Trials@uspto.gov
571.272.7822

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BUTAMAX™ ADVANCED BIOFUELS LLC,
Petitioner,

v.

GEVO, INC.,
Patent Owner.

Case IPR2013-00539
Patent 8,273,565 B2

Before RAMA G. ELLURU, CHRISTOPHER L. CRUMBLEY, and KERRY BEGLEY, *Administrative Patent Judges.*

BEGLEY, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

Butamax™ Advanced Biofuels LLC ("Petitioner") filed a Petition requesting *inter partes* review of claims 1–19 of U.S. Patent No. 8,273,565 B2 (Ex. 1001, "the '565 patent"). Paper 4 ("Pet."). Pursuant to 35 U.S.C. § 314(a), we determined the Petition showed a reasonable likelihood that Petitioner would prevail in establishing the unpatentability of claims 1–9 and 11–19 of the '565 patent, and instituted an *inter partes* review of these

claims on certain asserted grounds of unpatentability. Paper 9 ("Inst. Dec."). We, however, did not institute review of claim 10 of the '565 patent, because we determined the Petition did not show a reasonable likelihood that Petitioner would prevail in establishing the claim to be unpatentable. *Id.* at 27–29.

Patent Owner Gevo, Inc. ("Patent Owner") then filed a Patent Owner Response. Paper 19 ("PO Resp."). Petitioner filed a Reply to Patent Owner's Response. Paper 21 ("Reply").

An oral hearing was held on October 28, 2014, pursuant to a request by Petitioner. Paper 32 ("Tr."); Petitioner Butamax's Request for Oral Argument (Paper 23); Order – Trial Hearing (Paper 24), at 1. During the oral hearing, Petitioner presented argument; Patent Owner rested on its arguments in the Patent Owner Response. Tr. 40:3–13; *see id.* at 39:7–42:18; Order – Conduct of the Proceeding (Paper 25).

We issue this Final Written Decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons that follow, we determine Petitioner has shown by a preponderance of the evidence that claims 1–9 and 11–19 of the '565 patent are unpatentable.

I. BACKGROUND

A. THE '565 PATENT

The '565 patent, titled "Methods of Increasing Dihydroxy Acid Dehydratase Activity to Improve Production of Fuels, Chemicals, and Amino Acids," is directed to recombinant yeast microorganisms with increased activity of dihydroxy acid dehydratase ("DHAD"). Ex. 1001, [57], 1:29–2:25. DHAD is an enzyme that catalyzes steps in various biosynthetic pathways that produce metabolites, such as isobutanol, a

common fuel additive. *Id.* at [57], 1:46–66, Fig. 1. Increased DHAD activity is favorable for producing these metabolites. *Id.* at 1:65–2:20, 24:31–33. The patent also discloses methods of producing such metabolites by cultivating the disclosed recombinant microorganisms in a culture medium containing a carbon source feedstock. *Id.* at [57], 8:55–63.

The specification of the '565 patent discloses recombinant microorganisms with increased DHAD activity resulting from alterations in the regulation, expression, or activity of either or both the *GRX3* and *GRX4* genes, which encode the proteins monothiol glutaredoxin-3 ("Grx3") and monothiol glutaredoxin-4 ("Grx4"), respectively. *Id.* at 24:36–50; *see id.* at 23:30–57, 24:1–30. For example, in one embodiment, the Grx3 protein, the Grx4 protein, or both the Grx3 and Grx4 proteins are "deleted or attenuated." *Id.* at 24:9–11. The specification also discloses recombinant microorganisms with improved DHAD activity resulting from overexpression of either or both the transcriptional activator genes *AFT1* and *AFT2*, which encode activator of ferrous transport ("Aft") proteins, Aft1 and Aft2, respectively. *Id.* at 2:9–25, 4:14–26, 15:49–54. The DHAD in these embodiments may be localized in either the cytosol or the mitochondria of the microorganisms. *Id.* at 3:30–46, 16:33–34, 24:36–45. Further, the recombinant microorganisms may be one of various disclosed yeast genera and species, including *Saccharomyces cerevisiae*. *See id.* at 7:49–8:54.

B. ILLUSTRATIVE CLAIM

Claim 1, the only independent claim of the '565 patent, is illustrative of the challenged claims:

> 1. A recombinant yeast microorganism comprising a recombinantly overexpressed polynucleotide encoding a dihydroxy acid dehydratase (DHAD),

> wherein said recombinant yeast microorganism is engineered to comprise at least one inactivated monothiol glutaredoxin selected from the group consisting of monothiol glutaredoxin-3 (GRX3) and monothiol glutaredoxin-4 (GRX4),
>
> and wherein said inactivated monothiol glutaredoxin results from the deletion of one or more nucleotides of an endogenous gene encoding said monothiol glutaredoxin, the insertion of one or more nucleotides into an endogenous gene encoding said monothiol glutaredoxin, or combinations thereof.

Id. at 91:15–26 (line breaks added).

C. INSTITUTED GROUNDS OF UNPATENTABILITY

We instituted *inter partes* review of the '565 patent on the following grounds of unpatentability asserted in the Petition. Inst. Dec. 29.

Claim[s]	Basis	Reference[s]
1–4, 6–8, and 11–19	§ 102(e)	Flint
1–4, 6–8, 11, 13, 14, and 16–19	§ 103(a)	Anthony, Puig, and Ojeda
5	§ 103(a)	Anthony, Puig, Ojeda, and Li
9	§ 103(a)	Anthony, Puig, Ojeda, and van Maris

These instituted grounds rely on the following prior art references:

Anthony	US 2010/0081179 A1	Apr. 1, 2010	Ex. 1005
Li	US 2009/0163376 A1	June 25, 2009	Ex. 1015
Flint	WO 2011/103300 A2	Aug. 25, 2011	Ex. 1003

Antonius J. A. van Maris et al., *Directed Evolution of Pyruvate Decarboxylase-Negative* Saccharomyces cerevisiae, *Yielding a C_2-Independent, Glucose-Tolerant, and Pyruvate-Hyperproducing Yeast*, 70 APPLIED & ENVTL. MICROBIOLOGY 159 (2004). (Ex. 1008, "van Maris.")

Sergi Puig et al., *Coordinated Remodeling of Cellular Metabolism During Iron Deficiency Through Targeted mRNA Degradation*, 120 CELL 99 (2005). (Ex. 1006, "Puig.")

Luis Ojeda et al., *Role of Glutaredoxin-3 and Glutaredoxin-4 in the Iron Regulation of the Aft1 Transcriptional Activator in* Saccharomyces cerevisiae, 281 J. BIOLOGICAL CHEMISTRY 17661 (2006). (Ex. 1007, "Ojeda.")

II. ANALYSIS

A. LEVEL OF ORDINARY SKILL IN THE ART

We begin our analysis by addressing the level of ordinary skill in the art, which is relevant to the governing standards we apply in the remainder of our analysis. Petitioner proposes a standard for one of ordinary skill in the art. Pet. 6; *see* Ex. 1002 (Decl. of Dennis J. Thiele, Ph.D.) ¶ 17. Patent Owner has not contested this proposal or proffered an alternative standard. We adopt Petitioner's proposed standard and, therefore, determine that one of ordinary skill in the art would have had either: (1) "a Ph.D. in the life sciences or a similar related discipline, and . . . familiarity, training, and experience in molecular biology, microbial genetics and/or microbial metabolism," or (2) "a scientific background such as a Bachelor's degree in the life sciences (e.g., biology, microbiology, molecular biology or biochemistry) or a similar related discipline, and . . . substantial familiarity, training, and experience in molecular biology, microbial genetics and/or microbial metabolism." Pet. 6; *see* Ex. 1002 ¶ 17.

B. CLAIM INTERPRETATION

We next address the meaning of the claims. The Board interprets claims using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see In re Cuozzo Speed Techs., LLC*, No. 2014-1301, 2015 WL 448667, at *5–*8 (Fed. Cir. Feb. 4, 2015). We presume a claim term carries its "ordinary and customary meaning," which is "the meaning that the term

would have to a person of ordinary skill in the art in question" at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). This presumption, however, is rebutted when the patentee acts as a lexicographer by giving the term a particular meaning in the specification with "reasonable clarity, deliberateness, and precision." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "INACTIVATED"

Petitioner asserts that "inactivated," as used in the following limitation of claim 1, "said recombinant yeast microorganism is engineered to comprise at least one *inactivated* monothiol glutaredoxin selected from the group consisting of monothiol glutaredoxin-3 (GRX3) and monothiol glutaredoxin-4 (GRX4)," Ex. 1001, 91:17–21 (emphasis added), "should be construed to mean that the GRX3 and/or GRX4 protein lacks *all* activity and excludes GRX3 and/or GRX4 proteins having reduced, attenuated or partial activities." Pet. 7. Petitioner supports its argument with statements in an Examiner-Initiated Interview Summary in the prosecution history of the '565 patent in which Patent Owner "noted that the meaning of 'inactivate' is to render inactive so that GRX3 and GRX4 protein have no activity thereof," and the Patent Examiner "agree[d]." *Id.* at 7; Ex. 1012, Examiner-Initiated Interview Summary (May 17, 2012). Patent Owner has not responded to Petitioner's assertions regarding the meaning of "inactivated" or proposed a construction for the term. *See generally* PO Resp.

The plain and ordinary meaning of "inactivated" is having destroyed biologic activity; chemically or biologically inert; non-functional. *See* Ex. 3005 (*The American Heritage Medical Dictionary* 402 (Rev. ed. 2007)) (defining "inactivate" as "[t]o render nonfunctional"); Ex. 3006 (*Stedman's*

Medical Dictionary 959 (28th ed., Lippincott Williams & Wilkins 2006)) (defining "inactivate" as "[t]o destroy the biologic activity or the effects of an agent or substance"); Ex. 3007 (*Merriam-Webster's Collegiate Dictionary* 584 (10th ed. 2000)) (defining "inactivate" as "to make inactive," and "inactive" as "chemically" or "biologically inert"); Ex. 3008 (*Dictionary of Science and Technology* 1092 (Christopher Morris, ed. 1992)) (defining "inactivate" as "to render inactive; destroy the activity of"). This customary meaning, thus, requires a lack of all activity or functionality.

The usage of "inactivated" and related terms in the specification of the '565 patent neither elucidates the meaning of the term nor indicates any deviation from its ordinary and customary meaning. Dependent claims 9 and 10 recite the term "inactivate" in a manner similar to "inactivated" in claim 1: "said recombinant yeast microorganism is further engineered to *inactivate* one or more endogenous pyruvate decarboxylase (PDC)" (claim 9) and "glycerol-3-phosphate dehydrogenase (GPD)" (claim 10). Ex. 1001, 91:58–65 (emphasis added). These claims, therefore, offer no further clarity regarding the meaning of the term. Likewise, references to the term in other portions of the specification do not define or otherwise explicate its meaning. Upon review of the record, we are not persuaded that the inventors of the '565 patent acted as their own lexicographer to alter the ordinary and customary meaning of the term "inactivated."

Accordingly, to the extent Petitioner's proposed construction of "inactivated" requires a "lack[of] *all* activity," we conclude that it is consistent with the plain and ordinary meaning of the term as well as its usage in the '565 patent specification. Pet. 7. We, however, reject the remainder of Petitioner's proffered construction, "exclud[ing] GRX3 and/or

GRX4 proteins having reduced, attenuated or partial activities," because it is directed to the scope of claim 1, rather than the meaning of the term "inactivated." *Id.*

For these reasons, we construed "inactivated" to mean lacking all activity or functionality in our Decision to Institute. Inst. Dec. 8–10. Neither party has challenged this construction. *See generally* PO Resp.; Reply. Having considered whether this construction should be changed in light of the evidence introduced during trial, we are not persuaded any modification is necessary. Therefore, we maintain our construction of "inactivated" as lacking all activity or functionality.

2. OTHER CLAIM TERMS

Petitioner also proposes a construction for the final limitation of claim 1, asserting that the recited inserted or deleted nucleotides could not occur in "regulatory regions associated with the endogenous genes." Pet. 8–11. In our Decision to Institute, we determined that we need not address Petitioner's proposed construction, because whether the inserted or deleted nucleotides can occur in regulatory regions does not impact Petitioner's asserted grounds of unpatentability. Inst. Dec. 10–11. Neither party has challenged this determination. *See* Reply 1; *see generally* PO Resp. Having considered the issue in light of the evidence adduced during trial, we are not persuaded that any modification of our determination is necessary.[1]

[1] The Petition also argues that claim 1 encompasses at least the yeast genera and species recited in dependent claims 17 and 18, and at least DHAD localized in either the cytosol or the mitochondria, as recited in dependent claims 11 and 12, respectively. Pet. 9–10. Although we agreed with Petitioner in our Decision to Institute, this interpretation is not necessary to our final decision. *See* Inst. Dec. 11–12; Pet. 24–25; *infra* n.5.

C. INSTITUTED GROUNDS OF UNPATENTABILITY

We turn to the merits of the instituted grounds of unpatentability.

1. ANTICIPATION BY FLINT — CLAIMS 1–4, 6–8, AND 11–19

We begin with the instituted ground asserting that claims 1–4, 6–8, and 11–19 of the '565 patent are unpatentable under 35 U.S.C. § 102(e)[2] as anticipated by Flint. Pet. 12–29; Inst. Dec. 12–18, 29. Flint, PCT Application No. WO 2011/103300 A2, was filed on February 17, 2011, and claims priority to U.S. Provisional Application No. 61/305,333 ("'333 provisional" or "Flint '333 provisional"), filed on February 17, 2010. Ex. 1003, [10], [22], [30], [43]. Therefore, Flint's earliest claimed effective filing date is February 17, 2010.

The '565 patent was filed on September 27, 2011 as a divisional of U.S. Application Serial Nos. 13/228,342, filed September 8, 2011, and 12/953,884, filed November 24, 2010. Ex. 1001, [22], [62], 1:9–12. The '565 patent further claims priority to two provisional applications: U.S. Provisional Application Serial Nos. 61/350,209 ("'209 provisional"), filed June 1, 2010, and 61/263,952 ("'952 provisional"), filed November 24, 2009. *Id.* at [60], 1:12–17.

Thus, Flint—with the benefit of the filing date of the '333 Flint provisional (February 17, 2010)—is prior art to the '565 patent under § 102(e) unless the '565 patent is entitled to the benefit of the filing date of the '952 provisional (November 24, 2009). *See* 35 U.S.C. § 102(e); Pet. 12.

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[2] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284 (2011), revised 35 U.S.C. §§ 102–103, effective March 16, 2013. Because the '565 patent has an effective filing date before March 16, 2013, our references and citations to §§ 102–103 in this decision are to their pre-AIA version.

Accordingly, in addition to arguing that Flint and the ’333 provisional disclose each limitation of claims 1–4, 6–8, and 11–19 of the ’565 patent, the Petition further contends that the ’565 patent claims are not entitled to the benefit of the filing date of either the ’952 provisional or the ’209 provisional, because neither provides written description support for claim 1, the sole independent claim, of the ’565 patent. Pet. 12–29.

In the Response, Patent Owner disputes Petitioner’s assertion that Flint is prior art to the ’565 patent, arguing that the ’565 patent is entitled to the benefit of the filing date of the ’952 provisional, because both the ’952 and ’209 provisionals provide written description support for the ’565 patent claims. PO Resp. 2–3, 5–15. Patent Owner, however, does not contest that Flint and the ’333 provisional disclose each limitation of claims 1–4, 6–8, and 11–19 of the ’565 patent. *See id.* at 2–3, 15.

We consider first whether Flint is prior art to the ’565 patent, then whether Flint’s disclosure is anticipatory.

a. PRIOR ART STATUS OF FLINT

In this *inter partes* review, Petitioner has the burden of persuasion to establish unpatentability—including “all issues relating to the status of [Flint] as prior art,” *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576–78 (Fed. Cir. 1996)—by a “preponderance of the evidence,” 35 U.S.C. § 316(e). This burden of persuasion remains with Petitioner, while the burden of production—the burden to come forward with evidence—shifts between the parties. *See Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327–29 (Fed. Cir. 2008); *Mahurkar*, 79 F.3d at 1576–77; *Corning Inc. v. DSM IP Assets B.V.*, Case IPR2013-00053, slip op. at 6–8 (PTAB May 1, 2014) (Paper 66) (“[T]hough the patent owner bears the burden of production in

antedating a reference, the burden of persuasion to prove unpatentability . . . remains with the petitioner."). Now, "with all of the evidence from both sides before [us]"—the burden of production having shifted back and forth between the parties—Petitioner bears the ultimate burden of persuasion to establish by a preponderance of the evidence that Flint is prior art to the '565 patent, including that the '565 patent is not entitled to the benefit of the earlier filing date of the '952 provisional. *Tech. Licensing*, 545 F.3d at 1327–29; *Mahurkar*, 79 F.3d at 1578. We determine that Petitioner has met its burden, as we explain below.

i. Written Description Support for the '565 Patent Claims in the '952 and '209 Provisionals

Petitioner argues that claim 1 of the '565 patent, along with its dependent claims, is not entitled to the benefit of the filing date of either the '952 or '209 provisional based on a lack of written description support for the following limitations of the claim:

> wherein said recombinant yeast microorganism is engineered to comprise at least one inactivated monothiol glutaredoxin selected from the group consisting of monothiol glutaredoxin-3 (GRX3) and monothiol glutaredoxin-4 (GRX4),
>
> and wherein said inactivated monothiol glutaredoxin results from the deletion of one or more nucleotides of an endogenous gene encoding said monothiol glutaredoxin, the insertion of one or more nucleotides into an endogenous gene encoding said monothiol glutaredoxin, or combinations thereof.

Pet. 12–24; Ex. 1001, 91:15–26. Petitioner, with supporting testimony from its expert, Dr. Dennis J. Thiele, asserts that the provisionals describe, at best, only complete deletion of endogenous *GRX3* and *GRX4* genes. Pet. 17–24; Ex. 1002 ¶¶ 29–49. According to Petitioner, neither provisional provides

precise definitions—such as the type, location, or size—of the insertions, deletions, or insertion and deletions of nucleotides in these genes that would result in "inactivated" Grx3 and Grx4 proteins. Pet. 17–24; Ex. 1002 ¶¶ 29–49. Petitioner, therefore, urges that the "'952 and '209 provisional applications fail to describe adequately the full scope of the broadly claimed deletions, insertions, or combinations of deletions and insertions in the endogenous GRX3 and GRX4 genes" encompassed by claim 1 of the '565 patent. Pet. 20. In response, Patent Owner "directs [our] attention" to a list of disclosures in the '952 and '209 provisionals, which Patent Owner argues demonstrates that the inventors were in possession of the full scope of claimed insertions and deletions of nucleotides in the *GRX3* and *GRX4* genes as of the filing date of each provisional. PO Resp. 7–15. Patent Owner also argues that one of ordinary skill would have been familiar with gene deletions and insertions as techniques for "inactivating a gene" and, thus, Petitioner's arguments overlook that it is not necessary to disclose in detail what was well known in the art. *Id.* at 13–15.

A claim in a later-filed patent application is entitled to the benefit of the filing date of an earlier-filed provisional application only if the provisional application, and all applications in the chain leading back to the provisional application, satisfy the written description requirement of 35 U.S.C. § 112 for the invention claimed in the later-filed application. *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294–97 (Fed. Cir. 2002); *see* 35 U.S.C. §§ 119(e)(1), 120; *Hollmer v. Harari*, 681 F.3d 1351, 1355 (Fed. Cir. 2012). This requirement prevents an inventor from "overreaching" in a later-filed application as to the scope of what was invented at the time of the earlier-filed application by requiring that the

invention be described in "such detail that . . . future claims can be determined to be encompassed within the . . . original creation." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991). Specifically, to satisfy the written description requirement, the disclosure of the earlier-filed application must "reasonably convey[]" to one of ordinary skill in the art that, as of the filing date sought, "the inventor had possession" of the subject matter now claimed. *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351–52 (Fed. Cir. 2010); *Vas-Cath*, 935 F.2d at 1563–64. The test for written description, therefore, requires "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art" to determine whether the specification "show[s] that the inventor [had] actually invented," or possessed, each feature now included as a claim limitation. *Ariad Pharm.*, 598 F.3d at 1351; *see New Railhead Mfg.*, 298 F.3d at 1295.

The Federal Circuit has established specific requirements for written description of genus claims, i.e., claims encompassing two or more embodiments, that "use functional language to define the[ir] boundaries." *Ariad Pharm.*, 598 F.3d at 1349–50; *see Billups-Rothenberg, Inc. v. Associated Reg'l & Univ. Pathologists, Inc.*, 642 F.3d 1031, 1037 (Fed. Cir. 2011). Claim 1 of the '565 patent is a functionally-defined genus claim because it recites the function, or desired or useful result, of "inactivat[ion]" of "at least one" Grx3 and Grx4 proteins, and further recites that this inactivation "results from" any one of a number of different means: "deletion of one or more nucleotides of an endogenous gene encoding" the protein, "insertion of one or more nucleotides into an endogenous gene encoding" the protein, or "combinations thereof." Ex. 1001, 91:15–26; *see*

Tr. 8:6–7, 11:3–4; *Billups-Rothenberg*, 642 F.3d at 1037; *Ariad Pharm.*, 598 F.3d at 1349–50. We, therefore, must determine whether the '952 and '209 provisionals meet the governing standards for written description support of this genus claim.

Evaluating written description support for genus claims presents the issue of whether the disclosure in the specification demonstrates that the inventor had possession of species sufficient to support a claim to the totality of the functionally-defined genus. *Carnegie Mellon Univ. v. Hoffman-La Roche Inc.*, 541 F.3d 1115, 1126 (Fed. Cir. 2008); *Ariad Pharm.*, 598 F.3d at 1349–50. To meet the written description requirement for such claims, the specification must disclose either: (1) "a representative number of species falling within the scope of the genus," "precise[ly] defin[ed], such as by structure, formula, chemical name, physical properties, or other properties," or (2) "structural features common to the members of the genus." *Ariad Pharm.*, 598 F.3d at 1350; *Carnegie Mellon*, 541 F.3d at 1122–26; *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566–69 (Fed. Cir. 1997). A functionally-defined genus claim also can "meet the written description requirement if a reasonable structure-function correlation is established, whether by the inventor as described in the specification or known in the art at the time of the filing date." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014); *see Ariad Pharm.*, 598 F.3d at 1350. These standards are premised on the basic principle that one of ordinary skill in the art "must be able to 'visualize or recognize the identity of the members of the genus'" upon reviewing the disclosure. *Carnegie Mellon*, 541 F.3d at 1124 (quoting *Eli Lilly*, 119 F.3d at 1569); *see Ariad Pharm.*, 598 F.3d at 1350.

Here, the disclosures of the '952 and '209 provisionals cited by the parties as relevant to claim 1 of the '565 patent divide into two categories. One category includes disclosures regarding inserting or deleting nucleotides of genes—not specific to the *GRX3* or *GRX4* gene. Ex. 1010 ¶¶ 67–68, 213, 229, 258–264, 268; Ex. 1011 ¶¶ 73–74, 244, 260, 289–295, 299; *see* Pet. 20–23; PO Resp. 7–12; Reply 2–4. For example, the '952 and '209 provisionals define "engineer" to include "*inserting a polynucleotide and/or polypeptide* heterologous to the microorganism and *mutating a polynucleotide and/or polypeptide* native to the microorganism." Ex. 1010 ¶ 67; Ex. 1011 ¶ 73 (emphases added). The provisionals, in turn, define "mutation," to include, for example, "*deletions, or insertions of single or multiple residues in a polynucleotide*," or "*an insertion, or a deletion of part or all of a gene*." Ex. 1010 ¶ 68; Ex. 1011 ¶ 74 (emphases added). The provisionals explain that "an engineered or modified microorganism can also include *alteration, disruption, deletion, or knocking-out of a gene or polynucleotide*." Ex. 1010 ¶ 213; Ex. 1011 ¶ 244 (emphasis added). The provisionals further refer to "known deletion techniques" and include a section, titled "Genetic insertions and deletions," which references known techniques to "introduce" or "integrat[e]" genes or "nucleic acid molecule[s]" into yeast and to "remove[]" such "introduced marker genes." Ex. 1010 ¶¶ 258–263, 268; Ex. 1011 ¶¶ 289–294, 299.

The other category includes disclosures specifically referring to deleting, attenuating, or reducing either or both the *GRX3* and *GRX4* genes. Ex. 1010 ¶¶ 28, 154–58, claim 56; Ex. 1011 ¶¶ 31, 178, 180–82, claim 56; *see* Pet. 17–24; PO Resp. 7–12; Reply 2–4. For example, the '952 provisional states that the disclosed recombinant microorganism "may

be engineered to delete and/or attenuate one or more genes selected from the group consisting of *GRX3* and *GRX4*, or homologs thereof." Ex. 1010 ¶ 28. The later-filed '209 provisional adds that these genes may be reduced, specifically disclosing that the microorganism "may be engineered to delete, reduce, and/or attenuate" either or both the *GRX3* and *GRX4* genes. Ex. 1011 ¶ 31.

Petitioner, with supporting testimony from Dr. Thiele, takes the position that one of ordinary skill in the art would understand these disclosures in the '952 and '209 provisionals regarding reduction and attenuation of the *GRX3* and *GRX4* genes to accomplish "less than complete inactivation" of the corresponding protein. Pet. 17–18; Ex. 1002 ¶ 29. Patent Owner does not dispute this testimony or otherwise address the meaning of reduction or attenuation to a person of ordinary skill in the art. *See* PO Resp. 5–15; Reply 2. We credit Dr. Thiele's testimony on this point and, therefore, find that the Grx3 and Grx4 proteins in yeast engineered to reduce or attenuate either or both *GRX3* and *GRX4* genes would not be "inactivated" within the meaning of claim 1 of the '565 patent. Ex. 1002 ¶¶ 29–30; *see supra* Section II.B.1. Accordingly, the disclosed reduced or attenuated *GRX3* and *GRX4* genes do not fall within the scope of claim 1 of the '565 patent, and do not provide written description support for the claim.

As to the disclosures in the '952 and '209 provisionals regarding deletion of the *GRX3* and *GRX4* genes, Petitioner argues that one of ordinary skill would understand the disclosures directed to deleting either or both the *GRX3* and *GRX4* genes "to only encompass, at best, a complete deletion of the GRX3 and/or GRX4 genes." Pet. 18–19; Ex. 1002 ¶ 31. Patent Owner contests Petitioner's interpretation, citing to the disclosures in the

provisionals regarding "a deletion of part or all of a gene." PO Resp. 9–10, 13–14 (emphasis omitted); *see* Ex. 1010 ¶ 68; Ex. 1011 ¶ 74. We agree with Patent Owner. Petitioner's proposed interpretation takes an overly narrow view of the relevant disclosures that is unjustified in light of other statements in each provisional. In each, the disclosures that microorganisms may be "*engineered* to delete" either or both *GRX3* and *GRX4* genes (Ex. 1010 ¶¶ 28, 158; Ex. 1011 ¶¶ 31, 182 (emphasis added)) ties to the definitions of "engineer," which "includes . . . mutati[ons]" (Ex. 1010 ¶ 67; Ex. 1011 ¶ 73), and "mutation," which includes "deletions, or insertions of single or multiple residues in a polynucleotide," or "an insertion, or a deletion of part or all of a gene" (Ex. 1010 ¶ 68; Ex. 1011 ¶ 74). Therefore, based on the express language of the provisionals, we find that one of ordinary skill in the art would understand the references to deleting either or both the *GRX3* and *GRX4* genes to refer to deleting "all or part" of these genes—more specifically, both complete gene deletion (deletion of all nucleotides of the gene) and partial gene deletion (deletion of only a subset of nucleotides of the gene). Even so, however, the disclosures of the '952 and '209 provisionals fall short of the required standards for written description, for the reasons we explain below.

First, the disclosures in the '952 and '209 provisionals do not disclose a representative number of species falling within the scope of the claimed genus and, thus, fail to show that the inventors had "conceived and described sufficient representative species encompassing the breadth of the genus" of insertions, deletions, and combinations of insertions and deletions in either or both the *GRX3* or *GRX4* genes that inactivate the corresponding protein. *AbbVie*, 759 F.3d at 1300. Starting with deletions, the '952 and

'209 provisionals do reference both complete and partial deletion of the *GRX3* and *GRX4* genes, as we noted above. Complete deletion of the *GRX3* or *GRX4* genes results in non-expression of the corresponding protein, making the protein "inactive," as recited in claim 1. *See* Ex. 1002 ¶¶ 31–32. Based on the disclosures in the '952 and '209 provisionals regarding "eliminat[ion]" of genes according to "known deletion techniques" and specifically regarding "delet[ion]" of either or both *GRX3* and *GRX4* genes, together with Petitioner's acknowledgement that complete deletion of the *GRX3* and *GRX4* genes was known in the art when the provisionals were filed, we find that the provisionals sufficiently disclose species involving complete deletion of the *GRX3* gene, the *GRX4* gene, and the *GRX3* and *GRX4* genes, which fall within the scope of claim 1. *See* Ex. 1010 ¶¶ 28, 154–158, 268; Ex. 1011 ¶¶ 31, 178–182, 299; Ex. 1002 ¶¶ 31–32, 37, 40–41; Tr. 10:15–17; *see also Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, 746 F.3d 1302, 1314–15 (Fed. Cir. 2014) (explaining that patentee may rely upon information well known in the art for purposes of satisfying written description requirement).

Unlike complete deletion of the *GRX3* and *GRX4* genes, the references to partial deletion of the *GRX3* and *GRX4* genes in the provisionals do not "precise[ly] defin[e]" a species falling within the scope of the claimed genus.[3] *Ariad Pharm.*, 598 F.3d at 1350; *see Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004); *Eli*

[3] We note that even if the '952 and '209 provisionals described both complete and partial deletion of the *GRX3* and *GRX4* genes to inactivate the respective protein, we still would find that the provisionals do not disclose a representative number of species falling within the scope of the genus, because neither provisional discloses insertions, or insertions and deletions of nucleotides, falling within the scope of claim 1, as we explain below.

Lilly, 119 F.3d at 1566–69. In contrast to complete gene deletion, not all partial deletions of a gene result in inactivation of the corresponding protein. *See, e.g.*, Ex. 1002 ¶¶ 31, 46; Tr. 8:6–13, 10:3–12. Yet, as Dr. Thiele explains, "other than . . . deletion of the entire gene," the disclosures in the '952 and '209 provisionals "do not provide any description of the type, location, or size of a deletion in . . . an endogenous GRX3 and/or GRX4 gene that would result in an inactive protein." Ex. 1002 ¶ 41; *see id.* ¶¶ 32, 37, 39–40.

Similar to partial deletion of the *GRX3* or *GRX4* genes, the '952 and '209 provisionals also lack disclosures regarding the remaining scope of the claimed genus. In particular, the provisionals do not include any disclosure regarding insertions of one or more nucleotides into the *GRX3* or *GRX4* genes that would inactivate the corresponding protein. *See id.* ¶ 42. Likewise absent is any disclosure regarding a combination of insertions and deletions of one or more nucleotides in the *GRX3* or *GRX4* genes that would result in an inactivated protein. *See id.* ¶¶ 43–44.

Based on the analysis above, the only species falling within the scope of claim 1 that is defined with any precision in the disclosures of the '952 and '209 provisionals is complete deletion of either or both the *GRX3* and *GRX4* genes. With this exception, the '952 and '209 provisionals make no reference to which of a multitude of nucleotides can be inserted, deleted, or inserted and deleted in the *GRX3* and *GRX4* genes, or the locations where such alterations can be made, to effect the recited function of inactivating either or both the Grx3 and Grx4 proteins. *See* Tr. 10:3–12. Nor do the provisionals reference that these alterations were known in the art. Generic disclosures referring to known means to insert or delete nucleotides—not

specific to the *GRX3* or *GRX4* genes—are insufficient. *See* Ex. 1002 ¶¶ 39–40; Ex. 1010 ¶¶ 67–68, 213, 229, 258–264, 268; Ex. 1011 ¶¶ 73–74, 244, 260, 289–295, 299; *see, e.g.*, *Univ. of Rochester*, 358 F.3d at 927 (holding that specification disclosing, *inter alia*, tests for screening compounds to identify those that selectively inhibit enzyme lacked written description support for claimed methods involving administering such compounds because it "does not disclose just *which* peptides, polynucleotides, and small organic molecules have the desired characteristic") (quotations and citation omitted). Indeed, other than references to deleting the *GRX3* and *GRX4* genes, the disclosures do not refer to any goal, purpose, or intention to inactivate, in any form, Grx3 and Grx4 proteins, making it unclear that inactivation of these proteins by anything other than complete deletion of the corresponding gene was even a "wish or plan," much less in the inventors' possession. *Eli Lilly*, 119 F.3d at 1566–67.

The disclosed species—limited to complete deletion of either or both the *GRX3* and *GRX4* genes—do not represent adequately the full scope of the genus recited in claim 1, which also extends to inactivated proteins resulting from deleting less than all nucleotides, inserting one or more nucleotides, and combinations of deleting and inserting nucleotides in either or both genes. As the Federal Circuit explained in *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299–300 (Fed. Cir. 2014), "analogizing the genus to a plot of land," the "disclosed species only abide in a corner" of the plot or the genus—leaving undisclosed the remainder of the vast genus, claiming a variety of alterations to the *GRX3* and *GRX4* genes that inactivate the respective protein. The disclosed species, therefore, do "not describe[] the genus sufficiently to show that the

inventor[s] invented, or had possession of" the wide breadth of the genus. *AbbVie*, 759 F.3d at 1299–300.

In addition, the disclosures do not meet the alternative means of satisfying the written description requirement. The '952 and '209 provisionals do not disclose any structural features common to members of the recited genus. *See* Ex. 1002 ¶ 38. Similarly, there is no disclosed correlation between the structure of endogenous *GRX3* or *GRX4* genes with one or more inserted, deleted, or inserted and deleted nucleotides and a resulting function of inactivating the respective protein. *See id.* ¶¶ 47–48. Nor does "the record here . . . indicate such an established correlation." *AbbVie*, 759 F.3d at 1301; *see* Tr. 8:6–9, 8:22–24, 11:1–14. This lack of any disclosed common structural features, and known or disclosed structure-function correlation, was not disputed in this case. *See generally* PO Resp.

In sum, we are persuaded that one of ordinary skill in the art, upon reading either the '952 provisional or '209 provisional, would not be able to "visualize or recognize" members of the claimed genus with the exception of complete deletion of either or both the *GRX3* and *GRX4* genes. *See* Ex. 1002 ¶ 47. The evidence in this record demonstrates that the provisionals do not reasonably convey to one of ordinary skill in the art that, at the time of filing, the inventors possessed the scope of the genus later recited in claim 1 of the '565 patent. *See id.* ¶ 49. Patent Owner's conclusory, unsupported attorney argument asserting the contrary is not persuasive. *See* PO Resp. 7–13; Reply 2–4.

We note that even if the disclosures in the '952 and '209 provisionals would have rendered obvious, or enabled one of ordinary skill to make and use, the full scope of the claimed genus, the disclosures still would be

insufficient to satisfy the written description requirement. *See Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350 (Fed. Cir. 2013); *Ariad Pharm.*, 598 F.3d at 1352, 1356; *Eli Lilly*, 119 F.3d at 1567. The written description issue we consider here does not address whether claim 1 of the '565 patent is "an obvious variant of that which is disclosed" in the provisionals. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997) (holding that "a description which renders obvious the invention" does not satisfy the written description requirement because "[o]ne shows that one is in possession of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious") (emphasis, quotations, and citations omitted). Nor do we address whether "one of ordinary skill in the art presented with the [provisionals] would have been enabled" to determine, without undue experimentation, nucleotides to insert, delete, or insert and delete in order to inactivate the Grx3 and Grx4 proteins. *Novozymes*, 723 F.3d at 1350; *see* Tr. 9:5–14, 10:21–11:5.

Finally, we are not persuaded by Patent Owner's contention that Petitioner's arguments contradict Federal Circuit precedent holding that the written description requirement does not require disclosure of what was well known in the art, because one of ordinary skill would have known various methods for "inactivating a gene, including: gene deletions (including partial gene deletions) and gene insertions." PO Resp. 13–15; *see* Tr. 41:9–42:8. We recognize that "[b]ecause the specification is viewed from the perspective of one of skill, . . . a patentee may rely on information that is well-known in the art for purposes of meeting the written description requirement." *Butamax(TM)*, 746 F.3d at 1314–15 (citation and quotation omitted)). Yet, Patent Owner merely restates that general techniques for

deleting or inserting nucleotides in a gene to inactivate the corresponding protein were known in the art—which is not disputed in this case. *See* Tr. 9:5–14, 10:13–11:5; Pet. 20–21; Ex. 1002 ¶¶ 38–39. Patent Owner's argument is not specific to knowledge of the inventors, or persons of ordinary skill in the art, with respect to the particular subject matter recited in claim 1—alterations to the *GRX3* and *GRX4* genes to inactivate their respective proteins. *See* PO Resp. 13–15 (lacking any reference to the *GRX3* gene, *GRX4* gene, Grx3 protein, or Grx4 protein).

In contrast to the cases on which Patent Owner's argument relies, there is no evidence in this case that, with the exception of complete deletion of either or both the *GRX3* and *GRX4* genes, the particular subject matter recited in the relevant limitation of claim 1 was known in the art, or that one of ordinary skill would have understood from the disclosures in the '952 and '209 provisionals that the inventors had possession of this subject matter. *See Capon v. Eshhar*, 418 F.3d 1349, 1350–52, 1354–61 (Fed. Cir. 2005) (reversing decision that specifications of patent and application claiming chimeric DNA did not meet written description requirement where both parties presented testimony from "expert witnesses" and "scientific literature" demonstrating that "nucleotide sequence of claimed DNA . . . [wa]s already known in the field"); *Vas-Cath*, 935 F.2d at 1557, 1561–67 (reversing summary judgment determination of insufficient written description where expert declaration explained that drawing in application conveyed to one of ordinary skill in the art that inventor had possession of "claimed range," and plaintiffs "submitted no technical evidence to refute

[expert]'s conclusions").[4] Here, Patent Owner did not put forward the testimony of any expert, or anyone of ordinary skill in the art. In addition, Patent Owner did not take the opportunity to depose Dr. Thiele, Petitioner's expert. Patent Owner also has not submitted any relevant prior art references.

In sum, Petitioner presented comprehensive and persuasive expert testimony and supporting analysis that the disclosures in the '952 and '209 provisionals would not have conveyed to one of ordinary skill in the art that the inventors possessed the claimed scope of alterations to the *GRX3* and *GRX4* genes. Ex. 1002 ¶¶ 29–49; Pet. 13–24. In response, Patent Owner has presented no evidence—only attorney argument—regarding what one of ordinary skill in the art would have known and understood the disclosures to convey at the time of filing. Patent Owner's imprecise attorney argument does not refute Petitioner's detailed showing, with evidentiary support.

We find Petitioner has shown by a preponderance of the evidence that the '952 and '209 provisionals do not provide written description support for independent claim 1 of the '565 patent.[5] Thus, the provisionals also do not

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[4] Patent Owner also cites *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986), which involves enablement, not written description. Nonetheless, we note that there was evidence in that case that the "monoclonal antibodies used in the invention were known in the art." *Id.*

[5] We note that we are not persuaded by Petitioner's two other theories of lack of written description in the provisionals for claims 12 and 18 and, thus, claim 1 and other dependent claims. Pet. 24–25. The argument for each theory is conclusory and not supported sufficiently. *E.g.*, Ex. 1011 ¶¶ 232–239 ("Mitochondrially Localized DHAD"). Also, neither case Petitioner cited in the hearing stands for the proposition that if a feature in a dependent claim (e.g., a species (claim 18), location (claim 12)) lacks written

meet the written description requirement for claims 2–4, 6–8, and 11–19, which depend from claim 1. Accordingly, these claims are not entitled to the benefit of the filing date of either provisional, and have an effective filing date no earlier than November 24, 2010, making Flint—with the benefit of the effective filing date of the Flint '333 provisional, February 17, 2010, *see infra* Section II.C.1.b—prior art under § 102(e).

b. FLINT'S ANTICIPATORY DISCLOSURE

We now address the anticipatory disclosure of Flint. Patent Owner does not dispute that Flint is entitled to the benefit of the filing date of the '333 provisional or that Flint discloses the limitations of the '565 patent claims. *See* PO Resp. 2–3, 15. As we outline below, Petitioner has shown by a preponderance of the evidence that Flint, and the '333 provisional, disclose each limitation of claims 1–4, 6–8, and 11–19 of the '565 patent and, thus, that Flint is entitled to the benefit of the filing date of the '333 provisional for the relevant disclosures.

i. Flint

Flint and the '333 provisional disclose "increased specific activity of [DHAD]" in recombinant yeast cells of various genera and species. Ex. 1003, [57], ¶¶ 3, 12, 25, 103–116, 129; Ex. 1004 ¶¶ 1, 11, 24, 98–111

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description, the independent claim and other dependent claims—that do not recite that feature—also lack support *even if* the specification describes other such features (e.g., other species, locations). *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1372–79 (Fed. Cir. 2009) (specification described "only medical valves with spikes"); *The Gentry Gallery, Inc. v. The Berkline Corp.*, 134 F.3d 1473, 1478–80 (Fed. Cir. 1998) (specification identified console "as the only possible location for the controls"); Tr. 12:19–14:22.

(pp. 39–44).[6] The applications explain that the specific activity of DHAD in these recombinant yeast cells is increased by "delet[ing], mutat[ing], express[ing], up-regulat[ing], or down-regulat[ing]" Fe-S cluster genes, including the *GRX3* and *GRX4* genes. Ex. 1003 ¶ 123, Table 8; Ex. 1004 ¶ 163, Table 8; *see* Ex. 1003 ¶¶ 240–242; Ex. 1004 ¶¶ 154–155. Both applications also discuss methods of making isobutanol by providing a recombinant host cell and putting the cell in contact with a fermentable carbon source substrate. Ex. 1003 ¶ 16; Ex. 1004 ¶ 15.

ii. Flint's Disclosure of Claims 1–4, 6–8, and 11–19

Flint and the '333 provisional disclose the subject matter recited in claim 1. *See* Pet.26–27; Ex. 1002, 27–30. Specifically, the disclosure in each application that DHAD may be overexpressed by "over-express[ing] the recombinant polynucleotide" in a "recombinant host cell" meets the first limitation of the claim, "[a] recombinant yeast microorganism comprising a recombinantly overexpressed polynucleotide encoding . . . DHAD." Ex. 1003 ¶¶ 3, 113; Ex. 1004 ¶¶ 1, 108 (p. 43); *see* Ex. 1003 ¶¶ 9, 103–116, 229–233; Ex. 1004 ¶¶ 8, 98–111 (pp. 39–44), 144–148. Flint and the '333 provisional disclose the remaining limitations of claim 1, regarding inactivated Grx3 and Grx4 proteins resulting from insertions, deletions, or insertions and deletions in the corresponding endogenous gene, based on the discussion in each application of "delet[ion]" of Fe-S cluster genes—particularly the *GRX3* and *GRX4* genes. Ex. 1003 ¶¶ 123, 237–242, Tables 8, 10; Ex. 1004 ¶¶ 152–155, 163, Tables 8, 10. Deleting the *GRX3* or *GRX4*

[6] Certain paragraph numbers in Exhibit 1004, the Flint '333 provisional, repeat. Therefore, we include page numbers, in addition to paragraph numbers, as necessary.

gene results in inactivation of the respective protein, as recited in claim 1. Ex. 1002 ¶ 57.

The additional limitations of claims 2–4 and 6–8, reciting an "isobutanol producing metabolic pathway" with enzymes catalyzing steps of the pathway, also are found in Flint and the '333 provisional. *See* Pet. 27; Ex. 1002, 30–35. Specifically, both applications discuss an "isobutanol biosynthetic pathway," as recited in claim 2, that includes the conversion of: (a) "pyruvate to acetolactate," as catalyzed by "acetolactate synthase" (claim 3); (b) "acetolactate to 2,3-dihydroxyisovalerate," as catalyzed by "acetohydroxy acid isomeroreductase," which Dr. Thiele explains is a ketol-acid reductoisomerase (claim 4); (c) "2,3-dihydroxyisovalerate to α-ketoisovalerate," as catalyzed by DHAD; (d) "α-ketoisovalerate to isobutyraldehyde," as catalyzed by "branched-chain α-keto acid decarboxylase," which Dr. Thiele explains is a 2-keto acid decarboxylase (claim 6), and (e) "isobutyraldehyde to isobutanol," as catalyzed by a branched-chain alcohol dehydrogenase (claim 7). Ex. 1003 ¶¶ 138–145; Ex. 1004 ¶¶ 111–118 (pp. 60–61). In addition, Flint and the '333 application incorporate by reference U.S. Patent Application Publication No. 2007/0092957 A1, which discloses branched-chain alcohol dehydrogenases utilizing NADH, thereby disclosing the additional limitation of claim 8 that the "alcohol dehydrogenase" of step (e) be "NADH-dependent." Ex. 1003 ¶¶ 143–145; Ex. 1004 ¶¶ 116–118 (p. 61); Ex. 1018 ¶ 88; Ex. 1002, 34–35; *see Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1382 n.3 (Fed. Cir. 2007) (explaining that "material [that] is incorporated by reference" in a prior art reference "may . . . be considered for purposes of anticipation").

Flint and the ’333 provisional also disclose that the DHAD may be in the locations in recombinant yeast and from the bacterium recited in claims 11–14. *See* Pet. 27–28; Ex. 1002, 35–36. Specifically, Flint and the ’333 provisional explain that in some embodiments, the DHAD is “expressed in the cytosol,” as recited in claim 11. Ex. 1003 ¶¶ 13, 25, 118; Ex. 1004 ¶¶ 12, 24, 113 (p. 45). In addition, the DHAD in Flint and the ’333 provisional is expressed in the mitochondria—as recited in claim 12. *See* Ex. 1003 ¶ 6; Ex. 1004 ¶ 4; Ex. 1002, 35; Tr. 5:10–6:2. In particular, Flint and the ’333 provisional explain that DHAD natively is located in the mitochondria, and do not refer to removing the mitochondrial targeting sequence for DHAD that directs its transport to the mitochondria. Ex. 1003 ¶ 6; Ex. 1004 ¶ 4; Ex. 1002, 35; Tr. 5:10–6:2; *see generally* Exs. 1003, 1004. Likewise, both applications explain that the DHAD may be from “*Lactococccus lactis*” and “*S. mutans*,” i.e., *Streptococcus mutans*, thereby disclosing the additional limitations of claims 13 and 14, respectively. Ex. 1003 ¶¶ 97, 99, 229–233, Table 4b; Ex. 1004 ¶¶ 93–94, 144–148, Table 4b.

In addition, Flint and the ’333 provisional disclose the additional limitations of claims 15 and 16 that the yeast recited in claim 1 is “further engineered to comprise increased expression of one or more polynucleotides encoding one or more . . . Aft[] proteins” and “to express one or more polynucleotides encoding one or more constitutively active . . . Aft[] proteins,” respectively. *See* Pet. 27–28; Ex. 1002, 36–38. Specifically, Flint and the ’333 provisional discuss “upregulat[ing]” the *AFT1* and *AFT2* gene, as well as AFT1 and AFT2 being “co-expressed” with DHAD. Ex. 1003 ¶¶ 123, 130, Table 8; Ex. 1004 ¶¶ 103 (p. 57), 163; Table 8. The applications also disclose “expression” of the “constitutive mutant[s],”

"AFT1 L99A, AFT1 L102A, AFT1 C291F, AFT1 C293F." Ex. 1003 ¶¶ 130, 246; Ex 1004 ¶¶ 103, 158; *see* Ex. 1003 ¶¶ 243–246; Ex. 1004 ¶¶ 156–161.

Flint and the '333 provisional also explain that the disclosed recombinant yeast microorganism may be the yeast genera and species recited in claims 17 and 18. *See* Pet. 28; Ex. 1002, 38–39. Specifically, both applications state that the yeast strain used in the disclosed invention can be one of the following genera recited in claim 17, *Saccharomyces*, *Schizosaccharomyces*, *Hansenula*, *Candida*, *Kluyveromyces*, *Yarrowia*, *Issatchenkia*, and *Pichia*, and one of the following species recited in claim 18, *Saccharomyces cerevisiae*, *Kluyveromyces thermotolerans*, *Candida glabrata*, *Pichia stipitis*, and *Yarrowia lipolytica*. Ex. 1003 ¶¶ 12, 25, 108, 129; Ex. 1004 ¶¶ 11, 24, 103 (p. 40).

Finally, Flint and the '333 provisional disclose the "method of producing isobutanol" recited in claim 19. *See* Pet. 28–29; Ex. 1002, 39–40. In particular, the applications disclose "methods of making isobutanol" by putting the disclosed recombinant host cell in contact with a "fermentable carbon substrate in a fermentation medium," with "carbon substrates," and "recovering" the isobutanol. Ex. 1003 ¶¶ 16, 150; Ex. 1004 ¶¶ 15, 121; *see* Ex. 1003 ¶¶ 159, 163; Ex. 1004 ¶¶ 130, 134; Ex. 1002, 39–40.

Accordingly, the disclosures of both Flint and the '333 provisional encompass claims 1–4, 6–8, and 11–19 of the '565 patent.

c. CONCLUSION

In conclusion, having considered the arguments and evidence of record, we find Petitioner has shown by a preponderance of the evidence that claims 1–4, 6–8, and 11–19 of the '565 patent are anticipated by Flint.

2. OBVIOUSNESS GROUNDS

We turn to the instituted obviousness grounds, which allege that claims 1–9, 11, 13, 14, and 16–19 would have been obvious as of November 24, 2009, the earliest claimed effective filing date of the '565 patent. Inst. Dec. 19–29; Pet. 29–47; *see* Pet. 30 (explaining knowledge in the art "[a]s of the earliest asserted priority date of November 24, 2009"); Ex. 1002 ¶¶ 66, 80 ("[a]s of November 24, 2009").[7] We start by addressing the prior art status of the relevant references. Petitioner asserts, and Patent Owner does not dispute, that Anthony, Puig, Ojeda, Li, and van Maris are prior art to the '565 patent, regardless of whether the patent is entitled to the benefit of the filing date of the '952 or '209 provisionals. *See* Pet. 29–30 & n.5, 47–48 & n.8. We agree. *See* Inst. Dec. 19.

We consider each of the instituted obviousness grounds in turn.

a. ANTHONY, PUIG, AND OJEDA — CLAIMS 1–4, 6–8, 11, 13, 14, AND 16–19

We first address the instituted ground challenging claims 1–4, 6–8, 11, 13, 14, and 16–19 of the '565 patent as unpatentable under 35 U.S.C. § 103 over Anthony, Puig, and Ojeda. Pet. 29–47.

i. Independent Claim 1

We focus our discussion on independent claim 1, the center of the parties' dispute. Petitioner argues that based on the combined teachings of Anthony, Puig, and Ojeda, it would have been obvious to a person of ordinary skill in the art to delete the *GRX3* gene, the *GRX4* gene, or both the

[7] Because Petitioner has argued and established obviousness as of November 24, 2009, the earliest claimed effective filing date of the '565 patent, our obviousness determination is not contingent on our determination that the '565 patent is entitled to an effective filing date no earlier than November 24, 2010. *See supra* Section II.C.1.a.i.

GRX3 and the *GRX4* gene, thereby inactivating the respective protein or proteins, in a recombinant yeast recombinantly overexpressing DHAD. *See id.* at 34–39; Ex. 1002 ¶¶ 73–81. For the reasons explained below, we conclude Petitioner has shown by a preponderance of the evidence that claim 1 would have been obvious because, based on the knowledge of one of ordinary skill in the art and the teachings of Anthony, Puig, and Ojeda, it would have been obvious to inactivate *both* the Grx3 and Grx4 proteins by deletion of their respective genes in a recombinant yeast overexpressing DHAD. Because this conclusion is sufficient to render claim 1 obvious, we need not and do not reach the issue of whether it would have been obvious to delete only either the *GRX3* gene or the *GRX4* gene. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2006) ("If the claim extends to what is obvious, it is invalid under § 103."); *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 963 (Fed. Cir. 2014) (holding that party challenging patent "had the burden of showing that any compounds within the broad genus claimed by the . . . patent . . . were obvious at the time of the invention").

(a) The Prior Art's Teaching of the Claim Limitations

Turning to the prior art's teachings, Petitioner argues that Anthony teaches the first limitation of claim 1, which recites: "[a] recombinant yeast microorganism comprising a recombinantly overexpressed polynucleotide encoding a dihydroxy acid dehydratase (DHAD)." Ex. 1001, 91:15–17; Pet. 35; Ex. 1002 ¶ 75. Patent Owner does not counter this assertion. *See* PO Resp. 15–16; *see generally id.* We agree with Petitioner and find that Anthony's disclosure of a "recombinant yeast cell[] engineered" to increase activity of an expressed heterologous DHAD protein teaches this limitation. Ex. 1005 ¶¶ 38, 74–75; *see id.* ¶¶ 6, 13; Ex. 1002 ¶ 75.

Petitioner relies on Ojeda for the remaining limitations of claim 1. *See* Pet. 39; Ex. 1002 ¶ 81. Patent Owner does not contest that Ojeda teaches or suggests the limitations. *See* PO Resp. 20–22; *see generally id.* We find that Ojeda teaches the remaining limitations based on its disclosure of yeast in which both Grx3 and Grx4 proteins are inactivated as a result of deletion of their respective genes. *See* Ex. 1007, 17662, Table 1 (explaining Δ*grx3*Δ*grx4* yeast strains, in addition to Δ*grx3* and Δ*grx4* yeast strains, used in the disclosed study); *id.* at 17663, Fig. 1 (discussing "lack[]" or "absence of Grx3 and Grx4 proteins" in Δ*grx3*Δ*grx4* yeast cells, as well as absence of Grx3 protein in Δ*grx3* yeast cells and Grx4 protein in Δ*grx4* yeast cells).

(b) Reason to Combine

Petitioner argues that one of ordinary skill would have had reason to combine these teachings of Anthony and Ojeda, along with the teachings of a third reference, Puig, to reach the recombinant yeast recited in claim 1. *See* Pet. 34–39; Ex. 1002 ¶¶ 66–81. Patent Owner disputes this assertion. *See* PO Resp. 15–22.

To start, Petitioner has established that Anthony, Puig, and Ojeda are in the same field with interrelated teachings, given that each of the references relates to altered expression of Fe-S cluster proteins in yeast, specifically *Saccharomyces cerevisiae*. *See* Pet 34–39; Ex. 1002 ¶¶ 74–81; Ex. 1005, [57], ¶¶ 38, 74–76; Ex. 1006, 99, 101; Ex. 1007, 17661, 17667. Likewise, Petitioner, with supporting testimony from Dr. Thiele, has shown that one of ordinary skill in the art would have wanted to increase the specific activity of one Fe-S cluster protein, DHAD—a goal on which both "industry and academia focused a great deal of attention." Pet. 34, 38;

Ex. 1002 ¶¶ 72, 80. With this goal in mind, we turn to the teachings of Anthony, Puig, and Ojeda.

(1) Anthony

Anthony, as the parties agree, explains a reason for the focus on increased DHAD activity, namely that increased activity of DHAD—which catalyzes a step in biosynthetic pathways producing isobutanol—increases isobutanol production in yeast containing such a pathway. Ex. 1005, [57], ¶¶ 3, 38, 112–119; Ex. 1002 ¶ 75; Pet 35; PO Resp. 15. Further, Anthony discloses that increased activity of expressed heterologous Fe-S cluster proteins, including DHAD, results from "reduced expression" of at least one endogenous Fe-S cluster protein—a teaching the parties also agree upon. Ex. 1005, [57], ¶¶ 13, 38, 74–77; Ex. 1002 ¶¶ 75–77; Pet. 35; PO Resp. 15. In particular, Anthony reports that heterologous DHAD expression improved with inactivation of either the endogenous gene encoding DHAD (*ILV3*), or isopropylmalate isomerase (or dehydratase) (*LEU1*). Ex. 1005 ¶ 74. Anthony discloses other exemplary endogenous Fe-S cluster proteins, along with their encoding genes, that may be targets for reduced expression, such as aconitase (*ACO1*), lipoate synthase (*LIPS*), succinate dehydrogenase (*SDH2*), ubiquinol-cytochrome-c reductase (*RIP1*), and ABC protein Rli1 (*RLI1*). *Id.* ¶¶ 9, 77; Ex. 1002 ¶ 79; Pet. 36. Anthony's disclosure also includes exemplary ways to reduce expression of such Fe-S cluster proteins, including "gene disruption, deletion or inactivation." Ex. 1005 ¶ 53; *see id.* ¶¶ 77–97; Ex. 1002 ¶ 77; Pet. 36.

We credit and are persuaded by Dr. Thiele's testimony that one of ordinary skill in the art, reading Anthony with the goal of increasing isobutanol production by increasing DHAD activity, would have considered

alternative, known means to reduce expression of endogenous Fe-S proteins other than these exemplary techniques disclosed in Anthony. Ex. 1002 ¶¶ 77–78, 80; Pet. 36–37. Dr. Thiele explains that a reason for considering alternative techniques is that one of ordinary skill would have understood that individually deleting genes encoding Fe-S proteins, as disclosed in Anthony, "would have potentially negative implications on cell growth and yield." Ex. 1002 ¶ 78; Pet. 37.

(2) Puig

Puig teaches one such alternative technique for reducing the expression of endogenous Fe-S cluster proteins. Specifically, Puig discloses that the Cth2 protein in yeast downregulates specific mRNAs of certain genes encoding Fe-S cluster proteins—including many Fe-S cluster proteins Anthony explicitly lists as targets for reduced expression, such as the *ILV3* gene encoding DHAD, as well as the *LEU1*, *ACO1*, *LIPS*, *SDH2*, *RIP1*, and *RLI1* genes. Ex. 1006, 99, 101, 107, Table 1; *see* Ex. 1005 ¶¶ 9, 77; Ex. 1002 ¶ 79; Pet. 37, 45; PO Resp. 17–19. Puig explains that this downregulation occurs because the Cth2 protein binds to, and targets for degradation, AU-rich elements ("AREs") in the three-prime untranslated region ("3'UTR") of specific mRNAs. Ex. 1006, 99, 104, 107; Ex. 1002 ¶ 102; Reply 10. Puig also lists putative AREs of genes downregulated by the Cth2 protein, including the *ILV3* gene. Ex. 1006, Table 1; Reply 10.

In addition, as Petitioner and Patent Owner agree, Puig explains that it was known in the art that Aft1 and Aft2 induce expression of the iron regulon, a collection of genes, including the *CTH2* gene that encodes the Cth2 protein. Ex. 1006, 99 ("[C]ells utilize . . . Aft1 and Aft2 to induce expression of the so-called iron regulon . . . ."); *id.* at 100–01, Fig. 2;

Ex. 1002 ¶¶ 69, 79–80; Pet. 37; PO Rep. 16–19 ("On its face, Puig teaches that Aft1 and Aft2 . . induce expression of the iron regulon, including Cth2."); *see also* Ex. 1007, 17661 ("Aft1 and Aft2 . . . induce expression of more than 20 genes that are referred to as the iron regulon . . . ."); *id.* at 17663, Table 2 (identifying the *CTH2* gene as an "iron regulon gene[]").

Petitioner, with supporting testimony from Dr. Thiele, has established that one of ordinary skill would understand that Puig's teaching regarding the Cth2 protein downregulating genes encoding Fe-S cluster proteins is directed to *endogenous* Fe-S cluster proteins encoded by *endogenous* genes—not *recombinant* Fe-S cluster proteins encoded by a *recombinant* gene using well-known techniques for recombinant protein expression. Ex. 1002 ¶¶ 80, 100–105; Pet. 38, 45–47; Reply 7–10. As Dr. Thiele explains, in "standard techniques for recombinant protein expression," a recombinant Fe-S cluster protein is "encoded by an mRNA that lacks an endogenous 3'-untranslated region"—which Puig discloses is the location at which the Cth2 protein targets and binds mRNA. Ex. 1002 ¶ 103; Ex. 1006, 99, 104, 107; *see* Ex. 1006, 109 (discussing cloning a gene "sequence with no 3'UTR"). Accordingly, one of ordinary skill would have understood that the Cth2 protein would not downregulate *recombinant* Fe-S cluster genes lacking the 3'UTR to which the Cth2 protein binds and targets for degradation. Ex. 1002 ¶¶ 80, 103. As a result, one of ordinary skill would have expected that expression of the Cth2 protein would lower levels and activity of *endogenous* Fe-S cluster proteins—encoded by *endogenous* mRNAs with the 3'UTR that the Cth2 protein degrades—but would increase levels and activity of *recombinant* Fe-S cluster proteins—encoded by *recombinant* mRNAs lacking the 3'UTR that the Cth2 protein degrades—as

a result of less competition with endogenous Fe-S cluster proteins for Fe-S binding. *Id.* ¶¶ 80, 102–104. In sum, one of ordinary skill would have recognized that Cth2 protein expression would be a means to increase the number and activity of recombinant Fe-S cluster proteins, including DHAD. *Id.* ¶¶ 80, 102–104.

Accordingly, based on the teachings of Anthony and Puig, one of ordinary skill in the art would have been motivated to recombinantly express DHAD, encoded by mRNA lacking the 3'UTR, and to induce expression of the Cth2 protein, including by activating Aft1 and Aft2. *See* Ex. 1002 ¶¶ 77–80; Pet. 38–39; Reply 7–8.

(3) Ojeda

Ojeda, in turn, reports data confirming that iron regulon genes—including *CTH2*—are "fully induced" and show "constitutive expression" in yeast as a result of the "absence of Grx3 and Grx4 proteins" when their respective genes are deleted. Ex. 1007, 17661–63, Table 1; *id.* at 17662 ("The induced expression of iron regulon genes . . . was due to the absence of Grx3 and Grx4 . . . ."); *id.* at Table 2 (listing data for "iron regulon genes"—including *CTH2*—"document[ing] that the iron regulon genes are induced in Δ*grx3*Δ*grx4* cells"); *id.* at 17667–68 ("[T]he iron regulon genes are . . . fully induced in the absence of both [Grx3 and Grx4] proteins."); Pet. 39; Ex. 1002 ¶ 81. In addition, Ojeda's data show that Aft1 is "fully" or "constitutively active" in yeast lacking the Grx3 and Grx4 proteins, and suggest corresponding activity for Aft2. Ex. 1007, Fig. 1 ("Aft1 is . . . fully activated in cells lacking both glutaredoxins."); *id.* at 17663, 17664 ("[D]epletion of Grx3 and Grx4 resulted in constitutive Aft1 activity . . . ."); Pet. 39; Ex. 1002 ¶ 81.

(4) Combination of Anthony, Puig, and Ojeda

Based on the teachings of Anthony, Puig, and Ojeda and the knowledge in the art discussed above, we conclude Petitioner has demonstrated that one of ordinary skill would have been motivated to create the yeast recited in claim 1, and would have had a reasonable expectation of success in doing so, by inactivating Grx3 and Grx4 proteins through deletion of the endogenous *GRX3* and *GRX4* genes—as taught by Ojeda—in a yeast recombinantly overexpressing DHAD—as taught by Anthony. Specifically, one of ordinary skill, wanting to increase DHAD activity and ultimately isobutanol production, would have had reason to combine Anthony's teaching that in recombinant yeast, increased activity of expressed heterologous DHAD results from reduced expression of one or more endogenous Fe-S cluster proteins; with Puig's teaching that reduced expression of certain genes encoding endogenous Fe-S cluster proteins is caused by the Cth2 protein, whose expression is induced by Aft1 and Aft2; and Ojeda's teaching that the *CTH2* gene is induced, and Aft is activated, in cells lacking the Grx3 and Grx4 protein as a result of gene deletion. *See* Ex. 1002 ¶ 81; Pet. 39; Reply 8. Given these "interrelated teachings" of Anthony, Puig, and Ojeda and the "background knowledge" and motivations of one of ordinary skill in the art, we determine that there was sound reason, with "rational underpinning," to combine elements known in the art in the manner recited in claim 1. *See KSR*, 550 U.S. at 418.

We, therefore, disagree with Patent Owner's assertion that Petitioner "impermissibly forecasts" that one of ordinary skill would have considered alternative means to reduce expression of endogenous Fe-S cluster proteins beyond that disclosed in Anthony, and that Petitioner has not proffered a

"salient rationale" to look to Ojeda to cure the failure of both Anthony and Puig to disclose inactivated Grx3 and Grx4 proteins. PO Resp. 16, 20. Patent Owner's attorney argument provides no reliable evidence to dispute Petitioner's proposed combination, which is supported by the interrelated teachings of the references as well as the testimony of Dr. Thiele.

Patent Owner's other arguments disputing the combination of Anthony, Puig, and Ojeda also are not convincing. Patent Owner contends that Anthony does not provide sufficient direction regarding which endogenous Fe-S cluster protein's expression should be reduced to increase the activity of DHAD, and neither Anthony nor Puig teaches or suggests inactivating Grx3 or Grx4 proteins. *Id.* at 15–17. This attack on Anthony and Puig individually, however, does not support Patent Owner's nonobviousness arguments because Ojeda—not Anthony or Puig—provides the relevant teaching regarding inactivating Grx3 and Grx4 proteins, as we found above. *See In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references."); Reply 5–8; *see also Banner Eng'g Corp. v. Tri-Tronics Co.*, Nos. 93-1115, 93-1116, 93-1158, 1993 WL 432383, at *3 (Fed. Cir. Oct. 27, 1993) (holding that a party's "attack on the prior art—reference by reference—[wa]s not persuasive" because in assessing obviousness, "references are read not in isolation but for what they fairly teach in combination"). Further, we are not persuaded by Patent Owner's more general argument that Anthony lacks direction as to which endogenous Fe-S cluster protein should be targeted for reduced expression to increase DHAD activity. *See* PO Resp. 16. As discussed above, Anthony provides a

list of exemplary Fe-S cluster proteins that may be targets for reduced expression and specifically reports that heterologous DHAD expression improved with reduced expression of either of two specific endogenous genes: (1) the *ILV3* gene encoding DHAD, or (2) the *LEU1* gene encoding isopropylmalate isomerase (or dehydratase). Ex. 1005 ¶¶ 74–77; Reply 6–7.

(c) Alleged Teaching Away

Patent Owner also counters Petitioner's obviousness arguments by asserting that both Puig and Ojeda teach away from overexpression of DHAD and inactivation of either or both the Grx3 and Grx4 proteins, as recited in claim 1. PO Resp. 16–22. Specifically, as to Puig, Patent Owner agrees with Petitioner that Puig discloses that the Cth2 protein, whose expression is induced by activated Aft, downregulates genes encoding Fe-S cluster proteins. *Id.* at 16–19. According to Patent Owner, however, because heterologous DHAD is an Fe-S cluster protein and Puig does not provide any teaching distinguishing the binding of the Cth2 protein to endogenous versus heterologous DHAD mRNA, Puig teaches one of ordinary skill that induced expression of the Cth2 protein decreases the production of heterologous DHAD. *Id.* Patent Owner further argues that we should disregard Dr. Thiele's opinion that one of ordinary skill, reading Puig, would have understood that the Cth2 protein would degrade endogenous DHAD—but not recombinant DHAD expressed using standard techniques—because Dr. Thiele does not cite scientific literature or data for this point, which is "contrary to the plain teachings of Puig." *Id.* at 19; *see id.* at 17–18. Instead, according to Patent Owner, "the teachings of Puig must be taken on their face." *Id.* at 19.

Similarly, Patent Owner argues that Ojeda "explicitly teaches away" from deriving the yeast recited in claim 1 based on the following statements. *Id.* at 20. First, Ojeda explains that the enzymatic activity of aconitase, sulfite reductase, and isopropylmalate isomerase was "decreased" or "depressed" in yeast lacking *both* the Grx3 and Grx4 proteins, but was "normal" or "wild type" in yeast lacking *either* the Grx3 or Grx4 protein. Ex. 1007, 17667; *see* PO Resp. 20. Second, Ojeda reports that other Fe-S cluster enzymes similarly were "unaffected" in yeast lacking *either* the Grx3 or the Grx4 protein. Ex. 1007, 17668; PO Resp. 20–21. Patent Owner argues that one of ordinary skill would have expected that inactivating either or both the Grx3 and Grx4 proteins would impact the activity of DHAD, an Fe-S cluster enzyme, in a manner similar to the Fe-S cluster enzymes reported in Ojeda and, therefore, would have been dissuaded from doing so. *See* PO Resp. 20–21.

In reply, Petitioner argues that Patent Owner's teaching away argument—supported only by attorney argument—"fundamentally misunderstands and misapplies the knowledge and routine practice of a skilled practitioner in the field of eukaryotic recombinant gene expression," particularly with respect to endogenous versus recombinant Fe-S cluster proteins. Reply 12; *see id.* at 8; Ex. 1002 ¶¶ 101, 105; Pet. 45. Petitioner reiterates Dr. Thiele's opinion and argues that it is substantiated by the prior art, including Puig, as well as the knowledge and common practice in the field. Reply 9–10. Further, Petitioner asserts that Patent Owner's attempt to limit the knowledge of one of ordinary skill to "the four corners of a reference" is contrary to Supreme Court precedent in *KSR*. *Id.* at 10–11.

We first note that Puig and Ojeda are each silent as to whether the Fe-S cluster genes and proteins being discussed are endogenous or recombinant. *See generally* Ex. 1006; Ex. 1007. Therefore, Petitioner's position, with supporting testimony from Dr. Thiele, that one of ordinary skill would understand Puig and Ojeda to be referring to *endogenou*s Fe-S cluster genes and proteins and would know that *recombinant* Fe-S cluster genes and proteins, encoded using standard techniques for recombinant protein expression, would behave differently is not "contrary to the plain teachings" of the references—as Patent Owner contends. PO Resp. 19. Instead, Dr. Thiele's testimony merely explains how one of ordinary skill in the art would understand and interpret the teachings of the references. *See* Ex. 1002 ¶¶ 80, 100–105; Reply 9–13.

Further, we agree with Petitioner that Patent Owner's suggestion to take the references "on their face" is contrary to controlling precedent. PO Resp. 16–22; *see* Reply 10–11. The Supreme Court, in *KSR*, "required an analysis that reads the prior art in context, taking account of . . . 'the background knowledge possessed by a person having ordinary skill in the art,' and 'the inferences and creative steps that a person of ordinary skill in the art would employ.'" *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (quoting *KSR*, 550 U.S. at 418); *see KSR*, 550 U.S. at 417–19. Indeed, *KSR* held that "the knowledge of such 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." *Randall Mfg.*, 733 F.3d at 1362 (emphasis added). Therefore, we consider, as we must, the background knowledge possessed by one of ordinary skill in the art reading Puig and Ojeda.

Dr. Thiele explained the background knowledge of one of ordinary skill in detail in his declaration. Patent Owner asks us to reject Dr. Thiele's opinion, yet offers no legal precedent to support its argument and no evidence—only attorney argument—as to how one of ordinary skill would understand the references. *See* PO Resp. 16–22. We decline to do so, because we conclude that the prior art of record is consistent with and supports Dr. Thiele's testimony. Further, Patent Owner's proposed view of the references, in which one of ordinary skill would not distinguish endogenous and recombinant Fe-S cluster protein expression, lacks support in the record and takes an improperly narrow view of the knowledge of one of ordinary skill in the art.

We credit and are persuaded by Dr. Thiele's testimony that one of ordinary skill would have understood Puig's teaching regarding Fe-S cluster genes being downregulated by the Cth2 protein, and Ojeda's teaching regarding the activity of Fe-S cluster enzymes being decreased or unaffected by inactivation of either or both Grx3 and Grx4 proteins, to be directed to *endogenous* Fe-S cluster proteins encoded by *endogenous* genes. Ex. 1002 ¶¶ 80, 102–105. As Dr. Thiele explains, one of ordinary skill would have understood that, using standard techniques for recombinant protein expression, *recombinant* Fe-S proteins encoded by *recombinant* mRNA lacking the 3'UTR—which Puig teaches is what Cth2 binds to and degrades—would not be downregulated by induced expression of the Cth2 protein, including through the means taught by Ojeda, namely inactivating the Grx3 and Grx4 proteins. Ex. 1002 ¶¶ 80, 103; Pet. 38, 46; Reply 7; Ex. 1006, 99, 104, 107. Thus, one of ordinary skill in the art would have expected that such induced expression of Cth2 would result in lower levels

and activity of *endogenous* Fe-S cluster proteins—encoded by *endogenous* mRNAs with the 3'UTR that the Cth2 protein degrades—but greater levels and activity of *recombinant* Fe-S cluster proteins—encoded by *recombinant* mRNAs lacking the 3'UTR that the Cth2 protein degrades—with less competition from endogenous Fe-S cluster proteins for Fe-S binding. Ex. 1002 ¶¶ 80–81, 102–104; *see* Pet. 38, 45–47; Ex. 1007, 17661–63, Table 1–2. In other words, Ojeda's disclosure regarding decreased activity of Fe-S cluster enzymes in yeast lacking Grx3 and Grx4 proteins would have been entirely expected for *endogenous* Fe-S cluster enzymes, yet the opposite effect would have been expected for *recombinant* Fe-S cluster enzymes. Ex. 1002 ¶¶ 100–105; *see* Pet. 43–47; Reply 12–13. Thus, neither Puig's nor Ojeda's disclosures regarding reduced expression of Fe-S cluster genes and proteins would have dissuaded one of ordinary skill from inactivating the Grx3 and Grx4 proteins in yeast recombinantly overexpressing DHAD. Ex. 1002 ¶¶ 80, 100–105.

Dr. Thiele's position is consistent with and supported by the evidence of record.[8] As Petitioner points out, Puig discloses that the means by which the Cth2 protein downregulates mRNAs of Fe-S cluster genes is by binding to AREs within the 3'UTR. Ex. 1006, 101, 104, 107, Table 1. Thus, as Puig

[8] In reaching this conclusion, we do not consider Exhibit 1025 (Joseph Sambrook et al., Molecular Cloning: a Laboratory Manual (2d ed. 1989)), which Petitioner submitted with its Reply. Exhibit 1025 is relevant to Petitioner's affirmative obviousness arguments presented in the Petition and Dr. Thiele's declaration, *see* Pet. 38; Ex. 1002 ¶ 80, and Petitioner gave no reason why this evidence could not have been submitted with the Petition. *See* Tr. 19:17–22:8; *see generally* Reply. Accordingly, we determine this evidence is untimely and outside the proper scope of a reply. *See* 37 C.F.R. § 42.23(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012).

states, "*CTH2*-dependent mRNA downregulation under low Fe conditions is dependent on the presence of specific AREs located in the 3'UTR." *Id.* at 104. In addition, Puig lists putative AREs in the 3'UTR for various Fe-S cluster genes, including the *ILV3* gene encoding DHAD. *Id.* at Table 1. Significantly, Puig also expressly discusses cloning a gene "sequence with no 3'UTR." *Id.* at 109. These disclosures bolster Petitioner and Dr. Thiele's position that one of ordinary skill would know to, and be motivated to, recombinantly express DHAD, encoded by mRNA lacking the 3'UTR, and would appreciate that the resulting difference in the 3'UTR in mRNA would prevent the Cth2 protein from downregulating recombinant DHAD. In addition to Puig's teachings, Anthony is directed to *increased* activity of expressed *heterologous* Fe-S cluster proteins resulting from *reduced* expression of *endogenous* Fe-S cluster proteins. *See* Ex. 1005 ¶¶ 38, 74. In fact, Anthony specifically reports that heterologous DHAD expression improved with inactivation of the endogenous gene encoding DHAD (*ILV3*). *Id.* ¶ 74. Anthony's teachings, therefore, further support Petitioner and Dr. Thiele's position that one of ordinary skill in the art would have understood that endogenous and recombinant proteins behave differently.

In sum, the cited prior art, including Anthony and Puig, and Dr. Thiele's opinion demonstrate that one of ordinary skill, upon reading Puig and Ojeda, would not have been "discouraged from following the path set out in [Puig and Ojeda], or . . . led in a direction divergent from the path" taken by the inventors of the '565 patent. *In re Mouttet*, 686 F.3d 1322, 1333–34 (Fed. Cir. 2012) (quotations omitted); *accord Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1332 (Fed. Cir. 2008). Patent Owner's argument that Puig and Ojeda teach away from deriving the yeast recited in

claim 1 lacks factual and legal support, and is contrary to the evidence of record. We find by a preponderance of the evidence that neither Puig nor Ojeda teaches away from deriving the recombinant yeast recited in claim 1 in which DHAD is recombinantly overexpressed and both Grx3 and Grx4 proteins are inactivated by deletion of their respective genes.

(d) Purported Evidence of Secondary Considerations

In its final dispute of Petitioner's obviousness arguments, Patent Owner submits Exhibit 2001, U.S. Patent Application Publication No. 13/837,921 ("the '921 application"), Petitioner's pending patent application, which claims priority to the Flint '333 provisional. Ex. 2001, [21], [60]. Patent Owner directs our attention to paragraphs 290 and 291 of the '921 application:

> *Surprisingly, DHAD specific activity* in the crude extract in strains with a *deletion in* either the FRA2 or *the GRX3 gene increased by 2- to 3-fold, which was unexpected* as many of the deletions tested did not increase DHAD specific activity. . . .
>
> Another *unexpected finding is the effect of a Grx3 deletion on DHAD activity*. It has been shown that Grx3 and Grx4 are equivalent in function. While double mutations in both GRX3 and GRX4 genes resulted in drastic activation of the Fe regulon, mutation in Grx4 alone confers minimal phenotype (Pujol-Carrion, et al, *J Cell Sci.* 119:4554-4564 (2006); Ojeda, et al, *J Biol. Chem.* 281:17661-17669 (2006)). As shown in Table 10 above, *GRX3 deletion alone leads to significant improvement in DHAD specific activity*.

Id. ¶¶ 290–291 (emphases added); *see* PO Resp. 24–25. Patent Owner cites dependent claims 65 and 71, which involve increased DHAD activity and "at least one deletion, mutation or substitution in" one or a combination of

several endogenous genes, including *GRX3*, respectively. Ex. 2001, 77; PO Rep. 23–24. Patent Owner urges us to treat Petitioner's representations in the '921 application as a "party admission" regarding "the unexpected ability of GRX3 deletion to increase DHAD activity." PO Resp. 23–25 (emphasis omitted). Thus, Patent Owner essentially asks us to treat these representations as evidence of secondary considerations, specifically unexpected results, to rebut Petitioner's obviousness showing.

We, however, are not persuaded that the '921 application has any impact on this case for several reasons. We first note that Petitioner's statements in the '921 application regarding the "unexpected" or "surprising[]" effects on DHAD activity involve only deletions in the *GRX3* gene. Ex. 2001 ¶¶ 290–291. Our conclusion that Petitioner has shown that claim 1 would have been obvious rests on Petitioner's showing that it would have been obvious to inactivate *both* the Grx3 and Grx4 proteins, by deletion of *both* the *GRX3* and *GRX4* genes. *See supra* Section II.C.2.a.i. Accordingly, Petitioner's statements and representations regarding *GRX3* gene deletion alone do not contradict, and have no impact on, our obviousness conclusion in this case.

Nor are we persuaded that the statements and claims in the '921 application—when viewed in context—contradict Petitioner's position in this trial that one of ordinary skill would have known that deleting the *GRX3* gene would increase DHAD activity. It is reasonable to interpret the statements in paragraphs 290 and 291 of the '921 application to mean that what is "surprising[]" and "unexpected" is the *extent* of the increase in DHAD activity, specifically that this activity was "significant[ly] improve[d]" by "2-to3-fold," not that DHAD activity increased at all.

Ex. 2001 ¶¶ 290–291; Tr. 34:12–17. Patent Owner has not shown otherwise. As to the claims of the '921 application to which Patent Owner cites,[9] Petitioner correctly points out in its Reply that claims 65 and 71 are *separate* dependent claims. Reply 14; Ex. 2001, 77. Claim 71 relates to "at least one deletion, mutation, or substitution" in an endogenous *GRX3* gene, whereas claim 65 involves DHAD activity. Ex. 2001, 77. Therefore, Patent Owner has not directed us to any particular claim in the '921 application that contradicts Petitioner's position in this case that it would have been obvious to delete the *GRX3* gene to increase DHAD activity.

Yet, even if we agreed with Patent Owner that the representations in the '921 application are contrary to Petitioner's position in this case and are evidence of unexpected results, this evidence would not save the claims of the '565 patent for two reasons. To rebut Petitioner's obviousness showing, evidence of secondary considerations, including unexpected results, "must be reasonably commensurate with the scope of the claims." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011); *see In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (holding showing of unexpected results insufficient because "[e]ven assuming that the results were unexpected," applicant failed "to show results covering the scope of the claimed range"); Pet. 56–58. Here, the purported evidence of unexpected results relates exclusively to deletions in the *GRX3* gene—not the *GRX4* gene, or the *GRX3* and *GRX4* genes. *See* Ex. 2001 ¶¶ 290–291; PO Resp. 23 (referring to the "unexpected ability of *GRX3 deletion* to increase DHAD activity") (emphasis added); *id.* at 25 (arguing that "Petitioner considers the increased DHAD activity brought

[9] Petitioner clarified during the oral hearing that the claims in the '921 application were amended after publication of Exhibit 2001. Tr. 31:3–13.

about by inactivation of *GRX3* to be an 'unexpected finding'") (emphasis added). Accordingly, this purported evidence of unexpected results is not reasonably commensurate with the scope of the genus recited in claim 1.

In sum, the '921 application does not impact the obviousness of claim 1.

(e) Conclusion

Based on our review of the arguments and evidence of record, we conclude Petitioner has shown by a preponderance of the evidence that claim 1 is unpatentable as obvious over Anthony, Puig, and Ojeda.

ii. Dependent Claims 2–4, 6–8, 11, 13, 14, and 16–19

Petitioner asserts that Anthony teaches or suggests the additional limitations of dependent claims 2–4, 6–8, 11, 13, 14, and 17–19, and Puig teaches or suggests the additional limitation of claim 16. *See* Pet. 34–43; Ex. 1002 ¶¶ 82–92. Patent Owner does not dispute these assertions. *See* PO Resp. 15–22. Based on our review of the arguments and evidence, we determine that Petitioner has demonstrated that each of the additional limitations recited in claims 2–4, 6–8, 11, 13, 14, and 17–19 are taught by Anthony and the additional limitation of claim 16 is taught by Puig, for the reasons set forth in the Petition as well as Dr. Thiele's supporting declaration. *See* Pet. 34–43; Ex. 1002 ¶¶ 82–92.

For these reasons, in addition to our reasoning outlined above regarding the obviousness of claim 1, we conclude that Petitioner has shown by a preponderance of the evidence that claim 2–4, 6–8, 11, 13, 14, and 16–19 are unpatentable as obvious over Anthony, Puig, and Ojeda.

b. ANTHONY, PUIG, OJEDA, AND LI — CLAIM 5

Next, we consider Petitioner's assertion that claim 5 of the '565 patent is unpatentable under 35 U.S.C. § 103 as obvious over the combination of Anthony, Puig, Ojeda, and Li. Pet. 47–49. In response to this asserted ground of unpatentability, Patent Owner does not put forward any arguments or evidence unique to the additional limitation of claim 5 or to the teachings of Li, the additional reference Petitioner relies upon in this asserted ground. *See* PO Resp. 22. Instead, Patent Owner relies on its challenges to Petitioner's contention that claim 1 would have been obvious over Anthony, Puig, and Ojeda—which we have addressed and found unpersuasive above. *See id.*; *supra* Section II.C.2.a.i.

Li discloses ketol–acid reductoisomerase ("KARI") enzymes that preferentially bind to the cofactor NADH instead of NADPH. Ex. 1015 ¶¶ 2, 10–11. Li further discusses methods of producing such KARI enzymes as well as methods of using these enzymes in recombinant yeast microorganisms in the isobutanol biosynthetic pathway disclosed in Anthony. *Id.* ¶¶ 11, 32–39, 126–144; *see* Ex. 1005 ¶¶ 112–119. Li explains that using KARI enzymes that bind to NADPH, rather than NADH, "enhance[s] the productivity of the isobutanol biosynthetic pathway by capitalizing on the NADH produced by the existing glycolytic and other metabolic pathways in most commonly used microbial cells." Ex. 1015 ¶ 6.

Claim 5 of the '565 patent depends from claim 4 and further requires that the KARI of the recited recombinant yeast be "an NADH–dependent ketol–acid reductoisomerase." Ex. 1001, 91:45–49. We find that Li's disclosure of KARI enzymes that preferentially bind to the cofactor NADH, instead of NADPH, teaches this additional limitation of claim 5. *See*

Ex. 1015 ¶¶ 2, 10–11; Ex. 1002 ¶ 94. We also are persuaded by Dr. Thiele's opinion that one of ordinary skill would have had reason to combine this teaching of Li with the teachings of Anthony, Puig, and Ojeda in a manner that yields the recombinant yeast recited in claim 5, with a reasonable expectation of success. Specifically, Dr. Thiele opines that one of ordinary skill would look to combine the references, because Anthony and Li are directed to recombinant yeast with the same isobutanol biosynthetic pathway, and Li discloses the benefits of using KARI enzymes that bind to the cofactor NADH for isobutanol production. *See* Ex. 1002 ¶¶ 93–94.

Accordingly, we conclude Petitioner has shown by a preponderance of the evidence that claim 5 of the '565 patent is unpatentable as obvious over Anthony, Puig, Ojeda, and Li.

c. ANTHONY, PUIG, OJEDA, AND VAN MARIS — CLAIM 9

Finally, we address Petitioner's assertion that claim 9 of the '565 patent is unpatentable under 35 U.S.C. § 103(a) as obvious over Anthony, Puig, Ojeda, and van Maris. Pet. 49–51. As with the instituted ground of unpatentability challenging claim 5, Patent Owner has not proffered any arguments or evidence specific to the additional limitation of claim 9 or to the additional reference relied upon in this ground, van Maris—again relying exclusively on its arguments that the combination of Anthony, Puig, and Ojeda does not render independent claim 1 obvious. *See* PO Resp. 22–23.

Van Maris discloses that in *Saccharomyces cerevisiae* yeast, deleting the *PDC1*, *PDC5*, and *PDC6* genes results in significantly decreased production of ethanol, but increased production of pyruvate. Ex. 1008, Abstract, 159, 163, Fig. 1, Table 2. Specifically, van Maris reports a

theoretical yield of ethanol of less than 0.01 mmol in *Saccharomyces cerevisiae* lacking the *PDC* genes. *Id.* at Table 2. Van Maris further explains that these results occur because deleting the genes impairs a pathway that converts pyruvate to ethanol. *Id.* at Fig. 1.

In claim 9 of the '565 patent, which depends from claim 2, the yeast is "further engineered to inactivate one or more endogenous pyruvate decarboxylase (PDC)." Ex. 1001, 91:58–61. We find that van Maris's disclosure of deleting *PDC1*, *PDC5*, and *PDC6* genes in yeast teaches this additional limitation of claim 9. *See* Ex. 1008, Abstract, 159, 163, Fig. 1, Table 2; Ex. 1002 ¶ 97. In addition, we credit and find persuasive Dr. Thiele's opinion that one of ordinary skill in the art would have combined Anthony, Puig, Ojeda, and van Maris to reach the claimed invention. Ex. 1002 ¶¶ 95–97. In particular, Dr. Thiele opines that Anthony and van Maris involve yeast fermentation products with pyruvate as a starting substrate. *Id.* ¶ 95; *see* Ex. 1005 ¶ 113. Further, van Maris's disclosure of decreased ethanol production in yeast lacking PDC would have motivated one of ordinary skill, using the isobutanol pathway in Anthony with pyruvate as a starting substrate, to delete PDC genes to direct pyruvate away from ethanol production and towards isobutanol production. *See* Ex. 1002 ¶¶ 95–97. We likewise find persuasive Dr. Thiele's explanation that one of ordinary skill would have had a reasonable expectation of success in deleting *PDC*, because yeast strains lacking *PDC* activity were available commercially before the earliest claimed effective filing date of the '565 patent. *Id.* ¶ 97.

For these reasons, in addition to our reasoning outlined above regarding the obviousness of claims 1 and 2, we conclude Petitioner has

shown by a preponderance of the evidence that claim 9 would have been obvious over Anthony, Puig, Ojeda, and van Maris.

III. CONCLUSION

In conclusion, Petitioner has shown by a preponderance of the evidence that claims 1–9 and 11–19 of the '565 patent are unpatentable. Specifically, Petitioner has established that: (1) claims 1–4, 6–8, and 11–19 are anticipated by Flint; (2) claims 1–4, 6–8, 11, 13, 14, and 16–19 would have been obvious over Anthony, Puig, and Ojeda; (3) claim 5 would have been obvious over Anthony, Puig, Ojeda, and Li; and (4) claim 9 would have been obvious over Anthony, Puig, Ojeda, and van Maris.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has shown by a preponderance of the evidence that claims 1–9 and 11–19 of the '565 patent are unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

PETITIONER:

Deborah A. Sterling
Peter A. Jackman
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
dsterlin-PTAB@skgf.com
pjackman-PTAB@skgf.com

PATENT OWNER:

Erich E. Veitenheimer, Ph.D.
Chris Holly, Ph.D.
COOLEY LLP
eveitenheimer@cooley.com
IPR2013-00539@cooley.com