

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIFESCAN GLOBAL CORPORATION,
Petitioner,

v.

IKEDA FOOD RESEARCH, LTD., and PHC CORPORATION,
Patent Owners.

PGR2019-00032
Patent 9,976,125 B2

Before ERICA A. FRANKLIN, ROBERT A. POLLOCK, and
DAVID COTTA, *Administrative Patent Judges*.

COTTA, *Administrative Patent Judge*.

DECISION
Final Written Decision
Granting-in-Part and Denying-in-Part
Patent Owners' Motion to Amend
35 U.S.C. § 328

I. INTRODUCTION

On January 30, 2019, Lifescan Global Corporation (“Petitioner”) filed a Petition requesting a post grant review of claims 1–10 of U.S. Patent No. 9,976,125 B2 (Ex. 1005, “the ’125 patent”). Paper 1 (“Pet.”). On May 22, 2019, Ikeda Food Research Co., Ltd., and PHC Corporation (“Patent Owners”) filed a statutory disclaimer under 35 U.S.C. § 253(a) disclaiming claims 1–7, 9, and 10 of the ’125 patent. Ex. 2009. Shortly thereafter, Patent Owners filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”). We determined, based on the information presented in the Petition and Preliminary Response, that there was a reasonable likelihood that Petitioner would prevail in showing that claim 8, the only remaining claim, was unpatentable. Pursuant to 35 U.S.C. § 324, the Board instituted trial on August 15, 2019. Paper 11 (“Institution Decision” or “Inst. Dec.”).

Patent Owners did not file a Response to the Petition. Instead, Patent Owners filed a non-contingent Motion to Amend seeking cancellation of claim 8 and proposing substitute claim 11. Paper 18, 1. Patent Owner’s motion included a request for preliminary guidance from the Board, in accordance with the New Pilot Program Concerning Motion to Amend Practice. *Id.* at 2; *see also* 84 Fed. Reg. 9,497 (Mar. 15, 2019) (notice regarding New Pilot Program). Petitioner challenged the patentability of proposed new claim 11 in an Opposition (Paper 26), and we provided a Preliminary Guidance, in which we set forth our “preliminary, non-binding views” on whether Patent Owners had shown “a reasonable likelihood” that they had “satisfied the statutory and regulatory requirements associated with filing a motion to amend in a post-grant review” as well as our views on “whether Petitioner (or the record) establishe[d] a reasonable likelihood that the substitute claims are unpatentable” (Paper 27, 2).

After entry of our Preliminary Guidance, Patent Owners filed a Revised Motion to Amend, reiterating their request for cancellation of claim 8 and proposing entry of a revised claim 11 on a “noncontingent basis.” Paper 28, 1 (“R. Mot.”). Petitioner filed an Opposition to Patent Owners’ Revised Motion to Amend (Paper 30, “Opp.”), Patent Owners filed a Reply to Petitioner’s Opposition (Paper 34, “Reply”), and Petitioner filed a Sur-reply to Patent Owner’s Reply (Paper 36, “Sur-reply”). On June 18, 2020, the parties presented arguments at an oral hearing. The transcript of the hearing has been entered into the record. Paper 37 (“Tr.”).

We have jurisdiction under 35 U.S.C. § 6. We issue this Final Written Decision pursuant to 35 U.S.C. § 328(a) and 37 C.F.R. § 42.73. For the reasons discussed below, Patent Owner’s Motion to Amend is *granted* with respect to cancellation of claim 8, and *denied* with respect to proposed substitute claim 11.

A. Real Parties in Interest

Petitioner identifies LifeScan Global Corporation and its affiliates, as the real parties-in-interest. According to Petitioner these parties include:

Platinum Equity Capital Partners IV, L.P.; Platinum LifeScan Principals, LLC; DUV Holding Corporation; DUV Intermediate Holding Corporation; DUV Intermediate Holding II Corporation; LifeScan, Inc.; LifeScan China, LLC; LifeScan IP Holdings, LLC; LifeScan Holding Limited; LifeScan Holding II Limited; LifeScan Europe GmbH; LifeScan Scotland Limited; LifeScan Institute, LLC; LifeScan Foreign Holdings, LLC; LifeScan U.K. Limited; LifeScan Canada ULC; LifeScan Deutschland GmbH; LifeScan Italy S.R.L.; LifeScan Belgium BVBA; LifeScan France SAS; LifeScan Malaysia SDN. BHD; LifeScan Spain, S.L.; LifeScan U.K. Limited LIFESCAN – podružnica Croatia; LifeScan U.K. Limited, LIFESCAN YIIOKATAΣTHMA EΛΛAΔΣ; LifeScan U.K. Limited (spółka z ograniczoną odpowiedzialnością) Oddział w Polsce; LifeScan U.K. Limited Ireland Branch; LifeScan U.K. Limited South Africa Branch; LifeScan U.K. Limited Argentina Branch; LifeScan Russia Limited

Liability Company; LifeScan Czech Republic s.r.o.; LifeScan Mexico, S. de R.L. de C.V.; LifeScan Mexico Servicios S. de R.L. de C.V.; LifeScan Japan KK; LifeScan Brasil Equipamentos para diagnosticos, pesquisa e desenvolvimento Ltd; LifeScan Portugal, Unipessoal LDA; and LIFESCAN MEDICAL DEVICES INDIA PRIVATE LIMITED.

Pet. 7–8.

Patent Owners identify Ikeda Food Research Co., Ltd.; PHC Corporation; Ikeda Tohka Industries Co., Ltd.; PHC Holdings Corporation; and Ascensia Diabetes Care Holdings AG as the real parties in interest. Paper 3, 1.

B. Related Proceedings

Petitioner represents that it is unaware of any other matters related to the '125 patent. Pet. 8. Patent Owners identify U.S. Patent Nos. 8,492,130, 8,882,978, 9,340,816, and 9,663,811; U.S. Patent Application No. 15/955,650; PCT Publication No. WO 2008/001903 A1; and Japanese Publication Nos. 4665235 B2, 4773578 B2, 5209087 B2, 5792214 B2, 6438519 B2, 2016019529 A, and 2018093872 A (now Japanese Patent No. 6535075) as relating to the '125 patent. Paper 3, 2; Paper 16, 1–2.

C. The '125 Patent (Ex. 1005)

The '125 patent issued May 22, 2018, identifying Takako Yada, Koji Miyamoto, and Michinari Honda as joint inventors. Ex. 1005, code (72). The patent “relates to a novel gene (polynucleotide) encoding a flavin adenine dinucleotide (FAD) conjugated glucose dehydrogenase. . . [and] a biosensor for use in the determination of glucose . . . characterized by using the enzyme.” *Id.* at 1:6–14.

The '125 patent teaches that “blood glucose level is an important marker for diabetes” and that diagnostic kits using glucose dehydrogenase were “recommended” for determining blood glucose levels. *Id.* at 1:18–32. Glucose dehydrogenase may be coenzyme-conjugated or coenzyme-unconjugated. *Id.* at

1:33–39. Coenzyme-conjugated glucose dehydrogenase is preferred because its determination sensitivity is high, it is less likely to be affected by impurities than coenzyme-unconjugated glucose dehydrogenase, and it can, in principle, be used to produce a low cost point-of-care testing device. *Id.* at 1:33–45. Coenzyme-conjugated glucose dehydrogenase “requires pyrroloquinoline quinone (PQQ), flavin adenine dinucleotide (FAD) or the like as a coenzyme.” *Id.* at 1:33–39.

Notably, in biosensors using glucose dehydrogenase to determine blood glucose levels, it is desirable that glucose dehydrogenase not react with maltose. *Id.* at 1:46–56. “Maltose is a sugar used in an infusion, and when . . . glucose dehydrogenase reacts with maltose, a blood glucose POCT [point-of-care testing] device displays a higher blood glucose level than the actual value.” *Id.* at 1:48–50.

According to the ’125 patent, FAD-conjugated glucose dehydrogenase has been purified from several different bacterial strains. *Id.* at 2:4–3:22. FAD-conjugated glucose dehydrogenase enzymes purified from *Agrobacterium tumefaciens*, *Cytophaga marinoflava*, *Agaricus bisporus*, and *Macrolepiota rhacodes* “have a high activity for maltose, and have a low selectivity for glucose.” *Id.* at 2:4–18. FAD-conjugated glucose dehydrogenase purified from *Burkholderia cepacia* similarly has a “high activity for maltose.” *Id.* at 2:19–21. In contrast, FAD-conjugated glucose dehydrogenase purified from *Aspergillus terreus* “has excellent substrate (glucose) recognition performance, . . . and also has a low activity for maltose,” but “the production amount of the enzyme is extremely small” and, because of the sugars linked to the enzyme, “the activity of the enzyme is difficult to detect (the enzymatic activity is low).” *Id.* at 2:28–61. The “existence of a coenzyme-conjugated glucose dehydrogenase derived from *Aspergillus oryzae* was suggested in 1967,” however, “only partial enzymatic

properties were revealed, . . . although a property that the enzyme does not act on maltose was suggested.” *Id.* at 2:62–67.

The ’125 patent states that “an object of the invention is to . . . provide a novel gene (polynucleotide) encoding an FAD-conjugated glucose dehydrogenase having . . . excellent reactivity to glucose, excellent thermal stability, . . . excellent substrate-recognition performance and . . . a low activity for maltose.” *Id.* at 3:59–65. The ’125 patent discloses that:

The present inventors made intensive studies in order to achieve the above object, and as a result, they found that in order to significantly express an FAD-conjugated glucose dehydrogenase in an *Aspergillus oryzae* strain, it was necessary that an amino acid sequence (AGVPWV) be contained in a polypeptide encoding a gene of the enzyme, and also confirmed that the activity was substantially lost when at least one amino acid residue in the amino acid sequence was deleted, and thus, the invention was completed.

Id. at 4:7–15. According to the ’125 patent, “using the polynucleotide of the invention, an FAD-conjugated glucose dehydrogenase having excellent properties that it has excellent substrate (glucose) recognition performance and also has a low activity for maltose can be produced uniformly in a large amount by, for example, a recombinant DNA technique.” *Id.* at 5:34–39.

D. Challenged Claim

At the time of our Institution Decision, following Patent Owners’ statutory disclaimer of claims 1–7, 9, and 10 (Ex. 2009), claim 8 was the only claim remaining in the ’125 patent. For the reasons discussed *infra*, we grant Patent Owners’ request to cancel claim 8. As the patentability of claim 8 is thus no longer at issue, we focus our analysis on the patentability of proposed substitute claim 11. Proposed substitute claim 11 is reproduced below, with ~~strikeout text indicating text that has been deleted from original claim 8~~ and underlined text indicating text that has been added to original claim 8.

11. A biosensor comprising a recombinant FAD-conjugated glucose dehydrogenase, wherein the recombinant FAD-conjugated glucose dehydrogenase ~~is selected from: (a) a polypeptide which comprises the amino acid sequence represented by SEQ ID NO: 1; and (b) consists of a polypeptide which comprises an amino acid sequence~~ having the sequence of an FAD-conjugated glucose dehydrogenase of *Aspergillus oryzae* NBRC 30104, wherein the sequence is set forth in SEQ ID NO:1 except that amino acid residue R at position 121 is replaced with an S and amino acid residue V at position 129 is replaced with an I, ~~a homology of 90% or more to the amino acid sequence (a)~~ and has an FAD-conjugated glucose dehydrogenase activity;

wherein the recombinant FAD-conjugated glucose dehydrogenase has a value of enzymatic activity for maltose of ~~10%~~ 5% or less with a value of enzymatic activity for D-glucose taken as 100%; and

wherein the biosensor is capable of detecting glucose by a pH change.

R. Mot. 18 (proposed substitute claim 11); Ex. 1005, 35:10–27, 36:22–23 (original claim 8).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of substitute claim 11 on the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
11	103(a) ¹	Omura ² , knowledge of POSA ³
11	103(a)	Omura, Tsuji ⁴ , knowledge of

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the application from which the ’987 patent issued was filed before this date, the pre-AIA version of § 103 applies.

² Omura et al., U.S. Patent No. 7,514,250 B2, issued Apr. 7, 2009 (Ex. 1010, “Omura”).

³ Person of ordinary skill in the art (“POSA”).

⁴ Tsuji et al., U.S. Patent Publication No. 2008/0014612 A1, published Jan 17, 2008 (Ex. 1007, “Tsuji”).

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
		POSA

Petitioner submits the Second Declaration of Dr. Jeffrey T. LaBelle (Ex. 1031) in support of its Opposition to Patent Owners’ Revised Motion to Amend.⁵

F. Person of Ordinary Skill in the Art

Factual indicators of the level of ordinary skill in the art include “the various prior art approaches employed, the types of problems encountered in the art, the rapidity with which innovations are made, the sophistication of the technology involved, and the educational background of those actively working in the field.” *Jacobson Bros., Inc. v. United States*, 512 F.2d 1065, 1071 (Ct. Cl. 1975); *see also Orthopedic Equip. Co., v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983) (quoting with approval *Jacobson Bros.*).

Petitioner contends that the person of ordinary skill would have “a PhD in molecular biology (or a related discipline, such as biochemistry) with at least 2 years of post-doctoral experience, or an equivalent amount of combined education and laboratory experience.” Pet. 22–23. Petitioner contends that the person of ordinary skill would also have “experience using recombinant DNA techniques to express proteins and a familiarity with protein chemistry and biosensors.” *Id.*

In their Preliminary Response, Patent Owners asserted that Petitioner used “an overly broad and insufficiently experienced definition of a POSA [person of ordinary skill in the art].” Prelim. Resp. 9. According to Patent Owners, Petitioner’s proposal that the POSA would have a “PhD in molecular biology” was insufficiently specific for an invention “directed to the use of enzymes in biosensors for measuring glucose levels.” *Id.* at 10. Patent Owners asserted that

⁵ Petitioner also provided the Declarations of Dr. Jeffrey T. LaBelle (Ex. 1008) and Dr. Anthony Edward George Cass (Ex. 1021) in support of its Petition.

the POSA should have more than just a “familiarity” with enzyme-based biosensors and protein chemistry. *Id.* Rather, the POSA should have ordinary skill in enzymology and biosensors. *Id.* Thus, according to Patent Owners:

[A] POSA would have a PhD in the field of biological chemistry or a related discipline. The POSA would also have research experience and/or knowledge in enzymology, recombinant DNA techniques, and biosensors. The POSA would further understand that enzyme-based glucose biosensors were known and would understand how they work.

Id.

In our Institution Decision, we agreed with the position Patent Owners took in their Preliminary Response – i.e., that the focus of the challenged claims was enzyme-based biosensors and thus the POSA would have more than just a familiarity with enzyme-based biosensors and protein chemistry. Inst. Dec. 8–9. Accordingly, based on the record before us at the time, we accepted the definition provided in Patent Owners’ Preliminary Response, which was consistent with the level of skill reflected in the asserted prior art references and in the specification of the ‘987 patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself can reflect the appropriate level of ordinary skill in the art).

Neither party challenges the identification of the POSA set forth in our Institution Decision. *See generally*, R. Mot.; Opp.; Reply; Sur-reply. Additionally, we find that the fully developed trial record supports the POSA identification we made in our Institution Decision. Accordingly, in this decision, we apply the identification of the POSA set forth in our Institution Decision. Inst. Dec. 9.

E. Claim Construction

In a post grant review, we construe the claims “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b).” 37 C.F.R. § 42.200. Therefore, we construe the

challenged claims under the framework set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Id.*

Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). For purposes of this decision, we need not expressly construe any claim terms.

II. CANCELLATION OF CLAIM 8

Patent Owners’ Motion to Amend requests that claim 8 be cancelled.⁶

R. Mot. 1. The Motion is not contingent on any finding by the Board regarding the patentability of claim 8. *Id.* Rather, the Motion seeks to replace challenged claim 8 with substitute claim 11 without precondition. *Id.* (“Patent Owners . . . request cancellation of claim 8 of U.S. Patent No. 9,976,125 (‘the ’125 Patent,’ Ex. 1005) and entry of new claim 11 on a noncontingent basis.”).

“A motion to amend may cancel a challenged claim” 35 U.S.C. § 316(d)(1)(A); 37 C.F.R. § 42.121(a)(3). Petitioner does not oppose the cancelation of claim 8. Accordingly, we grant Patent Owner’s Revised Motion to Amend with respect to the request to cancel challenged claim 8.

III. PATENTABILITY OF SUBSTITUTE CLAIM 11

⁶ Petitioner challenged claims 1–10 in the Petition. As noted above, prior to our decision on institution, Patent Owners filed a statutory disclaimer under 35 U.S.C. § 253(a) disclaiming claims 1–7, 9, and 10 of the ’125 patent. Accordingly, we declined to institute post-grant review with respect to disclaimed claims 1–7, 9 and 10. Inst. Dec. 6–7.

Petitioner contends that substitute claim 11 is unpatentable on two grounds: first, substitute claim 11 would have been obvious over Omura in view of the knowledge of the POSA, and second, substitute claim 11 would have been obvious over the combination of Omura and Tsuji in view of the knowledge of the POSA. Opp. 7–24. We have considered the question of patentability in view of all the evidence and arguments presented in this proceeding. Based on the record developed during this proceeding, we determine that Petitioner has shown by a preponderance of the evidence that substitute claim 11 would have been obvious over the combination of Omura, Tsuji, and the knowledge of the POSA. Because Petitioner has proven that substitute claim 11 would have been obvious, as discussed in detail below, we do not consider whether Patent Owners’ motion otherwise complies with the statutory and regulatory requirements for a motion to amend. *See*, 35 U.S.C. § 326(d)(1)(B) (requiring that the amendment propose a “reasonable number of substitute claims” and requiring that the substitute claims do “not enlarge the scope of the claims of the patent or introduce new matter”); 37 C.F.R. § 42.221 (additionally providing, *inter alia*, that a motion to amend “may be denied where . . . [t]he amendment does not respond to a ground of unpatentability involved in the trial”). Similarly, because we have determined that substitute claim 11 would have been obvious over the combination of Omura, Tsuji, and the knowledge of the POSA, as discussed in detail below, we do not reach the question of whether substitute claim 11 would also have been obvious over only Omura in view of knowledge of the POSA.

A. Principles of Law

In a post grant review, amended claims are not added to a patent as of right, but rather must be proposed as a part of a motion to amend. 35 U.S.C. § 326(d). The Board must assess the patentability of proposed substitute claims “without

placing the burden of persuasion on the patent owner.” *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1328 (Fed. Cir. 2017) (en banc); *see also Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 15 at 3–4 (PTAB Feb. 25, 2019) (precedential). Subsequent to the issuance of *Aqua Products*, the Federal Circuit issued a decision in *Bosch Automotive Service Solutions, LLC v. Matal*, 878 F.3d 1027 (Fed. Cir. 2017) (“Bosch”), as well as a follow-up order amending that decision on rehearing. *See Bosch Auto. Serv. Sols., LLC v. Iancu*, No. 2015-1928 (Fed. Cir. Mar. 15, 2018) (Order on Petition for Panel Rehearing).

In accordance with *Aqua Products*, *Bosch*, and *Lectrosonics*, a patent owner does not bear the burden of persuasion to demonstrate the patentability of the substitute claims presented in the motion to amend. Rather, ordinarily, “the petitioner bears the burden of proving that the proposed amended claims are unpatentable by a preponderance of the evidence.” *Bosch*, 878 F.3d at 1040 (as amended on rehearing); *Lectrosonics*, Paper 15 at 3–4. In determining whether a petitioner has proven unpatentability of the substitute claims, the Board focuses on “arguments and theories raised by the petitioner in its petition or opposition to the motion to amend.” *Nike, Inc. v. Adidas AG*, No. 2019-1262, 2020 WL 1802796, at *6 (Fed. Cir. Apr. 9, 2020).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of

nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Objective evidence of nonobviousness may include the following: “commercial success, long felt but unsolved needs, failure of others, etc.”⁷ *Id.*

We analyze the patentability of substitute claim 11 in accordance with the above-stated principles.

B. Scope and Content of the Prior Art

Knowledge of the POSA

FAD-conjugated glucose dehydrogenase purified from *Aspergillus oryzae* was known at least as early as 1966. Ex. 1001, 1 (journal article published in 1967 stating: “[a] glucose dehydrogenase which catalyzes the oxidation by 2,6-dichlorophenol indophenol (DCIP) of glucose to gluconic acid was purified from induced mycelia of *Aspergillus oryzae* . . . The enzyme contained I mole of FAD as prosthetic group per mole of enzyme”); *see also*, Ex. 1031 ¶ 25 (Dr. LaBelle’s well supported testimony that “[g]lucose reactivity of FAD-conjugated GDH [glucose dehydrogenase] derived from *Aspergillus oryzae* and biosensors using that reactivity were known well in advance of the ’125 Patent’s earliest priority dates”); *see also* Ex. 1002, 1; Ex. 1003, 1; Ex. 1004, 4–5; Ex. 1007. 3:28–32 (“it has already been observed that a glucose dehydrogenase whose coenzyme is a flavin adenine dinucleotide exists in a cytoplasm fraction and a culture of *Aspergillus oryzae*”).

The *Aspergillus oryzae* strain NBRC 30104 was known at least as early as 1976, when it was submitted to the NBRC culture collection database by Hideya Murakami after he successfully characterized and classified various strains of

⁷ We do not address objective indicia of nonobviousness in this opinion because Patent Owners did not present any evidence or arguments directed to objective indicia of nonobviousness during this proceeding.

Aspergillus oryzae. Ex. 1037; Ex. 1031 ¶ 22 (Dr. LaBelle testimony regarding NBRC culture collection database).

Omura

Omura discloses, in relevant part, a “biosensor [that] may be any sensor having a reaction layer containing the inventive coenzyme-binding glucose dehydrogenase as an enzyme.” Ex. 1010, 18:54–55. Omura states, “[t]he coenzyme which is bound to the inventive glucose dehydrogenase may for example be a flavin compound, including a coenzyme such as flavin adenine dinucleotide.” *Id.* at 3:10–13. Omura also states, “the inventive coenzyme-binding glucose dehydrogenase may also be a synthetic coenzyme-binding glucose dehydrogenase or a recombinant coenzyme-binding glucose dehydrogenase obtained by a gene engineering technology.” *Id.* at 17:15–19. Omura teaches that “a biosensor can be constructed so that the chromogenic intensity or pH change is detected.” *Id.* at 19:3–4.

As to the source of its coenzyme-binding glucose dehydrogenase, Omura discloses that “[i]t has already been observed that a glucose dehydrogenase whose coenzyme is a flavin dinucleotide exists in a cytoplasm fraction and a culture of *Aspergills oryzae*.” *Id.* at 3:28–32. According to Omura, this enzyme has “poor stability” and can only be quenched using a heavy metal, which creates problems with waste disposal. *Id.* at 3:35–41. Omura discloses that the “coenzyme-binding glucose dehydrogenase discovered in [its] invention is characterized by its higher stability when compared with that of the known *Aspergillus orzyae*-derived coenzyme-binding glucose dehydrogenase, and also by a favorably convenient handling for quenching.” *Id.* at 3:41–48. The microorganism from which Omura’s coenzyme-binding glucose dehydrogenase is derived is “preferably a eukaryotic microorganism, more preferably, genus *Aspergillus*, further preferably, *Aspergillus*

terreus, and most preferably, the deposited strain FERM BP-08578.” *Id.* at 3:51–56.

Tsuji⁸

Tsuji discloses that “[i]t is an object of [Tsuji’s] invention to provide a method for efficiently producing the practically more advantageous enzyme for the blood glucose sensor.” Ex. 1007 ¶ 7. To this end, the inventors in Tsuji, “isolated the gene encoding the flavin-binding glucose dehydrogenase derived from *Aspergillus oryzae*.” *Id.* ¶ 27; *id.* ¶ 8 (disclosing that Tsuji’s inventors “acquired a glucose dehydrogenase gene derived from *Aspergillus oryzae* by utilizing [the] database of [the] National Center for Biotechnology Information (NCBI) and found that glucose dehydrogenase derived from *Aspergillus oryzae* could be acquired from *Escherichia coli* using the gene”). The enzyme isolated in Tsuji “does not act upon maltose in a broad sense and is suitable for the glucose sensor.” *Id.* ¶ 85; *see also, id.* ¶ 81 Table 1 (showing glucose reactivity of 100 and maltose reactivity of 0.4).

C. *Analysis*

Omura discloses a biosensor similar to that recited in substitute claim 11, with the principal differences between Omura’s biosensor and the claimed biosensor being that Omura does not disclose the use FAD-conjugated glucose dehydrogenase derived from the claimed strain of *Aspergillus oryzae*, and that the FAD-conjugated glucose dehydrogenase in Omura’s biosensor does not have the

⁸ At one point in this proceeding, Patent Owner challenged the status of Tsuji as prior art. *See, e.g.*, R. Mot. 12–13. At the hearing, Patent Owner represented that it no longer contends that Tsuji is not prior art. Tr. 32:21–33:4; *see also*, Opp. 15–18 (explaining Petitioner’s position as to why Tsuji constitutes prior art). As this point is no longer contested, and for the reasons set forth in our analysis in the Preliminary Guidance on the Motion to Amend (Paper 27, 7–8), we treat Tsuji as prior art to the ’125 patent.

amino acid sequence recited in substitute claim 11. The contested issues in this case focus principally on these differences. In particular, the parties dispute: 1) whether it would have been obvious to use FAD-conjugated glucose dehydrogenase derived from the claimed strain of *Aspergillus oryzae*, and 2) whether, as Patent Owners contend, the POSA would have faced insurmountable obstacles in trying to obtain the claimed amino acid sequence from *Aspergillus oryzae* strain NCBR 30104. We address these arguments in the context of analyzing the record with respect to each individual claim limitation recited in claim 11. We address each limitation in the sequence in which it is presented in the claim.

“A biosensor comprising recombinant FAD-conjugated glucose dehydrogenase . . .”

Substitute claim 11 recites a “biosensor comprising a recombinant FAD-conjugated glucose dehydrogenase.” Petitioner contends that both Omura and Tsuji disclose biosensors using recombinant FAD-conjugated glucose dehydrogenase. Opp. 7–8, 18–19.

Patent Owners do not contest that Omura and Tsuji disclose this element. *See generally*, R. Mot.; Reply.

We find that the evidence of record supports that both Omura and Tsuji disclose biosensors using recombinant FAD-conjugated glucose dehydrogenase. Ex. 1010, 18:54–55 (Omura disclosing biosensor containing “coenzyme-binding glucose dehydrogenase”); *id.* at 3:10–13 (disclosing that the coenzyme may be “flavin adenine dinucleotide.”); *id.* at 17:15–19 (disclosing that the coenzyme-binding glucose dehydrogenase may be obtained recombinantly); Ex. 1007 ¶ 7 (Tsuji disclosing objective to obtain an enzyme for the blood glucose sensor); *id.*

¶ 27 (disclosing isolation of gene encoding flavin-binding glucose dehydrogenase); *id.* ¶ 8 (disclosing that enzyme can be produced in *Escherichia coli*).

“ . . . wherein the recombinant FAD-conjugated glucose dehydrogenase consists of a polypeptide having the sequence of an FAD-conjugated glucose dehydrogenase of *Aspergillus oryzae* NBRC 30104 . . . ”

Substitute claim 11 recites that the “recombinant FAD-conjugated glucose dehydrogenase consists of a polypeptide having the sequence of an FAD-conjugated glucose dehydrogenase of *Aspergillus oryzae* NBRC 30104.” Neither Omura nor Tsuji disclose a biosensor that uses FAD-conjugated glucose dehydrogenase from the specifically recited strain of *Aspergillus oryzae*. Petitioner contends, however, that the POSA would have been aware that *Aspergillus oryzae* was a source for FAD-conjugated glucose dehydrogenase, and that a POSA, “equipped with the disclosure of recombinant FAD-conjugated GDH-based biosensors as in Tsuji and Omura[,] would have found it obvious to produce a biosensor having FAD-conjugated GDH comprising the amino acid sequence [from] . . . a previously known strain of *Aspergillus oryzae*, NBRC 30104.” Opp. 21–22.

More specifically, Petitioner contends that “[t]he functionality of the FAD-conjugated GDH from *Aspergillus oryzae* NBRC 30104 is indistinguishable from other strains of *Aspergillus oryzae*.” Opp. 22 (citing Ex. 1031 ¶¶ 26, 43); *id.* at 10–11 (“The ’125 Patent fails to demonstrate the advantage of NBRC 30104 over any of the other active FAD-conjugated GDH enzymes isolated from *Aspergillus oryzae*.”). Petitioner thus argues that it would have been obvious and “relatively simple” to substitute FAD-conjugated glucose dehydrogenase derived from the claimed strain of *Aspergillus oryzae* for FAD-conjugated glucose dehydrogenase derived from *Aspergillus terreus* as disclosed in Omura. *Id.* at 23; *see also* Sur-

reply 6 (arguing that “[t]he substitution of one element known in the art for a known equivalent is obvious”). Indeed, according to Petitioner, “any strain . . . would have been obvious to use in a known biosensor construction for detecting glucose.” Opp. 23. Petitioner contends that the POSA would have expected success “based on the similarities in characteristics of the enzymes.” Ex. 1031 ¶ 49 (cited at Opp. 23).

Patent Owners argue that there are over 185 species of *Aspergillus* and over 600 strains of *Aspergillus oryzae* and thus the POSA would have “no reason to select the FAD-GDH of the NBRC 30104 strain to produce the claimed recombinant sequence.” Reply 6. According to Patent Owners, “Petitioner and its expert are throwing darts,” as there is no indication in the cited art which of the possible 600 strains of *Aspergillus oryzae* would be most promising to try. *Id.* at 6–7. Patent Owners argue that “neither Petitioner nor its expert provide any motivation as to why a POSA would have chosen the FAD-GDH of the NBRC 30104 strain over the other 599 strains.” *Id.* at 6.

Particularly given the relatively high degree of skill in the art, which includes “research experience and/or knowledge in enzymology . . . and biosensors,” we agree with Petitioner that it would have been obvious to a POSA to substitute FAD-conjugated glucose dehydrogenase derived from the claimed strain of *Aspergillus oryzae* for FAD-conjugated glucose dehydrogenase derived from *Aspergillus terreus* as disclosed in Omura.

As an initial matter, the evidence of record supports that it was known to use FAD-conjugated glucose dehydrogenase from *Aspergillus oryzae* to detect glucose. In particular, Tsuji discloses that glucose dehydrogenase sourced from *Aspergillus oryzae* “does not act upon maltose in a broad sense,” “is suitable for the glucose sensor,” and can be produced “on a large scale by the use of recombinant

Escherichia coli.” Ex. 1007 ¶ 85; *see also id.* ¶¶ 7, 8; Ex. 1004, 4–5 (disclosing that “[p]referred sources” of FAD-conjugated glucose dehydrogenase for sensing glucose “include *Aspergillus oryzae* strain ATC 9102”); Ex. 1010, 3:28–31 (“It has already been observed that a glucose dehydrogenase whose coenzyme is a flavin adenine dinucleotide exists in a cytoplasm fraction and a culture of *Aspergillus oryzae*.”); Ex. 1002, 3 (disclosing that FAD-conjugated GDH enzyme derived from *Aspergillus oryzae* strain reacted with glucose but did not react with maltose “to measurable extents”).

We recognize that Omura discloses that *Aspergillus terreus* strain FERM BP-08578 is the most preferred source of FAD-conjugated glucose dehydrogenase, but this does not negate the general teaching of the genus *Aspergillus* as a preferred source. Ex. 1010, 3:53–56; *Merck & Co. Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (“[I]n a section 103 inquiry, ‘the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.’”) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)); *see also, Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (“A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination.”). Moreover, as discussed above, Tsuji discloses that glucose dehydrogenase sourced from *Aspergillus oryzae* “does not act upon maltose in a broad sense,” “is suitable for the glucose sensor,” and can be produced “on a large scale by the use of recombinant *Escherichia coli*. Ex. 1007 ¶ 85.

We also acknowledge that there is no evidence of record that *Aspergillus oryzae* strain NBRC 30104 was used to sense glucose prior to the filing of Patent Owner’s priority application. However, the record does include evidence

supporting that the POSA would have understood that enzyme activity toward glucose and maltose is preserved across the genus *Aspergillus* and, more specifically, that glucose dehydrogenase enzymes derived from different species of *Aspergillus* can be used in a glucose biosensor. Ex. 1010, 3:53–54 (Omura identifying the “genus *Aspergillus*” as a preferred microorganism source of “coenzyme-binding glucose dehydrogenase” for use in Omura’s invention), 3:28–55 (identifying *Aspergillus oryzae* as a source of FAD-conjugated glucose dehydrogenase and singling out *Aspergillus terreus* strain FERM BP-08578 as the most preferred source of FAD-conjugated glucose dehydrogenase because it exhibits high stability and is conveniently quenched);⁹ Ex. 1004, 3–4 (disclosing sensing glucose, teaching that the “glucose dehydrogenase enzymes may be obtained from any microorganism containing these enzymes,” and identifying the genus *Aspergillus* as a source of E.C.1.1.99.10, i.e., FAD-conjugated glucose dehydrogenase); Ex. 1030, 5–6 (disclosing that FAD-conjugated glucose dehydrogenase sourced from *Aspergillus niger* has low maltose activity as compared to glucose). This evidence supports Dr. LaBelle’s testimony that “there appears to be some appreciation in the art that functional difference[s], while they do exist, are relatively minor and do not vary much with respect to activity toward glucose and maltose at the genus and even species level.” Ex. 1031 ¶ 27.

In view of the evidence that enzyme functionality is preserved at the genus level, Dr. LaBelle persuasively concludes that “it would . . . follow that little difference would . . . exist among the strains within a particular species.” *Id.* More

⁹ Dr. LaBelle explains, in persuasive and un rebutted testimony, that these teachings from Omura would have suggested to a POSA that “FAD-conjugated GDH of *Aspergillus oryzae* does not differ functionally from *Aspergillus terreus* in relation to activity toward glucose and maltose but that differences rested with stability.” Ex. 1031 ¶ 27.

specifically, Dr. LaBelle testifies that the POSA “would recognize the high probability that FAD-conjugated GDH would be functionally the same toward glucose across *Aspergillus oryzae* strains.” Ex. 1031 ¶ 28. This testimony is un rebutted and persuasive.

Patent Owners do not direct us to persuasive evidence that the POSA would expect active glucose dehydrogenase sourced from different strains of *Aspergillus oryzae* to function differently when used to sense glucose that would undermine Petitioner’s persuasive showing. Indeed, Patent Owners concede that strains of *Aspergillus oryzae* with active glucose dehydrogenase are functionally equivalent. Tr. 29 (“JUDGE COTTA: So, counsel, as between those strains that do have activity, is there any evidence that they are not functional equivalents of each other? MR. GEORGE: No, I mean, the strains that have activity are functionally equivalent of each other.”).

At oral argument, the parties and the panel discussed whether Table 1 of the ’125 patent, which is reproduced below, showed differences among strains of *Aspergillus oryzae*. Tr. 10:24–13:16, 15:21–17:8, 21:10–23:12, 30:3–30:26.

TABLE 1		
Strain (<i>Aspergillus oryzae</i>)	Presence or absence of FAD-conjugated glucose dehydrogenase activity in culture supernatant or CFE	Presence or absence of amino acid sequence: AGVPWV
NBRC 5375	Presence	Presence
NBRC 100959	Absence	Absence
NBRC 4079	Presence	Presence
NBRC 4203	Presence	Presence
NBRC 4214	Presence	Presence
NBRC 4268	Presence	Presence
NBRC 5238	Presence	Presence
NBRC 6215	Presence	Presence
NBRC 30104	Presence	Presence
NBRC 30113	Presence	Presence
NBRC 4181	Absence	Absence
NBRC 4220	Absence	Absence

Table 1 presents results from the inventors’ attempts to confirm glucose dehydrogenase activity for each of twelve strains of *Aspergillus oryzae*. Ex. 1005, 19:50–20:19. Table 1 also correlates these results with the presence or absence of

amino acid sequence AGVPWV, a sequence that the '125 patent teaches is critical to glucose dehydrogenase activity. *Id.* at 4:6–16, 6:14–19, and 21:10–14. The results provided in Table 1 indicate that the inventors were able to confirm glucose dehydrogenase activity in 9 out of 12 strains of *Aspergillus oryzae*.

Patent Owners did not provide argument that Table 1 evidenced differences among strains of *Aspergillus oryzae* in their briefing on their motion to amend. *See generally* R. Mot.; Reply. Accordingly, any such argument is waived.¹⁰ However, even if we were to consider it, and to credit Table 1 as showing that some strains of *Aspergillus oryzae* lack active glucose dehydrogenase,¹¹ we would still find the claimed biosensor obvious. When balanced against the evidence that several strains of *Aspergillus oryzae* were understood to produce active glucose

¹⁰ At oral argument, Patent Owners also discussed Tsuji's inability to obtain functional glucose dehydrogenase from *Aspergillus oryzae* strain RIB 40. Tr. 27:14–28:21, 30:18–31:5. To the extent Patent Owners argue that the RIB 40 strain evidence differences among strains of *Aspergillus oryzae*, such argument is waived because it was not included in Patent Owners' briefing. But even if we were to consider Tsuji's discussion of the RIB 40 strain, and credit it as evidence that the strain does not have active glucose dehydrogenase rather than simply as evidence that Tsuji failed to sequence glucose dehydrogenase from the RIB 40 strain, we would consider it cumulative of the evidence provided by Table 1 of the '125 patent.

¹¹ Dr. LaBelle testifies that the absence of glucose dehydrogenase activity in some of the strains in Table 1 may be due to growth conditions and/or the medium on which the organism is cultured. Ex. 1031 ¶¶ 30–32. This testimony is potentially at odds with the teaching in the '125 patent that the amino acid sequence AGVPWV is critical to expression of glucose dehydrogenase and that the three inactive strains in Table 1 lack this critical sequence. Ex. 1005, 4:6–16, 6:14–19, 20:1–19, and 21:10–14. While we note this potentially conflicting evidence, for purposes of our discussion of the evidence in Table 1, we credit Table 1 as evidencing a lack of activity in three strains of *Aspergillus oryzae*.

dehydrogenase (*see, e.g.*, Ex. 1001, 1;¹² Ex. 1004, 4; 1007 ¶ 7, 8, 85; Ex. 1010 3:28–31) and that that glucose dehydrogenase activity was understood to be preserved at the genus level (*see, e.g.*, Ex. 1010, 3:53–54, 3:28–32, 3:53–55; Ex. 1004, 3–4; Ex. 1031 ¶ 27), the existence of certain strains of *Aspergillus oryzae* that lack glucose dehydrogenase activity does not defeat the reasonable expectation of success of a POSA in practicing the claimed invention. *See* Ex. 1031 ¶ 28 (unrebutted testimony of Dr. LaBelle that the POSA “would recognize the high probability that FAD-conjugated GDH would be functionally the same toward glucose across *Aspergillus oryzae* strains”).

Moreover, methods of testing the activity of glucose dehydrogenase with respect to glucose were known well before Patent Owners filed their priority application. *See e.g.*, Ex. 1001, 2 (“Glucose dehydrogenase activity was measured as described previously . . .”); Ex. 1002, 2; Ex. 1003, 2; Ex. 1007 ¶¶ 62–64 (“the glucose dehydrogenase activity is measured under the following condition[s] . . .”); Ex. 1010, 17:45–18:16 (describing “Enzymatic Activity Measurement Method 1” and “Enzymatic Activity Measurement Method 2”); Ex. 1004, 7–8, 9.

Accordingly, the POSA would have known to identify strains of *Aspergillus oryzae* that have active glucose dehydrogenase using known methods and to use strains of *Aspergillus oryzae* with active rather than inactive glucose dehydrogenase as a source of enzymes for use in biosensor. Ex. 1031 ¶ 29 (Dr. LaBelle testimony that “so long as there is a functional FAD-conjugated glucose dehydrogenase isolated from *Aspergillus oryzae*, a POSA would be able to utilize it within the biosensor as recited in PO’s substitute claim 11 and have a reasonable expectation of achieving success.”). Accordingly, even if we were to consider

¹² Exhibits 1002 and 1003 also disclose active glucose dehydrogenase sourced from *Aspergillus oryzae*, but appear to rely on the same strain of *Aspergillus oryzae* as Ex. 1001. *See*, Ex. 1002, 2 n.2; Ex. 1003, 2 n.1.

Patent Owner's argument that Table 1 of the '125 patent illustrates active and inactive strains of *Aspergillus oryzae*, we would still find that it obvious to use glucose dehydrogenase derived from the NBRC 30104 in a biosensor.

In sum, the evidence supports that FAD-conjugated glucose dehydrogenase from the genus *Aspergillus* and, more specifically, from the species *Aspergillus oryzae*, was known to have active FAD-conjugated glucose dehydrogenase that could be used in a glucose sensor. The evidence also supports that the POSA "would recognize the high probability that FAD-conjugated GDH would be functionally the same toward glucose across *Aspergillus oryzae* strains." Ex. 1031 ¶ 28. In view of this evidence, we agree with Dr. LaBelle that it would have been obvious to use the claimed strain of *Aspergillus oryzae* in Omura's biosensor. Dr. LaBelle explains:

Given the known properties of FAD-conjugated GDH from *Aspergillus* in general, and specifically *Aspergillus oryzae*, a POSA would have been motivated to use the FAD-conjugated GDH from any *Aspergillus oryzae* strain, including NBRC 30104 instead of the FAD-conjugated GDH from *Aspergillus terreus* in the FAD-conjugated GDH-based biosensors described in Omura based on the similarities in characteristics of the enzyme and the desire to industrially produce a coenzyme-binding glucose dehydrogenase in a commercial expression vector.

Id. ¶ 41; *see also id.* ¶¶ 47–49 (discussing motivation provided by Tsuji). We further agree with Dr. LaBelle that the POSA would reasonably have expected this substitution of known equivalents to be successful "based on the similarities in characteristics of the enzymes." *Id.* ¶ 49; *see also id.* ¶ 42.

"... wherein the sequence is set forth in SEQ ID NO:1 except that amino acid residue R at position 121 is replaced with an S and amino acid residue V at position 129 is replaced with an I ..."

Substitute claim 11 recites that the polypeptide sequence “is set forth in SEQ ID NO:1 except that amino acid residue R at position 121 is replaced with an S and amino acid residue V at position 129 is replaced with an I.” Petitioner contends that “the sequence recited in claim 11 is necessarily present in the NBRC 30104 strain, is well within the skill of a POSA to obtain, and would therefore necessarily be 100% identical to that of the FAD-conjugated GDH found in the NBRC 30104 strain.” Opp. 6 (citing Ex. 1031 ¶¶ 33, 34), 19–20 (citing Ex. 1007 ¶¶ 24–28; Ex. 1010, 17:19–36). Petitioner then asserts that with the sequence in hand, a POSA would have been able to produce the FAD-conjugated GDH recombinantly. *Id.* at 9 (“a POSA only needs to obtain the amino acid sequence for the FAD-conjugated GDH of *Aspergillus oryzae* in order to produce a recombinant GDH enzyme”), 20 (“a POSA can obtain the amino acid sequence of FAD-conjugated GDH of *Aspergillus oryzae* . . . in order to produce a recombinant GDH enzyme thereof.”).

Patent Owners do not contest that the claimed sequence is inherently present in *Aspergillus oryzae* NBRC 30104. Nor do Patent Owners contest that with the claimed sequences, the POSA would be able to produce a recombinant enzyme. Instead, Patent Owners contend that Petitioner and Dr. LaBelle “improperly conflate (i) the prior existence of the *A. oryzae* NBRC 30104 mold organism with (ii) possession of the requisite NBRC 30104 FAD-GDH amino acid sequence or gene sequence information (which was not known), and possession of recombinant NBRC 30104 FAD-GDH itself (which was also not known).” Reply 2. According to Patent Owner, “[s]imply being in possession of *A. oryzae* NBRC 30104 mold does not put a POSA in possession of NBRC 30104 FAD-GDH amino acid sequence information, which is needed to produce the claimed recombinant FAD-GDH.” *Id.*

We agree with Petitioner that the claimed sequence is necessarily present in the NBCR 30104 strain, that it would have been well within the skill of a POSA to obtain, and that once in possession of the sequence, the POSA would have been able to produce FAD-conjugated GDH recombinantly.

With respect to the identity of the claimed sequence to the sequence present in FAD-conjugated glucose dehydrogenase derived from NBCR 30104, Petitioner's position is supported by the testimony of Dr. LaBelle, who testifies:

The specific amino acid sequence of FAD-conjugated GDH enzyme from a known source, *Aspergillus oryzae* NBRC 30104, is inherent[ly] present. As such, the FAD-conjugated GDH of NBRC 30104 would therefore necessarily have 100% identity with the amino acid sequence recited in PO's substitute claim 11.

Ex. 1031 ¶ 34. Dr. LaBelle's testimony on this point is consistent with the record, including the description in the '025 patent of the claimed sequences as being "derived from *Aspergillus oryzae* NBRC 30104." See e.g, Ex. 1005, 20:31–41. Patent Owners do not direct us to contradictory evidence or provide argument that calls Dr. LaBelle's testimony into question. Accordingly, we credit Dr. LaBelle's testimony that FAD-conjugated glucose dehydrogenase derived from *Aspergillus oryzae* strain NBRC 30104 would have an amino acid sequence 100% identical to that recited in substitute claim 11.

With respect to the ability of the POSA to obtain the claimed sequence, Omura teaches that "[t]hose skilled in the art can obtain the coenzyme-binding glucose dehydrogenase readily based on the disclosure of the protein or its salt derived from the physiochemical characteristics of the inventive coenzyme." Ex. 1010, 17:19–23. Omura also discloses that its coenzyme may be "recombinant" and can be produced "industrially using a gene engineering method in which a gene segment of the coenzyme-binding glucose dehydrogenase is inserted into a

known expression vector.” *Id.* at 17:15–36. This supports that the POSA would have been able to obtain the claimed sequence and express it recombinantly.

Tsuji also supports that the POSA would have been able to obtain the claimed sequence. It discloses a method by which the gene and amino acid sequence of FAD-conjugated glucose dehydrogenase derived from *Aspergillus oryzae* was determined, even though “the amino acid sequence and the base sequence encoding the Flavin-binding glucose dehydrogenase derived from *Aspergillus oryzae* were not specified in the NCBI database.” Ex. 1007, ¶¶ 24 (disclosing absence of sequence in NCBI database), 69–71 (summarizing method of obtaining sequence), 75–79 (detailed discussion of obtaining the sequence).

In addition to the disclosures in the art supporting that a POSA would have been able to obtain the claimed sequence, Dr. LaBelle testifies that it was “well within the knowledge of a POSA to obtain an amino acid sequence of an enzyme known to exist in an organism” or to obtain “the DNA sequence encoding that particular enzyme.” Ex. 1031 ¶ 34. As this testimony is consistent with the art, and not persuasively rebutted, we credit it.

To counter this evidence, Patent Owners direct us to the disclosure in Tsuji that one of the methods that Tsuji used to try to obtain the sequence of FAD-conjugated glucose dehydrogenase from *Aspergillus oryzae* was unsuccessful. According to Patent Owners, “Tsuji shows that in 2006, POSAs encountered insurmountable technical hurdles in trying to directly obtain even a partial amino acid sequence of FAD-GDH from both *Aspergillus terreus* and *Aspergillus oryzae* using conventional sequencing techniques.” Reply 9. Patent Owners argue that Tsuji’s “contemporaneous statements regarding the POSA’s complete failure with conventional sequencing methods in 2006 directly contradict the Petitioner’s (and Prof. LaBelle’s) blasé assertions 13 years later that ‘a POSA *only* needs to obtain

the amino acid sequence for the FAD-conjugated GDH of *Aspergillus oryzae* in order to produce a recombinant GDH enzyme.” *Id.*

We acknowledge that one of the methods used by Tsuji was unsuccessful in obtaining the sequence of FAD-conjugated glucose dehydrogenase. *See* Ex. 1007 ¶ 26 (disclosing that the inventors “had no choice but to give up the cloning utilizing the partial amino acid sequence”); *see also, id.* ¶¶ 67, 68, 73, 74.

However, we do not find this persuasive of the inability of the POSA to obtain the claimed sequence because Tsuji’s disclosure also includes a method that was successful in obtaining the sequence of FAD-conjugated glucose dehydrogenase. *Id.* ¶¶ 27 (“the present inventors isolated the gene encoding the flavin-binding glucose dehydrogenase derived from *Aspergillus oryzae* and completed the present invention”), 69–71, 75–79.

Patent Owners argue that Tsuji’s second, successful method does not provide a viable path by which a POSA could obtain the claimed sequence. Reply 10–11. In Tsuji’s second method, Tsuji’s inventors used a FAD-conjugated glucose dehydrogenase amino acid sequence from *P. lilacinoechinulatum*, a microorganism from an entirely different genus, as a base for comparing to polypeptides isolated from *Aspergillus oryzae*. Ex. 1007 ¶¶ 77–79. Patent Owners argue that this should not have worked as the sequence from *P.*

lilacinoechinulatum had only 49% sequence similarity when compared to *Aspergillus oryzae*’s sequence, far below the 80% similarity that Patent Owners contend is the “yardstick for homology cloning.” Reply 11 (citing Ex. 2022).

Patent Owners thus contend that a “POSA would have viewed Tsuji’s experiments as a lucky break, and would not view them as a viable path forward.” *Id.* at 11.

This argument is not persuasive for two reasons.

First, Patent Owners neglect to consider that Tsuji is prior art, and thus the POSA would have knowledge of all that Tsuji discloses, including an amino acid sequence for FAD-linked glucose dehydrogenase derived from *Aspergillus oryzae*. See, e.g., Ex. 1007 (SEQ ID NO: 4).¹³ The availability of this sequence as a starting point for sequencing efforts vitiates Patent Owners' argument that the POSA would not have viewed Tsuji's as providing a "viable path forward."

Second, Patent Owners' contention is based entirely on attorney argument. As discussed above, Petitioner's position is supported by the testimony of Dr. LaBelle and by the prior art of record. Particularly given the relatively high level of skill in the art, which includes experience with "recombinant DNA techniques," we credit Dr. LaBelle's well supported testimony that it was "well within the knowledge of a POSA to obtain an amino acid sequence of an enzyme known to exist in an organism" and also to "obtain the DNA sequence encoding that particular enzyme," over Patent Owners' unsupported attorney argument to the contrary. Ex. 1031 ¶ 34.

In sum, the evidence supports Petitioner's position that "the sequence recited in claim 11 is necessarily present in the NBRC 30104 strain, is well within the skill of a POSA to obtain, and would therefore necessarily be 100% identical to that of the FAD-conjugated GDH found in the NBRC 30104 strain." Opp. 6.

The evidence also supports that once such sequence was obtained, a POSA would be capable of, and motivated to, use the sequence to produce the enzyme recombinantly industrially. Ex. 1007 ¶ 85; Ex. 1010, 17:15–36.

"... and has an FAD-conjugated glucose dehydrogenase activity; wherein the recombinant FAD-conjugated glucose dehydrogenase has a value of enzymatic

¹³ Petitioner asserts that SEQ ID NO:4 of Tsuji was 100% identical to SEQ ID NO:1 of the '125 patent. Pet. 42; see also Ex. 1008 ¶ 34; Ex. 1021 ¶ 32.

activity for maltose of 5% or less with a value of enzymatic activity for D-glucose taken as 100% . . .”

Substitute claim 11 recites that the polypeptide “has an FAD-conjugated glucose dehydrogenase activity” and that “the recombinant FAD-conjugated glucose dehydrogenase has a value of enzymatic activity for maltose of 5% or less with a value of enzymatic activity for D-glucose taken as 100%.” Petitioner contends that the relative enzymatic activity is “an inherent functional property that necessarily results from a known FAD-conjugated GDH enzyme.” Opp. 11–12. More specifically, Petitioner contends that a biosensor that uses a sequence identical to that recited in substitute claim 11 would “necessarily possess the [claimed] relative enzymatic activity toward maltose and glucose.” *Id.* at 12. Petitioner also provides evidence that it was known that “the FAD-conjugated GDH enzyme present in *Aspergillus* generally, and more specifically *Aspergillus oryzae*, exhibited low or reduced enzymatic activity towards maltose as compared to glucose.” *Id.*

Patent Owners do not contest that a biosensor having the recited amino acid sequence would necessarily have the claimed relative enzymatic activity. *See generally* R. Mot.; Reply.

We find that the evidence of record supports that a biosensor that used FAD-conjugated glucose dehydrogenase having the recited amino acid sequence would necessarily have the claimed relative activity level. Ex. 1031 ¶ 35 (Dr. LaBelle’s un rebutted testimony that “the activity level demonstrated in FAD-conjugated glucose dehydrogenase enzymes from *Aspergillus oryzae* flows directly as a result of the protein sequence” and that “the activity level demonstrated toward glucose and maltose are properties of the particular protein sequence”).

“... and wherein the biosensor is capable of detecting glucose by a pH change.”

Substitute claim 11 recites that “the biosensor is capable of detecting glucose by a pH change.” Petitioner contends that Omura discloses this element. Opp. 13, 21.

Patent Owners do not contest that Omura discloses this element. *See generally* R. Mot.; Reply.

We find that the evidence of record supports that Omura discloses a biosensor capable of detecting glucose by a pH change. Ex. 1010, 19:3–4 (Omura disclosure that “a biosensor can be constructed so that the chromogenic intensity or pH change is detected.”); Ex. 1031 ¶ 45 (Dr. LaBelle’s testimony that “[g]lucose biosensors operable by detecting a pH change [are] also known in the art and described in Omura.”).

D. Summary with Respect to Obviousness

Having fully considered the parties’ arguments and the evidence of record, we find that it would have been obvious to use FAD-conjugated glucose dehydrogenase from any strain of *Aspergillus oryzae* having active glucose dehydrogenase, including strain NBRC 30104, in a biosensor like that described in Omura that detects glucose by a pH change. We further find that a POSA would have been capable of obtaining the amino acid sequence of FAD-conjugated glucose dehydrogenase in strain NBRC 30104, and motivated to do so in order to express it recombinantly at scale. Finally we find that FAD-conjugated glucose dehydrogenase so expressed would inherently have the claimed sequence and relative activity toward glucose and maltose. We thus find that the Petitioner has established, by a preponderance of the evidence, that a POSA would have found

substitute claim 11 obvious over the combination of Omura, Tsuji, and the knowledge in the art. Accordingly, we deny Patent Owners' motion to enter proposed substitute claim 11.

IV. CONCLUSION

For the foregoing reasons, we grant Patent Owners' request to cancel claim 8, and deny Patent Owners' request to enter proposed substitute claim 11, as summarized in the following table:

Motion to Amend Outcome	Claim(s)
Original Claims Cancelled by Amendment	8
Substitute Claims Proposed in the Amendment	11
Substitute Claims: Motion to Amend Granted	
Substitute Claims: Motion to Amend Denied	11
Substitute Claims: Not Reached	

IV. ORDER

Accordingly, it is

ORDERED that Patent Owners' Motion to Amend is *granted* as to its non-contingent request to cancel claim 8;

FURTHER ORDERED that Patent Owners' Motion to Amend is *denied* as to substitute claims 11.

PGR2019-00032
Patent 9,976,125 B2

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