 1004 ¶¶ 38–41). Both Kurrle and Queen 1990 teach the design of humanized antibodies with low immunogenicity (*see* Ex. 1050, 6:21–25 (stating the resulting humanized antibody is "substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen"); Ex. 1071, 3:11–12 (stating the resulting humanized antibody is "essentially a human antibody with a much lower immunogenicity in patients")). Because Kurrle and Queen 1990 ((as well as Chothia & Lesk, and Chothia 1985) teach overlapping, and potentially complimentary, sets of candidate amino acids for mouse-to-human

substitution, we agree with Petitioners that an ordinary artisan would have had a reason to combine the teachings of those references.

a) Claims 4, 62, and 69

Claim 62 recites "[a] humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a consensus human variable domain." *See also* claims 4 and 69. With respect to Ground 3, Patent Owner argues that "the asserted references do not teach the consensus sequence limitations" of the challenged claims. PO Resp. 47–49. But as discussed in section II(E)(5)(c), above, we find that one of ordinary skill in the art would recognize Queen 1990 as disclosing a consensus sequence approach for generating humanized antibodies. Accordingly, Patent Owner provides insufficient support for its contention that "the asserted references," collectively, fail to teach this limitation.

Although not necessary to our determination, we also find persuasive Petitioner's evidence that prior to the critical date, "the very first antibody humanized in both chains, which was also the first humanized antibody administered to a patient, had a consensus light chain." Ex. 1202 ¶12; *see id.* at ¶¶ 12, 41, 61, 79, 82, 119, 162; Pet. Reply 27; Ex. 1002-5:2500 (referencing Ex, 1069[25]); Ex. 1193, 106[26] ("The CDR sequences from the kappa light chain were combined with consensus human kappa frameworks.").

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[25] Riechmann et al., *Reshaping Human Antibodies for Therapy*, 332(6162) NATURE 323–27 (1988).
[26] Foote, *Humanized Antibodies*, 61 Nova Acta Leopoldine, 269, 103–110 (1989).

b) Claims 33 and 62

With respect to claims 33 and 62, Patent Owner contends that Queen 1990 does not expressly or inherently disclose an antibody with the claimed framework substitutions and non-human CDRs that "bind an antigen" as required by the claims. PO Resp. 49–50. As an initial matter, we note that claim 62 is challenged under Ground 3, based on the combination of Queen 1990 and Kurrle. As indicated in section II(F)(2), above, Kurrle inherently discloses substitutions 4L, 69H, 71H, 73H and 76H of the Markush group of claim 63 as binding antigen. Given that claim 62 is of similar scope to claim 63 and has an identical Markush group, our analysis applies equally to both claims.

With respect to claim 33, challenged under Ground 8, we have previously determined that one of ordinary skill in the art applying the teachings of Queen 1990 would have necessarily arrived at substitutions for residues 98L and determined that they bind antigen. *See* section II(F)(4), above. Because the Markush group of claim 30, from which claim 33 depends, includes residue 98L, the same analysis applies.

c) Claim 77

In Ground 5, Petitioners rely on Kurrle, Queen 1990, and Chothia & Lesk, which teaches the importance of certain framework residues, including 4L, 62L, 73L, 4H, 36H, 69H, 78H and 92H, for maintaining antibody structure. Ex. 1062, 902, Table 4. Insofar as claim 77 recites amino acid framework substitution comprising residues 71H, 73H, and 78H, Petitioners point to Chothia & Lesk as teaching the importance of residue 78H "for maintaining antibody conformation, and thus antigen binding and specificity." Pet. 53 (citing Ex. 1062, 3, Abstract; Ex. 1003 ¶ 236); *see*

Ex. 1001, 3:1–8 (citing Chothia & Lesk for determining residues "critically affecting the conformation of particular CDRs and thus their contribution to antigen binding").

With respect to claim 77, Patent Owner argues that "Petitioners offer no reason (other than hindsight) why a person of ordinary skill [in the art] would have chosen the specific framework substitutions recited in claim [77] from among the numerous possibilities allegedly disclosed in the asserted references." PO Resp. 52–56. In section II(E)(3)(a), we determined that, in the context of anticipation, the selection of an antibody having substitutions at both 71H and 73H amounts to improper "picking and choosing." A similar analysis applies here: Petitioners do not persuade us that the teachings of Kurrle, Queen 1990, and Chothia & Lesk provide any guidance or motivation for the selection of substitutions at each of 71H, 73H, and 78H, as required by claim 77. As noted above, the 48 potential single substitutions disclosed in Kurrle alone provide more than 1000 potential two-way combinations, and the number of three-way combinations, such as required by claim 77, is substantially larger. *See* section II(F)(2)(a), above. Considering the evidence for unpredictability of framework region substitutions (*see* PO Resp. 54 (citing Ex. 2039, 310:2–10; Ex. 1071, 8:41–42; Ex. 2041 ¶¶ 236–237); Ex. 1071, 8:41–42), we conclude that the effects of substituting framework region residues for any particular antibody were—and quite possibly remain—unpredictable. But despite Dr. Foote's testimony that one of ordinary skill "faced with a set of candidates for substitution . . . . would try the candidates individually and then in combination" (Ex. 1202 ¶ 126), Petitioners do not persuade us that creating and testing this many combinations of variants is less than undue

experimentation. Accordingly, Petitioners have not demonstrated that the three-part substitution of claim 77 is drawn from "a finite number of identified, predictable solutions," nor that the relevant universe is "small or easily traversed." *See* PO Resp. 54–55 (quoting *KSR*, 550 U.S. at 421; *Ortho-McNeil Pharm., Inc v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

d) Claims 30, 31, and 33

Ground 8 addresses whether claims 30, 31, and 33 are obvious over the combination of Queen 1990 and Hudziak. Each of claims 30, 31, and 33 recites a single framework region substitution and requires an antibody that binds $p185^{HER2}$. Ex. 1001, 87:18–28, 87:29–32, 87:36–37, 18:54–55, 19:23–24.

Hudziak discusses the role of $p185^{HER2}$'s role in carcinoma development and discloses that 4D5, "a monoclonal antibody directed against the extracellular domain of $p185^{HER2}$ specifically inhibits the growth of breast tumor-derived cell lines overexpressing the *HER2/c-erbB*-2 gene product." Ex. 1021, Abstract, 1165. In characterizing 4D5, Hudziak reports that "resistance to the cytotoxic effect of tumor necrosis factor alpha, which has been shown to be a consequence of *HER2/c-erbB*-2 overexpression, is significantly reduced in the presence of this antibody." *Id.*, Abstract. According to Hudziak, "4D5 strongly inhibits the growth of several breast tumor cell lines and furthermore sensitizes $p185^{HER2}$-overexpressing breast carcinoma cell lines SK-BR-3 and MDA-MB-175-VII to the cytotoxic effects of TNF-α." *Id.* at 1171. Hudziak concludes that "[m]onoclonal antibodies specific for $p185^{HER2}$ may therefore be useful therapeutic agents for the treatment of human neoplasias." *Id.*

According to Petitioner, in light of Hudziak, one of ordinary skill in the art understood that, as of the filing date of the '231 patent, *HER2* "was a ripe target for therapeutic development." *See* Pet. 57–58 (citing, e.g., Ex. 1004 ¶ 53; Ex. 1003 ¶¶ 331–332, 342). Accordingly, given "the strength of 4D5 as a clinical target, the logical and necessary next step would have been to humanize 4D5." *Id.* at 59 (citing Ex. 1004 ¶ 70; Ex. 1003 ¶ 334).

Patent Owner argues that "Petitioners have presented no evidence that any of [the] framework substitutions recited in claims 30–31, [or] 33 . . . would have been obvious for an antibody that binds $p185^{HER2}$," as such reasoning "would make obvious a humanize antibody for any antigen," in light of the teachings of Kurrle and/or Queen 1990. PO Resp. 62–63 (emphasis omitted). We do not find Patent Owner's argument persuasive. In light of Hudziak, one of ordinary skill in the art would have recognized the benefits of humanizing mouse anti-HER2 4D5 antibodies for human clinical use. Having done so, we agree with Petitioners that it would have been routine to transfer those CDRs to a human framework. *See* Pet. Reply 24–25. And, because Kurrle and Queen 1990 provide general guidance for optimizing any such mouse-human combination, one of ordinary skill in the art would have reasonably applied the principles of Kurrle and/or Queen along with routine testing to arrive at antibodies having one or more of the framework amino acid substitutions recited in claim 30 and its dependent claims 31 and 33. *See id.*

2. Secondary Considerations

Patent Owner argues that objective indicia demonstrate that the challenged claims would not have been obvious based on evidence of unexpected results and commercial success. PO Resp. 64–68. Evidence of

objective indicia, when present, "must always . . . be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983). "For objective evidence of secondary considerations to be accorded substantial weight, its proponents must establish a nexus between the evidence and the merits of the *claimed invention*." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (*quoting Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Establishing nexus, however, requires that the proffered evidence is "commensurate in scope with the claims which the evidence is offered to support." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014) (citations omitted); *see e.g., In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978) ("Establishing that one (or a small number of) species gives unexpected results is inadequate proof, for 'it is the view of this court that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support."'); *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018) ("commensurate in scope" test applied to evidence of commercial success).

According to Patent Owner, the '213 patent provides a "broadly-applicable platform," which "unexpectedly allowed numerous different antibodies to be humanized from a single consensus sequence—without regard to how similar that consensus sequence is to the original non-human antibody." PO Resp. 64–65. We do not find this argument persuasive because, as Petitioners point out, the claims are not directed to a platform or method for humanizing antibodies, but to specific antibodies with specific framework region substitutions. Pet. Reply 25. Moreover, to the extent the independent claims invoke a consensus sequence, that limitation is taught in

the art. *See* Section II(F), above. We also find persuasive Petitioners' argument that "there is no evidence that the 'consensus' approach has ***any*** advantage over the 'best fit' approach in terms of binding affinity or immunogenicity." *See* Pet. Reply 26 (citing Ex. 1197, 184:16–185:7, 187:21–193:6; Ex. 1199, 131:10–141:22; Ex. 1198, 83:7–18; Ex. 1194, 979;[27] Ex. 1002-3, 1362; Ex. 1196, 319–20); *see also id.* at 16 (discussing Dr. Foote's explanation that "there is no meaningful difference between a humanized antibody generated using the 'consensus' and 'best fit' approaches, as the same sequence can arise from both"); Ex. 1202 ¶¶ 62–63.

Patent Owner also argues that "[a]ntibodies embodying the '213 invention lacked immunogenicity even after prolonged use and demonstrated ***superior*** binding affinity to the original non-human antibody." PO Resp. 66; *see* Paper 72, 13. Any evidence for this assertion, however, is limited to claims 30, 31, and 33, which are directed to an antibody that binds $p185^{HER2}$. *See* Ex. 1001, 51:48–53 ("The most potent humanized variant designed by molecular modeling, huMAb4D5-8, contains 5 FR residues from muMAb4D5. This antibody binds the $p185^{HER2}$ ECD 3-fold more tightly than does muMAb4D5 itself."); Ex. 2041 ¶¶ 76–77, 268. We accept Patent Owner's contention that this antibody, specifically, "HuMAb4D5-8[,] was put into clinical development and subsequently approved by the FDA as the drug Herceptin®." Prelim. Resp. 31; *see* PO Resp. 36 n.7, 67–68;

[27] Kolbinger, *et al., Humunization of a Mouse Anti-Human IgE Antibody: A Potential Therapeutic for IgE-Mediated Allergies,* 6(8) PROTEIN ENGINEERING 971–980 (1993).

Ex. 2017 ¶¶ 4, 77; Ex. 2016 ¶ 51; Ex. 1197, 149:18–15:2.[28] Petitioners do not reasonably dispute that huMAb4D5-8 is the active ingredient in Herceptin. *See* Pet. 67–68.

With respect to commercial success, Patent Owner relies on paragraphs 267 and 268 of Dr. Wilson's Declaration in contending that some of its "most successful antibodies embody the '213 claims, including Herceptin®, Perjeta®, Avastin®, Lucentis®, and Xolair®, together generating billions of dollars in revenue annually." PO Resp. 67; Ex. 2029, 2. With the exception of Herceptin, however, Dr. Wilson does little to establish that the recited antibody products embody any claim of the '231 patent. *See* Ex. 2041 ¶¶ 267–268; Ex. 1197, 248:3–12; *see also* Ex. 1198, 39:2–15; Ex. 1199, 43:23–44:4. At best, the referenced paragraphs recite that "[a]ntibodies for a variety of disease conditions made using the '213 invention lacked immunogenicity even after prolonged use and demonstrated ***superior*** binding affinity to the original non-human antibody." Ex. 2041 ¶ 268. This statement, however, goes to unexpected results, rather than commercial success and is supported largely by citations relating to Herceptin and the underlying p185HER2 antibody. *See id.* (citing Ex. 1002-7, 3439–41; Ex. 1001, 51:50–53). Nevertheless, having considered the parties arguments and evidence, we conclude that Herceptin embodies the invention recited in claims 30, 31, and 33.

[28] Patent Owner also points to the declaration of Dr. Shak submitted during the prosecution of the '231 patent. PO Resp. 66 (citing Ex. 1002–7, 3439–41). Although Dr. Shak presents evidence consistent with reduced immunogenicity of Herceptin antibodies (Ex. 1002–7, 3439–40 ¶¶ 2–4), he provides no evidence that any other antibody embodies a claim of the '231 patent (*see id.* at 5–9).

But despite linking huMAb4D5 / Herceptin to claims 30, 31, and 33, Petitioners reasonably argue that Patent Owner has failed to establish the requisite nexus to the claimed invention for two reasons. *See* Pet. 67–68; Pet. Reply 25–29; Ex. 1003 ¶ 353; Ex. 1197, 272:18–274:9. First, as set forth in the '213 Specification, HuMAb4D5 / Herceptin has substitutions at positions 71H, 73H, 78H, 93H, 102H, 55L, and 66L, of which all but 55L and 102H fall within the framework region. *See* Ex. 1001, Table 3; Pet. 67; Prelim. Resp. 65. Of these five framework substitutions, only 78H is recited in the Markush group of claim 30, from which claims 31 and 33 depend. Patent Owner presents no evidence that this particular substitution is sufficient, or even necessary, for the alleged unexpected results and commercial benefits of huMAb4D5 / Herceptin. Conversely, Patent Owner provides no evidence suggesting that substitutions of 102H and 55L in the CDR region of huMAb4D5 / Herceptin are not required for its superior binding affinity.

Second, the Markush group of claim 30 encompasses 27 other single site framework substitutions, thousands of combinations of the recited framework substitutions, and an unknown number of potential non-human CDRs. Given the vast number of species encompassed by the claims, even if Patent Owner had linked the substitution at position 78H to the properties or success of huMAb4D5 / Herceptin, we are not persuaded that such result would inform the full scope of the claims. Thus, in view of the limited evidence for nexus, and the enormous breadth of claims 30, 31, and 33, we accord little weight to Patent Owner's evidence of secondary considerations.

In sum, Patent Owner's secondary considerations evidence is germane only to claims 30, 31, and 33, and where it applies, we accord it little weight.

Balancing all the evidence, we conclude that Petitioners have demonstrated by a preponderance of the evidence that claims 30, 31, and 33 are obvious over the combination of Queen 1990 and Hudziak.

3. Conclusion

Considering all the evidence, Petitioners have demonstrated by a preponderance of the evidence that the following claims are unpatentable: claims 1, 2, 25, 29, 63, 66, 67, 72, 80, and 81 as anticipated by Kurrle; claims 1, 2, 4, 29, 62–64, 80, and 81 as anticipated by Queen 1990; claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 72, 78, 80, and 81 as obvious over Kurrle and Queen 1990; and claims 30, 31, 32 as obvious in view of Queen 1990 and Hudziak.

Petitioners have not demonstrated by a preponderance of the evidence the unpatentability of claims 12, 42, 60, 65, 71, 73–77, and 79.

II. MOTIONS

A. Petitioners' Motion to Exclude Evidence

Petitioners filed one motion to exclude evidence. Paper 67. Patent Owner opposed (Paper 72) and Petitioners submitted a reply in support of their motion (Paper 75).

1. Evidence of Secondary Considerations

In Paper 67, Petitioners seek to exclude Patent Owner's "secondary considerations" evidence (Ex. 2016 ¶¶ 5, 51–53; Ex. 2017 ¶¶ 4, 77–79; Ex. 2041 ¶¶ 83–87, 263–268; Ex. 2029) as "irrelevant (FRE 402), lacking sufficient reliability for expert testimony (FRE 702), and for failing to show supporting facts and/or data (37 C.F.R. § 42.65)." Paper 67, 5. At core, however, is Petitioners' contention that Patent Owner's evidence lacks nexus

to the challenged claims which, as Patent Owner points out, relates to the merits of the case. *See id.* at 5–7; Paper 72, 12. In section II(G)(2), above, we address the merits of Patent Owner's secondary considerations positions. Having already addressed the objected-to evidence on the merits, we see no reason to decide whether any of this evidence should be excluded. Accordingly, we dismiss Petitioners' motion as moot.

2. Notebooks and Internal Documents Relating to Patent Owner's Antedation Proofs (Exhibits 2001–2015)

Petitioners seek to exclude Exhibits 2001–2015 (and testimony predicated thereon) as not authenticated and unreliable. Paper 67, 7–13; Paper 75, 1–4). These documents encompass the inventors notebooks (Ex. 2001–2004) and the notebooks of Genentech technicians (2005–2009), whereas Exhibits 2010–2015 are other internal Genentech documents such as copies of emails, synthetic DNA request forms, project status reports, and meeting minutes. For the reasons set forth at pages 1–12 of Patent Owner's opposition brief (Paper 72), and as discussed above in section II(D)(2)(c), we do not find Petitioners' arguments persuasive.

In particular, we credit Patent Owner's argument that Genentech's records custodian sufficiently authenticated Exhibits 2001–2015 and established their admissibly as business records. Paper 72, 3. We also credit Patent Owner's argument that the inventors themselves authenticated Exhibits 2001–2004 as their own laboratory notebooks (*see id.* at 2), and Exhibits 2010–2015 as internal business records that they recognize from their work at Genentech (*see id.* at 10–11).[29] That Genentech cannot, as

[29] Petitioners appear to conflate authentication with corroboration in arguing that inventors cannot authenticate their own laboratory notebooks. *See*

Petitioners argue, prove the chain of custody for these records since their inception, or that they in some ways deviate from Genentech's record keeping policies does not, standing alone, deprive them of authenticity as internal business records. *See* Paper 67, 8–12.

We are likewise unpersuaded by Petitioners' suggestion that the produced versions of some of the laboratory notebooks differ in some substantive way from those microfilmed in the early 1990s. *See* Paper 67, 2, 8–9.[30] Patent Owner presents a reasoned explanation for the two sets of documents and points out that despite having possession of the second set of documents at the deposition of Genentech's records custodian, Petitioners neither asked the witness about the microfilmed versions, nor attempted to enter them into evidence. *See* Paper 72, 10. Nor did Petitioners at any time seek guidance from the Board regarding the status of the microfilmed versions, request their production, or otherwise investigate any potentially relevant differences between the produced and microfilmed versions of the documents. In light of the arguments and evidence before us, we give no credence to Petitioners' implication that Genentech substantively altered the laboratory notebooks relied on here.[31]

Paper 67, 7–8. At best, the cases Petitioners cite apply to cases involving uncorroborated inventor testimony as discussed on pages 4–6 of Patent Owner's opposition brief.

[30] Petitioners do not contend that the antedation evidence is fraudulent. *See* Tr. 54:18–55:10.

[31] As noted in section II(C)(2)(c), above, the circumstances surrounding Dr. Presta's changing a date in one notebook do not cause us to doubt authenticity of that document.

In sum, having reviewed the challenged documents as a whole, along with the supporting testimony, we are persuaded of their authenticity and reliability. Accordingly, we deny Petitioners' motion to exclude Exhibits 2001–2015 and related testimony.

3. Dr. Wilson's Opinions

Petitioners seek to exclude the totality of Dr. Wilson's opinion testimony based on an interchange at his deposition in which Dr. Wilson "admitted that in conducting his validity analysis he applied a standard requiring ***every*** framework region substitution recited in a claim to be disclosed or obvious." Paper 67, 13–14. We do not find Petitioners' arguments persuasive for the reasons set forth in Patent Owner's opposition brief. Paper 72, 14. As Petitioners would have us read the testimony, Dr. Wilson would only find anticipation if a reference disclosed every substitution recited in a Markush group. Even if true, Petitioners do not explain with specificity how this would impact the opinions in his expert report which, moreover, encompasses opinions on the prior art and claim limitations other than the Markush groups as well as obviousness of the claimed subject matter.

In addition, reading the testimony as a whole, it is not clear whether Dr. Wilson applied an incorrect standard in his declaration, misspoke, or was confused by the questioning. *See* Ex. 1197, 82:7–93:12. Indeed, as Patent Owner points out, during that same line of questioning, Dr. Wilson's testimony did reflect the proper standard with respect to the Markush groups. *See id.* at 84:11–15 (agreeing that "a humanized antibody that has only one of these substitutions listed still would fall within the claims").

Accordingly, we deny Petitioners' motion.

4. Dr. Carter's and Dr. Wilson's Errata

Petitioners seek to exclude errata to Dr. Carter's and Dr. Wilsons's deposition testimony as improper substantive changes to their testimony. Paper 67, 14–15. As we do not expressly rely on the objected-to testimony, we consider Petitioners' request moot.

Moreover, Patent Owner reasonably argues that, when read in context, the errata do not reflect substantive changes in the underlying testimony. Paper 72, 14–15. And to the extent the changes are substantive, Petitioners do not explain their relevance to the outcome of this proceeding. Indeed, that Petitioners did not contact the Board to request a follow-up deposition or other means of clarification, further suggests that the objected-to testimony is of limited relevance. Accordingly, we deny Petitioners' motion.

B. Patent Owner's Motion to Exclude Evidence

Patent Owner filed one motion to exclude evidence. Paper 63. Petitioners opposed (Paper 70) and Patent Owner submitted a reply in support of its motion (Paper 74).

1. The Declaration of Mr. Buss (Ex. 1004)

Patent Owner seeks to exclude paragraphs 15, 16, 18, 30–33, 43–35, 53–55, 63, and 69–70 of Dr. Buss's declaration (Ex. 1004), and testimony relying thereon on grounds that Petitioners have not shown that Mr. Buss is one of ordinary skill in the art, or that they are the product of reliable principles and methods. Paper 63. *Inter alia*, Patent Owner argues that Mr. Buss "copied nearly verbatim the substantive analysis" of Dr. Edward Ball, M.D submitted in *Mylan Pharms. v. Genentech, Inc.*, IPR2016-01694, and "performed no independent research or analysis regarding the subject matter

of the '213 patent." *Id.* at 2. Patent Owner further argues that Mr. Buss lacks the credentials of one of ordinary skill in the art; is not an oncologist like Dr. Ball, does not hold an advanced degree in any relevant field and "his purported expertise derives entirely from the on-the-job experience as a lab technician." *Id.* at 4–5.

Petitioners respond that "Mr. Buss is an 'independent consultant in the antibody engineering field" with "more than 25 years of practical and research experience specializing in antibody design, humanization, and expression," was a "Higher Scientific Officer under Sir Gregory Winter at the Cambridge Centre for Protein Engineering," and has experience "equivalent of a Ph.D. in molecular biology." Paper 70, 2. Petitioners concede that Mr. Buss "based the language in his declaration on that of the declaration of Dr. Edward Ball," but presents evidence that Mr. Buss "conducted his own review and performed his own analysis." *Id.* at 3–4.

As an initial matter, we note that there is no requirement that the Board exclude the testimony of an expert that does not qualify as one of ordinary skill in the art. To the contrary, as recently noted in the August 13, 2018 update to our Trial Practice Guide:

> An expert witness must be qualified as an expert by knowledge, skill, experience, training, or education to testify in the form of an opinion. Fed. R. Evid. 702. There is, however, no requirement of a perfect match between the expert's experience and the relevant field. *SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010). A person may not need to be a person of ordinary skill in the art in order to testify as an expert under Rule 702, but rather must be "qualified in the pertinent art." *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008).

See Notice of Update to Office Patent Trial Practice Guide, 83 Fed. Reg. 156, (Aug. 13, 2018) (text of update available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf).

In the present case, we agree with Petitioners that Dr. Buss is qualified to provide expert testimony based on his background and experience, and Patent Owner's objections go to the weight, not admissibility of this testimony. Although we do take into account the evidence that Buss substantially copied the declaration of another expert from a related case, and the amount of time he spent on his declaration, this also goes the weight we accord his opinions. With respect to that weight, we find compelling Petitioners' argument that Mr. Buss's opinions (most particularly, those relied on in our Decision) are undisputed. *See* Paper 70, 1, 4–5. Accordingly, Patent Owner's motion is denied.

2. Allegedly Improper Reply Evidence Set Forth in Patent Owner's Motion to Strike

Patent Owner moves to exclude the arguments and evidence subject to its motion to strike (Paper 61), which relates to allegedly new arguments set forth in Petitioners' Reply brief. Paper 63, 7–8; Paper 74, 5. We agree with Petitioners that "a motion to exclude is not a proper vehicle for a party to raise the issue of arguments exceeding the permissible scope of a reply." Paper 70 (quoting *Blackberry Corp. v. Zipit Wireless, Inc.*, IPR2014-01508, Paper 49 at 40 (Mar. 29, 2016)). Patent Owner's arguments are also redundant or subsumed by its motion to strike. Accordingly, we deny Patent Owner's motion.

C. Patent Owner's Motion to Strike

Patent Owner filed an authorized motion to strike Exhibit 1193 (Foote 1989) testimony related thereto as improper new evidence presented in the Reply, as well as the allegedly new argument that Kurrle discloses a humanized antibody with a consensus sequence. Paper 61. We do not find Patent Owner's arguments persuasive for the reasons set forth in Petitioners' brief in opposition (Paper 73), which we adopt. Petitioners argue persuasively that Patent Owner waived its objections to the scope of Drs. Foote and Wilson's deposition testimony. *See* Paper 73, 4–6. Petitioners also persuade us that much of the disputed evidence, while not highlighted in the Petition, can be reasonably ascertained from the Petition and Dr. Foote's supporting declaration. *See id.* at 6–7. Finally, we agree with Petitioners that arguments and evidence subject to the motion to strike fairly responds to arguments and evidence in the Patent Owner Response—most clearly in response to Patent Owner's "unexpected results" argument and its contention that the "consensus" approach is superior to the "best fit" approach. *See id.* at 7–9. Accordingly, we deny Patent Owner's motion in its entirety.

D. Motions to Seal (Papers 43, 54, and 66)

In Paper 25 we granted Patent Owner's unopposed motion to seal Exhibits 2001 through 2018 and Ordered that the Modified Default Standing Protective Order set forth in Exhibit 2030 shall govern the conduct of this proceeding. Paper 25, 3. The parties have since submitted three unopposed motions to seal: Paper 43 (Patent Owner), and Papers 54 and 66 (Petitioner).

The Board's standards for granting motions to seal are discussed in *Garmin International v. Cuozzo Speed Technologies, LLC*, IPR2012-00001

(PTAB Mar. 14, 2013) (Paper 34). In summary, there is a strong public policy for making all information filed in *inter partes* review proceedings open to the public, especially because the proceeding determines the patentability of claims in an issued patent and, therefore, affects the rights of the public. *Id*. at slip op. 1–2. Under 35 U.S.C. § 316(a)(1) and 37 C.F.R. § 42.14, the default rule is that all papers filed in an *inter partes* review are open and available for access by the public; a party, however, may file a concurrent motion to seal and the information at issue is sealed pending the outcome of the motion. It is only "confidential information" that is protected from disclosure. 35 U.S.C. § 316(a)(7); *see* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012). The standard for granting a motion to seal is "for good cause." 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof in showing entitlement to the requested relief, and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

We remind the parties of the expectation that confidential information relied upon or identified in a final written decision will be made public. *See* Office Trial Practice Guide, 77 Fed. Reg. 48756, 48761 (Aug. 14, 2012). Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. A party seeking to maintain the confidentiality of the information may file a motion to expunge the information from the record prior to the information becoming public. 37 C.F.R. § 42.56.

1. Petitioners' Motions to Seal (Papers 54 and 66)

Petitioners move to seal the non-redacted versions of Exhibits 1198, 1199, 1200, 1201, 1202, and Paper 67 because they "contain[] references to

subject matter filed under seal by Patent Owner, Genentech, Inc." Paper 54, 1; Paper 66, 1. Petitioners provide no other justification for why the redacted portions of the cited documents should be kept confidential and, thus, fail to satisfy the good cause requirement. Accordingly, Petitioners' motions are denied without prejudice to Patent Owner.

Patent Owner is invited to file, within 14 days of this Decision, a motion to seal any presently confidential portion of Exhibits 1198, 1199, 1200, 1201, 1202, and Paper 67. The motion shall attest that the material sought to be protected is not directly or indirectly relied on in this Decision, or, to the extent we rely on any of the material sought to be protected in this Decision, provide sufficient justification that outweighs the heightened public interest in understanding the basis for our decision on patentability. Together with the motion to seal, Patent Owner shall file narrowly redacted public versions of any documents sought to be sealed.

2. Patent Owner's Motions to Seal (Paper 43) and Modification of Previous Order on Patent Owner's Motion to Seal

Patent Owner requests that the non-redacted version of its Patent Owner Response (Paper 44) remain under seal pursuant to the Modified Default Standing Protective Order. Paper 43. As justification for its motion, Patent Owner merely states that the redacted portions contain "'confidential research [and] development . . . information' pursuant to FRCP 26(c)(1)(G)." Paper 43, 2–3. Patent Owner's motion is denied without prejudice. Moreover, to the extent we rely on any of the material sought to be protected in this Decision, we modify our previous Order (Paper 25) in accord with this Decision. For example, Patent Owner affirmatively relies

upon certain exhibits, including the inventor's notebooks (Exhibits 2001–2004), which we address in this Decision.

Patent Owner may, within 14 days of this Decision, renew its motion to seal any portion of its Patent Owner Response and the presently protected exhibits that are discussed in this Decision. Because the public has a heightened interest in understanding the basis for our decision on patentability, any renewed motion shall attest that the material sought to be protected is not directly or indirectly relied on in this Decision, or, to the extent we rely on any of the material sought to be protected in this Decision, provide sufficient justification that outweighs the heightened public interest in understanding the basis for our decision on patentability. Together with the renewed motion to seal, Patent Owner shall file narrowly redacted public versions of any exhibits sought to be sealed.

In the absence of any action on the part of Patent Owner, at the expiration of 14 days from the date of this Decision, the exhibits-at-issue will be made available to the public.

3. Redaction of the Final Written Decision

Subject to the same conditions as in sections III(D)(1) and (2), above, the parties may, within 14 days of this Decision, jointly propose redactions for this Final Written Decision. In the absence of such proposal, at the expiration of 14 days from the date of this Decision, the entirety of the Final Written Decision will be made available to the public.

III. CONCLUSION

Having considered all the evidence, Petitioners have demonstrated by a preponderance of the evidence that the following claims are unpatentable:

claims 1, 2, 25, 29, 63, 66, 67, 72, 80, and 81 as anticipated by Kurrle; claims 1, 2, 4, 29, 62–64, 80, and 81 as anticipated by Queen 1990; claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 72, 78, 80, and 81 as obvious over Kurrle and Queen 1990; and claims 30, 31, 33, as obvious in view of Queen 1990 and Hudziak.

Petitioners have not demonstrated by a preponderance of the evidence the unpatentability of claims 12, 42, 60, 65, 71, 73–77, and 79.

The parties' motions to exclude evidence and to seal are addressed in the following Order.

IV. ORDER

In consideration of the foregoing, it is:

ORDERED that claims 1, 2, 4, 30, 31, 33, 25, 29, 62–64, 66, 67, 69, 72, 78, 80, and 81 of the '213 patent are unpatentable;

FURTHER ORDERED that Petitioners' motion to exclude "secondary considerations" evidence in Exhibit 2016 ¶¶ 5, 51–53, Exhibit 2017 ¶¶ 4, 77–79, Exhibit 2041 ¶¶ 83–87, 263–68, and Exhibit 2029, is dismissed as moot.

FURTHER ORDERED that Petitioners' motion to exclude Exhibits 2001–2015 is denied.

FURTHER ORDERED that Petitioners' motion to exclude the opinion testimony of Dr. Wilson (Ex. 2041 ¶¶ 163–262) is denied.

FURTHER ORDERED that Petitioners' motion to exclude the errata of Dr. Wilson (Ex. 1197, 137) and Dr. Carter (Ex. 1198, 100) is denied.

FURTHER ORDERED that Patent Owner's motion to exclude portions of the declaration of Mr. Buss (Ex. 1004 ¶¶ 15-16, 18, 30–33, 43–45, 53–55, 63, 69–70), and testimony reliant thereon, is denied.

FURTHER ORDERED that Patent Owner's motion to exclude the allegedly improper Reply evidence subject to its motion to strike, is denied.

FURTHER ORDERED that Patent Owner's motion to strike is denied.

FURTHER ORDERED that we modify our prior order on Patent Owner's motion to seal (Paper 25) in accord with the following:

Within 14 days of this Decision, Patent Owner may file/renew its motion to seal any presently redacted or otherwise confidential portions of Exhibits 1198, 1199, 1200, 1201, 1202, 2001–2018, Paper 44, and Paper 67. Any such motion must explain why the information sought to be protected is truly confidential and attest that such information is not directly or indirectly relied on in this Decision. Petitioners may file a response within one week of Patent Owner's motion. The Exhibits and Papers will remain designated Board and Parties Only for 21 days from the date of this Decision or until consideration of any such motion and reply.

FURTHER ORDERED that Patent Owner may file/renew its request to seal any confidential information as instructed in this Decision; and

FURTHER ORDERED that, because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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