

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MOTIF FOODWORKS, INC.,
Petitioner,

v.

IMPOSSIBLE FOODS INC.,
Patent Owner.

IPR2023-00321
Patent 10,689,656 B2

Before ULRIKE W. JENKS, CHRISTOPHER M. KAISER, and
KIMBERLY McGRAW, *Administrative Patent Judges*.

McGRAW, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Motif Foodworks, Inc. (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting an *inter partes* review of claims 1–28 of U.S. Patent No. 10,689,656 B2 (Ex. 1002, “the ’656 patent”). Impossible Foods Inc. (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

We have authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314(b); 37 C.F.R. § 42.4(a). The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a), which provides that an *inter partes* review may not be instituted unless “there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.”

After considering the Petition, the Preliminary Response, and the evidence of record, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail with respect to at least one challenged claim. Accordingly, we do not institute an *inter partes* review of any challenged claim on any asserted ground.

II. BACKGROUND

A. *Related Matters*

The parties identify *Impossible Foods Inc. v. Motif FoodWorks, Inc.*, No. 22-cv-00311 (D. Del.) and IPR2023-00322, involving U.S. Patent No. 10,273,492, as related matters. Pet. 78; Paper 4 (Patent Owner’s Mandatory Notice), 1–2. Patent Owner also identifies IPR2022-00887 (involving U.S. Patent No. 10,863,761), IPR2023-00206 (involving U.S. Patent No. 9,943,096), IPR2023-00207 (involving U.S. Patent No. 11,224,241), IPR2023-00208 (involving U.S. Patent No. 11,013,250), IPR2023-00209

(involving U.S. Patent No. 10,039,306), and opposition proceedings in EP2943072 as related matters. Paper 4, 1–2.

B. Real Parties in Interest

Petitioner identifies its real party in interest as Motif FoodWorks, Inc. Pet. 77. Patent Owner identifies Impossible Foods Inc. as its real party in interest. Paper 4, 1.

C. Overview of the '656 patent

The '656 patent states that it relates to the use of *Pichia pastoris* yeast strains that overexpress the transcriptional activator called methanol expression regulator 1 (“Mxr1” or “Mxr1p”) from an alcohol oxidase 1 (“AOX1”) promoter to increase expression of transgenes that also are expressed from the AOX1 promoter. *See* Ex. 1002, 1:38–42. The Specification explains that expression of the Mxr1 from the AOX1 promoter creates a positive feedback loop that allows for expression of other transgenes from the AOX1 promoter in the absence of methanol when repressing carbon sources are depleted. Thus, expression of Mxr1 results in a significant increase in the amount of protein expressed. Ex. 1002, 1:47–49.

D. The Challenged Claims

Petitioner challenges claims 1–28 of the '656 patent. Pet. 1. Claims 1 and 26 are the only independent claims and are reproduced below, with bracketed letters¹ and formatting added:

1. A methylotrophic yeast cell comprising

¹ The bracketed letters used in this Decision differ slightly from the bracketed letters used by the parties. All references in this Decision to claim elements refer to the elements as indicated by the bracketing set forth below.

- [a] a recombinant nucleic acid molecule, wherein the recombinant nucleic acid molecule comprises a first exogenous nucleic acid encoding a methanol expression regulator 1 (Mxr1) transcriptional activator operably linked to at least one methanol-inducible promoter element comprising a sequence to which the Mxr1 transcriptional activator binds,
- [b] wherein the recombinant nucleic acid molecule comprises a second exogenous nucleic acid encoding a heterologous polypeptide operably linked to at least one methanol-inducible promoter element.

Ex. 1002, 87:31–41.

26. A methylotrophic *Pichia* yeast cell comprising a recombinant nucleic acid molecule, wherein the recombinant nucleic acid molecule comprises:
- [a] a nucleic acid encoding a Mxr1 transcriptional activator sequence from *P. pastoris*;
 - [b] a nucleic acid encoding a member of globin family PF00042; and
 - [c] a nucleic acid encoding at least one polypeptide involved in heme biosynthesis,
 - [d] wherein each nucleic acid is operably linked to a methanol-inducible promoter element, wherein the methanol-inducible promoter element comprises at least one sequence to which a Mxr1 transcriptional activator binds.

Ex. 1002, 90:1–13; Certificate of Correction (Ex. 1002, 60).

E. Evidence

Petitioner submits evidence including:

Evidence	Exhibit No.
Declaration of Dr. Carl Batt, Ph.D.	1003
Declaration of Dr. Geoffrey P. Lin-Cereghino, Ph.D.	1004
Regulation of <i>Pichia pastoris</i> promoters and its consequences for protein production, New Biotechnology, Vol. 30:4, May 2013 (“Vogl”)	1005

Evidence	Exhibit No.
Mxr1p, a Key Regulator of the Methanol Utilization Pathway and Peroxisomal Genes in <i>Pichia pastoris</i> , Molecular and Cellular Biology, Feb. 2006 (“Lin-Cereghino”)	1006
U.S. Patent No. 5,824,511 (Oct. 20, 1998) (“Mattoon”)	1008
U.S. Appl. Pub. No. 2011/0287467 A1 (published Nov. 24, 2011) (“Crane”)	1010
U.S. Appl. Pub. No. 2011/0129874 A1 (published Jun. 2, 2011) (“Tsutsumi”)	1024
Optimizing cofactor availability for the production of recombinant heme peroxidase in <i>Pichia pastoris</i> Microbial Cell Factories 14:4 (2015) (“Krainer”)	1031

F. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §	Reference(s)
1–17, 21, 23–25	103 ²	Tsutsumi, Lin-Cereghino, Mattoon
18–20	103	Tsutsumi, Lin-Cereghino, Mattoon, Crane
22	103	Tsutsumi, Lin-Cereghino, Mattoon, Krainer
26, 28	103	Mattoon, Vogl
27	103	Mattoon, Vogl, Crane

Pet. 5.

² The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), amended 35 U.S.C. § 103. The earliest claimed priority date for the ’646 patent is after the effective date of the applicable AIA amendment. *See* Ex. 1002, (60). Thus, we refer to the AIA version of 35 U.S.C. § 103.

G. The Prior Art

1. Tsutsumi (Ex. 1024)

Tsutsumi is a U.S. Patent Publication directed to variants of the *Pichia* DAS methanol-inducible promoter having increased copies of an “upstream activation sequence” (“UAS”) for increasing expression of a polypeptide of interest. Ex. 1024, Abstract, ¶ 7. Tsutsumi explains that induction of methanol-inducible promoters normally requires the presence of (1) methanol and (2) transcription factors, but that the exact role transcription factors play in induction is not yet known. *Id.* ¶ 41 (stating transcription factor Mxr1p “has been described as a key positive regulator required for methanol utilization” but that the “exact mechanism of action for such factors has not been elucidated”).

Tsutsumi also describes the preparation and use of DNA constructs having both (1) a nucleotide sequence encoding a functional part of a methanol-inducible DAS promoter as well as (2) upstream activation sequence (“UAS”) to express polypeptides of interest. *See id.* ¶¶ 2, 8, 137–145.

2. Lin-Cereghino (Ex. 1006)

Lin-Cereghino is a 2006 article titled “Mxr1p, a Key Regulator of the Methanol Utilization Pathway and Peroxisomal Genes in *Pichia pastoris*.” Ex. 1006, 1. The article identifies genes required for the expression of AOX1, including the gene encoding Mxr1. Ex. 1006, 1. Lin-Cereghino concludes that Mxr1 is a transcription factor that is necessary for the activation of a number of genes whose products are involved in the metabolism of methanol by *P. pastoris*. *Id.* Lin-Cereghino describes *P. pastoris* strains with Mxr1p under the control of methanol-inducible

promoters P_{AOX1} or P_{PEX8}. *Id.* at 11 (stating a strain produced with Mxr1p under control of “the strong methanol-regulated AOX1 promoter” did not grown on methanol and did not induce Mxr1p in response to methanol but that a strain expressing Mxr1 under control of the less strongly methanol regulated P_{PEX8} gene was able to grow on methanol).

3. *Mattoon (Ex. 1008)*

Mattoon is a U.S. Patent directed to a method of improving production of hemoproteins in yeast cells. Ex. 1008, 1:5–11. In one disclosed embodiment, yeast cells are transfected with a vector that encodes both a heme-rate limiting enzyme as well as a heme-binding agent. *See* Ex. 1008, 5:34–46.

4. *Crane (Ex. 1010)*

Crane is a U.S. Patent Publication that discloses methods of producing recombinant heme-binding proteins. Ex. 1010, (54). In one disclosed embodiment, yeast cells are transfected with a vector that encodes both a recombinant heme-binding protein and recombinant ferro-chelataase. *See* Ex. 1010 ¶¶ 34, 35, 74.

5. *Vogl (Ex. 1005)*

Vogl is a 2013 review article titled “Regulation of *Pichia pastoris* promoters and its consequences for protein production.” Ex. 1005, 1. Vogl discusses “[c]lassic *P. pastoris* promoters” including the methanol-inducible AOX1 promoter and the constitutive³ GAP promoter (Ex. 1005, 1–8), and

³ Petitioner explains that promoters can be either “constitutive” (active regardless of external stimuli) or “inducible” (more or less active in response to external stimuli, such as a chemical (e.g., methanol)). *See* Pet. 7.

“[a]lternative promoters” including the methanol-inducible DAS promoter (Ex. 1005, 8–11).

6. *Krainer (Ex. 1031)*

Krainer is a 2015 article titled “Optimizing cofactor availability for the production of recombinant heme peroxidase in *Pichia pastoris*.” Ex. 1031, 1. Krainer discusses optimizing heme availability through the overexpression of heme protein horseradish peroxidase (“HRP”) and through iron supplementation. Ex. 1031, 2, 6.

III. ANALYSIS

A. *Claim Construction*

Neither party proposes express constructions for any claim terms in this proceeding. *See generally* Pet.; Prelim. Resp. 4. For purposes of this Decision, we determine that no claim terms need to be construed to resolve any controversies in dispute. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (stating only those claim terms that are in controversy need to be construed, and only to the extent necessary to resolve the controversy).

B. *Level of Skill in the Art*

Petitioner asserts that a person of ordinary level of skill in the art (“POSITA”) would have at least a Bachelor of Science in biochemistry, chemistry, biological sciences, or an equivalent area of study and at least three years of graduate study or professional experience with recombinant techniques for protein production or general genetic modification experience. Pet. 28 (citing Ex. 1003 ¶ 36); *see also* Ex. 1004 ¶ 29

(providing similar definition). Patent Owner does not dispute Petitioner's definition.

We adopt Petitioner's definition of a POSITA, except that we delete the qualifier "at least" to eliminate vagueness as to the appropriate level of education or experience. The qualifier expands the range without an upper bound (e.g., encompassing a Ph.D. degree and beyond) and thus does not meaningfully indicate the level of ordinary skill in the art. This definition of a person of ordinary skill in the art is supported by the testimony of Dr. Batt and Dr. Lin-Cereghino and appears to be commensurate with the level of ordinary skill as reflected in the prior art and the '656 patent. *See* Ex. 1003 ¶ 36; Ex. 1004 ¶ 29.

C. Asserted Unpatentability of Claims 1–17, 21, and 23–25 over Tsutsumi, Lin-Cereghino, and Mattoon (Ground 1)

Petitioner contends that independent claim 1 and dependent claims 2–17, 21, and 23–25 are unpatentable under 35 U.S.C. § 103 over Tsutsumi, Lin-Cereghino, and Mattoon. Pet. 29–67. Patent Owner responds that the challenged claims are not unpatentable because the cited art does not teach all of the claimed limitations and because Petitioner failed to provide a reason to combine the teachings of the asserted art to arrive at the claimed subject matter. *See* Prelim. Resp. 8–31. For the reasons set forth below, we determine Petitioner has not shown a reasonable likelihood that any of the challenged claims are unpatentable under Ground 1.

1. Claim 1

a) A recombinant nucleic acid molecule having both a first and second exogenous nucleic acid

Claim 1 requires a recombinant nucleic acid molecule that comprises both (1) the "first exogenous nucleic acid" as recited in claim element 1[a]

(i.e., a nucleic acid encoding a methanol expression regulator 1 (Mxr1) transcriptional activator operably linked to at least one methanol-inducible promoter element comprising a sequence to which the Mxr1 transcriptional activator binds) and (2) the “second exogenous nucleic acid” as recited in claim element 1[b] (i.e., a nucleic acid encoding a heterologous polypeptide operably linked to at least one methanol-inducible promoter element).

Patent Owner argues that Petitioner fails to show that the asserted art discloses or suggests a single recombinant acid molecule having both the first and second exogenous nucleic acids required by claim elements 1[a] and [b]. For the reasons explained below, we agree with Patent Owner.

Petitioner first argues that Tsutsumi alone teaches a single recombinant nucleic acid molecule comprising both of the exogenous nucleic acids required by limitations 1[a] and [b]. Pet. 31 (citing Ex. 1003 ¶ 126). In particular, Petitioner asserts that Tsutsumi claims a “DNA construct” that includes Mxr1 under control of a promoter (i.e., the first exogenous nucleic acid) and a polypeptide under control of a DAS promoter (i.e., the second exogenous nucleic acid). Pet. 30–31 (citing Ex. 1024, claim 15; Ex. 1003 ¶ 126).

This argument is not persuasive. Contrary to Petitioner’s and Dr. Batt’s assertions, Tsutsumi’s dependent claim 15, which incorporates the limitations of claims 1, 10, 12 and 13, does not suggest a single “DNA construct” that includes Mxr1 under control of a promoter and a polypeptide under control of a DAS promoter,” (i.e., the claimed first and second exogenous nucleic acids). *See* Pet. 30; Ex. 1003 ¶ 126. Claim 10 does recite a “DNA construct.” However, it does not appear that claim 15, or any of the

claims from which claim 15 depends, require that the Mxr1 gene recited in claim 15 be located on the same DNA construct recited in claim 10.

For example, claim 1 of Tsutsumi is directed to an isolated polynucleotide having a DAS promoter sequence and at least one additional UAS. Ex. 1024, claim 1. Claim 10 is directed to a “DNA construct” having the polynucleotide of claim 1 operably linked to a gene encoding a polypeptide of interest. Ex. 1024, claim 10. Claim 12 is directed to a yeast cell “comprising an expression vector of claim 10.” Ex. 1024, claim 12. Claim 13 is directed to a method of producing a polypeptide comprising “cultivating the host cell of claim 12.” Ex. 1024, claim 13. Claim 15 is directed to a method according to claim 13 that further requires that “expression of the positive regulator Mxr1 is increased by controlling the expression of Mxr1 or by increasing the copy number of the gene encoding Mxr1.” There is no requirement in claim 15 that the gene encoding the positive regulator Mxr1 be located on the DNA construct recited in claim 10. Nor has Petitioner provided any persuasive argument to support such a finding. *See generally* Pet.; *see also* Ex. 1003 ¶¶ 126, 143, 165 (citing claim 15 but not providing persuasive argument that the gene encoding Mxr1 be located on the DNA construct recited in claim 10). Thus, we disagree with Petitioner’s and Dr. Batt’s contention that Tsutsumi’s claim 15 teaches a DNA construct that includes both Mxr1 under control of a promoter and a polypeptide under control of a DAS promoter, as required by claim 1.

To the extent Petitioner contends that integration of Tsutsumi’s multiple vectors into the yeast genome results in a single recombinant nucleic acid molecule comprising both of the nucleic acids required by limitations 1[a] and [b], this argument also fails. *See* Pet. 30 (stating

“Tsutsumi teaches *Pichia* transformed with multiple expression vectors, which a POSITA would understand are integrated into the *Pichia* genome”); *see also* Ex. 1003 ¶¶ 126 (stating that a POSITA would understand that Tsutsumi’s vectors are integrated into the *Pichia* genome and “[a]ccordingly, Tsutsumi teaches *Pichia* comprising a recombinant nucleic acid molecule that comprises the claimed two exogenous nucleic acid sequences”).

Petitioner has not explained how Tsutsumi’s multiple vectors would have integrated into the yeast genome to result in a *single* nucleic acid molecule comprising the first and second exogenous nucleic acids required by claim 1. Indeed, it appears from the record that the genome *P. pastoris* comprises four separate chromosomes. *See* Ex. 1031, 2, Table 1. Thus, any argument that Tsutsumi’s multiple vectors would have integrated into a *single P. pastoris* chromosome, and thus into a single nucleic acid molecule, is undeveloped and unsupported.

Petitioner also contends, to the extent Tsutsumi does not expressly disclose a recombinant nucleic acid molecule comprising the two exogenous nucleic acid sequences, that it would have been obvious to prepare such a construct as there are “ample teachings” of this recombinant technique and preparing such a vector and a POSITA would have been able to engineer such a vector “using the familiar Sambrook Laboratory Manual” (“Sambrook”). Pet. 31 (citing Ex. 1003 ¶¶ 126–130); *see also* Pet. 31, n.4 (citing Ex. 1003 ¶ 131; Ex. 1010 (Crane) ¶¶ 34, 35, 74).

We disagree. None of the evidence cited by Petitioner teaches a single nucleic acid molecule encoding both the Mxr1 transcriptional activator as well as a second endogenous nucleic acid or provides a reason

why a POSITA would have prepared such a construct. For example, Crane teaches a single expression vector encoding both heme-binding protein and a recombinant ferrochelatase but not Mxr1. *See* Ex. 1010 ¶¶ 34, 35, 74.

Petitioner fails to provide any particularized argument as to how Sambrook⁴ teaches creation of a single nucleic acid construct comprising Mxr1.

Moreover, Petitioner does not articulate a sufficient reasonable basis as to *why* a POSITA would have sought to create a single nucleic acid encoding both a transcriptional activator such as Mxr1 as well as a second exogenous nucleic acid. Rather, Petitioner's arguments and evidence are directed to the general concept of providing a vector that encodes more than one gene of interest and do not address why one of the genes would encode a transcription factor, let alone a transcription factor such as Mxr1. Dr. Batt does identify some benefits from using a single vector to express "more than one heterologous gene sequence," including (1) increased efficiency (i.e., only one transformation to introduce multiple heterologous gene sequences into a host cell) and (2) increased control (as use of such constructs affords a POSITA more control over the levels of the different gene's respective expression levels, as double transfection events may lead to different levels of vector incorporation in a cell). *See* Ex. 1003 ¶ 128. Dr. Batt, however, does not provide any explanation as to how these benefits apply to a nucleic acid sequence encoding transcription factors such Mxr1. *See e.g., id.* ¶¶ 126–131 (discussing creation of a single expression vector comprising multiple gene sequences of interest, but providing no discussion of genes encoding transcription factors). Thus, Petitioner has not sufficiently shown

⁴ Sambrook was not provided as an Exhibit. Thus, it is unclear what particular "ample teachings" in Sambrook Petitioner relies upon.

that Tsutsumi teaches or suggests a single nucleic acid molecule encoding both the first and second endogenous nucleic acids required by claim 1.

Petitioner also asserts that the combination of Tsutsumi and Mattoon teaches this limitation. Petitioner asserts that Mattoon teaches “inducible or constitutive promoters” that are “‘operatively linked’ to the nucleic acid sequences” and that Mattoon teaches that both “the nucleic acid sequence encoding the ‘heme’ rate-limiting enzyme as well as the heme-binding agent can be present on one expression vector.” Pet. 32 (citing Ex. 1008, 2:41–44, 5:34–46, 5:51–59, 6:9–63; Ex. 1003 ¶ 132). Petitioner asserts that a POSITA “would understand that Mattoon’s teachings could be readily applied to Tsutsumi/Lin-Cereghino” and that a POSITA would be motivated to combine Mattoon’s teaching (reflecting a general knowledge in the art) with Tsutsumi/Lin-Cereghino” with a reasonable expectation of success. Pet. 32 (citing Ex. 1003 ¶ 134; Pet. § V.A.⁵).

This argument is also not persuasive. Although Mattoon does teach a single expression vector encoding two separate proteins, Mattoon’s vectors do not encode both a transcriptional activator such as Mxr1 and a second endogenous nucleic acid. Rather, Mattoon teaches two genes encoding *two heme-associated polypeptides*—a heme enzyme and a heme-binding agent—present on one expression vector. See Ex. 1008, 5:34–46. As such, Mattoon does not disclose single nucleic acid encoding a transcriptional activator such as Mxr1 and a heterologous polypeptide as required by claim 1. Nor has Petitioner sufficiently articulated a reasoned basis as to why a POSITA would have made such a modification. Although Petitioner states that

⁵ Section V.A. discusses the Claims and Specification of the ’656 patent. See Pet. 24–27.

Mattoon’s teachings “could be” readily applied to Tsutsumi (Pet. 32), Petitioner fails to adequately explain or support *why* a POSITA would have applied Mattoon’s teachings to Tsutsumi to create a single nucleic acid construct encoding both the first and second nucleic acids required by claim elements 1[a] and 1[b]. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (stating “obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed inventions”). Petitioner’s conclusion that a “POSITA would thus be motivated to combine Mattoon’s teachings (reflecting the general knowledge in the art) with Tsutsumi/Lin-Cereghino with a reasonable expectation of success” is conclusory and unsupported. Pet. 32; Ex. 1003 ¶ 134.

Nor does the Petition provide any persuasive evidence to support an argument that the combined teachings would yield predictable results or that a POSITA would have had a reasonable expectation of success of combining the asserted art to arrive at claim 1. *See generally* Pet.; *see also* Pet. 29 (stating a POSITA would have been motivated to combine the asserted references with a reasonable expectation of success and citing Ex. 1003 ¶¶ 112–116); *see also* Ex. 1003 ¶¶ 112–116 (failing to provide persuasive evidence to support such an assertion). As such, Petitioner’s allegations, without more, do not articulate a reasonable reason why a POSITA would have combined the teachings of the prior art to provide a single nucleic acid molecule comprising the first and second nucleic acids recited in claim elements 1[a] and 1[b]. For at least this reason, Petitioner has not shown a reasonable likelihood that claim 1 would have been obvious over Tsutsumi, Lin-Cereghino, and Mattoon.

- b) *A recombinant nucleic acid molecule comprising a first exogenous nucleic acid encoding Mxr1 operably linked to a methanol-inducible promoter to which Mxr1 binds*

Claim element 1[a] requires a “first exogenous nucleic acid encoding a methanol expression regulator (Mxr1) transcriptional activator operably linked to at least one methanol-inducible promoter element comprising a sequence to which the Mxr1 transcriptional activator binds.” Petitioner contends that Tsutsumi in view of Lin-Cereghino teaches this limitation. *See* Pet. 33 (citing Ex. 1003 ¶¶ 135–158); *see also* Pet. 33–42.

Petitioner first asserts that Tsutsumi’s Example 5 discloses co-expression, in the same cells, of (1) the polypeptide *Humicola Insolens* Cutinase under the control of a methanol-inducible DAS promoter, to which the Mxr1 transcriptional activator binds, and (2) Mxr1 under control of a *GAP* promoter. Pet. 33–34 (citing Ex. 1024 ¶¶ 37, 140, 145; Ex. 1003 ¶¶ 140–142). Example 5, however, discloses that the vector encoding polypeptide under control of the methanol-inducible DAS promoter is on a *different vector* than the vector encoding the Mxr1 under control of *GAP* promoter. Thus, Example 5 does not disclose a nucleic acid molecule encoding Mxr1 operably linked to DAS. Thus, Tsutsumi does not disclose a first exogenous nucleic acid encoding Mxr1 operably linked to a methanol-inducible promoter to which Mxr1 binds as required by claim element 1[a].

Petitioner also asserts that, in addition to Example 5’s teaching of a *GAP* promoter used to control Mxr1, Tsutsumi also teaches “using a methanol-inducible system” and that promoters “suitable for the above activation may in particular be . . . induced by methanol.” Pet. 34 (quoting Ex. 1024 ¶ 108). This argument is not persuasive as Petitioner does not sufficiently explain why the statement that “the above activation . . . may be

induced by methanol” refers to activation of a gene that is not under control of a methanol-induced promoter. Rather, it appears that the statement discussing inducing activation by methanol would refer to the activation of genes under the control of a methanol-inducible promoter.

To the extent Petitioner argues that one of skilled in the art would understand that Tsutsumi’s GAP promoter is a methanol-induced promoter, this argument is not persuasive. *See* Pet. 34–35 (stating a “POSITA would understand that Tsutsumi discloses . . . Mxr1 under the control of a promoter element, which may be constitutive or methanol-inducible”). The art provided by Petitioner states that the GAP promoter is a constitutive promoter, not a methanol-induced promoter. *See, e.g.*, Ex. 1031, 3 (“using the strong constitutive promoter *PGAP*”). Indeed, even Petitioner’s own declarant refers to the GAP promoter as a constitutive promoter. *See* Ex. 1003 ¶ 105 (discussing Vogl’s “constitutive promoters of the *GAP* . . . gene[]”), ¶ 107 (discussing Takagi’s “strong constitutive *GAP* promoter”).

To support its argument that the GAP promoter is a methanol-induced promoter, Petitioner points to a statement in Vogl that “there is a clear influence of the carbon source on the expression strength” of the GAP promoter and that “in studies^[6] of *P. pastoris* alternative respiration, there were *indications* that P_{GAP} drive expression is not entirely constitutive but regulated under certain conditions.” Pet. 34–35 (citing Ex. 1005, 8⁷; Ex. 1003 ¶ 144) (emphasis added). However, neither of these statements constitute a clear declaration that the GAP promoter is a methanol-induced

⁶ Notably, Petitioner does not provide the publication that reports actual studies themselves.

⁷ This Decision refers to the page number of the Exhibit added by Petitioner in the lower right hand corner of the page.

promoter. Indeed, even Petitioner's declarant does not state that Tsutsumi's GAP promoter is methanol-induced. Rather, Dr. Batt merely states that a GAP promoter-driven expression of Mxr1 in Tsutsumi Example 5 "*could be at least partly* methanol-induced." Ex. 1003 ¶ 144 (emphasis added). Thus, the above cited portions of Vogl and declarant's qualified statements do not sufficiently show that Tsutsumi's GAP promoter *is* a methanol-inducible promoter.

Moreover, even if the GAP promoter is methanol-inducible, Petitioner makes no argument that Mxr1 binds to a GAP promoter as required by claim 1. Thus, we disagree that Tsutsumi discloses a yeast cell with Mxr1 under the control of a methanol-inducible promoter element. Pet. 35 (citing Ex. 1003 ¶ 144).

Petitioner next asserts that it would have been obvious to combine Tsutsumi with Lin-Cereghino, which discloses the use of a methanol-inducible promoter that binds to Mxr1 to drive expression of Mxr1. *See* Pet. 36–42. Petitioner explains that Lin-Cereghino teaches yeast strains with Mxr1p under control of either P_{AOX1} (a strong methanol-inducible promoter) or P_{PEX8} (a weaker methanol-inducible promoter) and that a yeast strain "with Mxr1p under regulation of P_{PEX8} grew on methanol and produced 'relatively high levels of the product.'" Pet. 37 (citing Ex. 1006, 885; Ex. 1003 ¶ 148; Ex. 1005, 9, Table 1). Petitioner concludes that a POSITA would therefore be motivated to substitute Tsutsumi's GAP promoter controlling Mxr1 with a fully methanol-inducible promoter that binds to Mxr1, as taught by Lin-Cereghino, to "tightly control and further overexpress Mxr1 that would bind to the methanol-inducible promoter and would have a [reasonable expectation of success] in doing so." Pet. 38

(citing Ex. 1003 ¶¶ 150–153; Ex. 1004 ¶¶ 76–79); *see also* Ex. 1004 ¶ 77 (predicting Mxr1p expressed under the control of P_{AOX1} would create “a positive feedback system” and further drive expression of Mxr1p because Lin-Cereghino (Ex. 1006, 9) teaches that overexpression of Mxr1p under the control of P_{PEX8} “led to ‘relatively high levels’ of Mxr1p in those cells”). Petitioner also asserts that a POSITA would know that an expression system constructed with Mxr1p controlled by a strong promoter is desirable and reasonably expected to succeed and that the methanol-induced promoters P_{PEX8}, P_{DAS}, and P_{AOX1} are “natural alternatives” to Mxr1 controlled expression under PGAP. Pet. 38–40 (citing Ex. 1003 ¶¶ 146, 150–158; Ex. 1004 ¶¶ 63–65, 67, 76–79; Ex. 1006, 5, 9–10; Ex. 1024 ¶¶ 5–6, 145). Petitioner further asserts that a POSITA looking to employ such expression systems would use “well-known strategies to control protein expression . . . with carbon sources,” such as growing cells to a high density and “only then inducing” gene expression by adding methanol. Pet. 42 (citing Ex. 1003 ¶ 158; Ex. 1004 ¶ 70; Ex. 1005, 2–3).

These arguments are not persuasive. Lin-Cereghino itself taught that yeast strains expressing Mxr1 under the methanol-inducible promoter P_{AOX1} did not grow. *See* Ex. 1006, 11 (stating that “this strain . . . did not grow on methanol and did not induce Mxr1p . . . in response to methanol” and that “[a]pparently, high levels of Mxr1p are toxic to *P. pastoris*”). Thus, the art itself shows that a POSITA would not have a reasonable expectation of success of expressing Mxr1 under control of a strong methanol-inducible promoter such as P_{AOX1}.

Petitioner cites to Dr. Lin-Cereghino's⁸ testimony stating that this teaching would not deter a POSITA from "attempting to improve heterologous protein expression in *P. pastoris* by overexpressing Mxr1p under strong promoters" such as P_{AOX1}. Ex. 1004 ¶ 41 (citing, *inter alia*, by Pet. 19–20). Dr. Lin-Cereghino further testifies that a POSITA would recognize that "further investigation would be needed" to determine the reason why a strain expressing Mxr1 under control of the P_{AOX1} promoter did not grow and provides examples of other studies that were able to express Mxr1 under control of other strong (albeit constitutive) promoters. Ex. 1004 ¶¶ 39–41.

Dr. Lin-Cereghino's testimony does not establish that a POSITA would have had a reasonable expectation of success of expressing Mxr1p under methanol-induced promoters. At best, it shows that a POSITA would have had a reason to investigate and to try the use of methanol-induced promoters to control the expression of Mxr1. However, attempting to try is not the standard when determining obviousness. Indeed, the very art cited by Petitioner shows that transcription pathways in *P. pastoris* was not well understood. *See, e.g.*, Ex. 1005, 17 (discussing transcription in *P. pastoris* and stating that the "majority of molecular mechanisms investigated up to now, are still art from being completely understood"); *id.* at 7 (stating data of various authors was "not entirely consistent and would require further investigation to clarify the activating mechanism of Mxr1p").

Nor are we persuaded that a POSITA would have found it obvious to grow cells to a high density and only then express the genes under control of

⁸ Dr. Lin-Cereghino is the named author of the Lin-Cereghino reference (Ex. 1006). *See* Ex. 1004 ¶ 34.

the methanol-induced promoter. *See* Pet. 42 (citing Ex. 1003 ¶ 158; Ex. 1004 ¶ 70). Petitioner provides no persuasive analysis as to why such general teachings would be applicable to cells expressing Mxr1 under the control of a methanol-inducible promoter. Rather, from the record before us, it appears that is only with the benefit of hindsight that a person of skill in the art would have had a reasonable expectation of success in modifying the art as asserted by Petitioner.

Thus, for the foregoing reasons, Petitioner does not show that the combination of Tsutsumi, Lin-Cereghino, and Mattoon teaches or suggests a recombinant nucleic acid molecule encoding a transcriptional activator Mxr1 operably linked to a methanol-inducible promoter element comprising a sequence to which the Mxr1 transcriptional activator binds, as required by claim element 1[a]. Thus, for this additional reason, Petitioner does not establish a reasonable likelihood of prevailing that claim 1 would have been obvious over Tsutsumi, Lin-Cereghino, and Mattoon.

2. *Claims 2–17, 21, and 23–25*

Petitioner presents no arguments or evidence with respect to dependent claims 2–17, 21, or 23–25 that would remedy the defects noted above with respect to independent claim 1. *See* Pet. 45–60. Thus, Petitioner has failed to demonstrate a likelihood that the subject matter of claims 2–17, 21, and 23–25 would have been obvious over Tsutsumi, Lin-Cereghino, and Mattoon.

D. Asserted Unpatentability of Claims 18–20 over Tsutsumi, Lin-Cereghino, Mattoon, and Crane (Ground 2) and of Claim 22 over Tsutsumi, Lin-Cereghino, Mattoon, and Krainer (Ground 3)

Petitioner contends that dependent claims 18–20 are unpatentable under 35 U.S.C. § 103 over Tsutsumi, Lin-Cereghino, Mattoon, and Crane

and that dependent claim 22 is unpatentable over Tsutsumi, Lin-Cereghino, Mattoon, and Krainer. *See* Pet. 60–67. Each of these challenged claims depend upon claim 1. Petitioner’s arguments regarding these dependent claims do not remedy the deficiencies regarding independent claim 1 set forth above. Accordingly, Petitioner does not show a reasonable likelihood of prevailing on either grounds 2 or 3.

E. Asserted Unpatentability of Claims 26 and 28 Over Mattoon and Vogl (Ground 4)

Petitioner contends that independent claim 26 and dependent claim 28 are unpatentable under 35 U.S.C. § 103 over Mattoon and Vogl. Pet. 67–74. Patent Owner responds, *inter alia*, that the challenged claims are not unpatentable because the cited art does not teach all of the claimed limitations and because Petitioner failed to provide a reason to combine the teachings of the asserted art to arrive at the claimed subject matter. *See* Prelim. Resp. 31–43. For the reasons set forth below, we determine Petitioner has not shown a reasonable likelihood that any challenged claims are unpatentable under Ground 4.

1. Claim 26

a) A recombinant nucleic acid molecule having three nucleic acid sequences

Claim 26 recites a methylotrophic yeast cell comprising, *inter alia*, “a recombinant nucleic acid molecule” that comprises three nucleic acids (1) “encoding a Mxr1 transcriptional activator sequence from *P. pastoris*” (claim element 26[a], the “first nucleic acid”); (2) “encoding a member of globin family PF00042” (claim element 26[b], the “second nucleic acid”); and (3) “encoding at least one polypeptide involved in heme biosynthesis” (claim element 26[c], the “third nucleic acid”). Ex. 1002, 90:1–13.

Petitioner contends that Vogl teaches the first nucleic acid (Pet. 68–70) and that Mattoon teaches the second and third nucleic acids (Pet. 70–71).

As to the requirement that all three nucleic acids be on the same nucleic acid molecule, Petitioner refers to its arguments made in Ground 1 and further asserts that Mattoon teaches “that more than one nucleic acid ‘can be present on one expression vector’” and a POSITA “would thus understand that the nucleic acids” of claim 26 “can be present on one recombinant nucleic acid molecule.” Pet. 70 (citing Pet. § VI.B; Ex. 1003 ¶ 277 and stating a POSITA would understand that the nucleic acids of claim elements 26[a] and [b] can be present on one nucleic acid molecule); Pet. 71 (citing Pet. §§ VI.B(1), IX.B.; Ex. 1003 ¶ 280 and stating that a POSITA would understand that the nucleic acids of claim elements 26[a–c] can be on the same nucleic acid molecule).

Petitioner’s reliance on its arguments set forth in Ground 1 are not persuasive for the same reasons set forth above in Section III.C.1.a. Petitioner does not articulate a sufficient reasonable basis as to *why* a POSITA would have sought to create a single nucleic acid that encodes a Mxr1 transcriptional activator as required by claim element 26[a] as well as nucleic acids encoding other polypeptides, such as those recited in claim elements 26[b]–[c]. Rather, Petitioner’s arguments and evidence are directed to the general concept of providing a vector that encodes more than one gene of interest and do not address why one of the genes would encode a transcriptional activator, let alone a transcriptional activator such as Mxr1.

For at least this reason, Petitioner has not shown a reasonable likelihood that claim 26 would have been obvious over Mattoon and Vogl.

b) Each of the three nucleic acids are “operably linked to a methanol-inducible promoter element” that

comprises “at least one sequence to which a Mxr1 transcriptional activator binds”

Claim element 26[d] requires that *each* of the three nucleic acids of claim elements 26[a–c] are “operably linked to a methanol-inducible promoter element” that “comprises at least one sequence to which a Mxr1 transcriptional activator binds.”

Citing its arguments set forth in Ground 1, Petitioner first asserts that Mattoon discloses “each nucleic acid is operably linked to a methanol-inducible promoter” with at least one sequence to which Mxr1 binds. Pet. 72 (citing Ex. 1003 ¶ 281; Ex. 1008, 2:41–44, 5:51–59, 6:9–63; Pet. §§ IV.B, VI.B). Petitioner next asserts Vogl would have motivated a POSITA to select a methanol-inducible promoter, such as P_{AOX1}, P_{DAS}, or P_{PEX8}, to control the expression of the nucleic acids recited in claim elements 26[a–c]. Pet. 72–73 (citing Ex. 1003 ¶¶ 282–283; Ex. 1005, 1–3, 7; Ex. 1008, 2:41–44, 5:51–59, 6:9–63). Petitioner asserts that Vogl would have motivated a POSITA to incorporate methanol-inducible promoters (e.g., P_{AOX1}, P_{DAS}, or P_{PEX8}) in Mattoon’s *P. pastoris* expression system to produce recombinant heme-containing proteins. Pet. 73 (citing Ex. 1003 ¶ 284; Ex. 1004 ¶¶ 63–67). Petitioner concludes that, for the same reasons set forth in its arguments regarding Ground 1, a POSITA would have had a reasonable expectation of success in operably linking each nucleic acid to a methanol-inducible promoter using routine techniques and well-known materials. Pet. 73 (citing Ex. 1003 ¶ 824; Ex. 1004 ¶¶ 63–67; Pet. §§ V.A, VI.B.).

These arguments are not persuasive for the same reasons set forth above in Section III.C.1. While Vogl may teach the gene encoding the Mxr1 transcriptional activator operably linked to the constitutive GAP promoter and also teach other genes operably linked to a methanol-inducible promoter

that binds to Mxr1, Petitioner has not sufficiently shown that Vogl teaches operably linking the gene encoding Mxr1 with a methanol-inducible promoter that binds to Mxr1, let alone also operably linking the nucleic acids recited in claim elements 26[b] and [c] to the same methanol-inducible promoter. *See* Ex. 1003 ¶¶ 282–284. As discussed above in Section III.C.1.b, Petitioner does not sufficiently show that a skilled artisan would have had a reasonable expectation of success of expressing Mxr1p under methanol-induced promoters as required by the claims. *See id.* Thus, for this additional reason, Petitioner has not shown a reasonable likelihood that it would prevail in showing that claim 26 is unpatentable over Mattoon and Vogl.

2. *Claim 28*

Claim 28 depends from claim 26. Petitioner's arguments regarding claim 28 do not remedy the deficiencies described above regarding claim 26. *See* Pet. 73–74. Because we conclude that Petitioner has not established a reasonable likelihood of prevailing in showing that independent claim 26 is unpatentable over Mattoon and Vogl, we likewise conclude that the information presented in the Petition fails to establish a reasonable likelihood that Petitioner would prevail in showing that dependent claim 28 is unpatentable over Mattoon and Vogl.

F. Asserted Unpatentability of Claim 27 over Mattoon, Vogl, and Crane (Ground 5)

Petitioner contends that claim 27, which depends from claim 26, is unpatentable under 35 U.S.C. § 103 as obvious over Mattoon, Vogl, and Crane. Pet. 74–75. Petitioner's contentions do not cure the deficiency noted above with respect to independent claim 26. Therefore, for the same reasons discussed above, we determine that the information presented in the Petition

fails to establish a reasonable likelihood that Petitioner would prevail in showing that dependent claim 27 is unpatentable over Mattoon, Vogl, and Crane.

G. Discretion under 35 U.S.C. § 325(d)

Patent Owner requests that the Board exercise its discretion under 35 U.S.C. § 325(d) to deny institution because the same or substantially the same prior art or arguments were previously presented to the Office. Prelim. Resp. 43–48. Because we deny institution on the merits, we do not reach Patent Owner’s § 325(d) argument.

IV. CONCLUSION

For the reasons set forth above, we determine that Petitioner has not demonstrated a reasonable likelihood of prevailing with respect to at least one challenged claim of the ’656 patent. Accordingly, we do not institute an *inter partes* review on any challenged claims.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied as to all challenged claims and no trial is instituted.

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