United States Patent and Trademark Office
Before the Patent Trial and Appeal Board

INARI AGRICULTURE, INC.
(Petitioner)
v.
CORTEVA AGRISCIENCE LLC
(Patent Owner)

Post-Grant Review

No. PGR2023-00022 | **U.S. Patent No. 11,371,055**

Petitioner's Demonstrative Exhibits

Inari Exhibit 1046
Inari v. Corteva
PGR2023-00022

July 25, 2024

Petition Grounds

GROUND	BASIS	CLAIMS
1	§112(a) (written description)	1-33
2	§112(a) (enablement)	1-33

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Claim 1 of the ’055 Patent

1. A transgenic plant cell comprising a recombinant polynucleotide that encodes an AAD-12 protein that exhibits aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide, further wherein said AAD-12 protein comprises:

i) an amino acid sequence having at least 85% sequence identity with SEQ ID NO: 2; and

ii) an AAD-12 motif having the general formula of:

$HX_{109}D(X)_{111\text{-}134}T(X)_{136\text{-}261}H(X)_{263\text{-}272}R$, wherein

X_{109} represents a single amino acid at position 109, relative to the sequence of SEQ ID NO: 2;

$(X)_{111\text{-}134}$ represents a sequence of 24 amino acids;

$(X)_{136\text{-}261}$ represents a sequence of 126 amino acids; and

$(X)_{263\text{-}272}$ represents a sequence of 10 amino acids.

’055 patent, claim 1

Petition Grounds – Written Description: No Structure-Function Correlation

> pyridyloxy auxin herbicide," no clear link between the recited "AAD-12" motif and the novel ability to enzymatically degrade both phenoxy and pyridyloxy auxin herbicides is disclosed. Silverstone, ¶¶42-50, 79. Indeed, the defined residues of

Petition, page 29

Petition Grounds – Written Description: No Representative Species

> The claimed genus encompasses up to 2.4 x 10^{106} species, as discussed below, yet the specification discloses only two species, and tests only one, that meet the structural requirements of the claims and possess the required functional features; the native AAD-12, and an AAD-12 variant that differs only by the addition of a single alanine residue near the N-terminus of the protein, 99.7% identical to the native AAD-12. Ex. 1001, SEQ ID NOS: 2, 4; Silverstone, ¶80, fn.

Petition, pages 27-28

Petition Grounds – Enablement

> Reaching the full scope of the claims of the '055 patent would require the testing of all proteins comprising an amino acid sequence having at least 85% sequence identity with SEQ ID NO: 2 and an AAD-12 motif having the general formula of: $HX_{109}D(X)_{111\text{-}134}T(X)_{136\text{-}261}H(X)_{263\text{-}272}R$ to determine whether they had aryloxyalkanoate dioxygenase activity as claimed. *See* Ex. 1001, Cl. 1. Because

Petition, page 39

Institution Decision – Written Description

> Nor are we persuaded that the two examples with 99.3% and 100% identity to SEQ ID NO: 2 are sufficient description for a genus of possible polypeptides with up to 15% sequence variation. It is clear that the disclosed SEQ ID NOs: 2 and 4 function as claimed, but it is unclear to the skilled artisan how far from 99.3% identity the polypeptide can deviate while still retaining the ability to degrade herbicides, including by stating design parameters that would indicate the inventors possessed this ability.

Institution Decision, page 39

Institution Decision – Enablement

regard, we are persuaded by the testimony of Dr. Silverstone regarding the *Wands* factors and the details regarding the extensive effort required to identify embodiments at the 85% end of the claim scope in light of the guidance provided in the '055 patent's Specification. *See* Ex. 1003 ¶¶ 56–93. Dr. Silverstone testifies, and we are persuaded on this record, that with the guidance in the '055 patent's Specification, the skilled artisan would not have been able to predict whether a modified SEQ ID NO: 2 at the lower (e.g., 85% identity level) would have been able to retain the function of degrading the recited herbicides. *Id.*

Institution Decision, page 52

Overview

The ‘055 Patent claims are invalid under § 112:

1. Written Description
    a. Failing to disclose a structure-function relationship while claiming an “astronomical” number of species
    (Petition, 27-34; Reply, 2-12, 16-17)
    b. Disclosing only two near-identical species at one end of the claimed range
    (Petition, 30-32; Reply, 15-16)
2. Enablement
    a. Claiming an unpredictable genus and failing to disclose a common quality
    (Petition, 39-49, 54; Reply, 2-12, 16-18, 20-25)
    b. Providing only a research plan for further trial-and-error testing
    (Petition, 46-49; Reply, 24-27)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Written Description – Corteva's Evidence Shows That AAD-12 Motif and Sequence Identity Are Not Correlated to Functionality

Table A



Petitioner's Reply, page 9; Ex. 1045 (Silverstone Reply Decl.), ¶ 9 (red box added)

Written Description – AAD-12 Amino Acids that Bind the Claimed Herbicides Are Not Known

pyridyloxy) recited in the Challenged Claims. Corteva's expert, Dr. Bollinger, admitted that even today (let alone in 2005) it is not known which of AAD-12's 292 residues bind to 2,4-D or triclopyr (Bollinger Dep., 37:22-24, 38:21-23, 39:8-14), which are phenoxy and pyridyloxy herbicides, respectively, described in the '055 patent (Ex. 1001, 2:45-54, Tables 10, 11, 13, 18, 19, 28). Dr. Bollinger admitted that

Petitioner's Reply, page 3

Q Was it known in 2005 which amino acids in AAD-12 bind to triclopyr?
A No.

Ex. 1043 (Bollinger Dep. Tr.), 38-39

Q Was it known in 2005/2006 which amino acids in AAD-12 bind to 2, 4-D?
A No.

Ex. 1043 (Bollinger Dep. Tr.), 39

Written Description – AAD-12 Amino Acids that Bind the Claimed Herbicides Are Not Known

an AAD-12 motif having the general formula of:

$HX_{109}D(X)_{111\text{-}134}T(X)_{136\text{-}261}H(X)_{263\text{-}272}R$, wherein

'055 Patent, Claim 1

1 2 3 4 5

patent (Ex. 1001, 2:45-54, Tables 10, 11, 13, 18, 19, 28). Dr. Bollinger admitted that rather than binding to herbicides the AAD-12 motif's five residues bind to alpha-ketoglutarate ("αKG") and to iron. Bollinger Dep., 32:16-33:2, 33:16-34:1.

Petitioner's Reply, page 3

chemical reactions. The Patent Owners only include part of the active site, the catalytic iron binding site, but not active site amino acids required for binding the auxin herbicide substrates, in the structure disclosed for the genus. Substitutions in

Ex. 1003 (Silverstone Decl.), ¶ 83 (cited in Petition, 46, 48)

Written Description – AAD-12 Fixed Spacing Is Not Correlated to Function

Enzyme	Active-Site Motif	% Seq Identity to AAD-12
AAD-12	$HX_{109}D(X)_{111\text{-}134}T(X)_{136\text{-}261}H(X)_{263\text{-}272}R$	100%
tfdA	$HX_{115}D(X)_{117\text{-}140}T(X)_{142\text{-}262}H(X)_{264\text{-}273}R$	37%
AAD-2	$HX_{116}D(X)_{118\text{-}141}T(X)_{143\text{-}263}H(X)_{265\text{-}274}R$	35%
AAD-1	$HX_{112}D(X)_{114\text{-}137}T(X)_{139\text{-}269}H(X)_{271\text{-}280}R$	30%
TauD	$HX_{100}D(X)_{102\text{-}125}T(X)_{127\text{-}254}H(X)_{256\text{-}265}R$	26%

113. Accordingly, as the '055 patent discloses, the conserved residues and fixed spacing of the AAD-12 motif differ from the active-site motif of other αKG-dependent dioxygenases and correlate with the claimed dual herbicide-degrading function.

Ex. 2011 (Bollinger Decl.), ¶¶ 112-113

Written Description – AAD-12 Fixed Spacing Is Not Correlated to Function

αKG Enzyme	Residues between H and D	Residues between D and T	Residues between T and H	Residues between H and R	Ability to Degrade 2,4-D (Efficiency Constant)
AAD-12	1	24	126	10	500,000
tfdA	1	24	121	10	125,000,000[3]
AAD-2	1	24	121	10	2,200
AAD-1	1	24	131	10	27,000
TauD	1	24	128	10	N/A
Bollinger Dep. Cites	65:13-16	65:21-66:18	68:11-69:16	66:19-67:7	78:4-10; 79:12-80:6

Petitioner's Reply, page 7 (red box added for emphasis)

Q Yeah. So the question was: Do you think there's a correlation between the spacer lengths of TfdA and AAD-2 for the third spacer and the efficiency of their abilities to degrade 2, 4-D?

A Well, for those two, I mean, that would be a pretty lame correlation, but if -- you know, they both degrade 2, 4-D, so in that sense it's correlated.

Ex. 1043 (Bollinger Dep. Tr.), 81 (cited in Petitioner's Reply, 7)

Written Description – AAD-12 Motif Residues Not Correlated to Function

Dr. Bollinger also incorrectly assumed [redacted]

[redacted]

[redacted]

[redacted]

Bollinger Dep., 170:7-171:3 [redacted]

[redacted] Ex. 2092

Petitioner's Reply, pages 10-11

an AAD-12 motif having the general formula of:

$HX_{109}D(X)_{111\text{-}134}T(X)_{136\text{-}261}H(X)_{263\text{-}272}R$, wherein

'055 Patent, Claim 1

1 2 3 4 5

Written Description – AAD-12 Motif Residues Not Correlated to Function

[redacted]

Ex. 2085 ([redacted]), slide 2 (cited in Petitioner's Reply, page 4)



Ex. 2092 at 8 (cited in Petitioner's Reply, page 11)

Written Description – No Structure-Function Correlation

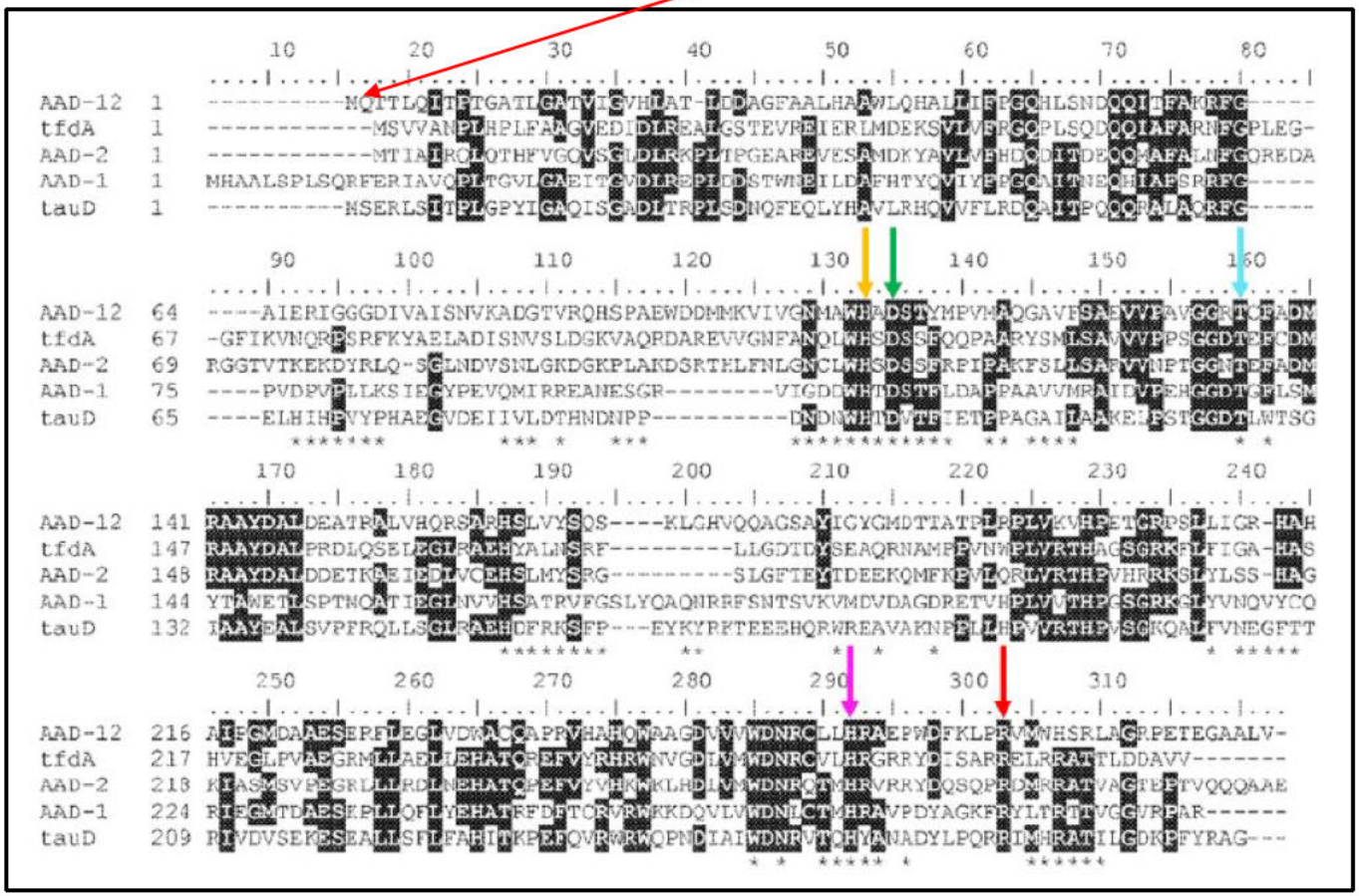


PO's Sur-reply, page 11

Written Description – Two Near-Identical Species Not Representative

sequence AAD-12 (v1) (SEQ ID NO:3) was developed that encodes a protein (SEQ ID NO:4) which is the same as the native SEQ ID NO:2 except for the addition of an alanine residue at the second position (underlined in SEQ ID NO:4).

'055 Patent, 35:10-13



Ex. 2011 (Bollinger Decl.), ¶ 111 (annotating AAD-12 motif in Fig. 2 of '055 Patent)

Written Description – Specification Discloses Testing Just One Species

> Q. So all the examples that described testing any kind of tolerance in the '055 patent only described testing in the AAD-12(v1) gene, right?
>
> A. That is correct.

Ex. 1044 (Christou Dep. Tr.), 80 (cited in Petitioner's Reply, page 16)

Not Enabled – Corteva's Experts Confirmed the Genus Is Unpredictable

Q So the same question for the T, what if you substituted the T in the motif with -- and that's the only change you made with some other amino acid, would it still have the dual functionality?

A Well, again, I want to point out that would not be, so it's a hypothetical outside the scope of the patent --

Q That's right.

A -- as the previous one was, and again, it would depend on what one would change it to. With the R in place, I suspect you could get some activity with the residue other than T.

Q What if you changed T to F?

A To F, probably not.

Q Why not?

A Too bulky.

Ex. 1043 (Bollinger Dep. Tr.), 170 (cited in Petitioner's Reply, pages 5, 20-21)



Ex. 2092 at 8 (cited in Petitioner's Reply, page 11)

Not Enabled – Corteva's Experts Confirmed the Genus Is Unpredictable

Q. And you wouldn't expect the AAD-12 variants within the scope of claim 1 to have an activity level that are 1 percent of the AAD-12(v1) gene, right?

MR. FLIBBERT: Objection to form.

A. It's the same enzyme. I think it will be very hard for me to imagine that I would see drastic changes in enzymatic activity.

Ex. 1044 (Christou Dep. Tr.), 82 (cited in Petitioner's Reply, page 11)

Table A

[redacted]

Petitioner's Reply, page 9; Ex. 1045 (Silverstone Reply Decl.), ¶ 9

Not Enabled – Corteva's Research Plan Is Insufficient

contrary, Dr. Bollinger detailed the principles skilled artisans used in making function-conserved variants in his declaration:

1. Maintain high sequence identity in view of the known sequence-function correlations for enzymes;
2. Maintain the active-site motif;
3. Retain other non-motif residues that are highly conserved across related enzymes (e.g., as shown in Figure 2 of the '055 patent); and
4. Retain surface charge distribution and steric bulk.

PO's Sur-reply, page 10

Studies of the SWISS-PROT Database Are Inapposite

> Q Where do the enzymes that are cataloged in there come from? Are they natural evolved? Are they made in a lab? Are they both?

...

> A I would think most of them come from a natural source.

Ex. 1043 (Bollinger Dep. Tr.), 101-102 (cited in Petitioner's Reply, 14)

Studies of the SWISS-PROT Database Are Inapposite

> Q Does that imply that enzymes that have evolved typically evolve to have a function?

...

> A I think that enzymes are -- in nature are generally subjected to evolutionary pressure for functionality, so yes.

Ex. 1043 (Bollinger Dep. Tr.), 104 (cited in Petitioner's Reply, 14)

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Studies of the SWISS-PROT Database Are Inapposite

1. A transgenic plant cell comprising a recombinant polynucleotide that encodes an AAD-12 protein that exhibits

'055 Patent, Claim 1

Q What does "transgenic" mean?

A My understanding is it means introduction of a gene not normally found in an organism into that organism.

Ex. 1043 (Bollinger Dep. Tr.), 17-18 (cited in Petitioner's Reply, 14)