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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANOFI-AVENTIS U.S. LLC AND
REGENERON PHARMACEUTICALS, INC.,
Petitioners,
v.

GENENTECH, INC. AND CITY OF HOPE,
Patent Owners.

Case IPR2015-01624
Patent 6,331,415 B1

Before LORA M. GREEN, ERICA A. FRANKLIN, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges.*

PAULRAJ, *Administrative Patent Judge.*

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

I. INTRODUCTION

Sanofi-Aventis U.S. LLC. and Regeneron Pharmaceuticals, Inc. (collectively, "Petitioners") filed a Petition (Paper 1, "Pet."), requesting institution of an *inter partes* review of claims 1–4, 9, 11, 12, 14–20, and 33 of U.S. Patent No. 6,331,415 B1 (Ex. 1001, "the '415 patent"). Genentech, Inc. and City of Hope (collectively, "Patent Owners") timely filed a Preliminary Response (Paper 14, "Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that Petitioners have 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

The parties have identified several district court and PTO proceedings related to the '415 patent. Pet. 7–17; Paper 6, 1–4.

Of particular relevance, the '415 patent was the subject of a merged *ex parte* reexamination proceeding, Control Nos. 90/007,542 and 90/007,859. *Id.* During the course of the reexamination, the claims of the '415 patent were initially rejected based on prior art 4,399,216 ("Axel," Ex. 1018) and 5,840,545 ("Moore," Ex. 1019), Rice & Baltimore (Ex. 1020), and Ochi (I) (Ex. 1021) on the grounds including obviousness-type double patenting, anticipation and obviousness. These rejections were overcome and a

reexamination certificate issued on May 19, 2009, which confirmed the patentability of claims 1–20 and 33–36, and determined that claims 21–32 are patentable as amended. Ex. 1026, Reexam Cert.

B. 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.

C. Illustrative Claims

Petitioners challenge claims 1–4, 9, 11, 12, 14–20, and 33 of the '415 patent. Independent claims 1 and 18 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.

D. The Asserted Grounds of Unpatentability

Petitioners challenge the patentability of the claims of the '415 patent on the following grounds:

References	**Basis**	**Claims challenged**
Bujard[1]	§ 102(e)	1, 3, 4, 9, 11, 15, 16, 17, 19, and 33
Bujard 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
Cohen & Boyer[4] and Riggs & Itakura	§ 103(a)	1, 3, 4, 11, 12, 14, and 33

II. DISCUSSION

A. Claim Construction

We interpret claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R.

[1] Bujard (Ex. 1002) Bujard et al., US 4,495,280, issued Jan. 22, 1985 (Ex. 1002).
[2] Arthur D. Riggs and Keiichi Itakura, *Synthetic DNA and Medicine*, 31 Am J. Hum Genet, 531–538 (1979) (Ex. 1003).
Riggs & Itakura (Ex. 1003)
[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*, J. Molecular and Applied Genetics, Vol.1, 327–341 (1982) (Ex. 1004).
[4] Cohen et al., US 4,237,224, issued Dec. 2, 1980 (Ex. 1005).

§ 42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015), *cert. granted*, No. 15-446 (U.S. Jan. 15, 2016) ("Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA,"[5] and "the standard was properly adopted by PTO regulation."). Under the broadest reasonable construction standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *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).

Neither party has proposed the construction of any particular claim terms. *See* Pet. 16–17; Prelim. Resp. 9–10. Petitioners and Patent Owners agree that the term "immunoglobulin" is interchangeable with "antibody." Pet. at 4 n.1; Prelim. Resp. 9 n.2. Moreover, while we note some ambiguity with respect to the term "independently expressing" recited in claims 1 and 33, both parties have treated that term as synonymous with "co-expressing" the first and second DNA sequences in a single host cell. *See* Pet. 50 (noting that claims 1 and 33 "are both directed to co-expression of heavy and light chains in a single host cell"); Prelim. Resp. 46 (arguing that "Petitioners

[5] The Leahy-Smith America Invents Act, Pub. L. No. 112–29, 125 Stat. 284 (2011) ("AIA").

have failed to establish that Bujard ***necessarily*** discloses the co-transformation and co-expression of an immunoglobulin heavy chain and light chain from the same host cell."). In other words, there does not appear to be any requirement that either the heavy or light chain should be capable of being expressed without the concomitant expression of the other chain. We apply that common understanding in our analysis here.

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

We analyze the proposed grounds of unpatentability in accordance with the following stated principles.

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).

1. Law of Anticipation

The Court of Appeals for the Federal Circuit summarized the analytical framework for determining whether prior art anticipates a claim as follows:

> To anticipate a claim, a single prior art reference must expressly or inherently disclose each claim limitation. *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). But disclosure of each element is not quite enough—this court has long held that "[a]nticipation requires the presence in a single prior art disclosure of all elements of a claimed invention *arranged as in the claim*." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (citing *Soundscriber Corp. v. United States*, 175 Ct. Cl. 644, 360 F.2d 954, 960 (1966) (emphasis added)).

Finisar Corp. v. DirecTV Grp., Inc., 523 F.3d 1323, 1334–35 (Fed. Cir. 2008). "Thus, it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 n.5 (Fed. Cir. 2008). "The requirement that the prior art elements themselves be 'arranged as in the claim' means that claims cannot be 'treated . . . . as mere catalogs of separate parts, in disregard of the part-to-part relationships set forth in the claims and that give the claims their meaning.'" *Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (quoting *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1459 (Fed. Cir. 1984)).

2. Law of Obviousness

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

Petitioners rely 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, 5:11–12. 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. This 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 "molecular 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 "[f]ree light chains" separately. *Id.* at 5:27.

2. Riggs & Itakura (Ex. 1003)

Riggs & Itakura discusses the bacterial production of human insulin. 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. Ex. 1003, 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]ybridomas 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.

4. Cohen & Boyer (Ex. 1005)

Cohen & Boyer describes generally the replication and expression of exogenous (foreign) genes in a microorganism for protein synthesis. Ex. 1005, 1:34–42. Cohen & Boyer teaches that host cells can be transformed

by introducing a plasmid vehicle bound to the foreign gene in order to produce proteins of interest. *Id.* at 1:56–59, 4:29–38, 5:59–65, 6:43–47, claim 1. In particular, Cohen states that "[b]y introducing one or more exogenous genes into a unicellular organism, the organism will be able to produce polypeptides and proteins ('poly(amino acids)') which the organism could not previously produce." *Id.* at 9:12–15. Cohen & Boyer lists antibodies among the "poly(amino acids) of interest." *Id.* at 9:28–34. Cohen & Boyer further notes: "the subject method provides means for preparing enzymes and enzymic products from bacteria where the natural host is not as convenient or efficient a source of such product. . . . Besides enzymes, other proteins can be produced such as antibodies." *Id.* at 16:54–64.

D. Analysis of Petitioners' Patentability Challenges

1. Anticipation of Claims 1, 3, 4, 9, 11, 12, 15–17, 19, and 33 Based on Bujard

Petitioners contend that claims 1, 3, 4, 9, 11, 12, 15–17, 19, and 33 are anticipated by Bujard. Pet. 35–44. In support, Petitioners rely upon the teachings of Bujard, as well as the Declaration of Jefferson Foote, Ph.D. (Ex. 1006). Petitioners include a claim chart for claims 1, 15, 17, and 33, but point to the same disclosures in Bujard for each of these claims. Pet. 41–43.

Independent claims 1 and 33 require the recombinant production of an immunoglobulin molecule (i.e., an antibody) or immunologically functional fragment by "independently expressing" DNA sequences encoding at least the variable domains of the immunoglobulin heavy and light chains within a "single host cell," while independent claim 15 requires a vector comprising

the DNA sequences encoding the variable domains of the heavy and light chains located "at different insertion sites."

Patent Owners argue that Bujard fails to teach a) transforming a single host cell with DNA sequences encoding the heavy and light chains of an immunoglobulin, b) independently expressing those sequences within the single host cell as separate molecules, and c) assembling the immunoglobulin chains to produce an intact antibody or an immunologically functional fragment. Prelim. Resp. 39–40. According to Patent Owners, "[t]he cited passages from Bujard make clear that the techniques being described by Petitioners are general ones; they do not show a particular application of the techniques to produce immunoglobulins in the manner required by the claims of the Cabilly '415 patent." *Id.* at 41. Patent Owners assert that the Petition does not establish that the claim elements missing from Bujard are necessarily present, and that Petitioner improperly relied upon the testimony of Dr. Foote to fill in the missing elements. *Id.* at 43.

Patent Owners also contend that, as the PTO found in the prior reexamination with respect to the Axel[6] reference, "the mere use of the words 'genes' and 'immunoglobulin' in a reference does not convey to the skilled person an actual description of how to produce a functional immunoglobulin or fragment by independent expression of its constituent heavy and light chains in a single transformed host cells." *Id.* at 29. Patent Owners assert that Petitioners rely upon the same "linguistic" arguments with respect to Bujard's disclosure of "genes" and "immunoglobulins" that have already been rejected. *Id.* at 31–38.

[6] Axel et al., US 4,399,216, issued Aug. 16, 1983 (Ex. 1018).

We determine that Petitioners have not demonstrated a reasonable likelihood of prevailing with respect to this anticipation challenge. Bujard describes generally the expression of "structural genes" using a vector containing a high signal strength promoter, and further identifies immunoglobulins among a "representative list of proteins of interest." Ex. 1002, 4:14–37. Bujard, however, does not describe a specific process or a vector that is "arranged as in the claim[s]" of the '415 patent. *Connell*, 722 F.2d at 1548. Although Bujard identifies the structure of immunoglobulins as including heavy and light chains (e.g., IgG with a molecular formula of $\gamma_2\lambda_2$ or $\gamma_2\kappa_2$), Bujard does not teach—either expressly or inherently—that genes encoding for both the heavy and light chains must be incorporated into the same vector or otherwise expressed within a single host cell. Ex. 1002, 5:10–27.

Petitioners' anticipation arguments require us to draw inferences that are not required by Bujard's generalized teachings. In particular, Petitioners assume, based on "common knowledge," "simple logic," and "common sense," that the skilled artisan would interpret Bujard's listing of immunoglobulins to mean that the different genes encoding for the heavy and light chains should both be present in the same vector and expressed within the same host cell. Pet. 38 (citing Ex. 1006 ¶ 91). But that type of analysis falls within the purview of obviousness, not anticipation. We recognize that Bujard suggests that a "plurality of genes, including multimers and operons" can be inserted between the promoter and terminators sequences of the vector. Ex. 1002, 3:46–48. We further recognize that Bujard suggests that it is "desirabl[e to] hav[e] at least one stop codon on the upstream side of the terminator" so that "one or more

structural genes may be introduced between the promoter and terminator." *Id.* at 7:60–63; *see also id.* at 3:15–21. Petitioners, however, do not point to any teaching that all the genes encoding for the different subunits (polypeptides) of the "proteins of interest" identified in Bujard must *necessarily* be expressed within the same host cell. To the contrary, Bujard indicates that "[t]he strategy described above . . . can be used with one or more hosts for gene expression . . . ." *Id.* at 8:1–3.

We find Bujard's teachings to be more specific and robust than the Axel reference that was previously considered by the PTO. *Contra* Prelim. Resp. 36–37. As explained below, we determine that Petitioners have demonstrated a reasonable likelihood of prevailing in their assertion that Bujard, in combination with the Riggs & Itakura or Southern references, renders certain of the challenged claims obvious. Nonetheless, in order to arrive at the claimed invention, a skilled artisan would have been required to selectively apply the general teachings of Bujard to the specific production of immunoglobulins and, in doing so, would have made choices based on inferences gleaned from outside the reference. This is insufficient for anticipation. *See Therasense*, 593 F.3d at 1332 (prior art disclosure of individual elements that merely "could have been arranged" in the claimed manner is not anticipatory).

We, therefore, determine that Petitioners have not demonstrated a reasonable likelihood of prevailing with respect to this anticipation challenge.

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

Petitioners contend that claims 1, 3, 4, 11, 12, 14, 19, and 33 are obvious based on the combined teachings of Bujard and Riggs & Itakura. Pet. 44–47. In addition to the teachings of the references, Petitioners also rely upon Dr. Foote's Declaration in support of this challenge. For this obviousness challenge, Petitioners focus on those claims of the '415 patent that require (or broadly allow for) the first and second DNA sequences to be present in a single vector within a host cell.

Petitioners assert that "even if a [skilled artisan] would not interpret Bujard to teach assembly of the chains into an immunoglobulin tetramer, [the skilled artisan] would nevertheless be motivated to combine Bujard with the *in vitro* assembly disclosures in Riggs & Itakura." *Id.* at 45. In particular, based on Bujard's suggestion that "individual [protein] subunits" can be "joined together in appropriate ways," Petitioners rely upon Riggs & Itakura as teaching a specific *in vitro* assembly technique that is applicable to Bujard. *Id.* at 45–46 (citing Ex. 1002, 4:20–21; Ex. 1002, 537–38; Ex. 1006, ¶¶ 99–101). Although Riggs & Itakura demonstrated the *in vitro* assembly of insulin A and B chains, and not immunoglobulin heavy and light chains, Petitioners assert 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 46. Petitioners also point to the conclusion 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 47 (citing Ex. 1003, 537; Ex. 1006 ¶ 102).

Patent Owners contend that Riggs & Itakura does not cure the deficiencies of Bujard. More specifically, Patent Owners assert that "nothing in Riggs & Itakura suggests that the *in vitro* techniques described therein to combine proteins expressed in separate host cells would also be suitable for combining *in vitro* different proteins expressed in the same host cell." Prelim. Resp. 49. Because Riggs & Itakura expressed the insulin A and B chains in separate host cells, Patent Owners argue that the references lead the skilled artisan away from the claimed invention of the '415 patent. Patent Owners also assert that there is "no explanation why one of skill in the art would rely upon Riggs & Itakura for some teachings (e.g., how to assemble a multimeric protein), but ignore the overarching strategy it advances for producing multimeric proteins." *Id.*

We determine that Petitioners have demonstrated a reasonable likelihood of prevailing with respect to this obviousness challenge. Although we do not consider Bujard's teachings to be anticipatory for the reasons discussed above, we determine that Petitioners have made a sufficient showing of obviousness for purposes of our institution of *inter partes* review when those teachings are combined with the *in vitro* assembly technique taught by Riggs & Itakura and applied to produce an immunoglobulin molecule.

We are unpersuaded by Patent Owners' preliminary arguments regarding this challenge. Patent Owners do not appear to take into account that Bujard itself suggests the incorporation of a plurality of structural genes encoding for the subunits of a multimeric protein, such as immunoglobulin

heavy and light chains, within a vector that would be placed in a single host cell. Ex. 1002, 3:46–48; *see also* Ex. 1006 ¶¶ 67–68 (Dr. Foote stating that the term "multimer" as used in Bujard would be understood by the skilled artisan as referring to genes encoding for proteins with more than one subunit). Moreover, Bujard teaches the desirability of inserting "translational stop codons e.g. oop or nonsense codons" in one or more reading frames of the vector, which would allow for the multiple structural genes to be translated into separate polypeptides.[7] Ex. 1002, 2:8–13, 3:15–21, 7:57–63. When these general teachings of Bujard are taken into consideration with the specific identification of immunoglobulins among "proteins of interest," Petitioners have demonstrated a reasonable likelihood that the skilled artisan would have found it obvious to insert the genes encoding for the heavy and light chains, separated by a stop codon, between the promoter and terminator sequences of the vector, which would permit the independent expression of those genes as separate molecules in the transformed host cell. *See* Ex. 1006 ¶ 92.

We recognize that, by utilizing separate host cells for the production of insulin chains, Riggs & Itakura takes a different approach than the "single host cell" approach required by the claims. There is no support identified, however, for Patent Owners' contention that the *in vitro* assembly technique disclosed therein is only applicable when the polypeptide chains are

[7] In *O'Farrell*, Judge Rich explained succinctly the role of stop codons within the mechanism of protein translation: "Like periods at the end of a sentence, these sequences signal the end of the polypeptide chain, and they are therefore called *stop codons*. . . . When a stop codon is reached [during translation], the polypeptide chain is complete and detaches from the ribosome." 853 F.2d at 897.

produced in separate host cells. Prelim. Resp. 49. Nor does Riggs & Itakura teach away from the claimed invention by merely presenting an alternative option. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). To be sure, it is possible that a skilled artisan could have chosen to express the genes for the heavy and light chains in separate host cells, as also suggested by Bujard (Ex. 1002, 8:1–3), but there is an insufficient basis on this record for us to conclude that that approach would have been considered the only appropriate method for the production of immunoglobulins. Rather, the current record demonstrates a reasonable likelihood that the expression of genes encoding for both immunoglobulin chains in a single host cell would have been among the "known options within [the skilled artisan's] technical grasp" that the skilled artisan would have chosen to pursue. *KSR*, 550 U.S. at 421.

We note there is a dispute as to whether the prevailing "mindset" of those skilled in the art prior to April 1983 was to make multimeric proteins using a single host cell or separate host cells. *See* Pet. 21–25; Prelim. Resp. 18–25.[8] Based on the foregoing, however, we find that at least the Bujard reference suggests that the skilled artisan's mindset would include making multimeric proteins within a single host cell. Thus, based on the current

[8] Petitioners contend that a person of ordinary skill in the art "at the time of the earliest effective filing date of the '415 patent would have a Ph.D. in molecular biology (or a related discipline, such as biochemistry) with 1 or 2 years of post-doctoral experience, or an equivalent amount of combined education and laboratory experience," and "would also have experience using recombinant DNA techniques to express proteins and familiarity with protein chemistry, immunology, and antibody production, structure, and function." Pet. 16 (citing Ex. 1006 ¶ 23). Patent Owners do not contest the level of ordinary skill in the art at this stage. Prelim. Resp. 10 n.3.

record, we determine that Petitioners have made a sufficient showing for institution on this obviousness challenge.

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

Petitioners contend that claims 1, 2, 18, 20 and 33 are obvious based on the combined teachings of Bujard and Southern. Pet. 47–50. In addition to the teachings of the references, Petitioners also rely upon Dr. Foote's Declaration in support of this challenge. For this obviousness challenge, Petitioners focus on those claims of the '415 patent that require (or broadly allow for) the first and second DNA sequences to be present in different vectors within the same host cell.

> Petitioners assert that the skilled 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 48 (citing Ex. 1006 ¶ 103). Petitioners further assert 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.* Petitioners contend 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 49 (citing Ex. 1006 ¶ 104).

We have considered Patent Owners' preliminary arguments regarding this challenge, but do not find them persuasive. Patent Owners argue that that Southern does not remedy the deficiencies of Bujard concerning the "production of a single vector containing DNA sequences encoding both the heavy and the light chains of an antibody, [their] expression in a single host cell . . . , or production of a functional antibody." Prelim. Resp. 51. As discussed above, we determine that Petitioners have demonstrated a reasonable likelihood that Bujard at least suggests the co-expression of the heavy and light chains in a single host cell. Patent Owners further argue that "Southern discloses the introduction of two ***selectable markers*** into a host cell, ***not*** the introduction of two DNA sequences that are meant to be co-expressed from a single host cell," and there would be no reason for the skilled artisan "to use Southern's technique . . . to produce multiple desired proteins." *Id.* at 52. We note, however, that Southern appears to teach the general applicability of its disclosed co-transformation technique by "inserting *genes of interest* into vector DNAs designed to express neo or gpt." Ex. 1004, 339 (emphasis added). Additionally, Petitioners have identified evidence that Southern's pSV2gpt and pSV2neo vectors were adopted by independent research groups for single chain immunoglobulin expression prior to the filing date of the '415 patent. Pet. 21 (citing Ex. 1020, Ex. 1021, Ex. 1031); Ex. 1006 ¶ 87. Accordingly, Petitioners have shown a reasonable likelihood that the skilled artisan would have found it obvious to use Southern's two-vector technique to express both the heavy and light immunoglobulin chains in a single host cell.

Based on the current record, we determine that Petitioners have a sufficient showing for institution on this obviousness challenge.

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

Petitioners contend that claims 1, 3, 4, 11, 12, 14, and 33 are obvious over the combination of Cohen & Boyer and Riggs & Itakura. Pet. 50–57. In addition to the teachings of the references, Petitioners also rely upon Dr. Foote's Declaration in support of this challenge. Petitioners include a claim chart for independent claims 1 and 33 in support of this challenge, but point to the same teachings of Cohen & Boyer with respect to both claims. *Id.* at 52–53.

The generalized teachings of Cohen & Boyer that Petitioners rely upon for this challenge are similar to Bujard's teachings. *See, e.g.*, Ex. 1005, 5:59–65 (noting that "[t]he [foreign] DNA fragment may include one or more genes or one or more operons"); *id.* at 9:12–30 ("Other poly(amino acids of interest include . . . globulin e.g. gamma-globulins or antibodies."). Indeed, Cohen & Boyer appears to teach less than Bujard. For example, there is no disclosure identified concerning the incorporation of "stop codons" or "multimer" genes in the vector. *Cf.* Ex. 1002, 3:15–20, 46–48. Moreover, Petitioners rely upon Riggs & Itakura's *in vitro* assembly technique in the same manner as with respect to the obviousness challenge based on the Bujard/Riggs & Itakura combination discussed above. Pet. 55–56. Petitioners also acknowledge that "[t]he bases for a [skilled artisan's] reasonable expectation of success are no different than the bases discussed . . . with respect to combining Bujard and Riggs & Itakura." *Id.* at 56.

Patent Owners argue that that this obviousness challenge is redundant. Prelim. Resp. 59–60. Patent Owners further assert that Cohen & Boyer was previously considered during the reexamination of the '415 patent. *Id.* at

53–54. Patent Owners' other arguments are similar to those they make with respect to Bujard. *Id.* at 54–58.

Board rules require us to "secure the just, speedy, and inexpensive resolution of every proceeding." 37 C.F.R. § 42.1(b). Petitioner has not pointed to any material differences between this challenge and the challenge based on the Bujard/Riggs & Itakura combination discussed above to justify the use of Board and party resources to proceed on both challenges. We, therefore, exercise our discretion and decline to institute on the basis of this additional obviousness challenge.

E. 35 U.S.C. § 325(d)

Patent Owners also ask us to "deny institution because the Petition presents the same arguments that were raised and fully addressed in prior Office proceedings involving the Cabilly '415 patent." Prelim. Resp. 58. However, the particular combination of references upon which we institute were not previously addressed during prosecution or reexamination. As noted above, we find Bujard's teachings to be more specific than the Axel reference previously considered.

Denial of institution under § 325(d) is discretionary. Here, based on the different arguments and evidence relied upon in the Petition, we decline to exercise that discretion.

III. CONCLUSION

For the foregoing reasons, we determine that Petitioners have demonstrated that the information presented in the Petition and in the Preliminary Response shows that there is a reasonable likelihood that they 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, the Board has not made a final determination as to the patentability of any challenged claim or any underlying factual and legal issues.

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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