UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BAYER CROPSCIENCE LP, MONSANTO COMPANY, AND INARI AGRICULTURE, INC.[1]

Petitioners,

v.

CORTEVA AGRISCIENCE LLC,

Patent Owner.

Case No. IPR2023-01038
U.S. Patent No. 11,299,745

PETITIONERS' REPLY TO PATENT OWNER'S RESPONSE

[1] The Board joined Inari Agriculture, Inc. as a party (Petitioner) to this proceeding via a Motion for Joinder in IPR2024-00181.

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INTRODUCTION

As its opening salvo, Patent Owner Corteva Agriscience LLC's ("Corteva") Response declares that Corteva's "groundbreaking invention" was to show that the known protein RdpA could degrade both phenoxy auxin herbicides (including (*R*)-enantiomers) and (*R*)-aryloxyphenoxypropionates ("(*R*)-FOPs"). Paper 22, 1. That, however, is not what Corteva claimed. Rather, Corteva claimed genera covering at least 20^{44} *variants* of RdpA that may or may not have such dual activity. Paper 2, 31. Corteva's Response underscores its inability to address this fundamental gap in its priority claim, rendering the claims unpatentable.

First, Corteva argues that the law only requires disclosure of a "correlation" between structure and function. Paper 22, 44-48 (discussing *Ajinomoto Co. v. ITC*, 932 F.3d 1342 (Fed. Cir. 2019)). But neither Corteva's 2004 and 2005 applications ("2004/2005 Applications," EXS1004-1005), nor the patent specification claiming priority to those documents, discloses *any* correlation between structure and the *claimed* (*R*)-enantioselective activity. Nor do the 2004/2005 Applications or patent identify a single amino acid involved in RdpA's (*R*)-enantioselectivity, even though they emphasize that (*R*)-enantioselectivity is what distinguishes RdpA from other αKG dioxygenases. EX1004, [0017], [0051]; EX1005, [0018], [0074]; EX1003, 4:48-62, 8:19-25. Nor do they disclose the importance of maintaining RdpA's 285 arginine, a residue that Corteva argued during prosecution of the '555 patent was

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"critical" to RdpA's activity. EX1008, -452, -455; Paper 12, 36 n.23, 50. Because the claimed (*R*)-enantioselective structure-function relationship was "unknown," Corteva cannot rely on any purported "correlation" to save its claims. *PureCircle USA Inc. v. SweeGen, Inc.*, No. 2022-1946, 2024 WL 20567, at *4 n.10 (Fed. Cir. Jan. 2, 2024) (nonprecedential) (discussing *Ajinomoto*); *see Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366-67 (Fed. Cir. 2011).

Second, Corteva abandons its 2004 priority date (April 2004) and alleges that the "prior art" Schleinitz 2004 publication (EX1042, dated September 2004) discloses both the AAD-1 motif and a 285 arginine as part of that motif (also referred to as "R285" or "$X_{282\text{-}284}$R"). Paper 22, 3-4 (Schleinitz 2004 is "*prior art*"),[2] 16-17, 39-42, 48-49, 58-59. That is factually incorrect. But the argument also harms Corteva's own cause. Corteva treats the disclosures of the 2004/2005 Applications (and the as-filed '555 patent specification) as identical for purposes of whether there is any description of the AAD-1 motif and R285 limitations. Paper 22, 30, 33, 36-38. Thus, by relying on Schleinitz 2004 to supply the AAD-1 limitations (with and without $X_{282\text{-}284}$R), *Corteva tacitly admits that they are not disclosed in the 2004 provisional—or, concomitantly, the 2005 application*. That is fatal to Corteva's position, because prior art cannot be used to supply limitations that are absent from

[2] Emphasis added unless indicated otherwise.

the specification. *Rivera v. ITC*, 857 F.3d 1315, 1322 (Fed. Cir. 2017).

By treating Schleinitz 2004 as prior art, Corteva also reinforces the absence of any (*R*)-enantioselective structure-function "correlation." Schleinitz 2004 states explicitly that the amino acids responsible for RdpA's (*R*)-enantioselectivity were unknown: "The basis of the enantiospecificity of the dichlorprop-cleaving enzymes is *not known*." EX1042, 5362-63. The Institution Decision quoted that very language as undermining Corteva's position. Paper 12, 49.

Third, Corteva asserts that Tian (EX2019)—which is nowhere cited in the patent—discloses a "universal principle" that if two enzymes have 60% sequence identity, the POSA would expect them to have the same activity 90% of the time. Paper 22, 1-2, 30-32. Corteva's failure to mention that "principle" in its years of prosecution or Preliminary Response is readily explained: the position is meritless.

As an initial matter, Corteva cannot rely on Tian because the notion that sequence identity alone predicts function is "directly contradict[ed]" by the specification, which provides that the type of substitution matters to variant function. *See Bos. Sci.*, 647 F.3d at 1366.

Also, while Corteva asserts that the specification references Tian's finding, Paper 22, 2-3, 21, 31, that is incorrect. The specification mentions 60%, but that number is not connected to Tian's 60% lower limit, as it lists every number between 49%-99%. EX1003, 37:24-42; EX1004, [00116]; EX1005, [00142]. As for the

discussion regarding 85-98% being "highly identical," EX1003, 44:5-30, not only does Tian nowhere specify 85% or 85-98%, but the discussion in the specification on its face concerns generic "α-ketoglutarate dioxygenase activity" for "[r]esistance to [the achiral compound] 2,4-D"—*i.e.*, not (*R*)-enantioselectivity, *see id.*; EX1005, [00171]; EX1070, ¶¶ 35-36.

Furthermore, Corteva's reliance on Tian is inapt because Tian describes relationships among *naturally occurring proteins*, which are subject to evolutionary selection; its analysis does not address the artificial variants encompassed by the claims. *See* EX2019, 863-65, 876-77; EX1070, ¶¶ 33-34, 37-41, 45. Recognizing this deficiency, Corteva points to Minshull (EX2025) to try to connect Tian to "protein engineering." Paper 22, 10. But Minshull—which likewise requires Corteva to abandon any 2004 priority claim—does not help Corteva. Minshull nowhere cites Tian or espouses its 60% threshold. Instead Minshull warns that "*[p]rediction of protein function from sequence and structure is a difficult problem*, because homologous proteins often have different functions," and invites trial-and-error experimentation. EX2025, 203.

Rather than focus on Tian, the POSA would credit Saari 1999, which teaches that even a handful of amino acid changes can alter (*R*)-enantioselective activity of αKG dioxygenases. Paper 2, 37; Paper 12, 40; EX1041, 421, 427; EX1070, ¶ 51. That dovetails with Schleinitz 2004, which provides that RdpA's (*R*)-enantiomer

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substrate specificity is "likely" "determined by only a few amino acids." EX1042, 5363; Paper 12, 49. And the fact that those amino acids were "not known" reinforces the unpredictability of ascertaining which RdpA variants exhibit the claimed (*R*)-enantioselectivity. EX1070, ¶¶ 29, 56.

As for Grounds IIA-IIB, Corteva misperceives the evidence supporting obviousness and proposes objective evidence not commensurate with the claims' vast scope.

ARGUMENT

I. GROUNDS IA-IB

Corteva does not dispute that, if claims 1-29 are not entitled to pre-October 2016 priority—*i.e.*, if they are not supported by the 2004/2005 Applications—then the Board should find every claim anticipated and obvious based on Corteva '437, published in November 2005. *See* Paper 2, 41-55; Paper 22, 28-30. Corteva is also in general agreement with Petitioners' POSA definition, and Dr. Hausinger's opinions would not change to the extent there are differences. Paper 22, 26; EX1070, ¶ 7; EX1073. Thus, the only issue for Grounds IA-IB is whether the 2004/2005 Applications provide written-description support. They do not.

A. Corteva Misapplies the Legal Standard

Although the Institution Decision rejected Corteva's arguments regarding *Ajinomoto* and other cases addressing "well-known" structure-function

relationships, Paper 12, 52-54, Corteva emphasizes that written description only requires a "reasonable" structure-function "correlation," not "perfect correspondence," Paper 22, 44-48. However, this is not a case of less-than-perfect correspondence or a "well-known" structure-function relationship. The 2004/2005 Applications and prior art *identified no correlation whatsoever* between structure and the claimed (*R*)-enantioselective activity. EX1070, ¶¶ 19-27. Indeed, the 2004/2005 Applications and the patent specification assert that activity against (*R*)-FOPs was novel, EX1004, [0017]; EX1005, [0018]; Paper 12, 54 (quoting EX1003, 4:55-58), yet never identify the amino acids correlating to (*R*)-enantioselective activity. As the Institution Decision observed, Schleinitz 2004 confirms that "[t]he basis of the enantiospecificity of the dichlorprop-cleaving enzymes is not known." EX1042, 5362-63 (disclosing it "likely" "that substrate specificity is determined by only a few amino acids" and "[s]ite-specific mutagenesis studies are needed to reveal the molecular basis of the substrate specificity and stereospecificity of RdpA and SdpA"); Paper 12, 49.

Corteva's selective discussion of *PureCircle* underscores its misapplication of the law. Corteva quotes *PureCircle* as stating, "*Ajinomoto* stands for the idea that where there are structural features common to a genus, the structure-function correlation does not need to be perfect and some testing—appropriate to the knowledge of a POSA—is allowed." Paper 22, 46-47. However, Corteva omits the

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remainder of the sentence, which reads: "*not that an unknown structure-function correlation along with extensive testing can satisfy written description*." *PureCircle*, 2024 WL 20567, at *4 n.10. Corteva's omission is telling. Given that the structure-function relationship for the claimed (*R*)-enantioselective activity of RdpA was unknown as of 2004/2005, extensive testing would be needed to ascertain which proteins having the claimed structure also possess the claimed activity. EX1070, ¶¶ 29-30.

While Corteva cites multiple Board decisions, it ignores the Informative decision in *Ex Parte Porro*, where the "at least about 90% identity" limitation lacked support because the "Specification does not provide guidance regarding what structural features are *responsible for* the enzymatic activity." Appeal No. 2008-0184, 2008 WL 2259960 at *2-3 (BPAI Mar. 11, 2008) (Informative). And the cases cited by Corteva do not aid its cause. In *Ex Parte Campbell*, the 90% lower limit was supported because the specification disclosed an embodiment with even lower (87%) identity—a stark difference from the specification here. *See* No. 2021-000865, Decision on Appeal, 15 n.3 (PTAB July 20, 2021). In *Lifescan Global Corp. v. Ikeda Food Research, Ltd.*, the specification "identifie[d] a portion of the claimed sequence believed to be critical to its activity." PGR2019-00032, Paper 11, 32 (PTAB Aug. 15, 2019). The specification here does not disclose what residues are important to (*R*)-enantioselective activity. And *Boehringer Ingelheim Animal*

Health USA Inc. v. Kansas State University is inapposite, as the claims recited no functional limitation. PGR2022-00021, Paper 13, 20 (PTAB Mar. 22, 2023).

B. Common Structural Features.

Corteva's arguments regarding common structural features fail.[3]

1. No pre-October 2016 support for the AAD-1 motif, with or without R285.

The 2004/2005 Applications' disclosures of the prior-art consensus motif ($HX(D/E)X_{23\text{-}26}(T/S)X_{114\text{-}183}HX_{10\text{-}13}R$), and the RdpA sequence (SEQ ID NO: 9), do not disclose the claimed AAD-1 motif. Paper 2, 11-14, 24-30; Paper 12, 32-34; EX1070, ¶ 13. At best, an "obviousness" analysis would be required, which is insufficient. *Rivera*, 857 F.3d at 1322; *see* Paper 12, 32-36.

Corteva's Response abandons any pretense that the 2004/2005 Applications disclose the AAD-1 motif or R285. Instead, Corteva suggests they were known in the art based on Schleinitz 2004. Paper 22, 3-4, 15-18, 39-44, 48-49, 58-60; *id.*, 40 (citing *Bos. Sci.*, 647 F.3d at 1366). That is wrong.

First, Corteva's reliance on a September 2004 publication, Schleinitz 2004,

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[3] Corteva argues that the "Petition does not dispute enablement of the full claim scope." Paper 22, 28 n.3. That is irrelevant. The claims lack pre-October 2016 support; Petitioners had no need to cite non-enablement as an additional basis. As Corteva knows, Petitioners raised non-enablement defenses in the district court.

as prior art effectively concedes that Corteva's April 2004 provisional—and, consequently, the 2005 application, *see* Paper 2, 11-14—cannot support the AAD-1 motif, with or without R285. Indeed, Schleinitz 2004 is nowhere referenced in the patent specification.

Second, and accordingly, the disclosures Corteva relies upon from Schleinitz 2004 are legally irrelevant. Corteva cites Schleinitz 2004 to supply claim limitations that it concedes are missing from the specification. That forecloses Corteva's position as a matter of law: "The knowledge of ordinary artisans may be used to inform what is actually in the specification, *but not to teach limitations that are not in the specification*, even if those limitations would be rendered obvious by the disclosure in the specification." *Rivera*, 857 F.3d at 1322.

Third, even were Corteva's gap-filling approach legally permissible, Schleinitz 2004 does not disclose the AAD-1 motif, with or without R285. Schleinitz 2004 never discloses any motif that is "new and unique" and generalizable from RdpA to other proteins. EX1042, 5357, 5362-63; EX1070, ¶¶ 8-10, 12-14; *see* Paper 12, 32-34. Instead, as the Institution Decision observed, Schleinitz 2004 merely "discuss[es] the αKGD consensus motif." Paper 12, 49. That is demonstrated by its text, which compares the sequences of several αKG dioxygenases with varying substrates and stereospecificities, and identifies the locations of the five amino acids from the "functionally essential" prior-art αKG

dioxygenase motif. EX1042, 5357, 5360, 5362-63; EX1070, ¶¶ 13-14, 19. It is also consistent with Dr. Nair's prosecution declaration, which cited Schleinitz 2004 as disclosing the consensus motif, but never suggested it disclosed the claimed AAD-1 motif, with or without R285. EX1008, 590-598, ¶ 6. Indeed, it would have been surprising to the POSA for Schleinitz 2004 to define a new "RdpA motif" while simultaneously noting that the basis for RdpA's (*R*)-enantioselectivity was unknown. EX1070, ¶ 15. While Corteva suggests Dr. Hausinger's deposition somehow supports its position, Paper 22, 17, he merely testified where the five conserved residues from the consensus motif appear in RdpA and how far apart they are, not that Schleinitz 2004 discloses a new RdpA motif, *see* EX2016, 22:1-26:14; EX1070, ¶ 27.

Nor does Schleinitz 2004 disclose $X_{282\text{-}284}R$. Schleinitz 2004 defines the consensus motif without reference to an additional arginine. EX1042, 5357, 5362. While Corteva points to Figure 2, that does not help Corteva. Figure 2 depicts an alignment of TfdA, TauD, SdpA and RdpA, in which a gray-highlighted arginine residue is present in TfdA, TauD, and (at position 285) RdpA, and a black arrow is located underneath the alignment. EX1042, 5360. Importantly, Corteva ignores the figure caption, which explains: "Black arrows indicate 2,4-D binding residues *in TfdA*." EX1042, 5360. The text does not provide that the black arrows also indicate binding residues in RdpA, even though RdpA is in Figure 2; the most straightforward

reading is that R285 had no known role for RdpA in binding to 2,4-D. EX1070, ¶¶ 16-17. And the arginine's involvement in TfdA's (an (*S*)-enantioselective enzyme) binding to 2,4-D (an achiral substrate) indicates that it *cannot* be responsible for RdpA's (*R*)-enantioselectivity. EX1042, 5360; EX1070, ¶ 18.

Corteva also asserts that Schleinitz 2004 suggests that spacing somehow determines enantioselectivity. Paper 22, 16-17. That is wrong. Schleinitz 2004 states that the basis for RdpA's enantioselectivity is "not known." EX1042, 5362-63. If anything, Schleinitz 2004 undermines any relationship between spacing and enantioselectivity: it discloses that TfdA and SdpA share (*S*)-enantioselectivity, yet have different spacings. *Id.*, 5360; EX1070, ¶¶ 23-25. Corteva's position is further undermined by Dr. Hausinger's article (EX1025), which discloses αKG dioxygenases with identical spacings, but different substrates. Paper 22, 43; EX1025, 22, EX1070, ¶ 26.

Finally, in *Yeda Research & Development Co. v. Abbott GmbH & Co.*, it was "undisputed" that the claims encompassed only one protein, for which the specification disclosed a partial sequence and a method for obtaining the remainder. 837 F.3d 1341, 1345 (Fed. Cir. 2016). Here, claim 1 covers at least 20^{44} sequences. EX1054, ¶ 79; Paper 2, 31.

2. No pre-October 2016 support for at least 85% sequence identity to RdpA.

In the Institution Decision, the Board invited Corteva to address whether there

was a "universal principle" that "if at least 85% amino acid identity, the POSA would expect the same properties." Paper 12, 40. In response, Corteva presents an entirely new argument premised on Tian, which according to Corteva "consolidated and built on" various earlier references. Paper 22, 9. Tian performed an analysis regarding percentage sequence identity using proteins from the Swiss-Prot database. EX2019, 865, 876-877. Swiss-Prot contains naturally occurring protein sequences annotated with Enzyme Classification ("EC") numbers; it does not include artificial variants, much less a vast number of hypothetical variants of known sequences, such as those recited in the claims. EX1070, ¶¶ 33, 37-38; EX1074, 53; EX1075. Tian determined that "above 60% sequence identity is needed to have above 90% accuracy." EX2019, 876. From that, Corteva asserts the sweeping conclusion that the POSA could predict the function of any enzyme with at least 60% identity, including the artificial sequences recited in the challenged claims. Paper 22, 10, 32-33. Corteva is mistaken.

a. Tian does not make the prediction that Corteva asserts. *Infra* Section I.B.2.c. But, even if it did, such predictions would not provide written description as a matter of law. One cannot receive a patent on a "research plan" for obtaining what is claimed. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014). A patent is not a "hunting license"; it "requires a description of an invention, not an indication of a result that one might

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achieve if one made that invention." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350, 1353 (Fed. Cir. 2010) (en banc) (citation omitted). A bare prediction that (i) a certain percentage of enzyme sequences above (ii) a certain sequence-identity threshold would have (iii) a given activity is an insufficient "research plan."

Indeed, Corteva's expert Dr. Bollinger testified that the patent proposes nothing more than a research plan with an obvious result, explaining that if one "follow[ed] established principles" for "***designing*** *enzyme variants*" that "conserve function," one would "have reasonably expected" to obtain proteins with dual-activity. EX2015, ¶ 134 (cross-referencing Section V.B.2 (¶¶ 52-59)); *id.*, ¶ 18 ("reasonable expectation" part of obviousness).

b. Tian and the other database references cited by Corteva lie outside "the four corners of the specification," further undermining Corteva's position. *Ariad*, 598 F.3d at 1351.

Indeed, the specification "directly contradict[s]" Tian's purported principle that sequence identity alone predicts function, thereby foreclosing reliance on Tian to support written description. *Bos. Sci.*, 647 F.3d at 1366. While Tian focuses on *sequence identity* as the sole predictor of function, the patent specification provides that the *type of substitution* matters. EX1070, ¶ 30. The specification discloses that "[c]onservative" "substitutions can be tolerated/made to not adversely affect the activity." EX1003, 38:3-28; *see* EX1004, [00118]; EX1005, [00144]. However, it

caveats that "[c]onservative substitutions" are only part of the invention "*so long as* the substitution is not adverse to the biological activity," thereby requiring extensive experimentation for the POSA to ascertain which variants exhibit the claimed activity. *Id.*; EX1070, ¶¶ 30-32. Moreover, the specification adds, without further explanation, that "non-conservative substitutions" can in "some instances" be made without adversely affecting activity. EX1003, 38:25-28. Even Corteva and Dr. Bollinger recognize that the type of substitution matters. Paper 22, 13; EX2015, ¶ 58. Accordingly, because the claims facially permit both conservative and non-conservative substitutions of any type, sequence identity would not be expected to be sufficient to predict activity—a point reflected in the specification itself. EX1070, ¶¶ 28-31.

While Corteva attempts to link Tian to the specification, that effort fails. Corteva cites the patent's unsupported statement that "amino acid identity will typically be at least 60%." Paper 22, 21 (citing EX1003, 37:24-35). But while Tian treats 60% as a lower limit, the specification does not: "at least 60%" appears in a discussion of every whole percentage from 49%-99%, which has no connection to Tian. EX1003, 37:24-42; *see* EX1004, [00116]; EX1005, [00142].

Corteva also relies on statements that "85-98%" sequence identity is "highly identical" and that "only sequences with high homology would be expected to retain similar properties." Paper 22, 2-3, 21 (citing EX1003, 44:12-24). But Tian does not

discuss "85%" as a threshold or "85-98%" as a range, reflecting the absence of any connection. EX1070, ¶¶ 35-36. Moreover, the discussion in question refers to a search for proteins with general "α-ketoglutarate dioxygenase activity" to "[i]mpart [r]esistance to *2,4-D*," an *achiral* compound, EX1003, 44:5-15; *see* EX1005, [00171]. As such, the discussion is not directed to (*R*)-enantioselectivity, thereby further disconnecting it from the claims, EX1070, ¶¶ 35-36.

c. Corteva also factually misinterprets Tian.

First, Swiss-Prot—analyzed both in Tian and the Rost 2002 (EX2028) reference focused on by Corteva—contains *naturally occurring proteins*, not artificial variants like those in the claims. *Supra* p. 13. Tian found that, within Swiss-Prot, two naturally occurring proteins needed to have at least 60% sequence identity for there to be a 90% likelihood of sharing an assigned EC number (a proxy for activity). EX2019, 865; EX1070, ¶¶ 33, 37-39, 43. But Tian never suggests the same applies to *artificial variants* like in the challenged claims. EX1070, ¶¶ 39-45. Tian never suggests, and the POSA would not have accepted, the proposition that the function of a synthetic variant can be assumed based on a percentage sequence identity threshold, because that would treat every modification as equivalent, irrespective of which amino acid is involved or what type of change is made. *Id.*

That Tian—as well as the other references relied on by Corteva—investigated naturally occurring proteins is a critical limitation. EX1070, ¶¶ 40-45. As Dr.

Hausinger explains, due to natural selection, naturally occurring proteins represent a highly biased and tiny subset of the universe of possible sequences. EX1070, ¶¶ 11, 38-41. That subset is quite different than the at least 20^{44} sequences encompassed by the claims, which have not been subject to natural selection that would filter out inactive variants. *Id*. Dr. Bollinger concurs with this point, testifying that "enzymes that have evolved over time to perform the same function (or similar functions) can span a relatively broad range of sequence space" because "any amino acid changes" that "disturbed the enzyme's overall structure or replaced amino acids that promoted the reaction would have led to a loss or reduction of the enzyme's activity, likely with negative consequences for the organism." EX2015, ¶ 42; *see* EX1070, ¶¶ 38, 50. Thus, neither Tian nor the other references cited by Corteva can be extended to predict the function of artificial variants. EX1070, ¶¶ 44-45.

Dr. Bollinger's testimony reinforces the flaw in Corteva's position. He acknowledged that his opinions regarding whether enzymes with 85% identity have the "same function" are premised on whether sequence changes would cause the "enzyme to make a different product." EX1072, 7:14-9:5. That framing ignores sequence changes yielding no product, *i.e.*, inactive variants. *Id.* However, the law does not grant a patentee a mulligan every time an inactive variant is produced. *See Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350 (Fed. Cir. 2013). And here, given (1) the absence of critical structure-function information

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in the specification concerning (*R*)-enantioselectivity and R285; and (2) the disclosure that both conservative and non-conservative substitutions may or may not preserve function, *supra* pp. 14-15, Dr. Bollinger's decision to ignore inactive variants wholly undermines his priority analysis.

Second, apparently recognizing Tian's inapplicability to the claims, Corteva cites Minshull for the proposition that analysis regarding "[h]omologous sequences" can be applied to "protein engineering." Paper 22, 10 (citing EX2025, at 202-03). The argument is misplaced. Corteva does not explain why Minshull—an article from April 28, 2005, nowhere cited in the patent—was "well known" by the May 2, 2005 PCT application. Moreover, Minshull never references Tian's 60% finding. Instead, Minshull teaches that "orthologous protein[]" sequences—*i.e.*, naturally occurring sequences with shared evolutionary ancestry that catalyze the same reaction—are "a potentially rich source of information regarding sequence changes that are acceptable without drastically disrupting protein function." EX2025, 203; EX1070, ¶¶ 46-47. Minshull observes that one can use such sequences as inputs to artificially generate new sequences, *e.g.*, through DNA shuffling, but as Minshull explains, such artificial sequences must still be screened for activity, thus requiring extensive testing. EX2025, 202-03; EX1070, ¶¶ 47-48. Minshull never proposes that the POSA should assume the artificial variants would have the same activity as the original sequence so long as they stayed above a certain percentage sequence

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identity. Corteva elides that deficiency, replacing "orthologous proteins" (which connotes that the proteins are naturally occurring) from the above quotation with the generic phrases "related proteins" or "related sequences." Paper 22, 11, 53 (citing EX2025, 202-03). Minshull therefore reinforces that Corteva's written description arguments constitute nothing more than a "research plan." *AbbVie*, 759 F.3d at 1300; *supra* Section I.B.2.a.

Corteva asserts that *AbbVie* and other "antibody" cases are "inapposite." Paper 22, 47-48. However, the Federal Circuit has applied *AbbVie* in cases involving enzymes, including *PureCircle*, 2024 WL 20567, at *4. Corteva itself cites *AbbVie* for the "standard for common structure." Paper 22, 44-45.

Third, as the Institution Decision recognized, prior art concerning herbicide-degrading αKG dioxygenases (Saari 1999) showed that sequences with more than 85% identity can have *opposite stereoselectivities*. Paper 12, 40 (citing EX1041, 421, 427 (86% and 95% identity respectively); *see* Paper 2, 37; EX1054, ¶¶ 54, 90-91, 109. That is consistent with Schleinitz 2004, which teaches that only a few (unknown) amino acids are responsible for RdpA's (*R*)-enantiomer substrate specificity. EX1042, 5362-63. The POSA would not ignore these teachings in favor of Tian, which does not discuss enantioselective αKG dioxygenases. EX1070, ¶¶ 34, 51. Indeed, because Tian limited its analysis to curated sets of proteins with assigned, complete EC numbers, EX2019, 865, 876, it could not have included

RdpA or SdpA, as their EC numbers were assigned in 2013, or TfdA, because its EC number is incomplete. EX1070, ¶ 42; EX1076, 11-12; EX1077, 3.

Recognizing that Saari 1999 is inconsistent with its position, Corteva attempts (unsuccessfully) to undermine it. Corteva questions Saari 1999's data because the study involved "crude cell extracts." Paper 22, 50. But cell extracts were commonly used when purified proteins were unavailable, and Saari 1999 included additional experiments confirming that the *A. denitrificans* cell extracts contained an herbicide-degrading, (*R*)-enantioselective, αKG dioxygenase. EX1041, 425-427 & Fig. 4; EX1070, ¶¶ 52-54; *see* EX1040, 71-89. Corteva also asserts that "later researchers" "predict[ed] enzymatic function" based on sequence, Paper 22, 50-51, but it fails to identify a single paper rejecting Saari's findings. Vedler never references Saari, nor does Vedler even hint that predictions based on sequence identity are more reliable than biochemical assays; to the contrary, Vedler reflects the flaw in predicting (*R*)-enantioselectivity based on sequence identity. EX1046; EX1070, ¶ 55. Schleinitz 2004 observes that further research could be done to investigate the *A. denitrificans* enzyme discussed in Saari, but it does not report any findings contradicting Saari's; rather, Schleinitz 2004 teaches that enantioselectivity depends on a few yet-to-be-identified amino acids, which is consistent with Saari. EX1042, 5362-63; EX1070, ¶ 56.

Moreover, in view of the aforementioned teachings, Corteva's emphasis on

whether RdpA and SdpA only have 30% overall sequence identity is a non-sequitur. *See* Paper 22, 50. The percentage sequence identity between RdpA and SdpA would tend to make it harder, not easier, for the POSA to identify which few amino acids are important to RdpA's (*R*)-enantioselectivity. EX1070, ¶ 57.

Furthermore, as "precedent" for its conclusions, Saari 1999 cites Nakajima, which describes two enzymes with 64% sequence identity that catalyze reactions with opposite stereochemistry. EX1041, 427-428; EX2053, 4876. Tian references Nakajima as an example to which Tian's conclusions are inapplicable. EX2019, 880-881 (identifying "1.1.1.206 (Tropine dehydrogenase)" and "1.1.1.236 (Tropinone reductase)" as "[e]nzyme functions indistinguishable from each other by sequence identity (above 60% global identity)"). Corteva tries to portray Nakajima as a unique exception, *see* Paper 22, 50-51 (citing EX2015, ¶¶ 123-124 (citing in turn EX2053)), but other prior art similarly reported that a small number of amino acid changes could have significant impacts on reaction stereochemistry, EX1079; EX1081. This literature, like Saari 1999 and Schleinitz 2004, underscores for the POSA that Tian's analysis does not hold with respect to stereospecificity. EX1070, ¶¶ 58-61; EX1078.

Fourth, Corteva's arguments regarding a "twilight zone" add nothing. *See* Paper 22, 7-8, 18 (citing EXS2021, 2023-2024). The cited art referred to a "twilight zone" where it became difficult to tell if naturally occurring proteins "evolved from

a common precursor," Paper 22, 7; it does not address artificial sequences. EX1070, ¶ 49.

Finally, Corteva's criticisms of Dr. Hausinger are unfounded. Corteva questions Dr. Hausinger's opinions regarding unpredictability, *e.g.* Paper 22, 33, but that is based on Corteva's erroneous analysis of Tian. Corteva also criticizes Dr. Hausinger's 20^{44} calculation, but offers no contrary calculation. Understandably so. *PureCircle* held that Dr. Bollinger's proposal of 9,000 enzymes still resulted in too much testing. 2024 WL 20567, at *3.

C. Representative Species.

The Institution Decision recognized that SEQ ID NOS: 10-11, which vary from RdpA by 1-2 residues, are insufficiently representative. Paper 12, 46-47. Corteva's Response fails for essentially the same reasons that its arguments regarding common structural features fail: it baselessly assumes the conclusion that the at least 20^{44} sequences covered by the claims are "highly identical." Paper 22, 56. Nothing in the patent or the prior art supports such a conclusion. Paper 2, 30-31. And while Corteva references the patent's "twenty-six examples," Paper 22, 22-23, the Institution Decision recognized those examples still only involve three enzymes, Paper 12, 47 n.27.

Corteva also raises several meritless arguments about post-priority evidence:

1. Corteva misperceives the applicability of post-priority evidence.

Written description is judged based on the state of the art as of the priority date. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1373-74 (Fed. Cir. 2017). However, a challenger can use post-priority evidence to show lack of written description. *Id.*

2. Petitioners do not assert that three-dimensional structural information is required. *See* Paper 22, 52-55. Instead, three-dimensional information is a potential way (another being mutagenesis studies) to try to ascertain which residues are responsible for the claimed (*R*)-enantioselectivity—something the named inventors did not do, instead leaving a research project for others to perform. *See* EX1054, ¶¶ 88-91. While Corteva suggests that such a research project could involve sequence alignments, Paper 22, 53 (citing Minshull regarding orthologous proteins), there was no other prior-art protein with RdpA's dual activity that could be used for such an alignment, *supra* pp. 6-7; EX1070, ¶¶ 20-22.

3. Corteva suggests that Petitioners' post-priority work as published in Larue somehow supports the claims, because it references earlier work from Dr. Wright. Paper 22, 57-58 (discussing EX1052). That is wrong. Petitioners' post-priority work—and the related sequence of events—refute Corteva's priority claim, as well as Corteva's copying allegations (*infra* Section II):

- The sequences with 89-91% identity to RdpA that Corteva (via Dr. Bollinger) refers to from Larue (EX2015, ¶ 136) were first published years earlier, in April 2016, in a Bayer/Monsanto application, EX1017;

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EX1070, ¶¶ 62-63; EX1084.

- Between 2004-2015, Corteva pursued claims with at least *95% identity* to RdpA. Paper 2, 1-2, 11-13; EXS1004-1008. However, in October 2016—six months after Bayer/Monsanto's application was published—Corteva filed the '406 application, seeking for the first time claims with at least *85% identity*.
- Internal documents submitted by Corteva show that, [redacted] EX1008, 457-474, [redacted] *e.g.*, EX2002, 433-444; EX2004. [redacted] *Id.*; EX1070, ¶¶ 65-68. [redacted] EX2002, 864-865. [redacted]
- In another document, Corteva [redacted] EX2004, -580. Likewise, [redacted]

[redacted]

[redacted] *Id.*

- Corteva ignores that Larue explains that "approximately 4000 enzyme variants" were prepared as part of the research project it discusses. EX1052, 2089; EX1070, ¶ 64. To the extent there is any link between that work and the 2004/2005 Applications, it shows the applications amount to, at best, an insufficient invitation to pursue extensive testing.

D. Claim 2 Lacks Support.

Claim 2 recites an AAD-1 motif that further requires $X_{282\text{-}284}R$. Paper 22, 58. However, that claim lacks support for the reasons discussed previously, including because Corteva improperly relies on prior art to supply a limitation [redacted] *Supra* Section I.B; EX2004, -580; Paper 2, 11-14, 24-30, 34.

* * *

In sum, the challenged claims lack pre-October 2016 support, rendering them unpatentable. Moreover, Corteva's position fails under what it calls the "three main issues for factual development." Paper 22, 26-28. Contrary to Corteva's arguments, (1) no "universal principle" exists that artificial variants with at least 85% sequence identity to RdpA would be expected to have the claimed (*R*)-enantioselectivity; (2) the 2004/2005 Applications do not disclose the claimed AAD-1 motif, with or

without $X_{282\text{-}284}R$; and (3) Saari 1999's disclosures are consistent with Schleinitz 2004 and further undermine Corteva's priority claim.

II. GROUNDS IIA-IIB

Corteva asserts lack of motivation because efforts to transform TfdA were a "commercial failure." Paper 22, 67-69. However, obviousness does not require commercial feasibility. *Grit Energy Sols., LLC v. Oren Techs., LLC*, 957 F.3d 1309, 1323 (Fed. Cir. 2020). Corteva further contends there was no motivation to confer tolerance to (*R*)-phenoxy auxins, Paper 22, 68-69, but Saari suggests exactly that, as the Institution Decision recognized, EX1041, 422, 427; Paper 12, 62. As for *InTouch Technologies, Inc. v. VGo Communications, Inc.*, 751 F.3d 1327, 1354 (Fed. Cir. 2014), the "could be" testimony in that case involved a mere possibility, not a proposal.

Corteva also does not contest that a plant successfully transformed to express RdpA would degrade an (*R*)-FOP. Instead, Corteva argues that various factors could affect enzyme activity or expression. Paper 22, 65-67. While Corteva frames these arguments in terms of "inherency," they really question whether the POSA could successfully transform plants to express RdpA. However, the patent admits that plant transformation methods were "well known." Paper 2, 57 (citing EX1003, 39:32-37; *Koninklijke Philips NV v. Google LLC*, 948 F.3d 1330, 1339 (Fed. Cir. 2020). Those same admissions undermine Corteva's arguments regarding

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dependent claims that further require, *e.g.*, herbicide tolerance.

Furthermore, Corteva's objective evidence is nowhere near commensurate with the claims. *See* Paper 22, 69-72; Paper 2, 64. The specific evidence that Corteva cites also fails, *e.g.*, because it demonstrates that Corteva copied Petitioners, not vice-versa. *Supra* Section I.C.3.

Finally, while Corteva questions the POSA's expectations because (*R*)-FOPs are larger, Paper 22, 62-63, those arguments further undermine Corteva's priority claim, as the patent provides no explanation regarding how to account for such size differences in preparing RpdA variants with the claimed function. EX1070, ¶ 69.

III. CONCLUSION

Petitioners respectfully request that claims 1-29 be cancelled.

July 2, 2024

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[redacted]

PATENT OWNER'S SECOND UPDATED EXHIBIT LIST

Exhibit No.	Description
EX1001	U.S. Patent No. 10,947,555
EX1002	U.S. Patent No. 11,149,283
EX1003	U.S. Patent No. 11,299,745
EX1004	U.S. Provisional Application No. 60/567052
EX1005	U.S. Application No. 11/587893 and File History
EX1006S	U.S. Application No. 12/951813 and File History
EX1007	U.S. Application No. 14/820893 and File History
EX1008	Certified U.S. Application No. 15/288,406 and File History
EX1009	U.S. Application No. 17/143,824 and File History
EX1010	Certified U.S. Application No. 17/175,966 and File History
EX1011	Certified U.S. Application No. 17/403,476, and File History
EX1012	Accession No. AAS49436.1, submitted Feb. 04, 2004
EX1013	Accession No. AF516751, published Aug. 6, 2002
EX1014	Accession No. AF516752, published Aug. 6, 2002
EX1015	Accession No. AJ628856, published March 3, 2004
EX1016	Accession No. Q8KSC8, published Oct. 1, 2002
EX1017	U.S. Patent Pub. No. 2016/0108422

Exhibit No.	Description
EX1018	C. Bayley et al., *Engineering 2,4-D Resistance into Cotton*, 83 THEORETICAL & APPLIED GENETICS 645-649 (1992)
EX1019	J.R. Chekan et al., *Molecular Basis for Enantioselective Herbicide Degradation Imparted by Aryloxyalkanoate Dioxygenases in Transgenic Plants*, 27 PROC. NAT'L ACAD. SCI. 13299-13304 (2019)
EX1020	J.R. Chekan et al., *Supplementary Information, Molecular Basis for Enantioselective Herbicide Degradation Imparted by Aryloxyalkanoate Dioxygenases in Transgenic Plants*, 27 PROC. NAT'L ACAD. SCI. 13299-13304 (2019)
EX1021	U.S. Patent Pub. No. 2005/107437
EX1022	BIOLOGICALLY ACTIVE NATURAL PRODUCTS: AGROCHEMICALS (H.G. Cutler & S.J. Cutler, eds. 1999)
EX1023	J.M. Elkins, R.P. Hausinger et al., *X-ray Crystal Structure of* Escherichia coli *Taurine/α-Ketoglutarate Dioxygenase Complexed to Ferrous Iron and Substrates*, 41 BIOCHEMISTRY 5185-5192 (2002)
EX1024	F. Fukumori & R.P. Hausinger, Alcaligenes Eutrophus JMP134 *"2,4-Dichlorophenoxyacetate Monooxygenase" Is an α-Ketoglutarate-Dependent Dioxygenase*, 175 J. BACTERIOLOGY 2083-2086 (1993)
EX1025	R. Hausinger, *Fe(II)/α-Ketoglutarate-Dependent Hydroxylases and Related Enzymes*, 39 CRIT. REV. BIOCHEM. MOLECULAR BIO. 21-68 (2004)
EX1026	S.S.Q. Hee & R.G. Sutherland, I PHENOXYALKANOIC HERBICIDES: CHEMISTRY, ANALYSIS, AND ENVIRONMENTAL POLLUTION (1981)

Exhibit No.	Description
EX1027	D.A. Hogan, R.P. Hausinger et al., *Site-Directed Mutagenesis of 2,4-Dichlorophenoxyacetic Acid/α-Ketoglutarate Dioxygenase. Identification of Residues Involved in Metallocenter Formation and Substrate Binding*, 275 J. BIO. CHEM. 12400-12409 (2000)
EX1028	J.C. Dunning Hotopp & R.P. Hausinger, *Alternative Substrates of 2,4-Dichlorophenoxyacetate/α-Ketoglutarate Dioxygenase*, 15 J. MOLECULAR CATALYSIS B: ENZYMATIC 155-162 (2001)
EX1029	J.C. Dunning Hotopp & R.P. Hausinger, *Probing the 2,4-Dichlorophenoxyacetate/α-Ketoglutarate Dioxygenase Substrate Binding Site by Site-Directed Mutagenesis and Mechanism-Based Inactivation*, 41 BIOCHEMISTRY 9787-9794 (2002)
EX1030	U.S. Patent Pub. No. 2003/0041357
EX1031	H.P.E. Kohler, Sphingomonas herbicodovorans *MH: A Versatile Phenoxyalkanoic Acid Herbicide Degrader*, 23 J. INDUS. MICROBIO. & BIOTECH. 336-340 (1999)
EX1032	B.R. Lyon et al., *Expression of a Bacterial Gene in Transgenic Tobacco Plants Confers Resistance to the Herbicide 2,4-Dichlorophenoxyacetic Acid*, 13 PLANT MOLECULAR BIO. 533-540 (1989)
EX1033	B.R. Lyon et al., *Cotton Plants Transformed with Bacterial Degradation Gene Are Protected from Accidental Spray Drift Damages by the Herbicide 2,4-Dichlorophenoxyacetic Acid*, 2 TRANSGENIC RES. 162-169 (1993)
EX1034	R.H. Müller et al., *Physiological and Genetic Characteristics of Two Bacterial Strains Utilizing Phenoxypropionate and Phenoxyacetate Herbicides*, 156 MICROBIO. RES. 121-131 (2001)

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Exhibit No.	Description
EX1035	T.A. Müller, R.P. Hausinger et al., *Structural Basis for the Enantiospecificities of* R- *and* S-*Phenoxypropionate/α-Ketoglutarate Dioxygenases*, 15 PROTEIN SCI. 1356-1368 (2006)
EX1036	K. Nickel et al., *Involvement of Two α-Ketoglutarate-Dependent Dioxygenases in Enantioselective Degradation of (*R*)- and (*S*)-Mecoprop by* Sphingomonas herbicidovorans *MH*, 179 J. BACTERIOLOGY 6674-6679 (1997)
EX1037	E. Otoxby & M.A. Hughes, *Engineering Herbicide Tolerance into Crops*, 8 TIBTECH 61-65 (1990)
EX1038	E.J. Perkins et al., *Use of* Alcaligenes eutrophus *as a Source of Genes for 2,4-D Resistance in Plants*, 35 WEED SCI. 12-18 (1987)
EX1039	PRINCIPLES OF WEED SCIENCE (V.S. Rao, ed., 2d ed. 2000)
EX1040	R.E. Saari, Substrate Specificity and Spectroscopic Properties of 2,4-Dichlorophenoxyacetic Acid/α-Ketoglutarate Dioxygenase, Doctoral Thesis, Mich. State Univ. (July 6, 1998)
EX1041	R.E. Saari, R.P. Hausinger et al., *Stereospecific Degradation of the Phenoxypropionate Herbicide Dichlorprop*, 6 J. MOLECULAR CATALYSIS B: ENZYMATIC 421-428 (1999)
EX1042	K.M. Schleinitz et al., *Localization and Characterization of Two Novel Genes Encoding Stereospecific Dioxygenases Catalyzing 2(2,4-Dichlorophenoxy)Propionate Cleavage in* Delftia acidovorans *MC1*, 70 APPLIED & ENVTL. MICROBIO. 5357-5365 (2004)
EX1043	U.S. Patent No. 6,153,401
EX1044	W.R. Streber et al., *Analysis, Cloning, And High-Level Expression of 2,4-Dichlorophenoxyacetate Monooxygenase Gene*

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Exhibit No.	Description
	tfdA *of* Alcaligenes eutrophus *JMP134*, 169 J. BACTERIOLOGY 2950-2955 (1987)
EX1045	W.R. Streber & L. Willmitzer, *Transgenic Tobacco Plants Expressing a Bacterial Detoxifying Enzyme Are Resistant to 2,4-D*, 7 BIOTECHNOLOGY 811-816 (1989)
EX1046	E. Vedler et al., *The Completely Sequenced Plasmid pEST4011 Contains a Novel IncP1 Backbone and a Catabolic Transposon Harboring* tfd *Genes for 2,4-Dichlorophenoxyacetic Acid Degradation*, 186 J. BACTERIOLOGY 7161-7174 (2004)
EX1047	A. Westendorf et al., *The Two Enantiospecific Dichlorprop/α-Ketoglutarate Dioxygenases from* Delftia acidovorans *MC1-Protein and Sequence Data of RdpA and SdpA*, 157 MICROBIO. RES. 317-322 (2002)
EX1048	A. Westendorf et al., *Purification and Characterization of the Enantiospecific Dioxygenases from* Delftia acidovorans *MC1 Initiating the Degradation of Phenoxypropionate and Phenoxyacetate Herbicides*, 23 ACTA BIOTECHNOLOGICA 3-17 (2003)
EX1049	Public Version of Stipulation and Proposed Order for Leave to File First Amended Complaint and to Amend Scheduling Order, *Corteva Agriscience LLC v. Monsanto Co.*, No. 1:22-cv-1046-GBW (D. Del.), D.I. 66
EX1050	Public Version of First Amended Complaint, *Corteva Agriscience LLC v. Monsanto Co.*, No. 1:22-cv-1046-GBW (D. Del.), D.I. 68
EX1051	R.F. Krausz et al., *Soybean* (Glycine max) *Tolerance to 2,4-D Ester Applied Preplant*, 7 WEED TECH. 906-910 (1993)
EX1052	C.T. Larue et al., *Development of Enzymes for Robust Aryloxyphenoxypropionate and Synthetic Auxin Herbicide*

[redacted]

Exhibit No.	Description
	Tolerance Traits in Maize and Soybean Crop, 75 PEST MGMT. SCI. 2086-2094 (2019)
EX1053	Admin. Office of the U.S. Courts, United States District Courts—National Judicial Caseload Profile, https://www.uscourts.gov/sites/default/files/data_tables/fcms_na_appprofile0331.2023.pdf (Mar. 31, 2023)
EX1054	Declaration of Dr. Robert P. Hausinger, Ph.D.
EX1055	Curriculum Vitae of Robert P. Hausinger, Ph.D.
EX1056	Joint Claim Construction Chart, *Corteva Agriscience LLC v. Monsanto Co.*, No. 1:22-cv-1046-GBW (D. Del.), D.I. 82
EX1057	OCLC WorldCat Search
EX1058	OCLC WorldCat Entry for R.E. Saari, Substrate Specificity and Spectroscopic Properties of 2,4-Dichlorophenoxyacetic Acid/α-Ketoglutarate Dioxygenase, Doctoral Thesis, Mich. State Univ. (July 6, 1998)
EX1059	OCLC FirstSearch Entry for R.E. Saari, Substrate Specificity and Spectroscopic Properties of 2,4-Dichlorophenoxyacetic Acid/α-Ketoglutarate Dioxygenase, Doctoral Thesis, Mich. State Univ. (July 6, 1998)
EX1060	R.E. Saari, Substrate Specificity and Spectroscopic Properties of 2,4-Dichlorophenoxyacetic Acid/α-Ketoglutarate Dioxygenase, Doctoral Thesis, Mich. State Univ. (July 6, 1998)
EX1061	Declaration of Alicia Julian

[redacted]

Exhibit No.	Description
EX1062	*Finding Dissertations and Theses: Home*, MICH. STATE UNIV., https://libguides.lib.msu.edu/ dissertations (accessed June 14, 2023)
EX1063-EX1069	Intentionally Omitted
EX1070	Reply Declaration of Robert P. Hausinger (PROTECTIVE ORDER MATERIAL)
EX1071	Intentionally Omitted
EX1072	Deposition Transcript of J. Martin Bollinger (June 21, 2024)
EX1073	Curriculum Vitae of Robert P. Hausinger, Ph.D. (updated)
EX1074	A. Bairoch & R. Apweiler, *The SWISS-PROT Protein Sequence Data Bank and Its Supplement TrEMBL in 1999*, 27 Nucleic Acids Res. 49-54 (1999)
EX1075	*Does UniProt KB Contain All Protein Sequences?*, UNIPROT, https://www.uniprot.org/help/uniprotkb_coverage (last updated Apr. 27, 2022)
EX1076	*Proposed Changes to the Enzyme List*, NOMENCLATURE COMM. OF THE INT'L UNION OF BIOCHEMISTRY & MOLECULAR BIO., https://iubmb.qmul.ac.uk/enzyme/supplements/sup2013/ newenz4.html#1141144 (last updated Mar. 1, 2024)
EX1077	P10088 TFDA_CUPPJ, UNIPROT, https://www.uniprot.org/ uniprotkb/P10088/entry (last updated Mar. 27, 2024)
EX1078	K. Nakajima et al., *Site-directed Mutagenesis of Putative Substrate-binding Residues Reveals a Mechanism Controlling the*

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Exhibit No.	Description
	Different Stereospecificities of Two Tropinone Reductases, 23 J. BIO. CHEM. 16563-16568 (1999)
EX1079	K. Valmsen et al., *Structural and Functional Comparison of 15* S- *and 15* R-*Specific Cyclooxygenases from the Coral* Plexaura Homomalla, 271 EUR. J. BIOCHEM. 3533-3538 (2004)
EX1080	G. Coffa et al., *On the Relationships of Substrate Orientation, Hydrogen Abstraction, and Product Stereochemistry in Single and Double Dioxygenations by Soybean Lipoxygenase-1 and Its Ala542Gly Mutant*, 280 J. BIO. CHEM. 38756-38766 (2005)
EX1081	Y. Ijima et al., *Inversion of Enantioselectivity of Asymmetric Biocatalytic Decarboxylation by Site-Directed Mutagenesis Based on the Reaction Mechanism*, 2005 CHEM. COMM. 877-879
EX1082	A. Baerga-Ortiz et al., *Directed Mutagenesis Alters the Stereochemistry of Catalysis by Isolated Ketoreductase Domains from the Erythromycin Polyketide Synthase*, 13 CHEM. & BIO. 277-285 (2006)
EX1083	M. Weiss et al., *The Physiology and Habitat of the Last Universal Common Ancestor*, 1 NAT. MICROBIOL. 16116 (2016)
EX1084	Annotated Excerpt of U.S. Patent Publication No. 2016/0108422 (EX1017), Figs. 6A-6E

WORD COUNT CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I hereby certify that the foregoing Petitioners' Reply to Patent Owner's Response contains 5,583 words as measured by the word processing software used to prepare the document, excluding the parts exempted from the word count by 37 C.F.R. § 42.24(c)(1).

July 2, 2024

/Dov P. Grossman/
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CERTIFICATE OF SERVICE

I hereby certify that on July 2, 2024, I caused the foregoing Petitioners' Reply to Patent Owner's Response, Petitioners' Second Updated Exhibit List, and Exhibits 1070, 1072-1084 to be served on counsel for Patent Owner and Petitioner Inari Agriculture, Inc. via e-mail:

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