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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*.

YANG, *Administrative Patent Judge*.

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

INTRODUCTION

Celltrion, 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 2 ("Pet."). Genentech, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 7 ("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 established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claims, we institute an *inter partes* review of the challenged claims.

Related Proceedings

Petitioner has concurrently filed IPR2017-01373, challenging the same claims of the '213 patent based on different prior art references. Paper 3, 4.

The '213 patent is the subject of IPR2016-01693 and IPR2016-01694, filed by Mylan Pharmaceuticals Inc. Paper 3, 4. Those two proceedings were terminated before institution due to settlement. *Mylan Pharmaceuticals Inc. v. Genentech, Inc.*, IPR2016-01693 (PTAB March 10, 2017) (Paper 24); IPR2016-01694 (PTAB March 10, 2017) (Paper 23).

The '213 patent is also the subject of the following pending matters: IPR2017-01488 and IPR2017-01489, brought by Pfizer, Inc.; IPR2017-02031 and IPR2017-02032 brought by Boehringer Ingelheim Pharmaceuticals, Inc.; and IPR2017-02139 and IPR2017-02140, brought by Samsung Bioepis Co., Ltd.

The parties have identified no district court cases involving the ’213 patent. We note, however, that the petitioner in IPR2017-01488 represents that 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.). IPR2017-01488, Paper 16, 1. The parties are encouraged to update their mandatory disclosures.

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 1:33–35.

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.

Illustrative Claim

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.

Ex. 1001, 85:44–52.

Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability (Pet. 4):

Ground	Claim(s)	Basis	Reference(s)
1	1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80, and 81	§ 102	Kurrle[1]
2	1, 2, 4, 29, 62–64, 80, and 81	§ 102	Queen 1990[2]

[1] Kurrle, et al., European Patent Application Publication No. 0403156, published December 19, 1990. Ex. 1071.
[2] 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	Queen 1990 and Kurrle
4	12	§ 103	Queen 1990, Kurrle, and Furey [3]
5	65, 73, 74, 77, 79	§ 103	Queen 1990, Kurrle, and Chothia & Lesk,[4] and Chothia 1985[5]
6	30, 31, and 33	§ 103	Queen 1990 and Hudziak[6]
7	42		Queen 1990, Kurrle, Hudziak and Furey
8	60		Queen 1990, Hudziak, and Chothia & Lesk

In support of its patentability challenges, Petitioner relies on the Declarations of its technical experts, Dr. Lutz Riechmann, Ph.D (Ex. 1003) and Dr. Robert Charles Fredrick Leonard, M.D. (Ex. 1004).

Patent Owner relies on the Declarations of named inventors Dr. Leonard G. Presta (Ex. 2016) and Dr. Paul J. Carter (Ex. 2017), research technician Mr. John Ridgway Brady (Ex. 2018).

[3] 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.
[4] Chothia and Lesk, *Canonical Structures for the Hypervariable Regions of Immunoglobulins*, 196 J. MOL. BIOL. 901–17 (1987). Ex. 1062.
[5] Chothia et al., *Domain Association in Immunoglobulin Molecules: The Packing of Variable Domains*, 186 J. MOL. BIOL. 651–63 (1985). Ex. 1063.
[6] 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.

ANALYSIS

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Petitioner proposes the construction of several claim terms. Pet. 13–15. Patent Owner states that "[n]o construction of those terms is necessary, but Patent Owner does not dispute Celltrion's proposed constructions for purposes of this proceeding." Prelim. Resp. 18. We agree with Patent Owner that those terms do not need express construction. *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).

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. According to Patent Owner, "[t]hat construction comes directly from the definition

provided in the ’213 patent.” *Id.* at 18–19 (citing Ex. 1001, 11:32–38). For purposes of this Decision, we adopt Patent Owner’s proposed construction.

Prior-Art Status of Kurrle and Queen 1990

Petitioner asserts that Kurrle and Queen 1990 are prior art. *See, e.g.*, Pet. 1, 7. Patent Owner disagrees. Prelim. Resp. 2, 12, 13, 20–42.

In an *inter partes* review, the burden of persuasion is on the petitioner to prove unpatentability by a preponderance of the evidence, and that burden never shifts to the patentee. *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 1378–79. 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)).

A threshold issue, then, is 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 application No. 07/715,272 (“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 the July 26, 1990 publication of Queen 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). Patent Owner argues that Queen 1990 and Tramontano do not qualify as prior art under § 102(b). Prelim. Resp. 40. According to Patent Owner, even though the ’213 patent issued from a continuation-in-part of the ’272 application, the challenged claims are entitled to the priority date of June 14, 1991, the filing date of the ’272 application. *Id.* at 40–42. For purposes of this Decision, we assume, without deciding, that the challenged claims are entitled to the priority date of June 14, 1991.

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. 2016–2018). 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 Patent Owner's witnesses has been cross-examined regarding the antedating evidence. Thus, the better course of action is to permit the parties to fully develop the record during trial before determining whether Patent Owner's evidence of prior invention is sufficient to disqualify Kurrle and Queen 1990 as prior art.

Level of Ordinary Skill in the Art

The parties propose similar definitions of a person of ordinary skill for the '213 patent. *See* Pet. 12–13; Prelim. Resp. 17–18. 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." Prelim. Resp. 17–18.

We further note that, in this case, the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings 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)).

Anticipation by Kurrle

Kurrle discloses "humanised and civilised versions" of monoclonal antibodies against the human alpha/beta T-cell receptor. Ex. 1071, Abstract; *see* Ex. 1003 ¶ 111. In particular, Kurrle discloses the production of chimeric antibodies, i.e., those "having mixed murine and human characteristics in order to improve their effectiveness and/or lower their immunogenicity in patients." Ex. 1071, 3:3–5. In one embodiment, "[o]nly the complementarity deter[min]ing regions and selected framework amino acids necessary for antigen binding are maintained murine. The remaining framework regions are converted to human sequences." *Id.* at 3:9–11. Such alterations to the framework regions "can advantageously be made in the sequence immediately before and after the CDRs." *Id.* at 8:25–26. In particular,

> 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; *See* Pet. 17 & n.5; Ex. 1003 ¶¶ 111–113, 144–160, Exhibit C, 4–7.

Relying on these disclosures, Petitioner asserts that Kurrle anticipates claims 1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80, and 81. Pet. 25–31. Patent Owner only challenges the merits of Petitioner's assertion regarding claim 63. Prelim. Resp. 45–47; *see also id.* at 2 ("[e]ven if Celltrion could rely on Kurrle . . . Celltrion has failed to demonstrate a reasonable likelihood of success for claim 63 in Ground 1")*;* Prelim. Resp. 45 n.8. 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.

In sum, based on the current record, we are satisfied that Petitioner has shown a reasonable likelihood to prevail in its assertion that claim 1 is anticipated by Kurle. We, thus, institute an *inter partes* review of the claims challenged under this ground.

Obviousness over Queen 1990 and Kurrle

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. 38–49. 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. 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 "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 12:17–14:25. 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.

Petitioner asserts that Queen 1990 provided both "explicit motivation" and "a detailed roadmap with specific criteria used in designing humanized

immunoglobulins." Pet. 31–32, 40 (citing Ex 1003 ¶¶ 162–71, 145–53, 197; Ex. 1050, 6:21–26, 12:9–15). Petitioner further asserts that "Kurrle employed a similarly detailed roadmap" to obtain a humanized antibody. *Id.* at 43 (citing Ex. 1071, 8:16–18, 8:25–40; Ex. 1003 ¶¶ 110–113, 198)). "Using these guidelines, Kurrle made a total of 13 substitutions in the light chain framework region and 18 substitutions in the heavy chain framework region,"[7] including those at positions 4L, 69H, 71H, 73H, and 76H, as recited in the challenged claims. *Id.* at 41 (citing Ex. 1003 ¶¶ 144–147, 199, Exhibit C, 4–7); *see* Ex. 1003 ¶ 113.

> According to Petitioner:
>
> > A POSA would have been motivated to combine the teachings of Queen 1990 and Kurrle because of the similarity in the approaches implemented in these references and to improve on the successes of both. Ex. 1003 at ¶¶199–200. The 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", Ex. 1071 at 3:11–12, while maintaining the binding affinity and specificity of the donor monoclonal antibody, and targeted the very species residues satisfying the claim 1 genus.

Id. at 41.

Patent Owner counters that Petitioner "never says what teaching absent from Queen 1990 is supposedly remedied by Kurrle, 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.

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[7] We note that Petitioner's expert identifies 13 human to mouse substitutions in the light chain framework region and 20 in the heavy chain framework region, defined as including a two-amino acid insertion between Kabat positions 103 and 104 of the heavy chain. *See* Ex. 1003 ¶ 199 & n.7.

Kurrle teaches methods of producing humanized antibodies. Ex. 1071, 8:27–47; Ex. 1003 ¶¶ 111–113, Exhibit C, 4–7. 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 ¶¶ 113 & n.4, Exhibit C, 4–7.

Queen 1990 similarly teaches methods of designing humanized antibodies. Ex. 1050, 14:14–17:2. As Patent Owner points out, "Celltrion does not point to any antibody sequence disclosed in Queen 1990 that contains the claimed framework substitutions." Prelim. Resp. 50. 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. 31–33 (citing Ex. 1050, 14:1–12; Ex. 1003 ¶ 161–171, Exhibit C, 8–9). According to Petitioner's expert, even taking into account the slightly different CDR boundaries assigned by Kabat as compared to Chothia and Lesk, only 24 amino acid residues are immediately adjacent to CDR regions: residues 23L, 35L, 49L, 57L, 88L, 98L, 30H, 36H, 49H, 66H, 94H and 103H as according to Kabat, plus the addition of residues 25L, 33L, 49L, 53L, 90L, 97L, 25H, 33H, 52H, 56H, 95H and 102H according to Chothia. Ex. 1003 ¶ 167.

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. 24 (citing Ex. 1050, 3:30–33; Ex. 1073, 9:12–19; Ex. 1003 ¶¶ 87–90; Ex. 1004 ¶¶ 33–34). 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, 71, 75, 76, 78, 80, and 81. *See* Prelim. Resp. 45 n.8. After reviewing the record, we are satisfied that Petitioner has met its burden at this stage with regard to these claims. *See* Pet. 38–49

We acknowledge the evidence of secondary considerations and Patent Owner's argument that such evidence establishes the non-obviousness of the challenged claims. Prelim. Resp. 63–65. Indeed, evidence of secondary considerations, 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). Here, the secondary-considerations evidence Patent Owner relies on is first presented together with the Preliminary Response, and Petitioner has not yet had an opportunity to respond to the 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 the combination of Queen 1989 and Kurrle. We, thus, institute an *inter partes* review of the claims challenged under this ground.

Anticipation by Queen 1990

Petitioner asserts that 1, 2, 4, 29, 62–64, 80, 81 are anticipated by Queen 1990. Pet. 31–38. Patent Owner disagrees. Prelim. Resp. 50–54.

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. 31–33 (citing Ex. 1050, 14:1–12; Ex. 1003 ¶¶ 145–153, 161–171, Exhibit C, 8–9). Patent Owner responds that Criterion III of Queen 1990 is a "broad rule encompass[ing] substitutions at any of 23 different positions (Ex. 1003 ¶ 167)—literally ***thousands*** of different combinations and permutations of possible substitutions, only a small fraction of which overlap with the challenged claims." Prelim. Resp. 50–51. 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. Riechmann'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 ¶ 167. 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 pages 50–51 of the Preliminary Response.

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

Obviousness over Queen 1990, Kurrle, and Furey

Claim 12 depends on claim 1 and further recites "wherein the residue at site 66L has been substituted." Ex. 1001, 86:50–51. Petitioner argues that claim 12 would have been obvious over the combination of Kurrle, Queen 1990, and Furey. Pet. 49–50. We find Petitioner's argument persuasive and adopt it for purposes of this Decision.

Furey teaches the structural importance of framework residues that established hydrogen bonding with CDR residues. Ex. 1125, Abstract, 673–674; Ex. 1003 ¶ 128. In particular, Furey reports 66L as a residue for interacting with CDR2 of the light chain. *Id.* at Table 4; Ex. 1003 ¶¶ 205–206. 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. 49–50 (citing Ex. 1003 ¶¶ 206). This, together with Dr. Riechmann'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 ¶ 206.

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. 54–55 (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.* at 55. 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, 550 U.S. at 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.

Obviousness over Queen 1990, Kurrle, Chothia & Lesk, and Chothia 1985

Petitioner asserts that claims 65, 73, 74, 77, and 79 would have been obvious over the combination of Kurrle, Queen 1990, Chothia & Lesk, and Chothia 1985. Pet. 50–53. 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. 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.

Petitioner argue that, 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. 51–52. Petitioner relies on Chothia & Lesk for teaching the substitution at 78H (*id.* at 50 (citing Ex. 1062, 903, Table 4; Ex. 1003 ¶ 232–233)), and Chothia 1985 for teaching the substitution at 93H (*id.* at 51 (citing Ex. 1063, Table 4; Ex. 1003 ¶¶ 227–228)).

Based on the current record, we are satisfied that Petitioner has shown a reasonable likelihood to 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. We, thus, institute an *inter partes* review of the claims challenged under this ground.

Obviousness Based on Queen 1990, Hudziak, Kurrle, Furey, Chothia & Lesk

Petitioner asserts that claims 30, 31, and 33 would have been obvious over the combination of Queen 1990 and Hudziak; claim 42 would have been obvious over the combination of Queen 1990, Kurrle, Furey and Hudziak; and claim 60 would have been obvious over the combination of Queen 1990, Chothia & Lesk, and Hudziak. Pet. 54–60. Patent Owner

disagrees. Prelim. Resp. 60–62. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in each of these assertions with respect to at least one challenged claim.

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, 87:54–55, 88:23–24. 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. 55–56 (citing Ex. 1004 ¶ 48; 1003 ¶¶ 321–22.). 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 56 (citing Ex. 1004 ¶ 62; Ex. 1003 ¶ 324). 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. 60–62. 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.

Based on the current record, we are satisfied that Petitioner has shown a reasonable likelihood to prevail in its assertion with respect to at least one claim under each ground. We, thus, institute an *inter partes* review of the claims challenged under each ground based on Queen 1990, Hudziak, Kurrle, Furey, and Chothia & Lesk.

CONCLUSION

For the foregoing reasons, the information presented in the Petition and accompanying evidence establishes a reasonable likelihood that Petitioner would prevail in showing the unpatentability of at least one challenged claim.

At this stage of the proceeding, the Board has not made a final determination as to the construction of any claim term or the patentability of any challenged claim.

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, 71, 75, 76, 78, 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 Queen 1990 and Kurrle;

3. claims 1, 2, 4, 29, 62–64, 80, 81 as anticipated by Queen 1990;
4. claim 12 as obvious over the combination of Queen 1990, Kurrle, and Furey;
5. claims 65, 73, 74, 77, and 79 as obvious over the combination of Queen 1990, Kurrle, 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 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.

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