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 No. 6,716,602

PATENT OWNER GENENTECH'S PRELIMINARY RESPONSE TO BIOEQ'S PETITION FOR INTER PARTES REVIEW

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LIST OF EXHIBITS

Patent Owner's Exhibit #	***Description***
2001	Laemmli, U.K., "Cleavage of Structural Proteins during the Assembly of the Head of Bacteriophage T4," *Nature* 227: 680–85 (1970)
2002	Herendeen *et al.*, "Levels of Major Proteins of *Escherichia coli* During Growth at Different Temperatures," *J. Bacteriol.* 139(1):185–194 (1979)
2003	Reynolds and Tanford, "The Gross Conformation of Protein-Sodium Dodecyl Sulfate Complexes," *J. Biological Chem.* 245(19): 5161–65 (1970)
2004	Towbin, *et al.*, "Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: Procedure and some applications," *Proceedings of the National Academy of Sciences USA* 76 (9): 4350–54 (1979)
2005	Pierce and Suelter, "An Evaluation Of The Coomassie Brilliant Blue G-250 Dye-Binding Method for Quantitative Protein Determination," *Analytical Biochemistry* 81: 478–80 (1977)
2006	Kahn and Rubin, "Quantitation of Submicrogram Amounts of Protein Using Coomassie Brilliant Blue R on Sodium Dodecyl Sulfate-Polyacrylamide Slab-Gels," *Analytical Biochemistry* 67: 347–52 (1975)
2007	Sachdev and Chirgwin, "Properties of Soluble Fusions Between Mammalian Aspartic Proteinases and Bacterial Maltose-Binding Protein," *J. Protein Chem.* 18(1): 127–136 (1999)

2008	Schrodel and de Marco, "Characterization of the aggregates formed during recombinant protein expression in bacteria," *BMC Biochemistry* 6:10 (2005)

I. Introduction

Pursuant to 35 U.S.C. § 313 and 37 C.F.R. § 42.107(a), Patent Owner Genentech, Inc. submits this Preliminary Response to the Petition for *Inter Partes* Review of U.S. Pat. No. 6,716,602 filed by Petitioner bioeq IP AG.

The Petition should be denied because it fails to show "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). Petitioner relies on a single prior art reference, Seeger (Exh.1010), as the primary basis for each of its allegations of unpatentability under 35 U.S.C. §§ 102 and 103. But, contrary to Petitioner's arguments, Seeger fails to disclose reducing the metabolic rate at the time of induction of polypeptide expression. All of the asserted grounds of unpatentability are predicated on this same incorrect characterization of Seeger, and all should fall together. Moreover, Seeger fails to disclose anything regarding properly folded polypeptide. This glaring deficiency is an independent reason why Seeger cannot be an invalidating reference, either by itself or as part of any § 103 combination.

The '602 Patent, which claims priority to a November 3, 2000 application, describes and claims a method for increasing polypeptide yield produced from recombinant host cells regulated by an inducible system. Unlike the prior art, the method of the '602 Patent increases yield of properly folded polypeptides,[1] including polypeptides of interest having "more than about 10 amino acids." '602 Patent (Exh. 1001) at 5:20–22. The inventors achieved this by culturing the cells under high metabolic and growth rate conditions, and then reducing the metabolic rate at the time of induction of expression.

Seeger describes work with a fundamentally different goal. Seeger is entitled "Comparison of temperature- and isopropyl-β-D-thiogalacto-pyranoside-induced synthesis of basic fibroblast growth factor in high-cell-density cultures of recombinant *Escherichia coli*." Seeger (Exh. 1010) at 3. True to its title, all of the data reported by Seeger pertain to experiments comparing two methods of inducing polypeptide expression—

[1] For the sake of simplicity, this preliminary response uses the terms "polypeptide" and "protein" interchangeably to refer to the products of gene expression in recombinant host cells.

temperature and IPTG[2]—in *E. coli*. In making the comparison, Seeger asks which method results in more expression of polypeptides, with no regard to whether those polypeptides are properly folded or misfolded. Indeed, a person of ordinary skill in the art reading Seeger would be unable to evaluate proper folding because, as explained in Part VI.A. below, Seeger's analytical techniques were based on SDS-PAGE, *see* Seeger (Exh. 1010) at 5:2:15–33, persons of ordinary skill would have understood SDS-PAGE denatures polypeptides and analyzes them in a linearized (*i.e.*, unfolded) state. *See* Laemmli (Exh. 2001) at 1. Seeger did not subject the polypeptides produced to any technique that distinguishes properly folded polypeptides from improperly folded polypeptides—for example, Seeger did not use the high performance liquid chromatography ('602 Patent (Exh. 1001) at 15:62–64) or affinity chromatography disclosed by the '602 Patent (*id.* at 17:33–40). Consequently, Seeger does not disclose or suggest the increased yield of properly folded polypeptide required by each claim of the '602 Patent.

The particular expression system in Seeger that Petitioner focuses on has another key characteristic that is fatal to Petitioner's

[2] IPTG stands for isopropyl-β-D-thiogalacto-pyranoside.

challenge: it is temperature-induced. Persons of ordinary skill have known at least since 1979 that within the temperature range used in Seeger, increasing the fermentation temperature increases both the growth rate and metabolic rate of *E. coli*. *See* Herendeen (Exh. 2002) at 1, 6–7. Thus, while Seeger includes a description in Figure 3 of a reduction in the glucose feed rate, Seeger also states that product formation was induced in that fermentation "by temperature shift from 30 to 42°C." Seeger (Exh. 1010) at 6, Figure 3 legend. Seeger provides no information on whether the net effect of the reduction in feed rate and increase in temperature was to decrease or increase the metabolic rate. Again, this is unsurprising because Seeger was trying to answer different questions.

For at least these reasons, Seeger does not anticipate the independent claims or any of the other claims that Petitioner challenges in Ground #1. Neither the general knowledge of those skilled in the art asserted in Ground #2 nor the secondary references asserted in the obviousness combinations of Grounds #3 and 4 fill these gaps. Petitioner proffers the secondary references solely to address additional limitations recited in the dependent claims, not to address the deficiencies in Seeger with respect to the limitations in the independent claims addressed above.

It is not reasonably likely that Petitioner will be able to demonstrate that any challenged claim is anticipated or obvious. For these reasons, and the reasons set forth below, Genentech respectfully requests that the Board deny institution.

II. The '602 Patent

The '602 Patent relates to fermentation methods for increasing yield of properly folded polypeptide produced by recombinant host cells. The expression of the polypeptide of interest is regulated by an inducible system. '602 Patent (Exh. 1001) at Abstract.

The '602 Patent explains that "upon induction, high protein expression rates may not always lead to high rates of formation of active, properly formed products." '602 Patent (Exh. 1001) at 1:58–60. "Thus, there is a need in the art to increase the yield of usable recombinant protein production." *Id.* at 2:14–15. To achieve this, the inventors explored conducting their fermentations with an initial phase during which the recombinant host cells were cultured under conditions permitting high growth and metabolic rates, so as to increase the protein production capacity of the culture. *Id.* at 3:14–16. They then changed the fermentation conditions to introduce a downward metabolic rate shift at the time of

inducing protein expression. *Id.* at 3:16–17 and 30–34. By coordinating a decrease in metabolic rate (for example, by manipulating oxygen transfer rate or glucose feed rate) with timing of induction of protein expression, the inventors found that yields of properly folded polypeptide molecules increased. *Id.* at 3:20–24. This "advantageously and unexpectedly" permitted "high levels of protein synthesis, assembly and folding." *Id.* at 2:16–19.

The inventors were able to confirm increases in yield of properly folded polypeptides because they employed analytical techniques that distinguished between properly folded and misfolded proteins. The inventors did not, as Petitioner and its expert improperly do, simply assume that any polypeptides found in "the soluble fraction of the cell lysate" were properly folded. *See* Petition at 22, 37. Instead, the inventors subjected the protein from the soluble fraction of whole cell extracts to analytical techniques informative of the quantity and quality of the expressed polypeptide molecules. *See, e.g.*, '602 Patent (Exh. 1001) at 5:1–19. In one experiment, for the anti-CD18 Fab'2 protein, they analyzed the soluble fraction on a carboxy-sulfon (CsX) column that allowed them to quantify the amount of a properly folded protein structure known as a leucine zipper,

which is a three-dimensional domain formed by two polypeptide strands twisting around one another. *Id.* at 16:15–21. In another example, the inventors analyzed the "supernatants"—the soluble fraction— on a column that had been coated with the protein target (VEGF) of the Fab antibody (anti-VEGF) that they had expressed. *Id.* at 17:33–41. Only properly folded (and presumably functional) anti-VEGF antibody would be able to recognize and bind to the VEGF target, thus permitting measurement of the amount of properly folded polypeptides. *See id.*

III. Claim Construction

Independent Claim 1 recites:

> 1. A method for increasing product yield of a properly folded polypeptide of interest produced by recombinant host cells, wherein expression of the polypeptide 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 and 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 results in increased yield of properly folded polypeptide.

The terms Petitioner proposes to construe are addressed below. Each of Petitioner's proposed constructions attempts to import additional limitations and thus is inconsistent with the broadest reasonable interpretation standard that applies here. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016).

A. "Wherein the Reduction in Metabolic Rate Results in Increased Yield of Properly Folded Polypeptide" (Claims 1, 16, 25)

Independent Claim 1 concludes with the clause: "wherein the reduction in metabolic rate results in increased yield of properly folded polypeptide."

During prosecution, Genentech added similar wherein clauses to Independent Claims 16 and 25. File History (Exh. 1004) at 27–29. The '602 Patent issued without the wherein clauses that Genentech had added to claims 16 and 25. To correct this mistake, Genentech has requested the Board's permission to submit a Request for Certificate of Correction Under

35 U.S.C. § 254. The mistake is apparent on the face of the prosecution history: The Amendment of August 1, 2003 included the amendments, File History (Exh. 1004) at 27–29, and the Notice of Allowability acknowledged them, *id.* at 6, but not all of the claims of the issued patent included the added language. Petitioner acknowledges all of this. *See* Petition at 14 nn.4–5, 20 n.8.

1. The Concluding Wherein Clause Is Limiting

First, a wherein clause is limiting if it gives "meaning and purpose to the manipulative steps" and "relate[s] back to and clarif[ies] what is required" by the claim. *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002). The wherein clause at issue here satisfies this test by stating the "meaning and purpose" of the recited method: namely, to increase the yield of properly folded polypeptide. The preamble contains similar language—"a method for increasing product yield of a properly folded polypeptide of interest"—and Genentech respectfully submits that the preamble likewise is limiting for reasons explained below. But if the Board concludes that the preamble is not limiting, then the wherein clause is even more significant as the portion of the claim that "relate[s] back to and clarif[ies]" the increased yield requirement. *See id.*

Second, when such a clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005) (discussing "whereby" clause). The prosecution history demonstrates that the wherein clause was material to patentability. After Genentech added language regarding increasing yield of a "properly folded" polypeptide to the preamble of Claim 1, *see* File History (Exh. 1004) at 138, the Examiner expressed doubts about whether the preamble should be accorded patentable weight, *id.* at 47. Genentech responded by submitting a further amendment that added the wherein clause to the body of the claim. *Id.* at 26. The remarks accompanying the amendment made clear that Genentech considered the wherein clause limiting and indeed relied on it to overcome an obviousness rejection:

> The unobvious result of the manipulations claimed herein is that total protein expression is not changed, but rather the yields of properly folded product are increased. Such increased yields resulting from reducing the metabolic rate in step (b) of claims 1, 15, and 24 [issued claims 1, 16 and 25] are now specified in the body of the claims and

> not merely recited in the preamble. Since neither the primary reference nor any of the secondary references discloses or suggests this unexpected result of reducing metabolic rate late in the process, which is now specifically claimed, the invention herein is not obvious over any of the references.

File History (Exh. 1004) at 33 (emphasis added). The Examiner responded by withdrawing the rejections and allowing the claims. *Id.* at 6–9.

Neither case cited by Petitioner supports treating the wherein clause as non-limiting. *Texas Instruments, Inc. v. USITC*, 988 F.2d 1165, 1172 (Fed. Cir. 1993) states that a wherein clause is non-limiting if it "adds nothing to the patentability or substance of the claim," but in this case the wherein clause adds substance, and moreover the Examiner determined the claims to be patentable after Genentech added it. In *Minton v. NASD*, 336 F.3d 1373, 1381 (Fed. Cir. 2003), the Court held that the whereby clause there "does not inform the mechanics" of the method claim, and "nothing in the specification or the prosecution history suggests otherwise." In this case, the prosecution history shows that "wherein the reduction in metabolic rate

results in increased yield of properly folded polypeptide" was a material addition that limits the claims.

Third, even if the wherein clause of Independent Claims 1, 16, and 25 is not limiting, the parallel language of the preamble is limiting. The preamble of all of the claims of the '602 Patent recites "increasing product yield of a properly folded polypeptide." Genentech added "properly folded" during prosecution to clarify that the claimed methods "aim to increase the yield of properly folded protein, not just of total protein." File History (Exh. 1004) at 138, 142–143. As noted above, the Examiner expressed doubts about whether the preamble should be accorded patentable weight, *id.* at 47, but Genentech's statement quoted above made clear that Genentech intended the amendment to be limiting. The preamble defines the intended purpose and is not superfluous. *See Manning v. Paradis*, 296 F.3d 1098, 1103 (Fed. Cir. 2002).

Furthermore, "[w]hether to treat a preamble as a limitation is a determination 'resolved only on review of the entire[] . . . patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim.'" *Catalina Mktg Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (internal citations omitted). The

specification makes clear from the outset of the detailed description that the inventors invented a method for "increasing product yield of a properly folded" polypeptide, and intended the claims to encompass this: "The present invention advantageously provides a method for increasing yield of a heterologous recombinant protein produced by recombinant host cells by first increasing the polypeptide production capacity of 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," '602 Patent (Exh. 1001) at 3:12–18 (emphasis added).

2. "Increased Yield of Properly Folded Polypeptide"[3]

Petitioner argues, in the alternative, that "increased yield of properly folded polypeptide" should be construed to mean "increasing the total quantity of properly-folded (i.e., useful, soluble) polypeptide produced

[3] As explained above, this language is part of the concluding wherein clause of claim 1, and Genentech has requested permission to submit a Request for a Certificate of Correction to reflect that, during prosecution, Genentech added corresponding wherein clauses containing this language to Claims 16 and 25.

by a fermentation method that includes a metabolic rate shift, as compared to a fermentation method that does not incorporate such a shift." Petition at 22. However, this imports limitations into the claims that are contrary to the intrinsic record and ignores other claim terminology. Moreover, Petitioner fails to show how Seeger meets each and every element of its proposed construction, and thus fails to justify adoption of that proposed construction. As explained in detail below, the plain meaning of "increased yield of properly folded polypeptide" is clear within the context of the claims and requires no further construction.

First, "increased yield of properly folded polypeptide" refers back to the preamble language "increasing product yield of a properly folded polypeptide of interest." Thus, "polypeptide" in the body of the claim means "polypeptide of interest." In context, it is clear that both phrases call for an increased quantity of properly folded polypeptide of interest relative to the total quantity expressed.

Second, there is no basis for importing the parenthetical "(i.e., useful, soluble)," which seeks to define properly folded as useful or soluble. Here, the claims already identify what is useful, namely, "properly folded polypeptide," and do not need to be further embellished.

As to "soluble," Petitioner asserts that "[a] POSA would have understood that the soluble fraction of the cell lysate would contain soluble (i.e., properly folded) polypeptides." Petition at 22. But "soluble" is not synonymous with "properly folded." While a POSA would have understood that the soluble fraction of a cell lysate would contain properly folded polypeptide of interest, he or she would also have understood that the soluble fraction could also contain misfolded polypeptide of interest. As explained in Part VI.A. below, misfolded polypeptides are also found in the soluble fraction of cell lysates and solubility is not proof of proper folding. This is why the inventors of the '602 Patent did not merely assume in their Examples that solubility could be equated with proper folding. Instead, after obtaining the soluble fraction, they loaded it onto a CsX or affinity column to separate properly folded from misfolded polypeptides, identified the peak containing the properly folded polypeptide and measured the amount of it by comparing the peak against a standard. '602 Patent (Exh. 1001) at 16:14–21, 17:33–41.

Third, there is no basis for importing the lengthy phrase "produced by a fermentation method that includes a metabolic rate shift, as compared to a fermentation method that does not incorporate such a

shift." It is not any metabolic rate shift that is called for by the claim, but rather "reducing the metabolic rate . . . at the time of induction of polypeptide expression" (emphasis added), after having "culture[d] the recombinant host cells under conditions of high metabolic and growth rate." Moreover, this requirement, as quoted in the preceding sentence, is already recited in the claims, so incorporating it in a construction of "increased yield of properly folded polypeptide" is both unnecessary and confusing.

As to its proposed phrase "as compared to a fermentation method that does not incorporate such a shift," Petitioner effectively attempts to tack onto the claims of the '602 Patent two additional steps: (1) running of an identical fermentation but without a metabolic rate shift, and (2) comparing the yields of properly folded polypeptide produced under each condition, that is, with and without a metabolic rate shift. But, as written, the claims do not recite these additional steps implicitly required by Petitioner's proposed construction. The '602 Patent teaches that a reduction in metabolic rate at the time of induction will result in an increased yield of properly folded polypeptide. A would-be infringer can take advantage of

this teaching by practicing the claimed methods with no need to perform the additional steps implied in Petitioner's proposed construction.

Genentech submits that the claim terms "increasing product yield of a properly folded polypeptide of interest" and "increased yield of a properly folded polypeptide" are sufficiently clear from the context of the claims, and that these phrases do not require further construction.

B. "Culturing the Recombinant Host Cells Under Conditions of High Metabolic and Growth Rate" (Claims 1, 16, 25)

Petitioner's contentions regarding the construction of this term are not material to any issue addressed in this preliminary response, and thus do not need to be addressed at this preliminary response stage. Genentech notes, however, that Petitioner once again attempts to import limitations. The specification states that "'culturing the host cells under conditions of high metabolic and growth rate' means establishing the host cell culture conditions to favor growth, *e.g.*, by providing unrestricted or relatively high feed rates of nutrients energy and oxygen, such that the cells have rapid growth and metabolic rates prior to reducing the metabolic rate to increase 'product yield.'" '602 Patent (Exh. 1001) at 4:49–55. Neither the specification nor the prosecution history provides any basis for adding the

further sentence proposed by Petitioner: "This interpretation encompasses high metabolic and growth rates at *any* point before the step of reducing the metabolic rate in step (b)." Petition at 24 (emphasis in original). It should be rejected as at best unnecessary and at worst misleading.

C. "Reducing the Metabolic Rate" (Claims 1, 16, 25)

Here Petitioner argues for an overly complex "bifurcated definition," Petition at 24, that once again attempts to import limitations from the specification. The specification states: "As used herein, 'reducing metabolic rate' or 'shifting down metabolic rate' means altering the host cell culture conditions such that the host cells undergoing rapid growth and expansion reduce (or stop) growth and expansion." '602 Patent (Exh. 1001) at 4:12–15. Thus, Genentech submits that "reducing the metabolic rate" should be construed using these same words: "altering the host cell culture conditions such that the host cells undergoing rapid growth and expansion reduce (or stop) growth and expansion."

Petitioner attempts to rely on the next sentence of the specification, stating that "[f]or the case of cells already in a reduced growth state, the rates of oxygen uptake and the corresponding rates of uptake of a carbon/energy source are reduced." '602 Patent (Exh. 1001) at 4:15–18.

This is an example of a way to reduce the metabolic rate for such cells (all other things being equal) and is not meant to be definitional. To the contrary, the very next sentence states: "Since, 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 reactions." *Id.* at 4:18–22 (emphasis added). Moreover, as explained in Part VI.A. below, persons of skill in the art have known at least since 1979 that there are other factors, for example temperature, that affect the metabolic rate. Limiting the availability of oxygen and carbon/energy will not necessarily succeed in reducing the metabolic rate in the presence of those factors. Thus, limiting the availability of oxygen and carbon/energy is neither a necessary nor a sufficient condition for reducing the metabolic rate.

D. "Assembled" (Claims 11, 35)

This term appears only in dependent claims 11 and 35. Petitioner's contentions regarding the construction of this term are not material to any issue addressed in this preliminary response, and thus do not need to be addressed at this preliminary response stage. Genentech notes, however, that Petitioner's proposed construction—"assembled" means "the

polypeptide is produced by the cell as functional," Petition at 27—improperly conflates "assembly" with functionality. A polypeptide can be assembled from its constituents in a way that is functional (for example, properly folded) or it can be assembled in a way that is not functional (for example, misfolded). This is shown in the same portion of the specification that Petitioner cites, which refers to "properly assembled antibody"; "a properly assembl[ed] growth factor, hormone or cytokine"; and "properly folded or assembled functional protein." '602 Patent (Exh. 1001) at 5:11–16 (emphasis added). Persons of ordinary skill would have understood that an "assembled" polypeptide is one in which the constituent polypeptide chains have associated with each other.

IV. Person of Ordinary Skill in the Art

Petitioner's contention regarding the person of ordinary skill in the art is not material to any issue addressed in this preliminary response, and thus does not need to be addressed for purposes of this preliminary response. Genentech notes, however, that Petitioner's listing of relevant areas of specialization—biochemistry, microbiology, or chemical engineering, *see* Petition at 4–5—is unduly restrictive because it does not include biochemical engineering. For example, one of the inventors, Dr.

Bradley R. Snedecor, has a doctorate in Biochemical Engineering. *See* https://www.gene.com/scientists/our-scientists/brad-snedecor.

V. The Relied Upon References

A. Seeger

Seeger compares temperature- and IPTG-inducible systems for producing recombinant basic fibroblast growth factor (bFGF) in high cell density cultures of *E. coli*. In particular, Petitioner relies on the temperature-inducible system, in which Seeger reported decreasing the glucose feed rate while bFGF expression was induced by increasing the temperature. Seeger (Exh. 1010), Figure 3. As explained in Part VI.A. below, Seeger does not disclose whether the net effect of the increased temperature and reduced feed rate was to reduce the metabolic rate. In addition, Seeger does not disclose whether use of the conditions of Figure 3 had any effect on amount of properly-folded bFGF produced.

B. Makrides

Makrides reviews methods for achieving high-level protein expression in *E. coli*. Petitioner cites Makrides for its teaching of the *phoA* promoter, induced by low levels of phosphate in the culture medium, and for its general teachings about periplasmic expression of proteins in *E. coli*.

C. Cabilly

Cabilly describes the production of functional Fab fragments in *E. coli*. Petitioner cites Cabilly because it "discloses using simple methodology for the design and production of antibodies, specifically Fab fragments composed of κ-chains and truncated heavy chains, in *E. coli* to obtain soluble, properly-folded protein," and teaches "assembly of recombinantly-produced Fab fragments." Petition at 53–54.

VI. Petitioner Has Failed to Show a Reasonable Likelihood that the Challenged Claims Were Anticipated By Seeger or Would Have Been Obvious Over Seeger in View of the General Knowledge in the Art or in Combination with Either of the Secondary References

Petitioner has not demonstrated the requisite reasonable likelihood that it would prevail with respect to any of the challenged claims. The following analysis addresses two of the fundamental deficiencies in Seeger that are fatal to all of Petitioner's arguments. Genentech expressly reserves the right to rely on further deficiencies in Seeger and the other prior art, and rebut further portions of Petitioner's characterization and arguments, if the Board elects to institute a trial.

A. Ground #1: Claims 1, 3-4, 6, 9, 15-16, 20, 22, 24-25, 27-28, 30, 33 and 39 Are Not Anticipated by Seeger

1. Seeger Fails to Disclose "Reducing the Metabolic Rate … at the Time of Induction of Polypeptide Expression" as Stated in Claim 1 and Fails to Disclose the Corresponding Limitations of Claims 16 and 25

As explained above, the term "reducing the metabolic rate" should be construed, as defined in the '602 specification, to mean "altering the host cell culture conditions such that the host cells undergoing rapid growth and expansion reduce (or stop) growth and expansion." The portions of Seeger that Petitioner cites concern the temperature-inducible bFGF expression system. Reducing the glucose feed rate in such a system will not necessarily reduce the metabolic rate, because, as explained below, increasing temperature increases the growth rate. Thus, whether the metabolic rate is increased or reduced depends on whether the magnitude of the rate increase caused by the upward temperature shift is greater or less than the magnitude of the decrease caused by the reduced feeding. Seeger did not consider this question (because that was not the purpose of Seeger's experiments), and Seeger's results do not suggest an answer.

(a) Seeger's Method of Induction—Temperature Increase—Increases Growth Rate

Seeger induced protein expression from the λ promoter by increasing temperature. Seeger (Exh. 1010), 6, Figure 3. By at least 1979 and certainly by the time of Seeger's experiments, it was well-known in the art that the growth rate of *E. coli* varies with the temperature at which it is cultured. Within a certain temperature range, one could predict a direct correlation between higher temperatures and higher growth rates. Herendeen (Exh. 2002) at 1. Note that the horizontal scale is inverse to temperature, and thus negative slope denotes increasing growth in the chart below:

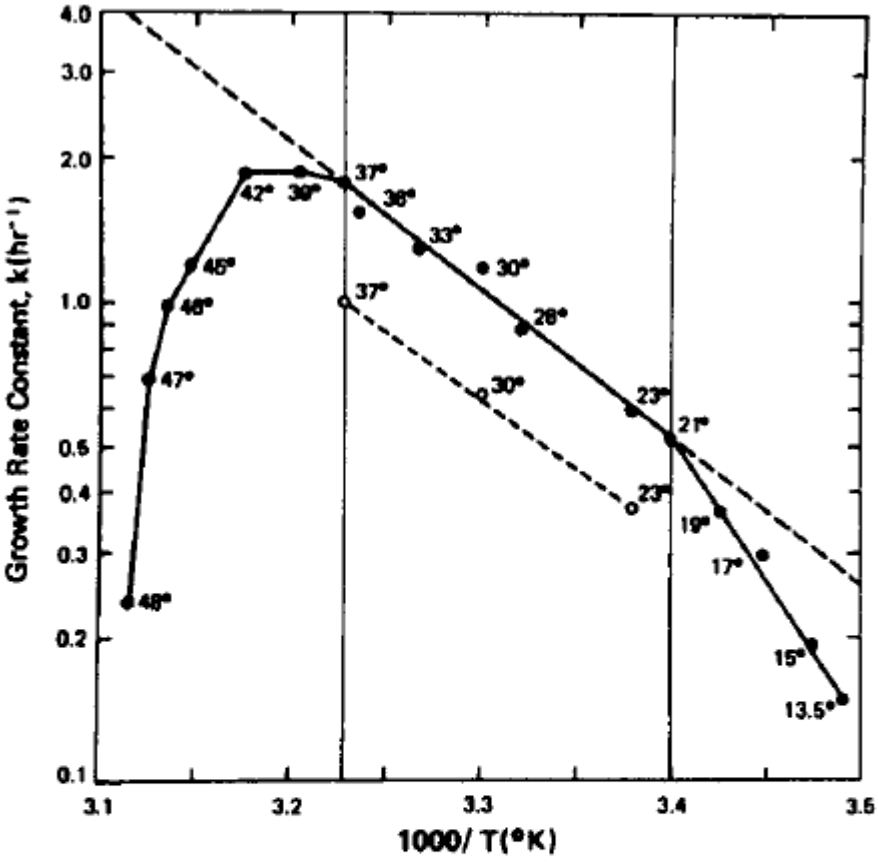

FIG. 1. ***Growth rate of E. coli B/r as a function of temperature. Cultures were grown to steady state at each temperature, and the rate of growth was measured. The logarithm of the growth rate constant, k (h^{-1}), is plotted on the ordinate against the inverse of the absolute temperature (°K) on the abscissa. Individual data points are marked with the corresponding degrees Celsius. (●) Strain NC3 in glucose-rich medium; (○) strain NC81 (identical to strain NC3 except for lacI lacP37 lacP5 thi) in glucose minimal medium.***

The legend of Figure 1 explains that the respective sets of data points represent *E. coli* strains grown in glucose-rich and glucose minimal media.

Id. at 2. In both cases, growth rate increases with temperature between 30°C and 37°C and plateaus between 37°C and 42°C before declining. Thus, a person of ordinary skill would have understood that when Seeger *et al.* raised the temperature of their fermentations from 30°C to 42°C to induce bFGF expression, the *E. coli* cells increased their growth rate.

(b) Seeger Does Not Teach or Suggest Whether the Competing Effects of the Temperature Increase and Feed Rate Decrease Resulted in Reduction or Increase of the Metabolic Rate

As noted above, Seeger induced polypeptide expression by increasing the temperature: "Product formation (phase 2) was induced at 45 g l^{-1} DCW by temperature shift from 30°C to 42°C." Seeger (Exh. 1010), 6, Figure 3. As taught by Herendeen et al., such an increase in temperature increases the growth and metabolic rate. Seeger also reduced the glucose feed rate: "Feeding was reduced in phase 2 of the fed-batch process such that a specific growth rate of $\mu_{set} = 0.08\ h^{-1}$ would have been maintained at 30°C." *Id.* But Seeger did not maintain the temperature at 30°C; Seeger increased it to 42°C. And Seeger did not account for the competing effects of the temperature increase and the feed rate reduction, leaving unanswered

the question of whether Seeger actually reduced the metabolic rate at the time of induction.

Likewise, Petitioner ignores the effects of the temperature increase on the metabolic rate. *See* Petition at 32–36. Its argument is constructed around a calculation performed by its expert, Dr. Rosenberg, regarding reduction in the glucose uptake rate that does not consider or address the countervailing effect of the temperature shift. *See id.* at 34; Rosenberg Declaration (Exh. 1002) at 117–18. Dr. Rosenberg modeled the glucose uptake rate as a function of time, based on Seeger's reported growth rate set point (μ_{set}), dry cell weight (DCW), density (X_F), reactor volume (V_F), and grams of glucose. *Id.* Importantly, Dr. Rosenberg's model does not take into account the variable of temperature. The variable for growth rate, μ, is expressed as a function of time, rather than as a function of both time and temperature. *Id.* at 117 (Equation 2[4]). Therefore, the glucose uptake rate calculated by Dr. Rosenberg and displayed as a graph of "Seeger: Temp Induction-gm glucose/gm DCW/hour" does not reflect the

[4] Equation 2 states: $Q_s(t) = \left(\frac{1}{Y_{xls}}\mu(t) + m_E\right)X(t)$.

true metabolic rate of the temperature-induced *E. coli* fermentation conducted by Seeger. *Id.* at 40; Petition at 35.

Given the temperature increase, Dr. Rosenberg's calculation provides no basis for concluding that there was a reduction in metabolic rate. Moreover, Herendeen teaches that there is no need for *E. coli* to synthesize more enzymes when it undergoes an increase in temperature from 30°C to 37°C (within Seeger's range of 30°C to 42°C) – that is, the cells need not consume more glucose to feed enzyme synthesis – to increase the metabolic rate. Instead, the increase in temperature from 30°C to 37°C raises the activity of enzymes already present in the cell, thereby increasing the metabolic rate. Herendeen (Exh. 2002) at 1, 6–7. Consequently, Dr. Rosenberg's calculated decrease in glucose uptake, even assuming it is correct, does not conclusively demonstrate a decrease in metabolic rate. Based on the knowledge in the art dating back to 1979, a person of ordinary skill reading Seeger's disclosure at the priority date of the '602 Patent could not have concluded that Seeger's decreased glucose feed rate and any decrease in glucose uptake it may have engendered, actually decreased the metabolic rate, when the increased temperature of induction would have had an offsetting effect. To the contrary, as to the temperature upshift from

30°C to 37°C, a person of skill would likely have concluded that a concomitant increase in metabolic rate had taken place.

2. Seeger Fails to Disclose "Increasing Product Yield of a Properly Folded Polypeptide" or "Increased Yield of Properly Folded Polypeptide" as Stated in Independent Claim 1, and Fails to Disclose the Corresponding Limitations of Independent Claims 16 and 25

Petitioner's "increased yield" argument also fails for at least the reason that Seeger only reported the total expression of polypeptide with no regard to whether the polypeptides are properly folded or misfolded. Because Seeger used quantification methods that rely on denaturing polypeptides before measuring them, Seeger does not and cannot provide any teaching regarding the amounts of properly folded polypeptides.

Seeger only measures denatured polypeptides and thus provides no information regarding amounts of properly folded polypeptides. Seeger discloses two measurement techniques: (1) immunodetection and (2) gel band densitometry. Seeger (Exh. 1010) at 5:2:15–33. Both of these techniques begin with use of the denaturing agent SDS to prepare the polypeptides for analysis by polyacrylamide electrophoresis (PAGE). Seeger notes its use of SDS-PAGE. *Id.* at 5:2:15–

17. Persons of skill in the art would have understood that SDS-PAGE linearizes protein molecules, that is, it eliminates the folding. The seminal paper on SDS-PAGE describes "the capability of SDS to break down proteins into their individual polypeptide chains" and dates from 1970. Laemmli (Exh. 2001) at 1. Once unfolded by interaction with SDS, proteins within a mixture all adopt a uniform shape, that of a linear chain of amino acids. *See* Reynolds and Tanford (Exh. 2003) at 1 ("[H)ydrodynamic studies suggest that the [SDS-protein] complex is a rodlike particle, the length of which varies uniquely with the molecular weight of the protein moiety."). The uniform shape of the SDS-denatured proteins facilitates their separation by size, without the potentially confounding effects of varying shapes. *Id.*

Immunoblotting, also known as Western blotting, begins with SDS-PAGE, and Seeger notes that "for immunodection of bFGF, samples were run on 9 to 16% SDS-PAGE gels." Seeger (Exh. 1010), 949:2:24-25. After the SDS-denatured proteins have been separated by gel electrophoresis, they are transferred to a membrane such as nitrocellulose (the "immunoblot") for antibody detection. *See* Towbin (Exh. 2004) at 1. In this "solid-phase immunoassay," denatured proteins remain stably bound to

the filter, where they are bound by a first antibody, which is then bound by a second, labeled antibody for purposes of detection. *Id.* Because it begins with the protein-denaturing method of SDS-PAGE, immunoblotting cannot distinguish between properly folded and misfolded proteins.

Gel band densitometry is a technique for measuring the intensity of staining with a protein-binding dye such as the one used by Seeger, Coomassie Brilliant Blue R250. *See* Pierce and Suelter (Exh. 2005) at 1. The technique is used after the polypeptides are denatured using SDS-PAGE. *See* Kahn and Rubin (Exh. 2006) at 1. Thus, whatever limited quantitative value gel band densitometry may have for measuring total protein, it provides no information whatsoever about the original protein structure or whether it was properly folded or misfolded. Again, because the SDS has denatured all the protein molecules into a linearized state, the technique is incapable of quantifying the amounts of properly and improperly folded proteins prior to denaturation. Both techniques measure total protein as linearized molecules and say nothing about the state of protein folding prior to denaturation with SDS.

Petitioner argues that proper folding can be inferred from Seeger's disclosure of bFGF levels in the "soluble cell fraction," Petition at

37 (citing Seeger (Exh. 1010), 9:1:13–26), and cites Dr. Rosenberg, who asserts that "[a] POSA would have understood that the soluble fraction of the cell lysate would contain soluble (i.e., properly folded) polypeptides." Rosenberg Declaration (Exh. 1002) at ¶ 26. Dr. Rosenberg attempts to support this assertion by citing Seeger (Exh. 1010) at 5:1:4 and Figure 3 legend, but neither these nor any passages of Seeger support the notion that polypeptide found in the soluble cell fraction must be properly folded. Misfolded proteins are also sometimes found in the soluble fraction of cell lysates and solubility is not proof of proper folding. *See* Sachdev and Chirgwin (Exh. 2007) at 2 ("[T]he soluble fusions lacked detectable proteinase activity, suggesting that the aspartic proteinase portions were nonnative."); Schrodel and de Marco (Exh. 2004) at 4 ("the SEC experiments showed that both aggregated and functional forms of the fusion protein were present in both the three fractions corresponding to the insoluble GFP-GST and the (soluble) fraction 1") (emphasis added). Thus, Seeger does not expressly or inherently address proper folding of proteins.

Dr. Rosenberg also cites the '602 Patent, noting that "[t]he specification also assesses the quantity of polypeptide (*e.g.*, an antibody) produced by the claimed fermentation methods by obtaining 'the soluble

fraction of the [cell] lysate.'" Rosenberg Declaration (Exh. 1002) at ¶ 26 (quoting '602 Patent (Exh. 1001) at 15:60–16:14). However, Petitioner and Dr. Rosenberg neglect the full teachings of the '602 specification. After the inventors obtained the soluble fraction, they loaded it onto a CsX column to separate properly folded from misfolded polypeptides, identified the peak containing the properly folded polypeptide and measured the amount of it by comparing the peak against a standard. '602 Patent (Exh. 1001) at 16:14–21. The inventors thus recognized that that solubility does not imply proper folding; further analysis is needed. Seeger did not perform or even suggest performing such analysis.

B. Grounds #2, 3 and 4: Claims 7-8, 10-14, 18, 23, 31-32 and 34-38 Would Not Have Been Obvious Over Seeger Combined With Makrides, Cabilly or the Alleged General Knowledge in the Prior Art

The same gaps in Seeger that are fatal to Petitioner's anticipation argument are also fatal to its obviousness arguments. Moreover, Seeger teaches away from the claimed invention.[5]

[5] As noted above, this preliminary response addresses fundamental deficiencies in Seeger that are fatal to all of Petitioner's arguments. Genentech reserves the right to rely on further deficiencies in Seeger and

Petitioner's obviousness arguments rely on Seeger for all of the limitations set forth in independent claims 1, 16, and 25. Petitioner uses the secondary references—Makrides, Cabilly and the alleged "general knowledge in the prior art"—only to argue that limitations recited in certain other challenged dependent claims were known in the art, as set forth in the table below:

Claim	***Ground for Challenge***	***Depends from***	***Additional limitations for which Petitioner cites secondary references***
Claim 7	Seeger + General Knowledge	Claim 1	"growing the cells to maximum density in step (a)"
Claim 8	Seeger + General Knowledge	Claim 7	"the metabolic rate is reduced by about half in step (b)"
Claim 10	Seeger + Makrides	Claim 1	"the inducible system is a phosphate depletion inducible system"
Claim 11	Seeger + Cabilly	Claim 1	"the polypeptide is assembled in the host cell"

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the other prior art if the Board institutes a trial. Genentech does not concede that there exists any motivation to combine the cited references.

Claim	***Ground for Challenge***	***Depends from***	***Additional limitations for which Petitioner cites secondary references***
Claim 12	Seeger + Makrides	Claim 9	"the polypeptide is secreted into the periplasm of the host cell"
Claim 13	Seeger + Cabilly	Claim 1	"the polypeptide is an antibody"
Claim 14	Seeger + Cabilly	Claim 1	"the polypeptide is selected from the group consisting of an Fab'2 antibody and an Fab antibody or other form of antibody"[6]
Claim 18	Seeger + Cabilly	Claim 16	"the antibody is an Fab antibody"
Claim 23	Seeger + Makrides	Claim 16	"the inducible system is a phosphate depletion inducible system"
Claim 31	Seeger + General Knowledge	Claim 25	"growing the cells to maximum density in step (a)"

[6] Note that the final phrase "or other form of antibody" was deleted by amendment during prosecution in the Amendment of August 1, 2003 and Genentech has requested permission to submit a request for Certificate of Correction to correct this error.

Claim	***Ground for Challenge***	***Depends from***	***Additional limitations for which Petitioner cites secondary references***
Claim 32	Seeger + General Knowledge	Claim 31	"the metabolic rate is reduced by about half in step (b)"
Claim 34	Seeger + Makrides	Claim 25	"the inducible system is a phosphate depletion inducible system"
Claim 35	Seeger + Cabilly	Claim 25	"the polypeptide is assembled in the host cell"
Claim 36	Seeger + Makrides	Claim 33	"the polypeptide is secreted into the periplasm of the host cell"
Claim 37	Seeger + Cabilly	Claim 25	"the polypeptide is an antibody"
Claim 38	Seeger + Cabilly	Claim 25	"the polypeptide is selected from the group consisting of an Fab'2 antibody and an Fab antibody or other form of antibody"[7]

[7] Note that the final phrase "or other form of antibody" was deleted by amendment during prosecution in the Amendment of August 1, 2003 and Genentech has requested permission to submit a request for Certificate of Correction to correct this error.

Because none of the tabulated phrases in the dependent claims addressed the limitations in each independent claim that Seeger lacks, the secondary references, in combination with Seeger, do not render any of the claims obvious. For this reason alone, Petitioner has not met its burden of showing a reasonable likelihood that any of the challenged claims would have been obvious, and a trial should not be instituted.

Furthermore, Seeger teaches away. Seeger stated: "A further reduction in the exponential feeding rate $\mu_{set} = 0.04\ h^{-1}$ after a temperature shift to 42°C did not permit expression of bFGF (data not shown)." Seeger (Exh. 1010) at 8:2:8–10 (emphasis added). Thus, when Seeger reduced the feeding rate from $0.08\ h^{-1}$ to $0.04\ h^{-1}$, bFGF expression was eliminated. Seeger teaches that a manipulation that Petitioner characterizes as causing a reduction of metabolic rate actually inhibits protein expression. This is the exact opposite of the effect disclosed in the '602 Patent that reduction in metabolic rate has on protein expression. As taught in the '602 Patent, the reduction in metabolic rate does not eliminate protein expression, but rather, results in an increased yield of properly folded polypeptides.

VII. Conclusion

For the foregoing reasons, Petitioner has failed to demonstrate a reasonable likelihood that any of the challenged claims of the '602 Patent are unpatentable. The Board should therefore deny the Petition and decline to institute an *inter partes* review.

Dated: November 30, 2016

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing PATENT OWNERS' PRELIMINARY RESPONSE complies with the type volume limitation of 37 C.F.R. § 42.24(b)(1) because it contains 6,905 words as determined by the Microsoft® Office Word 2010 word-processing system used to prepare the brief, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a)-(b).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), the undersigned certifies that on November 30, 2016, a true and correct copy of the foregoing PATENT OWNER'S PRELIMINARY RESPONSE, along with all exhibits supporting and filed with the Preliminary Response, was served by email on the following counsel of record for Petitioner:

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