United States Court of Appeals for the Federal Circuit

AGILENT TECHNOLOGIES, INC.,
Appellant

v.

SYNTHEGO CORP.,
Appellee

2023-2186, 2023-2187

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2022-00402, IPR2022-00403.

Decided: June 11, 2025

MARK A. LEMLEY, Lex Lumina PLLC, Los Angeles, CA, argued for appellant. Also represented by DENISE MARIE DE MORY, AARON HAND, Bunsow De Mory LLP, Redwood City, CA; REBECCA EMILY WEIRES, Morrison & Foerster LLP, Los Angeles, CA.

EDWARD R. REINES, Jones Day, Palo Alto, CA, argued for appellee. Also represented by DEREK C. WALTER, San Francisco, CA.

Before PROST, LINN, and REYNA, *Circuit Judges*.

PROST, *Circuit Judge*.

Agilent Technologies, Inc. ("Agilent") appeals from two final written decisions of the Patent Trial and Appeal Board ("Board") determining that all claims of U.S. Patent Nos. 10,337,001 ("the '001 patent") and 10,900,034 ("the '034 patent") are unpatentable. Because the Board did not commit legal error and substantial evidence supports its factual findings, we affirm.

BACKGROUND

I

The technology at issue relates to CRISPR-Cas[1] systems for gene editing. At a high level, the CRISPR-Cas system at issue here includes three components: (1) "non-coding RNA species referred to as CRISPR RNA ('crRNA')"; (2) "trans-acting RNA ('tracrRNA')"; and (3) the CRISPR-associated ("Cas") protein. '001 patent col. 1 ll. 23–36. The guide RNA, also known as "gRNA" or "double-molecule gRNA," is made up of two parts: a crRNA and a tracrRNA. *Id.* at col. 1 ll. 33–36, 49–51. A single-molecule gRNA, also known as a "sgRNA," combines the crRNA and tracrRNA on a single strand through a linker loop. *Id.* at col. 1 ll. 49–51; J.A. 473.

The CRISPR-Cas system permits one to selectively cleave DNA at particular target sites. The gRNA and the Cas protein bind to form a single complex. '001 patent col. 1 ll. 36–37. The gRNA directs the gRNA-Cas complex to a targeted DNA sequence, binds with the target DNA, and then the Cas protein cleaves the DNA sequence at that location. *Id.* at col. 1 ll. 36–43. For the CRISPR-Cas system to work effectively, it needs to be able to bind to the target

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[1] "CRISPR" stands for "clusters of regularly interspaced short palindromic repeats." '001 patent col. 1 ll. 18–19.

polynucleotide sequence, the gRNA needs to remain stable and resist degradation, and the gRNA needs to maintain its functionality. *Id.* at col. 1 ll. 60–67.

The '001 patent issued on July 2, 2019, claims priority to a series of provisional applications, the earliest of which was filed on December 3, 2014, and is assigned to Agilent. The '034 patent issued on January 26, 2021, claims priority to a series of provisional applications, the earliest of which was filed on December 3, 2014, and is assigned to Agilent. The '001 and '034 patents are directed to chemically modified gRNAs and their use in the CRISPR-Cas system. Representative claim 1 in each of the '001 and '034 patents is reproduced below:

> A synthetic CRISPR guide RNA having at least one 5′-end and at least one 3′-end, the synthetic guide RNA comprising:
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> > (a) one or more modified nucleotides within five nucleotides from said 5′-end, or
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> > (b) one or more modified nucleotides within five nucleotides from said 3′-end, or
> >
> > (c) both (a) and (b);
> >
> > wherein said guide RNA comprises one or more RNA molecules, and has *gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to a target polynucleotide*, wherein the modified nucleotide has a modification to a phosphodiester linkage, a sugar, or both.

'001 patent claim 1 (emphasis added).

> A synthetic CRISPR guide RNA comprising:
>
> > (a) a crRNA segment comprising (i) a guide sequence capable of hybridizing to a target

> sequence in a polynucleotide, (ii) a stem sequence; and
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> (b) a tracrRNA segment comprising a nucleotide sequence that is partially or completely complementary to the stem sequence,
>
> wherein the synthetic guide RNA has *gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to the target sequence*, and comprises one or more modifications in the guide sequence, wherein the one or more modifications comprises a 2′-O-methyl.

'034 patent claim 1 (emphasis added). The dependent claims narrow the modifications of the nucleotides to particular types of phosphodiester linkage or sugar modifications and combinations thereof. *See, e.g.*, '001 patent claim 8 ("The synthetic guide RNA of claim 1 wherein said guide RNA comprises a modified internucleotide linkage or a modified terminal phosphate group selected from a phosphonocarboxylate, a phosphonoacetate, and a phosphonothioacetate group."); '034 patent claim 6 ("The synthetic guide RNA of claim 1, wherein said one or more modifications comprises a 2′-O-methyl nucleotide with a 3′-phosphonoacetate.").

II

The key prior art relevant to the Board's anticipation determination is Pioneer Hi-Bred.[2] Pioneer Hi-Bred was filed on August 20, 2014, by Pioneer Hi-Bred International, Inc. and is titled "Genome Modification Using Guide

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[2] Int'l Pub. No. WO 2015/026885 A1 ("Pioneer Hi-Bred"), J.A. 2588–2736.

Polynucleotide/Cas Endonuclease Systems and Methods of Use." Pioneer Hi-Bred Title (capitalization omitted). Pioneer Hi-Bred discloses "[c]ompositions and methods" for "employing a guide polynucleotide/Cas endonuclease system for genome modification of a target sequence in the genome of a cell or organism, for gene editing, and for inserting a polynucleotide of interest into the genome of a cell or organism." *Id.* at 2 ll. 1–5.[3] It also defines "guide polynucleotide" to mean "a polynucleotide sequence that can form a complex with a Cas endonuclease and enables the Cas endonuclease to recognize and optionally cleave a DNA target site." *Id.* at 24 ll. 6–8. A "guide polynucleotide" "can be a single molecule or a double molecule" and a "guide polynucleotide that solely comprises ribonucleic acids is also referred to as a 'guide RNA.'" *Id.* at 24 ll. 8–9, 19–20. In Example 4, Pioneer Hi-Bred discloses "modifying the nucleotide base, phosphodiester bond linkage or molecular topography of the guiding nucleic acid component(s) of the guide polynucleotide/Cas endonuclease system" "for increasing cleavage activity and specificity." *Id.* at 104 l. 19–105 l. 2. "To increase the effective lifespan or stability of the nucleic acid component(s) of the guide polynucleotide/Cas endonuclease system *in vivo*, nucleotide and/or phosphodiester bond modifications may be introduced to reduce unwanted degradation." *Id.* at 106 ll. 14–17.

Relevant to this appeal, there are two additional prior-art references that the Board relied on to determine certain claims were unpatentable for obviousness: Threlfall[4] and

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[3] The pages cited correspond to the page numbers of Pioneer Hi-Bred itself.

[4] Richard N. Threlfall et al., *Synthesis and Biological Activity of Phosphonoacetate- and Thiophosphonoacetate-modified 2'-O-methyl Oligoribonucleotides*, 10 Org. Biomol. Chem., 746–54 (2011) ("Threlfall"), J.A. 2773–81.

Deleavey.[5] Threlfall is a scientific article published on November 29, 2011. Threlfall describes "[c]himeric 2′-O-methyl oligoribonucleotides (2′-OMe ORNs) containing internucleotide linkages which were modified with phosphonoacetate (PACE) or thiophosphonoacetate (thioPACE)." J.A. 2773. Threlfall explains that "[o]ligoribonucleotides with a 2′-O-methyl modification (2′-OMe ORNs) are known to be nuclease resistant and increase the stability of a duplex which is formed with complementary RNA." J.A. 2773 (footnote omitted). And Threlfall notes that in "a previous study, [oligodeoxynucleotides] modified with PACE or thioPACE were shown to be nuclease resistant." J.A. 2773.

Deleavey is a scientific article published on August 24, 2012. According to Deleavey, there were several "obstacles" with using chemically modified oligonucleotides, including RNA molecules, for gene regulation purposes, such as: "(1) their poor extracellular and intracellular stability, (2) low efficiency of intracellular delivery to targets cells or tissues, and (3) the potential for 'off-target' gene silencing, immunostimulation, and other side effects." J.A. 2737. To overcome these "obstacles," Deleavey discusses "a vast array" of chemical modifications that have been developed, J.A. 2737, including specific chemical modifications to internucleotide linkages, J.A. 2743 (Fig. 4), and to nucleotide sugars, J.A. 2746 (Fig. 6).

III

Synthego Corp. ("Synthego") filed two petitions for inter partes review ("IPR") of all claims of the '001 and '034 patents. J.A. 448, 9106. After instituting review on all

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[5] Glen F. Deleavey et al., *Designing Chemically Modified Oligonucleotides for Targeted Gene Silencing*, 19 Chem. & Bio. Review, 937–54 (2012) ("Deleavey"), J.A. 2737–54.

claims, the Board found that every claim in both the '001 and '034 patents is unpatentable. J.A. 1–143.[6] In particular, the Board found that Pioneer Hi-Bred anticipated claims 1–7, 9–10, 12–15, 17–18, 20–25, and 27–30 of the '001 patent and claims 1–5, 8–21, and 24–33 of the '034 patent. The Board reasoned that Pioneer Hi-Bred both discloses a functional gRNA and is enabling. The Board also found Synthego had shown that claims 8, 11, 16, 19, and 26 of the '001 patent and claims 6–7 and 22–23 of the '034 patent would have been obvious in view of Pioneer Hi-Bred and Threlfall or Deleavey. The Board relied on "Pioneer Hi-Bred for the limitations of the independent claims and Threlfall and Deleavey for their disclosure of 'phosphonoacetate' and 'phosphonothioacetate' (i.e., PACE and thioPACE) modifications as recited in claims 8 and 16 and '2[′]-O-methyl-3[′]-phosphonoacetate' and '2[′]-O-methyl-3[′]-phosphonothioacetate' nucleotides as recited in claims 11, 19, and 26" of the '001 patent. J.A. 58; *see also* J.A. 133 (similar for claims 6–7 and 22–23 of the '034 patent).

Agilent timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

"We review the Board's legal determinations de novo and its fact findings for substantial evidence." *Provisur Techs., Inc. v. Weber, Inc.*, 50 F.4th 117, 124 (Fed. Cir. 2022). Because "[a]nticipation is a question of fact," we review "the Board's determination of what is taught in the prior art at issue" for substantial evidence. *St. Jude Med., LLC v. Snyders Heart Valve LLC*, 977 F.3d 1232, 1238

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[6] The two final written decisions at issue in this appeal are substantially similar. In this opinion, we will cite to the final written decision in IPR No. 2022-00402 (J.A. 1–67), unless the record of IPR No. 2022-00403 (J.A. 68–143) provides a relevant difference.

(Fed. Cir. 2020); *see also* Oral Arg. at 5:14–40 (Agilent agreeing substantial-evidence review applies to determine whether Pioneer Hi-Bred expressly discloses the claimed gRNA functionality).[7] "Whether a prior[-]art reference is enabling is a question of law based on underlying factual findings." *In re Morsa*, 803 F.3d 1374, 1376 (Fed. Cir. 2015). "For obviousness, the ultimate determination is a legal one reviewed de novo, but underlying factual determinations are reviewed for substantial-evidence support." *St. Jude Med.*, 977 F.3d at 1238. Whether there is a reasonable expectation of success is a question of fact. *Teva Pharms. USA v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1380–81 (Fed. Cir. 2021). "Substantial[-]evidence review asks whether a reasonable fact finder could have arrived at the agency's decision and requires examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1366 (Fed. Cir. 2016) (cleaned up). "Where two different conclusions may be warranted based on the evidence of record, the Board's decision to favor one conclusion over the other is the type of decision that must be sustained by this court as supported by substantial evidence." *In re Chudik*, 851 F.3d 1365, 1371 (Fed. Cir. 2017) (quoting *In re Bayer Aktiengesellschaft*, 488 F.3d 960, 970 (Fed. Cir. 2007)).

Agilent raises three main issues on appeal. First, it argues that substantial evidence does not support the Board's finding that Pioneer Hi-Bred expressly discloses gRNA functionality. Second, it argues that, even if the Board did not err in finding that Pioneer Hi-Bred discloses gRNA functionality, Pioneer Hi-Bred is not enabling. Third, it contends that substantial evidence does not support the Board's finding that a skilled artisan would

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[7] No. 23-2186, https://oralarguments.cafc.uscourts.gov/default.aspx?fl=23-2186_03072025.mp3.

reasonably expect PACE and thioPACE modifications to gRNA in a CRISPR-Cas system to be successful. We address each argument in turn.

I

As to the first issue—whether Pioneer Hi-Bred expressly discloses the claimed functional gRNA—we conclude that substantial evidence supports the Board's finding.

The Board found that Pioneer Hi-Bred discloses the claimed gRNA functionality, i.e., associating with a Cas protein and targeting the gRNA:Cas protein complex to a target polynucleotide. It explained that "Pioneer Hi-Bred discloses that the guide polynucleotides described therein can: (1) form a complex with a Cas endonuclease; and (2) enable the endonuclease to recognize a DNA target site. That disclosure reads on both the associating and targeting aspects of the 'gRNA functionality' recited" in the challenged claims. J.A. 18. Specifically, the Board cited to the modified sequences in Examples 4 and 5 of Pioneer Hi-Bred. J.A. 18. Example 4 is titled "[m]odifying nucleic acid component(s) of the guide polynucleotide/Cas endonuclease system to increase cleavage activity and specificity," J.A. 2693, and Example 5 is titled "[e]xamining the effect of nucleotide base and phosphodiester bond modifications to the guide polynucleotide component of the guide polynucleotide/Cas endonuclease system in maize," J.A. 2697. The Board found that "Pioneer Hi-Bred refers to the modified sequences in Examples 4 and 5 as 'modified guide nucleotides,' indicating that those sequences have [the claimed gRNA] functionality." J.A. 18. The Board also cited to several statements in Pioneer Hi-Bred further supporting its findings. *See, e.g.*, J.A. 18 (citing Pioneer Hi-Bred at 107 ll. 14–24 (explaining that modified guide polynucleotides may be delivered with the other components of the "guide polynucleotide/Cas endonuclease system" to "form a functional complex capable of binding and/or

cleaving a chromosomal DNA target site"); Pioneer Hi-Bred at 107 l. 24–108 l. 2 ("Modified guide polynucleotides described above may also be delivered simultaneously in multiplex to target multiple chromosomal DNA sequences for cleavage or nicking.")). The Board clarified that "[w]hile the claimed 'gRNA functionality' does not require cleavage, the fact that cleavage occurs at a target site indicates that a gRNA is capable of associating with a Cas endonuclease and targeting it to a particular site." J.A. 18 n.9.

Agilent contends that Pioneer Hi-Bred does not expressly disclose the gRNA functionality, but only discusses a research plan to *test* for functionality of modified guide polynucleotides, such as Example 5, J.A. 2697, and falls short of stating that any particular modified guide would actually exhibit gRNA functionality. Agilent argues that the statements in Pioneer Hi-Bred relied on by the Board cannot be read as disclosures of functionality largely because Pioneer Hi-Bred does not differentiate functional from non-functional guides. *See, e.g.*, Appellant's Br. 30–32; Reply Br. 1–12.

Agilent also argues that data in Pioneer Hi-Bred showing no cleavage for a particular modified gRNA (and some later testing of other modified guide polynucleotides disclosed in Pioneer Hi-Bred that did not show cleavage) demonstrates that Pioneer Hi-Bred does not disclose gRNA functionality. The Board rejected these arguments. It held that cleavage "is not required for the 'gRNA functionality'" in the challenged claims and also cited Agilent's own expert admitting that "just because a gRNA in Table 4 [in Pioneer Hi-Bred] lacks cleavage activity does not demonstrate that it also lacks the ability to bind a Cas protein and target that complex to target polynucleotide." J.A. 25. The Board found that "the data in Table 4 of [Pioneer Hi-Bred's] [s]pecification showing a lack of cleavage activity does not demonstrate that the corresponding gRNA lacks the claimed 'gRNA functionality.'" J.A. 26. The disclosure of some non-working examples in Pioneer Hi-Bred does not

undermine the disclosure of other examples that were disclosed as functional. Agilent has not demonstrated that this finding lacks substantial evidence.

The Board also found Pioneer Hi-Bred's statements as express disclosures of functionality. *See, e.g.*, J.A. 18 (citing Pioneer Hi-Bred at 107 l. 24–108 l. 2 ("Modified guide polynucleotides described above may also be delivered simultaneously in multiplex to target multiple chromosomal DNA sequences for cleavage or nicking.")), J.A. 12 (citing Pioneer Hi-Bred at 106 ll. 17–21 ("Examples of nuclease resistant nucleotide and phosphodiester bond modifications are shown in Table 7 and may be introduced . . . at the 5' and 3' ends of any one of the nucleic acid residues comprising the VT or GER domains to inhibit exonuclease cleavage activity.")), J.A. 12–13 ("According to Pioneer Hi-Bred, these modified guide polynucleotides may be used 'in any organism subject to genome modification with the guide polynucleotide/Cas endonuclease system.'" (quoting Pioneer Hi-Bred at 108 ll. 3–5)).

To the extent that Agilent argues that Pioneer Hi-Bred does not disclose gRNA functionality because a person of ordinary skill in the art would not know how to create a functional modified guide from the disclosure because of the number of non-working examples, we view this argument as one related to whether Pioneer Hi-Bred is an enabling anticipatory reference rather than whether Pioneer Hi-Bred expressly discloses the claimed gRNA functionality. We address why Pioneer Hi-Bred is an enabling anticipatory reference in Section II of this opinion's Discussion.

For the foregoing reasons, substantial evidence supports the Board's finding that Pioneer Hi-Bred expressly discloses the claimed gRNA functionality, i.e., associating

with a Cas protein and targeting the gRNA:Cas protein complex to a target polynucleotide.[8]

II

Turning to the Board's enablement analysis, we see no error in the Board's conclusion that Pioneer Hi-Bred is enabling.

A finding of anticipation "does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). "[P]roof of efficacy is not required in order

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[8] Agilent also argues that the Board violated the requirements of notice and an opportunity to respond found in the Administrative Procedure Act ("APA"). Appellant's Br. 32–34; Reply Br. 12–14. Specifically, Agilent argues that the final written decisions were "the first time either Synthego or the Board explained that it read the mere use of the term 'modified guide polynucleotide' as an express disclosure of the claimed functionality." Reply Br. 12. The notice and opportunity-to-be-heard provisions of the APA have been applied "to mean that 'an agency may not change theories in midstream without giving respondents reasonable notice of the change' and 'the opportunity to present argument under the new theory.'" *Belden v. Berk–Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015) (quoting *Rodale Press, Inc. v. FTC*, 407 F.2d 1252, 1256–57 (D.C. Cir. 1968)). Here, the Board did not "change theories in midstream." The Board based its decision on more than just the definition of "guide polynucleotide" in Pioneer Hi-Bred. *See, e.g.*, J.A. 18, 20–21. And the question of whether the modified guide polynucleotide met the gRNA functionality limitation was central to the entire IPR proceedings. *See, e.g.*, J.A. 489–90 (petition), 698 (Board's institution decision). We thus reject Agilent's APA-based arguments.

for a reference to be enabled for purposes of anticipation." *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005). "Enablement of prior art requires that the reference teach a skilled artisan—at the time of filing—to make or carry out what it discloses in relation to the claimed invention without undue experimentation." *In re Morsa*, 803 F.3d at 1377. "For a prior-art reference to be enabling, it need not enable the [challenged] claim in its entirety, but instead the reference need only enable a single embodiment of the claim." *Id.*; *see also Schering*, 339 F.3d at 1381 ("An anticipatory reference need only enable subject matter that falls within the scope of the claims at issue, nothing more."). Prior art disclosures are presumed enabling. *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008) (reaffirming that an anticipating prior art patent is presumptively enabled); *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012) (extending the presumption to printed publications).

In assessing whether undue experimentation is required, the Board considered the *Wands* factors and found that the "record demonstrates that a [person of ordinary skill in the art], as of December 2014, could practice these disclosures without undue experimentation." J.A. 29; *see also* J.A. 29 n.13 (citing *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)). The Board rejected Agilent's argument that it would have been "extremely challenging for a [person of ordinary skill in the art] to chemically synthesize the claimed chemically-modified gRNA." J.A. 30 (cleaned up). It noted that the '001 and '034 patents' specifications "refer[] to the use of click chemistry and TC chemistry techniques," which both parties' experts agreed were techniques "known in the prior art for synthesizing long oligonucleotides." J.A. 29–30. The Board also found that "while it appears that Examples 4 and 5 in Pioneer Hi-Bred are prophetic, as opposed to working[] examples, that fact alone does not undermine the presumption that Pioneer Hi-Bred is enabled." J.A. 31. And it also rejected Agilent's argument that

"the nascent state of the art demonstrates that undue experimentation would be required." J.A. 32. It found that "[i]t is undisputed that the use of gRNA in a CRISPR/Cas system was a relatively new discovery first published in mid-2012. That said, the record demonstrates that by December 2014 substantial research into such systems had been published and would have been known to a [person of ordinary skill in the art]." J.A. 32 (internal citations omitted). The Board also found that:

> [W]hile the art was somewhat unpredictable in December 2014, it was far from a blank slate with a [person of ordinary skill in the art] understanding how the different elements of a CRISPR/Cas system are used and function together, including the role of gRNA; the types of chemical modifications that had been successfully used in other systems to reduce RNA degradation, while preserving functionality; and standard techniques for making gRNAs with the modifications disclosed and exemplified in Pioneer Hi-Bred.

J.A. 32. Considering these findings, the Board concluded that "undue experimentation would not have been required to make and use a gRNA with the recited chemical modifications and functionality." J.A. 33.

On appeal, Agilent argues that *Impax* is analogous to the facts here. We disagree and conclude there are important distinctions between that case and this one. One of the issues in *Impax* was whether a prior-art patent was an enabling prior-art reference. We affirmed the district court's finding that the prior-art patent was not an enabling prior-art reference. *Impax*, 545 F.3d at 1316. The prior-art patent in *Impax* "disclose[d] hundreds or thousands of compounds and several diseases," as well as "broad and general" dosage guidelines "without sufficient direction or guidance to prescribe a treatment regimen." *Id.* at 1315. Unlike the prior-art reference at issue in

Impax, "Pioneer Hi-Bred exemplifies particular crRNA sequences having the recited chemical modifications at the recited locations and teaches that gRNA comprising such may be used as guide polynucleotides in a CRISPR Cas system." J.A. 33; *see also* Pioneer Hi-Bred at 107 (Table 7) (disclosing five types of "[n]ucleotide base and phosphodiester bond modifications to decrease unwanted nuclease degradation"); *id.* at 109–10 (Table 8) (disclosing exemplary sequences of chemically modified crRNAs described in Table 7). The Board found that "the particular types of chemical modifications disclosed in Pioneer Hi-Bred and recited in the challenged claims had been known and used for decades to stabilize RNA against unwanted degradation in other systems." J.A. 32.

Agilent also likens this case to *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023).[9] In *Amgen*, the asserted claims were entirely functionally defined such that the patentee "s[ought] to monopolize an entire class of things defined by their function—every antibody that both binds to particular areas of the sweet spot of PCSK9 and blocks PCSK9 from binding to LDL receptors." *Id.* at 613. The patentee claimed the entire genus of antibodies that performed the claimed functions. *Id.* at 602. As a result of the breadth of the asserted claims, the Supreme Court concluded that a person of ordinary skill in the art would have been "forced to engage in painstaking experimentation to see what works." *Id.* at 614 (cleaned up). The Supreme Court qualified its holding by stating that a specification does not "always" have to "describe with particularity how to make and use every single embodiment within a claimed class." *Id.* at 610–11. "Nor is a specification necessarily inadequate just because it leaves the skilled artist to engage in some measure of adaptation or testing." *Id.* at 611. Indeed, "[a]

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[9] *Amgen* issued after the Board's final written decisions issued.

specification may call for a reasonable amount of experimentation to make and use a patented invention," and "[w]hat is reasonable in any case will depend on the nature of the invention and the underlying art." *Id.* at 612.

This case is different in two meaningful ways. First, the issue in *Amgen* was whether the asserted claims were sufficiently enabling to be valid under 35 U.S.C. § 112, not whether a prior-art reference was enabling and could thus support anticipation. These are two separate inquiries. *See Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005). The reason for this distinction "is that [§] 112 'provides that the specification must enable one skilled in the art to "use" the invention whereas [35 U.S.C. §] 102 makes no such requirement as to an anticipatory disclosure.'" *Rasmusson*, 413 F.3d at 1325 (quoting *In re Hafner*, 410 F.2d 1403, 1405 (CCPA 1969)).[10] Second, while the patent in *Amgen* required "painstaking experimentation to see what works," here the Board found a person of ordinary skill in the art understood "how the different elements of a CRISPR/Cas system are used and function together, including the role of gRNA; the types of chemical modifications that had been successfully used in other systems to reduce RNA degradation, while

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[10] Indeed, in *Amgen*, the issue before the Supreme Court was whether the patents' specifications at issue "enable[d] the full scope of the invention as defined by its claims." *Amgen*, 598 U.S. at 610. In the § 112 context, enablement ensures the patentee does not obtain a broader monopoly than the specification teaches. *Id.* at 613 ("For if our cases teach anything, it is that the more a party claims, the broader the monopoly it demands, the more it must enable."). That is not a concern in the enabling anticipatory prior art context. Rather, an enabling anticipatory prior-art reference "need only enable a single embodiment of the claim." *In re Morsa*, 803 F.3d at 1377.

preserving functionality; and standard techniques for making gRNAs with the modifications disclosed and exemplified in Pioneer Hi-Bred." J.A. 32.[11] This finding is supported by substantial evidence.

Agilent also argues that "Pioneer Hi-Bred discloses many inoperable guides," and "[a] skilled artisan reading Pioneer Hi-Bred would have known this because the reference both discloses data that would lead them to doubt that guide DNA works at all and acknowledges uncertainty about which of the remaining modified guides in Examples 4 and 5 would work." Appellant's Br. 30. Agilent's argument is unpersuasive because the testing data Agilent cites is only applicable to synthetic *DNA* sequences, not to the modified *RNA* sequences at issue in the challenged claims. The Board also rejected Agilent's argument and found:

> Pioneer Hi-Bred discloses both DNA and RNA-based embodiments. The Petition is premised on the latter. Even if we accept [Agilent's] argument that the DNA-based examples lack gRNA functionality, that fact does not suggest that a [person of ordinary skill in the art] would doubt that the RNA-based embodiments, e.g., crRNAs comprising sequences 64–69 in Table 8, lack such functionality.

J.A. 22. Agilent has not demonstrated that this finding lacks substantial evidence.

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[11] Agilent primarily argues that Pioneer Hi-Bred theoretically discloses "over a quadrillion quadrillion" possible combinations. Appellant's Br. 2. But Agilent's framing of the issue is not consistent with our case law. The relevant question is whether, for a person of ordinary skill in the art, undue experimentation is required to make and use a gRNA with the claimed chemical modifications and functionality given the relevant disclosures in Pioneer Hi-Bred.

Agilent additionally argues that Pioneer Hi-Bred does not enable "a single guide RNA" or "sgRNA" found in claim 2 of the '001 patent and claim 4 of the '034 patent. Appellant's Br. 59–60. In addition to all the reasons why the Board found the relevant disclosures of Pioneer Hi-Bred enabling, J.A. 27–33, the Board separately found that Pioneer Hi-Bred discloses a chemically-modified sgRNA, J.A. 34. The Board found that "Pioneer Hi-Bred specifically states that the modifications in Table 8 can also be introduced in a 'long guide RNA,' i.e., a sgRNA." J.A. 34. The Board concluded that "while sequences 64–69 are described as part of a crRNA, a [person of ordinary skill in the art] would have immediately envisioned that those sequences could also be implemented in the corresponding domains of a sgRNA." J.A. 34. And as the Board explained, Agilent's challenged patents did not "disclose any new techniques for synthesizing chemically-modified gRNAs." J.A. 30. Having affirmed the Board's determination that Pioneer Hi-Bred discloses and enables a modified guide polynucleotide, the statement in Pioneer Hi-Bred that this can also be accomplished on a sgRNA is also supported by substantial evidence.

Agilent's remaining arguments regarding whether Pioneer Hi-Bred is enabling are unpersuasive. Substantial evidence supports the Board's findings that the anticipatory disclosures of Pioneer Hi-Bred were enabling, and the Board provided adequate explanation and reasoning for its enablement finding. We also discern no legal error in the Board's determination of enablement of the relevant disclosures in Pioneer Hi-Bred.

For the foregoing reasons, we affirm the Board's determination that Pioneer Hi-Bred's disclosure is enabling.

III

Next, Agilent argues that the Board erred in determining claims 8, 11, 16, 19, and 26 of the '001 patent and claims 6–7 and 22–23 of the '034 patent would have been obvious

in view of Pioneer Hi-Bred in combination with either Threlfall or Deleavey. J.A. 58–61, 133–36. These dependent claims recite a PACE or thioPACE modification with the claimed functionality. The Board relied on Threlfall and Deleavey for their disclosure of PACE and thioPACE modifications. J.A. 58.

Agilent makes two main arguments: (1) Pioneer Hi-Bred does not expressly disclose the functionality of the claimed PACE- or thioPACE-modified guides; and (2) the Board failed to explain its reasonable-expectation-of-success finding. Neither of these arguments is persuasive.

As to Agilent's first argument, it submits that Synthego's obviousness ground concerning Pioneer Hi-Bred, Threlfall, and Deleavey fails because "Pioneer Hi-Bred does not mention PACE or thioPACE modifications with the claimed functionality and so cannot serve as a prophetic hook for gRNA functionality in the alleged obviousness combination." Appellant's Br. 40.[12] We disagree with Agilent. Relevant to this appeal, the Board analyzed whether the challenged dependent claims would have been *obvious* in view of Pioneer Hi-Bred and Threlfall or Deleavey, not whether Pioneer Hi-Bred *anticipated* the challenged dependent claims. Agilent's argument assumes that express disclosure of PACE and thioPACE modifications in Pioneer Hi-Bred is required, but the Board found the dependent claims unpatentable as obvious, which does not necessarily require all the claimed limitations to be expressly disclosed in Pioneer Hi-Bred. *See, e.g.*, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("[T]he analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can

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[12] Agilent also argues that "Pioneer Hi-Bred fails to disclose the functionality of any particular guide," Appellant's Br. 40, but as discussed in Section I of this opinion's Discussion, we reject that argument.

take account of the inferences and creative steps that a person of ordinary skill in the art would employ."). Indeed, the Board provided a comprehensive analysis explaining why a person of ordinary skill in the art would have been motivated to combine Pioneer Hi-Bred with the teachings in Threlfall and Deleavey. J.A. 60–61; *see also* J.A. 60 ("The teachings in Threlfall and Deleavey support Dr. Furneaux's [Synthego's expert] testimony regarding the benefits, e.g., increased resistance to degradation and enhanced cellular uptake, that would have motivated a [person of ordinary skill in the art] to use such modifications in Pioneer Hi-Bred's gRNA." (cleaned up)); J.A. 44–51.

Contrary to Agilent's second argument, the Board provided a thorough analysis as to why a person of ordinary skill in the art would reasonably expect success in combining Pioneer Hi-Bred with either Threlfall or Deleavey. The Board found that "a [person of ordinary skill in the art] would reasonably expect PACE and thioPACE modifications to gRNA in a CRISPR/Cas system would be successful." J.A. 60. To support its obviousness analysis, the Board cross-referenced its earlier discussion addressing Agilent's "global arguments" concerning motivation to combine and reasonable expectation of success. J.A. 44 n.16; *see also* J.A. 44–51. For example, the Board found that:

> [B]y December 2014, several studies had shown that the CRISPR/Cas system could successfully tolerate modifications. While these studies describe different types of modifications than those in the challenged claims, such evidence nevertheless supports Dr. Furneaux's testimony that a [person of ordinary skill in the art] would have expected that chemical modifications could be made at the 5[′] and 3[′]-ends of a gRNA while preserving the Cas enzyme's gene editing function.
>
> The record further demonstrates that shortly after the discovery of the CRISPR/Cas system for gene

> editing and prior to December 2014, there were already a number of researchers in addition to the authors of the Pioneer Hi-Bred publication suggesting the use of the claimed chemical modifications to improve the resistance of gRNA to degradation. [Agilent's] expert, Dr. Marshall, conceded as much on cross-examination. The fact that multiple groups of researchers independently suggested the same types of gRNA modifications recited in the challenged claims evidences that a [person of ordinary skill in the art] would have had a reasonable expectation those modifications could be successfully employed in a CRISPR/Cas system. Moreover, while [Synthego] points to multiple references suggesting such modifications to gRNA, neither [Agilent] nor Dr. Marshall identify any reference expressing doubt that such modifications could be successfully implemented in a CRISPR/Cas system. This contrast undermines [Agilent's] argument that a [person of ordinary skill in the art] would not have reasonably expected the prior art modifications to work in a CRISPR/Cas system.

J.A. 49–50 (cleaned up). On this record, we conclude that substantial evidence supports the Board's finding of reasonable expectation of success.

CONCLUSION

We have considered Agilent's remaining arguments and find them unpersuasive. For the foregoing reasons, we affirm the Board's determination that all claims of the '001 and '034 patents are unpatentable.

AFFIRMED