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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC. and CITY OF HOPE,
Patent Owner.

Case IPR2016-00710
Patent 6,331,415 B1

Before TONI R. SCHEINER, LORA M. GREEN, and SUSAN L. MITCHELL, *Administrative Patent Judges.*

GREEN, *Administrative Patent Judge.*

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

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition (Paper 2, "Pet."), requesting institution of an *inter partes* review of claims 1–4, 11, 12, 14, 18–20, and 33 of U.S. Patent No. 6,331,415 B1 (Ex. 1001, "the '415 patent"). Petitioner also filed a Motion for Joinder, seeking joinder with IPR2015-01624. Paper 3, 1. Genentech, Inc. and City of Hope (collectively, "Patent Owner") did not file a Preliminary Response, but did file an Opposition to the Motion for Joinder. Paper 8. In addition, Petitioners in IPR2015-01624, Sanofi Aventis U.S. LLC and Regeneron Pharmaceuticals, Inc., filed an opposition to the Motion for Joinder in that proceeding (Paper 25). Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a); *see* 37 C.F.R. § 42.108.

Upon consideration of the Petition, as well as the papers related to joinder, for the reasons explained below, we determine that Petitioner has shown that there is a reasonable likelihood that they would prevail with respect to at least one of the challenged claims. We, thus, institute an *inter partes* review of claims 1–4, 11, 12, 14, 18–20, and 33 of the '415 patent.

A. Related Proceedings

Petitioner identifies IPR2015-01624, IPR2016-00383, and IPR2016-00460 as all challenging claims of the '415 patent. Pet. 44. Note that IPR2015-01624, to which IPR2016-00460 was joined, has been terminated (Paper 43). The Board declined to institute trial in IPR2016-00383 (Paper 16).

Patent Owner identifies U.S. patent applications, as well as issued patents, that relate to the '415 patent. Paper 7, 2–3. In addition, Patent Owner identifies other proceedings before the Office, such as interferences and reexaminations, that may relate to the '415 patent. *Id.* at 3. Patent Owner also identifies several district court proceedings that may relate to the '415 patent. *Id.* at 3–6.

B. Motion for Joinder (Paper 25)

Petitioner seeks joinder to IPR2015-01624, asserting that its Petition "raises the same grounds of unpatentability over the same prior art as those instituted by the Board in [IPR2015-01624]." Paper 3, 1. We note, however, that at the request of the involved parties, we terminated IPR2015-01624 on September 2, 2016 (Paper 43). Thus, Petitioner's Motion for Joinder is moot. We do, however, for the reasons set forth below, as well as in the Decision on Institution in IPR2015-01624 (Paper 15), institute on the same grounds we instituted in IPR2015-01624.

C. The '415 Patent (Ex. 1001)

The '415 patent issued on December 18, 2001, and claims priority to an application filed on April 8, 1983. *See* Ex. 1001, Title Page. It names Shmuel Cabilly, Herbert L. Heyneker, William E. Holmes, Arthur D. Riggs, and Ronald B. Wetzel, as the inventors. *Id.*

The '415 patent relates generally to processes for producing immunoglobulin molecules in a host cell transformed with a first DNA sequence encoding the variable domain of the heavy chain and a second DNA sequence encoding the variable domain of the light chain, as well as vectors and transformed host cells used in such processes. More specifically, the first and second DNA sequences are present in either

different vectors or in a single vector, and independently expressed so that the immunoglobulin heavy and light chains are produced as separate molecules in the transformed single host cell. *See id.*, cols. 1, 15, 18, 21, and 33.

According to the Specification of the '415 patent, there were two major sources of vertebrate antibodies that could be generated *in situ* by the mammalian B lymphocytes or in cell culture by B-cell hybrids (hybridomas). *Id.* at 1:42–45. The Specification notes, however, that monoclonal antibodies produced by these two sources suffer from disadvantages, including contamination with other cellular materials, instability, production of an undesired glycosylated form, high cost, and an inability to manipulate the genome. *Id.* at 2:40–66. The Specification recognizes that "the use of recombinant DNA technology can express entirely heterologous polypeptides—so-called direct expression—or alternatively may express a heterologous polypeptide fused to a portion of the amino acid sequence of a homologous polypeptide." *Id.* at 4:33–37.

The Specification states that "[t]he invention relates to antibodies and to non-specific immunoglobulins (NSIs) formed by recombinant techniques using suitable host cell cultures," which can "be manipulated at the genomic level to produce chimeras of variants which draw their homology from species which differ from each other." *Id.* at 4:53–59. The Specification further indicates that "[t]he ability of the method of the invention to produce heavy and light chains or portions thereof, in isolation from each other offers the opportunity to obtain unique and unprecedented assemblies of immunoglobulins, Fab regions, and univalent antibodies." *Id.* at 12:58–62.

D. Illustrative Claims

Petitioner challenges claims 1–4, 11, 12, 14, 18–20, and 33 of the '415 patent. Independent claims 1 and 18, the only independent claims challenged, are illustrative, and reproduced below:

> 1. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell, comprising the steps of:
>
> (i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and
>
> (ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell.
>
> 18. A transformed host cell comprising at least two vectors, at least one of said vectors comprising a DNA sequence encoding at least a variable domain of an immunoglobulin heavy chain and at least another one of said vectors comprising a DNA sequence encoding at least the variable domain of an immunoglobulin light chain.

Ex. 1001, 28:35–49; 29:31–36.

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of the challenged claims of the '415 patent on the following grounds (Pet. 3):

References	Basis	Claims challenged
Bujard[1] and Riggs & Itakura[2]	§ 103(a)	1, 3, 4, 11, 12, 14, 19, and 33
Bujard and Southern[3]	§ 103(a)	1, 2, 18, 20 and 33

Petitioner relies also on the Declaration of Jefferson Foote, Ph.D. (Ex. 1006), as well as the Declaration of Dr. Kathryn Calame, Ph.D. (Ex. 1059). Pet 3. Petitioner relies on the Declaration of Dr. Calame "to preserve its right to rely on expert testimony in the event that joinder is not granted or in the case that the Sanofi IPR is settled." *Id.*

II. DISCUSSION

A. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the Specification of the patent in which they appear. *See* 37 C.F.R. §42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–2145 (2016) (upholding the use of the broadest reasonable interpretation standard). Under the broadest reasonable construction standard, claim terms are presumed to have their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire

[1] Bujard et al., US 4,495,280, issued Jan. 22, 1985 (Ex. 1002) ("Bujard").

[2] Arthur D. Riggs and Keiichi Itakura, *Synthetic DNA and Medicine*, 31 AM. J. HUM. GENET. 531–538 (1979) (Ex. 1003) ("Riggs & Itakura").

[3] P.J. Southern and P. Berg, *Transformation of Mammalian Cells to Antibiotic Resistance with a Bacterial Gene Under Control of the SV40 Early Region Promoter*, 1 J. MOLECULAR AND APPLIED GENETICS327–341 (1982) (Ex. 1004) ("Southern").

disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). "Absent claim language carrying a narrow meaning, the PTO should only limit the claim based on the specification . . . when [it] expressly disclaim[s] the broader definition." *In re Bigio*, 381 F.3d 1320, 1325 (Fed Cir. 2004). "Although an inventor is indeed free to define the specific terms used to describe his or her invention, this must be done with reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner states it "does not believe that any special meanings apply to the claim terms in the '415 patent." Pet. 18. Petitioner notes that the term "immunoglobulin" is interchangeable with "antibodies." Pet., 4 n.1. Moreover, for purposes of this decision and consistent with our Decision on Institution in IPR2015-01624 (Paper 15, 6–7), with respect to the term "independently expressing" recited in claims 1 and 33, we construe that term as not requiring that either the heavy or light chain is capable of being expressed without the concomitant expression of the other chain.

We determine that no explicit construction of any other claim term is necessary to determine whether to institute a trial in this case. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). At this stage of the proceeding, we have not made a final determination as to the construction of any claim term.

B. Principles of Law

An *inter partes* review may be instituted only if "the information presented in the [Petition and Preliminary Response] shows that there is a

reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). We analyze the proposed grounds of unpatentability in accordance with the following stated principles.

The legal question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In *KSR International Co. v. Teleflex Inc.*, the Supreme Court stated that, under certain circumstances, an invention may be found obvious if *trying* a course of conduct would have been considered obvious to a person having ordinary skill:

> 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. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. 398, 421 (2007). In this regard, "[o]bviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)).

As the court noted in *Kubin*, "[t]he Supreme Court's admonition against a formalistic approach to obviousness in this context actually resurrects this court's own wisdom in *In re O'Farrell* . . . ." *Id.* In

O'Farrell, the court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under § 103. First, obviousness is not shown when

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

O'Farrell, 853 F.2d at 903. Second, obviousness is also not shown when

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id.

C. Prior Art Relied Upon

Petitioner relies upon the following prior art in its challenges.

1. Bujard (Ex. 1002)

Bujard relates to a process for producing polypeptides in a transformed host cell using a plasmid vector that is optimized to have a high signal strength T5 phage promoter and a balanced terminator. Ex. 1002, Abstract. More particularly, the structure of the vector taught by Bujard is "a strong promoter, followed by a DNA sequence of interest, optionally followed by one or more translational stop codons in one or more reading frames, followed by a balanced terminator, followed by a marker allowing for selection of transformants." *Id.* at 2:8–13.

Bujard explains that the plasmid vector may have the strong promoter and terminator separated by "more than one gene, that is, a plurality of

genes, including multimers and operons." *Id.* at 3:45–48. Further, Bujard indicates that "[d]esirably, the gene is followed by one or a plurality of translational stop codons e.g. oop or nonsense codons, or preferably a plurality, usually up to about six, more usually from about two to five, where there is at least one stop codon in each reading frame." *Id.* at 3:15–19. These stop codons aid in the efficiency of termination at both the transcription and expression levels. *Id.* at 3:19–21. Bujard also states:

> For hybrid DNA technology it would be useful to have a plasmid having a unique restriction site between a T5 promoter and a terminator, desirably having at least one stop codon on the upstream side of the terminator. In this manner, one or more structural genes may be introduced between the promoter and terminator.

Id. at 7:57–63. The strategy described in Bujard "provides a vehicle which can be used with one or more hosts for gene expression." *Id.* at 8:1–3. The host cells employed for Bujard's process may be either bacterial or mammalian cells. *Id.* at 6:23–35.

Bujard indicates that a "wide variety of structural genes are of interest for production of proteins," and that "[t]he proteins may be prepared as a single unit or as individual subunits and then joined together in appropriate ways." *Id.* at 4:14–21. Among the "proteins of interest," Bujard includes "immunoglobulins e.g. IgA, IgD, IgE, IgG and IgM and fragments thereof," and further spells out the "Mol. formula" for each of those immunoglobulins. *Id.* at 4:30–5:27. For example, Bujard identifies immunoglobulin G (IgG) as having the formula $\gamma_2\lambda_2$ or $\gamma_2\kappa_2$, which corresponds to the two light chains and two heavy chains of the antibody molecule. *Id.* at 5:11–14. Bujard also lists "Free light chains" separately. *Id.* at 5:27.

2. Riggs & Itakura (Ex. 1003)

Riggs & Itakura discusses the bacterial production of human insulin. Ex. 1003, 531. Specifically, Riggs & Itakura made two *E. coli* strains, each constructed by cloning vectors containing chemically synthesized genes encoding the insulin A chain or B chain, and further showed that the separately purified chains can be joined by air oxidation *in vitro* to produce active insulin. *Id.* at 532 (FIG. 1). Among the potential practical applications, Riggs & Itakura states that the recombinant DNA techniques discussed therein can be used to produce antibodies from hybridoma, stating "[h]ybridoma will provide a source of mRNA for specific antibodies. Bacteria may then be used for the production of the antibody peptide chains, which could be assembled in vitro and used for passive immunization." *Id.* at 537–38.

3. Southern (Ex. 1004)

Southern describes the transformation of mammalian host cells to confer resistance to neomycin-kanamycin antibiotics. Ex. 1004, 327 (Summary). In particular, Southern utilized known selection markers for co-expressing the bacterial genes gpt and neo using two separate vectors—pSV2-gpt and pSV2-neo—within a single host cell. *Id.* at 337, Table 3. Southern teaches that "vectors containing these markers provide a way to cotransduce other genes whose presence and/or expression can not be selected." *Id.* at 338. Southern concludes that "[c]otransformation with nonselectable genes can be accomplished by inserting genes of interest into vector DNAs designed to express neo or gpt," and further states that "[t]he schemes used to select for the expression of gpt and neo [described therein]

are complementary and experiments that exploit the possibilities of a double and dominant selection are now in progress." *Id.* at 339.

D. Analysis of Petitioner's Patentability Challenges

1. Obviousness of Claims 1, 3, 4, 11, 12, 14, 19, and 33 Based on Bujard and Riggs & Itakura

Petitioner contends that claims 1, 3, 4, 11, 12, 14, 19, and 33 are obvious based on the combined teachings of Bujard and Riggs & Itakura. Pet. 34–38. In addition to the teachings of the references, Petitioner also relies upon the Declarations of Dr. Foote and Dr. Calame in support of this challenge. For this obviousness challenge, Petitioner focuses on those claims of the '415 patent that require (or allow for) the first and second DNA sequences to be present in a single vector within a host cell. Pet. 34–35.

Petitioner relies on Bujard as teaching the production of a protein of interest, including an immunoglobulin, "in a transformed host cell using a plasmid vector that is optimized to increase the efficiency of expression." Pet. 35 (citing Ex. 1002, 2:1–20, 3:9–14, 3:61–62, 4:14–16, 4:30–36, 5:11–27; Ex. 1006 ¶ 91; Ex. 1059 ¶ 16). In particular, Petitioner notes that Bujard teaches that the protein may be produced in a single cell transformed with a single plasmid that contains a plurality of genes. *Id.* (citing Ex. 1002, 3:46–48, 3:61–62, 6:23–37; Ex. 1006 ¶ 91; Ex. 1059 ¶ 16).

According to Petitioner, the ordinary artisan "would have been motivated to combine Bujard with the *in vitro* assembly disclosures in Riggs & Itakura, with a reasonable expectation of success in achieving the purported invention of the challenged claims, thus rendering the claims obvious." *Id.* at 36 (reference omitted) (citing Ex. 1003, 537–38; Ex. 1006 ¶ 99; Ex. 1059 ¶ 16).

In particular, based on Bujard's suggestion that "'individual [protein] subunits' can be 'joined together in appropriate ways,'" Petitioner relies upon Riggs & Itakura as teaching a specific *in vitro* assembly technique that is applicable to Bujard. *Id.* at 36–37 (citing Ex. 1002, 4:20–21; Ex. 1003, 537–38; Ex. 1006 ¶¶ 100–101; Ex. 1059 ¶ 16). Although Riggs & Itakura demonstrated the *in vitro* assembly of insulin A and B chains, and not immunoglobulin heavy and light chains, Petitioner asserts that the reference is nonetheless relevant because it "addresses the same problem of joining unassociated [polypeptide] chains separately produced in microorganism host cells." *Id.* at 36–37. Petitioner also points to the statement in Riggs & Itakura that the *in vitro* recombinant DNA techniques disclosed therein are applicable for antibodies, wherein hybridomas would be a source of mRNA for the antibody peptide chains (i.e., heavy and light chains) that are produced in bacteria and assembled *in vitro*. *Id.* at 37 (citing Ex. 1003, 531–32, 537–38; Ex. 1006 ¶ 101; Ex. 1059 ¶ 16).

We determine that Petitioner has sufficiently demonstrated a reasonable likelihood of prevailing with respect to this obviousness challenge. That is, we determine that Petitioner has made a sufficient showing of obviousness for purposes of our institution of *inter partes* review when Bujard's teachings are combined with the *in vitro* assembly technique taught by Riggs & Itakura and applied to produce an immunoglobulin molecule.

2. Obviousness of Claims 1, 2, 18, 20 and 33 Based on Bujard and Southern

Petitioner contends that claims 1, 2, 18, 20 and 33 are obvious based on the combined teachings of Bujard and Southern. Pet. 39–41. In addition to the teachings of the references, Petitioner also relies upon Dr. Foote's and

Dr. Calame's Declarations in support of this challenge. For this obviousness challenge, Petitioner focuses on those claims of the '415 patent that require (or allow for) the first and second DNA sequences to be present in different vectors within the same host cell. Pet. 39.

Petitioner asserts that the ordinary artisan would "have been motivated to combine (1) Bujard's teaching of a mammalian host cell transformed with two DNA sequences (for heavy and light chains), both in a single vector with (2) the co-transformation approach taught in Southern, i.e., a mammalian host cell transformed with two vectors, each with a different selectable marker and gene of interest." *Id.* at 39 (citing Ex. 1006 ¶ 103; Ex. 1059 ¶ 16). Petitioner asserts further that the skilled artisan would have had a reason "to modify Bujard accordingly by splitting the heavy and light chain DNA sequences into two separate vectors to be transformed in a single mammalian host cell." *Id.* at 39–40. Petitioner contends that the skilled artisan "would have known that the expression machinery in cells works universally, regardless of any difference in genes (heavy/light chain versus non-immunoglobulin polypeptides) or whether they are on separate vectors (instead of one)." *Id.* at 40–41 (citing Ex. 1006 ¶ 104; Ex. 1059 ¶ 16).

Based on the foregoing, we determine that Petitioner has sufficiently demonstrated a reasonable likelihood of prevailing with respect to this obviousness challenge.

III. CONCLUSION

For the foregoing reasons and the reasons set forth in the institution decision in IPR2015-01624 (Paper 15), we determine that the Petition demonstrates that there is a reasonable likelihood that Petitioner would

prevail in proving the unpatentability of claims 1–4, 11, 12, 14, 18–20, and 33 of the '415 patent for obviousness.

At this stage of the proceeding, we have not made a final determination as to the patentability of any challenged claim or any underlying factual or legal issue.

IV. ORDER

Accordingly, it is:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted as to claims 1–4, 11, 12, 14, 18–20, and 33 of U.S. Patent No. 6,331,415 (Ex. 1001) based on the following grounds of unpatentability:

A. Claims 1, 3, 4, 11, 12, 14, 19, and 33 under 35 U.S.C. § 103(a) as obvious over Bujard and Riggs & Itakura; and

B. Claims 1, 2, 18, 20 and 33 under 35 U.S.C. § 103(a) as obvious over Bujard and Southern.

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

FURTHER ORDERED that the trial is limited to the grounds of unpatentability listed above, and no other grounds of unpatentability are authorized for *inter partes* review.

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