No. 25-

IN THE

Supreme Court of the United States

AGILENT TECHNOLOGIES, INC.,

Petitioner,

v.

SYNTHEGO CORP.,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

DENISE M. DE MORY
Counsel of Record
AARON R. HAND
ABIGAIL LUBOW
KENNETH WANG
BUNSOW DE MORY LLP
701 El Camino Real
Redwood City, CA 94063
(650) 351-7248
ddemory@bdiplaw.com

Counsel for Petitioner, Agilent Technologies, Inc.

387449

COUNSEL PRESS
(800) 274-3321 • (800) 359-6859

QUESTIONS PRESENTED

A party challenging the validity of an issued patent in district court or in an *inter partes* review ("IPR") proceeding before the Patent Trial and Appeals Board ("PTAB") bears the burden of proving invalidity. 35 U.S.C. §§ 282, 316(e). To anticipate a claim of an issued patent, a prior art printed publication must disclose and enable said claim. *Seymour v. Osborne*, 78 U.S. (11 Wall.) 516, 538 (1870); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003) ("a non-enabled disclosure cannot be anticipatory (because it is not truly prior art)"). The questions presented are:

1. Should printed publications be presumed to be enabling when a party challenging the validity of issued patent claims asserts that a printed publication is anticipatory prior art, such that the burden of proving that the printed publication is nonenabling lies with the patentee?

2. Should the holding in *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005), that "proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation," be vacated or significantly narrowed?

PARTIES TO THE PROCEEDINGS BELOW

The caption of the case contains the names of all the parties to the proceedings.

RULE 29.6 CORPORATE DISCLOSURE STATEMENT

Agilent Technologies, Inc. has no parent corporations and no publicly held companies own 10% or more of its stock.

RELATED PROCEEDINGS

This petition is taken from a judgment of the Court of Appeals for the Federal Circuit entered in a consolidated proceeding involving two United States Patents, Nos. 10,337,001 and 10,900,034, assigned to Agilent Technologies, Inc.:

- *Agilent Technologies, Inc. v. Synthego Corp.*, Nos. 2023-2186 & 2023-2187, judgment dated June 11, 2025.

These Federal Circuit appeals arose from Final Written Decisions of the Patent Trial and Appeal Board entered May 17, 2023 in two corresponding *Inter Partes* Review proceedings:

- *Synthego Corporation v. Agilent Technologies, Inc.*, IPR2022-00402; and

- *Synthego Corporation v. Agilent Technologies, Inc.*, IPR2022-00403.

The patent claims found invalid by the Patent Trial and Appeal Board in the above proceedings were the subject of a declaratory judgment action for non-infringement filed by Synthego against Agilent in U.S. District Court for the Northern District of California. Agilent filed a counterclaim for infringement of the two patents. The action is stayed pending resolution of the above-referenced PTAB proceedings and the appeals therefrom:

- *Synthego Corporation v. Agilent Technologies, Inc.*, No. 3:21-cv-07801 (filed Oct. 5, 2021).

Agilent filed suit against Synthego in a patent infringement action in the U.S. District Court for the District of Delaware alleging infringement of the two patents. The case was transferred to the Northern District of California and later consolidated with the declaratory judgment case:

- *Agilent Technologies, Inc. v. Synthego Corporation*, No. 1:21-cv-01426 (filed Oct. 6, 2021).

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PETITION FOR WRIT OF CERTIORARI

Agilent Technologies, Inc. respectfully petitions for a writ of certiorari to review a judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The consolidated opinion of the Court of Appeals for the Federal Circuit disposing of case numbers 2023-2186 and 2023-2187 (App. 1a–24a) is reported in the Federal Reporter at 139 F.4th 1319.

The Final Written Decisions of the Patent Trial and Appeal Board for proceeding numbers IPR2022-00402 (App. 25a–96a) and IPR2022-00403 (App. 97a–177a) are not reported.

JURISDICTIONAL STATEMENT

The Federal Circuit entered judgment on June 11, 2025. This Petition is timely filed. This Court has jurisdiction under 28 U.S.C. § 1254(1).

STATUTORY AND CONSTITUTIONAL PROVISIONS INVOLVED

U.S. Const. art. I , § 8, cls. 8 & 18 provide:

> The Congress shall have power . . .
>
> * * *
>
> To promote the progress of science and useful arts, by securing for limited times to authors

> and inventors the exclusive right to their respective writings and discoveries;
>
> * * *
>
> To make all laws which shall be necessary and proper for carrying into execution the foregoing powers, and all other powers vested by this Constitution in the government of the United States, or in any department or officer thereof.

35 U.S.C. § 102(a)(1) provides:

> **(a) Novelty; Prior Art.—**A person shall be entitled to a patent unless—
>
> **(1)** the claimed invention was patented, described in a printed publication, . . . or otherwise available to the public before the effective filing date of the claimed invention; or

35 U.S.C. § 112(a) provides:

> **(a) In General.—**
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

35 U.S.C § 282(a) provides:

> **(a) In General.—**
>
> A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

35 U.S.C § 316(e) provides:

> **(e) Evidentiary Standards.—**
>
> In an inter partes review instituted under this chapter, the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.

I. INTRODUCTION

In the decision below, the Federal Circuit held that printed publications are presumed to be enabling when asserted as prior art against issued patent claims in *inter partes* review ("IPR") proceedings. Patentees now bear the burden of proving that any printed publication asserted to anticipate their claims is not enabling. This directly conflicts with provisions of the Patent Act allocating the burden of proving invalidity to the party challenging a patent, both in IPR and district court trials. The decision below also creates conflict between the burdens of persuasion for anticipation and obviousness, since the Federal Circuit elsewhere held that for obviousness assertions in IPR and district court proceedings, the burden never rests with the patentee because the Patent Act's provisions control.

In addition to shifting the burden of proof to the patentee, the decision's additional holding that "proof of efficacy" is not required to prove enablement of a prior art printed publication renders the patentee's new burden almost impossible to meet. Even if the patentee produces actual or circumstantial evidence that the disclosure in the printed publication does not work, or likely will not work, this evidence of "lack of efficacy" will not overcome the presumption because "proof of efficacy" is not required as a matter of law. The decision below puts future investment in important technologies at risk: "Making prior-art enablement challenges infeasible with respect to non-patent prior art unnecessarily restricts the universe of inventions that can be patented and subverts achievement of the policies justifying patent law." Henry H. Perritt, Jr., *Literary Fantasies as Prior Art, Eclipsing True*

Invention, 104 J. Pat. & Trademark Off. Soc'y 453, 456 (2024).

Two Agilent patents that claim improvements to synthetic guide RNAs ("gRNA") that are a core component of the CRISPR-Cas genome-editing system, and recognized in the industry as "seminal" and "landmark," were found invalid because Agilent could not overcome the presumption that a prophetic, abandoned patent application enabled the challenged claims. Agilent's patents claim specific chemical modifications that can be applied to gRNA to resist degradation; the claims also require that the modified gRNA remain functional in the CRISPR-Cas system. Using Agilent's patent claims as a guide, four sequences having the recited modifications were identified in that prior publication—but it was undisputed that those sequences had not been tested or otherwise determined to function as claimed by Agilent. It was the hindsight matching of sequences alone, without regard to whether they met the express functionality requirements of the claims, that shifted the burden to Agilent to prove nonenablement of the asserted prior art. But the exclusion of "efficacy" as a relevant enablement factor made this an impossible task. The absurdity is highlighted by the PTAB's reasoning, as affirmed by the Federal Circuit:

> Thus, 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. *See Antor Media*, 689 F.3d at 1289–90.

App. 59a, 133a. The decision below effectively rules that prior public disclosure of a genetic sequence or chemical compound alone is anticipatory, without regard for whether it will work for a claimed purpose.

The framework established in the opinion below directly conflicts with this Court's precedent in *Seymour v. Osborne*, 78 U.S. (11 Wall.) 516, 555 (1870), which requires that a printed publication must describe and enable the challenged invention to anticipate it. And the Federal Circuit's burden shifting stands in reckless disregard of the statutory evidentiary burdens governing challenges to patent validity in district court and *inter partes* review proceedings set forth in 35 U.S.C. §§ 282 and 316(e), respectively, which the court below did not address when adopting its rule.

The implications of the lower court's decision are of paramount concern. Consider the ability of Artificial Intelligence ("AI") tools to generate an exhaustive list of chemical compounds that can currently be manufactured and that have ever been contemplated in any academic research to be "cancer-curing chemical compounds." Publishing that list is trivial. Under the decision below, a pharmaceutical company that expended considerable resources in not only the discovery and synthesis of a drug compound, but also the testing necessary to demonstrate efficacy in curing cancer, would be foreclosed from protecting that innovation if its drug compound appeared in that prior published list. Had it secured a patent, its issued claims would be easily lost when an accused infringer used the patent as a guide to identify the allegedly anticipatory compound in that list. After all, it was expressly disclosed and could be manufactured.

And not only would the publication be presumed enabling of the later-claimed drug for the purpose of anticipation, but the pharmaceutical company would be hard-pressed to rebut that presumption absent a proof of efficacy requirement for a prior art enablement. Indeed, this hypothetical played out in real life—albeit absent AI—in the proceedings here.

This is of serious concern for industry. A recent Patent and Trademark Office request for comment ("RFC") regarding the impacts of AI received a robust response.[1] America's innovators loudly and uniformly identified the presumption of prior art enablement during prosecution as a significant legal issue with public and economic implications so compelling that they urged a revisiting of the rule to avoid subversion of our patent system's principles.[2] And although the RFC solicited

1. *See* Request for Comments Regarding the Impact of the Proliferation of Artificial Intelligence on Prior Art, the Knowledge of a Person Having Ordinary Skill in the Art, and Determinations of Patentability Made in View of the Foregoing, 89 F.R. 34217 (Apr. 30, 2024), *at* https://www.regulations.gov/docket/PTO-P-2023-0044.

2. *See* Corey Salsberg, Novartis, *Comment Letter on Impact of AI on Prior Art and PHOSITA* (July 26, 2024), at 2–3, *at* https://www.regulations.gov/comment/PTO-P-2023-0044-0037 ("[M]aterials—which, in our field, could perhaps include large, autonomously generated lists of *theoretical compounds, genetic sequences or antibodies—should not be treated as invalidating prior art if they are speculative, inoperable, non-enabling*, or do not exhibit practical utility. Treating such references as prior art would conflict with the policy aims of the patent system, destroying the enabling role of patents as an incentive to not only invent new subject matter that is actually useful and operable, but to invest in developing and commercializing it to advance human

feedback regarding impacts of AI generated art and inventions, IBM's response was not so limited: "[G]iven that enablement concerns have been expressed for both AI-generated and human-authored disclosures, neither should be entitled to a presumption of enablement if cited by an Examiner as a prior art printed publication."[3] These expressed policy concerns regarding presumptive enablement of prior art *during prosecution* ring even louder when the presumption is applied to *issued patents*, especially given Congress's express directives regarding the party that must bear the evidentiary burden.

The framework applied in the proceedings below is contrary to the statutory burdens imposed by Congress, and this Court's long-established precedent in *Seymour* that alleged prior art must enable the challenged claims in order to anticipate them. That framework also places

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progress.") (emphasis added); Ann M. Mueting, President, American Intellectual Property Law Association, *Comment Letter on AI and Inventorship RFC*, at 4 (July 29, 2024), *at* https://www.regulations.gov/document/PTO-P-2023-0044-0048 ("[T]he sheer number of these publications, and the resultant burden on a patent applicant to prove lack of enablement for large numbers of references, may have significant negative impact on the patent system."); *see also* Keith Moore, President, IEEE-USA, *Comment Letter on AI and Inventorship RFC* (July 22, 2024), *at* https://www.regulations.gov/document/PTO-P-2023-0044-0025 ("[T]he issue is whether 'prior art flooding' with 'wholly' automatically generated, edited, and published combinations and permutations should qualify as section 102 disclosure ...."); BSA Software Alliance, *Response to USPTO Solicitation of Comments on AI and Patentability* (July 26, 2024), at 5, *at* https://www.regulations.gov/comment/PTO-P-2023-0044-0034).

3. Mark Valone & Lisa Ulrich, IBM Corp., *Comment Letter on Proliferation of AI* (July 29, 2024), at 5, *at* https://www.regulations.gov/document/PTO-P-2023-0044-0042 (footnotes omitted).

the patent system at risk of failing its constitutional purpose by improperly affording more societal weight to a non-enabling publication than to inventors that bring "new designs and technologies into the public domain through disclosure" for the benefit of all. *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 151 (1989). Companies will be loath to invest in identifying and proving that new compounds work for their intended purpose if they cannot secure patent protection for their endeavors.

This petition should be granted.

II. STATEMENT OF THE CASE

A. Seven Ph.D. Scientists from Agilent invented fundamental improvements for the CRISPR-Cas System.

The Agilent patents at issue here claim improvements to the synthetic guide RNAs that are a core component of the CRISPR-Cas gene-editing system. Those improvements were recognized in the industry as "seminal" and "landmark."

In the CRISPR-Cas system, bacteria store a "library" of encountered pathogens as a series of DNA base sequences within their own DNA, from which CRISPR gets its name (**C***lustered* **R***egularly* **I***nterspaced* **S***hort* **P***alindromic* **R***epeats*). CRISPR-associated ("Cas") proteins are used to read and write into the library, and to carry out immunological response; the Cas9 protein functions to cleave pathogenic DNA. App. 2a. In 2012, U.C. Berkeley and Broad Institute researchers demonstrated

how the natural Cas proteins could be reimagined as tools for altering targeted DNA sequences.[4] The approach involved synthesizing a guide RNA—a short RNA molecule designed to pair at a specific section of target DNA—and then binding it to a Cas9 protein to form a "complex" essential for targeting and then cutting DNA. Once the gRNA-Cas9 complex pairs with DNA at the target site, the Cas9 protein functions to precisely cleave the target. App. 27a.

Because Cas proteins do not naturally occur in humans or many other organisms, their cells can treat Cas proteins as invaders. Cells are also naturally hostile to foreign RNA; anti-RNA proteins called nucleases rapidly degrade unprotected RNA—having the potential effect of preventing the targeting or editing process entirely. App. 27a–28a. Scientists suggested that guide RNAs might be able to be modified to resist such attack. But any modifications to the guide could impact its ability to perform the functions critical to the CRISPR system, including the ability to complex with the Cas protein and/or accurately target the desired genomic sequence. Determining whether, where, and how to apply chemical modifications to gRNAs to resist degradation while preserving the desired CRISPR functionality was arduous—and the technology for doing so was nascent in 2012. App. 54a. But Agilent's inventors took on this task.

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4. In June 2012, Jennifer Doudna and Emmanuelle Charpentier published a paper in the journal *Science* demonstrating that CRISPR technology could be used for *in vitro* gene editing, for which they were later granted the Nobel Prize in Chemistry. Martin Jinek et al., *A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 Science 816 (2012), *at* https://doi.org/10.1126/science.1225829.

While chemical modifications had been tested in other biological systems to varying success, no successful predictive model existed. To determine whether a particular chemical modification would remain functional in the CRISPR-Cas system, empirical testing using synthesized modified gRNA candidates was necessary. Between 2012 and 2014, Agilent scientists conducted exhaustive assays to determine which modifications conferred the desired nuclease resistance without impacting guide RNA functionality (Cas association, gRNA structure, or DNA targeting). Their work resulted in U.S. Patent Nos. 10,337,001 and 10,900,034. The patents describe and enable the claimed inventions, supported by synthesis, testing, and validation—the hallmarks of true experimentation and invention.

Each claim of the Agilent patents recites a gRNA with specific modifications that is functional to (1) associate with a Cas protein, and (2) target that Cas-complex to a target polynucleotide—the prerequisites for cleavage and editing. For example, claim 1 of the '001 patent recites:

> A synthetic CRISPR guide RNA having at least one 5′-end and at least one 3′-end, the synthetic guide RNA comprising:
>
> (a) one or more modified nucleotides within five nucleotides from said 5′-end, or
>
> (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.

App. 3a–4a (emphasis added).

B. The Agilent inventions were recognized as "landmark" and "seminal," and copied by Synthego.

Shortly after the patents were filed, the Agilent inventors reported their inventions, and the success of their chemically modified gRNA in editing human cells in collaborative research with Stanford researchers, in a 2015 paper published in *Nature Biotechnology*.[5] Their work was hailed as "landmark" and "seminal." Statistics provided by its publisher rank the paper in the top one-percentile by citation—over 1,000 in the decade since its publication.[6] App. 80a.

Notwithstanding the positions taken in its IPRs, Synthego, too, recognized the importance of Agilent's

5. Ayal Hendel et al., *Chemically Modified Guide RNAs Enhance CRISPR-Cas Genome Editing in Human Primary Cells*, 33 Nature Biotechnology 985 (2015), *at* https://doi.org/10.1038/nbt.3290.

6. Nature Biotechnology Metrics for *Chemically Modified Guide RNAs Enhance CRISPR-Cas Genome Editing in Human Primary Cells*, *at* https://www.nature.com/articles/nbt.3290/metrics (last visited Nov. 2, 2025.)

research and inventions. Synthego copied the chemical modifications reported by Agilent's inventors, and its website called them "the method of choice" for CRISPR-Cas9 editing in primary human cells. App. 83a. Agilent's inventions were the foundation on which Synthego built its business and through which Synthego directly competed against Agilent—bragging about its "very disruptive price."

After licensing discussions failed, patent infringement litigation ensued, and Synthego filed two IPR petitions.

C. Synthego's IPRs rely on a prophetic printed publication.

Synthego's petitions relied primarily on a reference that Synthego called "Pioneer Hi-Bred," an international patent application published under the Patent Cooperation Treaty. It never issued as a patent because it was abandoned.

In lieu of RNA guides, Pioneer Hi-Bred proposed DNA or "DNA-RNA combination sequences" as CRISPR guides. App. 18a–19a, 38a–39a. Unlike RNA—which is single-stranded, chemically reactive, and unstable *in vivo*—DNA's double-stranded, deoxyribose backbone confers greater stability. This fundamental difference makes RNA more difficult to synthesize and employ as a guide.

The 146-page Pioneer Hi-Bred publication is, at best, a test plan. The authors propose every known type of potential chemical modification, in every possible position in the guide, for every known purpose. In the

IPR proceedings it was undisputed that Pioneer Hi-Bred disclosed 6^{39}—over a quadrillion quadrillion—possible combinations, with no way to choose among them. App. 18a. Pioneer Hi-Bred provides the results of a single test. Its results show that the authors' preferred approach of using DNA as the guide did not work. App. 45a.

Synthego asserted that Pioneer Hi-Bred anticipated Agilent's patent claims via express disclosure.[7] App. 29a; App. 101a–102a. Working backward from Agilent's claims, Synthego identified four RNA sequences in Pioneer Hi-Bred with modifications that matched modifications required by Agilent's claim limitations. These sequences were in a list in a section that described "methods for evaluating" how proposed modifications would impact functionality.

It is undisputed that Pioneer Hi-Bred lacked test data or other express confirmation that the four sequences that allegedly expressly disclosed Agilent's claims—or any of the quadrillions of modified guides proposed—have "gRNA functionality" as required by the claims. App. 18a–19a & n.11. In contrast, for two of the four identified sequences, Agilent established that the opposite was true. App. 46a; App. 120a. Agilent pointed to test data in its own patents demonstrating that two of these four sequences were not functional. *Id.*

7. Synthego did not assert that Pioneer Hi-Bred alone rendered the claims obvious, nor did Synthego allege that the functionality of the identified sequences was inherent. Synthego's IPRs do include obviousness grounds for some dependent claims, but they are all predicated on the same Pioneer Hi-Bred disclosures. App. 7a–8a; *see also* App. 29a–30a, 101a–103a. Thus, the issues presented here are outcome determinative as to all claims.

As to the other two, Agilent submitted evidence suggesting that a POSITA would not have expected them to work. Dr. Doudna's seminal paper reported that the CRISPR guide region was about 20 nucleotides long. The identified Pioneer Hi-Bred sequences were only 17 nucleotides long. Agilent submitted uncontested evidence that 16-nucleotide guides were nonfunctional, and that 17 nucleotides was the minimum-length guide that could work, but for only *unmodified* guides. App. 50a, 124a. Because there is no evidence that Pioneer Hi-Bred or anyone else tested the prophetic modified 17-nucleotide guides, it is unknown, even today, if they would be functional.[8]

Agilent also submitted extensive expert testimony regarding the nascent state of CRISPR, the unpredictability of the art, and how and why a POSITA would understand that the mechanisms of CRISPR were unique from other systems in which chemical modifications had been identified (through testing) to resist degradation and remain functional. *See Regents of the Univ. of Cal. v. Broad Inst., Inc.*, 903 F. 3d 1286, 1292–93 (Fed. Cir. 2018); App. 14a–15a, 74a–75a, 154a–155a.

D. The PTAB invalidated all claims.

To meet the functionality limitation required to find express disclosure, the PTAB ultimately relied on a theory not advanced by Synthego—that because the

8. The Board ultimately dismissed this evidence because it did not prove nonenablement, and instead used *Agilent's* specifications to conclude that Pioneer Hi-Bred's sequences might work, thereby negating nonenablement. App. 48a–51a; App. 122a–125a.

Pioneer Hi-Bred authors called their proposals "guide polynucleotides," that was sufficient to disclose actual functionality as guides.[9] App. 44a–45a.

As to enablement, the PTAB relied on Federal Circuit precedent to conclude that Pioneer Hi-Bred is "presumed to be enabled," citing *In re Antor Media Corp.*, 689 F.3d 1282, 1287–88 (Fed. Cir. 2012), and quoting from *Apple Inc. v. Corephotonics, Ltd.*, 861 Fed. App'x 443, 450 (Fed. Cir. 2021) ("[R]egardless of the forum, prior art patents and publications enjoy a presumption of enablement, and the patentee/applicant has the burden to prove nonenablement for such prior art."). The PTAB considered, and waved away, Agilent's evidence (including the test data in Agilent's patents that refuted functionality) by casting doubt on the results. The PTAB found the disclosures in Pioneer Hi-Bred enabled based on a myriad of justifications—none of which showed efficacy of the relied-upon synthesized gRNAs. App. 45a–54a, 56a–61a, 118a–128a, 129a–135a. The PTAB concluded:

> Here, Petitioner asserts that the RNA-based embodiments disclosed in Examples 4 and 5 of Pioneer Hi-Bred are anticipatory. *Those disclosures are presumed enabling and Patent Owner has not shown otherwise.*

App. 56a, 130a (emphasis added). The Board did so even though it acknowledged that Examples 4 and 5 were prophetic, determining that this did not undermine the presumption that they were functional:

9. Agilent maintains that this is not express disclosure of the claimed functionality, and that it was a violation of the Administrative Procedure Act, which the Federal Circuit rejected. App. 12a n.8.

> Thus, 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. *See Antor Media*, 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 to perform the claimed invention.").

App. 59a, 133a.

E. The Federal Circuit affirmed and issued a published opinion confirming that printed publications are presumed enabled.

Citing the "substantial evidence standard," the Federal Circuit accepted the PTAB's findings that Pioneer Hi-Bred's definitional say-so constituted "express disclosures of functionality." App. 11a–12a. Agilent maintains that this decision was in error because no modified guides with the claimed functionality were disclosed or enabled.

As to enablement, the court held that the asserted prior art was presumed enabled, placing the burden on Agilent to demonstrate *non*enablement. App. 14a. The court also relied on its jurisprudence that "proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation." App. 13a (citing *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005)). This combined prior art enablement jurisprudence amounts to a Sisyphean task: a patentee bears the burden

of proving that functional claims are not enabled by the prior art, but functionality (i.e., efficacy) is not required for prior art to be enabled.

III. THE PETITION SHOULD BE GRANTED

A. The decision below results in an unprecedented and improper expansion of what qualifies as invalidating prior art that threatens innovation.

1. The decision below is wrong because the Patent Act provides that the burden of proving invalidity always rests with the patent challenger.

To anticipate a patent claim, a printed publication must both disclose and enable the claimed invention:

> Patented inventions cannot be superseded by the mere introduction of a foreign publication of the kind, though of prior date, *unless the description and drawings contain and exhibit a substantial representation of the patented improvement, in such full, clear, and exact terms as to enable any person skilled in the art or science to which it appertains, to make, construct, and practice the invention* to the same practical extent as they would be enabled to do if the information was derived from a prior patent. . . . [T]he knowledge supposed to be derived from the publication must be *sufficient to enable those skilled in the art or science to understand the nature and operation of the invention, and to carry it into practical*

> *use*. . . . [T]he account published, to be of any effect to support such a defense, *must be an account of a complete and operative invention capable of being put into practical operation*.

Seymour, 78 U.S. at 555 (emphasis added). The holding in *Seymour* remains the law today:

> A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. Long ago our predecessor court recognized that a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to "enable one of skill in the art to reduce the disclosed invention to practice."

Amgen, 314 F.3d at 1354 (citations omitted). Thus, disclosure and enablement are both affirmative elements of an anticipation defense. Indeed, enablement is so central to anticipation that a non-enabled disclosure "is not truly prior art." *Id.*

Section 282, which applies to district court proceedings, provides: "The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282. "[B]y its express terms, § 282 establishes a presumption of patent validity, and it provides that a challenger must overcome that presumption to prevail on an invalidity defense." *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 100 (2011). In patent infringement proceedings, this presumption of validity cannot be overcome "except by clear and cogent evidence." *Id.* at 101.

Section 316(e), which applies to *inter partes* review proceedings, states that "the petitioner shall have the burden of proving a proposition of unpatentability" by a preponderance of the evidence. 35 U.S.C. § 316(e). In *Cuozzo Speed Technologies, LLC v. Lee*, this Court held that "[t]he challenger bears the burden of proving unpatentability." 579 U.S. 261, 278–79 (2016).

The decision below impermissibly shifted the burden to Agilent, the patentee, to prove nonenablement of the alleged prior art publication. That decision cannot stand and should be vacated on this basis alone.

2. The decision below should be vacated because it is not supported by precedent.

The decision below should be vacated for the additional reason that the cases on which it rests do not support its holding. The Federal Circuit relied on *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008) (reaffirming that an anticipating prior art patent is presumptively enabled), and *Antor Media*, 689 F.3d at 1288 (extending the presumption to printed publications), in support of its holding that Agilent bore the burden of proving nonenablement. Neither case supports that result.

Impax is inapposite. In *Impax*, a prior art *patent* was asserted—not a printed publication. Whether a patent challenger can rely on a presumption of enablement when a prior art patent is asserted as anticipatory art is not at issue here.

Antor Media, involving an appeal of a reexamination proceeding, is also inapposite.[10] The appeal here involved an *inter partes* review. "In an *inter partes* review, the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' 35 U.S.C. § 316(e), and that burden never shifts to the patentee." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364 (Fed. Cir. 2016) (quoting *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)).[11]

But even if *Impax* and *Antor Media* applied, the decision should still be vacated because neither is supported by sound precedent. *Impax* and *Antor Media* both trace their origin to *Amgen*, 314 F.3d at 1354–55, which provides no reasoned or sound basis for the result here. *See Impax Labs.*, 545 F.3d at 1316; *Antor Media*, 689 F.3d at 1288.

In *Amgen*, the defendant asserted that certain unclaimed subject matter in a prior art patent anticipated Amgen's patent claims. 314 F.3d at 1354–55. Amgen countered that the defendant had not proven that the

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10. 35 U.S.C. § 132 governs the content of communications from the examiner in reexamination proceedings and during patent prosecution. It does not establish any burden of proof, but specifies the level of notice that must be provided to the applicant to allow for consideration and response.

11. The same is true in patent infringement cases in district court. The burden of proof never shifts to the patentee. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012) (reversing obviousness determination because "the court imposed a burden-shifting framework in a context in which none exists").

unclaimed subject matter in the patent was enabling and therefore had not established anticipation because enablement is a required element of the defense. The question before the Federal Circuit was which party had the burden of establishing whether the *unclaimed* subject matter was enabling. *Id.* at 1355–56.

Although issued patents are entitled to a presumption of enablement under 35 U.S.C. § 282, Amgen argued that the presumption was not operative in its case because the presumption extended only to claimed subject matter in issued patents. *Amgen*, 314 F.3d at 1355. Thus, Amgen contended that the defendant bore the burden of establishing enablement, which it had failed to do. *Id.*

The Federal Circuit disagreed, holding that the unclaimed subject matter was entitled to a presumption, and that Amgen, the patentee, had the burden of proving that it was not enabling. *Id.* The Federal Circuit was explicit that its ruling was not premised on the prior art patent also having a presumption of validity pursuant to Section 282. *Id.* at 1354 ("We agree that prior art patents are presumed enabled, but under authority going beyond § 282.").

Instead, the Federal Circuit purported to base its decision on its own jurisprudence. *Id.* at 1355. Specifically, the Federal Circuit relied on a proposition from *In re Sasse*, 629 F.2d 675, 681 (C.C.P.A. 1980), describing patent office procedure during the application process: "[W]hen the PTO cited a disclosure which expressly anticipated the present invention . . . the burden was shifted to the applicant. He had to rebut the presumption of the operability of [the prior art patent] by a preponderance of

the evidence." (citation omitted). The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled. *Id.* Citing *In re Sasse*, the court noted: "In patent prosecution the examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled or whether or not it is the claimed material (as opposed to the unclaimed disclosures) in that patent that are at issue." After making this observation, the Federal Circuit made the following leap:

> We hold that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff. *Thus, a court cannot ignore an asserted prior art patent in evaluating a defense of invalidity for anticipation, just because the accused infringer has not proven it enabled.*

Amgen, 314 F.3d at 1355 (emphasis added). But this is remarkably wrong. Indeed, just a page earlier in the same decision, the Federal Circuit confirmed that proof of enablement is a requirement to qualify as prior art: "Long ago our predecessor court recognized that a non-enabled disclosure cannot be anticipatory (because it is not truly prior art)." *Id.* at 1354. Thus, a court can and must ignore prior art "just because the accused infringer has not proven it enabled," because that means it *is not* prior art.

The Federal Circuit then proposed a procedure to determine whether a *patentee* met its burden of proving nonenablement:

> Like the applicant in *ex parte* prosecution, however, the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and therefore are not pertinent prior art. If a patentee presents evidence of nonenablement that a trial court finds persuasive, the trial court must then exclude that particular prior art patent in any anticipation inquiry, for then the presumption has been overcome.

Id. at 1355. Given that there is no back-and-forth in district court proceedings (unlike in prosecution practice), it is unclear under what procedural rules or mechanisms this would even occur in district court. But regardless, as noted above with regard to *Antor Media*, reexamination procedures have no bearing on the statutory burden of proof in IPR proceedings.

The only other rationale the court offered is in a footnote:

> Additionally, we think it unwise as a matter of policy to force district courts to conduct a mini-trial on the proper claim construction of a prior art patent every time an allegedly anticipating patent is challenged for lack of enablement. As we frequently revisit district courts determinations in matters of claim construction and validity, we are certainly aware that *such a task can occupy a great deal of a court's resources*. In any event, because the presumption outlined here does not rely on § 282, we see no reason to impose these burdens on litigants and the district courts.

Id. n.21 (emphasis added). But work avoidance cannot justify ignoring controlling law. *Amgen* is not sound precedent to support the decision below, which must be vacated.[12]

3. The decision below is at odds with Federal Circuit decisions regarding the burden of proof for obviousness.

Magnum Oil Tools addressed the question of whether the patentee ever bears the burden of persuasion in an IPR proceeding concerning obviousness. *Magnum Oil Tools*, 829 F.3d at 1375. The patentee asserted that the PTAB improperly shifted the burden to him in its obviousness analysis, and that the decision had to be vacated because the challenger never established by a preponderance of the evidence that the patent was invalid. *Id.* The Federal Circuit held that the burden of persuasion never shifts to the patentee as to the elements of an invalidity claim. *Id.*

Moreover, *Magnum Oil Tools* expressly rejects the notion that the burden-shifting patent office procedure proposed in *Amgen* has any relevance to district court proceedings:

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12. Relying on *Antor Media*, *Impax*, and *Amgen*, in *Apple Inc. v. Corephotonics, Ltd.*, 861 F. App'x at 450, the Court reversed a PTAB decision for requiring that Apple, the petitioner, establish the pedigree of its proffered prior art. The Court held: "We do not see a principled distinction between our cases holding that this presumption [of enablement] and burden apply during patent examination and in district court litigation, and AIA trial proceedings." But *Corephotonics* is not sound precedent for the same reasons as *Amgen*.

> We have noted that "a burden-shifting framework makes sense in the prosecution context," where "[t]he prima facie case furnishes a 'procedural tool of patent examination, allocating the burdens of going forward as between examiner and applicant.'" *Id.* at 1080 n. 7 (citing *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992)). As the PTO concedes, however, that burden-shifting framework does not apply in the adjudicatory context of an IPR. Intervenor Br. at 30 (citing *In re Jung*, 637 F.3d 1356, 1362 (Fed. Cir. 2011) (holding the prima facie case during patent examination "is merely a procedural device that enables an appropriate shift of the burden of production" from the PTO to the patent applicant)).

Id. Ultimately, the Federal Circuit held that the patent challenger always has the burden to prove obviousness by a preponderance of the evidence pursuant to Section 316(e), and reversed the outcome in the IPR. *Id.* at 1378–79. The burden never shifts to the patentee.

In addition to *Magnum Oil Tools*, many other Federal Circuit decisions confirm that the burden never shifts to patentee for obviousness. *See, e.g., Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373, 1378 (Fed. Cir. 2023) ("We have routinely held that the petitioner has the burden of proving unpatentability."); *E.I. du Pont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1007 (Fed. Cir. 2018) ("[T]here was no dispute that the burden of persuasion remained with the patent challenger."); *FanDuel, Inc. v. Interactive Games LLC*, 966 F.3d 1334, 1341 (Fed. Cir. 2020) ("[T]he burden of

proving invalidity in an IPR remains on the petitioner throughout the proceeding."); *Aqua Prods., Inc. v. Matal*, 872 F.3d 1290, 1306 (Fed. Cir. 2017).

The decision below is in conflict, and cannot be reconciled with these obviousness cases that correctly apply the burdens of proof established by the Patent Act. The decision must be reversed for this reason as well.

B. The decision below should be vacated because *Rasmusson* is either inapplicable and its narrow application should be clarified, or it conflicts with *Seymour* and should be overruled.

After applying Federal Circuit law to shift the burden to Agilent, the PTAB relied on the Federal Circuit's pronouncements in *Rasmusson*, 413 F.3d at 1326, to summarily dismiss the vast majority of evidence that Agilent brought forth to meet its burden. It did so by classifying Aligent's evidence as relating to "proof of efficacy," while also holding that proof of efficacy was not a necessary element of prior art enablement.

The opinion below cites *Rasmusson* to support its finding of "no error in the Board's conclusion that Pioneer Hi-Bred is enabling," because "[p]roof of efficacy is not required in order for a reference to be enabled for purposes of anticipation." App. 13a. This essentially negated *any* requirement for utility in an enabling prior art disclosure. It justified the finding that Pioneer Hi-Bred's disclosure was enabled without undue experimentation, because all that was required was the ability to make one guide that had the claimed modifications. The PTAB and Federal Circuit used this bright-line rule to dismiss Agilent's

evidence as irrelevant to the inquiry of whether a prior art reference is enabled for purposes of anticipation. App. 13a (citing *Rasmusson,* 413 F.3d at 1326).

The decision below should be vacated in view of its reliance on unsound precedent, or inapposite precedent. *Rasmusson*'s broad proclamation that "proof of efficacy is not required to enable a prior art reference for purposes of anticipation" is unsound, or inapposite. At a minimum, *Rasmusson*'s holding should be expressly confined to "failure to establish enablement due to a failure to demonstrate sufficient utility of a chemical or therapeutic compound pursuant to Section 101." *Rasmusson*, 413 F.3d at 1323. The decision should also be vacated because it conflicts with *Seymour v. Osbourne*, which requires a patent challenged to prove that a printed publication discloses "an operative invention capable of being put into practical operation."

Rasmusson arose from an appeal of an interference proceeding related to patents for treating prostate cancer. The misapplication and confusion that has resulted from the overstated holdings of *Rasmusson* is a matter of semantics and the Federal Circuit's contortion of the Board's results to affirm them. In *Rasmusson*, the Board determined that certain of Rasmusson's applications were not enabled, and hence, he was not entitled to priority of those applications. As the Federal Circuit explained the enablement rejection:

> With respect to enablement, the Board found that none of the applications filed before the ninth application "would have enabled a person of ordinary skill in the art as of

> each of the respective filing date[s] to treat human prostate cancer by administering a therapeutically effective amount of finasteride to a human in need thereof without undue experimentation." The Board based that finding on its determination that a person of ordinary skill in the art *would have had no basis as of the filing date of the eighth application for believing that finasteride could be used to treat prostate cancer in light of the state of the art* and *in light of Rasmusson's failure to provide any data to demonstrate the effects of finasteride in treating prostate cancer.*

Rasmusson, 413 F.3d at 1322 (emphasis added). In response, Rasmusson argued that the lack of efficacy was only related to Section 101 (i.e., utility), and that because the rejection was not based on Section 101, the Board erred.

The Federal Circuit disagreed, explaining that utility under Section 101 is incorporated by reference into the "use" part of Section 112. "As this court has explained, 'the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention.'" Thus, "efficacy," which was really "utility," now became associated with "enablement," because "utility" is incorporated into "enablement."

"Efficacy" in *Rasmusson*, in each instance that the term is used, is about "utility" or usefulness (i.e., Section 101), whether it is incorporated into the "use" prong of the enablement requirements or not. The

Federal Circuit ultimately sustained the use/enablement rejection, and found the Board's enablement rejection incorporated utility, and the utility requirement was not met because of the lack of proof of efficacy. Efficacy in *Rasmusson* is shorthand for utility or usefulness only in the context of chemical compounds and therapeutics, and the only relationship between efficacy and enablement is the *Rasmusson* court's holding that Section 101 is incorporated by reference into enablement.

Rasmusson then turned to consideration of whether the Rasmusson applications, that had just been determined to be not enabled because they failed to show utility/efficacy, could nonetheless anticipate the SmithKline applications that were the subject of the interference proceeding. And, citing *Hafner*, the court determined that they could.

> [A] disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law, *entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim*.

Rasmusson, 413 F.3d at 1325 (citing *In re Hafner*, 410 F.2d 1403, 1405 (C.C.P.A. 1969)). The court noted that since *Hafner*, also cited in the decision below, the Federal Circuit "has continued to recognize that a prior art reference need not demonstrate utility in order to serve as an anticipating reference under section 102." *Id.* at 1326.

The final reference to efficacy in the case relates to the parties' debate about the breadth of *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368 (Fed. Cir. 2001). It is here that the Federal Circuit agrees with *Rasmusson* that "proof of efficacy is not required in order for a reference to be enabled for purposes of anticipation." *Rasmusson*, 413 F.3d at 1326. And efficacy means the same thing here: utility.

Rasmusson, and the cases cited therein, are interference proceedings, involving chemical compounds or therapeutics, where the question of efficacy or effectiveness is a question of utility. They have no application outside of this realm, and should be limited to such.

To the extent that these cases, including *Rasmusson*, have applicability outside the scope of interference proceedings, then at least *Rasmusson* was wrongly decided because it conflicts with *Seymour*, discussed above in Sections III.A.1 and III.A.3. In *Seymour*, this Court set forth the test for test for enablement of a printed publication for purposes of anticipation. To anticipate, a publication must "*enable those skilled in the art or science to understand the nature and operation of the invention, and to carry it into practical use*. . . . [T]he account published, to be of any effect to support such a defense, *must be an account of a complete and operative invention capable of being put into practical operation*." 78 U.S. at 555 (emphasis added). To the extent *Rasmusson* is interpreted to state that functionality (which is an express element of the Agilent claims, in any event) is not required for purposes of establishing that a publication is enabled for purposes of anticipation, it conflicts with *Seymour* and must be overruled.

IV. THIS CASE IS AN IDEAL VEHICLE.

This case is an ideal vehicle for resolving a recurring and outcome-determinative question of patent law: whether printed publications are presumed enabling when asserted as anticipatory prior art, and further, whether excluding "efficacy" as an enablement factor is good law or policy.

The dispute below turned on whether the key prior art reference (*a printed publication*) was enabling. Both the Patent Trial and Appeal Board and the Federal Circuit addressed that issue directly, with the Federal Circuit devoting substantial analysis to affirming a distinct standard of enablement for § 102, complete with citations to the factual record and some accounting as to the legal reasoning of the Federal Circuit. App. 17a–20a. There are no factual or procedural obstacles that might prevent this Court from reaching the core legal question. The record contains the prior art reference itself and extensive expert testimony on what it taught (or failed to teach) concerning functional guide RNAs, and the standards applied by the Federal Circuit.

Moreover, Petitioner consistently argued that Pioneer Hi-Bred lacked a practical enabling disclosure—even invoking this Court's recent decision in *Amgen Inc. v. Sanofi,* 598 U.S. 594 (2023), by analogy, preserving this issue for review. Repudiating this Court's recent jurisprudence on § 112 enablement, the Federal Circuit squarely rejected Agilent's arguments because they turned on § 112 rather than § 102, ignoring what may be this Court's attempted harmonization of the law of enablement in adversarial proceedings.

Importantly, the outcome of this case hinges on the presumption of enablement for printed publications that should be applied by the Federal Circuit and the PTAB. If *Seymour*'s standard had been applied, the primary reference (which merely proposed guides without any data showing their CRISPR efficacy) would be deemed not enabling under § 112 standards and thus not prior art. Petitioner's patents would have survived, as no *truly enabling* disclosure predated the inventions claimed therein. But, under the Federal Circuit's enablement standard, the same reference was found sufficient to anticipate because a skilled artisan could *theoretically* find "at least one embodiment" that works by routine experimentation. Thus, the legal presumption of enabled anticipatory prior art was outcome determinative here. A Supreme Court ruling that the correct standard is the one articulated in *Seymour* would require reversal in the present case. There is no doubt that the issue is squarely presented and material to the judgment, satisfying the Court's ideal vehicle criteria.

Finally, the question carries exceptional national importance. Notwithstanding the *significant* concerns voiced by tech, biotech, and industry regarding the presumption of enablement for printed publications, the ruling below threatens to undermine American innovation fundamentally, especially in the unpredictable arts. Clarifying that the burden falls on the petitioner in litigation would restore coherence to patent law, ensure fairness in adversarial proceedings, and reaffirm the patent system's constitutional balance between public disclosure and genuine innovation. Moreover, given the nature of review in patent law, there is unlikely to be any meaningful circuit split forthcoming. Therefore this case,

where a pioneering CRISPR invention was invalidated by an abandoned prophetic application, offers the ideal vehicle for this Court to restore coherence and integrity to the law of enablement.

V. THIS CASE IS OF SIGNIFICANT IMPORTANCE AND SHOULD BE REVIEWED.

This petition presents a question of exceptional importance concerning a foundational bargain in the U.S. patent system. The Federal Circuit has reaffirmed the presumption that printed publications are enabling, shifting the burden to patent owners—and moreover, obviated "efficacy" as a dispositive factor when patent owners try to rebut. The result is a doctrinal double standard: patent applicants must disclose enough to teach the public how to practice the invention, yet alleged prior art may invalidate those same claims on the basis of speculative or prophetic disclosure with no supporting data. In this case, the functional gRNA limitations recited in Agilent's issued patents were deemed anticipated by an abandoned patent application, which included no evidence that the sequences recited therein (which contained unpredictable modifications), were in fact functional.

Two Federal Circuit errors require this Court's review. First, the Federal Circuit's adoption of a presumption of enablement for printed publications contravenes the burden on patent challengers established by this Court in *Seymour*, and is contrary to §§ 282 and 316(e), which assign the burden of proof to the challenger.

Second, the Federal Circuit's holding articulated in *Rasmusson* that "proof of efficacy is not required

in order for a reference to be enabled for anticipation" fundamentally misapprehends the appropriate boundaries of the holding in *Rasmusson*, which should be vacated or limited, and ignores long-standing interpretations of operative language surrounding the correct enablement standard for § 102.

This error by the Federal Circuit invites the publication of "paper" disclosures—speculative, inoperative disclosures that could never support patentability but may later be weaponized to invalidate genuine, working inventions. Left uncorrected, this approach undermines congressional intent, distorts prosecution practice, and erodes confidence in the patent system.

The Federal Circuit's error originated in a demonstrable misreading of this Court's precedent and has become entrenched in the nation's sole appellate court for patent law, precluding any possibility of correction without this Court's intervention. As the Federal Circuit is, for many patent law topics, the court of both first and last resort, the institutional reality makes this Court's review not merely important, but essential.

A. The Federal Circuit's doctrine ignores federal statutory directives designed to fulfill the Intellectual Property Clause.

The Federal Circuit's inconsistent logic and legally unsupportable enablement presumption fails on multiple independent grounds.

First, the Federal Circuit's insistence on shifting the burden to Patent Owners to disprove enablement during

adversarial proceedings stands contrary to statutory language in Sections 282 and 316(e)—mandating that the patent challenger bears the burden of proof, and must be addressed by the Court.

Second, this Court must untangle the complex web of exceptions built by the Federal Circuit in maintaining that "no efficacy is required" for a reference to be enabled—and re-establish a standard of prior art enablement in accord with this Court's holding in *Seymour* for challenges in district court and PTAB trials.

Without the guidance of this Court, the Federal Circuit's entrenched self-made presumption will continue to reward thin, hypothetical "paper" disclosures to the detriment of true innovators.

B. The Federal Circuit's prior art enablement framework forecloses practical application of this Court's precedent to counter anticipation challenges premised on non-enabled publications.

This Court's ruling in *Seymour* should serve as the blueprint for prior art enablement under Sections 102 and 103 of the Patent Act. *Seymour* held that a prior publication can defeat a patent only if it discloses the challenged invention "in such full, clear, and exact terms as to enable any person skilled in the art … to make, construct, and practice the invention." 78 U.S. at 555. Stated differently, prior art must be enabling to the same degree that § 112 requires of a patent specification.

As discussed in Section III.B above, the Federal Circuit departed from *Seymour*, relying instead on *Rasmusson* and *Hafner* to justify dismissing the vast majority of evidence that Agilent brought to meet the burden imposed upon it, reasoning that the distinction between Sections 112 and 102/103 was warranted because "§ 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.'" App. 17a (quoting *Rasmusson*, 413 F.3d at 1325). But in *Hafner*, the CCPA justified the split standard through a superficial textual analysis of the Patent Act and ignored this Court's established precedent in *Seymour*. Thus, the Federal Circuit's ruling in the below case rests on foundational textual and historical error and should be reversed.

Reaffirming the principles established in *Seymour* will correct a decades-old judicial distortion and realign patent law with the statutory text. Crucially, it will protect genuine, operative inventions from being undone by incomplete and inoperative disclosures. In an era where artificial intelligence can generate vast volumes of technical material at unprecedented speed, the issue of invalidating "paper" disclosures (presumed to be enabled) will undoubtedly predominate unless addressed by this Court now. This Court, by clarifying that non-enabling disclosures are insufficient to anticipate, can restore the constitutional bargain and ensure that the patent system rewards innovators like Agilent who place truly useful knowledge into the public domain.

C. The Federal Circuit's doctrine perverts the incentives that our patent laws were designed to foster.

Congress designed the Patent Act to promote efficient examination and reward genuine innovation. But the Federal Circuit's ruling threatens both objectives. By improperly shifting the burden of proof and adopting a dismissive "proof of efficacy is not required" enablement standard for printed publications, the Federal Circuit created a doctrinal gulf that distorts patent incentives and undermines advancement of the useful arts.

Section 112 defines the baseline for the enablement inquiry during prosecution: a patent may issue only when the specification teaches those skilled in the art to "make and use" the invention in "full, clear, concise, and exact terms." 35 U.S.C. § 112(a); *Amgen*, 598 U.S. at 605 ("So today, just as in 1790, the law secures for the public its benefit of the patent bargain by ensuring that, 'upon the expiration of [the patent], the knowledge of the invention [i]nures to the people, who are thus enabled without restriction to practice it.'") (quoting *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 187 (1933)). Properly applied, that standard discourages speculative or prophetic filings and ensures that patents correspond to operable, demonstrated inventions. It also guards against "omnibus" applications that attempt to claim every conceivable variation of a concept without teaching how to realize it—a concern magnified now that AI can generate vast pseudo-technical disclosures in seconds.

The Federal Circuit's presumption of enablement for printed publications invites the very behavior § 112

was designed to prevent. If a minimally described and non-enabled disclosure can later serve as fully "enabled" prior art, entities seeking to clear a particular field could simply flood the patent office with sprawling, speculative publications. These "paper patents," even if abandoned, are prior-art landmines, capable of invalidating genuine, fully enabled inventions years later.

The Federal Circuit's presumption has far-reaching consequences for all stages of the patent process. At the beginning, this doctrine threatens to overwhelm already overburdened examiners, frustrate efficient prosecution, and reward bad-faith actors who weaponize untested disclosures as presumptively enabled prior art. By the end, accused infringers will seek outcomes like in the below case that threaten to forestall American invention. The result is a less innovative patent landscape—one in which volume and speculation replace substance and proof.

Only this Court's intervention can restore the correct standard within the statutory framework of the Patent Act. Reaffirming that prior art must meet the same enablement standard that governs patent applicants under § 112 would realign the statutory balance between disclosure and innovation, deter strategic abuse, and preserve the efficiency and integrity of the patent system that Congress envisioned.

VI. CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

Denise M. De Mory
Counsel of Record
Aaron R. Hand
Abigail Lubow
Kenneth Wang
Bunsow De Mory LLP
701 El Camino Real
Redwood City, CA 94063
(650) 351-7248
ddemory@bdiplaw.com

Counsel for Petitioner,
Agilent Technologies, Inc.

Date: November 8, 2025

APPENDIX

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OPINIONS AND ORDERS

USPTO DECISIONS

OPINION, U.S. COURT OF APPEALS FOR THE FEDERAL CIRCUIT (JUNE 11, 2025)

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

AGILENT TECHNOLOGIES, INC.,

Appellant,

v.

SYNTHEGO CORP.,

Appellee.

No. 2023-2186, 2023-2187

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

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 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

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

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:

(a) one or more modified nucleotides within five nucleotides from said 5′-end, or

(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

(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 inter-nucleotide 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′-phos-phonoacetate.").

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 Polynucleotide/ Cas Endonuclease Systems and Methods of Use." Pioneer Hi-Bred Title (capitalization omitted). Pioneer Hi-Bred discloses "[c]ompo-

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

sitions 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

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

obviousness: Threlfall[4] and 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 modifi-

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[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.

[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.

cations 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 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 'phosphono-acetate' and 'phosphonothioacetate' (i.e., PACE and thio-PACE) 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).

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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.

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 (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,

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

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 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]

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[8] Agilent also argues that the Board violated the requirements of notice and an opportunity to respond found in the Administra-

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 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

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tive 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.

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 experimen-

tation 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 sev-

eral 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

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

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] 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

[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

"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 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:

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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.

[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.

> 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.

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 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

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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.

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

JUDGMENT, U.S. COURT OF APPEALS FOR THE FEDERAL CIRCUIT (JUNE 11, 2025)

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

AGILENT TECHNOLOGIES, INC.,

Appellant,

v.

SYNTHEGO CORP.,

Appellee.

No. 2023-2186, 2023-2187

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

JUDGMENT

THIS CAUSE having been considered, it is

ORDERED AND ADJUDGED:

AFFIRMED

FOR THE COURT

/s/ Jarrett B. Perlow
Clerk of Court

Date: June 11, 2025

FINAL WRITTEN DECISION ON IPR2022-00402, PATENT 10,337,001 B2, U.S. PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD (MAY 17, 2023)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNTHEGO CORPORATION,

Petitioner,

v.

AGILENT TECHNOLOGIES, INC.,

Patent Owner.

IPR2022-00402
Patent 10,337,001 B2

Before: Robert A. POLLOCK, David COTTA, and Michael A. VALEK, Administrative Patent Judges.

VALEK, Administrative Patent Judge.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable

35 U.S.C. § 318(a)
Granting Joint Motion to Seal; Granting Patent Owner's Motion to Seal Portions of Sur-reply Brief
37 C.F.R. §§ 42.14, 42.54

I. Introduction

Synthego Corporation ("Petitioner") filed a Petition (Paper 1, "Pet."), seeking *inter partes* review of claims 1–30 of U.S. Patent No. 10,337,001 B2 (Ex. 1001, "the '001 patent"). We instituted trial on all of the grounds in the Petition. Paper 11, 31.

Following institution, Agilent Technologies, Inc. ("Patent Owner") filed a Response (Paper 17, "Resp."), Petitioner filed a Reply (Paper 29, "Reply"), and Patent Owner filed a Sur-reply (Paper 32, "Sur-reply"). We held a hearing on March 1, 2021, and a transcript is of record. Paper 48 ("Tr.").

In addition, the parties have jointly moved to seal Exhibits 1053–1058 and portions of the Reply (Paper 28) and Patent Owner has moved to seal portions of the Sur-reply (Paper 33).

After considering the parties' arguments and evidence, we find that Petitioner has shown by a preponderance of the evidence that the challenged claims of the '001 patent are unpatentable. *See* 35 U.S.C. § 316(e). We also grant both motions to seal. Our reasoning is explained below.

II. Background

A. Real Parties in Interest

Petitioner and Patent Owner identify themselves as the only real parties in interest. Pet. 15; Paper 4, 2.

B. The '001 Patent

The '001 patent issued on July 2, 2019, and claims priority to a utility application filed on December 3, 2015 as well as a series of provisional applications filed within a year of that date. Ex. 1001, codes (60) (63).

The '001 patent relates to "modified guide RNAs and their use in clustered, regularly interspaced, short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems." Ex. 1001, Abstr. The Specification explains that "[i]n the native prokaryotic system" from which CRISPR technology is derived "the guide RNA ('gRNA') comprises two short, non-coding RNA species referred to as CRISPR RNA ('crRNA') and transacting RNA ('tracrRNA')." *Id.* at 1:33–36. The native CRISPR-Cas system may also be engineered to use a single guide RNA (sgRNA) that combines the crRNA and tracrRNA into a single molecule. *Id.* at 1:49–51. The guide RNA forms a complex with a Cas nuclease that is able to bind to a target DNA site adjacent a protospacer adjacent motif ("PAM") sequence and cleave the target DNA at that specific site. *Id.* at 1:35–43, 2:14–27; *see also* Ex. 1003 ¶¶ 44–48; Ex. 2003 ¶¶ 49–54 (declarant testimony from both parties offering similar technical background on guide RNA and its function in CRISPR-Cas systems).

According to the Specification, "there is a need for providing gRNA, including sgRNA, having increased resistance to nucleolytic degradation, increased binding affinity for the target polynucleotide, and/or reduced off-target effects while, nonetheless, having gRNA functionality." Ex. 1001, 1:63–67. The Specification states that Patent Owner's "invention is based, at least in part, on an unexpected discovery that certain chemical modifications to gRNA are tolerated by the

CRISPR-Cas system." *Id.* at 3:34–36. These modifications are "believed to increase the stability of the gRNA, to alter the thermostability of a gRNA hybridization interaction, and/or to decrease the off-target effects of Cas:gRNA complexation" and "do not substantially compromise the efficacy of Cas:gRNA binding to, nicking of, and/or cleavage of the target polynucleotide." *Id.* at 3:34–42.

C. Challenged Claims

The Petition challenges claims 1–30. Of these, claims 1 and 12 are independent. Claim 1 is illustrative and reads as follows:

> 1. A synthetic CRISPR guide RNA having at least one 5′-end and at least one 3′-end, the synthetic guide RNA comprising:
>
> (a) one or more modified nucleotides within five nucleotides from said 5′-end, or
>
> (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.

Ex. 1001, 243:11–24. Claim 12 is similar, but recites "a synthetic CRISPR crRNA molecule comprising a 5′-end, a 3′-end, and a guide sequence capable of hybridi-

zing to a target polynucleotide" in its preamble. *Id.* at 244:19–33.

D. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/ Basis
1–7, 9, 10, 12–15, 17, 18, 20–25, 27–30	102	Pioneer Hi-Bred[2]
9, 18, 25	103	Pioneer Hi-Bred and Krutzfeldgt,[3] Deleavey,[4] Soutschek,[5] Yoo[6]

[1] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. §§ 102 and 103 that became effective prior to the filing of the application that led to the '001 patent. Therefore, we apply the AIA versions of 35 U.S.C. §§ 102 and 103.

[2] WO 2015/026885 A1, published February 26, 2015 (Ex. 1006) ("Pioneer Hi-Bred").

[3] Jan Krützfeldt et. al, "Specificity, Duplex Degradation and Subcellular Localization of Antagomirs," 35 Nucleic Acids Research 2885–2892 (2007) (Ex. 1009) ("Krützfeldt").

[4] Glen F. Deleavey et. al., "Designing Chemically Modified Oligonucleotides for Targeted Gene Silencing," 19 Chem. & Bio. Review 937–954 (2012) (Ex. 1007) ("Deleavey").

[5] Jürgen Soutschek et. al., "Therapeutic Silencing of an Endogenous Gene by Systemic Administration of Modified siRNAs," 432 Nature 173–178 (2004) (Ex. 1012) ("Soutschek").

[6] Byong Hoon Yoo et al., "2′-O-methyl-modified Phosphorothioate

8, 11, 16, 19, 26	103	Pioneer Hi-Bred and Threlfall[7] or Deleavey
2, 29, 30	103	Pioneer Hi-Bred and Knowledge of Person of Ordinary Skill in the Art ("POSA")
9, 18, 25	103	Pioneer Hi-Bred and Knowledge of POSA

In support of these grounds, Petitioner relies on declarations from Henry Morrice Furneaux submitted with the Petition (Ex. 1003) and Reply (Ex. 1059). Patent Owner relies on declarations from William S. Marshall submitted with its Preliminary Response (Ex. 2003) and Response (Ex. 2025). Patent Owner also relies on a declaration from one of the inventors named on the '001 patent, Jeffrey R. Sampson (Ex. 2029).

Antisense Oligonucleotides Have Reduced Non-specific Effects *In Vitro*," 32 Nucleic Acids Research 2008–2016 (2004) (Ex. 1011) ("Yoo").

[7] Richard N. Threlfall et al., "Synthesis and Biological Activity of Phosphonoacetate-and Thiophosphonoacetate-modified 2′-O-methyl Oligoribonucleotides," 10 Org. Biomol. Chem., 746–754 (2012) (Ex. 1010) ("Threlfall").

III. Analysis of the Asserted Grounds

A. Legal Standards

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

i. Anticipation

To establish anticipation, each limitation in a claim must be found in a single prior art reference, arranged as recited in the claim. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Although the elements must be arranged or combined in the same way as in the claim, "the reference need not satisfy an *ipsissimis verbis* test." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009).

Further, to be anticipating, a prior art reference must be enabling. *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015). "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." *Id.* (citing *In re Antor Media Corp.*, 689 F.3d 1282, 1289–90 (Fed. Cir. 2012)). Prior art disclosures are presumed enabling. *In re Antor Media Corp.*, 689 F.3d 1282, 1287–88 (Fed. Cir. 2012); *Apple Inc. v. Corephotonics, Ltd.*, 861 Fed. Appx. 443, 450 (Fed. Cir. 2021) ("[R]egardless of the forum, prior art patents and publications enjoy a presumption of

enablement, and the patentee/applicant has the burden to prove nonenablement for such prior art.").

ii. Obviousness

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when in evidence, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

Subsumed within the *Graham* factors is the requirement that the skilled artisan would have had a reasonable expectation of success in combining the prior art references to achieve the claimed invention. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–4 (Fed. Cir. 1988). Moreover, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

On the other hand, a patent claim "is not proved obvious merely by demonstrating that each of its

elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. An obviousness determination requires finding "both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (citation omitted).

B. Level of Ordinary Skill in the Art

Relying on the testimony of its declarant, Dr. Furneaux, Petitioner contends that a POSA "as of December 3, 2014 (the earliest possible priority date of the '001 Patent) would have had a Ph.D. in molecular biology, biochemistry, or a related discipline." Pet. 12 (citing Ex. 1003 ¶ 60). Petitioner further asserts that "[a] POSA would have understood the chemical structure of nucleic acids, such as DNA and RNA, and would have understood the role of such nucleic acids in cellular biology" and been aware of various prior art "methods to chemically modify RNA, including gRNAs for use in gene regulation." *Id.* at 12–13 (citing Ex. 1003 ¶¶ 61–72, 80).

Patent Owner agrees that a POSA would have this educational level. Resp. 24. Patent Owner "also agrees that a POSA would have knowledge of prior art RNA based gene regulating technologies, but disagrees that the teachings of those technologies are relevant in the manner that Dr. Furneaux [and Petitioner] attempt[] to apply them" in the Petition's grounds. *Id.*

We find the parties' agreed understanding of the level of ordinary skill in the art to be supported by the record and apply that description in our analysis

herein. To the extent the parties may disagree regarding the application of a POSA's general knowledge of nucleic acids and related prior art techniques to the Petition's grounds, such disputes are addressed in our analysis below.

C. Claim Construction

The parties assert that all of the claim terms have their plain and ordinary meaning and that no formal claim construction is necessary. *See* Pet. 17; Resp. 24–25. Nevertheless, both sides accuse the other of misconstruing the "gRNA functionality" recited in the challenged claims. *See* Resp. 25; Reply 17; Sur-reply 2–5. Accordingly, we begin by briefly clarifying the gRNA functionality required by the claims.

Independent claims 1 and 12 recite a guide RNA or crRNA molecule having "gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to a target polynucleotide." Ex. 1001, 243:20–22, 244:28–31. This claim language makes clear that the recited "gRNA functionality" requires a molecule that can: (1) associate with a Cas protein, and (2) target that complex to a target polynucleotide. To the extent Petitioner suggests that a gRNA "need *only* bind to the Cas protein" to have "gRNA functionality," we disagree because the claims additionally recite the above-quoted targeting functionality. *See* Reply 17 (emphasis added).

At the same time, we agree with Petitioner that "a gRNA need not cleave the target DNA" to have the claimed "gRNA functionality." Reply 17. The Specification defines "gRNA functionality" as "one or more functions of naturally occurring guide RNA, such as associating with a Cas protein, or a function per-

formed by the guide RNA in association with a Cas protein" and lists various gRNA functions, *e.g.*, "associating," "targeting," "binding," "nicking," and "cleaving," that may be present "in certain embodiments" of the invention. Ex. 1001, 6:36–40. However, as noted above, the claims recite "gRNA functionality comprising" only the associating and targeting functions. Thus, while a molecule may have additional functions such as cleaving a target polynucleotide, it need only exhibit the recited "associating" and "targeting" functions to have the "gRNA functionality" in claims 1 and 12.

Our determination that "gRNA functionality" requires the recited "associating" and "targeting" functions, but not additional, unrecited functions such as cleaving, is also consistent with the parties' position that the claim language has its plain and ordinary meaning. *See* Pet. 17; Resp. 24–25. The parties do not dispute the construction of any other terms, nor do we discern that any further claim construction is necessary to resolve the issues in this proceeding. *See Nidec Motor Corp. v. Zhongshan Broad OceanMotor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (explaining that it is only necessary to "construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

D. Overview of the Cited References

i. Pioneer Hi-Bred

Pioneer Hi-Bred is a publication of a PCT application filed August 20, 2014. Ex. 1006, code (22). Patent Owner does not dispute Petitioner's assertion

that Pioneer Hi-Bred is prior art to the challenged claims. Pet. 14.

Pioneer Hi-Bred describes "methods and compositions employ[ing] a guide polynucleotide/Cas endonuclease system to provide an effective system for modifying or altering target sites within the genome of a cell or organism." Ex. 1006, Abstr. Pioneer Hi-Bred defines the term "guide polynucleotide" as "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 24:6–8.[8] Pioneer Hi-Bred teaches that the polynucleotide "can be a single molecule or a double molecule" and that "[a] guide polynucleotide that solely comprises ribonucleic acids is also referred to as a 'guide RNA.'" *Id.* at 24:9–20.

Pioneer Hi-Bred discloses a guide RNA with a variable targeting domain (VT domain) having a 3′ end "that is complementary to a nucleotide sequence in a target DNA" and a Cas endonuclease recognition domain (CER domain) having a 5′ end "that interacts with a Cas endonuclease." Ex. 1006, 24:21–25: 28, Fig. 1A–1B (depicting single and duplex guide polynucleotides). Pioneer Hi-Bred explains that "[t]he VT domain is responsible for interacting with the DNA target site through direct nucleotide-nucleotide base pairings while the CER domain is required for proper Cas endonuclease recognition (Figure 3A and Figure 3B)." *Id.* at 105:5–8. Pioneer Hi-Bred teaches that these domains in the guide polynucleotide "function to link

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[8] Unless otherwise indicated, the pinpoint cites in this decision refer to the page number in the original document as opposed to the number in the exhibit label.

DNA target site recognition with Cas endonuclease target site cleavage." *Id.* at 105:9–11; *see also id.* at Fig. 3A-3B (depicting complexes formed between a single and duplex guide RNA and a Cas9 endonuclease).

Pioneer Hi-Bred also discloses that the guide polynucleotide may contain "synthetic, non-natural, or altered nucleotide bases." Ex. 1006, 61:19–20. In Example 4, Pioneer Hi-Bred describes "modifying the nucleotide base, phosphodiester bond linkage or molecular topography of the guiding nucleic acid component(s) of the guide polynucleotide/Cas endonuclease system." *Id.* at 104:15–105:2. Table 7 of Example 4 provides "[e]xamples of nuclease resistant nucleotide and phosphodiester bond modifications," including "2′-O-Methyl RNA Bases" and "Phosphorothioate bond[s]," that may be introduced in order "to reduce unwanted degradation" of the guide polynucleotide. *Id.* at 106:13–107:5. Pioneer Hi-Bred discloses that

> [m]odifications may be introduced at the 5′ and 3′ ends of any one of the nucleic acid residues comprising the VT or CER domains to inhibit exonuclease cleavage activity, can be introduced in the middle of the nucleic acid sequence comprising the VT or CER domains to slow endonuclease cleavage activity or can be introduced throughout the nucleic acid sequences comprising the VT or CER domains to provide protection from both exo-and endo-nucleases.

Id. at 106:19–25. 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." *Id.* at 108:3–5.

In Example 5 of Pioneer Hi-Bred, "some the nucleotide base and phosphodiester bond modifications described in Example 4 are introduced into the VT domain and/or CER domain of a crNucleotide." Ex. 1006, 108:16–18. Table 8 of Example 5, reproduced in part below, describes crRNA sequences with modifications, including modifications "near ends" or "at ends" of the VT and CER domains (*i.e.*, sequences 64–69).

Table 8. crRNA and crDNA nucleotide base and phosphodiester linkage modifications.

Nucleic Acid Type	Modification	crRNA or crDNA Sequence and Corresponding Modification	
		VT Domain	CER Domain
crRNA	None	GCGUACG CGUACGU GUG (SEQ ID NO: 62)	GUUUU AGA GCUAU GCUGU UUUG (SEQ ID NO: 63)
crRNA	Phosphorothioate bonds near ends	G*C*G*UA CGCGUACG UGUG (SEQ ID NO: 64)	GUUUUAGA GCUAUGCU GUU*U*U*G (SEQ ID NO: 65)

crRNA	2′-O-Methyl RNA nucleotides at ends	mGmCmG UACGCGU ACGUGUG (SEQ ID NO: 66)	GUUU UAGAG CUAUG CUG UUmU mUmG (SEQ ID NO: 67)
crRNA	2′-O-Methyl RNA nucleotides for each nucleotide	mGm CmGm UmAm CmGm CmGm UmAm CmGm UmGmUm G (SEQ ID NO: 68)	mGm Um UmUm UmAm GmAm GmCm UmAm UmGm CmUm GmUm UmUm UmG (SEQ ID NO: 69)

Id. at 109. The excerpt from Table 8 above shows modifications comprising phosphorothioate bonds (denoted with a "*") and 2′-O-methyl RNA nucleotides (denoted with a "m") to particular nucleotides of a crRNA sequence. *See id.* at 109–110, n.1. The first nucleotide in the sequences in the VT Domain column is at the 5′ end of the crRNA and the last nucleotide in the sequences in the CER Domain column is at the 3′ end. *See* Ex. 1006, Fig. 1A; Ex. 1002 ¶¶ 126–29, 131–34. Thus, for example, sequence 66 discloses a crRNA with 2′-O-methyl modifications to the sugars of the

three nucleotides at the 5′ end and sequence 67 discloses a crRNA with 2′-O-methyl modifications to the sugars of the three nucleotides at the 3′ end.

Pioneer Hi-Bred discloses that modifications "similar to those illustrated in Example 5 Table 8 can be introduced individually or in combination into the crRNA, crDNA, tracrRNA, tracrDNA, long guide RNA or long guide DNA nucleic acid components of the guide polynuclease system and synthesized per standard techniques." Ex. 1006, 113:25–29.

ii. Krutzfeldt

Krutzfeldt was published in 2007. Ex. 1009. Patent Owner does not dispute that Krutzfedlt is prior art to the challenged claims.

According to Krutzfeldt, "MicroRNAs (miRNAs) are an abundant class of 20–23-nt long regulators of gene expression." Ex. 1009, Abstr. Krutzfeldt describes analogs of these miRNAs referred to as "antagomirs." *Id.* at 2885. These antagomirs "differ from normal RNA by complete 2′-*O*-methylation of sugar, phosphorothioate backbone and a cholesterol-moiety at 3′-end." *Id.* at 2885. Krutzfeldt discloses the combination of 2′-O-methyl and phosphorothioate modifications on nucleotides at the 5′ and 3′ ends of its antagomirs. *Id.* at 2886 (Table 1 disclosing antagomir sequences with a lower case letters indicating a 2′-O-methyl modification and a superscript indicating a phosphorothioate linkage). Krutzfeldt teaches these modifications "protect against different RNAse activities" that would otherwise degrade the RNA strand. *See id.* at 2889 (teaching "phosphorothioate modification to protect against exonucleases" and 2′-O-methyl sugar modification "to protect against endonuclease activity").

iii. Deleavey

Deleavey is a review article published in 2012. Ex. 1007. Patent Owner does not dispute that Deleavey is prior art to the challenged claims.

Deleavey teaches that oligonucleotides (ONs) such as small interfering (siRNAs) and microRNA-targeting ONs (anti-miRNAs) "and their chemically modified mimics, are now routinely used in the laboratory" and "under active investigation in the clinic." Ex. 1007, 937. Deleavey teaches that an array of ON chemical modifications have been developed to overcome the "therapeutically limiting features" of RNAs. *Id.*

In particular, Deleavey explains that RNAs "are rapidly degraded in cells . . . leading to shortened duration of activity and systemic delivery challenges." Ex. 1007, 941. Deleavey teaches that chemical modifications to both the internucleotide linkage, *e.g.*, phosphorothioate and phosphonoacetate (PACE), and sugar, *e.g.*, 2′-O-methyl nucleosides, had been shown to improve stability in various RNA applications. *See id.* at 942–47.

iv. Soutschek

Soutschek was published in 2004. Ex. 1012, 173. Patent Owner does not dispute that Soutschek is prior art to the challenged claims.

Soutschek describes chemically modified short interfering RNAs (siRNAs). Ex. 1012, 173. Soutschek teaches that "[c]hemically stabilized siRNAs with partial phosphorothioate backbone and 2′-O-methyl sugar modifications on the sense and antisense strands showed significantly enhanced resistance towards

degradation by exo-and endonucleases in serum and tissue homogenates." *Id.*; *see also id.* at 177 (listing sequences of chemically-modified siRNAs with phosphorothioate and 2′-O-methyl sugar modifications on certain nucleotides).

v. Yoo

Yoo was published in 2004. Ex. 1011, 2008. Patent Owner does not dispute that Yoo is prior art to the challenged claims.

Yoo describes antisense oligodeoxynucleotides (ODNs) having both phosphorothioate and 2′-O-methyl sugar modifications. Ex. 1011, 2008. Yoo teaches that "the addition of 2′-O-methyl groups to a phosphorothioate-modified ODN is advantageous because of increased stability of binding and reduced non-specific effects." *Id.*

vi. Threlfall

Threlfall was published in 2012. Ex. 1010, 746. Patent Owner does not dispute that Threlfall is prior art to the challenged claims.

Threlfall describes "[c]himeric 2′-O-methyl oligoribonucleotides (2′-OMe ORNs) containing internucleotide linkages which were modified with phosphonoacetate (PACE) or thiophosphonoacetate (thioPACE)" at their ends. Ex. 1010, 746; *see also id.* at 747 (Table 1 showing chemically modified sequences). Threlfall explains that "[o]ligoribonucleotides with a 2′-O-methyl modification . . . are known to be nuclease resistant and increase the stability of a duplex which is formed with complementary RNA." *Id.* at 746. Moreover, Threlfall teaches that "ODNs modified with PACE or

thioPACE [had been] shown to be nuclease resistant" in a prior study. *Id.* at 747. Threlfall reports results from tests on ORNs combining these chemical modifications "into chimeric 2′-OMe ORNs as PACE or thioPACE modifications." *Id.* at 752. According to Threlfall, "the chimeric ORNs formed stable duplexes with complementary RNA, and the majority of these duplexes had higher thermal melting temperatures than an unmodified RNA:RNA control duplex." *Id.*

E. Ground 1: Anticipation by Pioneer Hi-Bred

Petitioner contends that claims 1–7, 9, 10, 12–15, 17, 18, 20–25, and 27–30 are anticipated by Pioneer Hi-Bred. *See* Pet. 17–51. As explained below, Petitioner has shown by a preponderance of the evidence that these claims are anticipated by Pioneer Hi-Bred.

i. Claims 1 and 12

Petitioner has shown that Pioneer Hi-Bred discloses guide RNA and crRNA molecules having the chemical modifications recited in claims 1 and 12. *See, e.g.*, Pet. 19–24, 27–29 (showing for claims 1 and 12). In particular, Table 8 in Pioneer Hi-Bred discloses exemplary crRNA molecules comprising phosphorothioate modifications of the phosphodiester linkage within five nucleotides of the 5′ and 3′-ends (*i.e.*, sequences 64 and 65) and crRNA molecules comprising 2′-O-methyl modifications of the sugar within five nucleotides of the 5′ and 3′-ends (*e.g.*, sequences 66–69). Ex. 1006, 109. Pioneer Hi-Bred teaches that crRNAs, including those in Table 8, are paired with a tracrRNA to form a duplex guide RNA. *Id.* at 8:22–31, 24:32– 25:10, 109:4–9; Ex. 1003 ¶¶ 119, 126, 131, 138–39. Pioneer

Hi-Bred further discloses embodiments in which modifications similar to those exemplified in Table 8 are introduced into a long guide RNA (*i.e.*, a single guide RNA). *Id.* at 113:25–29; *see also id.* at Fig. 3B, 10:8–13 (depicting a "Long guide RNA" as a "fused crRNA and tracrRNA")); Ex. 1003 ¶¶ 117–18, 140, 147– 50.

Petitioner has also shown that Pioneer Hi-Bred discloses the recited "gRNA functionality." *See* Pet. 24–26 (Ex. 1003 ¶¶ 138–41). Pioneer Hi-Bred defines the term "guide polynucleotide" as "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." Ex. 1006, 24:6–8. Thus, 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 claims 1 and 12.

Pioneer Hi-Bred refers to the modified sequences in Examples 4 and 5 as "modified guide polynucleotides," indicating that those sequences have this functionality. Ex. 1006, 107:14–18:11; *see also id.* at 109:4–6 (referring to the complex formed by the "modified crRNA or crDNA components described in Table 8" as a "modified guide polynucleotide/Cas endonuclease complex"). Other statements in these examples confirm this understanding. *See id.* at 107:14–24 (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"); 107:24–108:2 ("Modified guide polynucleotides described above may also be delivered simultaneously in multiplex to target multiple chromosomal DNA sequences for cleavage or nicking.").[9]

Accordingly, we agree with Petitioner that Pioneer Hi-Bred discloses synthetic guide RNA and crRNA molecules as recited in claims 1 and 12. In its Response, Patent Owner contends that Pioneer Hi-Bred does not disclose the recited "gRNA functionality" and is non-enabling. *See* Resp. 30–45. As explained below, both of these arguments are unavailing.

1. Whether Pioneer Hi-Bred discloses a functional gRNA

Patent Owner argues that "Pioneer Hi-Bred does not disclose *a single functional modified gRNA*." Resp. 31. According to Patent Owner, Pioneer Hi-Bred tested only a single modified guide polynucleotide made of DNA, which subsequent testing revealed was not successful. *See id.* at 31–35. Patent Owner argues that Examples 4 and 5 "do not reveal any actual testing" and are "simply an invitation to experiment . . . that precludes a finding of anticipation because functionality is not disclosed." *Id.* at 35–37.

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[9] While 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. *See* Ex. 1059 ¶ 31 (explaining that "Agilent's cleavage experiments [in the Specification of the '001 patent] that show cleavage activity for certain gRNAs establish that 'gRNA functionality' is present for gRNAs," but the absence of cleavage activity "does not mean that it does not have 'gRNA functionality' because such a gRNA may nonetheless form a complex with Cas without effecting target cleavage").

Patent Owner argues that Petitioner did not assert "anticipation by inherency" for the gRNA functionality limitation. Resp. 37. According to Patent Owner, this is because "some of the sequences identified in Table 8 exhibited no functionality, including some 2′-O[-m]ethyl claims, so it cannot be assumed that this combination will work." *Id.* Patent Owner points to results in the Specification of the challenged patent showing that the use of chemically modified gRNAs with 26 and 37 consecutive 2′-O-methyl-modified nucleotides at the 5′ end did not result in cleavage activity. *Id.* at 38 (referring to Table 4 results for entry nos. 150 and 151 in Ex. 1001). According to Patent Owner, these results show "the proposed modifications in sequences 68 and 69 [in Table 8] together are non-functional." *Id.*

Patent Owner further contends that "a POSA would doubt" that sequences 64–69 in Table 8 of Pioneer Hi-Bred "would function at all because each design is both truncated and is also modified." Sur-reply 8 (citing Ex. 2025 ¶¶ 201–03, 221, 242–46); Ex. 1026, Ex. 1033, Ex. 2044, Ex. 2045). Patent Owner's expert, Dr. Marshall testifies that "a putative guide sequence is 20 nt in length," whereas the VT domain sequences in Pioneer Hi-Bred's sequences 64, 66, and 68 are "each only 17 nt long." Ex. 2025 ¶ 201. According to Patent Owner and Dr. Marshall, this means "the nucleotides being edited in Pioneer Hi-Bred are 4, 5, and 6 because 1, 2, and 3 have already been truncated from the end. But Nishimasu found that positions 4, 5, and 6 were crucial positions in the context of gRNA

associating and targeting." Resp. 39–40; *see also* Ex. 2025 ¶¶ 202–03.[10]

Petitioner replies, urging that testing data is not required for a prior art reference to be anticipatory. *See* Reply 3–6 (citing cases). Petitioner argues that Pioneer Hi-Bred provides a targeted disclosure that identifies only five types of modifications for decreasing unwanted nuclease degradation and "explains precisely why those modifications should be used." *Id.* at 14–15 (citing Ex. 1006, 107 (Table 7)). Moreover, Petitioner urges that Pioneer Hi-Bred "presents exemplary embodiments of gRNAs [in sequences 64–69 of Table 8] containing those modifications and the precise positions where those modifications ought to be placed, including the types and locations of modifications that anticipate" the challenged claims. *Id.* at 15–16 (citing Ex. 1006, 109).

Regarding Patent Owner's argument that the cleavage data in the '001 patent Specification shows that Pioneer Hi-Bred's sequences 68 and 69 lack functionality, Petitioner points out that the "gRNA functionality" in claims 1 and 12 does not require cleavage. Reply 17. Thus, Petitioner urges there is not "a shred of evidence that the sequences 68 and 69 in Pioneer Hi-Bred do not show the type of 'gRNA functionality'" in claims 1 and 12. *Id.* at 18 (citing Ex. 1060, 129:17–23; Ex. 1061, 105:15–25, 106:16–24, 107:14–25, 108:13–109:11).

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[10] The Response does not cite evidence for these arguments. However, based on the string cite in the Sur-reply, it appears Patent Owner is relying on Dr. Marshall's testimony and that "Nishimasu" refers to Exhibit 1026.

Petitioner replies to Patent Owner's truncation argument and the related testimony of Dr. Marshall with evidence from Dr. Furneaux. *See* Ex. 1059 ¶¶ 73–75. According to Dr. Furneaux, the record does not support Dr. Marshall's assumption that the sequences in Table 8 are truncated because Pioneer Hi-Bred teaches that the VT domain varies in length and is "designed based on the target sequence," which for the crRNAs in Table 8 is the 17 nucleotides long. *Id.* ¶ 74. Dr. Furneaux further testifies that the references Dr. Marshall cites as showing that truncated gRNAs do not work actually "support the opposite conclusion, that gRNAs with target sequences of 17 nucleotides are functional." *Id.* ¶ 75.

We find Petitioner's arguments and evidence persuasive. It is well established that "anticipation does not require actual performance of suggestions in a disclosure." *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005); *see also In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). Moreover, the Petition need not assert that "gRNA functionality" is inherently disclosed because Petitioner has shown that Pioneer Hi-Bred's expressly discloses this limitation. Pet. 24–26. There is no additional requirement that this express disclosure be backed by test data in order for the reference to be anticipatory. *See, e.g.*, *Novo*, 424 F.3d at 1355; *Rasmusson v. Smithkline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) ("[P]roof of efficacy is not required in order for a reference to be enabled for purposes of anticipation.").

Patent Owner suggests we should ignore what it calls a "bald assertion" of gRNA functionality in Pioneer Hi-Bred because either that assertion is incor-

rect or a POSA would doubt that it was true. *See* Resp. 1–2. We disagree. To begin with, Patent Owner's reliance on the purported failure of Pioneer Hi-Bred's DNA-based embodiments is unavailing. Pioneer Hi-Bred discloses both DNA and RNA-based embodiments. The Petition is premised on the latter. Even if we accept Patent Owner's argument that the DNA-based examples lack gRNA functionality, that fact does not suggest that a POSA would doubt that the RNA-based embodiments, *e.g.*, crRNAs comprising sequences 64–69 in Table 8, lack such functionality.

Patent Owner's argument that a POSA would doubt whether Pioneer Hi-Bred's RNA-based embodiments have gRNA functionality because the VT domain in sequences 64, 66, and 68 is truncated is also unpersuasive. First, Pioneer Hi-Bred does not state that these sequences are truncated, nor does the record support Patent Owner's argument that these sequences are necessarily truncated because they are 17 nt, as opposed to 20 nt, long. To the contrary, Pioneer Hi-Bred teaches that the VT domain may vary in length from 12 to 30 nt. Ex. 1006, 3:19–20, 98:19–23. In addition, Pioneer Hi-Bred explains that the sequences in Table 8 are designed to target the "LIGCas-3" site in Maize, which is 17 nt long. *Id.* at 109:4–9; *see also id.* at 99:15–18 (Table 1 identifying 17 nt target site sequence for LIGCas-3). Thus, the record supports, and we credit, Dr. Furneaux's testimony that the VT domain for these sequences is 17 nt because it is designed to target a 17 nt sequence—not because it has been truncated.[11] Ex. 1059 ¶ 74.

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[11] Patent Owner asserts that Dr. Furneaux "adopted the definition of 'truncated gRNAs' as those with 'regions of target

Second, even if those sequences were truncated, the record does not support Patent Owner's argument that a POSA would doubt that they have gRNA functionality. Patent Owner's argument is premised on Dr. Marshall's testimony that these sequences "are truncated to a point that would render them non-functional. Ex. 2025 ¶ 200. But the references he cites do not support that position. *See* Ex. 2025 ¶ 202 (citing Ex. 1033 ("Fu"); Ex. 2044 ("Cencic"); and Ex. 2045 ("Mali")). To the contrary, Fu evidences that "truncated gRNAs, with shorter regions of target complementarity <20 nucleotides in length" are functional and that truncation to 17 nt is beneficial. Ex. 1033, Abstr.; *see also id.* at 283 ("[W]e found that [truncated] gRNAs with 17 or 18 nucleotides of complementarity generally function efficiently at the intended target site and have improved specificities."). Cencic and Mali likewise do not suggest that a 17 nt VT domain would lack gRNA functionality. *See* Ex. 2025 ¶ 202 (citing Cencic as showing "truncated gRNA tests showed that a guide sequence of only 16 nucleotides" abolished cleavage activity); Ex. 2045, Supp. Fig. 10 ("1-3 bp 5′ [gRNA] truncations are indeed well tolerated, but larger deletions lead to loss of activity"). Accordingly, we credit Dr. Furneaux's testimony (*see, e.g.*, Ex. 1003 ¶ 79, Ex. 1059 ¶¶ 73–75) over the competing testimony offered by Dr. Marshall on these points.

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complementarity <20 nucleotides in length" in paragraph 79 of his opening declaration. Sur-reply 8 n. 1. We disagree. The testimony in paragraph 79 refers to the particular results in Fu. *See* Ex. 1003 ¶ 79 (citing Ex. 1033). We see nothing there that suggests Dr. Furneaux agrees with Patent Owner's position that any gRNA with a VT region of less than 20 nt is truncated.

At oral argument, Patent Owner took its argument a step further asserting not only that a POSA would doubt their functionality, but also that that the record shows that Pioneer Hi-Bred sequences 64–67, in fact, lack gRNA functionality because they combine truncation with chemical modifications to the 4, 5, and 6 nucleotides of the untruncated gRNA. *See* Tr. 41:3–48:16 (urging that "Nishimasu" (Ex. 1026) shows that the nucleotides at this position are critical to gRNA functionality). This new argument is unavailing.[12] First, as explained above, the record does not support Patent Owner's argument that the VT domain in these sequences is truncated. Second, there is test data in the record demonstrating gRNA functionality for both truncated gRNAs and gRNAs with modifications to the 4, 5, and 6 nucleotides. *See, e.g.*, Ex. 1033, 283; Ex. 2045, Supp. Fig. 10; Ex. 1001, Tables 3 and 4 (Patent Owner's Specification showing cleavage activity for truncated gRNAs with a 17 nt target sequence and gRNAs with chemical modifications at the 4, 5, and 6 nucleotides). While not prior art, this

[12] In its papers, Patent Owner asserts that a POSA would "doubt" the gRNA functionality of sequences 64–69 for this reason. Sur-reply 8; *see also* Resp. 40 (arguing this combination "would have been unpredictable" and thus gRNA functionality was not "inherent"); Ex. 2025 ¶ 203 ("[A] POSA would seriously question whether the guide sequence designs of Table 8 would be functional"). But at the hearing, Patent Owner stated it was asserting "both" that a POSA would doubt their functionality and that these sequences do not, in fact, exhibit gRNA functionality and that the record demonstrates such. Tr. 41:3–16. This latter point is a new argument that was not clearly presented in the Response and has therefore been waived. Even if it had been timely presented, we find that the record does not support Patent Owner's position that Pioneer Hi-Bred's sequences 64–69 are nonfunctional.

data does tend to rebut Patent Owner's argument that sequences 64–67 lack gRNA functionality because it shows that both truncation to 17 nt and modifications to the 4, 5, and 6 nucleotides can be individually tolerated without losing cleavage activity.

We also disagree with Patent Owner's argument that the cleavage data in its Specification shows that a crRNA corresponding to Pioneer Hi-Bred's sequences 68 and 69 would lack "gRNA functionality." Resp. 38. The data Patent Owner points to shows only that cleavage did not occur. Cleavage, however, is not required for the "gRNA functionality" recited in claims 1 and 12. Patent Owner's expert, Dr. Sampson admitted on cross-examination that just because a gRNA in Table 4 lacks cleavage activity does not demonstrate that it also lacks the ability to bind a Cas protein and target that complex to target polynucleotide:

> Q. [T]he handful of guide RNAs that you identified in Table 4 of the ['001] patent as not exhibiting cleavage, those may nonetheless bind with a Cas protein and form a complex with the target DNA; correct?
>
> A. Yeah. I can't, you known, answer that definitively.
>
> Q. All we know is that it might or might not happen; right? We don't know one way or the other?
>
> A. There is no objective evidence that would be able to indicate that.
>
> ***
>
> Q. I just want to be clear, the handful of guide RNAs that you point out as being

nonfunctional, you don't actually know whether they actually have gRNA functionality as claimed in the claims; right?

A. What I'd say is that I can't – there's no objective evidence that allows you for a determination of whether the guides bind to Cas9 or direct the programmed Cas9 to the target site.

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Q. You can't say one way or another whether the guide RNAs that you say are not functional actually lack that gRNA functionality as claimed in the claims; right?

A. I can state that I have no evidence to differentiate between whether they would bind to the Cas or direct the Cas to a target sequence.

Ex. 1060, 106:16–109:11 (objections omitted); *see also* Ex. 1059 ¶ 31 (similar testimony from Dr. Furneaux). Thus, the data in Table 4 of the Specification showing a lack of cleavage activity does not demonstrate that the corresponding gRNA lacks the claimed "gRNA functionality."

Moreover, Patent Owner's argument only applies to a crRNA that combines sequences 68 and 69 "together" resulting in a crRNA with 39 consecutive 2′-O-methyl modifications. Resp. 38. However, Pioneer Hi-Bred discloses that these modifications may be introduced "individually or in combination." Ex. 1006, 113:25–29. If introduced individually, a crRNA having the modifications in sequence 68 would have 17 2′-O-methyl modifications and a crRNA having the

modifications in sequence 69 would have 22 such modifications. This is closer to the number of modifications in sequences that the data in the Specification shows do have cleavage activity (*e.g.*, Table 4 Entry #s 146–150 having 20 consecutive 2′-O-methyl modifications) than it is to the sequences Patent Owner identifies as lacking cleavage activity. *See* Resp. 38 (citing Ex. 1001, 119 (Table 4 Entry #s 151 and 152 having 26 and 37 consecutive sugar modifications). Therefore, the data in the Specification does not show that a crRNA comprising sequence 68 or 69 would lack cleavage activity, much less the broader "gRNA functionality" recited in the challenged claims.

For these reasons, we determine that Pioneer Hi-Bred discloses functional, chemically-modified gRNAs as recited in claims 1 and 12.

2. Whether Pioneer Hi-Bred is enabled

Patent Owner contends that Pioneer Hi-Bred is not enabled. Resp. 41– 45. More specifically, Patent Owner asserts that "[a] POSA encountering Pioneer Hi-Bred could not make the claimed inventions of the '001 [patent] without undue experimentation" because it "discloses a laundry list of chemical modifications, that can be made alone or in combination, and applied literally anywhere in the disclosed guides." *Id.* at 43–44. According to Patent Owner, the "art was new, complicated and unpredictable," "not 'mechanistically analogous' to anything that came before it," and "a POSA would have been circumspect about making the claimed modifications without testing because what was known about the nature of the interactions between the Cas Protein and the gRNA suggested the

gRNA would be very sensitive to modifications, especially in the guide portion." *Id.* at 45 (no citations provided). Thus, argues Patent Owner, "the *Wands* factors lean[] heavily in favor of a finding that Pioneer Hi-Bred would not enable one to make the claims of the '001 Patent without undue experimentation." *Id.* (italics added).

Petitioner contends the anticipating disclosures in Pioneer Hi-Bred are enabled. Reply 6–19. In particular, Petitioner urges that Pioneer Hi-Bred discloses only five types of chemical modifications for decreasing unwanted nuclease degradation in Table 7 and provides exemplary embodiments of gRNAs, including those having "the types and locations of modifications that anticipate the '001 Patent claims," in Table 8. *Id.* at 14–16. Petitioner points to testimony from Patent Owner's declarants showing that the techniques for making such gRNAs were known in the art and a POSA could use "commercially available instruments that could churn out multiple [chemically-modified] gRNAs in a single day." *Id.* at 9–10.

Petitioner also cites evidence that the chemical modifications disclosed in Pioneer Hi-Bred had been used for decades prior to the filing of the '001 patent "to stabilize RNA against nucleases" and that "CRISPR gRNA stabilization presented a new iteration of an old problem with a tried and true solution." *Id.* at 10–13. According to Petitioner, "the testing data in the patent drives home just how predictable this field was" because only 7 of the roughly 250 gRNAs Patent Owner tested lacked cleavage functionality. *Id.* at 13–14, 17 (referring to the inventors "roughly 97% success rate in predicting which modified gRNAs would work" based on prior art teachings).

We again find Petitioner's evidence and argument persuasive. For a prior art reference to be enabling, "the reference need only enable a single embodiment of the claim." *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015). "In other words, a prior art reference need not enable its full disclosure; it only needs to enable the portions of its disclosure alleged to anticipate the claimed invention." *In re Antor Media Corp.*, 689 F.3d 1282, 1290 (Fed. Cir. 2012). Here, Petitioner asserts that the RNA-based embodiments disclosed in Examples 4 and 5 of Pioneer Hi-Bred are anticipatory. Those disclosures are presumed enabling and Patent Owner has not shown otherwise.

Indeed, he record demonstrates that a POSA, as of December 2014, could practice these disclosures without undue experimentation.[13] As explained above, Table 7 of Pioneer Hi-Bred teaches modifications, including 2′-O-methyl modifications to the sugar and phosphorothioate bond modifications, that can be used to decrease unwanted nuclease degradation of a gRNA in a guide polynucleotide/Cas endonuclease system. And Table 8 discloses exemplary sequences of such chemically-modified crRNAs that read on claims 1 and 12. Pioneer Hi-Bred teaches that gRNAs having the modifications in Table 8 and similar modifications

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[13] The question of undue experimentation involves consideration of certain factors identified in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include: the quantity of experimentation, the amount of direction or guidance present, the presence or absence of working examples, the state of the prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. *Id.* To the extent they are applicable here, we have considered these and the other *Wands* factors in our analysis below.

can be "synthesized per standard techniques." Ex. 1006, 113:25–29.

While Pioneer Hi-Bred does not further describe these standard techniques, the record demonstrates such techniques were known in the art and a POSA would have been able to use them to make the gRNAs disclosed in Pioneer Hi-Bred without undue experimentation. Both sides' experts testify that techniques such as "click chemistry" and "TC chemistry" were known in the prior art for synthesizing long oligonucleotides. Ex. 1059 ¶¶ 33–38; *see* Ex. 1061, 188:9–190:17). Moreover, the Specification of the '001 patent cites references describing these known techniques to explain how its chemically-modified gRNAs may be synthesized. Ex. 1001, 47:35– 65; *see also In re Morsa*, 803 F.3d at 1378 (explaining that statements in the specification evidencing the knowledge of a POSA may be relied upon to show that a prior art reference is enabled). The record further evidences that the inventors were able to employ such techniques to make an individual gRNA in about a day's time and that commercially-available "synthesizers" were available, allowing dozens of different gRNAs to be synthesized at the same time. Ex. 1069 ¶ 41; *see* Ex. 1060, 87:6–18, 88:3–16 (Dr. Sampson testifying that synthesizers capable of making as many as 48 gRNAs at a time were commercially-available), 191:16–192:14 (testifying that multiple guides can be made in a day).

Patent Owner argues that its inventors were uniquely-skilled in the synthesis of long RNAs and thus "it would have been extremely challenging for a POSA to chemically synthesize the claimed chemically-modified gRNA." *See* Resp. 11–13. This argument is unavailing for several reasons. First, the Specification

of the '001 patent does not disclose any new techniques for synthesizing chemically-modified gRNAs, but instead refers to the use of click chemistry and TC chemistry techniques already taught in other references. Ex. 1001, 47:35–65. Second, while Dr. Sampson points to challenges he and the other inventors allegedly had to overcome to make these molecules (*see* Ex. 2029 ¶¶ 12–14), none of those challenges are mentioned in the Specification of the '001 patent. *See In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) (holding "the Board's observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art references supports the Board's finding that one skilled in the art would have known how to implement the features of the references"). Moreover, when cross-examined about these purported challenges, Dr. Sampson was either unable to remember how the inventors addressed them or he testified they were overcome by increasing the reaction time, which was "[j]ust kind of a pretty standard thing that you do." Ex. 1061, 115:3–118:19. Third, in order to anticipate, Pioneer Hi-Bred "need only enable a single embodiment of the claim." *In re Morsa*, 803 F.3d at 1377. Petitioner's arguments that its team of inventors spent over a year to synthesize "hundreds" of gRNAs does not show that the experimentation required to make any one of the anticipating gRNAs disclosed in Pioneer Hi-Bred, *e.g.*, the exemplary crRNAs in Table 8, would be undue. For these reasons, we credit Dr. Furneaux's testimony that undue experimentation would not be required to make the anticipating, chemically-modified gRNAs taught in Pioneer Hi-Bred (*see* Ex. 1059 ¶¶ 32–47) over the competing testimony of Patent Owner's declarants.

So too, the fact that Pioneer Hi-Bred "contains no data regarding any testing of the sequences in Table 8" does not demonstrate that the crRNAs disclosed there are not enabled. *See* Resp. 35–37. "It is not . . . necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement." *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir.1985). Thus, 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. *See Antor Media,* 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 to perform the claimed invention").

To the extent Patent Owner contends that the nascent state of the art demonstrates that undue experimentation would be required, we disagree. *See* Resp. 45. It is undisputed that the use of gRNA in a CRISPR/Cas system was a relatively new discovery first published in mid-2012. *See* Pet. 2; Resp. 52–53. That said, the record demonstrates that by December 2014 substantial research into such systems had been published and would have been known to a POSA Ex. 1003 ¶ 79; Ex. 1059 ¶¶ 20–23, 65–72 (citing references). A POSA would also know that gRNA was subject to degradation, which could limit the efficiency of a CRISPR/Cas system. *See, e.g.*, Ex. 1003 ¶¶ 66, 71; Ex. 1061, 200:14–201:11. Moreover, 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. Ex. 1003 ¶¶ 51–52, 62–71; *see also* Ex. 1061, 214:6–16. Thus, while the art was somewhat unpredictable in December 2014, it was far from a blank slate with a POSA 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.

Finally, Patent Owner's attempt to analogize the present facts to those in *Impax Laboratories*[14] is unavailing. *See* Resp. 43. The claims in *Impax Laboratories* were directed to methods of using a particular compound to treat a particular disease. 545 F.3d at 1314. However, the allegedly anticipating prior art disclosed "hundreds or thousands of compounds and several diseases" along with "broad and general" dosage guidelines and "without sufficient direction or guidance to prescribe a treatment regimen." *Id.* at 1315–16. On those facts, the Federal Circuit affirmed the district court's finding that the prior art did not enable the particular method recited in the claims. *Id.* In contrast, 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.

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[14] *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008).

In sum, given the guidance in Pioneer Hi-Bred, the existing knowledge in the art, including knowledge of standard techniques and equipment/reagents for making the chemically modified RNA sequences taught in Pioneer Hi-Bred, and the relatively high level of training of a POSA, we find that undue experimentation would not have been required to make and use a gRNA with the recited chemical modifications and functionality. Because Pioneer Hi-Bred discloses functional, chemically-modified gRNAs as recited in claims 1 and 12, and that disclosure is enabled, Petitioner has demonstrated that claims 1 and 12 are anticipated by Pioneer Hi-Bred.

ii. Claim 2

Claim 2 depends from claim 1 and recites that the synthetic guide RNA is a "single guide RNA (sgRNA)." Ex. 1001, 243:25–26. Petitioner asserts that Pioneer Hi-Bred discloses a sgRNA and teaches that chemical "modifications, such as 2′-O-methyl and 3-phosphorothioate, can be made in a sgRNA." Pet. 30–31 (citing Ex. 1006, 24:6–19, 25:11–15, 113:25–29, Figs. 1B and 3B). We agree that Pioneer Hi-Bred discloses a chemically-modified sgRNA as recited in claim 2.

Patent Owner argues that claim 2 is not anticipated because "[s]equences 64, 65, 66, 67, 68, and 69 [in Pioneer Hi-Bred Table 8] are disclosed only as a portion of a duplex or two-part guide." Resp. 29.[15] Patent Owner's argument is unavailing. Pioneer Hi-

[15] To the extent Patent Owner reasserts the same arguments for claim 2 and the other dependent claims that it does for claims 1 and 12, those arguments are unavailing for the reasons already addressed in our analysis above.

Bred's disclosure is not limited to a two-part guide with the crRNA sequences in Table 8. It discloses that its guide polynucleotides can be implemented as "a single molecule or a double molecule." 1006, 24:8–9. Moreover, Pioneer Hi-Bred specifically states that the modifications in Table 8 can also be introduced in a "long guide RNA," *i.e.*, a sgRNA. Ex. 1006, 113:25–27; *see* Ex. 1003 ¶ 150 (explaining that a sgRNA is also referred to as a long guide RNA). Accordingly, while sequences 64–69 are described as part of a crRNA, a POSA would have immediately envisioned that those sequences could also be implemented in the corresponding domains of a sgRNA.

Accordingly, Petitioner has shown by a preponderance of the evidence that claim 2 is anticipated by Pioneer Hi-Bred.

iii. Claims 3–7, 10, 13–15, 17, and 20

Claims 3–7, 10, 13–15, 17, and 20 depend from claims 1 and 12 and further limit the type and location of the chemical modifications. Petitioner cites evidence showing that Pioneer Hi-Bred discloses the additional limitations in each of these claims. *See* Pet. 32–35, 38, 43–44.

Petitioner's contentions are sufficiently supported by the record and persuasive. Indeed, each of the additional limitations recited in claims 3–7, 10, 13–15, 17, and 20 is disclosed in one or more of the exemplary sequences 65–69 in Table 8 of Pioneer Hi-Bred. That is, sequences 64, 66, and 68 disclose a modification "at the first nucleotide" of the 5′-end as recited in claims 3, 6, and 13. Sequences 65, 67, and 69 disclose a modification of "at least two consecutive modified nucleotides within five nucleotides" of the 3′-end as

recited in claims 3, 6, and 13. Sequences 64 and 65 disclose phosphorothioate modifications as recited in claims 5 and 15. Sequences 66–69 disclose 2′-O-methyl modifications as recited in claims 10 and 17.

Patent Owner does not dispute Petitioner's showing for most of these claims separately from its arguments for the independent claims, which are unavailing. However, Patent Owner asserts that claims 4, 7, 14, and 20 are not disclosed by the crRNA sequences in Pioneer Hi-Bred Table 8 because they "include a limitation requiring at least one modified nucleotide that is a '2′-O-methyl-' nucleotide with an additional modification type to the same nucleotide." *See* Resp. 27. Patent Owner is incorrect.

Claim 4 depends from claim 3 and recites that the "one modified nucleotide" specified in claim 3 is selected from a group of modifications that includes "a 2′-O-methyl nucleotide." Ex. 1001, 243:34–36. Sequences 66–69 of Pioneer Hi-Bred disclose that limitation. Ex. 1006, 109.

Claim 7 depends from claim 6 and recites that the "one or more modified nucleotides within five nucleotides from the 3-end" are selected from a group of modifications that includes "a 2′-O-methyl nucleotide." Ex. 1001, 243:53–56. Sequences 65 and 69 disclose that limitation Ex. 1006, 1009.

Claim 14 depends from claim 13 and recites that the "one modified nucleotide" specified in claim 13 is selected from a group of modifications that includes "a 2′-O-methyl nucleotide." Ex. 1001, 244:42–44. Sequences 66–69 disclose that limitation. Ex. 1006, 109.

Claim 20 depends from claim 12 and recites that the "modified nucleotides" are selected from a group of modifications that includes "a 2′-O-methyl nucleotide." Ex. 1001, 243:53–56. Sequences 66–69 disclose that limitation. Ex. 1006, 109.

Accordingly, Petitioner has shown by a preponderance of the evidence that claims 3–7, 10, 13–15, 17, and 20 are anticipated by Pioneer Hi-Bred.

iv. Claims 9 and 18

Claims 9 and 18 depend from claims 1 and 12 and recite that the modified nucleotide is a "2′-O-methyl-3′-phophorothioate nucleotide." Ex. 1001, 243:65–67, 244:63–65.

Petitioner cites the disclosure in Tables 7 and 8 of Pioneer Hi-Bred, urging that these examples disclose "five types of nucleotide base (or sugar) and/or phosphodiester bond modifications including the phosphorothioate and 2′-O-methyl modifications." Pet. 35–36. Relying on Pioneer Hi-Bred's teaching that these modifications can be introduced throughout the VT and CER domains and in "combination," Petitioner asserts that "Tables 7 and 8 disclose thirty-one different ways to combine the five modifications, and eight of these combinations contain both a 3′-phosphorothioate modified nucleotide and a 3′-phosphorothioate modified nucleotide." *Id.* at 36–37 (citing Ex. 1003 ¶¶ 171–74; Ex. 1006, 106:13–19, 113:25–29). Petitioner relies on a similar mathematical analysis based on another teaching in Pioneer Hi-Bred that "yields 2047 ways to combine the [disclosed modifications], 512 of which contain a 2′-O-methyl-3′phosphorothioate modification in the guide sequence." *Id.* at 37–38 (citing Ex. 1003 ¶ 173; Ex. 1006, 24:6–

19). According to Petitioner, a POSA would "immediately envisage combining these modifications in one nucleotide near the 5′ and/or 3′-ends of a gRNA" given "the high fraction of combinations containing the combined [modifications] and Pioneer Hi-Bred's express teachings of combining" them. *Id.* at 38 (citing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)).

Patent Owner argues that "Pioneer Hi-Bred does not disclose any 2′-O-Methyl and 3′-phosphodiester linkage on the same nucleotide" as recited in these claims. Resp. 27. In its Sur-reply, Patent Owner further asserts that *Kennametal* "is inapposite since [there] it was undisputed that all claim elements were disclosed in the prior art but for a single structural element," whereas here "it is undisputed that Pioneer Hi-Bred lacks the structural limitations and the 'gRNA functionality' limitation." Sur-reply 26. However, Patent Owner does not challenge Dr. Furneaux's calculations, nor Petitioner's argument based on those calculations that a high fraction of the possible combinations would have both modifications. *See* Reply 2 (noting that Patent Owner "presents no analysis or argument" regarding these claims).

Petitioner's contentions are sufficiently supported by the record and persuasive. Sequences 64 and 65 in Pioneer Hi-Bred disclose phosphorothioate modifications to the three nucleotides at the 5′-end (sequence 64) and 3′-end (sequence 65) of a crRNA. Ex. 1006, 109. Sequences 66 and 67 disclose 2′-O-Methyl modifications at the same locations. *Id.* While none of the exemplary sequences in Table 8 disclose the combination of these two modifications to the same nucleotide, Pioneer Hi-Bred discloses that "[n]ucleotide

base *and*/or phosphodiester bond modifications similar to those illustrated in Example 5 Table 8 can be introduced individually or *in combination* into the crRNA." *Id.*at 113:25–27 (emphases added). The combination of the modifications in sequences 64 and 66, for example, would result in a crRNA 2′-O-methyl-3′-phosphorothioate nucleotides at the 5′-end. Similarly, Petitioner shows that a high fraction of the possible combinations in Table 7 result in the combination of 2′-O-methyl and 3′-phosphorothioate modifications. Pet. 36–37 (citing Ex. 1003 ¶¶ 171–74). This showing, which Patent Owner does not specifically dispute, sufficiently demonstrates that a POSA would immediately envisage the combination of modifications recited in claims 9 and 18. Accordingly, Petitioner has shown by a preponderance of the evidence that claims 9 and 18 are anticipated by Pioneer Hi-Bred.

v. Claims 21–25 and 27

Claim 21 recites a method for modifying a DNA sequence, regulating the expression of a gene of interest, or cleaving a target polynucleotide using the gRNA of claim 1 to form a gRNA:Cas protein complex that is then contacted with the target polynucleotide. Ex. 1001, 245:8–18. Claim 27 depends from claim 21 and recites that the gRNA:Cas protein is formed "outside or inside a cell" and contacted with the target polynucleotide "in a cell." *Id.* at 246:18–20.

Petitioner cites evidence showing that Pioneer Hi-Bred discloses the method recited in claims 21 and 27. *See* Pet. 45–49. Patent Owner does not dispute Petitioner's showing for these claims separately from its arguments for claim 1.

Petitioner's contentions are sufficiently supported by the record and persuasive. As explained above, Pioneer Hi-Bred discloses a synthetic gRNA with the chemical modifications and gRNA functionality recited in claim 1. Pioneer Hi-Bred discloses methods of using such a gRNA to modify a DNA sequence as recited in claim 21. Ex. 1006, 41:23–32, 128:8–14 (claim 28); Ex. 1003 ¶¶ 195–207 (explaining how Pioneer Hi-Bred discloses the steps of claim 21). Pioneer Hi-Bred also discloses that the gRNA/Cas endonuclease system can be used to regulate expression of a specific gene or cleave a target polynucleotide. *See id.* at 30:17–22 (cleave by "introduc[ing] a double strand break at said target site"); 47:15–29 (regulate expression). Regarding claim 27, Pioneer Hi-Bred discloses that the Cas endonuclease may be "paired with the modified nucleic acid components" (*i.e.*, the chemically-modified gRNA) and co-delivered into a cell. Ex. 1006, 112:30– 31. Dr. Furneaux offers testimony, which we credit, explaining that this would result in the gRNA:Cas protein complex being formed outside the cell and that the complex would contact the target polynucleotide inside the cell upon co-delivery. Ex. 1003 ¶¶ 217–18. The teachings Petitioner relies upon in Pioneer Hi-Bred are presumptively enabling. *See, e.g.*, *Antor Media*, 689 F.3d at 1287–88. Patent Owner does not challenge that presumption separately from its arguments for independent claims 1 and 12, which are unavailing as explained above.

Claims 22–25 depend from claim 21 and recite limitations on the type and location of the chemical modifications on the gRNA that are the same as those in claims 3–5 and 9. *Id.* at 245:19–246:12. Petitioner relies on the same showing for claims 22–25 as it does

for these other claims. That showing is sufficient for the same reasons explained above.

Accordingly, Petitioner has shown by a preponderance of the evidence that claims 21–25 and 27 are anticipated by Pioneer Hi-Bred.

vi. Claim 30

Claim 30 recites "[a] set or a library comprising at least two guide RNAs of claim 1." Ex. 1001, 246:25–26.

Petitioner relies on Pioneer Hi-Bred's teaching that the "modified guide polynucleotides described [therein] may also be delivered *simultaneously in multiplex* to target multiple chromosomal DNA sequences for cleavage or nicking." Pet. 50 (quoting Ex. 1006, 107:24– 108:2). In addition, Petitioner cites Pioneer Hi-Bred's teaching that the guide polynucleotide/Cas system can be used "for producing transgenic trait loci *comprising multiple transgenes*." *Id.* at 50–51 (quoting Ex. 1006, 78:19– 26). Petitioner and Dr. Furneaux assert that "[a] POSA would have understood [these teachings] as an express instruction to prepare a library of modified gRNAs comprising multiple modified gRNAs" as recited in claim 30. Pet. 51; Ex. 1003 225–27.

In response, Patent Owner asserts "[s]equences 65-69 not comprise [sic] a set or library of two or more synthetic guide RNAs, and there [sic] cannot anticipate claim 30." Resp. 29. Patent Owner does not respond to Petitioner's argument that Pioneer Hi-Bred teaches its modified gRNAs may be delivered in multiplex. *See* Reply 2–3 (noting that "Patent Owner

presents no rebuttal to Petitioner's citation" to this disclosure).

Petitioner's contentions are sufficiently supported by the record and persuasive. As we understand it, Patent Owner's argument against Petitioner's showing for claim 30 is that a single gRNA comprising one of sequences 65–69 of Pioneer Hi-Bred Table 8 would not itself be a set or library comprising at least two guide RNAs. But that misses the point. Pioneer Hi-Bred specifically teaches that its modified gRNA may be delivered simultaneously in multiplex to target multiple different sequences. Ex. 1006, 107: 24–108:2. Dr. Furneaux offers testimony, which we credit, explaining that a POSA would understand this to be an instruction to prepare a library of multiple, modified gRNAs. Ex. 1003 ¶ 227. Accordingly, Petitioner has shown by a preponderance of the evidence that claim 30 is anticipated by Pioneer Hi-Bred.

F. Ground 2: Obviousness over Pioneer Hi-Bred and Krutzfeldt, Deleavey, Soutschek, or Yoo

Petitioner contends claims 9, 18, and 25 are obvious over Pioneer Hi-Bred in combination with any of Krutzfeldt, Deleavey, Soutschek, or Yoo. Pet. 51–64. More specifically, Ground 2 relies on Pioneer Hi-Bred for the limitations of the independent claims and each of the other references for their disclosure of modified nucleotides comprising a 2′-O-methyl-3′-phosphorothioate nucleotide as recited in dependent claims 9, 18, and 25. *Id.*

Petitioner asserts that "[a] POSA would have been motivated to incorporate the 2′-O-methyl-3′phophorothioate modifications disclosed in Krutzfeldt,

Deleavey, Soutschek, or Yoo's RNA molecules with the modified gRNAs taught in Pioneer Hi-Bred for multiple reasons." Pet. 55. Petitioner's reasoning includes that it was "well known to use such modified nucleotides within five nucleotides of the 3′ and 5′-ends and the 2′-O-methyl-3′-phosphorothioate modifications in these secondary references "reflect the types of modifications to gRNA that are already taught and suggested in Pioneer Hi-Bred." *Id.* at 55–58. Petitioner further contends that a POSA would have been motivated to make the combination because the references teach that such modifications provide benefits such as improved stability and resistance towards nuclease degradation and increased editing efficiency. *Id.* at 58–60.

According to Petitioner, a POSA would have had a reasonable expectation of success because "it is undisputed that gRNAs with 2′-O-methyl and phosphorothioate modifications are inherently functional for this purpose." Pet. 61. Petitioner also refers to Pioneer Hi-Bred's teaching that both types of modifications can be used in a gRNA. *Id.* at 62. Finally, Petitioner urges that the "use of 2′-O-methyl-3′-phosphorothioate modifications at or near the 3′ and/or 5′-ends of various types of RNAs, such as siRNA, AONs, and anti-miRNA, in the field of gene regulation" was "widespread" and therefore a POSA would have anticipated that the same modifications "would not only have been functional" to hybridize to DNA in a cellular environment, but also would have had" additional benefits such as increasing stability and binding specificity. *Id.* at 63–64 (citing Ex. 1003 ¶¶ 259–68).

Petitioner's contentions are sufficiently supported by the record and persuasive. Krutzfeldt, Deleavey, Soutschek, and Yoo each disclose chemically modified RNA sequences having a "2′-O-methyl-3′-phosphorothioate nucleotide" as recited in claims 9, 18, and 25. Ex. 1009, 2886 (Table 1); Ex. 1007, 943 (Fig. 4), 948; Ex. 1012, 173, 177; Ex. 1011, 2008. Moreover, as Petitioner points out, these references teach that such modifications, particularly when made to nucleotides near the end of an RNA molecule, provide a number of benefits including increased resistance to nuclease degradation. Ex. 1009, 2889; Ex. 1007, 937; Ex. 1012, 173; Ex. 1011, 2008. This dovetails with Pioneer Hi-Bred's teaching that such modifications decrease unwanted nuclease degradation in a guide polynucleotide. *See* Ex. 1006, 107. Accordingly, the combination of Pioneer Hi-Bred with any of Krurtzfeldt, Deleavey, Soutschek, or Yoo teaches all of the limitations of these claims and the record supports Petitioner's rationale for combining them.

Patent Owner raises several arguments in its Response some of which were already addressed in our analysis of Ground 1. Patent Owner urges that the Petitioner's obviousness grounds fail because they rely exclusively on Pioneer Hi-Bred for the claimed functionality requirements. *See* Resp. 49– 50. However, as explained above, Pioneer Hi-Bred discloses synthetic gRNA and crRNA molecules having the recited "gRNA functionality" and the anticipating disclosure is enabled as to both Patent Owner's composition and method claims. Accordingly, Patent Owner's functionality arguments are unavailing.

Patent Owner also challenges Petitioner's motivation to combine and reasonable expectation of

success showing and offers evidence of objective indicia of non-obviousness. *See* Resp. 45–49, 50–66. We address these issues in turn.[16]

1. Whether there would have been a motivation to combine and reasonable expectation of success

Patent Owner argues that Petitioner "relies on the claims as a roadmap" and "regardless of the number of or variety of modifications in a challenged claim" the alleged motivation to combine is always the same, *i.e.*, that Pioneer Hi-Bred envisions other combinations and "the modifications in the prior art reference would enhance against degradation." Resp. 51. According to Patent Owner, "protecting against degradation is a function the disclosed modifications in Pioneer Hi-Bred were already providing so a POSA would have no need or motivation to look elsewhere to an already fulfilled need." *Id.*

Patent Owner's argument is unavailing for several reasons. First, at least with respect to claims 9, 18, and 25, Pioneer Hi-Bred teaches the same modifications (*i.e.*, 2′-O-methyl sugar and phosphorothioate linkage modifications) taught by the secondary references in Ground 2. Thus, the choice between Pioneer Hi-Bred's modifications and those taught in the Krutzfeldt, Delevey, Soutschek, and Yoo that Patent Owner's argument envisions is an illusory one.

Second, even if the combination involved the use of modifications not already taught in Pioneer Hi-

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[16] These are global arguments Patent Owner collectively argues for all of the obviousness grounds. Our analysis below considers the claims in all of those grounds.

Bred,[17] it is well-established that substitution of one element for another known to provide the same benefit may provide a rationale for combining references. *See KSR*, 550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."). So too, "the normal desire to improve upon what is already generally known" may provide a reason to employ additional types of modifications as in claims 8, 11, 16, 19, and 26, or to combine modifications as in claims 9, 18, and 25, where such strategies had been shown to prevent degradation in prior art RNA systems. *Jazz Pharms., Inc. v. Amneal Pharms.,* LLC, 895 F.3d 1347, 1368 (Fed. Cir. 2018).

Third, along with protecting against degradation, Petitioner points to teachings in these references that their chemical modifications provide other benefits, *e.g.*, increased specificity and cell penetration, that would have motivated a POSA to employ such modifications in Pioneer Hi-Bred's synthetic gRNAs. *See* Pet. 59 (referring to Yoo's teaching regarding "reduced non-specific effects"); 66–68 (referring to Threlfall's teaching regarding "greater efficacy and ability to penetrate cells" and "increased cellular uptake"); Ex. 1003 ¶¶ 259–64 (Ground 2); 285–87 (Ground 3). Moreover,

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[17] This is the case for the PACE and thioPACE modifications taught by Threlfall and Delevey in Ground 3. Pioneer Hi-Bred does not teach those modifications, but Petitioner asserts that it would have been obvious to use them in Pioneer Hi-Bred's synthetic gRNAs because "they would provide the same benefits to gRNAs that Pioneer Hi-Bred seeks to achieve." Pet. 67.

Dr. Furneaux provides testimony explaining why a POSA would understand that the various benefits these modifications provide to be desirable within the context of a CRISPR/Cas system. Ex. 1003 ¶¶ 254–55 (Ground 2); 286–87 (Ground 3). This testimony is credible and further supports Petitioner's reasoning for combining the references.

Patent Owner also argues there would have been no reasonable expectation of success in making the chemical modifications in Petitioner's obviousness combinations. *See* Resp. 52–64. According to Patent Owner, "[w]hether a particular combination of chemical modifications in at [sic] particular nucleotide positions . . . would adversely impact functionality was entirely unpredictable at the time Agilent started its work, and there was no guarantee of success that it would make the discoveries that led to the claimed inventions." *Id.* at 52. Patent Owner explains that "CRISPR was a nascent technology in 2014, and the structure-function relationships among the gRNA and Cas protein were still being investigated." *Id.* at 54–59 (citing references). Therefore, urges Patent Owner, "a POSA would know that the result of modifications would be unpredictable and would need to be tested." *Id.* at 55.

Regarding Petitioner's reliance on modifications known to be successful in prior art RNA systems, Patent Owner contends that a POSA would not have regarded such systems as "'mechanistically analogous' such that modifications that maintained functionality in other systems would work in the CRISPR-Cas system." Resp. 60–61 (citing Ex. 2025 ¶¶ 132–47). Patent Owner argues that Dr. Furneaux's testimony that "prior art siRNA, miRNA, AON" systems are

"mechanistically analogous" to CRISPR/Cas systems is flawed because "notably absent from his [declaration] *is any description of the mechanisms of the systems that are allegedly 'mechanistically analogous.'*" *Id.* at 61–62 (citing Ex. 1003 ¶¶ 43–50). Patent Owner urges that Petitioner and Dr. Furneaux's "entire 'mechanistically analogous' analysis reduces simply to noting that RNA, which is common to all these systems, faces the same problems, such as potential degradation." *Id.* at 62.

Finally, Patent Owner argues that "Agilent's own process confirms that arriving at the claimed combinations was anything but predictable or that a POSA would have had a reasonable likelihood of success." Resp. 63 (referring to Dr. Sampson's testimony). According to Patent Owner, this was "an iterative process as to which there was no assurance of success via which Agilent was able to test its various modified guides across a series of assays sufficient to appraise the public on how to improve CRISPR gRNAs." *Id.* at 64.

In reply, Petitioner argues that Patent Owner's arguments and Dr. Marshall's testimony regarding the complexity of the CRISPR/Cas system and mechanistic differences with prior art systems are "theoretical concerns . . . that were never actually expressed in the literature." Reply 23–24. According to Petitioner, by asserting that these "speculative and contrived concerns can defeat obviousness, Patent Owner effectively applies a heightened standard that goes beyond reasonable expectation of success." *Id.* at 24. Instead, "the law is clear that 'the expectation of success need only be reasonable, not absolute.'" *Id.*

(quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007)).

Petitioner urges that the record supports such a finding here because:

> [r]esearchers had been using the claimed chemical modifications in other relevant gene regulation contexts long before the conception of CRISPR as a gene editing tool. Then, when Doudna and co-workers published CRISPR for gene editing,[18] multiple researchers *immediately* proposed to use such chemical modifications with gRNAs, including the specific claimed 2′-O-methyl and phosphorothioate modifications.

Reply 25 (citing Pet. 12, 81; Ex. 1003 ¶¶ 71–72; Ex. 1061, 112:1–5, 113:3–8, 116:5–10, 211:14–218:8). According to Petitioner, "[i]f there were no reasonable expectation of success, it would not be the case that a chorus of researchers would so quickly propose using chemical modifications with gRNAs while none would warn against it." *Id.* at 26. In addition, Petitioner points to evidence that prior art "studies ha[d] shown that modifications at the 5′ or 3′-ends of gRNAs do not inhibit Cas9 function" and that the "crystal structure of Cas9 shows that it tolerates a large number of mutations to the gRNA, including multiple modifica-

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[18] "In 2012, Jennifer Doudna and Emmanuelle Charpentier discovered [and published] that CRISPR associated enzyme (more specifically, the Cas9 protein) could be programmed to target nearly any portion of a genome using lab-made guide RNA sequences." Ex. 2025 ¶ 77. Their work was published in June 2012. Resp. 52; Reply 19.

tions to single nucleotides." *Id.* (citing Ex. 1003 ¶¶ 78; Ex. 1026, 941; Ex. 1033, 279; Ex. 1034, 235).

Petitioner's arguments and evidence are persuasive. As Petitioner points out, by December 2014, several studies had shown that the CRISPR/Cas system could successfully tolerate modifications. Ex. 1026, 941; Ex. 1033, 279. While these studies describe different types of modifications[19] than those in the challenged claims, such evidence nevertheless supports Dr. Furneaux's testimony that a POSA 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. Ex. 1003 ¶¶ 79, 265–70, 288–89.

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. Ex. 1003 ¶ 72 (identifying examples of patent publications with filing dates prior to December 2014 describing 2′-O-methyl and phosphorothioate modifications to gRNA); Ex. 1019 ¶¶ 193–96, claim 171; Ex. 1020 ¶¶ 570–71, 1657; Ex. 1022 ¶ 260; Ex. 1023 ¶ 362. Patent Owner's expert, Dr. Marshall, conceded as

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[19] As Patent Owner points out, the "mutations" referred to in Exhibit 1026 are changes to the RNA bases, as opposed to modifications to the sugar or phosphodiester linkages in the backbone. Sur-reply 12 (citing Ex. 1026, 942–43 (Fig. 4D)). Exhibit 1033 describes truncation, *i.e.*, removal of nucleotides, within the gRNA.

much on cross-examination. Ex. 1061, 113:3–8, 116:5–10, 211:14–213:8. The fact that multiple groups of researchers independently suggested the same types of gRNA modifications recited in the challenged claims evidences that a POSA would have had a reasonable expectation those modifications could be successfully employed in a CRISPR/Cas system. Ex. 1059 ¶ 18; *see also Regents of the Univ. of California v. Broad Institute, Inc.*, 903 F.3d 1286, 1295 (Fed. Cir. 2018) (explaining that "simultaneous invention" may bear on the obviousness analysis because "it is evidence of the level of skill in the art"). Moreover, while Petitioner points to multiple references suggesting such modifications to gRNA, neither Patent Owner nor Dr. Marshall identify any reference expressing doubt that such modifications could be successfully implemented in a CRISPR/Cas system. This contrast undermines Patent Owner's argument that a POSA would not have reasonably expected the prior art modifications to work in a CRISPR/Cas system.

Nevertheless, Patent Owner maintains "there was no guarantee of success" and therefore testing was required to confirm that such modifications would work. *See* Resp. 52. That argument is unavailing because "only a reasonable expectation of success, not a guarantee, is needed" to show obviousness. *Pfizer*, 480 F.3d at 1364 (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). The facts of the *Pfizer* case are instructive. There, the lower court had concluded that there would have been no expectation of success in making the claimed drug salt "because there was no reliable way to predict the influence of a particular salt species on the active part of the compound." *Id.* The Federal Circuit reversed, explaining that while it

accepted the lower court's finding that "it was generally unpredictable as to whether a particular salt would form and what its exact properties would be," the "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art." The court observed that

> a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt—including those specifically listed in the [prior art reference]—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute.

Id.

The current proceeding presents analogous facts. We do not doubt that there would have been some degree of unpredictability because, as Patent Owner points out, the interactions in a CRISPR/Cas system are complex and that there are mechanistic differences from the prior art RNA systems in Petitioner's secondary references. *See* Resp. 52–64. However, Petitioner has shown that a POSA would have understood that these systems share features in common with CRISPR/Cas, including that their efficacy and functionality is limited by the fact that the RNA used in them is subject to unwanted degradation. *See, e.g.*, Ex. 1003 ¶¶ 66–68, 71–73, 254–55, 285–87. Thus, the fact that the claimed modifications reduced degradation, while maintaining functionality, in these prior art systems supports a finding that the same modifications could also be successful in a CRISPR/Cas

system. To the extent Dr. Marshall testifies that the successful use of these modifications in prior art systems does not evidence at least a reasonable expectation they could also be successfully used in a CRISPR/Cas system (*see, e.g.*, Ex. 2025 ¶¶ 132, 147), we credit Dr. Furneaux's testimony (Ex. 1003 ¶¶ 62–79, 256– 70 (Ground 2), 287–88 (Ground 3)) and the evidence noted above over Dr. Marshall's testimony on this issue.

For these reasons, Petitioner has sufficiently shown that a POSA would have had both a motivation for and reasonable expectation of success in combining the cited references.

2. Consideration of objective indicia of nonobviousness

Patent Owner argues that "[t]here is overwhelming evidence of secondary consideration of nonobviousness, particularly as it relates to no question about [sic] industry praise, copying, and commercial success." Resp. 46. Patent Owner's objective indicia arguments center on the Hendel paper (Ex. 1005). *See id.* at 46–49. Patent Owner explains that "[t]he Agilent inventions" were "first made public" in this paper, which was co-authored with researchers at Stanford. *Id.* at 19. According to Patent Owner, "publications citing the Hendel paper have called Agilient's work 'pioneering,' 'seminal,' and 'a major contribution.'" *Id.* at 46–47 (quoting Ex. 2050, 4; Ex. 2028, 681). Patent Owner also offers evidence that the Hendel paper has been cited almost 900 times since its publication in 2015, which is in the 94th, 98th, or 99th percentile according to various indices of "tracked articles of a similar age." *Id.* at 20, 47 (citing Ex. 2025 ¶ 57; Ex. 2032, Ex. 2056).

Regarding copying and commercial success, Patent Owner points to evidence of statements by Petitioner that it contends "tout the benefits of Agilent's inventions" and suggest that the reason Petitioner uses chemically modified gRNA in its products is the study published in the Hendel paper. *Id.* at 20–21, 48–49 (quoting statements by Synthego's Head of Synthetic Biology in Ex. 2033, 3:05–4:45[20] and citing Ex. 2034, 6). Patent Owner also asserts that "[t]here is . . . no doubt that Petitioner Synthego has been successful" as result of using Patent Owner's inventions. Resp. 49.

In its Reply, Petitioner urges that the fact that multiple researchers "*immediately* proposed to use chemical modifications with gRNAs" after the initial publication of CRISPR for gene-editing "proves obviousness." Reply 19 (citing *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010)). Moreover, Petitioner asserts that the evidence of praise for the Hendel paper is "surprisingly thin" with one of the two references Patent Owner cites praising it as "'pioneering'" having been "coauthored by Hendel himself." Reply. 20–21 (referring to Ex. 2050). According to Petitioner,

> Patent Owner's scientists may well have been the first to synthesize some chemically modified gRNAs and do some testing experiments, and they may have been the first to report such work in an article that has been frequently cited over the years. But Patent Owner points to no evidence that this

[20] Exhibit 2033 is a video. The pinpoint citation refers to the time in the video at which these statements occur, *i.e.*, beginning at 3 minutes and 5 seconds.

> frequent citation stems from a belief among scientists that the authors had done something inventive as opposed to merely generating confirmatory data.

Id. at 21–22.

Petitioner further contends that it did not copy the Hendel paper, but "simply uses the same tried and true techniques that had long been known in the art." According to Petitioner, the claimed chemical modifications and the idea to use them in gRNA were already in the prior art therefore "such modifications lack the required nexus for secondary considerations." *Id.* at 22 (citing *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)). Finally, Petitioner asserts that the evidence of objective indicia of nonobviousness "simply cannot overcome" the strength of the other evidence demonstrating obviousness. *Id.* (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)).

In its Sur-reply, Patent Owner argues that the data in the Specification presents unexpected results. Sur-reply 21–22. Patent Owner further contends that Petitioner and its experts "suffer from gross credibility problems, ignoring Synthego's admissions of non-obviousness" and "contradicting Synthego's own praise for the Hendel paper" as a "'landmark'" publication. *Id.* at 22–23 (quoting Ex. 2033, 3:05–4:45).

We assess the parties' objective indicia arguments below and then weigh any evidence of such with the other evidence of record to reach a conclusion on Petitioner's obviousness grounds.

Beginning with commercial success, we find Patent Owner's evidence and argument unavailing.

First, Patent Owner cites no evidence to support its factual assertions regarding Synthego's success. *See* Resp. 49 (asserting without citation to evidence of record that Synthego "has raised almost $500 million in funding and recently announced the opening of a 20,000 square foot GMP facility to add to its capacity."). Nor has Patent Owner identified sales or profits stemming either from its own products or any allegedly infringing products to support its allegations of commercial success. Second, even if there was evidence of commercial success, we agree with Petitioner that "there is no basis to believe Petitioner's market performance is due [to] the use" of the claimed chemical modifications as opposed to other factors. Reply 22; *see also* Ex. 1059 ¶ 81 (identifying other business factors to which Petitioner contributes its market performance). Accordingly, Patent Owner's commercial success arguments carry no weight.

Patent Owner's industry praise and copying arguments fare somewhat better. The record supports that the Hendel paper has been heavily cited and that Petitioner's own head of synthetic biology referred to it as a "landmark paper" in a video presentation. Ex. 2025 ¶ 57; Ex. 2033, 3:05–4:45; *see also* Ex. 2034, 6 (stating that the Hendel paper "study set the bar for chemically modified guide RNAs as the method of choice for CRISPR-Cas9 in primary human immune cells"). In the same presentation, Petitioner's executive states that the study in the Hendel paper is the reason Petitioner uses "single guide RNAs in a chemically modified format." Ex. 2033, 3:05–4:45. As such, we agree that Patent Owner has presented some evidence of industry praise and copying related to the Hendel paper.

There are, however, significant questions regarding whether there is a nexus between the Hendel paper and any novel aspects of the challenged claims, which limit the probative value of this evidence. "Before secondary considerations can carry the day" the proponent of that evidence must establish a nexus with the patent claims at issue. *Huai-Hung Kao*, 639 F.3d at 1068. "Where the secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus." *Id.* In this case, the use of 2′-O-methyl and phosphorothioate modifications, as well as other types of modifications to the sugar and internucleotide linkage, in a gRNA was already taught in the prior art. Ex. 1003 ¶ 72 (citing earlier-filed applications suggesting the use of such modifications in gRNA); Ex. 1006, 107–113. This suggests that any praise or copying of the Hendel paper may actually result from its use of these prior art ideas as opposed to any novel aspect of the challenged claims.

In addition, the Hendel paper describes tests of "[c]hemical modifications comprising 2′-O-methyl (M), 2′-O-methyl 3′phosphorothioate (MS), or 2′-O-methyl 3′thioPACE (MSP) . . . at three terminal nucleotides at both the 5′ and 3′ ends." Ex. 1005, 1. The MS modifications correspond to the modifications recited in the claims in Ground 2 and the MSP modifications are within the scope of the modifications recited in the claims in Ground 3. But it is unclear whether Petitioner's evidence of praise for the Hendel paper results from the MS and MSP modifications in those claims as opposed to other aspects of that study, *e.g.*, the use

of M modifications alone.[21] Similarly, Patent Owner's copying evidence suggests that Petitioner uses chemically modified gRNAs, but does not show that those chemically modified gRNAs have the particular modifications recited in the Ground 2 claims or the Ground 3 claims as opposed to other modifications. For these reasons, we give some weight to the evidence of industry praise and copying, however that weight is diminished by the tenuous nexus to the challenged claims.

Moreover, the fact that multiple research groups, nearly simultaneously proposed the use of chemically modified gRNA is itself objective evidence that the challenged claims would have been obvious. *See Regents*, 903 F.3d at 1295 (explaining that "simultaneous invention" is "objective evidence that person of ordinary skill in the art understood the problem and a solution to that problem"); *Geo. M. Martin*, 618 F.3d at 1305–6 ("Independently made, simultaneous inventions made within a comparatively short space of time are persuasive evidence that a claimed apparatus was the product of ordinary mechanical or engineering skill.") (internal quotations omitted). As explained above, we credit Petitioner's showing that a POSA would have reasonably expected that such modifications

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[21] According to Patent Owner, out of the 895 citations to the Hendel paper only a fraction of those include terms relating to the particular modifications in recited in the claims challenged in Grounds 2 and 3. Resp. 47 (noting that only 276 of the citing papers include the term "phosphorothioate" and only 67 include the term "thioPACE"). This diminishes the argument that there is a nexus between the particular modifications in those dependent claims and the praise that may be inferred from the fact that numerous authors have cited the Hendel paper.

could be successfully made to the gRNA in a CRISPR /Cas system. Thus, the fact that multiple researchers simultaneously proposed making 2′-O-methyl, phosphorothioate, and other modifications to gRNA and did so close in time to the initial publication describing the CRISPR/Cas system for gene editing suggests that this was an obvious solution to a known problem.

Finally, the unexpected results arguments in Patent Owner's Sur-reply are unavailing. Sur-reply 21–22. As an initial matter, these arguments were not presented in the Response such that Petitioner could address them in the Reply. For this reason, Patent Owner's unexpected results argument is untimely and has been waived. Even so, we disagree with Patent Owner's assertion that Petitioner "did not rebut the Patent's explicit discussion of the 'surprising' results obtained or why they were unpredictable." *Id.* (citing Ex. 1001, 3:34–36, 66:27–32, 66:61–67:6). It is Patent Owner as the proponent of this evidence who has the burden to show a nexus between its objective indicia evidence and the merits of the claimed invention. *Kao*, 639 F.3d 1057, 1068; *see also In re* Klosak, 455 F.2d 1077, 1088 (CCPA 1972) ("[T]he burden of showing unexpected results rests on he who asserts them."). The threadbare assertion in the Sur-reply does not do so. Moreover, Petitioner points out that the results in the Specification show that almost all of the chemically modified gRNAs Patent Owner tested exhibited cleavage activity. Reply 13–14, 17, Ex. 1059 ¶ 47 ("97% of the experiments that Agilent ran showed at least some cleavage activity"). This would seem to be exactly the result a POSA would expect in view of the teachings in Pioneer Hi-Bred and the other references

cited in the Petition. For these reasons, Patent Owner's unexpected results arguments carry no weight.

3. Conclusion for Ground 2

Considering the totality of the evidence regarding claims 9, 18, and 25, including objective indicia of non-obviousness, we determine that Petitioner has established, by a preponderance of the evidence, that these claims would have been obvious over the combination of Pioneer Hi-Bred with any of Krutzfeldt, Deleavey, Soutschek, or Yoo. Indeed, even if Patent Owner had established a sufficient nexus between these claims and its industry praise and copying evidence such that it was entitled to more weight, we would reach the same conclusion given the relative strength of Petitioner's showing. *See, e.g.*, *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1329 (Fed. Cir. 2017) (weighing evidence of unexpected results and copying together with other evidence, including "strong evidence of a motivation to make the claimed combination" in the cited prior art, to conclude that combination was obvious); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1247 (Fed. Cir. 2010) (listing cases where objective indicia evidence did not overcome a strong case of obviousness).

G. Ground 3: Obviousness over Pioneer Hi-Bred and Threlfall or Deleavey

Petitioner contends claims 8, 11, 16, 19, and 26 are obvious over Pioneer Hi-Bred in combination with either Threlfall or Deleavey. Pet. 64– 70. More specifically, Ground 3 relies 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 thio-PACE) 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. *Id.*

Petitioner asserts that "[a] POSA would have been motivated to use the PACE and thioPACE modifications within five nucleotides of the 5′ and/or 3′-ends of the RNA molecules" as taught in Threlfall and Deleavey in Pioneer Hi-Bred's gRNA and crRNA molecules "because they would provide the same benefits to gRNAs that Pioneer Hi-Bred seeks to achieve," including "[r]esistance to cellular degradation and increased cellular permeability." Pet. 67–68 (citing Ex. 1003 ¶ 286). In addition, Petitioner contends that "Threlfall reports successful cellular uptake of RNAs with the PACE and thioPACE modifications" and therefore "a POSA would have understood that combining and synthesizing gRNAs with the PACE and thioPACE modifications . . . such as the gRNAs with the 2′-O-methyl modifications within five nucleotides of the 5′ and/or 3′-ends of Pioneer Hi-Bred, would result in similarly increased cellular uptake of these modified gRNAs." *Id.* at 68 (citing Ex. 1003 ¶ 287; Ex. 1010, 7).

According to Petitioner, a POSA would have had a reasonable expectation of success because "RNAs including such modifications had been previously synthesized in Threlfall" and "such synthesis methods were commercially available." Pet. 68–69 (citing Ex. 1003 ¶ 288). Moreover, Petitioner contends that because of the "previous widespread use of PACE and thioPACE modifications . . . in various types of RNA molecules in the field of gene regulation, a POSA would have

reasonably expected that such modifications when applied at or near the 3′ and/or 5′-ends of the gRNAs [in Pioneer Hi-Bred] would have resulted in modified gRNAs that are functional with the Cas system." *Id.* at 69 (citing Ex. 1003 ¶ 289).

Petitioner's contentions are sufficiently supported by the record and persuasive. As explained above, Pioneer Hi-Bred discloses all of the limitations of the independent and other claims from which claims 8, 11, 16, 19, and 26 depend. Regarding the additional limitations in claims 8, 11, 16, 19, and 26, Threlfall and Deleavey teach that PACE and thioPACE modifications to RNA enhance resistance to degradation and are tolerated in prior art systems. Ex. 1007, 8; Ex. 1010, 1–2. Threlfall further teaches the combination of such modifications with 2′-O-methyl modified nucleotides at the 3′ and 5′-ends of an RNA molecule. Ex. 1010, 2 (Table 1). Thus, the combination of references articulated in the Petition teaches or suggests all of the limitations of claims 8, 11, 16, 19, and 26.

Moreover, the record supports Petitioner's rationale for combining the references. The teachings in Threlfall and Deleavey support Dr. Furneaux's testimony (Ex. 1003 ¶¶ 286–87) regarding the benefits, *e.g.*, increased resistance to degradation and enhanced cellular uptake, that would have motivated a POSA to use such modifications in Pioneer Hi-Bred's gRNA. *See, e.g.*, Ex. 1007, 8 (teaching PACE modified RNA exhibits "enhanced nuclease resistance); Ex. 1010, 7 (teaching "cellular uptake was notably more efficient" with 2′-O-methyl thioPACE modified nucleotides). As Petitioner point out, these are the amongst the same benefits that Pioneer Hi-Bred suggests chemical modification

of gRNA can achieve. *See* Ex. 1006, 107. As explained above, Patent Owner's arguments against Petitioner's showing for combining the references are unavailing. *See supra* § III.F.1.

Petitioner has also sufficiently shown that a POSA would reasonably expect PACE and thioPACE modifications to gRNA in a CRISPR/Cas system would be successful. As explained above, we credit the supporting testimony of Dr. Furneaux and other evidence cited in the Petition over the competing testimony of Dr. Marshall in this regard. *See supra* § III.F.1.

Patent Owner offers the same objective indicia evidence discussed in § III.F.2 above for the claims in Ground 3. As explained there, the weight of this evidence is limited because Patent Owner has not established a sufficient nexus to the particular modifications recited in claims 8, 11, 16, 19, and 26. Considering the totality of the evidence, including objective indicia of non-obviousness, we determine that Petitioner has established, by a preponderance of the evidence, that claims 8, 11, 16, 19, and 26 would have been obvious over the combination of Pioneer Hi-Bred and Threlfall or Deleavey.[22]

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[22] Even if Patent Owner had established a sufficient nexus between these claims and its industry praise and copying evidence such that it was entitled to more weight, we would reach the same conclusion given the relative strength of Petitioner's showing.

H. Ground 4: Obviousness of claims 2, 29, and 30 over Pioneer Hi-Bred in View of the Skill of a POSA

To the extent they are not anticipated, Petitioner argues claims 2, 29, and 30 would have been obvious over Pioneer Hi-Bred in combination with the knowledge of a POSA. Pet. 70–75. More specifically, Petitioner offers evidence and argument that each of the additional limitations in these claims, *i.e.*, an sgRNA (claim 2), forming the gRNA:Cas protein complex outside a cell (claim 29), and a library of at least two gRNA (claim 30) was well known in the art and would have been obvious to implement in view of Pioneer Hi-Bred's disclosure. *Id.* (citing Ex. 1003 ¶¶ 299–317).

Patent Owner advances the global arguments addressed above with respect to Petitioner's other grounds, but does not specifically dispute that the additional limitations in claims 2, 29, and 30 would have been known to a POSA. *See* Resp. 67.

Petitioner's contentions are sufficiently supported by the record and persuasive. As explained above, Pioneer Hi-Bred anticipates claims 2, 29, and 30 because it discloses the additional limitations in these claims and a POSA would have immediately envisioned embodiments meeting the same. To the extent one might argue otherwise, Petitioner has shown that claims 2, 29, and 30 would have been obvious because the additional elements they recite were well known to a POSA and taught in Pioneer Hi-Bred. In this regard, we credit Petitioner's contentions and the supporting the testimony of Dr. Furneaux (*i.e.*, Ex. 1003 ¶¶ 299–320). Thus, considering the totality of the evidence, including objective indicia of non-obviousness, we determine that Petitioner has established, by a

preponderance of the evidence, that claims 2, 29, and 30 would have been obvious over Pioneer Hi-Bred.

I. Ground 5: Obviousness of claims 9, 18, and 25 over Pioneer Hi-Bred in View of the Skill of a POSA

Petitioner further asserts that claims 9, 18, and 25 would have been obvious over Pioneer Hi-Bred in view of the skill of a POSA. Pet. 76–83.

Having already determined that these claims are anticipated for the reasons in Ground 1 and obvious for the reasons in Ground 2, we need not decide Petitioner's additional challenge to claims 9, 18, and 25 in Ground 5. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App'x 984, 990 (Fed. Cir. 2020) (nonprecedential) ("We agree that the Board need not address [alternative grounds] that are not necessary to the resolution of the proceeding.").

IV. Motions to Seal

The parties jointly request that Exhibits 1053–1058 and portions of Petitioner's Reply discussing those exhibits be sealed. Paper 28 ("Joint Motion"). These exhibits "are excerpts of the deposition of Dr. Daniel Ryan, a named inventor on the '001 [patent], along with certain exhibits to his deposition transcript." *Id.* at 1–2. "Patent Owner avers that the documents from the Ryan deposition provide information on proprietary research, as well as confidential information about Patent Owner's business practices." *Id.* at 3. The parties also represent that the district court in a

related proceeding "explicitly ruled that the Ryan transcript and exhibits that are the subject of this Motion to Seal have been properly designated as confidential." *Id.* (quotations omitted).

Along with their motion, the parties submit a proposed protective order. *Id.* at App. A. This order follows the guidelines in Appendix B of the Trial Practice Guide,[23] but modifies the highly confidential designation "by eliminating access by 'persons who are named parties to the proceeding,' 'party representatives,' and 'in-house counsel.'" *Id.* at 4–5. The parties represent that this modification aligns the designations in this proceeding with those that have been entered in the related district court proceeding and therefore "will aid in the efficient administration of justice, and will be more straightforward and expedient than preparing a 'two level' protective order for" the parties' IPR proceedings. *Id.* at 5.

A party may move to seal confidential information including, *e.g.*, confidential research, development, or commercial information. TPG 19; 37 C.F.R. § 42.54. It is the movant's burden to show good cause for sealing such information, and we balance the party's asserted need for confidentiality with the strong public interest in open proceedings. *Argentum Pharms. LLC v. Alcon Research, Ltd.*, IPR2017-01053, Paper 27 at 4 (PTAB Jan. 19, 2018) (informative).

The parties provide a sufficient explanation and have shown good cause for sealing exhibits 1053–1058 and the related portions of Petitioner's Reply.

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[23] Consolidated Trial Practice Guide (Nov. 2019), 64, available at https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf ("TPG").

Moreover, Petitioner provides a public version of its Reply (Paper 30) with redactions limited to a few paragraphs discussing these exhibits so the record may remain clear and reasonably open. We also determine that the proposed protective order with the agreed modification limiting access to outside counsel and the parties' experts is appropriate under these circumstances.

Patent Owner additionally moves to seal a paragraph in its Sur-reply, "which discusses documents as to which sealing was jointly requested" in the Joint Motion. Paper 33. Petitioner provides a public version of its Sur-reply (Paper 34) with redactions limited to a single paragraph. We find that Patent Owner has shown good cause for granting its motion.

Accordingly, Exhibits 1053–1058, Petitioner Reply (Paper 29), and Patent Owner's Sur-reply (Paper 32) are sealed, and the protective order, Appendix A to Paper 28, is entered.

V. Conclusion[24]

Petitioner has shown, by a preponderance of the evidence, that claims 1–30 of the '001 patent are unpatentable.

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[24] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this Decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated

Claims	35 U.S.C. §	Reference(s)/ Basis	Claims Shown Unpatentable
1–7, 9, 10, 12–15, 17, 18, 20–25, 27–30	102	Pioneer Hi-Bred	1–7, 9, 10, 12–15, 17, 18, 20–25, 27–30
9, 18, 25	103	Pioneer Hi-Bred, Krutzfeldgt, Deleavey, Soutschek, Yoo	9, 18, 25
8, 11, 16, 19, 26	103	Pioneer Hi-Bred, Threlfall, Deleavey	8, 11, 16, 19, 26
2, 29, 30	103	Pioneer Hi-Bred	2, 29, 30
9, 18, 25[25]	103	Pioneer Hi-Bred	
Overall Outcome			1-30

VI. Order

Accordingly, it is:

ORDERED that Petitioner has shown that claims 1–30 of U.S. Patent 10,337,001 B2 are unpatentable;

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mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), 42.8(b)(2).

[25] As explained above, we do not reach this ground.

FURTHER ORDERED that the Joint Motion to Seal (Paper 28) and Patent Owner's Motion to Seal Portions of the Sur-reply (Paper 32) are *granted*; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

FINAL WRITTEN DECISION ON IPR2022-00403, PATENT 10,900,034 B2, U.S. PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD (MAY 17, 2023)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNTHEGO CORPORATION,

Petitioner,

v.

AGILENT TECHNOLOGIES, INC.,

Patent Owner.

IPR2022-00403
Patent 10,900,034 B2

Before: Robert A. POLLOCK, David COTTA, and Michael A. VALEK, Administrative Patent Judges.

VALEK, Administrative Patent Judge.

Judgment
Final Written Decision

Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)
Granting Joint Motion to Seal
Granting Patent Owner's Motion to Seal Portions of
Sur-reply Brief *37 C.F.R. §§ 42.14, 42.54*

I. Introduction

Synthego Corporation ("Petitioner") filed a Petition (Paper 1, "Pet."), seeking *inter partes* review of claims 1–33 of U.S. Patent No. 10,900,034 B2 (Ex. 1001, "the '034 patent"). We instituted trial on all of the grounds in the Petition. Paper 11, 31.

Following institution, Agilent Technologies, Inc. ("Patent Owner") filed a Response (Paper 18, "Resp."), Petitioner filed a Reply (Paper 30, "Reply"), and Patent Owner filed a Sur-reply (Paper 33, "Sur-reply"). We held a hearing on March 1, 2021, and a transcript is of record. Paper 48 ("Tr.").

In addition, the parties have jointly moved to seal Exhibits 1053–1058 and portions of the Reply (Paper 29) and Patent Owner has moved to seal portions of the Sur-reply (Paper 34).

After considering the parties' arguments and evidence, we find that Petitioner has shown by a preponderance of the evidence that the challenged claims of the '034 patent are unpatentable. *See* 35 U.S.C. § 316(e). We also grant both motions to seal. Our reasoning is explained below.

II. Background

A. Real Parties in Interest

Petitioner and Patent Owner identify themselves as the only real parties in interest. Pet. 15; Paper 4, 2.

B. The '034 Patent

The '034 patent issued on January 26, 2021, and claims priority to a utility application filed on December 3, 2015, as well as a series of provisional applications the earliest of which was filed on December 3, 2014. Ex. 1001, codes (60) (63).

The '034 patent relates to "modified guide RNAs and their use in clustered, regularly interspaced, short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems." Ex. 1001, Abstr. The Specification explains that "[i]n the native prokaryotic system" from which CRISPR technology is derived "the guide RNA ('gRNA') comprises two short, non-coding RNA species referred to as CRISPR RNA ('crRNA') and transacting RNA ('tracrRNA')." *Id.* at 1:41–44. The native CRISPR-Cas system may also be engineered to use a single guide RNA (sgRNA) that combines the crRNA and tracrRNA into a single molecule. *Id.* at 1:57–59. The guide RNA forms a complex with a Cas nuclease that is able to bind to a target DNA site adjacent a protospacer adjacent motif ("PAM") sequence and cleave the target DNA at that specific site. *Id.* at 1:44–49, 2:21–34; *see also* Ex. 1003 ¶¶ 44–48; Ex. 2003 ¶¶ 49–54 (declarant testimony from both parties offering similar technical background on guide RNA and its function in CRISPR-Cas systems).

According to the Specification, "there is a need for providing gRNA, including sgRNA, having increased resistance to nucleolytic degradation, increased binding affinity for the target polynucleotide, and/or reduced off-target effects while, nonetheless, having gRNA functionality." Ex. 1001, 2:4–8. The Specification states that Patent Owner's "invention is based, at least in part, on an unexpected discovery that certain chemical modifications to gRNA are tolerated by the CRISPR-Cas system." *Id.* at 3:51–53. These modifications are "believed to increase the stability of the gRNA, to alter the thermostability of a gRNA hybridization interaction, and/or to decrease the off-target effects of Cas:gRNA complexation" and "do not substantially compromise the efficacy of Cas:gRNA binding to, nicking of, and/or cleavage of the target polynucleotide." *Id.* at 3:50–59.

C. Challenged Claims

The Petition challenges claims 1–33. Of these, claims 1 and 19 are independent. Claims 1 and 19 are illustrative and read as follows:

1. 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

   (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.

19. A synthetic CRISPR crRNA molecule comprising

a guide sequence capable of hybridizing to a target sequence in a polynucleotide, wherein the synthetic crRNA molecule comprises one or more modifications in the guide sequence;

wherein the synthetic crRNA molecule has gRNA functionality comprising associating with a Cas protein and targeting the gRNA :Cas protein complex to the target sequence; and wherein the one or more modifications comprises a 2′-O-methyl.

Ex. 1001, 257:34–47, 259:1–9.

D. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claims Challenged	35 U.S.C. §[1]	Reference(s)/ Basis
1-5,	102	Pioneer Hi-Bred[2]

[1] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), included revisions to 35 U.S.C. §§ 102 and 103 that became effective prior to the filing of the application that led to the '001 patent. Therefore, we apply the AIA versions of 35 U.S.C. §§ 102 and 103.

[2] WO 2015/026885 A1, published February 26, 2015 (Ex. 1006)

8-21, 24-33		
5, 8-13, 18, 20, 21, 24-28, 32	103	Pioneer Hi-Bred and Krutzfeldgt,[3] Deleavey,[4] Soutschek,[5] Yoo[6]
6, 7, 22, 23	103	Pioneer Hi-Bred and Threlfall[7] or Deleavey

("Pioneer Hi-Bred").

[3] Jan Krützfeldt et. al, "Specificity, Duplex Degradation and Subcellular Localization of Antagomirs," 35 Nucleic Acids Research 2885–2892 (2007) (Ex. 1009) ("Krützfeldt").

[4] Glen F. Deleavey et. al., "Designing Chemically Modified Oligonucleotides for Targeted Gene Silencing," 19 Chem. & Bio. Review 937–954 (2012) (Ex. 1007) ("Deleavey").

[5] Jürgen Soutschek et. al., "Therapeutic Silencing of an Endogenous Gene by Systemic Administration of Modified siRNAs," 432 Nature 173–178 (2004) (Ex. 1012) ("Soutschek").

[6] Byong Hoon Yoo et al., "2′-O-methyl-modified Phosphorothioate Antisense Oligonucleotides Have Reduced Non-specific Effects *In Vitro*," 32 Nucleic Acids Research 2008–2016 (2004) (Ex. 1011) ("Yoo").

[7] Richard N. Threlfall et al., "Synthesis and Biological Activity of Phosphonoacetate-and Thiophosphonoacetate-modified 2′-*O*-methyl Oligoribonucleotides," 10 Org. Biomol. Chem., 746–754 (2012) (Ex. 1010) ("Threlfall").

3, 4	103	Pioneer Hi-Bred and Knowledge of Person of Ordinary Skill in the Art ("POSA")
5, 8–13, 20, 21, 24–28	103	Pioneer Hi-Bred and Knowledge of POSA
14, 29	103	Pioneer Hi-Bred and Knowledge of POSA

In support of these grounds, Petitioner relies on declarations from Henry Morrice Furneaux submitted with the Petition (Ex. 1003) and Reply (Ex. 1059). Patent Owner relies on declarations from William S. Marshall submitted with its Preliminary Response (Ex. 2003) and Response (Ex. 2025). Patent Owner also relies on a declaration from one of the inventors named on the '034 patent, Jeffrey R. Sampson (Ex. 2029).

III. Analysis of the Asserted Grounds

A. Legal Standards

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016). This burden of persuasion never shifts to patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015).

i. Anticipation

To establish anticipation, each limitation in a claim must be found in a single prior art reference, arranged as recited in the claim. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). Although the elements must be arranged or combined in the same way as in the claim, "the reference need not satisfy an *ipsissimis verbis* test." *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009).

Further, to be anticipating, a prior art reference must be enabling. *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015). "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." *Id.* (citing *In re Antor Media Corp.*, 689 F.3d 1282, 1289–90 (Fed. Cir. 2012)). Prior art disclosures are presumed enabling. *In re Antor Media Corp.*, 689 F.3d 1282, 1287–88 (Fed. Cir. 2012); *Apple Inc. v. Corephotonics, Ltd.*, 861 Fed. Appx. 443, 450 (Fed. Cir. 2021) ("[R]egardless of the forum, prior art patents and publications enjoy a presumption of enablement, and the patentee/applicant has the burden to prove nonenablement for such prior art.").

ii. Obviousness

A claim is unpatentable for obviousness if, to one of ordinary skill in the pertinent art, "the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550

U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art; any differences between the claimed subject matter and the prior art; the level of ordinary skill in the art; and (4) when in evidence, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

Subsumed within the *Graham* factors is the requirement that the skilled artisan would have had a reasonable expectation of success in combining the prior art references to achieve the claimed invention. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). "Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–4 (Fed. Cir. 1988). Moreover, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

On the other hand, a patent claim "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. An obviousness determination requires finding "both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016) (citation omitted).

B. Level of Ordinary Skill in the Art

Relying on the testimony of its declarant, Dr. Furneaux, Petitioner contends that a POSA "as of December 3, 2014 (the earliest possible priority date of the '034 Patent) would have had a Ph.D. in molecular biology, biochemistry, or a related discipline." Pet. 11 (citing Ex. 1003 ¶ 59). Petitioner further asserts that "[a] POSA would have understood the chemical structure of nucleic acids, such as DNA and RNA, and would have understood the role of such nucleic acids in cellular biology" and been aware of various prior art "methods to chemically modify RNA, including gRNAs for use in gene regulation." *Id.* at 11–12 (citing Ex. 1003 ¶¶ 60–69). Petitioner further asserts that a POSA would "have known about uses of chemically modified gRNA in CRISPR-Cas applications," "about making libraries of such modified gRNAs," and "attaching fluorophores at the 5′-ends . . . for purposes of tracking them." *Id.* at 12–13 (citing Ex. 1003 ¶¶ 70– 80).

Patent Owner agrees that a POSA would have this educational level. Resp. 23. Patent Owner "also agrees that a POSA would have knowledge of prior art RNA based gene regulating technologies, but disagrees that the teachings of those technologies are relevant in the manner that Dr. Furneaux [and Petitioner] attempt[] to apply them" in the Petition's grounds. *Id.* at 23– 24.

We find the parties' agreed understanding of the level of ordinary skill in the art to be supported by the record and apply that description in our analysis herein. To the extent the parties disagree regarding the application of a POSA's general knowledge of nucleic acids and related prior art techniques to the

Petition's grounds, such disputes are addressed in our analysis below.

C. Claim Construction

The parties assert that all of the claim terms have their plain and ordinary meaning and that no formal claim construction is necessary. *See* Pet. 17; Resp. 24. Nevertheless, both sides accuse the other of misconstruing the "gRNA functionality" recited in the challenged claims. *See* Resp. 24–25; Reply 16; Surreply 2–4. Accordingly, we begin by briefly clarifying the gRNA functionality required by the claims.

Independent claims 1 and 19 recite a guide RNA or crRNA molecule having "gRNA functionality comprising associating with a Cas protein and targeting the gRNA:Cas protein complex to the target sequence." Ex. 1001, 257:42–44, 259:5–7. This claim language makes clear that the recited "gRNA functionality" requires a molecule that can: (1) associate with a Cas protein, and (2) target that complex to a target sequence in a polynucleotide. To the extent Petitioner suggests that a gRNA "need *only* bind to the Cas protein" to have "gRNA functionality," we disagree because the claims additionally recite the above-quoted targeting functionality. *See* Reply 16 (emphasis added).

At the same time, we agree with Petitioner that "a gRNA need not cleave the target DNA" to have the claimed "gRNA functionality." Reply 16. The Specification defines "gRNA functionality" as "one or more functions of naturally occurring guide RNA, such as associating with a Cas protein, or a function performed by the guide RNA in association with a Cas protein" and lists various gRNA functions, *e.g.*, "associating," "targeting," "binding," "nicking," and "cleaving," that

may be present "in certain embodiments" of the invention. Ex. 1001, 6:56–7:1. However, as noted above, the claims recite "gRNA functionality comprising" only the associating and targeting functions. Thus, while a molecule may have additional functions such as cleaving a target polynucleotide, it need only exhibit the recited "associating" and "targeting" functions to have the "gRNA functionality" in claims 1 and 19.

Our determination that "gRNA functionality" requires the recited "associating" and "targeting" functions, but not additional, unrecited functions such as cleaving, is also consistent with the parties' position that the claim language has its plain and ordinary meaning. *See* Pet. 17; Resp. 24. The parties do not dispute the construction of any other terms, nor do we discern that any further claim construction is necessary to resolve the issues in this proceeding. *See Nidec Motor Corp. v. Zhongshan Broad OceanMotor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (explaining that it is only necessary to "construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

D. Overview of the Cited References

i. Pioneer Hi-Bred

Pioneer Hi-Bred is a publication of a PCT application filed August 20, 2014. Ex. 1006, code (22). Patent Owner does not dispute Petitioner's assertion that Pioneer Hi-Bred is prior art to the challenged claims. Pet. 14.

Pioneer Hi-Bred describes "methods and compositions employ[ing] a guide polynucleotide/Cas endonuclease system to provide an effective system for modifying or altering target sites within the genome of a cell or organism." Ex. 1006, Abstr. Pioneer Hi-Bred defines the term "guide polynucleotide" as "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 24:6–8.[8] Pioneer Hi-Bred teaches that the polynucleotide "can be a single molecule or a double molecule" and that "[a] guide polynucleotide that solely comprises ribonucleic acids is also referred to as a 'guide RNA.'" *Id.* at 24:9–20.

Pioneer Hi-Bred discloses a guide RNA with a variable targeting domain (VT domain) having a 3′-end "that is complementary to a nucleotide sequence in a target DNA" and a Cas endonuclease recognition domain (CER domain) having a 5′-end "that interacts with a Cas endonuclease." Ex. 1006, 24:21–25: 28, Fig. 1A–1B (depicting single and duplex guide polynucleotides). Pioneer Hi-Bred explains that "[t]he VT domain is responsible for interacting with the DNA target site through direct nucleotide-nucleotide base pairings while the CER domain is required for proper Cas endonuclease recognition (Figure 3A and Figure 3B)." *Id.* at 105:5–8. Pioneer Hi-Bred teaches that these domains in the guide polynucleotide "function to link DNA target site recognition with Cas endonuclease target site cleavage." *Id.* at 105:9–11; *see also id.* at

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[8] Unless otherwise indicated, the pinpoint cites in this decision refer to the page number in the original document as opposed to the number in the exhibit label.

Fig. 3A-3B (depicting complexes formed between a single and duplex guide RNA and a Cas9 endonuclease).

Pioneer Hi-Bred also discloses that the guide polynucleotide may contain "synthetic, non-natural, or altered nucleotide bases" as well as other modifications such as "a fluorescent label." Ex. 1006, 27:3–19, 61:19–20. In Example 4, Pioneer Hi-Bred describes "modifying the nucleotide base, phosphodiester bond linkage or molecular topography of the guiding nucleic acid component(s) of the guide polynucleotide/Cas endonuclease system." *Id.* at 104:15–105:2. Table 7 of Example 4 provides "[e]xamples of nuclease resistant nucleotide and phosphodiester bond modifications," including "2′-O-Methyl RNA Bases" and "Phosphorothioate bond[s]," that may be introduced in order "to reduce unwanted degradation" of the guide polynucleotide. *Id.* at 106:13–107:5. Pioneer Hi-Bred discloses that

> [m]odifications may be introduced at the 5′ and 3′ ends of any one of the nucleic acid residues comprising the VT or CER domains to inhibit exonuclease cleavage activity, can be introduced in the middle of the nucleic acid sequence comprising the VT or CER domains to slow endonuclease cleavage activity or can be introduced throughout the nucleic acid sequences comprising the VT or CER domains to provide protection from both exo-and endo-nucleases.

Id. at 106:19–25. 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." *Id.* at 108:3–5.

In Example 5 of Pioneer Hi-Bred, "some the nucleotide base and phosphodiester bond modifications described in Example 4 are introduced into the VT domain and/or CER domain of a crNucleotide." Ex. 1006, 108:16–18. Table 8 of Example 5, reproduced in part below, describes crRNA sequences with modifications, including modifications "near ends" or "at ends" of the VT and CER domains (*i.e.*, sequences 64–69).

Table 8. crRNA and crDNA nucleotide base and phosphodiester linkage modifications.

Nucleic Acid Type	Modification	crRNA or crDNA Sequence and Corresponding Modification	
		VT Domain	CER Domain
crRNA	None	GCGUACG CGUACGU GUG (SEQ ID NO:62)	GUUUU AGAGCU AUGCUG UUUUG (SEQ ID NO: 63)
crRNA	Phosphorothioate bonds near ends	G*C*G*UA CGCGUAC GUGUG (SEQ ID NO: 64)	GUUUU AGAGCU AUGCUG UU*U*U* G (SEQ ID NO:65)
crRNA	2′-O-Methyl RNA nucleotides at ends	mGmCmG UACGCG UACGUG UG (SEQ ID NO:66)	GUUUUA GAGCUAU GCUGUU mUmUmG (SEQ ID NO:67)
crRNA	2′-O-Methyl RNA nucleotides for each nucleotide	mGm CmGm UmAm CmGm CmGm UmAm	mGm Um UmUm UmAm GmAm GmCm

		CmGm UmGmUm G (SEQ ID NO: 68)	UmAm UmGm CmUm GmUm UmUm UmG (SEQ ID NO: 69)

Id. at 109. The excerpt from Table 8 above shows modifications comprising phosphorothioate bonds (denoted with a "*") and 2′-O-methyl RNA nucleotides (denoted with a "m") to particular nucleotides of a crRNA sequence. *See id.* at 109–110, n.1. The first nucleotide in the sequences in the VT Domain column is at the 5′ end of the crRNA and the last nucleotide in the sequences in the CER Domain column is at the 3′ end. *See* Ex. 1006, Fig. 1A; Ex. 1002 ¶¶ 126–29, 131–34. Thus, for example, sequence 66 discloses a crRNA with 2′-O-methyl modifications to the sugars of the three nucleotides at the 5′ end and sequence 67 discloses a crRNA with 2′-O-methyl modifications to the sugars of the three nucleotides at the 3′ end.

Pioneer Hi-Bred discloses that modifications "similar to those illustrated in Example 5 Table 8 can be introduced individually or in combination into the crRNA, crDNA, tracrRNA, tracrDNA, long guide RNA or long guide DNA nucleic acid components of the guide polynuclease system and synthesized per standard techniques." Ex. 1006, 113:25–29.

ii. Krutzfeldt

Krutzfeldt was published in 2007. Ex. 1009. Patent Owner does not dispute that Krutzfedlt is prior art to the challenged claims.

According to Krutzfeldt, "MicroRNAs (miRNAs) are an abundant class of 20–23-nt long regulators of gene expression." Ex. 1009, Abstr. Krutzfeldt describes analogs of these miRNAs referred to as "antagomirs." *Id.* at 2885. These antagomirs "differ from normal RNA by complete 2′-*O*-methylation of sugar, phosphorothioate backbone and a cholesterol-moiety at 3′-end." *Id.* at 2885. Krutzfeldt discloses the combination of 2′-O-methyl and phosphorothioate modifications on nucleotides at the 5′ and 3′ ends of its antagomirs. *Id.* at 2886 (Table 1 disclosing antagomir sequences with a lower case letters indicating a 2′-O-methyl modification and a superscript indicating a phosphorothioate linkage). Krutzfeldt teaches these modifications "protect against different RNAse activities" that would otherwise degrade the RNA strand. *See id.* at 2889 (teaching "phosphorothioate modification to protect against exonucleases" and 2′-O-methyl sugar modification "to protect against endonuclease activity").

iii. Deleavey

Deleavey is a review article published in 2012. Ex. 1007. Patent Owner does not dispute that Deleavey is prior art to the challenged claims.

Deleavey teaches that oligonucleotides (ONs) such as small interfering (siRNAs) and microRNA-targeting ONs (anti-miRNAs) "and their chemically modified mimics, are now routinely used in the laboratory" and "under active investigation in the

clinic." Ex. 1007, 937. Deleavey teaches that an array of ON chemical modifications have been developed to overcome the "therapeutically limiting features" of RNAs. *Id.*

In particular, Deleavey explains that RNAs "are rapidly degraded in cells . . . leading to shortened duration of activity and systemic delivery challenges." Ex. 1007, 941. Deleavey teaches that chemical modifications to both the internucleotide linkage, *e.g.*, phosphorothioate and phosphonoacetate (PACE), and sugar, *e.g.*, 2′-O-methyl nucleosides, had been shown to improve stability in various RNA applications. *See id.* at 942–47.

iv. Soutschek

Soutschek was published in 2004. Ex. 1012, 173. Patent Owner does not dispute that Soutschek is prior art to the challenged claims.

Soutschek describes chemically modified short interfering RNAs (siRNAs). Ex. 1012, 173. Soutschek teaches that "[c]hemically stabilized siRNAs with partial phosphorothioate backbone and 2′-O-methyl sugar modifications on the sense and antisense strands showed significantly enhanced resistance towards degradation by exo-and endonucleases in serum and tissue homogenates." *Id.*; *see also id.* at 177 (listing sequences of chemically-modified siRNAs with phosphorothioate and 2′-O-methyl sugar modifications on certain nucleotides).

v. Yoo

Yoo was published in 2004. Ex. 1011, 2008. Patent Owner does not dispute that Yoo is prior art to the challenged claims.

Yoo describes antisense oligodeoxynucleotides (ODNs) having both phosphorothioate and 2′-O-methyl sugar modifications. Ex. 1011, 2008. Yoo teaches that "the addition of 2′-O-methyl groups to a phosphorothioate-modified ODN is advantageous because of increased stability of binding and reduced non-specific effects." *Id.*

vi. Threlfall

Threlfall was published in 2012. Ex. 1010, 746. Patent Owner does not dispute that Threlfall is prior art to the challenged claims.

Threlfall describes "[c]himeric 2′-O-methyl oligoribonucleotides (2′-OMe ORNs) containing internucleotide linkages which were modified with phosphonoacetate (PACE) or thiophosphonoacetate (thioPACE)" at their ends. Ex. 1010, 746; *see also id.* at 747 (Table 1 showing chemically modified sequences). Threlfall explains that "[o]ligoribonucleotides with a 2′-O-methyl modification . . . are known to be nuclease resistant and increase the stability of a duplex which is formed with complementary RNA." *Id.* at 746. Moreover, Threlfall teaches that "ODNs modified with PACE or thioPACE [had been] shown to be nuclease resistant" in a prior study. *Id.* at 747. Threlfall reports results from tests on ORNs combining these chemical modifications "into chimeric 2′-OMe ORNs as PACE or thioPACE modifications." *Id.* at 752. According to Threlfall, "the chimeric ORNs formed stable duplexes

with complementary RNA, and the majority of these duplexes had higher thermal melting temperatures than an unmodified RNA:RNA control duplex." *Id.*

E. Ground 1: Anticipation by Pioneer Hi-Bred

Petitioner contends that claims 1–5, 8–21, and 21–33 are anticipated by Pioneer Hi-Bred. *See* Pet. 17–47. As explained below, Petitioner has shown by a preponderance of the evidence that these claims are anticipated by Pioneer Hi-Bred.

i. Claims 1 and 19

Petitioner has shown that Pioneer Hi-Bred discloses guide RNA and crRNA molecules having 2′-O-methyl modifications as recited in claims 1 and 19. *See, e.g.*, Pet. 17–30, 44 (showing for claims 1 and 19). In particular, Table 8 in Pioneer Hi-Bred discloses exemplary crRNA molecules comprising 2′-O-methyl modifications in the VT domain (*e.g.*, sequences 66 and 68). Ex. 1006, 109. The VT domain corresponds to the "guide sequence" in claims 1 and 19 because it is "complementary to a nucleotide sequence in a target DNA" meaning that it hybridizes to a target sequence in that polynucleotide. *Id.* at 24:23–28, 97:17–18, Fig. 3A–B; Ex. 1003 ¶¶ 130– 33. Pioneer Hi-Bred teaches that crRNAs, including those in Table 8, also have a CER domain (*i.e.*, a stem sequence) that is complementary to and paired with a tracrRNA to form a duplex guide RNA. *Id.* at 8:22–31, 24:32– 25:10, 109:4–9, Fig. 1A, 3A; Ex. 1003 ¶¶ 129–33, 138. Pioneer Hi-Bred further discloses embodiments in which modifications similar to those exemplified in Table 8 are introduced into a long guide RNA (*i.e.*, a single guide RNA) in

which the crRNA and tracrRNA are fused together. *Id.* at 113:25–29; *see also id.* at 10:8–13, Fig. 1B, 3B (depicting a "Long guide RNA" as a "fused crRNA and tracrRNA")); Ex. 1003 ¶¶ 125–29, 135–37.

Petitioner has also shown that Pioneer Hi-Bred discloses the recited "gRNA functionality." *See* Pet. 25–26 (Ex. 1003 ¶¶ 128–29, 142–46). Pioneer Hi-Bred defines the term "guide polynucleotide" as "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." Ex. 1006, 24:6–8. Thus, 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 claims 1 and 19.

Pioneer Hi-Bred refers to the modified sequences in Examples 4 and 5 as "modified guide polynucleotides," indicating that those sequences have this functionality. Ex. 1006, 107:14–18:11; *see also id.* at 109:4–6 (referring to the complex formed by the "modified crRNA or crDNA components described in Table 8" as a "modified guide polynucleotide/Cas endonuclease complex"). Other statements in these examples confirm this understanding. *See id.* at 107:14–24 (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"); 107:24–108:2 ("Modified guide polynucleotides described above may also be delivered simultaneously in multiplex to

target multiple chromosomal DNA sequences for cleavage or nicking.").[9]

Accordingly, we agree with Petitioner that Pioneer Hi-Bred discloses synthetic guide RNA and crRNA molecules as recited in claims 1 and 19. In its Response, Patent Owner contends that Pioneer Hi-Bred does not disclose the recited "gRNA functionality" and is non-enabling. *See* Resp. 29–44. As explained below, both of these arguments are unavailing.

1. Whether Pioneer Hi-Bred discloses a functional gRNA

Patent Owner argues that "Pioneer Hi-Bred does not disclose *a single functional modified gRNA*." Resp. 30. According to Patent Owner, Pioneer Hi-Bred tested only a single modified guide polynucleotide made of DNA, which subsequent testing revealed was not successful. *See id.* at 30–34. Patent Owner argues that Examples 4 and 5 "do not reveal any actual testing" and are "simply an invitation to experiment . . . that precludes a finding of anticipation because functionality is not disclosed." *Id.* at 34–36.

Patent Owner argues that Petitioner did not assert "anticipation by inherency" for the gRNA

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[9] While 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. *See* Ex. 1059 ¶ 31 (explaining that "Agilent's cleavage experiments [in the Specification of the '034 patent] that show cleavage activity for certain gRNAs establish that 'gRNA functionality' is present for gRNAs," but the absence of cleavage activity "does not mean that it does not have 'gRNA functionality' because such a gRNA may nonetheless form a complex with Cas without effecting target cleavage").

functionality limitation. Resp. 36. According to Patent Owner, this is because "some of the sequences identified in Table 8 exhibited no functionality, including some 2′-O-Methyl modifications, so it cannot be assumed that this combination will work." *Id.* Patent Owner points to results in the Specification of the challenged patent showing that the use of chemically modified gRNAs with 26 and 37 consecutive 2′-O-methyl-modified nucleotides at the 5′ end did not result in cleavage activity. *Id.* at 37 (referring to Table 4 results for entry nos. 151 and 152 in Ex. 1001). According to Patent Owner, these results show "the proposed modifications in sequences 68 and 69 [in Table 8] together are non-functional." *Id.*

Patent Owner further contends that "a POSA would doubt" that sequences 64–69[10] in Table 8 of Pioneer Hi-Bred "would function at all because each design is both truncated and is also modified." Sur-reply 8 (citing Ex. 2025 ¶¶ 201–03, 221, 242–46); Ex. 1026, Ex. 1033, Ex. 2044, Ex. 2045). Patent Owner's expert, Dr. Marshall testifies that "a putative guide sequence is 20 nt in length," whereas the VT domain sequences in Pioneer Hi-Bred's sequences 64, 66, and 68 are "each only 17 nt long." Ex. 2025 ¶ 201. According to Patent Owner and Dr. Marshall, this means "the nucleotides being edited in Pioneer Hi-Bred are 4, 5, and 6 because 1, 2, and 3 have already been truncated from the end. But Nishimasu found that positions 4, 5, and 6 were crucial positions in the context of gRNA

[10] Sequences 64 and 65 disclose phosphorothioate modifications. While not recited in claims 1 and 19, such modifications are recited in some of the dependent claims. *See* Ex. 1001, 257:62–64, 258:41–57, 259:15–17, 259:24– 260:10 (claims 5, 9–13, 21, and 24–28). We address them here for completeness.

associating and targeting." Resp. 38–39; *see also* Ex. 2025 ¶¶ 202–03.

Petitioner replies, urging that testing data is not required for a prior art reference to be anticipatory. *See* Reply 2–5 (citing cases). Petitioner argues that Pioneer Hi-Bred provides a targeted disclosure that identifies only five types of modifications for decreasing unwanted nuclease degradation and "explains precisely why those modifications should be used." *Id.* at 13–14 (citing Ex. 1006, 107 (Table 7)). Moreover, Petitioner urges that Pioneer Hi-Bred "presents exemplary embodiments of gRNAs [in sequences 64–69 of Table 8] containing those modifications and the precise positions where those modifications ought to be placed, including the types and locations of modifications that anticipate" the challenged claims. *Id.* at 14–15 (citing Ex. 1006, 109).

Regarding Patent Owner's argument that the cleavage data in the '034 patent Specification shows that Pioneer Hi-Bred's sequences 68 and 69 lack functionality, Petitioner points out that the "gRNA functionality" in claims 1 and 19 does not require cleavage. Reply 16–17. Thus, Petitioner urges there is not "a shred of evidence that the sequences 68 and 69 in Pioneer Hi-Bred do not show the type of 'gRNA functionality'" in claims 1 and 19. *Id.* at 17 (citing Ex. 1060, 129:17–23; Ex. 1061, 105:15–25, 106:16–24, 107:14–25, 108:13–109:11).

Petitioner replies to Patent Owner's truncation argument and the related testimony of Dr. Marshall with evidence from Dr. Furneaux. *See* Ex. 1059 ¶¶ 73–75. According to Dr. Furneaux, the record does not support Dr. Marshall's assumption that the sequences in Table 8 are truncated because Pioneer Hi-Bred

teaches that the VT domain varies in length and is "designed based on the target sequence," which for the crRNAs in Table 8 is the 17 nucleotides long. *Id.* ¶ 74. Dr. Furneaux further testifies that the references Dr. Marshall cites as showing that truncated gRNAs do not work actually "support the opposite conclusion, that gRNAs with target sequences of 17 nucleotides are functional." *Id.* ¶ 75.

We find Petitioner's arguments and evidence persuasive. It is well established that "anticipation does not require actual performance of suggestions in a disclosure." *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005); *see also In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). Moreover, the Petition need not assert that "gRNA functionality" is inherently disclosed because Petitioner has shown that Pioneer Hi-Bred's expressly discloses this limitation. Pet. 25–26 (citing evidence). There is no additional requirement that this express disclosure be backed by test data in order for the reference to be anticipatory. *See, e.g.*, *Novo*, 424 F.3d at 1355; *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) ("[P]roof of efficacy is not required in order for a reference to be enabled for purposes of anticipation.").

Patent Owner suggests we should ignore what it calls a "bald assertion" of gRNA functionality in Pioneer Hi-Bred because either that assertion is incorrect or a POSA would doubt that it was true. *See* Resp. 2. We disagree. To begin with, Patent Owner's reliance on the purported failure of Pioneer Hi-Bred's DNA-based embodiments is unavailing. Pioneer Hi-Bred discloses both DNA and RNA-based embodiments. The Petition is premised on the latter. Even if

we accept Patent Owner's argument that the DNA-based examples lack gRNA functionality, that fact does not suggest that a POSA would doubt that the RNA-based embodiments, *e.g.*, crRNAs comprising sequences 64–69 in Table 8, lack such functionality.

Patent Owner's argument that a POSA would doubt whether Pioneer Hi-Bred's RNA-based embodiments have gRNA functionality because the VT domain in sequences 64, 66, and 68 is truncated is also unpersuasive. First, Pioneer Hi-Bred does not state that these sequences are truncated, nor does the record support Patent Owner's argument that these sequences are necessarily truncated because they are 17 nt, as opposed to 20 nt, long. To the contrary, Pioneer Hi-Bred teaches that the VT domain may vary in length from 12 to 30 nt. Ex. 1006, 3:19–20, 98:19–23. In addition, Pioneer Hi-Bred explains that the sequences in Table 8 are designed to target the "LIGCas-3" site in Maize, which is 17 nt long. *Id.* at 109:4–9; *see also id.* at 99:15–18 (Table 1 identifying 17 nt target site sequence for LIGCas-3). Thus, the record supports, and we credit, Dr. Furneaux's testimony that the VT domain for these sequences is 17 nt because it is designed to target a 17 nt sequence—not because it has been truncated.[11] Ex. 1059 ¶ 74.

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[11] Patent Owner asserts that Dr. Furneaux "adopted the definition of 'truncated gRNAs' as those with 'regions of target complementarity <20 nucleotides in length" in paragraph 79 of his opening declaration. Sur-reply 8 n. 1. We disagree. The testimony in paragraph 79 refers to the particular results in Fu. *See* Ex. 1003 ¶ 78 (citing Ex. 1033). We see nothing there that suggests Dr. Furneaux agrees with Patent Owner's position that any gRNA with a VT region of less than 20 nt is truncated.

Second, even if those sequences were truncated, the record does not support Patent Owner's argument that a POSA would doubt that they have gRNA functionality. Patent Owner's argument is premised on Dr. Marshall's testimony that these sequences "are truncated to a point that would render them nonfunctional." Ex. 2025 ¶ 200. But the references he cites do not support that position. *See* Ex. 2025 ¶ 202 (citing Ex. 1033 ("Fu"); Ex. 2044 ("Cencic"); and Ex. 2045 ("Mali")). To the contrary, Fu evidences that "truncated gRNAs, with shorter regions of target complementarity <20 nucleotides in length" are functional and that truncation to 17 nt is beneficial. Ex. 1033, Abstr.; *see also id.* at 283 ("[W]e found that [truncated] gRNAs with 17 or 18 nucleotides of complementarity generally function efficiently at the intended target site and have improved specificities."). Cencic and Mali likewise do not suggest that a 17 nt VT domain would lack gRNA functionality. *See* Ex. 2025 ¶ 202 (citing Cencic as showing "truncated gRNA tests showed that a guide sequence of only 16 nucleotides" abolished cleavage activity); Ex. 2045, Supp. Fig. 10 ("1-3 bp 5′ [gRNA] truncations are indeed well tolerated, but larger deletions lead to loss of activity"). Accordingly, we credit Dr. Furneaux's testimony (*see, e.g.*, Ex. 1003 ¶ 78, Ex. 1059 ¶¶ 73–75) over the competing testimony offered by Dr. Marshall on these points.

At oral argument, Patent Owner took its argument a step further asserting not only that a POSA would doubt their functionality, but also that that the record shows that Pioneer Hi-Bred sequences 64–67, in fact, lack gRNA functionality because they combine truncation with chemical modifications to the 4, 5, and

6 nucleotides of the untruncated gRNA. *See* Tr. 41:3–48:16 (urging that "Nishimasu" (Ex. 1026) shows that the nucleotides at this position are critical to gRNA functionality). This new argument is unavailing.[12] First, as explained above, the record does not support Patent Owner's argument that the VT domain in these sequences is truncated. Second, there is test data in the record demonstrating gRNA functionality for both truncated gRNAs and gRNAs with modifications to the 4, 5, and 6 nucleotides. *See, e.g.*, Ex. 1033, 283; Ex. 2045, Supp. Fig. 10; Ex. 1001, Tables 3 and 4 (Patent Owner's Specification showing cleavage activity for truncated gRNAs with a 17 nt target sequence and gRNAs with chemical modifications at the 4, 5, and 6 nucleotides). While not prior art, this data does tend to rebut Patent Owner's argument that sequences 64–67 lack gRNA functionality because it shows that both truncation to 17 nt and modifications to the 4, 5, and 6 nucleotides can be individually tolerated without losing cleavage activity.

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[12] In its papers, Patent Owner asserts that a POSA would "doubt" the gRNA functionality of sequences 64–69 for this reason. Sur-reply 8; *see also* Resp. 39 (arguing that the "combination of truncation and modifications would have been unpredictable" and thus gRNA functionality was not "inherent"); Ex. 2025 ¶ 203 ("[A] POSA would seriously question whether the guide sequence designs of Table 8 would be functional"). But at the hearing, Patent Owner stated it was asserting "both" that a POSA would doubt their functionality and that these sequences do not, in fact, exhibit gRNA functionality and that the record demonstrates such. Tr. 41:3–16. This latter point is a new argument that was not clearly presented in the Response and has therefore been waived. Even if it had been timely presented, we find that the record does not support Patent Owner's position that Pioneer Hi-Bred's sequences 64–69 are non-functional.

We also disagree with Patent Owner's argument that the cleavage data in its Specification shows that a crRNA corresponding to Pioneer Hi-Bred's sequences 68 and 69 would lack "gRNA functionality." Resp. 36–37. The data Patent Owner points to shows only that cleavage did not occur. Cleavage, however, is not required for the "gRNA functionality" recited in claims 1 and 12. Patent Owner's expert, Dr. Sampson admitted on cross-examination that just because a gRNA in Table 4 lacks cleavage activity does not demonstrate that it also lacks the ability to bind a Cas protein and target that complex to target polynucleotide:

> Q. [T]he handful of guide RNAs that you identified in Table 4 of the ['034] patent as not exhibiting cleavage, those may nonetheless bind with a Cas protein and form a complex with the target DNA; correct?
>
> A. Yeah. I can't, you known, answer that definitively.
>
> Q. All we know is that it might or might not happen; right? We don't know one way or the other?
>
> A. There is no objective evidence that would be able to indicate that.
>
> ***
>
> Q. I just want to be clear, the handful of guide RNAs that you point out as being non-functional, you don't actually know whether they actually have gRNA functionality as claimed in the claims; right?
>
> A. What I'd say is that I can't – there's no objective evidence that allows you for a determi-

> nation of whether the guides bind to Cas9 or direct the programmed Cas9 to the target site.
>
> ***
>
> Q. You can't say one way or another whether the guide RNAs that you say are not functional actually lack that gRNA functionality as claimed in the claims; right?
>
> A. I can state that I have no evidence to differentiate between whether they would bind to the Cas or direct the Cas to a target sequence.

Ex. 1060, 106:16–109:11 (objections omitted); *see also* Ex. 1059 ¶ 31 (similar testimony from Dr. Furneaux). Thus, the data in Table 4 of the Specification showing a lack of cleavage activity does not demonstrate that the corresponding gRNA lacks the claimed "gRNA functionality."

Moreover, Patent Owner's argument only applies to a crRNA that combines sequences 68 and 69 "together" resulting in a crRNA with 39 consecutive 2′-O-methyl modifications. Resp. 37. However, Pioneer Hi-Bred discloses that these modifications may be introduced "individually or in combination." Ex. 1006, 113:25–29. If introduced individually, a crRNA having the modifications in sequence 68 would have 17 2′-O-methyl modifications and a crRNA having the modifications in sequence 69 would have 22 such modifications. This is closer to the number of modifications in sequences that the data in the Specification shows do have cleavage activity (*e.g.*, Table 4 Entry #s 146–150 having 20 consecutive 2′-O-methyl modifications) than it is to the sequences Patent Owner identifies as lack-

ing cleavage activity. *See* Resp. 37 (citing Ex. 1001, 119 (Table 4 Entry #s 151 and 152 having 26 and 37 consecutive sugar modifications). Therefore, the data in the Specification does not show that a crRNA comprising sequence 68 or 69 would lack cleavage activity, much less the broader "gRNA functionality" recited in the challenged claims.

For these reasons, we determine that Pioneer Hi-Bred discloses functional, chemically-modified gRNAs as recited in claims 1 and 19.

2. Whether Pioneer Hi-Bred is enabled

Patent Owner contends that Pioneer Hi-Bred is not enabled. Resp. 39–44. More specifically, Patent Owner asserts that "[a] POSA encountering Pioneer Hi-Bred could not make the claimed inventions of the '034 [patent] without undue experimentation" because it "discloses a laundry list of chemical modifications, that can be made alone or in combination, and applied literally anywhere in the disclosed guides." *Id.* at 43. According to Patent Owner, the "art was new, complicated and unpredictable," "not 'mechanistically analogous' to anything that came before it," and "a POSA would have been circumspect about making the claimed modifications without testing because what was known about the nature of the interactions between the Cas Protein and the gRNA suggested the gRNA would be very sensitive to modifications, especially in the guide portion." *Id.* at 44 (no citations provided). Thus, argues Patent Owner, "the *Wands* factors lean[] heavily in favor of a finding that Pioneer Hi-Bred would not enable one to make the claims of the '034 Patent without undue experimentation." *Id.* (italics added).

Petitioner contends that the anticipating disclosures in Pioneer Hi-Bred are enabled. Reply 5–18. In particular, Petitioner urges that Pioneer Hi-Bred discloses only five types of chemical modifications for decreasing unwanted nuclease degradation in Table 7 and provides exemplary embodiments of gRNAs, including those having "the types and locations of modifications that anticipate the '034 Patent claims," in Table 8. *Id.* at 13–15. Petitioner points to testimony from Patent Owner's declarants showing that the techniques for making such gRNAs were known in the art and a POSA could use "commercially available instruments that could churn out multiple [chemically-modified] gRNAs in a single day." *Id.* at 8–9.

Petitioner also cites evidence that the chemical modifications disclosed in Pioneer Hi-Bred had been used for decades prior to the filing of the '034 patent "to stabilize RNA against nucleases" and that "CRISPR gRNA stabilization presented a new iteration of an old problem with a tried and true solution." *Id.* at 9–12. According to Petitioner, "the testing data in the patent drives home just how predictable this field was" because only 7 of the roughly 250 gRNAs Patent Owner tested lacked cleavage functionality. *Id.* at 12–13, 16 (referring to the inventors "roughly 97% success rate in predicting which modified gRNAs would work" based on prior art teachings).

We again find Petitioner's evidence and argument persuasive. For a prior art reference to be enabling, "the reference need only enable a single embodiment of the claim." *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015). "In other words, a prior art reference need not enable its full disclosure; it only needs to enable the portions of its disclosure alleged to anticipate the

claimed invention." *In re Antor Media Corp.*, 689 F.3d 1282, 1290 (Fed. Cir. 2012). Here, Petitioner asserts that the RNA-based embodiments disclosed in Examples 4 and 5 of Pioneer Hi-Bred are anticipatory. Those disclosures are presumed enabling and Patent Owner has not shown otherwise.

Indeed, the record demonstrates that a POSA, as of December 2014, could practice these disclosures without undue experimentation.[13] As explained above, Table 7 of Pioneer Hi-Bred teaches modifications, including 2′-O-methyl modifications to the sugar and phosphorothioate bond modifications, that can be used to decrease unwanted nuclease degradation of a gRNA in a guide polynucleotide/Cas endonuclease system. And Table 8 discloses exemplary sequences of such chemically-modified crRNAs that read on claims 1 and 12. Pioneer Hi-Bred teaches that gRNAs having the modifications in Table 8 and similar modifications can be "synthesized per standard techniques." Ex. 1006, 113:25–29.

While Pioneer Hi-Bred does not further describe these standard techniques, the record demonstrates such techniques were known in the art and a POSA would have been able to use them to make the gRNAs disclosed in Pioneer Hi-Bred without undue experi-

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[13] The question of undue experimentation involves consideration of certain factors identified in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include: the quantity of experimentation, the amount of direction or guidance present, the presence or absence of working examples, the state of the prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. *Id.* To the extent they are applicable here, we have considered these and the other *Wands* factors in our analysis.

mentation. Both sides' experts testify that techniques such as "click chemistry" and "TC chemistry" were known in the prior art for synthesizing long oligonucleotides. Ex. 1059 ¶¶ 33–38; *see* Ex. 1061, 188:9–190:17). Moreover, the Specification of the '034 patent cites references describing these known techniques to explain how its chemically-modified gRNAs may be synthesized. Ex. 1001, 48:4–33; *see also In re Morsa*, 803 F.3d at 1378 (explaining that statements in the specification evidencing the knowledge of a POSA may be relied upon to show that a prior art reference is enabled). The record further evidences that the inventors were able to employ such techniques to make an individual gRNA in about a day's time and that commercially-available "synthesizers" were available, allowing dozens of different gRNAs to be synthesized at the same time. Ex. 1069 ¶ 41; *see* Ex. 1060, 87:6–18, 88:3–16 (Dr. Sampson testifying that synthesizers capable of making as many as 48 gRNAs at a time were commercially-available), 191:16–192:14 (testifying that multiple guides can be made in a day).

Patent Owner argues that its inventors were uniquely-skilled in the synthesis of long RNAs and thus "it would have been extremely challenging for a POSA to chemically synthesize the claimed chemically-modified gRNA." *See* Resp. 11–13. This argument is unavailing for several reasons. First, the Specification of the '034 patent does not disclose any new techniques for synthesizing chemically-modified gRNAs, but instead refers to the use of click chemistry and TC chemistry techniques already taught in other references. Ex. 1001, 48:4–33. Second, while Dr. Sampson points to challenges he and the other inventors allegedly had to overcome to make these molecules

(*see* Ex. 2029 ¶¶ 12–15), none of those challenges are mentioned in the Specification of the '034 patent. *See In re Epstein*, 32 F.3d 1559, 1568 (Fed. Cir. 1994) (holding "the Board's observation that appellant did not provide the type of detail in his specification that he now argues is necessary in prior art references supports the Board's finding that one skilled in the art would have known how to implement the features of the references"). Moreover, when cross-examined about these purported challenges, Dr. Sampson was either unable to remember how the inventors addressed them or he testified they were overcome by increasing the reaction time, which was "[j]ust kind of a pretty standard thing that you do." Ex.1061, 115:3–118:19. Third, in order to anticipate, Pioneer Hi-Bred "need only enable a single embodiment of the claim." *In re Morsa*, 803 F.3d at 1377. Petitioner's arguments that its team of inventors spent over a year to synthesize "hundreds" of gRNAs does not show that the experimentation required to make any one of the anticipating gRNAs disclosed in Pioneer Hi-Bred, *e.g.*, the exemplary crRNAs in Table 8, would be undue. For these reasons, we credit Dr. Furneaux's testimony that undue experimentation would not be required to make the anticipating, chemically-modified gRNAs taught in Pioneer Hi-Bred (*see* Ex. 1059 ¶¶ 32–47) over the competing testimony of Patent Owner's declarants.

So too, the fact that Pioneer Hi-Bred "contains no data regarding any testing of the sequences in Table 8" does not demonstrate that the crRNAs disclosed there are not enabled. *See* Resp. 34–36. "It is not . . . necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the

enablement requirement." *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir.1985). Thus, 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. *See Antor Media,* 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 to perform the claimed invention").

To the extent Patent Owner contends that the nascent state of the art demonstrates that undue experimentation would be required, we disagree. *See* Resp. 44. It is undisputed that the use of gRNA in a CRISPR/Cas system was a relatively new discovery first published in mid-2012. *See* Pet. 2; Resp. 52–53. That said, the record demonstrates that by December 2014 substantial research into such systems had been published and would have been known to a POSA Ex. 1003 ¶ 78; Ex. 1059 ¶¶ 20–23, 65–72 (citing references). A POSA would also know that gRNA was subject to degradation, which could limit the efficiency of a CRISPR/Cas system. *See, e.g.*, Ex. 1003 ¶¶ 66, 71; Ex. 1061, 200:14–201:11. Moreover, 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. Ex. 1003 ¶¶ 50–52, 61–70; *see also* Ex. 1061, 214:6–16. Thus, while the art was somewhat unpredictable in December 2014, it was far from a blank slate with a POSA 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.

Finally, Patent Owner's attempt to analogize the present facts to those in *Impax Laboratories*[14] is unavailing. *See* Resp. 42–43. The claims in *Impax Laboratories* were directed to methods of using a particular compound to treat a particular disease. 545 F.3d at 1314. However, the allegedly anticipating prior art disclosed "hundreds or thousands of compounds and several diseases" along with "broad and general" dosage guidelines and "without sufficient direction or guidance to prescribe a treatment regimen." *Id.* at 1315–16. On those facts, the Federal Circuit affirmed the district court's finding that the prior art did not enable the particular method recited in the claims. *Id.* In contrast, 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.

In sum, given the guidance in Pioneer Hi-Bred, the existing knowledge in the art, including knowledge of standard techniques and equipment/reagents for making the chemically modified RNA sequences taught in Pioneer Hi-Bred, and the relatively high level of training of a POSA, we find that undue experimentation would not have been required to make and use a

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[14] *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008).

gRNA with the recited chemical modifications and functionality. Because Pioneer Hi-Bred discloses functional, chemically-modified gRNAs as recited in claims 1 and 19, and that disclosure is enabled, Petitioner has demonstrated that claims 1 and 19 are anticipated by Pioneer Hi-Bred.

ii. Claims 2 and 33

Claim 2 recites a method comprising the steps of: (a) contacting a DNA sequence, gene of interest, or target polynucleotide with a CRISPR-associated (Cas) protein and the gRNA of claim 1, and (b) editing, regulating, cleaving, or binding the DNA sequence, gene of interest, or target polynucleotide. Ex. 1001, 257:48–56. Claim 33 recites the same method using the crRNA of claim 19. *Id.* at 260:20–28.

Petitioner cites evidence showing that Pioneer Hi-Bred discloses the method recited in claims 2 and 33. *See* Pet. 30–32, 47. Patent Owner does not dispute Petitioner's showing for these claims separately from its arguments for claims 1 and 19.[15]

Petitioner's contentions are supported by the record and persuasive. As explained above, Pioneer Hi-Bred discloses a synthetic gRNA and crRNA with the chemical modifications and gRNA functionality recited in claims 1 and 19. Pioneer Hi-Bred discloses methods of using such to modify a DNA sequence. Ex. 1006, 41:23–32, 128:8–14 (claim 28); Ex. 1003 ¶¶ 157–58. Pioneer Hi-Bred also discloses that the gRNA/Cas

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[15] To the extent Patent Owner reasserts the same arguments for claims 2, 33, and the other dependent claims that it does for claims 1 and 19, those arguments are unavailing for the reasons already addressed in our analysis above.

endonuclease system can be used to regulate expression of a specific gene or cleave a target polynucleotide. *See* Ex. 1006, 30:17–22 (cleave by "introduc[ing] a double strand break at said target site"); 47:15–29 (regulate expression); Ex. 1003 ¶¶ 159–61. Moreover, Dr. Furneaux offers testimony, which we credit, explaining how Pioneer Hi-Bred discloses both the contacting and editing, regulating, cleaving, or binding steps recited in claims 2 and 33. Ex. 1003 ¶¶ 162–66. The teachings Petitioner and Dr. Furneaux rely upon are presumptively enabling. *See, e.g.*, *Antor Media*, 689 F.3d at 1287–88. Patent Owner does not challenge that presumption separately from its arguments for independent claims 1 and 19, which are unavailing as explained above.

Accordingly, Petitioner has shown by a preponderance of the evidence that claims 2 and 33 are anticipated by Pioneer Hi-Bred.

iii. Claim 3

Claim 3 recites "[a] set or a library comprising two or more synthetic guide RNAs of claim 1." Ex. 1001, 257:57–58.

Petitioner relies on Pioneer Hi-Bred's teaching that the "modified guide polynucleotides described [therein] may also be delivered *simultaneously in multiplex* to target multiple chromosomal DNA sequences for cleavage or nicking." Pet. 32 (quoting Ex. 1006, 107:24– 108:2). In addition, Petitioner cites Pioneer Hi-Bred's teaching that the guide polynucleotide/Cas system can be used "for producing transgenic trait loci *comprising multiple transgenes*." *Id.* at 50–51 (quoting Ex. 1006, 78:19– 26). Petitioner and Dr. Furneaux assert that "[a] POSA would have

understood [these teachings] as an express instruction to prepare a library of modified gRNAs comprising multiple modified gRNAs" as recited in claim 30. Pet. 32; Ex. 1003, 166–70.

In response, Patent Owner asserts "[s]equence 66 and 68 do not comprise a library of two or more synthetic guide RNAs, and there [sic] cannot anticipate claim 3." Resp. 28. According to Patent Owner, "Pioneer Hi-Bred does not disclose even one synthetic guide RNA that meets all of the limitations of Claim 1. By necessity, then, it cannot disclose 'two or more' such guide RNAs" as recited in claim 3. *Id.* at 45. Patent Owner does not respond to Petitioner's argument that Pioneer Hi-Bred teaches its modified gRNAs may be delivered in multiplex. *See* Reply 2–3 (noting that "Patent Owner presents no rebuttal to Petitioner's citation" to this disclosure).

Petitioner's contentions are sufficiently supported by the record and persuasive. As explained above, Pioneer Hi-Bred discloses synthetic gRNA comprising a guide sequence with the recited modifications and gRNA functionality and specifically exemplifies such in sequences 66 and 68 of Table 8. As we understand it, Patent Owner's argument against Petitioner's showing for claim 3 is that a single gRNA comprising either sequence 66 or 68 would not itself be a set or library comprising at least two guide RNAs. But that argument misses the point. Pioneer Hi-Bred specifically teaches that its modified gRNA may be delivered simultaneously in multiplex to target multiple different sequences. Ex. 1006, 107: 24–108:2. Dr. Furneaux offers testimony, which we credit, explaining that a POSA would understand this to be an instruction to prepare a library of multiple, modified gRNAs. Ex.

1003 ¶ 227. Accordingly, Petitioner has shown by a preponderance of the evidence that claim 3 is anticipated by Pioneer Hi-Bred.

iv. Claim 4

Claim 4 depends from claim 1 and recites that the synthetic guide RNA is a "single-guide RNA (sgRNA)." Ex. 1001, 257:60–61. Petitioner asserts that "Pioneer Hi-Bred discloses a single-guide RNA (also known as 'long guide RNA') comprising a VT domain and CER domain" and teaches that "nucleotide modifications, such as 2′-O-methyl and 3-phosphorothioate modifications, *e.g.*, as shown in Table 8, can be made in the guide sequence (VT Domain) of an sgRNA." Pet. 33–34 (citing Ex. 1006, 24:6–19, 25:11–15, 113:25–29, Figs. 1B and 3B; Ex. 1003 ¶¶ 171–76). We agree that the cited evidence shows that Pioneer Hi-Bred discloses a chemically-modified sgRNA as recited in claim 4.

Patent Owner argues that claim 4 is not anticipated because "[s]equences 64, 65, 66, 67, 68, and 69 [in Pioneer Hi-Bred Table 8] are disclosed only as a portion of a duplex or two-part guide." Resp. 29.[16] Patent Owner's argument is unavailing. Pioneer Hi-Bred's disclosure is not limited to a two-part guide with the crRNA sequences in Table 8. It discloses that its guide polynucleotides can be implemented as "a single molecule or a double molecule." 1006, 24:8–9. Moreover, Pioneer Hi-Bred specifically states that the

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[16] To the extent Patent Owner reasserts the same arguments for claim 2 and the other dependent claims that it does for claims 1 and 12, those arguments are unavailing for the reasons already addressed in our analysis above.

modifications in Table 8 can also be introduced in a "long guide RNA," *i.e.*, a sgRNA. Ex. 1006, 113:25–27; *see* Ex. 1003 ¶ 150 (explaining that a sgRNA is also referred to as a long guide RNA). Accordingly, while sequences 64–69 are described as part of a crRNA, a POSA would have immediately envisioned that those sequences could also be implemented in the corresponding domains of a sgRNA. Thus, Pioneer Hi-Bred anticipates claim 4.

v. Claims 5, 8–13, 20, 21, and 24–28

Claims 5, 8–13, 20, 21, and 24–28 further recite the use of at least one phosphorothioate modification along with the existing 2′-O-methyl modification required by the independent claims. More specifically, claims 5 and 21 recite that the "one or more modifications" in their respective independent claims "comprise[] a 2′-O-methyl nucleotide with a 3′-phosphorothioate." Ex. 1001, 257:62–64, 259:15–17. Claims 8 and 20 recite that the gRNA and crRNA in their respective independent claims further comprise at least one "phosphorothioate internucleotide linkage, phosphonoacetate (PACE) internucleotide linkage, and/or thiophosphonoacetate (thioPACE) internucleotide linkage." *Id.* at 258:37–40, 259:10–14. Claims 9–11 and 24–26 recite that the gRNA and crRNA in their respective independent claims comprise "up to"[17] a specified number (*i.e.*, 3, 7, or 10) of the

[17] The phrase "up to" puts an upper limit on the number of internucleotide linkage modifications. Accordingly, these claims encompass gRNA and crRNA having anywhere from one such modification "up to" the recited number of modifications. Neither party addresses whether the "up to" language puts any lower limit on the required number of internucleotide linkage modifications, *i.e.*, whether the disclosure of a synthetic gRNA or

same set "internucleotide linkage" modifications "in the guide sequence." *Id.* at 258:41–49, 259:24–260:3. Similarly, claims 12, 13, 27, and 28 recite "up to five consecutive" internucleotide linkage modifications at the 5′-end (claims 12 and 13) and 3′-end (claims 23 and 28). *Id.* at 258:50–57, 260:4–11.

For all these claims, Petitioner points to disclosure in Tables 7 and 8 of Pioneer Hi-Bred, urging that they disclose "five types of nucleotide chemical modifications including the phosphorothioate and 2′-O-methyl modifications." Pet. 34–35 (citing Ex. 1003 ¶ 178–82); *see also id.at* 38 (explaining that sequence 64 in Table 8 discloses "consecutive phosphorothioate internucleotide linkages in the gRNA guide sequence (VT domain) at the 5′-end"). Relying on Pioneer Hi-Bred's teaching that these modifications can be introduced in "combination," Petitioner cites Dr. Furneaux's calculations showing that "Tables 7 and 8 disclose thirty-one different ways to combine the five modifications, and eight of these combinations contain both a 3′-phosphorothioate modified nucleotide and a 3′-phosphorothioate modified nucleotide." *Id.* at 35–36 (citing Ex. 1003 ¶¶ 183–185; Ex. 1006, 108:25–27, 113:25–29). Petitioner relies on a similar mathematical analysis based on another teaching in Pioneer Hi-Bred that "yields 2047 ways to combine the [disclosed modifications], 512 of which contain a 2′-O-methyl-3′phosphorothioate modification in the guide sequence." *Id.* at 36

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crRNA as recited in the independent claims, but with *none* of the recited internucleotide linkage modifications would anticipate claims 9–13 and 24–28 because zero is less than the recited threshold. We need not resolve this issue because we find that Pioneer Hi-Bred discloses molecules with both 2′-O-methyl and at least one phosphorothioate modification in the guide sequence.

(citing Ex. 1003 ¶ 191; Ex. 1006, 24:6–19). According to Petitioner, a POSA would "immediately envisage combining these modifications in one nucleotide of the guide sequence" given "the high fraction of combinations containing the combined [modifications] and Pioneer Hi-Bred's express teachings of combining" them. *Id.* at 36–37 (citing *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)).

Patent Owner argues that sequences 66 and 68 in Table 8 disclose only 2′-O-methyl modifications and therefore cannot anticipate claims 5, 8– 13, 20, 21, and 24–28. *See* Resp. 27–28. According to Patent Owner, "Pioneer Hi-Bred simply does not disclose any of the combinations of chemical modifications" required by these claims and "Petitioner admits as much in its analysis" by relying on "Dr. Furneaux's calculation that there are 2047 possible combinations of the 11 specified chemical modifications early in the reference, but notably not in Examples 4 and 5." *Id.* at 28 (citing Ex. 2025 ¶¶ 255–57).

In its Sur-reply, Patent Owner further asserts that *Kennametal* "is inapposite since [there] it was undisputed that all claim elements were disclosed in the prior art but for a single structural element," whereas here "it is undisputed that Pioneer Hi-Bred lacks the structural limitations and the 'gRNA functionality' limitation." Sur-reply 26. However, Patent Owner does not challenge Dr. Furneaux's calculations, nor Petitioner's argument based on those calculations that a high fraction of the possible combinations would have both modifications. *See* Reply 2 (noting that Patent Owner "presents no analysis or argument" regarding these claims).

Petitioner's contentions are sufficiently supported by the record and persuasive. Sequence 64 in Table 8 exemplifies phosphorothioate modifications between the three nucleotides at the 5′-end of the guide sequence (VT domain). Ex. 1006, 109. Sequence 66 discloses 2′-O-Methyl modifications at the same location. *Id.* While none of the exemplary sequences in Table 8 disclose the combination of these two modifications to the same nucleotide, Pioneer Hi-Bred discloses that "[n]ucleotide base *and*/or phosphodiester bond modifications similar to those illustrated in Example 5 Table 8 can be introduced individually or *in combination* into the crRNA." *Id.* at 113:25–27 (emphases added). The combination of the modifications in sequences 64 and 66, for example, would result in a crRNA having 2′-O-methyl-3′-phosphorothioate nucleotides at the 5′-end of the guide sequence.

Regarding claims 13 and 28, sequence 65 in Table 8 exemplifies phosphorothioate modifications between the three nucleotides at the 3′-end of a crRNA. Ex. 1006, 109. The combination of modifications in sequences 65 and 66, for example, would result in a crRNA having 2-O-methyl modifications in its guide sequence and phosphorothioate modifications at the 3′-end of the crRNA. Thus, Pioneer Hi-Bred discloses the recited structural limitations (*i.e.*, 2′-O-methyl and phosphorothioate internucleotide linkage modifications) and expressly teaches that they can be combined in the guide sequence of a guide polynucleotide.[18] For this reason, Patent Owner's attempt to distinguish

[18] As explained above, Pioneer Hi-Bred discloses that its guide polynucleotides have the recited "gRNA functionality." *Supra* § III.E.i.

Kennametal is unavailing. *See Kennametal*, 780 F.3d at 1382 (explaining that where a reference discloses all of the claim elements "with the exception of" the recited combination of two of those elements "the question for purposes of anticipation is whether the number of categories and components disclosed in [the reference] is so large that the [recited] combination . . . would not be immediately apparent to one of ordinary skill in the art") (internal quotations omitted).

Here, Petitioner shows that a high fraction of the possible combinations disclosed in Tables 7 and 8 and elsewhere in Pioneer Hi-Bred result in the recited combinations of 2′-O-methyl and 3′-phosphorothioate modifications. Pet. 34–38 (citing Ex. 1003 ¶¶ 171–74). This showing, which Patent Owner does not specifically dispute, sufficiently demonstrates that a POSA would immediately envisage the combination of modifications recited in claims 5, 8–13, 20, 21, and 24–28. Accordingly, Petitioner has shown by a preponderance of the evidence that Pioneer Hi-Bred anticipates these claims.

vi. Claims 14 and 29

Claims 14 and 29 depend from claims 1 and 19 and further recite "a fluorophore at a 5′-end" of the gRNA or crRNA. Ex. 1001, 258:57–58, 60:12–13.

Petitioner contends that "Pioneer Hi-Bred teaches that fluorophore modifications can be combined with 2′-O-methyl modifications in the guide sequence." Pet. 41 (citing Ex. 1006, 27:3–19). According to Petitioner, "the guide sequence (VT domain) is found at either the 5′ or 3′-end of the gRNA." *Id.* (citing Ex. 1003 ¶ 211). Thus, "a POSA would immediately envisage gRNAs

with a combination of 2′-O-methyl modifications in the guide sequence and fluorophores at the 5′-end." *Id.*

Patent Owner disputes Petitioner's contention. According to Patent Owner, "[t]he only section in Pioneer Hi-Bred that Petitioner identifies" as disclosing this limitation "provides neither an explicit nor inherent disclosure of 'a fluorophore at a 5′-end of the [guide RNA/crRNA].'" Resp. 45 (alterations in original).

Petitioner's contentions are sufficiently supported by the record and persuasive. Pioneer Hi-Bred discloses modifying the VT domain of a guide polynucleotide to provide for "tracking" by adding the benefit of "a fluorescent label." Ex. 1006, 27:3–19. In the same section, Pioneer Hi-Bred teaches that such modifications may be used in "combination" with other modifications to the VT domain such as "a 2′-O-Methyl RNA nucleotide." *Id.* Thus, Pioneer Hi-Bred discloses the combination of 2′-O-methyl and fluorophore modifications in the VT domain of a gRNA and crRNA molecule.

Patent Owner does not clearly explain why, in its view, the disclosure Petitioner cites fails to disclose "a fluorophore at the 5′-end." To the extent Patent Owner contends that it doesn't specify a particular location for the fluorophore, we disagree. Dr. Furneaux offers testimony, which Patent Owner does not specifically dispute, that a POSA would understand that the VT domain is either at the 3′ or the 5′ end of the molecule. Ex. 1003 ¶ 211. Given that Pioneer Hi-Bred discloses adding a fluorescent label to the VT domain, and that a POSA would know that the VT domain is at one of the two ends of the molecule, Dr. Furneaux testifies "[a] POSA can immediately envisage guide RNAs comprising a 2′-O-methyl modified nucleotide in the

guide sequence in combination with a fluorophore at the 5′ end." Ex. 1003 ¶¶ 210–11. We find this explanation to be credible and supported by the record. Accordingly, Petitioner has shown by a preponderance of the evidence that claims 14 and 29 are anticipated by Pioneer Hi-Bred.

vii. Claims 15–17, 30 and 31

Claim 15 depends from claim 1 and recites that the gRNA comprises "one or more end modification." Ex. 1001, 258:59–60. Petitioner has shown that Pioneer Hi-Bred discloses a gRNA with an end modification. For example, sequences 66 and 68 in Table 8 disclose 2′-O-methyl modifications of the nucleotides at the 5′ end of a crRNA. Ex. 1006, 109. Patent Owner does not dispute Petitioner's showing for claim 15 separately from its arguments for the independent claims, which are unavailing as explained above.

Claims 16 and 30 recite "at least 2 consecutive 2′-O-methyl modifications." Ex. 1001, 258:62–63, 260:14–15. Petitioner again points to sequences 66 and 68 in Table 8, which it contends disclose this limitation. Pet. 42, 46.

Petitioner's contentions are sufficiently supported by the record and persuasive. Sequence 66 discloses a crRNA with three consecutive 2′-O-methyl modifications in the guide sequence. Ex. 1006, 109. Sequence 68 discloses a crRNA with seventeen consecutive 2′-O-methyl modifications in the guide sequence. *Id.*

Claims 17 and 31 recite "at least six 2′-O-methyl modifications." Ex. 1001, 258:64–67, 260:16–17. Sequence 68 discloses this limitation. Thus to the extent Patent Owner contends that Pioneer Hi-Bred

does not disclose the "multiple '2′-O-methyl modifications' recited in" claims 16, 17, 30, and 31, it is plainly incorrect. *See* Resp. 46. Accordingly, Petitioner has shown by a preponderance of the evidence that claims 15–17, 30 and 31 are anticipated by Pioneer Hi-Bred.

viii. Claims 18 and 32

Claims 18 and 32 recite "at least twenty 2′-O-methyl modifications." Ex. 1001, 258:66–67, 260:18–19. Petitioner argues that Pioneer Hi-Bred discloses: (1) "making 2′-O-methyl modifications at every position of the guide sequence (VT domain)" and (2) "that the length of the target sequence, and therefore the length of the guide sequence, can be at least twenty nucleotides." Pet. 43–44 (Ex. 1003 ¶¶ 215–18). In support of its argument, Petitioner cites the sequences in Table 8 and further quotes the description of Table 7, which provides that "modifications can be introduced throughout the nucleic acid sequences comprising the VT or CER domains." *Id.* (quoting Ex. 1006:13–25). Based on this disclosure, Petitioner contends "[a] POSA would immediately envisage utilizing at least twenty 2′-O-methyl modifications when [sic] guide sequences that are at least twenty nucleotides in length." *Id.* at 44 (citing Ex. 1003 ¶ 218).

Patent Owner disputes Petitioner's contentions, explaining that sequences 66 and 68 disclose three and seventeen 2′-O-methyl modifications, but not the "at least twenty" such modifications recited in these claims. Resp. 46. According to Patent Owner, Petitioner's argument is flawed because "modification 'throughout the nucleic acid sequences' does not mean more than twenty modifications. Rather the phrase could just as easily mean less than twenty modifications interspersed

throughout the entire length of the polynucleotide." *Id.* (referring to Petitioner's reliance on the disclosure at Ex. 1006, 106:13–25).

Petitioner's contentions are sufficiently supported by the record and persuasive. Sequence 68 in Table 8 discloses 2′-O-methyl modifications to every nucleotide in the guide sequence (*i.e.*, the VT domain). Ex. 1006, 109. That disclosure supports Petitioner's reading of the phrase "modifications . . . introduced throughout the nucleic acid sequence comprising the VT domain" to mean that every nucleotide in the VT domain is modified. Pet. 43 (quoting Ex. 1006, 106:13–25). The particular guide sequence exemplified in sequence 68 is only 17 nt long, but Pioneer Hi-Bred teaches that the VT domain may vary in length from 12 to 30 nt. Ex. 1006, 3:19–20, 98:19–23. Thus, the record supports Petitioner's argument that a POSA would understand Pioneer Hi-Bred to also disclose gRNAs having a guide sequence of at least twenty nucleotides and we credit Dr. Furneaux's testimony that a POSA would immediately envisage gRNAs with guide sequences of at least 20 nt in which every nucleotide has a 2′-O-methyl modification like exemplary sequence 68. Ex. 1003 ¶ 216–18. Accordingly, Petitioner has shown by a preponderance of the evidence that claims 18 and 32 are anticipated by Pioneer Hi-Bred.

F. Ground 2: Obviousness over Pioneer Hi-Bred and Krutzfeldt, Deleavey, Soutscheck, or Yoo

Petitioner contends that claims 5, 8–13, 18, 20, 21, 24–28, and 32 are obvious over Pioneer Hi-Bred in combination with any of Krutzfeldt, Deleavey, Soutschek, or Yoo. Pet. 47–67.

For claims 5, 8–13, 20, 21, and 24–28, Ground 2 relies on Pioneer Hi-Bred for the limitations of the independent claims and any one of the other references for their disclosure of modified nucleotides comprising a 2′-O-methyl nucleotide with one or more phosphorothioate modifications. Petitioner asserts that "[a] POSA would have been motivated to incorporate the 2′-O-methyl-3′phophorothioate modifications disclosed in Krutzfeldt, Deleavey, Soutschek, or Yoo's RNA molecules with the modified gRNAs taught in Pioneer Hi-Bred for multiple reasons." Pet. 52. Petitioner's reasoning includes that it was "well known to use such modified nucleotides in the targeting sequences of several types of RNA molecules" and the 2′-O-methyl-3′-phosphorothioate modifications in these secondary references "reflect the types of modifications to gRNA that are already taught and suggested in Pioneer Hi-Bred." *Id.* at 52–53. Petitioner further contends that a POSA would have been motivated to make the combination because the references teach that such modifications provide benefits such as improved stability and resistance towards nuclease degradation and increased editing efficiency. *Id.* at 54–56.

According to Petitioner, a POSA would have had a reasonable expectation of success because "it is undisputed that gRNAs with 2′-O-methyl and phosphorothioate modifications in the guide sequences are inherently functional for this purpose." Pet. 57. Petitioner also relies on Pioneer Hi-Bred's teaching that both types of modifications can be used in a gRNA. *Id.* at 57–58. Finally, Petitioner urges that the "use of 2′-O-methyl-3′-phosphorothioate modifications in the targeting sequences of various types of RNAs, such as

siRNA, AONs, and anti-miRNA, in the field of RNA therapeutics" was "widespread" and therefore a POSA would have anticipated that the same modifications "would not only have been functional, but also would have had . . . additional benefits" such as increasing stability and binding specificity. *Id.* at 58–59 (citing Ex. 1003 ¶¶ 267–79).

For claims 18 and 32, Ground 2 relies on same disclosure in Pioneer Hi-Bred noted above in Ground 1 and further cites Krutzfeldt as evidence that it was "known in other gene regulation applications that the entire RNA oligonucleotide can be comprised of 2′-O-methyl nucleotides" to support its argument that a gRNA with "at least twenty 2′-O-methyl nucleotides" would have been obvious. *Id.* at 64 (citing Ex. 1003 ¶ 299; Ex. 1009, 2886). Petitioner further asserts that "it was known that the guide sequence for Cas9 gRNAs is commonly 20 nucleotides long." *Id.* at 64–65 (citing Ex. 1013, 827). According to Petitioner,

> Given Pioneer Hi-Bred's express teachings to make gRNAs with guide sequences entirely composed of 2′-O-methyl nucleotides and to target sequences at least twenty nucleotides long, a POSA would have been motivated to make a gRNA with twenty 2′-O-methyl modifications in the guide sequence. A POSA would understand that using the same number of 2′-O-methyl modifications as the number of nucleotides in the target site produces recognizable and measurable effects in gene regulatory activity. Therefore, the number of 2′-O-methyl modifications, is a result-effective variable which, when changed, achieves a recognized result.

Id. at 65 (citing Ex. 1003 ¶¶ 301–04).

Petitioner's contentions are sufficiently supported by the record and persuasive. Beginning with claims 5, 8–13, 20, 21, and 24–28, Krutzfeldt, Deleavey, Soutschek, and Yoo each disclose chemically modified RNA sequences having both 2′-O-methyl and phosphorothioate modifications, including those comprising a "2′-O-methyl nucleotide with a 3′-phosphorothioate nucleotide" as recited in claim 5. Ex. 1009, 2886 (Table 1), 2889 (Fig. 5A); Ex. 1007, 943 (Fig. 4), 948; Ex. 1012, 173, 177; Ex. 1011, 2008. Moreover, as Petitioner points out, these references teach that such modifications, particularly when made to nucleotides near the end of an RNA molecule, provide a number of benefits including increased resistance to nuclease degradation. Ex. 1009, 2889; Ex. 1007, 937; Ex. 1012, 173; Ex. 1011, 2008. This dovetails with Pioneer Hi-Bred's teaching that such modifications decrease unwanted nuclease degradation in a guide polynucleotide. *See* Ex. 1006, 107. Accordingly, the combination of Pioneer Hi-Bred with any of Krutzfeldt, Deleavey, Soutschek, or Yoo teaches all of the limitations of these claims and the record supports Petitioner's rationale for combining them.

Regarding claims 18 and 32, we agree with Petitioner that Krutzfeldt teaches anti-miRNAs having 20 or more nucleotides wherein every nucleotide in the sequence has a 2′-O-methyl modification. Ex. 1009, 2886 (Table 1 using lower case letters to indicate 2′-O-methyl-modified nucleotides). Krutzfeldt refers to these as "antagomirs," which it describes as "RNA-like oligonucleotides that harbor various modifications for RNAse protection and pharmacologic properties such as enhanced tissue and cellular uptake." *Id.* at 2885;

see also id. at 2889 (teaching these modifications protect against exonucleases and endonucleases). Moreover, Krutzfeldt teaches that antagomirs having 2′-O-methyl modifications at every nucleotide and numerous phosphorothioate modifications can still form a duplex with the complementary miRNA. Ex. 1009, 2890-91; *see also* Ex. 1007, 948 (citing Krutzfeldt as showing that such antagomirs are "a successful strategy for targeting miRNAs"). Dr. Furneaux offers testimony, which we credit, that this fact supports that a POSA would have reasonably expected "that a guide RNA with the same modification in its targeting sequence (*i.e.*, the guide sequence) would bind to a complementary region of a polynucleotide in vivo." *Id.* ¶¶ 274-77.

Accordingly, the disclosure in Krutzfeldt adds to the existing teachings in Pioneer Hi-Bred that 2′-O-methyl modifications can be made to every nucleotide in the guide sequence. Ex. 1006, 109 (Table 8 sequence 68), 106:13–25. Given that Pioneer Hi-Bred teaches that the length of the guide sequence is variable and can be 20 or more nt long depending on the target, we agree that these teachings support Petitioner's obviousness argument. Ex. 1006, 32:1–3; *see also id.* at 3:19–20, 98:19–23. That is, even if a POSA would not have immediately envisaged a gRNA having at least 20 2′-O-methyl modifications in its guide sequence from the disclosure in Pioneer Hi-Bred, they would have considered such a gRNA to be the obvious result of routine optimization to a slightly longer guide sequence having at least 20 nt. Ex. 1003 ¶¶ 301–03.

Patent Owner raises several arguments in its Response some of which were already addressed in our analysis of Ground 1. For example, Patent Owner urges that all of Petitioner's obviousness grounds fail

because they rely exclusively on Pioneer Hi-Bred for the claimed functionality requirements. *See* Resp. 50–51. However, as explained above, Pioneer Hi-Bred discloses synthetic gRNA and crRNA molecules having the recited "gRNA functionality" and the anticipating disclosure is enabled as to both Patent Owner's composition and method claims. Accordingly, Patent Owner's functionality arguments are unavailing.

Patent Owner also challenges Petitioner's motivation to combine and reasonable expectation of success showing and offers evidence of objective indicia of non-obviousness. *See* Resp. 47–50, 51–63. We address these issues in turn.[19]

1. Whether there would have been a motivation to combine and reasonable expectation of success

Patent Owner argues that Petitioner "relies on the claims as a roadmap" and "regardless of the number of or variety of modifications in a challenged claim" the alleged motivation to combine is always the same, *i.e.*, that Pioneer Hi-Bred envisions other combinations and "the modifications in the prior art reference would enhance the protection against degradation." Resp. 51–52. According to Patent Owner, "protecting against degradation is a function the disclosed modifications in Pioneer Hi-Bred were already providing so a POSA would have no need or motivation to look elsewhere to an already fulfilled need." *Id.* at 52.

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[19] These are global arguments Patent Owner collectively argues for all of the obviousness grounds. Our analysis below considers the claims in all of those grounds.

Patent Owner's argument is unavailing for several reasons. First, at least with respect to claims 5, 8–13, 18, 20, 21, 24–28, and 32 Pioneer Hi-Bred teaches the same modifications (*i.e.*, 2′-O-methyl sugar and phosphorothioate linkage modifications) taught by the secondary references in Ground 2. Thus, the choice between Pioneer Hi-Bred's modifications and those taught in the Krutzfeldt, Delevey, Soutschek, and Yoo that Patent Owner's argument envisions is an illusory one.

Second, even if the combination involved the use of modifications not already taught in Pioneer Hi-Bred,[20] it is well-established that substitution of one element for another known to provide the same benefit may provide a rationale for combining references. *See KSR*, 550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."). So too, "the normal desire to improve upon what is already generally known" may provide a reason to employ additional types of modifications as in claims 6, 7, 22, and 23; to combine modifications as in claims 5, 8–13, 20, 21, and 24–28; or to use more of the same modifications as in claims 18 and 32, where such strategies had been shown to prevent degradation in prior art RNA systems. *Jazz*

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[20] This is the case for the PACE and thioPACE modifications taught by Threlfall and Delevey in Ground 3. Pioneer Hi-Bred does not teach those modifications, but Petitioner asserts that it would have been obvious to use them in Pioneer Hi-Bred's synthetic gRNAs because "they would provide the same benefits to gRNAs that Pioneer Hi-Bred seeks to achieve." Pet. 70.

Pharms., Inc. v. Amneal Pharms., LLC, 895 F.3d 1347, 1368 (Fed. Cir. 2018).

Third, along with protecting against degradation, Petitioner points to teachings in these references that their chemical modifications provide other benefits, *e.g.*, increased specificity, cell penetration or tracking, that would have motivated a POSA to employ such modifications in Pioneer Hi-Bred's synthetic gRNAs. *See* Pet. 51 (referring to Yoo's teaching regarding "reduced non-specific effects"); 69–70 (referring to Threlfall's teaching regarding "greater efficacy and ability to penetrate cells" and "increased cellular uptake"); 85–86 (citing references showing that "attaching fluorophores to biological molecules . . . was well-known and commonly done, *e.g.*, for purposes of tracking"); Ex. 1003 ¶¶ 267–72 (Ground 2); 323– 25 (Ground 3); 391–93 (Ground 6). Moreover, Dr. Furneaux provides testimony explaining why POSA would understand that the various benefits these modifications provide to be desirable within the context of a CRISPR/Cas system. Ex. 1003 ¶¶ 261–62 (Ground 2); 324–25 (Ground 3); 394 (Ground 6). This testimony is credible and further supports Petitioner's reasoning for its obviousness combinations.

Patent Owner also argues there would have been no reasonable expectation of success in making the chemical modifications in Petitioner's obviousness combinations. *See* Resp. 52–63. According to Patent Owner, "[w]hether a particular combination of chemical modifications in at [sic] particular nucleotide positions on the give [sic] would adversely impact functionality was entirely unpredictable at the time Agilent started its work, and there was no guarantee of success that it would make the discoveries that led to the claimed

inventions." *Id.* at 52–53. Patent Owner explains that "CRISPR was a nascent technology in 2014, and the structure-function relationships among the gRNA and Cas protein were still being investigated." *Id.* at 54–59 (citing references). Therefore, urges Patent Owner, "a POSA would know that the result of modifications would be unpredictable and would need to be tested." *Id.* at 55.

Regarding Petitioner's reliance on modifications known to be successful in prior art RNA systems, Patent Owner contends that a POSA would not have regarded such systems as "'mechanistically analogous' such that modifications that maintained functionality in other systems would work in the CRISPR-Cas system." Resp. 59–60 (citing Ex. 2025 ¶¶ 132–47). Patent Owner argues that Dr. Furneaux's testimony that "prior art siRNA, miRNA, AON" systems are "mechanistically analogous" to CRISPR/Cas systems is flawed because "notably absent from his [declaration] *is any description of the mechanisms of the systems that are allegedly 'mechanistically analogous.'*" *Id.* at 61–62 (citing Ex. 1003 ¶¶ 43–49, 61– 78). Patent Owner urges that Petitioner and Dr. Furneaux's "entire 'mechanistically analogous' analysis reduces simply to noting that RNA, which is common to all these systems, faces the same problems, such as potential degradation." *Id.* at 62.

Finally, Patent Owner argues that "Agilent's own process confirms that arriving at the claimed combinations was anything but predictable or that a POSA would have had a reasonable likelihood of success." Resp. 63 (referring to Dr. Sampson's testimony). According to Patent Owner, this was "an iterative process as to which there was no assurance of success

via which Agilent was able to test its various modified guides across a series of assays sufficient to appraise the public on how to improve CRISPR gRNAs." *Id.*

In reply, Petitioner argues that Patent Owner's arguments and Dr. Marshall's testimony regarding the complexity of the CRISPR/Cas system and mechanistic differences with prior art systems are "theoretical concerns . . . that were never actually expressed in the literature." Reply 23–25. According to Petitioner, by asserting that these "speculative and contrived concerns can defeat obviousness, Patent Owner effectively applies a heightened standard that goes beyond reasonable expectation of success." *Id.* at 25. Instead, "the law is clear that 'the expectation of success need only be reasonable, not absolute.'" *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007)).

Petitioner urges that the record supports such a finding here because;

> [r]esearchers had been using the claimed chemical modifications in other relevant gene regulation contexts long before the conception of CRISPR as a gene editing tool. Then, when Doudna and co-workers published CRISPR for gene editing,[21] multiple researchers *immediately* proposed to use such chemical modifications with gRNAs,

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[21] "In 2012, Jennifer Doudna and Emmanuelle Charpentier discovered [and published] that CRISPR associated enzyme (more specifically, the Cas9 protein) could be programmed to target nearly any portion of a genome using lab-made guide RNA sequences." Ex. 2025 ¶ 77. Their work was published in June 2012. Resp. 53; Reply 20.

> including the specific claimed 2′-O-methyl and phosphorothioate modifications.

Reply 26 (citing Pet. 12, 81; Ex. 1003 ¶¶ 71–72; Ex. 1061, 112:1–5, 113:3– 8, 116:5–10, 211:14–212:8). According to Petitioner, "[i]f there were no reasonable expectation of success, it would not be the case that a chorus of researchers would so quickly propose using chemical modifications with gRNAs while none would warn against it." *Id.* at 26. Petitioner also points to evidence that prior art "studies ha[d] shown that modifications at the 5′ or 3′-ends of gRNAs do not inhibit Cas9 function" and "crystal structure analysis of Cas9 show[ed] that it tolerates a large number of mutations to the gRNA, including multiple modifications to single nucleotides." *Id.* at 27 (citing Ex. 1003 ¶¶ 78; Ex. 1026, 941; Ex. 1033, 279; Ex. 1034, 235).

Petitioner's arguments and evidence are persuasive. As Petitioner points out, by December 2014, several studies had shown that the CRISPR/Cas system could successfully tolerate modifications. Ex. 1026, 941; Ex. 1033, 279. While these studies describe different types of modifications[22] than those in the challenged claims, such evidence nevertheless supports Dr. Furneaux's testimony that a POSA would have expected that the recited chemical modifications could be made to a gRNA while preserving the Cas enzyme's

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[22] As Patent Owner points out, the "mutations" referred to in Exhibit 1026 are changes to the RNA bases, as opposed to modifications to the sugar or phosphodiester linkages in the backbone. Sur-reply 12 (citing Ex. 1026, 942–43 (Fig. 4D)). Exhibit 1033 describes truncation, *i.e.*, removal of nucleotides, within the gRNA.

gene editing function. Ex. 1003 ¶¶ 78, 273–79, 301-03, 326-28, 395.

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. Ex. 1003 ¶ 71 (identifying examples of patent publications with filing dates prior to December 2014 describing 2′-O-methyl and phosphorothioate modifications to gRNA); Ex. 1019 ¶¶ 193–96, claim 171; Ex. 1020 ¶¶ 570–71, 1657; Ex. 1022 ¶ 260; Ex. 1023 ¶ 362. Patent Owner's expert, Dr. Marshall, conceded as much on cross-examination. Ex. 1061, 113:3–8, 116:5–10, 211:14–213:8. The fact that multiple groups of researchers independently suggested the same types of gRNA modifications recited in the challenged claims evidences that a POSA would have had a reasonable expectation those modifications could be successfully employed in a CRISPR/Cas system. Ex. 1059 ¶ 18; *see also Regents of the Univ. of California v. Broad Institute, Inc.*, 903 F.3d 1286, 1295 (Fed. Cir. 2018) (explaining that "simultaneous invention" may bear on the obviousness analysis because "it is evidence of the level of skill in the art"). Moreover, while Petitioner points to multiple references suggesting such modifications to gRNA, neither Patent Owner nor Dr. Marshall identify any reference expressing doubt that such modifications could be successfully implemented in a CRISPR/Cas system. This contrast undermines Patent Owner's argument that a POSA

would not have reasonably expected the prior art modifications to work in a CRISPR/Cas system.

Nevertheless, Patent Owner maintains "there was no guarantee of success" and therefore testing was required to confirm that such modifications would work. *See* Resp. 51–52. The problem with that argument is that "only a reasonable expectation of success, not a guarantee, is needed" to show obviousness. *Pfizer*, 480 F.3d at 1364 (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). The facts of the *Pfizer* case are instructive. There, the lower court had concluded that there would have been no expectation of success in making the claimed drug salt "because there was no reliable way to predict the influence of a particular salt species on the active part of the compound." *Id.* The Federal Circuit reversed, explaining that while it accepted the lower court's finding that "it was generally unpredictable as to whether a particular salt would form and what its exact properties would be," the "case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art." The Federal Circuit observed that

> a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt—including those specifically listed in the [prior art reference]—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute.

Id.

The current proceeding presents analogous facts. We do not doubt that there would have been some degree of unpredictability because, as Patent Owner points out, the interactions in a CRISPR/Cas system are complex and that there are mechanistic differences from the prior art RNA systems in Petitioner's secondary references. *See* Resp. 53–63. However, Petitioner has shown that a POSA would have understood that these systems share features in common with CRISPR/Cas, including that their efficacy and functionality is limited by the fact that the RNA used in them is subject to unwanted degradation. *See, e.g.*, Ex. 1003 ¶¶ 65–66, 70–72, 261–62, 323–25. Thus, the fact that the claimed modifications reduced degradation, while maintaining functionality, in these prior art systems supports a finding that the same modifications could also be successful in a CRISPR/Cas system. To the extent Dr. Marshall testifies that the successful use of these modifications in prior art systems does not evidence at least a reasonable expectation they could also be successfully used in a CRISPR/Cas system (*see, e.g.*, Ex. 2025 ¶¶ 132, 147, 157), we credit Dr. Furneaux's testimony (Ex. 1003 ¶¶ 61–80, 263–79, 303 (Ground 2), 326–28 (Ground 3), 395 (Ground 6)) and the evidence noted above over Dr. Marshall's testimony on this issue.

For these reasons, Petitioner has sufficiently shown that a POSA would have had both a motivation for and reasonable expectation of success for its obviousness combinations.

2. Consideration of objective indicia of nonobviousness

Patent Owner argues that "[t]here is overwhelming evidence of secondary consideration of nonobviousness, particularly as it relates to the question about [sic] industry praise, copying, and commercial success." Resp. 47–48. Patent Owner's objective indicia arguments center on the Hendel paper (Ex. 1005). *See id.* at 48–50. Patent Owner explains that "[t]he Agilent inventions" were "first made public" in this paper, which was coauthored with researchers at Stanford. *Id.* at 19. According to Patent Owner, "publications citing the Hendel paper have called Agilent's work 'pioneering,' 'seminal,' and 'a major contribution.'" *Id.* at 48 (quoting Ex. 2050, 4; Ex. 2028, 681). Patent Owner also offers evidence that the Hendel paper has been cited almost 900 times since its publication in 2015, which is in the 94th, 98th, or 99th percentile according to various indices of "tracked articles of a similar age." *Id.* at 20, 47 (citing Ex. 2025 ¶ 57; Ex. 2032; Ex. 2056).

Regarding copying and commercial success, Patent Owner points to evidence of statements by Petitioner that it contends "tout the benefits of Agilent's inventions" and suggest that the reason Petitioner uses chemically modified gRNA in its products is the study published in the Hendel paper. Resp. 20, 48–49 (quoting statements by Synthego's Head of Synthetic Biology in Ex. 2033, 3:05–4:45[23] and citing Ex. 2034, 6). Patent Owner also asserts that "[t]here is . . . no

[23] Exhibit 2033 is a video. The pinpoint citation refers to the time in the video at which these statements occur, *i.e.*, beginning at 3 minutes and 5 seconds.

doubt that Petitioner Synthego has been successful" as result of using Patent Owner's inventions. *Id.* at 50.

In its Reply, Petitioner urges that the fact that multiple researchers "*immediately* proposed to use chemical modifications with gRNAs" after the initial publication of CRISPR for gene-editing undermines Patent Owner's objective indicia arguments. *See* Reply 20–22. Moreover, Petitioner asserts that the evidence of praise for the Hendel paper is "surprisingly thin" with one of the two references Patent Owner cites praising it as "'pioneering'" having been "co-authored by Hendel himself." *Id.* at 21 (referring to Ex. 2050). According to Petitioner,

> Patent Owner's scientists may well have been the first to synthesize some chemically modified gRNAs and do some testing experiments, and they may have been the first to report such work in an article that has been frequently cited over the years. But Patent Owner points to no evidence that this frequent citation stems from a belief among scientists that the authors had done something inventive as opposed to merely generating confirmatory data.

Id. at 22.

Petitioner further contends that it did not copy the Hendel paper, but "simply uses the same tried and true techniques that had long been known in the art." According to Petitioner, the claimed chemical modifications and the idea to use them in gRNA were already in the prior art therefore "such modifications lack the required nexus for secondary considerations." Reply 23 (citing *In re Huai-Hung Kao*, 639 F.3d 1057,

1068 (Fed. Cir. 2011)). Finally, Petitioner asserts that the evidence of objective indicia of nonobviousness "simply cannot overcome" the strength of the other evidence demonstrating obviousness. *Id.* (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)).

In its Sur-reply, Patent Owner argues that the data in the Specification presents unexpected results. Sur-reply 21–22. Patent Owner further contends that Petitioner and its experts "suffer from gross credibility problems, ignoring Synthego's admissions of non-obviousness" and "contradicting Synthego's own praise for the Hendel paper" as a "'landmark'" publication. *Id.* at 22–23 (quoting Ex. 2033, 3:05–4:45).

We assess the parties' objective indicia arguments below and then weigh any evidence of such with the other evidence of record to reach a conclusion on Petitioner's obviousness grounds.

Beginning with commercial success, we find Patent Owner's evidence and arguments unavailing. First, Patent Owner cites no evidence to support its factual assertions regarding Synthego's success. *See* Resp. 50 (asserting without citation to evidence of record that Synthego "has raised almost $500 million in funding and recently announced the opening of a 20,000 square foot GMP facility to add to its capacity."). Nor has Patent Owner identified sales or profits stemming either from its own products or any allegedly infringing products to support its allegations of commercial success. Second, even if there was evidence of commercial success, we agree with Petitioner that Patent Owner has not shown that such success is attributable to its use of the claimed chemical modifications as opposed to other factors. *See* Reply

23; *see also* Ex. 1059 ¶ 81 (identifying other business factors to which Petitioner contributes its market performance). Accordingly, Patent Owner's commercial success arguments carry no weight.

Patent Owner's industry praise and copying arguments fare somewhat better. The record supports that the Hendel paper has been heavily cited and that Petitioner's own head of synthetic biology referred to it as a "landmark paper" in a video presentation. Ex. 2025 ¶ 57; Ex. 2033, 3:05–4:45; *see also* Ex. 2034, 6 (stating that the Hendel paper "study set the bar for chemically modified guide RNAs as the method of choice for CRISPR-Cas9 in primary human immune cells"). In the same presentation, Petitioner's executive states that the study in the Hendel paper is the reason Petitioner uses "single guide RNAs in a chemically modified format." Ex. 2033, 3:05–4:45. As such, we find that Patent Owner has presented some evidence of industry praise and copying related to the Hendel paper.

There are, however, significant questions regarding whether there is a nexus between the Hendel paper and any novel aspects of the challenged claims that limit the probative value of this evidence. "Before secondary considerations can carry the day" the proponent of that evidence must establish a nexus with the patent claims at issue. *Huai-Hung Kao*, 639 F.3d at 1068. "Where the secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus." *Id.* In this case, the use of 2′-O-methyl and phosphorothioate modifications, as well as other types of modifications to the sugar and internucleotide linkage, in a gRNA was already taught in the prior

art. Ex. 1003 ¶ 71 (citing earlier-filed applications from other researchers suggesting the use of such modifications in gRNA), ¶ 394 (citing earlier and contemporaneously-filed applications from other researchers suggesting the use of a fluorophore at the 5′ end of a gRNA); Ex. 1006, 27:3–18, 107–113. This suggests that any praise or copying of the Hendel paper may actually result from its use of these prior art ideas as opposed to any novel aspect of the challenged claims.

In addition, the Hendel paper describes tests of "[c]hemical modifications comprising 2′-O-methyl (M), 2′-O-methyl 3′phosphorothioate (MS), or 2′-O-methyl 3′thioPACE (MSP) . . . at three terminal nucleotides at both the 5′ and 3′ ends." Ex. 1005, 1. The MS modifications correspond to the modifications recited in the claims in Ground 2 and the MSP modifications are within the scope of the modifications recited in the claims in Ground 3. But it is unclear whether Petitioner's evidence of praise for the Hendel paper results from the MS and MSP modifications in those claims as opposed to other aspects of that study, *e.g.*, the use of M modifications alone.[24] Similarly, Patent Owner's copying evidence suggests that Petitioner uses chemically modified gRNAs, but does not show that

[24] According to Patent Owner, out of the 895 citations to the Hendel paper only a fraction of those include terms relating to the particular modifications in recited in the claims challenged in Grounds 2 and 3. Resp. 47 (noting that only 276 of the citing papers include the term "phosphorothioate" and only 67 include the term "thioPACE"). This diminishes the argument that there is a nexus between the particular modifications in those dependent claims and the praise that may be inferred from the fact that numerous authors have cited the Hendel paper.

those chemically modified gRNAs have the particular modifications recited in the Ground 2, Ground 3, or Ground 6 claims as opposed to other modifications. For these reasons, we give some weight to the evidence of industry praise and copying, however that weight is diminished by the tenuous nexus to the challenged claims.

Moreover, the fact that multiple research groups, nearly simultaneously proposed the use of chemically modified gRNA is itself objective evidence that the challenged claims would have been obvious. *See Regents*, 903 F.3d at 1295 (explaining that "simultaneous invention" is "objective evidence that person of ordinary skill in the art understood the problem and a solution to that problem"); *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305–6 (Fed. Cir. 2010) ("Independently made, simultaneous inventions made within a comparatively short space of time are persuasive evidence that a claimed apparatus was the product of ordinary mechanical or engineering skill.") (internal quotations omitted). As explained above, we credit Petitioner's showing that a POSA would have reasonably expected that such modifications could be successfully made to the gRNA in a CRISPR/Cas system. Thus, the fact that multiple researchers simultaneously proposed making 2′-O-methyl, phosphorothioate, fluorophore, and other modifications to gRNA close in time to the initial publication describing the CRISPR/Cas system for gene editing suggests that this was an obvious solution to a known problem.

Finally, the unexpected results arguments in Patent Owner's Sur-reply are unavailing. Sur-reply 21–22. As an initial matter, these arguments were not presented in the Response such that Petitioner could

address them in the Reply. For this reason, Patent Owner's unexpected results argument is untimely and has been waived. Even so, we disagree with Patent Owner's assertion that Petitioner "did not rebut the Patent's explicit discussion of the 'surprising' results obtained or why they were unpredictable." *Id.* (citing Ex. 1001, 3:34–36, 66:27–32, 66:61–67:6). It is Patent Owner as the proponent of this evidence who has the burden to show a nexus between its objective indicia evidence and the merits of the claimed invention. *Kao*, 639 F.3d 1057, 1068; *see also In re* Klosak, 455 F.2d 1077, 1088 (CCPA 1972) ("[T]he burden of showing unexpected results rests on he who asserts them."). The threadbare assertion of allegedly unexpected results in the Sur-reply does not do so. Moreover, Petitioner points out that the results in the Specification show that almost all of the chemically modified gRNAs Patent Owner tested exhibited cleavage activity. Reply 13–14, 17, Ex. 1059 ¶ 47 ("97% of the experiments that Agilent ran showed at least some cleavage activity"). This would seem to be exactly the result a POSA would expect in view of the teachings in Pioneer Hi-Bred and the other references cited in the Petition. For these reasons, Patent Owner's unexpected results arguments carry no weight.

3. Conclusion for Ground 2

Considering the totality of the evidence regarding claims 5, 8–13, 18, 20, 21, 24–28, and 32, including objective indicia of non-obviousness, we determine that Petitioner has established, by a preponderance of the evidence, that these claims would have been obvious over the combination of Pioneer Hi-Bred with any of Krutzfeldt, Deleavey, Soutschek, or Yoo. Indeed, even if Patent Owner had established a suffi-

cient nexus between these claims and its industry praise and copying evidence such that it was entitled to more weight, we would reach the same conclusion given the relative strength of Petitioner's showing. *See, e.g.*, *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1329 (Fed. Cir. 2017) (weighing evidence of unexpected results and copying together with other evidence, including "strong evidence of a motivation to make the claimed combination" in the cited prior art, to conclude that combination was obvious); *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1247 (Fed. Cir. 2010) (listing cases where objective indicia evidence did not overcome a strong case of obviousness).

G. Ground 3: Obviousness over Pioneer Hi-Bred and Threlfall or Deleavey

Petitioner contends claims 6, 7, 22, and 23 are obvious over Pioneer Hi-Bred in combination with either Threlfall or Deleavey. Pet. 67–73. More specifically, Ground 3 relies 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 6, 7, 22, and 23. *Id.*

Petitioner asserts that a POSA would have been motivated to use the PACE and thioPACE modifications taught in Threlfall and Deleavey in Pioneer Hi-Bred's gRNA and crRNA molecules "because they would provide the same benefits to gRNAs that Pioneer Hi-Bred seeks to achieve," including "[r]esistance to cellular degradation and increased cellular permeability" and

"increased binding affinity." Pet. 70–73 (citing Ex. 1003 ¶¶ 324, 330–33). In addition, Petitioner contends that "Threlfall reports successful cellular uptake of RNAs" with these modifications and therefore "a POSA would have understood that combining and synthesizing gRNAs with" these modifications in the guide sequences of gRNAs "would result in similarly increased cellular uptake of these modified gRNAs." *Id.* at 70; *see also id.* at 73 (urging that a POSA would have understood that PACE and thioPACE "modifications in the targeting sequence would have had similar effects as noted in Threlfall and Deleavey").

According to Petitioner, a POSA would have had a reasonable expectation of success because "RNAs including such modifications had been previously synthesized in Threlfall" and "such synthesis methods were commercially available." Pet. 71 (citing Ex. 1003 ¶ 326). Moreover, Petitioner contends that because of the "previous widespread use" of such modifications "in various types of RNA molecules in the field of gene regulation, a POSA would have reasonably expected" gRNAs containing such modifications "to be functional with the gRNA/Cas system." *Id.* 71–72 (citing Ex. 1003 ¶ 289).

Petitioner's contentions are sufficiently supported by the record and persuasive. As explained above, Pioneer Hi-Bred discloses all of the limitations of the independent and other claims from which claims 6, 7, 22, and 23 depend. Regarding the additional limitations in claims 6, 7, 22, and 23, Threlfall and Deleavey teach that PACE and thioPACE modifications to RNA enhance resistance to degradation and are tolerated in prior art systems. Ex. 1007, 8; Ex. 1010, 1–2. Threlfall further teaches the combination of such

modifications with 2′-O-methyl modified nucleotides at the 3′ and 5′ ends of an RNA molecule. Ex. 1010, 2 (Table 1). Thus, the combination of references articulated in the Petition teaches or suggests all of the limitations of claims 6, 7, 22, and 23.

Moreover, the record supports Petitioner's rationale for combining the references. The teachings in Threlfall and Deleavey support Dr. Furneaux's testimony (Ex. 1003 ¶¶ 320–25, 332–34) regarding the benefits, *e.g.*, increased resistance to degradation and enhanced cellular uptake, that would have motivated a POSA to use such modifications in Pioneer Hi-Bred's gRNA. *See, e.g.*, Ex. 1007, 8 (teaching PACE modified RNA exhibits "enhanced nuclease resistance); Ex. 1010, 7 (teaching "cellular uptake was notably more efficient" with 2′-O-methyl thioPACE modified nucleotides). As Petitioner points out, these are the among the same benefits that Pioneer Hi-Bred suggests chemical modification of gRNA can achieve. *See* Ex. 1006, 107. As explained above, Patent Owner's arguments against Petitioner's showing for combining the references are unavailing. *See supra* § III.F.1.

Petitioner has also sufficiently shown that a POSA would reasonably expect PACE and thioPACE modifications to gRNA in a CRISPR/Cas system would be successful. As explained above, we credit the supporting testimony of Dr. Furneaux and other evidence cited in the Petition over the competing testimony of Dr. Marshall in this regard. *See supra* § III.F.1.

Patent Owner offers the same objective indicia evidence discussed in § III.F.2 above for the claims in Ground 3. As explained there, the weight of this evidence is limited because Patent Owner has not estab-

lished a sufficient nexus. Considering the totality of the evidence, including objective indicia of non-obviousness, we determine that Petitioner has established, by a preponderance of the evidence, that claims 8, 11, 16, 19, and 26 would have been obvious over the combination of Pioneer Hi-Bred and Threlfall or Deleavey.[25]

H. Ground 4: Obviousness of claims 3 and 4 over Pioneer Hi-Bred in View of the Skill of a POSA

To the extent they are not anticipated, Petitioner argues claims 3 and 4 would have been obvious over Pioneer Hi-Bred in combination with the knowledge of a POSA. Pet. 74–77. More specifically, Petitioner offers evidence and argument that each of the additional limitations in these claims, *i.e.*, a set or library comprising two or more synthetic gRNA (claim 3), and a sgRNA (claim 4), was well known in the art and would have been obvious to implement in view of Pioneer Hi-Bred's disclosure. *Id.* (citing Ex. 1003 ¶¶ 338–49).

Patent Owner advances the global arguments addressed above with respect to Petitioner's other grounds, but does not specifically dispute that the additional limitations in claims 3 and 4 would have been known to a POSA. *See* Resp. 66.

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[25] Even if Patent Owner had established a sufficient nexus between these claims and its industry praise and copying evidence such that it was entitled to more weight, we would reach the same conclusion given the relative strength of Petitioner's showing.

Petitioner's contentions are sufficiently supported by the record and persuasive. As explained above, Pioneer Hi-Bred anticipates claims 3 and 4 because it discloses the additional limitations in these claims and a POSA would have immediately envisioned embodiments meeting the same. To the extent one might argue otherwise, Petitioner has shown that claims 3 and 4 would have been obvious because the additional elements they recite were well known to a POSA and taught in Pioneer Hi-Bred. In this regard, we credit Petitioner's contentions and the supporting the testimony of Dr. Furneaux (*i.e.*, Ex. 1003 ¶¶ 338–49). Thus, considering the totality of the evidence, including objective indicia of non-obviousness, we determine that Petitioner has established, by a preponderance of the evidence, that claims 3 and 4 would have been obvious over Pioneer Hi-Bred in view of the skill of a POSA.

I. Ground 5: Obviousness of claims 5, 8–13, 20, 21, and 24–28 over Pioneer Hi-Bred in View of the Skill of a POSA

Petitioner further asserts that claims 5, 8–13, 20, 21, and 24–28 would have been obvious over Pioneer Hi-Bred in view of the skill of a POSA. Pet. 77–85.

Having already determined that these claims are anticipated for the reasons in Ground 1 and obvious for the reasons in Ground 2, we need not decide Petitioner's additional challenge to these claims in Ground 5. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding that a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App'x 984, 990 (Fed. Cir. 2020) (nonprece-

dential) ("We agree that the Board need not address [alternative grounds] that are not necessary to the resolution of the proceeding.").

J. Ground 6: Obviousness of claims 14 and 29 over Pioneer Hi-Bred in View of the Skill of a POSA

To the extent they are not anticipated, Petitioner argues claims 14 and 19 would have been obvious over Pioneer Hi-Bred in combination with the knowledge of a POSA. Pet. 85–86. More specifically, Petitioner offers evidence and argument that the additional limitations in these claims, *i.e.*, a fluorophore at a 5′ end, was well known in the art and would have been obvious to implement in view of Pioneer Hi-Bred's disclosure. *Id.* (citing Ex. 1003 ¶¶ 391–95).

Patent Owner advances the global arguments addressed above with respect to Petitioner's other grounds, but does not specifically dispute that the additional limitations in claims 14 and 29 would have been known to a POSA. *See* Resp. 66–67.

Petitioner's contentions are sufficiently supported by the record and persuasive. As explained above, Pioneer Hi-Bred anticipates claims 14 and 29 because it discloses the addition of a fluorophore to the VT domain and a POSA would have understood that the VT domain may be at either the 3′ or 5′ end. *Supra* § III.E.vi. Thus, a POSA would have immediately envisioned embodiments meeting the same. To the extent one might argue otherwise, Petitioner has shown that claims 14 and 29 would have been obvious because the additional elements they recite were well known to a POSA and taught in Pioneer Hi-Bred. In this regard, we credit Petitioner's contentions and the

supporting the testimony of Dr. Furneaux (*i.e.*, Ex. 1003 ¶¶ 391–95). Thus, considering the totality of the evidence, including objective indicia of non-obviousness, we determine that Petitioner has established, by a preponderance of the evidence, that claims 14 and 29 would have been obvious over Pioneer Hi-Bred in view of the skill of a POSA.

IV. Motions to Seal

The parties jointly request that Exhibits 1053–1058 and portions of Petitioner's Reply discussing those exhibits be sealed. Paper 29 ("Joint Motion"). These exhibits "are excerpts of the deposition of Dr. Daniel Ryan, a named inventor on the . . . '034 [patent], along with certain exhibits to his deposition transcript." *Id.* at 1–2. "Patent Owner avers that the documents from the Ryan deposition provide information on proprietary research, as well as confidential information about Patent Owner's business practices." *Id.* at 3. The parties also represent that the district court in a related proceeding "explicitly ruled that the Ryan transcript and exhibits that are the subject of this Motion to Seal have been properly designated as confidential." *Id.* (quotations omitted).

Along with their motion, the parties submit a proposed protective order. *Id.* at App. A. This order follows the guidelines in Appendix B of the Trial Practice Guide,[26] but modifies the highly confidential designation "by eliminating access by 'persons who are named parties to the proceeding,' 'party represent-

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[26] Consolidated Trial Practice Guide (Nov. 2019), 64, available at https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf ("TPG").

atives,' and 'in-house counsel.'" *Id.* at 4–5. The parties represent that this modification aligns the designations in this proceeding with those that have been entered in the related district court proceeding and therefore "will aid in the efficient administration of justice, and will be more straightforward and expedient than preparing a 'two level' protective order for" the parties' IPR proceedings. *Id.* at 5.

A party may move to seal confidential information including, *e.g.*, confidential research, development, or commercial information. TPG 19; 37 C.F.R. § 42.54. It is the movant's burden to show good cause for sealing such information, and we balance the party's asserted need for confidentiality with the strong public interest in open proceedings. *Argentum Pharms. LLC v. Alcon Research, Ltd.*, IPR2017-01053, Paper 27 at 4 (PTAB Jan. 19, 2018) (informative).

The parties provide a sufficient explanation and have shown good cause for sealing exhibits 1053–1058 and the related portions of Petitioner's Reply. Moreover, Petitioner provides a public version of its Reply (Paper 31) with redactions limited to a few paragraphs discussing these exhibits so the record may remain clear and reasonably open. We also determine that the proposed protective order with the agreed modification limiting access to outside counsel and the parties' experts is appropriate under these circumstances.

Patent Owner additionally moves to seal a paragraph in its Sur-reply, "which discusses documents as to which sealing was jointly requested" in the Joint Motion. Paper 34. Petitioner provides a public version of its Sur-reply (Paper 35) with redactions limited to

a single paragraph. We find that Patent Owner has shown good cause for granting its motion.

Accordingly, Exhibits 1053–1058, Petitioner Reply (Paper 30), and Patent Owner's Sur-reply (Paper 33) are sealed, and the protective order, Appendix A to Paper 29, is entered.

V. Conclusion[27]

Petitioner has shown, by a preponderance of the evidence, that claims 1–33 of the '034 patent are unpatentable.

Claims	35 U.S.C. §	Reference(s) /Basis	Claims Shown Unpatentable
1-5, 8-21, 24-33	102	Pioneer Hi-Bred	1-5, 8-21, 24-33
5, 8-13, 18, 20, 21, 24-28, 32	103	Pioneer Hi-Bred, Krutzfeldgt, Deleavey, Soutschek, Yoo	5, 8-13, 18, 20, 21, 24-28, 32

[27] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this Decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), 42.8(b)(2).

6, 7, 22, 23	103	Pioneer Hi-Bred, Threlfall, Deleavey	6, 7, 22, 23
3, 4	103	Pioneer Hi-Bred	3, 4
5, 8–13, 20, 21, 24–28[28]	103	Pioneer Hi-Bred	
14, 29	103	Pioneer Hi-Bred	14, 29
Overall Outcome			1–33

VI. Order

Accordingly, it is:

ORDERED that Petitioner has shown that claims 1–33 of U.S. Patent 10,900,034 B2 are unpatentable;

FURTHER ORDERED that the Joint Motion to Seal (Paper 29) and Patent Owner's Motion to Seal Portions of the Sur-reply (Paper 33) are *granted*; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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[28] As explained above, we do not reach this ground.