

**IN THE UNITED STATES DISTRICT COURT
FOR DISTRICT OF DELAWARE**

IMPOSSIBLE FOODS INC.,	)	
	)	
Plaintiff,	)	C.A. No. 22-311 (WCB)
	)	
v.	)	
	)	
MOTIF FOODWORKS, INC.,	)	
	)	
Defendant.	)	
	)	
	)	

REPLY DECLARATION OF HAL ALPER, PH.D.

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I. INTRODUCTION AND QUALIFICATIONS

1. I, Hal Alper, Ph.D., submit this declaration in support of plaintiff Impossible Foods Inc.'s ("Impossible") Claim Construction Reply Brief. I offer this declaration as an expert in the fields of genetic engineering, synthetic promoter design, yeast engineering, and synthetic biotechnology. My qualifications and experience in these areas among others are set out in my June 14, 2023 Declaration (D.I. 107) and my curriculum vitae (D.I. 107-1, Ex. A).

II. DOCUMENTS AND INFORMATION CONSIDERED

2. As my initial declaration indicates, counsel for Impossible has asked for my opinion on the disputed terms of the Yeast Patents (U.S. Patent Nos. 10,273,492 and 10,689,656) based on the understanding of a person of ordinary skill in the art ("POSA") as of the relevant timeframe. I further have been asked to provide my opinion on the statements in the June 28, 2023 Declaration of Dr. Carl Batt ("Batt") (D.I. 123) and accompanying Exhibits B1-B24 (D.I. 123-1), defendant Motif FoodWorks, Inc.'s ("Motif") Responsive Claim Construction Brief (D.I. 120), and the Declaration of Dr. Carl Batt in support of Motif's petitions for *inter partes* review ("IPR") of the '492 (Ex. 24¹) and '656 patent (Ex. 23²).

3. I have formed my opinions using my education, knowledge, and experience together with my review of the materials cited in this declaration as well as my initial declaration. In my analysis throughout this declaration, I have followed the same legal principles set out in my initial declaration.

4. I have based my opinions in this declaration on the information and evidence currently available to me. I reserve the right to change, amend, and supplement my opinions in

¹ Attached to Plaintiff Impossible Foods' Reply Claim Construction Brief.

² Attached to Plaintiff Impossible Foods' Reply Claim Construction Brief.

response to any new information or evidence made available to me; additional scientific analysis that leads me to conclude that supplementation is necessary; new issues that may arise; and any additional discovery, arguments, evidence, or testimony presented in this case, including any evidence or testimony presented prior to or during trial. I reserve the right to testify with regard to my qualifications, experience, and the materials I have reviewed.

III. SUPPLEMENTATION OF OPINIONS

5. I have reviewed the materials discussed above and note that none of these materials has changed any of the opinions I provided in my June 14, 2023 declaration.

A. Terms 18-20

1. A POSA Would Understand the Distinction Between “Mxr1 transcriptional activator sequence” (Term 18) & “a nucleic acid molecule encoding a Mxr1 transcriptional activator” (Terms 19-20)

6. As I discussed in my initial declaration, the term “a Mxr1 transcriptional activator sequence from *P. pastoris*” (term 18) refers to a nucleic acid sequence to which the Mxr1 transcriptional activator protein binds, *e.g.*, a motif or consensus sequence. Terms 19 and 20, in contrast, refer to the nucleic acid sequence encoding the Mxr1 protein itself. The intrinsic record confirms this understanding, and Motif and its expert have not shown otherwise. For example, the Yeast Patents use the phrase “a nucleic acid molecule *encoding* a Mxr1 transcriptional activator” when defining the sequence of Mxr1. *E.g.*, ’492 patent, cl. 14 (emphasis added); *see also* Alper Decl.³, ¶¶ 48-49, 54-55.

7. Motif’s expert, Dr. Batt, disagrees with my understanding of term 18, which appears in claims 1 and 14 of the ’492 patent, based on the language of the ’656 patent. *See* Batt, ¶¶ 131-32. Dr. Batt points to claim 26 of the ’656 patent, which recites the limitation “wherein

³ D.I. 107.

the methanol-inducible promoter element comprises at least one sequence to which a Mxr1 transcriptional activator binds.” *Id.*, ¶ 130. Rather than focus on the language of the relevant claims of the ’492 patent, I note that Dr. Batt’s analysis focuses on the language of ’656 patent claims in discussing term 18. While the Yeast Patents share the same specification, they claim distinct inventions, and the nomenclature between them is not strictly uniform.

8. Even so, Motif’s expert’s approach of comparing the language of the ’492 patent to that of the ’656 patent in fact supports my understanding that “a Mxr1 transcriptional activator sequence from *P. pastoris*” (term 18) refers to a different molecular component of the expression system than terms 19-20. Claim 14 of the ’492 patent recites two distinct components of transcriptional activation in the claimed invention: (1) the “nucleic acid molecule **encoding** a Mxr1 transcriptional activator” and (2) the motif or consensus sequence to which Mxr1 binds, “a Mxr1 transcriptional activator sequence.” *See* Alper Decl., ¶¶ 52-54. The below side-by-side comparison of claim 14 of the ’492 patent to the corresponding elements of claim 26 of the ’656 patent shows that the same components are present: (1) a nucleic acid **encoding** a Mxr1 transcriptional activator sequence (in bold) and (2) an Mxr1 transcriptional activator sequence (in red).

'492 Patent Claim 14	'656 Patent Claim 26
The yeast cell of claim 1, further comprising a nucleic acid molecule encoding a Mxr1 transcriptional activator operably linked to a promoter element from <i>P. pastoris</i> and a Mxr1 transcriptional activator sequence from <i>P. pastoris</i>.	A methylotrophic <i>Pichia</i> 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 <i>P. pastoris</i>; [b] a nucleic acid encoding a member of globin family PF00042; and a nucleic acid encoding at least one polypeptide involved in heme biosynthesis, 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.

While Dr. Batt correctly observes that the word “binds” appears in claim 26 of the ’656 patent, I disagree with Dr. Batt’s conclusory statement that a POSA “would understand that if Impossible wanted to claim a sequence to which a Mxr1 transcriptional activator binds, it will use terminology such as Mxr1 binding site.” Batt, ¶ 130.

9. Dr. Batt does not provide any other support for his disagreement with respect to term 18. For his statement that “[t]he specification also *repeatedly* describes a ‘Mxr1 nucleic acid sequence’ that encodes Mxr1—not the binding site for Mxr1,” Dr. Batt points to a lone example, an excerpt that does not even contain the term “Mxr1 nucleic acid sequence” and that explicitly refers to “expression of Mxr1,” *i.e.*, production of the transcriptional activator protein. *Id.*, ¶ 131 (emphasis added). Once again, I note that expression of the transcriptional activator protein Mxr1 is distinct from the binding of (the transcriptional activator protein) Mxr1 to a

nucleic acid sequence in order to upregulate expression of other genes. *See* Alper Decl., ¶ 29 (“Mxr1 interacts with the alcohol oxidase I (‘AOX1’) promoter (‘P_{AOX1}’) or promoter element through binding sites known as ‘motifs’ or ‘consensus sequences’ and enhances the rate of transcription of downstream genes.”); *id.* (“It is important to emphasize two components of this interaction: activation requires (1) an Mxr1 binding target, which consists of a consensus sequence or motif, and (2) Mxr1 protein, which itself is encoded by a nucleic acid sequence.”).

10. Motif’s expert states that a POSA “would understand claim 14 to be referring to an embodiment in which more than one Mxr1 transcriptional activator is encoded by the nucleic acid molecule.” Batt, ¶ 134; *see also id.*, ¶¶ 88, 89 (describing recombinant protein production from a “gene encoding” a “protein of interest”). But Dr. Batt offers no explanation and does not cite any support from the intrinsic record to resolve the fact that “Motif’s proposed construction would render two limitations in claim 14 duplicative.” Alper Decl., ¶ 55 (illustrating claims 1 and 14 of the ’492 patent). Moreover, Motif’s expert clearly understands that the term “encoding” indicates a nucleic acid that corresponds to the Mxr1 transcriptional activator (terms 19-20). *See* Batt, ¶¶ 130-34 (repeatedly using the word “encoding” or “encodes” in reference to the sequence used to produce Mxr1 protein). Term 18 does not include the word “encoding.” This is because, as I have explained above and in my initial declaration, term 18 describes a distinct component: a nucleic acid sequence to which Mxr1 binds, *e.g.*, a motif or consensus sequence, and **not** a nucleic acid encoding Mxr1 itself. *See* Alper Decl., ¶¶ 53-56.

2. A POSA Would Not Interpret Terms 18-20 To Require “Native”

11. As I stated in my initial declaration, a POSA would be aware that “a Mxr1 transcriptional activator sequence from *P. pastoris*” (term 18), “a first exogenous nucleic acid encoding a methanol expression regulator 1 (Mxr1) transcriptional activator” (term 19), and “a

nucleic acid encoding a Mxr1 transcriptional activator sequence from *P. pastoris*” (term 20) need not be native sequences. *See* Alper Decl., ¶¶ 57-62.

12. Motif’s proposed constructions and the opinions of its expert appear to be based on a misapprehension of the term “native” with respect to the Yeast Patents. The shared specification states:

For example, an exogenous nucleic acid can be a nucleic acid from one microorganism (e.g., one genus or species of methylotrophic yeast) that is introduced into a different genus or species of methylotrophic yeast, however, an exogenous nucleic acid also can be a nucleic acid from a methylotrophic yeast that is introduced recombinantly into a methylotrophic yeast as an additional copy despite the presence of a corresponding native nucleic acid sequence.

’656 patent, 4:9-17; *see also id.*, 5:21-37 (defining a “nucleic acid sequence that is **not native**” as, e.g., “a nucleic acid from one microorganism (e.g., one genus or species of methylotrophic yeast) that is introduced into a different genus or species of methylotrophic yeast”) (emphasis added). Thus, the analysis of whether a nucleic acid sequence is “native” or “non-native” depends on a comparison of the genus and species of (1) the host organism and (2) the relevant nucleic acid sequence. Based on prior statements in related IPR proceedings, Motif shares this understanding. *See, e.g.*, Ex. 23, ¶ 186 (“As a POSITA would recognize, the Lin-Cereghino reference teaches that *MXR1* has its origins in the *P. pastoris* genome. Indeed, Lin-Cereghino teaches the discovery of the MXR1 gene in the search for genes that **natively** regulate [*i.e.*, in the host cell] the expression of methanol-inducible genes in *P. pastoris*.”) (emphasis added).

13. Motif’s expert avoids the specification’s express teachings and states: “the disclosure of the specification . . . shows that a heterologous nucleic acid sequence, *i.e.*, a nucleic acid sequence native to a species other than that of the host, can be introduced into a host yeast cell of a genus or species different from the one in which the nucleic acid sequence is native.” Batt, ¶ 128 (discussing ’656 patent, 5:31-37). This statement is puzzling and appears to

circumvent the obvious: a sequence that is “native to a species *other than* that of the host” and that is engineered into the recombinant constructs of the Yeast Patent claims, is not necessarily native to the host. *Id.* (emphasis added). This, of course, would depend in part on the identity of the host organism and the organism from which the relevant nucleic acid is derived.

14. Informed with a correct understanding of the term “native,” a POSA would understand that the exogenous nucleic acid sequences recited in the Yeast Patent claims may or may not be native to the host cell. *See* Alper Decl., ¶¶ 57-62. This observation does not “conflate the claims’ recitation of a host cell of the genus *Pichia*” with terms 18-20, as Motif’s expert contends. Batt, ¶ 129. Rather, my interpretation is grounded in my analysis of the intrinsic evidence in light of what a POSA would understand with respect to Motif’s proposed “native” limitation. According to the plain language of the claims, the Yeast Patents describe yeast cell hosts and do not require that terms 18-20 be sequences native to those yeast cell hosts. Claim 1 of the ’492 patent requires “[a] methylotrophic *Pichia* yeast cell” and “a Mxr1 transcriptional activator sequence from *P. pastoris*.” Claim 1 of the ’656 patent likewise does not include the term “native” and, with respect to the host organism, requires only “[a] methylotrophic yeast cell.” Claim 26 of the ’656 patent requires “[a] methylotrophic *Pichia* yeast cell” and “a nucleic acid encoding a Mxr1 transcriptional activator sequence from *P. pastoris*.” In all of these claims, the relevant nucleic acid sequences may (or may not) originate from a different organism than the methylotrophic yeast cell host organism.

15. I further note that the shared specification of the Yeast Patents teaches modifications to terms 18-20 such that the relevant sequences can be “from *P. pastoris*,” according to the language of the claims, but with potential differences—the result of genetic engineering efforts. *See, e.g.*, ’656 patent, 25:4-26:11 (Example 15 (describing *Pichia*

production strains containing the Mxr1 sequence, “from genomic DNA isolated from *Pichia pastoris*,” but engineered such that “6 additional amino acids were introduced at the N-terminus of Mxr1”). I also note the false dichotomy in Motif’s expert’s view that the language “from *P. pastoris*” is incompatible with “a variant or mutant” sequence. Batt, ¶ 129. As the shared specification shows, a sequence can be “from *P. pastoris*,” according to the language of the claims, **and also** can be “human-engineered” (e.g., through deletions, additions, substitutions) to yield the constructs comprising the claimed inventions. See ’656 patent, 25:4-26:11 (Example 15). Such sequences would not be “native” though they are “from *P. pastoris*.”

16. For the same reasons I discuss above as well as those in my initial declaration, the intrinsic evidence is inconsistent with introducing the word “native” into terms 18-20.

Accordingly, I disagree with Motif’s expert’s statement that a POSA would understand term 18 to mean “the sequence of the native *P. pastoris* Mxr1 transcriptional activator.” On this basis, I also disagree with Motif’s and its expert’s addition of the same “native” limitation into terms 19 and 20.

B. Term 26: “Promoter Element”

17. It is my opinion that a POSA would know that “promoter element” refers to a nucleic acid sequence that regulates transcription of downstream genes. This understanding is based on the specification, file history, and claim language of the Yeast Patents, as I described in my initial declaration. Alper Decl., ¶¶ 63-68.

18. I disagree with Dr. Batt’s opinion that a POSA could not be certain of the meaning of “promoter element.” See Batt, ¶¶ 135-36. I also disagree with the analytical process of Motif’s expert, who arrives at his opinions using a framework that prioritizes non-technical extrinsic literature over the teachings of the Yeast Patents themselves.

19. Motif’s expert begins his analysis of “promoter element” by stating that an “‘element’ commonly refers to a component of any larger structure” (Batt, ¶ 135) and referencing the New Oxford American Dictionary, 3rd Ed. (*id.*, ¶ 138 (citing D.I. 123-1, Ex. B18)), an extrinsic source with limited utility in a specialized art involving “recombinant techniques for protein production” and “genetic modification.” *Id.*, ¶ 63; *see also id.*, ¶ 135 (“‘Element’ does not imply a particular size, structure, or function for the component. . . . ‘POSITAs give [*sic*] term ‘element’ its common, generic meaning even in technical literature . . . [.]”); *id.*, ¶ 138 (“I see that the word ‘element’ has many possible meanings, as exemplified in the dictionary definition reproduced below.”). Further, Motif’s expert conducts a piecemeal analysis of “promoter element” by providing a lay dictionary definition of “element” divorced from “promoter.” This is unhelpful in determining a POSA’s understanding of the term and would be like providing a lay dictionary definition of “acid” to explain the meaning of “nucleic acid,” *e.g.*, DNA. *See, e.g.*, Ex. F⁴ at IF_0014114.

20. Contrary to the approach Motif’s expert has taken in interpreting the meaning of term 26, I understand that the claim construction inquiry prioritizes intrinsic evidence over extrinsic sources and looks to a POSA’s understanding of the relevant term (as a whole) in the **context** of the patent claim language, specification, and prosecution industry, *i.e.*, the intrinsic record. *See* Alper Decl., ¶ 24 (“Counsel has advised me that this analysis focuses on the . . . intrinsic evidence[.]. I also understand that dictionaries or other sources can be helpful in determining the plain and ordinary meaning of a term but cannot override a meaning that is clear from the intrinsic evidence.”).

⁴ “Acid,” New Oxford American Dictionary, 3rd Ed. (Stevenson & Lindberg eds), p. 13 (Oxford University Press 2010) (IF_0014112-114).

21. Motif's expert looks to the technical literature and concludes that, "***without reference*** to any specific part of the promoter or function thereof," an "'element' of a promoter is therefore subjective" and "based on empirical experimental results or the interests of the scientist." Batt, ¶ 135 (emphasis added). As I stated in my initial declaration, the intrinsic evidence provides the context or "reference" that Motif's expert describes. See Alper Decl., ¶¶ 33, 36, 40-43, 48, 64-66. Neither Motif nor its expert has contradicted this understanding.

22. Motif's expert states that "'expression element' itself does not inherently have the property of directing or regulating expression" but requires "localization," while disregarding the language of the claims and specification that provides such localization and specificity. Batt, ¶ 185. Motif's expert offers no supportable counterargument to my discussion of the intrinsic evidence, including the claims' recitation of a "methylotrophic yeast cell" and "a methanol expression regulator (Mxr1)" as well as the specification's statement that the "***promoter or other expression element(s)*** [is] positioned relative to a nucleic acid coding sequence in such a way as to ***direct or regulate expression*** of the nucleic acid," among other disclosures. '656 patent, 4:47-51 (emphases added); *id.*, cl. 1; *id.*, 6:57-61 ("It would be understood by the skilled artisan that a combination of inducible (e.g., methanol-inducible) and constitutive promoters (or promoter elements therefrom) can be combined to further increase the expression of any of the nucleic acids operably linked thereto."); *see also* Alper Decl., ¶ 65. In addition, the Yeast Patents draw a distinction over the prior art with respect to the claimed invention's recitation of "a methanol expression regulator (Mxr1) transcriptional activator, a methanol-inducible ***promoter element to which the Mxr1 transcriptional activator binds***, and a nucleic acid encoding a heterologous polypeptide." D.I. 107-2, Ex. E at IF_0007678 (emphasis added); *see also* Alper Decl., ¶ 64.

23. Accordingly, I disagree with Dr. Batt’s view that the Yeast Patents’ “specification does not describe the boundaries of a ‘promoter element’ or *any required characteristics* thereof.” Batt, ¶ 144 (emphasis added). On the same basis, I disagree with the statement that a POSA would understand that “promoter element” “does not have *any function*.” *Id.*, ¶ 153 (emphasis added); *see* ’656 patent, 4:47-50 (“[The] promoter or other expression element(s) [is] positioned relative to a nucleic acid coding sequence in such a way as to direct or regulate expression of the nucleic acid.”).

24. Motif’s expert asserts that term 26 “has no consistent meaning or structure in the art” and states that “[my initial] declaration supports [his] opinions” that a POSA “would not be reasonably certain of a ‘promoter element’s’ metes and bounds as it is used within the [Yeast Patents’] claims.” Batt, ¶ 186. I disagree. First, I note that the absence of a uniform meaning in dictionaries and technical literature does not compel Dr. Batt’s conclusion that a POSA would not understand the meaning of “promoter element” in the context of the intrinsic record. As discussed above, the Yeast Patents provide a description of term 26 sufficient to inform a POSA as to the meaning of “promoter element.” Second, it is important to clarify that the art is not inconsistent or ambiguous in the manner Motif’s expert suggests.

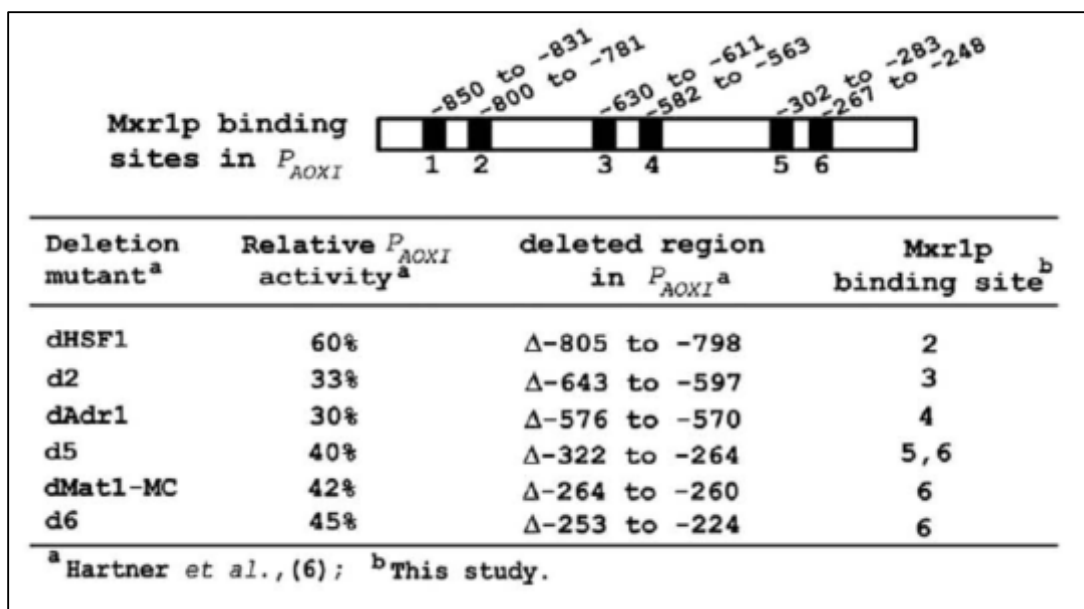
25. Motif’s expert states that a POSA “could not suggest that a sequence of DNA was a ‘promoter element’ without scientific knowledge and experimental validation.” Batt, ¶ 176. Dr. Batt points to a 2008 publication by Hartner *et al.*⁵ to show inconsistency in the meaning of “promoter element.” D.I. 123-1, Ex. B22 (“Hartner”). There were meaningful developments in yeast cell genetic engineering postdating the Hartner publication and leading up to the priority

⁵ Hartner, et al., “Promoter library designed for fine-tuned gene expression in *Pichia pastoris*,” *Nucleic Acids Res.*, 36(12):e76 (2008).

date of the Yeast Patents. *See, e.g.*, D.I. 107-2, Ex. D; D.I. 107-1, Ex. C at IF_0013972-973 (summarizing investigations into regulatory regions and specific consensus sequences within the AOX1 promoter). Such research would have informed a POSA as to the mechanism by which transcriptional activators like Mxr1 enhance gene expression and subsequently desired protein production. *See* Alper Decl., ¶ 29; *see generally* D.I. 107-1, Ex. B; *id.*, Ex. C.

26. Following Hartner’s identification of “[a] number of promoter sequences involved in methanol-inducible expression of P_{AOX1},” Kranthi *et al.*⁶ identified “key DNA elements involved in promoter recognition by Mxr1p” as “an important step in understanding its function as a master regulator of the methanol utilization pathway in *P. pastoris*.” Ex. G at IF_0014058. Specifically, Kranthi reports that “[i]n the AOX1 promoter, Mxr1p binds at six different regions” via “a consensus sequence . . . consisting of a core 5’ CYCC 3’ motif.” *Id.* Kranthi illustrates the “[c]orrelation between Mxr1p binding sites identified” and the “[e]ffect of deletion of different regions of AOX1 promoter on methanol-inducible P_{AOX1} activity *in vivo* as reported by Hartner et al.” as follows:

⁶ Kranthi, et al., “Identification of key DNA elements involved in promoter recognition by Mxr1p, a master regulator of methanol utilization pathway in *Pichia pastoris*,” *Biochimica et Biophysica Acta* 1789:460-468 (2009) (IF_0014058-066) (“Kranthi”).



Id. at IF_0014062 (Figure 4). “[A] number of promoter deletions which resulted in a significant decrease in P_{AOX1} activity *in vivo* involved deletions within Mxr1p binding sites.” *Id.* at IF_0014063. “In view of the strong correlation between deletions within Mxr1p binding sites and decrease in P_{AOX1} function, [Kranthi *et al.*] named the six P_{AOX1} Mxr1p binding sites . . . as **P_{AOX1} [promoter] Mxr1p response elements** (P_{AOX1} MXREs).” *Id.* (emphasis added); *see also id.* (“Analysis of the nucleotide sequence of the P_{AOX1} MXREs revealed that the sequence 5’ CYCC 3’ . . . is conserved in all the six P_{AOX1} MXREs []. A single point mutation within this **conserved motif** . . . abrogated Mxr1p binding, indicating a critical role for this sequence in Mxr1p-DNA interactions.” (emphasis added)).

27. Thus, Kranthi expanded upon the findings of Hartner and defined the conserved sequence necessary for the transcriptional activator protein Mxr1, in the language of the Yeast Patents, to be “operably linked to the promoter it activates.” ’656 patent, 2:43-45. I note that I discussed this consensus sequence or motif in my initial declaration. *See, e.g.*, Alper Decl., ¶ 29; *see also* D.I. 107-1, Ex. B at IF_0013553 (describing “DNA elements required for initiating gene transcription,” including “elements that play positive roles in transcription” by “provid[ing] the

binding sites for transcriptional activators that increase the levels of gene transcription”); D.I. 107-1, Ex. C at IF_0013973 (“Based on analysis of the Aox1 promoter sequence, a consensus sequence for Mxr1 binding consisting of a 5’ -CYCC-3’ motif was identified (Kranthi et al. 2009; Kranthi, Kumar and Rangarajan 2010).”).

28. Hartner itself also shows that a POSA would know the meaning of “promoter element” in the context of the Yeast Patent claims. For example, Hartner discusses the protein expression profiles of “short synthetic promoter variants, which were constructed using P_{AOX1}-derived *cis-acting elements*.” D.I. 123-1, Ex. B22 at 13 (emphasis added); *see also id.* at 2 (discussing “the *cis*- or *trans*-acting elements” of the AOX1 promoter); *id.* (“Deletion analysis . . . resulted in the identification of three *cis-acting elements in that promoter*, two upstream repression sites (URS1 and URS2) and one upstream activation sequence (UAS).”) (emphasis added); *id.* (“*Cis-acting elements sensitive to methanol induction* were also identified in the promoter sequences . . . [.]”) (emphasis added); *id.* at 10 (“Since the core promoter containing the transcription initiation site is also a key *cis-acting element crucial for efficient transcription*[], we first analysed three different core promoter fragments.”) (emphasis added); *id.* at 3 (describing materials and methods used to generate “[t]runcated AOX1 promoter variants”).

29. While I acknowledge that the art does not provide unequivocal data regarding the effects of mutagenesis of every single base pair within the relevant promoter—as Dr. Batt’s discussion of Hartner’s deletion libraries illustrates (*id.*, ¶¶ 166-76)—counsel has informed me that for a claim to be valid and not indefinite, the relevant standard is one of “reasonable certainty.” The intrinsic and extrinsic evidence would provide a POSA with at least “reasonable

certainty,” as I discussed above and in my initial declaration. *See, e.g.*, Alper Decl., ¶¶ 29-30, 56.

30. I further note that in related IPR proceedings, Motif’s expert made statements that undercut the opinions in his present declaration. *See, e.g.*, Ex. 23, ¶ 141 (“Tsutsumi discloses the recombinant methods it used to co-express Mxr1 in Example 5’s cutinase-expressing yeast cells under the control of a promoter element.”); *id.*, ¶ 149 (“A POSITA would further understand . . . that Mxr1 binds to at least one sequence in the *PEX8* and *AOX1* promoters . . . [and] systematic analysis for Mxr1p binding sites prior to 2015 revealed Mxr1 binding sites in, among others, the promoters of [*DAS*] and [*PEX8*]” (internal quotation marks omitted)); *id.* (“Consequently, for example, a POSITA would recognize that the *PEX8* promoter-driven expression of Mxr1 as taught in Lin-Cereghino reflects the methanol-inducible expression of Mxr1 by a promoter element (*PEX8*) to which Mxr1 itself binds.”). Dr. Batt understood that “[t]he ’656 patent refers to several promoter elements that can be constructed into the claimed expression system . . . [and] provides that the *AOX1* promoter can be used to direct gene expression in methylotrophic *P. pastoris*.” *Id.*, ¶ 44; *see also* Ex. 24, ¶¶ 41, 154, 157, 221.

31. Though Motif’s expert attempts to qualify his prior statements in support of Motif’s IPR petition, he nevertheless acknowledges that “it is [] possible to identify ‘elements’ of a promoter with some role in the promoter’s activity.” Batt, ¶ 136, n.2. This groundwork existed in the art, as my above discussion indicates. Moreover, Motif’s expert testified that a POSA “would reasonably expect success” in combining prior art disclosures to “drive expression of Mxr1 in *P. pastoris*” *even though* one of the references “does not expressly disclose Mxr1 under control of a methanol-inducible promoter element comprising a sequence to which the Mxr1 transcriptional activator binds.” Ex. 23, ¶ 138 (internal quotation marks omitted). In Dr.

Batt's words, "Mxr1 was known to activate methanol-inducible promoters" and can "drive expression of a heterologous polypeptide by binding and activating its methanol-inducible promoter if the promoter comprises a Mxr1 binding site." *Id.*, ¶ 161; *see also id.* ("A POSITA would be aware of Mxr1 [*sic*] bindings sites as they had previously been characterized . . . [.]"). It is difficult to reconcile these statements with Dr. Batt's present position that a POSA somehow "would not be reasonably certain of the meaning of a 'promoter element.'" Batt, ¶ 172.

32. For the above reasons, I disagree with Motif and its expert's assertion that "promoter element" is indefinite. A POSA would understand the meaning of this term based on the disclosures of the Yeast Patents together with the knowledge in the art as set out here and in my initial declaration. *See* Alper Decl., ¶¶ 64-66.

IV. CONCLUSION

33. For the reasons stated above, it remains my opinion that each of the disputed terms of the Yeast Patents should be accorded its plain and ordinary meaning.

Dated: July 7, 2023



Hal Alper, Ph.D.