

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORP.,

Petitioner,

v.

CHEMGENES CORP.,

Patent Owner.

IPR2023-00490

Patent 9,884,885 B2

Before JOHN G. NEW, ZHENYU YANG, and
CYNTHIA M. HARDMAN, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION

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

I. INTRODUCTION

Petitioner Shanghai Hongene Biotech Corp. (“Petitioner”) has filed a Petition (Paper 1, “Pet.”) seeking *inter partes* review of claims 1–5 of US Patent 9,884,885 B2 (Ex. 1001, the “’885 patent”). Patent Owner ChemGenes Corp. (“Patent Owner”) did not file a Preliminary Response.

Under 35 U.S.C. § 314, the Board “may not authorize an *inter partes* review to be instituted unless ... the information presented in the petition ... and any response ... shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” Upon consideration of the Petition and the evidence of record, we determine that the evidence presented demonstrates a reasonable likelihood that Petitioner would prevail in establishing the unpatentability of at least one challenged claim of the ’885 patent. We consequently institute *inter partes* review.

II. BACKGROUND

A. *Real Parties-in-Interest*

Petitioner identifies Shanghai Hongene Biotech Corp. as the real party-in-interest. Paper 1 at x. Patent Owner identifies ChemGenes Corp. as the real party-in-interest. Paper 4 at 2.

B. *Related Matters*

Patent Owner and Petitioner each identify an infringement action filed by Patent Owner against Petitioner, Case No. 1-22-cv-10290 (D. Mass.), asserting infringement of certain patents, including the ’885 patent. Pet. x;

Paper 6 at 2. Petitioner notes that, on July 7, 2022, ChemGenes filed a notice of voluntary dismissal of this district court action. Pet. x.

Patent Owner additionally acknowledges that it filed a reissue application relating to the '885 patent, Appl. No. 18/130,902, with the USPTO on April 5, 2023.

C. The Asserted Grounds of Unpatentability

Petitioner contends that claims 1–5 of the '885 patent are unpatentable, based upon the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1	102(b) ¹	Reddy ²
2	2	103(a)	Crooke ³ , Pitsch ⁴ , Fan ⁵

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the application from which the '885 patent issued has an effective filing date prior to that date, the pre-AIA versions of §§ 102 and 103 apply.

² Reddy et al. (US 5,808,039, September 15, 1998) (“Reddy”) Ex. 1016.

³ Crooke (US 5,898,031, April 27, 1999) (“Crooke”) Ex. 1017.

⁴ S. Pitsch et al., *Reliable Chemical Synthesis of Oligoribonucleotides (RNA) with 2'-O-[(Triisopropylsilyl)oxy]methyl(2'-O-tom)-Protected Phosphoramidites*, 84 HELVETICA CHIMICA ACTA 3773–95 (2001) (“Pitsch”) Ex. 1018.

⁵ Y. Fan et al., *Transient Silylation of the Guanosine O6 and Amino Groups Facilitates N-Acylation*, 6(15) ORGANIC LETTS. 2555–57 (2004) Ex. 1019.

3	2	103(a)	Vater ⁶ , Pitsch
4	3	103(a)	Crooke, Pitsch, Fan, Scaringe ⁷
5	4	103(a)	Scaringe, Pitsch, Fan
6	5	102(b)	Gaur ⁸

Petitioner also relies upon the Declaration of Dr. Phil S. Baran (the “Baran Declaration,” Ex. 1003).

D. The '885 Patent

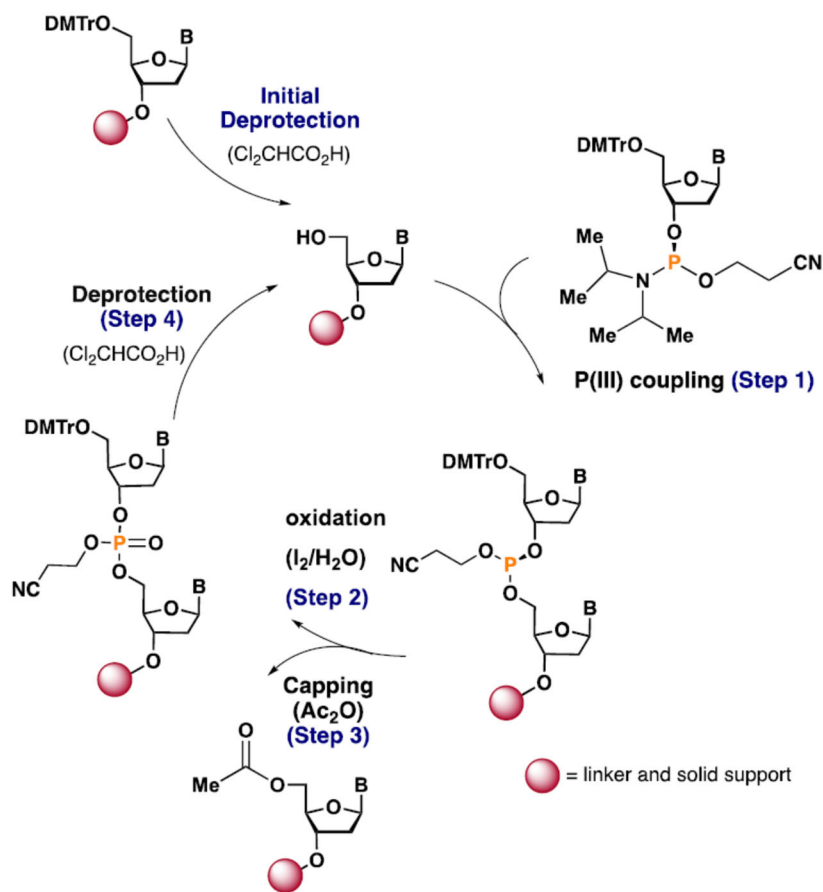
The '885 patent is directed to methods of synthesis of RNA oligonucleotides utilizing N-2-acetyl protected guanine as nucleoside base, and their nucleosides, succinates, phosphoramidites, and corresponding solid supports that are suitable for oligo deoxynucleoside and RNA oligonucleotide synthesis. Ex. 1001, Abstr. Briefly, the '885 patent claims a synthetic route that allows obtaining desired (n-acetyl) nucleosides without any contamination with unwanted impurities. The N-2-acetyl protected guanosine nucleosides and other N-2 acetyl protected nucleosides having

⁶ Vater et al. (US 7,879,991 B2, February 1, 2011) (“Vater”) Ex. 1020.

⁷ S.A. Scaringe et al., *Chemical Synthesis of Biologically Active Oligoribonucleotides using β -Cyanoethyl Protected Ribonucleoside Phosphoramidites*, 18(18) NUCLEIC ACIDS RES. 5433-41 (1990) (“Scaringe”) Ex. 1022.

⁸ R.K. Gaur et al., *Novel Solid Phase Synthesis of 2'-O Methylribonucleoside 5'-Triphosphates and their α -Thio Analogues*, 33(23) TETRAHEDRON LETTS. 3301-04 (1992) (“Gaur”) Ex. 1024.

various 2'-protecting groups as discussed or 2'-modification, such as 2-fluoro or 2'-amino groups, can be combined with cyanoethyl phosphate protecting group and utilized in high purity RNA synthesis. Ex. 1001, cols. 17–18, ll. 62–3. These compounds, when combined with either succinates or phosphoramidites can be used to either tether a given nucleoside to either a solid structure or to another nucleotide in an oligonucleotide chain, respectively. *See, e.g.*, Pet. Fig. 5, which is reproduced below:



The “canonical cycle” of solid-phase oligonucleotide synthesis using phosphoramidites as nucleotide as a protecting group.

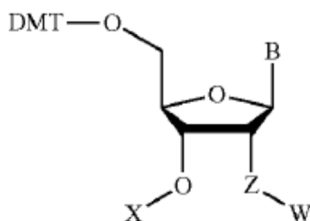
Pet. 14.

The use of phosphoramidites as protecting groups helps to prevent errors and branching in the formation of oligonucleotide chains and permits high-purity oligonucleotide synthesis. Ex. 1001, col. 12, ll. 3–6.

E. Representative Claim

Claim 1 is representative of the challenged claims, and recites:

1. Derivatized nucleoside and phosphoramidite of general formula 1,



Formula 1

where B is selected from the group consisting of guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;

Z is oxygen and W is methyl; and

X is cyanoethyl dialkyl phosphoramidite.

Ex. 1001, col. 25, ll. 25–47.

F. Priority History of the '885 Patent

The '885 patent issued from US Application Ser. No. 13/261,029 (the “'029 application”) filed on May 19, 2010 (Ex. 1001, codes 21–22), and claims the priority benefit of US Provisional Application Ser. No. 61/216,491, which was filed on May 18, 2009. *Id.*, code (60).

The patent issued on February 6, 2018. Ex. 1001, code (45).

III. ANALYSIS

A. *Claim Construction*

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). *See* 37 C.F.R. § 100(b) (2020). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is “less significant than the intrinsic record in determining ‘the legally operative meaning of claim language.’” *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

Petitioner offers no express construction of any of the claim terms. Pet. 17. We consequently construe the claim terms as having their “ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips*, 415 F.3d at 1312–13.

B. *A Person of Ordinary Skill in the Art*

Petitioner contends that, as of the May 18, 2009, filing date of the ’885 patent, a person of ordinary skill in the art would have had a Ph.D. (or equivalent degree) in organic or medicinal chemistry, and two to three years of post-graduate work experience in medicinal chemistry, synthetic organic

chemistry, and nucleic acid chemistry, including the development of oligonucleotide therapeutics, diagnostics, or building blocks. Pet. 17 (citing Ex. 1003 ¶ 24). Alternatively, proposes Petitioner, an individual holding a Bachelor's or Master's degree in organic chemistry or medicinal chemistry, who had extensive work experience in those fields, and who had gained a thorough understanding of the development of nucleic acid-based materials, would also have qualified as a person of ordinary skill in the art. *Id.*

Petitioner's proposed definition of the level of ordinary skill in the art appears to be consistent with the level of skill presented in the cited prior art. *See, e.g.*, Exs. 1017–1020, 1022, 1024. For the purposes of this Decision, then, we adopt Petitioner's definition, quoted above, as the definition of a person of ordinary skill in the art.

IV. ANALYSIS

A. *Principles of Law*

1. Burden of Proof

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016 (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity ... the evidence that supports the grounds for the challenge to each claim”))). Therefore, in an *inter partes* review, the burden of proof is on the Petitioner to show that the challenged claims are unpatentable; that burden never shifts to the patentee. *See* 35 U.S.C. § 316(e); *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375

(Fed. Cir. 2016) (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015)). At the institution stage, Petitioner must show reasonable likelihood that it would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314.

2. Anticipation

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373 (Fed. Cir. 2003) (quoting *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987)). It is well settled that “a reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.”

Kennametal, Inc. v. Ingersoll Cutting Tool Co., 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962)).

3. Obviousness

To ultimately prevail in its challenge to Patent Owner’s patent claims, Petitioner must demonstrate by a preponderance of the evidence⁹ that the claims are unpatentable. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). A patent

⁹ The burden of showing something by a preponderance of the evidence requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence before the trier of fact may find in favor of the party who carries the burden. *Concrete Pipe & Prods. of Cal., Inc. v. Constr. Laborers Pension Tr. for S. Cal.*, 508 U.S. 602, 622 (1993).

claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *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) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In determining obviousness when all elements of a claim are found in various pieces of prior art, “the factfinder must further consider the factual questions of whether a person of ordinary skill in the art would be motivated to combine those references, and whether in making that combination, a person of ordinary skill would have had a reasonable expectation of success.” *Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1380 (Fed. Cir. 2015); *see also WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999) (“When an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references.”). “Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *see also In re Magnum Oil Tools*, 829 F.3d at 1381, 1381 (finding a party that petitions the Board for a determination of unpatentability based on obviousness must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and

that the skilled artisan would have had a reasonable expectation of success in doing so”) (internal quotations and citations omitted).

An obviousness analysis “need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418; *see also In re Translogic Tech., Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person of ordinary skill in the art:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. “*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless ‘the improvement is more than the predictable use of prior art elements according to their established functions.’” *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

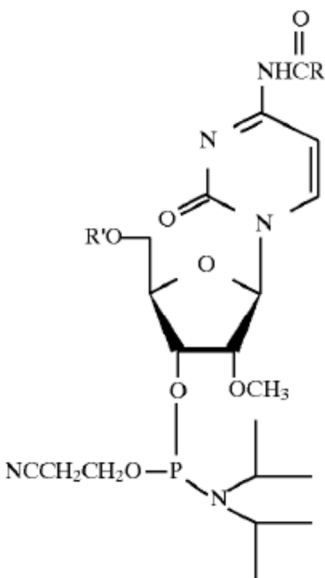
B. Ground 1: Anticipation under 35 U.S.C. § 102(b) of Claim 1 by Reddy (Ex. 1016)

1. Overview of the Prior Art

a. Reddy

Reddy is US 5,808,039, issued on September 15, 1998, and is prior art to the '885 patent. Reddy is directed to:

A compound of the general formula:



wherein R is alkyl of 1 to about 10 carbons and R' is selected from the group consisting of trityl and pixyl, for use in the synthesis of 2'-OMe RNA sequences. Fast cleavage and deprotection of oligonucleotides is facilitated by the use of a reagent comprising methylamine as active component in place of the traditional reagent ammonium hydroxide.

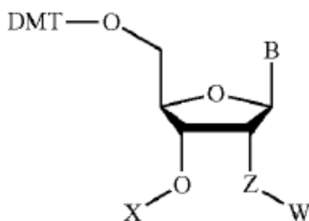
Ex. 1016, Abstr.

Reddy discloses that “oligonucleotides containing 2'-OMe ribonucleotides of [this general] formula have widespread applications in both diagnostics and therapeutics, in particular because of their strong affinity for complementary strands and resistance toward unwanted

nuclease degradation.” Ex. 1016, col 1, ll. 9–23. Reddy further discloses that such compounds “possess high chemical stability and are resistant to hydrolysis by alkali and nucleases.” *Id.* at col. 1, ll. 23–25. Reddy discloses that its claimed compounds are useful in the synthesis of 2′-OMe RNA sequences, and that fast cleavage and deprotection of the oligonucleotides is facilitated by the use of methylamine or a mixture of methylamine/ammonium hydroxide in place of the then-traditional reagent ammonium hydroxide. *Id.* at col. 2, ll. 21–26.

2. Petitioner’s argument

Petitioner argues that Reddy anticipates claim 1 of the ’885 patent. Pet. 23. Petitioner first points to the compound claimed as Formula 1 of challenged claim 1 of the ’885 patent:



Formula 1 of challenged claim 1

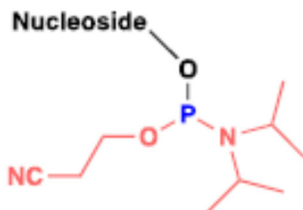
Pet. 23.

Petitioner argues that, in Formula 1, “B” is used to denote one of a named group of nucleobases or modified nucleobases (as is customary in the field of nucleic acid chemistry) and thus constitutes a Markush group.

Pet. 23 (citing Ex. 1003 ¶ 89). Petitioner notes that, when a claim element recites a Markush group, the entire element is disclosed by the prior art if one member of the Markush group is disclosed by the prior art. *Id.* (citing

Fresenius USA, Inc. v. Baxter Int'l, Inc., 582 F.3d 1288, 1298 (Fed. Cir. 2009)).

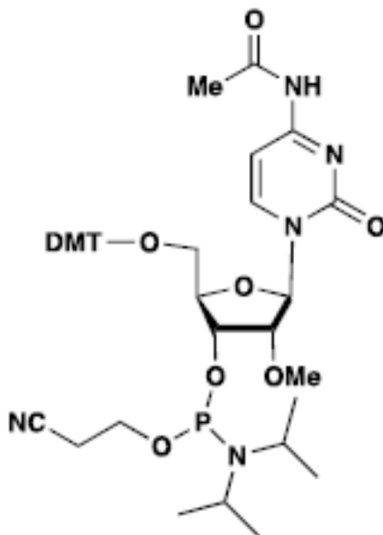
Petitioner also contends that, in the claimed Formula 1 of the '885 patent, “Z” is oxygen, “W” is methyl, and “X” is a cyanoethyl dialkyl phosphoramidite. Pet. 24 (citing Ex. 1003 ¶¶ 90–92). Petitioner asserts that the most well-known cyanoethyl dialkyl phosphoramidite is 2-cyanoethyl N,N-diisopropyl phosphoramidite, which has “been used virtually exclusively in phosphoramidite-based solid phase nucleotide synthesis.” *Id.* at 25 (quoting Ex. 1009, 3857; and citing Ex. 1003 ¶ 92). 2-cyanoethyl N,N-diisopropyl phosphoramidite has the structure depicted below:



2-cyanoethyl N,N-diisopropyl phosphoramidite

Id. (citing Ex. 1003 ¶ 92; Ex. 1009, 3857).

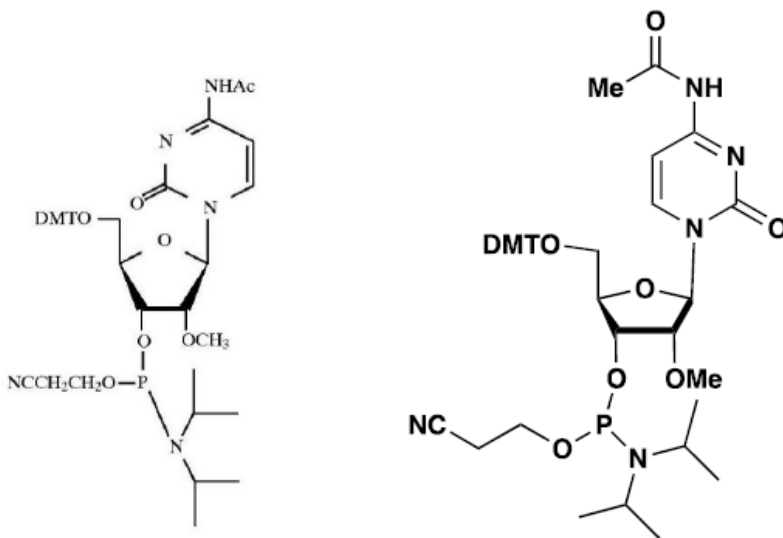
Consequently, Petitioner argues, when “B” is cytosine-N-acetyl, and “X” is 2-cyanoethyl N,N-diisopropyl phosphoramidite, Formula 1 of challenged claim 1 assumes the form depicted below:



Formula 1 of challenged claim 1, in which “B” is cytosine-N-acetyl, and “X” is 2-cyanoethyl N,N-diisopropyl phosphoramidite

Pet. 25.

Petitioner argues that Reddy discloses the identical molecule and a scheme for its synthesis. Pet. 26. Petitioner asserts that Reddy discloses that this molecule is identified as “DMT CAc-2’-OMe-3’cyanoethyl-phosphoramidite,” or as “CAc-2’-OMe phosphoramidite.” *Id.* (citing Ex. 1016, col. 3, ll. 5–25; Ex. 1003 ¶ 98). In the diagram below, Reddy’s disclosed CAc-2’-OMe phosphoramidite compound is depicted on the left, and the compound of challenged claim 1 in which “B” is cytosine-N-acetyl, and “X” is 2-cyanoethyl N,N-diisopropyl phosphoramidite (as depicted above) is illustrated on the right:



Side-by-side comparison of Reddy's disclosed CAC-2'-OMe phosphoramidite (left) and Formula 1 of challenged claim 1 in which "B" is cytosine-N-acetyl, and "X" is 2-cyanoethyl N,N-diisopropyl phosphoramidite (right)

Pet. 27.

Petitioner argues further that Reddy would have enabled a person of ordinary skill in the art to make and use the compound depicted above.

Pet. 28. According to Petitioner, Reddy provides a detailed methodology, "Scheme I," for the synthesis of CAC-2'-OMe phosphoramidite. *Id.* (citing Ex. 1016, cols. 3–5, ll. 5–20; Ex. 1003 ¶ 105). Petitioner asserts that Reddy also includes citations to supporting scientific literature, and detailed description of the structures of the starting materials; the structures of the intermediates; the reagents, catalysts, and reaction media; the reaction conditions; the synthetic organic chemistry techniques employed; and the percent yield at each step. *Id.*

Petitioner contends that, based upon this disclosure and a general knowledge of synthetic organic chemistry, a person of ordinary skill in the

art, comprehending the disclosures of Reddy's Scheme 1, would have had to engage in little or no experimentation to synthesize the molecule claimed in challenged claim 1 of the '885 patent (in which "B" is cytosine-N-acetyl and "X" is 2-cyanoethyl N,N-diisopropyl phosphoramidite). *Id.* (citing Ex. 1003 ¶ 106).

Petitioner additionally contends that a skilled artisan would also have understood that Reddy discloses how to use CAC-2'-OMe phosphoramidite. Pet. 29. Petitioner asserts that Reddy discloses that this compound was "successfully utilized in the synthesis of 2'-OMe oligonucleotides on an automated DNA synthesizer using a 15 minute coupling time," and further discloses alternate deprotection conditions. *Id.* (citing Ex. 1016, col. 5, ll. 22–31). According to Petitioner, the method of using of CAC-2'-OMe phosphoramidite as a building block in oligonucleotide synthesis would have been known to even less experienced chemists or technicians, who would simply have had to load such a building block into an automated oligonucleotide synthesizer and followed the parameters set forth in Reddy. *Id.* (citing Ex. 1003 ¶ 107).

3. Analysis

Based upon the evidence of record, as developed at this stage of the proceeding, we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing at trial in showing that challenged claim 1 is anticipated by Reddy. As explained and depicted above, Reddy expressly discloses and depicts the identical compound recited by challenged claim 1 in which "B" is cytosine-N-acetyl and "X" is 2-cyanoethyl N,N-diisopropyl phosphoramidite. *See* Ex. 1016, col. 3, ll. 10–25.

Furthermore, the evidence shows that Reddy likely enables this compound. Reddy discloses a scheme of synthesizing CAc-2'-OMe phosphoramidite that would not likely require undue experimentation to replicate and, indeed, would seem to leave little to the imagination of a person of ordinary skill in the art, as defined at this stage of the proceeding. *See id.* at cols. 3–5, ll. 5–20.

Reddy also discloses methods of using CAc-2'-OMe phosphoramidite in automated oligonucleotide synthesis. *Id.* at col 5., ll. 22–40. Based upon the evidence of record as presently developed, then, we conclude that Petitioner has met its burden of reasonably demonstrating that it can show at trial that Reddy anticipates challenged claim 1 of the '885 patent.

V. CONCLUSION

For the reasons we have explained, we conclude that Petitioner has demonstrated a reasonable likelihood of prevailing in demonstrating that at least challenged claim 1 of the '885 patent is unpatentable as being anticipated by Reddy. Furthermore, because Patent Owner has not filed a Preliminary Response to the Petition, there are no additional arguments to respond to. We also find that Petitioner has set forth sufficient contentions regarding the remaining claims to sustain our Decision to Institute.

We consequently determine that Petitioner has shown a reasonable likelihood of prevailing at trial in demonstrating that at least one claim is unpatentable on at least one of the stated Grounds, and we institute *inter partes* review of all challenged claims of the '681 patent, based on all of the Grounds identified in the Petition. *See SAS Inst., Inc. v. Iancu*, 138 S.Ct. 1348, 1359–60 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360

(Fed. Cir. 2018) (interpreting the statute to require “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition”).

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED, pursuant to 35 U.S.C. § 314(a), that the Petition for *inter partes* review of the challenged claims of US Patent 9,884,885 B2 is

GRANTED with respect to all grounds in the Petition; and

FURTHER ORDERED that *inter partes* review is instituted.

IPR2023-00490
Patent 9,884,885 B2

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