

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 SUR-REPLY

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I. INTRODUCTION

ChemGenes respectfully submits this Sur-Reply to Hongene's Reply ("Reply") (Paper 20) to the Patent Owner Response ("POR") (Paper 16).

II. CHEMGENES' POSA DEFINITION IS PROPER

ChemGenes' POSA definition is proper because the subject claims are directed to P(III) nucleosides and POSAs should have the proposed experience in P(III) nucleoside chemistry and synthesis and a background in medicinal chemistry is not necessary. Dr. Baran ("Baran") testified he viewed the POSA definition as "malleable" and that he "had no problem" with the "other definitions" proposed. (Ex. 2032, 177:17-178:1). ChemGenes prevails under either definition.

III. BARAN IS BIASED AND HRDLICKA'S TESTIMONY SHOULD BE GIVEN MORE WEIGHT

A. Hongene and Baran Concealed Dr. Baran's Significant Business Relationships with Hongene¹

It was recently discovered that on January 20, 2023, the day after Hongene filed its Petition, Hongene contacted Baran to discuss "work[ing] together." (Ex. 2033).

¹ Section III.A. and related exhibits are filed under seal because Hongene argued they contain "Outside Attorneys' Eyes Only" information under the Protective Order (Paper 26), which ChemGenes disputes.

On August 7, 2023, Hongene agreed to pay Baran \$70,000 for service on its “Advisory Board” over the course of 1-year, which can renew. (Ex. 2032, 121:3-4; Ex. 2034, HONG_0000031). Baran did not disclose this arrangement during his September 13, 2023 deposition or in his January 19, 2024 Reply Declaration (Ex. 1033).

Baran testified during his February 20, 2024 deposition that Hongene’s counsel “knew about the SAB” but the information was withheld because “none of us thought it was relevant” (Ex. 2035, 121:14-20). Hongene’s counsel erroneously instructed Baran not to answer follow-up questions on the basis of “privilege[],” “work product, et cetera.” (*Id.*, 121:21-122:1).

Also recently discovered, Elsie Biotechnologies (of which Baran is a co-founder) has been [REDACTED]
[REDACTED]
[REDACTED]. (*Id.*, 145:23-146:4; Ex. 2039, HONG_0000014; Ex. 2038, HONG_0000017).

It was also discovered that [REDACTED] and Hongene have been engaged in discussions during the pendency of this case regarding evaluation of “[REDACTED]
[REDACTED]” for use with [REDACTED]. (Ex. 2035, 149:8-150:4).

Hongene and Baran withheld this information from the record despite Baran being asked direct questions during his January 22 deposition that invited its

disclosure. (Ex. 2032, 114:23-115:8, 160:19-161:7). ChemGenes discovered this information only after obtaining limited document discovery and questioning Baran during his February 20 deposition. When asked why he did not disclose this information, Baran testified it was as relevant as his “favorite color sweater ...” (Ex. 2035, 151:5-21).

Baran owns approximately “10%” and “3 million” shares of Elsie and testified he would “personally financially benefit if Elsie does well” which is where his “conflict of interest or individual ability to profit comes from.” (Ex. 2032, 85:16-21, 112:5-9; Ex. 2035, 157:20-158:13).

He also testified during his January 22 deposition he had no other agreements in place with Hongene and was first contacted by Hongene in July 2023, but it was later discovered he had executed a “CDA” with Hongene on February 9, 2023. (Ex. 2035, 122:12-123:23; Ex. 2036, HONG_0000030).

Despite all this, Baran testified that he has “nothing to hide” contemptuously stating “you can check my DNA ... whatever you like ... I think it’s all funny.” (Ex. 2035, 141:8-15, 153:6).

B. Baran Lacks Significant Experience in P(III) Nucleoside Synthesis

Other than conclusory statements, the record does not show Baran has significant experience in *P(III) nucleoside chemistry and synthesis*, as neither Hongene nor Baran identify specific papers, companies, consultancies, awards,

patents, or other facts that demonstrate he does. Nonetheless, Baran, prone to overstatement, repeatedly belittles this complex and unpredictable technology as “simple,” “trivial,” “undergraduate,” “pedestrian,” and “beneath the skills of our group.” (Ex. 2032, 185:2-19; Ex. 2009, 161:6-12).

Baran’s financial and business interests with Hongene, Hongene and Baran’s concealment of those interests, and Baran’s lack of experience in P(III) nucleoside synthesis, should be strongly considered when evaluating the weight of his testimony and his bias. *See, e.g.*, 4 Weinstein’s Federal Evidence §607.04 (“the trier of fact must be sufficiently informed of the underlying relationships [(including “business” relationships)], circumstances, and influences operating on the witness to determine whether a modification of testimony reasonably could be expected as a probable human reaction.”)

This all contrasts with Dr. Hrdlicka (“Hrdlicka”) who has spent his entire career in P(III) nucleoside chemistry and synthesis, is and was a POSA in the 2009 timeframe under any definition, is an objective witness with no affiliation to ChemGenes other than his service on this case, and his opinions should therefore be given more weight. (Ex. 2008, ¶¶87-88).

IV. P(III) CHEMISTRY IS HIGHLY COMPLEX AND UNPREDICTABLE

Hongene argues POSAs “would have been well-equipped to manage” the unpredictable nature of **SPOS** (Reply, 2), but is silent regarding the same for **P(III)**

reagent synthesis, which is at issue here. As Hrdlicka explained, developing new P(III) reagents was highly unpredictable in 2009 (and is now), involving numerous complex synthetic steps to reach a desired reagent. (POR, 6-8; Ex. 2008, ¶¶65-70). Pitsch did not teach otherwise, merely describes 2'-TOM phosphoramidites used in SPOS, and is silent on the complexity and unpredictability of developing P(III)-based nucleosides.

V. HONGENE ADMITS IT DID NOT APPLY THE LEAD COMPOUND ANALYSIS

Remarkably, Hongene and Baran admit they did not apply the Federal Circuit's lead compound analysis ("LCA") to support any of Hongene's grounds in this case on the basis that LCA is not "relevant" to "reagents." (Reply, 4, 6, 28; Ex. 2035, 29:21-30:3, 31:25-32:3, 94:4-95:20). Hongene now invites the Board to adopt its rigid rule. (Reply, 4, 6, 28). The Board should not accept Hongene's invitation.

First, contrary to Hongene's argument that phosphoramidites are simply "reagents" and not "therapeutic compounds" (*id.*, 4), phosphoramidites carry "important" oligonucleotide monomers that once installed have therapeutic effect within the oligonucleotide, as Baran admitted (Ex. 2035, 50:25-51:9, 52:4-53:19). Accordingly, the subject nucleosides contain compounds with therapeutic potential and Hongene mischaracterizes them to suit its unsupported legal theory.

The Federal Circuit uniformly applies LCA to “new chemical compound[s]” in order to protect against the dangers of “hindsight bias.” *Otsuka Pharm. Co., v. Sandoz, Inc.*, 678 F.3d 1280, 1291-93 (Fed. Cir. 2012) (quoting *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007)). Hongene’s reliance on *UCB, Inc. v. Accord Healthcare, Inc.* and *Otsuka* is misplaced because *UCB* involved racemic mixtures (not “new compounds” as here) and *Otsuka* **applied** LCA when the challenge included “selecting and modifying *particular* prior art compounds” (as Hongene does here). 890 F.3d 1313, 1329 (Fed. Cir. 2018); 678 F.3d at 1291-93 (emphasis added).

Hongene also misapplies *NOF Corp. v. Nektar Therapeutics*, IPR2019-01397, Paper 70 (P.T.A.B. Aug. 5, 2021) where petitioner argued obviousness based on a prior art genus (“branched polymers”) as applied to claimed species. *Id.* at 12. The *NOF* Panel explained that the law of “species ... over ... genus” patentability “is less than clear,” and “therefore” looked to “the general law of obviousness for guidance.” *Id.* at 11. Here, there is a “species-to-species” challenge and the referenced “species over genus” issues are not at play. The *NOF* panel did not hold LCA was not applicable to reagents, and appears to have applied the first prong of LCA, i.e., whether POSAs “would have had (1) a reason to select the [prior art compounds] for further development” *Id.* at 14.

Moreover, other courts have applied LCA to non-“therapeutic” compounds. *See, e.g., Ex Parte Ryan A. Littich*, App. No. 2017-004796, *1 (P.T.A.B. May 30, 2019) (surfactants, see, U.S. Patent No. 10,501,429 1:25-51)); *AAT Bioquest, Inc. v. Texas Fluorescence Lab’ys, Inc.*, No. 14-cv-03909-DMR, 2015 WL 1738402, at *1 (N.D. Cal. Apr. 13, 2015) (calcium ion indicators (i.e., fluorescent dyes)).

Whether to apply LCA is not a binary choice as LCA exists within the flexible *KSR* framework to protect against hindsight, but it should not be completely ignored as Hongene has done. LCA applies here because: (1) Claims 2, 3 and 4 claim “new chemical compounds”; (2) no rigid rule that LCA does not apply to “reagents” exists; and (3) the claimed compounds should be protected from cancelation via hindsight bias.

The dangers of hindsight are prevalent here. There is no dispute there were thousands of phosphoramidites and nucleosides available for use in SPOS in 2009. (POR, 12; Ex. 2008, ¶78). Hongene now identifies even more complexity POSAs would have faced in selecting and modifying related compounds including alleged “myriad motivations” relating to oligonucleotide properties.² (Reply 5-6). Hongene

² Hongene identifies new alleged “motivations” (Reply, 4-6) not raised in its Petition and should therefore not support Hongene’s *prima facie* case. (PTAB Consolidated Trial Practice Guide (2019) (“T.P.G.”), 73-75).

provides no reason or motivation why POSAs would have selected the compounds it relies on from this large universe none of which are identified as leads even within their own respective disclosures.

If the Board determines LCA applies, Grounds II through V fail because Hongene intentionally did not apply or satisfy it (including its first prong). ChemGenes addresses all of Hongene's substantive arguments and would prevail whether LCA is applied or not.³

³ As the *NOF* Panel explained, "a party may take several different paths" to support its obviousness grounds and in that case the ***petition*** applied "standard principles of obviousness." *NOF*, at 10-11. Here Hongene did not cite ***to a single case or identify a specific obviousness theory*** in its Petition, which is misleading and prejudicial to ChemGenes in defending against Grounds II-V, violating 35 U.S.C. §312(a)(3) which requires the Petition to identify with "particularity" "the grounds on which the challenge to each claim is based" See *Intelligent Biosystems Inc. v. Illumina Cambridge, Ltd.*, 821 F.3d. 1359, 1369 (Fed. Cir. 2016) ("it is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition" comply with 35 U.S.C. §312(a)(3)).

VI. GROUND II

A. Selecting Compound x was Driven by Hindsight

First, Hongene misrepresents ChemGenes' argument. ChemGenes did not argue LCA requires a "single" lead compound and stated just the opposite by identifying a class of '031 Patent "compounds" that could be leads. (POR, 23).

Second, Hongene's argument that Compound x would have been selected due to its "utility" in SPOS "alone" is hindsight-driven. (Reply, 6). Any of the numerous phosphoramidites available in 2009 had similar utility, and Hongene provides no rationale why a POSA would have chosen Compound x from among them. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1360 (Fed. Cir. 2007).

Furthermore, Compound x (a 2'-fluoro-2'-deoxyribonucleotide phosphoramidite) caused known degradation problems that would have "directed [POSAs] away" from Compound x, issues that Baran admitted he did not consider in his opening declaration. *Takeda*, 492 F.3d at 1359; (Ex. 2035, 61:1-62:5; *see also* Ex. 2024, 83; Ex. 2025, 833).

Third, contrary to Hongene's argument, as Hrdlicka established and sustained through cross-examination, Examples 12.iii, 13.iii, 13.v and 14.i **do not specify Compound x**, could have applied to any 2'-F-phosphoramidite (e.g., 2'-F-U, 2'-F-C^{PG}, 2'-F-A^{PG}), and provide no indication Compound x was ever used to synthesize the oligonucleotides in those examples. (Ex. 1035, 67:4-75:5).

Fourth, Hongene admits the '031 Patent figures “do not present data on any oligoribonucleotides containing 2'-fluoro monomers” but misleadingly downplays the detailed figures as merely “illustrative.” (Reply, 8). That the '031 Patent did not disclose data for Compound x further shows POSAs would not have been motivated to select and modify it.

Fifth, Hongene concedes the '031 Patent does not disclose deprotection rates, but now argues the 24-hour deprotection period “would have prompted POSAs to explore shortening that period.” (*Id.*, 8). This argument is new (not allowed under T.P.G., 73-75) and baseless, and Baran’s cited testimony that base deprotection occurs **at each cycle** of SPOS is contradicted by his other testimony that base deprotection occurs **in one step after SPOS is complete**. (Ex. 2009, 31:7-25).

Sixth, Hongene’s argument Compound x would have been selected for its biological properties contradicts its argument that LCA does not apply to phosphoramidite “reagents” (Reply, *cf.* 9 and 4) and again fails to support why POSAs would choose Compound x from numerous other phosphoramidites having similar “utility.”

B. Hongene Fails to Carry its Burden to Show Motivation for Multiple Independent Reasons

1. POSAs Would not have been Motivated to Use Acetyl on 2'-fluoro-2'-deoxyguanosine

First, Hongene's argument that Pitsch "universal[ly]" applies to all nucleosides is baseless. (Reply, 9, 14). Pitsch studied 2'-TOM-protected phosphoramidites (used for RNA) **only**, and did not study 2'-fluoro-2'-deoxyguanosine or even 2'-deoxyguanosine (used for chimeras and DNA, respectively, **but not** RNA). (POR, 30-36; Ex. 2035, 63:5-64:3, 67:6-9).

Despite this, Baran speciously argues Pitsch taught acetyl could "be used on **virtually any** nucleobase, regardless of the sugar substitution or type of nucleobase," while admitting Pitsch does not state this or provide any data beyond "2-prime-tom RNA nucleosides," and that he relied on "Merriam-Webster" to interpret the term "universal," (Ex. 2035, 65:9-67:9) thereby baselessly exaggerating Pitsch well beyond its teachings. (See POR, 30-38; Ex. 1035, 139:15-140:10).

Hongene further mischaracterizes Pitsch arguing it teaches "**use**" of acetyl in SPOS under "robust" basic conditions (Reply, 9), but Pitsch only discloses its **removal** after basic conditions are introduced (Ex. 1018, 3778).

Second, Hongene incorrectly argues Khorana's pioneering work in phosphodiester chemistry eschewing acetyl to protect the N2-position of deoxyguanosine "did not apply to phosphoramidite-based synthesis." (Reply 10). As

Hrdlicka testified, supported by exemplary references (POR, 25-27), Khorana's teachings regarding acetyl "inspired the field" as it progressed into P(III) phosphoramidite chemistry (Ex. 2008, ¶¶107-111).

Baran likened Nobel Laureate Khorana's teachings to "the earth is flat" and useful only for "historical" and "classroom" purposes. (Ex. 2035, 71:19-72:10). Baran also testified he did not need to consider any other literature after he "identified Pitsch." (*Id.*, 73:10-18). This myopic approach ignores the broader "scope and content of the prior art" that a POSA would have considered and demonstrates classic hindsight.

Hongene's argument Khorana used "harsh deprotection conditions" (Reply, 10) is also incorrect because Khorana's study used ammonia during deprotection, which as Baran acknowledged, is milder (less basic) than methylamine used in Pitsch. (Ex. 2035, 22:17-20; Ex. 2011, 240; Ex. 1035, 112:3-114:8, 125:6-127:8).

Furthermore, Hongene erroneously relies on Schulhof which features **2'-phenoxyacetyl** (PAC) as an alternative to isobutyryl to protect the N2-position of 2'-deoxyguanosine and lists over a dozen additional alternative protecting groups, ***none of which are acetyl***. (See Ex. 2013).

Moreover, Hongene's argument "phosphodiester conditions were problematic for RNA oligonucleotide synthesis" (Reply, 11) is misplaced because the 2'-fluoro-

2'-deoxyguanosine compounds at issue would not have been used for RNAs (POR, 33-36).

Third, Hongene relies on Pitsch and the '719 Patent to argue acetyl was used “after Khorana,” but provides ***no evidence*** or argument acetyl was used to protect N2-guanine for non-RNA nucleosides like 2'-fluoro-2'-deoxyguanosine (or even 2'-deoxyguanosine). Furthermore, Hongene’s argument ChemGenes “ignores” Compound 5 (Reply, 11) from the '991 Patent in its summary of exemplary literature fails because Compound 5 is an ***acetyl-protected cytosine***, a known application for acetyl, and is therefore inapt because it is not a guanine-based nucleoside (POR, 61-64).

Fourth, contrary to Hongene’s argument, the cited exemplary literature before and after Pitsch indeed demonstrates the field followed the teachings of Khorana not to use acetyl to protect the N2-position of guanine. (*E.g.*, Ex. 2019 (Scaringe) (2004); Ex. 2023 (Culf) (2008); Ex. 2006 (Hogrefe) (2013)).

2. POSAs Would Not Have Been Motivated to Make Compound x Less Soluble in Organic Solvents

First, the known solubility problem for 2'-fluoro-2'-deoxyguanosine is not “refuted” by Pitsch which studied totally different “RNA”-based compounds. (Reply, 12). Pitsch’s Compound 20 had large hydrophobic 2'-O-TOM groups at its 2'-position making it “more lipophilic” than 2'-fluoro-2'-deoxyguanosine (as Baran

testified) and therefore less likely to fail during synthesis due to insolubility. (Ex. 2035, 78:20-79:4).

Second, Hongene's argument a "high degree" of solubility is "not needed" in SPOS is ambiguous (providing no parameters for "high degree") and based solely on Baran's unsupported testimony. (Reply, 12). Given the known solubility problems of guanine-based-nucleosides, especially those lacking 2'-protecting groups, POSAs would not have been motivated to use acetyl because it would have made Compound x less soluble in organic solvents. (POR, 27-29; Ex. 2008, ¶¶112-116).

Third, contrary to Hongene's argument, Sinha and Schaller explicitly identify "[p]roblems associated with solubility of deoxyguanosine-phosphoramidites" (Ex. 2018, 14) and using acetyl with 2'-deoxyguanosine caused "failure ... due to [] insolubility" (Ex. 2012, 3822, fn. 21). Reference to Pitsch is inapt because Pitsch teaches different RNA-based molecules with large hydrophobic 2'-TOM groups and Sinha and Schaller teach compounds lacking 2'-protecting groups (like 2'-fluoro-2'-deoxyguanosine) having known solubility issues. (POR, 28-29).

Fourth, Hongene's reliance on Donga is misplaced because, like Pitsch, Donga teaches RNA with protecting groups for 2'-OH but not less soluble 2'-deoxyguanosine or 2'-fluoro-2'-deoxyguanosine, which do not require lipophilic 2'-

protecting groups. (Ex. 1029; Ex. 2035, 78:20-79:10 (acknowledging Compound 20 would be “more lipophilic” than same compound but with 2'-fluorine)).

3. Pitsch and Fan Studied RNA, not 2'-Fluoro-2'-Deoxynucleosides or 2'-Deoxynucleosides

First, Hongene and Baran’s “RNA like” theory to bolster its motivation theory is new (not allowed under T.P.G., 73-75) and baseless. (Reply, 14). Baran omits Kawasaki’s teachings that show “CD Spectra” and “thermal” data related to “2'-deoxy-2'-fluorocytidine, -uridine, inosine, and -adenosine,” **but not -guanosine**. (Ex. 2025, 831-32).

Remarkably, Baran’s new theory (not allowed under T.P.G., 73-75) that 2'-fluoro-2'-deoxyguanosine is “more closely related to RNA than DNA” (Ex. 1033, ¶56) directly contradicts his other theory that 2'-fluoro-2'-deoxyguanosine would react “similarly” to DNA (*id.*, ¶78). It is also baseless because 2'-deoxyguanosine was known to have greater depurination risk during SPOS than guanosine (RNA with 2'-OH) as Baran admitted. (Ex. 2035, 58:13-59:13; Ex. 2016, 10 (“2'-OH has a **significant effect** on the nucleoside’s susceptibility to depurination”) (emphasis added)).

Second, Hongene stretches Pitsch as teaching acetyl would “universally” apply to all bases of all nucleoside amidites. (Reply, 9, 14). Pitsch did not suggest use of acetyl with a single alternative nucleoside beyond the TOM-protected ones it

studied and to read Pitsch to apply to ***all possible nucleosides*** is an absurdly broad reading of this limited study. (POR, 30-38; Ex. 1035, 139:15-140:10).

Third, Hongene asserts another new theory (not allowed under T.P.G., 73-75) that the 2'-group and N2-protecting groups are so “chemically distant” they would not “affect each other’s reactivities,” relying on Baran’s testimony, “common sense,” and Zhu (Ex. 1038, 1235) that allegedly shows “little or no variation in reaction times, regardless of the 2' group.” (Reply, 14). **But Table 1 of Zhu, below, shows a 300% increase in silylation and benzoylation time (0.5-1.5 hrs and 2-6 hours, respectively) going from guanosine to 2'-deoxyguanosine (the only difference being a 2'-OH vs 2'-H) further demonstrating Hongene’s meritless argument. Baran admitted to this.** (Ex. 2035, 81:4-82:14).

Table 1. N-Benzoylation of ribo-, arabino-, 2'-deoxy-ribo nucleosides.

Entry	Substrate	TMSCI (eq.)	Silylation time (h)	Benzoylation time (h)	Yield (%)
1	adenosine	3.3	0.5	2	96
2	cytidine	3.6	0.5	4	95
3	guanosine	3.6	0.5	2	99
4	ara-adenosine	3.6	1.0	2	95
5	ara-cytidine	3.6	1.0	4	98
6	ara-cytidine monohydrochloride	3.6	1.0	4	93
7	2'-deoxycytidine monohydrochloride	2.4	0.5	4	96
8	2'-deoxycytidine monohydrate	2.4	0.5	4	81
		3.6	0.5	4	98
		4.8	0.5	4	95
9	2'-deoxyadenosine monohydrate	3.6	0.5	2	91
10	2'-deoxyguanosine monohydrate	3.6	1.5	6	98

(Ex. 1038, 1235) (highlighting added).

4. Hongene Admits Degradation Problems Existed for 2'-fluoro-2'-deoxyribonucleotides

Hongene admits 2'-fluoro-2'-deoxyribonucleotides had degradation problems, but baselessly characterized it as a “potential” problem that was solved. (Reply, 15).

Both Sinha (Ex. 2024, 83 (2'-fluoro-2'-deoxyribonucleotides of chimeras are “subject to depyrimidation” in methylamine)) and Kawasaki (Ex. 2025, 833 (observing “significant degradation of 2'-deoxy-2'-fluorpyrimidine nucleosides” in NH_4OH)) identify an actual, not “potential”, problem, which corroborates the statements in the '885 Patent (Ex. 1001, 10:63-11:54).

Hongene argues the problem was “minimized” using ethanolic ammonia rather than methylamine. (Reply, 15). However, POSAs would have understood that using Compound x (a 2'-fluoro-2'-deoxyribonucleotide) limited their choices for deprotection conditions only adding to its known “negative properties,” deterring a POSA from selecting it. *Takeda*, 492 F.3d at 1359.

5. Pitsch and Fan Would Not Have Motivated POSAs to Switch to Acetyl for Faster Deprotection

First, contrary to Hongene’s argument, as discussed above, Pitsch and Fan taught RNA-based building blocks with reactive -OH groups requiring protection, not 2'-deoxyguanosines (as in Khorana) or 2'-fluoro-2'-deoxyguanosines (as in Compound x). (POR, 30-36). A POSA would have therefore relied on Khorana’s teachings and progeny that using acetyl with 2'-deoxyguanosine (including 2'-fluoro-

2'-deoxyguanosines) was unstable. POSAs would not have been motivated to deviate from those teachings no matter how “fast” Pitsch and Fan (both RNA-based studies) allegedly deprotected acetyl. (*Id.*, 24-27).

Second, Fan teaches PAC deprotected ***over 57 times faster*** than acetyl (4.7 minutes vs. 270 minutes), and therefore, if speed was the motivating factor, POSAs would have chosen PAC over acetyl. (Ex. 1019, 2556). A POSA would have also known PAC was larger and more lipophilic than acetyl, and was considered a viable protecting group for non-RNA 2'-deoxyguanosine as taught by Schulhof and other literature. (POR, 28; Ex. 2008, ¶¶113-114; Ex. 2013, 401; Ex. 2023, 82).

Third, Hongene speculates that Fan chose deprotection conditions to facilitate comparison of deprotection rates (Reply, 16-17) and ignores ChemGenes’ argument that deprotection conditions in Fan were not compatible with oligonucleotides, thereby admitting the same. (See POR, 38; Ex. 2008, ¶135).

Finally, Hongene fails to rebut ChemGenes’ argument that Example 8 of the ’031 Patent omits deprotection rates and thus would not have motivated POSAs.

C. Hongene Fails to Carry its Burden to Show Reasonable Expectation of Success for Multiple Independent Reasons

1. Baran’s Synthesis Theory is Baseless

First, Hongene deflects by arguing Fan’s failures were based on yield and not synthesizing the subject compound. (Reply, 17). In doing so, it adds a new argument

to support its *prima facie* case (not allowed under T.P.G., 73-75) that TMSCl treatment (as in Fan) would be needed in Step ii of Example 4-d, but provides no explanation as to what effect adding TMSCl might have within that scheme. Hongene also erroneously argues Donga did not have difficulties “**obtaining**” acetylated guanosine (Reply, 18) but omits that Donga does not teach its synthesis or where it obtained it.

Second, remarkably, Hongene argues “Chemgenes has not shown that TBAF **would not work.**” (*Id.*, 18). This is Hongene’s burden. ChemGenes has nonetheless demonstrated through Hrdlicka’s testimony supported by literature that POSAs would have expected TBAF to cleave the unstable acetyl groups. (POR, 45-47; Ex. 2008, ¶¶154-57). Hongene’s attempt to distinguish Ober is flawed, again not justifying how the “pyridine buffered pyridine-HF complex,” eventually used in Ober through significant experimentation, would have reacted in Step iii and Example 4-d’s overall scheme. (Ex. 2015, 18144).

Third, contrary to Hongene’s argument, there is ample support from Hrdlicka and cited literature that POSAs would have understood unprotected guanine-based nucleosides are highly polar and not functionally soluble in organic solvents. (POR 27-29; Ex. 2008, ¶¶112-116).

Hongene attempts to rebut this under Baran’s new (not allowed under T.P.G., 73-75) and unsupported theory that “removing two carbon atoms” (i.e., “going from

isobutyryl to acetyl”) would not affect solubility in the subject synthesis scheme. (Reply, 18; Ex. 1033, ¶74). In doing so, Baran ignores that compound 4-d (iii) has **two** isobutyryl groups and therefore switching to acetyl groups would remove **four**, **not two** carbon atoms, and thus reduce solubility **twice** as significantly as Baran argues, which would have had a significant impact on its solubility. (POR, 47-48; Ex. 2008, ¶¶158-161).

Baran also relies on Pitsch and other references for the proposition that none report “solubility-induced reactivity challenges,” (Reply, 19; Ex. 1033, ¶74) while ignoring that the subject compounds had large hydrophobic 2’-protecting groups and not the more polar 2’-fluoro-deoxyguanosine compounds at bar (Ex. 1029; Ex. 2035, 78:20-79:10).

Fourth, Hongene’s sole reliance on Pitsch to argue that using sodium hydroxide in Step v. would not have caused “any problems” is meritless. (Reply, 19). Again, Pitsch teaches totally different molecules and 2'-substituents, and the results of that study are not reliably applicable to 2'-fluoro-2'-deoxyguanosine. (POR, 39; Ex. 2008, ¶138).

Also, as explained by Hrdlicka and supported by literature, POSAs would expect TBAF to cause **both** acetyl groups to cleave rather than a single acetyl under Example 4-d’s “selective deprotection” protocol. (POR, 45-47; Ex. 2008, ¶¶154-

157). Hongene fails to show how such selective deprotection would have occurred under its theory.

Hongene or Baran could have conducted tests to prove Baran's theory that the claimed molecule could have been synthesized by "simply" substituting acetic anhydride in Step ii. of Example 4-d, but at least Baran did not do so. (Ex. 2035, 92:15-93:7).

2. Hongene's Arguments Regarding Sivets Remain Meritless and Illogical

First, Hongene and Baran again fail to support their baseless theory that 2'-fluoro-2'-deoxyguanosine would "react similarly" to "regular" 2'-deoxyguanosine (DNA). (Reply, 20; Ex. 1003, ¶123). Hongene's new reliance on Zhu is erroneous because, as discussed above, Table 1 clearly shows the ***substituents had a 3-fold effect on reactivities***.

This theory is also contradicted by Baran's new theory that 2'-fluoro-deoxyguanosine was "RNA-like" and had reactivities ***more like*** RNA (having -OH) ***than DNA*** (having -H). (Reply, 14; Ex. 1033, ¶56). According to Hongene and Baran, 2'-fluoro-deoxyguanosine is "DNA-like" for purposes of their Sivets arguments and "RNA-like" for their arguments relating to Pitsch and Fan. (Reply, *cf.* 14 and 20). Both theories are meritless.

Second, ChemGenes' solubility arguments are scientifically sound and fully supported by Hrdlicka's testimony and cited literature. (*E.g.*, POR, 27-29, 47-48; Ex. 2008, ¶¶112-116, 158-60).

Third, Hongene's unsupported new theory that POSAs "would have expected the installation" of base protecting groups on "2'-deoxy- and 2'-F-monomers to be *easier*" than on monomers with "reactive oxygen-bound substituent at the 2' position" is contradicted by Hongene and Baran's other new theory that the 2'-substituents *are so "chemically distant" from the nucleobase protecting groups that they do not "affect each other's reactivities"* (Reply, 14, 20; new theories not allowed under T.P.G., 73-75).

Fourth, Hongene's baselessly argues the flawed Pitsch protocol was due to the "catalytic" nature of NaOH, as nothing in Baran's citation to Exhibit 1041 demonstrates such a phenomenon and he therefore reverts to reliance on mere "simple logic." (Reply, 21; Ex. 1033, ¶85).

Finally, Hongene again provides no evidence 2-fluoro-2'-deoxyguanosine was commercially available (POR, 51) and this argument therefore fails.

D. Secondary Considerations Further Establish the Patentability of Claim 2

First, the statements and scheme in the '885 patent (1) show the degradation problem existed and was experienced by others; (2) were made at the time of the

patent application; (3) were verified under oath; and (4) were not made in view of litigation and were therefore not “self-serving.” (Ex. 1001, 10:63-11:54; Ex. 1002, 7-9, 11, 24-26, 81-82).

Second, the '885 Patent identifies a presentation by “Nanda D. Sinha” at “Eurotides, 2005, Munich, Germany” demonstrating “depyrimidation” of “2'-fluoro-2'-deoxy pyrimidines” and the chapter in Exhibit 2024 (by the same author Nanda D. Sinha) identifies the “depyrimidation” problem. (Ex. 1001, 11:43-47; POR, 57). Exhibit 2024 therefore corroborates the statements in the '885 Patent.

Contrary to Hongene’s argument, the '885 inventors avoided depyrimidation by inventing a new chemical compound that could be used without having to resort to limited deprotection conditions (e.g., use of methanolic ammonia as in Kawasaki), which was an unexpected result. (POR, 58-60).

Third, the '885 Patent, Kawasaki, and Sinha all describe the challenges posed by depyrimidation/degradation and any cited workaround using limited deprotection conditions does not mean the challenge did not exist. (Ex. 1001, 10:63-11:54; Ex. 2025, 833; Ex. 2024, 83).

Fourth, the corroborative Sinha chapter and Kawasaki (from 1993 which Hongene ignores) plainly identify depyrimidation/degradation. (POR, 32, 57; Ex. 2024, 83; Ex. 2025, 833). Hongene’s “hand-in-hand” argument (Reply, 22-23) is

new (not allowed under T.P.G., 73-75) and directed to RNA, not 2-fluoro-2'-deoxyguanosine, and therefore does not carry any weight.

Fifth, the evidence shows that the sole N2-Acetyl-2'-fluoro-2'-deoxyG compound that was challenged by Petitioner caused unexpected results and addressed a longstanding need, thereby demonstrating a “legally and factually” significant connection between the challenged compound and evidence presented which is probative of non-obviousness. *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Finally, ChemGenes did not argue others tried but failed to make the **subject compound**, but instead, failed to satisfy **the demand** addressing an industry need which is “particularly probative” of non-obviousness. *Millenium Pharm., Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017).

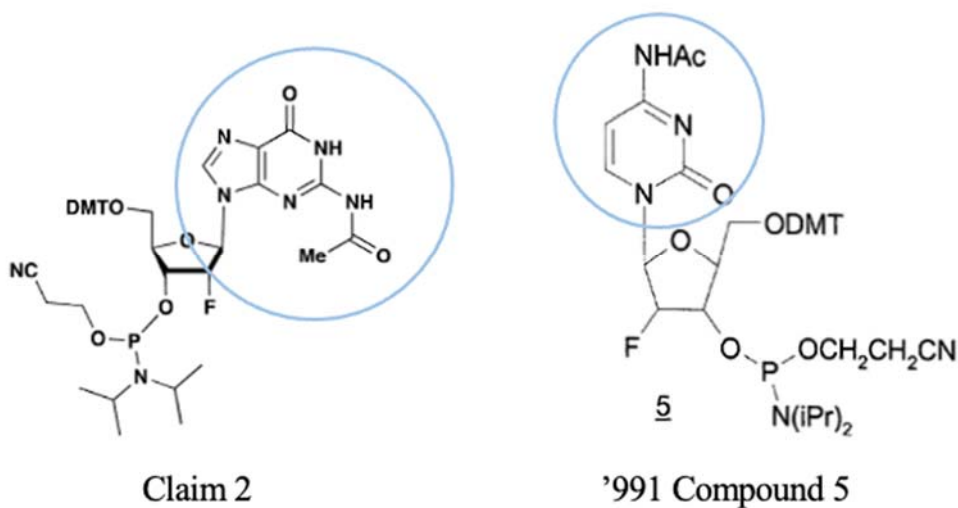
VII. GROUND III

A. A POSA Would Not Have Been Motivated to Make the Challenged Claim 2 Compound

First, Hongene baselessly argues Claim 2's 2'-fluoro-2'-deoxyguanosine compound would have been prepared “simply using D-guanosine as starting material instead of L-cytosine” under the “same procedures” (Reply, 23), failing to identify any exemplary “D-guanosine” compounds, “procedures,” or reaction conditions to support their argument (Ex. 1033, ¶97).

Moreover, Hongene's incorrect argument that Compound 5 would not react differently during SPOS (Reply, 23-24) is meritless because it ignores the different L- vs. D- configurations of the compounds and provides no evidence that L-configured phosphoramidites introduced onto growing oligonucleotides having D-configured nucleosides would somehow react similarly (or even what reactions they refer to).

Second, Hongene doubles down on its original argument that Compound 5 is “almost identical” to the claimed N2-Acetyl-2'-F-2'-deoxyG phosphoramidite. (Pet., 40; Reply, 24). Recall the compounds at issue:



As Hrdlicka explained, these compounds are completely different and not “almost identical,” as Baran agreed. (Ex. 2008, ¶¶197-207; Ex. 2009, 170:21-25).

Despite this, Hongene still argues “the two are closely structurally related” and “are identical” **“except for”** their nucleobase and stereochemistry, which are

quite significant differences. (Reply, 24). This baseless attorney argument that Baran did not support should not be afforded any weight.

Baran also does not support Hongene's new (not allowed under T.P.G., 73-75) argument POSAs would have been "immediately motivated" "by Compound 5" to make a "guanosine homolog." (Reply, 24). Nowhere does Baran refer to those compounds as "homologs," which they are not,⁴ and the unsupported attorney argument should be afforded no weight. (Ex. 1033, ¶¶100-101).

Third, Hongene again ignores LCA and argues "utility" of Compound 5 was "alone" enough for POSAs to select it. (Reply, 25). Again, Hongene provides no reason why POSAs would have selected Compound 5 from the '991 Patent's disclosures or the thousands of other phosphoramidites and other nucleosides available and its argument therefore fails.

Fourth, Hongene admits that the '991 Patent "conveys a preference" for "2'-F-modified" **pyrimidines** and acknowledges its "silence" regarding purines (Reply,

⁴ See, e.g., *Brenner v. Manson*, 383 U.S. 519, 522, fn. 3 (1966) (explaining homologs are "related compounds" that "var[y] **from member to member by CH(2)** (one atom of carbon and two atoms of hydrogen).") Here, Compound 5 plainly differs from the claimed compound by much more than a CH(2).

25), further making ChemGenes' point that the '991 Patent would not have motivated POSAs to make 2'-F-modified-guanine (purine).

Fifth, Hongene quotes the passage "can either be D- nucleic acids or L- nucleic acids" (Reply, 26) but omits the immediately following sentence: "***The nucleic acids are preferably L nucleic acids.***" (Ex. 1020, 11:33-34). This further establishes POSAs would not have been motivated to pursue D- over L-configured nucleic acids including for the additional reason the '991 Patent ***claims L-, not D-, configured compounds.*** (*Id.*, Cols. 179-182)

B. Hongene Fails to Carry its Burden to Show Reasonable Expectation of Success

Hongene relies on the same reasonable expectation of success arguments it made for Ground II (Reply, 26), which are without merit for at least the reasons ChemGenes provided for Ground II and Claim 2.

C. Secondary Considerations Further Establish Patentability of Claim 2

Hongene relies on the same arguments it made for Ground II (Reply, 26), which are without merit for at least the reasons ChemGenes provided for Ground II and Claim 2.

VIII. GROUND IV

A. Hongene Fails to Carry its Burden to Show Obviousness

First, Hongene's Claim 3 arguments relating to Claim 2's compound fail for at least the reasons for at least the reasons ChemGenes provided for Claim 2.

Second, Hongene's argument that POSAs would have expected "convert[ing] nucleosides to their corresponding phosphoramidites" would have "work[ed] better" with "2'-F-substituted species" (Reply, 27) is new (not allowed under T.P.G., 73-75) and only supported by Baran's conclusory statement, and therefore should be given little or no weight.

For at least the reasons in the POR and above, POSAs would not have been motivated by Scaringe, which Hongene relies upon solely for its teachings on succinates.

IX. GROUND V

A. A POSA Would Not Have Selected Compound 5(c)

First, as explained above, LCA should apply and ChemGenes does not argue LCA requires a "single" lead as Hongene erroneously argues, evidenced by ChemGenes argument POSAs would have viewed "Compounds 5(a) or 5(b) as leads" listed in Table 4. (POR, 74).

Second, Scaringe fails to provide any experimental data relating to Compound 5(c) further showing POSAs would not have selected it as a lead. (POR, 73-74).

B. A POSA Would Not Have Been Motivated to Make the Challenged Claim 4 Compound

First, Hongene relies on arguments it provided for Ground II (Reply, 29), which are without merit for at least the reasons ChemGenes provided regarding Claim 2.

Second, Hongene's argument that substituting the protecting group on the N2-position of guanine would not be affected by the O2'-TBDMS protecting group lacks merit for at least the reasons ChemGenes provided in the POR, which Hongene ignored (POR, 75).

C. Hongene Fails to Carry its Burden to Show Reasonable Expectation of Success for Claim 4

First, Hongene never argued how POSAs would have synthesized the "5'-O'DMT-2'-O-TBDMS N2-acetyl guanosine" in its Petition. (Pet., 51-52). Hongene now relies on its arguments for Claim 3 to allege reasonable expectation of success of Claim 4, a new argument not allowed under T.P.G., 73-75. (Reply, 29).

Moreover, Claim 3 involves a 2'-fluoro-succinate not a 2'-OTBDMS-succinate as in Claim 4, which are different molecules, and Hongene provides no argument accounting for this gap, even in its Reply. If this argument is considered, which it should not be, it also fails for the reasons provided in the POR and above regarding Claim 3.

X. CONCLUSION

Hongene failed to carry its burden of proving unpatentability by a preponderance of the evidence for at least the reasons in the POR and above.⁵

⁵ Hongene's Reply cites nearly exclusively to Dr. Baran's reply declaration but not to any of the exhibits Dr. Baran relies on, and many of the Reply's citations lack spacing (e.g., "Ex.1033 ¶9", "POR17," etc.), providing Hongene a significantly unfair word-count advantage.

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this Patent Owner Sur-Reply complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This Patent Owner Sur-Reply contains 5,600 words as calculated by the “Word Count” feature of Microsoft® Word for PC Version 2401 Build 16.0.1723.20194, the word processing program used to create it. Pursuant to the Trial Practice Guide (November 2019), 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 Sur-Reply has been prepared in a proportionally spaced typeface using Microsoft Word 365 in Times New Roman 14-point font.

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