

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

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

DECLARATION OF DR. CARL BATT

IN SUPPORT OF MOTIF'S ANSWERING CLAIM CONSTRUCTION BRIEF

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I, Carl Batt, Ph.D., hereby declare:

I. BACKGROUND

1. I have been retained by Quinn Emanuel Urquhart & Sullivan LLP on behalf of Defendant Motif FoodWorks, Inc. (“Motif”) as an independent expert in this litigation which is pending before the United States District Court for the District of Delaware (“Litigation”). I understand that the parties are presently engaging in claim construction proceedings in the Litigation.

2. I understand that, in this Litigation, Motif is offering constructions of certain terms in claims 1, 5, 7, and 14 of U.S. Patent No. 10,273,492, and claims 1, 10, 11, 26, and 28 of U.S. Patent No. 10,689,656 (“Expression System Patents”). I further understand that Motif is offering constructions of certain terms in claims including terms in claims 1-3 of U.S. Patent No. 9,943,096 (the “’096 patent”), claims 14 and 27 of U.S. Patent No. 10,039,306 (the “’306 patent”), claims 1 and 12 of U.S. Patent No. 10,863,761 (the “’761 patent”), claims 1 and 13 of U.S. Patent No. 11,013,250 (the “’250 patent”), and claims 1, 7, and 22-23 of U.S. Patent No. 11,224,241 (the “’241 patent”) (“Foodstuff Patents”). Based on my review of the first page of each of these patents, I understand them to be assigned to Impossible Foods Inc. (“Plaintiff”).

3. I have been asked to provide this declaration in support of certain positions advanced by Motif in these claim construction proceedings (“Declaration”). I reserve the right to amend or supplement my opinions in this Declaration in response to any positions that Plaintiff or its experts may take in the claim construction proceedings, the Litigation, or in response to any order of the District Court.

II. QUALIFICATIONS AND EXPERTISE

4. Ex. B1 accompanying this Declaration is a true and correct copy of my current CV. It describes in greater detail my education, publications, employment and research history, and professional activities and awards.

5. I have over 35 years of experience in microbiology, molecular biology, protein engineering, cell culture and food science. In 1975, I was awarded Bachelor of Science Degree in Microbiology from Kansas State University in Manhattan, Kansas. In 1981, I was awarded a Doctor of Philosophy Degree in Food Science from Rutgers University in New Brunswick, New Jersey. I was a postdoctoral research associate from 1982-1984 in the Department of Nutrition and Food Science and a research scientist from 1984-1985 in the Department of Applied Biological Sciences at Massachusetts Institute of Technology.

6. In 1985, I joined the faculty of Cornell University as an Assistant Professor in the Department of Food Science, where I was promoted to Associate Professor in 1991 and Professor in 1998.

7. While at Cornell University, I founded the Cornell University/Ludwig Institute for Cancer Research Partnership and served as its Director from 1999-2011. As Director, I managed the design, construction and operation of a Good Manufacturing Practice (“GMP”) facility on the Cornell University Ithaca campus, which resulted in the production of recombinant proteins using microbial expression systems, including *Pichia pastoris*, that have been used in clinical trials.

8. I have conducted research in several areas that span the life and physical sciences. My work includes pioneering efforts in the fields of microbiology, molecular biology, and nanotechnology. One area of research that I have focused on is the use of protein engineering and expression systems for producing recombinant anti-cancer therapeutics and proteins in general. For the past 35, years, my laboratory has been engaged in protein expression using a variety of

host systems including bacteria, yeast, fungi, and higher eukaryotic cells. Our work in *P. pastoris* began in the early 1990's and is documented in publications expressing various proteins using this versatile expression system.

9. The major area of research currently underway in my laboratory concerns exploring parallel routes for the expression of therapeutic agents and constructing rational approaches to scale-up of these systems. Our major focus is on the development and optimization of microbial-based expression systems for tumor antigens and tumor-specific antibody fragments. Our Biologics Production Facility enables us to carry out large-scale production of highly-purified immunotherapeutics suitable for early-phase human clinical trials.

10. Over the course of my career, I have authored or co-authored more than 300 peer-reviewed articles, book chapters and reviews. I have given more than 100 invited lectures worldwide. I am a named inventor on three United States patents.

11. I have been fortunate to receive a number of distinctions during my career. In 1990, I was awarded the Samuel Cate Prescott Award from the Institute of Food Technologists which is given to the outstanding scientist in my field under the age of 35. In 2000, I was named a Liberty Hyde Bailey Professor in the College of Agriculture and Life Sciences, a named chair created to honor the most outstanding faculty in the college. It is an honor that I hold for the time I am on the Cornell faculty. Today that distinction is held by only five professors among the 1,629 faculty at Cornell University.

12. I am co-founder of the Nanobiotechnology Center ("NBTC") at Cornell University, a National Science Foundation supported science and technology center, and was co-Director of NBTC from 1999-2004. I am also co-founder of Main Street Science, a not-for-profit corporation

established to develop and distribute K-12 science learning materials, and the founder of Nanooze, a science magazine for children.

13. In 2007, I was an NSF Discovery Corps Fellow in recognition of both my extraordinary research accomplishments and my efforts to communicate advances in science and technology to the general public. In addition, I have been the recipient of a number of awards from Cornell University for teaching (Teaching Excellence Award, 1990), service (Faculty Fellows in Service, 2001; Kaplan Family Distinguished Faculty Fellowship in Service-Learning, 2003), and diversity (CALS Kathy Berggren Diversity and Inclusion Award, 2008).

14. In addition to my teaching responsibilities, I have mentored over 50 graduate students, including 45 PhD students and over 100 undergraduates in my laboratory, many of whom now hold significant positions in academia, government and the private sector, both in the United States and internationally.

15. I served as Chief Editor for Food Microbiology (1987-2000), a peer-reviewed journal. I also served as Editor for the Encyclopedia of Food Microbiology (1996-1999) and Chief Editor of its 2nd Edition (2009-2015). I served as Editor of Elsevier's Food Microbiology, Food Science Reference Module (2015-2016). I have also been on the Editorial Boards of the peer-reviewed journals: Food Biotechnology (1987-1992), Journal of Food Science (2001-2008), and Protein Expression and Purification (2001-2004).

16. As a champion of making scientific concepts understandable for the general public, especially young students, I lead a team that developed a series of public exhibitions including "It's a Nanoworld," which was on a five-year tour in the United States after a six-month residency at EPCOT in Walt Disney World, and "Too Small To See," which is also on tour after opening in EPCOT in 2007. Subsequently I designed and oversaw the construction of two additional exhibits,

“Take a Nanooze Break” (2010-2020) and “Nanooze Labs” (2011-2014) that were on exhibit at Walt Disney World and Disneyland respectively.

III. SCOPE OF ASSIGNMENT

17. As explained in greater detail below, I have been asked to describe the relevant technical literature and state of the art regarding certain terms recited in some or all of the Expression System Claims and Foodstuff Claims, and to provide my opinions regarding the meaning of such terms as they would have been understood by a person of ordinary skill in the art for the respective patents (a “POSITA”).

18. In connection with the preparation of this Declaration, I have reviewed the Declaration of Dr. Hal Alper, which I understand to have been submitted in support of Impossible’s claim construction positions relating to terms recited in the Expression System Claims, and the Exhibits cited by Dr. Alper. Dr. Alper refers to the Expression System Patents as the Yeast Patents. I disagree with Dr. Alper’s opinions as explained below and respond to certain positions in his Declaration.

19. I am being compensated at my customary rate of \$375 per hour for my work in this matter. This compensation is in no way contingent upon the outcome of this matter or upon the opinions I offer in this Declaration. All of the opinions expressed in this Declaration are my own.

IV. SUMMARY OF OPINIONS

20. My opinions are set forth in greater detail below. Briefly, in my opinion:

A. “Animal” Terms

21. The parties dispute certain terms which relate to “animal” or “non-animal” limitations. I may refer to these terms as the “Animal Terms.” The parties’ respective proposed constructions for these terms are set forth below:

Impossible's Term No.	Claim Term	Impossible's Proposed Construction	Motif's Term No.	Motif's Proposed Construction
1	"a non-animal heme-containing protein" ('306 patent, cl. 14, 27; '250 cl. 1, 13)	"a heme-containing protein that contains no proteins the synthesis of which occurred inside an animal"	1	"a heme-containing protein that does not have the amino acid sequence of any animal heme-containing protein"
2	"free of animal heme-containing protein" ('241 patent, cl. 1, 22)	"free of proteins the synthesis of which occurred inside an animal"	1	"free of any protein that has the amino acid sequence of any animal heme-containing protein"
3	"no animal products" ('096 patent, cl. 1; '761 patent, cl. 12)	"no proteins the synthesis of which occurred inside an animal"	1	"no products that are the same (e.g., amino acid sequence) as those found in an animal"
4	"free of animal products" ('241 patent, cl. 23)	"free of proteins the synthesis of which occurred inside an animal"	1	"free of any products that are the same (e.g., amino acid sequence) as those found in an animal"
5	"wherein the heme-containing protein is selected from the group consisting of ... a myoglobin ..." ('096 patent, cl. 2)	Plain and ordinary meaning.	1	Indefinite.
6	"wherein the heme-containing protein comprises [an] amino acid sequence having at least 80% sequence identity to a polypeptide set forth in SEQ ID NO[: 18]." ('096 patent, cl. 3; '241 patent, cl. 7)	Plain and ordinary meaning.	1	Indefinite.

22. In my opinion, Motif's claim constructions are correct and clarify a POSITA's understanding of the terms and claims as a whole. They are supported by the Foodstuff Patents' specifications and the general understanding in the art.

23. As I explain below, the ordinary meaning of "animal protein" broadly refers to protein with "animal" genetic identity and is not limited to animal-sourced protein. Prior to advances in genetic engineering, an animal's proteins were produced only in the respective animal. As genetically-modified organisms and recombinant foodstuffs have been widely developed, however, POSITAs have recognized the importance of linguistic clarity in distinguishing between the "animal protein" and its source. This understanding is reflected in the FDA's approach to genetically modified organisms and recombinant proteins used in food. This understanding is consistent with Impossible's recitation of "animal" or "non-animal" proteins or products in the Foodstuff Patent claims.

B. "Mxr1 Transcriptional Activator" Terms

24. The parties' respective proposed constructions for these terms are set forth below:

Impossible's Term No.	Claim Term	Impossible's Proposed Construction	Motif's Term No.	Motif's Proposed Construction
18	"a Mxr1 transcriptional activator sequence from <i>P. pastoris</i> " ('492 patent, cl. 1, 14; '656 patent, cl. 1, 26)	Plain and ordinary meaning	4	"the sequence of the native <i>P. pastoris</i> Mxr1 transcriptional activator"
19	"a first exogenous nucleic acid encoding a methanol expression regulator 1 (Mxr1) transcriptional activator" ('656 patent, cl. 1,)	Plain and ordinary meaning	4	"a first exogenous nucleic acid sequence of a native Mxr1 transcriptional activator"

Impossible's Term No.	Claim Term	Impossible's Proposed Construction	Motif's Term No.	Motif's Proposed Construction
20	"a nucleic acid encoding a Mxr1 transcriptional activator sequence from <i>P. pastoris</i> " ('656 patent, cl. 26)	Plain and ordinary meaning	4	"a nucleic acid encoding the sequence of the native <i>P. pastoris</i> Mxr1 transcriptional activator"

25. In my opinion, Motif's claim constructions are correct and clarify a POSITA's understanding of the terms and claims as a whole. They are supported by the '492 and '656 Patents' specifications and the general understanding in the art.

26. I have reviewed Dr. Alper's opinions regarding construction of the "Mxr1 transcriptional activator" terms. I disagree with his opinions. Among other things, Dr. Alper's opinions conflict with the claim language reciting that the Mxr1 transcriptional activator is "from" *P. pastoris* ('492 Patent, claim 1, '656 Patent, claims 1 and 26) as opposed to some other species. They also conflict with the patents' disclosure that the Mxr1 transcriptional activator sequence would be native to *P. pastoris* ('492 Patent, claim 1, '656 Patent, claim 26), or native to some other organism ('656 Patent, claim 1), as opposed to a variant or mutant form of Mxr1. In addition, Dr. Alper's opinion that an "Mxr1 transcriptional activator sequence" is a sequence to which Mxr1 binds, rather than the sequence that encodes Mxr1, contradicts the patents' teachings and how Impossible has used "Mxr1 transcriptional activator sequence" in other claims.

C. "Promoter Element" Term

27. The parties' respective proposed constructions for these terms are set forth below:

Impossible's Term No.	Claim Term	Impossible's Proposed Construction	Motif's Term No.	Motif's Proposed Construction

26	“promoter element” (’492 patent, cl. 1, 5, 7, 14; ’656 patent, cl. 1, 10, 11, 26, 28)	Plain and ordinary meaning.	8	Indefinite.
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28. The term “promoter element” is indefinite, as that term is used in the context of the Asserted Expression System Patent claims. The Expression System Patents and intrinsic record do not define a “promoter element” and this term is not consistently used in the art. They do not describe any structural or functional boundaries for a “promoter element” or even an “element” of a promoter. As a result, a POSITA would not be reasonably certain of whether any particular nucleic acid sequence practices the “promoter element” term. Motif’s claim construction is therefore correct.

29. I have reviewed Dr. Alper’s opinions regarding construction of the “promoter element” term. I disagree with his opinions. Dr. Alper’s opinions combine selected teachings from the patents based on the patents’ disclosure of other terms. His opinion ignores contrary teachings in the patents, the art, and the generic ordinary meaning of “element,” each of which indicate that “promoter element” has no consistent, well understood meaning.

V. LEGAL UNDERSTANDING

30. In this section I describe my understanding of certain legal principles that I have relied upon in forming my opinions set forth in this Declaration. I have been informed of these legal standards by attorneys for Motif. I am not an attorney and I have not researched the law on patent invalidity. I am relying only on Motif’s attorneys relating to these legal standards.

B. Person of Ordinary Skill in the Art (“POSITA”)

31. I understand that patent validity is determined from the perspective of a person of ordinary skill in the pertinent art at the time of the invention (“POSITA”). I understand that a

POSITA is a hypothetical person who is presumed to be aware of all pertinent art, conventional wisdom in the art, and is a person of ordinary creativity—not an automaton.

32. In deciding the level of ordinary skill in the art, I am informed that the following factors may be considered: the levels of education and experience of persons working in the field; the types of problems encountered in the field; and the sophistication of the technology.

C. Claim Construction

33. I understand that claim construction is a matter of law for the Court to decide.

34. I understand that claim construction begins with the presumption that claim terms are given their ordinary and customary meaning, and that the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art at the time of the invention (*i.e.*, the effective filing date), viewed in the context of the patent. I understand that to determine the ordinary and customary meaning of claim terms, courts may consult a variety of sources, including the claims themselves, the specification, and the prosecution history (collectively, referred to as “intrinsic evidence”), as well as relevant dictionaries and treatises, and expert testimony (collectively, referred to as “extrinsic evidence”). I also understand that intrinsic evidence is the most important source for determining the meaning of claim terms, but that extrinsic evidence may, in some circumstances, also be useful when considered in the context of the intrinsic record. I understand that extrinsic evidence cannot be used to contradict an unambiguous meaning provided in the intrinsic evidence.

35. I understand that, under some circumstances, an inventor may clearly define a claim term in the specification or the prosecution history to mean something other than its ordinary meaning. Similarly, I understand that under some circumstances, an inventor may clearly and intentionally disclaim certain claim scope within the specification or prosecution history.

36. I understand that the claim language must be considered in the context of the entire patent, including the specification and the prosecution history. Specifically, I understand that the usage of a claim term within the specification and prosecution history may provide guidance as to the inventor's understanding of the meaning of the term and context which could assist a person of ordinary skill to ascertain the plain meaning of the claim language. At the same time, I understand that the specification usually cannot be used to import limitations into the claims, and that it is also generally improper to read limitations out of the claims.

37. I further understand that a patent may include two types of claims, independent claims and dependent claims. An independent claim stands alone and includes only the limitations it recites. A dependent claim can depend from an independent claim or another dependent claim. I am informed that a dependent claim includes all the limitations that it recites, in addition to the limitations recited in the claim from which it depends.

38. I understand that claim terms should usually be read and understood in a manner that gives meaning to all of the words in the claim and, further, gives each independent claim a distinct meaning and scope from its dependent claims. Thus, other claims (and claim elements) of the patent in question, both asserted and unasserted, can inform the meaning of a claim term. For example, because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims. Differences among claims can also be a useful guide in understanding the meaning of particular claim terms.

D. Indefiniteness

39. I am informed that patent law requires that the claims of the patent must meet the definiteness requirement. I understand that a patent is invalid for indefiniteness if its claims, read in the light of the specification and prosecution history, fail to inform with reasonable certainty a POSITA about the scope of the invention.

VI. THE FOODSTUFF PATENTS

40. I have reviewed the claims, specifications, and file histories of the Foodstuff Patents. I discuss certain aspects of these patents and the intrinsic record below. I reserve the right to amend or supplement my analysis below, for example, in response to any position Impossible may take in this litigation.

A. Person of Ordinary Skill in the Art for the Foodstuff Patents

41. The Foodstuff Patents are directed to the art of food science. In my opinion, a POSITA for the Foodstuff Patents would have a Master's degree or Ph.D. in food science or at least three years of experience working as a food scientist. A POSITA could also be part of a team of food scientists, including flavor chemists. In this Declaration, I provide my opinions based on the knowledge and understanding of a POSITA for the Foodstuff Patents.

42. I at least meet the qualifications of a POSITA.

B. Claims

43. I have reviewed the Foodstuff Patents' claims. Claim 1 from each patent is reproduced below. As shown below, certain claims recite limitations relating to "animal" protein or "animal" products. I emphasize these limitations. Independent claim 1 of both the '306 and '250 patents recite "a non-animal heme-containing protein." Independent claim 1 of the '096 patent recites that the claimed food flavor additive composition contains "no animal products." Similarly, dependent claim 12 of the '761 patent recites that the claimed beef replica contains "no animal products." Claim 1 of the '241 patent recites that the claimed "meat-like food product is free of animal heme-containing protein."

44. Claim 1 of the **'096 patent** recites (Ex. B2):

A food flavor additive composition comprising:

a) an isolated heme-containing protein;

b) a compound selected from glucose, ribose, fructose, lactose, xylose, arabinose, glucose-6-phosphate, maltose, maltodextrin, and galactose, and mixtures of two or more thereof; and

c) a compound selected from cysteine, cystine, thiamine, methionine, and mixtures of two or more thereof;

wherein the flavor additive composition *contains no animal products*; and

wherein cooking the food flavor additive composition results in the production of at least two volatile compounds which have a meat-associated aroma.

45. Claim 1 of the **'306 patent** recites (Ex. B3):

A method for imparting a beef-like aroma to a meat replica matrix,

wherein the meat replica matrix comprises one or more plant proteins,

a sugar selected from glucose, ribose, sucrose, fructose, xylose, maltodextrin, and combinations thereof,

and at least one sulfur compound selected from methionine, cysteine and thiamine,

the method comprising adding 0.01%-5% (by weight of the meat replica matrix) of *a non-animal heme-containing protein* to the meat replica matrix,

wherein, upon cooking of the meat replica matrix, at least two volatile compounds are generated that are associated with a beef-like aroma, thereby imparting a beef-like aroma to the meat replica matrix.

46. Claim 1 of the **'250 patent** recites (Ex. B4):

A meat replica matrix comprising:

one or more plant proteins;

a sugar selected from glucose, ribose, sucrose, fructose, xylose, maltodextrin, and combinations thereof;

at least one sulfur compound selected from methionine, cysteine, and thiamine;

and 0.01%-5% (by weight of the meat replica matrix) of *a non-animal heme-containing protein*,

wherein, upon cooking of the meat replica matrix, at least two volatile compounds are generated that are associated with a beef-like aroma.

47. Claim 1 of the **'241 patent** recites (Ex. B5):

A meat-like-food product produced by a method comprising:

providing one or more plant proteins; and

combining, with the one or more plant proteins:

a composition comprising a heme-containing protein, wherein the composition comprises at least 60% of the heme-containing protein on a dry weight basis;

a compound selected from glucose, ribose, fructose, lactose, xylose, arabinose, glucose-6-phosphate, maltose, and galactose, and mixtures of two or more thereof;

and a compound selected from cysteine, cystine, thiamine, methionine, and mixtures of two or more thereof in a concentration of at least 1.5 mM;

wherein the meat-like food product is *free of animal heme-containing protein*; wherein cooking the meat-like-food-product results in the production of at least two volatile compounds which have a meat-associated aroma; and

wherein the meat-like food product is in a form selected from the group consisting of a hotdog, a burger, ground meat, a sausage, a steak, a filet, a roast, a meatball, a meatloaf, or bacon.

48. Claim 1 of the **'761 patent** recites (Ex. B6):

A beef replica product, comprising:

a) a muscle replica comprising 0.1%-5% of a heme-containing protein, at least one sugar compound and at least one sulfur compound; and

b) a fat tissue replica comprising at least one plant oil and a denatured plant protein,

wherein said muscle replica and fat tissue replica are assembled in a manner that approximates the physical organization of meat.

Dependent claim 12 of the '761 patent recites "wherein said beef replica product *contains no animal products* and less than 5% carbohydrates."

49. The dependent claims recite different aspects or features of the claimed products and methods. Certain dependent claims recite limitations that refer to or implicate “animal” or “non-animal” identity. For example, certain dependent claims recite that “the non-animal heme-containing protein has a UV-VIS spectrum that is substantially similar to that of myoglobin from an animal.” *E.g.*, Ex. B3, ’306 patent claim 3.

50. Dependent claim 2 of the ’096 patent recites that “the heme-containing protein is selected from the group consisting of ... a myoglobin,” among other proteins. Ex. B2. Myoglobin is well-known to POSITAs to be an animal protein.

51. Dependent claim 3 of the ’096 patent and dependent claim 7 of the ’241 patent recite that “the heme-containing protein comprises amino acid sequence having at least 80% sequence identity to a polypeptide set forth in SEQ ID NOs: 1-26.” I observe that the patents teach that SEQ ID NO: 18 is a “*Bos taurus*” sequence, specifically “a mammalian myoglobin protein such as the *Bos taurus* (SEQ ID NO:18) myoglobin.” *E.g.*, Ex. B5, ’241 patent 10:50-51.

C. **Intrinsic Record**

52. I observe that the Foodstuff Patent specifications are not identical, though I understand Impossible contends that these patents are related. Although the Foodstuff Patent specifications are not identical, in my opinion they describe the claimed Animal Terms consistently such that a POSITA would understand that “animal” and “non-animal” have the same meanings for each of the patents.

53. The Foodstuff Patent specifications do not define the terms “animal” or “non-animal.” Certain disclosures are informative, however.

54. In a section of the ’306 patent titled “Proteins,” the specification describes preparing “*non-animal* proteins (*e.g.*, plant proteins)...” Ex. B3, ’306 patent §III.B, 20:19-24. The patents provide examples of these proteins, including myoglobin, hemoglobin, leghemoglobin, and

others. *E.g.*, Ex. B3, '306 patent 21:15-35; 22:14-23; Ex. B5, '241 patent 9:40-48 (similar); Ex. B6, '761 patent 2:33-54. A POSITA would understand that certain proteins are found in animal genomes, such as myoglobin, a well-known animal muscle protein. Similarly, a POSITA would understand that certain proteins are found in plant genomes, such as leghemoglobin (legume hemoglobin).

55. The “Proteins” section further describes certain proteins in terms of their genetic identity—specifically, the native amino acid sequence of these proteins. Ex. B3, '306 patent 23:7-40 (listing different species’ protein sequences); Ex. B5, '241 patent 10:25-58 (same). The specification explains, for example, that heme-proteins can have certain “sequence identity to the amino acid sequence of the corresponding wild-type” heme-protein, including “a leghemoglobin such as that from *Glycine max* (SEQ ID NO:4), *Pisum sativum* (SEQ ID NO:16), or *Vigna unguiculata* (SEQ ID NO:17),” “or a **mammalian myoglobin protein** such as the *Bos taurus* (SEQ ID NO:18) myoglobin, *Sus scrofa* (SEQ ID NO:19) myoglobin, or *Equus caballus* (SEQ ID NO:20) myoglobin”). *E.g.*, Ex. B3, '306 patent 23:12-35; Ex. B6, '761 patent 3:8-52. The claims similarly recite “one or more plant proteins,” which are described in terms of their genetic identity and not how they are produced. Ex. B3, '306 patent 23:12-19, 23:22-24.

56. The patents do not define “animal” or “non-animal” proteins by the method of their production. In fact, the patent identifies that any particular method of protein production is optional. For example, the “Proteins” section explains that these (non-animal) “**proteins can be isolated from** one or more other components of a **non-animal source**.” Ex. B3, '306 patent 20:32-33; 20:64-21:6. For example, “a protein fraction may be isolated from an isolate of a plant.” Other methods may also be used.

isolated and purified proteins also can be recombinantly produced using polypeptide expression techniques (e.g., heterologous expression techniques using

bacterial cells, insect cells, fungal cells such as yeast cells, plant cells, or mammalian cells). In some cases, standard polypeptide synthesis techniques (e.g., liquid-phase polypeptide synthesis techniques or solid-phase polypeptide synthesis techniques) can be used to produce proteins synthetically. In some cases, cell-free translation techniques can be used to produce proteins synthetically.

Ex. B3, '306 patent 20:64-21:6.

57. I observe that the patents do not describe the “invention” to require production only using “non-animal sources.” In fact, the patents state that the invention can include embodiments “partially” or “substantially derived from animal sources.”

In alternative embodiments, the muscle, fat, and/or connective tissue replica, or the meat substitute products comprising one or more of the replicas, are partially derived from animal sources but supplemented with ingredients derived from non-animal sources. In some embodiments, *as much as 90% of the food product is derived from animal sources*. In some embodiments about 75% of the food product is derived from animal sources. In some embodiments, about 50% of the food product is derived from animal sources. In some embodiments about 10% of the food product is derived from animal sources. In yet other alternative embodiments, the invention provides meat products substantially derived from animal sources (e.g., a beef, chicken, turkey, or a pork product) that are supplemented with one or more of a muscle tissue replica, a fat replica, and/or a connective tissue replica, wherein the replicas are derived substantially or entirely from non-animal sources.

Ex. B3, '306 patent, 9:50-10:2 (emphasis added). The patents further provide that recombinant protein expression can occur in “mammalian cells.” Ex. B3, '306 patent 20:64-21:1.

58. Rather, the patents teach that production in non-animal sources is an optional aspect of the methods. Under a section titled “Sources of Components of the Consumable,” for example, the '306 patent provides that “proteins *can be* derived from non-animal sources” such as plants, fungi, genetically modified organisms, or even *in vitro* chemical synthesis. Ex. B3, '306 patent 18:4-6 & §III.A; *see also id.* 24:25-34, 47:20-25 (“Non-animal sources *can* provide some or all of the protein ...”); 17:58-67 (“A consumable ... *may be* substantially or entirely composed of ingredients derived from non-animal sources...”); Ex. B5, '241 patent 11:41-12:28 (listing

“embodiments” of how proteins “can” be produced, including that they “*can* be extracted from the source material”); Ex. B6, ’761 patent 2:55-65; 5:66-6:4 (“In *some embodiments*, said protein content is derived from one or more non-animal sources. In particular *embodiments*, said one or more non-animal sources is a plant source. In other particular *embodiments*, said one or more non-animal sources is a genetically modified yeast or bacteria.”).

59. The patents contain little description of “animal products.” I see certain examples, “e.g., butter, cream, lard, and/or suet.” Ex. B3, ’306 patent 33:37-38. The patents explicitly provide that “[f]ood products described herein can be free of *animal products (e.g., animal heme-containing proteins* or other animal products).” Ex. B5, ’241 patent 18:56-58. Thus, I understand that one kind of animal “product” is an animal heme-containing protein.

60. From my review of the Foodstuff Patents’ prosecution history, the patents’ prosecution is consistent with a POSITA’s interpretation of “animal” and “non-animal.” I understand, for example, that when the claims of the ’306 patent application were allowed, the Examiner amended the claims to recite “*non-animal* heme-containing protein” and, at the same time, to *delete* the animal protein “myoglobin” from all dependent claims. This amendment is excerpted below. I understand that Impossible’s representative, Angela Parsons, gave permission for this amendment.

Authorization for this examiner's amendment was given in an interview with Angela Parsons on 2 March 2018.

The application has been amended as follows:

Claim 1:

A method for imparting a beef-like aroma to a meat replica matrix, wherein the meat replica matrix ~~contains no animal products and~~ comprises one or more plant proteins, a sugar selected from glucose, ribose, sucrose, fructose, xylose, maltodextrin, and combinations thereof, and at least one sulfur compound selected from methionine, cysteine and thiamine, the method comprising

adding 0.01%-5% (by weight of the meat replica matrix) of a non-animal heme-containing protein to the meat replica matrix,

wherein, upon cooking of the meat replica matrix, at least two volatile compounds are generated that are associated with a beef-like aroma, thereby imparting a beef-like aroma to the meat replica matrix.

Claim 4:

The method of claim 1, wherein the heme-containing protein is selected from the group consisting of ~~an androglobin, a cytoglobin, a globin E, a globin X, a globin Y, a hemoglobin, a leghemoglobin, a flavohemoglobin, Hell's gate globin I, a myoglobin, an erythrocrurin, a beta hemoglobin, an alpha hemoglobin, a protoglobin, a cyanoglobin, a cytoglobin, a histoglobin, a neuroglobins, a chlorocruorin, a truncated hemoglobin, a truncated 2/2 globin, and a hemoglobin 3, a cytochrome, and a peroxidase.~~

Ex. B7 (U.S. Application No. 14/796,970, Examiner amendment dated 4/4/2018 of allowed claims 1, 4, 7, 11, 47, 50). I further understand that Impossible deleted "mammalian" heme-containing protein from certain claims while simultaneously amending them to recite "no animal products." This amendment is excerpted below.

31. (Currently Amended) A food flavor additive composition comprising:

a) an isolated heme-containing protein;

b) ~~a compound sugar, sugar alcohol, sugar acid, or sugar derivative~~ selected from glucose, ribose, fructose, lactose, xylose, arabinose, glucose-6-phosphate, maltose, maltodextrin, and galactose, and mixtures of two or more thereof; and

c) a compound selected from cysteine, cystine, ~~selenocysteine~~, thiamine, methionine, and mixtures of two or more thereof;

wherein the flavor additive composition contains no animal products ~~tissue derived components~~; and

~~wherein the flavor additive composition is packaged and is in the form of a liquid, a gel, an emulsion, a powder, or a bouillon cube~~

wherein cooking the food flavor additive composition results in the production of at least two volatile compounds which have a meat-associated aroma.

36. (Currently Amended) The food flavor additive composition of claim 31, wherein the heme-containing protein is a plant, ~~a mammalian~~, a yeast or filamentous fungi, or bacterial heme-containing protein.

Ex. B8 ('096 patent File History, Sept. 25, 2017 Supplemental Amendment, claims 31, 36).

61. I further understand that, during the course of prosecution, Impossible has expressly defined certain claims in terms of proteins' source. Exemplary claims are excerpted below.

- 13. The meat substitute composition of claim 1, wherein said one or more isolated and purified proteins are not isolated from an animal.
- 14. The meat substitute composition of claim 13, wherein said one or more isolated and purified proteins are isolated from a single plant source.
- 15. The meat substitute composition of claim 14, wherein said one or more isolated and purified proteins are isolated from multiple plant sources.
- 16. The meat substitute composition of claim 13, wherein said one or more isolated, purified proteins are isolated from a genetically modified organism.
- 17. The meat substitute composition of claim 16, wherein said genetically modified organism is a genetically modified bacteria or yeast organism.

Ex. B9 ('211 Application, as-filed claims dated 7/12/2013).

167. (Original) The meat substitute product of claim 166, wherein said protein content is derived from a non-animal source.

168. (Original) The meat substitute product of claim 167, wherein said non-animal source is a plant source, or a genetically modified yeast or bacteria.

Ex. B10 ('211 Application, Claims 167-168 dated 5/25/2016).

VII. THE EXPRESSION SYSTEM PATENTS

62. I have reviewed the claims, specifications, and file histories of the Expression System Patents. I discuss certain aspects of these patents and the intrinsic record below. I reserve the right to amend or supplement my analysis below, for example, in response to any position Impossible may take in this litigation.

A. Person of Ordinary Skill in the Art for the Expression System Patents

63. Based on my review of the '492 and '656 patents, the patents are directed to the art of recombinant protein production. In my opinion, a person of ordinary skill in this art (a

“POSITA”) for the ’492 and ’656 patents would have a Bachelor of Science degree in biochemistry, chemistry, biological sciences, or an equivalent area of study. A POSITA would also have at least three years of graduate study or professional experience with recombinant techniques for protein production or general genetic modification experience.

64. I meet or exceed the qualifications of a POSITA for these patents.

65. In rendering my opinions in this Declaration, I have applied the perspective of a POSITA for the ’492 and ’656 patents in 2015.

B. Claims

66. The independent claims of both Expression System Patents are reproduced below.

Claim 1 of the **’492 Patent** recites (Ex. B11):

A methylotrophic *Pichia* yeast cell comprising:

a nucleic acid molecule encoding a heme-containing protein operably linked to a promoter element from *P. pastoris* and a Mxr1 transcriptional activator sequence from *P. pastoris*; and

a nucleic acid molecule encoding at least one polypeptide involved in heme biosynthesis operably linked to a promoter element from *P. pastoris* and a Mxr1 transcriptional activator sequence from *P. pastoris*.

67. Claim 1 of the **’656 Patent** recites (Ex. B12):

A methylotrophic yeast cell comprising a recombinant nucleic acid molecule,

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

wherein the recombinant nucleic acid molecule comprises a second exogenous nucleic acid encoding a heterologous polypeptide operably linked to at least one methanol-inducible promoter element.

68. Claim 26 of the **’656 Patent** recites:

A methylotrophic *Pichia* yeast cell comprising a recombinant nucleic acid molecule, wherein the recombinant nucleic acid molecule comprises:

a nucleic acid encoding a Mxr1 transcriptional activator sequence from *P. pastoris*;
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.

C. Intrinsic Record

69. The Expression System patents provide a summary of the claimed methods as follows:

This disclosure describes the use of *P. pastoris* strains that overexpress the transcriptional activator, Mxr1, from the AOX1 promoter to increase expression of transgenes that also are expressed from the AOX1 promoter, which significantly improves the recombinant production of one or more proteins. In addition, expression of Mxr1 from the AOX1 promoter creates a positive feedback loop that allows for expression of other transgenes from the AOX1 promoter in the absence of methanol, the normally obligate inducer, when repressing carbon sources are depleted. Expression of Mxr1 results in a significant increase in the amount of protein produced.

Ex. B12, '656 patent 1:37-49.

70. The '454 and '656 patents describe and distinguish recombinant protein expression systems, particularly in the context of producing the protein Mxr1. For example, Example 16 of the '492 and '656 patents describes an expression system engineered to express "Native Mxr1." Ex. B12, '656 patent 26:13-47. In contrast, Example 18 of the patents describes an expression system engineered to express "variant Mxr1." *Id.* 27:8-32. Each time the patents reference a recombinant system engineered to express a non-native Mxr1 protein, the patents qualify it as "modif[ied]" or "variant." *Id.* 4:21-22; 27:8-32. When referring to native Mxr1, the patents simply say "Mxr1." *Id.* 4:18-20; 26:14-47.

71. Mxr1 functions primarily as a transcriptional activator, and is native to *P. pastoris* and other organisms. It generally controls a promoter called “AOX1,” which the patents explain can be used to initiate transcription of recombinant genes when they are placed downstream of the AOX1 promoter. *E.g.*, Ex. B11, ’492 patent 1:38-42. An Mxr1 binding site also can be engineered into a recombinant expression construct to activate transcription.

72. Mxr1 activates transcription when methanol enters the cell typically after its addition to the growth medium. The patents describe using this feature of methylotrophic yeast to produce large quantities of recombinant proteins. One way the patent describes doing this is using a positive feedback loop that links a methanol-inducible promoter (activated by Mxr1 transcriptional activator) to a gene that codes for the Mxr1 transcription, resulting in elevated levels of Mxr1 that in turn may result in higher expression of the protein of interest expressed using the AOX1 promoter. *E.g.* Ex. B11, ’492 patent 3:50-57. That way, more Mxr1 protein is produced in the presence of methanol, allowing for higher levels of transcription of the gene encoding the protein of interest. The patents’ specifications describe this as follows:

Without being bound by any particular mechanism, the methods described herein create a positive feedback loop where the low level native expression of a transcriptional activator induces a promoter that is operably linked to a transcriptional activator. This leads to an increased expression of the transcriptional activator as well as one or more target polypeptides that are operably linked to the same inducible promoter.

Ex. B11, ’492 Patent 3:50-57. The patents explain in the “Summary” of the purported inventions that:

This disclosure describes the use of *P. pastoris* strains that overexpress the transcriptional activator, Mxr1, from the AOX1 promoter to increase expression of transgenes that also are expressed from the AOX1 promoter, which significantly improves the recombinant production of one or more proteins. In addition, expression of Mxr1 from the AOX1 promoter creates a positive feedback loop that allows for expression of other transgenes from the AOX1 promoter in the absence of methanol, the normally obligate inducer, when repressing carbon sources are

depleted. Expression of Mxr1 results in a significant increase in the amount of protein produced.

Ex. B11, '492 patent 1:37-48.

73. The patents provide additional examples of expressing genes that encode Mxr1 as part of the purported invention, for example:

Transcriptional activators such as Mxr1 may be normally expressed at low levels. Therefore, it is desirable to place the exogenous nucleic acid (i.e., the transcriptional activator) under control of a promoter that is inducible. As used herein, “operably linked” means that a promoter or other expression element(s) are positioned relative to a nucleic acid coding sequence in such a way as to direct or regulate expression of the nucleic acid (e.g., in-frame).

Ex. B11, '492 patent 4:44-52.

74. The Expression System Patents refer to both “promoters” and “promoter elements *therefrom*.” The patents state that certain promoters are known in the art and can be accessed via the GenBank database.

There are a number of inducible promoters that can be used when genetically engineering methylotrophic yeast. For example, a methanol-inducible ***promoter, or a promoter element therefrom***, can be used. Methanol inducible ***promoters are known in the art***. For example, a commonly used methanol-inducible ***promoter*** from *P. pastoris* is the promoter, ***or a portion thereof***, from the alcohol oxidase 1 (AOX1) gene, which is strongly transcribed in response to methanol. Other methanol-inducible promoters, or promoter elements therefrom, however, can be used, including, without limitation, the alcohol oxidase (AOD1) ***promoter*** from *Candida boidinii* (see, for example, GenBank Accession No. YSAAOD1A), the alcohol oxidase (MOX) ***promoter*** from *Hansenula polymorpha* (see, for example, GenBank Accession No. X02425), the MOD1 or MOD2 ***promoter*** from *Pichia methanolica* ..., the DHAS ***promoter*** from *P. pastoris* (see, for example, GenBank Accession No. FJ752551) or a promoter element therefrom, the formaldehyde dehydrogenase (FLD1) ***promoter*** from *Pichia pastoris* (see, for example, GenBank Accession No. AF066054), or the PEX8 promoter from *P. pastoris* All of these ***promoters*** are known to be induced by methanol.

Ex. B12, '656 patent 4:52-5:11.

75. The Expression System Patents do not define the term “promoter element.” The specification discusses a different term, “expression element” (*e.g.*, Ex. B12, ’656 patent 9:66-10:8):

Expression elements include nucleic acid sequences that direct and regulate expression of nucleic acid coding sequences. One example of an expression element is a promoter sequence. Expression elements also can include introns, enhancer sequences, response elements, or inducible elements that modulate expression of a nucleic acid. Expression elements can be of bacterial, yeast, insect, mammalian, or viral origin, and vectors can contain a combination of elements from different origins.

The patents also provide that expression elements may be “operably linked”: “As used herein, “operably linked” means that a promoter or other expression element(s) are positioned relative to a nucleic acid coding sequence in such a way as to direct or regulate expression of the nucleic acid (*e.g.*, in-frame).” Ex. B12, ’656 patent 4:47-51.

VIII. TECHNICAL BACKGROUND

76. I review below certain principles that support my opinions in this Declaration.

A. Scientific Nomenclature

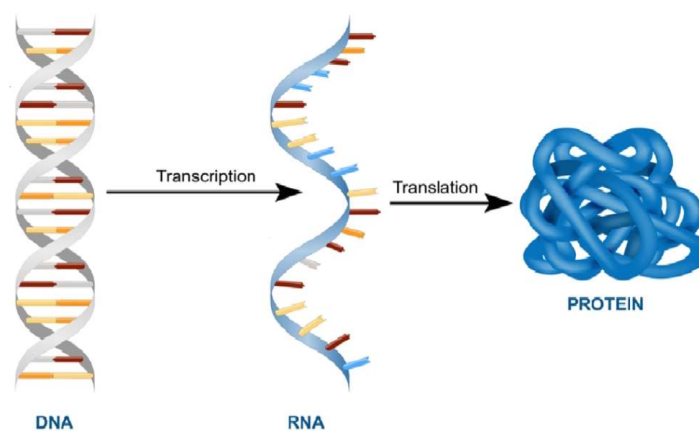
77. POSITAs commonly use what is referred to as binomial nomenclature, or a two-name naming system, to give what is colloquially referred to as a “scientific name” or “Latin name” to living things. There are many levels to the “scientific name” that help to organize all living things. At the top of the taxonomic rank is the term “domain” and at the bottom “species” (and even subspecies). Within any given rank, different organisms are grouped together based upon a number of characteristics. Subsequent discrimination at a lower rank is again a grouping based upon a more narrow set of characteristics. Today genome sequences helps to guide taxonomic classifications. Specific to the ‘scientific name’, the first part of the name identifies the genus, a level of classification that lies below “family” but above species. The second part of the “scientific name” identifies the species. For example, modern humans belong to the genus

Homo and the species *sapiens*. Thus, the “scientific name” for modern humans is *Homo sapiens*. POSITAs often abbreviate the “scientific name” to the first letter of the genus, capitalized, followed by the species, lowercase—all italicized. For example, *Homo sapiens* is commonly abbreviated as *H. sapiens*.

78. The methylotrophic yeast referenced in the preambles of ’492 patent claim 1 and ’656 patent claim 26 belongs to the genus *Pichia*. It should be noted that recently *P. pastoris* has been renamed to *Komagataella pastoris* and in other cases *Komagataella phaffi*, but for my opinion I will refer to it as *P. pastoris*. Those claims also recite a Mxr1 transcriptional activator sequence from *P. pastoris*, which a POSITA would understand is yeast of the genus *Pichia* and the species *pastoris*. There are also other species of *Pichia*.

B. Gene Expression

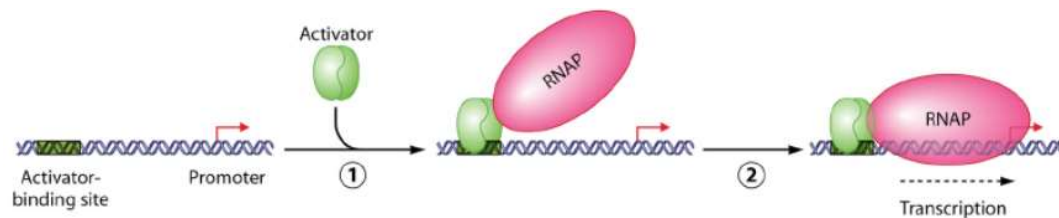
79. Each organism contains a genome, which is the complete set of genetic material for that organism. Chemically, the genome is made of deoxyribonucleic acid, or DNA. DNA sequences are made of four building blocks: “A,” “C,” “T,” and “G.” Information encoded in certain DNA sequences (a “gene”) is converted into messenger RNA (mRNA) through a process called “transcription” or “expression.”



80. As shown in the figure above, proteins are made from the blueprint which is encoded in the respective gene. Genes can exist in the genome of a cell, or can be introduced exogenously into a cell on a nucleic acid vector, among other ways.

81. Whether or not a gene is transcribed to start the protein production process can be controlled by different factors. One such factor is called a “transcriptional activator.” Transcriptional activators are proteins that can turn a gene “on” if it is not being transcribed, or can increase transcription. Some genes require transcriptional activators before any transcription can occur.

82. Transcriptional activators typically bind to DNA near the protein-coding region of a gene, to what POSITAs know as “activator binding sites.” This facilitates the access of part of the cell’s transcription machinery, called an RNA polymerase, to a “promoter.” The promoter is where the polymerase (and possibly additional proteins) binds to start transcription of the gene. This process is illustrated below:



83. In nature, gene expression is primarily controlled by the gene’s promoter. Typically, a promoter is the non-coding region of DNA adjacent to and upstream of the gene. Other sequences which are often not located near the gene, called “enhancer” sequences, can also affect expression.

84. Promoters are often described as constitutive or inducible. Constitutive promoters are “on” regardless of external stimuli (*i.e.*, constitutively active). Inducible promoters can be

made more or less active in response to external stimuli, such as temperature, oxygen, or chemicals.

C. **Methylotrophic Yeast Expression Systems**

85. *Pichia*, including *P. pastoris*, are what POSITAs classify as “methylotrophic” yeast cells. Methylotrophic yeast are able to utilize methanol as a sole source of carbon and energy.

86. Cells are largely composed of compounds that contain carbon. Carbon is essential for most cellular functions. While many organisms require more complex sugars to provide necessary carbon, methylotrophic yeast can utilize methanol, a simple alcohol with the formula $\text{CH}_3\text{-OH}$, as their carbon source.

87. Methylotrophic yeast have several features that make them suitable for producing proteins. Among those features, methylotrophic yeast are fast growing and can be grown in relatively simple growth medium. They can be easily genetically manipulated to produce proteins that are “heterologous” or not native in the yeast cell’s genome.

88. Expressing genes to produce heterologous proteins is often referred to as “recombinant” expression. Recombinant production of proteins commonly involves introducing an exogenous nucleic acid, usually contained in a DNA vector, that contains a gene encoding the protein of interest into a host yeast cell. The host cell’s machinery transcribes the DNA into messenger RNA (“mRNA”), and the mRNA is translated into a polypeptide that is folded into the protein. This process is illustrated above.

89. Recombinant expression systems can be used to (1) introduce more than one copy of the gene encoding the protein of interest, (2) to produce proteins that do not natively occur in the host cell, (3) to produce variants of the protein of interest whose amino acid sequence is non-native, or (4) to produce completely novel proteins that do not exist in nature.

D. **Recombinant Protein Production for Foodstuffs**

90. Over the past several decades, recombinant DNA technology has been used in the food industry in order to make food ingredients or to genetically modify plants and animals (genetically modified organisms, or GMOs) to improve properties such as shelf-life and nutritional value. In a 1993 article titled *Foods of the Future: The New Biotechnology and FDA Regulation*, scientists recognized various potential benefits of GMO technology.

Several years ago, the FDA polled more than 100 American biotechnology experts from industry, government, and academia and identified over 800 discrete developments emerging in food biotechnology. The anticipated innovations included recombinant DNA (gene-splicing)-based diagnostics for food-borne pathogens; crops that are genetically engineered to resist frost, drought, or insect pests; fats and oils with lower calories or enhanced nutritional profiles, such as rapeseed that is manipulated to yield canola oil with increased levels of unsaturated fatty acids; and new crop varieties that are slightly altered genetically to enhance vegetable quality, such as tomatoes that are engineered to eliminate an enzyme that makes them mushy or rotten, or strawberries with enhanced levels of ellagic acid, an anticarcinogen.

Ex. B13 (Miller), 911.

91. Various GMOs have been manufactured over the years. Some organisms are designed for consumption. One famous example is the “FLAVR SAVR” tomato, which was designed to reduce the enzymes that naturally cause the tomatoes to soften. Crops such as rice have been modified to be fortified with iron.

92. Other GMOs have been designed to express proteins. Certain microbial gene expression systems have become particularly popular. *Escherichia coli* (*E. coli*) was an early favorite and is still used for many applications. In my research during the 1980s and 1990s, my laboratory used *E. coli* to produce a whey protein that could be used for human consumption.

93. By the early 2000s, the yeast *Pichia pastoris* was recognized as one of the most commonly used yeast species in the production of recombinant proteins. The FDA has approved recombinant proteins expressed by *P. pastoris* as safe for use in humans and animals.

IX. **A POSITA WOULD UNDERSTAND “ANIMAL” PROTEINS HAVE ANIMAL GENETIC IDENTITY**

A. **The Ordinary Meaning of “Animal” or “Non-Animal” Protein Relates to the Protein’s Genetic Identity (Sequence)**

94. In my opinion, a POSITA would understand that when “animal” is used as an adjective to modify a protein, this usage means that the protein is encoded in an animal genome. An “animal” protein has the same sequence as a protein found in an animal, regardless of where the protein is synthesized. Conversely, when the adjective “non-animal” modifies a protein, this usage means that the protein is encoded in the genome of a species that is not an animal, such as a plant species.

1. ***Animal Protein Sequence Alone Defines Its “Animal” Identity***

95. The adjectives “animal” and “non-animal” are relatively simple. As shown in the exemplary dictionary definition below, “animal” broadly means “of, relating to, or characteristic of animals.”

► **adj.** [attrib.] of, relating to, or characteristic of animals: *the evolution of animal life* | *animal welfare*.
 ■ of animals as distinct from plants: *tissues of animal and vegetable protein*. ■ characteristic of the physical and instinctive needs of animals; of the flesh rather than the spirit or intellect: *a crude surrender to animal lust*.
 – **ORIGIN** Middle English: as a noun from Latin *animal*, based on Latin *animalis* ‘having breath,’ from *anima* ‘breath’; as an adjective via Old French, from Latin *animalis*.

Ex. B14, (Oxford Am. Dictionary), 62.

96. This broad meaning of “animal” is consistent with the genetic identity of animal proteins because an animal protein’s sequence defines that protein as an animal protein. A protein’s sequence confers its identity regardless of where the protein is made.

97. As a specific example, the bovine myoglobin protein is encoded in the genome of a domestic cow and is ordinarily expressed in the cow. With recombinant technology, bovine

myoglobin can be produced elsewhere. But regardless of its source—yeast cells, plant cells, bacterial cells—the bovine myoglobin protein has the same amino acid sequence as the protein that is produced in cow muscle tissues. This sequence fundamentally identifies the protein as bovine myoglobin.

98. Using a protein's amino acid sequence, a POSITA could ascertain the protein's species of origin. One widely-used tool that could be used for this purpose is the National Cancer and Biotechnology Institute's BLAST database. A scientist can enter a protein sequence into the BLAST database and obtain a probability score reflecting the species in which the protein is naturally encoded. For example, entering bovine myoglobin's amino acid sequence in BLAST will confirm that the protein is bovine myoglobin.

99. Moreover, to communicate meaningfully, scientists and POSITAs use language clearly indicating the source of the protein when the source is not the usual source. The issue has been complicated because of genetic engineering. Before the advent of recombinant technology, proteins were extracted from a given organism, the protein encoded by the native gene within that organism. With genetic engineering, that is no longer the case. As a matter of common sense, there is a need to describe the origin of the protein of interest, and, separately, how it is made. Otherwise no one would be able to distinguish a specific protein from its source. In this scenario, for example, if bovine myoglobin were expressed in *Pichia*, it might be called a *Pichia* protein.

100. This is not how such proteins are described. Doing so would create ambiguities and uncertainties in communication. Indeed, for regulatory purposes, the protein's origin would dictate that it be called bovine myoglobin. For example, Impossible labels its leghemoglobin as 'soy leghemoglobin' even though this protein is produced in *Pichia*.

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Cook to taste. Fully cooked when interior is 160°F.

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Nutrition Facts		Amount/serving	%DV	Amount/serving	%DV
3 servings per container	Total Fat	14g	18%	Total Carb.	9g 3%
	Saturated Fat	8g	40%	Dietary Fiber	3g 11%
	Trans Fat	0g		Total Sugars	<1g
Serving size 4oz. (113g)	Cholesterol	0mg	0%	Incl. <1g Added Sugars	1%
	Sodium	370mg	16%	Protein	19g 31%
Calories per serving 240	Vitamin D 0mcg 0% • Calcium 170mg 15% • Iron 4.2mg 25%				
	Potassium 610mg 15% • Thiamin 2350% • Riboflavin 15%				
	Niacin 50% • Vitamin B6 20% • Folate 30%				
	Vitamin B12 130% • Phosphorus 15% • Zinc 50%				

INGREDIENTS: WATER, SOY PROTEIN CONCENTRATE, COCONUT OIL, SUNFLOWER OIL, NATURAL FLAVORS, 2% OR LESS OF: POTATO PROTEIN, METHYLCELLULOSE, YEAST EXTRACT, CULTURED DEXTROSE, FOOD STARCH MODIFIED, SOY LEGHEMOGLOBIN, SALT, SOY PROTEIN ISOLATE, MIXED TOCOPHEROLS (VITAMIN E), ZINC GLUCONATE, THIAMINE HYDROCHLORIDE (VITAMIN B1), SODIUM ASCORBATE (VITAMIN C), NIACIN, PYRIDOXINE HYDROCHLORIDE (VITAMIN B6), RIBOFLAVIN (VITAMIN B2), VITAMIN B12

CONTAINS: SOY GLUTEN FREE

Manufactured by: Impossible Foods Inc. 400 Saguero Dr Redwood City, CA 94063 Hello@ImpossibleFoods.com
 KEEP REFRIGERATED. IF PURCHASED FROZEN, THAW IN REFRIGERATOR AND USE SEALED WITHIN 10 DAYS. 20-0004183

8 16697 02100 2

MADE WITH RECOMBINANT MEAT

HALAL KOSHER PAREVE

INGREDIENTS: WATER, SOY PROTEIN CONCENTRATE, COCONUT OIL, SUNFLOWER OIL, NATURAL FLAVORS, 2% OR LESS OF: POTATO PROTEIN, METHYLCELLULOSE, YEAST EXTRACT, CULTURED DEXTROSE, FOOD STARCH MODIFIED, SOY LEGHEMOGLOBIN, SALT, SOY PROTEIN ISOLATE, MIXED TOCOPHEROLS (VITAMIN E), ZINC GLUCONATE, THIAMINE HYDROCHLORIDE (VITAMIN B1), SODIUM ASCORBATE (VITAMIN C), NIACIN, PYRIDOXINE HYDROCHLORIDE (VITAMIN B6), RIBOFLAVIN (VITAMIN B2), VITAMIN B12

CONTAINS: SOY GLUTEN FREE

101. The rationale for preserving the origins of the protein to its native host are in part regulatory. As stated the FDA regulates food ingredients by assuring they are safe for human consumption. In general a food ingredient that was ‘safe’ when produced in its native host would likely to be deemed safe if it was produced in an approved recombinant host. On the other hand a food ingredient that was **not** safe when it was extracted from its native host, could never be ‘safe’ if it was produced in a ‘safe’ recombinant host.

102. From my review of relevant literature, I see that when the adjectives “animal,” “plant” and the like modify “protein,” they indicate the protein’s genetic identity (encoded by the native host’s genome). In contrast, when the writer intends to identify the protein’s source, the source is separately and clearly identified.

103. For example, in a 2009 article titled *Production of recombinant proteins by microbes and higher organisms*, Demain *et al.* note that “[i]n the 1970s, most of the enzymes used were traditionally derived from plant and animal sources,” and, with recombinant technology, “plant and animal enzymes could be made by microbial fermentations.” Ex. B15 (Demain), 298. Similarly, “[m]ammalian chymosin was cloned and produced by *A. niger* or *E. coli*...,” which are microbial expression systems. *Id.*, 298.

104. In discussing FDA approval of recombinant foodstuffs, other scientists observed the distinction between the gene’s identity and the identity of its source:

The question of ***animal genes*** in new crop varieties is somewhat more complex, and we are reviewing the comments on this issue submitted to the FDA. However, it seems clear from a scientific perspective that a single ***non-plant gene***—for example, an ***insect luciferase gene*** as a marker or a ***piscine protein*** introduced to change the plant’s freezing characteristics—introduced into a plant does not alter its fundamental nature.

Ex. B13, (Miller), 912 (emphasis added).

105. In referring to an “animal” protein, therefore, a POSITA would understand that the protein has a sequence encoded in the animal’s genome (*e.g.*, the protein’s amino acid sequence). If a POSITA intended to indicate that the protein is obtained from a host that does not produce the protein natively, the POSITA would refer to the source explicitly. This distinction is consistent with common parlance and necessary to communicate successfully and precisely. Impossible Food’s product ingredient label has “soy leghemoglobin” to indicate the ingredient originally came from soy while it is now produced in a recombinant yeast strain.

106. Precise usage of this terminology is also important for practical and safety considerations. A POSITA would be aware of such concerns in obtaining FDA approval for foods containing recombinant products, as I discuss below.

2. ***Recombinant Animal Proteins Are Commercially Approved Based on their Identity to Animal Sourced Proteins***

107. Recombinant proteins have been used as food and food ingredients for several decades. As the Food and Drug Administration (FDA) is charged with regulating the safety of food ingredients and some foods, a POSITA would be aware of regulatory considerations relating to use of these proteins in human foods.

108. As an example, the first recombinant protein approved by the FDA for use as a food ingredient was the chymosin or rennet and originally isolated from the calf stomach. Chymosin is used to make cheese and other dairy products. Traditionally, chymosin was sourced from cow stomach tissue. As this process was difficult and dependent on availability of calves, in the mid-1980s researchers expressed chymosin recombinantly in microorganisms. As examples, I excerpt several portions of an review article below.

The U.S. Food and Drug Administration (FDA) has accumulated substantial experience with biopharmaceuticals, and now it has some with engineered food ingredients as well: it formally approved the first food ingredient made via recombinant DNA technology just over a year ago (55 Fed. Reg. 10932, March 23, 1990). The product is a chymosin enzyme (rennin) preparation derived from *Escherichia coli* K-12 carrying the bovine prochymosin gene.

Ex. B16 (Flamm), 349. As shown above, Flamm distinguishes the identity of the gene (bovine prochymosin) from the host in which it is made (*E. coli* K-12 strain).

109. As noted in Flamm below, the FDA determined that chymosin produced in microorganisms (*E. coli*) was “the same” as chymosin extracted in animal tissues (rennet). Thus, the FDA approved recombinant chymosin based on its identity.

FDA has received three petitions for chymosin derived from microorganisms, starting in 1987. The first (GRASP 8G0337) requested GRAS [Generally Recognized As Safe] affirmation for a chymosin preparation derived from *Escherichia coli* K-12. After reviewing information in the petition and in the published literature, FDA concluded that ***the principal active component of the chymosin preparation is the same as that of rennet***, and that the impurities of the chymosin preparation, which differ from the impurities of rennet, do not render the

substance unsafe for its intended use. FDA therefore affirmed this preparation as GRAS for use as a replacement for rennet.

Ex. B16 (Flamm), 349 (emphasis added).

One FDA concern was to determine whether the cloned chymosin is identical to the chymosin in rennet. The petitioners provided published scientific data documenting that the prochymosin gene had been cloned and that it is properly expressed in its microbial hosts to make functional chymosin. The petitioners used three lines of evidence to show that the correct gene had been cloned. The cloned DNA was digested with restriction enzymes and the resulting fragments were found to be the sizes predicted by the DNA sequence of the prochymosin gene. The cloned DNA, and RNA synthesized from it, hybridized appropriately with the calf prochymosin gene. Finally, the sequence of the cloned DNA corresponded to the amino acid sequence of the prochymosin protein. The cloned prochymosin gene produced chymosin of the expected size and biological activity. Cloned chymosin has the same molecular weight as chymosin derived from calf rennet ... Cloned chymosin also has the same functional activity as chymosin derived from calf rennet

Ex. B16 (Flamm), 349 (emphasis added) (footnotes omitted).

After a comprehensive review of the information in the published literature, FDA concluded that the calf chymosin gene cloned into *E. coli* K-12 is expressed, that ***the gene product is chemically and biologically indistinguishable from calf chymosin***, and that the impurities in the microbial chymosin preparation do not make the preparation unsafe. As for any food ingredient that is new or made by a new method, FDA reviewed the manufacturing method to determine product purity and identity. From its review of this chymosin preparation and other new biotechnology-derived food ingredients, the Food and Drug Administration [sic] is finding that the review of the safety, purity, and ***identity of these products is fundamentally no different from that of analogous products derived from unmodified or traditionally modified organisms.***

Ex. B16 (Flamm), 351.

110. The story of chymosin approval is representative. It is my understanding that, even in the present day, the FDA continues to approve recombinant proteins today based on the proteins' identity to the protein from the original source.

3. ***A POSITA Would Distinguish Protein Identity from Protein Source For Safety Reasons***

111. POSITA would also be aware of potential safety considerations associated with proteins, including recombinant proteins. Proteins which are allergens (*e.g.*, they cause an allergenic response in humans) are regulated as allergens regardless of the production host.

112. By the early 1990s, the FDA was aware of concerns relating to allergens. As shown below, these concerns relate to the identity of the recombinant molecule—*e.g.*, animal genes in a plant, or gluten (a well-known allergen) in a plant where it does not normally exist.

Labeling.—The FDA’s labeling policy for foods from new plant varieties has stirred controversy. A common objection is, ***Why shouldn’t consumers be informed that their food is genetically engineered, especially when new tomatoes might contain animal genes?*** The FDA’s general position is that the information on labels must be accurate but also material, a criterion that in the agency’s view does not apply to plant-breeding techniques. Such information not only provides no useful insights into the composition or properties of the food, but would also be impractical. For example, wheat varieties developed with different techniques would have to be segregated during production, storage, distribution, and processing. Moreover, the difficulties would be magnified as varieties developed with different techniques were crossed in breeding programs. The FDA’s policy, however, does call for labeling to identify significant changes in composition, safety, or usage. For example, ***if wheat gluten were introduced into potatoes, labeling would be required to inform consumers with celiac sprue, who are sensitive to gluten.***

Ex. B13 (Miller), 912 (emphasis added).

Allergenicity.—The question of possible allergenicity, long a concern both to plant breeders and to the FDA, has been misrepresented. Many foods elicit an allergic response in some individuals, including milk, eggs, fish, crustacea, mollusks, nuts, wheat, and legumes. ***Since all known food allergens are proteins, the transfer of proteins from one food source to another could therefore confer allergenic properties from the donor plant.*** This is true of the “old biotech” wide crosses and hybridizations; likewise, it is true for the newer techniques.

Ex. B13 (Miller), 912 (emphasis added).

113. It is clear that the FDA recognized that the wheat gluten protein is an allergen regardless of the host and that the product label should contain a warning about the presence of

this allergen. A POSITA would be aware of these concerns and the related importance of identifying a protein based on its native source and not its recombinant host.

114. A POSITA would also be aware of different safety concerns from the host used to produce the food ingredient and that is part of the evaluation process used by the FDA. In describing those concerns, however, the POSITA would refer to the source.

* * * * *

115. Collectively, the principles above make clear that animal origin of a gene encoding for a protein of interest does not change simply because the protein is recombinantly produced in a non-animal host. Nor would a POSITA identify a recombinant protein in terms of its production host.

B. The Foodstuff Patents' Intrinsic Record Is Consistent with the Ordinary Meaning of Non-Animal Protein

116. From my review of the Foodstuff Patent specifications summarized above (Section VI.C), I see that the applicant referred to proteins in terms of their identity, such as animal or plant. In some parts of the disclosure, the patents identify specific proteins by their genetic sequence.

117. In other parts of the disclosure, the patents identify methods in which proteins are made. The patents teach that proteins can be manufactured in certain types of sources, such as genetically engineered cells. They disclose that proteins can be isolated or extracted from these sources.

118. The Foodstuff Patents therefore distinguish two different concepts: a protein's identity on the one hand, and the source or host used for its production on the other. This is consistent with my observations above. Thus, for reasons I explain above, it is my opinion that a POSITA would understand "animal protein" to refer to the animal identity of the protein (*i.e.*, having the same sequence as a protein encoded in an animal genome). A POSITA would not

understand “animal protein” to mean “animal-sourced protein” unless explicitly stated that an animal was the source from which the protein was extracted. Conversely, a POSITA would understand that “non-animal” proteins are simply proteins encoded for by genes that originated from non-animal organisms (hosts).

119. I am not aware of another basis in the Foodstuff Patents to read “animal” and “non-animal” in a way that is different from how a POSITA would normally understand them. In particular, I am not aware of any reason to define these proteins in terms of their source. From my review of the Foodstuff Patents, for example, they do not teach that the use of non-animal-sourced proteins or products is essential or even important to the methods and techniques disclosed in the patent. In fact, as I explain above, the patents describe using animal-sourced materials in foodstuff compositions—and in large quantities. Thus, the patents do not show or suggest that the patentee viewed its invention as requiring the use of non-animal sources.

120. I further understand that, during prosecution of the ’306 patent, the Examiner amended the pending independent claims of the ’306 patent to recite “non-animal” heme-containing protein and, at the same time, to delete “myoglobin” from certain dependent claims. These amendments are consistent with each other because the independent claims exclude animal heme-containing protein, and myoglobin is well known to be an animal muscle protein encoded in an animal’s genome.¹

121. Moreover, as I explain above (Section VI.C), during prosecution of the Foodstuff Patent families, Impossible crafted certain claims to recite the specific source of the proteins. Impossible therefore knew how to define its invention in terms of source.

¹ Ex. B17, Ordway & Garry, *Myoglobin: an essential hemoprotein in striated muscle*, 207 J. Exp. Bio. 3441 (2004).

122. Consistent with my observations above, the Foodstuff Patents do not teach that changing an “animal” protein’s source of manufacture changes its animal identity to “non-animal.” For example, the patents do not disclose that “mammalian myoglobin” becomes a “fungal” protein when expressed recombinantly in yeast. A POSITA would not have that understanding either. For reasons I explain above, a POSITA would be aware of concerns regarding shellfish, egg, peanut, or other allergens. A consumer with a specific allergy would develop an allergic response if they consumed a plant-based product containing that allergen (protein) regardless of the host used to produce that allergen. Thus, a POSITA would be careful to identify proteins based on their identity, and not their source.

123. I understand that some claims recite animal “products.” I see from the specification that animal “products” is defined to include “animal proteins.” Thus, “animal proteins” are a subset of “animal products.” A POSITA would understand that “products” is a broader term than “proteins” and could include, for example, products that are made from animals such as butter, milk, and cheese. Ex. B3, ’306 patent 33:37-39. The use of the term “products” does not change my view regarding the meaning of the adjective “animal,” however. “Animal” refers to identity, which encompasses materials that are identical to animal-sourced counterparts or are directly sourced from animals. The Foodstuff Patents do not teach that the use of the term “products” changes “animal’s” ordinary meaning.

X. THE MXR1 TERMS REFER TO NATIVE MXR1

A. A POSITA Would Understand The Terms To Refer To Native, Not Variant, Mxr1

124. In my opinion, Motif’s construction reflects a POSITA’s understanding, as underscored in the patents’ specifications, distinguishing between native (wild-type) Mxr1 proteins and engineered or mutant variants of it. The specification explains that “*P. pastoris*

contains an endogenous nucleic acid encoding a Mxr1 transcriptional activator.” Ex. B12, ’656 patent 4:18-19. A POSITA would understand this endogenous nucleic acid is native to *P. pastoris*. In addition, Example 16 is titled “Construction of Native Mxr1 Expression Vector” and describes construction of “[a] plasmid containing the Mxr1 transcription regulator gene under the control of the pAOX1 promoter.” *Id.*, 26:13-47. A POSITA would understand that this, too, describes a Mxr1 transcriptional activator sequence that is native to *P. pastoris*. In contrast, Example 18 describes a “variant Mxr1,” distinguishing it from a native Mxr1 because it has additional sequence that is not found in native Mxr1, and therefore is distinct from the native Mxr1. *Id.*, 27:5-32; Ex. 23 (SEQ ID NO:1).

125. In my opinion, a POSITA would understand that the sequence encoding the native *P. pastoris* Mxr1 transcriptional activator is the Mxr1 sequence that is has been reported in *P. pastoris*. As set forth above, native Mxr1 sequences can be endogenous, meaning they originate within the host cell, or exogenous, meaning they originate outside the host cell but are introduced into the host cell. Non-native Mxr1 variants also can be exogenously introduced into the host cell.

126. I note that no opinions in Dr. Alper’s June 14, 2023 declaration dispute the opinions I offer in this section.

B. A POSITA Would Understand The Term “From *P. Pastoris*” To Refer To Mxr1 Native To *P. Pastoris*, Not Some Other *Pichia* Genus

127. In my opinion, Motif’s construction aligns with the claim language, which requires that the claimed Mxr1 sequence is “from” *P. pastoris*. That is the only way a POSITA would understand this limitation. In my opinion, Impossible’s argument that the claim preamble extends the term Mxr1 to any *Pichia* species conflates the *Pichia* host cell of the preamble with the Mxr1 transcriptional activator. A POSITA would understand that the Mxr1 transcriptional activator is a

separate claim element that is part of the expression system in the host cell but not required to be from the particular host.

128. It is my further opinion that the disclosure of the specification that Impossible and Dr. Alper (at paragraphs 58, 60) rely on 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.

That passage states:

Similar to the exogenous nucleic acid encoding the transcriptional activator, a heterologous nucleic acid refers to any nucleic acid sequence that is not native to the genome or in the genome of an organism (e.g., a heterologous 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).

Ex. B12, '656 patent 5:31-37.

129. In my opinion, Impossible and Dr. Alper's construction contradicts the claim language and specification and does not reflect how a POSITA would understand this term. Dr. Alper's opinions, at paragraphs 57-60, seem to conflate the claims' recitation of a host cell of the genus *Pichia*, which include other species in addition to *pastoris*, with the Mxr1 transcriptional activator sequence, which the claims say must be of the species *P. pastoris*. I disagree that a POSITA would understand that because the host cell may be any *Pichia* species, the Mxr1 transcriptional activator "from *P. pastoris*" does not actually have to be from *P. pastoris*. Such an interpretation renders the claim meaningless and is at odds with the patent disclosure I cite in the preceding paragraph. Moreover, if the recited Mxr1 is not native, in other words if it is a variant or mutant Mxr1, then it is not "from *P. pastoris*" but rather is something that was human-engineered likely using another host such as *E. coli*.

C. A POSITA Would Understand That A Mxr1 Sequence Is The Sequence That Encodes Mxr1, Not The Activator Binding Site

130. In my opinion, a POSITA would understand that the language of '492 patent claim 1 refers to the Mxr1 “*sequence*,” not its “binding site,” which Impossible and Dr. Alper’s construction proposes. I note that other Impossible claims make this distinction clear. For example, claim 26 of the '656 patent, *e.g.*, distinguishes between a “Mxr1 sequence,” which encodes Mxr1, and a Mxr1 binding site, to which Mxr1 binds. Specifically, the claim reads:

26. A methylotrophic *Pichia* yeast cell comprising a recombinant nucleic acid molecule, wherein the recombinant nucleic acid molecule comprises:

a nucleic acid encoding a Mxr1 transcriptional activator sequence from *P. pastoris*;

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.

A POSITA 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.

131. The specification also repeatedly describes a “Mxr1 nucleic acid sequence” that encodes Mxr1—not the binding site for Mxr1. For example:

This disclosure describes the use of *P. pastoris* strains that overexpress the transcriptional activator, Mxr1, from the AOX1 promoter to increase expression of transgenes that also are expressed from the AOX1 promoter, which significantly improves the recombinant production of one or more proteins. In addition, expression of Mxr1 from the AOX1 promoter creates a positive feedback loop that allows for expression of other transgenes from the AOX1 promoter in the absence of methanol, the normally obligate inducer, when repressing carbon sources are depleted. Expression of Mxr1 results in a significant increase in the amount of protein produced.

Ex. B11, '492 patent 1:37-48.

132. I disagree with Dr. Alper's opinion, in paragraphs 53 and 56 of his declaration, that "Mxr1 transcriptional activator sequence" is the sequence to which Mxr1 binds in the context of the claims. Rather, a POSITA would understand that the Mxr1 transcriptional activator sequence is the sequence that encodes Mxr1. This is consistent with other claims, as explained in the preceding paragraph, and the repeated disclosure of the specification describing positive feedback loops, as I describe in section VII.C of my declaration.

133. I disagree with Dr. Alper's opinion in paragraph 54 that the patents only "use the phrase 'a nucleic acid molecule encoding a Mxr1 transcriptional activator' when defining the sequence of Mxr1." Even Dr. Alper's opinion itself reflects the fact that "the sequence of Mxr1" is the sequence that encodes it. Moreover as explained in the preceding paragraphs a POSITA would understand "Mxr1 transcriptional activator sequence" to be the sequence that encodes Mxr1, not the sequence to which it binds, which Impossible claims using very different terminology.

134. I further disagree with Dr. Alper's reading of '492 patent claim 14, in paragraph 55 of his declaration. There, Dr. Alper contends that Motif's construction would render "a nucleic acid molecule encoding a Mxr1 transcriptional activator" duplicative. But, in fact, a POSITA 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—one native to *P. pastoris* and another that may be of a different origin. The claim states:

14. The yeast cell of claim 1, further comprising a nucleic acid molecule encoding a Mxr1 transcriptional activator operably linked to a promoter element from *P. pastoris* and a Mxr1 transcriptional activator sequence from *P. pastoris*.

XI. "PROMOTER ELEMENT" IS INDEFINITE

A. The Term "Promoter Element" Is Indefinite

135. In my opinion, a POSITA for the Expression System Patents would not be reasonably certain of the meaning of “promoter element” as that term is used in the patents’ claims and specification. As explained in more detail below, “element” commonly refers to a component of any larger structure. “Element” does not imply a particular size, structure, or function for the component. With respect to the term “promoter,” POSITAs give term “element” its common, generic meaning even in technical literature—*i.e.*, without reference to any specific part of the promoter or function thereof. An “element” of a promoter is therefore subjective and identified as such based on empirical experimental results or the interests of the scientist. Any function ascribed to a particular nucleic acid sequence cannot be computationally validated and must be experimentally tested because of the context of the surrounding sequences. Consequently, an “promoter element” within a particular promoter lacks definition because its function is dependent upon its context with respect to the neighboring sequences. A “promoter element” may act as an activator of transcription, *e.g.*, but this activity depends on the “promoter element’s” context within the other sequences that are required for transcription. Stripped of those other sequences, the “promoter element” would not function as an activator. Therefore, the term “promoter element” is subjective and has no consistent, well-known meaning in the art. I note that, consistent with my opinions, Dr. Alper does not even attempt to establish that “promoter element” has a consistent or well understood meaning in the art.

136. Furthermore, from my review of the Expression System Patents and intrinsic record, the patents do not provide a meaning to this term beyond its generic meaning. Rather, the patents describe other features of the technology—some of which may or may not relate to a “promoter element.” They do not describe any structural or functional boundaries for a “promoter element” or even an “element” of a promoter. As a result, a POSITA would not be reasonably

certain of whether any particular nucleic acid sequence practices the “promoter element” term. Accordingly, the claim term “promoter element” is indefinite.²

137. I list below several considerations that support my opinion.

4. ***“Element” Is A Generic Term for Component and Does Not Imply Structure or Function***

138. I see that the word “element” has many possible meanings, as exemplified in the dictionary definition reproduced below. For example, the first definition states that an “element” is “a part or aspect of something abstract, esp. one that is essential or characteristic.” This broad definition does not impose structural or functional limits on the “something” of which it is “a part or aspect.”

el-e-ment /'eləmənt/ ► **n.** 1 a part or aspect of something abstract, esp. one that is essential or characteristic: *the death had all the elements of a great tabloid story* | *there are four elements to the proposal.* ■ a small but significant presence of a feeling or abstract quality: *it was the element of danger he loved in flying.* ■ **(elements)** the rudiments of a branch of knowledge: *legal training may include the elements of economics and political science.* ■ [usu. with modifier] **(often elements)** a group of people of a particular kind within a larger group or organization: *extreme right-wing elements in the army.* ■ **Mathematics & Logic** an entity that is a single member of a set.

Ex. B18 (Oxford Am. Dictionary), 561.

² In *inter partes* reviews of the '492 and '656 patents, I discussed the teachings of the art with respect to the patents' claims. In doing so, I necessarily used the claim term “promoter element” to identify corresponding disclosures in the art. My statements in these proceedings are not contrary to my opinions in this Declaration as my opinions in those proceedings refer to prior art promoters, some component of which can be generically referred to as an “element.” As I explain in this Declaration, it is also possible to identify “elements” of a promoter with some role in the promoter's activity. But “promoter element” itself does not have a common, well-understood, or consistent meaning in the art.

139. Following the common use of “element”, therefore, a “promoter element” is some “part or aspect” of a promoter. But the addition of the word “element” itself does not imply any particular structure or functional component of the promoter. In discussing promoters and “promoter elements,” for example, the patents refer generically to “a portion thereof” of the familiar AOX1 promoter. Ex. B12, ’656 patent 4:56-60.

140. In fact, as I explain below, the function of different parts of the promoter depends not only on any particular part, but on their structural relationship with each other within the context of the full promoter. Changing even one or two nucleotides within the context of a promoter (that can be thousands of nucleotides in length) can significantly affect the promoter’s activity. Removing any part from the promoter and putting it in a different context will likely result in a loss of function.

5. *A “Promoter Element” Is Not the Same As a Promoter*

141. The term “promoter” is familiar to a POSITA, as I explain in this Declaration. As explained above, at its most basic structural level, a promoter is a DNA sequence composed of the familiar DNA building blocks (nucleotides) “A,” “C,” “T,” and “G.” Promoters are typically hundreds or thousands of nucleotides (sometimes called “base pairs” or simply “bp”) in length. Promoters are so defined because they direct gene expression, as I explain above. A promoter for a gene of interest is typically identified through systematic study of the region of the genome adjacent to the gene using both computational and experimental methods. Through such investigation, promoters for many genes have been identified and they are annotated in public databases such as GenBank.

142. A POSITA would understand a promoter “element” to be a “part” of a promoter as I explain above, with the understanding that the “element’s” identity would be clarified through experimental methods.

143. Consistent with a POSITA's general understanding, the Expression System Patents make clear that a "promoter *element*" is something distinct from a promoter itself. Ex. B12, '656 patent 4:52-5:11 (reciting promoters "*or* a promoter *element therefrom*"); 6:28-51 (similar); 6:57-61 (similar). The plain language of the patents alone is sufficient to clarify that a "promoter" and a "promoter element" do not have the same meaning. As a matter of linguistics, a POSITA reading the Expression System Patents' specification would recognize that these terms have a different scope at least because the patent's named inventors are using both the familiar word "promoter" and, separately, the different term "promoter element[s] therefrom."

144. But the Expression System Patents' specification does not describe the boundaries of a "promoter element" or any required characteristics thereof. From my review of the specifications, the patents do not contain an express definition of a "promoter element." As explained further below, the patents do not identify any features that define the term "promoter element" with respect to function, size, composition, or any other feature that would permit a POSITA to identify a "promoter element" within any promoter either as part of a native gene or an artificial construct.

145. Dr. Alper's proposed definition of "promoter element" is premised on a misreading of the specification, fails to establish that a POSITA would be reasonably certain of the scope of "promoter element" either based on the specification or the technical literature, and is incorrect as I explain further below.

6. *A "Promoter Element" Is Not the Same As a Binding Site*

146. A POSITA reading the Expression System Patents would understand that a transcription factor binding site is not a required feature of a "promoter element." Likewise, Dr. Alper does not opine that a transcription factor binding site is a required feature for this term.

147. **First**, the patents’ specifications do not state that a “promoter element” contains a transcription factor binding site. Nor do they state that a “promoter element” directs and regulates expression. Dr. Alper’s opinion ignores contrary teachings from the patents.

148. One part of the specification concerns “expression element.” This term is not the same as a “promoter element” as I explain below, but it is informative. In particular, the patents state that “[e]xpression elements **include** nucleic acid sequences that direct and regulate expression of nucleic acid coding sequences.” Ex. B12, ’656 patent 9:66-10:2. The patents therefore do not **require** an expression element to have this activity.

149. Additionally, the patents provide that “expression elements” can include sequences such as “introns,” which may affect gene expression without functioning as a binding site for a transcription factor.³

150. **Second**, the claims do not require a “promoter element” to include a binding site. Claim 1 of the ’656 patent recites “at least one methanol-inducible promoter element comprising a sequence to which the Mxr1 transcriptional activator binds.” Independent claim 26 of the ’656 patent similarly recites that “the methanol-inducible promoter element comprises at least one sequence to which a Mxr1 transcriptional activator binds.” In contrast, independent claim 1 of the ’492 patent recites “a promoter element from *P. pastoris*” without further structural context.

151. The contrast between these two sets of independent claims illustrates that some “promoter elements” **may** include a binding site—e.g., a binding site for the Mxr1 transcription factor—and some may not. Regardless, a binding site is not a required feature of a “promoter

³ For example, introns’ role is reviewed in Shaul, *How introns enhance gene expression*, 91 Int’l J. Cell Biochem. & Cell Biol. 145-55 (2017) (Ex. B19). Shaul explains that “[i]n many eukaryotes, including mammals, plants, yeast, and insects, **introns can increase gene expression without functioning as a binding site for transcription factors.**” *Id.*, Abstract (emphasis added).

element” as reflected in the ’492 patent claims. At most, a binding site may be a component of a “promoter element,” but it is not a defining characteristic.

152. Relatedly, a “promoter element” is not co-extensive with a binding site. As a matter of language, the terms “promoter element” and “sequence to which a Mxr1 transcriptional activator binds” (a Mxr1 binding site) are different. Therefore, by implication, the “promoter element” of the ’656 patent claims has a broader meaning than just a Mxr1 binding site, and a Mxr1 binding site is merely one feature of the ’656 patent claims’ “promoter element.”

153. **Third**, a POSITA would understand from the claims that a “promoter element” does not have any particular function. For example, dependent claim 5 from the ’492 patent recites that “the promoter element from *P. pastoris* is a constitutive promoter element from *P. pastoris* or a methanol-inducible promoter element from *P. pastoris*.” This distinction is significant because a POSITA would understand that constitutive promoters (which are “always on”) have a different structure (nucleic acid sequence) than methanol-inducible promoters (which are only “on” in certain circumstances, *i.e.*, when methanol is present).

154. A POSITA would therefore understand that any given “promoter element” would not necessarily have the same structural features, or function, as any other “promoter element.” For example, Mxr1 is well-known to induce expression in the presence of methanol. Ex. B20 (Vogl), 387 (identifying Mxr1 as “a positive regulator of methanol inducible genes”).

155. Accordingly, a POSITA would understand that a constitutive “promoter element” would not contain a functional Mxr1 binding site. But this exclusion does not define any “element” of a constitutively active promoter.

7. ***A “Promoter Element” Is Not Defined As Having Unique Structural Features***

156. As I note above, the claimed “promoter element” is indefinite because it is not defined to have structural distinguishing features such that a POSITA would be able to identify a “promoter element.” This problem is particularly troublesome with respect to specific sequences that are not commonly recognized as a component of a promoter. Through scientific efforts a number of “conserved” sequences have been identified, functions assigned to them and verified through experimentation.

157. For example, one portion of the *AOXI* promoter shown in Vogl is the so-called “TATA box.” The name TATA box refers to a short sequence of four nucleotides—“T,” “A,” “T,” and “A”—which, when located at within a promoter, can suggest where gene expression can begin.

158. A TATA box is not unique to a yeast such as *P. pastoris*. Scientists have long known that the TATA box is ubiquitous in most eukaryotes, including mammalian and yeast promoters, and that the TATA box is important for initiating gene transcription. *E.g.*, Ex. B21 (Sचना), 973 (excerpt below) (emphasis added, footnotes omitted); Ex. B22 (Hartner), 4 (referring to a “TATA element”).

The general promoter factors are a set of four proteins known as transcription factors IID, IIA, IIE and IIB. These factors are thought to bind promoters in a stepwise manner 1 and are apparently required for accurate and efficient transcription initiation at all promoters transcribed by polymerase II. ***Transcription studies in vitro have shown, for example, that TFIID binds directly to the promoter element known as the TATA-box*** (fig. 1A). ***The TATA-box, which is found in nearly all eukaryotic promoters***, is located about 30 bp upstream of the transcription start site in mammalian promoters and somewhat further and more variably upstream (40 120 bp) of the start site in yeast promoters.

Thus, the “TATA box” is a functional component of a promoter and even described as a promoter element when it is found within the context of a promoter. Not every TATA sequence functions as a TATA box unless it is located within the context of the other important components of a

promoter. It is not clear from the Expression System Patents, however, whether a TATA box—found in virtually every species—meets the “promoter element” limitation.

159. The ’492 patent claims illustrate the lack of clarity facing a POSITA. Claim 1 is reproduced below, with the “promoter element” terms highlighted:

A methylotrophic *Pichia* yeast cell comprising:
 a nucleic acid molecule encoding a heme-containing protein operably linked to a promoter element from *P. pastoris* and a Mxr1 transcriptional activator sequence from *P. pastoris*; and
 a nucleic acid molecule encoding at least one polypeptide involved in heme biosynthesis operably linked to a promoter element from *P. pastoris* and a Mxr1 transcriptional activator sequence from *P. pastoris*.

As explained above, the promoters of *P. pastoris* genes, as well as the genes of many other eukaryotic species, contain a TATA box. Undisputedly, a TATA box is known to play a functional role when it is positioned within the context of these promoters and, in that context, is involved in the regulation of gene expression.

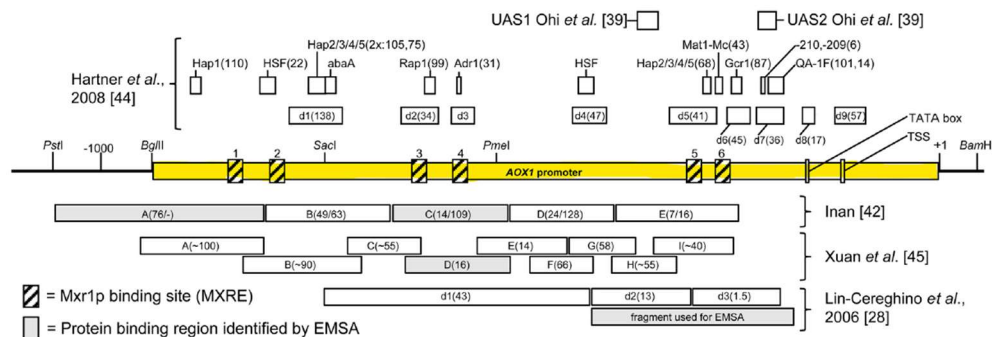
160. A POSITA would not be reasonably certain, however, whether (any) TATA box (which is found in promoters of many diverse species) which might be found or placed in an expression construct practices the “promoter element” term in claim 1 of the ’492 patent, which requires a promoter element “*from*” one particular species, *P. pastoris*. For example, a hypothetical expression construct which has a native or an introduced TATA box could arguably practice the ’492 patent claim, even though that construct does not contain any component originating from a *P. pastoris* promoter (and therefore not originating from another species’ promoter). In that case, a POSITA would not be reasonably certain about what makes the TATA box “*from P. pastoris*” as compared to “from” any other organism.

8. *Scientists Use Different Approaches to Study Promoters*

161. Certain literature uses the terms “element” of a promoter or “promoter element.” This art does not support finding that the Expression System patents’ claim term “promoter

element” has a well-understood or consistent meaning in the art. Scientists approach the study of promoters differently. Accordingly, their findings concerning a “promoter element” must be understood in the context of each study.

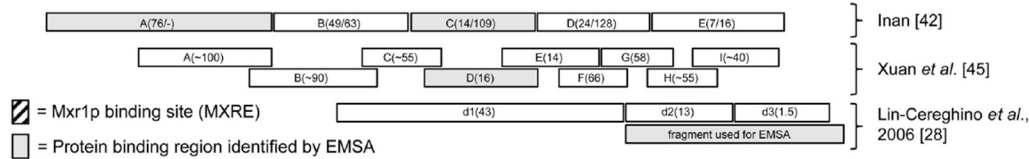
162. To understand why, it is helpful to understand the vast array of methods that are used to identify “promoters” writ large. As an example, I reproduce below a schematic of *Pichia pastoris*’s *AOX1* gene promoter from a 2015 review article by Vogl and Glieder. Vogl and Glieder summarized the work of a number of other studies which employed different techniques to identify different regions of the *AOX1* promoter and ascribe specific functions. The various components of the *AOX1* promoter are shown below.



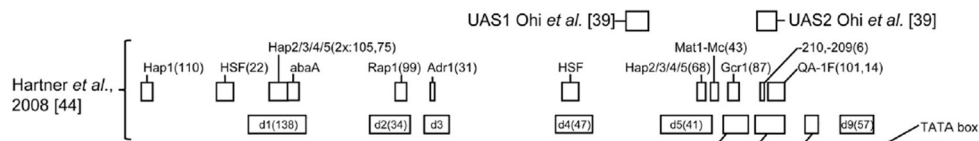
Ex. B20 (Vogl), 387 (Figure 1).⁴

163. Vogl’s schematic and the research it cites illustrates how scientists approach promoter study differently. The Inan, Xuan, and Lin-Cereghino groups each characterized different components of the *AOX1* promoter using different methods, as represented by the different boxes below:

⁴ The schematic above shows various features in the *AOX1* promoter. For readability, the *AOX1* promoter is highlighted in yellow. The promoter contains several sequences within the *AOX1* promoter to which the Mxr1 transcription factor binds, shown as hashed squares. The promoter is located on the “strand ruler,” which shows the relative location of nucleotides.



In the cases of Inan, Xuan, and Lin-Cereghino they carved out specific regions of the AOX1 promoter to experimentally analyze their impact on AOX1 expression. In contrast, the Hartner group ascribed function to regions of the *AOX1* promoter using a computational approach:⁵



164. The differences in approach (experimental vs. computational) are relevant to my opinions because each research group identifies an “element” differently depending on their research methodology.

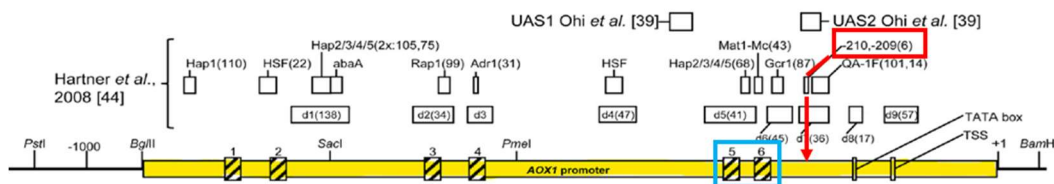
165. The relationship between promoter structure (*e.g.*, sequence and location thereof) and promoter function (*e.g.*, effect on gene expression) is determined empirically. In other words, even if a relationship between structure and function can be predicted through sequence analysis, it can’t be known for sure until an experiment is performed. In the experiment, scientists may modify or delete regions of DNA within the suspected “promoter” in order to establish the portions of that region affect gene expression. From these experiments, that region can be identified as the gene’s promoter. But these studies do not show that an “element” of a promoter can be defined with a consistent meaning. In fact, they show the opposite. I discuss this observation in detail with respect to the Hartner (2008) study below.

9. *Even Minor Changes to a Promoter Can Affect Expression Dramatically*

⁵ The Hartner group’s research illustrates the impossibility of defining a “promoter element” unless the “element” is in used in context. I discuss it further below.

166. Even very minor changes to the nucleotide sequence of a promoter—only a few nucleotides—can affect promoter activity. Certain researchers may therefore refer to those regions containing nucleotides as an “element.” This is shown in the work of Hartner, below. A POSITA would not be reasonably certain of whether a few nucleotides is a “promoter element” within the meaning of the Expression System Patent claims.

167. The Hartner researchers studied how modifications of very short sequences in the *AOX1* promoter resulted in major changes to the promoter’s activity as measured using a ‘reporter’ (GFP) which had a fluorescent read out. They report that “when we deleted (or mutated) nucleotides surrounding position –209 to –210 (numbers are relative to the start of the *AOX1* coding sequence), the promoter activity dropped to ~6–30% of the wild-type activity.” Ex. B22 (Hartner) at 12.⁶



Most remarkably, a deletion of nucleotides –209 and –210 (TA), referred to as d737-38 in Figure 1B (below), within the PAOX1 sequence resulted in a drop of GFP fluorescence to ~6% of wild-type.⁷

Ex. B22 (Hartner), 7. I reproduce Figure 1B from Hartner (2008) below. Figure 1B further illustrates how modifying the *AOX1* promoter can affect the expression of a downstream gene.

⁶ Hartner’s finding is reported in Vogl Fig. 1 below. The location of the modified site within the promoter (yellow) is indicated with a red arrow. This site is not part of, and is in fact some distance away from, the identified Mxr1 binding sites (hashed squares in a blue box).

As I note above, “promoter element” is not defined by the presence of a binding site. This is consistent with Hartner’s showing that modifications to other parts of a promoter can affect function.

⁷ Here, “GFP fluorescence” is a proxy (reporter) for gene expression.



168. The boxes above show how either the deletion or substitutions of just two nucleotides can have a significant effect on promoter activity. The native, wild type (“WT”) promoter sequence is indicated in a blue box, and its activity (100%) is indicated at the right. Three modified promoter sequences are indicated in a red box. Specifically, when two nucleotides (737T,738A) are deleted (“d737-38”) or are altered (“737AT” and “737GC”) the relative activity decreases, 6.0, 5.6 and 29% respectively.

169. Hartner *et al.* comment on the surprising nature of these findings:

While we expected to strongly downregulate the promoter activity upon deletion of the putative TATA box, *we did not expect such a large number of regions where a mutation can decrease promoter activity by >50%*, some of the effects being even more dramatic than in the case of the TATA box deletion. For instance, *when we deleted (or mutated) nucleotides surrounding position –209 to –210, the promoter activity dropped to ~6–30% of the wild-type activity, depending on the mutation* (Figure 1B). In addition, these results are consistent with previous studies where promoter activity dropped with stepwise truncations and which effects observed in the case of larger deletions of the whole AOX1 promoter sequence.

Id., 12 (footnotes omitted, emphasis added). Thus, even a change to *just two nucleotides, –209 and –210*, in the AOX1 promoter sequence affected gene expression significantly.

170. Elsewhere, Hartner paper reports other changes in activity resulting from small changes to the promoter structure.

A promoter library consisting of several AOX1 promoter variants fused to GFP displayed a broad range of activities (from ~6% to >160%) with *small increments* between the individual promoter variants.

Ex. B22 (Hartner), 12.

We identified seven regions within the AOX1 promoter where a deletion of *either small core sequences* of the putative TFBS *or* the deletion of *a larger stretch* covering the whole putative TFBS resulted in a decrease in promoter activity of >50%.

Ex. B22 (Hartner), 12.

171. Hartner refers to these few nucleotides as an “element” of the *AOX1* promoter. For example, Hartner studies five “sequences” to determine their role in promoter function:

[O]ur next goal towards the design of fully synthetic promoter variants was to determine the effect of selected putative cis-acting sequences on the expression of the basal AOX176 region. Based on the results of the deletion libraries as well as the similarity of predicted sites to the matrix of the TFBS, we chose: (i) the 201–214 bp fragment, (ii) the **737 region**, (iii) the STRE element, (iv) the putative binding site for Adr1p, (v) the putative binding site for Gcr1p and (vi) the putative binding site for Mat1- Mc to be inserted upstream of the basal promoters.

Ex. B22 (Hartner), 11. The “737 region” refers to the two-nucleotide deletion (d373-38) discussed above. Hartner concludes that the “verified five cis-acting *elements* within the AOX1 promoter [(i) through (v) above) cause different effects.” *Id.*

172. The results reported in Hartner illustrate how a POSITA would not be reasonably certain of the meaning of a “promoter element.” Hartner discloses that changing just one or two nucleotides in a promoter have functional consequences—these changes reduce gene expression dramatically. Hartner refers to these few nucleotides as an “element.” But the Expression System Patents do not make clear if these two specific nucleotides would be defined as an “element.” Indeed, the patents do not describe the “promoter element” as having any particular size. Accordingly, a POSITA would not be reasonably certain of whether a few nucleotides can constitute the claimed “promoter element.” Moreover a POSTIA would not designate these two

nucleotides (737T,738A) as a promoter element regardless of context; the sequences before or after these two nucleotides.

10. ***Regulation of Expression Depends on Localization of Promoter Structures, Not Just the Structures Themselves***

173. In my experience, portions of a promoter that contribute to function only do so within the context of the promoter as a whole. Excising any particular portion and transplanting it elsewhere in the genome have a predictable outcome when present in a different context.

174. Hartner's research is consistent with my understanding. As shown below, the authors report that their findings may result from changing the relative position of various portions of the promoter.

We introduced deletions into the promoter sequence, which possibly modified positioning of trans-acting factors that work in a concerted fashion to achieve full induction (e.g. facilitating the binding of partner factors or bending of DNA). Thus, ***the observed effects are not necessarily caused by the deletion of a cis-acting element, but may result simply from changes in spacing between authentic elements.***

Ex. B22 (Hartner), 12-13.

Taken together, the above results demonstrate that we closely located a major cis-acting element within the region between -253 and -184 of the AOX1 promoter sequence positioned around -210 and also minor cis-acting elements surrounding the major -210 region. ***Remarkably, the expression effects of the individual deletions are largely dependent on their extension and exact location*** (Figure 1B).

Ex. B22 (Hartner), 8.

175. Hartner et al. also observe the importance of considering promoter function holistically and refer to "authentic" elements as defined by experimental work.

There 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.*** The new promoter variants are especially useful for tailoring a production strategy that is specific to the needs of the individual protein.

Ex. B22 (Hartner), 13.

176. The function of a specific piece of DNA is dependent upon its sequence and the context of that sequence with respect to the surrounding DNA sequences. As Hartner *et al.*'s research shows, combining portions of nucleic acid sequences often leads to surprising and unexpected results. Because function is dependent on context, a sequence that is a functional "element" in one context may not be a functional "element" in another context. Thus, a POSITA would not be reasonably certain of the meaning of "promoter element" taken out of context. A POSITA could not suggest that a sequence of DNA was a "promoter element" without scientific knowledge and experimental validation

177. Relatedly, I see that Dr. Alper cites the "Ma" review. Ma uses "element(s)" multiple times but, in every case, element is modified to allow it to be understood within a specific context. For example Ma describes "insulator elements" that "can prevent 'unwanted' communications between enhancers and promoters ...; [and] an insulator is a DNA element that can block the communication between an enhancer (or a silencer) and a promoter when the insulator is located between them, but not when it is located outside the enhancer-promoter unit" Ex. B23. Accordingly, an "insulator element's" function is dependent and its definition as a "element" upon its position between an enhancer and a promoter. Outside of that context, an insulator element would not be an insulator element and a POSITA could not identify it as such based solely upon its sequence.

11. ***Dr. Alper Fails to Establish that "Promoter Element" Has A Well-Known or Consistent Meaning in the Art***

178. I have reviewed the "Relevant Background" of the technology provided in Section IV.A of the Alper Declaration and the exemplary references he cites therein. Ex. B24. This section does not explain what a "promoter element" means with respect to a promoter. Indeed, Dr. Alper

does not even attempt to establish that the term “promoter element” has a well-known or commonly accepted meaning in the art.

179. In this section, Dr. Alper states that “the transcriptional activator Mxr1 interacts with the alcohol oxidase I (“AOX1”) promoter (“PAOX1”) or promoter element through binding sites known as ‘motifs’ or ‘consensus sequences’ and enhances the rate of transcription of downstream genes.” Ex. B25, Alper Decl. 29 (emphasis added). The *AOX1* promoter is known to contain as many as six Mxr1 binding sites. But, even in this limited context, Dr. Alper does not explain what distinguishes a “promoter element” from a “promoter” or even from a “binding site,” or whether a “promoter element” must have any particular motif or consensus sequence. Accordingly, his analysis of the technical literature does not establish that the term “promoter element” has any consistent meaning in the art whatsoever, much less as the name for any particular structure or component of in a promoter such as the *AOX1* promoter.

B. Dr. Alper’s Purported “Promoter Element” Definition Is Unsupported and Fails to Clarify the Metes and Bounds of the Claimed “Promoter Element”

180. Dr. Alper’s analysis and opinions concerning the definition of term “promoter element” are incorrect for several reasons. I note, consistently with my own review of the Expression System Patents’ specification, that Dr. Alper does not identify an express definition for a “promoter element” in the patents. Rather, he combines pieces of the disclosure in order to reach a definition that ascribes a function to the “promoter element” without clarifying the metes and bounds of what a “promoter element” actually are.

181. *First*, Dr. Alper conflates the “promoter element” term with a different phrase, “expression element.” The patents’ disclosure of “expression element” is reproduced below. Notably, “expression element” is also not a defined term. Rather, the patents state that “[e]xpression elements *include* nucleic acid sequences that direct and regulate expression of

nucleic acid coding sequences.” By implication, therefore, expression elements are *not limited to* sequences that direct and regulate expression.

Expression elements include nucleic acid sequences that direct and regulate expression of nucleic acid coding sequences. One example of an expression element is a *promoter sequence*. Expression elements also can include introns, enhancer sequences, response elements, or inducible elements that modulate expression of a nucleic acid.

Ex. B12, '656 patent 9:51-10:8 (emphasis added).

182. As emphasized above, the patents explain that a “promoter sequence” is an expression element. They do not state that a “promoter element” is an expression element. Even assuming that a “promoter element” could be an “expression element,” the patents do not make clear the definition of a “promoter element”. Following the disclosure of “expression element,” a “promoter element” could *include, but not be limited to*, sequences that direct and regulate expression. As stated above there is therefore no a priori definition of promoter element let alone linkage to any obvious definition of expression element.

183. Indeed, a POSITA would understand that an “expression element” refers to a broader set of features than some mere quantum of a promoter. For example, an expression element can be an “enhancer.” Promoters and enhancers are different structures with different roles in gene expression. Consistent with the specification, Schena (1989) explains (Ex. B21, 973, footnotes omitted):

Though promoters themselves are sufficient to direct basal level gene expression, vigorous and regulable transcription requires the assistance of a second set of proteins known as regulatory proteins. One of the two classes of regulatory proteins, known as activators, stimulate transcription by binding to specific DNA sequences known as upstream regulatory elements. Upstream regulatory elements that confer positive promoter regulation (i.e. bind activators) are known as upstream promoter elements or enhancers in mammalian cells, and as upstream activator sequences (UASs) in yeast. Upstream promoter elements and UASs are usually located within several hundred base pairs of linked promoters (fig. 1B), whereas mammalian enhancers may reside as far as several thousand bases upstream or

downstream from a given promoter. Though these DNA sequences may function slightly differently, one may collectively view them as members of a single class of upstream regulatory elements that function in the context of a bound activator to stimulate promoter activity (fig. 1B).

Thus, the broad description of “expression element” does not refine or objectively define the scope of a “promoter element”. An “expression element” can also be an “intron,” which does not require a transcription binding site. Ex. B19 (Shaul), *supra*. Moreover, the patents refer to promoters and, generically, to “a portion thereof” of when discussing “promoter elements.” Ex. B12, ’656 patent 4:56-60, 6:36-41. A POSITA would not be reasonably certain of the metes and bounds of a “portion” of a promoter—e.g., size, function, or any other attribute—as explained above.

184. **Second**, Dr. Alper’s purported definition of “promoter element” is unsupported because he draws from a definition of a different term, “operably linked.” The patents’ definition of “operably linked” is reproduced below.

Transcriptional activators such as Mxr1 may be normally expressed at low levels. Therefore, it is desirable to place the exogenous nucleic acid (i.e., the transcriptional activator) under control of a promoter that is inducible. As used herein, “operably linked” means that a promoter or other expression element(s) are positioned relative to a nucleic acid coding sequence in such a way as to direct or regulate expression of the nucleic acid (e.g., in-frame).

’656 patent 4:44-50. This definition of “operably linked” merely clarifies the situation in which an expression element (which is not the same thing as a “promoter element”) is positioned—e.g., in order to direct or regulate expression. It does not define the metes and bounds of the expression element itself. Nor does it define the metes and bounds of a “promoter element” within a promoter.

185. Moreover, consistent with my observations above, this disclosure indicates that an “expression element” itself does not inherently have the property of directing or regulating expression. Rather, the localization of the “expression element” is necessary to achieve any particular function.

186. Accordingly, in my view, Dr. Alper's declaration supports my opinions that the term "promoter element" has no consistent meaning or structure in the art and that a POSITA would not be reasonably certain of a "promoter element's" metes and bounds as it is used within the Expression System Patents' claims.

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

Dated: 6/28/23


Dr. Carl Batt