Filed: August 16, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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BAYER CROPSCIENCE LP, MONSANTO COMPANY, AND

INARI AGRICULTURE, INC.

Petitioners,

v.

CORTEVA AGRISCIENCE LLC,
Patent Owner.

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IPR2023-01038[1]
U.S. Patent No. 11,299,745

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**PATENT OWNER'S SUR-REPLY**

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[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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## I. Introduction

On a full trial record, Petitioners failed to establish that Corteva '437 qualifies as prior art. Petitioners' priority challenge is based on legal error, imposing an incorrect legal standard requiring more than a *reasonable correlation* between structure and function under *Ariad* and *Ajinomoto*. Petitioners also err by demanding disclosure of common structures correlated to an unrecited "(R)-enantioselectivity" feature rather than the recited function of *degrading* the two required classes of herbicides. Petitioners further fail to establish (i) that skilled artisans would have expected any significant functional diversity within 85% and higher sequence identity to SEQ ID NO: 9, (ii) that Corteva's 2004 and 2005 Priority Applications lack disclosure of the AAD-1 active-site motif, or (iii) that the AAD-1 *active-site* motif lacks correlation to the claimed degradation *activity*. Grounds 1A and 1B are thus fatally flawed and should be rejected.

At institution, the Board initially found Grounds 2A and 2B "threadbare" and unpersuasive. ID, 61-69. On a full trial record, Petitioners have not sought to remedy any of the deficiencies the Board and Corteva identified. Grounds 2A and 2B should therefore also be rejected. Corteva thus respectfully asks that the Board confirm the patentability of all challenged claims.

## II. Grounds 1A and 1B: Petitioners Failed to Prove that the Challenged Claims Lack Priority or Are Unpatentable

Corteva '437 is not prior art if the challenged claims are entitled to priority to the 2004 or 2005 Priority Applications. ID, 28. Because Petitioners failed to establish lack of priority to either application, Grounds 1A and 1B should be rejected.

### A. Petitioners' Priority Challenge Is Based on Legal Error

#### 1. Petitioners Apply an Incorrect Legal Standard for Function-Correlated Common Structure

As detailed in Corteva's Response, the Federal Circuit requires only a reasonable *correlation* between common structure and function under *Ariad* and *Ajinomoto*—not the higher *causation* standard Petitioners applied in demanding that each common structure be "responsible for" or "determinative" of function. POR, 44-48. In *Ajinomoto*, a common consensus sequence was not necessary or *responsible for* producing stronger promoters (i.e., some promoters further from the consensus sequence were stronger). *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342, 1360 (Fed. Cir. 2019). The consensus sequence was nonetheless *related* to promoter strength. *See* POR, 45-46. That reasonable correlation is all the law requires. *Ajinomoto*, 932 F.3d at 1360 ("we have spoken more modestly of a '*correlation* between structure and function'" (emphasis in original)) (quoting *Ariad*, 598 F.3d at 1350).

Petitioners continue to apply an incorrect legal standard, arguing that the law requires disclosure of structural features "responsible for" a claimed function. Reply, 7. The only authority Petitioners cite, however, is a pre-*Ariad* BPAI decision, which evaluated claims without any structural motif or consensus sequence limitations. *See Ex Parte Porro*, 2008 WL 2259960 at *2-3 (BPAI Mar. 11, 2008) (informative). Petitioners identify no legal basis for departing from the reasonable-correlation standard set forth in the Federal Circuit's *en banc Ariad* decision and the precedential *Ajinomoto* decision; none exists.

Petitioners thus continue to invite legal error and have failed to establish that the AAD-1 motif and at least 85% sequence identity limitations lack correlation to the dual herbicide-degrading function under a proper legal standard.

### 2. Petitioners Disregard the Claim Language and Rely on an Impermissible *Sub Silentio* Claim Construction

Petitioners further commit legal error by failing to sufficiently address the requirements of the '745 patent claims. Instead of analyzing the claimed function of *degrading* phenoxy auxin and FOP herbicides, Petitioners focus their written-description arguments on something different, i.e., "(R)-enantioselectivity" or "(R)-enantiospecificity," which are terms that do not appear in any of the '745 patent claims. Indeed, Dr. Hausinger refers to these terms 50+ times in his reply declaration while barely mentioning the actual claim limitations. *See* Ex. 1070. That is legal

error because a written description analysis requires evaluating the specification for disclosure of what is claimed, not other unrecited features. *Ariad*, 598 F.3d at 1351; *United Therapeutics Corp. v. Liquidia Techs., Inc.*, 74 F.4th 1360, 1371 (Fed. Cir. 2023) (affirming denial of written-description challenge based on features "not recited in the claims").

Dr. Hausinger has a history of overreaching with his opinions in this manner. In a previous litigation, he contended that AAD-1 had "monooxygenase" activity rather than dioxygenase activity. Ex. 2066, 50:8-51:13, 53:8-23, 55:3-59:1, 63:14-64:14. He took that position at Bayer's behest, notwithstanding that (i) the differences between monooxygenases and dioxygenases had been known for over 50 years, (ii) he had personally conducted research to confirm that enzymes in the same family as RdpA/AAD-1 are αKG-dependent *dioxygenases*, and (iii) he had conceded that it would be "scientifically invalid or misleading" to call an αKG-dependent dioxygenase a "monooxygenase." *Bayer CropScience AG v. Dow Agrosciences, LLC*, No. 10-1045, 2012 WL 4498527, *3 n.5 (Sept. 27, 2012). Rejecting Dr. Hausinger's testimony about AAD-1 allegedly having "monooxygenase" activity, the court in that case granted summary judgment against Bayer's infringement claim, crediting Dr. Bollinger's opinions instead. *Id.* at *6-8.

Here, while acknowledging that claim 1 does not include the terms "(R)-enantioselective" or "(R)-enantiospecific," Dr. Hausinger asserted during

cross-examination that he was reading such requirements into the claims because they were allegedly inherently present. Ex. 2066, 31:17-32:23. Dr. Hausinger applied these "(R)-enantioselective" and "(R)-enantiospecific" terms strictly in his analysis, stating that in claim 1, a skilled artisan would "probably assume that it means [AAD-1 is] *only acting on (R)-enantiomers*." *Id.*, 32:13-23.[2] The '745 patent claims, however, also include degradation of non-(R)-enantiomeric substrates, such as 2,4-D. Ex. 1003, claim 11 ("wherein said phenoxy auxin herbicide is an achiral phenoxy auxin selected from the group consisting of 2,4-D and MCPA"), 3:52-54. Dr. Hausinger reiterated his incorrect understanding of the claims during Petitioners' redirect questioning. Ex. 2066, 80:6-18 ("the claims really focused on (R)-enantiospecificity"); Ex. 1070, ¶ 19 ("claimed (R)-enantioselective activity").

Petitioners and their expert Dr. Hausinger have thus conducted their written-description analysis by improperly reading strict (R)-enantioselectivity and (R)-enantiospecificity limitations into the claims. Such *sub silentio* claim constructions are improper. Under the Board's rules, Petitioners had to present any claim construction positions in the original Petition. 37 C.F.R. § 42.104(b)(3) (the Petition

[2] When asked about enzymes that were not strictly enantiospecific, Dr. Hausinger refused to characterize them as having enantiospecificity. He instead discussed their activity in terms of enantiomer "preference." *See, e.g.*, Ex. 2066, 17:5-18:10.

"must identify the following … (3) How the challenged claim is to be construed."). But the Petition here identified no terms for construction. Pet., 17. Nor were any such terms raised in claim construction in the related litigation. *See id.*; ID, 11 n.4, 25-26. Grounds 1A and 1B should thus be rejected as improperly based on a claim construction position never presented in the Petition. *See, e.g.*, *GCE Gas Control Equip. Inc. v. VBox, Inc.*, IPR2023-00326, Paper 27 at 10-11, 26-27 (PTAB June 18, 2024).

Petitioners' (R)-enantioselectivity arguments also lead them to further error in their written-description analysis. Petitioners demand that the Priority Applications disclose residues providing the "basis for RdpA's (R)-enantioselectivity," pointing to the Muller publication as illustrating such residues. Reply, 2, 10; Ex. 1070, ¶¶ 9, 22. But to explain RdpA's greater activity on (R)-enantiomers, Muller identified residues that *prevent (S)-enantiomers from binding*. Ex. 1035, 1364 ("For RdpA variants, Gln93, Ile106, and Phe171 are proposed to sterically exclude binding by the incorrect enantiomer"); Ex. 2066, 27:21-28:8 ("It means that the glutamine 93 is disallowing the wrong enantiomer from binding."); *see* Ex. 1003, Table 5; Ex. 2016, 44:24-45:23. Such information is legally irrelevant to written description—Petitioners cite no authority requiring disclosure of amino acid residues explaining why *unclaimed substrates* (e.g., (S)-enantiomers) are not degraded.

In addition to their legal errors above, Petitioners presented no scientific evidence that residues providing a "basis for (R)-enantioselectivity" needed to be identified and precluded from substitution to maintain the claimed function. In Muller, at most, a few substitutions in *SdpA* relaxed its steric blocking so that it had, in addition to activity on the (S)-enantiomer, also a small amount of activity on the (R)-enantiomer. Ex. 2066, 24:4-27:5, 28:10-29:4; Ex. 1035, Table I. But even if a similar effect were reported for RdpA variants, Petitioners fail to explain how the ability to additionally degrade a small amount of an (S)-enantiomer would take such variants outside the scope of the claims. *See* Ex. 1003, 52:8-54:59, Table 4 (reporting AAD-1 activity on (S)-cyhalofop). Ex. 2066, 31:7-15.

Accordingly, Petitioners' priority challenge is based on legal error and directed to subject matter not recited in the claims.

### B. The Specification Discloses Function-Correlated Common Structures

Under a proper legal standard, the Priority Applications disclose both the AAD-1 motif and the at least 85% sequence identity limitations, and those common structures are correlated to the claimed dual herbicide-degrading function. *Ariad*, 598 F.3d at 1350. Petitioners have therefore failed to meet their burden of proving that the disclosures of the 2004 and 2005 Priority Applications are insufficient. POR, 28.

### 1. The Specification Discloses the AAD-1 Motif

The Priority Applications amply disclose the AAD-1 motif. As Dr. Bollinger testified without rebuttal, skilled artisans understood that each αKG-dependent dioxygenase has the distinctive characteristic of a specific active-site motif within the variable αKG dependent dioxygenase motif. Ex. 2015, ¶¶ 110-112. It is undisputed there is only one such set of active-site residues in SEQ ID NO: 9—i.e., the claimed AAD-1 motif—and therefore no selections are necessary. *Id.*, ¶¶ 84, 113. Petitioners' argument that an obviousness-type analysis would have been required is thus incorrect. Reply, 8-9.

Dr. Bollinger's testimony that a skilled artisan would have readily recognized the AAD-1 motif in SEQ ID NO: 9 is undisputed. Ex. 2015, ¶ 113. Petitioners did not cross-examine Dr. Bollinger on this testimony (they barely cross-examined him at all). His opinion is supported by Schleinitz 2004, which confirms that skilled artisans had *already identified the RdpA (AAD-1) motif* by 2004 and published the location of those active-site residues and their spacing in the RdpA sequence, as confirmed by the testimony of both parties' experts. *Id.*, ¶¶ 114, 72-74; Ex. 2016, 24:19-26:7; Ex. 1042, 5360. Petitioners' argument that Schleinitz only discloses the consensus αKG dependent dioxygenase motif is thus incorrect. Reply, 9-10.

Petitioners' suggestion that Corteva relies on Schleinitz 2004 for "gap-filling" or to "supply" claim limitations is wrong. Reply, 9. Schleinitz 2004 is unrebutted

confirmatory evidence that skilled artisans would know the AAD-1 motif from the RdpA sequence alone, just as Dr. Bollinger testified. Ex. 2015, ¶ 113. To the extent anything further is required, Schleinitz 2004 also confirms that a skilled artisan would have come to SEQ ID NO: 9 in the specification equipped with the knowledge of where the residues of the AAD-1 motif in that sequence were located. That is the legally required "lens" through which written description is assessed—not gap-filling. *Ossia, Inc. v. Energous Corp.*, PGR2016-00024, Paper 20, 37-38 (PTAB Nov. 29, 2016) ("[c]entral to the analysis is looking at the [written-description] issue through the lens of one" skilled in the art (citing *Ariad*, 598 F.3d at 1351)).

### 2. The Disclosed AAD-1 Motif Is Correlated to the Dual-Herbicide Degrading Function

The AAD-1 motif, which marks the active site of AAD-1 enzymes, is also amply correlated to the claimed function, i.e., enzymatic activity that "*degrades* a phenoxy auxin herbicide and an (R)-aryloxyphenoxypropionate herbicide." Ex. 1003, claim 1.

Dr. Bollinger rebutted Petitioners' allegation that the AAD-1 motif lacks structure-function correlation. As he testified, the defined residues and fixed spacing of the AAD-1 motif set the contours for the enzymes' active site. Ex. 2015, ¶¶ 111-112, 65-66, 149. That active site accommodates the required reactants for the enzymatic degradation reaction to occur: α-ketoglutarate, oxygen, ferrous iron, and

the herbicide (either a phenoxy auxin or a FOP). *Id.*; Ex. 2016, 35:6-17 ("one requires the correct coordination of alpha-ketoglutarate"), 32:13-21 (αKG "is what really drives the reaction"). Petitioners presented no contrary evidence in reply. Dr. Bollinger's testimony that skilled artisans would have recognized the *active site* of AAD-1 enzymes to be correlated to their *activity* is unrebutted. Ex. 2015, ¶¶ 115-116; Ex. 1003, 18:43-62 (the role of the active-site motif is "essential for catalytic activity"); Ex. 1004, ¶ [0059]; Exs. 1005-1010, 1021, ¶ [0085].

Indeed, by 2004, the active-site motif residues of RdpA (AAD-1) were already recognized as "*functionally important*" and "*functionally essential*." Ex. 1042, 5357, 5362. The '745 patent inventors then investigated AAD-1's mechanism of action and reported that AAD-1 degrades (R)-FOP herbicides in a similar way as phenoxy auxin herbicides—i.e., via an αKG- and $Fe^{II}$-dependent oxidation reaction coordinated by the active-site motif residues. Ex. 1003, 49:21-50:45; Ex. 2015, ¶¶ 88-90. The inventors' disclosure of a common, AAD-1-catalyzed degradation pathway for both phenoxy auxin and (R)-FOP herbicides supported by the same active site confirms the correlation between the AAD-1 active-site motif and the claimed dual-herbicide degrading function. Ex. 2015, ¶¶ 116-118.

Within the AAD-1 motif, Petitioners also fail to establish that the particular spacings between the required residues are unrelated to function. *Certain L-Tryptophan, L-Tryptophan Products, and Their Methods of Production*, Inv. No.

337-TA-1005, 2018 WL 8648370, at *25 (USITC Jan. 11, 2018) (rejecting written-description challenge as failing to establish that a consensus sequence was "*unrelated*" to a claimed function), *aff'd*, 932 F.3d at 1360. Indeed, the consistent *conservation* of the AAD-1 motif residues and their specific spacing, including by Petitioners themselves in their RdpA variants, undercuts their position that the unique residue spacing within the AAD-1 motif does not matter to the claimed function. POR, 54-55; Ex. 2015, ¶¶ 65-66, 116.

While Dr. Hausinger sought to identify examples of αKG-dependent dioxygenases having the same motif spacing but different functions, he could only identify one such pair—TauD and AtsK. Ex. 1070, ¶ 26. Neither has the same motif as AAD-1. Moreover, in his declaration, Dr. Hausinger omitted that TauD and AtsK share only 33% sequence identity, i.e., where different function is generally expected. Ex. 2066, 47:19-48:7; POR, 7. Nowhere did Dr. Hausinger identify any enzymes having the same motif spacing *and* at least 85% sequence identity as having different functions, as the claims require here. *See also* Ex. 2066, 43:19-46:18 (Dr. Hausinger acknowledging that the other plant enzymes he cited did not have a motif within the variable ranges of the consensus αKG motif).

### 3. The Disclosed Common Structural Feature of at Least 85% Sequence Identity with SEQ ID NO: 9

#### a. At Least 85% Sequence Identity with SEQ ID NO: 9 Is Correlated to Function

In addition to having the common AAD-1 active-site motif, the AAD-1 enzymes of the claims must be highly identical in sequence, having at least 85% sequence identity to SEQ ID NO: 9. Petitioners cite no evidence that such high sequence identity is *unrelated* to conserving enzyme function, particularly when also maintaining the same active-site motif residues and spacing. *See L-Tryptophan Products*, 2018 WL 8648370, at *25. Instead, Petitioners present a piecemeal analysis addressing the two common structural features of the ’745 patent claims separately, rather than together “as a whole” as the law requires. *See* Ex. 1070, §§ III.A, III.C; *seeSandoz Inc. v. Boehringer Ingelheim Int’l GmbH*, PGR2022-00037, Paper 13 at 7 (PTAB Feb. 23, 2023).

The Priority Applications disclose that *variants*—i.e., not just natural proteins—having the “same or similar activity” of exemplified proteins like AAD-1 will typically have at least 60% sequence identity, including 85% or higher sequence identity. Ex. 1003, 37:24-43; Ex. 1004, ¶ [0116]; Exs. 1005-1010, 1021, ¶¶ [0142]. They further disclose that among αKG-dependent dioxygenases, enzymes having 85% and higher are “highly identical” and expected to have similar properties (i.e., sequence-function correlation). Ex. 1003, 44:11-24; Exs. 1005-1010, 1021, ¶ [0171].

In other words, the AAD-1 enzymes of the claims have the *same active-site motif* and cannot vary much from the overall sequence of SEQ ID NO: 9. Petitioners' case is thus even more deficient than the challenger's in *Lifescan*, where the Board found a written-description challenge unpersuasive where an enzyme sequence had 593 amino acids, permitted 59 substitutions, and had a functionally important motif that was not recited in the claims. PGR2019-00032, Paper 11 at 18-19, 28-30. Here, SEQ ID NO: 9 is shorter (295 amino acids), only up to 44 substitutions are permitted, and the five amino acid AAD-1 motif is required by the claims and has fixed residues and spacing, unlike the motif in *Lifescan*.

The Priority Applications' disclosures comport with the understanding of skilled artisans. Dr. Bollinger testified without rebuttal that skilled artisans recognized a general trend that higher sequence identities more strongly correlate to conservation of enzyme function. Ex. 2015, ¶ 100; Ex. 1072, 7:20-9:1. Indeed, the Board correctly noted at institution that SEQ ID NO: 9 must be correlated to the claimed dual-herbicide degrading function. ID, 53. Skilled artisans would have recognized that sequences closer to SEQ ID NO: 9 would be more likely to maintain that function than sequences having more distant sequence identity. Ex. 2015, ¶ 100; POR, 37-38; *Ajinomoto*, 932 F.3d at 1360 (finding adequate structure-function correlation where sequences closer to a consensus sequence generally—but not always—had stronger activity). As Dr. Bollinger testified, that expectation is further

strengthened by additionally conserving the AAD-1 active-site motif. Ex. 2015, ¶ 112. On a full trial record, Dr. Hausinger identified no enzymes that have the AAD-1 motif, at least 85% sequence identity to SEQ ID NO: 9, and catalyze a different reaction than AAD-1. *Id.* Accordingly, Petitioners' original conclusory theory about "*massive and diverse* genera covered by the claims" remains devoid of evidentiary support on a full record. Ex. 1054, ¶ 76.

#### b. Petitioners Fail to Establish Functional Diversity Within 85% Sequence Identity to SEQ ID NO: 9

The complete trial record further establishes that functional variation between enzymes having high sequence identity is rare, as Dr. Bollinger testified. Ex. 2015, ¶ 123. Dr. Hausinger sought to identify examples of such variation in his reply declaration. But across the entire field of enzymology, he identified only five in total (and none alleged to have an αKG motif). Ex. 1070, ¶ 60-61 (citing Exhibits 1078-1082); *compare* Ex. 2027, 1113 (reporting a study on *486,000* pairs of proteins). For two out of those five examples, Dr. Hausinger cited later, non-prior art studies. Ex. 1082; Ex. 1080. Moreover, none of these studies evaluated enzymes' ability to accept different enantiomeric substrates, and thus they are irrelevant even under Petitioners' legally incorrect (R)-enantioselectivity theory. *Supra* § II.A.2. Instead, the enzymes in these studies accepted the *same substrate*, differing only in their enantiomeric reaction product ratios. Ex. 2066, 12:17-23, 13:17-20, 19:17-23:3.

Petitioners therefore place incorrect reliance on Schleinitz's speculation that "only a few residues" are responsible for RdpA's substrate specificity, as such situations are rare in the art. *See* Reply, 19. Indeed, on a full trial record, that speculation has not been shown to be true. Petitioners also fail to establish that skilled artisans would have attributed an unexpected (R)-enantiospecificity to a particular sequence in a crude mixture of proteins from *A. denitrificans* when Saari 1999 did not even make that attribution. Ex. 2015, ¶¶ 122-130. In his own work, and contradicting his testimony in this case, Dr. Hausinger has been critical of researchers seeking to attribute a particular function to an enzyme without purifying it and characterizing it in isolation. Ex. 2066, 61:12-62:25 ("They did not purify the protein and characterize it. So that's what we wanted to do."). Indeed, the prior art rejected any notion that a particular *A. denitrificans* sequence had (R)-specific activity, stating it was "not supported." Ex. 1042, 5362.

#### c. Petitioners' Criticism of Sequence-Function Correlation Studies Is Misplaced

Rather than meaningfully addressing the specification's disclosure that variants having sequence identities of 85% and higher correlate to having the same or similar function, Petitioners devote far more of their Reply to a prior-art background study by Tian 2003. Reply, 11-18. Petitioners' arguments miss the forest for the trees.

At institution, the Board invited evidence on whether, for enzymes other than TfdA, there was a "more universal principle" that highly identical (85-98%) sequences would be expected to retain similar properties. ID, 40. As Corteva detailed in its Response, enzymes in general are indeed unique in that they exhibit strong conservation of function at high sequence identities—a feature not shared with other types of proteins. POR, 30-35; Ex. 2015, ¶¶ 41-44. Petitioners present no evidence that RdpA/AAD-1 is any different in this manner. Indeed, its related (S)-counterpart enzyme, SdpA, shares only 30% sequence identity with RdpA. Ex. 2015, ¶¶ 123-124.

While Petitioners pick at aspects of Tian's study, they ignore that enzymologists in the field had devoted extensive time and resources towards assessing the extent to which sequence identity is correlated to enzyme function. Ex. 2015, ¶¶ 29-40; Ex. 2028, 596 ("[G]iven an alignment between protein A and B, and given the experimental annotation for the enzyme A, what is the probability that B has the same enzymatic activity as A?"); Ex. 1070, ¶¶ 33-50. Indeed, those enzymologists:

- Used the best available, standardized evidence of enzyme function for analyzing enzymes across the entire enzymology field. *E.g.*, Ex. 2019, 864 (EC numbers are the "best developed and most widely used functional classification scheme").

- Used the best available and quality-controlled protein/enzyme databases. *E.g.*, Ex. 2019, 864 (SWISS-PROT is the "gold standard"); Ex. 2026, 98 (FSSP database).

- Adjusted their enzyme datasets to avoid over-representation of particular enzyme families, making their results more representative and generalizable. *E.g.*, Ex. 2028, 595-596, 605-606; Ex. 2019, 863-865.

- Analyzed conservation of function based on (i) enzyme sequences alone and also (ii) combined enzyme/non-enzyme datasets. *E.g.*, Ex. 2019, 866 (analyzing "enzyme–non-enzyme sequence pairs").

- Conducted studies both with and without multifunction/multidomain enzymes. *E.g.*, Ex. 2028, 605; Ex. 2026, 99; Ex. 2066, 22:1-11; Ex. 2015, ¶ 33.

- Continued to refine and build upon previous studies, including by Devos 2000 (Ex. 2026), Wilson 2000 (Ex. 2024), Todd 2001 (Ex. 2027), Rost 2002 (Ex. 2028), and Tian 2003 (Ex. 2019), with all of them consistently finding a high degree of sequence-function correlation at 85% and higher sequence identity. POR, 31-32; Ex. 2028, 604 (Fig. 5).

Petitioners fail to identify any evidence suggesting that these sequence-function correlation studies were irrelevant for enzyme variants. Instead, Petitioners legally err by assuming that a *skilled artisan* would exercise *no skill* by randomly substituting all 20 amino acids at every possible location to come up with their

calculation of $20^{44}$ sequences, while also treating "every modification as equivalent." Reply, 15-16. Petitioners further assert that one would then need to rely on "sequence identity alone [to] predict[] function," which again legally errs by analyzing sequence identity in isolation, divorced from the AAD-1 motif requirement of the challenged claims. *Id.*, 13.

One of skill would readily understand that the types and locations of substitutions can matter. As Dr. Bollinger testified without rebuttal, artisans exercising ordinary skill routinely made variants that *maintained the function of a natural parent enzyme*. Ex. 2015, ¶¶ 58-59. Such skill required only basic, known principles: maintaining the active-site motif and other highly conserved residues, and avoiding substitutions to oppositely charged residues or to dramatically different sized residues. *Id.*; POR, 13. On a full trial record, Petitioners have not disputed any aspect of this ordinary skill in this field. Nor could they, as Dr. Bollinger's testimony is amply supported. *E.g.*, POR, 35, 11-13; Ex. 2025, 204-205 ("changes at key active site residues or other highly conserved residues are generally deleterious"); *see Lifescan*, PGR2019-00032 at 30 (crediting testimony that skilled artisans could look at variant enzyme sequences and "make a fair guess" whether it would maintain qualitatively similar activity as a parent enzyme).

Petitioners fail to diminish the importance of sequence-activity relationships for enzyme variants. Reply, 17-18. Minshull repeatedly discloses that alignments to

"related" and "homolog" sequences are valuable, including both orthologous and paralogous sequences (e.g., SdpA), which were well known in the art. Ex. 2025, 203 (citing the "successful philosophy of using substitutions found in homologs"), 204-205 (using the "[d]egree of amino acid conservation at positions in related proteins"); Ex. 1042, Fig. 2; Ex. 1035, 1357-58. Furthermore, Dr. Hausinger's misplaced assertion about the purported need for screening ignores Minshull's conclusion that sequence-activity relationships *minimize* any experimentation needed:

| Dr. Hausinger's Testimony | Minshull (Ex. 2025) |
|---|---|
| "Minshull recognizes that artificially generated variants (for example, through the use of DNA shuffling) *had to be screened* for activity." Ex. 1070, ¶ 48 (citing Ex. 2025, 202-203). | Concluding that "the use of sequence-activity relationships *should free protein engineers from the expenses and inaccuracies of high-throughput screens* . . . ." Ex. 2025, 207. |

Dr. Hausinger also overreaches by assuming that insolubility experienced with a set of AAD-1 variants prepared for isolation and testing (i.e., outside their normal cellular environment) means that they lack the claimed dual-herbicide degrading activity. Ex. 1070, ¶¶ 65-68; Reply, 23-24. As Dr. Hausinger conceded during cross-examination, many routine techniques are available for improving

solubility to the extent needed to run an assay, including using maltose-binding protein (MPB) or adjusting buffer solution components, temperature, or pH—none of which he evaluated in the context of the AAD-1 variants here. Ex. 2066, 34:25-42:12. Nor did he evaluate whether potentially deleterious substitutions had been made to highly conserved residues in those variants. Ex. 2066, 72:10-78:14; Ex. 2025, 204-205.

### C. The Disclosed AAD-1 Species Are Representative of the Limited Claimed Genus

Corteva's Response explained that the claimed genus of AAD-1 enzymes is essentially the opposite of a structurally or functionally diverse genus—it is a group of *highly identical* enzymes with a conserved active-site motif. POR, 56-58. The disclosed AAD-1 species are thus amply representative of the genus of AAD-1 enzymes, which are all of a similar type. *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1165 (Fed. Cir. 2019) (the law "allow[s] relatively few representative examples or formulas to support a claim on a structurally similar genus").

As detailed above, Petitioners fail to establish that any significant structure-function diversity exists within 85% identity to SEQ ID NO: 9. *Supra* § II.B.3.b. Petitioners thus fail to establish that the disclosed AAD-1 variants are not representative of the claimed genus.

### D. Claim 2 Is Adequately Described

Petitioners repeat their incorrect "gap-filling" argument regarding the claim 2 motif, which includes an additional arginine at position 285. Reply, 9-10. As Corteva's Response established, the significance of this arginine was well-documented in the prior art. POR, 58-60.

Elkins previously reported that this conserved arginine is "conserved across a range" of αKG-dependent dioxygenases and serves as a substrate ligand in the enzyme TauD. Ex. 2015, ¶ 140; Ex. 1023, 5189-5190. Hotopp reported that the arginine also had a substrate-ligand role in the enzyme TfdA. Ex. 2015, ¶ 141; Ex. 1029, 9792. Schleinitz 2004 then published an alignment of RdpA with TfdA and TauD, showing that this arginine is also conserved in RdpA, indicating it serves a similar role in RdpA. Ex. 2015, ¶¶ 141-142; Ex. 1042, Fig. 2. Indeed, Schleinitz expressly discloses that a substrate-binding arginine similar to TfdA's "was present" in RdpA. Ex. 1042, 5362; *Rivera v. Int'l Trade Comm'n*, 857 F.3d 1315, 1322-23 (Fed. Cir. 2017) (a skilled artisan's knowledge is permissibly relied upon for written description when it "*inform[s]* what is actually in the specification").

Dr. Hausinger asserts that skilled artisans would have ignored all of the accumulated knowledge about the role of this well-characterized arginine residue. Ex. 1070, ¶¶ 16-17. But his testimony again contradicts his own previous disclosures outside of this proceeding, where he relied on the same literature detailed above to

advocate that this arginine residue serves the same, known role in RdpA. Ex. 1035, 1364 ("Comparable Arg residues are conserved in many $Fe^{II}$/αKG-dependent dioxygenases, where they play a dual role of binding the primary substrate and the C1 carboxyl group of αKG . . . Such a dual role is predicted for Arg285 of RdpA") (citing Elkins, Ex. 1023).

### E. Grounds 1A and 1B Are Also Fatally Flawed in View of Petitioners' Inconsistent Positions Regarding Anticipation

In their Reply, Petitioners advanced an extreme position denying the existence of any AAD-1 motif and asserting that the five active-site residues and their spacing in the RdpA sequence cannot disclose the claimed AAD-1 motif. Reply, 10; Ex. 1070, ¶ 27; Ex. 2066, 70:12-21. Grounds 1A and 1B should therefore also be rejected because Petitioners' allegations directly contradict their anticipation positions. *See Google LLC v. Uniloc USA, Inc.*, IPR2017-02082, Paper 10, 12-14 (PTAB Mar. 29, 2018) (rejecting anticipation ground based on "Petitioner's inconsistent and contradictory arguments" about a reference's disclosure).

For anticipation, Petitioners contend that the 2005 Priority Application, Corteva '437, discloses the AAD-1 motif because SEQ ID NOs: 9 and 10 have the required residues and their required spacing. Pet., 44-45. For written description, however, Petitioners contend the opposite, denying those same disclosures in the

same Corteva ’437 application. During cross-examination, Dr. Hausinger rejected the basis of Petitioners’ anticipation contentions:

| Petitioners’ Anticipation Position Regarding Corteva ’437 and the AAD-1 Motif | Dr. Hausinger’s Testimony Regarding Corteva ’437 and the AAD-1 Motif |
|---|---|
| “SEQ ID NO: 9-10 have a histidine (H) at position 111, aspartic acid (D) at position 113, threonine (T) at position 138, histidine (H) at position 270, and arginine (R) at position 281.”<br>Pet., 44-45. | Q. “[D]oes the disclosure in Seq. ID No. 10 with the histidine at position 111, aspartic acid at position 113, threonine at position 138, histidine at position 270, arginine at position 281 disclose the AAD-1 motif of the challenge claims?<br>**A. And I would say no.**”<br>Ex. 2066, 71:12-18; 69:16-70:3 (similar for SEQ ID NO: 9). |
| “Corteva ’437 discloses that SEQ ID NOS:9 and 10 have the required amino acids at those positions.”<br>Ex. 1054, ¶ 122. | Q. [I]t's not sufficient . . . for Seq. ID 10 to have the required amino acids at those positions, correct?<br>**A. In my opinion, there is no AAD-1 motif denoted in this patent.**” |

| | |
|---|---|
| | Ex. 2066, 71:19-24, 70:12-21 (similar for SEQ ID NO: 9). |

Petitioners cannot have the same disclosures in Corteva ’437 mean different things depending on which argument they are advancing at a given time. *Jaguar Land Rover N. Am., LLC v. Blitzsafe Tex., LLC*, IPR2018-00544, Paper 8, 21-22 (PTAB Aug. 10, 2018) (rejecting petitioners’ inconsistent positions about the prior art as impermissibly vacillating depending on the issue at hand). Anticipation requires a reference to “clearly and unequivocally disclose” the claimed invention to a skilled artisan. *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). Petitioners cannot meet that exacting standard in view of their position that Corteva ’437’s SEQ ID NOs: 9 and 10 do not disclose the AAD-1 motif, even under the less-strict standard for written description. ID, 34-35 (written description permits reliance on well-known information from the prior art). Petitioners raised no other inherency or obviousness arguments directed to the AAD-1 motif and cannot raise such arguments now. *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016).

On a full trial record, Petitioners have not met their burden of proving anticipation in view of their self-contradictory arguments and testimony. Grounds

1A and 1B should thus be rejected for this additional reason, independent of the flaws in Petitioners' priority challenge.

## III. Grounds 2A and 2B: Petitioners Failed to Establish Obviousness of Any Challenged Claim

At institution, the Board found Grounds 2A and 2B unpersuasive. ID, 64-68. On a full trial record, Petitioners' allegations have not improved, and therefore these grounds should be rejected.

No inherency: Petitioners' "threadbare" inherency theory remains legally insufficient. ID, 65; POR, 63-64. Dr. Hausinger testified that many factors affect enzyme activity and expression (including in transgenic plants)—none of which were addressed in the Petition or Petitioners' Reply. Ex. 2016, 57:16-58:22; *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) ("[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient" for inherency).

No response to Corteva's arguments: In their Reply brief, Petitioners present no evidence to buttress their threadbare inherency theory (POR, 64-65), no evidence suggesting a POSA would have reasonably expected success in achieving the dual herbicide-degrading activity (POR, 61-63; Ex. 1072, 17:5-14), and no evidence that Streber's plant-transformation method was usable with RdpA (POR, 65-66). Dr. Hausinger devoted only a single paragraph of his reply declaration to Grounds

2A and 2B, and he did not seek to remedy any of the deficiencies that the Board and Corteva identified in Petitioners' positions. Ex. 1070, ¶ 69. Petitioners also provide essentially no response to Corteva's arguments regarding lack of motivation and the Petition's failure to allege inherency with respect to any of the dependent claims requiring herbicide tolerance. POR, 66-69.

Objective evidence of nonobviousness: Petitioners' own scientists have cited and credited the '745 patent's inventors as pioneering the use of RdpA/AAD-1 in agriculture, determining that FOP herbicides are suitable substrates, and establishing AAD-1's mechanism of action, just as the inventors originally disclosed in the Priority Applications and then published in the literature by 2010—long before Petitioners published any RdpA variants. POR, 71-72; Ex. 2059, 256. On a full trial record, Petitioners have not argued that any of their purportedly thousands of RdpA variants lack the AAD-1 motif or have less than 85% sequence identity to SEQ ID NO: 9, confirming that Corteva's objective evidence has ample nexus to the scope of the claims.

## IV. Conclusion

Corteva respectfully requests that the Board reject Petitioners' unpatentability grounds and confirm the patentability of all claims of the '745 patent.

Respectfully submitted,

Dated: August 16, 2024

/Pier D. DeRoo/
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## CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Pier D. DeRoo, certify that **Patent Owner's Sur-Reply** contains 5,555 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: August 16, 2024

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## CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Sur-Reply** was served electronically via email on August 16, 2024, in its entirety on the following:

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