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Paper No. 85
Entered: November 29, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01374
Patent 6,407,213 B1

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

ORDERS

Denying Patent Owner's Motion to Exclude (Paper 60)
37 C.F.R. § 42.64(c)

Denying Petitioner's Motion to Exclude (Paper 62)
37 C.F.R. § 42.64(c)

Denying Patent Owner's Motion to Strike (Paper 58)
37 C.F.R. § 42.5

Denying Patent Owner's Motion to Seal (Paper 36) without Prejudice
37 C.F.R. § 42.55

Denying Petitioner's Motions to Seal (Papers 51, 61, and 74)
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 Petitioner has demonstrated by a preponderance of the evidence that claims 1, 2, 4, 25, 29, 30, 31, 33, 62–64, 66, 67, 69, 72, 78, 80, and 81 of the '213 patent are unpatentable. Petitioner has not made that showing with respect to claims 12, 42, 60, 65, 71, 73–77, and 79.

A. Procedural History

Petitioner, Celltrion, 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 2 ("Pet."). Patent Owner, Genentech, Inc., timely filed a Preliminary Response. Paper 7 ("Prelim. Resp."). Based on the record before us at the time, we instituted trial with respect to all challenged claims. Paper 15, 23–24 ("Dec.").

After institution of trial, Patent Owner filed its Patent Owner Response (Paper 37, "PO Resp.") and Petitioner filed a Reply to the Patent Owner Response (Paper 52, "Pet. Reply"). Patent Owner filed a motion to strike evidence and argument presented in Petitioner's Reply. Paper 58. Petitioner opposed. Paper 70.

With respect to technical experts, Petitioner relies on the declarations of Lutz Riechmann, Ph.D. (Exs. 1003, 1143) and Robert Charles Frederick Leonard, Ph.D. (Ex. 1004); Patent Owner relies on the declarations of Drs. Leonard G. Presta (Ex. 2016), Paul J. Carter (Ex. 2017), and Ian A. Wilson (Ex. 2041). Patent Owner further relies on the testimony of research technician, Mr. John Ridgway Brady (Ex. 2018). With respect to records management and authentication, Petitioner relies on the testimony of Mathew Miner, Ph.D. (Ex. 1133); 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. Riechmann (Paper 65), to which Petitioner responded (Paper 69).

Patent Owner submitted one motion to exclude evidence. Paper 60. Petitioner opposed (Paper 67), and Patent Owner submitted a reply in support of its motion (Paper 71). Petitioner also submitted one motion to

exclude evidence. Paper 62. Patent Owner opposed (Paper 68), and Petitioner submitted a reply in support of its motion (Paper 81).

Patent Owner submitted a first, unopposed motion to seal (Paper 8), which we granted (Paper 14) 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 36 (by Patent Owner); Papers 51, 61, and 74 (by Petitioner).

We heard oral argument on July 16, 2018, in a joint proceeding involving this case and IPR2017-001373. A transcript of that proceeding is entered as Paper 82 ("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.) (dismissed); *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01407 (D. Del.); *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01471 (D. Del.); and *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.) (appeal docketed, No. 18-2160 (Fed. Cir. July 16, 2018); *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.). *See, e.g.*, Paper 83, 1–2; Paper 84, 1–2.

In addition to the present case, the '213 patent is the subject of the following pending matters: IPR2017-01373 brought by Celltrion, Inc.; IPR2017-01488 and IPR2017-01489, brought by Pfizer, Inc.; and IPR2017-02139 and IPR2017-02140, brought by Samsung Bioepis Co., Ltd.

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. The '213 patent was also the subject of IPR2017-02031 and IPR2017-02032 brought by Boehringer Ingelheim Pharmaceuticals, Inc., which we terminated in light of the Petitioner's 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, (45), (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 (V_H and V_L) 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 sequences. In particular, 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 1:60–63), 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.[1]

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.

[1] 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. 60 n.12 (citing Ex. 2041 ¶¶ 83, 220).

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:[2]

Ground	Claim(s)	Basis	Reference(s)
1	1, 2, 25, 29, 63, 65, 66, 71, 75, 76, 78, 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	65, 73, 74, 77, and 79	§ 103	Kurrle, Queen 1990, and Chothia & Lesk[6], and Chothia 1985[7]

[2] Petitioner did not expressly recite claim 65 in its statement of grounds in the Petition, nor did we initially institute on this claim in our Decision. Both parties, however, present arguments and evidence presuming the inclusion of claim 65 in this proceeding, and Patent Owner has not objected to our order at oral hearing including claim 65 in Ground 1. *See* Tr. 5:10–7:6.
[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.

Ground	Claim(s)	Basis	Reference(s)
6	30, 31, and 33	§ 103	Queen 1990 and Hudziak[8]
7	42	§ 103	Queen 1990, Kurrle, Hudziak, and Furey
8	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]

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[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.

[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.

Finisar Corp. v. DirecTV Grp., Inc., 523 F.3d 1323, 1334 (Fed. Cir. 2008). That "single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002). 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 with respect to the '213 patent. *See* Pet. 12–13; Prelim. Resp. 17–18; PO Resp. 17–18. 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. 10–11. Petitioner does 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. 18. Petitioner does not contest this definition in their Reply.

Patent Owner's proposed construction derives from the '213 patent's definition of consensus sequence as "refer[ing] to an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." Ex. 1001, 11:32–38. In the context of the patent as a whole, however, we do not understand the term to require a consensus of "all" human immunoglobulins in the literal sense because the embodiments in the patent were generated using the most common residue at each position

identified in Kabat 1987.[11] *See id.* at 10:34–63, 11:55–60; Ex. 2016 ¶¶ 25–26. 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. *See* PO Resp. 47. Moreover, at oral argument, Patent Owner did not contest Petitioner's assertion 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." Tr. 15:4–16:4.[12]

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." Consistent with claim 63's

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[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.

[12] In a parallel proceeding involving the same patent, 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.

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, 61:57–61. 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. 43 (citing Ex. 1094 (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").

We previously stated that the language of claim 63, "refer[s] to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody." IPR2017-01488, Paper 27 at 10–12. Patent Owner does not dispute this interpretation. *See* PO Resp. 19. Petitioner argues that the recited reduction in immunogenicity is both an inherent aspect of the claimed humanized antibodies, and "the stated goal of all humanization projects, including that of Queen 1990 and Kurrle." Pet. Reply, 28, 43. Petitioner also contends that the term is not a claim limitation

and "simply a statement of the intended result of the claimed compositions," but, nevertheless, states: "For the purpose of the present petition only, Petitioner will assume that the preambles are limiting." Pet. 13 n.3.

On balance, we see no need to 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. Nevertheless, to the extent Petitioner is correct that the preambles should be accorded no weight, such a determination would not alter the outcome of this proceeding.

3. Other Limitations

On pages 13–15 of its Petition, Petitioner proposes constructions for "humanized" antibodies (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) [13]; and "up to 3-fold more" (claim 65). Patent Owner does not dispute Petitioner's proposed constructions, but asserts that "[n]o construction of those terms is necessary." Prelim. Resp. 19; PO Resp. 18. On the present

[13] Petitioner states that the '213 Patent "ties its numbering system to" both Kabat 1987 and Kabat 1991 (Kabat, et al. *Sequences of Proteins of Immunological Interest 5th Ed., 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*, (National Institutes of Health, Bethesda, Md.) (1991) (Ex. 1055)), but concedes that the priority application relies only on Kabat 1987 and that there are no significant differences between the two numbering systems. Pet. 14–15 & n.4; Ex. 1003 ¶ 167 n.5.

record, we agree with Patent Owner that the terms identified by Petitioner 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

Petitioner asserts that Kurrle and Queen 1990 are prior art for all challenged claims. *See e.g.*, Pet. 1, 4. Patent Owner disagrees, at least with respect to claims 12, 42, 60, 65, 71, 73–74, and 79.[14] PO Resp. 22–44. 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 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

[14] 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. 22–23).

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 Petitioner 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, Petitioner has satisfied its 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.

Petitioner notes "[t]he only examples in the '272 application are the eight variants of the humanized 4D5 antibody," designated huMAb4D5-1 through huMAb4D5-8. *See* Pet. Reply 6 (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. 41–44. 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, Petitioner broadly contends that the '272 application fails to support the full scope of the claims because claims 12, 42, 60, 65, 71, 73–74, and 79 are broader than the exemplified embodiments huMAb4D5-1 through huMAb4D5-8, which "do not disclose to a POSA the applicability of these substitutions to a different antibody." Pet. Reply 6. We do not find Petitioner's 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. 42–44 (citing Ex. 2032, 87–90, 93; Ex. 2041 ¶¶ 91–95).

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. 22–44. 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.*[15] Considering Patent Owner's detailed references to the proffered evidence, we are persuaded that that HuMAb4D5-5 and HuMAb4D5-8 embody claims 12, 42, 60, 65, 71, 73–74, and 79. *See, e.g.*, PO Resp. 35–39 (claim chart and other comparisons between claim elements and record evidence).

Petitioner argues that we should reject Patent Owner's antedation evidence for lack of sufficient corroboration. In particular, Petitioner attacks 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 Petitioner's arguments persuasive, we address only the first two of these arguments here, whereas Petitioner's authenticity contentions are addressed in the context of its motion to exclude evidence. *See* section III(A)(1), below.

With respect to credibility, Petitioner argues that the inventors' notebooks do not support Dr. Carter's testimony that "on May 6, 1990, he 'provided [] clones to Dr. Gorman and Mr. Brady with instructions for them to express Variants 2–6 in a mammalian cell line and have assays performed as we had done with Variant 1."[16] Pet. Reply 5 (quoting Ex. 2017, ¶ 75). But despite some discrepancy regarding the date Dr. Carter distributed certain clones for testing, Petitioner does not reasonably challenge Patent

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[15] 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. 1002-3, 707–15, 721.

[16] HuMAb4D5-5 and HuMAb4D5-8 correspond to "variant 1" and "variant 6," respectively, in Patent Owner's antedation proofs. *See e.g.*, Ex. 2017 ¶¶ 31, 76, 77.

Owner's assertion that "[b]y July 6, 1990, Mr. Brady had expressed the full-length antibodies corresponding with all six humanized 4D5 variants, and he provided samples to Monique Carver, who ran assays demonstrating their p185^{HER2} binding affinity." PO Resp. 32–33 (citations omitted). Accordingly, we do not find Petitioner's argument persuasive.

In challenging Patent Owner's evidence of corroboration, Petitioner argues that, in contravention of Genentech policy, none of the laboratory notebooks relied on are witnessed or countersigned by a non-inventor. Pet. Reply 4–5. While an "unwitnessed" notebook alone is insufficient to support reduction to practice (*see Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 998-99 (Fed. Cir. 2009)) and 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)), Patent Owner's evidence is not limited to the inventors' notebooks and testimony. And though we agree that witnessed and countersigned notebook entries are preferred, the absence of such indicia does not require us to *a priori* disregard Patent Owner's evidence. To the contrary, "[i]ndependent 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." *Medichem S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1171 (Fed. Cir. 2006) (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." *Id.* at 1170 (emphasis added).

As the Federal Circuit recently explained, the rule of reason 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 (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.

Considering the evidence as a whole, 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 Petitioner's grounds depends on Kurrle and/or Queen 1990, Petitioner has 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

Petitioner challenges each of claims 1, 2, 25, 29, 80, and 81 as anticipated and obvious over Kurrle and/or Queen 1990. *See* Pet. 4; Pet. Reply 1. 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. 19-20.

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 Petitioner's 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 Petitioner ***has 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, ***has*** 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, Petitioner challenges claims 63, 66, 75, 76, 78 as anticipated by Kurrle (*see* Pet. 25–31) and claims 4, 62, 63, and 64 as anticipated by Queen. *See* Pet 31–38.

1. Overview of Kurrle (Ex. 1071)

Kurrle discloses "humanised and civilised versions" of monoclonal antibodies against the human alpha/beta T-cell receptor.[17] 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

[17] 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.

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.

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. *See* Ex. 2029, 295:14–21, 297:14–19; Ex. 2041 ¶¶ 128, 130–131; Ex. 1003 ¶¶ 113 & fn.3, 144–147, 154–155, 199.

Kurrle 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, whereas Kurrle implicates a total of 48 positions for framework substitution. Ex. 2041 ¶¶ 64, 130–134. According to Petitioner's expert, Dr. Riechmann, "Kurrle made a total of 13 framework substitutions in the light chain and 20 framework substitutions in the heavy chain," plus a further insertion of amino acids at two framework positions to fill the gap between the human and mouse sequences. Ex. 1003 ¶ 113. Dr. Riechmann further states that Kurrle's antibodies involved "the substitution of the human framework residues, including at claimed residues including **4L, 69H, 71H, 73H, 76H** and **93H** according to the Kabat numbering system," i.e., "where a few select residues in the human framework region were switched back to mouse." *Id*. at ¶¶ 29, 99.

2. Analysis of Ground 1

a) Non-human CDRs which Bind Antigen

Petitioner challenges claims 63, 66, 75, 76, 78 as anticipated by Kurrle. Pet. 25–31. Patent Owner contends that this challenge fails "because Petitioner has 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. 44. 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, 44–46. 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 human to mouse substitutions. *Id.* at 45 (citing Ex. 1071, 8:42–43; Ex. 2041 ¶¶ 127–31, 164; Ex. 2039, 349:21–350:19). According to Patent Owner, "Kurle states that other humanized antibodies incorporating the same CDRs [but fewer framework substitutions] were unable to bind antigen." *Id.* (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 45–46 (citing Ex. 1072;[18] Ex. 2041 ¶¶ 133, 163).

In response, Petitioner argues that "[t]he claim language 'bind an antigen' encompasses binding to any degree," and notes that Dr. Wilson's testimony that "one approach to try to regain the binding affinity . . . was to make additional substitutions back to mouse in the human framework." Pet. Reply 12 (citing Ex. 1138, 28:2–8). As we understand Petitioner's argument, it is irrelevant that Kurrle presents no binding data for EUCIV4 in particular, because Kurrle discloses substitutions of residues within the Markush groups of the challenged claims and, as conceded by Dr. Wilson, it would have required nothing more than routine skill and experimentation to identify specific residues that would work (i.e., bind antigen) in a given humanization project. *Id.* at 8 (citing Ex. 1138, 116:1–122:1, Ex. 1142, 97:14–98:22); *see* Ex. 1143 ¶ 20. As such, one of ordinary skill in the art

[18] 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).

following the teachings of Kurrle, would inherently arrive at the claimed invention.

We find Petitioner's inherency argument persuasive with respect to claims 63, 66, and 78, which require single substitutions at position 4L, 69H, 71H, 73H or 76H. One of ordinary skill in the art applying Kurrle would necessarily identify substitutions of claims 63, 66, and 78 as binding antigen. 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. As acknowledged by the '213 patent:

> Since it is not entirely possible to predict in advance what the exact impact of a given substitution will be it may be necessary to make the substitution and assay the candidate antibody for the desired characteristic. These steps, however, are per se routine and well within the ordinary skill of the art.

Ex. 1051, 10:28–33; *see also* 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."). 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.[19]

[19] The same analysis applies to claims 4 and 12, discussed below.

We do not, however, find Petitioner's argument persuasive with respect to claims 75 and 76, which require substitutions at position 71H and 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.[20] Petitioner does 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.

[20] 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) "lacks immunogenicity"

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. Petitioner contends that lacking immunogenicity compared to a non-human parent antibody is both "an explicity stated goal of all antibody humanization projects" and "an inherent aspect of the claimed humanized antibodies." Pet. 28; *see* Ex. 1003 ¶¶ 152–153. According to Petitioner, "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 to treat a chronic disease in that patient') is also present." Pet. 28. Petitioner, thus, argues that claim 63 is anticipated because "one of ordinary skill in the art would thus know that Kurrle's humanized antibodies would also 'lack immunogenicity compared to a non-human parent antibody upon repeated administration.'" *Id.* at 29.

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. 58 (citations omitted). Patent Owner further points to Dr. Riechmann's admission that, absent testing, "[y]ou cannot predict the immune response of any antibody when given to a patient." *Id.* (citing Ex. 2039, 243:13–244:5).

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 Petitioner that the property of reduced immunogenicity would also be present. Pet. 28–29. 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 Petitioner has shown by a preponderance of the evidence that claims 63, 66, 67, and 72 are anticipated by Kurrle. Petitioner has 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.[21] 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

[21] 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

Petitioner challenges claims 4 and 62–64 as anticipated by Queen 1990. Pet. 31–37.

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 sequence with the framework substitutions recited in non-human CDRs that 'bind an antigen.'" PO Resp. 48–49. We do not find Patent Owner's arguments persuasive.

As an initial matter, we credit Petitioner's argument that Queen 1990 Criterion III explicitly taught the substitution of framework sites immediately adjacent to CDRs, which applying the numbering system of Kabat 1987, include 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. *See* Pet. 32–33. Further, each of claims 4 and 62–

64 requires, *inter alia*, at least one framework region substitution. *See id*. at 36–37 (considering additional elements of claim 64).

With respect to antigen binding, Petitioner asserts that binding affinity of an antibody is an inherent property of the claimed invention and notes that Queen 1990 "discloses '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.'" Pet. Reply 12–13 (citing Ex. 1050, 9:3–7).

Considering the evidence presented, we find Petitioner's arguments persuasive for essentially the same reasons discussed in section II(F)(2)(a), above.

a) "lacks immunogenicity"

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. 58. For essentially the same reasons as set forth in section II(F)(2), above, we agree with Petitioner 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. 35–36.

b) "consensus human variable domain,"

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 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 Petitioner has 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. 46–48 (citing Ex. 1050, 12:19–20, 13:3–11; Ex. 2041 ¶¶ 207–208).[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 using all sequences. *Id*. at 48 (citing Ex. 1050, 13:22–33; Ex. 2041 ¶¶ 205–211).

Petitioner, however, points out that Queen 1990 "explicitly discloses the use of a consensus sequence as the human framework in a humanization project." Pet. Reply 13–14 (citing Pet. 36–37); *see* Ex. 1003 ¶ 216. In particular, 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*," and, thus,

[22] Although the heading on page 46 of the Patent Owner Response refers to a plurality of asserted references, the arguments appear limited to Queen 1990.

distinguishes between a best fit/homologous approach and a consensus sequence approach. Ex. 1050, 12:17–20; *see* Pet. 36–37; *see also* Ex. 1003 ¶ 216 (Dr. Riechmann testifying that the disclosure in Queen 1990 "Criterion I that '[a]s acceptor, … use ***a consensus framework*** from many human antibodies,' . . . is the definition of 'consensus sequence'").

Petitioner further argues that the instructions of Criterion I relating to the consensus approach are not limited to only a subset of human antibodies and that Patent Owner has offered no evidence that this approach was any different from the approach taken by the inventors of the '213 patent, "which was to take the 'many human antibodies' disclosed in Kabat 1987 and use them to make a consensus framework." Pet. Reply 14 (citing Ex. 1142, 27:14–28:13, 32:17–20, 35:9–20). Relying on the testimony of Dr. Riechmann, Petitioner further explains that Queen 1990's reference to "a representative collection" of human heavy chains does not refer to the consensus sequence framework but to the alternative approach set forth in Criterion I. *Id.* at 14 (citing Ex. 1050, 13:3–11; Ex. 1143 ¶ 15).

Petitioner also argues that Queen 1990's discussion of rare or unusual amino acids in Criterion II is in reference to the best fit/homologous sequence approach rather than to the consensus approach and, in any event, Queen 1990 teaches that "[t]hese criteria may be used singly, or when necessary in combination, to achieve the desired affinity or other characteristics." *See* Pet. Reply 14–15; Ex. 1050, 12:12–15; Ex. 1143 ¶ 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 Petitioner 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 Petitioner has shown by a preponderance of the evidence that claims 4 and 62–64 are anticipated by Queen 1990.

G. Obviousness (Grounds 3, 5, and 6)

Of the remaining claims at issue, Petitioner challenges 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, Chothia & Lesk, and Chothia 1985 (Ground 5); and claims 30, 31, and 33 as obvious in view of Queen 1990 and Hudziak (Ground 6). Pet. 38–60. We need not specifically address Grounds 4, 7, and 8 for the reasons set forth in sections II(D) and II(E), above.

Grounds 3, 5, and 6 each rely on the combination of Kurrle and Queen 1990. Pet. 38–58. Petitioner asserts 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,'" comprising Criterion I through IV, and provides "explicit motivation to follow these steps to obtain a monoclonal antibody that can be used in human therapeutics." Pet. 38–40 (citing Ex. 1050; Ex. 1003 ¶¶ 121–125, 196, 197). According to Petitioner and Petitioner's expert, Dr. Riechmann, "Kurrle largely followed the steps of Queen 1990," and thus employed a similar roadmap to obtain a humanized antibody within the scope of the challenged claims. Pet. 40–41; Ex. 1003 ¶ 198–199. As Dr.

Riechmann testifies, one of ordinary skill in the art "would have been motivated to combine Queen 1990 with Kurrle based on the similarity of the approaches used in both references . . . to further improve on the successes of both . . . and provide a more comprehensive list of possible residues to modify." Ex. 1003, 200. 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. 21–22, 50–53.

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 Petitioner that an ordinary artisan would have had a reason to combine the teachings of those references.

1. Specific Framework Substitutions

Patent Owner contends that although certain of the challenged claims recite one (claims 72 and 78) or more than one (claims 75, 76, and 77) specific framework region substitutions selected from a broad genus of potential candidates, "'there is nothing in the disclosure of [the reference] suggesting that one should select' the claimed species.'" PO Resp. 50 (quoting *In re* Baird, 16 F.3d 380, 382 (Fed. Cir. 1994). With respect to

Queen 1990, for example, Patent Owner references 23 single-site substitutions in connection with Criterion III and 19 associated with Criterion IV, and contends that the asserted references overall give rise to "literally millions of potential combinations and permutations of framework substitutions." *Id.* at 50–51. Patent Owner contends that other than hindsight, Petitioner provides no reason why a person of ordinary skill would have chosen the specific framework region substitutions recited in claims 72, 75, 76, 77, and 78. *Id.* at 51–52.

As Petitioner points out, however, the '213 patent also instructs a person of ordinary skill in the art to choose framework region substitutions from a large genus, in particular, "to identify residues that, because of their positions within the V_H and V_L domains, could alter binding affinity, and then conduct trial-and-error mutagenesis to see which of those substitutions improve binding." Pet. Reply 8–10 (citations omitted). Noting that Kurrle expressly discloses residues satisfying the Markush group limitations of claims 72, 75, and 78 as candidates for substitution, Petitioner argues that nothing more than routine skill and experimentation would have been required to use these methods to identify the specific residues(s) that would work in a given humanization project. *See id.* at 8 (citing Ex. 1138, 116:1–122:1; Ex. 1142, 97). Similarly, with respect to the cited references, a skilled artisan would have been able to identify from the list of potential framework region substitutions, "residues that would be appropriate to modify in any given project. It would have been routine for a POSA to select the residues that were most likely to provide optimal binding and confirmation for the target antibody." Ex. 1003 ¶ 200. As Petitioner notes, "PO offers no rationale why the selection process required by the patent is

any less complex than the selection process disclosed in the prior art." Pet. Reply 10.

According to Petitioner's expert, Dr. Riechmann, the selection process for any particular antibody could have been done "quite quickly" by those of ordinary skill in the art because "[t]he level of skill is high, and it was known (both in research labs and commercial labs) how to engage in the types of molecular modeling needed to engage in the humanization process, and which particular areas/residues to target." Ex. 1003 ¶ 194. Thus, "[w]hile the number of residues may seem large to a lay person" one of ordinary skill in the art would readily identify the appropriate residues to target. *Id.*

On balance, we find Petitioner's arguments persuasive with respect to claims 72 and 78, which require at least one of the framework region substitutions expressly disclosed in Kurrle. For reasons similar to those discussed in section II(F)(2), above, we are not persuaded by Petitioner's arguments with respect to claims 75–77, which require multiple framework region substitutions. In particular, Petitioner has presented insufficient evidence that creating and testing this many combinations of variants is less than undue experimentation. Accordingly, Petitioner has not demonstrated that the multiple framework substitutions required for claims 75–77 is drawn from "a finite number of identified, predictable solutions," nor that the relevant universe is "small or easily traversed." *See* PO Resp. 53–54 (quoting *KSR*, 550 U.S. at 421; *Ortho-McNeil Pharm., Inc v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

2. Non-human CDRs which Bind Antigen

Patent Owner also contends that Petitioner's obviousness challenges to claims 4, 33, 62–64, 66, 67, 69, 72, 75, 76, and 78 fail because Queen 1990 does not disclose binding affinity data for any antibody having the claimed framework region substitution, Kurrle does not disclose antibody binding data for EUCIV4, and the effect of any single substitution on antibody binding is unpredictable. PO Resp. 44–45, 48–49. For the reasons set forth in section II(F)(2), above, we find Patent Owner's argument persuasive with respect to claims 75, 76, and 77, which require the substitution of more than one framework region amino acid, but not with respect to claims 4, 33, 62–64, 66, 67, 69, 72, and 78, which do not require simultaneous substitution at multiple framework region positions.

3. "a consensus human variable domain"

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." Claims 4, 33, 64, and 69 incorporate similar language. With respect to Grounds 3 and 6, Patent Owner argues that "the '213 patent provides a specific definition of the claimed human 'consensus sequence,'" which is not obvious in light of the cited references. *See* PO Resp. 46–48. For the reasons set forth in section II(F)(4)(b), above, we do not find Patent Owner's argument persuasive but that Queen 1990 describes a consensus human variable domain.

Although not necessary to our determination, we also find persuasive Petitioner's evidence that prior to the critical date, Dr. Reichmann constructed a humanized antibody having a light chain made using a

consensus human variable domain. Pet. Reply 18; Ex. 1143 ¶ 30; Ex. 1193, 106[23] ("The CDR sequences from the kappa light chain were combined with consensus human kappa frameworks."); Ex. 1138, 193:20–197:14 (referencing June 23, 1997 amendment at Ex. 1002-2, 340); *see* Paper 70, 8.

4. "lacks immunogenicity"

Patent Owner contends that the prior art does not render obvious "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient," as set forth in claim 63. PO Resp. 57–60. For the reasons set forth in section II(F)(2)(b), we do not find Patent Owner's argument persuasive.

5. An Antibody that Binds $p185^{HER2}$

Ground 6 addresses whether claims 30, 31, and 33 are obvious over the combination of Queen 1990 and Hudziak. Claim 30, from which claims 31 and 32 depend, recites a single framework region substitution and requires an antibody that binds $p185^{HER2}$. *See* 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

[23] Foote, *Humanized Antibodies*, 61 Nova Acta Leopoldine, 269, 103–110 (1989).

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, including certain mammary carcinomas, which are characterized by the overexpressing of $p185^{HER2}$." *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. 55–56 (citing Ex. 1003 ¶¶ 321–322); *see* Ex. 1004 ¶¶ 41–60; Pet. Reply 17–18. In sum, "[g]iven the understanding that an antibody must be humanized before use as a therapeutic agent, the published accounts regarding other monoclonal antibody humanization efforts, and the strength of 4D5 as a clinical target, the logical and necessary next step would have been to humanize 4D5." *Id.* at 56 (citing Ex. 1004 ¶ 62; Ex. 1003 ¶ 324).

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. 61–62 (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 Petitioner that it would have

been routine to transfer those CDRs to a human framework and apply the humanization teachings of Queen 1990. *See* Pet. 58; Pet. Reply 17–18. Because Queen 1990 provides general guidance for optimizing any such mouse-human combination, one of ordinary skill in the art would have reasonably applied the principles of Queen 1990 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.

H. 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. 62–65. 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 the claims are not directed to a platform or method for humanizing antibodies, but to specific antibodies with specific framework region substitutions. Moreover, to the extent the independent claims invoke a consensus sequence, that limitation is taught in Queen 1990. We also find persuasive Petitioner's argument that "there is no evidence that humanization using a consensus sequence was superior to the 'closest homolog' approach that PO concedes was in the prior art." Pet. Reply. 18–19 (citing, *e.g.*, Ex. 1142, 36:11–37:13, 139:11–17; Ex. 1196, 319–20; Ex. 1138, 184:16–185:7).

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. 63 (citing Ex. 1002 ¶¶ 2–9; Ex. 1001, 51:50–53). 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, 265. Although Petitioner argues that "PO has not

established that Herceptin is an embodiment of the claims," it does not reasonably dispute that huMAb4D5-8 is the active ingredient in Herceptin. *See* Pet. 63; Pet. Reply 20. Considering the evidence of record, 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 (citations omitted); *see* PO Resp. 35 n.8, 65; Ex. 2017 ¶¶ 4, 77; Ex. 2016 ¶ 51; Ex. 2041 ¶ 263.

With respect to commercial success, Patent Owner relies on paragraphs 264 and 265 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. 64; Ex. 2029, 2. As an initial matter, we agree with Petitioner that Patent Owner presents sales figures for these various products "without putting them in context of the market as a whole." Pet. Reply 21. Moreover, with the exception of Herceptin, Dr. Wilson does little to establish that the recited antibody products embody any claim of the '231 patent. *See* Ex. 2041 ¶ 263–265. 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 ¶ 265. 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.

Further, despite linking huMAb4D5 / Herceptin to claims 30, 31, and 33, Patent Owner fails to establish the requisite nexus to the claimed invention. *See* Pet. 63. 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. 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 Petitioner has demonstrated by a preponderance of the evidence that claims 30, 31, and 33 are obvious over the combination of Queen 1990 and Hudziak.

2. Conclusion

Considering all the evidence, Petitioner has demonstrated by a preponderance of the evidence that the following claims are unpatentable: claims 1, 2, 25, 29, 63, 66, 78, 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 in view of Kurrle and Queen 1990; and claims 30, 31, 32 as obvious in view of Queen 1990 and Hudziak.

Petitioner has not demonstrated by a preponderance of the evidence the unpatentability of claims 12, 42, 60, 65, 71, 73, 74–77, and 79.

III. MOTIONS

A. Petitioner's Motion to Exclude Evidence

Petitioner filed one motion to exclude evidence. Paper 62. Patent Owner opposed (Paper 68) and Petitioner submitted a reply in support of their motion (Paper 81).

1. Notebooks and Internal Documents Relating to Patent Owner's Antedation Proofs (Exhibits 2001–2009, 2014 and 2015)

Petitioner seeks to exclude Exhibits 2001–2009, 2014–2015 (and testimony predicated thereon in Exhibits 2016–2018) as not authenticated and unreliable. Paper 62, 7–13; Paper 81, 1–4. These documents encompass the inventors notebooks (Ex. 2001–2004) and the notebooks of Genentech technicians (Exs. 2005–2009), whereas Exhibits 2014 and 2015

comprise an internal Genentech project status report, and meeting minutes, respectively. For the reasons set forth at pages 1–10 of Patent Owner's opposition brief (Paper 68), and as discussed above in section II(D)(2), we do not find Petitioner's arguments persuasive.

In particular, we credit Patent Owner's argument that Genentech's records custodian sufficiently authenticated Exhibits 2001–2009 and established their admissibly as business records. Paper 68, 2, 6–8. We also credit Patent Owner's argument that the inventors themselves authenticated the laboratory notebooks of Exhibits 2001–2006 (*see id.* at 1–2), and Exhibits 2014–2015 as internal business records that they recognize from their work at Genentech (*see id.* at 9–10). That Genentech cannot, as Petitioner argues, prove the chain of custody for these records since their inception, does not, standing alone, deprive them of authenticity as internal business records. *See* Paper 62, 2–5.

We are likewise unpersuaded by Petitioner's suggestion that the color scans of some of the laboratory notebooks differ in some substantive way from those microfilmed in the early 1990s. *See* Paper 62, 2–5. 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, Petitioner neither asked the witness about the microfilmed versions, nor attempted to enter them into evidence. *See* Paper 68, 1–6. Nor did Petitioner 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 Petitioner's

implication that Genentech substantively altered the laboratory notebooks relied on here.[24]

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 Petitioner's motion to exclude Exhibits 2001–2009, 2014–2015 and related testimony.

2. Dr. Presta's and Mr. Brady's Testimony Regarding Project Status

Petitioner seeks to exclude paragraphs 23, 49, and 50 of Exhibit 2016 and paragraphs 21 and 22 of Exhibit 2018 under FRE 602 for lack of evidence "that Dr. Presta had personal knowledge of Dr. Carter's knowledge or activities," or "that Mr. Brady had personal knowledge of the activities of Monique Carver," respectively. Paper 62, 7. We do not find Petitioner's arguments persuasive for the reasons set forth on pages 10–11 of Patent Owner's opposition brief (Paper 68). Moreover, we note that Petitioner had ample opportunity to question the declarants about these statements at deposition. *See* Papers 42 and 43. Accordingly, we deny Petitioner's motion to exclude the recited portions of Exhibits 2016 and 2018.

3. Non-prior art documents

Petitioner asserts that Exhibits 2021, 2053, 2059, and 2060 are not prior art to the '213 patent and should be excluded as irrelevant. Paper 62, 7–9. The disputed documents, however, relate to the development of antibody-based treatments including Herceptin, and are, thus, within the

[24] As indicated in section II(D)(2), above, the date discrepancy Petitioner identifies between Dr. Carter's testimony and the inventor's notebooks do not cause us to doubt the authenticity of those documents.

same general field as the '213 patent. Moreover, as Patent Owner points out, arguments concerning the relevance of documents based on post-filing publication dates relate to the weight we accord that evidence rather than its admissibility. *See* Paper 68, 11–12. Petitioner also asserts that we should exclude Exhibits 2021, 2053, 2059, and 2060 under FRE 402 and 403 because their "probative value . . . is substantially outweighed by the undue prejudice stemming from Patent Owner's improper reliance on the non-prior art documents to show purported prior art practices or the knowledge of a person of ordinary skill in the art." Paper 62 at 9. We disagree with Petitioner's assessment. Moreover, the Board can rely on evidence other than just prior art in considering the knowledge, motivations, and expectations of a person of ordinary skill in the art. *See Yeda Research v. Mylan Pharm. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018) (noting that the Board correctly "recognized that non-prior art evidence of what was known 'cannot be applied, independently, as teachings separately combinable' with other prior art, but "can be relied on for their proper supporting roles, e.g., indicating the level of ordinary skill in the art, what certain terms would mean to one with ordinary skill in the art, and how one with ordinary skill in the art would have under-stood a prior art disclosure") (citation omitted).

Accordingly, we deny Petitioner's motion to exclude Exhibits 2021, 2053, 2059, and 2060.

4. Exhibits Not Addressed in the Patent Owner Preliminary Response or Patent Owner Response

Petitioner seeks to exclude Exhibits 2042, 2043, 2055, 2061, and 2062 under FRE 401 and 402 because "Patent Owner did not rely on any of them in either its Patent Owner's Preliminary Response or its Patent Owner's

Response." Paper 62, 10–11; Paper 81, 5. In response, Patent Owner withdraws Exhibits 2042–2044, argues that Exhibit 2062 is relevant to assessing Dr. Riechmann credibility, and that Exhibits 2055 and 2061 are addressed in Dr. Riechmann's and Dr. Leonard's deposition testimony. Paper 68, 13–14. As we do not expressly rely on the cited deposition testimony or on the objected-to Exhibits, we deny Petitioner's request as moot.

5. Exhibit 2029

According to Patent Owner, Exhibit 2029 is an excerpt from Roche, Inc's 2016 Finance Report. Paper 68, 13. Petitioner seeks to exclude Exhibit 2029 under FRE 901 and 802 for lack of authentication and as inadmissible hearsay. Paper 62, 11–12; Paper 81, 5. We do not find Petitioner's arguments persuasive for the reasons set forth on pages 13–14 of Paper 68. Accordingly, we deny Petitioner's request with respect to Exhibit 2029.

6. Dr. Wilson's Opinions

Petitioner seeks to exclude paragraphs 25, 36, 37, 48, 65, 172, 180, 186, and 231 of Dr. Wilson's declaration (Exhibit 2041) under FRE 403 and 602 "to the extent that they lack foundation or rely on improper evidence." Paper 63, 13. But, as Patent Owner points out, "Petitioner never describes the contents of those paragraphs, where they were relied on by Patent Owner, how they relate to the Board's determination of patentability here, why the particular statements require citations to evidence, or how the statements prejudice Petitioner," as set forth in our Trial Practice Guide. Paper 68, 15 (citing *Patent Trial Practice Guide*, 77 Fed. Reg. 48,765 at

48,767). Accordingly, we deny Petitioner's request to exclude paragraphs 25, 36, 37, 48, 65, 172, 180, 186, and 231 of Exhibit 2041.

B. 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 regarding Foote 1989's disclosure of the use of a consensus sequence in creating a humanized antibody. Paper 58. We do not find Patent Owner's arguments persuasive for the reasons set forth in Petitioner's brief in opposition (Paper 70), which we adopt. Petitioner persuades us that the basis of the disputed evidence, while not highlighted in the Petition, can be reasonably ascertained from the Petition and Dr. Foote's supporting declaration. Paper 70, 4–5. We also agree with Petitioner 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.

C. Motions to Seal

In Paper 14, 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 14, 3. The parties have since submitted four unopposed motions to seal: Paper 36 (Patent Owner), and Papers 51, 61, and 74 (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. Petitioner's Motions to Seal (Papers 51, 61, and 74)

Petitioner moves to seal the non-redacted versions of Exhibits 1139–1142 and portions of Paper 52, Exhibit 1143, Paper 62, and Paper 73

because they "reflect information that Patent Owner has marked Confidential pursuant to the Modified Default Standing Protective Order." Paper 51, 1; Paper 61, 1; Paper 74, 1. Petitioner provides 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, Petitioner's 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 1139–1143 and Papers 52, 62, and 73. 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 the documents sought to be sealed.

2. Patent Owner's Motions to Seal (Paper 36) 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 37) remain under seal pursuant to the Modified Default Standing Protective Order. Paper 36. 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 36, 1–2. 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 14)

granting Patent Owner's motion to seal Exhibits 2001–2018 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 (Paper 37) and Exhibits 2001–2018 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 the 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(C)(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.

IV. CONCLUSION

Having considered all the evidence, Petitioner has 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.

Petitioner has 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.

V. ORDER

In consideration of the foregoing, it is:

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

FURTHER ORDERED that Petitioner's motion to exclude Exhibits 2001–2009, 2014–2015 and related testimony is denied.

FURTHER ORDERED that Petitioner's motion to exclude paragraphs 23, 49, and 50 of Exhibit 2016 and paragraphs 21 and 22 of Exhibit 2018 is denied.

FURTHER ORDERED that Petitioner's motion to exclude Exhibits 2021, 2053, 2059, and 2060 is denied.

FURTHER ORDERED that Petitioner's motion to exclude Exhibits 2042, 2043, 2055, 2061, and 2062 is denied as moot.

FURTHER ORDERED that Petitioner's motion to exclude Exhibit 2029 is denied.

FURTHER ORDERED that Petitioner's motion to exclude paragraphs 25, 36, 37, 48, 65, 172, 180, 186, and 231 of Exhibit 2041 is denied.

FURTHER ORDERED that Patent Owner's motion to strike Exhibit 1193 and testimony related thereto is denied.

FURTHER ORDERED that we modify our prior order on Patent Owner's motion to seal (Paper 14) in accord with the following: Within 14 days of this Decision, Patent Owner may renew its motion to seal any presently redacted or otherwise confidential portions of Exhibits 2001–2018 and Paper 37. 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. Petitioner may file a response within one week of Patent Owner's motion. The Exhibits and Paper 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, within 14 days of this Decision, Patent Owner may file a 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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