UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/463,687	08/20/2014	Andrew Mark Cigan	BB2284-US-NP	5241

27310 7590 06/26/2020

PIONEER HI-BRED INTERNATIONAL, INC.
7250 NW 62ND AVENUE
PO BOX 552
JOHNSTON, IA 50131-0552

EXAMINER
UYENO, STEPHEN G

ART UNIT	PAPER NUMBER
1662	

NOTIFICATION DATE	DELIVERY MODE
06/26/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPsupport@corteva.com
sue.smith@corteva.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANDREW MARK CIGAN, SAVERIO CARL FALCO, HUIRONG GAO, ZHONGSEN LI, ZHAN-BIN LIU, L. ALEKSANDER LYZNIK, JINRUI SHI, SERGEI SVITASHEV, and JOSHUA K. YOUNG

Appeal 2019-003067
Application 14/463,687
Technology Center 1600

Before ERIC B. GRIMES, TIMOTHY G. MAJORS, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims to a method of modifying a target site in the genome of a plant cell that have been rejected for anticipation under 35 U.S.C. § 102 and obviousness under 35 U.S.C. § 103. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM, but designate our affirmance a new ground of rejection under 37 C.F.R. § 41.50(b).

---

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies Pioneer Hi-Bred International, Inc. and E.I. DuPont de Nemours & Company as the real parties in interest. Appeal Br. 3.

STATEMENT OF THE CASE

"Recombinant DNA technology has made it possible to insert foreign DNA sequences into the genome of an organism, thus, altering the organism's phenotype." Spec. 1. According to the Specification, "[a]lthough several approaches have been developed to target a specific site for modification in the genome of a plant, there still remains a need for more efficient and effective methods for producing a fertile plant, having an altered genome comprising specific modifications in a defined region." *Id.* at 2.

Appellant's Specification describes "compositions and methods for genome modification of a target sequence in the genome of a plant or plant cell" that "employ a guide RNA/Cas endonuclease system, wherein the Cas endonuclease is guided by the guide RNA to recognize and optionally introduce a double strand break at a specific target site into the genome of a cell." Spec. 27. A Cas endonuclease is a protein encoded by a "CRISPER-associated (Cas)" gene such as Cas9. *Id.* at 28–29.

Claims 6 and 15–17 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claim 6 is illustrative of the claims on appeal. It reads as follows:

> 6. A method for modifying a target site in the genome of a plant cell, the method comprising providing a guide RNA and a Cas endonuclease to said plant cell, wherein said guide RNA and Cas endonuclease form a complex that enables the Cas endonuclease to introduce a double strand break at said target site.

Appeal Br. 21.

Appellant filed its Appeal Brief seeking review of Examiner's rejection of claims 6 and 15–17 as obvious over Zhang[2] and Hein.[3] Appeal Br. 7. In the Answer, Examiner introduced a new ground rejecting claim 6 under 35 U.S.C. § 102 as anticipated by Zhang. Ans. 3. Appellant elected to maintain the appeal, responding to Examiner's anticipation rejection in its Reply Brief. *See* 37 CFR § 41.39(b)(2). Both rejections are before us now.[4]

I. ZHANG'S DISCLOSURE

Before we address Appellant's arguments concerning the anticipation and obviousness rejections, we must first clarify the scope of the disclosure in Zhang that qualifies as prior art to Appellant's application. Both of Examiner's rejections are based on Zhang, an issued U.S. patent, which claims priority to a series of four provisional applications. Examiner, however, does not articulate support for the rejections by citing to the disclosure in Zhang. Instead, Examiner cites only to the disclosure in one of Zhang's provisional applications, i.e., no. 61/736,527 (the "'527 Provisional"). *See* Final Act. 2–4; Ans. 3–4, 6–7. Appellant likewise does not address the disclosure in Zhang and responds only to Examiner's findings premised on the disclosure in the '527 Provisional. *See* Appeal Br. 7 (noting that "[c]onsistent with the Examiner's citations in the Final Office Action . . . all citations of Zhang by Appellants are to the specification of

---

[2] US 8,697,359 B1, issued Apr. 15, 2014 ("Zhang").
[3] US 5,959,177, issued Sept. 28, 1997 ("Hein").
[4] Examiner's Answer additionally refers to certain non-statutory double patenting rejections. *See* Ans. 9–13. Appellant explains that it filed terminal disclaimers to overcome those rejections (Reply Br. 13) and Examiner's Advisory Action mailed August 2, 2018 indicates those rejections were previously overcome. Thus, those rejections are not before us now.

61/736,527").

But according to statute, it is the issued patent, not the provisional application, that is considered prior art. *See* 35 U.S.C. § 102(a)(2) ("A person shall be entitled to a patent unless . . . the claimed invention was described in a patent issued under section 151 . . in which the patent . . . names another inventor and was effectively filed before the effective filing date of the claimed invention."). In this case, the distinction between the patent and the provisional application is significant because the disclosure in Zhang is materially broader than that in just the '527 Provisional. Of particular relevance to Appellant's claims and arguments on appeal, Zhang provides additional disclosure regarding the use of CRISPR-Cas systems to edit the genome of plant cells (*see, e.g.,* Zhang 26:55–27:31) as well as an example describing methods for "[u]sing Cas9 to Target and Manipulate Plant Genes" (*id.* at 54:27–67:56 (Ex. 7)). These disclosures are not part of the '527 Provisional.

Instead, the additional plant-related disclosures and example noted above seem to originate in Zhang provisional application no. 61/835,931 (the "'931 Provisional"). *Compare* Zhang 26:55–27:31; 54:27–67:56 *with* '931 Provisional ¶¶ 148–150; 475–491 (Ex. 15). The '931 Provisional has a filing date of June 17, 2013, and is the last-filed of Zhang's four provisional applications. However, like all of Zhang's provisional applications, the filing date of the '931 Provisional antedates the earliest possible effective filing date of Appellant's present application.[5]

[5] Indeed, Zhang's non-provisional filing date (i.e., October 15, 2013) antedates all but two of the five provisional applications to which Appellant's present application claims priority. We do not analyze whether

The Federal Circuit has explained the conditions under which an issued patent is entitled to the filing date of a provisional application for prior art purposes, stating

> that for a non-provisional application to claim priority to a provisional application for prior art purposes, 'the specification of the *provisional* [application] must contain a written description of the invention . . . in such full, clear, concise, and exact terms, to enable an ordinarily skilled artisan to practice the invention claimed in the *non-provisional* application.' Further, we have previously stated that 'for the non-provisional utility application to be afforded the priority date of the provisional application . . . the written description of the provisional must adequately support the claims of the non-provisional application.

Amgen Inc. v. Sanofi, 872 F.3d 1367, 1380 (Fed. Cir. 2017) (quoting *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) and *New Railhead Mfg., LLC v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002)) (alterations in original). Thus, if the

---

Appellant's claims are entitled to the benefit of its two earliest-filed provisional applications (i.e., Appl. No. 61/868,706 filed August 22, 2013 and Appl. No. 61/882,532 filed September 25, 2013) because we determine that Zhang is prior art at least as of the filing date of the '931 Provisional and therefore necessarily antedates the present application. We leave it to Examiner to consider whether Appellant's claims are indeed entitled to the benefit of its earliest-filed provisional applications should the issue arise upon continued prosecution. *See* MPEP 211.05(A) ("*If the filing date of the earlier provisional application is necessary*, for example, in the case of an interference or to overcome a reference, care must be taken to ensure that the disclosure filed as the provisional application adequately provides (1) a written description of the subject matter of the claim(s) at issue in the later filed nonprovisional application, and (2) an enabling disclosure to permit one of ordinary skill in the art to make and use the claimed invention in the later filed nonprovisional application without undue experimentation.") (emphasis added).

above requirements are satisfied for Zhang's provisional applications, Zhang is prior art at least as of the filing date of the last-filed provisional, i.e., the '931 Provisional.

On the present record, we determine that Zhang meets the above requirements. Zhang claim 1 recites a method of using a CRISPR-Cas9 system to alter expression of a gene product in a eukaryotic cell. Zhang, 139:1–22. Appellant does not dispute that the '527 Provisional provides sufficient support for this method in animal cells. *See* Appeal Br. 11 ("[The '527 Provisional] contemplated non-plant vectors, organisms, transfected cell lines, and host cells (mentioned in Paragraphs [0049], [0078], [00054-0055], [0061], and [0052) along with contemplated genomic targets in over one hundred pages (*e.g.*, Table A and Pages 143–260)."). Indeed, in addition to extensive disclosure regarding CRISPR-Cas systems, Zhang's provisional applications provide a number of detailed examples demonstrating the use of CRISPR-Cas systems to edit target sites within the genome of eukaryotic cells and thereby alter the expression of a gene product. *See, e.g.,* '527 Provisional ¶¶ 150–203; Provisional Appl. No. 61/748,427 ¶¶ 155–235; Provisional Appl. No. 61/791,409 ¶¶ 175–255; '931 Provisional ¶¶ 185–491.

Regarding plant cells specifically, the '931 Provisional explains that the same CRISPR-Cas9 systems it demonstrates for use in animal cells can also be used to edit eukaryotic cells in plants. '931 Provisional ¶ 148 (stating that "reference herein to animal cells may also apply, mutatis mutandis, to plant cells unless otherwise apparent"). In addition, the '931 Provisional incorporates by reference techniques for plant transformation from other references (*see id.* ¶ 148) and provides an example describing

methods of using a CRISPR-Cas9 system to alter the expression of a gene product in micro-algae, i.e., plant cells (*id.* ¶¶ 475–491). All of these disclosures, which are incorporated into Zhang from its provisional applications, "are presumptively enabling." *See In re Antor Media Corp.*, 689 F.3d 1282, 1287 (Fed. Cir. 2012). As explained below, Appellant has not provided persuasive argument nor evidence to overcome that presumption.

For these reasons, we determine that Zhang's provisional applications provide adequate description for and are sufficient to enable Zhang claim 1. Therefore, Zhang is prior art to the present application. *See Amgen*, 872 F.3d at 1380. This means that it is Zhang, the issued patent and not just the disclosure in the '529 Provisional, which should be evaluated in considering whether Zhang anticipates or renders obvious Appellant's claims. We do so below.

II. ANTICIPATION REJECTION

Issue

The issue for this rejection is whether a preponderance of the evidence supports Examiner's conclusion that Zhang anticipates the method of using a guide RNA and a Cas endonuclease to modify a target site in the genome of a plant cell as recited in claim 6.

Findings of Fact

FF1. Zhang discloses "systems, methods and compositions for altering expression of target gene sequences and related gene products" including "methods of directing CRISPR complex formation in eukaryotic cells and methods for utilizing the CRISPR-Cas system." Zhang, Abstr. Zhang explains that

> [t]he CRISPR/Cas or the CRISPR-Cas system (both terms are used interchangeably throughout this application) does not require the generation of customized proteins to target specific sequences but rather a single Cas enzyme can be programmed by a short RNA molecule to recognize a specific DNA target, in other words the Cas enzyme can be recruited to a specific DNA target using said short RNA molecule.

Id. at 2:13–20.

FF2. Zhang discloses methods for "altering or modifying expression of one or more gene products" comprising

> introducing into a eukaryotic cell containing and expressing DNA molecules encoding the one or more gene products an engineered, non-naturally occurring vector system comprising one or more vectors comprising: a) a first regulatory element operably linked to one or more Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)--CRISPR associated (Cas) system guide RNAs that hybridize with target sequences in genomic loci of the DNA molecules encoding the one or more gene products, b) a second regulatory element operably linked to a Type-II Cas9 protein, wherein components (a) and (b) are located on same or different vectors of the system, whereby the guide RNAs target the genomic loci of the DNA molecules encoding the one or more gene products and the Cas9 protein cleaves the genomic loci of the DNA molecules encoding the one or more gene products, whereby expression of the one or more gene products is altered; and, wherein the Cas9 protein and the guide RNAs do not naturally occur together. The invention comprehends the expression of two or more gene products being altered and the vectors of the system further comprising one or more nuclear localization signal(s) (NLS(s)). The invention comprehends the guide RNAs comprising a guide sequence fused to a tracr sequence. The invention further comprehends the Cas9 protein being codon optimized for expression in the eukaryotic cell.

Zhang, 2:30–56. Zhang further explains that the Cas enzyme and guide RNA form a "complex" that is directed by the guide RNA to a target sequence in the genome of the eukaryotic cell being edited. *See, e.g.,* Zhang, 3:44–67; 6:47–59.

FF3. Zhang discloses that in a CRISPR-Cas system, the Cas protein "directs cleavage of one or two strands at the location of the target sequence" of the guide RNA. Zhang, 4:27–29, 6:26–28; *see also id.* at 18:32–47 (teaching that Cas9 can be modified "from a nuclease that cleaves both strands to a nickase (cleaves a single strand)").

FF4. Zhang discloses that the organism whose genome is modified using the methods it describes "may be a plant." Zhang, 6:45; *see also id.* at 26:3–8 (explaining that "one or more vectors described herein are used to produce a . . . transgenic plant.").

FF5. Zhang discloses that "[w]ith recent advances in crop genomics, the ability to use CRISPIR-Cas systems to perform efficient and cost effective gene editing and manipulation will allow the rapid selection and comparison of single and multiplexed genetic manipulations to transform such genomes for improved production and enhanced traits." *Id.* at 26:55–60. Zhang explains that the "present invention" provides "plant breeders . . . with a new tool to induce mutations." *Id.* at 27:25–26. "Accordingly, one skilled in the art can analyze the genome of sources of resistance genes, with more precision than previous mutagenic agents and hence accelerate and improve plant breeding programs." *Id.* at 27:26–32.

FF6. Zhang further teaches that methods for producing transgenic plants are known in the art (Zhang, 26:9–10) and incorporates by reference the disclosures in "U.S. Pat. No. 6,603,061—*Agrobacterium*-Mediated Plant

Transformation Method; U.S. Pat. No. 7,868,149—Plant Genome Sequences and Uses Thereof and US 2009/0100536—Transgenic Plants with Enhanced Agronomic Traits" and "Morrell et al 'Crop genomics: advances and applications' Nat Rev Genet. 2011 Dec. 29; 13(2):85-96." *Id.* at 26:60–27:3.

FF7. Zhang discloses Example 7, which is titled "Engineering of Plants (Micro-Algae) Using Cas9 to Target and Manipulate Plant Genes." Zhang, 54:29–31. In Example 7, Zhang discloses three methods for delivering Cas9 and a guide RNA into plant cells. *See id.* at 54:33–47. Zhang further provides the nucleotide sequences for cassettes that include the Cas9 endonuclease as well as the sequence for a guide RNA that may be used in these methods. *Id.* at 54:48–62:11.

FF8. Zhang Example 7 also discloses a method for producing "a line of *Chlamydomonas reinhardtii*," i.e., algae, "that expresses Cas9 constitutively." *See* Zhang, 62:12–67:56. Zhang discloses that "[t]his can be done by using pChlamy1 (linearized using PvuI) and selecting for hygromycin resistant colonies" and provides the nucleotide sequence for "pChalmyl1 containing Cas9." *Id.* According to Zhang, "to achieve gene knockout" in such Cas9-expressing algae "one simply needs to deliver RNA for the guide RNA" and "for homologous recombination" one "deliver[s] guideRNA as well as a linearized homologous recombination template." *Id.* at 62:17–20.

Analysis

We agree with Examiner that claim 6 is anticipated by Zhang. In particular, Example 7 of Zhang discloses methods for modifying a target cite in the genome of a plant cells comprising the delivery of a guide RNA and Cas endonuclease to a plant cell. FF7–FF8. In addition, Zhang teaches that

the guide RNA and Cas endonuclease form a complex that enables to the Cas endonuclease to introduce a double strand break at the site targeted by the guide RNA. FF2–FF3.

We are not persuaded by Appellant's argument that Examiner's anticipation rejection is premised on "mere speculation." *See* Reply Br. 5–6. Zhang specifically describes methods for modifying a target site in the genome of a plant cell comprising the step of providing a guide RNA and Cas9 endonuclease to such cells. FF4–FF8. Moreover, with respect to the "wherein" clause of claim 6, Zhang explains that in the CRISPR-Cas systems it describes the guide RNA and Cas9 endonuclease form a complex that enables Cas9 to introduce a double strand break in the DNA at a target cite in the genome. FF2–FF3. Thus, Zhang, in fact, discloses all of the elements of claim 6 "arranged or combined in the same way as in the claim." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (quotations omitted).

Appellant's argument that Zhang does not provide an enabling disclosure for plant cells is also unpersuasive. *See* Reply Br. 6–8. First, Zhang describes the use of CRISPR-Cas systems to introduce double strand breaks as specific sites within the genome of eukaryotic cells. FF1–FF3. Second, Zhang teaches that these techniques can be used in plant cells and incorporates additional disclosure from a number of references relating to the generation of transgenic plants. FF4–FF6. Third, Zhang discloses an example specifically directed to the application of a CRISPR-Cas system and other techniques to produce modified plant cells. FF7–FF8. These disclosures are presumed to be enabled and sufficient to establish a prima facie case of anticipation. *See Antor*, 689 F.3d at 1289. "[T]he burden

[then] shifts to the applicant to submit rebuttal evidence of nonenablement." *Id.*

Appellant has failed to persuasively explain, much less provide evidence, showing that Zhang's disclosures are not enabled for plant cells. Appellant asserts that Zhang "did not provide adequate instruction for how an RNA-guided Cas endonuclease complex could be provided or used in plant cells without undue experimentation" and that "[t]he step in Claim 6 of 'providing a guide RNA and a Cas endonuclease to said plant cell' was not taught by Zhang's mentioning of a generic method of introducing DNA into a cell." Reply Br. 8. Those arguments, however, ignore the methods taught in Zhang Example 7. FF7–FF8. Nor does Appellant address the other plant-related disclosure (*see* FF4–FF6) that Zhang provides and incorporates by reference. In a single sentence in its Reply Brief, and without further explanation, Appellant asserts that "a prophetic description for unicellular microalgae . . . do[es] not satisfy the enabling requirement."[6] Reply Br. 7. However, even assuming Zhang Example 7 is a prophetic example, as opposed to a working one, that example and the other plant-related disclosures in Zhang are still presumptively enabled. *See Antor*, 689 F.3d at 1289–90 ("[T]he mere use of forward-looking language (such as terms like 'should') does not show one way or another whether a person of ordinary skill in the art would have to engage in undue experimentation" because "the invention in a prior art publication need not have actually been made or

[6] We note that this is the only time in its briefing Appellant appears to acknowledge Zhang's broader disclosure regarding the use of CRISPR-Cas systems in plant cells, beyond that which Examiner cited to in the '529 Provisional.

performed to satisfy enablement."). Appellant has not shown that undue experimentation would be required to follow those teachings.

Instead, Appellant contrasts what it characterizes as "vague references scattered across Zhang" with the present Specification that, according to Appellant, "provides forty examples of specific compositions and detailed methods for creating modifications in a plant cell using an RNA-guided Cas endonuclease." Reply Br. 7. That comparison, however, is unpersuasive. First, Appellant's comparison does not distinguish claim 6 because claim 6 is not limited to any particular method for using a RNA-guided Cas endonuclease to modify the genome of a plant cell and therefore directly reads on the methods disclosed in Zhang Example 7. Second, Appellant has not identified any particular disclosure that it contends is: (1) necessary to enable Zhang's teachings regarding the use of CRISPR-Cas systems in plant cells; and (2) not expressly disclosed, nor incorporated by reference, in Zhang. It may be that Appellant's Specification provides additional disclosure pertinent to the use of an RNA-guided Cas endonuclease that Zhang lacks, but claim 6 does not recite such. Moreover, Appellant has not provided sufficient argument and evidence to overcome the presumption that Zhang's teachings, including the particular methods taught in Zhang Example 7, are enabled.

For these reasons, we determine that the preponderance of the evidence supports a determination that claim 6 is anticipated by Zhang and therefore affirm the rejection. Because our rationale for affirming the rejection is substantially based on disclosure in Zhang that was not previously cited by Examiner, we designate this affirmance a new ground of rejection.

III. OBVIOUSNESS REJECTION

Issue

Appellant does not argue Examiner's rejection of claims 15–17 separately from claim 6. Thus, claims 15–17 stand or fall with claim 6. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Accordingly, the issue before us is whether a preponderance of the evidence supports Examiner's conclusion that Zhang in combination with Hein renders the method in claim 6 obvious.

Additional Findings of Fact

FF9. Hein "relates to expression and assembly of foreign multimeric proteins—*e.g.*, antibodies—in plants, as well as to transgenic plants that express such proteins." Hein, Abstr. Hein teaches various methods for producing transgenic plants containing a multimeric protein by introducing DNA to transform the genome of a plant cell. *See id.* at 10:28–15:57.

FF10. Hein teaches that the methods it describes for producing transgenic plants can be used in dicots, including tobacco, tomato, legumes, and alfalfa; monocots, including grasses, corn, oats, wheat, and barley; as well as "lower plants" such as algae. Hein, 19:20–29.

Analysis

Examiner finds

> Zhang teaches a method providing a vector system comprising one or more vectors, wherein the vector system comprises (a) a regulatory element operably linked to a guide [RNA] sequence, that when expressed, directs sequence-specific binding of a CRISPR complex to a target sequence in a eukaryotic cell, wherein the CRISPR complex comprises a [Cas] enzyme complexed with the guide sequence . . . .

Ans. 7 (citing '527 Provisional ¶ 4). Examiner further determines that Zhang "contemplates applying their method in transgenic plants," but "does not expressly teach transformed monocots such as maize or transformed dicots such as soybean." *Id.* at 7 (citing '527 Provisional ¶ 79). Examiner concludes that it would have been obvious for a skilled artisan to combine Zhang's "method of introducing double strand breaks into the genome of eukaryotic cells" using a CRISPR-Cas system "with the teachings of Hein to modify the genome of other plants that are routinely transformed," including both monocots and dicots as recited in Appellant's dependent claims. *Id.*

We agree with Examiner's findings (*see* FF1–FF10) and conclusion of obvious. In addition to the teachings Examiner cites from '527 Provisional, we note that Zhang expressly teaches that its methods for using CRISPR-Cas systems to induce double stand breaks at target locations in genome provide a new tool for plant breeders to produce transgenic crops with improved traits and incorporates by reference various disclosures relating to techniques for producing transgenic plants. FF5–FF6. As such, Zhang provides an express motivation to combine its teachings with those in Hein. In addition, Zhang provides specific methods for delivering a Cas9 endonuclease and guide RNA into plant cells (FF7–FF8) and teaches that in such systems the Cas9 complex introduces a double strand break at the location targeted by the guide RNA (FF2–FF3).

We are not persuaded by Appellant's arguments that "[t]he sole appearance of the word 'plant' in the '527 [Provisional] is in Paragraph [0079]" and "Zhang does not provide any method for testing of CRISPR-Cas compositions in plants, or for modification of a plant cell genome with a Cas endonuclease and guide RNA complex." *See* Appeal Br. 10–14. While

Appellant's characterization of the '527 Provisional is correct, Appellant's arguments ignore the disclosure in Zhang regarding the use of CRISPR-Cas systems in plant cells. *See* FF4–FF8.

Appellant's argument that a skilled artisan would not have a reasonable expectation of success "because of plant cell/animal cell differences" is likewise unpersuasive. *See* Appeal Br. 14–15. As explained above, Zhang teaches that CRISPR-Cas systems can be used in both animal and plant cells and provides specific methods and vectors for doing so. *See* FF1–FF8. Zhang's teachings are sufficient to support a prima facie case of obviousness for claim 6, particularly given that "[t]he reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success." *Par Pharm., Inc. v. TWI Pharms., Inc*., 773 F.3d 1186, 1198 (Fed. Cir. 2014). Thus, while it is no doubt true that "plant cells are different from animal cells" (Appeal Br. 14), Appellant has not provided sufficient, evidence–backed argument to demonstrate that any of those differences would have resulted in one of ordinary skill in the art to lacking a reasonable expectation that Zhang's CRISPR-Cas systems could be successfully used in plants.

Appellant's reliance on the Appellees' arguments to the Federal Circuit in Appeal No. 2017-1907 ("CAFC Brief") does not demonstrate otherwise. *See* Appeal Br. 14. The arguments Appellant cites in the CAFC Brief relate to differences between prokaryotic and eukaryotic cells and whether one of skill in the art would have had a reasonable expectation of successfully engineering a CRISPR-Cas system for eukaryotes. *Id.* Appellant asserts that the "difference in cell type" between plant and animal cells is "analogous to the challenges alleged by [Appellees] when comparing

Cas endonuclease mediated genome editing of eukaryotic cells versus prokaryotic cells." *Id.* That assertion, however, is merely attorney argument. *See In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984) (explaining that arguments and conclusions unsupported by factual evidence carry no evidentiary weight). Appellant has not provided evidence demonstrating how, if at all, the arguments regarding prokaryotic and eukaryotic cells in the CAFC Brief are relevant to whether a skilled artisan would reasonably expected that Zhang's teachings could be successfully applied in plants.

Appellant's reliance on Shukla[7] and the Zhang Article[8] (*see* Appeal Br. 15–17) is similarly unpersuasive because Appellant has not persuasively shown that the subject matter of these articles relates to whether one of ordinary skill in the art would have had a reasonable expectation that Zhang's teachings regarding CRISPR-Cas systems could be successfully applied to plants. Shukla describes the use of a different technology, i.e., Zinc-Finger Nucleases ("ZFNs") to edit the genome of a species of maize. *See* Shukla, 437. According to Appellant, ZFNs "had previously been described as a gene editing tool in mammalian (human) cells," but Shukla evidences that "additional ZFN method development was necessary for use in plant cells." Appeal Br. 16. The Zhang Article describes experiments with another technology, Transcription Activator-Like Effector Nucleases ("TALENs"). Zhang Article, 20. Similar to its argument concerning

[7] Shukla et al., *Precise Genome Modification in the Crop Species Zea Mays Using Zinc-Finger Nucleases*, 459 Nature 437–41 (2009) ("Shukla").
[8] Zhang et al., *Transcription Activator-Like Effector Nucleases Enable Efficient Plant Genome Engineering*, 161 Plant Physiology 20–27 (2013) ("Zhang Article").

Shukla, Appellant urges that the Zhang Article shows additional development was necessary before TALENs could be successfully used in plants. *See* Appeal Br. 16–17. The problem with both arguments is that even if we assume the premise is correct, i.e., some amount of additional work was required to adapt ZFNs and TALENs before those technologies could be successfully used in plants, Appellant has not persuasively demonstrated how the any of the difficulties allegedly encountered with adapting ZFNs and TALENs to work in plants relates to Zhang's teachings regarding the use of CRISPR-Cas systems. Again, these are different technologies and Appellant offers nothing other than attorney argument in its attempt to relate them to the teachings in Zhang.[9]

Moreover, even if Appellant had provided evidence to connect the arguments between the different types of cells in the CAFC Brief and the different technologies in Shukla and the Zhang Article to facts of the rejections here, Appellant still has not addressed how any of this overcomes Zhang's express teaching that its CRISPR-Cas systems can be used to edit the genome of crops and other plants (FF4–FF7) and particular methods for doing so described in Example 7 (FF7–FF8). It may be, as Appellant urges, that the examples in the "instant application [demonstrates successful genome editing of a plant cell with a Cas endonuclease and guide RNA . . . with specific compositions and methods," but the present claims are not limited to any specific composition or method in those examples. *See*

[9] We further note Zhang's teaching that unlike other gene editing technologies CRISPR-Cas systems do not require the creation of customized proteins to target specific sequences, but rather are targeted by changing the guide RNA. FF1.

Appeal Br. 11. Thus, Appellant's arguments do not distinguish the present claims over the asserted combination of Zhang and Hein.

For these reasons, we determine that the preponderance of the evidence supports Examiner's conclusion that claims 6 and 15–17 are obvious over Zhang and Hein. However, as before, we recognize that much of the disclosure in Zhang supporting our affirmance was not previously cited by Examiner. Accordingly, in order to provide Appellant an opportunity to fully respond, we designate our affirmance a new ground of rejection.

DECISION SUMMARY

Claims Rejected	**35 U.S.C. §**	**Reference(s)/Basis**	**Affirmed**	**Reversed**	**New Ground**
6	102	Zhang	6		6
6, 15–17	103	Zhang, Hein	6, 15–17		6, 15–17
Overall Outcome			6, 15–17		6, 15–17

FINALITY AND RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. . . .
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

AFFIRMED; 37 C.F.R. § 41.50(b)