

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.,
Petitioner,

v.

REGENTS OF THE UNIVERSITY OF MINNESOTA,
Patent Owner.

IPR2017-01753
Patent 8,815,830 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* YANG.

Opinion Dissenting filed by *Administrative Patent Judge* PAULRAJ.

YANG, *Administrative Patent Judge*.

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

INTRODUCTION

Gilead Sciences, Inc. (“Petitioner”) filed a Petition (Paper 1 (“Pet.”)), seeking an *inter partes* review of claims 1–9, 11–21, 23, 24, and 26–28 of U.S. Patent No. 8,815,830 B2 (Ex. 1101, “the ’830 patent”). Regents of the University of Minnesota (“Patent Owner”) filed a Preliminary Response. Paper 33 (“Prelim. Resp.”).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a) (2012).

For the reasons provided below, we determine that Petitioner has not demonstrated a reasonable likelihood that it would prevail with respect to at least one of the claims challenged in the Petition. Accordingly, we deny institution of an *inter partes* review.

Related Matters

According to the parties, Patent Owner asserted the ’830 patent against Petitioner in *Regents of the University of Minnesota v. Gilead Sciences, Inc.*, No. 16-cv-02915 (D. Minn.). Pet. x; Paper 3, 1. The case was later transferred to the U.S. District Court for Northern District of California and was docketed as *Regents of the University of Minnesota v. Gilead Sciences, Inc.*, No. 3:17-cv-06056 (N.D. Ca.). Paper 20, 1.

Petitioner also filed three other petitions (IPR2017-01712, IPR2017-02004, IPR2017-02005), all challenging the claims of the ’830 patent. Paper 12, 1.

Case History

Petitioner filed the Petition on July 7, 2017. Paper 5. With our authorization, the parties briefed the issue of whether the doctrine of sovereign immunity applies in this proceeding such that we should grant Patent Owner's Motion to Dismiss the Petition. Papers 14, 15, 16.

While the Motion to Dismiss in this case was pending, the Board denied Patent Owner's motions to dismiss based on sovereign immunity in several other *inter partes* review proceedings. *LSI Corp. v. Regents of the Univ. of Minn.*, IPR2017-01068, Paper 19 (PTAB Dec. 19, 2017); *Ericsson Inc. v. Regents of the Univ. of Minn.*, IPR2017-01186, -01197, -01213, -01214, -01200, -01219 (PTAB Dec. 19, 2017). On February 12, 2018, Patent Owner filed a Notice of Appeal, seeking immediate appellate review of those decisions. *See, e.g.*, IPR2017-01186, Paper 22.

Under such circumstances, and at the request of Patent Owner, we suspended this proceeding in view of the appellate adjudication of the state-sovereign-immunity issue. Papers 17, 22, 25, 28. Petitioner then sought, and was granted, leave to intervene in those appeals. Paper 26, 2.

On June 14, 2019, the Federal Circuit affirmed the Board's decision denying Patent Owner's motion to dismiss in those proceedings. *Regents of the Univ. of Minn. v. LSI Corp.*, 926 F.3d 1327, 1330 (Fed. Cir. 2019). On January 13, 2020, the Supreme Court denied Patent Owner's petition for writ of certiorari. *Regents of the Univ. of Minn. v. LSI Corp.*, 140 S. Ct. 908 (Jan. 13, 2020) (No. 19-337). The next day, we denied Patent Owner's Motion to Dismiss and lifted the stay order in this proceeding. Paper 32.

Because Petitioner filed four petitions, challenging largely overlapping claims of the '830 patent, we requested Petitioner to rank them in the order in which it wishes the panel to consider the merits. Paper 38, 2 (citing Office Patent Trial Practice Guide, July 2019 Update,¹ 26). We also invited Patent Owner to respond to Petitioner's notice. *Id.* at 3. The parties have since filed their respective papers. Papers 39, 40.

The '830 Patent

The '830 patent relates to nucleosides with antiviral and anticancer activity. Ex. 1101, 1:1–2.

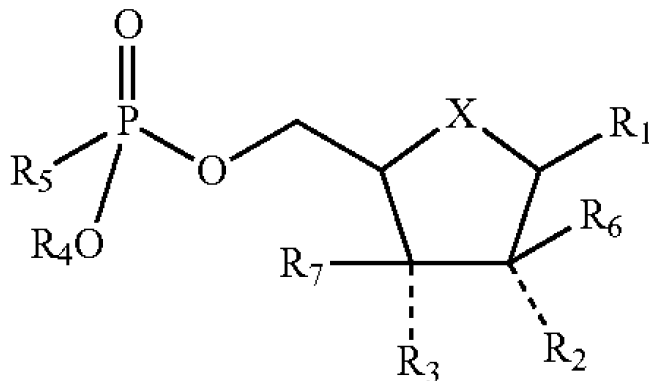
The '830 patent acknowledges that “U.S. Pat. No. 6,475,985 reports certain specific nucleoside phosphoramidate analogs having anticancer and/or antiviral properties.” *Id.* at 1:61–63. It states that there were other, continued interests “in phosphoramidate nucleoside analogs due to their demonstrated utility as prodrugs of antiviral and anticancer nucleoside monophosphates, or pronucleotides.” *Id.* at 1:63–66. But despite the prior-art studies on this topic, there was still “a need for chemotherapeutic agents with antiviral and[/]or anticancer properties.” *Id.* at 2:6–8. According to the '830 patent, its invention provides such “compounds that act as antiviral and[/]or anticancer agents.” *Id.* at 2:48–49.

¹ 84 Fed. Reg. 33,926 (July 16, 2019), available at <https://www.uspto.gov/TrialPracticeGuide3>.

Illustrative Claim

Claim 1 is independent and is reproduced below:

1. A compound of formula I:



wherein:

R₁ is guanine, cytosine, thymine, 3-deazaadenine, or uracil, optionally substituted by 1, 2, or 3 U; wherein each U is independently halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, hydroxy(C₁-C₆)alkyl, —(CH₂)₁₋₄P(=O)(OR_w)₂, aryl, aryl(C₁-C₆)alkyl, or NR_xR_y;

R₂ is halo;

R₆ and R₇ are independently H or (C₁-C₆)alkyl;

R₃ is hydroxy;

R₄ is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, aryl(C₁-C₆)alkyl, or 2-cyanoethyl;

R₅ is an amino acid;

X is oxy, thio, or methylene;

each R_w is independently hydrogen or (C₁-C₆)alkyl;

R_x and R_y are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, phenethyl, or (C₁-C₆)alkanoyl; or R_x and R_y together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino;

wherein any (C₁-C₆)alkyl of R₁, R₄-R₇, R_w, R_x, and R_y is optionally substituted with one or more halo, hydroxy,

(C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, oxo (=O), (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkyl(C₁-C₆)alkyl, (C₁-C₆)alkyl-S—(C₁-C₆)alkyl-, aryl, heteroaryl, alkyl(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl, or NR_{aj}R_{ak}; wherein each R_{aj} and R_{ak} is independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl;

and wherein any aryl or heteroaryl may optionally be substituted with one or more substituents selected from the group consisting of halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, and amino;

or a pharmaceutically acceptable salt thereof.

Asserted Ground of Unpatentability

Petitioner challenges claims 1–9, 11–21, 23, 24, and 26–28 under a single ground, alleging they are unpatentable for obviousness over the combined teachings of the '985 patent,² Maruyama,³ and Sato.⁴

In support of its patentability challenge, Petitioner relies on the Declaration of David MacMillan, Ph.D. Ex. 1107.

² Wagner et al., U.S. Pat. No. 6,475,985, issued November 5, 2002 (Ex. 1102).

³ Tokumi Maruyama et al., *Synthesis and Anti-HIV Activity of 6-Substituted Purine 2'-Deoxy-2'-Fluororibosides*, 13 NUCLEOSIDES & NUCLEOTIDES 527 (1994) (Ex. 1103).

⁴ Yoshiko Sato et al., *Synthesis and Hypnotic and Anti-Human Immunodeficiency Virus-1 Activities of N3-Substituted 2'-Deoxy-2'-fluorouridines*, 42 CHEM. PHARM. BULL. 595 (1994) (Ex. 1104).

ANALYSIS

Discretionary Denial

Patent Owner contends that we should exercise our discretion and deny institution because Petitioner filed four petitions to challenge the claims of the '830 patent. Prelim. Resp. 9. According to Patent Owner, “[f]our parallel petitions are inappropriate and have placed a substantial and unnecessary burden on the Board and Patent Owner.” *Id.*

Petitioner points out that all four petitions were filed in 2017, before the Office started to disfavor multiple petitions against the same patent. Paper 39, 1. According to Petitioner, but for Patent Owner’s “efforts to stop these proceedings before they began” by asserting sovereign immunity, these proceedings would have concluded before the policy shift. *Id.* at 1–2.

Under such circumstances, and because, as explained below, we deny institution based on substantive analysis of the Petition, we decline to consider whether institution should be denied on a discretionary basis.

Claim Construction

In an *inter partes* review based on a petition filed before November 13, 2018, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b) (2017);⁵ *Cuozzo*

⁵ The final rule changing the claim construction standard does not apply here, as the Petition was filed before the effective date of the final rule, November 13, 2018. *See* Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51,340 (Oct. 11, 2018) (amending 37 C.F.R. § 42.100(b) effective November 13, 2018).

Speed Techs., LLC v. Lee, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

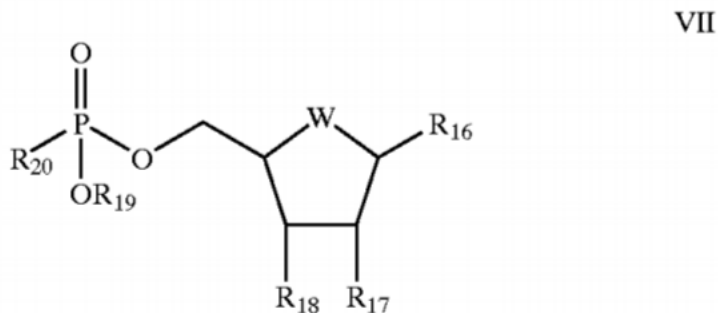
Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to construe any term expressly.

Prior-Art Disclosures

The '985 Patent

The '985 patent teaches nucleosides that possess antiviral and anticancer activity. Ex. 1102, Abstract. Claims 75 and 78 of the '985 patent are reproduced below:

75. A therapeutic method comprising treating breast cancer by administering to a mammal in need of such therapy, an effective amount of a compound of formula VII:



wherein

R₁₆ is adenine, guanine, cytosine, thymine, 3-deazaadenine, or uracil, optionally substituted by 1, 2, or 3 U; wherein each is independently halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, hydroxy(C₁-C₆)alkyl, -(CH₂)₁₋₄P(=O)(OR_w)₂ aryl, aryl(C₁-C₆)alkyl, or NR_xR_y;

one of R₁₇ and R₁₈ is hydroxy and the other is hydrogen, halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, -N(R_z)C(=O)N(R_{aa})(R_{ab}), -N(R_z)C(=O)OR_{ac}, or NR_{ad}R_{ae};

R₁₉ is hydrogen, (C-C)alkyl, (C-C)cycloalkyl, aryl, aryl(C-C₆)alkyl, or 2-cyanoethyl, wherein any aryl ring may optionally be substituted by 1, 2, or 3 halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoxy, (C₁-C₆)alkanoyloxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, or amino;

R₂₀ is an amino acid or a peptide;

W is oxy, thio, or methylene;

each R_w is independently hydrogen or (C₁-C₆)alkyl;

R_x and R_y are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, phenethyl, or (C₁-C₆)alkanoyl; or R_x and R_y together with the nitrogen to which they are attached are pyrrolidino, piperdino or morpholino;

R_z is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl;

R_{aa} and R_{ab} are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached are pyrrolidino, piperdino or morpholino; and

R_{ac} is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; and

R_{ad} and R_{ae} are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, phenethyl, or (C₁-C₆)alkanoyl;

or R_{ad} and R_{ae} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino;

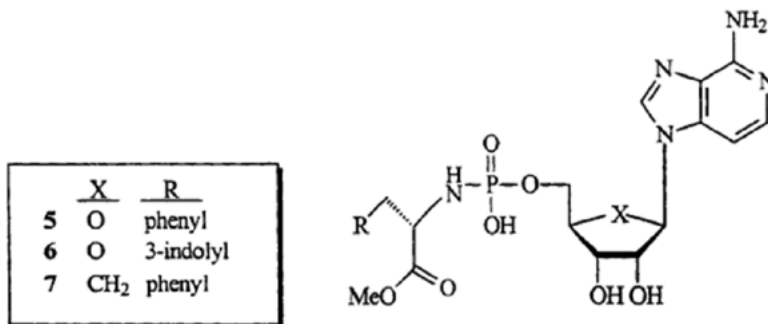
or a pharmaceutically acceptable salt thereof.

....

78. The method of claim 75 wherein R_{18} is hydroxy.

Id. at 45:1–65, 46:13.

Figure 1 of the '985 patent shows several representative compounds:



The figure above illustrates the structures of compounds 5, 6, and 7 of the '985 patent. According to the '985 patent,

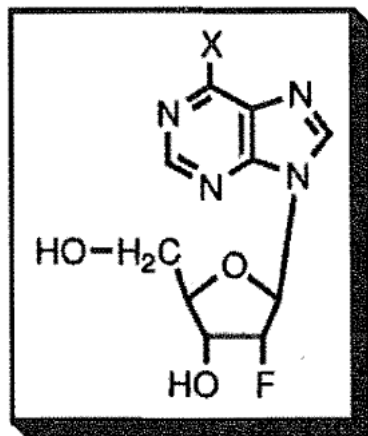
[T]he phosphoramidates, 5, 6 and 7 (FIG. 1), were able to effectively inhibit HIV-1 viral growth in peripheral blood lymphocytes. The tryptophan phosphoramidate, 6, is nearly forty-fold more active than DZA, while the phenylalanine derivative, 5, is nearly ten-fold more active than DZA. As was observed for AZT-phosphoramidates, the DZA phosphoramidates exhibited no detectable cytotoxicity to PBMCs at concentrations as high as 10 μ M, while the CC_{80} for DZA is 1 μ M. Surprisingly, unlike DZA, phosphoramidates of DZA did not exhibit activity against AZT resistant HIV-1.^[6]

Id. at 18:27–38 (footnote added).

⁶ The parties do not dispute that DZA is a known anti-HIV agent and AZT is a known and FDA-approved HIV drug. Pet. 38; Prelim. Resp. 18.

Maruyama

Maruyama teaches the syntheses of 6-substituted purine 2'-deoxy-2'-fluororibosides. Ex. 1103, 528–29. It reports the inhibition of HIV-1 plaque formation by the following compounds:



6 series

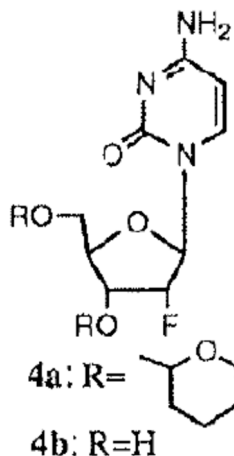
a ; X=Cl, b ; X=NH₂

c ; X=NMe₂, d ; X=SH

The figure above shows the structures of compounds 6a–6d of Maruyama. *Id.* at 531, Table 1. According to Maruyama, “[b]oth 6a and 6b displayed indications of activity against HIV-1 in this series.” *Id.* at 529.

Sato

Sato reports the synthesis of, among others, 2'-deoxy-2'-fluorocytidine (compound 4b). Ex. 1104, 595–96. Compound 4b has the following structure:



The figure above shows the structures of compounds 4a and 4b of Sato. *Id.* at 595. According to Sato, “[c]ompound 4b showed moderate antiviral activity” against HIV-1. *Id.*, Abstract; *see also id.* at 596, Table II (showing in plaque inhibition assay, compound 4b displayed 43% reduction against HIV-1 at 10 μ M).

Analysis

Petitioner asserts that claims 1–9, 11–21, 23, 24, and 26–28 would have been obvious over the combination of the ’985 patent, Maruyama, and Sato. Pet. 31–64. Based on this record, we determine Petitioner has not established a reasonable likelihood that it would prevail in this assertion.

Petitioner argues that compounds 5 and 6 of the ’985 patent are lead compounds. *Id.* at 33–39. According to Petitioner, they are “nucleoside phosphoramidates with proven activity against HIV” and favorable cytotoxicity profile. *Id.* at 37–38 (citing Ex. 1102, 18:25–32, 20:9–53; Ex. 1107 ¶ 104). Petitioner explains that in the nomenclature of the ’830 patent, each of compounds 5 and 6 contains an oxygen heteroatom in the sugar ring at X, a 3-deazaadenine base at R₁, hydroxy at R₂ and R₃, and hydrogen at R₄, R₆, and R₇. *Id.* at 33–35 (citing Ex. 1102, Figure 1; Ex. 1107

¶¶ 109–111). And at R₅, compound 5 contains a methyl-ester of phenylalanine, and compound 6 contains a methyl-ester of tryptophan, both of which are amino acids. *Id.*

Petitioner concludes that “[c]ompounds 5 and 6 of the prior art ’985 patent are fully within the scope of claim 1 of the ’830 patent, with one exception,” that is, claim 1 of the ’830 patent “limits R₂—the 2’-‘down’ position on the sugar ring—to halo (fluoro for claims 6 and 18),” whereas each of compounds 5 and 6 has a hydroxy there. *Id.* at 35. Petitioner argues that “[t]he only ‘further development effort’ necessary to bring the ’985 patent compounds 5 and 6 wholly within the scope of the claims of the ’830 patent would have been the substitution of a secondary fluorine for the secondary hydroxy group at R₂.” *Id.* at 38–39. According to Petitioner, the prior art “provides clear motivation” for this modification and an ordinarily skilled artisan would have had a reasonable expectation of success in doing so. *Id.* at 39–48.

Patent Owner contends that Petitioner’s obviousness challenge fails because (1) the Petition fails to establish that compounds 5 and 6 are lead compounds; (2) even if compounds 5 and 6 are considered lead compounds, the Petition fails to establish that an ordinarily skilled artisan would have modified them to arrive at the claimed compounds; and (3) there is no reasonable expectation of success. Prelim. Resp. 10–66. For purposes of this Decision, we determine that even if compounds 5 and 6 are lead compounds, the Petition has failed to demonstrate adequately for institution a reason to modify the lead compounds with a reasonable expectation of successfully arriving at the claimed compounds.

Alleged Reason to Modify Based on the '985 Patent

Petitioner argues that the '985 patent teaches a secondary fluorine substitution as one of several options at the 2' position. Pet. 39–40 (citing Ex. 1102, 5:24–30, claim 75). Petitioner also refers to the '985 patent for teaching that “substituents at the 2' and 3' positions of the nucleosides of the invention can have any stereo orientation.” *Id.* at 40 (quoting Ex. 1102, 8:37–39). According to Petitioner, thus, “the '985 patent itself, in both its specification and claims, teaches that a secondary fluorine (**halo**) substitution is one of several possible selections at the 2'-position (**R₁₇**) that a person of skill would consider, including at the 2'-‘down’ position.” *Id.* at 39 (citing Ex. 1107 ¶ 117). We are not persuaded by this argument for three reasons.

First, Petitioner relies on compounds 5 and 6 of the '985 patent as the lead compounds for further modification. In each of those two compounds, the potential variables identified in formula VII are predetermined. Petitioner does not explain sufficiently why an ordinarily skilled artisan would have maintained the predetermined **R₁₆**, **R₁₈**, **R₁₉**, **R₂₀**, and **W**, and only modified **R₁₇**.

Second, the '985 patent teaches that **R₁₇** of formula VII, which corresponds to **R₂** in challenged claim 1, could be “hydrogen, halo, hydroxy, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyloxy, (C₁-C₆)alkanoyl, (C₁-C₆)alkanoyloxy, trifluoromethyl, azido, cyano, –N(**R_z**)C(=O)N(**R_{aa}**)(**R_{ab}**), –N(**R_z**)C(=O)OR_{ac}, or NR_{ad}R_{ae}.” Ex. 1102, 5:24–29, 45:24–30. It further teaches that

R_z is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl;

R_{aa} and R_{ab} are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; or R_{aa} and R_{ab} together with the nitrogen to which they are attached are pyrrolidino, piperdino or morpholino; and

R_{ac} is hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, or phenethyl; and

R_{ad} and R_{ae} are each independently hydrogen, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, phenyl, benzyl, phenethyl, or (C₁-C₆)alkanoyl; or R_{ad} and R_{ae} together with the nitrogen to which they are attached are pyrrolidino, piperidino or morpholino.

Id. at 5:46–60, 45:49–64. Thus, the “several options” at the 2' position, according to Petitioner’s characterization (Pet. 39), in fact include thousands of possibilities. As Patent Owner correctly points out, “the ’985 Patent discloses many different substituents for the 2' position and expresses no preference for the particular substituent (fluorine) [Petitioner] picked.” Prelim. Resp. 40.

Third, as Petitioner acknowledges, the ’985 patent teaches that substituents at the 2' position “can have any stereo orientation.” Pet. 40 (quoting Ex. 1102, 8:37–39). According to Patent Owner, the fact that substituents at the 2' position can be either “up” or “down” not only doubles the already large number of possible substituents, but also affects the resulting compounds’ activities. Prelim. Resp. 40–41. Indeed, Marquez I,⁷ a prior art reference Petitioner relies on, teaches that “[w]hile 2'-F-ddA (II) was stable to acid catalyzed decomposition at pH 1, the addition of a

⁷ Victor E. Marquez et al., *Rapid Communications: 2', 3'-Dideoxy-2'-Fluoro-Ara-A. An Acid-Stable Purine Nucleoside Active Against Human Immunodeficiency Virus (HIV)*, 36 BIOCHEM. PHARMACOL. 2719 (1987) (Ex. 1111, “Marquez I”).

fluorine atom in this ‘down’ configuration reduced the protective effect against HIV to 13% of that seen with ddA and produced a compound more toxic than the parent drug.” Ex. 1111, 2721. In contrast, “[a] change in the stereochemistry of fluorine at the 2'-position to the ‘up’ configuration produced dramatically different activity results as well as acid stability.” *Id.* Thus, we agree with Patent Owner that “[d]ifferent stereoisomers (e.g., ‘up’ or ‘down’) of the otherwise same molecule can have vastly different anti-HIV activity, toxicity and/or chemical stability.” Prelim. Resp. 41.

In sum, Petitioner has not sufficiently explained why, based on the teachings of the '985 patent, an ordinarily skilled artisan would have substituted a fluorine at the 2' down position of compounds 5 and 6.

Alleged Reason to Modify Based on Maruyama and Sato

Petitioner also contends that “Maruyama and Sato report that substitution of the specific halogen, fluorine, at the 2’-‘down’ position (with hydrogen at the 2’-‘up’ position) conveys anti-HIV activity to natural nucleosides.” Pet. 40. Petitioner explains that in the nomenclature of the '830 patent, at R₁, compound 6b of Maruyama contains an adenine base, and compound 4b of Sato contains a cytosine. *Id.* Each of these two compounds contains an oxygen heteroatom in the sugar ring at X, fluorine at R₂, hydroxy at R₃, and hydrogen at R₆ and R₇. *Id.* Petitioner points out that the prior art reported anti-HIV activity in both compound 6b of Maruyama and compound 4b of Sato. *Id.* at 41–43 (citing Ex. 1103, Table 1; Ex. 1104, Table II). Petitioner concludes:

The import of Maruyama and Sato is that each reference teaches a person of skill that the exact same modification proposed to lead compounds 5 and 6 of the '985 patent (substituting a

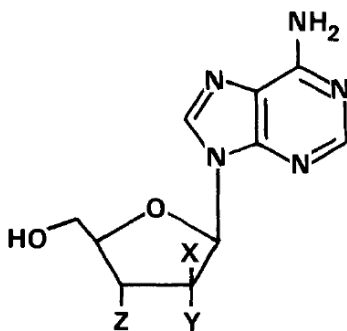
secondary fluorine at the 2'-"down" position) has been done before and was known in the art to impart anti-HIV activity.

Id. at 43 (citing Ex. 1107 ¶ 118).

Patent Owner disagrees, emphasizing that Petitioner has not shown sufficiently that an ordinarily skilled artisan, aware of the prior art as a whole, and not just Maruyama and Sato, would have substituted fluorine at the 2' down position of compounds 5 and 6 of the '985 patent. *See* Prelim. Resp. 45, 55–61. We find Patent Owner's arguments more persuasive. Indeed, prior art, including those references Petitioner relies on, teaches that substituting fluorine at the 2' down position of several compounds with anti-HIV activity not only renders the compounds inactive, but also increases their toxicity.

Petitioner relies on Marquez I and Marquez II⁸ in support of its argument that an ordinarily skilled artisan would have substituted fluorine at R₂ for its "stabilizing effects." Pet. 44 (citing Ex. 1111), 46 (citing Ex. 1119); *see infra* at 21–22. Marquez I teaches the synthesis of two monofluoro 2'-diastereomers of ddA, compounds II and III. Ex. 1111, 2719–21. The structures of the compounds are:

⁸ Victor E. Marquez et al., *Acid-stable 2'-Fluoro Purine Dideoxynucleosides as Active Agents against HIV*, 33 J. MED. CHEM. 978 (1990) (Ex. 1119, "Marquez II").



I, X = H; Y = H; Z = H
II, X = H; Y = F; Z = H
III, X = F; Y = H; Z = H

The figure above shows the structure of compounds I, II, and III of Marquez I. *Id.* at 2719. Compound I is ddA, which is potent and effective in inhibiting the cytopathic effect of HIV. *Id.* Compounds II and III are ddA derivatives, with fluorine at the 2' down position and the 2' up position, respectively. *Id.* at 2721. Marquez I reports:

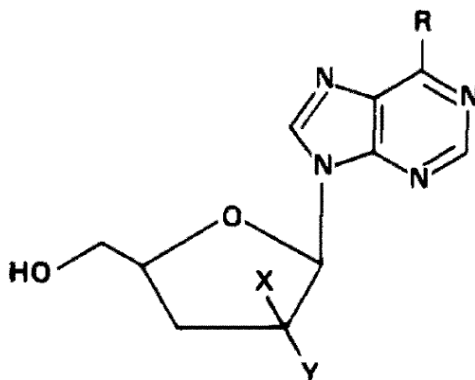
While 2'-F-ddA (II) was stable to acid-catalyzed decomposition at pH 1, the addition of a fluorine atom in this “down” configuration reduced the protective effect against HIV to 13% of that seen with ddA and produced a compound more toxic than the parent drug.

A change in the stereochemistry of fluorine at the 2'-position to the “up” configuration produced dramatically different activity results as well as acid stability. 2'-F-ara-ddA (III) was approximately as active and potent as AZT (1) or ddA . . . in protecting ATH8 cells against the cytopathic effect of HIV under conditions of substantial viral excess. Furthermore, the antiviral effect of III was as durable as that of the parent compound, I.

Id.

Marquez II reports similar results. Marquez II investigated the effect of adding a fluorine atom to the 2'-position of ddA by preparing the fluorine-

containing 2'-*erythro* and 2'-*threo* isomers of ddA. Ex. 1119, Abstract. The structures of the compounds are:



- 1, X=Y=H; R=OH (ddl)
- 2, X=Y=H; R=NH₂ (ddA)
- 3, X=F; Y=H; R=NH₂ (2'-F-dd-ara-A)
- 4, X=F; Y=H; R=OH (2'-F-dd-ara-I)
- 5, X=H; Y=F; R=NH₂

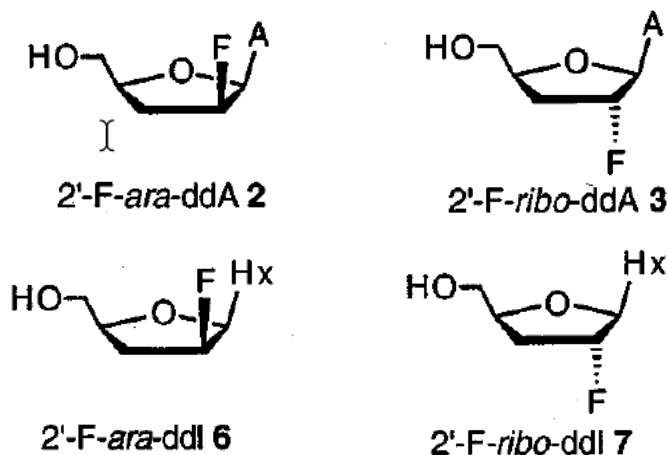
The figure above shows the structures of compounds 1–5 of Marquez II. *Id.* at 979. Compound 2 is ddA, which according to Marquez II, “shows potent activity and better selectivity in vitro against HIV than AZT in ATH8 cells.” *Id.* Compounds 3 and 5 are ddA derivatives, with fluorine at the 2' down position and the 2' up position, respectively. *Id.*

Marquez II reports that compounds 3 and 5 are “completely inert” to acid hydrolysis under the conditions that rapidly hydrolyzed ddA. *Id.* “Evaluation of [compounds] 3 and 5 in the ATH8/HIV system,” however, “indicated that only the *threo* isomer ([compound] 3, 2'-F-dd-ara-A) was an effective anti-HIV agent.” *Id.*; see also *id.* at Abstract (reporting that “the fluorine-containing *erythro* isomer, [compound] 5, was inactive,” but the *threo* isomer (compound 3) was “just as potent and active in protecting

CD4+ ATH8 cells from the cytopathogenic effects of HIV-1 as the parent drug[]”).

In addition to the two references cited in the Petition, Patent Owner presents two other references, Meier⁹ and Marquez III,¹⁰ to show that fluorine at the 2' down position renders the resulting compounds inactive.

Meier determined the antiviral property of several compounds, including compounds 2, 3, 6, and 7, reproduced below.



The figure above shows the structures of compounds 2, 3, 6, and 7 of Meier. Ex. 2123, 1617. According to Meier, ddA and ddI had been used clinically for the treatment of AIDS. *Id.* at 1615. Meier reports that compounds 3 (2'-F-ribo-ddA) and 7 (2'-F-ribo-ddI), each of which contains a fluorine at the 2' down position, “were devoid of any antiretroviral

⁹ Chris Meier et al., *cycloSal-Pronucleotides of 2'-Fluro-ara- and 2'-Fluro-ribo-2',3'-dideoxyadenosine as a Strategy to Bypass a Metabolic Blockade*, 42 J. MED. CHEM. 1615 (1999) (Ex. 2123).

¹⁰ Victor E. Marquez et al., *Conformational Studies and Anti-HIV Activity of Mono- and Difluorodideoxy Nucleosides*, Nucleoside and Nucleotide as Antinumor and Antiviral Agents (Plenum Press, New York, 1993), pp. 265–84 (Ex. 2124, “Marquez III”).

activity,” whereas compounds 2 (2'-F-*ara*-ddA) and 6 (2'-F-*ara*-ddI), each of which contains a fluorine at the 2' up position, “proved to be equally active against HIV-1- and HIV-2-induced cytopathogenicity in CEM cells.” *Id.* at 1619.

Marquez III reviewed the literature on monofluoro dideoxynucleosides and their anti-HIV activity. Ex. 2124, 266, Table 1. It observed that “[f]or various aglycon moieties, a fluorine atom at positions 3'-‘down’ or 2'-‘up’ correlates with anti-HIV activity (Table 1). On the other hand, fluorine atoms at the same positions, but with inverted stereochemistry, consistently produced inactive compounds (Table 1).” *Id.* at 267.

In sum, the prior art consistently teaches that the type of modification proposed by Petitioner, that is, substituting a fluorine at the 2' down position of a compound that already exhibited anti-HIV activity, destroys the activity and increases the toxicity of the compound. *See* Prelim. Resp. 55. Thus, we determine that Petitioner has not met its burden of showing that Maruyama and Sato provide a reason to modify compounds 5 and 6 of the '985 patent as proposed.

Alleged Reason to Modify Based on the “Stabilizing Effects”

Petitioner further contends that an ordinarily skilled artisan would have modified compounds 5 and 6 of the '985 patent because “a secondary fluorine substitution at R₂ would have stabilizing effects.” Pet. 44–47. Citing Marquez I, Petitioner argues that “[n]ucleoside stability was a known problem in the art.” *Id.* at 44 (citing Ex. 1111). According to Petitioner, each of compounds 5 and 6 contains a hemiaminal carbon. *Id.* at 45 (citing

Ex. 1107 ¶ 119). Petitioner argues that introducing a fluorine at the carbon adjacent to a hemiaminal group “would enhance the stability of the β -N1-glycosidic bond,” which “could impact the pharmaceutical properties of lead compounds 5 and 6 in the ’985 patent.” *Id.* at 45–46. As support, Petitioner points to Marquez II’s statement that “ddA had a half-life of less than 1 min at pH 1 and 37 °C. The 2’-fluorinated analogue, however, was shown to be stable indefinitely under these conditions.” *Id.* at 46 (citing Ex. 1119).

Patent Owner disagrees. According to Patent Owner, “[t]here are two kinds of stability of pharmaceutical compounds – chemical and enzymatic,” and Petitioner “does not identify a consistent theory of unpatentability based on either type of stability.” Prelim. Resp. 47–51. Patent Owner also advances other rebuttal arguments. *Id.* at 51–54. We do not need to resolve these disputes because, as discussed above, both Marquez I and Marquez II teach that a fluorine substitution at the 2’ down position renders the compounds inactive and toxic. *See supra* at 17–20. Petitioner has not shown sufficiently for institution that an indefinitely stable but inactive and toxic compound would have motivated an ordinarily skilled artisan to make the same modification to compounds 5 and 6 of the ’985 patent.

In sum, Petitioner’s proposed modification appears to be based on impermissible hindsight, and not on what an ordinarily skilled artisan would have been motivated to do based on the prior art and the knowledge in the art at the time of the invention.

Reasonable Expectation of Success

Petitioner argues that an ordinarily skilled artisan would have had a reasonable expectation that (1) “the replacement of a secondary alcohol with

a secondary fluorine at the 2’-‘down’ position on compounds 5 or 6 would be synthetically possible,” and (2) “based on the actual anti-HIV activity data in Maruyama and Sato, . . . such a substitution would impart anti-HIV activity.” Pet. 48.

Petitioner is correct that “Maruyama and Sato report that substitution of the specific halogen, fluorine, at the 2’-‘down’ position (with hydrogen at the 2’-‘up’ position) conveys anti-HIV activity to natural nucleosides.” Pet. 40. Petitioner’s argument, however, fails to consider that the prior art as a whole, including references Petitioner relies on, teaches that substituting fluorine at the 2' down position renders numerous anti-HIV compounds inactive, and increases their toxicity. *See supra* at 17–20. Thus, Petitioner has not met its burden to show that an ordinarily skilled artisan would have had a reasonable expectation that modified compounds 5 and 6 of the ’985 patent with a fluorine at the 2' down position would retain their anti-HIV activity and lack toxicity. *See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (stating that “the success was finding a compound that had high activity, few side effects, and lacked toxicity”).

Responses to the Dissent

The dissent criticizes that we adopt a “piecemeal approach” because we “separately discuss[] alleged reasons to modify the compounds based on: 1) the ’985 patent itself, 2) Maruyama and Sato, and 3) ‘stabilizing effects’ as taught by Marquez I and Marquez II.” Dissent at 2. But in a case such as this, “it’s the petitioner, not the Director, who gets to define the contours of

the proceeding.” *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355 (2018). We merely evaluate Petitioner’s arguments as presented. *See* Pet. 5, 25–26.

The dissent also criticizes that we find persuasive Patent Owner’s arguments even though they are “based on attorney argument about what the prior art teaches and not supported by expert testimony.” Dissent at 3. In the dissent’s view, the prior art suggests that a fluorine substitution at the 2' down position merely “reduces (but not necessarily ‘destroys’) activity and increases toxicity of the compound.” *Id.* at 4. But the statements in the prior art are more than, as the dissent characterizes, “potential[ly] ‘negative.’” *Id.* at 1. For example, Marquez II reports that the compound with such a substitution “was inactive” (Ex. 1119, Abstract), and Meier teaches that compounds with such a substitution “were devoid of any antiretroviral activity” (Ex. 2123, 1619). And although Marquez I describes that such a substitution “reduced” the anti-HIV effect, it specifies that the reduction is to 13% activity of the parent compound. Ex. 1111, 2721. Indeed, Marquez III, after reviewing publications on this topic, summarizes that such a substitution “*consistently* produced inactive compounds.” Ex. 2124, 267 (emphasis added).¹¹ When the statements in the prior art are clear and easily

¹¹ The dissent states that “at least in light of Maruyama and Sato, it is not clear based on the present record ‘that the prior art *consistently* teaches that the type of modification proposed by Petitioner, that is, substituting a fluoride at the 2' down position of a compound that already exhibited anti-HIV activity, destroys the activity and increases the toxicity of the compound.’” Dissent at 3 (quoting *supra* at 21) (emphasis added by the dissent). Maruyama and Sato, however, as Petitioner acknowledges, do not discuss compounds that already exhibit anti-HIV activity, as compounds 5

understandable, “expert testimony is not required.” *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1079 (Fed. Cir. 2015).

The dissent further criticizes that we impose “too high a burden on Petitioner to identify and preemptively address any potential ‘negative’ statements from the prior art in the Petition itself.” Dissent at 1. In an *inter partes* review, we generally do not require a petitioner to proactively address all possible arguments a patent owner might raise. A party, however, may not selectively point to one portion of an exhibit to buttress its argument, while disregarding another part of the same document that undermines its contention. *See In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965).

Here, Petitioner relies on certain disclosures of Marquez I and Marquez II to support its argument that “a secondary fluorine substitution at R₂ would have stabilizing effects,” Pet. 44 (citing Ex. 1111), 46 (citing Ex. 1119). Petitioner, however, fails to address the data in those references showing that a fluorine at the 2' down position renders the compounds inactive and toxic. Because “[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art,” we determine Petitioner has not met its burden. *See Wesslau*, 353 F.2d at 241.

and 6 of '985 do. Pet. 40 (stating Maruyama and Sato teach that fluorine at the 2' down position “conveys anti-HIV activity to natural nucleosides,” which “are not active against HIV-1”).

CONCLUSION

For the reasons explained above, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that at least one of the challenged claims is unpatentable as obvious over the combination of the '985 patent, Maruyama, and Sato.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Petition is denied, and we do not institute *inter partes* review of any claim of the '830 patent based on the ground asserted in the Petition.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GILEAD SCIENCES, INC.,
Petitioner,

v.

REGENTS OF THE UNIVERSITY OF MINNESOTA,
Patent Owner.

IPR2017-01753
Patent 8,815,830 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges*.

PAULRAJ, *Administrative Patent Judge*, dissenting.

In my view, Petitioner has demonstrated a reasonable likelihood of prevailing with respect to the challenges presented in the Petition. The majority imposes too high a burden on Petitioner to identify and preemptively address any potential “negative” statements from the prior art in the Petition itself.

Taking a step back, Petitioner’s obviousness theory is based on a single modification to prior art compounds 5 and 6 taught in the ’985 patent,

i.e., the substitution of a halogen (in particular fluorine) for the hydroxy group at the corresponding 2' position (claimed "R₂") of the nucleoside core. *See* Pet. 1. Compounds 5 and 6 are otherwise identical to the claimed compound, and the majority does not contend Petitioner has not demonstrated sufficiently that they are appropriate lead compounds for the analysis. Rather, the majority's primary basis for denial is that "Petitioner has failed to demonstrate adequately for institution a reason to modify the lead compounds with a reasonable expectation of successfully arriving at the claimed compounds." Majority Op. 13. The majority separately discusses alleged reasons to modify the compounds based on: 1) the '985 patent itself, 2) Maruyama and Sato, and 3) "stabilizing effects" as taught by Marquez I and Marquez II. *Id.* at 13–22. The majority's piecemeal approach, however, gives selective weight to certain prior art teachings while disregarding others.

For instance, with respect to the '985 patent, the majority focuses on the fact that the 2' position of the compounds (i.e., R₁₇) generically disclosed therein includes "thousands of possibilities," and contends that "Petitioner does not explain sufficiently why an ordinarily skilled artisan would have maintained the predetermined R₁₆, R₁₈, R₁₉, R₂₀, and W, and only modified R₁₇" specifically in compounds 5 and 6. *Id.* at 14–15. Although I agree that the '985 patent includes a large number of possible substituents at the 2' position, it nonetheless specifically identifies and claims a "halo" group among those possible substituents. Pet. 39–40 (citing Ex. 1102, 5:24–30, 8:37–39, 45:25–30; Ex. 1107 ¶ 117).

Moreover, Petitioner's obviousness challenge is not based on the '985 patent alone, but further relies upon additional prior art teachings as providing a specific motivation to include a fluoro group at the 2' position. In particular, Petitioner contends that "Maruyama and Sato report that substitution of the specific halogen, fluorine, at the 2'-'down' position (with hydrogen at the 2'-'up' position) conveys anti-HIV activity to natural nucleosides." Pet. 40. The majority acknowledges this contention and the teachings of Maruyama and Sato, but the majority finds that other "prior art, including those references Petitioner relies on, teaches that substituting fluorine at the 2' down position of several compounds with anti-HIV activity not only renders the compounds inactive, but also increases their toxicity." Majority Op. 17. For example, the majority points to the statement in Marquez I that "the addition of a fluorine atom in this 'down' configuration reduced the protective effect against HIV to 13% of that seen with ddA and produced a compound more toxic than the parent drug." *Id.* at 18 (quoting Marquez I, 2721). But at least in light of Maruyama and Sato, it is not clear, based on the present record, "that the prior art *consistently* teaches that the type of modification proposed by Petitioner, that is, substituting a fluoride at the 2' down position of a compound that already exhibited anti-HIV activity, destroys the activity and increases the toxicity of the compound." *Id.* at 21 (emphasis added). Patent Owner's arguments to this effect that have been adopted by the majority are based on attorney argument about what the prior art teaches and are not supported by expert testimony. *See Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1380 (Fed. Cir. 2009) (noting that "unsworn attorney argument . . . is not evidence"). Regardless, even if one of ordinary skill in the art would have been discouraged by the prior art's

suggestion that a fluoride substitution at the 2' down position reduces (but not necessarily “destroys”) activity and increases toxicity of the compound, the skilled artisan may nonetheless have found reason to attempt such a substitution in order to increase the stability of the compound, which the majority acknowledges is also suggested by Marquez I and Marquez II. Majority Op. 17–19; *see Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (explaining that “a given course of action often has simultaneous advantages and disadvantages, and this does not necessarily obviate motivation to combine”).

The stringent standard that the majority imposes upon the Petitioner in this case is perhaps best captured by its statement that “[a] party . . . may not selectively point to one portion of an exhibit to buttress its arguments, while disregarding another part of the same document that undermines its contention.” Majority Op. 25. The majority acknowledges, however, that “we generally do not require a petitioner to proactively address all possible arguments a patent owner might raise.” *Id.* Here, the additional prior art teachings that the majority finds to undermine Petitioner’s contentions were first identified in Patent Owner’s Preliminary Response. They are not limited to only prior art references identified in the Petition. *Id.* at 19–20 (addressing Patent Owner’s arguments based on Meyer (Ex. 2123) and Marquez III (Ex. 2124)). As such, there appears to be no reason why Petitioner should have preemptively addressed those prior art teachings or anticipated Patent Owner’s arguments as to why they undermine Petitioner’s contentions.

This is not to say that Petitioner has met its ultimate burden of proving unpatentability of the challenged claims. In determining whether to institute

an *inter partes* review, we must only assess whether “there is a *reasonable* likelihood that the petitioner would prevail.” 35 U.S.C. § 314(a) (emphasis added); *cf. Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 21 (PTAB Dec. 20, 2019) (precedential) (“For institution of an *inter partes* review, a petitioner must establish a reasonable likelihood that a reference is a printed publication. If trial is instituted, the petitioner will ultimately have the burden to prove that the reference is a printed publication by a preponderance of the evidence.”). If a trial had been instituted in this proceeding, Petitioner would have been afforded an opportunity to respond to Patent Owner’s arguments regarding the additional prior art teachings in its Reply and Patent Owner could have responded to Petitioner’s arguments in its Sur-Reply. As recognized by our reviewing court, “the introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings. . . . The development of evidence in the course of the trial is in keeping with the oppositional nature of an *inter partes* review proceeding.” *Genzyme Therapeutic Prod. Ltd. P’ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1367 (Fed. Cir. 2016). In the absence of a full evidentiary record, which would include the cross-examination of Petitioner’s expert and testimony from Patent Owner’s own expert, I am reluctant to resolve the type of factual dispute that the majority does in Patent Owner’s favor at this preliminary stage.

For these reasons, I respectfully dissent.

IPR2017-01753
Patent 8,815,830 B2
FOR PETITIONER:

Alicia Russo
Frederick Millett
Robert S. Schwartz
VENABLE LLP
arusso@venable.com
gilead830ipr@venable.com
rschwartz@Venable.com

Adam K. Mortara
J. Scott McBride
Nevin M. Gewertz
BARTLIT BECK LLP
adam.mortara@bartlit-beck.com
scott.mcbride@bartlit-beck.com
nevin.gewertz@bartlit-beck.com

FOR PATENT OWNER:

Edward Gates
Richard Giunta
Gerald Hrycyszyn
WOLF, GREENFIELD & SACKS, P.C.
egates-ptab@wolfgreenfield.com
rgiunta-ptab@wolfgreenfield.com
ghrycyszyn-ptab@wolfgreenfield.com