

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

***Bayer CropScience LP, Monsanto Company, and
Inari Agriculture, Inc.***

v.

Corteva Agriscience LLC

IPR2023-01036

IPR2023-01037

IPR2023-01038

CORTEVA'S TRIAL DEMONSTRATIVES

September 24, 2024

The '555 Patent Claims

1. A transgenic 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 (R)-aryloxyphenoxypropionate herbicide, 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:

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

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

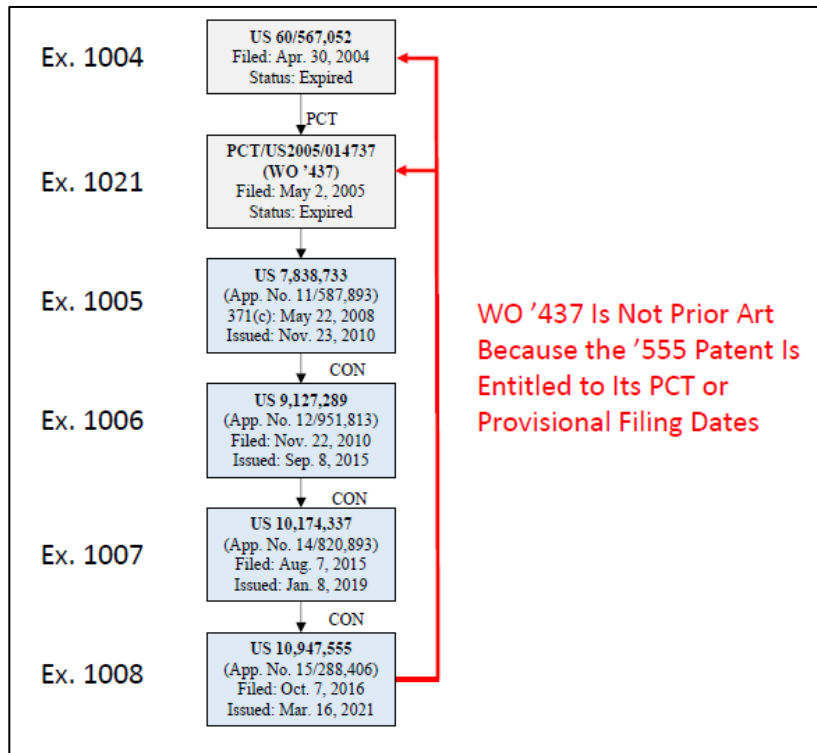
$(X)_{114-137}$ represents a sequence of 24 amino acids;

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

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

Ex. 1001 ('555 patent), claim 1

Grounds 1A/1B



Institution Decision

“Patent Owner contends, and for purposes of this Decision we agree, if the '555 patent's challenged claims are entitled to priority to the PCT application (filed in 2005) or the '052 Provisional (filed in 2004), then Corteva '437 is not prior art. Prelim. Resp. 19–20. The parties do not identify additional, distinct disclosures (or lack thereof) in the intervening applications that affect the priority analysis. Thus, the question here distills to whether the challenged claims have written description support in the PCT application (i.e., Corteva '437).”

POR, 29; IPR2023-01036 ID (Paper 11), 25-26.

Written Description – Reasonableness Standard



Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)

- Written description requires that the specification “**reasonably convey**[] to those skilled in the art that the inventor had possession of the claimed subject matter.”



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.”



Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co., 276 F. Supp. 3d 629, 646, 652-53 (E.D. Tex. 2017) (Bryson, J.), *aff’d*, 739 F. App’x 643 (Fed. Cir. 2018)

- Found a “very large” genus adequately described in view of common structures shared by members of the genus.

POR, 29, 35, 44-45.

The *Ajinomoto/Ariad* Reasonableness Standard



Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019)

- **Applied common-structure analysis for a “consensus sequence.”**
- **Found “more potent promoter” term adequately described.**

Claim at issue in *Ajinomoto*:

9. A recombinant *Escherichia coli* bacterium, which has the ability to accumulate aromatic L-amino acid in a medium, wherein the aromatic L-amino acid production by said bacterium is enhanced by enhancing activity of a protein in a cell of said bacterium beyond the levels observed in a wild-type of said bacterium,

...

wherein the activity of the protein is enhanced by ... replacing the native promoter which precedes the DNA on the chromosome of the bacterium with a **more potent promoter**, or by introduction of multiple copies of the DNA encoding said protein into the chromosome of said bacterium to express the protein in said bacterium.

POR, 45-46.

The *Ajinomoto/Ariad* Reasonableness Standard



Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019)

- Found adequate written description where the evidence showed that “deviations toward the consensus sequence generally increase promoter strength.”

Challenger's Arguments

- “[A] promoter closer to the consensus sequence will not always be stronger than one farther from that sequence.”  **NOT REQUIRED**
- “[S]imilarity to the consensus sequence ‘is still not enough to predict the ... strength of [a] promoter from a given sequence’”  **NOT REQUIRED**
- “[T]he strongest promoters in *E. coli*, do not necessarily adhere to the consensus sequence.”  **NOT REQUIRED**

POR, 45-46.

The *Ajinomoto/Ariad* Reasonableness Standard



Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019)

- Adequate written description does not require a perfect correspondence between the members of the genus and the asserted common structural feature; for a functionally defined genus like the one at issue here, **we have spoken more modestly of a "correlation between structure and function."**
- Found adequate written description where the evidence showed that “deviations toward the consensus sequence **generally increase** promoter strength.”



In the Matter of Certain L-Tryptophan, L-Tryptophan Prods., 2018 WL 8648370, *25 (ITC Jan. 11, 2018)

- “[W]hile Respondents may be able [to] establish that the consensus sequence does not necessarily provide the *most* potent promoter for the *yddG* gene of *E. coli* bacteria, **Respondents do not show by clear and convincing evidence that the consensus sequence is unrelated to promoter strength**”

Perspective of Skilled Artisans

Dr. Bollinger:

VI. Level of Skill in the Art

75. Regarding aspects of the '555 patent relating to enzymology, particularly α KG-dependent dioxygenases (e.g., RdpA/AAD-1) and variants thereof, a person skilled in the art would have generally 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 α KG-dependent dioxygenases. This need for a background in enzymology and familiarity with α KG-dependent dioxygenases is reflected in the scientific literature from 2004-2005. *E.g.*, Ex. 1023 (Elkins); Ex. 2019 (Tian); Ex. 2028 (Rost 2002); Ex. 2025 (Minshull); Ex. 1042 (Schleinitz).



Ariad, 598 F.3d at 1351

- “[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”

Ex. 2015, ¶ 75; POR, 25-26, 41



Ossia, Inc. v. Energous Corp., PGR2016-00024, Paper 20, 37-38 (PTAB Nov. 29, 2016)

- “Central to the analysis is looking at the [written-description] issue through the lens of one” skilled in the art.

AAD-1 Enzymes

“Preferred enzymes and genes for use according to the subject invention are referred to herein as AAD-1 (Aryloxy Alkanoate Dioxygenase) genes and proteins.”

“[P]roteins and genes of the subject invention are referred to herein as AAD-1 proteins and genes.”

“[T]he subject invention also relates to ‘plant optimized’ genes that encode proteins of the subject invention.”

Ex. 1001, 18:15-18, 19:52-54, 20:30-32; Ex. 1021, ¶¶ [0086], [0095], [0099]; POR, 20, 30

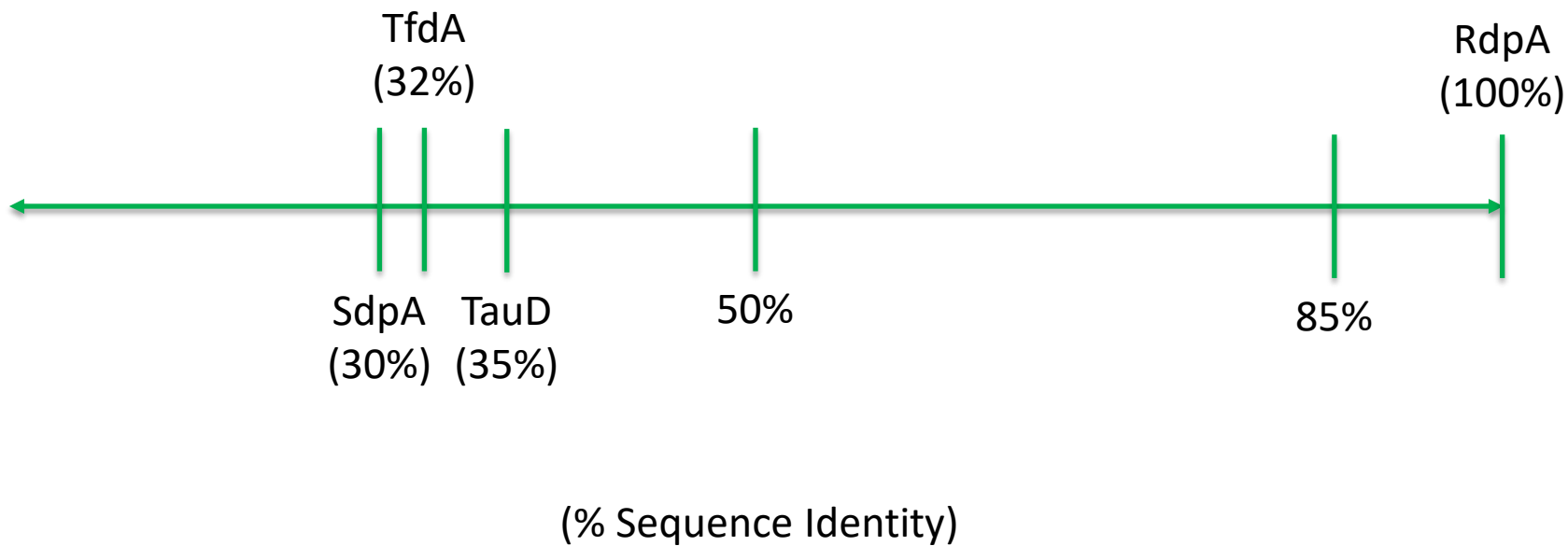
AAD-1 Enzymes

Certain proteins of the subject invention have been specifically exemplified herein. As these proteins are merely exemplary of the proteins of the subject invention, it should be readily apparent that the subject invention comprises variant or equivalent proteins (and nucleotide sequences coding for equivalents thereof) having the same or similar activity of the exemplified proteins. Equivalent proteins will have amino acid similarity (and/or homology) with an exemplified protein. The amino acid identity will typically be at least 60%, preferably at least 75%, more preferably at least 80%, even more preferably at least 90%, and can be at least 95%. Preferred proteins of the subject invention can also be defined in terms of more particular identity and/or similarity ranges. For example, the identity and/or similarity can be 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% as compared to a sequence exemplified or suggested herein. Any number listed above can be used to define the upper and lower limits.

Ex. 1001, 37:36-55;
Ex. 1021, ¶ [0142];
POR, 30

ID at 35: "There is no dispute that AAD-1 v1 (SEQ ID NO: 9) and its variants (AAD-1 v2 and v3) would be understood as the 'exemplary' AAD-1 proteins."

Lack of Structural/Functional Diversity



POR, 40; Ex. 2015, ¶ 115.

The AAD-1 Active Site Motif

tfdA proteins, for example. Even though this enzyme has very low homology to tfdA, the genes of the subject invention can still be generally classified in the same overall family of α -ketoglutarate-dependent dioxygenases. This family of proteins is characterized by three conserved histidine residues in a “HX(D/E)X₂₃₋₂₆(T/S)X₁₁₄₋₁₈₃HX₁₀₋₁₃R” motif which comprises the active site. The histidines coordinate Fe⁺² ion in the active site that is essential for catalytic activity (Hogan et al., 2000). The preliminary in vitro expression experiments discussed herein were tailored to help select for novel attributes.

More specifically, the subject invention relates in part to the use of an enzyme that is not only capable of degrading 2,4-D, but also AOPP herbicides. No α -ketoglutarate-dependent dioxygenase enzyme has previously been reported to have the ability to degrade herbicides of different chemical classes and modes of action. Preferred enzymes and genes for use according to the subject invention are referred to herein as AAD-1 (AryloxyAlkanoate Dioxygenase) genes and proteins. As disclosed herein a peptide of SEQ ID NO:

Ex. 1001, 17:66-18:18;

Ex. 1021, ¶ [0085];

Sur-Reply, 10

Minshull (Ex. 2025):

“Changes at key active site residues or other highly conserved residues are generally deleterious.”

Ex. 2025, 204-05; POR, 43

The AAD-1 Active Site Motif

RdpA	MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAPH	50
TauD	-----MSLTIQIPISPALGAIVSGIDLGAFLDDTGQRAIEQALL	38
TfdA	-----MSVVANPLHPLFAAGVEDIDLREALGSTEVREIERLMD	38
SdpA	-----MQTTLQITPTGATLGATVTGVHLAT-LDDAGFAALHAAWL	39
RdpA	TYQVIYFPGQAITNEQHIAFSRRFGPVPDPVPLLSIEGYPEVQIMIRREAN	100
TauD	EHQVLFFRDQSLEPRSQARFAARFGDLHIHPIYPSVPEQPEVIVLDTAVT	88
TfdA	EKSVLVFRGQPLSQDQQIAFARNFGPLEGGFIKVNQRPSRFKYAELADIS	88
SdpA	QHALLIFPGQHLSNDQQITFAKRFGAIERIGGGDIVAISNVKADGTVRQH	89
RdpA	ESGRV-----IGDDWHTDSTFLDAPPAAVVMRAIDVPEHG	135
TauD	DVR-----DNAIWHTDVTFLETALGAVLAAKQLPPYG	121
TfdA	NVSLDGGKVAQRDAREVVGNFANQLWHSDDSSFQQPAARYSMLS AVVVP	138
SdpA	SPAEWDDMMKVIVG-----NMAWHADSTYMPVMAQGAVFSAEVVPAVG	132
RdpA	GD [†] TGFLSMYTAWETLSPTMQATIEGLNVVHSATRVFGSLYQAQNRREFSNT	185
TauD	GD [†] TLWASSTAAYEALSAPLRRLLDGLTATHDIGKSFP---RERFGVTEAD	168
TfdA	GD [†] TEFCDMRAAYDALPRDLQSELEGLRAEHYALNSRF-----LLGD	179
SdpA	GRT [†] CFADMRAAYDALDEATRALVHQRSARHSLVYSQS---KLGHVQQAG	178
RdpA	SVKVMVDVADGRETVHPLVVTHPGSGRKGLYVNQVYQRIEGMTDAESKP	235
TauD	LARLEEARLKNPPRSHPVVRTHPVTGRKGLFVSDGFTTRINELEPAESDA	218
TfdA	TDYSEAQRNAMPPVNWPLVRTHAGSGRKFLFIG-AHASHVEGLPVAEGRM	228
SdpA	SAYIGYGMDTTATPLRPLVKVHPETGRPSLLIG-RHAHAIPGMDAAESER	227
RdpA	LLQFLYEHATRFDEF [†] TCVRWKKDQVLVWDNLCTM [†] HRAVPDYAGKFRYLTR	285
TauD	LLKFLFAHATRPEFTVRWRWQENDVAFWDNRVTQH [†] YAVDDYR [†] QRRVMHR	268
TfdA	LLAELLEHATQREFVYRHRWNVGD [†] LVMWDNRCVL [†] HRRYR [†] DISARRELRR	278
SdpA	FLEGLVDWACQAPRVHAHQW [†] AAGDVVVWDNRC [†] LLHRAEPWDFKLPR [†] VMWH	277
RdpA	TTVGGVRPAR-----	295
TauD	ATILGDKPF-----	277
TfdA	ATTLD [†] DAVV-----	287
SdpA	SRLAGR [†] PETEGAALV	292

Dr. Bollinger: “In 2004-2005, RdpA’s primary amino acid sequence alone was sufficient for a skilled artisan to recognize the RdpA (AAD-1) motif.”

Ex. 1042, 5360; Ex. 2015, ¶¶ 71-72; POR, 16-17

Dr. Hausinger & Schleinitz 2004

HX₁₁₂**D**(X)₁₁₄₋₁₃₇**T**(X)₁₃₉₋₂₆₉**H**(X)₂₇₁₋₂₈₀**R**

19 Q. Let's now look at the RdpA sequence in
20 Schleinitz's Figure 2.
21 The first motif residue shaded in black is
22 a histidine at position 111. Correct?
23 A. RdpA has a histidine at 111, correct.
24 Q. And RdpA, the second motif residue is an
25 aspartate at position 113. Correct?
1 A. RdpA does have an aspartate at position
2 113.
3 Q. The histidine at position 111 and the
4 aspartate at position 113 are separated by one
5 amino acid at position 112. Correct?
6 A. There is a threonine at position 112 in
7 RdpA.
8 Q. In RdpA, the third motif residue
9 highlighted in black is a threonine at position
10 138. Correct?
11 A. RdpA does have a threonine highlighted in
12 black at position 138, yes.

Ex. 2016, 24:19-25:12; POR, 17

Dr. Hausinger & Schleinitz 2004

HX₁₁₂**D**(X)₁₁₄₋₁₃₇**T**(X)₁₃₉₋₂₆₉**H**(X)₂₇₁₋₂₈₀**R**

13 Q. The second motif residue at position 113
14 and the third motif residue at position 138 are
15 separated by residues 114-137. Correct?

16 A. That's how the math works, yes.

17 Q. In RdpA, the fourth motif residue is a
18 histidine at position 270. Correct?

19 A. There is a histidine at 27 -- residue 270
20 in RdpA, yes.

21 Q. And it's separated from the third motif
22 residue by residues 139-269. Correct?

23 A. That is how it works out, yes.

24 Q. In RdpA, the fifth residue highlighted in
25 black is an arginine at position 281. Correct?

1 A. RdpA does have an arginine at 281,
2 correct.

3 Q. And it's separated from the fourth motif
4 residue at position 270 by residues 271-280.
5 Correct?

6 A. Those residues do separate the two
7 conserved residues, yes.

Ex. 2016, 25:13-26:7; POR, 17

“Functionally Important”

Schleinitz 2004 (Ex. 1042):

homologous to dioxygenases of this family. The functionally important motif HX(D/E)X₂₃₋₂₆(T/S)X₁₁₄₋₁₈₃HX₁₀₋₁₃R/K, which is conserved throughout group II α KG-dependent dioxygenases (18), is present in both RdpA and SdpA. In TfdA of *R. eutropha* it includes the three Fe(II)-binding residues His114, Asp116, and His263, and the two α KG-binding residues Thr141 and Arg274 (Fig. 2). All of these residues were conserved in RdpA and SdpA, representing the putative Fe(II) and α KG-binding residues in these enzymes. Arg278, His214, Ser117, Lys95, and Lys71 of TfdA are known to interact with 2,4-D (8, 10). Ser117 homologues were identified in both dichlorprop-cleaving enzymes. A homologue for Arg278 was present only in RdpA, one for His214 was found in SdpA. The

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 AAD-1 Active Site Motif

2.3—HPLC Results.

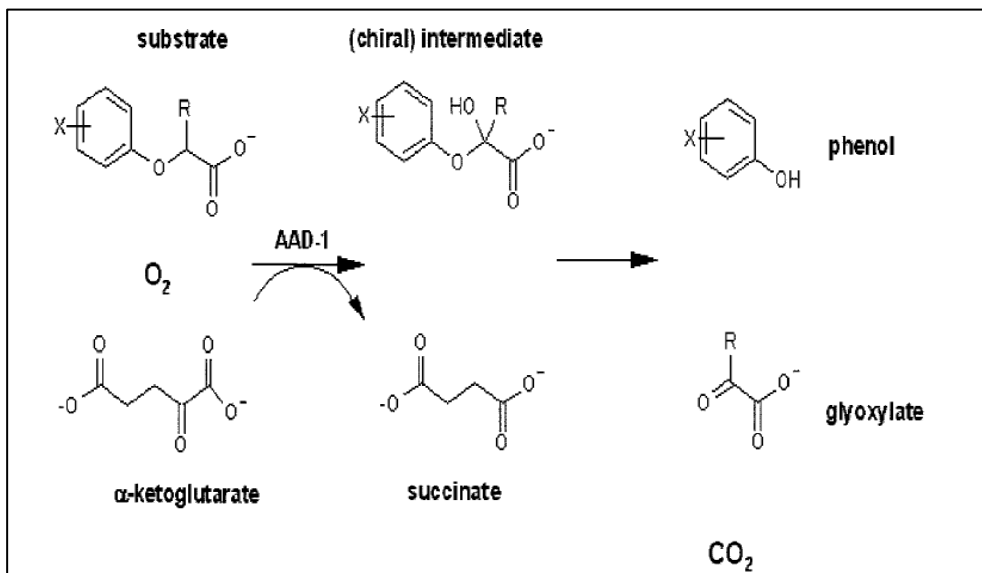
From the literature, it was known that dioxygenase enzymes in this class require α -ketoglutarate as a co-substrate (for a general scheme, see FIG. 1) and ferrous ion to bind in the active site. Other experiments in the literature have shown that the addition of ascorbate increased the enzymatic activity by maintaining the iron in the reduced state, thus preventing the enzyme from being degraded. Based on this previous work, initial assays were set up under the assumption that the subject enzyme would work in the same way as other members of this general class of enzyme.

ACCase inhibitors, haloxyfop and diclofop, were then tested using the same conditions as with 2,4-D. (The corresponding phenol metabolites co-eluted with the parent compound under the HPLC conditions used.) The bioassay results from these samples showed loss of herbicidal activity against both haloxyfop (FIG. 3) and diclofop. These results were also confirmed by the colorimetric assay, which was also used to test a wider sampling of these compounds.

Ex. 1001, 49:30-50:43; Ex. 1021, ¶¶ [00191]-[00195] POR, 19-20

The AAD-1 Degradation Reaction

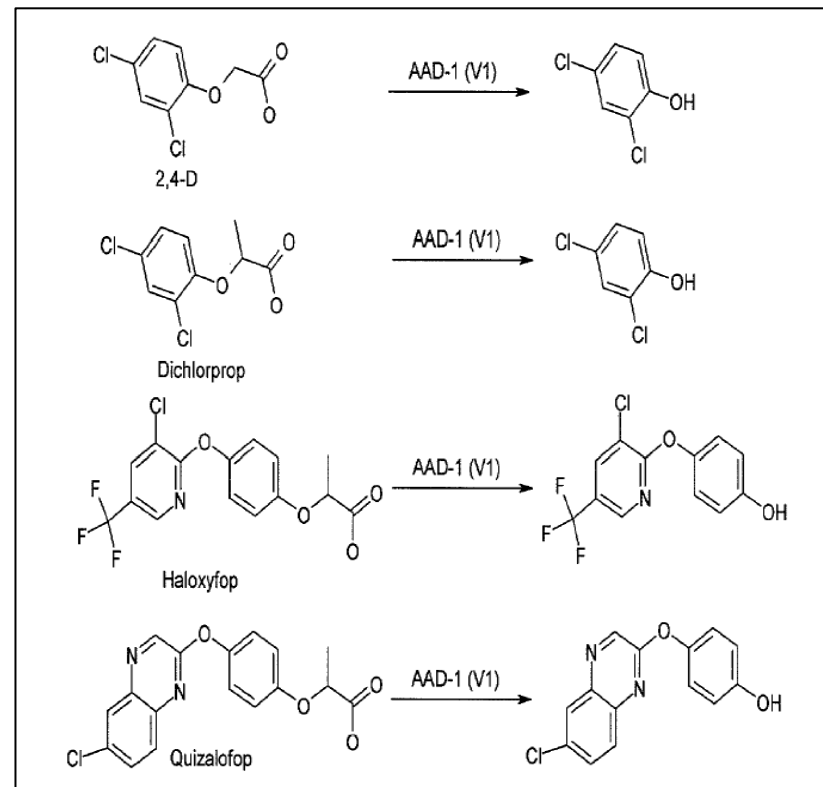
Figure 1



Dr. Hausinger:

- “The alpha-ketoglutarate is what really drives the reaction”
- “[O]ne requires the correct coordination of alpha-ketoglutarate”

Figure 4



Ex. 1001, Figs. 1 and 4; POR, 14, 19-20; Ex. 2016, 32:13-21, 35:6-17

The AAD-1 Active Site Motif

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

Dr. Bollinger:

116. Skilled artisans intuitively understood in 2004-2005 that an enzyme's active-site residues are correlated to its activity. Minshull 2005, for example, confirmed that when making enzyme variants, "changes at key active site residues" were "generally deleterious." Ex. 2025 (Minshull), 204-205. Moreover, Dr. Hausinger and others in the field had often reported the different spacing of the active-site motif residues in α KG-dependent dioxygenases and related enzymes, which results in binding pockets of different sizes and different configurations for catalyzing a diversity of reactions. Ex. 1025 (Hausinger 2004), 21-22 (Table 1); Ex. 1023 (Elkins 2002), 5190 (Fig. 5); Ex. 1042 (Schleinitz 2004), 5360 (Fig. 2).

Ex. 2015, ¶¶ 115-116; POR, 40-41, 43

The AAD-1 Active Site Motif

Dr. Bollinger:

111. Dr. Hausinger states that “[t]he POSA would not have looked to the generic α KG consensus motif, which describes characteristics that are commonly shared by α KG dioxygenases, for guidance on the characteristics that distinguish RdpA’s activity from that of other α KG dioxygenases.” Ex. 1054, ¶ 102. His statement misses the point. Skilled artisans understood that each α KG-dependent dioxygenase has the distinctive characteristic of a specific motif, which is strongly correlated to its function. The contours of an individual α KG-dependent dioxygenase’s active site would be defined by the spacing and residues of its specific motif. A skilled artisan thus would not look to the generic consensus motif, as Dr. Hausinger asserts, instead of the more specific motif within that enzyme’s sequence.

The AAD-1 Active Site Motif – Bayer's Sequences

RdpA	MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFFGQ
FT_5	MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFFGQ
FT_C	MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFFGQ
FT_R	MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFFGQ
FT_T	MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFFGQ
FT_Tv3	MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFFGQ
FT_Tv7	MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFFGQ
	*****:***:::.. * *****
RdpA	AITNEQHIAFSRRFGFVDPVPLLSIEGYFEVQMIIRREANESGRVIGDDWHTDSTFLDAP
FT_5	AITNEQHIAFSRRFGFVDPVPLLSIEGYFEVQMIIRREANESGRVIGENWHTDSTFLDAP
FT_C	AITNEQHIAFSRRFGFVDPVPLLSIEGYFEVQMIIRREANESGRVIGDDWHTDSTFLDAP
FT_R	AITNEQHIAFSRRFGFVDPVPLLSIEGYFEVQMIIRREANESSRVIGDDWHTDSTFLDAP
FT_T	AITNEQHIAFSRRFGFVDPVPLLSIEGYFEVQMIIRREANESSRFIGDDWHTDSTFLDAP
FT_Tv3	AITNEQHIAFSRRFGFVDPVPLLSIEGYFEVQMIIRREANESSRYIGDDWHTDSTFLDAP
FT_Tv7	AITNEQHIAFSRRFGFVDPVPLLSIEGYFEVQMIIRREANESSRYIGDDWHTDSTFLDAP
	*****:***:::.. * **:-***:*****
RdpA	PAAVVMRAIDVPEHGGDTGFLSMYTAWETLSPTMQATIEGLNVVHSATRVFGSLYQAQNR
FT_5	PAAVVMYAKEIPFYGGDTLFTSMYTAWETLSPTMQATIEGLNVVHSATRVFGSLYQAQNR
FT_C	PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
FT_R	PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
FT_T	PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
FT_Tv3	PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
FT_Tv7	PAAVVMRAIEVPEYGGDTGFLSMYSAWETLSPTMQATIEGLNVVHSATKVFGSLYQATNW
	***** * :*: * :*** * ***:*****:***** *
RdpA	RFSNTSVKVMVDVDAGDRETVHPLVVTHPGSGRKGLYVNQVYCQRIEGMTDAESKPLLQFL
FT_5	RFSNTSVKVMVDVDAGDRETVHPLVVTHPETGRKGLYVNQVYCQRIEGMSEKSEPLLQFL
FT_C	RFSNTSVKVMVDVDAGDRETVHPLVVTHFVTGRRALYCNQVYCQKIQGMTDAESKPLLQFL
FT_R	RFSNTSVKVMVDVDAGDRETVHPLVVTHFVTGRRALYCNQVYCQKIQGMTDAESKPLLQFL
FT_T	RFSNTSVKVMVDVDAGDRETVHPLVVTHFVTGRRALYCNQVYCQKIQGMTDAESKPLLQFL
FT_Tv3	RFSNTSVKVMVDVDAGDRETVHPLVVTHFVTGRRALYCNQVYCQKIQGMTDAESKPLLQFL
FT_Tv7	RFSNTSVKVMVDVDAGDRETVHPLVVTHFVTGRRALYCNQVYCQKIQGMTDAESKPLLQFL
	:**:***:..** *****:***::: **:-**:**
RdpA	YEHATRFDFTCRVRWKKDQVLVWDNLCTMRAVPDYAGKFFYLTRTTVGGVRPAR
FT_5	FAHATKPEFTCRVRWQEGDVLVWDNLCTQYAVPDYAGKFFYLTRTTVGGVRPAR
FT_C	YEHATKFDFTCRVRWKKDQVLVWDNLCTMRAVPDYAGKFFYLTRTTVAGDKPSR
FT_R	YEHATKFDFTCRVRWKKDQVLVWDNLCTMRAAPDYAGKFFYLTRTTVAGDKPSR
FT_T	YEHATKFDFTCRVRWKKDQVLVWDNLCTMRAVPDYAGKFFYLTRTTVAGDKPSR
FT_Tv3	YEHATQFDFTCRVRWKKDQVLVWDNLCTMRAVPDYAGKFFYLTRTTVAGDKPSR
FT_Tv7	YEHATQFDFTCRVRWKKDQVLVWDNLCTMRAVPDYAGKFFYLTRTTVAGDKPSR
	: ***: :*****:::***** * _*****: * :*

Ex. 2015, ¶ 136; Exs. 2012-2014, 2048-2050, 2061; POR, 55

Known Principles for Maintaining Function

1. Maintain high sequence identity.
2. Maintain the active site motif.
3. Retain residues that are highly conserved across related enzymes.
4. Maintain charge distribution and steric bulk.

Ex. 2015, ¶¶ 52-59, 107; POR, 12-13, 35

Lifescan Global Corp. v. Ikeda Food Research, Ltd.

<i>Lifescan</i>	The instant case
Enzyme sequence contained 593 amino acids	SEQ ID NO: 9 contains 295 amino acids
Number of permitted mutations encompassed by the claims: 59	Claim 1 (at least 85% sequence identity) permits up to 44 mutations
Motif: six amino acids	AAD-1 motif: five amino acids with fixed spacing



***Lifescan Global Corp. v. Ikeda Food Rsch., Ltd.*, PGR2019-00032, Paper 11 at 26, 30 (PTAB 2019)**

- **“Dr. Cass also testifies that ‘[a] POSA could look at a given sequence, different from SEQ ID 1 and make a fair guess whether it would have a qualitatively similar behavior or not’”**

Lifescan at *30; POR, 36, 49-50; Sur-Reply, 13, 18

AbbVie v. Janssen

AbbVie	The instant case
Claims directed to antibodies	Claims require AAD-1 enzymes
Purely functional claims - no sequence identity limitations included	Claims require at least 85% sequence identity to SEQ ID NO: 9
Claims did not require conserving any active-site motif residues	Claims require AAD-1 motif: five amino acids with fixed spacing
No evidence of antibody sequence-function correlation presented	Dr. Bollinger testified regarding the spec's disclosures regarding the AAD-1 motif, enzyme sequence-function correlation, and background literature in the field

AbbVie, 759 F.3d at 1300-01; POR, 47-48, 57; Pet. 31, 39



Ajinomoto Co. v. Int'l Trade Comm'n, 932 F.3d 1342, 1360 (Fed. Cir. 2019)

- “The cases cited by CJ in which we have held genus claims to lack an adequate written description are **inapposite** In **AbbVie**, there was ‘no evidence to show any described antibody to be structurally similar to, and thus representative of,’ an antibody accused of coming within the claim”

POR, 47-48

Juno v. Kite

<i>Juno</i>	The instant case
Claims directed to scFvs (single chain antibodies)	Claims require AAD-1 enzymes
Purely functional claims - no sequence identity limitations included. No amino acid sequences disclosed for any scFv.	Claims require at least 85% sequence identity to SEQ ID NO: 9
Claims did not require conserving any active-site motif residues	Claims require AAD-1 motif: five amino acids with fixed spacing
No evidence of antibody sequence-function correlation presented	Dr. Bollinger testified regarding the spec's disclosures regarding the AAD-1 motif, enzyme sequence-function correlation, and background literature in the field

POR, 47-48, 58; Pet., 24



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”

PureCircle v. SweeGen

PureCircle	The instant case
Claims directed to UDP-glucosyltransferase enzymes	Claims require AAD-1 enzymes
Purely functional claims - no sequence identity limitations included	Claims require at least 85% sequence identity to SEQ ID NO: 9
Claims did not require conserving any active-site motif residues. No active-site residues disclosed.	Claims require AAD-1 motif: five amino acids with fixed spacing

POR, 46-47



PureCircle USA Inc. v. SweeGen, Inc., slip op. (Fed. Cir. Jan. 2, 2024)

- Using homology modeling and “[l]ooking at the model of a working enzyme, PureCircle argues, a person of ordinary skill in the art (POSA) could find the active site where that enzyme converts Reb D to Reb X”

Claim 2 Motif - Arginine

Elkins 2002 (Ex. 1023):

- TauD's "Arg270 is partially conserved across a range of the group II dioxygenases"
- TfdA: "Interactions with the 2,4-D carboxylic acid are proposed to involve Arg278..."

Hotopp 2002 (Ex. 1029):

- TfdA: “We conclude that Lys71 and Arg278 have important roles in binding the carboxylate of 2,4-D...”
- “Residues homologous to Arg278 are conserved in several other aKG dependent dioxygenases”

Schleinitz 2004 (Ex. 1042):

- “A homologue for Arg278 was present only in RdpA...”

RdpA LLQFLYE[•]HAT[•]RFD[•]FTCRVR[•]WK[•]KDQVLVDN[•]LC[•]TM[•]HRAVPDYAGKFRYL[•]TR 235
TauD LLKFLFAHATRPEFTVRWRWQENDVAFWDNRVTOHYAVDDYR[•]QRRVM[•]TR 238
TfdA LLAELLEHATQREFVYRHRWNVGD[•]LVMWDNRCVL[•]H[•]RGRRYDISARREL[•]TR 278
SdpA FLEGLVDWACQAPRVHAHQWAAGD[•]VVVVDNRCLL[•]HRAEPWDFKLP[•]RV[•]M[•]WH[•] 277
↑

Ex. 2015, ¶¶ 140-142; Ex. 1023, 5189-5190; Ex. 1029, 9792; Ex. 1042, 5360; POR, 59

Claim 2 Motif - Arginine

Dr. Hausinger in this Proceeding	Dr. Hausinger Outside this Proceeding
“The authors’ decision to limit the statement in the caption to TfdA would indicate that R285 in RdpA does not necessarily bind to 2,4-D; the most straightforward reading of the caption for the POSA is that there was no known role for R285 in binding to 2,4-D.” Ex. 2066, ¶ 17.	“Comparable Arg residues are conserved in many Fe^{II}/αKG-dependent dioxygenases, where they play a dual role of binding the primary substrate and the C1-carboxyl group of αKG (Valegard et al. 1998; Elkins et al. 2002; O'Brien et al. 2003; Hausinger 2004; Muller et al. 2004a). Such a dual role is predicted for Arg285 of RdpA.” Ex. 1035, 1364.

Schleinitz 2004 (Ex. 1042):

- “A homologue for Arg278 was present only in RdpA...”

RdpA	LLQFLYEHATRFDFTCRVRWKKDQVLVWDNLCTMHR	AVPDYAGKFRYL	TR	235
TauD	LLKFLFAHATRPEFTVRWRWQENDVAFWDNRVTQ	HYAVDDYRPQRRVM	MR	258
TfdA	LLAELLEHATQREFVYRHRWNVGDLMWDNRCVL	HGRGRRYDISARREL	RR	278
SdpA	FLEGLVDWACQAPRVHAHQWAAGDVVVWDNRCLL	HRAEPWDFKLPRVM	WH	277
			↑	

Ex. 2015, ¶ 141; POR, 59; Sur-Reply, 21-22

Dr. Hausinger's (R)-Enantioselectivity Testimony

Q: Do you see the term “(R)-enantioselective” in Claim 1 or is that something you're interpreting?

A: That term is not part of Claim 1.

Q: Is the term “(R)-enantiospecific” part of Claim 1?

A: That term “(R)-enantiospecific” is not part of Claim 1. And I think it would be inherent in -- a POSA looking at this would assume that they are seeking specific chemistry here that is for the (R)-enantiomers. And so probably assume that it means it's only acting on (R)-enantiomers.

Ex. 2066, 32:5-23; Sur-Reply, 4-5

(R)-Enantioselectivity – Muller 2006 (Ex. 1035)

Basis of the substrate-binding specificity of RdpA and SdpA

Examination of the mutant forms of RdpA and SdpA also provided insights into the specificity for the distinct mecoprop enantiomers. For RdpA variants, Gln93, Ile106, and Phe171 are proposed to sterically exclude binding by the incorrect enantiomer, whereas the Q93A variant yields results consistent with inhibition by (S)-mecoprop. Similarly, the results with the SdpA mutants are consistent with Glu69, Asn98, and Arg207 and His208 acting to prevent binding of the (R) enantiomer. In particular, the E69A, R207A, and G97I/N98G variants exhibited activity with the incorrect substrate, (R)-mecoprop. Hydrophobic interactions are also likely to be critical for substrate discrimination. For example, Val80 and Leu83 in RdpA are predicted to be well positioned to interact with the propanoic acid methyl group, whereas Glu69 and Ala72 occupy these positions in SdpA. We conclude that several residues in each protein play a role in dictating the substrate enantiospecificity.

Ex. 1035, 1364; Sur-Reply, 6

Saari 1999 – *A. Denitrificans*

4. Discussion

The above studies demonstrate that the herbicide-degrading activity of *A. denitrificans* exhibits opposite stereochemistry than that found in strains JMP134 or RASC; yet, each of these activities are α -KG-dependent and the enzymes are likely to be genetically related. The present work extends the conclusions derived from studies with a strain of *Sphingomonas herbicidovorans* that is capable of degrading both enantiomers of mecoprop [32]. In that strain, two α -KG-dependent dioxygenases appear to be present, each specific for a separate enantiomer of the substrate [33]. Based on our findings, it is probable that the two *S. herbicidovorans* enzymes are closely related in sequence. The abil-

Ex. 1041, 427; Ex. 2015, ¶ 125; POR, 50-51; Sur-Reply, 15

Dr. Bollinger's Testimony – *A. Denitrificans*

125. Saari 1999 never specifically attributed (*R*)-enantioselective activity to the *A. denitrificans* enzyme sequence that they presented. There was good reason for that caution—the only functional characterization of the (*R*)-enantioselective activity in *A. denitrificans* involved the use of cell extracts, i.e., breaking open cells and examining substrate transformation in the crude mixture that comes out. *See* Ex. 1041, 426-27. Because cell extracts can contain hundreds of different proteins, attributing an activity to a particular enzyme in that mixture without purifying and testing that particular enzyme in isolation is fraught with potential for misattribution.

Ex. 2015, ¶ 125; POR, 50-51; Sur-Reply, 15

Contemporaneous Criticism – Schleinitz 2004

DISCUSSION

Two novel genes encoding the enantiospecific dichlorprop and mecoprop cleaving dioxygenases RdpA and SdpA in *D. acidovorans* MC1 were identified. The characterization of genes shown to be involved in the cleavage of these chiral herbicides has not previously been reported. To date, *tfdA* genes or genes closely related in sequence to *tfdA* were proposed to be involved in *R*-dichlorprop cleavage in *Alcaligenes denitrificans* (39). This suggestion was based on the observations that a *tfdA* gene is present in *Alcaligenes denitrificans* and that dichlorprop cleavage is catalyzed by an α KG-dependent dioxygenase in this strain as well as in *S. herbicidovorans* MH (38). However, it was not supported by *tfdA* expression studies or amino acid sequences of the *R*-dichlorprop cleaving dioxygenase. The *rdpA* and *sdpA* genes of strain MC1 showed no

Ex. 1042, 5362; Ex. 2015, ¶ 129; POR, 50-51; Sur-Reply, 15

Lack of Structural/Functional Diversity

Example 1

deposited. Using default settings, this search returns upwards of 100 homologous protein sequences at varying levels. These range from highly identical (85-98%) to very low identity (23-32%) at the amino acid level. Traditionally only sequences with high homology would be expected to retain similar properties to the input sequence. In this case we chose only those sequences with $\leq 50\%$ homology. We go

* * *

A single gene (rdpA) was identified from the NCBI database (see the ncbi.nlm.nih.gov website; accession #AF516752) as a homologue with only 28% amino acid identity to tfdA from *Ralstonia eutropha*. Percent identity was determined by first translating both the rdpA and tfdA DNA sequences deposited in the database to proteins, then using ClustalW in the VectorNTI software package to perform the multiple sequence alignment.

Ex. 1001, Example 1; Ex. 1021, ¶¶ [00171]-[00172]; POR, 40.

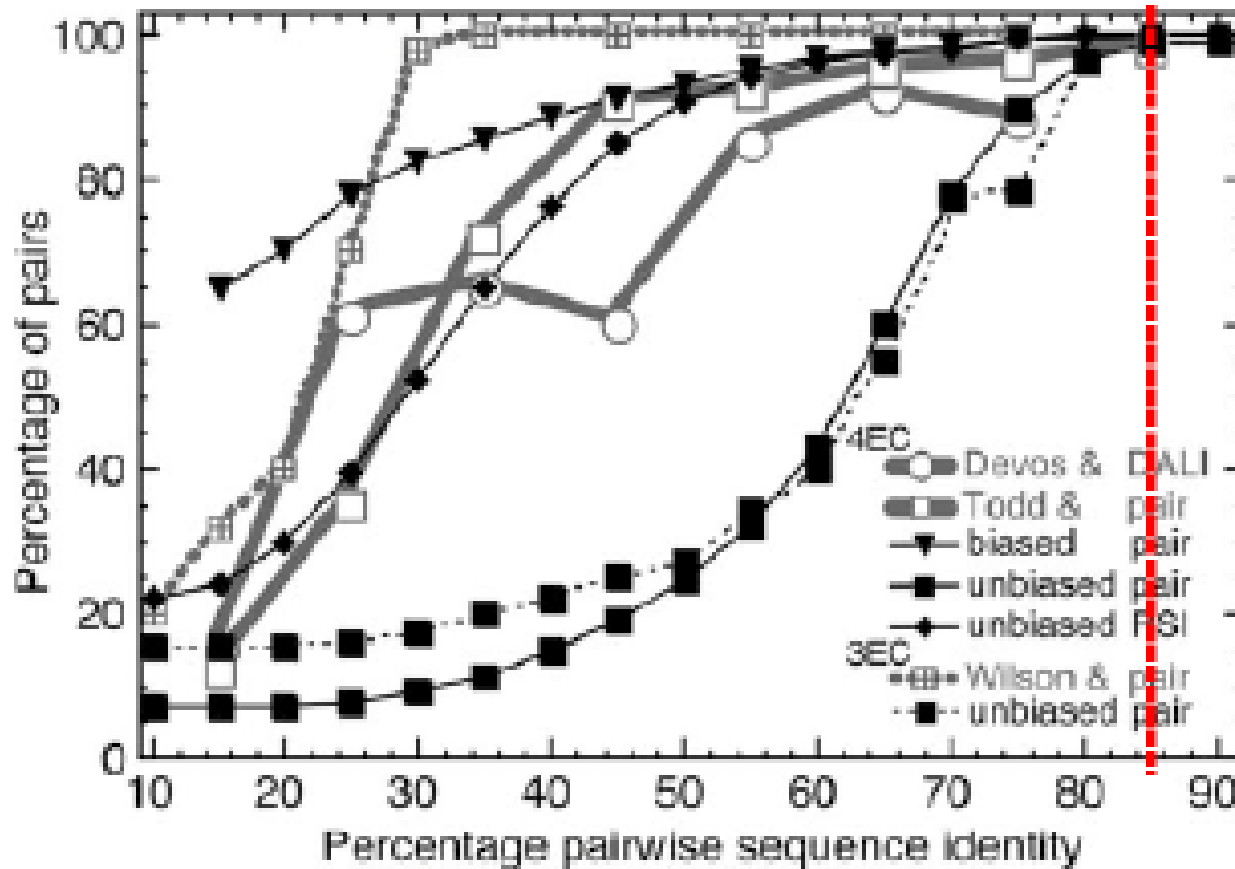
Enzyme Sequence-Function Correlation

Dr. Bollinger:

2019 (Tian 2003), 863; Ex. 2026 (Devos), 102. In other words, there was a recognized trend that higher sequence identities correlated more strongly to conserved enzyme function than lower sequence identities, and 85% was a particularly high level of sequence identity from which skilled artisans would have expected the same enzyme function.

to the active site. Sequence alignments can thus provide guidance as to regions of the enzyme that are likely to tolerate substitutions without loss of function and other regions in which any substitution, or particular classes of substitutions, will likely disrupt the enzyme's structure and cause a loss of activity. *See e.g.*, Ex. 1023 (Elkins), 5190 (Fig. 5); Ex. 1042 (Schleinitz), 5360 (Fig. 2).

Enzyme Sequence-Function Correlation



POR, 32; Ex. 2028, 604 (annotated Fig. 5)

Enzyme Sequence-Function Correlation

Devos 2000 (Ex. 2026):

“The comparison of protein sequences is *widely used* to infer protein structure and function.”

Rost 2002 (Ex. 2028):

Ex. 2026, 98, 105; POR, 33-34; Ex. 2015, ¶¶ 29, 31, 104

“[E]stimates for the sequence conservation of enzyme function may provide important benchmarks for everyday sequence analysis.”

Tian 2003 (Ex. 2019):

Ex. 2028, 595; POR, 8-9; Ex. 2015, ¶ 102

- “[S]equence identity is also *widely used* as an indication of functional similarity”
- “[B]ecause the percentage of sequence identity is *simple, quick and widely accepted* by the biologist, *several groups have examined the extent to which pairwise sequence identity [to] function similarity can be inferred.*”

Ex. 2019, 864, 872; POR, 11, 31, 34; Ex. 2015, ¶ 101



Lifescan Global Corp. v. Ikeda Food Rsch., Ltd., PGR2019-00032, Paper 11 at 26, 30 (PTAB 2019) (crediting expert testimony that skilled artisans could identify enzymes within a claim by making a “fair guess” based on sequence)

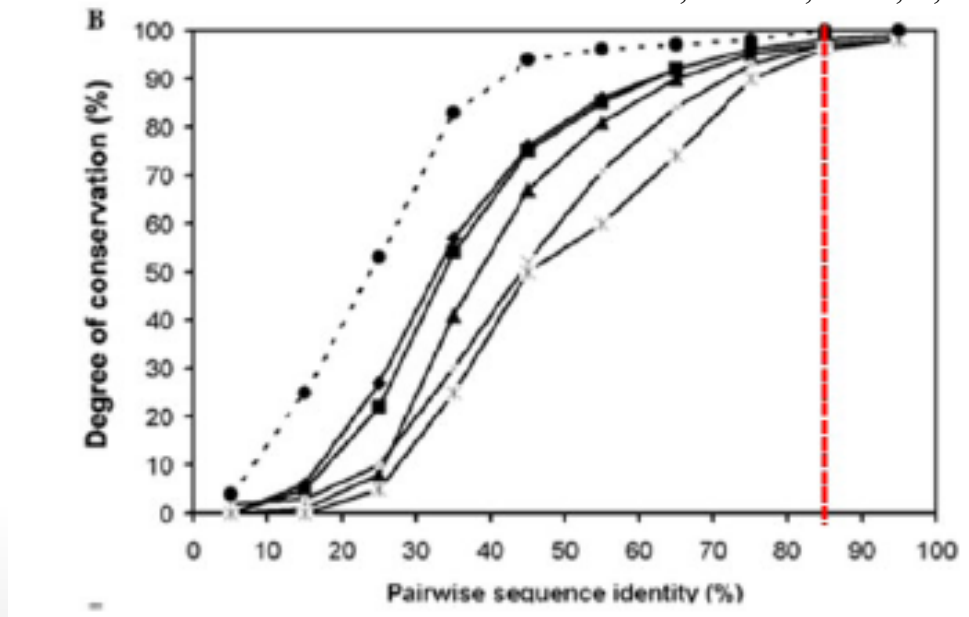
POR, 49-50; Sur-Reply, 18

Enzyme Sequence-Function Correlation

Tian 2003 (Ex. 2019):

- Purpose: “derive the threshold of sequence identity necessary to transfer function from a protein of known function to an unknown protein.”
- “Because the Enzyme Commission (EC) is the best developed and most widely used functional classification scheme, EC numbers have been employed to explore the threshold of sequence identity necessary for accurate function transfer.”

Ex. 2019, 863-64; POR, 6, 9-10, 31; Ex. 2015, ¶¶ 23, 29, 35



Ex. 2019, 866 (Figure 1(B) “includes both enzyme-enzyme and enzyme-non-enzyme sequence pairs”); Ex. 2015, ¶ 103; POR, 2

Variants and Sequence Comparisons

Minshull (Ex. 2025):

- “There are two main reasons to try to predict an enzyme’s function from its sequence ... the second is to create enzymes with specific properties.”
- “[C]hanges at key active site residues or other highly conserved residues are generally deleterious.”
- “When the functional similarity of 486,000 homologous protein pairs were compared, very little variation in EC number was observed in sequences sharing more than 40% identity.”

Ex. 2025, 202, 204-205; Ex. 2015, ¶¶ 58, 107, 116; POR, 31, 43

Ng (Ex. 2044):

- “SIFT presumes that important amino acids will be conserved in the protein family, and so changes at well-conserved positions tend to be predicted as deleterious.”

Ex. 2044, 3812; Ex. 2015, ¶¶ 56-58; POR, 12

Variants and Sequence-Activity Relationships

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

J. Martin Bollinger, Ph.D.

- Enzymologist and Professor at Penn State University, Department of Chemistry and Department of Biochemistry and Molecular Biology
- Endowed Russell and Mildred Marker Professor of Natural Products Chemistry
- Ph.D. from Massachusetts Institute of Technology, 1993
- N.I.H.-sponsored postdoctoral fellow at Harvard Medical School, 1993-1995
- Fellow of the American Association for the Advancement of Science
- Research team specializes in enzymes that use transition metals to react with oxygen gas to transform substrate compounds.
- 20+ years of research and 39 publications concerning α KG-dependent oxygenases, including in *Science* and *Nature*



Ex. 2015, ¶¶ 1-20; POR, 5.

Dr. Hausinger Lacks Credibility



Bayer CropScience AG v. Dow AgroSciences LLC, 2012 WL 4498527, *3 n.5
(D. Del. Sept. 27, 2012)

3 Q. In the next sentence you said that
4 DAS's argument that its AAD proteins were
5 dioxygenases rather than monooxygenases was,
6 quote/unquote, "simply indefensible."

7 That was the word you used, correct?

10 THE WITNESS: That is the word that I
11 incorporated there.

12 BY MR. DeROO:

13 Q. Did the Court in this previous Bayer
14 litigation agree with your argument that AAD-1
15 had the monooxygenase activity required by the
16 '401 patent claims?

17 A. I know that the -- the case was
18 viewed in favor of Dow. I don't know how they
19 weighed all the different components of it.

"Q: And how long in your judgment has
[the difference between monooxygenase
and dioxygenase] been known?

DR. HAUSINGER: Over 50 years."

"Q: You said if somebody knows [that the
TfDA enzyme is a dioxygenase] and they
go ahead and call it a monooxygenase,
you said that's scientifically invalid or
misleading. Yes or no?

DR. HAUSINGER: It's incorrect.

Q: But you said it's scientifically invalid or
misleading not just incorrect.

A: It is...."

Ex. 2066, 58:3-19; Sur-Reply, 4-5

Inconsistent Positions Regarding Solubility

Dr. Hausinger's Reply Decl.

“Given that Seq 10-Seq 18 were **insoluble** and yielded no purified protein . . . the POSA would understand from the data that they do not exhibit the herbicide degrading activity required by the claims of the challenged patents.”

Ex. 1070, ¶ 67; Ex. 2066, 35:1-36:11;
Ex. 1027, 12400; Sur-Reply, 19-20

Dr. Hausinger's Deposition

Q. And enzymes typically exist in cells in nature, not in a purified form, correct?

A. That is correct.

Q. What is **maltose-binding protein**?

A. It's a protein that is often used in protein engineering studies because it's highly soluble. And so **when you fuse this protein to a desired protein it can retain its solubility of that desired protein....**

Dr. Hausinger's Hogan 2000 Publication

Variant “forms of TfdA formed inclusion bodies when overproduced in *Escherichia coli* DH5a; however, these proteins were soluble when fused to the maltose-binding protein (MBP).”

Inconsistent Positions Regarding the AAD-1 Motif

Petitioners' Anticipation Position Regarding Corteva '437 and the AAD-1 Motif	Dr. Hausinger's Testimony Regarding Corteva '437 and the AAD-1 Motif
"Corteva '437 discloses that SEQ ID NOS:9 and 10 have the required amino acids at those positions." Ex. 1054, ¶ 122.	Q. [I]t's not sufficient . . . for Seq. ID 10 to have the required amino acids at those positions, correct? A. In my opinion, there is no AAD-1 motif denoted in this patent." Ex. 2066, 71:19-24, 70:12-21 (similar for SEQ ID NO: 9).

Sur-Reply, 23-24

Grounds 2A/2B

No Reasonable Expectation of Success in the Prior Art

Institution Decision:

- “Petitioner’s argument that the POSA would have expected RdpA to degrade phenoxy auxins and (*R*)-FOPs ‘via the same mechanism’ **lacks a sufficient explanation and is wanting for persuasive evidentiary support.**”
- “Using an applicant’s discovery as evidence of the POSA’s expectations **looks like hindsight.**”

Corteva’s PO Response:

- “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.”
- Dr. Hausinger conceded that the prior art “did not report testing of RdpA on (*R*)-aryloxyphenoxypropionate substrates.” (Ex. 1054, ¶ 219)
- “The structural differences between phenoxy auxin and FOP herbicides are significant ... These structural differences are reflected in their significantly different chemical properties.”

No Inherency in the Prior Art

Institution Decision:

- “Based on the dearth of explanation in the Petition, we find that Petitioner is not reasonably likely to prevail in establishing that the POSA would have expected the recited AAD-1 activity against both phenoxy auxins and (*R*)-FOPs. That leaves Petitioner with its inherency theory”

Corteva’s PO Response:



Honeywell Int’l Inc. v. Mexichem Amanco Holdings S.A., 865 F. 3d 1348, 1355 (Fed. Cir. 2017)

- Held 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.”
- “What is important regarding properties that may be inherent, but unknown, is whether they are unexpected.”

No Inherency in the Prior Art

Institution Decision:

- “Petitioner’s inherency argument about the claimed activity is little more than a single sentence”
- “Threadbare as Petitioner’s inherency theory is, we will revisit the issue on a full record.”

Corteva’s PO Response:

- Petitioner failed to address any of the factors that Dr. Hausinger conceded could affect enzyme activity or expression.
- Petitioner failed to present any evidence that using Streber’s *Agrobacterium* transformation method would work with RdpA. *See* ID, 61.
- Petitioner failed to address any dependent claims requiring herbicide tolerance.

ID, 60-61; POR, 64-66

Lack of Motivation in the Prior Art

Corteva's PO Response:

- “Petitioners’ reliance on a half-sentence from Saari 1999—i.e., that . . . 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.”
- Even with TfdA, “little interest has been shown in any [crop] but cotton” and TfdA-transgenic plants had “significantly reduced” growth rates and poor herbicide tolerance.

From Petitioners' Own Scientists

Oxygenase Enzymes for Agricultural Biotechnology Applications

Clayton T. Larue

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The use of RdpA and SdpA in agriculture biotechnology was first demonstrated by Wright *et al.* (2010). In this work, RdpA from *S. herbicidivorans* (renamed by Wright *et al.* (2010) as aryloxyalkanoate dioxygenase-1 or AAD-1) and SdpA from *D. acidovorans* (renamed by Wright *et al.* (2010) as AAD-12) were further characterized and expressed in *Arabidopsis thaliana*, corn (maize) and soybean plants. Further characterization of the substrate specificity of these enzymes confirmed that these enzymes were selective based on the nature and chirality of alkanoic acid side chain, but forgiving regarding the substituents on the aromatic ring, including being able to accept members of the FOP herbicides which have additional ring structures as substituents on the aromatic ring (Wright *et al.*, 2010). RdpA was

* * *

normal field use rates (Wright *et al.*, 2010). This work in both corn and soybeans nicely illustrates the potential value these dioxygenase enzymes could bring to agriculture biotechnology.

POR, 71; Ex. 2059, 256

Compelling Unexpected Results

Corteva's PO Response:

- “[T]he claimed invention produced unexpected results with transgenic 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 advantageous provided broad-spectrum weed control.”
- “[T]he references Petitioners assert are the closest prior art (e.g., Streber, Schleinitz, and Saari) disclose no FOP-degrading activity.”



In re Albrecht, 514 F.2d 1389, 1395-96 (CCPA 1975)

- Held claims nonobvious in view of a compound's unexpected dual activity of exhibiting antiviral and anesthetic properties.

POR, 69-70; Ex. 2015, ¶¶ 159-161