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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01488
Patent 6,407,213 B1

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

POLLOCK, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Pfizer, Inc. ("Petitioner") 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 of U.S. Patent No. 6,407,213 B1 ("the '213 patent," Ex. 1001). Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 6 ("Prelim. Resp."). We review the Petition, Preliminary Response, and accompanying evidence under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has demonstrated a reasonable likelihood that at least claim 1 of the '213 patent is unpatentable, we institute an *inter partes* review of the challenged claims.

A. Related Proceedings

According to Petitioner, the '213 Patent is at issue in *Amgen Inc. v. Genentech, Inc.*, No. 2-17-cv-07349 (C.D. Cal.); *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01407 (D. Del.); *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01471 (D. Del.). Paper 16, 1.

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

In addition to the present case, the '213 patent is presently the subject of seven pending matters: IPR2017-01489, brought by Pfizer, Inc.; IPR2017-01373 and IPR2017-01374, brought by Celltrion, Inc.; IPR2017-

02031 and IPR2017-02032 brought by Boehringer Ingelheim Pharmaceuticals, Inc.; and IPR2017-02139 and IPR2017-02140, brought by Samsung Bioepis Co., Ltd. Paper 4, 4; Paper 16, 1.

B. The '213 Patent and Relevant Background

The '213 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." Ex. 1001, 1:12–14.

A naturally occurring antibody (immunoglobulin) comprises two heavy chains and two light chains. *Id.* at 1:18–20. Each heavy chain has a variable domain (V_H) and a number of constant domains. *Id.* at 1:21–23. Each light chain has a variable domain (V_L) and a constant domain. *Id.* at 1:23–24.

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

Before the '213 patent, monoclonal antibodies targeting a specific antigen, obtained from animals, such as mice, had been shown to be antigenic in human clinical use. *Id.* at 1:51–53. The '213 patent recognizes efforts to construct chimeric antibodies and humanized antibodies in the prior art. *Id.* at 1:59–2:52. According to the '213 patent, chimeric antibodies are "antibodies in which an animal antigen-binding variable

domain is coupled to a human constant domain" (*id.* at 1:60–62), whereas "humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies" (*id.* at 2:32–35).

The '213 patent also acknowledges the following as known in the prior art:

1. In certain cases, in order to transfer high antigen binding affinity, it is necessary to not only substitute CDRs, but also replace one or several FR residues from rodent antibodies for the human CDRs in human frameworks. *Id.* at 2:53–61.

2. "For a given antibody[,] a small number of FR residues are anticipated to be important for antigen binding" because they either directly contact antigen or "critically affect[] the conformation of particular CDRs and thus their contribution to antigen binding." *Id.* at 2:62–3:8.

3. In a few instances, a variable domain "may contain glycosylation sites, and that this glycosylation may improve or abolish antigen binding." *Id.* at 3:9–12.

4. 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.

5. The antigen binding affinity of a humanized antibody can be increased by mutagenesis based upon molecular modelling. *Id.* at 3:44–46.

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.

C. Illustrative Claims

Among the challenged claims, claims 1, 30, 62–64, 66, 79, and 80 are independent. Claim 1 is illustrative and is reproduced below:

> 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.[1]

D. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 6–7):

Ground	Claim(s)	Basis	Reference(s)
1	1, 2, 25, 29, 63, 66, 67, 71, 72, 75, 76, 80, and 81	§ 102	Kurrle[2]
2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990[3]

[1] *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").
[2] Kurrle, et al., European Patent Application Publication No. 0403156, published December 19, 1990. Ex. 1071.
[3] Queen, et al., International Publication No. WO 1990/07861, published July 26, 1990. Ex. 1050.

Ground	Claim(s)	Basis	Reference(s)
3	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81	§ 103	Kurrle and Queen 1990 and
4	12	§ 103	Kurrle, Queen 1990, and Furey [4]
5	73 and 77	§ 103	Kurrle, Queen 1990, and Chothia & Lesk[5]
6	74	§ 103	Kurrle, Queen 1990, and Chothia 1985[6]
7	79 and 65	§ 103	Kurrle, Queen 1990, Chothia & Lesk, and Chothia 1985
8	30, 31, 33, and 42	§ 103	Queen 1990 and Hudziak[7]
9	42	§ 103	Queen 1990, Hudziak and Furey
10	60	§ 103	Queen 1990, Hudziak, and Chothia & Lesk

In support of its patentability challenges, Petitioner relies on the Declarations of its technical experts, Dr. Jefferson Foote (Ex. 1003) and Mr. Timothy Buss (Ex. 1004). Petitioner further relies on the Declarations of Amanda Hollis, Christopher Lowden, and Karen Younkins for record authentication. Exs. 1187, 1188, and 1184, respectively.

[4] 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.
[5] Chothia and Lesk, *Canonical Structures for the Hypervariable Regions of Immunoglobulins*, 196 J. MOL. BIOL. 901–17 (1987). Ex. 1062.
[6] Chothia et al., *Domain Association in Immunoglobulin Molecules: The Packing of Variable Domains*, 186 J. MOL. BIOL. 651–63 (1985). Ex. 1063.
[7] 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.

Patent Owner relies on the Declarations of named inventors Dr. Leonard G. Presta and Dr. Paul J. Carter (Exs. 2016 and 2017, respectively), research technician Mr. John Ridgway Brady (Ex. 2018), and Ms. Irene Loeffler (Ex. 2019) with respect to authentication of records.

II. ANALYSIS

To anticipate a claim under 35 U.S.C. § 102, "a single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Group, 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).

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). In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *Id.* at 418.

A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "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) (internal quotations and citations omitted).

A. Person of Ordinary Skill in the Art

The parties propose similar definitions of a person of ordinary skill for the '213 patent. *See* Pet. 15–16; Prelim. Resp. 18. For purposes of this Decision, we adopt Patent Owner's proposed definition 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." *Id.*

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 regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

B. Claim Construction

In 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); *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)).

On pages 16–18 of its Petition, Petitioner proposed the construction of "humanized" (*see* claims 1, 30, 62–64, 66, 79, 80); "and further comprising a framework region (FR) amino acid substitution at a site selected from the group consisting of" (claims 1, 30, 62, 63, 66, 79, and 80); "numbering

system set forth in Kabat" (claims 1, 30, 62, 63, 66, 79, and 80); and "up to 3-fold more" (claim 65). Patent Owner does not dispute Petitioner's proposed constructions "for purposes of this proceeding," but asserts that "[n]o construction of those terms is necessary." Prelim. Resp. 19. On the present 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).

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. Patent Owner correctly points out that this "construction comes directly from the definition provided in the '213 patent." *Id.* at 19 (citing Ex. 1001, 11:32–38). For purposes of this Decision, we adopt Patent Owner's proposed construction.

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." Although neither party proposes an express definition of this phrase, Patent Owner appears to suggest that it refers to a complete lack of immunogenicity. *See* Prelim.

Resp. 45 (arguing that "lack[ing] immunogenicity compared to a non-human parent antibody" cannot be an inherent property of humanized antibodies because "even humanized antibodies may produce an immunogenic response"); *see also, id.* at 45–46 (arguing that Petitioner must show that antibodies produced according to techniques disclosed in [Kurrle and/or Queen 1990] will *necessarily* lack immunogenicity"). We find no support for this construction in the Specification or in the plain reading of the claim language.

Claim 63 does not merely recite "[a] humanized antibody which lacks immunogenicity," but expressly compares the immunogenicity of the claimed humanized antibody to that of its parent. Consistent with the plain language of the claim, the Specification states that one object of the invention is to "to provide methods for the preparation of antibodies which are less antigenic in humans than non-human antibodies but have desired antigen binding and other characteristics and activities." Ex. 1001, 4:24–28. The Specification similarly states that embodiments within the scope of the claims have "low immunogenicity," or are designed to "minimize the potential immunogenicity of the resulting humanized antibody in the clinic." *Id.* at 52:54–58, 61:56–61. Moreover, with reference to claim 63 in particular, Patent Owner states that "[t]he '272 application explains that the purpose of humanizing antibodies using its consensus sequence approach is to reduce immunogenicity versus the non-human parent antibody. (*Id.*, 6:24–30, 84:24–30.)." Prelim. Resp. 42 (citing Ex. 2032 (File History for U.S. Patent Application No. 07/715,272 ("the '272 application")); *see also id.* at 38 (indicating that the limitation is satisfied where "[o]nly 1 out of 885

patients experienced an immunogenic response . . . which was a substantial improvement over the murine 4D5 antibody"). Accordingly, for the purpose of institution, we interpret "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient," as referring to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody.

C. Prior-Art Status of Kurrle and Queen 1990

Petitioner asserts that Kurrle and Queen 1990 are prior art. Pet. 1–2 & n.3, 13, 19–23, 27. Patent Owner disagrees. Prelim. Resp. 2, 12, 14, 20–43.

"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 prior art under 35 U.S.C. § 102. *Id.* at 1379. Once the petitioner has met 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. *Id.* (citing *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008)). We therefore address the threshold issue of whether Petitioner

has met its initial burden to show that Kurrle and Queen 1990 are prior art to the challenged claims.

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 shown on the face of the '213 patent. Thus, we determine that Petitioner has satisfied its initial burden of showing that Kurrle and Queen 1990 qualify as prior art to the challenged claims.

Patent Owner attempts to disqualify Kurrle and Queen 1990 as prior art, arguing that the challenged claims were actually reduced to practice before either Kurrle or Queen 1990 was published, i.e., before July 26, 1990. Prelim. Resp. 20–43. As a preliminary matter, we note that this avenue of 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). According to Patent Owner, even though the '213 patent issued from a continuation-in-part of the '272 application, the challenged claims are only entitled to the priority date of June 14, 1991, the filing date of the '272 application. Prelim. Resp. 40–42. Thus, Patent Owner argues, Kurrle and Queen 1990 do not qualify as prior art under § 102(b). *Id.* at 40. For purposes of this Decision, we assume, without deciding, that the challenged claims are entitled to the priority date of June 14, 1991. Nevertheless, based on the current record,

Patent Owner has not sufficiently shown that the challenged claims were actually reduced to practice before the July 26, 1990, publication of Queen 1990.

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). A showing of prior invention requires corroboration. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996). Sufficiency of corroboration is determined by using a "rule of reason" analysis, under which all pertinent evidence is examined when determining the credibility of an inventor's testimony. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1170 (Fed. Cir. 2006). Corroboration may be 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. *Id.* at 1171.

To support its argument of prior invention, Patent Owner relies on numerous confidential internal documents, including laboratory notebooks or excerpts of laboratory notebooks, and other documents relating to internal research. Prelim. Resp. 20–40 (citing Exs. 2001–2015); *see also* Paper 8 (seeking to seal Exhibits 2001–2015). Patent Owner also relies on the Declarations of the inventors and another employee scientist. *Id.* (citing

Exs. 2016 (Presta Declaration), 2017 (Carter Declaration), 2018 (Brady Declaration)). These declarations, according to Patent Owner, "pertain[] to confidential research and development activities related to the invention described and claimed." Paper 8, 3–4 (seeking to seal Exhibits 2016–2018).

At this early stage of the proceeding, none of the antedating evidence has been developed or tested. Merely by way of example, Petitioner relies on Kurrle's disclosure for creating humanized mouse monoclonal antibodies in which the framework residues at 4L and 69H are murine, as set forth in claim 1. Pet. 19–20. It is not clear whether any of the antedating evidence relates to those substitutions. *See* Prelim. Resp. 20–40. To the contrary, Patent Owner states that the antedating evidence does not show substitution at 69H "because the murine . . . antibody and human consensus sequences are the same at those positions." Prelim. Resp. 36. It appears the substitution at 69H was only made "subsequently," as evinced in a 1997 publication. *Id.*, n.6; Ex. 2016 ¶ 52; Ex. 2021.[8] As a result, based on the current record, we determine that Patent Owner's evidence of prior invention is insufficient to disqualify Kurrle and Queen 1990 as prior art.

D. Anticipation by Kurrle (Ground 1)

Kurrle discloses "humanised and civilised versions" of monoclonal antibodies against the human alpha/beta T-cell receptor. Ex. 1071, Abstract; *see* Ex. 1003 ¶ 122. In particular, Kurrle discloses the production of chimeric antibodies, i.e., those "having mixed murine and human

[8] Presta et al., Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders, 57 Cancer Res. 4593–99 (1997).

characteristics in order to improve their effectiveness and/or lower their immunogenicity in patients." Ex. 1071, 3:3–5. In one embodiment, "[o]nly the complementarity deter[min]ing regions and selected framework amino acids necessary for antigen binding are maintained murine. The remaining framework regions are converted to human sequences." *Id.* at 3:9–11. Such alterations to the framework regions "can advantageously be made in the sequence immediately before and after the CDRs." *Id.* at 8:25–26. In particular,

> 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 the subgroup consensus model, Kurrle discloses substitution of human framework residues for mouse residues, including at positions 4L, 69H, 71H, 73H, and 76H. *Id.* at Tables 6A, 6B; Ex. 1003 ¶¶ 111, 123–124, 158, Exhibit D.

Relying on these disclosures, Petitioner asserts that Kurrle anticipates claims 1, 2, 25, 29, 63, 66, 67, 71, 72, 75, 76, 80, and 81. Pet. 12, 28–34. Patent Owner only challenges the merits of Petitioner's assertion regarding claim 63. Prelim. Resp. 45–46; *see also id.* at 2 ("even if Pfizer could rely

on Kurrle . . . Pfizer has failed to demonstrate a reasonable likelihood of success for claim 63 in Ground 1"); Prelim. Resp. 44, n.8. On this record, we are satisfied that Petitioner has established a reasonable likelihood that Kurrle anticipates at least claim 1.

We also are satisfied that Petitioner has shown sufficiently that Kurrle discloses all the elements of claim 63. Claim 63 recites:

> 63. A humanized antibody which *lacks immunogenicity compared to a non-human parent antibody upon repeated administration* to a human patient in order to treat a chronic disease in that patient, wherein the humanized antibody comprises non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

Ex. 1001, 88:36–48.

Petitioner presents evidence that Kurrle discloses substitution of framework residues at positions 4L, 69H, 71H, and 76H, thus encompassing four of the amino acid substitutions recited in claim 63. *See* Pet. at 20; Ex. 1071, Tables 6A, 6B; Ex. 1003 ¶¶ 111, 123, 124 & n.12, 155–172, Exhibit D.

Petitioner further contends that "lacking immunogenicity compared to a non-human parent [antibody is] an inherent aspect of the claimed humanized antibodies." Pet. 31; *see* Ex. 1003 ¶¶ 162–164. According to 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 in order to treat a chronic disease in that patient') is also present." Pet. 30–31. Petitioner also refers to Kurrle for stating that after humanization of the variable regions, the resulting chimeric antibody is "essentially a human antibody with a much lower immunogenicity in patients." *Id.* (quoting Ex. 1071, 3:8–12).

Patent Owner argues that Petitioner has failed to establish inherent anticipation because Petitioner has not shown that "antibodies produced according to techniques disclosed in [Kurrle] will *necessarily* lack immunogenicity." Prelim. Resp. 45–46. According to Patent Owner, Kurrle's assertion that "[t]he humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans," is merely an "aspirational statement[] of intended results," and an "unsupported prediction." *Id.* at 45. Patent Owner argues that during prosecution, Applicants successfully distinguished similar aspirational statements in Riechmann,[9] and "[t]he same result should apply here." *Id.* at 46 (citing Ex. 1002, 2485, 3431–3432; Ex. 1069, 1). We are not persuaded.

During prosecution of the '213 patent, the examiner rejected certain claims as obvious over the combination of several references, including Riechmann. Ex. 1002, 2483–87. According to the examiner, those references "clearly teach reduced immunogenicity associated with the humanized antibody." *Id.* at 2485. Specifically, the examiner relied on a passage from Riechmann, which states that "the use of human rather than

[9] Riechmann, et al., *Reshaping Human Antibodies for Therapy*, 332 NATURE 323–27 (1988) (Ex. 1069).

mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies." Ex. 1069, 323; Ex. 1002, 245 (citing "Riechmann et al. page 323, column 2, lines 5–8"); *see also* Prelim. Resp. 6, 46 (explaining anti-globulin responses are immunogenic response). Applicants argued that in Isaacs,[10] a follow-on publication of Riechmann, "three out of four patients treated with [Riechmann's] humanized . . . antibody . . . developed antiglobulins that were able to inhibit the binding of [the antibody] to its antigen." Ex. 1002, 3432 (citing Ex. 2025, 751). Patent Owner now relies on the same statement in Isaacs to support the proposition that "even humanized antibodies may produce an immunogenic response." Prelim. Resp. 45 (citing Ex. 2025, 751).

We note, however, that claim 63 does not require an absolute *lack* of immunogenicity, but only a *reduction* in immunogenicity as compared to a non-humanized parent antibody. *See* section II(B)(ii), above. Accordingly, Petitioner need not demonstrate that antibodies produced according to Kurrle "lack immunogenicity" as Patent Owner asserts.

We further note that Patent Owner does not argue that the humanized antibody taught in Riechmann and tested in Isaacs contains any substitution of framework residues at positions recited in claim 63. In contrast, Kurrle explicitly discloses the substitution of framework residues at positions 4L, 69H, or 76H, as recited in claim 63. *See* Pet. 20 (citing Ex. 1071, 25–26, Tables 6A and 6B; Ex. 1003 ¶¶ 123, 155–172). Moreover, Kurrle recognizes that the humanized antibody disclosed therein is "essentially a

[10] Isaacs, et al., *Humanised Monoclonal Antibody Therapy for Rheumatoid Arthritis*, 340 THE LANCET 748–52 (1992). Ex. 2025.

human antibody with a much lower immunogenicity in patients." Ex. 1071, 3:11–12. And 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). Thus, on the current record, we are persuaded that Petitioner has established a reasonable likelihood that Kurrle discloses all the elements of claim 63.

In view of the above, we are satisfied that Petitioner has shown a reasonable likelihood to prevail in its assertion that at least one claim would have been anticipated by Kurle. We, thus, institute inter partes review of claims 1, 2, 25, 29, 63, 66, 67, 71, 72, 75, 76, 80, and 81 challenged under this ground.

E. Obviousness over Kurrle and Queen 1990 (Ground 3)

Petitioner asserts that claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81 would have been obvious over the combination of Kurrle and Queen 1990. Pet. 41–51. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion with respect to at least claim 1.

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.[11] To account for this observation, Queen

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

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 "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, 12:9–13. 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, to 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 (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 9:21–25.

Citing the Declaration of Dr. Foote, Petitioner asserts that Queen 1990 provided the "motivation to humanize monoclonal antibodies along with a detailed roadmap for production of humanized monoclonal antibodies" that can be used in human therapeutics, (Pet. 42 (citing Ex. 1003 ¶¶ 203–204)), and that "Kurrle employed a similar roadmap" to obtain a humanized antibody. *Id.* at 43 (citing Ex. 1071, 8:16–40). According to Petitioner, "[u]sing these guidelines, Kurrle made a total of 13 substitutions in the light chain framework region and 18 substitutions in the heavy chain framework

region,"[12] including those at positions 4L, 69H, 71H, 73H, and 76H, as recited in the challenged claims. *Id.* (citing Ex. 1003 ¶¶ 155–158, 206); *see id*. at 20.

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

Patent Owner counters that Petitioner "never says what teaching absent from Kurrle is supposedly remedied by Queen 1990, or vice versa—let alone explains how the skilled artisan would purportedly combine the teachings of these two references." Prelim. Resp. 52. We are not persuaded by Patent Owner's argument.

[12] We note that Petitioner's expert identifies 13 human to mouse substitutions in the light chain framework region and 19 in the heavy chain framework region, plus one insertion between Kabat positions 103 and 104 of the heavy chain. *See* Ex. 1003 ¶ 124 & n.11.

Kurrle teaches methods of producing humanized antibodies. Ex. 1071, 8:27–46; Ex. 1003 ¶¶ 122–123. It explicitly discloses mouse for human substitution of framework residues at specific positions: 1L, 3L, 4L, 42L, 46L, 47L, 48L, 63L, 70L, 71L, 81L, 100L, 106L, 27H, 28H, 30H, 38H, 40H, 48H, 66H, 67H, 69H, 71H, 73H, 76H, 83H, 89H, 90H, 91H, 94H, 105H and 107H. Ex. 1071, Tables 6A, 6B; Ex. 1003 ¶¶ 124 & n.12, 158, Exhibit D.

Queen 1990 similarly teaches methods of designing humanized antibodies. Ex. 1050, 14:14–17:2. As Patent Owner points out, however, Queen 1990 does not expressly disclose any antibody sequence that contains the claimed framework substitutions. Prelim. Resp. 49–51. Petitioner, instead, relies on Queen 1990 for teaching substitution of framework residues "immediately adjacent" to the CDRs as taught in Queen 1990's Criterion III. Pet. 35–36 (citing Ex. 1050, 14:1–12; Ex. 1003 ¶ 173–183, Exhibit E). According to Petitioner's expert, even taking into account the slightly different CDR boundaries assigned by Kabat as compared to Chothia and Lesk, only 12 framework residues of the light chain and 12 residues of the heavy chain are immediately adjacent to CDR regions, including the 98L and 36H positions recited in claim 1. Ex. 1003 ¶ 179.

As Petitioner points out, before the '213 patent, "[t]he field recognized that earlier efforts (e.g., chimeric antibodies, CDR grafting) often resulted in non-or poor binding, with immunogenicity remaining a concern." Pet. 27 (citing Ex. 1050, 3:30–33; Ex. 1073, 9:12–19; Ex. 1003 ¶¶ 252–253; Ex. 1004 ¶¶ 38–41). Both Kurrle and Queen 1990 teach the design of humanized antibodies with low immunogenicity (*see* Ex. 1050, 6:21–25

(stating the resulting humanized antibody is "substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen"); Ex. 1071, 3:11–12 (stating the resulting humanized antibody is "essentially a human antibody with a much lower immunogenicity in patients")). Because Kurrle and Queen 1990 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.

Patent Owner does not dispute Petitioner's assertion that the combination of Kurrle and Queen 1990 teaches or suggests all limitations in each of claims 1, 2, 25, 29, 66, 67, 71, 72, 75, 80, and 81. *See* Pet. 6, 28–51; Prelim. Resp. 44 n.8. Patent Owner also does not address the obviousness challenge to claim 78, which is directed to "[a]n antibody comprising the humanized variable domain of claim 66." Ex. 1001, 90:1–2. After reviewing the record, we are satisfied that Petitioner has met its burden at this stage with regard to these claims.

Patent Owner challenges Petitioner's assertion that the combination of Kurrle and Queen 1990 teaches or suggests all limitations in each of claims 4, 62–64 and 69. Prelim. Resp. 45–53. We are not persuaded by Patent Owner's argument with regard to these claims. Each of claims 4, 62–64 and 69 requires "a consensus human variable domain" or, more broadly, "a human variable domain" (claim 64). Ex. 1001, 85:59–61, 88:27–35, 88:49–62, 89:14–16. Petitioner relies on Queen 1990 for teaching using "a consensus framework from many human antibodies" as the acceptor for

humanizing antibody. Pet. 41, 45–47 (quoting Ex. 1050, 12:17–20). Patent Owner contends "that is Queen 1990's only mention of a 'consensus framework.'" Prelim. Resp. 47. In our obviousness analysis, we evaluate the content of the prior art teaching, and not the number of times it was repeated.

Patent Owner further asserts that "Queen 1990 is not referring to the type of consensus sequence expressly defined and claimed in the '213 patent." *Id.* But Patent Owner presents no evidence in support of this contention and we accord little weight to unsupported attorney arguments.

With respect to claim 63, we are also satisfied that Petitioner has shown sufficiently that the combination of Kurrle and Queen 1990 teaches "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration." *See* Ex. 1001, 88:36–38. Patent Owner argues that Petitioner has failed to establish inherency because Petitioner has not shown that "antibodies produced according to techniques disclosed in [Kurrle and Queen 1990] will *necessarily* lack immunogenicity." Prelim. Resp. 45. As explained in section II(D), above, we are not persuaded by Patent Owner's argument.

Kurrle explicitly discloses substitution of framework residues at positions 4L, 69H, and 76H, as recited in claim 63 (*see* Ex. 1071, Tables 6A, 6B; Ex. 1003 ¶¶ 124&n.12, 158, Exhibit D.); and an ordinary artisan would have understood Queen 1990 for teaching substitution at positions 36H and 98L, also as recited in claim 63 (*see* Ex. 1003 ¶ 179–182, 188). Thus, on the current record, we are persuaded that Petitioner has established a reasonable likelihood that claim 63 would have been obvious over the combination of

Kurrle and Queen 1990. *See Atlas Powder*, 190 F.3d at 1347 (explaining that "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").

Patent Owner argues that objective indicia demonstrate that the challenged claims would not have been obvious. Prelim. 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)). Where objective indicia "result[ ] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *Id*. On the present record, Patent Owner has not sufficiently shown the nexus between the alleged unexpected results or commercial success and the claimed invention.

Moreover, because the secondary-considerations evidence Patent Owner relies on is presented in its Preliminary Response, Petitioner has not yet had an opportunity to respond to those evidence and arguments. Thus, in this case, a better course of action is to permit the parties to fully develop the record during trial before further weighing the alleged evidence of secondary considerations.

Based on the current record, we are satisfied that Petitioner has shown a reasonable likelihood to prevail in its assertion that claim 1 would have been obvious over Kurrle. We, thus, institute an *inter partes* review of the claims challenged under this ground.

F. Anticipation by Queen 1990 (Ground 2)

Petitioner asserts that claims 1, 2, 4, 29, 62–24, 80, and 81 are anticipated by Queen 1990. Pet. 34–40. Patent Owner opposes (Prelim. Resp. 49–51) and further argues that Grounds 2 and 3 are duplicative (*id.* at 52–53). With respect to claim 1, Petitioner argues that Criterion III of Queen 1990 explicitly taught the substitution of framework residues immediately adjacent to CDR, thus encompassing the claimed framework residues 98L and 36H. Pet. 35–36 (citing Ex. 1050, 14:1–12; Ex. 1003 ¶¶ 173–183, Exhibit E). Patent Owner responds that Criterion III of Queen 1990 is a "broad rule encompass[ing] substitutions at any of 23 different positions (Ex. 1003 ¶ 179)—literally ***thousands*** of different combinations and permutations of possible substitutions, only a small fraction of which overlap with the challenged claims." Prelim. Resp.50. On this record, we do not find Patent Owner's argument persuasive.

Claim 1 recites "[a] humanized antibody variable domain . . . further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: . . . 98L . . . 36H." On the present record, we accept Dr. Foote's testimony that one of ordinary skill in the art would understand Queen 1990 to disclose 24 positions "immediately adjacent to CDR regions" including 98L and 36H. *See* Ex. 1003 ¶ 179. Because the Markush group of claim 1 is introduced with open-ended

'comprising" language, it is irrelevant whether these 24 positions may be selected in "literally thousands" of multi-substitution combinations as Patent Owner suggests on page 50 of the Preliminary Response.

Based on the current record, we are satisfied that Petitioner has shown a reasonable likelihood to prevail in its assertion that at least claim 1 would have been anticipated by Queen 1990. We, thus, institute an *inter partes* review of the claims challenged under this ground.

G. Obviousness over Kurrle, Queen 1990, and Furey (Ground 4)

Claim 12 depends on claim 1 and further recites "wherein the residue at site 66L has been substituted." Ex. 1001, 86:51–52. Petitioner argues that claim 12 would have been obvious over the combination of Kurrle, Queen 1990, and Furey. Pet. 51–52. We find Petitioner's argument persuasive and adopt it for purposes of this Decision.

Specifically, Furey teaches the structural importance of framework residues that established hydrogen bonding with CDR residues. Ex. 1125, Abstract, 673–674; Ex. 1003 ¶ 139. In particular, Furey reports 66L as a residue for interacting with CDR2 of the light chain. *Id.* at Table 4; Ex. 1003 ¶ 233–234. Petitioner argues that Kurrle and Queen 1990 provide an ordinary artisan the motivation to substitute framework region positions that are close enough to either influence CDR conformation or to interact directly with antigen. Pet. 52 (citing Ex. 1003 ¶ 234). This, together with Dr. Foote's testimony that, in light of Furey, "one of ordinary skill in the art would have understood position **66L** to be on the list of substitutable residues, and would have substituted it if it was necessary," supports Petitioner's contention that claim 12 is obvious. *See* Ex. 1003 ¶ 234.

Patent Owner points out "Furey states that the 'most important' hydrogen-bonding interactions 'seem to be the two involved in the salt-bridge between Arg62 [*i.e.*, 61L] and Asp83 [*i.e.*, 82L].'" Prelim. Resp. 54 (quoting Ex. 1125, 672). Patent Owner faults Petitioner for not explaining "why a skilled artisan would have selected [residue] 66L instead of the five other hydrogen bonding interactions that Furey identified in addition to 66L," or the 31 and 23 potential substitutions suggested in Kurrle and Queen 1990, respectively. *Id.* We are not persuaded.

As the Supreme Court instructed,

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007). Here, both Kurrle and Queen 1990 recognize the need to substitute framework residues in order to reduce immunogenicity. *See* Ex. 1050, 6:21–26; Ex. 1071, 3:11–12. Based on that design need, the finite number of potential substitutions, and the "detailed roadmap" taught in Kurrle and Queen 1990, we determine Petitioner has established a reasonable likelihood that it would prevail in its assertion that claim 12 would have been obvious over the combination of Kurrle, Queen 1990, and Furey.

H. Obviousness over Kurrle, Queen 1990, Chothia & Lesk, and Chothia 1985 (Grounds 5–7)

Petitioner asserts that claims 65, 73, 74, 77, and 79 would have been obvious over Kurrle and Queen 1990, in combination with Chothia & Lesk,

and/or Chothia 1985. Pet. 52–56. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion with respect to at least claims 73 and 74.

Claims 73 and 74 require specific substitutions at 78H and 93H, respectively. Ex. 1001, 89:23–24, 89:25–26. Petitioner relies on Chothia & Lesk for teaching the substitution at 78H (Pet. 53 (citing Ex. 1062, Abstract, 901; Ex. 1003 ¶ 236); *see* Ex. 1062, Table 4), and Chothia 1985 for teaching the substitution at 93H (*id.* at 54 (citing Ex. 1063, 660, Table 4; Ex. 1003 ¶¶ 242–243)). Chothia & Lesk teaches certain framework residues, including 4L, 62L, 73L, 4H, 36H, 69H, 78H and 92H, as recited in the challenged claims, for maintaining antibody structure. Ex. 1062, 902, Table 4. Chothia 1985 teaches 12 "buried" residues that are involved in the VL and VH interface, and "are absolutely or very strongly conserved in all immunoglobulin sequences." Ex. 1063, Abstract, Table 4.

According to Petitioner, in light of the motivation provided by Kurrle and Queen 1990 to substitute certain framework region residues, it would have been obvious for an ordinary artisan to substitute residues 78H and 93H, as claimed in claims 73 and 74, respectively. *See* Pet. 53–54. Patent Owner's arguments are similar to those advanced in rebutting the obviousness of claim 12 based on Kurrle, Queen 1990, and Furey. *See* Prelim. Resp. 55–59. For the reasons explained above, we are not persuaded. *See* section II(G), above. Thus, we determine Petitioner has established a reasonable likelihood that it would prevail in its assertion that claims 73 and 74 would have been obvious over the combination of Kurrle, Queen 1990, Chothia & Lesk, and Chothia 1985.

Based on the current record, we are satisfied that Petitioner has shown a reasonable likelihood to prevail in its assertion that at least one claim would have been obvious over Kurrle and Queen 1990, in combination with Chothia & Lesk, and/or Chothia 1985. We, thus, institute an *inter partes* review of the claims challenged under Grounds 5–7.

I. Obviousness Based on Queen 1990, Hudziak, Furey, and Chothia & Lesk (Grounds 8–10)

Petitioner asserts that claims 30, 31, 33, and 42 would have been obvious over the combination of Queen 1990 and Hudziak; claim 42 would have been obvious over the combination of Queen 1990, Furey and Hudziak; and claim 60 would have been obvious over the combination of Queen 1990, Chothia & Lesk, and Hudziak. Pet. 7, 56–62. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in these assertions.

Each of claims 30, 31, 33, 42, and 60 requires an antibody that binds $p185^{HER2}$. Ex. 1001, 87:18–28, 87:29–32, 87:36–37, 18:54–55, 19:23–24. Hudziak discusses the role of $p185^{HER2}$'s role in carcinoma development and discloses 4D5, "a monoclonal antibody directed against the extracellular domain of $p185^{HER2}$ specifically inhibits the growth of breast tumor-derived cell lines overexpressing the *HER2/c-erbB*-2 gene product." Ex. 1021, Abstract, 1165. In characterizing 4D5, Hudziak reports that "resistance to the cytotoxic effect of tumor necrosis factor alpha, which has been shown to be a consequence of *HER2/c-erbB*-2 overexpression, is significantly reduced in the presence of this antibody." *Id.*, Abstract. According to Hudziak, "4D5, strongly inhibits the growth of several breast tumor cell lines and furthermore sensitizes $p185^{HER2}$-overexpressing breast carcinoma cell lines

SK-BR-3 and MDA-MB-175-VII to the cytotoxic effects of TNF-α." *Id.* at 1171. Hudziak concludes that "[m]onoclonal antibodies specific for $p185^{HER2}$ may therefore be useful therapeutic agents for the treatment of human neoplasias." *Id.*

According to Petitioner, Hudziak and other prior art demonstrated that *HER2* "was a ripe target for therapeutic development." Pet. 58 (citing Ex. 1004 ¶ 53; 1003 ¶¶ 331–332; 342.). Given "the strength of 4D5 as a clinical target," Petitioner contends, "the logical and necessary next step would have been to humanize 4D5." *Id.* at 59 (citing Ex. 1004 ¶70; Ex. 1003 ¶ 334). Patent Owner does not dispute these arguments. Instead, Patent Owner repeats its contention that Queen 1990 does not suggest the substitution at the specific residues claimed, and that the additional references do not cure that deficiency. Prelim. Resp. 59–61. We are not persuaded by Patent Owner's argument. As explained above, we determine that Petitioner has met its burden of showing that Queen 1990 teaches substituting certain framework residues, including those recited in claims 30, 31, 33, 42, and 60. *See* section II(F), above. Thus, after reviewing the entire record, we determine Petitioner has established a reasonable likelihood that it would prevail in its obviousness challenges of claims 30, 31, 33, 42, and 60.

J. Constitutionality of *Inter Partes* Review Proceedings

Patent Owner objects to the constitutionality of *inter partes* review in light of the pending review of that issue by the United States Supreme Court. Prelim. Resp. 66 (citing *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, 137 S. Ct. 2239 (Mem) (2017)). As of the date of this

Decision, the Supreme Court has not issued a decision addressing this issue, and Patent Owner's argument is foreclosed under existing Federal Circuit precedent. *See MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284 (Fed. Cir. 2015) (holding *inter partes* review does not violate Article III or the Seventh Amendment right to a jury trial). Patent Owner's objection is, however, sufficient to preserve this issue for appeal.

III. CONCLUSION

After considering the evidence and arguments presented in the Petition and Preliminary Response, we determine that Petitioner has demonstrated a reasonable likelihood of success in proving that at least one challenged claim of the '213 Patent is unpatentable. In keeping with our mission of resolving patent validity disputes in a just, speedy, and inexpensive manner, we exercise our discretion to institute *inter partes* review on all of the challenged claims and on all of the asserted grounds, as raised in the Petition.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted on the following grounds:

1. claims 1, 2, 25, 29, 63, 66, 67, 71, 72, 75, 76, 80, and 81, as anticipated by Kurrle;
2. claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81, as obvious over the combination of Kurrle and Queen 1990;
3. claims 1, 2, 4, 29, 62–64, 80, and 81 as anticipated by Queen 1990

4. claim 12 as obvious over the combination of Kurrle, Queen 1990, and Furey;
5. claims 65 and 79 as obvious over the combination of Kurrle, Queen 1990, Chothia & Lesk, and Chothia 1985;
6. claims 30, 31, and 33 as obvious over the combination of Queen 1990 and Hudziak;
7. claim 42 as obvious over the combination of Queen 1990, Furey, and Hudziak; and
8. claim 60 as obvious over the combination of Queen 1990, Chothia & Lesk, and Hudziak; and

FURTHER ORDERED that no other ground of unpatentability is authorized in this *inter partes* review;

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the ’158 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; and

FURTHER ORDERED that the parties shall, within two weeks of the entry date of this Order file a joint statement indicating which, if any, portions of this Decision are requested to remain sealed subject to the protective order entered in this case.

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