

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

Inari Agriculture, Inc.
v.
Corteva Agriscience LLC

PGR2023-00022

U.S. Patent No. 11,371,055

CORTEVA'S TRIAL DEMONSTRATIVES

July 25, 2024

Structural Limitations of the '055 Patent Claims

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:

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

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

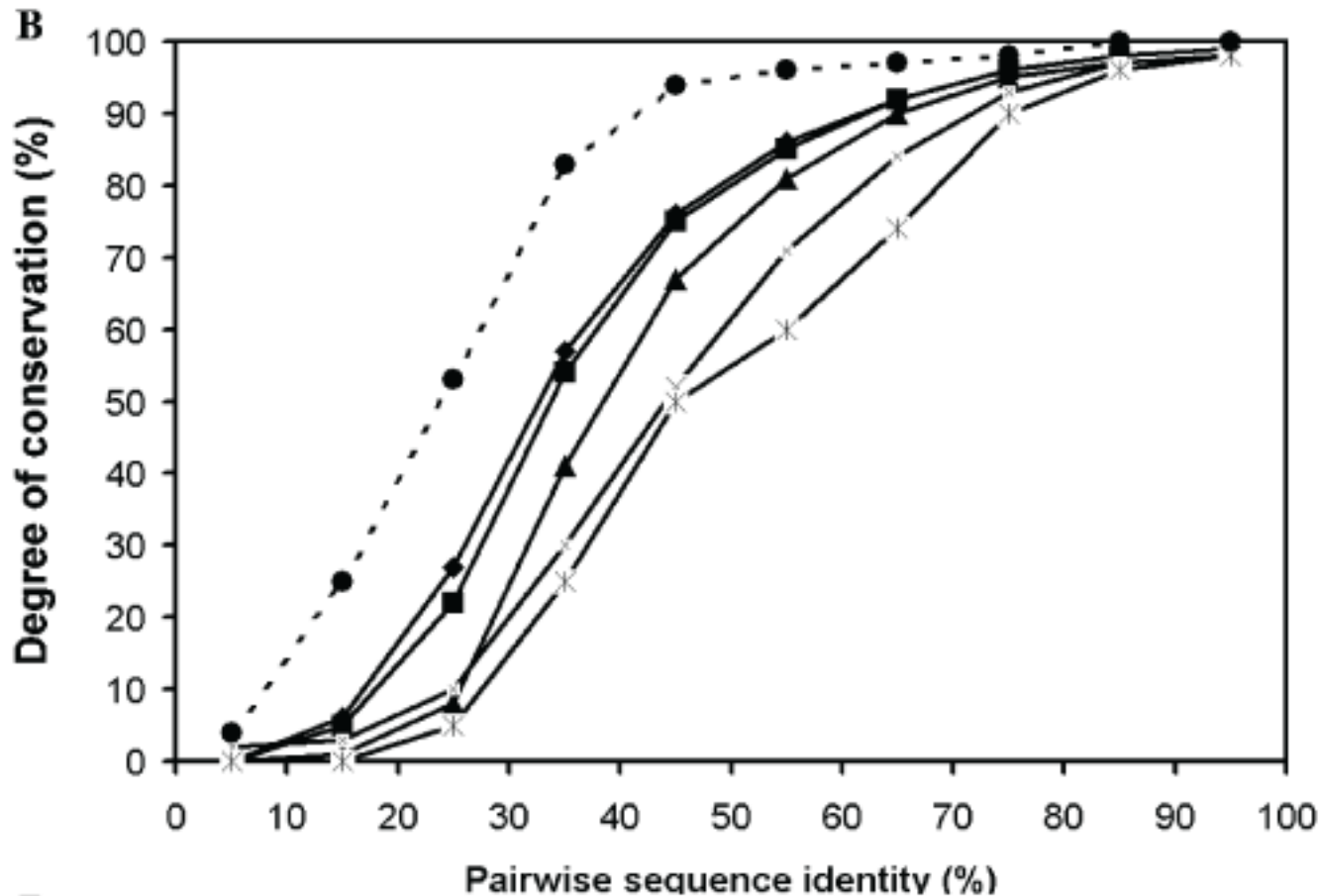
$(X)_{111-134}$ represents a sequence of 24 amino acids;

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

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

Ex. 1001 ('055 patent), claim 1

Relationship Between Enzyme Sequence and Function



Ex. 2019, 866; POR, 10; Ex. 2011, ¶ 34

'055 Patent – High Sequence Identity

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 ('055 patent), 21:41-60; POR, 22, 35-36; Sur-Reply, 4; Ex. 2011, ¶ 95

'055 Patent – High Sequence Identity

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, only sequences with $\leq 50\%$ homology were chosen. As exemplified herein, cloning and recombinantly expressing homologues with as little as 31% amino acid conservation (relative to *tfdA* from *Ralstonia eutropha*) can be used to impart commercial levels of resistance not only to the intended herbicide, but also to substrates never previously tested with these enzymes.

Ex. 1001 ('055 patent), 31:55-32:22; POR, 21, 35-36; Sur-Reply, 4; Ex. 2011, ¶ 95

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, 39; Ex. 2011, ¶ 157

“[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, 9; Ex. 2011, ¶ 98

- “[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, 38; Ex. 2011, ¶¶ 35, 97



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)

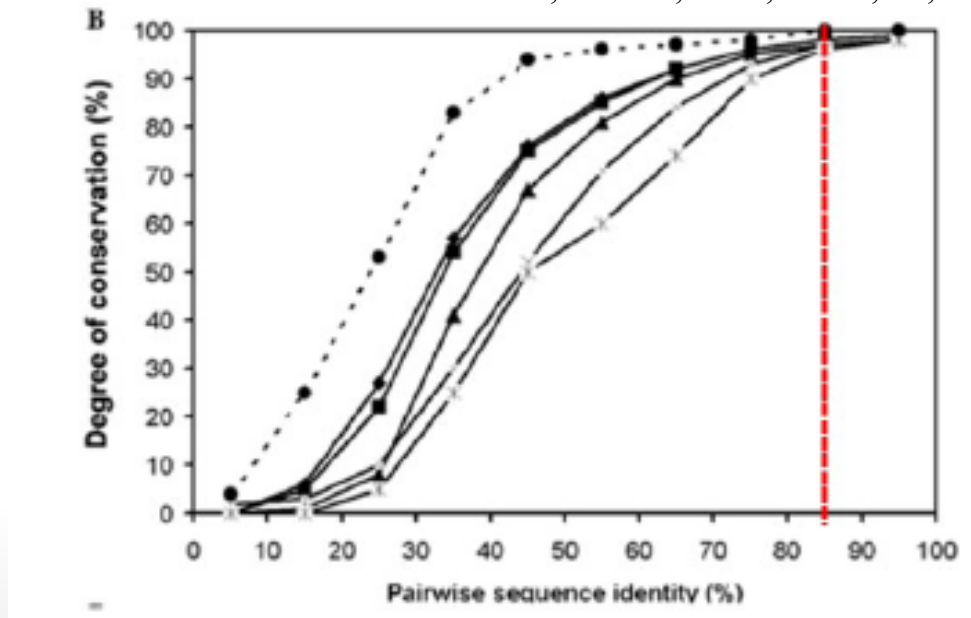
POR at 46

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, 10-11, 31; Sur-Reply, 6; Ex. 2011, ¶¶ 23, 34



Ex. 2019, 866 (Figure 1(B) “includes both enzyme-enzyme and enzyme-non-enzyme sequence pairs”); Ex. 2011, ¶ 99;
POR, 37

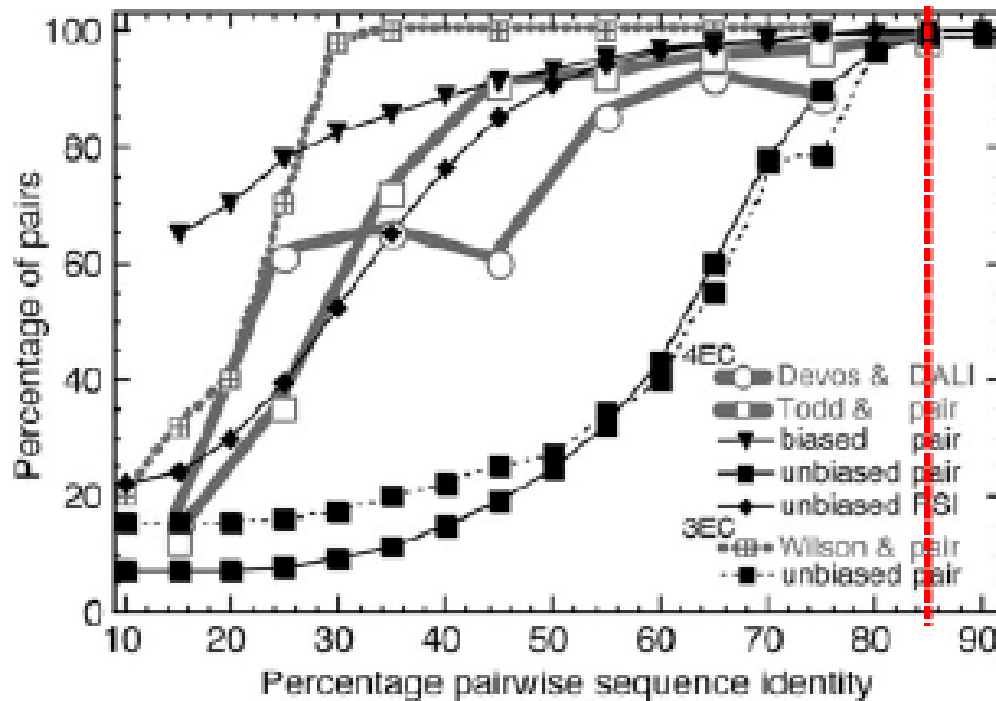
Enzyme Sequence-Function Correlation

Rost 2002 (Ex. 2028):

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

Ex. 2028, 595; POR, 9; Sur-Reply, 6;

Ex. 2011, ¶¶ 97-99

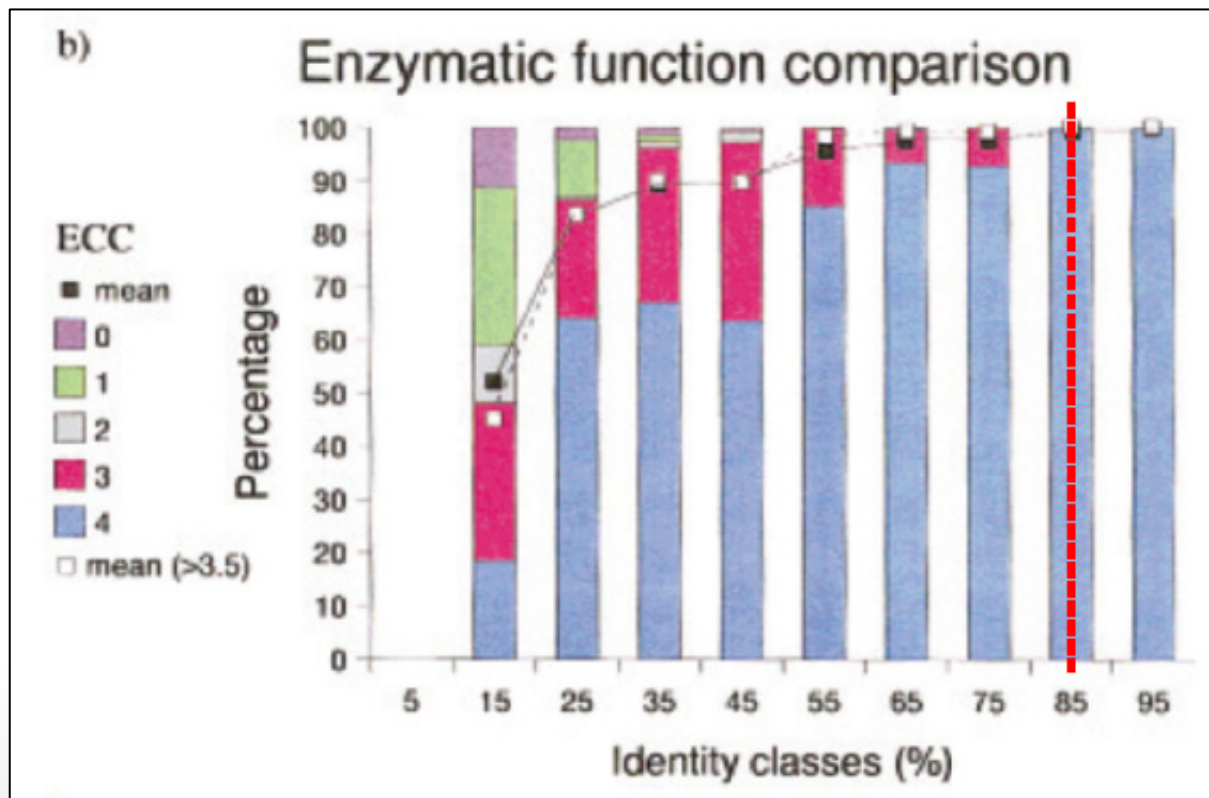


Ex. 2011, ¶ 99; Ex. 2028, 604; POR, 37

Enzyme Sequence-Function Correlation

Devos 2000 (Ex. 2026):

- “The comparison of protein sequences is widely used to infer protein structure and function.”
- “Structural similarity is conserved even at very low levels of sequence similarity.”



Ex. 2026, 98, 105;
POR, 39; Ex. 2011,
¶¶ 100, 158

Ex. 2026, 99-101 (Fig. 1(b) (red annotation at 85% added)); Ex. 2011, ¶¶ 31-39; Sur-Reply, 8.

Enzyme Sequence-Function Correlation

Petition	Tian 2003
“[I]t would be <i>nearly impossible</i> to reliably predict whether any other sequence within the scope of the claim would work.” Pet., 40. “Due to the <i>highly unpredictable correlation</i> between amino acid sequence and function, combined with the highly unpredictable effects of mutations, . . . all amino acid sequences falling within the scope of the claims would have to be meticulously tested over a period of years” Pet., 49.	“Using pairwise sequence comparison, <i>several studies suggested that when the sequence identity is above 40%, enzyme function is well conserved.</i>” Ex. 2019, 863. “[T]he percentage of sequence identity is <i>simple, quick and widely accepted by the biologist</i>” for inferring enzymatic function. <i>Id.</i>, 872.

POR, 38

Enzyme Structure and Sequence Identity

Wilson (Ex. 2024):

“Structure is always more highly conserved than sequence, so usually a given amount of structural similarity is not as significant as a corresponding amount of sequence similarity.”

Ex. 2024, 238; Ex. 2011, ¶ 101; POR, 39

Rost 2002 (Ex. 2028):

- “When two sequences are very similar we can safely infer that they have similar structures.”
- “In general, transfer of structure is almost guaranteed to be correct above the twilight zone, e.g., all known pairs of proteins with more than 33 residues in 100 identical have similar structure.”

Ex. 2028, 604, 596; Ex. 2011 ¶ 101; POR, 39

Devos 2000 (Ex. 2026):

- “Structural similarity is conserved at very low levels of sequence similarity.”
- “The comparison of protein sequences is widely used to infer protein structure and function.”

Ex. 2026, 105, 98; POR, 39; Ex. 2011, ¶¶ 100, 157

Dr. Bollinger's Testimony

Enzyme Sequence-Function Correlation

118. The scope of AAD-12 proteins encompassed by the '055 patent claims is narrow. The at least 85% sequence identity requirement limits the AAD-12 proteins to those falling within a closely confined sequence space at which skilled artisans would expect to maintain the same or similar function, just as the specification discloses. Ex. 1001 ('055 Pat.), 21:41-60, 32:1-6; Ex. 2013, ¶¶ [0093], [00123]; Exs. 2014, 2017, ¶¶ [00102], [00150]; Ex. 2015, ¶¶ [00105], [00153]; Ex. 2016, ¶¶ [00108], [00156]. Indeed, skilled persons in 2005-2006 recognized that high levels of sequence identity, including 85%, were predictive of common function. Ex. 2019 (Tian); Ex. 2028 (Rost 2002); Ex. 2024 (Wilson). Enzymes having at least 85% sequence identity would have been considered highly identical and would have been presumed to be essentially the same enzyme having the same function.

Ex. 2011 (Dr. Bollinger's Declaration), ¶ 118; POR, 73

'055 Patent – AAD-12 Motif

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

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

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

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

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

Ex. 1001 ('055 patent), claim 1; 10:61-11:34

Dr. Bollinger's Testimony:

- “Q. What is a motif in simple terms? A. In general, *it's a stretch or sequence of amino acids* in which some are specified and some can be any identity that *relates to a function*.”
- “[S]killed artisans understood that *active site* residues are, as their name reflects, correlated to an enzyme's *activity*.”

Ex. 2011, ¶¶ 154-156; Ex. 1043, 22:18-22; POR, 74

'055 Patent's Disclosures of Figure 2, Motif, and Conserved Residues

Specific changes to the “active site” of the enzyme can be made to affect the inherent functionality with respect to activity or stereospecificity (see alignment FIG. 2). Muller et. al. (2006). The known tauD crystal structure was used as a model dioxygenase to determine active site residues while bound to its inherent substrate taurine. Elkins et al. (2002)

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

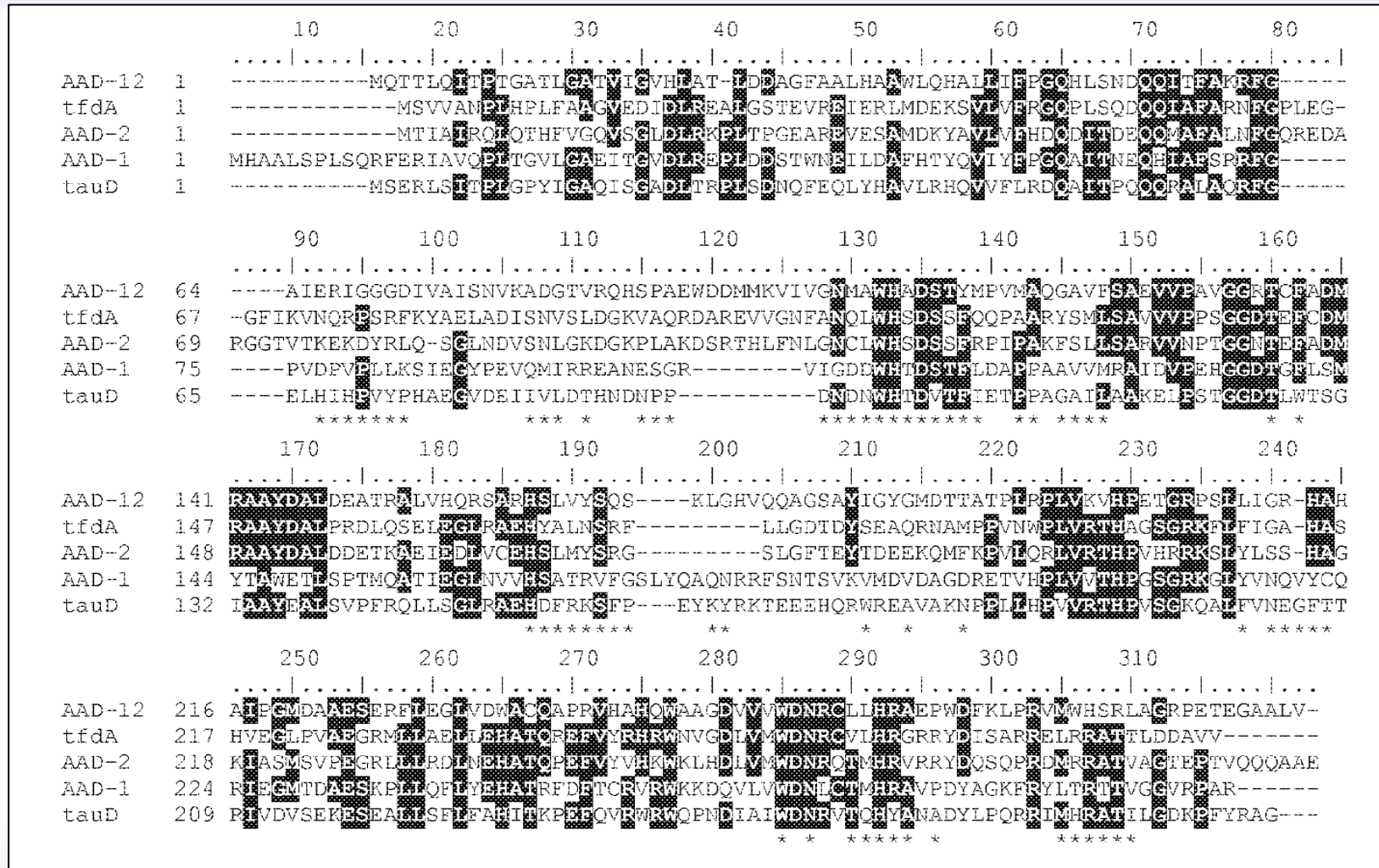
Ex. 1001 ('055 patent), 20:23-34, 11:1-6; POR, 22-23, Ex. 2011, ¶ 71

Minshull (Ex. 2025):

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

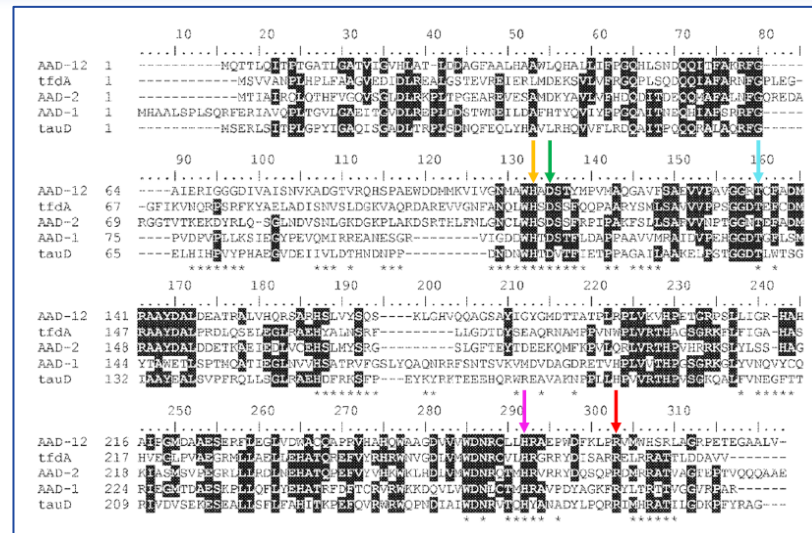
Ex. 2025, 204-205; Ex. 2011, ¶¶ 56, 119, 138, 156, 160; POR, 74; Sur-Reply, 16

Figure 2: Motif and Conserved Residues



Ex. 1001 ('055 patent), Fig. 2, 31:55-32:22; Ex. 2011, ¶¶ 83, 111-112; POR, 44; Sur-Reply, 7

Figure 2: Motif and Conserved Residues



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

Ex. 1001 ('055 patent), 31:55-32:22; Ex. 2011, ¶¶ 111-112; POR, 44; Sur-Reply, 7

Technical Background - Motif

Hausinger (Ex. 2054):

TABLE 1 Metal ligands and α KG-binding residues of selected Fe(II)/ α KG-dependent hydroxylases and related enzymes						
Enzyme	Ligand 1	Ligand 2	Spacing	Ligand 3	Spacing	α KG C-5 stabilization
Human prolyl 4-hydroxylase	His 412	Asp 414	68	His 483	9	Lys 493
Human lysyl hydroxylase	His 638	Asp 640	49	His 690	9	Arg 700
Human HIF α -specific prolyl	His 135	Asp 137	58	His 196	8	Arg 205

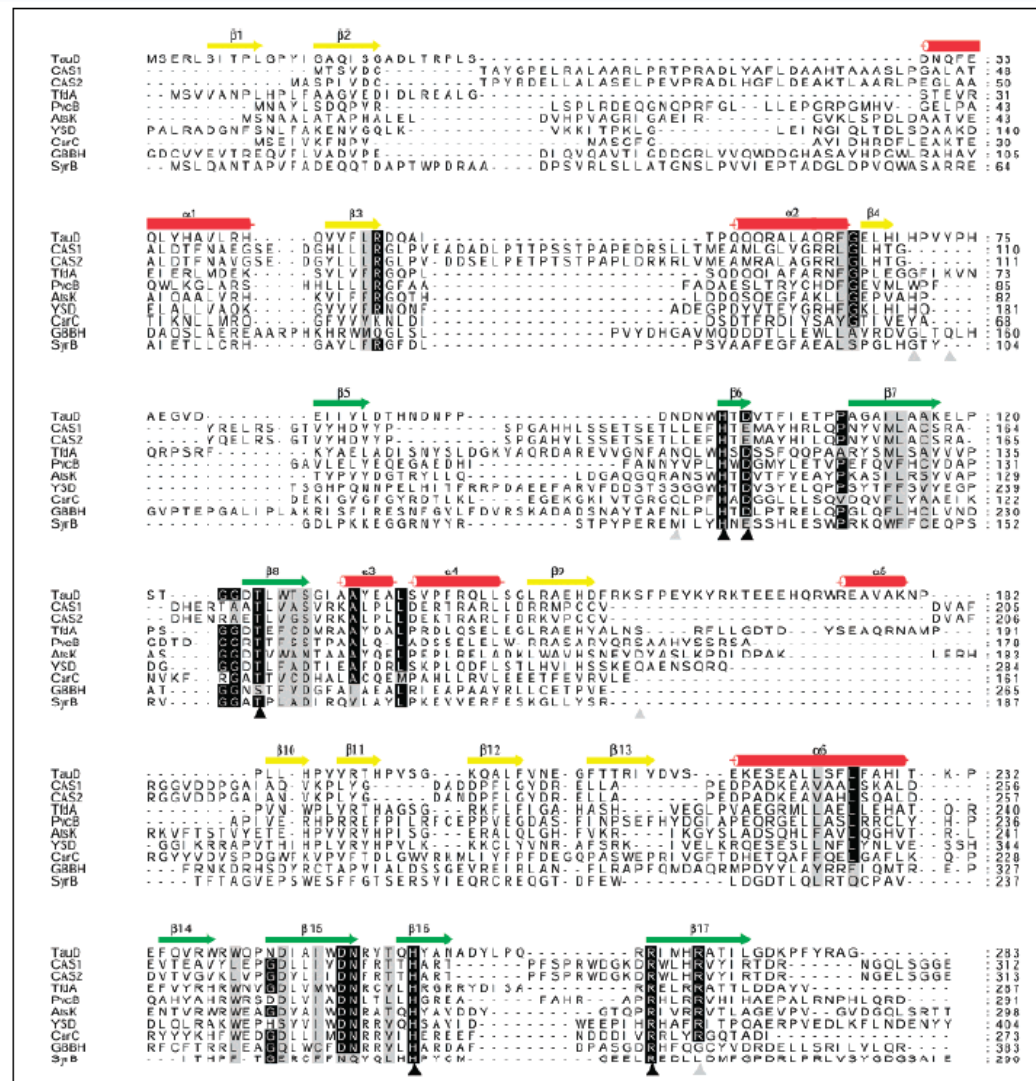
Ex. 2054, 22 (annotated); Ex. 2011, ¶ 66; POR, 14

Muller (Ex. 1020)

“The high degree of active-site sequence identity and strong orientation of key side chains by interactions with the Fe^{II} are supportive of the active site being the most conserved and structurally accurate part of the RdpA and SdpA models.”

Ex. 1020, 1358; POR, 29

Motif and Conserved Secondary Structures



Ex. 2022 (Elkins), 5190 (Fig. 5); Ex. 2011, ¶¶ 83, 110, 124; POR at 75

Sequence Comparisons & Protein Variants

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. 2011, ¶¶ 29, 56, 103, 119, 138, 156, 160; POR, 8, 49

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. 2011, ¶¶ 54-56; POR, 12-13

Amgen Inc. v. Sanofi

<i>Amgen</i>	The instant case
Claims directed to antibodies	Claims require AAD-12 enzymes
Purely functional claims - no sequence identity limitations included	Claims require at least 85% sequence identity to SEQ ID NO: 2
Claims did not require conserving any active-site motif residues	Claim require AAD-12 motif: five amino acids with fixed spacing
No evidence of antibody sequence-function correlation presented	Dr. Bollinger testified regarding the '055 patent's disclosures of the AAD-12 motif and enzyme sequence-function correlation and background literature in the field (e.g., Tian, Rost, Devos, Wilson, Todd)

Amgen, 598 U.S. at 602, 613-14; POR, 1, 6-11, 33-46

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

<i>Lifescan</i>	The instant case
Enzyme sequence contained 593 amino acids	SEQ ID NO: 2 contains 293 amino acids
Number of permitted mutations encompassed by the claims: 59	Claim 1 (at least 85% sequence identity) permits up to 43 mutations
Motif: six amino acids	AAD-12 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, 46

Perspective of Skilled Artisans

VI. Level of Skill in the Art

72. Regarding aspects of the '055 patent relating to enzymology, particularly α KG-dependent dioxygenases (e.g., SdpA/AAD-12) 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 2005-2006. E.g., Ex. 1019 (Hogan); Ex. 1020 (Müller); Ex. 2019 (Tian); Ex. 2028 (Rost 2002); Ex. 2025 (Minshull).

Ex. 2011 (Dr. Bollinger's Declaration), ¶ 72; POR, 29.

Perspective of Skilled Artisans

All variants exhibiting any level of the dual herbicide-degrading activity would broadly be “winners” because they would fall within the scope of the claims. Ex. 2035 (Chaparro-Riggers), 185 (discussing use of sequence comparisons to identify residues “that can tolerate mutation without radically affecting function”). A skilled artisan would only need to avoid total loss of activity. The '055 patent significantly guards against loss of activity by precluding substitution of the AAD-12 active site motif residues, which a skilled artisan would expect to be deleterious to function. Ex. 2025 (Minshull), 6. In addition, a skilled artisan would be guided by the '055 patent's sequence alignments to avoid deleterious changes to other strictly conserved residues. Ex. 1001, Fig. 2; Exs. 2014-2017, Fig. 2.

Ex. 2011 (Dr. Bollinger's Declaration), ¶ 135; POR, 60.

'055 Patent – Twenty Four Examples

AAD-12 Transformation of Monocot and Dicot Plants

- Arabidopsis – Example 7
- Corn – Example 8
- Tobacco – Example 10
- Soybean – Example 11
- Cotton – Example 12
- Rice – Example 21
- Canola – Example 22
- AAD-12 as Selectable Marker – Examples 7 and 24

In Vitro Assays – Examples 5 and 6

Codon Optimization – Example 2

Identification of AAD-12 (SdpA) – Example 1

- Proteins investigated “range from highly identical (85-98%) to very low identity (23-32%).”
- “In this case only sequences with $\leq 50\%$ homology were chosen.”
- SdpA was identified “as a homologue with only 31% amino acid identity to TfdA.”

Ex. 1001 ('055 patent), 31:55-102:49; POR, 23-26; Ex. 2011, ¶¶ 85-90

Paul Christou, Ph.D. – Plant Transformation Expert

- Endowed Professor, Catalan Institution for Research and Advanced Studies at the University of Lleida, Spain.
- Ph.D. in Plant Biochemistry, The University of London, University College, 1980.
- Generated the first stably transformed soybean line in the world by particle bombardment. Published in Nature Biotechnology, 1988.
- Led industry group to generate the first commercialized transgenic soybean crop, RoundUp Ready soybean.
- Recipient of grants from the Bill & Melinda Gates Foundation and the European Research Council
- Serves on the International Advisory Board of the Max Planck Institute of Plant Physiology
- Awarded 2020 Narcís Monturioll Medal for excellence in scientific research
- 286 peer-reviewed publications



Plant Transformation

'055 Patent:

“A large number of techniques are available for inserting DNA into a plant host cell.”

Ex. 1001, 24:25-62 (describing microparticle bombardment (biolistics), *Agrobacterium*, etc.); POR, 24

Dr. Christou (in Altpeter 2005):

“[P]article bombardment is a versatile and effective transformation method, not limited by cell type, species or genotype. There are no intrinsic vector requirements so transgenes of any size and arrangement can be introduced, and multiple gene cotransformation is straightforward.”

Ex. 2075, 305-306; POR, 19

Plant Transformation

Dr. Christou:

92. Plant transformation generally involves steps of (1) building an expression cassette to drive transgene expression, (2) transforming plant cells, and (3) regenerating (under selection in most cases) the post-transformation plant cells into whole plants. The transgene may optionally be codon optimized. By 2005-2006, the techniques required for each of these steps were readily available and routinely used by skilled artisans to successfully generate transgenic monocot and dicot plants. *Supra* § VI.B.2. Validation of successful transformation using a selectable marker was also straightforward and well established. *Supra* §§ VI.B.3-5.

Ex. 2012, ¶ 92; POR, 19-21

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. 2011, ¶¶ 1-19; POR, 5.

Principles for Generating Variants & Retaining Function

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

Ex. 2011, ¶¶ 56, 123-128; POR, 12-13; Sur-Reply, 2

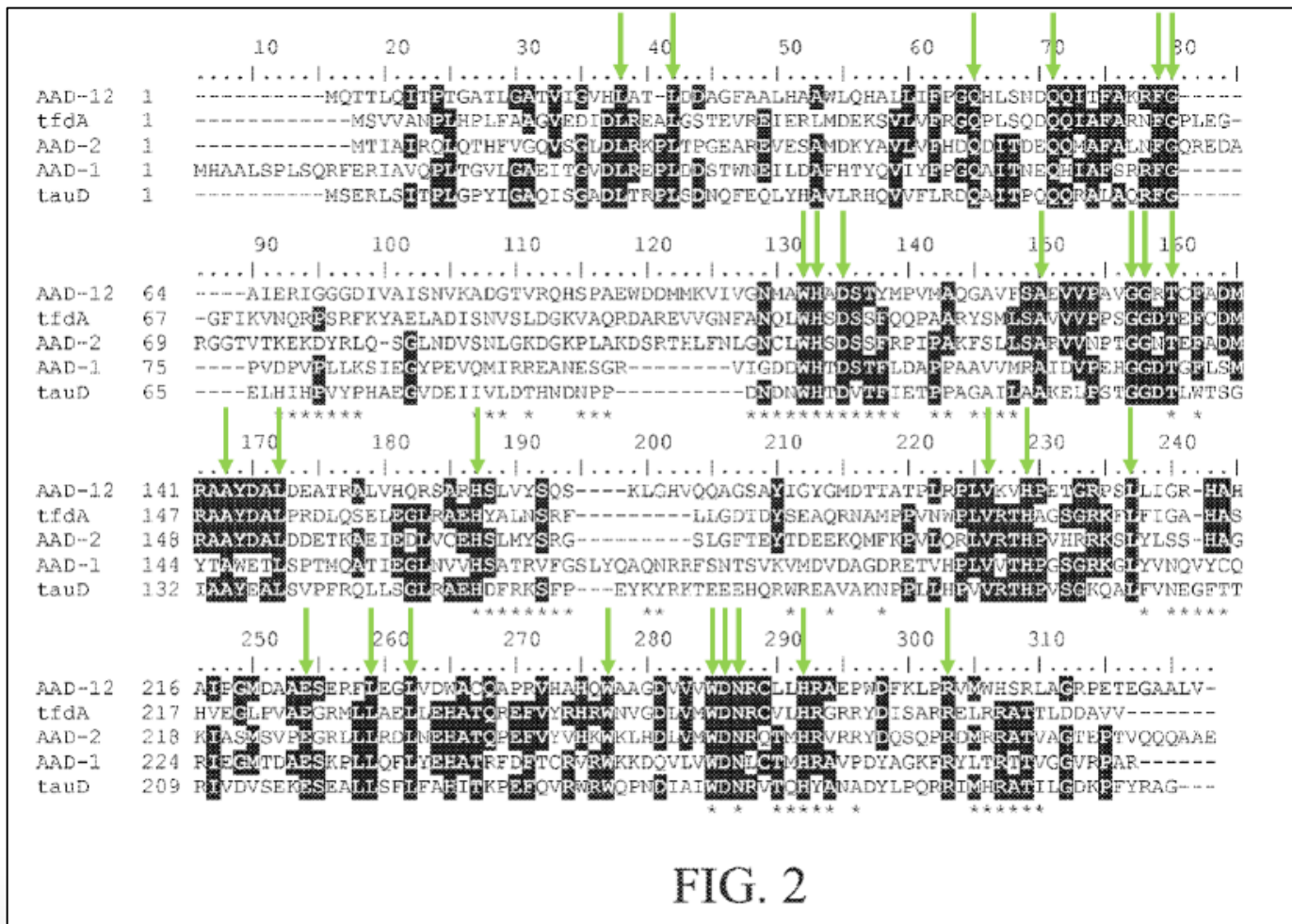
Generating Variants & Retaining Function

Dr. Bollinger's Testimony:

Skilled artisans would readily identify in Figure 2 the residues that are identical across all five enzymes and generally avoid making substitutions to those strictly conserved residues. In the annotated Figure 2 below, green arrows are used to indicate the strictly conserved residues across AAD-12, tfdA, AAD-2, AAD-1, and TauD disclosed in the '055 specification. Indeed, skilled artisans understood that the sequences of related proteins are often a “rich source of information regarding sequence changes that are acceptable without drastically disrupting protein function.” Ex. 2025 (Minshull), 2-3.

Ex. 2011, ¶ 125; POR, 51-52; Sur-Reply, 11

Generating Variants & Retaining Function



Ex. 2011, ¶ 125; POR, 51-52; Sur-Reply, 11

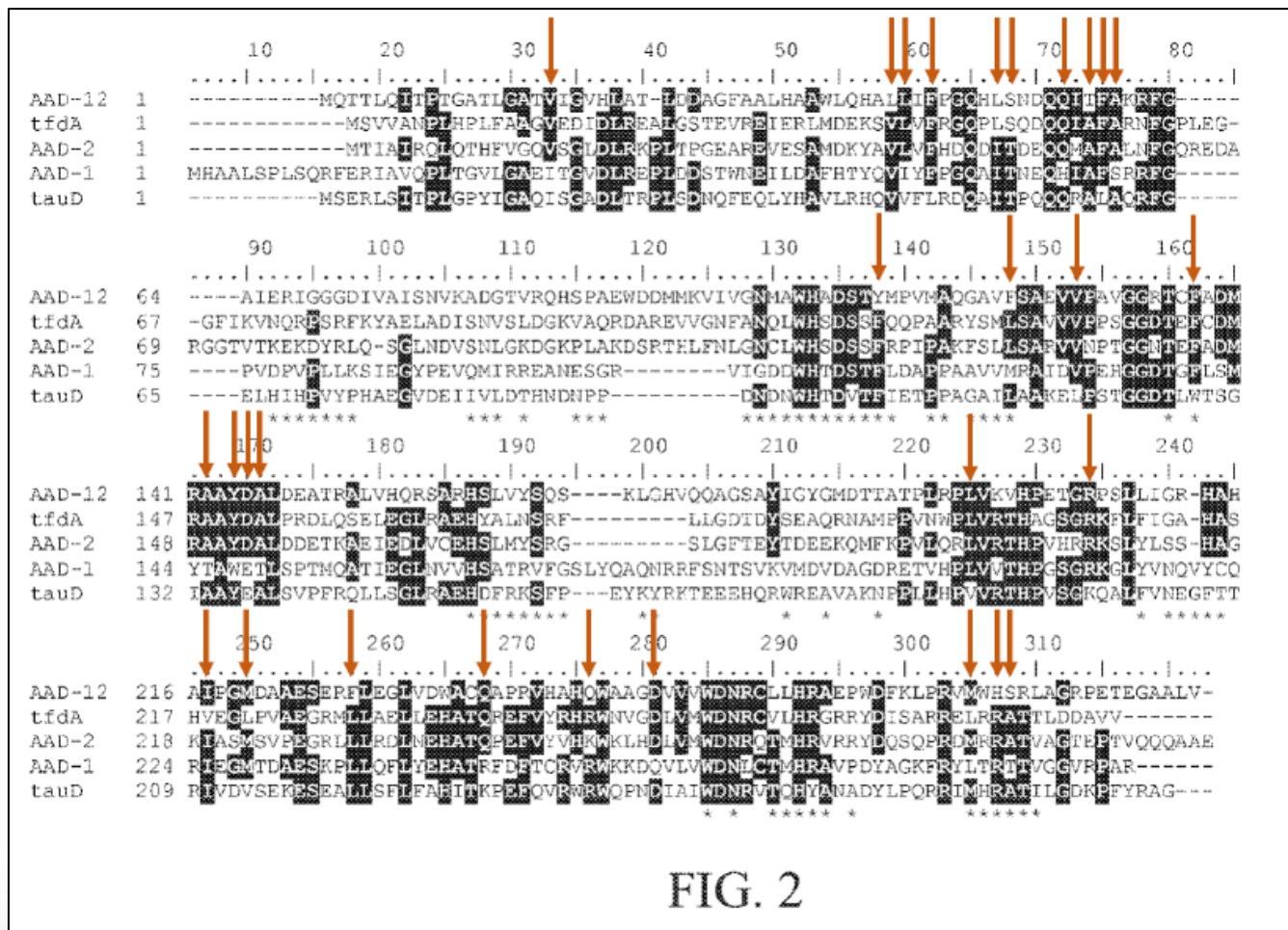
Generating Variants & Retaining Function

Dr. Bollinger's Testimony:

126. A skilled artisan would also understand from Figure 2 that there are many shaded residues (marked in red below) that are not strictly conserved across the sequences of all five enzymes. These residues are somewhat conserved but have been shown to tolerate conservative changes to similar amino acids as shown in the sequence alignment (e.g., L to I or V; S to G; etc.), providing guidance to skilled artisans that these residues may be preferentially left unsubstituted or conservatively substituted.

Ex. 2011, ¶ 126; POR, 51-52; Sur-Reply, 12

Generating Variants & Retaining Function



Ex. 2011, ¶ 126; POR, 51-52; Sur-Reply, 12

Generating Variants & Retaining Function

Dr. Bollinger's Testimony:

127. A skilled artisan would further understand from Figure 2 that the unshaded residues would likely tolerate a broader range of amino acid substitutions, particularly when overall sequence identity is kept at 85% or higher. For example, as shown among the unshaded residues in Figure 2, position 51—H, E, L or Y (different charge and L is non-polar and hydrophobic); position 112—R, D, E or H (different charge); position 215—M, R, K, D or V (hydrophobic, positive charge, positive charge, negative charge, hydrophobic).

Ex. 2011, ¶ 127; POR, 52; Sur-Reply, 10

Dr. Silverstone

- No academic degree or scientific training in enzymology or protein engineering.
- No publications in enzymology or protein engineering.
- No invited talks regarding enzymology or protein engineering.
- Could not recall what Enzyme Commission (EC) numbers mean.
- His CV, which accurately reflects how he holds himself out to the industry, does not mention any expertise in enzyme engineering or enzymology.
- Omitted enzymology from his proposed level of skill.

POR, 29, 31-32, 47

Dr. Silverstone

Time Period for His Analysis:

A. . . . I used March 24, 2017, as the date for my evaluation.

Q. That's what you were instructed to use by counsel, correct?

A. That is correct. Counsel advised me to use that date.

Perspective for His Analysis:

Ex. 2009, 88:13-18; POR, 31

“In my opinion, analysis of Wands factor (6) the relative skill of those in the art shows that a very high level of skill in the biochemical arts is required for the genetic modification of plants”

Enzymology and EC numbers:

Ex. 1003, ¶ 62; POR, 47

Q. EC numbers generally have four digits; is that right?

A. I don't remember if that's the case.

Q. Do you know what each of the four digits of an EC number indicates?

A. I don't remember. It's been a long time since I used them, so I don't remember what each category is.

Q. Do you know how many options there are for the first digit in an EC number?

A. I don't know how many options there are. I don't remember.

Ex. 2009, 107:23-108:9; POR, 31-32

α KG-Dependent Dioxygenases

- **Hydroxylation**
- **Dealkylation**
- **Desaturation**
- **Epoxidation**
- **Epimerization**
- **Halogenation**
- **Cyclization**
- **Peroxide formation**
- **Ring expansion/contraction reactions**

Ex. 1003, ¶ 48; Ex. 2011, ¶ 102; POR, 39-40