UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

CORTEVA AGRISCIENCE LLC,
Patent Owner.

U.S. Patent No. 10,947,555
"Herbicide Resistance Genes"

U.S. Patent No. 11,149,283
"Herbicide Resistance Genes"

U.S. Patent No. 11,299,745
"Herbicide Resistance Genes"

REPLY DECLARATION OF ROBERT P. HAUSINGER, PH.D.

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I, Robert P. Hausinger, Ph.D., declare as follows:

I. INTRODUCTION

1. This is my second declaration in connection with Petitions filed by Petitioners Bayer CropScience LP and Monsanto Company (collectively, "Bayer") for inter partes review ("IPR") of U.S. Patent No. 10,947,555 (the "'555 patent"), U.S. Patent No. 11,149,283 (the "'283 patent"), and U.S. Patent No. 11,299,745 (the "'745 patent") (collectively, "the Corteva patents" or "the challenged patents"). Because there are a number of common issues across the three IPR Petitions, I am providing a single reply declaration in connection with all three Petitions.

2. I understand that the Board has instituted trial on each of the Grounds for all three patents. Those Grounds are identified in my first declaration.

3. I have been asked to respond to the opinions that Dr. Bollinger has provided on behalf of the patent owner, Corteva Agrisciences LLC ("Corteva"). I understand that Dr. Bollinger has submitted a separate declaration in each of the three proceedings for the Corteva patents, but that those declarations are largely identical. I will respond to all three of Dr. Bollinger's declarations here. I also understand that the exhibit number EX2015 and paragraph numbering for all three of Dr. Bollinger's declarations is the same across the three proceedings. I therefore will provide a single citation and paragraph number for citations to his declarations. I likewise understand that the exhibit numbers for the exhibits that I cite are the same

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across all three proceedings. When citing to the challenged patents, for convenience I will cite to the ’555 patent, unless there is a reason to specifically refer to the ’283 or ’745 patents.

4. To the extent that I do not address every opinion set forth in one or more of Dr. Bollinger’s declarations, I do not mean to suggest that I agree with those opinions. I disagree with Dr. Bollinger’s opinions that the claims of the challenged patents are not anticipated or rendered obvious for the reasons stated in my first declaration (EX1054), and I do not repeat all of those reasons in this reply declaration.

5. My compensation has not changed since I submitted my first declaration. My current CV is submitted as EX1073.

6. In undertaking my analyses, I have considered the materials cited in my first declaration, the materials listed in Appendix A to that first declaration, Dr. Bollinger’s declarations, the materials cited in Dr. Bollinger’s declarations, EX2015, and the materials cited in this declaration and the attached Appendix 1. I have also relied upon my education, training, and experience.

II. PERSON OF ORDINARY SKILL IN THE ART

7. In my first declaration, I provided my opinion regarding the qualifications of the POSA, or hypothetical person to whom the challenged patents are directed. EX1054, ¶ 29. Dr. Bollinger’s description of the level of skill in the

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art is similar to my definition. EX2015, ¶ 75. To the extent there are any differences, I am qualified to offer opinions from the perspective of the POSA regarding the issues I address, and my opinions would not change under Dr. Bollinger's description. As indicated in my first declaration, I have familiarity with α-ketoglutarate ("αKG")-dependent dioxygenases and structure-function relationships in enzymology. EX1054, ¶ 30.

III. GROUNDS IA-IB

8. My first declaration specified that if the claims of the challenged patents are entitled to a priority date no earlier than October 7, 2016—which is the date the patent applicant first mentioned an "AAD-1 motif" in submissions to the Patent Office—then the Corteva '437 publication, published in November 2005, leads to conclusions of anticipation and obviousness. Dr. Bollinger does not disagree with this notion, but instead focuses on whether the claims of the challenged patents can claim priority to Corteva's 2004 and 2005 patent applications ("2004/2005 Applications") (EXS1004-1005). I disagree with Dr. Bollinger, as I discuss in detail in this reply declaration. In my opinion, the claims of the challenged patents are invalid in light of Corteva '437. That opinion does not change regardless of whether Dr. Bollinger is relying on Corteva's April 30, 2004 application (EX1004) or Corteva's May 2, 2005 application (EX1005). Dr. Bollinger does not identify any differences between these applications that matter to the written description analysis,

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and I am not aware of any.[1] As I discuss elsewhere in this reply declaration, the additional art cited by Dr. Bollinger that is dated between the two filing dates of those two applications (including Schleinitz 2004 (EX1042)) supports my opinions.

9. As explained in more detail in my first declaration, the 2004/2005 Applications did not describe an "AAD-1 motif" or a genus of AAD-1 proteins having that motif. Each of the 2004/2005 Applications, as well as the specification of the '555 patent when it was filed in October 2016, disclosed the sequence of RdpA (SEQ ID NO: 9) and emphasized that RdpA, unlike other known αKG dioxygenases, was able to degrade the particular set of herbicide substrates required by the claims. EX1054, ¶ 73; EX1001 ('555 Pat.), 4:32-36, 4:39-42, 8:10-17, 17:62-66, 18:10-20, 50:58-67, 51:1-53:13, Figs. 6A-6B, Tbls. 3-4; EX1004 ('052 Provisional Appl.), [0017], [0051], [0059]-[0060], [00168]-[00181], Figs. 6A-6B; Tbls. 3-4; EX1005 ('7893 Appl. & File History), [0018], [0074], [0085]-[0086], [00198]-[00211], Figs. 6A-6B, Tbls. 3-4. However, the applications do not identify which amino acids or structural features were important to RdpA's (*R*)-enantioselective activity against

[1] I am aware that the 2004 provisional application does not contain the "highly identical (85-98%)" and "similar properties" language that Dr. Bollinger focuses on, and that the language was added to the 2005 application. *Compare* EX1004, [00145], *with* EX1005, [00171]-[00172].

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phenoxy auxin herbicides and (*R*)-aryloxyphenoxypropionates ("(*R*)-FOPs"). EX1054, ¶¶ 74-75, 87-88. Further investigation would have been required to begin identifying those features, such as the RdpA homology modeling/mutagenesis work we published in Müller 2006 (EX1035), or an RdpA crystal structure analysis, which was not published until 2019.

10. Dr. Bollinger responds that the POSA would have been able to glean additional information from various references, including an article published by Schleinitz et al. in September 2004. EX2015, ¶¶ 113-118. I disagree that the references cited by Dr. Bollinger described for the POSA an "AAD-1 motif" or what characteristics were important to RdpA's (*R*)-enantioselective activity. The POSA would not have understood the features responsible for RdpA's unique activity to be the features it shared with TfdA or other αKG dioxygenases that lack that activity. EX1054, ¶ 102.

11. Dr. Bollinger also relies on what he describes as a "general rule" that enzyme sequences above a certain percentage sequence identity would be expected to catalyze the same reactions. EX2015, ¶¶ 40, 109, 123. As support, Dr. Bollinger relies on Tian (EX2019), which he says "built upon" analyses from earlier references. EX2015, ¶¶ 29-38, 40, 100-101. However, these references, which do not discuss RdpA or any other herbicide-degrading αKG dioxygenases, were directed to annotation of naturally occurring protein sequences identified through

genome sequencing projects. Because naturally occurring protein sequences are limited to those proteins that have survived natural selection, they represent a small and biased dataset that is not analogous to an artificially generated set of variants having a certain percent sequence identity to a known protein, such as the recombinant amino acid sequences set forth in the claims of the challenged patents. Thus, the POSA would not have assumed that the conclusions of these papers would extend to the set of at least 20^{44} hypothetical artificial recombinant variants of RdpA whose sequences are covered by the claims of the challenged patents. *See* EX1054, ¶¶ 79-80.

A. Neither the 2004/2005 Applications nor the prior art, including Schleinitz 2004, disclosed an "AAD-1 motif," with or without R285

12. Dr. Bollinger equates the presence of the generic αKG dioxygenase consensus motif in RdpA's sequence as a description of a new "AAD-1 motif" or "RdpA motif" that is "strongly correlated to its function." EX2015, ¶ 111. For example, he offers the opinion that "RdpA's primary amino acid sequence alone was sufficient for a skilled artisan to recognize the RdpA (AAD-1) motif," because, in his opinion, the POSA would have recognized that RdpA included a generic αKG dioxygenase consensus motif. EX2015, ¶ 113. He also states that the Schleinitz 2004 paper "published that information in 2004, illustrating the exact residues and spacing of the RdpA motif as compared to other Group II αKG-dependent dioxygenases." EX2015, ¶ 114.

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13. As I explained in my first declaration, the ’555 patent specification as originally filed in October 2016, the relevant part of which is the same as the 2004/2005 Applications, does not disclose the “AAD-1 motif” of claim 1 ($HX_{112}D(X)_{114\text{-}137}T(X)_{139\text{-}269}H(X)_{271\text{-}280}R$). EX1054, ¶¶ 63-68; EX1004 (’052 Provisional Appl.), [0059]; EX1005 (’7893 Appl. & File History), [0085]; EX1008 (’406 Appl. & File History], [0085]. Instead, they disclose the generic consensus prior art motif and the amino acid sequence for RdpA (SEQ ID NO: 9). *Id.*; EX1004 (’052 Provisional Appl.), SEQ ID NO: 9; EX1005 (’7893 Appl. & File History), SEQ ID NO: 9; EX1008 (’406 Appl. & File History), SEQ ID NO: 9. In that respect, the above statements from Dr. Bollinger ignore the important distinction between observing that RdpA’s sequence includes an instance of the generic αKG dioxygenase consensus motif versus describing a new and unique “RdpA motif” or “AAD-1 motif” that is characteristic of proteins like RdpA with (*R*)-enantioselective activity that degrades phenoxy auxin herbicides and (*R*)-FOP herbicides. As I explained in my first declaration, the POSA would not have expected that the variables in the generic αKG-dioxygenase consensus motif, or a derivative of it, would define and describe a genus of proteins with the claimed (*R*)-enantioselective activity. I stated, “[B]ecause most αKG dioxygenases do not have (*R*)-stereospecific activity, the αKG dioxygenase consensus motif would not be expected to capture the characteristics important to that stereospecificity. The POSA would have

understood this, and would not have expected the variables in that consensus motif, or a derivative of it, to define and describe a genus of AAD-1 proteins limited to those with the claimed activity." EX1054, ¶ 102. Although the POSA would have known that the five conserved amino acids in the consensus motif were involved in coordinating the metal center and binding the α-ketoglutarate, and thus are functionally important to αKG dioxygenases generally, the POSA would not have mistaken those residues or the spacing between them for the features that define the set of substrates that a particular αKG dioxygenase such as RdpA will use. I discuss this issue in more detail below. *See* ¶¶ 19-27.

14. The Schleinitz 2004 paper relied on by Dr. Bollinger confirms that observing an instance of the generic consensus motif is not the same thing as defining a new motif. Dr. Bollinger focuses on Figure 2, which depicts the sequences of RdpA, TfdA, TauD, and SdpA, and indicates the locations of the five conserved residues required by the generic consensus motif. EX2015, ¶ 114; EX1042 (Schleinitz 2004 (pp. 5360, 5362)). Schleinitz 2004's text explains that Figure 2 shows that RdpA and SdpA belong to the αKG dioxygenase family and that they each include the consensus motif. EX1042 (Schleinitz 2004 (p. 5362)). If Dr. Bollinger were correct that the instance of the consensus motif in RdpA's sequence constitutes a description of a new "motif" characteristic of RdpA-like enzymes, then Schleinitz 2004 would surely have discussed that motif. However, there is nothing

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in Schleinitz 2004 that supports that assertion. The generic αKG dioxygenase consensus motif is the only "motif" that is discussed in Schleinitz 2004, which would reflect to the POSA that the authors did not think they had described a new and unique "motif" that is generalizable to other enzymes. EX1042 (Schleinitz 2004 (p. 5362)) ("The functionally important motif $HX(D/E)X_{23\text{-}26}(T/S)X_{114\text{-}183}HX_{10\text{-}13}R/K$, which is conserved throughout group II αKG-dependent dioxygenases (18), is present in both RdpA and SdpA."); EX1042 (Schleinitz 2004 (p. 5357)).

15. The above understanding is reinforced by Schleinitz 2004's recognition that the basis for RdpA's (*R*)-enantioselective activity was unknown. Dr. Bollinger describes a "motif" as a pattern shared by "a set of enzymes with the same or similar functions." EX2015, ¶ 39. It would have been surprising to the POSA if the authors of Schleinitz 2004 had attempted to define a new "motif" characteristic of RdpA-like enzymes based on just one enzyme sequence (RdpA) while at the same time concluding that "the basis of the enantiospecificity of the dichlorprop-cleaving enzymes is not known" and that "studies are needed to reveal the molecular basis of the substrate specificity and stereospecificity of RdpA and SdpA." EX1042 (Schleinitz 2004 (pp. 5362-5363)). If the authors of Schleinitz 2004 had believed the information in Figure 2, or elsewhere in the prior art, identified a new "motif" shared by RdpA and other enzymes with its same activity, then the POSA would expect that they would have presented that new motif, explained how it was distinct

from the generic consensus motif, and explained their reasoning in the article text. The fact that the authors did not do so confirms that the POSA would not have understood Schleinitz 2004 to describe a new RdpA or AAD-1 "motif." EX1042 (Schleinitz 2004 (pp. 5357, 5362-5363)).

16. For similar reasons, I disagree with Dr. Bollinger's opinion that the prior art, including Schleinitz 2004,[2] discloses a motif that includes an additional arginine at R285 or otherwise indicates that R285 (or $X_{282\text{-}284}R$, as Corteva uses in claim 2 of each of the challenged patents) is functionally important in RdpA. *See* EX2015, ¶¶ 138-142. The only motif discussed in Schleinitz 2004 is the generic consensus motif, which does not include an additional arginine. EX1042 (Schleinitz 2004 (pp. 5357, 5360, 5362-5363)). In Figure 2, the 285 arginine in RdpA is highlighted gray, while the consensus motif residues are highlighted black. EX1042 (Schleinitz 2004 (p. 5360)). Similarly, neither '555 patent specification as originally filed nor the 2004/2005 Applications disclose the $X_{282\text{-}284}R$ limitation. EX1054, ¶ 68. I therefore disagree with Dr. Bollinger's suggestion that either of the 2004/2005 Applications or Schleinitz 2004 provides a description of the $X_{282\text{-}284}R$

[2] I understand that Corteva is taking the position that Schleinitz 2004 is "prior art." I further understand that means that Corteva is relying on the 2005 application (EX1005) for its priority claim, as Schleinitz 2004 was published in September 2004.

[redacted]

limitation in claim 2 of each of the challenged patents.

17. I likewise disagree with Dr. Bollinger's assertion that Figure 2 shows that R285 was understood to be functionally significant in RdpA. *See* EX2015, ¶¶ 141-142. The caption to Figure 2 explains that "Black arrows indicate 2,4-D binding residues in TfdA," which is only one of the four enzymes depicted (RdpA, TauD, TfdA, SdpA):

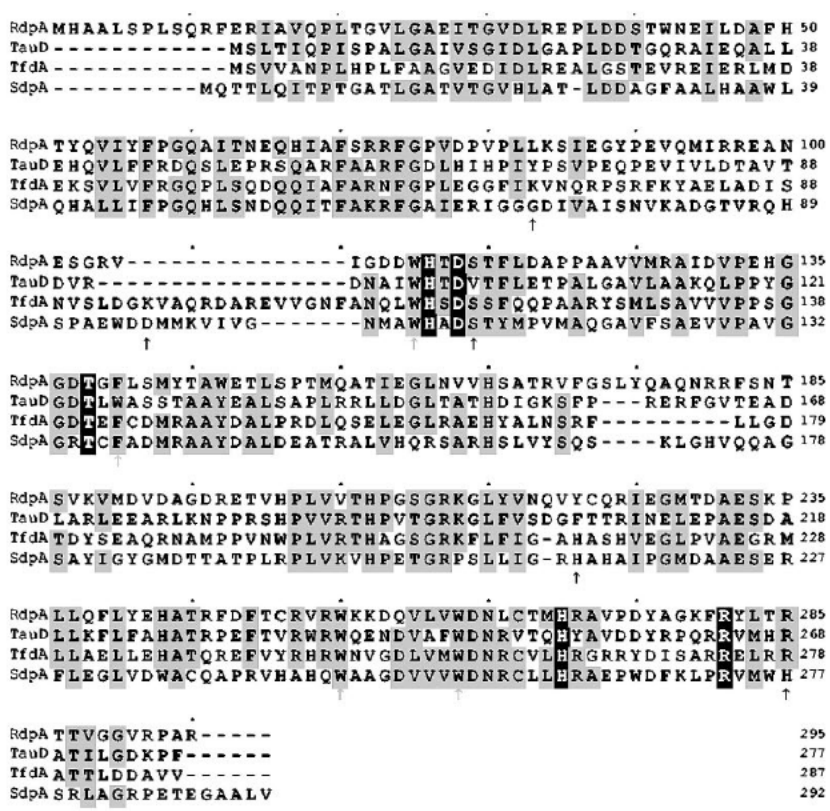

FIG. 2. Sequence alignment of RdpA and SdpA with other group II αKG-dependent dioxygenases. TfdA, *R. eutropha* 2,4-D/αKG dioxygenase (accession no. A27082); TauD, *P. aeruginosa* taurine/αKG dioxygenase (accession no. NP_252624). Conserved Fe(II)- and αKG-binding residues are shaded in black; other conserved regions are shaded in gray. Black arrows indicate 2,4-D binding residues in TfdA; gray arrows indicate residues undergoing posttranslational hydroxylation in TauD or TfdA. Amino acid positions numbers are shown to the right of each line. The alignment was created with CLUSTAL W.

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EX1042 (Schleinitz 2004 (p. 5360 & Fig. 2) (highlighting added)). I disagree with Dr. Bollinger that this "strongly indicat[es] a similar function for Arg285 in RdpA." *See* EX2015, ¶ 141. If the authors wanted to indicate that the residue performed a particular function in RdpA, they would have identified RdpA in the relevant part of the caption. 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.

18. Dr. Bollinger also relies on Elkins (EX1023) and Hotopp 2002 (EX1029), but those articles do not support his opinions. *See* EX2015, ¶¶ 140-141. These papers addressed the role of a number of additional residues in two enzymes with activity different from RdpA's: TauD, which degrades taurine, and TfdA, which degrades 2,4-D but not (*R*)-phenoxy auxins or (*R*)-FOPs (because it is (*S*)-enantioselective). These papers do not indicate to the POSA that the arginine at 285 in RdpA is essential to RdpA's activity or is part of an RdpA-specific "motif." Like Schleinitz 2004, the consensus motif discussed in these papers does not include an additional arginine. EX1023 (Elkins (p. 5185)); EX1029 (Hotopp 2002 (p. 9878)). Furthermore, I note that even if the POSA might have hypothesized that RdpA's R285 could bind 2,4-D, that would not have supported the conclusion that R285 is involved in RdpA's distinctive (*R*)-enantioselective activity because TfdA has (*S*)-

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enantioselectivity and 2,4-D is achiral. *See* EX1054, ¶ 74.

B. Neither the 2004/2005 Applications nor the prior art, including Schleinitz 2004, identified the structural features involved in RdpA's (*R*)-enantioselective activity

19. Neither the '555 patent specification as originally filed in October 2016, nor the 2004/2005 Applications to which it claims priority, ever identify which of RdpA's 295 amino acids are important to the claimed (*R*)-enantioselective activity. *E.g.,* EX1054, ¶¶ 74-75. Dr. Bollinger does not disagree with that opinion. Instead, he focuses on Schleinitz 2004. However, and contrary to Dr. Bollinger's opinion, the POSA would not have mistaken Schleinitz 2004's description of the generic αKG motif residues as "functionally important" to RdpA, *see* EX2015, ¶ 39 (citing Schleinitz 2004 (p. 5357)), as a statement that those residues are "functionally important" to RdpA's ability to act in an (*R*)-stereoselective manner on phenoxy auxin herbicides and (*R*)-FOPs. Although the conserved residues in the consensus motif are involved in the general αKG dioxygenase function (three residues coordinate the metal center, and the other residues interact with the α-ketoglutarate), those residues do not define the set of substrates that a particular αKG dioxygenase such as RdpA will use. As the challenged patents and 2004/2005 Applications emphasize, there is a difference between the (*R*)-enantioselective activity of RdpA, which degrades the herbicide substrates required by the claims, and the activities of other known αKG dioxygenases, including TfdA, which has (*S*)-enantioselective

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activity. EX1054, ¶ 73; EX1001 ('555 Pat.), 4:32-36, 4:39-42, 8:10-17, 17:62-66, 18:10-20, 50:58-67, 51:1-53:13, Figs. 6A-6B, Tbls. 3-4; *see* EX1004 ('052 Provisional Appl.), [0017], [0051], [0059]-[0060], [00168]-[00181], Figs. 6A-6B; Tbls. 3-4; EX1005 ('7893 Appl. & File History), [0018], [0074], [0085]-[0086], [00198]-[00211], Figs. 6A-6B, Tbls. 3-4. The POSA would not have mistaken Schleinitz 2004's description of the αKG motif residues, which are characteristics that RdpA *shares* with other αKG dioxygenases, to be a description of the characteristics that *distinguish* RdpA from other αKG dioxygenases lacking the claimed (*R*)-enantioselective activity, particularly given Schleinitz 2004's statements that "the basis of the enantiospecificity of the dichlorprop-cleaving enzymes is not known" and that "studies are needed to reveal the molecular basis of the substrate specificity and stereospecificity of RdpA and SdpA." EX1042 (Schleinitz 2004 (pp. 5362-5363)).

20. Dr. Bollinger suggests that the POSA could have relied on sequence alignments of orthologous proteins to identify which amino acids in RdpA's sequence are important to the claimed activity. EX2015, ¶¶ 46-51, 55-56. I disagree. The challenged patents do not include a sequence alignment or suggest that such an alignment indicates the features responsible for RdpA's (*R*)-enantioselective activity. The POSA would have understood from the challenged patents that a sequence alignment would not be of much use because, as noted above,

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they state that RdpA is the first αKG dioxygenase to be determined to have the claimed dual herbicide-degrading activity. While several bacterial species had RdpA genes, all of those genes encoded the identical amino acid sequence, including the two genes cited by Dr. Bollinger. EX2015, ¶ 71. As I explained in my first declaration, the genes encoding RdpA from *Delftia acidovorans* MC1 (formerly known as *Comomonas acidovorans* MC1) and *Rhodoferax* P230 encode the same amino acid sequence as *Sphingomonas herbicidovorans* RdpA. *See* EX1054, ¶ 55; EX1001 ('555 Pat.), 31:61-64; EX1042 (Schleinitz 2004 (p. 5362)). Because the amino acid sequences of the known RdpA orthologues with (*R*)-enantioselective activity were the same, the POSA would not expect that comparing them to one another would provide useful information about which residues were important to RdpA's (*R*)-enantioselective activity.

21. The sequence alignments on which Dr. Bollinger relies, Elkins Figure 5 and Schleinitz 2004 Figure 2, do not support Dr. Bollinger's opinions. Elkins Figure 5 does not include RdpA. EX1023 (Elkins (p. 5190 & Fig. 5)). Schleinitz 2004 Figure 2 compared RdpA to other αKG dioxygenases that lack the claimed (*R*)-enantioselective herbicide-degrading activity. EX1042 (Schleinitz 2004 (p. 5360 & Fig. 2)). That alignment identifies certain amino acids shared by RdpA and the other αKG dioxygenases, but, again, the POSA would not have understood the features responsible for RdpA's (*R*)-enantioselective activity to be features shared with other

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αKG dioxygenases lacking that activity. As recognized in Schleinitz 2004, it was not known which of the many differences between these sequences were responsible for RdpA's (*R*)-enantioselective activity. EX1042 (Schleinitz 2004 (pp. 5362-5363)).

22. Dr. Bollinger's reliance on three-dimensional structural features shared by αKG dioxygenases, such as the jellyroll folds discussed in Elkins, *see* EX2015 ¶ 70, suffers from similar flaws. Elkins does not discuss RdpA's sequence or structure, and a description of structural features common to other αKG dioxygenases is not a description of the structural features that distinguish RdpA from other αKG dioxygenases lacking the claimed (*R*)-enantioselective activity. The challenged patents do not provide any information on RdpA's three-dimensional structure or which aspects of that structure may be important to RdpA's (*R*)-enantioselective activity, and that information was not available in the prior art. The challenged patents note that "[v]arious properties and three-dimensional features of the protein can also be changed without adversely affecting the activity/functionality of the protein," but they fail to provide any further information that would identify the three-dimensional features contemplated by that statement. EX1001 ('555 Pat.), 38:6-8; *see* EX1004 ('052 Provisional Appl.), [00118]; EX1005 ('7893 Appl. & File History), [00144]. In order to understand which of RdpA's structural features were important to that activity, the POSA would have had to undertake a significant

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research project, such as the structural model and mutagenesis study we did for *Sphingomonas* RdpA and SdpA, EX1035 (Müller 2006), EX1054, ¶ 88, or the crystal structure of RdpA, which confirmed the importance of several key residues we had identified in Müller 2006, EX1054, ¶ 88, EX1019 (Chekan 2019). Likewise, Dr. Bollinger does not accurately characterize the situation when he suggests that the variant RdpA sequences in the claims would have been expected to have similar three-dimensional structure and therefore would have the same (*R*)-enantioselective activity. *See* EX2015, ¶ 105. The POSA would have understood that enzymes with similar three-dimensional structures can catalyze different reactions. *See, e.g.*, EX2053 (Nakajima 1998 (Abstract, pp. 4876, 4880-4881)) (two enzymes with "overall folding" that is "almost identical" catalyze reactions with opposite stereospecificities); ("Comparison of the two TR structures made clear that opposite reaction stereospecificities can be acquired in enzymes that have a conserved overall folding, by changing the amino acids in the substrate binding site").

23. Dr. Bollinger also offers the opinion that the POSA would have ascribed functional significance to the distances between the conserved amino acids in the consensus motif because they were believed to "strongly correlate[]" to substrate specificity. EX2015 ¶ 111; *see* EX2015, ¶¶ 66, 69, 74, 115, 149. I disagree that the POSA would have had that understanding.

24. To support his opinion, Dr. Bollinger cites Figure 2 of Schleinitz 2004,

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which shows that RdpA, TfdA, SdpA and TauD have the same distances between the first and second conserved residues (one amino acid), and between the fourth and fifth conserved residues (ten amino acids) of the αKG dioxygenase consensus motif. EX2015, ¶¶ 72-74; EX1042 (Schleinitz 2004 (p. 5360 & Fig. 2)). Only the distance between the second and third conserved residues in the consensus motif is different for each enzyme, with RdpA having 131 amino acids.[3] As I explained in my first declaration, the POSA would not have understood that the length of this region is responsible for enantioselectivity. EX1054, ¶¶ 98-102.

25. Contrary to Dr. Bollinger's view, Schleinitz 2004 supports my opinion: the authors never suggest a connection between the spacing of the consensus motif depicted in Figure 2 and the activities of RdpA or SdpA on different enantiomers. Instead, they conclude that the basis of RdpA's (*R*)-enantiospecificity is "unknown," that it is "likely that 2,4-D and dichlorprop-cleaving enzymes are structurally very similar and that substrate specificity is determined by only a few amino acids," and

[3] Dr. Bollinger states that "RdpA is the only enzyme in the alignment having no gaps, illustrating a difference in its active site motif as compared to other enzyme family members." EX2015, ¶ 74. The POSA would have recognized that the "gaps" in Figure 2 are merely a visual convention permitting the alignment of sequences of different lengths, and would not have considered them functionally significant.

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that "[s]ite-specific mutagenesis studies are needed to reveal the molecular basis of the substrate specificity and stereospecificity of RdpA and SdpA." EX1042 (Schleinitz 2004 (pp. 5362-63)). Figure 2 also shows that SdpA and TfdA, which are both (*S*)-enantioselective enzymes, have different spacings, further supporting my opinion that consensus motif spacing is not determinative of enantioselectivity. EX1042 (Schleinitz 2004 (p. 5360 & Fig. 2).

26. Dr. Bollinger also relies on a table of selected αKG dioxygenases from my 2004 review article, observing that two of the enzymes listed in the table, TauD and CarC, have different spacing and act on different substrates. EX2015, ¶¶ 66, 69; EX1025 (Hausinger 2004 (Table 1, p. 22)). I disagree with Dr. Bollinger's interpretation of my review. For example, he fails to mention that Table I includes multiple examples of enzymes having *identical* spacing in the consensus motif, but acting on different substrates. For example, TauD has the same spacing as the enzyme immediately below it, *Pseudomonas putida* AtsK, but TauD acts on taurine (2-aminoethanesulfonate) and AtsK acts on alkyl sulfates. EX1025 (Hausinger 2004 (Table 1, pp. 22, 39)). In addition, Table 1 includes other groups of plant enzymes with identical spacings that were known to catalyze different reactions and use different substrates: *Citrus unshiu* flavonol synthase, *Arabidopsis thaliana* ANS (anthocyanidin synthase), *Cucurbita maxima* gibberellin 7-oxidase, and *Cucurbita maxima* gibberellin 20-oxidase; *Caranthus roseus* desacetoxyvindoline-4-

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hydroxylase and *Petunia hybrida* flavanone 3,β-hydroxylase; and *Hyoscyamus niger* hyoscyamine 6,8-hydroxylase and tomato ACC oxidase (an enzyme that is related to the αKG dioxygenases, but does not require α-ketoglutarate). EX1025 (Hausinger 2004 (Table 1, pp. 22, 32-34, 36, 43)). As these examples show, my 2004 review does not support that a particular spacing "strongly correlates" to a unique set of substrates, or that the POSA would have assumed that αKG dioxygenases with identical spacing would have identical function.

27. I understand that Corteva has suggested in briefing to the Board that, at my deposition, I somehow acknowledged that Figure 2 of Schleinitz 2004 discloses the AAD-1 motif. I disagree with that characterization. During my deposition, I was asked to look at Elkins, and then asked about where the consensus motif residues were located in different enzymes in that paper, including TfdA. EX2016, 11:13-18:25. I was then asked to look at Figure 2 of Schleinitz 2004, where I identified in RdpA where the five amino acid residues of the consensus motif were located, as well as what the spacing was between the residues. EX2016, 22:1-26:14. Counsel for Corteva did not ask me whether Figure 2 or any other part of Schleinitz 2004 disclosed any kind of motif derived from RdpA, let alone whether Schleinitz 2004 disclosed the AAD-1 motif identified in the claims of the challenged patents, and I never agreed (and do not agree) that Schleinitz 2004 discloses such a motif.

[redacted]

C. The POSA would not agree that an 85% sequence identity threshold would describe a set of artificial variant sequences having the claimed (*R*)-enantioselective activity

28. Dr. Bollinger offers the opinion that the artificial variant sequences in the claims of the challenged patents would be expected to have the claimed function because they have at least 85% sequence identity. EX2015, ¶ 109. He asserts that 85% or more sequence identity "was recognized to be correlated to enzyme function and used for making enzyme variants that maintain function," and that "[s]killed artisans would therefore have expected AAD-1 enzyme variants to retain their dual herbicide degrading activity when they shared the common structural feature of having at least 85% sequence identity to SEQ ID NO: 9." EX2015, ¶ 109. He adds that "[a] skilled artisan would have considered the claimed set of AAD-1 enzymes as essentially the same enzyme with the same function based on their high sequence identity (85% or more) to SEQ ID NO: 9 and conserved AAD-1 motif." EX2015, ¶ 133. I disagree.

29. Contrary to Dr. Bollinger's opinion, the POSA would not have expected a set of artificial variant sequences to have the same activity as the original sequence simply because they meet a particular sequence identity threshold. The POSA would have recognized that the problem with using a sequence identity threshold in this manner, which Dr. Bollinger does not address, is that it treats each amino acid change as equivalent to, and interchangeable with, any other change. A

sequence identity cutoff does not account for which amino acids are changed or how they are changed (for example, if a substitution is conservative or non-conservative, or if an addition or deletion is made). *See* EX1054, ¶¶ 82-86. The POSA would have known that different types of changes at different locations in the sequence can have varied and unpredictable effects. EX1054, ¶ 90. Dr. Bollinger acknowledges this concept, stating, for example, that in his opinion the POSA would prefer to make changes that maintain similar charge or bulkiness. EX2015, ¶ 58. In addition, the POSA would have understood that it was critical to retain the amino acids that are important to RdpA's (*R*)-enantioselective activity. However, the sequence identity threshold does not distinguish those amino acids from the rest. The POSA would not know based on the 2004/2005 Applications or the prior art whether a given variant sequence retained those amino acids, because those amino acids are not identified in the application and were not known in the prior art, nor are they required by the claims to be maintained. EX1042 (Schleinitz 2004 (pp. 5362-5363)). Schleinitz 2004 taught that the (*R*)-enantioselective activity of RdpA was likely due to "only a few amino acids," EX1042 (Schleinitz 2004 (pp. 5362-5363)), which would reinforce for the POSA that one could not predict which of the variants with as many as 44 changes to the sequence (*i.e.*, 85% or more identity) would exhibit the claimed (*R*)-enantioselective activity. For these reasons, the POSA would not have been able to predict that a variant sequence would have the claimed (*R*)-

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enantioselective activity just because it has at least 85% sequence identity to RdpA. Nor would the POSA have been able to predict that a variant sequence would have the claimed (*R*)-enantioselective activity just because it has at least 85% sequence identity to RdpA and maintained the claimed AAD-1 motif. The POSA would not expect that the set of at least 20^{44} sequences with at least 85% sequence identity to RdpA would have the claimed (*R*)-enantioselective activity, or consider that set to be "essentially the same enzyme," irrespective of whether the sequences in that set were also required to maintain the claimed AAD-1 motif. *See* EX2015, ¶ 133.

30. Contrary to Dr. Bollinger's opinion, the challenged patents do not support the proposition that the POSA would have expected that any given variant sequence with at least 85% identity to RdpA would have the claimed (*R*)-enantioselective activity, irrespective of the nature of the changes in the sequence. The challenged patents instead recognize that, as the POSA would have known, the nature of the changes to a given variant matters. For example, the challenged patents state that "[c]onservative substitutions can be tolerated/made to not adversely affect the activity." EX1001 ('555 Pat.), 38:8-27; *see* EX1004 ('052 Provisional Appl.), [00118]; EX1005 ('7893 Appl. & File History), [00144]. However, the challenged patents further note, "Conservative substitutions whereby an amino acid of one class is replaced with another amino acid of the same type fall within the scope of the subject invention *so long as* the substitution is not adverse to the biological activity

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of the compound." *Id.* (emphasis added). In other words, the challenged patents recognize that conservative substitutions can be "adverse to the biological activity," but they do not specify in which cases that would happen, thereby leaving it up to the POSA to test each artificial variant to evaluate whether there has been an adverse change to the biological activity. *See* EX1054, ¶ 90. Similarly, the challenged patents state that "[i]n some instances, non-conservative substitutions can also be made." EX1001 ('555 Pat.), 38:28-31; *see* EX1004 ('052 Provisional Appl.), [00119]; EX1005 ('7893 Appl. & File History), [00145]. However, they do not identify the "instances" in which non-conservative substitutions can be made, further reinforcing for the POSA not only the unpredictability of whether sequences that have 85% or greater sequence identity to RdpA would have the claimed (*R*)-enantioselective activity, but also that extensive experimentation would be required to evaluate which artificial variants have the claimed (*R*)-enantioselective activity. As such, the notion that sequence identity alone can predict the function of an artificial variant (discussed in more detail in the context of Dr. Bollinger's reliance on Tian) is contradicted by the approach taken in the challenged patents, which provide that the type of substitution matters to the function of the variant.

31. Dr. Bollinger asserts that the POSA would have preferred to make certain types of changes when generating variant sequences such as amino acid changes that would maintain charge and steric bulk, and outlines a proposed process

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for preparing enzyme variants. *See* EX2015, ¶¶ 45, 52-59. Not only does Dr. Bollinger's proposed process describe an extensive research project, but his opinions ignore that the claims of the challenged patents are not limited to variant sequences with certain types of changes. The only limitations the claims place on amino acid substitutions are to retain the five or six amino acids required by the AAD-1 motifs, and to retain at least 85% sequence identity to RdpA (SEQ ID NO: 9). The claims do not require conservative substitutions, or substitutions that maintain charge or bulkiness or other properties. *See* EX1054, ¶ 78. Indeed, as noted above, the challenged patents explain that conservative substitutions may or may not be adverse to activity, and that in some instances non-conservative substitutions are acceptable, but they provide no further guidance as to particular substitutions that will preserve the claimed (*R*)-enantioselective activity of RdpA. EX1001 ('555 Pat.), 38:8-31; *see* EX1004 ('052 Provisional Appl.), [00118], [00119]; EX1005 ('7893 Appl. & File History), [00144], [00145].

32. The POSA's knowledge that the functional properties of an enzyme can be affected by changes as small as a single amino acid is demonstrated by prior art studies using mutagenesis to investigate the function of individual amino acids, such as our work in Hotopp 2002. It is also reflected in the testing performed by Corteva during prosecution of the '555 patent, which indicated that replacing the arginine at position 285 of RdpA eliminated activity against 2,4-D and (*R*)-quizalofop. EX1008

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[redacted]

('406 Appl. & File History), COR-AAD1-00000472-74 (Wright-I Decl. App'x III); EX1054, ¶ 97.

D. The POSA would not have extended Tian's findings to artificial RdpA variants

33. Dr. Bollinger relies on papers, in particular Tian, which discuss whether naturally occurring gene sequences discovered in genome sequencing projects and added to public databases could be annotated with predicted functions, based on inferences about these sequences' evolutionary relationships. EX2015, ¶¶ 83, 106, 123 (citing EX2019 (Tian)); *see also* EX2015, ¶¶ 30-35, 100-103 (citing EX2024 (Wilson); EX2026 (Devos); EX2027 (Todd); EX2028 (Rost 2002)). These studies conducted statistical analyses of sets of enzyme sequences that had been deposited in public databases. As an indicator of function, they relied on Enzyme Commission ("EC") numbers, a system of standardized nomenclature used to identify different biochemical reactions. *See* EX2015, ¶¶ 23, 101. Tian, which Dr. Bollinger states "consolidated and built upon the prior studies by Devos (EX2026), Wilson (EX2024), Todd (EX2027), and Rost (EX2028)," EX2015, ¶ 35, considered whether the percentage sequence identity between two protein sequences in a database could be used to predict whether they had been assigned to the same EC number, determining that "above 60% sequence identity is needed to have above 90% accuracy," EX2015 ¶ 101; EX2019 (Tian (p. 876)). Dr. Bollinger describes these database analyses as "foundational literature in the field for predicting function

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based on sequence identity," EX2015, ¶ 106, and offers the opinion that "Tian, Rost, and other researchers demonstrated that, for enzymes having 85% or more sequence identity, a skilled artisan would have expected conserved function," EX2015, ¶¶ 106, 109. I disagree. As explained below, the POSA would not have extended the conclusions of Tian regarding naturally occurring protein sequences to artificial RdpA variants as in the claims of the challenged patents.

34. First, the POSA would not have regarded Tian to be particularly informative because it does not address the structure or function of αKG dioxygenases. Even if the POSA had considered Tian or the other database analyses relied on by Dr. Bollinger, the POSA would have regarded them to be far less relevant than the studies we and other groups had published on enantioselective herbicide-degrading αKG dioxygenases, such as Saari 1998, Saari 1999, and Schleinitz 2004.

35. Second, the challenged patents do not cite or discuss Tian or the references it built upon, and would not have suggested to the POSA that they are relevant to RdpA variants. Dr. Bollinger notes that the challenged patents mention 60% sequence identity, EX2015, ¶¶ 83, 99, but nothing in the challenged patents points to Tian as the source of this number. Moreover, 60% is one of many sequence identity values listed, ranging from 49% to 99%, EX1054, ¶ 71; EX1001 ('555 Pat.), 37:36-55; *see* EX1004 ('052 Provisional Appl.), [00116]; EX1005 ('7893 Appl. &

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File History), [00142]. The fact that the challenged patents include percentage sequence identity values as low as 49% does not comport with Dr. Bollinger's opinion that the challenged patents are somehow referencing Tian, since Tian used 60% sequence identity as the lower limit.

36. Dr. Bollinger also refers to the discussion in the challenged patents of sequences with "85-98%" identity being "highly identical" and that "[t]raditionally only sequences with high homology would be expected to retain similar properties." EX2015, ¶¶ 83 (citing EX1001 ('555 Pat.), 44:26-29; EX1002 ('283 Pat.), 44:5-8; EX1003 ('745 Pat.), 44:20-23), 99 (citing EX1001 ('555 Pat.), 44:17-35; EX1002 ('283 Pat.), 43:63-44:9; EX1003 ('745 Pat.) 44:11-25). He offers the opinion that the discussion is somehow a reference to Tian and the earlier references it built upon. EX2015, ¶¶ 83, 99. I disagree. Tian does not discuss 85% or 85-98% sequence identity or recommend relying on such a threshold or range, which reflects the lack of any connection between Tian and the challenged patents. In addition, the POSA would recognize that the above discussion regarding 85-98% being "highly identical" is made in reference to proteins with generic "α-ketoglutarate dioxygenase activity" and not (*R*)-enantioselective activity in particular. EX1001 ('555 Pat.), 44:17-20; EX1002 ('283 Pat.), 43:63-66; EX1003 ('745 Pat.) 44:11-14); *see* EX1005, [00171('7893 Appl. & File History), [00171]. That would be reinforced for the POSA by the title of the example (Example 1), which is "Method for

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Identifying Genes that Impart Resistance to 2,4-D in Plants." EX1001 ('555 Pat.), 44:10-13; *see* EX1005, -0102 ('7893 Appl. & File History). Specifically, the fact that 2,4-D is an achiral substrate supports the notion that the discussion in the example refers to generic "α-ketoglutarate dioxygenase activity" and not (*R*)-enantioselective activity. Thus, the references to generic "α-ketoglutarate dioxygenase activity" and "Genes that Impart Resistance to 2,4-D" would further reinforce the absence of any connection between the above discussion and the claims of the challenged patents, the latter of which require (*R*)-enantioselective activity.

37. Third, Dr. Bollinger's suggestion that Tian and earlier database analyses represent "foundational literature in the field for predicting function based on sequence identity," EX2015, ¶ 106, ignores that they focused on a specific context that is not at issue here. As Dr. Bollinger acknowledges, Tian and earlier database analyses addressed the annotation of new protein sequences discovered through genome sequencing. *See* EX2015, ¶ 29 ("By the 2000s, genome sequencing was identifying new genes encoding proteins much faster than researchers could empirically determine the activities of those proteins."); EX2019 (Tian (pp. 863-864)) (explaining that Tian is directed to genome sequence annotation); EX2019 (Tian (p. 876)). Dr. Bollinger fails to mention that Tian expressly tailors its conclusion to the specific context of "function annotation on genome sequences." EX2019 (Tian (p. 876)) ("Our results suggest that ***for function annotation on***

genome sequences, . . . to transfer all four digits of an EC number, above 60% sequence identity is needed to have above 90% accuracy.") (emphasis added). Consistent with this stated purpose, Tian's conclusions were based on analyses of naturally occurring protein sequences, not artificial variants that had been generated by making changes to known sequences. The sequences Tian analyzed, for example, were a subset of the database Swiss-Prot. EX2019 (Tian (pp. 865, 876)). Swiss-Prot is a curated database of naturally occurring protein sequences that excludes synthetic or artificial sequences. EX1074 (Bairoch (p. 53)) ("Another category of data which will not be included in SWISS-PROT are synthetic sequences."); EX1075 (UniProt Website). Rost 2002, which Dr. Bollinger also focuses on, EX2015, ¶¶ 102-103, similarly analyzed a subset of sequences from the Swiss-Prot database, EX2028 (Rost 2002 (p. 605)).

38. This context is important because, as Dr. Bollinger explains, a typical enzyme is a product of evolution over a long time period. EX2015, ¶ 42. At a high level, evolution involves the survival of individual organisms with desirable properties, and the elimination of individual organisms with undesirable properties. The set of naturally occurring protein sequences that have survived to be expressed in organisms today, and would be included in Swiss-Prot, have undergone this process of natural selection. That set does not include all the variant sequences that have not survived, such as those with amino acid changes that led to a loss or

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reduction of enzyme activity. *See* EX2015, ¶ 42 ("any amino acid changes (mutations) appearing over time that disturbed the enzyme's overall structure or replaced amino acids that promoted the reaction would have led to a loss or reduction of the enzyme's activity, likely with negative consequences for the organism that depended on the enzyme").

39. The claims of the challenged patents, however, are not limited to naturally occurring RdpA proteins. They involve a much larger set of artificial sequences that could be generated by making changes to RdpA's sequence. As I explained in my first declaration, a rough lower estimate of the number of possible RdpA variants with an AAD-1 motif and any naturally occurring amino acid at 44 positions (just over 85% sequence identity to SEQ ID NO: 9) might be 20^{44}. EX1054, ¶ 79. This is a huge set of sequences that has not undergone natural selection or any other process that would eliminate variants with undesirable properties, such as inactive variants. In contrast, Tian's conclusions were based on a set of just 22,645 naturally occurring enzyme sequences. EX2019 (Tian (pp. 876-877)).

40. The POSA would have realized that it would not make sense to extend Tian's conclusions, which were based on naturally occurring protein sequences that have survived evolution, to a hypothetical set of artificially generated variants that have not undergone that process. That approach would wrongly extend conclusions

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from a biased set of amino acid sequences (*i.e.*, ones which had survived evolution) to a larger dataset of proteins that has not been subject to natural selection.

41. Tian and the Rost 2002 paper cited by Dr. Bollinger recognize the dangers of such database bias. The authors attempted to compensate for a different source of bias: the tendency for certain families of enzymes to be overrepresented or underrepresented in sequence data relative to the frequency with which those enzymes occur in nature. EX2028 (Rost 2002 (p. 596)) ("A principal problem of any database analysis is that of bias related to the experimental focus of the groups that deposit their information. . . . If we reduce the bias, we compare one representative of each family against all others."); EX2019 (Tian (Abstract, pp. 863-864, 871)) ("Thus, SWISSPROT is a biased database dominated by a few functional families"), ("the distribution of enzyme sequences in the SWISSPROT database is biased and different from that in a real genome"). The authors attempted to reduce this source of bias by adjusting their datasets to be more representative of the naturally occurring proteins that they sought to annotate: "If we want to estimate the accuracy in transferring function ***in the context of genome annotation***, we have to base our analysis on data sets that have a redundancy similar to that of entire proteomes." EX2028 (Rost 2002 (pp. 605-606)) (emphasis added); *see* EX2019 (Tian (Abstract, pp. 863, 873)) ("we employ a strategy similar to Rost's to reduce the database bias; however, we classify enzyme families based not only on sequence

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similarity, but also on functional similarity"). This does not mean, however, that their results can be further extended to artificial variant sequences (and the authors did not suggest doing so).

42. The POSA would have had additional reservations about extending the conclusions of Tian to variants of RdpA. As Dr. Bollinger emphasizes, Tian relied on sequences with EC classifications, using the EC classification as a proxy for function. EX2015, ¶¶ 30-35. Tian, for example, limited its analysis to a subset of sequences that had been assigned EC numbers, while excluding sequences that lacked EC numbers or that were assigned incomplete or multiple EC numbers. EX2019 (Tian (pp. 865, 876)). Due to this methodology, Tian would have excluded RdpA from its dataset: the EC numbers assigned to RdpA and SdpA were added to the list of EC numbers by amendment in 2013. EX1076, 11-12 (IUBMB Website) ("EC 1.14.11.43 (S)-dichlorprop dioxygenase (2-oxoglutarate) (22 October 2013); EC 1.14.11.44 (R)-dichlorprop dioxygenase (2-oxoglutarate) (22 October 2013)"). Tian's dataset also would have excluded TfdA, which has not been assigned a complete (four-digit) EC number. EX1077, 3 (UniProtKB P10088 TFDA_CUPPJ) ("EC:1.14.11.-"). Dr. Bollinger has not provided any reason to believe that RdpA or any other herbicide-degrading αKG dioxygenase was considered by Tian or any of the other papers.

43. Finally, Tian did not indicate, and the POSA would not assume, that

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each protein having the same EC number will degrade an identical set of substrates. As Dr. Bollinger states, a four-digit EC number typically specifies a chemical reaction on a particular substrate. EX2015, ¶ 23. However, the EC number does not specify the details of a particular protein's activity, such as the complete list of substrates it can use. Thus, "there may be considerable variation between two proteins of identical EC numbers." EX2028 (Rost 2002 (p. 605)) ("[T]he full EC number does not describe all the details about a particular function: there may be considerable variation between two proteins of identical EC numbers."). Tian affirmatively excluded "multifunctional" enzymes that had been assigned multiple EC numbers, and the authors did not describe any analysis of the remaining enzymes that could support the assumption that all the proteins assigned to a given EC number use the same set of substrates. That matters here because the claims of the challenged patents require degradative activity on multiple substrates (achiral phenoxy auxins like 2,4-D, (*R*)-phenoxy auxins, and (*R*)-FOPs).

44. As already noted, Tian itself states that its findings are applicable to the annotation of newly discovered genomic sequences, not artificial sequences. EX2019 (Tian (p. 876)) ("Our results suggest that ***for function annotation on genome sequences***, . . . to transfer all four digits of an EC number, above 60% sequence identity is needed to have above 90% accuracy.") (emphasis added). Dr. Bollinger does not cite any reference that applies Tian's conclusions (or the

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conclusions of Tian's predecessors) to a set of artificial sequence variants.

45. For similar reasons, the other papers cited by Dr. Bollinger do not support the notion that a sequence identity threshold could be used to predict the function of artificial RdpA variants. EX2015, ¶¶ 101-103. Like Tian, those papers addressed the evolutionary relationships between proteins identified through genome sequencing projects, and the challenges of annotating those sequences. *E.g.*, EX2028 (Rost 2002 (p. 605)) ("The differences between the biased and unbiased estimates impact estimates for errors in genome annotations."); EX2024 (Wilson (p. 245)) ("The sequence-structure and sequence-function relationships described here provide practical information for genome annotation in terms of folds and functions."); EX2026 (Devos (p. 106)) ("In addition to the practical implications for function annotation, the results presented here can be interpreted in terms of protein evolution."); EX2027 (Todd (Abstract, p. 1113)) (exploring "the mechanisms for generating functional diversity during evolution" and "[t]he implications of functional diversity within superfamilies for the structural genomics projects"). They considered EC numbers as a proxy for function, relied on information from Swiss-Prot and other databases which were dominated by naturally occurring protein sequences, and in most cases focused on sequences corresponding to known structures or particular protein families. EX2024 (Wilson (Abstract, pp. 233, 242)) (considering "~30,000 pairs of protein domains with known structure and

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function"); EX2027 (Todd (Abstract, pp. 1113, 1115, 1136-1137)) (considering sequences from "enzyme superfamilies for which structural data are available" and noting that "[o]ur work depends upon both the reliability of annotation in SWISS-PROT, and the accuracy of crystal structure and mutagenesis studies from which catalytic residues and reaction mechanisms are inferred"); EX2028 (Rost 2002 (p. 605)) (relying on sequences from Swiss-Prot); EX2026 (Devos (pp. 99-100) (relying on "7,162 alignments . . . selected" from a protein structure alignment database and EC numbers or functional keywords from Swiss-Prot). As such, these studies are no more generalizable to artificially generated variant sequences than Tian.

46. Dr. Bollinger's only cited support for the proposition that the POSA would have applied a sequence identity threshold to "new protein variants" is Minshull, an article published around April 2005. EX2015, ¶¶ 52, 107, 109; EX2025 (Minshull 2005). However, I disagree that Minshull suggests that the POSA would have extended the findings of Tian or the articles it builds upon to artificial variants.

47. Minshull does not refer to Tian or otherwise suggest that Tian's 60% threshold of sequence identity could be used to predict the function of an artificially generated variant sequence. Minshull observes that evolutionarily related proteins (homologues) with similar functions can be useful as inputs (or "donors") for protein engineering, such as through the use of DNA shuffling. EX2025 (Minshull (pp. 203-

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204)). Minshull states that "orthologous protein[]" sequences, naturally occurring sequences with shared evolutionary ancestry that catalyze the same reaction, "are thus a potentially rich source of information regarding sequence changes that are acceptable without drastically disrupting protein function." EX2025 (Minshull (pp. 202-03)). But Minshull observes that "***[p]rediction of protein function from sequence and structure is a difficult problem***, because homologous proteins often have different functions." EX2025 (Minshull (p. 203)) (emphasis added). Minshull further observes that, "[i]n the absence of ***reliable*** functional assignments," "the simplest method for identifying potential donors" for a protein engineering research project is to look for sequences "with reasonable amino acid identity." EX2025 (Minshull (p. 204)) (emphasis added) (citing Todd, discussed above).

48. Minshull's discussion of evolutionarily related sequences as possible inputs or "donors" for an extensive protein engineering research project would not have suggested to the POSA that one could use a sequence identity threshold to predict the function of artificially generated variant sequences. The passage Dr. Bollinger cites about "orthologous" sequences is discussing naturally occurring proteins, not artificial variants, and Minshull recognizes that, even then, predicting protein function is a "difficult problem." (Minshull (pp. 202-03)). Minshull recognizes that artificially generated variants (for example, through the use of DNA shuffling) had to be screened for activity. *E.g.*, EX2025 (Minshull (pp. 202-03))

("[L]ibraries of 10,000 or more recombinants must typically be screened to identify those with useful improvements. High-throughput screening of protein function itself presents some problems, primary amongst which is the frequent lack of good correlation between a screen that is simple and one that accurately predicts function under application conditions."). Thus, Minshull illustrates that the POSA would not have relied on a sequence identity threshold to predict the activity of artificially generated variants.

49. I note that Dr. Bollinger also cites prior art referring to a "twilight zone" where it is difficult to tell if naturally occurring proteins evolved from a common ancestor based on a comparison of their amino acid sequences. EX2015, ¶ 28 (citing EX2021 (Rost 1999 (p. 85)), EX2023 (Chung (p. 1123))). The cited literature discusses the use of sequence comparisons to illuminate the "evolutionary relatedness of proteins," not to predict the function of artificially generated variants. *See* EX2023 (Chung (p. 1123)) ("The twilight zone is an operationally defined term. It represents a range of sequence identity that sets the boundary of confidence levels for detecting evolutionary relatedness of proteins in sequence alignment analysis."); EX2021 (Rost 1999 (p. 85)) (contrasting a "midnight zone" of proteins "that may have become similar by convergent or divergent evolution" with the "twilight zone" and asking "is the twilight zone defined by a particular feature of evolution?"); EX2024 (Wilson (p. 234)) ("the 'twilight zone,' the region of sequence similarity

that does not reliably imply structural homology").

50. I understand that Corteva has suggested in a brief to the Board that, at my deposition, I indicated I was "not surprised" that enzymes with about 60% sequence identity had the same function, and that this somehow supports the use of a sequence identity threshold to predict variant function. I disagree with that characterization of my testimony. At my deposition, I was asked about a paper I published in 1993 which notes that Fe-protein sequences identified in five species are approximately 60% identical. EX2016, 70:18-72:19; EX2043 (Hausinger 1993 (pp. 13486-13487)). Referring to this paper, counsel for Corteva asked if it was "surprising to you to see that proteins having 60 percent identity had the same function," and I responded that "I was not surprised that these enzymes had this level of sequence identity." EX2016, 72:13-72:19. Counsel for Corteva did not ask me why I was not surprised, but the reason is that this particular enzyme family is believed to be very old. The members of the family are distantly related over millions of years of evolution, which has allowed the sequences to diverge while retaining activity. *See* EX1083 (Weiss) (suggesting that a nitrogenase enzyme was present in the last universal common ancestor). Counsel for Corteva did not ask me if I agree that a threshold of 60% sequence identity can be used to predict the function of artificially generated variant sequences, and my opinion is that a threshold cannot be used in this way.

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[redacted]

E. The prior art showed that herbicide degrading αKG dioxygenases with at least 85% sequence identity can have different enantioselectivities

51. In addition to the issues discussed above, Saari 1998 and Saari 1999 would have caused the POSA not to extend Tian's conclusions to the RdpA variants in the claims of the challenged patents. The Saari references reported that enantioselective herbicide-degrading αKG dioxygenases with sequence identities of at least 85% had different enantioselectivities. EX1041 (Saari 1999 (Abstract, pp. 421, 426-427)); EX1040 (Saari 1998 (Abstract, pp. 71-74, 86-94)); EX1054, ¶¶ 54, 90-91, 109. That is consistent with the discussion in Schleinitz 2004 that while "[t]he basis of the enantiospecificity of the dichlorprop-cleaving enzymes is not known," it is "likely" that "substrate specificity is determined by only a few amino acids." EX1042 (Schleinitz 2004 (pp. 5362-5363)). The POSA would have considered studies of enantioselective herbicide-degrading αKG dioxygenases such as Saari 1998, Saari 1999, and Schleinitz 2004 to be more relevant and informative to the claimed RdpA variants than any "general rule" derived from Tian or the papers it built upon. The POSA would not have ignored this information and simply assumed that a sequence with at least 60% identity to RdpA would have the claimed (*R*)-enantioselective activity, or that a sequence with at least 85% identity to RdpA would have the claimed (*R*)-enantioselective activity, as Dr. Bollinger suggests, irrespective of whether those sequences also maintained the AAD-1 motif set forth

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[redacted]

in the claims. *See* EX2015, ¶¶ 109, 123.

52. Dr. Bollinger offers three general criticisms of Saari 1999. First, he states that "Saari 1999 never specifically attributed (*R*)-enantioselective activity to the *A. denitrificans* enzyme sequence that they presented." EX2015, ¶ 125. Dr. Bollinger is mistaken, because Saari 1999 does attribute the (*R*)-enantioselective activity to the *A. denitrificans* sequence. For example, the Abstract states:

> Although the *A. denitrificans* activity exhibited stereospecificity opposite to that of the JMP134 and RASC strains, its cofactor requirements were found to be characteristic of an a-KG-dependent dioxygenase. ***A PCR amplification product from the DNA of this strain was shown to encode an amino acid sequence that was 95% and 86% identical to the corresponding region of TfdA in RASC and JMP134, respectively. Thus, closely related herbicide-degrading gene products appear to be capable of exhibiting opposite stereochemical degradative capabilities.***

EX1041 (Saari 1999 (Abstract, p. 421)) (emphasis added).

53. Second, Dr. Bollinger suggests that Saari's conclusions are somehow unsupported because "the only functional characterization of the (*R*)-enantioselective activity in *A. denitrificans* involved the use of cell extracts," as opposed to purified recombinant enzymes. EX2015, ¶ 125. I disagree that the POSA would have discounted our findings on this basis. The POSA would have appreciated that cell extracts are commonly used when purified proteins are not

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available. *E.g.*, EX1036 (Nickel 1997); EX1031 (Kohler 1999); EX1001 ('555 Pat.), 22:11-22, 46:8-28. In addition, we employed several different approaches to ensure that the activity we reported was due to an (*R*)-enantioselective herbicide-degrading αKG dioxygenase.

54. As I observed during my deposition, care must be taken when using cell extracts in colorimetric assays, because if other substances are present they could potentially give false readings due to nonspecific activity. EX2016, 41:19-43:12; EX2015, ¶ 127. For this reason, the study reported in Saari did not rely solely on colorimetric assays. We also used high-performance liquid chromatography ("HPLC") to quantify the substrate (*R*)-dichlorprop as it was degraded. EX1041 (Saari 1999 (pp. 425-427 & Fig. 4)) ("Dichlorprop was quantitated by using chiral HPLC"). We varied the iron and cofactor concentrations to confirm that the *A. denitrificans* herbicide-degrading activity displayed the hallmarks of an αKG dioxygenase, EX1041 (Saari 1999 (p. 426)) ("The *A. denitrificans* activity was dependent on α-KG and ferrous ion, and was rapidly lost (in 2 min) in the absence of ascorbic acid. These cofactor requirements are characteristic of α-KG-dependent dioxygenases"), and we confirmed that the herbicide-degrading activity we observed was selective for the substrate (*R*)-dichlorprop, EX1041 (Saari 1999 (pp. 425-427 & Fig. 4)); *see* EX1040 (Saari 1998 (pp. 71-89)). These techniques served to confirm that we were not seeing nonspecific activity due to other substances in the extract.

Dr. Bollinger did not address these aspects of Saari or explain why he thinks the POSA would have considered them deficient. *See* EX2015, ¶ 125. He also does not point to any scientific evidence that would suggest that the (*R*)-enantioselective *A. denitrificans* activity is attributable to a protein encoded by a different amino acid sequence than the protein we identified in Saari, and I am not aware of any such scientific evidence.

55. Third, Dr. Bollinger offers the opinion that his criticisms of Saari find support in Vedler and Schleinitz 2004. EX2015, ¶¶ 128-129. I disagree. As I noted in my first declaration, Vedler provided the full-length sequence of the *A. denitrificans* TfdA-like protein we had identified. EX1054, ¶ 109. Vedler did not perform any functional characterization of that enzyme or offer any findings inconsistent with ours. Instead, Vedler simply made a prediction that the *A. denitrificans* TfdA-like protein would have TfdA-like activity based on its percentage sequence identity compared to that of other TfdA enzymes. EX1046 (Vedler (pp. 7162-7165 & Table 1)). Vedler never cites Saari, much less criticizes Saari's findings, and Vedler never suggests that predictions based on sequence data are more reliable than Saari's biochemical assays. To the contrary, Vedler would have reinforced for the POSA the problem with relying on sequence identity to predict function.

56. Likewise, Schleinitz 2004 did not state that Saari 1999's conclusions

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were somehow unreliable or present inconsistent data. As already discussed above, the authors of Schleinitz 2004 reached conclusions about RdpA that are entirely consistent with Saari's conclusions: They agreed that the enantioselectivity of herbicide-degrading αKG dioxygenase enzymes likely depends on a relatively small number of unidentified amino acids in the sequence. *See* EX1042 (Schleinitz 2004 (pp. 5362-5363)) ("the basis of the enantiospecificity of the dichlorprop-cleaving enzymes is not known"), (it is "likely . . . that substrate specificity is determined by only a few amino acids"), ("studies are needed to reveal the molecular basis of the substrate specificity and stereospecificity of RdpA and SdpA"); EX1041 (Saari 1999 (Abstract, pp. 421, 427)) ("closely related herbicide-degrading gene products appear to be capable of exhibiting opposite stereochemical degradative capabilities"), ("the ability for closely related enzymes to recognize opposite stereoisomers has precedent. . . . closely related enzymes exhibit opposite substrate stereoselectivities due to differences in a few charged residues at the active site"); EX1054, ¶ 91. Thus, rather than undermining Saari 1999 as Dr. Bollinger suggests, Schleinitz 2004 would have reinforced to the POSA that sequence identity cannot be used to predict the (*R*)-enantioselective activity required by the claims of the challenged patents. The POSA would have understood Schleinitz 2004's observation that our findings in Saari were "not supported by *tfdA* expression studies or amino acid sequences of the *R*-dichlorprop cleaving dioxygenase" in context, as recognizing that additional

[redacted]

investigation remained to be done on the *A. denitrificans* enzyme we had discussed in Saari.[4] EX1042 (Schleinitz 2004 (p. 5362)).

57. I disagree with Dr. Bollinger that because RdpA and SdpA have approximately 30% sequence identity, Saari 1999 "has essentially no bearing on RdpA (AAD-1)." EX2015, ¶ 124. Saari 1999 was one of the few prior art papers reporting (*R*)-enantioselective herbicide-degrading αKG dioxygenase activity. The POSA would have considered the findings in Saari 1999 (and Saari 1998) highly relevant to RdpA, the only other (*R*)-enantioselective herbicide-degrading αKG dioxygenase reported in the prior art. The POSA would have understood from Saari that herbicide-degrading αKG dioxygenases with sequence identities of at least 85% could have opposite stereoselectivity and that reaction stereochemistry depends on relatively few amino acids. EX1041 (Saari 1999 (Abstract, pp. 421, 427)) ("closely related herbicide-degrading gene products appear to be capable of exhibiting opposite stereochemical degradative capabilities"), ("the ability for closely related enzymes to recognize opposite stereoisomers has precedent. . . . closely related enzymes exhibit opposite substrate stereoselectivities due to differences in a few

[4] The discussion at EX2015, ¶ 129 appears to incorrectly equate *D. acidovorans*, discussed on p. 5357 of Schleinitz 2004, with *A. denitrificans*. They are two different bacterial species.

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charged residues at the active site"). This information would be relevant to the POSA on the question of whether the challenged patents described the set of (*R*)-enantioselective herbicide-degrading αKG dioxygenase enzymes having at least 85% sequence identity. Because neither the challenged patents nor the 2004/2005 Applications identify any amino acids that were responsible for RdpA's (*R*)-enantioselective activity, and because the amino acids responsible for such activity were not known in the prior art, *see* EX1042 (Schleinitz 2004 (pp. 5362-5363)), the POSA had no way to know without trial-and-error experimentation whether any given variant with at least 85% identity to RdpA would degrade (*R*)-herbicides, as required by the claims. If anything, the large number of differences between the RdpA and SdpA amino acid sequences would have made it harder, not easier, to identify the amino acids that are important to RdpA's (*R*)-enantioselective activity. Dr. Bollinger never asserts, and neither the challenged patents nor the prior art could support, that the POSA would have believed that *only* variants with 30% identity to RdpA or less could have (*S*)-enantioselective activity. Saari reported that TfdA-like sequences with much greater percentage sequence identity had opposite enantioselectivity, and Schleinitz 2004 supported that conclusion, stating that the different activities of RdpA and SdpA were "likely" attributable to "a few amino acids." EX1042 (Schleinitz 2004 (pp. 5362-5363)).

58. Dr. Bollinger's opinions are further negated by the fact that our findings

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[redacted]

in Saari 1998 and Saari 1999 had precedent in the prior art. To illustrate this, we cited work by Nakajima et al., which demonstrates how reaction stereochemistry can depend on only a handful of amino acids. EX1041 (Saari 1999 (pp. 427-428)); EX2053 (Nakajima 1998). Dr. Bollinger acknowledges that the two TR enzymes discussed in Nakajima share 64% sequence identity, but catalyze reactions with opposite stereochemistry. EX2015, ¶ 123. However, Dr. Bollinger suggests that this information is not relevant because 64% is "well below the 85% minimum sequence identity disclosed in" the challenged patents. EX2015, ¶ 123. I disagree with that opinion.

59. First, Nakajima 1998 demonstrates why the POSA would not have relied on the 60% sequence identity threshold discussed in Tian in the way proposed by Dr. Bollinger. Tian itself indicates that even though the TR enzymes discussed in Nakajima have greater than 60% sequence identity, they have different EC numbers and functions. EX2019 (Tian (pp. 880-882 & Table A1)):

Global sequence identity 60–70%				
1.1.1.1 (Alcohol dehydrogenase)	1.1.1.2 (Alcohol dehydrogenase ($NADP^+$))	ADH1_ALLMI	ADH4_RANPE	62
1.1.1.149 (20-α-Hydroxysteroid dehydrogenase)	1.1.1.188 (Prostaglandin-F synthase)	PE2R_RAT	PGF2_BOVIN	67
1.1.1.149 (20-α-Hydroxysteroid dehydrogenase)	1.1.1.50 (3-α-Hydroxysteroid dehydrogenase (B-specific))	PE2R_RAT	DIDH_RAT	67
1.1.1.149 (20-α-Hydroxysteroid dehydrogenase)	1.3.1.20 (*trans*-1,2-Dihydrobenzene-1,2-diol dehydrogenase)	PE2R_RAT	DBDD_HUMAN	68
1.1.1.188 (Prostaglandin-F synthase)	1.1.1.50 (3-α-Hydroxysteroid dehydrogenase (B-specific))	PGF2_BOVIN	DIDH_RAT	69
1.1.1.206 (Tropine dehydrogenase)	1.1.1.236 (Tropinone reductase)	TRN1_DATST	TRN2_DATST	61
1.1.1.27 (L-lactate dehydrogenase)	1.1.1.37 (Malate dehydrogenase)	LDH_BOTBR	MDH_RHILV	68
1.1.1.50 (3-α-Hydroxysteroid dehydrogenase (B-specific))	1.3.1.20 (*trans*-1,2-Dihydrobenzene-1,2-diol dehydrogenase)	DIDH_RAT	DBDD_HUMAN	69
1.13.11.31 (Arachidonate 12-lipoxygenase)	1.13.11.33 (Arachidonate 15-lipoxygenase)	LOXE_MOUSE	LOX1_HUMAN	66

Thus, the POSA would have recognized that Tian's 60% sequence identity threshold

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does not apply to these enzymes.[5]

60. Second, Nakajima 1998 does not support the proposition that the difference in the TR enzymes' activities is due to having an overall sequence identity of less than 85%. Based on the x-ray crystal structures of the two TR enzymes and additional structural modeling work, the authors concluded that the TR enzymes' overall structure was almost identical, so the reaction stereochemistry likely depended on less than a dozen amino acids involved in substrate binding. EX2053 (Nakajima 1998 (Abstract, pp. 4876, 4878-4879 & Fig. 3, 4880-4881)). Thus, Nakajima indicates that the difference in activity is due to less than 11 amino acids, which is less than 5% of each TR enzyme's amino acid sequence. EX2053 (Nakajima 1998 (p. 4879 & Fig. 3)); *see* EX1078 (Nakajima 1999 (p. 16563)). In June 1999, around the same time we published Saari 1999, the same research group reported the results of a follow-up study involving site-directed mutagenesis of the TR enzymes. EX1078 (Nakajima 1999). They reported that "[s]ubstitution of five amino acid residues resulted in an almost complete reversal of stereospecificity."

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[5] Tian Table A1 provides a "global identity" of 61% for the TR enzymes, while Nakajima 1998 provides a value of 64%. EX2053 (Nakajima 1998 (Abstract, p. 4876)). As Tian recognizes, sequence identity can be calculated in multiple ways, EX2019 (Tian (p. 865)), but both values exceed the 60% threshold in Tian.

EX1078 (Nakajima 1999 (Abstract, p. 4876)). This reinforces the work reported in Nakajima 1998 and demonstrates that variant sequences differing by just 5 amino acids (approximately 2% of each TR enzyme's sequence) can catalyze different reactions.

61. Dr. Bollinger tries to discount this precedent by asserting that the POSA would have viewed Nakajima as a "rare exception[]" to the "general rule." EX2015, ¶ 123. He does not cite any support for that characterization, and I disagree with his opinion. It was well known in 2004-2005 that stereospecificity can depend on a few amino acids. *E.g.*, EX1079 (Valmsen); EX1081 (Ijima); *see also* EX1082 (Baerga-Ortiz) (published 2006); EX1080 (Coffa) (published September 2005). From such literature, the POSA would have understood that variants with 85% or more sequence identity can catalyze different reactions. Saari 1998 and Saari 1999 demonstrated that this principle applies in the particular context of enantioselective herbicide-degrading αKG dioxygenases, and the discussion in Schleinitz 2004 regarding the amino acids responsible for RdpA's (*R*)-enantioselectivity supports that understanding.

F. The challenged patents do not disclose representative species

62. Dr. Bollinger offers the opinion that the "AAD-1 enzymes" in the challenged patents "would have been considered representative of the AAD-1 enzymes of the claims, which is further confirmed by the consistent conservation of

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the AAD-1 motif and high (89-90%) sequence identity in Bayer's FT (AAD-1) enzymes." EX2015, ¶¶ 136-137. As I explained in my first declaration, I disagree that the sequences in the challenged patents are representative of the claimed "AAD-1 proteins." EX1054, ¶¶ 81-87. In addition, I disagree with Dr. Bollinger that Bayer/Monsanto's work suggests otherwise.

63. While Dr. Bollinger cites Larue 2019 (EX1052), the six FT sequences he discusses were published several years earlier, on April 21, 2016, in a Bayer/Monsanto patent application. EX1017 ("April 2016 publication"). The April 2016 publication predated Corteva's October 2016 submission of claims to proteins defined by an "AAD-1 motif" and 85% sequence identity. EX1054, ¶¶ 60-62. Figures 6A-6E of the April 2016 publication include the amino acid sequence of RdpA (SEQ ID NO:60) and twenty-two engineered amino acid sequences. EX1017, Figs. 6A-6E, [0020]. As I have indicated in the attached annotated copy of Figures 6A-6E (EX1084), and as shown in the excerpt below, the engineered amino acid sequences in Figs. 6A-6E include the six FT sequences cited by Dr. Bollinger (FT_5, FT_T, FT_R, FT_C, FT_Tv3, and FT_Tv7):

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RdpA     SEQ ID NO:60   MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:1    MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLSDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:4    MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQQIAF 70
         SEQ ID NO:7    MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLSDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:9    MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLSDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
FT_5     SEQ ID NO:11   MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
FT_T     SEQ ID NO:14   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
FT_R     SEQ ID NO:18   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:22   MHAALSPLSQRFERIAVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:25   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
FT_C     SEQ ID NO:28   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:31   MHAALSPLSQKYRFIDVQPLTGVLGAEITGVTLREPLDDNTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:34   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:37   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:40   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPAQQITNEQHISF 70
         SEQ ID NO:43   MHAALTPLTNKYRFIDVQPLCGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:46   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
FT_Tv3   SEQ ID NO:47   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:48   MHAALTPLTNKYRHIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:49   MHAALTPLTNKYRHIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:50   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
FT_Tv7   SEQ ID NO:51   MHAALTPLTNKYRFIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70
         SEQ ID NO:52   MHAALTPLTNKYRHIDVQPLTGVLGAEITGVDLREPLDDSTWNEILDAFHTYQVIYFPGQAITNEQHIAF 70

         Consensus      MHAAL·PL·····I·VQPLtGVLGAEITGVdLREPLdDsTWNEILDAFHTYQVIYFPgQaITNEQhIaF 70
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FIG.6A

EX1084; *see* EX1017, Figs. 6A-6E; EX1052 (Larue 2019 (p. 2088)); EX2015, ¶¶ 136-137; EX2061. I have highlighted the residues in the six FT sequences (but not the other sixteen sequences) that differ from the residues in RdpA; these are the same modifications depicted in Dr. Bollinger's sequence alignment (EX2061). EX1084; EX2061.

64. As Dr. Bollinger emphasizes, the Bayer/Monsanto FT enzymes in the April 2016 publication have approximately 89%-90% sequence identity to RdpA, EX2015, ¶¶ 136-137; in contrast, the sequences in the challenged patents are approximately 99% identical to RdpA, EX1054, ¶¶ 82-83 (citing EX1008 ('406

[redacted]

Appl. & File History), COR-AAD1-00000471 (Wright-I Decl. App'x II)). As explained in the April 2016 publication and Larue 2019, the Bayer/Monsanto FT enzymes resulted from extensive research performed by Bayer/Monsanto scientists. That work involved mutagenesis, making and testing thousands of amino acid sequences and performing multiple rounds of screening, and generating crystal structures. *See* EX1017, [0065]-[0074], [0081]-[0094]; EX1052 (Larue 2019 (pp. 2087-2092)).

G. Corteva's internal data

65. In my first declaration, I explained that during the prosecution of the application that issued as the '555 patent, one of the named inventors, Dr. Terry Wright, submitted two declarations to the Patent Office. EX1054, ¶ 97. Dr. Wright's first declaration, dated April 10, 2019, included test results for nine "AAD-1 variants," designated as "Seq 01" through "Seq 09," with "~94-95%" sequence identity to "AAD-1 (SEQ ID NO: 9)." EX1008 ('406 Appl. & File History), COR-AAD1-00000462-63, COR-AAD1-00000472-74 (Wright-I Decl. ¶¶ 14-15, App'x III); EX1054, ¶ 97. In Seq 01, Seq 02, and Seq 03, the "AAD-1 motif" from claim 2 was "intact." *Id.* In Seq 04 through Seq 09, the "AAD-1 motif" from claim 2 was modified by substituting one of the required amino acids with a different amino acid ("single aa change to motif residues"). *Id.*

66. The document at pp. 433-44 of EX2002 is [redacted]

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[redacted]

[redacted] EX2002, pp. 433-44. This document shows that [redacted] EX2002, pp. 434. [redacted] *Id.* [redacted] EX2002, p. 434; *see* EX1008, COR-AAD1-00000472-74 (Wright-I Decl. App'x III).

67. The [redacted] document indicates that [redacted]

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[redacted]

[redacted]

EX2002, pp. 435-437.

68. For the reasons explained in my first declaration and above, the POSA would conclude that Corteva's named inventors did not have possession of the claimed "AAD-1" proteins prior to at least October 7, 2016, even without reviewing Corteva's internal documents. Nevertheless, Corteva's internal documents would

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[redacted]

further reinforce the POSA's conclusion in that regard.

IV. GROUNDS IIA-IIB

69. Dr. Bollinger offers the opinion that "[a]s of 2004-2005, a person of ordinary skill in the art would not have reasonably expected that RdpA could degrade FOP herbicides, which are a unique class of herbicides compared to phenoxy auxins." EX2015, ¶ 144. In support of that opinion, he notes that "FOPs are significantly larger than phenoxy auxins" and adds that "[t]he additional steric bulk in the FOPs would have led a person of skill in the art to doubt that an enzyme that efficiently degrades a phenoxy auxin would also degrade a FOP." EX2015, ¶ 145. As discussed in Sections III.A-III.B above, neither the challenged patents nor the prior art identify the amino acids responsible for RdpA's (*R*)-enantioselective activity, and therefore the POSA would have lacked information critical to understanding which RdpA variants with at least 85% identity to RdpA and the claimed "AAD-1 motif" would have the function required by the challenged claims. In addition, the challenged patents fail to explain how the differences in size between phenoxy auxin herbicides and (*R*)-FOPs, which Dr. Bollinger focuses on, are accounted for in preparing such variants in order for a given variant to have the activity required by the challenged claims.

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[redacted]

70. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

71. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: July 1, 2024

Robert P. Hausinger

Robert P. Hausinger, Ph.D.

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APPENDIX 1

[redacted]

TABLE OF EXHIBITS

Exhibit No.	Short Citation	Full Citation
EX1001	’555 Pat.	U.S. Patent No. 10,947,555
EX1002	’283 Pat.	U.S. Patent No. 11,149,283
EX1003	’785 Pat.	U.S. Patent No. 11,299,745
EX1004	’052 Provisional Appl.	U.S. Provisional Application No. 60/567052
EX1005	’7893 Appl. & File History	U.S. Application No. 11/587893 and File History
EX1006	’813 Appl. & File History	U.S. Application No. 12/951813 and File History
EX1007	’0893 Appl. & File History	U.S. Application No. 14/820893 and File History
EX1008	’406 Appl. & File History	Certified U.S. Application No. 15/288,406 and File History
EX1009	’824 Appl. & File History	U.S. Application No. 17/143,824 and File History
EX1010	’966 Appl. & File History	Certified U.S. Application No. 17/175,966 and File History
EX1011	’476 Appl. & File History	Certified U.S. Application No. 17/403,476, and File History

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Exhibit No.	Short Citation	Full Citation
EX1012		Accession No. AAS49436.1, submitted Feb. 04, 2004
EX1013	Schleinitz	Accession No. AF516751, published Aug. 6, 2002
EX1014		Accession No. AF516752, published Aug. 6, 2002
EX1015		Accession No. AJ628856, published March 3, 2004
EX1016		Accession No. Q8KSC8, published Oct. 1, 2002
EX1017	April 2016 Publication	U.S. Patent Pub. No. 2016/0108422
EX1018	Bayley 1992	C. Bayley et al., *Engineering 2,4-D Resistance into Cotton*, 83 THEORETICAL & APPLIED GENETICS 645-649 (1992)
EX1019	Chekan 2019	J.R. Chekan et al., *Molecular Basis for Enantioselective Herbicide Degradation Imparted by Aryloxyalkanoate Dioxygenases in Transgenic Plants*, 27 PROC. NAT'L ACAD. SCI. 13299-13304 (2019)
EX1020	Chekan 2019 Suppl. Info.	J.R. Chekan et al., Supplementary Information, *Molecular Basis for Enantioselective Herbicide Degradation Imparted by Aryloxyalkanoate Dioxygenases in Transgenic Plants*, 27 PROC. NAT'L ACAD. SCI. 13299-13304 (2019)
EX1021	Corteva '437	U.S. Patent Pub. No. 2005/107437
EX1022	Cutler 1999	BIOLOGICALLY ACTIVE NATURAL PRODUCTS: AGROCHEMICALS (H.G. Cutler & S.J. Cutler, eds. 1999)

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EX1023	Elkins 2002	J.M. Elkins, R.P. Hausinger et al., *X-ray Crystal Structure of* Escherichia coli *Taurine/α-Ketoglutarate Dioxygenase Complexed to Ferrous Iron and Substrates*, 41 BIOCHEMISTRY 5185-5192 (2002)
EX1024	Fukumori & Hausinger 1993	F. Fukumori & R.P. Hausinger, Alcaligenes Eutrophus *JMP134 "2,4-Dichlorophenoxyacetate Monooxygenase" Is an α-Ketoglutarate-Dependent Dioxygenase*, 175 J. BACTERIOLOGY 2083-2086 (1993)
EX1025	Hausinger 2004	R. Hausinger, *Fe(II)/α-Ketoglutarate-Dependent Hydroxylases and Related Enzymes*, 39 CRIT. REV. BIOCHEM. MOLECULAR BIO. 21-68 (2004)
EX1026	Hee 1981	S.S.Q. Hee & R.G. Sutherland, I PHENOXYALKANOIC HERBICIDES: CHEMISTRY, ANALYSIS, AND ENVIRONMENTAL POLLUTION (1981)
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EX1028	Hotopp 2001	J.C. Dunning Hotopp & R.P. Hausinger, *Alternative Substrates of 2,4-Dichlorophenoxyacetate/α-Ketoglutarate Dioxygenase*, 15 J. MOLECULAR CATALYSIS B: ENZYMATIC 155-162 (2001)
EX1029	Hotopp 2002	J.C. Dunning Hotopp & R.P. Hausinger, *Probing the 2,4-Dichlorophenoxyacetate/α-Ketoglutarate Dioxygenase Substrate Binding Site by Site-Directed Mutagenesis and Mechanism-Based Inactivation*, 41 BIOCHEMISTRY 9787-9794 (2002)

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EX1031	Kohler 1999	H.P.E. Kohler, Sphingomonas herbicodovorans *MH: A Versatile Phenoxyalkanoic Acid Herbicide Degrader*, 23 J. INDUS. MICROBIO. & BIOTECH. 336-340 (1999)
EX1032	Lyon 1989	B.R. Lyon et al., *Expression of a Bacterial Gene in Transgenic Tobacco Plants Confers Resistance to the Herbicide 2,4-Dichlorophenoxyacetic Acid*, 13 PLANT MOLECULAR BIO. 533-540 (1989)
EX1033	Lyon 1993	B.R. Lyon et al., *Cotton Plants Transformed with Bacterial Degradation Gene Are Protected from Accidental Spray Drift Damages by the Herbicide 2,4-Dichlorophenoxyacetic Acid*, 2 TRANSGENIC RES. 162-169 (1993)
EX1034	Müller 2001	R.H. Müller et al., *Physiological and Genetic Characteristics of Two Bacterial Strains Utilizing Phenoxypropionate and Phenoxyacetate Herbicides*, 156 MICROBIO. RES. 121-131 (2001)
EX1035	Müller 2006	T.A. Müller, R.P. Hausinger et al., *Structural Basis for the Enantiospecificities of* R- *and* S-*Phenoxypropionate/α-Ketoglutarate Dioxygenases*, 15 PROTEIN SCI. 1356-1368 (2006)
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EX1038	Perkins 1987	E.J. Perkins et al., *Use of* Alcaligenes eutrophus *as a Source of Genes for 2,4-D Resistance in Plants*, 35 WEED SCI. 12-18 (1987)
EX1039	Rao 2000	PRINCIPLES OF WEED SCIENCE (V.S. Rao, ed., 2d ed. 2000)
EX1040	Saari 1998	R.E. Saari, Substrate Specificity and Spectroscopic Properties of 2,4-Dichlorophenoxyacetic Acid/α-Ketoglutarate Dioxygenase, Doctoral Thesis, Mich. State Univ. (July 6, 1998)
EX1041	Saari 1999	R.E. Saari, R.P. Hausinger, et al., *Stereospecific Degradation of the Phenoxypropionate Herbicide Dichlorprop*, 6 J. MOLECULAR CATALYSIS B: ENZYMATIC 6 421-428 (1999)
EX1042	Schleinitz 2004	K.M. Schleinitz et al., *Localization and Characterization of Two Novel Genes Encoding Stereospecific Dioxygenases Catalyzing 2(2,4-Dichlorophenoxy)Propionate Cleavage in* Delftia acidovorans *MC1*, 70 APPLIED & ENVTL. MICROBIO. 5357-5365 (2004)
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EX1047	Westendorf 2002	A. Westendorf et al., *The Two Enantiospecific Dichlorprop/α-Ketoglutarate Dioxygenases from* Delftia acidovorans *MC1-Protein and Sequence Data of RdpA and SdpA*, 157 MICROBIO. RES. 317-322 (2002)
EX1048	Westendorf 2003	A. Westendorf et al., *Purification and Characterization of the Enantiospecific Dioxygenases from* Delftia acidovorans *MC1 Initiating the Degradation of Phenoxypropionate and Phenoxyacetate Herbicides*, 23 ACTA BIOTECHNOLOGY 3-17 (2003)
EX1050		First Amended Complaint, *Corteva Agriscience LLC v. Monsanto Co.*, No. 1:22-cv-1046-GBW (D. Del.), D.I. 68, excluding exhibits
EX1051	Krausz 1993	R.F. Krausz et al., *Soybean* (Glycine max) *Tolerance to 2,4-D Ester Applied Preplant*, 7 WEED TECH. 906-910 (1993)
EX1052	Larue 2019	C.T. Larue et al., *Development of Enzymes for Robust Aryloxyphenoxypropionate and Synthetic Auxin Herbicide Tolerance Traits in Maize and Soybean Crop*, 75 PEST MGMT. SCI. 2086-2094 (2019)
EX1055		Curriculum Vitae of Robert P. Hausinger, Ph.D.

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EX1056		Joint Claim Construction Chart, *Corteva Agriscience LLC v. Monsanto Co.*, No. 1:22-cv-1046-GBW (D. Del.), D.I. 82
EX1062	MSU Library Website	*Finding Dissertations and Theses: Home*, MICH. STATE UNIV., https://libguides.lib.msu.edu/dissertations (accessed June 14, 2023)
EX1072		Deposition Transcript of J. Martin Bollinger, Ph.D. (June 21, 2024)
EX1073		Curriculum Vitae of Robert P. Hausinger, Ph.D. (updated)
EX1074	Bairoch	A. Bairoch & R. Apweiler, *The SWISS-PROT Protein Sequence Data Bank and Its Supplement TrEMBL in 1999*, 27 Nucleic Acids Res. 49-54 (1999)
EX1075	UniProt Website	*Does UniProt KB Contain All Protein Sequences?*, UNIPROT, https://www.uniprot.org/help/uniprotkb_coverage (last updated Apr. 27, 2022)
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EX1077	UniProtKB P10088 TFDA_CUPPJ	P10088 TFDA_CUPPJ, UNIPROT, https://www.uniprot.org/uniprotkb/P10088/entry (last updated Mar. 27, 2024)
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EX1083	Weiss	M. Weiss et al., *The Physiology and Habitat of the Last Universal Common Ancestor*, 1 NAT. MICROBIOL. 16116 (2016)
EX1084		Annotated Excerpt of U.S. Patent Publication No. 2016/0108422 (EX1017), Figs. 6A-6E
EX2001	Fukumori	F. Fukumori & R.P. Hausinger, *Purification and Characterization of 2,4-Dichlorophenoxyacetate/α-Ketoglutarate Dioxygenase*, 268 J. Biol. Chem., 24311-24317 (1993)

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EX2002, pp. 432-444		Sealed Version of Defendants' Counterclaims to Plaintiff's Second Amended Complaint, *Corteva Agriscience LLC v. Monsanto Co.*, No. 22-cv-1046-GBW (D. Del.), D.I. 143 (excerpted pages 38 to 65 and accompanying exhibits) (CONFIDENTIAL – FILED UNDER SEAL)
EX2004		"Protein Sequences" (CONFIDENTIAL – FILED UNDER SEAL)
EX2012		GenBank Accession No. MH043112
EX2013		GenBank Accession No. MH043114
EX2014		GenBank Accession No. MH043115
EX2015		Declaration of J. Martin Bollinger (June 21, 2024)
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EX2018	Robinson	P.K. Robinson, *Enzymes: Principles and Biotechnological Applications*, 59 ESSAYS BIOCHEM. 1-41 (2015)
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EX2024	Wilson	C.A. Wilson et al., *Assessing Annotation Transfer for Genomics: Quantifying the Relations Between Protein Sequence, Structure and Function Through Traditional and Probabilistic Scores*, 297 J. MOL. BIOL. 233-249 (2000)
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EX2033	Dym	O. Dym & D. Eisenberg, *Sequence-Structure Analysis of FAD-Containing Proteins*, 10 PROTEIN SCI. 1712-1728 (2001)
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EX2035	Chaporro-Riggers	J.F. Chaparro-Riggers et al., *Better library Design: Data-Driven Protein Engineering*, 2 BIOTECHNOL. J. 180-191 (2007)
EX2037	Wedege	E. Wedege & L.O. Frøholm, *Human Antibody Response to a Group B Serotype 2a Meningococcal Vaccine Determined by Immunoblotting*, 51 INFECTION & IMMUNITY 571-578 (1986)
EX2038	Chica	R.A. Chica et al., *Semi-Rational Approaches to Engineering Enzyme Activity: Combining the Benefits of Directed Evolution and Rational Design*, 16 CURR. OPIN. BIOTECHNOL. 378-384 (2005)
EX2040	Altschul	S.F. Altschul et al., *Gapped BLAST and PSI-BLAST: A New Generation of Protein Database Search Programs*, 25 NUCLEIC ACIDS RES. 3389-3402 (1997)
EX2041	Müller	T. Müller & M. Vingron, *Modeling Amino Acid Replacement*, 7(6) J. COMPUTATIONAL BIO. 761-776 (2000)
EX2042	Schleinitz Excerpt	"Excerpt of Ex. 1042"

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EX2044	Ng	P.C. Ng & S. Henikoff, *SIFT: Predicting Amino Acid Changes that Affect Protein Function*, 31 NUCLEIC ACIDS RES. 3812-3814 (2003)
EX2045		U.S. Patent No. 8,343,747 to Silverstone et al. (issued Jan. 1, 2013)
EX2046	Paine	J.A. Paine et al., *Improving the Nutritional Value of Golden Rice Through Increased Pro-Vitamin A Content*, 23 NATURE BIOTECH. 482-487 (2005)
EX2047	Llewelyn	M.B. Llewelyn et al., *Monoclonal Antibodies in Medicine*, 305 BRIT. MED. J. 1269-1272 (1992)
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EX2052	Last & Llewellyn	D.I. Last & D.J. Llewellyn, *A Detoxification Gene in Transgenic* Nicotiana tabacum *Confers 2,4-D Tolerance*, 47 WEED SCIENCE 401-04 (1999)
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EX2056	Herbicide Handbook	Weed Sci. Soc'y of Am., *Herbicide Handbook*, 111-115, 133-135, 281-283, 453-454 (W.K. Vencill ed., 8th ed. 2002)
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EX2058		MERRIAM-WEBSTER'S COLLEGIATE DICTIONARY 994-995 (10th ed. 2001)
EX2059	Larue 2023	C. Larue, *Oxygenase Enzymes for Agricultural Biotechnology Applications*, 9 AGRICULTURAL BIOCATALYSIS: ENZYMES IN AGRICULTURE AND INDUSTRY 245, 253-265 (2023)
EX2060	Cox	C. Cox, *Mecoprop (MCPP)*, 24 J. PESTICIDE REFORM 10-14 (2004)
EX2061		"Sequence Alignment of Sequences from Exs. 2012-2014 and 2048-2050"

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Second Unopposed Motion to Seal** was served electronically via email on July 3, 2024, in its entirety on the following:

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