

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MOTIF FOODWORKS, INC.,
Petitioner,

v.

IMPOSSIBLE FOODS, INC.,
Patent Owner.

Case IPR2023-00322
Patent No. 10,273,492

**PATENT OWNER'S PRELIMINARY RESPONSE
PURSUANT TO 37 C.F.R. § 42.107**

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I. INTRODUCTION

The Board should not institute *inter partes* review of claims 1-14 of U.S. Patent No. 10,273,492 (EX1001, “’492 patent”) because Petitioner Motif FoodWorks, Inc. fails to show that it has a reasonable likelihood of prevailing. Petitioner’s grounds engage in impermissible hindsight by cherry-picking select aspects of a reference without consideration of other teachings from the same reference that undermine the proposed combinations and thus provide no supportable motivation or rationale to combine the cited references to achieve what is claimed.

Each of the challenged claims recites, in relevant part, a methylotrophic yeast cell comprising nucleic acid molecules encoding a heme-containing protein and at least one polypeptide involved in heme biosynthesis that are each operably linked to a promoter element and a Mxr1 transcriptional activator sequence from *P. pastoris*. Attempting to reach this particularly claimed combination, the petition improperly disregards what its very own references teach about recombinant protein expression systems.

For instance, each of Petitioner’s grounds depend on a review article (Vogl) describing numerous activators and promoters. Petitioner plucks out the pieces it desires from Vogl, while ignoring other aspects, including Vogl’s description on the known disadvantages to methanol-inducible promoters, uncertainties as to

expression of Mxr1 in yeast, and the need to carefully consider the particular aspects of the recombinant expression system. Vogl's review of yeast recombinant protein expression state of the art is in stark contrast to the petition's hindsight-driven approach, which amounts to a haphazard combination of any available transcriptional activator with any available promoter for any protein of interest. The complexity of the regulatory mechanisms underlying the numerous transcriptional activators and promoter elements were well-known, and still not understood at the critical date. Accordingly, the choice of which transcriptional activator and promoter element to use required a deliberative, evidence-based analysis specific to the expression system. The petition fails to provide one even today, much less demonstrate that the claimed combination would have been obvious to a POSA before the critical date.

For the reasons detailed below, institution of *inter partes* review should be *denied*.

II. CLAIM CONSTRUCTION

A claim subject to *inter partes* review receives its plain and ordinary meaning, interpreted in light of the specification of the patent in which it appears. *See* 37 C.F.R. § 42.100(b). Petitioner asserts that no claim construction is required. Pet., 26. Patent Owner submits that no constructions are needed for the Board to reach a decision denying institution.

III. OVERVIEW OF THE TECHNOLOGY

Petitioner's deficient analysis of the challenged claims relies on an oversimplification and lack of understanding of the technology at issue. Petitioner wrongly treats recombinant yeast protein expression systems as if they were predictable and readily interchangeable during the relevant timeframe of May 11, 2015. See Pet., 34-35 (alleging recombinant technologies "only require[s] routine techniques, known methods, and readily available materials"). However, as Petitioner's own cited art demonstrates, recombinant systems for the expression of heterologous proteins using yeast transcriptional activators, particularly the Mxr1 transcriptional activator, and promoter elements in recombinant systems were recognized as complex and not fully understood. In fact, "[t]he majority of molecular mechanisms investigated up to now, are still far from being completely understood." EX1005, 400-401. Indeed, Petitioner's own cited art emphasizes the complexity of yeast protein expression systems, particularly methanol-inducible systems, including then-known existing methanol-responsive yeast transcriptional activators. *Id.* When considering the art in its totality, work in this field was not predictable as noted by Petitioner's own references, further highlighting Petitioner's failure to set forth an articulated rationale that is supported by the references. *Id.*

For instance, Vogl (EX1005) explains that the control and expression of yeast transcriptional activators, including Mxr1, was not fully understood and therefore unpredictable. *See* EX1005, 400. In discussing the work of Takagi (EX1007), for example, Vogl specifically highlights uncertainties surrounding work by Takagi regarding the control and mechanism of action of two transcriptional activators, PRM1 and Mxr1. *See id.*, 391 (noting Takagi’s experiments failed to provide for “comparison to methanol induction or comparative biomass production”). Vogl also particularly noted the disconnect of Takagi’s findings with Lin-Cereghino (EX1006), which showed that high levels of expression of Mxr1 using the strong methanol-inducible promoter AOX1 was toxic to *P. pastoris* cells, “caus[ing] a growth defect on methanol and inhibited expression of MUT genes.”¹ *Id.* Vogl concluded from these studies, both of which

¹ Petitioner attempts to negate Lin-Cereghino’s explicit teachings of Mxr1 toxicity through the *post hoc* testimony of present-day Dr. Lin-Cereghino (EX1004). *See* Pet., 17-18 (citing EX1004, ¶¶37-39) (alleging “we did not perform any additional experiments to test or confirm this hypothesis” and a POSA “would recognize that further investigation would be needed to determine what caused this strain not to grow”). Dr. Lin-Cereghino’s hindsight testimony ignores that subsequent experiments were performed using lower Mxr1 expression levels

were cited by Petitioner, the data available at the time was “not entirely consistent and would require further investigation to clarify the activating mechanism of Mxr1p.” *Id.* Vogl’s message, which was closest in time to the critical date, reinforced the position that overexpression of Mxr1 was harmful to yeast cells and therefore cautioned those in the art that the effects of incorporating Mxr1 in protein expression systems were unpredictable, not well understood, and potentially harmful to its host.

Further, utilizing various genetic elements such as transcriptional promoters for driving expression in methylotrophic yeast cells was far from routine. Even limiting consideration to transcriptional promoters, the cited references report that a POSA would have been faced with many different promoters and would have had to first determine the compatibility of inducible and constitutive promoters with heterologous protein expression and transcriptional activators. For example, Vogl provides a table listing over twenty different promoters known at the time. As Vogl evidences, a promoter that works for a particular protein may not work for

with the weak promoter *PEX8* that rescued yeast cells, with no indication that culture conditions differed (*see* EX1006, 884 (Materials & Methods)), providing strong support for what Lin-Cereghino unequivocally concluded: “Apparently, high levels of Mxr1p are toxic to *P. pastoris*.” EX1006, 893.

a different protein. *See* EX1005, 392 (“Furthermore the strong expression from P_{AOX1} and P_{GAP} is not always the most favorable condition for heterologous protein production.”); *see also* EX1042, 4-5 (“Thus, we are no longer confident as we were 18 years ago that simplicity will eventually emerge from complexity. The extreme sophistication of cellular mechanisms will challenge cell biologists throughout the new century....”); EX1022, 145 (“Each protein expression system offers a unique set of properties....”). Using a transcriptional promoter for the purpose of increasing expression may not even work, and may even provide deleterious effects, such as toxicity. *See* EX1005, 391; EX1017, Abstract, e76 (“little is known about the regulation of the AOX1 promoter at the molecular level”); *id.*, e76 (“the regulatory properties of the promoter variant, the target protein and the production process have to be seen as a whole,” noting certain promoters can cause toxic effects). In other words, the art showed that it was not a matter of simple substitution with predictable results. Petitioner’s own references report that genetic expression systems including recombinant insertion of a transcriptional promoter for expression of a given protein was complex and challenging, not a mere matter of simple and predictable substitutions of mechanical components.

IV. GROUND 1A FAILS

Petitioner's Ground 1A challenges claims 1 and 4-11 based on the combination of Mattoon (EX1008) and Vogl (EX1005). Pet., 1, 27. Petitioner fails to establish a reasonable likelihood of prevailing on this ground.

As explained below, Petitioner's Ground 1A fails against claim 1 because Petitioner's proposed combination is premised on a conclusory rationale that selectively picks and chooses disclosure from Vogl to reach the claimed invention. By failing to grapple with (or even acknowledge) disclosure in Vogl that expressly taught the uncertainty surrounding the regulatory mechanism underlying Mxr1 and the evidence that high levels of Mxr1 expression were known to "cause[] a growth defect on methanol and inhibit[] expression of MUT genes" (EX1005, 391), Petitioner's Ground 1A fails.

A. Petitioner's combination of Mattoon and Vogl is transparent hindsight

Petitioner's purported reasoning why a POSA would have been motivated to combine Mattoon and Vogl to arrive at the claimed invention is premised on impermissible hindsight. Petitioner's analysis starts with Mattoon (Pet., 28-29, 35-36), which provides an example where two constructs, pCTT1 expressing catalase T from CTT1 (allegedly, the claimed "heme-containing protein") and pHEM2 expressing ALA dehydratase from HEM2 (allegedly, the claimed "polypeptide involved in heme biosynthesis"), are co-expressed. See EX1008, 7:51-64.

Petitioner then turns to Vogl to further operably link to each construct “a promoter element from *P. pastoris*” (in particular, the methanol-inducible promoter element P_{AOX1}) and “a Mxr1 transcriptional activator sequence from *P. pastoris*,” in which the expression of Mxr1 is under the control of the constitutive promoter element P_{GAP}. Pet., 33-34, 37. As detailed below, Petitioner fails to establish why a POSA would have been motivated to express CTT1 and HEM2 in Mattoon’s system and Mxr1 with a reasonable expectation of success.

1. Petitioner’s motivation to combine Mattoon and Vogl is deficient

Petitioner’s arguments that a POSA would have been motivated to incorporate the use of the methanol-inducible promoter element P_{AOX1} and the Mxr1 transcriptional activator in Mattoon’s expression system based on Vogl’s teachings rely on misleadingly combining together snippets of Vogl’s text, which fails to support a motivation to combine with Mattoon. See Pet., 30-32.

Mattoon relates to methods for “enhancing the production of hemoproteins” by (1) “increasing the production of heme by eliminating the rate-limiting step or steps in the heme biosynthetic pathway” (*e.g.*, increase ALA dehydratase encoded by the HEM2 gene), and (2) “reducing the concentration of free heme within the cell by ‘trapping’ such heme using the ability of apoproteins” (*e.g.*, heme-binding agents such as a catalase encoded by CTT1), “thereby reducing the occurrence of heme-feedback inhibition.” EX1008, 3:33-40; 2:9-30; *see also id.*, Abstract.

Mattoon provides an example where yeast cells are transformed simultaneously with a plasmid encoding ALA dehydratase (pHEM2) and a plasmid encoding a catalase (pCTT1). *See id.*, 7:62-65.

Petitioner relies on Vogl to modify Mattoon to operably link each of the nucleic acids encoding CTT1 and HEM2 to the methanol-inducible promoter P_{AOX1} that is regulated by Mxr1 expressed under the control of the promoter element P_{GAP}. *See Pet.*, 33-34, 37. When taken as a whole, however, Petitioner fails to provide sufficient evidence as to why a POSA would have been motivated to specifically select, among the many options for promoters, a methanol-inducible promoter that is regulated by Mxr1 for each of the nucleic acids in the proposed combination. *See Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (“[T]he petition has the burden from the onset to show with particularity why the patent it challenges is unpatentable.”).

As Petitioner acknowledges, “Vogl provides a comprehensive review of prior studies using promoters and transcription factors from *P. pastoris* to regulate recombinant protein production.” *Pet.*, 34. While Petitioner provides out-of-context quotes describing the purported benefits to using methanol-inducible promoters and Mxr1 as a transcriptional activator (*see Pet.*, 31-33), Vogl instead teaches that the selection of these elements is context-specific and many factors go into guiding the choice for a particular element. For example, Vogl notes that “the

combination of promoter and protein of interest can have a strong influence on the expression levels” and provides a table of numerous different constitutive or inducible *P. pastoris* promoters that can be utilized to express a protein of interest. EX1005, 396, Table 1. Consistent with Vogl, Hartner 2008 explains that “[t]here **is no general optimal promoter**: the regulatory properties of the promoter variant, the target protein and the production process have to be seen as a whole.” EX1017, 13 (emphasis added). Further, “production strateg[ies]” are tailored to be “specific to the needs of the individual protein.” *Id.* For example, “stronger variants would be useful for the expression of non-toxic proteins” and “[w]eaker variants could be favourable for the expression of proteins, which cause deleterious effects to the host cell.” *Id.* Thus, while Petitioner selects, with the benefit of hindsight, methanol-inducible promoters in its proposed combination, citing to general statements in Vogl describing such promoters, Petitioner conveniently ignores the art’s acknowledgement that such selection should be made with the protein of interest in mind. *See id.* In this regard, Petitioner provides no analysis as to why a POSA would have been motivated to pluck methanol-inducible promoters from among the listed promoters to express the *specific* proteins in the proposed combination (*i.e.*, CTT1 and HEM2).

Furthermore, Petitioner ignores that regulation via Mxr1 was not well understood at the time. *See* EX1005, 400. For example, with respect to the AOX1

promoter, P_{AOX1}, Vogl describes the identification of activators Mxr1 and Prm1, but makes clear that “there exist also additional, so far uncharacterized regulators of Mxr1p” and “other aspects of P_{AOX1} regulation are only partially understood,” indicating “a highly complex regulation pattern of P_{AOX1} and other MUT genes, that involves multiple activating and repressing factors.” *Id.* Ignoring this clear teaching that regulation via Mxr1 was not well understood at the time, Petitioner selectively relies on one experiment from Takagi (EX1007) to support an alleged motivation for combining a “Mxr1 transcriptional activator sequence” with the pCTT1 or pHEM2 of Mattoon. Pet., 33, 37. In the described experiment, Takagi co-expressed Mxr1 under the control of the constitutive GAP promoter with a phytase under the control of the methanol-inducible promoter AOX1. EX1005, 391. Although the co-expression purportedly resulted in a 7.6-fold increased activity of the phytase, Petitioner fails to acknowledge that Vogl found these results inconsistent with an experiment performed in Lin-Cereghino (EX1006). EX1005, 391. Specifically, Vogl referenced Lin-Cereghino for overexpressing Mxr1 under the control of the AOX1 promoter, which “caused a growth defect on methanol and inhibited expression of MUT genes.” *Id.*, 391. Vogl summarized the findings of Takagi and Lin-Cereghino as “***not entirely consistent*** and would require further investigation to ***clarify the activating mechanism of Mxr1p.***” *Id.*

(emphasis added). Petitioner fails to recognize and reconcile the inconsistencies between Takagi and Lin-Cereghino referenced by Vogl.

Furthermore, Vogl teaches that the use of methanol is both complex and dangerous. EX1005, 392 (methanol induction “increases the process time and handling efforts” and “the induction with methanol (a toxic and flammable compound) was considered problematic for safety reasons, especially for large-scale production”). Indeed, Petitioner’s own cited art suggested that “[c]onstitutive expression eases process handling, omits the use of potentially hazardous inducers and provides continuous transcription of the gene of interest.” EX1029, 5304. Thus, while Petitioner focuses on the supposed advantages of Mxr1 and methanol-inducible promoters mentioned in Vogl, Petitioner ignores its own disclosure, including in Vogl, related to the known disadvantages of Mxr1 and methanol-inducible promoters. Pet., 31-32. Petitioner’s conclusory statement that a POSA “would have been motivated to incorporate Mxr1p in Mattoon’s nucleic acid construct to express a heme-containing protein” and a “polypeptide involved in heme biosynthesis” in *P. pastoris* by “expressing Mxr1p under P_{GAP}, to regulate P_{AOX1}-controlled expression” of the proteins rests on cherry-picked citations to Vogl’s disclosure and fails to address disclosure counseling against the modification. *Id.*, 33.

Accordingly, for this reason, Petitioner's rationale for combining Mattoon and Vogl fails to satisfy its burden in establishing a reasonable likelihood of success on the merits.

2. Petitioner fails to establish that a POSA would have been motivated to combine Mattoon and Vogl with a reasonable expectation of success

Petitioner argues that a POSA would have reasonably expected success with the proposed modifications because they would have involved "routine techniques." Pet., 34-35, 37. As noted above, however, protein expression systems are not predictable: "[e]ach protein expression system offers a unique set of properties, and for successful production of a heterologous protein, it is often required to tailor a process specifically based on the properties of the protein to be produced and the expression system used." EX1022, 145; *supra*, section III.

For example, overexpression of certain proteins can be toxic to a cell, and thus render that expression system unsuitable for use with that particular protein. See EX1006, 893 ("high levels of Mxr1p are toxic to *P. pastoris*"). Petitioner's combination proposes the use of Mxr1 to upregulate the co-expression of Mattoon's CTT1 and HEM2 proteins. See Pet., 33-34, 37. However, because Mattoon teaches increased co-expression of HEM2 (to increase heme production) and CTT1 (to trap free heme) (EX1008, 3:33-56), Petitioner's combination relies on Mxr1 to drive expression of **both** HEM2 and CTT1. Yet, the art taught that

high levels of Mxr1 “are toxic to *P. pastoris*,” thus undermining Petitioner’s assertions regarding a POSA’s motivation to use Mxr1 with a reasonable expectation of success. EX1006, 893.

Moreover, with respect to production of heme-containing proteins, it was known that improving recombinant protein production was not straightforward, and that simply “co-overexpress[ing] genes of the endogenous heme biosynthesis pathway d[oes] not improve the recombinant production of active heme protein.” EX1031, Abstract. Neither Mattoon nor Vogl provide any reason for a POSA, who would have been aware of the uncertain aspects of recombinant protein production, to reasonably expect success in selecting Mxr1 and the particular promoter elements picked out by Petitioner from Vogl’s review for the successful production of a heme-containing protein and a polypeptide involved in heme biosynthesis, absent further affirmative evidence. Instead, a POSA would recognize the “potential pitfalls connected to metabolic pathway engineering, such as the additional metabolic burden upon overexpression of multiple genes as well as an accumulation of free intracellular porphyrin intermediates which can lead to the formation of reactive oxygen species.” *Id.*, 1.

Accordingly, Petitioner’s Ground 4 fails for this additional reason.

B. Petitioner fails to establish Mattoon and Vogl disclose a “heme-containing protein operably linked to a promoter element from *P. pastoris*”

Petitioner asserts that Mattoon discloses a nucleic acid sequence encoding “heme-containing protein” (CTT1) that is “‘controllable by inducible or constitutive promoters’ that are ‘operatively linked’ to the nucleic acid sequences encoding proteins-of-interest.” Pet., 29 (emphasis omitted). However, to reach this limitation, Petitioner must stitch together statements in Mattoon regarding the use of promoters generally. *Id.* Other than conclusory statements from its expert, Petitioner provides no further evidence that the CTT1 gene of Mattoon is “operably linked to a promoter element from *P. pastoris*” as required by the ’492 claims. *See id.* (citing EX1003, ¶127) (“A POSITA would have understood from Mattoon that the expression levels of the genes encoding proteins of interest can be under the control of a promoter using the preferable *P. pastoris* host cell”).

For at least these reasons, Ground 1A fails.

V. GROUND 1B FAILS

Ground 1B relies on Mattoon, Vogl, and Crane as allegedly rendering obvious dependent claims 2-3 and 12-13. Pet., 1, 45. The petition challenge to these dependent claims relies on the petition challenge to claim 1 and fails for the same reasons described above with respect to claim 1.

VI. GROUND 1C FAILS

Ground 1C relies on Mattoon, Vogl, and Lin-Cereghino as allegedly rendering obvious dependent claim 14. Pet., 1, 50. The petition challenge to this dependent claim relies on the petition challenge to claim 1 and fails for the same reasons described above with respect to claim 1.

VII. GROUND 2A FAILS

Petitioner also challenges claims 1-13 based on the combination of Crane (EX1010), and Vogl (EX1005). Pet., 1, 54. Petitioner's obviousness analysis for Ground 2A largely follows the same analysis applied with respect to Ground 1, except Mattoon is replaced with Crane. *See id.*, 54. Like with Mattoon, Petitioner alleges that "Crane expressly discloses every limitation of claim 1 except 'a Mxr1 transcriptional activator sequence from *P. pastoris*' (which is taught by Vogl)." *Id.* Petitioner then advances the same arguments as in Ground 1A: a POSA would have turned to Vogl and selected a methanol-inducible promoter, such as P_{AOX1}, to control expression of a heme-binding protein and a polypeptide involved in heme biosynthesis, and further would select Mxr1, expressed using P_{GAP}, to regulate P_{AOX1}. *Id.*, 57-58, 60.

As explained below, Petitioner's Ground 2A fails because Petitioner's proposed combination fails to establish that a POSA would have been motivated to

combine the references to arrive at the claims of the '492 patent with a reasonable expectation of success. For this reason, Petitioner's Ground 2A fails.

A. Petitioner's motivation to combine Crane and Vogl is deficient

As with Ground 1A, Petitioner's analysis with respect to Crane and Vogl is again limited to reproducing snippets of Vogl's text, which are misleadingly combined together in the petition. *See* Pet., 57. Petitioner relies on the same selective disclosures of Vogl describing the purported benefits to using methanol-inducible promoters and Mxr1 as a transcriptional activator (*see id.*, 57-58), yet ignores Vogl's teaching that the selection of these elements is context-specific and many factors go into guiding the choice for a particular promoter or transcriptional activator. *See supra*, section IV.A.1. Petitioner also ignores that regulation via Mxr1 was not well understood at the time, with Vogl acknowledging that findings regarding Mxr1 were "not entirely consistent and would require further investigation to clarify the activating mechanism of Mxr1p," and that the use of methanol was recognized as both complex and dangerous. EX1005, 391, 392; EX1029, 5304 (noting "[c]onstitutive expression eases process handling, omits the use of potentially hazardous inducers and provides continuous transcription of the gene of interest").

Furthermore, Petitioner acknowledges that Crane already identifies several suitable promoters, none of which Petitioner alleges are methanol inducible. Pet.,

56-57 (citing EX1010, [0047]). Indeed, Petitioner acknowledges that Crane identifies glyceraldehyde-3-phosphate dehydrogenase (or P_{GAP}) as one such suitable promoter. *Id.* Yet, Petitioner argues, in a conclusory statement, that a POSA “would understand that Crane was ripe for modifications that would yield ‘a high level of transcription’ of heme-containing proteins” (Pet., 57), and thus would have used P_{AOX1} instead. This argument, however, ignores that (1) Vogl identifies P_{GAP} as a strong constitutive promoter that provides high expression levels (EX1005, Table 1), and (2) the known disadvantages with methanol-inducible systems described above.

Thus, while Petitioner focuses on the supposed advantages of Mxr1 and methanol-inducible promoters mentioned in Vogl (*see* Pet., 31-32, 57, 63), Petitioner ignores its own reference’s disclosure, including in Vogl, related to the known disadvantages of methanol-inducible promoters, and the uncertainties regarding the Mxr1 transcriptional activator in particular. *See* EX1005, 391, 392, 400. Petitioner’s conclusory statement that a POSA “would have been motivated to incorporate an Mxr1 sequence in Crane’s *P. pastoris* expression system to produce recombinant heme-containing proteins” by “expressing Mxr1p under P_{GAP},[] to improve P_{AOX1}-controlled expression” of the proteins rests on cherry-picked citations to Vogl’s disclosure and fails to address disclosure counseling against the modification. *See* Pet., 58.

Accordingly, for these reasons, Petitioner's Ground 2A fails.

B. Petitioner fails to establish that a POSA would have been motivated to combine Crane and Vogl with a reasonable expectation of success

Moreover, for the same reasons discussed above for Ground 1A, Petitioner fails to establish that a POSA would have been motivated to combine Crane and Vogl with a reasonable expectation of success. *See supra*, section IV.A.2. As with Ground 1A, Petitioner argues that a POSA would have reasonably expected success with the proposed modifications because they would have involved “routine techniques.” Pet., 58-59. However, as noted above, protein expression systems are not predictable, including in the production of heme proteins, and overexpression of certain proteins, including Mxr1, were known to be toxic to *P. pastoris*. *See supra*, sections III, IV.A.2.

Moreover, Petitioner points to a generic statement in Crane provided after its specific listing of suitable promoters to justify its *carte blanche* approach to the selection of any promoter element and transcriptional activator to express the proteins of interest in Crane with a reasonable expectation of success. Pet., 58 (stating “Crane further teaches that ‘any plasmid vector containing yeast-compatible promoter, origin of replication and termination sequences is suitable’”) (quoting EX1010, [0047]). But Vogl directly undermines this approach by cautioning that “the combination of promoter and protein of interest can have a

strong influence on the expression levels”. EX1005, 396; *see also id.*, 392 (“Furthermore the strong expression from P_{AOX1} and P_{GAP} is not always the most favorable condition for heterologous protein production.”).

Petitioner asserts that Vogl “teaches that Mxr1p is essential for recombinant protein expression . . . and that *high levels of Mxr1p expression results in in higher expression of a protein-of-interest controlled by a promoter regulated by Mxr1p, such as P_{AOX1}.*” Pet. 57, citing to EX1005, 391, 400. Petitioner ignores that Vogl (EX1005) specifically refers to yeast transcriptional activators, including Mxr1, as not fully understood and therefore unpredictable. *See* EX1005, 391; *see* Section III, *supra*. Vogl specifically noted the findings of Lin-Cereghino (EX1006), which showed that high levels of expression of Mxr1 using the same strong methanol-inducible promoter AOX1 relied on by Petitioner as *toxic* to *P. pastoris* cells, “caus[ing] a growth defect on methanol and inhibited expression of MUT genes.” EX1005, 391. Lin-Cereghino’s original reference unequivocally stated that “high levels of Mxr1p are toxic to *P. pastoris*.” EX1006, 893. Petitioner’s attempt to sweep aside and ignore the clear statements of toxicity in relation to high expression of Mxr1 in their own cited prior art undercuts their motivation to combine arguments with Crane. *See* Section III, Fn 1, resorting to post-hoc statements by Lin-Cereghino [Ex1004] and Batt [EX1003].

In view of Vogl, a POSA would not have combined *any* transcriptional activator with *any* promoter of Crane. The studies in the art would have instead cautioned the operable linking of an Mxr1 transcriptional activator to a protein expression system, including a heme-containing protein” and “heme biosynthesis” polypeptide as claimed because the high expression of Mxr1 as a transcriptional activator, which Petitioner recognizes was needed for efficient expression of heterologous proteins from *Pichia* yeast cells, was known and recognized to be potentially harmful to its host.

Thus, Petitioner’s conclusory selection of P_{AOX1} as a promoter element and Mrx1 as a transcriptional activator to express the particular proteins of Crane is, without more, insufficient to establish a motivation to combine those elements with a reasonable expectation of success. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (“[W]here a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness.”).

Accordingly, for the same reasons discussed above with respect to Ground 1A, Petitioner fails to establish that a POSA would have been motivated to combine Crane and Vogl in the manner proposed with a reasonable expectation of success.

VIII. GROUND 2B FAILS

Ground 2B relies on Crane, Vogl, and Lin-Cereghino (EX1006) as allegedly rendering obvious dependent claim 14. Pet., 1, 68. The petition challenge to this dependent claim relies on the petition challenge to claim 1 and fails for the same reasons described above with respect to claim 1.

IX. INSTITUTION SHOULD BE DENIED UNDER § 325(D)

Petitioner alleges no discretionary denial under § 325(d) because “Mattoon and Vogl, alone or in combination, were not cited in any IDS or otherwise considered during prosecution of the ’492 patent,” and, while “Crane and Lin-Cereghino were cited in the IDS,” they “were not relied upon or discussed substantively in any office action for this patent.” Pet., 70.

Petitioner, however, fails to point out that Petitioner relies on Vogl’s discussion of Takagi (EX1007) as supplying an alleged reason to use Mxr1 to express a heme-containing protein and a polypeptide involved in heme biosynthesis as claimed. *See, e.g.*, Pet., 33. Takagai was cited in an IDS and before the Examiner during prosecution. *See* EX1001, (56); EX1039, 1151 (citing WO2008/090211); *cf.* EX1007, (87). Petitioner’s statement that the disclosure of Vogl was not “considered during prosecution of the ’492 patent” is thus incorrect, insofar as Petitioner relies on Takagi, which was considered during prosecution, via Vogl.

X. CONCLUSION

Accordingly, for at least the reasons set forth above, institution of *inter partes* review should be *denied*.

Respectfully submitted,

Date: May 9, 2023

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
Reg. No. 52,182

CERTIFICATE OF COMPLIANCE

Pursuant to §42.24(d), the undersigned certifies that this paper contains no more than 14,000 words, not including the portions of the paper exempted by §42.24(b). According to the word-processing system used to prepare this paper, the paper contains 4,618 words.

Respectfully submitted,

Date: May 9, 2023

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
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CERTIFICATE OF SERVICE

I certify that the foregoing Patent Owner's Preliminary Response was served on this 9th day of May, 2023, on the Petitioner at the following electronic service addresses:

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/ Michael T. Rosato /
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