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Paper No. 11
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOEQ IP AG,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2016-01608
Patent 6,716,602 B2

Before TONI R. SCHEINER, ERICA A. FRANKLIN, and MICHELLE N. ANKENBRAND, *Administrative Patent Judges*.

FRANKLIN, *Administrative Patent Judge*.

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

I. INTRODUCTION

bioeq IP AG ("Petitioner") filed a Petition requesting an *inter partes* review of claims 1, 3–4, 6–16, 18, 20, 22–25, 27–28, and 30–39 of U.S. Patent No. 6,716,602 B2 (Ex. 1001, "the '602 patent"). Paper 3 ("Pet."). Genentech, Inc. ("Patent Owner") filed a Preliminary Response to the Petition. Paper 9 ("Prelim. Resp."). Petitioner filed an authorized Reply to Patent Owner's Preliminary Response, Paper 10 ("Reply"), to address corrections to the '602 patent claims requested by Patent Owner in its Request for Certificate of Correction Under 35 U.S.C. § 254, Ex. 2009, submitted to the Director after the filing of the Petition.

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." 35 U.S.C. § 314(a).

Upon considering the Petition, Preliminary Response, and Reply, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of at least one of the challenged claims. Accordingly, we deny the Petition and decline to institute an *inter partes* review.

A. Related Proceedings

Petitioner and Patent Owner indicate that there are no related matters to this proceeding. Pet. 65; Paper 6, 2.

B. The ’602 Patent

The ’602 patent is directed to methods for increasing the yield of a heterologous recombinant protein produced by recombinant host cells. Ex. 1001, 3:12–14. The Specification explains that those methods involve “first increasing the protein production capacity of the cells in culture by culturing the cells at a high growth rate, and then decreasing metabolic rate of the cells (rate shift) to permit proper folding or assembly of the heterologous protein.” *Id*. at 3:14–18. Properly folded or assembled functional protein can be revealed by activity assays. *Id*. at 5:11–12.

C. Illustrative Claim

Claim 1 is representative of the challenged claims and is reproduced below:

> 1. A method for increasing the product yield of a properly folded polypeptide of interest produced by recombinant host cells, wherein expression of the polype[]ptide by the recombinant host cells is regulated by an inducible system, which method comprises
>
> (a) culturing the recombinant host cells under conditions of high metabolic growth rate; and
>
> (b) reducing the metabolic rate of the cultured recombinant host cells at the time of induction of polypeptide expression, wherein reducing the metabolic rate comprises reducing the feed rate of a carbon/energy source, or reducing the amount of available oxygen, or both, and wherein the reduction in metabolic rate result in increase yield of properly folded polypeptide.

Ex. 1001, 18:11–24.

D. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1, 3–4, 6–16, 18, 20, 22–25, 27–28, and 30–39 of the ’602 patent on the following grounds:

Reference(s)	Basis	Claim(s) challenged
Seeger[1]	§ 102(b)	1, 3–4, 6, 9, 15–16, 20–22, 24–25, 27–28, 30, 33, 39
Seeger	§ 103(a)	7–8, 31–32
Seeger and Makrides[2]	§ 103(a)	10, 12, 23, 34, 36
Seeger and Cabilly[3]	§ 103(a)	11, 13–14, 18, 35, 37–38

Petitioner also relies on the declaration of Dr. Morris Z. Rosenberg (Ex. 1002).

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the

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[1] Anke Seeger et al., *Comparison of temperature- and isopropyl-ß-D-thiogalacto-pyranoside-induced synthesis of basic fibroblast growth factor in high-cell-density cultures of recombinant Escherichia coli*, 17 ENZYME & MICROBIAL TECH. 947–53 (1995) (Ex. 1010).
[2] Savvas C. Makrides, *Strategies for Achieving High-Level Expression of Genes in Escherichia coli*, 60 MICROBIOLOGICAL REVIEWS 512–38 (1996) (Ex. 1023).
[3] Shmuel Cabilly, *Growth at sub-optimal temperatures allows the production of functional, antigen-binding Fab fragments in Escherichia coli*, 85 GENE 553–57 (1989) (Ex. 1032).

invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner proposes a construction for the claim phrase "reducing the metabolic rate," that is recited in each of the challenged independent claims.[4] Pet. 24. According to Petitioner, a person of ordinary skill in the art would have understood from the Specification that claim phrase means "altering the fermentation conditions to reduce or stop the growth/expansion of cells undergoing rapid growth and expansion, *or* for cells no longer undergoing rapid growth and expansion, reducing the oxygen uptake rate and/or the corresponding uptake of the corresponding carbon/energy source by the cells." *Id*. at 25–26 (emphasis added).

Patent Owner asserts that Petitioner argues for "an overly complex 'bifurcated definition'" that "attempts to import limitations from the specification." Prelim. Resp. 18. According to Patent Owner, the phrase "reducing the metabolic rate" should be construed as defined by the Specification, i.e., "altering the host cell culture such that the host cells undergoing rapid growth and expansion reduce (or stop) growth and expansion." *Id*. (quoting Ex. 1001, 4:12–15).

We agree with Patent Owner that the Specification provides an explicit definition for the claim phrase "reducing the metabolic rate." The Specification states, "[a]s used herein, 'reducing metabolic rate' or 'shifting down metabolic rate' means altering the host cell culture such that the host

[4] *See* Ex. 1001, 18:10–20:32; Ex. 2009, 7.

cells undergoing rapid growth and expansion reduce (or stop) growth and expansion." Ex. 1001, 4:12–15. Following that definition, the Specification describes "the case of cells already in a reduced growth state," explaining that "the rates of oxygen uptake and the corresponding rates of uptake of a carbon/energy source are reduced." *Id*. at 4:15–18. The Specification then states, "[s]ince, in the case of respiring cells, the metabolic rates are determined primarily by the rate at which the cell oxidizes the available carbon/energy source using the available oxygen, the metabolic rate can be reduced by limiting either of these two reactants." *Id*. at 4:18–22. Thus, the Specification provides an explicit definition for the phrase "reducing metabolic rate," followed by instructions for achieving that reduction in a particular circumstance. We disagree with Petitioner that the instructions provided by the Specification for reducing the metabolic rate in an exemplary situation serve to modify the express definition disclosed. Specifically, we do not find that the Specification provides an alternative definition of the claim phrase, as indicated by Petitioner's use of the term "or" in its proposed construction of the phrase. Pet. 26.

Accordingly, we determine that the '602 patent expressly defines the claim phrase "reducing [the] metabolic rate" as meaning "altering the host cell culture such that the host cells undergoing rapid growth and expansion reduce (or stop) growth and expansion," Ex. 1001, 4:12–15, and that definition is "set forth with reasonable clarity, deliberateness, and precision," *see In re Paulsen*, 30 F.3d at 1480.

In view of our analysis, we determine that no additional claim terms require construction for the purpose of this Decision. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (Only terms

which are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. Anticipation by Seeger

Petitioner asserts that Seeger discloses a method that meets each element of claims 1, 3–4, 6, 9, 15–16, 20–22, 24–25, 27–28, 30, 33, and 39. Pet. 28–43. Patent Owner disagrees. Prelim. Resp. 23–33.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). "Inherency … may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *MEHL/Biophile Int'l. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) (*quoting In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)).

1. Seeger

Seeger is a journal article discussing a comparison of two different expression systems for the expression of the cDNA encoding human basic fibroblast growth factor (bFGF) using *E. coli* as the host organism. Ex. 1010, Abstract. The bFGF structural gene was cloned into two vectors with different promoters, and the resulting expression systems were studied in high-cell density cultures. *Id.* Cells were grown at 30°C in a fed-batch procedure, with a predetermined exponential feeding rate to ensure constant specific growth rates. *Id.* Seeger explains that product formation was induced by shifting either the temperature from 30°C to 42°C, or by adding isopropyl-ß-D-thiogalacto-pyranoside (IPTG). *Id.* Seeger observes acetic acid accumulation in response to temperature-induced product expression. *Id.* at 952. To prevent that accumulation, and allow expression of bFGF, the

exponential feeding rate was reduced from $\mu_{set} = 0.12\ h^{-1}$ to $\mu_{set} = 0.08\ h^{-1}$ after the temperature shift to 42°C. *Id*. Seeger notes that a further reduction in the exponential feeding rate did not allow expression of bFGF. *Id*.

Upon comparison, Seeger determined that the temperature-induced production of bFGF "generated more total and more soluble bFGF compared to IPTG-induced cultures." *Id*. at 953. Seeger determined that the majority of bFGF produced was in the soluble cell fraction of the temperature-induced cultures. *Id*. at 952–953. The soluble and insoluble fractions were subjected to SDS-PAGE analysis, revealing that the formation of inclusion bodies and soluble bFGF occurred simultaneously after the temperature shift. *Id*. at 953.

2. Analysis

Petitioner asserts that Seeger's temperature-induced production of bFGF meets every element of claims 1, 3–4, 6, 9, 15–16, 20–22, 24–25, 27–28, 30, 33, and 39, including "reducing the metabolic rate of the cultured recombinant host at the time of induction . . . wherein the reduction in metabolic rate results in increased yield of properly folded polypeptide," recited by each of the challenged independent claims.[5] Pet. 28. In particular, Petitioner asserts that "Seeger specifically discloses reducing the metabolic rate of cultured recombinant *E. coli* host cells at the time of induction of polypeptide expression by reducing the feed rate of a carbon/energy source—glucose." *Id*. In support of that assertion, Petitioner relies on the description in the '602 patent for "reducing metabolic rate," and the testimony of its declarant, Dr. Rosenberg, that Seeger's reduction in the amount of available glucose resulted in a decreased rate of glucose uptake

[5] *See* Ex. 1001, 18:10–20:32; Ex. 2009, 7.

by the recombinant host cells. Pet. 28, 32–36. To support his opinion, Dr. Rosenberg used Seeger's data "to calculate the specific glucose uptake rate (GUR) by the *E. coli* cells during growth and induction." Ex. 1002 ¶ 56 (citing *id.* at App. A). According to Dr. Rosenberg, his calculation revealed that GUR decreased in Seeger's phases 1 and 2, indicating a reduction in the metabolic rate at the time of induction. *Id.*

Regarding the claim recitation, "wherein the reduction in metabolic rate results in increased yield of properly folded polypeptide," Petitioner asserts that is an intended result of the positively-recited method steps and does not impart patentable weight to the claims. *Id*. at 28, 36. Petitioner asserts further that even if considered a claim limitation, "Seeger's metabolic rate shift results in increased yield of soluble, i.e., properly-folded, bFGF polypeptide." *Id*. at 28. In support of that assertion, Petitioner states that "Seeger quantified the yield of bFGF following temperature shift induction at '70% of the bFGF produced . . . present in the soluble cell fraction." *Id*. at 37 (quoting Ex. 1010, 953:1–2). According to Petitioner and Dr. Rosenberg, that percentage of bFGF produced in the soluble cell fraction represents properly folded bFGF. *Id*. (citing Ex. 1002 ¶¶ 57, 73).

Patent Owner argues that Seeger fails to disclose reducing the metabolic rate at the time of induction of polypeptide expression. Prelim. Resp. 23. According to Patent Owner, Seeger's method of inducing expression by increasing temperature introduced another variable affecting the growth rate. *Id*. In particular, Patent Owner asserts that it was well known in the art that increasing temperature, within the range disclosed by

Seeger, increases the growth rate of *E. coli*. *Id*. at 24–26 (citing Herendeen,[6] Ex. 2002, 1). Patent Owner asserts that, although Seeger reduced the glucose feeding rate in phase 2 of the fed-batch process, Seeger did not address the competing effect of increasing temperature on the growth rate, "leaving unanswered the question of whether Seeger actually reduced the metabolic rate at the time of induction." *Id*. at 26–27.

Additionally, Patent Owner asserts that Dr. Rosenberg's GUR calculation does not reflect the true metabolic rate of Seeger's temperature-induced *E. coli* fermentation because Dr. Rosenberg's model does not take into account the variable of temperature. *Id*. at 27–28. Specifically, Patent Owner asserts that Dr. Rosenberg's calculation included the variable for growth, μ, as a function of time, rather than as a function of both time and temperature. *Id*. at 27 (citing Ex. 1002, App. A, Equation 2). According to Patent Owner, given the temperature increase in Seeger's method, "Dr. Rosenberg's calculation provides no basis for concluding that there was a reduction in metabolic rate," as required by each of the challenged claims. Prelim. Resp. 28.

Further, Patent Owner asserts that Seeger reports the total expression of polypeptide without disclosing whether the polypeptides are properly folded. *Id*. at 29. In particular, Patent Owner asserts that Seeger's two measuring techniques employed the denaturing agent, sodium dodecyl sulfate (SDS), to prepare the polypeptides for analysis by polyacrylamide electrophoresis (PAGE). *Id*. (citing Ex. 1010, 949). Thus, Patent Owner

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[6] Sherrie L. Herendeen et al., *Levels of Major Proteins of Escherichia coli During Growth at Different Temperatures*, 139 J. BACTERIOLOGY 185–94 (1979) (Ex. 2002).

asserts, "Seeger only measures denatured polypeptides and thus provides no information regarding amounts of properly folded polypeptides." *Id*. (emphasis omitted). According to Patent Owner, a person of skill in the art would have understood that SDS-PAGE linearized protein molecules, i.e., eliminates any folding. *Id*. at 30 (citing Laemmli,[7] Ex. 2001, 1).

Moreover, Patent Owner asserts that Seeger's disclosure of bFGF levels in the "soluble cell fraction" does not necessarily amount to a disclosure of the yield of properly folded polypeptide. Prelim. Resp. 32. According to Patent Owner, a person of ordinary skill in the art would have understood that misfolded proteins may also be found in the soluble fraction of the cell lysates and that solubility is not proof of proper folding." *Id*. (citing, e.g., Sachdev, Ex. 2007,[8] 2; Schrodel, Ex. 2008,[9] 4). Patent Owner asserts that, in the '602 patent, the inventors recognized that solubility does not imply proper folding, and further analyzed the soluble fraction by loading it onto a CsX column to separate properly folded polypeptides from misfolded ones prior to quantifying the properly folded portion. Prelim. Resp. 33 (citing Ex. 1001, 16:14–21). Thus, Patent Owner asserts that Seeger does not expressly or inherently address proper folding of proteins. *Id.*

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[7] U.K. Laemmli, *Cleavage of Structural Proteins during the Assembly of the Head of Bacteriophage T4*, 227 NATURE 680–85 (1970) (Ex. 2001).
[8] Deepali Sachdev et al., *Properties of Soluble Fusions Between Mammalian Aspartic Proteinases & Bacterial Maltose-Binding Protein*, 18 J. PROTEIN CHEMISTRY 127–36 (1999) (Ex. 2007).
[9] Schrodel et al., *Characterization of the aggregates formed during recombinant protein expression in bacteria*, 6:10 BMC BIOCHEMISTRY 1–11 (2005) (Ex. 2008).

Based upon our review of the arguments and evidence, we are persuaded that Petitioner has not established that Seeger discloses *reducing the metabolic rate* of the cultured recombinant host cells at the time of induction of polypeptide expression, as required by the challenged claims, for the reasons discussed by Patent Owner. In particular, Petitioner relies upon the disclosure of the '602 patent describing reducing metabolic rate in cells already in a reduced growth state by reducing the rates of oxygen uptake and the corresponding rates of uptake of a carbon/energy source. Pet. 32–36 (citing Ex. 1001, 4:15–18). However, Petitioner has not addressed adequately how Seeger's method of inducing expression by increasing temperature from 30 to 42°C may have affected the metabolic rate. *Id*. at 32–36.

In the Reply, Petitioner acknowledges that temperature is one of the "external factors that influence[s] the metabolic rate," along with amount of glucose and oxygen supplied. Reply 2. According to Petitioner, Dr. Rosenberg's GUR calculation is a "'read-out' of the cells' metabolic rate," and accounts for each of those external factors, including temperature. *Id*. In support of that contention, Petitioner states, "Dr. Rosenberg calculated GUR throughout Seeger's fed-batch phases, i.e., before and after temperature change induced bFGF expression, thus accounting for temperature." *Id*. at 2–3 (citing Ex. 1002 ¶ 56) (emphasis omitted).

Petitioner's assertion is not supported by the evidence of record. Dr. Rosenberg's discussion of his calculation for the GUR in the paragraph cited by Petitioner explains only that Seeger increased the temperature, without describing or suggesting that he considered that temperature increase in his calculation or conclusions. Ex. 1002 ¶ 56. Moreover, as Patent Owner has asserted, Dr. Seeger's calculation set forth in Appendix A does not include a

variable accounting for the temperature shift. Ex. 1002, App. A. Thus, Petitioner has not shown persuasively that a person of skill in the art would have understood Seeger's method to have included reducing the metabolic rate of the cultured recombinant host cells at the time of expression induction. *See MEHL/Biophile Int'l. Corp.*, 192 F.3d at 1365.

In that vein, even if we accept Petitioner's position that the claim recitation "wherein the reduction in metabolic rate results in increased yield of properly folded polypeptide" is an intended result of the positively-recited method steps, Pet. 28, 36, Petitioner has not shown persuasively that Seeger discloses the positive step of reducing the metabolic rate so as to achieve that result. Moreover, if considered a limitation, Petitioner has not shown sufficiently that Seeger discloses such a result for the same reason. Further, for the reasons discussed by Patent Owner, Petitioner has not shown persuasively that Seeger's soluble fraction of bFGF necessarily represents properly folded polypeptide. Prelim. Resp. 29–33.

Therefore, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that Seeger anticipates claims 1, 3–4, 6, 9, 15–16, 20–22, 24–25, 27–28, 30, 33, and 39. Consequently, we decline to institute an *inter partes* review of claims 1, 3–4, 6, 9, 15–16, 20–22, 24–25, 27–28, 30, 33, and 39 based on this ground.

C. Obviousness over Seeger Alone or in Combination with Additional References

Each of Petitioner's obviousness grounds is directed to a set of dependent claims. Pet. 27. Petitioner relies upon Seeger alone as disclosing the elements of the independent claims from which those challenged claims depend. *Id*. at 43–57. Indeed, Petitioner does not address the elements recited in the independent claims in any of the obviousness grounds. *Id*. To

the extent that Petitioner cites Makrides or Cabilly, those references are relied upon only to address additional elements of dependent claims, and are not asserted to cure any deficiencies of Seeger with respect to elements of the independent claims. *Id*. at 46–58.

Therefore we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing in showing the unpatentability of dependent claims 7–8 and 31–32 over Seeger, dependent claims 10, 12, 23, 34, and 36 over Seeger and Makrides, or dependent claims 11, 13–14, 18, 35, and 37–38 over Seeger and Cabilly, under 35 U.S.C. § 103(a), for the same reasons discussed regarding the independent claims from which they depend. Consequently, we decline to institute an *inter partes* review of claims 7–8, 10–14, 18, 23, 31–32, and 34–38 based on the respective ground challenging those claims.

III. CONCLUSION

For the foregoing reasons, we conclude that Petitioner has not established a reasonable likelihood of prevailing in showing the unpatentability of any challenged claim.

ORDER

Accordingly, it is hereby:

ORDERED that Petitioner's request for an *inter partes* review of claims 1, 3–4, 6–16, 18, 20, 22–25, 27–28, and 30–39 of the '602 patent is *denied*.

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