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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

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Case IPR2017-01373
Patent 6,407,213 B1

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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 9 ("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 IPR2017-01374, 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 1:33–34.

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.

*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.

*Asserted Grounds of Unpatentability*

Petitioner asserts the following grounds of unpatentability:

| Claim(s) | Basis | Reference(s) |
|---|---|---|
| 1, 2, 12, 25, 29, 63, 66, 67, and 71–81 | § 103 | Queen 1989[1] and Protein Data Bank (PDB database) |
| 1, 2, 4, 12, 25, 29, 62–67, 69, and 71–81 | § 103 | Queen 1990[2] and PDB database |

[1] Queen et al., *A Humanized Antibody that Binds to the Interleukin 2 Receptor*, 86 PRO. NAT'L ACAD. SCI. 10029–33 (1989) (Ex. 1034).
[2] Queen et al., International Publication No. WO 90/07861 A1, published July 26, 1990 (Ex. 1050).

| Claim(s) | Basis | Reference(s) |
|---|---|---|
| 65, 75–77, and 79 | § 103 | Queen 1989, PDB database, and Tramontano[3] |
| 65, 75–77, and 79 | § 103 | Queen 1990, PDB database, and Tramontano |
| 4, 62, 64, and 69 | § 103 | Queen 1989, PDB database, and Kabat 1987[4] |
| 30, 31, 42, and 60 | § 103 | Queen 1989, PDB database, and Hudziak[5] |
| 30, 31, 33, 42, and 60 | § 103 | Queen 1990, PDB database, and Hudziak |

Pet. 4.

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

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

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[3] Tramontano, A. et al., *Framework Residue 71 is a Major Determinant of the Position and Conformation of the Second Hypervariable Region in the VH Domains of Immunoglobulins*, 215 J. MOL. BIOL. 175–82 (1990) (Ex. 1051).

[4] Kabat, et al., Sequences of Proteins of Immunological Interest 4th Ed., Tabulation and Analysis of Amino Acid and Nucleic Acid Sequences of Precursors, V-Regions, C-Regions, J-Chain, T-Cell Receptor for Antigen, T-Cell Surface Antigens (National Institutes of Health, Bethesda, Md.) (1987) (Ex. 1052).

[5] 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. 13–16. 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. 17. According to Patent Owner, "[t]hat construction comes directly from the definition

provided in the ’213 patent.” *Id.* at 17–18 (citing Ex. 1001, 11:32–38). For purposes of this Decision, we adopt Patent Owner’s proposed construction.

*Prior-Art Status of Queen 1990 and Tramontano*

Petitioner asserts that Queen 1990 and Tramontano are prior art. *See, e.g.*, Pet. 4. Patent Owner disagrees. Prelim. Resp. 19–42.

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 Queen 1990 and Tramontano 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 national stage on November 17, 1993, from a PCT application filed on June 15, 1992. Ex. 1001, (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 (21), (63). Queen 1990 was published on July 26, 1990 (Ex. 1050, (43)), and Tramontano was published on September 5, 1990 (Exs. 1051, 2027), 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 Queen 1990 and Tramontano qualify as prior art to the challenged claims.

Patent Owner attempts to disqualify Queen 1990 and Tramontano as prior art, arguing that the challenged claims were actually reduced to practice before either Tramontano or Queen 1990 was published, i.e., before July 26, 1990. Prelim. Resp. 19–42. As a preliminary matter, we note that the 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, 1170–71 (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.*

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. 20–39 (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. Prelim. Resp. 20–39 (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 Queen 1990 and Tramontano 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; Prelim. Resp. 17. 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.

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)).

*Disclosures of the Asserted Prior Art*

Queen 1989

Queen 1989 teaches constructing a humanized antibody by combining the CDRs of a murine antibody with human framework and constant regions. Ex. 1034, Abstract, 3–4. According to Queen 1989, "[f]or the humanized antibody, sequence homology and molecular modeling were used to select a combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity." *Id.* at 1. In Queen 1989, the human framework regions were chosen to maximize homology with the murine antibody sequence. *Id.* at Abstract, 3. In addition, based on a computer model, Queen 1989 identified "several amino acids which, while outside the CDRs, are likely to interact with the CDRs or antigen. These mouse amino acids were also retained in the humanized antibody." *Id.* at Abstract, 3. Further, Queen 1989 teaches substituting an unusual amino acid in the human framework region if the corresponding

positions in the murine antibody "actually has a residue much more typical of human sequences." *Id.* at 4.

Queen 1990

Queen 1990 teaches the following four criteria for designing humanized antibodies that "have a very strong affinity for a desired antigen:"

> 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 one or more of the 3 CDR[]s in the primary sequence of the humanized immunoglobulin chain, the donor amino acid(s) 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.

Ex. 1050, 14:9–16:25. 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 8:21–25.

PDB Database

According to Petitioner, the Protein Data Bank (PDB) database was established in 1971 as a computer archival service managed by the Brookhaven National Laboratory. Pet. 19–20; Ex. 1003 ¶ 129 (citing Ex. 1080). "The purpose of the Bank is to collect, standardize, and distribute atomic co-ordinates and other data from crystallographic studies." Ex. 1080, 1. Dr. Riechmann testifies that the PDB database "is a repository of protein crystal atomic co-ordinates available to the public." Ex. 1003 ¶ 129. "The information provided in the PDB database was only a list of residues and their coordinates, but this was computer-readable data that could be directly inputted into distance calculation and graphic programs . . . for use in visualization and comparison studies." *Id.* According to Dr. Riechmann, in 1991, an ordinary artisan "relied on and contributed to the PDB database." *Id.*

Tramontano

Tramontano teaches that "the major determinant of the position of H2 [i.e., CDR2 of the heavy chain] is the size of the residue at site 71, a site that is in the conserved framework of the $V_H$ domain." Ex. 1051, Abstract. According to Tramontano, "[u]nderstanding the relationship between the residue at position 71 and the position and conformation of H2 has applications to the prediction and engineering of antigen-binding sites of immunoglobulins." *Id.*

Kabat 1987

Kabat 1987 is a compilation of known antibody sequences. Ex. 1052. For a given type of immunoglobulin, Kabat 1987 identifies the most common amino acids occurring at each position. *See, e.g.*, *id.* at 8. It also teaches the FR and CDR boundaries within the variable domains. *See, e.g.*, *id.* at 6–11.

Hudziak

Hudziak teaches $p185^{HER2}$'s role in carcinoma development. Ex. 1021, Abstract. Hudziak shows that 4D5, "a monoclonal antibody directed against the extracellular domain of $p185^{HER2}$ specifically inhibits the growth of breast tumor-derived cell lines overexpressing the *HER2*/c-*erbB*-2 gene product." *Id.* In addition, 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.* Hudziak states that "[m]onoclonal antibodies specific for $p185^{HER2}$ may therefore be useful therapeutic agents for the treatment of human neoplasias." *Id.* at 7.

*Obviousness over Queen 1989 and PDB Database*

Petitioner argues that claims 1, 2, 12, 25, 29, 63, 66, 67, and 71–81 would have been obvious over the combination of Queen 1989 and PDB database. Pet. 26–49. 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.

Relying on the Declaration of Dr. Riechmann, Petitioner asserts that

> Queen 1989 taught that framework residues that (1) are close enough to influence CDR conformation; (2) interact directly with the antigen; and/or (3) are more 'human' in the mouse or donor immunoglobulin than the residue at the same position in human antibody variable domain (i.e., conserved) are candidates for substitution with the donor antibody residue in the humanization process.

Pet. 27 (citing Ex. 1034, 3–4; Ex. 1003 ¶ 247). According to Petitioner, an ordinary artisan "would have used those simple rules to determine which residues in a human FR region could be switched back to mouse." *Id.* (citing Ex. 1003 ¶¶ 247–250).

"[F]ollowing the teachings of Queen 1989" and using antibodies well-known prior to the '213 patent, Petitioner continues, Dr. Riechmann was able to identify CDR-contacting framework residues that were targets for substitution. Pet. 30 (citing Ex. 1003 ¶¶ 254–258). These include residues 4L, 58L, 62L, 66L, 67L, 69L,[6] 73L, 85L, and 105L in the light chain, and residues 2H, 24H, 39H, 45H, 69H, 71H, 73H, 76H, 78H, 93H, and 103H in

[6] Even though the Petition states that Dr. Riechmann found "8 light (L) chain" residues and does not lists 69L (Pet. 30), Dr. Riechmann actually testifies he found nine residues, including 69L, in the light chain (Ex. 1003 ¶ 255).

the heavy chain. *Id.* As Petitioner points out, residues 4L, 58L, 66L, 67L, 69L, 73L, 2H, 45H, and 69H are recited in claim 1. *Id.*

Patent Owner argues that Queen 1989 contradicts Petitioner's obviousness theory. Prelim. Resp. 44–45. According to Patent Owner, Queen 1989 teaches nine substitutions, none of which corresponds to those recited in the challenged claims. *Id.* at 44 (citing Ex. 1034, 3). We are not persuaded by Patent Owner's argument.

First, Queen 1989 teaches more than the nine substitutions referred to by Patent Owner. For example, Queen 1989 teaches substituting 93H, which is a residue recited in claim 66. Ex. 1034, 4. Second, a person of ordinary skill would have read a reference for all that it teaches, including uses beyond its primary purpose. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418–21 (2007); *see also Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) (stating that a prior art reference is relevant "for all that it teaches" to those of ordinary skill in the art). Here, Queen 1989 teaches a general method to humanize antibodies. We agree with Petitioner that applying the criteria taught in Queen 1989 to antibodies known before the '213 patent, one of ordinary skill in the art would have identified nine positions in the light chain and eleven in the heavy chain as candidates for substitution, including those recited in the challenged claims.

Patent Owner next contends that 20 is a "large number" of possible framework substitutions. Prelim. Resp. 46. According to Patent Owner, because only "[l]ess than half" of them are claimed, Petitioner has not explained why an ordinary artisan "would have been drawn to the specific substitutions recited in the challenged claims." *Id.* We are not persuaded by this argument, either.

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. Here, Queen 1989 recognize the need to substitute framework residues in order to "reduce immunogenicity while retaining high binding affinity." *See* Ex. 1034, 1. Based on that design need, the finite number of potential substitutions, and the methodology taught in Queen 1989, we are persuaded by Petitioner that an ordinary artisan would have had a reason to combine the teachings of Queen 1989 and PDB database, and that the combination teaches or suggests all limitations in claim 1.

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 (*see* Prelim. Resp. 63–65 (citing Exs. 2025, 2029)), 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.

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 would have been obvious over the combination of Queen 1989 and PDB database. We, thus, institute an *inter partes* review of the claims challenged under this ground.

*Obviousness over Queen 1990 and PDB Database*

Petitioner argues that claims 1, 2, 4, 12, 25, 29, 62–67, 69, and 71–81 would have been obvious over the combination of Queen 1990 and PDB database. Pet. 32–49. 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.

Petitioner asserts that Queen 1990 teaches substituting "framework region positions that are adjacent to or can contact the CDRs" and "maintaining conserved residues in the human acceptor framework" in order to decrease immunogenicity. Pet. 33 (citing Ex. 1003 ¶¶ 123, 259–260; Ex. 1050, 15:22–37, 16:1–36). Petitioner contends "Queen 1990 thus provided a detailed rationale for substituting particular amino acids, and *how* to do it in a detailed and objective way." *Id.* Petitioner further points out that Queen 1990 "explicitly instructed" an ordinary artisan to look to the PDR Database to identify candidate framework residues for substitution. *Id.* (citing Ex. 1050, 14:21–25, 15:22–37, 16:1–12). According to Petitioner, following this roadmap, an ordinary artisan would have determined 19 light chain residues and 23 heavy chain residues as candidates. *Id.* at 33–34. Among those, 4L, 58L, 66L, 67L, 69L, 73L, 98L, 2H, 36H, 45H, and 69H are recited in claim 1. *Id.* at 34 (citing Ex. 1003 ¶¶ 164–165, 259–260).

Patent Owner's arguments in rebuttal are similar to those advanced in countering the obviousness ground based on Queen 1989. Prelim. Resp. 48–50. As explained above, we are not persuaded by those arguments. *See supra* at 15–18. After reviewing the record, we are satisfied that Petitioner has met its burden at this stage with regard 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 would have been obvious over the combination of Queen 1990 and PDB database. We, thus, institute an *inter partes* review of the claims challenged under this ground.

*Obviousness over Queen 1989 or Queen 1990, PDB Database, and Tramontano*

Petitioner argues that claims 65, 75–77, and 79 would have been obvious over the combination of Queen 1989 or Queen 1990, PDB database, and Tramontano. Pet. 49–51. Claim 75 specifies substitution at site 71H. According to Petitioner, Tramontano independently confirms the criticality of residue 71H "to maintain the H2 loop and antigen binding." *Id.* at 50 (citing Ex. 1051, Abstract). Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in this obviousness assertion with respect to at least claim 75. We, thus, institute an *inter partes* review of the claims challenged under this ground.

*Obviousness over Queen 1989, PDB Database, and Kabat 1987*

Each of claims 4, 62, 64, and 69 requires "a consensus human variable domain." Petitioner argues that these claims would have been obvious over the combination of Queen 1989, PDB Database, and Kabat 1987. Pet. 51–52. Specifically, Petitioner asserts:

> [R]ecognizing the importance of maintaining FR conservation to reduce immunogenicity and "make the antibody more human," Queen 1989 explicitly taught moving towards a consensus framework region, observing that replacing amino acid residues with ones that are "more typical" and common would make the resulting antibody more human and less immunogenic.

*Id.* at 51 (citing Ex. 1003 ¶ 310). According to Petitioner, combining this teaching of Queen 1989 with those of Kabat 1987, "which provided all consensus amino acids at each framework region position," an ordinary artisan would have substituted residues in the framework region itself "with the most common amino acid in human antibodies to maximize a reduction in immunogenicity." *Id.* at 51–52 (citing Ex. 1003 ¶ 310).

Patent Owner contends that "Queen 1989's reliance on identifying a human sequence 'most homologous' to the specific non-human sequence to be humanized is the ***opposite*** of a consensus sequence," and that Queen 1989's teachings of "***modifying*** a sequence to include 'more typical' residues is not the consensus sequence approach of the '213 patent" either. Prelim. Resp. 58. Because these are merely unsupported attorney arguments, we are not persuaded at this stage of the proceeding.

In sum, based on the current record, we are satisfied that Petitioner has shown a reasonable likelihood to prevail in its assertion that at least one of claims 4, 62, 64, and 69 would have been obvious over the combination of Queen 1989, PDB database, and Kabat 1987. We, thus, institute an *inter partes* review of the claims challenged under this ground.

*Obviousness over Queen 1989 or Queen 1990, PDB Database, and Hudziak*

Petitioner asserts that claims 30, 31, 33, 42, and 60 would have been obvious over the combination of Queen 1989 or Queen 1990, PDB database,

and Hudziak. Pet. 52–57. Based on the current record, we determine Petitioner has established a reasonable likelihood that it would prevail in these assertions.

Claim 30 requires an antibody that binds $p185^{HER2}$. It also requires amino acid substitution at a site selected from a group including those sites recited in claim 1. According to Petitioner, Hudziak and other prior art demonstrated that *HER2* "was a ripe target for therapeutic development." Pet. 53 (citing Ex. 1004 ¶ 61). Petitioner contends that given "the strength of 4D5 as a clinical target, the logical and necessary next step" would have been to humanize 4D5. *Id.* at 54 (citing Ex. 1004 ¶ 63).

Patent Owner does not dispute these arguments. Instead, Patent Owner repeats its contention that neither Queen 1989 nor Queen 1990 discloses the substitution at the specific residues claimed, and that the additional references do not cure that deficiency. Prelim. Resp. 62–63. We are not persuaded by Patent Owner's argument. As explained above, we determine that, at this stage of the proceeding, Petitioner has met its burden in showing Queen 1989 or Queen 1990 teaches and suggests substituting certain framework residues, including those recited in claim 30. *See supra* 15–19. After reviewing the entire record, we determine Petitioner has established a reasonable likelihood that it would prevail in its obviousness challenges of claim 30. We, thus, institute an *inter partes* review of the claims challenged under this ground.

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, 12, 25, 29, 63, 66, 67, and 71–81 as obvious over the combination of Queen 1989 and PDB database;
2. claims 1, 2, 4, 12, 25, 29, 62–67, 69, and 71–81 as obvious over the combination of Queen 1990 and PDB database;
3. claims 65, 75–77, and 79 as obvious over the combination of Queen 1989, PDB database, and Tramontano;
4. claims 65, 75–77, and 79 as obvious over the combination of Queen 1990, PDB database, and Tramontano;
5. claims 4, 62, 64, and 69 as obvious over the combination of Queen 1989, PDB database, and Kabat 1987;
6. claims 30, 31, 42, and 60 as obvious over the combination of Queen 1989, PDB database, and Hudziak; and
7. claims 30, 31, 33, 42, and 60 as obvious over the combination of Queen 1990, PDB database, and Hudziak; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the ’213 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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