UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOEQ IP AG

Petitioner

v.

GENENTECH, INC.

Patent Owner

Case No. IPR2016-01608

U.S. Patent No. 6,716,602

PETITIONER'S REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE

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Petitioner submits this Reply to address corrections to claims 14, 16, 21, 25, 28, and 38 of the '602 patent (BEQ1001), newly introduced by Patent Owner's December 1, 2016 Request for Certificate of Correction Under 35 U.S.C. § 254 (EX2009). Petitioner confirms that its Petition (Paper 3) challenges claims 14, 16, 25, 28, and 38 as-issued, and this Reply, authorized by the Board, demonstrates how the claims as presented in EX2009 are unpatentable. Petitioner also seeks to add claim 21 to its original Ground 1—but for Patent Owner's dilatory efforts to file its Request, Petitioner would have challenged claim 21 in its Petition.

I. Seeger anticipates claims 16, 25, and 28

Seeger anticipates claims 16, 25, and 28—amended or not. Amended claims 16 and 25 include the same step (b) and same terminal "wherein" clause recited in claim 1, modified to refer to "antibody, growth factor, or protease" (claim 16) or "mammalian polypeptide" (claim 25). (EX2009, 2, 3, 7; BEQ1001, 18:23-24.) Claim 28 would depend from claim 25, not 27. (EX2009, 3, 7; BEQ1001, 20:1-2.) As explained in the Petition and Declaration (BEQ1002), Seeger anticipates claims 16, 25, and 28. (Paper 3, 28-41; BEQ1002, ¶¶68-74; 88-89; 98-99; 103-104.)

Seeger discloses every element of claims 16, 25, and 28, arranged as claimed and in a manner enabling to a POSA. (Paper 3, 28-41; BEQ1002, ¶¶68-74; 88-89; 98-99; 103-104.) The Petition and Declaration show that Seeger describes inducible expression of mammalian growth factor bFGF in recombinant host cells,

by first culturing the cells "under conditions of high metabolic and growth rate," and then "reducing the metabolic rate of the host cells at the time of induction" by reducing the amount of available glucose. (Paper 3, 29, 32-35; BEQ1010, 951:2:1, 950:2, Figure 3; BEQ1002, ¶¶4, 29, 52-57, 68-69, 71-72, 76). Dr. Rosenberg's calculations show that reducing available glucose resulted in a reduction in the host cells' specific glucose uptake rate (GUR). (Paper 3, 34-35; EX1002, ¶56.) Indeed "a reduction in [] GUR represents a reduction in the metabolic rate." (Paper 3, 34-35; BEQ1002, ¶71.) Thus, the Petition shows that Seeger reduced metabolic rate of the cells at the time of induction.

Genentech posits that Dr. Rosenberg's GUR calculation "does not reflect the true metabolic rate" of Seeger's cells because it "ignores the effects of the temperature increase on the metabolic rate." (Paper 9, 27-28). Genentech is wrong. As Dr. Rosenberg explains, "a metabolic rate of a bacterial cell is closely related to a rate with which the cell consumes and oxidizes [] glucose," e.g., GUR. (BEQ1002, ¶37; Paper 3, 8.) And, "a magnitude of change in GUR [] can serve as a proxy for the magnitude of change in a metabolic rate." (BEQ1002, ¶81; Paper 3, 41.) Thus, GUR is a "read-out" of the cells' metabolic rate. It accounts for any external factors that influence the metabolic rate—amount of supplied glucose, oxygen, or temperature. Dr. Rosenberg calculated GUR *throughout* Seeger's fed-batch phases, i.e., before and after the temperature change that induced bFGF

expression, thus accounting for temperature. (Paper 3, 34-35; BEQ1002, ¶56.) Indeed, "when the temperature was raised from 30° to 42°C [in Seeger's method], there was a reduction in the actual growth rate." (BEQ1020, 64.)

Seeger also teaches the added "wherein" clause of claims 16 and 25. (Paper 3, 36-37; BEQ1002, ¶¶43, 55, 57, 73.) This clause imparts no patentable weight—it is an intended outcome. (Paper 3, 20-21, 36.) Indeed, Genentech itself admits unequivocally that "a reduction in metabolic rate at the time of induction ***will result*** in an increased yield of properly folded polypeptide." (Paper 9, 16, emphasis added.) But even if considered a limitation, Seeger teaches the "wherein" clause.

Dr. Rosenberg explains that shifting the exponential glucose feeding rate at the time of induction resulted in an increased bFGF expression in a soluble fraction—from ***zero*** without the shift. (Paper 3, 37; BEQ1002, ¶¶43, 57, 73.) A POSA would have understood that the soluble fraction contained properly-folded bFGF. (Paper 3, 37; BEQ1002, ¶73.) And Genentech agrees: "a POSA would have understood that the soluble fraction of a cell lysate ***would contain*** properly folded polypeptide of interest." (Paper 9, 15, emphasis added.) Indeed, Seeger's goal was to "optimize the production of soluble and thus biologically active bFGF." (BEQ1020, 80.) Claims 16 and 25 do not require a percentage of properly-folded polypeptide—***any*** increase in properly folded polypeptide is within the scope of claims 16 and 25.

II. Seeger renders obvious claims 14 and 38

The proposed corrections to claims 14 and 38 leave intact the phrase "the polypeptide is selected from the group consisting of an Fab'2 antibody and an Fab antibody." (EX2009, 7; BEQ1001, 18:52-54, 20:27-29; BEQ1002, ¶¶18:52-54, 20:27-29.) The Petition and Dr. Rosenberg's Declaration confirm that a POSA reading Seeger and Cabilly, would have had a reason to produce Fab antibody fragments as recited in claims 14 and 38, with a reasonable expectation of success. (Paper 3, 53-57; BEQ1002, ¶¶144-163.) Genentech does not dispute these teachings, and instead argues that Seeger teaches away. (Paper 9, 37.) But it does not. Teaching away is measured in the art as a whole. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2016). And Seeger clearly describes decreasing the exponential feeding rate—and thus the metabolic rate—at the time of induction to produce soluble, properly-folded bFGF protein.

III. Seeger anticipates claim 21

Amended claim 21 would depend from claim 20 instead of claim 19. (EX2009, 3, 4, 7; BEQ1001, 19:11-12.) The Petition did not challenge claim 19 but did challenge claim 20. (Paper 3, 40.) Because Patent Owner now seeks to amend claim 21, Petitioner requests that the Board also institute IPR of claim 21.

Claim 21 states that "the carbon/energy source is glucose." (EX2009, 3, 4; BEQ1001, 19:11-12.) Seeger teaches a glucose carbon/energy source, anticipating

claim 21. (Paper 3, 28; BEQ1002, ¶¶77-78, 103-104.) And Petitioner challenged *the same limitation* in claims 4 and 28 (Paper 3, 40-41; BEQ1002, ¶¶77-78):

				Seeger (BEQ1010) describes each element:
Challenged dependent claim	4	**21**	28	949:1:1, 950:2, Figure 3 legend, 952:1, Table 2
Depends from	3	20	27	951:2:1-2, 950:2, Figure 3 legend
Depends from	1	16	25	947, Abstract, 948:1:3, 948, Table 1, 948:2:1-3, 950:2, 951:2:1-2, 952:1:1-952:2:2, 953:1:2

The Board has discretion to find claim 21 unpatentable in view of the prior art and information provided in the Petition.[1] *Cuozzo Speed Techs, LLC v. Lee*, 136 S. Ct. 2131, 2140 (2016). Any prejudice to Patent Owner by such a finding is minimal because the Petition provided notice that a glucose carbon source is in the art. The same cannot be said for Petitioner. Had Patent Owner corrected claim 21 in the more than 12 years since issuance, the Petition would have included the claim. It is manifestly unjust to reward Patent Owner's delay by not adding claim 21 here.

Respectfully submitted,
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[1] The excess claim fee ($600) for claim 21 is paid with this filing.

CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e), 42.105(a))

The undersigned hereby certifies that the above-captioned "Petitioner's Reply to Patent Owner's Preliminary Response" was served in its entirety on December 9, 2016, upon the following counsel of record via electronic mail:

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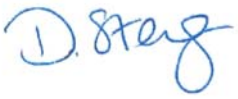

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