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Paper: 35
Date: July 18, 2024

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*.

JUDGMENT
Final Written Decision
Determining Challenged Claims 1–5 Unpatentable
Granting Petitioner's Motion to Seal
35 U.S.C. § 318(a)

I. INTRODUCTION

We have jurisdiction to hear this *inter partes* review under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner Shanghai Hongene Biotech Corp. ("Petitioner") has established, by a preponderance of the evidence, that challenged claims 1–5 of Patent Owner ChemGenes Corp.'s ("Patent Owner") U.S. Patent No. 9,884,885 B2 (Ex. 1001, the "'885 patent") are unpatentable.

A. Procedural History

On January 19, 2023, Petitioner filed its Petition (Paper 1, "Petition") seeking *inter partes* review of claims 1–5 of the '885 patent. Patent Owner did not file a Preliminary Response and, on July 20, 2023, and pursuant to 35 U.S.C. § 314, we instituted *inter partes* review of challenged claims 1–5 of the '885 patent. Paper 7 ("Institution Decision" or "Dec.").

After institution of trial, Patent Owner filed a Response (Paper 16, "PO Resp."), to which Petitioner filed a Reply (Paper 20, "Pet. Reply"), and Patent Owner, in turn, filed a Sur-Reply (Paper 27, "Sur-Reply").

On October 17, 2023, Patent Owner filed a Motion to Amend claims 1 and 5 with substitute new claims 6 and 7. Paper 17. Petitioner filed an Opposition to Patent Owner's Motion to Amend (Paper 22). We entered Preliminary Guidance on Patent Owner's Motion to Amend on February 5, 2024 (Paper 23). On February 28, 2024, upon Patent Owner's request, we entered an Order authorizing the withdrawal of Patent Owner's Motion to Amend the claims. Paper 28. As specified in that Order, Patent Owner's arguments with respect to its Motion to Amend will not be considered or

addressed in this Final Written Decision. *Id.* at 5. Oral argument was heard on April 23, 2024 and a transcript of the hearing is of record.

Petitioner filed a Motion to Seal (Paper 31) portions of the Sur-Reply, as well as four related Exhibits (Exs. 2035, 2036, 2038, and 2039). Petitioner filed redacted versions of the Sur-Reply. Paper 32. Petitioner's Motion to Seal is *granted*.

II. BACKGROUND

B. Real Parties-in-Interest

Petitioner identifies itself, Shanghai Hongene Biotech Corp., as the real party-in-interest. Pet. x. Patent Owner identifies itself, ChemGenes Corp., as the assignee and real party-in-interest. Paper 25 at 2.

C. Related Matters

Petitioner and Patent Owner each identify *ChemGenes Corp. v. Hongene Biotechnology Ltd.*, 1-22-cv-10290 (D. Mass. 2022) as a related matter. Pet. x, Paper 25 at 2. Patent Owner represents that this litigation was voluntarily dismissed by Patent Owner on July 7, 2022. Paper 25 at 2.

On April 5, 2023, Patent Owner filed a reissue application with the USPTO relating to the '885 patent, which the Office has assigned U.S. Reissue Application No. 18/130,902. On September 1, 2023, the Office notified Patent Owner that it was suspending, *sua sponte*, the examination of U.S. Reissue Application No. 18/130,902 for a period of six months from the September 1, 2023 notice date, in view of this *inter partes* review. Ex. 3001, 2. That suspension was renewed by the Office for another 6 months on February 28, 2024. Ex. 3004, 2.

D. 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	Crooke[3], Pitsch[4], Fan[5]
3	2	103	Vater[6], Pitsch
4	3	103	Crooke, Pitsch, Fan, Scaringe[7]
5	4	103	Pitsch, Fan, Scaringe

[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) ("Fan") Ex. 1019.

[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 (1991) ("Scaringe") Ex. 1022.

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
6	5	102(b)	Gaur[8]

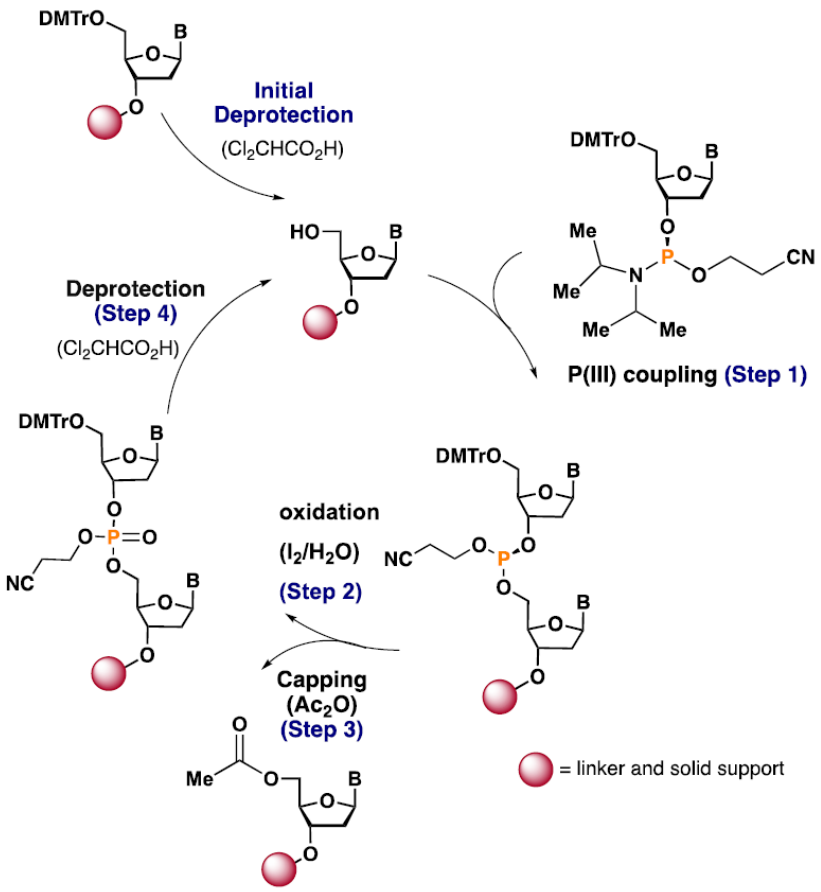
Petitioner also relies upon the Declaration of Dr. Phil S. Baran (the "Baran Declaration," Ex. 1003). Patent Owner relies upon the Declaration of Dr. Patrick J. Hrdlicka (the "Hrdlicka Declaration," Ex. 2008). We have reviewed the credentials of Petitioner's and Patent Owner's declarants, and consider each to be qualified to provide the opinions for which their testimony has been submitted.

E. 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 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

[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.

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:



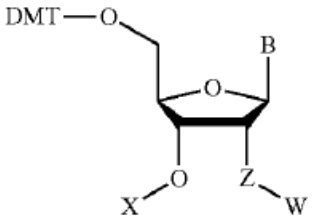
The "canonical cycle" of solid-phase oligonucleotide synthesis using phosphoramidites as nucleotide as a protecting group.

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.

F. 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.

G. Priority History of the '885 Patent

The '885 patent issued from U.S. 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 U.S. 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)).

Both parties agree that the terms of the challenged claims should be given the ordinary and customary meaning of such terms as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent. Pet. 17; PO Resp. 15 (both citing 37 C.F.R. § 42.100). Accordingly we see no need for explicitly construing any of the terms of the challenged claims beyond that standard.

Furthermore, both Petitioner and Patent Owner agree that clear errors exist in the wording of challenged claims 3–5. Both parties agree that a person of ordinary skill in the art would have recognized that the limitation reciting "where M is selected from the group consisting of *succinyl*, oxalyl, and hydroquinolynyl" should properly read "where M is selected from the group consisting of *ethyl*, oxalyl, and hydroquinolynyl." Pet. 18–20; PO Resp. 15. Both parties further agree that the language of claim 5 mistakenly omits the italicized portions of the limitation reciting "NH is *capable of being attached to a solid support with a spacer selected from the group*

consisting of C1–C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy," as is expressly recited in claims 3 and 4. Pet. 21–22 (citing Ex. 1003 ¶ 158); PO Resp. 15.

We agree with both parties' reasoning with respect to these errors, and we construe the claims as reciting the corrected language, such that claims 3–5 read, in relevant part "where M is selected from the group consisting of *ethyl*, oxalyl, and hydroquinolynyl" and claim 5 additionally reads "NH is *capable of being attached to a solid support with a spacer selected from the group consisting* of C1–C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy." *See Fitbit, Inc. v. Valencell, Inc.*, 964 F.3d 1112, 1119–20 (Fed. Cir. 2020) (holding that the Board erred in not correcting a "conspicuous" and undisputed error in claim).

B. The Level of Ordinary Skill in the Art

Petitioner argues that a person of ordinary skill in the art would have had a Ph.D. (or equivalent degree) in organic or medicinal chemistry, and 2 to 3 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). Petitioner further proposes that an individual with a Bachelor's or Master's degree in organic chemistry or medicinal chemistry, and possessing extensive work experience in these fields, with 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.*

Patent Owner disagrees, arguing that a person of ordinary skill in the art would have had a Ph.D. (or equivalent degree) in organic chemistry, and

at least 2 to 3 years of post-graduate work experience in the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through solid phase oligonucleotide synthesis ("SPOS"), pursuant to P(III) chemistry. PO Resp. 19.

Alternatively, Patent Owner contends, a person of ordinary skill in the art would have been someone with a Ph.D. (or equivalent degree) in organic chemistry, and who focused on the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through SPOS pursuant to P(III) chemistry during his or her Ph.D. studies. PO Resp. 19. Additionally, argues Patent Owner, someone with a Bachelor's or Master's degree in organic chemistry who had at least 5 years of extensive work experience in these fields, and who had gained a thorough understanding of the syntheses of nucleic acid-based materials pursuant to P(III) chemistry, would also have qualified as a an artisan of ordinary skill. *Id.*

In support of its proposed definition, Patent Owner points to the Declaration of its expert, Dr. Hrdlicka, who opines that, in 2009, skilled artisans who developed synthetic schemes, and who managed the syntheses of nucleosides, phosphoramidites and oligonucleotides in connection with P(III) chemistry, are those who would provide the most relevant viewpoints on aspects relating to whether the compounds claimed in the '885 patent would have been obvious, including with respect to knowledge, skills, motivations, and reasonable expectations. PO Resp. (citing Ex. 2008 ¶ 88).

In contrast, argues Patent Owner, the viewpoints of those who have instead focused on using oligonucleotides for therapeutic and diagnostic

purposes after their production, but who were not skilled in the art of developing synthesis schemes for, and managing or conducting the syntheses of, nucleosides, phosphoramidites or oligonucleotides pursuant to P(III) chemistry, are not as applicable to the central inquiries at bar, since the challenged claims in the '885 patent are directed to nucleoside and phosphoramidite compounds themselves based on P(III) chemistry and not their therapeutic and diagnostic uses or syntheses based on P(V) oligonucleotide chemistry. *Id.* ¶ 89.

As a side effect of this argument, Patent Owner contends that Petitioner's declarant, Dr. Baran, was not himself a person of ordinary skill in the art in 2009, and does not appear to have a deep background in P(III) chemistry. PO Resp. 17. According to Patent Owner, Dr. Baran has characterized himself as a professor in organic chemistry and an expert in medicinal chemistry, but has also testified that only 14 of the over 250 papers he authored in his career relate to oligonucleotide synthesis and the earliest of those papers was just 5 years ago. *Id.* (citing Ex. 2009, 75, 73, 97, 99–100). Patent Owner additionally asserts that the focus of the most prominent of those papers appears to be on P(V) chemistry which, as Dr. Baran acknowledged, is a fundamentally different synthesis platform than the P(III) chemistry at bar. *Id.* (citing Ex. 2009, 109).

Petitioner responds to this latter argument by stating that Dr. Baran is one of the world's preeminent synthetic organic chemists and has an extensive background in the field and his groundbreaking work on P(V) chemistry for oligonucleotide chemistry, which earned him prestigious awards, built on, and required a deep understanding of, P(III) chemistry. Reply 1 (citing Ex. 1033 ¶¶ 7–8). Petitioner adds that Dr. Baran was

exposed to nucleoside chemistry as an undergraduate in 1996, and in the interval from 2003 to 2009, he both taught classes, and consulted with companies, concerning nucleotide synthesis. *Id.* (citing Ex. 1033 ¶ 8).

Patent Owner replies that its definition is proper because the subject claims are directed to P(III) nucleosides and POSAs should have the proposed experience in P(III) nucleoside chemistry and synthesis and a background in medicinal chemistry is not necessary. Sur-Reply 1. Patent Owner asserts that Dr. Baran testified he viewed the definition of one of ordinary skill in the art as "malleable" and that he "had no problem" with the "other definitions" proposed. *Id.* (citing Ex. 2032, 177–178).

First, we are not persuaded by Patent Owner's argument that a doctorate in the field "medicinal chemistry" is irrelevant to the definition of a person of ordinary skill in the art. Medicinal chemistry being necessarily a subset of the larger field of organic chemistry, we find that a person with a doctorate in medicinal chemistry would have the necessary academic preparation to undertake the experience of practicing the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through SPOS.

However, we prefer Patent Owner's definition of the required 2–3 years of experience in "the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through solid phase oligonucleotide synthesis ('SPOS')" to Petitioner's more generalized requirement of having experience in "medicinal chemistry, synthetic organic chemistry, and nucleic acid chemistry, including the development of oligonucleotide therapeutics, diagnostics, or building blocks." Both parties acknowledge that the level of

skill in the art is very high. *See, e.g.*, Resp. 17; Reply 2. We find that, to achieve a level of ordinary skill in the art, a person with the requisite educational background would require 2–3 years of experience for one possessing a doctorate in the relevant field, or 3–5 years for one with a lesser degree (to compensate for the additional educational experience gained by achieving a doctorate) in the specific techniques recited by Patent Owner. We reject the terminal clause "pursuant to P(III) chemistry" proposed by Patent Owner as redundant in that a person engaged for a number of years in "the development and syntheses of nucleosides, nucleotides, and nucleic acids" including SPOS, would likely have an operant knowledge of P(III) chemistry.

Consequently we adopt the following definition of a person of ordinary skill in the art: "A person of ordinary skill in the art having a Ph.D. (or equivalent degree) in organic or medicinal chemistry, and 2 to 3 years of post-graduate work experience in the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through solid phase oligonucleotide synthesis ('SPOS')" and, alternatively, "a person of ordinary skill in the art would have a Bachelor's or Master's degree in organic or medicinal chemistry who had at least 5 years of extensive work experience in these fields."

As for Dr. Baran, we are not persuaded by Patent Owner's argument that Dr. Baran is not sufficiently experienced or qualified to opine with respect to the claimed subject matter. A review of Dr. Baran's extensive curriculum vitae (Ex. 1003, 79–137), indicates that he is deeply experienced and extensively published in the field of oligonucleotide synthesis. Patent Owner's argument that Dr. Baran is principally experienced in P(V)

techniques presupposes that experience in that technique indicates an ignorance of P(III) methodologies. We do not find this position consistent with the breadth of Dr. Baran's C.V. We will weigh Dr. Baran's testimony, and that of Dr. Hrdlicka, against the cumulative weight of the evidence of record in this *inter partes* review in assessing the credibility and probative value of their respective testimonies.

C. 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)).

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

A patent claim is unpatentable under 35 U.S.C. § 103(a) 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 multiple 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 Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *see also In re Magnum Oil Tools*, 829 F.3d at 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").

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 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 challenges to patentability in accordance with the above-stated legal principles.

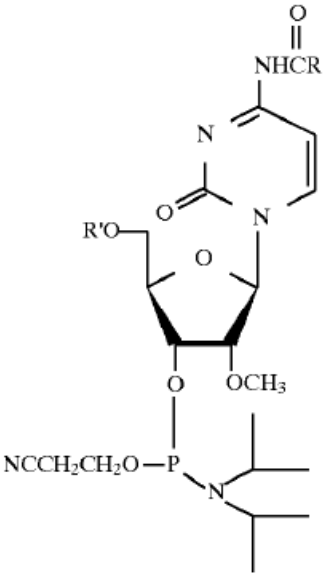
D. Ground 1: Anticipation of challenged claim 1 over Reddy

1. Overview of the Prior Art

a. Reddy

Reddy is U.S. patent 5,808,039, issued on September 15, 1998, and is prior art to the '885 patent. Ex. 1016, code (45). Reddy is directed to:

A compound of the general formula:



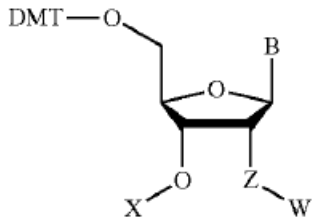
> wherein R is alkyl of 1 to about 10 carbons and R′ is selected from the group consisting of trityl and pixyl, for use in the synthesis of 2′-OMe RNA sequences. Fast cleavage and deprotection of oligonucleotides is facilitated by the use of a reagent comprising methylamine as active component in place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

Id., 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:



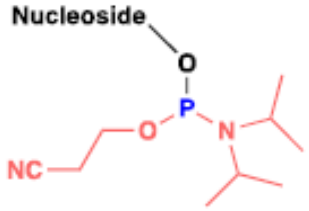
Formula 1 of challenged claim 1

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)).

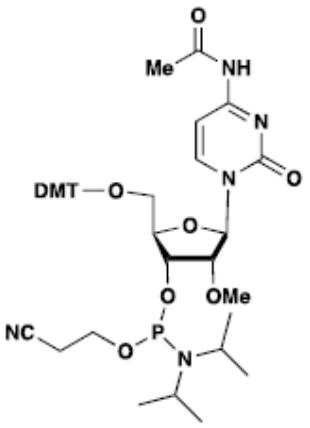
Petitioner also contends that, in the claimed Formula 1 of the '885 patent, "Z" is oxygen, "W" is methyl, and "X" is a cyanoethyl dialkyl phosphoramidite. Pet. 24 (citing Ex. 1003 ¶¶ 90–92). Petitioner asserts that the most well-known cyanoethyl dialkyl phosphoramidite is 2-cyanoethyl N,N-diisopropyl 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).

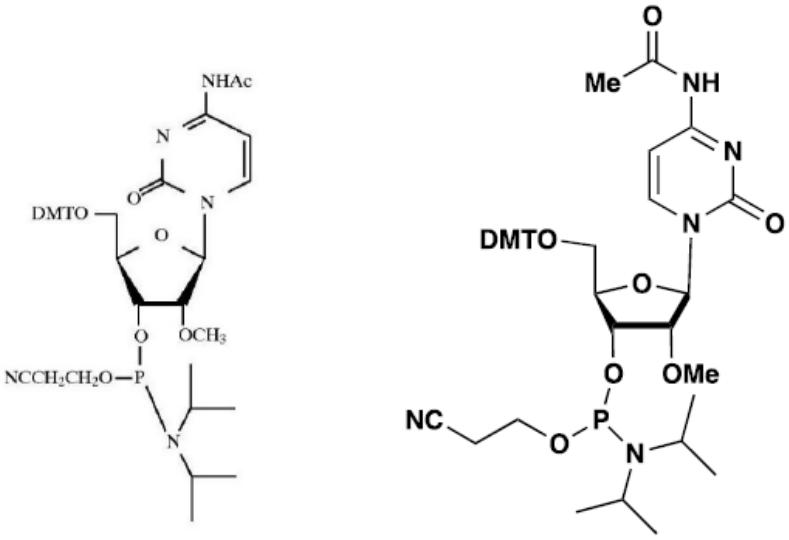
Consequently, Petitioner argues, when "B" is cytosine-N-acetyl, and "X" is 2-cyanoethyl N,N-diisopropyl phosphoramidite, Formula 1 of challenged claim 1 assumes the form depicted below:



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).

3. Patent Owner's Response

In its Patent Owner Response, Patent Owner did not substantively challenge Ground 1, in view of its then-pending Motion to Amend. Specifically, Patent Owner states that, without prejudice to Patent Owner's rights to the other patentably distinct compounds in Claim 1's Markush group (e.g., where "B" in Formula 1 is guanine-N-acetyl, adenine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl), or Patent Owner's rights to those compounds secured under at least U.S. Reissue Application No. 18/130,902, Ground 1 is rendered moot in view of its (now-withdrawn) Motion to Amend. PO Resp. 20–21.

4. Analysis

Based upon Petitioner's arguments, and the evidence of record, we conclude that Petitioner has demonstrated, by a preponderance of the evidence, 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.

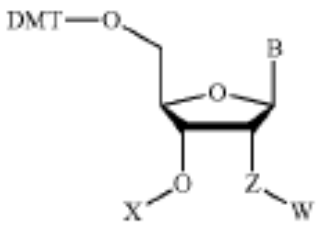
Furthermore, the evidence shows that Reddy enables this compound. Reddy discloses a scheme of synthesizing CAc-2′-OMe phosphoramidite that would likely not require undue experimentation to replicate and, indeed,

would seem to leave little to the imagination of a person of ordinary skill in the art. *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.

We therefore conclude that Petitioner has met its burden of demonstrating, by a preponderance of the evidence, that Reddy anticipates challenged claim 1 of the ’885 patent.

E. Ground 2: Obviousness of challenged claim 2 over Crooke, Pitsch, and Fan

Claim 2 of the ’885 patent recites:

> 2. Derivatized nucleoside and phosphoramidite of general formula 1,
>
> (Formula 1)
>
> 
>
>
> where B is Guanine-N-acetyl , or adenine-N-acetyl ;
>
> Z = ribo fluoro or ara fluoro, and
>
> W is absent; and
>
> X is cyanoethyl dialkyl phosphoramidite.

Ex. 1001, col. 25, ll. 59–62.

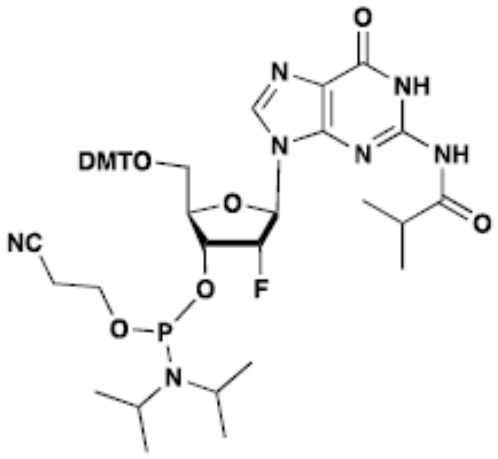
1. Overview of the Prior Art

a. Crooke

Crooke is U.S. Patent 5,898,031, issued on April 27, 1999, and is prior art to the ’885 patent. Ex. 1017, code (45). Crooke is directed to

"Oligomeric compounds including oligoribonucleotides and oligoribonucleosides … that have subsequences of pentoribofuranosyl nucleosides that activate dsRNase." *Id.*, Abstr.

Specifically, in the final synthetic step x of example 4-d, Crooke teaches the synthesis of a guanosine phosphoramidite, N-isobutyryl-9-(2′-deoxy-2′-fluoro-5′-O-4.4-dimethoxytrityl-guanosine-3′-O-N,N-diisopropyl-3-D-cyanoethyl phosphoramidite ("compound x"). Ex. 1017, cols. 27–28, ll. 63–19. The structure of compound x is illustrated below:



Structure of N-isobutyryl-9-(2′-deoxy-2′-fluoro-5′-O-4.4-dimethoxytrityl-guanosine-3′-O-N,N-diisopropyl-3-D-cyanoethyl phosphoramidite ("compound x")

See Pet. 37 (citing Ex. 1003 ¶ 115).

b. Pitsch

Pitsch is a journal article entitled *Reliable Chemical Synthesis of Oligoribonucleotides (RNA) with 2′-O-[(Triisopropylsilyl)oxy]methyl(2′-O-tom)-Protected Phosphoramidites*. Ex. 1018. Pitsch was published in Helvetica Chimica Acta in 2001, and is prior art to the '885 patent. *Id.*

Pitsch is directed to the use of protecting groups to protect the 2′-O-positions of the phosphoramidite building block during SPOS. Ex. 1018, 3773–74. These protecting groups are subsequently removed following synthesis of the oligonucleotide (i.e., "deprotection"). *Id.* Pitsch reports that there is a large number of known 2′-O-ribonucleoside protecting groups, which can essentially be divided into acid-, photo-, and fluoride-labile groups. Pitsch describes in detail the preparation of 2′-O-([(triisopropylsilyl)oxy]methyl)-protected (2′-O-tom-protected) phosphoramidites of the four canonical ribonucleosides. *Id.* at 3774.

Pitsch teaches addition of an acetyl protecting group to protect the exocyclic amine group of a nucleobase as the first step in "[t]he preparation of the phosphoramidite building blocks from the four ribonucleosides." Ex. 1018, 3774-75, Scheme 1). Pitsch also outlines the specific steps for synthesizing a nucleobase-protected N2-acetylguanosine. *Id.* at 3775.

Pitsch compares the deprotection half-lives of 2′-O-acetyl- and 2′-O-tom-protected nucleobases. Ex. 1018, 3778. Specifically, Pitsch teaches that:

> Prior to the synthesis of oligonucleotides, we established the conditions required for the removal of the base-protecting Ac groups with $MeNH_2$ (10 in H_2O/EtOH 1:1, 25°). By UV measurements and reversed-phase HPLC, we determined half-lives of <2 min for the 2′-O-tom-protected N4-acetylcytidine and N6-acetyladenosine derivatives, and a half-life of 4 min for the 2′-O-tom-protected N2-acetylguanosine, respectively (Scheme 3). These values indicated that complete base-deprotection of oligonucleotide sequences can be achieved within 1 h (equal to 15 half-lives for the acetylated guanosine residues) and demonstrated that the Ac group, in combination with $MeNH_2$, is indeed suited for a labile universal nucleobase protection. Under the deprotection conditions with $MeNH_2$, the

> 2′-O-tom group was completely stable for a period of at least 48 h.

Id.

c. Fan

Fan is a journal article entitled *Transient Silylation of the Guanosine O6 and Amino Groups Facilitates N-Acylation*. Ex. 1019. Fan was published in the journal Organic Letters in 2004, and is prior art to the '885 patent. *Id.*

Fan teaches that "[s]ynthetic methods for the preparation of fully protected ribonucleosides with the labile N-acyl groups that are preferred for RNA synthesis are not yet optimal, particularly for guanosine." Ex. 1019, 2555 (footnote omitted).

Fan compares deprotection rates of the guanine N-isobutyryl, acetyl, and phenoxyacetyl groups in samples of N-acetyl-3′,5′-O-di-tert-butylsilylene-2′-O-TBS-guanosine and the corresponding phenoxyacetyl and isobutyryl derivatives. Ex. 1019, 2556. Table 1 of Fan, reproduced below, displays the results.

Table 1. Deprotection of *N*-Acylguanosine Derivatives

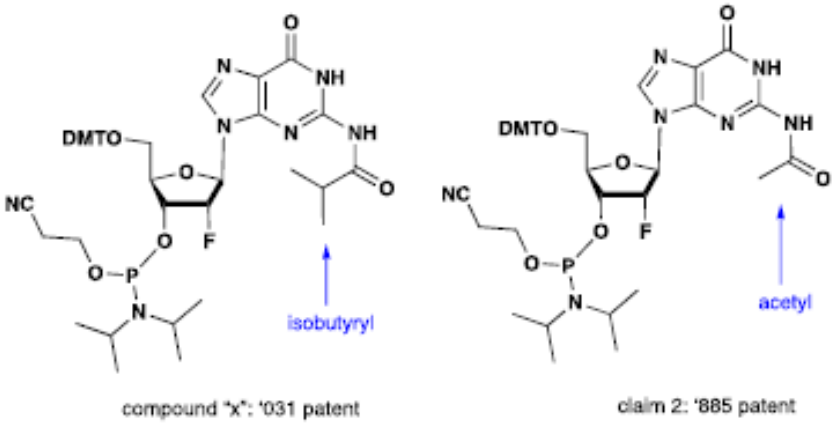
N-acyl group	time required for 50% deprotection
isobutyryl	18 h
acetyl	4.5 h
phenoxyacetyl	4.7 min

Table 1 shows that the time required for 50% deprotection of the N-isobutyryl, acetyl, and phenoxyacetyl deprotecting groups was 18 hours, 4.5 hours, and 4.7 minutes, respectively.

Fan concludes that its described experimental procedures for N-acylation provide a new high-yield route for preparation of guanosine nucleobases. Ex. 1019, 2557.

2. Petitioner's arguments

Petitioner argues that the only difference between the compound x of Example 4-d in Crooke and the molecule recited in challenged claim 2 of the '885 patent, where "B" is guanine-N-acetyl and "Z" is ribo Fluoro, is the identity of the protecting group on the exocyclic NH_2 group of the guanine base: Crooke's compound x has an isobutyryl group, whereas the claimed compound has an acetyl group. Pet. 33 (citing Ex. 1003 ¶ 117). Petitioner provides an annotated side-by-side comparison of the two molecules, which is reproduced below:



Petitioner's annotated side-by-side comparison of Crooke's compound x (left) and the compound of challenged claim 2 (right)

Petitioner contends that using an acetyl protecting group to shield the exocyclic NH_2 group of a nucleobase was well known in the art at the time of filing of the '885 patent, and a person of ordinary skill in the art would

also have understood the advantage of an acetyl protecting group. Pet. 34 (citing Ex. 1003 ¶ 118).

In support of this argument, Patent Owner points to Pitsch, which, Petitioner asserts, teaches that the installation of an acetyl protecting group to protect the exocyclic NH_2 group of a nucleobase is the first step in "[t]he preparation of the phosphoramidite building blocks from the four ribonucleosides [which] was carried out by stepwise introduction of the base-protecting acetyl group, …, and finally the 3′-(2-cyanoethyl diisopropylphosphoramidite) moiety." Pet. 34 (quoting Ex. 1018, 3774–75; and citing *id.* at Scheme 1, steps "a)", "b)", "c)"; Ex. 1003 ¶ 119). Petitioner argues that Pitsch also teaches the specific steps for synthesizing a nucleobase-protected N2-acetylguanosine. *Id.* (citing Ex. 1018, 3775).

According to Petitioner, Pitsch explains that the acetyl protecting group ("Ac group") was chosen for its rapid deprotection speed; stating that "complete base-deprotection of oligonucleotide sequences can be achieved within 1 h (equal to 15 half-lives for the acetylated guanosine residues) and demonstrated that the acetyl group, in combination with $MeNH_2$, is indeed suited for a labile universal nucleobase protection." Pet. 35 (quoting Ex. 1018, 3778). Petitioner notes that this rapid deprotection compares favorably against the 24-hour deprotection period for the removal of the isobutyryl protecting group from 2′-O-methyl Guanosine in Example 8 of Crooke. *Id.* (citing Ex. 1003 ¶ 119; Ex. 1017, col. 40, ll. 41–52).

Petitioner also points to Fan as teaching a direct comparison of the respective deprotection rates of N-acylguanosine derivatives with N-isobutyryl, acetyl, and phenoxyacetyl protecting groups and reporting that the "time required for 50% deprotection" for N-acetyl (4.5 h) was only 25%

of that for N-isobutyryl (18 h). Pet. 35 (citing Ex. 1019, 2556–57, Table 1; Ex. 1003 ¶ 120).

Petitioner argues that a person of ordinary skill in the art would have found it obvious, in view of the respective teachings of Pitsch and Fan, to synthesize a substitute an acetyl protecting group for the isopropyl protecting group of Crooke's guanosine phosphoramidite compound x. Pet. 36. Petitioner contends that a skilled artisan would have been motivated to make such a substitution to take advantage of the significant improvement in deprotection speeds taught by Pitsch and Fan. *Id.*

Petitioner also argues that a person of ordinary skill in the art would have had a reasonable expectation of successfully synthesizing the molecule in challenged claim 2, and would have regarded the conditions and yield for the installation of an acetyl protecting group as simple and similar to those for an isobutyryl group. Pet. 36. By way of example, Petitioner points to step "ii" in Crooke's Example 4-d, which teaches the addition of the isobutyryl protecting group *via* the addition of isobutyric anhydride, in a process to convert 9-(3′, 5′-[1, 1, 3, 3-tetraisopropyldisilox-1, 3-diyl]-β-D-arabinofuranosyl)guanine into N2-isobutyryl-9-(2′-O-isobutyryl-3′, 5′-[1, 1, 3, 3-Tetraisopropyldisilox-1, 3-diyl]-β-D-arabinofuranosyl)guanine. *Id.* (citing Ex. 1017, cols. 25–26, ll. 61–10).

Petitioner asserts that Pitsch analogously teaches the installation of the acetyl protecting group through the addition of acetic anhydride: "A convenient synthesis of N2-acetylguanosine (3) was achieved by peracetylation of guanosine with Ac_2O [acetic anhydride] in DMF/pyridine, followed by cleavage of the O-bound Ac groups with NaOH in THF/MeOH/H_2O." Pet. 37 (citing Ex. 1018, 3775, Scheme 1, step "c)").

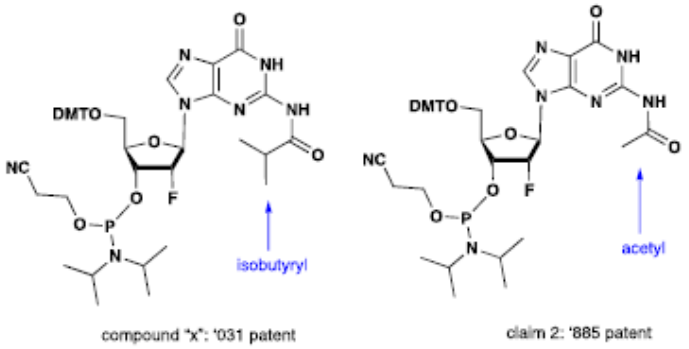
Petitioner argues that a person of ordinary skill in the art could have simply substituted acetic anhydride (for isobutyric anhydride) in step "ii" of Crooke's Example 4-d and thereafter performed remaining steps "iii" through "x" to synthesize the molecule of challenged claim 2 of the '885 patent, where "B" is guanine-N-acetyl and "Z" is ribo fluoro. *Id.* Petitioner notes that a skilled artisan would have further recognized that an acetyl protecting group could be easier to add due to its smaller physical size and lower molecular weight than an isobutyryl group, and would therefore have been less disruptive to the bulk properties of the molecule. *Id.* (citing Ex. 1003 ¶ 122).

3. Patent Owner's Response

Patent Owner makes a number of arguments with respect to Ground 2, which we address in our analysis below.

4. Analysis

There is no real dispute between the parties as to whether compound x of Crooke's Example 4-d is identical to the compound recited in challenged claim 2, with the sole exception that Crooke's compound x has an isobutyryl protecting group, and the claimed compound has an acetyl protecting group. Petitioner's annotated side-by-side comparison of the two compounds is reproduced below:



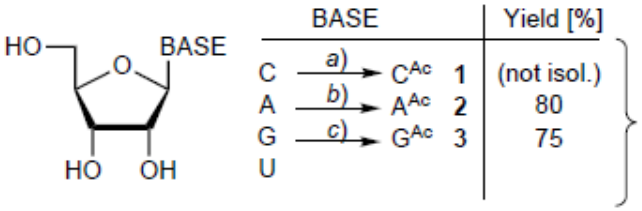
Annotated side-by-side comparison of Crooke's compound x (left) and the compound of challenged claim 2 (right)

Pet. 34.

We find that the prior art cited by Petitioner as the basis of Ground 2 sufficiently supports its argument that Crooke's compound x would have been a logical starting point for the proposed modification, because compound x is expressly designed by Crooke to be used for the same purpose as the compound of challenged claim 2, i.e., the formation of oligonucleotides. Indeed, both Crooke and the '885 patent teach that 2′-fluoro-substituted nucleosides are useful in oligonucleotide synthesis. *See* Ex. 1017, col. 12, ll. 3–56 ("A further particularly useful 2-substituent group for increasing the binding affinity is the 2′-fluoro group"); Ex. 1001, Abstr. ("This approach is designed to lead to high purity large scale therapeutic grade oligonucleotide chimeras which consist of fluoro sugar modification in conjunction with deoxynucleosides, ribonucleosides, modified base and modified sugar nucleosides").

The question that presents itself with respect to Ground 2, then, is whether it would have been obvious to a person of ordinary skill in the art to replace the isobutyryl protecting group of Crooke's compound x with an acetyl protecting group.

Pitsch describes "in detail the preparation of 2′-O-{[(triisopropylsilyl)oxy]methyl}-protected (i.e., 2′-O-tom-protected) phosphoramidites of the four canonical ribonucleosides[9] and summarize[s] all necessary information required for their application in the routine synthesis of oligoribonucleotides." Ex. 1018, 3774. Pitsch teaches that "[t]he preparation of the phosphoramidite building blocks from the four ribonucleosides was carried out by stepwise introduction of the base-protecting acetyl group, the 5′-O-$(MeO)_2$Tr group, the tom group, and finally the 3′-(2-cyanoethyl diisopropylphosphoramidite) moiety." *Id.* at 3774–75. The initial acylation step is depicted in the detail of Pitsch's Scheme 1, which is reproduced below:



Initial Step of Scheme 1 of Pitsch depicting the acylation of the guanine base (G to GAc) of guanosine

Specifically, Pitsch teaches that a "convenient synthesis of N2-acetylguanosine (3) was achieved by peracetylation of guanosine with Ac_2O in DMF/pyridine, followed by cleavage of the *O*-bound Ac groups with NaOH in THF/MeOH/H_2O." *Id.* at 3775.

Pitsch also explains its reason for selecting an acetyl protecting group: "For protection of the exocyclic NH_2 functions of the nucleobases, we have chosen the Ac group, *which, as a protecting group for cytosine nucleosides,*

[9] The five canonical nucleobases of the nucleic acids DNA and RNA are, of course, adenine, guanine, cytosine, thymine and uracil.

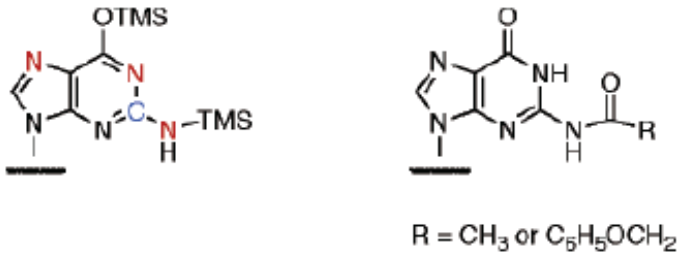
is already used in combination with a convenient deprotection scheme involving a mixture of aqueous NH_3 solution and $MeNH_2$." Ex. 1018, 3778 (emphasis added). Pitsch teaches the deprotection half-lives of its nucleobases, including "a half-life of 4 min[utes] for the 2′-O-tom 2′-protected N2-acetylguanosine" and adds that "[t]hese values indicated that complete base-deprotection of oligonucleotide sequences can be achieved within 1 h[our] (equal to 15 half-lives for the acetylated guanosine residues) and demonstrated that the Ac group, in combination with $MeNH_2$, *is indeed suited for a labile universal nucleobase protection*." *Id.* at 3778, Scheme 3 (emphasis added).

Pitsch thus teaches that use of an acetyl moiety as a protecting group to shield the exocyclic NH_2 groups of nucleobases, including guanosine, was well known and practiced in the art, could be successfully used in the synthesis of RNA oligonucleotides, and had advantageous deprotection qualities in terms of a rapid half-life.

Fan teaches:

> The formation of a guanosine derivative silylated at both the O6 and amino groups…. This intermediate allows facile reaction with acetyl chloride or phenoxyacetyl chloride to give in high yield the corresponding N-protected guanosine derivatives, suitable for use in RNA synthesis. The acetyl and phenoxyacetyl amino protecting groups are, respectively, 4 and 230 times more labile than the isobutyryl group to methylamine/ethanol deprotection.

Ex. 1019, Abstr. (internal reference omitted). Fan schematizes the steps this process as depicted below:



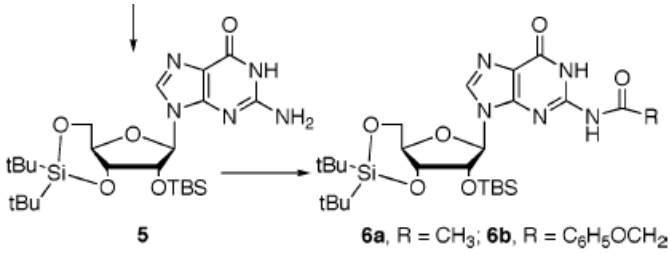
Intermediate (left) and end product (right) of Fan's synthetic scheme. R=CH_3 indicates an acetyl protecting group, whereas $C_5H_5OCH_2$ indicates phenoxyacetyl

Id.

Fan teaches that:

> [A]cylation of guanosine with these labile groups, using TMS [trimethylsilyl] transient protection, is known to proceed smoothly. When we then explored treatment of the 3′,5′-di-tert-butylsilylene derivative **5** with TMSCl before acylation, we found that these acylations also proceeded smoothly, without generation of dark mixtures. Unlike acetylation of guanosine, which is problematic in part for reasons of solubility of the starting material and product, **5** is more soluble in a variety of solvents, so that reaction with TMSCl must be doing something beyond aiding solubility.

Ex. 1019, 2555–2556. Intermediate compound 5 in the acetylation of guanosine (compound **6a**) is depicted in Fan's scheme 2:



Id., Scheme 2 (detail).

Table 1 of Fan (reproduced below) demonstrates the deprotection rates for N-acylguanosine derivatives with isobutyryl, acetyl, and phenoxyacetyl protecting groups:

Table 1. Deprotection of *N*-Acylguanosine Derivatives

N-acyl group	time required for 50% deprotection
isobutyryl	18 h
acetyl	4.5 h
phenoxyacetyl	4.7 min

Table 1 shows that the time required for 50% deprotection of the N-isobutyryl, acetyl, and phenoxyacetyl deprotecting groups was 18 hours, 4.5 hours, and 4.7 minutes, respectively.

Fan concludes that its "experimental procedures for N-acylation [of guanosine] provide a new high-yield route for preparation of these important compounds." Ex. 1019, 2557.

We conclude that the evidence of record establishes, by a preponderance of the evidence, that a person of ordinary skill in the art, having comprehended the teachings of Crooke, Pitsch, and Fan would have found it obvious to substitute an acetyl protecting group for the isobutyryl protecting group of Crooke's compound x. Pitsch and Fan both teach methods of adding an acetyl protecting group to the pyrimidine guanine base, and both comment that the use of acetyl protecting groups are well known in the art and, indeed, Pitsch comments that its method of acetylating guanosine is "suited for a labile universal nucleobase protection." Ex. 1018, 3778; Ex. 1019, Abstr., 2555–2556.

We also conclude that a person of ordinary skill in the art would have been motivated to combine the references. Both Pitsch and Fan teach that acetyl protecting groups can be rapidly removed (essential to the synthesis of a functional oligonucleotide) and Fan teaches that the deprotection rate of acetyl-protected guanosine (4.5 hours for 50% deprotection) is much more rapid than for isobutyryl-protected guanosine (18 hours for 50%

deprotection). *See* Ex. 1018, 3778; Ex. 1019, Table 1. We acknowledge that Fan teaches that deprotection of phenoxyacetyl-protected guanosine is even more rapid; nevertheless, acetyl deprotection still remains significantly more rapid than isobutyryl deprotection. Ex. 1019, Table 1. However, in performing an obviousness analysis, "all disclosures of the prior art, including unpreferred embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)). Finally, as both Pitsch and Fan agree, using an acetyl moiety as a protecting group was well known in the art.

Furthermore, we conclude that a person of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Both Pitsch and Fan teach the successful acetylation of guanosine, as well as details of their synthetic schemes, and, again, Pitsch expressly states that its synthetic scheme is "suited for a labile universal nucleobase protection." Ex. 1018, 3778; *see also generally*, Ex. 1018, 1019. We conclude that, based upon the teachings of Fan, a person of ordinary skill in the art would have a reasonable expectation of successfully substituting an acetyl protecting group for the isobutyryl protecting group of Crooke's compound x, and thus arrive at the compound recited in challenged claim 2.

Patent Owner makes numerous arguments with respect to whether: (a) a person of skill in the art would have selected Crooke's compound x as a lead compound; (b) a skilled artisan would have been motivated to use the teachings of Pitsch and Fan to substitute an acetyl protecting group for the isobutyryl protecting group of Crooke's compound x; (c) a person of

ordinary skill in the art would have had a reasonable expectation of success in combining the references; and (d) objective secondary evidence supports a conclusion of non-obviousness. *See* PO Resp. 12–54; Sur-Reply 9–22. We now address each of these arguments in turn.

a. Selection of Crooke's compound x

Patent Owner contends that, under the lead compound test that our reviewing court first set forth in *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007), a patent challenger must show that a person of ordinary skill in the art (1) would have selected a lead compound that was the "most promising to modify in order to improve upon its [] activity and obtain a compound with better activity"; (2) "would have had a reason to select [the lead compound] from the panoply of known compounds in the prior art"; and (3) would have found the lead compound to have been "a natural choice for further development efforts." *Otsuka Pharm. Co., v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012); *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009).

We are not persuaded that the lead compound analysis is an appropriate one for the case before us. However, we need not decide the aptness of applying *Takeda* and its progeny in performing our analysis, because we conclude that, to a person of ordinary skill, Crooke's compound x would have been an obvious starting point for modification. As we have explained above, guanosine is one of the five canonical nucleotides of the nucleic acids DNA and RNA that are the essential building blocks of oligonucleotide synthesis, and they are a natural, obvious starting place for any artisan seeking to build oligonucleotides. Consequently, a person of

ordinary skill in the art, seeking to synthesize oligonucleotides *via* SPOS would start with phosphoramidites of these four nucleosides, depending upon whether they wished to build a DNA or RNA oligonucleotide. Phosphoramidites of the canonical nucleotides are, simply put, essential.

Moreover, Crooke teaches that fluoridated nucleobases are desirable modifications, and are well known in the art for their increased activity and binding affinity in oligonucleotide synthesis. *See* Ex. 1017, col. 12, ll. 3–56 ("A further particularly useful 2-substituent group for increasing the binding affinity is the 2′-fluoro group."). Crooke teaches a fluoro-substituted guanosine phosphoramidite that is identical to the compound recited in challenged claim 2, with the exception that the isobutyryl protecting group of Crooke's compound x is replaced by an acetyl protecting group in the claimed compound. Crooke's compound x is the result of the final step in the synthetic scheme taught by Crooke for making fluoro-substituted guanosine that can be used in the SPOS synthesis of oligonucleotides in Example 4-d. *See* Ex. 1017, col. 21, ll. 40–44 ("2′-fluoro substituted nucleoside amidites are prepared as follows in Examples 4-a through 4-d[10] or alternately as per the method of Kawasaki[11] "). *Id.* (citing Ex. 2025, 831–41, Ex. 1001, cols. 27–28, ll. 61–129).

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[10] Examples 4-a through 4-c provide synthetic steps for other canonical 2′ fluoro-substituted ribonucleobases; adenosine, uracil, and cytosine, respectively. Ex. 1017 cols. 21–25, ll. 46–30.

[11] A.M. Kawasaki et al., *Uniformly Modified 2′-Deoxy-2′-fluoro Phosphorothioate Oligonucleotides as Nuclease-Resistant Antisense Compounds with High Affinity and Specificity for RNA Targets*, 36 J. MED. CHEM. 831-41 (1993) ("Kawasaki") Ex. 2025.

Pitsch and Fan together teach that acetyl protecting groups can be linked to guanosine, and that acetyl has a more rapid, and therefore advantageous, rate of deprotection than isobutyryl protecting groups. Ex. 1018, 3778; Ex. 1019, Table 1. Where a skilled artisan merely pursues "known options" from a "finite number of identified, predictable solutions," obviousness under § 103 arises. *KSR*, 550 U.S. at 421.

Consequently, we are not persuaded by Patent Owner's argument that a person of ordinary skill in the art would not have selected Crooke's compound x as a starting point for modification of the protecting groups.

b. Patent Owner's arguments that a person of ordinary skill in the art would not have been motivated to use acetyl as a protecting group on Crooke's compound x

i. Prior art teaches away

Patent Owner first argues that the prior art teaches away from the use of acetyl protecting groups. PO Resp. 24–27. A reference teaches away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

Specifically, Patent Owner and its expert, Dr Hrdlicka rely upon Khorana's[12] teaching that "The N-acetyl group was introduced some years

[12] H. Weber and H.G. Khorana, *Total Synthesis of the Structural Gene for an Alanine Transfer Ribonucleic Acid from Yeast. Chemical Synthesis of an Icosadeoxynucleotide Corresponding to the Nucleotide Sequence 21 to 40*, 72 J. MOL. BIOL. 219-49 (1972) ("Khorana") Ex. 2011.

ago … but its disappearance to a significant extent during the course of synthetic and isolation procedures has repeatedly been observed," and that further investigation showed "the N-isobutyryl group to be considerably more stable than the N-acetyl group." PO Resp. 25 (quoting Ex. 2011, 221).

However, the Khorana reference upon which Patent Owner relies was published in 1972, thirty-seven years prior to the claimed priority date of the '885 patent. Furthermore, as Petitioner points out, and Dr. Hrdlicka confirms, Khorana's reported abandonment of acetyl protecting groups was discussed in the context of conducting phosphodiester coupling chemistry, years before the advent of the phosphoramidite (PIII) coupling chemistry, which was developed in the 1980s. *See* Pet. Reply 10; Ex. 1033, 39–40; Ex. 1035 at 113–115 ("Certainly [phosphodiester chemistry is] a different chemistry than – it's different, but protecting groups remain isobutyryl and acetyl that are discussed here in this paper."); Ex. 1007.

Most importantly, Pitsch and Fan expressly teach the successful synthesis and use of acetyl protecting groups with guanosine nucleoside phosphoramidites. We acknowledge that Fan does briefly discuss problems with acetylation of guanosine compared to isobutyryl:

> We have used the Beigelman procedure to protect the guanosine amino group with an isobutyryl group in excellent yield, just as reported. In contrast, when we attempted to introduce more labile amino protecting groups, such as acetyl … or phenoxyacetyl…, the reaction mixtures were dark and the yields were unsatisfactory.

Ex. 1019, 2555 (footnote omitted). However, Fan also expressly teaches how these difficulties were surmounted:

> Yet acylation of guanosine with these labile groups, using TMS transient protection, is known to proceed smoothly. When we then explored treatment of the 3′,5′-di-tert-butylsilylene

> derivative **5** with TMSCl before acylation, we found that these acylations also proceeded smoothly, without generation of dark mixtures.

Id. at 2556 (footnote omitted).

Most importantly, Fan teaches that use of acetyl protecting groups is advantageous in that it has a considerably faster rate of deprotection that isobutyryl. *Id.* at Table 1. Pitsch also praises acetyl protecting groups as "suited for a labile universal nucleobase protection," and as having rapid deprotection rates. Ex. 1018, 3778.

In short, the teachings of the cited prior art in Ground 2 make clear that, by 2009, the field of oligonucleotide synthesis had moved on from the 1972 methods and teachings of Khorana, and that acetyl protecting groups for guanosine nucleobases were known and accepted as advantageous in the art. We consequently reject Patent Owner's teaching away argument.

ii. A skilled artisan would not have been motivated to switch from an isobutyryl group to an acetyl group to protect the N2- position of guanine on compound x because doing so would have made compound x less soluble in organic solvents

Petitioner relies primarily upon its expert Dr. Hrdlicka's opinion that a person of ordinary skill in the art would have known that solubility of nucleosides in organic solvents is critical during the synthesis of nucleosides and during SPOS. PO Resp. 28–29 (citing Ex. 2008 ¶ 112). According to Dr. Hrdlicka, the addition of the smaller, more polar acetyl protecting group would render guanosine less soluble than isobutyryl in organic solvents. *Id.* at 29 (citing Ex. 2008 ¶¶ 113–114).

Dr. Hrdlicka's expert opinion, however, is contradicted by the teachings of Pitsch and Fan. As we explained in the previous section, Fan teaches that, using its method, acetylation of guanosine "proceeded smoothly." Ex. 1019, 2556. Nor does Pitsch describe any solubility issues in its acetylation method for guanosine. Ex. 1018, 3775 ("A convenient synthesis of N2-acetylguanosine (3) was achieved by peracetylation of guanosine with Ac_2O in DMF/pyridine, followed by cleavage of the O-bound Ac groups with NaOH in THF/MeOH/H_2O"). In view of these teachings, and the additional teachings of these references that acetylation can be advantageous in view of its rapid deprotection rates (as explained above), we conclude that, Dr. Hrdlicka's opinion notwithstanding, a person of ordinary skill in the art would have been motivated to combine the teachings of Crooke, Pitsch, and Fan to arrive at the claimed invention.

iii. Pitsch and Fan do not study 2′-deoxynucleosides or 2′-deoxynucleotides and would have produced completely different oligonucleotides than produced by Crooke's compound x

Patent Owner contends that, unlike compound x of Crooke, compound 20 of Pitsch has an O2′-(triisopropylsilyl)oxy-methyl ("TOM") group at its 2′-position (not fluoro) and an acetyl group bound to the N2- guanine. PO Resp. 30 (citing Ex. 1018, 3775 (Scheme 1); Ex. 2008 ¶ 118). Likewise, argues Patent Owner, Fan's compound 6a was a nucleoside derivative (not a phosphoramidite) that could not have been used during SPOS unless transformed into a phosphoramidite. *Id.* at 31 (Ex. 1019, 2556; Ex. 2008 ¶ 119). Patent Owner asserts that neither reference teaches 2′-deoxyribonucleotides. *Id.* at 32.

Patent Owner also argues that, in 2009, a persistent problem existed with at least 2′-fluoro-2′-deoxyribonucleotides, in which oligonucleotides with those monomers would degrade. PO Resp. 32–33 (citing Ex. 2024, 83).

We do not find these arguments persuasive. The only structural difference between corresponding RNA and DNA nucleosides is the presence of a hydroxyl group at the 2′ position on the 5 carbon ribose sugar of RNA nucleosides that is absent in the 2′ deoxyribose of DNA. Ex. 1045, col. 3, ll. 35–38. This site is chemically distant from the 2′ amino group of the guanine molecule that is the site of attachment of the acetyl protecting group. Moreover, Pitsch and Fan concentrate on acetylation of the guanine molecule at the 2′N position. *See, generally*, Ex. 1018; Ex. 1019. Patent Owner adduces no persuasive evidence that the presence or absence of a hydroxyl group at a site distant from the amino moiety requiring protection on the guanine molecule would affect acetylation at that site.

Moreover, "[t]he test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference…. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425 (C.C.P.A. 1981). Crooke teaches the compound recited in challenged claim 2, with the exception of having an isobutyryl group at the 2′N site of the guanine molecule instead of an acetyl. As we have explained above, Pitsch and Fan teach methods by which guanine can be advantageously acetylated at that site. Pitsch, in particular, teaches that acetylation at this site by its method is "indeed suited for a labile *universal nucleobase protection*." Ex. 1018, 3778 (emphasis added).

As for Patent Owner's argument that degradation was a persistent problem in 2′-fluoro-2′-deoxyribonucleotides, Sinha[13], which was published in 2013 and is not prior art to the '885 patent, notes that "[t]he 2′-F modification is subject to depyrimidation (especially with methylamine or ammonia/methylamine deprotection)." Ex. 2024, 83. However, Sinha also teaches that "[t]hese side reactions [i.e., depyrimidation] resulting from methylamine or methylamine/ammonium hydroxide-based C&D [cleavage and deprotection] can often be minimised by using ethanolic ammonia solution (7M) for C&D." Ex. 2024, 83–85. Likewise, Kawasaki reports only the potential for degradation, but also reports successfully using "methanolic ammonia at room temperature," noting that "protecting groups were cleanly removed by methanolic ammonia," including from guanosine. Ex. 2025, 833. Notably, Crooke also teaches this method, stating that "[t]reatment in methanolic ammonia for 24 hrs at room temperature was then done to deprotect all bases…." Ex. 1017, col. 40, ll. 48–52. We consequently find Patent Owner's arguments not persuasive.

iv. A skilled artisan would not have been motivated by Pitsch or Fan to modify Crooke's compound x to make the claimed invention

Patent Owner first argues that neither Pitsch nor Crooke, alone or in combination, compares base deprotection rates of acetyl and isobutyryl protecting groups. PO Resp. 36–38. Patent Owner also argues that Fan

[13] H. Cramer et al., *Oligonucleotide Impurities and their Origin*, in ANALYSIS OF OLIGONUCLEOTIDES AND THEIR RELATED SUBSTANCES (G. Okafo et al., eds.) (2013). ("Sinha") Ex. 2024.

discloses deprotection rates on a fundamentally different compound than compound x under deprotection conditions that a person of ordinary skill in the art would have never used on an oligonucleotide. PO Resp. 39–40.

Patent Owner is quite correct that neither Crooke nor Pitsch compares base deprotection rates between acetyl and isobutyryl protecting groups. However, Pitsch provides deprotection rates for acetyl protecting groups in different nucleosides, including guanosine, and notes the rapidity of the deprotection rates, which causes Pitsch to state that acetyl protecting groups are suitable "for a labile universal nucleobase protection." Ex. 1018, 3778.

With respect to Fan, Patent Owner argues that Fan discloses syntheses and deprotection of nucleoside derivatives, which were completely different molecules than compound x, and does not teach syntheses of corresponding phosphoramidites, or syntheses or deprotection of any oligonucleotide. PO Resp. 39. Patent Owner also argues that Fan uses "1.3% methylamine, 2.6% ethanol, and 96% methylene chloride by weight" to deprotect the N-acyl groups from the N2-position of the subject guanosine derivatives. PO Resp. 39–40 (citing Ex. 1019, 2556; Ex. 2008 ¶ 139). Patent Owner and Dr. Hrdlicka argue that these are unusual deprotection conditions that were not applicable for deprotection of oligonucleotides during SPOS because of the risk of precipitation. *Id.* at 40 (citing Ex. 2008 ¶ 139; Ex. 2009, 151–152).

Although the conditions used by Fan may not necessarily be suitable for the deprotection of oligonucleotides, Fan provides *relative* deprotection rates for acetyl, isobutyryl, and phenoxyacetyl protecting groups on guanosine. We find that that information would have been useful to a person of ordinary skill in the art, and would, in view of the teachings of Crooke and Pitsch, have motivated a person of ordinary skill to attempt the

substitution an acetyl protecting group for the isobutyryl protecting group of Crooke's compound x.

c. Patent Owner's arguments regarding a lack of reasonable expectation of success

i. Use of acetic anhydride in step ii of Example 4-d of Crooke would have caused the synthetic scheme to fail

Patent Owner argues that, contrary to Petitioner's expert, Dr. Baran's proposed synthetic scheme, substituting acetic anhydride for isobutyric anhydride in step ii of Crooke's Example 4-d and executing the subsequent synthetic transformations (steps iii-x) to achieve the compound recited in claim 2, would have resulted in failure. PO Resp. 40–42 (citing Ex. 2008 ¶ 146).

Specifically, Dr. Hrdlicka opines that a skilled artisan would have understood that in step i of Example 4-d, compound i is synthesized from unprotected guanosine, with a silyl group simultaneously protecting the 3′- and 5′-positions of the ribose ring, and the 2′-OH and the N2 amine of the guanine base unprotected. PO Resp. 43 (citing Ex. 2008 ¶¶ 147–149). According to Dr. Hrdlicka, compound i would have then been converted to compound ii by the introduction of, *inter alia*, isobutyric anhydride. *Id.* at 44 (citing Ex. 1017, 25; Ex. 2008 ¶ 150). Patent Owner argues that a skilled artisan would have expected that using acetic anhydride in step ii of the complex synthesis scheme in Example 4-d of Crooke, as proposed by Petitioner's expert, Dr. Baran, would have failed. *Id.* at 40.

Patent Owner also argues that Fan teaches that isobutyrylation of guanosine derivatives (like compound i) using isobutyryl in its scheme worked well, but acetylation (i.e., addition of acetyl groups) of guanosine

derivatives did not ("the reaction mixtures were dark and the yields were unsatisfactory"). PO Resp. 44–45 (citing Ex. 1019, 2555; Ex. 2008 ¶ 151). Patent Owner therefore argues that, in view of the teachings of Fan, a skilled artisan would not have had a reasonable expectation of success in acylating guanosine.

We fail to see the relevance of this argument. What is claimed in challenged claim 2 of the '885 patent is the compound itself, and not a method of its synthesis. Moreover, the question is not whether Petitioner's expert's proposed scheme would work, but what a person of ordinary skill in the art would have understood in view of the teachings of the prior art. *Keller*, 642 F.2d at 425. As we have explained above, both Pitsch and Fan teach successful acylation of the guanine molecule. Ex. 1018, 3778; Ex. 1019, 2555–2556. And we have also explained how Fan, while acknowledging one failure, as Patent Owner points out, also reports successful acylation of guanine. Ex. 1019, 2555-2556 ("Yet acylation of guanosine with these labile groups, using TMS transient protection, is known to proceed smoothly. When we then explored treatment of the 3′,5′-di-tert-butylsilylene derivative **5** with TMSCl before acylation, we found that these acylations also proceeded smoothly, without generation of dark mixtures").

The teachings of the prior art indicate that acylation of guanosine was well known in the art and could be practiced successfully. Patent Owner's arguments are not persuasive.

ii. Using TBAF in step iii of Crooke's Example 4-d would have cleaved the labile acetyl groups and failed

Patent Owner next argues that, in step iii of Crooke's Example 4-d, compound ii would have been converted to compound iii, by the introduction of, *inter alia*, tetra-n-butylammonium fluoride ("TBAF"). PO Resp. 45. Dr. Hrdlicka points to Ober[14] in support of his position that a person of ordinary skill in the art would have expected that removing the 5′-O, 3′-O-silyl protecting groups in step iii with TBAF also would have seriously risked the undesirable removal of the O2′- and/or N2-acetyl groups, given the disclosed basic/nucleophilic conditions disclosed, derailing the subsequent synthetic transformations towards the N2-acetyl analogue of compound x. PO Resp. 46–47 (citing, e.g., Ex. 2015, 18144; Ex. 2008 ¶¶ 155–158).

We find Patent Owner's reading of the evidence to be too selective. Ober indeed teaches that "[t]he subsequent deprotection of the TBDMS groups proved to be difficult due to parallel cleavage of the acetyl protecting group under basic fluoride deprotection conditions such as TBAF in THF." Ex. 2015, 18144. However, Ober goes on to state that "the cleavage reaction was finally possible with pyridine buffered pyridine-HF complex in ethyl acetate." *Id.* Ober thus relates how it was able to overcome the encountered difficulties and its teachings would point the way for a person of ordinary skill to overcome the problem. Patent Owner's argument in this respect is not persuasive.

[14] M. Ober et al., *Base Pairing and Replicative Processing of the Formamidopyrimidine-dG DNA Lesion*, 127(51) J. AM. CHEM. SOC. 2005 18143–49 (2005) ("Ober") Ex. 2015.

iii. The acetyl group would render compound iii less soluble in organic solvents and cause the synthesis to fail

Patent Owner next repeats its argument above that acetylated guanosine, with its small, polar acetyl group would have rendered the composition less soluble in organic solvents. PO Resp. 47–48 (citing Ex. 2009, 176; Ex. 2008 ¶ 158).

We have explained, in Section III.E.4.(b).ii above why we are not persuaded by this argument, and we repeat that reasoning here. Patent Owner's argument is not persuasive in view of the teachings of Pitsch and Fan which report either no solubility issues in the acetylation of guanosine (Ex. 1018, 3778) or overcoming solubility issues so that acylation proceeded "smoothly." Ex. 1019, 2555–2556.

iv. Using sodium hydroxide in step v of Crooke's Example 4-d would have cleaved the 2′ and/or n2 acetyl protecting groups and caused the synthesis to fail

Patent Owner next points to step v of Example 4-d, in which compound iv is converted to compound v by the introduction of, *inter alia*, NaOH. PO Resp. 49. Patent Owner argues, citing Büchi[15], that had two acetyl groups been present on compound iv, instead of the two isobutyryl

[15] H. Büchi et al., *CV. Total Synthesis of the Structural Gene for an Alanine Transfer Ribonucleic Acid from Yeast. Chemical Synthesis of an Icosadeoxyribonucleoside Corresponding to the Nucleoside Sequence 31 to 50*, 72 J. MOL. BIOL. 251–88 (1972) ("Büchi") Ex. 2020.

groups, the use of sodium hydroxide to remove the O2′-acetyl group in step v of Example 4-d would have caused concomitant removal of the N2-acetyl group, given the basic/nucleophilic conditions disclosed, which include an over 10-fold molar excess of sodium hydroxide (NaOH) relative to the reactant nucleoside. *Id.* at 50 (citing Ex. 2020, 252, 279; Ex. 2008 ¶ 164).

Patent Owner's argument is not persuasive because Pitsch teaches the use of NaOH at the analogous step in its synthesis, obtaining a 77% yield, and not reporting any problems. Ex. 1018, 3787 ("N2-Acetylguanosine"). Furthermore, Büchi teaches only partial deacetylation of deoxyguanosine-5′-phosphates in NaOH; after two hours in a molar excess of NaOH[16], only 18% had been deacetylated—an 82% yield. Ex. 2020, Table 1. Patent Owner's arguments that a person of ordinary skill in the art would not have had a reasonable expectation of success in arriving at the compound recited in challenged claim 2 are not persuasive.

v. Petitioner's additional arguments lack evidentiary bases

Finally, Patent Owner argues that Petitioner's argument that a skilled artisan "could have also synthesized the molecule claimed in Claim 2 … by starting with 2′-fluoro-2′-deoxyguanosine, either acquired from a

[16] Petitioner's expert, Dr. Baran, notes that both Büchi and step v of Crooke's Example 4-d employ a molar excess of sodium hydroxide for the same two-hour exposure period. Ex. 1033 ¶ 76 (citing Ex. 1017, col. 26, ll. 49–50; Ex. 2020, Table 1).

commercial source or synthesized according to Sivets,[17]" lacks support, is speculative, and constitutes hindsight reconstruction. PO Resp. 51–54 (quoting Pet. 37–38, which in turn cites Ex. 1028, compound 17).

Patent Owner points to Dr. Hrdlicka's testimony that a skilled artisan would have known that compound 17 of Sivets is not an N9-linked 2′-fluoro-2′-deoxyguanosine, as recited in claim 2, but is instead an isomeric N7-linked 2′-fluoro-2′-deoxyguanosine, and each are completely different molecules. PO Resp. 51 (citing Ex. 1028, 1821; Ex. 2008 ¶ 168).

Moreover, Patent Owner argues, even if, *arguendo*, 2′-fluoro-2′-deoxyguanosine would react similarly to 2′-deoxyguanosine, then it follows that a person of skill in the art would have understood that 2′-fluoro-2′-deoxyguanosine would have suffered from similar solubility problems as 2′-deoxyguanosine during acetylation. PO Resp. 52–53 (citing Ex. 2012, 3822; Ex. 2008 ¶ 171). Dr. Hrdlicka testifies that an artisan of ordinary skill would have known that 2′-fluoro-2′-deoxyguanosine and 2′-deoxyguanosine would have had markedly different electronegativities, and would have expected those differences to have had a significant effect on the conformations of the resulting nucleosides and their reactivities. *Id.* at 53 (citing Ex. 2014, 1421; Ex. 2008 ¶ 171).

We are not persuaded. As an initial matter, we have addressed above Patent Owner's arguments regarding the purported decreased solubility of acetylated guanosine, and we find them no more persuasive upon repetition.

[17] G.G. Sivets et al., *Synthesis and Conformational Analysis of 1′- and 3′-Substituted 2-Deoxy-2-fluoro-d-ribofuranosyl Nucleosides*, 90 HELVETICA CHIMICA ACTA 1818–36 (2007) ("Sivets") Ex. 1028.

With respect to Dr. Hrdlicka's reliance upon Guschlbauer[18] to support his opinion that a skilled artisan would have known that 2′-fluoro-2′-deoxyguanosine and 2′-deoxyguanosine would have had markedly different electronegativities with a significant effect on the conformations of the resulting nucleosides and their reactivities, we do not agree. *See* PO Resp. 53 (citing Ex. 2014). Patent Owner does not point to, nor can we discern, any teaching or suggestion in Guschlbauer that addresses the relative reactivity of 2′-fluoro-2′-deoxy and 2′-deoxy nucleosides. Indeed, Example 4-d of Crooke teaches that protecting groups can be added to the 2′-fluoro-2′-deoxyguanosine, and Patent Owner offers no persuasive evidence that an acetyl protecting group could not have been added as a substitute for the isobutyryl protecting group taught by Crooke. Ex. 1017, cols. 25–26, ll. 33–23. And, as we have explained, Pitsch and Fan, which both teach acetylation of guanosine and guanine, strongly suggest that it could be substituted.

d. Patent Owner's arguments that objective secondary evidence supports a conclusion of non-obviousness

Finally, Patent Owner argues that secondary indicia of non-obviousness further establish that claim 2 is not obvious. PO Resp. 54. Dr. Hrdlicka testifies that, when describing their invention in the '885 patent's Specification, the inventors explained that peers in the oligonucleotide field were experiencing difficulty in obtaining pure chimeric oligoribonucleotides. PO Resp. 55 (citing Ex. 1001, cols. 10–11, ll. 65–4;

[18] W. Guschlbauer et al., *Nucleoside Conformation is Determined by the Electronegativity of the Sugar Substituent*, 8(6) NUCLEIC ACIDS RES. 1421–33 (1980) ("Guschlbauer") Ex. 2014.

Ex. 2008 ¶ 184). Patent Owner notes that the inventors further explained that the 2′-fluoro atom on 2′-fluoro-2′-deoxyribonucleotide monomers of chimeric oligoribonucleotides was lost (as hydrogen fluoride) under "usual deprotection conditions," thus resulting in the formation of chimeric oligonucleotides with monomers lacking fluorine. *Id.* (citing Ex. 1001, col. 11, ll. 15–17; Ex. 2008 ¶ 185). According to the inventors, under the strongly basic conditions, there was a loss of fluorine molecules as well as depyrimidation of uracil and cytosine, an issue also recognized in the literature. *Id.* at 55–57 (citing Ex. 1001, col. 11, ll. 12–47; Ex. 2024, 83; Ex. 2008 ¶¶ 186, 187).

Dr. Hrdlicka testifies that, in addressing this longstanding industry need, the applicants of the '885 patent reported the following unexpected results:

> Our data shows that by utilizing n-acetyl-guanine protected ribonucleoside phosphoramidites, used in oligo with 2′-fluoro substitution, high quality full length RNA were obtained. It is therefore imperative to utilize 2′-fluoro-2′-deoxy nucleosides and corresponding phosphoramidites with guanine protecting groups having N-2 acetyl guanine for mild and shorter base deprotection protocol.

PO Resp. 57–58 (quoting Ex. 1001, col. 11, ll. 48–55; and citing Ex. 2008 ¶ 188). Dr. Hrdlicka testifies the results cited in the '885 Specification were unexpected compared to the properties of Petitioner's alleged closest prior art, Crooke's compound x. *Id.* at 58 (citing Ex. 2008 ¶ 189).

Dr. Hrdlicka further opines that this result is supported by Kawasaki, which reports "significant degradation of the 2′-deoxy-2′-fluoropyrimidine nucleosides" while under "the usual oligonucleotide deprotection conditions

(concentrated NH_4OH, 55°C)." PO Resp. 58 (quoting Ex. 2025, 833; and citing Ex. 2008 ¶ 190).

Patent Owner concludes that, because at least one of the molecules described in the '885 patent satisfied a long-felt industry need and demonstrated unexpected results, the same phosphoramidite recited in challenged claim 2 is entitled to a presumption of a nexus between the asserted evidence and the patent claim. PO Resp. 59 (citing *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019); *Henny Penny Co. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019); Ex. 2008 ¶ 195).

We do not find Patent Owner's arguments persuasive. We have addressed Dr. Hrdlicka's arguments concerning Kawasaki above, finding that Kawasaki reports only the potential for depyrimidation and offers a solution to that issue.

With respect to the secondary objective evidence of nonobviousness, our reviewing court has recognized that such evidence can include commercial success, industry praise, unexpected results, copying, industry skepticism, licensing, and long-felt but unsolved need. *See Apple Inc. v. Samsung Electronics Co., Ltd*., 839 F.3d 1034, 1052 (Fed. Cir. 2016). As evidence of nonobviousness, Patent Owner offers only the statements of the applicants during prosecution of the application that matured into the '885 patent, in which the then-applicants quote the '885 Specification. Such evidence, is not *objective* evidence of nonobviousness as required by the Federal Circuit. Dr. Baran notes, and we agree, that Patent Owner does not point to any statements from any independent third-party asserting that any long-felt need to obtain pure chimeric oligoribonucleotides when using 2′-fluoro-2′-deoxyribonucleotides. *See* Ex. 1033 ¶ 87. The '885 Patent cites

two conference presentations as examples of this alleged difficulty, but does not provide any details concerning the actual reaction conditions employed. *Id.* (citing PO Resp. 57; Ex. 1001, col. 11, ll. 37–47 Ex. 2008 ¶ 187). Nor does Patent Owner provide any copies of these presentations as evidence of record

Patent Owner argues further that Sinha corroborates these conference presentations. *See* PO Resp. 57. However, and as we have explained, Sinha was published in 2013, and is not prior art to the '885 patent. But to the extent that Sinha does teach difficulties with degradation associated with deprotection, Sinha's publication date (2013) suggests that any perceived long-felt need in the field was not, indeed, satisfied by the disclosures of the '885 patent, which claims a priority date of 2009. And, as we have also explained above, Sinha (as well as Kawasaki) expressly teaches how to avoid degradation of oligonucleotides that contain 2′- fluoro-2′-deoxyribonucleotides by using different deprotection conditions. Ex. 2024 at 83–86; Ex. 2025, 831–41.

Furthermore, its arguments to the contrary notwithstanding, Patent Owner has not persuasively shown that anyone tried and failed to make the claimed compound. To be sure, Sinha and Kawasaki describe problems with degradation, however, and as we have explained above, they also demonstrate how such problems could be overcome. And, as we have noted, Sinha is not prior art to the '885 patent and so does not reflect the state of the field, including any long-felt need, at the time of filing. Ex. 2024 at 83–86; Ex. 2025, 831–41.

Patent Owner's arguments concerning its alleged unexpected results are similarly not persuasive. *See* PO Resp. 57–58. As we have explained

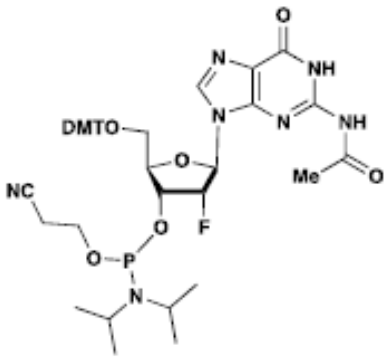
above, a person of ordinary skill in the art, upon comprehending the teachings of the cited prior art, would have had a reasonable expectation of success in synthesizing the claimed compound. Moreover, Patent Owner's claim of unexpected results in obtaining "high quality full length RNA" is not commensurate in scope with claim 2, which claims only phosphoramidite compounds and does not claim RNA oligonucleotides, or any process for synthesizing them.

To the extent that Patent Owner has thus presented secondary objective evidence of nonobviousness, we find it is not of sufficient probative weight to overcome Petitioner's showing, by a preponderance of the evidence, that the challenged claim 2 is obvious over the cited prior art. *See Leapfrog Enters. Inc. v. Fisher-Price Inc.,* 485 F.3d 1157, 1162 (Fed. Cir. 2007) (holding that "given the strength of the prima facie obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion" of obviousness).

We consequently conclude that Petitioner has established, by a preponderance of the evidence, that claim 2 is obvious over the prior art cited in Ground 2 and that Patent Owner's arguments do not overcome our conclusion.

F. Ground 3: Obviousness of challenged claim 2 over Vater and Pitsch

As we related above, challenged claim 2 recites a derivatized nucleoside and phosphoramidite where "B" is, *inter alia*, guanine-N-acetyl and "Z" is ribo fluoro. The claimed molecule is depicted again below:



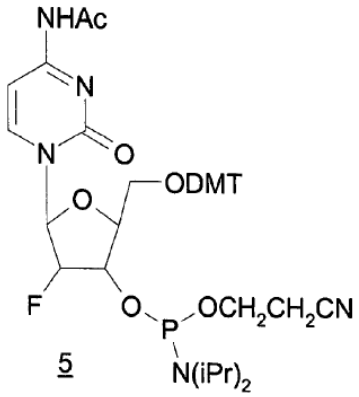
Claimed molecule recited in challenged claim 2 where "B" is guanine-N-acetyl and "Z" is ribo fluoro

Pet. 39.

1. Overview of the prior art

a. Vater

Vater is U.S. Patent 7,879,991 B2, issued on February 1, 2011. Among other things, Vater teaches 2′-fluoro-L-cytidine phosphoramidite. This molecule is depicted in Figure 16(5) of Vater and reproduced below:



2′-fluoro-L-cytidine phosphoramidite; "iPr" is an abbreviation for an isopropyl group

2. Petitioner's arguments

Petitioner argues that the only difference between the phosphoramidite in challenged claim 2 of the '885 patent (where "B" is guanine-N-acetyl and "Z" is ribo fluoro) and the 2′-fluoro-L-cytidine phosphoramidite in Figure 16(5) of Vater is the nucleobase present: the former has a guanine ("G") base whereas the latter has a cytosine ("C") base. Pet. 40 (Ex. 1003 ¶ 127).

Petitioner contends that a person of ordinary skill in the art would have recognized that the purpose of a phosphoramidite compound was to serve as a building block for incorporating the corresponding nucleobase into a growing oligonucleotide chain through automated SPOS. Pet. 40. According to Petitioner, such a skilled artisan would also have known that the synthesis of most oligonucleotides would require the incorporation of all four canonical nucleobases. *Id.* Therefore, argues Petitioner, the 2′-fluoro-L-cytidine phosphoramidite disclosed in Figure 16(5) of Vater would have motivated a POSA to build the structurally analogous 2′-fluoro-guanosine phosphoramidite claimed in challenged claim 2 of the '885 patent, especially in view of Pitsch, which would have informed one of ordinary skill about the advantages of using an acetyl protecting group to protect the exocyclic NH_2 group of the guanine nucleobase. *Id.* at 40–41 (citing Ex. 1003 ¶ 128).

Petitioner also contends that, as argued in the previous section with respect to challenged claim 2, a person of ordinary skill in the art would have had a reasonable expectation of successfully synthesizing the molecule in claim 2 of the '885 patent. Pet. 41.

3. Patent Owner's Response

Patent Owner first argues that Vater teaches a totally different molecule than that recited in challenged claim 2 of the '885 patent. PO Resp. 61. Patent Owner argues further that a person of ordinary skill in the art would have recognized that Vater's compound 5 in Figure 16 is an L-configured nucleoside, as disclosed by Vater. *Id.* at 62 (citing Ex. 1020, col. 16, ll. 38–40; 45:45–48; Ex. 1003 ¶ 127; Ex. 2009, 180; Ex. 2008 ¶ 199). Dr. Hrdlicka, Patent Owner's expert, opines that a skilled artisan would have also understood that the compound recited in challenged claim 2 of the '885 patent is a D-configured nucleoside. *Id.* (citing Ex. 2008 ¶¶ 201–205).

Patent Owner argues that a person of ordinary skill in the art would have understood that these molecules would have had to been prepared completely differently, would have had opposite stereochemical configurations, would have required different starting materials for their synthesis (i.e., enantiomeric starting materials), and would have reacted completely differently during SPOS. PO Resp. 63–64 (citing Ex. 2008 ¶ 207).

Patent Owner also again argues that Petitioner fails to provide any reasoning why a skilled artisan would have selected Vater's compound 5 as a lead compound. PO Resp. 64 (citing Ex. 2008 ¶ 208; Pet. 40). Patent Owner again argues that this suggests impermissible hindsight reconstruction on Petitioner's part. *Id.*

Patent Owner further argues that a person of ordinary skill in the art would not have been motivated by Vater and Pitsch to synthesize the N2-acetyl-2′-F-2′-deoxyguanosine of challenged claim 2. PO Resp. 65. Patent

Owner argues that Petitioner's arguments are illogical and its expert's testimony conclusory. *Id.* Petitioner also recapitulates its arguments concerning Pitsch that it advanced with respect to Ground 2 above. *Id.*

Furthermore, argues Patent Owner, a skilled artisan would have understood that Vater teaches that pyrimidine nucleotides were to be configured with F at the 2′-position. PO Resp. at 65–66 (citing Ex. 1020, 12; Ex. 2008 ¶ 213). However, Patent Owner asserts, the guanine base of challenged claim 2 of the '885 patent is a purine, not a pyrimidine base, and therefore Vater would not have motivated a skilled artisan to synthesize a N2-Acetyl-2′-F-2′-deoxyguanosine, as recited in challenged claim 2. *Id.*

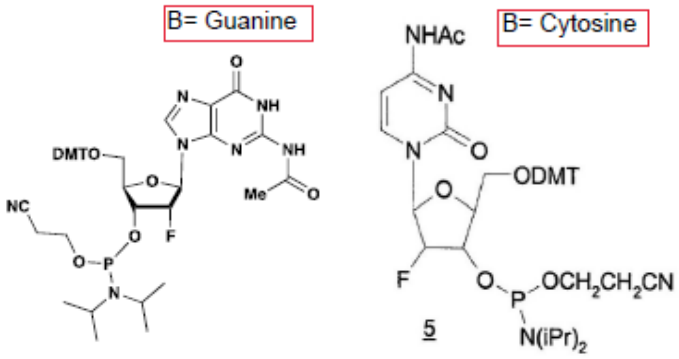
Patent Owner also contends that Vater would not have motivated a skilled artisan because Vater is directed to L-configured nucleic acids, not D-configured phosphoramidites (as in challenged claim 2), and thus teaches instability of D-configured nucleic acids in aqueous solutions and biological systems. PO Resp. 66 (citing Ex. 2008 ¶ 214; Ex. 1020, 12).

Patent Owner contends that a person of ordinary skill in the art also would not have had a reasonable expectation of successfully synthesizing the molecule in challenged claim 2 based on Vater. PO Resp. 67. Patent Owner contends that nowhere in its Petition does Petitioner provide sufficient evidence or reasoning for a reasonable expectation of success based on Vater or its compound 5, which is a completely different molecule from compound x of Crooke and the molecules disclosed in Pitsch. *Id.* (citing Ex. 2008 ¶ 217).

Finally, Patent Owner repeats its arguments from Ground 2 with respect to objective evidence of nonobviousness. PO Resp. 67.

4. Analysis

Having reviewed the parties' arguments and the evidence of record, we conclude that Petitioner has established, by a preponderance of the evidence of record, that challenged claim 2 is obvious over Vater and Pitsch. The compounds recited in challenged claim 2 and in Figure 16(5) (compound 5) of Vater are depicted side-by-side below:



Petitioner's annotated diagram comparing the compound recited in claim 2 of the '885 patent (left) with compound 5 of Vater (right)

We agree with Patent Owner that phosphoramidite compound 5 has a pyrimidine cytidine molecule as its base, rather than the purine guanine residue of challenged claim 2. But we find persuasive Petitioner's argument that a person of ordinary skill in the art, preparing phosphoramidite nucleobases as a prelude to oligonucleotide synthesis, would find it equally obvious to prepare phosphoramidite nucleobases of each of the canonical nucleobases, because all of these may be necessary to the synthesis of a given completed oligonucleotide.

For the same reason, a skilled artisan would have been motivated to combine the teachings of Vater and Pitsch to arrive at the compound recited in challenged claim 2. Pitsch expressly teaches that acetyl groups are useful as protecting groups in cytosine-based phosphoramidites: "For protection of

the exocyclic NH_2 functions of the nucleobases, we have chosen the [acetyl] group, which, as a protecting group for cytosine nucleosides, is already used in combination with a convenient deprotection scheme involving a mixture of aqueous NH_3 solution and $MeNH_2$." Ex. 1018, 3778. Pitsch teaches that the deprotection half-life of 2′-O-tom-protected N4-acetylcytidine is less than 2 minutes. *Id.* And, again, Pitsch teaches that "the [acetyl] group, in combination with $MeNH_2$, is indeed suited for a labile *universal nucleobase protection*." *Id.* (emphasis added).

Furthermore, the references themselves establish a reasonable expectation of success in arriving at the claimed compound. Pitsch expressly teaches that an acetyl protecting group can be used equally effectively with cytosine and guanosine nucleobases. Ex. 1018, 3778. Consequently, we conclude that a person of ordinary skill in the art, knowing that phosphoramidite nucleobases of all of the canonical nucleobases, including cytosine (as taught by Vater) and guanosine (as taught by Crooke) are necessary for oligonucleotides, and further knowing that both cytosine and guanosine phosphoramidites can be acetylated (and subsequently deprotected) by the method of Pitsch, would have had a reasonable expectation of success in combining the teachings of the references to arrive at the claimed invention.

We do not find Patent Owner's arguments to the contrary persuasive. We have addressed some of those arguments in the preceding discussion of Ground 2. With respect to Patent Owner's contention that Vater teaches an L-configured phosphoramidite, rather than a D-configured phosphoramidite, as in challenged claim 2, Vater teaches that "[t]he nucleic acids according to the present invention can either be D nucleic acids or L nucleic acids," and

that "parts of these longer nucleic acids can be either a D nucleic acid or an L nucleic acid[, and such parts] can have a function, [such as] immobilizing, cross-linking, proof or amplification." Ex. 1020, (Ex. 1020, col. 11, ll. 32–67). As such, a person of ordinary skill in the art would have understood that either D- or L- enantiomers are equally contemplated within the scope of Vater's teachings.

With respect to Patent Owner's allegation that Petitioner has employed impermissible hindsight reasoning:

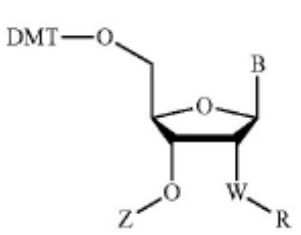
> Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.

In re McLaughlin, 443 F.2d 1392, 1395 (C.C.P.A. 1971). In its arguments, Patent Owner does not point to any knowledge that could have been gleaned only from the Specification of the '885 patent. Its hindsight allegation, consequently, is without merit.

Finally, we have addressed Patent Owner's arguments concerning its secondary indicia of nonobviousness in Section III.E.4.d. above. We incorporate by reference those arguments with respect to Ground 3 as well, and arrive at the same conclusion that Patent Owner's arguments in this respect are insufficient to overcome Petitioner's showing that claim 2 is obvious over Vater and Pitsch.

G. Ground 4: Obviousness of challenged claim 3 over Crooke, Pitsch, Vater and Scaringe

Claim 3 recites:

> 3. Derivatized nucleosides, succinates and solid supports
>
> of general formula 2,
>
> 
>
> (Formula 2)
>
> where B is Guanine-N-acetyl , or adenine-N–acetyl
>
> W = ribo fluoro or ara fluoro, and R is absent
>
> Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of [ethyl[19]], oxalyl, and hydroquinolynyl
>
> and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1–C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

Ex. 1001, cols. 25–26, ll. 64–17.

1. Overview of the prior art

b. Scaringe (Ex. 1022)

Scaringe is an article entitled *Chemical Synthesis of Biologically Active Oligoribonucleotides using β-Cyanoethyl Protected Ribonucleoside Phosphoramidites*, and published in the journal Nucleic Acids Research on September 25, 1990. Ex. 1022, 5433. Scaringe is directed to "[t]he preparation of fully protected diisopropylamino β-cyanoethyl ribonucleoside phosphoramidites." *Id.* at Abstr. Scaringe notes that "the need to protect the

[19] *See* Pet. 18–20; PO Resp. 15; *see also* Section III.A, *supra*.

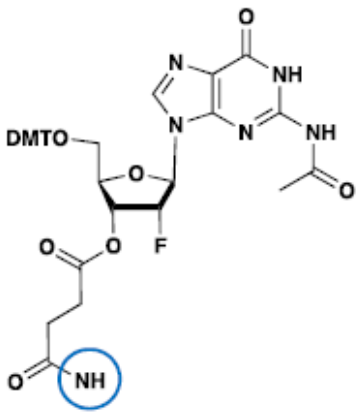
additional 2′-hydroxyl group in RNA has hindered the development of a practical method to synthesize RNA." *Id.* at 5433.

Scaringe explains how to convert each of the four canonical RNA nucleosides, including an N2-isobutyryl, 2′-O-TBDMS protected guanosine, to either its corresponding phosphoramidite or succinylated derivative. Ex. 1022, 5434, 5440. Scaringe also teaches that the succinylated derivatives are coupled to LCAA-CPG to prepare the solid supports for SPOS. *Id.* at 5435.

Scaringe concludes "that the ribonucleoside phosphoramidites 2a-d are > 99.95% isomerically pure. We have further demonstrated that the protecting group strategy used led to the successful preparation, deprotection, and isolation of RNA." Ex. 1022, 5438.

2. Petitioner's argument

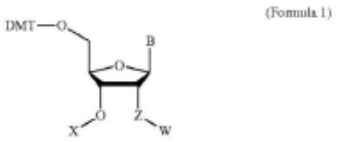
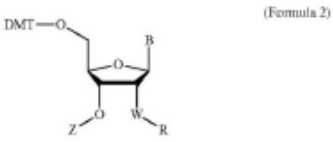
Petitioner argues that a person of ordinary skill in the art would have understood that the compound recited in challenged claim 3, in which "B" is guanine-N-acetyl, "W" is ribo fluoro, and "Z" is a succinyl group bound to "-NH" (i.e., such that "M" is ethyl), claims the following molecule:



Compound of claim 3 in which "B" is guanine-N-acetyl, "W" is ribo fluoro, and "Z" is a succinyl group bound to "—NH"

Pet. 42, 43 (citing Ex. 1003 ¶ 138).

Petitioner argues that the -NH group (circled in blue in the above illustration) on the succinyl group is capable of being attached to a solid support with a spacer selected from the group of spacers recited in challenged claim 3. Pet. 43 (citing Ex. 1003 ¶ 139). Petitioner argues that challenged claims 2 and 3 claim nearly identical structures, as shown by the following table:

Claim 2	Claim 3
Derivatized nucleoside and **phosphoramidite** of general formula 1,	Derivatized nucleosides, **succinates and solid supports** of general formula 2,
 (Formula 1)	 (Formula 2)
where B is Guanine-N-acetyl, or adenine-N-acetyl;	where B is Guanine-N-acetyl, or adenine-N-acetyl;
Z=ribo Fluoro or ara fluoro, and	W=ribo fluoro or ara fluoro,
W is absent; and	and R is absent;
X is cyanoethyl dialkyl phosphoramidite.	Z is C(O)-M-C(O)—NH,
	where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl,
	and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

Pet. 44 (citing (Ex. 1003 ¶ 142). The above table compares the limitations of claims 2 and 3, to show the similarity between the limitations of these claims. Petitioner contends that the compounds recited in claims 2 and 3 differ only with respect to the moiety bound to the 3′-O of the sugar ring: in

claim 2, "X" is cyanoethyl dialkyl phosphoramidite, whereas in claim 3, "Z" can be a succinyl-NH in which the NH is capable of attachment to a solid support with one of the recited spacers. *Id.* (citing Ex. 1003 ¶ 143).

Petitioner repeats its arguments with respect to Ground 2 above, that: (1) the guanosine phosphoramidite made in Crooke's Example 4-d has an isobutyryl protecting group at the exocyclic NH_2 group of the guanine base of that molecule; (2) a person of ordinary skill in the art would have been motivated by the respective teachings of Pitsch and Fan to make and use a similar guanosine phosphoramidite, but with an acetyl instead of an isobutyryl protecting group; and (3) such a skilled artisan would have had a reasonable expectation of successfully arriving at the nucleoside and phosphoramidite recited in claim 2 of the '885 patent, in which "B" is guanine-N-acetyl and "Z" is ribo fluoro. Pet. 45 (citing Ex. 1003 ¶ 141).

Petitioner contends that a person of skill in the art would have understood that it was well known in the art that, in solid phase oligonucleotide synthesis using phosphoramidite chemistry, the side group bound to the O on the 3′ C of a nucleoside (i.e., "X" in Claim 2 and "Z" in claim 3) could be either a phosphoramidite (as recited in claim 2) or a succinate (as recited in claim 3). Pet. 45 (citing Ex. 1003 ¶ 144). Petitioner contends that Scaringe explains how to convert each of the four canonical RNA nucleosides, including an N2-isobutyryl, 2′-O-TBDMS protected guanosine, to either its corresponding phosphoramidite or succinylated derivative. *Id.* at 45–46 (citing Ex. 1022, 5434, 5440). Petitioner asserts that Scaringe further explains that the succinylated derivatives are coupled to LCAA-CPG to prepare the solid supports for SPOS: "All solid phase syntheses were performed on commercially available DNA synthesizers …

on a 0.5 μmol scale using derivatized 1000 Å CPG [] solid supports. These supports were prepared by the coupling of compounds 5a-d to LCAA-CPG." *Id.* at 46 (citing Ex. 1022, 5435, 5440).

Petitioner contends that it was known in the art that LCAA-CPG stands for "long chain alkyl amine controlled pore glass," a commonly used solid support used in SPOS, in which the "long chain alkyl" functions as a spacer attaching the "amine" group to the "controlled pore glass." Pet. 47 (citing Ex. 1003 ¶ 146; Ex. 1023, 74). Petitioner argues that a skilled artisan would also have regarded a C6 alkyl as a suitable long chain alkyl spacer which falls within the claimed "C1–C20 alkyl" recited in claim 3. *Id.* (citing Ex. 1003 ¶ 147; Ex. 1007, 2229 (molecule #40)).

Petitioner therefore asserts that Scaringe demonstrates that those of ordinary skill would have had a reasonable expectation of success of: (1) synthesizing the molecule recited in challenged claim 3 of the '885 patent (where "B" is guanine-N-acetyl and "W" is ribo fluoro); and (2) attaching that molecule to a "long chain alkyl amine controlled pore glass." Pet. 47.

3. Patent Owner's Response

Patent Owner repeats its arguments with respect to Ground 2 above, contending that: (1) Petitioner fails to provide a rationale as to why a skilled artisan would have chosen Crooke's compound x as a lead compound; (2) neither Pitsch nor Fan would have motivated a POSA to modify compound x to make the compounds claimed in claim 2; (3) a POSA would not have had a reasonable expectation of success in synthesizing the compounds recited in claim 2; and (4) secondary indicia of non-obviousness also establish that

challenged claim 3 is not unpatentable. PO Resp. 69 (citing Ex. 2008 ¶ 224).

Patent Owner argues further that Scaringe does not disclose 2′-F groups and instead uses an O2′-TBDMS group and only teaches using an isobutyryl protecting group, and not acetyl, to protect the N2-position of the guanine nucleobase, and does not disclose deprotection rates. PO Resp. 70 (citing Ex. 1022, 5434; Ex. 2008 ¶ 226).

4. Analysis

We conclude that Petitioner has established, by a preponderance of the evidence, that claim 3 is obvious over the cited prior art. As Petitioner notes, compound 5 of Scaringe's Figure 1 and the recited compound of challenged claim 3 are identical[20], with the exception that the functional group at the 3′-O position is either cyanoethyl dialkyl phosphoramidite in challenged claim 2 or is C(O)-M-C(O)-NH, where M is selected from the group consisting of ethyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy in challenged claim 3.

We have explained at length above why we conclude that Petitioner has successfully established that the compound of challenged claim 2 is obvious over Crooke, Pitsch, and Fan, and why Patent Owner's arguments

[20] This despite the different letters used to indicate various subgroups between the two claims, e.g., Z/W for "ribo fluoro or ara fluoro" and W/R "is absent."

are insufficient to overcome Petitioner's showing. *See* Section III.E.4, *supra*. We incorporate our same reasoning here with respect to Ground 4.

That leaves us with only the question of whether the limitation reciting "Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of [ethyl], oxalyl, and hydroquinolynyl and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1–C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy" is obvious over the prior art.

Scaringe expressly teaches how to convert each of the four canonical RNA nucleosides, including an N2-isobutyryl, 2′-O-TBDMS protected guanosine, into either its corresponding phosphoramidite or succinylated derivative. *See, e.g.*, Ex. 1022, 5440 ("Synthesis of 5′-O(dimethoxytrityl)-2′-O-(*t*-butyldimethylsylyl) ribonucleoside 3′-O-succinates (5a-d)"). We also agree with Petitioner that a person of ordinary skill in the art would have understood that Scaringe teaches that its succinylated nucleosides were coupled to LCAA-CPG so as to permit SPOS, and that Scaringe's 6C alkyl LCAA chain spacer falls within the claimed C1–C20 alkyl spacer of challenged claim 4.

As we have explained with respect to Ground 2 above, we conclude that a person of ordinary skill in the art would have been motivated to select and modify Crooke's compound x, in view of the teachings of Fan and Pitsch, to substitute an acetyl protecting group for the isobutyryl group taught by Crooke, with a reasonable expectation of success in arriving at the claimed invention. *See* Section III.E.4, *supra*. We further conclude, in view of the teachings of Scaringe, that a person of ordinary skill would have been motivated to add Crooke's modified compound x, a succinyl group at the 3′-

O position of the nucleoside to facilitate attachment of the C6 LCAA-CPG alkyl spacer for attachment in process of solid phase oligonucleotide synthesis (SPOS) and, as Scaringe teaches, would have had a reasonable expectation of success in doing so. *See* Ex. 2022, 5440.

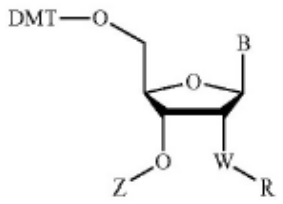
Patent Owner's arguments are not persuasive. In addition to its repeated arguments with respect to Ground 2, which we have addressed in Section III.E.4 above, Patent Owner argues: (1) that Scaringe does not disclose 2′-F groups and instead uses an O2′-TBDMS group; (2) teaches using an isobutyryl protecting group, and not acetyl, to protect the N2-position of the guanine nucleobase; and (3) does not disclose deprotection rates. *See* PO Resp. 70.

With respect to (1), Crooke's compound x is 2′-fluoro-substituted guanosine, and Crooke further teaches that 2′-fluoro substituted nucleobases are very useful due to their increased binding affinity. *See* Ex. 1017, cols. 25–28, ll. 34–19, col. 12, ll. 3–31. Patent Owner adduces no evidence of record that substituting a fluoro group at the 2′ position would render Scaringe's methods inoperable. We agree with Patent Owner that Scaringe teaches using an isobutyryl protecting group (2) but, as we have explained with respect to Ground 2, a person of ordinary skill in the art would have been motivated to substitute an acetyl protecting group to obtain a likely faster deprotection rate. And with respect to (3), although Scaringe does not disclose deprotection rates, such rates are not recited in, or required by, the challenged claims. Furthermore, and as we have explained with respect to Ground 2 above, both Fan and Pitsch suggest that acetyl protecting groups have more rapid rates of deprotection that isobutyryl. *See* Section III.E.4, *supra*. We consequently conclude that Patent Owner's arguments in this

respect are insufficient to overcome Petitioner's showing that claim 3 is obvious over the cited prior art.

H. Ground 5: Obviousness of challenged claim 4 over Scaringe, Pitsch, and Fan

Challenged claim 4 recites:

> 4. Derivatized nucleosides, succinates and solid supports of general formula 2,
>
> (Formula 2)
>
> 
>
>
> wherein, 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;
>
> W is Oxygen
>
> and R is selected from the group consisting of t-butyldimethyl silyl, acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and
>
> Z is C(O)-M-C(O)—NH,
>
> where M is selected from the group consisting of [ethyl[21]], oxalyl, and hydroquinolynyl,
>
> and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1–C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy

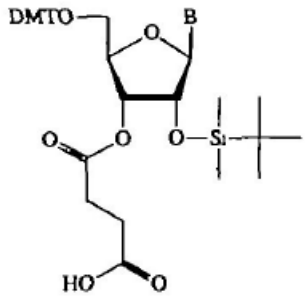
Ex. 1001, col. 26, ll. 18–43.

[21] *See* fn.16, *supra*.

1. Petitioner's arguments

Petitioner points to compound 5 of Scaringe's Figure 1 as disclosing an almost identical compound to that recited in challenged claim 4, in which "B" is guanine-N-isobutyryl. Pet. 50. Compound 5 of Scaringe's Figure 1 is reproduced below:

a) B = N^6-Benzoyl adenine
b) = N^4-Benzoyl cytosine
c) = N^2-Isobutyryl guanine
d) = Uracil



Compound 5 of Scaringe's Figure 1

Petitioner argues that Scaringe's compound 5(c) differs from the compound recited in challenged claim 4 only with respect to the protecting group on the exocyclic NH_2 of the guanine base: compound 5(c) has an isobutyryl protecting group, whereas claim 4 claims an acetyl-N-guanine. Pet. 50 (citing Ex. 1003 ¶ 153).

Petitioner repeats its arguments with respect to both Ground 2 and 4 above, contending that a person of ordinary skill would have been motivated by the teachings of Pitsch and Fan to substitute an acetyl protecting group for the isobutyryl protecting group of Scaringe's compound 5(c). Pet. 51. Petitioner also argues that a skilled artisan would have recognized that the substitution of the protecting group on the exocyclic NH_2 group of the guanine base would not be affected by the 2′-O-TBDMS protecting group, which was commonly used to shield the 2′-OH. *Id.* (citing Ex. 1003 ¶ 155). Petitioner argues that this substitution of the protecting group on the exocyclic NH_2 group of the guanine base would have resulted in a 5′-O-

DMT-2′-O-TBDMS N2-acetyl-guanosine 3′-O-succinate. *Id.* (citing Ex. 1003 ¶ 155). Petitioner again argues that Scaringe discloses the coupling of this succinate to LCAA-CPG to prepare the solid support for SPOS, and that a person of ordinary skill would have regarded a C6 alkyl as a suitable spacer. *Id.* at 51–52 (citing Ex. 1003 ¶ 156; Ex. 1022, 5435; Ex. 1007, 2229 (molecule #40)).

2. Patent Owner's arguments

Patent Owner argues that Petitioner makes no showing as to why a person of ordinary skill in the art would have selected compound 5(c) as a lead compound as the "most promising to modify in order to improve upon its [] activity and obtain a compound with better activity," or why a skilled artisan "would have had a reason to select [compound 5(c)] from the panoply of known [nucleoside building blocks] in the prior art." PO Resp. 73 (citing *Takeda Chem.*, 492 F.3d at 1357; *Otsuka*, 678 F.3d at 1292).

Patent Owner's expert, Dr. Hrdlicka, opines that a skilled artisan would not have chosen compound 5(c) as a lead compound. PO Resp. 73 (citing Ex. 2008 ¶ 234). According to Dr. Hrdlicka, Scaringe teaches that the syntheses of RNA oligoribonucleotides via SPOS, which for RNA proceeds in the 3′ to 5′ direction and that, in SPOS, the 3′-end would have been bound, *via* the succinate, to a solid support. PO Resp. 73–74 (citing Ex. 2008 ¶ 235). Dr. Hrdlicka points to Scaringe's Table 4 as disclosing the synthesis of four RNA sequences, none of which shows a guanosine on the 3′-end. Dr. Hrdlicka contends that there is no evidence of guanosine being bound to a solid support, through a succinate or otherwise. *Id.* at 74 (citing Ex. 2022, 5436; Ex. 2008 ¶ 236). Patent Owner therefore argues that a

person of ordinary skill in the art would not have viewed compound 5(c) of Scaringe as a lead compound. *Id.*

3. Analysis

Having reviewed the parties' arguments and the evidence of record, we conclude that Petitioner has established, by a preponderance of the evidence, that claim 4 is obvious over the combined cited prior art. We have explained above why a person of ordinary skill in the art, in view of the teachings of Pitsch and Fan, would have been motivated to substitute an acetyl protecting group for an isobutyryl group to possibly obtain a more rapid deprotection rate, and why such an artisan would have a reasonable expectation of success in doing so.

Patent Owner's arguments are not persuasive. As we explained earlier, we are skeptical of Patent Owner's "lead compound" theory of the case but, our skepticism notwithstanding, Scaringe teaches the synthesis of 5′-O-(dimethoxytrityl)-2′-O-(*t*-butyldimethylsylyl) ribonucleoside 3′-O-succinates, *including guanosine* as the nucleoside. Ex. 1022, 5440, Fig. 1 (compound 5(c)). Scaringe teaches that the purpose of the succinate compounds (including compound 5(c)) is to be coupled to LCAA-CPG to prepare supports for SPOS:

> All solid phase syntheses were performed on commercially available DNA synthesizers (see experimental). Syntheses were conducted on a 0.5/μmol scale using derivatized 1000 Å CPG (average loading = 10–15/μmol g^{-1}) solid supports. These supports were prepared by the *coupling of compounds* ***5a-d*** *to LCAA-CPG*.

Ex. 1022, 5435 (emphasis added). Scaringe thus expressly contemplates the use of succinated guanosine nucleobase as the attachment point at the 3′ end

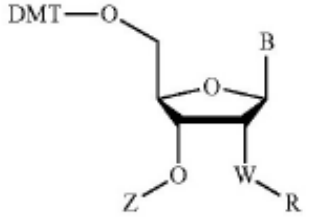
of oligonucleotide synthesis. Consequently, a person wishing to start their SPOS nucleotide with guanosine would use the succinated nucleoside to tether the molecule to LCAA-CPG, as taught by Scaringe. *Id.*

That Scaringe did not list an oligonucleotide beginning with guanosine on the 3′ end of its examples in its Table 4 is of no moment. "[A] reference is not limited to the disclosure of specific working examples." *In re Mills*, 470 F.2d 649, 651 (C.C.P.A. 1972). In this case, Scaringe expressly teaches the synthesis of guanosine succinate for use in SPOS. We conclude that a person of ordinary skill in the art would have chosen to synthesize 5′-O-(dimethoxytrityl)-2′-O-(*t*-butyldimethylsylyl) guanosine 3′-O-succinate in the course of synthesizing, *via* SPOS, an oligonucleotide with guanosine on the 3′ end.

We consequently conclude that Petitioner has established, by a preponderance of the evidence, that challenged claim 4 is obvious over the cited prior art, and that Patent Owner's arguments do not overcome Petitioner's showing that the challenged claim is obvious.

I. Ground 6: Anticipation of challenged claim 5 by Gaur

Claim 5 recites:

> 5. Derivatized nucleosides, succinates and solid supports of general formula 2,
>
> (Formula 2)
>
> 
>
>
> wherein B is selected from the group consisting of Guanine-Nacetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-

> isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;
>
> W is Oxygen and R is methyl; and
>
> Z is C(O)-M-C(O)-NH,
>
> where M is selected from the group consisting of [ethyl[22]], oxalyl, and hydroquinolynyl,
>
> and NH is [is capable of being attached to a solid support with a spacer selected from the group consisting of[23]] C1–C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

Ex. 1001, col. 26, ll. 43–65.

1. Overview of the prior art

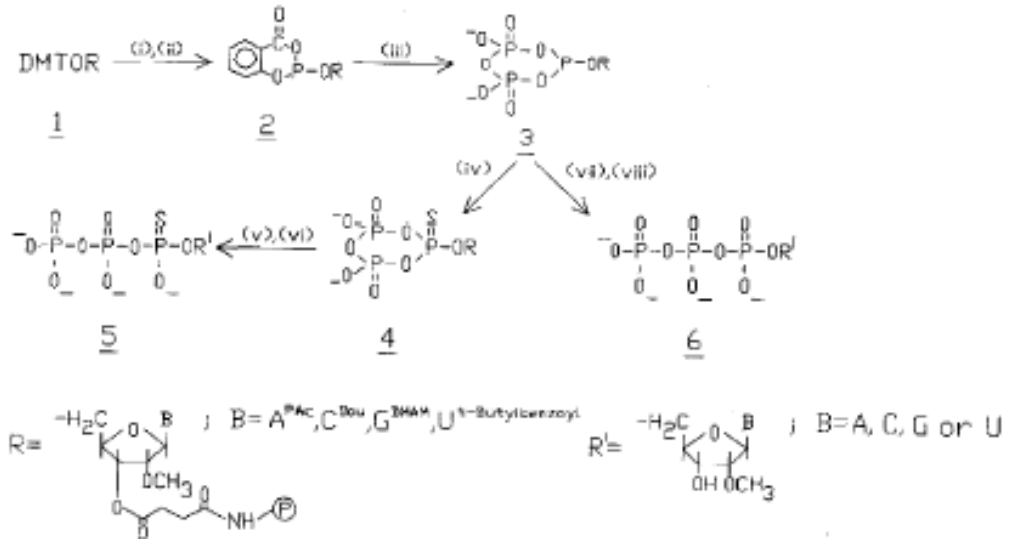
a. Gaur

Gaur is an article entitled *Novel Solid Phase Synthesis of 2′-O-Methylribonucleoside 5′-Triphosphates and their A-Thio Analogues*, which was published in the journal Tetrahedron Letters in 1992. Ex. 1024, 3301. Gaur teaches a "[s]imple, versatile and convenient syntheses of 2′-O-methylribonucleoside 5′-triphosphates." *Id.*, Abstr.

Gaur teaches its general synthetic scheme as Scheme 1, which is depicted below:

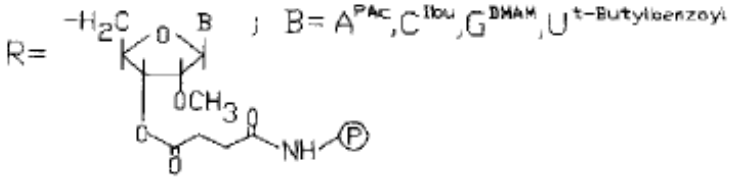
[22] *See* fn.16, *supra*.

[23] *See* Pet. 21–22; PO Resp. 15.



Ex. 1024, Scheme 1.

Gaur teaches, as its starting point, compound 1 ("compound 1"), which is DMTOR, or DMT-O-R. DMT is a 4, 4′-dimethoxytrityl protecting group, and R is a ribonucleoside having a 2′-O-Me and a 3′-O-succinyl-NH, where the NH is also attached to a circled P (i.e., a polymer support for SPOS).

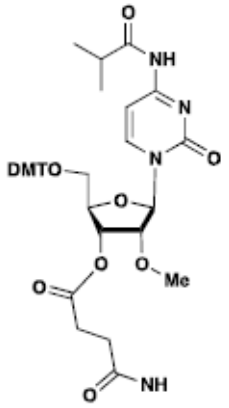


Detail of scheme 1 of Gaur

In this compound, "B" is a nitrogenous base consisting of "A^{PAC}" phenoxyacetylatyed adenine, "C^{Ibu}" isobutyrylated cytosine, "G^{DMAM}" dimethylaminomethylidenated guanine, or "$U^{t\text{-}butybenzoyl}$" *t*-butybenzoylated uracil. Ex. 1024, Scheme 1.

2. Petitioner's Arguments

Petitioner argues that the compound recited in claim 5, in which "B" is cytosine-N-isobutyryl and "Z" is a succinyl group bound to "—NH," claims the molecule depicted below.



Pet. 53 (citing Ex. 1002 ¶ 164). Petitioner argues that compound 1 of Gaur is identical to the molecule recited in challenged claim 5 of the '885 patent, in which "B" is cytosine-N-isobutyryl and "Z" is a succinyl group bound to "-NH." Pet. 55 (citing Ex. 1003 ¶ 170). Petitioner therefore argues that Gaur anticipates claim 5. *Id.*

Petitioner also argues that Gaur enables its compound 1. According to Petitioner, the third reference cited in Gaur is Sproat[24]. Pet. 55 (citing Ex. 1024 at 3301, n.3). Petitioner asserts that Sproat, in turn, cites Inoue[25], which teaches the synthesis of N-acylated 2′-O-methyloligoribonucleotides in detail. *Id.* at 56. (citing Ex. 1025, n.4; Ex. 1026, 6132–35, Scheme 1).

[24] B.S. Sproat et al., *2'-O-alkyloligoribonucleotides Synthesis and Applications in Studying RNA Splicing*, 10 (1–3) NUCLEOSIDES AND NUCLEOTIDES 25–36 (1991) ("Sproat") Ex. 1025.

[25] H. Inoue et al., Synthesis and Hybridization Studies on Two Complementary Nona(2′-O-Methyl)Ribonucleotides, 15(15) Nucleic Acids Res. 6131–48 (1987) ("Inoue") Ex. 1026.

Petitioner notes that Inoue also teaches the conversion of these compounds to their corresponding 3′-succinates. *Id.* (citing Ex. 1025, 6135, Scheme 2). Petitioner argues that the teachings of Gaur, Sproat, and Inoue demonstrate that the chemical synthesis of compound 1 of Gaur would have been within the technical ability of those of ordinary skill in the art. *Id.* (citing Ex. 1003 ¶ 173).

3. Patent Owner's Response

In its Patent Owner Response, Patent Owner did not substantively challenge Ground 6, in view of its then-pending Motion to Amend. Specifically, Patent Owner states that, subject to the Board's claim construction, and without prejudice to Patent Owner's rights to the other patentably distinct compounds in Claim 5's Markush group, or Patent Owner's rights to those compounds secured under at least U.S. Reissue Application No. 18/130,902, Ground 6 is rendered moot in view of its (now-withdrawn) Motion to Amend. PO Resp. 77.

4. Analysis

We conclude that Petitioner has demonstrated, by a preponderance of the evidence, that Gaur's compound 1 anticipates the compound recited in claim 5, in which "B" is cytosine-N-isobutyryl and "Z" is a succinyl group bound to "-NH." We also conclude that Gaur enables its compound 1. We therefore conclude that Gaur anticipates claim 5.

IV. CONCLUSION[26]

For the reasons we have explained, we conclude that Petitioner has demonstrated by a preponderance of the evidence, that challenged claims 1–5 of the '885 patent are unpatentable.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that based on a preponderance of the evidence, claims 1–5 of the '885 patent are unpatentable;

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

Claims	35 U.S.C. §	References	Claims Shown Unpatentable	Claims Not shown Unpatentable
1	102(b)	Reddy	1	
2	103	Crooke, Pitsch, Fan	2	
2	103	Vater, Pitsch	2	
3	103	Crooke,	3	

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

		Pitsch, Fan, Scaringe		
4	103	Scaringe, Pitsch, Fan	4	
5	102(b)	Gaur	5	
Overall Outcome			1–5	

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