UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BIOEQ IP AG

Petitioner

v.

GENENTECH, INC.

Patent Owner

Case No. Unassigned

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

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,716,602 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.1-.80, 42.100-.123

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1002	Declaration of Morris Z. Rosenberg, DSC.
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1004	File History for U.S. Patent No. 6,716,602
1005	Knorre, W.A., *et al.*, "High Cell Density Fermentation of Recombinant *Escherichia coli* with Computer-Controlled Optimal Growth Rate," *Annals New York Academy of Sciences* 646: 300-306 (1991)
1006	Jackson, D.A., *et al.*, "Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of *Escherichia coli*," *Proceedings of the National Academy of Sciences* 69(10): 2904-2909 (1972)
1007	Donovan, R.S., *et al.*, "Review: Optimizing inducer and culture conditions for expression of foreign proteins under the control of the *lac* promoter," *Journal of Industrial Microbiology* 16: 145-154 (1996)
1008	Korz, D.J., *et al.*, "Simple fed-batch technique for high cell density cultivation of *Escherichia coli*," *Journal of Biotechnology* 39: 59-65 (1995)
1009	Verma, R., *et al.*, "Antibody engineering: Comparison of bacterial, yeast, insect, and mammalian expression systems," *Journal of Immunological Methods* 216: 165-181 (1998)
1010	Seeger, A. *et al.*, "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*," *Enzyme and Microbial Technology* 17: 947-953 (1995)

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1011	Luli, G.W., *et al.*, "Comparison of Growth, Acetate Production, and Acetate Inhibition of *Escherichia coli* Strains in Batch and Fed-Batch Fermentations," *Applied and Environmental Microbiology* 56(4): 1004-1011 (1990)
1012	Akesson, M., *et al.*, "A simplified probing controller for glucose feeding in *Escherichia coli* cultivations," *Decision and Control* 5: 4520-4525 (2000)
1013	Strittmatter, W., *et al.*, "Process for the Preparation of Recombinant Proteins in *E. coli* by High Cell Density Fermentation," U.S. Patent No. 6,410,270 (International Filing Date November 28, 1996; Issued June 25, 2002)
1014	Smirnova, G.V., *et al.*, "Influence of Acetate on the Growth of *Escherichia coli* Under Aerobic and Anaerobic Conditions," *Mikrobiologiya* 54(2): 205-209 (1985)
1015	Rinas, U., *et al.*, "Glucose as a substrate in recombinant strain fermentation technology," *Applied Microbiology and Biotechnology* 31: 163-167 (1989)
1016	CURRENT PROTOCOLS IN MOLECULAR BIOLOGY pp. 1.1.1- 1.15.8 and 16.1-16.21 (Frederick M. Ausubel, *et al.*, eds., Volume I, Supplement 3, 1995)
1017	Roszak, D.B., *et al.*, "Survival Strategies of Bacteria in the Natural Environment," *Microbiological Reviews* 51(3): 365-379 (1987)
1018	Akesson, M., *et al.*, "A probing feeding strategy for *Escherichia coli* cultures," *Biotechnology Techniques* 13: 523-528 (1999)
1019	Wangsa-Wirawan, N.D., *et al.*, "Novel fed-batch strategy for the production of insulin-like growth factor 1 (IGF-1)," *Biotechnology Letters* 9(11): 1079-1082 (1997)

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1020	Seeger, A., "Production of the Basic Fibroblast Growth Factor (bFGF) in a High Cell Density Process by means of Recombinant *Escherichia coli*," Dissertation submitted to the Department of Mechanical Engineering and Electrical Engineering of the Technical University of Carolo-Wilhelmina (1995)
1021	Lin, H., "Cellular responses to the induction of recombinant genes in *Escherichia coli* fed-batch cultures," Dissertation submitted to Martin-Luther-Universitat Halle-Wittenberg Faculty of Mathematics and Natural Sciences Department of Biochemistry and Biotechnology (2000)
1022	Sawers, G., *et al.*, "Alternative regulation principles for the production of recombinant proteins in *Escherichia coli*," *Applied Microbiology Technology* 46: 1-9 (1996)
1023	Makrides, S.C., "Strategies for Achieving High-Level Expression of Genes in *Escherichia coli*," *Microbiological Reviews* 60(3): 512-538 (1996)
1024	Wanner, B.L., "Gene Regulation by Phosphate in Enteric Bacteria," *Journal of Cellular Biochemistry* 51: 47-54 (1993)
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1026	Carter, P., *et al.*, "High Level *Escherichia coli* Expression and Production of a Bivalent Humanized Antibody Fragment," *Biotechnology* 10: 163-167 (1992)
1027	Better, M., *et al.*, "*Escherichia coli* secretion of an active chimeric antibody fragment," *Science* 240: 1041 (1988)
1028	Shimuzu, N., *et al.*, "Fed-Batch Cultures of Recombinant *Escherichia coli* with Inhibitory Substance Concentration Monitoring," *Journal of Fermentation Technology* 66: 187-191 (1988)

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1029	Bauer, K.A., *et al.*, "Improved Expression of Human Interleukin-2 in High-Cell-Density Fermentor Cultures of *Escherichia coli* K-12 by a Phosphotransacetylase Mutant," *Applied and Environmental Microbiology* 56: 1296-1302 (1990)
1030	Huston, J.S., *et al.*, "Protein engineering of antibody binding sites: recovery of specific activity in an anti-digoxin single-chain Fv analogue produced in *Escherichia coli*," *Proceedings of the National Academy of Sciences* 85: 5879 (1988)
1031	BIOPROCESS ENGINEERING PRINCIPLES pp. 257-296 (Pauline M. Doran, ed., 1995)
1032	Cabilly, S., "Growth at sub-optimal temperatures allows the production of functional, antigen-binding Fab fragments in *Escherichia coli*," *Gene* 85: 553-557 (1989)
1033	Boss, M.A., *et al.*, "Assembly of functional antibodies from immunoglobulin heavy and light chains synthesized in *E. coli*," *Nucleic Acids Research* 12:3791-3806 (1984)
1034	Cabilly, S., *et al.*, "Generation of anybody activity from immunoglobulin polypeptide chains produces in *E. coli*," *Proceedings of the National Academy of Sciences* 81: 3273-3277 (1984)
1035	Akesson, M., *et al.*, "On-Line Detection of Acetate Formation in *Escherichia* coli Cultures Using Dissolved Oxygen Responses to Feed Transient," *Biotechnology and Bioengineering* 64: 590-598 (1999)
1036	Hoffman, F., *et al.*, "Minimizing inclusion body formation during recombinant protein production in *Escherichia coli* at bench and pilot plant scale," *Enzyme and Microbial Technology* 34: 235-241 (2004)

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1037	Jensen, E.B., *et al.*, "Production of Recombinant Human Growth Hormone in *Escherichia coli:* Expression of Different Precursors and Physiological Effects of Glucose, Acetate, and Salts," *Biotechnology and Bioengineering* 36: pp. 1-11 (1990)
1038	Turner, C., *et al.*, "A Study of the Effect of Specific Growth Rate and Acetate on Recombinant Protein Production of *Escherichia coli,* JM107," *Biotechnology Letters* 16: 891-896 (1994)
1039	GENES III pp. 183-218 and 732 (Benjamin Lewin ed., Third Edition, 1987)
1040	Qiu, J., *et al.,* "Expression of Active Human Tissue-Type Plasminogen Activator in *Escherichia coli*," *Applied and Environmental Microbiology* 64: 4891-4896 (1998)
1041	Nan Chang, C., *et al.*, "High-level secretion of human growth hormone by *Escherichia coli*," *Gene* 55: 189-196 (1987)
1042	Ulrich, H.D., *et al.*, "Expression studies of catalytic antibodies," *Proceedings of the National Academy of Sciences* 92: 11907-11911 (1995)
1043	ESSENTIAL IMMUNOLOGY pp. 31-54 (Ivan Roitt ed., Sixth Edition, 1988)
1044	Rosano, G.L., *et al.*, "Recombinant protein expression in *Escherichia coli*: advances and challenges," *Frontiers in Microbiology* 5: pp. 1-17 (2014)
1045	Henry, N.G., "Effect of Decreasing Growth Temperature on Cell Yield of *Escherichia coli,*" *Journal of Bacteriology* 98: 232-237 (1969)
1046	Kovářová, K., *et al.*, "Temperature-Dependent Growth Kinetics of *Escherichia coli* ML 30 in Glucose-Limited Continuous Culture," *Journal of Bacteriology* 178: 4530-4539 (1996)

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1047	Ko, Y.-F., *et al.*, "A Metabolic Model of Cellular Energetics and Carbon Flux During Aerobic *Escherichia coli* Fermentation," *Biotechnology and Bioengineering* 43: 847-855 (1994)
1048	Skerra, A., "Use of tetracycline promoter for the tightly regulated production of a murine antibody fragment in *Escherichia coli*," *Gene* 151: 131-135 (1994)

I. Introduction

bioeq IP AG ("Petitioner") submits this Petition for *Inter Partes* Review ("IPR") seeking cancellation of claims 1, 3-4, 6-16, 18, 20, 22-25, 27-28, and 30-39 of U.S. Patent No. 6,716,602 ("the '602 patent") (BEQ1001). These claims are unpatentable under 35 U.S.C. §§ 102 and 103. And the reason is simple: a § 102(b) prior art reference (Seeger, BEQ1010), neither cited nor considered by the Examiner during prosecution, describes the *exact* limitation Patent Owner argued was missing from the cited prior art—reducing the metabolic rate of the cultured host cells *at the time of induction* of polypeptide expression.

To be clear, Patent Owner admitted that the primary reference relied upon by the Examiner (Knorre, BEQ1005) *expressly* taught reducing metabolic rate by controlling the bacterial growth rate (through a glucose feed-rate reduction), just not *at the time of induction*. Yet, as this Petition demonstrates, Seeger describes (or in combination with additional references renders obvious) each and every limitation of the challenged claims, including this element.

The challenged claims recite methods for increasing product yield of a properly-folded polypeptide of interest produced by recombinant host cells, where expression of the polypeptide by the host cells is regulated by an inducible system. The methods comprise only two steps: (i) culturing the recombinant host cells under conditions of high metabolic and growth rate and (ii) reducing the metabolic

rate of the cultured host cells at the time of induction of polypeptide expression. (*See*, *e.g.*, BEQ1001, 18:16-17.)[1] Step (ii) is achieved by either reducing the feed rate of a carbon/energy source or reducing the amount of available oxygen, or both, as has been part of the practiced art long before the earliest effective filing date of the '602 patent.[2] (*See*, *e.g.*, BEQ1001, 18:18-21.)

Seeger used an inducible expression system to induce expression of a mammalian polypeptide, basic fibroblast growth factor, in a high cell density culturing system by first culturing the recombinant host cells under conditions of high metabolic and growth rate. Then, to reduce the metabolic rate of the host cells upon induction, Seeger controlled the bacterial growth rate by reducing the feed rate of a carbon/energy source—glucose. Thus, Seeger described using the exact

[1] Citations to patent literature provided as BEQ10XX, YYY:Z-Z indicate citations to column Y, at lines Z-Z. Citations to non-patent literature provided as BEQ10XX, Y:Z:Z' indicate citations to page number Y, at column number Z, and paragraph number Z'.

[2] Petitioner does not concede that the '602 patent is entitled to a filing date of November 3, 2000. However, the '602 patent cannot be entitled to any filing date earlier than November 3, 2000.

technique (reducing glucose feed-rate) to reduce metabolic rate that Patent Owner admitted was in the prior art, and Seeger did so at the time of induction.

And, before November 3, 2000, a POSA running *E. coli* fermentations would have had a reason to apply Seeger's reduced metabolic rate fermentation strategies to produce other recombinant proteins, such as antibodies and antibody fragments like Fab, or using well-known inducible promoter systems, such as phosphate depletion inducible systems (e.g., *phoA*), as recited in the dependent claims. This is so because Seeger specifically aimed to address a problem that had been identified and solved well-before the earliest priority date of the '602 patent, namely: reduce toxic by-product accumulation, particularly acetic acid, which significantly limits host cell growth and recombinant protein production. Seeger succeeded in doing so by reducing the metabolic rate of the host cells at the time of induction of polypeptide expression.

Moreover, a POSA would have successfully arrived at the limitations recited in the dependent claims identified herein with a reasonable expectation of success because recombinant *E. coli* fermentation strategies had long been used to produce numerous commercially-important proteins, including growth factors, antibodies, and antibody fragments. Indeed, the field had selected *E. coli* as "the most important" and versatile host for production of commercially-important proteins.

Finally, no objective indicia of nonobviousness weigh in favor of patentability. Accordingly, Petitioner requests that the Board institute trial because Petitioner is reasonably likely to prevail with respect to at least one challenged claim based on the Grounds asserted in this Petition.

II. Grounds for standing (37 C.F.R. § 42.104(a))

Petitioner certifies that the '602 patent is available for IPR, and Petitioner is not barred or estopped from requesting IPR of any of the challenged claims.

III. Statement of the precise relief requested and the reasons therefore

The Office should institute IPR under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80 and 42.100-42.123, and cancel claims 1, 3-4, 6-16, 18, 20, 22-25, 27-28, and 30-39 of the '602 patent as unpatentable under pre-AIA 35 U.S.C. § 102(b) and 103(a) for the reasons explained below. This petition is accompanied and supported by the Declaration of Dr. Morris Rosenberg (BEQ1002) and related materials. Petitioner's detailed full statement of the reasons for relief requested is set forth in § VI.

IV. Overview

A. POSA

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the '602 patent, a POSA would typically have had a Ph.D. or a D.Sc. and at least two years of experience, or an M.S. and at least

four years of experience, in recombinant protein production, specializing in biochemistry, microbiology, or chemical engineering. (BEQ1002, ¶19.) A POSA would have also typically worked as part of a multi-disciplinary team to solve a given problem, drawing upon not only his or her own skills, but also certain specialized skills of others in the team. (BEQ1002, ¶20.) For example, such a team may be comprised of a chemical engineer, microbiologist, biochemist, and/or molecular biologist. (*Id*.)

Before November 3, 2000, the state of the art of which a POSA would have been aware included teachings provided by the references discussed in this Petition and by Dr. Rosenberg. Additionally, a POSA, based on then existing literature, would also have had general knowledge of recombinant protein production and methods of producing recombinant polypeptides. (*Id*.)

B. Scope and content of the art before November 3, 2000

In his Declaration, Dr. Rosenberg describes prior art teachings confirming the general knowledge of a POSA as of November 3, 2000. *See In re Khan*, 441 F.3d 977, 988 (Fed. Cir. 2006) (stating that a person of ordinary skill possesses the "understandings and knowledge reflected in the prior art"); *see also Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) ("[T]he knowledge of [a person of ordinary skill in the art] is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been

obvious."). And Petitioner's grounds rely on the prior art teachings, as explained below and supported by Dr. Rosenberg. (*See* BEQ1002, ¶¶10, 18.)

1. *E. coli:* "the most important" host for bacterial production of recombinant proteins, including growth factors, antibodies, and antibody fragments

The field of recombinant protein production advanced considerably over several decades before November 3, 2000. (*See* BEQ1006, 2904-2909; BEQ1007, 145:1; BEQ1023, 512:1-2; BEQ1002, ¶33.) Indeed, scientists routinely used bacteria—primarily *E. coli*—for recombinant protein production of a wide variety of commercially-important proteins, including mammalian polypeptides, such as growth factors, antibodies, and antibody fragments. (*See* BEQ1007, 145:1:2; BEQ1002, ¶33.) And the field had selected *E. coli* as "the most important" and versatile host for recombinant protein production because, e.g., it grows at a very fast rate allowing for high-volume protein production over a short time. (*See* BEQ1008, 59:1:1; BEQ1002, ¶34.) Thus, a POSA had a wealth of knowledge about this versatile host and would have preferred it for recombinant protein production. (*See* BEQ1007, 145:1:2; BEQ1002, ¶34.)

E. coli host cells also presented a POSA with an ability to express a diverse array of recombinant proteins in the cytoplasm or to target these proteins to the periplasm, using a signal sequence like the PhoA signal peptide. (*See* BEQ1009, 170:1:3; BEQ1023, 520:2:3-4; BEQ1002, ¶¶49, 64-65.) This versatility is

particularly important for recombinant antibodies and antibody fragments, which tend to precipitate in the reducing environment of the bacterial cytoplasm. (*See* BEQ1009, 170:1:3; BEQ1023, 518:1:5, 518:2:3, 520:2:2; BEQ1002, ¶¶49, 63.) Periplasmic targeting enabled production of Fab fragments (an antibody fragment) as assembled, soluble dimeric proteins that did not precipitate in the periplasm. (*See* BEQ 1023, 520:2:3; BEQ1042, 11909:2:3; BEQ1002, ¶¶49, 64.)

Typical fermentation methods for producing recombinant proteins in *E. coli* involved (and still do) a growth phase, where logarithmic or exponential growth of the host cells occurs at a constant doubling rate, and a recombinant protein production phase, which can begin when the host cells are in logarithmic or exponential growth or when the host cells have reached a stationary growth phase. (*See* BEQ1017, 368:1:2; BEQ1016, 1.1.1:2; BEQ1002, ¶35.) The field used high cell density culturing (HCDC) of the *E. coli* host cells as a strategy to obtain "efficient recombinant protein formation." (*See* BEQ1013, 1:21-23; BEQ1002, ¶36.) But by November 3, 2000, a POSA would have known that excess glucose feeding during either the growth phase or production phase of, e.g., an HCDC, presented a central obstacle in *E. coli*-based recombinant protein production methods. (*See* BEQ1010, 947:1-1; BEQ1011, 1004, 1:1 and 1009:1:4; BEQ1014, 206:2 and Figure 1; BEQ1015 163:Summary; BEQ1018: 523:1:1; BEQ1028, Abstract; BEQ1029, Abstract; BEQ1038, Abstract; BEQ1002, ¶¶36-38.)

2. Excess glucose during bacterial fermentation causes acetate accumulation and limits high host cell densities and recombinant protein production

Because *E. coli* grow faster on glucose than other carbon sources, media used for recombinant protein production in *E. coli* usually include substantial concentrations of glucose to obtain high-density bacterial cultures. (*See* BEQ1011, 1004, 1:1; BEQ1002, ¶36.) However, excess glucose provided to *E. coli* host cells grown in HCDC in the presence of oxygen (i.e., aerobic conditions), can cause the formation of acidic by-products, such as acetate (or acetic acid). (*Id*.)

Acetate accumulation during HCDC *E. coli* fermentation presents a central obstacle to recombinant protein production because it detrimentally affects both host cell growth and recombinant protein production. (*See* BEQ1010, 947:1-1; BEQ1011, 1004, 1:1 and 1009:1:4; BEQ1014, 206:2 and Figure 1; BEQ1015 163:Summary; BEQ1018: 523:1:1; BEQ1028, Abstract; BEQ1029, Abstract; BEQ1038, Abstract; BEQ1002, ¶¶36-38.) The acetate accumulation results from an imbalance between a host cell's glucose metabolism and respiration, which are intimately linked. (*See* BEQ1011, 1009:1:3; BEQ1002, ¶37.) This is because a host cell uses oxygen to metabolize glucose, which means that as the glucose uptake rate ("GUR") decreases, so does the oxygen uptake rate ("OUR"). (*See* BEQ1018, 525:Figure 1; BEQ1035, 591:Figure 1; BEQ1012, 4520:2:3 and Figure 2; BEQ1002, ¶37.) Moreover, a POSA would have known that the rate at which an *E.*

coli host cell consumes and oxidizes a carbon source (e.g., glucose) closely correlates to the metabolic rate of that host cell. (*Id*.)

3. Glucose-limited fed-batch fermentation minimizes acetate accumulation and maximizes cell densities and recombinant protein production

To avoid this central obstacle (acetate accumulation) to recombinant protein production methods, scientists in the field had developed methods based on a fed-batch fermentation. (*See* BEQ1021, 1:2(11:2); BEQ1010, 947:2:2-948:1:1; BEQ1002, ¶39.) Fed-batch fermentation allowed for controlled addition of media components, "to control growth conditions, such as overflow metabolism, accumulation of toxic compounds and oxygen availability," to minimize acetate accumulation and increase cell mass. (*Id*.) Indeed, by 2000, "[f]ed-batch procedures ha[d] proved to be the most effective means of maximizing cell mass concentration." (BEQ1010, 947:2:2; BEQ1002, ¶39.) And, "controlled addition of the carbon source, e.g., by glucose limited fed-batch strategies" provided a simple means to control acetate accumulation. (*See* BEQ1021, 5:3(15:3)[3]; BEQ1010, 947:2:2-948:1:1; BEQ1002, ¶40.)

In a fed-batch process, a base media supports initial bacterial growth ("batch

[3] Pincites in parenthesis for BEQ1021 refer to page numbers as indicated on the label in the right-hand side in the bottom of the page.

phase"), and a feed media is added to prevent nutrient depletion and to sustain a protein production phase ("fed-batch phase"). (*See* BEQ1011, 1004:1:1; BEQ1002, ¶39.) To control acetate accumulation, researchers in the field, as of 2000, routinely used high glucose amounts during batch phase and low glucose amounts during fed-batch phase, to produce numerous pharmaceutically-important proteins. (*See* BEQ1021, 4:3(14:3); BEQ1010, 948:1:2; BEQ1020, 2:3; BEQ1002, ¶¶40-43.)

One of many examples is Seeger, which describes a fed-batch, HCDC fermentation process to produce a recombinant human growth factor, basic fibroblast growth factor ("bFGF"), in *E. coli*. (BEQ1010, 947, Abstract, 948:1:3; BEQ1002, ¶43.) Seeger avoided "accumulation of toxic levels of acetic acid" by using a three phase fed-batch process comprising a batch phase, characterized by unlimited *E. coli* growth (μ_{max} = 0.51 h^{-1}), followed by two fed-batch phases of successively-reduced growth rates (μ_{set} = 0.12 h^{-1} to 0.08 h^{-1}). (BEQ1010, 925:1:1-2:1, 950:2 Figure 3, 952:2:1; BEQ1002, ¶¶ 43, 55.) At the time of induction of bFGF polypeptide expression, Seeger shifted the growth rate from 0.12 h^{-1} to 0.08 h^{-1} which "was sufficient to prevent accumulation of acetic acid during fed-batch phase 2 and to allow expression of bFGF." (BEQ1010, 952:2:1; BEQ1002, ¶¶43, 57.) Thus, Seeger provided one of several examples of production of "more total and more soluble" recombinant protein by *limiting* glucose availability in HCDC

fermentation at the time of recombinant protein induction to limit growth rate. (BEQ1010 953:1:3; BEQ1002, ¶43.)

4. Control of recombinant protein expression used well-known inducible promoters, such as the phosphate-inducible promoter *phoA*

As of November 3, 2000, researchers in the field achieved high yields of recombinant proteins using inducible promoter systems. (BEQ1007, 145:2:1; BEQ1002, ¶45.) Inducible promoters, as compared to constitutive promoters, allow for separation of cell growth from the recombinant protein production phase and generally avoid the metabolic burden associated with coordinated cell growth and recombinant protein production. (BEQ1007, 145:1:3 and 145:2:1; BEQ1016, 16.1.1:1:4; BEQ1002, ¶45.) This facilitates increased cell mass accumulation before recombinant protein production and thus, higher total recombinant protein yields. (BEQ1007, 145:2:1; BEQ1002, ¶45.)

And researchers had available a number of inducible promoters (or inducible expression systems) suitable for *E. coli*. (BEQ1022, Table 4; BEQ1023 1996, Table 1; BEQ1002, ¶46.) For example, Makrides disclosed a list of twenty-nine inducible promoters, including *phoA*, a phosphate-depletion inducible promoter. (BEQ1023, Table 1; BEQ1002, ¶62.) The art provided guidance for choosing a promoter: 1) the promoter must be strong (e.g., "resulting in the accumulation of protein making up to 10-30% or more of the total cellular protein"); 2) "exhibit a

minimal level of basal transcriptional activity"; and 3) induction should be simple and cost-effective. (BEQ1023, 513:2:2-514:1:2; BEQ1002, ¶¶46, 62.) As confirmed by Dr. Rosenberg, a POSA aware of this guidance would have easily selected a suitable promoter from Makrides' twenty-nine commonly-used promoters. (BEQ1002, ¶¶46, 62, 129.)

For example, a POSA knew that the *phoA* promoter satisfied several of these criteria. (BEQ1022, Table 4; BEQ1023 1996, Table 1; BEQ1024, 48:1:Table I; BEQ1026, 163:2:4; BEQ1042, 11900:1:2 and Abstract; BEQ1002, ¶¶46, 62, 129.) Not only does the *phoA* promoter induce protein expression at "more than 1000-fold," it is "essentially silent," exhibiting minimal basal transcriptional activity. (BEQ1022, 5:2:2; BEQ1002, ¶47.) And because induction is simple, requiring only limiting the phosphate concentration, the promoter had been used routinely to produce several recombinant proteins in HCDC. (*See* BEQ1022, 5:2:2; BEQ 1023, 513:2:2-514:1:2; BEQ1040, Abstract and 4892:2:2; BEQ1041, Abstract; BEQ1042, 11900:1:2 and Abstract; and BEQ1026, Abstract; BEQ1002, ¶¶47, 62.)

C. The '602 patent

Against this background in which the prior art described well-established methods for avoiding acetate accumulation to increase recombinant protein yields in "the most important" host cell (*E. coli*) in the field of recombinant protein production, Andersen *et al.* filed a patent application. The '602 patent recites

methods "for increasing product yield of a polypeptide of interest produced by recombinant host cells" and issued on April 6, 2004. (BEQ1001, Abstract.) The '602 patent asserts its earliest priority claim to November 3, 2000. According to the Office's electronic assignment records, Genentech, Inc. ("Genentech" or "Patent Owner") owns the '602 patent by assignment.

1. The '602 patent claims

The '602 patent has 39 issued claims, 3 independent and 36 dependent. Challenged independent claim 1 is reproduced below:

> 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.

(BEQ1001, 18:11-23.)

Challenged independent claim 16 is similar to claim 1. It differs in that it specifies that the host cell is *E. coli* and that the expressed polypeptide is a properly folded antibody, growth factor, or mammalian protease, and it does not recite the wherein clauses of claim 1.[4] (*Id.*, 18:58-67.)

Challenged independent claim 25 is similar to claim 1. It differs in that it specifies that the polypeptide is mammalian and does not recite the wherein clauses of claim 1.[5] (*Id.*, 19:20-28.)

The challenged dependent claims recite several art-recognized aspects of recombinant protein production, and these claims generally group as follows: 3,

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[4] Patent Owner amended step (b) during prosecution as follows: "reducing the metabolic rate of the cultured recombinant host cells at the time of induction of antibody, growth factor, or protease expression, wherein the reduction in metabolic rate results in increased yield of properly folded antibody, growth factor, or protease." (BEQ1004, 28 (amendments underlined).) Despite the Office's acknowledgment of the 2003-08-01 Amendment, the '602 patent issued *without* Patent Owner's amendments. (BEQ1004, 6.)

[5] Patent Owner amended step (b) during prosecution as shown in note 3 *supra*; however, the '602 patent issued *without* Patent Owner's amendments. (BEQ1004, 29, 6.)

20, and 27 ("reducing the metabolic rate comprises decreasing available carbon/energy sources to the host cells"); 4 and 28[6] ("the carbon/energy source is glucose"); 6, 22, and 30 ("the metabolic rate is reduced by about half in step (b)"); 7 and 31 ("growing the cells to maximum density in step (a)"); 8 and 32 ("the metabolic rate is reduced by about half in step (b)"); 9 and 33 ("the recombinant host cell is a bacterial cell selected from the group consisting of *E. coli* and Salmonella"); 10, 23, and 34 ("the inducible system is a phosphate depletion inducible system"); 11 and 35 ("the polypeptide is assembled in the host cell"); 12 and 36 ("the polypeptide is secreted into the periplasm of the host cell"); 13 and 37 ("the polypeptide is an antibody"); 14 and 38 ("the polypeptide is selected from the group consisting of an Fab'_2 antibody and an Fab antibody or other form of antibody[7]"); 15, 24, and 39 ("the metabolic and growth rate of the host cells is

[6] Despite an amendment to alter the dependency of claim 28 (then claim 27) from claim 25 to 27 (then claims 24 and 26) during prosecution, the '602 patent issued without this amendment. (BEQ1004, 29, 6.)

[7] Patent Owner amended claims 14 and 38 (then claims 13 and 36, respectively) during prosecution to remove the phrase "or other form of antibody" and to alter dependency from claims 1 and 25 to 13 and 37, respectively (then claims 1 and 24 to 38 and 39, respectively). (BEQ1004, 27 and 30.) However, the

maximized in step (a)"); 18 ("the antibody is an Fab antibody").

2. Summary of the prosecution of the '602 patent

Patent Owner filed the '602 patent as U.S. Patent Appl. No. 10/000,655 ("the '655 application"), claiming priority to U.S. Provisional Patent Appl. No. 60/245,962. (BEQ1001, 1:5-7.) The originally-filed claims were directed to, *inter alia*, methods for increasing product yield of a polypeptide of interest produced by recombinant host cells, wherein expression of the polypeptide by the recombinant host cells is regulated by an inducible system, comprising (a) culturing the recombinant host cells under conditions of high metabolic and growth rate; and (b) reducing metabolic rate of the recombinant host cells at the time of induction. (BEQ1004, 325.) Original dependent claims recited mostly identical limitations as those discussed above. (*Id.*, 325-27.)

Upon examination, the Examiner rejected the claims as, *inter alia*, obvious over "Knorre [(BEQ1005), which] specifically teaches a growth rate shift from 0.45 h^{-1} to 0.11 h^{-1} (page 303, second full paragraph), which is about ½." (BEQ1004, 169.) And while the Examiner noted that Knorre did not teach inducible expression, a second reference (Skerra (BEQ1048)) taught inducible

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patent issued with this phrase intact and the dependency unchanged. (BEQ1004, 6.)

expression of a Fab antibody in *E. coli* host cells "when the culture has reached a density considered to be optimal for expression of the recombinant protein." (*Id.*)

In response, Patent Owner amended claim 1 to require a properly-folded polypeptide of interest and to specify how the metabolic rate is reduced (reducing the metabolic rate comprises reducing the feed rate of the carbon/energy source, or reducing the amount of available oxygen, or both). (BEQ1004, 138.) Patent Owner then admitted that "both Knorre and Skerra describe good recombinant protein expression at a reduced growth rate of host cells, either by limiting glucose (Knorre/Skerra) and/or oxygen (Knorre)," and attempted to distinguish these prior art references on the basis that "neither coordinate induction of protein expression at the time of reducing the *metabolic* rate." (*Id.*,146-47.)

The Examiner maintained the rejection, reasoning that "combining the teachings of Knorre with *any* teaching of an inducible expression system, to *induce protein expression in the fed-batch phase*, at the time *when the metabolic rate (i.e. specific growth rate) of the host cells is reduced* and protein expression is optimal" would have been obvious to a POSA. (BEQ1004, 46 (emphases added).) Responding to Patent Owner's argument that the combination of Knorre and Skerra does not "teach coordinate induction of protein expression at the time of reducing the metabolic rate," the Examiner pointed out that "Applicant concedes, Skerra teaches induction of protein expression as biomass approaches maximum . .

. which is precisely the point at which metabolic rate begins to decline in the fed-batch system of Knorre." (*Id.*, 47-48.)

Patent Owner next amended claims 1, 16, and 25 to include the phrase "wherein the reduction in metabolic rate results in increased yield of properly folded polypeptide"; however, this amendment does not appear in issued claims 16 and 25. (BEQ1004, 26-29.) And, Patent Owner argued and admitted that the prior art taught reducing metabolic rates as basic background science:

> *Knorre represents a basic teaching involving reducing metabolic rates* early in fermentations (about 10 to 20 OD) to prevent toxic byproduct accumulation, such as acetate. Avoiding toxic byproduct accumulation is a key goal of Knorre, along with controlling oxygen demand, as seen from page 300, second paragraph, page 301, first full paragraph, page 305, Figure 5, and the summary on page 306 of Knorre. Likewise, *inducing product expression at near maximum cell densities* (about 200 OD), as Skerra and others disclose, *is a basic teaching in this field. This much represented by the prior art can be acknowledged as basic background science*.

(*Id.*, 32:4 (emphases added); *see also* 33:3 ("Knorre only teaches reducing metabolic rate relatively early in the fermentation . . . [not] a further reduction at the time of art-recognized induction of protein expression.")

Patent Owner sought to distinguish Knorre, stating that the claimed method allegedly advances the art by "reducing metabolic rate (beyond the initial reduction

taught by Knorre needed to prevent byproduct accumulation) at or near the time of induction of protein expression" and allegedly "confers an unexpected benefit on the fermentation (increased yield of properly folded product). . . . This is a feature not taught or suggested by any of the cited references." (*Id.*, 33.) Then the Examiner allowed the application, noting that "it would not [have] be[en] obvious to the skilled artisan to reduce metabolic rate of the culture at the time of induction of polypeptide expression." (BEQ1004, 8:3 (emphasis in original).)

So, during prosecution, Patent Owner admitted that 1) reducing the metabolic rate as a fermentation strategy and 2) inducing product expression at or near maximal cell densities "can be acknowledged as basic background science." (*Id.*, 32:4.) And, Patent Owner explicitly acknowledged that Knorre "teaches reducing metabolic rates relatively early in the fermentation," by "controlling the growth rate" through a reduction in glucose feeding. (*Id.*, 32, 33, and 148.) Patent Owner admitted this, and the Examiner acquiesced having *only* the Knorre and Skerra references before him.

However, armed with the additional prior art discussed in this Petition, the Examiner would not have so relented. This is because the newly cited prior art in this Petition describes—in one reference—not just reducing metabolic rate of the culture *at the time of induction of* polypeptide expression, but also increasing yield

of properly folded polypeptide. This prior art is exactly what the Examiner did not have before him. As such, the challenged claims should not stand.

V. Claim construction

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretations in light of the specification of the '602 patent. *See Cuozzo Speed Techs., LLC, v. Lee*, No. 15-446 (2016). The terms of the '602 patent, except those discussed below, are plain on their face and should be construed to have their ordinary meanings. *See Chef America, Inc. v. Lamb-Weston, Inc*., 358 F.3d 1371, 1373 (Fed. Cir. 2004).

Claim 1 recites an intended result: Claim 1 recites the phrase "*wherein* the reduction in metabolic rate results in increased yield of properly folded polypeptide."[8] (BEQ1001, 18:22-23 (emphasis added).) The transitional word "wherein" signifies an intended outcome of the positively recited method step of

[8] As discussed in n.4 and 5 *supra*, Patent Owner amended step (b) of claims 16 and 25 to include this phrase. (BEQ1004, 27-29 (amendments underlined).) Yet, the '602 patent issued without it. Because claims 16 and 25 issued without this phrase, it cannot limit the scope of the claims. However, even if these claims contained this phrase, it is an intended outcome and imparts no patentable weight to the claims.

reducing the metabolic rate of the cultured recombinant host cells at the time of induction of polypeptide expression. Therefore, the phrase "wherein the reduction in metabolic rate results in increased yield of properly folded polypeptide" imparts no patentable weight to claim 1. *See Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n.*, 988 F.2d 1165, 1172 (Fed. Cir. 1993) ("[a] 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."); *see also Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) (finding that a clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited).

To the extent that the Board determines that this intended outcome (increased yield of properly-folded polypeptide) is a limitation included in claim 1, it should be construed according to its plain and ordinary meaning in light of the specification as follows[9]:

The specification explicitly defines "product yield" as "the quantity of useful recombinant protein produced by a fermentation system." (BEQ1001, 5:1-3.) The '602 patent further states that "the metabolic rate shift increases the yield of

[9] Petitioner has analyzed the unpatentability of claim 1 giving weight to the intended outcome, regardless.

properly folded and, if appropriate, assembled protein," effected "by shifting the metabolic rate compared to the titers obtained by running the fermentation at a previously favorable, constant metabolic rate." (BEQ1001, 3:20-23, 4:3-6.) Thus, the specification compares product yield from the claimed methods (i.e., with a metabolic rate reduction) to yields obtained without reduction. (BEQ1002, ¶25.)

The '602 patent also assesses the quantity of a polypeptide by obtaining "the soluble fraction of the [cell] lysate." (BEQ1001, 15:60-16:14.) A POSA would have understood that the soluble fraction of the cell lysate would contain soluble (i.e., properly-folded) polypeptides. (BEQ1010, 949:1:4 and Figure 2 (legend); BEQ1002, ¶26.) Consistent with the specification then, a POSA would have understood the broadest reasonable interpretation of "increased yield of properly folded polypeptide" to mean increasing the total quantity of properly-folded (i.e., useful, soluble) polypeptide produced by a fermentation method that includes a metabolic rate shift, as compared to a fermentation method that does not incorporate such a shift. (BEQ1002, ¶26.)

Culturing the recombinant host cells under conditions of high metabolic and growth rate: Claims 1, 16, and 25 recite "culturing [the recombinant][10] host cells under conditions of high metabolic and growth rate." (BEQ1001, 18:16-17, 63-64, 19:25-26.) The specification explicitly defines this phrase:

> "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 metabolic rate to increase "product yield."

(BEQ1001, 4:49-55.)

The patent further provides: "prior to expression of the polypeptide of interest, the host cells inoculated into the fermentor are grown under favorable growth conditions, e.g., with all of the available oxygen and carbon/energy sources (or, preferably, source), along with essential nutrients and pH control, necessary for logarithmic growth." (BEQ1001, 13:39-44.)

Thus, a POSA would have understood the phrase "culturing [the

[10] Claim 16 does not recite the phrase "the recombinant" found in claims 1 and 25. The inclusion of this phrase, or not, does not alter the proposed construction in the text.

recombinant] host cells under high metabolic and growth rate" to mean culturing the cells under conditions that favor growth, such that the cells have rapid growth and metabolic rates prior to the step of reducing the metabolic rate. (BEQ1002, ¶27.) This interpretation encompasses high metabolic and growth rates at *any* point before the step of reducing the metabolic rate in step (b). (BEQ1002, ¶28.)[11]

Reducing the metabolic rate: Claim 1 recites "reducing the metabolic rate of the cultured recombinant host cells" and claims 16 and 25 recite "reducing metabolic rate of the recombinant host cells." (BEQ1001, 18:18-19, 18:65-66, 19:27-28.)

The '602 patent recites a bifurcated definition of this phrase depending on whether the cells are (i) undergoing rapid growth and expansion, or (ii) are already in a reduced growth state. (*See* BEQ1001, 4:12-18.) For (i), reducing the metabolic rate means altering the fermentation conditions to reduce or stop the growth/expansion of cells. (*See id.*, 4:12-15.) For (ii), reducing the metabolic rate

[11] Patent Owner asserted during prosecution that "a reduction of the metabolic rate . . . further increases protein yield even 'for the case of cells already in a reduced growth state.'" (BEQ1004, 147). Patent Owner's argument acknowledges, therefore, that step (a) does not need to occur immediately before step (b).

means reducing the oxygen uptake rate and the corresponding uptake of the corresponding carbon/energy source by the cells. (*See id.*, 4:15-18.)

The '602 patent also 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 reactants***. So reduction of metabolic rate can result from inter alia (1) reducing the amount of available oxygen in the cell culture (i.e., fermentation); (2) reducing the amount of available carbon/energy sources; or (3) reducing both.***

(BEQ1001, 4:18-26 (emphasis added).) The patent further elaborates:

> After reaching target cell density, two manipulations of the fermentation occur. The first is to provide the signal to induce expression of the polypeptide of interest . . . . The second manipulation (which can result from the first) is to downshift or reduce the host cell metabolic rate. Since during logarithmic growth the metabolic rate is directly proportional to availability of oxygen and a carbon/energy source, reducing the levels of available oxygen or carbon/energy sources, or both, will reduce metabolic rate.

(BEQ1001, 13:49-58.)

Thus, a POSA would have understood the phrase "reducing the metabolic rate" to mean 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. (BEQ1002, ¶30.) And this metabolic-rate reduction is achieved by reducing the amount of available oxygen in the fermentation, reducing the amount of available carbon/energy source, or both. (*Id*.)

Not only is this interpretation consistent with the '602 patent definition, it is also consistent with Patent Owner's statements during prosecution. (*Id*.) For example, Patent Owner distinguished an Examiner-cited prior art reference (Knorre (BEQ1005)) by pointing to the specification and stating "that a reduction in the metabolic rate by decreasing the rate of oxygen uptake and/or rate of uptake of the carbon source further increases protein yield even 'for the case of cells already in a reduced growth state' (see specification at page 6, lines 9-11)." (BEQ1004, 147.)

"Assembled" polypeptide: Claims 11 and 35 recite that "the polypeptide is assembled in the host cell." (BEQ1001, 18:46-47, 20:20-21.) While not defined, the '602 patent states that "the metabolic rate shift increases the yield of properly folded and, if appropriate, assembled protein" and that "[a]ctivity assays can reveal properly folded or assembled functional protein." (BEQ1001, 3:21-23, 5:11-12.) The specification also states "properly assembled antibody may bind antigen,

preferably with similar affinity as a control antibody." (*Id.*, 5:12-14). And, "[a] properly assembly [sic] growth factor, hormone, or cytokine will bind its cognate receptor and induce cell signaling, again in a manner comparable to that of wild-type." (*Id.*, 5:14-16). Thus, a POSA would have understood the term "assembled" to mean the polypeptide is produced by the cell as functional. (BEQ1002, ¶31.)

VI. Identification of challenge (37 C.F.R. § 42.104(b))

Petitioner requests IPR of claims 1, 3-4, 6-16, 18, 20, 22-25, 27-28, and 30-39 of the '602 patent on the grounds of unpatentability listed in the table below. Copies of the cited prior art references accompany the Petition. 37 C.F.R. § 42.6(c). The Declaration of Dr. Morris Rosenberg (BEQ1002), an expert in the field of recombinant polypeptide production, with almost 30 years of experience, accompanies this Petition. Each of the Grounds shows a reasonable likelihood that one or more of the '602 patent claims is unpatentable.

Ground	35 U.S.C. Section (pre-3/16/2013)	Claims	Index of References
1	102(b)	1, 3-4, 6, 9, 15-16, 20, 22, 24-25, 27-28, 30, 33, and 39	Seeger (BEQ1010)
2	103(a)	7-8 and 31-32	Seeger (BEQ1010)
3	103(a)	10, 12, 23, 34, and 36	Seeger (BEQ1010) and Makrides (BEQ1023)
4	103(a)	11, 13-14, 18, 35, and 37-38	Seeger (BEQ1010) and Cabilly (BEQ1032)

A. Ground 1: Seeger anticipates claims 1, 3-4, 6, 9, 15-16, 20, 22, 24-25, 27-28, 30, 33, and 39

Seeger anticipates claims 1, 3-4, 6, 9, 15-16, 20, 22, 24-25, 27-28, 30, 33, and 39. (BEQ1002, ¶¶68-111.) Seeger published on October 10, 1995, and qualifies as prior art under 35 U.S.C. § 102(b) to the '602 patent claims. As confirmed by Dr. Rosenberg, Seeger discloses every element of these claims, arranged as claimed and in a manner enabling to a POSA. (*Id*.)

1. Seeger anticipates claim 1

During prosecution, Patent Owner admitted that the cited prior art lacked only a teaching to reduce metabolic rate *at the time of induction* of polypeptide expression. (*See* § IV.C.2.) But, as discussed below, 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. Furthermore, Seeger's metabolic rate shift results in increased yield of soluble, i.e., properly-folded, bFGF polypeptide.

Claim 1 also recites the phrase "*wherein* the reduction in metabolic rate results in increased yield of properly folded polypeptide." (BEQ1001, 18:22-23.) (emphasis added). As discussed in § V., this feature is an intended result of the positively-recited method steps—namely, reducing the metabolic rate of the cultured recombinant host cells at the time of induction of polypeptide

expression—and not a separate or independent limitation. *Minton*, 336 F.3d at 1381; *Texas Instruments*, 988 F.2d at 1172. However, to the extent that the Board construes claim 1 to include this limitation, Seeger still renders claim 1 anticipated, as discussed below.

(a) Seeger teaches expression of a polypeptide of interest in recombinant host cells regulated by an inducible system

Seeger describes a temperature-inducible expression system "in high-cell density cultures of *recombinant E. coli* synthesizing basic fibroblast growth factor (bFGF[12])." (BEQ1010, 948:1:3 (emphases added); BEQ1002, ¶¶53, 68.) Specifically, Seeger expressed bFGF "using *Escherichia coli* [K12 strain] TG1 as host organism," in a fed-batch procedure induced by "a temperature shift from 30 to 42°C." (BEQ1010, 947, Abstract, 951:2:1; BEQ1002, ¶¶52, 69.) Seeger used the temperature-inducible expression vector pCYTEXP1 with bFGF under control of the $\lambda P_R P_L$ promoter. (BEQ1010, 949:2:3, 951:1-3; BEQ1002, ¶¶52, 69.)

So, Seeger specifically discloses expression of a polypeptide of interest (bFGF) by recombinant host cells (*E. coli*) regulated by an inducible system (temperature-inducible promoter $\lambda P_R P_L$). (BEQ1002, ¶69.)

[12] The '602 patent lists bFGF as an exemplary polypeptide of interest, growth factor, *and* mammalian polypeptide. (BEQ1001, 5:20-27, 51.)

(b) Seeger teaches culturing the recombinant host cells under conditions of high metabolic and growth rate

Seeger cultured the recombinant *E. coli* host cells under conditions of high metabolic and growth rate (BEQ1010, 948:2:3-949:1:3 and 951:2:1; BEQ1002, ¶¶53, 70.) As discussed above, the '602 patent explicitly defines this phase as "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." (BEQ1001, 4:50-54 (emphases added); BEQ1002, ¶70.)

Seeger describes cultivating the cells in batch phase "with *maximal specific growth rates* (TG1:pλFGFB: $\mu_{set} = 0.51\ h^{-1}$ . . .)" with an initial glucose concentration of 25 g/L. (BEQ1010, 951:2:1, 950:2, Figure 3 legend (referring to batch mode as "*unlimited growth* . . . ($\mu_{max} = 0.51\ h^{-1}$)") (emphases added); BEQ1002, ¶¶53, 86.) Moreover, Seeger states that the "dissolved oxygen concentration was maintained at 40% of air saturation by increasing the stirrer speed," during this initial, batch phase of the high-cell-density fermentation. (BEQ1010, 948:2:3; BEQ1002, ¶¶53, 70.) Dr. Rosenberg confirmed that these conditions would have favored maximal or unlimited growth. (BEQ1002, ¶¶53, 70.) Thus, Seeger establishes culture conditions to favor maximal or unlimited growth by providing unrestricted or relatively high feed rates of nutrients glucose and oxygen. (BEQ1002, ¶¶53, 70.)

Moreover, Patent Owner acknowledges the correlation between high growth rate and metabolic rate in the ’602 patent: “during logarithmic growth the metabolic rate is directly proportional to availability of oxygen and a carbon/energy source.” (BEQ1001, 13:54-58; BEQ1002, ¶87.) Explicit statements made in the public record, i.e., in the patent itself or its prosecution history are binding on Patent Owner. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582-1583 (Fed. Cir. 1996); *In re Cygnus Telecomm. Tech., LLC, Patent Litig.*, 536 F.3d 1343, 1354 (Fed. Cir. 2008). As such, Patent Owner cannot contend that Seeger’s supply of unrestricted or relatively high feed rates of nutrients glucose and oxygen to favor maximal or unlimited growth—which squarely aligns with the patent’s explicit definition and teachings—are not conditions of high metabolic and growth rate. And as confirmed by Dr. Rosenberg, a POSA would have also known that when cells are growing at a high specific growth rate, their metabolic rate is also high. (BEQ1047, 847:2:2; BEQ1002, ¶70.)

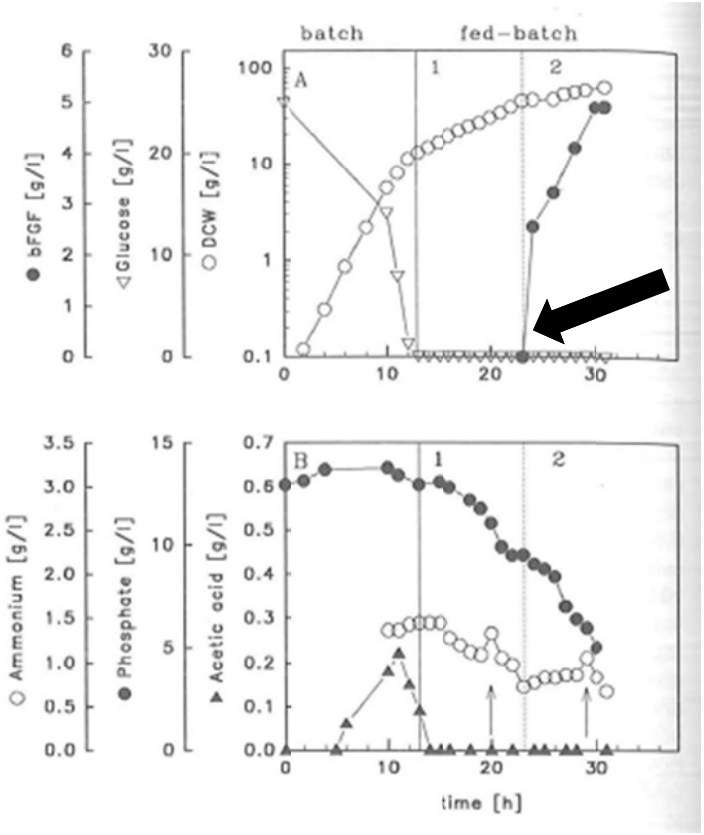
Therefore, Seeger describes culturing recombinant host cells under conditions of high metabolic and growth rate as recited in claim 1. (BEQ1002, ¶70.)

(c) Seeger teaches reducing the metabolic rate of the cultured recombinant host cells at the time of induction of polypeptide expression

Seeger describes reducing the metabolic rate of the cultured recombinant *E. coli* host cells at the time of induction of bFGF. (BEQ1010, 951:2:1; BEQ1002, ¶¶55, 72.) As discussed above in § V., the '602 patent defines "reducing the metabolic rate" for cells already in a reduced growth state as "the rates of oxygen uptake and the corresponding rates of uptake of a carbon/energy source are reduced." (BEQ1001, 4:16-18; BEQ1002, ¶29.) And this is achieved by reducing the amount of available oxygen in the fermentation, reducing the amount of available carbon/energy source, or both. (BEQ1002, ¶29.)

Seeger reduces the metabolic rate of its cultured recombinant host cells by reducing the amount of available glucose during the fed-batch fermentation phase. Specifically, following unlimited growth during batch phase and consumption of available glucose, Seeger initiated "***carbon-limited growth*** . . . with a constant specific growth rate of $\mu_{set} = 0.12\ h^{-1}$ (phase 1; see *Table 2*)." (BEQ1010, 951:2:1 (emphasis added); *see also* 950:2, Figure 3 legend ("After unlimited growth during batch mode ($\mu_{max} = 0.51\ h^{-1}$), fed-batch mode was started with a desired specific growth rate of $\mu_{set} = 0.12\ h^{-1}$ (phase 1)."; BEQ1002, ¶¶54, 71.) Thus, a POSA would have considered cells growing in Seeger's fed-batch phase 1 to be in a reduced growth state. (BEQ1002, ¶71.)

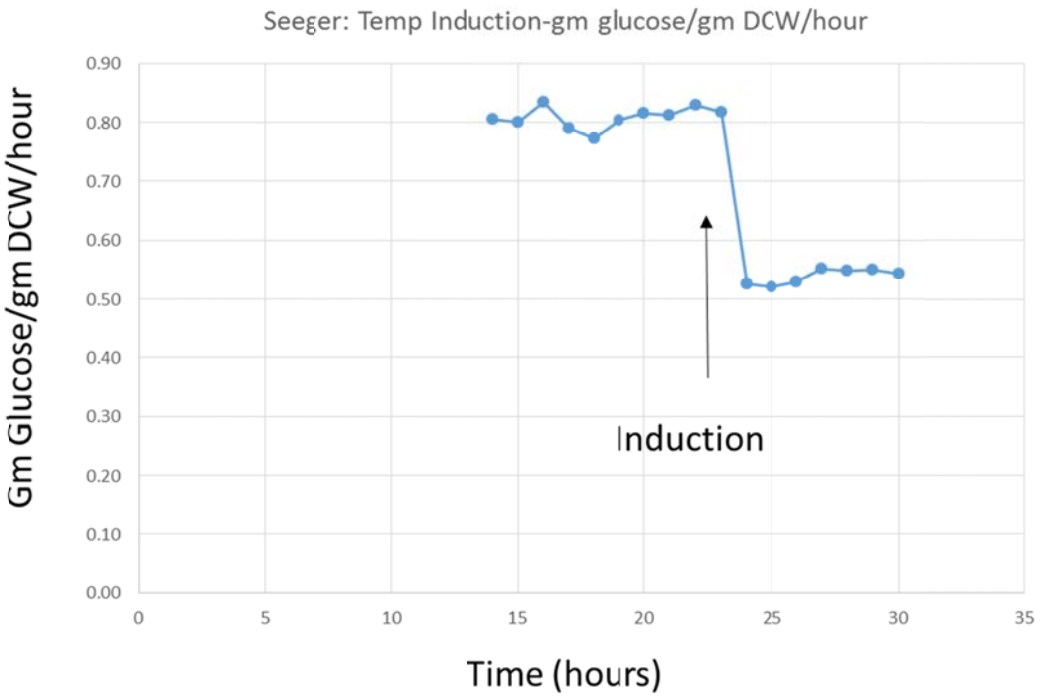
Then, at the same time as induction of bFGF, Seeger *limited available glucose further* "in phase 2 of the fed-batch process. . . . to [a specific growth rate of] $\mu_{set} = 0.08\ h^{-1}$ after the temperature shift to 42°C." (BEQ1010, 952:2:1(emphasis added); *see also* 951:2:2 ("Product formation (phase 2; *Figures 3 and 4*) was induced . . . by temperature shift from 30°C to 42°C (TG1:pλFGFB) . . . ."); BEQ1002, ¶¶55, 72.) Figure 3, reproduced below, shows expression of bFGF at the same time as fed-batch phase 2 initiation where Seeger reduced the amount of available glucose (bold arrow added).



Patent Owner admitted during prosecution that reducing the metabolic rate as a fermentation strategy "can be acknowledged as basic background science" and

explicitly acknowledged that Knorre "teaches reducing metabolic rates" by "controlling the growth rate" through a reduction in glucose feeding, which is exactly what Seeger did. (*See* § IV.C.2.) *Vitronics*, 90 F.3d at 1582-1583. And Dr. Rosenberg confirmed that Seeger's reduction in the amount of available glucose in fed-batch phase 1 and further limitation in fed-batch phase 2 resulted in a decreased rate of glucose uptake by the recombinant host cells. (BEQ1002, ¶71.)

Using the data in Seeger's Figure 3 and Table 2, Dr. Rosenberg calculated the specific glucose consumption rate for the temperature-induced recombinant *E. coli* cells. (BEQ1002, ¶56.) As reproduced below, the specific glucose consumption rate decreases on a per-cell basis from about 0.8 g glucose/g dry cell weight/hour in fed-batch phase 1 to about 0.54 g glucose/g dry cell weight/hour in fed-batch phase 2. (*Id*.) This decrease occurs at the time of induction of bFGF and is maintained through fed-batch phase 2. (*Id*.)



Therefore, Seeger describes reducing the metabolic rate of recombinant host cells in a reduced growth state by reducing the amount of available glucose, and consequently the rate of glucose uptake by the recombinant host cells[13], at the time of induction, as recited in claim 1. (BEQ1002, ¶¶52-57, 71-72.)

[13] To the extent the Board reads "reducing the metabolic rate" of cells in a reduced growth state as requiring a reduction in both oxygen uptake rate and glucose uptake rate, a POSA would have understood that Seeger's reduction in glucose uptake rate also resulted in a reduction in the oxygen uptake rate. (BEQ 1035, Figure 1; BEQ1002, ¶71.)

(d) Seeger reduces the metabolic rate by reducing the feed rate of the carbon/energy source

Seeger describes reducing the metabolic rate of recombinant *E. coli* TG1 cells by reducing the feed rate of glucose. (BEQ1010, 952:2:2; *see also* 950:2, Figure 3 legend; BEQ1002, ¶¶56, 69, 71, 76.) Following unlimited growth during batch phase, Seeger adjusted glucose feeding rate "in such a way that ***carbon-limited growth*** continued with a constant specific growth rate of $\mu_{set} = 0.12\ h^{-1}$ (phase 1; see *Table 2*)." (BEQ1010, 951:2:1 (bolded emphasis added); *see also* 950:2, Figure 3 legend; BEQ1002, ¶¶54, 71.) Seeger then reduced the glucose feeding rate further (to $\mu_{set} = 0.08\ h^{-1}$) at the time of induction of bFGF. (BEQ1010, 952:2:1; BEQ1002, ¶¶55, 71.)

Therefore, Seeger describes reducing the metabolic rate by reducing the feed rate of glucose. (BEQ1002, ¶71.)

(e) Seeger's method of reducing metabolic rate results in increased yield of properly-folded polypeptide

As discussed in § V., the phrase "wherein the reduction in metabolic rate results in increased yield of properly folded polypeptide" imparts no patentable weight to claim 1 because it is an intended result. However, to the extent that the Board considers that it is a limitation, it is interpreted as increasing the total quantity of properly-folded (i.e., useful, soluble) polypeptide produced by a fermentation system using a metabolic rate shift compared to a fermentation

system that does not. (BEQ1001, 5:1-3; BEQ1002, ¶26.) Seeger provides such an increase.

When not incorporating a metabolic rate shift, i.e., maintaining the glucose feeding rate (μ_{set}) at 0.12 h^{-1} in fed-batch phases 1 and 2, Seeger describes the immediate accumulation of acetic acid and subsequent accumulation of glucose (BEQ1010, 952:1:1-2:1; BEQ1002, ¶¶55, 73.) Dr. Rosenberg confirmed that Seeger was unable to express bFGF at this growth rate because of acetic acid accumulation. (BEQ1002, ¶¶55, 73.) To minimize the detrimental acetic acid effect on bFGF expression, Seeger further reduced the glucose feeding rate (and, as such, the metabolic rate) at the time of induction "in phase 2 of the fed-batch process" to μ_{set} = 0.08 h^{-1}. (BEQ1010, 951:2:2; BEQ1002, ¶¶ 55, 73.) This reduction in metabolic rate "was sufficient ***to prevent accumulation of acetic acid during fed-batch phase 2*** and ***to allow expression of bFGF*** (*Figure 3*). (BEQ1010, 952:2:1 (bolded emphases added); BEQ1002, ¶¶43, 57, 73.) And, Seeger quantified the yield of bFGF following temperature shift induction at "70% of the bFGF produced . . . present in the soluble cell fraction," where bFGF is properly folded. (BEQ1010, 953:1:2 (bolded emphases added); BEQ1002, ¶¶57, 73.) Thus, as confirmed by Dr. Rosenberg, Seeger's fermentation strategy achieved increased production of soluble, properly-folded bFGF. (BEQ1002, ¶73.)

(f) A POSA would have been able to use Seeger's fermentation strategy without undue experimentation

Dr. Rosenberg confirmed that a POSA would have been able to use Seeger's high-cell-density fed-batch fermentation strategy to increase the yield of soluble, properly-folded bFGF without undue experimentation. (BEQ1002, ¶74.) This is because Seeger provides a specific disclosure of the methods for high-cell-density fed-batch fermentation. (BEQ1010, 947:2:2; BEQ1002, ¶74.) Moreover, a POSA would have viewed using Seeger's fed-batch fermentation strategy of carbon-limited growth to minimize acetate production as well-known and routine in the art. (BEQ1010, 947:2:2- 948:1:3; BEQ1011, 1004:1:1; BEQ1021, 1:2(11:2) and 5:4 (15:4); BEQ1019, 1079:1:1; BEQ1002, ¶¶39-44, 74.) And because the recombinant protein production field was well-established in November 3, 2000, and fed-batch fermentation strategies like Seeger's had been in use since at least the early 1990s, a POSA would have had experience, and a high level of predictability, in producing recombinant proteins in high-cell-density fed-batch fermentations as those described in Seeger. Thus, a POSA would not have had to perform undue experimentation to use Seeger's method of high-cell-density fed-batch fermentation. (BEQ1002, ¶74; *see*, *e.g.*, BEQ1010, 947:2:2- 948:1:3; BEQ1011, 1004:1:1; BEQ1021, 1:2(11:2) and 5:4 (15:4); BEQ1019, 1079:1:1.)

2. Seeger anticipates claims 3-4, 6, 9, 15-16, 20, 22, 24-25, 27-28, 30, 33, and 39

Claim 16: Claim 16 differs from claim 1 in that claim 16 recites "a properly folded antibody, growth factor, or mammalian protease produced by a recombinant *E. coli* host cell" instead of, e.g., "a properly folded polypeptide of interest" and "recombinant host cells." (BEQ1001, 18:58-60 and 11-13.) As discussed above for claim 1, Seeger anticipates claim 1 because, *inter alia*, it describes a method of increasing the yield of soluble, properly-folded growth factor bFGF produced by recombinant *E. coli* host cells. (BEQ1010, 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; BEQ1002, ¶¶ 69-73, 88-89.) Thus, for the same reasons that Seeger anticipates the broader polypeptide genus of claim 1, it also anticipates the growth factor species or subgenus of claim 16. (BEQ1002, ¶¶88-89.) Moreover, as confirmed by Dr. Rosenberg, Seeger explicitly discloses the method steps of claim 16 arranged as claimed and in a manner enabling to a POSA. (*Id.*)

Claim 25: Claim 25 differs from claim 1 in that claim 25 recites a "mammalian polypeptide of interest" instead of a "polypeptide of interest." (BEQ1001, 19:20-21 and 18:12.) As discussed above for claim 1, Seeger anticipates claim 1 because, *inter alia*, it describes a method of increasing the yield of soluble, properly-folded mammalian polypeptide bFGF produced by recombinant *E. coli* host cells. (BEQ1010, 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; BEQ1002 ¶¶ 69-73, 98-99.) Thus, for the same reasons that Seeger anticipates the broader genus of claim 1 (polypeptide of interest), it also anticipates the species or subgenus of claim 25 (mammalian polypeptide of interest) because bFGF is a human polypeptide. (BEQ1010, 947, Abstract; BEQ1002, ¶99.) Moreover, as confirmed by Dr. Rosenberg, Seeger explicitly discloses the method steps of claim 25 arranged as claimed and in a manner enabling to a POSA, for the same reasons as discussed above for claim 1. (BEQ1002, ¶¶98-99.)

Claims 3, 20, and 27: As discussed above, Seeger anticipates claims 1, 16, and 25. Claims 3, 20, and 27 depend from claims 1, 16, and 25, respectively, and further specify that "reducing the metabolic rate comprises decreasing available carbon/energy sources to the host cells." (BEQ1001, 18:27-29, 19:8-10, and 19:32-34.) Seeger describes reducing the metabolic rate of recombinant *E. coli* TG1 cells by decreasing available glucose from fed-batch phase 1 ($\mu_{set} = 0.12\ h^{-1}$) to phase 2 ($\mu_{set} = 0.08\ h^{-1}$). (BEQ1010, 951:2:1-2 *see also* 950:2, Figure 3 legend; BEQ1002, ¶¶76, 92, 102.) So, Seeger describes decreasing available glucose to maintain carbon-limited growth and anticipates claims 3, 20, and 27. (BEQ1002, ¶¶75-76, 90-92, 100-102.)

Claims 4 and 28: As discussed above, Seeger anticipates claims 1 and 25. Claims 4 and 28 depend indirectly from claims 1 and 25, respectively, and further

specify that "the carbon/energy source is glucose." (BEQ1001, 18:30-31, 19:11-12, 20:1-2.) Seeger describes reducing the metabolic rate of recombinant *E. coli* TG1 cells by decreasing available glucose, anticipating claims 4 and 28. (BEQ1010, 949:1:1, 950:2, Figure 3 legend, 952:1, Table 2; BEQ1002, ¶¶77-78, 103-104.)

Claims 6, 22, and 30: As discussed above, Seeger anticipates claims 1, 16, and 25. Claims 6, 22, and 30 depend from claims 1, 16, and 25, respectively, and further specify that "the metabolic rate is reduced by about half in step (b)." (BEQ1001, 18:35-36, 19:13-14, 20:7-8.) As discussed in § VI.A.1(c)-(d), Seeger describes reducing the metabolic rate of recombinant *E. coli* TG1 cells by reducing the glucose feeding rate at the time of induction of bFGF expression. (BEQ1010, 947, Abstract, 948:1:3; 948, Table 1, 948:2:1-3, 950:2, Figure 3 legend, 951:2:1-2, 952:1:1-952:2:2, 953:1:1; BEQ1002, ¶¶69-73, 89.) As confirmed by Dr. Rosenberg, Seeger decreased the metabolic rate by about half. (BEQ1002, ¶¶81, 94, 106.) This is because a POSA would have understood that a magnitude of change in glucose uptake rate or oxygen uptake rate can serve as a proxy for the magnitude of change in metabolic rate. (BEQ1002, ¶81.) Indeed, the '602 patent appears to correlate a reduction of approximately 50% in oxygen uptake rate to a metabolic rate reduction of about half. (*See* BEQ1001, Fig. 5A; BEQ1002, ¶81.) Thus, Seeger anticipates claims 6, 22, and 30. (BEQ1002, ¶¶79-81, 93-94, 105-106.)

Claims 9 and 33: As discussed above, Seeger anticipates claims 1 and 25. Claims 9 and 33 depend from claims 1 and 25, respectively, and further specify that "the recombinant host cell is a bacterial cell selected from the group consisting of *E. coli* and Salmonella." (BEQ1001, 18:41-43, 20:14-16.) Seeger describes using recombinant *E. coli* TG1 cells, thus anticipating claims 9 and 33. (BEQ1004, 947, Abstract, 948:1:3, 951:1-2, 952:1, Table 2, 953:1:2; BEQ1002, ¶¶69-72, 82-83, 107-108.)

Claims 15, 24, and 39: As discussed above, Seeger anticipates claims 1, 16, and 25. Claims 15, 24, and 39 depend from claims 1, 16, and 25, respectively, and further specify that "the metabolic and growth rate of the host cells is maximized in step (a)." (BEQ1001, 18:55-57, 19:17-19, 20:30-32.) Seeger describes maximizing the metabolic and growth rate of the recombinant *E. coli* TG1 cells: "[c]ultivation started as a batch process with cells growing at 30°C with *maximal specific growth rates* (TG1:pλFGFB: μ_{max} = 0.51 h^{-1}. . . ." (BEQ1010, 951:2:1, 950:2, Figure 3 legend (describing "unlimited growth during batch mode (μ_{max} = 0.51 h^{-1})"), 952:1, Table 2; BEQ1002, ¶¶86-87, 95-97, 109-111; *see* § VI.A.1(b).) Further, Seeger maintains the dissolved oxygen concentration "at 40% of air saturation by increasing the stirrer speed," during batch phase of the high-cell-density fermentation. (BEQ1010, 948:2:3; BEQ1002, ¶¶53, 70.)

As confirmed by Dr. Rosenberg, Seeger's supply of unrestricted or relatively

high feed rates of glucose and oxygen favor maximal or unlimited growth and provide a maximal metabolic and growth rate. (BEQ1002, ¶¶87, 97, 111.) And this is because "during logarithmic growth the metabolic rate is directly proportional to availability of oxygen and a carbon/energy source." (BEQ1001, 13:54-58; BEQ1002, ¶87.) Therefore, Seeger describes maximizing metabolic and growth rate of the recombinant cells during the batch phase (step (a)) and anticipates claims 15, 24, and 39. (BEQ1002, ¶¶86-87, 95-97, 109-111.)

B. Ground 2: Claims 7-8 and 31-32 would have been obvious over Seeger in view of the general knowledge in the prior art

Viewing the teachings of Seeger, in view of the general knowledge in the prior art, a POSA would have had a reason and the know-how to arrive at the methods of claims 7-8 and 31-32, with a reasonable expectation of success. (BEQ1002, ¶¶116-125.) This is because it was well-understood in the art that protein expression should be induced at or near maximum cell density, which Patent Owner admitted "is a basic teaching in the field." (BEQ1004, 32:4; BEQ1002, ¶¶116-125; *see* § IV.C.2.)

Claims 7 and 31: Claims 7 and 31 depend from claims 1 and 25, respectively, and further specify "growing the cells to maximum density in step (a)." (BEQ1001, 18: 38, 20:10-11.) As discussed by Dr. Rosenberg, a POSA would have had a reason to grow recombinant *E. coli* host cells (like those of Seeger) to maximum density before inducing protein expression. (BEQ1002, ¶¶118, 122.)

This is because, as of November 3, 2000, a POSA routinely grew *E. coli* host cells to or near maximum cell density in the growth phase before inducing polypeptide expression. (*See, e.g.*, BEQ1007, 145:2:1 (Donovan stating that inducible expression systems "allow[] for the separation of cell growth from the product synthesis or induction phase of the fermentation[, where a]fter obtaining *a high concentration of cells in a fermenter during the growth phase*, the foreign gene can then be induced resulting in higher total yields of the recombinant protein" (emphasis added); BEQ1002, ¶45.)

And Patent Owner confirmed as much during prosecution: "*inducing product expression at near maximum cell densities* (about 200 OD), as Skerra and others disclose, *is a basic teaching in the field*." (*See* BEQ1004, 32:4 (emphasis added).) *Vitronics*, 90 F.3d at 1582-1583. Thus, not only would a POSA have had a reason to grow cells to maximum density before inducing protein expression, he or she would have done so with a reasonable expectation of success. (BEQ1002, ¶¶119, 123.)

Seeger provides a detailed disclosure of reducing the metabolic rate of *E. coli* cells at the time of induction of bFGF polypeptide expression by reducing the feed rate of glucose as recited in claims 1 and 25. (BEQ1010, 948:1:4-949:2:3; BEQ1002, ¶119.) Moreover, as discussed in § VI.A.1.(f), Seeger's protocol was routine for a POSA to follow. (*Id.*, ¶¶74, 119.) And glucose-limited, high-cell-

density fermentations in the field of recombinant protein production were well-developed and predictable as of November 3, 2000. (*Id.*, ¶74.)

So, in addition to the reasons outlined above for claims 1 and 25, a POSA would have had a reason to grow Seeger's *E. coli* cells to maximum density in the growth phase as recited in claims 7 and 31, with a reasonable expectation of success. (BEQ1002, ¶¶116-119, 122-123.)

Claims 8 and 32: Claims 8 and 32 depend from claims 7 and 31, respectively, and further specify "the metabolic rate is reduced by about half in step (b)." (BEQ1001, 18:35-36, 20:13-14.) In addition to the reasons outlined above for claims 7 and 31, a POSA would have had a reason to reduce the metabolic rate of the *E. coli* cells by about half in the fed-batch phase as recited in claims 8 and 32 and would have done so with a reasonable expectation of success. (BEQ1010, 951:2:1; BEQ1002, ¶¶71, 81, 121, 125.) This is so because Seeger describes reducing the metabolic rate of recombinant cells by reducing the glucose feeding rate at the time of induction of bFGF expression. (BEQ1010, 951:2:2; 950:2, Figure 3 legend, 952:1, Table 2; BEQ1002, ¶¶56, 72; § VI.A.1(c)-(d).) As confirmed by Dr. Rosenberg, Seeger decreases the metabolic rate by about half. (*See* § VI.A.2; BEQ1002, ¶¶81, 121, 125.) And, for the same reasons as discussed above for claims 7 and 31, Seeger's detailed disclosure of reducing the metabolic

rate of *E. coli* cells at the time of induction of bFGF polypeptide expression, provided a routine protocol for a POSA to follow. (*Id.*, ¶¶74, 119.)

Therefore, a POSA would have had a reason to reduce the metabolic rate of Seeger's *E. coli* cells by about half as recited in claims 8 and 32, with a reasonable expectation of success. (*Id.*, ¶¶120-121, 124-125.)

C. Ground 3: Claims 10, 12, 23, 34, and 36 would have been obvious over Seeger and Makrides

Viewing the teachings of Seeger and Makrides in light of the knowledge in the art, a POSA would have had a reason and the know-how to successfully arrive at the methods of claims 10, 12, 23, 34, and 36 (BEQ1002, ¶¶126-143.) Makrides published in September 1996, and qualifies as prior art under 35 U.S.C. § 102(b) to the '602 patent claims. Each of Seeger and Makrides is directed to high-level production of foreign proteins in *E. coli* using, *inter alia*, inducible expression systems. (*Id.*, ¶¶57, 62, 129.)

A POSA reading Seeger's disclosure of growing recombinant *E. coli* cells in high-cell density cultures at high metabolic and growth rates and then reducing the metabolic rate at the time of induction of recombinant polypeptide expression to increase expression of total, soluble polypeptide would have had a reason to look to Makrides. (BEQ1002, ¶¶128, 136, 139, 141.) This is because Makrides describes the many advantages of *E. coli* that make it "a valuable organism for the high-level production of recombinant proteins" and, as discussed below, provides

reasons to use any one of twenty-nine inducible promoters (including *phoA*) and/or periplasmic protein expression to achieve this high-level production. (BEQ1023, 512:1:2 and Table 1, 520:2:3; BEQ1002, ¶¶62, 64, 129, 135.) *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (holding that a POSA would have had a reason to combine a reference disclosing a besylate salt among 53 pharmaceutically-acceptable anions with other references to render obvious claims to a besylate salt compound).

Therefore, a POSA would have sought to apply Makrides's teachings to Seeger's high cell density fermentations of recombinant *E. coli* to produce polypeptides using a phosphate inducible expression system or secretion to the periplasmic space, with predictable results. (BEQ1002, ¶¶127-131, 138-141.)

Claims 10, 23, and 34: Claims 10, 23, and 34 depend from claims 1, 16, and 25, respectively, and further specify that "the inducible system is a phosphate depletion inducible system." (BEQ1001, 18:44-45, 19:15-16, 20:18-19.) Makrides teaches "[t]he many advantages of *Escherichia coli* have ensured that it remains a valuable organism for the high-level production of recombinant proteins." (BEQ1023, 512:1:2 and Table 1; BEQ1002, ¶¶62, 129.) And Makrides describes engineering efficient *E. coli* expression vectors, stating that "[t]here are many promoters available for gene expression in *E. coli*," and references Table 1, which describes 29 well-known promoters for high-level gene expression, including the

phosphate starvation (i.e., phosphate depletion) promoter *phoA*. (BEQ1023, 512:1:2 and Table 1; BEQ1002, ¶¶62, 129.) With reference to these promoters, Makrides states:

> A useful promoter exhibits several desirable features: it is strong, it has a low basal expression level (i.e., it is tightly regulated), it is easily transferable to other *E. coli* strains to facilitate testing of a large number of strains for protein yields, and its induction is simple and cost-effective.

(BEQ1023, 513:1:1; *see also* 513:2:2-514:1:2 (discussing three important promoter characteristics: strength, minimal basal transcriptional activity, and simple and cost-effective induction); BEQ1002, ¶¶46, 62.)

A POSA would have had a reason to combine Seeger and Makrides—as they are in the same field of endeavor—and would have had a reasonable expectation of success in practicing the methods of claims 10, 23, and 34. (BEQ1002, ¶¶128-131, 136, 139, 141.) A POSA would have readily modified Seeger's high-cell density fermentations of recombinant *E. coli*, where the cells are first grown in high-cell density cultures at high metabolic and growth rates and then polypeptide expression is induced, to use a phosphate inducible expression system, such as the *phoA* promoter described in Makrides. (*Id.*, ¶¶128, 136, 139, 141.) This is because Makrides teaches that "[l]arge-scale gene expression preferably employs cell growth to high density and minimal promoter activity,

followed by induction or derepression of the promoter." (BEQ1023, 513:2:3; BEQ1002, ¶¶62, 128.) Moreover, Makrides provided a POSA with a list of twenty-nine inducible promoters routinely used for "high-level expression of genes in *E. coli*," which included the commonly-used *phoA* promoter. (BEQ1023, 514, Table 1; BEQ1002, ¶¶62, 129.)

Under similar facts, the Federal Circuit held that a POSA would have had a reason to combine a reference disclosing 53 pharmaceutically-acceptable anions, including that used to create besylate salts, with other references to render obvious claims to a besylate salt compound. *Pfizer*, 480 F.3d at 1364. There, the court noted that the prior art reference's list of "FDA-approved anions at the time was small, i.e., only 53," and additional prior art publications established, by clear and convincing evidence, that a POSA "would have favorably considered benzene sulphonate because of its known acid strength, solubility, and other know chemical characteristics." *Id.*, 1363.

Here, as in *Pfizer*, a preponderance of the evidence demonstrates that Makrides's list of twenty-nine inducible promoters routinely used for "high-level expression of genes in *E. coli*" was small. (BEQ1002, ¶129.) And, a POSA would have favorably considered *phoA* (and a phosphate-inducible expression system) because of its art-recognized advantages: 1) it is a strong promoter (protein expression can be induced more than 1000-fold), 2) it has minimal basal

transcriptional activity (it is essentially silent at high phosphate concentrations), and 3) it is a simple and cost-effective induction system (its activity can be readily manipulated by limiting phosphate concentration). (BEQ1022, 5:1:2 and 5:2:2; BEQ1002, ¶¶47, 129.) Thus, for the same reasons applied by the Federal Circuit in *Pfizer*, a POSA would have had a reason to combine Seeger and Makrides and would have favorably chosen *phoA* as a phosphate-inducible system. (BEQ1002, ¶¶47, 129.) *Pfizer*, 480 F.3d at 1364 (Fed. Cir. 2007).

In addition, Seeger provides a detailed disclosure of reducing the metabolic rate of *E. coli* cells at the time of induction of bFGF polypeptide expression by reducing the feed rate of glucose, which as discussed above in § VI.A.1.(f), was routine for a POSA to follow. (BEQ1002, ¶74.) And glucose-limited, high-cell-density fermentations in the field of recombinant protein production was well-developed and predictable as of November 3, 2000. (*Id.*) Similarly, a POSA knew of the common and routine use of the *phoA* promoter in the field at that time, which generally was "applicable to the production of any of the categories of recombinant protein." (BEQ1022, 5:2:2; BEQ1002, ¶¶47, 130.)

So, in addition to the reasons outlined above for claims 1, 16, and 25, a POSA would have had a reason to arrive at the phosphate depletion inducible system recited in claims 10, 23, and 34, with a reasonable expectation of success. (BEQ1002, ¶¶126-131, 138-139, 140-141.)

Claims 12 and 36: Claims 12 and 36 depend from claims 9 and 33, respectively, and further specify "the polypeptide is secreted into the periplasm of the host cell." (BEQ1001, 18:48-49, 20:22-23.) Makrides discusses progress "in the areas of extracellular secretion and disulfide bond formation" to address efficient release (secretion) of expressed protein into the culture medium and proteins that require "extensive" disulfide bond formation. (BEQ1023, 512:2:1; BEQ1002, ¶63.) And Makrides discloses the several advantages of periplasmic expression of recombinant proteins in *E. coli*: 1) the target protein is "effectively concentrated" in the periplasm and "its purification is considerably less onerous"; 2) "[t]he oxidizing environment of the periplasm facilitates the proper folding of proteins"; and 3) [p]rotein degradation in the periplasm is also less extensive." (BEQ1023, 520:2:3; BEQ1002, ¶¶64, 135.) Moreover, Makrides indicates that "[a] wide variety of signal peptides *have been used successfully* in *E. coli* for protein translocation to the periplasm," including the prokaryotic signal sequence *E. coli* PhoA signal. (BEQ1023, 520:2:4 (emphasis added); BEQ1002, ¶¶65, 137.)

As discussed above, a POSA would have had a reason to combine both Seeger and Makrides and would have had a reasonable expectation of success in arriving at the subject matter of claims 12 and 36. (BEQ1002, ¶¶132-137, 142-143.) A POSA would have readily modified Seeger's high cell density fermentations of recombinant *E. coli*, where the cells are first grown in high-cell

density cultures at high metabolic and growth rates and then polypeptide expression is induced, to target secretion of the produced polypeptide to the periplasm as described in Makrides. (*Id.*, ¶¶134-135, 143.) This is because Makrides teaches the onerous nature of cytoplasmic polypeptide production, including: (i) formation of inclusion bodies as "a significant barrier to gene expression in the cytosol"; (ii) an unfavorable reducing environment for mammalian proteins which may result in an incorrect conformation in the bacterial cytoplasm"; (iii) an increased likelihood of protein degradation as compared to other cellular compartments; and (iv) purification from a large pool of intracellular proteins. (BEQ1023, 518:1:5; 518:2:3; 520:2:1; BEQ1002, ¶135.) Instead of cytoplasmic expression, Makrides offered several advantages to target expression to the *E. coli* periplasm, as discussed above, providing a POSA with reasons to do so. (BEQ1002, ¶¶64, 135.)

In addition, Seeger provides a detailed disclosure of reducing the metabolic rate of *E. coli* cells at the time of induction of bFGF polypeptide expression by reducing the feed rate of glucose, which as discussed in § VI.A.1.(f), was routine for a POSA to follow. (BEQ1002, ¶74.) And glucose-limited, high-cell-density fermentations in the field of recombinant protein production was well-developed and predictable as of November 3, 2000. (*Id.*, ¶74.) Similarly, Makrides provided a POSA with a wide-variety of signal peptides, including the prokaryotic signal

sequence *E. coli* PhoA signal, successfully used in *E. coli* for protein translocation to the periplasm." (BEQ1023, 520:2:4; BEQ1002, ¶¶65, 135, 143.)

So, in addition to the reasons outlined above for claims 9 and 33, a POSA would have had a reason to arrive at secreting the recombinant polypeptide into the periplasm of *E. coli* cells as recited in claims 12 and 36, with a reasonable expectation of success. (BEQ1002, ¶¶132-137, 142-143.)

D. Ground 4: Claims 11, 13-14, 18, 35, and 37-38 would have been obvious over Seeger and Cabilly

Viewing the teachings of Seeger and Cabilly, in view of the knowledge in the art, a POSA would have had a reason and the know-how to successfully arrive at the methods of claims 11, 13-14, 18, 35, and 37-38. (BEQ1002, ¶¶144-163.) Cabilly published December 28, 1989, and qualifies as prior art under 35 U.S.C. § 102(b) to the '602 patent claims. Each of Seeger and Cabilly is directed to expression of foreign proteins in *E. coli*. (*Id.*, ¶148.)

A POSA reading Seeger's disclosure of growing recombinant *E. coli* cells in high-cell density cultures at high metabolic and growth rates and then reducing the metabolic rate at the time of induction of recombinant polypeptide expression to increase expression of total, soluble polypeptide would have had a reason to look to Cabilly. (BEQ1002, ¶¶146-147, 152, 155, 157, 159, 161, 163.) This is because Cabilly 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. (BEQ1032, 553, Abstract, 556:1:2; BEQ1002, ¶¶59-60, 147.) Therefore, a POSA would have sought to apply Cabilly's teachings to Seeger's high cell density fermentations of recombinant *E. coli* to produce soluble, properly-folded and assembled antibodies, including Fab fragments, with predictable results. (BEQ1002, ¶¶146-147, 152, 155, 157, 159, 161, 163.)

Claims 11 and 35: Claims 11 and 35 depend from claims 1 and 25, respectively, and further specify "the polypeptide is assembled in the host cell." (BEQ1001, 18:46-47, 20:20-21.) As discussed in § V., a POSA would have understood the term "assembled" to mean the polypeptide is produced by the cell as functional. (BEQ1002, ¶31.) Seeger in view of Cabilly renders these claims obvious. This is because Cabilly teaches assembly of recombinantly-produced Fab fragments. Specifically, Cabilly sought to improve the assembly of the recombinant Ig polypeptides by designing a single plasmid harboring both genes (encoding the κ-chain and Fd fragments). (BEQ1032, 554:1:2-4 and Figure 1 legend; BEQ1002, ¶60.) And, Cabilly demonstrates that the "bacterially-produced Fab has the same antigen binding site [in carcinoembryonic antigen] as that of the monoclonal antibody from which it was derived," was produced at an amount "equivalent to 5-10% of the total protein," and these functional Fab fragments

retained activity "upon storage at 4 °C for more than two months." (BEQ1032, 556:1:2, *see also* 553, Abstract; BEQ1002, ¶¶60, 147.)

A POSA would have had a reason to combine both Seeger and Cabilly—as they are in the same field of endeavor—and would have had a reasonable expectation of success in arriving at the subject matter of claims 11 and 35. (BEQ1002, ¶¶147-149, 159.) A POSA would have readily modified Seeger's high cell density fermentations of recombinant *E. coli* to produce antibodies and antibody fragments as in Cabilly. (*Id.*, ¶¶147-149, 159.) Seeger provides a detailed disclosure of reducing the metabolic rate at the time of induction of recombinant polypeptide expression to increase expression of total, soluble polypeptide which as discussed in § VI.A.1.(f), was routine for a POSA to follow, and Cabilly teaches using simple methodology for the design and production of antibodies, specifically Fab fragments, in *E. coli* to obtain assembled antibody fragments. (BEQ1032, 553, Abstract, 554:1:4, 556:1:2; BEQ1002, ¶¶60, 71, 146-147.) Indeed, a POSA would have had a reason to produce antibodies and antibody fragments in *E. coli* cells at high cell density fermentation, as disclosed in Seeger, to obtain assembled recombinant antibodies and antibody fragments at increased quantities. (*Id.*, ¶¶146-148, 159.)

So, in addition to the reasons outlined above for claims 1 and 25, a POSA would have had a reason to arrive at producing assembled recombinant antibodies

and antibody fragments as recited in claims 11 and 35, with a reasonable expectation of success. (BEQ1002, ¶¶146-149, 159.)

Claims 13-14, 18, and 37-38: Claims 13 and 37 depend from claims 1 and 25, respectively, and further specify "the polypeptide is an antibody." (BEQ1001, 18:50-51, 20:25-26.) The '602 patent defines the term "antibody" to include antibody fragments "Fab'$_2$, Fab, scFv single chain antibodies, and the like." (BEQ1001, 6:1-6.) And claims 14, 18, and 38 depend from claims 1, 16, and 25, respectively, and further specify "the polypeptide is selected from the group consisting of an Fab'$_2$ antibody and an Fab antibody or other form of antibody" (claims 14 and 38) or "the antibody is an Fab antibody" (claim 18). (*Id.*, 18:52-54, 20:24-26, 19:3-4.)

As discussed above, Cabilly teaches proper assembly of recombinantly-produced Fab fragments by designing a single plasmid harboring immunoglobulin genes encoding the κ-chain and Fd fragments. (BEQ1032, 554:1:2-4 and Figure 1 legend; BEQ1002, ¶60.) And, for the same reasons as discussed above, a POSA would have had a reason to combine Seeger and Cabilly (same field of endeavor) and would have had a reasonable expectation of success in arriving at the subject matter of claims 13-14, 18, and 37-38—antibodies and specifically an Fab fragment. (BEQ1002, ¶¶147-149, 152, 155, 157, 161, 163.)

A POSA would have readily modified Seeger's high cell density fermentations of recombinant *E. coli* to produce antibodies, particularly an Fab fragment, as in Cabilly. (*Id.*) And, Seeger discloses reducing the metabolic rate at the time of induction of recombinant polypeptide expression to increase expression of total, soluble polypeptide, which as discussed in § VI.A.1.(f), was routine for a POSA to follow, while Cabilly teaches using simple methodology for the design and production of antibodies, specifically Fab fragments, in *E. coli* to obtain assembled protein. (BEQ1032, 553, Abstract, 554:1:4, 556:1:2; BEQ1002, ¶¶60, 71, 146-147, 152.) A POSA would have had a reason to produce antibodies and Fab antibody fragments in *E. coli* cells at high cell density fermentation, as disclosed in Seeger, to obtain recombinant antibodies and antibody fragments at increased quantities. (*Id.*, ¶¶152, 155, 157, 161, 163.)

So, in addition to the reasons outlined above for claims 1, 16, and 25, a POSA would have had a reason to arrive at producing Fab antibody fragments as recited in, and encompassed by, claims 13-14, 18, and 37-38, with a reasonable expectation of success. (BEQ1002, ¶¶150-157, 160-163.)

E. Objective indicia do not support patentability

In addition to Petitioner's strong showing of *prima facie* obviousness outlined above (*see* §§ VI.B.-D.), objective indicia must be taken into account as "*part of* the whole obviousness analysis," although it does not control the

obviousness conclusion. *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1199 (Fed. Cir. 2014) (quoting *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013); *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). In cases where, as here, a strong showing of *prima facie* obviousness exists, the Federal Circuit has repeatedly held that even relevant secondary considerations supported by substantial evidence may not amount to a showing of non-obviousness. *See, e.g., Leapfrog Enterprises Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). Further, "the objective indicia 'must be tied to the novel elements of the claim at issue' and must 'be reasonably commensurate with the scope of the claims.'" *Medtronic v. Nuvasive,* IPR2014-00073, Paper 48, at 22 (citing *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013)); *see also Gnosis v. SAMSF,* IPR2013-00118, Paper 64, at 38 ("Objective evidence that results from something [that] is not 'both claimed and novel in the claim' lacks a nexus to the merits of the invention." (citing *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)).

Patent Owner may argue that secondary considerations of unexpected superior results, long-felt but unmet need, failure of others, or industry praise exist. They do not.[14]

1. No unexpected superior results

Nonobviousness of an invention can be demonstrated by showing that the claimed invention exhibits a superior property or advantage, i.e., unexpectedly superior results, over the closest prior art. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). Any such rebuttal argument for claims 7-8, 10-14, 18, 23, 31-32, and 34-38 fails.

During prosecution, Patent Owner asserted that it was unexpected that "[t]he 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 . . . [which is an] unexpected result of reducing metabolic rate late in the process." (BEQ1004, 33:2.) In support, Patent Owner relied on the results presented in the '602 patent, Example 2. But that example compares to a "standard method," where "the fermenter conditions did not change with time," rather than

[14] Any rebuttal evidence or arguments by Patent Owner do not apply to Ground 1, which is based on anticipation by Seeger. Thus, any argument to rebut a *prima facie* case of obviousness would have to be made against Grounds 2-4.

the closest prior art—Seeger. (BEQ1001, 16:65-66, Table 2; BEQ1002, ¶167.) *See, e.g.*, *Bristol-Myers Squib Co. v. Teva Pharmaceuticals USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (noting that "[t]o be particularly probative, evidence of unexpected results must establish . . . a difference between the results obtained and those of the closest prior art").

Had Patent Owner compared Example 2, or any disclosure from the '602 patent, to Seeger, the results obtained would not have been unexpected. (BEQ1002, ¶¶168, 170.) This is because Seeger described a method for increasing the amount of properly-folded polypeptides produced by recombinant *E. coli*, which included reducing the metabolic rate of *E. coli* at the time of induction. (BEQ1010, 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; BEQ1002, ¶168.) And Genentech argued during prosecution that the distinguishing feature over the "standard method" is "reducing the metabolic rate late in the process," which is what Seeger did. (BEQ1004, 33:2; BEQ1002, ¶168.) Thus, Patent Owner has not demonstrated that the claimed invention exhibits a superior property or advantage over the closest prior art.

Even if Patent Owner had made such a showing, the results are neither superior nor unexpected. Dr. Rosenberg confirmed the results presented in Table 2 of the '602 patent, represent merely a difference in degree, not in kind. (BEQ1002, ¶¶169-170.) *Bristol-Myers Squib*, 752 F.3d at 977 ("And 'differences in degree' of

a known and expected property are not as persuasive in rebutting obviousness as differences in 'kind.'"). The '602 patent asserts that "[t]hese data demonstrate a statistically significant improvement in titer as a result of the OUR shifts compared to the standard protocol." (BEQ1001, 17:46-48.) Yet, the 30% or so increase in the amount of soluble protein represented in Table 2 is a difference in degree (i.e., quantity), not in kind (i.e., new or dissimilar property). (BEQ1002, ¶169.) *Id.* Moreover, Dr. Rosenberg confirmed this difference in degree is slight. (*Id*.) And, Seeger achieved this quantitative difference: the method "was sufficient to prevent accumulation of acetic acid . . . and *to allow expression of bFGF*" compared to maintaining the same metabolic rate in fed-batch phases 1 and 2. (BEQ1010, 952:2:1 (emphasis added); BEQ1002, ¶170.)

The additional elements recited in claims 7-8, 10-14, 18, 23, 31-32, and 34-38 do not provide unexpected results, as these were well-known in the art and do not impart any unexpected properties to the method for increasing the amount of properly-folded polypeptides. (BEQ1002, ¶170.) Any such arguments by Patent Owner in this proceeding should fail for the same reasons.

2. No long-felt need or failure of others

A showing of a long-felt and unmet need requires that the need must have been a persistent one recognized by a POSA. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). Also, the long-felt need must not have

been satisfied by another before the invention. *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopedics, Inc*., 976 F.2d 1559, 1574-75 (Fed. Cir. 1992). And the invention must in fact satisfy the long-felt need. *Id.*, 1575. Failure of others to find a solution to the problem which the patent purports to solve is also relevant in determining nonobviousness. *Id.* There is no evidence of either as of November 3, 2000. (BEQ1002, ¶¶172-175).

First, by 2000 researchers in the field had successfully-produced a wide variety of recombinant mammalian proteins, such as growth factors and immunoglobulins, in *E. coli*, on a commercial scale (i.e., in high yields and properly-folded). (*See, e.g.*, BEQ1007, 145:1:2; BEQ1002, ¶172).

Second, to the extent that Patent Owner argues there was a persistent need to develop a method to increase the yield of properly-folded, i.e., soluble polypeptide, in cultured recombinant *E. coli* host cells, the '602 patent did not satisfy that need. Instead, it was Seeger that specifically disclosed—at least five years before the '602 patent—reducing the metabolic rate at the time of induction of mammalian polypeptide (bFGF) expression by reducing the feed rate of a carbon/energy source (glucose). (*See* § VI.A.1.(c)-(d); BEQ1010, 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; BEQ1002, ¶¶69-73 and 76.) But to the extent Patent Owner disagrees, it cannot prevail because researchers continue to develop and improve methods to obtain higher yields of properly-

folded recombinant proteins even to this day. (*See, e.g.*, BEQ1036, 235:2:1 (stating that "process conditions *must be found* which balance heterologous protein production and host physiology *to optimize the overall yield of active product*" (emphases added)); *see also* BEQ1044, Abstract and the entire content of the article; BEQ1002, ¶173.)

Finally, there was no recognized need to develop the fermentation strategies recited in dependent claims 7-8, 10-14, 18, 23, 31-32, and 34-38 as prior art disclosed the additional elements of these claims long before the '602 patent. (*See* BEQ1007, 145:1:2; BEQ1023, Table 1; BEQ1032, Abstract; BEQ1002, ¶¶170, 172.)

Thus, others did not fail to find a solution to the problem that the patent purports to solve, and there was no long-felt and unmet need, because Seeger succeeded at increasing the yield of properly-folded in cultured recombinant *E. coli* host cells by reducing the metabolic rate at the time of induction of polypeptide expression. (BEQ1002, ¶¶172-175.) As such, any of Patent Owner's arguments of long-felt but unmet need or failure of others must fail.

3. There is no other evidence of nonobviousness

As discussed by Dr. Rosenberg, there is no other publicly-available evidence to consider. For example, there is no evidence of praise by the industry or experts in the field for the claimed methods. (BEQ1002, ¶176.) It is unclear if anyone in

the field has even used the claimed methods outside the two examples recited in the '602 patent. (*Id*.)

VII. Conclusion

Claims 1, 3-4, 6-16, 18, 20, 22-25, 27-28, and 30-39 are either anticipated or would have been obvious over the art discussed above. Ground 1 demonstrates that every element of claims 1, 3-4, 6, 9, 15-16, 20, 22, 24-25, 27-28, 30, 33, and 39 was disclosed in a single reference, arranged as claimed and in a manner enabling to a POSA. Grounds 2-4 demonstrate that a POSA would have had a reason and the know-how to arrive at each of claims 7-8, 10-14, 18, 23, 31-32, and 34-38 over the asserted prior art with a reasonable expectation of success. Thus, the Board should institute IPR for each challenged claim.

VIII. Mandatory notices (37 C.F.R. § 42.8(a)(1))

The Real Parties-In-Interest (37 C.F.R. § 42.8(b)(l)) are: bioeq IP AG, bioeq GmbH, Santo Holding AG, and Swiss Pharma International AG. Swiss Pharma International AG is a subsidiary owned by Medana Pharma SA, Polfa Warsaw SA (also known and registered as Warszawskie Zakłady Farmaceutyczne Polfa S.A.) and Pharmaceutical Works Polpharma SA (also known and registered as Zakłady Farmaceutyczne Polpharma SA). Polfa Warsaw SA and Medana Pharma SA are in turn owned by Zakłady Farmaceutyczne Polpharma SA (also known as Pharmaceutical Works Polpharma SA).

Related Matters (37 C.F.R. § 42.8(b)(2)): Judicial: None.

Administrative: None.

Designation of Lead and Back-up Counsel (37 C.F.R. § 42.8(b)(3)):

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Notice of Service Information (§ 42.8(b)(4)): Please direct all correspondence to lead counsel and back-up counsel at the above address. Petitioner consents to email service at: dsterlin-PTAB@skgf.com, tshea-PTAB@skgf.com, jfrueauf-PTAB@skgf.com, and opartington-PTAB@skgf.com.

Procedural Statements: This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed are a Power of Attorney and Exhibit List under 37 C.P.R. § 42.10(b) and § 42.63(e), respectively. The required fee is paid through.

Deposit Acct. No. 19-0036 (Customer ID No. 45324). The Office is authorized to charge any fee deficiency, or credit any overpayment, to the same.

Word Count Certification (37 C.F.R. § 42.24(a)(1)(i)): Petitioner certifies that this Petition is 13,747 words in length, as determined by Microsoft Word® word count feature, excluding any table of contents, mandatory notices under § 42.8, certificate of service or word count, or appendix of exhibits or claim listing.

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

The undersigned hereby certifies that the above-captioned "Petition for *Inter Partes* Review of U.S. Patent No. 6,716,602 under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123," was served in its entirety on August 16, 2016, upon the following parties via Express Mail:

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Patent owner's correspondence address of record for U.S. Patent No. 6,716,602

Respectfully submitted,
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