No. 25-570

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

BRIEF IN OPPOSITION

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QUESTIONS PRESENTED

Petitioner frames the questions presented as:

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?

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INTRODUCTION

The CRISPR-Cas system revolutionized the field of gene editing when it was discovered in 2012. But the invalidated Agilent patents are *not* directed to that foundational discovery. They are instead directed to routine chemical modifications that had been known for decades to enhance the stability of RNA molecules that can be used with CRISPR and other systems. Agilent sought to patent these routine modifications, when used in the context of CRISPR, to corner the burgeoning CRISPR field.

Because those modifications were routine and well known, Agilent was far from the first to disclose their use in conjunction with CRISPR. As the Patent Trial and Appeal Board found—and the Federal Circuit agreed—a prior art reference known as Pioneer Hi-Bred had already disclosed the modified guide-RNA sequences that Agilent claimed (as did other prior art references introduced by Synthego). The Board also found—and the Federal Circuit again agreed—that Pioneer Hi-Bred was enabling: That is, it taught the skilled artisan how to make and use the claimed invention without undue experimentation. Accordingly, the Board concluded that Pioneer Hi-Bred anticipated Agilent's claims because any putative invention was already disclosed, and held them invalid under 35 U.S.C. § 102. The Federal Circuit affirmed, concluding comfortably that the Board's fact-intensive analysis was backed by substantial evidence.

The petition asks this Court to take up two issues that Petitioner did not even raise below. The first question presented challenges the application of a

well-established presumption of prior art enablement to the facts of this case. The second question presented challenges the application of the rule that ex ante proof of efficacy—i.e., some definitive demonstration to show that the claimed invention works—is not a necessary prerequisite to finding that prior art is enabled. But before the Federal Circuit, Agilent *never* contested the Board's application of the presumption of enablement, and it *affirmatively conceded* that proof of efficacy is not a prerequisite to enablement. This Court should decline to review issues that were not even contested below.

This case is also a poor vehicle because the answers to the questions presented do not matter to the outcome—which is likely why Agilent never raised them before. The Board expressly placed the burden of persuasion on Synthego, noting that burden "*never* shifts to [the] patent owner." App.31a (emphasis added); App.103a. And its decision rests upon *findings* showing that Pioneer Hi-Bred is enabling; it recited (App.104a), but did not rest on (App.128a-135a), the presumption of prior art enablement. Regardless, the presumption of prior art enablement allocates a burden of *production* which can and does shift, not the immutable burden of *persuasion*, which does not. Agilent's petition confuses these two different burdens.

The Board likewise followed well-settled precedent in concluding that Pioneer Hi-Bred was enabling. App.133a-134a. It did so notwithstanding a lack of working examples because of the predictable state of the art and the well-known nature of the modifications. *Id.* Pioneer Hi-Bred's disclosure indeed showed that it worked; after all, it involved tried-and-

true modifications. And though Agilent sought to raise questions about Pioneer Hi-Bred's disclosure as it relates to DNA molecules, that argument was irrelevant. The claims involve *RNA* molecules—not *DNA* molecules—and Synthego invoked only Pioneer Hi-Bred's RNA disclosures as anticipatory. The Federal Circuit, in turn, held that the evidence sufficiently backed the Board's decision. App.14a-20a.

But even were this petition an adequate vehicle, neither question presented warrants this Court's review. Each involves a fact-intensive application of well-established doctrines that serve valuable evidentiary functions, that promote the procedurally efficient litigation of invalidity claims, and that patent practitioners have relied on for half a century. Petitioner's new assertions that those doctrines are somehow inconsistent with the Patent Act are wrong. Regardless, Petitioner also deprived the en banc Federal Circuit from considering those contentions by declining to file a petition for rehearing. This petition should be denied.

STATEMENT

A. Factual Background

The proceedings below concern chemical modifications to synthetic nucleic acids to improve their stability for use in CRISPR-Cas systems. App.2a. The CRISPR-Cas system permits the selective modification of DNA at a particular target. *Id.* To do so, guide-RNA (or "gRNA") directs a Cas protein to the targeted DNA sequence, and then the Cas protein can cleave the DNA sequence at that location. *Id.* It is important for gRNA to remain stable and resist degradation during that process. *Id.*

For decades prior to the invention of the CRISPR-Cas system, researchers had known that synthetic nucleic acids were vulnerable to degradation and instability. App.5a; App.16a. In particular, enzymes known as nucleases may cleave the bonds holding the synthetic nucleic acid strand together, thereby degrading the molecule and rendering it ineffective for its intended use. App.37a; App.42a; App.55a. And for almost as long, well-known chemical modifications have been used to successfully reduce RNA degradation in other systems. App.18a; App.55a.

Those known modifications often shared specific features. For instance, it is advantageous to modify nucleotides near the 3' or 5' end (the two different sides of the RNA string) because certain kinds of nucleases (called exonucleases) attack RNAs from the end of the nucleotide chain. App.37a. And to reduce interior cleavage from other kinds of nucleases (called endonucleases), one could alter the phosphate group through phosphorothioate modifications, and alter the ribose sugar in the individual nucleotide through 2'-O-methyl modifications. App.41a-42a. These well-known modifications can work in tandem: modifying the 5' or 3' ends of an RNA molecule prevents an exonuclease from attacking the RNA sequence at the termini, while placing an O-methyl modification at the adjacent 2' position prevents an endonuclease from cleaving the interior. App.40a. By the early 2010s, it was well known how to use such modifications to stabilize RNA molecules. App.6a.

Almost immediately after the CRISPR-Cas system was introduced, "multiple researchers rapidly suggested using chemically modified guide RNAs with CRISPR." No. 23-2186, Doc. 26 (Pub. App'x) at

Appx1203 (admission of Agilent's expert); *see also id.* at Appx1139-50 (collecting admissions regarding well-known state of the art).

One publication (among others) on this subject is "Pioneer Hi-Bred," which is an international patent application that described "compositions and methods" that "employ[] 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." App.5a. The term "guide polynucleotide" was defined in Pioneer Hi-Bred 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.*

Just like the Agilent patents did later, Pioneer Hi-Bred earlier taught using nucleotide modifications to increase the stability of the guide polynucleotides, explaining that such modifications "reduce unwanted degradation." *Id.* Pioneer Hi-Bred described these methods in Example 4 of the patent application, which disclosed "modifying … nucleic acid component(s) of the guide polynucleotide/Cas endonuclease system for increasing cleavage activity and specificity." *Id.*

In Example 4, Pioneer Hi-Bred specifically described "nuclease resistant" modifications "to decrease unwanted nuclease degradation." App.56a. Reflecting the well-understood role of 2'-O-methyl and phosphorothioate modifications in reducing degradation, Pioneer Hi-Bred included both of these alterations in a table, and explained how they could

make the guide polynucleotide more resistant to nucleases. *Id*. (Table 7).

In another table, Pioneer Hi-Bred listed several examples of modified sequences (some later claimed as inventions in the Agilent patents), including sequences containing a 2'-O-methyl modification or a phosphorothioate modification near the 3'-end or 5'-end. App.38a (Table 8). Pioneer Hi-Bred further explained that nucleotide base and phosphodiester bond modifications "similar to those illustrated in [Table 8] can be introduced individually or in combination" into the CRISPR-Cas system. App.40a.

In sum, Pioneer Hi-Bred provided a targeted description of the gRNA later claimed in Agilent's patents as its inventions, identifying not just the specific chemical modifications that should be used with CRISPR gRNAs, but also the particular locations where they ought to be used and the rationale for why the modifications would work.

B. Agilent's Patents

Agilent, among others, also proposed to use known, modified RNAs with CRISPR shortly after the publication of the CRISPR discovery. App.3a-4a. To this end, Agilent confirmed that the numerous tried-and-true modifications that had worked in other systems would work in CRISPR too. Specifically, Agilent scientists synthesized and tested roughly 250 different gRNAs. App.129a; App.55a. Because both the modifications and the procedures for synthesizing RNA were so well understood at the time, the entire process—from first identifying the most promising modifications to synthesizing, validating, and testing them, for over 250 distinct molecules—took only about

a year. App.132a. And because the modifications predictably preserved the functionality of the gRNA, as the prior art had long understood, *97%* of the sequences tested by Agilent were successful for their intended purpose. App.167a ("97% of the experiments that Agilent ran showed at least some cleavage activity," which is "exactly the result a [skilled artisan] would expect in view of the teachings in Pioneer Hi-Bred and the other references cited").

Agilent sought to patent practically the entire field of modified gRNA. Agilent's two invalidated patents are: U.S. Patent No. 10,337,001 (the '001 patent) and U.S. Patent No. 10,900,034 (the '034 patent). App.1a. Both patents cover the application of well-understood nucleotide modifications to synthetic gRNA molecules.

The claims themselves recite little more than familiar nucleotide modifications—particularly 2'-O-methyl and phosphorothioate modifications—at the ends of the nucleotide sequence. Claim 1 of the '001 patent is representative:

> 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.

App.3a.

Claim 1 thus applies to *any* gRNA that is functional in the sense that it can "associate[] with a Cas protein" and then "target[] … a target polynucleotide," and where a nucleotide near either the 5'-end or the 3'-end of the strand contains any modification to a phosphodiester linkage or a sugar. *Id*. The dependent claims tack on nothing more than other standard modifications long used in the art, such as 2'-O-methyl, phosphorothioate, phosphonocarboxylate, phosphonoacetate, and phosphonothioacetate. App.4a.

C. Proceedings Below

Synthego is a pioneering CRISPR solutions provider dedicated to advancing the frontiers of cell and gene therapy. In 2021, Agilent threatened Synthego with an infringement action, demanding that Synthego purchase a license from Agilent for all of Synthego's services using modified gRNA. Synthego responded by filing a case in the Northern District of California that sought a declaratory judgment of noninfringement. *Synthego Corp. v. Agilent Techs., Inc.*, No. 3:21-cv-07801 (Oct. 5, 2021). In turn, Agilent filed its own infringement action in the District of Delaware, seeking an injunction to stop Synthego's use of gRNA modifications. *Agilent Techs., Inc. v. Synthego Corp.*, No. 1:21-cv-01426 (Oct. 6, 2021).

With that backdrop, Synthego filed two inter partes review (IPR) petitions in 2022, one challenging all

claims in the '001 patent (IPR2022-00402; App.25a) and the other challenging all claims in the '034 patent (IPR2022-00403; App.97a). Synthego explained that the relevant claims of each of the '001 and '034 patents were anticipated by Pioneer Hi-Bred. App.7a.[1] Like the patents at issue here, Pioneer Hi-Bred disclosed that functional gRNA can be modified by employing 2'-O-methyl or phosphorothioate modifications near the 3'-end or the 5'-end of the nucleotide sequence. App.4a-5a; App.35a-40a.

The Board agreed, "find[ing] that Petitioner has shown by a preponderance of the evidence that the challenged claims … are unpatentable." App.26a.[2] In doing so, the Board placed the burden of persuasion squarely on the petitioner, explaining that "the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable," and emphasizing that "[t]his burden of persuasion never shifts to the patent owner." App.31a. To anticipate a claim, the Board explained, "each limitation in a claim must be found in a single prior art reference, arranged as recited in the claim." *Id.* That prior art reference "must be enabling." *Id.* The Board explained that Pioneer Hi-Bred, in fact, disclosed each element of the challenged claims, thereby anticipating them. App.117a-119a; App.135a-147a.

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[1] The obviousness ruling as to other claims is not at issue in this petition.

[2] The Board issued two final written decisions—one for each IPR petition. As the Federal Circuit correctly observed, those decisions are "substantially similar." App.7a n.6. This brief cites to them interchangeably as the panel did below. *See id.*

The Board rejected Agilent's contention that Pioneer Hi-Bred is not enabling. "The record demonstrates," the Board found, "that a [skilled artisan], as of December 2014, could practice these disclosures without undue experimentation." App.130a. "Indeed," the Board continued, "Pioneer Hi-Bred teaches that gRNAs having [the relevant modifications] can be synthesized per standard techniques." *Id.* The Board found that "such techniques were known in the art" and that "a POSA would have been able to use them to make the gRNAs disclosed." App.130a-131a (explaining those specific techniques). "The record further evidences," the Board continued, "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." App.131a. The Board rejected the contrary testimony of Agilent's expert for lack of credibility. App.131a-132a.

The Board also rejected Agilent's contention that Pioneer Hi-Bred was not enabling because it "contains no data regarding any testing of the sequences" at issue. App.132a-133a. Enablement, the Board explained, concerns whether the skilled artisan can make and use the invention without undue experimentation. And, under settled precedent, that does not require "that an invention disclosed in a publication shall have actually been made." App.132a-133a. The Board then explained why that was the case here, again highlighting 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." App.133a-134a. And it agreed that their application in the CRISPR context simply "presented a new iteration of an old problem with a tried and true solution." App.129a.

Indeed, the Board emphasized the "persuasive" fact that "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." App.129a. The skilled artisan, the Board found, would have expected "exactly [that] result" based on Pioneer Hi-Bred. App.167a. "In sum," the Board concluded, "we find that undue experimentation would not have been required to make and use a gRNA with the recited chemical modifications and functionality." App.134a-135a. Thus Pioneer Hi-Bred's "disclosure is enabled." *Id*.

The Board also emphasized that Pioneer Hi-Bred "discloses functional, chemically-modified gRNAs" as recited in the patented claims. App.54a. Agilent argued that Pioneer Hi-Bred was not functional because it disclosed both DNA and RNA-based guides, asserting that the DNA-based guides would fail. App.49a. But the Board rejected that argument because Synthego's challenge was squarely premised on *RNA*—not *DNA*—guides of Pioneer Hi-Bred. *Id*. So "[e]ven if [the Board] accept[ed] Patent Owner's argument that the DNA-based examples lack gRNA functionality," the Board found, "the fact does not suggest that a [skilled artisan] would doubt that the RNA-based embodiments … lack such functionality." *Id*. Indeed, the Board explained why the skilled

artisan would (correctly) understand Pioneer Hi-Bred's RNA-based embodiments to have gRNA functionality based on the disclosure. App.49a-54a.

Reviewing that fact-intensive analysis for substantial evidence—and without Agilent ever complaining of the burdens and presumptions applied by the Board—the Federal Circuit affirmed. The panel agreed that Pioneer Hi-Bred was enabled. Pioneer Hi-Bred, the panel explained, "exemplifies … 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." App.16a (emphasis omitted). And it reiterated the Board's finding 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." App.16a.

Taking the teachings of Pioneer Hi-Bred in light of the prior art, the panel thus "s[aw] no error in the Board's conclusion that Pioneer Hi-Bred is enabling." App.13a. The panel also observed that even if Pioneer Hi-Bred disclosed "some non-working examples" (DNA, not RNA guides), that "does not undermine the disclosure of other examples that were disclosed as functional." App.11a.

Agilent did not file a petition for panel rehearing or rehearing en banc.

REASONS FOR DENYING THE PETITION

The petition takes aim at the longstanding presumption of prior art enablement, arguing that it is an improper burden-shifting framework. Pet.20-27. The petition also asserts that a lack of working

examples, or some other definitive "proof of efficacy," should necessarily bar anticipation, notwithstanding the predictable and well-known state of the art. Pet.27-31. The Court should decline to review either question presented.

First, Petitioner misstates the law. The presumption of prior art enablement describes a burden of *production*, not a burden of *persuasion*. The petition errs by conflating the two. As the Board correctly explained, the "burden of persuasion *never* shifts to [the] patent owner." App.31 (emphasis added). The burden of production, on the other hand, is an essential evidentiary tool that can shift in the right circumstances and is fully consistent with the ultimate burden of persuasion.

Petitioner's "proof of efficacy" argument is similarly confused. Petitioner's argument seems to be a fact-bound one: that Pioneer Hi-Bred did not sufficiently show that it worked. But Agilent's evidence related to *DNA* guides of Pioneer Hi-Bred that are not at issue because Synthego relied on *RNA* guides that unquestionably worked. Regardless, Petitioner's argument makes little sense because Pioneer Hi-Bred taught the skilled artisan how to make and use the patented claims in the context of a predictable art. Agilent offers no authority whatsoever to show that its actual testing—of already tried-and-true compounds—was necessary or inventive so as to justify a monopoly over the entire field.

Second, this case is a poor—indeed, improper—vehicle for the questions presented because Petitioner failed to raise either of the asserted issues below. The reason why is clear: neither issue mattered in light of

the findings below. The evidence of enablement was powerful. And the relevant RNA guides of Pioneer Hi-Bred worked as the skilled artisan expected they would.

Third, the questions presented do not warrant review. There is no split of authority. Nor did the Petitioner ask the Federal Circuit to reconsider either question en banc. Indeed, Petitioner does not point to any dissenters, commentators, amici, or practitioners calling for an overhaul of that Court's established anticipation precedents, which offer a workable and orderly procedure for adjudicating invalidity contentions. To be sure, Petitioner speculates about the supposed potential future implications of anticipation law in the context of Artificial Intelligence (AI) to try to garner interest in this otherwise routine invalidation of Agilent's patents. Pet.6-8, 37. But Petitioner also admits that the invention here did not involve—and has nothing to do with—AI. Pet.7. Even then, Petitioner accedes that the political branches are attuned to the novel issues that AI may pose in patent law. Pet.7-8. Those branches are best positioned to evaluate and consider in the first instance how and whether to confront any future challenges. The Federal Circuit, too, is well positioned to evaluate how to apply its precedent in the context of AI.

I. THE FEDERAL CIRCUIT'S PRECEDENT IS CORRECT AND PETITIONER OFFERS NO VALID REASON FOR UPENDING IT.

1. An inventor is granted a limited-term monopoly over a discovery in exchange for disclosing it to the public. *Amgen Inc. v. Sanofi*, 598 U.S. 594, 605 (2023).

But if prior art has already disclosed the claimed invention, that bargain no longer makes sense. When "the claimed invention was" previously "described in a printed publication," it is not patentable because it is in the public domain. 35 U.S.C. § 102(a). To describe a claimed invention, the prior art must disclose "each and every element" of the patented claim. *E.g.*, *Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662 (Fed. Cir. 2023). And that prior art disclosure must similarly enable the skilled artisan to make and use the claimed invention without undue experimentation—that is, the prior art must be enabling. *In re Morsa*, 803 F.3d 1374, 1377 (Fed. Cir. 2015). Prior art need not enable a patented claim in its entirety to anticipate it—a single embodiment suffices. *Id.*

A patent challenger bears the burden of persuasion—that is, showing that a patented claim is invalid by a preponderance of the evidence—in IPR proceedings. *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); 35 U.S.C. § 316(e). That burden "never shifts to [the] patent owner." App.31a (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)). When anticipation is at issue, a presumption of enablement serves as an evidentiary tool that allocates the burden of *production*. Once the patent challenger meets its initial burden to introduce a prior art reference shown to describe the claimed invention, the presumption of enablement kicks in. The patent holder may defeat that presumption by offering any "non-frivolous argument that cited prior art is not enabling." *In re Morsa*, 713 F.3d 104, 110 (Fed. Cir. 2013). The challenger must then overcome those

arguments and show that the prior art is enabled. That framework has been well established for at least half a century. *See, e.g.*, *Impax Lab'ys, Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008); *In re Morsa*, 713 F.3d at 110; *In re Antor Media Corp.*, 689 F.3d 1282, 1287-88 (Fed. Cir. 2012); *In re Sasse*, 629 F.2d 675, 681 (C.C.P.A. 1980); *Application of Jacobs*, 318 F.2d 743, 745-46 (C.C.P.A. 1963).

Petitioner argues that the presumption of enablement impermissibly shifts the burden of proof established by 35 U.S.C. § 316(e) to the patentee. Pet.20. Not so, because the presumption only affects the burden of *production*—an often-used evidentiary tool—not the burden of *persuasion*—which the patent challenger always bears. *See Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 100 n.4, 103 (2011) (explaining these different burdens); *In re Morsa*, 713 F.3d at 110 (describing the presumption of prior art enablement as a "procedural" tool). The burdens of persuasion and production "are two distinct burdens." *Dynamic Drinkware*, 800 F.3d at 1378. The "burden of persuasion 'is the ultimate burden assigned to a party who must prove something to a specified degree of certainty.'" *Id.* (quoting *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326-27 (Fed. Cir. 2008)). The "burden of production," by contrast, "is a shifting burden, 'the allocation of which depends on where in the process of the trial the issue arises.'" *Id.* "The burden of production may entail 'producing additional evidence' and 'presenting persuasive argument based on new evidence or evidence already of record.'" *Id.* Section 316(e)'s "preponderance of the evidence" burden is a classic assignment of the burden of persuasion. *See id.* at 1378. It says nothing about

the procedural tools, like the burden of production, that may be used to assist with that inquiry.

Petitioner's failure to grasp the difference between a burden of production and a burden of persuasion is fatal to most of its arguments. Petitioner also argues (Pet.18-20) that the presumption of enablement is contrary to this Court's decision in *Seymour v. Osborne*, 78 U.S. 516 (1870). But *Seymour* simply explains that prior art cannot invalidate a patented invention unless it is enabling. *Id.* at 555. It says nothing about who bears either the burden of persuasion or production in demonstrating the enablement of a prior art reference. *Id.* Nor does *Seymour* say anything about the evidentiary tools that may be used in conducting the enablement inquiry. *Id.* Petitioner likewise asserts (Pet.25-27) that there is a tension between the burden of proof in the anticipation context and the burden of proof in the obviousness context. That is wrong, and again reflects Petitioner's failure to separate out the burden of production from the burden of persuasion. In both contexts, "[t]his burden of persuasion never shifts to [the] patent owner." App.31a (citing *Dynamic Drinkware*, 800 F.3d at 1378).

Just last term, this Court showed how a burden shifting framework can work within an ultimate preponderance of the evidence standard. *See Ames v. Ohio Dep't of Youth Servs.*, 605 U.S. 303, 308 & n.2 (2025). In the *McDonnell Douglas* framework for employment discrimination, this Court explained, a plaintiff "bears the 'initial burden' of 'establishing a prima facie case' by producing enough evidence to support an inference of discriminatory motive." *Id.* at 308 (quoting *McDonnell Douglas Corp. v. Green*, 411

U.S. 792, 802 (1973)). That can be likened to the patent challenger's initial burden to come forward with a prior art reference that anticipates the challenged claim. Under *McDonnell Douglas*, the burden of production then "shifts to the employer to articulate some legitimate, nondiscriminatory reason for the employee's rejection." *Id.* at 309. That, too, is akin to the patentee's burden to "make[] a non-frivolous argument that cited prior art is not enabling." *In re Morsa*, 713 F.3d at 110. Finally, the *McDonnell Douglas* burden shifts back to the plaintiff to show that the stated reason is pretext for discrimination. *Ames*, 605 U.S. at 309. That is much like the patent challenger's task to ultimately prove enablement, including by defeating the patentee's non-frivolous arguments. Through the *McDonnell Douglas* framework, courts are thus "provide[d] a sensible, orderly way to evaluate the evidence" bearing on the "critical question," on which the Plaintiff bears the "ultimate burden of persuasion." *Id.* at 308 n.2. So too for the presumption of prior art enablement.[3]

Related patent law issues likewise show how the burden of persuasion and the burden of production work together. Consider contested priority dates. The patent challenger, "having the ultimate burden of proving … invalidity based on anticipating prior art, also ha[s] the initial 'burden of going forward with evidence that there is such anticipating prior art.'" *Dynamic Drinkware*, 800 F.3d at 1379 (quoting *Tech.*

[3] In a concurring opinion, Justice Thomas noted that *McDonnell Douglas* made less sense in the context of summary judgment as compared to a bench trial. *Ames*, 605 U.S. at 320, 322. That distinction is not implicated here, where the Board held a full trial on the merits.

Licensing Corp., 545 F.3d at 1327). In response, the patentee has "the burden of going forward with evidence either that the prior art does not actually anticipate, or … that it is not prior art because the asserted claim is entitled to the benefit of a filing date prior to the alleged prior art." *Id.* Then, the "burden of going forward again shifts to the proponent of the invalidity defense … to convince the court" of anticipation on the facts. *Id.* Again, that is the framework that applies here.

Notably, the distinction between these two burdens was apparent in the proceedings below. The Board was clear: the "burden of persuasion never shifts to [the] patent owner." App.31a; App.103a. But the petition *never* acknowledges that the Board assigned this burden to Synthego as the challenger.

The presumption of enablement is also essential to the workable and orderly resolution of patent cases. The patentee is generally better positioned than the challenger to show, whether through evidence or argument, why the disclosure is not enabling. *See In re Antor Media Corp.*, 689 F.3d at 1288 (emphasizing that "it is procedurally convenient" for the better-positioned patentee to come forward with evidence or argument). After all, whether prior art is enabling is often not disputed. But were the burden of production in this regard to be placed on the patent challenger, each and every prior art reference in each and every case would need to be analyzed before anticipation may be shown. As a practical matter, that would require the great burden and expense of expert testimony as to even the most mundane element of each claim, and it would send the cost of patent litigation to the roof. As the Federal Circuit has

emphasized, such a system "would be overly cumbersome, perhaps even impossible." *Id.* And it would effectively force a kind of enablement "mini-trial," whenever prior art is asserted, that would "occupy a great deal of a court's resources"—an "unwise," unworkable, and unneeded task. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 n.21 (Fed. Cir. 2003).

2. Petitioner's "proof of efficacy" argument is entirely misplaced. Pet.27. Before the Board, Petitioner contended that certain *DNA* guides of Pioneer Hi-Bred might not work. App.18a; App.39a. But there was no question that the *RNA* guides of Pioneer Hi-Bred that satisfied each element of the claimed invention *would* work, and *those* are the embodiments that Synthego relied on to prove anticipation below. App.18a; App.39a; *see In re Morsa*, 803 F.3d at 1377 ("For a prior-art reference to be enabling, it need not enable the claim in its entirety, but instead the reference need only enable a single embodiment of the claim."); *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003) ("An anticipatory reference need only enable subject matter that falls within the scope of the claims at issue, nothing more"); *see also* Matt Lincicum, *A Knot in the Eternal Golden Braid: Searching for Coherence in the Relationship Between Enablement, Anticipation, and Obviousness*, 23 HARV. J.L. & TECH. 589, 594 (2010) (explaining the "sensible" logic that "a patentee [cannot] claim an entire genus … if some of the covered species were not novel").

Petitioner's arguments about *Rasmusson* and *Seymour* are thus entirely untethered from the case at hand. *Rasmusson* addressed a discrete issue: whether

a prior art reference must meet the standard for utility under Section 101 for it to be enabling under Section 102. *See* 413 F.3d at 1322-23, 1326. That issue is not at play here, and Pioneer Hi-Bred unquestionably discloses the utility of the chemical modifications at issue for reducing nucleic acid degradation. *E.g.*, App.5a (Pioneer Hi-Bred discloses "modifying" molecules "to reduce unwanted degradation" of guide RNA). *Seymour*'s discussion nowhere allows an inventor to lay claim to broad fields when an anticipatory reference within its scope has already been disclosed. *See* 78 U.S. at 555.

II. THIS CASE IS A POOR VEHICLE.

A. Petitioner Did Not Raise The Questions Presented In The Federal Circuit, And That Court Is Best Positioned To Consider Them In The First Instance.

Petitioner argues that, by affirming the Board's decision, the Federal Circuit applied a presumption of prior-art enablement in an "unprecedented" way—an "improper expansion of what qualifies as invalidating prior art." Pet.18. Petitioner also argues that the Federal Circuit is wrong to hold that "proof of efficacy" is not dispositive to the enablement of prior art.

Neither issue was raised below, and Petitioner cannot raise them now. This Court is "a court of review, not of first view." *Moody v. NetChoice, LLC*, 603 U.S. 707, 726 (2024). When "the question presented was not pressed or passed upon below," that "precludes" a grant of certiorari. *United States v. Williams*, 504 U.S. 36, 41 (1992). Petitioner never challenged the application of the presumption of enablement to Pioneer Hi-Bred in the Federal Circuit.

In fact, the word "presumption" (including variants thereof) appears only once in Petitioner's opening brief below, and not at all in Petitioner's reply brief. No. 23-2186, Doc. 14 at 68 (Opening Brief); No. 23-2186, Doc. 23 (Reply Brief). And that usage is merely a quote from the Board's opinion. Opening Brief 68. That does not suffice to preserve Petitioner's arguments against the application of the presumption.

The record is even worse as to Petitioner's "proof of efficacy" argument. The Board observed that a prior art reference does not need to contain proof of efficacy to be enabling under Section 102. Petitioner *agreed* with that law before the Federal Circuit, affirmatively conceding the issue: "The Board is correct that a lack of testing data does not *necessarily* mean prior art is non-enabling." Opening Brief 68 (emphasis in original). Indeed, Petitioner proceeded to likewise admit that "the presence or absence of working examples" is not required. Opening Brief 68-69. And Petitioner also acknowledged the "general legal standard for whether a prior art disclosure is enabling," which is "that 'anticipation does not require actual performance of suggestions in a disclosure.'" Opening Brief 37. Indeed, Petitioner never even cited *Seymour*, which Petitioner now characterizes as *the* critical precedent from this Court bearing on both questions presented. Petitioner thus conceded the issue, and never challenged the application of the Federal Circuit's proof of efficacy requirement.

Petitioner may, in reply, assert that making these arguments to the Federal Circuit would have been futile. That contention would fail. In fact, it would contradict the Petition itself. As to the first question presented, Petitioner asserts that the application of a

presumption of efficacy in the context of the case below was supposedly "unprecedented," and that the Federal Circuit misapplied its own caselaw in doing so for the first time here. *E.g.*, Pet.18. Without resisting the supposed application of inapposite caselaw below, Petitioner cannot now be heard to complain of it. So too as to the second question presented. Petitioner argues that "*Rasmusson*, and the cases cited therein, are interference proceedings, involving chemical compounds or therapeutics" that "have no application outside of this realm." Pet.31. But again, Petitioner expressly accepted the application of that doctrine below, and did not seek to distinguish *Rasmusson* on the grounds that it now advances. It cannot do so for the first time on appeal.[4]

Moreover, this case is a prime example of the wisdom of the Court's refusal to consider issues that are not pressed below. Because the Petitioner did not challenge the application of the presumption of enablement below or the application of *Rasmusson*, those arguments have not yet been rejected by the Federal Circuit, and they remain available for a future litigant to advance. And to the extent that Agilent believed there to be a problem with binding Federal Circuit precedent, it should have presented that issue in the first instance to the en banc Federal Circuit. Petitioner provides no reason for this Court to take up

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[4] Even if Petitioner's arguments had been futile (contrary to the Petition's proffered distinctions), that would still be no excuse for failing to raise them below. An appellant has the obligation to preserve the issues and arguments that it seeks to raise in this Court. *See, e.g., Williams*, 504 U.S. at 44-45. The extraordinary exceptions to that rule are nowhere near applicable to the forfeiture and concession at hand. *See id.*

an issue that Agilent deprived the Federal Circuit of an opportunity to address by failing to file a petition for rehearing en banc.

In short, because Petitioner (a) never challenged the application of a presumption of efficacy below, and (b) conceded that the Board was "correct" that proof of efficacy is not required for enablement, the petition should be denied at the outset.

B. The Questions Presented Did Not Matter To The Proceedings Below.

There is a good reason that Petitioner declined to raise the questions presented before the Federal Circuit: They are immaterial to the outcome here. It makes little sense for this Court to decide the questions presented in the context of a case where they did not matter, and where their resolution would be merely advisory.

The Board's enablement decision turned on findings, not a presumption. The Board weighed all the evidence, assessed the credibility of the experts, and conducted a thorough analysis of all the relevant facts to affirmatively find that Pioneer Hi-Bred was enabling, concluding that: "[T]he record demonstrates that a [skilled artisan], as of December 2014, could practice [Pioneer Hi-Bred's] disclosures without undue experimentation." App.130a. In a careful and detailed opinion, the Board explains why: Tables 7 and 8 of Pioneer Hybrid each teach modifications that can be used to decrease nuclease degradation of guide RNA to be used in conjunction with CRISPR-Cas. App.130a. "The record," the Board continued, "demonstrates such techniques were known in the art and a [skilled artisan] would have been able to use them to make the

gRNAs disclosed in Pioneer Hi-Bred." App.130a-131a. Nor did doing so require undue experimentation: "The record further evidences," the Board found, that an individual gRNA could be made "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." App.57a.

The Board also found that the testimony of Agilent's expert to the contrary was not credible. App.131a-132a. Agilent's expert, for instance, failed to identify any new or undue challenges to synthesizing the chemically modified gRNAs. App.131a-132a. And it expressly gave "credit" to the testimony of Synthego's expert "that undue experimentation would not be required to make the anticipating, chemically-modified gRNAs taught in Pioneer Hi-Bred over the competing testimony of Patent Owner's declarants." App.132a.

The Board also rejected Agilent's argument that Pioneer Hi-Bred was not enabled for failure to disclose "data regarding any testing of the sequences in Table 8" because it is "not necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement." App.132a-133a. That was true here, the Board continued, because "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." App.133a. Thus, "it was far from a blank slate" for the skilled artisan, who would have expected the RNA modifications to work as anticipated. App.133a-134a.

To the extent that the Board mentioned the presumption of enablement at all, it did so in passing. The Board noted, for instance, that the disclosures of Pioneer Hi-Bred are presumed enabling before explaining why "the record demonstrates" that enablement is "indeed" the case here. App.129a-130a. Similarly, the Board explained that the lack of working examples "alone does not undermine the presumption that Pioneer Hi-Bred is enabled" because working examples are not always required for enablement. App.132a-133a. The Board then proceeded to explain that the state of the art was "far from a blank slate" and the evidence demonstrated enablement, notwithstanding the lack of working examples. Indeed, following the teachings of Pioneer Hi-Bred, 97% of the compounds tested by Agilent worked. App.55a-56a. In short, though the Board noted the presumption of enablement and that working examples are not required, its analysis went far beyond that assumption in evaluating the evidence at hand.

The Federal Circuit's fact-bound review of the Board's decision for substantial evidence similarly turned on the evidence at hand and did not rest on a presumption. "In assessing whether undue experimentation is required," the panel explained, "the Board considered the Wands factors and found that the 'record demonstrates that a [skilled artisan], as of December 2014, could practice these disclosures without undue experimentation.'" App.14a. It then reviewed the specific facts that supported that determination, including the Board's credibility determination, its determination that the relevant techniques were "known in the prior art," and that the

relevant art was sufficiently predictable despite the absence of working examples. App.14a-15a. Indeed, the Federal Circuit's sound affirmance of the Board's factual analysis would amply "suffice[] for [this Court] to affirm" without "going into fine details of molecular biology." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 596 (2013) (Scalia, J., concurring in part and concurring in the judgment).

The Federal Circuit's opinion mentions the presumption of enablement on only a single appendix page. First, the panel stated—in explaining prior art enablement and consistent with Petitioner's failure to contest the application of the presumption—that "[p]rior art disclosures are presumed enabling." App.14a. Second, the panel quoted the Board's observation that a lack of working examples "does not undermine the presumption that Pioneer Hi-Bred is enabled," before turning to the state of the art. App.14a-15a.

The same is true for the question of "proof of efficacy." The Board's decision quoted the "proof of efficacy" language in passing. App.48a. It also noted that Pioneer Hi-Bred itself disclosed the efficacy of the chemical modifications at issue. App.28a; App.44a ("[Synthego] has shown that Pioneer Hi-Bred discloses the recited 'gRNA functionality.'"). And it found that a skilled artisan "would [not] doubt that the RNA-based embodiments … lack such functionality." App.49a. The Federal Circuit mentioned "proof of efficacy" a single time, in passing, in discussing the standard of review. App.13a. And in reviewing the Board's decision, the panel emphasized the Board's finding that a skilled artisan would not doubt that the

relevant RNA-based embodiments would function as expected. App.18a-19a.

The upshot is that neither of the questions presented mattered to the disposition of the petition below. The resolution of the question presented is "irrelevant to the ultimate outcome of the case before the Court," counseling that "certiorari may be denied." Shapiro et al., SUPREME COURT PRACTICE § 4.4(g). This Court has observed that it is best positioned to resolve a question presented "in the context of meaningful litigation" and when presented "less abstractly." *The Monrosa v. Carbon Black Exp., Inc.*, 359 U.S. 180, 184 (1959). So too here.

III. THE DECISION BELOW DOES NOT WARRANT THE COURT'S REVIEW, AND THE SPECULATIVE IMPLICATIONS OF THE DECISION BELOW FOR ARTIFICIAL INTELLIGENCE ARE OVERSTATED AND NOT BEFORE THE COURT.

This request for error correction does not warrant this Court's review.

First, Petitioner repeatedly hitches the importance of the questions presented to the *possible* future implications of AI. *E.g.*, Pet.6-9. But that speculation about AI has *nothing* to do with the case at hand. Indeed, Petitioner admits that AI is "absent" from this case: the invention does not claim subject matter related to AI, and the prior art amply predates the present emerging use of AI tools. Pet.7. If this Court wishes to take on the implications of novel applications of AI in the context of patent law, it would be well served to wait for a case that actually involves AI.

In fact, the AI questions posed by Petitioner may be resolved before they reach this Court. Petitioner points to the Patent and Trademark Office's "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 Fed. Reg. 34217 (Apr. 30, 2024). The entire purpose of that request is to give the political branches an opportunity to address the implications of AI in the first instance, and, if warranted, to change the law accordingly. Indeed, as the USPTO explained, the comments "will help the Office evaluate the need for further guidance on these matters, aid in the development of any such guidance, and help inform the USPTO's work in the courts and in providing technical advice to Congress." *Id.* And the USPTO specifically invited comments about changes to the law in order to account for the impacts of AI: "Should title 35 of the U.S. Code be amended to account for any of the considerations set forth in this notice, and if so, what specific amendments do you propose, and why?" *Id.* at 34220.[5]

Second, this Court has repeatedly denied petitions presenting similar questions. *See, e.g.*, *Converter Mfg., LLC v. Tekni-Plex, Inc.*, No. 24-866; *Queen's Univ. at Kingston v. Samsung Elecs. Co.*, No. 18-190; *In re*

[5] The USPTO is far from alone in considering emerging AI questions. The Senate Judiciary Committee, for instance, has held hearings on Artificial Intelligence and Intellectual Property. *See, e.g.*, Artificial Intelligence and Intellectual Property—Part I: Patents, Innovation, and Competition, S. Hrg. 118-65 (June 7, 2024), available at https://www.govinfo.gov/content/pkg/CHRG-118shrg53115/pdf/CHRG-118shrg53115.pdf.

Finjan, Inc. No. 12-1245. Petitioner offers no reason why this case warrants any different result.

Third, Petitioner has not shown—even if the Federal Circuit's precedent is wrong—that the Federal Circuit is unable to correct it. For instance, Petitioner argues that the decision below is novel and does not reflect the Federal Circuit's prior precedent. But because Petitioner never made these arguments to the Federal Circuit, the challenged "holdings" are best characterized as dicta and may be revisited by a future panel. Moreover, Petitioner has not shown that these questions were ever properly presented to the Federal Circuit in a petition for rehearing en banc. If the Federal Circuit's precedent is wrong (and it is not), the Federal Circuit should be given the opportunity to correct it.

CONCLUSION

For the foregoing reasons, the Court should deny the petition.

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Respectfully submitted,

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