

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

IMPOSSIBLE FOODS INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
MOTIF FOODWORKS, INC.,	)	C.A. No. 22-311 (WCB)
	)	
and	)	
	)	
GINKGO BIOWORKS, INC.,	)	
	)	
Defendants.	)	

**SUPPLEMENTAL DECLARATION OF DR. CARL BATT
IN SUPPORT OF MOTIF’S SUR-REPLY CLAIM CONSTRUCTION BRIEF**

I, Dr. Carl Batt, declare as follows:

1. On June 28, 2023, I submitted a Declaration (“Decl.”) in support of Motif’s Answering Claim Construction Brief in this Litigation. I incorporate that Declaration, including my opinions therein, herein by reference. My opinions and analysis in my Declaration are unchanged. I also incorporate my curriculum vitae (Decl. Ex. B1) herein by reference.

I. SCOPE OF SUPPLEMENTAL ASSIGNMENT

2. I have been asked to supplement my opinions and analysis provided in my Declaration in response to positions taken by Plaintiff Impossible Foods and its experts in Reply claim construction briefing.

3. I have reviewed Impossible’s Reply Claim Construction Brief regarding the Animal Terms, the Mxr1 Terms, and “promoter element.” I disagree with Impossible’s positions in this brief as I explain further below.

4. I understand that Impossible’s expert, Dr. Paul Sarnoski, submitted a declaration in this Litigation on July 7, 2023 in support of Impossible’s Reply Claim Construction Brief. In this declaration (“Sarnoski Decl.”), I see that Dr. Sarnoski has responded to some of my statements and opinions in my Declaration regarding the Animal Terms. I have reviewed the Sarnoski Declaration and the exhibits Dr. Sarnoski has cited in support. I disagree with Dr. Sarnoski and respond to his positions below.

5. I also understand that Impossible’s expert, Dr. Hal Alper, submitted a declaration in this Litigation on July 7, 2023 in support of Impossible’s Reply Claim Construction Brief. In this declaration (“Alper Rep.”), I see that Dr. Alper has responded to some of my statements and opinions in my Declaration regarding the Mxr1 Terms and “promoter element.” I have reviewed

the Alper Reply and the exhibits Dr. Alper has cited in support. I disagree with Dr. Alper and respond to his positions below.

6. I reserve the right to further respond to opinions or positions taken by Plaintiff Impossible, Dr. Sarnoski, Dr. Alper, or other experts of Impossible in due course as this Litigation proceeds, or to amend or further supplement my opinions herein or in my Declaration as new information comes to my attention.

II. REBUTTAL OPINIONS

A. Supplemental Opinions Regarding Animal Terms

7. I have reviewed the Sarnoski Declaration with respect to the “Animal Terms.” As a preliminary matter, it is not clear to me that Dr. Sarnoski is a POSA for the Foodstuff Patents according to his own definition. Dr. Sarnoski opines that a “POSA would have at least a graduate degree in food science, biology, chemistry, or a similar discipline, plus 2 years of experience as a food scientist.” Sarnoski Decl. ¶19. Dr. Sarnoski states that he obtained his Ph.D. in 2010. I observe Dr. Sarnoski applies a priority date of July 12, 2011 for the ’761 patent and January 11, 2013 for the other Foodstuff Patents.¹ Accordingly, from his own admissions, it is not apparent that Dr. Sarnoski had 2 years of experience as a food scientist after receiving his graduate degree at the time of the ’761 patent’s priority date.

8. I disagree with paragraphs 79, 82-83, and 88 of the Sarnoski Declaration for reasons previously explained in my Declaration. As I previously opined, whether a food or a food ingredient is “animal” is a function of its genetic origins regardless of what host is used to produce it, as in the case with a recombinant host. Decl. §IX.A.1. *E.g.*, the patents teach that a non-animal

¹ I understand from Motif’s Answering Claim Construction Brief that Impossible has contended that all Foodstuff Patents are related. I am not aware, and Dr. Sarnoski does not explain, why he applies different priority dates for different Foodstuff Patents.

“source” is one way to produce animal proteins. Decl. ¶58. The patents thus distinguish between the protein’s identity and host used to produce it. The claims do not recite the latter concept. Decl. §§VI.C, IX.B. Dr. Sarnoski apparently disagrees with me but never provides any factual or evidentiary contradiction to my position that genetic identity dictates whether a protein is “animal.” Instead, although he does not say so directly, he apparently believes that the proteins’ source dictates whether they are “animal” or not, within the meaning of the Foodstuff Patent claims. I disagree as explained above.

9. Dr. Sarnoski discusses certain dependent claims in paragraph 80-81. To the extent certain claims exclude “animal” proteins or “animal” products, I disagree with Dr. Sarnoski that these terms are consistent with the independent claims. Myoglobin is well-known to be an animal protein, as I previously explained. Decl. ¶120. Even Impossible’s cited support recognizes this fact. *See, e.g.*, Reply Brief Exhibit 14, IF_0014526 (“Myoglobin is a 17.8-kD protein that is found exclusively in skeletal muscle Myoglobin (Mb) is a heme-containing globular protein that is found in abundance in myocyte cells of heart and skeletal muscle.”); IF_0014529 (“Myoglobin is an oxygen-binding protein located primarily in muscles.”); IF_0014530 (“Myoglobin is a low molecular weight oxygen binding heme protein that is found exclusively in heart and skeletal muscle cells.”). Dr. Sarnoski does not opine that myoglobin is not an animal protein.²

10. I further disagree with Dr. Sarnoski’s opinions in paragraphs 80-81. I see, for example, that the sequences highlighted by Dr. Sarnoski (SEQ ID NOS. 18-20) are among a total

² To the extent the patents discuss “myoglobins” from other species, it is unclear whether the patents mean myoglobin specifically or rather a “myoglobin-like” protein. Dr. Sarnoski offers no opinion on this point. Impossible’s cited support confirms that “myoglobin-like” proteins are found in non-animal organisms (“taxa” such as bacteria). Reply Brief page 2, Exhibit 14 (“Mb and *Mb-like* proteins are also found in many taxa, including bacteria, plants, fungi, and animals.”). It is not clear to me whether Impossible or Dr. Sarnoski are opining that “myoglobin” includes proteins encoded in non-animal species. Regardless, my opinions relating to the significance of

of 26 different sequences recited in the claims at issue. Sarnoski Decl. ¶¶80-81. Their inclusion in the dependent claims is suggestive of an error by the patent Examiner in failing to appreciate the internal inconsistency between the independent and dependent claims. For example, the Examiner may have overlooked SEQ ID NOS. 18-20 among the SEQ ID NOS. 1-26 recited in the dependent claims when allowing the claims.

11. As I explained in my Declaration, for example, the Examiner deleted “myoglobin” from a dependent claim in amending the respective independent claim to recite “non-animal” heme-containing protein. Decl. ¶¶60, 120. Dr. Sarnoski addresses my positions regarding this amendment. Sarnoski Decl. ¶90. I disagree with his characterization. He states, e.g., that he “would not understand such an [clarifying] amendment to change the substantive meaning of the claim.” *Id.* He does not further explain or identify any basis for his understanding. Nor is it apparent what expertise Dr. Sarnoski has that qualifies him to opine on whether a claim amendment is substantive or not, e.g., training in patent prosecution. Regardless, I disagree with Dr. Sarnoski. The evidence shows that the ’306 patent Examiner recognized that these terms are internally inconsistent with each other. In my view, failure to make similar amendments in other patent claims reflects an error by those patents’ Examiners.

12. I disagree with Dr. Sarnoski’s opinions regarding FDA Standards of Identity. Sarnoski Decl. ¶¶84-85. I previously explained, for example, that products such as milk (or butter or cheese) could be “animal products” without changing the meaning of “animal,” a term which relates to identity. Decl. ¶123. Dr. Sarnoski’s opinions do not address my explanation. Instead,

amendments of the claim term “myoglobin” are unchanged in light of the undisputed and abundant disclosure that myoglobin is an *animal* muscle protein.

he contrasts animal-sourced milk with plant-sourced “milk alternatives.” I disagree with the relevance of Dr. Sarnoski’s analysis as explained below.

13. I have reviewed Exhibit C to Dr. Sarnoski’s declaration, an FDA Guidance document titled “Labeling of Plant-Based Milk Alternatives and Voluntary Nutrient Statements: Guidance for Industry.” Exhibit C is dated February 2023 and therefore post-dates the Foodstuff Patents’ priority date(s) by a decade or more. The relevance of Exhibit C to Dr. Sarnoski’s opinions is therefore unclear. Exhibit C explains how a producer may label plant-based milk alternatives below. *See* Ex. C page 5 (emphasis added). I note that Exhibit C does not state that these milk alternatives can be produced by recombinant technology and most addresses soy milk and other extracts from plants.

Plant-based milk alternatives are made from *liquid-based extracts of plant materials*, such as tree nuts (e.g., almond, walnuts, macadamia), legumes (e.g., soybean), seeds (e.g., hemp, flax), or grains (e.g., rice, oat).

14. I am not certain what argument Dr. Sarnoski is advancing with respect to the milk-alternative SOI. Dr. Sarnoski’s comparison does not appear to be relevant to my opinions, however. In Dr. Sarnoski’s comparison, the two sets of products (animal milk and plant “milk alternative”) are materials produced by different sources (animals and plants), but these sources are the native sources of the respective products. My opinions relate to the question of whether, properly construed, a protein encoded in an animal genome is “animal” or “non-animal” within the meaning of the Foodstuff Patents’ claims when that protein is expressed in a non-animal source that does not naturally produce that protein. *E.g.*, Decl. §IX.A.1. Dr. Sarnoski’s milk-alternative example does not address this question.³ Milk is not just a mixture of specific proteins, lipids,

³ Also, milk is not just a mixture of specific proteins, lipids, sugars and other molecules. The U.S. Food and Drug Administration (FDA) defines milk as the lacteal secretion obtained from one or more healthy cows. The definition includes milk obtained by manual milking or by the use

sugars and other molecules. The U.S. Food and Drug Administration (FDA) defines “milk” as the lacteal secretion obtained from one or more healthy cows. The definition includes milk obtained by manual milking or by the use of mechanical means from cows that are in good health and are not under any treatment that could affect the milk’s safety. Taken in total, the process by which an animal produces “milk” and how it is collected is part of the definition of milk. Dr. Sarnoski does not offer any evidence (extrinsic or otherwise) to argue that recombinant production of a milk protein (*e.g.*, casein) naturally encoded and expressed in animal cells should be considered a “non-animal” protein. It is unclear that any such evidence, even if available, would be relevant to the meaning of the claimed “animal” or “non-animal” terms given the 2011-2013 priority date Dr. Sarnoski applies and I disagree with Dr. Sarnoski to the extent he opines that the subject matter of paragraphs 84-85 are relevant. The analogy has no merit because milk is not a single protein, and plant-based milks will never be considered to be the equivalent of milk, *i.e.*, lacteal secretion obtained from one or more healthy cows. The FDA may allow producers of plant-based milk alternatives to use the word ‘milk’ on their label but modified to reflect its origin (soy, cashew, etc.) with the added requirement of a comparative nutrition label to inform the consumer of the differences between the plant-based milk and milk. Further and in support of Motif’s claim that the origin matters, soy milk must be labeled ‘soy’ to alert consumers who might be allergic to soy proteins. I reserve all rights to respond to any further opinions he or another expert may offer on this subject.

15. Dr. Sarnoski states that Motif uses the term “plant based” to describe Motif’s products. Sarnoski Decl. ¶86. He cites only to a two-page print-out from a website that bears the

of mechanical means from cows that are in good health and are not under any treatment that could affect the milk’s safety. Taken in total the process by which an animal produces ‘milk’ is part of the definition of milk.

URL <https://www.nsf.org/food-beverage/food-beverage-product-certification/plant-based-certification>. See Sarnoski Decl. Ex. D. NSF is formerly known as National Sanitation Foundation, a private entity that, among other things, certifies various equipment and practices in the food industry. Their self-initiated ‘certificate’ is not sanctioned by any Federal agency and represents a certification that some individuals may choose to obtain from NSF for a fee. It is not to be confused with the National Science Foundation, also known (and more widely) as NSF. As with any private-party certification, the authority and value is in eyes of the beholder. The only date associated with Exhibit D is “7/7/23”—at least a decade or more after the priority dates applied by Dr. Sarnoski. I am not certain what argument Dr. Sarnoski is advancing with respect to this term. For example, it is not clear how “animal-derived” as used in Exhibit D is relevant to any claim term. Indeed, Dr. Sarnoski states that he “[is] *unsure* whether Motif is certified” by the NSF organization. There is no obvious rationale for probing if Motif has this certification, nor the value to Motif or any organization to having this certification as it relates to the matter at hand. Therefore, the relevance of Exhibit D to Dr. Sarnoski’s opinions on terms with a 2011-2013 priority date is wholly unclear to me and I disagree with Dr. Sarnoski to the extent he opines that the subject matter of paragraph 86 is relevant. I reserve all rights to respond to any further opinions he or another expert may offer on this subject.

16. Dr. Sarnoski states that “the papers cited by Dr. Batt [in my Declaration] do not tell a food scientist how the term “non-animal” should be interpreted in the context of the patents.” Sarnoski Decl. ¶87. I disagree. Dr. Sarnoski cites no support for this statement and it appears to be entirely conclusory. Nor does Dr. Sarnoski identify any specific statement or analysis from my Declaration that he disagrees with. I note that Dr. Sarnoski’s experience with recombinant technology, including in production of foodstuffs or proteins—if any—is not apparent from his

identified qualifications. In addition a POSITA would seek to be informed about the term ‘non-animal’ from a broader sense than just its context in these patents and more than likely seek guidance from FDA documentation. That documentation makes it clear that the origins of the protein with regard to where the original gene came from is of utmost importance.

17. Dr. Sarnoski states that “Dr. Batt and Motif are looking to outside sources and ignoring the focus and language of the patents.” Sarnoski Decl. ¶87. I disagree. I considered the Foodstuff Patents and their intrinsic record as explained in my Declaration. *E.g.*, Decl. §§VII, IX.B.

18. Dr. Sarnoski quotes twice from a response by Impossible to the Patent Office during prosecution of the ’241 patent. I am not certain what argument Dr. Sarnoski is advancing with respect to these statements. To the extent Dr. Sarnoski suggests they contradict my opinions, I disagree. For example, I see no statements in Exhibit 18 that address the question of whether a protein genetically encoded in an animal, and therefore “animal” in identity, becomes “non-animal” when it is synthesized in a non-animal source.

19. Indeed, Exhibit 18 refers to heme-proteins that are encoded by the same host that the native genes are expressed in. I excerpt the relevant portion of Impossible’s Exhibit 18 below (IF_0013133), with highlighting to indicate the proper context of the excerpt quoted by Dr. Sarnoski. Specifically, I see from my review of Exhibit 18 that the “Hsieh” prior art reference contained beef. Therefore, the heme-protein in Hsieh was both genetically encoded in beef and also synthesized in beef. I see that the Examiner argued it would be obvious to combine Hsieh with another reference, Proulx. As I understand from ’241 patent prosecution, the Examiner cited Proulx for its teaching of leghemoglobin, a protein whose gene is found in a plant (i.e., soybean) and can be isolated from it. Ex. B25 (U.S. Application No. 15/913,090, Non-Final Rejection dated

May 12, 2020, page 5 (citing “Proulx et al. (“Iron Bioavailability of Hemoglobin *from Soy Root Nodules* Using a Caco-2 Cell Culture Model”)), page 7 (“Proulx et al. teach leghemoglobin is a heme protein *identified in soybean root nodules* ... Proulx et al. disclose a *purified* leghemoglobin protein ... Proulx et al. teach that the bioavailability of *leghemoglobin from soy root nodules* is similar to that of heme iron from animal sources....”) (emphasis altered). With this context, it is clear to me that when Impossible was referring to “heme from a non-animal source,” Impossible was referring back to Proulx’s *plant-sourced plant protein* leghemoglobin. When the portion quoted by Dr. Sarnoski is considered in context, it says nothing about recombinant production or genetically modified yeast. In fact, Impossible originally sought to use leghemoglobin from soybean nodules but then opted to express soy leghemoglobin in a genetically modified yeast, retaining ‘soy’ as the descriptor for the ingredient to reflect its origins. I therefore disagree with Dr. Sarnoski’s characterization of Exhibit 18.

The teachings of Hsieh do not support the Examiner’s assertion that it would be obvious to modify the meat analog of Hsieh to include the non-animal leghemoglobin of Proulx. In fact, the meat analog of Hsieh would inherently contain heme by the addition of beef to the meat analog. As such, there would be no reason for Hsieh to modify their meat analog to contain heme from a non-animal source. Further, the Examiner does not provide any evidence that a person of ordinary skill would have had a motivation to combine Hsieh, Dinh, and/or Proulx with a reasonable expectation of success.

20. I also observe that Impossible points to Motif’s GRAS notice dated April 15, 2021 (Reply Brief pages 1-2) in support of certain arguments concerning the Animal Terms. Dr. Sarnoski does not mention this GRAS notice and Impossible’s brief does not rely on an opinion by him on this point. In my opinion, as explained above regarding the “milk alternative” and

“NSF” evidence cited by Dr. Sarnoski, the 2021 GRAS notice is irrelevant to how a POSITA would have understood the claims of the Foodstuff Patent roughly 10 years earlier.

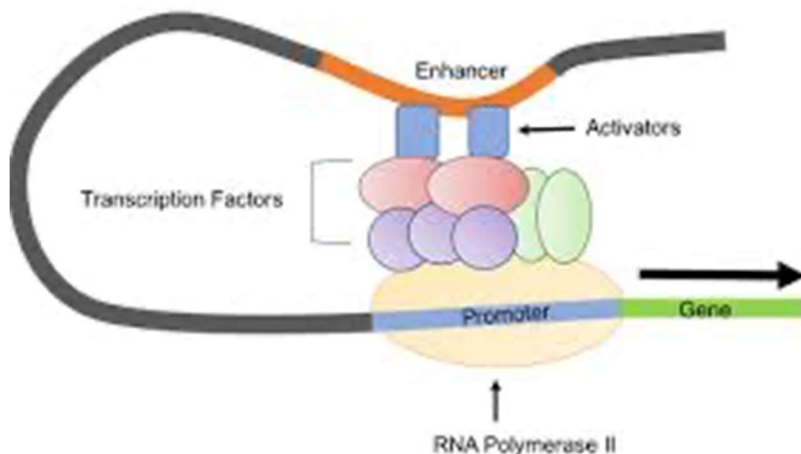
21. However, it is also my opinion that if the GRAS notice is relevant, Impossible is wrong about the significance of bovine myoglobin’s allergenicity reported in therein. As the GRAS notice explains, “[t]he myoglobin present in Motif FoodWorks’ Myoglobin Preparation is 100% identical to bovine myoglobin.” Reply Brief Ex. 12 at 25. In addressing potential allergenicity, for example, the notice discusses the protein’s “amino acid sequence homology” across “different animal species” in relation to whether the protein is an allergen. D.I. 142, Ex. 12 at 23. In a different disclosure of allergenicity, Impossible (through its attorneys only) argues that the yeast production system causes Motif’s protein to lack the α -Gal carbohydrate (α -Gal) sometimes associated with meat allergies. I disagree with this argument to the extent Impossible argues the myoglobin is thereby rendered “non-animal.” The α -Gal carbohydrate is a post-translational modification to the myoglobin protein. Thus, the protein’s fundamental genetic identity as an animal (*e.g.*, bovine) myoglobin is unchanged.

B. Supplemental Opinions Regarding Mxr1 Terms

(a) The Term “Mxr1 Transcriptional Activator Sequence” Refers to the Coding Nucleic Acid, Not the Binding Site

22. The patents never use the term “sequence” to refer to a location where Mxr1 binds. At most, the patents refer to the AOX1 promoter as the region where Mxr1 binds. ’492 patent 39:23-31. But they do not call the binding site itself a “sequence.” This is consistent with how a POSITA would describe a binding site—*i.e.*, a POSITA would call that region a “binding site.” In contrast, a POSITA would use “sequence” to describe the nucleic acid sequence that encodes the Mxr1 transcriptional activator itself or in general any nucleic acid sequence modified by a

description of the origins of that sequence, i.e., soy leghemoglobin sequence. This is depicted in the illustration below:



23. Further, I disagree with Dr. Alper’s reading of claim 14 in paragraph 6. The patents describe an embodiment in which Mxr1 transcriptional activator sequence, as used in that claim, refers to the protein that is encoded in the nucleic acid sequence rather than a binding site to which Mxr1 binds. ’492 patent, 4:18-22.

24. I disagree with Alper Reply paragraph 7. He claims I should not be using the ’656 patent claims as instructive in interpreting the ’492 patent claims. It is unclear what Dr. Alper means by “the nomenclature between [the patents] is not strictly uniform.” Even if the patents’ claims have some differences in phrasing, the relevant term at issue—the four words *Mxr1 transcriptional activator sequence*—are the same. This terminology, used in two different claim sets, arises from the same specification and should have the same meaning in both claim sets. Dr. Alper does not identify any support in any of the patents where this term—*Mxr1 transcriptional activator sequence*—refers to a binding site. The plain and simple meaning of *Mxr1 transcriptional activator sequence* is the sequence that codes for the Mxr1 activator. The plain and simple means to designate the region where Mxr1 binds would be the Mxr1 binding site.

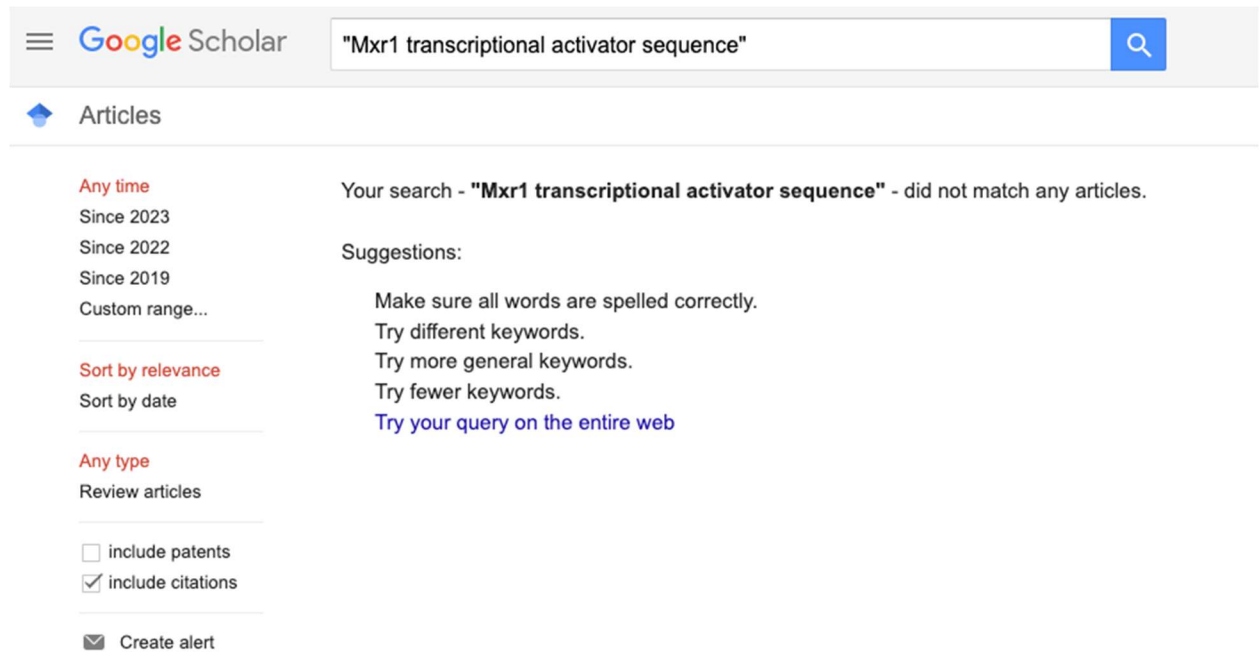
“Sequence” conveys a degree of certainty with respect to the nucleic acid sequence while in fact the six Mxr1 binding sites in the AOX1 promoter have very little similarity outside of a 4 nucleotide sequence CYCC (where Y is either a C or a T, ie CCCC)

25. I disagree with Alper Reply paragraph 8 because his comparison fails to account for the claims’ actual language. He compares the two terms he emphasizes red, but these terms are different. Instead, Dr. Alper should have compared the red language in claim 14 with the language I highlight in claim 26 below.

'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.

26. I disagree with Alper Reply paragraph 9 because none of Dr. Alper’s cited support uses the term at issue—*Mxr1 transcriptional activator sequence*. In fact, his cited disclosure supports my opinion that the patents describe binding sites with different terminology, specifically, “binding sites” and “binding target.” In fact “*Mxr1 transcriptional activator sequence*” fails to appear in any scientific publication as determined using a search of Google Scholar. Therefore a

POSITA would understand the phrase “*Mxr1 transcriptional activator sequence*” to mean the sequence coding for the Mxr1 transcriptional activator.



27. Alper Reply paragraph 10 because addressed my interpretation of ’492 patent claim 14 as referring to an embodiment in which more than one Mxr1 transcriptional activator is encoded by the nucleic acid molecule. Dr. Alper is incorrect that my interpretation would render two limitations in claim 14 duplicative. Dr. Alper does not appreciate the fact that claim 14 recites two different Mxr1 transcriptional activator sequences—one from *P. pastor* and one not limited to a species of origin, which may not be from *P. pastoris*. Those are Mxr1 transcriptional activators of different scope, they are not duplicative. I disagree with the remainder of Alper Reply 10 for reasons stated above.

(b) A POSITA Would Understand “Mxr1” to Refer to a Native Transcriptional Activator, not a Non-Natural Variant

28. As I noted in my Responsive Declaration at paragraphs 70, 124-26, the patents’ specifications consistently refer to native Mxr1 as “Mxr1” and distinguish it from variant Mxr1,

which the patents refer to as “variant Mxr1.” *E.g.*, Ex. B12, ’656 patent, 27:5-32; Ex. 23 (SEQ ID NO:1). That is consistent with a POSITA’s understanding that Mxr1 is a naturally occurring transcriptional activator native to *Pichia*, but variants are human-made proteins that are not “Mxr1”; rather they may have different sequences, functionality, activity, structure, or other characteristics that make them different than Mxr1.

29. I disagree with Alper Reply paragraphs 12-14. I do not dispute that Mxr1 native to one *Pichia* species can be recombinantly produced in *Pichia* of another species. But that misses the point. Dr. Alper does not dispute that a human-made variant Mxr1 is not “native” to *Pichia* of any species. Dr. Alper is confusing the issue of species to which Mxr1 is native—which the ’656 patent claims specify as “from *P. pastoris*”—with the fact that native proteins are not human-made variants. A POSITA would understand that human-made variant Mxr1 proteins are not native to any *Pichia* species.

30. In Alper Reply paragraph 15, Dr. Alper misguidedly points to Example 15 of the ’656 patent to argue a construct including the native Mxr1 sequence with “6 additional amino acids introduced at the N-terminus” is engineered but still Mxr1. However, Dr. Alper does not appreciate that Mxr1 in that construct retains its full and native sequence, as the construct was made to include “[t]he open reading frame encoding the Mxr1 protein ... from genomic DNA isolated from *Pichia pastoris*...” ’656 patent at 25:15-23. The construct did not vary the Mxr1 transcriptional activator—it remained the native sequence as coded in the open reading frame. 6 amino acids were introduced to the N-terminus during cloning, but the patent states it did not vary the native properties of the transcriptional activator, as “*Pichia* production strains containing the Mxr1 sequence having the additional 6 amino acids at the N-terminus and *Pichia* strains containing

the wild type Mxr1 (i.e., without the additional 6 amino acids at the N-terminus) were indistinguishable in fermentation tanks.” *Id.* at 26:7-11.

31. For the reasons in my Responsive Declaration and those set forth here, a POSITA, based on common understanding in the art and the disclosure of the ’492 and ’656 patents, would interpret the Mxr1 transcriptional activator terms, in the context of the claims, as construed by Motif. I disagree with Dr. Alper’s opinions to the contrary.

C. Supplemental Opinions Regarding “Promoter Element”

(a) My Approach to Claim Construction Is Correct

32. Dr. Alper insinuates that my approach to claim construction in my Declaration is legally incorrect. Alper Rep. ¶¶18-20. I disagree. As I explained in my Declaration, I understand from counsel that intrinsic evidence is the most important source for determining the meaning of claim terms, but that extrinsic evidence—which I am informed includes expert testimony such as my Declaration—may also be useful. Decl. ¶34.

33. In my Declaration, I reviewed the Expression System Patents’ intrinsic record and provided reasons why (1) Dr. Alper misinterprets the specifications, resulting in an incorrect definition of “promoter element” (Decl. §§VII, XI.B) and (2) a POSITA would not be reasonably certain of “promoter element” in view of the intrinsic record. *Id.* §XI.A. I did not “prioritize” extrinsic evidence. Rather, the intrinsic record does not explain or define what a “promoter element” is (as opposed to other concepts, such as “operably linked” or “expression element”). The question, therefore, is whether a POSITA would be reasonably certain of “promoter element’s scope” *despite* the patents’ lack of definition.

34. The answer to this question is no, as I explained in my Declaration. In support, I discussed specific examples from technical literature which I believe will aid the Court in understanding the complexity of this term as well as illustrate a POSITA’s confusion over whether

an expression system (either deliberately through design or by accidental inclusion) contains the claimed “promoter element.” Decl. §§XI.A.4-11.

35. I note Dr. Alper states that “the intrinsic evidence provides the context or ‘reference’” to establish the scope of “promoter element.” Alper Rep. ¶21. Dr. Alper evidently misunderstands my contrary position, which is that a “promoter element” *only* has meaning within the context of a known promoter (several are listed in the patents and available on GenBank), and that “promoter element” or “element” terminology is used subjectively throughout the technical literature. Decl. ¶135, §XI.A.8 (different approaches). Neither the intrinsic nor extrinsic evidence clarifies the metes and bounds of “promoter element” separate and apart from the known promoter, as I explained. *Id.* ¶135, 140, 163 & n.5, 176-77; §§XI.A.7 (TATA box location in context), XI.A.9 (minor changes affect expression), XI.A.10 (regulation depends on promoter localization). Dr. Alper’s understanding of “promoter element” is also fatally flawed by his misinterpretation of the intrinsic record, as explained below.

(b) **Dr. Alper’s Circular Analysis of the Intrinsic Record Confirms the Indefiniteness of “Promoter Element”**

36. Dr. Alper defines “promoter element” in terms of its supposed function (regulating transcription). Alper Rep. ¶17. Dr. Alper borrows this meaning from two *different* terms—“expression element” and “operably linked,” as I previously noted. Decl. ¶¶181-85. I explained the problems with Dr. Alper’s definition (Decl. §XI.B), but he does not meaningfully address my explanation in his Reply.

37. Instead, Dr. Alper disagrees with my opinion that “elements” require localization for function by arguing that the claims and specification “provides such localization and specificity.” Alper Rep. ¶22. His Reply argument is premised on three teachings: (1) the claims’ recitation of “methylotrophic yeast cell” and Mxr1, (2) the definition of the different term

“operably linked” (656 patent, 4:47-51) although he does not acknowledge this explicitly, and (3), a Mxr1 binding site. Alper Rep. ¶22. As in my Declaration, I disagree with Dr. Alper with respect to each of these teachings.

38. Regarding (1) and (3), as I previously explained, a Mxr1 binding site is neither required nor sufficient to define a “promoter element,” for example, in the ’492 patent claims that do not recite or contain a Mxr1 binding site. Decl. ¶¶150-55. I am not aware that Dr. Alper has made any argument regarding how a methylotrophic yeast cell clarifies the scope of the claimed “promoter element” but reserve rights to do so.

39. Dr. Alper does not argue, for example, that the intrinsic record teaches that a Mxr1 binding site will *always* regulate transcription *whenever* a gene of interest is linked to the Mxr1 binding site (as might be the case of a genetically engineered artificial construct). In fact, the literature (*e.g.*, Hartner (2008)) teaches that the location of a binding site can change its ability to regulate transcription. *See, e.g.*, Decl. §XI.A.10 and below.

40. Regarding (2), Dr. Alper’s argument is premised on the conflation of “promoter element” with another term, “operably linked,” and I disagree as explained in my Declaration (§XI.B). Dr. Alper’s Reply fails to clarify the circularity of using one term to define the other, both of which are purely functional (according to Dr. Alper). I provide an exemplary dilemma to illustrate the confusion that Dr. Alper did not address:

- (1) If (as in Hartner (2008)), a POSITA moves a binding site in a promoter, and the result is that transcription stops, is that binding site sequence a “promoter element” within the meaning of the Expression System Patent claims? The sequence still exists but no longer regulates promoter activity, so it would no longer be a “promoter element” under Dr. Alper’s definition.
- (2) Alternatively, is the binding site still a “promoter element” but simply no longer “operably linked” in such a way as to drive transcription? Instead, the binding site is linked, but not “operably linked.”

41. In failing to respond to my position the intrinsic record does not describe the boundaries of “promoter element” and that Dr. Alper’s declaration misinterprets the intrinsic record on this point (Decl. ¶136, §XI.B), Dr. Alper’s Reply likewise fails to demonstrate how a POSITA would be reasonably certain regarding the meaning of this term based on the disclosures of the intrinsic record.

42. Dr. Alper’s Reply analysis of the extrinsic evidence also fails as explained below.

(c) “Element,” As Used in “Promoter Element,” Is A Generic Term in the Art

43. Dr. Alper states that I “conduct[ed] a piecemeal analysis of ‘promoter element’ by providing a lay dictionary definition of ‘element’ divorced from ‘promoter,’” which Dr. Alper asserts “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.” Alper Rep. ¶19. It is not clear to me why Dr. Alper believes the dictionary definition of acid is unhelpful in the context he identifies. In fact, the specific dictionary definition of “acid” proffered by Dr. Alper (Ex. F to the Alper Reply) is useful to explain the meaning of “nucleic acid” because it informs the reader about the chemical properties that define the meaning of “acid” in nucleic acid (*e.g.*, that it can donate a proton or accept an electron pair). The functionality of a nucleic acid in providing the blueprint of every protein in a cell is dependent in part on its being an acid.

44. Dr. Alper’s criticism is misplaced, however, because the term “element” is used generically in the art cited by myself and Dr. Alper to refer to some portion of a promoter. *E.g.*, Alper Rep. Ex. G, Title (“key DNA elements”), 461 (“Mxr1p response elements”), 465 (“cis-acting elements”). In fact, Exhibit G to the Alper Reply does not use the term “promoter element” at all. Moreover, unlike nucleic acid—where acid is an integral part of the definition of a nucleic

acid—“element” is at best a component of a promoter which loses all meaning when it is not seen within the context of a known promoter, as I explained. *See supra* paragraph 35.

45. Likewise, the Alper Reply does not identify any uniform meaning of “promoter element.” Indeed, Dr. Alper acknowledges “*the absence of a uniform meaning in dictionaries and technical literature*” for this term. Alper Rep. ¶24 (emphasis added).

46. Dr. Alper asserts, however, that “the art is not inconsistent or ambiguous in the manner” explained in my Declaration. Alper Rep. ¶24. Dr. Alper is incorrect as explained below.

(d) **Dr. Alper Fails to Show that a POSITA Would Be Reasonably Certain of A “Promoter Element’s” Structural Features**

47. Dr. Alper again defines “promoter element” in terms of its function—*i.e.*, he opines “that ‘promoter element’ refers to a nucleic acid sequence that regulates transcription of downstream genes.” Alper Rep. ¶17. This definition is premised on his misinterpretation of the specification, which I previously explained. Decl. §XI.B. Dr. Alper does not address my explanation anywhere in the Alper Reply.

48. In my Declaration, I identified a variety of reasons why a POSITA would not be reasonably certain of “promoter element.” Dr. Alper does not address the issues that I raise in any meaningful way in his Reply. In fact, his Reply further illustrates the indefiniteness of “promoter element” as I explain below.

49. In support of his position, Dr. Alper refers to “developments” before the Expression System Patents’ priority date relating to “investigations” of regions and sequences within the AOX1 gene promoter, such as a Mxr1 “consensus sequence” and “core” 4-nucleotide motif (CYCC, in which Y is an abbreviation of either a C or a T). Alper Rep. ¶¶25-27. These “developments” relate to a specific binding site (Mxr1) *found within a known promoter*—the AOX1 promoter. It is unclear from the Alper Reply whether Dr. Alper believes the core 4-

nucleotide motif is a “promoter element,” whether the (unspecified) “consensus sequence” is, or both.

50. Regardless, to the extent Dr. Alper opines that these “developments” provide reasonable certainty of the scope of “promoter element,” I disagree. Dr. Alper identifies no basis for understanding how any particular discovery is a “promoter element” *outside the natural context of the AOX1 promoter*. For example, Dr. Alper does not point to literature showing that, *e.g.*, inserting the CYCC motif into an artificial expression construct, at any particular location, would “regulate” transcription, turning on transcription by the addition of methanol. As there are only four building blocks of DNA (A, C, T, and G), a POSITA would expect to find CYCC sequences frequently throughout artificial constructs (which are typically thousands of nucleotides long) and as well as cellular genomes (millions of nucleotides). If CYCC is a “promoter element” (Dr. Alper does not say), it is not clear whether Dr. Alper believes that CYCC is a promoter element each and every time it is found in the genome regardless of context (*i.e.*, located in a known promoter).

51. Moreover, a binding site is not a required or defining feature of a “promoter element” as I previously explained. Decl. §§XI.A.6-7. As one example, constitutive promoters do *not* contain binding sites for transcription factors that function to regulate inducible expression, such as the Mxr1 binding site. Decl. ¶¶150-55. But a transcription factor binding site is not the only sequence that can (in the context of a promoter) regulate expression. Sequences like introns, which are not transcription factor binding sites, also affect gene expression. *Id.* ¶¶149 & n.3, 183. Dr. Alper does not discuss these complexities at all in his Reply.

52. In his Reply, Dr. Alper points to the Hartner (2008) authors’ generic and subjective use of “elements” to refer to sequences that they identified to affect expression in the context of

the *AOX1* promoter. He “*acknowledge[s]* 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.” Alper Rep. ¶29. Thus, Dr. Alper agrees with my analysis at least to some extent.

53. Dr. Alper states, however, that a POSITA would be “reasonably certain” of “promoter element” for the other reasons he identifies. Alper Rep. ¶29. Thus, I disagree with Dr. Alper’s conclusion as explained herein and in my Declaration in response to the points he raises.

54. I disagree with Dr. Alper’s conclusion that, in view of Hartner (2008), a “POSA would know the meaning of ‘promoter element’ in the context of the Yeast Patent claims.”⁴ Alper Rep. ¶28. As I previously pointed out, Hartner (2008) shows changing even two nucleotides in a promoter (also not a binding site) can drastically affect gene expression. Decl. ¶167 & n.6. Critically, as Hartner (2008) exemplifies, transcription is the result *not only of nucleic acid structure but also the structure’s location* within the promoter. *Id.* §XI.A.10. Dr. Alper’s analysis fails to engage with the complex issues I identified and does not resolve the ambiguities and inconsistencies identified in the literature.

55. Rather, the portions of Hartner (2008) cited by Dr. Alper use the term “element” (*not* “promoter element”) generically to indicate specific pieces of the *AOX1* promoter. Alper Rep. ¶28. They do not clarify whether any particular sequence satisfies the claimed “promoter element” *when taken out of the context of that promoter*. See *supra* paragraph 35. Dr. Alper does not explain, for example, how a POSITA looking at a gene sequence *outside the AOX1*

⁴ Relatedly, Dr. Alper does not address how a POSITA would recognize a “promoter element” “*from P. pastoris*” if structures like the TATA box are considered a “promoter element.” As I explained, TATA box sequences are found in many different species, including but not limited to *P. pastoris*. Decl. §XI.A.7.

promoter would recognize that any particular “element” or sequence identified by Hartner satisfies the “promoter element” limitation. As I explain above, Dr. Alper’s opinion continues to conflate “promoter element” with “operably linked” and other patent terms in a way that muddies and obfuscates the meaning of “promoter element” instead of clarifying it.

(e) **My Statements in IPR Do Not Undercut My Opinions Regarding “Promoter Element” Indefiniteness**

56. Dr. Alper opines that, in IPRs of the Expression System Patents, I “made statements that undercut the opinions in” my Declaration. Alper Rep. ¶30. I disagree.

57. Here, Dr. Alper attempts to manufacture confusion where none exists. In my IPR declarations, I discussed *gene promoters* known in the prior art, such as the promoter of the *AOX1* gene (pAOX1) and the *PEX8* gene (pPEX8), and structural features thereof such as Mxr1 binding sites (which do not define “promoter elements” as explained above). As I opined in my Declaration, naturally occurring *promoters*, such as the promoters listed in the Expression System Patents, are familiar to a POSITA and drive gene expression. Decl. §XI.A.5. Scientists and POSITAs study such promoters to understand how portions of the promoter are relevant to that promoter’s activity and use the term “element” generically to refer to parts of the promoter. *Id.* §XI.A.8 (different scientific approaches), ¶135. In these studies, “elements” of a promoter are defined subjectively and with reference to the promoter itself. *Id.* My IPR testimony, which relates to gene *promoters*, is therefore not inconsistent with my opinions that the claim term “promoter element” is indefinite.

58. Dr. Alper also argues that my explanation of my IPR testimony is unpersuasive. Alper Rep. ¶31. I disagree because the testimony Dr. Alper cites relates to studies of gene promoters, as well as binding sites, which are neither necessary nor sufficient to define the scope

of a “promoter element.” Dr. Alper is therefore incorrect for reasons explained above and in my Declaration.

59. I also note that, in my declarations supporting Motif’s IPRs, I did not opine that “promoter element” is indefinite. I am informed that, legally, the definiteness of claims *cannot* be challenged in an IPR. I did not propose a definition of “promoter element” in my IPR declarations, however—a point Dr. Alper fails to mention. Moreover, I did not take a position as to what makes a sequence a “promoter element” outside the context of a full gene promoter, and Dr. Alper does not identify that I took any such position.

I hereby declare under penalty of perjury under the laws of the United States of America
that the foregoing is true and correct.

Dated: JULY 14, 2023



Dr. Carl Batt

CERTIFICATE OF SERVICE

I hereby certify that on July 14, 2023, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on July 14, 2023, upon the following in the manner indicated:

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