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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHRISTIAN SCHOPKE, GREG F. W. GOCAL, KEITH WALKER, and PETER R. BEETHAM

Appeal 2018-000616
Application 12/245,610
Technology Center 1600

Before JEFFREY N. FREDMAN, TAWEN CHANG, and DAVID COTTA, Administrative Patent Judges.

CHANG, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims.[2] We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Cibus US LLC. Appeal Br. 4.

[2] An oral hearing was held on Oct. 7, 2019.

BACKGROUND

> The nuclear-encoded chloroplast enzyme acetohydroxyacid synthase or acetolactate synthase (AHAS or ALS . . .) catalyses the first common step in the biosynthesis of the branched-chain amino acids leucine, isoleucine and valine. This enzyme . . . is the site of action for several distinct classes of herbicides, including the sulfonylureas, imidazolinones and triazolopyrimidines. Resistance to a sulfonylurea, chlorsulfuron, has been shown . . . to result from single amino acid substitutions within the AHAS enzyme.

Rutledge 31 (citations omitted).[3] The invention relates to "the field of herbicide resistant plants and seeds and more specifically to mutations in the acetohydroxyacid synthase (AHAS) gene and protein." Spec. ¶ 2.

CLAIMED SUBJECT MATTER

The claims are directed to a method for targeted alternation of a *Brassica napus* plant cell. Claim 152 is illustrative:

> 152. A method for targeted alteration of a *Brassica napus* plant cell, comprising:
>
> introducing into the plant cell gene repair oligonucleobase comprising at least one mismatch with respect to an acetohydroxyacid synthase (AHAS) I gene naturally present in the plant cell genome, the mismatch selected to introduce a tryptophan to leucine mutation in the AHAS I gene at a position corresponding to residue W574 of SEQ ID NO: 1;
>
> identifying a plant cell having substantially normal growth and AHAS catalytic activity in the presence of an AHAS-inhibiting

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[3] Robert G. Rutledge, *Molecular Characterization and Genetic Origin of* Brassica Napus *Acetohydroxyacid Synthase Multigene Family*, 229 MOLECULAR AND GENERAL GENETICS 31 (1991) ("Rutledge").

> herbicide as compared to a corresponding plant cell retaining the tryptophan at the position corresponding to residue W574 of SEQ ID NO: 1; and
>
> regenerating from the identified plant cell a non-transgenic herbicide-resistant *Brassica napus* plant having the tryptophan to leucine mutation at the position corresponding to residue W574 of SEQ ID NO: 1.

Appeal Br. 12 (Claims App.).

REJECTION

Claims 152 and 154[4] are rejected under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Hawkes,[5] Arntzen,[6] Rutledge, Beetham,[7] and Kochevenko.[8] Ans. 2.

DISCUSSION

The Examiner has rejected claims 152 and 154 as obvious over Hawkes, Arntzen, Rutledge, Beetham, and Kochevenko. The Examiner finds that Hawkes teaches "introducing a donor mutagenic nucleobase

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[4] Both the Examiner and Appellant state that it is claim *157*, in addition to claim 152, that is rejected an under appeal. Ans. 2; Appeal Br. 5. However, claim 157 has been cancelled, and claims 152 and *154* are the only claims that have not been cancelled or withdrawn. Appeal Br. 12 (Claims App.).
[5] Hawkes et al., GB 2 326 163 A, published Dec. 16, 1998 ("Hawkes").
[6] Arntzen et al., US 7,094,606 B2, issued Aug. 22, 2006 ("Arntzen").
[7] Beetham et al., US 6,870,075 B1, issued Mar. 22, 2005 ("Beetham").
[8] Andrej Kochevenko et al, *Chimeric RNA/DNA Oligonucleotide*-Based *Site-Specific Modification of the Tobacco Acetolacetate Syntase Gene*, 132 PLANT PHYSIOLOGY 174 (2003) ("Kochevenko").

wherein the duplex acceptor DNA sequence is an AHAS gene." Ans. 2.

The Examiner finds that Arntzen teaches

> a method for producing an herbicide-resistant plant comprising introducing into a plant cell a recombinagenic oligonucleobase that targets an ALS (syn. AHAS) gene, selecting a plant cell having substantially normal growth and catalytic activity as compared to a corresponding wild-type plant cell in the presence of an AHAS-inhibiting herbicide and regenerating a non-transgenic herbicide resistant plant having a mutated AHAS gene from said plant cell at claim 4; wherein the plant cell is a canola *(Brassica napus)* at claim 7. Arntzen . . . teach[es] that an alanine^{205}-to-aspartic acid, a tryptophan^{591}-to-leucine, a tryptophan^{591}-to-serine and a serine^{660}-to-asparagin mutation can be introduced into an ALS gene to confer sulfonylurea and imidazolinone herbicide resistance. Tryptophan^{591} of Arntzen corresponds to tryptophan^{574} of the instant claims. Arntzen . . . teach[es] that it is understood that in most plants the gene encoding ALS has been duplicated and that a mutation can be introduced into any allele of either ALS gene.

Id. at 3 (citation omitted). The Examiner finds that Rutledge teaches that "the coding sequence of the *Brassica napus* AHAS1, AHAS2, and AHAS3 genes were known in the art at the time of . . . Arntzen" and that Beetham teaches introducing a recombinagenic oligonuclobase into a plant cell. *Id.* Finally, the Examiner finds that Kochevenko teaches (1) "introducing a mixed [RNA] into a tobacco plant protoplast to modify an AHAS gene;" (2) substituting, in an AHAS gene, a leucine for a tryptophan corresponding to W^{574} in the SEQ ID NO: 1 of claim 152; and (3) "introducing into a plant cell a gene repair oligonucleobase, identifying a plant cell[,] and regenerating a non-transgenic herbicide-resistant plant having the tryptophan to leucine mutation." *Id.* at 3–4 (citation omitted).

Appellant contends that, based on the cited references, a skilled artisan would not have had "a reasonable expectation of success in producing a W574L mutation in *B. napus* AHAS I." Appeal Br. 10.

A. Issue

Whether, based on the cited combination of prior art, a skilled artisan would have had reason to introduce a tryptophan to leucine mutation in the AHAS I gene of a *Brassica napus* plant cell, at a position corresponding to residue W574 of SEQ ID NO: 1, with a reasonable expectation of success.

B. Findings of Fact

1. Hawkes teaches

> [a] method of producing plants which exhibit an agronomically desirable trait comprises mutating or otherwise modifying in situ in a plant cell at least one gene and regenerating from a cell exhibiting the said trait fertile morphologically normal whole plants, and is characterised in that a polynucleotide is introduced into the plant cell, the said polynucleotide comprising at least one region which is substantially complementary to the gene, which gene when mutated or otherwise modified provides for the agronomically desirable trait the region in the said polynucleotide containing at least one base mismatch in comparison with the like region in the said gene, so that the region in the said gene is altered by the DNA repair/replication system of the cell to include the said mismatch.

Hawke Abstract.

2. Hawkes teaches that "[t]he agronomically desirable trait may be herbicide resistance." *Id.*; *see also id.* at 1:24–25.

3. Hawkes teaches that "[t]he protein encoding region of the gene may encode an enzyme selected from a group consisting of EPSPS, GOX,

PAT, HPPD, ACC, ALS, BNX and protox and known mutated or variant forms thereof." *Id.* at 2:24–26. The Examiner finds, and Appellant does not dispute, that ALS is synonymous with AHAS. Ans. 3.

4. Hawkes teaches that the method of its invention may be applied to a cell of oilseed rape, which Appellant acknowledges to be *Brassica napus*. Hawkes 3:13-18; Appeal Br. 4.

5. Hawkes teaches using a mixed ribo-deoxyribonucleic acid to introduce a mutation into the target gene, wherein the mixed ribo-deoxyribonucleic acid has two regions homologous with the sequence of the target site, flanking an interposed heterologous region. Hawkes 5:20–28.

6. Hawkes teaches that "[t]he change to be introduced into the target gene is encoded by the heterologous region" and that "[t]he change to be introduced may be a change in one or more bases of the target gene sequence or the addition of one or more bases." *Id.* at 6:8–10.

7. Arntzen teaches "use of duplex oligonucleotides about 25 to 30 base pairs to introduce site specific genetic alterations in plant cells," wherein "plants having the genetic alteration can be generated from the altered cells" thereafter. Arntzen Abstract.

8. Arntzen teaches that its invention "allows the skilled practitioner to make a specific alteration of a specific pre-existing gene of a plant." *Id.* at 1:20–22.

9. In particular, Arntzen teaches using mixed duplex oligonucleotides (MDON) to effect genetic changes, wherein the MDON comprises sequences that are homologous to a first and second fragment of the target gene as well as a "region of difference, termed the 'heterologous region,'" which "can effect an insertion or deletion, or can contain one or

more bases that are mismatched with the sequence of target gene so as to effect a substitution," such that "the target gene becomes homologous with the sequence of the MDON." *Id.* at 1:31–58.

10. Arntzen teaches that the genetic changes effected by its invention can be used to introduce a selectable trait and that "[t]he selectable trait can . . . be . . . herbicide resistance." *Id.* at 7:49–50, 8:7–9.

11. Arntzen teaches that "[i]n one embodiment of the invention a MDON is used to introduce a mutation into an Acetolactate synthase (ALS) gene, which is also termed the aceto-hydroxy amino acid synthase (AHAS) gene." *Id.* at 8:31–34.

12. Arntzen teaches that "[s]ulfonylurea herbicides and imidazoline herbicides are inhibitors of the wild type ALS enzymes" but that prior art teaches "several mutations (hereinafter, a "Bedbrook Mutation") that were found to render yeast ALS enzymes resistant to sulfonylurea herbicides" and that are stated to "make[] a plant resistant to sulfonylurea and imidazoline herbicides when introduced into a plant ALS gene." *Id.* at 8:34–36, 40–46.

13. Arntzen teaches that

> [t]hree of the Bedbrook mutations were, in fact, shown to confer herbicide resistance in a plant, namely the substitutions Pro→Ala^{197} Ala→Asp^{205} and Trp→Leu^{591}. Rajasekaran reports that mutations Trp→Ser^{591} caused resistance to sulfonylurea and imidazoline and that Ser→Asn^{660} caused resistance to imidazoline herbicides. . . . According to the invention any substitution for the naturally occurring amino and [sic] at position 660 or one of the positions listed in Table 2 of Bedbrook, which is hereby incorporated by reference, can be used to make a selectable mutation in the ALS gene of a plant.

Id. at 8:49–54, 8:66–9:3.

14. The Examiner finds, and Appellant does not dispute that "Tryptophan[591] of Arntzen corresponds to tryptophan[574] of the instant claims." Ans. 3.

15. Arntzen teaches that "[i]t is understood that in most plants the gene encoding ALS has been duplicated" and that "[a] mutation can be introduced into any allele of either ALS gene." Arntzen 8:46–48.

16. The Examiner finds, and Appellant does not dispute, that Rutledge teaches the coding sequence of the AHAS1, AHAS2, and AHAS3 genes for *Brassica napus*. Ans. 3; Rutledge Fig. 2. The AHAS1 and AHAS3 genes of *B. napus* "share extensive homology." Rutledge Abstract, Fig. 2; *see also* Ouellet 321 (Teaching that "*AHAS1* and *AHAS3*, which are located in the C and A genomes, respectively, are highly conserved with respect to each other in nucleotide sequences.") (citing Rutledge).[9]

17. Beetham teaches production of a non-transgenic plant resistant to a particular type of herbicide by using a "recombinagenic oligonucleobase to make a desired mutation in the chromosomeal or episomal sequences of a plant in the gene encoding" a specific enzyme (EPSPS). Beetham Abstract.

18. Beetham teaches methods of introducing recombinagenic oligonucleobase into a plant cell. *Id.* at 4:22–24.

19. Beetham teaches that the recombinagenic oligonucleobase may be a single stranded oligodeoxynucleotide mutational vector (SSOMV). *Id.* at 10:1–4 (claim 3).

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[9] Therese Ouellet et al., *Members of the Acetohydroxyacid Synthase Multigene Family of* Brassica napus *Have Divergent Patterns of Expression*, 2 THE PLANT J. 321 (1992) ("Ouellet").

20. Kochevenko teaches that "[s]ingle amino acid substitutions at either of two crucial positions in acetolactate synthase (ALS) result in a chlorsulfuron-insensitive form of this enzyme and, as a consequence, a herbicide-resistant phenotype." (Kochevenko Abstract.) In particular, Kochevenko teaches that "[l]ines with proline-196-alanine, threonine, glutamine, or serine substitutions or with tryptophan-573-leucine substitutions were highly resistant at both cellular and whole plant levels." *Id.*

21. Kochevenko teaches that

> [t]he allotetraploid species tobacco has two genetically unlinked loci, *SuRA* and *SuRB,* for ALS. Mutations in either *SuRA* (Pro-196-Glu and Pro-196-Thr) or *SuRB* (Pro-196-Ser) locus result in single amino acid replacements at position 196 and a herbicide-resistant phenotype. It was also shown that the S4-Hra mutant of tobacco bearing two linked mutations within locus *SuRB* had amino acid substitutions at positions 196 (Pro-196-Ala) and 573 (Trp-573-Leu), and it was more resistant to chlorsulfuron. . . . Interestingly, the same type of amino acid change (Trp to Leu) in the conserved region near the C terminus of ALS (as a result of 1-bp substitution, G to T) resulted in sulfonylurea resistance in a *Xanthium* sp. and *Brassica napus*. Moreover, in cocklebur (*Xanthium*), all possible mutations affecting the Trp at this position were investigated using site-directed mutagenesis, and only Trp-Leu substitutions yielded an active, herbicide-insensitive form of ALS.

Id. at 175 (citations omitted).

22. Kochevenko teaches a strategy of gene alteration using chimeric RNA/DNA oligonucleotides (i.e., chimeras), wherein the chimera is identical to a targeted gene except for a single nucleotide, which "produces a mismatched base that is presumably recognized by endogenous repair machinery." *Id.* at 174.

23. Kochevenko teaches using "olionucleotide-mediated strategy to create single point mutations at different positions with ALS genomic sequences of tobacco," that "[s]equence analysis confirmed that application of oligonucleotides with various targeting sequences resulted in the production of predicted alterations, and that "assay of ALS activity in the leaves of resistant lines in the presence of chlorsulfuron demonstrated the appearance of an herbicide-insensitive form of the enzyme." *Id.* at 175.

24. In particular, Kochevendo designed two chimeric RNA/DNA oligonucleotides "to obtain separate targeted single-nucleotide conversion at two different positions within either [*SuRA* or *SuRB*]," wherein ChALS-588 and ChALS-1719 are respectively designed to lead to "amino acid changes Pro-Gln at position 196 and Trp-Leu at 573, respectively" and to an herbicide-insensitive form of ALS. *Id.*

25. Kochevenko teaches that its experiments "clearly demonstrated that single amino acid substitution Trp-573-Leu alone can provide a chlorsulfuron-resistant phenotype." *Id.* at 179.

26. Kochevenko teaches that "[c]hlorsulfuron-resistant plants were regenerated from calli after mesophyll protoplast electroporation or leaf tissue particle bombardment with these specifically constructed chimeras." *Id.* at Abstract.

C. Analysis

Unless otherwise noted, we adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (April 27, 2016 Office Act. 3–6; Ans. 2–10; FF1–26) and agree with the Examiner that claims 152 and 154 would have been obvious over the combination of

Hawkes, Arntzen, Rutledge, Beetham, and Kochevenko. Only those arguments timely made by Appellant in the briefs have been considered; arguments not so presented in the briefs are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived."). We address Appellant's arguments below.

Appellant concedes that the prior art discloses the W574L mutation in the *B. napus* AHAS III gene. Appeal Br. 6–7. However, Appellant contends that a skilled artisan would not have had "a reasonable expectation of success in producing a W574L mutation in *B. napus* AHAS I," because "[t]he literature indicates that the AHAS . . . genes . . . are not simply equivalent to one another such that a mutation in one is applicable to the other." Appeal Br. 6, 10; *see also* Reply Br. 4–5.

Appellant first argues that, while a W574L mutation of the *B. napus* AHAS III gene has long been known in the prior art, as evidenced by Tan[10] and Hattori,[11] such a mutation has never been described in the AHAS I gene recited in the claims. Appeal Br. 6–7; *see also* Reply Br. 4. Appellant argues that, while Hawkes mentions that ALS (i.e., AHAS) is a gene that may be targeted for mutation, it makes no specific reference to "any particular mutations within any AHAS gene," "AHAS in the context of *B.*

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[10] Siyuan Tan et al., *Imidazolinone-Tolerant Crops: History, Current Status and Future*, 61 PEST MGMT. SCI. 246 (2005).
[11] Jiro Hattori et al., *An Acetohydroxy Acid Synthase Mutant Reveals a Single Site Involved in Multiple Herbicide Resistance*, 246 MOLECULAR & GENERAL GENETICS 419 (1995).

napus," or "AHAS I in *B. napus*," much less any reference to "introducing a W574L mutation into *B. napus* AHAS I." Appeal Br. 8; *see also* Reply Br. 3. Appellant similarly argues that, while Arntzen teaches "general methods for introducing mutations into cells" and teaches that transgenic plants containing certain mutated yeast AHAS genes are herbicide resistant, "the present claims do not relate to transgenic plants, but rather to mutations in the endogenous *B. napus* genomic copy of AHAS I." Appeal Br. 8–9; *see also* Reply Br. 3. Finally, Appellant argues that Rutledge and Beetham also do not "make any reference to introducing a W574L mutation into *B. napus* AHAS I." Appeal Br. 9.

We are not persuaded. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

In this case, Appellant concedes that a W574L mutation in the *B. napus* AHAS III gene is known, Appeal Br. 6–7, and the prior art taken together teaches that this and corresponding Trp→Leu mutations in other plant AHAS genes confer herbicide resistance, FF12–14, FF20, FF21, FF24, and FF25, and also teaches that AHAS I and AHAS III genes are highly conserved in *B. napus*, FF16. The prior art further teaches a method of "mak[ing] a specific alteration of a specific pre-existing gene of a plant" such as the AHAS gene of *B. napus* in order to confer, e.g., herbicide resistance. *See* FF1–14, FF17–19, FF22, FF24, and FF25. Finally, the prior art teaches that "[i]t is understood that in most plants the gene encoding ALS

has been duplicated" and that "[a] mutation can be introduced into any allele of either ALS gene."[12] FF15.

Given all of the above, including particularly the highly conserved nature of the two AHAS genes and the teaching in Arntzen that a mutation can be introduced into any allele of the various AHAS genes, we agree with the Examiner that a skilled artisan would have had reason to introduce mutation corresponding to W574L in the AHAS I gene of *B. napus*, in order to confer herbicide resistance, with a reasonable expectation of success in doing so.

With respect to Appellant's contention that a mutation has never been described in the *B. napus* AHAS I gene despite the fact that the W574L mutation in the AHAS III gene has long been known in the prior art, *see, e.g.*, Appeal Br. 6–7, we note that Appellant has submitted no evidence that there has been a long-felt need to achieve the W574L mutation in the AHAS I gene in particular, given that W574L mutation in the AHAS III gene is known and provides the same benefit of herbicide resistance. *Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (explaining that "long-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem").

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[12] During oral argument, Appellant argued that the AHAS I and AHAS III genes in *B. napus* are not duplications. Tr. 10:12–11:2. In particular, Rutledge teaches that "*B. napus* is an allotetraploid believed to originate from an interspecific cross between *B. campestris*, the A genome donor and *B. oleracea*, the C genome donor." Rutledge 31. Rutledge further teaches that AHAS III originates from the A genome, while AHAS I originates from the C genome. *Id.* at Abstract. We are not persuaded, because, regardless of the origins of AHAS I and AHAS III genes, their nucleotide sequences are highly conserved as compared to each other. FF16.

Appellant argues that Kochevenko, together with van der Vyver[13] and Lee,[14] supports the argument that a skilled artisan would not have had a reasonable expectation of success in arriving at a W574L mutation in the *B. napus* AHAS I gene. Appeal Br. 9; *see also* Reply Br. 3, 4. In particular, Appellant notes that Kochevenko teaches mutations in an allotetraploid tobacco genome that contain two highly conserved AHAS genes, SuRA and SuRB. Appeal Br. 9. Appellant further notes that, "despite designing RNA/DNA oligonucleotides to achieve mutations in 'either of these genes,' [a Trp-Leu] mutation was obtained only in the SuRB gene; the equivalent mutation was not observed in the other 'highly conserved' SuRA gene." Appeal Br. 9; *see also* Reply Br. 3, 4. Appellant thus contends that Kochevenko, like Tan, demonstrates that simply because a particular mutation (W574L) was possible in one allopolyploid gene (tobacco SuRB, *B. napus* AHAS III), the same mutation may not be available in a different but highly conserved gene (tobacco SuRA, *B. napus* AHAS I). Appeal Br. 10; *see also* Reply Br. 4.

While we acknowledge Appellant's argument, we are not persuaded. As an initial matter, it is not clear that Kochevenko teaches that the Trp→Leu mutation occurred only in the SuRB gene. Appellant points to the portion in Kochevenko that teaches that, when chimeric oligonucleotide ChALS-1719, designed to alter the codon for Trp-573, was introduced into

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[13] Christell van der Vyver, *In vitro Selection of Transgenic Sugarcane Callus Utilizing a Plant Gene Encoding a Mutant Form of Acetolactate Synthase*, 49 IN VITRO CELLULAR & DEVELOPMENTAL BIOLOGY—PLANT 198 (2013) ("van der Vyver").

[14] Kathleen Y. Lee et al., *The Molecular Basis of Sulfonylurea Herbicide Resistance in Tobacco*, 7 THE EMBO J. 1241 (1988) ("Lee").

tobacco cells, "the observed change was limited to a single nucleotide substitution (G to T) at position 1,719." Appeal Br. 9. This statement, however, should be read in the context of the next sentence, i.e., that "the codon for Pro-196 was unchanged." *See* Kochevenko 177. Thus, this appears to be a statement that only the expected G to T substitution at position 1,719 was observed, and no substitution occurred at position 588, when ChALS-1719 was introduced into tobacco cells. It is not clear that the substitution only occurred in one of the AHAS genes but not the other.

Appellant argue, however, that Lee and van der Vyver make clear that the Trp-573 mutation occurred only in the SuRB gene. Tr. 13:14–23. While Lee teaches that "two separate substitutions, one at Pro-196 and a second at Trp-573 in the SuRB locus . . . result in an herbicide resistance phenotype," Lee was published before Kochevenko and does not address the results obtained by Kochevenko. Similarly, while van der Vyver cites to Kochevenko in stating that "[t]he mutant *ALS SurB* isoform (*alsb*) was isolated from tobacco cDNA" and the existence of the Trp-573-Leu amino acid substitution confirmed, van der Vyver does not teach that Kochevenko did not achieve a corresponding mutation in the SuRA gene. van der Vyver 201.

More importantly, assuming for argument's sake that the Trp→Leu mutation occurred only in the SuRB and not the SuRA gene in Kochevenko, Appellant has not provided any persuasive evidence, only attorney arguments, that a skilled artisan would not have reasonably expected to be able to achieve the corresponding mutation in either the SuRA gene in tobacco or the AHAS I gene in *B. napus* with routine experimentation. Attorney arguments cannot substitute for evidence. *In re Geisler*, 116 F.3d

1465, 1470 (Fed. Cir. 1997). Neither has Appellant pointed to any step in the claimed method that distinguishes the claimed method from the method taught in the prior art.

In this regard, we also note that Arntzen teaches that its method for introducing mutations "allows the skilled practitioner to make a specific alteration of a specific pre-existing gene of a plant." FF8. Likewise, Kochevenko teaches that its ChALS-1719 is designed to obtain a single-nucleotide conversion at position 1719 (leading to amino acid change Trp-Leu at 573) within either SuRA or SuRB gene. "[A] prior art printed publication cited by an examiner is presumptively enabling barring any showing to the contrary by a patent applicant," *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012), and Appellant has not provided persuasive evidence, only attorney argument, that prior art references such as Arntzen would not have allowed a skilled artisan to introduce a specific alteration (i.e., the nucleotide mutation(s) that would result in the Trp-573-Leu substitution) of a specific pre-existing gene of a plant (i.e., the AHAS I gene of *B. napus*).

Finally, Appellant contends in the Reply Brief that "achieving the W574L mutation in AHAS I is an unexpected result, based on literature." Reply Br. 5. We are not persuaded for the same reasons discussed above, namely that Appellant has only provided attorney argument, and not persuasive evidence, that achieving a W574L mutation in AHAS I is an unexpected result.

Accordingly, we affirm the Examiner's rejection of claims 152 over the combination of Hawkes, Arntzen, Rutledge, Beetham, and Kochevenko. Claim 154, which was not separately argued, falls with claim 152.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
152, 154	103(a)	Hawkes, Arntzen, Rutledge, Beetham, Kochevenko	152, 154	
Overall Outcome			152, 154	

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED