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Paper No. 11
Date: May 31, 2022

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*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

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"). Agilent Technologies, Inc. ("Patent Owner") filed a Preliminary Response. Paper 7 ("Prelim. Resp.").

In its Preliminary Response, Patent Owner requests that the Board apply discretion to deny institution under 35 U.S.C. §§ 325(d) and 314(a). *See* Prelim. Resp. 16–34, 52–61. Patent Owner also raises certain challenges to the merits of the grounds in the Petition. *Id.* at 35–52. With our authorization, Petitioner filed a reply to Patent Owner's arguments for discretionary denial under § 314(a) (Paper 8 ("Reply")) and Patent Owner filed a sur-reply (Paper 10 ("Sur-reply")).

After considering the arguments and evidence presented at this stage of the proceeding, we are persuaded that Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition and we decline to exercise discretion to deny institution under 35 U.S.C. §§ 325(d) or 314(a). Accordingly, we institute *inter partes* review.

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. Related Matter

The parties identify the following related matters involving the '001 patent: *Synthego Corp. v. Agilent Techs., Inc.*, 21-cv-07801 (N.D. Cal. filed

Oct. 5, 2021) and *Agilent Techs., Inc. v. Synthego Corp.*, 21-cv-01426 (D. Del. filed Oct. 6, 2021). Pet. 15, Paper 4, 2. Herein, we refer to the first of these two cases as the "California litigation."

The parties also identify IPR2022-00403, which was filed concurrently with the Petition here and challenges a related patent. Pet. 15; Paper 4, 2.

C. 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 (CRISPER)/ CRISPER-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 trans-acting 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.

D. Challenged Claims

The Petition challenges claims 1–30. Of these, claims 1 and 12 are independent. Claim 1 is illustrative of the subject matter the challenged claims 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 hybridizing to a target polynucleotide" in its preamble. *Id.* at 244:19–33.

E. 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 Krützfeldt,[3] Deleavey,[4] Soutschek,[5] or Yoo[6]
8, 11, 16, 19, 26	103	Pioneer Hi-Bred and Threlfall[7] or Deleavey

[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 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

Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
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

Petitioner further relies on the declaration of Henry Morrice Furneaux (Ex. 1003) submitted with the Petition. Patent Owner submits the declaration of Dr. William S. Marshall (Ex. 2003) in support of its Preliminary Response.

Before turning to our analysis of these grounds, we address Patent Owner's arguments that, notwithstanding the merits of the Petition, we should exercise discretion to deny institution under 35 U.S.C. §§ 325(d) and 314(a).

III. DISCRETION UNDER 35 U.S.C. § 325(D)

Patent Owner argues that "Pioneer Hi-Bred and Threlfall were disclosed to the Patent Office and considered by the Examiner" and "all the arguments made in each Ground were considered by the Examiner and overcome by Patent Owner during prosecution." Prelim. Resp. at 17. Patent Owner also contends that Petitioner "makes no attempt to show the Examiner erred." *Id.*

Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office. The statute states, in pertinent part, "[i]n

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Oligoribonucleotides," 10 Org. Biomol. Chem., 746–754 (2012) (Ex. 1010) ("Threlfall").

determining whether to institute . . . the Director may take into account whether, and reject the petition . . . because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d).

The question of whether the petition presents art or arguments that are "the same or substantially the same" as art or arguments previously presented to the Office is a factual inquiry, which may be resolved by reference to the factors set forth in *Becton, Dickinson*.[8] The precedential section of that decision sets forth the following non-exclusive factors ("*BD* Factors") for consideration:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

[8] *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR 2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("*Becton, Dickinson*").

Becton, Dickinson, 17–18.

Advanced Bionics[9] sets out a two-part framework for analyzing these factors. In the first part, we consider factors (a), (b), and (d) to determine whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, 8–10. "If, after review of factors (a), (b), and (d), it is determined that the same or substantially the same art or arguments previously were presented to the Office," then we move on to the second part of the analysis to determine "whether the petitioner has demonstrated a material error by the Office" in view of factors (c), (e), and (f). *Id.*

A. Advanced Bionics Part One

Petitioner asserts that "[t]he Examiner did not consider any of the prior art underlying the Grounds in th[e] Petition." Pet. 11. That assertion is plainly incorrect.

Both Pioneer Hi-Bred and Threlfall appear in the cited references section on the face of the '001 patent. Ex. 1001, code (56). As Patent Owner points out, these references were submitted by the Applicant in IDSs and the Examiner confirmed that they were considered during examination. Prelim. Resp. 20–21; Ex. 1002, 747, 805, 833 (Pioneer Hi-Bred), 209, 594 (Threlfall).

It is also clear that Pioneer Hi-Bred, and to a lesser extent Threlfall, are central to the challenges in the Petition. Pioneer Hi-Bred is the primary

[9] *Advanced Bionics, LLC v. Med-El Electromedizinishe Geräte GmbH*, IPR2019-01469, Paper 6 at 10 (Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

reference for all of Petitioner's grounds and the only reference cited in three of the Petition's five grounds. The combination of Pioneer Hi-Bred and Threlfall is asserted against the five claims not reached by the grounds relying on Pioneer Hi-Bred as the only cited reference. Thus, Petitioner's grounds collectively challenge all of the claims of the '001 patent based on either Pioneer Hi-Bred or the combination of Pioneer Hi-Bred and Threlfall. While the Petition cites other secondary references that were apparently not considered during prosecution, those references are asserted in the alternative or applied only to a few of the dependent claims already challenged in other grounds based primarily on Pioneer Hi-Bred.

For these reasons, we determine that, on the whole, the Petition presents the same or substantially the same art as that previously presented to the Office and proceed to the second part of the *Advanced Bionics* framework.

B. Advanced Bionics Part Two

Regarding *BD* Factor (c), we note that neither Pioneer Hi-Bred, nor Threlfall were the basis for any of the Examiner's rejections during prosecution. Thus, the full extent to which the Examiner considered these references is not clear. It appears, however, that the Examiner placed greater emphasis on other references, e.g., Zhang,[10] the '616 patent,[11] and Doudna,[12] which were cited in anticipation and obviousness rejections of the then-pending claims. *See* Ex. 1002, 571–572, 667–669.

[10] US 2014/0242664 A1, published Aug. 24, 2014 ("Zhang").
[11] US 8,906,616 B2, issued Dec. 9, 2015 ("the '616 patent").
[12] US 2017/0166893 A1, published June 15, 2017 (Ex. 1019) ("Doudna").

Petitioner provides a brief overview of the prosecution history, explaining that the rejection based on Zhang was overcome by Applicant's argument "that although [Zhang] disclosed modifying the gRNA with the claimed modifications, it did not direct the skilled artisan to make those modifications at the claimed locations in the gRNA, specifically, the 5'-end or 3'-ends of the gRNA." Pet. 11 (citing Ex. 1002, 697–699). According to Petitioner, "the Applicant secured allowance over the prior art based on nothing more than the idea that it was inventive to make modifications at the ends of the gRNA," which "was erroneous" because Pioneer Hi-Bred discloses such modifications. *Id.*

Patent Owner faults Petitioner for failing to expressly address the rejections based on the '616 patent and Doudna, which were also overcome. *See* Prelim. Resp. 22–29. Patent Owner contends that Petitioner "relies on disclosures in Pioneer Hi-Bred that are the same as those already traversed with regard to Doudna." *Id.* at 29. Patent Owner argues that by "having omitted any discussion of the Doudna reference . . . much less the details of how Patent Owner overcame it, Petitioner necessarily fails to sustain the burden required of each petitioner in the second part of the *Advanced Bionics* test: how the Examiner erred in its consideration of Pioneer Hi-Bred, Threlfall, and Doudna." *Id.* at 34–35.

We disagree with Patent Owner. Based on the current record, Petitioner has shown that Pioneer Hi-Bred discloses examples of synthetic guide RNA and crRNA molecules having the recited modifications at their 3' and 5' ends. *See* Pet. 20–24 (referring to Table 8 of Ex. 1006). That disclosure undermines the Applicant's arguments during prosecution that: (1) "a skilled person would not modify a CRISPR guide RNA or crRNA at

the particularly claimed positions," and (2) the reference to "'securing or steadying the structure' of RNA in [Zhang] relates to secondary structure" as opposed to "modifications at the claimed positions," i.e. within five nucleotides from one or both of the ends. Ex. 1002, 783. Both of these arguments were credited by the Examiner as reasons for withdrawing the rejection over Zhang. *Id.* at 783–784. Thus, Petitioner has sufficiently shown that the Examiner materially erred by not recognizing the relevance of Pioneer Hi-Bred's disclosure and in particular the crRNA examples in Table 8.

The rejections involving the '616 patent and Doudna were overcome before the Examiner entered the rejection over Zhang. The Applicant responded to the rejections involving the '616 patent and Doudna by amending claims 1 and 12 to specify that "the modified nucleotide has a modification to a phosphodiester linkage, a sugar, or both." Ex. 1002, 646. The Examiner then withdrew those rejections based on that additional limitation. *Id.* at 655; *see also* Prelim. Resp. at 29 (acknowledging that "the Examiner agreed to withdraw the '616 Patent and Doudna-based rejections in light of [this] limitation").

Petitioner has shown that Table 8 in Pioneer Hi-bred discloses examples with modifications to the phosphodiester linkage and to the sugar of nucleotides at both ends of the guide RNA. *See* Pet. 20–24 (referring to Table 8 of Ex. 1006). Thus, on the present record, Petitioner has shown that Pioneer Hi-Bred discloses the limitation the Examiner found lacking in the '616 patent and Doudna. For these reasons, Patent Owner's argument that the Petition is premised on disclosures that "are the same as those already

traversed with regard to Doudna" is not persuasive.[13] Prelim. Resp. at 29. For these reasons, we determine that Petitioner has sufficiently demonstrated a material error and therefore decline to exercise discretion to deny institution of *inter partes* review under 35 U.S.C. § 325(d).

IV. DISCRETION UNDER 35 U.S.C. § 314(A)

Patent Owner argues that we should exercise discretion under 35 U.S.C. § 314(a) to deny institution of *inter partes* review in view of the California litigation. Prelim. Resp. 52–62. Patent Owner contends that "[a]ll the issues raised in the Petition are already presented, and are already being litigated" in the California litigation, which Petitioner filed as a declaratory judgment action[14] approximately three months before it filed the Petition. *Id.* at 54. According to Patent Owner, it "acted promptly after being served with Petitioner's Answer and Reply Counterclaims," which raised invalidity challenges over the same references in the Petition, "to file

[13] Patent Owner points out that in a prior action the Examiner had also referred to Doudna's teachings regarding modifications to the sugar backbone. *See* Prelim. Resp. 24–25 (citing Ex. 1002, 571–572). It is unclear, however, whether the Examiner appreciated those teachings when agreeing to withdraw the '616 patent and Dounda rejections "based upon the recited limitation 'the modified nucleotide has a modification to a phosphodiester linkage, a sugar, or both.'" Ex. 1002, 646. In any event, Petitioner has sufficiently shown that the Examiner erred by not appreciating the relevance of the crRNA sequences in Table 8 of Pioneer Hi-Bred to Patent Owner's claims. *See, e.g.*, Pet. 20–24 (comparing the sequences in Table 8 to claim 1).

[14] Petitioner's declaratory judgment complaint did not seek a judgment of invalidity. Ex. 2012. Patent Owner's answer to that complaint included counterclaims for infringement and Petitioner's reply to those counterclaims raised invalidity. Ex. 2015 ¶ 11.

a Motion for Preliminary Injunction" that is currently scheduled to be heard on July 7, 2022. *Id.* at 55; Ex. 2013, 1 (May 12, 2022 order granting stipulated schedule for hearing and briefing on preliminary injunction motion).[15] Patent Owner further asserts that the California court has entered an "expedited schedule for discovery and claim construction" and "[t]here is no reason for the Board to hold proceedings that would duplicate those in the district court and that would take longer to complete." *Id.* at 56. For these and other reasons, Patent Owner urges that all six *Fintiv*[16] factors favor the exercise of discretion to deny institution under § 314(a). *Id.* at 62.

Petitioner generally disputes Patent Owner's assessment of the *Fintiv* factors and contends these factors do not favor the exercise of discretion to deny institution. *See* Reply 1–4.

The Board's precedential decision in *Fintiv* outlines factors that balance considerations of system efficiency, fairness, and patent quality when a patent owner raises an argument for discretionary denial due to the advanced state of a parallel proceeding, such as the California litigation here. *Fintiv*, 5–6. These factors are:

> 1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
>
> 2. proximity of the court's trial date to the Board's projected statutory deadline for a final written decision;

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[15] Patent Owner has filed two different exhibits labeled as Exhibit 2013. Here, we refer to the version of Exhibit 2013 filed with Patent Owner's Sur-Reply on May 19, 2022. Patent Owner has also filed two exhibits under exhibit number 2011. Patent Owner should work with the Board paralegals to resolve these duplications.

[16] *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (Mar. 20, 2020) (precedential) ("*Fintiv*").

> 3. investment in the parallel proceeding by the court and the parties;
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> 4. overlap between issues raised in the petition and in the parallel proceeding;
>
> 5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
>
> 6. other circumstances that impact the Board's exercise of discretion, including the merits.

Id. "[I]n evaluating the factors, the Board takes a holistic view of whether efficiency and integrity of the system are best served by denying or instituting review." *Id.* at 6.

We now consider these factors to assess whether to exercise discretion to deny institution under 35 U.S.C. § 314(a) in this case.

A. Factor 1: whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted

Patent Owner argues this factor favors discretionary denial because the judge in the California litigation, Judge Davila, "stated on the record at the January 20, 2022, case management conference that he is unlikely to issue a stay in that case pending the outcome of this IPR." Prelim. Resp. 57 (citing Ex. 2016, 10:3–10).

The portion of the transcript Patent Owner cites does not support its position. Read in context, Judge Davila was responding to a suggestion by Petitioner's counsel that litigation of the preliminary injunction motion, which had just been filed, be stayed pending the Board's institution decisions in this and the related IPR. *See* Ex. 2016, 5:6–11:14. Judge Davila responded that he was "probably not likely to do that." *Id.* at 10:6.

The district court did not, however, indicate that a stay of the litigation was unlikely in the event IPR were instituted and we decline to speculate as to how Judge Davila might rule if a motion for such were filed in view of this decision. Accordingly, this factor is neutral.

B. Factor 2: proximity of the court's trial date to the Board's projected statutory deadline for a final written decision

The projected statutory deadline for a final written decision in this case is one year after the entry of this decision, i.e., in May 2023.

We understand a trial date has not yet been set for the California litigation. According to the scheduling order submitted by Patent Owner, a "Trial Setting Conference" is set for September 1, 2022. Ex. 2005, 3. Fact discovery is set to close on September 30, 2022, expert discovery is set to close on December 9, 2022, and the dispositive motion deadline is January 6, 2023. *Id.* at 3–4.

Patent Owner asserts that the California litigation "will be ready for trial in early 2023." Prelim. Resp. 58. But that does not mean that trial will actually be set for early 2023, much less that a trial would occur prior to the issuance of a final written decision here.

On the other hand, Petitioner's argument that "Judge Davila's historical average time to trial in civil cases is nearly ***three years***" and therefore this factor weighs against institution is unpersuasive because it does not address the specifics of the California litigation. *See* Reply 2. In particular, Petitioner's suggestion that the district court would set the present schedule, but then wait eighteen months or longer after the discovery and dispositive motion deadlines to hold a trial seems unlikely.

On balance, the record before us does not support either party's view as to the proximity of the district court's trial date to the projected deadline for our final written decision. Accordingly, this factor is neutral.

C. Factor 3: investment in the parallel proceeding by the court and the parties

Patent Owner asserts that "Judge Davila is likely to have ruled on Patent Owner's Motion for Preliminary Injunction" by the time of the Board's institution decision. Prelim. Resp. 58. That argument is premised on an assumption that this decision would issue "in or around July 26, 2022." *Id.* As of today, however, the briefing on Patent Owner's preliminary injunction motion is not complete, the hearing on that motion has not occurred, and we have not been made aware of any ruling from the district court that touches on the issues presented in the Petition.

We recognize that considerable investment has been made by the parties and district court to file the preliminary injunction papers and to prepare for the hearing. *See* Sur-Reply 2 (referring to discovery taken in the California litigation). So too, investment has been made to prepare and exchange contentions and to appear for a case management conference. *See* Prelim. Resp. 59. However, like the parallel litigation in *Fintiv*, "much work remains" in the California litigation "as it relates to invalidity." *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 15, 14 (May 13, 2020) (informative). The deadlines for completing both fact and expert discovery are still many months away, final invalidity contentions have not been served, and claim construction has not yet occurred. *See* Ex. 2005, 3. Indeed, based on the evidence before us, the California litigation does not appear as close to completion as the parallel litigation in *Fintiv* where this factor was found to

weigh only "somewhat in favor of discretionary denial." *See Fintiv*, Paper 15, 14 (explaining that there a detailed claim construction order had already been issued and final contentions had been served).

We also determine that Petitioner was reasonably diligent in filing the Petition expeditiously while the California litigation was still in an early stage. The Petition was filed on January 5, 2022, i.e., only three months after the California litigation began and before Patent Owner filed its preliminary injunction motion. *See* Ex. 2017, 3, 5 (docket entry nos. 1 and 40). For these reasons, in view of the particular circumstances of this case, we find this factor weighs only marginally, if at all, in favor of exercising discretion to deny institution.

D. Factor 4: overlap between issues raised in the petition and in the parallel proceeding

Patent Owner asserts that "Petitioner is relying on *the same six alleged prior art* references" cited in the Petition in "seeking to invalidate" the same claims of the '001 patent in the California litigation. Prelim. Resp. 59–60 (citing Ex. 2015 ¶ 11; Ex. 2019, 10–22 (Petitioner's preliminary invalidity contentions)); *see also* Reply at 2 (acknowledging that the grounds in the Petition are a "subset" of the "invalidity arguments Petitioner presents in district court").

We agree there is overlap between the issues in the two proceedings and that this overlap weighs in favor of exercising discretion to deny institution.

E. Factor 5: whether the petitioner and the defendant in the parallel proceeding are the same party

The parties are the same in both proceedings. Because it is not clear whether a trial will occur in the California litigation before the parties receive a final written decision here, we assess this factor to be neutral.

F. Factor 6: other circumstances that impact the Board's exercise of discretion, including the merits

This factor accounts for other relevant circumstances, including whether "the merits of a ground raised in the petition seem particularly strong on the preliminary record," which favors institution. *Fintiv*, 14–15.

On the current record, we determine that the merits of Petitioner's anticipation ground appear to be particularly strong for the independent claims and for those dependent claims where Petitioner's arguments are similarly premised on the crRNA examples in Table 8 being anticipatory without any further modification. *See infra* § V.E (explaining that, on the current record, Petitioner has shown that Pioneer Hi-Bred Table 8 discloses presumptively-enabled examples that read on claims 1 and 12 as well as a number of the dependent claims). Accordingly, we find that this factor weighs strongly against exercising discretion to deny institution.

G. Weighing of Fintiv Factors

Considering the *Fintiv* factors as part of a holistic analysis of the factors discussed above, we are not persuaded that the interests of the efficiency and integrity of the system would be served by invoking our authority under 35 U.S.C. § 314(a) to deny institution of a potentially

meritorious Petition. Accordingly, we do not exercise our discretion to deny institution under § 314(a).

V. ANALYSIS OF THE ASSERTED GROUNDS

A. Legal Standards

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).

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).

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). Patent Owner's declarant, Dr. Marshall, applies the same definition for his analysis. Ex. 2003 ¶ 85. At this stage in the proceeding, we find this description of the level of ordinary skill in the art to be sufficiently supported by the record. Thus, for purposes of this decision, we adopt the description of a POSA noted above.

In addition to this description, Petitioner asserts that a POSA would also have "abundant knowledge relevant to the '001 Patent," including that "researchers had long prepared and studied various forms of modified oligonucleotides (such as RNAs)," that "synthetic RNAs were well known in the art," and that "[m]odifying gRNAs using 2'-O-methyl and/or 3'-phosphorothioate was well known by 2014." *See* Pet. 12–13 (citing Dr. Furneaux's testimony).

Patent Owner disagrees, arguing that Petitioner's assertions regarding "what a POS[]A would know about alleged 'state of the art' and allegedly available gRNA" are "lengthy and contrived" and that Dr. Furneaux's "conclusory opinions regarding the state of the art . . . directly contradict" other evidence of record. *See* Prelim. Resp. 36–39. Patent Owner contends that "[a]ll grounds can be rejected in view of Petitioner's faulty POS[]A definition." *Id.* at 36.

We need not adopt the assertions Petitioner makes regarding the knowledge of a POSA in its POSA definition to determine that Petitioner has met its burden for institution of *inter partes* review. Some of these assertions are disputed points best resolved upon further development at trial. Moreover, the assertions Petitioner makes regarding a POSA's

knowledge of particular types of modifications and motivations for applying those to guide RNA in CRISPR-Cas systems are better assessed in context of the disclosure and teachings in the cited references as opposed to trying to include them in the definition of one of ordinary skill. The parties are, nevertheless, welcome to revisit the definition of one of ordinary skill in the art in their subsequent papers.

C. Claim Construction

Neither party identifies any claim term for construction. Pet. 17; Prelim. Resp. 35. We agree that no formal claim construction is necessary at this stage of the proceeding. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor 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. References Relied Upon

i. Pioneer Hi-Bred

Pioneer Hi-Bred is a publication of a PCT application filed August 20, 2014. Ex. 1006, code (22). Petitioner asserts that Pioneer Hi-Bred qualifies as prior art under 35 U.S.C. § 102. Pet. 14. At this stage, Patent Owner does not dispute that Pioneer Hi-Bred is prior art to the challenged claims.

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 cites within the genome of a cell or organism." Ex. 1006, Abstr. Pioneer Hi-Bred explains that a "guide polynucleotide" as disclosed in that reference is "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. 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. According to Pioneer Hi-Bred, 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 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 of 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., SEQ ID NOs: 64–67).

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

Nucleic Acid Type	Modification	crRNA or crDNA Sequence and Corresponding Modification[1]	
		VT Domain	CER Domain
crRNA	None	GCGUACGCGUACGUGUG (SEQ ID NO: 62)	GUUUUAGAGCUAUGCUGUUUUG (SEQ ID NO: 63)
crRNA	Phosphorothioate bonds near ends	G*C*G*UACGCGUACGUGUG (SEQ ID NO: 64)	GUUUUAGAGCUAUGCUGUU*U*U*G (SEQ ID NO: 65)
crRNA	2'-O-Methyl RNA nucleotides at ends	mGmCmGUACGCGUACGUGUG (SEQ ID NO: 66)	GUUUUAGAGCUAUGCUGUUmUmUmG (SEQ ID NO: 67)
crRNA	2'-O-Methyl RNA nucleotides for each nucleotide	mGmCmGmUmAmCmGmCmGmUmAmCmGmUmGmUmG (SEQ ID NO: 68)	mGmUmUmUmUmAmGmAmGmCmUmAmUmGmCmUmGmUmUmUmUmG (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 in the crRNA sequence. *See id.* at 109–110, n.1.

ii. Secondary References

The Petition cites Krutzfeldt, Deleavey, Soutschek, and Yoo as "secondary references" in its second ground and Threlfall and Deleavey as "secondary references" in its third ground. Pet. 14–15. Petitioner contends that all of these references are prior art under 35 U.S.C. § 102. *Id.* At this stage, Patent Owner does not dispute these references are prior art to the challenged claims.

Petitioner contends that Krutzfeldt, Deleavey, Soutschek, and Yoo teach 2'-O-methyl-3'-phosphorothioate modifications in other types of RNA and that a POSA would have been motivated to incorporate such modifications into the guide RNAs taught in Pioneer Hi-Bred, thereby

achieving the guide RNA and crRNA molecules recited in claims 9, 18, and 25. *See* Pet. 51–64.

Petitioner contends that Threlfall and Deleavey teach "RNAs with phosphonoacetate and phosphonothioacetate modifications at or near the 3' and/or 5'-ends" and that a POSA would have been motivated to use such modifications in the guide RNAs taught in Pioneer Hi-Bred, thereby achieving the guide RNA and crRNA molecules recited in claims 8, 11, 16, 19, and 26. *See* Pet. 64–70.

E. Anticipation Ground

Petitioner contends claims 1–7, 9, 10, 12–15, 17, 18, 20–25, and 27–30 are anticipated by Pioneer Hi-Bred. *See* Pet. 17–51. Petitioner presents evidence and argument purporting to show that each of the limitations of these claims is disclosed in Pioneer Hi-Bred. *Id.*

Beginning with independent claims 1 and 12, we determine that Petitioner has met its burden for institution. Based on the current record, Petitioner has shown that Table 8 of Pioneer Hi-Bred discloses a synthetic guide RNA or crRNA molecule comprising one or more modifications of the phosphodiester linkage within five nucleotides of both the 5' and 3'-ends (i.e., SEQ ID NOs: 64 and 65) and a synthetic guide RNA or crRNA molecule comprising one or more modifications of the sugar within five nucleotides of both the 5' and 3'-ends (e.g., SEQ ID Nos: 66 and 67). *See, e.g.*, Pet. 19–24, 27–29 (showing for claim 1). Petitioner points to Pioneer Hi-Bred's disclosure that "the modified gRNAs of Table 8 and Table 7 can be used to edit cells such as maize cells," (*see* Pet. 26) thus demonstrating

sufficiently for institution that Pioneer Hi-Bred discloses that the modified crRNAs in Table 8 have guide RNA functionality in a CRIPSR-Cas system.

In its preliminary response, Patent Owner raises two arguments against the merits of Petitioner's anticipation ground. *See* Prelim Resp. 39–48. First, Patent Owner argues that the Petition fails to demonstrate that Pioneer Hi-Bred discloses modified guide RNAs with the functionality recited in independent claims 1 and 12, i.e., "(1) gRNA functionality comprising associated with a Cas protein, and (2) gRNA functionality comprising targeting the gRNA:Cas protein complex to the target sequence." *Id.* at 41 (citing Ex. 1001, 244:19–34) (emphasis omitted).

Patent Owner's first argument is unavailing on the current record. The Petition identifies a sufficient connection between the modified crRNA molecules in Table 8 and the disclosure of guide RNA functionality throughout Pioneer Hi-Bred. *See* Pet. 26; *see also* Ex. 1006, 24:6–11 (stating that a "guide polynucleotide" is 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"); 99:3–6 ("[e]xpression of both the Cas endonuclease gene and the crRNA and tracrRNA molecules allows for the formation of the duplex guide RNA/Cas endonuclease system"); Fig. 3A–3B (depicting guide RNA/Cas complexes). Indeed, Pioneer Hi-Bred states that its "modified guide polynucleotides" can be used with the various "components needed to form a functional guide polynucleotide/Cas endonuclease complex" and "to target multiple chromosomal DNA sequences for cleavage or nicking." Ex. 1006, 107:14–108:2. On the current record, this disclosure appears sufficient to read on the "gRNA functionality" recited in claims 1 and 12.

Patent Owner's second argument is that Pioneer Hi-Bred is not enabling. According to Patent Owner, Pioneer Hi-Bred does not disclose "any testing of the pertinent modifications" and therefore a POSA "would be left needing to make, use, and test each of the many potential modifications to determine the impact of the proposed modification on gRNA functionality." Prelim Resp. 44–46. In addition, Patent Owner argues that data in the '001 patent shows that one of the modified crRNAs in Table 8 of Pioneer Hi-Bred, i.e., proposed modifications in SEQ ID NOs 68 and 69, "are non-functional." *Id.* at 47–48. In Patent Owner's view, "[t]he fact that the '001 Patent establishes that the allegedly anticipatory designs of Pioneer Hi-Bred are not functional is 'strong evidence' that Pioneer Hi-Bred is nonenabling." *Id.* at 48 (citing *In re Donahue*, 766 F.2d 531, 533 (Fed. Cir. 1985)).

Patent Owner's second argument is also unavailing on the current record. Pioneer Hi-Bred's disclosure, including that the modified crRNA molecules in Table 8 have guide RNA functionality, is presumptively enabling. *In re Antor Media Corp.*, 689 F.3d 1282, 1287–88 (Fed. Cir. 2012); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003) ("both claimed and unclaimed materials disclosed in a patent are presumptively enabling" for purposes of determining anticipation). Even accepting Patent Owner's argument that the data in the '001 patent shows that the modified crRNA comprising SEQ ID NOs 68 and 69 lacks guide RNA functionality, Pioneer Hi-Bred still discloses two other examples (i.e., the crRNA comprising SEQ ID NOs 64 and 65 and the crRNA comprising SEQ ID NOs 66 and 67) that, at least on the current record, appear to read on the synthetic RNA molecules recited in claims 1

and 12. Patent Owner's Preliminary Response does not identify evidence sufficient to overcome the presumption the SEQ ID NO: 64 and 65 example and the SEQ ID NOs: 66 and 67 example are enabling.

To the extent Patent Owner suggests that test data confirming the "gRNA functionality" of these examples is necessary for Pioneer Hi-Bred to be enabling prior art, we are skeptical that position is consistent with precedent. Our reviewing court has explained,

> [t]he standard for enablement of a prior art reference for purposes of anticipation under section 102 differs from the enablement standard under 35 U.S.C. § 112. *Rasmusson v. SmithKline Beecham Corp*., 413 F.3d 1318, 1325 (Fed.Cir.2005) (citation omitted). While section 112 "provides that the specification must enable one skilled in the art to 'use' the invention," *id.* (quoting *In re Hafner*, 56 C.C.P.A. 1424, 410 F.2d 1403, 1405 (1969)), "section 102 makes no such requirement as to an anticipatory disclosure," *id.* Significantly, we have stated that "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art." *Bristol–Myers Squibb Co. v. Ben Venue Labs., Inc*., 246 F.3d 1368, 1379 (Fed.Cir.2001) (citing *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir.1985) ("It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.")).

Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp., 424 F.3d 1347, 1355 (Fed. Cir. 2005). The Federal Circuit has also explained that a prior art reference need not demonstrate the invention's utility to anticipate. *Rasmusson*, 413 F.3d at 1326. Thus, in the context of a method of treatment claim our reviewing court has explained that "proof of efficacy is not required" to show that the method disclosed in the prior art is enabling for purposes of anticipation. *Id.*

At least facially, such precedent suggests Pioneer Hi-Bred need not disclose test data to support its teaching that the modified crRNAs in Table 8 have the recited guide RNA functionality. We note, however, that this case is still at a preliminary stage and the record is not fully developed. We invite the parties to address the application of this precedent to the facts of this case in their subsequent papers. For now, we determine that Petitioner's showing is sufficient to meet its burden for claims 1 and 12.

We also determine that Petitioner's showing for dependent claims 2–7, 9, 10, 13–15, 17, 18, 20–25, and 27–30 is sufficient to meet the burden for institution. Indeed, for most of these claims Petitioner relies on the same examples from Pioneer Hi-Bred Table 8 discussed above and sufficiently shows how the modified crRNA sequences in those examples reads on the additional limitation(s) recited in these dependent claims. *See* Pet. 32–35 (claims 3–7), 38 (claim 10), 43–44 (claims 13–15, 17), 44–48 (claims 20–24), 48–51 (claims 27–30). At this stage, Patent Owner does not present any arguments against Petitioner's showing for these claims beyond its arguments for claims 1 and 12. As explained above, those arguments are unavailing on the current record.

Accordingly, based on the current record, Petitioner has established a reasonable likelihood it will prevail in demonstrating that claims 1–7, 9, 10, 12–15, 17, 18, 20–25, and 27–30 are anticipated by Pioneer Hi-Bred.

F. Obviousness Grounds

Petitioner presents four obviousness grounds collectively challenging claims 2, 8, 9, 11, 15, 18, 19, 25, 26, 29, and 30. *See* Pet. 51–83. For each of these grounds, Petitioner asserts that it would have been obvious to

combine the modified guide RNAs taught in Pioneer Hi-Bred in view of the teachings in one of the cited secondary references or the knowledge of a POSA to arrive at the claimed invention. *Id.* Petitioner supports these assertions by articulating various reasons why, in its view, a POSA would have been motivated to make the combination and have a reasonable expectation of success in doing so. *See id.* at 55–64 (ground two), 67–69 (ground three), 70–75 (ground four), 76–83 (ground five).

At this stage, Patent Owner argues that a POSA would not have had a reasonable expectation of success for the combinations in each of Petitioner's obviousness grounds because the additional references and knowledge of a POSA "cannot make up for the Petition's shortcomings with respect to the functionality requirements of the independent claims." Prelim. Resp. 49; *see also id.* at 52 (arguing that grounds four and five "do not make up for or add evidence to address the lack of showing of functionality and enablement of the independent claims"). In other words, Patent Owner contends the obviousness grounds fail because Petitioner has failed to meet its burden for its anticipation challenge of the independent claims in ground one. *See id.* at 49, n. 10 ("Each Ground fails because independent claims 1 and 12 . . . incorporated by reference into the Petition's discussion of Grounds 2 and 3, have not been shown to be anticipated.").

Because we determine that Petitioner has met its burden for institution on its anticipation ground, we find Patent Owner's arguments for the obviousness grounds in the Preliminary Response to be unavailing. We also determine that, based on the current record, Petitioner has met its burden for institution on all of the obviousness grounds in the Petition. That said, we express some skepticism regarding the Petition's showing for those

dependent claims, e.g., claims 8, 9, 11, 16, 18, 19, 25, and 26, where Petitioner's obviousness theory relies on combining modifications from other references or the knowledge of a POSA in ways that may not be exemplified or otherwise disclosed in Pioneer Hi-Bred. For those claims, Patent Owner's arguments regarding "the unpredictability of the effects of RNA modifications on various RNA or oligonucleotide types" may carry more weight and ultimately be persuasive to undermine Petitioner's showing that a POSA would have reasonably expected such modifications to successfully produce a functional guide RNA. *See* Prelim. Resp. 51. In any event, such issues would benefit from further development and we invite the parties to address them more fully in their papers at trial.

VI. CONCLUSION

Based on the current record, we determine Petitioner has shown a reasonable likelihood that it will prevail in establishing that at least one claim of the '001 patent is unpatentable. Accordingly, we institute review of all claims challenged on all of the grounds in the Petition. *See* Consolidated Trial Practice Guide (Nov. 2019), 64, available at https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing analysis could change upon completion of the record.

VII. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–30 of the '001 patent based on the unpatentability challenges presented in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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