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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-02032
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

Boehringer Ingelheim Pharmaceuticals, Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71–73, 75–78, 80, and 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 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 claim, we institute an *inter partes* review of claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 73, 75–78, 80, and 81.

Related Proceedings

According to the parties, the '213 patent is at issue in several district court cases, including *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01407 (D. Del.); *Amgen Inc. v. Genentech, Inc.*, No. 2-17-cv-07349 (C.D. Cal.); *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01471 (D. Del.); *Genentech, Inc. et al. v. Pfizer, Inc*. 1-17-cv-01672 (D. Del.); *Celltrion, Inc. v. Genentech, Inc.*, No. 18-cv-00274 (N.D. Cal.); and *Genentech, Inc. v. Celltrion, Inc.*, No. 18-cv-00095 (D. Del.). Paper 7, 5; Paper 8, 3; Paper 16, 2.

Petitioner has concurrently filed IPR2017-02031, challenging the same claims of the '213 patent based on different prior art references. Paper 1, 2.

The ’213 patent is the subject of IPR2016-01693 and IPR2016-01694, filed by Mylan Pharmaceuticals Inc. Paper 1, 2. We terminated those two proceedings before issuing an institution decision because the parties settled. *Mylan Pharm. 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: IPR2017-01373 and IPR2017-01374 brought by Celltrion, Inc.; and IPR2017-01488 and IPR2017-01489 brought by Pfizer, Inc. We previously instituted *inter partes* reviews in those cases, and joined IPR2017-02139 and IPR2017-02140, brought by Samsung Bioepis Co., Ltd., to IPR2017-01488 and IPR2017-01489, respectively.

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. This involves:

> a. obtaining the amino acid sequences of at least a portion of an import antibody variable domain and of a consensus variable domain;
>
> b. identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human variable domain sequences;
>
> c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
>
> d. aligning the amino acid sequences o(a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
>
> e. identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
>
> f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:
>
> 1. non-covalently binds antigen directly,

2. interacts with a CDR; or
3. participates in the V_L-V_H interface; and

g. for any non-homologous import antibody amino acid residue which is reasonably expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence.

Id. at 4:43–5:5.

Figures 1A and 1B of the '213 patent show alignments of light and heavy chain variable regions of mouse antibody muMAb4D5 with human antibody huMAb4D5, along with their resulting consensus sequences ($HUV_{Lκ}$I and HUV_HIII), respectively. *Id.* at 6:57–7:8.

Illustrative Claim

Among the challenged claims, claims 1, 62–64, 66, 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:

Ground	Claim(s)	Basis	Reference(s)
1	1, 2, 25, 29, 63, 66, 67, 71–73, 75–78, 80, 81	§ 103	Queen 1989[1] and Protein Data Bank (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).

Ground	Claim(s)	Basis	Reference(s)
2	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71–73, 75–78, 80, 81	§ 103	Queen 1990[2] and PDB database
3	75–77	§ 103	Queen 1989, PDB database, and Tramontano[3]
4	75–77	§ 103	Queen 1990, PDB database, and Tramontano
5	4, 62, 64, 69	§ 103	Queen 1989, PDB database, and Kabat 1987[4]
6	1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 73, 75–78, 80, 81	§ 102	The '101 patent[5]

Pet. 4.

In support of its patentability challenges, Petitioner relies on the Declaration of Dr. Geoffrey Hale (Ex. 1003).

ANALYSIS

Grounds 1–5

Patent Owner requests that we exercise our discretion under 35 U.S.C § 325(d) to deny institution with respect to Grounds 1–5 because "Boehringer copied Grounds 1–5 of this Petition from IPR2017-01373

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[2] Queen et al., International Publication No. WO 90/07861 A1, published July 26, 1990 (Ex. 1050).
[3] Tramontano 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] U.S. Patent No. 5,530,101, issued June 25, 1996 (Ex. 1136).

(Celltrion) and IPR2017-01489 (Pfizer), and copied Grounds 1–3 and 5 of IPR2017-02031 from IPR2017-01374 (Celltrion) and IPR2017-01488 (Pfizer)—without seeking joinder with those earlier-filed proceedings." Prelim. Resp. 1. According to Patent Owner, "[t]his redundancy would waste the Board's and Patent Owner's resources, and also would unfairly allow Boehringer to preview the parties' arguments before having to address them itself." *Id.* at 2. We find Patent Owner's argument persuasive.

In determining whether to institute an *inter partes* review, we "may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). As Patent Owner correctly points out, Grounds 1–5 asserted in the Petition "are essentially identical to those already instituted in" IPR2017-01373 and IPR2017-01489. Prelim. Resp. 12–13. Petitioner filed this Petition before we issued the decisions instituting *inter partes* reviews in IPR2017-01373 and IPR2017-01489. Thus, Petitioner could have sought to join the pending IPRs. Yet, it did not do so. *See* 37 C.F.R. § 42.122. The time for requesting joinder has since expired. *See id*. As such, we exercise our discretion under § 325(d) and deny the Petition with respect to Grounds 1–5.

Ground 6: Anticipation by the '101 Patent

Petitioner asserts that claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 73, 75–78, 80, and 81 are anticipated by the '101 patent. Pet. 52–60. Patent Owner does not respond on the merits, but argues that that we should deny institution of this ground under § 325(d). Prelim. Resp. 15–17. We address, in turn, Patent Owner's § 325(d) argument and the merits of Petitioner's challenge.

§ 325(d)

Patent Owner argues that we should deny ground 6 because "the PTO Already Determined that the '101 Patent is Not Prior Art." Prelim. Resp. 15. According to Patent Owner, the '101 patent "was not only specifically raised during prosecution, but antedated by Patent Owner." *Id.* As a result, Patent Owner contends that we should deny ground 6 under § 325(d). *Id.* at 16–17. We are not persuaded.

During prosecution, the examiner rejected the then pending claims under 35 U.S.C. 102(e) as anticipated by the '101 patent. Ex. 1002, 738–40. In response, the applicant submitted a Declaration under 37 C.F.R. §1.131, swearing behind the reference. *Id.* at 802–03. In the Declaration, the inventors stated that, prior to September 28, 1990, they had conceived and reduced to production a humanized antibody comprising "a[n] FR amino acid substitution at site 73H." *Id.* at 803. Thereafter, the examiner allowed the claims. *Id.* at 835.

Claim 1 recites an 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." Because 73H is not recited in the challenged claim 1, the § 1.131 Declaration submitted during prosecution cannot antedate the '101 patent.[6]

[6] We acknowledge that certain challenged claims, such as claims 66 and 80, recite amino acid substitution at site 73H as a member of a Markush group. For purpose of this Decision, however, we do not need to decide whether the § 1.131 Declaration is sufficient to antedate those claims. See 35 U.S.C. § 314(a) (authorizing institution when "there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition").

As a result, we decline to exercise our discretion under § 325(d) to deny ground 6.

Prior-Art Status of the '101 patent

Patent Owner argues that Petitioner "failed to meet its burden to establish that the '101 patent is prior art." Prelim. Resp. 16.

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)).

The '101 patent issued from an application No. 07/634,278, which was filed on December 19, 1990 and claims priority to a series of earlier applications. Ex. 1136, [63], 1:6–11. The earliest possible priority date of the challenged claims is June 14, 1991. Ex. 1001, (21), (63). Thus, we determine that Petitioner has satisfied its initial burden of showing that the '101 patent qualifies under § 102(e) as prior art to at least challenged claim 1.

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).

Claim 1 of the '231 patent recites "[a] humanized antibody variable domain . . . 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." Depending from claim 1, claim 4 limits the humanized antibody variable domain of claim 1 to "a consensus human variable domain."[7]

Petitioner reasons that "[b]ecause claim 1 requires substitutions in the variable domain, claim 4 must also require substitutions in the variable domain" such that the claim "encompass[] humanized antibody variable domains where only *some* of the residues in the sequence are 'consensus' residues, and where other, non-consensus residues are 'substitutions' in the consensus sequence." Pet. 7–8.

[7] Although we focus our analysis on claim 4, similar usages are found throughout the challenged claims. Claim 64, for example, recites "a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup . . . compris[ing] a Framework Region (FR) substitution."

Petitioner further argues "substitution," and the related term "substituted," do not require the intentional replacement of amino acids in a human consensus variable domain. *See id.* at 8–9. Rather, Petitioner argues, as used in the challenged claims, these terms invoke product-by-process limitations, which should be disregarded in the patentability analysis. *Id.* at 8, 53 (citing *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1353–54 (Fed. Cir. 2016); Ex. 1003 ¶ 321). Taken together, Petitioner argues that "any differences from the consensus sequence can be considered a 'substitution' of the consensus residue for a non-consensus reside, whether or not it was deliberately placed." *Id.* at 55.

Based on the current record, and for purposes of this Decision, we find Petitioner's argument reasonable and adopt Petitioner's interpretation of "substitution." We further construe claim 4 as encompassing humanized variable domains where only some of the residues in the sequence are amino acids of a consensus human variable domain.

Based on the current record, and for purposes of this Decision, no other claim term requires 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).

Analysis of Ground 6

Petitioner contends that "a prior art antibody prepared without intentional substitutions, but with the same sequence (and thus structure and function) as an antibody prepared according to the claims of the '213 patent, would anticipate those claims." Pet. 54. According to Petitioner, "[t]he '101 patent discloses just such a prior art antibody." *Id.*

The ’101 patent discloses “humanized immunoglobulins having one or more complementarity determining regions (CDR’s) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin.” Ex. 1136, Abstract. Specifically, the ’101 patent discloses a humanized CMV5 antibody. *Id.* at 60:45–64:26.

Petitioner refers us to Hale Exhibit R, which allegedly compares the consensus sequence (as shown in Fig 1A of the ’213 patent) with the sequences of Wo1, mouse CMV5, and humanized CMV5 (as shown in Figures 6A and 40A of the ’101 patent). Pet. 54–55. According to Petitioner, “this comparison [shows] there are both consensus and non-consensus residues in the humanized CMV5 variable domain.” *Id.* at 55. Relying on the testimony of Dr. Hale, Petitioner argues that the ’101 patent discloses humanized CMV5 antibody with substitutions “at least at 4L;58L;85L; and 69H,” among which “[a]t least residues 4L;58L; and 69H are the same as the corresponding murine residue at those locations. Pet. 54 (citing Ex. 1003 ¶ 126; Ex. 1003C, 780 (Hale Exhibit R)), *see also id.* at 23 (the same). Because 4L, 58L, and 69H are members of the Markush group recited in claim 1, Petitioner argues that the ’101 patent anticipates that claim. *Id.* at 55; *see also* Ex. 1003 ¶ 321 (“[S]o long as the humanized variable domain disclosed by the ’101 patent differs with the consensus variable domain at least at one of the sites recited by claim 1, then the ’101 patent meets the requirement for a ‘Framework Region (FR) amino acid substitution’ at that site.”).

Based on the current record, we find Petitioner’s arguments persuasive. Because we determine that Petitioner has shown a reasonable

likelihood that it would prevail in showing the unpatentability of at least claim 1 of the ’231 patent, we institute *inter partes* review to determine whether claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 73, 75–78, 80, and 81 are anticipated by the ’101 patent.

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 to determine whether claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 73, 75–78, 80, and 81 are anticipated by the ’101 patent;

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 ’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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