

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORPORATION,

Petitioner,

v.

CHEMGENES CORPORATION,

Patent Owner.

IPR2023-00490

U.S. Patent No. 9,884,885 B2

PATENT OWNER RESPONSE

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Fed. R. Evid. 702(b)-(d)	passim

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2002	D. Flood et al., <i>DNA Encoded Libraries: A Visitor's Guide</i> , ISRAEL J. CHEM 60(3):268-280 (Jan. 2020)
2003	D. Flood et al., <i>Expanding Reactivity in DNA-Encoded Library Synthesis via Reversible Binding of DNA to an Inert Quaternary Ammonium Support</i> , J. AM. CHEM. SOC. 141(25):9998-10006 (May 2019)
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2007	Second Amended Complaint, <i>ChemGenes Corp. v. Hongene Biotech Corp.</i> , 1:22-cv-10290, D.I. 18 (D. Mass. May 27, 2022)
2008	Expert Declaration of Patrick Hrdlicka, Ph.D.
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2012	H. Schaller et al., <i>The Stepwise Synthesis of Specific Deoxyribopolynucleotides (4). Protected Derivatives of</i>

	<i>Deoxyribonucleosides and New Syntheses of Deoxyribonucleoside-3' Phosphates</i> , J. AM. CHEM. SOC. 85(23):3821-27 (Dec. 1963)
2013	J.C. Schulhof et al., <i>The final deprotection step in oligonucleotide synthesis is reduced to a mild and rapid ammonia treatment by using labile base-protecting groups</i> , NUCLEIC ACID RES. 15(2):397-416 (Jan. 1987)
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2017	H. Köster, <i>N-Acyl Protecting Groups for Deoxynucleosides</i> , TETRAHEDRON 37(2):363-69 (1981)
2018	N.D. Sinha, <i>Labile exocyclic amine protection of nucleosides in DNA, RNA and oligonucleotide analog synthesis facilitating N-deacylation, minimizing depuration and chain degradation</i> , BIOCHIMIE 75(1):13-23 (1993)
2019	S. Scaringe, <i>Preparation of 5'-Silyl-2'-Orthoester Ribonucleosides for Use in Oligoribonucleotide Synthesis</i> , CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY 2:2.10.1-2.10.16 (May 2004)
2020	H. Weber & H. Khorana, <i>Total synthesis of the structural gene for an alanine transfer ribonucleic acid from yeast. Chemical synthesis of an icosadeoxynucleotide corresponding to the nucleotide sequence 31 to 50</i> , J. MOL. BIOL. 72(2):251-288 (Dec. 1972)
2021	L. McBride et al, <i>Amidine Protecting Groups for Oligonucleotide Synthesis</i> , J. AM. CHEM. SOC. 108:2040-48 (1986)

2022	R. Iyer et al., <i>Nucleobase Protection of Deoxyribo-and Ribonucleosides</i> , CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, 2.1.1-2.1.40 (2017)
2023	A. Culf et al., <i>Fast Deprotection of Synthetic Oligodeoxyribonucleotides Using Standard Reagents under Microwave Irradiation</i> , OLIGONUCLEOTIDES 18:81-92 (2008)
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2029	ChemGenes Corporation Catalog, Bio Technology Products & Manufacturer of DNA-RNA Intermediates 1999
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2031	R. T. Pon, <i>Solid-Phase Supports for Oligonucleotide Synthesis</i> , CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, 3.1.1-3.1.28 (2000)

Patent Owner ChemGenes Corporation (“Patent Owner” or “ChemGenes”) respectfully submits that Petitioner Shanghai Hongene Biotech Corporation (“Petitioner” or “Hongene”) has not carried its burden of demonstrating by a preponderance of the evidence that Claims 1-5 of U.S. Patent No. 9,884,885 (“the ’885 Patent”), as issued and amended, are unpatentable.

I. INTRODUCTION

Petitioner oversimplifies the highly complex and unpredictable P(III) chemistry at issue in this case and uses impermissible hindsight reasoning to reconstruct the ’885 Patent's innovative compounds. In doing so, Petitioner fails to carry its burden to show that a POSA would have first chosen Compound x to advance and then been motivated to replace its N2-isobutyryl group with an N2-acetyl group with a reasonable expectation of success.

In the 2009 timeframe, a POSA would have known that deep-rooted literature (including by Nobel Laureate H.B. Khorana) taught away from using acetyl as a protecting group for the N2-position of 2'-deoxyguanosine derivatives like Compound x because acetyl groups were too unstable. A POSA would have also known that switching to an N2-acetyl group would have made Compound x less soluble in organic solvents risking failure during nucleoside synthesis and SPOS.

Petitioner’s heavy reliance on Pitsch and Fan is misplaced because those references did not study 2'-deoxyguanosine (with 2'-fluoro substituents or otherwise)

like the Compound x and stood in stark contrast to the broader teachings in the prior art that uniformly taught isobutyryl and other groups were to be used to protect the N2-position of guanine nucleosides, but the acetyl group was not.

Petitioner also fails to carry its burden to show that a POSA would have had a reasonable expectation of success in synthesizing the claimed compounds. In connection with Claims 2 and 3, Petitioner's expert Dr. Baran offers a conclusory theory that it would have been "trivial" to a POSA to have synthesized the claimed compounds according to Example 4-d of the '031 Patent by "simply" substituting acetic anhydride for isobutyric anhydride in step ii. Dr. Baran justifies the fact that he did not conduct studies to test his unsupported theory on grounds that doing so would not have been needed because it was "undergraduate level chemistry." Contrary to Petitioner's unsubstantiated arguments, and as demonstrated by Patent Owner's expert Dr. Hrdlicka and established scientific literature, Dr. Baran's proposed approach would have caused the proffered synthesis to have failed for multiple independent reasons.

Moreover, secondary indicia further establish the non-obviousness of the challenged claims as evidenced by the '885 Patent and other literature showing the claimed N2-Acetyl-2'-F-2'-deoxyG nucleosides demonstrated unexpected results and addressed a longstanding industry need by preventing the degradation of

chimeric oligonucleotides during synthesis caused by loss of fluorine and pyrimidine bases.

For these and the other reasons stated herein, including for Claims 1, 4, and 5, Petitioner has not carried its burden of demonstrating by a preponderance of the evidence that Claims 1-5 of the '885 Patent, as issued and amended, are unpatentable.

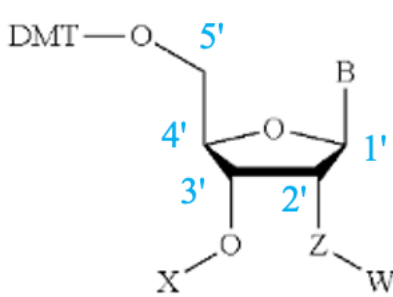
I. THE '885 PATENT AND PARTIES

ChemGenes Corporation is a Massachusetts-based company that has been an innovator in the field of nucleoside, P(III) phosphoramidite reagent, and oligonucleotide syntheses since 1981, at the dawn of the modern solid-phase oligonucleotide synthesis (“SPOS”) era.

ChemGenes has invented numerous novel nucleosides, phosphoramidite reagents, and oligonucleotides, which it has sold to pharmaceutical companies, biotechnology companies, academic institutions, and other partners since its founding. ChemGenes has consistently applied for and been granted patents in the U.S. and throughout the world over the years for its novel compounds.

Such compounds include those described and claimed in the '885 Patent. Ex. 1001. For example, as shown below, the Markush groups of Claims 2 and 3 cover phosphoramidites and succinates that feature fluoro (F) at the 2'-position of the sugar ring and acetyl at the N2-position of the guanine base (hereinafter “N2-Acetyl-2'-F-

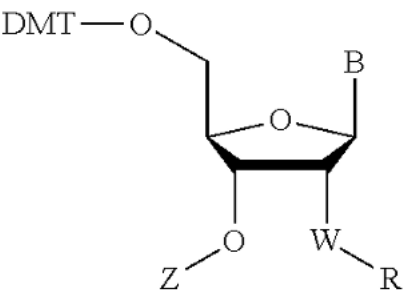
2'-deoxyG"). The Claim 2 phosphoramidite where "Z" is ribo fluoro and "B" is guanine-N-acetyl is provided as follows:¹

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, 25:44-64. Hongene, a direct competitor of ChemGenes, has previously sold at least N2-Acetyl-2'-F-2'-deoxyG phosphoramidite. Ex. 2007, ¶¶ 38-40.

¹ The 1', 2', 3', 4' and 5' annotations are provided to denote the corresponding positions of carbon on the sugar ring of Formula 1 and this nomenclature will be used throughout this Response when referring to the sugar rings of other nucleosides as well.

Similarly, the corresponding Claim 3 succinate where “W” is ribo fluoro and “B” is guanine-N-acetyl is provided as follows:

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 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.	

Ex. 1001, 25:64-26:18; Ex. 2008, ¶¶63-64.

II. STATE OF THE ART

A. Petitioner Oversimplifies the Highly Complex and Unpredictable Chemistry Involved in Synthesizing Nucleosides, Phosphoramidites and Oligonucleotides Via P(III) Chemistry

While Petitioner covers certain aspects of the history of SPOS, the Petition does not describe how complex and inherently unpredictable this science was in the 2009 timeframe (and is today), and the chemistry involved in this specialized field is by no means “simple” or “trivial,” as portrayed by Petitioner. Pet., 36; Ex. 2008, ¶65.

On the contrary, as discussed by pioneers such as Serge L. Beaucage, synthetic chemists have faced significant adversity developing SPOS over the decades. *See, e.g.*, Ex. 1007, 2223 (describing complex challenges); 2223-33 (same); 2233-42 (same); 2249-59 (same); 2259-93 (same); Ex. 2008, ¶66.

As Patent Owner’s expert, Dr. Patrick Hrdlicka, explains, while many hurdles have been overcome, this science is still developing and inherently unpredictable, and that was certainly the case in the 2009 timeframe when the inventors of the ’885 Patent developed the structures claimed in Claims 1-5. Ex. 2008, ¶67.

Then, and now, the syntheses of such structures and related oligonucleotides involve meticulous development, planning and execution of complex, multi-step synthetic routes, all subject to unpredictable outcomes and risk of failure, to produce

high-quality, stable nucleoside phosphoramidite reagents for use in SPOS to produce oligonucleotides of correct identity with high purity and optimum yield. *Id.*

According to Dr. Hrdlicka, synthetic routes for phosphoramidites, e.g., often include introduction of a diverse array of chemical reagents designed to transform a starting compound into a new compound (also called a synthetic intermediate), and in succeeding steps, more reagents are added to transform the newly created compound in the prior step into yet another new compound. *Id.*, ¶68.

Phosphoramidite synthesis can involve in the range of 5, 10, 20 or more synthetic steps to attempt to reach the desired compound, and each step, requires carefully selected and controlled reaction conditions to successfully produce the desired product. *Id.* High levels of unpredictability exist at many of these stages, and even minor changes in either the molecular structure of a substrate or reagent, or in the reaction conditions, can trigger undesirable and unforeseen reactions and cause the planned synthetic transformations to fail. *Id.*

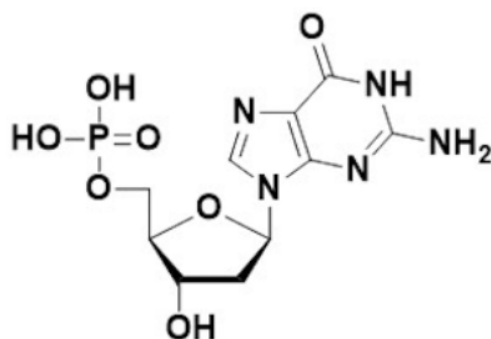
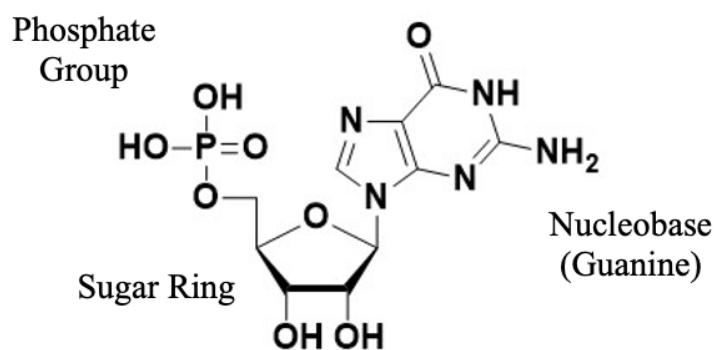
Furthermore, in the event a novel phosphoramidite is successfully synthesized, it may still not be useful as a reagent in SPOS to synthesize an oligonucleotide. *Id.*, ¶69. For example, a phosphoramidite may display low or no coupling efficiency during SPOS, a protecting group masking a reactive center may be prematurely removed resulting in undesirable production of branched or damaged oligonucleotides, or the resulting nucleotide monomer may be insoluble or unstable

during the SPOS and/or deprotection conditions. *Id.* Therefore, there are considerable variables and uncertainty in this work, and skilled artisans in this space have experienced, and continue to experience, major challenges. *Id.*

Accordingly, Petitioner’s arguments that a POSA would have found it “simple” or “trivial” to achieve the claimed inventions greatly oversimplifies the complex chemistry and challenges that a POSA would have faced in the 2009 timeframe. *Id.*, ¶70. Such hindsight-driven viewpoints are precisely what the Federal Circuit and PTAB have warned about as distorting the obviousness inquiry. *See, e.g., Otsuka Pharm. Co., v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012); *Gilead Sciences, Inc. v. Regents of the Univ. of Minn.*, IPR2017-01753, Paper 42, 22 (P.T.A.B. Apr. 22, 2020).

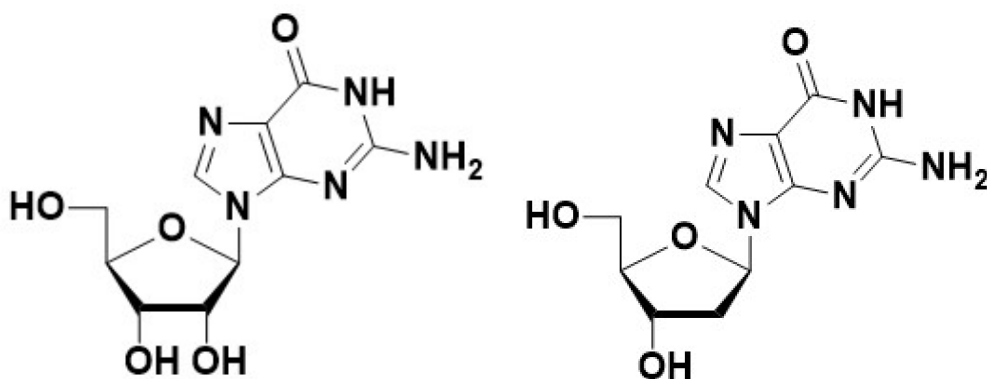
B. Overview of the Relevant Technology and Summary of Key Terminology Used in this Response

Nucleotides. Nucleotides have (1) a five-carbon sugar ring; (2) a phosphate group; and (3) one of four major nitrogen “nucleobases” (i.e., adenine (“A”), thymine (“T”), cytosine (“C”), or guanine (“G”) for DNA; and A, C, G, or uracil (“U”)) for RNA). Following are exemplary nucleotides, for RNA (2'-OH) and DNA (2'-H), having a guanine nucleobase:



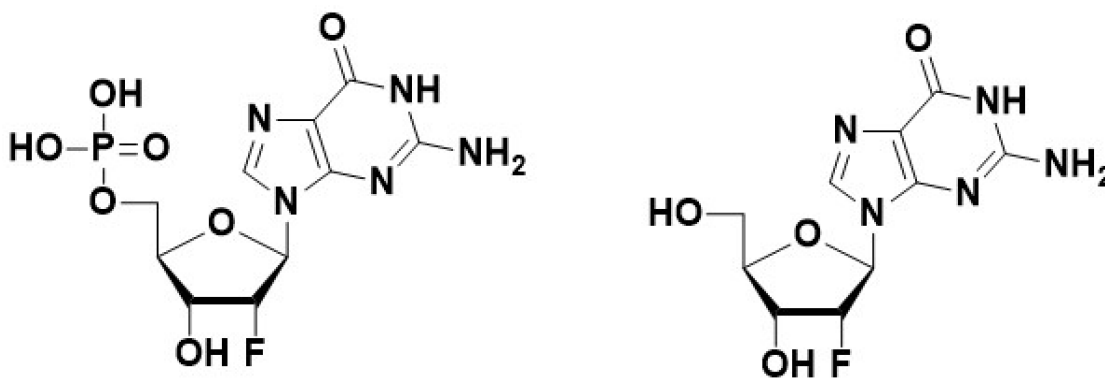
Ex. 2008, ¶71.

Nucleosides. Nucleosides are nucleotides without a phosphate group; following are two exemplary nucleosides having a guanine nucleobase, referred to as guanosine (2'-OH) and 2'-deoxyguanosine (2'-H):



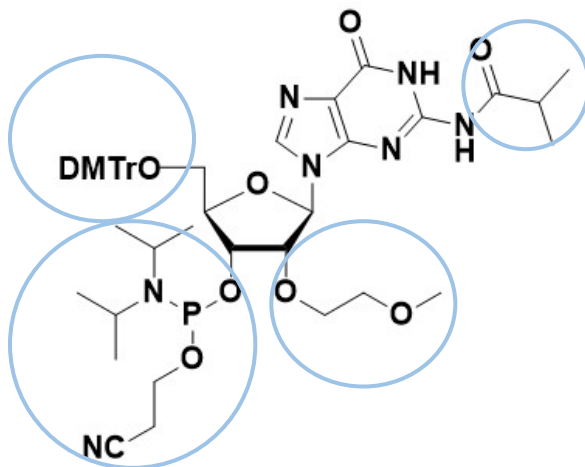
Id., ¶72.

2'-Fluoro Nucleotides and Nucleosides. Importantly, a ribonucleic acid (“RNA”) nucleotide has a hydroxyl (-OH) group at the 2'-position, and a deoxyribonucleic acid (“DNA”) nucleotide has a hydrogen (-H), at the corresponding 2'-position. Both “modified” RNA and DNA sequences can have nucleotides with non-naturally occurring groups, like fluoro, at the 2'-position, making 2'-fluoro nucleotides and nucleosides versatile compounds for SPOS (2'-fluoro-2'-deoxyguanosine nucleotide shown on the left, and 2'-fluoro-2'-deoxyguanosine nucleoside shown on the right):



Id., ¶73.

Phosphoramidites. Nucleoside phosphoramidites (or “phosphoramidites” or “amidites”) are derivatives of nucleosides used as reagents for SPOS to obtain oligonucleotides; following is an exemplary guanosine phosphoramidite:



Id., ¶74. As shown above, a phosphoramidite is characterized by having the general structure $(RO)_2PNR_2$, i.e., a phosphorus atom in a P(III) oxidation state having one P-N bond and two P-O bonds, and of the two oxygen-containing functionalities, one is usually a protecting group (typically a β -cyanoethyl group) and the other is a 3'-O of a nucleoside. *Id.*, ¶75.

Phosphoramidites have wide ranges of groups on the 2'-, 3'-, and 5'- positions of the sugar ring (here shown as methoxyethyl (MOE)) at the 2'-position, N,N-diisopropylamino-2-cyanoethoxyphosphinyl at the 3'-position, and 4,4-dimethoxytrityl (DMTr) at the 5'-position) and on the exocyclic amines $-NH_2$ of the nucleobase (here shown as N2-isobutyryl-protected guanine). *Id.*, ¶76.

Every position on the sugar ring can be additionally modified, such as the 2'-position which can have, e.g., a fluoro, methoxy, MOE, or other groups which do not require protecting groups. *Id.*, ¶77.

For *RNA synthesis*, the 2'-position has a hydroxyl group (-OH), which, because of its reactivity during SPOS, must be protected with groups such as t-butyldimethyl silyl (TBDMS), acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM), or O2'-(triisopropylsilyl)oxy-methyl (TOM). *Id.*

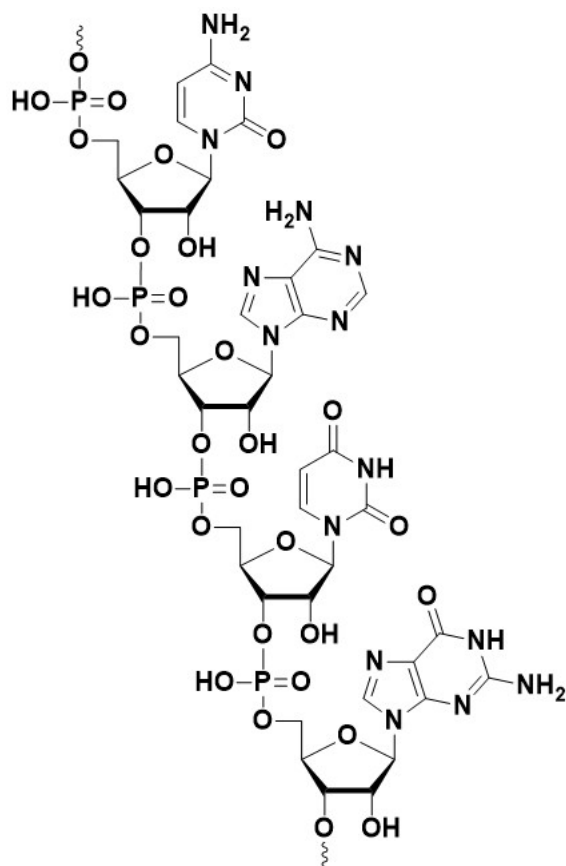
Most nucleobases (e.g., A, C, G) typically require protecting groups for successful use in conventional SPOS, such as N2-isobutyryl-G, and phosphoramidites can feature non-canonical nucleobases and chemically modified nucleobases such as 5-methylcytosine. *Id.*

Given the variety of options for protecting groups, and chemically modified sugars and nucleobases, there were thousands of different phosphoramidites and nucleosides available to a POSA in the 2009 timeframe. *Id.*, ¶78.

Oligonucleotides. Oligonucleotides are short polymeric single strands of nucleotides. Ex. 2008, ¶79. DNA-based oligonucleotides are referred to as “oligo*deoxy*nucleotides” or “oligo*deoxyribo*nucleotides” and RNA-based oligonucleotides are referred to as “oligo*ribo*nucleotides,” with RNAs having (-OH) at the 2'-position and DNAs having only (-H) (hence, the term “deoxy,” or without oxygen). *Id.*

Oligonucleotides vary in length and sequences and can possess tens or hundreds of nucleotides as compared to DNA and RNA sequences that can have

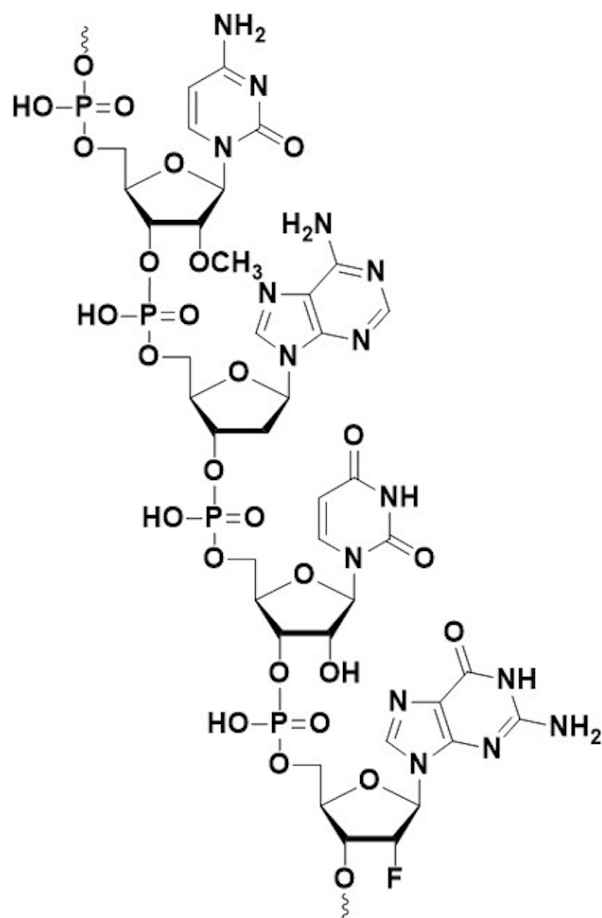
millions of nucleotides. *Id.* Following is a depiction of an oligoribonucleotide for RNA:



Id., ¶80.

The umbrella term “oligonucleotide” or “oligo” encompasses oligodeoxyribonucleotides (for DNA), oligoribonucleotides (for RNA), and “chimeric oligonucleotides” explained below. *Id.*, ¶81. The first nucleotide in an oligonucleotide is typically attached to a solid support through utilization of a succinyl and long chain amino alkyl linker at the 3'-position. *Id.*

Chimeric Oligonucleotides. Chimeric oligonucleotides are oligonucleotides that feature 2 or more different types of nucleotides; following is a depiction of a “chimeric” oligonucleotide having four different types of nucleotides:



Id., ¶82. This exemplary chimeric oligonucleotide shows, starting from top to bottom, has 2'-OMe-C (or 2'-O-Methylcytidine); 2'-deoxyadenosine (DNA); uridine (RNA); and 2'-fluoro-2'-deoxyguanosine. *Id.*, ¶83.

Chimeric oligonucleotides can have near limitless ranges of design and applicability, and non-natural nucleotides with, e.g., 2' groups like fluoro, can be used for synthesizing modified RNAs, DNAs, or oligonucleotides completely

comprised of non-naturally-occurring nucleotides (e.g., only having 2'-fluoro-2'-deoxyribonucleotides). *Id.*

III. CLAIM CONSTRUCTION: CLAIMS 1-5 SHOULD BE CONSTRUED IN ACCORDANCE WITH THEIR ORDINARY AND CUSTOMARY MEANINGS AND TO CORRECT CLEAR ERRORS

Claims 1-5 should be construed in accordance with “the ordinary and customary meaning of such claim[s] as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100.

In addition, Patent Owner agrees with Petitioner that a POSA would have recognized clear errors in Claims 3-5. Ex. 2008, ¶84. Specifically, for the reasons stated in the Petition, a POSA would have understood “M” should be “ethyl” in Claims 3-5 and that the last clause in Claim 5 should be construed to mean “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., 17-20; Ex. 2008, ¶84.

These corrections are: “[1] not subject to reasonable debate based on consideration of the claim language and the specification and [2] the prosecution history does not suggest a different interpretation of the claims.” *Novo Indus. v. Micro Molds Corp.*, 350 F.3d 1348, 1354 (Fed. Cir. 2003); *see, e.g., Netflix, Inc. v. Uniloc 2017 LLC*, IPR2020-00044, Paper 24 at 12 (P.T.A.B. Apr. 20, 2021). Should the Board agree with the proffered claim construction of Claims 3-5 as reflected

above, Patent Owner submits that Claims 3-5 are not unpatentable for at least the reasons stated in this Response.

Alternatively, should the Board not construe Claims 3-5 in this manner, then Petitioner's challenges to those claims (i.e., in Grounds IV, V, and VI) should fail because none of the prior art cited in **Ground IV** (i.e., the '031 Patent, Pitsch, Fan, and Scaringe), **Ground V** (i.e., Pitsch, Fan, or Scaringe) or **Ground VI** (i.e., Gaur), disclose compounds where "M" is succinyl or any of the remaining compounds listed in the Markush groups of Claims 3-5 (i.e., where M is "oxalyl" or "hydroquinolynyl"). *Arendi S.A.R.L. v. Apple, Inc.*, 832 F.3d 1355, 1366 (Fed. Cir. 2016) (holding missing elements would not have been supplied by the knowledge of a person of ordinary skill in the art); *Sanofi-Synthelab v. Apotex, Inc.*, 550 F.3d 1075, 1084 (Fed. Cir. 2008) (holding that a single prior art reference must disclose all claim elements to anticipate).

Accordingly, because all of the limitations of uncorrected Claim 3 are not taught by the prior art under this interpretation, Petitioner fails to make a *prima facie* case of obviousness in Grounds IV and V and anticipation in Ground VI.

IV. PETITIONER'S DEFINITION OF A POSA SHOULD BE MODIFIED

Patent Owner does not agree with Petitioner's definition of a POSA, i.e., that a POSA would have had a Ph.D. 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 (emphasis added).

Dr. Baran has characterized himself as a professor in organic chemistry and an expert in medicinal chemistry, but 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. Ex. 2009, 75:22-24; 73:21-23; 97:23-98:1; 99:15-100:7. Furthermore, 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.*, 109:4-6 (“Q. But the focus of this paper [Ex. 2001] is on P(V)? A. the focus of this paper is awakening people to the difference between P(V) and P(III).”); Ex. 2010, 1 (Dr. Baran et al. describing “P(V)-based reagent platforms” as “as a fundamentally different approach” as compared to “phosphorus(III)-based reagent systems.”). Ex. 2008, ¶¶85-86. Dr. Baran therefore was not himself a POSA in 2009 timeframe and does not appear to have a deep background in the P(III) chemistry at bar and, in any event, Patent Owner respectfully disagrees with Dr. Baran and his definition of a POSA.

Dr. Hrdlicka is, and was in the 2009 timeframe, highly skilled in developing synthesis schemes and directing the synthesis of nucleosides, nucleotides, and nucleic acids pursuant to P(III) chemistry, including, but not limited to, the synthesis

of oligonucleotides through SPOS, and is and was familiar with the level of skill of a POSA in the 2009 timeframe. Ex. 2008, ¶87.

According to Dr. Hrdlicka, skilled artisans in the 2009 timeframe who developed synthetic schemes for (e.g., as discussed in Section III.A.), 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 in the 2009 timeframe including with respect to knowledge, skills, motivations, and reasonable expectations. *Id.*, ¶88.

In contrast, the viewpoints of those who instead have 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 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.

Accordingly, Patent Owner respectfully proposes the following alternative definition for a POSA, shown as redline changes to the definition that Petitioner proposed:

As of May 18, 2009, a person of ordinary skill in the art (“POSA”) would have had a Ph.D. (or equivalent degree) in organic ~~or medicinal~~ 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. ~~medicinal chemistry, synthetic organic chemistry, and nucleic acid chemistry, including the development of oligonucleotide therapeutics, diagnostics, or building blocks.~~

Alternatively, 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.

Alternatively, 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 POSA ~~with a Bachelor’s or Master’s degree in organic chemistry or medicinal chemistry.~~

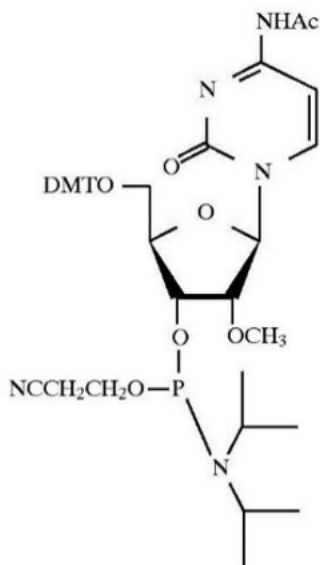
Id., ¶90. This definition would not exclude medicinal or other chemists so long as the chemist in question met the above requirements. *Id.*

Patent Owner respectfully submits that it would prevail under either definition of a POSA based on at least the reasons provided in this Response.

V. THE CHALLENGED CLAIMS ARE NOT UNPATENTABLE

A. Ground I is Moot Subject to Patent Owner's Motion to Amend Removing the Sole Compound in Claim 1 Being Challenged in the Petition

Petitioner has challenged one of six distinct compounds claimed by Claim 1's Markush group, based solely on anticipation under 35 U.S.C. § 102(b) by U.S. Patent No. 5,808,039 ("the 039 Patent"), which discloses the following compound:



Ex. 1016, 3:8-25. In response to this Ground, Patent Owner has contemporaneously filed a Motion to Amend under 37 C.F.R. § 42.121 ("Motion to Amend") to remove "B" as "cytosine-N-acetyl" from Claim 1's Markush group.

Accordingly, subject to the Board's ruling on Patent Owner's Motion to Amend, and 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 I is rendered moot.

B. Ground II: Claim 2 is not Obvious in View of the '031 Patent, Pitsch and Fan

1. Petitioner Fails to Carry its Burden to Show Why a POSA Would Have Selected Compound x in the '031 Patent as a Lead Compound and, in Any Event, a POSA Would Not Have Done So

The Federal Circuit applies a "lead compound" analysis when assessing whether new chemical compounds would have been obvious to a POSA, i.e.: (1) "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts," and (2) "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1291-92.

A lead compound is a prior art compound that a POSA (1) would have found "most promising to modify in order to improve upon its [] activity and obtain a compound with better activity," *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007), (2) "would have had a reason to select from the

panoply of known compounds in the prior art,” *Otsuka*, 678 F.3d at 1292, and (3) would have found to have been “a natural choice for further development efforts.” *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). The lead compound analysis is “guided by evidence of the compound’s pertinent properties” and “[a]bsent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection. ... Were it otherwise, the analysis would impermissibly rely upon *ex post* reasoning.” *Otsuka*, 678 F.3d at 1292 (citations omitted); *Ex Parte Ryan A. Littich*, App. No. 2017-004796, *4 (PTAB May 30, 2019).

Petitioner provides the following statement ostensibly to support why a POSA would have selected the compound listed in step “x” of Example 4-d from the ’031 Patent (“Compound x”) as a lead compound:

Since the advent of phosphoramidite chemistry in oligonucleotide synthesis in the 1980s, a POSA would have recognized that the purpose of the above phosphoramidite was to serve as a building block for incorporating a guanine base into a growing oligonucleotide chain through automated SPOS, as illustrated above in Figures 5 and 6.

Pet., 33. But Petitioner makes ***no showing*** as to ***why*** a POSA would have selected Compound x – out of the scores of nucleosides identified in the ’031 Patent and thousands of other nucleosides available in the prior art – as the most promising to

modify in order to improve upon its activity. *Takeda Chem.*, 492 F.3d at 1357. Ex. 2008, ¶101.

In either case, a POSA would not have selected Compound x as a lead compound as the most promising to modify to improve upon its activity (here, its base deprotection properties). As Dr. Hrdlicka explains, the '031 Patent discloses over 50 nucleosides and over 40 different general oligonucleotide structures, but does not disclose Compound x's base deprotection properties or data showing it being used to incorporate 2'-fluoro-2'-deoxyguanosine monomers into any oligonucleotides, as Dr. Baran acknowledged. Ex. 2009, 145:5-146:4 (“we don’t know what the absolute rate was”); 137:4-7 (Q. None of this data relates to 2 prime fluoromonomers; correct? A. The data on this figure, I don’t see it explicitly shown with the fluorine”); Ex. 2008, ¶¶102-104.

As Dr. Hrdlicka explains, if a POSA were to select any compound from the '031 Patent as a lead compound, a POSA would have selected the compounds that the '031 Patent provided data for, i.e., the chimeric phosphorothioate oligoribonucleotides of the general structure: “[2'-OMe]-[RNA]-[2'-OMe],” shown in Example 8, and 22-25 of the '031 Patent, which use Example 1’s “2'-O-Methyl nucleoside amidites” and “2'-OH (blocked as 2'-t-butyl dimethylsilyl derivative) nucleoside amidites” which are *not* 2'-fluoro phosphoramidites like Compound x. Ex. 1017, 17:25-53. Ex. 2008, ¶105.

Therefore, a POSA would not have been motivated to select Compound x over the '031 Patent's highlighted compounds or the "panoply of known" nucleosides in the prior art as "a natural choice for further development efforts" to improve upon its base deprotection rates or other activity. Petitioner has therefore used hindsight in selecting Compound x. *Altana*, 566 F.3d at 1008.

Accordingly, Petitioner has not met its burden to establish a *prima facie* case obviousness based on the first prong of the lead compound analysis, and Ground II should fail for this reason alone. *See Otsuka*, 678 F.3d at 1292.

2. A POSA Would Not Have Been Motivated by Pitsch or Fan to Use Acetyl as a Protecting Group for Guanine on Compound x of the '031 Patent

i. A POSA Would Have Known That the Prior Art Taught Away from Using an Acetyl Group to Protect N2- of 2'-Deoxyguanosine and Neither Pitsch Nor Fan Would Have Motivated a POSA to Switch to an N2-Acetyl Group for Compound x

As Dr. Hrdlicka explains, a POSA would have known that, long before Pitsch and Fan, oligonucleotide synthesis pioneers had attempted to use acetyl to protect the N2-position of the guanine nucleobase in nucleosides and nucleotides, but rejected that approach for sound scientific reasons. Ex. 2011, 221; Ex. 2008, ¶107. Specifically, a POSA would have well known that Nobel Laureate Har Gobind Khorana eschewed using acetyl groups to protect the N2-position of 2'-

deoxyguanosine due to the demonstrated instability of those groups under basic conditions.

The N-acetyl group was introduced some years ago ... and it has been used in all the synthetic work reported so far, *but its disappearance to a significant extent during the course of synthetic and isolation procedures has repeatedly been observed* ... In view of the extended nature of the present task, the use of an alternative group was highly desirable ... [Further investigation] showed the *N-isobutyryl group to be considerably more stable than the N-acetyl group* and this group has been used for the protection of all the deoxyguanosine residues in the present work ...

Ex. 2011, 221 (emphasis added). Ex. 2008, ¶107.

As confirmed by Dr. Hrdlicka, a POSA in the 2009 timeframe would have therefore been discouraged from using acetyl groups to protect 2'-deoxyguanosine, as Dr. Khorana explicitly taught away from that approach. *Millenium Pharm., Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017). Ex. 2008, ¶108.

As explained by Dr. Hrdlicka, following Dr. Khorana's discovery, isobutyryl and other base protecting groups, were used in the field to protect the N2- position of guanine, but acetyl was not one of those groups, as evidenced by the breadth of literature spanning the decades. *See, e.g.*, Ex 2011 (1972), 221 (describing acetyl as not stable for protecting the N2-position of 2'-deoxyguanosine derivatives and isobutyryl is used instead); Ex. 2020 (1972), 252 (same); Ex. 2017 (1981), 365

(describing numerous protecting groups for the N2-position of 2'-deoxyguanosine derivatives including isobutyryl, but not acetyl); Ex. 2021 (1986), 2047 (describing numerous protecting groups for the N2-position of 2'-deoxyguanosine derivatives including isobutyryl, but not acetyl); Ex. 2013 (1987), 401 (describing the use of phenoxyacetyl as a protecting group at the N2-position of 2'-deoxyguanosine derivatives, but not acetyl); Ex. 1007 (1991), 2256-58 (describing numerous protecting groups for the N2-position of guanine of nucleosides/nucleotides including isobutyryl, but not acetyl); Ex. 2018 (1993), 13-14 (describing the use of *t*-butylphenoxyacetyl as a protecting group for the N2-position of guanine of nucleosides/nucleotides over phenoxyacetyl, but not acetyl); Ex. 2016 (2001), 2.1.13 (describing isobutyryl as a “particularly valuable” protecting group for the N2-position of guanine in oligonucleotide synthesis, and listed numerous other N2-protecting groups, but not acetyl); Ex. 2019 (2004), 2.10.1 (identifying isobutyryl as a “standard” base protecting group for the N2-position of guanosine derivatives, but not acetyl); Ex. 2023 (2008), 82 (identifying isobutyryl and PAC as a “standard” protecting groups for the N2-position of 2'-deoxyguanosine derivatives, but not acetyl); Ex. 2008, ¶109.

As Dr. Hrdlicka further explains, even after the filing of the applications that led to the issuance of the '885 Patent, experts in the field still regarded isobutyryl, but not acetyl, as a standard base protecting group for the N2-position of guanine.

Ex. 2006 (2013), 327 (“Khorana et al. introduced protecting groups for the nucleosidyl exocyclic amines that are *known today as standard protecting groups: isobutyryl (iBu) for guanosine*, and benzoyl (Bz) for adenosine and cytidine. Although others exist, *these groups are those most commonly used*, with the possible exception of acetyl-protected cytidine, which is more readily and cleanly removed compared with Bz (Figure 1).”) (emphasis added); Ex. 2022 (2017), 2.1.22 (identifying isobutyryl as a “popular” and “efficient” protecting group for the N2-position of guanine of nucleosides/nucleotides, but not acetyl); Ex. 2008, ¶110. Dr. Baran acknowledged this during his deposition. Ex. 2009, 156:13-16 (“Okay. So is it fair to say that the standard protecting group for guanosine in the 2013 time frame was isobutyryl? A. For most applications, isobutyryl is fine.”).

A POSA would have therefore understood that the deep-rooted scientific literature taught away from using acetyl groups to protect the N2-position of guanine nucleosides and nucleotides, and would not have been motivated by Pitsch and Fan, which did not study 2'-deoxyribonucleosides like Compound x. Ex. 2008, ¶111.

ii. A POSA 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

As Dr. Hrdlicka explains, a POSA would have known that solubility of nucleosides in organic solvents is critical during the synthesis of nucleosides and

during SPOS. Ex. 2008, ¶112. That is because numerous organic solvents are used, e.g., to solubilize nucleoside derivatives while transforming them into phosphoramidites, and to solubilize phosphoramidites for SPOS, and should a molecule have solubility problems during any of these reactions, or during purification of reaction mixtures, it would “drop like a rock” (i.e., precipitate) in the solution and cause catastrophic failure to the subject synthesis scheme. *Id.*

A POSA would have readily understood nucleosides with guanine moieties were notoriously insoluble in organic solvents and lipophilic base protecting groups like isobutyryl or *tert*-butylphenoxyacetyl to protect the N2- position of nucleosides with guanine moieties would have enhanced the nucleoside’s solubility. Ex. 2018, 14 (“Problems associated with solubility of deoxyguanosine-phosphoramidites using other labile N-protecting groups are eliminated with the use of the more lipophilic t-butylphenoxyacetyl groups.”); Ex. 2008, ¶113.

According to Dr. Hrdlicka, a POSA would have known that acetyl groups would have made nucleoside derivatives ***less soluble*** in organic solvents than isobutyryl groups when used to protect the N2- position of guanine derivatives. Ex. 2008, ¶114. That is because acetyl groups are smaller, more polar groups, than isobutyryl groups and therefore less hydrophobic and less apt to solubilize nucleosides with guanine moieties, as Dr. Baran confirmed. Ex. 2009, 175:25-176:6 (“Q. And isobutyryl is more hydrophobic—isobutyryl group is more hydrophobic

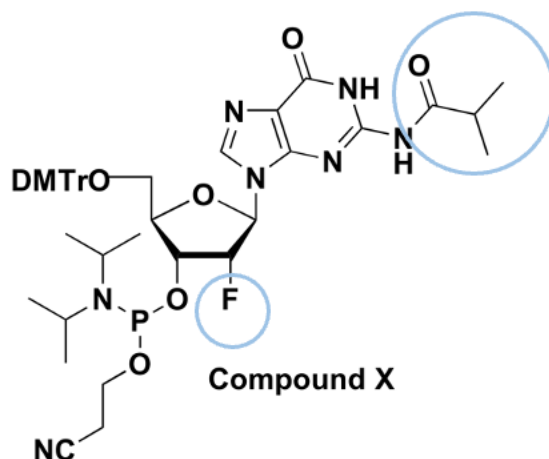
than an acetyl group; right? A. I would expect that to be the case, yes. Q. So an acetyl group is more polar than an isobutyryl group? That would be my expectation, yes.”); Ex. 2008, ¶114.

As Dr. Hrdlicka explains, a POSA would have understood that adding acetyl to (i.e., acetylation of) 2'-deoxyguanosine caused solubility problems. Ex. 2012, 3822-26 (stating that “[a]cetylation of deoxyguanosine so as to prepare N,3',5'-triacetyldeoxyguanosine did not proceed satisfactorily ... A part of the cause of failure to accomplish N-acetylation could be due to the insolubility of 3',5'-di-O-acetylguanosine which separates from the reaction mixture. ... The lack of N-acetylation was probably due to the insolubility of 3',5'-di-O-acetylguanosine in the solvent. ... In a parallel experiment benzoylation with [more lipophilic] benzoyl chloride did cause N-benzoylation as clearly shown”); Ex. 2008, ¶115.

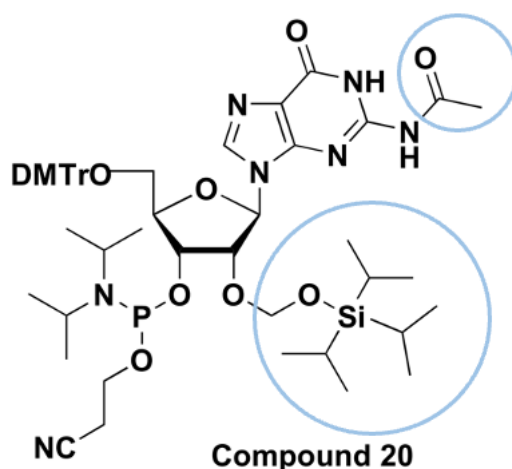
A POSA would therefore not have been motivated to use acetyl over isobutyryl for Compound x because doing so would have made Compound x *less soluble* in organic solvents. Ex. 2008, ¶116.

- iii. **A POSA Would Not Have Been Motivated by Pitsch and Fan Which Did Not Study 2'-Deoxynucleosides or 2'-Deoxynucleotides and Would Have Produced Completely Different Oligonucleotides Than Produced by Compound x**
- a. **Pitsch and Fan Did Not Study 2'-fluoro-2'-deoxynucleosides Like Compound x Which Involved Known Degradation Issues When Used to Make Chimeric Oligonucleotides**

A POSA would have known that Compound x, as shown below, was a phosphoramidite that had a fluoro (F) at its 2'-position and an isobutyryl group bound to the N2-position of guanine. Ex. 1017, 25:33-59. Ex. 2008, ¶117.



A POSA would have also understood that compound 20 from Pitsch (“Compound 20”), shown below, had an O2'-(triisopropylsilyl)oxy-methyl group, or “TOM” group at its 2'-position (*not fluoro*) and an acetyl group bound to the N2-guanine. Ex. 1018, 3775 (Scheme 1); Ex. 2008, ¶118.



A POSA would have further understood that compound 6a from Fan (“Compound 6a”), shown below, was a nucleoside derivative (not a phosphoramidite) that could not have even been used during SPOS unless transformed into a phosphoramidite (which is not described in Fan), and that had (1) *tert*-butyldimethylsilyl (interchangeably denoted as “TBS” or “TBDMS”) to protect the hydroxyl (-OH) group at the 2'-position (*not fluoro*); and (2) 3',5'-*O*-di-*tert*-butylsilylene to protect the hydroxyl (-OH) groups at the 3'- and 5'- positions, and an acetyl group bound to the N2-guanine. Ex. 1019, 2556; Ex. 2008, ¶119.

while under “the usual oligonucleotide deprotection conditions (concentrated NH₄OH, 55°C)”).

Accordingly, a POSA would have recognized that the unique challenges associated with oligonucleotides with 2'-fluoro nucleotides would not have been resolved by the fundamentally different studies described in Pitsch and Fan, each of which disclosed using methylamine during deprotection, and would therefore not have been motivated by those references to modify Compound x. Ex., 1018, 3778. Ex. 1019, 2556; Ex. 2008, ¶122.

b. A POSA Would Have Understood That Pitsch and Fan Were Focused on RNA Which Would Not Have Been Applicable to a Study of 2'-fluoro-2'-deoxynucleosides for Use in Modified Oligonucleotides Like Compound x

A POSA would have also understood that the phosphoramidites and nucleosides disclosed in Pitsch and Fan would have been used for synthesis of unmodified RNAs (i.e., with (-OH) at the 2'-position), not *modified* oligonucleotides produced using Compound x having 2'-fluoro-2'-deoxynucleotides. Ex. 2008, ¶123.

Below are illustrations of solid-support-bound oligonucleotides produced from Compound 20 (Fig. 1.a.) and a hypothetical phosphoramidite analogue of Compound 6a (Fig. 1.b.), showing each with acetyl at the N2-position of guanine

and different O2'-protecting groups (i.e., TOM and TBDMS) prior to base deprotection.²

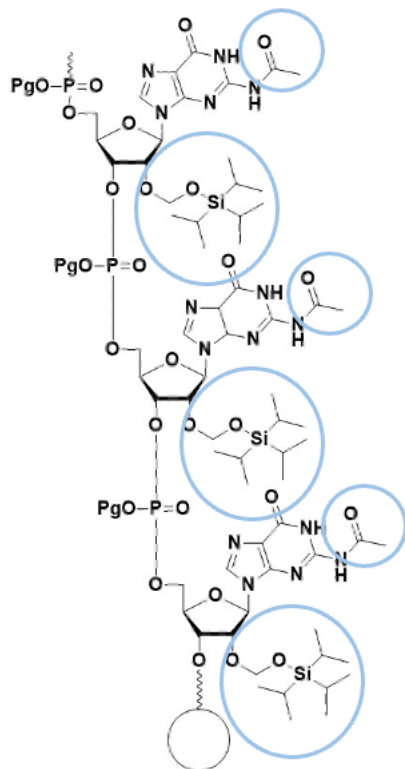


Fig. 1.a.

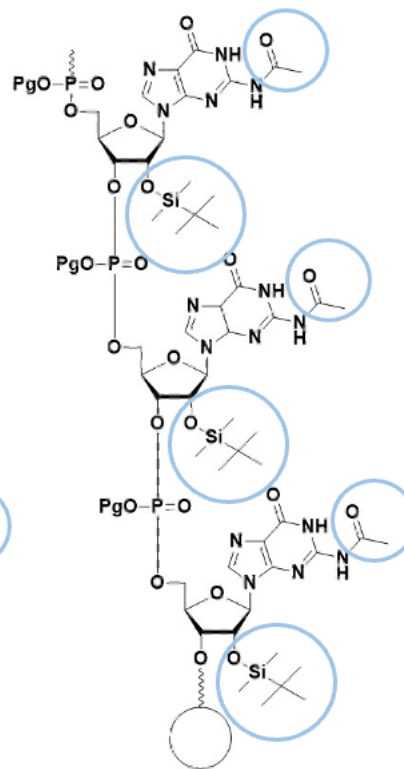


Fig. 1.b.

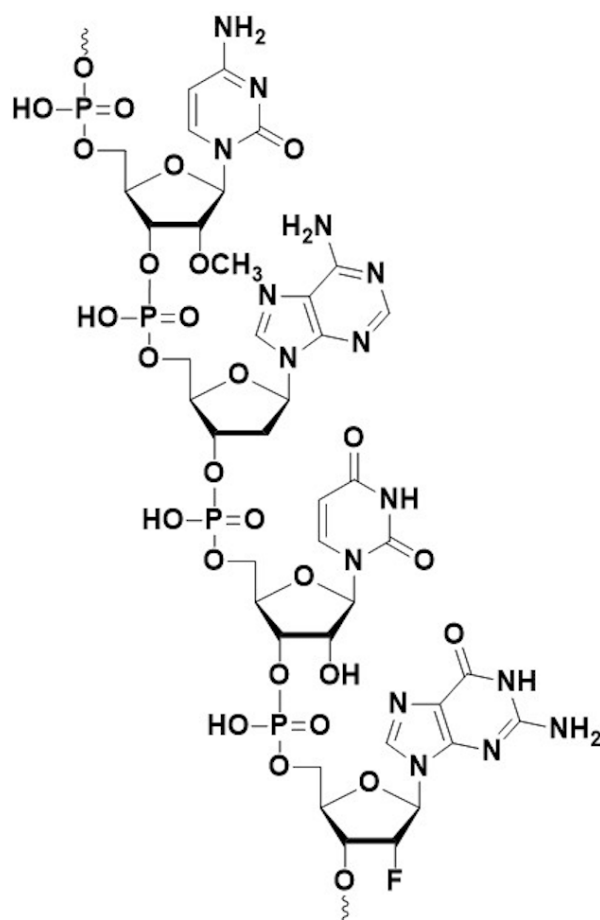
Id., ¶124.

A POSA would have readily known that these oligonucleotides—incorporating the Pitsch and Fan monomers—are directed to RNA because of the (-OH) functional groups at their 2'-positions and the related disclosures in Pitsch and

² “Pg” in Fig. 1 is an abbreviation for “protecting group.”

Fan that discuss “RNA” synthesis but not modified RNA or DNA or chimeric oligonucleotides. Ex. 1018, 3773; Ex. 1019, 2556. Ex. 2008, ¶125.

In contrast, a POSA would have understood that Compound x would have most certainly been used to incorporate modified nucleotides into oligonucleotides, such as a chimeric oligonucleotide shown below with 2'-fluoro-2'-deoxyribonucleotides (i.e., 2'-F) and an assortment of other nucleotides.



Ex. 2008, ¶126.

A POSA would have found the limited teachings of Pitsch and Fan, which only applied to protected ribonucleosides and phosphoramidites for RNA synthesis

having (-OH) functional groups at their 2'-positions, and not 2'-fluoro-2'-deoxyribonucleotide phosphoramidites for modified oligonucleotide synthesis, as not relevant (i.e., “apples and oranges”) to efforts in modifying a 2'-fluoro-2'-deoxyribonucleoside phosphoramidite like Compound x. Ex. 2008, ¶127.

As Dr. Hrdlicka explains, a POSA would have also expected that RNA-based phosphoramidites would have coupled differently during SPOS, and the oligonucleotide structures would have had different deprotection characteristics when the base protecting groups were removed after the targeted oligonucleotide sequence was synthesized, as compared to Compound x, further discouraging a POSA from relying on Pitsch and Fan to modify Compound x. *Id.*, ¶128.

Accordingly, for at least these reasons, a POSA would not have been motivated by Pitsch and Fan to modify Compound x to produce N2-Acetyl-2'-F-2'-deoxyG as claimed in Claim 2. *Id.*, ¶129.

iv. Petitioner Misapplies the Teachings of Pitsch and Fan and a POSA Would Not Have Been Motivated by those References to Modify Compound x to Make the Claimed Invention

a. Neither Pitsch Nor the '031 Patent, Alone or in Combination, Compare Base Deprotection Rates of Acetyl and Isobutyryl

Petitioner’s argument that the base deprotection rates of acetyl groups disclosed in Pitsch “compare[] favorably against the 24 hour deprotection period for

the removal of the isobutyryl protecting group from the 2'-O-methyl G in Example 8 of the '031 Patent” is misleading. Pet., 35.

Example 8 of the '031 Patent states:

Treatment in methanolic ammonia *for 24 hrs* at room temperature was then done to deprotect all bases and sample was again lyophilized to dryness.

Ex. 1017, 40:48-51; Ex. 2008, ¶131. As Dr. Baran admitted, a POSA would have understood that Example 8 of the '031 Patent *does not disclose base deprotection rates* for the subject molecule it references but instead merely provides the procedure for how the subject molecule was deprotected. Ex. 2009, 145:5-13 (“Q. But the 24-hour deprotection period disclosed in example 8 of the '031 patent is not a rate of deprotection; right? A. I mean, that is the length of time it took them before they isolated and purified. So in an absolute sense, it is the time they took, but what we don't know is what the absolute rate was. Maybe they only needed seven hours. Maybe they needed 19.2. We don't know that.”); Ex. 2008, ¶132.

Petitioner also indicates that the subject molecule in Example 8 represents “2'-O-methyl G” monomers. But, as Dr. Hrdlicka explains, that is not accurate because the Example 8 molecules are 2'-methoxy-2'-hydroxy-2'-methoxy phosphorothioate oligoribonucleotide “gapped” chimeric compounds, not O2'-methyl G monomers. Ex. 1017, 40:30-33 (subject molecule identified as “[2'-O-Me]/PS.[2'-OH]/PS.[-2'-OMe]/PS oligoribonucleotide”); Ex. 2008, ¶133.

Example 8's oligoribonucleotides also do not have 2'-fluoro-2'-deoxyribonucleotide monomers, yet alone 2'-fluoro-2'-deoxyguanosine monomers, and Example 8 therefore does not correspond to an oligoribonucleotide synthesized using Compound x. Ex. 2008, ¶134.

Moreover, as Dr. Hrdlicka explains, a POSA would have recognized that Pitsch does not disclose base deprotection rates for isobutyryl, or even discuss isobutyryl as a base protecting group for the N2-position of guanine. *Id.*, ¶135. A POSA would have also known that the base deprotection conditions between Pitsch and Fan are completely different. Ex. 1018, 3778 (disclosing “MeNH₂ (10M in H₂O/EtOH 1:1, 25°)”; Ex. 1019, 2556 (disclosing 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). Accordingly, a POSA would not be able to compare the teachings of Pitsch and Fan with any teachings of the '031 patent with respect to deprotection rates. ¶135.

Accordingly, neither the '031 Patent nor Pitsch, alone or in combination, disclose any comparisons of base deprotection rates for isobutyryl vs. acetyl for any phosphoramidites, nucleosides, oligonucleotides, 2'-fluoro monomers, or any other molecules, and Petitioner's arguments for motivation on these grounds are without merit.

b. Fan Discloses Deprotection Rates on a Fundamentally Different Compound Than Compound x Under Deprotection Conditions That a POSA Would Have Never Used on an Oligonucleotide

As Dr. Hrdlicka explains, Fan does not remedy the deficiencies of Pitsch and the '031 Patent and, as discussed in Section VI.B.2., a POSA would have understood that Fan discloses syntheses and deprotection of *nucleoside derivatives*, which were completely different molecules than Compound x, and did not even teach syntheses of corresponding phosphoramidites, or syntheses or deprotection of any oligonucleotides. Ex. 2008, ¶137.

First, as Dr. Hrdlicka confirms, a POSA would not have been motivated by the findings in Fan (or, for that matter, Pitsch) because, as any POSA in this field would have been well aware, data generated in connection with one nucleoside would not have reliably transposed to a different nucleoside, never mind to a different corresponding oligonucleotide. Ex. 2013, 400 (“[I]t is worth noting that the deprotection time of the free nucleoside may be quite different from that of the nucleoside inserted in the DNA chain.”); Ex. 2008, ¶138.

Furthermore, as Dr. Hrdlicka explains, a POSA would have recognized that the Fan study used deprotection conditions that are *incompatible with oligonucleotides*. *Id.*, ¶139. For example, a POSA would have known that the Fan study used “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. Ex. 1019, 2556; Ex. 2008, ¶139. A POSA would have understood that these were unusual deprotection conditions that were not applicable for deprotection of oligonucleotides during SPOS. Ex. 2008, ¶139.

Moreover, as Dr. Baran acknowledged, a POSA *would have never* used methylene chloride (having the chemical formula CH_2Cl_2) as a solvent when deprotecting a resulting oligonucleotide because of the risk that the solvent would lead to precipitation of the oligonucleotide, thus failing to accomplish nucleobase deprotection. Ex. 2009, 151:22-152:1 (“Q. If you try to deprotect oligonucleotide using the deprotection conditions of Fan, it wouldn’t work very well, would it? A. Nobody would do that. That’s not the point of the study.”); Ex. 2008, ¶140.

Accordingly, for at least these reasons, Fan would not have motivated a POSA to modify Compound x to make N2-Acetyl-2'-F-2'-deoxyG as claimed in Claim 2.

3. A POSA Would Not Have Had a Reasonable Expectation of Successfully Synthesizing the Compounds Claimed in Claim 2 of the '885 Patent

i. A POSA Would Have Expected That Using Acetic Anhydride in Step ii. of the Complex Synthesis Scheme in Example 4-d of the '031 Patent Would Have Failed

Petitioner argues that a POSA would have “simply substituted acetic anhydride (for isobutyric anhydride) in step ii’ and thereafter performed the remaining steps ‘iii’ through ‘x’” in Example 4-d of the '031 patent and would have

“regarded the conditions and yield for the installation of an acetyl protecting group as trivial and similar to those for an isobutyryl group.” Pet., 36-37. Petitioner’s argument is without merit.

Petitioner relies on speculation by its expert in alleging that substituting acetic anhydride in step ii. of the complex 10-step process set forth in Example 4-d of the ’031 Patent would have resulted in the claimed invention. Ex. 2008, ¶143.

Dr. Baran testified that he did not see a need to conduct any tests to prove his theory because he considered it “undergraduate level chemistry.” Ex. 2009, 161:6-12 (“And my question was whether you went into the lab to prove that theory. A. No, because this is undergraduate level chemistry, so there would be no need to even contemplate doing something like that. So the answer is no.”)

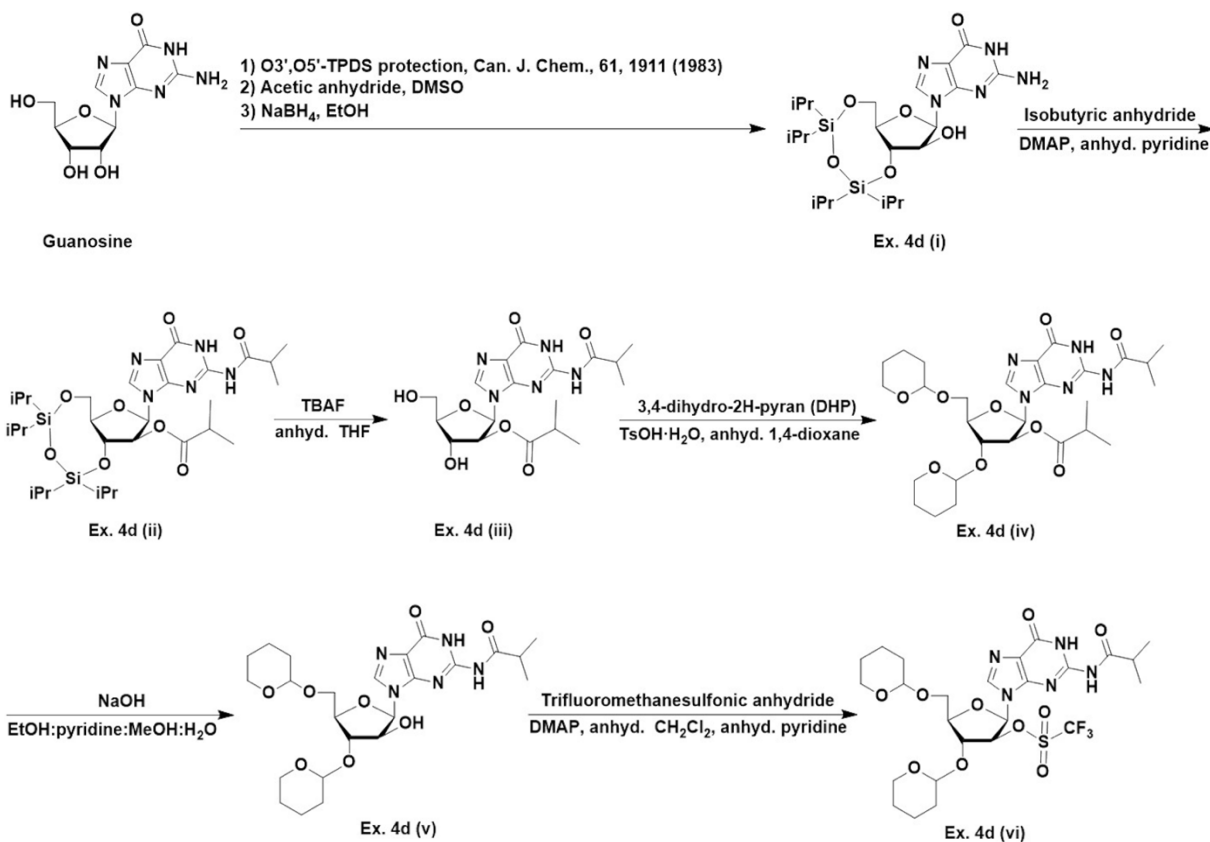
Petitioner does not provide any references, data, experimental evidence or technical reasoning to support Dr. Baran’s hindsight-based theory that the proffered modification to the Example 4-d scheme would have succeeded in resulting in the claimed compound. Dr. Baran’s testimony on this point should therefore be given little or no weight. 37 C.F.R. § 42.65(a); Fed. R. Evid. 702(b)-(d); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 (P.T.A.B. Aug. 24, 2022) (Precedential).

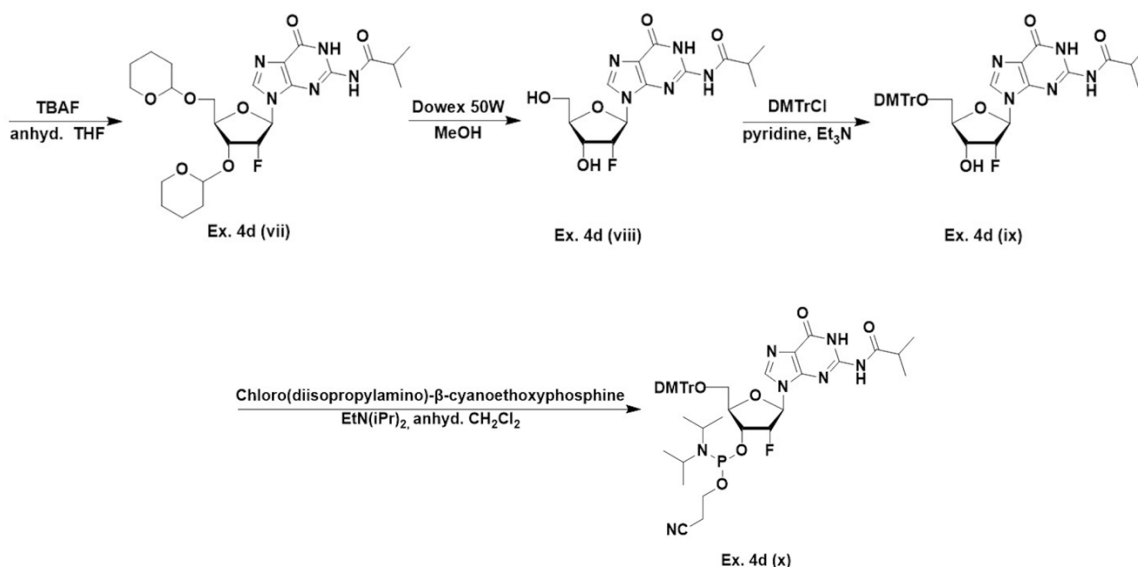
Contrary to Petitioner’s unsubstantiated arguments, a POSA would have instead expected that substituting acetic anhydride for isobutyric anhydride in step

ii. of Example 4-d in the '031 patent and executing the subsequent synthetic transformations (steps iii-x) would have resulted in failure. Ex. 2008, ¶146.

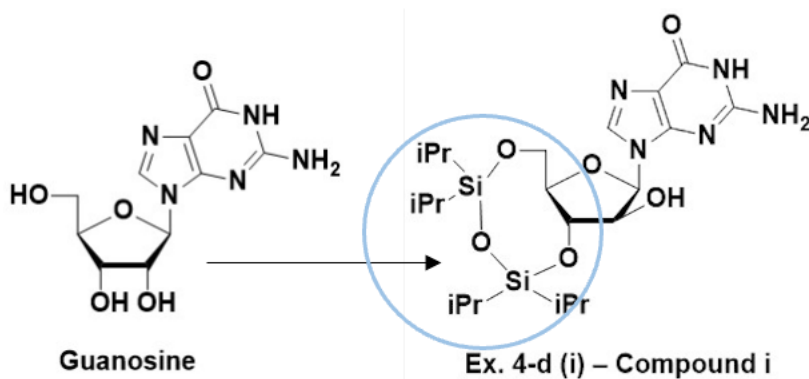
ii. A POSA Would Have Expected That Acetylating the Guanosine Derivative in Step ii. of Example 4-d of the '031 Patent Would Have Failed

In his declaration, Dr. Hrdlicka, provides a schematic overview of the complex 10-step synthesis scheme described by Example 4-d of the '031 Patent, reproduced as follows:



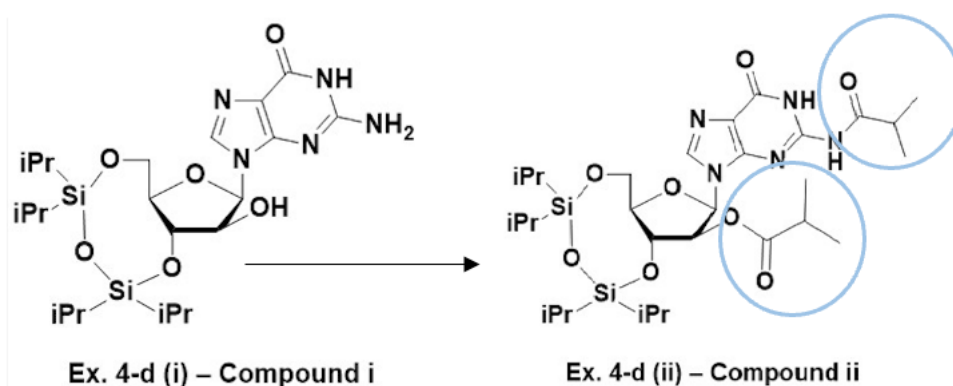


Ex. 2008, ¶147. As Dr. Hrdlicka explains, a POSA would have understood that in step i. of Example 4-d of the '031 Patent, “9-(3',5'-1,1,3,3-Tetraisopropylidisiloxy-1,3-diyl]-β-D-arabinofuranosyl)guanine,” (“Compound i”) is synthesized from unprotected guanosine.



Ex. 1017, Col. 25: 34-38; Ex. 2008, ¶148. A POSA would have further understood that the resulting Compound i would have had a silyl group simultaneously protecting the 3'- and 5'-positions of the sugar ring, and the 2'-OH and the N2 amine (-NH₂) of the guanine base would not have been protected. Ex. 2008, ¶149.

A POSA would have observed, as shown below, that in step ii. of Example 4-d of the '031 Patent, Compound i would have then been converted to “N²-Isobutyryl-9-(2'-O-isobutyryl-3',5'-1,1,3,3-tetraisopropylidisiloxy-1,3-diyl]-β-D-arabinofuranosyl)guanine” (“Compound ii”) by the introduction of, *inter alia*, isobutyric anhydride.



Ex. 1017, 25:61-62; Ex. 2008, ¶150. A POSA would have understood that the resulting modified guanosine Compound ii still would have had a 5'-O, 3'-O-silyl group protecting the 3'- and 5'-positions of the sugar ring, and the 2'-OH and the N2 amine (-NH₂) of the guanine base would have each been protected with isobutyryl groups. Ex. 2008, ¶150.

Petitioner’s argument that introducing an acetyl group via acetic anhydride in accordance with this step ii. would be successful is belied by one of Petitioner’s primary references, Fan, reporting that isobutyrylation (i.e., addition of isobutyryl groups) of guanosine derivatives (like Compound i) using isobutyryl in its scheme worked well, *but acetylation (i.e., addition of acetyl groups) of guanosine*

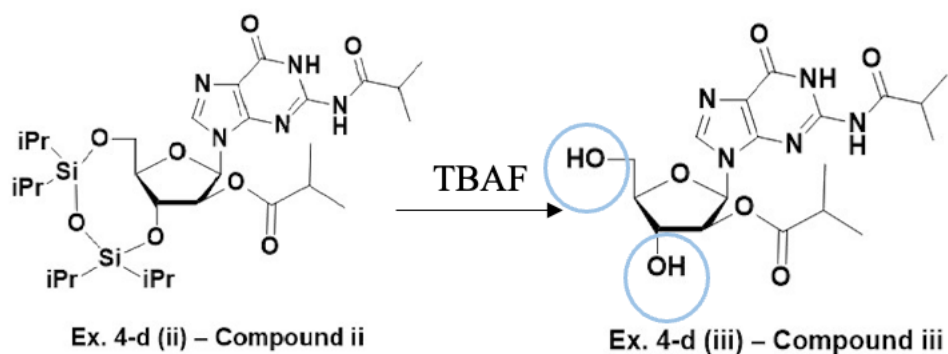
derivatives did not (“the reaction mixtures were dark and the yields were unsatisfactory.”). Ex. 1019, 2555. Ex. 2008, ¶151.

According to Dr. Hrdlicka, a POSA would have understood that a failure to attach acetyl groups (instead of isobutyryl groups) to the O2'- and/or N2-positions at this step would have completely derailed the subsequent synthetic transformations towards the N2-acetyl analogue of Compound x purported by Petitioner, as the reactive/nucleophilic O2'- and/or N2-positions would have reacted with reagents in some of the subsequent steps, to produce undesirable intermediates that would not have resulted in the synthesis of the N2-acetyl analogue Compound x. Ex. 2008, ¶152.

Accordingly, a POSA would not have had a reasonable expectation of success of synthesizing the N2-Acetyl-2'-F-2'-deoxyG of Claim 2 based on Petitioner's theory. *Id.*, ¶153.

iii. A POSA Would Have Expected That Using TBAF in Step iii. of Example 4-d of the '031 Patent Would Have Cleaved the Labile Acetyl Groups and Failed

As Dr. Hrdlicka explains, a POSA would have understood that in step iii. of Example 4-d of the '031 Patent, as shown below, Compound ii would have been converted to “N²-Isobutyryl-9-(2'-O-isobutyryl-β-D-arabinofuranosyl)guanine” (“Compound iii”) by the introduction of, *inter alia*, tetra-*n*-butylammonium fluoride (“TBAF”).



Ex. 1017, 26:12-18; Ex. 2008, ¶154.

A POSA would have also known that the TBAF would have been used to cleave the 5'-O, 3'-O-silyl protecting groups from the 3'- and 5'- positions of the sugar ring, while leaving the isobutyryl groups at the O2'- and N2- positions unharmed (i.e., with guanine remaining protected with an isobutyryl group). Ex. 2008, ¶154.

Even assuming, as per Petitioner's theory, that acetyl groups could have been successfully introduced in step ii. in place of the isobutyryl groups protecting the O2'- and N2- positions of guanine (which they would not have been), a POSA 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 basic/nucleophilic conditions disclosed. *See, e.g.*, Ex. 2015, 18144 ("The subsequent deprotection of the TBDMS groups proved to be difficult due to parallel cleavage of the [N2] acetyl protecting group under basic fluoride deprotection conditions such as TBAF in THF."); Ex. 2008, ¶155.

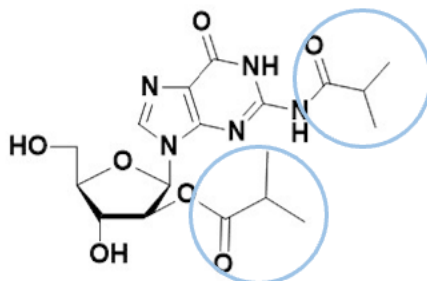
According to Dr. Hrdlicka, a POSA would have expected that the undesirable removal of the acetyl group(s) at the O2'- and/or N2- positions at this step would have completely derailed the subsequent synthetic transformations towards the N2-acetyl analogue of Compound x, as the presence of a reactive/nucleophilic 2'-OH and/or 2-NH₂ groups would have reacted with reagents in subsequent steps to produce undesirable intermediates that would not have resulted in the synthesis of the N2-acetyl analogue Compound x as Petitioner alleges. Ex. 2008, ¶156.

Accordingly, a POSA would not have had a reasonable expectation of success of synthesizing N2-Acetyl-2'-F-2'-deoxyG claimed by Claim 2 for this additional independent reason. *Id.*, ¶157.

iv. A POSA Would Have Expected the Acetyl Group to Have Rendered Compound iii Less Soluble in Organic Solvents and Cause the Synthesis to Fail

As discussed in Section VI.B.2.iii., a POSA would have understood that unprotected guanosine and its derivatives are highly polar and not functionally soluble in organic solvents absent hydrophobic protecting groups like isobutyryl groups. Ex. 2008, ¶158. A POSA would have also known that acetyl groups are smaller and more polar (i.e., more water-loving) than isobutyryl groups and therefore would have made guanosine derivatives less soluble in organic solvents. Ex. 2009, 176:4-6; Ex. 2008, ¶158.

Therefore, a POSA would have understood that, according to Petitioner's theory, Compound iii, shown here,



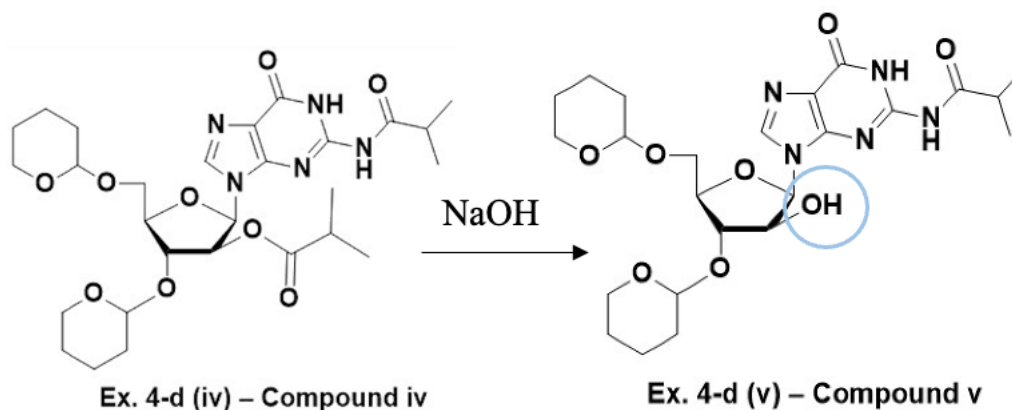
Ex. 4-d (iii) – Compound iii

would have had two acetyl groups at the O2'- and N2- positions instead of the two isobutyryl groups. Ex. 2008, ¶159. A POSA would have expected Petitioner's proposed molecule to be less soluble in organic solvents than Compound iii, which a POSA would have expected could have negatively affected purification and caused the synthesis to fail. *Id.*, ¶160. Additionally, a POSA would have also been concerned that the lower solubility of acetyl groups as compared to isobutyryl groups would have derailed the subsequent synthetic transformations and purifications (steps iv. – x.) of Example 4-d. *Id.*

Accordingly, a POSA would not have had a reasonable expectation of success of synthesizing the N2-Acetyl-2'-F-2'-deoxyG of Claim 2 for this additional independent reason. *Id.*, ¶161.

v. A POSA Would Have Expected That Using Sodium Hydroxide in Step v. Would Have Cleaved the 2' and/or N2 Acetyl Protecting Groups and Caused the Synthesis to Fail

As Dr. Hrdlicka explains, a POSA would have known that in step v. of Example 4-d of the '031 Patent, “N²-Isobutyryl-9-(2'-O-isobutyryl-3',5'-di-O-tetrahydropyran-2-yl-β-D-arabinofuranosyl)guanine” (“Compound iv”) is converted to “N²-Isobutyryl-9-(3',5'-di-O-tetrahydropyran-2-yl-β-D-arabinofuranosyl)guanine” (“Compound v”) by the introduction of, *inter alia*, NaOH (“sodium hydroxide”).



Ex. 1017 at 26:42-59; Ex. 2008, ¶162.

A POSA would have understood that the resulting Compound v, shown above, would have retained its tetrahydropyran-2-yl (THP) protecting groups at the 3'- and 5'- positions (installed during step iv.) and the isobutyryl protecting group at the N2-position, whereas the isobutyryl protecting group at the O2'- position was cleaved. Ex. 2008, ¶163. A POSA would have understood that this step indicates “selective

deprotection,” where only certain protecting groups (here, just O2'-isobutyryl) are cleaved, whereas others remain intact. *Id.*

A POSA would have expected that, had two acetyl groups been present on Compound iv. (as per Petitioner’s theory), instead of the two isobutyryl groups, and the scheme had not already failed in prior steps (which, as discussed above, a POSA would have expected it would have), 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. Ex. 2020, 252; 279 (“the N-isobutyryl group showed, as might have been expected, considerably higher stability than the N-acetyl group” when deprotected “in a mixture of pyridine (0.4 ml.) and water (0.6 ml.) at 4°C [and] Sodium hydroxide (1 ml. of 2 M), which had been cooled to 4°C [and] added with vigorous agitation.”); Ex. 2008, ¶164.

Accordingly, a POSA would not have had a reasonable expectation of success of synthesizing the N2-Acetyl-2'-F-2'-deoxyG compound of Claim 2 for this additional and independent reason. Ex. 2008, ¶165.

4. Petitioner's Additional Arguments for Reasonable Expectation of Success Lack Evidentiary Bases and are Without Merit

Petitioner further argues that instead of starting with Compound x, “a POSA could have also synthesized the molecule claimed in Claim 2 ... by starting with 2'-fluoro-2'-deoxyguanosine, either acquired from a commercial source or synthesized according to Sivets (2007).” Pet., 37-38 (citing Sivets, (Ex. 1028), compound 17). Petitioner's argument lacks support, is speculative, and constitutes classic hindsight reconstruction.

First, Dr. Baran's conclusory statement is not supported by any evidence (e.g., a product or catalogue disclosure) that shows 2'-fluoro-2'-deoxyguanosine was commercially available at the time of invention, and this aspect of Dr. Baran's testimony should therefore be given little or no weight. 37 C.F.R. § 42.65(a). *See also* Fed. R. Evid. 702(b)-(d); *Xerox*, IPR2022-00624 Paper 9 at 15.

Second, as Dr. Hrdlicka explains, a POSA would have known that compound 17 from Sivets (2007) (“Compound 17”) is not an *N9-linked* 2'-fluoro-2'-deoxyguanosine such as claimed in Claim 2, but is instead an *isomeric N7-linked* 2'-fluoro-2'-deoxyguanosine, and each are completely different molecules. Ex. 1028, 1821; Ex. 2008, ¶168. When this was posed to Dr. Baran during his deposition, he changed his testimony and referred to compound 15 disclosed in Sivets (2007) (“Compound 15”), without providing any other bases for his opinions now relating

to Compound 15. Ex. 2009, 166:15-21. In either case, Petitioner's arguments are without merit.

Petitioner argues that a POSA "would have reasonably expected that 2'-fluoro-2'-deoxyguanosine would react similarly to a 'regular' 2'-deoxyguanosine (*i.e.*, one with a 2'-H instead of the 2'-F substitution) in connection with the preparation of reagents for SPOS ..." Pet., 38. However, Petitioner's argument relies on the conclusory testimony of its expert and provides no references, data, or experimental evidence for the proposition that these completely different molecules "would react similarly." Ex. 2008, ¶169.

When asked about the basis for this testimony during his deposition, Dr. Baran testified that his testimony is based on "[t]ons of experience in the area and doing this chemistry through supervision and seeing it over the years" along with "literature" that he failed to identify in his declaration or during his deposition. Ex. 2009, 167:9-12. This aspect of Petitioner's argument, which is not supported by sufficient facts or data, should therefore be given little or no weight. 37 C.F.R. § 42.65(a). *See also* Fed. R. Evid. 702(b)-(d); *Xerox*, IPR2022-00624 Paper 9 at 15.

Even if the argument that 2'-fluoro-2'-deoxyguanosine would react similarly to a 'regular' 2'-deoxyguanosine was supported, which it is not, then it follows that a POSA would have understood that 2'-fluoro-2'-deoxyguanosine would have suffered

from similar solubility problems as “regular” 2'-deoxyguanosine during acetylation. Ex. 2012, 3822. Ex. 2008, ¶171.

As explained by Dr. Hrdlicka, and contrary to Petitioner’s unsupported argument, a POSA would have known, at the very least, that the different 2'-substituents of 2'-fluoro-2'-deoxyguanosine and ‘regular’ 2'-deoxyguanosine (i.e., 2'-F vs. 2'-H) 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 thus their reactivities. Ex. 2014, 1421 (stating “[n]ucleoside conformation[s are] determined by the electronegativity of the sugar substituent...”); Ex. 2008, ¶171.

The rest of Petitioner’s arguments in Section VI.B.4. are illogical. A POSA would have understood that neither Pitsch (Scheme 1, step “c”) molecule 3; step “d”), molecule 6); and Step “f”); Pitsch #2 (2001) (Support Protocol 2); nor the '031 Patent (Example 4-d, Step “x”) (Figure 3) teach the installation of protecting groups on “regular” 2'-deoxyguanosine. Pet., 38; Ex. 2008, ¶172. Accordingly, it does not make sense to cite to those protocols as being useful for the synthesis of “regular” 2'-deoxyguanosine (or, for that matter, 2'-fluoro-2'-deoxyguanosine). Ex. 2008, ¶172.

As Dr. Hrdlicka explains, Petitioner’s reliance on Pitsch, Scheme 1, step “c”) is misplaced since Pitsch teaches installing acetyl on a completely different molecule

than 2'-fluoro-2'-deoxyguanosine which is not instructive to synthesizing 2'-fluoro-2'-deoxyguanosine, and its teachings would therefore not have provided a POSA with a reasonable expectation of success in synthesizing the claimed compound. Ex. 2008, ¶173. Further discouraging a POSA, a POSA would have also recognized that Pitsch is based on a flawed protocol because, *inter alia*, it discloses an insufficient amount of sodium hydroxide (“0.2 mol”) to remove all of the O-acetyl groups of the peracetylated intermediate. Ex. 1018, 3787; Ex. 2008, ¶173.

Moreover, McBride (Ex. 1006) does not cure these deficiencies as it does not disclose 2'-fluoro-2'-deoxyguanosine or a cyanoethyl dialkyl phosphoramidite as specified by Claim 2, i.e., the phosphorous in McBride is connected to a methoxy group (-OCH₃), unlike N2-Acetyl-2'-F-2'-deoxyG in Claim 2 where phosphorous is connected to a cyanoethyl group (-OCH₂CH₂CN). Ex. 2008, ¶182; Ex. 1006, 245, 247.

Accordingly, a POSA would not have had a reasonable expectation of success of synthesizing the N2-Acetyl-2'-F-2'-deoxyG compound of Claim 2 for these additional reasons.

5. Secondary Indicia of Non-Obviousness Further Establish that Claim 2 is Not Obvious

Even if the Board concludes that Petitioner has made a *prima facie* case of obviousness under this Ground II, which Patent Owner respectfully submits it has

not, secondary indicia of non-obviousness further establish that Claim 2 would not have been obvious to a POSA and is therefore not unpatentable.

As Dr. Hrdlicka explains, in describing their invention in the '885 Patent's specification, the applicants explained that peers in the oligonucleotide industry were experiencing difficulty in obtaining pure chimeric oligoribonucleotides.

When oligo ribonucleotide chimeras comprise [sic] of mixed bases composed of 2'-fluoro and 2'-ribo bases they present a challenge in obtaining pure chimera oligonucleotides. It has been well documented by several recent reports that oligonucleotide chimeras having 2'-fluoro-2,'-deoxy [sic] bases along with natural ribo bases present difficulty in obtaining pure oligos.

Ex. 1001, 10:65-11:4; Ex. 2008, ¶184.

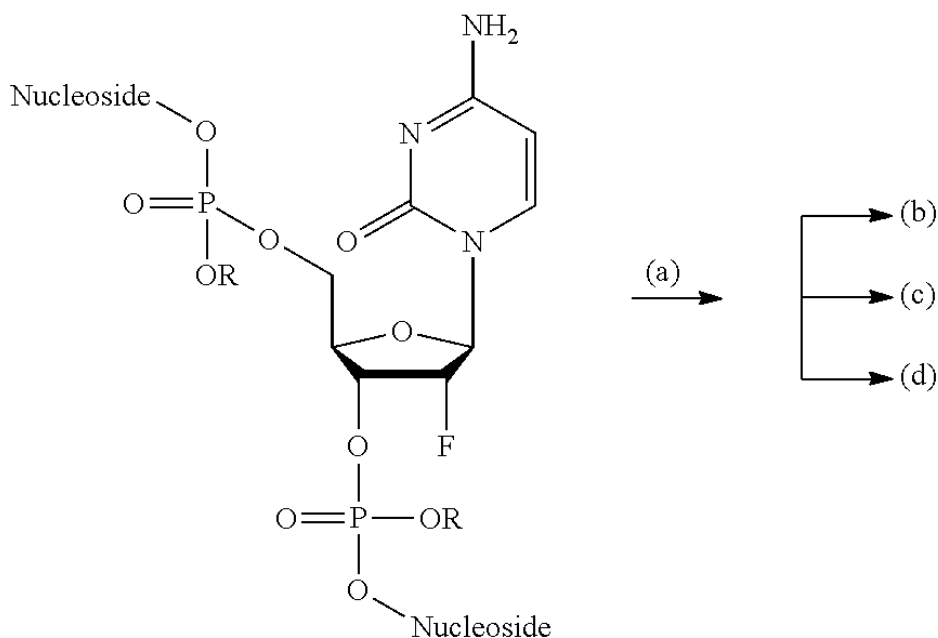
The applicants further explained that the 2'-fluoro atom on 2'-fluoro-2'-deoxyribonucleotide monomers of chimeric oligoribonucleotides was lost (as hydrogen fluoride (HF)) under “usual deprotection conditions,” thus resulting in the formation of chimeric oligonucleotides with monomers lacking fluorine. Ex. 1001, 11:15-17. Ex. 2008, ¶185.

The applicants also discussed the observed loss of pyrimidine nucleobases (i.e., uracil and cytidine) from 2'-fluoro-2'-deoxyribonucleotide monomers which caused damage to the nucleotides and the overall chimeric oligoribonucleotide products themselves.

It has been shown that with strongly basic conditions, there is ***significant loss of fluorine*** as loss of Hydrogen Fluoride (“HF”) is seen as M-20 peak in Mass spectral analysis. Besides it has also been shown that uracil and cytosine are eliminated to a significant extent, when oligo chimeras containing 2'-fluoro-2'-deoxy uridine and 2'-fluoro-2'-deoxy cytidine are part of chimeras (see scheme 3).

Ex. 1001, 11:4-11 (emphasis added); Ex. 2008, ¶186. The applicants also provided the following scheme to illustrate the problem:

Scheme 3. Graphic Representation of effect on quality of oligonucleotides containing 2'-fluoro nucleosides: (a) deprotection using methyl amine, the usual deprotection condition of protecting groups of bases, (b) loss of fluorine leading to loss of HF, generating significant amount of M-20, (c) loss of cytosine and uracil, the pyrimidine bases is observed quite frequently, d) with the loss of pyrimidine, subsequent cleavage of chain occurs.



Ex. 1001, 11:12-35; Ex. 2008, ¶186.

To further demonstrate the issue, applicants cited to studies presented at 2 conferences occurring in 2005 and 2007:

The studies as shown in scheme 3 were carried out independently by two groups recently. Ken Hill, Agilent Technologies, Boulder, Colorado [sic]; Identification of Process Related Impurities—Understanding Oligonucleotide Production, TIDES 2007, Las Vegas, Nev. The author showed depyrimidation of chimera oligonucleotides carrying 2'-fluoro-2'-deoxy pyrimidine in RNA's; and, Nanda D. Sinha, Avecia Biotechnologies Inc., Massachusetts—Depyrimidation, as well as loss of HF and chain cleavage in chimeras having 2'-fluoro-2'-deoxy pyrimidines in RNA sequences. Eurotides, 2005, Munich, Germany.

Ex. 1001, 11:36-47; Ex. 2008, ¶187.

These observations are corroborated by publications, including from one of the cited authors, Nanda D. Sinha. Ex. 2024, 83 (book chapter by Sinha et. al. stating that the 2'-fluoro-2'-deoxyribonucleotide of chimeric oligonucleotides “is subject to depyrimidation [] especially with methylamine or ammonia/methylamine deprotection...”). *Id.*, ¶187.

As Dr. Hrdlicka further explains, 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.

Ex. 1001, 11:48-55 (emphasis added); Ex. 2008, ¶188. The “2'-fluoro-2'-deoxy nucleosides and corresponding phosphoramidites with guanine protecting groups having N-2 acetyl” compounds referenced in this passage cover the exact N2-Acetyl-2'-F-2'-deoxyG phosphoramidite that Petitioner has challenged. Ex. 2008, ¶188.

According to Dr. Hrdlicka, the cited results were unexpected as compared to the properties of Petitioner’s alleged closest prior art— Compound x. Ex. 2008, ¶189. Based on the disclosures in the '885 Patent and other literature (e.g., Exs., 2024 and 2025) referencing oligoribonucleotide chimeras comprised of mixed 2'-fluoro and 2'-ribo bases presenting serious challenges in obtaining pure oligonucleotides, a POSA would have expected that using Compound x would have caused similar purity problems. *Id.*

As Dr. Hrdlicka explains, this is supported by at least Kawasaki, which observes “*significant degradation* of the 2'-deoxy-2'-fluorpyrimidine nucleosides” while under “the usual oligonucleotide deprotection conditions (concentrated NH₄OH, 55°C).” Ex. 2025, 833. Ex. 2008, ¶190. Kawasaki shows (in Scheme II) significant overlap with the synthesis schemes of Example 4-d of the '031 Patent

and both publications identified as originating from the same company (Isis Pharmaceuticals, Inc.). Ex. 1017, Cover; Ex. 2025, 831; Ex. 2008, ¶190.

While Compound x is not shown as synthesized in Kawasaki, its precursors are, and the Compound x structure—“N2-Isobutyryl-2'-deoxy-2'-fluoro-5'-O-(4,4'-dimethoxytrityl)guanosine 3'-[β-Cyanoethyl N,N-diisopropylphosphoramidite]”—is described in the experimental protocols. Ex. 2025, 839; Ex. 2008, ¶191. As Dr. Hrdlicka explains, it therefore appears the work disclosed in Kawasaki and the '031 Patent may be related and address the same structures including Compound x. Ex. 2008, ¶191.

Kawasaki also discloses using methanolic ammonia instead of NH₄OH, but did not disclose modifying the N2-protecting group, to attempt to address the degradation problem. Ex. 2025, 833. Ex. 2008, ¶192. Given that this publication was dated in 1993, the overall degradation problem therefore had persisted for at least 15 years before the filing of the application that led to the issuance of the '885 Patent. Ex. 2008, ¶192.

Moreover, POSAs routinely used methylamine to remove protecting groups from guanosine, but Sinha observed problems using methylamine, further demonstrating that the results using N2-Acetyl-2'-F-2'-deoxyG were unexpected. Ex. 2024, 83; Ex. 1001, 22:63-23:1 (using methylamine); Ex. 1018, 3778 (using methylamine); Ex. 1019, 2556 (using methylamine).

Accordingly, the results obtained by the applicants in utilizing N2-acetyl on 2'-fluoro-2'-deoxyguanosine to address this problem were surprising and unexpected as compared to the closest prior art which did not disclose using the novel claimed N2-Acetyl-2'-F-2'-deoxyG compound to address the longstanding industry need. Ex. 1001, Col. 11:15-17. Ex. 2008, ¶193.

Since at least one of the molecules described in these passages of the '885 Patent as satisfying a long-felt industry need and demonstrating unexpected results is *the same* N2-Acetyl-2'-F-2'-deoxyG phosphoramidite claimed in Claim 2, Patent Owner is entitled to a presumption of a nexus between the asserted evidence and patent claim. *Fox Factory*, 944 F.3d at 1373 (Fed. Cir. 2019). Ex. 2008, ¶195.

Furthermore, the evidence of long-felt need spanning over 15 years is “particularly probative” because it “demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy the demand.” *Millenium Pharm.*, 862 F.3d at 1369. Even if a nexus is not presumed, which it should be, the nexus nevertheless exists because there is a “‘legally and factually sufficient connection’ between the evidence and the patented invention” for the reasons stated herein. *Id.* (quoting *Henny Penny Co. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019)).

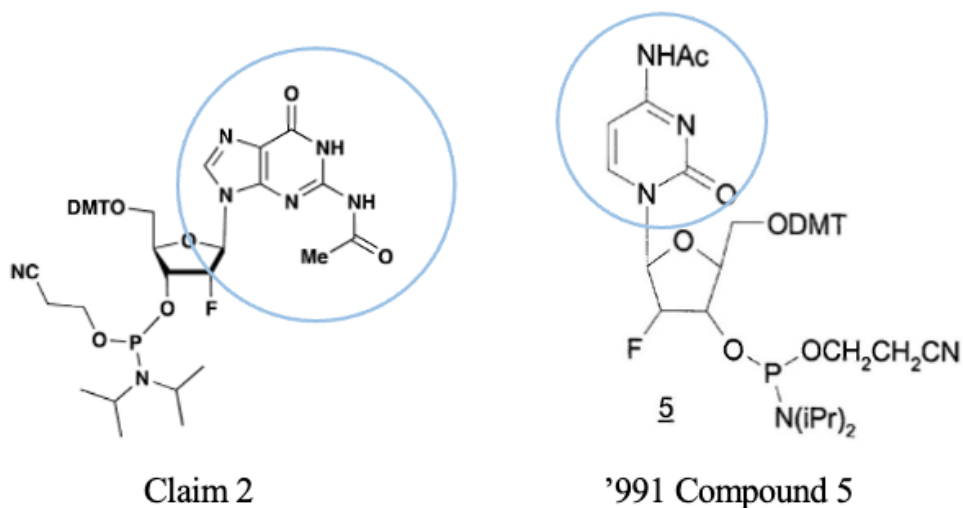
Accordingly, the inventors' advancement in developing the novel N2-Acetyl-2'-F-2'-deoxyG phosphoramidite, as claimed in Claim 2, was not obvious for this reason as well.

C. Ground III: Claim 2 Would Not Have been Obvious in View of U.S. Patent No. 7,879,991 and Pitsch

1. The '991 Patent Discloses a Totally Different Molecule than Claimed in Claim 2 of the '885 Patent

Contrary to Petitioner's argument, the compound disclosed in Figure 16 of U.S. Patent No. 7,879,991 (the '991 Patent) ("Compound 5") is not "almost identical" to Claim 2 "where 'B' is Guanine-N-acetyl and 'Z' is ribo Fluoro," and is instead starkly different. Pet., 40.

First, as shown in the figure below from the Petition, Claim 2 has a *guanine* base and Compound 5 has a *cytosine* base.



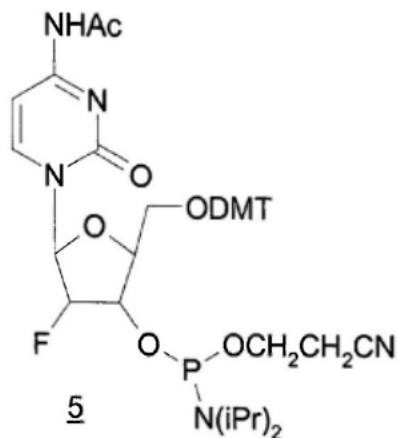
Pet., 39; Ex. 2008, ¶198. As Dr. Hrdlicka explains, a POSA therefore immediately known that Compound 5 was totally different from the compound claimed in Claim

2 where “B” is guanine-N-acetyl and “Z” is ribo fluoro, and therefore certainly not “almost identical.” Ex. 2008, ¶198.

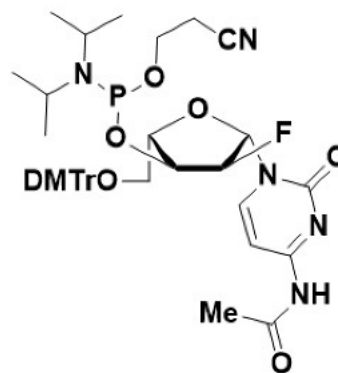
Further, a POSA would have recognized that Compound 5 is an *L-configured* nucleoside, as stated in the '991 Patent and admitted by Dr. Baran. Ex. 1020, Sheet 17, 16:38-40; 45:45-48; Ex. 1003, ¶127 (disclosing “2'-fluoro-L-cytidine phosphoramidite” in Figure 16); Ex. 2009, 180:8-16 (“Q. Right. So does that clarify for you that figure 16 shows L configured cytosine? A. Yes.”). Ex. 2008, ¶199.

In contrast, according to Dr. Hrdlicka, a POSA would have also understood that the compound claimed in Claim 2 of the '885 patent is a *D-configured* nucleoside. Ex. 2008, ¶¶201-205. As he explains, even assuming N2-acetyl-protected guanine was identical to a N4-acetyl-protected cytosine, which it is not, a POSA would have understood that such compounds would have been enantiomers (i.e., non-superimposable mirror images) of each other. *Id.*

For illustrative purposes, the image below (to the right) shows an alternative depiction of Compound 5, after having been turned over from the left to the right (e.g., like a hamburger patty), with C1' located in the upper right of the sugar ring and C4' located in the upper left of the sugar ring (i.e., with the sugar ring orientated in the same fashion as the N2-acetyl 2'-F-deoxyguanosine of Claim 2). Ex. 2008, ¶200.

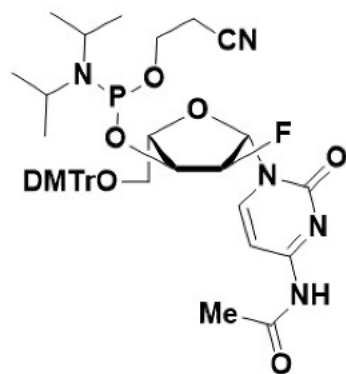


'991 Compound 5

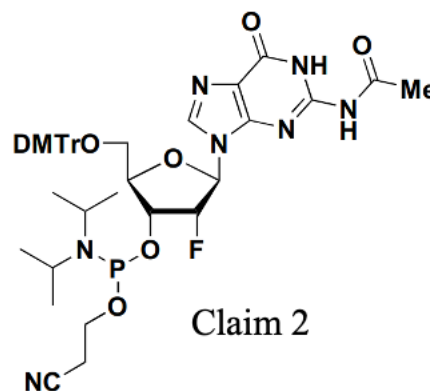


Alternative Compound 5

When the L-configured Compound 5, depicted in this way, is then compared to the D-configured N2-acetyl 2'-F-deoxyguanosine of Claim 2 (below), a POSA would have plainly seen how different these molecules are. Ex. 2008, ¶206.



Alternative Compound 5



Claim 2

Specifically, a POSA would have understood that these molecules would have had to have 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. *Id.*, ¶207.

2. Petitioner Fails to Carry its Burden to Show Why a POSA Would Have Selected Compound 5 of the '991 Patent as a Lead Compound and, in Any Event, a POSA Would Not Have Made That Selection

Petitioner again fails to provide any reasoning why a POSA would have selected Compound 5 as a lead compound other than the conclusory statement that a POSA would have viewed Compound 5 as a “building block” for a growing oligonucleotide chain. Ex. 2008, ¶208. Pet., 40.

Petitioner makes *no showing* as to *why* a POSA would have selected Compound 5 as the “most promising to modify in order to improve upon its [] activity and obtain a compound with better activity,” *Takeda Chem.*, 492 F.3d at 1357, or *why* a POSA “would have had a reason to select [Compound 5] from the panoply of known [oligonucleotide building block] compounds in the prior art” or from the compounds described in the '991 Patent. *Otsuka*, 678 F.3d at 1292. Ex. 2008, ¶208.

This again suggests improper hindsight reconstruction, and Petitioner’s argument should fail for this reason alone. *I-Mak, Inc. v. Gilead Pharmasset LLC*, IPR2018-00122, Paper 10 at 25 (P.T.A.B. May 21, 2018).

3. A POSA Would Not Have Been Motivated by the '991 Patent and Pitsch to Synthesize the N2-Acetyl-2'-F-2'-deoxyG of Claim 2

Petitioner argues that “[Compound 5] would have motivated a POSA to build the structurally analogous 2'-fluoro-guanosine phosphoramidite claimed in Claim 2, especially in view of Pitsch” Pet., 40-41.

Petitioner’s argument is illogical and Petitioner provides no support, other than Dr. Baran’s identical conclusory statements for why Compound 5, a totally different L-configured compound with a cytosine base, would have motivated a POSA to build the structurally different D-configured N2-Acetyl-2'-F-2'-deoxyG claimed in Claim 2. Ex. 2008, ¶211. 37 C.F.R. § 42.65(a); Fed. R. Evid. 702(b)-(d); *Xerox*, IPR2022-00624 Paper 9 at 15.

Petitioner’s argument that Pitsch would have motivated a POSA to make the N2-Acetyl-2'-F-2'-deoxyG compound claimed in Claim 2 is also without merit for at least the reasons set forth in Section VI.B. above, including that the prior art taught away from using acetyl groups to protect 2'-deoxyguanosine. Ex. 2011, 221; Ex. 2008, ¶212.

Furthermore, the teachings of the '991 Patent contradict Petitioner’s argument that a POSA would have been motivated by it to make the claimed invention. Ex. 2008, ¶213. For example, a POSA would have understood that the '991 Patent teaches that *pyrimidine* nucleotides were to be configured with F at the 2'-position:

A particularly advantageous modification [to nucleic acids] in connection with the present invention constitutes configuring the inventive nucleic acid(s), in which at least one, preferably more and ***most preferably all pyrimidine nucleotides*** forming the nucleic acid have a 2'-fluoro group at the 2' position of the ribose section of each nucleotide.

Ex. 1020 at 12:33-40 (emphasis added); Ex. 2008, ¶213. Here, a POSA would have known that the guanine base of Claim 2 of the '885 Patent is a ***purine***, not a ***pyrimidine*** base, and therefore the '991 Patent would not have motivated a POSA to synthesize a N2-Acetyl-2'-F-2'-deoxyG as claimed in Claim 2. Ex. 2008, ¶213.

Moreover, the '991 Patent would not have motivated a POSA in this way, is that the '991 Patent is directed to L-configured nucleic acids, not D-configured phosphoramidites (as in Claim 2), and thus teaches instability of D-configured nucleic acids in aqueous solutions and biological systems. *Id.*, ¶214.

The L nucleic acids are enantiomers of the naturally occurring nucleic acids. ***The D nucleic acids however are not very stable*** in aqueous solutions and in particular in biological systems or biological samples as a result of the broad distribution of nucleases.

Ex. 1020, 12:3-7 (emphasis added); *Millenium Pharm.*, 862 F.3d at 1366; Ex. 2008, ¶214. Accordingly, a POSA reading the '991 Patent would have been discouraged from pursuing D- over L-configured nucleic acids. Ex. 2008, ¶215.

Accordingly, for at least these reasons, a POSA would not have been motivated by the '991 Patent or Pitsch to make the N2-Acetyl-2'-F-2'-deoxyG phosphoramidite claimed in Claim 2.

4. Petitioner Fails to Carry its Burden Showing Why a POSA Would Have Had a Reasonable Expectation of Successfully Synthesizing the Molecule in Claim 2 Based on the '991 Patent

Petitioner relies on “Section VI.B.4” of its Petition to show a POSA would have had a reasonable expectation of success in synthesizing the molecule claimed in Claim 2 based on the '991 Patent or Compound 5. Pet., 41; Ex. 2008, ¶216.

But neither Section VI.B.4, nor anywhere else in the Petition, does Petitioner discuss or address reasonable expectation of success based on the '991 Patent or Compound 5. Ex. 2008, ¶216. Accordingly, Petitioner fails to provide sufficient (indeed, any) evidence or reasoning for reasonable expectation of success based on the '991 Patent or Compound 5 – a completely different molecule from Compound x from the '031 Patent and the molecules disclosed in Pitsch, Fan, Sivets (2007), Pitsch #2 (2001), and McBride (1983). *Id.*, ¶217. Dr. Baran’s conclusory testimony supporting this aspect of Ground III should be given little or no weight. 37 C.F.R. § 42.65(a); Fed. R. Evid. 702(b)-(d); *Xerox*, IPR2022-00624 Paper 9 at 15.

Should the Board determine the arguments in Section VI.B.4 may be used to support this Ground III, then Petitioner’s arguments fail for at least the reasons stated in Sections VI.B. herein for Ground II.

5. Secondary Considerations of Non-Obviousness Further Establish that Claim 2 is Not Obvious

Claim 2 would not have been obvious to a POSA for at least the reasons set forth for secondary considerations of non-obviousness for Ground II discussed in Section VI.B.5. Ex. 2008, ¶219.

D. Ground IV: Claim 3 Would Not Have Been Obvious in View of the '031, Pitsch, Fan, and Scaringe

1. Claim 3 Should be Interpreted Such That “M” Should be “Ethyl” and Ground IV Should Fail Under any Interpretation

As discussed in Section IV above, Patent Owner agrees with Petitioner’s contention that Claim 3 should be interpreted such that “M” should be “ethyl” and not “succinyl.” For the reasons stated below, Patent Owner respectfully submits that Petitioner has not met its burden to establish *prima facie* obviousness under this interpretation of Claim 3, and Claim 3 is not unpatentable.

Alternatively, should the Board not construe Claim 3 in this manner, then Ground IV should fail because none of the prior art references cited in Ground IV (i.e., the '031 Patent, Pitsch, Fan, and Scaringe) discloses compounds where “M” is succinyl or any of the remaining compounds listed in the Claim 3 Markush group (i.e., where M is “oxalyl” or “hydroquinolynyl”). Ex. 2008, ¶221. Accordingly, because all of the limitations of uncorrected Claim 3 are not taught by the prior art under this interpretation, and the missing element would not have been supplied by

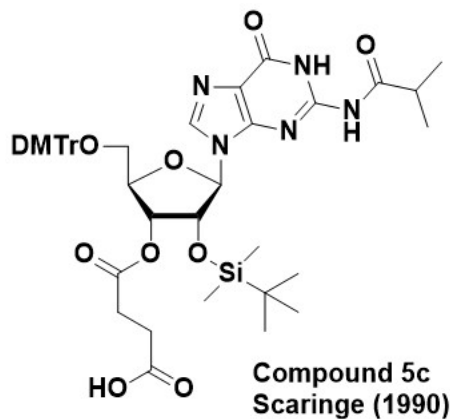
the knowledge of a POSA, Petitioner fails to make a *prima facie* case of obviousness for Ground IV. See *Arendi S.A.R.L.*, 832 F.3d at 1366.

2. Petitioner’s Arguments with Respect to Alleged Obviousness of Claim 3 Fail for at Least the Reasons its Arguments in Connection with Claim 2 Fail

The molecules in Claims 2 and 3 are identical except Claim 2 has a “cyanoethyl dialkyl phosphoramidite” at the 3'-position and Claim 3 has succinyl, solid support and spacer groups at the 3'-position. Pet., 44; Ex. 2008, ¶223. Petitioner mainly relies on its arguments under Ground II for the molecule claimed in Claim 2 where “B” is guanine-N-acetyl and “Z” is ribo fluoro to support its arguments in this Ground IV. Pet., 45.

Petitioner’s argument is therefore without merit for at least the reasons set forth in Section VI.B. (Ground II) above relating to Claim 2, i.e., (a) Petitioner fails to provide a rationale as to why a POSA would have chosen Compound x as a lead compound; (b) neither Pitsch nor Fan would have motivated a POSA to modify Compound x to make the compounds claimed in Claim 2; (c) a POSA would not have had a reasonable expectation of success in synthesizing the compounds claimed in Claim 2; and (d) secondary indicia of non-obviousness further establish that Claim 2 is not unpatentable. Ex. 2008, ¶224. Accordingly, because Petitioner fails to establish *prima facie* obviousness for Claim 2, Petitioner also fails to establish a *prima facie* obviousness for Claim 3 (Ground IV).

Furthermore, as Dr. Hrdlicka explains, the molecule disclosed in Scaringe (“Compound 5c”), shown below, is also different from the molecules covered by Claim 3 and the various molecules disclosed in the ’031 Patent, Pitsch, and Fan (discussed in Section VI.B. above).



Ex. 2008, ¶225. As shown above, Scaringe does not disclose 2'-F groups and instead uses an O2'-TBDMS group and only teaches using an isobutyryl group to protect the N2-position of the above guanine nucleobase, does not teach using an acetyl group, and does not disclose deprotection rates. *See, e.g.*, Ex. 1022, 5434. Ex. 2008, ¶226.

Accordingly, for at least these reasons, and the reasons provided in Section VI.B. above, a POSA would not have been motivated by Scaringe to synthesize the succinate claimed in Claim 3 where “B” is guanine-N-acetyl and “Z” is ribo fluoro, with a reasonable expectation of success.

3. Secondary Considerations

Secondary considerations of non-obviousness discussed in Section VI.B.5. for Claim 2 further establish that Claim 3 would not have been obvious.

The nexus between the claimed invention and secondary indicia including unexpected results and long-felt need is directly related to the core structure at issue (i.e., Claim 3 is the corresponding succinate of the phosphoramidite in Claim 2) and therefore the nexus should be presumed. *Fox Factory*, 944 F.3d at 1373; Ex. 2008, ¶229.

Even if a nexus is not presumed, which it should be, the nexus nevertheless exists because there is a “‘legally and factually sufficient connection’ between the evidence and the patented invention” for the reasons stated herein. *Fox Factory*, 944 F.3d at 1373 (citations omitted).

E. Ground V: Claim 4 Would Not Have Been Obvious in View of Scaringe, Pitsch, and Fan

1. Claim 4 Should be Interpreted Such That “M” Should be “Ethyl” and Ground V Should Fail Under any Interpretation

As discussed in Section IV. above, Patent Owner agrees with Petitioner that Claim 4 should be interpreted such that “M” should be “ethyl” and not “succinyl.” Ex. 2008, ¶230. For the reasons stated herein, Patent Owner respectfully submits that Petitioner has not met its burden to establish *prima facie* obviousness under this

interpretation of Claim 4, and Claim 4 is not unpatentable based on the Petitioner's proffered grounds.³

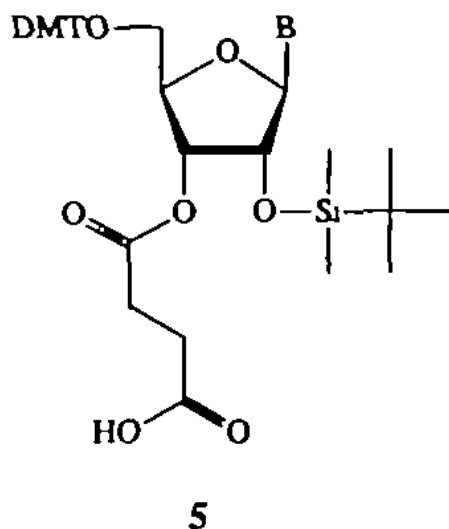
Alternatively, should the Board not construe Claim 4 in this manner (i.e., not correcting the error and instead requiring "M" to be succinyl and not ethyl), then Ground V fails because none of the prior art references cited in Ground V (i.e., the Scaringe, Pitsch, Fan) discloses compounds where "M" is succinyl or any of the remaining compounds listed in the Claim 4 Markush group (i.e., where M is "oxalyl" or "hydroquinolynyl"). Ex. 2008, ¶231. Accordingly, because all of the limitations of uncorrected Claim 3 are not taught by the prior art under this interpretation, and the missing element would not have been supplied by the knowledge of a POSA, Petitioner fails to establish *prima facie* obviousness for Ground V. *See Arendi S.A.R.L.*, 832 F.3d at 1366.

³ Patent Owner's arguments herein are directed at Petitioner's stated grounds for unpatentability only. Patent Owner has sought reissue of Claim 4 in U.S. Reissue Application No. 18/130,902 to remove a compound from Claim 4's Markush Group (where B is Cytosine-N-acetyl) based on a prior sale of that compound.

2. Petitioner Fails to Carry its Burden to Show Why a POSA Would Have Selected Compound 5(c) of Scaringe as a Lead Compound and, in Any Event, a POSA Would Not Have Made that Selection

Petitioner identified Compound 5(c) disclosed in Scaringe (1990) (“Compound 5(c)”) as its primary reference for this Ground V.

- a) B = N⁶-Benzoyl adenine
- b) = N⁴-Benzoyl cytosine
- c) = N²-Isobutyryl guanine
- d) = Uracil



Ex. 1022, at 3, Fig. 1, #5; Pet. at 48-52.

Petitioner fails to carry its burden and makes *no showing* as to *why* a POSA 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,” *Takeda Chem.*, 492 F.3d at 1357, or why a POSA “would have had a reason to select [Compound 5(c)] from the panoply of known [nucleoside building blocks] in the prior art.” *Otsuka*, 678 F.3d at 1292.

According to Dr. Hrdlicka, a POSA would not have chosen Compound 5(c) as a lead compound. Ex. 2008, ¶234. Scaringe reports the syntheses of RNA

oligoribonucleotides via SPOS, which for RNA proceeds in the 3' → 5' direction. *Id.*, ¶235. A POSA would know that the nucleotide on the 3'-end would have been bound to a solid support (and thus made via the succinate) and the remaining nucleotides would have been sequentially added in coupling steps in a 3' → 5' fashion (i.e., added using phosphoramidites). *Id.*, ¶235.

Scaringe discloses the synthesis of 4 RNA sequences as shown in Table 4 (the first four sequences shown below).

Table 4

Name	Sequence 5'-3'	Length
S	GCG CCG AAA CAC CGU GUC UCG AGC	24
R	GGC UCG ACU GAU GAG GCC C	18
μ-Helix	GGG GCU AUA GCU CUA GCU CCA CCA	24
m-Helix	GGG GCU AAG CCG UUC GAU CCC GCU UAG CUC CAC CA	35
1.	TTTTTrATTTT (2% 5'-2')	10
2.	TTTTTrATTTT	10
3.	TTTTTrGTTTT	10

Ex. 1022, 5436. According to Dr. Hrdlicka, none of those four sequences shows a guanosine on the 3'-end, and they all instead show C, C, A, and A at their 3'-ends, and there is no evidence of guanosine (or U) being bound to a solid support through a succinate or otherwise. Ex. 2022, 5436; Ex. 2008, ¶236. Thus, a POSA would not have viewed Compound 5(c) as a lead compound and would have instead viewed Compounds 5(a) or 5(b) as leads because they were demonstrated as bound to a solid support used for RNA synthesis.

Accordingly, for at least these reasons, Claim 4 is not unpatentable.

3. A POSA Would Not Have Been Motivated by Pitsch and Fan to Install an Acetyl Protecting Group on Compound 5(c) of Scaringe and Petitioner Fails to Provide any Rationale as to How a POSA Would Have Done So with a Reasonable Expectation of Success

A POSA would have also known, as discussed in Section VI.B., that the prior art taught away from using acetyl groups to protect the N2-position of guanosine derivatives based on the demonstrated instability of acetyl group and that acetyl groups would have made guanosine derivatives less soluble in organic solvents than isobutyryl. Ex. 2013, 400; Ex. 2008, ¶238. Accordingly, a POSA would not have been motivated by Pitsch and Fan to pursue a course antithetical to established teachings in the art. Pet., 51. Ex. 2008, ¶238.

Petitioner also argues that a “POSA would have recognized that the substitution of the protecting group on the exocyclic NH₂ group of the guanine base *would not be affected by* the O2'-TBDMS protecting group, which had been commonly used to shield the 2'-OH.” Pet., 51 (citing Ex. 1007). But Petitioner’s reliance on Beaucage (Ex. 1007) is misplaced because that reference does not disclose the use of an acetyl group on the N2-position of guanosine derivatives in conjunction with O2'-TBDMS protecting groups, never mind providing evidence that the substitution “would not be affected by the O2'-TBDMS protecting group.” *Id.*; Ex. 2008, ¶239.

Similarly, Petitioner fails to provide any rationale as to how a POSA would have synthesized the “5'-O-DMT-2'-O-TBDMS N2-acetyl guanosine 3'-O-succinate” molecule, and fails to provide any evidence or argument for reasonable expectation of success for that molecule. Ex. 2008, ¶240.

Therefore, Petitioner’s arguments on these points rely solely on the conclusory, hindsight-based testimony of Dr. Baran should be given little or no weight. 37 C.F.R. § 42.65(a). *See also* Fed. R. Evid. 702(b)-(d); *Xerox*, IPR2022-00624 Paper 9 at 15.

Accordingly, for at least these reasons, Claim 4 is not unpatentable.

F. Ground VI is Moot Subject to the Board’s Interpretation of Claim 5 and Patent Owner’s Motion to Amend

As discussed in Section IV above, Patent Owner agrees with Petitioner’s contention that Claim 5 should be interpreted such that “M” should be “ethyl” and not “succinyl.” Patent Owner also agrees that Claim 5 should be interpreted such that the last clause in Claim 5 should read “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. 2008, ¶242. This interpretation should apply in connection with the merits of the Motion to Amend which deletes “B” as “cytosine-N-isobutyryl” from Claim 5’s Markush group, in response to this ground.

Accordingly, subject to the Board's claim construction and ruling on Patent Owner's Motion to Amend, and without prejudice to Patent Owner's rights to the other patentably distinct compounds in Claim 5's Markush group (e.g., where "B" in Formula 2 is guanine-N-acetyl, adenine-N-acetyl, 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 VI is rendered moot.

Alternatively, should the Board not construe Claim 5 in this manner then Ground VI fails because the reference that Petitioner relies on for this Ground VI (i.e., Gaur (1992)), does not disclose a compound where "Z" is C(O)-M-C(O)-NH where "M" is succinyl or any of the remaining compounds listed in Claim 5's Markush group (i.e., where M is "oxalyl" or "hydroquinolynyl"). Accordingly, because all of the limitations of uncorrected Claim 5 are not taught by Gaur (1992) under this interpretation, Petitioner fails to make a case of anticipation for Ground VI. *Sanofi-Synthelab*, 550 F.3d at 1084.

VI. CONCLUSION

For the reasons set forth above, and in its Motion to Amend, Patent Owner respectfully requests that the Board affirm the validity of the challenged claims, as issued and amended.

Dated: October 17, 2023

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this Patent Owner Response complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This Patent Owner Response contains 13,929 words as calculated by the “Word Count” feature of Microsoft® Word for Mac Version 16.77.1, the word processing program used to create it. Pursuant to the Trial Practice Guide (August 2018 Update), the page and word count do not include the table of contents, table of authorities, mandatory notices under § 42.8, certificate of service, or appendix of exhibits or claim listings. The undersigned further certifies that this response complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This Patent Owner Response has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14-point font.

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CERTIFICATE OF SERVICE

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