Paper No. 22
Filed: April 16, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BAYER CROPSCIENCE LP, MONSANTO COMPANY, AND
INARI AGRICULTURE, INC.
Petitioner,

v.

CORTEVA AGRISCIENCE LLC,
Patent Owner.

IPR2023-01038[1]
Patent 11,299,745

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.

TABLE OF CONTENTS

I. Introduction 1

II. Scientific Background and State of the Art 5

A. Enzymes 5

1. Enzyme Classification 5

2. Enzyme Sequence-Function Relationships and Predicting Function Based on Sequence Identity 6

3. Enzyme Variants 11

4. α-Ketoglutarate-Dependent Dioxygenases and RdpA (AAD-1) 13

III. The ’745 Patent 18

A. AAD-1 Enzymes 18

B. The Specification’s Twenty-Six Examples 22

C. The Claims 23

IV. Level of Skill in the Art 26

V. Issues Raised in the Institution Decision 26

VI. Grounds 1A and 1B: Petitioners Failed to Establish that the Challenged Claims Lack Priority or Are Unpatentable 28

A. The ’745 Patent Discloses Common Structures Correlated to the Claimed Function 29

1. The Common Structural Feature of at Least 85% Sequence Identity with SEQ ID NO: 9 30

2. The Common AAD-1 Active-Site Motif 38

a. The Specification Describes the Active-Site Motif of AAD-1 Enzymes 38

b. The Disclosed AAD-1 Motif Is Correlated to Function 42

3. Petitioners' Common-Structure Arguments Are Legally Deficient 44

a. Petitioners Fail to Apply a Correct Legal Standard for Function-Correlated Structure 44

b. Petitioners' Arguments Based on Other AAD-1 Structures Are Also Based on Legal Error 48

c. Petitioners Erroneously Rely on Post-Filing Date Evidence 51

B. The Disclosed AAD-1 Enzymes Are Representative of the Narrow Claimed Genus 56

C. Claim 2 Is Adequately Described 58

VII. Grounds 2A and 2B: Petitioners Fail to Establish that the Challenged Claims Would Have Been Obvious 60

A. Petitioners Fail to Establish a Reasonable Likelihood of Success 61

B. Petitioners Fail to Establish Inherency 63

C. Petitioners Fail to Establish Motivation to Combine Streber, Saari, and Schleinitz 67

D. Objective Evidence Strongly Supports Nonobviousness 69

VIII. Conclusion 72

TABLE OF AUTHORITIES

Page(s)

Cases

AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.,
759 F.3d 1285 (Fed. Cir. 2014) ..... *passim*

In re Adams,
356 F.2d 998 (CCPA 1966) 64

Ajinomoto Co. v. ITC,
932 F.3d 1342 (Fed. Cir. 2019) ..... *passim*

In re Albrecht,
514 F.2d 1389 (CCPA 1975) 63, 70

Amgen Inc. v. Sanofi,
872 F.3d 1367 (Fed. Cir. 2017) 51, 57

Apple Inc. v. ContentGuard Holdings, Inc.,
IPR2015-00443, Paper 9 (PTAB July 9, 2015) 61

Ariad Pharms., Inc. v. Eli Lilly & Co.,
598 F.3d 1336 (Fed. Cir. 2010) (en banc) 29, 30, 31, 45

Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Rsch. Found.,
PGR2022-00021, Paper 13 (PTAB Mar. 22, 2023) 53, 59

Bos. Sci. Corp. v. Johnson & Johnson,
647 F.3d 1353 (Fed. Cir. 2011) 40

Brown v. Ent. Merchs. Ass'n,
564 U.S. 786 (2011) 45

Ex parte Campbell,
No. 2021-000865, Decision on Appeal (PTAB July 20, 2021) 53, 58

Capon v. Eshhar,
418 F.3d 1349 (Fed. Cir. 2005) 41

Certain L-Trytophan, L-Trytophan Products, and Their Methods of Production,
Inv. No. 337-TA-1005, 2018 WL 8648370 (USITC Jan. 11, 2018).....46

In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.,
676 F.3d 1063 (Fed. Cir. 2012) 69

Datamaxx Applied Techs., Inc. v. Brown & Brown, Inc.,
No. 21-13451, 2022 WL 3597311 (11th Cir. Aug. 23, 2022) 45

DIRECTV, LLC v. Qurio Holdings, Inc.,
IPR2015-02006, Paper 6 (PTAB Apr. 4, 2016) 61

Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.,
276 F. Supp. 3d 629 (E.D. Tex. 2017), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018) 35

Falko-Gunter Falkner v. Inglis,
448 F.3d 1357 (Fed. Cir. 2006) 41

Ex parte Hirahashi,
No. 2020-005092, 2021 WL 2549655 (PTAB June 18, 2021).....66

In re Hogan,
559 F.2d 595 (CCPA 1977) 54

Honeywell Int'l Inc. v. Mexichem Amanco Holdings S.A. De C.V.,
865 F.3d 1348 (Fed. Cir. 2017) 64, 65

Hospira, Inc. v. Fresenius Kabi USA, LLC,
946 F.3d 1322 (Fed. Cir. 2020) 66

Innovative Intelligent Prods., LLC v. Nat'l Prods. Inc.,
IPR2021-00767, Paper 8 (PTAB Oct. 21, 2021) 28

InTouch Techs., Inc. v. VGo Commc'ns, Inc.,
751 F.3d 1327 (Fed. Cir. 2014) 69

Janssen Pharms., Inc. v. Tolmar, Inc.,
No. 21-1784, 2024 WL 834762 (D. Del. Feb. 26, 2024) 28

Juno Therapeutics, Inc. v. Kite Pharma, Inc.,
10 F.4th 1330 (Fed. Cir. 2021), *cert. denied*, 143 S. Ct. 402 (2022).....47, 58

Leo Pharm. Prods., Ltd. v. Rea,
726 F.3d 1346 (Fed. Cir. 2013).....68

Lifescan Glob. Corp. v. Ikeda Food Rsch., Ltd.,
PGR2019-00032, Paper 11 (PTAB Aug. 15, 2019).....*passim*

In re Magnum Oil Tools Int'l, Ltd.,
829 F.3d 1364 (Fed. Cir. 2016).....48, 62

Medtronic, Inc. v. Teleflex Innovations S.À.R.L.,
IPR2020-00127, Paper 107 (PTAB June 17, 2021).....71

Millennium Pharms., Inc. v. Sandoz Inc.,
862 F.3d 1356 (Fed. Cir. 2017).....65

Ossia, Inc. v. Energous Corp.,
PGR2016-00024, Paper 20 (PTAB Nov. 29, 2016).....4, 41

Otsuka Pharm. Co. v. Sandoz, Inc.,
678 F.3d 1280 (Fed. Cir. 2012).....62

Par Pharm., Inc. v. TWi Pharms., Inc.,
773 F.3d 1186 (Fed. Cir. 2014).....60

PureCircle USA Inc. v. SweeGen, Inc.,
No. 2022-1946, slip op. (Fed. Cir. Jan. 2, 2024)..... 46, 47, 48, 54

Rivera v. ITC,
857 F.3d 1315 (Fed. Cir. 2017).....60

In re Smythe,
480 F.2d 1376 (CCPA 1973) 49

Snitzer v. Etzel,
465 F.2d 899 (CCPA 1972) 36, 37

In re Soni,
54 F.3d 746 (Fed. Cir. 1995) 70

In re Spormann,
363 F.2d 444 (CCPA 1966) 64, 65

Teva Pharms. Int'l GmbH v. Eli Lilly & Co.,
8 F.4th 1349 (Fed. Cir. 2021) 71

WBIP, LLC v. Kohler Co.,
829 F.3d 1317 (Fed. Cir. 2016) 71

Yeda Rsch. & Dev. Co. v. Abbott GmbH & Co.,
837 F.3d 1341 (Fed. Cir. 2016) 41, 42

Zhejiang Crystal-Optech Co. v. Viavi Sols. Inc.,
IPR2022-01184, Paper 8 (PTAB Feb. 7, 2023) 61

Statutes

35 U.S.C. § 103(a) 61

35 U.S.C. § 316(e) 28

I. Introduction

It is undisputed that before Corteva's groundbreaking invention, the prior art failed to disclose any enzyme reported to degrade FOP herbicides, let alone exhibit dual activity against FOPs and a *second* herbicide class (i.e., phenoxy auxins), as required by all challenged claims of the '745 patent. Instead, as Petitioners' own in-house scientists have acknowledged, it was Corteva's inventors who did the pioneering work of investigating RdpA (AAD-1), characterizing its mechanism of action against FOP herbicides, and creating transgenic soybean plants and plant cells expressing AAD-1 enzymes. Petitioners' contentions that the '745 patent claims are unpatentable for anticipation or obviousness should be rejected on a full trial record.

Petitioners' written-description-based priority challenge in Grounds 1A and 1B fails to establish that the asserted Corteva '437 reference qualifies as prior art. All challenged claims require AAD-1 enzymes having (i) at least 85% sequence identity and (ii) an AAD-1 active-site motif defined by particular amino acid residues having specific spacing between them. Petitioners failed to prove that either recited structural feature, let alone both, lacks correlation to the claimed function (dual herbicide-degrading activity). *Ajinomoto Co. v. ITC*, 932 F.3d 1342, 1360 (Fed. Cir. 2019).

After finding Petitioners' literal-disclosure challenge to the "at least 85% sequence identity" limitation unpersuasive at institution, the Board invited further

evidence regarding whether skilled artisans recognized that high sequence identity correlates to function. ID, 38-39, 40-41. As explained by Dr. Martin Bollinger, an expert in protein biochemistry and enzymology, several research groups in the early 2000s had indeed identified thresholds for reliably predicting enzyme function based on sequence identity. Their results—entirely ignored by Petitioners' declarant, Dr. Hausinger—consistently showed that even with only about 60% sequence identity, enzymatic function (including substrate specificity) was conserved with about 90% accuracy. With at least 85% sequence identity, as claimed here, the correlation was even stronger, above 90% accuracy:

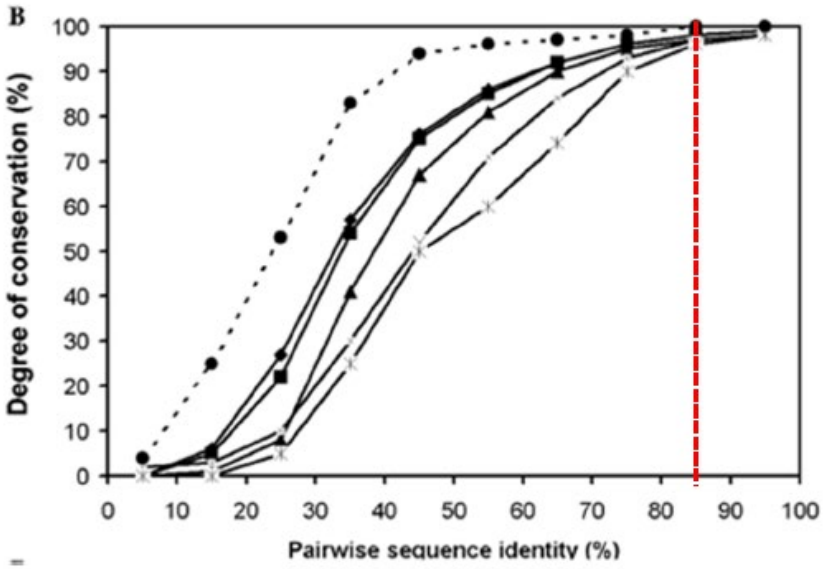


Figure 1, Ex. 2019, 866 (Fig. 1(B)) (graph of enzyme function conservation (y-axis) by percent sequence identity (x-axis); red annotation added)

Skilled artisans as of the 2004 and 2005 priority dates thus expected to retain the same or similar function among enzymes having at least 85% sequence identity

to SEQ ID NO: 9, *just as the '745 patent discloses*. Ex. 1003, 44:12-24 (enzymes at 85% identity are "highly identical" and "expected to retain similar properties").

Conserved function was further expected based on the AAD-1 motif, i.e., the catalytic active site defined by specific amino acid residues and their fixed spacing, which is distinctive to AAD-1 enzymes. There is only one such active-site motif in SEQ ID NO: 9, which a skilled artisan would have readily recognized. Indeed, Dr. Hausinger acknowledged during cross-examination that the prior art had *already published* the locations of the five active-site residues, identifying them individually in black:

```
RdpA MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFH 50
TauD ------------MSLTIQPISPALGAIVSGIDLGAPLDDTGQRAIEQALL 38
TfdA ------------MSVVANPLHPLFAAGVEDIDLREALGSTEVREIERLMD 38
SdpA ----------MQTTLQITPTGATLGATVTGVHLAT-LDDAGFAALHAAWL 39

RdpA TYQVIYFPGQAITNEQHIAFSRRFGPVDPVPLLKSIEGYPEVQMIRREAN 100
TauD EHQVLFFRDQSLEPRSQARFAARFGDLHIHPIYPSVPEQPEVIVLDTAVT 88
TfdA EKSVLVFRGQPLSQDQQIAFARNFGPLEGGFIKVNQRPSRFKYAELADIS 88
SdpA QHALLIFPGQHLSNDQQITFAKRFGAIERIGGGDIVAISNVKADGTVRQH 89

RdpA ESGRV---------------IGDDWHTDSTFLDAPPAAVVMRAIDVPEHG 135
TauD DVR-----------------DNAIWHTDVTFLETPALGAVLAAKQLPPYG 121
TfdA NVSLDGKVAQRDAREVVGNFANQLWHSDSSFQQPAARYSMLSAVVVPPSG 138
SdpA SPAEWDDMMKVIVG-------NMAWHADSTYMPVMAQGAVFSAEVVPAVG 132

RdpA GDTGFLSMYTAWETLSPTMQATIEGLNVVHSATRVFGSLYQAQNRRFSNT 185
TauD GDTLWASSTAAYEALSAPLRRLLDGLTATHDIGKSFP---RERFGVTEAD 168
TfdA GDTEFCDMRAAYDALPRDLQSELEGLRAEHYALNSRF---------LLGD 179
SdpA GRTCFADMRAAYDALDEATRALVHQRSARHSLVYSQS----KLGHVQQAG 178

RdpA SVKVMDVDAGDRETVHPLVVTHPGSGRKGLYVNQVYCQRIEGMTDAESKP 235
TauD LARLEEARLKNPPRSHPVVRTHPVTGRKGLFVSDGFTTRINELEPAESDA 218
TfdA TDYSEAQRNAMPPVNWPLVRTHAGSGRKFLFIG-AHASHVEGLPVAEGRM 228
SdpA SAYIGYGMDTTATPLRPLVKVHPETGRPSLLIG-RHAHAIPGMDAAESER 227

RdpA LLQFLYEHATRFDFTCRVRWKKDQVLVWDNLCTMHRAVPDYAGKFRYLTR 285
TauD LLKFLFAHATRPEFTVRWRWQENDVAFWDNRVTQHYAVDDYRPQRRVMHR 268
TfdA LLAELLEHATQREFVYRHRWNVGDLVMWDNRCVLHRGRRYDISARRELRR 278
SdpA FLEGLVDWACQAPRVHAHQWAAGDVVVWDNRCLLHRAEPWDFKLPRVMWH 277

RdpA TTVGGVRPAR-----                                    295
TauD ATILGDKPF------                                    277
TfdA ATTLDDAVV------                                    287
SdpA SRLAGRPETEGAALV                                    292
```

Ex. 1042, 5360 (Fig. 2); Ex. 2016, 24:19-26:7; *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)). Moreover, Petitioners' allegation that the *active-site motif* of AAD-1 enzymes is uncorrelated to their *dual activity* is incorrect, as skilled artisans had reported the motif as "functionally important" and "functionally essential." Ex. 1042. Petitioners' own dual-activity AAD-1 enzymes, for example, which they renamed as "FT" (FOP Tolerance) enzymes and published in 2019, uniformly maintain the AAD-1 motif.

Petitioners' Grounds 2A and 2B fail to establish that any challenged claim would have been obvious as of the 2004 priority date. None of the cited references disclose the dual herbicide-degrading activity required by all claims, and Petitioners impermissibly rely on hindsight (i.e., using the patent and prosecution history) to contend that the dual activity was allegedly expected in the prior art. Petitioners also cannot overcome the compelling objective evidence of nonobviousness of record, including the unexpected dual herbicide-degrading activity of AAD-1 enzymes—unprecedented in the agricultural biotechnology field—as well as praise and copying by Petitioners' own scientists.

At institution, the Board correctly found Grounds 2A and 2B "threadbare," "wanting," and "look[ing] like hindsight." ID, 64-66. The Board should again find

that Petitioners failed to meet their burden on Grounds 2A and 2B. Corteva respectfully requests that the Board confirm the patentability of all challenged claims.

II. Scientific Background and State of the Art

A. Enzymes

The following background on enzymes, including RdpA and αKG-dependent dioxygenases, is based on Dr. Bollinger's testimony. Ex. 2015, ¶¶ 1-20. Dr. Bollinger is an expert in protein biochemistry and enzymology, holding the endowed Russell and Mildred Marker professorship in the Department of Biochemistry and Molecular Biology at Penn State University. His research focuses on the structures and mechanisms of enzymes that use transition metals to react with oxygen to transform carbon compounds, which includes 20+ years of experience researching and publishing on αKG-dependent dioxygenases. *Id.*, ¶¶ 10-11. Dr. Bollinger has won many awards for his research, including the American Chemical Society Nobel Laureate Signature Award for Graduate Education in the Chemical Sciences. *Id.*, ¶ 5.

1. Enzyme Classification

Enzymes catalyze biochemical reactions. *Id.*, ¶ 21. They bind substrates at a location known as the "active site." Ex. 2018, 4. To form enzymes, amino-acid building blocks are connected in a linear chain in a specific sequence. An enzyme's

amino acid sequence is called its primary structure. *See id.* This linear chain then folds up into a "globular" (meaning more or less spherical) three-dimensional structure in order to function as an enzyme catalyst. Accordingly, an enzyme's structure and the reaction it catalyzes (its function) are generally dictated by its amino acid sequence. Ex. 2015, ¶¶ 22-24.

Enzymologists classify enzymes using a long-established nomenclature system. An enzyme's Enzyme Commission or "EC" number is a unique four-digit code that categorizes the chemical reaction catalyzed by the enzyme. *Id.*, ¶ 23; Ex. 2019, 864 ("[T]he Enzyme Commission (EC) is the best developed and most widely used functional classification scheme."). The first three digits of an EC number usually describe the overall type of enzymatic reaction, while the last digit usually represents the substrate specificity of the reaction. Ex. 2020, 36-37.

2. Enzyme Sequence-Function Relationships and Predicting Function Based on Sequence Identity

Skilled artisans have long analyzed structural and functional similarities between enzymes by comparing their amino acid sequences. By 2004-2005, they had arrived at a general consensus for how to describe the degree of relatedness of enzymes based on their amino acid sequences. Ex. 2015, ¶¶ 25-26.

Sequence identities between two or more enzymes may range from less than 10% (few matching residues) to 100% (identical). A sequence identity above 35%

or 40% is considered a relatively high level of sequence identity and indicates that two enzymes likely have similar structures and functions. *Id.*, ¶ 27; Ex. 2021, 85. Enzymes having less than 20% sequence identity generally have different structures and functions.

Decades of comparing protein sequences led to the observation of a "twilight zone" for sequence identity. Ex. 2023, 1123. The "twilight zone" represents a range of sequence identity (approximately 20-35%) in which the relatedness of proteins—how similar their structures are, whether they have the same function, and whether they evolved from a common precursor—can be more difficult to judge. *Id.*; Ex. 2021, 85. In other words, relationships between sequence and function are often more unpredictable when sequence identities fall within the twilight zone. Ex. 2015, ¶ 28.

Across the range of possible sequence identities (<10% to 100%), researchers established thresholds for predicting enzyme function in the early 2000s. *Id.*, ¶ 29. These efforts were prompted by genome-sequencing research, which was identifying genes believed to encode enzymes faster than researchers could empirically determine the enzymes' function. Skilled artisans therefore conducted studies to determine how reliably one could infer the function of a new enzyme by comparing its sequence the sequence of an enzyme having a known function. *Id.*, ¶¶ 30-40; Ex. 2025, 202.

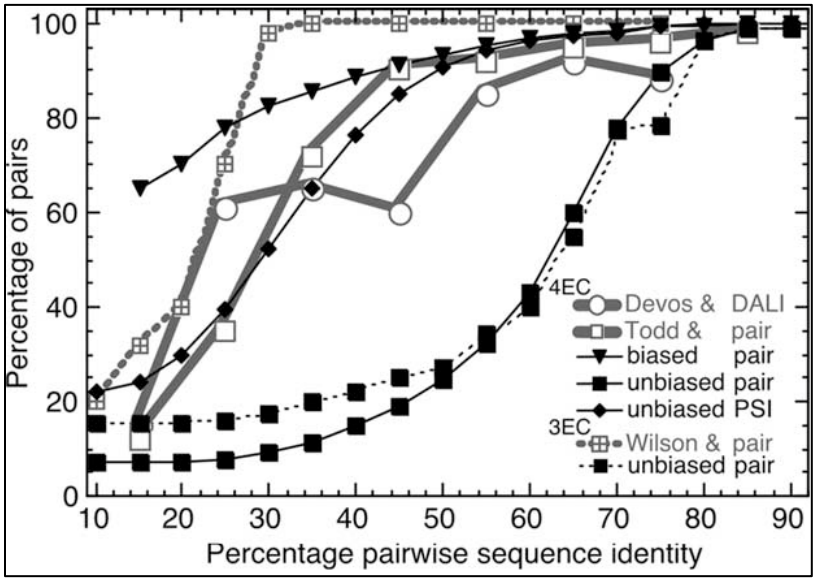
In 2000, Wilson et al. evaluated pairwise sequence, structure, and function comparisons on ~30,000 pairs of protein domains and corresponding EC numbers. Ex. 2024, 233, 242. Wilson found that full conservation of enzyme function can occur between two proteins with as low as ~40% sequence identity. *Id.*, 233. The authors concluded that percent identity is a useful predictor of function for proteins that are close in structure and outside the twilight zone. *Id.*, 245.

A study in 2000 by Devos analyzed a set of over 7,000 protein sequence alignments. Ex. 2026, 99. Devos found that, above a sequence identity threshold of 50-80%, at least the first three digits of an EC number were identical, and above 80% sequence identity, all four digits in the EC codes were "completely identical," meaning that two enzymes having this level of identity can confidently be assumed to have the same activity. *Id.*, 101-02.

In 2001, a study by Todd et al. assessed the functional variation of 31 diverse structural enzyme superfamilies using the EC classification scheme and found that functional variation is rare when sequence identity is above 40%. Ex. 2027, 1113. Todd reported that "conservation of chemistry does appear to be the dominant theme," i.e., high sequence identity between a pair of enzymes indicates they will catalyze the same reaction. *Id.*, 1138.

In 2002, Rost made a more conservative estimate for sequence-based conservation of enzyme function to provide "important benchmarks for everyday

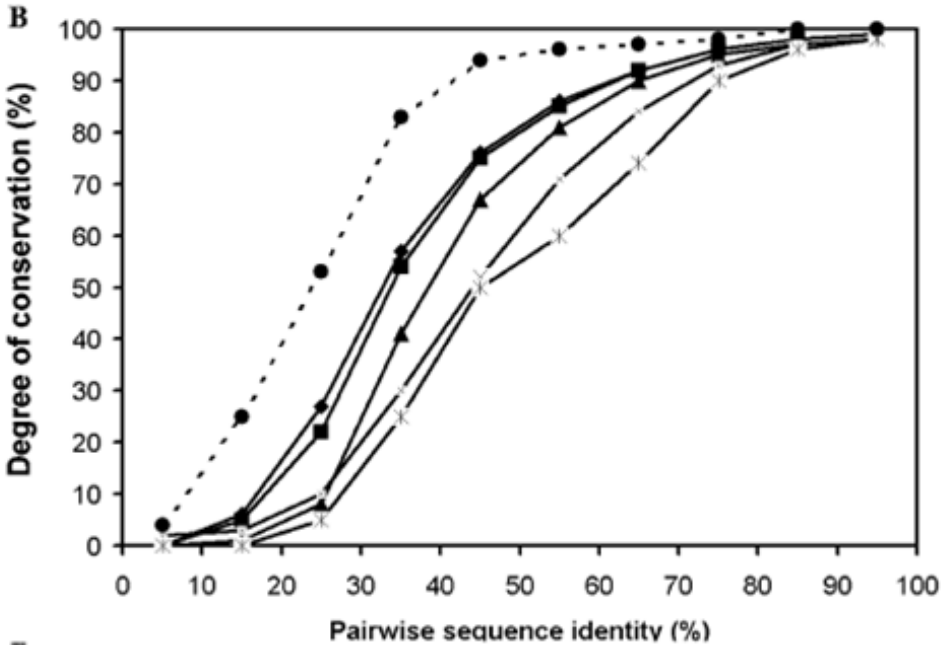
sequence analysis," suggesting that prior analyses were biased or too small. Ex. 2028, 595. Taking a different approach that considered sequence comparisons into the twilight zone, Rost found that, when the sequence identity is below 70%, EC numbers diverge more than others had reported. *Id.*, 603-04; Ex. 2019, 863. Nevertheless, Rost presented a graphical comparison between his results and those of Wilson, Devos, and Todd, confirming strong conservation of enzyme function at high levels of sequence identity, including at 85% or greater identity:



Ex. 2028, 604 (Fig. 5) (x-axis: sequence identity; y-axis: conservation of enzyme function).

A study by Tian in 2003 consolidated and built on the prior studies by Devos, Wilson, Todd, and Rost, analyzing thousands of protein sequences. Ex. 2019, 863-64. As Tian stated, it was "of great significance to establish the threshold of sequence identity above which functional similarity can be affirmed." *Id.* Tian found

that "above 60% global sequence identity," skilled artisans would have "above 90% accuracy" in predicting function, defined as all four digits of an EC number. *Id.*, 867.



Id., 866 (Fig. 1(B)) (x-axis: sequence identity; y-axis: conservation of enzyme function).

Highly identical enzyme sequences were therefore known to correlate well with conservation of enzyme structure and function, which enzymologists recognized and referred to as sequence-function relationships. Ex. 2015, ¶¶ 36-40. These well-established principles were routinely applied in protein engineering to make enzyme variants with conserved or even improved functional traits. *See infra* Section II.A.3; Ex. 2025, 202-03 ("Using homologous sequences for protein engineering").

Thus, by 2004-2005, skilled persons routinely predicted enzyme function based on sequence similarity to enzymes whose function had been experimentally determined. Ex. 2032, 779-80; Ex. 2033, 1712; Ex. 2034, 258. The studies detailed above show that this was a universal principle applied within the field of enzymology. *See, e.g.*, Ex. 2015, ¶ 36; Ex. 2026, 98; Ex. 2019, 864 ("[S]equence identity is … widely used as an indication of functional similarity."); Ex. 2030, 1; *see also* Ex. 1046, 7164 (Table 1 listing "predicted functions" based on percentage sequence identity); Ex. 1042, 5362 (Table 3 listing "predicted function" based on percentage sequence identity). Indeed, amino acid sequence comparisons were accepted as the "gold standard" for predicting protein function. Ex. 2029, 97; Ex. 2024, 233 ("percent identity is more effective at quantifying functional conservation" than other techniques).

3. Enzyme Variants

In 2004-2005, skilled artisans commonly developed enzymes with desired functional properties. Ex. 2015, ¶¶ 45-51. They generally analyzed an enzyme's amino acid sequence and compared it to other known, similar sequences. Ex. 2025, 202-203 (related sequences are "a potentially rich source of information regarding sequence changes that are acceptable without drastically disrupting protein function"); Ex. 2040, 3389; Ex. 2041, 761. It was particularly helpful to compare related amino acid sequences having lower levels of identity (e.g., ~30%) because

residues that remain conserved even at lower levels of sequence identity are likely important to enzyme structure and/or function. Ex. 2015, ¶ 55.

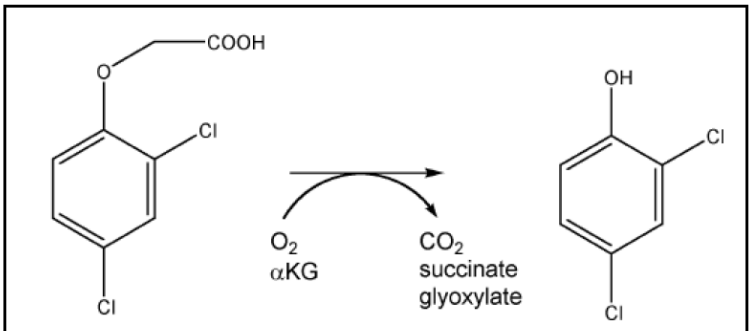
When making amino acid substitutions, skilled artisans had no need to randomly pick from among the 20 naturally occurring amino acids when making enzyme variants. *Id.*, ¶¶ 52-53. Instead, sequence comparisons to related proteins routinely identified the types of substitutions that may be tolerated at a given position. *Id.*, ¶ 51. For example, skilled artisans generally did not substitute or only conservatively substituted amino acid residues that were highly conserved across related enzymes. *Id.* For residues that were not conserved across related proteins, skilled artisans understood that a wider range of amino acid substitutions would likely be tolerated. *Id.* Moreover, matrices known since the 1970s detailed which amino acid replacements were accepted by the processes of natural selection. *Id.*, ¶¶ 50, 54-57; Ex. 2057, 345. By 2004-2005, these matrices were automated and computer-implemented, for example with the SIFT (**S**orting **I**ntolerant **F**rom **T**olerant) program, which predicts whether an amino acid substitution affects protein function by considering the position at which the change occurred and the type of amino acid change. Ex. 2044, 3812 (SIFT "relies solely on sequence for prediction, yet performs similarly to tools that use structure"); Ex. 2038, 378.

Thus, as Dr. Bollinger explains, skilled artisans in 2004-2005 applied established principles for making enzyme variants that maintain function. Ex. 2015,

¶¶ 58-59. In view of the known sequence-function relationships among enzymes, skilled artisans sought to maintain high sequence identity. *Id.* To maintain function, skilled artisans also sought to maintain the enzyme's active-site motif. *Id.* Skilled artisans also sought to retain (or only conservatively substitute) non-motif residues that were highly conserved across related enzymes, which were presumed to be functionally and/or structurally important. *Id.* And skilled artisans would avoid making substitutions with oppositely charged amino acids or substitutions with dramatically differently sized amino acids, which could distort surface charge or steric bulk. *Id.*

4. α-Ketoglutarate-Dependent Dioxygenases and RdpA (AAD-1)

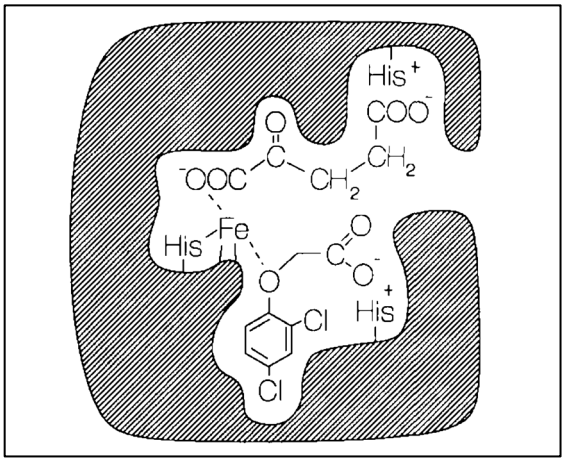
α-Ketoglutarate-dependent ("αKG-dependent") dioxygenase enzymes that degrade phenoxy auxin herbicides, such as 2,4-D, were known by 2004-2005. Examples include the enzymes TfdA, RdpA, and SdpA. *See, e.g.*, Exs. 1027, 1047. To have activity, these enzymes require the presence of Fe(II) as the metallocenter, as well as oxygen (O_2) and α-ketoglutarate as a co-substrate. Ex. 2001, 24311; Ex. 2016, 32:13-33:14. The enzymatically catalyzed oxidation reaction produces carbon dioxide, succinate, glyoxylate, and a phenol:



SCHEME 33.

Ex. 1025, 40; Ex. 2015, ¶¶ 60-63.

Researchers depicted an exemplary αKG-dependent dioxygenase active site (i.e., of TfdA) that accommodates the Fe(II), α-ketoglutarate, and 2,4-D substrate:



Ex. 2001, 24316 (Fig. 11). Through further investigations, researchers identified the particular active-site residues that anchor the Fe(II) metallocenter and the α-ketoglutarate co-substrate in the active site. Ex. 2015, ¶¶ 64-70. The substrates and Fe(II) are anchored in a configuration that orchestrates the oxidation reaction to cleave the primary substrate's ether bond. Ex. 2016, 35:6-17 ("one requires the correct coordination of alpha-ketoglutarate"), 32:13-21 (αKG "is what really drives

the reaction"). The motif residues are interspersed in different parts of the sequence, and the protein fold brings them together in the active site to orchestrate the reaction. The spacer sequences separating the motif residues thus set the contours for the active site, helping define the specificity of the enzyme for its primary substrate(s). Ex. 2015, ¶¶ 64-65.

By 2004, researchers had categorized enzymes within the αKG-dependent dioxygenase family into groups based on a variable "consensus sequence" or "motif" for their active sites: HX(D/E)$X_{23\text{-}26}$(T/S)$X_{114–183}$H$X_{10–13}$R. Ex. 1023, 5185; Ex. 2015 ¶¶ 66-69. αKG-dependent dioxygenases were thus known to have five common, conserved residues in their active sites with variable spacing, depending on the particular enzyme. Skilled artisans thus recognized that enzymes in the αKG-dependent dioxygenase family varied greatly in the number of amino acids in the spacers separating the required consecutive motif residues, reflecting the diversity of reactions catalyzed by these enzymes. *Id.*; Ex. 1025, 21-22 (Table 1 listing the differing motif spacers of TfdA, other αKG-dependent dioxygenases, and related enzymes). αKG dioxygenases were generally defined by their motif, which is a simple way of describing them and identifying the active site present in each individual enzyme. Ex. 2015, ¶¶ 64, 66 (citing Exs. 1025, 1023, 1042).

Researchers had also discovered αKG-dependent dioxygenases produced by soil bacteria that had been reported to degrade phenoxy auxin herbicides such as

2,4-D. These included RdpA enzymes having identical sequences from the bacteria *Sphingobium herbicidovorans* MH and *Delftia acidovorans* MC1. Ex. 1015; Ex. 1042; Ex. 1013.

By 2004, researchers had already identified the active-site motif (i.e., residues and spacers) in RdpA's amino acid sequence. Ex. 1042, Abstr., 5362 ("The functionally important motif … is present in both RdpA and SdpA."). As shown below, Schleinitz et al. published a sequence comparison of RdpA, SdpA, TauD, and TfdA, using black shading to identify the positions of the five motif residues in the amino acid sequence of these enzymes:

```
RdpA MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFH 50
TauD ------------MSLTIQPISPALGAIVSGIDLGAPLDDTGQRAIEQALL 38
TfdA ------------MSVVANPLHPLFAAGVEDIDLREALGSTEVREIERLMD 38
SdpA ----------MQTTLQITPTGATLGATVTGVHLAT-LDDAGFAALHAAWL 39

RdpA TYQVIYFPGQAITNEQHIAFSRRFGPVDPVPLLKSIEGYPEVQMIRREAN 100
TauD EHQVLFFRDQSLEPRSQARFAARFGDLHIHPIYPSVPEQPEVIVLDTAVT 88
TfdA EKSVLVFRGQPLSQDQQIAFARNFGPLEGGFIKVNQRPSRFKYAELADIS 88
SdpA QHALLIFPGQHLSNDQQITFAKRFGAIERIGGGDIVAISNVKADGTVRQH 89

RdpA ESGRV---------------IGDDWHTDSTFLDAPPAAVVMRAIDVPEHG 135
TauD DVR-----------------DNAIWHTDVTFLETPALGAVLAAKQLPPYG 121
TfdA NVSLDGKVAQRDAREVVGNFANQLWHSDSSFQQPAARYSMLSAVVVPPSG 138
SdpA SPAEWDDMMKVIVG-------NMAWHADSTYMPVMAQGAVFSAEVVPAVG 132

RdpA GDTGFLSMYTAWETLSPTMQATIEGLNVVHSATRVFGSLYQAQNRRFSNT 185
TauD GDTLWASSTAAYEALSAPLRRLLDGLTATHDIGKSFP---RERFGVTEAD 168
TfdA GDTEFCDMRAAYDALPRDLQSELEGLRAEHYALNSRF---------LLGD 179
SdpA GRTCFADMRAAYDALDEATRALVHQRSARHSLVYSQS----KLGHVQQAG 178

RdpA SVKVMDVDAGDRETVHPLVVTHPGSGRKGLYVNQVYCQRIEGMTDAESKP 235
TauD LARLEEARLKNPPRSHPVVRTHPVTGRKGLFVSDGFTTRINELEPAESDA 218
TfdA TDYSEAQRNAMPPVNWPLVRTHAGSGRKFLFIG-AHASHVEGLPVAEGRM 228
SdpA SAYIGYGMDTTATPLRPLVKVHPETGRPSLLIG-RHAHAIPGMDAAESER 227

RdpA LLQFLYEHATRFDFTCRVRWKKDQVLVWDNLCTMHRAVPDYAGKFRYLTR 285
TauD LLKFLFAHATRPEFTVRWRWQENDVAFWDNRVTQHYAVDDYRPQRRVMHR 268
TfdA LLAELLEHATQREFVYRHRWNVGDLVMWDNRCVLHRGRRYDISARRELRR 278
SdpA FLEGLVDWACQAPRVHAHQWAAGDVVVWDNRCLLHRAEPWDFKLPRVMWH 277

RdpA TTVGGVRPAR-----                                    295
TauD ATILGDKPF------                                    277
TfdA ATTLDDAVV------                                    287
SdpA SRLAGRPETEGAALV                                    292
```

Id., 5360; Ex. 2042; Ex. 2015, ¶¶ 71-72. As both parties' experts testified, the RdpA active-site motif residues illustrated in Schleinitz are H, D, T, H, and R, with a spacer residue at position 112 between the first two motif residues (H, D) and the other spacer residues are at positions 114-137, 139-269, and 271-280. Ex. 2015, ¶ 73; Ex. 2016, 24:19-26:7. In view of the gaps in the sequence alignment of RdpA, TauD, TfdA, and SdpA, skilled artisans recognized that each of these enzymes had different active-site motifs, which was unsurprising in view of their different substrate specificities. Ex. 2015, ¶ 74; *see infra* Section VI.A.2.a.

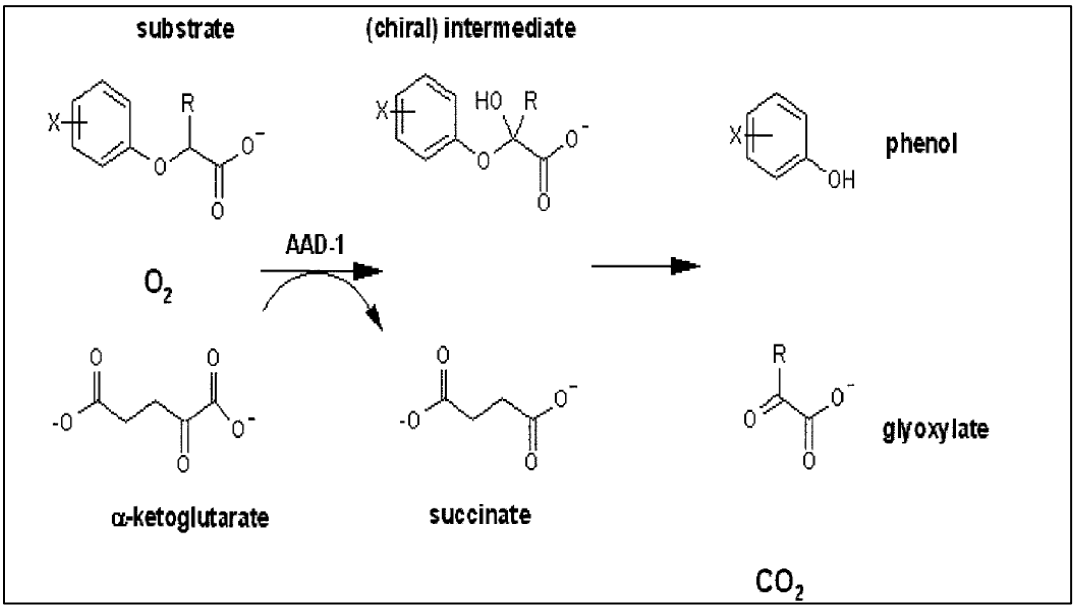
Accordingly, as of Corteva's 2004 and 2005 filing dates, skilled artisans had substantial knowledge of the structure and function of αKG-dependent dioxygenases. This knowledge included RdpA's amino acid sequence, its well-known and "functionally important" active-site motif, and its ability to degrade phenoxy auxin herbicides (e.g., 2,4-D and *R*-dichlorprop). Ex. 1042, Abstr., 5362; Ex. 2015, ¶¶ 73-74.

III. The '745 Patent

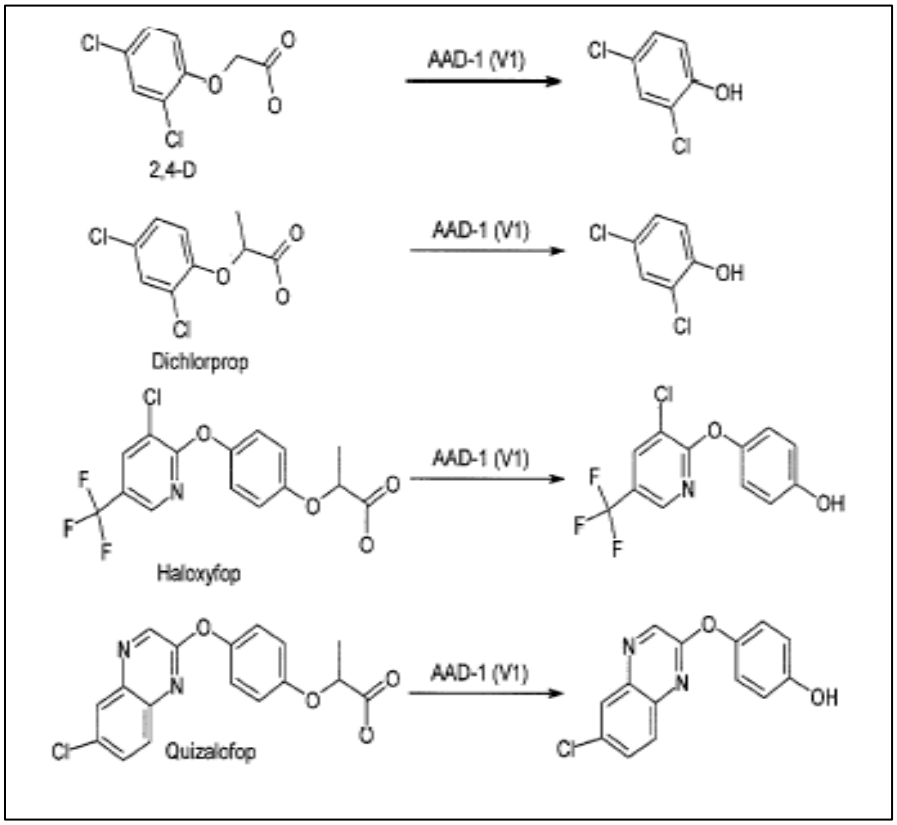
A. AAD-1 Enzymes

The '745 patent's inventors identified AAD-1 (RdpA) by broadly investigating αKG-dependent dioxygenase sequences ranging from "highly identical (85-98%) to very low identity (23-32%)" to TfdA. *Id.*, 44:9-42. The inventors thus searched into the more unpredictable twilight zone of lower identities to TfdA for potentially different enzyme functions, where they identified AAD-1 (RdpA) at 28% identity. *Id.* As reflected in the specification, the inventors performed *in vitro* and *in planta* characterizations of AAD-1 enzymes, determined their mechanism of action, and disclosed the wild-type AAD-1 amino acid sequence as SEQ ID NO: 9. Ex. 1003, 7:6-8; Ex. 2015, ¶¶ 86-94. The '745 patent further discloses that AAD-1 has the αKG-dependent dioxygenase active-site residues that coordinate the reaction requirements "essential for catalytic activity." Ex. 2015, ¶¶ 81-85; Ex. 1003, 18:39-51; *see supra* Section II.A.4.

The inventors investigated and disclosed AAD-1's mechanism of action. They reported that AAD-1 degrades FOP herbicides in a similar way as phenoxy auxin herbicides, via an αKG- and Fe^{II}-dependent oxidation reaction coordinated by the active-site motif residues. Ex. 2015, ¶¶ 89-90. The specification discloses that these enzymes require αKG and ferrous iron to "bind in the active site." Ex. 1003, 49:20-31. The specification reports that AAD-1 degrades 2,4-D *in vitro* and, as expected, produces a phenol product that was detected using a colorimetric assay. *Id.*, 49:32-50. The specification states that FOP herbicides—never previously reported as substrates for RdpA/AAD-1 (*id.*, 18:54-62)—were then tested using the same conditions and produced phenol products as confirmed by the colorimetric assay. *Id.*, 49:62-50:22. The '745 patent reported FOP-degradation reaction schemes in Figures 1 and 4:



Id., Fig. 1 (excerpt), 5:32-33 ("FIG. 1 shows a general scheme for dioxygenase cleavage of phenoxy auxin or AOPP herbicides.").



Id., Fig. 4. The '745 patent thus reports the inventors' discovery of a common, AAD-1-catalyzed degradation pathway for phenoxy auxin and FOP herbicides and its implementation in AAD-1 transgenic plants. *See id.*, 4:6-8.

The '745 patent describes a genus of closely related AAD-1 enzymes. *Id.*, 18;59-62, 19:9-13, 20:29-31 ("[P]roteins and genes of the subject invention are referred to herein as AAD-1 proteins and genes."), 20:52-56; 21:7-9 ("[T]he subject invention also relates to 'plant optimized' genes that encode proteins of the subject invention."); Ex. 2015, ¶ 83. The specification describes techniques for modifying

AAD-1 genes and proteins to create AAD-1 variants. *Id.*, 33:23-38:50. Beyond SEQ ID NOs: 9-11, the '745 patent provides detailed structural basis and guidance regarding variant enzymes "having the same or similar activity" of disclosed enzymes such as AAD-1. *Id.*, 37:24-52.

Consistent with established sequence-identity thresholds for conserved enzyme function, the '745 patent discloses that the sequence identity of variants having the same or similar activity to a disclosed sequence "will typically be at least 60%." Ex. 1003, 37:24-35; Ex. 2019, 863 (disclosing that "60% sequence identity is needed to have at least 90% accuracy" in predicting function); Ex. 2015, ¶ 83. The specification also discloses sequence identities of 85% and higher. Ex. 1003, 37:37-42. Indeed, for αKG-dependent dioxygenases, the '745 patent discloses that sequences having 85% to 98% identity are "highly identical" and that such enzymes are "expected to retain similar properties." *Id.*, 44:12-24.

The '745 patent also discloses the location of the known active-site motif in αKG-dependent dioxygenases such as AAD-1, which skilled artisans knew to maintain in variants with conserved function. Ex. 2015, ¶¶ 84, 58; Ex. 1003, 18:43-62, 49:22-50:45. The specification states that AAD-1 is "classified in the same overall family of α-ketoglutarate-dependent dioxygenases" that is characterized by a "'$HX(D/E)X_{23\text{-}26}(T/S)X_{114\text{-}183}HX_{10\text{-}13}R$' motif which comprises the active site." Ex. 1003, 18:43-62. There is only one such active-site motif in SEQ ID NO: 9.

Ex. 2015, ¶ 84. As detailed above, skilled artisans had already identified the motif in the RdpA sequence and other highly conserved residues across related enzymes. Ex. 1042, 5360 (Fig. 2), 5362. The specification also discloses that the AAD-1 active site coordinates the oxidation reaction that degrades phenoxy auxin and FOP herbicides. Ex. 1003, 49:22-50:45.

B. The Specification's Twenty-Six Examples

The '745 patent discloses twenty-six examples, including in soybean. *Id.*, 21:47-49 ("The transgenic expression of the subject AAD-1 genes is exemplified in, for example, *Arabidopsis*, corn (maize), tobacco, cotton, rice, soybean, and canola."), 44:5-129:45. The patent discloses standard *in vitro* assays for measuring AAD-1 activity, including a 96-well microplate format for performing enzyme assays measuring degradation activity against 2,4-D and FOP herbicides using 15-minute incubation times. *Id.*, 45:35-54:59 (Examples 2-4). The '745 patent also presents *in vitro* testing data showing that AAD-1 degrades "aryloxyphenoxypropionate [i.e., FOP] herbicides as well as phenoxy auxins." *Id.*, 51:55-52:6, Figs. 6A, 6B. The patent also describes how to codon-optimize the gene sequences for efficient expression of AAD-1 proteins in plant cells. *Id.*, 54:61-63:40 (Example 5); Ex. 2015, ¶¶ 87-88.

The '745 patent describes transformation of *Arabidopsis* plants with an AAD-1 gene. *Id.*, 63:43-78:10 (Example 6). The patent reports test data confirming

that AAD-1-transformed *Arabidopsis* exhibited tolerance to both 2,4-D and the FOP herbicides tested. *Id.*, 69:13-70:20 ("This provides the first in planta data that AAD-1 (v3) will provide [FOP] resistance.").

The '745 patent provides examples of other dicot and monocot plants transformed with AAD-1 genes, including corn, tobacco, soybeans, cotton, rice, turfgrass, and canola. *Id.*, Examples 7-9, 12-15, 19-20, 24-26. The '745 patent further discloses stacking AAD-1 traits with other herbicide tolerance traits (e.g., genes providing resistance to glyphosate, glufosinate, and/or imidazolinone herbicides) to confer multiple herbicide-tolerance traits in transformed plants. *Id.*, Examples 16, 21-23.

C. The Claims

The '745 patent claims are directed to transgenic soybean plants and plant cells comprising a recombinant polynucleotide encoding a structurally well-defined class of AAD-1 proteins. Ex. 2015, ¶¶ 76-80. The AAD-1 protein must have the defined AAD-1 motif with each of the specified active-site amino acid residues and their required spacing. The AAD-1 protein must also have at least 85% sequence identity with SEQ ID NO: 9. Claim 1, for example, recites:

> 1. A transgenic soybean plant cell comprising a recombinant polynucleotide that encodes an AAD-1 protein that exhibits aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy

auxin herbicide and an I-aryloxyphenoxypropionate herbicide, an (R)-aryloxyphenoxypropionate herbicide, which are aryloxyalkanoate herbicides, further wherein said AAD-1 protein comprises:

i) ***an amino acid sequence having at least 85% sequence identity with SEQ ID NO: 9***; and

ii) an AAD-1 motif having the general formula of:

$\boldsymbol{HX_{112}D(X)_{114\text{-}137}T(X)_{139\text{-}269}H(X)_{271\text{-}280}R}$, wherein

X_{112} represents a single amino acid at position 112, relative to the sequence of SEQ ID NO: 9;

$(X)_{114\text{-}137}$ represents a sequence of 24 amino acids;

$(X)_{139\text{-}269}$ represents a sequence of 131 amino acids; and

$(X)_{271\text{-}280}$ represents a sequence of 10 amino acids,

wherein said AAD-1 protein when expressed in a soybean plant cell renders said soybean plant cell tolerant to a phenoxy auxin herbicide and an (R)-aryloxyphenoxypropionate herbicide, as compared to an untransformed soybean plant cell.

Ex. 1003, claim 1[2]; *id.*, claim 29. The dependent claims recite additional features, including:

- An AAD-1 motif of the general formula $HX_{112}D(X)_{114\text{-}137}T(X)_{139\text{-}269}H(X)_{271\text{-}280}R(X)_{282\text{-}284}R$ (claim 2);
- A transgenic soybean plant comprising a plurality of the soybean plant cells of claim 1, wherein expression of the polynucleotide renders the plant tolerant to an aryloxyalkanoate herbicide (claim 3);

- Tolerance to particular herbicides or herbicide classes (claims 4-6);
- A transgenic plant having a second herbicide resistance gene (claims 7, 8);
- Methods of controlling at least one weed in a field, wherein the field contains at least one plant of claim 6 and the methods require certain herbicide resistance genes or applying certain herbicides (claims 9-24, 26); and
- Seeds, plants, progeny, etc., comprising a plurality of the plant cells of claim 1 (claims 25, 27, 28).

[2] Emphases added unless otherwise noted.

IV. Level of Skill in the Art

For purposes of this proceeding, a skilled artisan would have typically possessed a Ph.D. in molecular biology, biotechnology, or biochemistry, and 3-5 years of experience in the development of enzymes and enzyme variants as well as familiarity with αKG-dependent dioxygenases. Ex. 2015, ¶ 75. This proposed level of skill is generally consistent with Petitioners' proposed level of skill (e.g., "post-doc or higher"), but includes familiarity with αKG-dependent dioxygenases and structure-function relationships in enzymology, as reflected in the art. *E.g.*, Exs. 1023, 1042, 2019, 2025, 2028; *Lifescan Glob. Corp. v. Ikeda Food Rsch., Ltd.*, PGR2019-00032, Paper 11, 9 (PTAB Aug. 15, 2019) (correcting petitioner's overgeneralized POSA definition).

Petitioners do not define any level of skill regarding the aspects of the '745 patent relating to genetic transformation of plants. Nor does Dr. Hausinger purport to have any such expertise. Indeed, Grounds 1A and 1B do not allege any written-description deficiency regarding the transgenic soybean plant aspects of the claims.

V. Issues Raised in the Institution Decision

On the previously limited record before the Board, the Institution Decision found that at least one claim was more likely than not unpatentable based on Grounds 1A and 1B, which depend on Petitioners' priority challenge. The Board found

Petitioners' obviousness challenge in Grounds 2A and 2B unpersuasive at institution. ID, 68.

Regarding Petitioners' priority challenge, the Board identified three main issues for factual development:

- Whether the specification's disclosure that highly identical (85-98%) sequences would be expected to retain similar properties is a "more universal principle" for enzymes beyond TfdA. ID, 40.
- Whether the AAD-1 motif is disclosed in the specification, previously well known in the art, or if an obviousness-type analysis would have been required for a skilled artisan to discern the location of the AAD-1 motif residues in SEQ ID NO: 9. *Id.*, 32-34, 48-50.
- Whether a TfdA-like sequence from *A. denitrificans* has opposite stereoselectivity from TfdA, and whether any parallel exists for RdpA (AAD-1). *Id.*

Corteva has now fully addressed these issues, establishing that skilled artisans in 2004-2005 would have expected AAD-1 enzymes of 85% or higher sequence identity to maintain the claimed function as the specification discloses; that the *A. denitrificans* sequence was not confirmed or disclosed to have (*R*)-enantiospecificity and that it has no bearing on RdpA (AAD-1); and that the claimed

active-site motif was known and disclosed as a distinctive characteristic of RdpA (AAD-1) enzymes and their function.

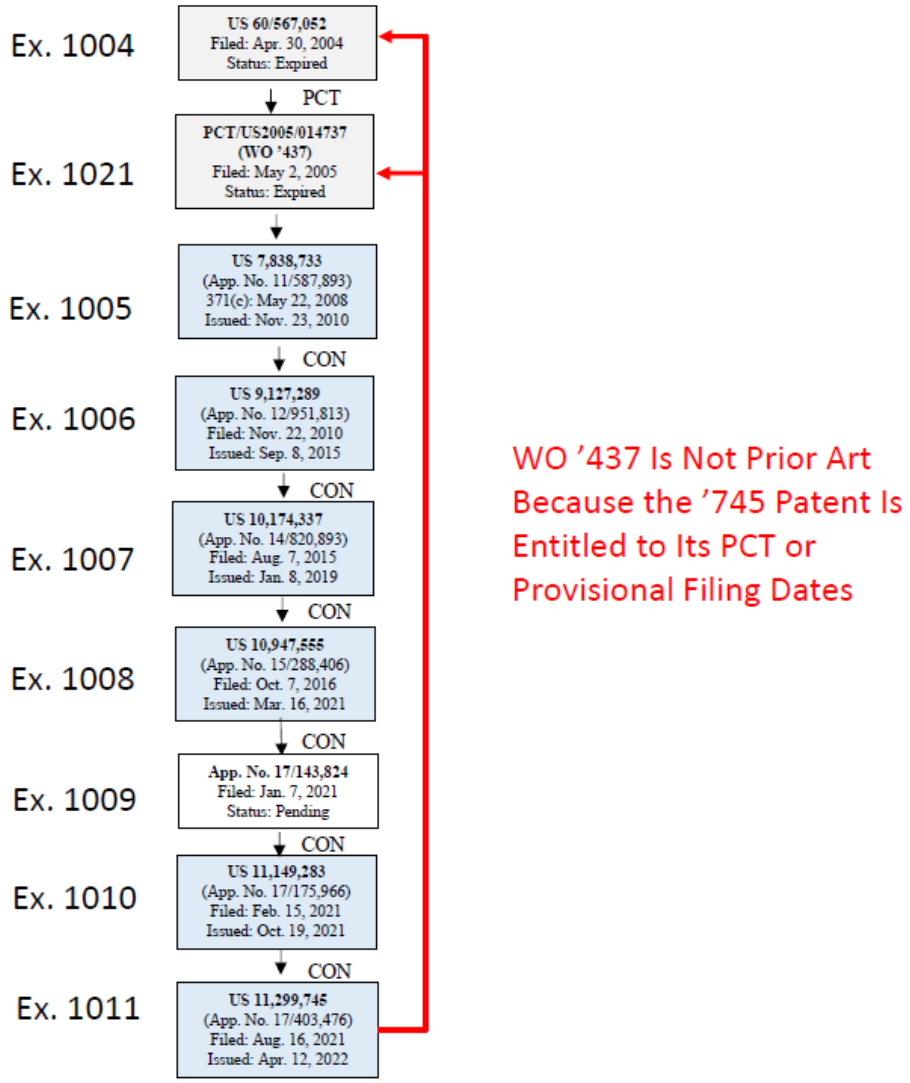
VI. Grounds 1A and 1B: Petitioners Failed to Establish that the Challenged Claims Lack Priority or Are Unpatentable

Grounds 1A and 1B, asserting anticipation and obviousness based on the published PCT application within the '745 patent's priority chain (Corteva '437), depend on Petitioners' written-description-based priority challenge.[3] Because Petitioners have not met their burden of establishing that the '745 patent claims lack priority to their May 2, 2005, PCT or April 30, 2004, provisional filing dates, Corteva '437 (published November 17, 2005) is not prior art and Grounds 1A and 1B should be rejected. ID, 28.[4]

---

[3] The Petition does not dispute enablement of the full claim scope. ID, 26 n.20.

[4] The burden of proof, as always, remains on Petitioners—particularly where priority was addressed during prosecution. 35 U.S.C. § 316(e); *Innovative Intelligent Prods., LLC v. Nat'l Prods. Inc.*, IPR2021-00767, Paper 8 at 18-24 (PTAB Oct. 21, 2021); *Janssen Pharms., Inc. v. Tolmar, Inc.*, No. 21-1784, 2024 WL 834762, at *9 (D. Del. Feb. 26, 2024) (Bryson, J.); *see* Ex. 1008, COR-AAD1-00000270-271, -631, -676 (examiner addressing priority during prosecution of the predecessor '406 Application).



A. The '745 Patent Discloses Common Structures Correlated to the Claimed Function

Written description requires that the specification "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). This standard is satisfied when the specification discloses a function-

correlated structure common to members of a claimed genus. *Id.* at 1350. Here, the Priority Applications disclose two such structures: at least 85% sequence identity to SEQ ID NO: 9 and the AAD-1 active-site motif. Grounds 1A and 1B therefore fail because Corteva '437 is not prior art in view of Petitioners' deficient priority challenge.

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

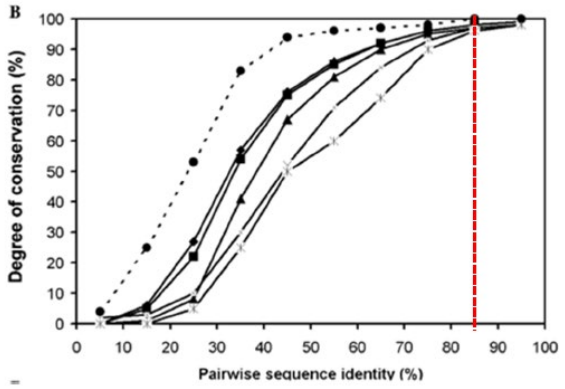
The Priority Applications disclose that the claimed invention includes a genus of AAD-1 enzymes, with high sequence identity as a common, function-correlated structural feature. Ex. 1003, 18:59-62, 19:9-13, 20:29-31 ("[P]roteins and genes of the subject invention are referred to herein as AAD-1 proteins and genes."), 20:52-56, 21:7-9; Ex. 1004, ¶ [0069]; Exs. 1005-1010, 1021, ¶ [0095]; Ex. 2015, ¶¶ 95-98. The specification discloses that enzymes having the "same or similar activity of the exemplified proteins" (e.g., AAD-1) typically have at least 60% sequence identity, including 85% or higher sequence identity. Ex. 1003, 37:24-52. The specification further discloses that among αKG-dependent dioxygenases like AAD-1, enzymes having sequence identities of 85% and higher are "highly identical" and expected to have similar properties (i.e., sequence-function correlation). *Id.*, 44:12-24, 37:24-52; Ex. 1004, ¶ [0116]; Exs. 1005-1010, 1021, ¶¶ [0142], [0171]; Ex. 2015, ¶ 99. While Petitioners ignored these disclosures, the

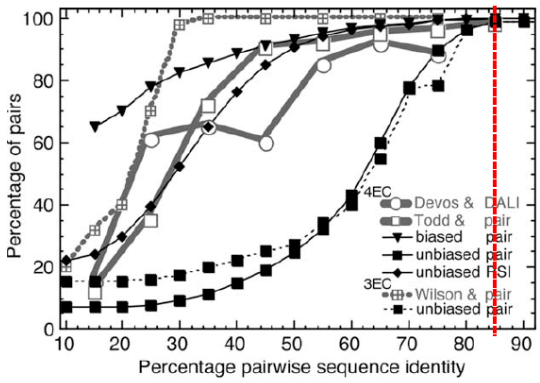
Board noted them and invited further evidence as to whether high sequence identity was a "more universal principle" for expecting conserved enzymatic function. ID, 40; Ex. 2015, ¶ 36 (Dr. Bollinger testifying that "extensive studies" showed that high sequence identity was indeed a universal principle for expecting the same enzyme function).

As Dr. Bollinger explains, a skilled artisan in 2004-2005 would have expected AAD-1 enzymes to retain the claimed function at 85% and higher sequence identity. Ex. 2015, ¶¶ 99-100. The specification's description of 85% sequence identity as highly identical and as conferring similar function comports with the contemporaneous understanding of persons skilled in the art. *Id.*; *Ariad*, 598 F.3d at 1351 (a written-description analysis must account for (1) existing knowledge in the field, (2) the prior art, (3) maturity of the science, and (4) predictability of the technology).

By 2004-2005, several research groups had extensively analyzed enzyme families and published on the strong correlation of high levels of sequence identity to conserved enzymatic function. Ex. 2019, 872, 864 ("[I]t is of great significance to establish the threshold of sequence identity above which functional similarity can be affirmed."); Ex. 2025, 204; Ex. 2015, ¶¶ 100-103. These studies consistently demonstrated that enzyme function and substrate specificity (e.g., all four digits of

an EC number) are conserved even at sequence identities extending well below the 85% threshold recited in the challenged claims:





Ex. 2019, 866 (annotated Fig. 1(B)). Ex. 2028, 604 (annotated Fig. 5).

For example, as Tian disclosed, only "*60% sequence identity is needed to have at least 90% accuracy*" in predicting common function and substrate specificity, defined as "all four digits of an EC number." Ex. 2019, 863; Ex. 2016, 72:16-19 (Dr. Hausinger conceding he was "not surprised" that enzymes having 60% sequence identity had the same function); Ex. 2043, 13486. Another study identified a threshold for conserved enzyme function of at least 70% identity—still substantially lower than the 85% minimum of the challenged claims. *Id.* (citing Ex. 2028); Ex. 2015, ¶¶ 102-103; *see also* Ex. 1042, 5362 (Table 3 reporting "predicted function" of enzymes in bacteria containing RdpA based on "% Amino acid identity"). As Dr. Bollinger testifies, enzymes having 85% or higher sequence identity were presumed to be essentially the same enzyme having the same function. Ex. 2015, ¶ 133.

As Dr. Bollinger also explains, this conservation of enzyme function is consistent with the strong conservation of enzyme structure at high levels of sequence identity, as the field recognized. *Id.*, ¶¶ 104-105.

- "When two sequences are very similar[,] we can safely infer that they have similar structures." Ex. 2028, 604, 596.
- "Sequence alignments unambiguously distinguish between protein pairs of similar and non-similar structure when the pairwise sequence identity is high (>40% for long alignments)." Ex. 2021, 85.
- "Structural similarity is conserved even at very low levels of sequence similarity." Ex. 2026, 105.

Accordingly, a skilled artisan in 2004-2005 would have considered enzyme variants having 85% or greater sequence identity as "highly identical" and as expected to confer similar properties to a reference sequence (e.g., SEQ ID NO: 9)—*just as the specification discloses*. Ex. 2015, ¶¶ 98-100, 109; Ex. 1003, 44:12-24, 37:24-52; Ex. 1004, ¶ [0116]; Exs. 1005-1010, 1021, ¶¶ [0142], [0171].

Dr. Hausinger's conclusory assertions about sequence-function unpredictability and a purportedly "massive and diverse" genus are thus contradicted by the specification and extensive pre-2005 literature from skilled enzymologists documenting established sequence-identity thresholds for conserving enzyme function.

Dr. Hausinger	Pre-2005 Literature
Alleging "*massive and diverse* genera covered by the claims." Ex. 1054, ¶ 76.	"Typically, enzymes that catalyze the same reaction often show *significant sequence and structural similarity*[.]" Ex. 2019, 877.
"If you have two sequences that are being considered in terms of function, I think you want to test the function and not just look at the sequences." Ex. 2016, 29:25-30:15.	"The comparison of protein sequences is *widely used* to infer protein structure and function." Ex. 2026, 105, 98. "[S]equence identity is also *widely used* as an indication of functional similarity." Ex. 2019, 864.
A skilled artisan "*would not have been able to predict* … whether any given amino acid sequence possessing the required motif and percent identity would have had the claimed activity." Ex. 1054, ¶ 91.	"Using pairwise sequence comparison, *several studies suggested that when the sequence identity is above 40%, enzyme function is well conserved*." *Id.*, 863.

Accordingly, Dr. Hausinger failed to account for the perspective of artisans skilled in enzymology, disregarding their ability to predict enzyme function based on sequence comparisons. Ex. 2016, 30:16-23, 29:25-30:15 (refusing to acknowledge any difference in enzyme-function expectations at 99% sequence identity versus 35% identity); Ex. 2015, ¶ 106.[5]

[5] Dr. Hausinger's opinions are also contradicted by joined Petitioner Inari's declarant, Dr. Aron Silverstone. *See* Paper 19, 5. In his own work, Dr. Silverstone

Dr. Hausinger also presents a conclusory, mathematical calculation (alleging at least 20^{44} possible sequences within the scope of the claims) that falsely assumes a *skilled artisan* would exercise *no skill* in randomly substituting all 20 alternative amino acids at every possible location. Ex. 1054, ¶¶ 77-80. As Dr. Bollinger explains, however, skilled artisans understood function-conserved enzyme variants differently and routinely made them in 2004-2005. Skilled artisans kept sequence identity high, conserved active-site residues, and relied on comparisons to the sequences of related enzymes to identify important conserved residues and residues that could be more freely substituted. Ex. 2015, ¶¶ 52-59, 107. All of this information would have been available and known to skilled artisans in 2004-2005 in view of the specification's disclosures and the state of the art. *Id.*, ¶¶ 50-59, 71-74; Ex. 1003, 18:39-62, 37:24-52, 44:21-24, 49:20-50:45, SEQ ID NO: 9; Ex. 1042, 5360; *see also Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 646, 652-53 (E.D. Tex. 2017) (finding even a "very large" genus adequately described in view of common structures shared by members of the genus), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018).

---

refers to sequences of 50+% identity as "substantially identical" (Ex. 2045, 48:55-66) and reported that it was "not surprising[]" for enzymes to have similar function at 89% identity (Ex. 2046, 484).

Petitioners' remaining argument regarding the "at least 85% sequence identity" limitation—a blaze-marks challenge—should also be rejected. The Board correctly found this argument unpersuasive at institution. ID, 38-39 ("[A] disclosure of an AAD-1 protein with at least 85% sequence identity can be reasonably pieced together without further blaze marks.").

The specification expressly discloses that enzymes having the same or similar activity include sequence identities of 85% and greater to exemplified proteins such as AAD-1. Ex. 1003, 37:24-52; Ex. 1004, ¶ [0116]; Exs. 1005-1010, 1021, ¶ [0142]. As *Snitzer v. Etzel* held, the express listing of a claim element represents a literal disclosure, and thus no blaze marks are required. 465 F.2d 899, 902-03 (CCPA 1972). The Board has likewise rejected arguments about sequence identity limitations similar to Petitioners' here. *See Lifescan*, PGR2019-00032, Paper 11, 25.

Regardless, to the extent any blaze-mark requirement applies, the Priority Applications contain more than ample disclosure. Ex. 2015, ¶¶ 108-109. They disclose a genus of AAD-1 proteins and genes as part of the "invention," referring to AAD-1 more than ***four hundred times*** throughout the specification. *See, e.g.*, Ex. 1003, 20:29-31 ("[P]roteins and genes of the subject invention are referred to herein as AAD-1 proteins and genes."); Ex. 1004, ¶ [0069], Examples 2-4, 6-9, 12-15, 17, 19-20; Exs. 1005-1010, 1021, ¶ [0095], Examples 2-4, 6-9, 12-15, 17, 19-20, 24-26. For such a genus, the specification expressly lists minimum sequence

identities including 85%, as claimed. Ex. 1003, 37:24-52; Ex. 1004, ¶ [0116]; Exs. 1005-1010, 1021, ¶ [0142].[6] The specification further calls out 85% sequence identity as a "highly identical" level of identity within this technical field that would lead one to expect "similar properties." Ex. 1003, 4:21-24; Exs. 1005-1010, 1021, ¶ [0171]. The law requires no further blaze marks than these, and indeed Petitioners cite no authority to the contrary. Accordingly, Petitioners' blaze-marks challenge fails.

The Board correctly pointed out in its Institution Decision that the three disclosed AAD-1 variants "must be correlated to the function of degrading phenoxy auxins and (*R*)-FOPs." ID, 53. As the specification and Corteva's rebuttal evidence detailed above illustrates, the claims here only extend to variants having a narrow range of sequence identities that skilled artisans would have considered "highly identical" with an expectation of the "same or similar properties." Ex. 1003, 44:12-24, 37:24-52; Ex. 1004, ¶ [0116]; Exs. 1005-1010, 1021, ¶¶ [0142], [0171]; Ex. 2015, ¶¶ 106-109. Accordingly, the disclosed and claimed requirement that AAD-1 proteins have at least 85% sequence identity to AAD-1 (SEQ ID NO: 9),

[6] Petitioners' assertion that there are more than "1,000 possible combinations" of sequence identity values (Pet., 12) is exactly the type of "hopelessly exaggerated" argument *Snitzer* rejected. 465 F.2d at 903.

which was well above established thresholds for conserved enzyme function, represents a common, function-correlated structural feature that runs throughout the claimed genus. *See Ajinomoto*, 932 F.3d at 1360 (finding function-correlated common structure where promoter sequences closer to a consensus sequence were generally stronger than promoter sequences farther from it).

2. The Common AAD-1 Active-Site Motif

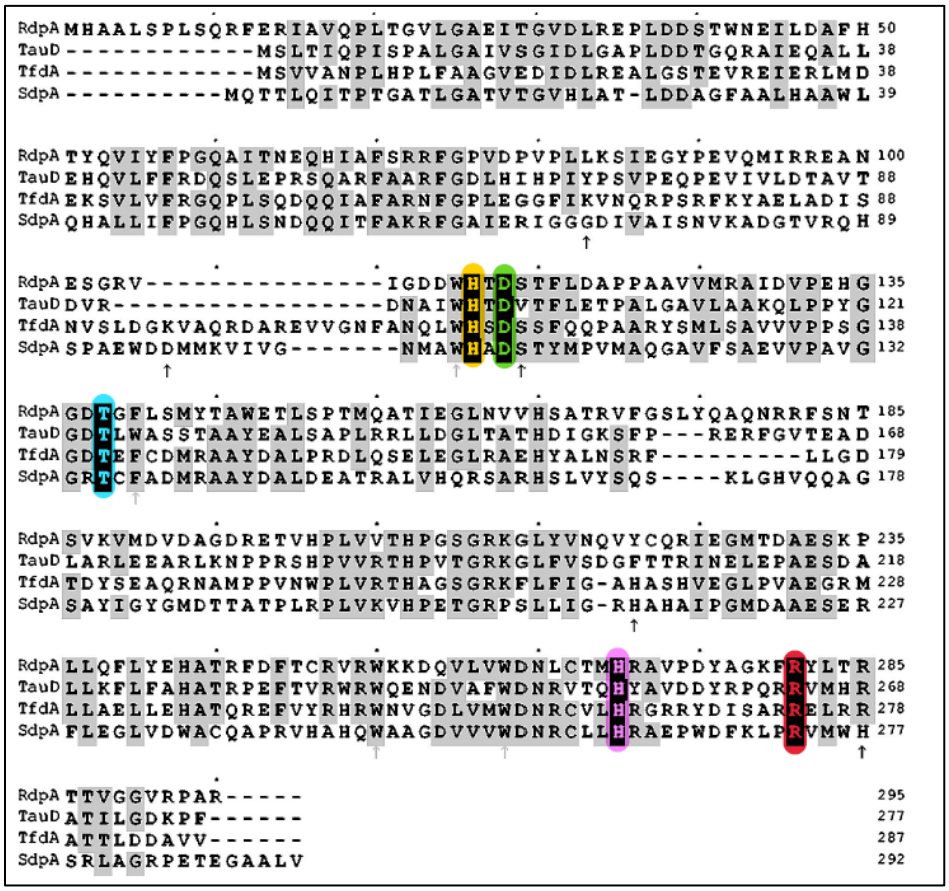
a. The Specification Describes the Active-Site Motif of AAD-1 Enzymes

The ’745 patent claims further require maintaining the active-site motif in the disclosed genus of AAD-1 enzymes: $HX_{112}D(X)_{114\text{-}137}T(X)_{139\text{-}269}H(X)_{271\text{-}280}R$. As Dr. Bollinger explains, skilled artisans understood that each αKG-dependent dioxygenase has the distinctive characteristic of a specific motif. Ex. 2015, ¶¶ 110-112. Skilled artisans thus knew where the motif was located in RdpA/AAD-1—no information beyond its primary amino acid sequence was required. *Id.*, ¶ 113. Here, the ’745 patent discloses SEQ ID NO: 9 and, to the extent any further guidance was necessary, it discloses that AAD-1 has the motif residues, the family motif that orients a skilled artisan to the motif residues’ locations, and the role of the AAD-1 active site in degrading phenoxy auxin and (*R*)-FOP herbicides. *Id.*; Ex. 1003, 18:43-62, 49:20-50:45.

At institution, the Board preliminarily suggested that an obviousness-type analysis would have been required for a skilled artisan to discern the location of the

AAD-1 motif residues. ID, 32-33. Corteva respectfully submits that no such analysis would have been required because a skilled artisan would have recognized that there was only one set of motif residues in SEQ ID NO: 9—no selections would have been necessary. Ex. 2015, ¶¶ 84, 113.

Moreover, the Petition failed to acknowledge that skilled artisans *had already identified the RdpA (AAD-1) motif* and published the location of those active-site residues in Schleinitz 2004, using black shading. The Board's preliminary finding that Schleinitz was only "discussing the αKGD consensus motif" is thus incorrect in view of the testimony of both Dr. Bollinger and Dr. Hausinger. *See* ID, 48-49; Ex. 2015, ¶¶ 114, 72-74; Ex. 2016, 24:19-26:7.



Ex. 1042, 5360 (Fig. 2) (annotated), 5362; Ex. 2015, ¶¶ 114, 72-74.

Enzyme	Active-Site Motif	% Seq Identity to AAD-1
AAD-1	$HX_{112}D(X)_{114\text{-}137}T(X)_{139\text{-}269}H(X)_{271\text{-}280}R$	100%
TauD	$HX_{98}D(X)_{100\text{-}123}T(X)_{125\text{-}252}H(X)_{254\text{-}263}R$	35%
TfdA	$HX_{115}D(X)_{117\text{-}140}T(X)_{142\text{-}262}H(X)_{264\text{-}273}R$	32%
SdpA	$HX_{109}D(X)_{111\text{-}134}T(X)_{136\text{-}261}H(X)_{263\text{-}272}R$	30%

Ex. 2015, ¶ 115.

A skilled artisan therefore would have already known the RdpA (AAD-1) motif. *Id.*, ¶ 114; *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (a patentee may rely on "well-known" information in satisfying the written-description requirement). A skilled artisan also would have understood that

the RdpA (AAD-1) motif differed from the motifs of the other aligned αKG-dioxygenase sequences having different functions, as shown by the gaps in Schleinitz's Figure 2 multiple sequence alignment. Ex. 2015, ¶¶ 72-74.

The '745 patent thus more than amply discloses the AAD-1 motif. That disclosure is further strengthened by the knowledge of a skilled artisan—the lens through which the written-description requirement is analyzed—who *already knew the location of the motif residues* in the RdpA/AAD-1 sequence. *Ossia*, PGR2016-00024, Paper 20, 37-38 ("[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)). Petitioners' demand for additional *in ipsis verbis* disclosure of the AAD-1 motif as a characteristic of AAD-1 enzymes is therefore legal error. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006) (the written-description requirement does not require "the forced recitation of known sequences in patent disclosures"); *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005) (repeating known sequence information is unnecessary).

The Federal Circuit has found adequate written description of particular amino acid residues based on lesser disclosures. In *Yeda*, the specification disclosed only a part of the N-terminus sequence of a TNFα protein, a protocol for obtaining the protein from a biological source, and the protein's biological activity. *Yeda Rsch. & Dev. Co. v. Abbott GmbH & Co.*, 837 F.3d 1341, 1344 (Fed. Cir. 2016). The court

nonetheless found claims reciting additional undisclosed N-terminal amino acid residues adequately described. It found that the protein identified in the specification was the "only protein with the same partial N-terminus sequence and additional traits [i.e., properties] disclosed," and thus the specification inherently disclosed the remaining N-terminal amino acids. *Id.* at 1345.

Here, the specification disclosed all five AAD-1 active-site motif residues in SEQ ID NO: 9, directed one where to locate them (Ex. 1003, 18:43-62), and confirmed that this active site coordinates the enzyme's dual herbicide-degrading activity (*id.*, 49:20-50:45)—all to a skilled artisan who *already knew* where the five active-site motif residues were located (Ex. 1042, 5360). Exs. 1004-1005, [0059]-[0060], [00163]-[00165]; Exs. 1006-1010, 1021 ¶¶ [0085]-[0086], [00192]-[00194]. The disclosures and background knowledge here thus far exceed the disclosures found sufficient in *Yeda*.

b. The Disclosed AAD-1 Motif Is Correlated to Function

The AAD-1 motif of the challenged claims requires keeping the active site of dual-activity AAD-1 proteins highly conserved: (1) the position of the motif is anchored to position 112 relative to SEQ ID NO: 9, (2) the distances between the motif residues are fixed (rather than variable), and (3) the key motif amino acids are identified (cannot be substituted). Ex. 2015, ¶ 112. Thus, even among "highly

identical" variants having at least 85% sequence identity to SEQ ID NO: 9, the claims further restrict the AAD-1 enzymes to those having the same active-site motif as the dual-herbicide degrading enzyme of SEQ ID NO: 9. *Id.*, ¶ 110.

As Dr. Bollinger explains, skilled artisans understood that the active-site motifs of αKG-dependent dioxygenases like RdpA (AAD-1) were correlated to their functions. *Id.*, ¶¶ 115-116. Hausinger 2004, Elkins 2002, and Schleinitz 2004, for example, all report the different spacing of motif residues in αKG-dependent dioxygenase and related enzymes, resulting in binding pockets of different sizes for catalyzing a diversity of reactions. Ex. 1025, 21-22; Ex. 1023, Fig. 5; Ex. 1042, Fig. 2. As Dr. Bollinger further explains, skilled artisans understood that an enzyme's *active-site residues* were correlated to enzyme *activity*. Ex. 2015, ¶¶ 38-40; Ex. 2025, 204-05 ("[C]hanges at key active site residues … are generally deleterious.").

The motif-function correlation among αKG-dependent dioxygenases was also recognized for RdpA. Schleinitz disclosed the AAD-1/RdpA motif and reported that it was "*functionally important*" and "*functionally essential*." Ex. 1042, Abstr., 5357, 5362. Petitioners have also acknowledged the functional importance of the RdpA/AAD-1 motif. Ex. 1054, ¶ 95 (Dr. Hausinger similarly acknowledging that "the five or six active site residues required by the consensus motif and AAD-1

motifs *are important to the function*"), ¶ 53 ("*critical interactions* exist between the enzyme's active site and the carboxyl end of the substrate").

At institution, the Board downplayed Schleinitz's disclosures and Petitioners' concessions as not relating to herbicide-degrading activity on (*R*)-FOP herbicides. ID, 48-49. But while the prior art did not report that RdpA degrades (*R*)-FOP herbicides, *the '745 patent does*. Ex. 2015, ¶ 117. It describes successful testing of AAD-1/RdpA on both (*R*)-FOP and phenoxy auxin herbicides and further reports that the AAD-1 "active site" coordinates the αKG and Fe^{II}-mediated degradation reaction on *both* of the recited classes of herbicides in a similar way. Ex. 1003, 49:20-50:45, 18:43-62 (the role of the active-site motif is "essential for catalytic activity"); Ex. 2015, ¶¶ 116-118.

Accordingly, the disclosed and claimed AAD-1 motif requirement represents a common, function-correlated structural feature that runs throughout the claimed genus. *Ajinomoto*, 932 F.3d at 1360-61.

3. Petitioners' Common-Structure Arguments Are Legally Deficient

a. Petitioners Fail to Apply a Correct Legal Standard for Function-Correlated Structure

The Petition never mentions or applies the Federal Circuit's reasonable-correlation standard for common structure. *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014) (the written-description

requirement is satisfied "if a reasonable structure-function correlation is established, whether by the inventor as described in the specification or known in the art at the time of the filing date"); *Ajinomoto*, 932 F.3d at 1359-60; *Ariad*, 598 F.3d at 1350.

Instead, Petitioners erroneously assert that a common structural feature must be *necessary* and *responsible for* the claimed function. Ex. 1054, ¶ 95 (requiring identification of residues "responsible for the stereoselective activity"), ¶ 103 ("responsible for"); Paper 8, 2-3 ("responsible for"), 4 ("responsible for"); Pet., 29 (requiring structural features "necessary for the (*R*)-enantioselective activity"). Petitioners thus essentially seek to elevate the *correlation* standard for common structure to a *causation* standard. Ex. 2058, 995 (defining "responsible" as "the cause or explanation"); Ex. 1054, ¶¶ 74, 109 (requiring a structural feature "*determinative of*" function). But that is not the law—it is axiomatic that correlation does not require causation. *Ariad*, 598 F.3d at 1350; *Datamaxx Applied Techs., Inc. v. Brown & Brown, Inc.*, No. 21-13451, 2022 WL 3597311, at *4 (11th Cir. Aug. 23, 2022) ("correlation does not imply causation" (citing *Merriam-Webster Dictionary* and *Brown v. Ent. Merchs. Ass'n*, 564 U.S. 786, 800 (2011))).

As *Ajinomoto* illustrates, the law requires only a relationship—i.e., a correlation—between structure and function, which the "at least 85% sequence identity" and AAD-1 motif features amply satisfy here. *See supra* Section VI.A. In that case, the ITC accepted that a "consensus sequence" did not necessarily provide

the most potent promoter within the scope of the claims. *Certain L-Trytophan, L-Trytophan Products, and Their Methods of Production*, Inv. No. 337-TA-1005, 2018 WL 8648370, at *25 (USITC Jan. 11, 2018). In other words, the consensus sequence was *not* necessary for—let alone *determinative* or *responsible for*—producing more potent promoters. *See id.* The ITC nonetheless reversed the ALJ's finding of inadequate written description, concluding that the challenger failed to establish that the consensus sequence was "*unrelated* to promoter strength" or failed to yield a more potent promoter, as claimed. *Id.*

The Federal Circuit affirmed. *Ajinomoto*, 932 F.3d at 1360-61. The patent challenger argued that similarity to a consensus sequence was "still not enough to predict the site and strength of [a] promoter from a given sequence," and that "a promoter closer to the consensus sequence will not always be stronger than one farther from that sequence." *Id.*; *compare* Ex. 1054, ¶ 91 (Dr. Hausinger making similar arguments). The Federal Circuit rejected those arguments as assuming "too strict a legal standard." *Ajinomoto*, 932 F.3d at 1360. Here, Petitioners' asserted requirement that a disclosed structural feature must be "necessary," "responsible for," and "determinative of" the claimed function demands the same level of "perfect correspondence" that *Ajinomoto* rejected. *Id.*

Indeed, in *PureCircle*, the court recently reiterated that "*Ajinomoto* stands for the idea that where there are structural features common to a genus," as here, "the

structure-function correlation does not need to be perfect and some testing—appropriate to the knowledge of a POSA—is allowed." *PureCircle USA Inc. v. SweeGen, Inc.*, No. 2022-1946, slip op. at 12 n.10 (Fed. Cir. Jan. 2, 2024). There, the Federal Circuit found that claims reciting a *purely functionally defined genus* of enzymes lacked written-description support where they contained no sequence limitations and a skilled artisan would have had to empirically determine the active site's location. *See id.* at 5-6. Here, in contrast, the '745 patent discloses the AAD-1 active-site motif and restricts the AAD-1 enzymes to those having highly identical (at least 85%) sequences.

Petitioners also incorrectly rely on the nonanalogous decisions in *AbbVie* and *Juno*, which involved purely functionally defined antibody claims. Pet., 23-24, 26, 28-29, 32. The Federal Circuit has already held that *AbbVie* is "inapposite" in the common-structure context. *Ajinomoto*, 932 F.3d at 1360-61. Indeed, in *AbbVie*, the Federal Circuit observed that there is no common structure in the antibody class that correlates to an antibody binding to a particular target. 759 F.3d at 1301. The court recognized the same fact in *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1339 (Fed. Cir. 2021) ("[A] different amino acid sequence would recognize a different antigen."), *cert. denied*, 143 S. Ct. 402 (2022). In contrast, AAD-1 enzymes are a distinctly different type of protein than the antibodies at issue in *AbbVie* and *Juno*. Ex. 2015, ¶¶ 41-44 (citing Exs. 2037, 2047). As the '745 patent discloses and

the field recognized, there was an established correlation between high sequence identity and conserved enzyme function, and the functional importance of active-site motifs—including in RdpA/AAD-1 specifically—was known. *See supra* Sections II and III. Petitioners have thus relied on inapposite case law and have not established that either high sequence identity to SEQ ID NO: 9 or the AAD-1 motif is uncorrelated to the claimed function. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016) (the ultimate burden of proving unpatentability remains with the petitioner and "that burden never shifts to the patentee").

b. Petitioners' Arguments Based on Other AAD-1 Structures Are Also Based on Legal Error

Petitioners further err in challenging the '745 patent's reasonable structure-function correlation based on *other* structures alleged to be important to function. For example, Petitioners cite the substitution of an additional residue (R285) to alanine in SEQ ID NO: 9 as resulting in an inactive enzyme. Pet., 33; ID, 49-50 (preliminarily stating that inactivity by substituting of R285 "undercut" written description). But the written-description requirement does not require ruling out any or all potentially inoperative embodiments. *PureCircle*, slip op. at 12 n.10 (reasonable testing of variants having a common structure is permitted); *Ajinomoto*, 932 F.3d at 1360-61. Petitioners ignore that R285 was recognized in the field as one

of a few highly conserved, function-correlated residues across RdpA/AAD-1, TfdA, and TauD.

Ex. 2015, ¶¶ 140-142; Ex. 1042, 5360 (Fig. 2 (excerpt)). In other words, R285 was precisely the type of residue that skilled artisans would avoid substituting or would only conservatively substitute when seeking to conserve enzyme function. Ex. 2015, ¶¶ 51-58, 139-142; *In re Smythe*, 480 F.2d 1376, 1385 (CCPA 1973) (written description does not require "an applicant to be so specific in his claims as to exclude materials known to be inoperative" (internal quotation marks and citation omitted)).

Moreover, Petitioners' argument based on the single R285 residue incorrectly presumes that the law requires disclosure of *all* structures (e.g., amino acids) correlated to function, which would again amount to the "perfect correspondence" standard that *Ajinomoto* held was not legally required. 932 F.3d at 1360. Indeed, the Federal Circuit and the Board have credited disclosures of partial, function-correlated amino acid sequences as sufficient to meet the written-description requirement. *See, e.g.*, *id.* at 1359-61 (crediting "consensus sequence" as sufficient disclosure); *Lifescan*, PGR2019-00032, Paper 11, 29 (rejecting written-description

challenge where the evidence suggested that a six-amino-acid sequence or a close variation of it was necessary for activity).

The Board cited a single sequence from *A. denitrificans* as potentially indicating that high sequence identity is not correlated to conserved function. ID, 40. As Dr. Bollinger explains, Petitioners' hypothesis that a TfdA-counterpart enzyme in *A. denitrificans* might have high sequence identity to TfdA while exhibiting opposite (*R*)-enantiospecificity is irrelevant and has no bearing on RdpA (AAD-1), which has only 30% identity to its (*S*)-enantiospecific counterpart enzyme, SdpA. Ex. 2015, ¶¶ 123-124 (citing Exs. 2053, 1035).

Moreover, Dr. Hausinger overreaches in seeking to attribute unexpected (*R*)-enantiospecificity to a particular TfdA-like (not RdpA-like) *A. denitrificans* amino acid sequence. Ex. 2015, ¶¶ 122-130; Ex. 1054, ¶ 109. Saari 1999 did not, and could not, attribute (*R*)-enantiospecificity to that sequence because the authors only tested crude cell extracts, not any purified protein. Ex. 1041, 421, 427; Ex. 2015, ¶ 125 ("cell extracts can contain hundreds of different proteins"). Notably, later researchers did not report any particular (*R*)-enantiospecific enzyme sequence. Instead, they continued to predict enzymatic function, including for TfdA-like

sequences in *A. denitrificans*, based on sequence identity. Ex. 2015, ¶¶ 128-129; *supra* Section II.A.2.

Accordingly, Petitioners' legally flawed arguments fail to rebut the strong correlation between the disclosed and claimed common structures and the dual herbicide-degrading activity of AAD-1 enzymes. To the contrary, Petitioners' reliance on alleged *anecdotal exceptions* to Corteva's structure-function evidence tends, if anything, to prove the *general correlation* of at least 85% sequence identity and the AAD-1 motif to the claimed function. *See Ajinomoto*, 932 F.3d at 1360 (holding that evidence that deviations from a consensus sequence "do not *always* decrease promoter strength" failed to disturb the general correlation between consensus sequence and promoter strength).

c. Petitioners Erroneously Rely on Post-Filing Date Evidence

Petitioners further err by analyzing the specification's sufficiency in view of the state of the art as late as 2019, long after the 2004-2005 filing dates. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1373-74 (Fed. Cir. 2017) ("[W]ritten description is judged based on the state of the art as of the priority date. Accordingly, evidence illuminating the state of the art subsequent to the priority date is not relevant to written description.").

Impermissibly relying on later-dated evidence detailing analyses of RdpA/AAD-1 enzymes—e.g., Müller 2006 (Ex. 1035), Chekan 2019 (Ex. 1019), and Larue 2019 (Ex. 1052)—Petitioners contend that three-dimensional structural data was necessary to identify residues important to the claimed function:

- "[T]he type of structural information that might have been used to identify the residues that are important to RdpA's activity" was published in Müller 2006, Chekan 2019, and Larue 2019. Ex. 1054, ¶ 88.
- "[T]he POSA would not have had the benefit of substrate-bound crystal structures or crystallography data until that information was published in 2019." *Id.*, ¶ 105.

See also Pet., 31 (citing Larue 2019 and suggesting that "three-dimensional structural data" was needed); Ex. 1054, ¶ 106. Petitioners' arguments are irrelevant and incorrect.

First, the law does not require disclosure of three-dimensional structural information, and Petitioners cite no authority supporting their position. Disclosures of motifs or other consensus sequences normally suffice in satisfying the written-description requirement. *See Ajinomoto*, 932 F.3d at 1360 ("consensus sequence"); *Lifescan*, PGR2019-00032, Paper 11, 18-19, 29 (six-amino-acid motif within a 593 amino acid protein). High sequence identity requirements also often suffice.

Ex parte Campbell, No. 2021-000865, Decision on Appeal, 15 (PTAB July 20, 2021); *Boehringer Ingelheim Animal Health USA Inc. v. Kan. State Univ. Rsch. Found.*, PGR2022-00021, Paper 13, 20-21 (PTAB Mar. 22, 2023). Here, the '745 patent discloses and claims *both* types of common structures correlated to function.

Second, while skilled artisans *could* rely on a three-dimensional enzyme crystal structure when making variants, they were not so limited. Ex. 2015, ¶¶ 45-59. Skilled artisans recognized that a "wide variety" of approaches could be used, including "sequence alignments." Ex. 2035, 180; Ex. 2025, 202-03 (sequences of related proteins are "a potentially rich source of information regarding sequence changes that are acceptable without drastically disrupting protein function"). The information presented in the '745 patent and known in the art provided ample guidance for making AAD-1 variants, particularly within the narrow sequence space (85% or higher identity to SEQ ID NO: 9) of the claims. Ex. 2015, ¶¶ 119-121; *supra* Sections II, III.

Third, Petitioners' argument that additional residues could also be functionally important fails to establish that the AAD-1 motif and "at least 85% sequence identity" features lack correlation to the claimed function. Instead, Petitioners' criticism of the specification in view of other identified residues in later-dated evidence simply repackages their legally incorrect attempt to impose a heightened, perfect-correspondence standard for written description. *Ajinomoto*, 632

F.3d at 1360; *PureCircle*, slip op. at 12 n.10; *supra* Section VI.A.3.a. Indeed, the law does not require disclosure of *all* structural features potentially relevant to function—it only requires that the *identified common structures* have a "reasonable structure-function correlation." *AbbVie*, 759 F.3d at 1301; *In re Hogan*, 559 F.2d 595, 606-07 (CCPA 1977) (warning that "[c]onsideration of a later existing state of the art in testing for compliance with § 112, first paragraph, … would wreak havoc" by discouraging further research and development if such later efforts could be used to "reach back" and invalidate an earlier-filed patent).

Fourth, Petitioners' later-dated evidence fails to support their argument that Corteva's disclosed structural features lack correlation to the claimed function. Petitioners point to their Larue 2019 publication as disclosing important three-dimensional crystal structure data. Ex. 1054, ¶ 88; Pet., 31. But they omit that the dual herbicide-degrading RdpA variants Petitioners made and reported with knowledge of that crystal structure nonetheless *uniformly retained* the disclosed common structures. Indeed, as Dr. Bollinger explains, all six dual herbicide-degrading FT enzymes have the AAD-1 motif's required residues and *exact spacing*.

```
RdpA      MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQ
FT_5      MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQ
FT_C      MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQ
FT_R      MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQ
FT_T      MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQ
FT_Tv3    MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQ
FT_Tv7    MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQ
          *****:**:::: * ********************************************

RdpA      AITNEQHIAFSRRFGPVDPVPLLKSIEGYPEVQMIRREANESGRVIGDDWHTDSTFLDAP
FT_5      AITNEQHIAFSRRFGPVDPVPLLKSIEGYPEVQMIRREANESGRVIGENWHTDSTFLDAP
FT_C      AITNEQHIAFSRRFGPVDPVPLLKSIEGYPEVQMIRREANESGRVIGDDWHTDSTFLDAP
FT_R      AITNEQHIAFSRRFGPVDPVPLLKSIEGYPEVQMIRREANESSRVIGDDWHSDSTFLDAP
FT_T      AITNEQHIAFSRRFGPVDPVPILKSIEGYPEVQMIRREANESSRFIGDDWHTDSTFLDAP
FT_Tv3    AITNEQHIAFSRRFGPVDPVPILKSIEGYPEVQMIRREANESSRYIGDDWHADSTFLDAP
FT_Tv7    AITNEQHIAFSRRFGPVDPVPILKSIEGYPEVQMIRREANESSRYIGDDWHADSTFLDAP
          **********************:********************.* **::**:********

RdpA      PAAVVMRAIDVPEHGGDTGFLSMYTAWETLSPTMQATIEGLNVVHSATRVFGSLYQAQNR
FT_5      PAAVVMYAKEIPPYGGDTLFTSMYTAWETLSPTMQATIEGLNVVHSATRVFGSLYQAQNR
FT_C      PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
FT_R      PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
FT_T      PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
FT_Tv3    PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
FT_Tv7    PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
          ****** * ::* :**** * ***:************************:******** *

RdpA      RFSNTSVKVMDVDAGDRETVHPLVVTHPGSGRKGLYVNQVYCQRIEGMTDAESKPLLQFL
FT_5      RFSNTSVKVMDVDAGDRETVHPLVVTHPETGRKGLYVNQVYCQRIEGMSEKESEPLLSFL
FT_C      RFSNTSVKVMDVDAGDRETVHPLVVTHPVTGRRALYCNQVYCQKIQGMTDAESKSLLQFL
FT_R      RFSNTSVKVMDVDAGDRETVHPLVVTHPVTGRRALYCNQVYCQKIQGMTDAESKSLLQFL
FT_T      RFSNTSVKVMDVDAGDRETVHPLVVTHPVTGRRALYCNQVYCQKIQGMTDAESKSLLQFL
FT_Tv3    RFSGTSVKVMDVDAGDRETVHPLVVTHPVTGRRALYCNQVYCQKIQGMTDAESKSLLQFL
FT_Tv7    RFSNTSVKVMDVDAGDRETVHPLVVTHPVTGRRALYCNQVYCQKIQGMTDAESKSLLQFL
          ***.************************ :**:.** ******:*:**:: **:.**.**

RdpA      YEHATRFDFTCRVRWKKDQVLVWDNLCTMHRAVPDYAGKFRYLTRTTVGGVRPAR
FT_5      FAHATKPEFTCRVRWQEGDVLVWDNLCTCHYAVPDYAGKFRYLTRTTVGGVRPAR
FT_C      YEHATKFDFTCRVRWKKDQVLVWDNLCTMHRAVPDYAGKFRYLTRTTVAGDKPSR
FT_R      YEHATKFDFTCRVRWKKDQVLVWDNLCTMHRAAPDYAGKFRYLTRTTVAGDKPSR
FT_T      YEHATKFDFTCRVRWKKDQVLVWDNLCTMHRAVPDYAGKFRYLTRTTVAGDKPSR
FT_Tv3    YEHATQFDFTCRVRWKKDQVLVWDNLCTMHRAVPDYAGKFRYLTRTTVAGDKPSR
FT_Tv7    YEHATQFDFTCRVRWKKDQVLVWDNLCTMHRAVPDYAGKFRYLTRTTVAGDKPSR
          : ***: :*******::.:********* * *.***************.* :*:*
```

Ex. 2015, ¶ 136; Exs. 2012-2014, 2048-2050, 2061. They all also have high sequence identity (~89-90%) to RdpA (SEQ ID NO: 9), which is unsurprising in view of long-recognized sequence-function correlations in the art. Ex. 2015, ¶ 136. The consistent retention of the claimed structural features in Petitioners' own enzymes strongly confirms that those structural features have ample correlation to function.

B. The Disclosed AAD-1 Enzymes Are Representative of the Narrow Claimed Genus

Petitioners' challenge also fails for an independent reason: the '745 patent's disclosed AAD-1 variants are representative of the claimed genus. *Ajinomoto*, 932 F.3d at 1358-59.

Disclosed species are representative when they reflect the diversity of a claimed genus. *AbbVie*, 759 F.3d at 1301. Here, the analysis is simpler than in most cases because 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. Ex. 2015, ¶¶ 131-135; Ex. 1003, 44:12-24 (85% and higher identity is "highly identical"), 37:24-52; Ex. 1004, ¶ [0116]; Exs. 1005-1010, 1021, ¶¶ [0142], [0171]; Ex. 2019, 863 ("[S]everal studies suggested that when the sequence identity is above 40%, enzyme function is well conserved."); Ex. 2028, 604 ("When two sequences are very similar[,] we can safely infer that they have similar structures."); Ex. 2021, 85; *Ajinomoto*, 932 F.3d at 1359 (finding disclosure of four exemplary promoters and "background knowledge in the art" sufficiently representative to support claims with no promoter sequence limitations). Petitioners' assertion that the claimed genus is "massive and diverse" is thus refuted by the evidence of record. Ex. 1054, ¶ 76.

In contrast to Petitioners' legally incorrect reliance on a later state of the art in analyzing written description (*see supra* Section VI.A.3.c), the Federal Circuit has recognized that post-filing date evidence can be properly used for the limited purpose of analyzing the scope of a genus and whether disclosed species are representative of that genus. *AbbVie*, 759 F.3d at 1300-01 (analyzing whether disclosed antibodies were sufficiently similar to challenger's Stelara antibody); *Amgen*, 872 F.3d at 1374-75. Here, Petitioners' own later evidence confirms that AAD-1 enzymes are essentially the opposite of a structurally or functionally diverse genus, and that the '745 patent's disclosed variants are thus representative of that genus.

In Larue 2019, submitted with the Petition, Petitioners' scientists disclosed additional RdpA variants, citing the prior work of the '745 patent's inventors on AAD-1 enzymes. Ex. 1052, 2087 (citing ref. 9, an article by T. Wright and J. Lira). Petitioners renamed these additional AAD-1 enzymes as "FT" (FOP tolerance) enzymes and submitted six sequences to GenBank. *Id.*, 2087, 2090 (Fig. 3). All six dual herbicide-degrading FT enzymes have the AAD-1 motif. Ex. 2015, ¶¶ 136-137. All are within 85% sequence identity of RdpA (SEQ ID NO: 9). *Id.* These additional AAD-1 (FT) enzymes thus further confirm that the claimed AAD-1 enzymes represent a genus of *highly identical* enzymes having the same or similar activity, just as the specification discloses. Ex. 1003, 44:12-24 (85% and higher identity is

"highly identical"), 37:24-52; Ex. 1004, ¶ [0116]; Exs. 1005-1010, 1021, ¶¶ [0142], [0171].

Petitioners' reliance on functionally defined genus cases such as *AbbVie* and *Juno* is misplaced. *E.g.*, Pet., 29. The claims there encompassed all antibodies *regardless of amino acid sequence* that exhibited the claimed activity. *AbbVie*, 759 F.3d at 1292; *Juno*, 10 F.4th at 1339. The broad diversity of the genus of antibodies in *AbbVie* and *Juno* thus bears no resemblance to this case, as skilled artisans would have expected enzymes having at least 85% sequence identity to be "highly identical" and have the same or similar activity as the specification discloses. Ex. 1003, 44:12-24, 37:24-52; Ex. 1042, 5360 (Fig. 2); Ex. 2019, 863; Ex. 2015, ¶¶ 41-44 (enzymes are "starkly different" than antibodies); *Campbell*, No. 2021-000865, Decision on Appeal, 15 (upholding claims requiring at least 90% sequence identity based on disclosure of two sequences, where sequence comparisons provided guidance on where amino acid substitutions could be made).

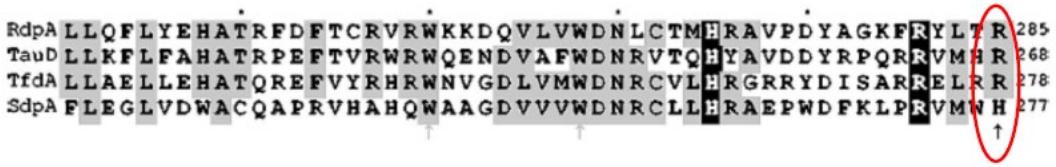
C. Claim 2 Is Adequately Described

Claim 2 depends from independent claim 1 and requires an additional arginine in the motif $HX_{112}D(X)_{114\text{-}137}T(X)_{139\text{-}269}H(X)_{271\text{-}280}R(X)_{282\text{-}284}R$, wherein $(X)_{282\text{-}284}$ represents a sequence of three amino acids.

In previous cases, the Board has rejected written-description challenges to broader claims (e.g., here, claim 1) while finding that narrower claims reciting an

additional feature (e.g., claim 2) lacked written description. *See Boehringer*, PGR2022-00021, Paper 13, 20-21 (denying challenge to claims requiring PCV3 proteins having at least 90% sequence identity and distinguishing a previous decision that held a related patent's claims with an additional functional limitation unpatentable for lack of written description). In this case, however, the Board should decline to find that claim 2 lacks priority or is unpatentable.

While the Board preliminarily criticized Hotopp's disclosure of an additional arginine important to function as insufficiently "well-known" to support written description, Corteva respectfully submits that the Board's concerns are misplaced. ID, 35-36. Indeed, a skilled artisan's knowledge would not have been limited to Hotopp because a sequence comparison had already been published showing that the additional arginine in TfdA was involved in substrate binding *and* that this residue was highly conserved in RdpA (i.e., SEQ ID NO: 9) as well as in TauD.



Ex. 2015, ¶¶ 138-142; Ex. 1042, 5360 (Fig. 2 (excerpt)); Ex. 1023, 5190; Ex. 2016, 26:15-27:10. This arginine was thus precisely the type of highly conserved residue that skilled artisans would have recognized as functionally important. Ex. 2015, ¶ 139. The law does not require an *in ipsis verbis* disclosure separately calling out

the additional arginine residue in SEQ ID NO: 9 when skilled artisans already understood its importance. *Rivera v. ITC*, 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").

Accordingly, for these reasons, the Board should reject Petitioners' priority challenge and find that all challenged claims are patentable over Corteva '437, which is not prior art.

VII. Grounds 2A and 2B: Petitioners Fail to Establish that the Challenged Claims Would Have Been Obvious

It is undisputed that, as of Corteva's April 30, 2004, filing date, the prior art failed to disclose the dual herbicide-degrading enzymatic activity required by all challenged claims. Ex. 1054, ¶ 219; Ex. 2015, ¶ 147. This fatal deficiency in Petitioners' challenge should end the obviousness analysis. *Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014) (motivation and reasonable expectation of success are considered *only if* the prior art discloses all claim elements). Indeed, at institution, the Board correctly found Petitioners' attempts to rectify this lack of prior-art disclosure unpersuasive, "[t]hreadbare," and "look[ing] like hindsight." ID, 64-65, 67-68. On a complete trial record, the Board should confirm that Petitioners failed to meet their burden, as they have not proven

reasonable expectation of success, inherency, motivation, or meaningfully addressed Corteva's compelling objective evidence of nonobviousness.

A. Petitioners Fail to Establish a Reasonable Likelihood of Success

Petitioners' reasonable-expectation analysis is legally deficient, failing to analyze the claimed invention "as a whole," as required. 35 U.S.C. § 103(a). Petitioners first allege that a POSA would have expected success in *transforming soybean plants* to express RdpA. Pet., 57. Then they circle back to contend that the "remaining limitations" of claim 1—including the required dual herbicide-degrading activity—were expected. *Id.*, 56. The Board routinely rejects this type of piecemeal analysis. *Zhejiang Crystal-Optech Co. v. Viavi Sols. Inc.*, IPR2022-01184, Paper 8, 9, 27 (PTAB Feb. 7, 2023); *DIRECTV, LLC v. Qurio Holdings, Inc.*, IPR2015-02006, Paper 6, 7-9, 13-14 (PTAB Apr. 4, 2016); *Apple Inc. v. ContentGuard Holdings, Inc.*, IPR2015-00443, Paper 9, 9-11 (PTAB July 9, 2015).

Regarding the claimed dual-herbicide degrading activity, Petitioners advance a conclusory, one-sentence argument that a POSA would have expected RdpA to degrade FOP herbicides "via the same mechanism" as phenoxy auxins. Pet., 58-59. The Board should reject this argument because, as the Institution Decision pointed out, Petitioners cite no supporting prior-art evidence. ID, 63-65. Instead, they rely on the file history's discussion of the '745 patent's studies regarding RdpA's

mechanism of action on FOP and phenoxy auxin herbicides. Ex. 1054, ¶¶ 219-220. Neither Saari nor any other cited reference discloses any investigation of substrate-degradation pathways for FOP herbicides, much less with RdpA specifically. Ex. 1054, ¶ 219 (Dr. Hausinger acknowledging the prior art "did not report testing of RdpA" on FOPs). Petitioners' reliance on the inventors' own work disclosed in the '745 patent and referenced during prosecution is impermissibly based on hindsight. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight." (citing 35 U.S.C. § 103(a))).

Dr. Hausinger's suggestion in a background section of his declaration—cited nowhere in Petitioners' obviousness analysis[7]—that an additional aryl group present on FOP herbicides would have been viewed as unlikely to affect binding—is also incorrect and based on impermissible hindsight. Ex. 1054, ¶¶ 45-57; *see* Pet., 55-58. The structural differences between phenoxy auxin and FOP herbicides are significant, not immaterial as Petitioners contend. Ex. 2015, ¶¶ 143-154. The

[7] The Institution Decision found that Petitioners' reasonable-expectation theory improperly incorporated by reference material that should have been presented in the Petition itself. ID, 67. Any further arguments by Petitioners outside of the scope of the Petition should be rejected. *Magnum Oil*, 829 F.3d at 1381.

additional aryl group present on FOP herbicides significantly increases the size of their aromatic substituents as compared to phenoxy auxins. *Id.* These structural differences are reflected in their significantly different chemical properties. Phenoxy auxins act by mimicking natural plant hormones whereas FOP herbicides inhibit fatty acid synthesis by intracellular acetyl-CoA carboxylase ("ACCase") enzymes. Ex. 2015, ¶ 146; Ex. 1054, ¶¶ 39, 43. As the '745 patent discloses, and Petitioners nowhere address, "these classes of herbicides are all quite distinct" and no prior art as of April 30, 2004, suggested that they followed common degradation pathways. Ex. 1003, 3:65-4:8.

Thus, as Dr. Bollinger explains, the dual herbicide-degrading activity of the claimed invention was indeed unexpected in view of the prior art and unique within the field of αKG-dependent dioxygenases as of 2004. Ex. 2015, ¶ 159. The claimed invention thus yields a difference-in-kind (i.e., new function) compared to the prior art, which strongly supports nonobviousness. *In re Albrecht*, 514 F.2d 1389, 1395-96 (CCPA 1975) (crediting a compound's unexpected dual activity of exhibiting antiviral and anesthetic properties as supporting nonobviousness).

B. Petitioners Fail to Establish Inherency

Petitioners' conclusory, single-sentence inherency theory also fails. Pet., 57-58. Because the dual herbicide-degrading activity of RdpA (AAD-1) was unknown and unexpected as of April 30, 2004, Petitioners cannot meet their burden of proving

inherency. *Honeywell Int'l Inc. v. Mexichem Amanco Holdings S.A. De C.V.*, 865 F.3d 1348, 1355 (Fed. Cir. 2017) (holding that the Board, "in dismissing properties of the claimed invention as merely inherent, without further consideration as to unpredictability and unexpectedness, erred as a matter of law").

Petitioners' inherency theory is threadbare and unsupported. The only paragraph of Dr. Hausinger's declaration that purportedly addresses inherency cites no supporting evidence. Ex. 1054, ¶ 120. To the extent Dr. Hausinger relies on the '745 patent's disclosures, his opinions boil down to alleging inherency merely because Corteva showed that its invention works. That, however, is not the law.

In *Adams*, the claimed invention produced an unexpected and unsuggested advantage, which the Office contended was inherent. *In re Adams*, 356 F.2d 998, 1002 (CCPA 1966). Finding that the Office's position was improperly based on hindsight, the court rejected the proposition that the claims were unpatentable merely because the invention "work[ed]." *Id.* (reversing inherency-based rejection where "[n]o reference" suggested the advantages of a claimed invention); *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (similarly reversing inherency-in-obviousness rejection where the prior art did not suggest an advantage alleged to be inherent). Thus, as the Federal Circuit has cautioned, applying inherency in the context of obviousness must be carefully circumscribed because the inherency of a claimed function (e.g., AAD-1 activity) and its obviousness are "entirely different

questions." *Spormann*, 363 F.3d at 448 ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."); *Honeywell*, 865 F.3d at 1355 ("What is important regarding properties that may be inherent, but unknown, is whether they are unexpected.").

Petitioners have also failed to meet their burden on inherency because the Petition nowhere addresses the factors Dr. Hausinger testified during cross-examination could affect enzyme activity or expression. 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).

At institution, the Board also questioned whether pairing Streber's transformation method with the *rdpA* gene might be ineffective or yield inactive protein. ID, 64. Despite having the burden of proof, Petitioners failed to present any evidence that using Streber's *Agrobacterium*-mediated transformation method would work with *rdpA* and yield active protein, much less establish inherent dual-herbicide degrading activity. *See* Pet., 57-58. Indeed, the '745 patent discloses an *Agrobacterium*-mediated transformation procedure for tobacco that uses different *Agrobacterium* strains, gene promoters, and regeneration-and-selection procedures, among other differences. *Compare* Ex. 1003, 95:45-96:16, *with* Ex. 1043, 30:37-61. Dr. Hausinger conceded that the choice of promoters can affect whether and to what

extent active protein is expressed. Ex. 2016, 58:23-59:19, 59:20-60:3 (Dr. Hausinger further testifying he has no experience using Streber's promoters); *see* Ex. 1003, Examples 7-9, 12-15, 19-20, 24-26 ('745 patent disclosing suitable promoters). Petitioners' reliance on *Hospira* is thus misplaced, as the challenger in that case supported its inherency allegations with test results showing that a claimed formulation-stability limitation was necessarily present *in the prior-art combination*. Pet., 58; *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1331-32 (Fed. Cir. 2020).[8] Petitioners have not come close to making the same type of showing here, much less with respect to soybean specifically.

Finally, Petitioners raise no inherency arguments with respect to the tolerance aspects of all challenged claims. For example, claim 1 (and all claims depending therefrom, as well as independent claim 29) require that the "AAD-1 protein when expressed in a soybean plant cell renders said soybean plant cell tolerant" to the recited herbicides.. Here again, Dr. Hausinger conceded that many factors can affect

[8] *Ex parte Hirahashi*, No. 2020-005092, 2021 WL 2549655, at *3 (PTAB June 18, 2021) (*see* Pet., 57-58), is also distinguishable because treatment of a claimed disease was inherently a subtype of a disease already disclosed for treatment in the prior art. Here, Petitioners here fail to identify any analogous prior-art AAD-1 activity, much less in transformed plants.

expression levels. Ex. 2016, 57:16-60:3; Ex. 1054, ¶ 137 (Dr. Hausinger asserting only that "at least some" plants had tolerance). Claims 25-28 require additional features such as a seed, plant, or progeny. Petitioners nowhere contend that these features would have been inherent in any prior-art combination. Indeed, the '745 patent discloses them as preferred embodiments, not as inherently present. Ex. 1003, 29:61-30:56 (transgenic plants preferably express an "effective amount" of an enzyme to confer tolerance), 42:19-21 (transgenic plants "*may* … be grown to seed and said seed *can* be used to establish future generations").

C. Petitioners Fail to Establish Motivation to Combine Streber, Saari, and Schleinitz

Petitioners fail to acknowledge that Streber's TfdA-transformation efforts to create 2,4-D-resistant crops, beginning in the late 1980s, were a commercial failure in view of their poor performance. Exs. 1043-1045. Regarding Streber's TfdA-transformed tobacco, "none of the researchers were interested in 2,4-D-tolerant tobacco," having used it only as a model crop. Ex. 2055, 165, 168 ("little interest has been shown in any [crop] but cotton"). When TfdA was used in cotton, the transformed plants had "significantly reduced" growth rates and poor 2,4-D tolerance. Ex. 2052, 404. Researchers questioned TfdA-transformed cotton's "agronomic usefulness," stating that better performance was "unlikely" because "among the strongest" promoters had already been tried. *Id.* No TfdA-resistant crop

was ever commercialized. Dr. Hausinger conceded he had no evidence that skilled artisans in the field of crop transformation were seeking to use any other αKG-dependent dioxygenase in soybean notwithstanding TfdA's poor performance. Ex. 2016, 63:6-8, 63:19-64:1. The art's struggles with TfdA-transformed plants over the 15+ years before the '745 patent's priority date fail to support motivation—to the contrary, they strongly support nonobviousness. Ex. 2015, ¶¶ 155-156; *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1359 (Fed. Cir. 2013) (identifying "intervening time" between the prior art and development of the claimed invention as supporting nonobviousness).

Ignoring these struggles with 2,4-D resistance and TfdA, Petitioners focus on possible tolerance to *R*-phenoxy auxins such as *R*-dichlorprop and *R*-mecoprop. Pet., 56. But at that time, glyphosate already conferred broad-spectrum control of both broadleaf (i.e., dicot) and grassy (i.e., monocot) weeds. Ex. 1003, 1:46-2:11, 17:12-13; Ex. 2015, ¶¶ 157-158. Petitioners cite no evidence that, as glyphosate-resistant weeds began to appear, skilled artisans viewed *R*-dichlorprop and *R*-mecoprop as possible alternatives. *Id.*, 2:12-57; Ex. 2016, 55:13-24 (Dr. Hausinger testifying he has no expertise in herbicide selection). Indeed, they were not. *R*-dichlorprop and *R*-mecoprop were limited-spectrum herbicides compared to 2,4-D's broader agricultural use. Ex. 2056, 113, 282, 453 (*R*-dichlorprop used to control certain broadleaf weeds in "brush control"

applications along fencerows, highways, etc.); Ex. 2060, 10 (*R*-mecoprop mainly used for broadleaf-weed control in weed-and-feed lawn products, as well as with certain cereal crops). Petitioners also cite no evidence that skilled artisans would have been motivated to genetically modify soybeans, in particular, with a recombinant herbicide-tolerance gene for *R*-phenoxy auxins such as *R*-dichlorprop and *R*-mecoprop.

Petitioners' reliance on a half-sentence statement from Saari 1999—i.e., that a gene encoding an *R*-specific enzyme-encoding gene "*could* be used" to develop genetically engineered crops—is thus legally insufficient and ignores past failures with TfdA-transformed crops and how dichlorprop and mecoprop were used in the art. Pet., 56 (citing Ex. 1041, 422); *InTouch Techs., Inc. v. VGo Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014) (rejecting similarly conclusory argument that a skilled artisan "*could* combine" certain references (emphasis in original)). The AAD-1-transformed plants of the '745 patent provided the first alternative to glyphosate-resistant crops by surprisingly conferring broad-spectrum weed control to both grassy weeds (e.g., using FOP herbicides) and broadleaf weeds (e.g., using 2,4-D). Ex. 1003, 20:41-47; Ex. 2015, ¶ 160.

D. Objective Evidence Strongly Supports Nonobviousness

Objective evidence must be considered before any making any determination regarding obviousness. *In re Cyclobenzaprine Hydrochloride Extended-Release*

Capsule Pat. Litig., 676 F.3d 1063, 1075-76 (Fed. Cir. 2012). Here, as detailed above, the claimed invention produced unexpected results with transgenic soybean plants exhibiting the AAD-1 activity of degrading two different classes of herbicides (FOPs and phenoxy auxins), which was unprecedented in the agricultural biotechnology field and advantageously provided broad-spectrum weed control. *See, e.g.*, Ex. 1003, 4:15-19, 4:48-5:5, 8:19-33 (AAD-1 is "unlike all tfdA homologues characterized to date"), 108:61-116:6 (Example 17), 99:49-104:35 (Example 13); Ex. 2015, ¶¶ 159-162. This is precisely the type of difference-in-kind from the prior art that strongly supports nonobviousness. *Albrecht*, 514 F.2d at 1395-96 (crediting a compound's unexpected dual activity of exhibiting antiviral and anesthetic properties).

Corteva's evidence of unexpected results, which remains unrebutted by Petitioners, persuasively supports nonobviousness. *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (when a patentee demonstrates substantially improved results and states that the results were unexpected, those results are established absent contrary evidence). Petitioners fail to identify *any* αKG-dependent dioxygenases in the prior art that degrade FOP herbicides, much less any that additionally degrade a second class of herbicides (e.g., phenoxy auxins). Ex. 1054, ¶ 219 (Dr. Hausinger conceding that the prior art "did not report testing of RdpA on (*R*)-aryloxyphenoxypropionate

substrates"); Pet., 64-65. Indeed, the references Petitioners assert are the closest prior art (e.g., Streber, Schleinitz, and Saari) disclose no FOP-degrading activity.

The unexpected results achieved by the claimed invention are entitled to a presumption of nexus and have actual nexus to the scope of the claims. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329, 1331 (Fed. Cir. 2016). The '745 patent claims only extend to a narrow sequence space of 85% or higher identity variants that skilled artisans would have considered "highly identical" with an expectation of having the "same or similar" properties. Ex. 1003, 44:12-24, 37:24-52; *supra* Sections VI.A-B. Within that narrow sequence space, the AAD-1 enzymes must further have the AAD-1 active site motif. Ex. 2015, ¶¶ 161, 110. The claims are thus restricted to a group of *highly identical* enzymes—the polar opposite of the broad, functionally defined antibody claims where courts have found nexus lacking. *Cf. Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1363-64 (Fed. Cir. 2021).

Additional objective evidence also supports nonobviousness: Petitioners' copying and praise of the claimed invention. *Medtronic, Inc. v. Teleflex Innovations S.À.R.L.*, IPR2020-00127, Paper 107, 46-48 (PTAB June 17, 2021) (petitioner's copying favors nonobviousness). Petitioners' scientists have cited and credited the '745 patent's inventors as pioneering the use of RdpA/AAD-1, determining that FOP herbicides are suitable substrates, and establishing AAD-1's mechanism of action. Ex. 2059, 256 ("The use of RdpA … in agriculture biotechnology was first

demonstrated by Wright *et al.*"); *id.* (Wright et al.'s "work in both corn and soybeans nicely illustrates the potential value these dioxygenase enzymes could bring to agriculture biotechnology."); Ex. 1052, 2087 (citing Wright (ref. 9) as showing that RdpA "provide[s] tolerance" to the two herbicide classes).

Only after learning of Corteva's surprising results did Petitioners seek to make additional AAD-1 enzymes, copying Corteva's invention. Ex. 2059, 256 (acknowledging that after Wright et al.'s work, Petitioners used "the RdpA scaffold" to make enzymes having FOP and 2,4-D degrading activity). Petitioners acknowledged the importance of the surprising FOP-degrading activity by renaming AAD-1 enzymes as "FT" (FOP tolerance) enzymes. Ex. 1052, 2087. As detailed above, Petitioners' scientists published six sequences of FT enzymes having the dual herbicide-degrading activity of the claimed invention. *Supra* Section VI.B. Each FT enzyme maintains the AAD-1 motif and has 89-90% sequence identity to SEQ ID NO: 9, further illustrating that Corteva's objective evidence of nonobviousness has ample nexus to the scope of the claims. *Id.*

VIII. 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: April 16, 2024

/Pier D. DeRoo/
Pier D. DeRoo
Reg. No. 69,340

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Pier D. DeRoo, certify that **Patent Owner's Response** contains 13,694 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: April 16, 2024

/Pier D. DeRoo/
Pier D. DeRoo
Reg. No. 69,340

CERTIFICATE OF SERVICE

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

Dov P. Grossman
Ben Picozzi
Williams & Connolly LLP
680 Maine Avenue SW
Washington, DC 20024
dgrossman@wc.com
bpicozzi@wc.com

Scott A. McKeown
Jonathan B. Roses
Charles T. Steenburg
Eric J. Rutt
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210-2206
SMcKeown-PTAB@WolfGreenfield.com
JRoses-PTAB@WolfGreenfield.com
Charles.Steenburg@WolfGreenfield.com
Eric.Rutt@WolfGreenfield.com

Petitioners have consented to service by email.

Dated: April 16, 2024

/William Esper/
William Esper
Case Manager and PTAB Coordinator
Finnegan, Henderson, Farabow,
Garrett & Dunner, LLP